Options After second and Third Generation ALK TKI RESISTANCE

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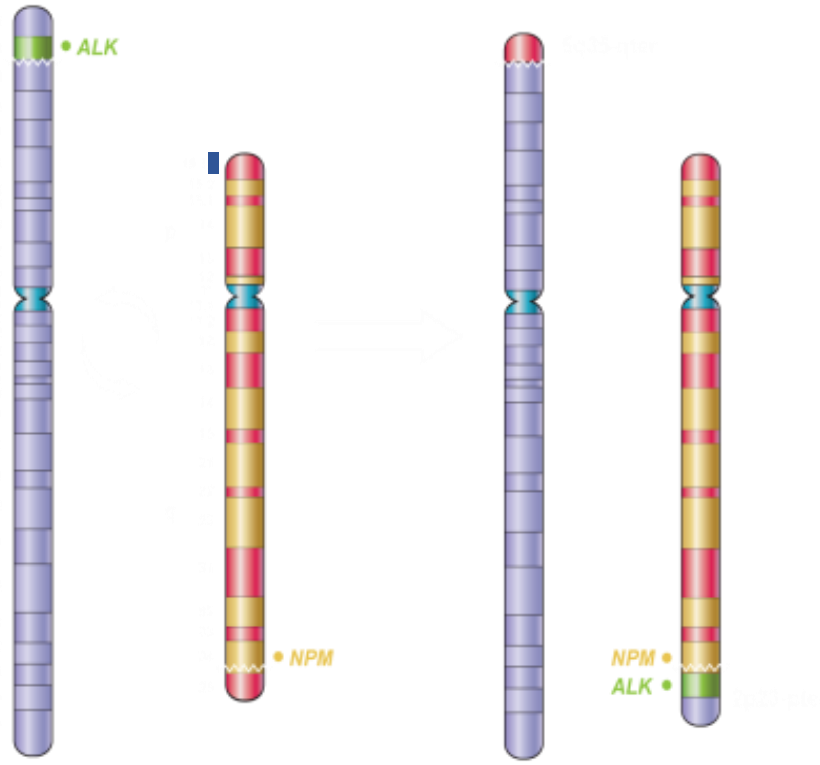
Background: Discovery of *ALK* in Lymphoma

- *ALK* first discovered in a subset of anaplastic large-cell lymphoma (ALCL), leading to the name *anaplastic lymphoma kinase*[1]
- *ALK* fused to the N-terminal portion of *nucleophosmin* (*NPM-ALK*), leading to constitutive activation of *ALK*[2]

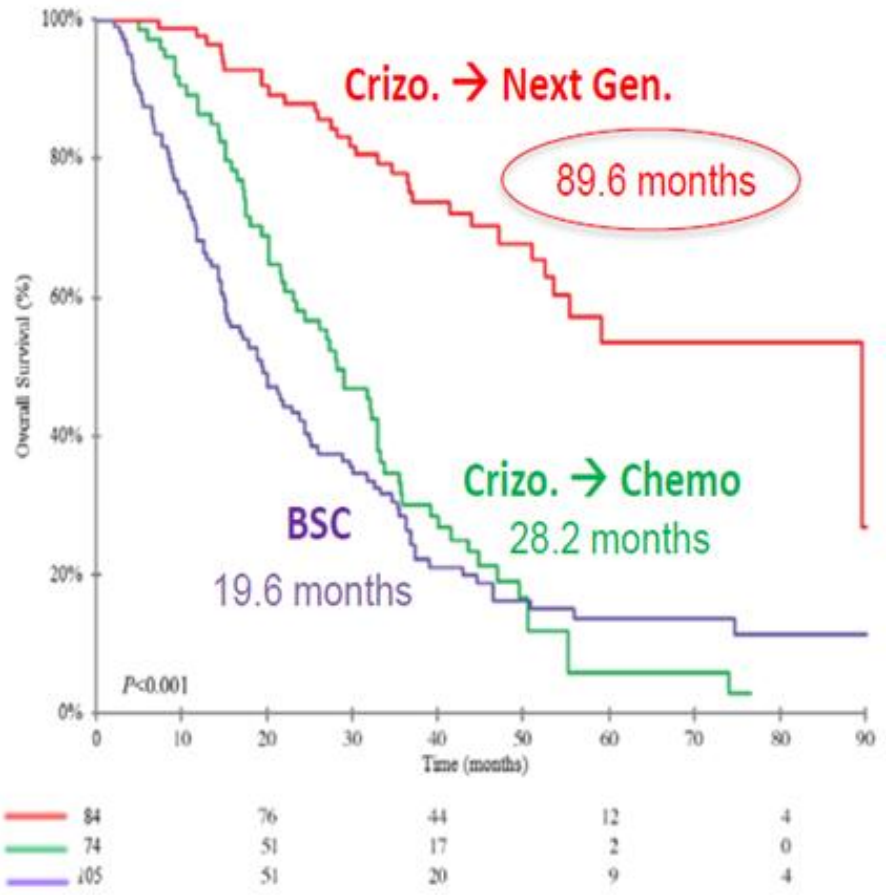


Adapted from Mathew P, *et al. Blood* 1997;89:1678–85

1. Johnson TW, et al. *J Med Chem* 2014;57:4720−44; 2. Mathew P, *et al. Blood* 1997;89:1678–85.

Overall survival according to subsequent systemic treatments

Overall survival from the diagnosis of metastatic disease in the 84 patients receiving next-generation ALK inhibitors after progression on crizotinib



Adapted from Oncotarget 2017:8:21903–17

Duruisseaux et al. Oncotarget 2017:8:21903–17

Case :

- 44 / Male , Non smoker
- Feb 2020
- RT lung mass with Effusion
- Biopsy : ALK positive IHC
- Started on Crizotinib
- PET June 2020 : PR
- PET nov 2020 PD
- Started on Alectnib
- Responded symptomatically ,

- PET nov 2020 PD
- Started on Alectnib
- Responded symptomatically ,
- PET 2021 Feb PR
- Pt developed cough
- Second opinion : second time
- Dose increased to full dose
- Clinically responded but lost response in next 3 months
- PET may 2021 new lesions previous lesion under remission

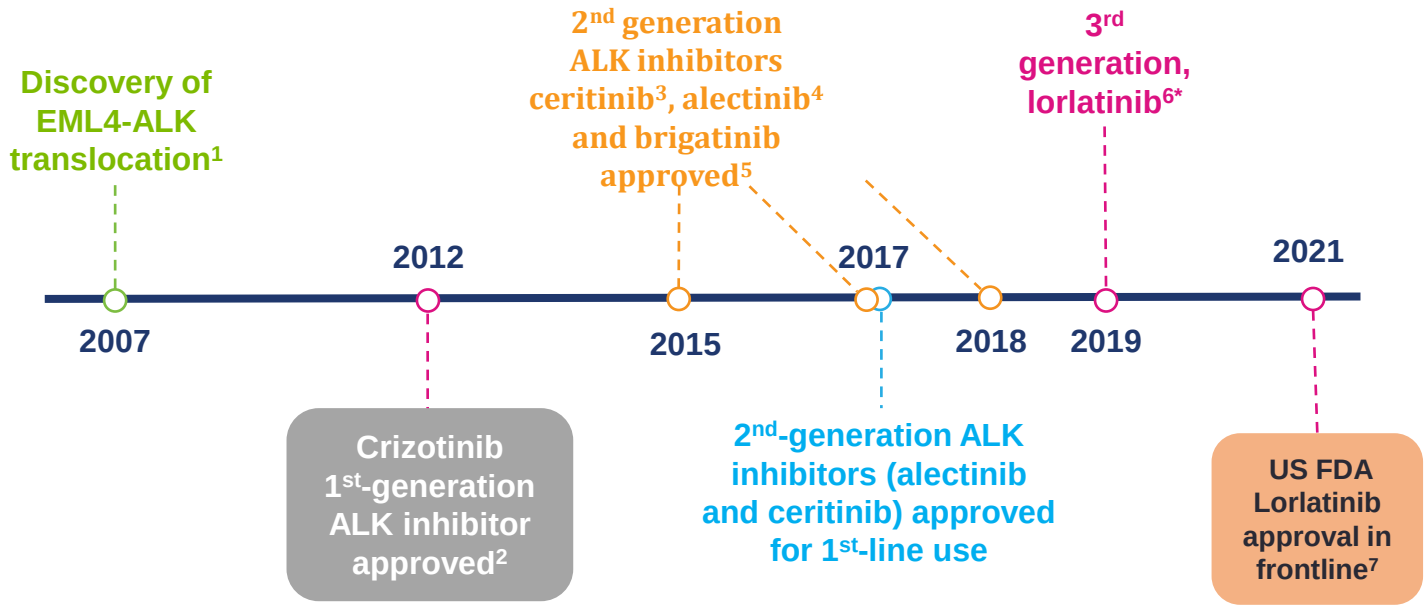
- PET : PD
- Biopsy done

- Report will discuss at end

- What options post CRIZOTINIB and ALECTINIB ?

Background on ALK

ALK inhibitor development timelines

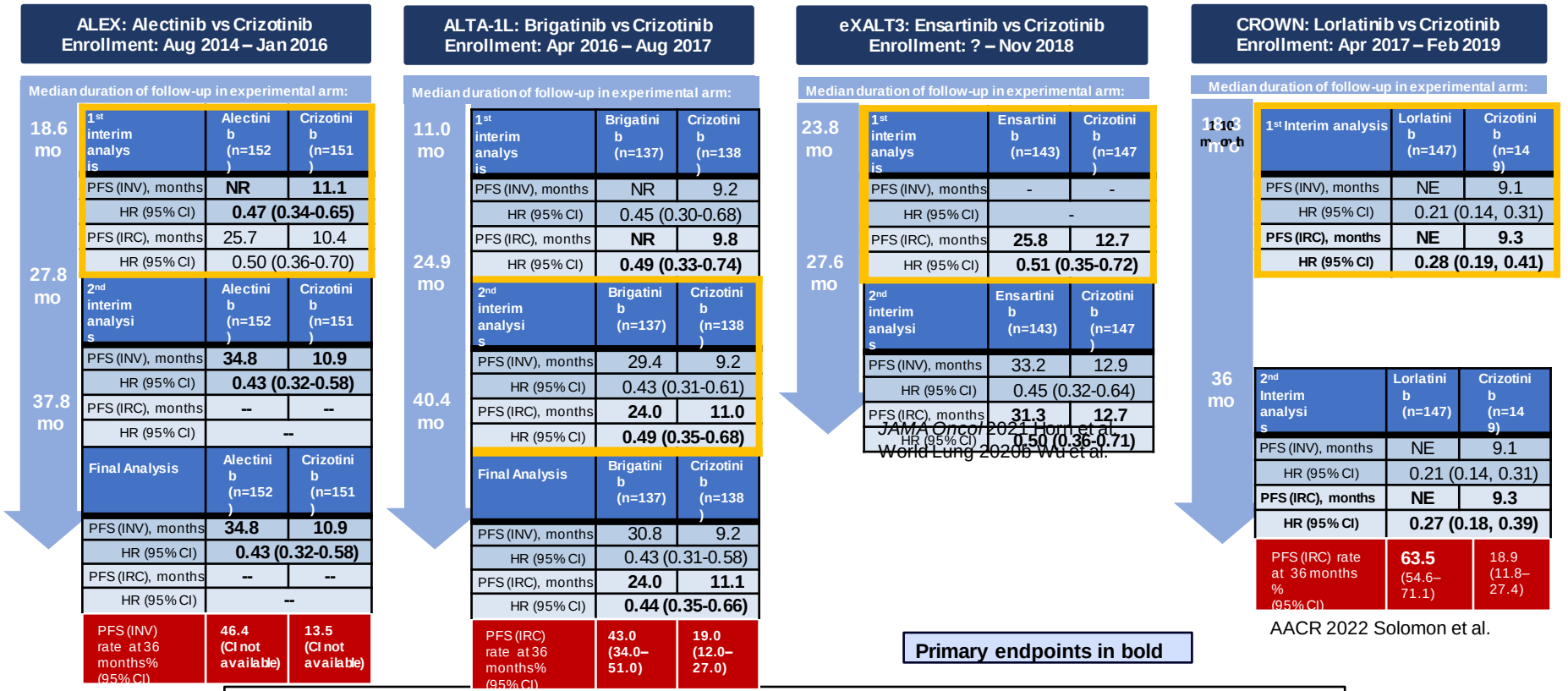


Dates refer to EMA approval, unless otherwise specified
* Approved in second line

1. Soda M et al. *Nature* 2007;448(7153):561–6; 2. crizotinib SmPC. accessed on 27th Aug 2021; 3. Ceritinib SmPC. accessed on 27th Aug 2021; 4. Alectinib SmPC. accessed on 27th Aug 2021; 5. Brigatinib SmPC. accessed on 27th Aug 2021; 6. https://www.pfizer.com/news/press-release/press-release-detail/european_commission_approves_lorviqua_lorlatinib_for_certain_adult_patients_with_previously_treated_alk_positive_advanced_non_small_cell_lung_cancer accessed on 27th Aug 2021 7. US FDA approves lorlatinib for metastatic ALK-positive NSCLC https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-lorlatinib-metastatic-alk-positive-nsclc (accessed on 27th Aug 2021

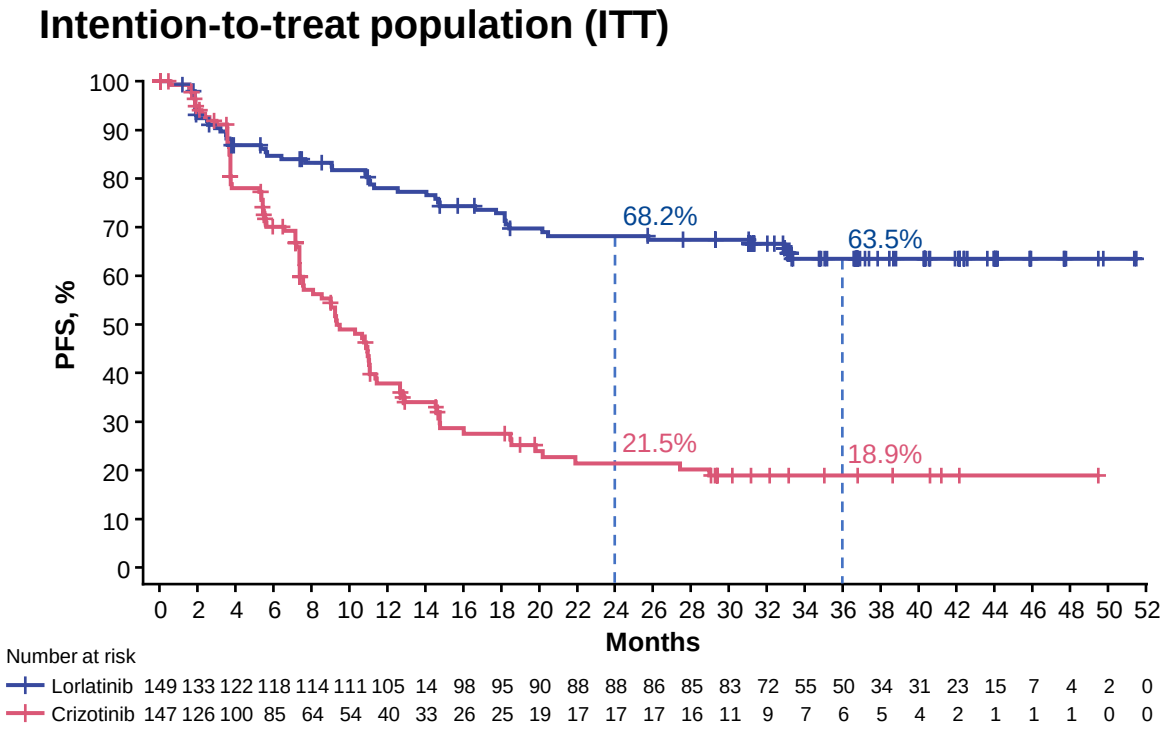
Please see summary of prescribing information on last slide

PFS Outcomes for ALEX, ALTA-1L, eXALT3, and CROWN Trials at Varying Levels of Data Maturity



NEJM 2017 Peters et al.
JTO 2019 Camidge et al.
ESMO 2019 Mok et al.

At 36.7 months of median follow-up in the lorlatinib arm, BICR assessed PFS remained significantly longer with lorlatinib than with crizotinib



	ITT	
	Lorlatinib (n=149)	**Crizotinib (n=147)**
Events	49	92
PFS, median (95% CI), months	NR (NR–NR)	9.3 (7.6–11.1)
HR (95% CI)	0.27 (0.184–0.388)	

- Confirmed ORR by BICR
  - 77.2% (lorlatinib) vs 58.5% (crizotinib)
- Median DOR, months
  - NR (lorlatinib) vs 9.6 months (crizotinib)

BICR- Blinded independent central review, PFS- Progression free survival, HR- Hazard ratio, DOR-Duration of response, ORR-Objective response rate, CI- Confidence interval, NR- Not reached

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Presented as poster

Progression on First generation ALK TKIs

- Although patients with ALK positive advanced NSCLC initially respond to ALK inhibitors, ALK-positive NSCLC remains an incurable disease, as patients ultimately develop resistance to ALK TKI due to resistance mutations, which are around 20-71% [1, 2]
- G1202R confers high levels of resistance to all currently available second-generation ALK inhibitor[1]
- Around 60% of ALK positive patients present with brain metastases upon progression after treatment with ALK inhibitor(s) and are associated with a poor prognosis
- CNS activity and activity against resistant mutations: Ideal Agent

1. Gainor JF et al. Cancer Discov; 6(10); 1118–33. 2. Solomon et al. Lancet Oncol 2018; 19: 1654–67

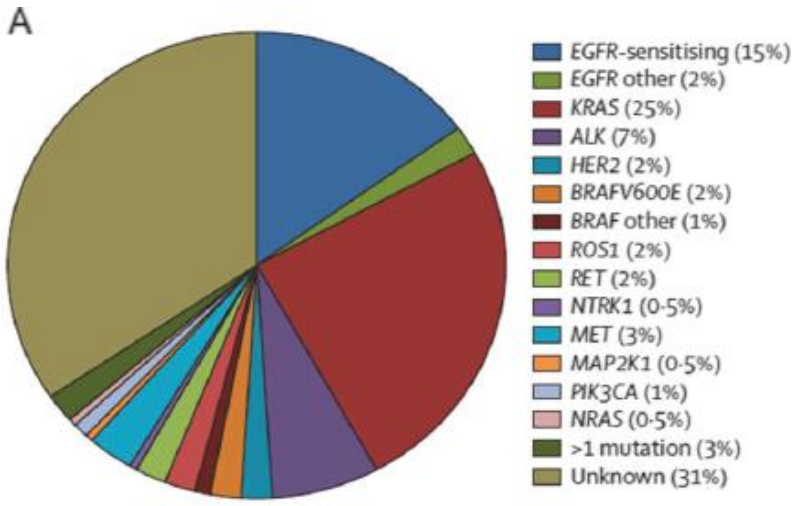
Resistance mechanism in ALK rearranged NSCLC

Mechanisms of Acquired Resistance to ALK Inhibitors

- Progression on ALK Inhibitors

- Despite 1L ALK inhibitors demonstrating high activity in ALK-rearranged NSCLC, disease progression occurs in a median of ~10 to 25 months[1-5]
- Patterns of resistance may include isolated CNS progression and various forms of extracranial progression[5]
- Mechanisms implicated in acquired resistance to ALK inhibitors include[5,6]:
  - ALK amplifications
  - ALK mutations
  - Activation of oncogenic bypass pathways including those involving EGFR, HER2, MET, KIT, and InsR
  - Drug efflux pumps in the CNS

Targetable mutations in adenocarcinoma[7]

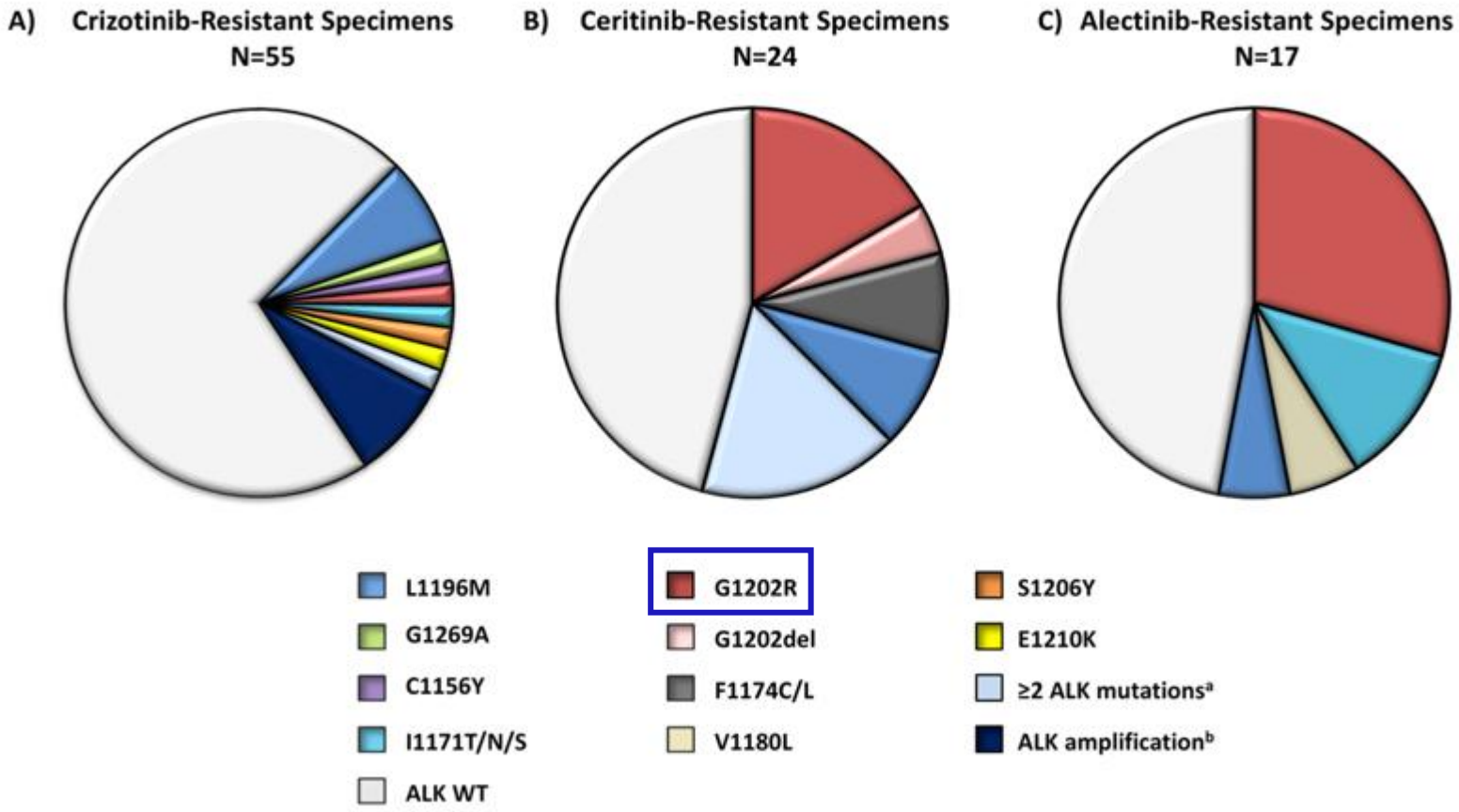


Adapted from Brainard J & Carol Farver C. Modern Pathology (2019) 32:S16–S26

•CNS, central nervous system.

1. Local product information for Crizotinib_ version 12. Pfizer India_ LPDCRI042020. 2. Ceritinib prescribing information. East Hanover, NJ: Novartis Pharmaceutical Corp.; 2019. 3. Alectinib prescribing information. Cambridge, MA: Takeda Pharmaceutical Company Ltd.; 2017. 4. Camidge DR et al. *N Engl J Med*. 2018;379(21):2027-2039 5. Rothenstein JM, et al. *Curr Oncol*. 2018;25(S1):S59-S67. 6. Thomas A et al. *Ann Oncol*. 2013;24(3):577-585. 7. Brainard J & Carol Farver C. Modern Pathology (2019) 32:S16–S26

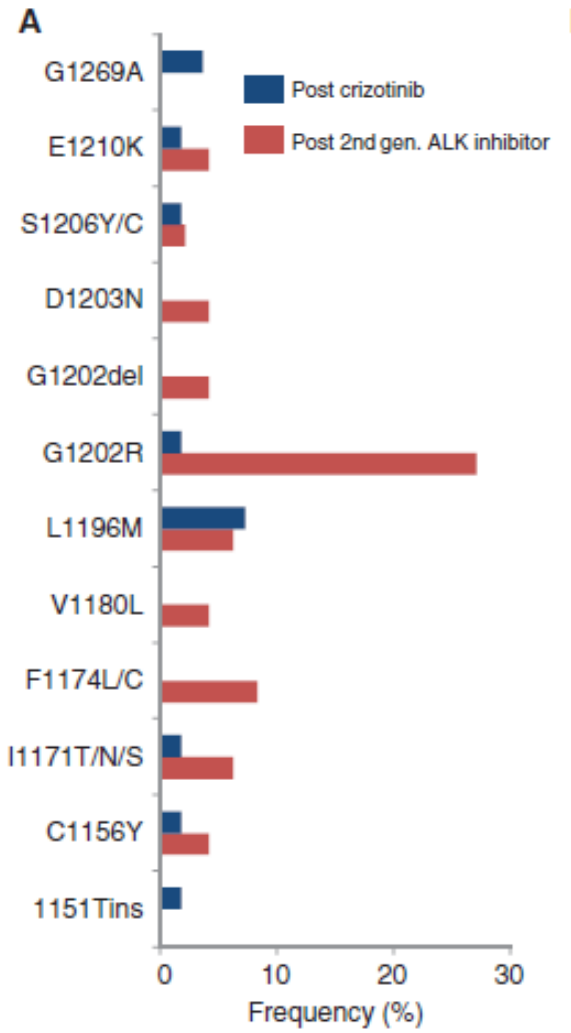
Resistance after treatment with ALK inhibitors



Adapted from Gainor JF et al. Cancer Discov; 6(10); 1118–33

Gainor JF et al. Cancer Discov; 6(10); 1118–33

Enrichment of G1202R in patients who progressed on next Gen ALKi



Adapted from Gainor JF et al. Cancer Discov; 6(10); 1118–33

Gainor JF et al. Cancer Discov; 6(10); 1118–33

Sequencing of ALK-TKI Generations Lead to More *ALK* Resistance Mutations

Clonal evolution of resistance to sequential *ALK*-targeting therapies.[1,2]

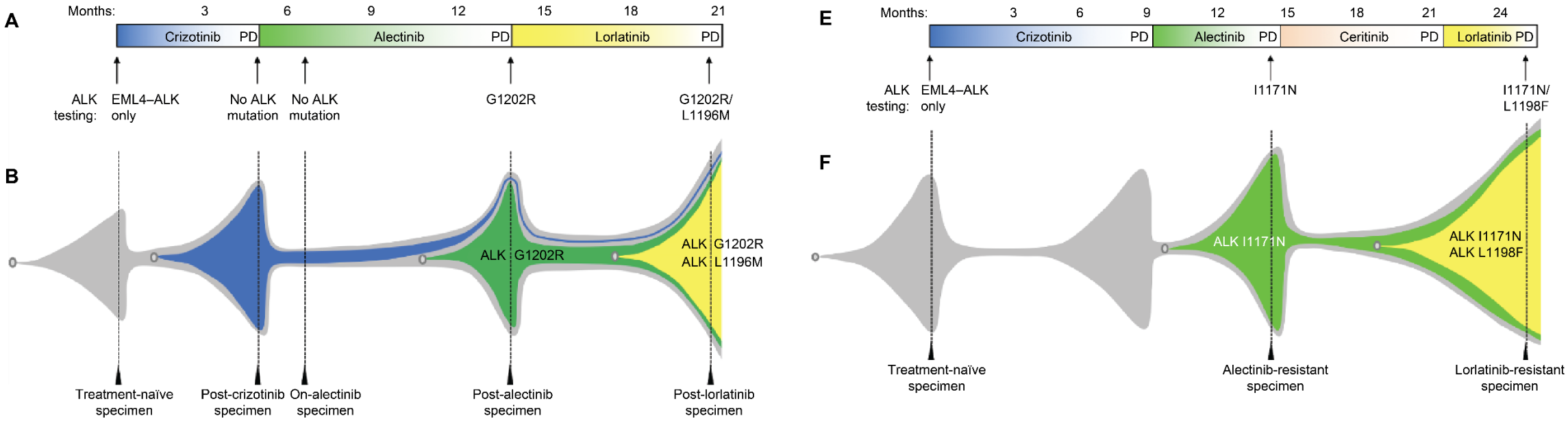


Image adapted from Yoda S, Lin JJ, *Cancer Discov.* 2018;8(6):714–729.

As more generations of *ALK*-TKI were sequenced, more "monster" *ALK* resistance mutations appeared.[2]

1. Yoda S, Lin JJ, *Cancer Discov.* 2018;8(6):714–729.
2. Ou SH S04.02. Presented at IASLC TTLC 2021

ALK: Ananaplastic lymphoma kinase;
TKI: Tyrosine kinase inhibitors.

Unmet need

- Most trials evaluate progression on crizotinib
- Development of complex mutations after multiple lines of ALK TKIs
- Brain frequent site of progression thus underlining need for drug with excellent CNS penetration

• *In vitro*, lorlatinib covers the broadest range of ALK resistance mutations of any ALK inhibitor

- Lorlatinib has broad-spectrum potency against most known ALK resistance mutations, including ALK G1202R1,2
- ALK positive patients also develop compound mutations upon treatment with ALK inhibitors

IC_{50} ≤50 nM IC_{50} >50–<200 nM IC_{50} ≥200 nM

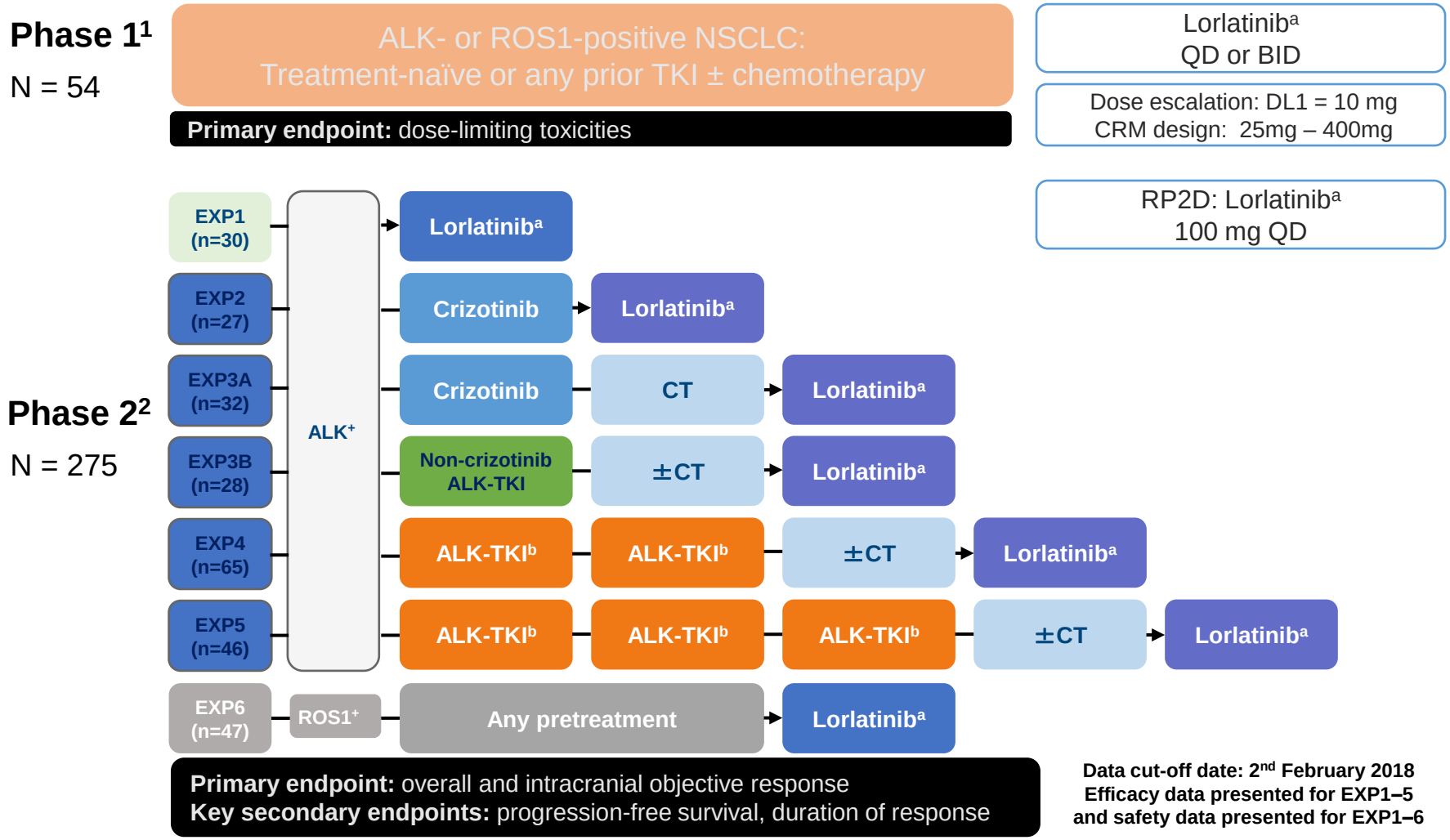
	Cellular ALK Phosphorylation Mean IC_{50} (nM)			
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Lorlatinib**
EML4-ALK	38.6	4.9	11.4	2.3
C1156Y	61.9	5.3	11.6	4.6
I1171N	130.1	8.2	397.7	49.0
I1171S	94.1	3.8	177.0	30.4
I1171T	51.4	1.7	33.6	11.5
F1174C	115.0	38.0[a]	27.0	8.0
L1196M	339.0	9.3	117.6	34.0
L1198F	0.4	196.2	42.3	14.8
G1202R	381.6	124.4	706.6	49.9
G1202del	58.4	50.1	58.8	5.2
D1203N	116.3	35.3	27.9	11.1
E1210K	42.8	5.8	31.6	1.7
G1269A	117.0	0.4	25.0	10.0

Adapted from Gainor JF, et al. *Cancer Discov* 2016;6:1118–33.

IC_{50}, half-maximal inhibitory concentration; ND, not done

Gainor JF, et al. *Cancer Discov* 2016;6:1118–33.

Clinical data: Efficacy



Adapted from Besse B, et al. Poster 9032 presented at ASCO 2018

Asymptomatic brain metastases were allowed in all cohorts. Different treatments may have been received in any order and not necessarily in the sequence depicted above e.g. CT may have been given prior to or after other therapy
aTreatment until PD or unacceptable toxicity. bLines of therapy (if the same TKI is given twice, this is counted as 2 prior lines of treatment).

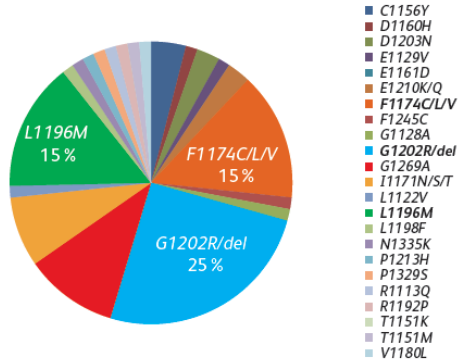
1. Shaw AT, et al. *Lancet Oncol* 2017;18(12):1590–99; 2. Besse B, et al. Poster 9032 presented at ASCO 2018 Congress, Chicago, USA, 1–5 June, 2018.

Please see summary of prescribing information on last slide

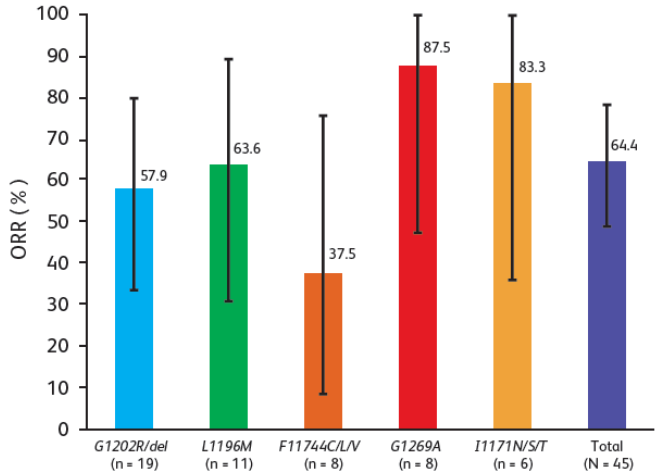
Lorlatinib Phase 2 Study 1001: Translational Outcomes

- Of 190[a] baseline plasma samples in pretreated *ALK*-positive patients, 45 (24%) had ≥1 detectable ALK kinase domain mutation
- A total of 75 *ALK* mutations (27 unique mutations) were detected, and G1202R/del was the most frequently observed (25%) mutation
- ORRs were observed across a range of *ALK* resistance mutations
  - Among 139 patients without a detectable *ALK* mutation in cfDNA, 63 patients (45%) responded to lorlatinib

ALK kinase domain mutations detected in cfDNA (EXP2–5)[b]



ORR in patients harboring the most frequent _ALK_ mutations in cfDNA (EXP2–5)[c]



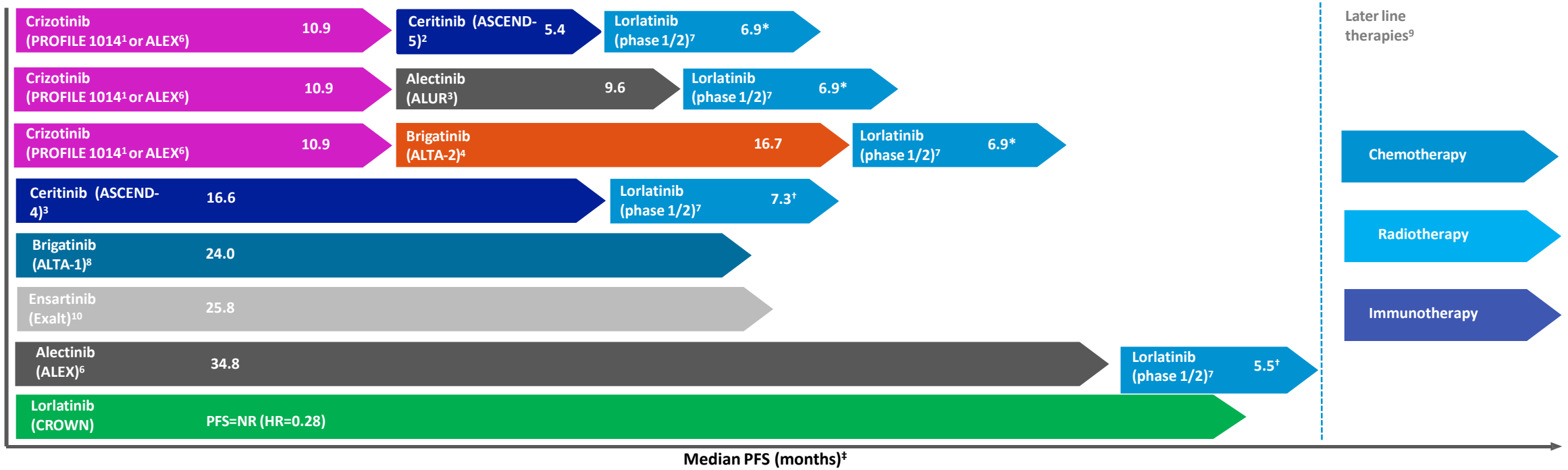
Adapted from Besse B, et al. Poster 9032 presented at ASCO 2018.

[a]Six patients had no-analyzable samples; [b]≥1 ALK kinase domain mutation was detected in 45 of 190 patients (24%); a total of 75 mutations were detected (used for the frequency denominator); [c]n is the number of patients with a mutation in cfDNA; patients may have had ≥1 mutation; bars represent 95% CIs.

Besse B, et al. Poster 9032 presented at ASCO 2018 Congress, Chicago, USA, 1–5 June, 2018.

Rapidly Evolving Clinical Evidence on ALK+ NSCLC Defines Treatment Sequence for Patients

The rapidly evolving ALK+ NSCLC landscape and a growing body of clinical evidence is defining the treatment sequence for patients.



*Data are from the EXP4 and EXP5 groups (two or three prior ALK TKIs ± chemotherapy); †Lorlatinib PFS data following ceritinib or alectinib in any line; ‡Adapted and updated from Ferrera, et al. 20189. **Brigatinib is currently not approved for use as a first-line treatment of ALK+ NSCLC in Singapore; Ensartinib is an investigational agent not yet approved in the first-line treatment of ALK+ NSCLC in Singapore; Lorlatinib is currently not approved for use as a first-line treatment option for ALK+ NSCLC in Singapore.** For illustration purposes only; note that cross-trial comparisons should be interpreted with caution due to the differences in study design, size, patient population, and data maturity; the IMpower150 regimen is not currently approved in the US

1. Solomon BJ, *et al*. *N Eng J Med*. 2014;371(23):2167–2177. 2. Shaw A, *et al*. *Lancet Oncol*. 2017;18(12):1590–1599. 3. Novello S, *et al*. *Ann Oncol*. 2018;29(6):1409–1416. 4. Huber RM, *et al. J. Clin. Oncol.* 2018;36(15):9061–9061. 5. Soria JC, *et al*. *Lancet.* 2017;389(10072):917–929. 6. Camidge DR, *et al. J Thorac Oncol*. 2019;14(7):1233–1243. 7. Besse B, *et al. J. Clin. Oncol.* 2018;36(15):9032–9032 8. Camidge DR, *et al. N Engl J Med*. 2018;379(21):2027–2039. 9. Ferrara R, *et al. J Thorac Oncol*. 2018;13(1):27–45. 10. Horn, L. IASLC WCLC 2020 Presidential Symposium.

ALK: Ananaplastic lymphoma kinase; NSCLC: Non-small– cell lung cancer; PFS: Progression-free survival.

Chemo post 2nd gen ALK TKI

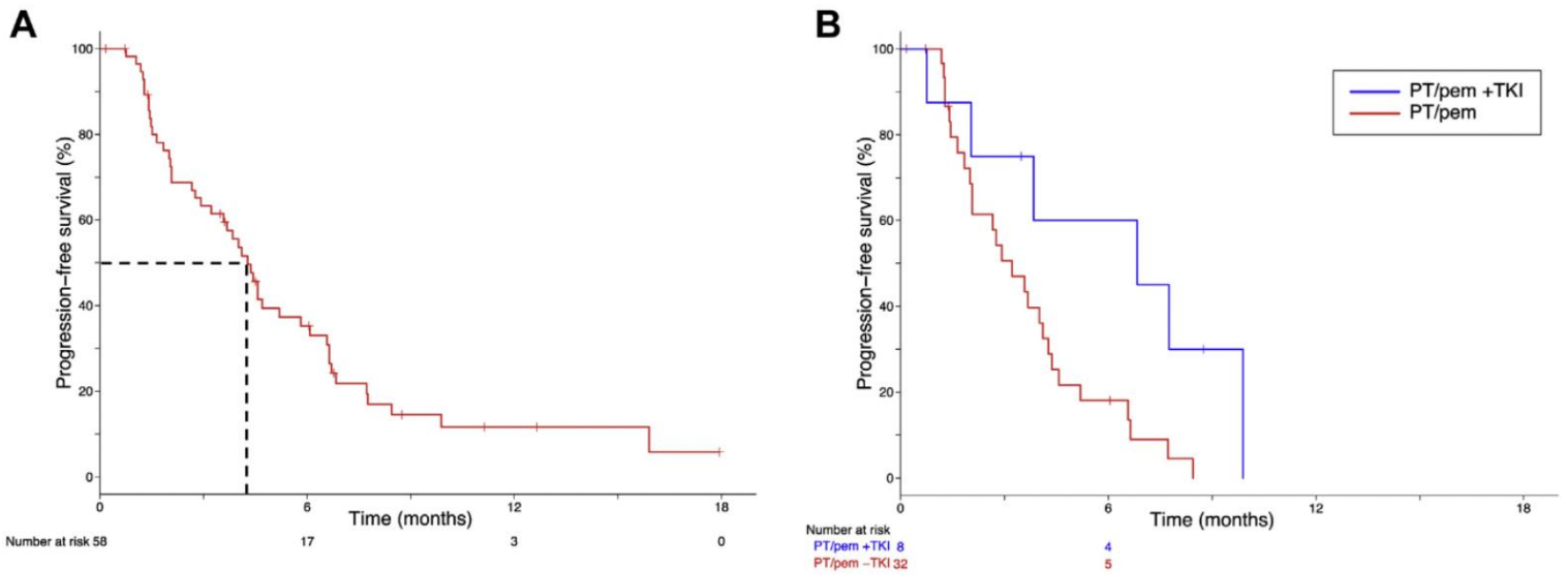


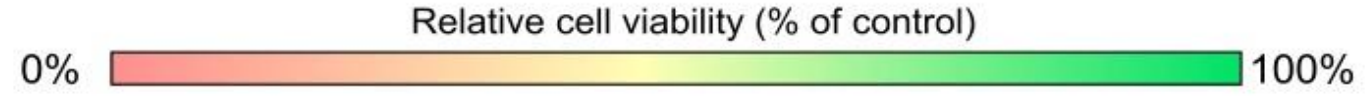
Figure 3. Progression-free survival (PFS) on chemotherapy. *A*, Overall PFS on platinum (PT)-pemetrexed (pem)-based chemotherapy for the entire study cohort. *Dotted lines* show the median PFS. *B*, PFS for patients who received PT/pem only (*red*) versus those who received PT/pem with an ALK TKI (*blue*).

Is LORLATINIB free from Acquired Resistance?

- Answer : NO
- C1156Y + L1198F and I1171N + L1256F led to resistance to LORLATINIB re-sensitization to crizotinib and alectinib, respectively
- I1171N + L1198F mutants are more sensitive to crizotinib than I1171N single mutants.
- Meanwhile, resistance to I1171N+L1196M can be overcome by ceritinib and brigatinib.
-
- I1171N + F1174I and I1171N + L1198H. PAN TKI RESISTANCE MUTATIONs

What is the answer for LORLATINIB RESISTANCE

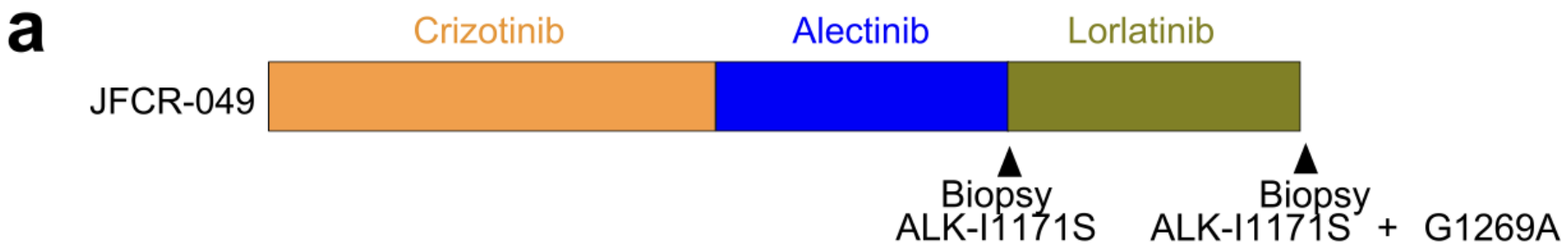
a



	Drugs	DMSO	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib	Entrectinib	Gilteritinib
BaF3 cells	Parent (+ IL-3)	100.0	88.2	77.5	83.3	81.1	82.4	78.4	95.2
	EML4-ALK WT	100.0	9.1	0.3	0.4	0.5	0.5	9.5	0.1
	EML4-ALK I1171N + F1174I	100.0	116.5	100.0	101.1	83.9	116.1	142.6	11.4
	EML4-ALK I1171N + L1198H	100.0	47.3	75.4	82.0	51.0	76.1	80.3	2.3
	Drugs	**Erlotinib**	**Gefitinib**	**Afatinib**	**Osimertinib**	**Vandetanib**	**Lenvatinib**	**Cabozantinib**	**Foretinib**
BaF3 cells	Parent (+ IL-3)	78.1	80.9	81.5	91.1	97.8	81.6	99.3	77.9
	EML4-ALK WT	111.5	98.7	132.0	81.9	139.0	91.8	142.0	92.7
	EML4-ALK I1171N + F1174I	114.1	155.6	112.1	122.4	114.9	114.2	152.5	100.2
	EML4-ALK I1171N + L1198H	87.5	74.1	83.7	87.2	90.3	89.9	86.7	83.8
	Drugs	**Imatinib**	**Ponatinib**	**Dasatinib**	**AEW541**	**OSI906**	**R428**	**Sunitinib**	**17-AAG**
BaF3 cells	Parent (+ IL-3)	81.6	64.8	49.6	83.2	104.8	84.1	83.1	81.6
	EML4-ALK WT	69.4	97.4	105.0	98.5	149.7	99.7	101.1	83.8
	EML4-ALK I1171N + F1174I	116.1	122.1	103.5	93.1	138.9	142.5	108.6	92.6
	EML4-ALK I1171N + L1198H	87.8	77.3	73.0	88.6	86.8	85.0	89.7	82.5

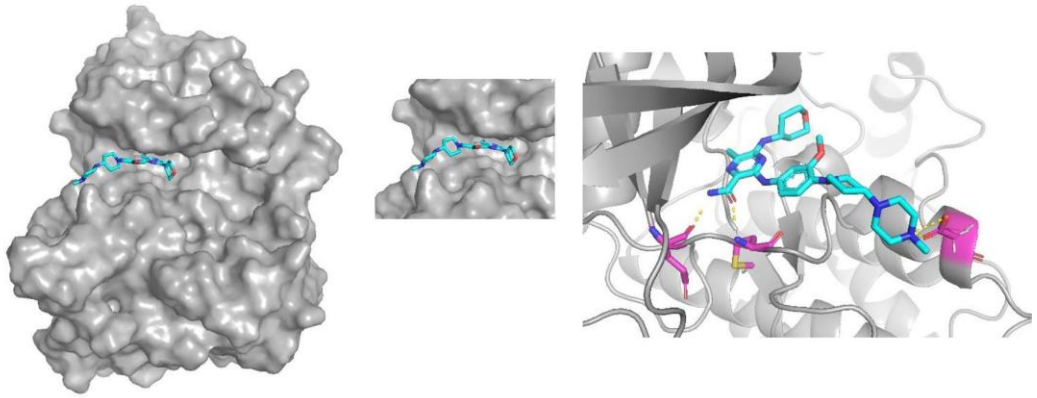
GILTERITINIB: TKI used in relapsed FLT3AML

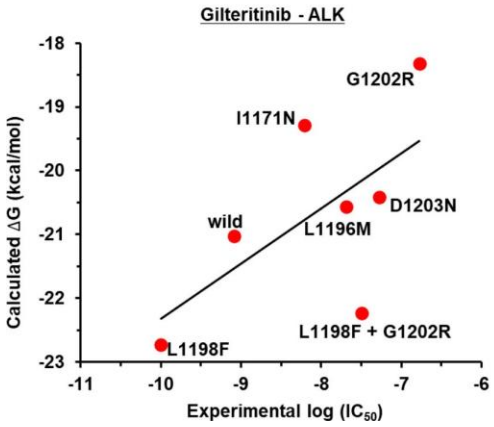
In clinic use

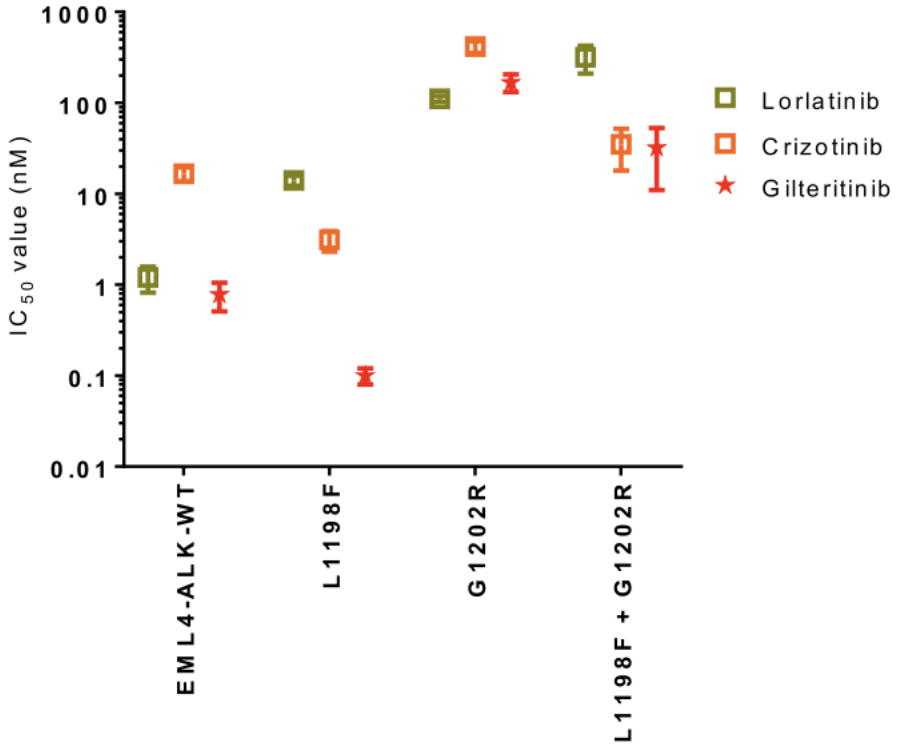


Sensitive To: Brigatinib Ceritinib and Gilteritinib

GILTERITINIB







FOUNDATIONONE® CDx

PATIENT
Viradia, Vipul

TUMOR TYPE
Lung adenocarcinoma
COUNTRY CODE
IN

REPORT DATE
06 Oct 2021
ORDERED TEST #
ORD-1201922-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT

DISEASE Lung adenocarcinoma
NAME Viradia, Vipul
DATE OF BIRTH 12 October 1976
SEX Male
MEDICAL RECORD # Not given

PHYSICIAN

ORDERING PHYSICIAN Bhosale, Bharat
MEDICAL FACILITY Bombay Hospital & Research Center
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 200979
PATHOLOGIST Pandey, Vinita

SPECIMEN

SPECIMEN SITE Pleura
SPECIMEN ID ADH-4137/21
SPECIMEN TYPE Block
DATE OF COLLECTION 15 September 2021
SPECIMEN RECEIVED 27 September 2021

Biomarker Findings

Microsatellite status - MS-Stable
Tumor Mutational Burden - 8 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix.

ALK **I1171M, G1269A, I1171T - subclonal, EML4-ALK fusion (Variant 1)†**
CTNNB1 **S37F**
MST1R **R1194H**
MUTYH **E466***
SETD2 **T305fs*4**
SMAD4 **E538fs*15**
TET2 **S21***
TP53 **R273H - subclonal, R248W, S127F†**

7 Disease relevant genes with no reportable alterations: *BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1*

† See About the Test in appendix for details.

3 Therapies with Clinical Benefit
3 Therapies with Resistance
20 Clinical Trials

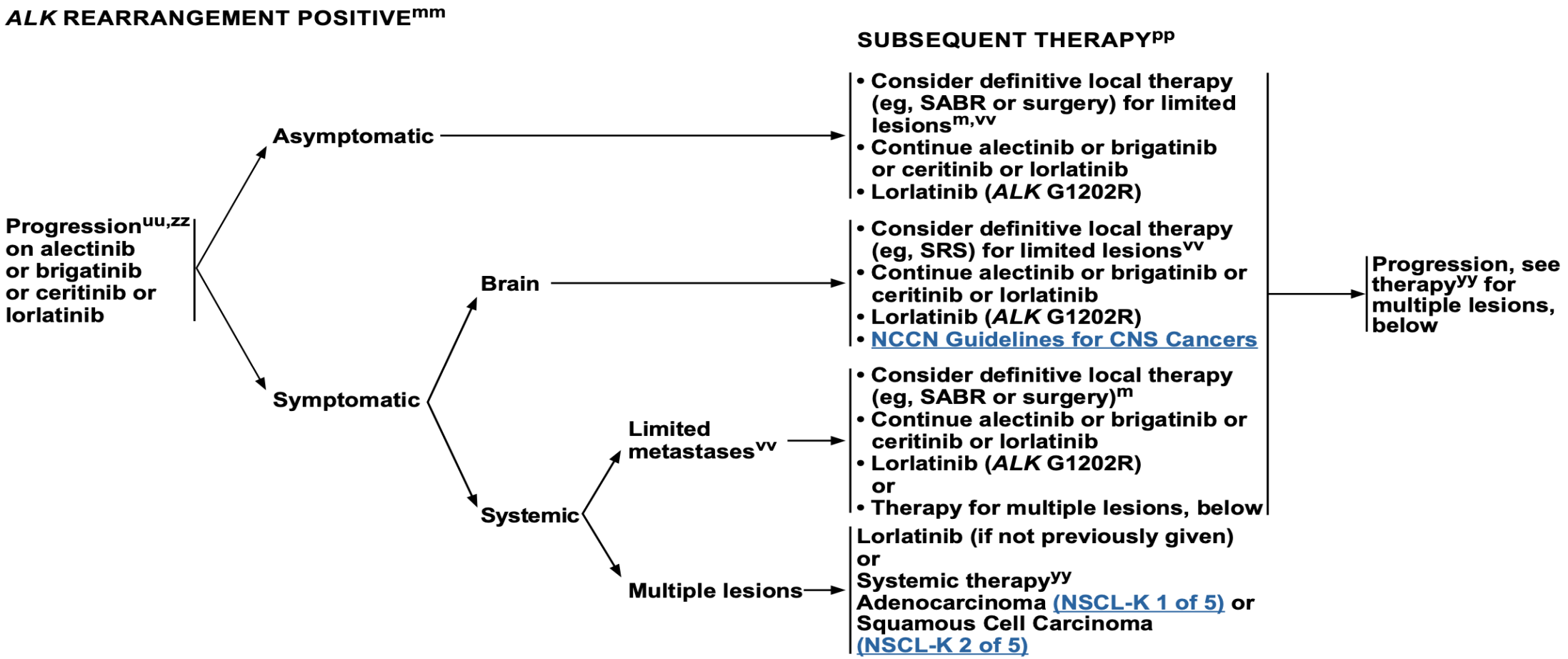
BIOMARKER FINDINGS	THERAPY AND CLINICAL TRIAL IMPLICATIONS
Microsatellite status - MS-Stable	**No therapies or clinical trials.** see Biomarker Findings section
Tumor Mutational Burden - 8 Muts/Mb	**No therapies or clinical trials.** see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL RELEVANCE (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL RELEVANCE (IN OTHER TUMOR TYPE)
***ALK* -** I1171M, G1269A, I1171T - subclonal, EML4-ALK fusion (Variant 1)	Brigatinib [1]	none
	Ceritinib [1]	
	Entrectinib	
	Alectinib ⊗	
	Crizotinib ⊗	
	Lorlatinib ⊗	
10 Trials *see p. 14*		
***CTNNB1* -** S37F	none	none
10 Trials *see p. 16*		

⊗ *Extensive evidence showing variant(s) in this sample may confer resistance to this therapy*

[ ] *NCCN category*

NCCN



[m] IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).

[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).

[uu] Beware of flare phenomenon in subset of patients who discontinue TKI. If disease flare occurs, restart TKI.

[vv] Limited number is undefined but clinical trials have included 3 to 5 metastases.

[yy] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR exon 19* deletion *or L858R, ALK*+ NSCLC.

Summary

1. Treating ALK positive Lung cancer is challenging task
2. CNS relapse and mutations causing resistance to available TKI
3. Best Agent first vs sequencing : Both strategies have been tried
4. Lorlatinib seems to be best upfront available options

Summary

1. Treating Lorlatinib resistant cases is unmet need now
2. Repeat Biopsy must be tried whenever feasible
3. Liquid Biopsy is promising tool to pick up Resistant mutations
4. Chemotherapy is always an option but in fit patients preferably with continuation of TKI

Thank you

Sunrise Oncology Centre