It’s Precisely the Time for More Precision in Genomic Testing and Targeted Treatment of NSCLC

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Post-test and Evaluation: **PeerView.com/NSCLC-Survey-NEN**

Your evaluation of the program is very important in helping us to better meet your current and future medical education needs. We welcome your opinions and comments.

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Why Test Lung Cancer Patients for Genomic Alterations?

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Genomic Alterations Are Common in NSCLC

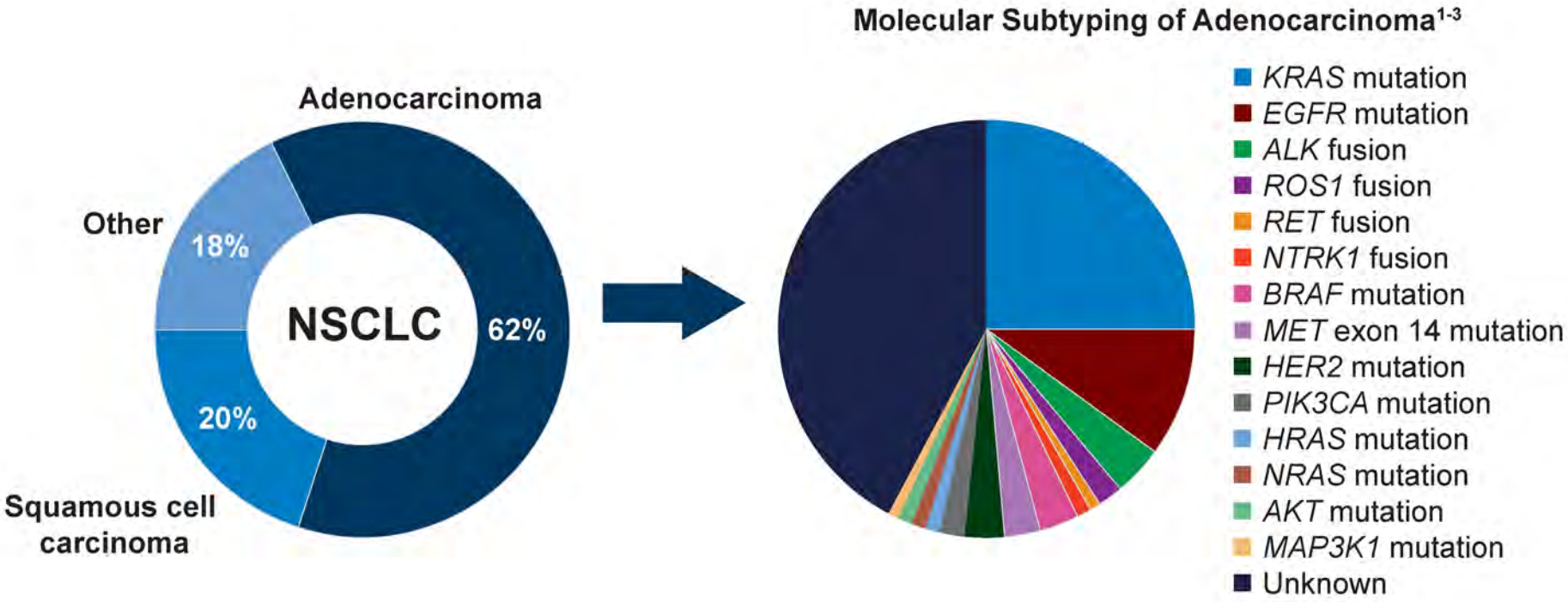
- French Cooperative Thoracic Intergroup (IFCT): 50% of NSCLC tested positive for genomic alterations
- Lung Cancer Mutation Consortium: 64% of NSCLC tested positive for genomic alterations

There are now 7 genomic alterations occurring in NSCLC with FDA-approved targeted therapies, and there are many more coming:

- *EGFR*
- *ALK*
- *ROS1*
- BRAF V600E
- *NTRK*
- *MET* exon 14 skipping (new)
- *RET* (new)

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NSCLC Is Complex and Heterogeneous



1. NCCN Clinical Practice Guidelines in Oncology. Non–Small Cell Lung Cancer. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
2. Lindeman NI et al. *J Thorac Oncol.* 2018;13:323-358. 3. Kalemkerian GP et al. *J Clin Oncol.* 2018;36:911-919.

PeerView.com

Targeted Therapies Produce Better Treatment Outcomes in NSCLC Patients With Genomic Alterations

Always try to match patients with targeted therapies

- Higher response rates, improved QoL
- May be able to avoid chemotherapy

Let's consider a few examples of outcomes seen with some of the targeted therapies:

Target	Drug	ORR, %
EGFR	Osimertinib[1]	77
ALK	Alectinib[2]	79
ROS1	Entrectinib[3]	77
BRAF V600E	Dabrafenib/trametinib[4]	64
MET exon 14 alterations	Capmatinib[5]	68
RET	Selpercatinib[6]	90
NTRK1/2/3	Larotrectinib[7]	81

1. Ramalingam S et al. *J Clin Oncol*. 2019;36:841-849. 2. Peters S et al. *N Engl J Med*. 2017;377:829-838. 3. Doebele R et al. International Association for the Study of Lung Cancer 19th World Conference on Lung Cancer (WCLC 2018). Abstract OA02.01. 4. Planchard D et al. *Lancet Oncol*. 2017;18:1307-1316. 5. Wolf J et al. ASCO 2019. Abstract 9004. 6. Goto K et al. ASCO 2020. Abstract 3584. 7. Lanssen U et al. ESMO 2018. Abstract 409O.

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Immunotherapy Has Low Efficacy in NSCLC With Genomic Alterations[1]

Progression-Free Survival According to Primary Oncogenic Driver From Initiation of ICI

	Event/N	Median PFS (95% CI), mo	6 mo PFS (95% CI)	12 mo PFS (95% CI)
KRAS	208/271	3.2 (2.7-4.5)	37.9 (32.1-49.8)	25.6 (20.2-31.3)
EGFR	117/125	2.1 (1.8-2.7)	18.4 (12.1-25.6)	6.4 (2.7-12.1)
BRAF	34/43	3.1 (1.8-4.6)	32.1 (18.3-46.6)	18.0 (7.2-32.7)
HER2	23/29	2.5 (1.8-3.5)	22.7 (8.9-40.2)	13.6 (3.6-30.1)
MET	26/36	3.4 (1.7-6.2)	36.5 (20.7-52.4)	23.4 (10.6-39.0)
ALK	21/23	2.5 (1.5-3.7)	11.8 (2.2-30.2)	5.9 (0.4-23.0)
ROS1	–	–	–	–
RET	15/16	2.1 (1.3-4.7)	14.1 (2.3-35.9)	7.0 (0.4-27.1)

1. Mazieres J et al. *Ann Oncol*. 2019;30:1321-1328.

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Immunotherapy Has a High Risk of Serious Adverse Events in Patients With Genomically Altered (*EGFR* Mutant) NSCLC[1]



- **Primary objective:** ORR of pembrolizumab prior to TKI
- **Secondary objectives:** safety, PFS, OS of pembrolizumab; safety and efficacy of subsequent EGFR TKI therapy

[a] Performed with 22C3 assay in a Clinical Laboratory Improvement Amendments (CLIA)–approved laboratory.

1. Lisberg AE et al. 2018 American Society of Clinical Oncology Annual Meeting (ASCO 2018). Abstract 9014.

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Potentially Fatal Pneumonitis With Anti-PD-1 With Subsequent EGFR TKI[1]

Pembrolizumab: Treatment-Related Adverse Events (TRAEs)

AE	Any TRAE n = 11, %	TRAE Grade 3-5 n = 11, %
Integument		
Rash	3 (27.3%)	0
Endocrine		
Adrenal insufficiency	1 (9.1%)	0
Gastrointestinal		
Diarrhea	2 (18.2%)	0
Other		
Flu-like symptoms	2 (18.2%)	0
Chills	1 (9.1%)	0
Laboratory abnormalities		
Alanine and aspartate Aminotransferase increased	1 (9.1%)	1 (9.1%)
Alkaline phosphatase increased	1 (9.1%)	0
Thyroid-stimulating hormone decreased	1 (9.1%)	0

Subsequent TKI: Treatment-Related Adverse Events (TRAEs)

AE	Any TRAE n = 7, %	TRAE Grade 3-5 n = 7, %
Integument		
Rash	4 (57.1%)	0
Respiratory		
Pneumonia	1 (14.3%)	1 (14.3%)
Gastrointestinal		
Diarrhea	2 (28.6%)	1 (14.3%)
Laboratory abnormalities		
Transaminitis	1 (14.3%)	1 (14.3%)

1. Lisberg AE et al. *J Clin Oncol*. 2018;36(suppl 15). Abstract 9014.

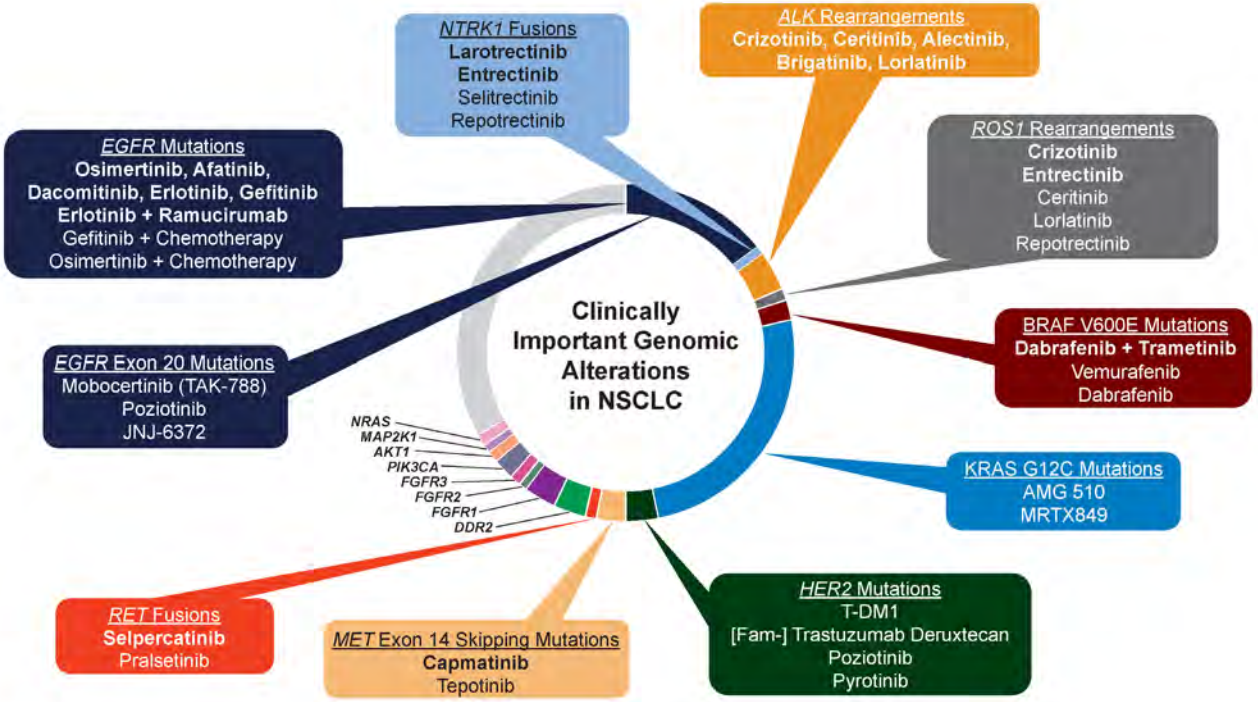
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Which Genomic Alterations Need to Be Tested?

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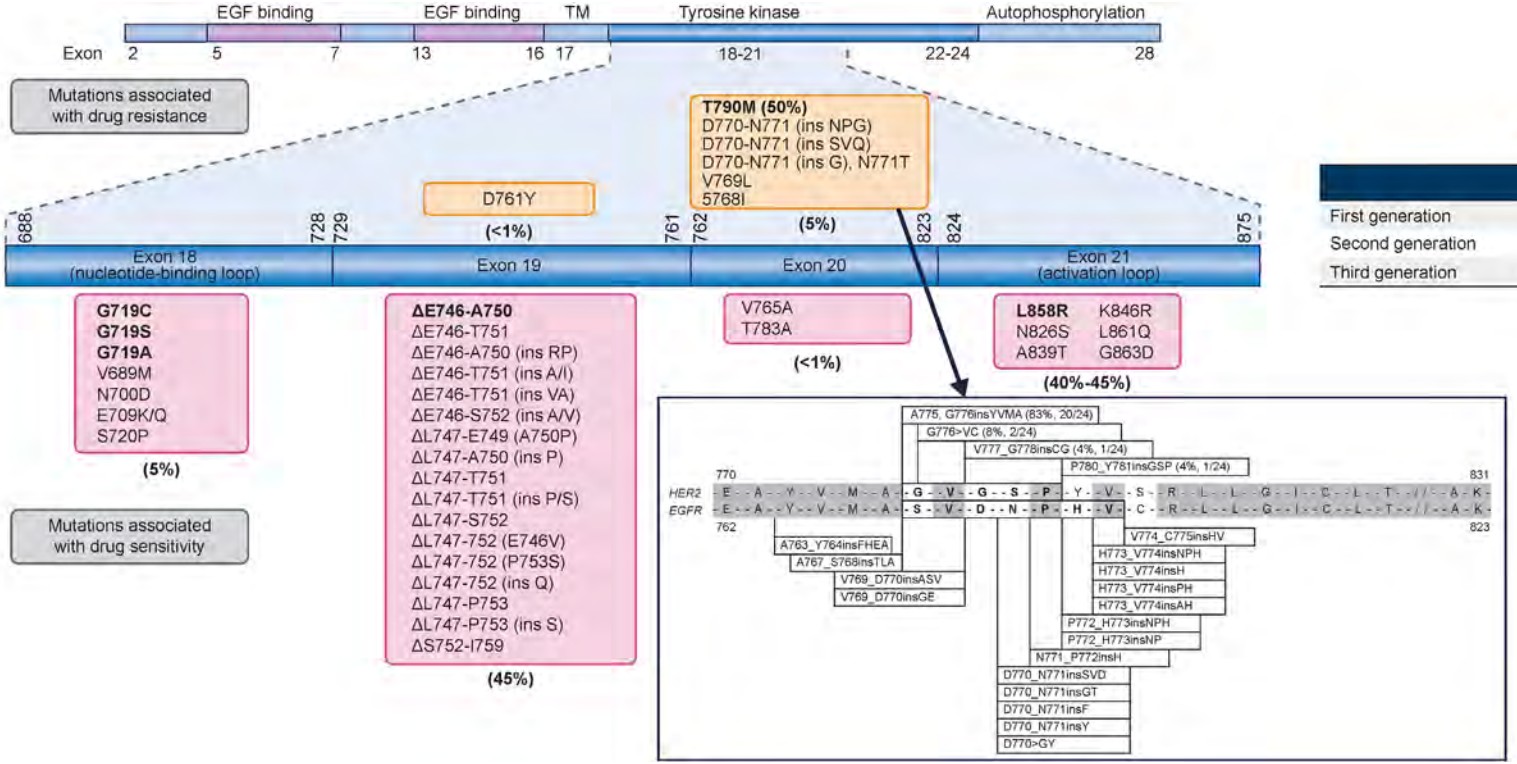
Which Molecular Alterations Need to Be Investigated?

- Molecular targets with FDA-approved therapies:
  - *EGFR*
  - *RET* (new)
  - *MET* exon 14 skipping (new)
  - *ALK*
  - *ROS1*
  - BRAF V600E
  - *NTRK*
- Emerging targets:
  - KRAS G12C
  - *HER2*



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Complexity of *EGFR* Alterations in Lung Cancer



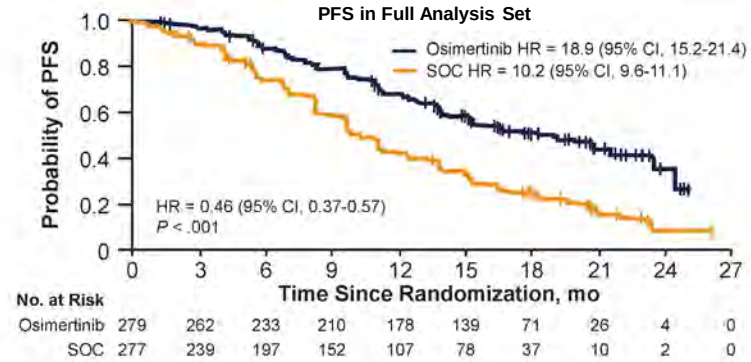
EGFR

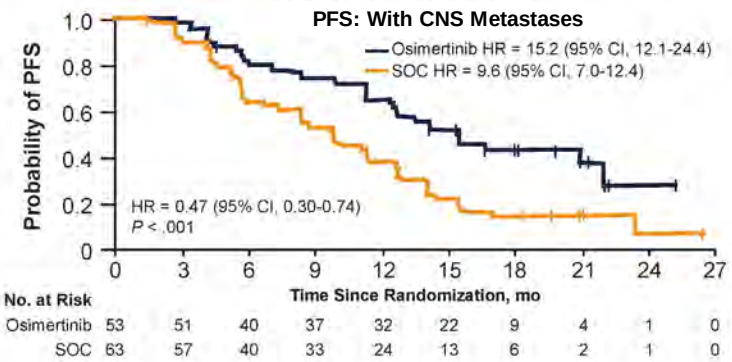
	Drug Names
First generation	Erlotinib, gefitinib
Second generation	Afatinib, dacomitinib
Third generation	Osimertinib (rociletinib), nazartinib

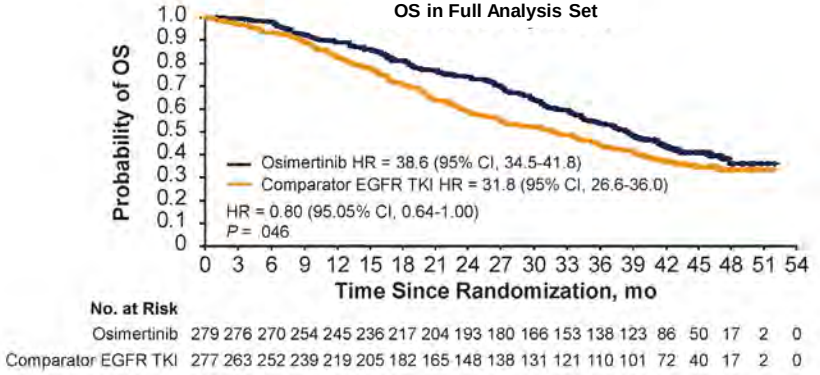
- Most commonly encountered *EGFR*-activating mutations are exon 19 deletion and L858R
- Many FDA-approved EGFR tyrosine kinase inhibitors (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib)

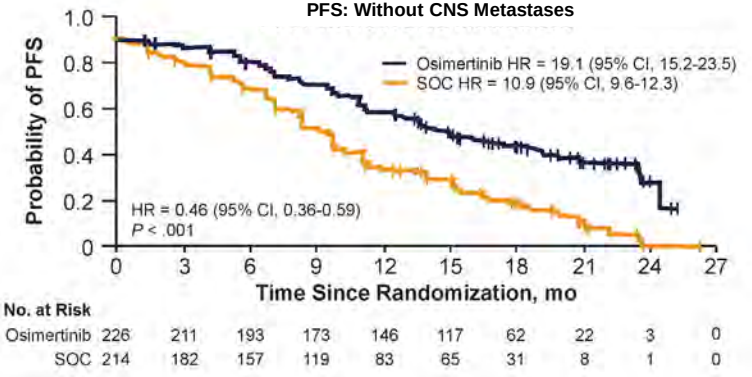
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EGFR Inhibitor: Osimertinib (FLAURA PFS)[1]







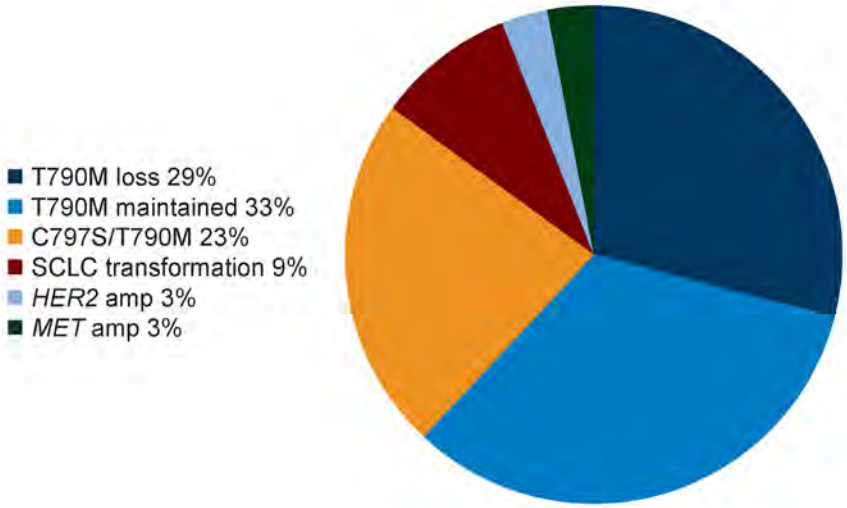


1. Soria JC et al. *N Engl J Med*. 2018;378:113-125.

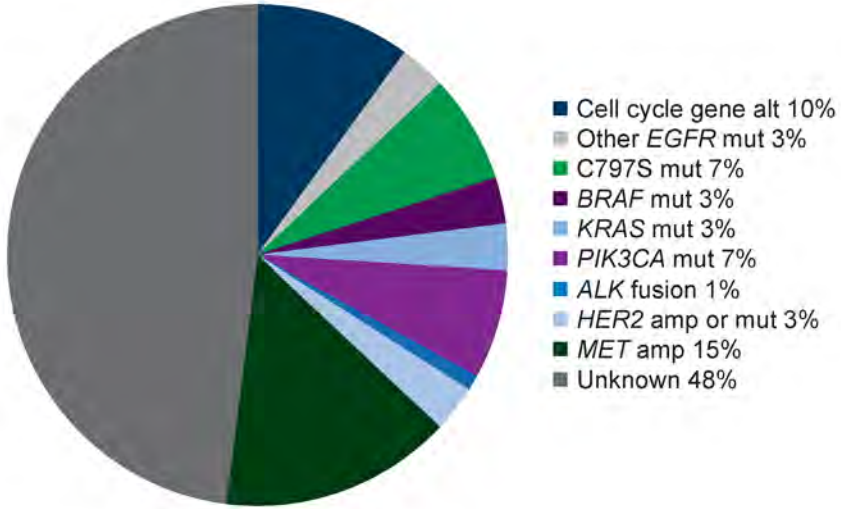
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Mechanisms of Resistance to Osimertinib: Frontline and Second-Line Administration

Resistance to First-Generation EGFR TKI Followed by Second-Line Osimertinib[1-5]



Resistance to Frontline Osimertinib[6]



1. Piotrowska Z, Sequist L. *Cancer J*. 2015;21:371-377. 2. Thress KS et al. *Nat Med*. 2015;21:560-562. 3. Yu H et al. *JAMA Oncol*. 2015;1:982-984. 4. Planchard D et al. *Ann Oncol*. 2015;26:2073-2078. 5. Kim TM et al. *J Thorac Oncol*. 2015;10:1736-1744. 6. Ramalingam SS et al. *Annals Oncol*. 2018;29(suppl 8):LBA50.

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Trials of EGFR Inhibitor–Based Combinations[1-9]

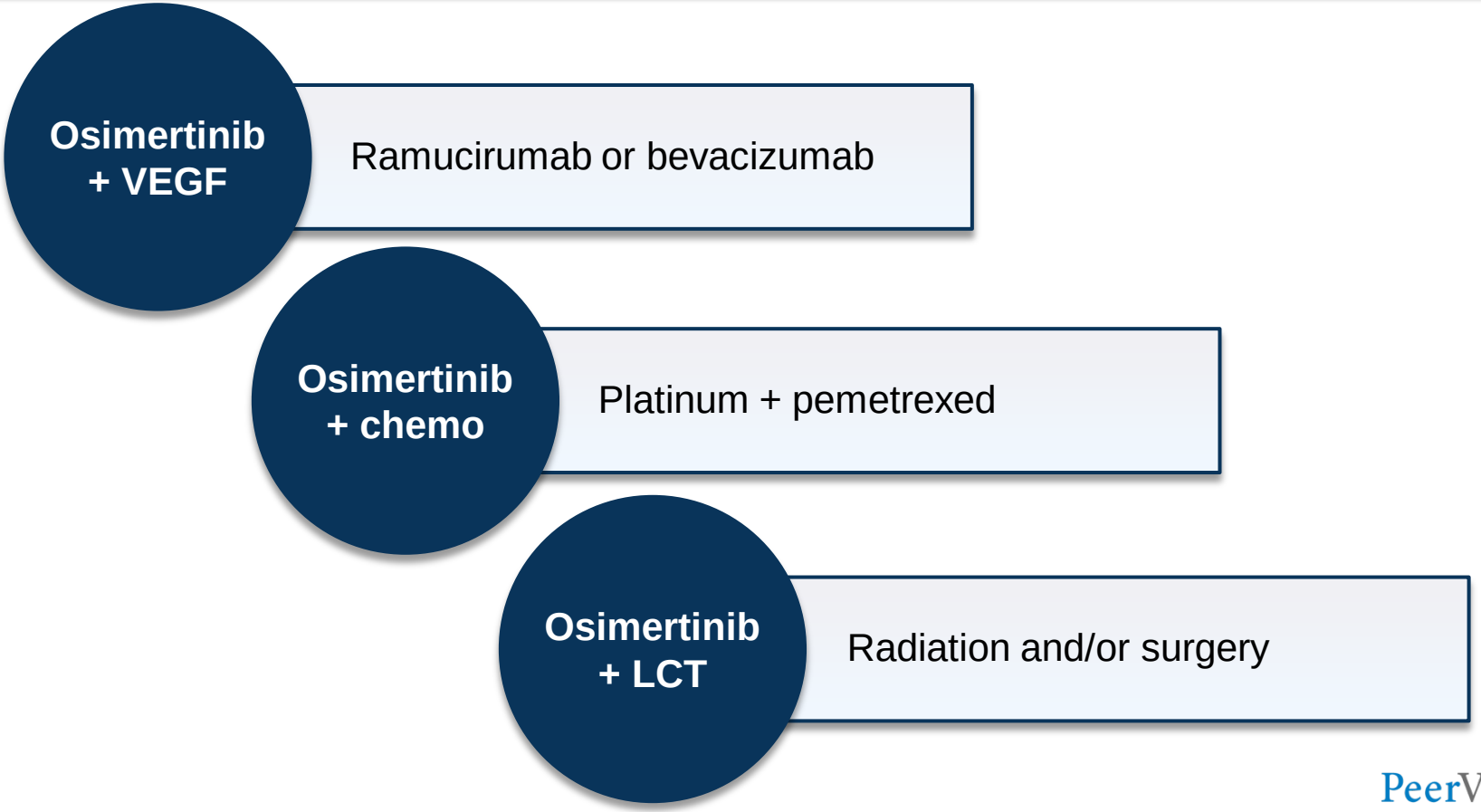
Outcome	Phase 3 NEJ026[1-3]		Phase 3 RELAY[4-6]		Phase 3 NEJ009[7]		Phase 3[8]	
	Erlotinib/ Bevacizumab (n = 112)	Erlotinib (n = 114)	Erlotinib/ Ramucirumab (n = 224)	Erlotinib (n = 225)	Gefitinib/ Carboplatin/ Pemetrexed (n = 169)	Gefitinib (n = 172)	Gefitinib/ Carboplatin/ Pemetrexed (n = 173)	Gefitinib (n = 177)
ORR, %	72	66	76.3	74.7	84	67	81	69
PFS, mo	16.9	13.3	19.4	12.4	20.9	11.2	16	8
HR (95% CI)	0.61 (0.42-0.88)		0.59 (0.46-0.76)		0.49 (0.39-0.62)		0.50 (0.39-0.65)	
PFS2, mo	28.6	24.3	–		20.9	20.7	–	
HR (95% CI)	0.80 (0.59-1.10)		–		0.97 (0.77-1.22)		–	
OS, mo	50.7	46.2	NR (interim)	NR (interim)	52.2	38.8	NR	18
HR (95% CI)	1.00 (0.68-1.48)		0.832 (0.53-1.30)		0.70 (NR)		0.45 (0.31-0.66)	

May 29, 2020: The FDA approved ramucirumab in combination with erlotinib for the first-line treatment of metastatic *EGFR* mutation–positive NSCLC based on efficacy data from RELAY trial[9]

1. Furuya N et al. ASCO 2018. Abstract 9006. 2. Saito H et al. *Lancet Oncol.* 2019;20:625-635. 3. Maemondo M et al. ASCO 2020. Abstract 9506. 4. Nakagawa K et al. ASCO 2019. Abstract 9000. 5. Nakagawa K et al. *Lancet Oncol.* 2019;20:1655-1669. 6. Nakahara Y et al. ASCO 2019. Abstract TPS9120. 7. Nakamura A et al. ASCO 2018. Abstract 9005. 8. Noronha V et al. ASCO 2019. Abstract 9001. 9. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-ramucirumab-plus-erlotinib-first-line-metastatic-nsclc.

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Other Osimertinib-Based Combinations Under Investigation



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EGFR Exon 20 Insertions in Lung Cancer

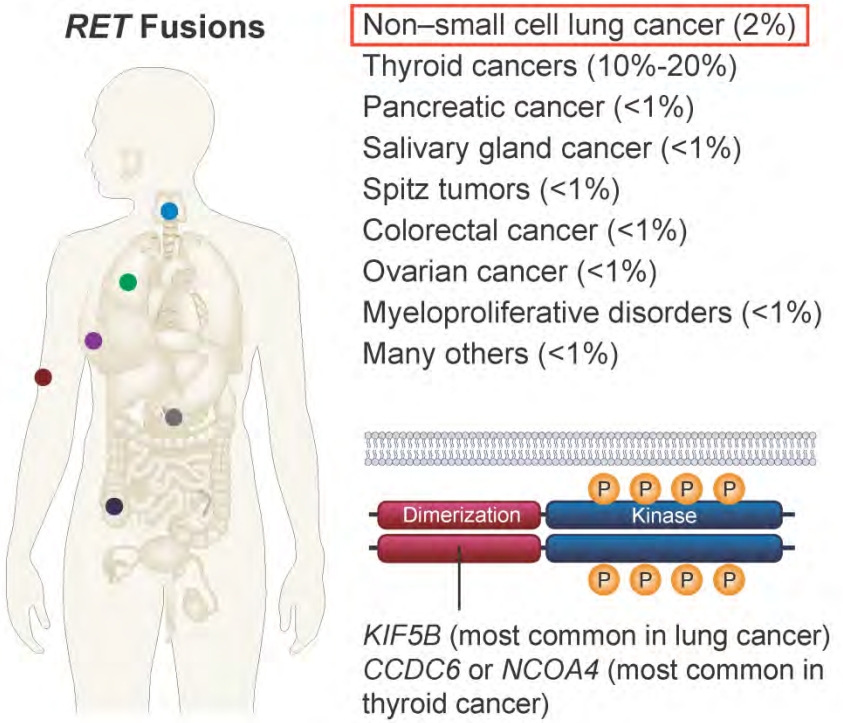
EGFR exon 20 insertions comprise 4%-10% of *EGFR*-mutant NSCLC and are generally refractory to first/second-generation EGFR TKIs, but other agents are showing clinical activity and tolerability in this setting

- **Osimertinib**
  - – Phase 2 EA5162 trial (NCT03191149)[1]
- **Poziotinib**
  - – Phase 2 trial (NCT03066206)[2]
  - – Phase 2 ZENITH20 trial did not meet primary endpoint in *EGFR* exon 20 cohort[3]
- **Mobocertinib (TAK-788)**
  - – Phase 1/2 trial "EXCLAIM" extension cohort (NCT02716116)[4]
- Breakthrough therapy designation based on ORR and long-term benefit seen in a phase ½ study in patients with exon20ins disease[5]
- **Amivantamab (JNJ-61186372)**
  - – Breakthrough therapy designation based on results from a phase 1 study (NCT02609776) demonstrating robust and durable antitumor activity in patients with exon20ins disease with a manageable safety profile[6]

1. Piotrowska Z et al. ASCO 2020. Abstract 9513. 2. Heymach JV et al. WCLC 2018. Abstract OA 02.06. 3. Le X et al. ASCO 2020. Abstract 9514. 4. Riely G et al. WCLC 2019. P1.01-127. 5. Janne PA et al. *J Clin Oncol.* 2019;37(suppl 15):9007.6. Park K et al. ASCO 2020. Abstract 9512.

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RET Fusions in Lung Cancer



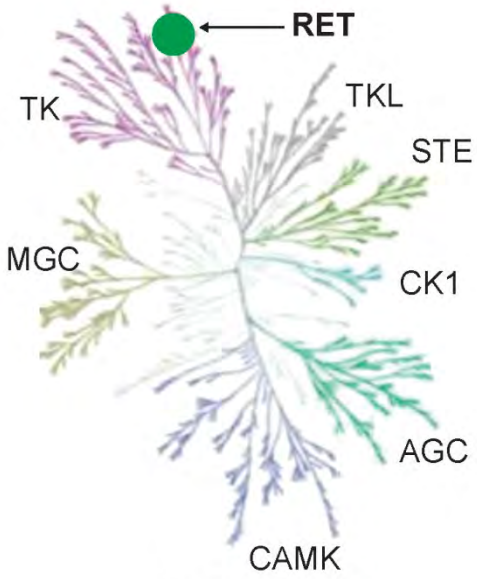
- ***RET* fusions are bona fide lung cancer drivers**
  - – Mutually exclusive with other driver alterations[1,2]
  - – Transforming and actionable in vitro and in vivo[3,4]
  - – Up to half of patients with advanced disease have
  - – brain metastases[5]

1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-167. 2. Wang R et al. *J Clin Oncol*. 2012;30:4352-4359. 3. Saito et al. *Carcinogenesis*. 2014;35:2452-2456. 4. Takahashi et al. *Cell*. 1985;42:581-588. 5. Drilon A et al. *J Clin Oncol*. 2017;35(suppl):9069.

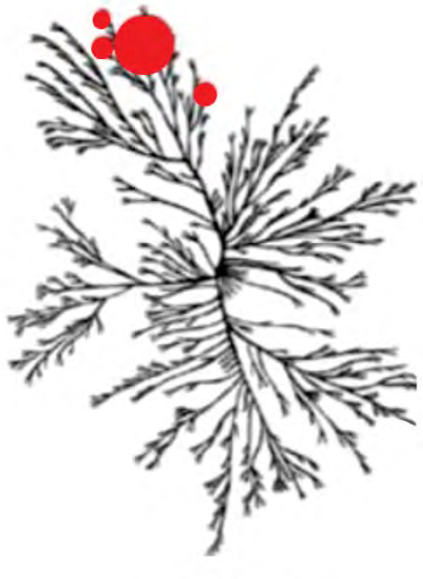
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First- and Second-Generation RET Inhibitors

	Drug Names
First generation	Alectinib, cabozantinib, lenvatinib, vandetanib
Second generation	Selpercatinib, pralsetinib



Selpercatinib
(LOXO-292)



Pralsetinib
(BLU-667)

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New FDA Approval for RET Inhibitor Selpercatinib[1]

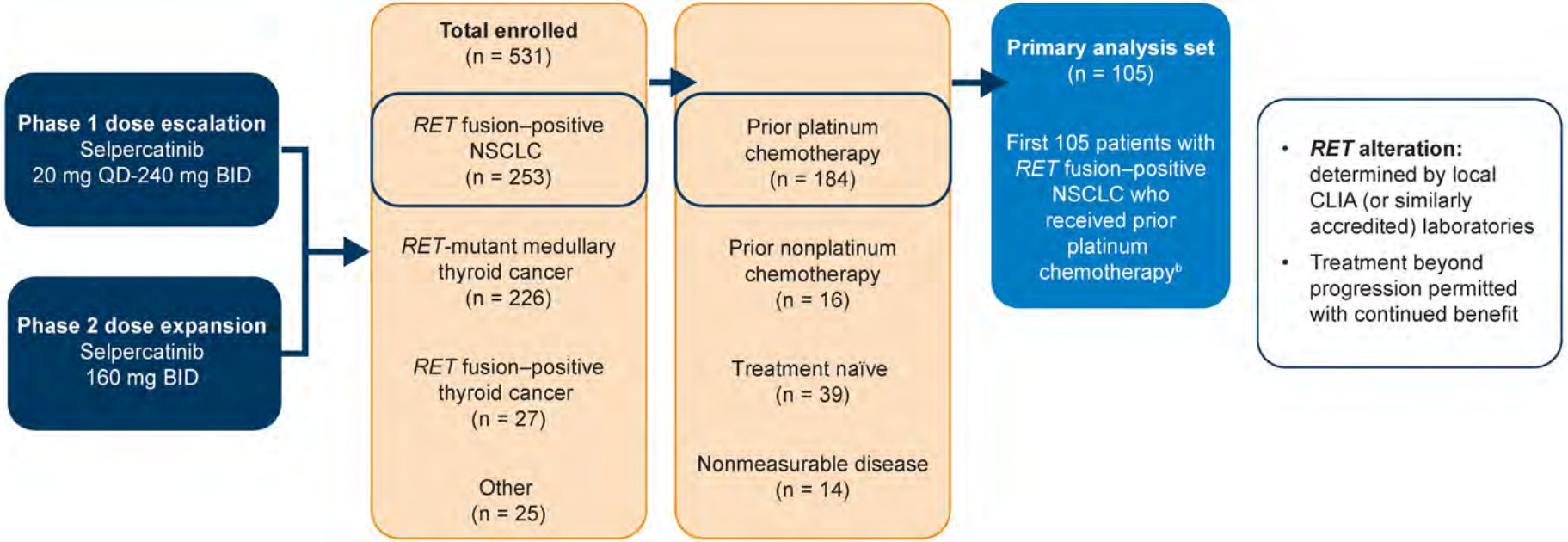
May 8, 2020: The FDA granted accelerated approval to selpercatinib for the treatment of adult patients with metastatic *RET* fusion–positive NSCLC

- Line agnostic
- Efficacy based on results of LIBRETTO-001 trial
- Main outcome measures were ORR and response duration determined by a blinded independent review committee using RECIST 1.1
- Identification of *RET* gene alterations was prospectively determined in local laboratories using either next-generation sequencing, polymerase chain reaction, or fluorescence in situ hybridization

1. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-selpercatinib-lung-and-thyroid-cancers-ret-genemutations-or-fusions.

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LIBRETTO-001:[a] Selpercatinib in *RET*-Altered Cancers[1]



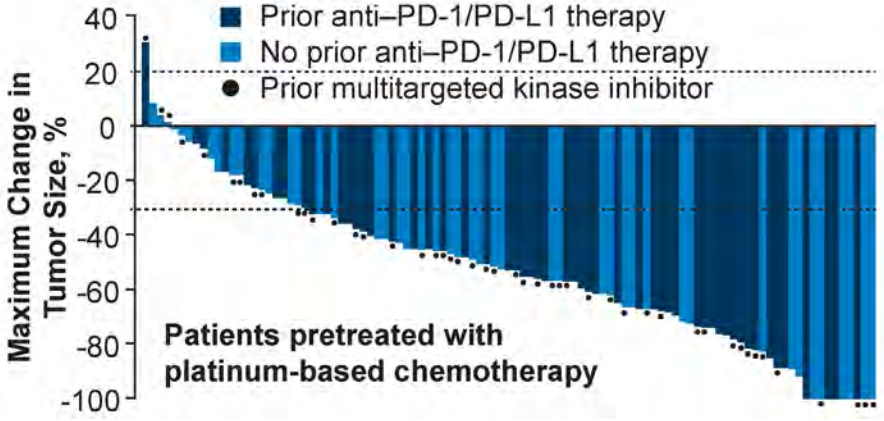
- **Primary endpoint:** ORR (RECIST 1.1)
- **Secondary endpoints:** duration of response, PFS, safety

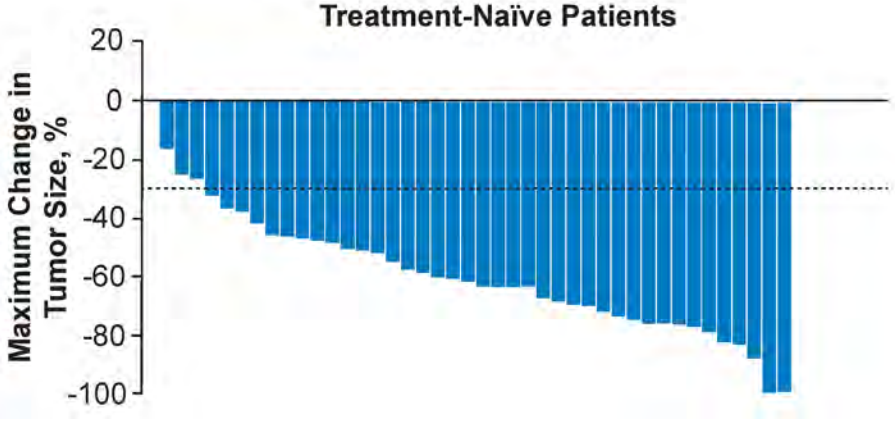
[a] NCT03157128; data cutoff: December 16, 2019.
[b] Per agreement with the FDA, patients with nonmeasurable disease enrolled during phase 1 dose escalation were eligible for the primary analysis set.
1. Goto K et al. ASCO 2020. Abstract 3584.

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LIBRETTO-001: Selpercatinib in *RET*-Altered Cancers[1]

Selpercatinib achieved marked and durable antitumor activity in patients with *RET* fusion+ NSCLC and was well tolerated





In 105 previously treated patients:
- ORR, 70% (95% CI, 60%-78%); responses did not differ by fusion partner or number or type of prior therapies, including anti–PD-1/PD-L1 agents and off-label multikinase inhibitor use
- Median DOR, 20.3 mo (95% CI, 15.6-24.0)

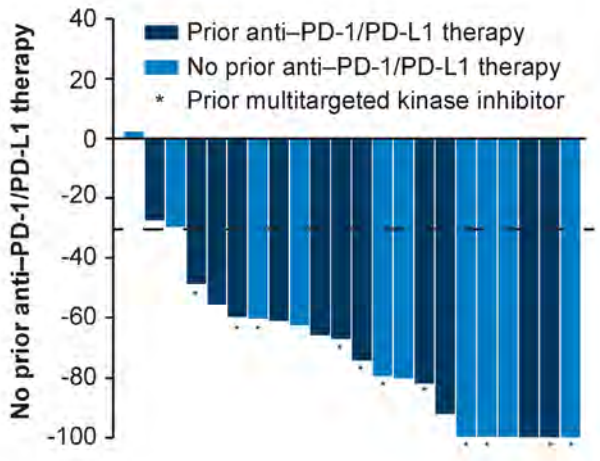
In 39 treatment-naïve patients:
- ORR, 90% (95% CI, 76%-97%)
- Median DOR, NR with 27 of 33 (82%) confirmed responses ongoing at a median follow-up of 7.4 mo

1. Goto K et al. ASCO 2020. Abstract 3584.

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Selpercatinib CNS Response in *RET* Fusion–Positive NSCLC: Updated Data From ASCO 2020[1]

- Selpercatinib had marked intracranial antitumor activity in *RET* fusion+ NSCLC patients with CNS metastases; tumor responses were durable, independently confirmed, and observed in patients with prior systemic chemotherapy
  - In patients with CNS metastases, intracranial ORR, 82% (n = 18); 95% CI, 60%-95%, including 5 CRs (23%) and 13 PRs (59%)
  - Median intracranial DOR, 9.4 mo (95% CI, 7.4-NE)



Status	*RET* Fusion–Positive NSCLC Patients With Measurable CNS Metastases (n = 22)[a]		
	Total (n = 22)	Without Prior CNS RT (n = 14)	With Prior CNS RT[b] (n = 8)
CNS best response of CR/PR, n	18	12	6
CNS duration of response, mo			
Median	9.4	9.4	NE
95% CI	7.4-NE	6.7-10.1	5.1-NE
CNS duration of follow-up, mo			
Median	9.5	15.7	9.5
25th, 75th percentile	9.2, 15.7	8.3, 15.7	9.2, 21.2
Response status, % (n)	44.4 (8)	41.7 (5)	50.0 (3)

[a] Patients had CNS measurable lesions per RECIST v1.1. [b] Of the 8 patients who received prior radiotherapy, 6 completed radiotherapy >2 months prior to treatment.

1. Subbiah V et al. ASCO 2020. Abstract 9516.

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New FDA Approval for RET Inhibitor Pralsetinib[1]

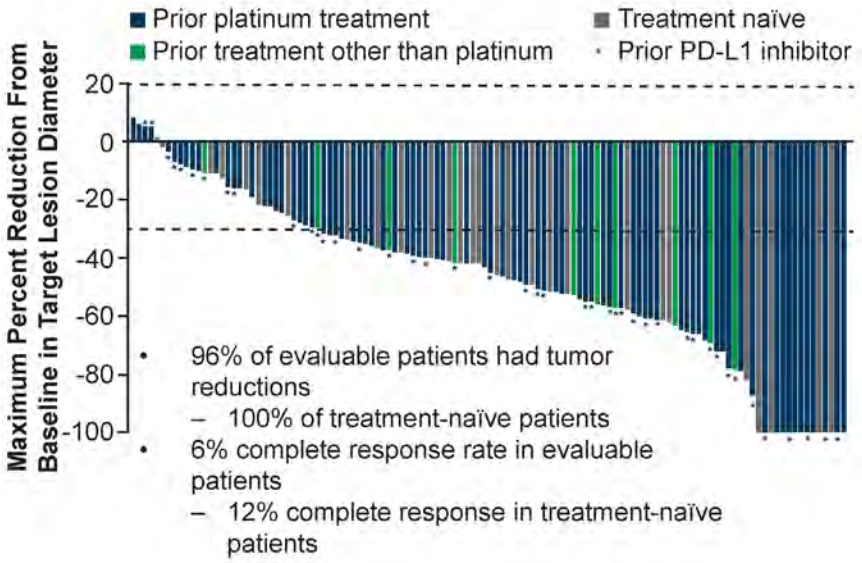
September 4, 2020: The FDA granted accelerated approval to pralsetinib for the treatment of adult patients with metastatic *RET* fusion–positive NSCLC

- Line agnostic
- Efficacy based on results of ARROW trial
- Main outcome measures were ORR and response duration determined by a blinded independent review committee using RECIST 1.1
- Identification of *RET* gene alterations was prospectively determined in local laboratories using either next-generation sequencing or fluorescence in situ hybridization

1. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pralsetinib-lung-cancer-ret-gene-fusions.

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RET Inhibitor: Pralsetinib (ARROW Trial)[1]



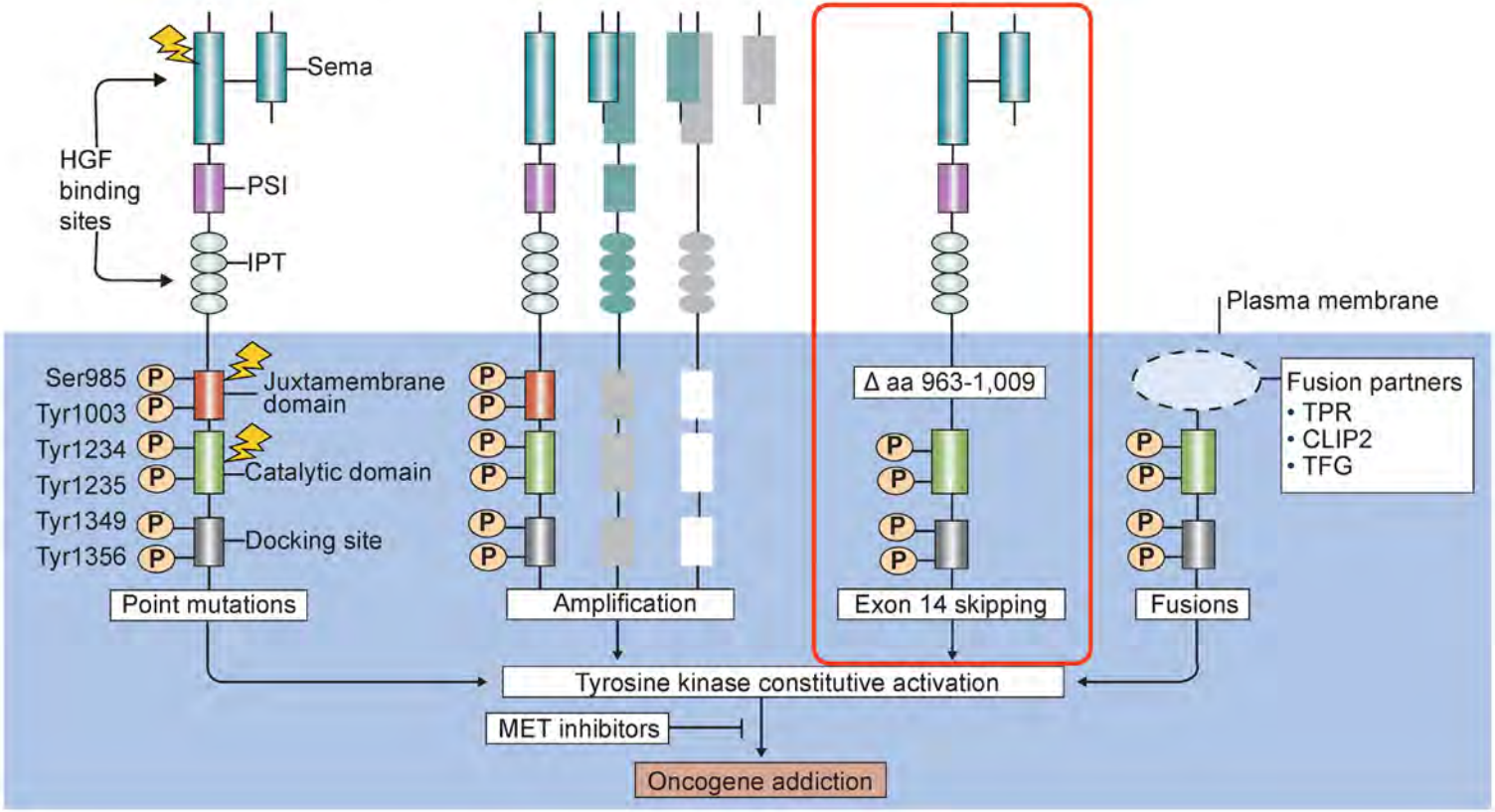
	Response-Evaluable Population		
	All NSCLC (n = 116)[a]	Prior Platinum (n = 80)	Treatment Naïve (n = 26)
ORR (95% CI)	65%[b] (55%-73%)	61%[b] (50%-72%)	73% (52%-88%)
Best overall response			
CR	6%	5%	12%
PR	59%[b]	56%[b]	62%
SD	28%	34%	15%
PD	7%	5%	12%
NE	0%	0%	0%
Disease control rate (95% CI)	93% (87%-97%)	95% (88%-99%)	88% (70%-98%)
Clinical benefit rate (95% CI)[c]	72% (62%-80%)	71% (60%-81%)	73% (52%-88%)

[a] Includes 10 patients with prior treatment other than platinum. [b] Includes 2 patients still on treatment with PRs pending confirmation. [c] CR or PR or SD ≥16 weeks.

1. Gainor J et al. ASCO 2020. Abstract 9515.

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MET Alterations in NSCLC[1]



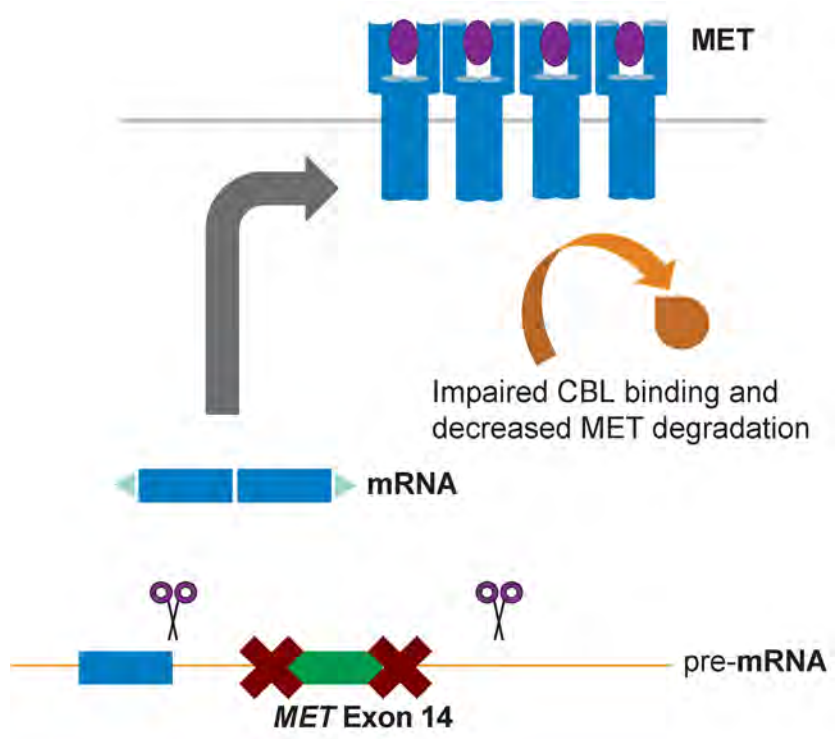
1. Comoglio PM et al. *Nat Rev Cancer*. 2018;18:341-358.

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MET Exon 14 Alterations in NSCLC[1-4]

MET mutations that lead to decreased MET degradation

- Deletions, insertions, or base substitutions
- Many disrupt splice sites flanking *MET* exon 14 → exon 14 skipping
- Increased MET receptor on the tumor cell surface



1. Drilon A. *Clin Cancer Res*. 2016;22:2832-2834. 2. Kong-Beltran M et al. *Cancer Res*. 2006;66:283-289. 3. Ma PC et al. *Cancer Res*. 2003;63:6272-6281.
4. Frampton GM et al. *Cancer Discov*. 2015;5:850-859.

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MET Inhibitors in Clinical Trials[1]

Agent	Other Molecular Targets	IC_{50}, nM
Type I		
Crizotinib	MET (type Ia), ALK, ROS1	<1
Capmatinib	Selective MET (type Ib)	0.13
Tepotinib	Selective MET (type Ib)	3
Savolitinib	Selective MET (type Ib)	5
Type II		
Cabozanitib	MET (type II), VEGFR, RET, TIE2, AXL, FLT3, KIT	1.3
Merestinib	MET (type II), MST1R, FLT3, MERTK, TEK, ROS1, DDR, NTRK, AXL	4.7

- Type I binds ATP-binding pocket in the active conformation; Ib more specific
- Type II binds ATP-binding pocket in the inactive conformation; potency is more valuable

1. Reungwtwattana T et al. *Lung Cancer*. 2017:103:27-37.

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New FDA Approval for *MET* Exon 14 Skipping Inhibitor to Treat NSCLC[1-3]

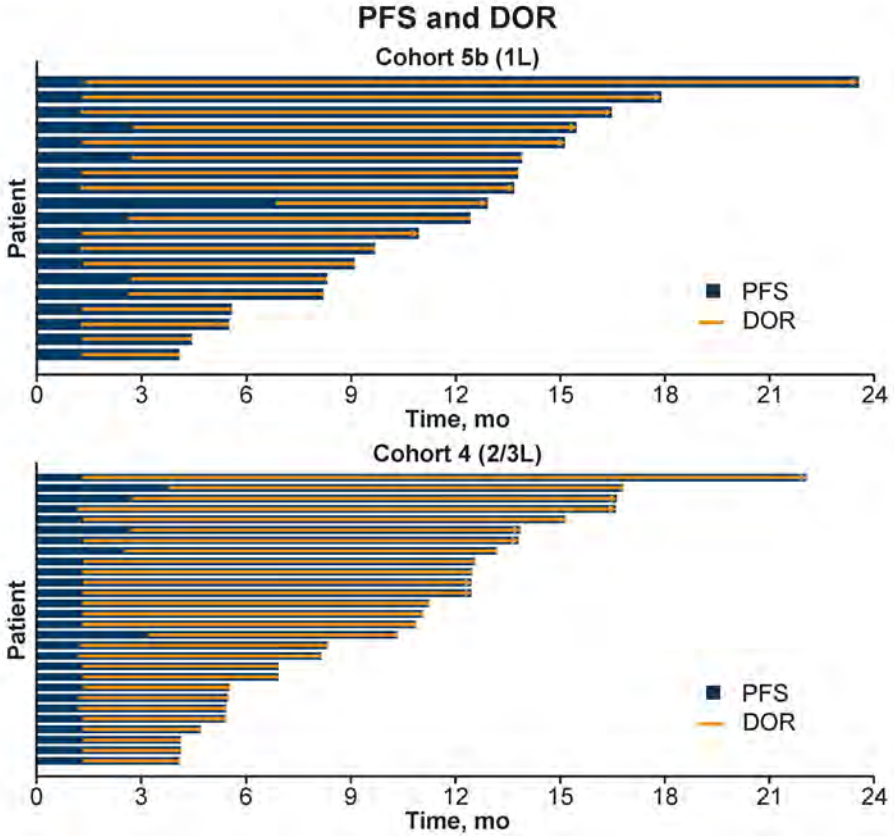
May 6, 2020: Capmatinib received FDA approval for the treatment of adult patients with metastatic *MET* exon 14 skipping NSCLC based on efficacy data from GEOMETRY trial

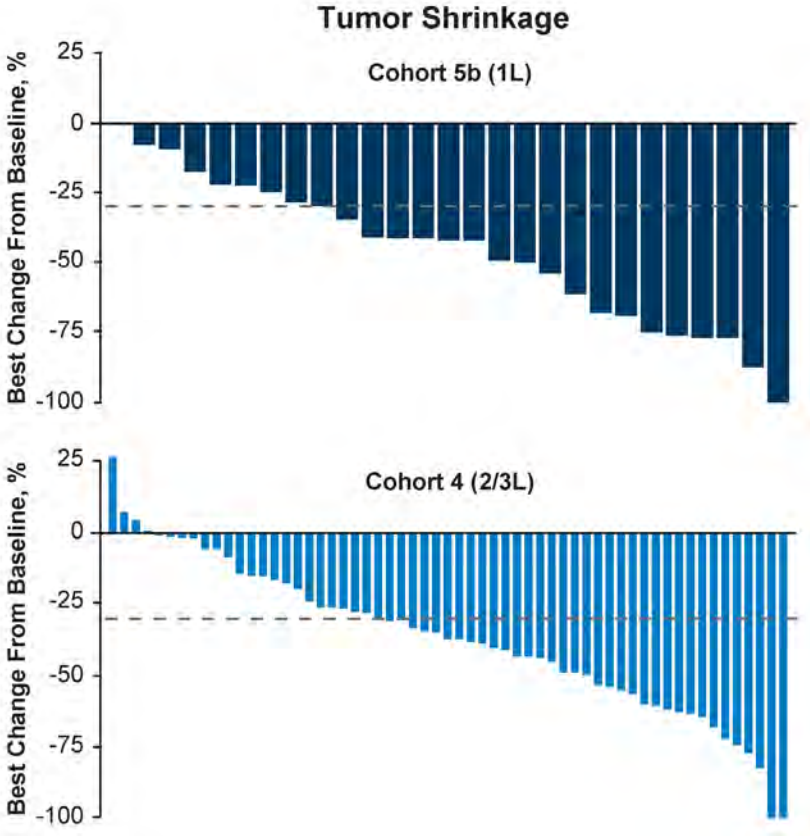
- The FDA also approved the FoundationOne CDx assay (F1CDx) as a companion diagnostic for capmatinib
- Primary efficacy outcome was ORR; secondary outcome was DOR
- In 28 treatment-naïve patients: ORR, 68% (95% CI, 48%-84%) with a response duration of 12.6 months (95% CI, 5.5-25.3 mo)
- In 69 previously treated patients: ORR, 41% (95% CI, 29%-53%) with a response duration of 9.7 months (95% CI, 5.5-13 mo)

1. https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-treat-aggressive-form-lung-cancer. 2. Wolf J et al. ASCO 2019. Abstract 9004. 3. https://www.targetedonc.com/news/fda-grants-priority-review-to-nda-for-capmatinib-inmet-exon-14-nsclc.

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Capmatinib in *MET* Exon 14 Skipping NSCLC[1]





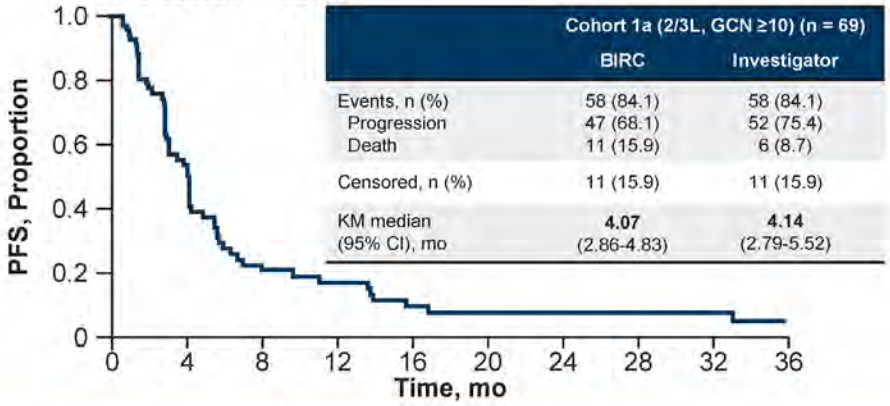
1. Wolf J et al. ASCO 2019. Abstract 9004.

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MET-Amplified Inhibitor: Capmatinib (GEOMETRY mono-1 study)[1]

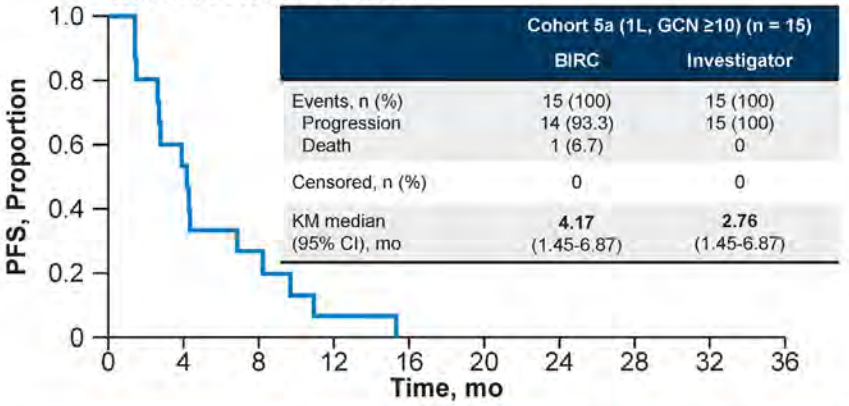
Capmatinib Demonstrates Activity in a Subset of Patients With High-Level *MET*-Amplified (GCN ≥10) NSCLC

Pretreated Patients



	Cohort 1a (2/3L, GCN ≥10) (n = 69)	
	BIRC	Investigator
Events, n (%)	58 (84.1)	58 (84.1)
Progression	47 (68.1)	52 (75.4)
Death	11 (15.9)	6 (8.7)
Censored, n (%)	11 (15.9)	11 (15.9)
KM median (95% CI), mo	**4.07** (2.86-4.83)	**4.14** (2.79-5.52)

Treatment-Naïve Patients



	Cohort 5a (1L, GCN ≥10) (n = 15)	
	BIRC	Investigator
Events, n (%)	15 (100)	15 (100)
Progression	14 (93.3)	15 (100)
Death	1 (6.7)	0
Censored, n (%)	0	0
KM median (95% CI), mo	**4.17** (1.45-6.87)	**2.76** (1.45-6.87)

	Cohort 1a (2/3L) (n = 69)		Cohort 5a (1L) (n = 15)	
	BIRC	Investigator	BIRC	Investigator
ORR, % (95% CI)	**29 (18.7-41.2)**	**27.5 (17.5-39.6)**	**40 (16.3-67.7)**	**40 (16.3-67.7)**
DCR, % (95% CI)	71.0 (58.8-81.3)	60.9 (48.4-72.4)	66.7 (38.4-88.2)	73.3 (44.9-92.2)
Median PFS, mo (95% CI)	4.07 (2.86-4.83)	4.14 (2.79-5.52)	4.17 (1.45-6.87)	2.76 (1.45-6.87)
Median DOR, mo (95% CI)	n = 20 8.31 (4.17-15.44)	n = 19 6.80 (4.21-20.73)	n = 6 7.54 (2.56-14.26)	n = 6 9.66 (4.01-17.08)

1. Wolf J et al. ASCO 2020. Abstract 9509.

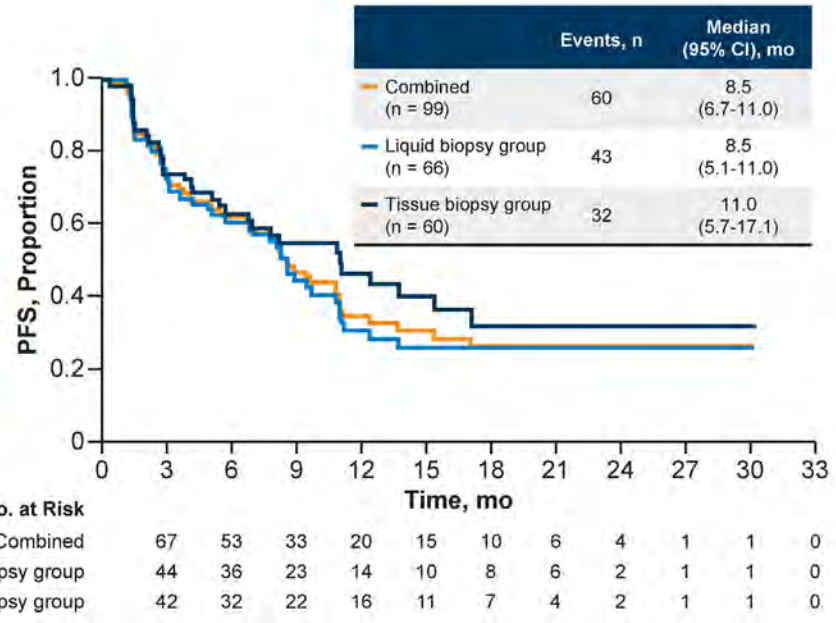
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MET Exon 14 Skipping Inhibitor: Tepotinib (VISION Trial)[1,2]

VISION study design (N = up to 120)

- Stage IIIB/IV NSCLC
  - – All histologies (including squamous and sarcomatoid)
  - – Exclusion of active brain metastases or brain as only measurable lesion
- Tissue- or blood-based *MET* alterations (central lab testing)
  - – *MET*ex14 skipping mutations detected
    - ➢ Plasma, LBx (DNA based)
    - ➢ Tissue, TBx (RNA based)
  - – *MET* amplification only
- First-, second-, third-line therapy
  - – Prior anti-MET therapy was not allowed
  - – Prior immunotherapy was allowed

Cohort A *MET*ex14 skipping mutation → Tepotinib 500 mg daily (21 day cycles until PD)

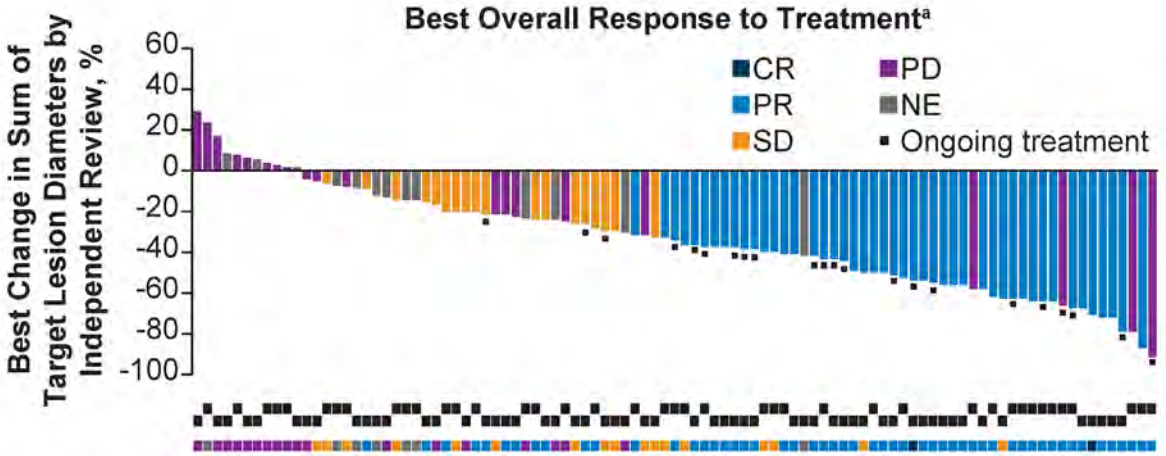


- In the combined group, median (95% CI) PFS was 8.5 (6.7-11.0) months by independent review and 8.6 (6.7-11.2) months by investigator assessment
- Median (95% CI) OS was 17.1 (12.0-26.8) months in the combined group,15.8 (9.5-NE) months in the liquid biopsy group, and 22.3 (15.3-NE) months in the tissue biopsy group

1. Paik PK et al. ASCO 2019. Abstract 9005. 2. Le X et al. ASCO 2020. Abstract 9556.

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Tepotinib: ORR and Duration of Response[1]



- Responses occurred early and were durable across treatment lines
- Patients with brain metastases at baseline benefited equally from treatment

	Liquid Biopsy Group (n = 66)[b]		Tissue Biopsy Group (n = 60)[c]		Combined[d] (n = 99)	
	IRC	INV	IRC	INV	IRC	INV
ORR, % (95% CI)	48.5 (36.0-61.1)	56.1 (43.3-68.3)	50.0 (36.8-63.2)	61.7 (48.2-73.9)	46.5 (36.4-56.8)	55.6 (45.2,-65.5)
DOR, median mo (95% CI)	9.9 (7.2-NE)	14.0 (7.3-NE)	15.7 (9.7-NE)	16.4 (9.7-NE)	11.1 (7.2-NE)	14.0 (9.7-18.3)
DCR, % (95% CI)	65.2 (52.4-76.5)	69.7 (57.1-80.4)	68.3 (55.0-79.7)	78.3 (65.8-87.9)	65.7 (55.4-74.9)	72.7 (62.9-81.2)

[a] Two patients are not shown, as baseline/on-treatment measurement was not available. [b] Two patients were liquid biopsy positive only. [c] 25 patients were tissue biopsy positive only; objective response rate by independent review was 40.0% (95% CI, 21.1-61.3) and 48.0 (95% CI, 27.8-68.7) by investigator assessment.
[d] Combined refers to liquid biopsy positive and/or tissue biopsy positive.

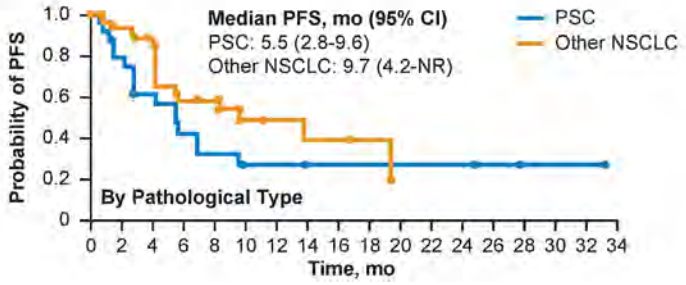
1. Le X et al. ASCO 2020. Abstract 9556.

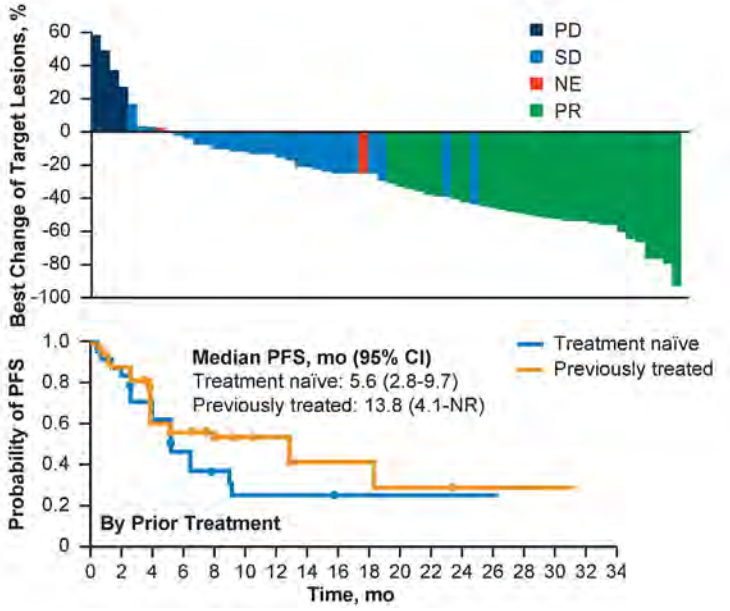
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Phase 2 Study of Savolitinib in PSC and Other Types of NSCLC Harboring *MET* Exon 14 Skipping Mutations[1]

- **Savolitinib (AZD6094)** is a highly selective oral MET tyrosine kinase inhibitor; its antitumor activity has been shown in combination with osimertinib in patients with *EGFR*-mutant, *MET*-amplified NSCLC[2]
- **Phase 2 study (NCT02897479):** savolitinib in patients with unresectable or metastatic *MET*ex14+ PSC and other NSCLC

Efficacy Evaluable Set	IRC (N = 61)	Investigator (N = 62)
Confirmed PR	30 (49.2)	32 (51.6)
SD	27 (44.3)	25 (40.3)
PD	4 (6.6)	5 (8.1)
Interim ORR, % (95% CI)	49.2 (36.1-62.3)	51.6 (38.6-64.5)
Interim DCR, % (95% CI)	93.4 (84.1-98.2)	91.9 (82.2-97.3)
Interim DOR,[a] mo (95% CI)	9.6 (5.5-NR)	6.9 (5.0-NR)



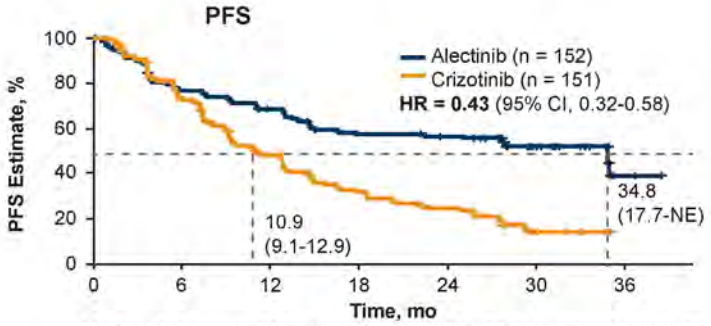


[a] DOR maturity: 40% and 40.6% by IRC and investigator assessment, respectively.

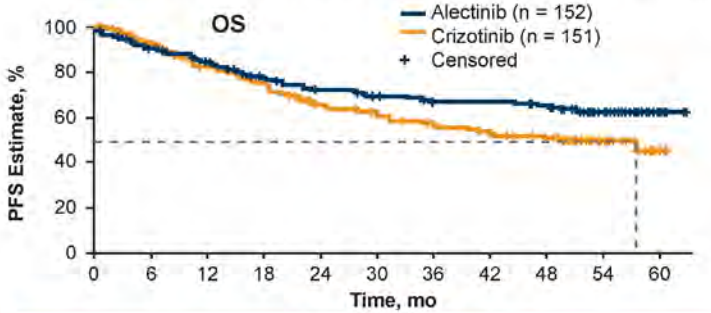
1. Lu S et al. ASCO 2020. Abstract 9519. 2. Yu H et al. 2019 American Association for Cancer Research (AACR) Annual Meeting. Abstract CT032.

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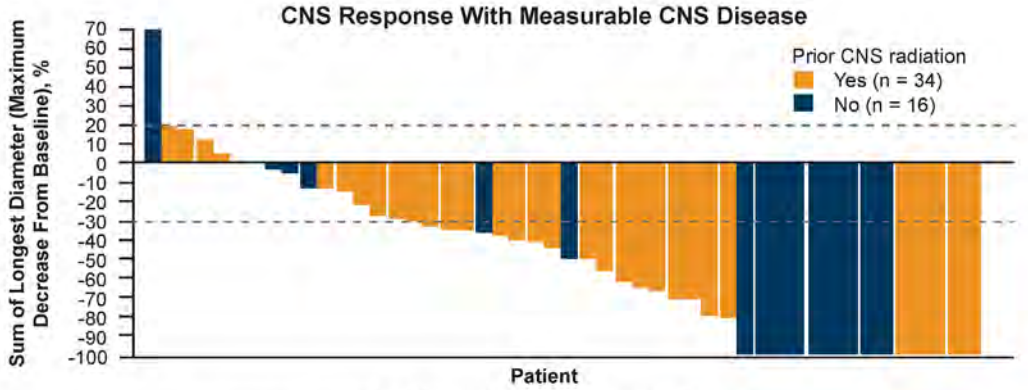
ALK Inhibitor: Alectinib (ALEX Trial)[1-5,a]

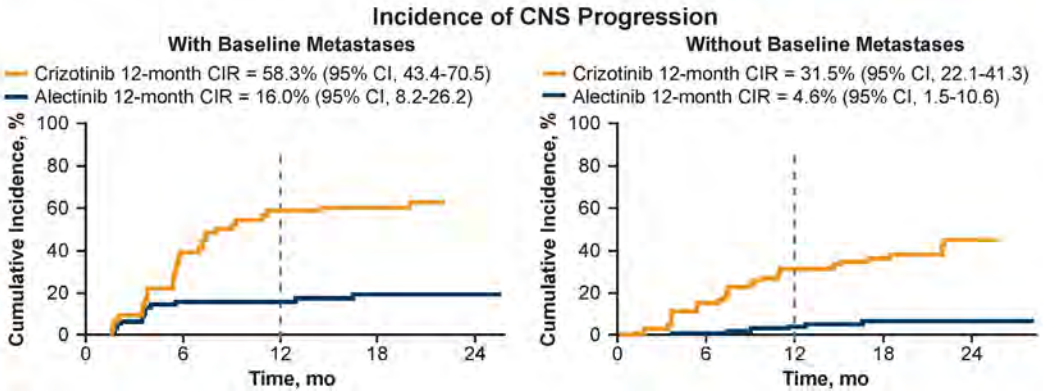


Median follow-up: 27.8 months (alectinib), 22.8 months (crizotinib)



ASCO 2020 Update:
5-y OS, 62.5% (95% CI, 54.3-70.8) with alectinib vs 45.5% (95% CI, 33.6-57.4) with crizotinib



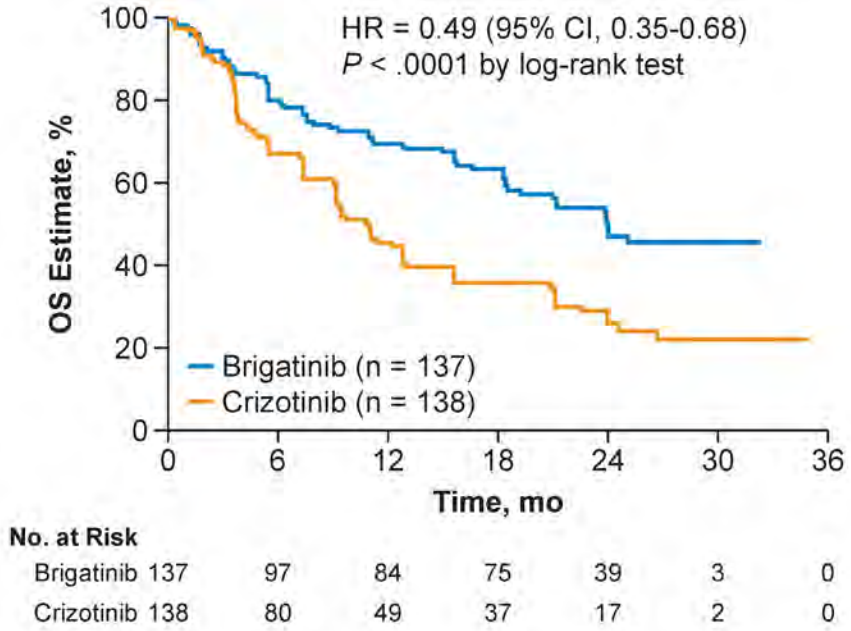


[a] ALEX study is the first to include prospective CNS assessments for all patients. 1. Camidge DR et al. ASCO 2018. Abstract 9043. 2. Gadgeel S et al. *J Clin Oncol.* 2016;34:4079-4085. 3. Peters S et al. *N Engl J Med.* 2017; 377:829-838. 4. Gadgeel S et al. *Ann Oncol.* 2018;29:2214-2222. 5. Peters S et al. ASCO 2020. Abstract 9518.

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ALK Inhibitor: Brigatinib (ALTA Trial)[1]

Primary Endpoint: BIRC-Assessed PFS



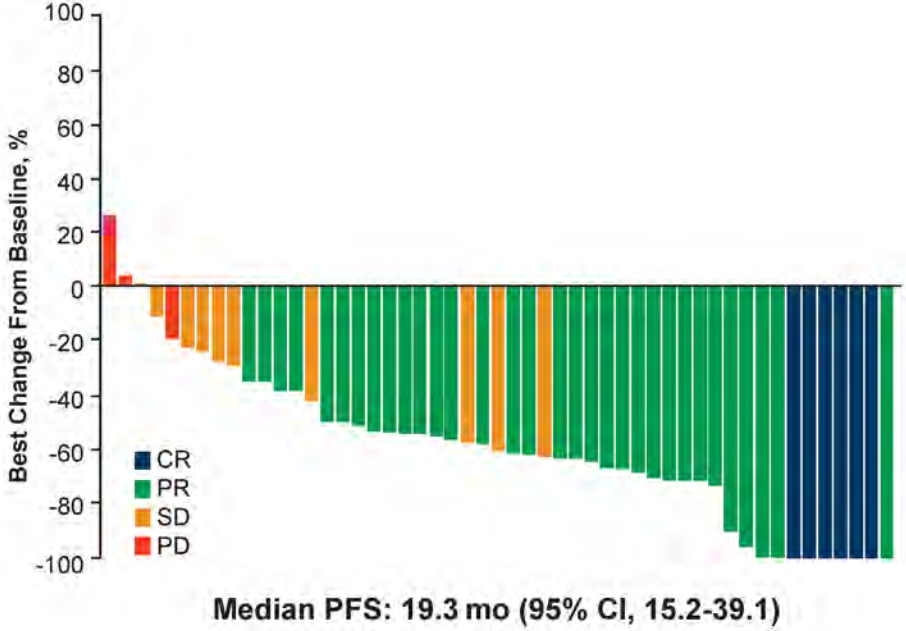
Treatment	Patients With Events, No. (%)	Median PFS (95% CI)	2-Year PFS, % (95% CI)
Brigatinib (n = 137)	63 (46)	24.0 mo (18.5-NR)	48 (39-57)
Crizotinib (n = 138)	87 (63)	11.0 mo (9.2-12.9)	26 (18-35)

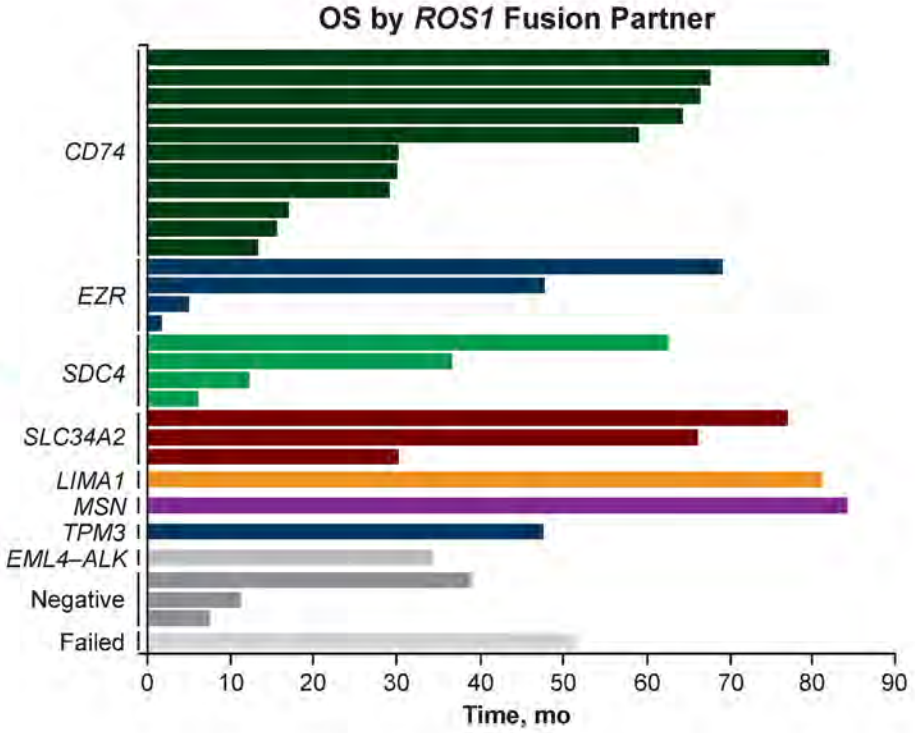
May 22, 2020: Brigatinib received FDA approval for 1L treatment of *ALK*+ NSCLC based on ALTA-1L (brigatinib vs crizotinib) showing PFS HR = 0.49, ORR 74%, and intracranial RR 78%

1. Camidge DR et al. ESMO Asia Congress 2019. Abstract LBA1.

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ROS1 Inhibitor: Crizotinib (PROFILE 1001 Trial)[1]



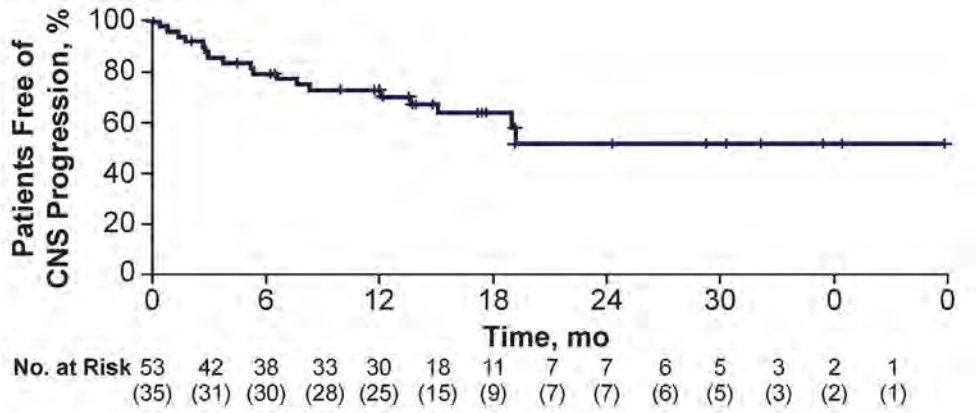


1. Shaw AT et al. *Ann Oncol.* 2019;30:1121-1126.

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ROS1 Inhibitor: Entrectinib (ALKA + STARTRK-1 + STARTRK-2 Trials)[1]

Integrated analysis of 53 patients with *ROS1* fusion–positive NSCLC enrolled in ALKA-372-001, STARTRK-1, and STARTRK-2



Endpoint	Integrated Dataset[a] (N = 53)
ORR, %	77
mPFS, mo	19
mDOR	24.6
Intracranial ORR, %	55
mPFS in patients with brain metastases	13

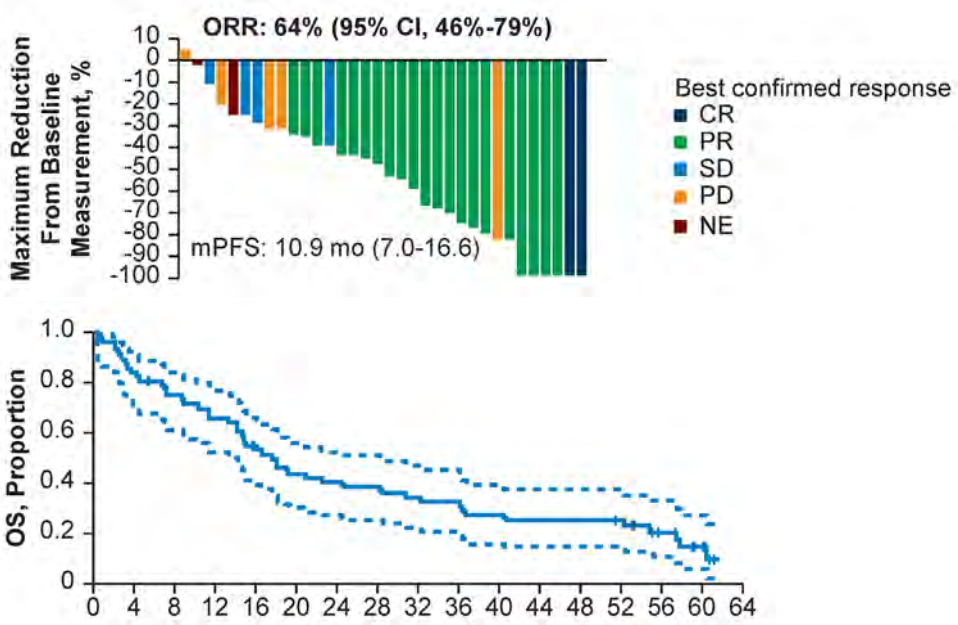
[a] Integrated analysis of data from the global multicenter trials (ALKA, STARTRK-1, STARTRK-2) in patients with *ROS1* fusion-positive NSCLC previously untreated with a ROS1 TKI.

1. Doebele R et al. WCLC 2018. Abstract OA02.01.

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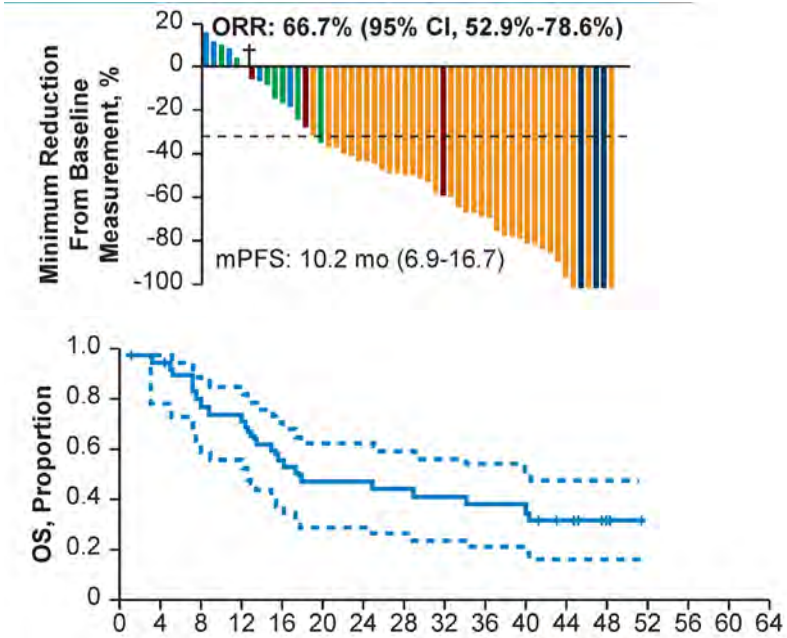
BRAF V600E Inhibitor: Dabrafenib + Trametinib (BRF113928 Trial)[1-4]

Treatment-Naïve Patients



mOS, 17.3 mo [(95% CI, 12.3-40.2); 3 y OS, 40%]

Pretreated Patients



mOS, 18.2 mo [(95% CI, 14.3-28.6); 3 y OS, 33%]

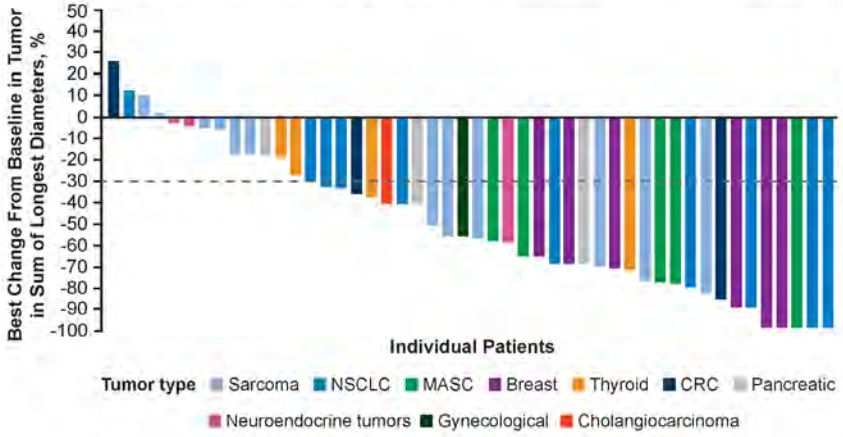
1. Planchard D et al. *Lancet Oncol*. 2017;18:1307-1316. 2. Planchard D et al. *Lancet Oncol*. 2016;17:984-993. 3. Planchard D et al. *J Clin Oncol*. 2017;35(suppl):abstr 9075. 4. Planchard D et al. ASCO 2020. Abstract 9593.

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TRK Inhibitors: Entrectinib and Larotrectinib[1,2]

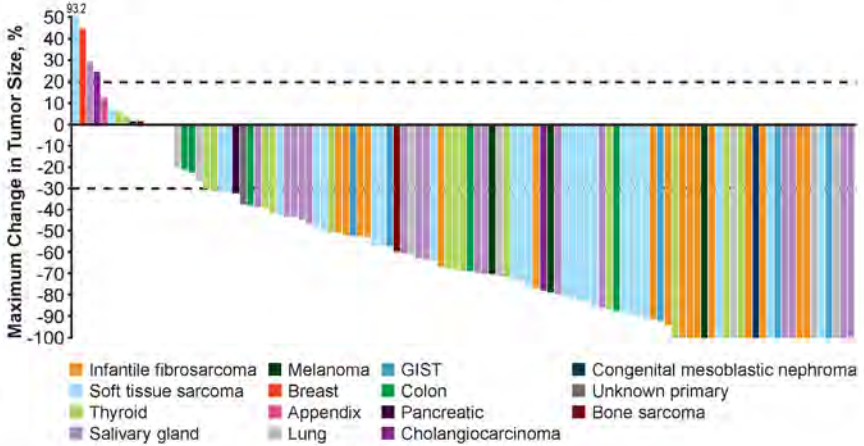
Entrectinib

	NTRK+ All Patients (n = 54)
ORR (95% CI), %	57.4 (43.21-70.77)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD, missing or unevaluable	10 (18.5)



Larotrectinib

	Integrated (n = 109)
ORR, % (95% CI)	81 (72-88)
Best response, %	
PR	63
CR	17

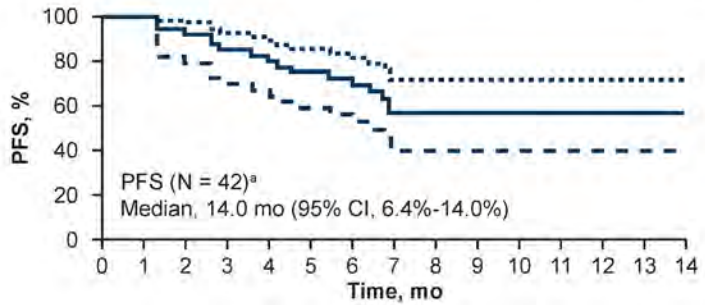


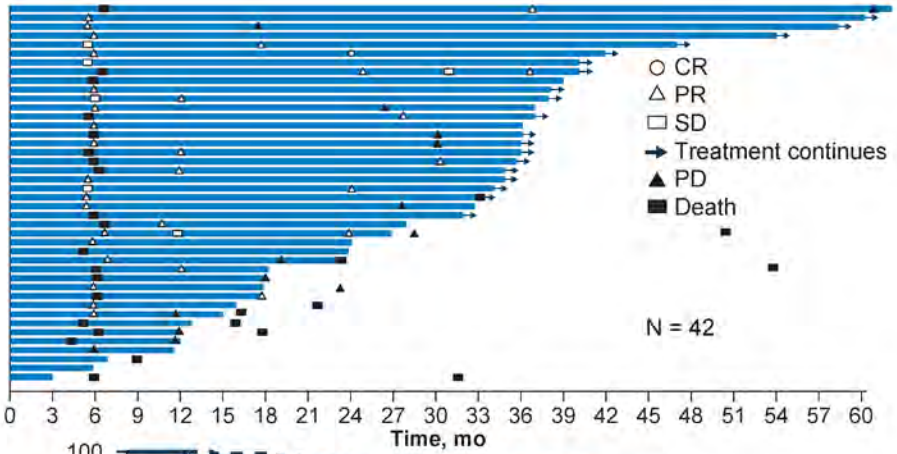
1. Demetri G et al. European Society for Medical Oncology (ESMO) 2018 Congress. Abstract LBA17. 2. Lanssen U et al. ESMO 2018. Abstract 409O.

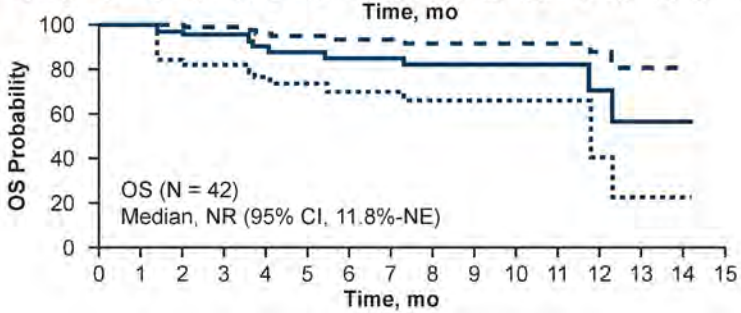
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HER2 Inhibitor: [Fam-] Trastuzumab Deruxtecan (DESTINY-Lung01 Trial)[1]

Confirmed ORR By ICR	Patients (N = 42) 61.9% (n = 26) (95% CI, 45.6%-76.4%)
CR	2.4% (n = 1)
PR	59.5% (n = 25)
SD	28.6% (n = 12)
PD	4.8% (n = 2)
NE	4.8% (n = 2)
DCR	NR (95% CI, 5.3 mo-NE)
DOR, median	NR (95% CI, 5.3 mo-NE)
PFS, median	14.0 mo (95% CI, 6.4-14.0 mo)





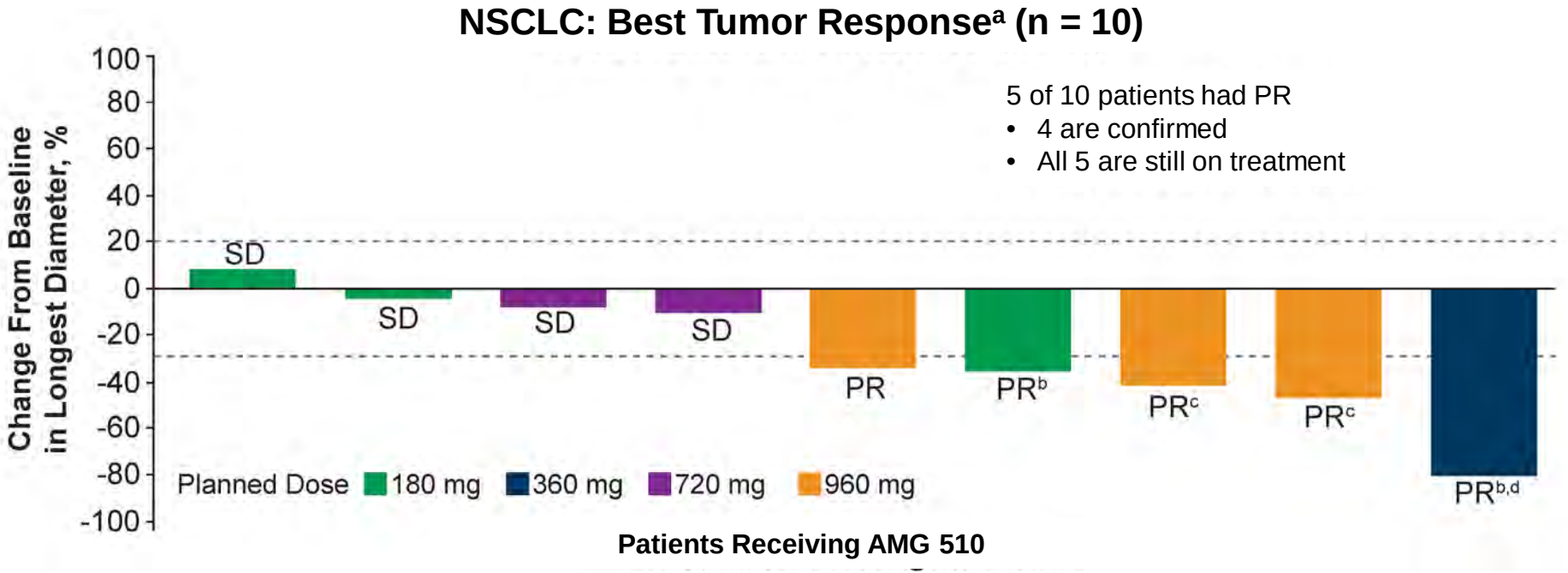


[a] Patients were censored if they discontinued treatment; the median is estimated by Kaplan–Meier analysis. Median follow-up, 8.0 months (1.4-14.2). Dashed lines indicate upper and lower 95% CI.

1. Smit EF et al. ASCO 2020. Abstract 9504.

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KRAS G12C Inhibitor: AMG 510 (CodeBreak Trial)[1]



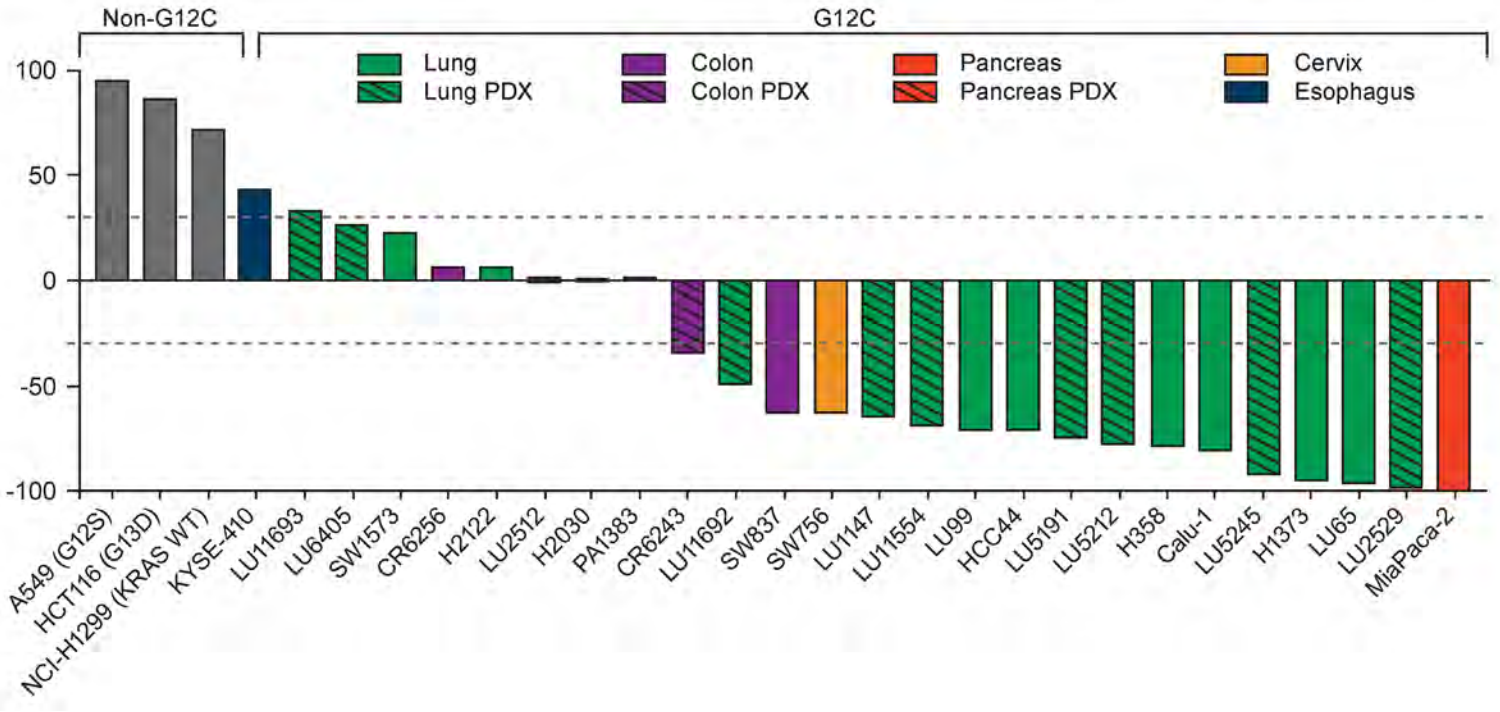
[a] Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria. One patient had clinical progression before week 6 and is not in this graph.
[b] Confirmed response. [c] Two additional patients had confirmed PR post data cutoff. [d] Patient had a CR of the target lesions at week 18, post data cutoff.

1. Govindan R et al. ESMO 2019. Abstract 446PD.

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KRAS G12C Inhibitor: MRTX849[1]

Tumor Assessment on Day 22 of Oral, Daily Dosing of MRTX849 (100 mg/kg)



1. Papadopoulos K et al. ASCO 2019. Poster 3161.

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Other Novel KRAS Inhibitors: Trials Enrolling

- **LY3499446:** a selective, covalent KRAS G12C inhibitor

  – A phase 1/2 study is underway of LY3499446 administered to patients with advanced solid tumors (including NSCLC) with KRAS G12C mutation (NCT04165031)[1]

- **JNJ-74699157**

  – A first-in-human study of the safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of JNJ-74699157 in participants with advanced solid tumors harboring the KRAS G12C mutation (NCT04006301)[2]

1. https://clinicaltrials.gov/ct2/show/NCT04165031. 2. https://clinicaltrials.gov/ct2/show/NCT04006301.

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Setting the Stage for the Testing Discussion

- Therapeutic options for lung cancer patients have been rapidly expanding over last 10 years
  - – Targeted therapies comprise the majority of new treatment options
  - – In patients with NSCLC with molecular alterations, therapies aimed at these targets are associated with better treatment outcomes—higher response rates and improved quality of life

But…

- Suboptimal testing rates; suboptimal use of targeted therapies even when testing is carried out, especially in community settings
- Barriers to successful widespread application of comprehensive genomic testing in community-based and academic cancer care settings

How can we overcome the existing unmet needs and barriers to broad-based implementation of genomic testing in lung cancer?

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Who Needs to Undergo Molecular Testing?

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Who Needs to Be Tested?

- Disease stage: Only test patients with advanced (stage IV) disease?
- Age: Only test younger patients?
- Histology: Only test adenocarcinoma?
- Smoking history: Only test nonsmokers?

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All Histologies Need to Be Tested

- Metastatic, nonsquamous, NSCLC—absolute standard of care: test every patient
- Adenosquamous NSCLC: test every patient
- Test all nonsmokers and light smokers with squamous and small-cell histologies
- Genetic alterations are found in squamous NSCLC with NGS[1]
- Targetable mutations are also found in sarcomatoid carcinomas[2,3]

NGS conducted on tumors of 7 patients with pulmonary sarcomatoid carcinomas (PSC)[2]

- 136 putative somatic variants and 1 gene fusion were identified
  - 16 variants were considered hot spot mutations: *EGFR*, *EML4-ALK*, *MET*, *BRAF*, *PIK3CA*, and *TP53*
  - *EML4-ALK* fusion and *EGFR* exon 19 deletion were confirmed by Ventana IHC
- Molecular-targeted therapy may be a useful treatment strategy for PSC with targetable alterations

Prevalence of *MET* ex14 skipping mutation investigated with NGS in 46 resected PSC patients without common targetable mutations in *EGFR*, *KRAS*, *ALK*, *ROS1*, and *RET*3

- *MET* ex14 skipping mutation was present in 4 patients (9%)

1. Sands JM et al. *Lung Cancer*. 2020;140;35-41. 2. Li X et al. *Sci Rep*. 2017;7:3947. 3. Yu Y et al. *J Cancer Res Ther*. 2019;15:909-913.

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Targeted Therapies Potentially Moving to Early-Stage NSCLC: Should We Be Testing Earlier?

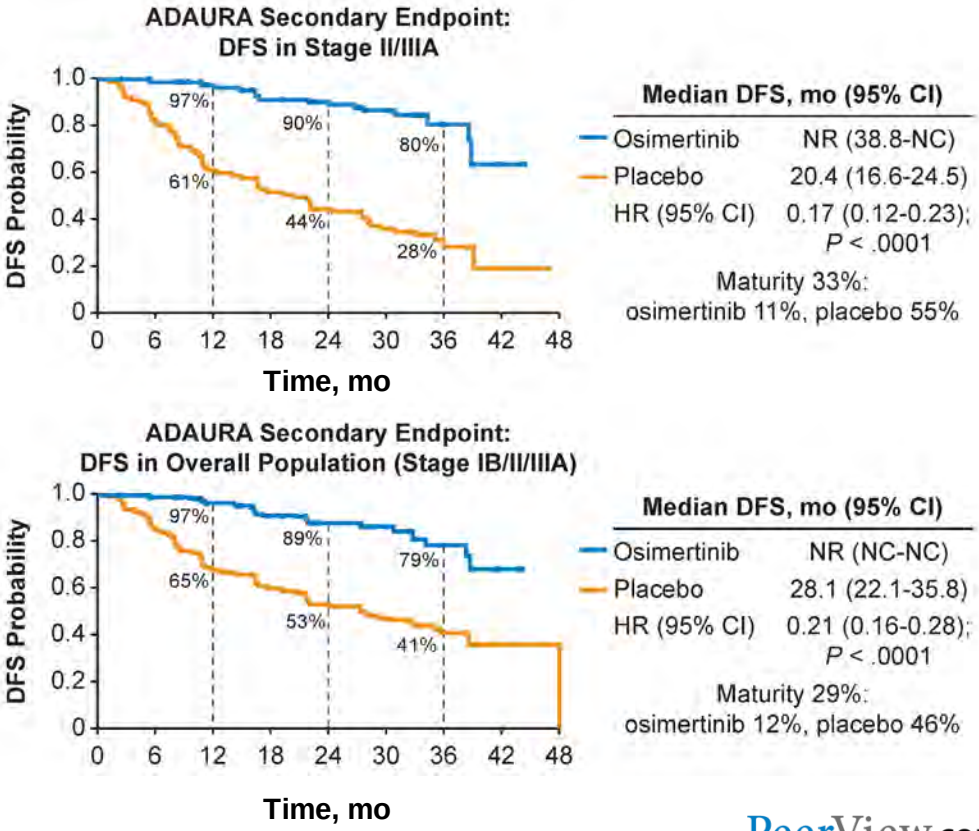
- **ADAURA1:** phase 3 trial in the adjuvant treatment of 682 patients with stage IB, II, IIIA *EGFR*mut NSCLC with complete tumor resection and optional, standard postoperative adjuvant chemotherapy; in the experimental arm, patients were treated with osimertinib for 3 years or until disease recurrence

  – Based on efficacy findings, study to be unblinded early under recommendation from an independent data monitoring committee

  – Plans for regulatory submission are under way for osimertinib based on these findings

- **Other early-stage trials under way: A**djuvant **L**ung **C**ancer **E**nrichment **M**arker **I**dentification and **S**equencing **T**rials (**ALCHEMIST**), a group of randomized clinical trials for patients with early stage resected/resectable NSCLC (NCT02194738)

- ***Potential implications for testing and treatment?***

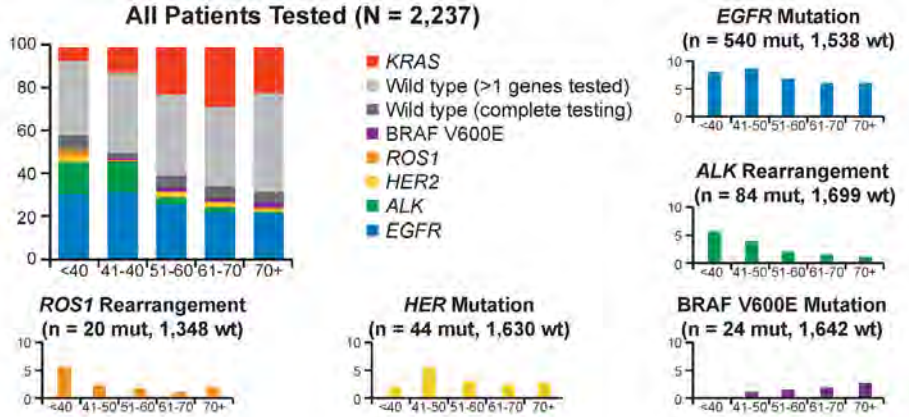


1. Herbst R. ASCO 2020. Abstract LBA5.

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Young and Old, Smokers and Nonsmokers: All Need to Be Tested

Relationship Between Age at Diagnosis and the Presence of a Targetable Genomic Alteration[1,2]



- *EGFR* mutations, *ALK* rearrangements, *ROS1* rearrangements, and *HER2* exon 20 insertions more common among young patients and frequency steadily decreases with age
- *KRAS*, BRAF V600, *MET* exon 14–mutated appear more common among older patients

Smokers With Genomic Alterations Derive Same Benefit From Targeted Therapy as Nonsmokers[3-6]

- 60 patients with a history of smoking derived similar survival benefit from targeted therapy for alterations in *EGFR/ALK/ROS1* when compared with 75 never smokers with the same alterations
- Preclinical study found that cigarette smoke augments oncogene addiction to cMET in NSCLC cells
  - MET inhibitors may show clinical benefits for lung cancer patients with a smoking history
- Although *EGFR*, *ALK*, *RET*, and *ROS1* NSCLC is more common in never smokers, *BRAF* and *KRAS* mutations are found in patients with and without a smoking history

1. Sacher AG et al. *JAMA Oncol*. 2016;2:313-320. 2. Awad MM et al. *J Clin Oncol*. 2016;34:721-730. 3. Aisner DL et al. *Clin Cancer Res*. 2017;24:1038-1047.
4. Tu CY et al. *Mol Oncol*. 2018;12:705-723. 5. Litvak AM et al. *J Thorac Oncol*. 2014;9:1669. 6. Riely GJ et al. *Clin Cancer Res*. 2008;14:5731-5734.

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How to Test for Genomic Alterations?

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How to Test for Genomic Alterations?

- One at a time vs NGS?
- DNA vs RNA?
- Tumor, liquid, or both?
- Only at initial diagnosis or at disease progression also?

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Which Molecular Testing Techniques to Use?[1]

	EGFR (sensitizing and T790M)	*HER2* Mutation	*MET* Exon 14 Mutation	*BRAF* Mutation	*KRAS* Mutation	*ALK* Rearrangement	*ROS1* Rearrangement	*MET* Amplification	*RET* Rearrangement	PD-L1 Protein Expression	*NTRK* Fusion
Tissue PCR sequencing	+	+	–	+	+	–	–	–	–	–	–
Tissue allele–specific PCR sequencing	++	++	++	++	++	–	–	–	–	–	–
Tissue FISH	–	–	–	–	–	++	++	++	++	–	++
Tissue IHC	–	–	–	–	–	++	–	–	–	++	+
Tissue NGS	++	++	++	++	++	+	+	+	+	–	+
ctDNA PCR	+	+	+	+	+	+	–	–	+	–	–
ctDNA NGS	+	+	+	+	+	+	+	+	+	–	+
Tissue RNA	+	+	++	+	+	++	++	+	++	–	++

++: Highest sensitivity +: Lower sensitivity (higher chance of false negative) –: Not useful

1. https://www.uptodate.com/contents/personalized-genotype-directed-therapy-for-advanced-non-small-cell-lung-cancer.

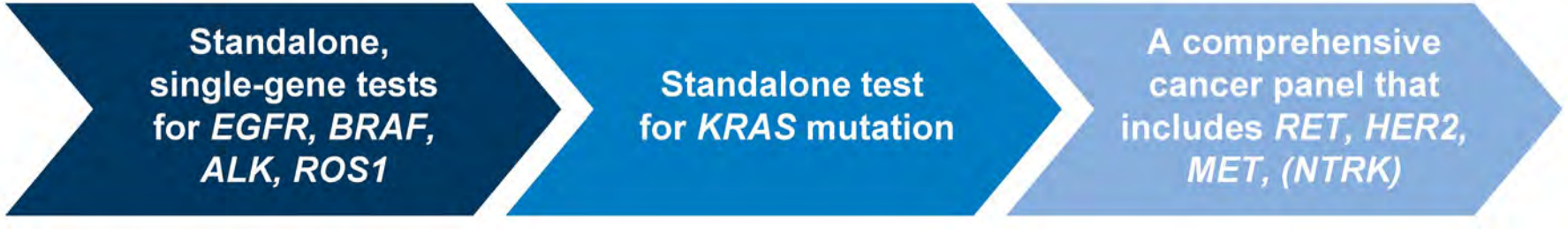
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One Test at a Time vs NGS?[1]

Institutions providing care for patients with lung cancer have a choice:

A comprehensive cancer panel that includes *EGFR, BRAF, ALK, ROS1, RET, HER2, KRAS, MET, NTRK*

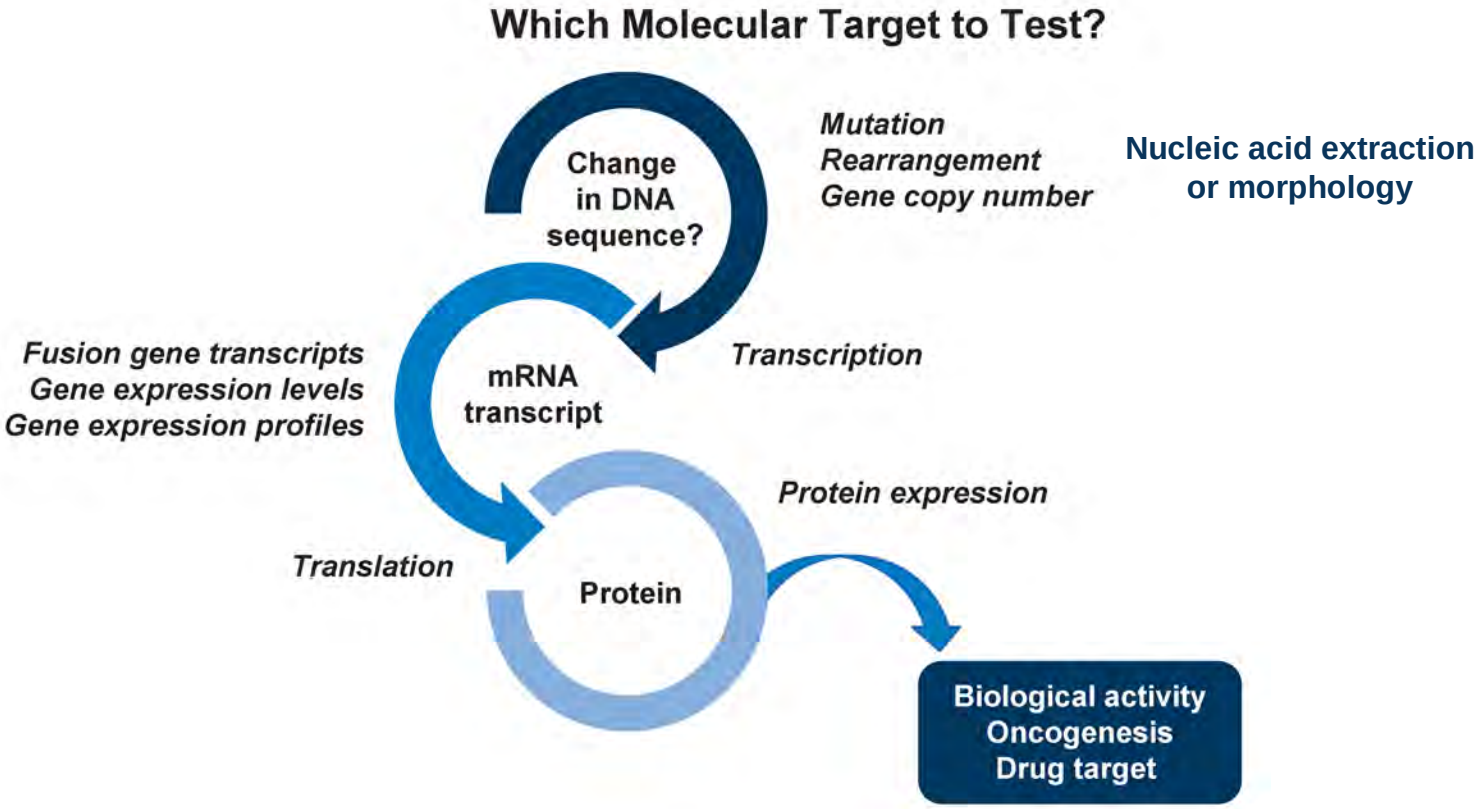
OR



1. Lindeman NI et al. *J Thorac Oncol.* 2018;13:323-358.

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DNA vs RNA?



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Limitations of NGS

- Mutations? (*EGFR*, *BRAF*, *MET* exon 14, *HER2*)
  - ✓ *Yes*
- Fusion genes? (*ALK*, *ROS1*, *NTRK*, *RET*)
  - ✓ *Probably but…*
- Gene amplification? (*MET*)
  - ✓ *Probably not yet…*
- Protein expression?
  - ✓ *No*

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Lung Cancer Genotyping: Tissue vs Plasma

- Tumor biopsies involve multiple steps:



- Liquid biopsies (plasma genotyping) involve fewer steps:



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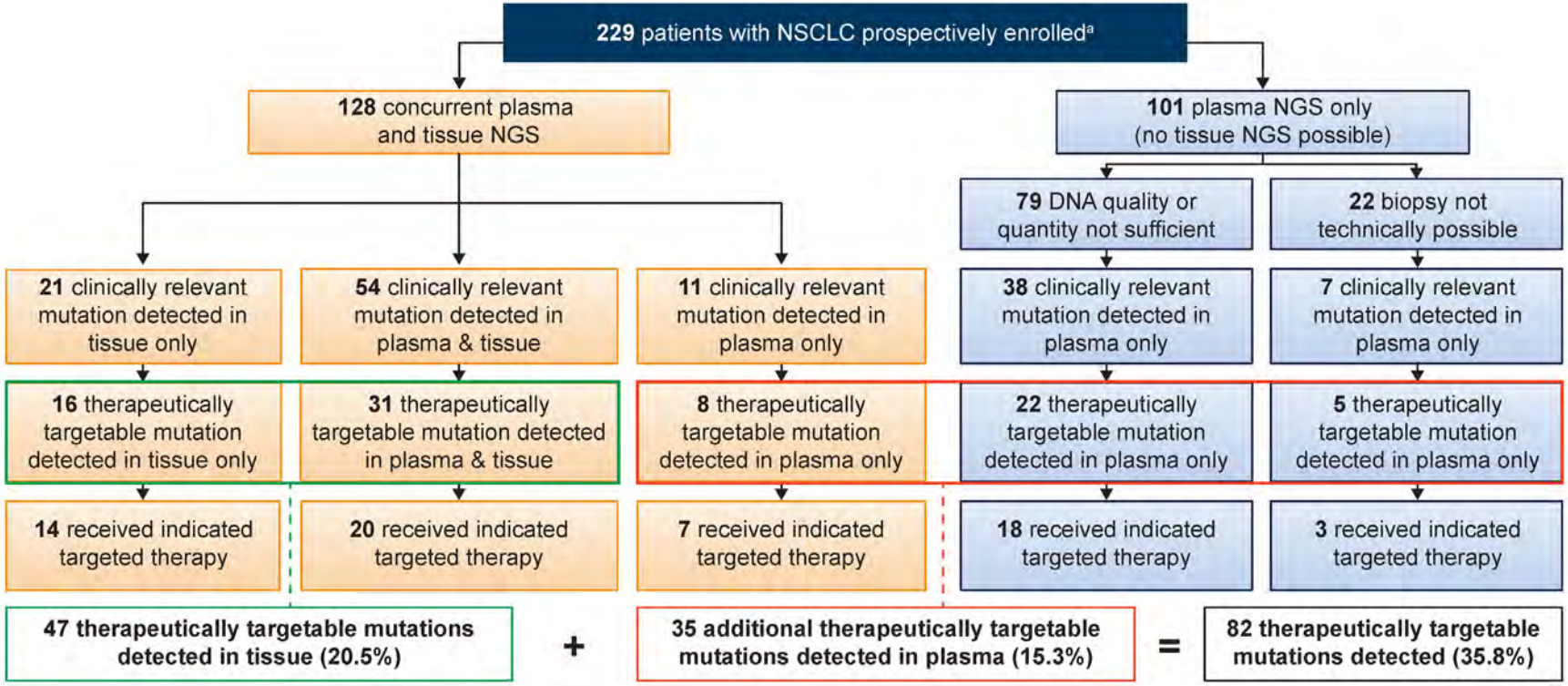
Plasma ctDNA Testing in Patients With Advanced NSCLC

- With high positive predictive value but imperfect sensitivity, plasma ctDNA genotyping is best used
  - As a screening test when tumor is unavailable
  - With reflex to tumor biopsy when negative
  - In patients in whom tumor DNA shed into plasma is more likely (eg, not for tiny lung nodules, early stage cancers, etc.)
- Simultaneously adding plasma ctDNA analysis to tissue testing in treatment-naïve patients can enhance the chances of detecting a relevant actionable mutation[1,2]
- Plasma-based testing is indicated for all patients with advanced-stage, treatment-naïve lung cancer for whom tissue sampling may be infeasible or insufficient[3]
- Plasma ctDNA testing is also useful to look for resistance mutations in the progressive disease setting[4]

1. Aggarwal C et al. *JAMA Oncol*. 2019;5:173-180. 2. Leighl NB et al. *Clin Cancer Res*. 2019;25:4691-4700. 3. NCCN Clinical Practice Guidelines in Oncology. Non–Small Cell Lung Cancer. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. 4. Oxnard GR et al. *J Clin Oncol*. 2016;34:3375-3382.

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Clinical Implications of Plasma ctDNA Testing in Metastatic NSCLC[1]



[a] Patients were either enrolled at time of initial diagnosis or at disease progression.

1. Aggarwal C et al. *JAMA Oncol.* 2019;5:173-180.

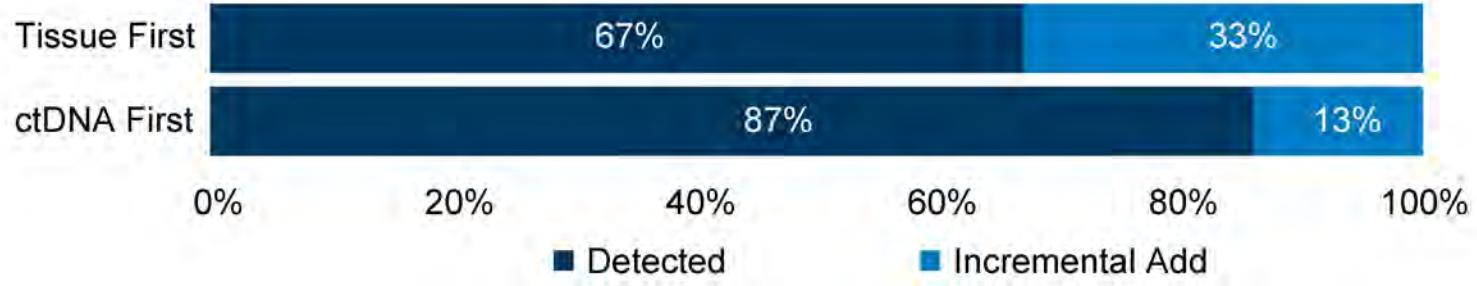
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NILE Study: Comparison of ctDNA to Tissue Genotyping[1]

Genomic Biomarker Positivity by Sample Type

Guideline-recommended biomarker positivity by sample type		Tissue		
		Positive	Negative	Total
ctDNA	Positive	48	29	**77**
	Negative	12	193	**205**
	Total	**60**	**222**	**282**

Percentage of Guideline-Recommended Biomarker Detected by Testing Modality



1. Leighl NB et al. *Clin Cancer Res*. 2019;25:4691-4700.

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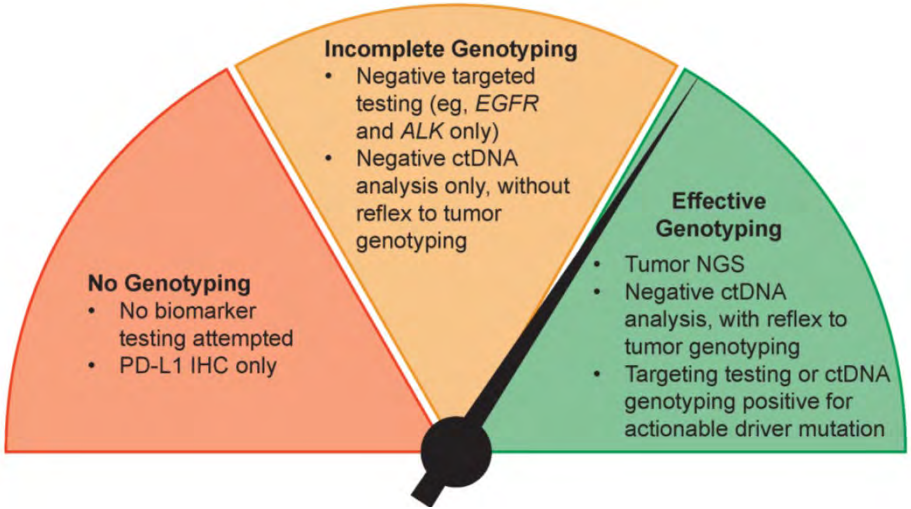
Best Practices For Molecular Testing in Patients With Advanced NSCLC

- Selecting an assay
  - – Make sure the test can detect gene fusions and other alterations in addition to mutations
  - – Consult and collaborate with your pathologists
- When to perform molecular testing
  - – All treatment-naïve patients should undergo genomic testing
  - – New tissue biopsy- and/or plasma-based test needs to occur when patients develop resistance/disease progression
- Communicate with colleagues who perform biopsies about the necessity of acquiring as much tissue as possible for DNA testing

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Achieving Effective Lung Cancer Genotyping[1]

- The availability of NGS assays with a high PPV means that, today, no patients with advanced NSCLC should receive no molecular testing or PD-L1 testing only, but the limitations of our genotyping assays must be recognized if we wish to avoid incomplete genotyping



- Targeted assays for common driver mutations can take time and exhaust tissue, making it harder to then test for rarer driver mutations if negative
- ctDNA analysis has imperfect sensitivity such that targetable driver mutations can be missed; these more limited assays can be useful if positive, but further testing must be pursued if they are negative

To offer our patients effective genotyping, the most reliable approaches involve either a panel-based assay tested on a high-quality tissue biopsy or ctDNA analysis first, followed by reflex totumor genotyping if the "liquid biopsy" is negative for a targetable driver mutation

1. Meador CB, Oxnard GR. *Clin Cancer Res*. 2019;25:4583-4585.

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Audience Q&A



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Please remember to complete and submit your Post-Test and Evaluation for CME/MOC/CC/CNE/CPE credit.

PeerView.com/NSCLC-Survey-NEN

Thank you and have a good day.

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Abbreviations

AE: adverse event

ARMS: amplification refractory mutation system

ATP: adenosine triphosphate

BID: twice daily

BIRC: blinded independent review committee

cfDNA: cell-free DNA

CR: complete response

CRC: colorectal cancer

ctDNA: circulating tumor DNA

DCR: disease control rate

DOR: duration of response

FFPE: formalin-fixed paraffin-embedded

FISH: fluorescence in situ hybridization

GIST: gastrointestinal stromal tumors

ICI: immune checkpoint inhibitor

IFCT: French Cooperative Thoracic Intergroup

IHC: immunohistochemistry

IR: interventional radiology

IRC: independent review committee

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Abbreviations (cont'd)

LBx: liquid biopsy test (maybe correct; see Slide 31)

MASC: mammary analogue secretory carcinoma

mDOR: median duration of response

mOS: median overall survival

mPFS: median progression-free survival

mRNA: messenger RNA

MTD: maximum tolerated dose

NE: not evaluable

NGS: next-generation sequencing

NR: not reached

NSCLC: non–small cell lung cancer

ORR: objective response rate

Pap: Papanicolaou

PCR: polymerase chain reaction

PD: progressive disease

PD-1: programmed cell death protein 1

PD-L1: programmed cell death ligand 1

PDX: patient-derived xenograft

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Abbreviations (cont'd)

PFS: progression-free survival

PPV: positive predictive value

PR: partial response

QoL: quality of life

RECIST: Response Evaluation Criteria in Solid Tumors

SCLC: small cell lung cancer

SD: stable disease

SOC: standard of care

TKI: tyrosine kinase inhibitor

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