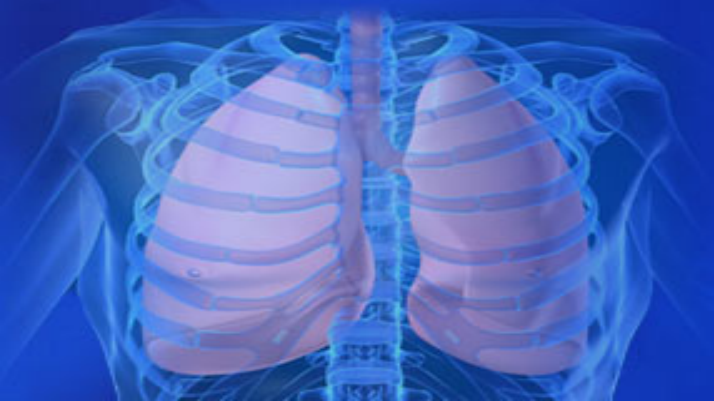
Precision Medicine Against ALK-Positive Non-Small Cell Lung Cancer

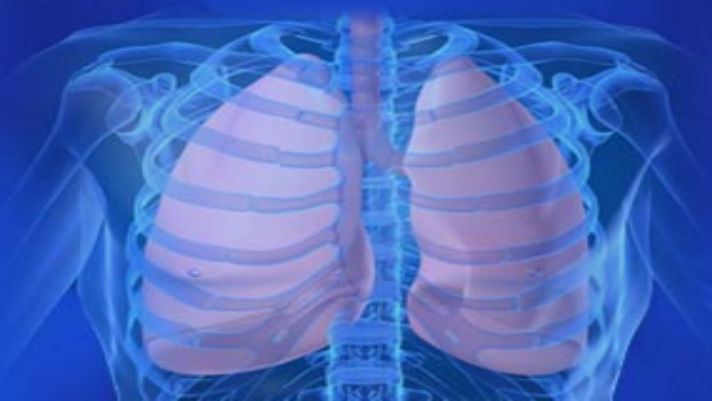
PROF. DR MILAN RANČIĆ, PROF. DR DAVORIN RADOSAVLJEVIĆ, PROF. DR BOJAN ZARIĆ, DOC. DR GORAN STOJANOVIĆ, NS PRIM. DR SCI. MED. DR NATALIJA SAMARDŽIĆ, PRIM. DR MARINA CEKIĆ



KME je podržan nezavisnim grantom ID:75681225 od strane kompanije Pfizer

Institute for pulmonary Diseases of Vojvodina
Clinic for Thoracic Oncology

Značaj molekularnog testiranja u eri preciznog lečenja karcinoma pluća i savremeni klinički vodiči



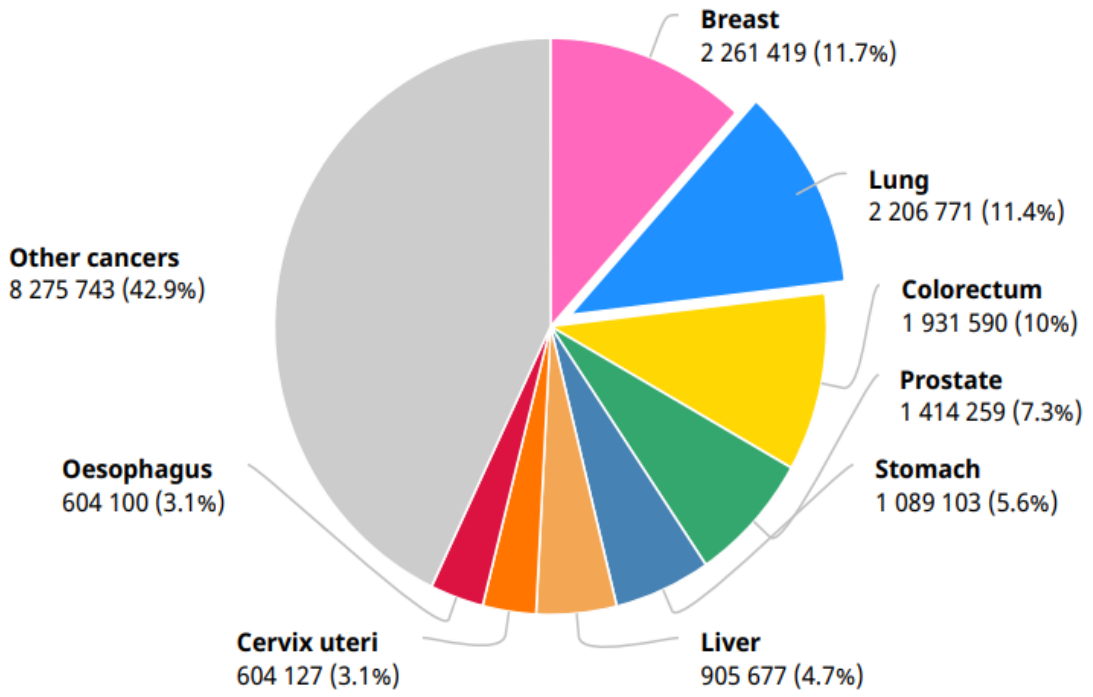
Doc dr. sc. med Goran Stojanović prim

International Agency for Research on Cancer
World Health Organization

Lung

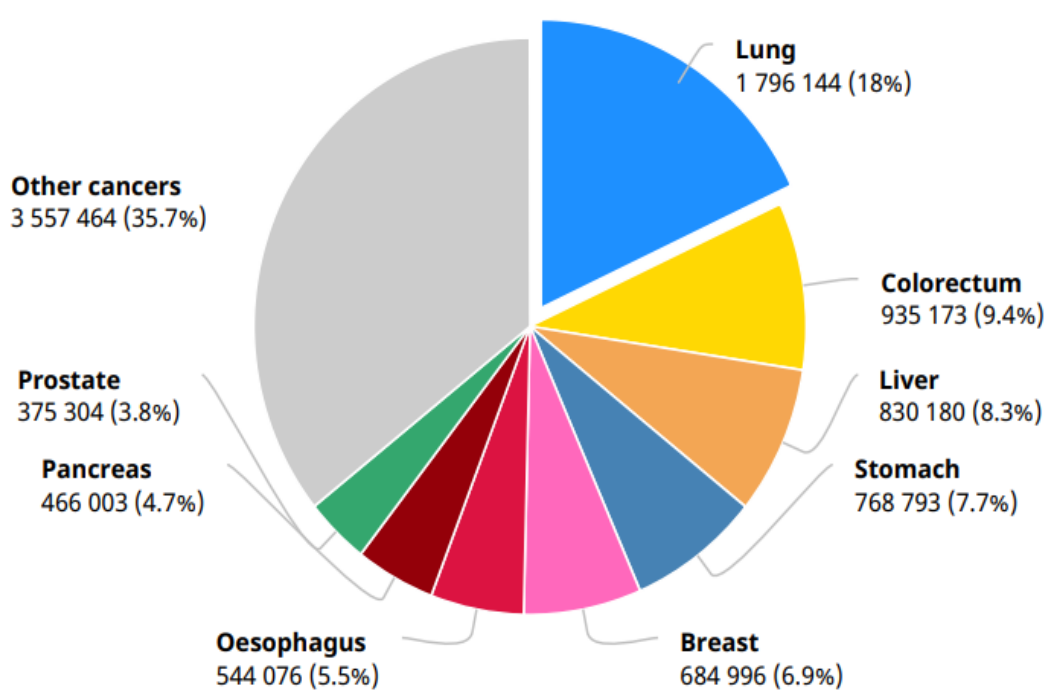
Source: Globocan 2020

Number of new cases in 2020, both sexes, all ages



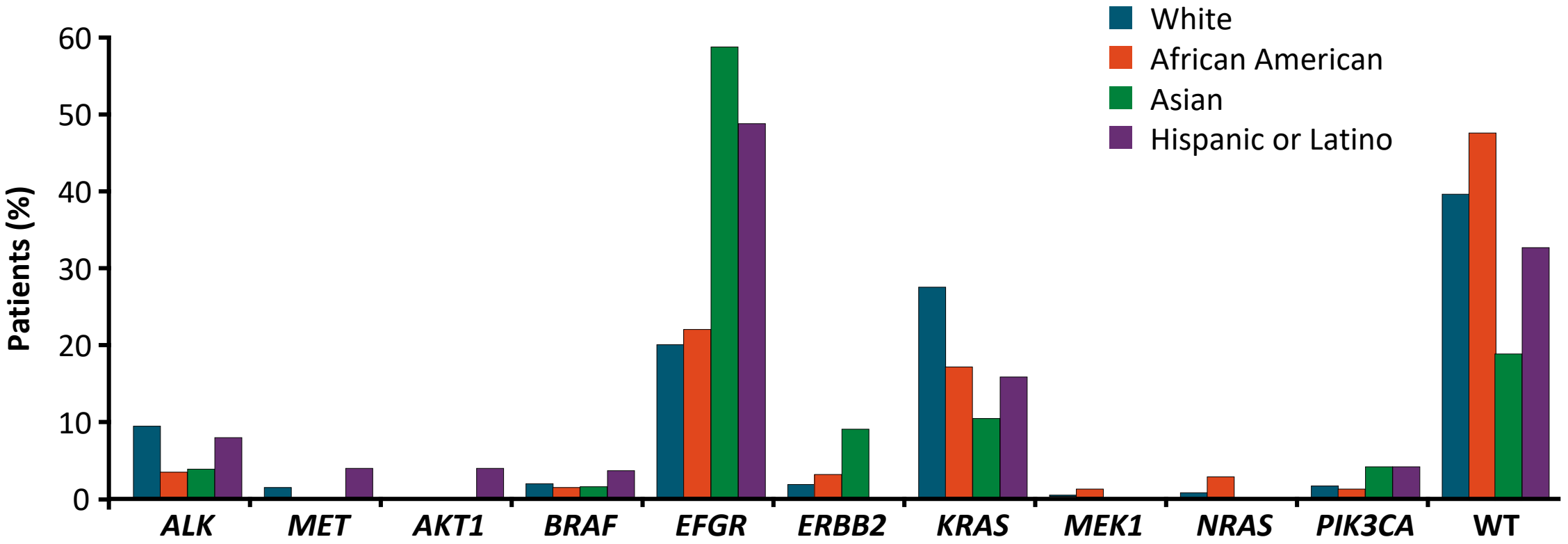
Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages



Total: 9 958 133 deaths

Mutational Prevalence by Race in Lung Adenocarcinoma



Steuer. Cancer. 2016;122:766.

Slide credit: clinicaloptions.com

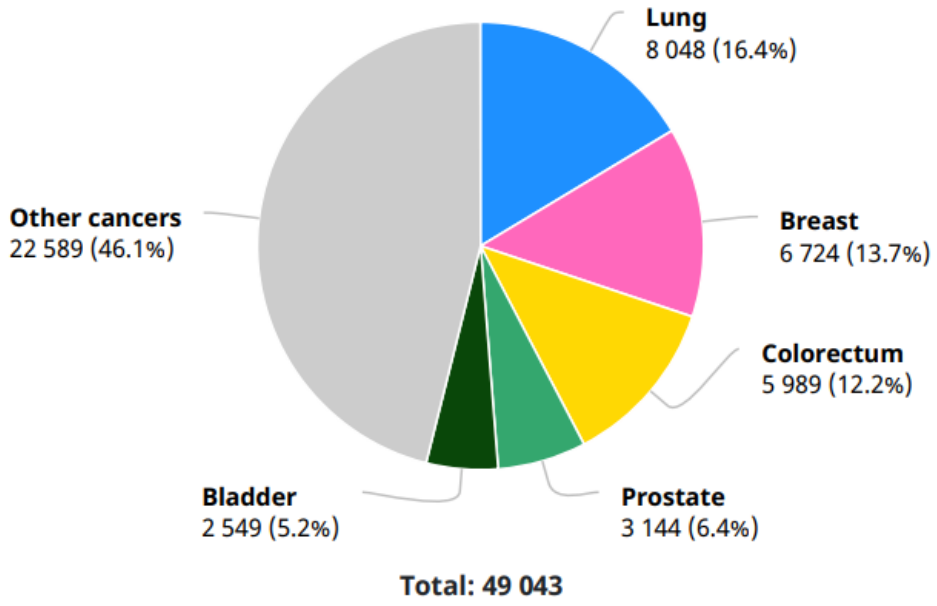
International Agency for Research on Cancer

World Health Organization

Serbia

Source: Globocan 2020

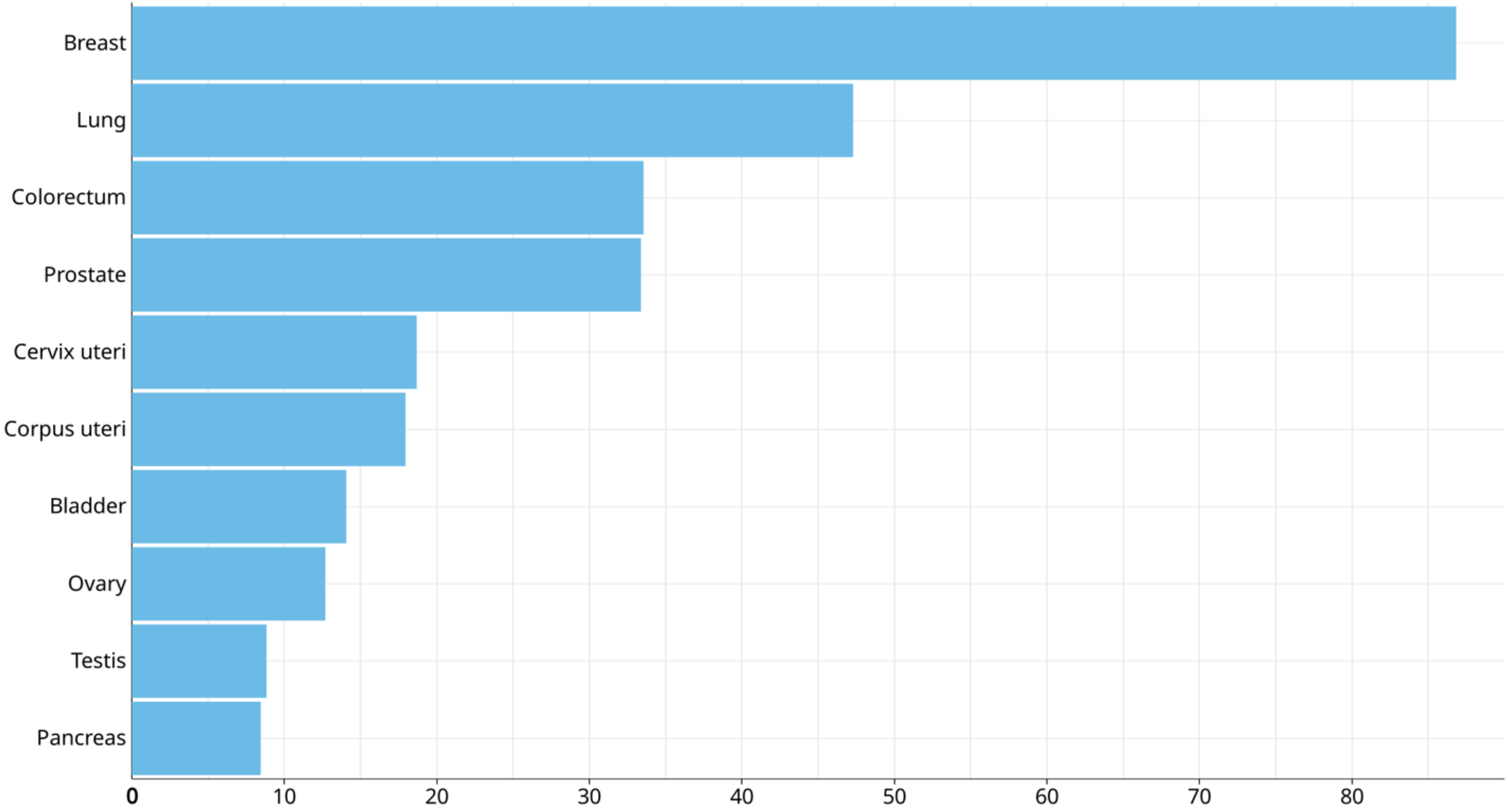
Number of new cases in 2020, both sexes, all ages



Total: 49 043

Geography

Estimated age-standardized incidence rates (World) in 2020, Serbia, both sexes, all ages (excl. NMSC)

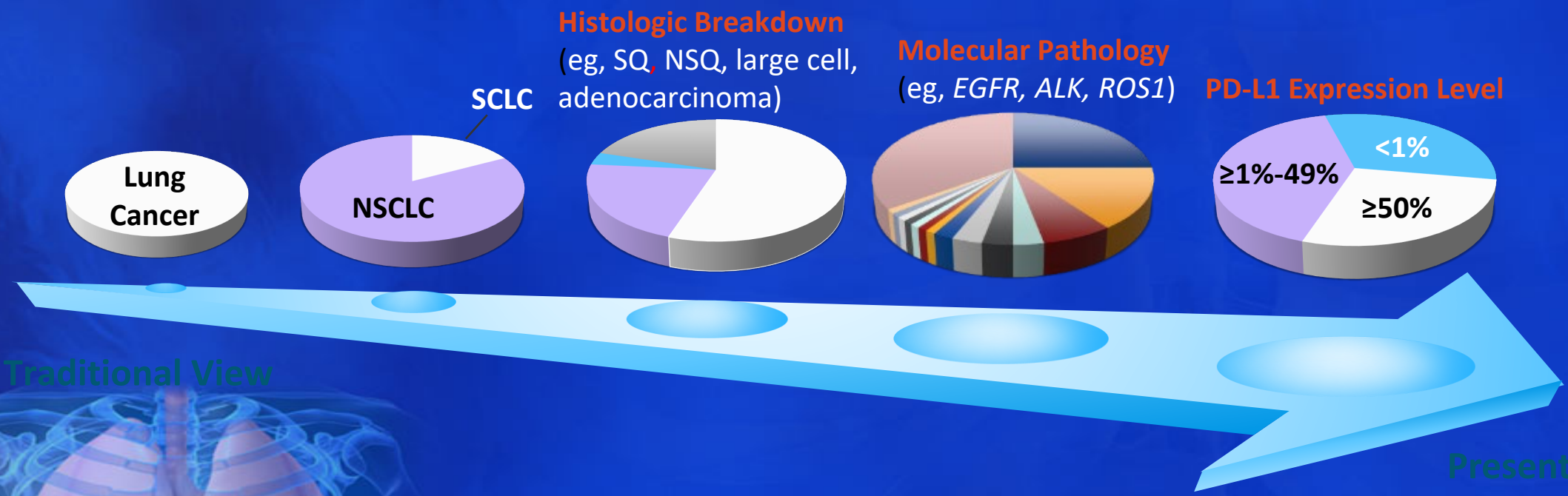


Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Can
World Health Organization

Evolution of Therapy in Lung Cancer

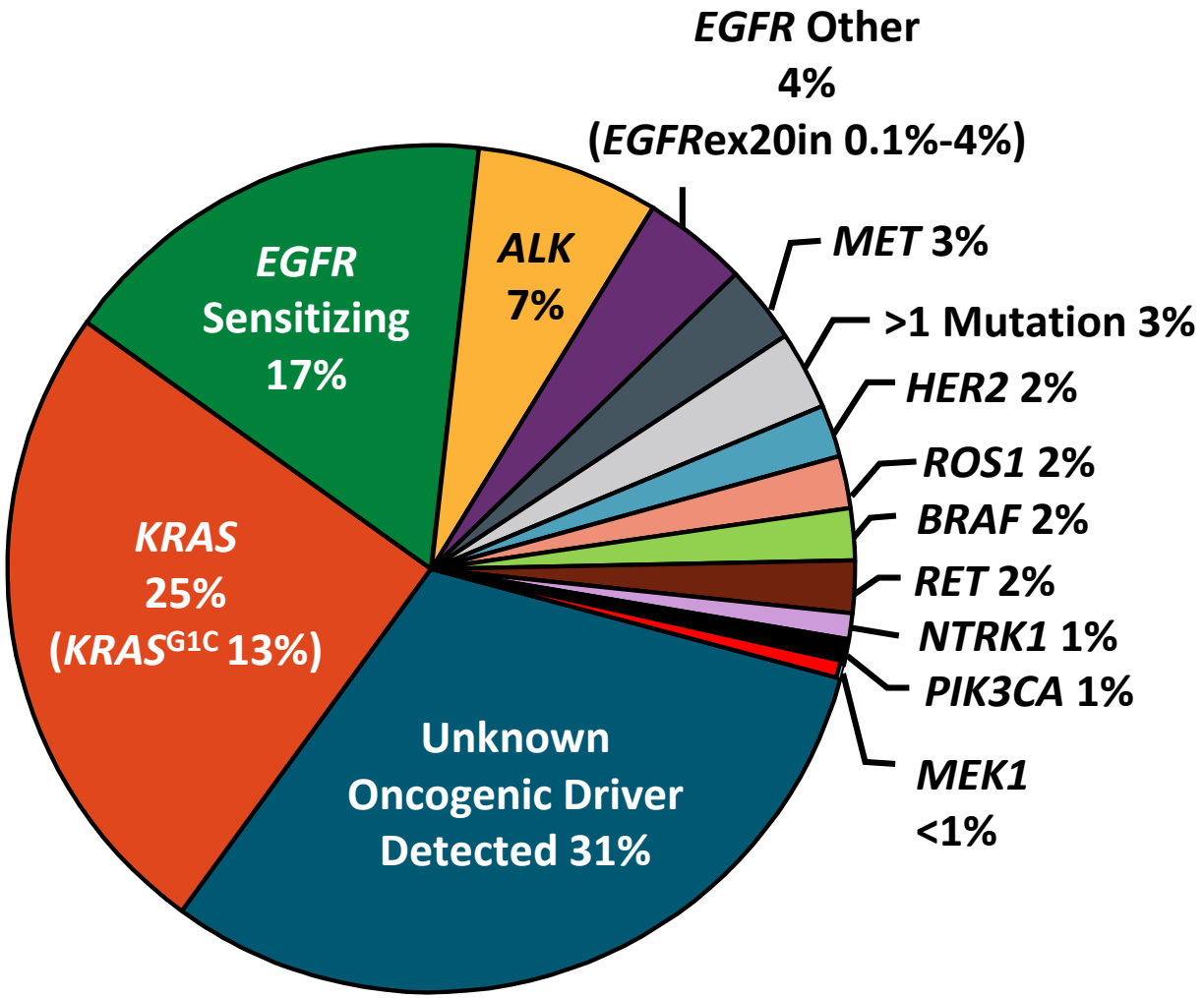
- Not one disease, but many



Cooper. Pathology. 2011;43:103. Langer. JCO. 2010;28:5311. Galon. Immunity. 2013;39:11. Pao. Lancet Oncol. 2011;12:175. Krigsfeld. AACR 2017. Abstr CT143.

Slide credit: clinicaloptions.com

~50% of Patients With Advanced Nonsquamous NSCLC Have an Actionable Driver Mutation



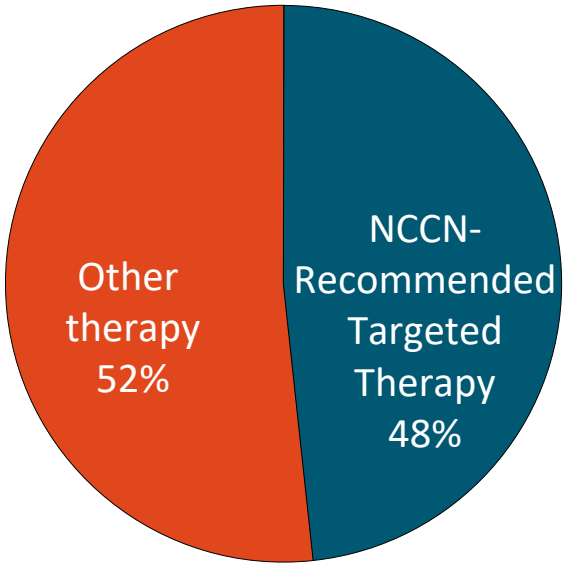
Li. JCO. 2013;31:1039. Tsao. JTO. 2016;11:613.
Burnett. PLoS One. 2021;16:e0247620. Nassar. NEJM. 2021;384:185.

Slide credit: clinicaloptions.com

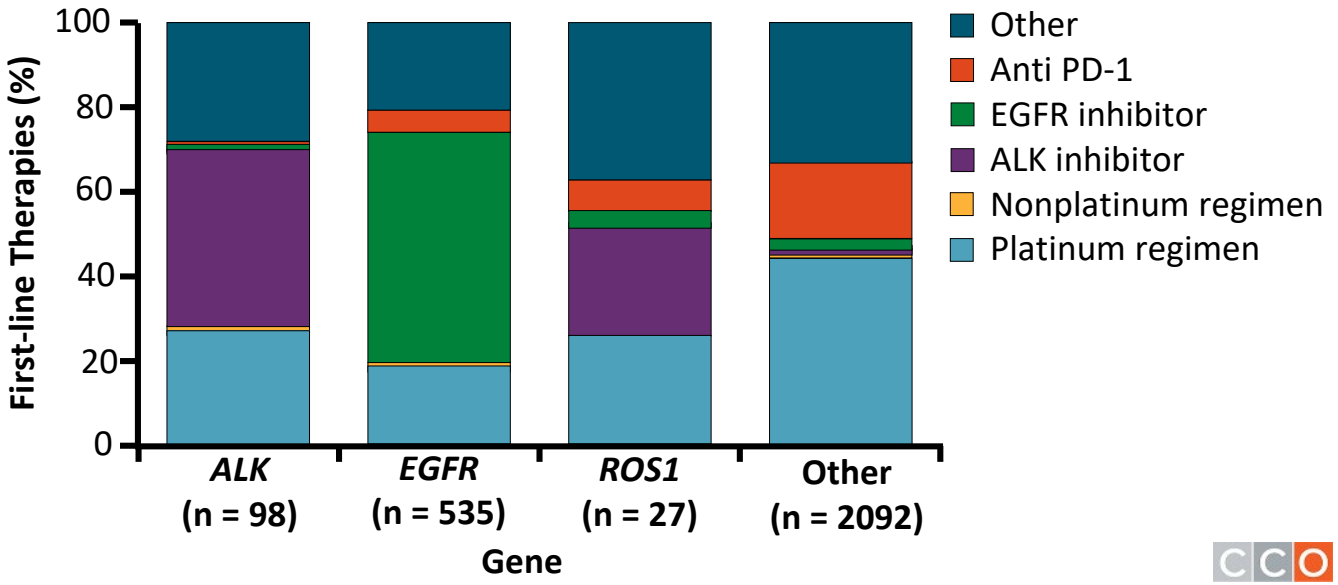
Why Does Upfront Testing Matter?

- Only 48% of patients with advanced NSCLC and a driver mutation received NCCN-recommended targeted therapy[1]
  - Alterations included *EGFR, ALK, ROS1, BRAF, MET, RET, ERBB2*
- Patients with driver mutations who received targeted therapy had an improved OS (18.6 mo vs 11.4 mo; *P* <.001)[1]
- **Always give the best treatment upfront**
  - ~30% of patients will NOT go on to receive second-line treatment[2]

Patients with NSCLC
(N = 1260)



First-line Therapy Received by Driver Mutation



1. Singal. JAMA. 2019;321:1391. 2. Ramalingam. NEJM. 2020;382:41.

Slide credit: clinicaloptions.com

Tissue Journey: Biopsy to Analysis

Preliminary diagnosis → **Biopsy methods and specimen processing** → **Morphologic assessment** → **Extraction** → **Analysis**

TISSUE
- **Resection**
- **Excision**
- **Small tissue biopsies**

→ **FFPE block**

CYTOLOGY
- **Fine-needle aspiration**
- **Exfoliative cytology** (cells shed from body surfaces)

→ **FFPE block**

LIQUID
- **Liquid biopsies**
  - Blood
  - Cyst fluid

→ **Non–cell block slide**

Histology

Cytology

Parallel diagnostics
- IHC (eg, PD-L1, dMMR)
- ISH/FISH

DNA →
- PCR
- Cancer gene panels
- MSI
- NGS (WGS, WES, targeted hotspot panel)

RNA →
- RT-qPCR
- Gene expression panels
- RNA-seq NGS

Protein →
- Proteomics
- FACS

- Data analytics

Assessment methods

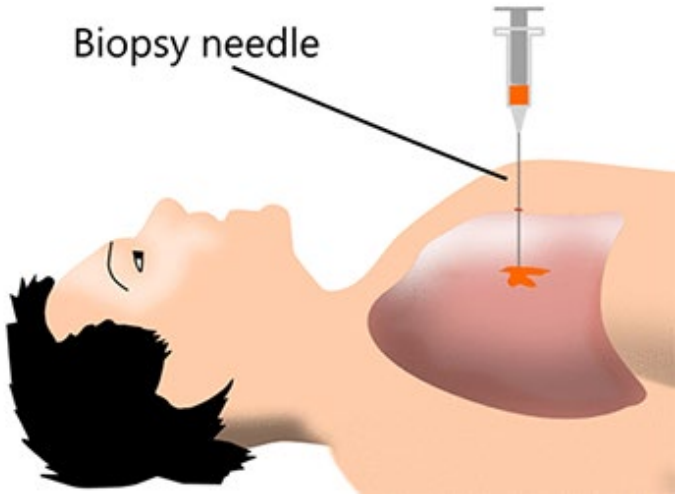
Ascierto. J Mol Diagn. 2019;21:756.

Slide credit: clinicaloptions.com

Tissue Testing in NSCLC

Benefits

- Tissue available from biopsy
- Considered "gold standard" for biomarker testing



Challenges

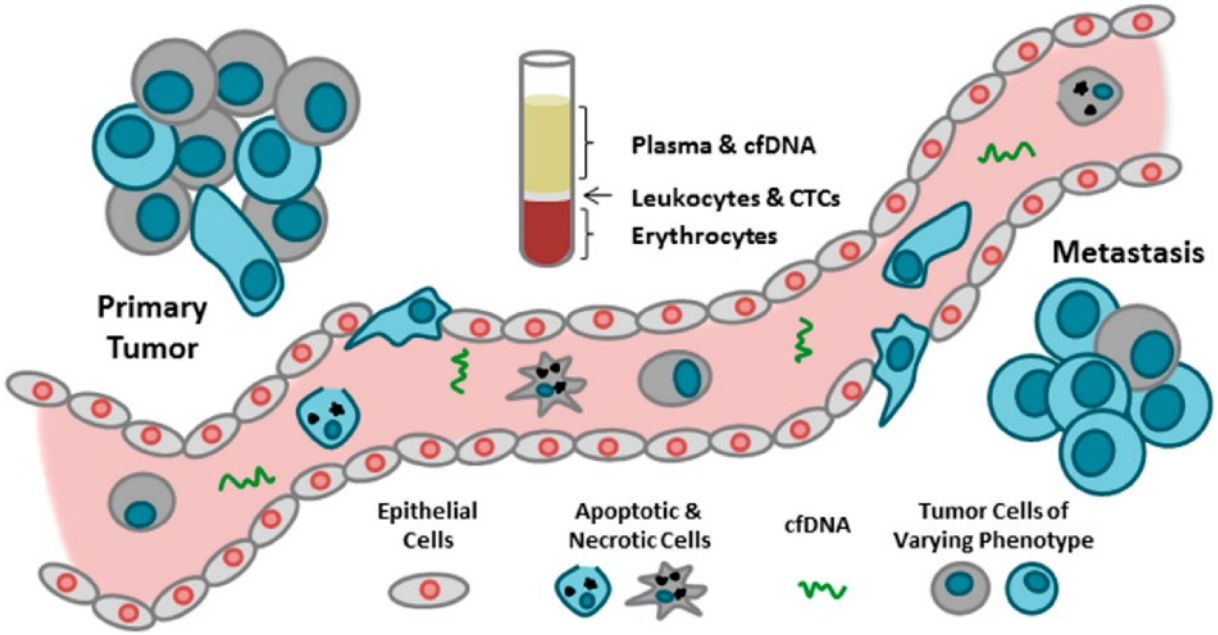
- Lung cancer biopsies are less cellular than other solid tumors
  - QNS: quality or quantity not sufficient (need 10%-20% of viable cancer cells in sample for reliable results)
- Bone biopsies yield poor samples due to decalcification, which degrades DNA
- Logistical: Timing of DNA sequencing can take weeks
  - Centralized vs sent to distant laboratory

Vanderlaan. Lung Cancer. 2014;84:39. Hiley. Lancet. 2016;388:1002.

Slide credit: clinicaloptions.com

Liquid Biopsy

- Blood sample containing cell-free DNA from multiple sources, including DNA shed from tumor



- **When do we use liquid biopsy?**
  - **Plasma-first approach**: for inadequate or no tissue biopsy—if negative, rebiopsy for tumor tissue
  - **Sequential approach**: tumor tissue adequate for genotyping—follow with cfDNA testing only when results from tissue incomplete
  - **Complementary approach**: increases rate of biomarker detection
  - Resistance to TKIs
- **Advantages:** minimally invasive, may overcome tumor heterogeneity
- **Limitations:** Sensitivity (70%-80%), specificity near 100%; negative result is noninformative; cannot assess histology or PD-L1

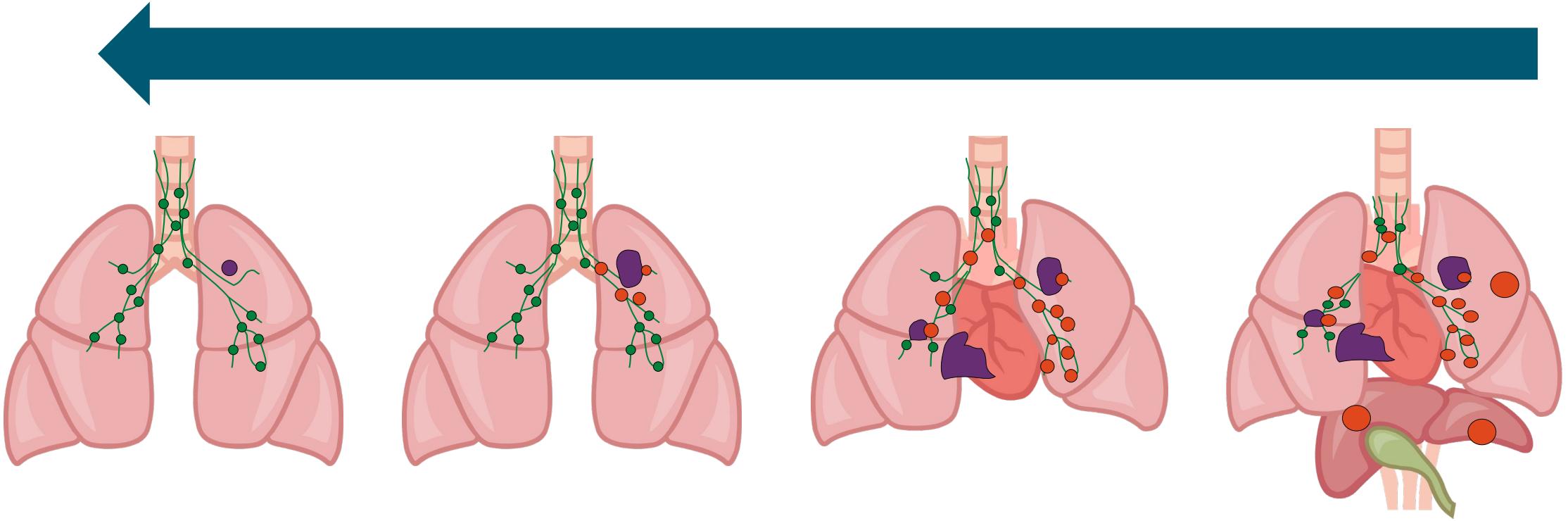
Slide credit: clinicaloptions.com

Biopsy: Establish Diagnosis, Determine Histologic Subtype, Biomarker Testing

- Histologic subtyping: squamous or nonsquamous?[1,2]
- **Test for *EGFR*, including *EGFR* ex20ins, *ALK*, *ROS1*, *BRAF* V600E, *NTRK*, *RET*, *MET*ex14, and *KRAS* in all nonsquamous NSCLC[3]**
  - **Use broad NGS testing to detect most mutations using least amount of tissue**
  - For squamous NSCLC, consider testing in young, never/light smokers or if biopsy specimen is of mixed histology
- **Test for PD-L1 expression in all NSCLC[3]**
  - TAT for PD-L1 much shorter than for NGS
- **Wait for results of NGS before acting on PD-L1 results**

1. Masters. JCO. 2015;33:3488. 2. Mukhopadhyay. Am J Surg Pathol. 2011;35:15.
3. Pennell. ASCO Educ Book. 2019;39:351.

Moving Targeted Therapy Earlier in Disease Course



Stage I **Stage II** **Stage III** **Stage IV**

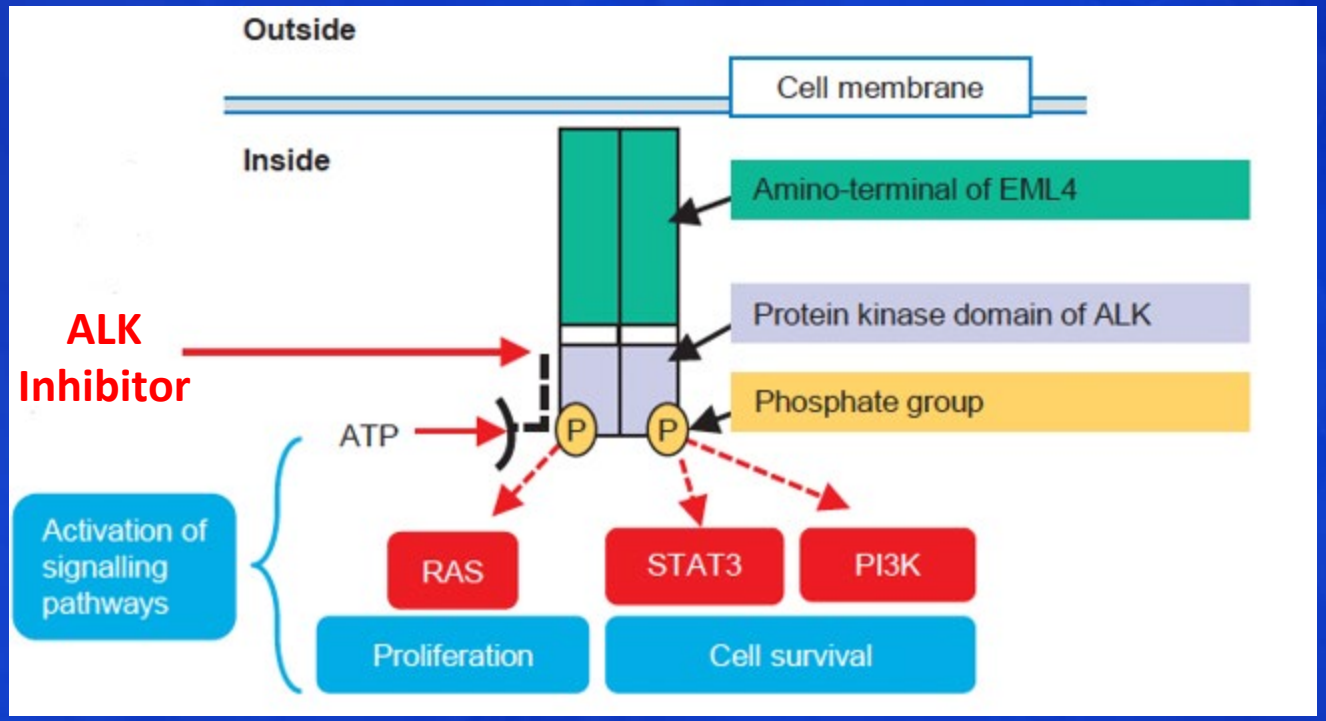
Tumors Nonmetastatic lymph nodes Regional/local metastatic lymph nodes/distant metastases

Slide credit: clinicaloptions.com

ALK Rearrangement in NSCLC

Pathophysiology

- ALK is a gene that fuses with other genes to create oncogenic fusion proteins, which induce malignant transformation of cells[1,2]
- ALK-rearranged NSCLC accounts for up to 3%-7% of NSCLCs[1-4]
- The most common ALK gene fusion partner is EML4[1,2]
- The EML4-ALK fusion protein (shown) triggers uncontrolled cell proliferation and survival[2]



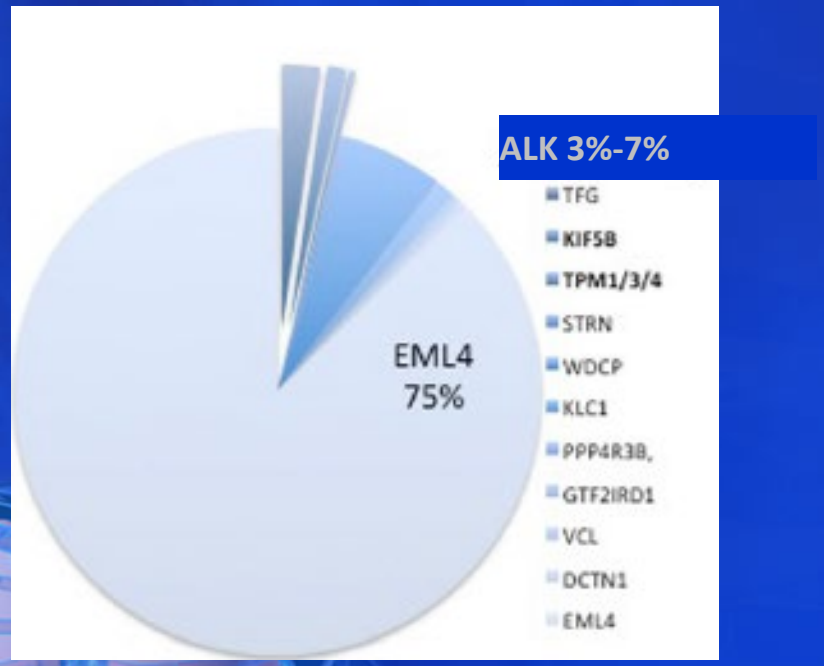
1. Millett RL, et al. *Anticancer Res*. 2018;38(9):4969-4975. 2. Personalized Medicine in Oncology. Alectinib: An Anaplastic Lymphoma Kinase (ALK) Inhibitor ALK Rearrangements in Lung Adenocarcinoma. Accessed February 4, 2021. http://www.personalizedmedonc.com/article/alectinib-an-anaplastic-lymphoma-kinase-alk-inhibitor/. 3. Ali R, et al. *Drug Des Devel Ther*. 2019;13:569-580. 4. Kris MG, et al. *J Am Med Assoc*. 2014;311(19):1998-2006.

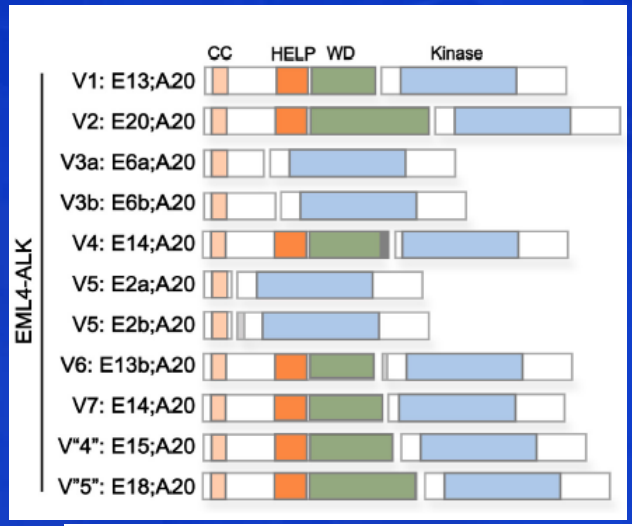
ALK Rearrangement in NSCLC

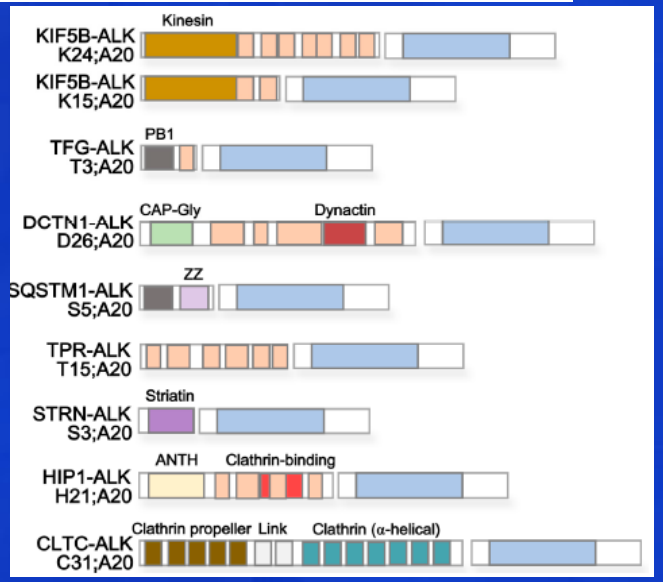
Other Fusion Partners

- Although EML4-ALK is the most common fusion gene, more than 30 other ALK fusion partners have been identified, some of which are shown here[1-3]

Prevalence of ALK With Partner Genes in Lung



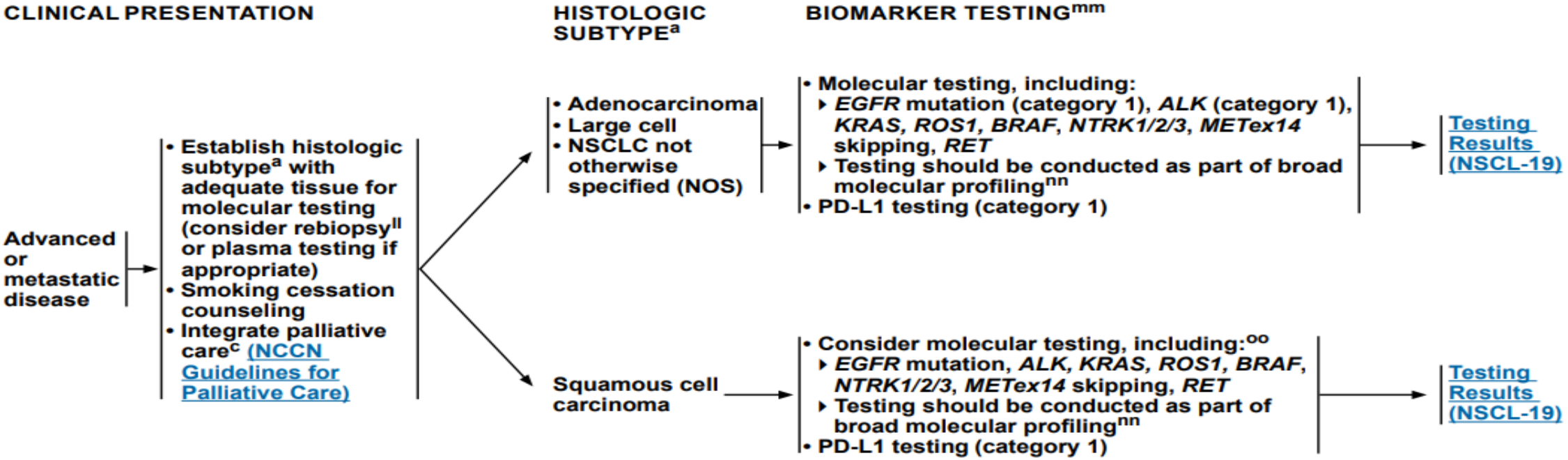




1. Childress MA, et al. *Mol Cancer Res*. 2018;16(11):1724-1736. 2. Cerrato A, et al. *Mol Cancer*. 2018;17(1):1-11. 3. Wu W, et al. *Cancers (Basel)*. 2017;9(12):164-181.

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

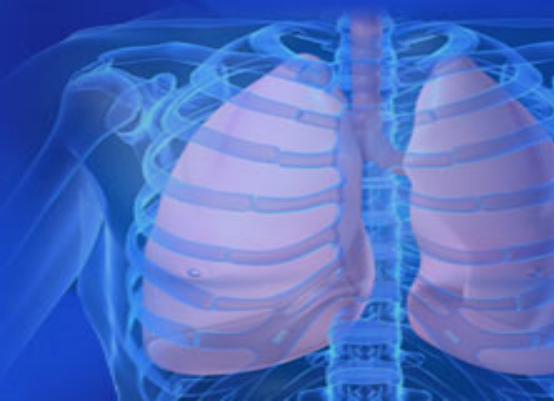


[a] Principles of Pathologic Review (NSCL-A).
[c] Temel JS, et al. N Engl J Med 2010;363:733-742.
[ll] If there is insufficient tissue to allow testing for all of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *and RET*, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[nn] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).
[oo] Lam VK, et al. Clin Lung Cancer 2019;20:30-36.e3; Sands JM, et al. Lung Cancer 2020;140:35-41.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

nscl.pdf (nccn.org)



TESTING RESULTS[ll,mm]

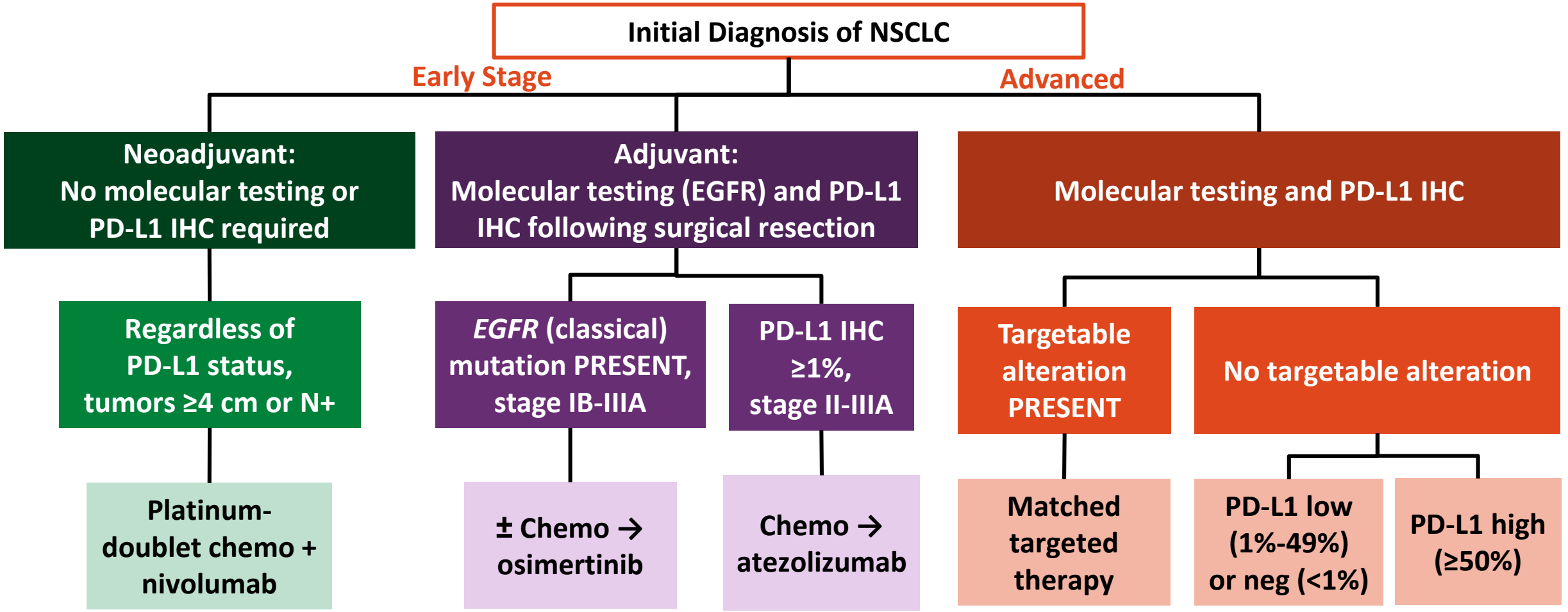
EGFR exon 19 **deletion or** ***L858R*** **mutation positive**	NSCL-20
EGFR S768I, L861Q, **and/or** ***G719X*** **mutation positive**	NSCL-23
EGFR exon 20 **insertion mutation positive**	NSCL-24
KRAS G12C **mutation positive**	NSCL-25
ALK **rearrangement positive**	NSCL-26
ROS1 **rearrangement positive**	NSCL-29
BRAF **V600E mutation positive**	NSCL-31
NTRK1/2/3 **gene fusion positive**	NSCL-32
METex14 **skipping mutation positive**	NSCL-33
RET **rearrangement positive**	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

[ll] If there is insufficient tissue to allow testing for all of *EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET,* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

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

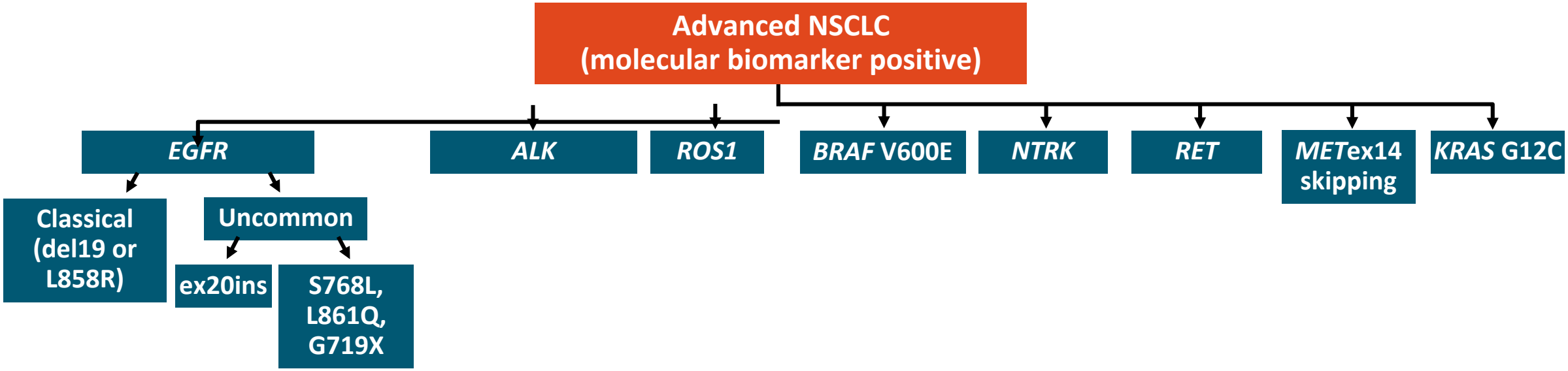
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Molecular and PD-L1 Testing at Initial Diagnosis to Guide Treatment in NSCLC



Slide credit: clinicaloptions.com

2022 Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



Biomarker testing to identify optimal first-line targeted therapy has improved survival for patients with advanced NSCLC in recent years

NCCN. Clinical practice guidelines in oncology: NSCLC. v.3.2022. nccn.org. Howlader. NEJM. 2020;383:640.

Slide credit: clinicaloptions.com

TARGETED THERAPY OR IMMUNOTHERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

EGFR Exon 19* Deletion or *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 Positive**
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

***KRAS G12C* Mutation Positive**
- Subsequent therapy
  - Sotorasib[14]

***ALK* Rearrangement Positive**
- First-line therapy
  - Alectinib[15,16]
  - Brigatinib[17]
  - Ceritinib[18]
  - Crizotinib[15,19]
  - Lorlatinib[20]
- Subsequent therapy
  - Alectinib[21,22]
  - Brigatinib[23]
  - Ceritinib[24]
  - Lorlatinib[25]

***ROS1* Rearrangement Positive**
- First-line therapy
  - Ceritinib[24]
  - Crizotinib[27]
  - Entrectinib[28]
- Subsequent therapy
  - Lorlatinib[29]
  - Entrectinib[28]

***BRAF* V600E Mutation Positive**
- First-line therapy
  - Dabrafenib/trametinib[30,31]
  - Dabrafenib[30]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[31,32]

***NTRK1/2/3* Gene Fusion Positive**
- First-line/Subsequent therapy
  - Larotrectinib[33]
  - Entrectinib[34]

***MET* Exon 14 Skipping Mutation**
- First-line therapy/Subsequent therapy
  - Capmatinib[35]
  - Crizotinib[36]
  - Tepotinib[37]

***RET* Rearrangement Positive**
- First-line therapy/Subsequent therapy
  - Selpercatinib[38]
  - Pralsetinib[39]
  - Cabozantinib[40,41]

PD-L1 ≥1%
- First-line therapy[d]
  - Pembrolizumab[42-44]
  - (Carboplatin or cisplatin)/pemetrexed/ pembrolizumab (nonsquamous)[45,46]
  - Carboplatin/paclitaxel/bevacizumab[c]/ atezolizumab (nonsquamous)[47]
  - Carboplatin/(paclitaxel or albumin-bound paclitaxel)/pembrolizumab (squamous)[48]
  - Carboplatin/albumin-bound paclitaxel/ atezolizumab (nonsquamous)[48]
  - Nivolumab/ipilimumab[49]
  - Nivolumab/ipilimumab/pemetrexed/ (carboplatin or cisplatin) (nonsquamous)[50]
  - Nivolumab/ipilimumab/paclitaxel/carboplatin (squamous)[50]

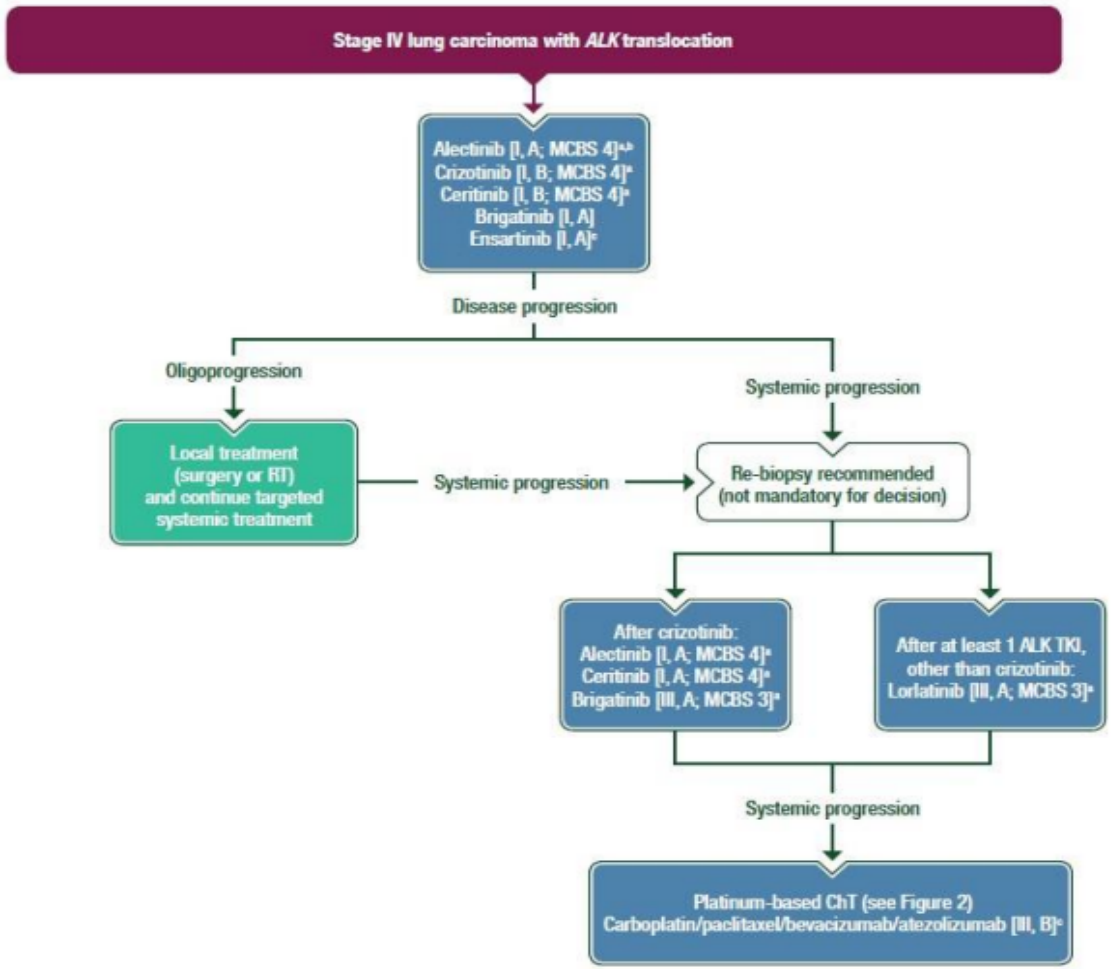
PD-L1 ≥50% (in addition to above)
- First-line therapy[d]
  - Atezolizumab[51]
  - Cemiplimab-rwlc[52]

[a] Monitoring During Initial Therapy: Response assessment after 2 cycles, then every 2–4 cycles with CT of known or high-risk sites of disease with or without contrast or when clinically indicated. Timing of CT scans within Guidelines parameters is a clinical decision.
[b] Monitoring During Subsequent Therapy or Maintenance Therapy: Response assessment with CT of known or high-risk sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[d] Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4–6 cycles, in the absence of disease progression.

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Figure 5. Treatment algorithm for stage IV lung carcinoma with ALK translocation.



[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[b]Preferred option [203a].
[c]Not EMA-approved.

Clinical Practice Living Guidelines – Metastatic Non-Small-Cell Lung Cancer | ESMO

ESMO 1L Treatment Algorithm for Stage IV Lung Carcinoma With ALK Translocation

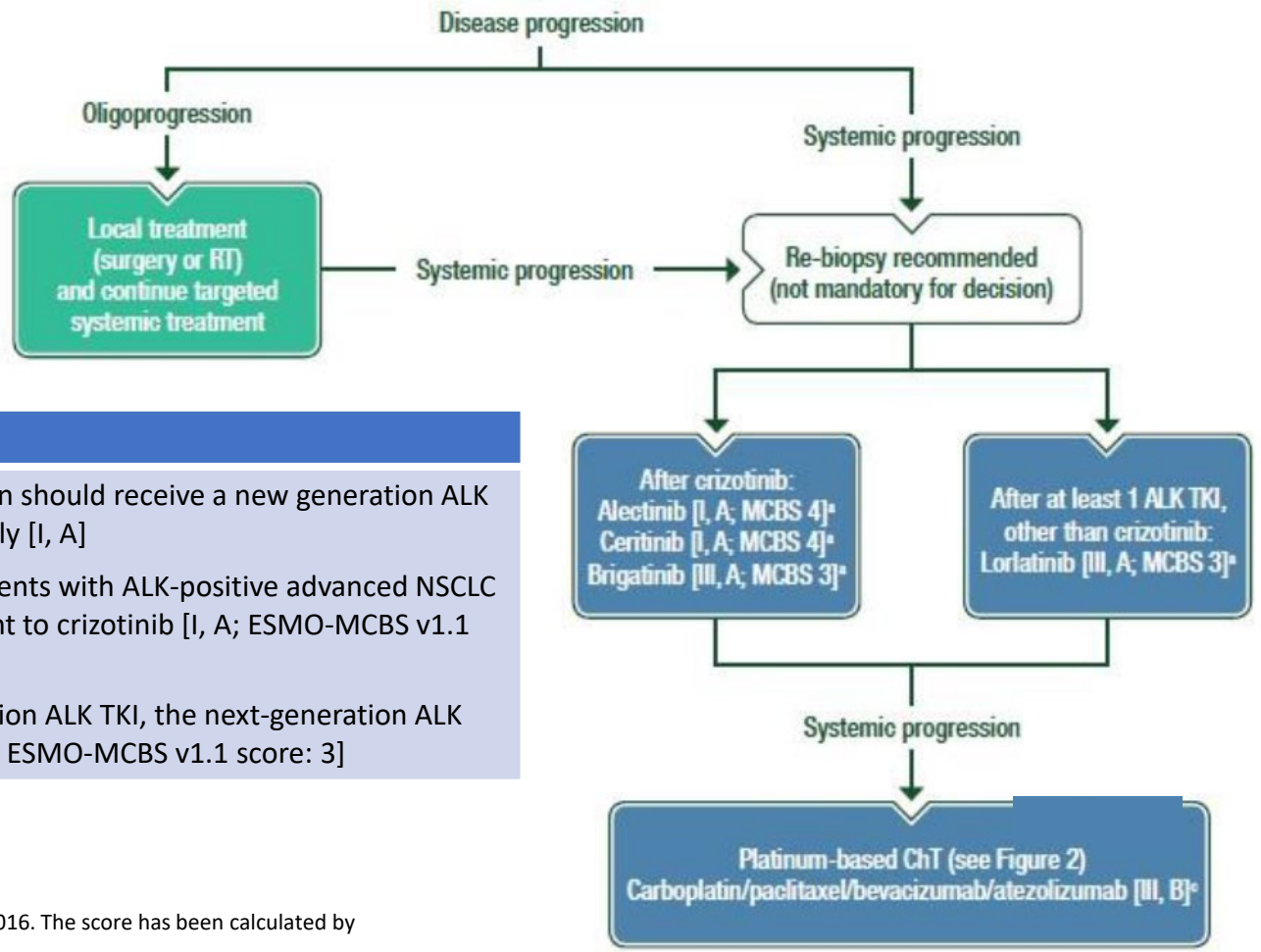
ESMO Treatment Recommendations	
1L Recommendations	• Patients with ALK-rearranged NSCLC should receive first-line ALK TKI including crizotinib [I, A; ESMO-MCBS v1.1 score: 4], ceritinib [I, B; ESMO-MCBS v1.1 score: 4], alectinib [I, A; ESMO-MCBS v1.1 score: 4] or brigatinib [I, A; EMA-approved]
CNS Activity	• In patients with CNS involvement, front-line use of ALK TKIs is effective, and alectinib [III, A], brigatinib [III, B] or ceritinib [IV, B] is recommended. Ceritinib represents a better treatment strategy than chemotherapy [I, B] and presumably crizotinib [IV, B]; alectinib represents a better treatment option than crizotinib [I, A]; brigatinib represents a better treatment option than crizotinib [I, A; EMA-approved]

Treatment	Level of Evidence	Grade of Recommendation	ESMO-MCBS v1.1 Score[a]
Alectinib	I	A (preferred option)	4
Crizotinib	I	A	4
Ceritinib	I	B	4
Brigatinib	I	A	NA
Lorlatinib	NA	NA	Not EMA-approved
Ensartinib	I	A	Not EMA-approved

[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

Planchard D, et al. *Ann Oncol*. 2018;29(January):iv192-iv237. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.
https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer. Updated September 15, 2020.

ESMO 2L+ Treatment Algorithm for Stage IV Lung Carcinoma With ALK Translocation



ESMO Treatment Recommendations	
2L+ Recommendations	• Any patient with NSCLC harbouring an ALK fusion should receive a new generation ALK TKI as next-line therapy, if not received previously [I, A] • Ceritinib and alectinib are recommended in patients with ALK-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [I, A; ESMO-MCBS v1.1 score: 4] • In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitor lorlatinib is an option if available [III, A; ESMO-MCBS v1.1 score: 3]

[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.

[b]Preferred option.

[c]Not EMA-approved.

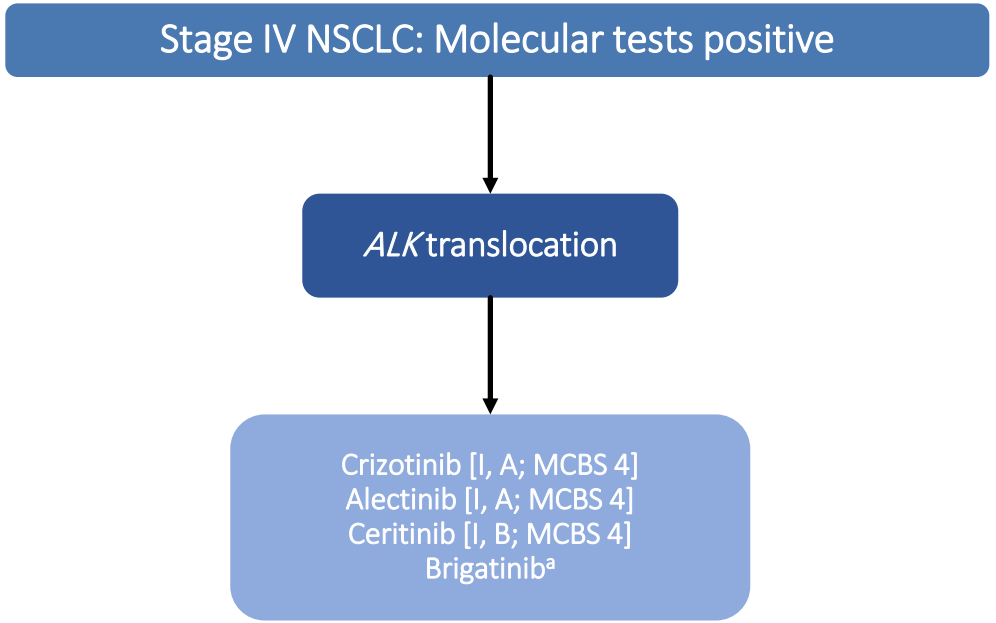
ALK, anaplastic lymphoma kinase; ChT, chemotherapy; EMA, European Medicines Agency; MCBS, ESMO-Magnitude of Clinical Benefit Scale; RT, radiotherapy; TKI, tyrosine kinase inhibitor.

Planchard D, et al. *Ann Oncol*. 2018;29(January):iv192-iv237. Metastatic Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. https://www.esmo.org/guidelines/lung-and-chest-tumours/clinical-practice-living-guidelines-metastatic-non-small-cell-lung-cancer. Updated September 15, 2020.

Pan-Asian Adapted Clinical Practice Guidelines for 1L Treatment of Stage IV Lung Carcinoma With ALK Translocation

1L Treatment Recommendations

- Patients with ALK-rearranged NSCLC should receive first-line treatment with an ALK TKI, including crizotinib [A=100% and I, A], ceritinib [A=100% and I, B] and alectinib [A=100% and I, A]
- Alectinib is associated with a longer PFS and lower toxicity than crizotinib and showed activity against CNS disease in previously untreated patients with ALK-positive NSCLC [A=100% and I, A]
- In patients with CNS involvement front-line use of ALK TKIs is effective, and alectinib [III, A] or ceritinib [IV, B] are recommended [A=100%]. Ceritinib represents a better treatment strategy than chemotherapy [I, B] and presumably crizotinib [IV, B]; alectinib represents a better treatment option than crizotinib [I, A]; brigatinib represents a better treatment option than crizotinib [I, B]
- In ALK-rearranged NSCLC patients with localized distant progression and ongoing systemic control, continuation of treatment with ALK TKI in combination with local treatment of the progressing metastatic sites may be considered [A=100% and III, B]



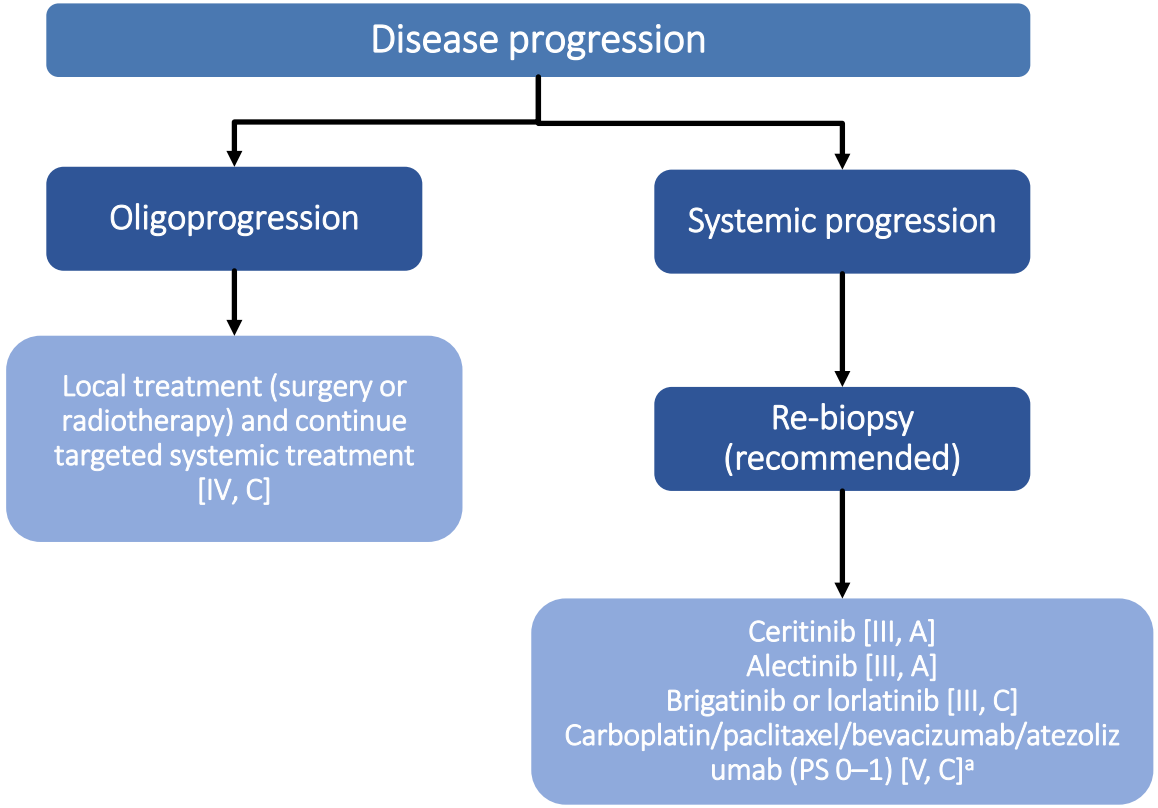
[a]Not approved for 1L treatment.

Wu YL, et al. *Ann Oncol*. 2019;30(2):171-210. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO, and TOS. https://www.annalsofoncology.org/article/S0923-7534(19)31046-4/fulltext.

Pan-Asian Adapted Clinical Practice Guidelines for 2L+ Treatment of Stage IV Lung Carcinoma With ALK Translocation

2L+ Treatment Recommendations

- Ceritinib and alectinib are recommended in patients with ALK-positive advanced NSCLC who progress on treatment with or are intolerant to crizotinib [I, A]
- In patients with ALK-positive NSCLC progressing on crizotinib with CNS progression, treatment should be a next-generation ALK TKI such as alectinib or ceritinib [I, A]
- In patients who progress after a second-generation ALK TKI, the next-generation ALK inhibitors such as brigatinib or lorlatinib are an option if available [III, C]. If not, pemetrexed and cisplatin should be considered
- Assessment of the molecular mechanisms of resistance could also have an impact in the decision-making process
- The optimal sequencing of ALK-targeted agents remains to be established
- Combination of atezolizumab and bevacizumab with carboplatin and paclitaxel might be considered as a therapeutic option in patients with ALK-mutated tumour, PS 0–1, in the absence of contraindications to use of immunotherapy after targeted therapies has been exploited [V, C after discussion]



[a]Depending on approval status and reimbursement.

Wu YL, et al. *Ann Oncol*. 2019;30(2):171-210. Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO-ESMO initiative endorsed by JSMO, KSMO, MOS, SSO, and TOS. https://www.annalsofoncology.org/article/S0923-7534(19)31046-4/fulltext.

ALK Inhibitor Key Clinical Data: 1L PFS Data Readouts

	XALKORI (crizotinib)		ZYKADIA (ceritinib)		ALECENSA (alectinib)		ALUNBRIG (brigatinib)		LORBRENA/LORVIQUA (lorlatinib)		Ensartinib	
Key study	Phase 3: PROFILE 1014		Phase 3: ASCEND-4		Phase 3: ALEX		Phase 3: ALTA-1L		Phase 3: CROWN		Phase 3: eXalt3	
Dosing	**XALKORI (N=172)** 250 mg BID	**Chemotherapy* (N=171)**	**ZYKADIA (N=189)** 750 mg QD	**Chemotherapy† (N=187)**	**ALECENSA (N=152)** 600 mg BID	**Crizotinib (N=151)** 250 mg BID	**ALUNBRIG (N=137)** 90 mg → 180 mg QD	**Crizotinib (N=138)** 250 mg BID	**LORBRENA (N=149)** 100 mg QD	**Crizotinib (N=147)** 250 mg BID	**Ensartinib (N=143)** 225 mg QD	**Crizotinib (N=147)** 250 mg BID
Efficacy Data												
Median PFS, months	Median follow-up: 17.4 mo[1]		Median follow-up: 19.7 mo[2]		Median follow-up: 18.6 mo[3]		Median follow-up, 11 mo[6]		Median follow-up, 18.3 mo[9]		Median follow-up, 23.8 mo[10]	
	10.9 (8.3, 13.9)	7.0 (6.8, 8.2)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)	NR (17.7, NE)	11.1 (9.1, 13.1)	NR (NR, NR)	9.8 (9.0, 12.9)	NR (NR, NR)	9.3 (7.6, 11.1)	25.8 (21.8, NR)	12.7 (9.2, 16.6)
	HR 0.45 (95% CI, 0.35, 0.60); *P*<0.001‡		HR 0.55 (95% CI, 0.42, 0.73); *P*<0. 00001‡		HR 0.47 (95% CI, 0.34, 0.65)**		HR 0.49 (95% CI, 0.33, 0.74); *P*<0.001‡		HR 0.28 (95% CI, 0.19, 0.41); P<0.001‡		HR 0.51 (95% CI, 0.35, 0.72); *P*=0.0001‡	
					Median follow-up: 27.8 mo[4]		Median follow-up, 24.9 mo[7]				Median follow-up, 27.6 mo[11]	
					34.8 (17.7, NE)	10.9 (9.1, 12.9)	24.0 (18.5, NE)	11.0 (9.2, 12.9)			31.3 (20.2, NR)	12.7 (9.2, 16.6)
					HR 0.43 (95% CI, 0.32, 0.58)**		HR 0.49 (95% CI, 0.35, 0.68)‡				HR 0.50 (95% CI, 0.36, 0.71); *P*=0.0001*	
					Median follow-up: 37.8 mo[5]		Median follow-up, 40.4 mo[8]					
					34.8 (17.7, NE)	10.9 (9.1, 12.9)	24.0 (18.5, 43.2)	11.0 (9.1, 13.0)				
					HR 0.43 (95% CI, 0.32, 0.58); P<0.0001**		HR 0.48 (95% CI, 0.35, 0.66)‡					

•*Pemetrexed 500 mg/m² and cisplatin 75 mg/m² or carboplatin AUC of 5 or 6 mg/mL·min by intravenous infusion every 3 weeks for up to 6 cycles. †Pemetrexed 500 mg/m² and investigator's choice of cisplatin 75 mg/m² or carboplatin AUC of 5-6 mg/mL·min administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m²) every 21 days. ‡By independent review. **By investigator review.

•CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached; PFS, progression-free survival.

•References in notes.

Pregled terapijskih opcija za lečenje ALK+ metastatic NSCLC pacijenata

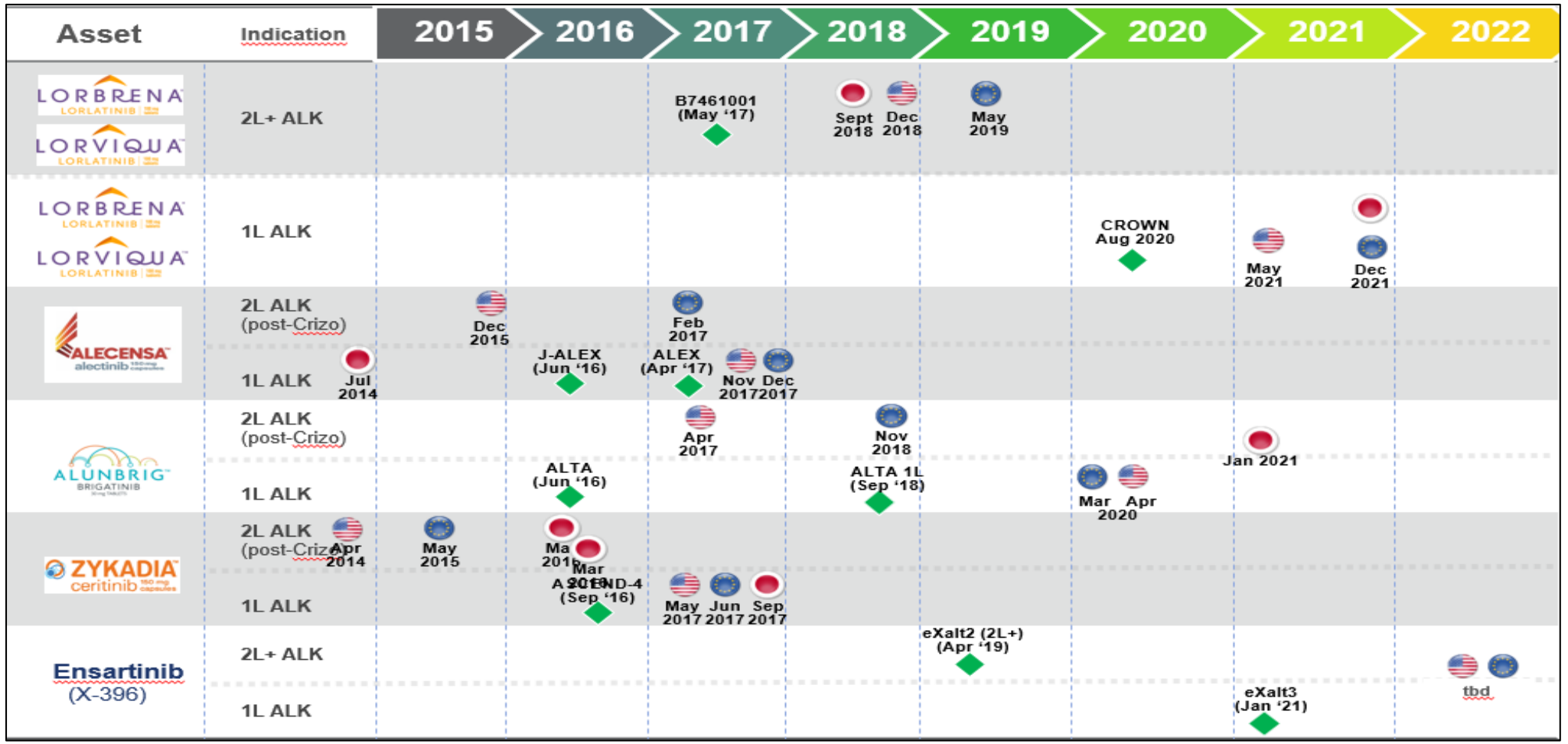
Prof. dr Davorin Radosavljević

Institut za Onkologiju i Radiologiju Srbije

On-line CME Medscape Srbija

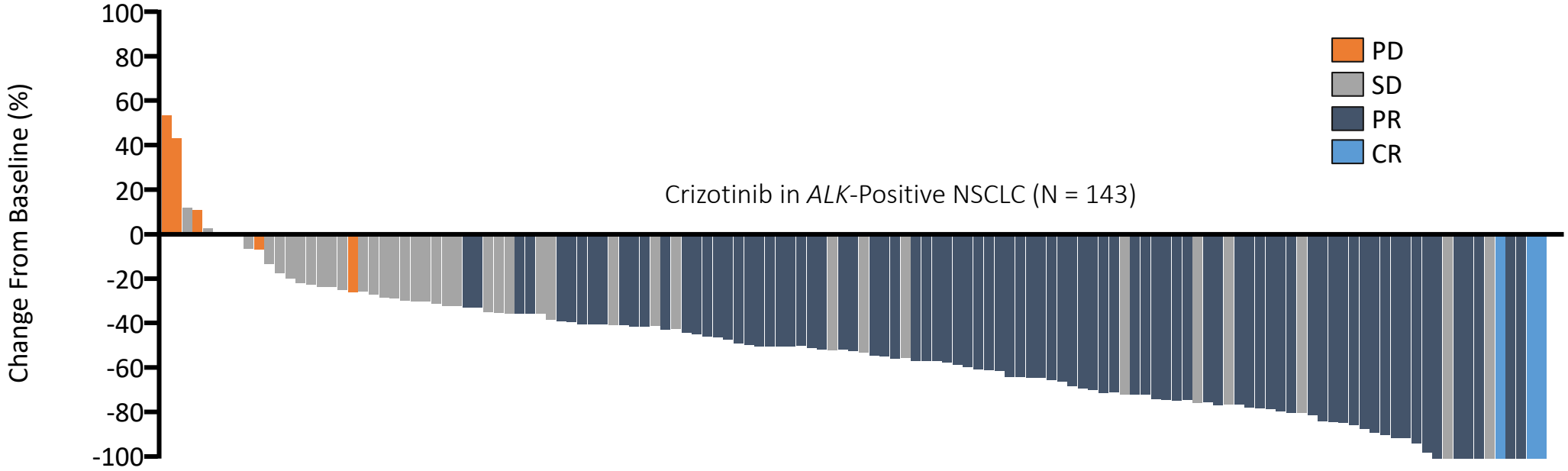
Current ALK+ Treatment Landscape

- Alectinib: entrenched as the SoC for ALK+ NSCLC, high response rates & including CNS efficacy; Brigatinib: 1L approval Q2 2020;
- Ensartinib: 6th ALK inhibitor to market; mPFS is 31.3



Tumor Responses to ALK Inhibitor Crizotinib in *ALK*+ Lung Cancer

- Most pts on study had already had **≥ 2 lines of previous therapy**
- Objective response rate: **60.8%**
- Median PFS: **9.7 mos** (95% CI: 7.7-12.8)



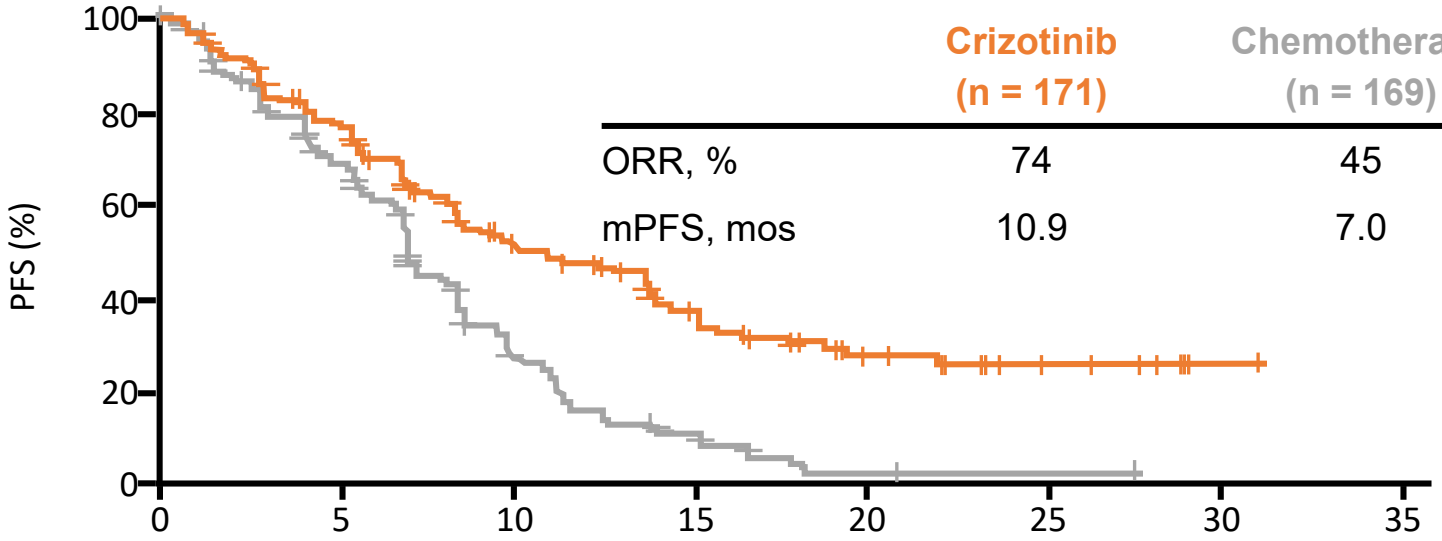
Camidge DR, et al. Lancet Oncol. 2012;13:1011-1019.

PROFILE 1014: Crizotinib vs Pemetrexed/ Platinum in Advanced Untreated NSCLC

Advanced ALK-positive nonsquamous NSCLC not previously treated (N = 343)

- Crizotinib 250 mg BID
- Pemetrexed + Cisplatin or Carboplatin q3w x 6 cycles

Primary endpoint: PFS

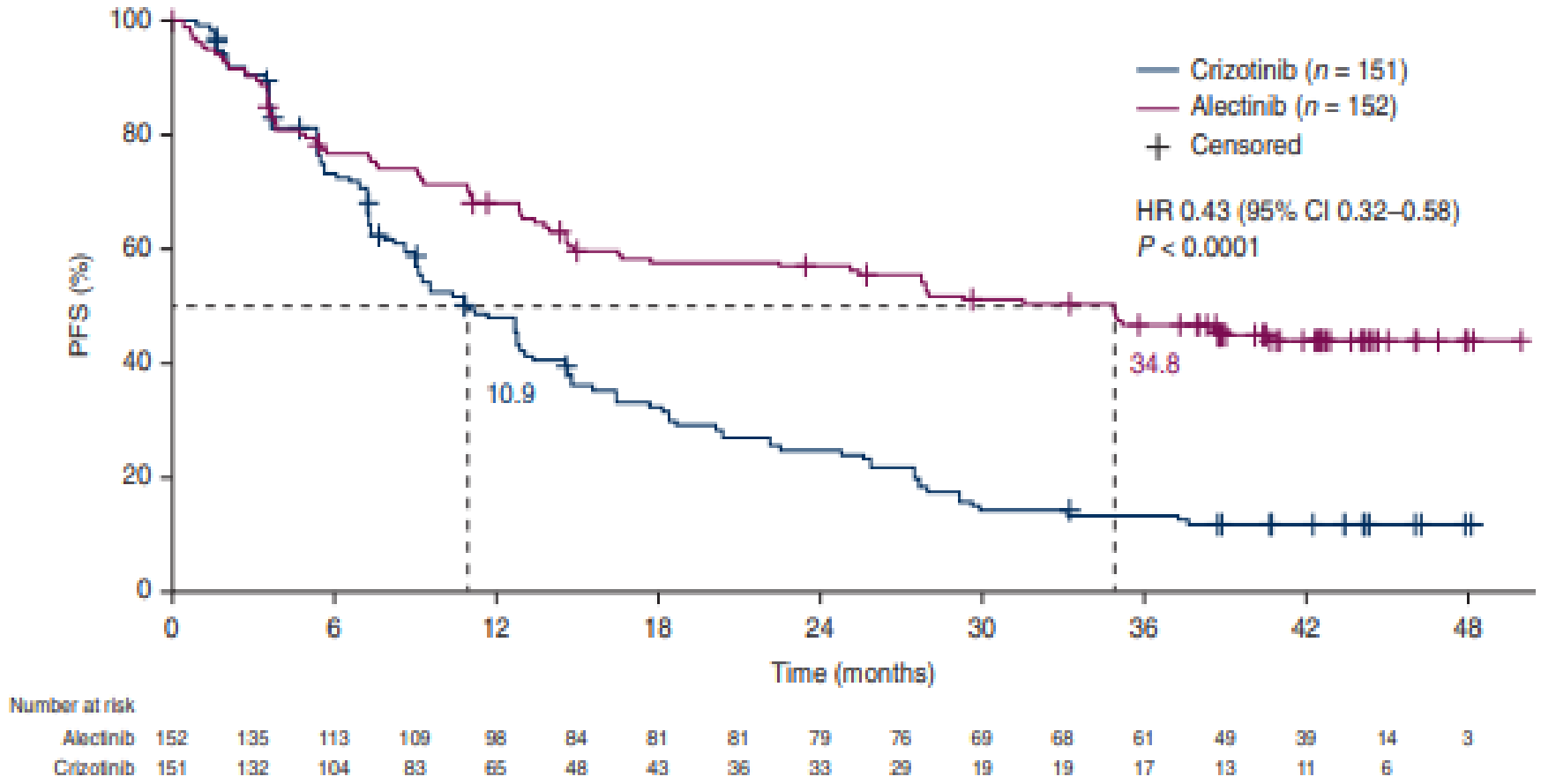


	Crizotinib (n = 171)	Chemotherapy (n = 169)	HR (95% CI)	*P* Value
ORR, %	74	45		
mPFS, mos	10.9	7.0	0.45 (0.35-0.60)	

Solomon BJ, et al. N Engl J Med. 2014;371:2167-2177. Mok T, et al. ASCO 2014. Abstract 8002.

ALEX: mature PFS results

T. Mok et al, Ann Oncol 2020.

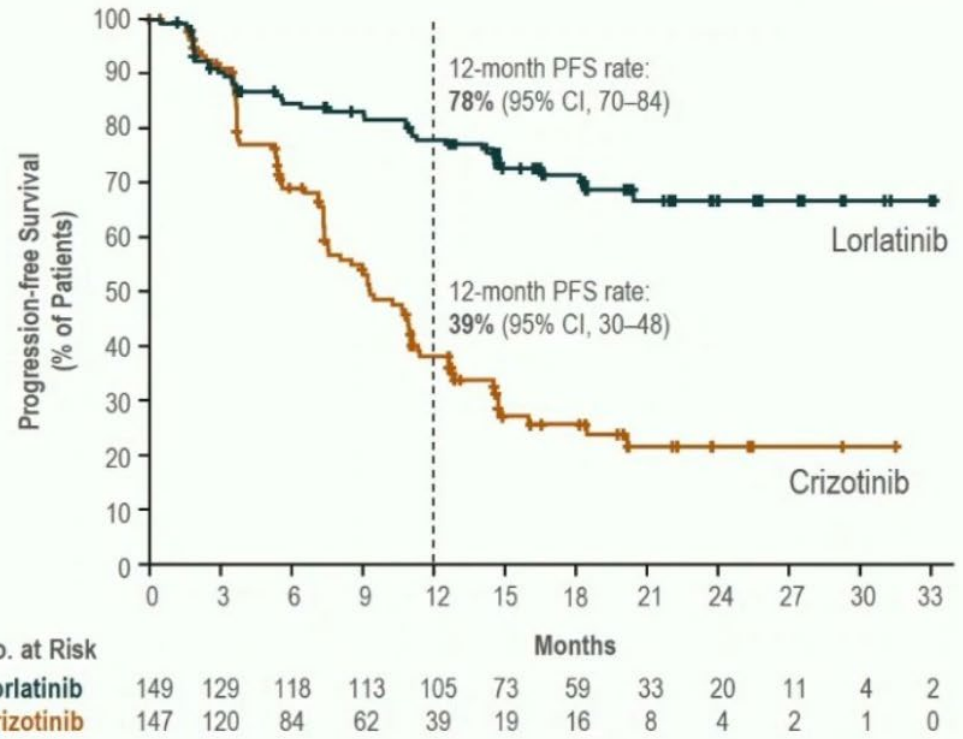


Lorlatinib vs Crizotinib in 1L ALK-positive NSCLC (CROWN study),

AT Shaw et al, NEJM 2020.

VIRTUAL 2020 ESMO congress

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.

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

ALEX trial: CNS results

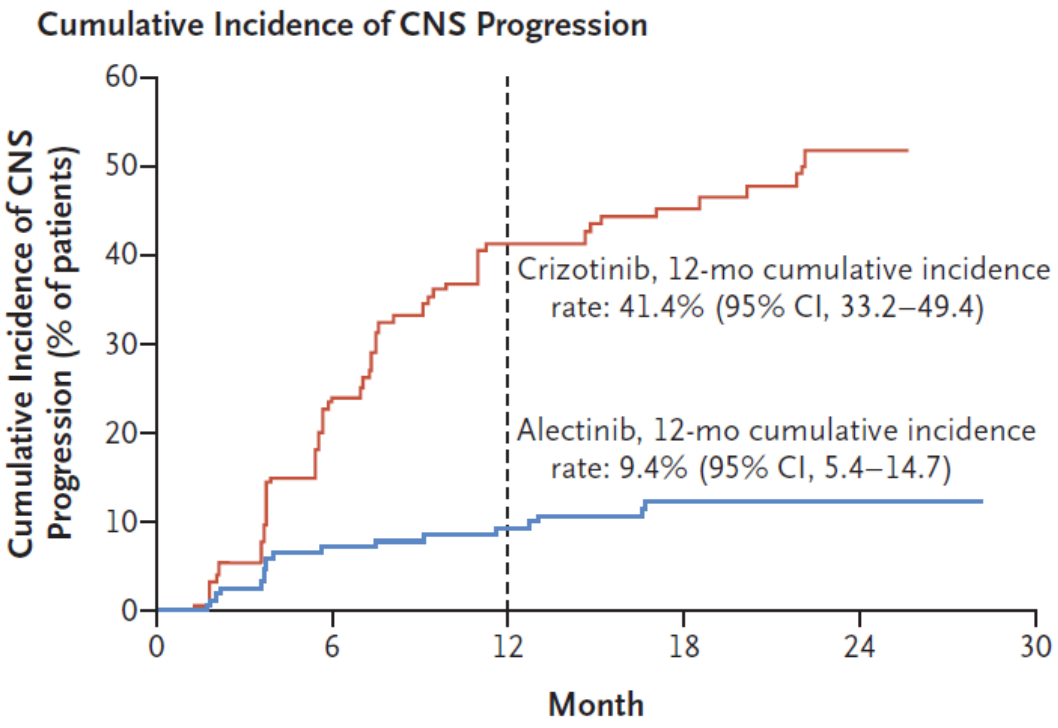


Table 2. Objective Response Rates in the Intention-to-Treat Population and among Patients with CNS Lesions at Baseline.*

Variable	Crizotinib	Alectinib
Intention-to-treat population		
No. of patients	151	152
Response		
No. of patients	114	126
% (95% CI)	75.5 (67.8–82.1)	82.9 (76.0–88.5)†
Complete response — no. (%)	2 (1)	6 (4)
Partial response — no. (%)	112 (74)	120 (79)
Stable disease — no. (%)	24 (16)	9 (6)
Median duration of response (95% CI) — mo	11.1 (7.9–13.0)	NE (NE)
Patients with measurable CNS lesions at baseline		
No. of patients	22	21
CNS response		
No. of patients	11	17
% (95% CI)	50 (28–72)	81 (58–95)
CNS complete response — no. (%)	1 (5)	8 (38)
Median duration of response (95% CI) — mo	5.5 (2.1–17.3)	17.3 (14.8–NE)
Patients with measurable or nonmeasurable CNS lesions at baseline		
No. of patients	58	64
CNS response		
No. of patients	15	38
% (95% CI)	26 (15–39)	59 (46–71)
CNS complete response — no. (%)	5 (9)‡	29 (45)§
Median duration of response (95% CI) — mo	3.7 (3.2–6.8)	NE (17.3–NE)

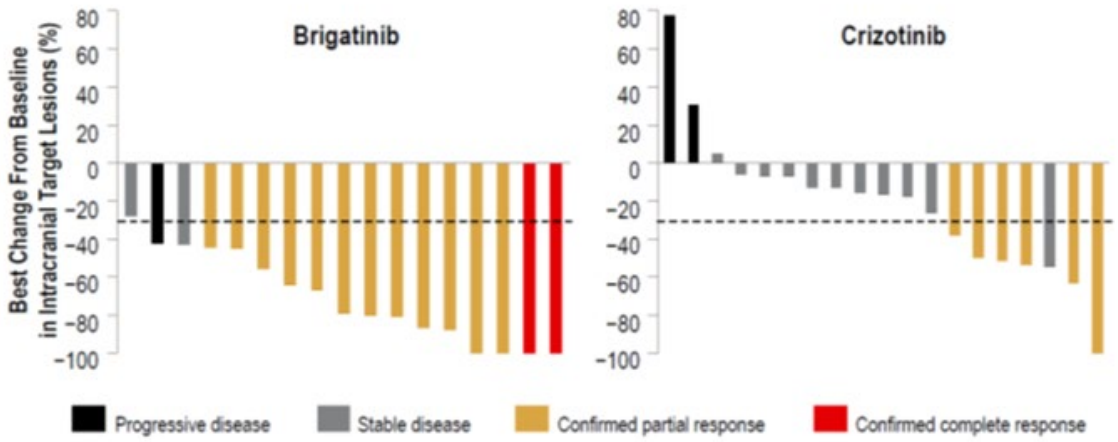
* Systemic responses (in the intention-to-treat population) were assessed by the investigator. CNS responses (in patients with CNS lesions at baseline) were assessed by the independent review committee. CI denotes confidence interval, and NE not estimable.
† P=0.09 for the comparison between crizotinib and alectinib.
‡ Of the 5 patients, 1 received previous brain radiotherapy and 1 received concomitant brain radiotherapy.
§ Of the 29 patients, 5 received previous brain radiotherapy and 1 received concomitant brain radiotherapy.

- CNS, central nervous system; CI, confidence interval; CR, complete response; ORR, objective response rate

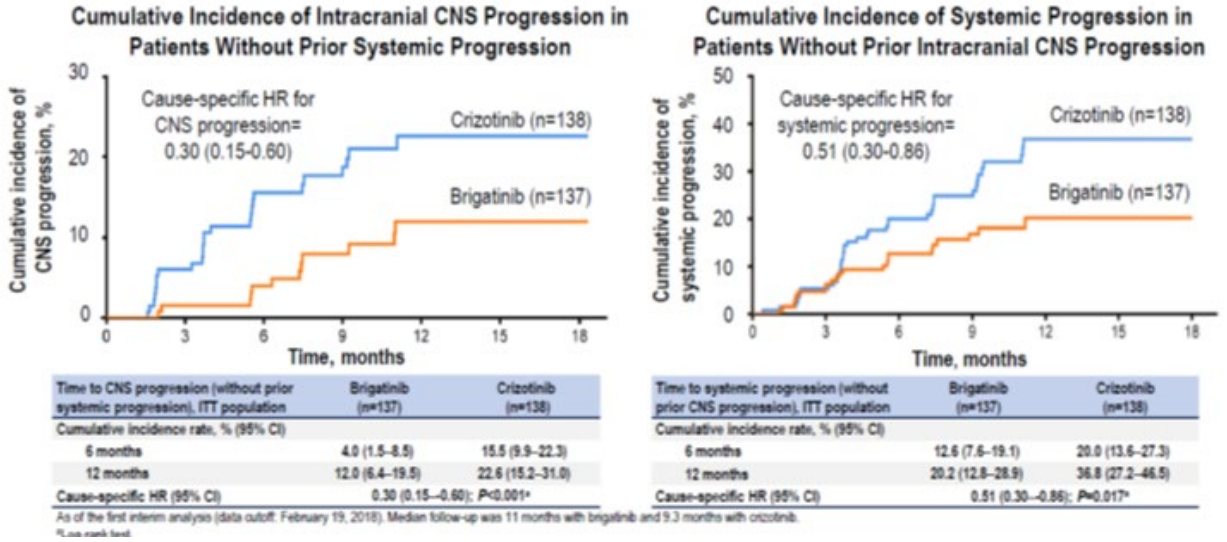
- Peters S, et al. N Engl J Med 2017;377:829–38

ALTA-1L: CNS results

Intracranial best target lesion response in patients with measurable brain metastasis



CNS and systemic efficiency: competing risks analysis



Time to CNS progression (without prior systemic progression), ITT population	Brigatinib (n=137)	Crizotinib (n=138)
Cumulative incidence rate, % (95% CI)		
6 months	4.0 (1.5–8.5)	15.5 (9.9–22.3)
12 months	12.0 (6.4–19.5)	22.6 (15.2–31.0)
Cause-specific HR (95% CI)	0.30 (0.15–0.60); P<0.001[a]	

Time to systemic progression (without prior CNS progression), ITT population	Brigatinib (n=137)	Crizotinib (n=138)
Cumulative incidence rate, % (95% CI)		
6 months	12.6 (7.6–19.1)	20.0 (13.6–27.3)
12 months	20.2 (12.8–28.9)	36.8 (27.2–46.5)
Cause-specific HR (95% CI)	0.51 (0.30–0.86); P=0.017[a]	

As of the first interim analysis (data cutoff: February 19, 2018). Median follow-up was 11 months with brigatinib and 9.3 months with crizotinib.

[a]Log-rank test.

- CNS, central nervous system; CI, confidence interval; CR, complete response; ic, intracranial; PR, partial response; ORR, objective response rate

- Califano R, presented at ELCC 2019. *Ann Oncol;* 2019;30(suppl_2):ii38-ii68

Lorlatinib vs Crizotinib in 1L ALK-positive NSCLC (CROWN study),

AT Shaw et al, NEJM 2020.

VIRTUAL 2020 ESMO congress

Intracranial-OR by BICR

	Patients with measurable or non-measurable brain metastases at baseline		Patients with measurable brain metastases at baseline	
	Lorlatinib (n=38)	**Crizotinib (n=40)**	**Lorlatinib (n=17)**	**Crizotinib (n=13)**
IC-responders, n (%)	**25 (66)**	**8 (20)**	**14 (82)**	**3 (23)**
(95% CI)	(49-80)	(9-36)	(57-96)	(5-54)
Odds ratio (95% CI)	8.41 (2.59-27.23)		16.83 (1.95-163.23)	
IC-CR, n (%)	**23 (61)**	**6 (15)**	**12 (71)**	**1 (8)**
Median DR, months (95% CI)	NE (NE–NE)	9.4 (6.0-11.1)	NE (NE–NE)	10.2 (9.4-11.1)

Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib
CR, complete response; DR, duration of response; IC, intracranial; NE, not evaluable; OR, objective response

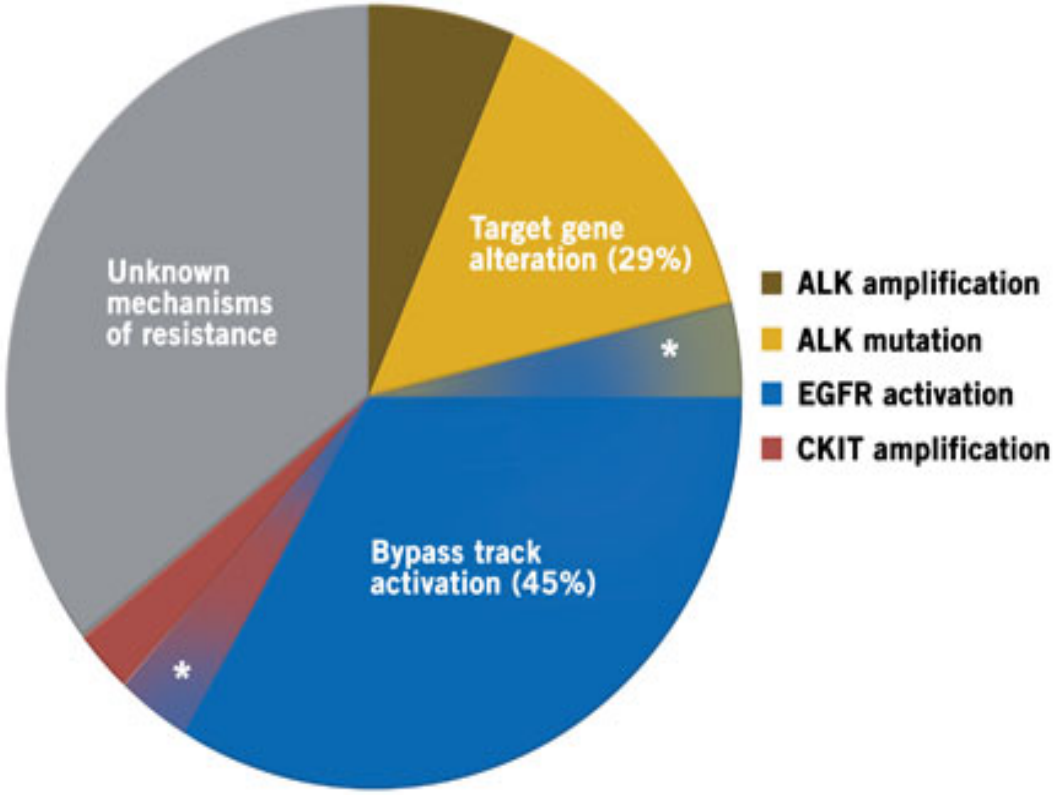
New generations of ALK inhibitors

- **Better CNS penetration**
- **More potent**
- **Active against resistance**

- **“on target”** mechanisms – kinase domain **mutations** and genomic **amplifications** of the ALK fusion;
- **„off target”** mechanisms – predominantly **“bypass”** signaling pathways

Prema podacima autora

ALK+ NSCLC resistance mechanisms

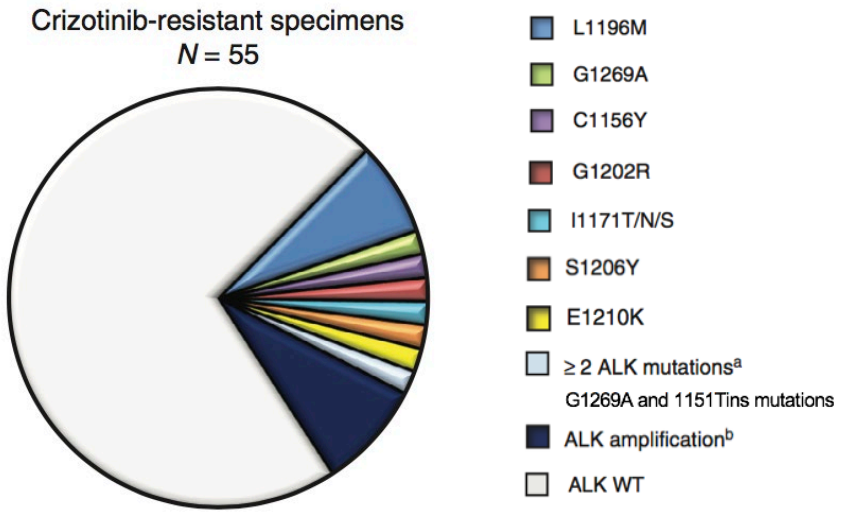


*Patients with more than one mechanism of resistance.

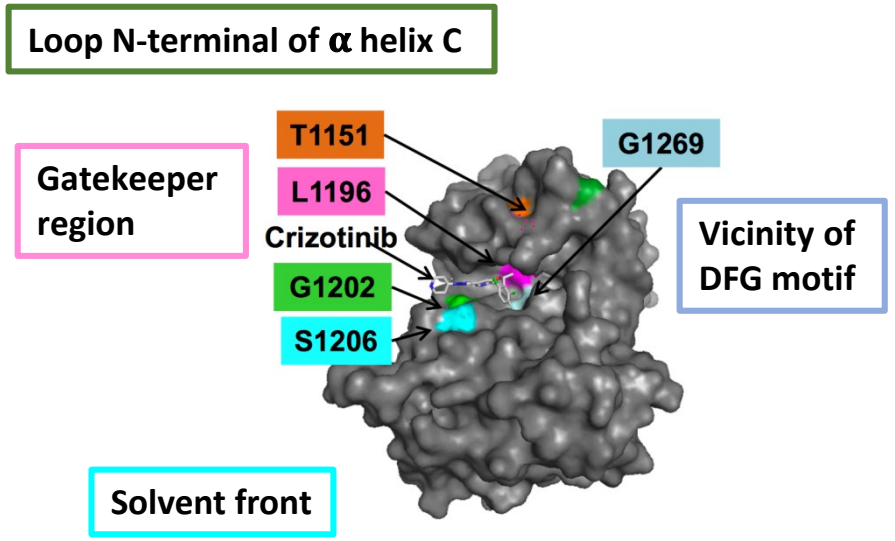
Prema podacima autora

Resistance to 1st generation (crizotinib)

Median PFS: 10.9 months



31% with ALK alteration



Gainor et al Cancer Discovery 2016; Katayama R Pharmaco Ther 2017

Gainor et al. *Cancer Discov.* 2016;6:1118–1133 and Iwama et al. *OncoTargets Ther.* 2014;7:375–385. demonstrated the appearance of resistance mechanisms during prolonged treatment with TKIs

They differ between first-generation and next-generation ALK TKIs:

- ✓ In patients who demonstrated treatment failure on the first-generation agent crizotinib, the main mechanisms of resistance include the **expression of other oncogenes, changes in the copy number of the *ALK* gene, and activation of alternative pathways such as epidermal growth factor receptor (EGFR) or KIT signaling**, while secondary *ALK* rearrangements were only found in 20% to 30% of patients.
- ✓ In contrast, ***ALK* resistance mutations** represented the major resistance mechanism (50% to 70%) in patients treated with ceritinib, alectinib, or brigatinib. This is thought to reflect the greater potency and selectivity of the next-generation TKIs compared to crizotinib

Lorlatinib has broad activity against ALK resistance mutations

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

- Secondary mutations in the ALK kinase domain can induce resistance to first- and second-generation ALK TKIs[1]
- **Lorlatinib has broad-spectrum potency against most known ALK resistance mutations, including ALK G1202R[1,2]**

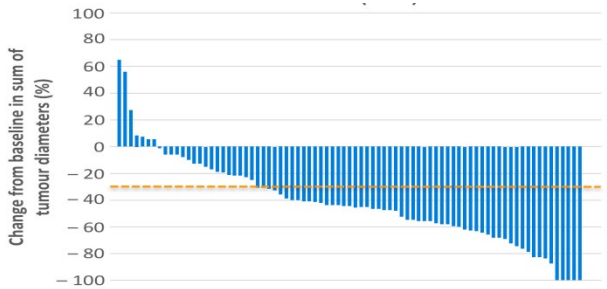
	Cellular ALK Phosphorylation Mean IC_{50} (nM)				
Mutation status	**Crizotinib**	**Ceritinib**	**Alectinib**	**Brigatinib**	**Lorlatinib**
EML4-ALK	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C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

1. Gainor JF, et al. *Cancer Discov.* 2016;6:1118–1133;
2. Johnson TW, et al. *J Med Chem.* 2014;57:4720–4744

Activity of 2nd generation ALK inhibitors, post-crizotinib

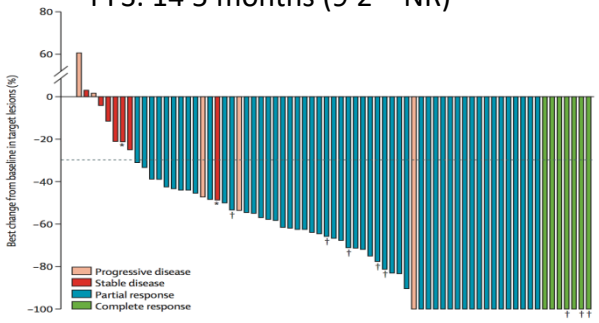
Ceritinib

ORR: 39.1% (30.2, 48.7)
PFS: 6.7 months (4.4, 7.9)



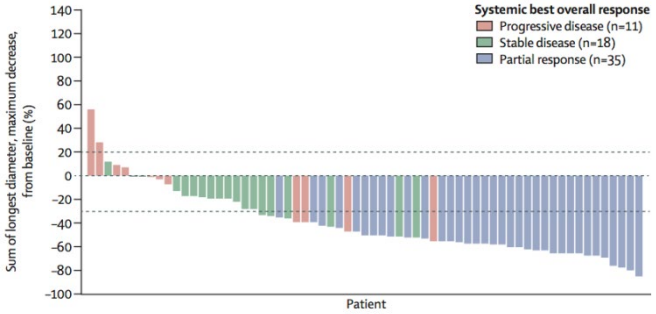
Brigatinib

ORR: 62% (50–73)
PFS: 14·5 months (9·2 – NR)



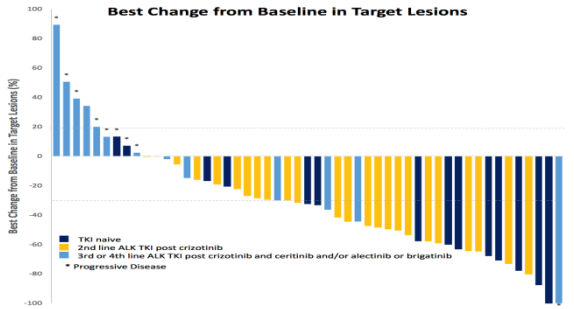
Alectinib

ORR: 48%, 95%CI (36 – 60)
PFS: 8.1 months, 95%CI (6.2 – 12.6)



Ensartinib

ORR: 64% (n=16/25)



Scagliotti ESMO 2016; Shaw et al. TLO 2016; Gettinger et al. TLO 2016; Horn et al. ESMO 2016

Lorlatinib – a third generation ALK TKI

- Phase II study: 5 cohorts with ALK+ and 1 cohort with ROS1+;
  - cohort 1, ALK+, **treatment naive**: **ORR 90%,** intracranial RR 75%
  - cohort 2 and 3A, ALK+, **previously crizotinib**, crizo+/-CT: **ORR 69%,** intracranial RR 68%
  - cohort 3B, ALK+, **previously non-crizotinib** TKI: **ORR 33%,** intracranial ORR 42%
  - cohort 4 and 5, ALK+, 2 or 3 prior TKI, +/-CT: ORR 39%, intracranial ORR 48%

Solomon B et al. J Clin Oncol 2017; 39: 9009.

FDA breakthrough designation, November 2, 2018.: **lorlatinib** for the treatment of patients with ALK+ metastatic NSCLC **previously treated with one or more ALK inhibitors**

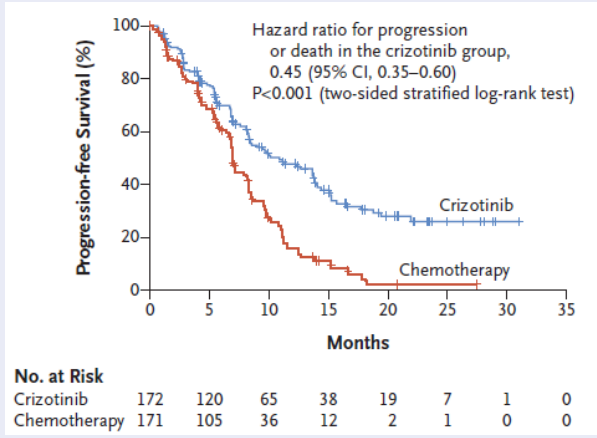
ALK Inhibitor 1L Indications

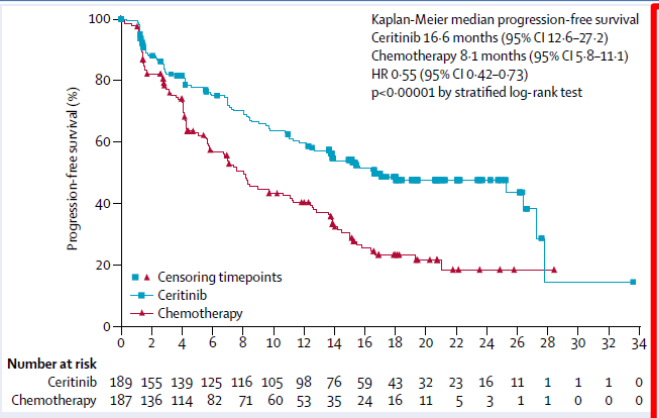
Updated 07.04.202

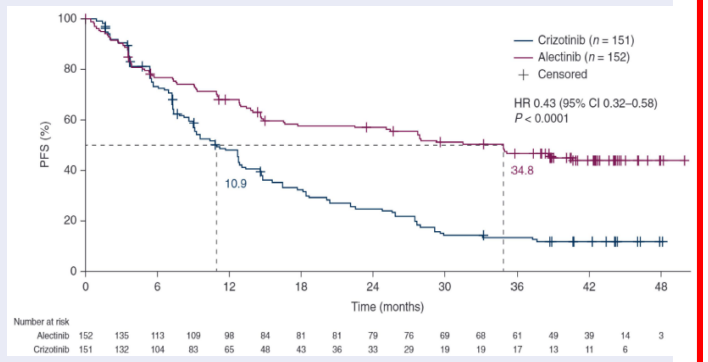
	XALKORI (crizotinib)[1-3]	ZYKADIA (ceritinib)[4-6]	ALECENSA (alectinib)[7-9]	ALUNBRIG (brigatinib)[10,11]	LORBRENA/LORVIQUA (lorlatinib)[12,13]	Ensartinib[14]
US	XALKORI is indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK+ or ROS1+ as detected by an FDA-approved test	ZYKADIA is indicated for the treatment of adult patients with metastatic NSCLC whose tumors are ALK+ as detected by an FDA-approved test	ALECENSA is indicated for the treatment of patients with ALK+ NSCLC as detected by an FDA-approved test	ALUNBRIG is indicated for the treatment of adult patients with ALK+ metastatic NSCLC as detected by an FDA-approved test	LORBRENA is a kinase inhibitor indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK positive as detected by an FDA-approved test	In clinical development in the 1L setting
EU	XALKORI is indicated for the 1L treatment of adults with ALK+ advanced NSCLC	ZYKADIA as monotherapy is indicated for the 1L treatment of adult patients with ALK+ advanced NSCLC	ALECENSA as monotherapy is indicated for the 1L treatment of adult patients with ALK+ advanced NSCLC	ALUNBRIG is indicated as monotherapy for the treatment of adult patients with ALK+ advanced NSCLC previously not treated with an ALK inhibitor	Lorviqua as monotherapy is indicated for the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor.	In clinical development
JPN	XALKORI is indicated for ALK-positive, unresectable, advanced or relapsed NSCLC	ZYKADIA is indicated for the treatment of unresectable advanced/ relapsed ALK fusion gene–positive NSCLC	ALECENSA is indicated for ALK fusion gene–positive, unresectable, recurrent or advanced NSCLC	N/A	N/A	N/A
Trial	**Phase 3:** PROFILE 1014	**Phase 3:** ASCEND-4	**Phase 3:** ALEX	**Phase 3:** ALTA-1L	**Phase 3:** CROWN	**Phase 3:** eXalt3

ALK Inhibitor Key Clinical Data: 1L PFS (1 of 2)

	XALKORI (crizotinib)[1,2]		ZYKADIA (ceritinib)[3,4]		ALECENSA (alectinib)[5-7]	
Key study	Phase 3: PROFILE 1014		Phase 3: ASCEND-4		Phase 3: ALEX	
Dosing	**XALKORI (N=172)** 250 mg BID	**Chemotherapy* (N=171)**	**ZYKADIA (N=189)** 750 mg QD	**Chemotherapy† (N=187)**	**ALECENSA (N=152)** 600 mg BID	**Crizotinib (N=151)** 250 mg BID
Efficacy Data						
Median PFS, months	10.9	7.0	16.6	8.1	34.8	10.9
	HR 0.45 (95% CI, 0.35, 0.60); *P*<0.001‡		HR 0.55 (95% CI, 0.42, 0.73); *P*<0.0001‡		HR 0.43 (95% CI, 0.32, 0.58); *P*<0.0001**	







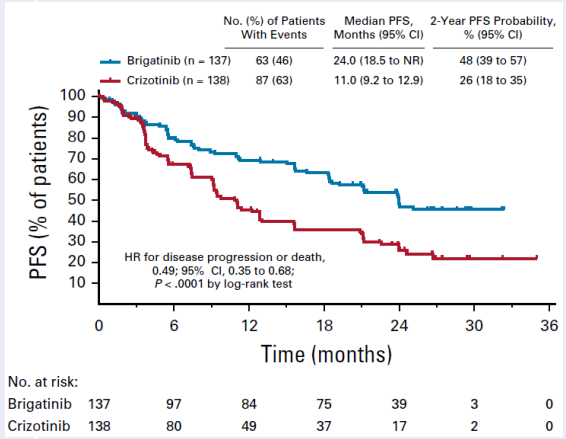
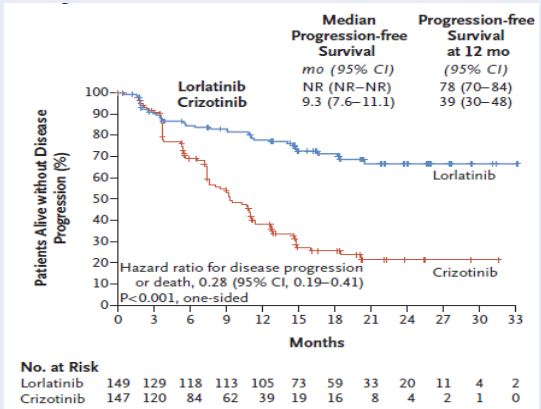
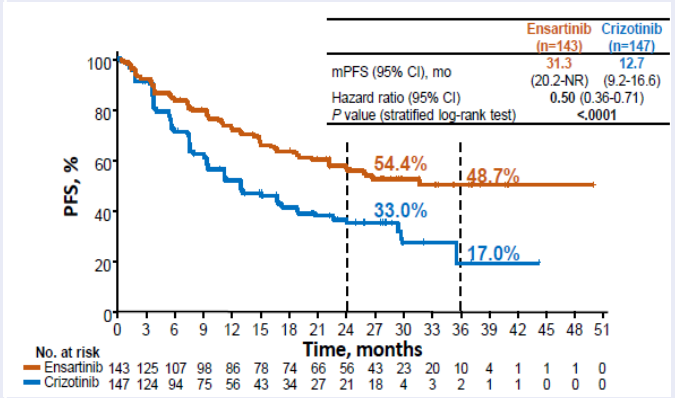
Cross trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results

•*Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC of 5 or 6 mg/mL·min by intravenous infusion every 3 weeks for up to 6 cycles. †Pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC of 5-6 mg/mL·min administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m^2) every 21 days. ‡By independent review. **By investigator review.

•CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

•1. XALKORI [prescribing information]. New York, NY: Pfizer Inc.; 2021. 2. Solomon BJ, et al. *N Engl J Med*. 2014;371(23):2167-2177. 3. ZYKADIA [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Corp.; 2019. 4. Soria JC, et al. *Lancet*. 2017;389(10072):917-929. 5. ALECENSA [prescribing information]. Cambridge, MA: Takeda Pharmaceutical Company Ltd.; 2018. 6. Camidge DR, et al. *J Clin Oncol*. 2018;36(26):2693-2701. 7. Mok T, et al. *Ann Oncol*. 2020;31(8):1056-1064.

ALK Inhibitor Key Clinical Data: 1L PFS (2 of 2)

	ALUNBRIG (brigatinib)[1]		LORBRENA/LORVIQUA (lorlatinib)[2]		Ensartinib[4]	
Key study	Phase 3: ALTA-1L		Phase 3: CROWN[3]		Phase 3 eXalt3 trial is ongoing[5]	
Dosing	**ALUNBRIG (N=137)** 180 mg QD after 7-day lead-in at 90 mg	**Crizotinib (N=138)** 250 mg BID	**LORBRENA/LORVIQUA (N=149)** 100 mg QD	**Crizotinib (N=147)** 250 mg BID	**ENSARTINIB (N=143)** 225 mg QD	**Crizotinib (N=147)** 250 mg BID
Efficacy Data						
Median PFS, months						
	24.0 (18.5, NR)	11.0 (9.2, 12.9)	NR (NR, NR)	9.3 (7.6, 11.1)	31.3 (20.2, NR)	12.7 (9.2, 16.6)
	HR 0.49 (95% CI, 0.35, 0.68); *P*<0.0001*		HR 0.28 (95% CI, 0.19, 0.41); *P*<0.001*		HR 0.50 (95% CI, 0.36, 0.71); *P*=0.0001*	

•NOTE: Ensartinib data are investigational; this agents is not approved in the 1L setting.

•*By independent review.

•CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

•1. Camidge R, et al. *J Clin Oncol*. 2020;38(31):3592-3603. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018-2029. 3. ClinicalTrials.gov. A study of lorlatinib versus crizotinib in first line treatment of patients with ALK-positive NSCLC (NCT03052608). Accessed February 4, 2021. 4. Wu Y, et al. Oral presentation at WCLC; January 2021. 5. ClinicalTrials.gov. eXalt3: Study comparing X-396 (ensartinib) to crizotinib in ALK positive non-small cell lung cancer (NSCLC) Patients (NCT02767804). Accessed February 4, 2021.

ALK Inhibitor Key Clinical Data: 1L DoR, ORR, and CNS (1 of 2)

	XALKORI (crizotinib)[1,2]		ZYKADIA (ceritinib)[3]		ALECENSA (alectinib)[4-6]	
Key study	Phase 3: PROFILE 1014		Phase 3: ASCEND-4		Phase 3: ALEX	
Dosing	**XALKORI (N=172)** 250 mg BID	**Chemotherapy* (N=171)**	**ZYKADIA (N=189)** 750 mg QD	**Chemotherapy† (N=187)**	**ALECENSA (N=152)** 600 mg BID	**Crizotinib (N=151)** 250 mg BID
Efficacy Data						
Median DoR, months	11.3	5.3	23.9	11.1	33.1	11.1
	NA		NA		NA	
ORR (%)	74	45	73	27	82.9	75.5
	P<0.001		NA		*P*=0.0936	
CNS Assessment‡	**N=39**	**N=40**	**N=28**	**N=27**	**N=152**	**N=151**
Intracranial PFS or TTP	Median TTP: 15.7 months	Median TTP: 12.5 months	NA	NA	12-month cumulative incidence CNS progression: 9.4%	12-month cumulative incidence CNS progression: 41.4%
	HR 0.45 (95% CI, 0.19, 1.07); *P*=0.063					
CNS ORR (%)	NA; 24-wk DCR: 56	NA; 24-wk DCR: 25	57	22	81	50
	P=0.006					
CRR (%)	NA	NA	7	7	38	5
Median DoR	NA	NA	16.6	NE	17.3	5.5

•*Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC of 5 or 6 mg/mL·min by intravenous infusion every 3 weeks for up to 6 cycles. †Pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC of 5-6 mg/mL·min administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m^2) every 21 days. ‡In patients with measurable CNS lesions at baseline except for patients in PROFILE 1014, in which outcomes were reported in patients with treated CNS metastases.

•CI, confidence interval; CNS, central nervous system; CRR, complete response rate; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; NA, not available; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; TTP, time to progression.

•1. XALKORI Sažetak Karakteristika Leka, Maj 2019 .; 2021. 2. Solomon BJ, et al. *J Clin Oncol*. 2016;34(24):2858-2865. 3. ZYKADIA Sažetak Karakteristika leka Maj 2019. 4. ALECENSA Sažetak Karakteristika Leka April 2018. 5. Peters S, et al. *N Engl J Med*. 2017;377(9):829-838. 6. Camidge DR, et al. *J Thorac Oncol*. 2019;14(7):1233-1243.

ALK Inhibitor Key Clinical Data: 1L DoR, ORR, and CNS (2 of 2)

	ALUNBRIG (brigatinib)[1]		LORBRENA/LORVIQUA (lorlatinib)[2,3]		Ensartinib[5]	
Key study	Phase 3: ALTA-1L		Phase 3: CROWN[4]		Phase 3 eXalt3 trial is ongoing[6]	
Dosing	**ALUNBRIG (N=137)** 180 mg QD after 7-day lead-in at 90 mg	**Crizotinib (N=138)** 250 mg BID	**LORBRENA/LORVIQUA (N=149)** 100 mg QD	**Crizotinib (N=147)** 250 mg BID	**ENSARTINIB (N=143)** 225 mg QD	**Crizotinib (N=147)** 250 mg BID
DoR, months	NR (95% CI, 19.4, NR)	13.8 (95% CI, 9.3, 20.8)	NE (95% CI, NE, NE)	11.0 (95% CI, 9.0, 12.9)	NR (95% CI, 22.05, NR)	27.3 (95% CI, 11.27, NR)
	NA		NA			
ORR (%)	74 (95% CI, 66, 81)	62 (95% CI, 53, 70)	76 (95% CI, 68-83)	58 (95% CI, 49-66)	75	67
	OR 1.73 (95% CI, 1.04, 2.88); *P*=0.0342		OR 2.25 (1.35-3.89)			
CNS Assessment*	**N=18**	**N=23**	N=17	N=13	**N=11**	**N=19**
Intracranial PFS or TTP	CNS PFS†: 24.0 (95% CI, 12.9, NR)	CNS PFS†: 5.6 (95% CI, 3.7, 7.5)	CNS TTP: NE (95% CI, NE, NE)	CNS TTP: 16.6 (95% CI, 11.1, NE)	NA	NA
CNS ORR (%)	78 (95% CI, 52, 94)	26 (95% CI, 10, 48)	82 (95% CI, 57, 96)	23 (95% CI, 5, 54)	64%	21%
CRR (%)	28	0	71	8	27%	11%
Median DoR, months	NR (95% CI, 5.7, NR)	9.2 (95% CI, 3.9, 9.2)	NE (95% CI, NE, NE)	10.2 (95% CI, 9.4, 11.1)	N/A	

- **NOTE: Ensartinib data are investigational; this agents is not approved in the 1L setting.**
- *In patients with measurable CNS lesions at baseline. †Any brain metastases (N=47 and N=49, respectively)
- CI, confidence interval; CNS, central nervous system; CRR, complete response rate; DoR, duration of response; HR, hazard ratio; NA, not available; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

- 1. Camidge R, et al. *J Clin Oncol*. 2020;38(31):3592-3603. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018-2029. 3. Solomon B et al. Oral presentation at ESMO Virtual Congress; September 19 – 21, 2020. LBA2. 4. ClinicalTrials.gov. A study of lorlatinib versus crizotinib in first line treatment of patients with ALK-positive NSCLC (NCT03052608). Accessed February 4, 2021. 5. Horn L, et al. Oral presentation at WCLC Virtual Presidential Symposium; August 8, 2020. 6. ClinicalTrials.gov. eXalt3: Study comparing X-396 (ensartinib) to crizotinib in ALK positive non-small cell lung cancer (NSCLC) Patients (NCT02767804). Accessed February 4, 2021.

ALK Inhibitor Key Clinical Data: 1L Safety

	XALKORI (crizotinib)[1]		ZYKADIA (ceritinib)[2]		ALECENSA (alectinib)[3]		ALUNBRIG (brigatinib)[4,5]		LORBRENA/LORVIQUA (lorlatinib)[6]		Ensartinib[7]	
Key study	Phase 3: PROFILE 1014 N=171 (XALKORI)		Phase 3: ASCEND-4 N=189 (ZYKADIA)		Phase 3: ALEX N=152 (ALECENSA)		Phase 3: ALTA-1L N=136 (ALUNBRIG)		Phase 3: CROWN N=149 (LORBRENA)		Phase 3: eXalt3 N=143	
Safety Data in Study Drug												
Dose modifications (%)	6		66		46.7		38		49% (interruption) 21% (reduction)		24 (reduction)	
Discontinuations due to ARs (%)	8		12		14.5		13		7		9	
SARs (%)	34		38		38.8		33		34		23	
Most common Grade 3-4 ARs (%)	**Grade 3-4* (%)**		**Grade 3-4† (%)**		**Grade 3-4 (%)**		**Grade 3-5†† (%)**		**Grade 3-4 (%)**		**Grade 3-5 (%)**	
	Diarrhea	2	Fatigue	7	Anemia	5.9	Increased blood creatinine kinase	24	Hypercholesterolemia	16	Rash	~12
	Vomiting	2	Vomiting	5	AST increase	5.3	Increased lipase	14	Hypertriglyceridemia	20	ALT increase	~4
	Constipation	2	Diarrhea	4.8	Pneumonia	4.6	Hypertension	12	Edema	4	Edema	~2
	Esophagitis	2	Abdominal pain	3.7	Urinary tract infection	3.9	Increased amylase	6	Increased weight	17	Nausea	~2
	ECG QT prolonged	2	Weight loss	3.7	Acute kidney injury	2.6						
					Rash	2.0			Hypertension	10		

•**NOTE: Ensartinib data are investigational; this agents is not approved in the 1L setting.**

•*Grade 3-4 laboratory abnormalities: Increased ALT (15%), neutropenia (11%), hypophosphatemia (10%), increased AST (8%), and lymphopenia (7%). †Grade 3-4 laboratory abnormalities (≥10%): Increased GGT (49%), increased ALT (34%), increased AST (21%), increased alkaline phosphatase (12%), hyperglycemia (10%). **Reported as grade 3-5 adverse events. ††Hematologic and non-hematologic events reported together.

• ARs, adverse reactions; ECG, electrocardiogram; RP2D, recommended phase 2 dose; SARs, serious adverse reactions.

•1. XALKORI Sažetak Karakteristika Leka, Maj 2019 . 2. ZYKADIA ZYKADIA Sažetak Karakteristika leka Maj 2019. 3. Mok T, et al. *Ann Oncol*. 2020;31(8):1056-1064.
4. ALUNBRIG Sažetak Karakteristika leka, Februar 202o.; 2020. 5. Camidge R, et al. *J Clin Oncol*. 2020;38(31):3592-3603. 6. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018-2029. 7. Horn L, et al. Oral presentation at WCLC Virtual Presidential Symposium; August 8, 2020.

PFS Outcomes for ALEX, ALTA-1L, eXALT3 and CROWN Trials at varying levels of data maturity

ALEX: Alectinib vs Crizotinib

Enrollment: Aug 2014 – Jan 2016

Median duration of follow-up in experimental arm:

18.6 mo

1st interim analysis	Alectinib (n=152)	Crizotinib (n=151)
PFS (INV), months	**NR**	**11.1**
HR (95% CI)	**0.47 (0.34-0.65)**	
PFS (IRC), months	25.7	10.4
HR (95% CI)	0.50 (0.36-0.70)	

27.8 mo

2nd interim analysis	Alectinib (n=152)	Crizotinib (n=151)
PFS (INV), months	**34.8**	**10.9**
HR (95% CI)	**0.43 (0.32-0.58)**	
PFS (IRC), months	--	--
HR (95% CI)	--	

37.8 mo

Final Analysis	Alectinib (n=152)	Crizotinib (n=151)
PFS (INV), months	**34.8**	**10.9**
HR (95% CI)	**0.43 (0.32-0.58)**	
PFS (IRC), months	--	--
HR (95% CI)	--	

NEJM 2017 Peters *et al*
JTO 2019 Camidge *et*
Ann Onco 2020 Mok *et al*

ALTA-1L: Brigatinib vs Crizotinib

Enrollment: Apr 2016 – Aug 2017

Median duration of follow-up in experimental arm:

11.0 mo

1st interim analysis	Brigatinib (n=137)	Crizotinib (n=138)
PFS (INV), months	NR	9.2
HR (95% CI)	0.45 (0.30-0.68)	
PFS (IRC), months	**NR**	**9.8**
HR (95% CI)	**0.49 (0.33-0.74)**	

24.9 mo

2nd interim analysis	Brigatinib (n=137)	Crizotinib (n=138)
PFS (INV), months	29.4	9.2
HR (95% CI)	0.43 (0.31-0.61)	
PFS (IRC), months	**24.0**	**11.0**
HR (95% CI)	**0.49 (0.35-0.68)**	

NEJM 2018 Camidge *et al*
JCO 2020 Camidge *et al*

eXALT3: Ensartinib vs Crizotinib

Enrollment: ? – Nov 2018

Median duration of follow-up in experimental arm:

23.8 mo

1st interim analysis	Ensartinib (n=143)	Crizotinib (n=147)
PFS (INV), months	-	-
HR (95% CI)	-	
PFS (IRC), months	**25.8**	**12.7**
HR (95% CI)	**0.51 (0.35-0.72)**	

27.6 mo

2nd interim analysis	Ensartinib (n=143)	Crizotinib (n=147)
PFS (INV), months	33.2	12.9
HR (95% CI)	0.45 (0.32-0.64)	
PFS (IRC), months	**31.3**	**12.7**
HR (95% CI)	**0.50 (0.36-0.71)**	

World Lung 2020 Horn *et al*
World Lung 2020b Wu *et al*

CROWN: Lorlatinib vs Crizotinib

Enrollment: Apr 2017 – Feb 2019

Median duration of follow-up in experimental arm:

18.3 mo

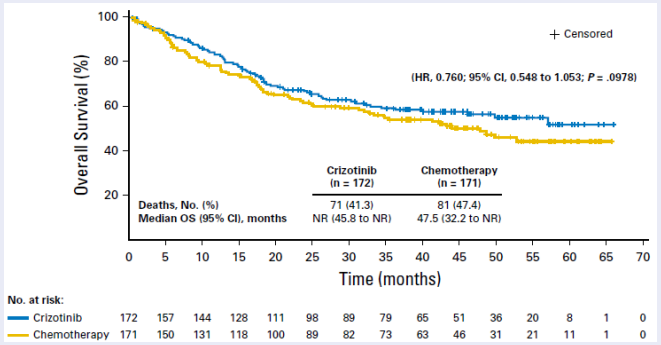
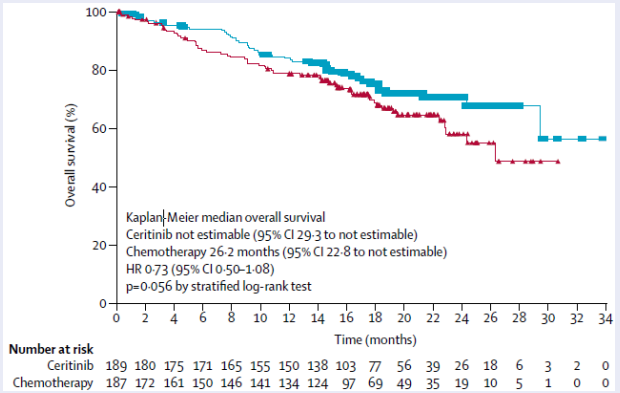
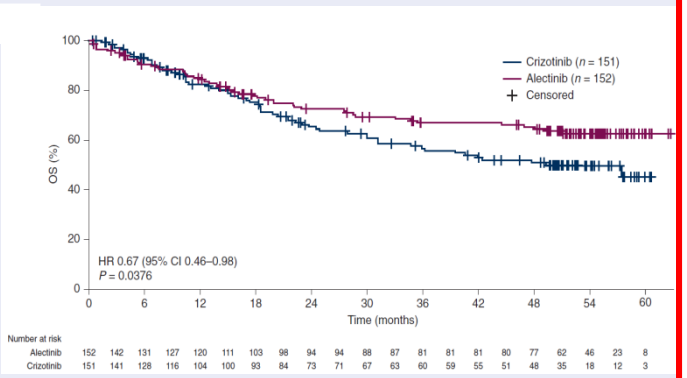
Interim analysis	Lorlatinib (n=147)	Crizotinib (n=149)
PFS (INV), months	NE	9.1
HR (95% CI)	0.21 (0.14, 0.31)	
PFS (IRC), months	**NE**	**9.3**
HR (95% CI)	**0.28 (0.19, 0.41)**	

NEJM 2020 Shaw *et al*

Primary end points in bold

Cross trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results

ALK Inhibitor Key Clinical Data: 1L OS (1 of 2)

	XALKORI (crizotinib)[1,2]		ZYKADIA (ceritinib)[3]		ALECENSA (alectinib)[4,5]	
Key study	Phase 3: PROFILE 1014		Phase 3: ASCEND-4		Phase 3: ALEX	
Dosing	**XALKORI (N=172)** 250 mg BID	**Chemotherapy* (N=171)**	**ZYKADIA (N=189)** 750 mg QD	**Chemotherapy† (N=187)**	**ALECENSA (N=152)** 600 mg BID	**Crizotinib (N=151)** 250 mg BID
Efficacy Data						
						
Median OS, months	NR	47.5	NE	26.2	NA‡	57.4
	HR 0.76 (95% CI, 0.548, 1.053); *P*=0.098		HR 0.73 (95% CI, 0.50, 1.08); *P*=0.056		HR 0.67 (95% CI, 0.46, 0.98); *P*=0.0376	

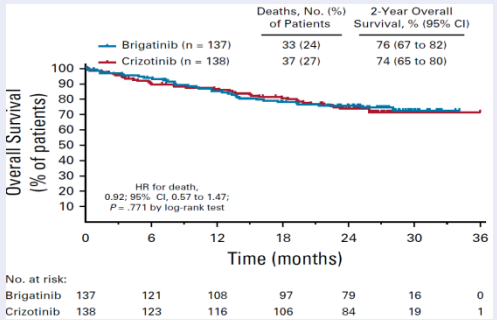
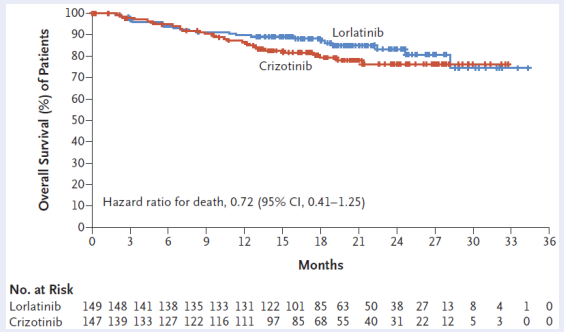
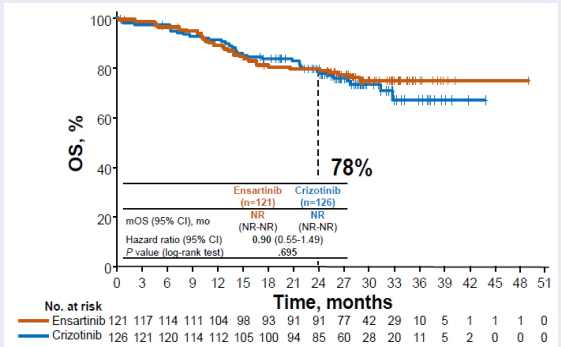
•*Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC of 5 or 6 mg/mL·min by intravenous infusion every 3 weeks for up to 6 cycles. †Pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC of 5-6 mg/mL·min administered on day 1 of each 21-day cycle for a maximum of 4 cycles followed by pemetrexed (500 mg/m^2) every 21 days. ‡OS data not yet mature as of most recent publication.

•CI, confidence interval; HR, hazard ratio; NA, not available; NE, not estimable; NR, not reached; OS, overall survival.

•1. XALKORI Sažetak Karakteristika Leka, Maj 2019 . 2. Solomon BJ, et al. *J Clin Oncol*. 2018;36(22):2251-2258. 3. Soria JC, et al. *Lancet*. 2017;389(10072):917-929. 4. Camidge RD, et al. *J Clin Oncol*. 2018;36(26):2693-2701. 5. Mok T, et al. *Ann Oncol*. 2020;31(8):1056-1064.

Cross trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results

ALK Inhibitor Key Clinical Data: 1L OS (2 of 2)

	ALUNBRIG (brigatinib)[1,*]		LORBRENA/LORVIQUA (lorlatinib)[2,*]		Ensartinib[4]	
Key study	Phase 3: ALTA-1L		Phase 3: CROWN[3]		Phase 3 eXalt3 trial is ongoing[5]	
Dosing	**ALUNBRIG (N=137)** 180 mg QD after 7-day lead-in at 90 mg	**Crizotinib (N=138)** 250 mg BID	**LORBRENA/LORVIQUA (N=149)** 100 mg QD	**Crizotinib (N=147)** 250 mg BID	**ENSARTINIB (N=143)** 225 mg QD	**Crizotinib (N=147)** 250 mg BID
Efficacy Data						
Median OS, months						
	2-yr OS: 76% (67, 82)	74% (65, 80)	NR	NR	NR (NR, NR)	NR (NR, NR)
	HR 0.92 (0.57-1.47, *P*=0.771)		HR 0.72 (95% CI, 0.41, 1.25)		HR 0.90 (0.55, 1.49); *P*=0.695	

Cross trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results

•NOTE: Ensartinib data are investigational; this agent is not approved in the 1L setting.

•*OS data are not yet mature.

•CI, confidence interval; DoR, duration of response; HR, hazard ratio; NR, not reached; OS, overall survival; TKI, tyrosine kinase inhibitor.

•1. Camidge R, et al. *J Clin Oncol*. 2020;38(31):3592-3603. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(21):2018-2029. 3. ClinicalTrials.gov. A study of lorlatinib versus crizotinib in first line treatment of patients with ALK-positive NSCLC (NCT03052608). Accessed February 4, 2021. 4. Wu Y, et al. Oral presentation at WCLC; January 2021. 5. ClinicalTrials.gov. eXalt3: Study comparing X-396 (ensartinib) to crizotinib in ALK positive non-small cell lung cancer (NSCLC) Patients (NCT02767804). Accessed February 4, 2021.

Intracranial efficacy outcomes in first-line Phase 3 clinical trials in ALK+ NSCLC

- **Intracranial response rates**

	ALEX*[1]		ALTA-1L†[2]		Exalt3‡[3]		CROWN§[4]	
Patients with any brain metastases at baseline	Alectinib (n=64)	Crizotinib (n=58)	Brigatinib **(n=47)**	Crizotinib **(n=49)**	Ensartinib	Crizotinib	Lorlatinib (n=38)	Crizotinib (n=40)
IC-ORR (BIRC), % (95% CI)	59 (46–71)	26 (15–39)	66 (51–79)	16 (7–30)	Not reported	Not reported	66 (49–80)	20 (9–36)
IC-CR (BIRC), %	45	9	45	4	Not reported	Not reported	61	15
IC-mDoR (BIRC), months (95% CI)	NE (17.3–NE)	3.7 (3.2–6.8)	24.0 (16.9–NR)	9.2 (3.9–NR)	Not reported	Not reported	NE (NE–NE)	9.4 (6.0–11.1)
Patients with measurable brain metastases at baseline	Alectinib (n=21)	Crizotinib (n=22)	Brigatinib (n=18)	Crizotinib (n=23)	Ensartinib (n=11)	Crizotinib (n=19)	Lorlatinib (n=17)	Crizotinib (n=13)
IC-ORR (BIRC), % (95% CI)	81 (58–95)	50 (28–72)	78 (52–94)	26 (10–48)	64	21	82 (57–96)	23 (5–54)
IC-CR (BIRC), %	38	5	28	0	Not reported	Not reported	71	8
IC-mDoR (BIRC), months (95% CI)	17.3 (14.8–NE)	5.5 (2.1–17.3)	NR (5.7–NR)	9.2 (3.9–9.2)	Not reported	Not reported	NE (NE–NE)	10.2 (9.4–11.1)

Cross trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results

*Based on a data cut-off of 09 February 2017 (first interim analysis); †Based on a data cut-off of 28 June 2019 (second interim analysis); ‡Based on a data cut-off of 01 July 2020; §Based on a data cut-off of 20 March 2020. BIRC, blinded independent central review; CI, confidence interval; IC-CR, intracranial complete response; IC-mDoR, intracranial median duration of response; IC-ORR, intracranial objective response rate; NE, not estimable; NR, not reached. 1. Peters S, et al. *N Engl J Med* 2017;377:829–38; 2. Camidge DR, et al. *J Clin Oncol* 2020;38:3592–603; 3. Horn L, et al. Presented at WCLC 2020 Presidential Symposium 2020, 08 August 2020; 4. Shaw A, et al. *N Engl J Med* 2020;383:2018–29.

Intracranial efficacy outcomes in first-line Phase 3 clinical trials in ALK+ NSCLC

- **CNS and non-CNS progression competing risks analysis**

	ALEX*[1]		ALTA-1L†[2,3]		Exalt3[4]		CROWN‡[5]	
Time to first event of CNS progression	Alectinib (n=152)	Crizotinib (n=151)	Brigatinib (n=137)	Crizotinib (n=138)	Ensartinib (n=143)	Crizotinib (n=146)	Lorlatinib (n=149)	Crizotinib (n=147)
12-month rate, % (95% CI)	9.4 (5.4–14.7)	41.4 (33.2–49.4)	7.8 (4.0–13.3)	22.4 (15.6–29.9)	Not reported	Not reported	2.8 (1.0–8.1)	33.2 (24.6–44.7)
HR (95% CI)	0.16 (0.10–0.28)		0.30 (0.17–0.53)		Not reported		0.06 (0.02–0.18)	
Time to first event of non-CNS progression								
12-month rate, % (95% CI)	Not reported	Not reported	19.5 (13.1–26.8)	31.3 (23.4–39.5)	Not reported	Not reported	15.4 (10.5–22.6)	44.3 (36.1–54.4)
HR (95% CI)	0.81 (0.49–1.31)		0.54 (0.36–0.82)		Not reported		0.30 (0.19–0.47)	

Cross trial comparisons have significant limitations. This information is presented in order to generate discussion, not to make comparisons between study results

*Based on a data cut-off of 09 February 2017 (first interim analysis); †Based on a data cut-off of 28 June 2019 (second interim analysis); ‡Based on a data cut-off of 20 March 2020.
CI, confidence interval; CNS, central nervous system; HR, hazard ratio.

1. Peters S, et al. *N Engl J Med* 2017;377:829–38; 2. Camidge DR, et al. *J Clin Oncol* 2020;38:3592–603; 3. EMA Assessment Report: Alunbrig® (brigatinib). www.ema.europa.eu/en/documents/variation-report/alunbrig-h-c-4248-ii-0003-epar-assessment-report-variation_en.pdf (Accessed 03 November 2020); 4. Horn L, et al. Presented at WCLC 2020 Presidential Symposium 2020, 08 August 2020; 5. Shaw A, et al. *N Engl J Med* 2020;383:2018–29 and supplementary appendix.

Differing tolerability profiles have established a need to optimise and understand therapy management of first-line ALK TKIs

- With increasing ALK TKIs available, each with their own individual tolerability profiles, there is a need to optimise and understand therapy management to ensure time on treatment is maximised for patients[1]

	ALEX*[2] Alectinib (n=152)	ALTA-1L†[3] Brigatinib (n=136)	Exalt3‡§[4] Ensartinib (n=143)	**CROWN¶[5] Lorlatinib (n=149)**
Most common all Grade AEs in each treatment arm (%)	Constipation (36)	Diarrhoea (52)	Rash	Hypercholesterolaemia\\ (70)
	Anaemia (22)	Increased blood CPK (46)	ALT increased	Hypertriglyceridaemia\\ (64)
	Fatigue (20)	Cough (35)	**AST increased**	**Oedema\\ (55)**
	Blood bilirubin increased (19)	Hypertension (32)	**Constipation**	**Weight increased (38)**
	Peripheral oedema (18)	Nausea (30)	Cough	Peripheral neuropathy\\ (34)
	ALT increased (17)	**AST level increased (26)**	Pruritus	Cognitive effects\\ (21)
	Myalgia (16)	Increased lipase (23)	**Nausea**	**Diarrhoea (21)**
	AST increased (16)	**ALT level increased (21)**	**Oedema**	**Dyspnoea (20)**
	Nausea (16)	Back pain (21)	**Anaemia**	**Anaemia (19)**
	Diarrhoea (13)	Headache (21)	**ALP increased**	**Fatigue\\ (19)**
	Rash (13)	Vomiting (21)	Pyrexia	Arthralgia (19)

• In patients treated with lorlatinib, the incidence of hypertension and hyperglycemia was 18% and 9%, respectively. While not within the most common all Grade AEs, a new Warning & Precaution has been added to the lorlatinib USPI as covered previously.

Please note, data are from unrelated studies, with different study designs and inclusion criteria. Therefore, cross trial comparisons should not be made.

•AE, adverse event; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate amino transferase; CPK, creatine phosphokinase.
*Based on a data cut-off of 1 December 2017; †Based on a data cut-off of 28 June 2019 (second interim analysis); ‡Exact data were not reported; §Based on a data cut-off of 01 July 2020; ¶Based on a data cut-off of

• 20 March 2020; \\cluster term.
1. Blackhall F, et al. Presented at ESMO Lung Preceptorship 2020, 19–21 October 2020; 2.Camidge DR, et al. J Thorac Oncol 2019;14(7):1233–43. Supplementary appendix; 3. EMA Assessment Report: Alunbrig® (brigatinib). www.ema.europa.eu/en/documents/variation-report/alunbrig-h-c-4248-ii-0003-epar-assessment-report-variation_en.pdf (Accessed 03 November 2020); 4. Horn L, et al. Presented at WCLC 2020 Presidential Symposium 2020, 08 August 2020; 5. Shaw A, et al. N Engl J Med 2020;383:2018–29 supplementary appendix.

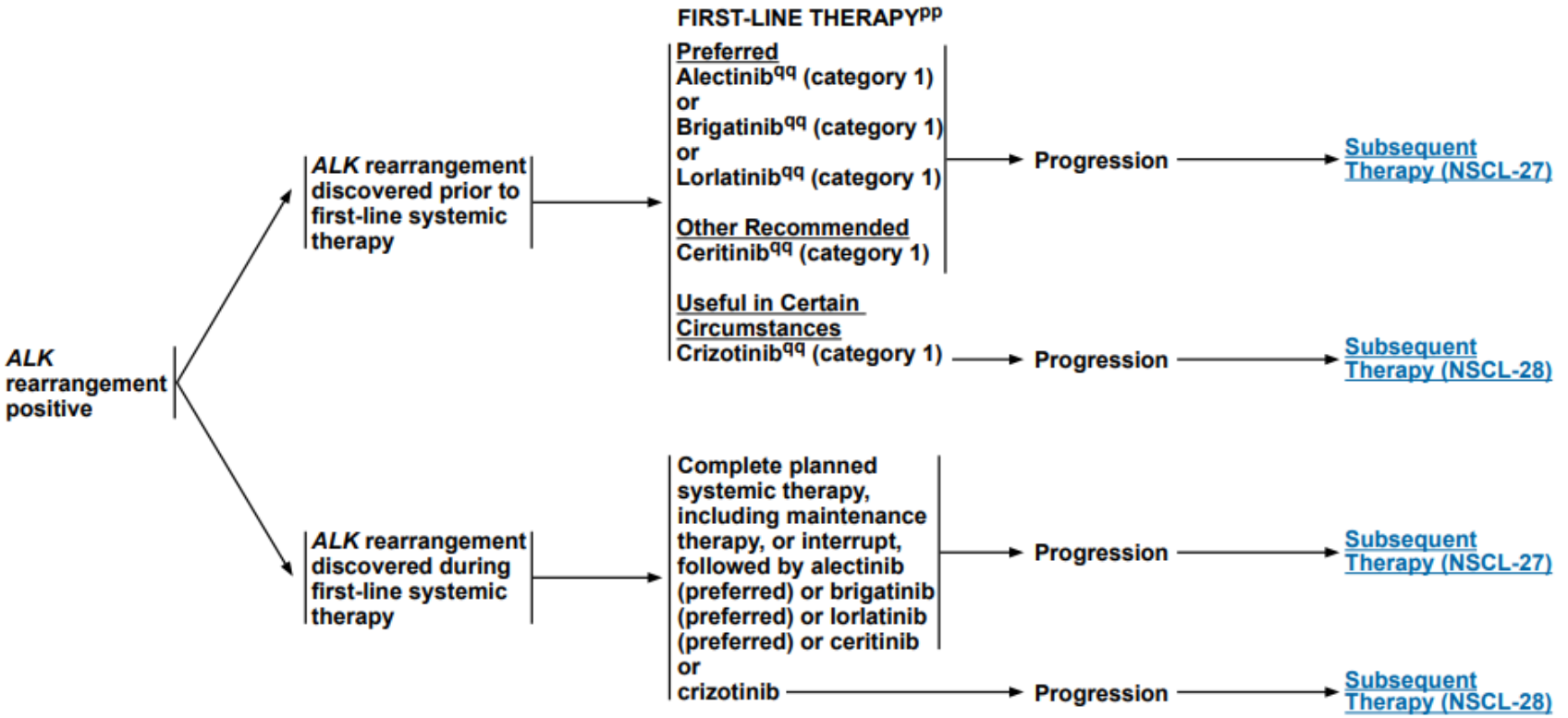
NCCN Guidelines Recommendations for the 1L Treatment of ALK Rearrangement–Positive NSCLC

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

***ALK* REARRANGEMENT POSITIVE**[mm]



[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).
[pp] Targeted Therapy or Immunotherapy for Advanced or Metastatic Disease (NSCL-J).
[qq] For performance status 0–4.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

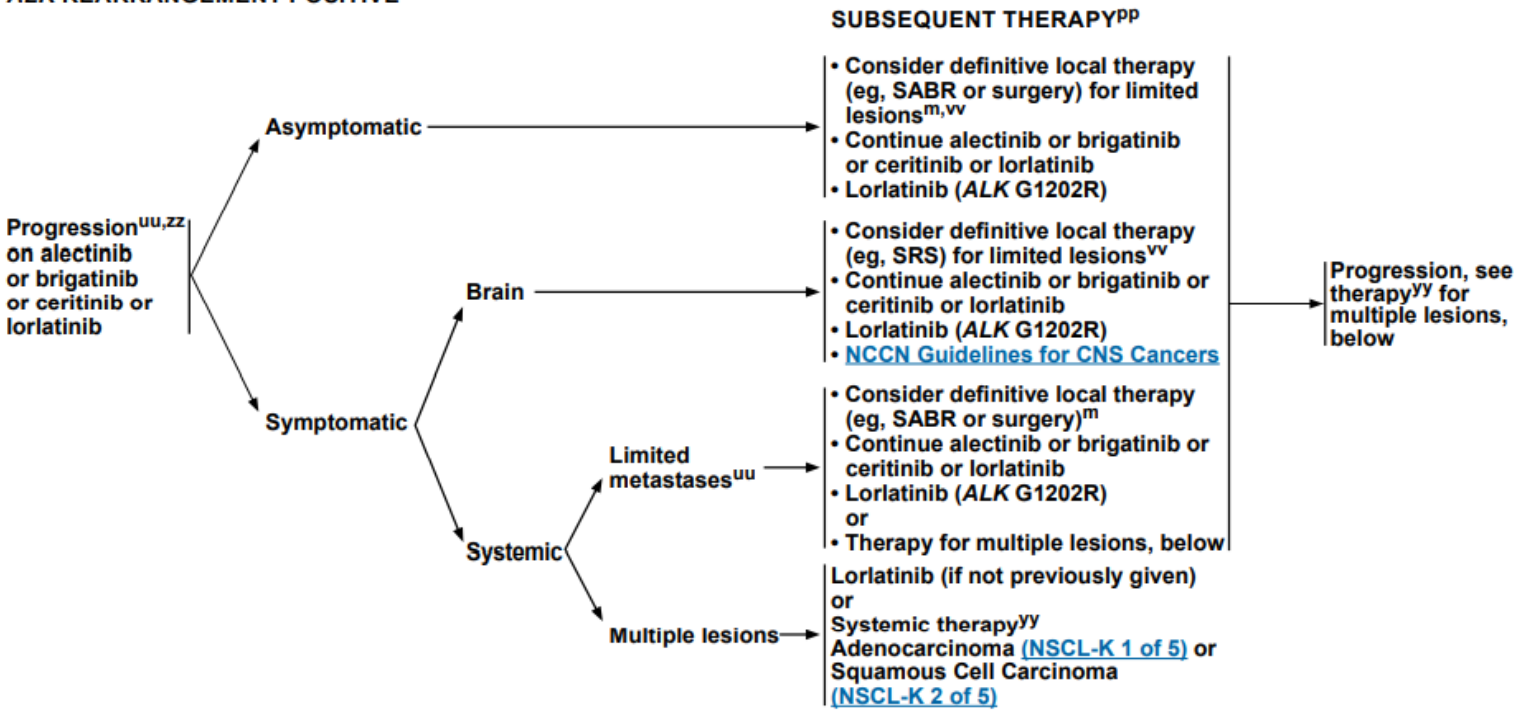
NCCN Guidelines Recommendations for the Treatment of ALK Rearrangement–Positive NSCLC: Progression on Crizotinib

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

***ALK* REARRANGEMENT POSITIVE[mm]**



[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.
[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

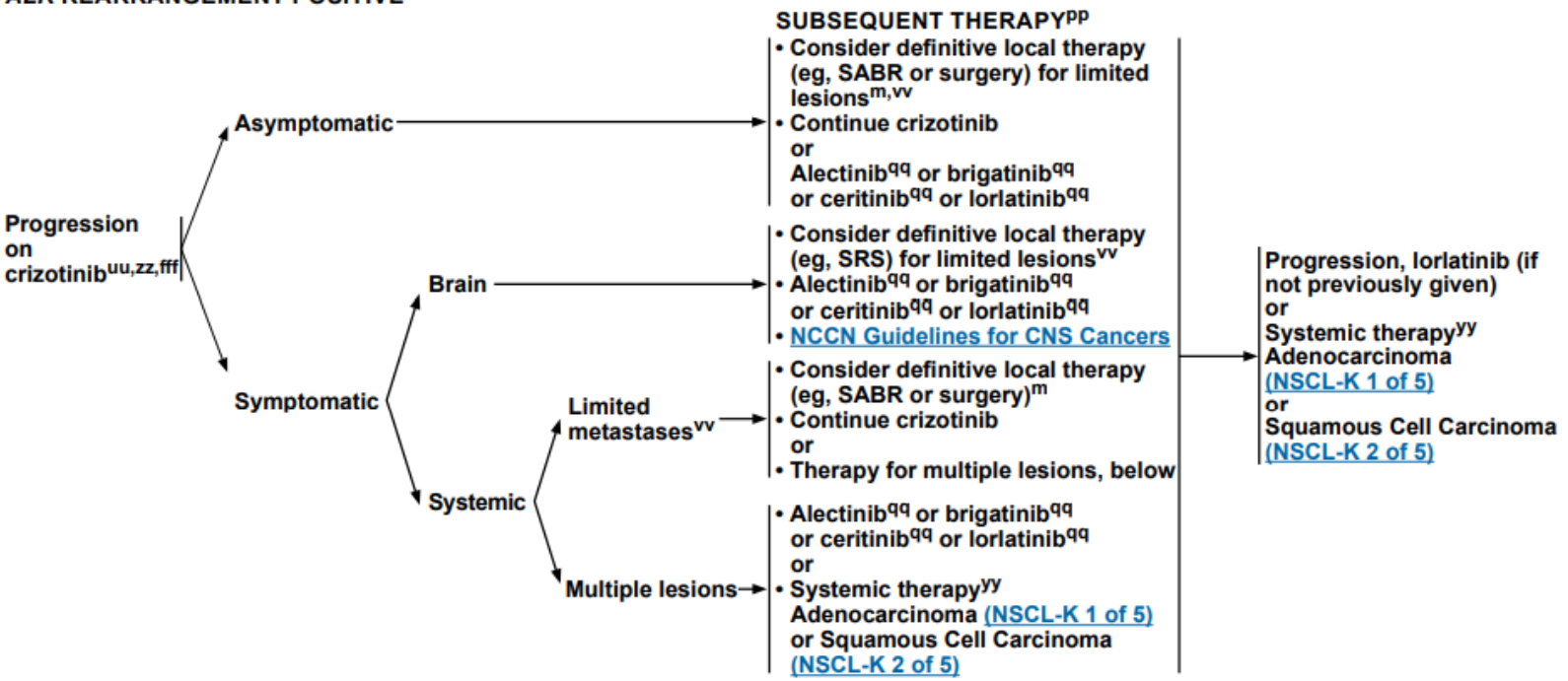
NCCN Guidelines Recommendations for ALK Rearrangement–Positive NSCLC: Progression on Alectinib, Brigatinib, Ceritinib, or Lorlatinib

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

***ALK* REARRANGEMENT POSITIVE[mm]**



[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).

[qq] For performance status 0–4.

[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.

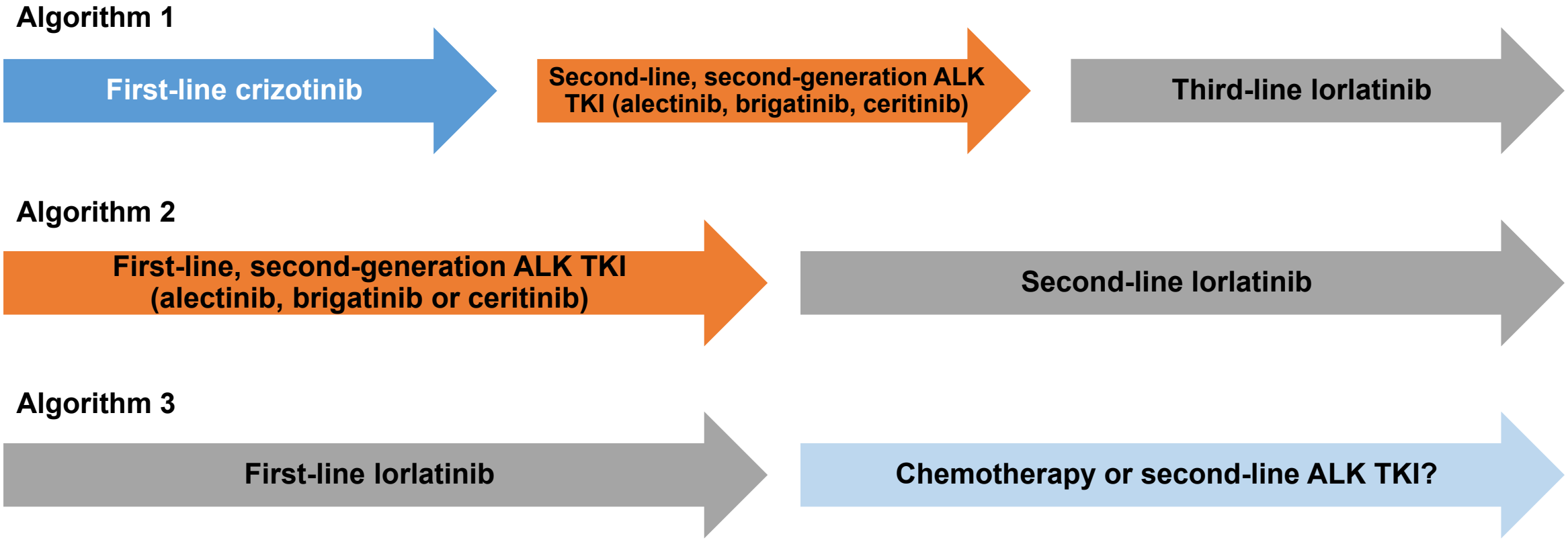
[yy] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR exon 19 deletion or L858R*, *ALK*+ NSCLC.

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

[fff] Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, brigatinib, or lorlatinib.

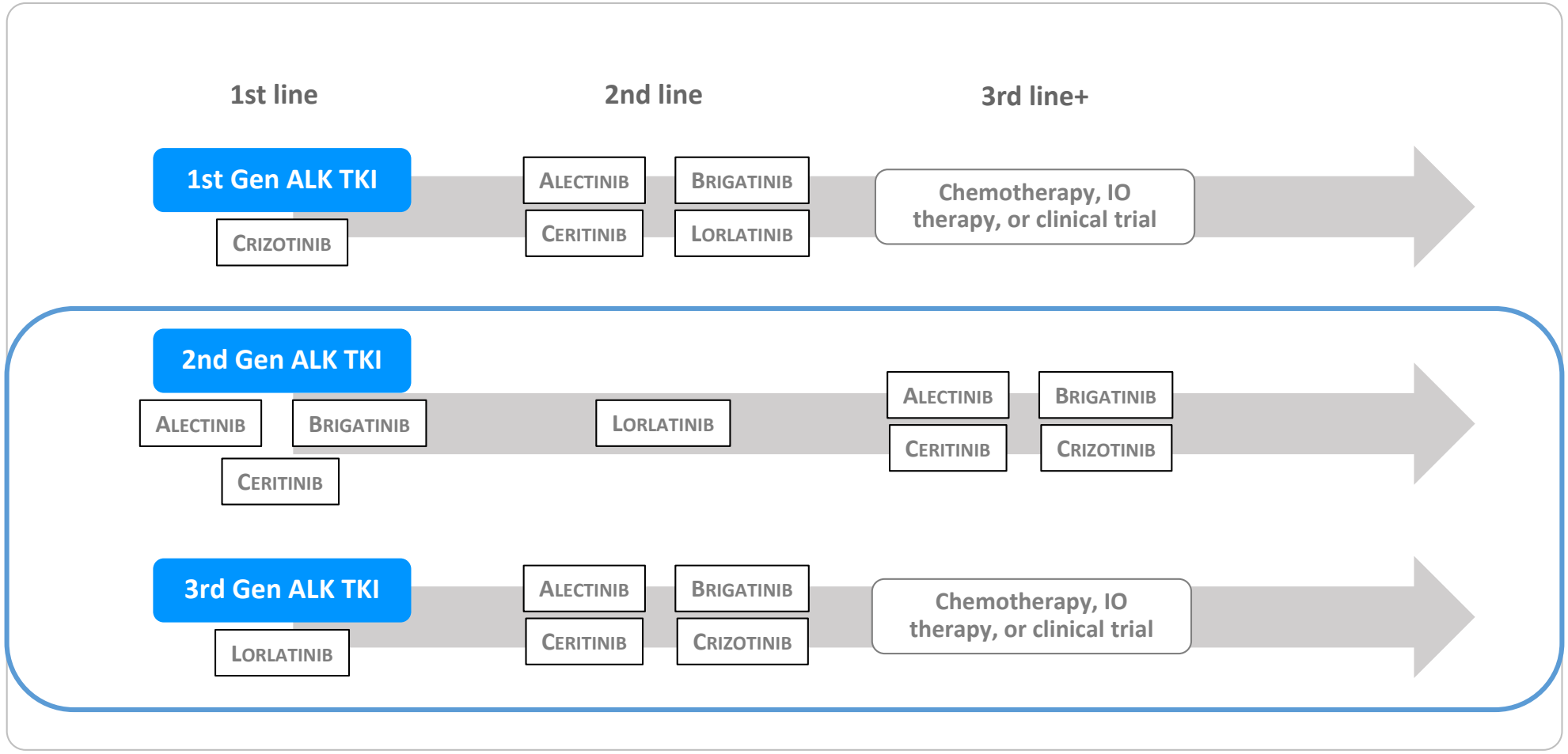
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Treatment sequence algorithms in ALK+ NSCLC*



- *Please note that these sequence algorithms are for illustrative purposes.

Potential Sequencing* in ALK+ Metastatic NSCLC



*Please note that these sequence algorithms are for illustrative purposes.

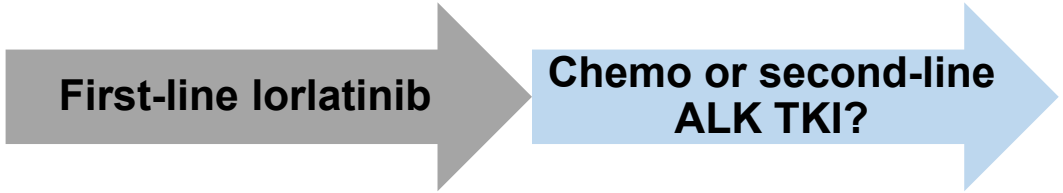
Modified from: Gristina V, et al. *Pharmaceuticals* (Basel). 2020;13(12):474–96.

Treatment sequencing considerations for lorlatinib

- **Positioning of lorlatinib in treatment algorithms is debated amongst physicians**

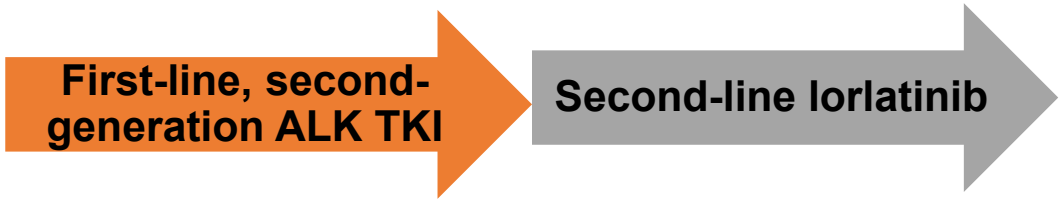
1. Use 'the best drug upfront' approach

- In patients with brain metastases at diagnosis, there is an argument that the ALK TKI with the best intracranial efficacy and greatest delay in time to CNS progression should be the first-line treatment of choice
- Given the marked intracranial activity of lorlatinib in the CROWN trial, positioning of lorlatinib in the **first line** may be particularly effective in treating and preventing the formation of brain metastases[1]
- Furthermore, lorlatinib's broad ALK resistance profile may delay the emergence of first-line resistance
  - However, there is a lack of knowledge and data surrounding post-first-line lorlatinib resistance and subsequent therapy options



2. 'Reserving lorlatinib for later lines' approach

- On the other hand, some physicians may prefer to reserve lorlatinib for **later lines**, once patients have progressed on second-generation ALK inhibitors, particularly for those who develop CNS metastases during the course of their disease
  - Given its current indication, many physicians have experience and are comfortable with prescribing lorlatinib in this setting



•CNS, central nervous system.

1. Shaw A, et al. *N Engl J Med* 2020;383:2018–29.

Najnoviji rezultati CROWN studije i značaj primene leka lorlatinib u lečenju pacijenata u prvoj liniji lečenja ALK

Prof. dr Bojan Zarić

Institut za Plućne Bolesti Vojvodine

Medicinski Fakultet, Univerzitet Novi Sad

Indikacija za lek lorlatinib

Indication

Lek Lorviqua® kao monoterapija indikovan je za lečenje odraslih pacijenata sa ALK (anaplastična limfomska kinaza) pozitivnim, uznapredovalim nemikrocelularnim kancerom pluća (engl. non-small cell lung cancer – NSCLC) koji ranije nisu lečeni inhibitorom ALK-a.

Lek Lorviqua kao monoterapija je indikovan za lečenje odraslih pacijenata sa ALK (anaplastična limfomska kinaza) pozitivnim, uznapredovalim NSCLC-om čija je bolest napredovala nakon primene:

- Alektiniba ili ceritiniba kao prve terapije inhibitorom ALK tirozin kinaze (engl. *tyrosine kinase inhibitor* – TKI) ili
- Krizotiniba i najmanje još jednog inhibitora ALK tirozin kinaze.

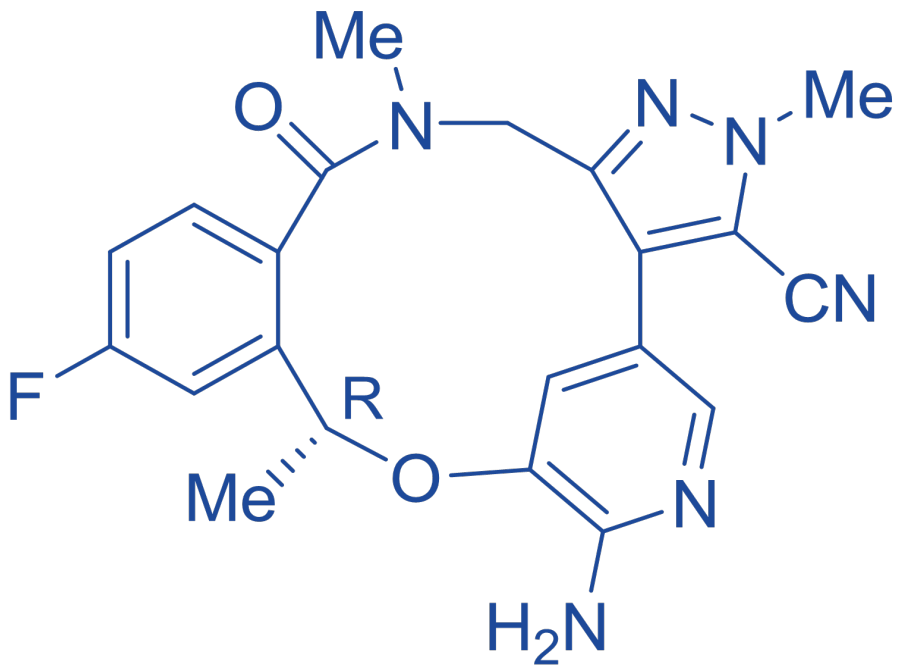
ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

LORVIQUA® Sažetak karakteristika leka; Pfizer, Maj 2022.

Lorlatinib, Inhibitor Kinaze: Mehanizam Dejstva

Indication

- Lorlatinib is a selective, adenosine triphosphate (ATP)-competitive inhibitor of ALK and c-ros oncogene 1 (ROS1) tyrosine kinases
- In non-clinical studies, lorlatinib inhibited catalytic activities of non-mutated ALK and clinically relevant ALK mutant kinases in recombinant enzyme and cell-based assays
- Lorlatinib demonstrated marked antitumour activity in mice bearing tumour xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T
- Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to alectinib, brigatinib, ceritinib, and crizotinib
- Lorlatinib was also capable of penetrating the blood-brain barrier
- Lorlatinib demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALKL1196M brain tumour implants



The correlation between lorlatinib in vitro data and clinical efficacy has not been established

ALK, anaplastic lymphoma kinase.

LORVIQUA® Sažetak karakteristika leka; Pfizer, Maj 2022;. LORBRENA [US Prescribing Information]. New York, NY: Pfizer Inc; 2021.

CROWN: Lorlatinib vs. Crizotinib in the First-Line Treatment of Patients with Advanced ALK+ NSCLC

CROWN: Introduction

Clinical Data

- ALK rearrangements occur in a subset of NSCLCs resulting in sensitivity to small-molecule ALK TKIs[1,2]
- Resistance to ALK TKIs commonly develops and often includes CNS progression[3–5]
- Lorlatinib is a highly potent, brain-penetrant, third-generation ALK TKI[6,7] with overall and intracranial activity in advanced ALK-positive NSCLC[3,7–9]
- The CROWN study is a randomized Phase 3 study comparing lorlatinib vs. crizotinib as first-line treatment in ALK-positive NSCLC[10,11]
  - 296 patients (104 study sites; 23 countries) were randomized from May 2017 to February 2019
  - Imaging assessments included chest, abdomen, and pelvis CT or MRI scans and brain MRI every 8 weeks
- Results presented here are from a planned interim analysis (data cutoff March 20, 2020), and from the unplanned, updated analysis of long-term data[10,11]
  - The primary endpoint of PFS was met in the CROWN trial primary analysis (median follow-up for PFS: 18.3 months for patients receiving lorlatinib and 14.8 months for patients receiving crizotinib); median PFS was not estimable for the lorlatinib arm and was 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (hazard ratio [HR], 0.28; 95% CI, 0.19-0.41;P<.001)[10]
  - Confirmed objective response was higher with lorlatinib (76%) than with crizotinib (58%) In patients with measurable baseline brain metastases, the frequency of confirmed IC response was greater with lorlatinib (82%) than crizotinib (23%)[10]
  - The unplanned analysis was performed at median follow-up of 36.7 months for patients on lorlatinib (29.3 months for patients on crizotinib)[11]
    - **Limitations: no formal hypothesis testing was performed given the PFS endpoint was previously met in the CROWN trial primary analysis; results are presented descriptively since the Type I error was spent at the primary analysis**

BICR, blinded independent central review; CNS, central nervous system; IC, intracranial response; NSCLC, non-small cell lung cancer; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Soda M, et al. *Nature*. 2007;448:561–6; 2. Kwak EL, et al. *N Engl J Med.* 2010;363:1693–703; 3. Dagogo-Jack I, et al. *J Clin Oncol*. 2020;38:9595; 4. Gainor JF, et al. *Cancer Discov*. 2016;6:1118–33; 5. Ali A, et al. *Curr Oncol*. 2013;20:e300–6; 6. Johnson TW, et al. *J Med Chem*. 2014;57:4720–44; 7. Shaw AT, et al. *Lancet Oncol*. 2017;18:1590–9; 8. Solomon BJ, et al. *Lancet Oncol*. 2018;19:1654–67; 9. Bauer TM, et al. *Target Oncol*. 2020;15:55–65; 10. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; 11. Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Study Design[1,2]

Key Eligibility Criteria

- Stage IIIB/IV ALK-positive NSCLC as identified by the VENTANA ALK (D5F3) CDx
- No prior systemic treatment for metastatic disease
- ECOG PS 0–2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST v1.1) with no prior radiation required
- Patients with severe acute or chronic psychiatric conditions were excluded*

N=296

1:1 RANDOMIZED

Lorlatinib 100 mg QD (n=149)

Crizotinib 250 mg BID (n=147)

Stratification factors

- Presence of brain metastases (yes vs. no)
- Ethnicity (Asian vs. non-Asian)

Treatment continued until disease progression or unacceptable toxicity

Primary Endpoint

- PFS† by BICR

Secondary Endpoints

- PFS (investigator assessed), ORR by BICR and investigator, ic-ORR, DOR and ic-DOR by BICR, ic-TTP by BICR, OS
- Safety: adverse reactions & lab abnormalities
- QoL

No crossover between treatment arms was permitted

Sample Size Determination and Interim Analysis

- The primary objective of this study was to demonstrate that lorlatinib is superior to crizotinib in prolonging PFS by BICR assessment per RECIST v1.1
- 177 PFS events (disease progression by BICR or death) were required for at least 90% power to detect a HR of 0.611 (assuming median PFS from 11 months with crizotinib and 18 months with lorlatinib)
- With a one-sided stratified log-rank test at a significance level of 0.025 (one-sided) and a 2-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries
- PFS interim analysis planned after 133 (≈75%) PFS events by BICR
  - Analysis run with 127 (72%) PFS events by BICR and a one-sided P value of 0.0081 used as significance threshold

*Including recent (within the past year) or active suicidal ideation or behavior

†Defined as the time from randomization to RECIST-defined progression or death due to any cause.

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Groups Performance Status; ic-DOR, intracranial duration of response; ic-ORR, intracranial objective response rate; ic-TTP, intracranial time to tumor progression; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

ClinicalTrials.gov number: NCT03052608 (Study B7461006); 1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 2. Shaw AT, et al. *N Engl J Med.* 2020;383(20):2018–29.

CROWN: Study Participants

296 Patients Were Randomized[1]

149 patients were assigned to receive lorlatinib	147 patients were assigned to receive crizotinib
149 received assigned treatment	142 received assigned treatment
	5 did not receive assigned treatment
46 patients discontinued treatment	111 patients discontinued treatment
26 had progressive disease	83 had progressive disease
10 had adverse events	12 had adverse events
4 withdrew consent	8 withdrew consent
6 died	4 died
	3 had global deterioration of health status
	1 had other reasons
Patient status at data cutoff:	**Patient status at data cutoff:**
103 continued to receive lorlatinib	31 continued to receive crizotinib
19 were being followed for survival after discontinuation of study treatment	68 were being followed for survival after discontinuation of study treatment
23 died	28 died
4 withdrew consent	18 withdrew consent
	2 were lost to follow-up

Analysis set	n
Intention-to-treat	149
Safety	149
Patient-reported outcomes	148

Analysis set	n
Intention-to-treat	147
Safety	142
Patient-reported outcomes	140

BICR, blind independent central review.

1. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29.

CROWN: Baseline Patient Characteristics [1,2]

Characteristic	Lorlatinib (n=149)	Crizotinib (n=147)
Age, years		
Mean (standard deviation)	59.1 (13.1)	55.6 (13.5)
Median (IQR)	61 (51–69)	56 (45–66)
Sex		
Female	84 (56)	91 (62)
Male	65 (44)	56 (38)
Race		
White	72 (48)	72 (49)
Asian	65 (44)	65 (44)
Black or African American	0 (0)	1 (1)
Missing	12 (8)	9 (6)
ECOG performance status		
0	67 (45)	57 (39)
1	79 (53)	81 (55)
2	3 (2)	9 (6)
Smoking status		
Never smoked	81 (54)	94 (64)
Previous smoker	55 (37)	43 (29)
Current smoker	13 (9)	9 (6)
Current stage of disease		
Stage IIIA	1 (1)	0 (0)
Stage IIIB	12 (8)	8 (5)
Stage IV	135 (91)	139 (95)
Other*	1 (1)	0 (0)
Histology		
Adenocarcinoma	140 (94)	140 (95)
Adenosquamous carcinoma	6 (4)	5 (3)
Large cell carcinoma	0 (0)	1 (1)
Squamous cell carcinoma	3 (2)	1 (1)
Prior anticancer drug therapy†	12 (8)	9 (6)
Prior brain radiotherapy	9 (6)	10 (7)
Brain metastases at baseline ‡	38 (26)	40 (27)

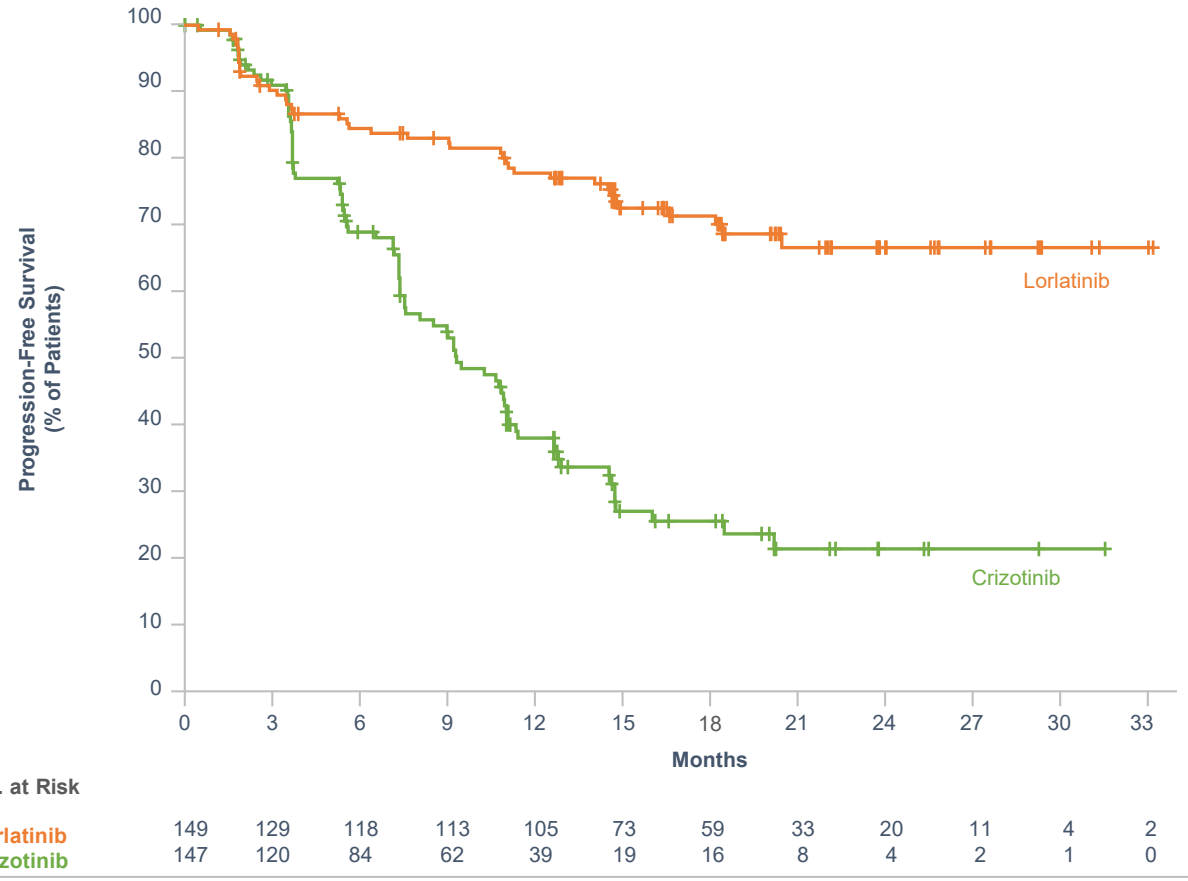
version 8.0, instead of AJCC, version 7.0, as required by the protocol. This stage was therefore classified as "other."; †According to the protocol, previous adjuvant or neoadjuvant anticancer therapy was allowed if it had been completed more than 12 months before randomization. One patient with metastatic disease who had received previous chemotherapy was reported as having a protocol violation. ‡21% of the patients with brain metastases had received prior brain radiotherapy on the lorlatinib arm and 25% on the crizotinib arm.

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group.

1. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29. 2. Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278.

CROWN Primary Endpoint: PFS by BICR (planned interim analysis)[1,2]

Clinical Data



Data cutoff: March 20, 2020

	Patients (n)	Events n (%)	mPFS (months)
Lorlatinib	149	41 (28)	NE (95% CI: NE–NE)
Crizotinib	147	86 (59)	9.3 (95% CI: 7.6–11.1)

Hazard ratio 0.28 (95% CI: 0.19–0.41; 1-sided *P* <0.0001*)

12-month PFS rate:

Lorlatinib : **78%** (95% CI: 70–84)

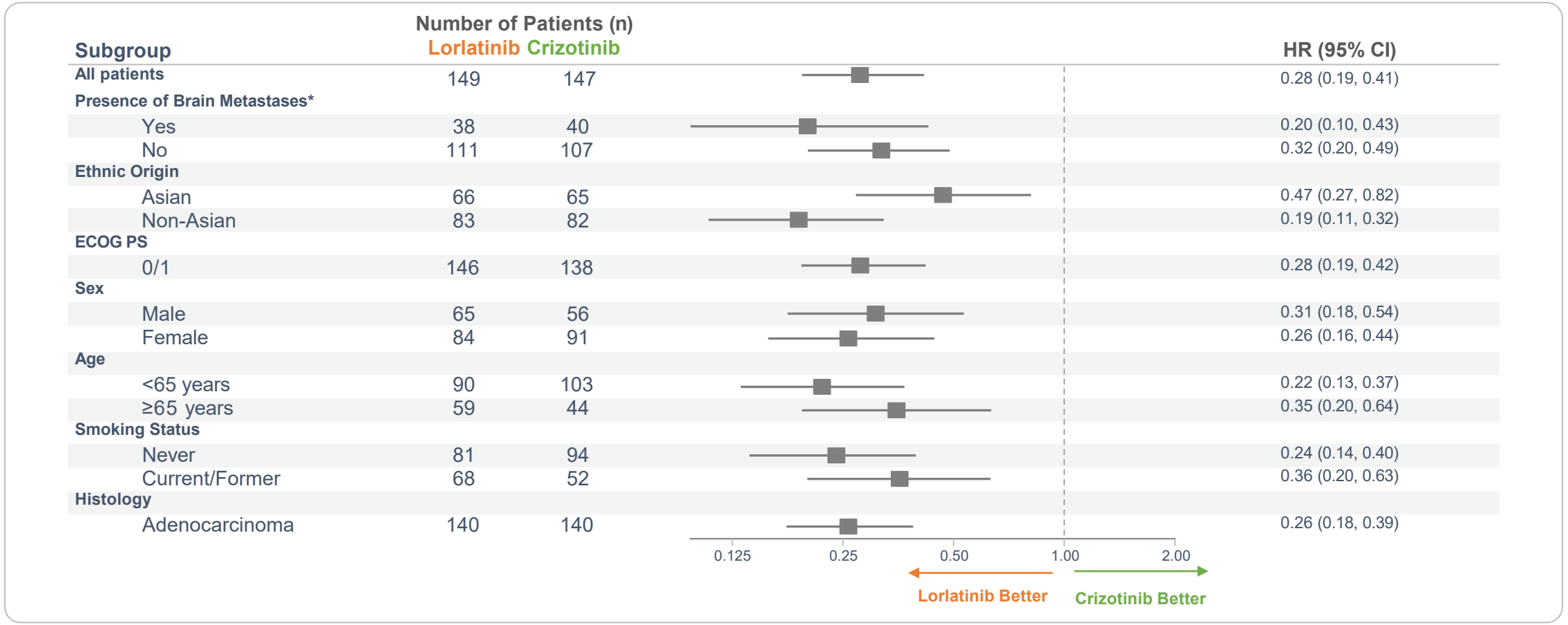
Crizotinib : **39%** (95% CI: 30–48)

*By stratified log-rank test.

BICR, blind independent central review; PFS, progression-free survival.

1. LORVIQUA® Sažetak karakteristika leka; Pfizer, Maj 2022; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29.

CROWN: PFS by BICR Subgroups (planned interim analysis)



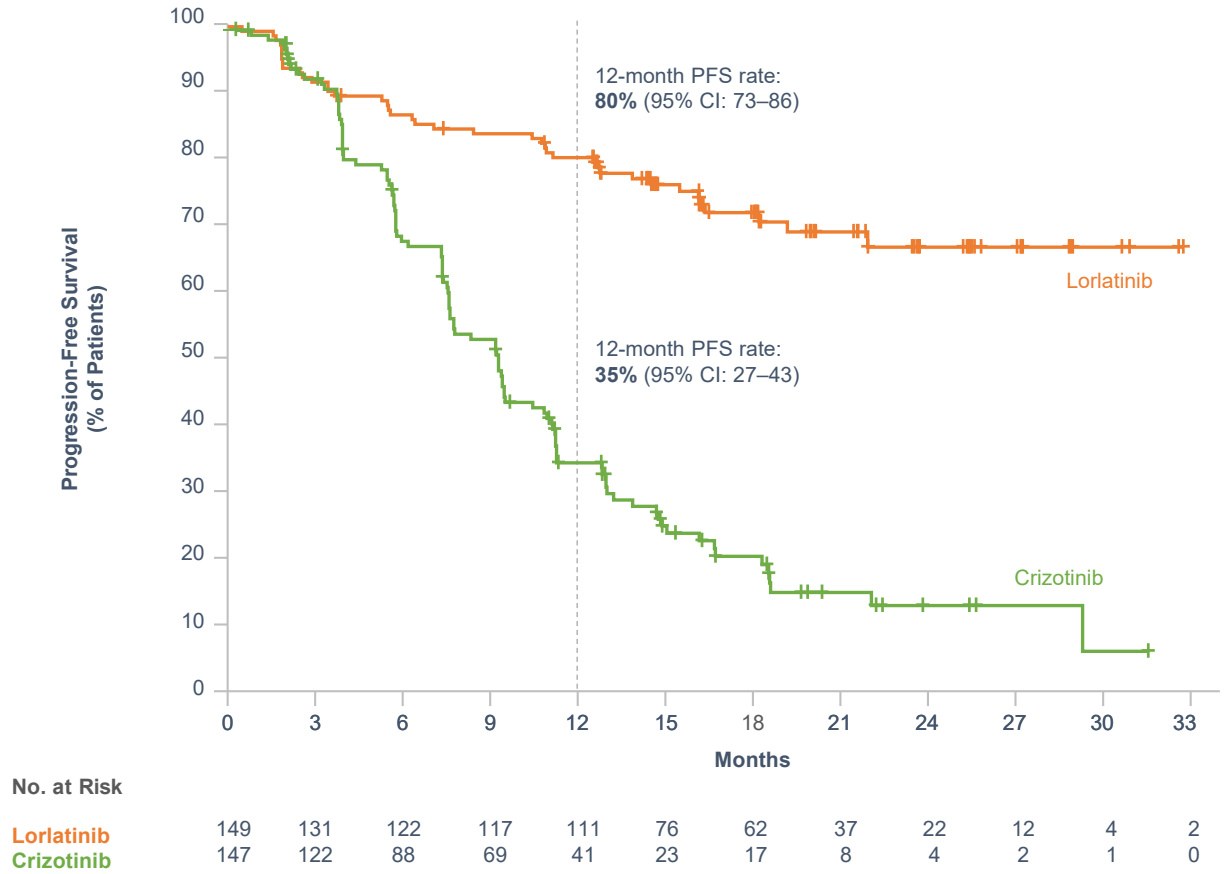
*Based on BICR assessment. Hazard ratios were not calculated due to insufficient numbers of events (<10 events on either treatment arm within the defined subset), as dictated by the Statistical Analysis Plan, for patients who had ECOG performance status of 2 (2 vs. 8 events), or histology of Non-Adenocarcinoma (5 vs. 5 events). This graph depicts exploratory subgroup analyses, only some of which were prespecified, from the ITT population in CROWN. Small patient numbers can be a limitation of subgroup analyses. These results are presented for descriptive purposes and cannot be interpreted as a demonstration of efficacy in any particular subgroup. The results show the variability of the observed treatment effect over several subgroups.

BICR, blind independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ITT, intention to treat; PFS, progression-free survival.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; Supplementary Appendix.

CROWN: PFS by Investigator Assessment (planned interim analysis)[1,2]

Clinical Data



Data cutoff: March 20, 2020

	Patients (n)	Events (n, %)	mPFS (months)
Lorlatinib	149	40 (27)	NR (95% CI: NR–NR)
Crizotinib	147	104 (71)	9.1 (95% CI: 7.4–10.9)

Hazard ratio 0.21 (95% CI: 0.14–0.31; 1-sided *P* <0.001*)

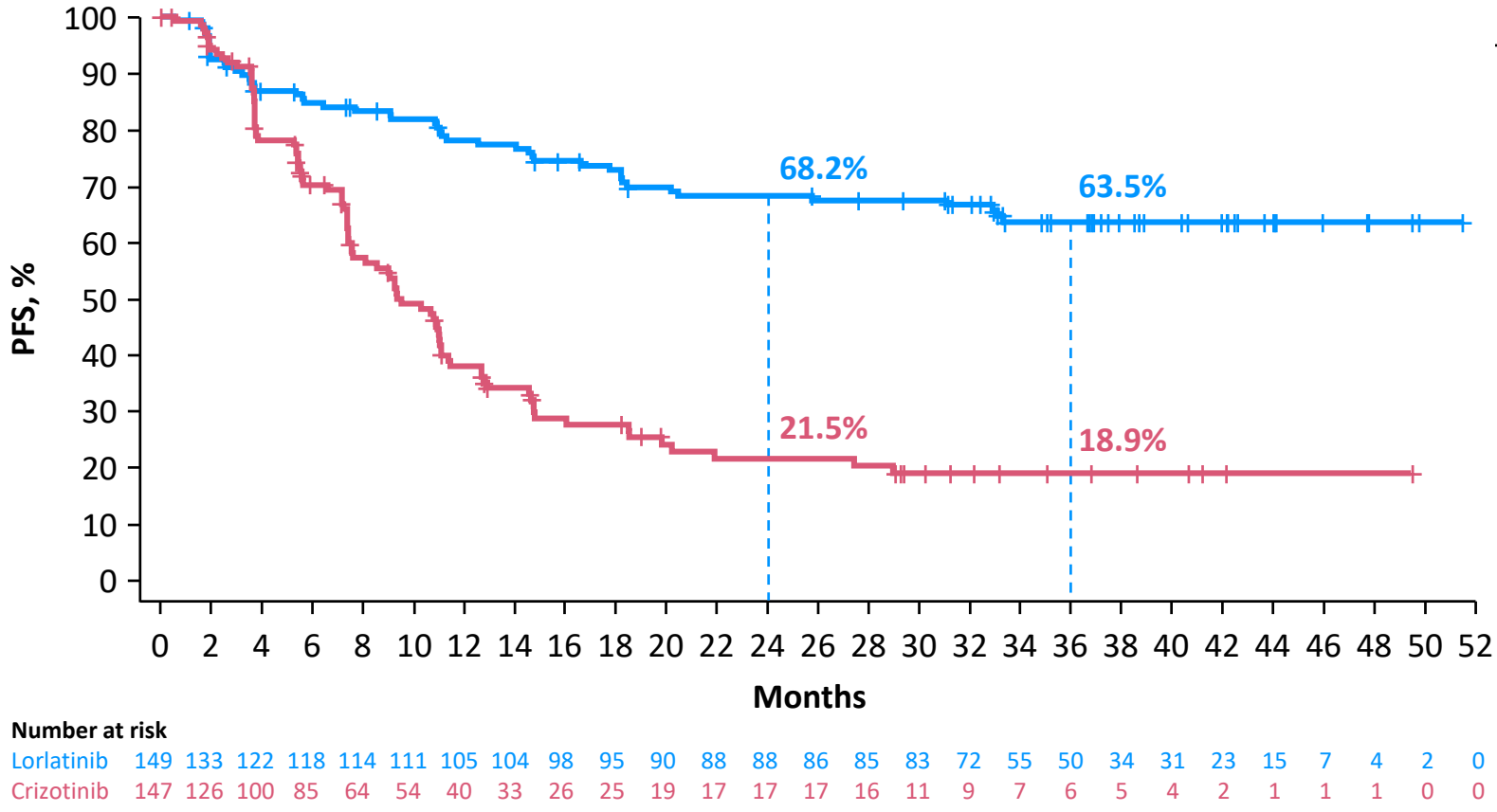
*By stratified log-rank test.

NR, not reached; PFS, progression-free survival.

1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; Supplementary Appendix.

CROWN Primary Endpoint: PFS by BICR (long-term follow up, ITT population)

Clinical Data



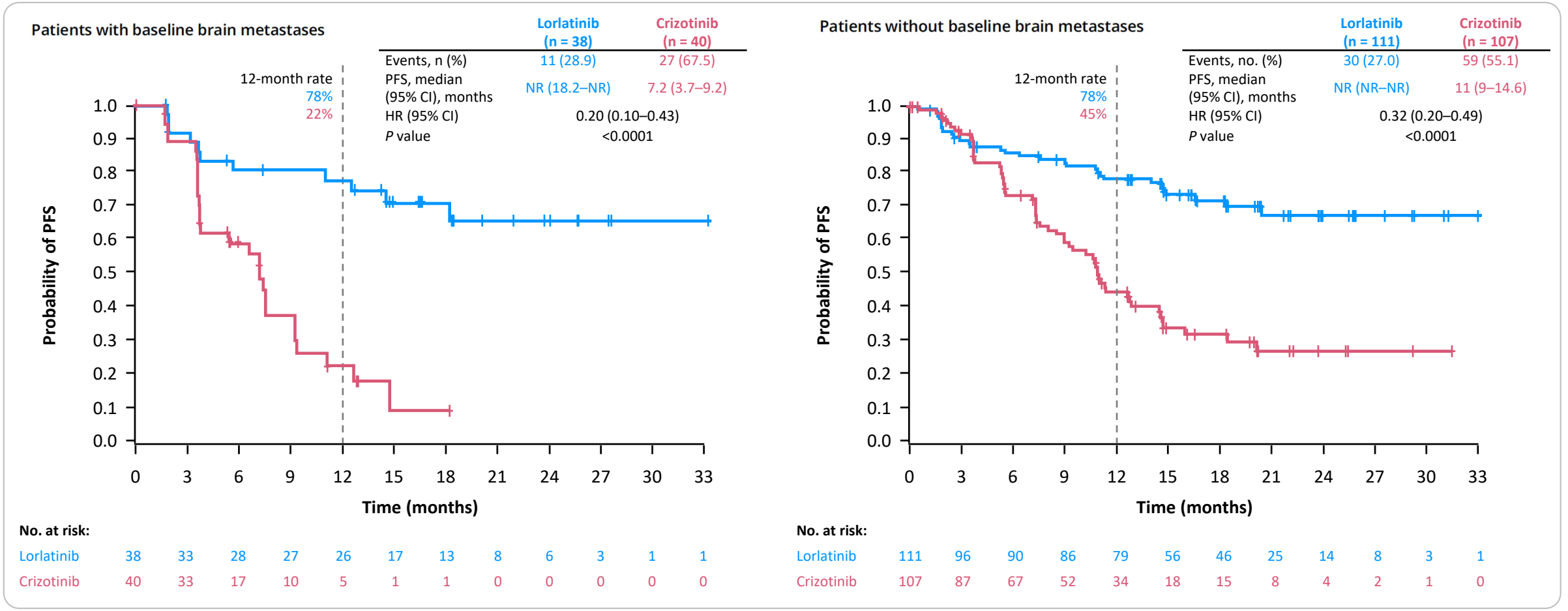
	Lorlatinib (n = 149)	Crizotinib (n = 147)
Events	49	92
PFS, median (95% CI), months	NR (NR–NR)	9.3 (7.6–11.1)
HR (95% CI)	0.27 (0.184–0.388)	

- PFS as assessed by the investigators was also longer with lorlatinib than crizotinib
  - Median PFS was NR (95% CI, NR-NR) with lorlatinib and 9.1 months (95% CI, 7.4-10.9 months) with crizotinib (HR, 0.19; 95% CI, 0.131-0.274)

Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by BICR: lorlatinib, 36.7 months; crizotinib, 29.3 months.
BICR, blinded independent central review; ITT, intent to treat; NR, not reached; PFS, progression-free survival.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: PFS by BICR in Patients with and without Brain Metastases at Baseline (post hoc analysis)

Clinical Data



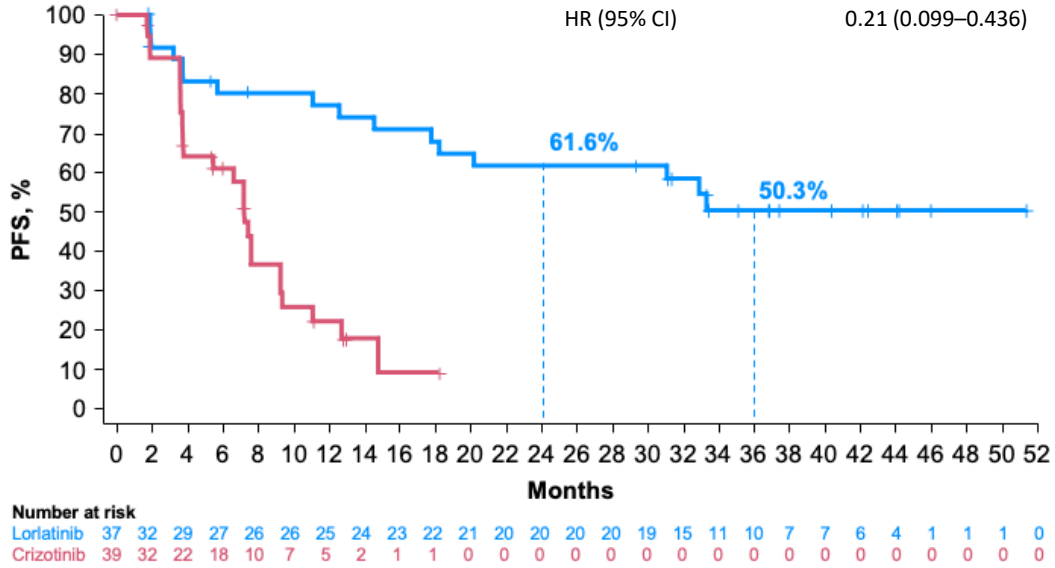
Data cutoff: March 20, 2020.
NR, not reached; PFS, progression-free survival.
Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278.

CROWN: PFS by BICR in Patients with and without Brain Metastases at Baseline (long-term follow up)

Clinical Data

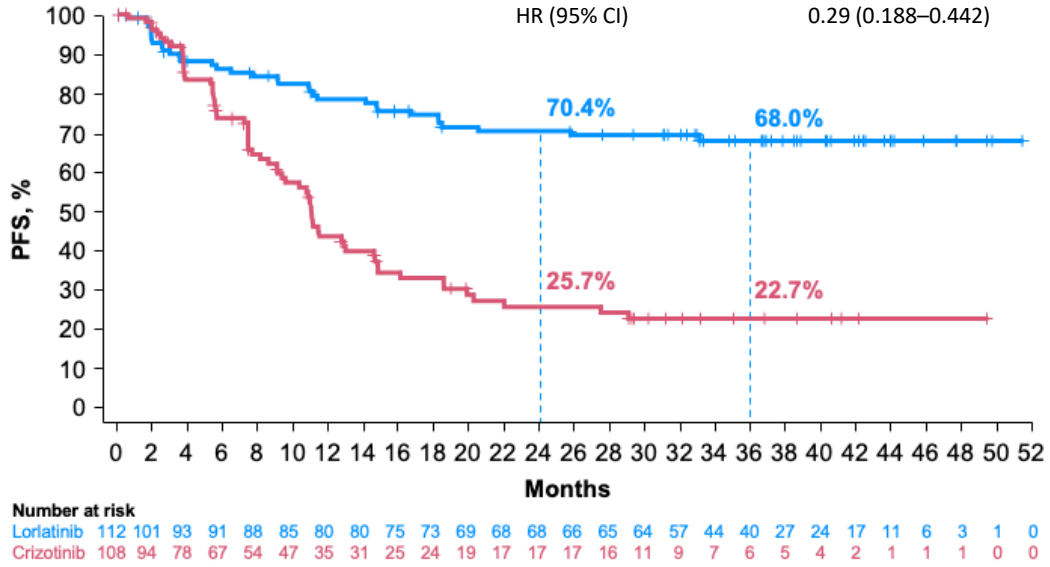
Patients with baseline brain metastases

	Lorlatinib (n = 37)	Crizotinib (n = 39)
Events	16	27
PFS, median (95% CI), months	NR (18.2–NR)	7.2 (3.7–9.2)
HR (95% CI)	0.21 (0.099–0.436)	



Patients without baseline brain metastases

	Lorlatinib (n = 112)	Crizotinib (n = 108)
Events	33	65
PFS, median (95% CI), months	NR (NR–NR)	11.0 (9.0–14.6)
HR (95% CI)	0.29 (0.188–0.442)	



Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by BICR: lorlatinib, 36.7 months; crizotinib, 29.3 months.
BICR, blinded independent central review; NR, not reached; PFS, progression-free survival.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: First Subsequent Systemic Anticancer Therapies (long-term follow up)

	Lorlatinib	Crizotinib
≥1 Subsequent therapy, n/N (%)	**33/149 (22.1)**	**103/147 (70.1)**
First subsequent therapy, n	**33**	**103**
ALK TKI, n/N (%)	21/33 (63.6)	96/103 (93.2)
Alectinib	12/21 (57.1)	65/96 (67.7)
Crizotinib	4/21 (19.0)	5/96 (5.2)
Ceritinib	3/21 (14.3)	3/96 (3.1)
Brigatinib	1/21 (4.8)	20/96 (20.8)
Lorlatinib	1/21 (4.8)	3/96 (3.1)
Chemotherapy ± anti-angiogenic drugs, n/N (%)	11/33 (33.3)	3/103 (2.9)
Chemotherapy/immunotherapy, n/N (%)	1/33 (3.0)	0
Other, n/N (%)	0	4/103 (3.9)
Duration of first subsequent systemic anticancer therapy, median (IQR), months	**9.6 (2.9–18.1)**	**13.3 (4.8–21.2)**
ALK TKIs as first subsequent therapy	9.6 (2.8–19.3)	14.0 (6.5–21.8)
Non-ALK TKIs* as first subsequent therapy	10.4 (3.4–15.1)	1.0 (0.8–1.8)

Response Rates to First Subsequent Anticancer Therapies

Data cutoff: September 20, 2021.

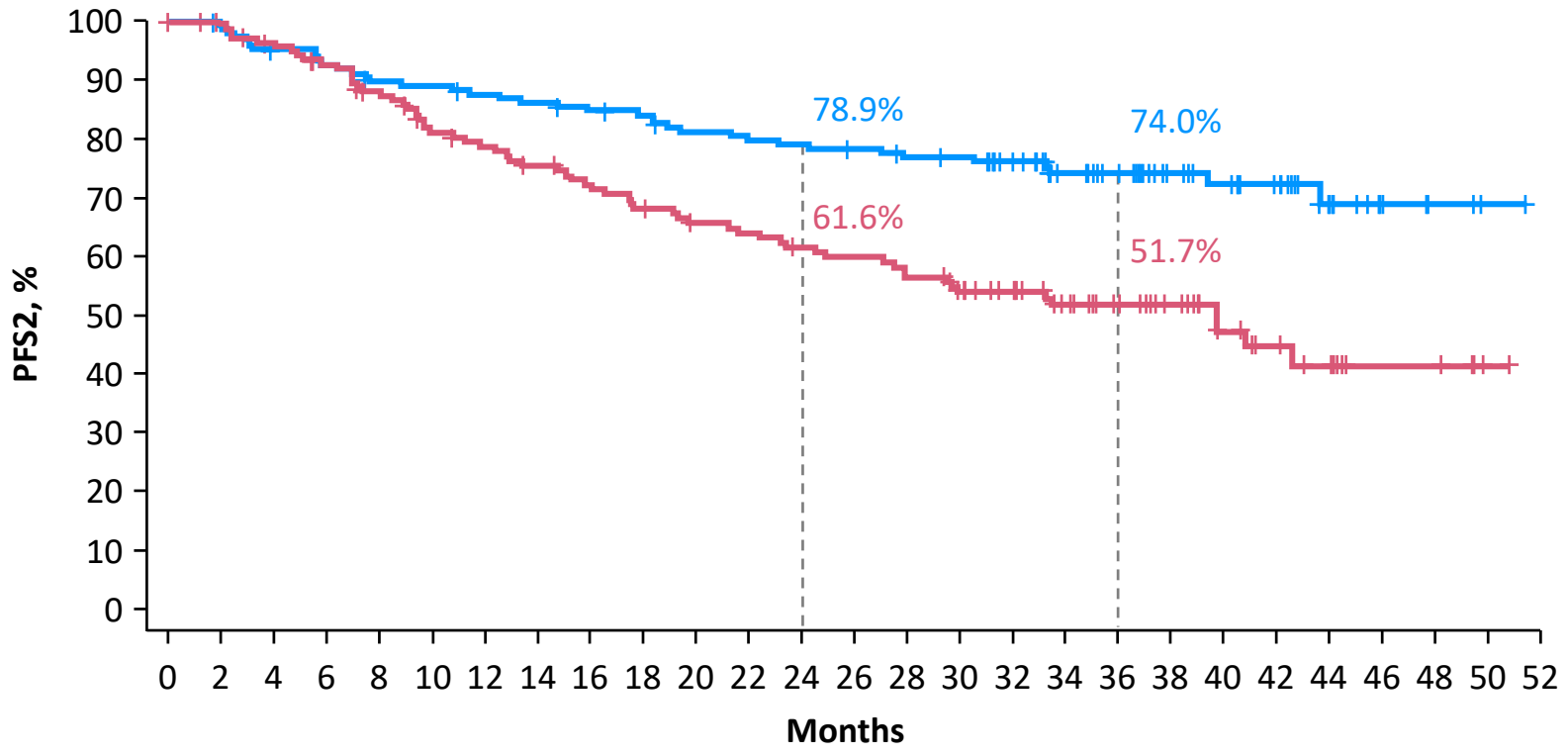
*Included chemotherapy and other therapies.

Median duration of treatment on first subsequent systemic anticancer therapy was 9.6 months (interquartile range [IQR], 2.9–18.1 months) for patients previously treated with lorlatinib and 13.3 months (IQR, 4.8–21.2 months) for patients previously treated with crizotinib.

ALK, anaplastic lymphoma kinase; IQR, interquartile range; TKI, tyrosine kinase inhibitor.

Solomon B, et al. ASCO Annual Meeting. June 3-7, 2022. Abstract 9069.

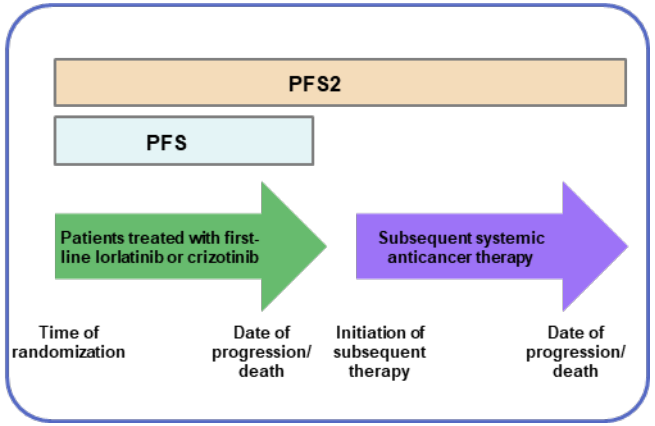
CROWN: PFS2* (long-term follow up)



No. at risk

Lorlatinib	149	145	137	133	128	127	124	122	119	117	112	110	109	106	103	102	89	71	63	43	37	28	18	8	4	2	0
Crizotinib	147	136	130	122	114	103	99	94	89	84	79	77	73	71	67	61	54	44	34	28	20	15	11	5	5	1	0

	Lorlatinib (n = 149)	Crizotinib (n = 147)
Events	38	64
PFS, median (95% CI), months	NR (NR–NR)	39.6 (27.4–NR)
HR (95% CI)	0.45 (0.298–0.672)	



[Response Rates to First Subsequent Anticancer Therapies]

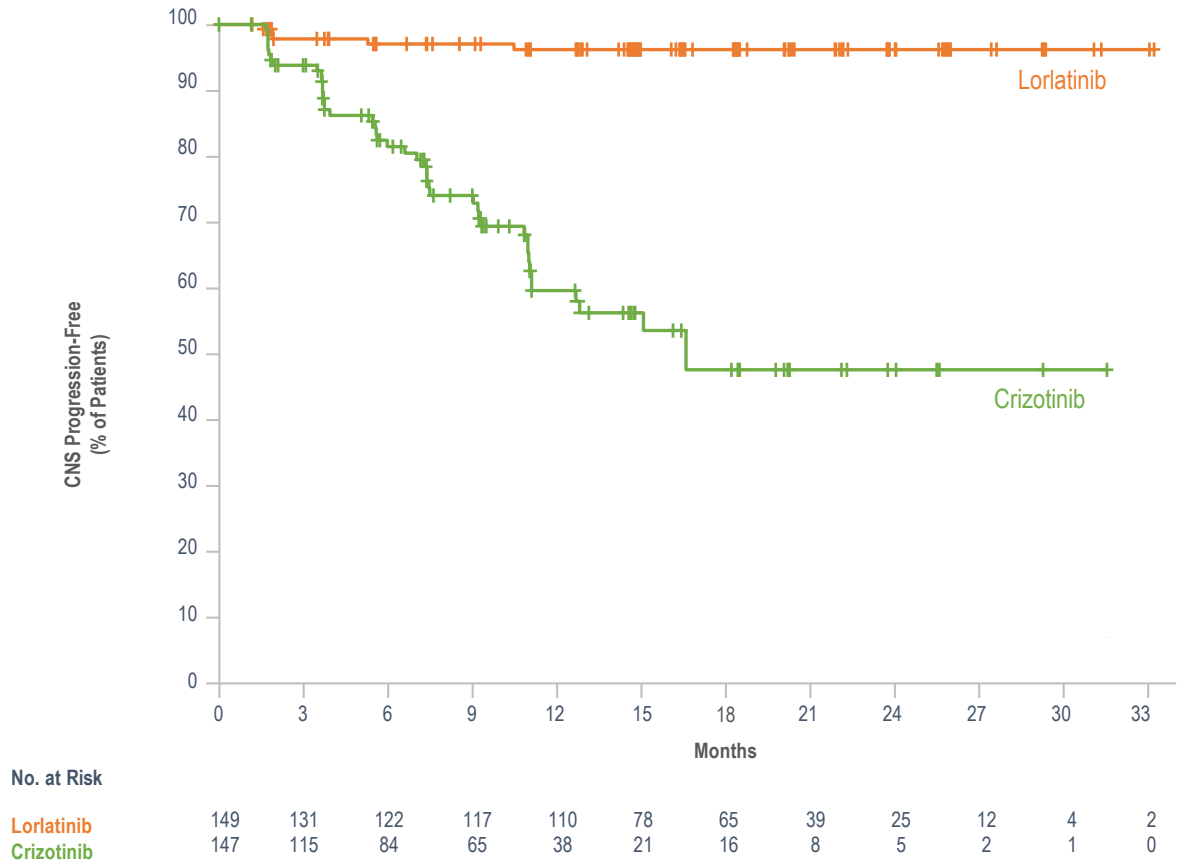
Data cutoff: September 20, 2021.

*Defined as time from randomization to the date of disease progression while receiving the first subsequent systemic anticancer therapy or death due to any cause.

CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Solomon B, et al. ASCO Annual Meeting. June 3-7, 2022. Abstract 9069.

CROWN: Time to IC Progression* by BICR (planned interim analysis)[1,2]



	Patients (n)	Events (n, %)	Median time to CNS Progression, Months (95% CI)
Lorlatinib	149	5 (3)	NE (NE–NE)
Crizotinib	147	45 (31)	16.6 (11.1–NE)

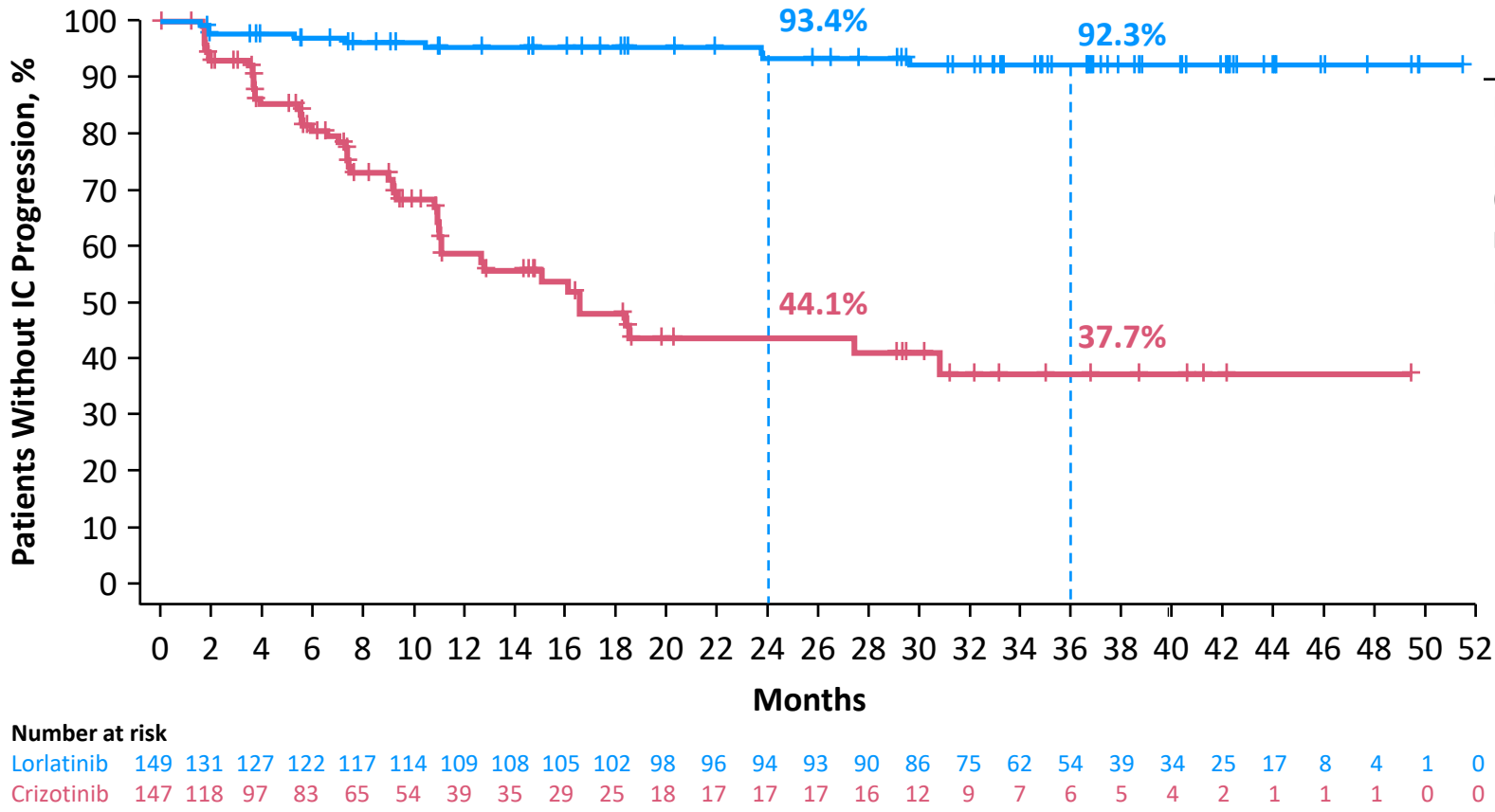
Hazard ratio 0.07 (95% CI: 0.03–0.17); 1-sided *P* <0.001[†]

Data formerly reported as Intracranial Time to Progression. *Time to CNS progression was defined as the time from randomization to the first objective progression of CNS disease (either new brain metastases or progression of existing brain metastases). The secondary endpoint of intracranial time to progression was not part of the statistical testing hierarchy. The small patient numbers are a limitation to this analysis. In addition, the clinical relevance of these data is unknown because they do not include disease status in the rest of the body. Therefore, these data were not included in the USPI by the FDA. These results are presented for descriptive purposes only and should be interpreted within this context. [†]By stratified log-rank test.

BICR, blind independent central review; CNS, central nervous system; NE, not estimable; USPI, United States prescribing information.

1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29.

CROWN: Time to IC Progression by BICR (long-term follow up, ITT Population)



	Lorlatinib (n = 149)	Crizotinib (n = 147)
Events	9	51
PFS, median (95% CI), months	NR (NR–NR)	16.6 (11.1–NR)
HR (95% CI)	0.08 (0.040–0.174)	

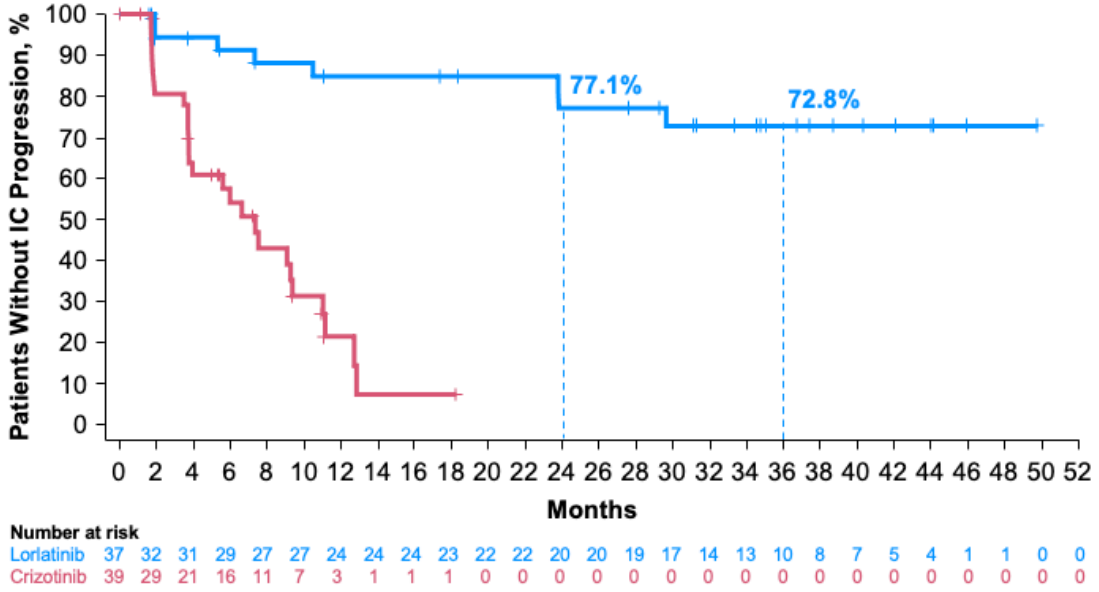
Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
BICR, blinded independent central review; IC, intracranial; ITT, intent to treat; NR, not reached; PFS, progression-free survival.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Time to IC Progression by BICR in Patients with and without Brain Metastases at Baseline (long-term follow up)

Clinical Data

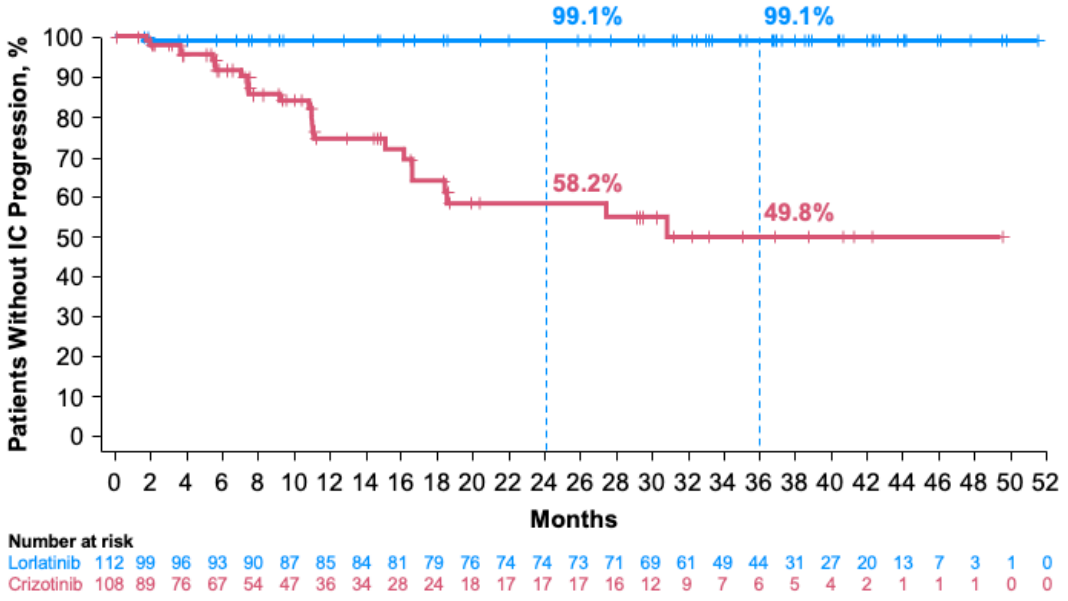
Patients with baseline brain metastases

	Lorlatinib (n = 37)	Crizotinib (n = 39)
Events	8	26
TTP, median (95% CI), months	NR (NR–NR)	7.3 (3.7–9.3)
HR (95% CI)	0.10 (0.037–0.268)	



Patients without baseline brain metastases

	Lorlatinib (n = 112)	Crizotinib (n = 108)
Events	1	25
TTP, median (95% CI), months	NR (NR–NR)	30.8 (18.4–NR)
HR (95% CI)	0.02 (0.002–0.136)	



Time to IC progression by BICR was longer with lorlatinib than crizotinib in patients with or without baseline brain metastases

- **8 of 37 patients had IC progression with lorlatinib treatment**
- **1 of 112 patients had IC progression with lorlatinib treatment**

Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
BICR, blinded independent central review; IC, intracranial; NR, not reached; TTP, time to tumor progression.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Tumor Response by BICR (planned interim analysis)

Characteristic	Lorlatinib (n=149)	Crizotinib (n=147)
Responders, n (%)[1,2]	113 (76)	85 (58)
(95% CI)[1,2]	(68–83)	(49–66)
Odds ratio*[1]	2.25 (1.35–3.89)	
CR, n (%)[1]	4 (3)	0 (0)
PR, n (%) [1]	109 (73)	85 (58)
SD, n (%)[1]	19 (13)	41 (28)
Non-CR/Non-PD, n (%)[1]	3 (2)	3 (2)
PD, n (%)[1]	10 (7)	7 (5)
NE, n (%)[1]	4 (3)	11 (7)
Median DOR, months (95% CI)[1]	NE (NE-NE)	11 (9.0-12.9)
Median time to response, months (IQR)[1]	1.8 (1.7–1.9)	1.8 (1.7–1.9)

*Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib.

BICR, blind independent central review; CR, complete response; DOR, duration of response; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; 2. LORVIQUA® Sažetak karakteristika leka; Pfizer, Maj 2022.

CROWN: Tumor Response by Investigator Assessment (planned interim analysis)

Characteristic	Lorlatinib (n=149)	Crizotinib (n=147)
Responders, n (%)	120 (81)	91 (62)
(95% CI)	(73–87)	(54–70)
Odds ratio*	2.50 (1.48–4.59)	
CR, n (%)	12 (8)	3(2)
PR, n (%)	108 (72)	88 (60)
SD, n (%)	16 (11)	39 (27)
Non-CR/Non-PD, n (%)	0 (0)	0 (0)
PD, n (%)	8 (5)	7 (5)
NE, n (%)	5 (3)	10 (7)

*Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib.

CR, complete response; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; Supplementary Appendix.

CROWN: Intracranial OR by BICR (planned interim analysis)

	Patients With Measurable or Non-Measurable Brain Metastases at Baseline[1]		Patients With Measurable Brain Metastases at Baseline[1,2]	
	Lorlatinib (n = 38)	**Crizotinib (n = 40)**	**Lorlatinib (n = 17)**	**Crizotinib (n = 13)**
Confirmed CNS Response, n (%)	25 (66)	8 (20)	14 (82)	3 (23)
(95% CI)	(49–80)	(9–36)	(57–96)	(5–54)
Odds ratio*	8.41 (2.59–27.23)		16.83 (1.95–163.23)	
CNS CR, n (%)	23 (61)	6 (15)	12 (71)	1 (8)
Median DOR, months (95% CI)	NE (NE–NE)	9.4 (6.0–11.1)	NE (NE–NE)	10.2 (9.4–11.1)
Median time to response, months (IQR)	1.9 (1.8–3.7)	1.8 (1.7–2.7)	1.9 (1.8–3.5)	1.9 (1.8–1.9)

*Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib.

BICR, blind independent central review; CNS, central nervous system; CR, complete response; DOR, duration of response; IQR, interquartile range; NE, not estimable; OR, overall response.

1. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; 2. LORVIQUA® Sažetak karakteristika leka; Pfizer, Maj 2022.

CROWN: Overall and IC Response by BICR (long-term follow up)

	Lorlatinib	Crizotinib
ITT population, n	**149**	**147**
Confirmed ORR by BICR, n (%)	115 (77.2)	86 (58.5)
Complete response	4 (2.7)	0
DOR, median (95% CI), months	NR (NR –NR)	9.6 (9.0 –12.9)
Patients with any brain metastases at baseline, n	**37**	**39**
Confirmed IC ORR by BICR, n (%)	24 (64.9)	7 (17.9)
Complete IC response	22 (59.5)	5 (12.8)
IC DOR, median (95% CI), months	NR (NR –NR)	9.4 (6.0 –11.1)
Patients with ≥1 measurable brain metastasis at baseline, n	**18**	**13**
Confirmed IC ORR by BICR, n (%)	15 (83.3)	3 (23.1)
Complete IC response	13 (72.2)	1 (7.7)
IC DOR, median (95% CI), months	NR (NR –NR)	10.2 (9.4 –11.1)

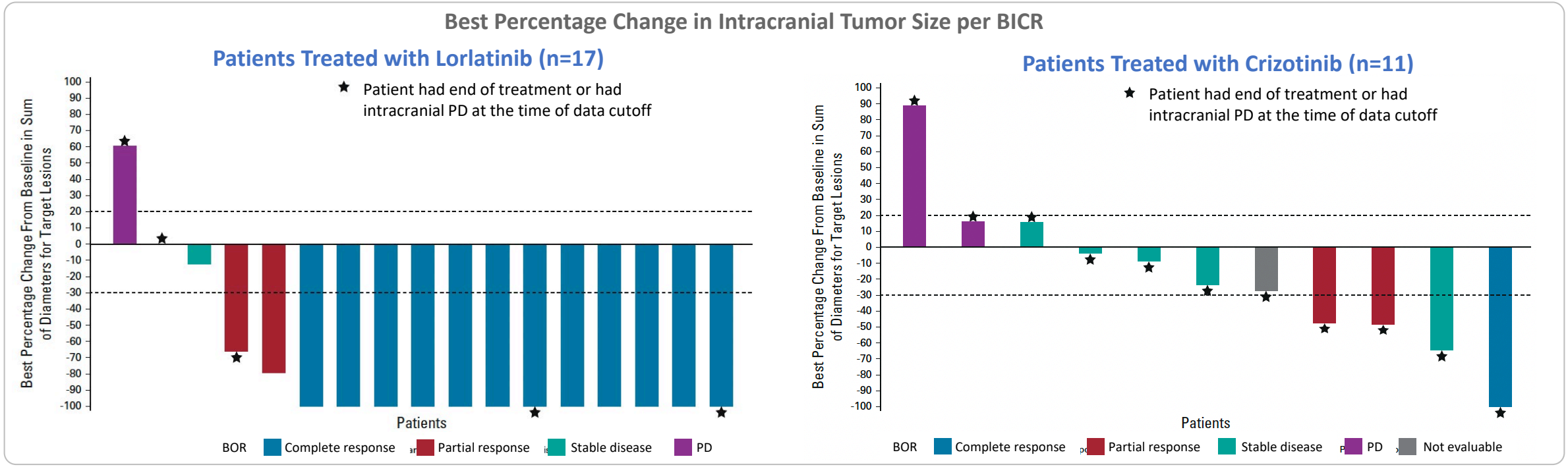
In patients with measurable baseline brain metastases, confirmed IC ORR by BICR was

83.3% with lorlatinib and 23.1% with crizotinib

72.2% and 7.7%, respectively, had a complete IC response

Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
BICR, blinded independent central review; DOR, duration of response; IC, intracranial; NR, not reached; ORR, objective response rate.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Intracranial Complete Responses* (post hoc analysis, ITT population)



- Complete CNS responses with lorlatinib were seen in 23/38 (61%) patients with any brain metastases at baseline, and in 12/17 (71%) patients with at least one measurable brain metastasis at baseline
  - Median DOR with lorlatinib in patients with complete responses and measurable brain lesions at baseline: NR (range 7.4–31.4 months)
  - 83% had a DOR ≥12 months; 42% had a DOR ≥18 months

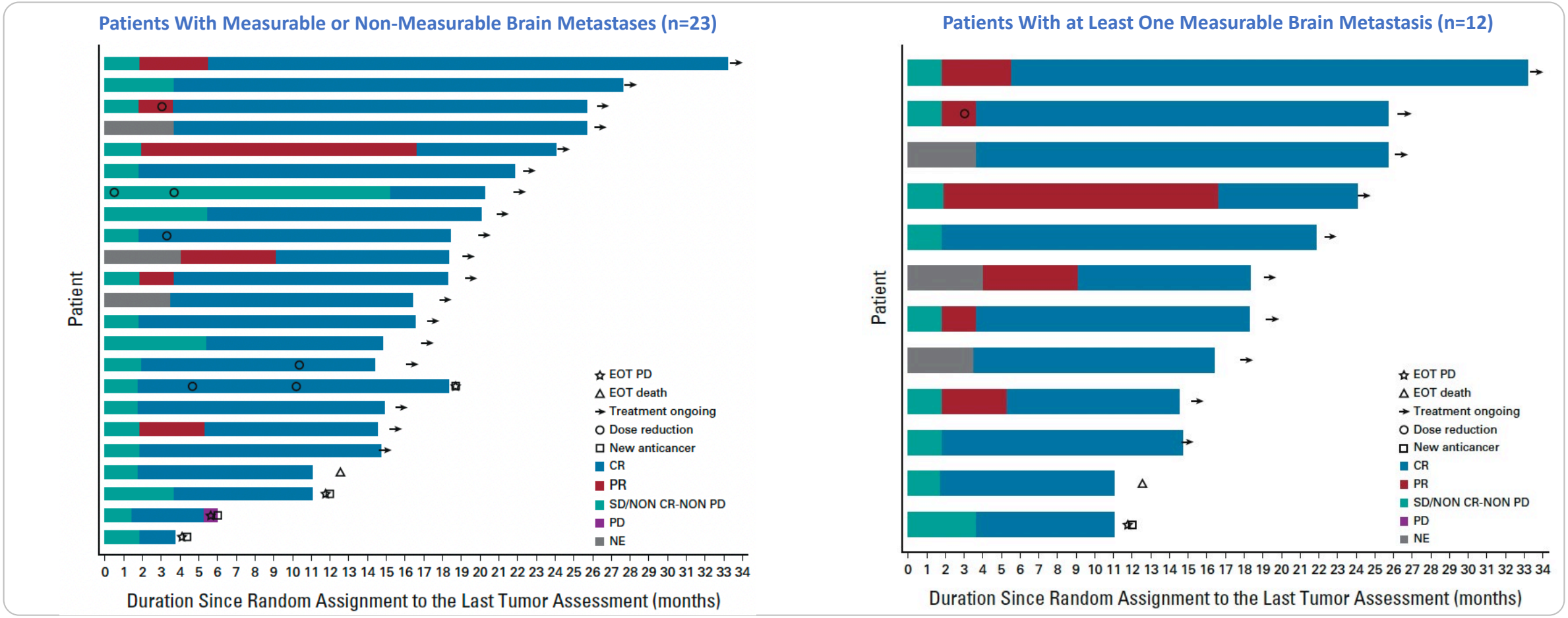
- Complete CNS responses with crizotinib were seen in 6/40 (15%) patients with any brain metastases at baseline, and in 1/13 (8%) patients with at least one measurable brain metastasis at baseline

*Only included patients with target lesions at baseline and at least one adequate post-baseline assessment up to the time of PD or new anti-cancer therapy. Two patients from the crizotinib arm were excluded from the plot as they did not have any post-baseline tumor assessment.

BICR, blinded independent central review; BOR, best overall response; CNS, central nervous system; DOR, duration of response; ITT, intent to treat; NR, not reached; PD, progressive disease.

Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278.

CROWN: Intracranial Complete Responses Over Time (post hoc analysis, ITT population)

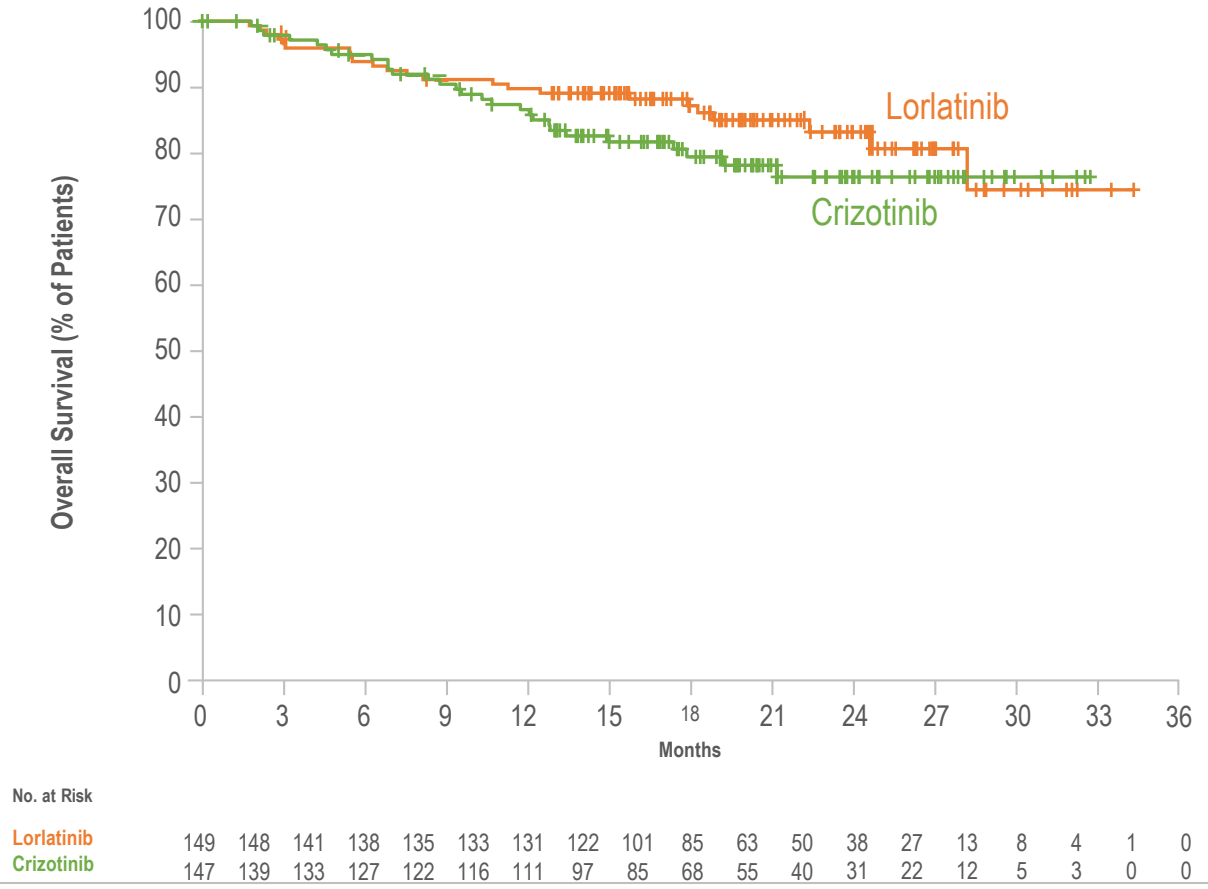


- **Most patients with intracranial responses were still receiving lorlatinib treatment at data cutoff**

CR, complete response; EOT, end of treatment; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278. Supplementary Appendix.

CROWN: Overall Survival (planned interim analysis) [1,2]

Clinical Data



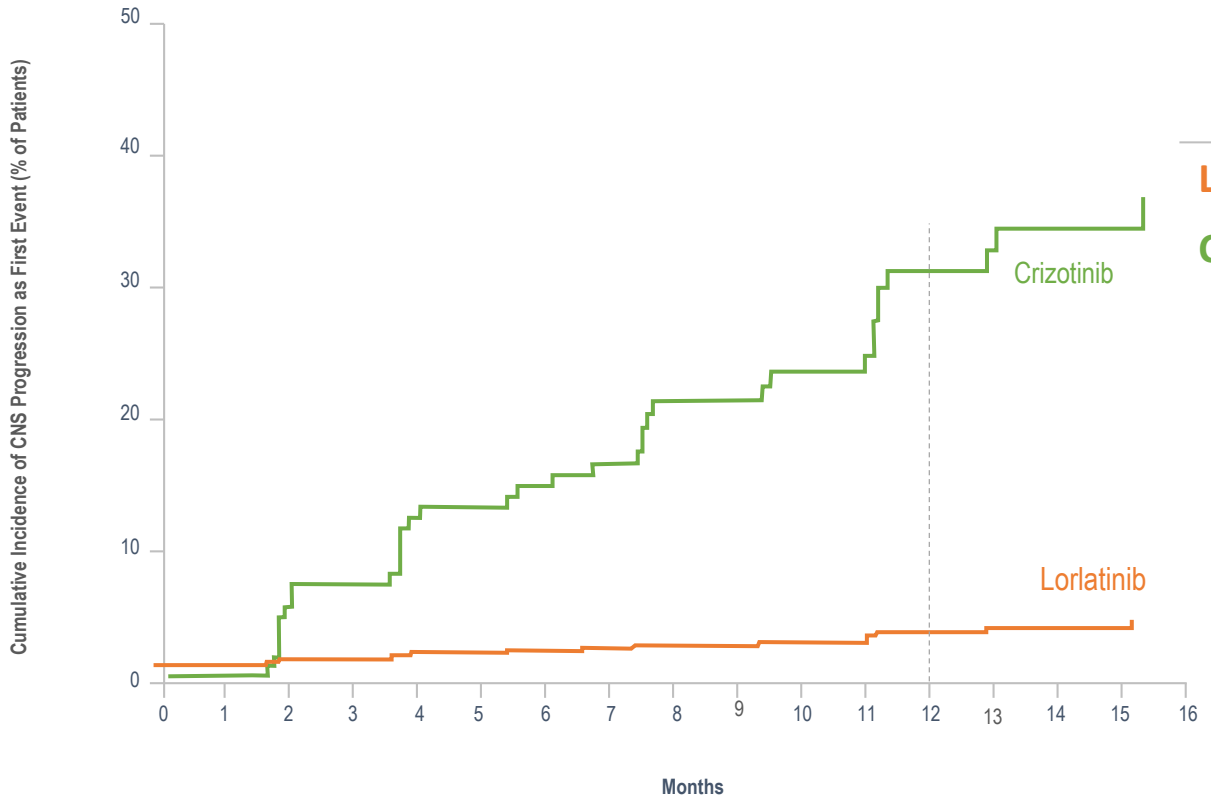
	Patients (n)	Events (n, %)	mOS (months)
Lorlatinib	149	23 (15)	NE (95% CI: NE–NE)
Crizotinib	147	28 (19)	NE (95% CI: NE–NE)

Hazard ratio 0.72 (95% CI: 0.41–1.25)

NE, not estimable; OS, overall survival.

1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 2. Shaw AT, et al. N Engl J Med. 2020;383(20):2018–29.

CROWN: Cumulative Incidence of CNS Progression as First Event*(planned interim analysis)



	Patients (n)	12-Month Cumulative Incidence Rate (95% CI)
Lorlatinib	149	2.8% (1.0–8.1)
Crizotinib	147	33.2% (24.6–44.7)

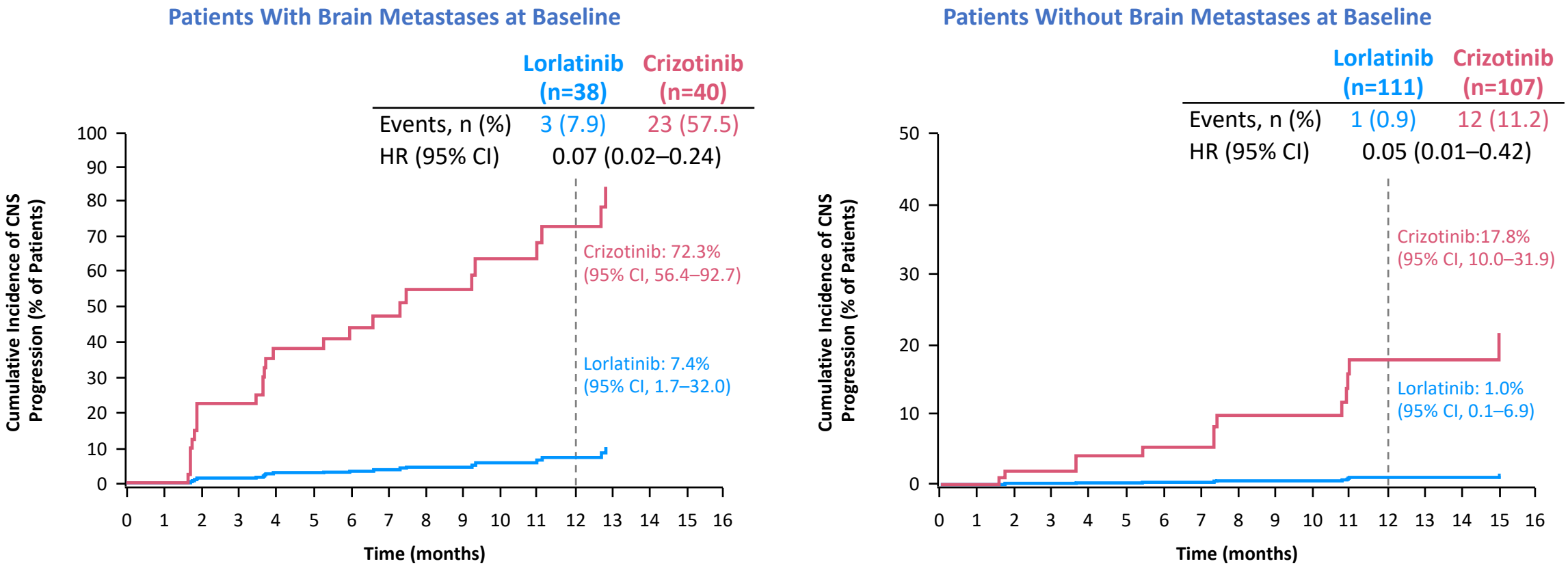
Hazard ratio for CNS progression without prior non-CNS progression or death 0.06 (95% CI, 0.02–0.18)

*The secondary endpoint of cumulative incidence of CNS progression as first event was not part of the statistical testing hierarchy. The small patient numbers are a limitation to this analysis. In addition, the clinical relevance of these data is unknown because they do not include disease status in the rest of the body. Therefore, these data were not included in the USPI by the FDA. These results are presented for descriptive purposes only and should be interpreted within this context.

CNS, central nervous system; USPI, United States prescribing information.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29.

CROWN: CNS Progression by Presence of Brain Metastases at Baseline (post hoc analysis)



Lorlatinib was also associated with lower cumulative incidence of non-CNS progression than crizotinib in patients regardless of presence of brain metastases at baseline

CNS, central nervous system.

Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278.

CROWN: Response Rates to First Subsequent Anticancer Therapies

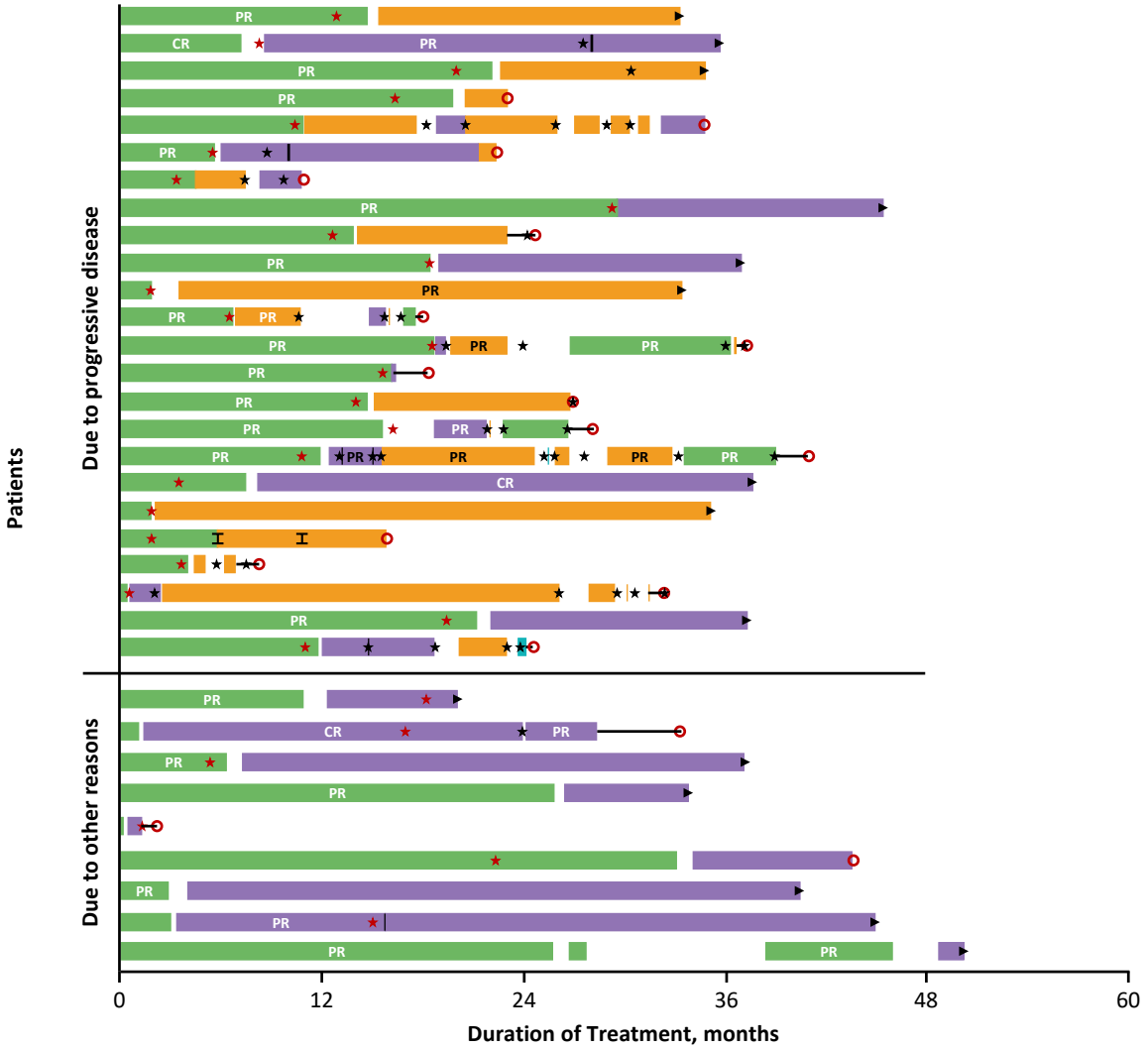
Clinical Data

	First Subsequent Therapy		ALK TKIs as First Subsequent Therapy		Non-ALK TKIs* as First Subsequent Therapy	
	Lorlatinib (n=33)	Crizotinib (n=103)	Lorlatinib (n=21)	Crizotinib (n=96)	Lorlatinib (n=12)	Crizotinib (n=7)
Best overall response, n (%)						
Complete response	2 (6.1)	1 (1.0)	2 (9.5)	1 (1.0)	0	0
Partial response	6 (18.2)	15 (14.6)	4 (19.0)	14 (14.6)	2 (16.7)	1 (14.3)
Stable disease	3 (9.1)	18 (17.5)	1 (4.8)	18 (18.8)	2 (16.7)	0
Progressive disease	8 (24.2)	10 (9.7)	6 (28.6)	8 (8.3)	2 (16.7)	2 (28.6)
Unknown	4 (12.1)	12 (11.7)	1 (4.8)	8 (8.3)	3 (25.0)	4 (57.1)
Not reported; therapy ongoing	10 (30.3)	47 (45.6)	7 (33.3)	47 (49.0)	3 (25.0)	0
Response rate (95% CI), %	24.2 (11.1–42.3)	15.5 (9.1–24.0)	28.6 (11.3–52.2)	15.6 (9.0–24.5)	16.7 (2.1–48.4)	14.3 (0.4–57.9)

*Included chemotherapy and other therapies.
Subsequent systemic therapy is ongoing in 30.3% of patients previously treated with lorlatinib and 45.6% of patients previously treated with crizotinib, and therefore response data are not available in these patients
CI, confidence interval; TKI, tyrosine kinase inhibitor.
Solomon B, et al. ASCO Annual Meeting. June 3-7, 2022. Abstract 9069.

CROWN: Best Overall Response in Patients Who Discontinued Treatment with Lorlatinib

Clinical Data



- In the lorlatinib arm, 2 patients had a CR and 4 patients had a PR on first subsequent therapy
  - 1 CR and 4 PR were observed in patients who discontinued due to progressive disease
  - 1 CR was observed in a patient who discontinued due to other reasons

CR, complete response; PD, progressive disease; PR, partial response; TKI, tyrosine kinase inhibitor.

Solomon B, et al. ASCO Annual Meeting. June 3-7, 2022. Abstract 9069.

CROWN: Safety Summary (planned interim analysis)

Clinical Data

	Lorlatinib (n=149)	Crizotinib (n=142)
Median treatment duration,* months (95% CI)[1,3]	16.7 (4 days, 34.4 months)	9.6 (7.6–11.1)
Patients remaining on treatment >12 months, n (%)[2]	113 (76)	49 (35)
Patients with, n (%)		
Any grade AR[1,2]	149 (100)	140 (99)
Grade 3/4 AR[1-3]	108 (72)	79 (56)
Serious AR[1-3]	51 (34)	39 (27)
Fatal AR[1-3]	5 (3.4)	7 (5)†
AR leading to permanent treatment discontinuation[1-3]	10 (7)	13 (9)
AR leading to temporary dose interruption[1-3]	73 (49)	67 (47)
AR leading to dose reduction[2,3]	31 (21)	22 (15)

- The most frequently reported **serious ARs** among patients treated with lorlatinib were pneumonia (4.7%), dyspnea (2.7%), respiratory failure (2.7%), cognitive effects (2.0%), and pyrexia (2.0%)[3]
- **Fatal ARs** occurred in 3.4% of patients treated with lorlatinib and included pneumonia (0.7%), respiratory failure (0.7%), cardiac failure acute (0.7%), pulmonary embolism (0.7%), and sudden death (0.7%)[3]
- The most frequent AR that led to **permanent discontinuation** of lorlatinib was cognitive effects (1.3%)[3]
- The most frequent ARs that led to **dose interruptions** of lorlatinib were hypertriglyceridemia (7%), edema (5%), pneumonia (4.7%) cognitive effects (4.0%), mood effects (4.0%), and hypercholesterolemia (3.4%)[3]
- The most frequent ARs that led to **dose reductions** were edema (5%), hypertriglyceridemia (4.0%), and peripheral neuropathy (3.4%)[3]

*Estimated using the Kaplan-Meier method.
†Incidence of adverse events.

1. Solomon B, et al. Lorlatinib vs. Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. ESMO September 2020; 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29. 3. LORBRENA [US Prescribing Information]. New York, NY: Pfizer Inc; 2021.

CROWN: Adverse Events in the Safety Population* (planned interim analysis, 1/2)

	Lorlatinib (n=149), n (%)					Crizotinib (n=142), n (%)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any adverse event	149 (100)	6 (4)	28 (19)	87 (58)	21 (14)	140 (99)	8 (6)	46 (32)	67 (47)	12 (8)
Hypercholesterolemia†	105 (70)	24 (16)	57 (38)	23 (15)	1 (1)	5 (4)	5 (4)	0	0	0
Hypertriglyceridemia†	95 (64)	28 (19)	37 (25)	19 (13)	11 (7)	8 (6)	5 (4)	3 (2)	0	0
Edema†	82 (55)	54 (36)	22 (15)	6 (4)	0	56 (39)	38 (27)	16 (11)	2 (1)	0
Increased weight	57 (38)	11 (7)	21 (14)	25 (17)	0	18 (13)	6 (4)	9 (6)	3 (2)	0
Peripheral neuropathy†	50 (34)	36 (24)	11 (7)	3 (2)	0	21 (15)	19 (13)	1 (1)	1 (1)	0
Cognitive effects†‡	32 (21)	20 (13)	9 (6)	3 (2)	0	8 (6)	7 (5)	1 (1)	0	0
Diarrhea	32 (21)	21 (14)	9 (6)	2 (1)	0	74 (52)	67 (47)	6 (4)	1 (1)	0
Anemia	29 (19)	16 (11)	9 (6)	4 (3)	0	11 (8)	3 (2)	4 (3)	4 (3)	0
Fatigue†	29 (19)	25 (17)	2 (1)	2 (1)	0	46 (32)	25 (18)	17 (12)	4 (3)	0
Hypertension	27 (18)	1 (1)	11 (7)	15 (10)	0	3 (2)	0	3 (2)	0	0
Vision disorder†	27 (18)	25 (17)	2 (1)	0	0	56 (39)	54 (38)	1 (1)	1 (1)	0
Increased ALT level	26 (17)	22 (15)	0	4 (3)	0	48 (34)	26 (18)	16 (11)	5 (4)	1 (1)
Constipation	26 (17)	24 (16)	2 (1)	0	0	42 (30)	30 (21)	11 (8)	1 (1)	0
Mood effects†§	24 (16)	14 (9)	8 (5)	2 (1)	0	7 (5)	4 (3)	3 (2)	0	0
Nausea	22 (15)	21 (14)	0	1 (1)	0	74 (52)	56 (39)	15 (11)	3 (2)	0

*Shown are adverse events that differed by more than 10 percentage points in frequency between the groups. Patients were counted only once per event. The listed events occurred after the first dose of trial treatment through the end of trial follow-up or the start of new anticancer therapy, whichever took place first. Data for all grades in the lorlatinib group are listed in decreasing order of frequency.

†This category comprised a cluster of adverse events that may represent similar clinical symptoms or syndromes.

‡Cognitive effects with a frequency of at least 1% included memory impairment, disturbance in attention, confusion, amnesia, cognitive disorder, and delirium.

§Mood effects with a frequency of at least 1% included anxiety, depression, affect liability, affective disorder, agitation, irritability, and altered mood.

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29.

CROWN: Adverse Events in the Safety Population* (planned interim analysis, 2/2)

	Lorlatinib (n=149), n (%)					Crizotinib (n=142), n (%)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Increased AST level	21 (14)	18 (12)	0	3 (2)	0	39 (27)	30 (21)	4 (3)	5 (4)	0
Vomiting	19 (13)	16 (11)	2 (1)	1 (1)	0	55 (39)	42 (30)	11 (8)	2 (1)	0
Hyperlipidemia	16 (11)	6 (4)	7 (5)	2 (1)	1 (1)	0	0	0	0	0
Dysgeusia	8 (5)	8 (5)	0	0	0	23 (16)	20 (14)	3 (2)	0	0
Decreased appetite	5 (3)	3 (2)	2 (1)	0	0	35 (25)	23 (16)	8 (6)	4 (3)	0
Bradycardia	2 (1)	2 (1)	0	0	0	17 (12)	15 (11)	2 (1)	0	0

*Shown are adverse events that differed by more than 10 percentage points in frequency between the groups. Patients were counted only once per event. The listed events occurred after the first dose of trial treatment through the end of trial follow-up or the start of new anticancer therapy, whichever took place first. Data for all grades in the lorlatinib group are listed in decreasing order of frequency.
AST, aspartate aminotransferase.
Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29.

CROWN: Serious Adverse Events (planned interim analysis)

Adverse Event,* n (%)	Lorlatinib (n=149)				Crizotinib (n=142)			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Any Serious Adverse Event	51 (34)	28 (19)	6 (4)	7 (5)	39 (27)	19 (13)	6 (4)	7 (5)
Pneumonia	7 (5)	2 (1)	1 (1)	1 (1)	5 (4)	3 (2)	1 (1)	0
Dyspnea	4 (3)	4 (3)	0	0	0	0	0	0
Respiratory failure	4 (3)	3 (2)	0	1 (1)	0	0	0	0
Cognitive effects†‡	3 (2)	1 (1)	0	0	0	0	0	0
Pyrexia	3 (2)	0	1 (1)	0	3 (2)	2 (1)	0	0
Back pain	2 (1)	1 (1)	0	0	0	0	0	0
Bronchitis	2 (1)	2 (1)	0	0	0	0	0	0
Cardiac failure	2 (1)	1 (1)	0	0	1 (1)	0	0	0
Hypertriglyceridemia†	2 (1)	0	2 (1)	0	0	0	0	0
Pericardial effusion	2 (1)	1 (1)	0	0	1 (1)	0	0	1 (1)
Pleural effusion	2 (1)	1 (1)	0	0	2 (1)	1 (1)	1 (1)	0
Pneumonitis†	2 (1)	0	0	0	2 (1)	1 (1)	0	0
Sepsis	2 (1)	1 (1)	1 (1)	0	0	0	0	0
Pulmonary embolism	1 (1)	0	0	1 (1)	2 (1)	1 (1)	0	0
Malignant neoplasm progression	0	0	0	0	2 (1)	0	0	2 (1)

*Serious adverse events occurring in ≥1% of patients in any treatment group; †Cluster term; ‡Cognitive effects include Grade 2 cognitive disorder in one patient, Grade 2 delirium in one patient, and Grade 3 confusion in one patient.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; Supplementary Appendix.

CROWN: Summary of Adverse Events (long-term follow up)

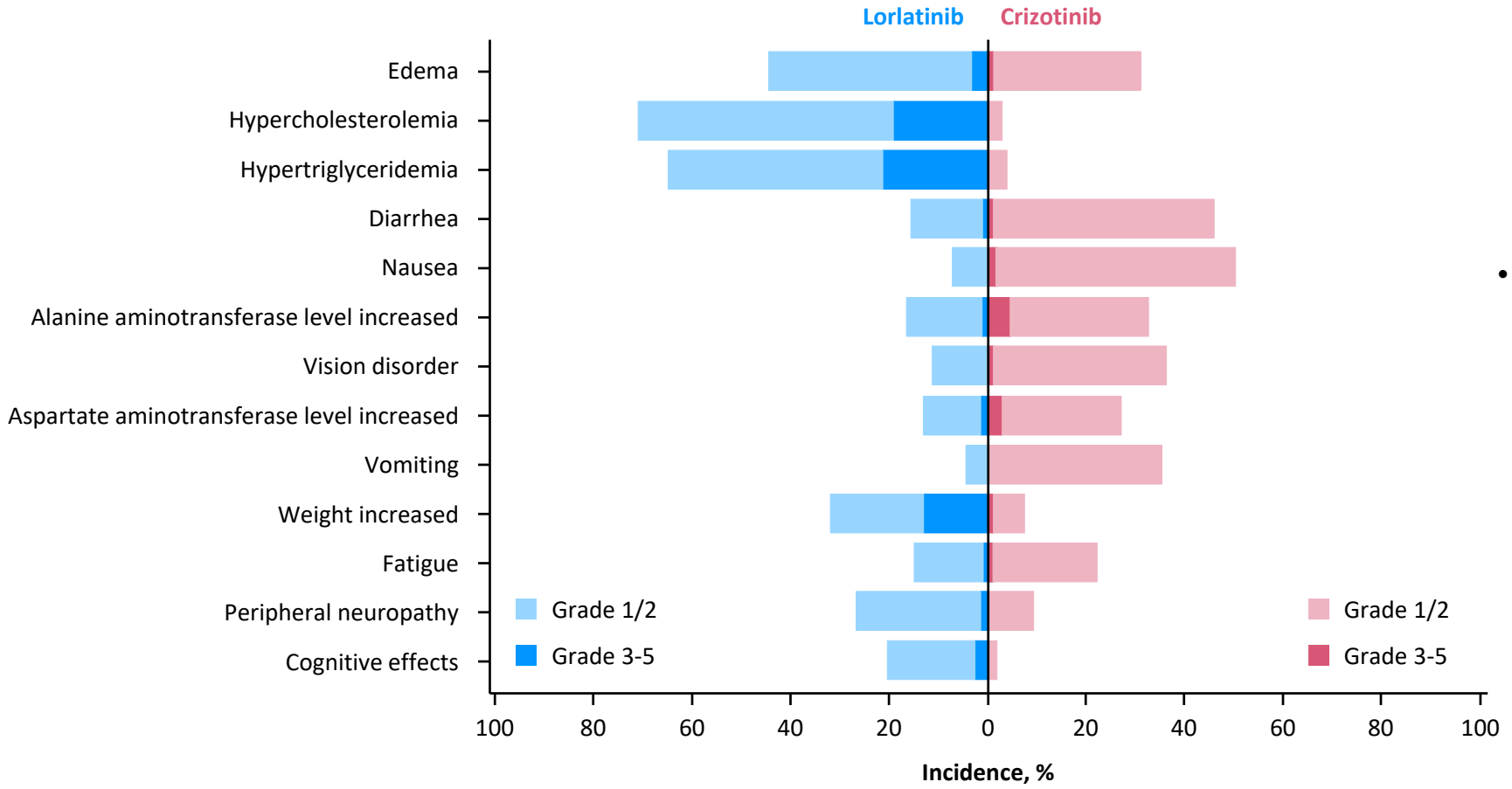
Event, n (%)	Lorlatinib (n = 149)	Crizotinib (n = 142)
Any-grade AE	149 (100.0)	140 (98.6)
Treatment related	145 (97.3)	133 (93.7)
Grade 3/4 AE	113 (75.8)	81 (57.0)
Treatment related	94 (63.1)	54 (38.0)
Death	10 (6.7)	7 (4.9)
Treatment related	2 (1.3)	0
Any serious AE	57 (38.3)	44 (31.0)
Treatment related	13 (8.7)	9 (6.3)
AEs leading to dose reduction	32 (21.5)	21 (14.8)
AEs leading to temporary discontinuations	84 (56.4)	69 (48.6)
AEs leading to permanent treatment discontinuation	11 (7.4)	14 (9.9)

- With longer follow-up, no new safety signals have emerged
- Grade 3/4 all-causality adverse events (AEs) occurred in 75.8% of patients in the lorlatinib arm and 57.0% in the crizotinib arm
- AEs leading to permanent treatment discontinuation were reported in 7.4% of patients in the lorlatinib arm and 9.9% in the crizotinib arm

Data cutoff: September 20, 2021. **Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months**. AE, adverse event.

Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Any Grade Treatment-Related Adverse Event in ≥20% of Patients within Either Treatment Arm (long-term follow up)



- Treatment-related cognitive effects occurred in 20.8% of patients in the lorlatinib arm; however, most (27 of 31) cognitive effects were grade 1/2 and no grade 4 event was observed

Data cutoff: September 20, 2021.
Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: CNS Adverse Events in the Lorlatinib Arm by Maximum Grade (post hoc analysis, safety population)

Adverse Event, n (%)	Lorlatinib (n = 149)			
	Grade 1	Grade 2	Grade 3	Total*
With any CNS adverse event†	32 (21)	15 (10)	5 (3)	52 (35)
Cognitive effects	20 (13)	9 (6)	3 (2)	32 (21)
Memory impairment	11 (7)	2 (1)	0	13 (9)
Disturbance in attention	5 (3)	2 (1)	0	7 (5)
Confusion	2 (1)	2 (1)	2 (1)	6 (4)
Amnesia	4 (3)	1 (1)	0	5 (3)
Cognitive disorder	1 (1)	1 (1)	1 (1)	3 (2)
Delirium	1 (1)	1 (1)	0	2 (1)
Disorientation	0	1 (1)	0	1 (1)
Mental impairment	1 (1)	0	0	1 (1)
Psychotic effects	4 (3)	1 (1)	0	5 (3)
Hallucination	3 (2)	0	0	3 (2)
Hallucination, visual	1 (1)	1 (1)	0	2 (1)
Hallucination, auditory	1 (1)	0	0	1 (1)
Delusion	1 (1)	0	0	1 (1)

CNS AEs (independent of causality) were reported in 52/149 (35%) patients receiving lorlatinib and in 15/142 (11%) patients who received crizotinib

*No patients had grade ≥4 CNS adverse events. †All causality.
COGNITIVE EFFECTS were any events from HLGT Cognitive and attention disorders and disturbances, Deliria (including confusion) or Mental impairment disorders; PSYCHOTIC EFFECTS were any events from SMQ narrow Psychosis and psychotic disorders or preferred term of Psychotic symptom. CNS, central nervous system.
Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278.

CROWN: CNS Adverse Events in the Lorlatinib Arm by Maximum Grade (post hoc analysis, safety population, cont.)

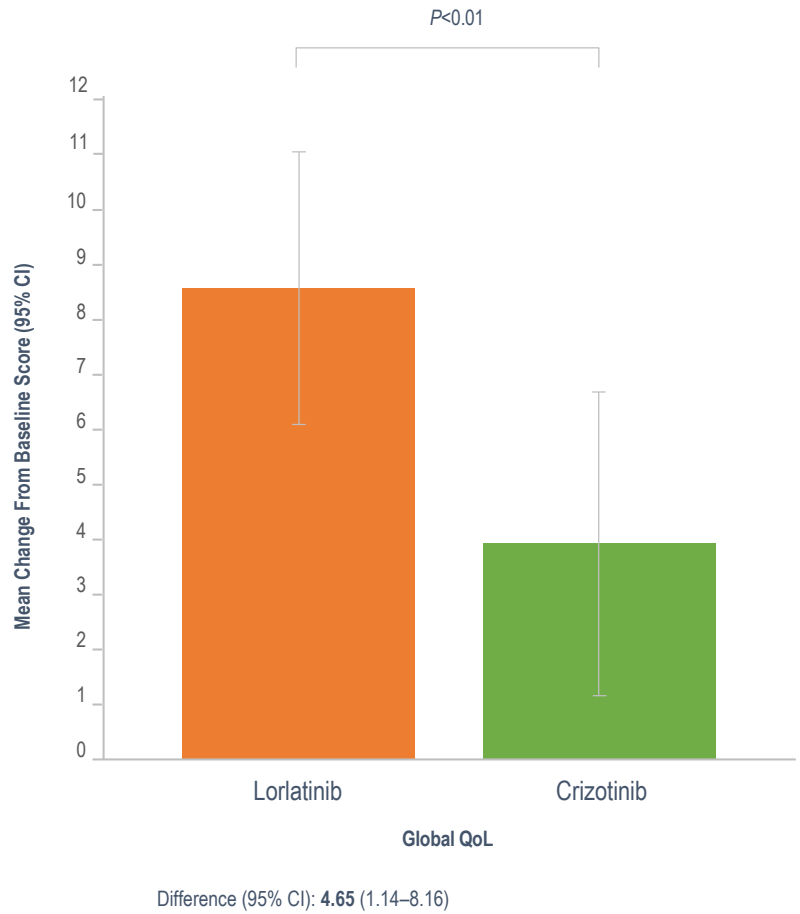
Adverse Event, n	Lorlatinib (n = 149)			
	Grade	Grade	Grade	
Mood effects	14 (9)	8 (5)	2 (1)	24 (16)
Anxiety	7 (5)	3 (2)	0	10 (7)
Depression	3 (2)	3 (2)	0	6 (4)
Affect lability	3 (2)	0	0	3 (2)
Affective disorder	1 (1)	1 (1)	0	2 (1)
Agitation	2 (1)	0	0	2 (1)
Irritability	1 (1)	0	1 (1)	2 (1)
Mood altered	2 (1)	0	0	2 (1)
Anger	0	1 (1)	0	1 (1)
Bipolar I disorder	0	0	1 (1)	1 (1)
Depressed mood	1 (1)	0	0	1 (1)
Depressive symptom	0	1 (1)	0	1 (1)
Euphoric mood	1 (1)	0	0	1 (1)
Mood swings	0	1 (1)	0	1 (1)
Stress	1 (1)	0	0	1 (1)

Adverse Event, n (%)	Lorlatinib (n = 149)			
	Grade 1	Grade 2	Grade 3	Total*
Speech effects	6 (4)	0	1 (1)	7 (5)
Dysarthria	4 (3)	0	0	4 (3)
Speech disorder	1 (1)	0	1 (1)	2 (1)
Slow speech	1 (1)	0	0	1 (1)

*No patients had grade ≥4 CNS adverse events.
MOOD EFFECTS were any events from HLGT Anxiety disorders and symptoms, Depressed mood disorders and disturbances, Manic and bipolar mood disorders and disturbances, Mood disorders and disturbances not elsewhere classified, or Personality disorders and disturbances in behavior; SPEECH EFFECTS were any events from HLT Speech and language abnormalities. CNS, central nervous system.

Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278.

CROWN: Change From Baseline in Global QoL Scores* (planned interim analysis)



*Using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30) in all patients who completed a baseline assessment and ≥1 post-baseline assessment.

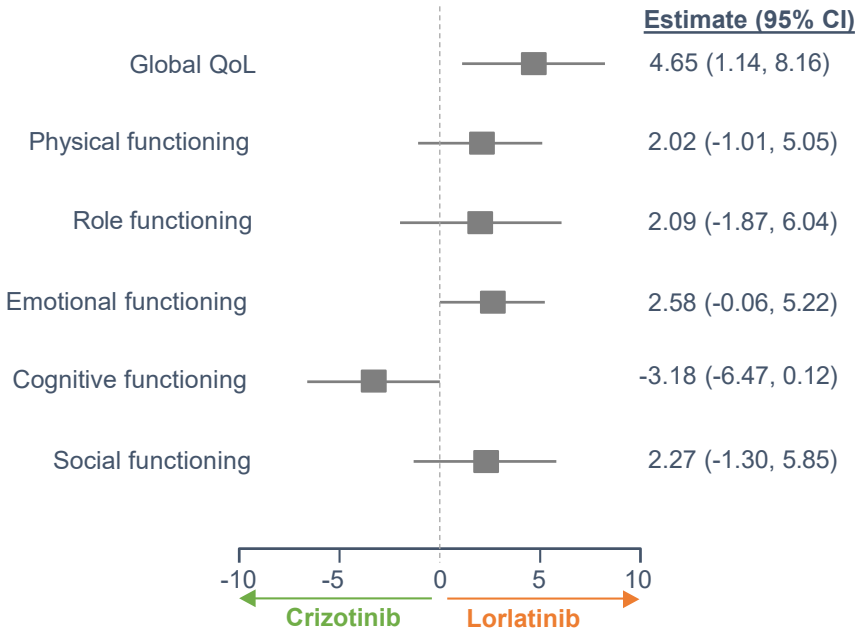
QoL, quality of life.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29; Supplementary Appendix.

CROWN: Differences In Change From Baseline Up To But Not Including EOT (Mixed Model*)

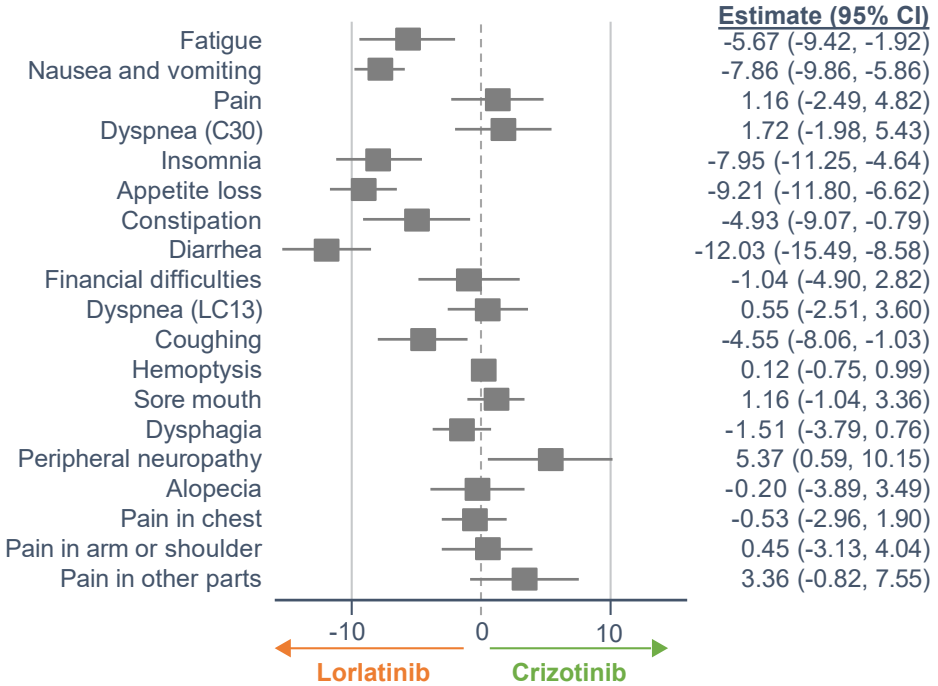
Clinical Data

EORTC QLQ-C30
(Global QoL and Functioning[a])



There were no differences between treatment arms in any functioning domain

EORTC QLQ-C30 and LC13
(Symptoms[b])



For diarrhea there was both a clinically meaningful and statistically significant difference favoring lorlatinib

Completion rates (defined as at least one question answered) were 100% at baseline and remained ≥96% through Cycle 18 in both treatment arms

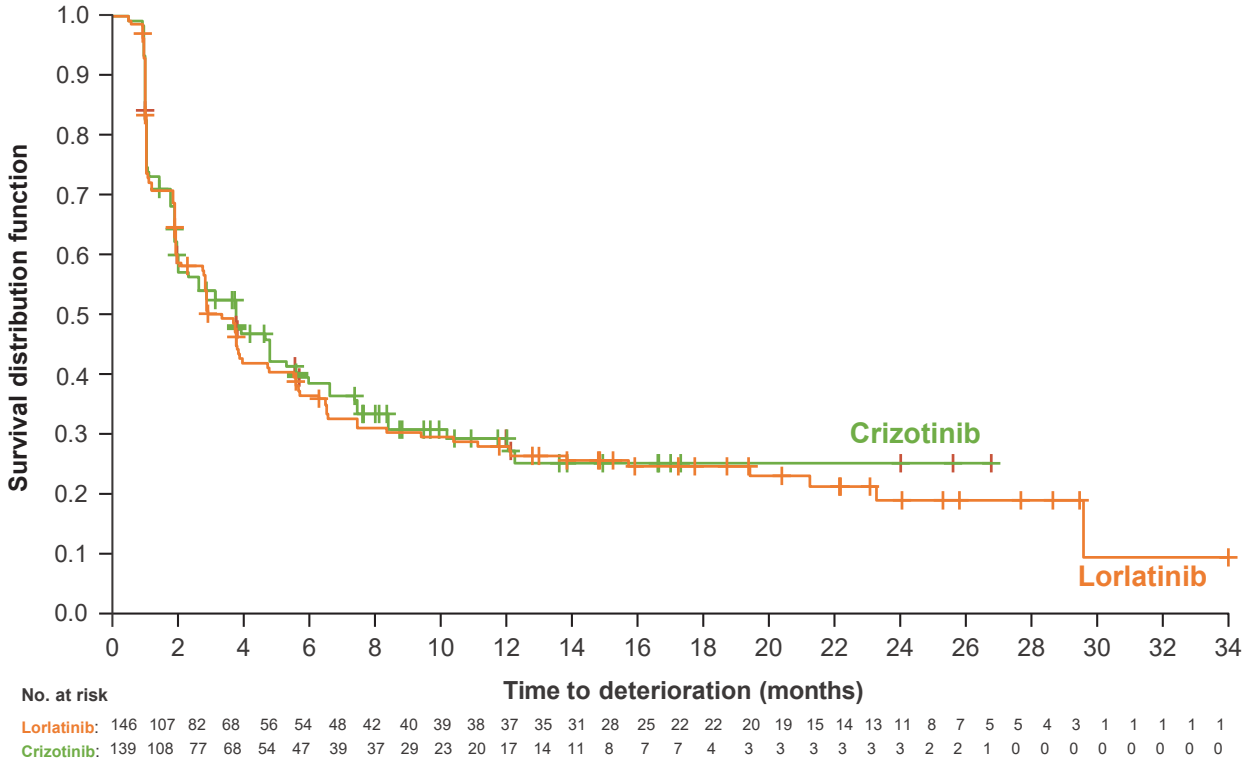
*Included patients in the EORTC QLQ-C30 PRO analysis set with a score at baseline and post-baseline assessment. Analysis based on random-intercept, random-slope, mixed-effects model with an intercept term, treatment, time (as a continuous variable), treatment-by-time, baseline and randomization stratification factors as covariates. Analysis model included post-baseline assessments up to EOT, but not including EOT. [a]Higher scores indicate greater global quality of life and functioning. [b]Higher scores indicate a greater presence of symptoms.

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire; EOT, end of treatment; QoL, quality of life.

Mazieres J, et al. Oral presentation at: WCLC Virtual Congress. January 28-31, 2021. Abstract MA11.08.

CROWN: Time to Deterioration in Composite Endpoint*

Clinical Data



Lorlatinib: Median 3.3 months (95% CI 2.1–4.7)
Crizotinib: Median 3.7 months (95% CI 2.0–5.5)

Hazard ratio 1.09 (95% CI 0.822–1.444; 1-sided *P* = 0.7293)

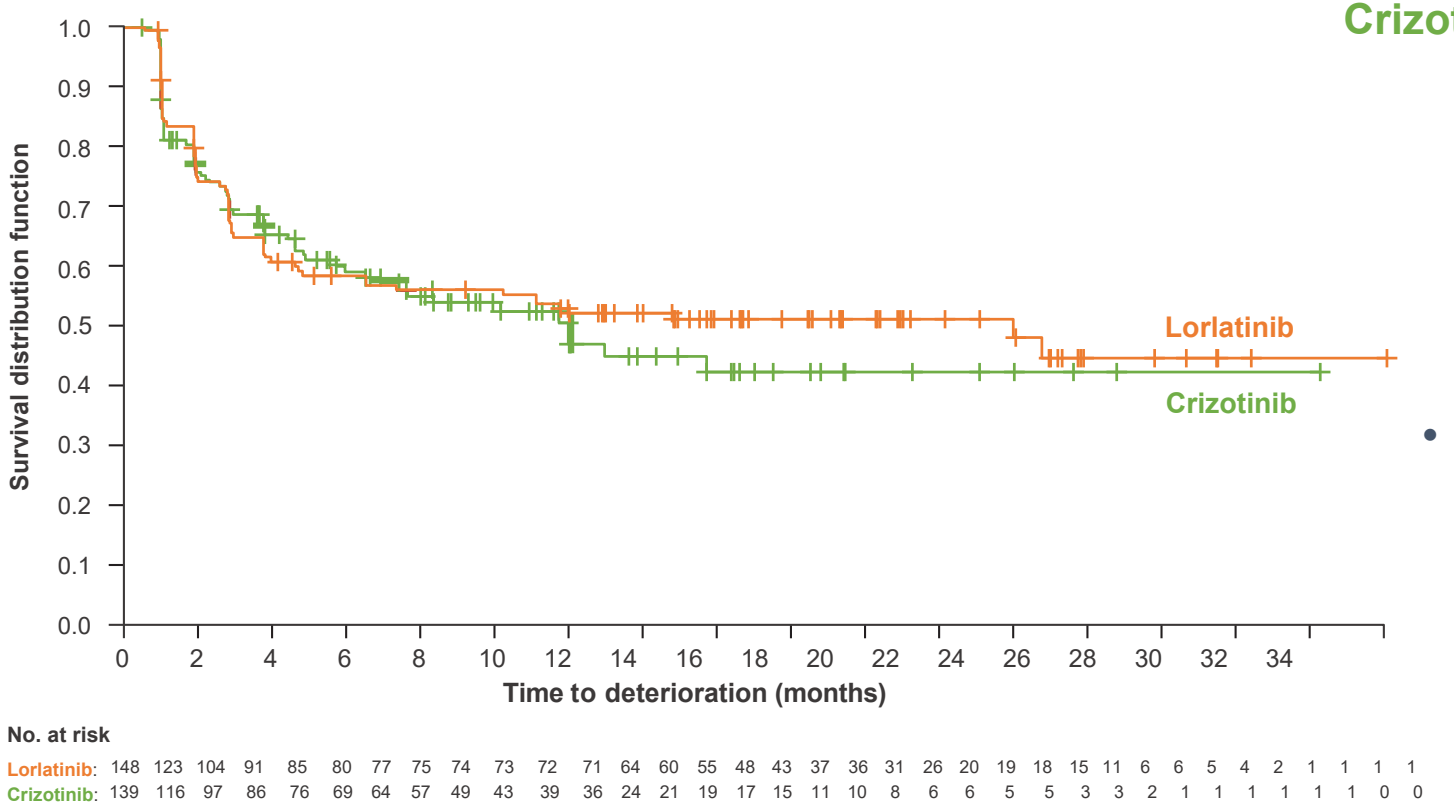
- There was no significant difference in time to deterioration in composite endpoint between lorlatinib and crizotinib

*Composite endpoint of lung cancer symptoms: cough, dyspnea, and pain in chest.
Mazieres J, et al. Oral presentation at: WCLC Virtual Congress. January 28-31, 2021. Abstract MA11.08.

CROWN: Time to Deterioration in Global QoL

Clinical Data

Lorlatinib: Median 24 months (95% CI: 6.5–NE)
Crizotinib: Median 12 months (95% CI: 6.5–NE)



Hazard ratio 0.92 (95% CI: 0.650–1.294 1-sided P = 0.3127)

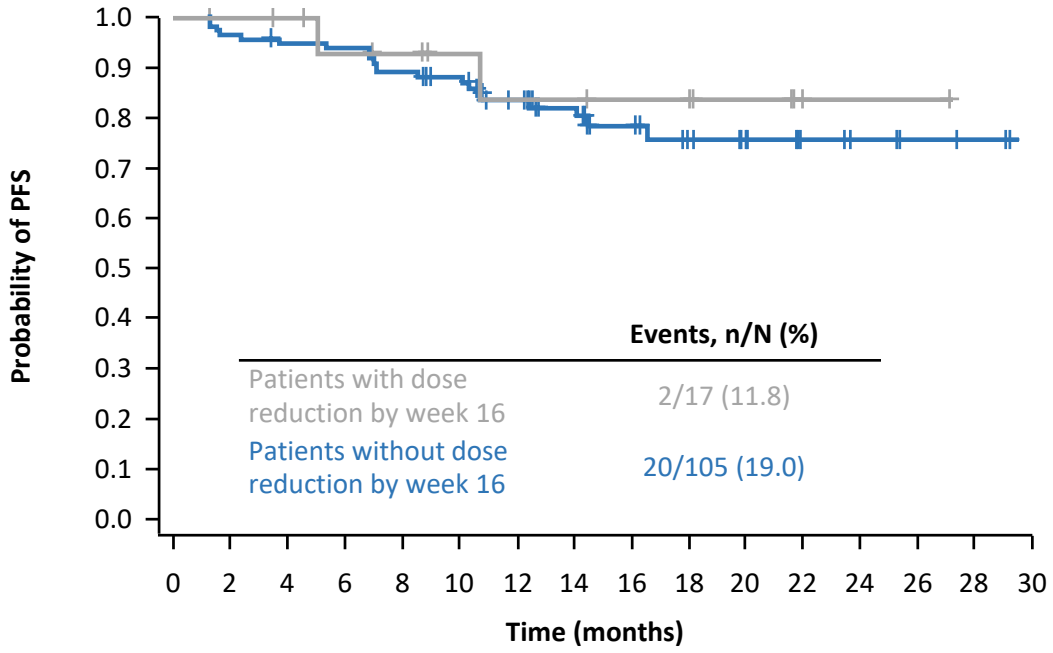
- There was no significant difference in time to deterioration in global QoL between lorlatinib and crizotinib

QoL, quality of life.

Mazieres J, et al. Oral presentation at: WCLC Virtual Congress. January 28-31, 2021. Abstract MA11.08.

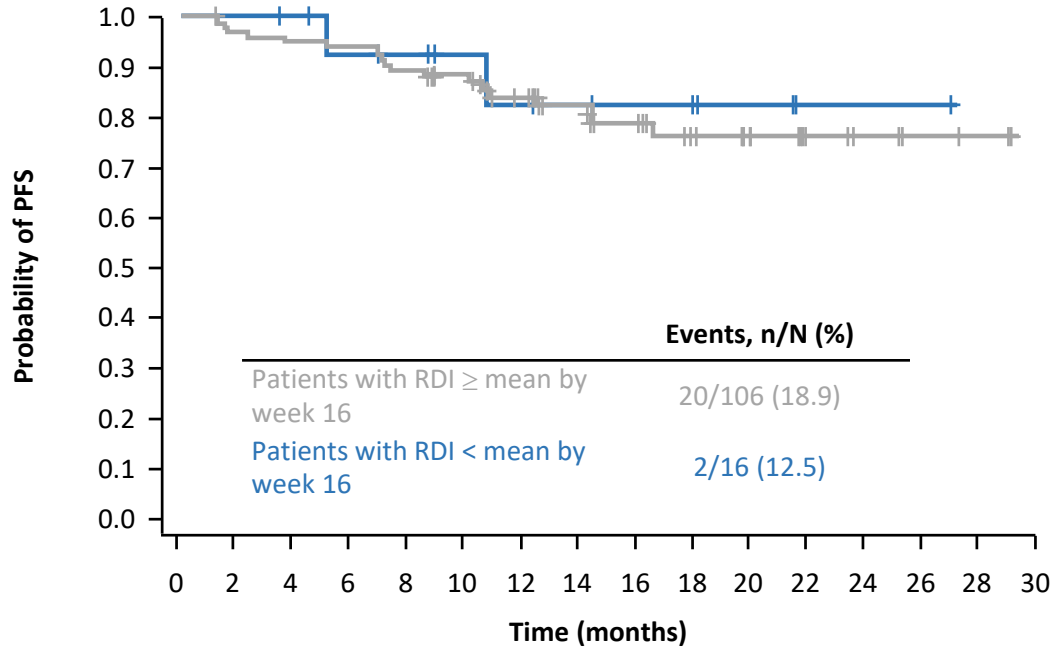
CROWN: Landmark Analysis of PFS per BICR Assessment by First Lorlatinib Dose Reduction and Mean RDI Within 16 Weeks (ITT Population)

PFS by First Lorlatinib Dose Reduction



No. at risk:																
Pts w/ reduction	17	17	16	14	13	10	9	8	6	6	4	1	1	1	0	0
Pts w/o reduction	105	101	98	97	92	82	63	51	36	25	16	10	7	3	2	0

PFS by Mean RDI



No. at risk:																
≥ mean	106	102	99	98	93	83	64	52	37	26	17	10	7	3	2	0
< mean	16	16	15	13	12	9	8	7	5	5	3	1	1	1	0	0

BICR, blinded independent central review; ITT, intent to treat; PFS, progression-free survival; RDI, relative dose intensity.

Solomon BJ, et al. *J Clin Oncol*. 2022; JCO2102278. Supplementary appendix.

Pristup lečenja ALK+NSCLC pacijenata sa CNS metastazama - prikaz slučaja

NS prim. dr sci. med Natalija Samardžić

Klinika za pulmolgiju UKCS

Beograd, 01.07.2022.

CNS metastaze kod ALK+ NSCLC

- Visoka incidenca **CNS metastaza** (MTS) NSCLC: ~ **30 % u momentu postavljanja dijagnoze**
  ~ 60% tokom lečenja
- Veća incidenca pojave CNS MTS kod pacijenata sa prisutnom ALK ekspresijom u odnosu na ostale NSCLC *driver* mutacije
- CNS MTS: Loša prognoza i kvalitet života
- Pacijenti sa inicijalnim CNS MTS imaju kraće ukupno preživljavanje (OS) u poredjenju sa onima koji MTS razviju kasnije (4.8 vs 9.8 meseci)
- **Terapijski pristup**
  - Lokalni tretman: operacija (OP) i radioterapija (RT)
  - Sistemska terapija (target)

  Cilj terapije, multidisciplinarni pristup:
  - Lokalna kontrola
  - Dobar kvalitet života i neurološke funkcije
  - Poboljšano preživljavanje

Najpoželjnije sekvencijalno ili kombinovano lečenje

ALK TKI

1. Generacija**: Krizotinib**
2. Generacija**: Alektinib, Brigatinib, Ceritinib**
3. Generacija**: Lorlatinib**

- Hemoterapija (HT) ima limitiranu intrakranijalnu (IC) aktivnost
  - IC stopa odgovora (*responce rate-RR*) ~ 27%, mPFS of 4.0-7.0 meseci sa IC MTS
- ALK tirozin kinazni inhibitori (TKI) su preporučeni za lečenje ALK+NSCLC
  - Krizotinib, ceritinib, alektinib, brigatinib, lorlatinib su opcija lečenja u 1L i 2L, u SAD i Evropi
- ALK TKI Krizotinib je prvi registrovan i dugo vremena zlatni standard lečenja ALK+ NSCLC, ali je klinička praksa pokazala nisku CNS efikasnost
- **Vodeći evropski i američki (ESMO i NCCN)** vodiči preporučuju 2. i 3. generaciju ALK TKI za 1L i ≥2L kod ALK+ NSCLC sa CNS metastazama

Solomon BJ, et al. *J Clin Oncol.* 2016;34:2858-2865; 2. Soria JC, et al. *Lancet*. 2017;389:917-929; 3. Economopoulou P, Mountzios G. *Transl Lung Cancer Res.* 2016;5:588-598; 4. Zhang I, et al. *Lancet Oncol.* 2015;16:e510-e521; 5. US Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-brigatinib-alk-positive-metastatic-nsclc. Accessed October 19, 2021; 6. Takeda Oncology
ALK- anaplasic lymphoma kinase; NSCLC- non-small cell lung cancer; BM- brain metastase;

[1]Johung et al.JCO 2016; [2]Nayak et al. Curr Oncol Rep. 2012 ; [3]Peters et al.Cancer Treat Rev 2016; [4]Walkers et al. Clin Lung Cancer 2017

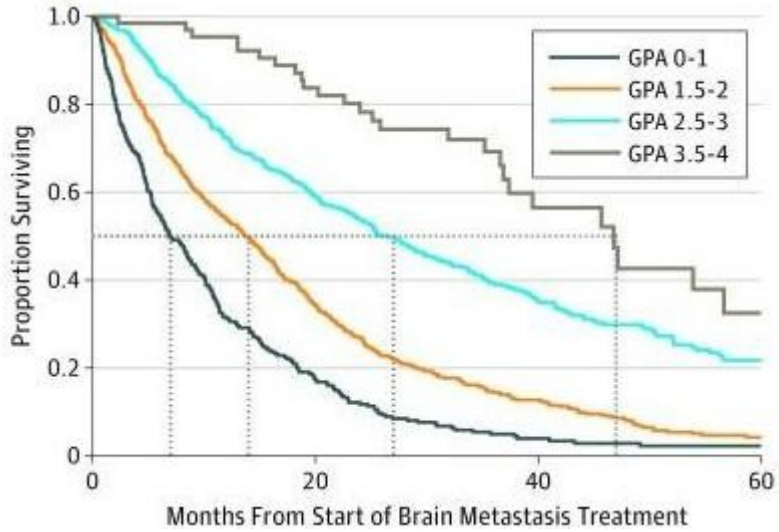
Gainor JF, et al. *J Thorac Oncol*. 2013;8:1570-1573; 2. Zhang I, et al. *Lancet Oncol*. 2015;16:e510-e521; 3. Johung KL, et al. *J Clin Oncol*. 2016;34:123-129; 4. Rangachari D, et al. *Lung Cancer*. 2015;88:108-1114; 5. Peters S, et al. *Cancer Treat Rev*. 2016;45:139-162; 6. Davies J, et al. *Curr Med Res Opin*. 2019;35:535-542; 7. Walker MS, et al. *Clin Lung Cancer*. 2017;19:139-147; 8. Costa DB, et al. *J Clin Oncol*. 2015;33:1881-1888; 9. Ali A, et al. *Curr Oncol*. 2013;20:e300-e306.

Prognostički faktori NSCLC sa CNS metastazama

Preživljavanje:
- Nelečene CNS MTS: mOS 1-2-meseca
- WBRT 4-6 meseca
- Sistemska (HT) terapija: 7-8 meseci

(Lung-mol)GPA:
- Starosna dob
- Ekstrakranijalne metastaze
- CNS MTS
- Karnofsky Performance Status
- Genske alteracije

Prognostic Factor	GPA Scoring Criteria[a]		
	0	0.5	1.0
Age, y	≥70	<70	NA
KPS	<70	80	90-100
ECM	Present		Absent
Brain metastases, No.	>4	1-4	NA
Gene status	*EGFR* neg/unk and *ALK* neg/unk	NA	*EGFR* pos or *ALK* pos



Lung-mol GPA[4]	0-1.0	1.5-2.0	2.5-3.0	3.5-4.0
mOS,m	6.9	13.7	26.5	46.8

BM- brain metastases; WBRT- whole brain radiotherapy; GPA- Graded Prognostic Assessment

[1]Zimm et al.Cancer. 1981; [2]Mehta et al. J Clin Oncol. 2003; [3]Brown et al. Neuro Oncol. 2013; [4]Sperduto et al. JAMA oncol 2017

Kvalitet života NSCLC pacijenata sa CNS MTS

CNS MTS ima negativan impact na HRQOL!

- Podaci ALKConnect baze podataka:

  QoL na trećem mestu po važnosti za pacijenta tokom procesa lečenja (PFS i RR prema prioritetu)

Opservaciona studija u SAD:

PRO uznapredovalog NSCLC sa/bez CNS MTS tokom godinu dana/FU

- CNS MTS: značajno lošiji rezultati (*P* <.02) HRQOL poredeći sa ostalim metastatskim lokalizacijama (izuzev MTS kostiju)

•PRO: S i g n i f i k a n t n o z n a č a j n a r e z l i k a (*P* <.05) u Q o L pacijenata sa CNS metastazama prisutnim inicijalno pri postavljanju dijagnoze bolesti

Terapijski pristup lečenja CNS metastaza kod ALK+NSCLC

Mogućnosti:

- Operacija (OP)
- Whole-brain radiation therapy (WBRT)
- Stereotaktična radiohirurgija (SRS)

Prednosti kombinovane WBRT i SRS u odnosu na SRS:

- Poboljšanje lokalne kontrole CNS
- Preživljavanje nije poboljšano
- Viši rizik od neurokognitivnih komplikacija

Efficacy Outcomes[3]	SRS + WBRT (n = 28)	SRS (n = 30)	*P*
OS			
Median OS, months	5.7	15.2	.003
1-year OS rate, %	21	63	.003
HR of death (95% CI)	2.47 (1.34-4.54)		.0036
1-Year local control rate, %	100	67	.012
1-Year distant control rate, %	73	45	.02
1-Year freedom from CNS recurrence, %	73	27	.0003

SRS:

- Približno preživljavanje uz bolju toleranciju u odnosu na WBRT
- Rizik od komplikacija (radijaciona nekroza)

(SRS: precizni tretman selektovanih promena visokim dozama zračenja, jednako efektivno kao i hirurški tretman u lokalnoj kontroli bolesti)

A Cochrane review: WBRT u odnosu na ostale terapijjske režime(novodijagnostikovanih CNS MTS):
Lošiji neurokognitivni ishodi , bez razlike u ukupnom peživljavanju u odnosu na aditivnu WBRT radiohirurgiji

WBRT- whole brain radiotherapy; SRS- stereotactic radiosurgery; CNS- central nervous system; BM- brain metastases; OS- overall survival

[1]Langer et al.2005; [2] Pirzkall et al. 1998; [3]Chang et al. 2009; [4]Aoyama et al.2006; [5]Minniti et al.2016; [6]Hughes et al. 2019; [7]Li et al. 2020; [8]Tsao et al.2018; ;[9]Churilla et al., 2019

Efikasnost Krizotiniba CNS MTS ALK+ NSCLC:

Faza 1: ORR 61%; mPFS 9.7 M

2L faze 3: mPFS 7.7M vs 3.0 m (HR 0.49; P<0.001)

1L faze 3: mPFS 10.9 mMvs 7.0 m (HR 0.45; P<0.001)

Ipak: Svi pacijenti progrediraju

- Do 60% razvije CNS MTS tokom terapije Crizotinibom
- Krizotinib ima limitiranu CNS aktivnost: niska koncnetracija u CNSu
  - Loša penetracija kroz hemato-encefalnu barijeru
  - Povišen efluks iz CNS-a (pGP supstrat)

Pulovane analize PROFILE 1005 i 1007:

ORR (18 vs. 53%),

DOR (26.4 vs. 47.9 nedelja), i

TTP (7.0 vs. 12.5 meseci)

Lošiji rezultati kod IC lezija u odnosu na EC

Brain progression rate (20 vs. 72%) u pacijenata sa BM vs BM baseline

CNS predstavlja dominantno mesto progresije kod ALK – pozitivnih pacijenata lečenih Krizotinibom

Anti-CNS MTS efekat kod ALK+ NSCLC ne zadovoljava

ORR- objective response rate; mPFS- median progression free survival; BM- brain metastases; CNS- central nervous system; DOR- duration of response; p-GP- P glycoprotein; IC- intracranial; TTP- time to progression; NSCLC- non-small cell lung cancer

[1]Camidge et al. 2012; [2]Shaw et al. 2013; [3]Solomon et al 2015; [4]Zhang et al. 2015; [5]Costa et al. 2011; [6]Baik et al. 2015

Tirozin kinazni inhibitori kod ALK+ NSCLC

Duže preživljavanje kod ALK+ NSCLC (sa/bez CNS MTS):

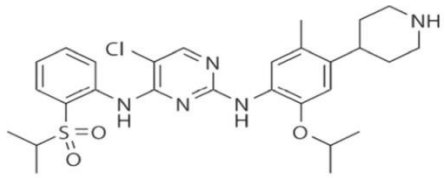
- Potvrdjena efikasnost, kvalitet života, pošteda kognitivnih funkcija
- OP i ili/RT CNS MTS mogu biti odložene (redukovanje komplikacija izazvane ovim tretmanima)
- SRS se preporučuje (toksičnost WBRT)

Dizajnirani lekovi – ALK TKI 2. i 3. generacija

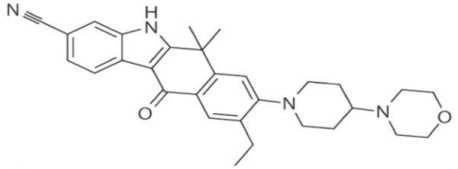
Bolja hemato-encefalna penetracija: preovladjuje makrociklična struktura

-P-GP supstrat (interakcije)

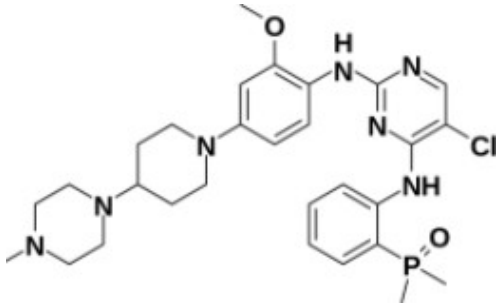
ceritinib



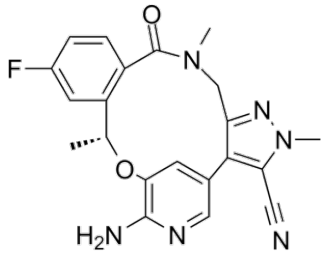
alectinib



brigatinib



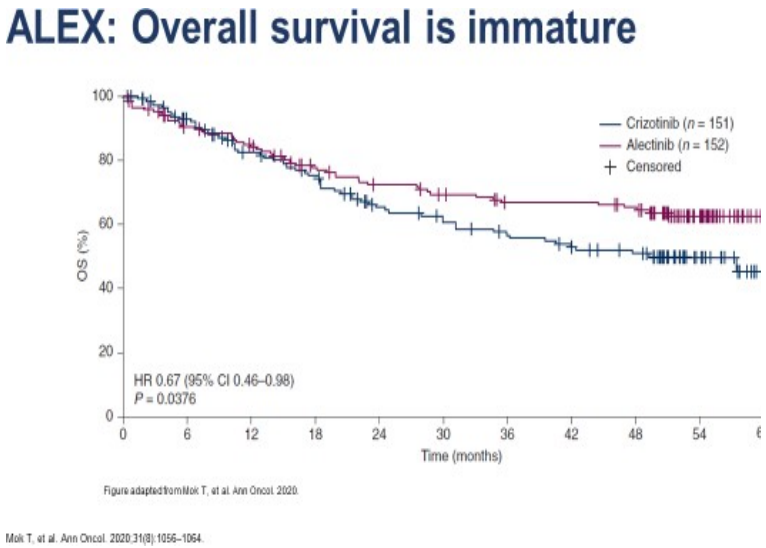
lorlatinib



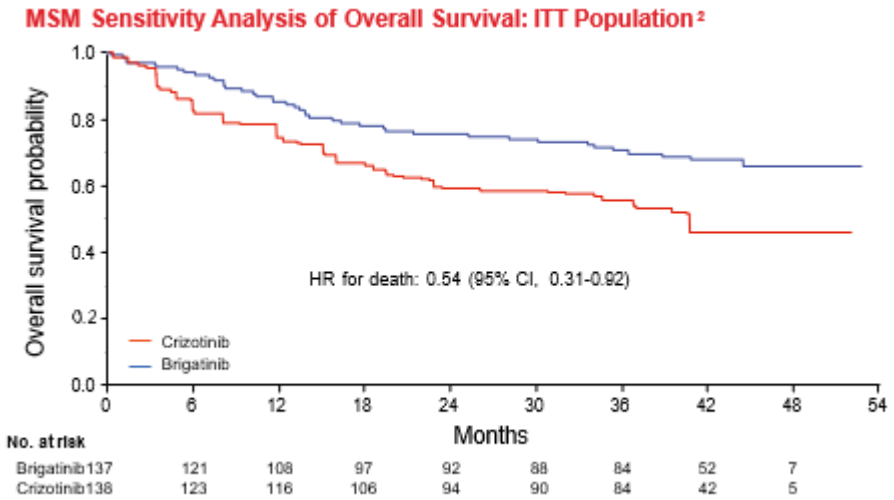
NSCLC- non-small cell lung cancer ; BM- brain metastases; WBRT- whole brain radiotherapy; SRS- stereotactic radiosurgery; TKI- tyrosine kinase inhibitors; p-GP- P glycoprotein

[1]Dempke et al. 2015; [2]Lexicomp Drug Interactions

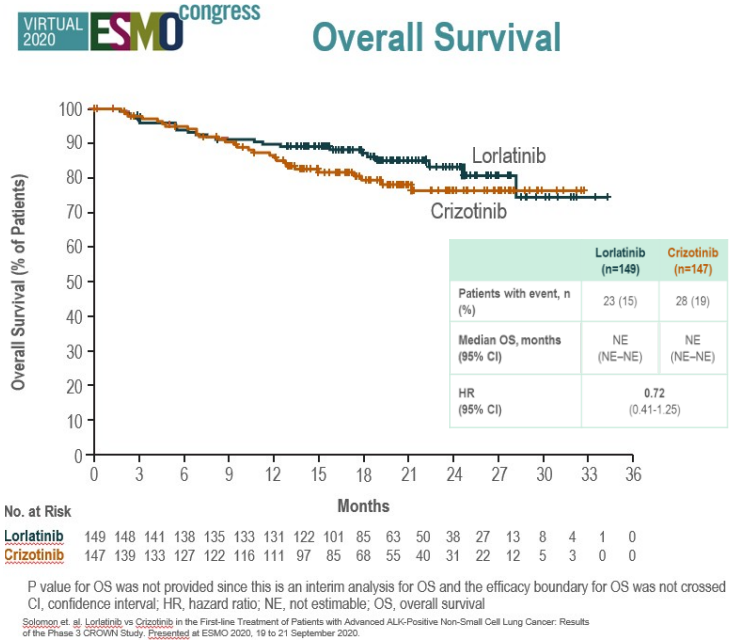
Ukupno preživljavanje ALK(+) NSCLC - prednost 2. i 3. generacije ALK TKI
ALEX, ALTA, CROWN



Mok T, et al. Ann Oncol. 2020;31(8):1056–1064.



Camidge et al J Thoracic Oncol . 2021;16(12):2091-2108.



P value for OS was not provided since this is an interim analysis for OS and the efficacy boundary for OS was not crossed
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival

Solomon et. al. Lorlatinib vs Crizotinib in the First-line Treatment of Patients with Advanced ALK-Positive Non-Small Cell Lung Cancer: Results of the Phase 3 CROWN Study. Presented at ESMO 2020, 19 to 21 September 2020.

Alektinib vs. Krizotinib
HR 0.67

Brigatinib vs. Krizotinib
HR 0.54

Lorlatinib vs. Krizotinib
HR 0.72;

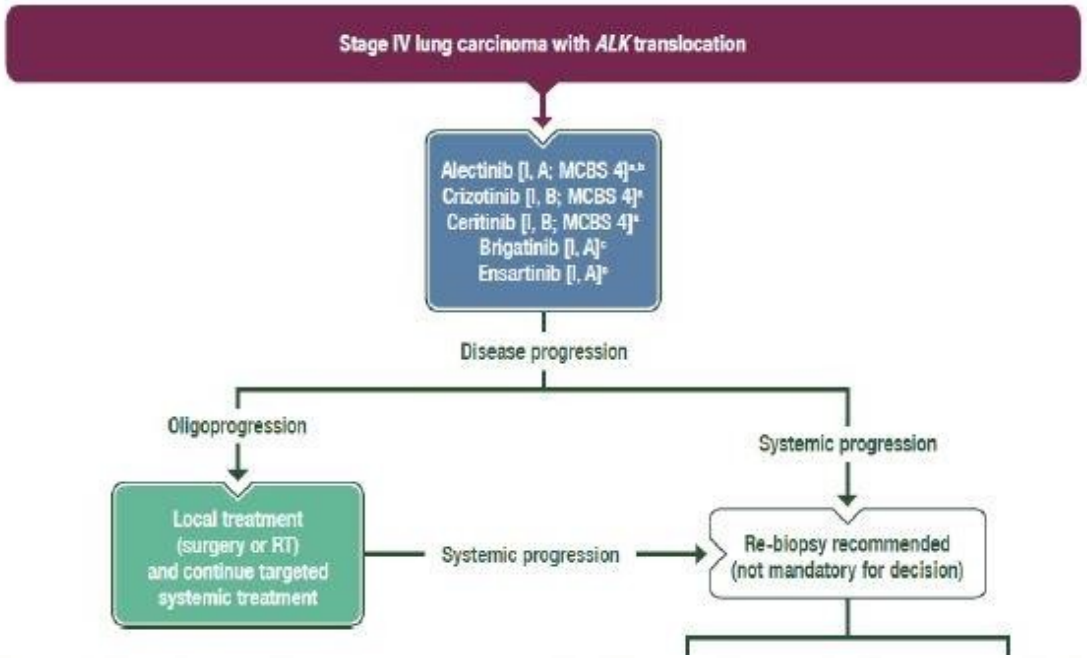
Presented data may contain information about medicines which are still not registered in EU and/or Adriatic countries and are for educational purposes only.

ESMO Klinički vodič - preporuke za lečenje 1L ALK+ NSCLC

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Updated version published 15 September 2020 by the ESMO Guidelines Committee

Figure 5. Treatment algorithm for stage IV lung carcinoma with ALK translocation.



[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[b]Preferred option [203a].
[c]Not EMA-approved.

*Brigatinib was approved as a first-line treatment for advanced *ALK*+ NSCLC in April 2020 by the EMA and in May 2020 by the FDA
MCBS = magnitude of clinical benefit scale

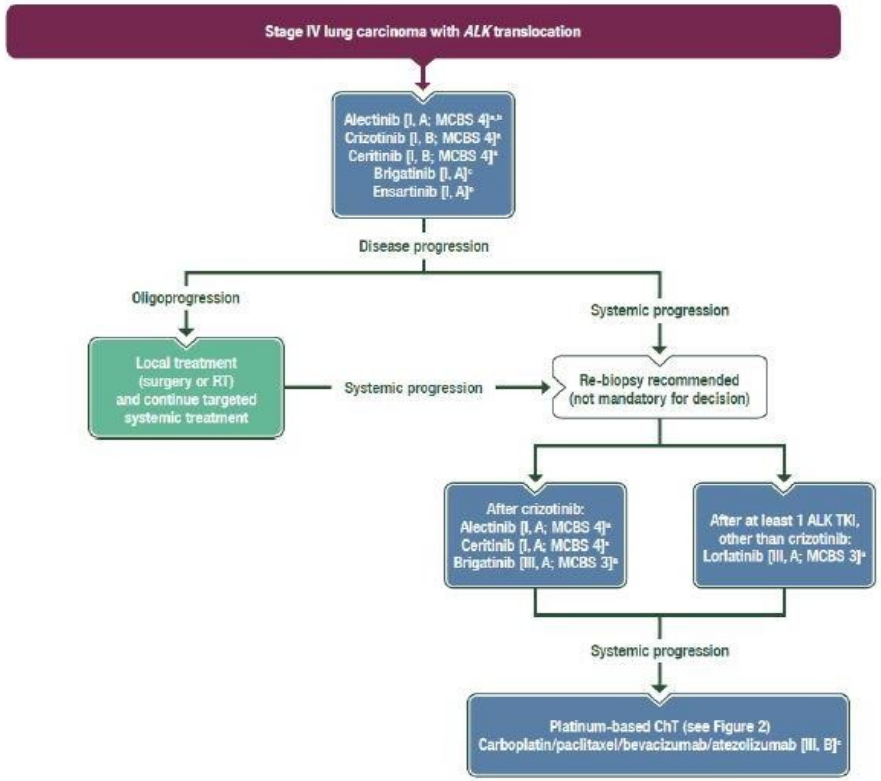
1. NCCN NSCLC guidelines V8 2020
2. Planchard, et al. Ann Oncol 2018 (last updated September 2020)

Tip progresije bolesti (oligo/sistemska progresija) odredjuje dalje lečenje – preporučuju klinički vodiči

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Updated version published 15 September 2020 by the ESMO Guidelines Committee

Figure 5. Treatment algorithm for stage IV lung carcinoma with ALK translocation.

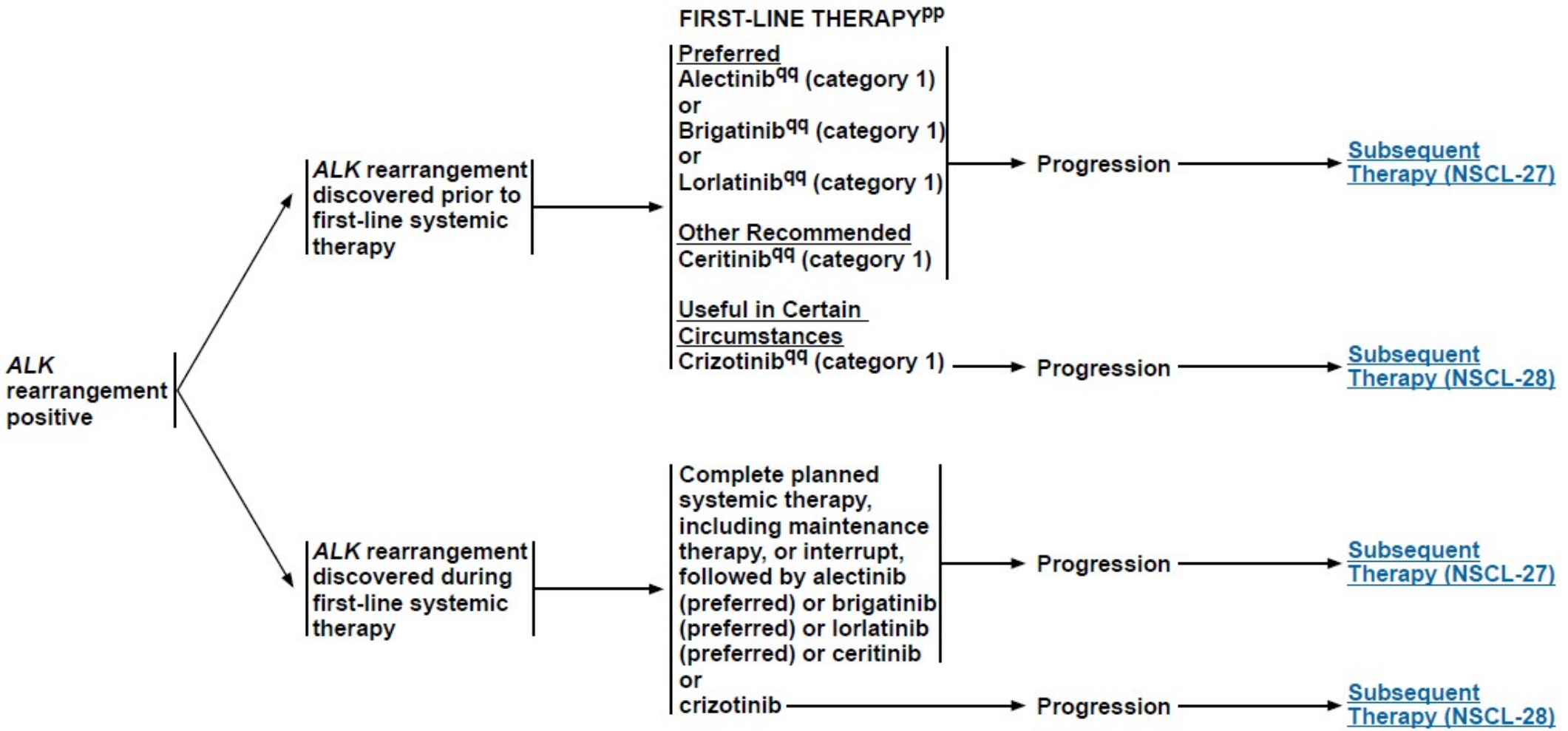


[a]ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA since 1 January 2016. The score has been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee.
[b]Preferred option [203a].
[c]Not EMA-approved.

*Brigatinib was approved as a first-line treatment for advanced *ALK*+ NSCLC in April 2020 by the EMA and in May 2020 by the FDA
MCBS = magnitude of clinical benefit scale

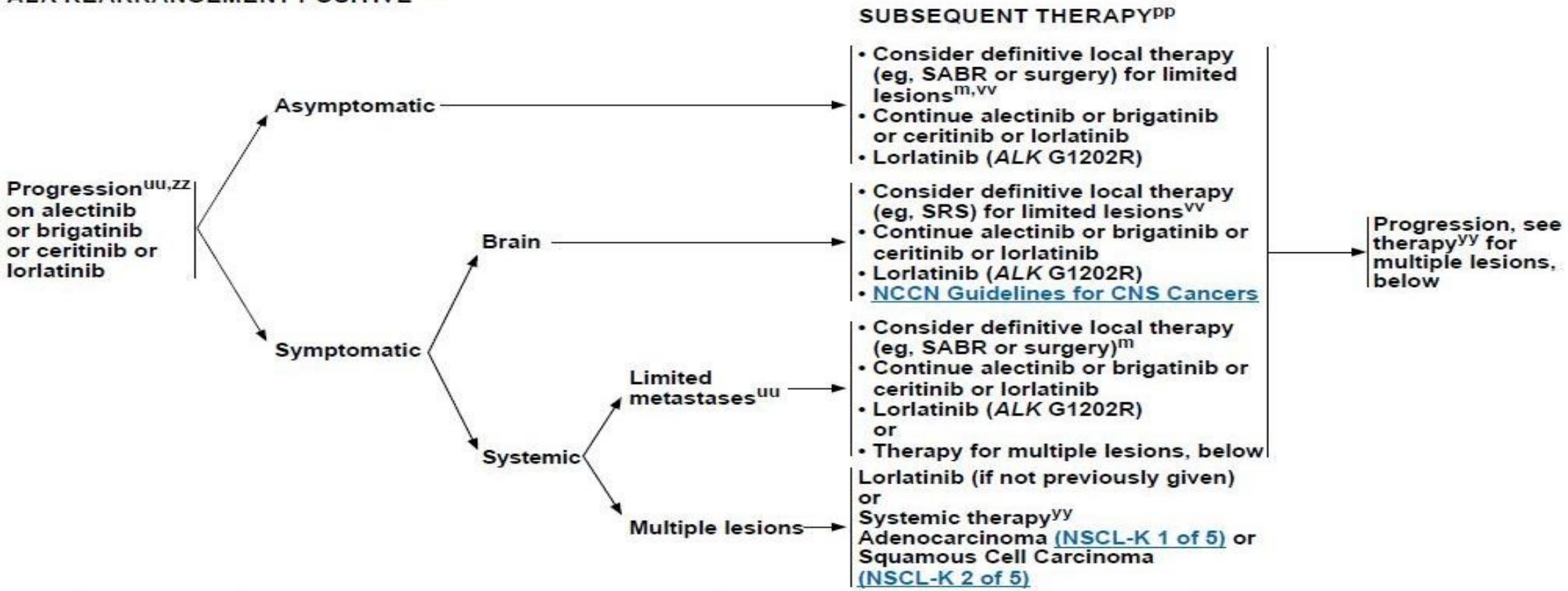
1. NCCN NSCLC guidelines V8 2020
2. Planchard, et al. Ann Oncol 2018 (last updated September 2020)

ALK REARRANGEMENT POSITIVE[mm]



See Evidence Blocks on NSCL-34A

ALK REARRANGEMENT POSITIVE[mm]



[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.

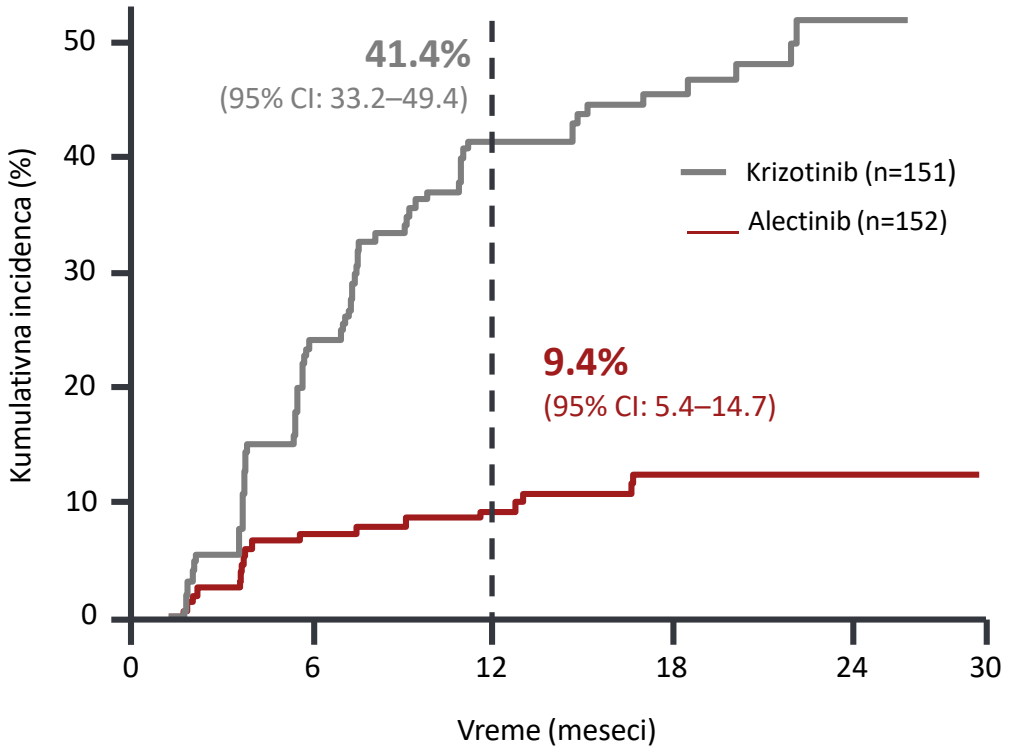
[yy] The data in the second-line setting suggest that PD-1/PD-L1 inhibitor monotherapy is less effective, irrespective of PD-L1 expression, in *EGFR exon 19* deletion *or L858R, ALK+* NSCLC.

[zz] Plasma or tissue-based testing via broad molecular profiling should be considered at progression for genomic resistance mechanisms. If plasma-based testing is negative, tissue-based testing with rebiopsy material is strongly recommended. Practitioners may want to consider scheduling the biopsy concurrently with plasma testing referral.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Alektinib je demonstrirao izrazito CNS protektivno dejstvo

	Alektinib (n=152)	Krizotinib (n=151)
Pacijenti sa događajem, n (%)	18(12)	68 (45)
Koeficijent rizika HR	**0.16** (95% CI: 0.10–0.28) p<0.0001	



Peters, et al. N Engl J Med 2017
Shaw, et al. ASCO 2017

PFS prema statusu CNS metastaza pre započinjanja terapije

Pacijenti sa CNS metastazama pre započinjanja terapije

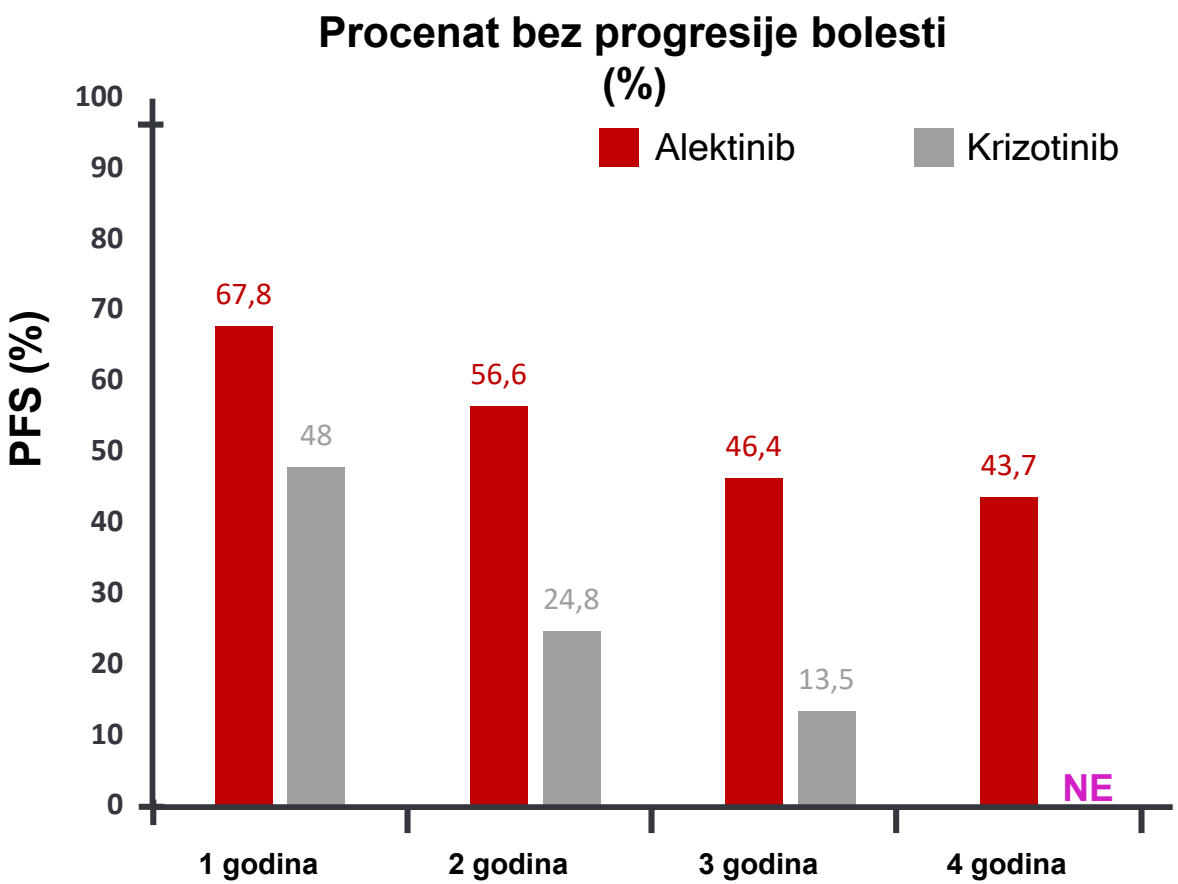
	Alektinib (n=64)	Krizotinib (n=58)
Medijana PFS (95% CI)	**25.4** (9.2–NE)	**7.4** (6.6–9.6)
HR (95% CI)	**0.37** (0.22–0.56)	

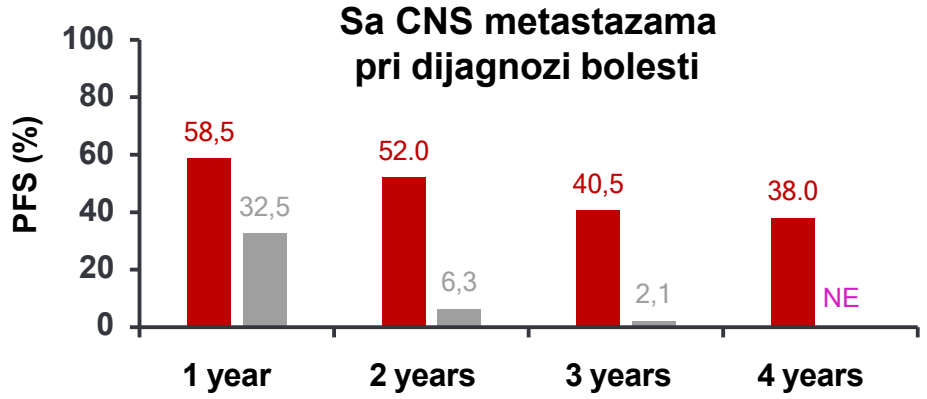
Pacijenti bez CNS metastaza pre započinjanja terapije

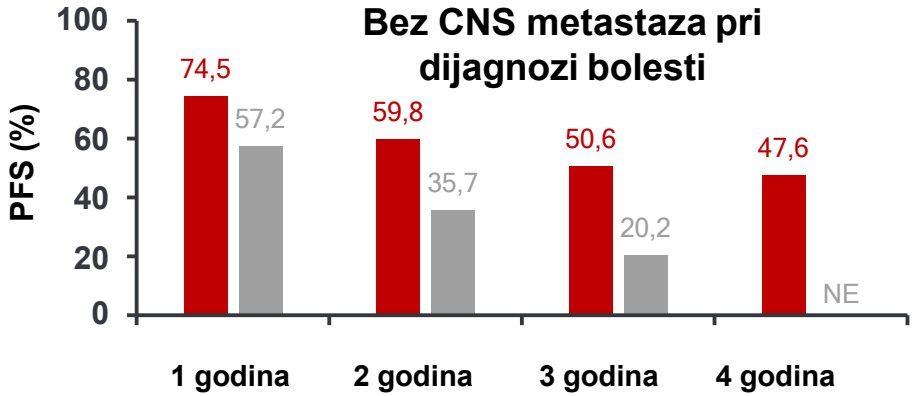
	Alektinib (n=88)	Krizotinib (n=93)
Medijana PFS (95% CI)	**38.6** (22.4–NE)	**14.7** (10.8–20.3)
HR (95% CI)	**0.46** (0.32–0.71)	

Mok, et al. ESMO 2019
Updated data cut-off (1 December 2017)

ALEX: Procenat pacijenata koji nisu doživeli progresiju bolesti (i dalje su na terapiji)







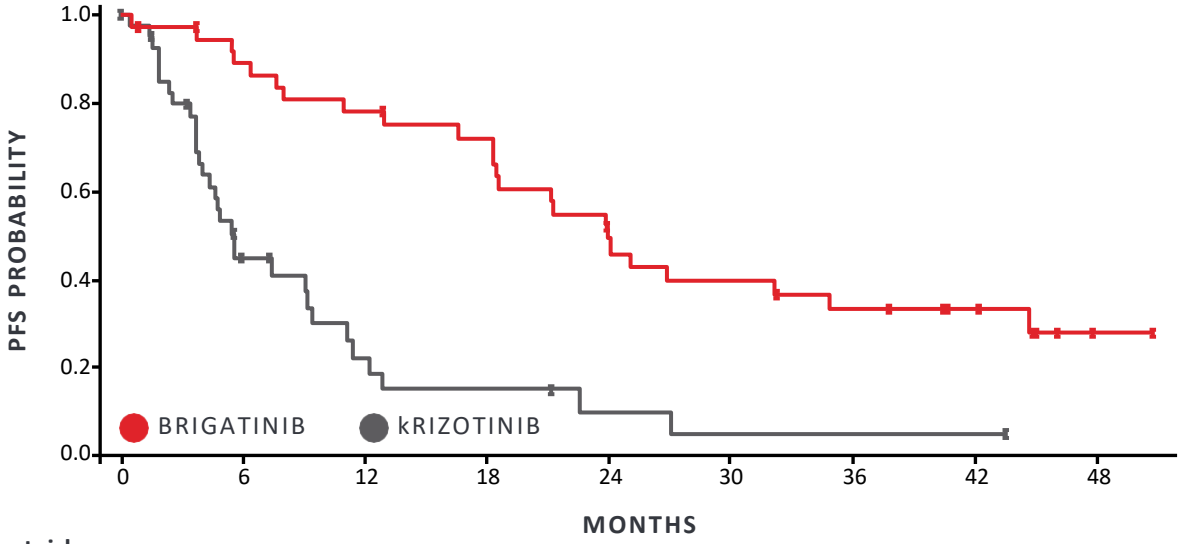
NE = not estimable
Exploratory data cut-off 2 (30 November 2018)
CNS = central nervous system; ITT = intention-to-treat; NE = non evaluable; PFS = progression-free survival

Mok, et al. ESMO 2019

Brigatinib ALTA-1L Trial

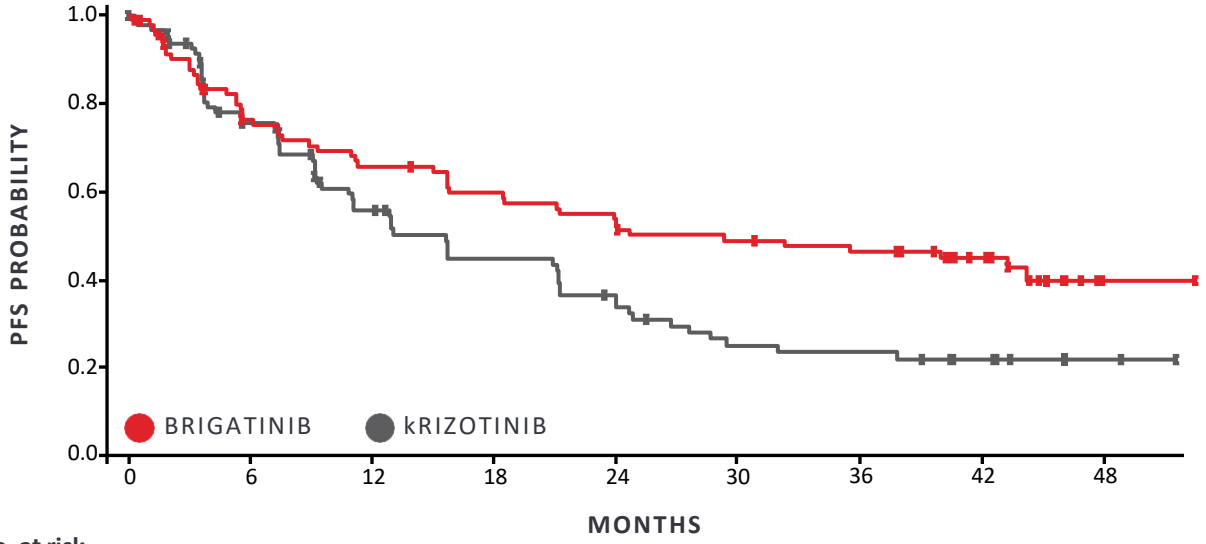
PFS: CNS MTS *inicijalno pre početka primene terapije* (BIRC)

Patients With Any Brain Metastases at Baseline



No. at risk									
Brigatinib	40	32	28	25	15	13	10	7	1
Crizotinib	41	15	6	4	2	1	1	1	0

Patients Without Brain Metastases at Baseline



No. at risk									
Brigatinib	97	65	56	50	44	40	37	23	1
Crizotinib	97	64	43	33	24	17	16	7	2

TREATMENT	MEDIAN PFS (95% CI), MONTHS	HR (95% CI)	3-YEAR PFS RATE (95% CI), %	4-YEAR PFS RATE (95% CI), %
Brigatinib (n = 40)[a]	24.0 (18.4-34.9)	**0.25** (0.14-0.46) *P* < .0001[b]	33 (18-49)	28 (13-45)
Krizotinib (n = 41)[a]	5.6 (3.8-9.2)		5 (0-20)	NE

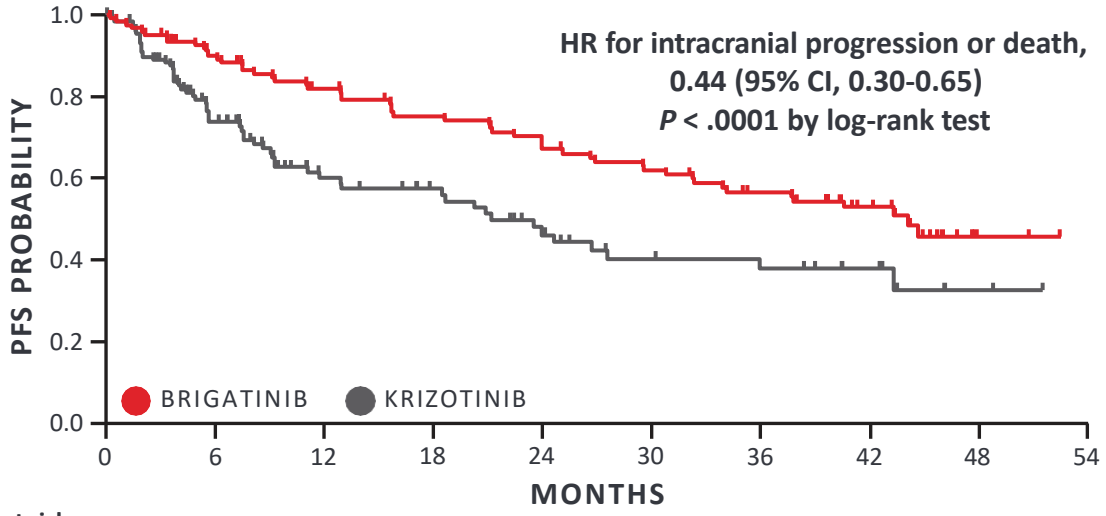
TREATMENT	MEDIAN PFS (95% CI), MONTHS	HR (95% CI)	3-YEAR PFS RATE (95% CI), %	4-YEAR PFS RATE (95% CI), %
Brigatinib (n = 97)[a]	29.3 (15.7-NE)	**0.62** (0.43-0.91) *P* = .0131[b]	47 (36-57)	40 (28-51)
Krizotinib (n = 97)[a]	15.6 (9.5-21.1)		24 (15-34)	22 (13-32)

Final analysis data cutoff: January 29, 2021. Median follow-up: 40.4 months in the brigatinib arm and 15.2 months in the crizotinib arm.

NE, not evalul.

Brigatinib ALTA-1L Trial
Intrakranijalni PFS (BIRC)

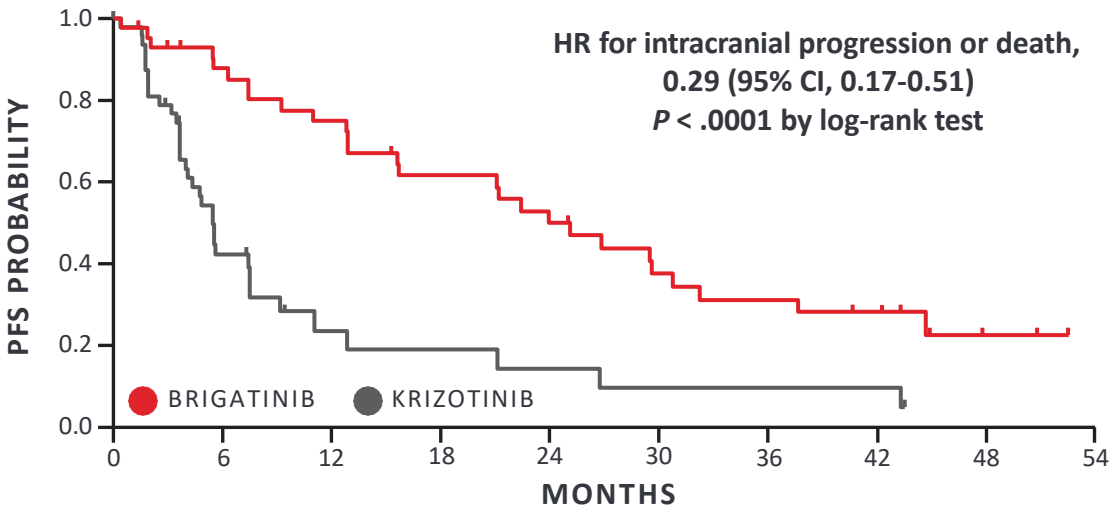
Intracranial PFS (ITT population)



No. at risk

Brigatinib 137	103	89	76	66	59	53	31	2
Crizotinib 138	76	45	37	26	19	17	9	2

Intracranial PFS (patients with any baseline brain metastases)



No. at risk

Brigatinib 47	34	29	22	17	12	10	7	2
Crizotinib 49	16	5	4	3	2	2	2	0

TREATMENT[a]	MEDIAN icPFS (95% CI), MONTHS	HR (95% CI)	3-YEAR icPFS RATE (95% CI), %	4-YEAR icPFS RATE (95% CI), %
Brigatinib (n = 137)	44.1 (32.2-NE)	**0.44** (0.30-0.65) *P* < .0001	56 (47-66)	46 (34-57)
Krizotinib (n = 138)	21.2 (12.9-35.9)		38 (27-49)	33 (19-47)

TREATMENT[a]	MEDIAN icPFS (95% CI), MONTHS	HR (95% CI)	3-YEAR icPFS RATE (95% CI), %	4-YEAR icPFS RATE (95% CI), %
Brigatinib (n = 47)	24.0 (12.9-30.8)	**0.29** (0.17-0.51) *P* < .0001	31 (17-47)	22 (9-39)
Krizotinib (n = 49)	5.5 (3.7-7.5)		9 (2-25)	NE

Final analysis data cutoff: January 29, 2021. Median follow-up: 40.4 months in the brigatinib arm and 15.2 months in the crizotinib arm.

icPFS, intracranial PFS.

[a] Intracranial reviewers are independent from systemic reviewers.Camidge DR, et al. *J Thorac Oncol.* [in press]. August 2021.

Brigatinib ALTA-1L Trial

Intrakranijalne stope odgovora: CNS MTS *inicijalno pre početka primene terapije*

MEASURABLE[b] BRAIN METASTASES AT BASELINE	BRIGATINIB (n = 18)	KRIZOTINIB (n = 23)	OR (95% CI)[c]; *P* VALUE
Confirmed intracranial ORR (95% CI), %	78 (52-94)	26 (10-48)	11.67 (2.15-63.27); .0014
CR, %	28	0	-
PR, %	50	26	-
Median DOR in confirmed responders (95% CI), months	27.9 (5.7-NE)	9.2 (3.9-NE)	-
2-year probability[d] of maintaining response (95% CI), %	64 (30-85)	(insufficient number of patients)	-
3-year probability[d] of maintaining response (95% CI), %	39 (10-67)	(insufficient number of patients)	-
ANY BRAIN METASTASES AT BASELINE	**(n = 47)**	**(n = 49)**	
Confirmed intracranial ORR (95% CI), %	66 (51-79)	14 (6-27)[e]	13.56 (4.70-39.11); < .0001
CR, %	45	2	-
PR, %	21	12	-
Median DOR in confirmed responders (95% CI), months	27.1 (16.9-42.8)	9.2 (3.9-NE)	-
2-year probability[d] of maintaining response (95% CI), %	59 (38-75)	33 (1-75)	-
3-year probability[d] of maintaining response (95% CI), %	38 (20-56)	(insufficient number of patients)	-

Final analysis data cutoff: January 29, 2021. Median follow-up: 40.4 months in the brigatinib arm and 15.2 months in the crizotinib arm.

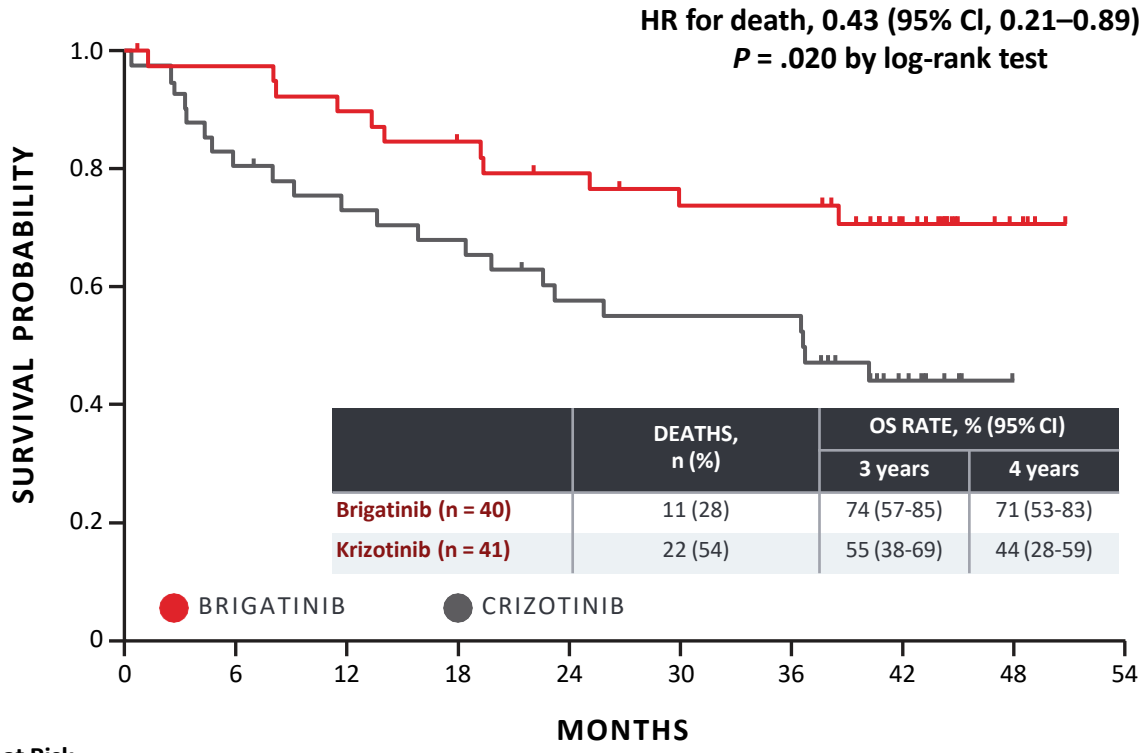
[a] Intracranial reviewers are independent from systemic reviewers; [b] ≥ 10 mm in diameter; [c] ORs (brigatinib vs crizotinib) and *P* values are from a Cochran-Mantel-Haenszel test stratified by presence of prior chemotherapy for locally advanced or metastatic disease; [d] Kaplan-Meier estimated probability of maintaining response; [e] The difference in CR rate from that reported in the second interim analysis is due to reclassification of response in one patient who received subsequent anticancer therapy before the complete response was observed.

1. Camidge DR, et al. *J Thorac Oncol*. [in press]. August 2021; 2. Takeda. Data on file (CSR AP26113-13-301, Table 15.2.3.2.1, Table 15.2.7.4, Table 15.2.3.2.5, Table 15.2.7.2).

Brigatinib ALTA-1L Trial

OS: CNS MTS *inicijalno pre početka primene terapije* (BIRC)

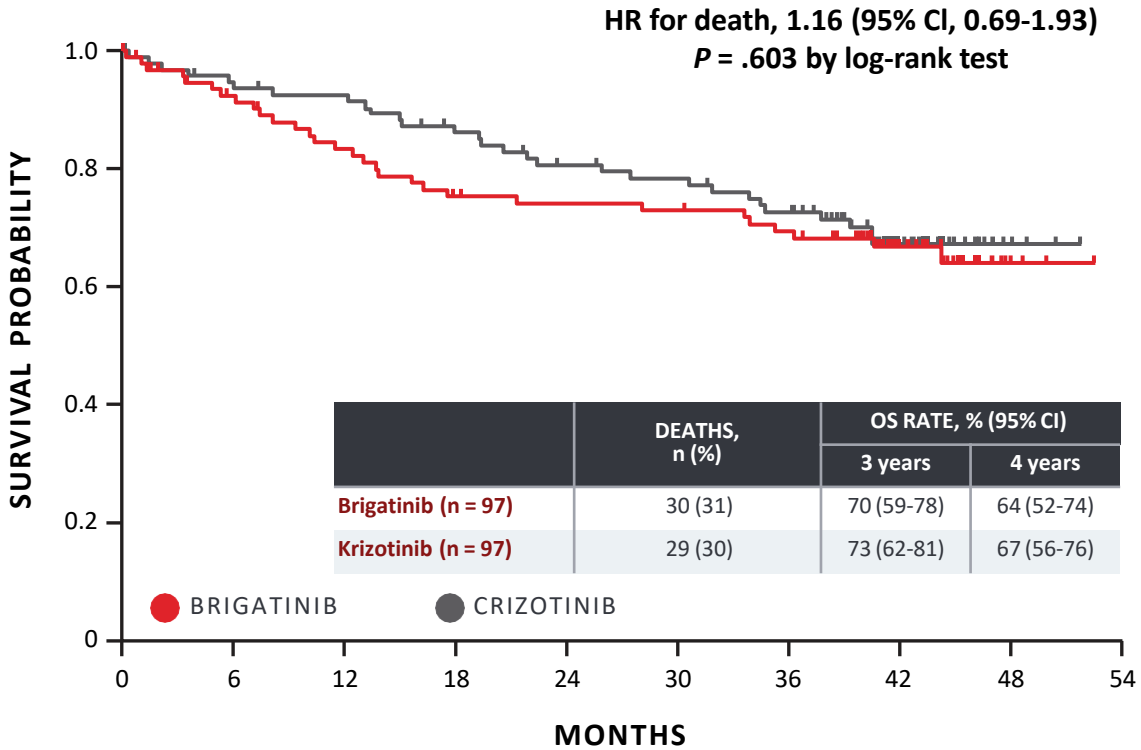
OS in Patients With Any Brain Metastases at Baseline[a]



	DEATHS, n (%)	OS RATE, % (95% CI)	
		3 years	4 years
Brigatinib (n = 40)	11 (28)	74 (57-85)	71 (53-83)
Krizotinib (n = 41)	22 (54)	55 (38-69)	44 (28-59)

No. at Risk										
Brigatinib	40	38	35	32	29	26	26	16	4	0
Krizotinib	41	33	29	27	22	21	21	9	1	0

OS in Patients Without Brain Metastases at Baseline[a]



	DEATHS, n (%)	OS RATE, % (95% CI)	
		3 years	4 years
Brigatinib (n = 97)	30 (31)	70 (59-78)	64 (52-74)
Krizotinib (n = 97)	29 (30)	73 (62-81)	67 (56-76)

No. at Risk										
Brigatinib	97	83	73	65	63	62	58	36	3	0
Krizotinib	97	90	87	79	72	69	63	33	4	0

Final analysis data cutoff: January 29, 2021. Median follow-up: 40.4 months in the brigatinib arm and 15.2 months in the crizotinib arm.

[a] Brain metastasis present at baseline based on INV assessment.

Camidge DR, et al. *J Thorac Oncol.* [in press]. August 2021.

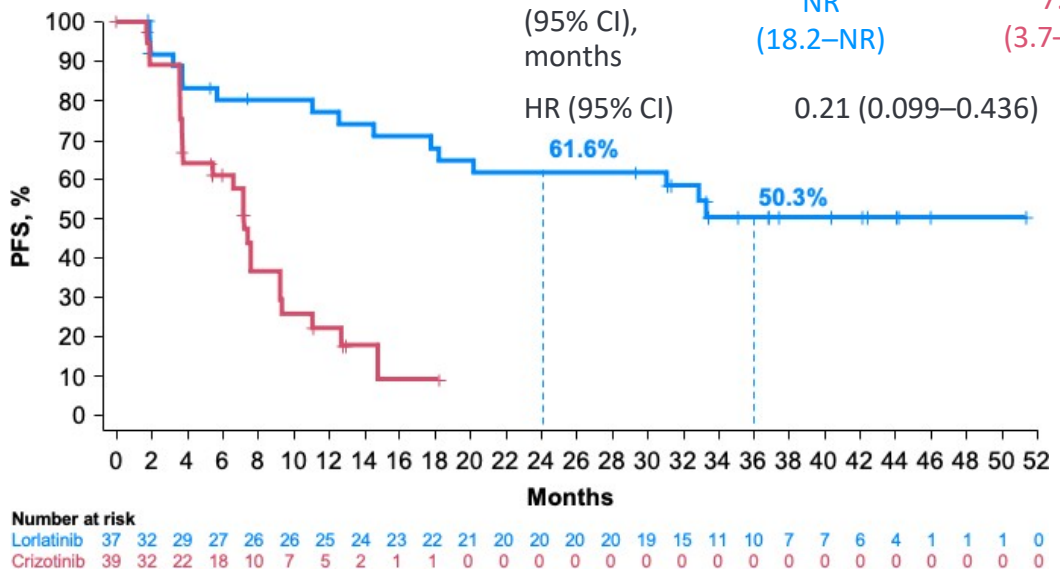
CROWN: PFS (BICR) kod pacijenata sa/bez CNS MTS *inicijalno pre početka primene terapije*

(long-term follow up): SUPERIORNA UKUPNA i IC EFIKASNOST Lorlatiniba u odnosu na Krizotinib

- 92% redukcije stope intrakranijalne progresije

Patients with baseline brain metastases

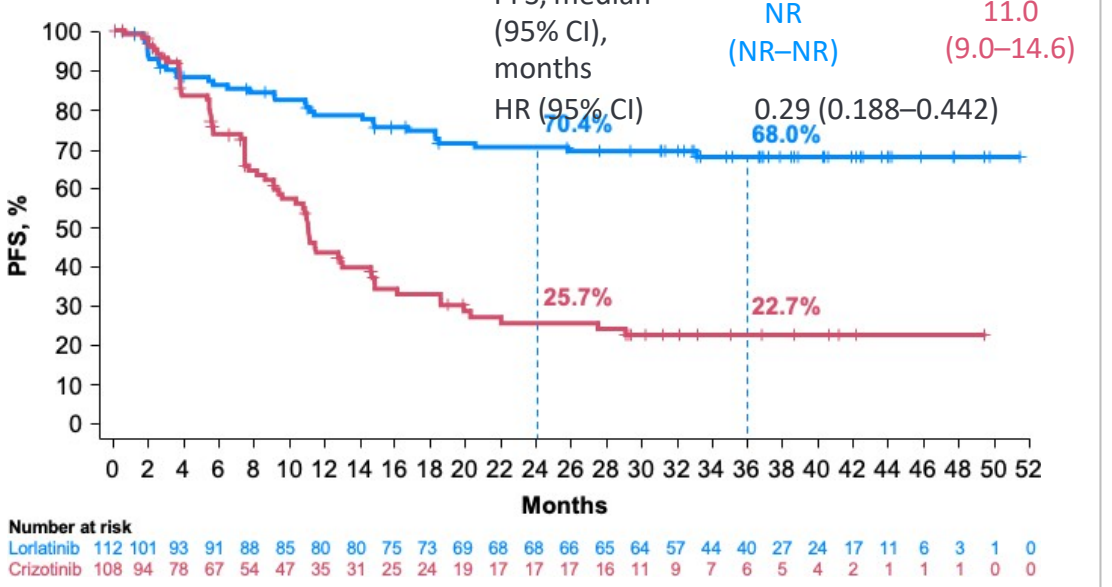
	Lorlatinib (n = 37)	Crizotinib (n = 39)
Events	16	27
PFS, median (95% CI), months	NR (18.2–NR)	7.2 (3.7–9.2)
HR (95% CI)	0.21 (0.099–0.436)	



Patients without baseline brain metastases

Data cutoff: September 20, 2021

	Lorlatinib (n = 112)	Crizotinib (n = 108)
Events	33	65
PFS, median (95% CI), months	NR (NR–NR)	11.0 (9.0–14.6)
HR (95% CI)	0.29 (0.188–0.442)	

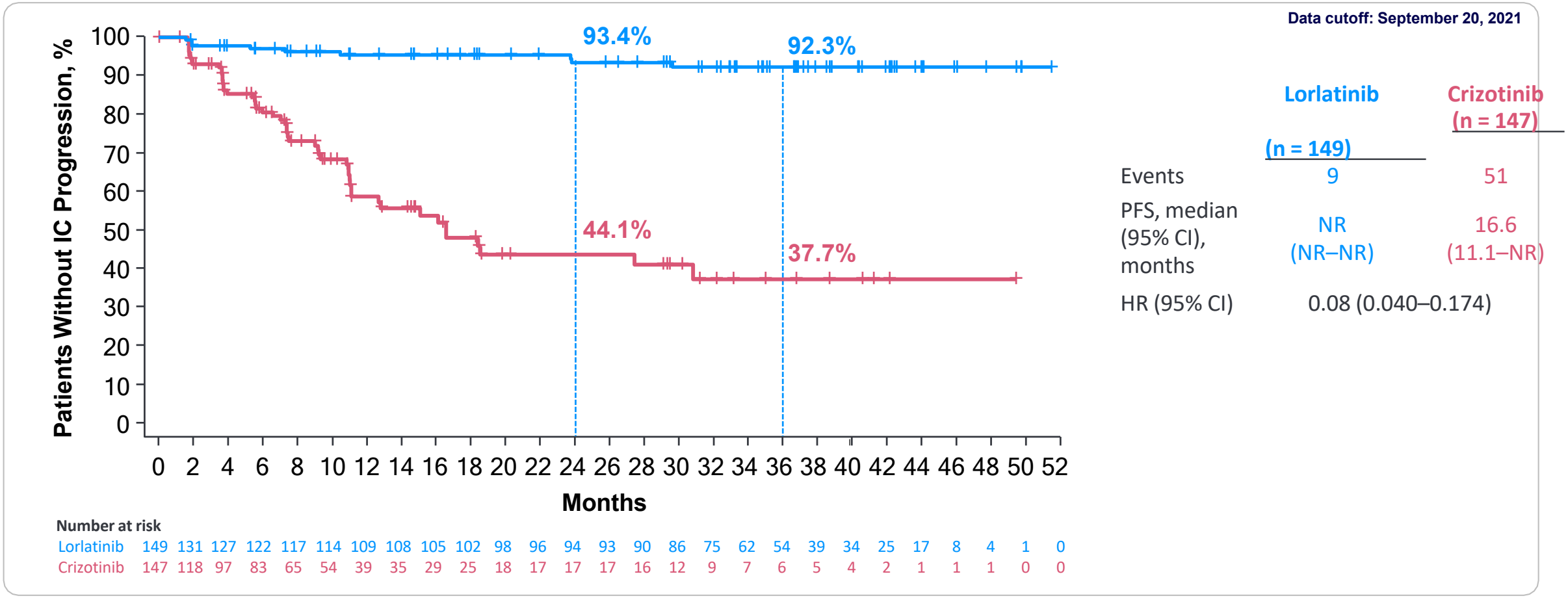


Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
Median duration of follow-up for PFS by BICR: lorlatinib, 36.7 months; crizotinib, 29.3 months.
BICR, blinded independent central review; NR, not reached; PFS, progression-free survival.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Vreme do IC progresije (BICR)

(long-term follow up, ITT populacija)

Lorlatinib kod pacijenata bez *inicijalnih* CNS MTS pri dijagnozi bolesti: 1 od 112 pacijenata ima **IC progresiju – protektivni efekat**



	Lorlatinib (n = 149)	Crizotinib (n = 147)
Events	9	51
PFS, median (95% CI), months	NR (NR–NR)	16.6 (11.1–NR)
HR (95% CI)	0.08 (0.040–0.174)	

Median duration of treatment: lorlatinib, 33.3 months; crizotinib, 9.6 months.
BICR, blinded independent central review; IC, intracranial; ITT, intent to treat; NR, not reached; PFS, progression-free survival.
Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

CROWN: Intrakranijalni OR (BICR)

(planirana interim analiza)

	Patients With Measurable or Non-Measurable Brain Metastases at Baseline		Patients With Measurable Brain Metastases at Baseline	
	Lorlatinib (n = 38)	Crizotinib (n = 40)	Lorlatinib (n = 17)	Crizotinib (n = 13)
Confirmed CNS Response, n (%)	25 (66)	8 (20)	14 (82)	3 (23)
(95% CI)	(49–80)	(9–36)	(57–96)	(5–54)
Odds ratio*	8.41 (2.59–27.23)		16.83 (1.95–163.23)	
CNS CR, n (%)	23 (61)	6 (15)	12 (71)	1 (8)
Median DOR, months (95% CI)	NE (NE–NE)	9.4 (6.0–11.1)	NE (NE–NE)	10.2 (9.4–11.1)
Median time to response, months (IQR)	1.9 (1.8–3.7)	1.8 (1.7–2.7)	1.9 (1.8–3.5)	1.9 (1.8–1.9)

*Odds ratio >1 indicates better outcome for lorlatinib relative to crizotinib.

BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DOR, duration of response; IQR, interquartile range; NE, not estimable; OR, overall response.

Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018-29

Pregled kliničkih studija u 1L ALK TKI (2. i 3. generacija): Pacijenti sa inicijalno dijagnostikovanim MTS CNS pre započinjanja terapije

Indirektna komparacija različitih kliničkih studija!

- Različiti *end-points* procene CNS efikasnosti
- Različiti kriterijumi za merljive CNS lezije inicijalno prisutne
- Neuniformna populacija pacijenata

	ALTA-1L[1]		ALEX[2-4]		CROWN[5]	
	Brigatinib (n=137)	Crizotinib (n=138)	Alectinib (n=152)	Crizotinib (n=151)	Lorlatinib (n=149)	Crizotinib (n=147)
PFS **with** baseline brain mets (INV-assessed), HR (95% CI)	0.24 (0.12–0.45)		0.37 (0.23–0.58)		IRC-assessed 0.20 (0.10–0.43)	
PFS **without** baseline brain mets (INV-assessed), HR (95% CI)	0.57 (0.38–0.84)		0.46 (0.31–0.68)		IRC-assessed 0.32 (0.20–0.49)	
OS **with** baseline brain mets (INV-assessed), HR (95% CI)	0.43 (0.21–0.89)		0.58 (0.34–1.00)		NR	
OS **without** baseline brain mets (INV-assessed), HR (95% CI)	1.16 (0.69–1.93)		0.76 (0.45–1.26)		NR	

PFS- progression free survival; INV- investigator assessed; IRC- independent review committee; OS- overall survival

[1]Camidge DR, et al. J Clin Oncol. 2020; [2]Peters S, et al. New Engl J Med. 2017; [3]Gadgeel S, et al. Ann Oncol. 2018; [4]Mok T, et al. Ann Oncol. 2020; [5]Solomon B, et al. ESMO 2020

Pregled kliničkih studija u 1L ALK TKI (2. i 3. generacija): CNS efikasnost

Indirektna komparacija različitih kliničkih studija!

- Različiti *end-points* procene CNS efikasnosti
- Različiti kriterijumi za merljive CNS lezije inicijalno prisutne
- Neuniformna populacija pacijenata

CNS TUMOUR RESPONSE ENDPOINTS (IRC)	ALTA-1L[1]		ALEX[2–4]		CROWN[5]	
Patients with measurable disease	Brigatinib (n=18)	Crizotinib (n=23)	Alectinib (n=21)	Crizotinib (n=22)	Lorlatinib (n=17)	Crizotinib (n=13)
CNS ORR, % (95% CI)	77.8 (52.4–93.6)	26.1 (10.2–48.4)	81.0 (58–95)	50.0 (28–72)	82 (57–96)	23 (5–54)
CR, %	27.8	0	38.1	4.5	71	8
CNS DOR, % (95% CI)	NE (5.7-NE)	9.2 (3.9–9.2)	17.3 (14.8–NE)	5.5 (2.1–17.3)	NE (NE–NE)	10.2 (9.4–11.1)

CNS TIME TO EVENT ENDPOINTS (IRC)	ALTA-1L[1]		ALEX[2–4]		CROWN[5]	
	Brigatinib (n=137)	Crizotinib (n=138)	Alectinib (n=152)	Crizotinib (n=151)	Lorlatinib (n=149)	Crizotinib (n=147)
Intracranial PFS (any brain metastases), HR (95% CI)	0.31 (0.17-0.56) Events – death, intracranial progression, radiotherapy to the brain					
Time to progression in CNS as first site of progression (ITT), HR (95% CI)			0.16 (0.10–0.28) Events – intracranial progression only, non-CNS progression censored			
Time to intracranial progression (ITT), HR (95% CI)					0.07 (0.03–0.17) Events – intracranial progression only	

*Based on best change from baseline; †mITT population reported

CNS- central nervous system; ORR- objective response rate; IRC- independent review committee; CR- complete response; DOR- duration of response; ITT- intention to treat population;

[1]Camidge DR, et al. J Clin Oncol. 2020; [2]Peters S, et al. New Engl J Med. 2017;[3]Gadgeel S, et al. Ann Oncol. 2018; [4]Mok T, et al. Ann Oncol. 2020; [5]Solomon B, et al. ESMO 2020

Postoji li i dalje potreba za sprovodjenjem RT metastaza CNS-a?

VOLUME 34 · NUMBER 2 · JANUARY 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Extended Survival and Prognostic Factors for Patients With *ALK*-Rearranged Non–Small-Cell Lung Cancer and Brain Metastasis

Kimberly L. Johung, Norman Yeh, Neil B. Desai, Terence M. Williams, Tim Lautenschlaeger, Nils D. Arvold, Matthew S. Ning, Albert Attia, Christine M. Lovly, Sarah Goldberg, Kathryn Beal, James B. Yu, Brian D. Kavanagh, Veronica L. Chiang, D. Ross Camidge, and Joseph N. Contessa

TKI

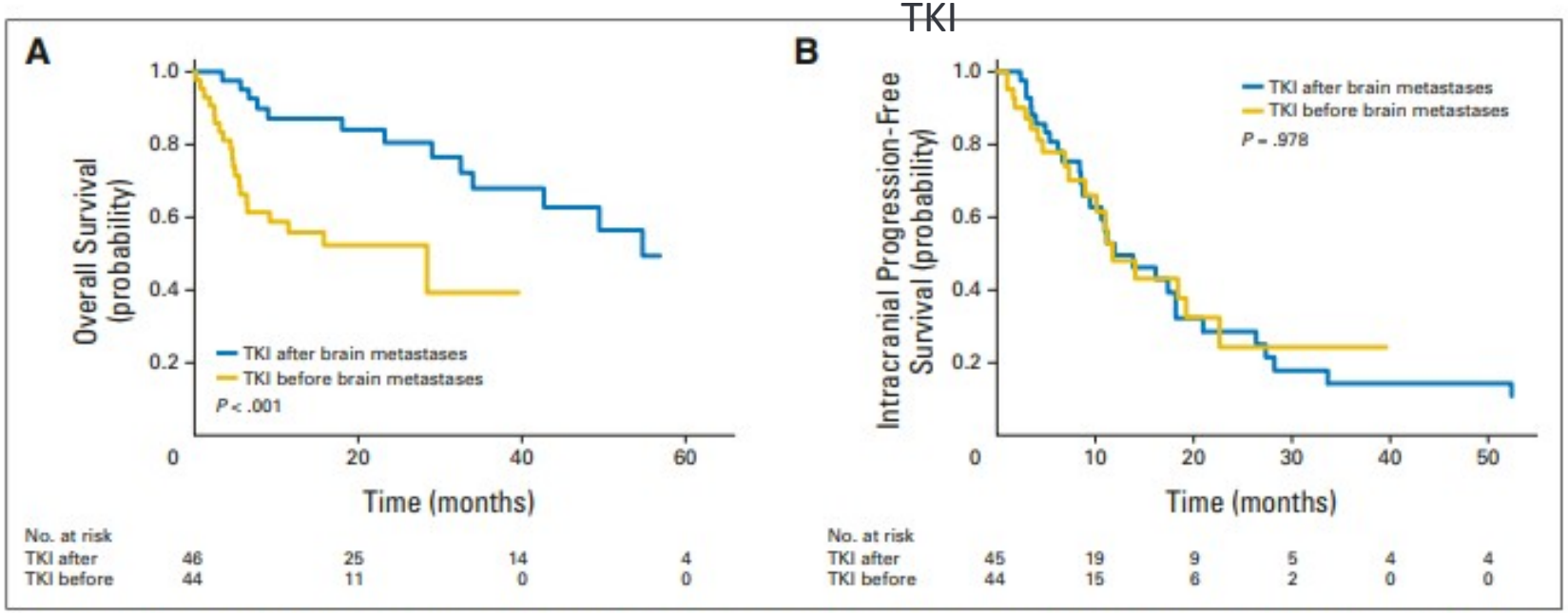


Fig 3. Kaplan-Meier estimate of (A) overall (B) and intracranial progression-free survival from date of diagnosis of brain metastasis, stratified by treatment with tyrosine kinase inhibitor (TKI) before development of brain metastasis or initiation of TKI after diagnosis of brain metastasis.

Johung et al. JCO 2016

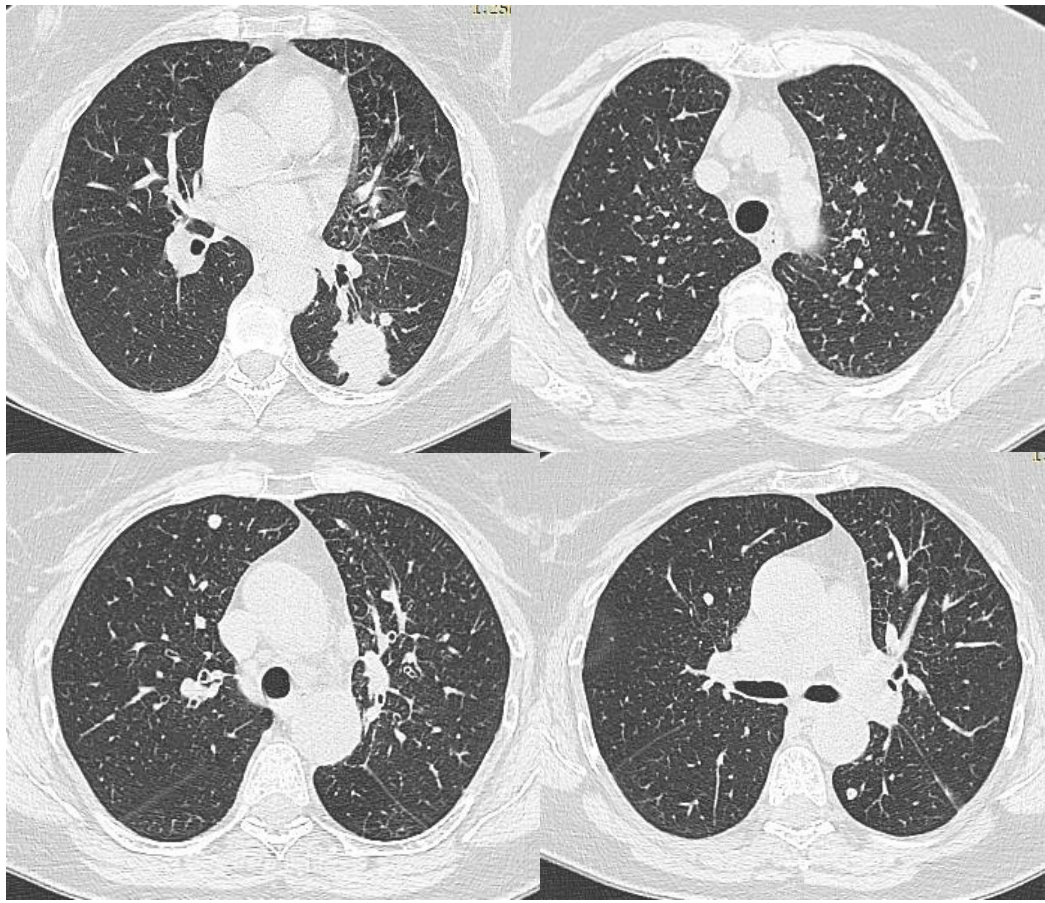
I prikaz slučaja: GM, 67 godina stara, nepušač

- Mart 2019 - suvi kašalj
- Diabetes mellitus, HTA
- CT thorax-a i abdomena (12.03.2019.)

TU 37mm u donjem levom lobusu, metastaze 6mm i 7mm u istom lobusu, u desnom gornjem režnju 5mm, bez medijastinalne limfadenopatije.

- 01.04.2019. leva donja lobektomija sa sistemskom limfadenektomijom
- PH adenocarcinoma, pT3N2Mx,

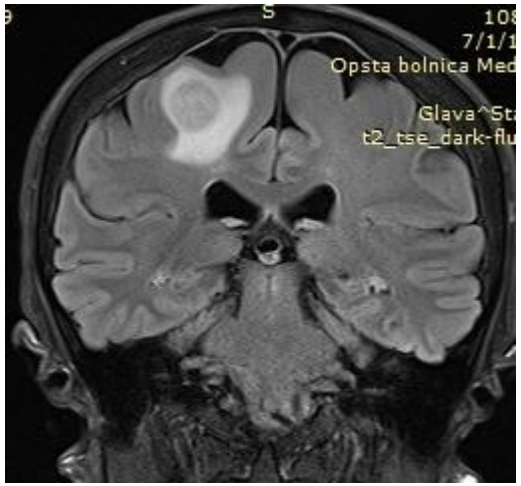
  svi LN pozitivni - 5, 6, 7, 9, 10, 12
- cT3N2M1a

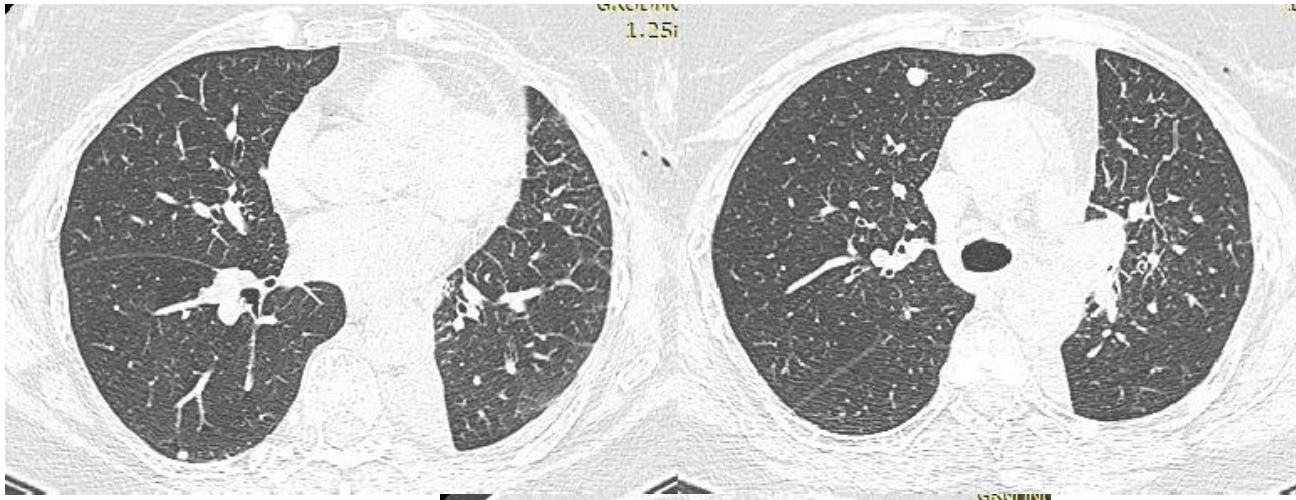


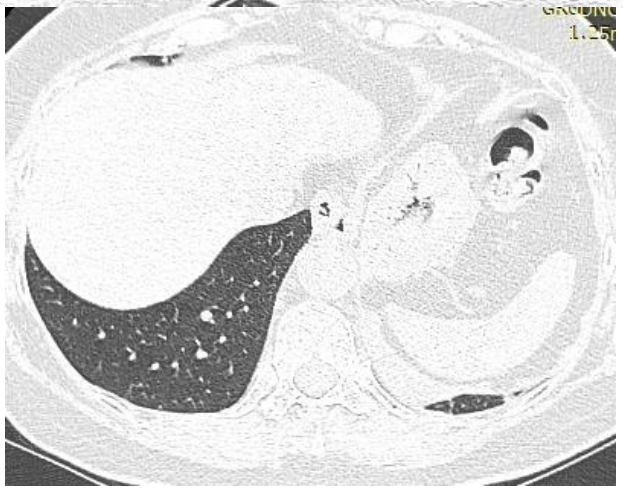
Source of data: UCCS Clinic for pulmonology lung cancer hospital registry

I prikaz slučaja - lečenje

- EGFRwt, ALK FISH ekspresija (60%)
- 1L alektinib
- Slabost leve ruke, kašalj
- CT thorax-a i abdomena (30.04.2019)
  multiple nodularne promene
- MR CNS (07.05.2019) - desno parijetalno metastaze 19mm sa perifokalnim edemom



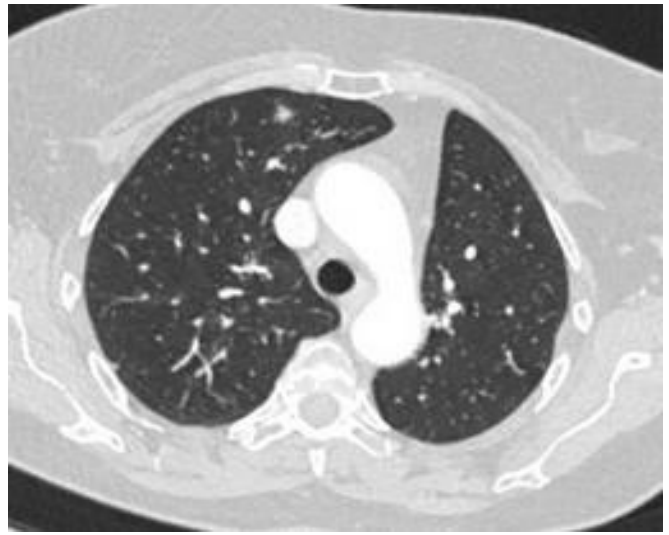




Source of data: UCCS Clinic for pulmonology lung cancer hospital registry

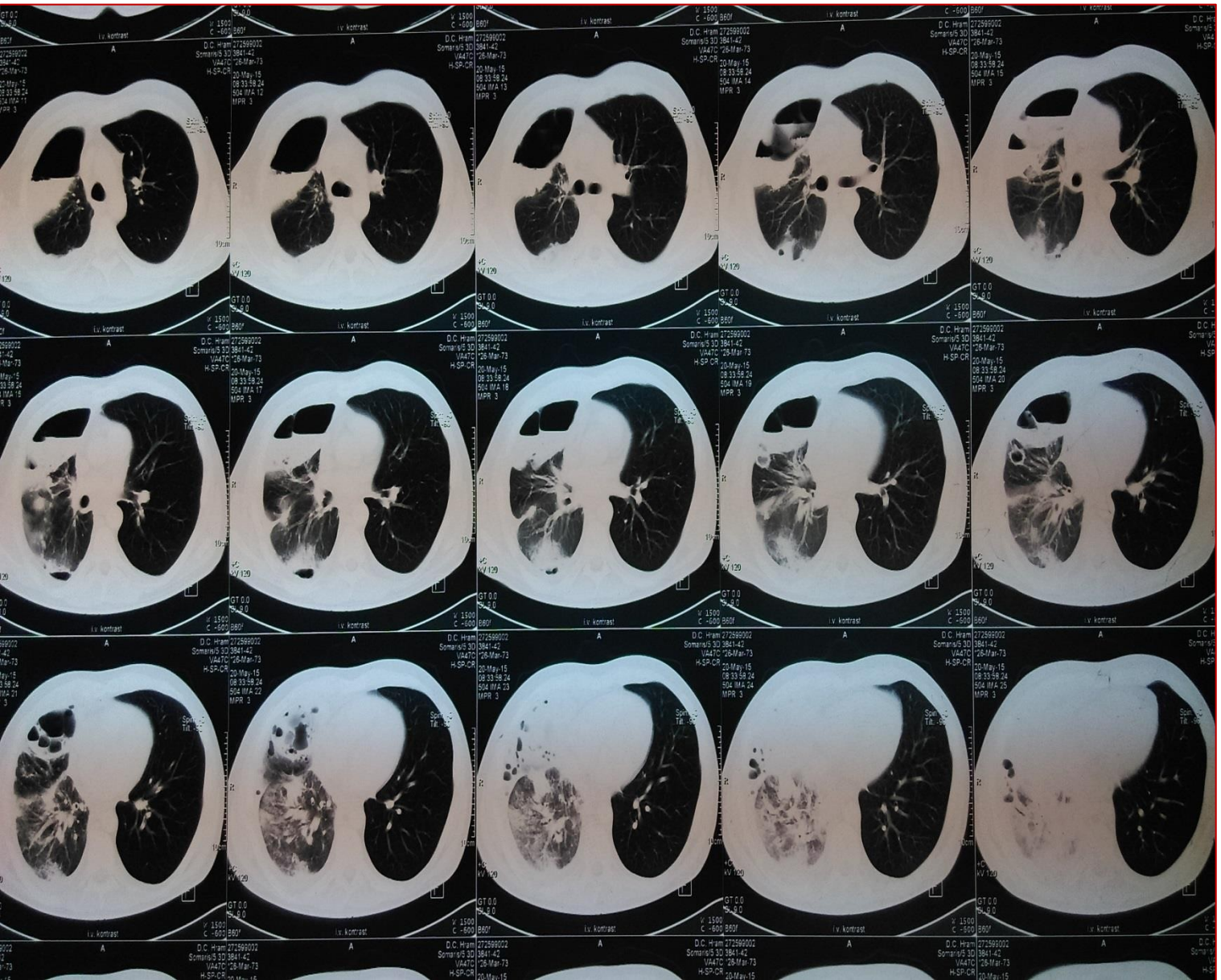
Kako nastaviti lečenje? Lokalna kontrola bolesti? Postoji li mogućnost primene 2L TKI?

- Gamma knife 22.05.2019
- **Lorlatinib (07.06.2019) – NPP (donacija)**
- CT thorax-a i abdomena : PR
- Gamma knife RT 10.12.2019 - retreatman metastaza desno parijetalno
- NMR CNS 06.03.2020 – suspektna progresija MTS desno parijetalno sa perifokalnim edemom ?
- NMR sa spektroskopijom i difuzijom 01.06.2020 - tretirane lezije sa postiradijacionom nekrozom
- **Lorlatinib in courso (3 godine)**
- 01.08.2019 ND - hyperholesterolemija, hypertriglyceridemija



Source of data: UCCS Clinic for pulmonology lung cancer hospital registry

ALK TKI sekvencijalno lečenje II prikaz slučaja: JŽ, 42 godine star iz Beograda



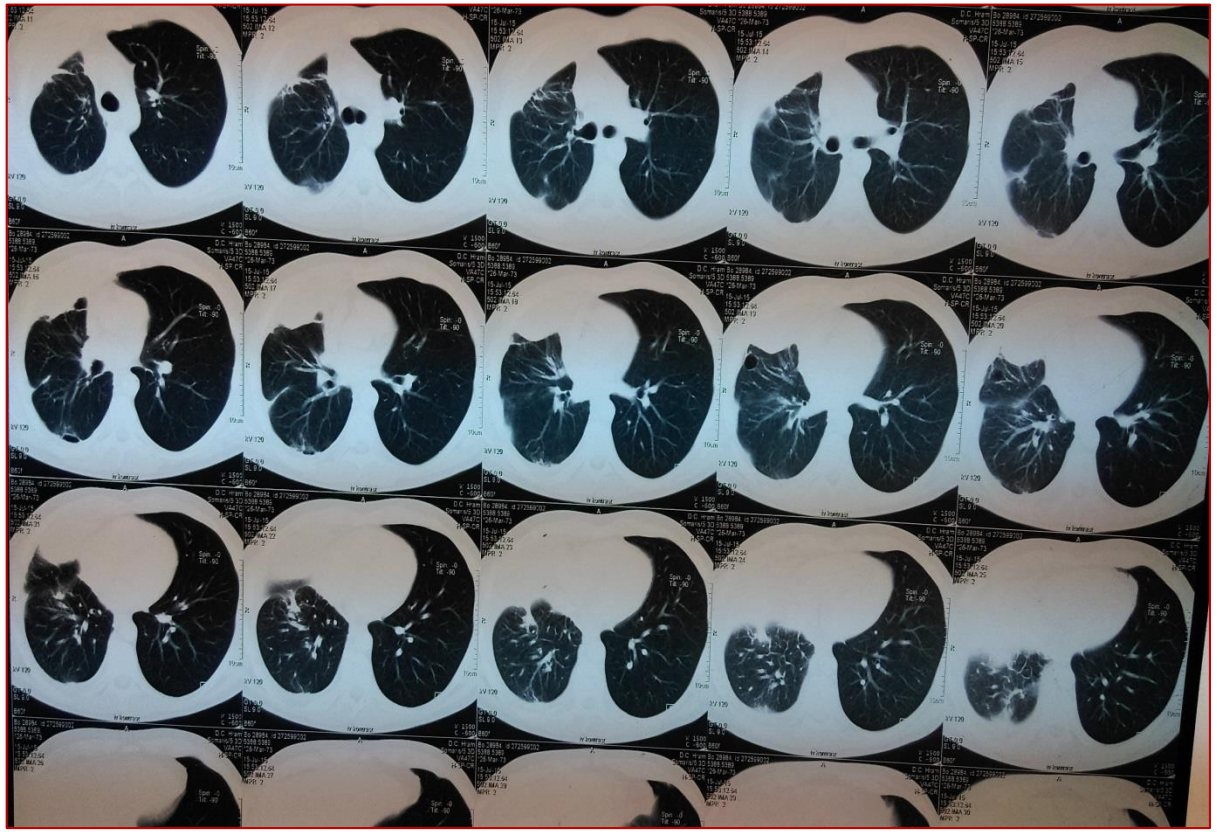
- Bez hroničnih bolesti i operacija
  Nepušač
  ECOG PS 1

•**Intenzivni bolovi u desnom hemitoraksu** Dg:
Carcinosis pleurae l dex pp **Adenocarcinoma** bronch.
VATS biopsio pleurae l dex ***14.04.2015.***
cT4N1M1a cIV
EGFR mutacija – nije detektovana
ALK ekspresija prisutna

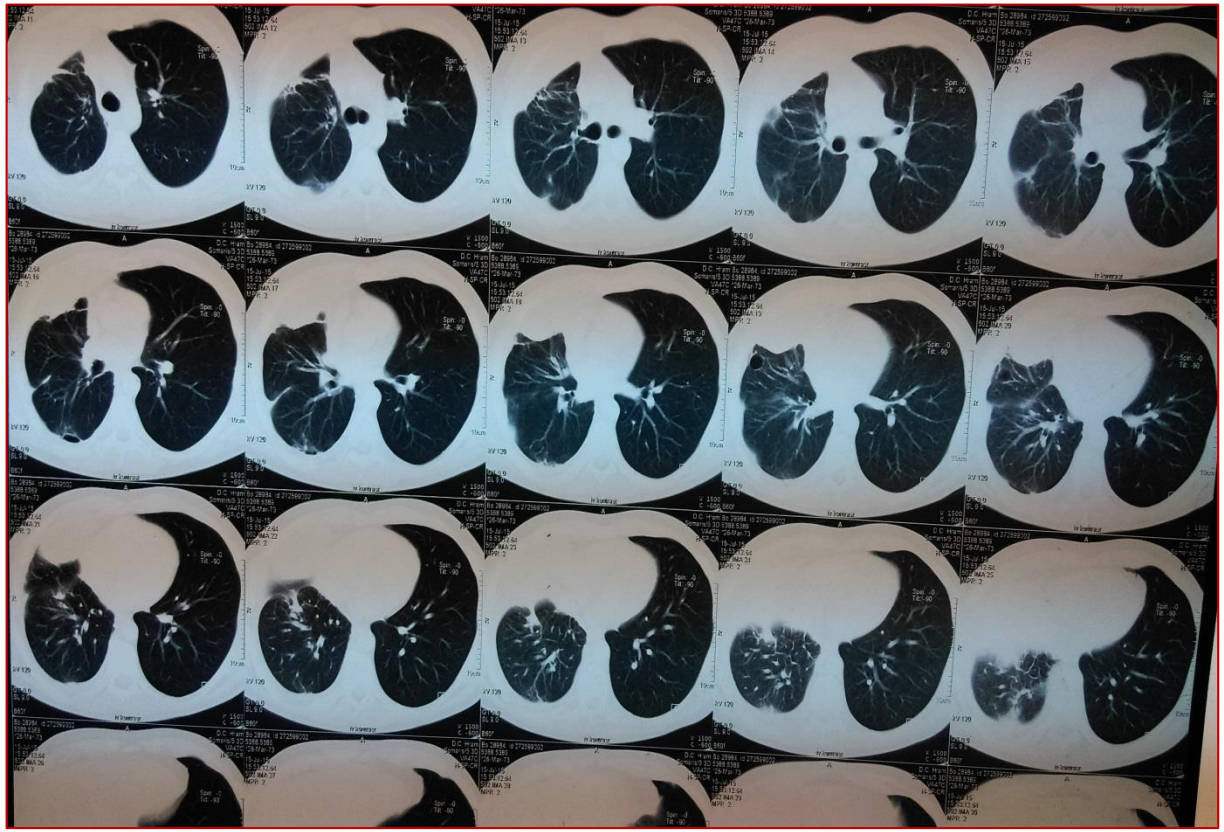
Source of data: UCCS Clinic for pulmonology lung cancer hospital registry

- TKI **Krizotinib** caps. a 250 mg **25.MAJ 2015 (Alex studija)**
- Klinički odličan odgovor (potpuno obezboljavanje)

JUL 2015: 2M PR

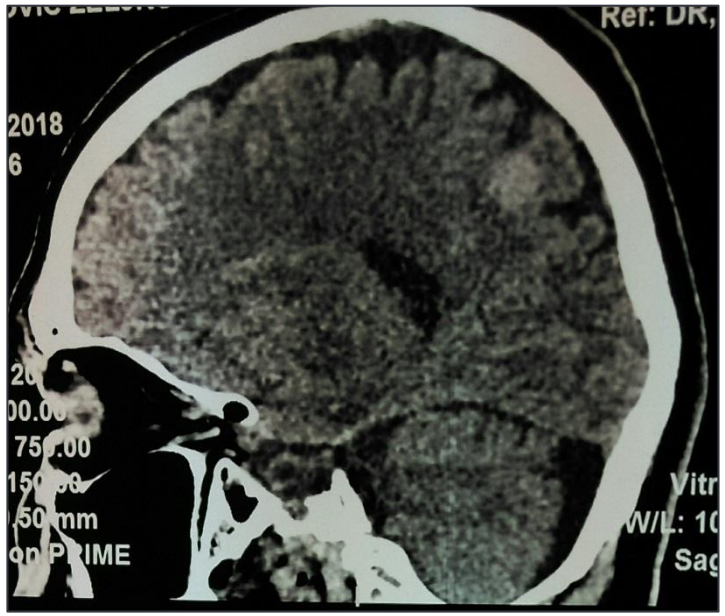


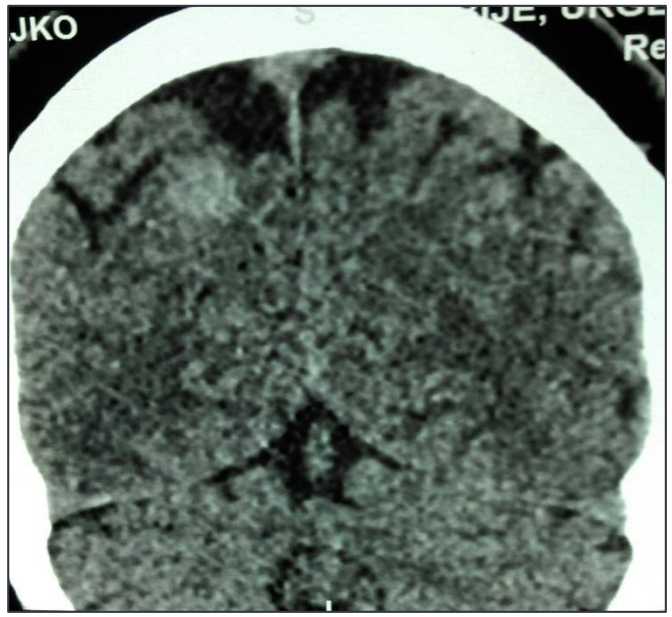
SEP 2015

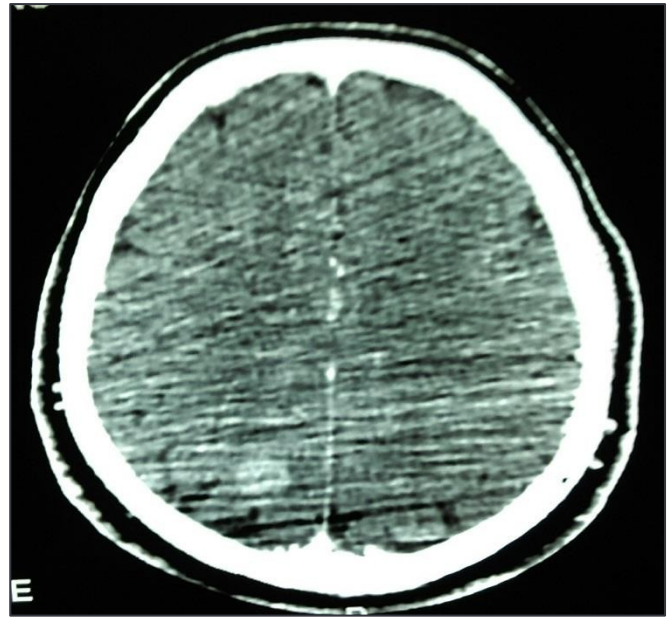


Source of data: UCCS Clinic for pulmonology lung cancer hospital registry

PFS 38 meseci - najbolji odgovor PR
ST post C38 TKI Krizotinib – PD
PD : Multiple MTS endokranijuma, održavanje PR u grudnom košu (**april 2018**)







- **RNH** – gamma knife (ST post gamma gladium)
- Pfizer *Compassionate Use Program* **TKI Lorlatinib tb (100 mg)**
- **Godinu dana kasnije AE** AVG 2019 holesterol 12.5 mmol/L trig 12.2 mmol/L
  Th: statini, dijetalni režim ishrane
- **Covid -19 infekcija,** hospitalno zbrinut u KBC "Zemum" 08.03. - 17.03.2021. - bilateralna intersticijska pneumonija srednjeg stepena.: **sve vreme prima TKI Lorlatinib**

Source of data: UCCS Clinic for pulmonology
lung cancer hospital registry

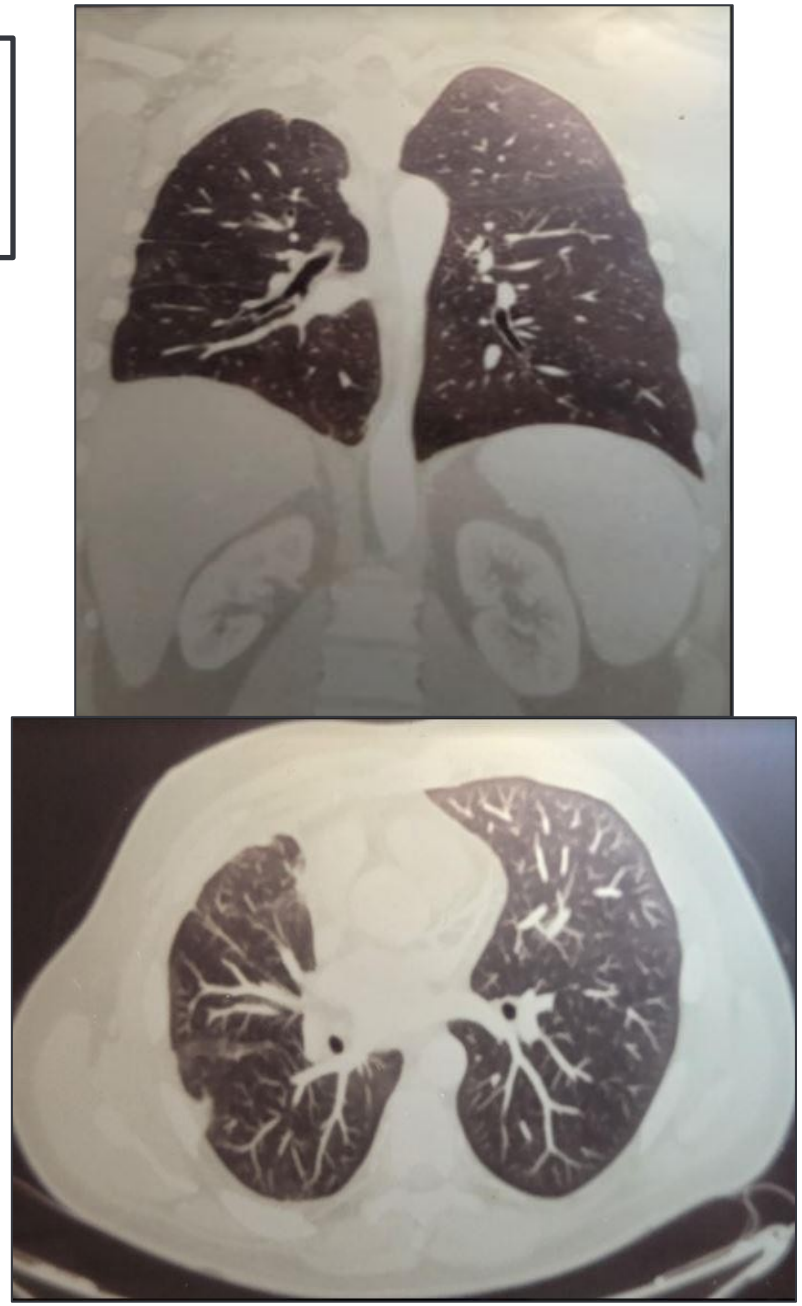
TKI KRIZOTINIB/LORLATINIB (1L/2L)
7 GODINA LEČENJA

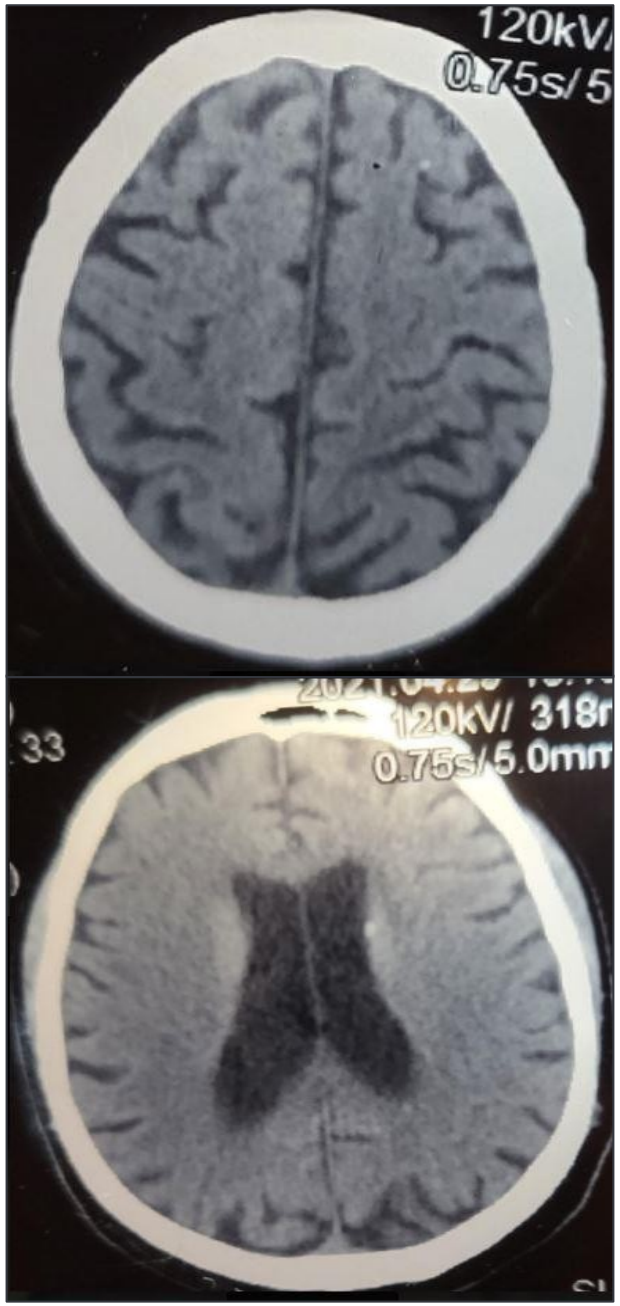
- **Dobar kvalitet života**

03.06.2022

CT thorax-a i gornjeg sp abdomena: promene po tipu ground glass u desnom pluću, ostali nalaz stacionaran: desni hemitoraks sužen sa iregularnim zadebljanjem kostalne pleure 6 mm, u desnom pleuralnom kavumu pleuralni izliv 10 mm

CT endokranijuma: ne vide se znaci hemoragije, neoplastičkog procesa





Odličan klinički, radiografski odgovor,
QoL

Source of data: UCCS Clinic for pulmonology
lung cancer hospital registry

Zaključak

ALK+ NSCLC: visoka incidenca CNS metastaza pri dijagnozi bolesti
(1/3 pacijenata ima inicijalno, pri postavljanju dijagnoze CNS metastaze)

Duže preživljavanje: viši rizik za neželjene efekte primenjenih terapijskih modaliteta lečenja

Prednost ALK TKI (target terapija) u odnosu na primenu hemoterapije:

- Superiorna intrakranijalna efikasnost
- Duže ukupno preživljavanje
- Bolji kvalitet života

Kombinacija **RT CNS + TARGET terapija (TKI)**: bolja intrakranijalna kontrola bolesti

Preporuka:

Nelečeni, asimptomatski ALK+ NSCLC sa CNS metastazama
***Primena 2. ili 3. generacije ALK TKI*, promptno nadziranje, mogućnost odlaganja lokalne terapije sve dok se postiže efikasno lečenje tirozin kinaznim inhibitorom**

Standard lečenja NSCLC ALK+ sa CNS metastazama:
TKI (TARGET) terapija uz lokalnu kontrolu bolesti personalizovanim pristupom

Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Značaj rezultata studija sa podacima iz kliničke prakse:

Prof. dr Milan Rančić
Klinika za pulmologiju
Univerzitetski klinički centar Niš

Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

- ALK-rearranged NSCLC, present in 3% to 5% of patients with advanced NSCLC
- The second most common oncogene-driven NSCLC [1]
- Oncogenic ALK fusions are amenable to targeted therapy by means of three generations of ALK-receptor tyrosine kinase inhibitors (ALK tyrosine kinase inhibitor [TKI]) [2]
- Clinical trial data clearly reveal the safety and efficacy of ALK TKI, but within the context of highly selected trial populations

- 1. Reynolds C, Masters ET, Black-Shinn J, et al. Real-world use and outcomes of ALK-positive crizotinib treated metastatic NSCLC in US community oncology practice: a retrospective observational study. J Clin Med. 2018;7:129.
- 2. Xing P, Wang S, Hao X, Zhang T, Li J. Clinical data from the real world: efficacy of crizotinib in Chinese patients with advanced ALK-rearranged non-small cell lung cancer and brain metastases. Oncotarget. 2016;7:84666– 84674.

Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

- Given the evidence for benefit in clinical trial populations, evaluation of realworld populations with ALK-rearranged NSCLC to determine whether clinical trial data are reflective of the real-world clinical setting is of critical importance [3]

- Challenges real word evidence:
  - Heterogeneity (demographic, geographic, clinical, socioeconomic) of patients encountered in clinical practice
  - The low incidence of ALK rearrangements among patients with NSCLC
  - The loss of diversity which occurs when retrospective reviews are conducted by means of single-center studies
  - limited analysis of patients from a particular region
  - therapy restricted to specific health care insurance providers

- 3. Gibson AJW, Box A, Dean ML, Elegbede AA, Hao D, Sangha R, Bebb DG. Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors. JTO Clinical and Research Reports 2021. 2(4): 100157

ORIGINAL ARTICLE

Retrospective Real-World Outcomes for Patients With *ALK*-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),[a] Adrian Box, MD, PhD,[a,b] Michelle L. Dean, BSc,[a] Anifat A. Elegbede, MSc,[a] Desiree Hao, MD,[a,c] Randeep Sangha, MD,[d,e] D. Gwyn Bebb, BMBCh, PhD[a,c,*]

[a]*Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[b]*Molecular Pathology Lab, Alberta Precision Laboratories, Calgary, Alberta, Canada*
[c]*Tom Baker Cancer Centre, Alberta Health Services, Calgary, Alberta, Canada*
[d]*Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada*
[e]*Cross Cancer Institute, Alberta Health Services, Edmonton, Alberta, Canada*

Received 29 October 2020; revised 1 February 2021; accepted 10 February 2021
Available online - 1 March 2021

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

Methods

- This study explored the use, safety, and efficacy of initial use of an ALK-inhibiting targeted therapy(ALK tyrosine kinase inhibitor [TKI]) in patients with ALK-rearranged NSCLC in a population-based, real-world clinical population within the province of Alberta, Canada.
- Demographic, clinical, treatment, and outcome data of the patients with advanced or metastatic ALK-rearranged NSCLC receiving their first ALK TKI between 2014 and 2019 were included in the analysis.
- Patient selection was refined to include only those positive for an ALK translocation
- Immunohistochemistry or with fluorescence in situ hybridization confirmation
- A first-line therapy for patients with treatment-naive ALK-rearranged disease: crizotinib or alectinib
- Comparator cohort of patients with ALK-wildtype disease, tested and confirmed negative for detectable ALK rearrangements, who underwent standard-of-care cytotoxic chemotherapy for their advanced or metastatic NSCLC

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

Methods

- ALK-rearranged cohort:
  - The American Joint Committee on Cancer eighth edition M-stage,
  - histological subtype,
  - sex,
  - Eastern Cooperative Oncology Group (ECOG),
  - smoking history, and
  - 5-year age group to the for survival analysis comparisons.

- **Survival metrics:**
- median post-advanced/metastatic disease discovery survival (median overall survival [mOS]),
- median post-ALK TKI initiation survival,
- median progression-free survival (mPFS)
- treatment events, response, best response, and outcomes were calculated
- Response was determined using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1
- AEs were recorded using Common Terminology Criteria for Adverse Events version 5.0 codes, descriptors, and grades,

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

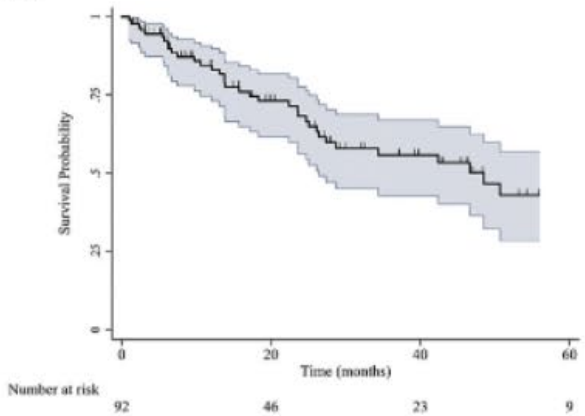
Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

Results

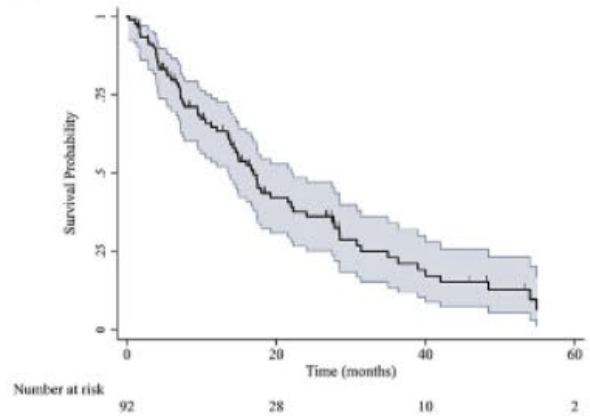
- Patients treated with alectinib and crizotinib did not exhibit significantly different demographic characteristics
  - Crizotinib-treated patients were more often given palliative-intent cytotoxic chemotherapy before initial ALK TKI treatment (20% versus 0%, p<0.002)
  - compared with alectinib, exhibited a higher overall rate of brain metastases development up to the time of analysis (70% versus 42%, p < 0.01).
  - crizotinib-treated patients experienced higher rates of treatment changes (26% versus 0%, p < 0.001)
- Neither mOS (48.5 months) nor mPFS (17.0 months) differed significantly between the two different initial ALK TKIs
- mPFS was found to significantly vary by initial disease presentation
  - patients receiving ALK TKI for relapsed early stage disease (recurrence with metastatic disease after curative-intent surgical resection [stage I, II, or III]) had significantly longer time to progression than did ALK TKI-treated patients presenting with de novo advanced NSCLC (mPFS: 30.8 versus 15.0 mo; p < 0.04)

A



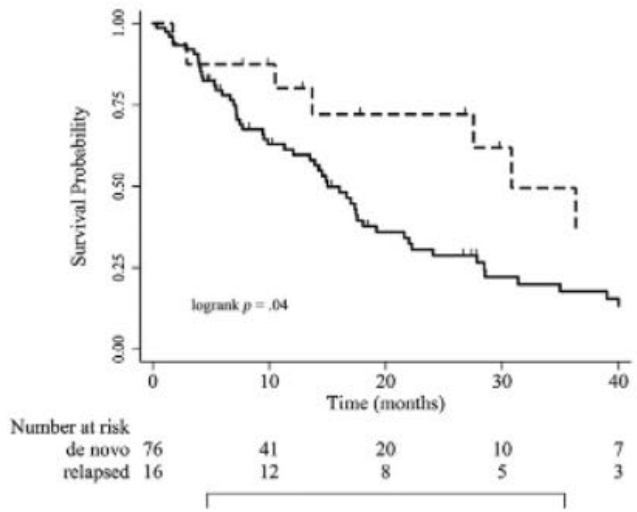
Median postmetastatic Disease Survival:
Aggregate: 48.5 months
[95% CI: 26.4 – not reached]
Frontline Crizotinib: 46.6 months
[95% CI: 25.1 – not reached]
Frontline Alectinib: 50.7 months
[95% CI: 50.7 – not reached]
Log-rank $p = 0.32$

B



Median Progression-free Survival:
Aggregate:17.0 months
[95% CI: 13.7 – 22.2]
Frontline Crizotinib: 16.0 months
[95% CI: 12.1 – 22.0]
Frontline Alectinib: 34.9 months
[95% CI: 6.6 – not reached]
Log-rank $p = 0.53$

C



Median Progression-free Survival:
Aggregate:17.0 months
[95% CI: 13.7 – 22.2]
Relapsed: 30.8 months
[95% CI: 13.7 – 54.9]
De novo: 15.0 months
[95% CI: 11.3 – 18.0]
Log-rank $p = 0.04$

	Relapsed Metastatic Disease (n = 16)	*de novo* Metastatic Disease (n = 76)	Statistical Comparison
Age median (IQR)	69.7 (53.3–72.7)	58.3 (51.6–68.7)	Z = 1.267 $p = 0.21$
Sex			$X^2 = 0.42$ df(1) $p = 0.52$
Male	7 (44%)	40 (53%)	
Female	9 (56%)	36 (47%)	
Smoking history			$X^2 = 0.89$ df(1) $p = 0.34$
Ever	9 (56%)	32 (42%)	
Never	7 (44%)	42 (58%)	
ECOG Performance Status			$X^2 = 2.18$ df(1) $p = 0.10$
ECOG: 0 or 1	15 (94%)	59 (78%)	
ECOG: 2 or 3	1 (6%)	17 (22%)	
TNM (eighth edition) M-stage			$X^2 = 9.80$ df(4) $p = 0.05$
M0	2 (13%)	8 (11%)	
M1a	5 (31%)	19 (25%)	
M1b	8 (50%)	24 (31%)	
M1c	1 (6%)	25 (33%)	

Figure 1. Survival outcomes for ALK-rearranged cohort. (*A*) Median postmetastatic disease survival. (*B*) Median progression-free survival. (*C*) Median progression-free survival relapsed versus de novo. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range.

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

Results

- A case-matching protocol identified a cohort of 41 matched cases
  - Patients with ALK-mutant NSCLC who received initial ALK TKI vs those with ALK-wildtype NSCLC initially treated with cytotoxic chemotherapy
  - (mOS: 46.8 m versus 14.2 m, log-rank $p < 0.001$)
  - ECOG PS greater than or equal to 2 was associated with reduced mPFS (7.4 versus 17.6 mo, log-rank $p < 0.02$)
- The most common reason for discontinuation of initial ALK TKI therapy at the time of analysis was progressive disease
  - 58% advancement of preexisting lesions
  - 30% exhibiting new metastatic brain metastasis
  - the most common site of metastatic spread

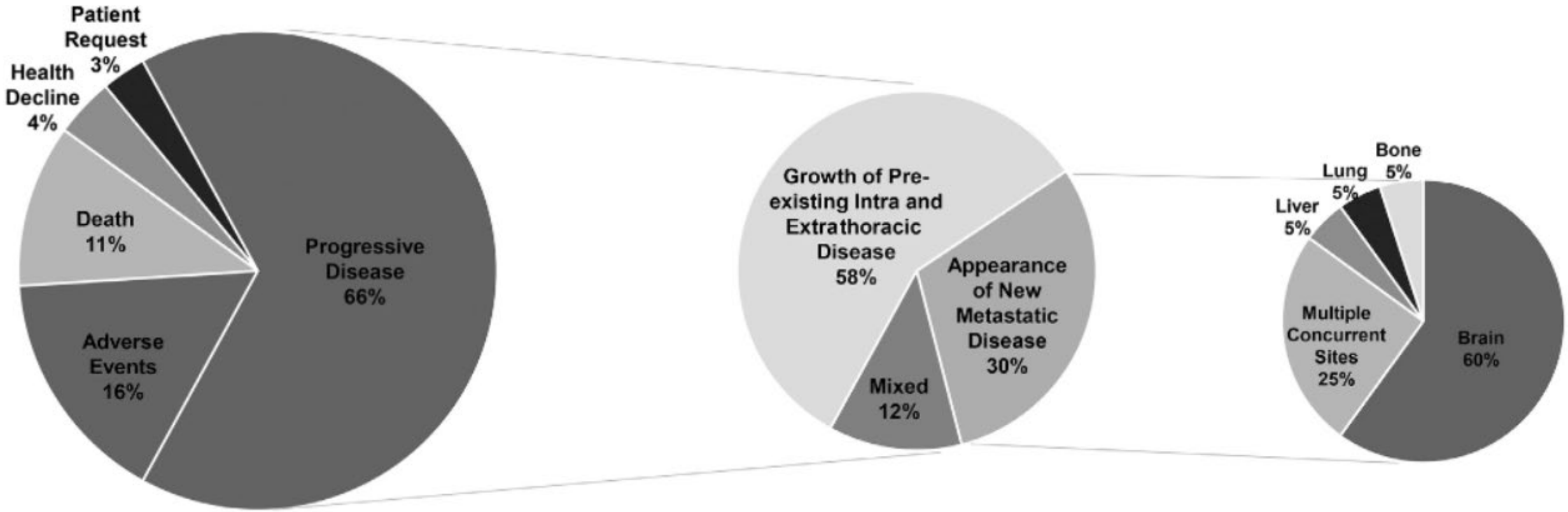
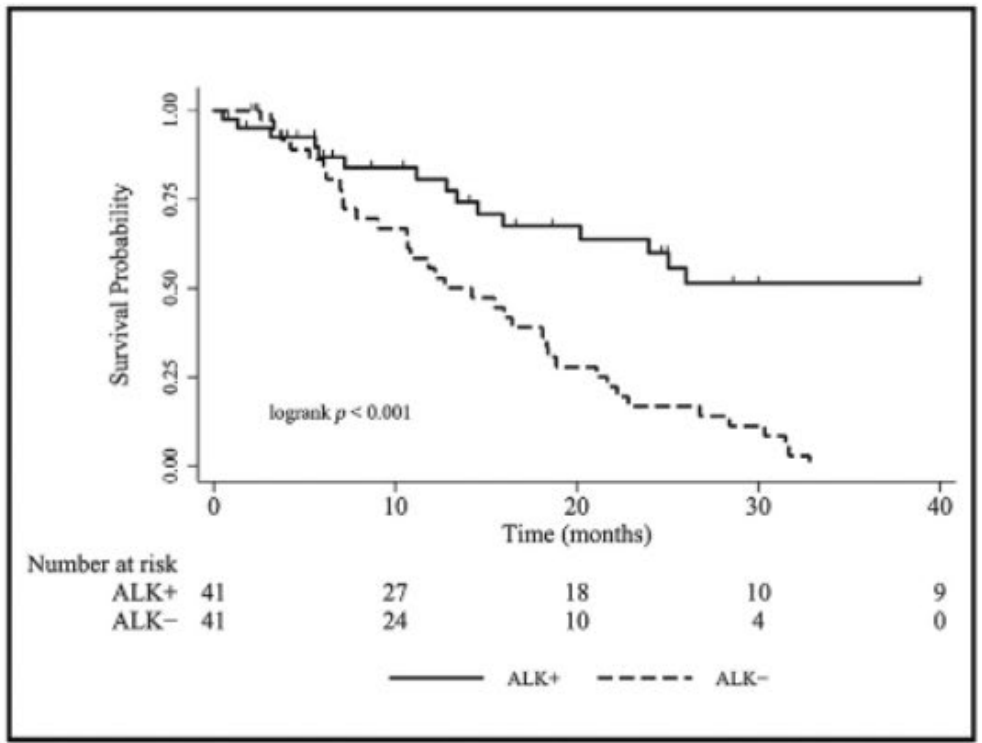


Figure 4. ALK TKI termination reasons and sites of failure. TKI, tyrosine kinase inhibitor.

- ***JTO Clinical and Research Reports Vol. 2 No. 4: 100157***



Median Post-Treatment Initiation Survival:
ALK-rearranged: 46.8 months [95% CI: 15.9 – not reached]
ALK-wildtype: 14.2 months [95% CI: 9.1–18.3]
Log-rank $p < 0.001$

	ALK-Rearranged on ALK TKI (n = 41)	ALK-wildtype on Cytotoxic Chemotherapy (n = 41)
Age median (IQR)	61.0 (51.9–70.6)	65.3 (58.7–70.2)
Sex		
Male	15 (37%)	15 (37%)
Female	36 (63%)	36 (63%)
Histology		
Adenocarcinoma	41 (100%)	41 (100%)
Smoking History		
Ever	35 (85%)	35 (85%)
Never	6 (15%)	6 (15%)
ECOG Performance Status		
ECOG: 0 or 1	33 (80%)	33 (80%)
ECOG: 2 or 3	8 (20%)	8 (20%)
TNM (eighth edition) M-stage		
M0	6 (15%)	6 (15%)
M1a	10 (24%)	10 (24%)
M1b	13 (32%)	13 (32%)
M1c	12 (29%)	12 (29%)

Figure 2. Case-matched cohort survival analysis and demographic features. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; TKI, tyrosine kinase inhibitor.

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

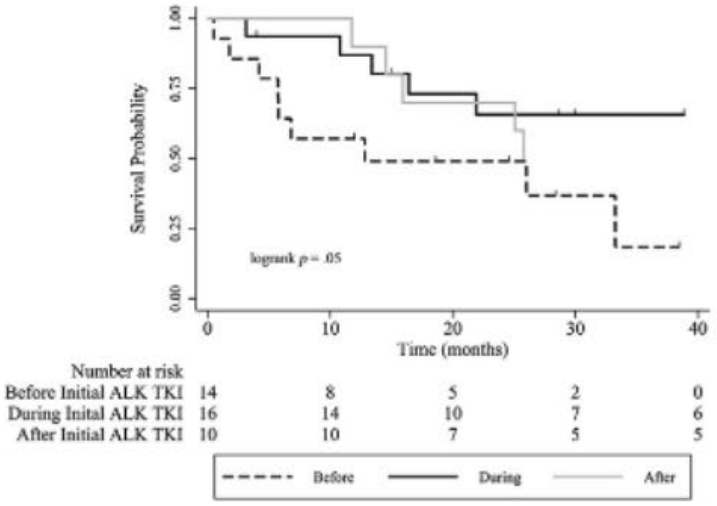
JTO Clinical and Research Reports Vol. 2 No. 4: 100157

Results

- the most common site of metastatic spread
- Within the crizotinib-treated cohort, 50% of the patients had brain metastases at the time of analysis
- median time to brain metastases onset was 16.4 months

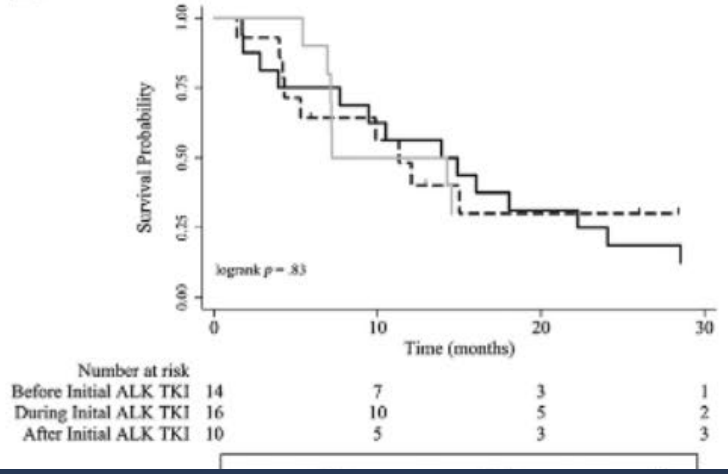
- Neither presence nor absence of brain metastases significantly affected median post-ALK TKI initiation survival or mPFS in the crizotinib-treated cohort
- Improved median post-ALK TKI initiation survival was observed in patients developing brain metastases during initial treatment with crizotinib, compared with those with brain metastases at baseline

A



Brain Metastases Onset	Median Post-ALK-inhibitor Initiation Survival [95% CI]	Pairwise Comparisons
At baseline	12.8 months [54.2–not yet reached]	**Baseline versus. During**: log-rank p=0.04*
During Initial ALK TKI	Not yet reached [16.4–not yet reached]	
Post-Initial ALK TKI	25.7 months [11.7–not yet reached]	**Baseline versus. Post**: log-tank p = 0.16 **During versus. Post**: log-rank p = 0.21
Any brain metastases	33.3 months [15.9–not yet reached]	**Any versus. None**: log-rank p = 0.62
No brain metastases to date	41.4 months [20.2–not yet reached]	

B



Brain Metastases Onset	Median Progression-free Survival [95% CI]	Pairwise Comparisons
At baseline	11.3 months [4.19–not yet reached]	**Baseline versus. During**: log-rank p=0.88
During Initial ALK TKI	13.9 months [3.9–22.4]	
Post-Initial ALK TKI	7.2 months [5.4–not yet reached]	**Baseline versus. Post**: log-tank p = 0.81 **During versus. Post**: log-rank p = 0.52
Any brain metastases	16.0 months [12.8–54.0]	**Any versus. None**: log-rank p = 0.08
No brain metastases to date	22.0 months [13.7–30.8]	

Figure 5. Impact of brain metastases on outcome. (A) Median survival after ALK TKI initiation. (B) Median progression-freesurvival. CI, confidence interval; TKI, tyrosine kinase inhibitor

	Total Cohort (n=92) n (%)	Crizotinib (n=72)	Alectinib (n=20)	p-value
Adverse Events				
Adverse Event(s) Occurred				
No	28 (30)	18 (25)	10 (50)	X^2, df(1) p=0.04*
Yes	64 (70)	54 (75)	10 (50)	
Highest Grade of Reported AE, per Patient				
None	28 (30)	18 (25)	10 (50)	X^2, df(4), p=0.3
Low (grade 1 or 2)	54 (59)	45 (63)	9 (45)	
Serious (grade 3 or 4)	10 (11)	9 (12)	1 (5)	
Number of Adverse Events per Patient				
Median (IQR)	2 (1-3)	2 (1-3)	1 (1-2)	Z = -1.7, p=0.07
Time to First Reported Adverse Event (days)				
Median (IQR)	27.5 (14-39)	27.5 (14-35)	23 (9-58)	Z = -0.1, p=0.9
Maximum Grade of Reported Adverse Event(s)				
Median, (IQR), range	2 (1-2), 1-4	2 (1-2), 1-4	1.5 (1-2), 1-3	Z = -0.74, p=0.5
Most Common AE (CTCAE 5.0 Category)				
Eye Disorders				
Yes	22 (24)	22 (31)	0 (0)	X^2, df(1) p<0.001*
No	70 (76)	50 (69)	20 (100)	
General Disorders				
Yes	17 (18)	15 (21)	2 (20)	X^2, df(1) p=0.2
No	75 (82)	57 (79)	18 (80)	
Gastrointestinal Disorders				
Yes	30 (33)	27 (38)	3 (15)	X^2, df(1) p=0.04*
No	62 (67)	45 (62)	17 (85)	

Gibson, A., Box, A., Dean, M. L., Elegbede, A. A., Hao, D., Sangha, R., & Bebb, D. G. (2021). Retrospective Real-World Outcomes for Patients With *ALK*-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors. *JTO clinical and research reports*, *2*(4), 100157. https://doi.org/10.1016/j.jtocrr.2021.100157

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

Results (overview)

- A total of 92 patients with ALK-rearranged NSCLC treated with ALK TKI (78% crizotinib, 22% alectinib) were identified.
- In the ALK-rearranged cohort, 1-year survival rate was 73% and
- Median overall survival (OS) was 48.5 months.
- Progression-free survival (PFS) was 17.0 months.
- An objective response rate of 49% was observed
- and adverse events were reported in 70% of the patients, primarily of low grade (84%).

Supplementary Data 1: Clinical Response and Outcome for ALK-rearranged NSCLC on initial ALK-TKI

	Total Cohort	Initial ALKTKI		
Initial ALK-TKI Treatment Characteristics and Response				
	Total Cohort (n=92) n (%)	**Crizotinib (n=72)**	**Alectinib (n=20)**	**p-value**
Survival Rate [95% CI]				
1-year	73% [62.4-81.2]	71% [58.6-79.9]	86% [53.9-96.2]	-
2-year	59% [57.5-69.1]	56% [43.7-66.7]	86% [53.9-96.2]	
Median time on Initial ALK-TKI				
Cycles, (ICR)	12.7 (6.5-26.6)	13.2 (6.9-27.9)	7.5 (4.1-21.4)	Z = -1.11 p=0.3
Adherence to Initial ALK-TKI				
Full Adherence	69 (75)	49 (74)	20 (100)	X^2, df(1) p=0.001*
Partial Adherence	23 (25)	23 (26)	0 (0)	
Treatment Breaks During Initial ALK-TKI				
No	73 (79)	53 (74)	20 (100)	X^2, df(1) p=0.001*
Yes	19 (21)	19 (26)	0 (0)	
Median duration (days), (IQR)	8 (7-28)	8 (7-28)	-	
Dose Adjustment During Initial ALK-TKI				
No	81 (88)	61 (85)	20 (100)	X^2, df(1) p=0.001*
Yes	11 (12)	11 (15)	0 (0)	
Median duration in months, (IQR)	14.5 (1-21)	14.5 (1-21)	-	
Best Response Metrics				
Complete response	4 (5)	1 (1)	3 (15)	
Partial response	40 (45)	31 (43)	9 (45)	X^2, df(4) p=0.06
Stable disease	26 (29)	24 (33)	2 (10)	
Progressive disease	8 (9)	6 (9)	2 (10)	
Non-evaluable	11 (12)	9 (14)	2 (10)	
Time to best response (days), (IQR)	58 (49-107)	56 (49-107)	67.5 (45.5-95)	Z = 0.22, p=0.8
Duration of best response (months), (IQR)	9.7 (3.2-17.6)	10.4 (4.0-22.8)	3.2 (0.12-14.3)	Z = -1.9, p=0.06
Disease Control Rate	76%	78%	70%	X^2, df(1) p=0.92
Objective Response Rate	48%	45%	60%	X^2, df(1) p=0.10

Gibson, A., Box, A., Dean, M. L., Elegbede, A. A., Hao, D., Sangha, R., & Bebb, D. G. (2021). Retrospective Real-World Outcomes for Patients With *ALK*-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors. *JTO clinical and research reports*, *2*(4), 100157.

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

key messages

- distinctions between the outcomes of patients with NSCLC with relapsed versus de novo metastatic disease
- crizotinib cohort in this study had a lower 1-year survival rate than crizotinib treatment cohort in the ALEX clinical trial (71% versus 83%)
- The aggregate ORR (48%) within this study is lower than the greater than 60% ORR observed in other clinial study and realworld cohorts.[1,2]

- DCR within this study :76%
- for the entire cohort, AEs accounted for 16% of all reasons for ALK TKI termination
  - higher rates of AEs in crizotinib-treated patients
- Median time-to-onset of brain metastases was 16.4 months after initiation of initial ALK TKI
  - previous real-world cohorts (range: 7–11 mo) [3,4]

1. Davis KL, et a. Curr Oncol. 2018;25:e40– e49
2. Zhou C, et al. Lancet Respir Med. 2019;7:437–466
3. Del Valle MFF, Chang AY. J Thorac Dis. 2019;11:3864–3873.
4. 8. Costa DB, et al. J Clin Oncol. 2015;33:1881–1888

Retrospective Real-World Outcomes for Patients With ALK-Rearranged Lung Cancer Receiving ALK Receptor Tyrosine Kinase Inhibitors

Amanda J. W. Gibson, BSc (Hons),a Adrian Box, MD, PhD,a,b Michelle L. Dean, BSc,aAnifat A. Elegbede, MSc,a Desiree Hao, MD,a,c Randeep Sangha, MD,d,eD. Gwyn Bebb, BMBCh, PhDa,

JTO Clinical and Research Reports Vol. 2 No. 4: 100157

conclusion

- **Case matching using patients with ALK-wildtype NSCLC receiving cytotoxic chemotherapy supports the conclusion that the improved prognosis comes only in the context of both ALK-rearrangement and ALK-inhibiting therapy**

GLASS: Global Lorlatinib for ALK(+) and ROS1(+) retrospective Study: real world data of 123 NSCLC patients

Lung Cancer 148 (2020) 48–54

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

GLASS: Global Lorlatinib for *ALK*(+) and *ROS1*(+) retrospective Study: real world data of 123 NSCLC patients

Nir Peled[a,b,*], Roni Gillis[a,b], Saadettin Kilickap[c], Patrizia Froesch[d], Sergei Orlov[e], Elena Filippova[e], Umut Demirci[f], Petros Christopoulos[g], Irfan Cicin[h], Fatma Bugdayci Basal[i], Cengiz Yilmaz[j], Moiseenko Fedor[k,l], Taner Korkmaz[m], Semra Paydas[n], Oliver Gautschi[o], Alisan Zirtiloglu[p], Yesim Eralp[m], Havva Yesil Cinkir[r], Ahmet Sezer[s], Mustafa Erman[c], Deniz Tural[p], Hande Turna[t], Julien Mazieres[u], Elizabeth Dudnik[v], Noemi Reguart[w], David Ross Camidge[x], Terry L. Ng[y], Filiz Çay Şenler[z], İsmail Beypınar[A], Doğan Yazılıtaş[B], Ahmet Demirkazık[z], Aziz Karaoğlu[C], Kerem Okutur[D], Hasan Şenol Coşkun[E], Mehmet Ali Nahit Şendur[B], Abdurrahman Isikdogan[E], Devrim Cabuk[I], Perran Fulden Yumuk[F], Ibrahim Yıldız[m], M. Ali Kaplan[E], Özgür Özyılkan[s], İlhan Öztop[C], Omer Fatih Olmez[G], Kübra Aydin[J], Adnan Aydıner[q], Nezih Meydan[H], Roxana Denisa Grinberg[a,b], Laila C. Roisman[a,b]

Table 1
Baseline characteristics and patient demographics. Data are in (%) in *ALK/ROS1* group, unless indicated otherwise. ECOG = Eastern Cooperative Oncology Group.

Characteristics	ALK (+) patients	ROS1 (+) patients
Age at diagnosis, Y		
Median	53	49
Mean (SD)	53 (12.7)	51 (10.7)
Range	19-84	22-70
Sex		
Male	53 (50%)	9 (53%)
Female	53 (50%)	8 (47%)
Smoking history		
Never	77 (73%)	11 (65%)
Current	5 (5%)	1 (6%)
Former	23 (21%)	5 (29%)
Unknown	1 (1%)	0 (%)
Histology		
Adenocarcinoma	103 (97%)	16 (94%)
Other NSCLC	3 (3%)	1 (6%)
Stage of disease at diagnosis		
Early	4 (4%)	1 (6%)
3-4	102 (96%)	16 (94%)
ECOG performance status at diagnosis		
0-1	65 (61%)	11 (65%)
2≤	15 (14%)	3 (18%)
NA	26 (25%)	3 (18%)
Brain metastasis at diagnosis		
Present	72 (68%)	11 (65%)
Absent	34 (32%)	6 (35%)
Method of diagnosis†		
FISH	81 (76%)	12 (71%)
IHC	33 (31%))	2 (12%)
NGS	8 (8%)	2 (12%)
PCR	14 (13%)	2 (12%)

† Few patients have been diagnosed by more than one method.

From March 2015 to January 2019, a total of 123 ALK or ROS1 positive NSCLC patients were enrolled from 8 countries (Table 1).

Several clinical endpoints were assessed.

- **Objective response rate (ORR)** was defined by the investigator using RECIST 1.1 as the proportion of patients achieving a best clinical response to lorlatinib of either CR or PR.
- **Disease control rate (DCR)** was defined as the patients achieved a best clinical response of CR + PR + SD.
- **Duration of therapy (DoT)** was defined as time from lorlatinib treatment initiation until treatment termination, including treatment beyond progression. Patients without a progression event were censored at the earlier of initiation of a new therapy or last available medical record.
- Finally, **overall survival (OS)** was calculated from initial diagnosis of metastatic disease with a data cut-off at January 2019. Patients who were still alive at the time of data cut off were censored at the date of the last available medical record.

Peled, N. et.al. Lung cancer 148 (2020)

Overview of therapies before treatment with Lorlatinib

Lung Cancer 148 (2020) 48–54

ALK (+) patients

Table 2
Last therapy before Lorlatinib treatment.

Last Therapy before Lorlatinib	Summary of cases	Lorlatinib as 2nd Line	Lorlatinib as 3rd Line	Lorlatinib as 4th Line	Lorlatinib as 5th Line	Lorlatinib as 6th Line	Lorlatinib as 7th Line	Lorlatinib as 8th Line
ALK(+) Patients								
Crizotinib	40 (38%)	12 (75%)	22 (55%)	4 (13%)	2 (18%)			
Alectinib	15 (14%)	1 (6%)	2 (5%)	8 (24%)	1 (9%)	1 (50%)		2 (67%)
Brigatinib	13 (12%)		1 (2%)	6 (18%)	4 (36%)		1 (100%)	1 (33%)
Ceritinib	25 (24%)	3 (19%)	9 (22%)	10 (30%)	2 (18%)	1 (50%)		
Chemotherapy	13 (12%)		6 (16%)	5 (15%)	2 (18%)			
Total ALK(+) cases	106 (100%)	16 (100%)	40 (100%)	33 (100%)	11 (100%)	2 (100%)	1 (100%)	3 (100%)
ROS1(+) Patients								
Crizotinib	12 (71%)	5 (83%)	5 (83%)				1 (100%)	1 (100%)
Ceritinib	2 (12%)	1 (17%)	1 (17%)					
Chemotherapy	3 (18%)			3 (100%)				
Total ROS1(+) cases	17 (100%)	6 (100%)	6 (100%)	3 (100%)			1 (100%)	1 (100%)

N (% from summary of line of treatment).

Lorlatinib was
2nd line in 16/106 patients (15 %), **3rd** line in 40/106 patients (38 %) and **4th** line in 33/106 (31 %), **≥5th** 17/106 (16%)

ECOG score was **0–1** in 65/106 **(61 %)** of the patients upon lorlatinib initiation

Last previous line prior to lorlatinib was **crizotinib** in 40/106 **(38 %)**, **ceritinib** in 25/106 **(24 %)**, **alectinib** 15/106 **(14 %)**, **brigatinib** 13/106 **(12 %)** and **chemotherapy** 13/106 **(12 %)**

Table 3A

Extracranial best response to Lorlatinib treatment.

Extracranial Best response to Lorlatinib treatment	Summary of cases	2nd Line	3rd Line	4th Line	5th Line	6th Line	7th Line	8th Line
ALK(+) Patients								
Objective Response Rate	52 (60%)	7 (64%)	21 (63%)	15 (54%)	7 (70%)	0 (0%)	0 (0%)	2 (67%)
Disease Control Rate	79 (91%)	11 (100%)	28 (88%)	24 (86%)	10 (100%)	2 (100%)	1 (100%)	3 (100%)
Complete Response	9 (10%)	2 (18%)	4 (13%)	1 (4%)	2 (20%)			
Partial Response	43 (50%)	5 (46%)	17 (53%)	14 (50%)	5 (50%)			2 (67%)
Stable Disease	27 (31%)	4 (36%)	7 (22%)	9 (32%)	3 (30%)	2 (100%)	1 (100%)	1 (33%)
Progressive Disease	8 (9%)	0 (0%)	4 (12%)	4 (14%)				
Summary of available data	87 (100%)	11 (100%)	32 (100%)	28 (100%)	10 (100%)	2 (100%)	1 (100%)	3 (100%)
Indeterminate/ Missing Data	19	5	8	5	1			
Total ALK(+) cases	106	16	40	33	11	2	1	3
ROS1(+) Patients								
Objective Response Rate	8 (62%)	1 (25%)	4 (100%)	1 (33%)			1 (100%)	1 (100%)
Disease Control Rate	12 (92%)	4 (100%)	4 (100%)	2 (67%)			1 (100%)	1 (100%)
Complete Response	0 (0%)							
Partial Response	8 (61%)	1 (25%)	4 (100%)	1 (33%)			1 (100%)	1 (100%)
Stable Disease	4 (31%)	3 (75%)		1 (33%)				
Progressive Disease	1 (8%)			1 (33%)				
Summary of available data	13 (100%)	4 (100%)	4 (100%)	3 (100%)			1 (100%)	1 (100%)
Indeterminate/ Missing Data	4	2	2					
Total ROS1(+) cases	17	6	6	3			1	1

All percentage calculations are from the total of patients with available evaluable data.
N (% from summary of line treatment).

Peled, N. et.al. Lung cancer 148 (2020)

Table 3B
Intracranial best response to Lorlatinib treatment.

Intracranial Best response to Lorlatinib treatment	Summary of cases	2nd Line	3rd Line	4th Line	5th Line	6th Line	7th Line	8th Line
ALK(+) Patients								
Objective Response Rate	40 (62%)	5 (50%)	12 (71%)	13 (52%)	7 (78%)	1 (50%)	1 (100%)	2 (67%)
Disease Control Rate	57 (88%)	10 (100%)	14 (83%)	20 (80%)	9 (100%)	2 (100%)	1 (100%)	3 (100%)
Best Overall Response								
Complete Response	10 (16%)	2 (25%)	2 (12%)	5 (20%)	1 (11%)			
Partial Response	30 (46%)	2 (25%)	10 (59%)	8 (32%)	6 (67%)	1 (50%)	1 (100%)	2 (67%)
Stable Disease	17 (26%)	4 (50%)	2 (12%)	7 (28%)	2 (22%)	1 (50%)		1 (33%)
Progressive Disease	8 (12%)		3 (17%)	5 (20%)				
Summary of available data	65 (100%)	8 (100%)	17 (100%)	25 (100%)	9 (100%)	2 (100%)	1 (100%)	3 (100%)
Indeterminate/ Missing Data	41	8	23	8	2			
Total ALK(+) cases	106	16	40	33	11	2	1	3
ROS1(+) Patients								
Objective Response Rate	6 (67%)	2 (67%)	2 (100%)	1 (33%)			1 (100%)	
Disease Control Rate	7 (78%)	3 (100%)	2 (100%)	1 (33%)			1 (100%)	
Best Overall Response								
Complete Response	1 (11%)		1 (50%)					
Partial Response	5 (56%)	2 (67%)	1 (50%)	1 (33%)			1 (100%)	
Stable Disease	1 (11%)	1 (33%)						
Progressive Disease	2 (22%)			2 (67%)				
Summary of available data	9 (100%)	3 (100%)	2 (100%)	3 (100%)			1 (100%)	
Indeterminate/ Missing Data	8	3	4				1	
Total ROS1(+) cases	17	6	6	3			2	

All percentage calculations are from the total of patients with available evaluable data.
N (% from summary of line treatment).

Peled, N. et.al. Lung cancer 148 (2020)

DoT

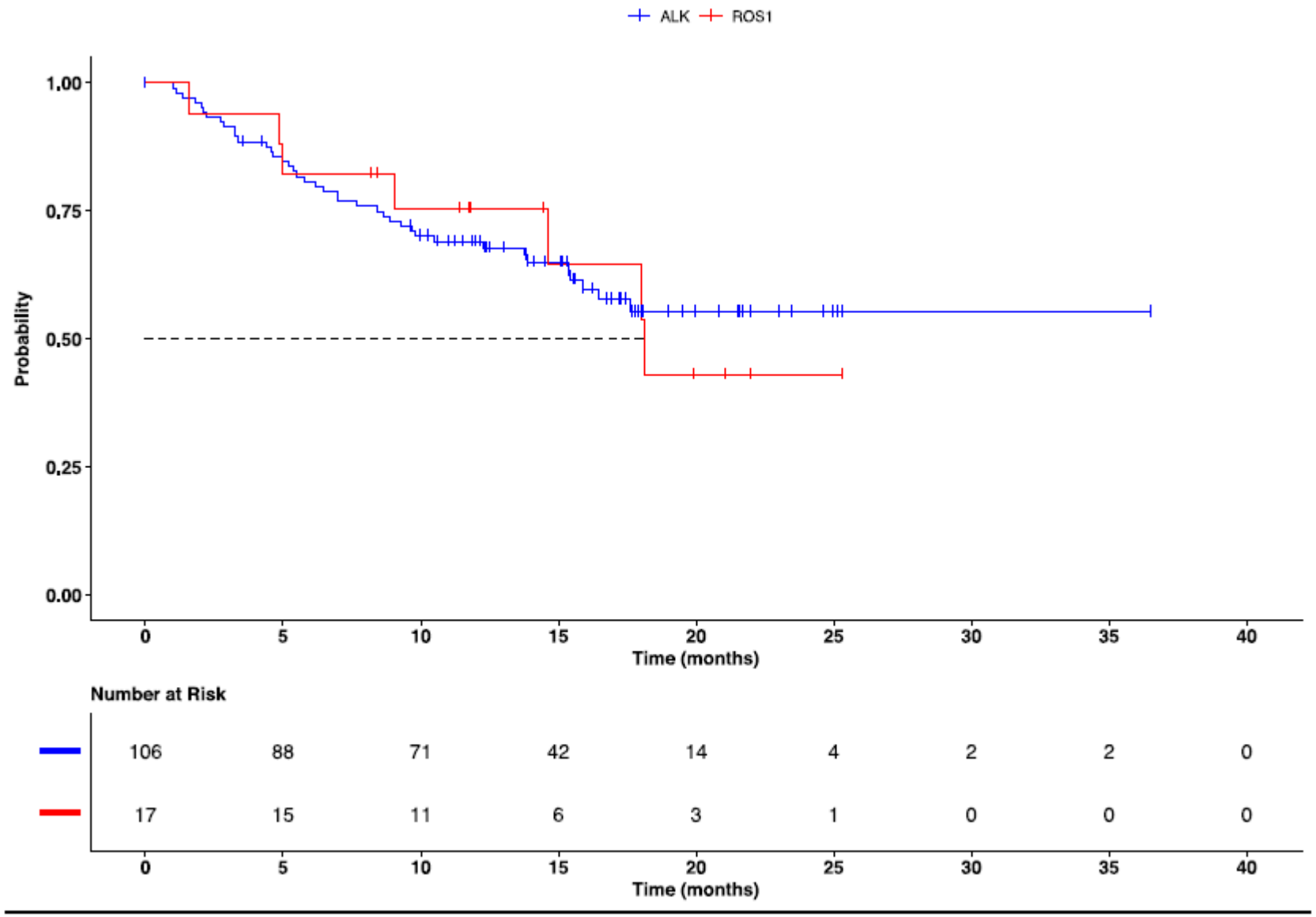


Fig. 1. Duration of Therapy (DoT) of Lorlatinib in ALK and ROS1 NSCLC patients.

ALK (+)

The median duration of therapy (DoT) was not reached with a mean **DoT of 23.9 ± 1.6 months** (95 % CI 20.9–27)

ROS (+)

The median duration of therapy **(DoT) was 18.1 ± 2.5 months** (95 % CI 13.2–23.1)

Peled, N. et.al. Lung cancer 148 (2020)

Overal Survival for the cohort in total

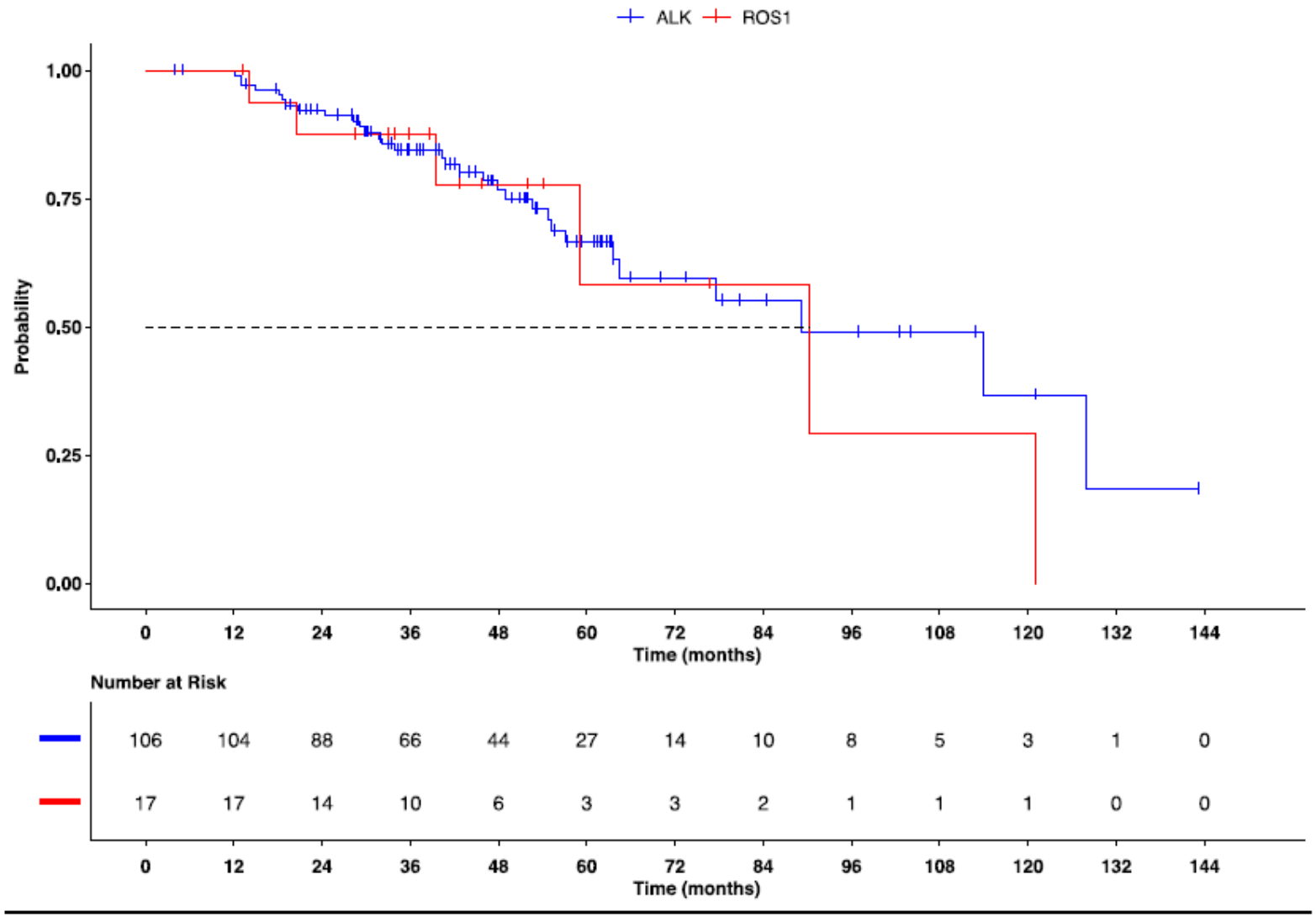


Fig. 2. Overall Survival (OS) since first diagnosis, all cohorts (ALK and ROS1 subgroups).

ALK (+)

median OS was 89.1 ± 19.6 months

(95 % CI 50.7–127.5)

OS and DoT were not significantly correlated with neither line of therapy nor with the previous type of therapy.

ROS (+)

median OS was 90.3 ± 24.4 months

(95 % CI 42.5–138.1)

OS and DoT were not significantly correlated with lorlatinib line of therapy.

Peled, N. et.al. Lung cancer 148 (2020)

Table 4
Lorlatinib's adverse events.

Adverse effect N = 123	Grade1 N (%)	Grade 2 N (%)	Grade 3 N (%)	Grade 4 N (%)
Hyperlipidemia	13 (11%)	35 (28%)	8 (6%)	3 (3%)
Hypercholesterolemia	12 (10%)	34 (28%)	7 (6%)	3 (3%)
Hypertriglyceridemia	25 (20%)	24 (20%)	2 (2%)	2 (2%)
Peripheral edema	27 (22%)	29 (24%)	2 (2%)	
Weight increased	23 (19%)	5 (4%)	2 (2%)	
Fatigue	23 (19%)	6 (5%)	1 (1%)	
Peripheral neuropathy	9 (7%)	4 (3%)	2 (2%)	
Cognitive effects	16 (13%)	6 (5%)		
Mood effects	16 (13%)	3 (2%)		
Diarrhea	6 (5%)	1 (1%)		
Arthralgia	6 (5%)	3 (2%)		
Increased AST	8 (6%)	2 (2%)		
Bronchial pain while breathing deeply	2 (2%)			
QTc prolongation		2 (2%)		
Creatinine elevation		1 (1%)		
Pleural and pericardial effusion		1 (1%)		
Systremma	1 (1%)			
Rash	2 (2%)			
Anemia	1 (1%)			
Dyspnea	1 (1%)			
Exanthema	1 (1%)			
Formication left arm	1 (1%)			
Ischemia	1 (1%)			
Dry skin	1 (1%)			
Double vision	1 (1%)			
Fever	1 (1%)			

HOW THE SAFETY PROFILE LOOK LIKE?

The most common lorlatinib treatment-related adverse events of any grade among all patients were:

hypercholesterolemia	**46 %** (56/ 123)
hypertriglyceridemia	**43 %** (53/123)
peripheral edema	**47 %** (58/123)
weight gain	**24 %** (30/123)
fatigue	**24 %** (30/123).

CNS adverse events such as cognitive effect of grade 1–2 were reported in 18 % (22/123) of patients.

Peled, N. et.al. Lung cancer 148 (2020)

This report confirms the activity of lorlatinib in ALK and ROS1 positive NSCLC both extracranial and intracranial:

- The **overall survival of 89 ± 19 months for ALK(+)** NSCLC patients treated with next generation TKIs, and
- it is the **first report** showing a **median OS of 90.3 ± 24.4 months for patients with ROS1(+) NSCLC where crizotinib was used first in most patients.**

The **extracranial ORR of 60 % and 62 %** respectively and the **intracranial ORR of 62 % and 67 % respectively** are as expected and in similarity with previous reports for lorlatinib both in the ALK and the ROS1 positive NSCLC [1]

ROS1 median DoT of 18.1 ± 2.5 months (95 % CI 13.2–23.1) showed in this cohort while previously reported 21.1 months (IQR 15·2–30·3) [2].

[1]A.T. Shaw, E. Felip, T.M. Bauer, et al., Lancet Oncol. 18 (2017) 1590–1599
[2]Alice T. Shaw, et al., Lancet Oncol. (2019)

Study has several limitations!!!

- It is retrospective and therefore imaging routine and standardization of previous lines were not feasible

- Likewise, the exact time of RECIST progression is limited, and therefore we discussed duration of therapy and not PFS, moreover there is a high degree of censoring which might reflect an over-estimation of the median DoT

- Survival data may overcome this limitation. Molecular profiling on progression was not available in most cases, and centrally assessed molecular testing or RECIST evaluation was not feasible

- Adverse events were collected and graded retrospectively.

The updated ALEX (Peters S, et al. for the ALEX Trial. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. N Engl J Med 2017; 377: 829-838 **) data shows a median PFS of 34.8 months for alectinib vs. 10.9 months for crizotinib and overall survival benefit for alectinib arm HR 0.67 (CI 0.46–0.98)**

The current report may emphasize the importance of preserving numerous therapeutic alternatives, particularly in countries with limited access to newer agents

Treatment strategy should be taken in caution and after considering all factors including existence of brain disease, mechanism of resistant and drug availability.

Bezbednosni profil ALK inhibitora i terapijski menadžment lekova: krizotinib, alektinib, brigatinib,ceritinib, lorlatinib

Dr Marina Cekić

Karakteristike pacijenata sa *ALK*+ NSCLC

Mlađi pacijenti[1–3]

Medijana starosti ~52 godine[1] u poređenju sa ~70 godina[3] za ostale tipove karcinoma pluća i bronha

Nepušači ili blagi pušači[1,2,4]

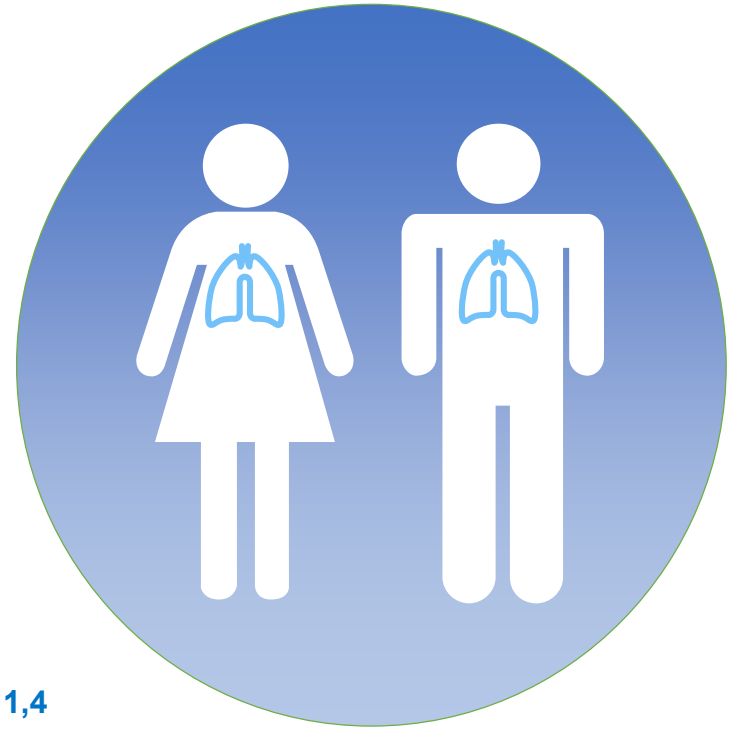
~70% *ALK*+ NSCLC pacijenata su nepušači

Histologija adenokarcinoma[1,4]

Odsustvo *EGFR* i *KRAS* mutacije[1]

Bolest otkrivena u uznapredovalom stadijumu[1,4]

- Pleuralni/perikardijalni izliv[1]
- Višestruke lezije/mesta[1,4]
- CNS metastaze[1,4]



1. Chia, et al. Clin Epidemiol 2014; 2. Mori, et al. Thorac Cancer 2019 3. Howlader, et al. SEER Cancer Statistics Review 2019 4. Digumarthy, et al. Cancers 2020

ALK = anaplastic lymphoma kinase; CNS = central nervous system *EGFR* = epidermal growth factor receptor; NSCLC = non-small-cell lung cancer

Terapijske opcije u 1L lečenja pacijenata sa *ALK*+ NSCLC

Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Key trial: **PROFILE 1014**[1]	Key trial: **ASCEND-4**[2]	Key trial: **ALEX**[3–5]	Key trial: **ALTA-1L**[6,7]	Key trial: **CROWN**[8]
Dose: 250mg BID	Dose: 450 / 750mg* QD	Dose: 600mg† BID	Dose: 180mg‡ QD	Dose: 100mg QD

1. Solomon, et al. N Engl J Med 2014; 2. Soria, et al. Lancet 2017 3. Peters, et al. N Engl J Med 2017; 4. Camidge, et al. J Thorac Oncol 2019 5. Mok, et al. Ann Oncol 2020; 6. Camidge, et al. N Eng J Med 2018
7. Camidge, et al. ESMO Asia 2019; 8. NCCN NSCLC guidelines. V6 2020 9. Planchard, et al. Ann Oncol 2019 8. Show et al 2020

	Alectinib	Brigatinib	Ceritinib	Lorlatinib
Clinical trial	ALEX[9,18]	ALTA-1L[17,22]	ASCEND-4[16]	CROWN[11]
OR (%) (95% CI)	82.9 (76.0–88.5)	74 (66–81)	72.5 (65.5–78.7)	76 (68–83)
Median DOR (months) (95% CI)	NE (NE)	33.2 (22.1 – NE)	23.9 (16.6 – NE)	NE (NE – NE)
Median PFS by ICR (months) (95% CI)	25.7 (19.9 – NE)	24.0 (18.5–43.2)*	16.6 (12.6–27.2)*	NE (NE – NE)*
Median PFS by IR (months) (95% CI)	34.8 (17.7 – NE)*	30.8 (21.3–40.6)	16.8 (13.5–25.2)	NE (NE – NE)
HR for disease progression or death (95% CI)	0.47 (0.34–0.65)	0.48 (0.35–0.66)	0.55 (0.42–0.73)	0.28 (0.19–0.41)
OS rates (%) (95% CI)	5-year OS rate 62.5% (54.3–70.8)	3 year-OS probability 71% (62–78)	2 year-OS probability 70.6% (62.2–77.5)	NA
Median OS, HR (95% CI)	0.67 (0.46–0.98)	0.81 (0.53–1.22)	0.73 (0.50–1.08)	0.72 (0.41–1.25)

Note: *Primary end point of the study.

Abbreviations: ICR, independent central review; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IR, investigator review; NA, no available data; NE, not estimable; OR, overall response; OS, overall survival; PFS, progression-free survival.

frontiers | Frontiers in Oncology

SYSTEMATIC REVIEW
published: 14 June 2022
doi: 10.3389/fonc.2022.921854

Beyond Crizotinib: A Systematic Review and Meta-Analysis of the Next-Generation ALK Inhibitors as First-Line Treatment for ALK-Translocated Lung Cancer

Emilio Francesco Giunta[1†], *Alessio Signori*[2†], *Howard Jack West*[3], *Giulio Metro*[4], *Alex Friedlaender*[5], *Kaushal Parikh*[6], *Giuseppe Luigi Banna*[1*‡] and *Alfredo Addeo*[5‡]

OPEN ACCESS

- U ovom sistematskom pregledu i metanalizi, ispitana je efikasnost i bezbednost ALK inhibitora sledeće generacije kod pacijenata sa nelečenim uznapredovalim ALK-translociranim karcinomom pluća, kroz baze podataka randomizovanih faze III kontrolisanih studija (PubMed, EMBASE i Cochrane biblioteka).

Bezbednost ALK inhibitora po studijskim podacima

Name of the trial	First author and year of publication	Treatment in the control arm: drug/ dose	Treatment in the experimental arm: drug/ dose	No of pts in the control arm	No of pts in the experimental arm	% of patients developing G≥3 AEs: control vs experimental arm		% of patients developing SAEs: control vs experimental arm		% of patients developing fatal AEs: control vs experimental arm		% of patients discontinuing drugs due to AEs: control vs experimental arm		% of patients needing dose reduction due to AEs: control vs experimental arm		% of patients interrupting drugs due to AEs: control vs experimental arm	
ALEX (19)	Peters et al., 2017	crizotinib 250 mg BID	alectinib 600 mg BID	151	152	50%	41%	29%	28%	5%	3%	13%	11%	21%	16%	25%	19%
J-ALEX (20)	Hida et al., 2017	crizotinib 250 mg BID	alectinib 300 mg BID	104	103	52%	26%	NA	NA	0	0	20%	9%	NA	NA	74%	29%
ALTA-1L (21)	Camidge et al., 2020	crizotinib 250 mg BID	brigatinib 180 mg QD (with 7-day lead-in at 90 mg QD)	137	136	61%	73%	NA	NA	NA	NA	9%	13%	25%	38%	NA	NA
ASCEND-4 (8)	Soria et al., 2017	platinum-based CT: cisplatin 75 mg/m2 or carboplatin AUC 5-6 + pemetrexed 500 mg/m2 q3w for 4 cycles followed by pemetrexed maintenance	ceritinib 750 mg QD	175	189	62%	78%	NA	NA	NA	NA	11%	5%	NA	NA	NA	NA
ALESIA (22)	Zhou et al., 2019	crizotinib 250 mg BID	alectinib 600 mg BID	62	125	43%	27%	26%	15%	5%	2%	10%	7%	23%	24%	27%	26%
eXalt3 (23)	Horn et al., 2021	crizotinib 250 mg BID	ensartinib 225 mg QD	146	143	40%	50%	6% (TR)	8% (TR)	3%	1%	7%	9%	20%	24%	NA	NA
CROWN (24)	Shaw et al., 2020	crizotinib 250 mg BID	lorlatinib 100 mg QD	142	149	56%	72%	27%	34%	5%	5%	9%	7%	15%	21%	47%	49%

AEs, adverse events; BID, bis in die; CI, confidence interval; G, grade; IA, investigator assessed; NA, not available; QD, quoque die; SAEs, serious advent events; TR, treatment-related.

Giunta et al. Beyond Crizotinib: A Systematic Review.
Front. Oncol., 14 June 2022 https://doi.org/10.3389/fonc.2022.921854

RR (relativni rizik) za bezbednosne ishode povezane sa ALKI sledeće generacije u poređenju sa kontrolnim terapijama.

(A) neželjeni događaji svih stepena

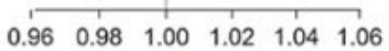
A

Study	Treatment Yes	Treatment No	Control Yes	Control No	RR with 95% CI	Weight (%)
ALEX, 2017	147	5	146	5	1.00 [0.96, 1.04]	9.15
ASCEND-4, 2017	189	0	170	5	1.03 [1.00, 1.06]	15.84
ALESIA, 2019	124	1	62	0	0.99 [0.96, 1.02]	14.15
ALTA-1L, 2020	135	1	137	0	0.99 [0.97, 1.01]	22.14
CROWN, 2020	149	0	141	1	1.01 [0.99, 1.03]	23.23
eXalt3, 2021	140	3	145	1	0.99 [0.96, 1.02]	15.49
Overall					1.00 [0.99, 1.02]	

Heterogeneity: $\tau^2 = 0.00$, $I^2 = 27.42\%$, $H^2 = 1.38$

Test of $\theta_i = \theta_j$: Q(5) = 6.65, p = 0.25

Test of $\theta = 0$: z = 0.39, p = 0.70



Random-effects REML model

(B) neželjeni događaji Gr. 3-4

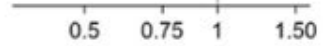
B

Study	Treatment Yes	Treatment No	Control Yes	Control No	RR with 95% CI	Weight (%)
ALEX, 2017	62	90	76	76	0.82 [0.64, 1.05]	14.46
ASCEND-4, 2017	147	42	109	67	1.26 [1.10, 1.44]	15.80
J-ALEX, 2017	27	76	54	50	0.50 [0.34, 0.73]	12.51
ALESIA, 2019	34	91	27	35	0.63 [0.42, 0.94]	11.99
ALTA-1L, 2020	99	37	84	53	1.20 [1.01, 1.42]	15.50
CROWN, 2020	107	42	80	62	1.29 [1.08, 1.53]	15.40
eXalt3, 2021	72	72	58	88	1.25 [0.97, 1.62]	14.33
Overall					0.96 [0.74, 1.26]	

Heterogeneity: $\tau^2 = 0.11$, $I^2 = 90.50\%$, $H^2 = 10.53$

Test of $\theta_i = \theta_j$: Q(6) = 37.98, p < 0.001

Test of $\theta = 0$: z = -0.26, p = 0.79

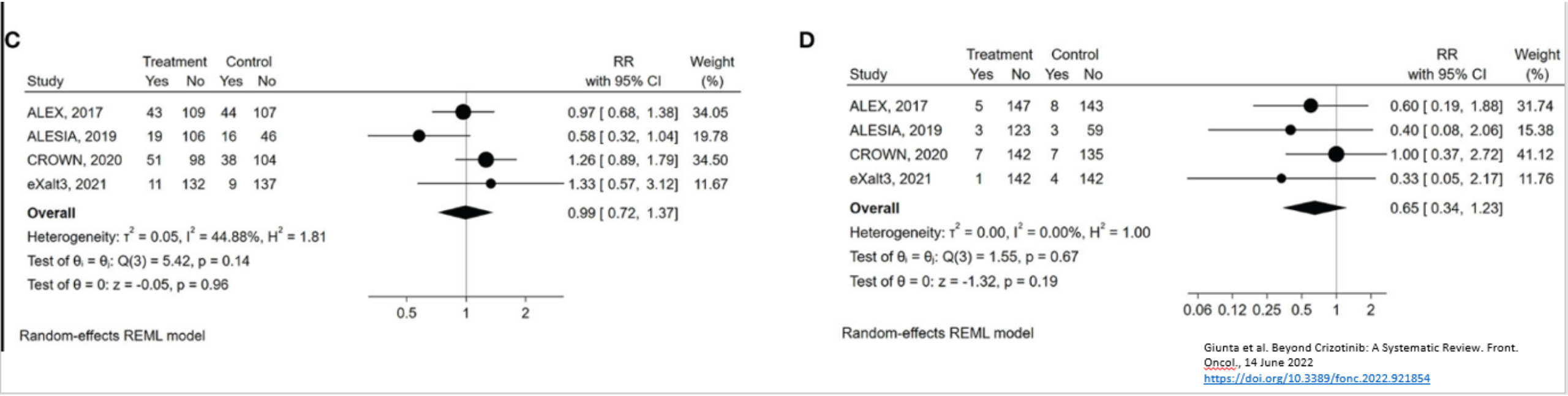


Random-effects REML model

U poređenju sa kontrolnom terapijom- krizotinibom, upotreba ALK inhibitora sledeće generacije nije bila povezana ni sa povećanim rizikom od neželjenih događaja za sve graduse niti za gr≥3.

Giunta et al. Beyond Crizotinib: A Systematic Review.
Front. Oncol., 14 June 2022 https://doi.org/10.3389/fonc.2022.921854

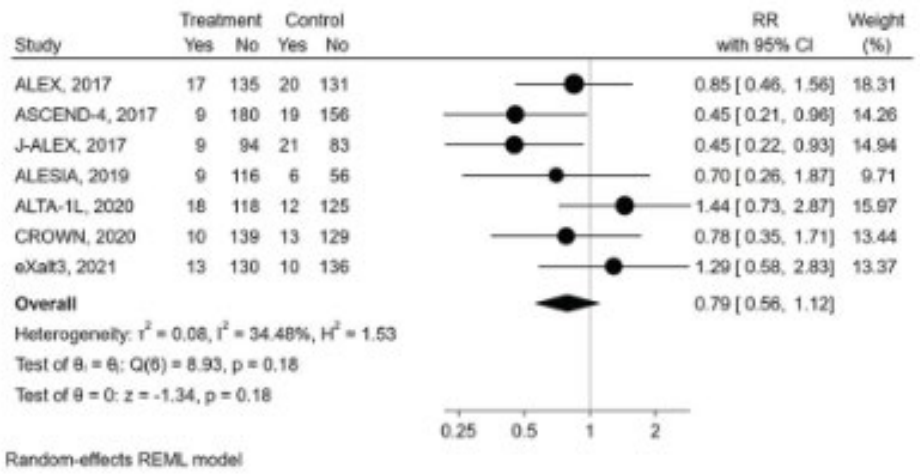
Fatalni neželjeni efekti (prijavljeni u pet studija) su takođe bili slični



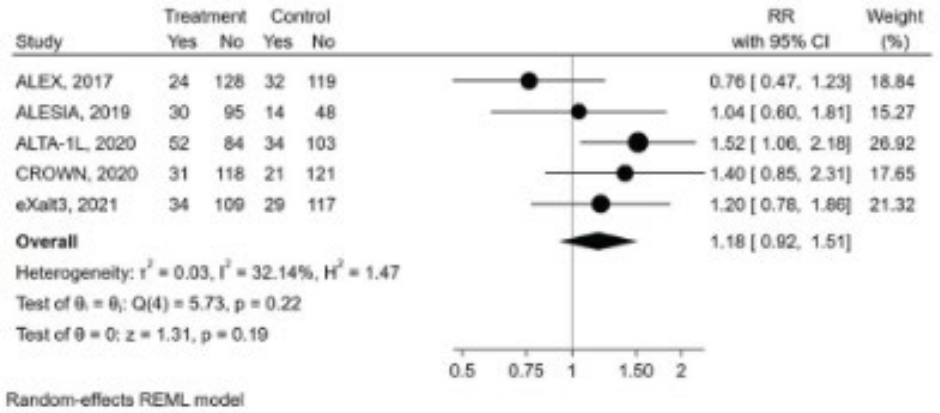
Giunta et al. Beyond Crizotinib: A Systematic Review.
Front. Oncol., 14 June 2022 https://doi.org/10.3389/fonc.2022.921854

RR za bezbednosne ishode povezane sa ALKI sledeće generacije u poređenju sa kontrolnim terapijama. (E) prekid upotrebe leka zbog neželjenih efekata. (F) smanjenje doze zbog neželjenih efekata. (G) prekid doze zbog neželjenih efekata

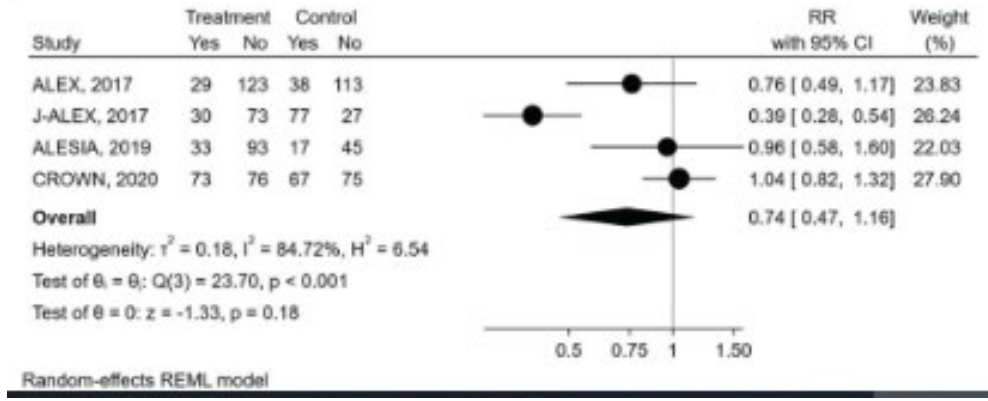
E



F



G



Sve studije su izvestile o prekidu uzimanja leka u vezi sa AE, pet o smanjenju doze i četiri o stopi prekida doze. Postojale su neznatne razlike između eksperimentalnog i kontrolnog leka za sve te parametre

Giunta et al. Beyond Crizotinib: A Systematic Review. Front. Oncol., 14 June 2022
https://doi.org/10.3389/fonc.2022.921854

Profil bezbednosti i toksičnosti ALK TKi

ALK TKi	Ozbiljni TRAEs, %	TRAE dovode do smanjenje doze, %	TRAE vode do prekida, %	TRAES Češći studijski lek vs krizotinib
Lorlatinib[1] 100 mg/day PO	Lorlatinib: 34 Crizotinib: 27	Lorlatinib: 21 Crizotinib: 15	Lorlatinib: 7 Crizotinib: 9	Hiperholesterolemija, hipertrigliceridemija, edem, povećanje telesne težine, periferna neuropatija, kognitivni efekti, anemija, hipertenzija, raspoloženje, hiperlipidemija
Alectinib[2,3] 600 mg BID PO	Alectinib: 39 Crizotinib: 32	Alectinib: 20 Crizotinib: 20	Alectinib: 15 Crizotinib: 15	Anemija, mijalgija, povećan bilirubin, povećana težina, mišićno-skeletni bol, reakcija fotosenzitivnosti
Brigatinib[4,5] 90 mg/day PO x 7 dana, zatim 180 mg/dnevno PO	-- --	Brigatinib: 44 Crizotinib: 25	Brigatinib: 13 Crizotinib: 9	Povećan CPK, kašalj, hipertenzija, povećana lipaza, rani početak ILD/pneumonitis
Ensartinib[6] 225 mg/dnevno PO	Ensartinib: 7.7 Crizotinib: 6.1	Ensartinib: 24 Crizotinib: 20	Ensartinib: 9 Crizotinib: 7	Osip (svi gradusi 68%, gradus 1/2 ~60%), pruritus, pireksija

1. Shaw. NEJM. 2020;383:2018. 2. Peters. NEJM. 2017;377:829. 3. Mok. Ann Oncol. 2020;31:1056.
4. Camidge. NEJM. 2018;379:21 5. Camidge. J Thorac Oncol. 2021;16:2091. 6. Horn. JAMA Oncol. 2021;7:1617.

ALECTINIB : Praćenje pacijenata zbog neželjenih reakcija:

PLUĆA	• Pacijente je potrebno pomno pratiti zbog moguće pojave pulmonarnih simptoma koji ukazuju na pneumonitis
JETRA	• Funkciju jetre, uključujući ALT, AST i ukupni bilirubin, treba proceniti na početku lečenja i pratiti svake 2 nedelje tokom prva 3 meseca lečenja. Nakon toga, navedene parametre treba pratiti periodično, jer neželjeni događaji mogu nastupiti i nakon 3 meseca. Procenu funkcije jetre potrebno je sprovoditi i češće kod pacijenata koji razviju povišene vrednosti transaminaza i bilirubina
SRCE	• Potrebno je kontrolisati srčanu frekvenciju i krvni pritisak u skladu sa kliničkim indikacijama
CPK	• Pacijente treba uputiti da prijave bilo kakav neobjašnjiv bol u mišićima, osetljivost mišića na dodir ili mišićnu slabost. Vrednosti CPK-a treba pratiti svake dve nedelje tokom prvog meseca lečenja, a zatim u skladu sa kliničkim indikacijama kod pacijenata koji prijave simptome

ALT = alanin transaminaza; AST = aspartat transaminaza; CPK = kreatin fosfokinaza

ALECTINIB: Bezbednosni profil

AE	ALECTINIB (ALEX)	
Najučestliji AE (svi gradusi)	Constipation (37%) Anemia (26%) Fatigue (22%) Povećanje bilirubina (22%)	Periferni edemi (19%) ALT povećanje (18%) AST povećanje (17%) Myalgia (17%) Nausea (16%)
% pacijenata sa gr ≥3 AEs	**52%**	
Najučestaliji gr ≥3 AEs	Anemia (6%) ALT povećanje (5%) AST povećanje (5%) Pneumonia (5%)	
% pacijenata sa redukcijom doze zbog AEs	**20%** **Mediana praćenja 48.2 m**	

ALIMS, Alecensa SmPC

ALEX : Bezbednosni profil

Safety population	alectinib (n=152)	crizotinib (n=151)
Median treatment duration, months	**28.1**	**10.8**
All grade AEs, n (%)	147 (96.7)	147 (97.4)
Serious AEs, n (%)	59 (38.8)	48 (31.8)
Grade 3–5 AEs, n (%)	79 (52.0)	85 (56.3)
Fatal AEs, n (%)	7 (4.6)	7 (4.6)
AEs leading to dose reduction, n (%)	31 (20.4)	30 (19.9)
AEs leading to dose interruption, n (%)	40 (26.3)	40 (26.5)
AEs leading to treatment discontinuation, n (%)	22 (14.5)	22 (14.6)

Uz **~3x duže trajanje lečenja lekom alektinib**, nivo redukcije doze leka, odlaganja terapije i prekida lečenja su bili slični u grupama pacijenata lečenih alektinibom i krizotinibom, čime je pokazano da se **alektinib dobro podnosi prilikom dugoročne upotrebe**

Third exploratory analysis (data cut-off: 29 November 2019)

1. Mok, et al. Ann Oncol 2020

Najčešći ND kod oba TKI:

Pacijenti sa ND, n (%)	ALECTINIB n=152	Crizotinib n=151
Konstipacija	56 (37)	51 (34)
Anemija	40 (26)	12 (8)
Umor	34 (22)	28 (19)
Povišen nivo bilirubina	33 (22)	2 (1)
Periferni edem	29 (19)	50 (33)
ALT povišen	27 (18)	51 (34)

ALEX : ND gradusa ≥3 sa incidencom ≥2% u obe grane

Pacijenti sa Gr.> 3ND	ALECTINIB %
Anemija	6%
ALT povišen	5%
AST povišen	5%
Pneumonija	5%
Infekcija urinarnog trakta	4%
Povišen CPK	3%

ALIMS, Alecensa SmPC

ALECTINIB: Modifikacija doze zbog neželjenih reakcija

Povišene vrednosti ALT-a ili AST-a gradusa ≥3 (>5 puta veće od GGN-a) uz ukupni bilirubin ≤2 puta veći od GGN-a	Privremeno odložiti primenu leka do oporavka na početnu vrednost ili gradus ≤1 (≤3 puta veća od GGN-a), a zatim nastaviti lečenje smanjenom dozom (videti Tabelu 1)
Povišene vrednosti ALT-a ili AST-a gradusa ≥2 (> 3 puta veće od GGN-a) uz porast vrednosti ukupnog bilirubina na > 2 puta iznad GGN-a, bez holestaze ili hemolize	Trajno obustaviti lečenje lekom Alecensa
Bradikardija* gradusa 2 ili stepena 3 (simptomatska, može biti teška i medicinski značajna, indikovana medicinska intervencija)	Privremeno odložiti primenu leka dok se bradikardija ne ublaži do gradusa ≤1 (asimptomatska bradikardija) ili dok srčana frekvencija ne bude ≥ 60 otkucaja u minuti. Proveriti istovremenu primenu lekova za koje se zna da uzrokuju bradikardiju, kao i antihipertenzivne lekove. Ako se utvrdi da je bradikardiji doprineo neki od istovremeno primenjivanih lekova i ako se njegova primena ukine ili se prilagodi doza, nastaviti lečenje dotadašnjom dozom nakon što se bradikardija ublaži do gradusa ≤1 (asimptomatska bradikardija) ili srčani ritam bude ≥ 60 otkucaja u minuti. Ako se utvrdi da bradikardiji nije doprineo nijedan od istovremeno primenjivanih lekova ili ako se ne ukine ili ne prilagodi doza istovremeno primenjivanih lekova koji su doprineli bradikardiji, nastaviti lečenje smanjenom dozom (videti Tabelu "Raspored smanjenja doze") nakon što se bradikardija ublaži do gradusa ≤1 (asimptomatska bradikardija) ili srčani ritam bude ≥ 60 otkucaja u minuti
Bradikardija* gradusa 4 (posledice opasne po život, indikovana urgentna intervencija)	Trajno obustaviti lečenje ako se utvrdi da bradikardiji nije doprineo nijedan od istovremeno primenjivanih lekova. Ako se utvrdi da je bradikardiji doprineo neki od istovremeno primenjivanih lekova i ako se njegova primena ukine ili prilagodi doza, nastaviti lečenje smanjenom dozom (videti Tabelu 1) nakon što se bradikardija ublaži do gradusa ≤1 (asimptomatska bradikardija) ili srčani ritam bude ≥ 60 otkucaja u minuti, uz često praćenje u skladu sa kliničkom indikacijom. U slučaju ponovnog javljanja, trajno obustaviti lečenje

ALIMS, Alectinib SmPC

ALECTINIB: Modifikacija doze zbog neželjenih reakcija

- Zbrinjavanje neželjenih dogadjaja može zahtevati smanjenje doze, privremeni prekid ili obustavu lečenja
- Dozu leka smanjivati postepeno u koracima od po 150mg dvaput na dan u skladu sa podnošljivošću leka

Raspored smanjenja doze	Nivo doze
Početna doza	alectinib 600mg dva puta dnevno
Prva redukcija doze	alectinib 450mg dva puta dnevno
Druga redukcija doze	alectinib 300mg dva puta dnevno

- Lečenje obustaviti u slučaju nepodnošenja doze od 300mg dva puta dnevno

BRIGATINIB: Bezbedonosni profil

- Ozbiljne neželjene reakcije su se javile kod 33% pacijenata koji su primali brigatinib.
- Najčešće ozbiljne neželjene reakcije bile su pneumonija (4,4%), ILD/pneumonitis (3,7%), pireksija (2,9%), dispneja(2,2%), plućna embolija (2,2%) i astenija (2,2%).
- Fatalne neželjene reakcije su se javile kod 2,9% pacijenata: pneumonija (1,5%), cerebrovaskularni inzult (0,7%) i sindrom višestruke disfunkcije organa (0,7%).

BRIGATINIB: Bezbedonosni profil

- U ALTA 1L, 13% pacijenata koji su primali brigatinib trajno je prekinulo dalje lečenje zbog neželjenih reakcija.
- Najčešće neželjene reakcije koje su dovele do prekida terapije bile su ILD/pneumonitis (3,7%) i pneumonija (2,2%).
- Kod ALTA 1L, 38% pacijenata je zahtevalo smanjenje doze zbog neželjenih reakcija.
- Najčešća neželjena reakcija koja je dovela do smanjenja doze bila je povećanje CPK (15%), povećanje lipaza (6,6%), povećana amilaza (4,4%), povećanje AST (2,2%), ILD/pneumonitis (2,2%) i hipertenzija (2,2%).
- Srednje trajanje lečenja bilo je 24,3 meseca.

BRIGATINIB: Idiopatska plućna fibroza/pneumonitis

- U ispitivanju prve linije faze 3: ILD/pneumonitis se javio kod 5,1% pacijenata koji su primali brigatinib.
- U roku od 8 dana od početka primene kod 2,9% pacijenata, sa reakcijama stepena 3-4 koje su se javile kod 2,2% pacijenata.
- U post-krizotinib fazi 2 ispitivanja: ILD/pneumonitis se javio kod 9,1% pacijenata.
- U roku od 9 dana od početka terapije brigatinibom (srednji početak je bio 2 dana) kod 6,4% pacijenata,sa reakcijama stepena 3- 4 koje se javljaju u 2,7%.

NEŽELJENA REAKCIJA I TEŽINA	MODIFIKACIJA DOZE
Hipertenzija Hipertenzija gr 3(SBP≥160 mmHg ili DBP ≥100 mmHg, indikovana medicinska intervencija, više od jednog antihipertenzivnog leka ili intenzivnija terapija nego što je prethodno korišćeno	Stop brigatinib dok se hipertenzija ne oporavi na ≤Gr 1 (SBP <140 mmHg i DBP <90 mmHg), a zatim nastavite sa lekom u istoj dozi •Ponavljanje: Stop do oporavka do ≤Gr 1, i nastaviti sa sledećom nižom dozom ili trajno prekinuti terapiju
Hipertenzija Hipertenzija gr. 4 (po život opasne posledice, indikovana hitna intervencija)	•Stop brigatinib do oporavka do ≤Gr 1 i nastaviti sa sledećom nižom dozom ili trajno prekinuti terapiju •Ponavljanje: Trajno prekinuti brigatinib zbog ponavljanja hipertenzije stepena 4
Bradikardija (HR <60 otkucaja u minuti) Simptomatska bradikardija	•Stop brigatinib do oporavka od asimptomatske bradikardije ili do otkucaja srca u mirovanju od 60 otkucaja u minuti ili više •Ako se identifikuje istovremeni lek za koji se zna da izaziva bradikardiju i prekine ga ili mu doza bude prilagođena, nastavite sa brigatinibom u istoj dozi nakon oporavka od asimptomatske bradikardije ili otkucaja srca u mirovanju od 60 otkucaja u minuti ili više •Ako se ne identifikuje nijedan prateći lek za koji se zna da izaziva bradikardiju, ili ako se prateći lekovi ne prekinu ili ne prilagode dozu, nastavite brigatinib na sledećem nižem nivou doze nakon oporavka od asimptomatske bradikardije ili otkucaja srca u mirovanju od 60 otkucaja u minuti ili više
Bradikardija (HR <60 otkucaja u minuti) Bradikardija sa životno opasnim posledicama, indikovana hitna intervencija	•Trajna obustava brigatiniba, ako se ne identifikuje nijedan prateći lek

BRIGATINIB: doziranje

- Preporučena doza za brigatinib je 90 mg oralno ,jednom dnevno prvih 7 dana; zatim se doza povećava do 180 mg oralno jednom dnevno.

LOPLATINIB: moždane metastaze

- Što se tiče pacijenata bez početnih metastaza u CNS-u, lorlatinib je najpoželjnija opcija lečenja.
- Lorlatinib pruža poboljšanu kontrolu bolesti CNS-a, 71% pacijenata koji su primali lorlatinib imalo je intrakranijalni CR u CROWN studiji [1]
- Povećana aktivnost lorlatiniba na moždanim metastazama pripisana je njegovoj sposobnosti da pređe hematoencefalnu barijeru
- Lorlatinib pokazuje antitumorsku aktivnost za sve poznate pojedinačne rezistentne mutacije na ALK .
- Ovi faktori mogu biti osnova za izraženu efikasnost lorlatiniba kao terapije prve linije.

1. Shaw A, Bauer T, de Marinis F, Felip E, Goto Y, Liu G, Mazieres J, Kim D, Mok T, Polli A*, Thurm H., Calella A.M., Peltz G., Solomon B.J., CROWN Trial Investigators.*: ALKFirst-Line Lorlatinib or Crizotinib in Advanced -Positive Lung Cancer 2020, 383(21):2018–2029, DOI: 10.1056/NEJMoa2027187.

LORLATINIB: Najčešće prijavljeni neželjeni događaji

- Hiperholesterolemia (70%)
- Hipertrigliceridemia (64%)
- Edem (55%)
- Dobijanje na težini (38%)
- Periferna neuropatija (34%)
- Cognitivni neželjeni efekti (21%)

LOPLATINIB: Doziranje

Preporučena doza je 100 mg lorlatiniba koji se uzima oralno jednom dnevno do progresije bolesti ili neprihvatljive toksičnosti

Tableta se guta cela. Ne žvakati, drobiti ili cepati tablete. Ne gutati tablete ako su slomljene, napukle ili na neki drugi način oštećene

U isto vreme svakog dana. Ako je doza propuštena, onda je treba uzeti čim se pacijent seti, osim ako nije prošlo manje od 4 sata pre sledeće doze, u kom slučaju pacijent ne bi trebalo da uzima propuštenu dozu

Pacijenti ne bi trebalo da uzimaju 2 doze istovremeno da bi nadoknadili propuštenu

Sažetak karakteristika leka Maj 2022.

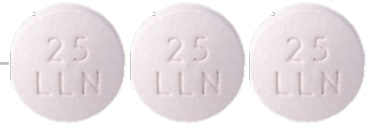
LORLATINIB: Modifikacija doza

Prekid doziranja ili smanjenje doze može biti potrebno na osnovu individualne bezbednosti i podnošljivosti

Preporučena doza

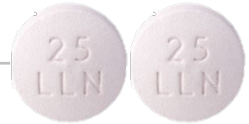
100 mg
oralno **jednom dnevno**

Prva redukcija
(ako je potrebna)



75 mg
oralno **jednom dnevno**

Druga redukcija
(ako je potrebno)



50 mg
oralno **jednom dnevno**

- Lorlatinib se isporučuje u obliku tableta koje sadrže 25 mg ili 100 mg lorlatiniba
- Lorlatinib treba permanentno isključiti ako pacijent ne može da toleriše dozu od 50mg jednom dnevno

Sažetak karakteristika leka Maj 2022

Preporučene doze orlatinib-a za neželjene dogadjaje* (1/4)

Hypercholesterolaemia or Hypertriglyceridaemia	
Blaga hiperholesterolemija (holesterol ULN – 300 mg/dL or ULN – 7.75 mmol/L) **OR** **Umerena hiperholesterolaemija** (holesterol 301– 400 mg/dL or 7.76 – 10.34 mmol/L)	• Uvesti ili modifikovati terapiju za snižavanje lipida† u skladu sa odgovarajućim informacijama o propisivanju • Nastaviti lorlatinib u istoj dozi
Blaga hipertriglyceridaemia (triglyceridi 150 – 300 mg/dL or 1.71 – 3.42 mmol/L) **ILI** **Umerena hipertriglyceridaemia** (triglyceridi 301 – 500 mg/dL or 3.43 – 5.7 mmol/L)	
Teška hipercholesterolaemia (holesterol 401 – 500 mg/dL or 10.35 – 12.92 mmol/L ILI **Teška hipertriglyceridaemia** (triglyceridi 501 – 1,000 mg/dL or 5.71 – 11.4 mmol/L)	• Uvesti primenu terapije za snižavanje lipida† • Ako ste trenutno na terapiji za snižavanje lipida, povećajte dozu ove terapije† u skladu sa odgovarajućim informacijama o propisivanju; ili pređite na novu terapiju za snižavanje lipida† • Nastavite sa uzimanjem lorlatiniba u istoj dozi bez prekida
Po život opasna hiperholesterolaemia (holesterol >500 mg/dL or >12.92 mmol/L) **ILI** **Po život opasna hipertriglyceridaemia** (triglyceridi>1,000 mg/dL or >11.4 mmol/L)	• Uvesti upotrebu terapije za snižavanje lipida† ili povećati dozu ove terapije† u skladu sa odgovarajućim informacijama o propisivanju ili preći na novu terapiju za snižavanje lipida† • Zaustavite lorlatinib do oporavka hiperholesterolemije i/ili hipertrigliceridemije do umerenog ili blagog stepena težine • Ponovo testirajte istu dozu lorlatiniba dok maksimizirate terapiju za snižavanje lipida† u skladu sa odgovarajućim informacijama o propisivanjuAko se teška hiperholesterolemija i/ili hipertrigliceridemija ponove uprkos maksimalnoj terapiji za snižavanje lipida† • u skladu sa odgovarajućim informacijama o propisivanju, smanjite lorlatinib za 1 nivo doze

Kategorije gradusa/stepena neželjenih dogadjaja su zasnovane na klasifikaciji Zajedničkih terminoloških kriterijuma za neželjene događaje (CTCAE) Nacionalnog instituta za rak (NCI)

® Sažetak karakteristika leka Maj 2022

Preporučene doze lorlatinib-a za neželjene dogadjaje* (2/4)

CNS neželjeni dogadjaji	
Grade 2: Umeren **ILI** **Grade 3: Težak**	• Zadržati dozu dok toksičnost ne bude manja ili jednka gr 1 • Prva redukcija lorlatinib-a
Grade 4: Životno ugrožavajući/Zahteva hitnu intervenciju	• Trajno isključiti Lorlatinib

Povećanje Lipasa/Amylasa	
Grade 4: Težak **ILI** **Grade 4: Životno ugrožavajući/Zahteva hitnu intervenciju**	• Zadržati dozu dok toksičnost ne bude manja ili jednka gr 1 • Prva redukcija lorlatinib-a

*Grade categories are based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) classifications.
® Sažetak karakteristika leka Maj 2022

Preporučene doze lorlatinib-a za neželjene dogadjaje* (3/4)

Interstitijalna bolest pluća/Pneumonitis	
Grade 1: blaga **ili** **Grade 2: Umerena**	• Zaustavite lorlatinib dok se simptomi ne vrate na početnu vrednost i razmislite o započinjanju terapije kortikosteroidima • Nastavite sa lorlatinibom sa 1 smanjenom dozom • Trajno prekinite uzimanje lorlatiniba ako se ILD/pneumonitis ponovi ili se ne oporavi nakon 6 nedelja uzimanja lorlatiniba i terapije steroidima
Grade 3: Teška **OR** **Grade 4: Životno ugrožavajući/Zahteva hitnu intervenciju**	• Trajno isključiti lorlatinib

Hyperglycaemia	
Grade 3 **ILI** **Grade 4** (stalna hyperglycaemia >250 mg/dLuprkos adekvatnoj terapiji	• Zaustavite lorlatinib dok se hiperglikemija ne kontroliše na odgovarajući način • Nastaviti sa lorlatinibom u sledećoj nižoj dozi • Ako se adekvatna kontrola hiperglikemije ne može postići optimalnim medicinskim tretmanom, trajno prekinuti sa lorlatinibom

*Grade categories are based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) classifications.
® Sažetak karakteristika leka Maj 2022

Preporučene doze lorlatinib-a za neželjene dogadjaje * (4/4)

Hipertenzija	
Grade 3 (SBP ≥160 mmHg or DBP ≥100 mmHg; naznačena medicinska intervencija; više od jednog antihipertenzivnog leka, ili intenzivniju terapiju nego što je prethodno korišćeno)	• Zaustaviti lorlatinib dok se hipertenzija ne oporavi na stepen 1 ili manje (SBP manji od 140 mmHg i DBP manji od 90 mmHg) • Nastaviti sa lorlatinibom u istoj dozi • Ako se hipertenzija stepena 3 ponovi, obustaviti lorlatinib do oporavka na stepen 1 ili manje • Nastavite sa lorlatinibom u smanjenoj dozi • Ako se adekvatna kontrola hipertenzije ne može postići optimalnim medicinskim tretmanom, trajno prekinite sa lorlatinibom
Grade 4 (Životno ugrožavajući/Zahteva hitnu intervenciju)	• Zaustaviti lorlatinib do oporavka do stepena 1 ili manje • Nastavite sa smanjenom dozom ili trajno prekinite sa lorlatinibom • Ako se hipertenzija 4. stepena ponovi, trajno prekinite sa lorlatinibom

Drugi neželjeni dogadjaji	
Grade 1: Blagi **ILI** **Grade 2: Umereni**	• Ne razmatrati modifikaciju doze ili smanjiti dozu za 1 nivo, kao što je klinički indikovano
≥ Grade 3: Teški	• Zaustavite lorlatinib dok se simptomi ne povuku na manje od ili jednake stepenu 2 ili početnoj liniji • Nastavite sa lorlatinibom sa 1 smanjenom dozom

*Grade categories are based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) classifications.
DBP, diastolic blood pressure; SBP, systolic blood pressure.
® Sažetak karakteristika leka Maj 2022

LORLATINIB: Modifikacije doze za interakcije sa lekovima

	Modifikacija doze
Upotreba snažnog CIP3A4/5 induktora sa lorlatinibom je kontraindikovana	• Istovremena upotreba lorlatiniba sa lekovima koji su jaki inhibitori CIP3A4/5 i proizvodima soka od grejpfruta i kantariona može povećati koncentraciju lorlatiniba u plazmi • Jaki CYP3A4/5 Inhibitori:rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin i kantarion, itraconazole, ketoconazole, voriconazole, ritonavir, lopinavir ili tipranavir. • početnu dozu lorlatiniba od 100 mg jednom dnevno treba smanjiti na dozu od 75 mg jednom dnevno • Ako se prekine istovremena upotreba snažnog inhibitora CIP3A4/5, lorlatinib treba nastaviti sa dozom koja je korišćena pre početka primene snažnog inhibitora CIP3A4/5 i nakon perioda ispiranja od 3-5 poluživota jakog CIP3A4/5 inhibitor
Jaki CYP3A4/5 Induktori	• **Istovremena upotreba lorlatiniba sa jakim induktorima CIP3A4/5 je kontraindikovana**

CYP, cytochrome P450.

LORVIQUA® Sažetak karakteristika leka Maj 2022.

Lorlatinib: Redukcija doze za tešku bubrežnu slabost

Modifikacija doze	
Teška bubrežna slabost **(eGFR <30 mL/min)**	• Redukovana doza Lorlatinib-a (startna doza 75 mg oralno)

eGFR, estimated glomerular filtration rate

Sažetak karakteristika leka Maj 2022.

LORLATINIB: opcija lečenja za pacijente sa ALK+ metastatskim NSCLC

• Lorlatinib je inhibitor kinaze indikovan za lečenje odraslih pacijenata sa metastatskim karcinomom ne-malih ćelija pluća (NSCLC) čiji su tumori pozitivni na anaplastičnu limfom kinazu (ALK), što je otkriveno testom koji je odobrila FDA.
•Lorlatinib je kontraindikovan kod pacijenata koji uzimaju jake CIP3A induktore, zbog potencijala ozbiljne hepatotoksičnosti
•Upozorenja i mere predostrožnosti uključuju rizik od ozbiljne hepatotoksičnosti uz istovremenu upotrebu jakih induktora CIP3A, efekte na CNS, hiperlipidemiju, AV blok, intersticijalnu bolest pluća/pneumonitis, hipertenziju, hiperglikemiju i embrio-fetalnu toksičnost
•Efikasnost lorlatiniba ustanovljena je kod 149 pacijenata koji nisu primali prethodnu sistemsku terapiju za ALK pozitivan metastatski NSCLC u otvorenoj, randomizovanoj, aktivno kontrolisanoj, multicentričnoj studiji (Studija B7461006; NCT03052608) i u podgrupi od ALK 215 pacijenata. -pozitivan metastatski NSCLC koji je prethodno lečen jednim ili više inhibitora ALK kinaze koji su bili uključeni u nerandomizovanu, multikohortnu, multicentričnu studiju sa rasponom doza i procenom aktivnosti (Studija B7461001; NCT01970865)
•U objedinjenoj bezbednosnoj populaciji, najčešće neželjene reakcije kod ≥ 20% od 476 pacijenata koji su primali lorlatinib bili su edem (56%), periferna neuropatija (44%), povećanje telesne težine (31%), kognitivni efekti (28%), umor (27%), dispneja (27%), artralgija (24%), dijareja (23%), efekti na raspoloženje (21%) i kašalj (21%)
•Nakon srednjeg trajanja praćenja PFS prema BICR-u od 36,7 meseci sa lorlatinibom i 29,3 meseca sa krizotinibom, srednji PFS prema BICR-u je bio NR (95% CI, NR-NR) sa lorlatinibom i 9,3 meseca (95% CI, 7,6 -11,1 meseci) sa krizotinibom (HR, 0,27; 95% CI, 0,184-0,388).
•Korist PFS od lorlatiniba u poređenju sa krizotinibom takođe je primećena kod pacijenata sa i bez početnih metastaza u mozgu.
•Bezbednosni profil lorlatiniba u analizi dužeg praćenja bio je u skladu sa onim u primarnoj analizi

ALK, anaplastic lymphoma kinase; AV, atrioventricular; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CYP, cytochrome 450; FDA, Food and Dug Administration; HR, hazard ratio; NSCLC, non-small cell lung cancer. NR, not reached; PFS, progression-free survival.

1. LORVIQUA® Sažetak karakteristika leka Maj 2022. 2. Shaw AT, et al. *N Engl J Med*. 2020;383(20):2018–29. 3. Solomon B, et al. AACR Annual Meeting. April 8-13, 2022. Abstract CT223.

ZAKLJUČAK

- Odobrenje druge i treće generacije ALK inhibitora dramatično je promenilo algoritam lečenja ALK+ NSCLC.
- U nedostatku direktnih poređenja između ALK inhibitora sledeće generacije, bilo koji ALK inhibitor sledeće generacije može se smatrati validnom opcijom kao terapija prve linije, i po efikasnosti i po bezbednosti
- Izbor preferiranog ALK inhibitora u prvoj liniji uglavnom se oslanja na procenu lekara zasnovanu na ličnom iskustvu i razlikama u bezbednosnim profilima ALK inhibitora