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Precision Medicine in NSCLC

Implications for Molecular Testing and Treatment – *Part 2*

This transcript has been edited for style and clarity and includes all slides from the presentation.

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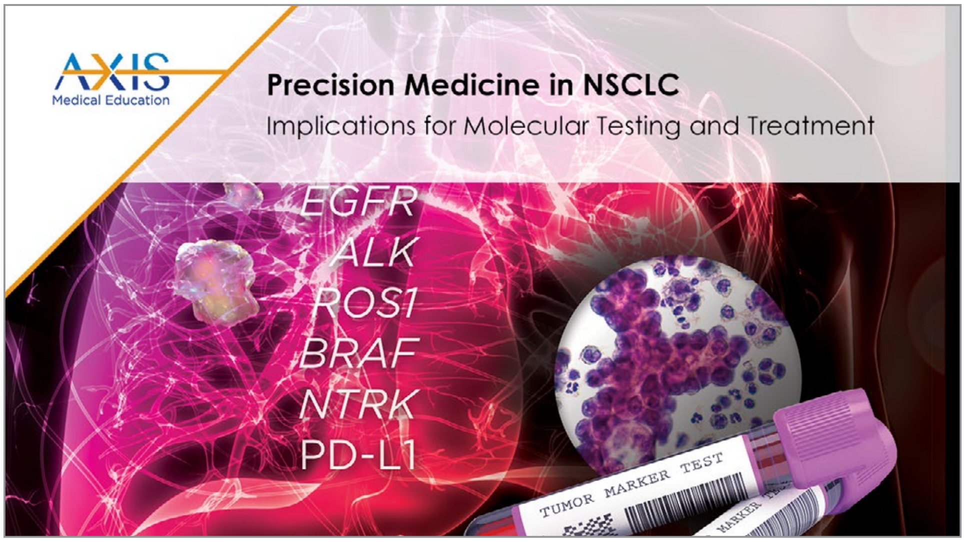
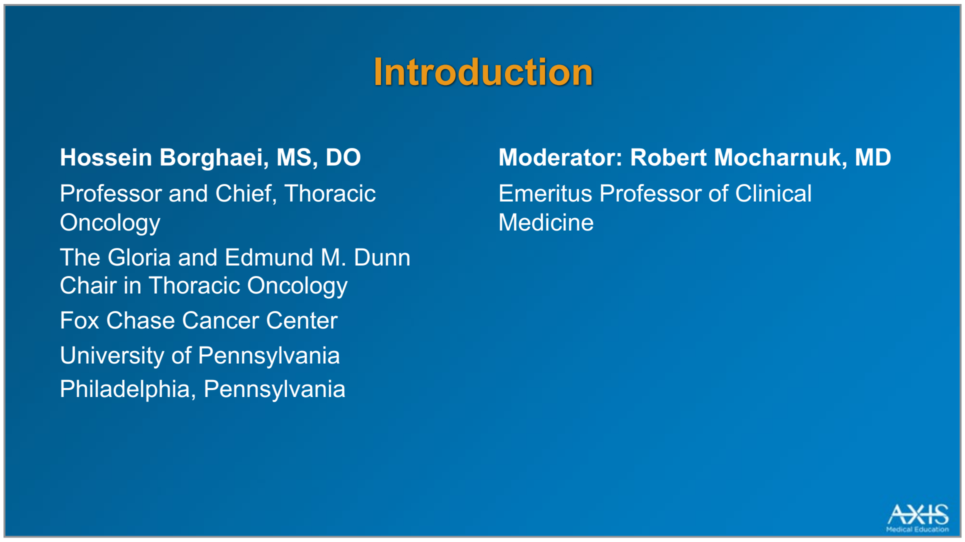
Precision Medicine in NSCLC: Implications for Molecular Testing and Treatment – Part 2

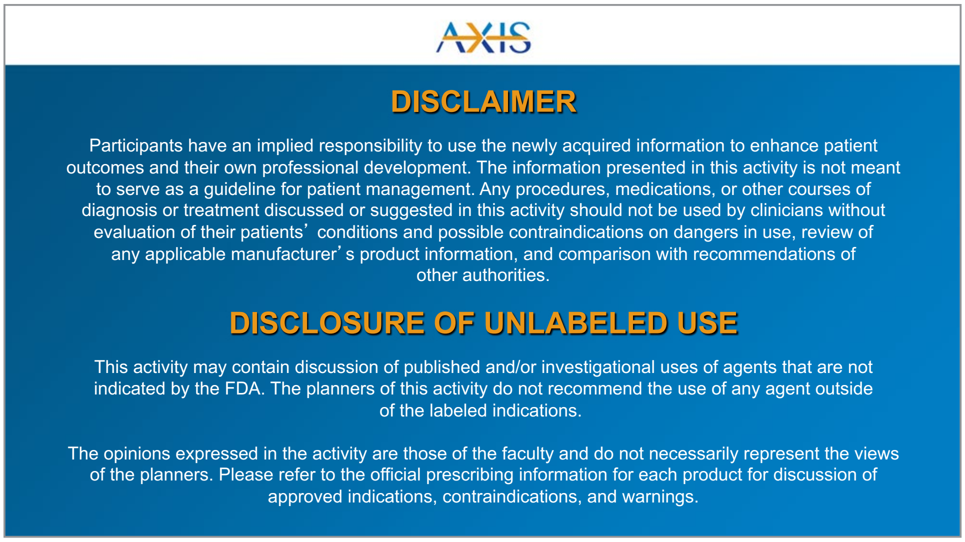
Hossein Borghaei, MS, DO



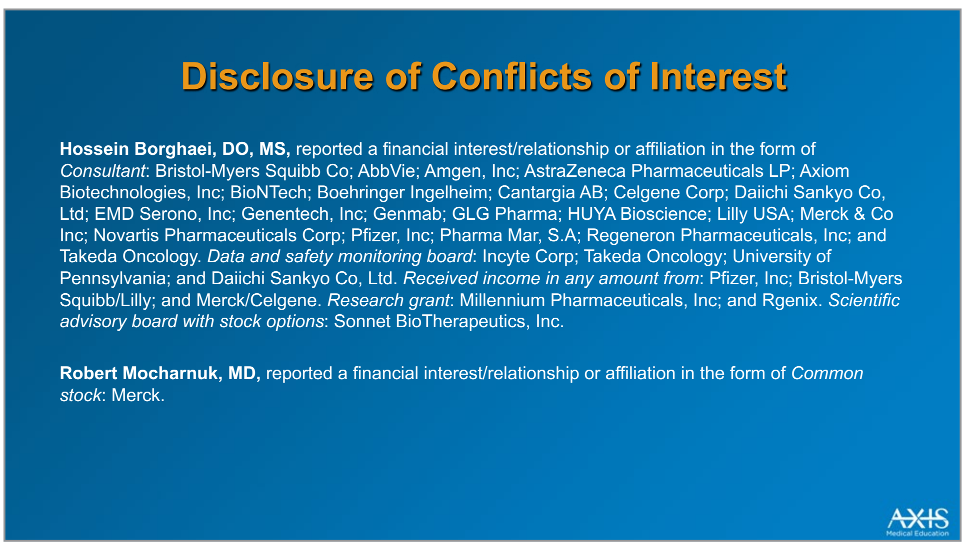
▶ **Robert Mocharnuk, MD:** Hello, and welcome to part two of this educational activity entitled *Precision Medicine in Non-Small Cell Lung Cancer: Implications for Molecular Testing and Treatment.*



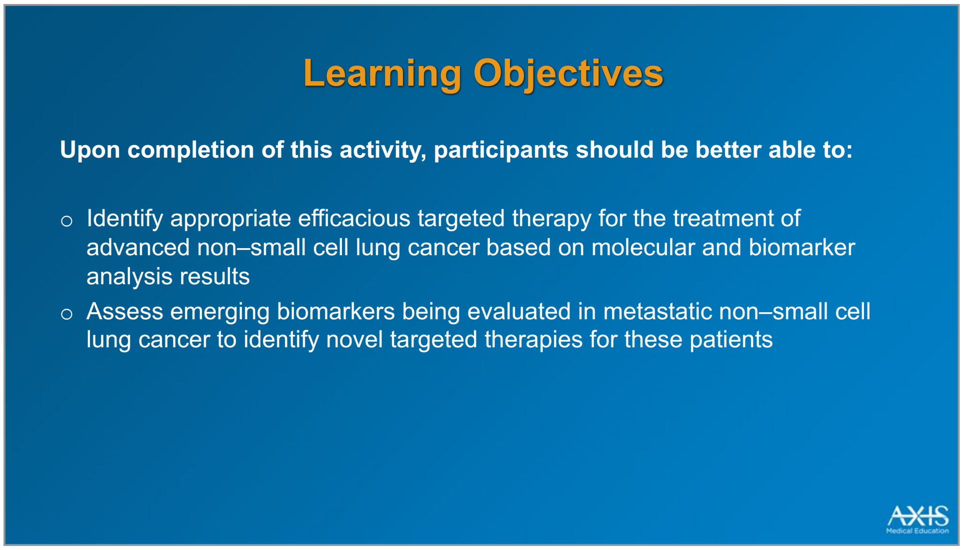
▶ I am Dr. Robert Mocharnuk, Emeritus Professor of Clinical Medicine, and I am joined today by Dr. Hossein Borghaei, Professor and Chief of Thoracic Oncology at the Fox Chase Cancer Center in Philadelphia, Pennsylvania.



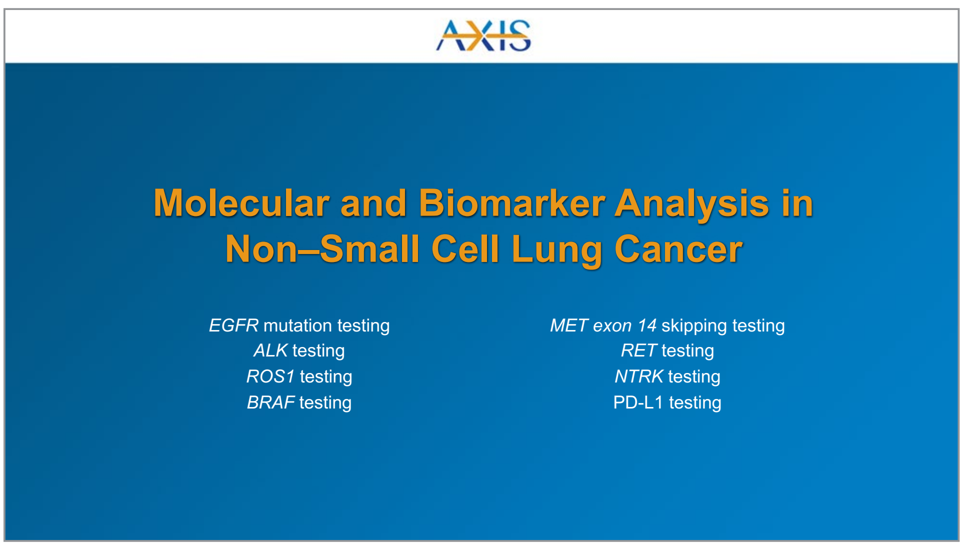
- Here is a disclaimer and disclosure indicating that we may be discussing off-label use of approved agents, or agents that are currently in development.



- Here is our financial disclosure information.



- Here are the learning objectives for this activity. Today, in part two of this activity, we will review and evaluate the most recent data and recommendations, and provide expert insights on targeted therapies for the treatment of advanced and metastatic non-small cell lung cancer that are currently available based on the presence of identified mutations and gene rearrangements.



- Dr. Borghaei, as we reviewed in part one, there are many gene alterations in non-small cell lung cancer that impact therapy selection, once identified through molecular and biomarker analysis. Will you take us through the available targeted therapies in advanced and metastatic non–small cell lung cancer, and briefly review the most pertinent data and guideline recommendations that support their use? Let's start with *EGFR* mutation-positive disease.

EGFR Mutation Positive

Drug (NCCN® Recommendation)	Trial(s)	Reference(s)
First-Line Therapy		
Afatinib (recommended)	LUX Lung 3 LUX Lung 6	Yang et al. *Lancet Oncol*. 2015;16:141-151.
Erlotinib (recommended)	EURTAC	Rosell et al. *Lancet Oncol*. 2012;13:239-246.
Dacomitinib (recommended)	ARCHER 1050	Wu et al. *Lancet Oncol.* 2017;18:1454-1466.
Gefitinib (recommended)	IPASS IFUM	Mok et al. *N Engl J Med.* 2009;361:947-957. Douillard et al. *Br J Cancer.* 2014;110:55-62.
Osimertinib (preferred)	FLAURA	Soria et al. *N Engl J Med*. 2018;378:113-125. Ramalingam et al. *N Engl J Med*. 2020;382:41-50.
Erlotinib + ramucirumab (recommended)	RELAY	Nakagawa et al. *Lancet Oncol*. 2019;20:1655-1669.
Erlotinib + bevacizumab (useful in certain circumstances)	NEJ026	Saito et al. *Lancet Oncol*. 2019;20:625-635.
Subsequent Therapy		
Osimertinib (T790M+)	AURA3	Mok et al. *N Engl J Med*. 2017;376:629-640.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

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Hossein Borghaei, DO, MS: One of the best-studied pathways in all of oncology is the EGFR pathway. In lung cancer, this has a significant place because it's one of the first mutations that we were able to identify—activating mutations in *EGFR*—that helped us figure out which patients will respond to EGFR-targeted therapies in terms of the oral agents we had available.

And this came as a result of several lines of well-documented investigation, but what you see are basically a number of trials over the past few years that have been published with different EGFR tyrosine kinase inhibitors (TKIs) for patients with specific *EGFR* mutations; many of these are phase 3 studies with a comparator arm. But in all of these, basically what we are finding is that patients who have an *EGFR* mutation, if they get the targeted therapy, they do better compared to patients who get chemotherapy.

The field has advanced to the stage that we have first-, second-, and now third-generation oral TKIs. What are the differences? Well, the first-generation TKIs were erlotinib and gefitinib. These were reversible inhibitors. The second generations include mostly afatinib, maybe dacomitinib. These are irreversible. And then, third generation includes osimertinib, which is also an irreversible inhibitor of the tyrosine kinase pathway.

Consistent Major Benefit of EGFR TKI over Chemotherapy in *EGFR* Mutation–Positive Advanced NSCLC

Generation	Author	Study	Agent	N (*EGFR* mutation+)	RR	Median PFS (mo)	Median OS (mo)
1st generation, reversible	Mok et al[1]	IPASS	Gefitinib	261	71.2% vs 47.3%	9.8 vs 6.4	21.6 vs 21.9
	Lee et al[2]	First-SIGNAL		42	84.6% vs 37.5%	8.4 vs 6.7	27.2 vs 25.6
	Mitsudomi et al[3]	WJTOG 3405		177	62.1% vs 32.2%	9.2 vs 6.3	35.5 vs 38.8
	Maemondo et al[4]	NEJGSG002		230	73.7% vs 30.7%	10.8 vs 5.4	30.0 vs 23.6
	Zhou et al[5]	OPTIMAL	Erlotinib	154	83% vs 36%	13.1 vs 4.6	22.6 vs 28.8
	Rosell et al[6]	EURTAC		154	54.5% vs 10.5%	9.2 vs 5.4	19.3 vs 19.5
2d generation, irreversible	Yang et al[7]	LUX-Lung 3	Afatinib	345	56% vs 23%	13.6 vs 6.9	31.6 vs 28.2
	Wu et al[8]	LUX-Lung 6		364	67% vs 23%	11.0 vs 5.6	23.6 vs 23.5

Consistent RR and PFS benefit versus chemo, but crossover likely to obscure OS benefit

NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; RR, response rate; TKI, tyrosine kinase inhibitor.

1. Mok et al. *N Engl J Med*. 2009;361:947-957. 2. Lee et al. WCLC meeting, 2009: PRS.4. 3. Mitsudomi et al. *Lancet Oncol*. 2010;11:121-128.
4. Maemondo et al. *N Engl J Med*. 2010:362:2380-2388. 5. Zhou et al. *Ann Oncol*. 2010;21(suppl 8):LBA13. 6. Rosell et al. *J Clin Oncol*. 2011;29(suppl): abstract 7503.
7. Yang et al. *J Clin Oncol*. 2012;30(suppl): abstract LBA7500. 8. Wu YL et al. *J Clin Oncol*. 2013;31(suppl): abstract 8016.

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- It's significant to look at the number of studies that have been done with all of these agents. All of them show the superiority of oral TKIs for patients with activating *EGFR* mutations, compared to chemo and other drugs.

EGFR Tyrosine Kinase Inhibitors

TKI	Indication	Salient Aspects
1st Generation: Gefitinib, Erlotinib	1st-line therapy	Reversible inhibition
2nd Generation: Afatinib, Dacomitinib	1st -line therapy	Irreversible inhibition
3rd Generation: Osimertinib	1st-line therapy 2nd-line therapy for T790M+ NSCLC	Irreversible inhibition

NSCLC, non–small cell lung cancer; TKI, tyrosine kinase inhibitor.

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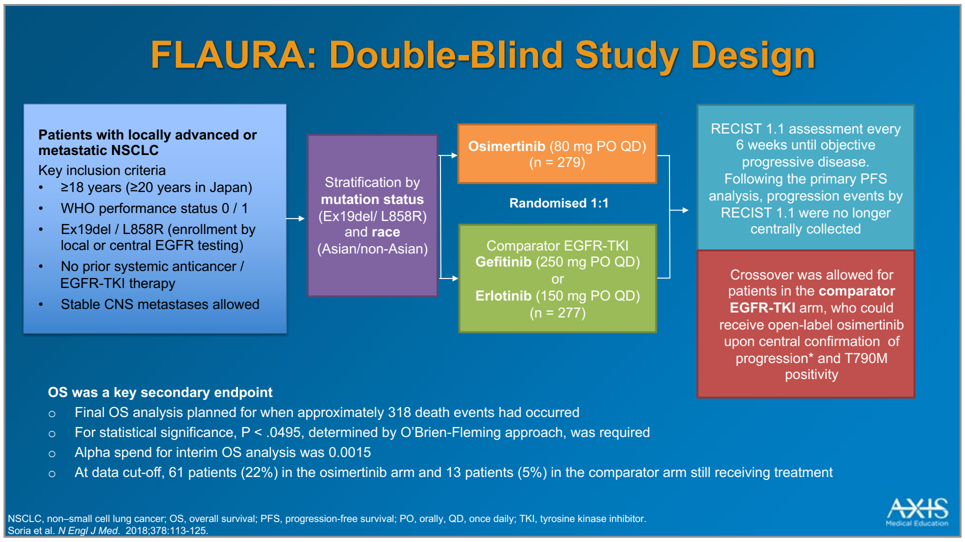
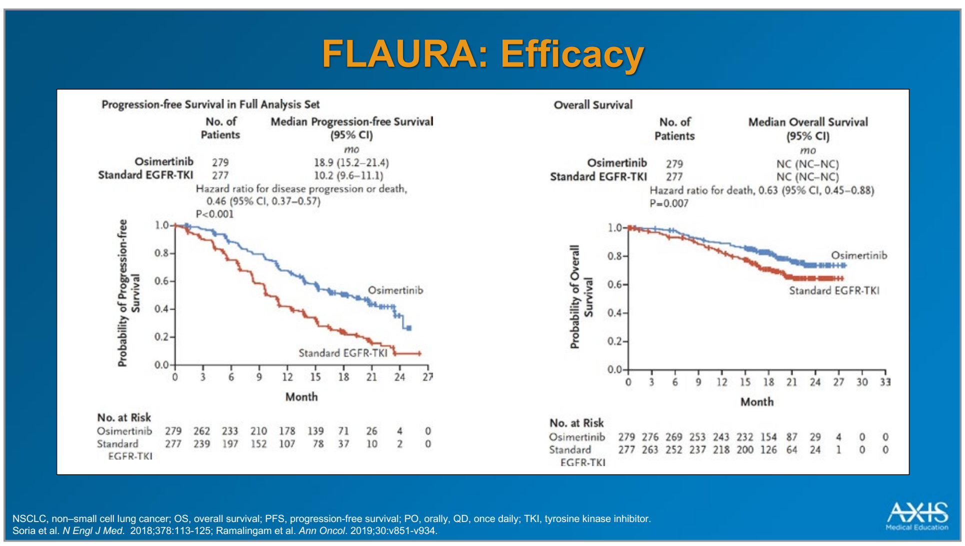
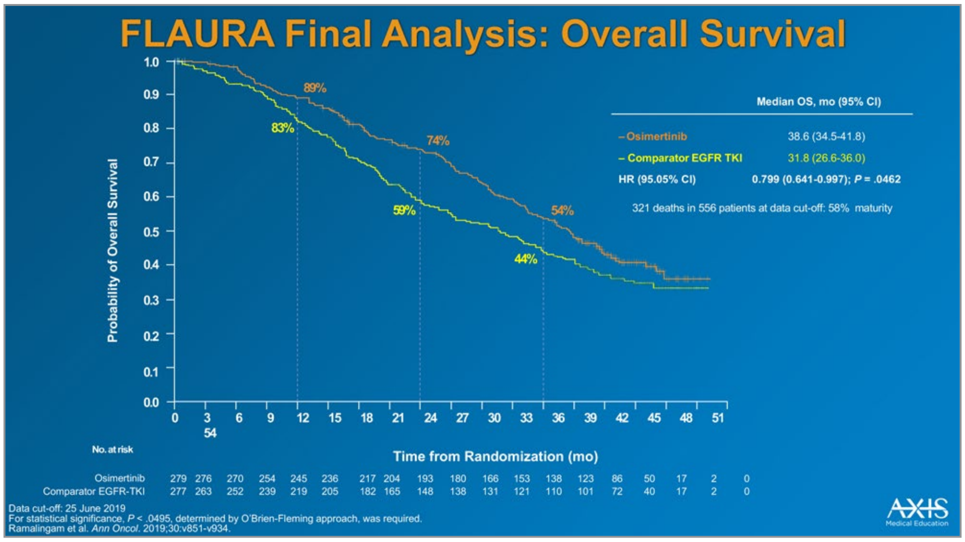
- This is the basic principle of first-, second-, and third-generation drugs and some of the characteristics, as I spoke to. Where are we now? Well, we know first- and second-generation drugs such as gefitinib and erlotinib work really well. Then osimertinib came to the scene. Initially osimertinib was for patients who had developed a particular mutation called T790M, which we normally were discovering following treatment on erlotinib or gefitinib. And this drug showed really good clinical activity there, but it was pretty obvious that osimertinib also had activity against *EGFR* mutations in patients who are treatment naïve.



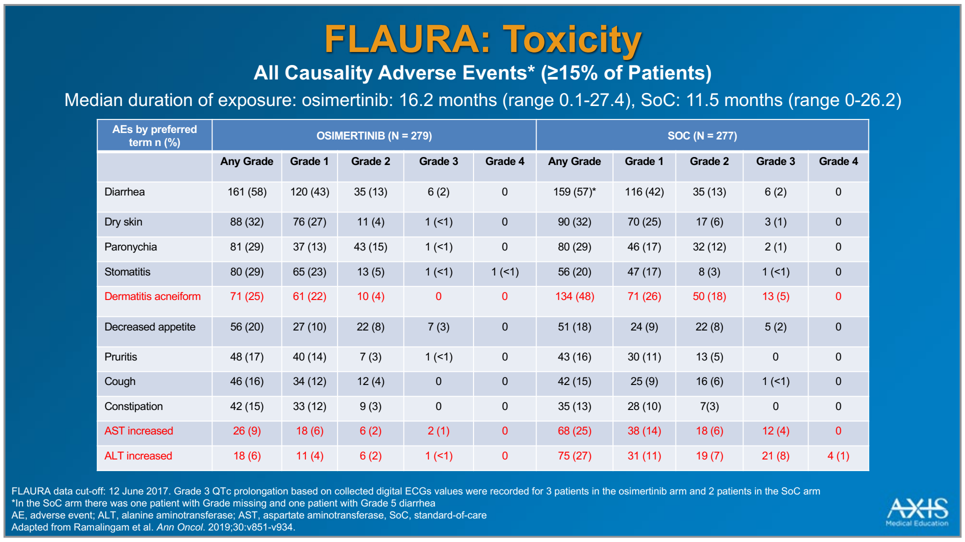
- The FLAURA study was a randomized phase 3 trial that compared osimertinib to either erlotinib or gefitinib.



- The efficacy endpoint, shown on the left, is progression-free survival (PFS). On the right is the interim overall survival, all indicating that osimertinib was superior to either erlotinib or gefitinib for the treatment of patients with *EGFR* mutations.



- The updated overall survival is shown here. With longer follow-up, we now have a median survival of almost 39 months for patients who were treated with osimertinib, versus about 32 months for patients who were treated with either erlotinib or an EGFR TKI. In most parts of the world where osimertinib is available, the results of this study led to a switch from using either gefitinib or erlotinib first line, to using osimertinib first line. In the United States and in my clinical practice for patients who have an activating *EGFR* mutation, osimertinib is the drug that is used.



FLAURA: Toxicity

All Causality Adverse Events* (≥15% of Patients)

Median duration of exposure: osimertinib: 16.2 months (range 0.1-27.4), SoC: 11.5 months (range 0-26.2)

AEs by preferred term n (%)	OSIMERTINIB (N = 279)					SOC (N = 277)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	161 (58)	120 (43)	35 (13)	6 (2)	0	159 (57)*	116 (42)	35 (13)	6 (2)	0
Dry skin	88 (32)	76 (27)	11 (4)	1 (<1)	0	90 (32)	70 (25)	17 (6)	3 (1)	0
Paronychia	81 (29)	37 (13)	43 (15)	1 (<1)	0	80 (29)	46 (17)	32 (12)	2 (1)	0
Stomatitis	80 (29)	65 (23)	13 (5)	1 (<1)	1 (<1)	56 (20)	47 (17)	8 (3)	1 (<1)	0
Dermatitis acneiform	71 (25)	61 (22)	10 (4)	0	0	134 (48)	71 (26)	50 (18)	13 (5)	0
Decreased appetite	56 (20)	27 (10)	22 (8)	7 (3)	0	51 (18)	24 (9)	22 (8)	5 (2)	0
Pruritis	48 (17)	40 (14)	7 (3)	1 (<1)	0	43 (16)	30 (11)	13 (5)	0	0
Cough	46 (16)	34 (12)	12 (4)	0	0	42 (15)	25 (9)	16 (6)	1 (<1)	0
Constipation	42 (15)	33 (12)	9 (3)	0	0	35 (13)	28 (10)	7(3)	0	0
AST increased	26 (9)	18 (6)	6 (2)	2 (1)	0	68 (25)	38 (14)	18 (6)	12 (4)	0
ALT increased	18 (6)	11 (4)	6 (2)	1 (<1)	0	75 (27)	31 (11)	19 (7)	21 (8)	4 (1)

FLAURA data cut-off: 12 June 2017. Grade 3 QTc prolongation based on collected digital ECGs values were recorded for 3 patients in the osimertinib arm and 2 patients in the SoC arm
*In the SoC arm there was one patient with Grade missing and one patient with Grade 5 diarrhea
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase, SoC, standard-of-care
Adapted from Ramalingam et al. *Ann Oncol*. 2019;30:v851-v934.
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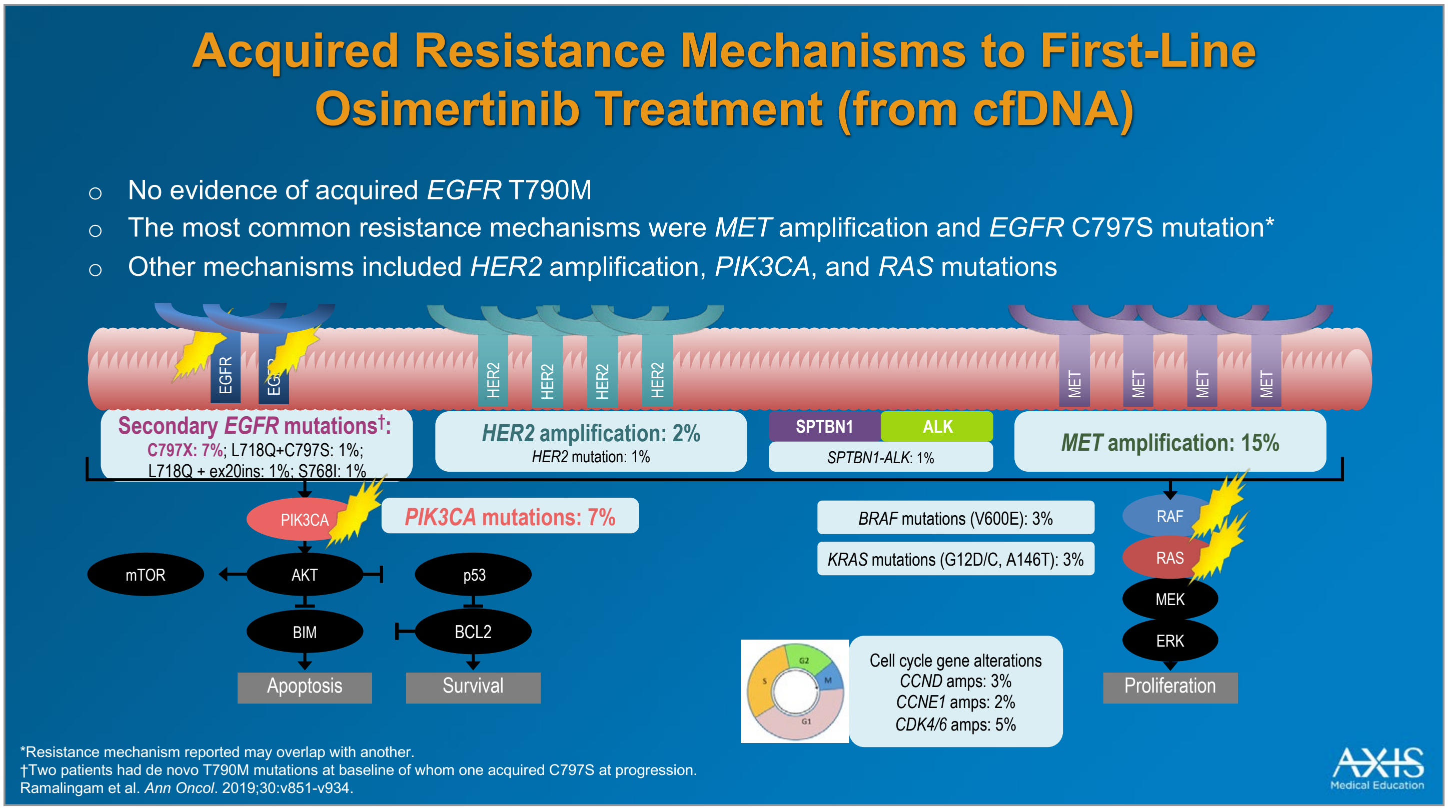
- Osimertinib is effective—it works a lot better than erlotinib or gefitinib; however, what about toxicity? This is a table from the initial presentation indicating a head-to-head comparison in terms of some of the more common toxicities that are associated with TKIs (rash and diarrhea) and it shows that osimertinib was slightly more tolerable.

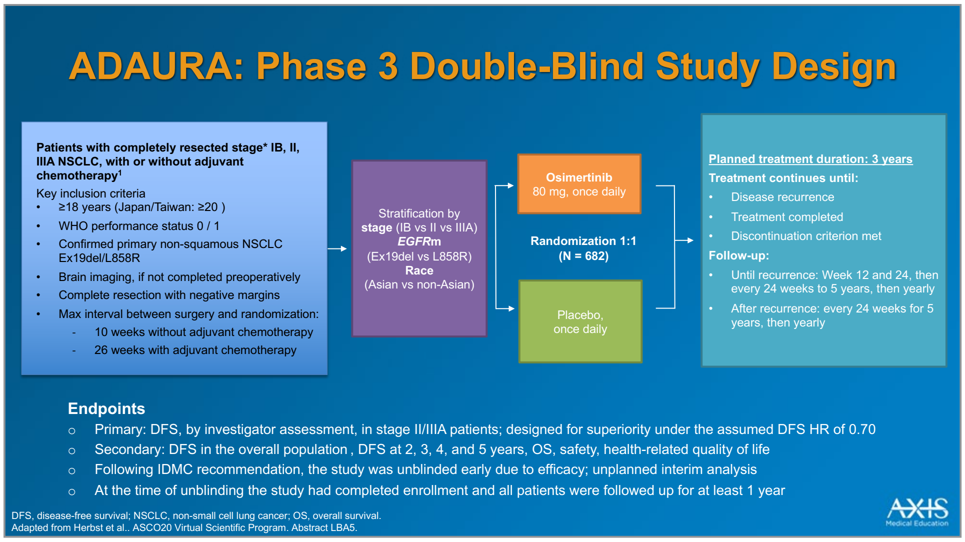
  So, it doesn't mean that the drug doesn't have side effects. Every drug, unfortunately, has some degree of side effect associated with it. What the table tells us is that compared to the first-generation drugs, osimertinib seems to be a better agent. So, toxicity is better, clinical activity is better. What isn't indicated on these slides is that patients with brain metastases can respond, which is a big deal in the world of non–small cell lung cancer, especially for patients with these sorts of mutations.



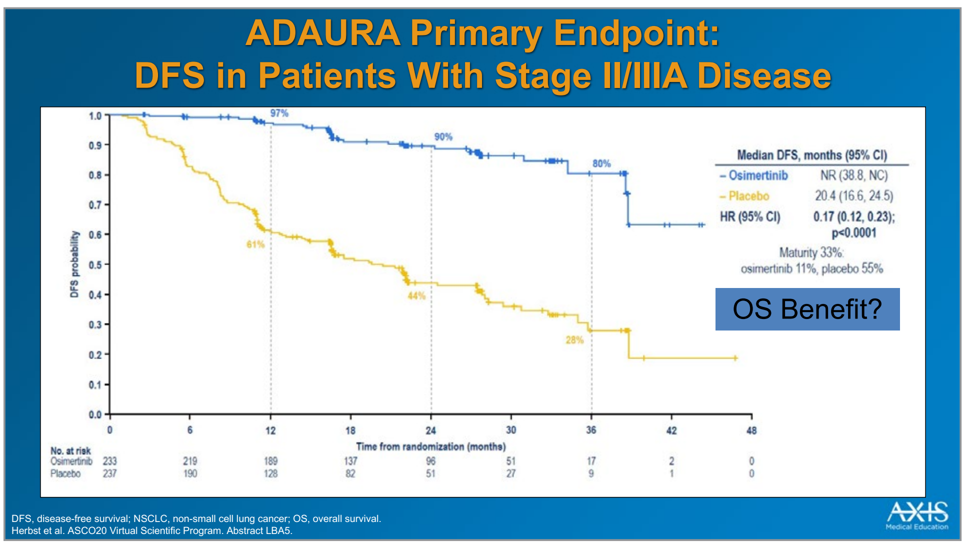
- If you put all of that together, it indicates that osimertinib is a really good first-line option for patients with an activating *EGFR* mutation. The problem is that unfortunately we're not curing our patients who have an *EGFR* mutation; eventually, there is disease progression. The question then becomes, why is there disease progression? As a result of multiple biopsies done at progression for patients who are on osimertinib, there are specific bypass mechanisms where the tumor can actually escape control as a result of treatment with osimertinib.

Some of these cases can now be addressed. About 15% of our patients end up having a met amplification as a resistance mechanism to osimertinib. Another 2% might have a *HER2* amplification. And other pathways can be altered or affected, as shown on this particular slide.

There are 2 reasons why this is important. It tells us that we should obtain biopsy specimens at the time of progression on osimertinib to figure out if they have one of these alterations. Why? Because if they have one of these alterations, we can address it right now in the form of clinical trials, but there are hopefully, down the road, going to be protocols we can offer our patients if they have one of these alterations.



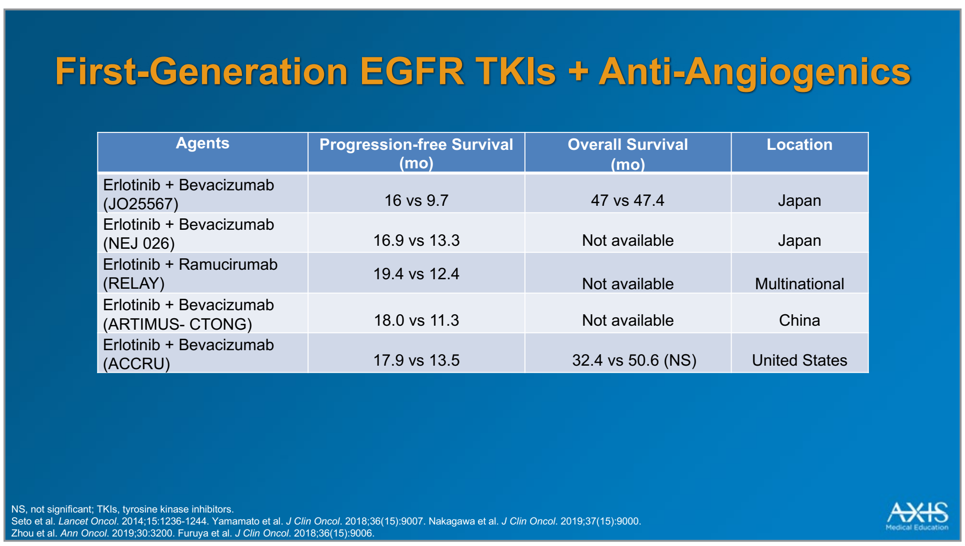
This is the design for the ADAURA study. This was an adjuvant clinical trial for patients who've had surgically resected non–small cell lung cancer with activating *EGFR* mutations. They could get adjuvant chemo as per the standard of care. Then the patients were randomized to either receiving osimertinib or placebo, which is doable because in the adjuvant setting we don't have any treatment after adjuvant chemotherapy.



The primary endpoint of this study was disease-free survival. This was just presented at the virtual ASCO meeting in 2020. The study had to be held early because of the significant difference in disease-free survival seen in patients treated with osimertinib compared to placebo, as shown on this particular graph. This has led to a lot of discussion in the field as to whether this is enough for us to switch our patients after adjuvant chemo and offer them osimertinib. Right now, we don't have approval in the adjuvant setting, but that might change.

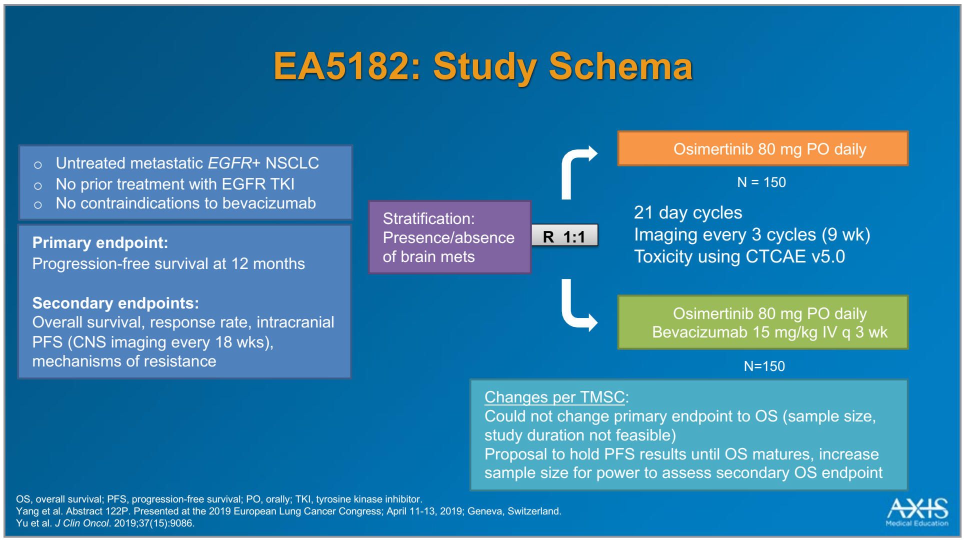
Is this enough, or should we have some overall survival data to compel us to change the treatment for this particular group of patients? That's something we're still debating. The discussions are ongoing. The study is ongoing. Hopefully, with more follow-up, we'll have a little bit more clarity. I think this is something that we should be aware of because we could potentially have a practice-changing protocol based on the results of this study.

- What do we do for disease that becomes resistant?



Agents	Progression-free Survival (mo)	Overall Survival (mo)	Location
Erlotinib + Bevacizumab (JO25567)	16 vs 9.7	47 vs 47.4	Japan
Erlotinib + Bevacizumab (NEJ 026)	16.9 vs 13.3	Not available	Japan
Erlotinib + Ramucirumab (RELAY)	19.4 vs 12.4	Not available	Multinational
Erlotinib + Bevacizumab (ARTIMUS- CTONG)	18.0 vs 11.3	Not available	China
Erlotinib + Bevacizumab (ACCRU)	17.9 vs 13.5	32.4 vs 50.6 (NS)	United States

- First, there are a number of different strategies that we have undertaken to see if we can improve the time that patients are actually receiving osimertinib. One approach is to use antiangiogenic agents. This table covers a number of different studies that we've done with, for instance, erlotinib versus bevacizumab, trying to see if there is a way for us to improve the outcome. Either the survival or PFS or things of that nature.



- As shown on the previous slide, where we were using, for instance erlotinib and bevacizumab, ECOG-ACRIN 5182 uses osimertinib plus bevacizumab, again as a method to see if we can delay disease progression.

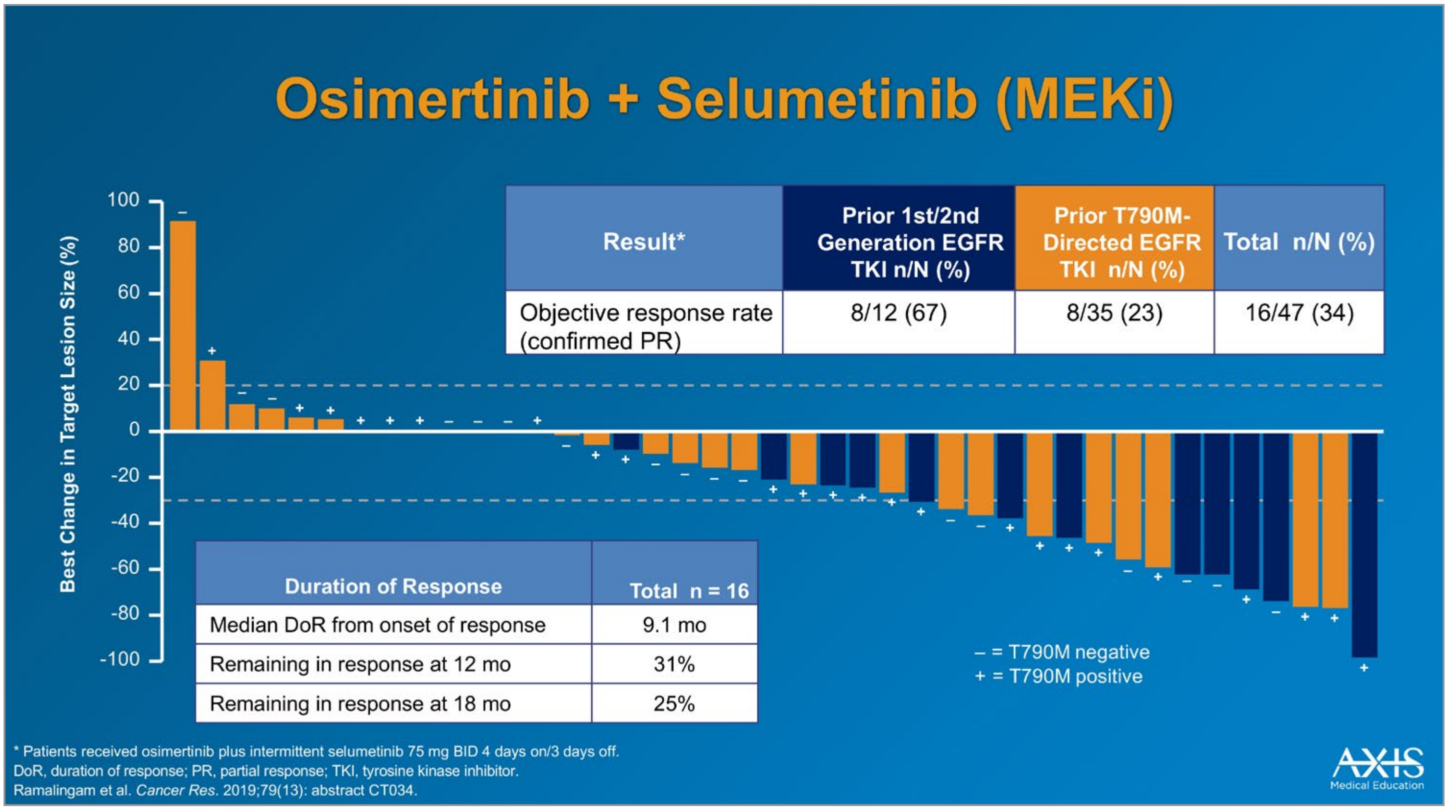
EGFR TKI + Chemotherapy

Study	Agent (n)	mPFS, mo	mOS, mo
NEJ 009*	Gefitinib (172)	11.2	38.8
	Chemo + Gefitinib (169)	20.9	52.2
Noronha et al†	Gefitinib (177)	8	18
	Chemo + Gefitinib (173)	16	NR (HR for death, 0.45)

*Nakamura et al. *J Clin Oncol*. 2018;36(15):9005.
†Noronha et al. *J Clin Oncol*. 2019;37(15):9001.
Chemo, chemotherapy; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; TKI, tyrosine kinase inhibitor.

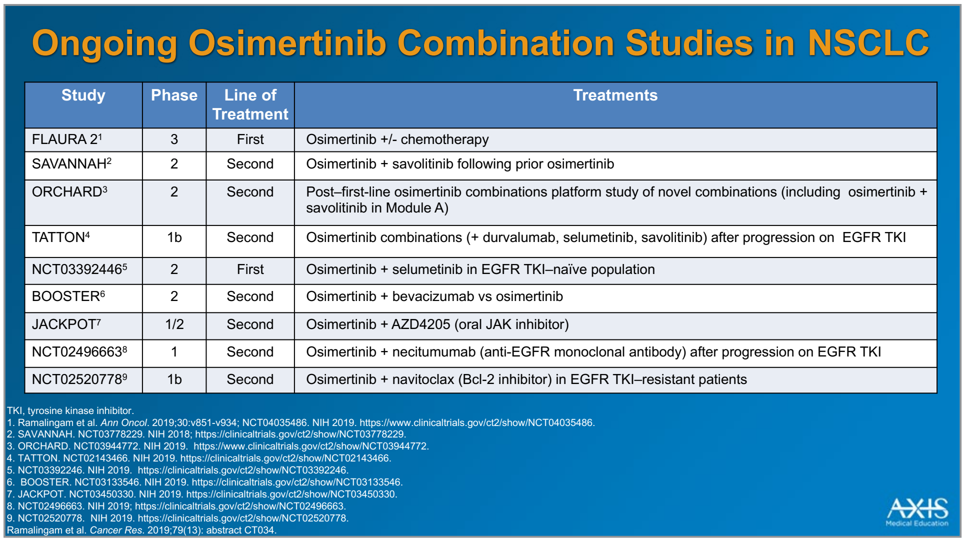
- Second, the other method that has been publicized and discussed is combination of an oral TKI, in this case gefitinib, plus chemotherapy. There are two studies, one from Japan, one from India, both large, randomized, phase 3 studies, both of which show the superiority of the combination with chemotherapy over TKI alone for management of patients.

  Again, this is something that's been debated as to whether a chemo combination would be a more appropriate way of going because of the improvement in the overall survival and PFS that's seen in some of these studies. More investigations are underway.



- One way to overcome resistance mechanisms that might arise is shown on this slide. This is from a larger study using osimertinib in combination with several different agents, in this case selumetinib, which is a MEK inhibitor, suggesting that patients who had evidence of disease progression on osimertinib, when treated with a combination, did have responses.

The number of patients in this study is a little bit small and obviously has to be extended. There are always toxicities to worry about, particularly in a combination setting. And there are different strategies to see if we can overcome some of these toxicities. This is just an example of some of the efforts that are underway to see if we can either delay disease progression using VEGF inhibition or with the addition of chemotherapy. Or when progression has happened, is there a way to rescue some of the patients with very specific pathway inhibition? For instance, MEK or MET inhibitors, and there are many examples of these kinds of studies that are ongoing, and we'll see what the results are.



Ongoing Osimertinib Combination Studies in NSCLC

Study	Phase	Line of Treatment	Treatments
FLAURA 2[1]	3	First	Osimertinib +/- chemotherapy
SAVANNAH[2]	2	Second	Osimertinib + savolitinib following prior osimertinib
ORCHARD[3]	2	Second	Post–first-line osimertinib combinations platform study of novel combinations (including osimertinib + savolitinib in Module A)
TATTON[4]	1b	Second	Osimertinib combinations (+ durvalumab, selumetinib, savolitinib) after progression on EGFR TKI
NCT03392446[5]	2	First	Osimertinib + selumetinib in EGFR TKI–naïve population
BOOSTER[6]	2	Second	Osimertinib + bevacizumab vs osimertinib
JACKPOT[7]	1/2	Second	Osimertinib + AZD4205 (oral JAK inhibitor)
NCT02496663[8]	1	Second	Osimertinib + necitumumab (anti-EGFR monoclonal antibody) after progression on EGFR TKI
NCT02520778[9]	1b	Second	Osimertinib + navitoclax (Bcl-2 inhibitor) in EGFR TKI–resistant patients

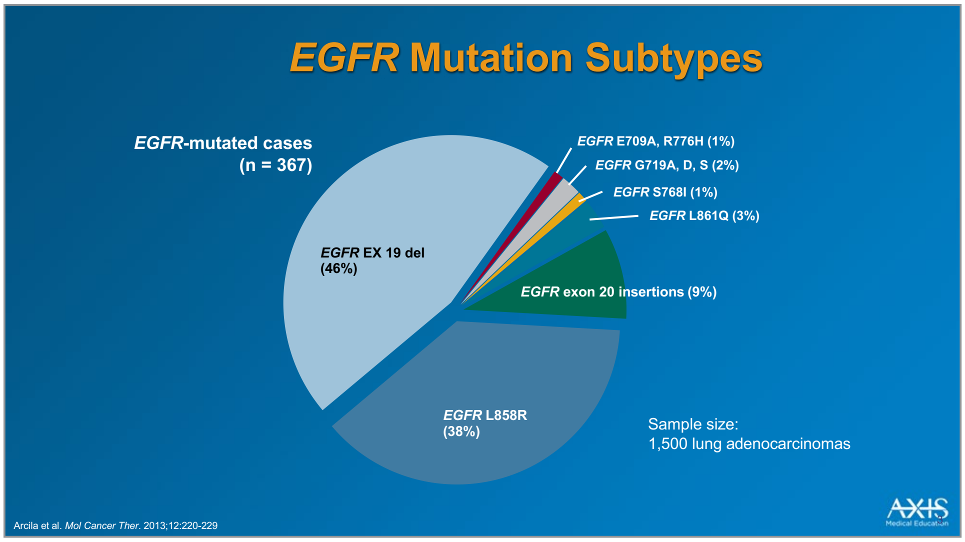
TKI, tyrosine kinase inhibitor.

1. Ramalingam et al. *Ann Oncol*. 2019;30:v851-v934; NCT04035486. NIH 2019. https://www.clinicaltrials.gov/ct2/show/NCT04035486.
2. SAVANNAH. NCT03778229. NIH 2018; https://clinicaltrials.gov/ct2/show/NCT03778229.
3. ORCHARD. NCT03944772. NIH 2019. https://www.clinicaltrials.gov/ct2/show/NCT03944772.
4. TATTON. NCT02143466. NIH 2019. https://clinicaltrials.gov/ct2/show/NCT02143466.
5. NCT03392246. NIH 2019. https://clinicaltrials.gov/ct2/show/NCT03392246.
6. BOOSTER. NCT03133546. NIH 2019. https://clinicaltrials.gov/ct2/show/NCT03133546.
7. JACKPOT. NCT03450330. NIH 2019. https://clinicaltrials.gov/ct2/show/NCT03450330.
8. NCT02496663. NIH 2019; https://clinicaltrials.gov/ct2/show/NCT02496663.
9. NCT02520778. NIH 2019. https://clinicaltrials.gov/ct2/show/NCT02520778.

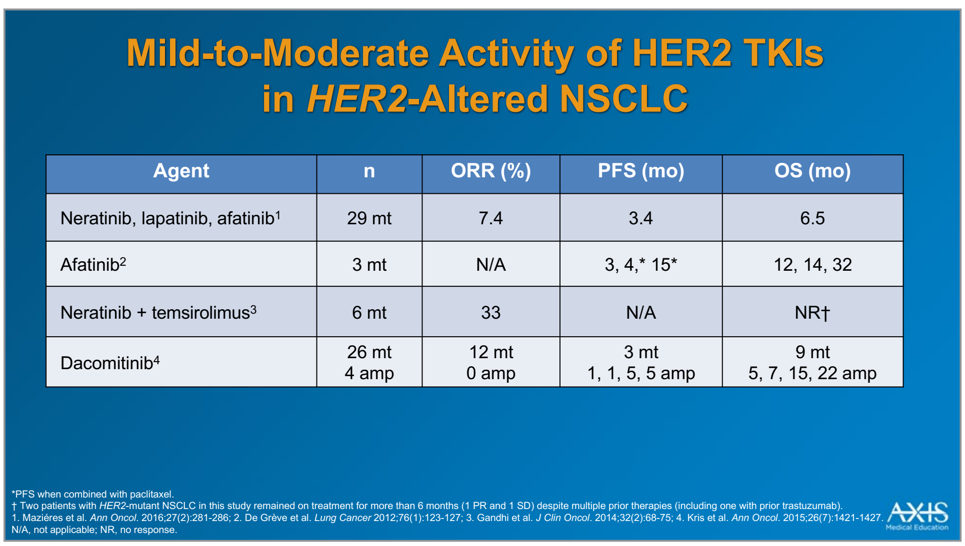
Ramalingam et al. *Cancer Res*. 2019;79(13): abstract CT034.

- These are some of the key ongoing studies with osimertinib. This is mostly for your reference, just to let you know that this is an area of active clinical investigation.

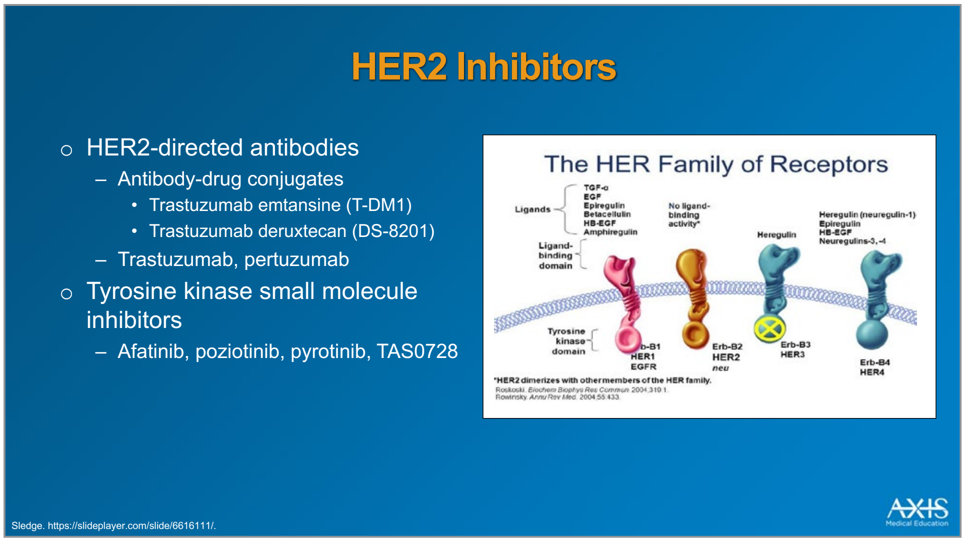
- What about some of the other gene alterations? For instance, exon 20 insertions.



- This is a pie chart of all the *EGFR* mutation subtypes. Exon 19, for instance, that we're all familiar with, the L858R, and these are the majority of the activating mutations that we see that are targeted with the oral TKIs. About 10% or so of our patients have these exon 20 insertion mutations.



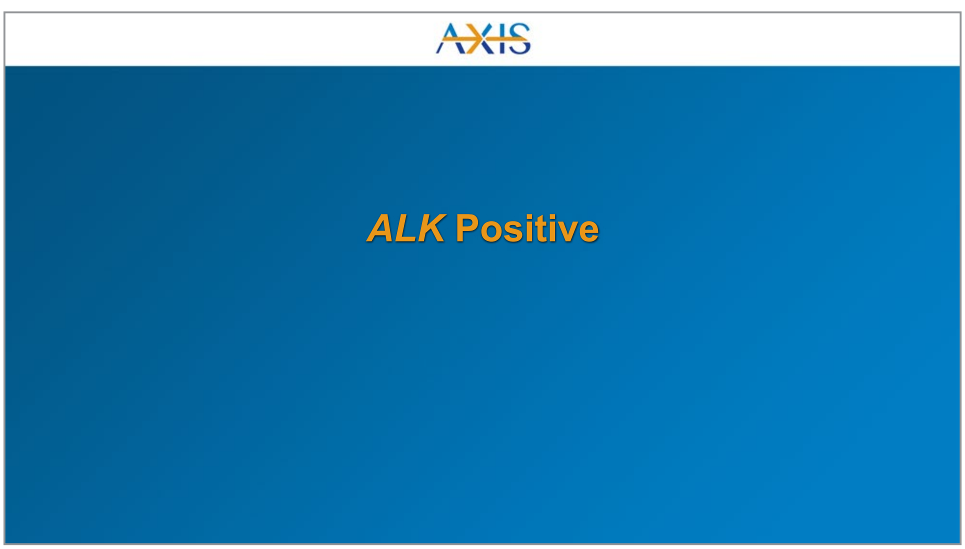
- A number of different agents have been tested, with mild-to-moderate activity. These are some of the studies that have been presented at various meetings. And you see the numbers. The number of patients participating in these studies was a little bit on the smaller side. There is an intense interest to come up with specific treatment options for this patient population.



- When we talk about the HER family of receptors, there are 4 separate receptors. If you concentrate on HER2-directed therapies, you'll see that this is, again, another area of active clinical investigation because we have many drugs in this category. We have many patients who qualify for these types of treatments.

  As far as HER2-directed antibodies are concerned, there are 2 antibody-drug conjugates. One is T-DM1 (ado-trastuzumab emtansine), which is commonly used for breast cancer. And the other is a newcomer, trastuzumab deruxtecan.

  The other antibodies include trastuzumab and pertuzumab. As far as small molecule inhibitors are concerned, there's a growing list, and some of them are shown on this slide.



- **Mocharnuk:** Next, let's talk about *ALK* rearrangement–positive non–small cell lung cancer.

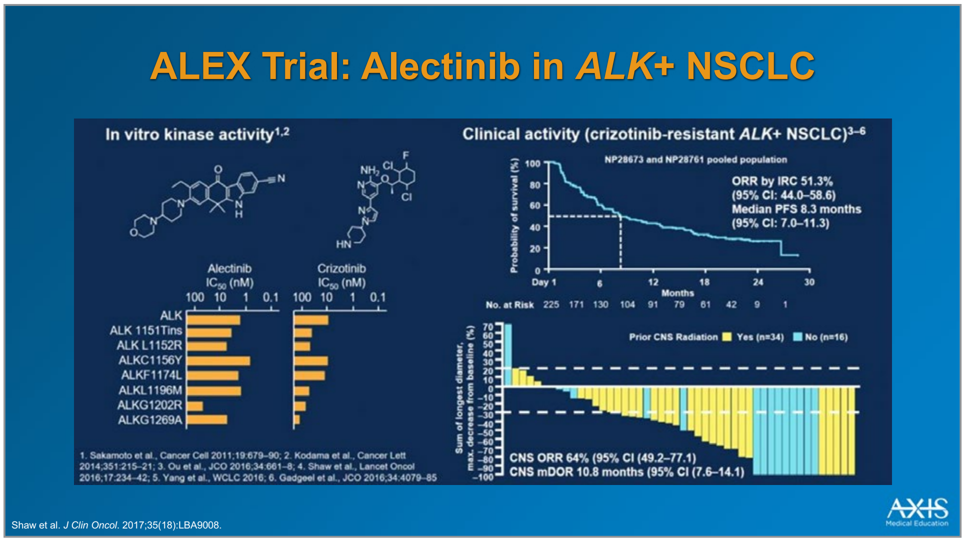
ALK Rearrangement Positive

Drug (NCCN® Recommendation)	Trial(s)	Reference(s)
First-Line Therapy		
Alectinib (preferred)	ALEX J-ALEX	Peters et al. N Engl J Med. 2017;377:829-838. Hida et al. Lancet. 2017;390(10089):29-39.
Brigatinib (recommended)	ALTA-1L	Camidge et al. N Eng J Med. 2018;379:2027-2039.
Ceritinib (recommended)	ASCEND-4	Soria et al. Lancet. 2017;389:917-929.
Crizotinib (useful in certain circumstances)	ALEX PROFILE 1014	Peters et al. N Engl J Med. 2017;377:829-838. Solomon et al. N Engl J Med. 2014;371:2167- 2177.
Subsequent Therapy		
Alectinib	NP28673 Phase 2	Ou et al. J Clin Oncol. 2016;34:661-668. Shaw et al. Lancet Oncol. 2016;17:234-242.
Brigatinib	Phase 2	Kim et al. J Clin Oncol. 2017;35:2490-2498.
Ceritinib	ASCEND-5	Shaw et al. Lancet Oncol. 2017;18:874-86.
Lorlatinib	Phase 2	Solomon et al. Lancet Oncol. 2018;19:1654-1667.

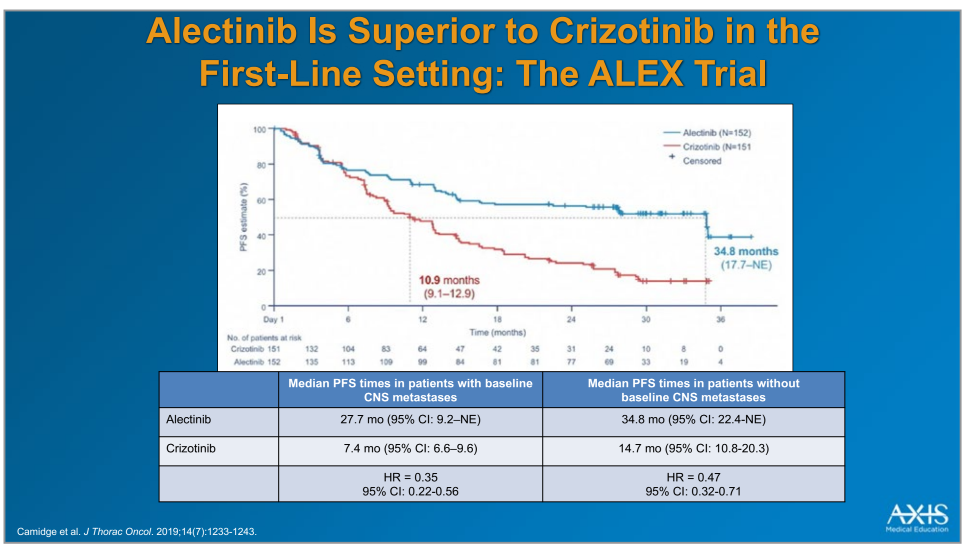
Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

Borghaei: Well, *ALK* is another major alteration or translocation that we look for in patients with non–small cell lung cancer. The list of ALK-directed therapies seems to be expanding. We have really good drugs in this category, including alectinib, brigatinib. Of course, the first drug was crizotinib, which basically changed the field. We now have lorlatinib. All of these drugs have either undergone extensive clinical investigation and are available as an FDA-approved drug or undergoing additional evaluations.

The big question here is, is there a drug that you have to start first, or is there a drug that you go to in a second line? So, for most of us, alectinib, at least now, seems to be the drug that we choose when we have somebody with non–small cell lung cancer and an *ALK* translocation. This drug has undergone several clinical investigations, including a head-to-head comparison versus crizotinib, which was the prototypical ALK inhibitor that we were using in the beginning.



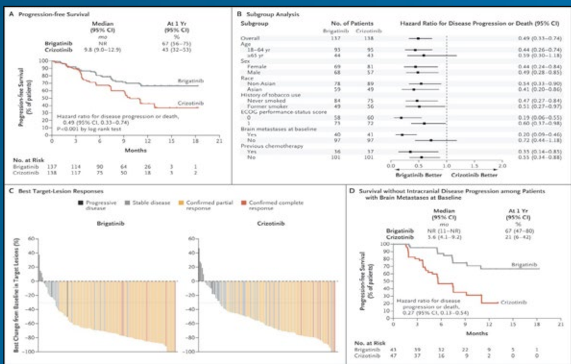
- This is the result of the ALEX trial.



	Median PFS times in patients with baseline CNS metastases	Median PFS times in patients without baseline CNS metastases
Alectinib	27.7 mo (95% CI: 9.2–NE)	34.8 mo (95% CI: 22.4-NE)
Crizotinib	7.4 mo (95% CI: 6.6–9.6)	14.7 mo (95% CI: 10.8-20.3)
	HR = 0.35 95% CI: 0.22-0.56	HR = 0.47 95% CI: 0.32-0.71

- Results of this study indicate that alectinib is superior to crizotinib for patients with newly diagnosed *ALK*-translocated non–small cell lung cancer, and the PFS curves are shown for your evaluation.

Brigatinib Is Superior to Crizotinib in the First-Line Setting: ALTA First-Line Trial



	Brigatinib	Crizotinib
ORR	71%	60%
Intracranial ORR	78%	29%
Estimated 12-mo PFS	67%	43%
HR	0.49 (95% CI, 0.33-0.74)	
P	<.001 by the log-rank test	

ORR, objective response rate; PFS, progression-free survival.
Camidge et al. *N Engl J Med*. 2018;379:2027-2039.

- Brigatinib is another drug. It also has undergone a number of clinical trials, including head-to-head comparison to crizotinib. This was the ALTA-1 first-line trial showing really good clinical activity for patients who are treatment naïve, comparing brigatinib to crizotinib.

Summary First Line

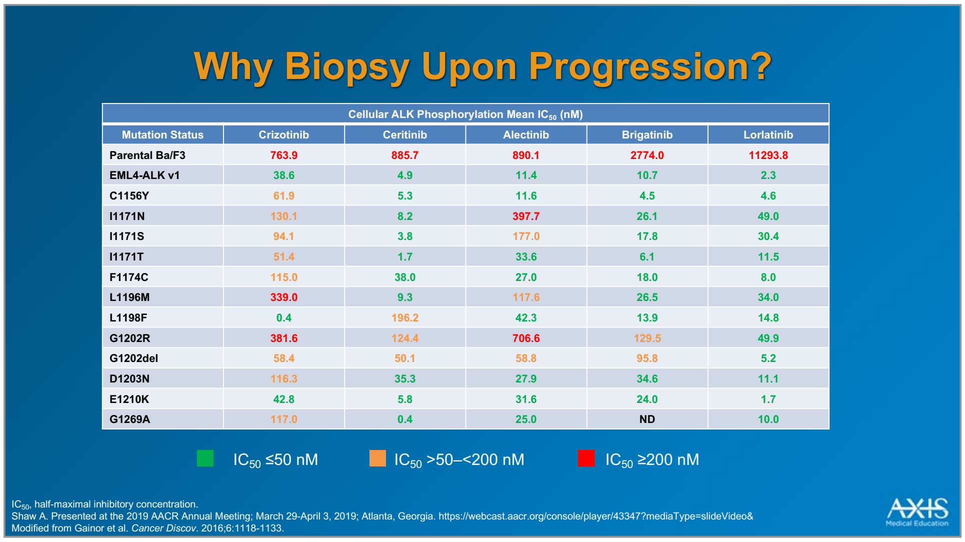
	Crizotinib	Ceritinib	Alectinib	Brigatinib
ORR	74%	73%	83%	71%
Median PFS	10.9 mo	16.6 mo	34.4 mo	NR
Intracranial ORR	Prior RT: 71.4% No RT: 40.0%	-	Prior RT: 85.7% No RT: 78.6%	78%
Safety	N/V, AST/ALT elevation, neutropenia	N/V, AST/ALT, amylase and GGT elevation	Constipation, myalgia, AST, ALT elevation	Pneumonitis, CPK amylase, lipase elevation
Dose Reduction/Discontinuation	6%/12%	45%/5%	16%/11%	29%/12%

Adapted from Leora Horn at 2019 ASCO Annual Meeting.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; GGT, gamma glutamyl transferase; NR, not reached; N/V, nausea/vomiting; ORR, overall response rate; PFS, progression-free survival; RT, radiation therapy.

- There are a number of these drugs. This is a slide from Dr. Leora Horn's presentation at last year's ASCO meeting, comparing responses, median PFS, and safety for some of the more commonly available drugs. You see head-to-head comparisons. And there is a little bit of a difference between the cost of some of these drugs, so that might become an issue down the road, given the way the healthcare system is moving.

  So, the issue here again is very similar to what we have with patients with *EGFR* mutations, which is that unfortunately we're not able to cure our patients with a diagnosis of *ALK* translocated non–small cell lung cancer. So what happens? Well, resistant mechanisms develop, again, much like what we saw with *EGFR* mutations except it's not so much that there are various pathways that are altered, although there is evidence for some of that.

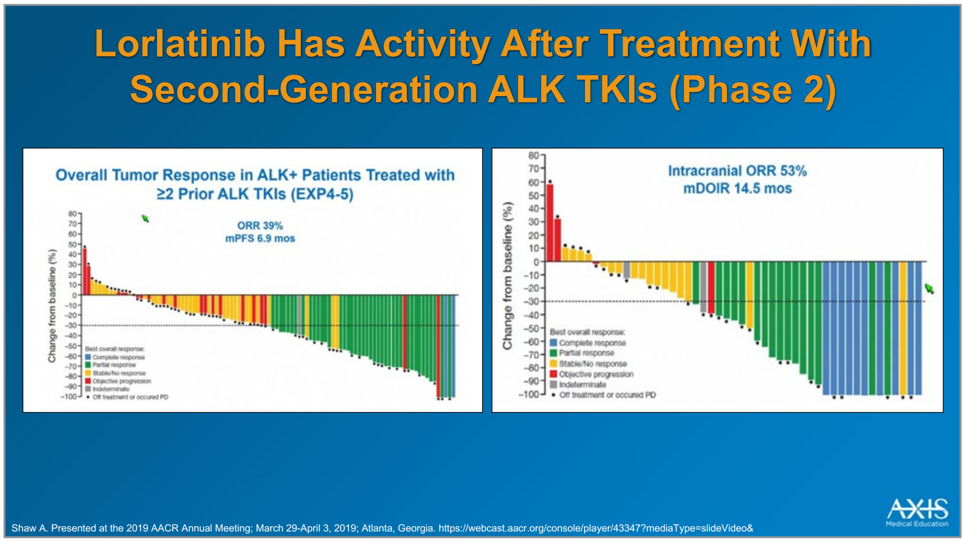
  As you can see on this table, specific mutations in the binding pocket may develop, and that might make the patient not respond to specifically ALK directed therapy that they're taking.



	Cellular ALK Phosphorylation Mean IC_{50} (nM)				
Mutation Status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4-ALK v1	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

- This table provides us with some way of trying to manage these progressions. This particular slide and publications seem to suggest that we should obtain a biopsy specimen at the time of progression, and I agree with that. You have to look for specific mutations to see if you can match the mutation with a particular drug.

  As you can see on the table here, lorlatinib, which is one of the ALK-directed drugs that we have available, seems to have good clinical activity against the majority of the mutations that we can detect. This becomes important because if someone has been treated with couple of different lines of treatment, it allows us to go to another drug that could potentially control the disease and give us good clinical activity, even after 1 or 2 lines of treatment.



- And that is shown on this slide—this is lorlatinib's clinical activity. What you see on the table on the right-hand side is that patients with brain metastases can actually respond, so intracranial responses have been established. Again, this is a smaller study. Nonetheless, it suggests that patients who've had a couple of lines of prior ALK TKIs can respond to lorlatinib.

ROS1 Positive

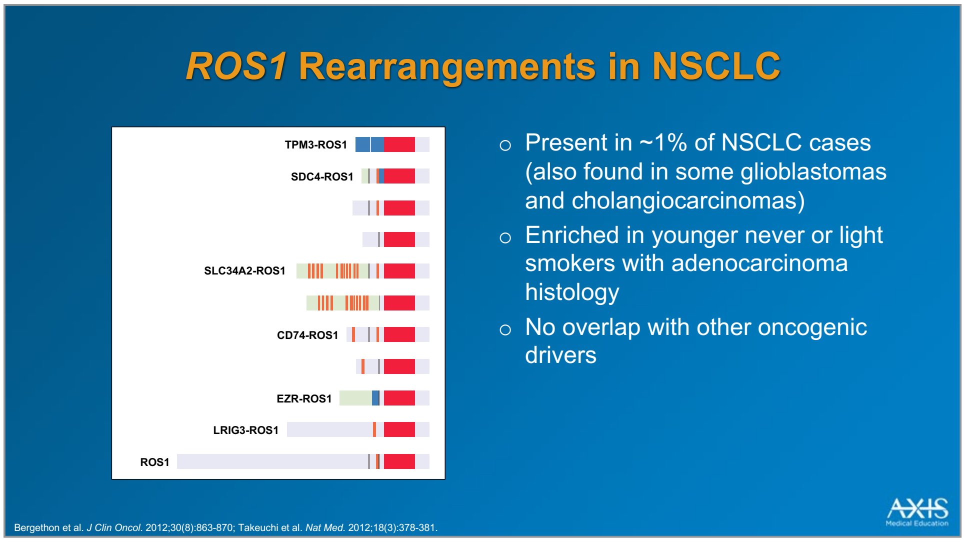
Mocharnuk: What about *ROS1* rearrangement–positive disease?

ROS1 Rearrangement Positive

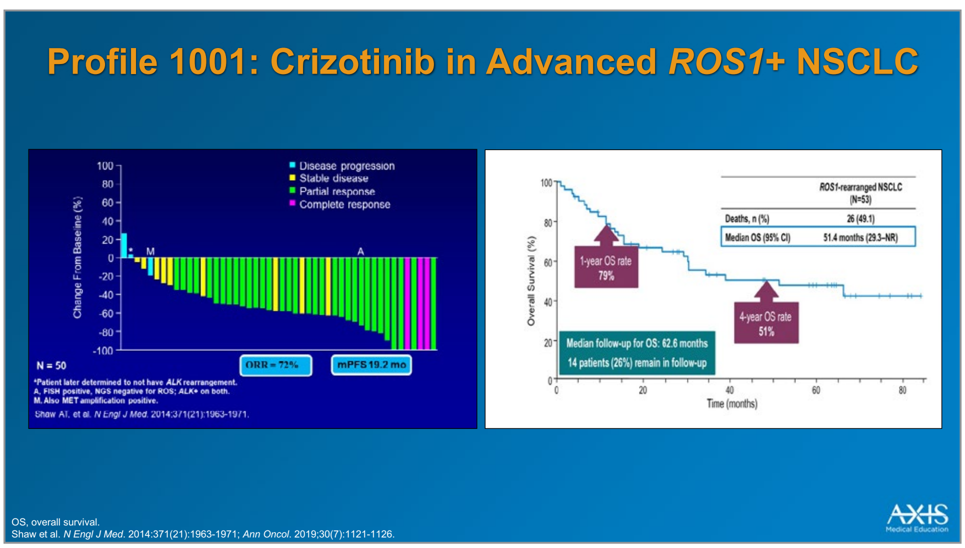
Drug (NCCN® Recommendation)	Trial(s)	Reference(s)
First-Line Therapy		
Ceritinib (preferred)	Phase 2	Lim et al. *J Clin Oncol*. 2017;35:2613-2618.
Entrectinib (preferred)	ALKA-372-001 STARTRK-1 STARTRK-2	Drilon et al. *Lancet Oncol*. 2020;21:261-270.
Crizotinib (recommended)	PROFILE 1001	Shaw et al. *N Engl J Med*. 2014;371:1963-1971.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

Borghaei: *ROS1* is again another one of the alterations and rearrangements that we look for when we have somebody with a diagnosis of advanced non–small cell lung cancer. Under this category, there are a couple of studies that we should consider. First of all, drugs such as ceritinib and crizotinib do seem to have activity. And then we have a drug, entrectinib, that also seems to have really good activity against ROS.



- So what is *ROS1*? It's another rearrangement that we see in about 1% of patients with non–small cell lung cancer. There seems to be an enrichment in the younger, never-smoker patient population. There is usually very little overlap with other oncogenic drivers.



- Crizotinib, the same drug that we were using, and initially at least in the *ALK*-translocated tumors does seem to have activity in *ROS1* rearrangement–positive disease. That's shown on the waterfall plot, and the overall survival, as you see there. So this has been a drug that for patients with a *ROS1* alteration.

Treatment of *ROS1*-Positive Disease After Progression on a First-Line ROS1 TKI

Agent	TKI-Naïve Response Rate	TKI-Pretreated Response Rate	Phase	Activity in TKI Pretreated Patients?
Ceritinib	20/30, 67%	0/2	2	Case report
Brigatinib	1/1	0/2	1/2	Case report
Entrectinib	12/14, 86%	0/6	1	
DS-6051b	8/10; 80%	0/3	1	
Lorlatinib	8/13, 61.5 %	9/34, 26.5%	2	YES
Repotrecinib	8/10; 80%	7/18; 39 %	1	YES

TKI, tyrosine kinase inhibitor.
Lim et al. *J Clin Oncol.* 2017;35:2613-2618; Hegde et al. *J Clin Oncol Precision Oncol.* 2019;3:1-6. Drilon et al. *Cancer Discov.* 2017;7(4):400-409. Nosaki et al. *J Thorac Oncol.* 2017:12:S1069. Ou et al. Abstract OA02.03. Presented at the IASLC 19th World Conference on Lung Cancer, 2018. Lin et al. Abstract OA02.02. Presented at the IASLC 19th World Conference on Lung Cancer, 2018.

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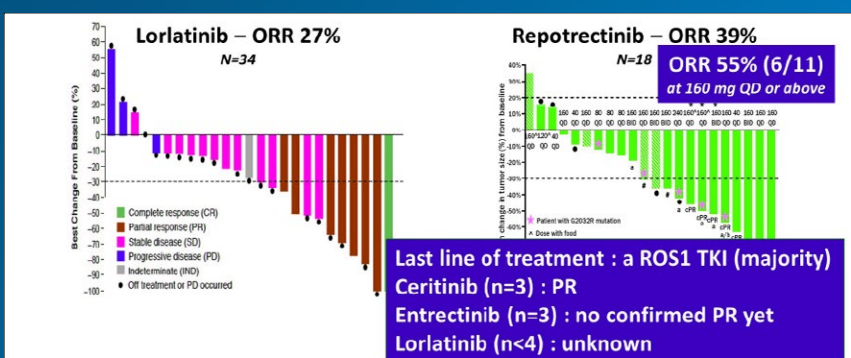
- The other drugs are shown on this table. Brigatinib, ceritinib, entrectinib, and a couple of the other drugs are being tested. You'll notice that some of these drugs we've been able to generate data in terms of the drug having activity in patients who are pretreated with other TKIs. In that category, lorlatinib and repotrectinib are the 2 drugs to keep in mind for your patients with *ROS1* translocations that have been treated with, let's say for instance, crizotinib in the first-line setting.

ROS1 Inhibitors in TKI-Pretreated Patients



ORR, overall response rate; TKI, tyrosine kinase inhibitor.
Shaw et al. *Lancet Oncol.* 2019;20(12):1691-1701. Ou et al. Abstract OA02.03. Presented at the IASLC 19th World Conference on Lung Cancer, 2018. Solomon et al. *Ann Oncol.* 2018;29:viii493-viii547.Abstract 1380PD. ESMO 2018. Cho et al. *J Clin Oncol.* 2019;37:9011.

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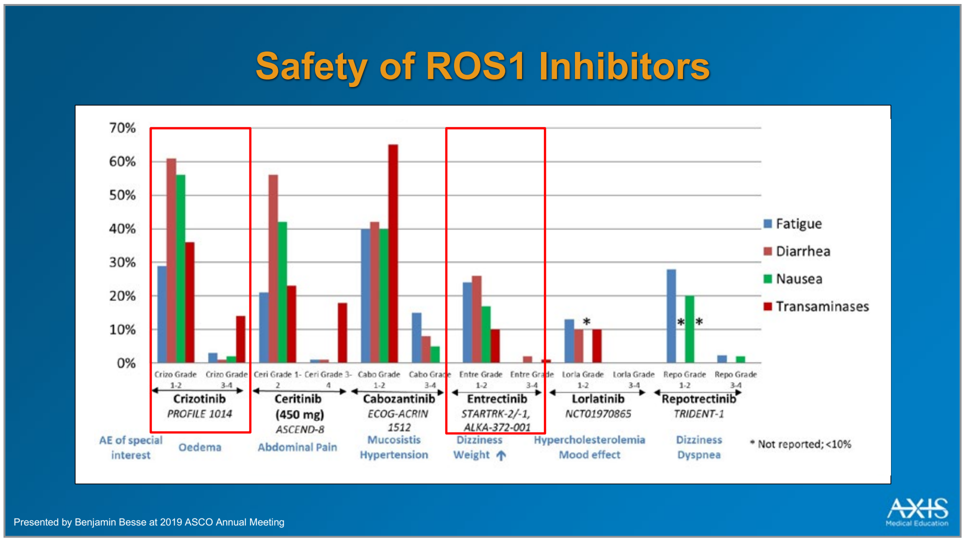
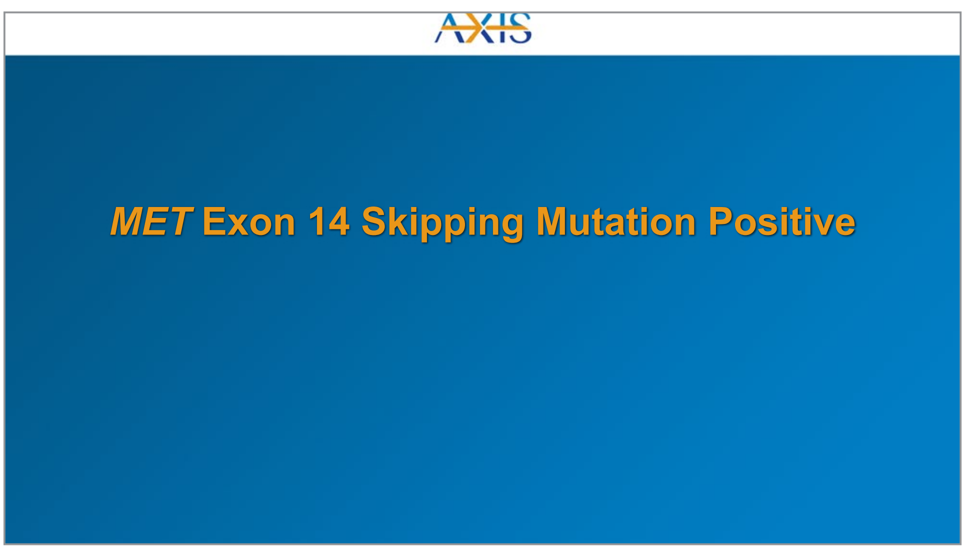
- The key thing is to identify patients or identify drugs that could be active in patients who have already been treated with oral TKIs. This slide shows you that lorlatinib could have an overall response rate around 27% in a *ROS1*-positive pretreated patient population. And repotrectinib can have a response rate of about 50%.

  This is good news because for a while, we did not really have a lot of options for our patients with *ROS1* alterations after crizotinib. It's important to see that some of these drugs we already have at our disposal for use in other diseases and other settings could have activity in *ROS1*-positive disease.



- What about the safety? Most of these drugs seem to have a very similar safety profile. Although as you can see on this particular slide, the entrectinib and lorlatinib and repotrectinib seem to have a little bit less in terms of side effects. The majority of side effects are thankfully grade 1 and 2, which can have an impact on a patient's quality of life. We have to pay attention to it and learn how to manage some of these toxicities.

  In terms of the kind of toxicities that are severe, leading to discontinuation of treatment, we don't see a whole lot of those. All of these drugs unfortunately have some level of toxicity—being familiar with how to mitigate and how to manage these toxicities becomes very important.



- **Mocharnuk:** What can you tell us about a relatively new target, *MET* exon 14?

MET Exon 14 Skipping Mutation

Drug (NCCN® Recommendation)	Trial(s)	Reference(s)
First-line/Subsequent Therapy		
Capmatinib (preferred)	GEOMETRY	Wolf et al. *J Clin Oncol.* 2019;37:abstract 9004.
Crizotinib (useful in certain circumstances)		Drilon et al. *Nat Med.* 2020;26:47-51.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

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- **Borghaei:** Well, I think MET is one of the pathways that we've had a lot of interest in for a very long time. I think one issue with *MET* is that there are many different forms of *MET* alteration. What we're going to talk about first today is *MET* exon 14 skipping mutation. And under that category, there are a couple of studies that I think we need to discuss. It is important to notice that capmatinib has been approved for treatment of patients with *MET* exon 14 skipping mutation.

*MET*ex14

- *MET* exon 14 skipping (*MET*ex14) alterations are reported in 3%-4% of patients with NSCLC[1]
  - Present in 8%-32% of sarcomatoid lung carcinomas[2,3]
- *MET*ex14 alterations can be conveniently detected using liquid biopsy (L+) or tissue biopsy (T+)
- *MET*ex14 alterations lead to aberrant activation of MET kinase, but remain sensitive to MET inhibition
  - MET inhibitors have shown clinical activity in patients with *MET*ex14 alterations [1,4-6]

1. Paik PK, et al. Cancer Discov. 2015;5:842–9; 2. Shrock AB, et al. J Thorac Oncol. 2016;11:1493–1502; 3. Tong JH, et al. Clin Cancer Res. 2016;22:3408–56; 4. Felip E, et al. SCLC 2018 [abs. OA12.01]; 5. Drilon A, et al. WCLC 2018 [abs. OA12.02]; 6. Wolf J, et al. Ann Oncol. 2018;29(Suppl 8) [abs. LBA52].
NSCLC, non-small cell lung cancer.

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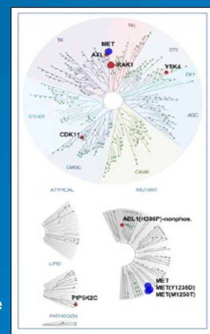
- So what are these? These are rare mutations, occurring in about 3% to 4% of patients with non–small cell lung cancer. Although if you have somebody with a sarcomatoid lung carcinoma, the rate of finding a *MET* exon 14 skipping mutation can be as high as 30%, depending on the literature that you're seeing. So, 3% to 4% is enough for us to say that we should be able to identify these patients. If you go back to part 1 of the discussion, using a broad next-generation sequencing panel is important to be able to identify these more rare mutations.

Capmatinib Background

- *MET* exon 14 skipping mutations (*MET*Δex14) are reported in 3%-4% of patients with NSCLC[1-4] and associated with both poor prognosis and poor responses to standard therapies including immunotherapy.[5-9]
- Capmatinib is a highly selective *MET* inhibitor with *in vitro* and *in vivo* activity seen against preclinical cancer models with *MET* activation.[10]
- Capmatinib is the most potent inhibitor against MET compared to other inhibitors.[11]

	Capmatinib	Savolitinib	Tepotinib	Cabozantinib	Crizotinib
IC_{50} (nM)	0.6	2.1	3.0	7.8	22.5

- Preliminary efficacy data from the phase 2, multi-cohort, multicenter GEOMETRY mono-1 study showed deep responses with capmatinib irrespective of the line of treatment as well as activity in the brain lesions of patients with METΔ*ex*14 mutated advanced NSCLC.[12]



1. Gelsomino F, et al. *Cancers* (Basel). 2014;6:2100–15; 2. Ma PC. *Cancer Discov*. 2015;5:802-5; 3. Reungwetwattana T, et al. *Lung Cancer*. 2017;103:27-37; 4. Tong JH, et al. *Clin Cancer Res*. 2016;22:3048-56; 5. Dimou A, et al. *PLoS One*. 2014; 9:e107677; 6. Guo B, et al. *PLoS One*. 2014;9:e99399; 7. Sabari JK, et al. *Ann Oncol*. 2018;29:2085-91; 8. Baba K, et al. *Thorac Cancer*. 2019;10:369-72; 9. Reis H, et al. *Clin Lung Cancer*. 2018;19:e441-e441-e63; 10. Baltschukat, et al. *Clin Cancer Res*. 2019; Epub; 11. Fujino T, et al. WCLC 2018, Poster P1.13-41; 12. Wolf J, et al. *Ann Oncol*. 2018; 29(Suppl 8): Abstract LBA52.
Wolf et al. *J Clin Oncol*. 2019;37:9004.

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- Capmatinib has been around for a while and has good activity against *MET*-positive disease.

GEOMETRY mono-1: A Phase 2 Trial of Capmatinib in Patients With Advanced NSCLC Harboring *MET* exon14 Skipping Mutation

- Stage IIIB/IV NSCLC
- *MET*Δex14 irrespective of *MET* GCN by central RT-PCR
- *EGFR* wt (for L858R and delE19) and *ALK* negative
- PS 0-1
- ≥1 measurable lesion (RECIST 1.1)
- Neurologically stable or asymptomatic brain metastases allowed

→ Capmatinib 400 mg BID tablet →

Cohort 4 (Pretreated, 2/3L) N = 69 Enrollment Closed

Cohort 5 (Treatment-naive) N = 28 Enrollment Closed

Primary endpoint
- ORR by blinded independent central review

Secondary endpoint
- Duration of response
- Progression-free survival
- Overall survival
- Safety

- Study methodology
  - Cohort 4 and 5b are each analyzed separately and have independent statistical hypothesis
  - Primary (ORR) and key secondary (DOR) endpoints based on BICR including 2 parallel independent radiology reviewers (+ additional one for adjudication)
  - Efficacy endpoints based on BICR and investigator assessment per RECIST 1.1

Data cut off: April 15, 2019; median duration of follow-up for DOR: 9.7 months in Cohort 4 and 9.6 months in Cohort 5b
Additional data on *MET* mutated patients will be generated in Cohort 6 (2L; N~27)
BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate.
Wolf et al. *J Clin Oncol*. 2019;37:9004.

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- GEOMETRY study results led to the approval of capmatinib in this setting. This was a phase 2 study looking at patients with advanced non–small cell lung cancer with *MET* exon 14 skipping mutations. There were multiple cohorts. What we are showing here are cohorts 4 and 5.

Cohort 4 included patients who had prior therapy, and cohort 5 included patients who were treatment naïve.

GEOMETRY mono-1: Best Overall Response

Pretreated cohort 4

All responses confirmed per RECIST 1.1
Response rates consistent between BICR and investigator assessment

	Cohort 4 (2/3L) N = 69	
	BIRC	Investigator
Best overall response, n (%)		
CR	0	1 (1.4)
PR	28 (40.6)	28 (40.6)
SD	25 (36.2)	22 (31.9)
Non-CR/non-PD	1 (1.4)	2 (2.9)
PD	6 (8.7)	7 (10.1)
Not evaluable	9 (13.0)	9 (13.0)
ORR, %	40.6	42.0
DCR, %	78.3	76.8

Treatment naïve cohort 5b

All responses confirmed per RECIST 1.1
Response rates consistent between BICR and investigator assessment

	Cohort 5b (1L) N = 28	
	BIRC	Investigator
Best overall response, n (%)		
CR	1 (3.6)	0
PR	18 (64.3)	17 (60.7)
SD	8 (28.6)	10 (35.7)
PD	1 (3.6)	1 (3.6)
ORR, %	67.9	60.7
DCR, %	96.4	96.4

BIRC, blinded independent review committee; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response, SD, stable disease.
Wolf et al. *J Clin Oncol.* 2019;37:9004.

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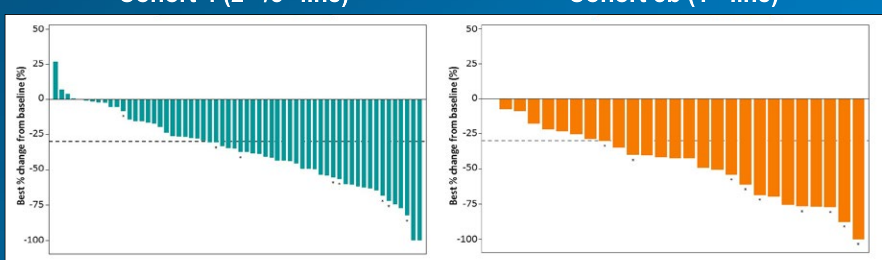
- A little bit of a smaller table, but the point is that whether you're looking at patients with treatment naïve or prior treatment, capmatinib works, and the response rates are shown and highlighted here.

  It does appear that if you identify patients who are treatment naïve and offer them capmatinib, the response rates seem to be a little bit higher compared to the previously treated patient population.

GEOMETRY mono-1: Tumor Shrinkage per BICR

Deep responses observed in a majority of patients across both cohorts

Cohort 4 (2nd/3rd line) **Cohort 5b (1st line)**



*Patients still on treatment
BICR, blinded independent central review.
Wolf et al. *J Clin Oncol.* 2019;37:9004.

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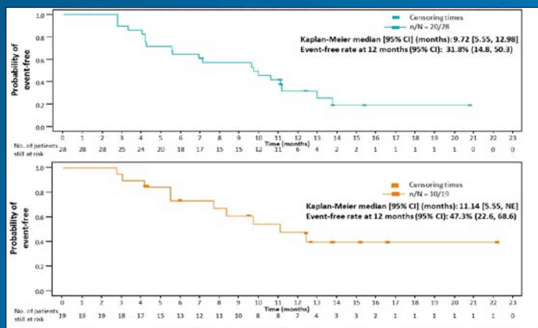
- If you look at the waterfall plot, you get the sense that majority of patients who are treatment naïve have some level of response to it.

GEOMETRY mono-1: Duration of Response per BICR

Median DOR was 9.72 months in Cohort 4 (2nd/3d line) and 11.14 months in Cohort 5b (1st line)

Cohort 4 (2nd/3d line)

Cohort 5b (1st line)



Median DOR per investigator was 8.31 months (95% CI: 4.34-12.06) in Cohort 4 and 13.96 months (95% CI: 4.27-NE) in Cohort 5b

BIRC, blinded independent central review; DOR, duration of response.
Wolf et al. *J Clin Oncol*. 2019;37:9004.

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- This is the durability of responses seen with this particular drug in both cohorts. As far as I can tell, these are really good, durable responses.

GEOMETRY mono-1: Safety Summary

Favorable and manageable safety profile

Most Common TRAEs (≥10%, all grades), n (%)	All Patients N = 334	
	All Grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

- Safety determined in the largest dataset of MET dysregulated** NSCLC patients (N = 334)
- Median treatment expose time: 14.9 weeks
- Capmatinib well tolerated with few grade 3/4 events
  - 15 patients (4.5% had grade 4 events)
- Dose adjustment due to treatment related AE:
  - 73 (21.9%)
- Discontinuation due to treatment-related AE:
  - 37 (11.1%)
  - Most frequent (≥1%): peripheral edema (n = 6, 1.8%), pneumonitis (n = 5, 1.5%) and fatigue (n = 5, 1.5%)
- Serious treatment related AEs:
  - 43 (12.9%)

*Capmatinib administered in fasting conditions; food restriction removed in new cohorts 6 and7
† Capmatinib is known to inhibit creatinine transporters
** *MET* mutated/amplified.
AE, adverse event.
Wolf et al. *J Clin Oncol*. 2019;37:9004.

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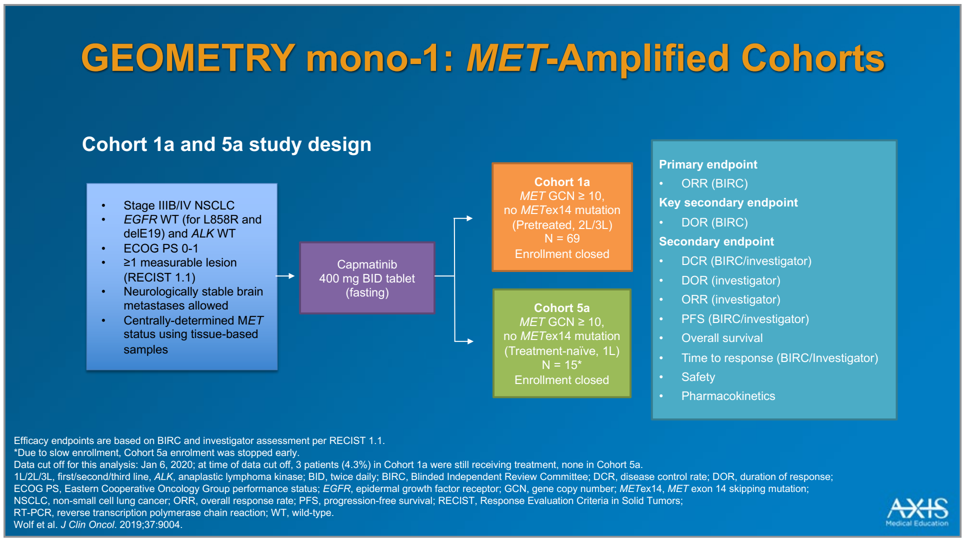
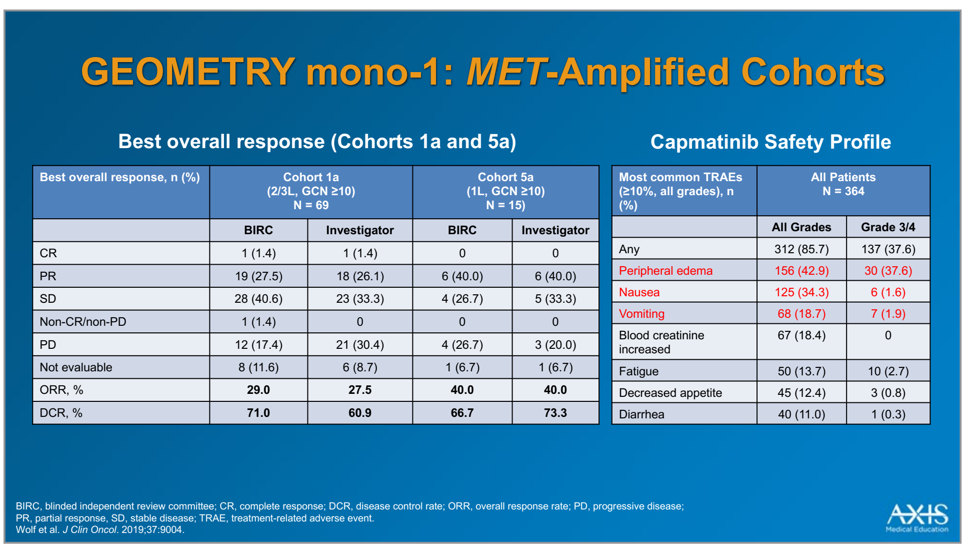
- What about toxicity? There is some peripheral edema associated with the use of this drug. Notice that grade 3 or 4 peripheral edema was reported in about 8% of patients who received this drug. There are various ways of managing the peripheral edema.



- GEOMETRY also had another study looking at *MET*-amplified, which is another way of detecting *MET*. So we have *MET* exon 14 mutations, and then we have *MET* amplification, and that's determined by gene copy number as was done in this particular study. This has multiple cohorts, as you see on the particular slide.

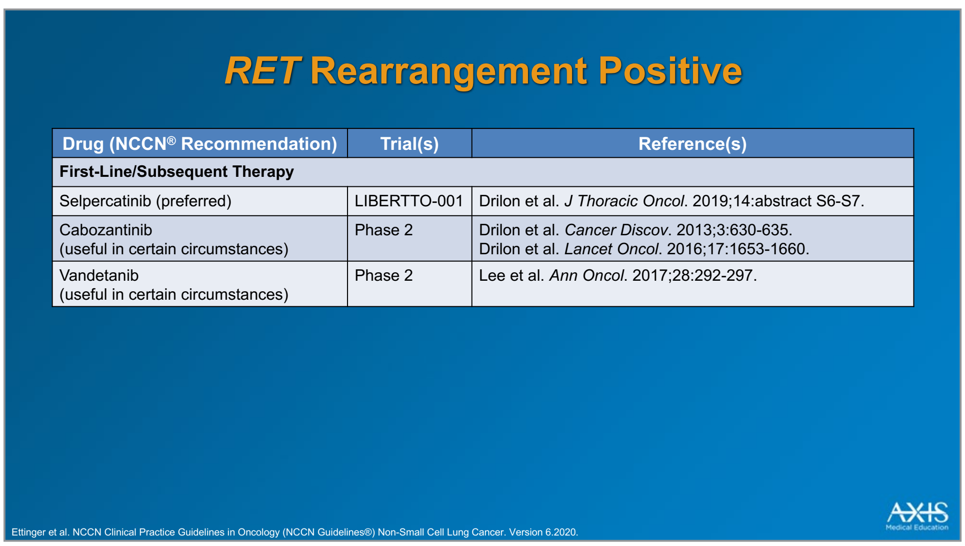


Best overall response, n (%)	Cohort 1a (2/3L, GCN ≥10) N = 69		Cohort 5a (1L, GCN ≥10) N = 15	
	BIRC	Investigator	BIRC	Investigator
CR	1 (1.4)	1 (1.4)	0	0
PR	19 (27.5)	18 (26.1)	6 (40.0)	6 (40.0)
SD	28 (40.6)	23 (33.3)	4 (26.7)	5 (33.3)
Non-CR/non-PD	1 (1.4)	0	0	0
PD	12 (17.4)	21 (30.4)	4 (26.7)	3 (20.0)
Not evaluable	8 (11.6)	6 (8.7)	1 (6.7)	1 (6.7)
ORR, %	**29.0**	**27.5**	**40.0**	**40.0**
DCR, %	**71.0**	**60.9**	**66.7**	**73.3**

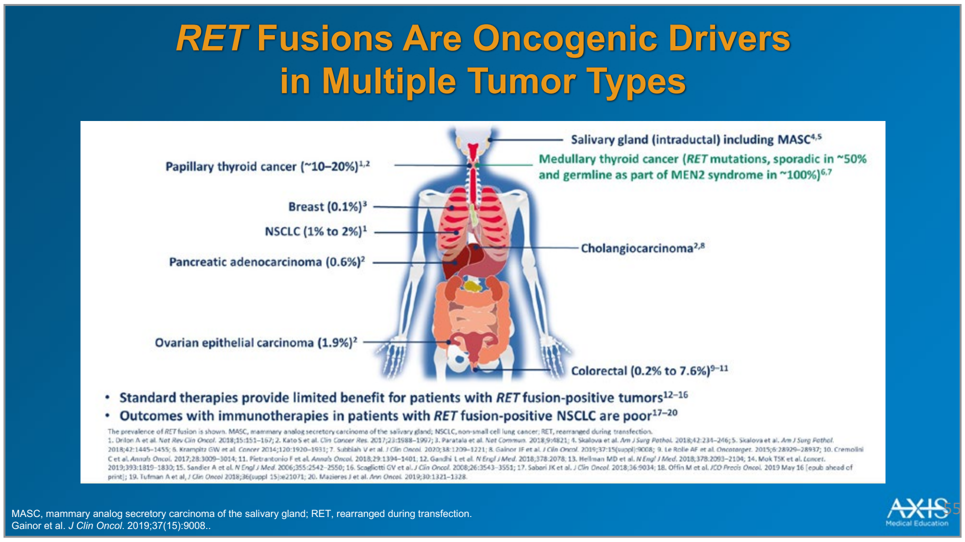
Most common TRAEs (≥10%, all grades), n (%)	All Patients N = 364	
	All Grades	Grade 3/4
Any	312 (85.7)	137 (37.6)
Peripheral edema	156 (42.9)	30 (37.6)
Nausea	125 (34.3)	6 (1.6)
Vomiting	68 (18.7)	7 (1.9)
Blood creatinine increased	67 (18.4)	0
Fatigue	50 (13.7)	10 (2.7)
Decreased appetite	45 (12.4)	3 (0.8)
Diarrhea	40 (11.0)	1 (0.3)

- Responses seem to be very reasonable regardless of the cohort that you're looking at. The side effect profile is very similar to what we saw initially. There is about 8% peripheral edema, and some nausea and vomiting.

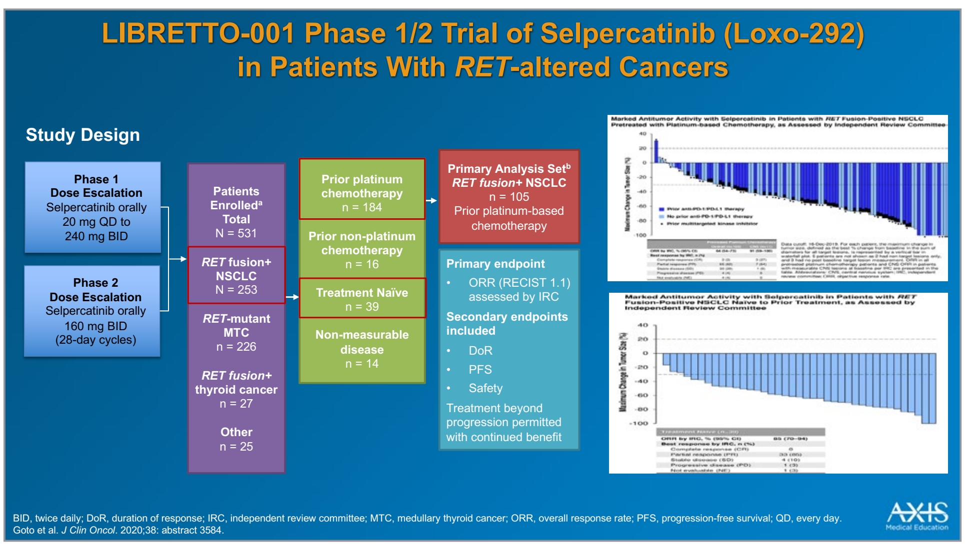
- **Mocharnuk:** What treatment options do patients with *RET* rearrangement–positive disease have?



- **Borghaei:** The other newcomer in terms of new approval is for *RET* alterations. And RET has also been a pathway that's been of interest. It is one of those tumor-agnostic alterations.



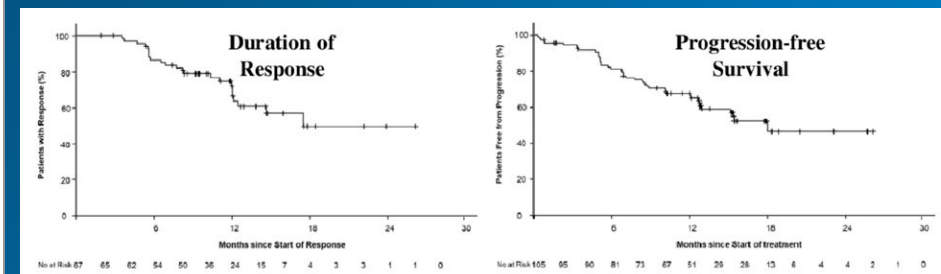
- These fusions can be found in patients with papillary thyroid cancer, non–small cell lung cancer, and a number of other malignancies, as you see on this slide.



- The LIBRETTO study investigated the clinical activity of selpercatinib, or Loxo-292, in patients with *RET* alteration. I've combined all of the trial design and the clinical activity in one slide just for ease of reference. And the bottom line is, as you can see, this is a highly active drug. Again, patients, whether they had prior therapy, or they were treatment naïve, responded to selpercatinib rather nicely. And this is the drug that's available for us.

  If we do not use these broad testing platforms, we're not going to be able to find the fusions that we need, and these patients do benefit from the use of these targeted drugs.

Sepercatinib Benefit in Platinum Chemotherapy-treated Patients With *RET* Fusion–Positive NSCLC, as Assessed by Independent Review Committee



Goto et al. *J Clin Oncol*. 2020;38: abstract 3584.

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- This is just the duration of response and PFS with selpercatinib as per the most recent ASCO meeting presentation.

Adverse Events in All Selpercatinib-treated Patients (N = 531)

AE, %	AE, regardless of attribution					TRAE		
Grade	1	2	3	4	Any	3	4	Any
Diarrhea	27	9	4	-	40	2	-	22
Dry mouth	33	5	-	-	38	-	-	33
Hypertension	4	14	17	<1	36	11	<1	24
AST increased	19	6	7	1	32	5	1	26
Fatigue	18	11	1	-	30	<1	-	18
ALT increased	15	5	9	1	30	7	1	25
Nausea	21	6	1	-	27	<1	-	11
Constipation	21	5	1	-	27	<1	-	12
Edema peripheral	22	4	<1	-	27	-	-	15
Headache	18	5	2	-	24	<1	-	8
Blood creatinine increased	15	5	-	<1	21	-	-	11
Abdominal pain	14	5	2	-	20	<1	-	5
Rash	15	3	1	-	19	1	-	12
Vomiting	14	4	<1	-	18	<1	-	5
Cough	14	2	-	-	16	-	-	1
ECG QT prolonged	5	7	4	-	16	3	-	12
Dyspnea	10	3	2	<1	16	-	-	1

Data cut-off: Dec. 16, 2019.
Total % for any given adverse event may be different than the sum of the individual grades, due to rounding.
AE, adverse event, ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
Goto et al. *J Clin Oncol*. 2020;38: abstract 3584.

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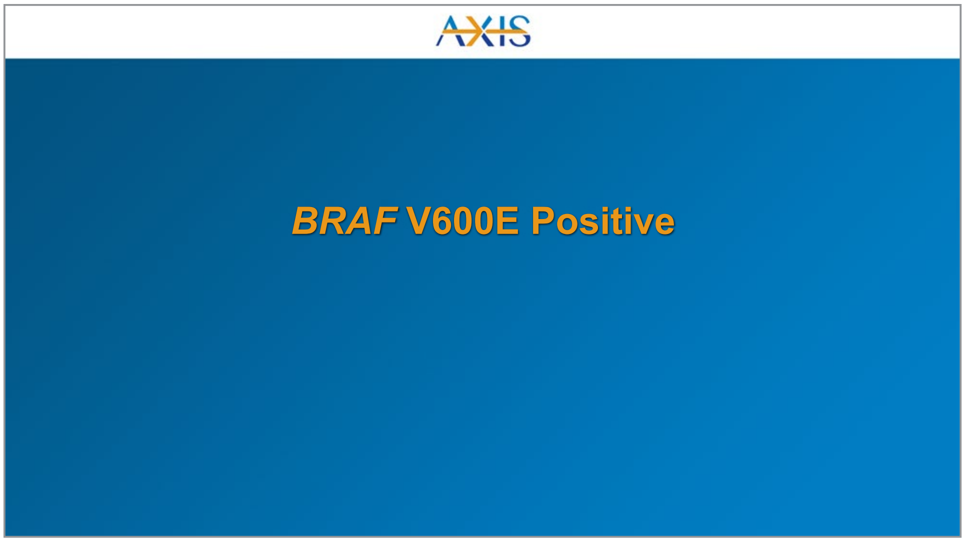
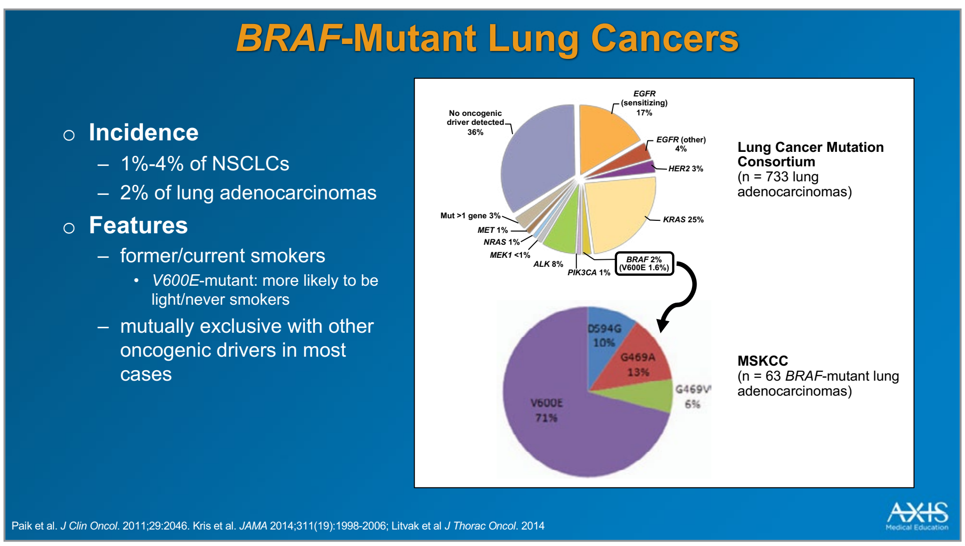
- What about toxicity? We have a database of 530 patients. And you notice that there are very few grade 3 and 4 toxicities, but there are some grade 1 and 2 toxicities, mostly diarrhea, dry mouth. There is a little bit of hypertension that we do have to pay attention to. But again, most of the other side effects are easily manageable.



▶ **Mocharnuk:** What about patients with *BRAF* V600E mutation–positive disease?



▶ **Borghaei:** *BRAF* is an interesting mutation. We all know that you can find *BRAF* mutations in patients with melanoma. Obviously in lung cancer, *BRAF* V600E has been identified. The rate is about 2% to 4% of patients with non–small cell lung cancer, perhaps 2% of adenocarcinomas.

BRAF V600E Mutation Positive

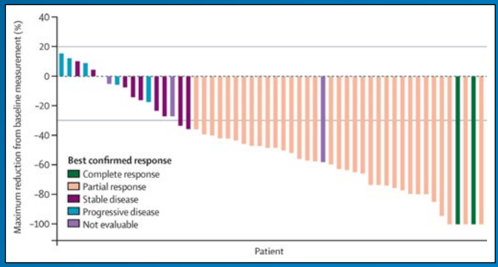
Drug (NCCN® Recommendation)	Trial(s)	Reference(s)
First-Line Therapy		
Dabrafenib/trametinib (preferred)	Phase 2	Planchard et al. *Lancet Oncol*. 2016;17:1307-1316.
Vemurafenib (other recommended)		Mazieres et al. *Ann Oncol*. 2020;31:289-294.
Dabrafenib (other recommended)	Phase 2	Planchard et al. *Lancet Oncol*. 2016;17:642-650.
Subsequent Therapy		
Dabrafenib/trametinib	Phase 2 BRF113928	Planchard et al. *Lancet Onol*. 2016;17:984-993. Planchard et al. *J Clin Oncol*. 2017;35:abstract 9075.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

- Why is it important to find this? Again, it's because we have really good, effective drugs. Some of the references are shown on this slide.

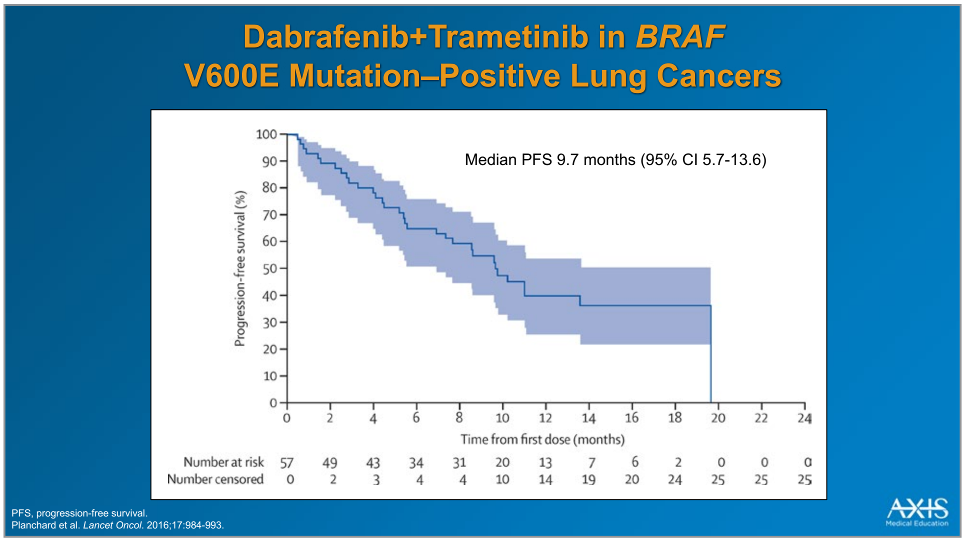
Dabrafenib+Trametinib in *BRAF* V600E Mutation–Positive Lung Cancers

- Multicenter single-arm phase 2 study
- Dabrafenib 150 mg twice daily + Trametinib 2 mg daily
- Primary endpoint:
  - Overall response: 63.2%
- 36 partial responses out of 57 patients with *BRAF* V600E mutation–positive disease

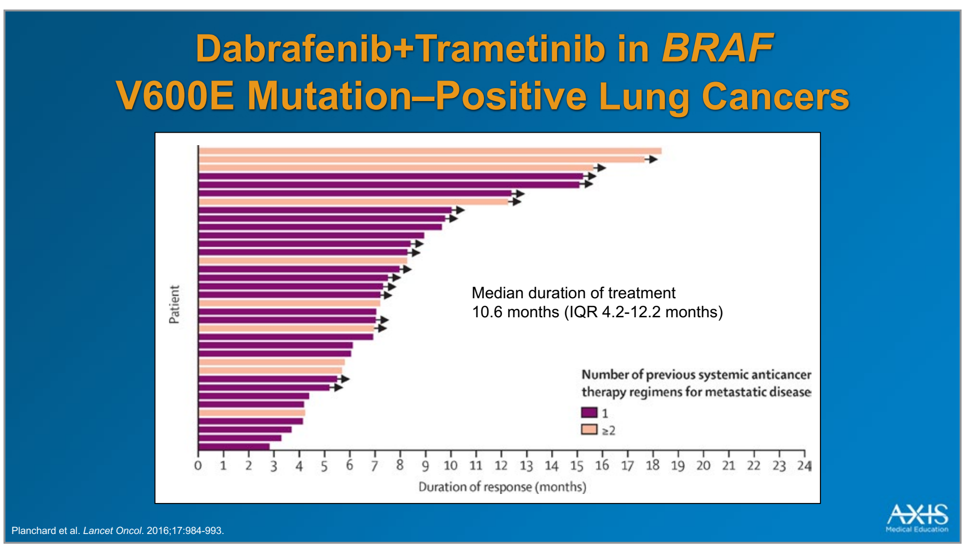


Planchard et al. *Lancet Oncol*. 2016;17:984-993.

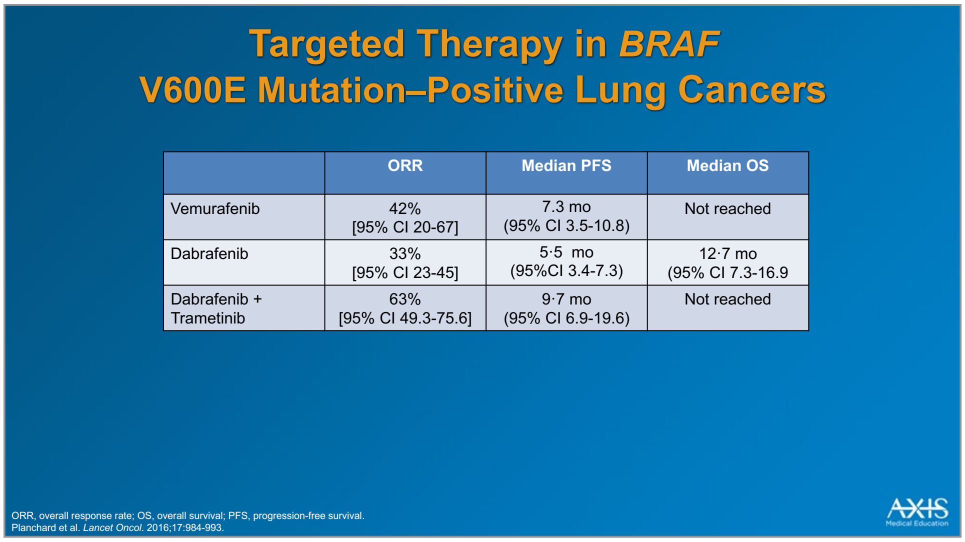
- But what we have arrived at is the fact that a combination of 2 targeted agents, dabrafenib and trametinib, is what we need for treatment of patients with *BRAF* V600E-mutated non–small cell lung cancer. Dabrafenib, by itself, can have some clinical activity. Trametinib, by itself, can have activity. But the combination for this particular mutation leads to particularly good clinical efficacy with an overall response rate in the 60% range, as you see based on this *Lancet Oncology* publication.



- The median PFS was around 10 months when patients were treated with this particular combination, with really good, durable responses.

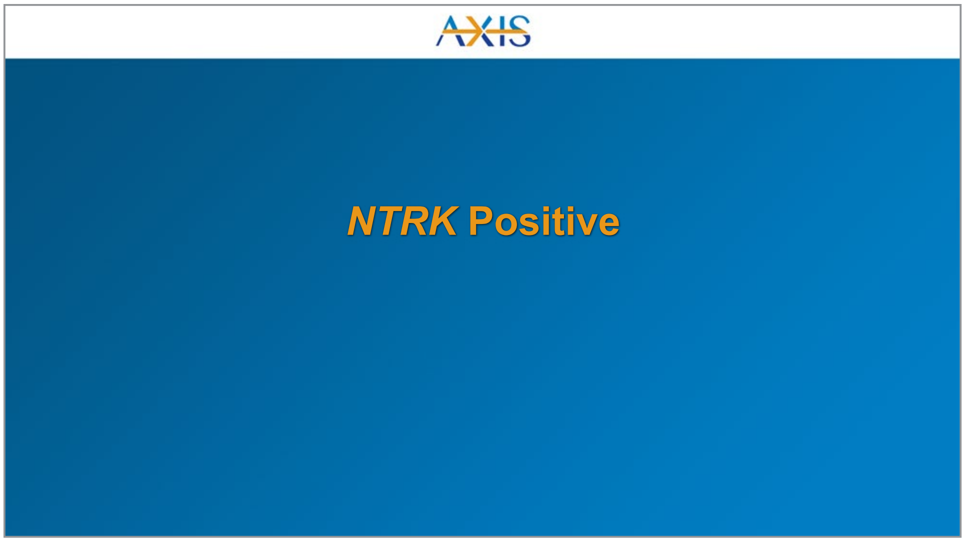


- Again, some patients were treatment naïve. Some had received prior therapy. There is clinical activity regardless of line of therapy.



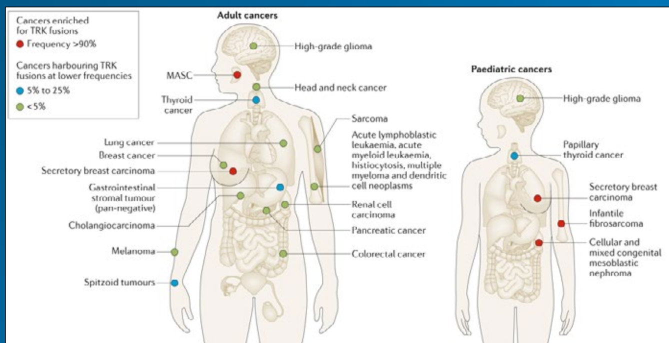
	ORR	Median PFS	Median OS
Vemurafenib	42% [95% CI 20-67]	7.3 mo (95% CI 3.5-10.8)	Not reached
Dabrafenib	33% [95% CI 23-45]	5·5 mo (95%CI 3.4-7.3)	12·7 mo (95% CI 7.3-16.9
Dabrafenib + Trametinib	63% [95% CI 49.3-75.6]	9·7 mo (95% CI 6.9-19.6)	Not reached

- These are the lists of the targeted therapies. In the interest of time, we cannot cover all of the data that's out there. But just to reference that these drugs have been investigated with good clinical activity.



- **Mocharnuk:** *NTRK* is an interesting and newer concept. Can you talk briefly about *NTRK* fusion–positive tumors?

NTRK Fusions Are Found Across Diverse Adult and Pediatric Cancers



Cocco et al. *Nat Rev Clin Oncol*. 2018;15:731-747.

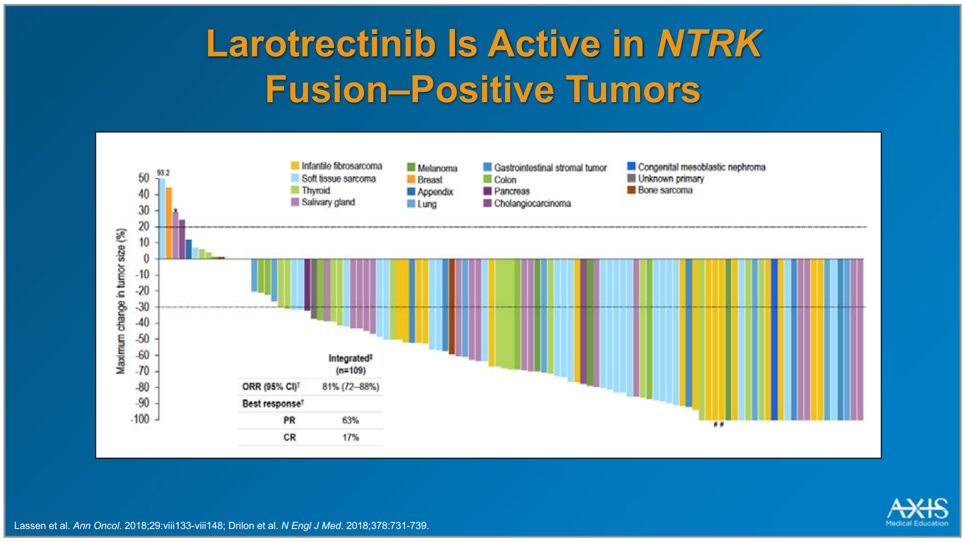
- **Borghaei:** *NTRK* is another one of these alterations that is sort of pan tumor. Interestingly, this one, the *NTRK* fusions can be found in both adult and pediatric cancers. And the list of malignancies that can potentially have *NTRK* fusions is shown on this slide.

NTRK Gene Fusion Positive

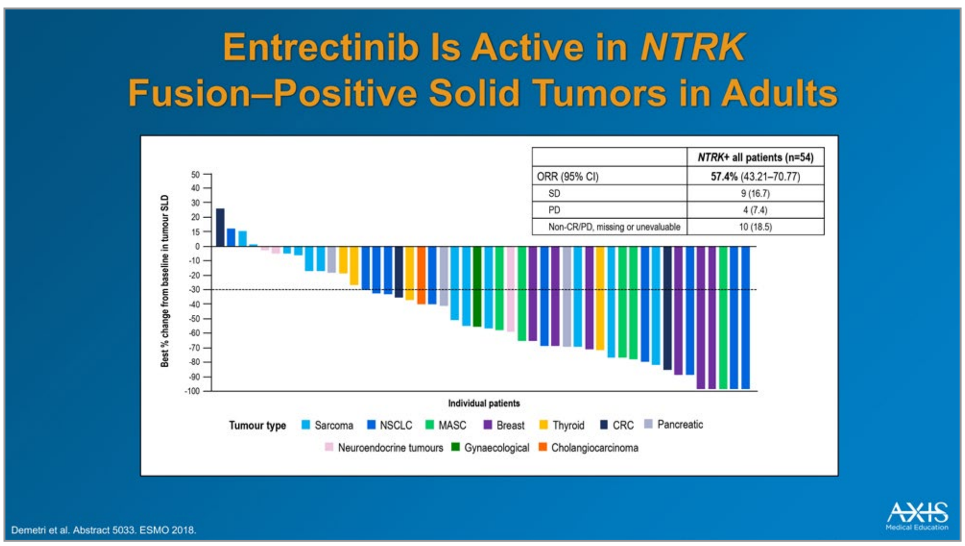
Drug (NCCN® Recommendation)	Trial(s)	Reference(s)
First-line/Subsequent Therapy		
Larotrectinib (preferred)	SCOUT NAVIGATE	Drilon et al. *N Engl J Med*. 2018;378:731-739.
Entrectinib (preferred)	ALKA-372-001 STARTRK-1 STARTRK-2	Doebele et al. *Lancet Oncol*. 2020;21:271-282.

Ettinger et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer. Version 6.2020.

- There are a couple of drugs under this category, larotrectinib and entrectinib. As you can see, they both have been heavily investigated.

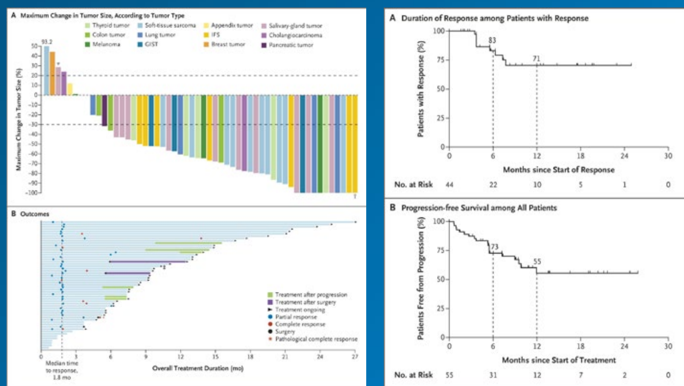


- Larotrectinib is highly active in *NTRK* fusion–positive tumors. A number of different malignancies have been tested as part of these trials. Because this is a pan tumor fusion, the clinical activity is overwhelming and very impressive.



- Entrectinib is another TRK inhibitor, and you can see activity across many different tumor types as long as you can find the alteration— it has a response rate approaching 60%.

Efficacy of Larotrectinib in *NTRK* Fusion–Positive Cancers in Adults and Children



Drilon et al. *N Engl J Med*. 2018;378:731-739.

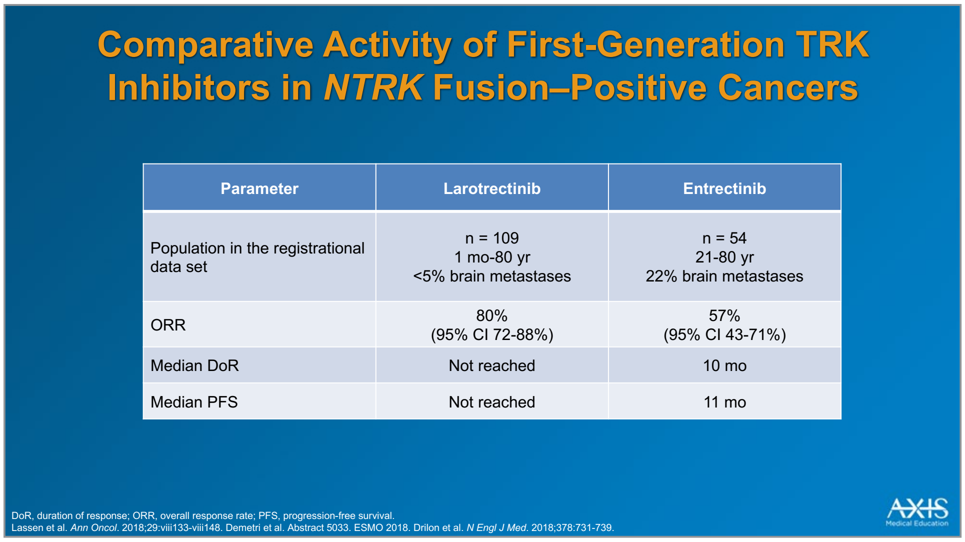
- This is from *The New England Journal of Medicine* publication of larotrectinib in *NTR*K fusion–positive cancers in both adults and children, again showing really good clinical activity with very durable responses and a very impressive PFS, all of which leads to the fact that, you know, we need to be able to identify these patients. You really need to ask your pathologists and your molecular lab to be certain that you can identify these genetic alterations.

Adverse Events*

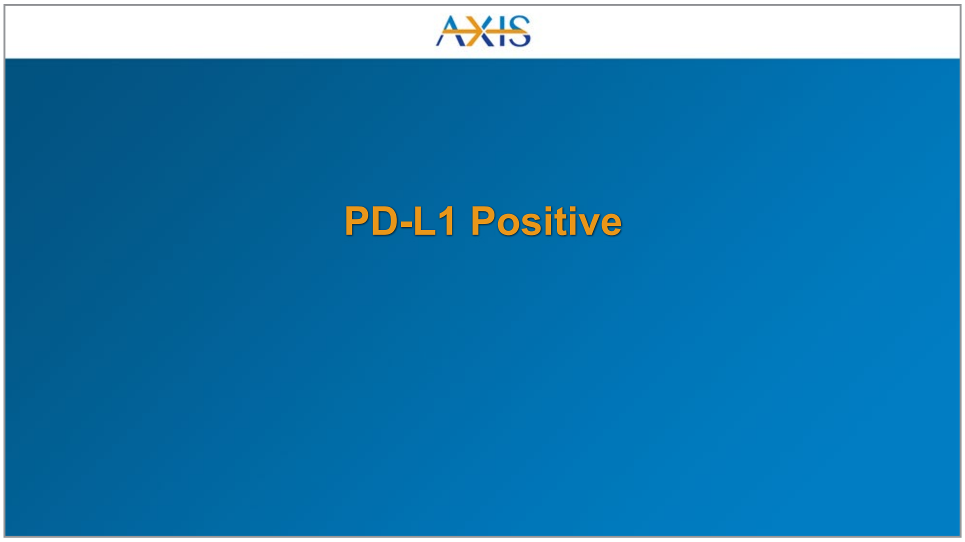
AE	AE, %					TRAE, %		
	Gr 1	Gr 2	Gr 3	Gr 4	Any Gr	Gr 3	Gr 4	Any Gr
Increased ALT or AST level	31	4	7	0	42	5	0	38
Fatigue	20	15	2	0	36	0	0	16
Vomiting	24	9	0	0	33	0	0	11
Dizziness	25	4	2	0	31	2	0	25
Nausea	22	7	2	0	31	2	0	16
Anemia	9	9	11	0	29	2	0	9
Diarrhea	15	13	2	0	29	0	0	5
Constipation	24	4	0	0	27	0	0	16
Cough	22	4	0	0	25	0	0	2
Increased body weight	11	5	7	0	24	0	0	11
Dyspnea	9	9	0	0	18	0	0	2
Headache	13	4	0	0	16	0	0	2
Pyrexia	11	2	2	2	16	0	0	0
Arthralgia	15	0	0	0	15	0	0	2
Back pain	5	9	0	0	15	0	0	0
Decreased neutrophil count	0	7	7	0	15	2	0	9

*The adverse events listed here are those that occurred in at least 15% of the patients, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gr, grade; TRAE, treatment-related adverse event.
Drilon et al. *N Engl J Med*. 2018;378:731-739.

- This is from the table that was published in *The New England Journal of Medicine*, indicating really good tolerability of this particular agent.



- Larotrectinib and entrectinib are the TRK inhibitors that we have. This is a little bit of a head-to-head comparison, but obviously we don't have a formal trial, head to head comparing, so we're doing cross-trial comparisons, showing both are highly clinically active.



- **Mocharnuk:** What are the options for patients who do not have any of the previously mentioned mutations, rearrangements, or fusions, but do express programmed cell death protein ligand 1 (PD-L1)?

Approved First-Line Therapy: PD-1/PD-L1 Inhibitors

Drug	FDA Approval Date	Trial	Indication
Pembrolizumab (PD-1)	October 2016	KEYNOTE-024	As a single agent for the first-line treatment of patients with **PD-L1–expressing** (TPS ≥50%) metastatic NSCLC with no *EGFR* or *ALK* genomic tumor aberrations
	April 2019	KEYNOTE-042	As a single agent for the first-line treatment of patients with stage III NSCLC, who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC, and whose tumors **express PD-L1 (TPS ≥1%)** as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations
	May 2017 (accelerated) August 2018	KEYNOTE-021 KEYNOTE-189	Combined with pemetrexed and platinum chemotherapy as first-line treatment of patients with metastatic **nonsquamous** NSCLC with no *EGFR* or *ALK* genomic tumor aberrations
	October 2018	KEYNOTE-407	Combined with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of patients with metastatic **squamous** NSCLC
Atezolizumab (PD-L1)	December 2018	IMpower150	Combined with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic **nonsquamous** NSCLC with no *EGFR* or *ALK* genomic tumor aberrations
	December 2019	IMpower130	Combined with nab-paclitaxel and carboplatin for the first-line treatment of adult patients with metastatic **nonsquamous** NSCLC with no *EGFR* or *ALK* genomic tumor aberrations
	May 2020	IMpower110	As first-line treatment of adult patients with metastatic NSCLC whose tumors have **high PD-L1 expression** (PD-L1 stained ≥50% of tumor cells or PD-L1 stained tumor-infiltrating immune cells covering ≥10% of the tumor area, with no *EGFR* or *ALK* genomic tumor aberrations
Nivolumab (PD-1)	May 2020	CheckMate-227	Combined with ipilimumab as first-line treatment for patients with metastatic NSCLC whose tumors **express PD-L1(≥1%)**, as determined by an FDA-approved test, with no *EGFR* or *ALK* genomic tumor aberrations
	May 2020	CheckMate-9LA	Combined with ipilimumab and 2 cycles of platinum-doublet chemotherapy as first-line treatment for patients with metastatic or recurrent NSCLC, with no *EGFR* or *ALK* genomic tumor aberrations

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release, 2016, 2017, 2018, 2019, 2020.

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Approved Second-Line Therapy: PD-1/PD-L1 Inhibitors

Drug	FDA Approval Date	Trial	Indication
Nivolumab	March 2015	CheckMate-017	metastatic **squamous** NSCLC that progresses on or after platinum-based chemotherapy
	October 2015	CheckMate-057	metastatic **nonsquamous** NSCLC that progresses on or after platinum-based chemotherapy
Pembrolizumab	October 2015 (accelerated) October 2016 (regular)	KEYNOTE-001 KEYNOTE-010	metastatic NSCLC that **express PD-L1** (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy
Atezolizumab	October 2016	OAK POPLAR	metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy

NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; TPS, tumor proportion score.
FDA News Release 2015, 2016.

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Borghaei: You know, talking about biomarkers, the other one that we also talk about a lot and use in the clinic is PD-L1. The PD-L1 test has been debated since its introduction when we started talking about immunotherapy. And it's an immunohistochemistry-based assay, and I agree that it's not a perfect biomarker, meaning that there are patients with low expression of PD-L1 that respond to immunotherapy. There are patients with high expression who sometimes unfortunately do not respond. So we know that tumor heterogeneity exists, and it's not a perfect marker.

However, the overwhelming amount of information that's out there, in my opinion, suggests that PD-L1 can be a fairly decent marker in identifying patients who actually can benefit from immunotherapy. And I think there's a long list of clinical trials that have looked at markers, this PD-L1 marker. And I again fully agree that there are different tests for different drugs, and it adds to the confusion or discomfort with PD-L1.

But nonetheless, regardless of the PD-1 or PD-L1 inhibitor that you're looking at, PD-L1 expression does seem to correlate with clinical efficacy for these drugs. So it's definitely something that we need to have. You can make treatment decisions based on it. For instance, if somebody has really high PD-L1 expression, you could potentially offer them single-agent immunotherapy and not have to go the chemotherapy route.

On the other hand, the data suggests that if the PD-L1 is not really high, then a combination of chemo plus immunotherapy can be more effective than chemotherapy. So there is a role for PD-L1 expression.

So, what are some of the key points and key takeaways? Again, if you don't test patients with a broad platform, you're not going to identify them. If you don't identify them, they cannot benefit from these targeted therapies that we have, and these are really good targeted therapies.

The list of fusions and amplifications and mutations is growing. And I think it requires active participation by multiple groups taking care of patients with non–small cell lung cancer, as we had discussed previously.

I think the field for *EGFR* mutations is still evolving. Whether we're going to use chemo combinations or VEGF inhibitors is something that clinical trials will address.

As far as *ALK* is concerned, is there a one single best drug to start with? We don't know. Clinical trials hopefully will show us the way. But right now, we have really good, effective therapies for these patients.

Rare fusions such as *NTRK* need to be identified because we have highly effective, well tolerated drugs for this patient population. So again, if you don't look for them, you're not going to find them. Keep in mind that a lot of these drugs have really good intracranial activity, which I think is really important for our patient population. Again, identifying them and offering them the best treatment option is the way to go.

And then finally, PD-L1—it's a newcomer, so to speak. But there are more and more data that are accumulating around this. And potentially, there will be other biomarkers for immunotherapy in the coming years. And with that, I thank you for your participation.

Mocharnuk: Thank you, Dr. Borghaei, for that excellent review of the numerous targeted agents and immunotherapies available for the treatment of advanced and metastatic non–small cell lung cancer. And thank you to our audience for your participation in this activity.

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AXIS Medical Education, Inc. is a full-service continuing education company that designs and implements live, web-based, and print-based educational activities for healthcare professionals. AXIS provides convenient opportunities to engage learners based on their individual learning preferences through a full spectrum of educational offerings.

The executive leadership of AXIS combines 75 years of experience in adult learning theory, curriculum design/implementation/assessment, continuing education accreditation standards, and medical meeting planning and logistics. Our team has a deep understanding of the governing guidelines overseeing the medical education industry to ensure compliant delivery of all activities. AXIS employs an experienced team of medical and scientific experts, medical writers, project managers, meeting planners, and logistics professionals. This team is dedicated to meeting the unmet educational needs of healthcare professionals, with the goal of improving patient outcomes.

AXIS believes that partnerships are crucial in our mission to deliver timely, relevant, and high-quality medical education to healthcare professionals. To that end, AXIS partners with other organizations and accredited providers to offer added expertise and assist in expanding access to our educational interventions. AXIS also partners with numerous patient advocacy organizations to provide recommended patient education and caregiver resources in specific disease areas. AXIS finds value in these partnerships because they complement our core clinical curriculum with validated and relevant supplemental resources for busy clinicians and their patients.

The mission of AXIS is to enhance the knowledge, skills, competence, and performance of the interprofessional healthcare team to ensure patients receive quality care, resulting in improved patient outcomes. We engage healthcare professionals in fair-balanced, scientifically rigorous, expert-led certified educational activities designed to foster lifelong learning that is applicable to clinical practice and patient-centered care.

To learn more and to see our current educational offerings, visit us online at www.AXISMedEd.com.

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