touch ONCOLOGY®

A moving target: Assessing the role of EGFR-TKIs in early-stage NSCLC

Transcript from a touchTALKS®

THE EXPERT

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INTRODUCTION

Watch Dr Stephen Liu present how the latest clinical evidence on the use of EGFR-TKIs in the adjuvant setting is shaping the treatment paradigm of early-stage NSCLC and how the collaborative approach of a multidisciplinary team is essential to integrate a personalized approach to patient management.

LEARNING OBJECTIVES

After watching this touchTALKS®, you should be better able to:

- Recall the latest efficacy and safety data for EGFR-TKIs for patients with early-stage *EGFR*-mutant NSCLC
- Describe how the evolving use of EGFR-TKIs may impact the current recommendations for mutation testing in NSCLC
- Discuss how EGFR-TKIs may be incorporated into the evolving treatment pathway for early-stage NSCLC, now and in the future

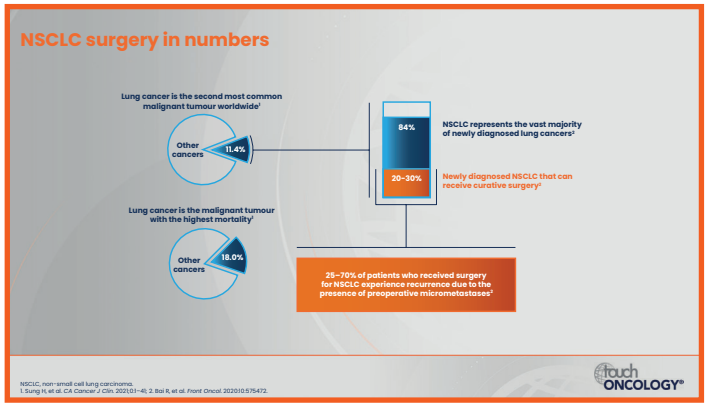
TOPICS DISCUSSED

- What do the latest data tell us about the role of targeted therapy in early-stage NSCLC?
- How do recent data impact the future mutation testing guidelines in NSCLC?
- How do recent data in early-stage NSCLC impact the current treatment pathway for *EGFR*-mutant NSCLC?

WHAT DO THE LATEST DATA TELL US ABOUT THE ROLE OF TARGETED THERAPY IN EARLY-STAGE NSCLC?

Hi, I'm Stephen Liu, Medical Oncologist from Georgetown University (Washington, DC, USA) and today we'll talk a bit about the role of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in early-stage non-small cell lung cancer (NSCLC).

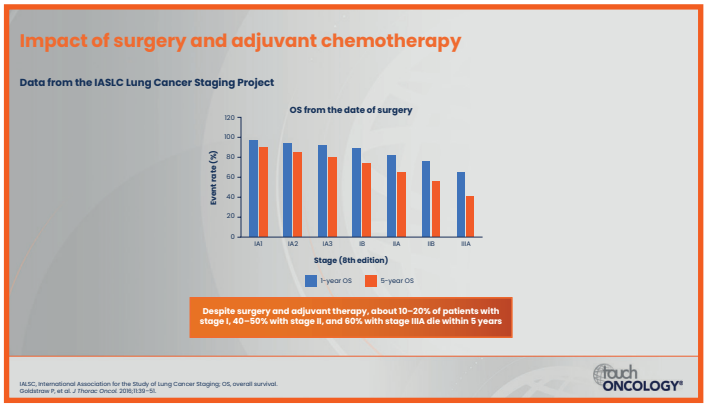
So what do the latest data tell us about the role of targeted therapy in early-stage NSCLC? Well, the unmet need is clear. Lung cancer is the second most common malignant tumour worldwide, accounting for about 11% of new cancer diagnoses, but it is disproportionately lethal, accounting for almost one in five cancer-related deaths. Lung cancer is the malignant tumour with the highest mortality by far.



When referring to lung cancer, we're typically referring to NSCLC, which represents about 84% of new lung cancer diagnoses. Among these, about 20% to 30% of newly diagnosed lung cancer can receive curative surgery. Unfortunately, our outcomes with surgery are still quite poor: 25% to 70% of patients who receive surgery for NSCLC experience recurrence. Cure is our intent, but not necessarily our expectation.

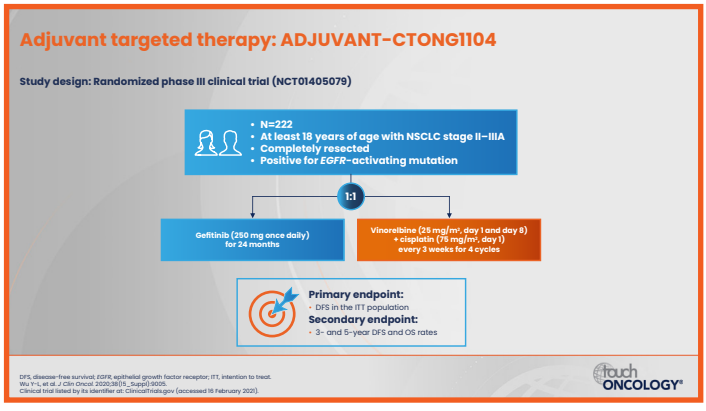
Recurrence is due to the presence of preoperative micrometastases, present at the time of surgery, but below our threshold for detection. This is the reason why our outcomes remain quite poor.

These are data from the International Association for the Study of Lung Cancer Staging (IASLC) Lung Cancer Staging Project, showing 1-year and 5-year survival rates by stage. What we can see is that despite surgery and adjuvant therapy, our 5-year survival rates for stage I lung cancer are only about 80%, for stage II, only 60% and for stage III, only 40%. We need to do better.



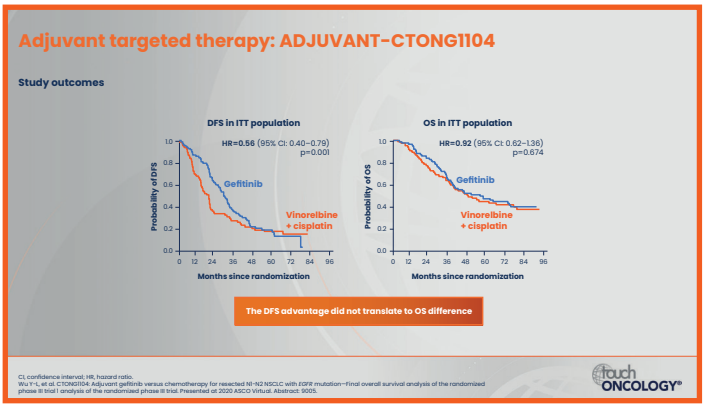
Are there some subsets of patients for whom we can introduce alternate adjuvant therapy approaches to improve outcomes? In the metastatic setting, an important development is the recognition that there are genomic subsets of NSCLC for which we can deliver targeted therapy, which is more effective and better tolerated than chemotherapy. Can targeted therapy play a role in a resected NSCLC that harbours a targetable, actionable alteration?

Well, this was the premise for the ADJUVANT-CTONG1104 study. In this study, which included 222 patients with *EGFR*-mutant NSCLC, stage II to IIIA, completely resected patients were randomized 1:1 to receive adjutant gefitinib at 250 mg daily for two years or chemotherapy: cisplatin and vinorelbine.

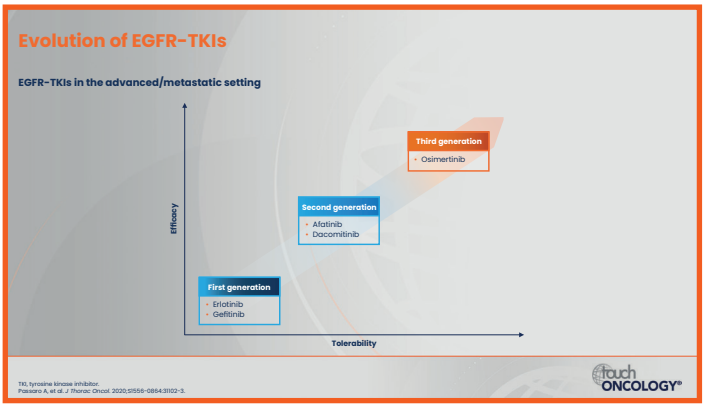


The primary endpoint for this study was disease-free survival (DFS) in the intent-to-treat population, with important secondary endpoints of 3- and 5-year DFS and overall survival (OS) rates. The results were quite interesting. When we look at DFS, giving adjuvant gefitinib significantly improved DFS compared with chemotherapy. The hazard ratio (HR) here is 0.56, but when we look at these DFS curves, we can see they separate early and

during the duration of treatment with gefitinib, that separation is widened. But after the 2-year mark, when gefitinib is stopped, we see those curves come together and in fact they do cross after about 4 years. Importantly, the OS was not different between these two arms: the HR for survival is 0.92, with curves that largely overlap. Adjuvant gefitinib in resected *EGFR*-mutant lung cancer significantly improved DFS but that did not translate to an OS difference.

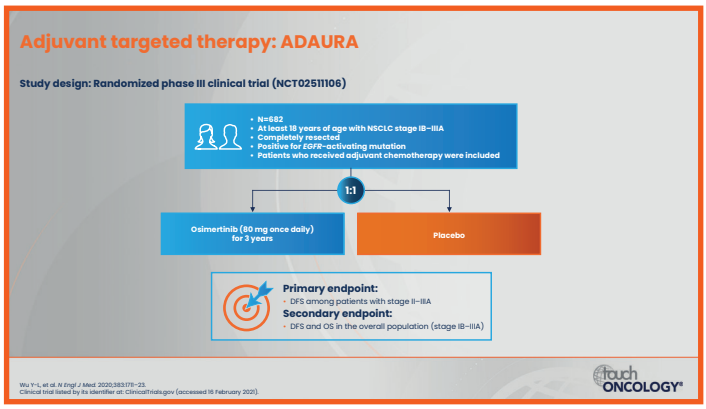


In our current practice, gefitinib is no longer our preferred standard. The third-generation EGFR-TKI, osimertinib is better tolerated, more potent and, in the stage IV setting, offers a significant progression-free survival (PFS) and an OS advantage. In addition, osimertinib is highly central nervous system (CNS)-penetrant. Would osimertinib in this setting offer different results?

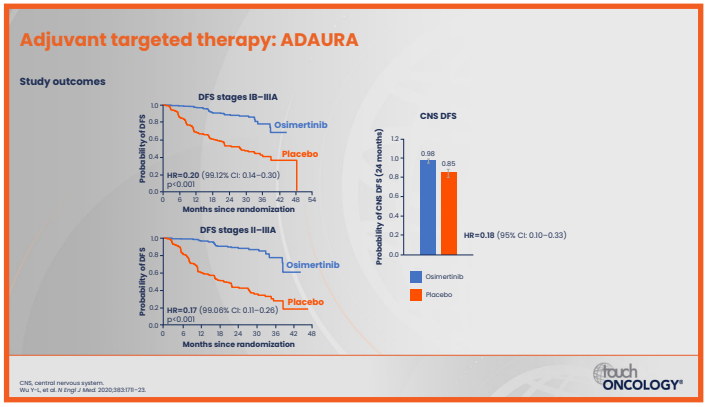


We have the answer to that question from the adjuvant ADAURA trial. This was a very large study with 682 patients with completely resected stage IB to IIIA NSCLC. Note that this used the IASLC seventh edition for staging.

Tumours harboured either an *EGFR* exon 19 deletion or an *EGFR* L858R point mutation. Patients could receive adjuvant chemotherapy, but were not mandated to do so. Postoperative radiation therapy was not permitted in the ADAURA study. Patients were randomized 1:1 after chemotherapy or after surgery for those who did not receive



chemotherapy, to receive osimertinib at the standard dose of 80 mg a day for three years, or placebo. The primary endpoint here was DFS in the higher-risk group of stage II to IIIA NSCLC with important secondary endpoints of DFS and OS in the overall population.



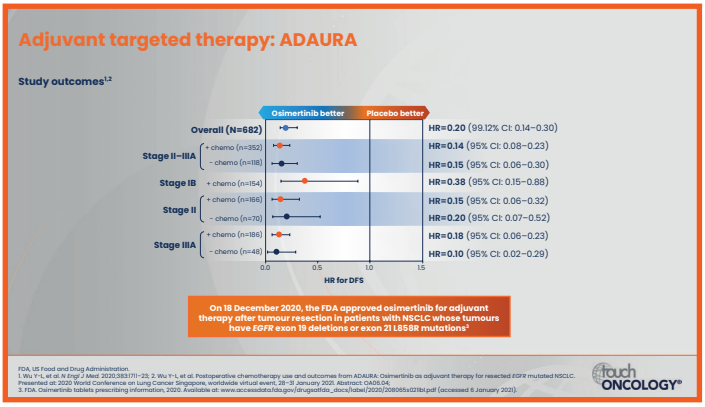
The results here were quite striking. Adjuvant osimertinib significantly improved DFS. If we look at the overall population of IB to IIIA, we have a HR for DFS of 0.20, and in that high-risk population, stage II to IIIA, we see a HR of 0.17. These DFS curves split immediately, and they widen with time.

These are impressive results and the data are still maturing. Remember, in ADAURA, patients received osimertinib for 3 years. We don't know what happens after the 3-year mark as the DFS median follow-up in this study is only 22 months. It'll be interesting to see how these curves change over time once osimertinib is stopped and, importantly, we still do need to see OS endpoints.

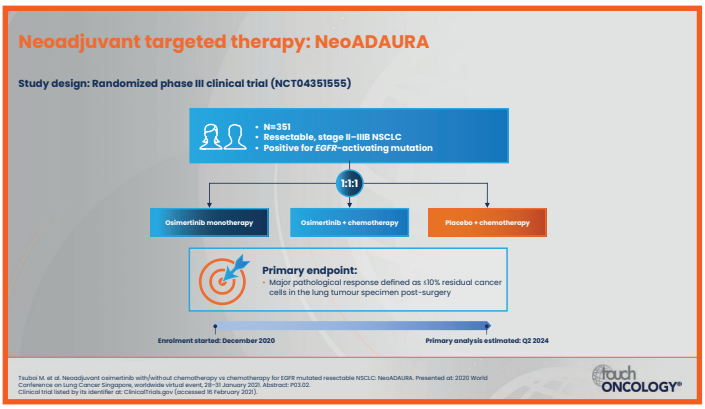
Osimertinib is a highly CNS-penetrant drug. Would it be able to prevent CNS recurrence? Would it be able to prolong CNS DFS? When we look at the CNS DFS rates between the two, we see an improvement with osimertinib with a HR of 0.18. Less CNS recurrence with the use of adjuvant osimertinib is yet another advantage of this strategy.

When we look at the different subgroups, we see a DFS benefit with adjuvant osimertinib in the overall population as well as in the high-risk stage II to IIIA

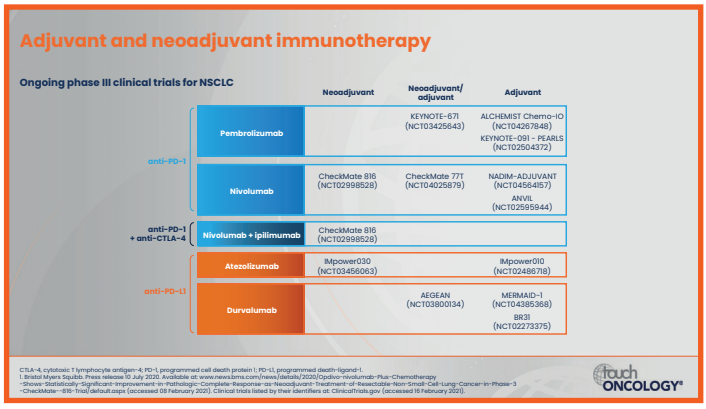
population, in stage II alone and in stage III alone, with or without chemotherapy. In the stage IB population, while the DFS benefit appears to be somewhat less for that group, the HR is still significant at 0.38. Based on these data, on December 18th, 2020, the US Food and Drug Administration (FDA) approved osimertinib for adjuvant therapy after resection in patients with a completely resected *EGFR*-mutant NSCLC, restricted to *EGFR* exon 19 deletion or *EGFR* L858R 21 point mutation.



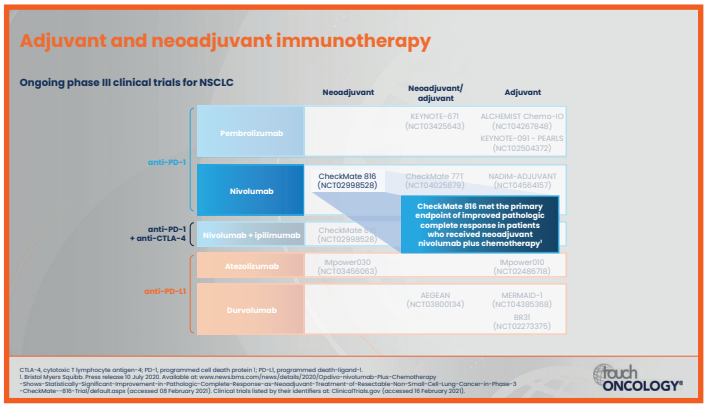
An alternate approach is to deliver systemic therapy before surgery. We call this a neoadjuvant approach, and this is the premise for the NeoADAURA trial. This randomized phase III trial will include 351 patients with resectable stage II and IIIB NSCLC that harbours an *EGFR*-activating mutation. This is a three-arm study with patients randomized to osimertinib alone, osimertinib with chemotherapy, or placebo with chemotherapy. The primary endpoint for this study is major pathologic response, which is defined as ≤10% residual cancer cells in the lung specimen post-surgery. Enrolment for this study began in December 2020; this will be an important addition to the data of perioperative targeted therapy.



We also have several important adjuvant and neoadjuvant immunotherapy trials. Ongoing clinical trials include programmed cell death protein-1 (PD-1) inhibitors, dual checkpoint blockade, and programmed death-ligand-1 (PD-L1) inhibitors.



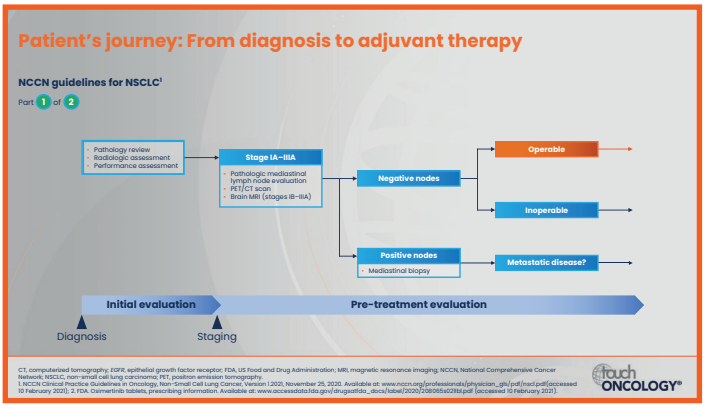
We are already seeing some results filter through. For example, we know from press releases that CheckMate 816 has met the primary endpoint of improved pathologic complete response in patients who receive neoadjuvant nivolumab plus chemotherapy. This is an important and exciting perioperative systemic therapy approach.



Targeted adjuvant therapy with osimertinib significantly improved DFS in patients with *EGFR*-mutant early-stage NSCLC, irrespective of prior chemotherapy. Clinical trials underway will assess the safety and efficacy of using that same targeted approach in the neoadjuvant setting and immunotherapy may represent an alternative to targeted therapy and chemotherapy in the adjuvant or neoadjuvant setting for tumours that do not harbour a targetable mutation.

HOW DO RECENT DATA IMPACT THE FUTURE MUTATION TESTING GUIDELINES IN NSCLC?

How do these new data impact future mutation testing guidelines in NSCLC? To do that, it is best to think of the patient's journey, from the time of diagnosis to making decisions about adjuvant therapy. Diagnosis begins with a biopsy and pathology review. This is how we establish the diagnosis of NSCLC, and initial radiographic assessment and initial performance assessment sets us on our way. For patients with a stage IA to stage III NSCLC, we then proceed typically with a positron emission tomography (PET)/computerized tomography (CT) scan and brain magnetic resonance imaging (MRI), with and without gadolinium, to properly stage that cancer.

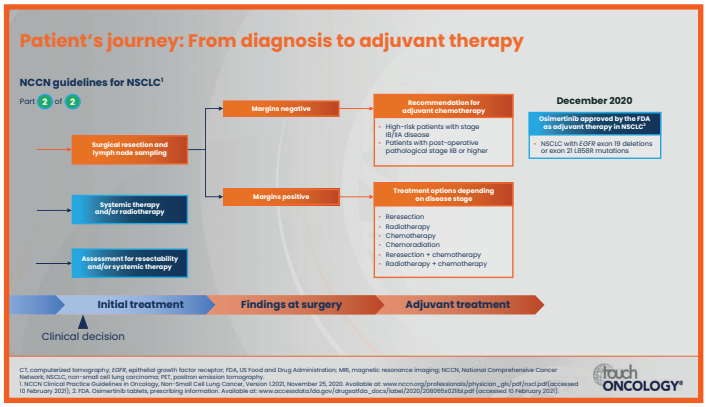


An important part of staging is pathologic mediastinal lymph node evaluation: a positive PET scan in the mediastinum and large nodes—not enough to rule in pathologic involvement; small lymph nodes, or PET negative nodes—not necessarily enough to rule out pathologic evaluation. The lymph node staging is critical to the proper staging of NSCLC.

If lymph nodes are positive, it is critical to ensure there is no metastatic disease, as those patients' tumours are much more likely to have spread outside of the thorax. If lymph nodes are negative, our decision is then based on its operable or inoperable status. Does the patient have comorbidities that might prevent surgery? Is the tumour itself resectable? Small tumours in the wrong location can sometimes be challenging for surgery.

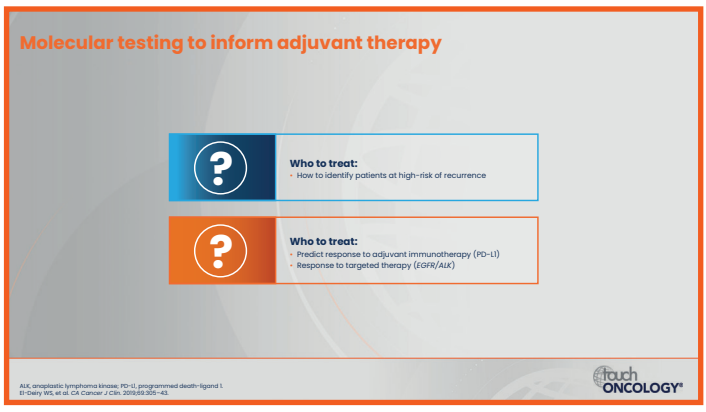
For node-positive tumours, systemic therapy will be an important part of treatment. We then must decide whether that happens before or after surgery. For inoperable or unresectable tumours, a current standard remains chemoradiation. When lymph nodes are not involved, our standard treatment is surgical resection with lymph node sampling at the same time.

We then turn towards margins. If the margins are positive, treatment options will really depend on disease stage and may involve re-resection, radiotherapy chemotherapy, or combination of those different modalities. If the margins are negative, we then need to make recommendations about adjuvant therapy. Different factors will influence that choice, including the stage. High-risk patients with stage IB to IIA may be considered for adjuvant therapy, and certainly most patients with stage IIB or higher NSCLC will be recommended to receive adjuvant therapy.



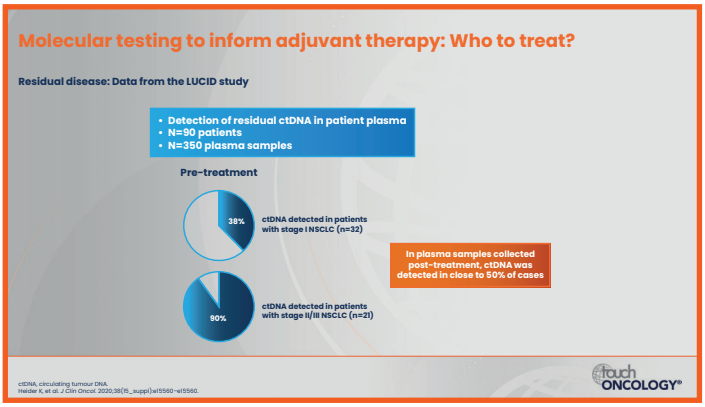
Historically, adjuvant therapy has been chemotherapy, but as of December 2020, osimertinib is now approved by the FDA for resected *EGFR*-mutant NSCLC and exon 19 deletion or exon 21 L858R point mutation: a targeted option that gives us another adjuvant option for NSCLC that's been resected.

Now, can molecular tests help guide these decisions? Is there a test that tells us who to treat? How do we identify those patients at higher risk of recurrence? How do we identify patients who will benefit from further therapy? And can tests tell us how to treat? Are there predictors of immunotherapy such as PD-L1 expression? Are there predictors of targeted therapy, such as mutations and genomic fusions?

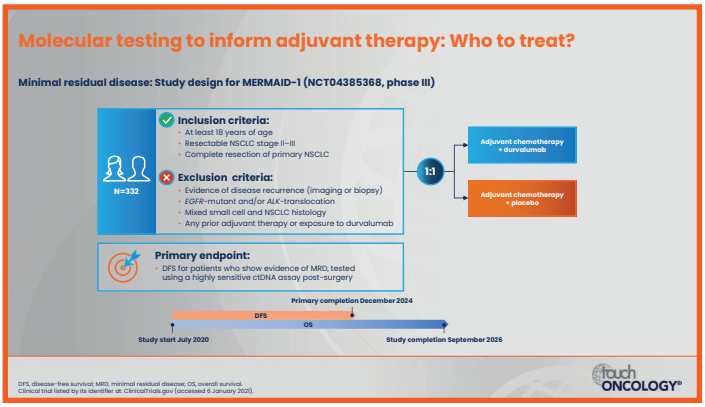


An important study to help give us a clue as to what the future may hold was the LUCID study.

This trial of 90 patients, which included 350 patient samples looked at circulating tumour DNA or ctDNA. In patients with stage I NSCLC, ctDNA was detected in 38% of cases. With higher stages, ctDNA is more prevalent. We see in patients with stage II or III NSCLC, 90% had detectable ctDNA. After treatment, 50% of the samples contained ctDNA. Does the presence of ctDNA after treatment predict patients who are at higher risk for recurrence? Does it predict patients who will benefit from adjuvant therapies?

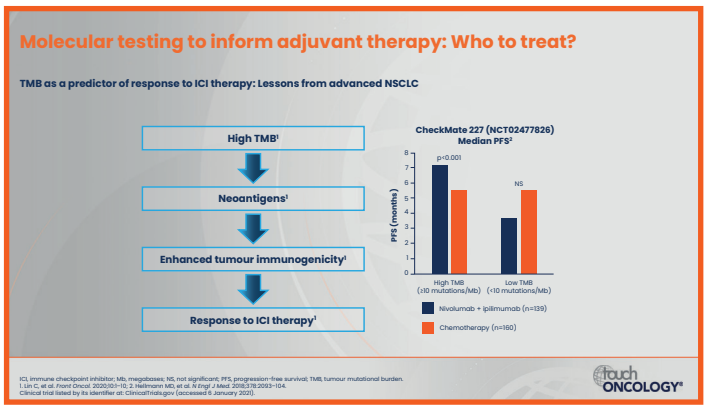


One study that will help answer this question is the MERMAID-1 trial. This phase III trial includes patients with stage II to III completely resected primary NSCLC. This study excluded patients with *EGFR* or *ALK* alterations because it explored immunotherapy. No prior adjuvant therapy was permitted prior to randomization. Patients were randomized to receive adjuvant chemotherapy alone or adjuvant chemotherapy with durvalumab, a PD-L1 inhibitor.

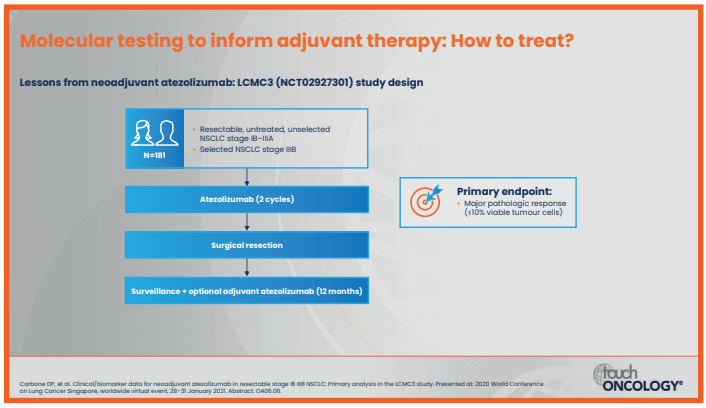


The primary endpoint here was DFS, but not in the entire population. It was DFS for patients who did show evidence of minimal residual disease using a highly-sensitive ctDNA assay. For patients with detectable ctDNA, will immunotherapy offer a DFS benefit in that population? This is an important question. It will be some time before we have these results, but good to see these studies are ongoing to answer the question—not just how, but also who.

Molecular testing may inform adjuvant therapy in many different ways. An important potential predictive biomarker is tumour mutational burden. High tumour mutational burden (TMB), a high rate of somatic tumour mutations, would presumably lead to more neoantigens. That would lead to presumably an enhanced tumour immunogenicity, which then could predict response to immune checkpoint inhibitor therapy. And we saw from CheckMate 227 that patients whose tumours had higher TMB did have a better PFS with the combination of nivolumab and ipilimumab. Will TMB play a role in the use of perioperative immunotherapy? This remains to be seen.

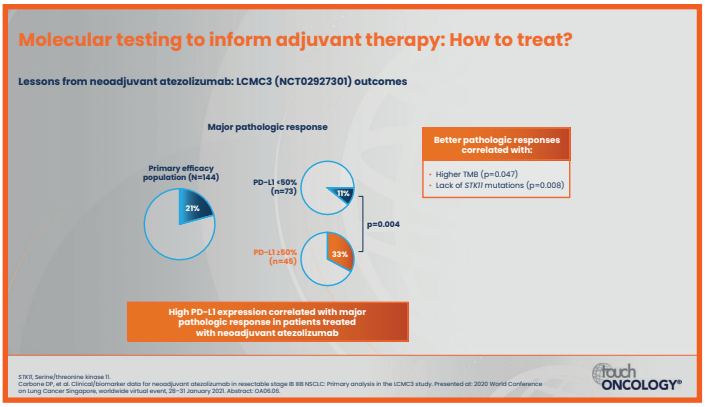


The largest study to date looking at neoadjuvant immunotherapy alone is LCMC3. This study included patients with resectable, untreated, unselected stage IB to IIIA NSCLC, and some selected stage IIIB NSCLC. Patients received only two doses of atezolizumab, the PD-L1 inhibitor alone, then went directly to surgery. That was followed by surveillance with the option for adjuvant atezolizumab for up to one year afterwards. The primary endpoint here was major pathologic response (MPR), which is defined as ≤10% viable tumour cells in the surgical specimen.

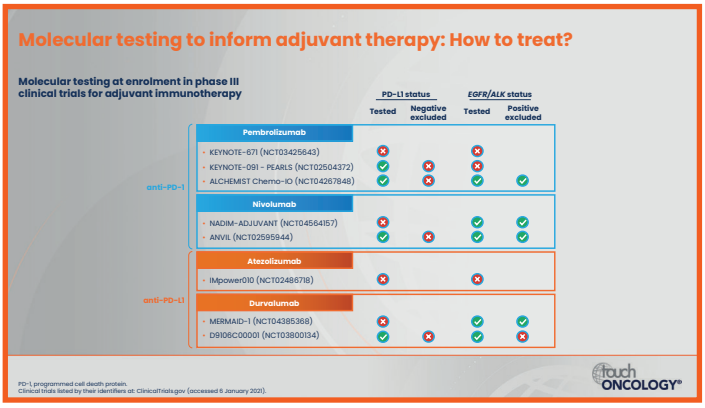


What we saw with the use of neoadjuvant atezolizumab was that the MPR rate was 21% in the primary efficacy population. If we break that down by PD-L1 expression, we see a lower

rate for PD-L1 negative at 11% (PD-L1 <50%), and for PD-L1 high, the MPR rate was 33%. That was a significant difference. High PD-L1 expression correlates with major pathologic response when we use neoadjuvant atezolizumab. Are there other biomarkers that can help predict who will derive greater benefit from it? What we saw in some correlative studies from LCMC3 is that higher TMB did correlate with better pathologic responses and the absence of an *STK11* mutation significantly correlated with a better response to neoadjuvant atezolizumab. We have yet to see whether this will translate to a difference in long-term survival, but these are certainly encouraging results.

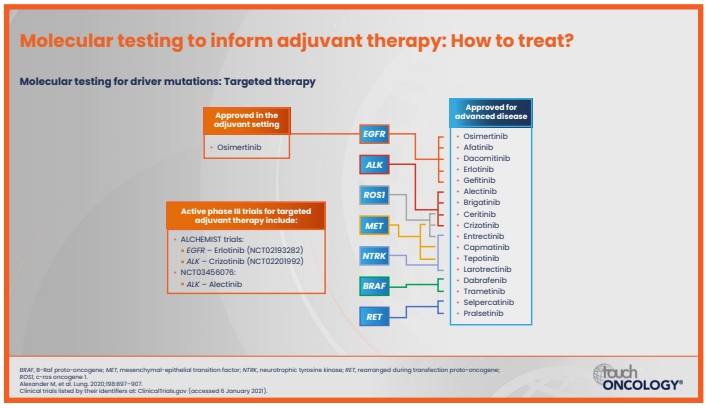


And this is one of only several trials looking at adjunct immunotherapy—some relying on PD-L1 to determine who derives that benefit; some excluding patients with *EGFR* or *ALK* alterations to try to enrich that population. But there are several trials with PD-1 and PD-L1 inhibitors looking at immunotherapy or immunotherapy with chemotherapy in that adjuvant space.

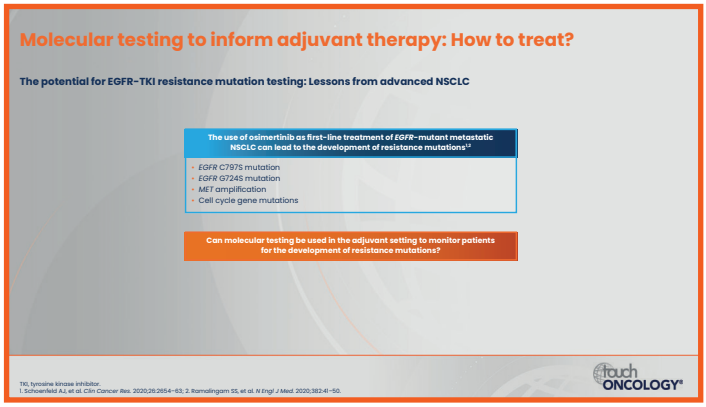


We also can explore adjuvant targeted therapy. We know from the ADAURA trial that the use of adjuvant osimertinib for tumours with an *EGFR* exon 19 deletion or L858R point mutation significantly improves DFS. But osimertinib is not the only EGFR kinase inhibitor, and *EGFR* is not the only alteration. Would the same apply to *ALK, ROS1, RET*? Will we see an improvement in DFS if we were to use alectinib or brigatinib, and would it be at the same magnitude for *ALK*-fusion positive NSCLC?

It may be hard to test all of these hypotheses, given the rarity of some of these alterations. *RET* fusion, for example, occurs in only 1% of NSCLC, but we have very selective, well-tolerated RET inhibitors like selpercatinib and pralsetinib. Would we see comparable results with adjuvant RET inhibition in a *RET*-fusion positive NSCLC? We simply do not know. Importantly, though, there are ongoing phase III trials that are seeking to answer some of these questions. In addition to *EGFR*, we have several studies looking at *ALK*-fusion positive NSCLC. It will be important to see and to compare the results from these studies with the ADAURA trial.



Today, we know that in stage IV NSCLC, osimertinib resistance is mediated by several detectable alterations, including C797S and *MET* amplification. Will we start to see some of these in the adjuvant space? How will the use of adjuvant osimertinib impact resistance at the time of recurrence? Important, but unanswered questions.



The diagnostic and treatment algorithm for NSCLC needs to identify who will benefit most from these adjuvant approaches. Markers such as TMB, PD-L1 expression and minimal residual disease are going to be important to inform whether a patient may be more or less likely to benefit from these strategies—a hypothesis that does need to be proven. PD-L1 expression or the presence of alterations such as *EGFR* or *ALK* may in the future help guide the use and the selection of patients to benefit from optimal adjuvant and perioperative systemic therapy strategies.

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

How do data in early-stage NSCLC impact our current treatment pathway for *EGFR*-mutant lung cancer? Well, it's important to consider this in the context of the multidisciplinary management of NSCLC. There are many factors that we must consider when formulating the optimal plan for a resectable early-stage NSCLC.

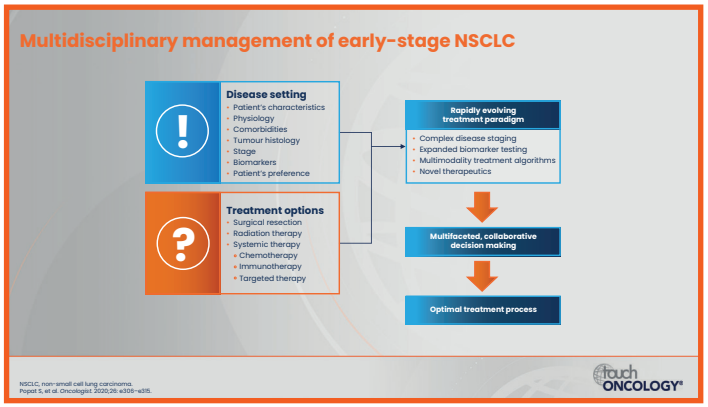
Some of the important characteristics have to do with the disease setting, such as the patient characteristics, their underlying physiology, lung function and comorbidities, as well as important factors for the tumour. The histology will guide systemic options and the prognosis. The stage clearly guides treatment options. Beyond the stage there's more granularity that can only be gleaned from incorporating a multidisciplinary team (MDT).

We don't treat all stage II or all stage III NSCLC the same. Some stage II lung cancer, while early-stage, is simply not resectable. If a stage II lung cancer is adherent to the pulmonary artery, it cannot be removed because there's no barrier there. Are we unable to get clean margins? Are we unable to resect based on underlying lung function? The treatment algorithms will vary. It really requires input from a MDT.

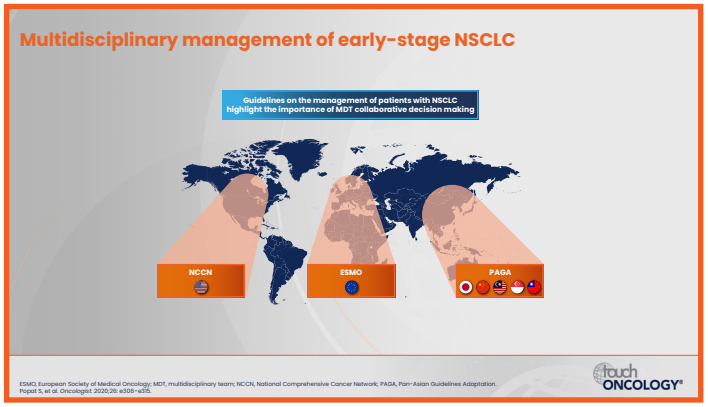
There are different biomarkers we consider now, with the option of targeted therapy in the perioperative setting, the presence or absence of molecular alterations, and certainly the patient's preference. We now employ a shared decision-making model—the patient has input on what the optimal treatment should be.

We have different treatment options that we can employ. Certainly, surgical resection has been our mainstay for early-stage lung cancer, but radiation therapy can certainly play a role, and we have different systemic options. Chemotherapy is the historic standard; we have the introduction of both immunotherapy and targeted therapy as possible options now and in the near future.

This is a rapidly evolving treatment paradigm. We have complex disease staging that is only growing increasingly complex as our tests grow increasingly sophisticated. The multi-modality treatment will continue to be an important highlight for early-stage NSCLC; biomarker testing is now critical and will expand in coming years. The field is moving very quickly with novel therapeutics being developed and integrated in the treatment for early stage NSCLC. It's important to stay up to date with the latest developments and the best outcomes. It really is a multifaceted, collaborative, decision-making process that is required for the optimal treatment process for patients with early-stage NSCLC.

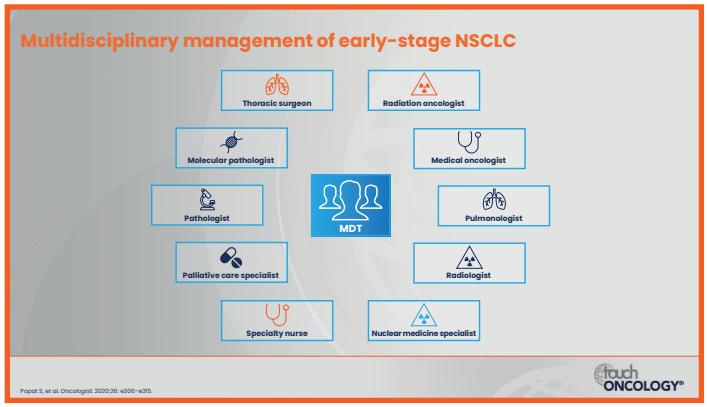


Current guidelines on the management of patients with NSCLC reflect the importance of a multidisciplinary tumour approach and collaborative decision-making, which really is an intervention in and of itself.



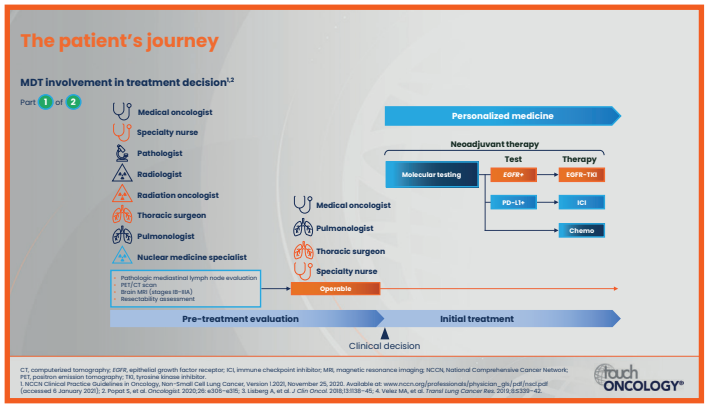
That MDT requires input from many different specialties. Historically, we considered our thoracic surgeons as those doing the resection, our radiation oncologists as those delivering radiation, and our medical oncologists as those delivering systemic therapy; but the optimal team, whenever possible, includes many more members. The pulmonologist is critical sometimes in establishing the diagnosis, certainly in establishing the nodal stage with invasive nodal techniques and in helping determine what the lung function is: what the lung function is now and what the lung function would be after the proposed intervention.

We rely on radiologists and nuclear medicine specialists to help interpret many of the staging studies with specific granularity. Specialty nurses and palliative care specialists can help guide symptom management and improve outcomes. Pathologists help establish the diagnosis, the histology, the grade, but increasingly we're relying on molecular pathologists to help give a diagnosis beyond just the histology to help look at the genomic subtype of these lung cancers.



All of these sub-specialties are not available in all settings, but whenever possible, they do make for a more balanced and an optimal approach. So how do these different members of the MDT come into play in a specific patient's journey? We will see that different specialties play different roles at every step of the way.

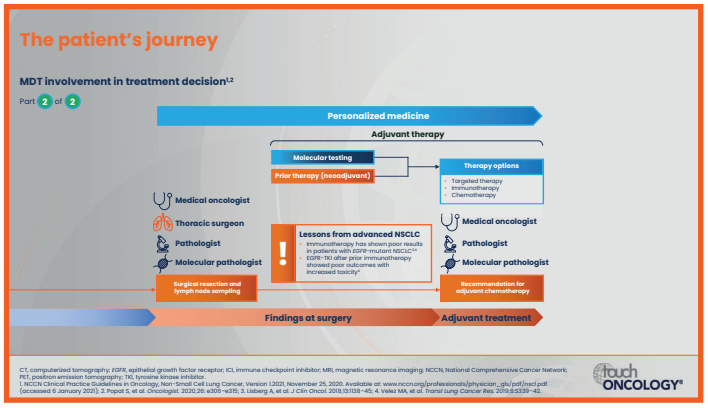
Our pre-treatment evaluation typically involves a biopsy. The biopsy needs to be evaluated by a pathologist and will be acquired by either a radiologist or a thoracic surgeon or, more frequently, a pulmonologist. Staging studies are done early on, PET/CT scans, MRIs, this will require input from our radiologists and from our nuclear medicine specialists. We then must make decisions about resectability with important input from our thoracic surgeons, but also from our pulmonologists.



If we decide that we're moving forward, we must now decide whether the tumour is resectable, whether the patient is operable. This requires input from our pulmonologists, from our thoracic surgeons, and often the entire package delivered to our medical oncologists to help determine whether systemic therapy can help improve outcomes pre- or post-surgery.

The initial treatment is often personalized when possible, and that will increasingly require molecular testing, knowing the underlying genotype, knowing whether, for example, an *EGFR* mutation is present, will help guide treatment decisions both before and after surgery, not just on what to deliver, but what to avoid. PD-L1 testing may play a role in the use of immune checkpoint inhibitors in the relatively near future, and certainly we rely on chemotherapy in that setting as well to improve outcomes.

When patients do proceed to surgery, after surgical resection interpretation of the results will be critical in deciding whether more therapy is needed. That will require assessment of the surgical specimen from our pathologists, but also our molecular pathologists and interpretation from our medical oncologists. We then must decide whether adjuvant therapy is needed. If molecular testing has not been done to date, it must be done now. The presence of an *EGFR* mutation, for example, predicting better DFS with the use of targeted therapy such as osimertinib.



We use molecular testing to guide treatment pre- and post-surgery while targeted therapy, and in the near future immunotherapy, are important options for patients with resected or resectable NSCLC. It's important these worlds do not collide. These really are two separate pathways and must be treated as such.

We learned important lessons from patients with metastatic NSCLC that targeted therapy is very

safe, but when delivered after immunotherapy, it becomes much more toxic; that immunotherapy is largely inactive in patients with an underlying driver mutation; and that the sequence of treatment is critical to delivering the best outcomes in a safe way.

It's because of this that we must know the *EGFR* mutation status and potentially any driver mutation status for patients before we integrate immunotherapy. If patients have an *EGFR* mutation and we implement a neoadjuvant or adjuvant immunotherapy strategy, we then make subsequent targeted therapy much more toxic, really compromising outcomes. To do that, we must know the *EGFR* mutation status before immunotherapy is deployed. That may be before surgery or it may be after surgery, but our workflow and our understanding of NSCLC has to evolve as these different modalities emerge.

Each patient's case really needs to be discussed within a MDT, and while not all patients and not all sites will have access to every member of the team, as many as possible will help improve outcomes. It really is a collaborative decision-making process from the beginning. We discuss patients at our multidisciplinary tumour board at my own institution and I encourage others to do the same whenever possible.

That MDT involvement should be considered as a medical intervention in its own right. Effective MDT decision-making and optimal patient management decisions require effective communication among these different specialties using a common language. It really is through a team approach that we can get the best possible outcomes for patients with early-stage NSCLC.

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