ALESIA – 5 year update & Optimal Sequencing of TKIs in ALK+ NSCLC

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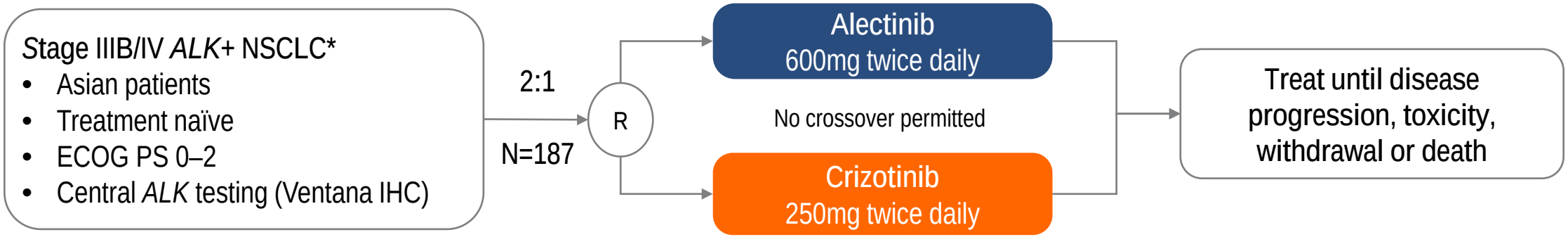
My subsequent reactions….

Alectinib vs crizotinib in Asian patients with treatment-naïve advanced ALK+ non-small cell lung cancer: 5-year update from the Phase 3 ALESIA study

Thanyanan B et. al ESMO ASIA 2022

ALESIA: alectinib vs crizotinib in treatment-naïve Asian patients with advanced *ALK*+ NSCLC



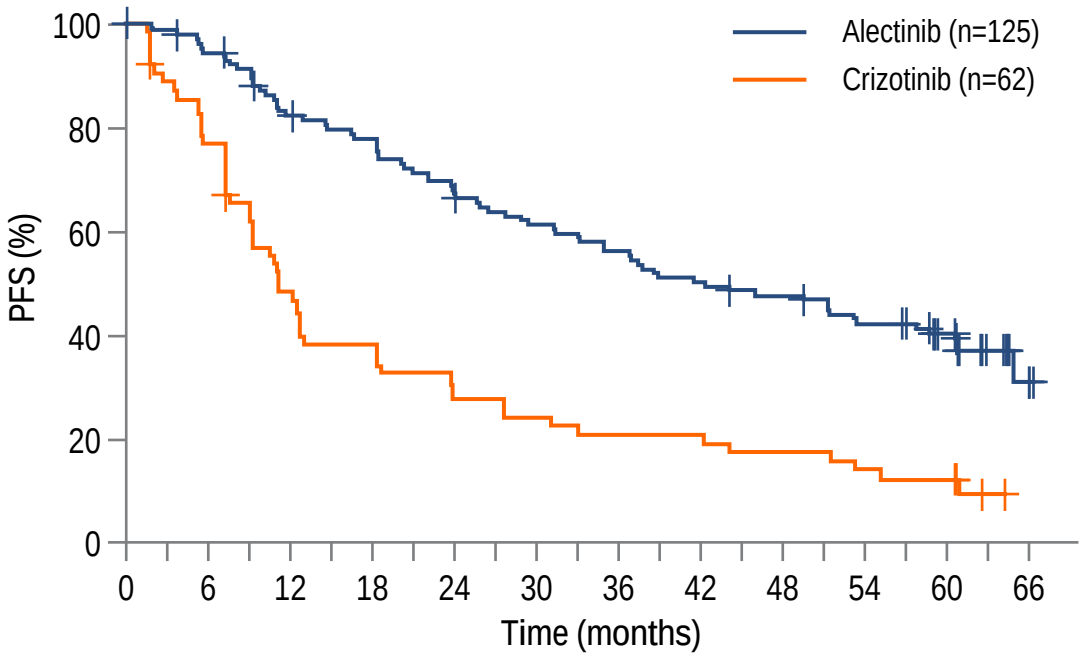
- Stratification factors: ECOG PS (0/1 vs 2) and CNS metastases at baseline (yes vs no)
- Primary endpoint: PFS by INV
- Secondary endpoints: Time to CNS progression by IRC, ORR by INV, DOR by INV, OS and safety
- Median duration of survival follow-up: 61 months alectinib vs 51 months crizotinib

Baseline demographics		Alectinib n=125	Crizotinib n=62
Age, years	Median (range)	51.0 (21–78)	49.0 (28–83)
Gender, %	Male / Female	51.2 / 48.8	54.8 / 45.2
ECOG PS, %	0–1 / 2	96.8 / 3.2	98.4 / 1.6
Smoking status, %	Active smoker / Non-smoker / Past smoker	3.2 / 67.2 / 29.6	4.8 / 72.6 / 22.6
CNS metastases by IRC, %	Yes	35.2	37.1
CNS metastases by INV, %	Yes	33.6	32.3
Prior brain radiation, %	Yes	6.4	8.1

Patients were enrolled from China, Thailand and South Korea. *Asymptomatic CNS metastases allowed.
Data cut-off 16 May 2022. ClinicalTrials.gov: NCT02838420. CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; INV, investigator IRC, independent review committee; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

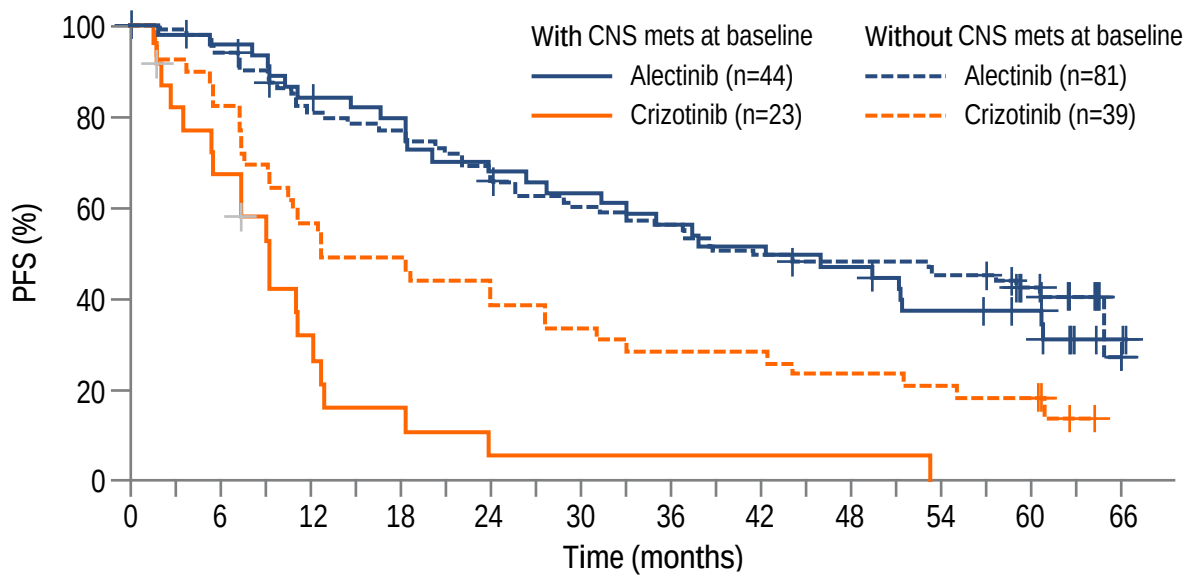
Updated analyses from ALESIA demonstrate durable PFS benefit for alectinib versus crizotinib, irrespective of CNS involvement at baseline

Updated PFS: ITT population



	Alectinib n=125	Crizotinib n=62
Median PFS, months (95% CI)	41.6 (33.1–58.9)	11.1 (9.1–18.4)
HR (95% CI)	0.33 (0.23–0.49)	

PFS according to CNS status at baseline

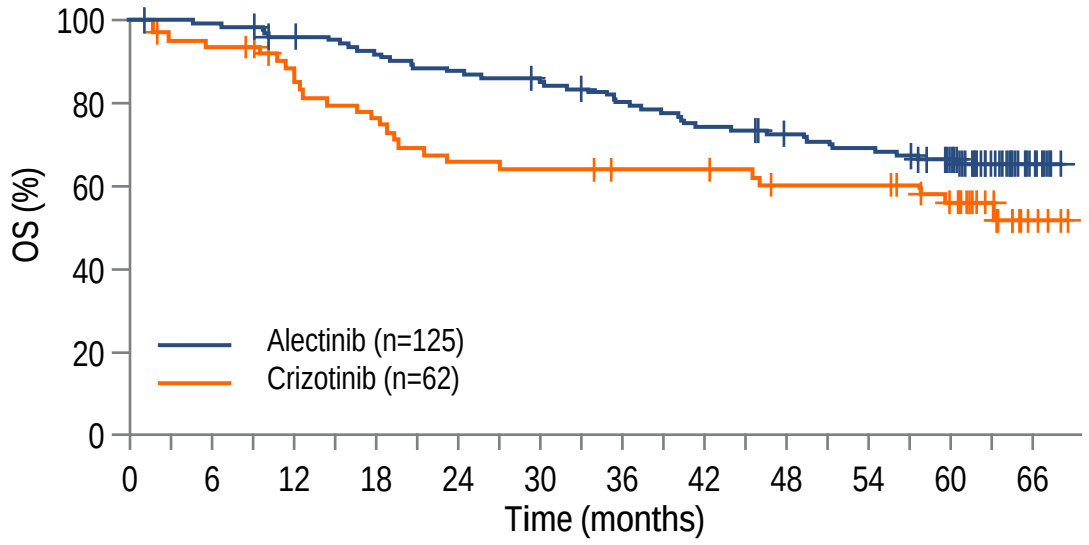


	With CNS mets at baseline		Without CNS mets at baseline	
	Alectinib n=44	Crizotinib n=23	Alectinib n=81	Crizotinib n=39
Median PFS, months (95% CI)	42.3 (27.8–60.7)	9.2 (5.5–12.2)	41.6 (29.5–64.9)	12.7 (9.2–27.6)
HR (95% CI)	0.17 (0.09–0.33)		0.45 (0.29–0.71)	

Data cut-off 16 May 2022. CI, confidence interval; CNS, central nervous system; HR, hazard ratio; ITT, intent-to-treat; mets, metastases; PFS, progression-free survival

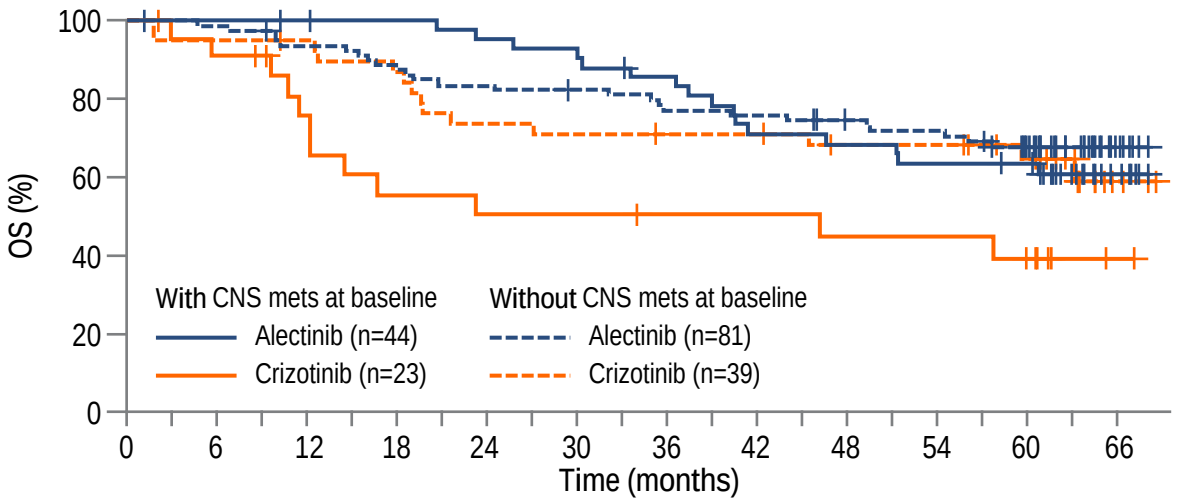
A clinically meaningful improvement in 5-year OS rate was observed for alectinib compared with crizotinib

Updated OS: ITT population



	Alectinib n=125	Crizotinib n=62
Pts with event, n (%)	41 (32.8)	26 (41.9)
Median OS, months (95% CI)	NE (NE–NE)	NE (45.5–NE)
HR (95% CI)	0.60 (0.37–0.99)	
5-year OS rate, % (95% CI)	66.4 (57.9–74.9)	56.0 (43.0–69.1)
Pts remaining at risk, n	69	25

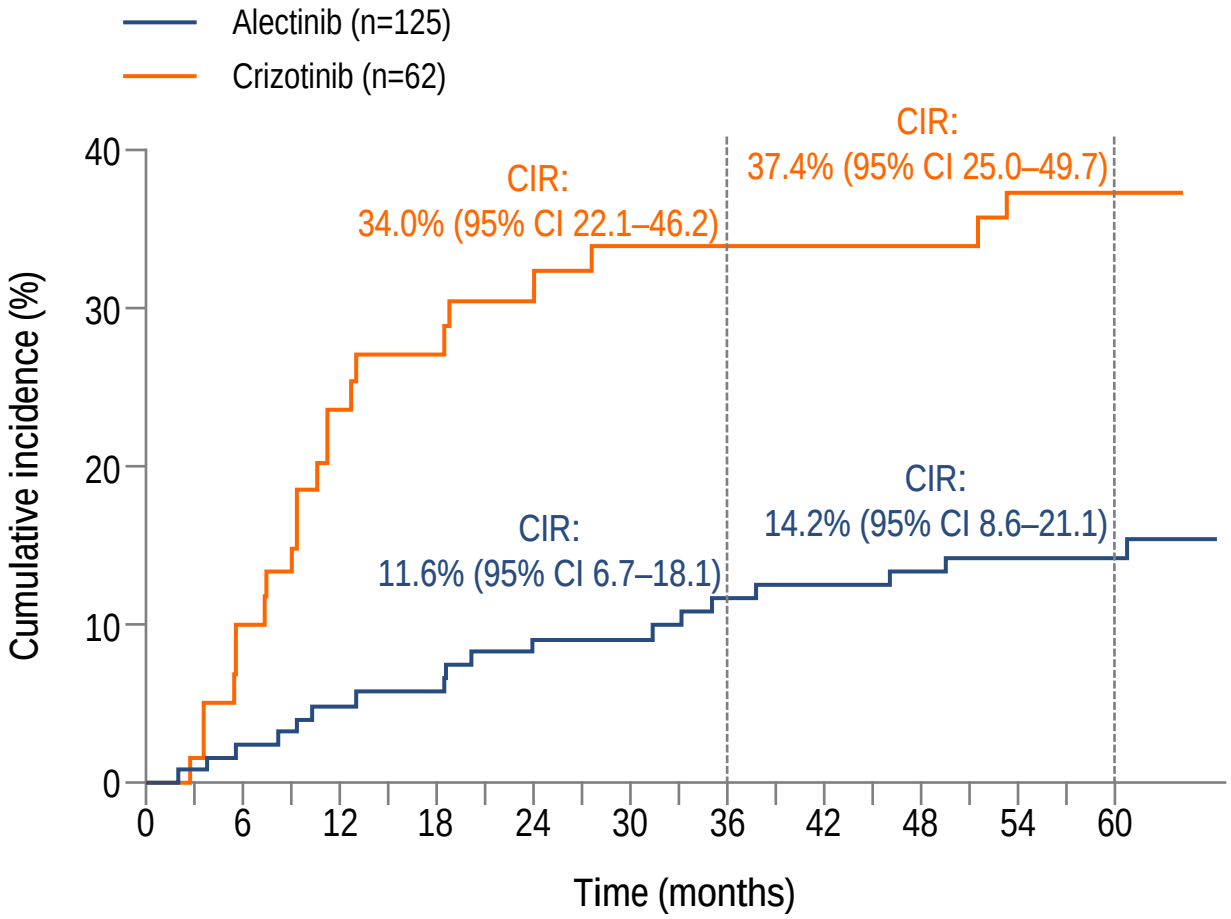
OS according to CNS status at baseline



	With CNS mets at baseline		Without CNS mets at baseline	
	Alectinib n=44	Crizotinib n=23	Alectinib n=81	Crizotinib n=39
Pts with event, n (%)	16 (36.4)	12 (52.2)	25 (30.9)	14 (35.9)
Median OS, months (95% CI)	NE (51.4–NE)	46.2 (12.2–NE)	NE (NE–NE)	NE (59.8–NE)
HR (95% CI)	0.40 (0.19–0.85)		0.81 (0.42–1.55)	
5-year OS rate, % (95% CI)	63.6 (48.9–78.3)	39.3 (17.4–61.2)	67.8 (57.4–78.2)	64.9 (49.3–80.4)
Pts remaining at risk, n	25	6	44	19

Data cut-off 16 May 2022. CI, confidence interval; CNS, central nervous system; HR, hazard ratio; ITT, intent-to-treat; mets, metastases; NE, not evaluable; OS, overall survival; pts, patients

Treatment with alectinib delayed the time to CNS progression*



	Alectinib n=125	Crizotinib n=62
CNS progression without prior systemic progression		
Patients with events, n (%)	18 (14.4)	22 (35.5)
Cause-specific HR (95% CI)	0.16 (0.08–0.32)	
Estimated cumulative incidence, % (95% CI)		
At 36 months	11.6 (6.7–18.1)	34.0 (22.1–46.2)
At 60 months	14.2 (8.6–21.1)	37.4 (25.0–49.7)

*Derived from investigators' assessment. CNS PD = CNS Target Lesion PD per RECIST version 1.1, appearance of new CNS lesion(s), and/or unequivocal PD of Non-Target CNS lesion(s)
Data cut-off 16 May 2022. CI, confidence interval; CIR, cumulative incidence rate; CNS, central nervous system; HR, hazard ratio; PD, progressive disease

Post-progression therapy

	Alectinib n=125	Crizotinib n=62
Patients with PD, n	68	48
Anti-cancer therapy after PD, n (%)	42 (61.8)	38 (79.2)
ALK inhibitor, n (%)	25 (36.8)	28 (58.3)
Alectinib	5 (7.4)	14 (29.2)
Lorlatinib	8 (11.8)	6 (12.5)
Brigatinib	6 (8.8)	7 (14.6)
Crizotinib	7 (10.3)	2 (4.2)
Ceritinib	3 (4.4)	4 (8.3)
Ensartinib	2 (2.9)	1 (2.1)
Investigational drug	1 (1.5)	0
Chemotherapy, n (%)	24 (35.3)	15 (31.3)
Anti-VEGF therapies, n (%)	9 (13.2)	3 (6.3)
Immunotherapy, n (%)	3 (4.4)	2 (4.2)
Other therapies, n (%)	6 (8.8)	7 (14.6)

More crizotinib patients (79.2% vs 61.8% alectinib) received at least one anti-cancer therapy post-progression
Approximately 30% of patients in the crizotinib arm received alectinib after their disease progressed

Data cut-off 16 May 2022. PD, progressive disease; VEGF, vascular endothelial growth factor

The safety profile of alectinib remained favourable with longer follow-up; no new safety signals were observed

Event, n (%)	Alectinib (n=125)	Crizotinib (n=62)
Patients with ≥1		
All grade AEs	125 (100)	62 (100)
Serious AEs	35 (28.0)	18 (29.0)
Grade ≥3 AEs	60 (48.0)	34 (54.8)
Fatal AEs	5 (4.0)*	3 (4.8)
AEs leading to treatment discontinuation	14 (11.2)	9 (14.5)
AEs leading to dose reduction	33 (26.4)	17 (27.4)
AEs leading to dose interruption	33 (26.4)	19 (30.6)

Grade ≥3 AEs with ≥3% difference in frequency between treatment arms, n (%)	Alectinib (n=125)	Crizotinib (n=62)
Weight increased	11 (8.8)	1 (1.6)
Blood creatine phosphokinase increased	8 (6.4)	2 (3.2)
ALT increased	3 (2.4)	4 (6.5)
Nausea	1 (0.8)	3 (4.8)
Neutrophil count decreased	0	9 (14.5)
ECG QT prolonged	0	3 (4.8)
White blood cell count decreased	0	3 (4.8)
Decreased appetite	0	3 (4.8)
Hyponatraemia	0	3 (4.8)
Interstitial lung disease	0	3 (4.8)
Vomiting	0	3 (4.8)
Bradycardia	0	2 (3.2)
Hepatic function abnormal	0	2 (3.2)

Median treatment duration was more than three-times greater for alectinib (42.3 months) compared to crizotinib (12.6 months)

*Three additional fatal events occurred during the longer follow-up: one was due to COVID-19 pneumonia, and the other two were reported as 'death' and not related to alectinib treatment
Data cut-off 16 May 2022. AE, adverse event; ALT, alanine aminotransferase; ECG, electrocardiogram

Conclusions: 5-year update from the Phase 3 ALESIA study

With **at least 5 years** of follow-up, 1L alectinib **600mg twice daily** continues to demonstrate clinical benefit to Asian patients with advanced *ALK*+ NSCLC, **consistent with** that observed in the **global ALEX study**

Treatment with alectinib also delayed the time to CNS progression

This clinical benefit, coupled with a tolerable and manageable safety profile, **confirms alectinib as standard-of-care treatment** for patients with advanced *ALK*+ NSCLC

Case scenario:

- 50-year old woman
- No history of smoking
- c/o severe left back pain, breathlessness and cough since 3 months
- CT shows mass in the left lower lobe and moderate ipsilateral pleural effusion
- Histopathology reveals moderately differentiated adenocarcinoma
- EGFR wild, ALK positive by IHC
- PET CT: Lung carcinoma with pleural effusion; brain and skeletal mets.
- Final diagnosis: NSCLC, stage IV, ALK rearranged

How do you diagnose ALK rearranged NSCLC?

- IHC
- IHC for screening and confirm by FISH
- FISH
- PCR
- NGS

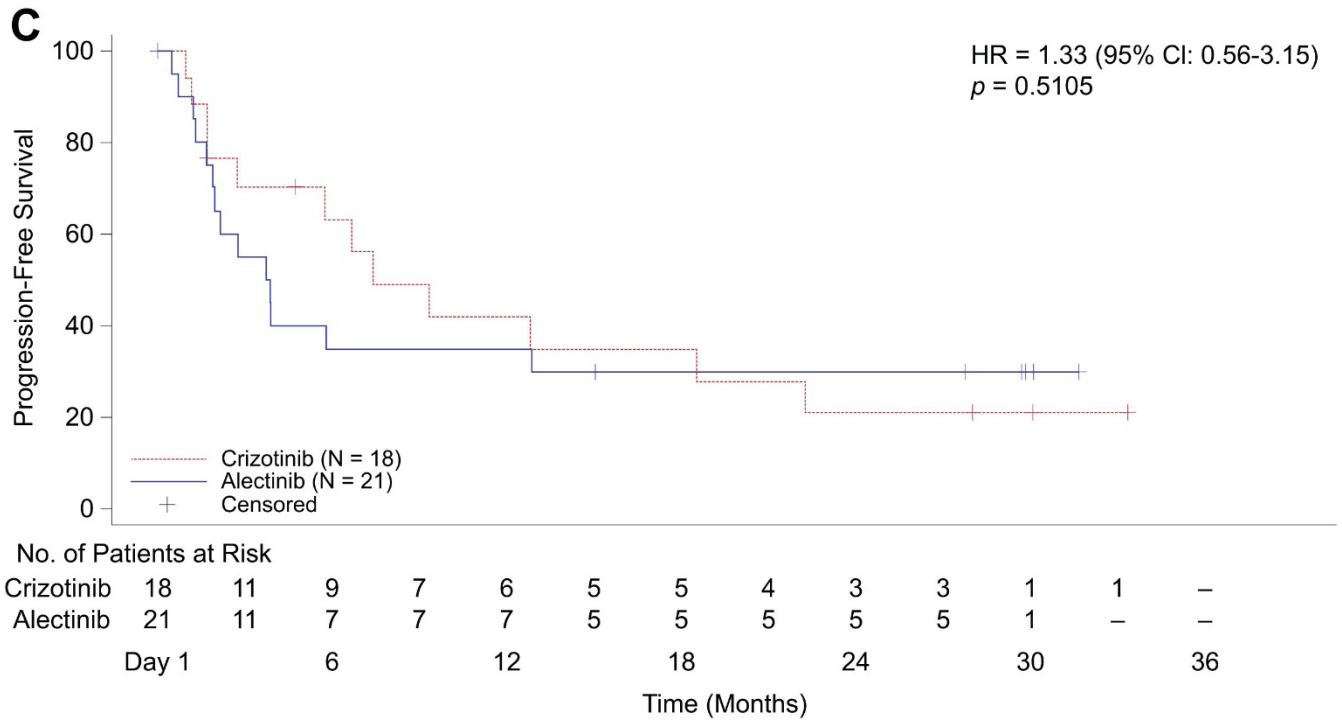
What is the ALK positivity rate in your centre??

Concordance between NGS and FISH and IHC???

PRINCIPLES OF MOLECULAR AND BIOMARKER ANALYSIS

- Molecular Targets for Analysis (continued)
  - *ALK* (anaplastic lymphoma kinase) Gene Rearrangements: ALK is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ALK kinase domain.
    - The most common fusion partner seen with ALK is echinoderm microtubule-associated protein-like 4 (EML4), although a variety of other fusion partners have been identified.
    - The presence of an *ALK* rearrangement is associated with responsiveness to oral ALK TKIs.
    - Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of an *ALK* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - Testing Methodologies: FISH break-apart probe methodology was the first methodology deployed widely. IHC can be deployed as an effective screening strategy. FDA-approved IHC can be utilized as a stand-alone test, not requiring confirmation by FISH. Numerous NGS methodologies can detect *ALK* fusions. Targeted real-time PCR assays are used in some settings, although it is unlikely to detect fusions with novel partners.
  - *ROS1* (ROS proto-oncogene 1) Gene Rearrangements: ROS1 is a receptor tyrosine kinase that can be rearranged in NSCLC, resulting in dysregulation and inappropriate signaling through the ROS1 kinase domain.
    - Numerous fusion partners are seen with *ROS1*, and common fusion partners include: *CD74, SLC34A2, CCDC6*, and GOPC (*FIG*).
    - The presence of a *ROS1* rearrangement is associated with responsiveness to oral ROS1 TKIs.
    - Some clinicopathologic features—such as smoking status and histology—have been associated with the presence of a *ROS1* rearrangement; however, these features should not be utilized in selecting patients for testing.
    - Testing Methodologies: FISH break-apart probe methodology can be deployed; however, it may under-detect the FIG-ROS1 variant. IHC approaches can be deployed; however, IHC for *ROS1* fusions has low specificity, and follow-up confirmatory testing is a necessary component of utilizing ROS1 IHC as a screening modality. Numerous NGS methodologies can detect *ROS1* fusions, although DNA-based NGS may under-detect *ROS1* fusions. Targeted real-time PCR assays are utilized in some settings, although they are unlikely to detect fusions with novel partners.

What about patients who are positive by IHC and Negative by FISH?



***ALK* IHC-positive and FISH-negative (n = 39)**

Inv assessed PFS HR=1.33 (95% CI: 0.6–3.2)

Alectinib = 3.8 mo [95% CI: 1.9–NE])

Crizotinib = 7.4 mo [95% CI: 2.7–22.1.

The Kaplan-Meier curves crossed, and median PFS times were low for both alectinib and crizotinib.

Note: The number of patients at risk was very small in these non-prespecified subgroups.

T. Mok et al JTO 2021

J Clin Pathol. 2021 Mar 22;jclinpath-2021-207408. doi: 10.1136/jclinpath-2021-207408. Online ahead of print.

IHC versus FISH versus NGS to detect ALK gene rearrangement in NSCLC: all questions answered?

Ullas Batra [1], Shrinidhi Nathany [2], Mansi Sharma [3], Sunil Pasricha [4], Abhishek Bansal [5], Parveen Jain [3], Anurag Mehta [6]

Affiliations + expand

PMID: 33753563 DOI: 10.1136/jclinpath-2021-207408

Abstract

Aims: Anaplastic lymphoma kinase (*ALK*) rearranged non-small cell lung carcinoma (NSCLC) is a distinct molecular subtype and rapid approval of *ALK* tyrosine kinase inhibitors (TKIs) has necessitated rapid and sensitive diagnostic modalities for the detection of this alteration. Gene rearrangements can be identified using many techniques including fluorescence in situ hybridisation (FISH), reverse transcriptase-PCR, next-generation sequencing (NGS) and immunohistochemistry (IHC) for fusion oncoprotein expression. We aimed to determine the concordance between IHC, FISH and NGS for *ALK* biomarker detection, and determine differences in sensitivity, and survival outcomes.

Methods: We analysed the concordance between IHC using D5F3 monoclonal antibody, FISH (break-apart) and NGS using a custom panel containing 71 different *ALK* variants.

Results: Among 71 cases included in this study, FISH was evaluable in 58 cases. The concordance of ALK IHC with FISH was 75.9% and that with NGS was 84.5%. The sensitivities of FISH and NGS were 75.6% and 87.5%, respectively. The median progression-free survival of ALK IHC-positive and FISH-negative group was 5.5 months and that of both positive was 9.97 months.

Conclusion: Although NGS offers a better throughput and visualisation, IHC still remains the

What are the key factors you consider when selecting the first line treatment for patients with advanced ALK+NSCLC?

Roche

Crizotinib

Ceritinib

Alectinib

Lorlatinib

chemotherapy

Don’t forget the comorbidities!!!

Lets discuss the pros and cons of all the available drugs….

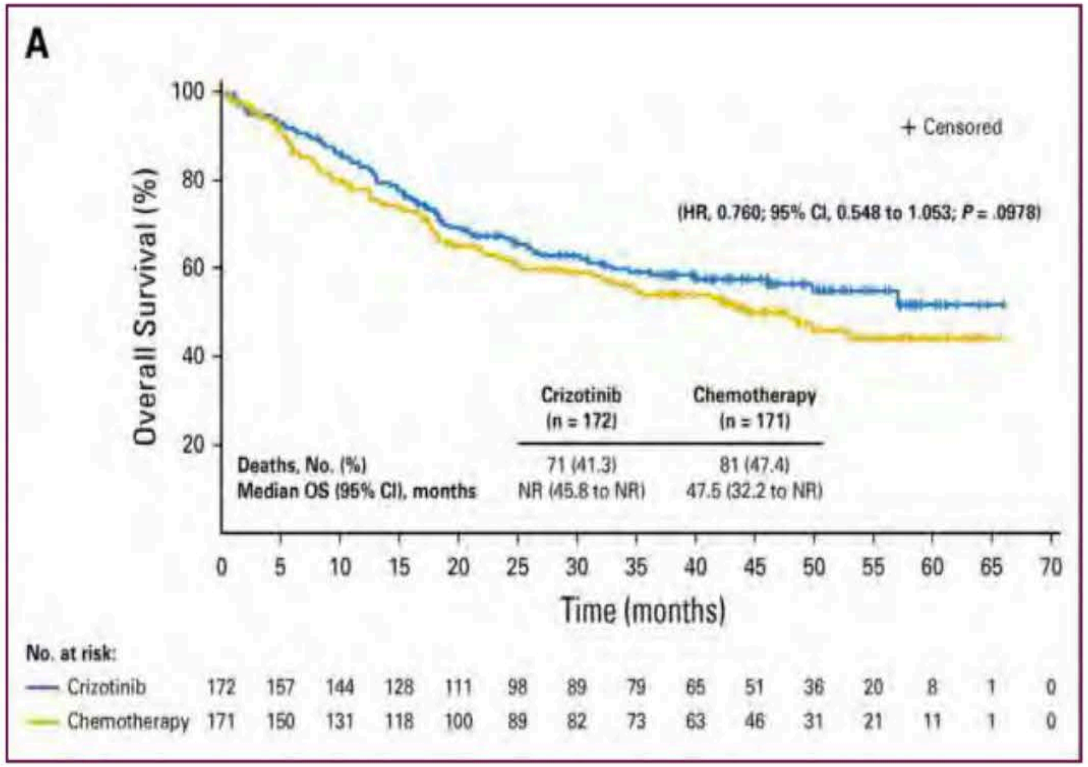
Pros and Cons of Crizotinib

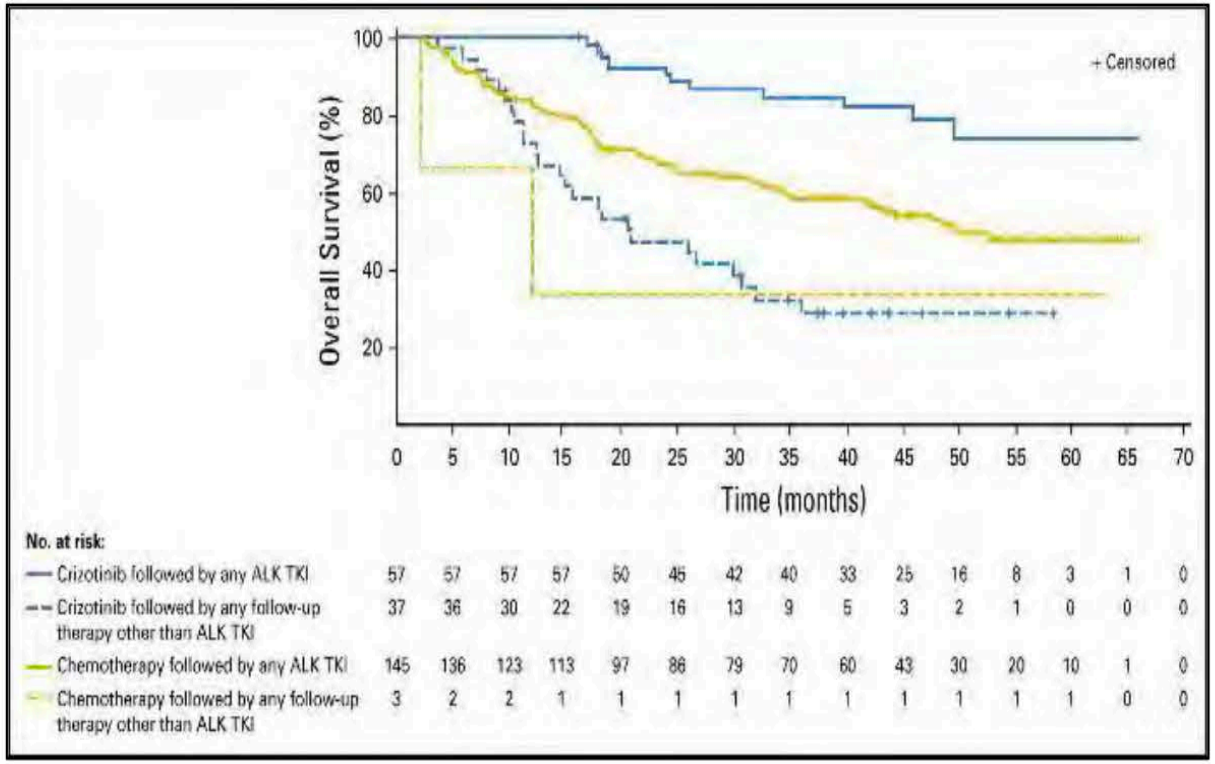
- PROs
- -the first mover advantage
- - relatively cost effective
- Good clinical experience
- -PFS – 10-12 months
- Toxicity profile- easy to manage

- CONS
  - PFS is only 10-12 months
  - Doesn’t cross Blood brain barrier
  - 10 months of crizalk- 6-8 months of 2ng gen TKIs- 6 month of 3rd gen TKIs- overall OS in RWE- 30-32 months
  - Hepatotoxicity could be a concern

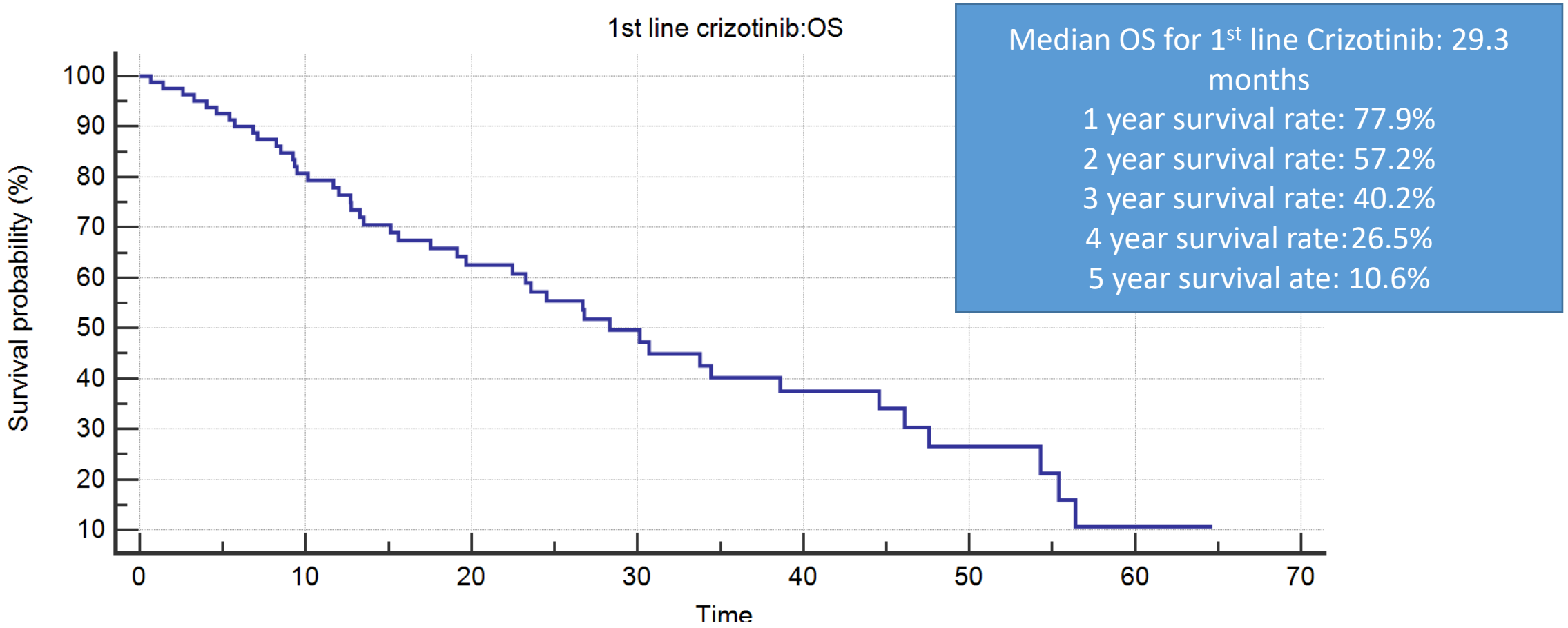
Final Overall Survival Analysis from PROFILE 1014

Solomon et al. JCO 2018

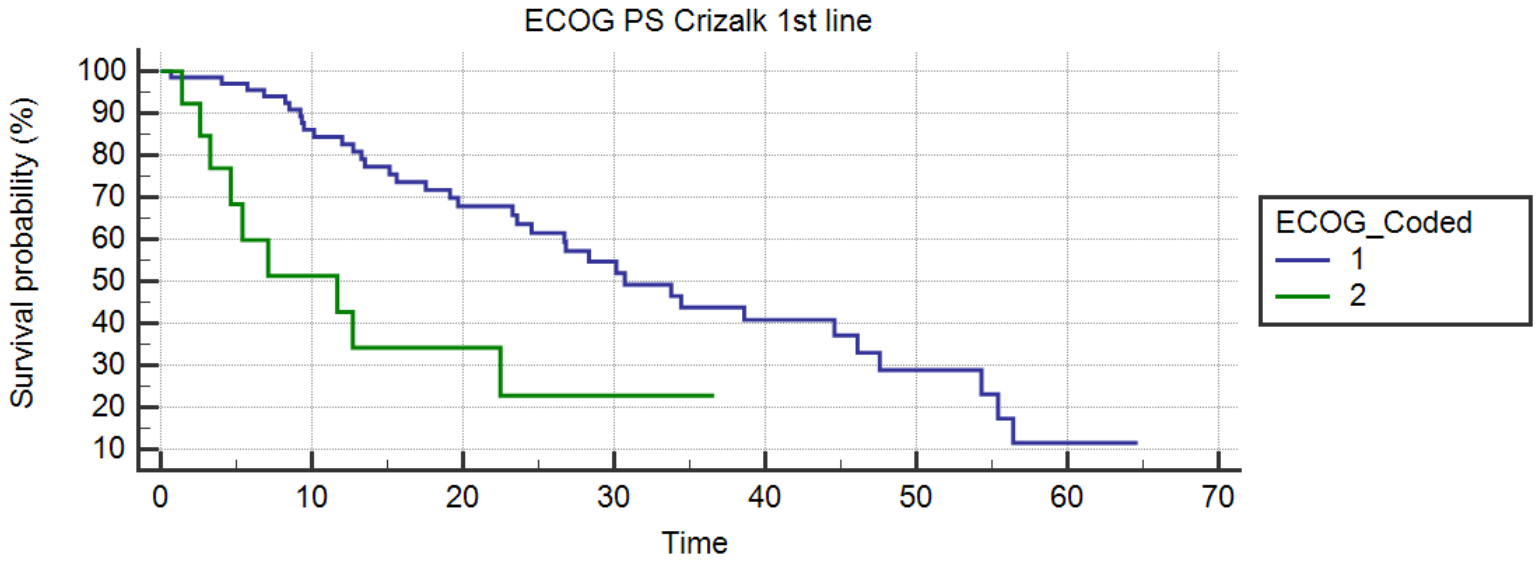




- Survival probability at 4 yrs = 56.6% (95% CI 48.3, 64.1) for crizotinib, median OS NR (45.8,NR)
- Median OS was longest (NR) in 57 patients who received crizotinib then another ALK TKI
- Median OS was 20.8 months in 37 patients who received crizotinib then treatment other than an ALK TKI
- No prospective, randomised data to support sequential crizotinib followed by a next generation ALKi versus a next generation ALKi alone



Median OS for 1st line Crizotinib: 29.3 months
1 year survival rate: 77.9%
2 year survival rate: 57.2%
3 year survival rate: 40.2%
4 year survival rate:26.5%
5 year survival ate: 10.6%



Median OS for 1st line Crizotinib ECOG PS
ECOG 0-2: 30.8months
ECOG 3-4: 11.8months

P value:0.001

Pros and Cons of Ceretinib

- PROs
  - PFS- 16.6 months
  - Has reasonable BBB activity
  - Cost effective in Indian scenario

- CONS
- -No head to head data with Crizalk
- -Toxicity profile
  - Hyperglycemia, nausea, vomiting, Hyperamylasemia
- What after Ceretinib?

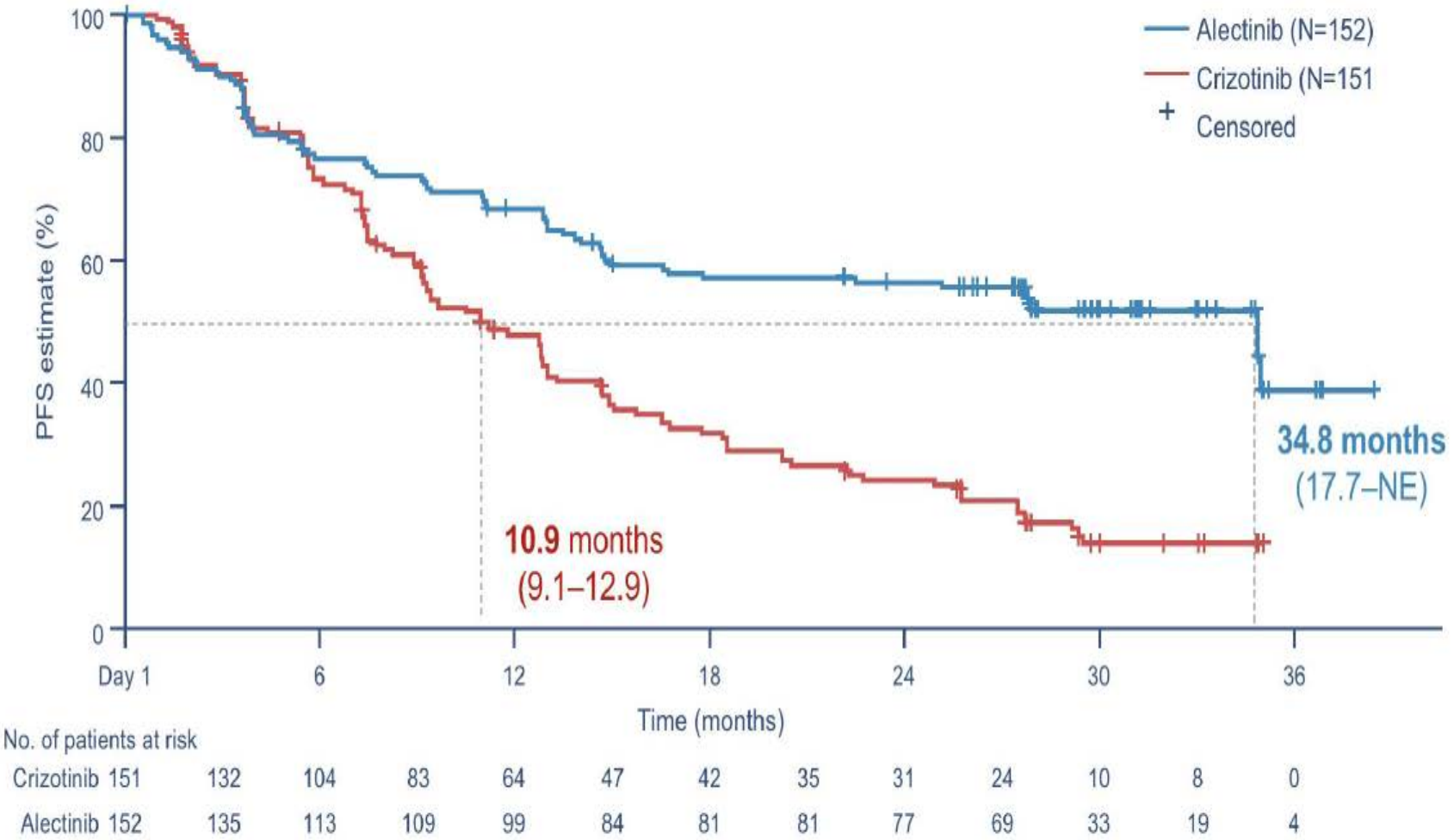
  -3rd Gen TKIs- 6 months- chemo- BSC

Pros and Cons of Alectinib…

- PROS
- - Impressive PFS
- Impressive Os
- Favorable toxicity profile
- Crosses BBB

- CONS
- The ideal dosage
- J ALEX vs ALEX
- What if CROWN surpasses ALEX!!!!

Alectinib is Superior to Crizotinib as First-Line Therapy: Updated Results of Global ALEX

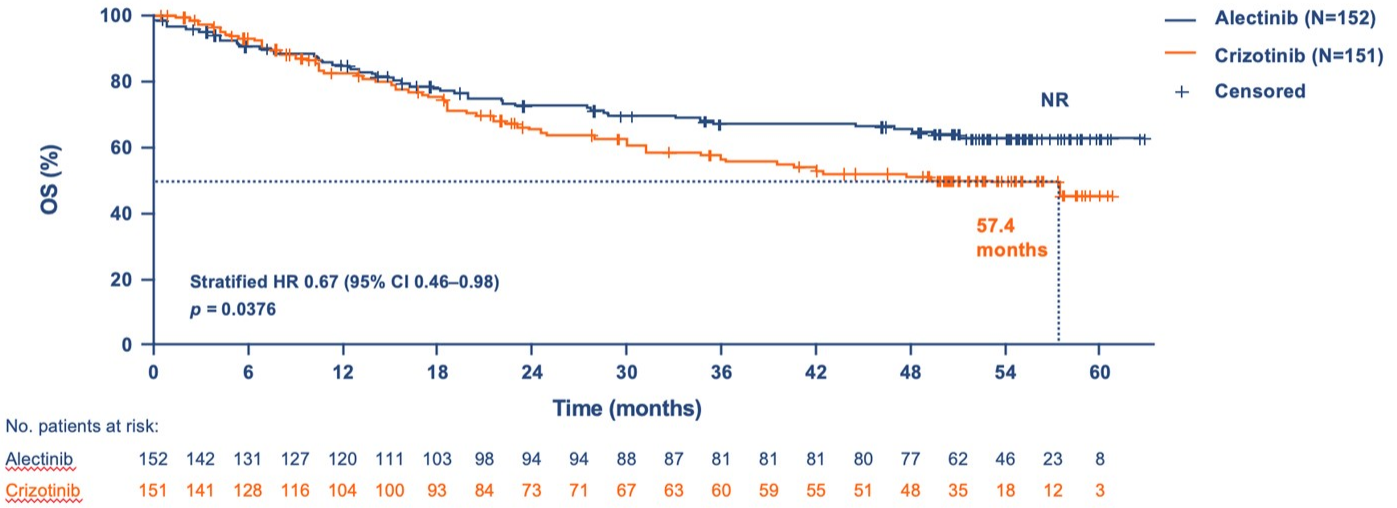


Camidge et al., ASCO 2018

9518

ALEX – updated OS

(median follow-up 48.2 mo)



OS data remain immature, with 37% of events recorded (stratified HR 0.67, 95% CI 0.46–0.98)

Median OS was not reached with alectinib vs 57.4 months with crizotinib (95% CI 34.6–NR)

NR, not reached

1st line alectinib

- Median os: NOT REACHED
- 1yr survival rate: 88.2%
- 2 yr survival rate: 69.3%
- 3 yr survival rate: 69.3%

1st line ceritinib

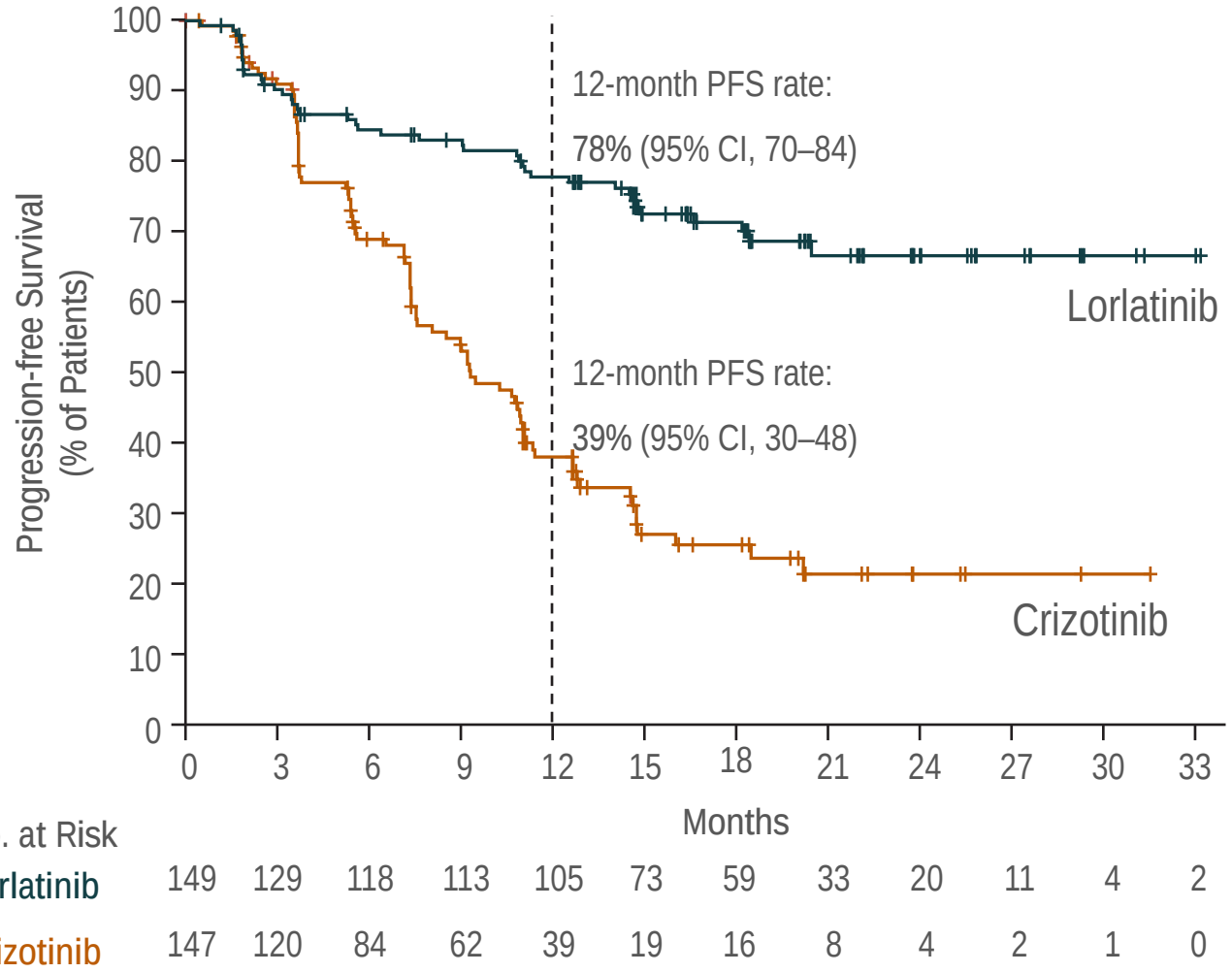
- Median os: 24.3 months
- 1yr survival rate: 76.5%
- 2 yr survival rate: 49.1%
- 3 yr survival rate: 48.7%

Pros and Cons of Lorlatinib

- PROS
- - Impressive HR for PFS
- Impressive HR for OS
- Crosses BBB

- CONS
- Unfavorable toxicity profile
- What after Lorlatinib
- Final Data remains to be seen

• Primary Endpoint: PFS by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	0.28 (0.19-0.41) <0.001	

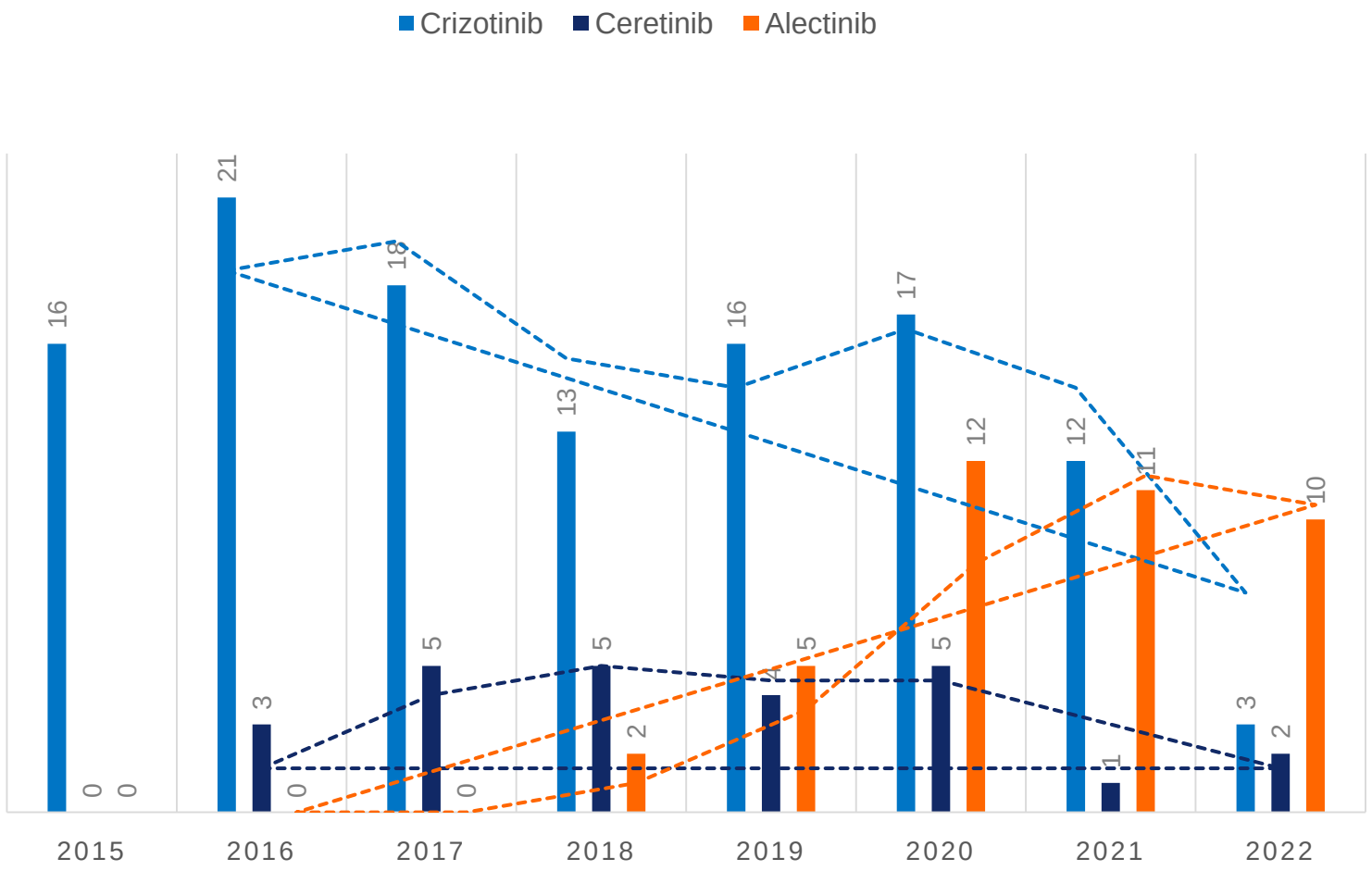
*By stratified log-rank test.

Data is still immature

Lorlatinib is not currently approved in 1L in India

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

Year wise usage of different 1st line TKI drugs



Caption

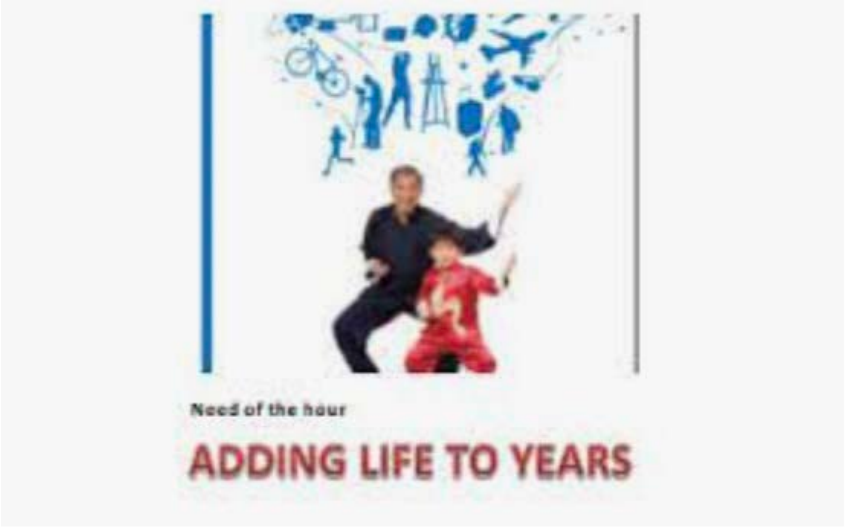
Feedback: Clinical experience with Alectinib

- How would you describe the impact /usage of first-line Alectinib on your patients' lives?

Feedback: Clinical experience with Alectinib

How does the safety and tolerability profile of Alectinib compare with other ALK inhibitors?

Any peculiar side effect that you have encountered??



Most common AEs and AEs of interest for 1L ALK inhibitors

Approved

Crizotinib (PROFILE 1014)[2,*]

- Vision disorders (71%)[¶]
- Diarrhoea (61%)
- Oedema (49%)
- Vomiting (46%)

Ceritinib (ASCEND-4)[3,*]

- Diarrhoea (85%)
- Nausea (69%)
- Vomiting (66%)
- ALT increase (60%)

Alectinib (ALEX)[1,*]

- Constipation (37%)
- Anaemia (26%)
- Fatigue (22%)

Lorlatinib (CROWN)[6,*]

- Hypercholesterolaemia (70%)
- Hypertriglyceridaemia (64%)
- Oedema (55%)
- Increased weight (38%)
- Cognitive effects (21%)

Brigatinib (ALTA-1L)[4,*]

- Diarrhoea (52%)
- CPK increase (46%)
- Cough (35%)
- Early-onset ILD/ pneumonitis[‖]

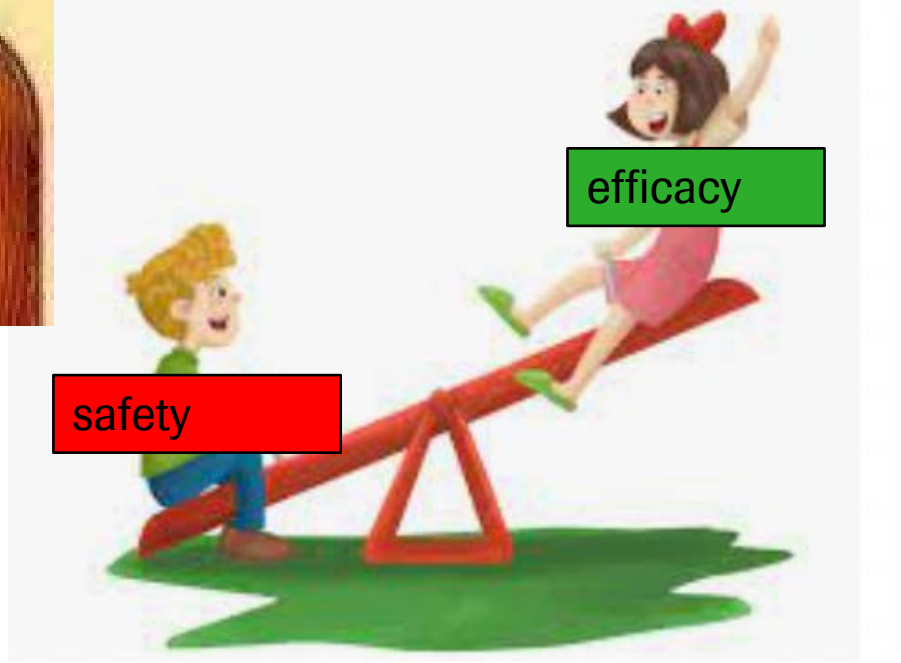
Cross-trial comparisons should be treated with caution due to differences in study designs and patient populations.
*Most common any-grade AEs shown; [†]Most common treatment-related AEs shown; [‡]Percentages not included in presentations; [¶]Comprising a cluster of adverse events including (in descending order): visual impairment, photopsia, blurred vision, vitreous floaters, reduced visual acuity, diplopia and photophobia; [‖]Brigatinib AE of interest: 3% (4/136) of patients on brigatinib had early-onset ILD/pneumonitis in the ALTA-1L study (0% on crizotinib)[4]; early-onset ILD/pneumonitis is a serious and potentially life-threatening event that is associated with brigatinib[4,7]
1L = first-line; AE = adverse event; ALK = anaplastic lymphoma kinase; ALT = alanine aminotransferase
AST = aspartate aminotransferase; CPK = creatine phosphokinase; ILD = interstitial lung disease

1. Mok, et al. Ann Oncol 2020; 2. Solomon, et al. N Engl J Med 2014
3. Soria, et al. Lancet Oncol 2017; 4. Camidge, et al. J Clin Oncol 2020
5. Horn, et al. WCLC 2020; 6. Shaw, et al. N Engl J Med 2020
7. Ng, et al. J Thorac Oncol 2020

1) What are your views on the safety data of Alectinib and o

nd efficacy data of Alectinib help y

run without any serious complicati



What about the sequencing approach??

- **Are there any takers for a sequencing approach (a La EGFR mutant NSCLC approach)-to start with crizotinib and follow on progression with alectinib??**

Would you reserve Alectinib for second line??

Clinical efficacy of 2nd generation ALK inhibitors in crizotinib resistant patients

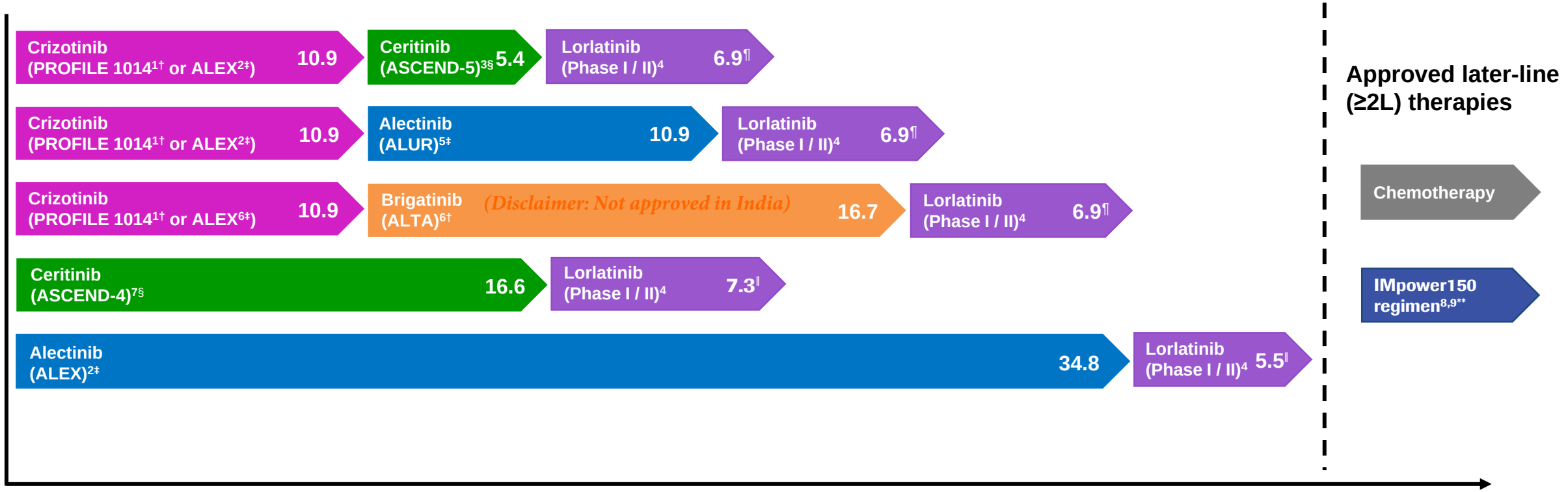
	Ceritinib		Alectinib		Brigatinib	
Reference	Kim et al. Lancet Oncol 2016	Crino et al. JCO 2016	Ou et al. JCO 2016	Shaw et al. Lancet Oncol 2016	Gettinger et al. Lancet Oncol 2016	Kim et al JCO 2017 (ALTA) 90mg/ 90*-180mg
Patients (N)	163	140	138	87	70	112 / 110
ORR (%)	56	38	50	48	71	45 / 54
Median PFS (mths)	6.9	5.7	8.9	8.1	13.4	9.2 / 12.9 16.7 mths**

**90mg 7 day run in then increase to 180mg*

***Updated analysis of ALTA ORR for Brigatinib on 180mg dose Ahn et al. JTO 2017*

Caution : Cross-trial comparisons cannot be made due to differences in trial design and study populations

There are now treatment sequence options for patients with advanced *ALK*+ NSCLC



Treating with 1L alectinib provides with the longest duration of disease control along with a defined treatment sequence, improving the prognosis for patients with advanced *ALK*+ NSCLC

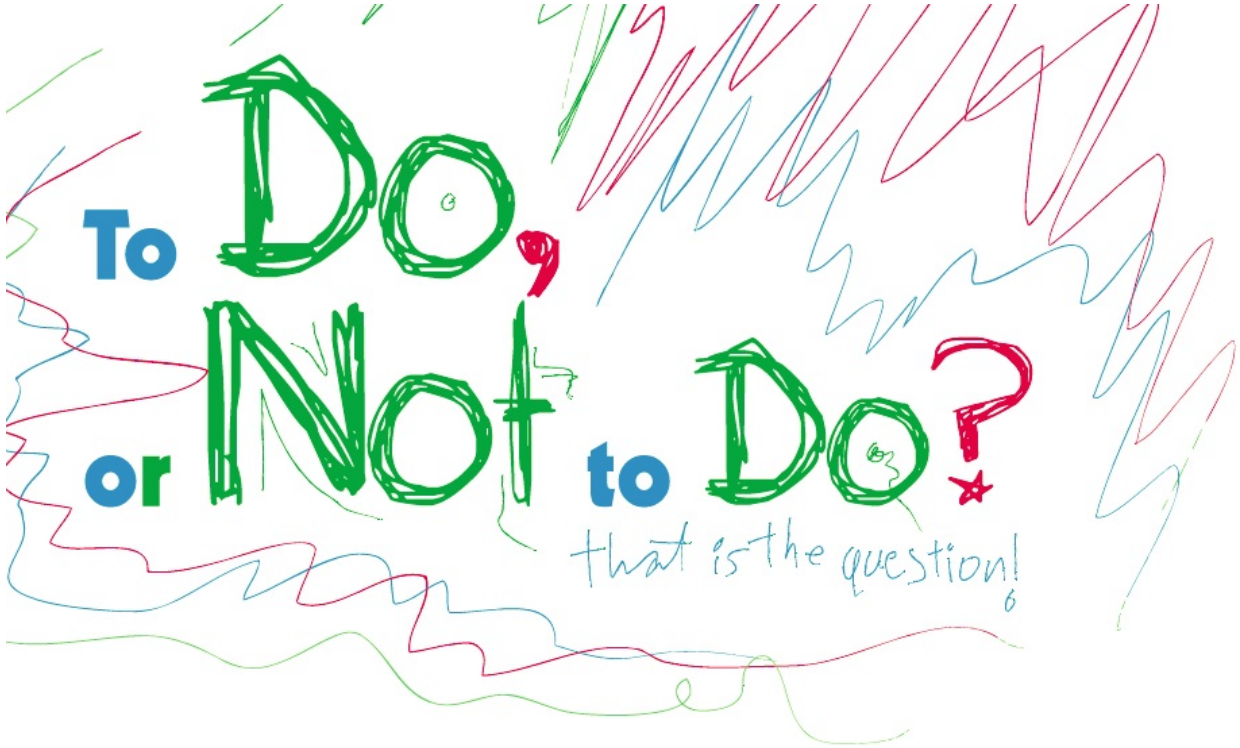
*Adapted and updated from Ferrara et al, 2018.[10] For illustration purposes only; **note that cross-trial comparisons should be interpreted with caution due to differences in study design, size, patient population and data maturity** Median PFS for ALK TKIs that are currently approved in the 1L or ≥2L setting are shown; †Median PFS by IRC; ‡Median PFS by INV; §Median PFS by BIRC; ¶Data from the EXP4 + EXP5 group (two or three prior ALK TKIs ± CT); ‖Lorlatinib PFS data following ceritinib or alectinib in any line;, many treatment options may not be available or approved in India, refer individual pack inserts of products for most updated information

1. Solomon, et al. N Eng J Med 2014; 2. Mok, et al. Ann Oncol 2020
3. Shaw, et al. Lancet Oncol 2017; 4. Besse, et al. ASCO 2018
5. Wolf, et al. WCLC 2019; 6. Huber, et al. J Thorac Oncol 2020
7. Camidge, et al. ESMO Asia 2019; 8. Socinski, et al. ASCO 2018
9. Ateolizumab Prescribing information December 2020 V 16; 10. Ferrara, et al. J Thorac Oncol 2018

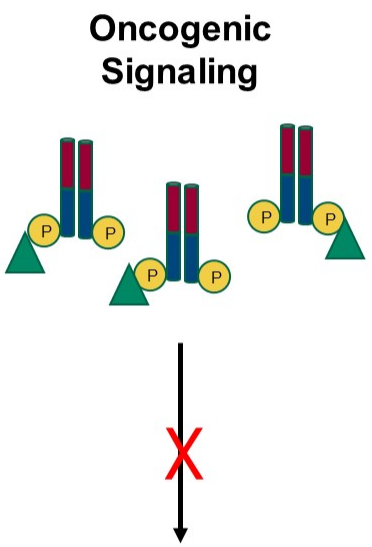
What about Progression on ALK TKIs??

- How would you treat progression on
  - First Generation ALK TKIs??
  - Second generation ALK TKIs
  - Third generation ALK TKIs??

  What is the role of Rebiopsy???



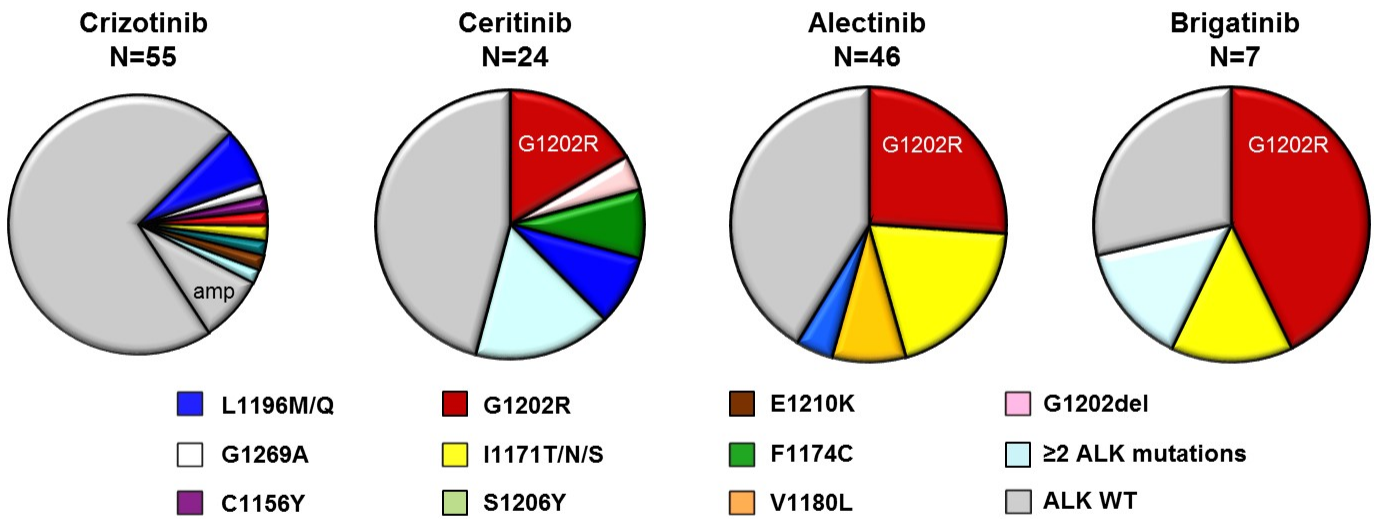
Framework for Resistance



On target resistance pathway

Off target resistance pathway

ALK Resistance Mutations are More Common After Progression on Second-Generation ALK inhibitors



1. Updated from Gainor JF, Dardaei L, et al. Cancer Discovery 2016;
2. Lin JJ, et al. ASCO 2018.

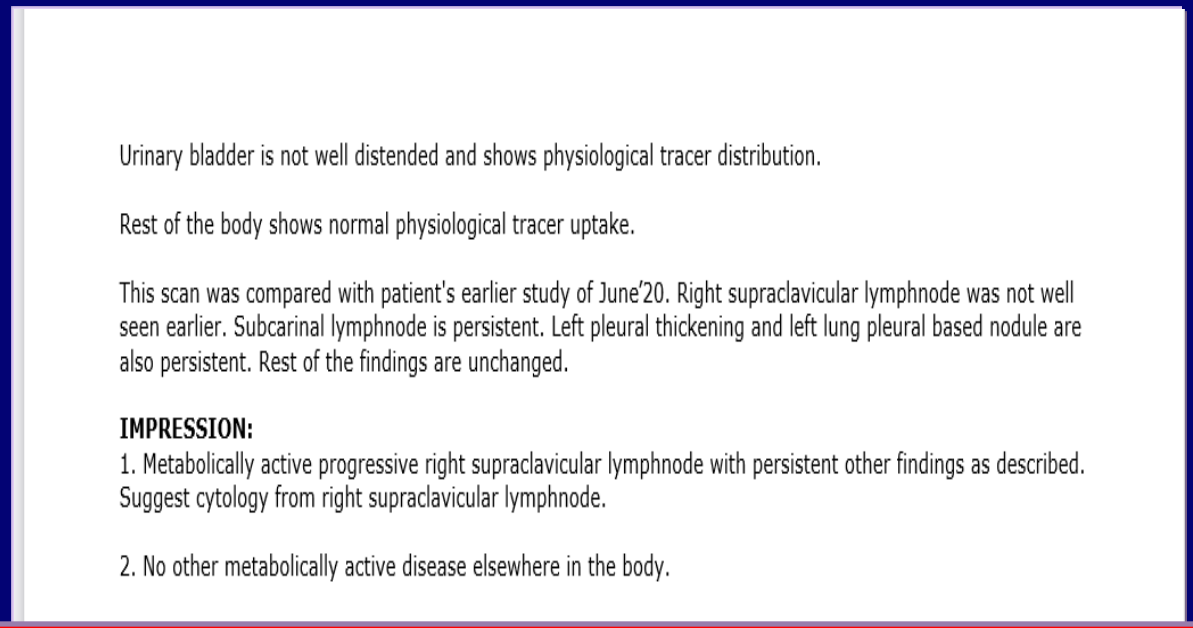
What does the future behold for ALK rearranged NSCLC??

Case 1

- 74 year old male, SS
- Diagnosed as NSCLC, ALK rearranged
- No brain mets at diagnosis
- Received Crizotinib for 10 months
- Now has extracranial and intra cranial progression
- your choice of treatment:
  - 2nd gen TKIs: Ceretinib/Alectinib
  - 3rd gen TKIs- Lorlatinib
  - Chemotherapy??
  - rebiopsy??

The case continues…

- **Patient was started on Alectinib**
- **PET CT after 6 months:**



Urinary bladder is not well distended and shows physiological tracer distribution.

Rest of the body shows normal physiological tracer uptake.

This scan was compared with patient's earlier study of June'20. Right supraclavicular lymphnode was not well seen earlier. Subcarinal lymphnode is persistent. Left pleural thickening and left lung pleural based nodule are also persistent. Rest of the findings are unchanged.

IMPRESSION:
1. Metabolically active progressive right supraclavicular lymphnode with persistent other findings as described. Suggest cytology from right supraclavicular lymphnode.

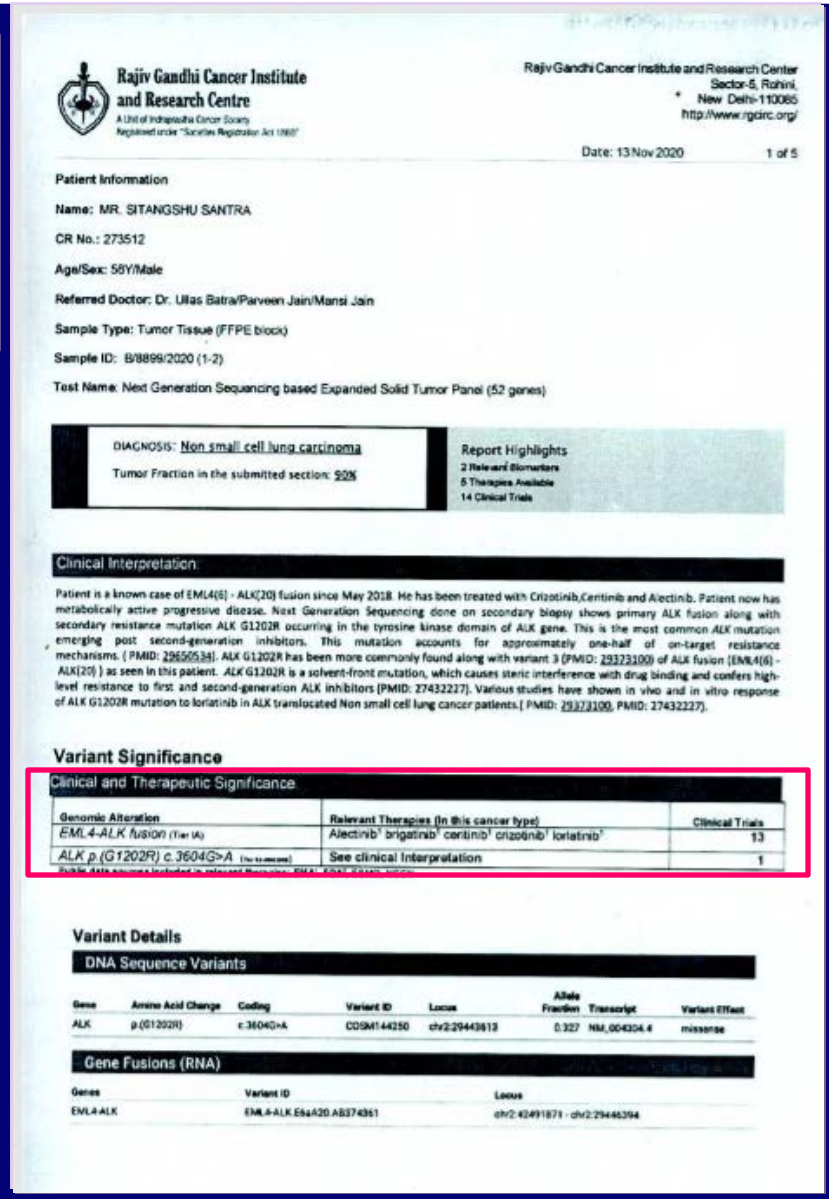
2. No other metabolically active disease elsewhere in the body.

Your management options
- Change of ALK TKI
- Rebiopsy
- RT to oligoprog site
- Any other??

The case continues…

The patient underwent Rebiopsy and RT to oligoprogressive site…

What next??



Rajiv Gandhi Cancer Institute and Research Centre

Rajiv Gandhi Cancer Institute and Research Center
Sector-5, Rohini,
New Delhi-110085
http://www.rgcirc.org/

Date: 13 Nov 2020 1 of 5

Patient Information

Name: MR. SITANGSHU SANTRA

CR No.: 273512

Age/Sex: 58Y/Male

Referred Doctor: Dr. Ullas Batra/Parveen Jain/Mansi Jain

Sample Type: Tumor Tissue (FFPE block)

Sample ID: B/8899/2020 (1-2)

Test Name: Next Generation Sequencing based Expanded Solid Tumor Panel (52 genes)

DIAGNOSIS: Non small cell lung carcinoma

Tumor Fraction in the submitted section: 90%

Report Highlights
2 Relevant Biomarkers
5 Therapies Available
14 Clinical Trials

Clinical Interpretation

Patient is a known case of EML4(6) - ALK(20) fusion since May 2018. He has been treated with Crizotinib,Ceritinib and Alectinib. Patient now has metabolically active progressive disease. Next Generation Sequencing done on secondary biopsy shows primary ALK fusion along with secondary resistance mutation ALK G1202R occurring in the tyrosine kinase domain of ALK gene. This is the most common *ALK* mutation emerging post second-generation inhibitors. This mutation accounts for approximately one-half of on-target resistance mechanisms. (PMID: 29650534). ALK G1202R has been more commonly found along with variant 3 (PMID: 29373100) of ALK fusion (EML4(6) - ALK(20)) as seen in this patient. *ALK* G1202R is a solvent-front mutation, which causes steric interference with drug binding and confers high-level resistance to first and second-generation ALK inhibitors (PMID: 27432227). Various studies have shown in vivo and in vitro response of ALK G1202R mutation to lorlatinib in ALK translocated Non small cell lung cancer patients.(PMID: 29373100, PMID: 27432227).

Variant Significance

Clinical and Therapeutic Significance

Genomic Alteration	Relevant Therapies (In this cancer type)	Clinical Trials
EML4-ALK fusion (Tier IA)	Alectinib[1] brigatinib[1] ceritinib[1] crizotinib[1] lorlatinib[1]	13
ALK p.(G1202R) c.3604G>A (Tier IIA)	See clinical interpretation	1

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Fraction	Transcript	Variant Effect
ALK	p.(G1202R)	c.3604G>A	COSM144250	chr2:29443613	0.327	NM_004304.4	missense

Gene Fusions (RNA)

Genes	Variant ID	Locus
EML4-ALK	EML4-ALK E6a:A20 AB374361	chr2:42491879 - chr2:29446394

Referred By : DR .

Status : OPD

PET-Regional (as part of Pet-MRI package)

Urinary bladder is not well distended and shows physiological tracer distribution.

Rest of the body shows normal physiological tracer uptake.

This scan was compared with patient's earlier study of Nov.'20. Right supraclavicular & subcarinal lymphnodes shows mild decrease in size & metabolic activity. Left pleural thickening and left lung pleural based nodule are also persistent. Rest of the findings are unchanged. No new abnormality seen.

IMPRESSION:

1. Partial metabolic response to treatment with residual lymphnodes & other associated findings as described.

2. No other metabolically active disease elsewhere in the body.

Dr.TARUNA & Dr.PARUL/Dr.ROHINI
SENIOR RESIDENT & ATTND.CONSULTANT

Dr.MANOJ GUPTA
CONSULTANT NUCLEAR MEDICINE

Dr.P.S.CHOUDHURY
DIRECTOR NUCLEAR MEDICINE

Dr.RAJIV KAPUR
SR. CONSULTANT RADIOLOGY

Approved by :Dr.Manoj 09-Mar-2021 5:27PM
Validated by : Dr.Manoj 09-Mar-2021 5:27PM
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Any Alternations will make the Report Void

Entered By :

Printed By :

lung cancer

DESERVES A CURE TOO

WARNING: To be sold by the retail on the prescription of an Oncologist only

ABRIDGED PRESCRIBING INFORMATION

(Alecensa ®) SUMMARY OF PRESCRIBING INFORMATION:

Generic Name: Alectinib Capsules

Brand Name: Alecensa®

Indications: Alecensa is indicated for the first-line treatment of patients with Anaplastic Lymphoma Kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC). Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)- positive, metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to Crizotinib. Type of Dosage Form: Alecensa® is supplied as hard capsules containing 150 mg of alectinib. Dosage and administration: Standard Dosage – The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally, twice daily (total daily dose of 1200 mg). Alecensa hard capsules should be taken with food, swallowed whole and must not be opened or dissolved. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg). Duration of Treatment – It is recommended that patients are treated with Alecensa until disease progression or unmanageable toxicity. If a planned dose of Alecensa is missed, patients can make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of Alecensa, patients should take the next dose at the scheduled time. Dose Modifications – Management of adverse events may require temporary interruption, dose reduction, or discontinuation of treatment with Alecensa. The dose of Alecensa should be reduced in steps of 150 mg twice daily based on tolerability. Alecensa treatment should be permanently discontinued if patients are unable to tolerate the 300 mg twice daily dose. Use in Special Populations: Pediatric use: The safety and efficacy of Alecensa in children and adolescents (<18 years) have not been studied. Geriatric use: No dose adjustment of Alecensa is required in patients ≥ 65 years of age. Renal Impairment – No dose adjustment is required in patients with mild or moderate renal impairment. Alecensa has not been studied in patients with severe renal impairment, however since alectinib elimination via the kidney is negligible, no dose adjustment is required in patients with severe renal impairment. Hepatic Impairment – No dose adjustment is required in patients with underlying mild or moderate hepatic impairment. Patients with underlying severe hepatic impairment should receive a dose of 450 mg given orally twice daily (total daily dose of 900 mg). Contraindications: Alecensa is contraindicated in patients with a known hypersensitivity to alectinib or any of the excipients. Warnings and Precautions: Interstitial lung disease (ILD)/Pneumonitis – Cases of ILD/pneumonitis have been reported in clinical trials with Alecensa. Patients should be monitored for pulmonary symptoms indicative of pneumonitis. Alecensa should be immediately interrupted in patients diagnosed with ILD/pneumonitis and should be permanently discontinued if no other potential causes of ILD/pneumonitis have been identified. Hepatotoxicity – Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 5 times the upper limit of normal (ULN) as well as bilirubin elevations of more than 3 times the ULN occurred in patients in pivotal clinical trials with Alecensa. In the pivotal Alecensa clinical trials, it was reported that three patients with Grade 3- 4 AST/ALT elevations had drug induced liver injury. Based on the severity of the adverse drug reaction, withhold Alecensa and resume at a reduced dose, or permanently discontinue Alecensa. Severe Myalgia and Creatine Phosphokinase (CPK) elevation – Myalgia or musculoskeletal pain was reported in patients in pivotal trials with Alecensa, including Grade 3 events. Assess CPK levels every two weeks for the first month of treatment and as clinically indicated in patients reporting symptoms. Based on the severity of the CPK elevation, withhold Alecensa, then resume or reduce dose. Bradycardia – Symptomatic bradycardia can occur with Alecensa. Heart rate and blood pressure should be monitored as clinically indicated. If patients experience symptomatic bradycardia or life-threatening events, concomitant medications known to cause bradycardia, as well as antihypertensive medications should be evaluated and Alecensa treatment should be adjusted. Photosensitivity – Photosensitivity to sunlight has been reported with Alecensa administration. Patients should be advised to avoid prolonged sun exposure while taking Alecensa and for at least 7 days after discontinuation of treatment. Patients should also be advised to use a broad spectrum Ultraviolet A (UVA)/ Ultraviolet B (UVB) sun screen and lip balm (SPF ≥50) to help protect against potential sunburn. Embryo-fetal toxicity – Alecensa may cause fetal harm when administered to a pregnant woman. When administrated to pregnant rats and rabbits, alectinib caused embryo-fetal toxicity. Female patients of child bearing potential, or women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa Use in Special population: Pregnancy Women of childbearing potential must be advised to avoid pregnancy while on Alecensa. No clinical studies of Alecensa in pregnant women have been performed. Based on its mechanism of action, Alecensa may cause fetal harm when administered to a pregnant woman. In animal studies, alectinib caused embryo-fetal toxicity. Contraception Female patients of child-bearing potential, or women of child-bearing potential who are partners of male patients receiving Alecensa, must use highly effective contraceptive methods during treatment and for at least 3 months following the last dose of Alecensa. Female patients or women who are partners of male patients receiving Alecensa, who become pregnant while taking Alecensa or during the 3 months following the last dose of Alecensa must contact their doctor and should be advised of the potential harm to the fetus. Labor and Delivery The use of Alecensa during labor and delivery has not been established. Lactation It is not known whether Alecensa is excreted in human breast milk. No studies have been conducted to assess the impact of Alecensa on milk production or its presence in breast milk. As many drugs are excreted in human milk and because of the potential harm to the infant, mothers should be advised against breastfeeding while receiving Alecensa. Undesirable Effects: The safety of Alecensa has been evaluated in 253 patients in pivotal phase II clinical trials (NP28761, NP28673) with ALK positive NSCLC treated with the recommended dose of 600 mg twice daily. The very common side effects are constipation, nausea, vomiting, diarrhea, edema, myalgia, increased blood creatinine phosphokinase, rash, photosensitivity reaction, increased bilirubin, increased AST, increased ALT, anemia and bradycardia. All side effects reported please refer to the full prescribing information. Post marketing experience: The adverse drug reaction of increased alkaline phosphatase was reported with Alecensa in the post-marketing period. Cases of increased alkaline phosphatase have been reported. The adverse drug reaction of hemolytic anemia was reported with Alecensa in the post marketing setting. Cases of hemolytic anemia have been reported in the Alecensa clinical trial (BO29554). Interactions with other medicinal products and other forms of interaction: Effects of alectinib on others drugs CYP substrates – In vitro studies indicate that neither alectinib nor its major active metabolite (M4) inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP2D6 at clinically relevant concentrations. Alectinib and M4 show weak time-dependent inhibition of CYP3A4. In vitro, alectinib exhibits a weak induction potential of CYP3A4 and CYP2B6 at clinical concentrations. Results from a clinical drug-drug interaction study in ALK-positive NSCLC patients demonstrated that multiple doses of alectinib had no influence on the exposure of midazolam, a sensitive CYP3A substrate. Therefore, no dose adjustment is required for co-administered CYP3A substrates. Although in vitro studies indicate that alectinib is an inhibitor of CYP2C8, physiologically based pharmacokinetic (PBPK) modeling supports that at clinically relevant concentrations alectinib does not have the potential to increase plasma concentrations of coadministered substrates of CYP2C8. P-gp and BCRP substrates – In vitro, alectinib and M4 are inhibitors of the efflux transporters P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Therefore, alectinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp or BCRP. When alectinib is co-administered with P-gp or BCRP substrates with narrow therapeutic index (e.g. digoxin, dabigatran, methotrexate), appropriate monitoring is recommended. Effects of other drugs on alectinib – Based on in vitro data, CYP3A4 is the primary enzyme mediating the metabolism of both alectinib and its major active metabolite M4. M4 has shown similar in vitro potency and activity to alectinib against ALK. CYP3A inducers – Co-administration of multiple oral doses of 600 mg rifampicin once daily, a strong CYP3A inducer, with a single oral dose of 600 mg alectinib exhibited a minor effect on combined exposure of alectinib and M4. Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inducers. CYP3A inhibitors – Co-administration of multiple oral doses of 400 mg posaconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 300 mg alectinib had a minor effect on combined exposure of alectinib and M4. Therefore, no dose adjustments are required when Alecensa is co-administered with CYP3A inhibitors. Medicinal products that increase gastric pH – A dedicated clinical drug-drug interaction study with 40 mg esomeprazole once daily, a proton pump inhibitor, demonstrated no clinically relevant effect on the combined exposure of alectinib and M4. Therefore, no dose adjustments are required when Alecensa is co-administered with proton pump inhibitors or other drugs which raise gastric pH (e.g. H2 receptor antagonists or antacids). Effect of transporters on alectinib disposition – Based on in vitro data, alectinib is not a substrate of P-gp. Alectinib and M4 are not substrates of BCRP or Organic anion-transporting polypeptide (OATP) 1B1/B3. In contrast, M4 is a substrate of P-gp. Alectinib inhibits P-gp, and therefore, it is not expected that co-medication with P-gp inhibitors has a relevant effect on M4 Exposure Overdose: Patients who experience overdose should be closely supervised and supportive care instituted. There is no specific antidote for overdose with Alecensa. Storage condition: Do not store above 30°C, keep in the original container to protect from light and moisture. Shelf life 36 months when stored at recommended storage conditions. Packs: Multipack: 224 capsules (contains 4 packs of 7 blisters and each blister contains 8 hard capsules 150mg). Please read the full prescribing information before usage. Details of Permission or License Number with date: IMP-ND-06/2017 dated 23 January 2017 Date of Revision: Current at March 2021; Version 8.0

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