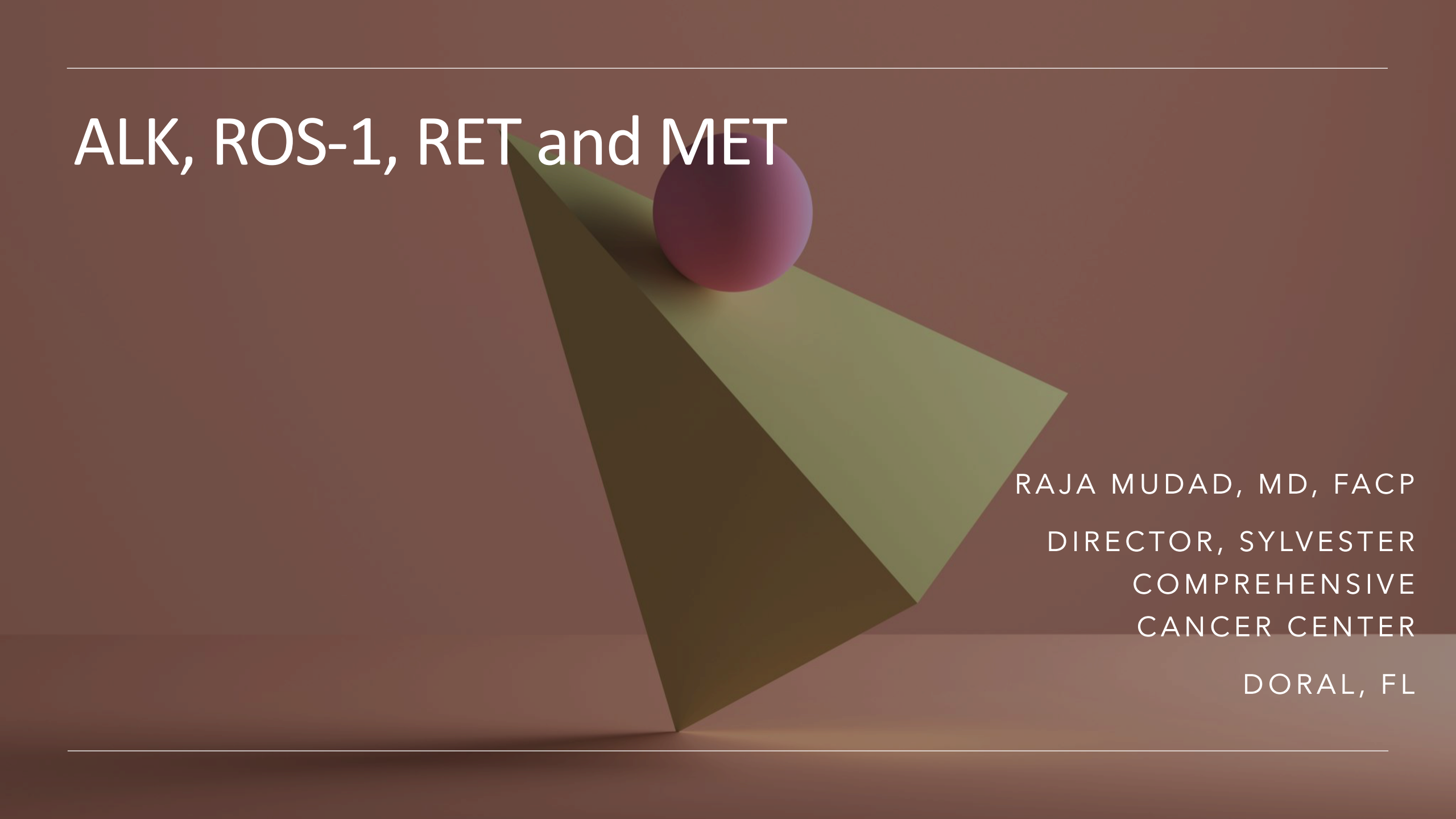
ALK, ROS-1, RET and MET



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ROS 1

Facts

- There is homology between ROS1 and ALK oncogenes
- Both are activated by gene rearrangements in NSCLC
- Both ROS1 and ALK belong to the insulin receptor superfamily
- They are evolutionary conserved
- They share >80% of their amino acid sequence within their ATP-binding sites
- TKIs often are active in both

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ROS1 epidemiology

- In non—small cell lung cancer (NSCLC), the incidence of *ROS1* rearrangements is approximately 1% to 2%
- It ranges from 2.4% to 2.9% in the adenocarcinoma subtype, being substantially lower (0.2%-0.6%) in non-adenocarcinoma tumors
- *ROS1* rearrangements are more prevalent in females, patients without smoking history, and at a younger age
- Unlike other genomic alterations, *ROS1* rearrangements do not correlate with worse prognosis

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ROS1 epidemiology

- Patients with *ROS1*-positive tumors have from 2.5- to 5-fold higher risk for thromboembolic events compared with EGFR or KRAS
- To date, 23 different *ROS1* fusion variants have been identified in NSCLC, *CD74-ROS1* being the most common occurring in up to 50% of cases
- The exact mechanism of ROS1 kinase activation in the fusion proteins has not been established
- ROS1 signaling mainly relies on ERK, PI3K/mTOR and JAK-STAT intracellular pathways
- The incidence of baseline brain metastases (BM) in treatment-naïve advanced *ROS1*-positive NSCLC patients ranges from 20% to 35%

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ROS1 epidemiology and detection

- Methods to detect *ROS1* fusion variants include immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR) and next-generation sequencing (NGS)
- IHC is recommended as initial *ROS1* screening, followed by FISH or a molecular test for confirmation
- Only one-third of *ROS1*-positive patients receive a TKI in first-line setting

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Current therapeutic strategy

- Several ROS1 tyrosine kinase inhibitors (TKIs) have been developed
- Two are already approved in the first-line setting: crizotinib (approved by both the Food and Drug Administration [FDA] and European Medicines Agency [EMA] in 2016) and entrectinib (approved by the FDA in 2019)
- Treatment with ROS1 TKIs in *ROS1*-positive NSCLC patients significantly improves OS
- Upfront ROS1 TKIs produce a better response rate (RR) and progression-free survival (PFS) than platinum-pemetrexed chemotherapy

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Shen L et al. JCO 201937.15 Supp.9101

Crizotinib

- Crizotinib showed a RR of 72%, median PFS of 19.3 months, and median OS of 51.4 months, with a 4-year OS of 51% (PROFILE 1001 study) confirmed by other trials
- Crizotinib showed a benefit in patient-reported quality of life (QoL) and a reduction in patient-reported lung cancer-related symptoms
- Poor CNS penetration
- Two main mechanisms of crizotinib failure exist:
  - On-target mutation –systemic failure
  - Progression in the central nervous system
- CNS is the first and only site of progression in 47% of *ROS1*-positive patients on crizotinib

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Shaw et al. N Engl J Med 2014;371: 1963–71

Mechanisms of acquired resistance to crizotinib

- Acquired *ROS1* resistance mutations occur in up to 60% of crizotinib-refractory patients
- To date, seven different crizotinib *ROS1* resistance mutations have been described in patient
- G2032R is the most common (41%)
- Other mechanisms of resistance are
  - Upregulation of bypass signaling pathways, such as *EGFR*, *KRAS* and *KIT*
  - Phenotypic changes, such as epithelial-mesenchymal transition (EMT)

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Gainor JF et al. JCO Precis. Oncol 2017;2017.

Mechanisms of acquired resistance to crizotinib

- Circulating tumor DNA (ctDNA) analysis is a useful tool to identify mechanisms of acquired resistance to ROS1 TKIs
- In the Guardant360 dataset, 56 ROS1 NSCLC patients were identified with ctDNA analysis, and 33% of plasma specimens at crizotinib relapse had ROS1 mutations
- ctDNA allowed the identification of potential mediators of crizotinib resistance in 44% of cases, with a frequency of secondary ROS1 mutations in plasma similar to that observed in tumor tissue

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Dagogo-Jack et al. J Thor Oncol 2019;14:816-24

Ceritinib

- Ceritinib is an ALK and ROS1 TKI
- ASCEND-4 trial: Ceritinib vs.chemotherapy
  - PFS 16.6 mo vs. 8.1 mos
- RR of 67%, median PFS of 19.3 months, and median OS of 24 months
- About 37% of patients presented grade ≥ 3 TRAEs, requiring dose reduction in 68% of cases, and the GI toxicity limits the use of this drug in daily clinical practice
- Recently, in the final report from the ASCEND-8 trial, ceritinib at 450 mg with food vs 750 mg fasted showed similar efficacy (RR 78% vs 73%, regardless the presence or absence of brain metastases) and a more favorable gastrointestinal tolerability

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Soria JC et al. Lancet 2017:389:917-29

Entrectinib

- Entrectinib is a potent TKI that promotes a durable and meaningful clinical benefit and intracranial activity in advanced ROS1-positive NSCLC patients and NTRK gene fusion-positive solid tumors
- RR of 77% and PFS of 19 months (26.3 mos with no brain metastases)
- The intracranial (ic)RR was 55%, and the median icPFS was 7.7 months
- The grade 3–4 TRAEs rate was 34%
- Approved in ROS1-positive patients, as well as adults and pediatric patients with NTRK-positive solid tumors
- KRAS G12C mutation causes entrectinib resistance in vitro and co-targeting ROS1 and MEK pathways is a proposed strategy to overcome this resistance

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Drilon A et al. Lancet Oncol 2020:21:261-70

Lorlatinib

- Selective third-generation ALK and ROS1 TKI specifically developed to penetrate the blood–brain barrier via the reduction of P-glycoprotein 1-mediated efflux
- RR in TKI-naïve patients is 62% vs 35% in pre-treated
- Median PFS is 21 months vs 8.5 mos
- The icRR of lorlatinib in TKI-naïve and crizotinib-pretreated patients is 64% and 50%, respectively
- Grade ≥ 3 TRAEs were registered in 49% of patients and were mainly grade 3–4, hypertriglyceridemia (19%) and hypercholesterolemia (14%)

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Shaw et al. Lancet Onco 2019:20:1691-701

Repotrectinib

- Repotrectinib is a ROS1/NTRK/ALK TKI, which can inhibit ROS1 with > 90-fold higher potency than crizotinib and designed to overcome the ROS1 G2032R mutation
- In 11 TKI-naïve ROS1-positive NSCLC patients, repotrectinib showed a RR of 82% (regardless of the dose) and icRR of 100%
- in 18 TKI-refractory patients the RR was 39% and reached 55% in crizotinib-pretreated patients at 160 mg

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Cho BC et al. LCO 2019:37:9011

DS-6051b

- DS-6051b is a new and selective ROS1/NTRK TKI, inducing a dramatic growth inhibition both in wild type and G2032R-mutant ROS1- or NTRK-rearranged cancers in vitro and in vivo
- In a phase I trial, among six crizotinib-refractory ROS1-positive NSCLC patients, 33% had partial response, 33% stable disease
- In another phase I trial, DS-6051b showed a RR of 58.3% in 12 patients with target lesions and of 66.7% in nine crizotinib-naïve patients

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Papadopoulos KP et al.JCO 2018.36:2514

Sequencing

- Sequential treatment strategies may impact patients' outcomes, although they remain to be defined in this subset since current evidence is derived from small cohorts
- The efficacy of lorlatinib in ROS1-positive tumors may be compromised by the previous ROS1 TKI and the occurrence of the G2032R mutation
- The efficacy of lorlatinib after a ROS1 TKI different than crizotinib is less prominent than after crizotinib (RR, 13% vs 35%; duration of response [DoR], 5.6 months vs 13.8 months)

Remon J, Pignataro D. et al: Cancer Treatment Reviews Volume 95 (April 2021) 102178
Shaw et al. Lancet Onco 2019:20:1691-701

Sequencing

- Repotrectinib showed preliminary clinical activity with response in 39% in 18 patients previously treated with a ROS1 TKI (crizotinib, ceritinib, entrectinib)
- Neither ceritinib nor entrectinib appear to be clinically active in crizotinib-resistant ROS1-positive tumors
- The crizotinib-lorlatinib sequence is emerging as a treatment strategy of choice, with an expected cumulated PFS of 28 months
- Lorlatinib does not seem to be superior to crizotinib in TKI-naïve patients, and the safety profile of crizotinib seems more favorable than that of lorlatinib
- This places crizotinib as the standard first-line treatment of choice for ROS1-positive advanced NSCLC patients

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Cho BC et al. LCO 2019:37:9011

Sequencing

- Lorlatinib is not active in tumors with the G2032R mutation
- DS-6051b and repotrectinib have been designed to overcome acquired solvent front mutations with a dramatic growth inhibition in G2032R/D2033N-mutant ROS1-positive cancers in vitro and in vivo
- Clinical data suggest that repotrectinib could be a potential treatment strategy in G2032R-mutant tumors (RR of 40%, N = 5) but more clinical evidence is needed
- The mechanisms of acquired progression on lorlatinib are
  - One-third acquiring ROS1 mutations
  - About 10% MET amplification

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Shaw et al. Lancet Onco 2019:20:1691-701

- Activity with or without brain metastases

Table 2. Clinical activity of ROS1 TKIs according to the presence or not of baseline brain metastases and the intracranial response rate.

TKI	RR (%)		PFS (months)		Intracranial RR (%)
	With BM	w/o BM	With BM	w/o BM	
Crizotinib [24]	74% N=23	71% N=104	10.2	18.8	NR
Ceritinib [34]	NR	NR	NR	NR	25% (N=8)
Entrectinib [37]	74% N=23	80% N=30	13.6	26.3	55% icDoR/PFS: 12.9/7.7 months
Lorlatinib [33] **in post-crizotinib**	25% N=24	50% N=16	NR	NR	50% icDoR: not reached

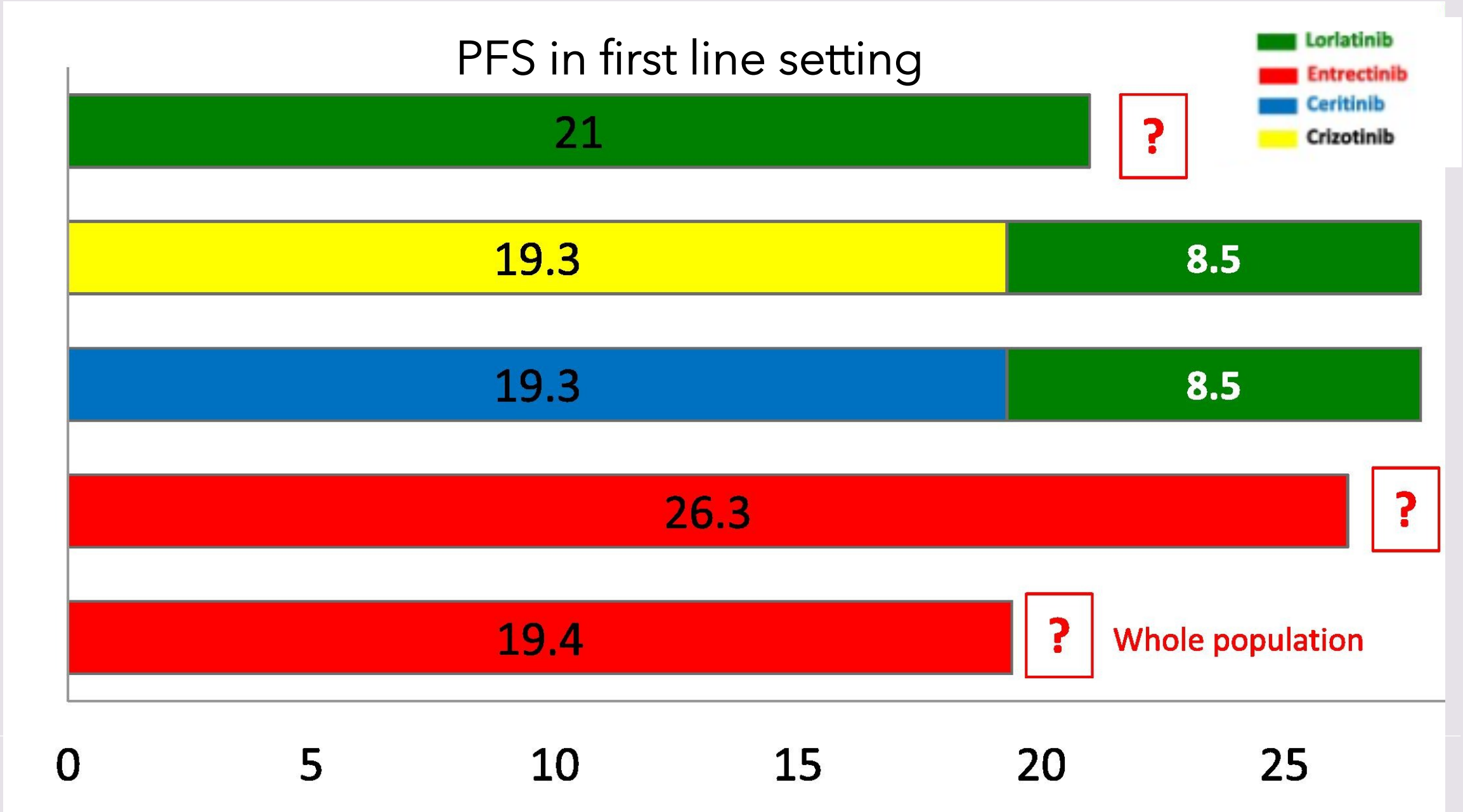
TKI, tyrosine kinase inhibitor; RR, response rate; PFS; progression-free survival; NR, not reported; icDoR/PFS: intracranial duration of response/progression-free survival; w/o, without.

- Activity and toxicity of ROS1 TKIs in treatment Naïve patients

Table 1. Clinical activity and toxicity of ROS1 TKIs in treatment-naïve advanced *ROS1*-positive NSCLC patients.

TKI	N	RR (%)	PFS (months)	OS (months)/1-y OS (%)	Grade 3–4 TRAE (%)	Discontinuation (%)
Crizotinib [22], [23]	53	72	19.3	51.4/79	36	0
Ceritinib [34]	30	67	19.3	24/56	37	3
Entrectinib [37]	53	77	19.0 (26.3 w/o BM)	NR/85	34	5
Lorlatinib [33]	21	62	21.0	NR	49	1
Repotrectinib [48]	10	82	NR	NR	12	2.4

TKI, tyrosine kinase inhibitor; RR, response rate; PFS; progression-free survival; OS, overall survival; TRAE, treatment-related adverse event; NR, not reported; w/o BM, without brain metastases.


PFS in first line setting
Lorlatinib
Entrectinib
Ceritinib
Crizotinib
21
?
19.3
8.5
19.3
8.5
26.3
?
19.4
?
Whole population
0
5
10
15
20
25

ALK

ALK epidemiology

- EML4-ALK rearrangements occur in about 3–8% of the overall NSCLC population
- Never/light smokers, younger age, and adenocarcinoma subgroups
- There are multiple (>15) EML4-ALK fusion variants (v),
  - v1 (40%),
  - v2 (10%)
  - v3a/b (30%)

Are among the most frequently reported

Remon J, D. et al: Cancer Treatment Reviews Volume 95 (April 2021) 102178
Li T et al. J Thor Oncol.2014:9:18-25

NCCN Guidelines Version 2.2023
Non-Small Cell Lung Cancer

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19 Deletion or Exon 21 L858R
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

EGFR S768I, L861Q, and/or G719X
- First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

EGFR Exon 20 Insertion Mutation
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

KRAS G12C Mutation
- Subsequent therapy
  - Sotorasib[14]
  - Adagrasib[15]

ALK Rearrangement
- First-line therapy
  - Alectinib[16,17]
  - Brigatinib[18]
  - Ceritinib[19]
  - Crizotinib[16,20]
  - Lorlatinib[21]
- Subsequent therapy
  - Alectinib[22,23]
  - Brigatinib[24]
  - Ceritinib[25]
  - Lorlatinib[26]

ROS1 Rearrangement
- First-line therapy
  - Ceritinib[27,28]
  - Crizotinib[29]
  - Entrectinib[30]
- Subsequent therapy
  - Lorlatinib[31]
  - Entrectinib[30]

BRAF V600E Mutation
- First-line therapy
  - Dabrafenib/trametinib[32]
  - Dabrafenib[32]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[33,34]

NTRK1/2/3 Gene Fusion
- First-line/Subsequent therapy
  - Larotrectinib[35]
  - Entrectinib[36]

MET Exon 14 Skipping Mutation
- First-line therapy/Subsequent therapy
  - Capmatinib[37]
  - Crizotinib[38]
  - Tepotinib[39]

RET Rearrangement
- First-line therapy/Subsequent therapy
  - Selpercatinib[40]
  - Pralsetinib[41]
  - Cabozantinib[42,43]

ERBB2 (HER2) Mutation
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[44]
  - Ado-trastuzumab emtansine[45]

PD-L1 ≥50% First-line Therapy

PD-L1 ≥1-49% First-line Therapy

reatment
Naive

TKI	Study	N	ORR	IC-ORR	mPFS (months)	mOS (months)	Grade 3–4 AE (%)
Crizotinib vs CT	PROFILE 1014 [77], [104]	343	74% vs 45%	NA	10.9 vs 7 (HR 0.45; 95% IC 0.35 to 0.60)	NR vs 47.5 (HR:0.76, 95% CI 0.54–1.05)	50.3% vs 53.3%
Alectinib vs Crizotinib	ALEX [82], [84]	303	82.9% vs 75.5%	59% vs 26%	34.8 vs 10.9 HR 0.43, 95% CI 0.32–0.58	NR vs NR (HR 0.67 95% CI 0.46–0.98)	41% vs 50%
	J-ALEX [85]	207	92% vs 79%	NA	34.1 vs 10.2 HR 0.37, 95% CI 0.26–0.52	NR vs 43.7	37% vs 61%
	ALESIA [86]	187	91% vs 77%	73% vs 22%	NR vs 11.1 HR 0·22, 95% CI 0·13–0·38	NR vs NR	29% vs 48%*
Brigatinib vs Crizotinib (BIRC)	ALTA-1 [88]	275	74% vs 62%	78% vs 26%	24.0 vs 11.0 HR 0.49, 95% CI 0.35–0.68	NR vs NR	73% vs 61%

Ensartinib vs Crizotinib (BIRC)	eXalt3 [89]	290	75% vs 67%	64% vs 21%	25.8 vs. 12.7 months, HR 0.51 (95%CI: 0.35–0.72), p<0.0001	NR VS NR	NR vs NR
Lorlatinib vs crizotinib (BIRC)	CROWN [95]	296	76% vs. 58%	83% vs 23%	NE vs 9.1 (HR 0.28 (0.19, 0.41)	NE vs NE HR 0.72 (0.41–1.25)	72% vs 56%
Ceritinib vs CT	ASCEND-4 [90]	376	73% vs 2–7%	72.7% vs 27.3%	16.6 vs 8.1 HR 0·55, 95% CI 0·42–0·73	NR vs 26.2	78% vs 62%

Clinical activity of ALK TKIs and chemotherapy in *ALK*-positive NSCLC patients who failed prior second-generation ALK TKIs.

TKI	Study		N	ORR	IC-ORR	mPFS (months)	mOS (months)
Lorlatinib	EXP 3B-5 [52]	Phase II	139	37%	53%	6.9*	NR
	ALKmut/ALK WT [75]	Retrospective	110	69%/27%	NR	11 /5.4	NR
Chemotherapy	Lin et al. [105]	Retrospective	58	29.7%	15.8%	4.3**	NR
Ceritinib	ASCEND-9 [94]	Retrospective	20	25%	NR	3.7	NR
Brigatinib	BRIGALK [106]	Retrospective	104	50%	NR	6.6	17.2
	Lin et al. [93]	Retrospective	22	17%	NR	4.4	NR
	UVEA-BRIG [107]	Retrospective	50	34.9%	NR	5.7	10.2
	ATOMIC [108]	Phase II	20	40%	NR	6.4	NR
Ensartinib	[109]	Phase I/II	16	25%	NR	1.9	NR

N, number of patients; ORR, objective response rate; IC-ORR intracranial objective response rate; mPFS, median progression-free survival; mOS, median overall survival.

ALK RESISTANCE

- Intra-tyrosine kinase secondary ALK mutations represent the main mechanism of resistance to second-generation ALK TKIs, reported in more than 50% of patient.
- Among them, p.G1202R accounts for 25%-30% of cases
- In the remaining patients, the occurrence of acquired resistance under second-generation
- ALK TKIs is driven by ALK-independent mechanisms
  - Bypass signaling (including EGFR, MET, c-KIT, SRC, RAS/ MAPK, and SHP2)
  - Histological (small cell lung cancer transformation) and/or phenotypical (EMT) changes

Remon J, et al: Cancer Treatment Reviews Volume 95 (April 2021) 102178
Gainor JF. Et al.Cancer Discov 2016.6:1118-33

Sequencing

- Alectinib is the preferred first-line treatment option in ALK-rearranged advanced NSCLC as it has shown the best balance of clinical activity and safety
- The third-generation ALK TKI lorlatinib, with a wide spectrum of activity against the majority of ALK secondary mutations, has focused new interest on the debate regarding the best first-line ALK TKI.
- Preventing the onset of resistance mechanisms with the use of the most potent TKI at the frontline has proven to be an effective strategy in patients with EGFR-mutated NSCLC
- No direct comparison between second- and third-generation ALK TKIs is currently available

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Gainor JF. Et al.Cancer Discov 2016.6:1118-33

Sequencing

- Lorlatinib showed higher ORR in mutation-positive (69%) vs mutation-negative NSCLC patients (27%)
- Molecular profiling at the time of disease progression to second- generation ALK TKIs may help physicians identify the best candidate to lorlatinib therapy and ultimately define genomic-driven therapeutic sequences
- In a recent study, MET amplification was detected in 15% of tumor biopsies from patients relapsing on next-generation ALK TKIs.
- Patients with acquired MET alterations may benefit from therapeutic agents targeting both ALK and MET like crizotinib

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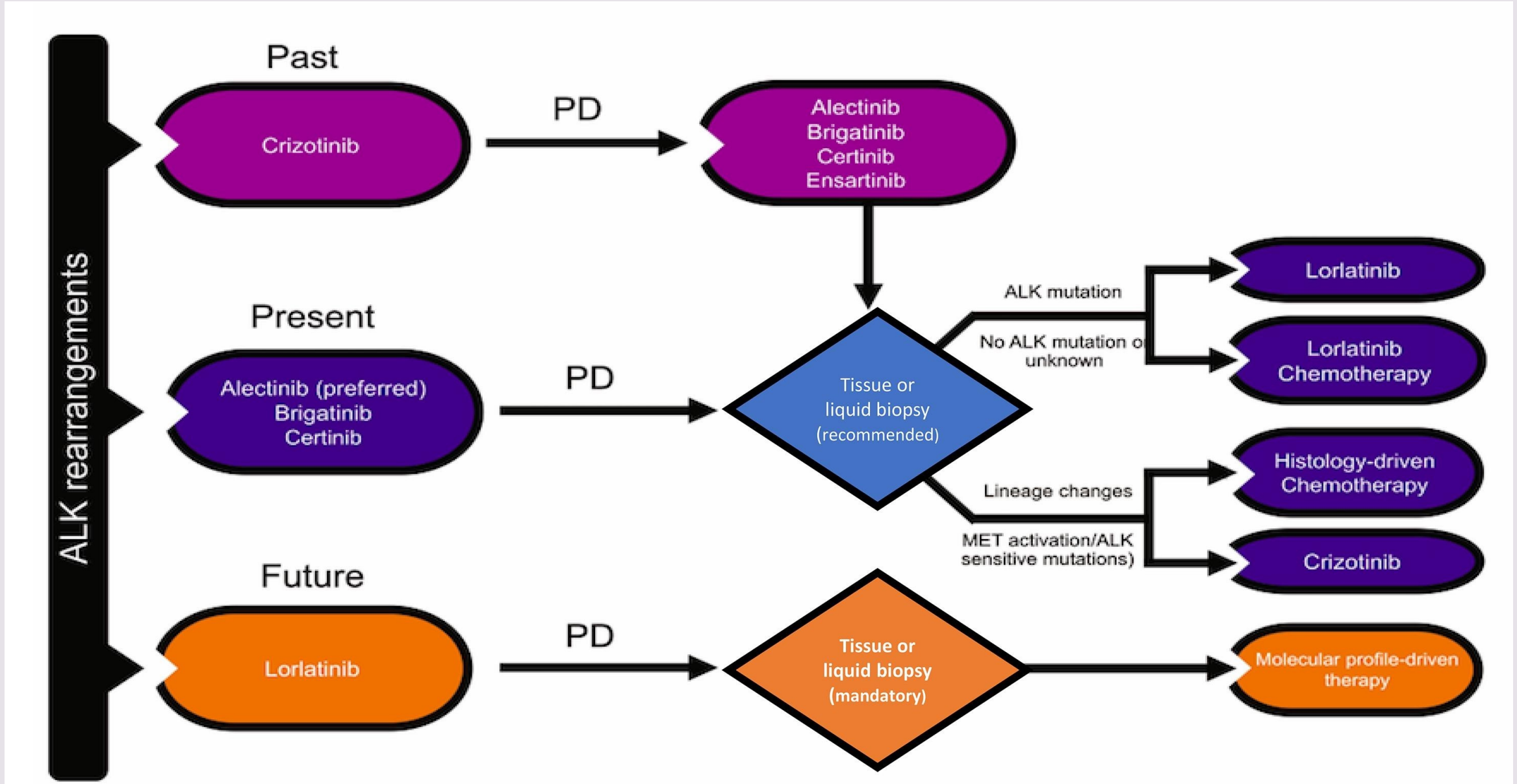
Gainor JF. Et al.Cancer Discov 2016.6:1118-33

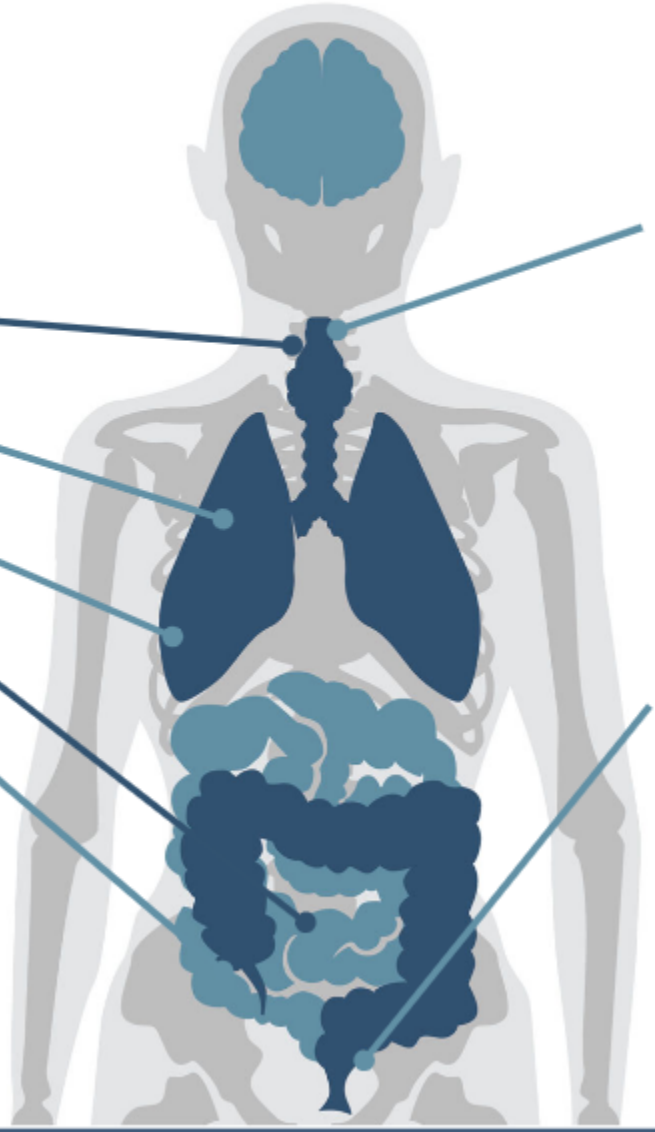


Tissue or
liquid biopsy

RET

RET is a known oncogenic driver in many cancers[1,2]

RET fusions make up 1%-2% of non–small cell lung cancer (NSCLC)[1]



PTC (≈10%-20%)[1,2*]

Breast (0.1%)[3*]

NSCLC (1% to 2%)[1*]

Pancreatic adenocarcinoma (0.6%)[2*]

Ovarian epithelial carcinoma (1.9%)[2*]

MTC (RET mutations, sporadic in ~50%[4] and germline as part of MEN2 syndrome in ~100%[5])

Colorectal (0.2%-7.6%)[6-8†]

*Includes RET fusions only.

†Includes both RET fusions and RET rearrangements.

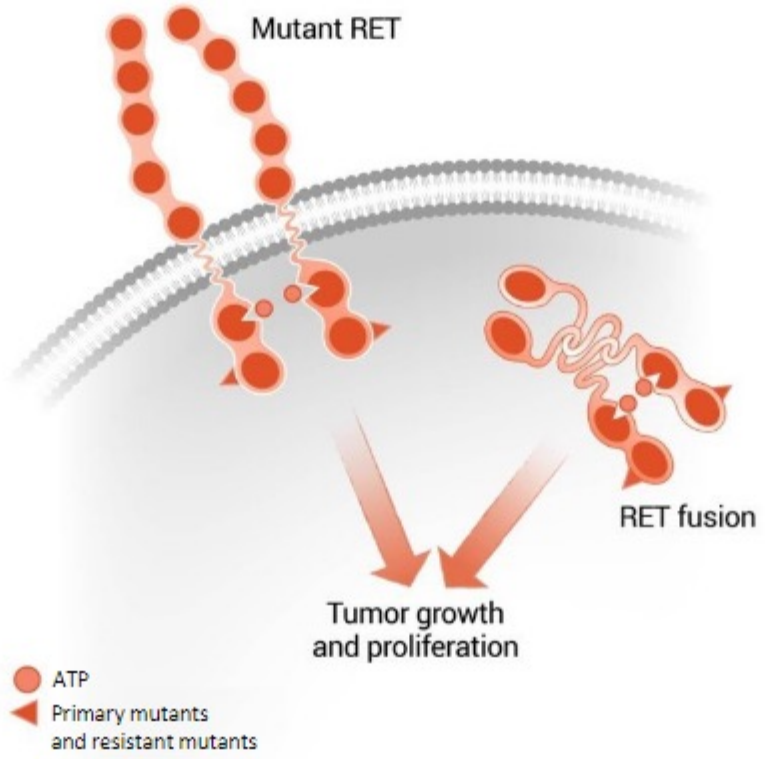
MTC=medullary thyroid cancer; PTC=papillary thyroid cancer.

References: 1. Drilon A, et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. **2.** Kato S, et al. *Clin Cancer Res*. 2017;23(8):1988-1997. **3.** Paratala BS, et al. *Nat Commun*. 2018;9:4821. **4.** Subbiah V, et al. *Cancer Discov*. 2018;8(7):836-849. **5.** Krampitz GW, et al. *Cancer*. 2014;120:1920–1931. **6.** Le Rolle A-F, et al. *Oncotarget*. 2015;6:28929-28937. **7.** Cremolini C, et al. *Ann Oncol*. 2017;28:3009-3014. **8.** Pietrantonio F, et al. *Ann Oncol*. 2018;29(6):1394-1401.

RET signaling can lead to tumor growth and proliferation[1-4]

Oncogenic RET Signaling

Oncogenic alterations in RET lead to ligand-independent kinase activation, driving tumor growth and proliferation



ATP=adenosine triphosphate.

References: 1. Mulligan LM. *Nat Rev Cancer*. 2014;14(3):173-186. **2.** Pützer BM, et al. In: Diamanti-Kandarakis E, ed. *Contemporary Aspects of Endocrinology*. IntechOpen; 2011. Accessed August 23, 2018. **3.** Pratilas CA, et al. *Proc Natl Acad Sci U S A*. 2009;106(11):4519-4524. **4.** Drilon A, et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167.

RET Fusions are Actionable Lung Cancer Drivers

- ~1–2% of patients with NSCLC have *RET* gene fusions (**Fig. 1**)[1-5]
- Definitive locoregional therapies +/- adjuvant chemotherapy, followed by surveillance is the current standard of care for patients with early-stage (IB-IIIA) disease[6]
- Although the use of targeted therapies in the early-stage setting is still being characterized, there is historical precedent for regulatory approval of adjuvant TKI therapy in lung cancer:
  - Osimertinib has been approved by FDA for resected NSCLC with EGFR mutation[7]

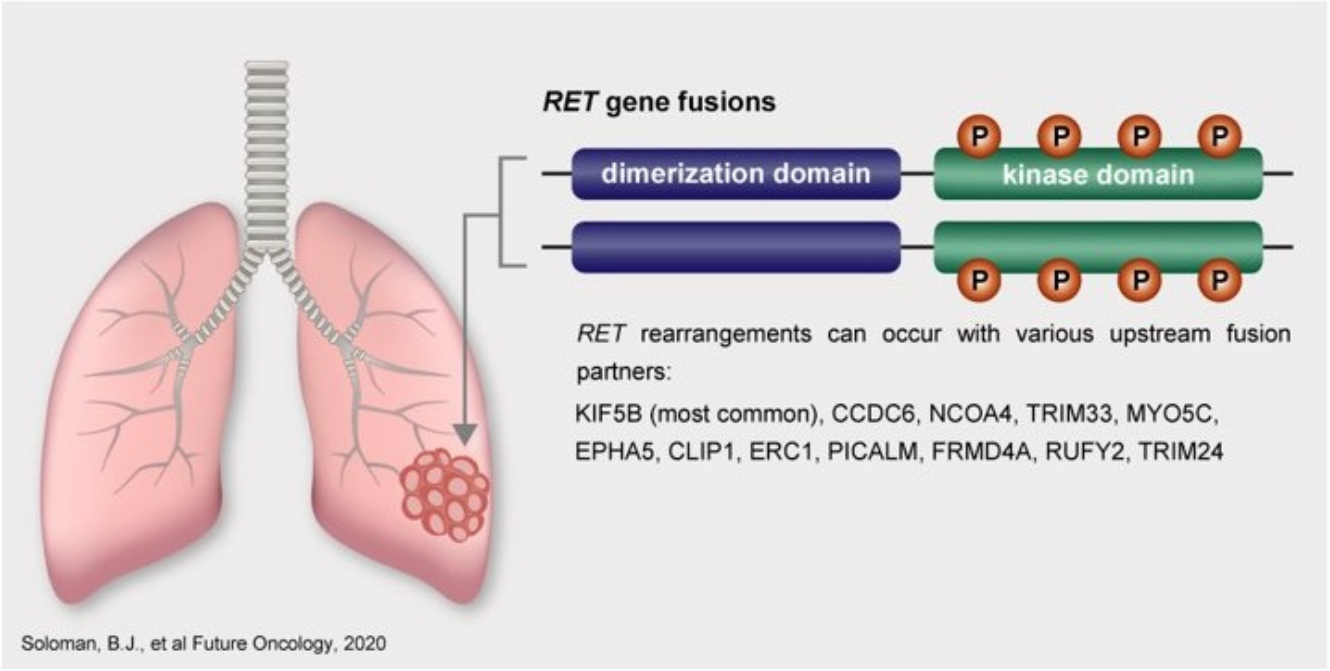


Fig 1. *RET* Fusions are the *RET* gene rearrangements identified in NSCLC

1. Bronte, G., et al. Lung Cancer (Auckl), 2019; 2. Ju, Y.S., et al. Genome Res, 2012; 3. Kohno, T., et al. Nat Med, 2012; 4. Lipson, D., et al. Nat Med, 2012; 5. Takeuchi, K., et al. Nat Med, 2012; 6. NCCN 2020; 7. Wu, Y., et al. N Engl J Med, 2020

Durable Efficacy of Selpercatinib in Patients (pts) with Medullary Thyroid Cancer (MTC): Update of the LIBRETTO-001 Trial

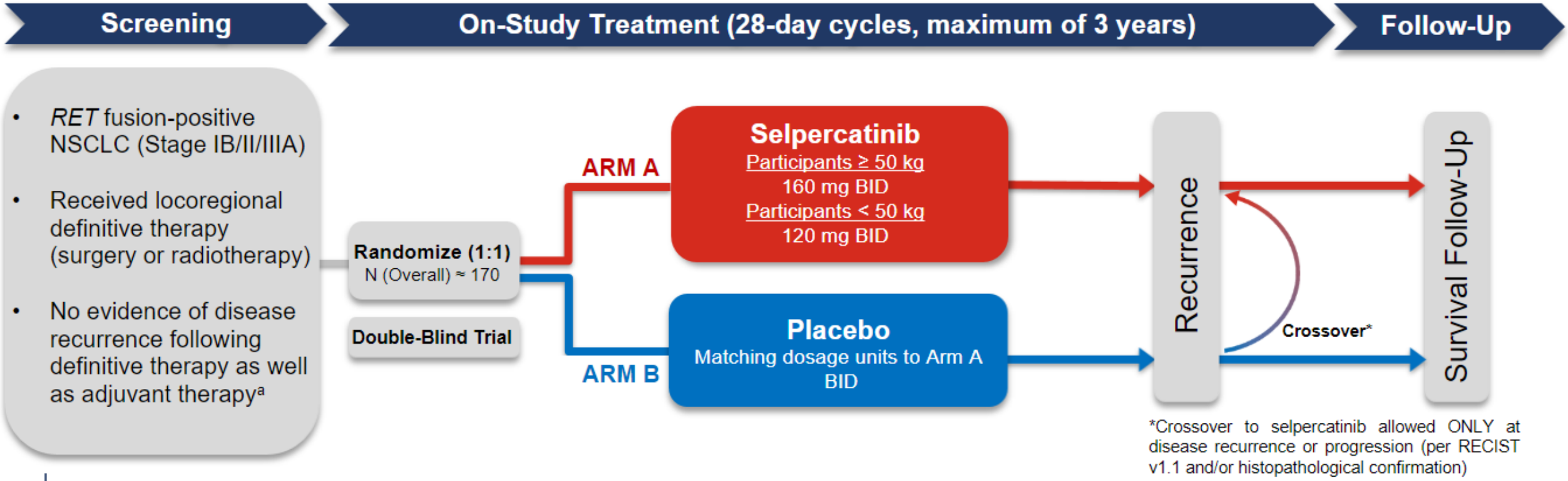
Matthias Kroiss[1], Eric Sherman[2], Lori J. Wirth[3], Maria E. Cabanillas[4], Bruce Robinson[5], Vivek Subbiah[4], Alexander Drilon[6], Yann Godbert[7], Nicolas Fasnacht[8], Victoria Soldatenkova[8], Chi-Wei Duann[8], Jennifer Wright[8], Daniela Weiler[9] and Manisha Shah[10]

[1]University Hospital Würzburg, Germany; University Hospital Munich, Germany; [2]Memorial Sloan Kettering Cancer Center, New York, USA; [3]Massachusetts General Hospital, Boston, USA; [4]The University of Texas M.D. Anderson Cancer Center, Houston, USA; [5]Royal North Shore Hospital, St. Leonards, NSW, Australia; [6]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, USA; [7]University of Bordeaux, France; [8]Eli Lilly and Company, Indianapolis, USA; [9]Cantonal Hospital, Luzern, Switzerland; [10]Ohio State University Comprehensive Cancer Center, Columbus, USA

Subbiah V et al. Lancet Oncology 2022 Oct 23 (10):1261-1273

Study Design

Figure 2. Trial design of LIBRETTO-432 (NCT04819100)



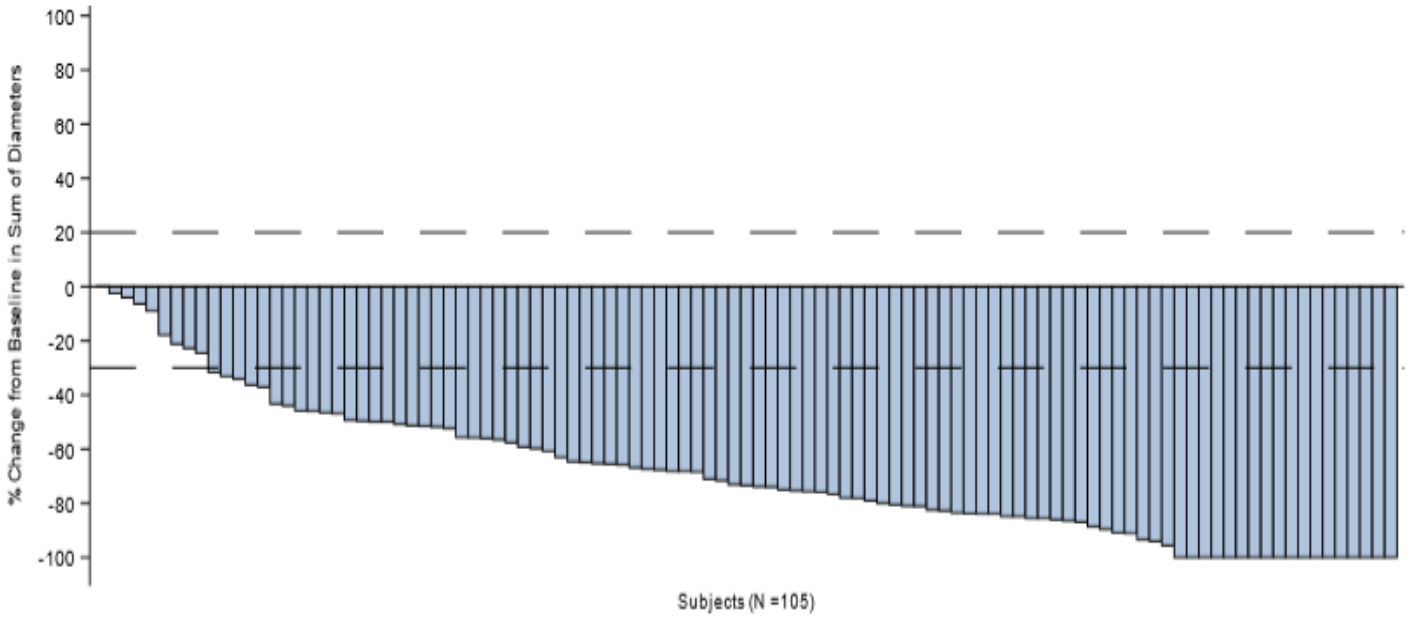
Stratification factors

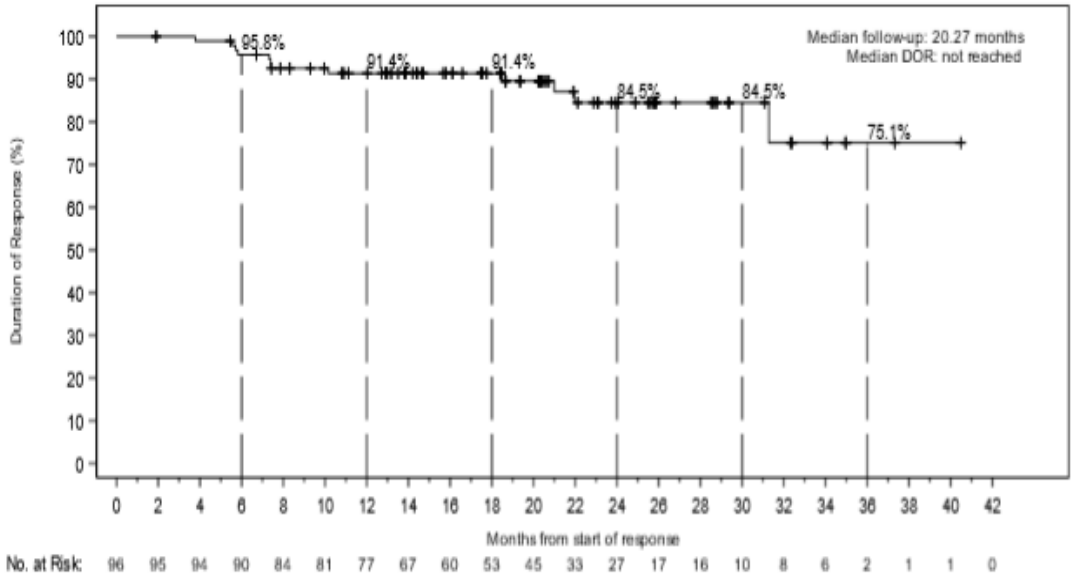
- Disease stage (Stage IB/II/IIIA)
- Prior definitive therapy (surgery, radiotherapy)

[a]Participants must have undergone the available anti-cancer therapy (including chemotherapy or durvalumab) or not be suitable for it, based on the investigator's discretion

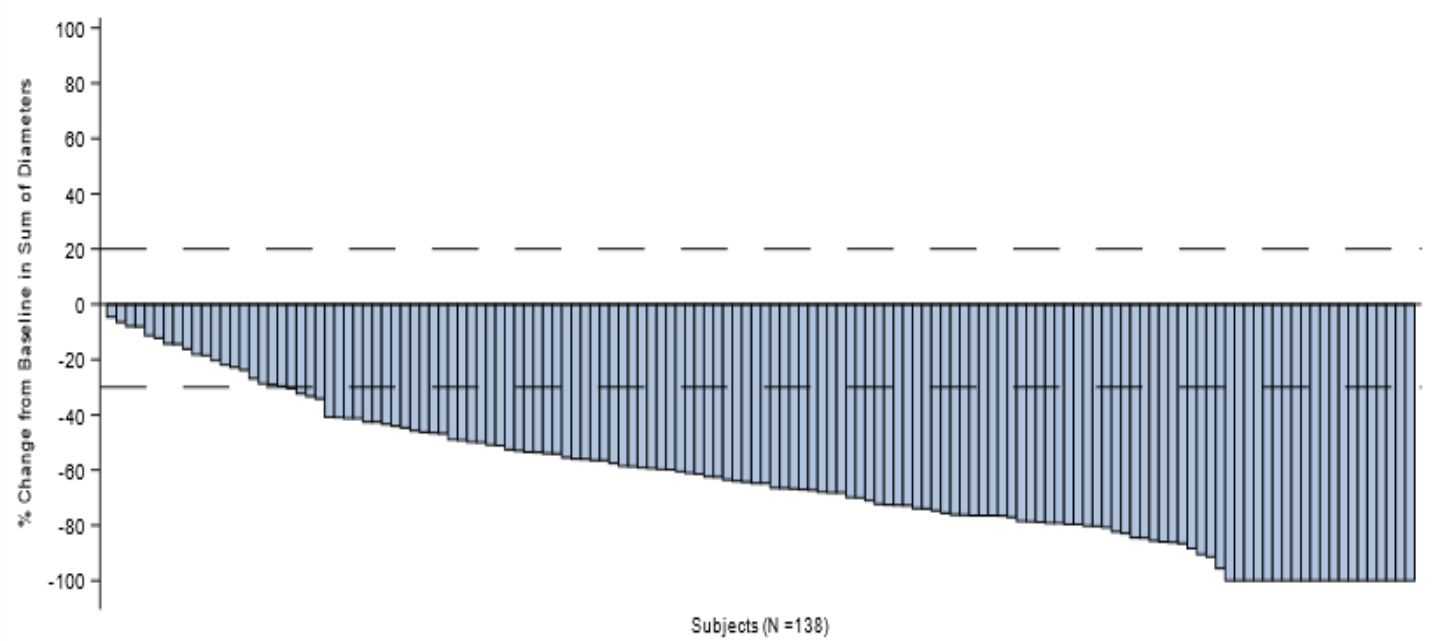
BID=twice daily; N=number of participants; NSCLC=non-small cell lung cancer; RECIST v1.1=Response Evaluation Criteria in Solid Tumors Version 1.1

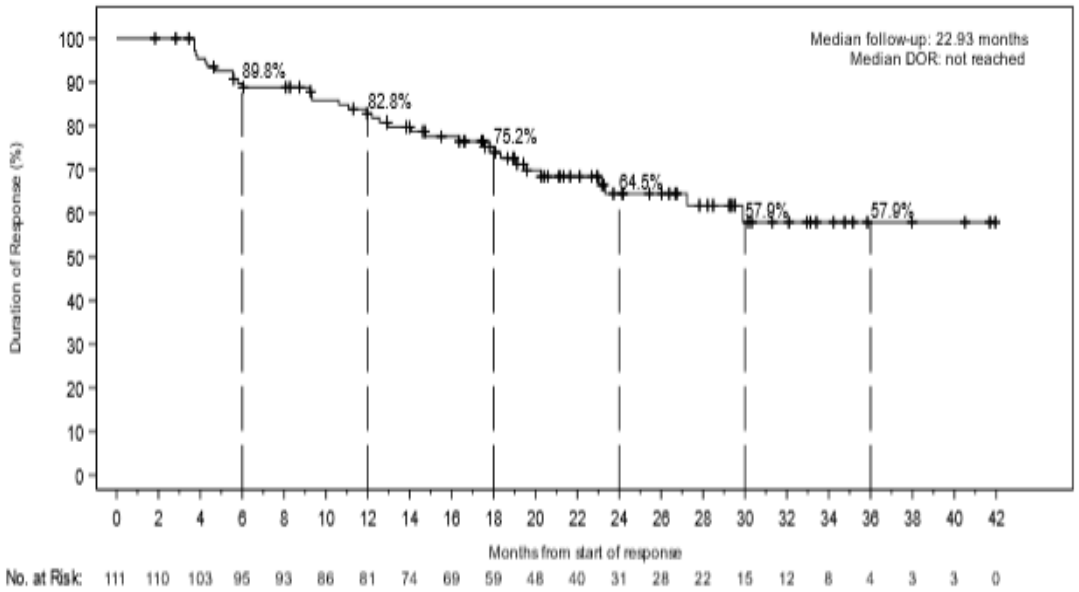
TREATMENT NAÏVE





PRIOR CAB AND/OR VAN





EFFICACY

Response	Cab/van naïve		Prior cab and/or van
	Overall N=142	Treatment naïve N=115	Overall N=151
Objective response rate, n (%) [95% CI]	115 (81.0) [73.6, 87.1]	96 (83.5) [75.4, 89.7]	111 (73.5) [65.7-80.4]
Best overall response, n (%)			
Complete response	22 (15.5)	20 (17.4)	14 (9.3)
Partial response	93 (65.5)	76 (66.1)	97 (64.2)
Stable disease	22 (15.5)	14 (12.2)	31 (20.5)
Progressive disease	2 (1.4)	2 (1.7)	2 (1.3)
Not evaluable	3 (2.1)	3 (2.6)	7 (4.6)
Duration of response (DoR)			
Median DoR, months [95% CI]	NE	NE [31.3-NE]	NE [27.2-NE]
Censored, n (%)	100 (87.0)	84 (87.5)	77 (69.4)
DoR rate at 24 months, % [95% CI]	83.7 [73.0-90.4]	84.5 [72.5, 91.6]	64.5 [52.9-73.9]
Median follow-up, months	20.3	20.3	22.9
Progression-free survival (PFS)			
Median PFS, months [95% CI]	NE	NE	34 [25.7-NE]
Censored, n (%)	118 (83.1)	97 (84.3)	94 (62.3)
PFS rate at 24 months, % [95% CI]	81.1 [72.4, 87.3]	81.6 [71.6-88.4]	64.4 [55.4-72.0]
Median follow-up, months	24.5	23.9	27.6
Overall survival rate at 24 months, % [95% CI]	95.0 [89.0-97.7]	94.7 [87.5-97.8]	77.2 [69.3-83.4]

TREATMENT-EMERGENT ADVERSE EVENTS

- In total, 23 patients (7.2%) discontinued treatment due to TEAEs, including 13 patients (4.1%) due to treatment-related AEs (TRAEs)
- 116 patients (36.4%) had a dose adjustment due to AEs

MTC safety population (N=319)				
	Treatment-emergent adverse events†		Treatment-related adverse events	
n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Edema	174 (54.5)	3 (0.9)	108 (33.9)	2 (0.6)
Fatigue	158 (49.5)	11 (3.4)	110 (34.5)	9 (2.8)
Diarrhea	143 (44.8)	20 (6.3)	79 (24.8)	6 (1.9)
Hypertension	143 (44.8)	69 (21.6)	102 (32.0)	46 (14.4)
Dry mouth	136 (42.6)	0	114 (35.7)	0
Constipation	130 (40.8)	1 (0.3)	68 (21.3)	0
Abdominal pain	121 (37.9)	6 (1.9)	48 (15.0)	1 (0.3)
Increased AST	112 (35.1)	23 (7.2)	84 (26.3)	18 (5.6)
Increased blood creatinine	110 (34.5)	4 (1.3)	57 (17.9)	1 (0.3)
Headache	104 (32.6)	7 (2.2)	46 (14.4)	3 (0.9)
Increased ALT	103 (32.3)	26 (8.2)	81 (25.4)	22 (6.9)
Rash	98 (30.7)	1 (0.3)	59 (18.5)	1 (0.3)
Cough	77 (24.1)	0	6 (1.9)	0
Vomiting	77 (24.1)	6 (1.9)	29 (9.1)	0

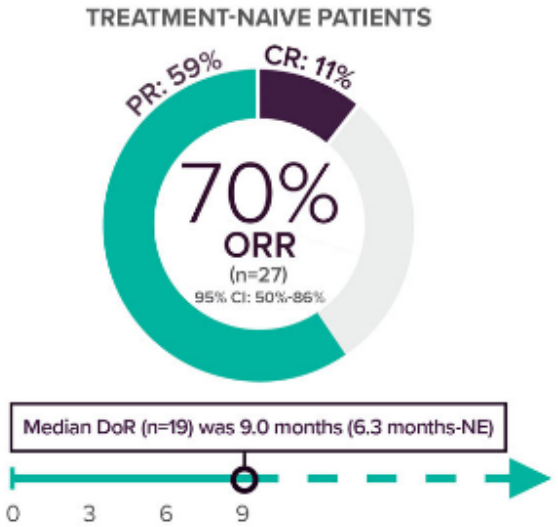
ARROW study design and demographics[1]

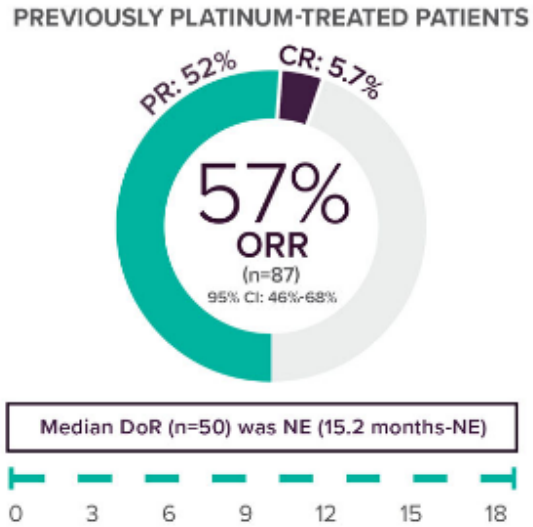
- Efficacy and safety with Pralsetinib 400 mg orally once daily) was evaluated in patients with RET fusion+ mNSCLC in the ARROW study, a phase 1/2, nonrandomized, open-label, single-arm, multicohort, multicenter clinical trial. Patients with asymptomatic central nervous system metastases, including patients with stable or decreasing steroid use within 2 weeks prior to study entry, were enrolled
- All patients were required to have a RET fusion as determined by local testing:
  - Patients with RET fusion+ NSCLC previously treated with platinum chemotherapy: 77% NGS (45% tumor samples, 26% blood or plasma samples, 6% unknown); 21% FISH; 2% other
  - Treatment-naive RET fusion+ NSCLC: 67% NGS (41% tumor samples, 22% blood or plasma, 4% unknown); 33% FISH
- Patients received a starting dose of 400 mg orally once daily

Gainor JF et al. Lancet oncol. 2021 Jul;22(7):959-969

Pralsetinib demonstrated robust and durable response with or without prior therapy[1]

The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as assessed by a blinded independent central review (BICR) according to RECIST v1.1.





CR=complete response; BICR=blinded independent central review; NE=not estimable; PR=partial response.

†Calculated using the proportion of responders with an observed duration of response at least 6 months or greater.

Response in previously platinum-treated patients regardless of RET fusion partner[1]

RET PARTNER | Exploratory analysis

KIF5B (n=65):

59% ORR

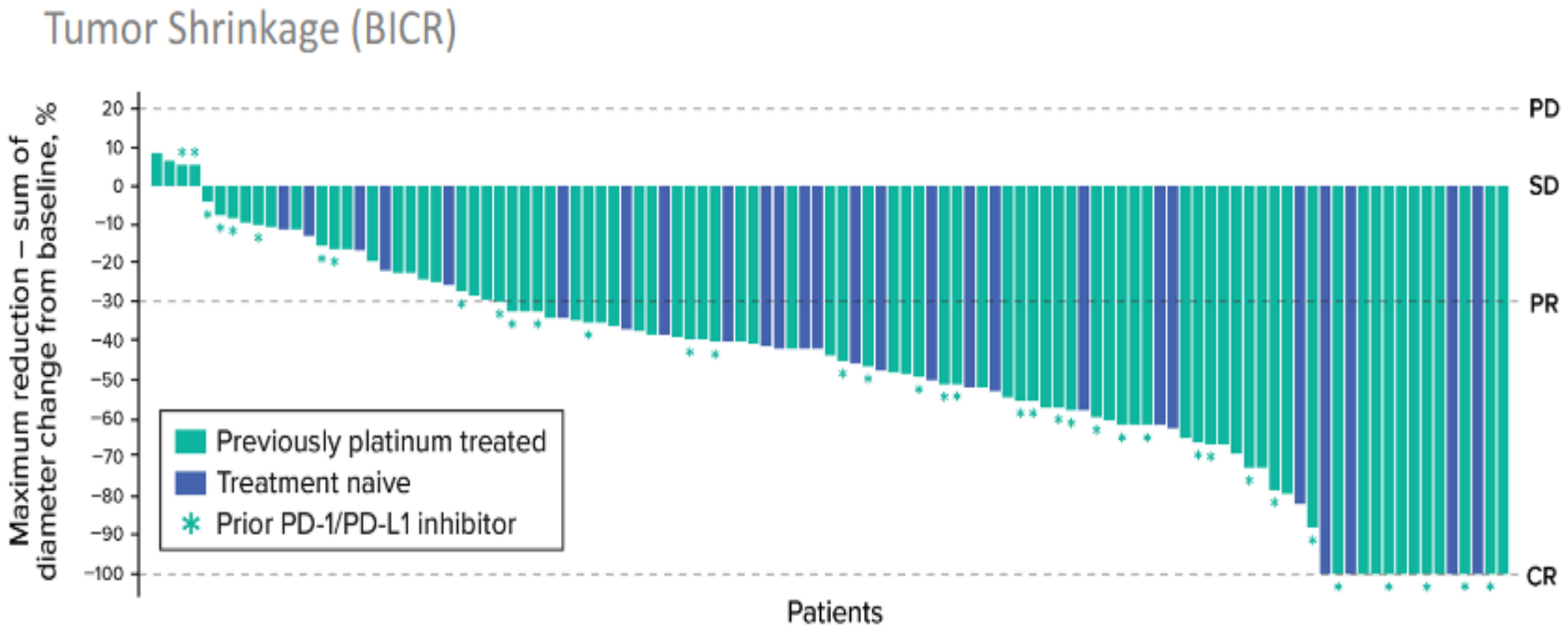
(95% CI: 46%-71%)

CCDC6 (n=15):

60% ORR

(95% CI: 32%-84%)

In RET+ mNSCLC, 96% of patients with measurable disease had a reduction in tumor size during treatment (n=109)[1]*



MET

MET

- c-Met is the tyrosine kinase receptor for hepatocyte growth factor.

- The intracellular c-Met juxta-membrane domain is encoded in part by *MET* exon 14 and contains critical regulatory elements
- Somatic mutations in the *MET* gene can cause exon 14 skipping, and the resulting mutant receptor demonstrates increased c-Met signaling and oncogenic potential
- Incidence in NSCLC is ~ 3% (Dana Farber cohort of 933 non-squamous lung cancer patients)
- None detected in squamous cell, small cell or neuroendocrine carcinomas.
- Nearly half the patients presented at Stage I. In late stages, more likely to be associated with strong c-Met expression than met exon 14 skipping.

Awad et al: JCO v34, Number 7, March1, 2016

Table 1. Clinical Characteristics of Patients With Lung Cancers Harboring *MET* Exon 14 Versus *EGFR* or *KRAS* Mutations

Characteristic	No. (%)		
	MET Exon 14 (n = 28)	*EGFR* (n = 99)	*KRAS* (n = 169)
Median age (range), years	72.5 (59-84)	61 (30-93)	65 (42-93)
Sex			
Male	9 (32)	30 (30)	62 (37)
Female	19 (68)	69 (70)	107 (63)
Smoking history, pack-years*			
Never-smoker	10 (36)	57 (58)	6 (4)
≤ 10	3 (11)	10 (10)	11 (7)
> 10	15 (53)	28 (28)	152 (90)
Race			
White, non-Hispanic	28 (100)	79 (80)	157 (93)
Asian	0 (0)	15 (15)	0 (0)
Black	0 (0)	1 (1)	5 (3)
White, Hispanic	0 (0)	3 (3)	3 (2)
Unknown	0 (0)	1 (1)	4 (2)
Histology			
Adenocarcinoma	18 (64)	92 (93)	150 (89)
Pleomorphic with adenocarcinoma component	4 (14)	0 (0)	3 (2)
NSCLC, poorly differentiated	5 (18)	4 (4)	10 (6)
Squamous	0 (0)	2 (2)	5 (3)
Adenosquamous	1 (4)	1 (1)	1 (1)
Stage at diagnosis			
I	13 (46)	9 (9)	12 (7)
II	2 (7)	3 (3)	12 (7)
III	4 (14)	9 (9)	44 (26)
IV	9 (32)	78 (79)	101 (60)

NOTE. Percentages may not add up to 100% because of rounding.
Abbreviation: NSCLC, non–small-cell lung cancer.
*Number of smoking pack-years was not available for four patients with *EGFR* mutations.

Awad et al: JCO v34, Number 7, March1, 2016

MOLECULAR AND BIOMARKER-DIRECTED THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19 Deletion or Exon 21 L858R
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

EGFR S768I, L861Q, and/or G719X
- First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

EGFR Exon 20 Insertion Mutation
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

KRAS G12C Mutation
- Subsequent therapy
  - Sotorasib[14]
  - Adagrasib[15]

ALK Rearrangement
- First-line therapy
  - Alectinib[16,17]
  - Brigatinib[18]
  - Ceritinib[19]
  - Crizotinib[16,20]
  - Lorlatinib[21]
- Subsequent therapy
  - Alectinib[22,23]
  - Brigatinib[24]
  - Ceritinib[25]
  - Lorlatinib[26]

ROS1 Rearrangement
- First-line therapy
  - Ceritinib[27,28]
  - Crizotinib[29]
  - Entrectinib[30]
- Subsequent therapy
  - Lorlatinib[31]
  - Entrectinib[30]

BRAF V600E Mutation
- First-line therapy
  - Dabrafenib/trametinib[32]
  - Dabrafenib[32]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[33,34]

NTRK1/2/3 Gene Fusion
- First-line/Subsequent therapy
  - Larotrectinib[35]
  - Entrectinib[36]

MET Exon 14 Skipping Mutation
- First-line therapy/Subsequent therapy
  - Capmatinib[37]
  - Crizotinib[38]
  - Tepotinib[39]

RET Rearrangement
- First-line therapy/Subsequent therapy
  - Selpercatinib[40]
  - Pralsetinib[41]
  - Cabozantinib[42,43]

ERBB2 (HER2) Mutation
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[44]
  - Ado-trastuzumab emtansine[45]

PD-L1 ≥50% First-line Therapy

PD-L1 ≥1-49% First-line Therapy

MET Treatment : Capmatinib

- Capmatinib a highly potent and selective inhibitor of the MET receptor, crosses the blood–brain barrier
- Geometry study
  - Given as 400 mg PO twice daily
  - Brain metastases allowed with stable steroid doses
  - Stratified by prior treatment
  - Stratified by type of MET alteration

Wolf et al.N Engl J Med 2020; 383:944-957

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	NSCLC with *MET* Exon 14 Skipping Mutation		NSCLC with *MET* Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)
Age							
Median (range) — yr	71 (49–90)	71 (57–86)	61 (33–76)	70 (49–86)	60 (36–76)	64 (39–84)	63 (38–78)
≥65 yr — no. (%)	55 (80)	25 (89)	28 (41)	10 (67)	13 (31)	24 (44)	14 (47)
Female sex — no. (%)	40 (58)	18 (64)	15 (22)	4 (27)	21 (50)	15 (28)	11 (37)
ECOG performance-status score — no. (%)†							
0	16 (23)	7 (25)	17 (25)	4 (27)	14 (33)	23 (43)	9 (30)
≥1	53 (77)	21 (75)	52 (75)	11 (73)	28 (67)	31 (57)	21 (70)
Smoking history — no. (%)							
Never smoked	40 (58)	18 (64)	5 (7)	2 (13)	7 (17)	11 (20)	7 (23)
Former smoking	27 (39)	9 (32)	54 (78)	8 (53)	29 (69)	34 (63)	20 (67)
Current smoking	2 (3)	1 (4)	10 (14)	5 (33)	6 (14)	9 (17)	3 (10)
Histologic findings — no. (%)							
Adenocarcinoma	53 (77)	25 (89)	57 (83)	11 (73)	35 (83)	48 (89)	22 (73)
Squamous-cell carcinoma	6 (9)	2 (7)	7 (10)	2 (13)	2 (5)	4 (7)	5 (17)
Large-cell carcinoma	1 (1)	0	2 (3)	1 (7)	1 (2)	0	1 (3)
Other	9 (13)	1 (4)	3 (4)	1 (7)	4 (10)	2 (4)	2 (7)
Brain metastases at baseline — no. (%)‡	11 (16)	3 (11)	26 (38)	7 (47)	14 (33)	18 (33)	6 (20)
No. of previous lines of antineoplastic therapy — no. (%)§							

Wolf et al.N Engl J Med 2020; 383:944-957

Table 2. Responses to Capmatinib Treatment, as Assessed by the Independent Review Committee.*

Response	NSCLC with *MET* Exon 14 Skipping Mutation		NSCLC with *MET* Amplification				
	Cohort 4 (N=69)	Cohort 5b (N=28)	Cohort 1a (N=69)	Cohort 5a (N=15)	Cohort 1b (N=42)	Cohort 2 (N=54)	Cohort 3 (N=30)
Progressive disease	6 (9)	1 (4)	12 (17)	4 (27)	15 (36)	21 (39)	6 (20)
Unknown or could not be evaluated	9 (13)	0	8 (12)	1 (7)	4 (10)	8 (15)	8 (27)
Overall response†							
No. of patients with overall response	28	19	20	6	5	5	2
Percent of patients (95% CI)	41 (29–53)	68 (48–84)	29 (19–41)	40 (16–68)	12 (4–26)	9 (3–20)	7 (1–22)
Disease control‡							
No. of patients with disease control	54	27	49	10	23	25	16
Percent of patients (95% CI)	78 (67–87)	96 (82–100)	71 (59–81)	67 (38–88)	55 (39–70)	46 (33–60)	53 (34–72)
Duration of response							
No. of events/no. of patients with response	23/28	11/19	15/20	6/6	3/5	4/5	2/2
Median duration of response (95% CI) — mo	9.7 (5.6–13.0)	12.6 (5.6–NE)	8.3 (4.2–15.4)	7.5 (2.6–14.3)	24.9 (2.7–24.9)	9.7 (4.2–NE)	4.2 (4.2–4.2)
Progression-free survival							
Progression or death — no. of patients	60	17	58	15	34	50	22
Median progression-free survival (95% CI) — mo	5.4 (4.2–7.0)	12.4 (8.2–NE)	4.1 (2.9–4.8)	4.2 (1.4–6.9)	2.7 (1.4–3.1)	2.7 (1.4–4.1)	3.6 (2.2–4.2)

Table 3. Adverse Events, According to Grade, Regardless of Causality, and Exposure to Capmatinib.*

Variable	NSCLC with *MET* Exon 14 Skipping Mutation				
	Cohort 4 (N=69)		Cohort 5b (N=28)		C
	Total	Grade 3 or 4	Total	Grade 3 or 4	Total
Adverse events					
Any event — no. (%)	68 (99)	52 (75)	28 (100)	21 (75)	67 (97)
Most common events — no. (%)†					
Peripheral edema	37 (54)	10 (14)	21 (75)	3 (11)	34 (49)
Nausea‡	32 (46)	0	13 (46)	0	32 (46)
Vomiting‡	18 (26)	0	7 (25)	0	24 (35)
Blood creatinine increased	23 (33)	0	10 (36)	0	16 (23)
Dyspnea	19 (28)	7 (10)	6 (21)	2 (7)	13 (19)
Fatigue	18 (26)	6 (9)	4 (14)	1 (4)	11 (16)
Decreased appetite‡	15 (22)	1 (1)	8 (29)	0	15 (22)
Constipation	10 (14)	2 (3)	4 (14)	0	16 (23)
Diarrhea	12 (17)	0	5 (18)	0	19 (28)
Cough	10 (14)	1 (1)	7 (25)	0	9 (13)
Back pain	11 (16)	2 (3)	4 (14)	0	8 (12)
Pyrexia	9 (13)	1 (1)	2 (7)	0	10 (14)
ALT increased	8 (12)	6 (9)	4 (14)	2 (7)	12 (17)

Pyrexia	9 (13)	1 (1)	2 (7)	0
ALT increased	8 (12)	6 (9)	4 (14)	2 (7)
Asthenia	6 (9)	3 (4)	4 (14)	2 (7)
Pneumonia	7 (10)	4 (6)	2 (7)	0
Weight loss	9 (13)	0	3 (11)	0
Noncardiac chest pain	5 (7)	1 (1)	1 (4)	0
Serious adverse event — no. (%)	36 (52)	30 (43)	14 (50)	12 (43)
Event leading to discontinuation — no. (%)	14 (20)	8 (12)	6 (21)	5 (18)
Exposure				
Median duration — wk	22.1		48.2	
Range — wk	0.4–136.0		4.0–117.4	

MET Treatment : Tepotinib

- Tepotinib is a once-daily, highly selective oral MET inhibitor
- Vision study
  - Given as 500 mg PO daily
  - Brain metastases allowed with tapering steroid doses
  - Untreated brain metastases, < 1 cm, asymptomatic
  - Stratified by prior treatment
  - Stratified by type of MET alteration

Paik et al. NEJM 2020 Sep 3;383(10):931-934

Table 1. Characteristics of the Patients at Baseline (Efficacy Population).*

Characteristic	Liquid Biopsy (N=66)	Tissue Biopsy (N=60)	Combined Biopsy (N=99)
Median age (range) — yr	74 (49–88)	74 (41–94)	74 (41–94)
Sex — no. (%)			
Male	32 (48)	39 (65)	54 (55)
Female	34 (52)	21 (35)	45 (45)
Race — no. (%)†			
Asian	11 (17)	15 (25)	21 (21)
White	52 (79)	44 (73)	74 (75)
Smoking history — no. (%)‡			
Yes	28 (42)	30 (50)	46 (46)
No	34 (52)	22 (37)	45 (45)
ECOG performance-status score — no. (%)§			
0	14 (21)	16 (27)	22 (22)
1	52 (79)	44 (73)	77 (78)
Histologic subtype — no. (%)¶			
Adenocarcinoma	58 (88)	56 (93)	89 (90)
Squamous	6 (9)	3 (5)	7 (7)
Sarcomatoid	1 (2)	0	1 (1)
Previous courses of therapy for advanced or metastatic disease — no. (%)			
0	29 (44)	27 (45)	43 (43)
1	22 (33)	19 (32)	33 (33)
≥2	15 (23)	14 (23)	23 (23)
Brain metastases as identified by independent review — no. (%)‖	9 (14)	3 (5)	11 (11)

MET Treatment : Tepotinib

- The response rate according to investigator assessment was 56% in the liquid biopsy group
- The response rate according to investigator assessment was 62% in the tissue biopsy group
- Tumor shrinkage was observed in 89% of patients
- Responses were rapid, onset within 6 weeks
- Median duration of response 11.1 months
- Median PFS 8.5 months
- Median OS 17.1 months

Paik et al. NEJM 2020 Sep 3;383(10):931-934

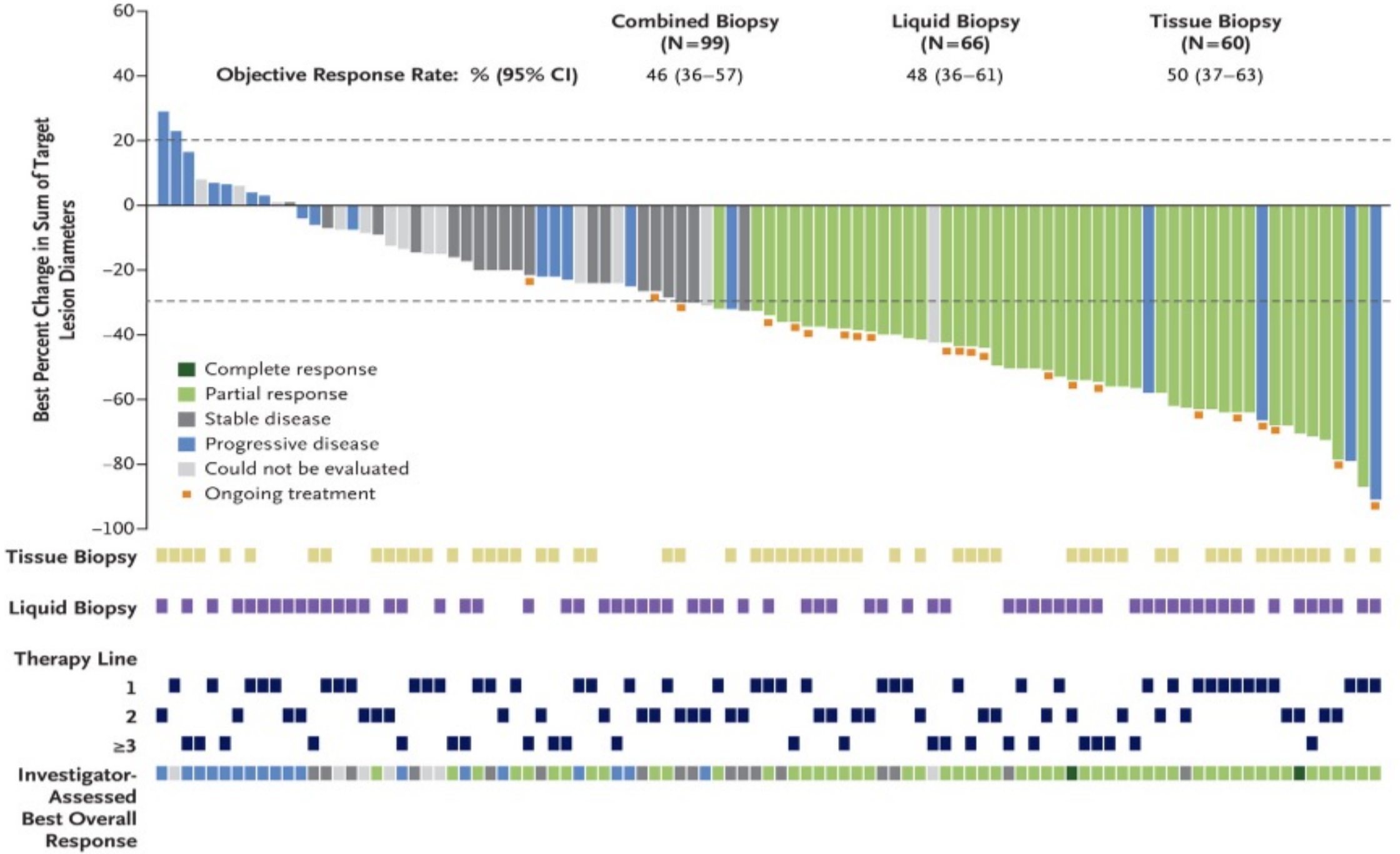

Combined Biopsy (N=99)
Liquid Biopsy (N=66)
Tissue Biopsy (N=60)
Objective Response Rate: % (95% CI)
46 (36–57)
48 (36–61)
50 (37–63)
Best Percent Change in Sum of Target Lesion Diameters
60
40
20
0
−20
−40
−60
−80
−100
Complete response
Partial response
Stable disease
Progressive disease
Could not be evaluated
Ongoing treatment
Tissue Biopsy
Liquid Biopsy
Therapy Line
1
2
≥3
Investigator-Assessed Best Overall Response

Table 2. Adverse Events (Safety Population).*

Adverse Events	Safety Population (N=152)			
	All Grades	Grade 1 or 2	Grade 3	Grade 4
	number of patients (percent)			
Any adverse event†	135 (89)	93 (61)	38 (25)	3 (2)
Peripheral edema	96 (63)	85 (56)	11 (7)	0
Nausea	39 (26)	38 (25)	1 (1)	0
Diarrhea	33 (22)	32 (21)	1 (1)	0
Blood creatinine increased	27 (18)	26 (17)	1 (1)	0
Hypoalbuminemia	24 (16)	21 (14)	3 (2)	0
Amylase increased	17 (11)	13 (9)	3 (2)	1 (1)
Lipase increased	13 (9)	9 (6)	4 (3)	0
Asthenia	12 (8)	11 (7)	1 (1)	0
Decreased appetite	12 (8)	11 (7)	1 (1)	0
Pleural effusion	12 (8)	8 (5)	4 (3)	0
Alopecia	12 (8)	12 (8)	0	0
Fatigue	11 (7)	10 (7)	1 (1)	0
Alanine aminotransferase increased	11 (7)	7 (5)	3 (2)	1 (1)
Aspartate aminotransferase increased	10 (7)	7 (5)	2 (1)	1 (1)
Vomiting	9 (6)	9 (6)	0	0
General edema	9 (6)	5 (3)	4 (3)	0
Upper abdominal pain	8 (5)	8 (5)	0	0

Conclusions

- Targeted agents have revolutionized the treatment of lung cancer by offering personalized therapy based on the specific molecular characteristics of an individual's cancer
- These drugs are designed to target specific molecules or pathways that are crucial for the growth and survival of cancer cells
- Resulted in improved efficacy and reduced toxicity compared to traditional chemotherapy
- Targeted agents have provided a valuable alternative for patients with advanced lung cancer who may not be eligible for surgery or radiation
- While these agents have significantly improved patient outcomes, continued research is necessary to identify new targets and develop more effective therapies for patients with lung cancer

The content of this slide was created by AI