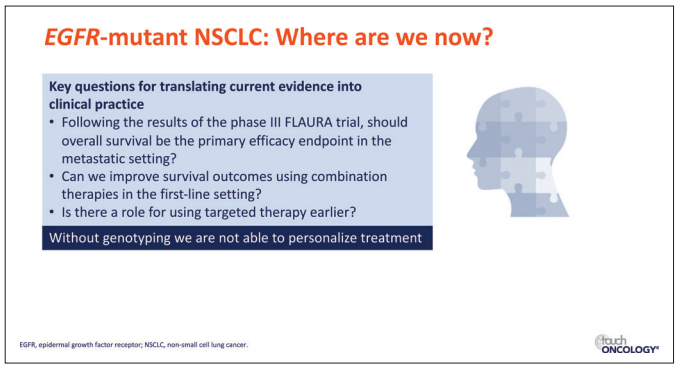
## Introduction and summary of key trials at ASCO20 Virtual

Hello, I'm Dr Roy Herbst, Chief of Medical Oncology and Professor of Medicine at the Yale Cancer Centre, Smilow Cancer Hospital, New Haven, Connecticut, USA.

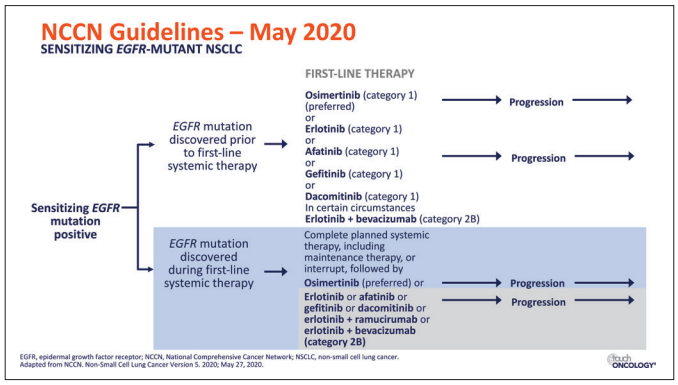
Thanks for joining me for this webinar: Progress in the management of *EGFR*-mutant NSCLC in 2020: Where are we now?

### *EGFR*-mutant NSCLC: Where are we now?




Where are we now with *EGFR*-mutant non-small cell lung cancer (NSCLC)? There are some key questions that remain for translating current evidence into clinical practice. Following the results of the phase III FLAURA trial, the question is should overall survival be the primary efficacy endpoint in a metastatic setting? Can we improve survival outcomes using combination therapies in the first-line setting? Is there a role for targeted therapy even earlier? We must remember that without genotyping, we're not able to personalize any treatment, because if we don't know who has *EGFR* mutation, we can't identify them for any of these treatment approaches.

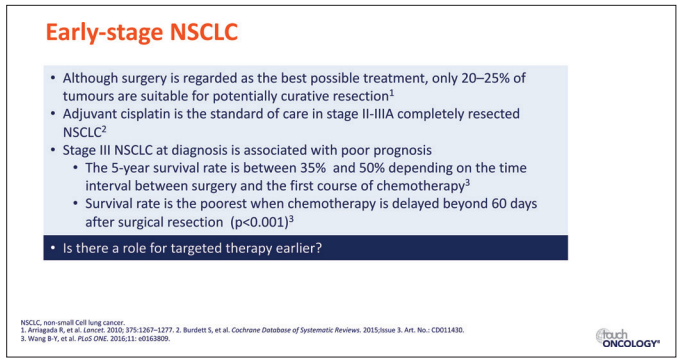
### NCCN Guidelines – May 2020




Let's start with the NCCN guidelines. I work here at the Yale Cancer Centre at Yale University; we are an NCCN institution and use these guidelines quite often. As you can see patients with sensitizing *EGFR*-mutation positive abnormalities are on the left and then there are two different groups: *EGFR* mutation is discovered prior to the first-line systemic therapy, or *EGFR* mutation is discovered during the first-line therapy. If you know the mutation beforehand (which I would contest is preferable, and is the reason why we should try to test everyone), there are five different drugs that have category 1 recommendations; erlotinib + bevacizumab is category 2B. Then of course when patients progress, the question is what to do then? For those patients with *EGFR* mutations discovered during systemic therapy, then one would complete the planned therapy and then I would switch. In both cases [EGFR mutation discovered prior to or during first-line systemic therapy], osimertinib is the preferred drug when one can use it.

## WILL TARGETED THERAPIES PLAY A SIGNIFICANT ROLE IN THE ADJUVANT SETTING?

### Early-stage NSCLC




What do we know about early-stage NSCLC? Although surgery is regarded as the best treatment option, only 20–25% of tumours are suitable for potentially curative resection, meaning many of these tumours will recur. Adjuvant cisplatin is the standard of care in stage II–IIIA completely resected NSCLC and in some stage IB disease. Stage 3 lung cancer diagnosis is associated with poor prognosis. The five-year survival rate is between 35–50%; depending on the time interval between surgery and the first course of chemotherapy, that might even be a little bit generous. Survival rate is the poorest when chemotherapy is delayed beyond 60 days after surgical resection. So the question is, is there a role for targeted therapy even earlier? I would say yes, there's clearly an unmet need.

### KINDLE: Contemporary management and associated outcomes of patients with stage III NSCLC in a real-world setting: A multicountry observational study

*Jazieh AR, et al.*

So, here are a couple of studies to help us frame this. This is the KINDLE study of contemporary management and associated outcomes of patients with stage III NSCLC in a real-world setting: a multicountry observational study. Basically, this looked at >3,000 patients, enrolled at 125 centres in three geographical

## KINDLE: Contemporary management and associated outcomes of patients with stage III NSCLC in a real-world setting: A multicounty observational study

Jazieh AR, et al.

**To characterize patients, treatment patterns and their associated outcomes for stage III NSCLC in a real-world setting in the pre-IO era**

**Study enrolment period:** January 1st, 2013 to December 31st, 2017

- KINDLE is a retrospective, multicountry, multicentre study capturing data on patient and disease characteristics, treatments and outcomes for stage III NSCLC

- 3151 patients enrolled at 125 centres in three geographical regions (≥9 months follow up):
  - Middle East and North Africa, n=1046
  - Asia, n=1874
  - Latin America, n=231

| Baseline characteristics | |
|---|---|
| Median age | 63 years (range 21–92) |
| Males | 76.5% |
| Smoking history | 69.2% |
| Stage IIIA (AJCC 7th ed.) | 55.9% |
| Adenocarcinoma | 53.7% |
| Squamous cell carcinoma | 36.6% |
| Curative surgical resection | 21.4% |

- **>25 first-line regimens**: cCRT = 29.4%, CT alone = 17%, sCRT = 10.4%, RT alone = 8.5%
- **Stage IIIA patients**: those eligible for and undergoing surgery + CT had longer mOS and mPFS than patients not undergoing surgery, and received other treatments
- **Stage IIIB patients**: mOS and mPFS significantly improved for cCRT vs CT alone or RT alone or sCRT
- Overall mOS in stage IIIA and stage IIIB were 43.8 mos and 27.7 mos, respectively
- Patients with complete resections had mPS and mOS of 21 months

**Real-world data reveal diversity of treatment practices in stage III NSCLC. Survival outcomes remain poor in stage III disease and there is a need for implementation of guidelines and improved access to innovative treatments to optimize outcomes**

cCRT, concurrent chemo-radiotherapy; CI, confidence interval; CT, chemotherapy; IO, immunotherapy; mos, months; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; RT, radiotherapy; sCRT, sequential chemo-radiotherapy.
Jazieh AR, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9043).

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regions. You can see the baseline characteristics in the middle. However, the bottom line is that there are >25 first-line regimens used in this stage III setting and the eligibility, outcomes and regimens are so variable across the world. Basically, real-world data reveal a diversity of treatment practices in stage III NSCLC. It's one of the reasons it is so hard to build new trials, because there is so much variation. Survival outcomes remain poor despite all these different regimens in stage III disease and there is a need for implementation of guidelines and improved access to innovative treatments to optimize therapy, perhaps even biologic therapies.

## ALCHEMIST: Adjuvant targeted therapy or immunotherapy for high-risk resected NSCLC

*Sands J, et al.*

The ALCHEMIST study is being run in the USA through our cooperative groups. There was an abstract at the ASCO virtual meeting, reporting enrolment to the ALCHEMIST trial offering concurrent adjuvant therapy,

## ALCHEMIST: Adjuvant targeted therapy or immunotherapy for high-risk resected NSCLC

Sands J, et al.

**To report updated enrolment to the ALCHEMIST platform: a trial offering concurrent immunotherapy with adjuvant chemotherapy**

- ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial)
- Screening trial A151216 enrols patients (n=5362 registered) with completely resected stage IB (≥4 cm)–IIIA (per AJCC 7) NSCLC – 3 studies ongoing:

| Study | Biomarker | Patients | Adjuvant vs observation |
|---|---|---|---|
| A081105 | *EGFR* mutations | 367 | Erlotinib |
| E4512 | *ALK* fusions | 109 | Crizotinib |
| EA5142 | PD-L1 status | 935 | Nivolumab |

- New adjuvant study A081801 (Spring 2020)
- Patients randomized to 1 of 3 treatment arms:
  - Chemo-IO with pembrolizumab during and after chemotherapy
  - Sequential chemotherapy followed by pembrolizumab
  - Chemotherapy alone

Early biomarker testing used to facilitate enrolment to targeted therapy trials

**Inclusion criteria:**
- Enrolled to A151216, negative for *EGFR* and *ALK* alterations, and with PD–L1 testing completed
- Aged >18 years, Eastern Cooperative Oncology Group performance status 0-1, standard organ function values

**Exclusion criteria:**
- Prior lung cancer therapy except surgery
- Pregnancy/ breastfeeding, active second malignancy <3 years

**By building off the ongoing ALCHEMIST platform, study aims to facilitate rapid enrolment to A081801 across participating NCTN sites**

ALK, anaplastic lymphoma kinase; Chemo-IO, chemo-immunotherapy; EGFR, epidermal growth factor receptor; NCTN, National Clinical Trials Network; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1.
Sands J, et al. *J Clin Oncol.* 2020;38:(suppl; abstr TPS9077).

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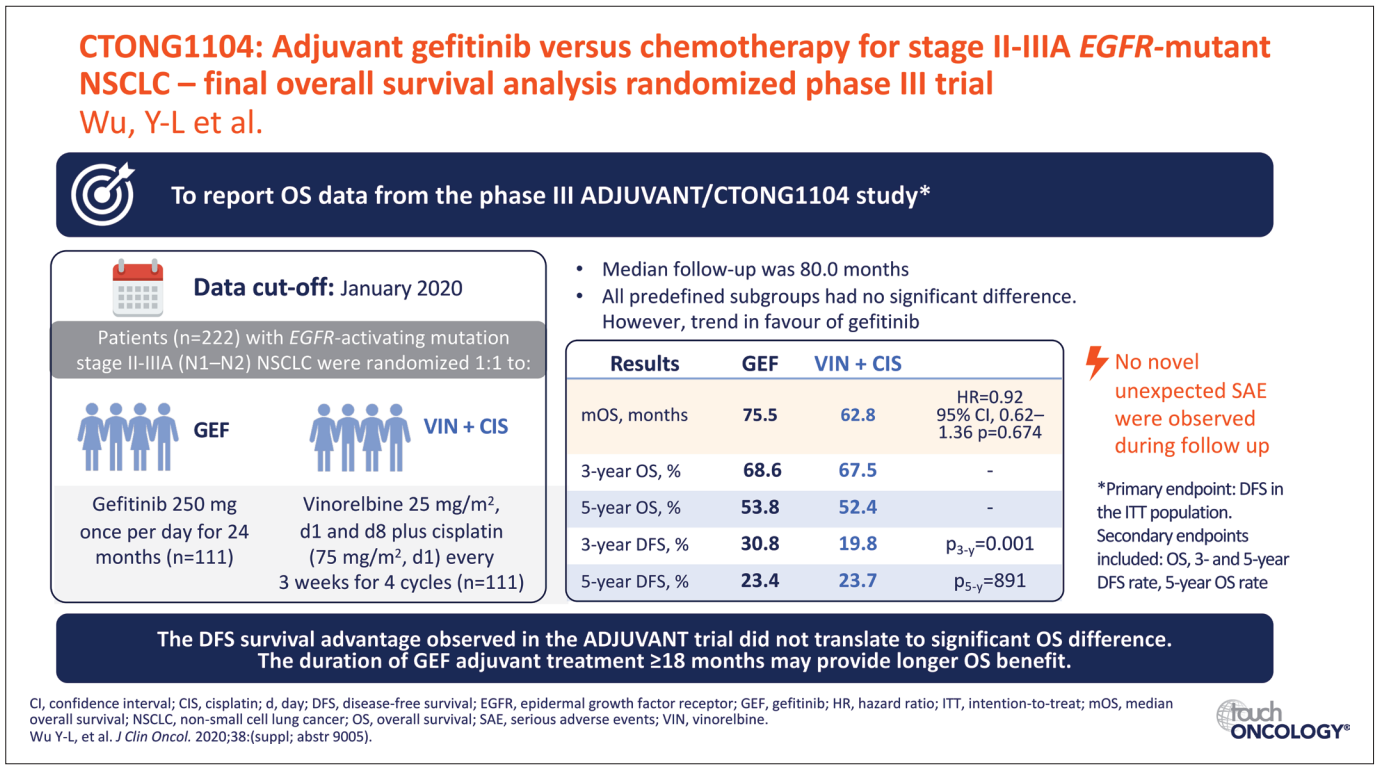
chemotherapy, immunotherapy or targeted therapy to patients. You can see on the left there are three arms to the ALCHEMIST study: patients with *EGFR* mutations are randomized to observation versus erlotinib, they have 367 patients enrolled as presented with this poster; *ALK* fusions, 109 patients randomized to control or to crizotinib, and then an arm that went very fast for approval as you can imagine, the biomarker being PD-L1 status, 935 patients to control or the immunotherapy nivolumab. The bottom line is that adjuvant approaches are being looked at in a number of different trials. This trial remains ongoing and is building to study and facilitate rapid enrolment across many sites in the USA and Canada.

## CTONG1104: Adjuvant gefitinib versus chemotherapy for stage II-IIIA *EGFR*-mutant NSCLC – final overall survival analysis randomized phase III trial

*Wu Y-L, et al.*

Well, here's CTONG1104. This is adjuvant treatment versus chemotherapy for stage II–IIIA *EGFR*-mutant NSCLC – final overall survival analysis of a randomized

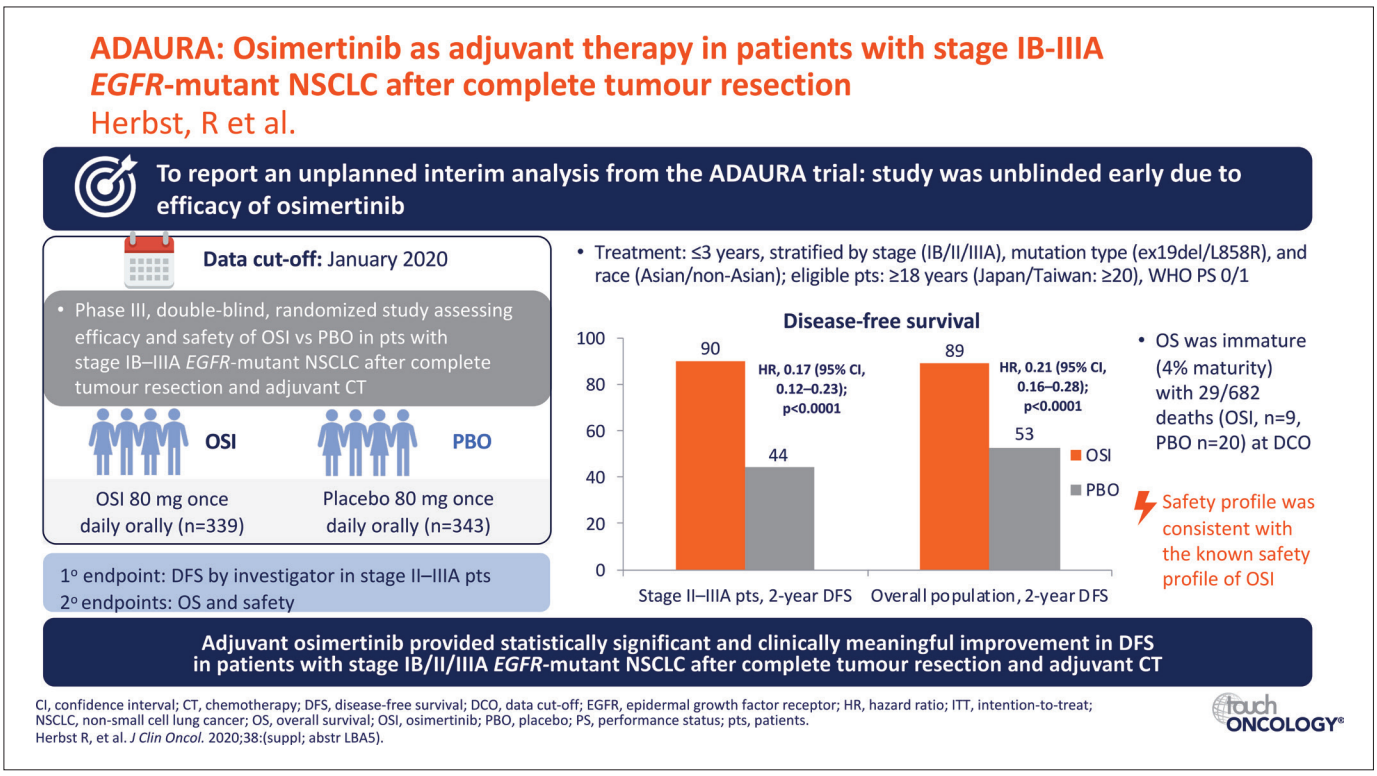



phase III trial. This was presented by my friend and colleague Yi-Long Wu from China. This is from data cut-off from January 2020. In this group of trial patients, >200 with *EGFR*-activating mutations, stage II–IIIA (N1–2 disease) were randomized 1:1 to either gefitinib 250 mg (an *EGFR* inhibitor), or standard platinum-based chemotherapy, in this case cisplatin plus vinorelbine at the doses shown. The median follow-up was a whopping 80 months, very mature data, all pre-defined subgroups had no difference. However, there was a trend in favour of gefitinib. You can see median overall survival (OS), there is a trend in favour of gefitinib, but it did not reach statistical significance; the hazard ratio is 0.92. Three-year OS, 5-year OS, you can see none of them met statistical significance. Interestingly, in this trial disease-free survival (DFS) at 3 years did meet significance – median 30.8 versus 19.8 months (p=0.001). However, 5-year median DFS values came together [no significant difference]. There were no novel, unexpected serious adverse events in this trial. Bottom-line, the DFS advantage observed in this trial did not translate into significant OS benefits. Much of this might be due to crossover effects. The duration of adjuvant treatment was >18 months, and there was a suggestion that perhaps even a longer treatment might be more beneficial. This trial suggests that at least this generation of EGFR inhibitor was not superior to chemotherapy. Of course, it did not ask the question, what if you used both?

## ADAURA: Osimertinib as adjuvant therapy in patients with stage IB-IIIA *EGFR*-mutant NSCLC after complete tumour resection

*Herbst R, et al.*

So now we have the ADAURA trial, one that I know incredibly well as I just presented it in the plenary session at the ASCO 2020 virtual meeting. This is a trial of osimertinib as adjuvant therapy in patients with stage IB–IIIA *EGFR*-mutant NSCLC after complete tumour resection. Chad presented on behalf of my co-steering committee members, Dr Yi-Long Wu and Masahiro Tsuboi, and a large panel of investigators and a study team from around the country and around the world, and of course patients from around

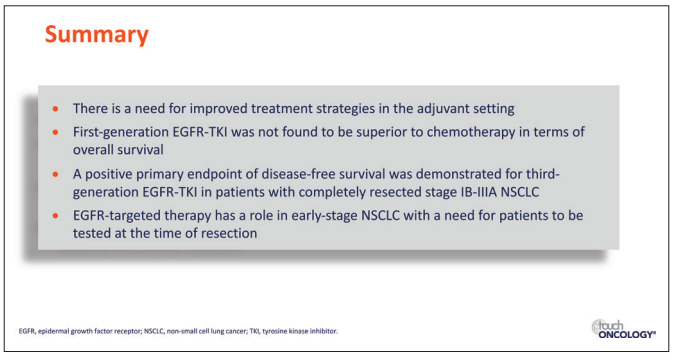



the world. This is a study that looked at osimertinib as an adjuvant therapy for patients with stage IB–IIIA NSCLC, non-squamous, who actually had their tumours completely resected. Patients could receive chemotherapy in the adjuvant setting with platinum as appropriate. As you can imagine, few patients did in stage I, but the majority did in stage II and III. Then they were randomized to osimertinib (80 mg once-daily, 339 patients) or placebo (80 mg once-daily, 343 patients). Why a placebo? As we've already discussed, there is no other treatment after adjuvant platinum therapy in patients with *EGFR*-mutant NSCLC after resection, here recurrence rates are high.

We weren't expecting to present this at ASCO this year. In fact, the trial still needed a couple more years to meet its target number of patients for analysis. However, the safety committee reviewing the data in April of 2020 noticed that there seemed to be an imbalance in efficacy in favour of the study drug. So, they asked for an early review, and those are the results that I am showing you today. You can see that the results clearly showed a positive primary endpoint of disease-free survival. If you look at the study group as a whole, stage IB–IIIA, the hazard ratio was 0.21, meaning a 79% improvement in disease-free survival in those patients treated with osimertinib. Looking at it graphically, you can see just looking at the stage II–IIIA group, in those patients, that hazard ratio was 0.17. That was in fact the primary analysis population. You can see that at 2 years, the disease-free survival was 90% for those patients who received osimertinib versus 44% for those who received the placebo. Then if you look at that overall population that I mentioned earlier, 89% versus 53%, not much difference, even though the much better prognosis stage-I patients are added. The OS was immature at the time of this analysis, only 4% maturity. So, not much we can say about that yet, we'll continue to follow. The safety profile was consistent with the known safety profile of osimertinib.

This trial was quite exciting because it was one of the first, if not the first, global randomized trial to show that a targeted therapy in lung cancer can improve disease-free survival. It shows that adjuvant osimertinib provided statistically significant and clinically meaningful improvement in disease-free survival in patients with stage IB–IIIA *EGFR*-mutant NSCLC after complete tumour resection and adjuvant chemotherapy.

## Summary



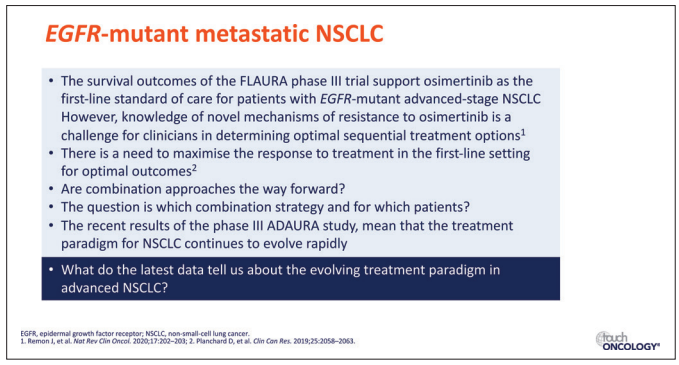

To summarize this first part, it is quite clear that EGFR-targeted therapy has a place now in the earliest stages of NSCLC. It will be important to test patients so that we can get them onto these drugs in the metastatic setting. Of course, that is already being done, but not to an equal extent throughout the world,

so that needs to continue to be promoted. Now it is even more critical, because we need to know who has *EGFR* mutations at the time of resection, because based on the data from ADAURA, it is quite clear that one would want to have the option to treat patients with EGFR therapy in the adjuvant setting. In that trial, the treatment duration plan was 3 years. So, clearly a great deal of progress. We will continue to learn more from the ADAURA study as it matures and as we look at the data in other ways, but clearly, we're making great progress in lung cancer.

I can tell you, from my personal experience, having done some of the earliest trials with gefitinib in the late 90s, to see EGFR therapy move from an untargeted oral therapy in lung cancer with some responders, to the discovery of the EGFR mutations in about 2004. Then of course, to the use of EGFR inhibitors in the second- and first-line metastatic setting with *EGFR*-mutation selection, leading to the FLAUR A study and osimertinib approval several years ago. Now, to see osimertinib in the front-line setting with results from FLAURA, I think is quite exciting. We expected there would be activity in the ADAURA trial, but to have a hazard ratio of 0.17 in the overall population was quite extraordinary. The trial was powered for a hazard ratio of 0.7, so an 83% improvement in disease-free survival.

## HOW IS THE TREATMENT LANDSCAPE EVOLVING IN METASTATIC *EGFR*-MUTANT NSCLC?

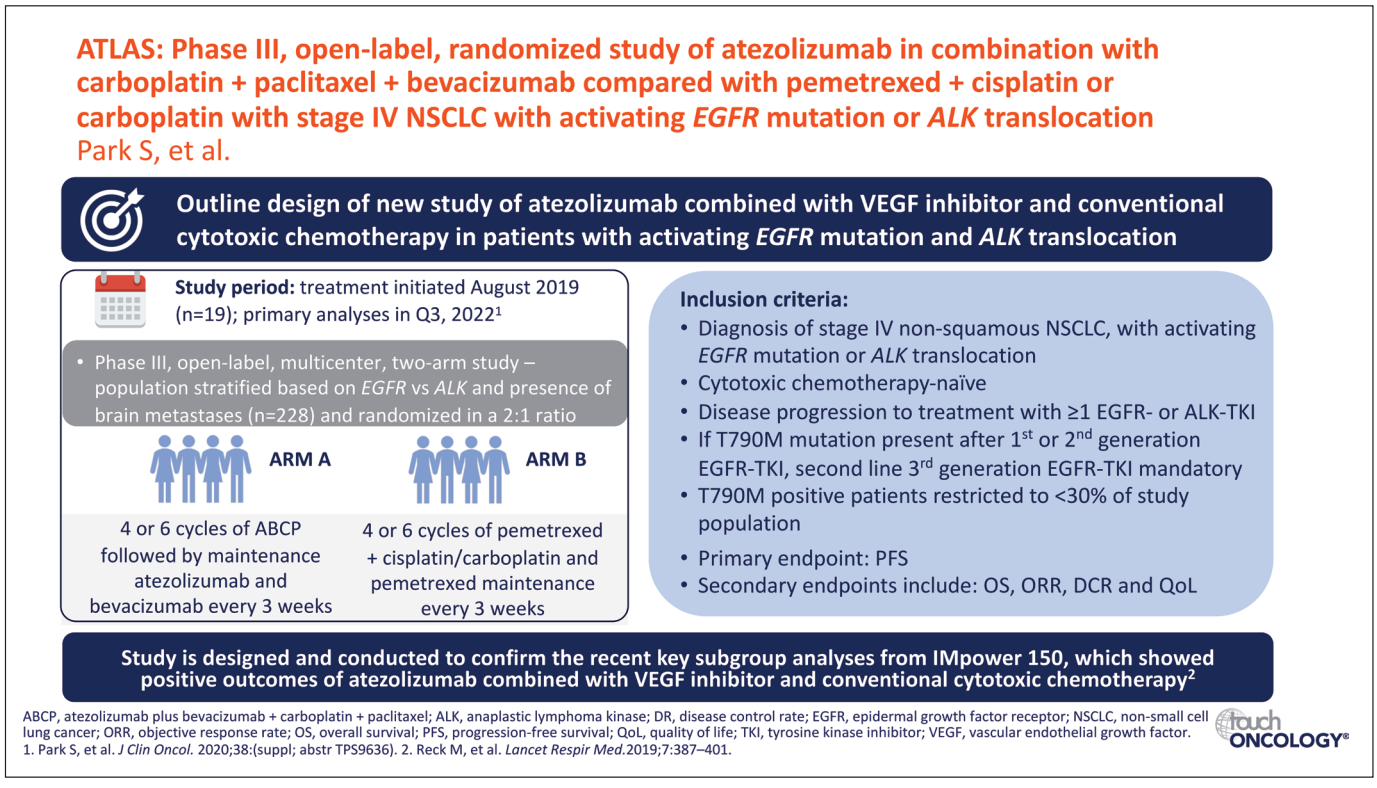
### *EGFR*-mutant metastatic NSCLC




### ATLAS: Phase III, open-label, randomized study of atezolizumab in combination with carboplatin + paclitaxel + bevacizumab compared with pemetrexed + cisplatin or carboplatin with stage IV NSCLC with activating *EGFR* mutation or *ALK* translocation

*Park S, et al.*

Here we have the ATLAS trial. This is a phase III experience ongoing in Asia. The study is designed and conducted to confirm the recent key subgroups from IMpower 150, which showed the positive outcomes for atezolizumab combined with vascular endothelial growth factor (VEGF) inhibitor bevacizumab in conventional cytotoxic chemotherapy. So, a very simple design, patients with *EGFR* mutation or *ALK* translocation are eligible, 2:1 randomization: arm A, the four-drug combination, including the atezolizumab; arm B, the three drugs (chemotherapy + bevacizumab, without the atezolizumab), and the primary endpoint is progression-free survival (PFS). There is some suggestion that this combination with immunotherapy and anti-angiogenic therapy will



have activity in patients with *EGFR* mutations, and *ALK* is being explored as well. This is important because if that is the case, or if we get to using this atezolizumab in those patients, we could perhaps start using it even in the refractory setting.

## RELAY+: Exploratory study of ramucirumab plus gefitinib in untreated patients with *EGFR*-mutant metastatic NSCLC

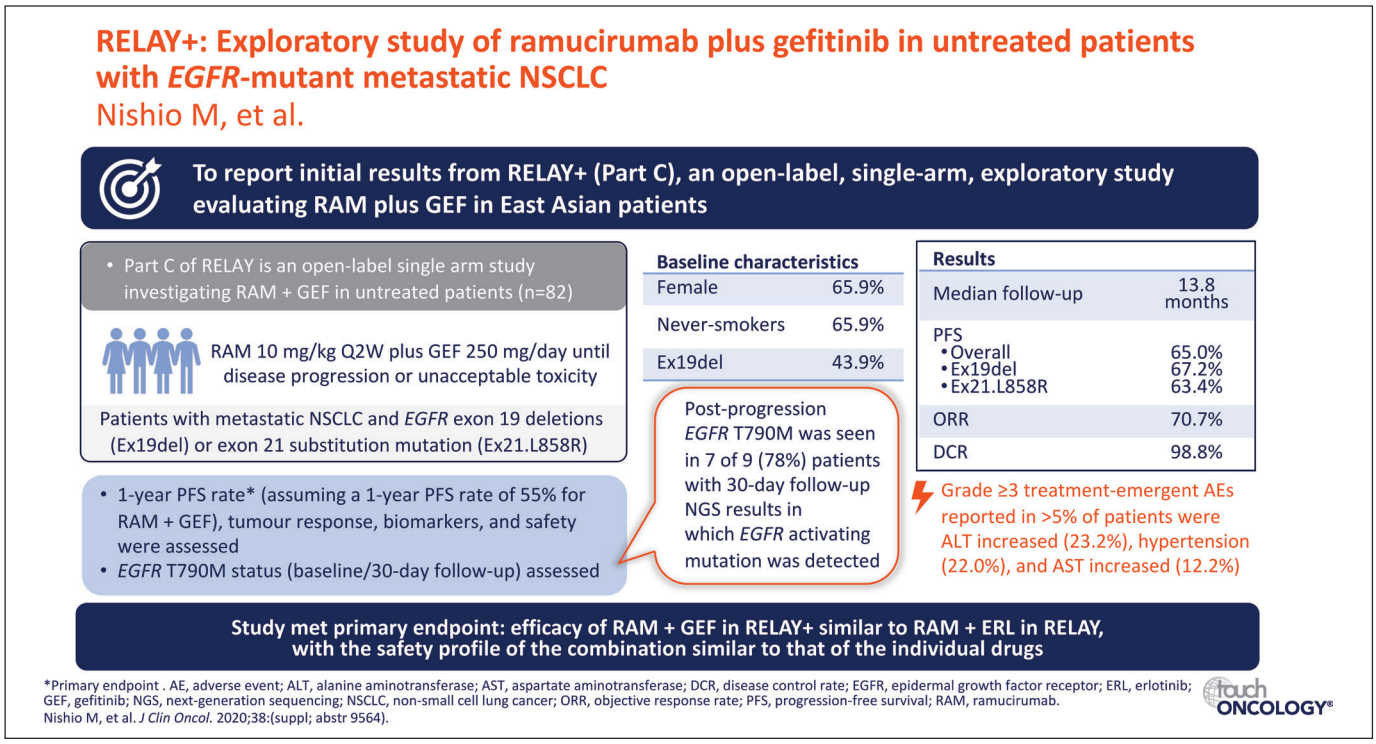
*Nishio M, et al.*

Here we have the RELAY+ trial, an exploratory analysis of ramucirumab, a VEGFR2 antibody, plus gefitinib, an EGFR tyrosine kinase inhibitor (TKI), in untreated patients with *EGFR*-mutant metastatic NSCLC. Erlotinib plus ramucirumab is an approved regimen now in the USA for untreated patients with *EGFR*-mutant disease. Here, the safety and efficacy of gefitinib is examined in a similar cohort of patients. As you can see, it is a very simple single-arm trial. The median follow-up is 13.8 months, but the PFS looks good, 65% at the time of follow-up. Overall response rate is 70.7%, disease control rate is nearly 100%. So, the study met its primary endpoint, meaning the efficacy of ramucirumab and gefitinib in RELAY+ is similar to ramucirumab and erlotinib in the larger RELAY, with the same safety profile of the combination, similar to that of the individual drugs. So, a very nice corollary to that study.

## NEJ026: Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harbouring activating *EGFR*-mutations

*Maemondo M, et al.*

Well, here's NEJ026. This is a final survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harbouring *EGFR* mutations. This is something near and dear to my heart. I actually did the first trial of bevacizumab plus erlotinib with Alan Sadler almost 20 years ago. We always knew, when the paper was published in *Lancet,* it was called the BeTa trial, that erlotinib and bevacizumab had improved PFS over erlotinib alone in *EGFR*-mutant patients. That's already been shown in the NEJ026 trial. However, what has been done now is to look at the survival




analysis, and cutting to the chase, if you look to the right, you can see the median OS was 50.7 months for the bevacizumab/erlotinib and 46.2 months for the erlotinib, and the hazard ratio is 1. So, even though there was a strong PFS benefit seen, and that was the primary endpoint of this trial, the key secondary endpoint of OS was not met. If you look at the PFS2, measuring PFS a little bit differently, it looks like it is not significant either, nor is median OS in the second-line setting. So, the additional effect of bevacizumab on erlotinib monotherapy for *EGFR*-mutant NSCLC, its efficacy is gradually decreased in the order of PFS, PFS2 and OS with no significant differences. Findings are concordant with the J025567 study, in that efficacy on OS unfortunately is not met.

## High-dose osimertinib for CNS progression in *EGFR*-mutant NSCLC: A multi-institutional experience

*Piper-Vallillo A, et al.*

Here is a study that looks at high-dose osimertinib for CNS progression in *EGFR*-mutant NSCLC, a multi-institutional experience. They did a retrospective study

## NEJ026: Final overall survival analysis of bevacizumab plus erlotinib treatment for NSCLC patients harbouring activating *EGFR*-mutations

Maemondo M, et al.

**To report overall survival in patients with *EGFR*-mutated NSCLC treated with bevacizumab + erlotinib vs erlotinib monotherapy**

**Data cut-off:** November 2019[1]

- Phase III, randomized trial in which CT-naïve patients (n=226) with advanced non-squamous EGFR-mutant NSCLC were randomly assigned to:

| **Bevacizumab + erlotinib (n=112)** | **Erlotinib (n=112)** |
|---|---|
| Erlotinib 150 mg daily + bevacizumab 15 mg/kg iv q3w | Erlotinib 150 mg daily |

1° endpoint: PFS; 2° endpoints: OS, RR, safety and QoL

| | Bevacizumab + erlotinib (BE) | Erlotinib (E) | HR (95% CI) |
|---|---|---|---|
| Median OS | 50.7 months (37.3–NR) | 46.2 months (38.2–NR) | 1.00 (0.68 to 1.49) |
| Median PFS2* | 28.6 months (22.1–35.9) | 24.3 months (20.4–29.1) | 0.773 (0.562 to 1.065) |
| Median OS 2nd line OSI | 50.7 months (38.0–50.7) | 40.1 months (29.5–NR) | 0.645 (0.40 to 1.03) |

- Median follow-up time 39.2 months

BE treatment induces T790M resistance. OSI treatment was equally efficacious after either BE or E treatment

**Additional effect of bevacizumab on erlotinib monotherapy for *EGFR*-mutant NSCLC, its efficacy gradually decreased in the order of PFS, PFS2 and OS, with no significant differences. Findings are concordant with J025567 study[2]**

*PFS2, median survival time between enrolment and progressive disease of second-line treatment. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; NR, not reached; OS, overall survival; OSI, osimertinib; PFS, progression-free survival; QoL, quality of life; RR, response rate.

1. Maemondo M, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9506). 2. Seto T, et al. *Lancet Oncol.* 2014;15:1236–44.

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looking at 105 patients with advanced *EGFR*-mutant NSCLC who were treated with osimertinib 160 mg daily. Looking back at groups (very small subgroups): one group who originally was on osimertinib 80 mg daily and then increased to 160 mg daily for CNS progression, but with no chemotherapy; a second group with the same regimen, but with chemotherapy; and the third group, where they started with osimertinib 160 mg daily as the initial dose, but without chemotherapy and radiation. Numbers are small, but the suggestion is that there is some activity in relation to the higher dose of osimertinib (160 mg daily). In cohort A, you can see the median CNS control was 3.8 months; in cohort B, 5.1 months, with some chemotherapy; and then cohort C, 4.2 months. There is some suggestion, very small, that dose escalation provides modest benefit, with a median of 3–4 months added to disease control. The important thing is there were no severe life-threatening side effects. So, more to come on this – it is certainly very interesting.

## High-dose osimertinib for CNS progression in *EGFR*-mutant NSCLC: A multi-institutional experience

Piper-Vallillo A, et al.

**To report multi-institutional experience with dose-escalation of osimertinib up to a maximum dose of 160 mg daily**

- Patients (n=105) with advanced *EGFR*-mutant NSCLC treated with OSI 160 mg daily were retrospectively reviewed to assess the CNS efficacy of dose escalation for CNS progression (CNS PD) – analysis focused on 3 cohorts:

| **A (n=24)** | **B (n=34)** | **C (n=11)** |
|---|---|---|
| OSI 80 mg to 160 mg for CNS PD without CT and/or RT | OSI 80 mg to 160 mg for CNS PD while receiving CT and/or RT | OSI 160 mg for CNS PD as initial dose without CT and/or RT |

- MedDurCNSCon defined as time from start of OSI 160 mg to CNS PD or discontinuation
- 69 (26 male, median age 57 years) *EGFR*-mutant NSCLC patients received OSI 160 mg for CNS PD
- 61 patients had isolated CNS/LMD PD, without systemic PD

| | MedDurCNSCon (mos) |
|---|---|
| Cohort A | |
| • OSI 160 mg monotherapy | 3.8 (95% CI, 1.7–5.8) |
| • Isolated LMD | 5.8 (95% CI, 1.7–9.1) |
| • Parenchymal metastases only | 2 (95% CI, 1–4.9) |
| Cohort B | 5.1 (95% CI, 3.1–6.5) |
| Cohort C | 4.2 (95% CI, 1.6–NA) |

**Dose escalation to OSI 160 mg daily provided modest benefit with median 3.8 months added CNS disease control, with no severe or life-threatening side effects**

CI, confidence interval; CT, chemotherapy; EGFR, epidermal growth factor receptor; LMD, leptomeningeal disease; MedDurCNSCon, median duration of central nervous system (CNS) disease control; NSCLC, non-small cell lung cancer; OSI, osimertinib; PD, progressive disease; RT, radiotherapy.

Piper-Vallillo A, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9586).

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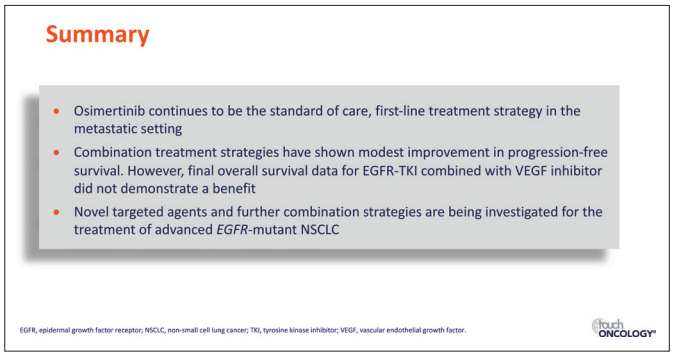
## Nazartinib in treatment-naïve *EGFR*-mutant NSCLC: Updated phase II results

*Shao-Weng Tan D, et al.*

Here is nazartinib in the treatment of naïve *EGFR*-mutant NSCLC, updated phase II results. In treatment-naïve patients with advanced *EGFR*-mutant lung cancer, the median OS was not reached at 33 months and the safety profile was quite manageable. If you look at the overall response rate, disease control and median, they all look quite favourable. The most frequent grade 3/4 adverse events were some rash and increased lipase, but no pancreatitis. Here is another third-generation drug that is being tested and there are several of them as well.

## Summary

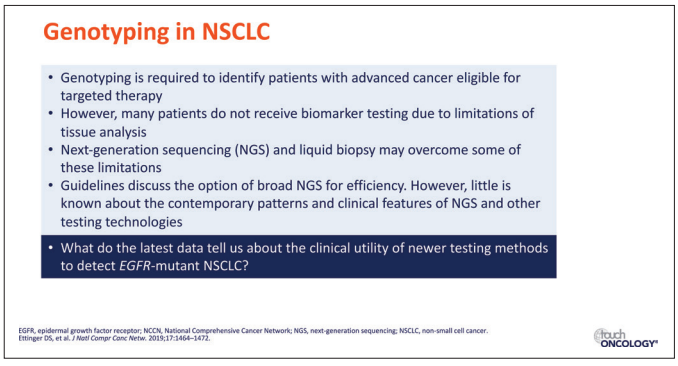


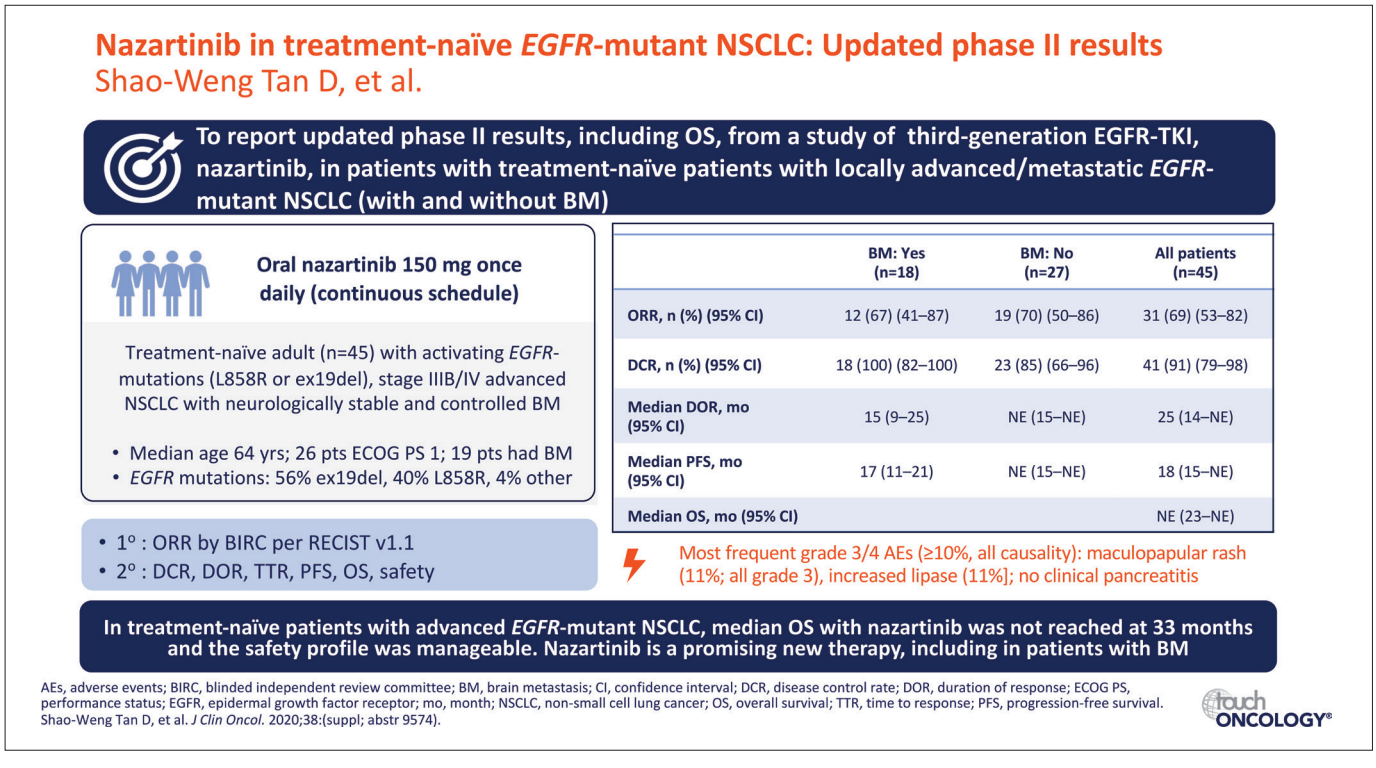

So, what do I conclude in the metastatic setting? We are continuing to use osimertinib as a front-line therapy. We have seen some activity now in brain metastases, which we've always known, perhaps increasing the dose will be important. There are so many other drugs on the horizon. Then some of the combinations with that, e.g. with VEGF inhibition, have shown some modest improvement. Certainly, the RELAY+ trial appears to be an approvable regimen in the USA. Now we see that can be used with gefitinib, which is more commonly done in Asia. Unfortunately, we did not see any improvement in survival despite the progression-free survival results for the Japanese trial of bevacizumab and erlotinib. I suspect in future years we will see many more combinations in the front- and second-line setting for *EGFR*-mutant disease to target both primary and acquired resistance.

## WHAT ADVANCES IN MUTATION TESTING WILL FURTHER SUPPORT PRECISION MEDICINE IN *EGFR*-MUTANT NSCLC?

So, let's move on to our third and final portion of this programme. What advances in mutation testing will further support precision medicine in *EGFR*-mutant NSCLC? This I think, is probably the most important part of all because everything I've talked about so far makes no difference if we do not test the patient for these mutations.

## Genotyping in NSCLC



So, the question is, what do the latest data from ASCO tell us about the clinical utility of newer testing methods to detect *EGFR*-mutant NSCLC?

## Genomic testing among patients with newly-diagnosed advanced NSCLC in the United States: A contemporary clinical practice patterns study

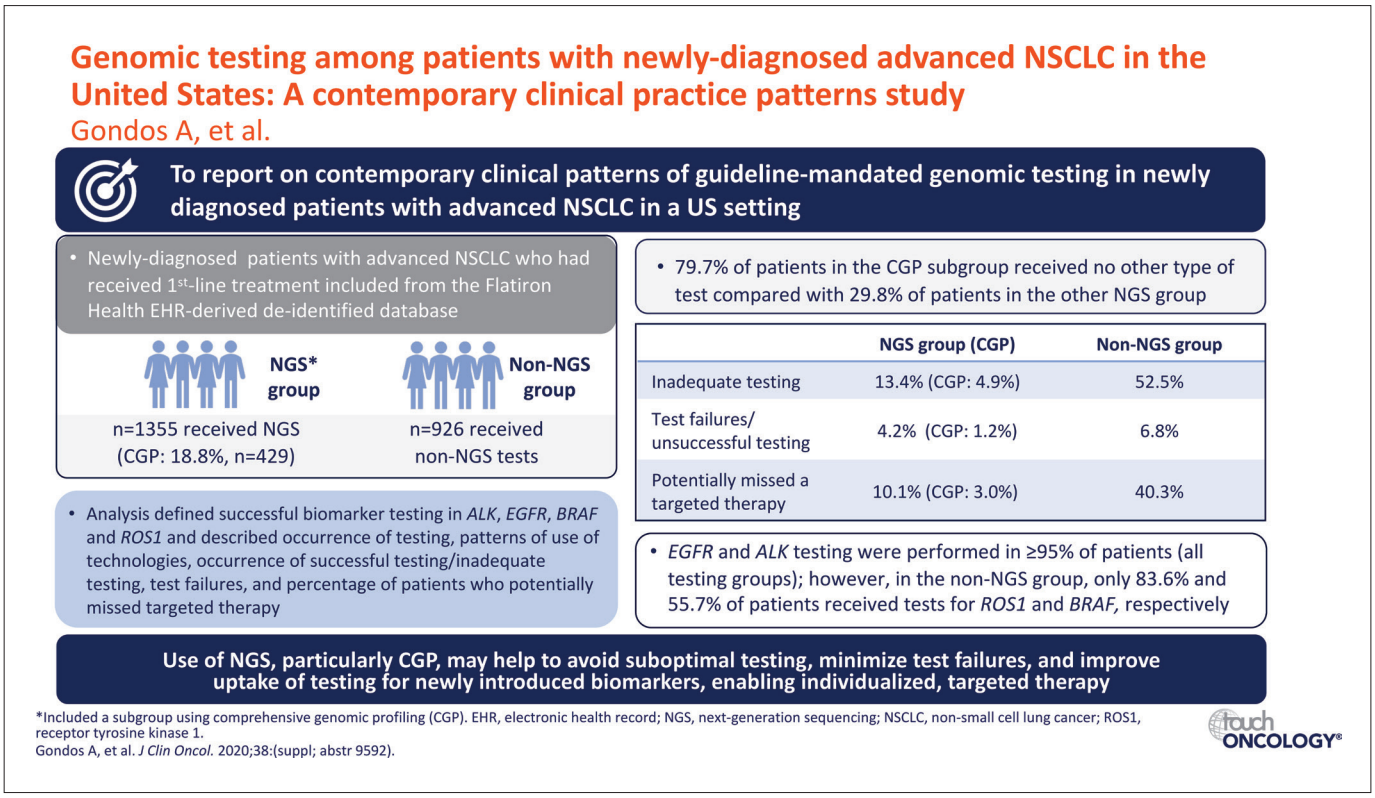
*Gondos A, et al.*

Here is a nice study from Gondos et al. – Genomic testing among patients with newly diagnosed advanced NSCLC in the United States: a contemporary clinical practice patterns study. This is using the Flatiron Health database, a large database that is assembled from hospitals around the world. Basically, they had a next-generation sequencing (NGS) group who received comprehensive genomic profiling (1,355 patients), then a non-NGS group (926 patients). So, the question is, are there differences between the two groups as far as adequacy of testing and completeness of testing? Overall, 79.7% of the patients in the comprehensive profiling group received no other type of test. So, once you have this, you don't need to have anything else, compared with 29% of patients in the non-NGS subgroup. You can see that inadequate testing was only seen in 13.4% of patients who received NGS versus >52% in those who did not. So much more adequacy of testing, if you did genomic profiling. If you look at test failures: 4.2% in the NGS group and 6.8% in the non-NGS group. That, of course, depends on the technique, which is about the same. However, look at this, potentially missed targeted therapy abnormalities: 10.1% in the NGS group, but a whopping 40.3% in the non-NGS group, suggesting that you can find more treatable abnormalities if you use NGS. The conclusion is that the use of NGS, particularly comprehensive genomic profiling, may help to avoid sub-optimal testing, minimize test failures and improve uptake of testing for newly introduced biomarkers, enabling individualized, personalized targeted therapy.

## Clinical performance of a comprehensive novel liquid biopsy test for identifying patients with NSCLC for treatment with osimertinib

*Gray JE, et al.*

This next study is quite interesting. What about clinical performance of comprehensive novel liquid biopsy tests? This is from Jhanelle Gray and colleagues. What was looked at were two trials that looked at osimertinib, one in the second-line, the AURA3, and one on the front-line, the FLAURA trial. You can see a large number of patients in both studies. If you start with FLAURA, and you look at the PFS (the outcome of the study), it looks the same with the G360, the liquid biopsy, looking at cell-free DNA in the blood versus the cobas assay, which is the approved assay in the plasma or in the tissue. Then if you look at AURA3, the second-line trial, same thing – the PFS values all look about the same. So, bottom line, the G360, which is the Guardant360® liquid biopsy test, accurately identifies patients with *EGFR*-mutant NSCLC for osimertinib therapy, while providing comprehensive genotyping for other molecular targets. That is the beauty, not only do you get what you need for the EGFR, but you can find other targets as well. Liquid biopsy, I believe, is a complement to tissue-based testing.



## Clinical performance of a comprehensive novel liquid biopsy test for identifying patients with NSCLC for treatment with osimertinib

Gray JE, et al.

**To report on a liquid biopsy test based on NGS of ctDNA to identify patients with *EGFR*-mutant NSCLC (ex19del, L858R mutations) or *EGFR* T790M eligible for treatment with osimertinib (OSI)**

**n=441/556 FLAURA trial**

1st-line OSI vs EGFR TKI in *EGFR*m NSCLC

**n=300/419 AURA3 trial**

OSI vs CT in NSCLC with T790M at progression on EGFR TKI

- Patients from FLAURA and AURA3 retrospectively tested with Guardant360 (G360), a 74-gene ctDNA NGS assay assessing single nucleotide variants, insertion-deletions, amplifications and fusions
- PFS of patients with *EGFR*m or T790M detected by G360 was compared with patients detected by cobas® *EGFR* Mutation Test using tissue or plasma

| FLAURA (ex19del/L858R) | PFS Hazard Ratio (95% CI) | p-value |
|---|---|---|
| • G360 | 0.42 (0.31, 0.55) | <0.0001 |
| • cobas plasma | 0.45 (0.35, 0.58) | <0.0001 |
| • cobas tissue | 0.43 (0.34, 0.54) | <0.001 |
| **AURA3 (T790M)** | | |
| • G360 | 0.39 (0.28, 0.57) | <0.0001 |
| • cobas plasma | 0.42 (0.28, 0.62) | <0.0001 |
| • cobas tissue | 0.37 (0.29, 0.48) | <0.0001 |

- G360 demonstrated clinical performance similar to that for cobas EGFR Mutation Test for identifying patients with *EGFR*-mutant or T790M
- Efficacy analyses were limited to tissue-positive patients

**G360 accurately identifies patients with *EGFR*-mutant NSCLC for osimertinib therapy while providing comprehensive genotyping for other therapeutic molecular targets. Liquid biopsy complements tissue-based testing**

CI, confidence interval; ctDNA, circulating tumour DNA; EGFRm, epidermal growth factor receptor mutant; ex19del, exon 19 deletions; HR, hazard ratio; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; OSI, osimertinib; PFS, progression-free survival.
Gray JE, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9553).

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## A model comparing the value of broad next-generation sequencing-based testing to single gene testing in patients with NSCLC in the US

*Pennell NA, et al.*

Here is a study I thought would be interesting to put up here, a comprehensive model comparing broad next-generation sequencing to single gene testing in patients with NSCLC in the US. This is from Dr Nathan Pennell and colleagues, who wanted to report a plausible testing model looking at configurations for exploring actionable driver mutations and looking at their implications for the population. They concluded that broad NGS testing compared to single gene testing for *EGFR* and *ALK* leads to larger gains in life years saved at reduced cost per life year gained. So, it [NGS testing] is better for saving lives and is less expensive [than single gene testing], supporting universal testing. This is a very intricate mathematical model. I'll be very anxious to see the full paper when this comes out to see all their different assumptions, but it is certainly consistent with what I've shown you

## A model comparing the value of broad next-generation sequencing-based testing to single gene testing in patients with NSCLC in the US

Pennell NA, et al.

**To report on plausible testing configurations for actionable driver oncogenes and discuss their implications for the US population**

- Simulation evaluated various testing with SGT or NGS on the basis of LYG and cost per LYG
- Expected prevalence of ADOs among nsNSCLC patients and survival distribution in the presence/absence of an ADO treatment strategy were calibrated
- Survival duration generated from Weibull distributions fit to statistical estimates of median and 5-year survival
- Weibull distributions with appropriate match between ADO and targeted treatment generated median additional 2 years of life
- **nsNSCLC patients for testing in US annually = 89,000**
- ADOs in NGS: *EGFR, ALK, ROS1, BRAF, RET, MET, NTRK*
- ADOs in SGT: *EGFR* and *ALK*

| Estimated patients with ADOs (*EGFR/ALK/ROS1/BRAF/RET/MET/NTRK*) | 26,300 |
|---|---|
| CMS reimbursement for NGS | $627.50 |
| CMS reimbursement for SGTs (*EGFR*+*ALK*) | $732.30 |
| Cost of treatment for 2 years | $10K/year = $20,000 |
| Estimated median and 5-year survival of patients with ADO with highly-effective treatment | 39 months and 25% |
| Estimated median and 5-year survival of patients with ADO who goes unidentified | 14 months and 5% |

- Each 10% increase in NGS instead of SGT = 2630 additional LYG and cost savings per LYG of -$49 to -$109
- At current 80% testing rate, replacing SGT with NGS = additional 21,019 LYG with reduced cost per LYG of -$599
- Increasing testing from 80% to 100% of patients would increase LYG by 15,017
- If 100% of patients were tested with NGS and every patient received treatment, cost per LYG of this strategy would be $16,641.57

**Broad NGS testing compared to SGT for *EGFR/ALK* leads to large gains in life years at reduced cost per LYG, supporting universal NGS testing for all patients with advanced non-squamous NSCLC**

ADOs, actionable driver oncogenes; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; LYG, life year gained; NGS, next-generation sequencing; nsNSCLC, non-squamous non-small cell lung cancer; NTRK, non-receptor tyrosine kinase; ROS1, receptor tyrosine kinase 1; SGT, single-gene testing.
Pennell NA, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9529).

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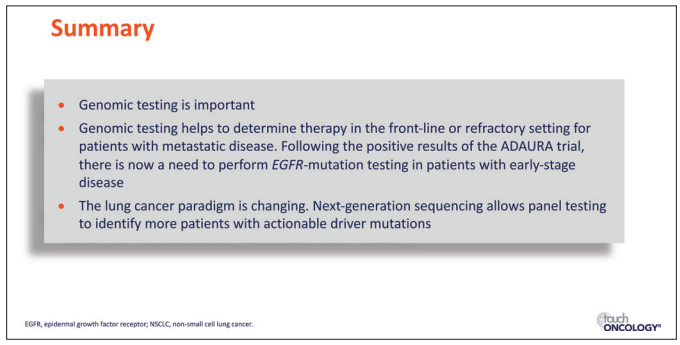
from some of the retrospective databases on the last few slides.

## Residual circulating tumour DNA after two months of therapy to predict progression-free and overall survival in patients on S1403 randomized to afatinib ± cetuximab

*Mack PC, et al.*

Finally, here is an abstract that comes from some work that I was involved in from the SWOG group in the USA and the lung SPORE group at Yale. Basically, Phil Mack put this poster in: Residual circulating tumour DNA after two months of therapy to predict progression-free and overall survival in patients on the S1403 randomized trial of afatinib ± cetuximab. This trial was begun, believing that in the front-line setting, afatinib plus cetuximab would be a superior regimen to afatinib alone. Unfortunately, it did not meet its primary endpoint. Clearance of cell-free DNA for EGFR was looked at. At Cycle 3 Day 1 (C3D1), you can see the median PFS for those patients who have clearance was 15.1, while it was 2.8 months for those who did not (residual); the overall survival was 27.2 versus 15 months, respectively. So, what does that tell you? Both of those look to be significant p values. It says that clearance of EGFR cell-free DNA after 60 days of therapy was associated with a substantial and statistically significant improvement in subsequent PFS and OS. More on this to come because I think this is going to be very important, as we follow patients with either single- or combination-agent EGFR-targeted therapies, deciding if and when to switch to different regimens.

## Summary




Testing is important. It is the biggest part of the puzzle, in my opinion, because that is where we will find the denominator. Those patients either with metastatic disease, who have *EGFR* mutations, but now patients with early disease who have these mutations. I think that will allow for more effective and quick therapy. The other thing though, is the paradigm for lung cancer has shifted, starting with *EGFR*, of course, but now there are almost ten different actionable mutations that are important to know, because they can help to determine therapy in the front-line or refractory setting. Now of course, even in the earliest stages of disease. So, all these next-generation panels, including blood-based panels are going to be critically important.

Thank you.

**Residual circulating tumour DNA after two months of therapy to predict progression-free and overall survival in patients on S1403 randomized to afatinib +/- cetuximab**

Mack PC, et al.

**To report on the predictive value of ctDNA clearance at Cycle 3 Day 1 (C3D1) following treatment with afatinib with/without cetuximab in patients with *EGFR*-mutant NSCLC**

- S1403: a 1st-line phase III study of afatinib with/without cetuximab in patients with *EGFR*-mutant NSCLC (n=168)
- Study closed early due to futility

- Plasma specimens prospectively collected at baseline, Cycle 3 Day 1 (C3D1; 8 weeks) and at progression
- Samples processed for batch analysis of ctDNA by NGS (Guardant360) – complete case analysis approach used

- Survival distributions (Kaplan-Meier) and HRs + CIs (Cox model) were estimated, and distributions compared (log-rank test); landmark analysis assessed predictive value of ctDNA clearance at C3D1
- 104 patients (62%) had analyzable baseline plasma specimens, with *EGFR* mutations detected in 83 (80%)

| Baseline | | | |
|---|---|---|---|
| | Detectable | Not-detectable | HR (CI) |
| PFS | 10.2 (7.3–13.5) | 14.7 (10.1–NR) | 1.80 (0.29–2.01) [p=0.03] |
| OS | 30.2 (25–NR) | NR | 2.10 (0.82–5.39) [p=0.1] |
| **Landmark analysis** | | | |
| | C3D1: clearance | C3D1: residual | HR (CI) |
| PFS | 15.1 | 2.8 | 0.24 (0.13–0.44) [p=0.00001] |
| OS | 27.2 | 15.0 | 0.30 (0.14–0.66) [p=0.003] |

- Of 62 cases with detectable ctDNA at baseline, 68% (42/62) became undetectable at C3D1 (ctDNA clearance)
- 70 patients had matching at-progression samples
- T790M mutations were observed at progression in 18/70 (25%) cases

**Clearance of *EGFR* ctDNA after 60 days of therapy was associated with a substantial and statistically significant improvement in subsequent PFS and OS**

CI, confidence interval; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; NGS, next-generation sequencing; NR, not reached; OS, overall survival; PFS, progression-free survival.
Mack PC, et al. *J Clin Oncol.* 2020;38:(suppl; abstr 9532).

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