# Optimal treatment strategy of ALK+ NSCLC


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GUSTAVE ROUSSY
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GRAND PARIS

Oncology

Lunch satellite symposium

**Dec. 7** 12:00-13:20

高雄展覽館 304A

# DISCLOSURES

**Consulting, advisory role or lectures:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

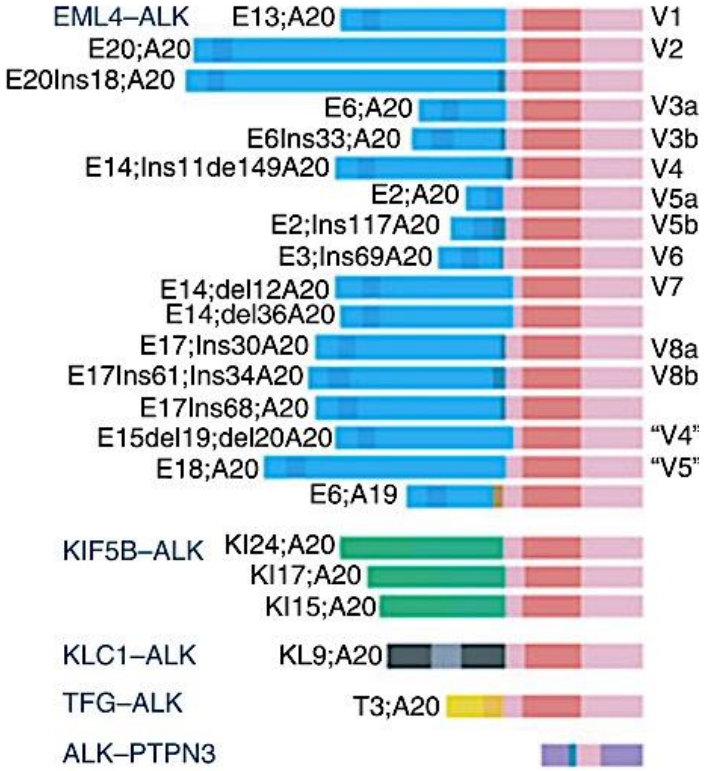
**Honoraria:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Merck, Novartis, Pfizer, prIME Oncology, Peer CME, Roche

**Clinical trials research:** AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, Roche, Medimmun, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo

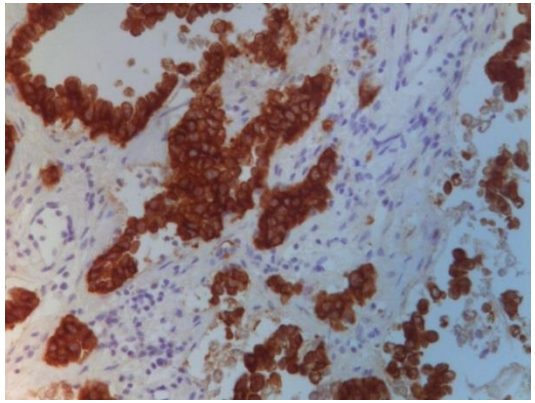
**Travel, Accommodations, Expenses:** AstraZeneca, Roche, Novartis, prIME Oncology, Pfizer

# *ALK* GENE REARRANGEMENTS IN NSCLC

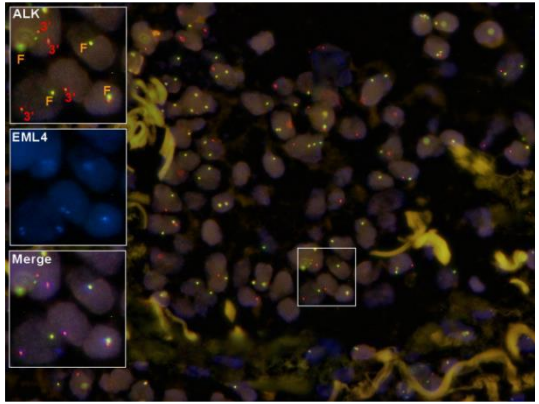
- Found in 3-7% of NSCLC
- Typically adenocarcinoma histology
- Younger patients
  (median age ~50 years)
- Often never or light smokers
- At least 15 EML4-ALK variants have been described in lung cancers.



# Diagnostics of ALK translocations



## IHC




## FISH

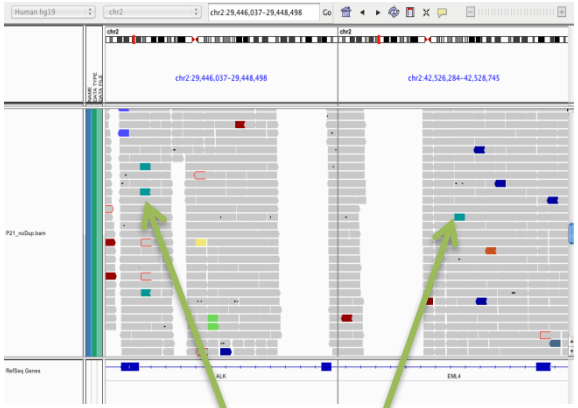
Break apart:

Orange:red/green fusion normal

Red: ALK 3´break

Zytovision

## NGS



**ALK**

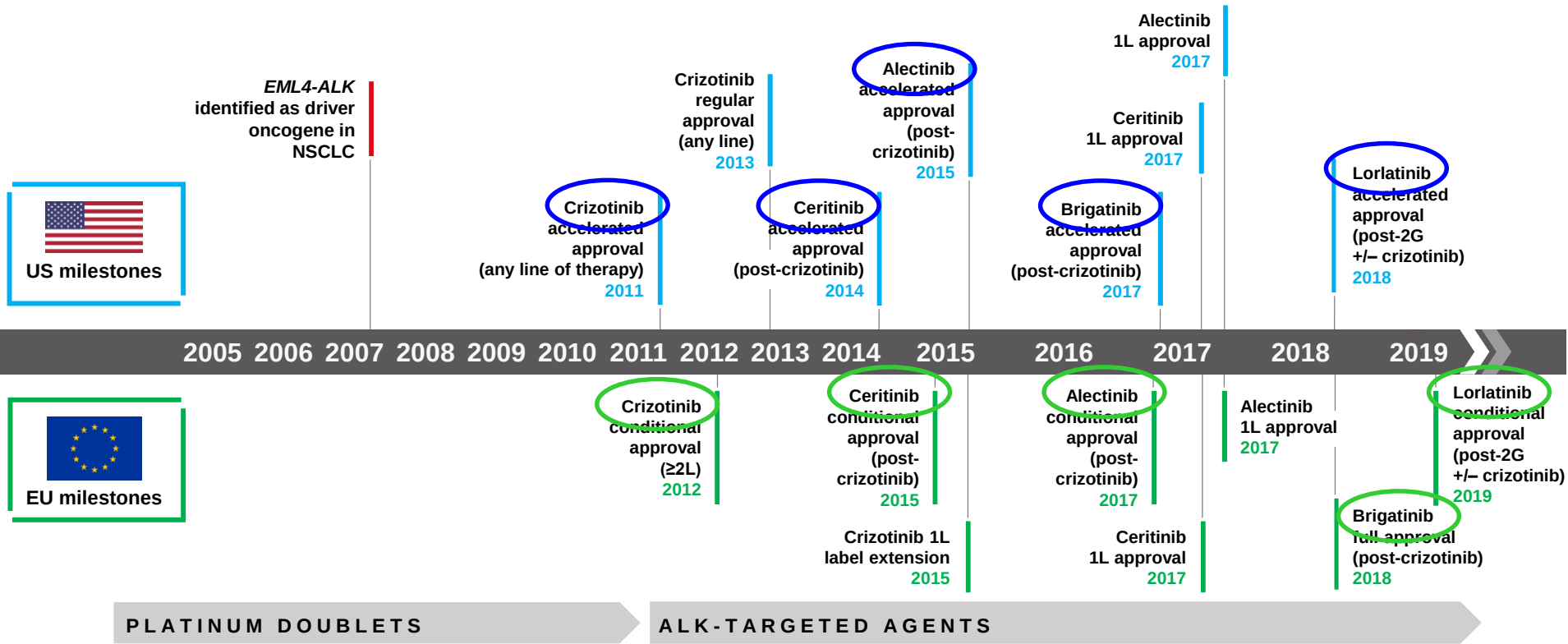
Reads marked in ALK to pair with region of EML4

**EML4**

Reads marked in EML4 to pair with region in ALK

Images courtesy of A. Scheel and R. Büttner, Cologne.

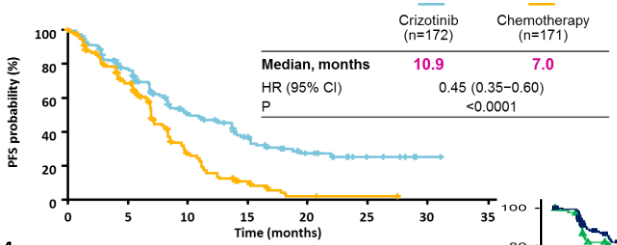
# Treatment Landscape in ALK+ NSCLC Is Evolving




1L, first line; 2L, second line; 2G, second generation; ALK, anaplastic lymphoma kinase; EML4, echinoderm microtubule-associated protein-like 4; NSCLC, non–small cell lung cancer.

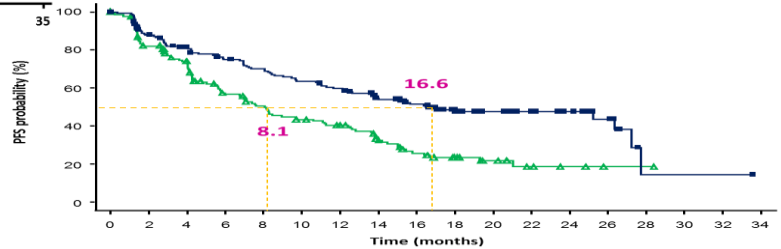
# ALK: 1L Treatment is changing

## Crizotinib



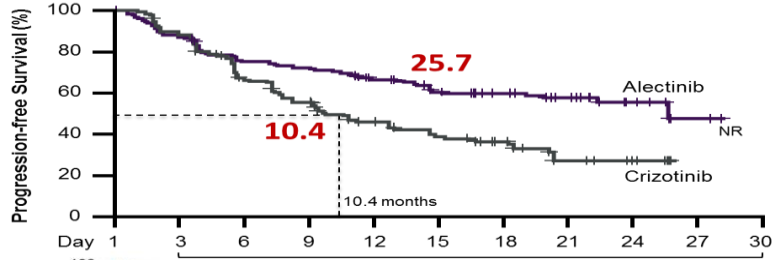

Solomon BJ, et al. *N Engl J Med* 2014

## Ceritinib



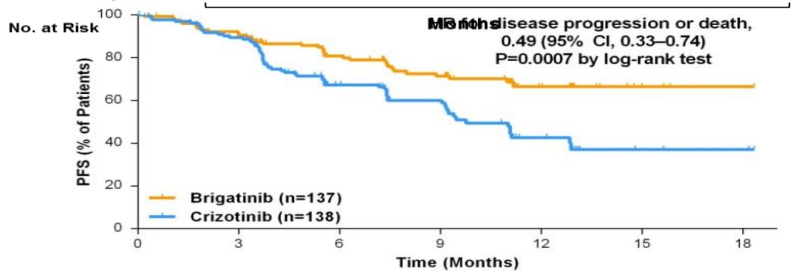

C Soria et al lancet 2017

## Alectinib




Peters S et al, NEJM 2017

## Brigatinib



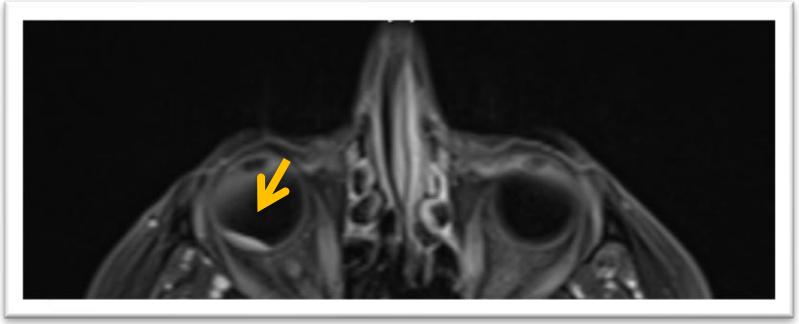

Camidge et al. NEJM 2018

# Medical History

- **59 year-old female patient, non smoker**
- No past history
- No exposition to asbestos

- **Jan. 2016**
  - 1st symptom: visual disturbance
  - Eye fund: right choroid lesion

- **CT scan:** right pulmonary mass + lymph nodes + liver metastases



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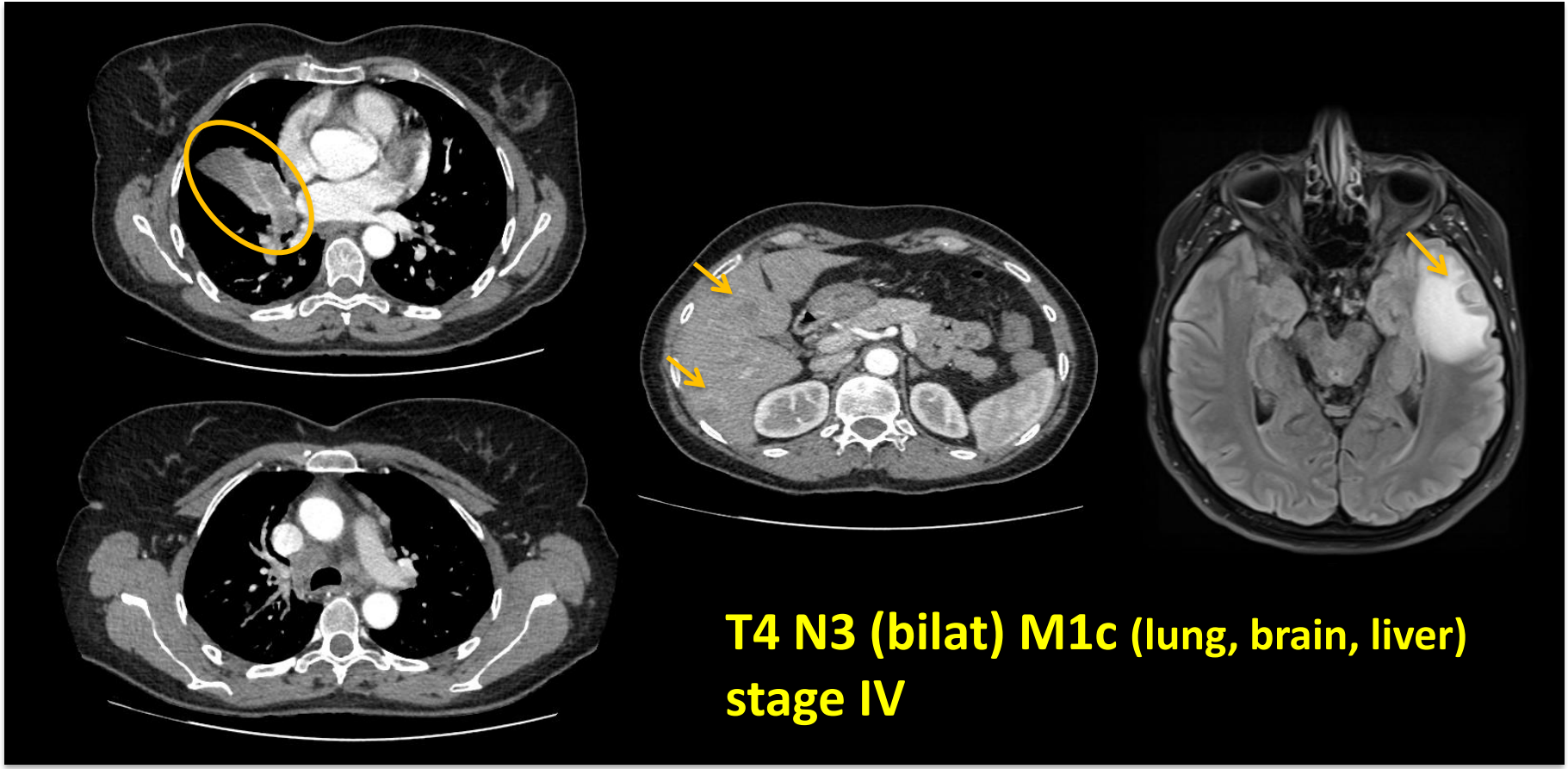
# Lung Cancer Staging

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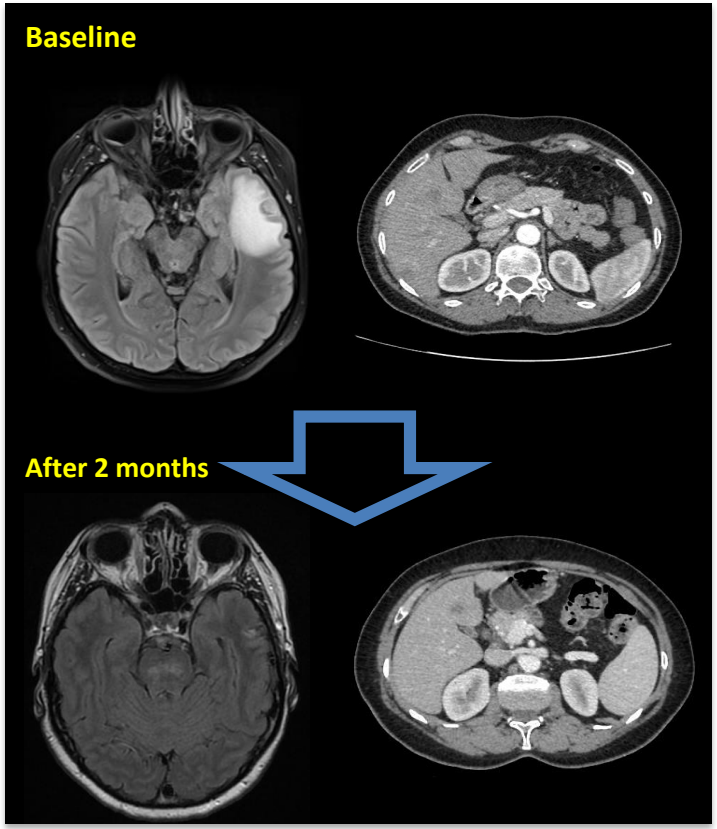
# *Molecular testing found ALK positivity (IHC and FISH), EGFR-, BRAF-, HER2-, ROS1- and PDL1+ (10%)*

- **March 2016**
  - PS 2 (abdominal pain)
  - **CRIZOTINIB 250mg bid**
  - Close interval follow-up with MRI

- **Front-line therapy:**
  - Clinical benefit: ↓ Symptoms (PS0)
  - Partial response after 2 months

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# Summury of crizotinib trials in ALK+ NSCLC

| | PROFILE 1001[1] (N=143) | PROFILE 1005[2] (N=259) | PROFILE 1007[3] (N=172) | PROFILE 1014[4] (N=172) |
|---|---|---|---|---|
| Phase | 1 | 2 | 3 | 3 |
| Line of therapy | Any line | 2nd line and beyond | 2nd line | 1st line |
| Response rate | 61% | 60% | 65% | 74% |
| PFS, median (mos) | 9.7 | 8.1 | 7.7 | 10.9 |
| Survival probability at 12 mos | 75% | NA | 70% | 84% |

Shaw, et al. N Engl J Med 2013 Benjamin J. Solomon et al, NEJM 2014

# ... after 10 months crizotinib

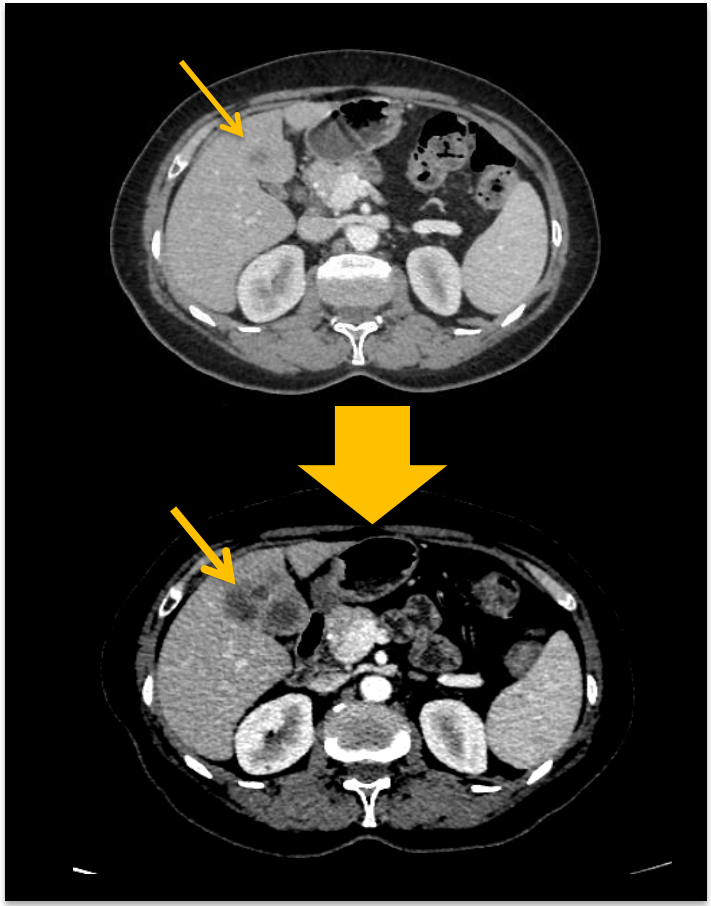
- **Nov 2016**

- **Symptoms +++**

- Abdominal pain

- **Body CT scan**

- Liver progression +++



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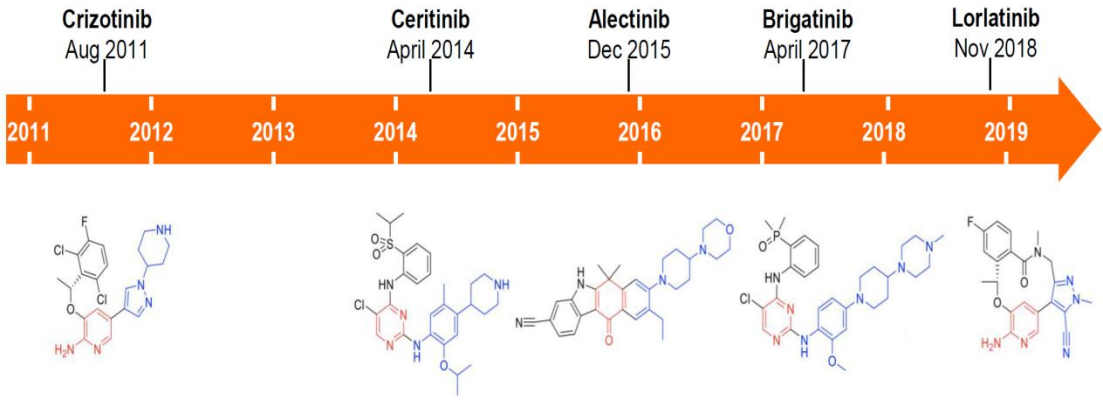
# Unmet need for 2-3rd-generation ALK inhibitors that:

## Have activity against crizotinib-resistance mutations

| | ALK TKI | ADDITIONAL TARGETS |
|---|---|---|
| 1st generation | Crizotinib | MET, ROS1 |
| 2nd generation | Alectinib | RET, LTK |
| | Brigatinib | Mutant EGFR, ROS1 |
| | Ceritinib | IGF-R1, IR, ROS1 |
| | Ensartinib | MET, ABL, AXL |
| | Entrectinib | NTRKs, ROS1 |
| 3rd generation | Lorlatinib | ROS1 |




**Timeline of FDA accelerated approvals**

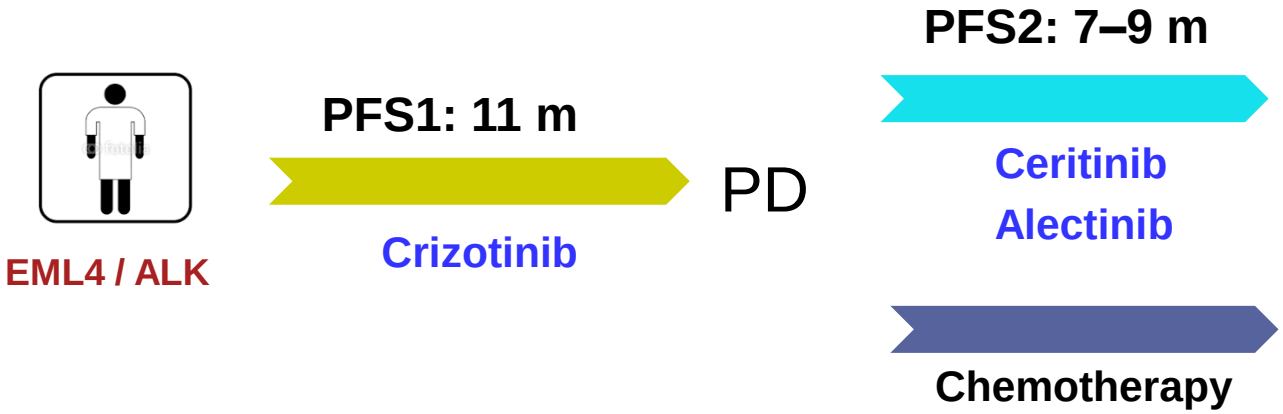
# 2nd generation ALK-TKI in crizotinib-refractory NSCLC

| Design/Assessment | Ceritinib Phase 1/2 | Alectinib Phase 2 | Brigatinib Phase 2 |
|---|---|---|---|
| Median PFS | **6.9M** (5.6-8.7) | **8.9M** (5.6-11.3) | **15.6M** (11.1-NR) |
| ORR | **56% (49-64)** | **50% (41-59)** | **55% (44-66)** |
| IC ORR | **36%** | **57%** | **67%** |
| Duration of Response | 8.3M | 11.2M | 14.8M |

Kim et al Lancet Oncology 2016; Shaw et al. Lancet Oncology 2016; Kim DW et al, JCO 2017

# Developing the optimal treatment sequence

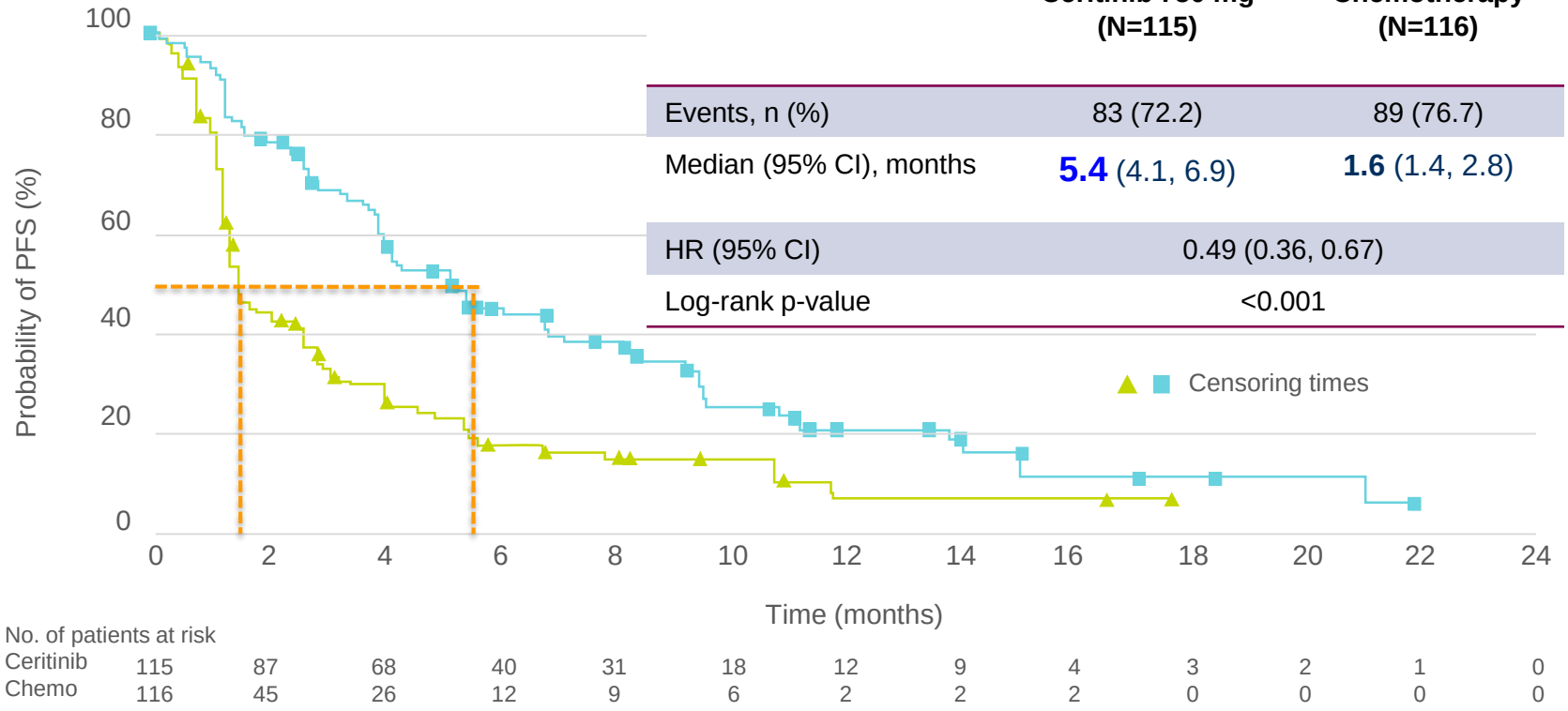
**Next-generation ALK inhibitor vs chemotherapy post-crizotinib**




**ASCEND-5** (NCT01828112)
Phase 3, advanced NSCLC (n = 231): ceritinib vs docetaxel/pemetrexed (primary endpoint: PFS)

**ALUR** (NCT02604342)
Phase 3, advanced NSCLC (n = 120): alectinib vs docetaxel/pemetrexed (primary endpoint: PFS)

# Phase III ASCEND-5 study
# Kaplan-Meier Plots of PFS (BIRC)




| | Ceritinib 750 mg (N=115) | Chemotherapy (N=116) |
|---|---|---|
| Events, n (%) | 83 (72.2) | 89 (76.7) |
| Median (95% CI), months | **5.4** (4.1, 6.9) | **1.6** (1.4, 2.8) |
| HR (95% CI) | 0.49 (0.36, 0.67) | |
| Log-rank p-value | <0.001 | |

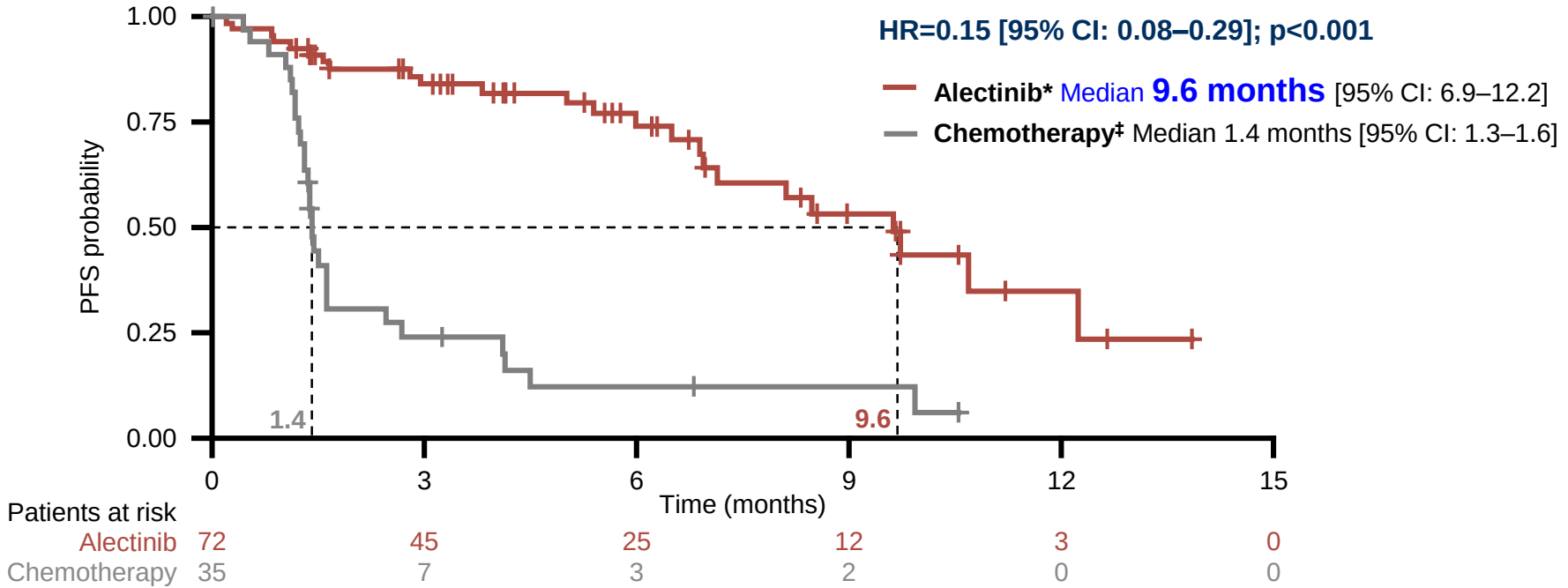
No. of patients at risk

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ceritinib | 115 | 87 | 68 | 40 | 31 | 18 | 12 | 9 | 4 | 3 | 2 | 1 | 0 |
| Chemo | 116 | 45 | 26 | 12 | 9 | 6 | 2 | 2 | 2 | 0 | 0 | 0 | 0 |

*Giorgio Scagliotti et al, ESMO 2016; Shaw AT et al, Lancet onco 2017*

# ALUR trial

# Primary endpoint: PFS (investigator-assessed)

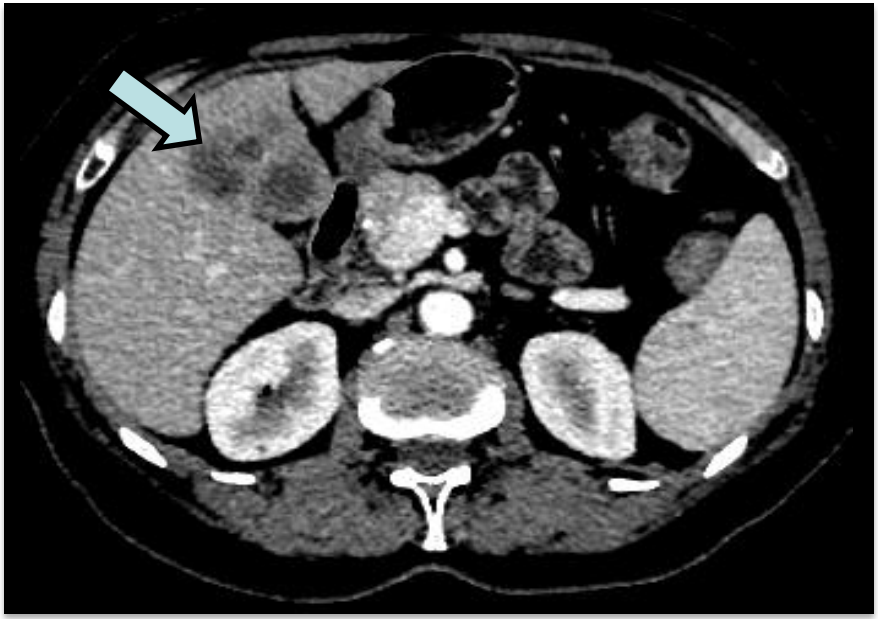



At data cut-off (26.01.17), median follow-up was 6.5 months with alectinib and 5.8 months with chemotherapy
Median time on treatment was 20 weeks (range: 0.4–62.1) in the alectinib arm and 6 weeks (range: 1.9–47.1) in the chemotherapy arm

*Silvia Novello et al ESMO 2017, annals of onco 2018*

# ... after 10 months of crizotinib

- Dec 2016
- Symptoms +++
  - Abdominal pain
- Body CT scan
  - Multifocal liver progression +++



- **Our proposal:**
  - Rebiopsy: MATCH-R protocol (NGS, CGH, WES)
  - 2nd line before we get results of molecular testing: **CERITINIB**

D.Planchard et al, Gustave Roussy

# ... after 8 months ceritinib

- **Good tolerance**
- **Partial response (55%)**

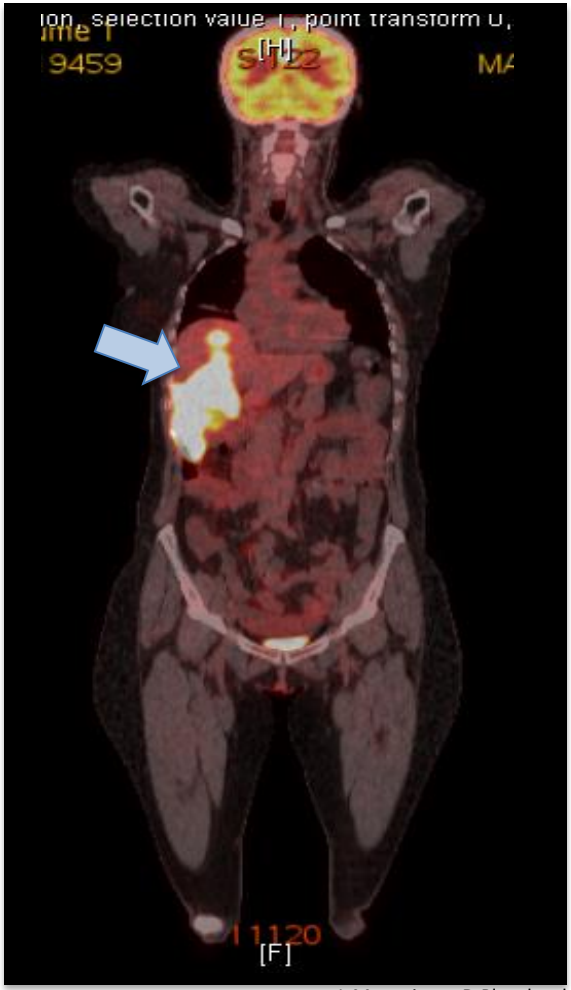
- **PET scan**

- Liver PD ++++

- **Biopsy:**

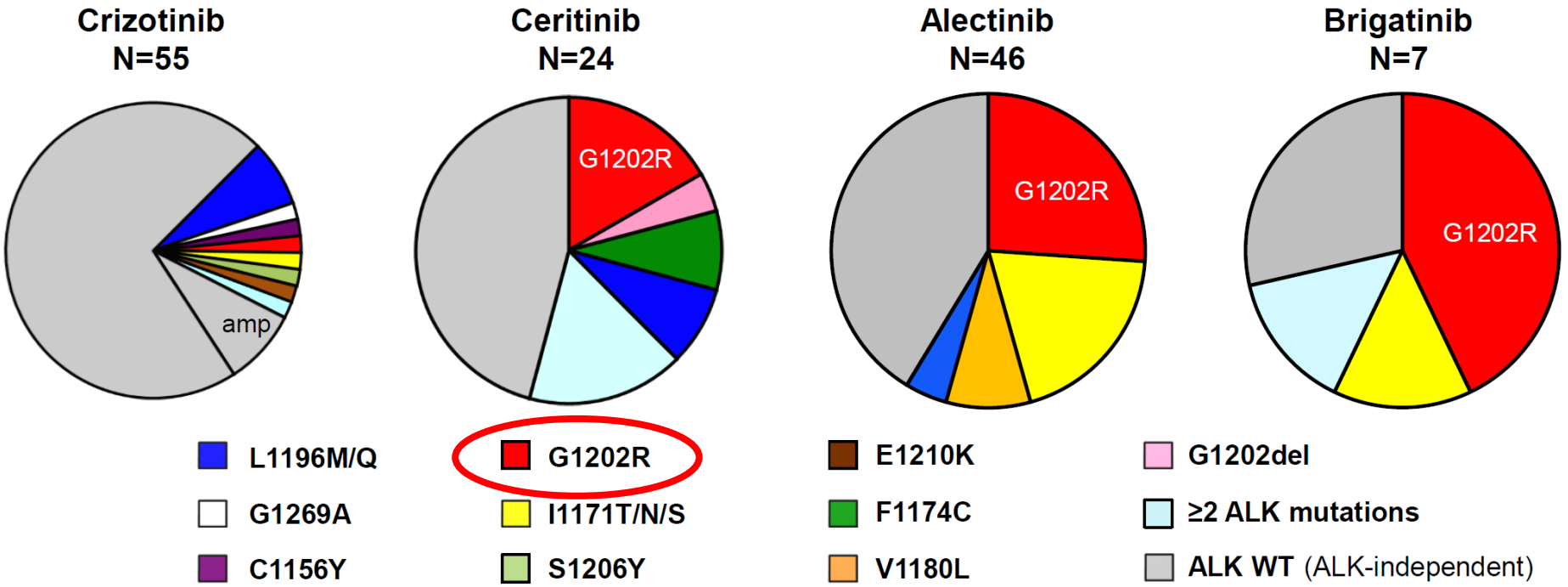
- Adenocarcinoma IHC ALK +++

  ***ALK*G1202R resistance mutation** → **MTB**




L.Mezquita D.Planchard et al, Gustave Roussy

# Disctinct profiles of ALK resistance mutations after failure of a second generation ALK TKI




updated from Gainor et al., Cancer Discov 6: 1118-33, 2016

# Lorlatinib Covers the Broadest Range of ALK Resistance Mutations

- 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]

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

| | Cellular ALK Phosphorylation Mean $IC_{50}$ (nM) | | | | |
|---|---|---|---|---|---|
| **Mutation status** | **Crizotinib** | **Ceritinib** | **Alectinib** | **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[a] | 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 |

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

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

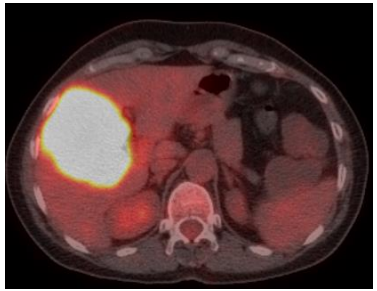
1. Gainor JF, et al. *Cancer Discov.* 2016;6:1118–1133.
2. Johnson TW, et al. *J Med Chem.* 2014;57:4720–4744.

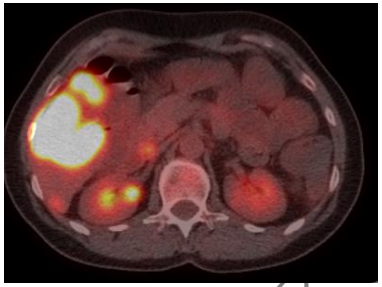
# *ALK* positive crizo-resistant NSCLC stage IV
# Primary resistance to Ceritinib

- **March 2017**
  - PS 1 (abdominal pain +++ liver)

- **Our options**:
  - ✓ **Expanded access to Brigatinib**
  - ✓ Expanded access to Lorlatinib *(not available)*
  - ✓ Platinum- based chemo

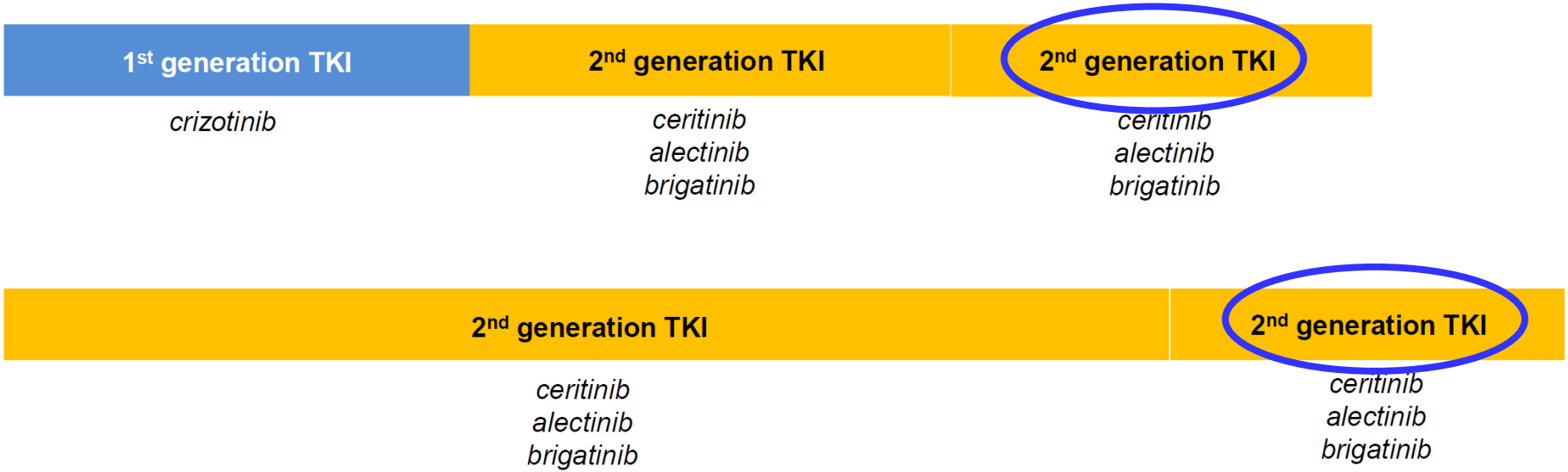
- **After 6 weeks Brigatinib:**
  - Hospitalization for clinical deterioration
  - *CT scan*:
  - Multifocal liver progression
  - Infradiaphragmatic nodal PD





D.Planchard et al, Gustave Roussy

# Are second generation ALK inhibitors active after failure of a prior second generation inhibitor ?



# Limited efficacy of second generation ALK TKIs after alectinib

| | Hida et al., 2018 (ASCEND-9)[1] | Yoshida et al., 2018 | Lin et al., 2018 |
|---|---|---|---|
| ALK TKI | ceritinib | ceritinib | brigatinib |
| Country | Japan | Japan | US |
| No. of patients | 20 | 9 | 22 |
| Median f/u | 11.6 mos | - | - |
| ORR | 25% | 16%* | 17% |
| Median PFS | 3.7 mos (1.9-5.3) | N/A | 4.4 mos (1.8-5.6) |
| Intracranial ORR | N/A | N/A | 1 of 4 (25%) |

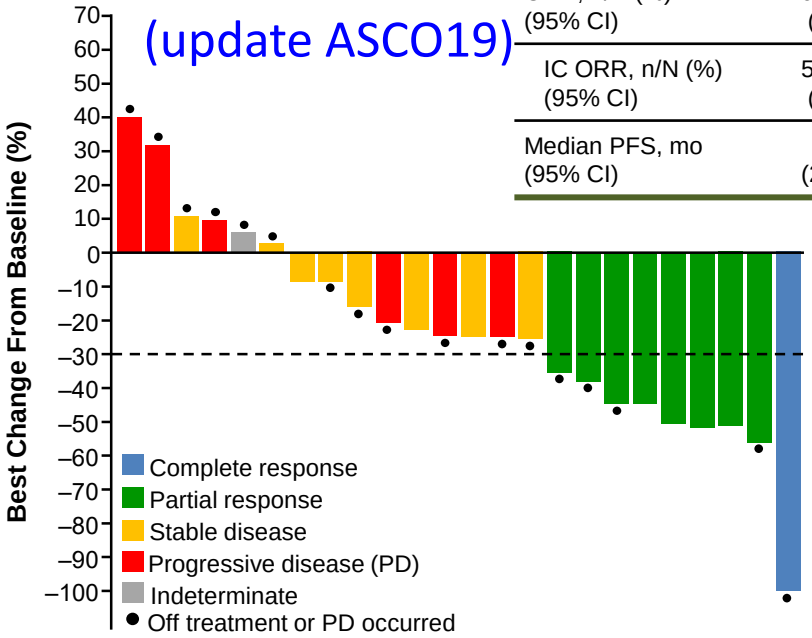
[1]Hida et al., Cancer Sci 109:2863-72, 2018; [2]Yoshida et al., In Vivo 32:158—90, 2018; [3]Lin et al., J Thorac Oncol 13:1530-38, 2018

# Efficacy Lorlatinib in ALK+ Pts Previously Treated with Prior Non-crizotinib ALK TKI ± CT (EXP3B)

Overall[a,b]

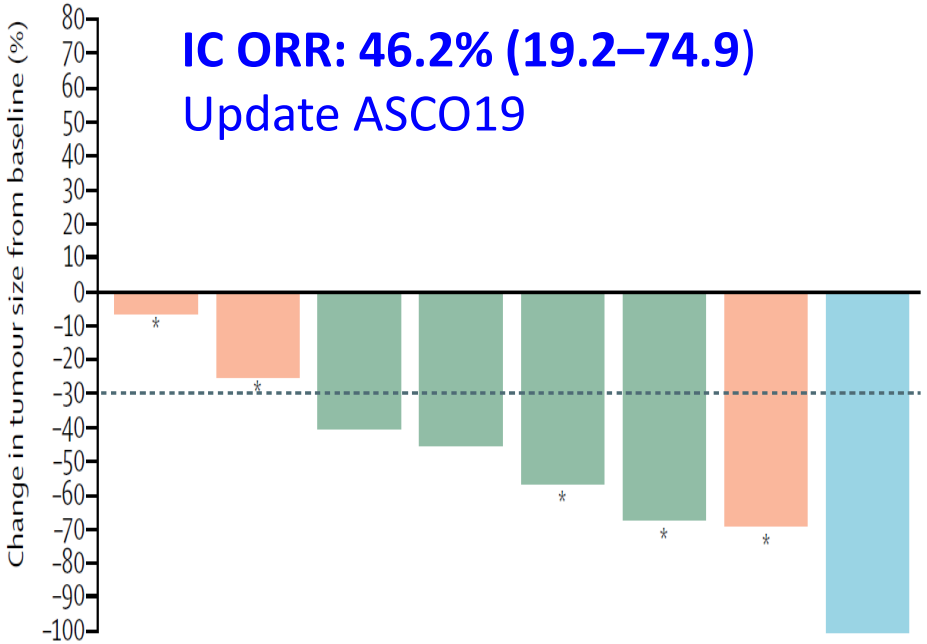
**ORR: 42.9%**
(update ASCO19)

| EXP3B: 1 non-crizotinib TKI ± chemo (n=27) | |
|---|---|
| ORR, n/N (%) (95% CI) | 9/27 (33) (16, 54) |
| IC ORR, n/N (%) (95% CI) | 5/12 (42) (15, 72) |
| Median PFS, mo (95% CI) | 5.5 (2.9, 9.0) |




Updated Efficacy and Safety: B.Besse et al, ASCO 2019

**IC ORR: 46.2% (19.2–74.9)**
Update ASCO19



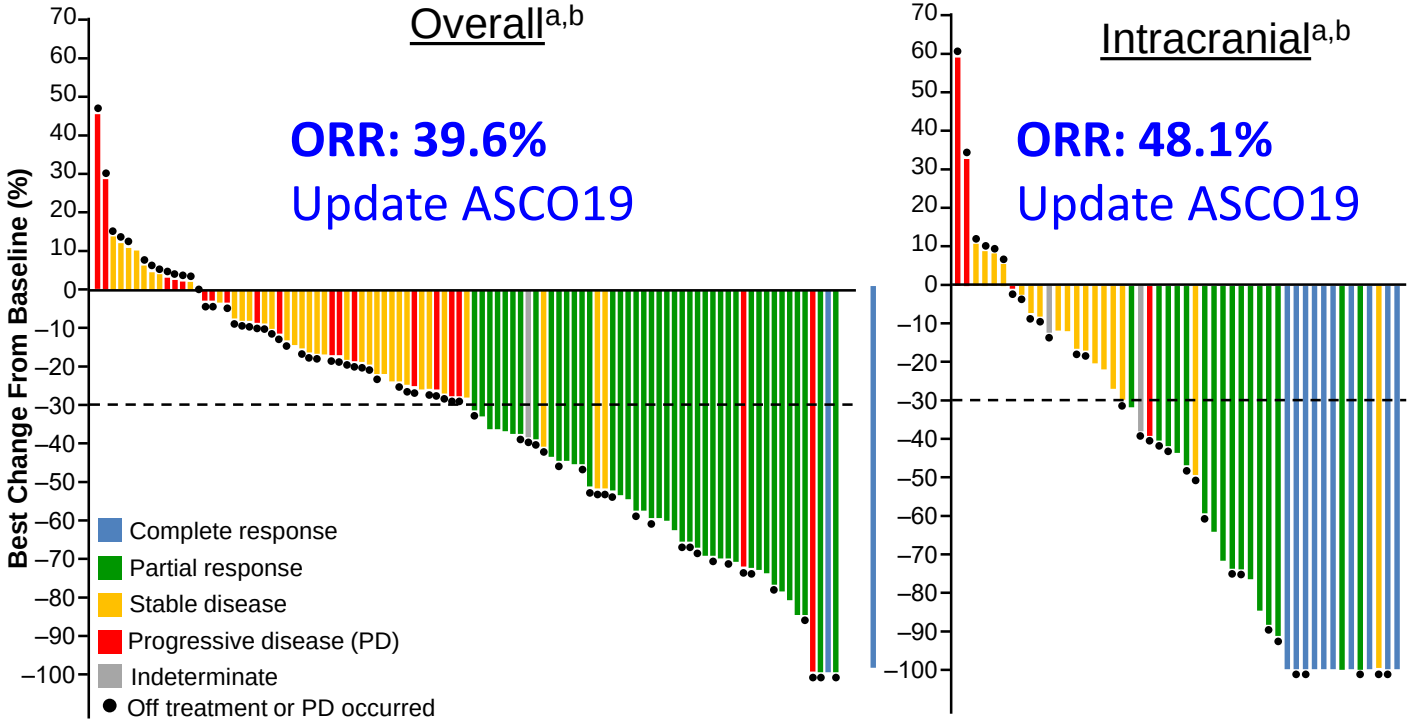

Solomon BJ, et al. J Thorac Oncol:2017;12:abs1756 (Data cut-off: 15 Mar 2017).

[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

# Efficacy Lorlatinib in ALK+ Pts Previously Treated with ≥2 Prior ALK TKIs ± CT (EXP 4-5)

| EXP4–5: ≥2 prior ALK TKIs ± chemo (n=111) | |
|---|---|
| ORR, n/N (%) (95% CI) | 43/111 (39) (30, 49) |
| IC ORR, n/N (%) (95% CI) | 40/83 (48) (37, 59) |
| Median PFS, mo (95% CI) | 6.9 (5.4, 9.5) |




- 83 patients (75%) had brain metastases at baseline.

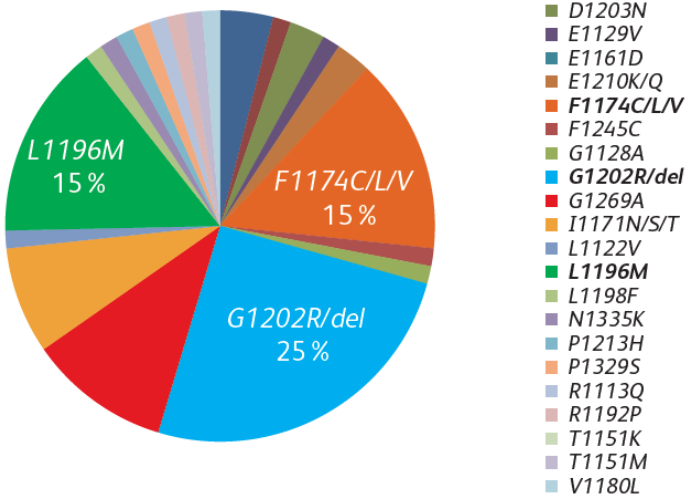
[a] Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.
[b] Complete response was defined as the disappearance of all target lesions; when nodal disease was included in target lesions, reversion to normal node size (<10 mm) prevented the percent change from baseline from reaching –100%. Some patients with a total change from baseline of –100% are shown as partial responses due to the inclusion of non-target lesions in the summary.

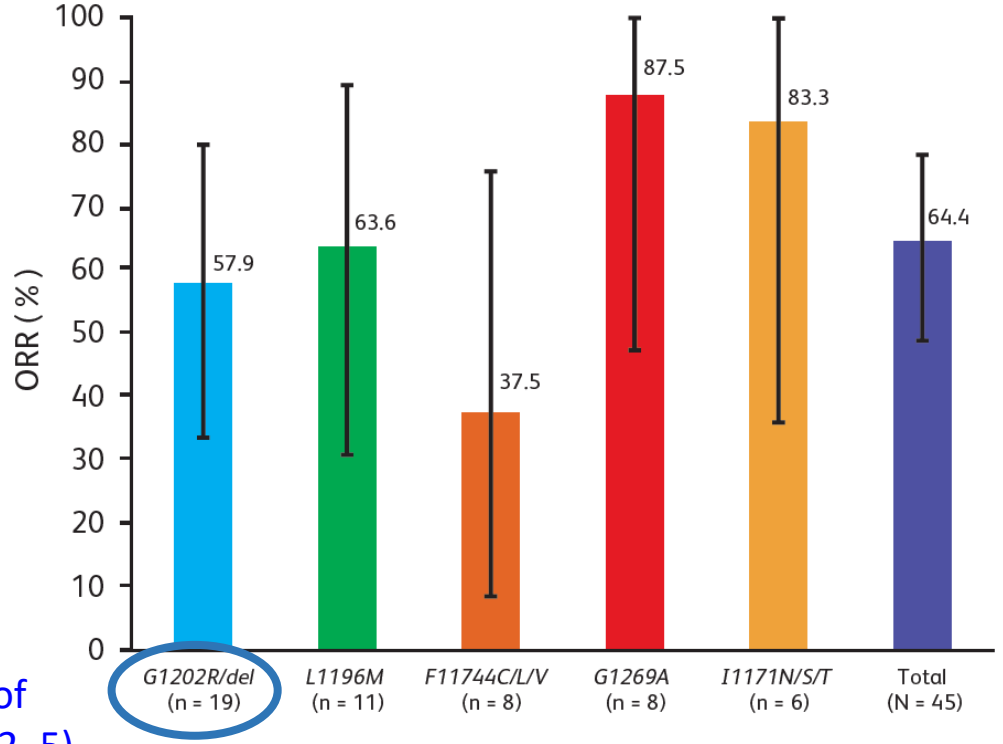
CI, confidence interval; CT, chemotherapy; DOR, duration of response; mo, months; NR, not reached.

Updated Efficacy and Safety: B.Besse et al, ASCO 2019

Benjamin J. Solomon et al, WCLC 2017; lancet onco 2018

# ORR in Previously Treated Patients With ALK+ NSCLC Harboring the Most Frequent ALK Mutations in cfDNA (EXP2–5)

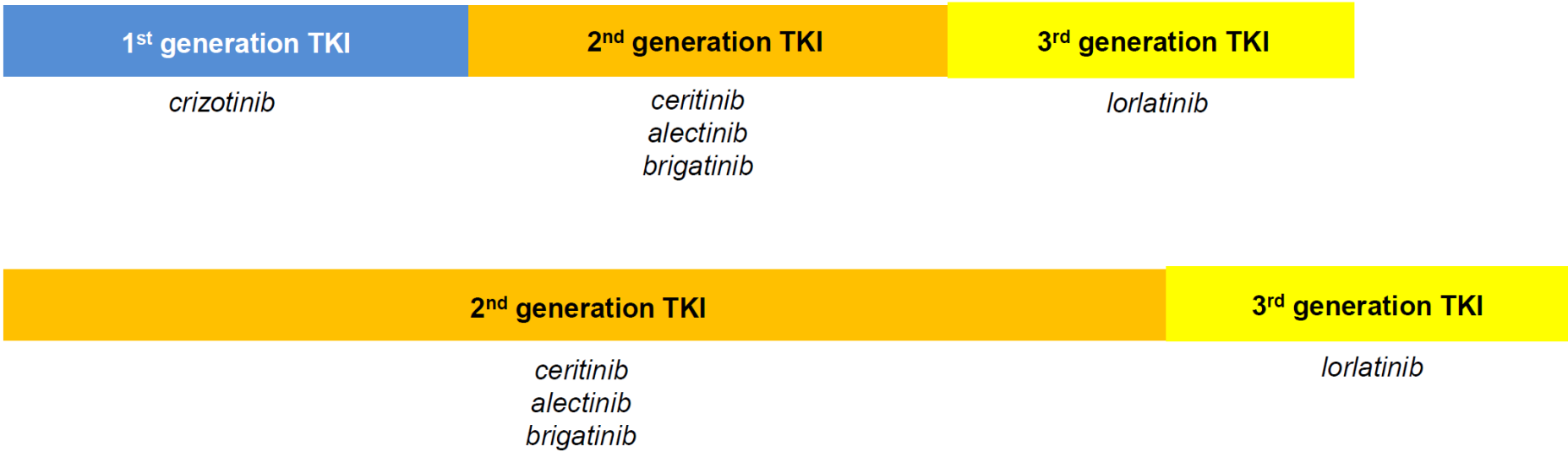



ALK Kinase Domain Mutations Detected in cfDNA of Previously Treated Patients With ALK+ NSCLC (EXP2–5)

Updated Efficacy and Safety: B.Besse et al, ASCO 2019

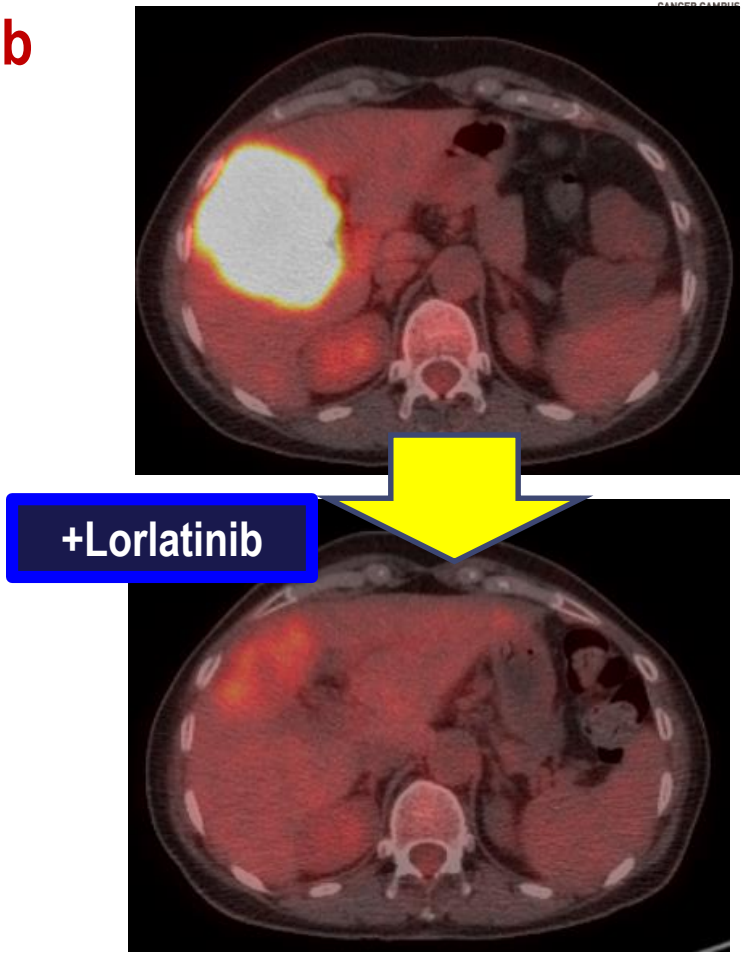
# The 3rd Generation ALK/ROS1 TKI Lorlatinib has become a standard therapy after 2nd Generation TKIs



# *ALK* positive crizo-resistant NSCLC stage IV
# Primary resistance to Ceritinib & Brigatinib

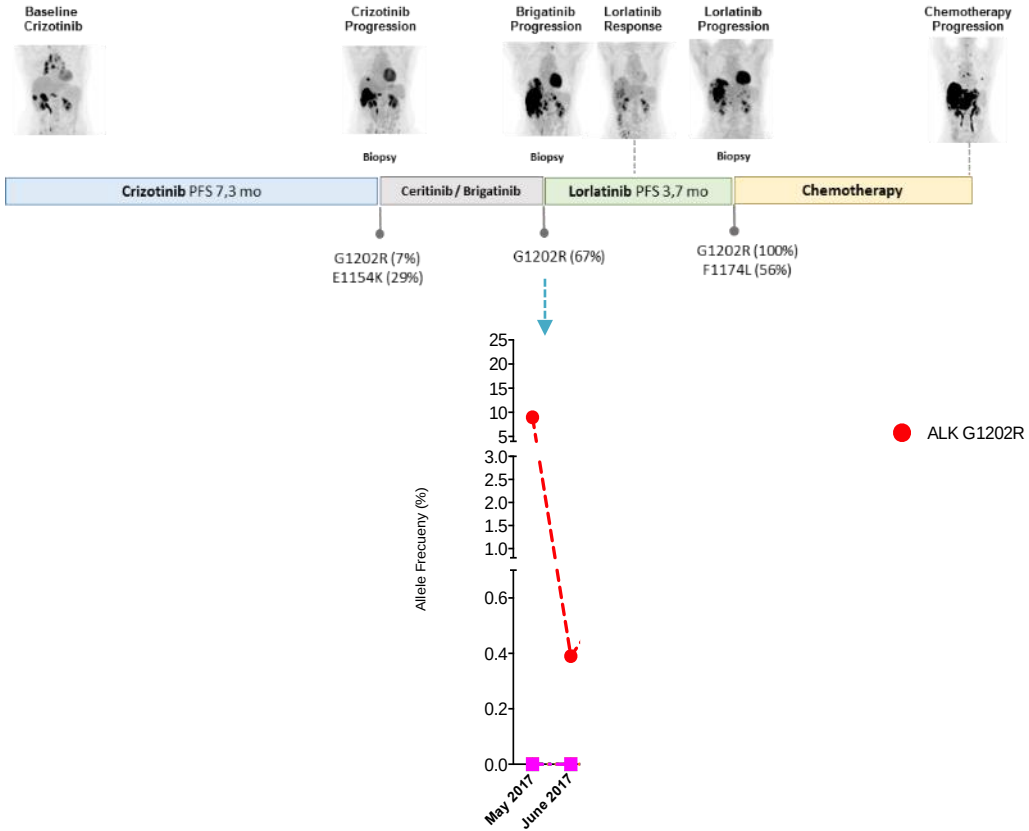
- **May 2017**
  - PS 2 (abdominal pain +++ liver)
  - Admitted in the hospital
    - **Blood for "liquid biopsy"**
      - ALK-EML v3 by RT-PCR
      - *ALK* G1202R mutation

- **Our options:**
  - ✓ **Expanded access to Lorlatinib**
  - ✓ Platinum- based chemo
  - ✓ Immunotherapy (+/- Chemo)



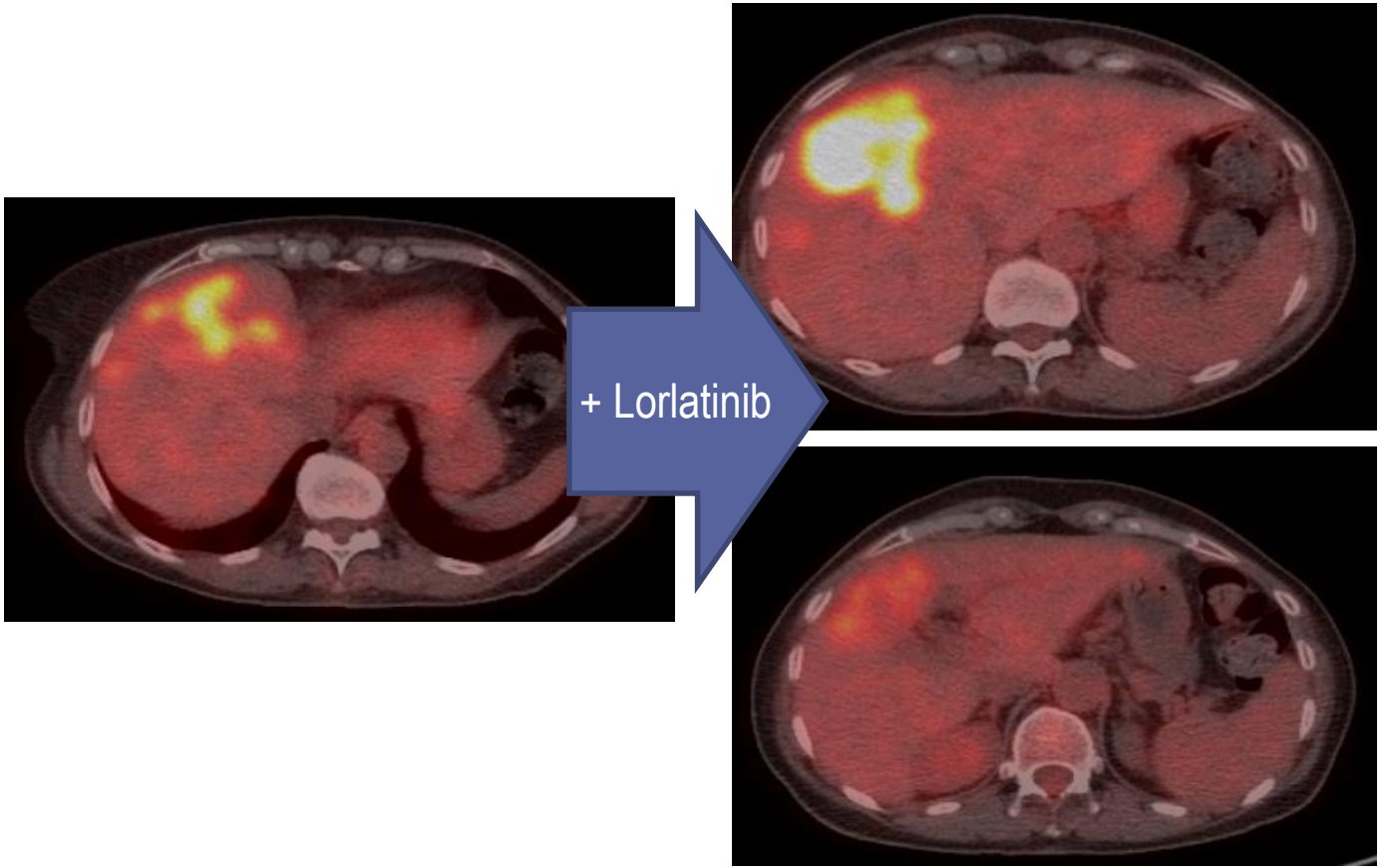

D.Planchard et al, Gustave Roussy

# ctDNA monitoring during treatment




D.Planchard et al, Gustave Roussy, L.Friboulet team at Gustave Roussy; G.Recondo et al, CCR 2019

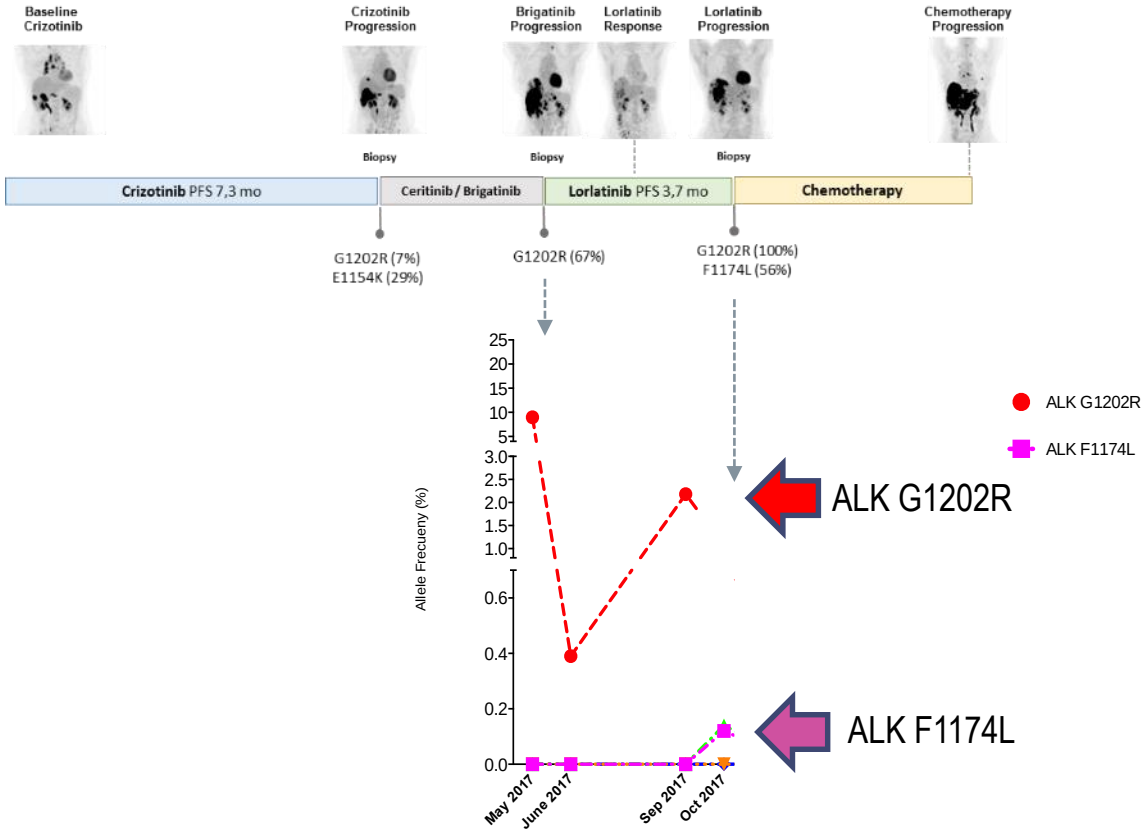
# 4 months of Lorlatinib…




**Tissu biopsy**
**+ Plasma sample**

D.Planchard et al, Gustave Roussy

# Emergence of 2 mutations ALK - G1202R and F1174L

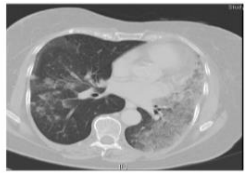


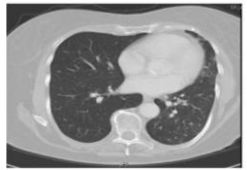

Unpublished data: do not post

D.Planchard et al, Gustave Roussy, L.Friboulet team at Gustave Roussy

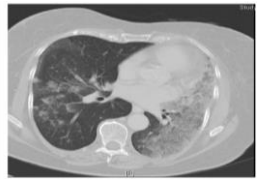
# MATCH-R program

**Patients with + biomarker tumor exposed to a targeted therapy and an initial response**





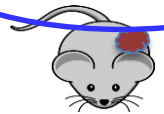
Sensitive



**Resistant**

**In vitro patient Cell lines**

**Mouse xenograft models**

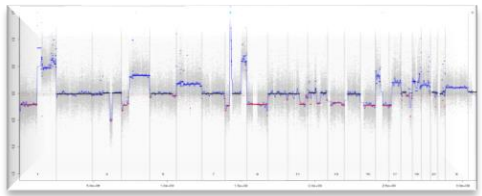


**Tumor biopy**

Whole-exome sequencing

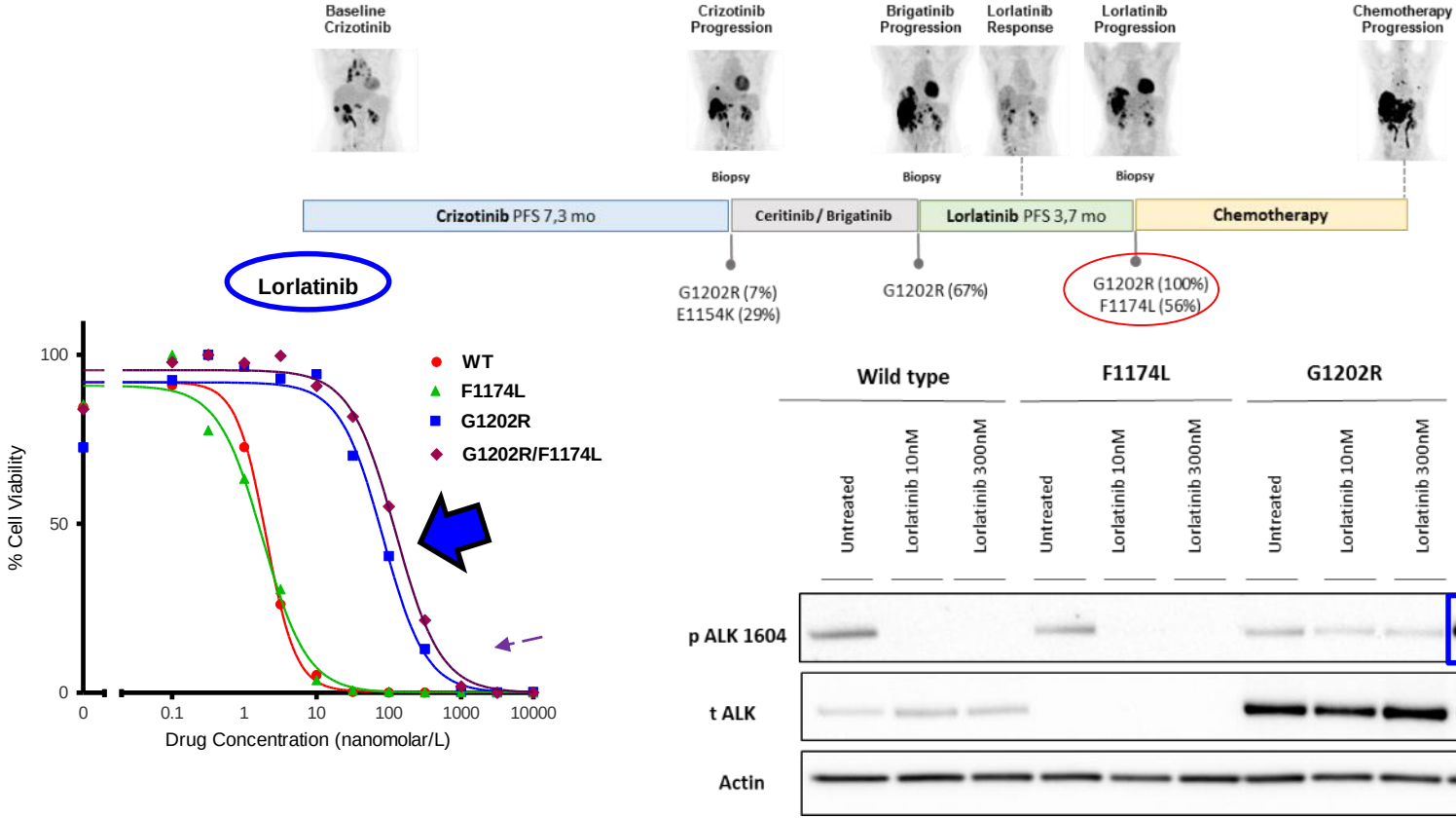
RNAseq

CGH

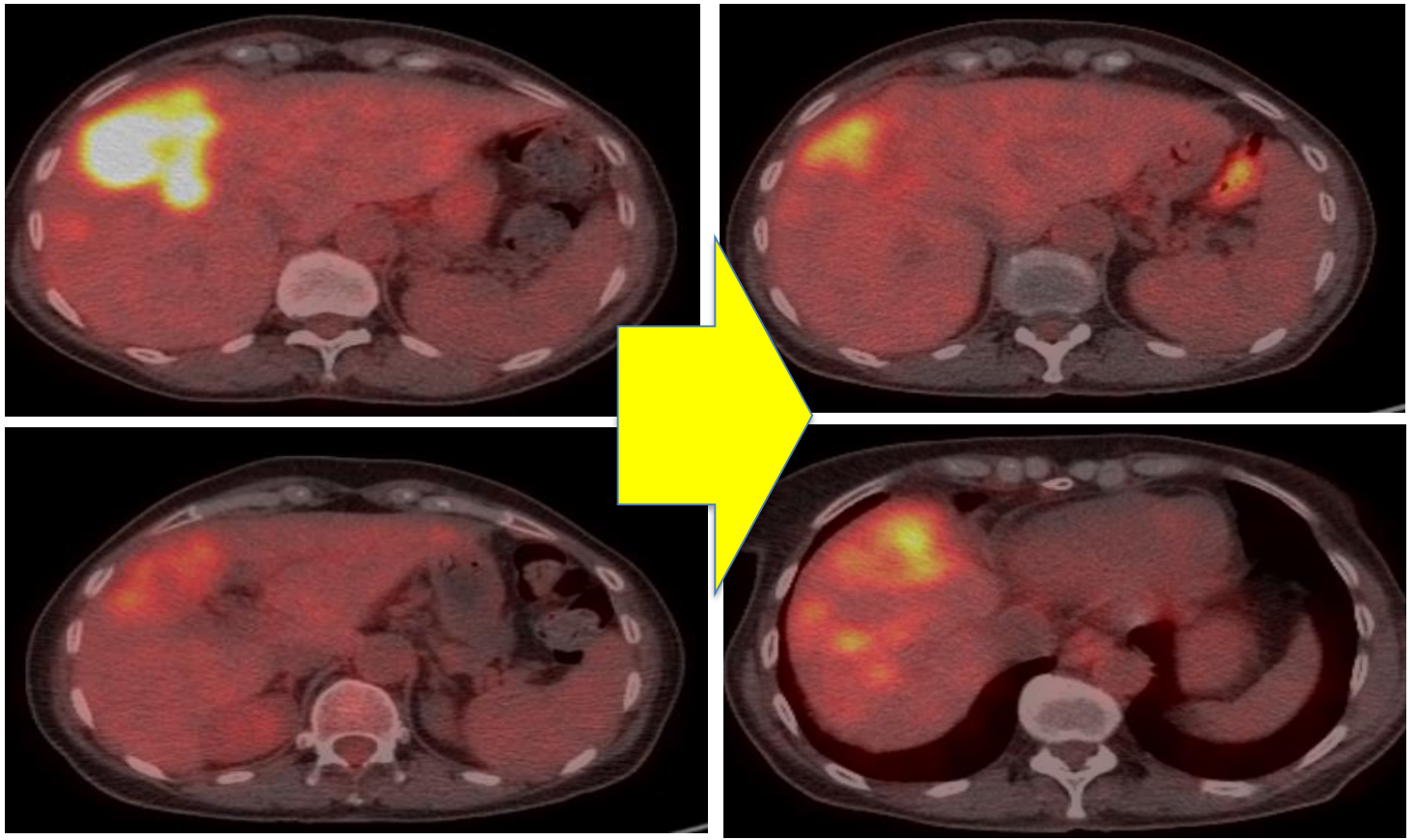
PI JC. Soria-F.André and B.Besse at Gustave Roussy

# Efficacy of ALK inhibitors on the novel G1202R/F1174L mutations



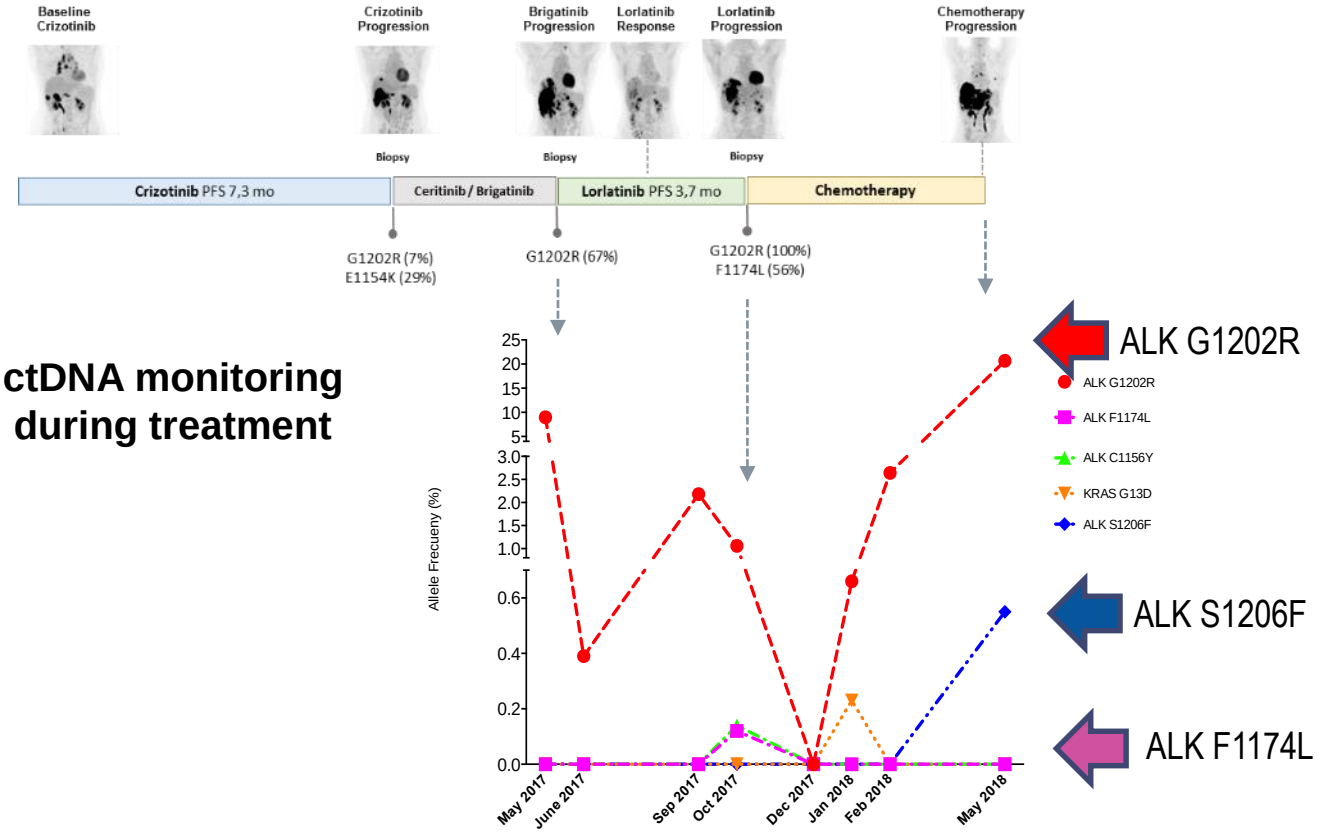

D.Planchard et al, Gustave Roussy, L.Friboulet team at Gustave Roussy; G.Recondo et al, CCR 2019

# **MTB Decision:** CDDP+Pemetrexed…



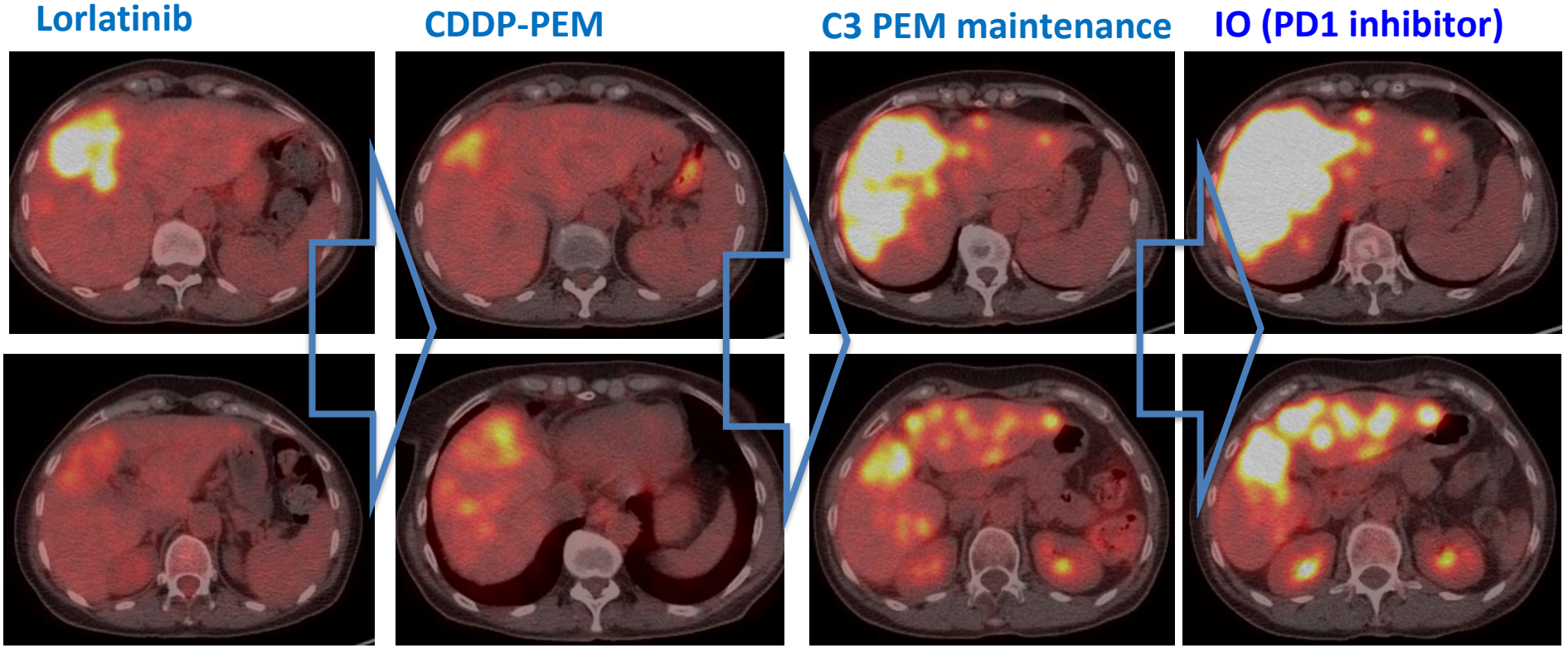
D.Planchard et al, Gustave Roussy

# Emergence of G1202R and S1206F mutations




D.Planchard et al, Gustave Roussy, L.Friboulet team at Gustave Roussy; G.Recondo et al, CCR 2019

# MTB decision: IO…



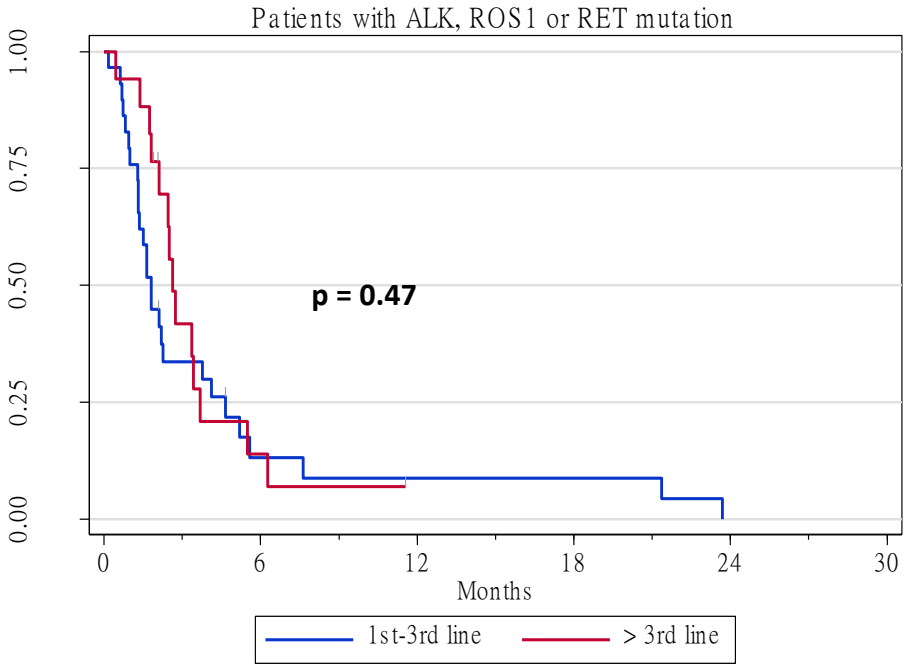

D.Planchard et al, Gustave Roussy

# IMMUNOTARGET cohort, *fusion*+ subgroup

## Outcomes in ALK/ROS1/RET + population

| Driver | N | ORR | mPFS (m) | mOS (m) |
|---|---|---|---|---|
| ALK | 23 | 0 | 2.5 | 17 |
| RET | 16 | 6% | 2.1 | 21.3 |
| ROS1 | 7 | 17% | - | - |

**PFS by N# line**

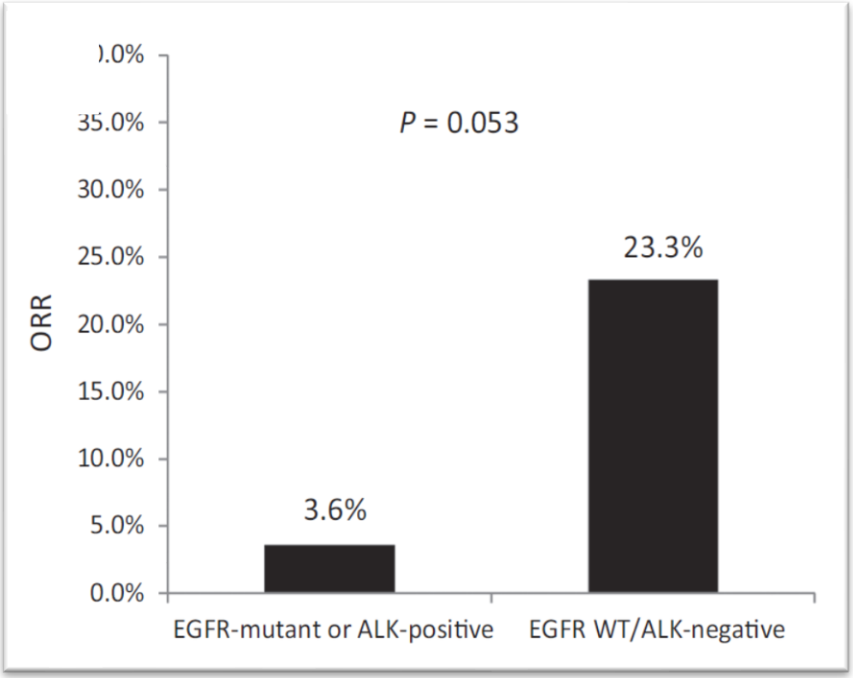



*Mazières ASCO 2018*

# ALK fusion and IO…

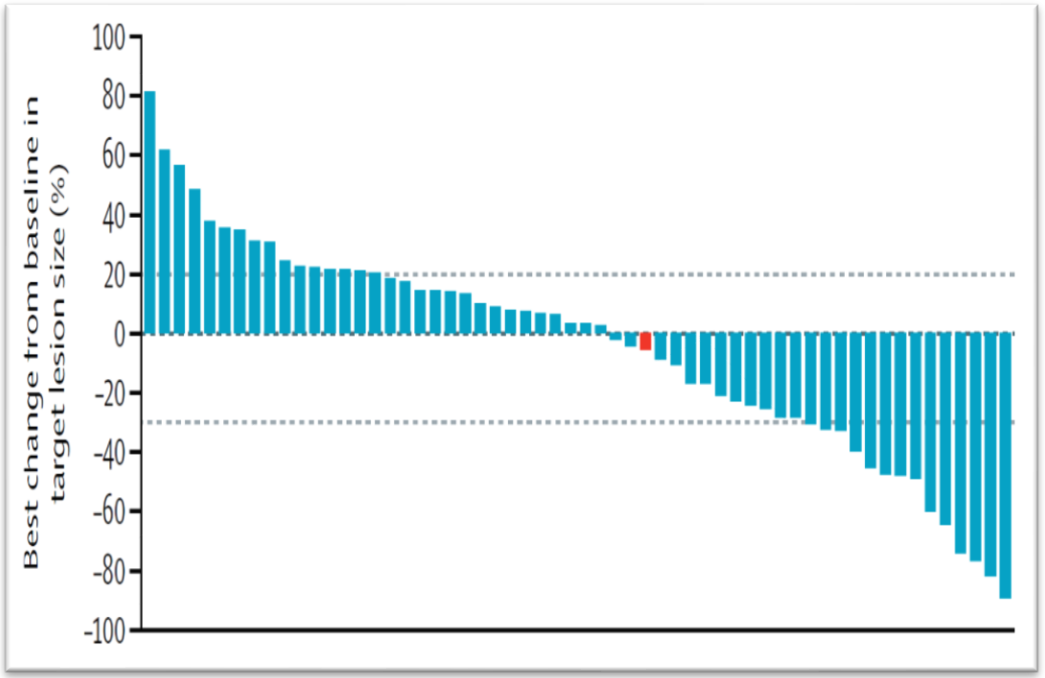
## EGFR+/ALK+

**ORR ALK+: 0/6**



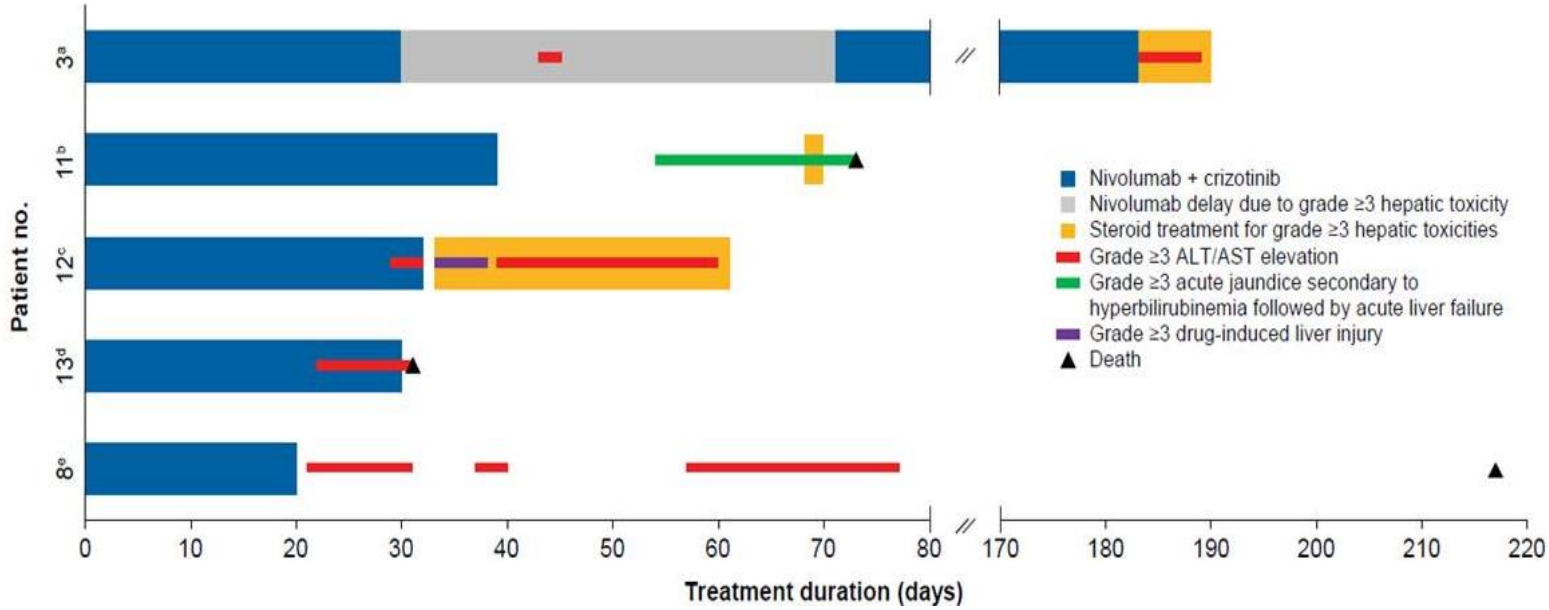

## EGFR+/ALK+ arm (ATLANTIC Trial)

**ORR ALK+ : 0/15**




*Gainor CCR 2016, Garassino Lancet Oncol 2018*

# CheckMate 370 (Nivolumab + Crizotinib): Closed Early due to toxicities




- 13 patients enrolled on study
- PR in 5/13 (38%) patients and SD in 2 (15%)
- 5 patients (38%) developed sever hepatic toxicities

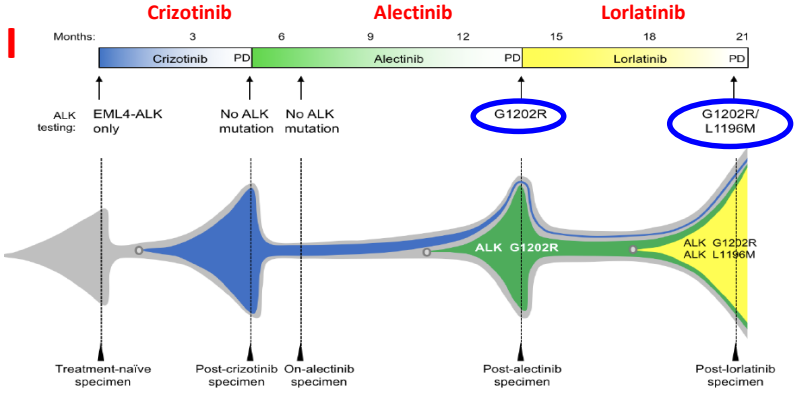
Spigel et al, JTO 2018

# Oncologist against Cancer

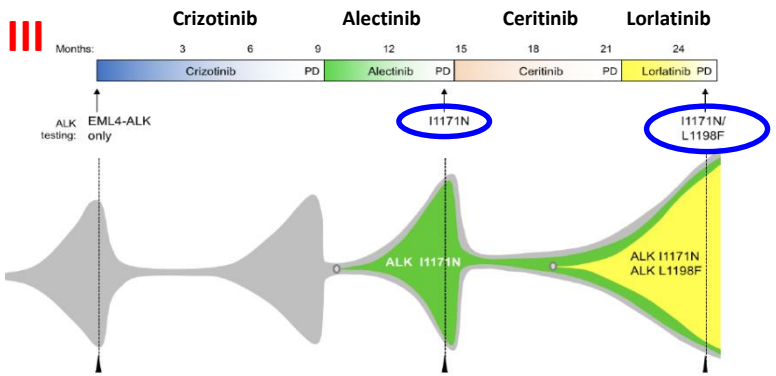
# Clonal evolution of resistance to sequential ALK targeted therapies

GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS

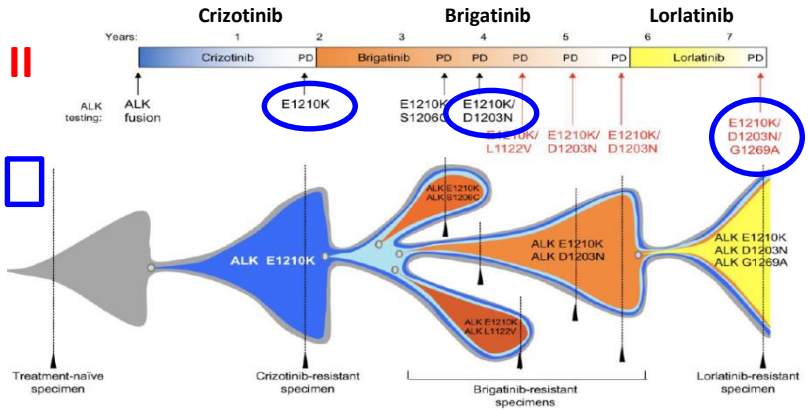
## Pts I



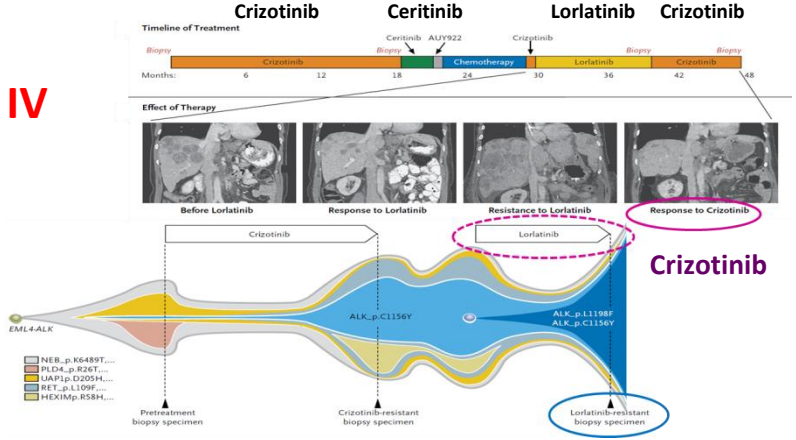

## Pts III




## Pts II




## Pts IV

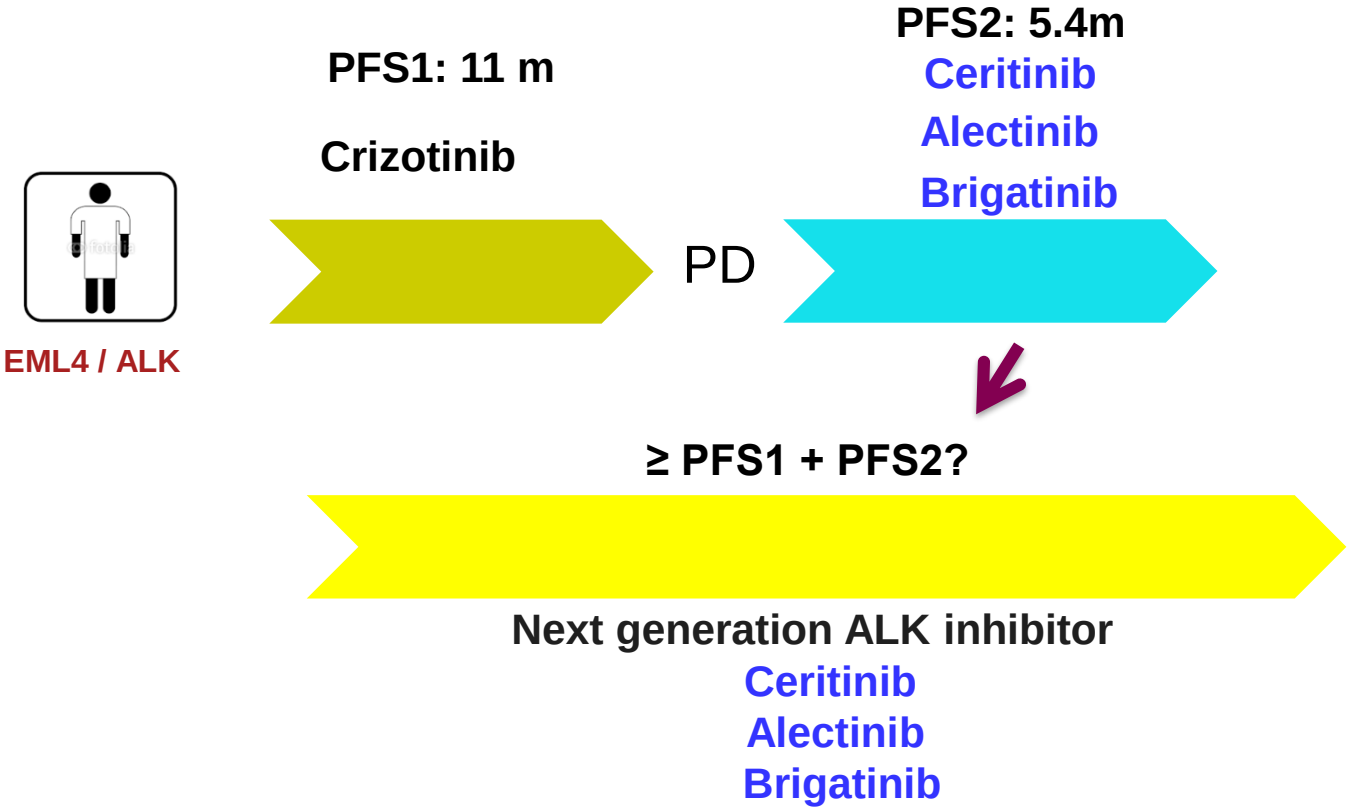



Crizotinib

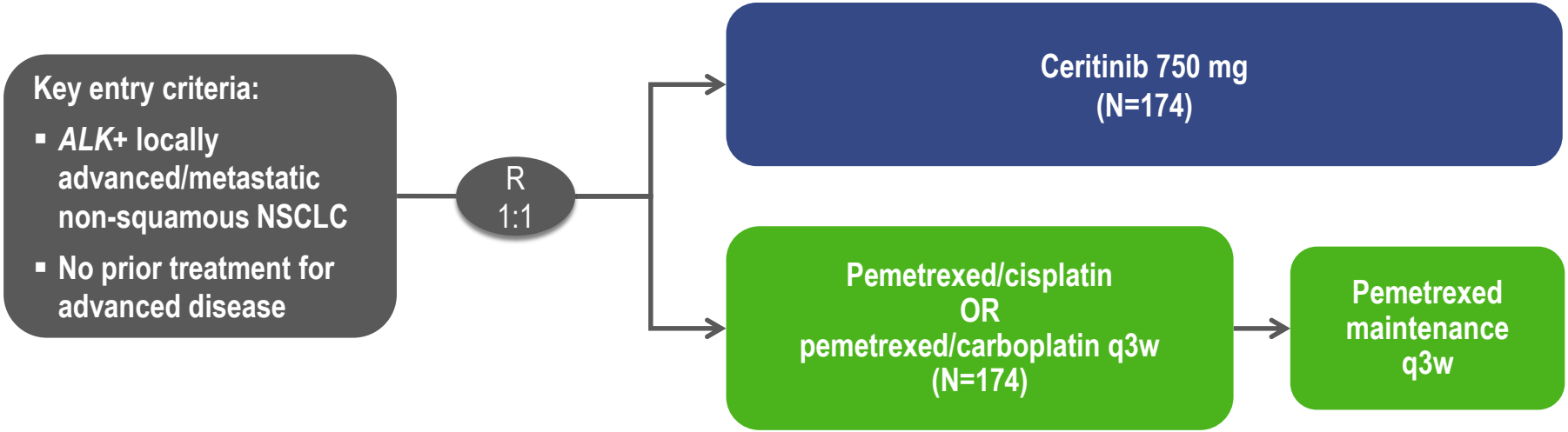
Alice T. Shaw et al NEJM 2016 Satoshi Yoda et al, cancer discovery 2018

# Developing the optimal treatment sequence

## Next-generation ALK inhibitor as 1st-line treatment



# CERITINIB vs CHEMOTHERAPY IN THE 1ST-LINE SETTING (ASCEND-4)

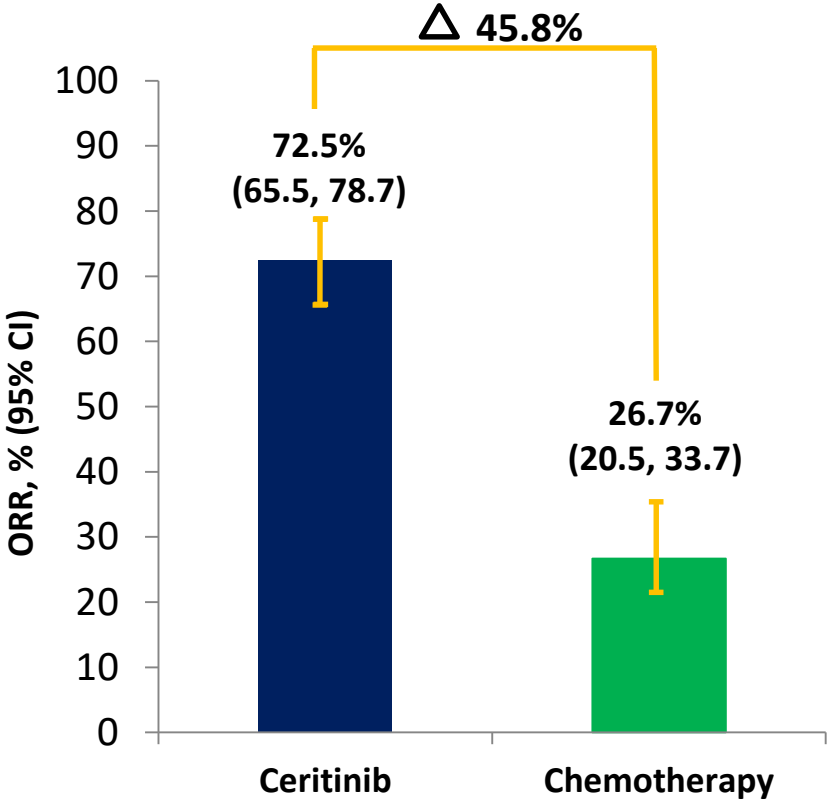



Soria JC *et al. Lancet* 2017;389:917–929

Primary endpoint = PFS
q3w, every 3 weeks

# Objective Tumor Response (BIRC)

## High Response Rate and Rapid time to Responses With Ceritinib




| | Ceritinib (n=189) | Chemotherapy (n=187) |
|---|---|---|
| **ORR (CR+PR), n (%) [95% CI]** | **137 (72.5) [65.5, 78.7]** | **50 (26.7) [20.5, 33.7]** |
| CR, n (%) | 1 (0.5) | 0 |
| PR, n (%) | 136 (72.0) | 50 (26.7) |
| SD, n (%) | 23 (12.3)* | 88 (47.1)† |
| PD, n (%) | 19 (10.1) | 26 (13.9) |
| UNK, n (%) | 10 (5.3) | 23 (12.3) |
| **Median time to first response (in responders), weeks (range)** | 6.1 (5.1- 61.7) | 13.4 (5.1-90.1) |

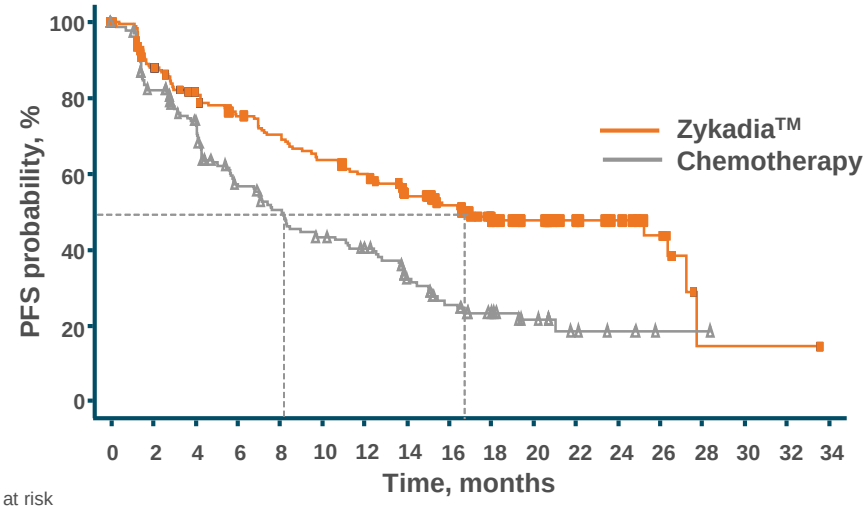
*3 NCRNPD cases are based on patients with non-measurable disease
†9 NCRNPD cases are based on patients with non-measurable disease

Gilberto de Castro Jr et al, IASLC 2016 Soria JC et al, lancet 2017

# Primary Endpoint: PFS by BIRC

## Progression-Free Survival

| | Zykadia™ (n = 189) | Chemotherapy (n = 187) |
|---|---|---|
| Events, n (%) | 89 (47.1) | 113 (60.4) |
| Median (95% CI), months | **16.6** (12.6- 27.2) | 8.1 (5.8-11.1) |
| Hazard ratio (95% CI) = 0.55 (0.42-0.73) | | |
| Stratified Log-rank *P* value < .001 | | |

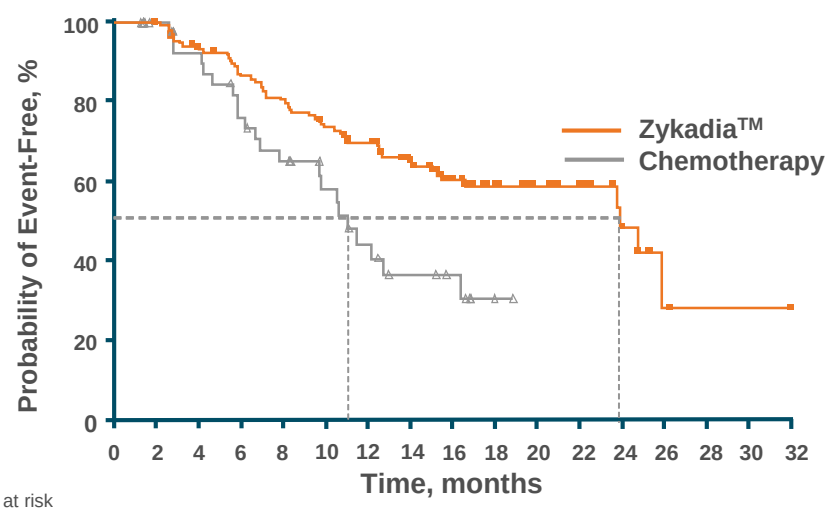



No. at risk

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zykadia™ | 189 | 155 | 139 | 125 | 116 | 105 | 98 | 76 | 59 | 43 | 32 | 23 | 16 | 11 | 1 | 1 | 1 | 0 |
| Chemotherapy | 187 | 136 | 114 | 82 | 71 | 60 | 53 | 35 | 24 | 16 | 11 | 5 | 3 | 1 | 1 | 0 | 0 | 0 |

## Duration of Response

| | Zykadia™ (n = 137) | Chemotherapy (n = 50) |
|---|---|---|
| Events, n (%) | 54 (39.4) | 22 (44.0) |
| Median (95% CI), months | **23.9** (16.6-NE) | 11.1 (7.8-16.4) |
| Estimated 21-month DOR rate (95% CI), % | 59.0 (49.3-67.4) | NE* |




No. at risk

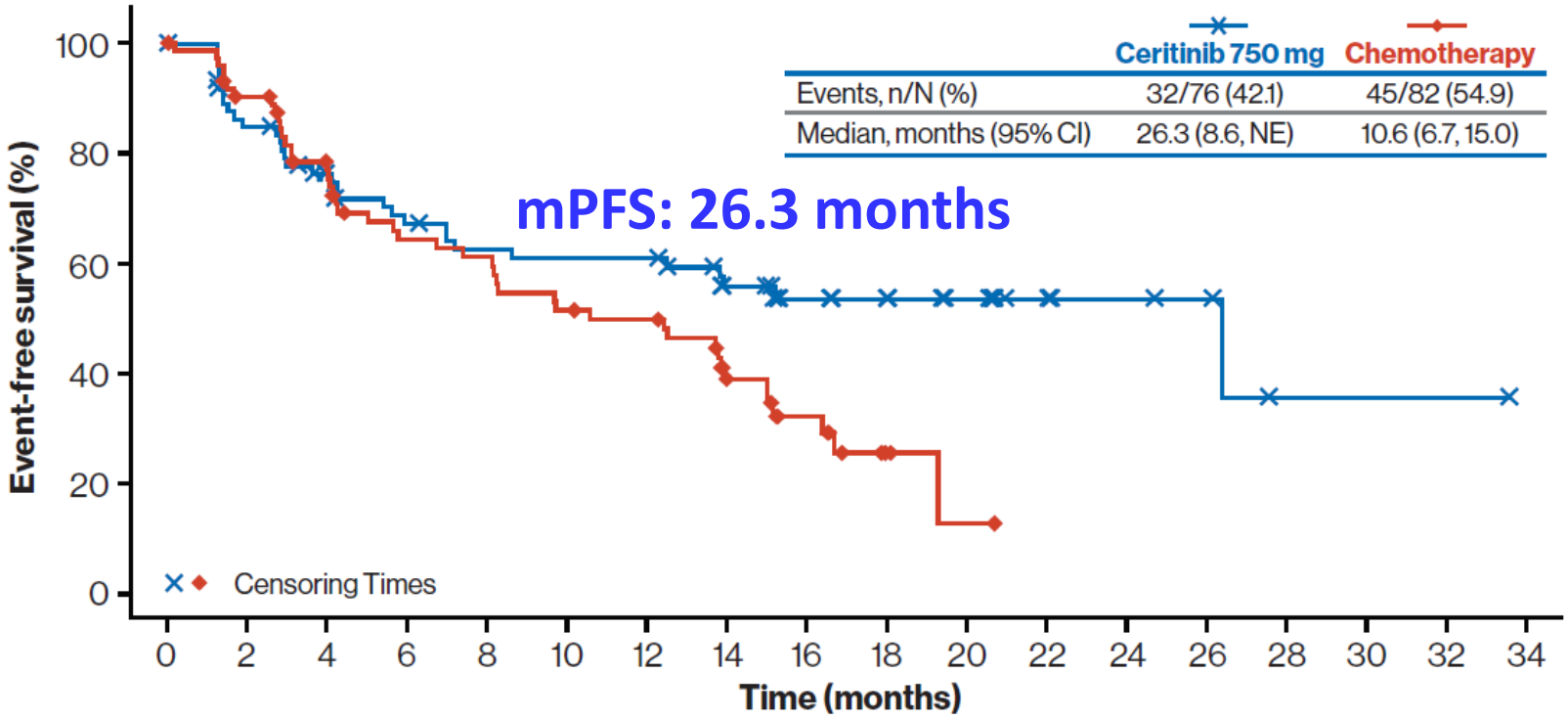
| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Zykadia™ | 137 | 137 | 125 | 114 | 106 | 96 | 87 | 62 | 45 | 32 | 20 | 16 | 8 | 2 | 1 | 1 | 0 |
| Chemotherapy | 50 | 42 | 35 | 28 | 23 | 17 | 12 | 8 | 6 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |


1.de Castro Jr. G, et al. WCLC 2016 [abstract PL03.07]
2.Soria JC, et al. *Lancet*. 2017 Jan 23. [Epub ahead of print].

# ASCEND-4 – Asian group analysis (PFS – per BIRC)

ORR: 65.8 vs 29.3%

| | Ceritinib 750 mg | Chemotherapy |
|---|---|---|
| Events, n/N (%) | 32/76 (42.1) | 45/82 (54.9) |
| Median, months (95% CI) | 26.3 (8.6, NE) | 10.6 (6.7, 15.0) |



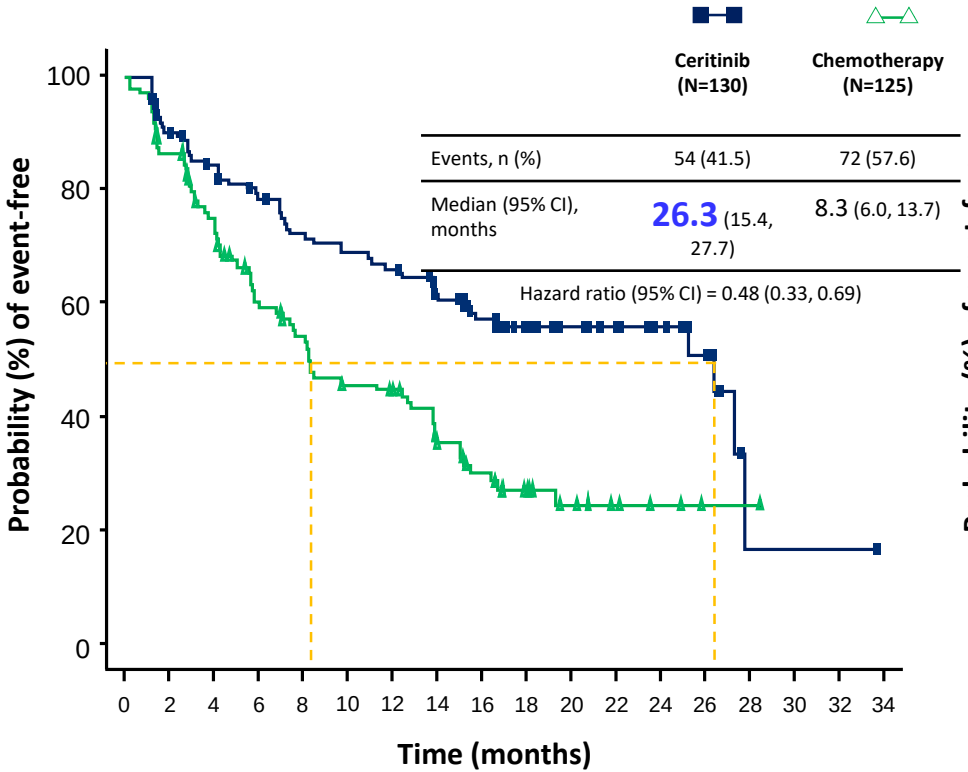

No. of patients still at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ceritinib | 76 | 61 | 51 | 44 | 40 | 39 | 39 | 28 | 21 | 18 | 13 | 8 | 5 | 4 | 1 | 1 | 1 | 0 |
| Chemotherapy | 82 | 63 | 51 | 40 | 38 | 32 | 30 | 18 | 11 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Daniel SW Tan et al, ESMO 2019

# PFS By BIRC in Patients Without and With BM

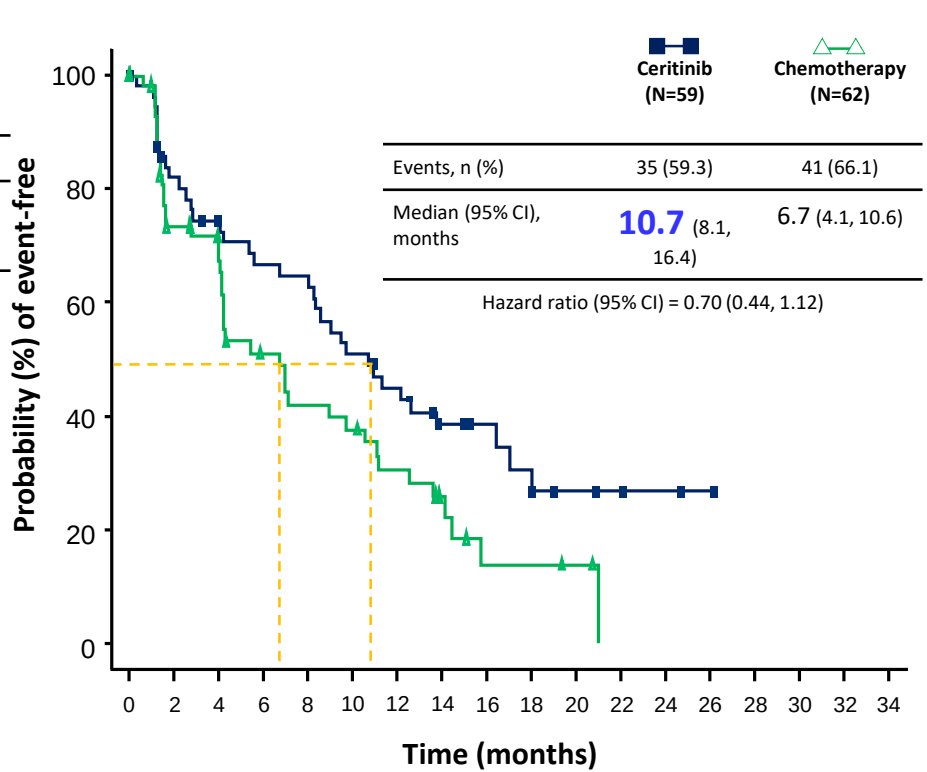
## No Brain metastases at baseline




No. at risk

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ceritinib | 130 | 111 | 101 | 91 | 83 | 79 | 76 | 62 | 49 | 35 | 28 | 20 | 14 | 10 | 1 | 1 | 1 | 0 |
| Chemotherapy | 125 | 96 | 79 | 59 | 52 | 43 | 40 | 28 | 21 | 13 | 9 | 5 | 3 | 1 | 1 | 0 | 0 | 0 |

## With Brain metastases at baseline




No. at risk

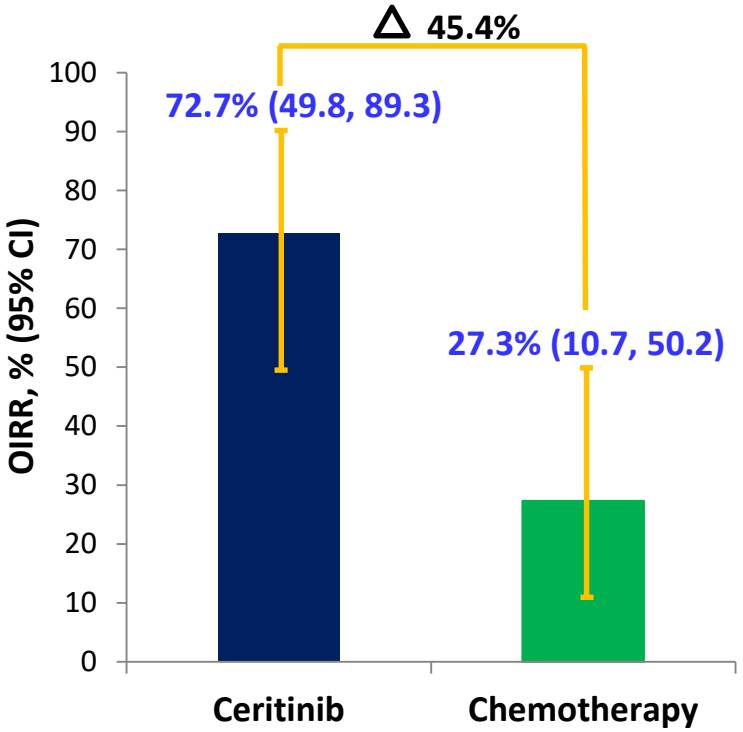
| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ceritinib | 59 | 44 | 38 | 34 | 33 | 26 | 22 | 14 | 10 | 8 | 4 | 3 | 2 | 1 | 0 | 0 | 0 | 0 |
| Chemotherapy | 62 | 40 | 35 | 23 | 19 | 17 | 13 | 7 | 3 | 3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Gilberto de Castro et al, IASLC 2016; JC Soria et al lancet 2017

# Intracranial Response by BIRC Neuro-radiologist

## High Response and Durable Clinical Benefit in the Brain with Ceritinib

- Intracranial response was assessed by BIRC neuro-radiologist as per modified RECIST 1.1 (a maximum of 5 target lesions located in the brain could be selected at baseline)



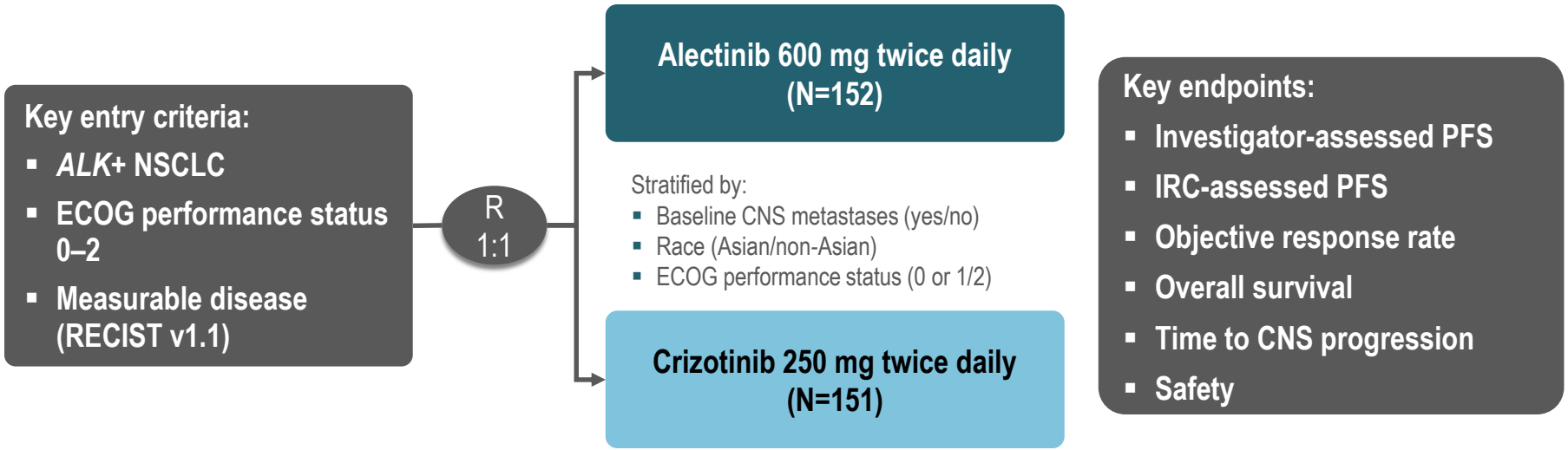

| Patients with measurable brain lesions* | Ceritinib (n=22) | Chemotherapy (n=22) |
|---|---|---|
| **OIRR, n (%) (95% CI)** | **16 (72.7) (49.8, 89.3)** | **6 (27.3) [10.7, 50.2]** |
| CR, n (%) | 2 (9.1) | 2 (9.1) |
| PR, n (%) | 14 (63.6) | 4 (18.2) |
| SD, n (%) | 3 (13.6) | 14 (63.6) |
| PD, n (%) | 1 (4.5) | 1 (4.5) |
| UNK, n (%) | 2 (9.1) | 1 (4.5) |
| **Median DOIR, months (95% CI)** | **16.6 (8.1, NE)** | **NE** (1.5, NE)** |
| **ICBR at ≥24 weeks, n (%) (95% CI)** | **19 (86.4) (65.1, 97.1)** | **11 (50.0) (28.2, 71.8)** |

ICBR = CR or PR or SD or Non-CR/Non-PD

*Baseline and ≥1 post-baseline scan

Gilberto de Castro Jr et al, IASLC 2016 Soria JC et al, lancet 2017

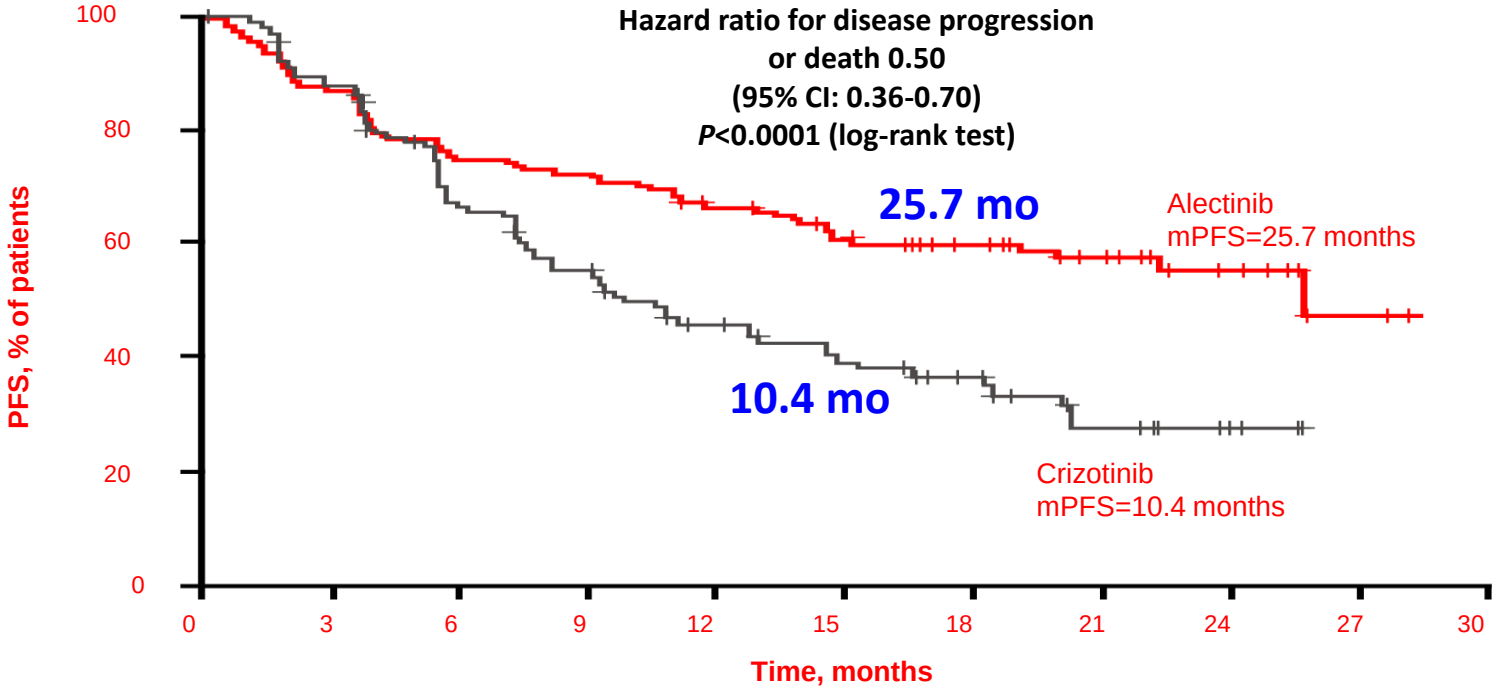
# ALECTINIB IN THE 1ST-LINE SETTING (ALEX)




Peters S *et al. N Engl J Med* 2017;377:829–838

ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; RECIST, response evaluation criteria in solid tumors

# ALEX: Progression-Free Survival at Primary Analysis (by Independent Review Committee)




**Patients at risk**

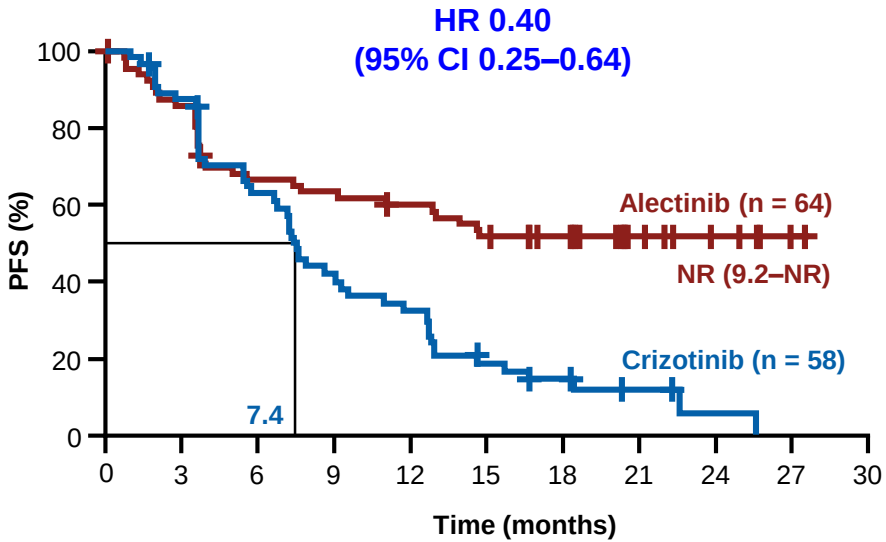
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Crizotinib | 151 | 128 | 92 | 74 | 57 | 46 | 33 | 12 | 4 | 0 | 0 |
| Alectinib | 152 | 132 | 1 12 | 108 | 95 | 83 | 69 | 35 | 15 | 2 | 0 |

Median follow up time: alectinib 17.6 months; crizotinib 18.6 months

Peters S, et al. *N Engl J Med*. 2017;377:829-838.

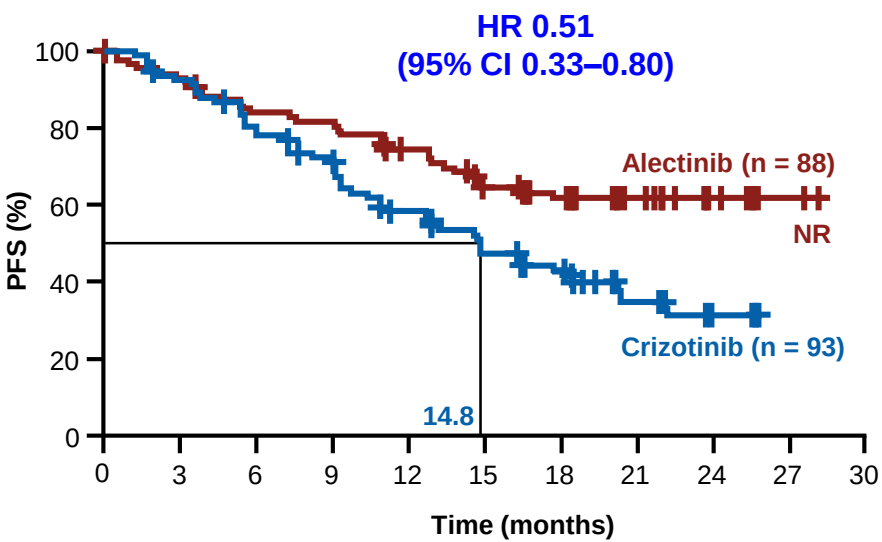
# ALEX: PFS by baseline CNS metastases status[a]

## Patients With CNS Metastases at Baseline




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Crizotinib | 58 | 48 | 33 | 22 | 17 | 9 | 6 | 3 | 1 | |
| Alectinib | 64 | 54 | 41 | 39 | 36 | 31 | 24 | 10 | 4 | 1 |

## Patients Without CNS Metastases at Baseline

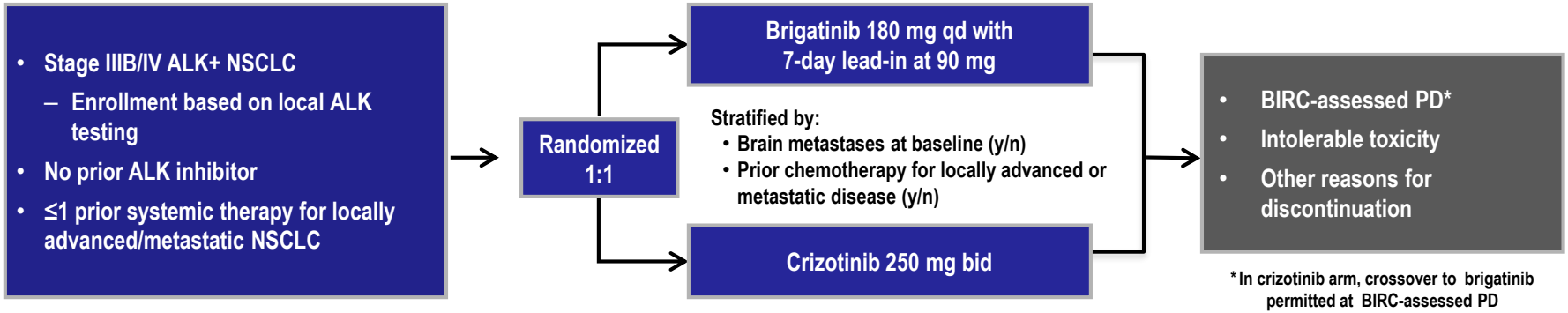



| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Crizotinib | 93 | 84 | 71 | 62 | 48 | 37 | 29 | 13 | 4 | |
| Alectinib | 88 | 81 | 72 | 70 | 61 | 50 | 43 | 25 | 11 | 2 |

[a] Investigator assessment.

Shaw A, et al. ASCO 2017. Abstract LBA9008.

# ALTA-1L: Phase 3, Open-label, Randomized, Multicenter Study (NCT02737501)




Disease assessment every 8 weeks, including brain MRI for all patients

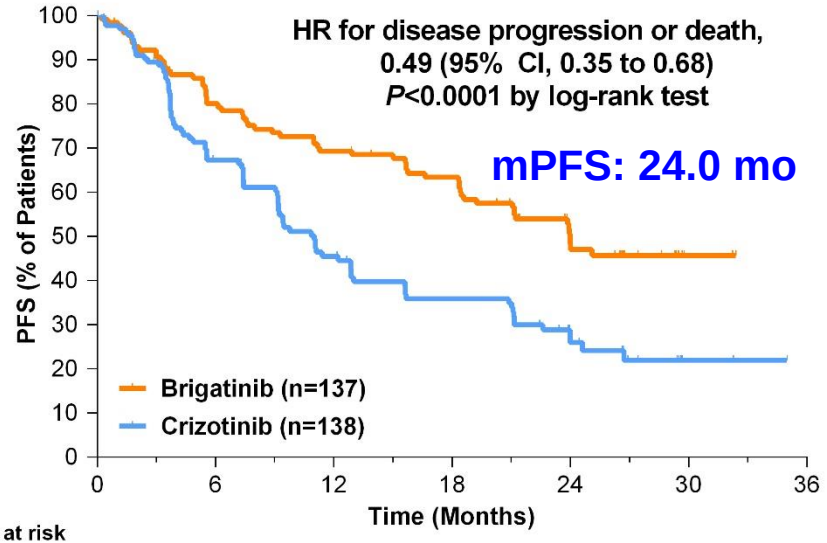
- Primary endpoint[a]: Blinded independent review committee (BIRC)–assessed PFS per RECIST v1.1
- Key secondary endpoints: Confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability
- Statistical considerations: ≈270 total patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses at 99 (50%) and 149 (75%) total expected events

**Trial fully accrued in August 2017 (N=275)**

[a] Statistical significance for the primary endpoint was achieved at the first interim analysis

# ALTA-1L (Brigatinib vs crizo), Primary Endpoint: BIRC-Assessed PFS
# Updated PFS (ESMO Asia)

## BIRC-Assessed PFS (Primary Endpoint)

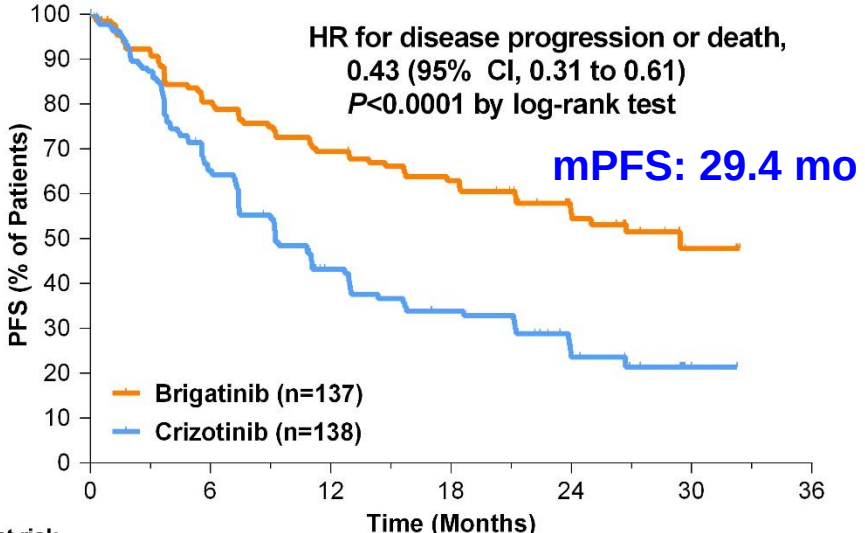



No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Brigatinib | 137 | 97 | 84 | 75 | 39 | 3 | 0 |
| Crizotinib | 138 | 80 | 49 | 37 | 17 | 2 | 0 |

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

## Investigator-Assessed PFS




No. at risk

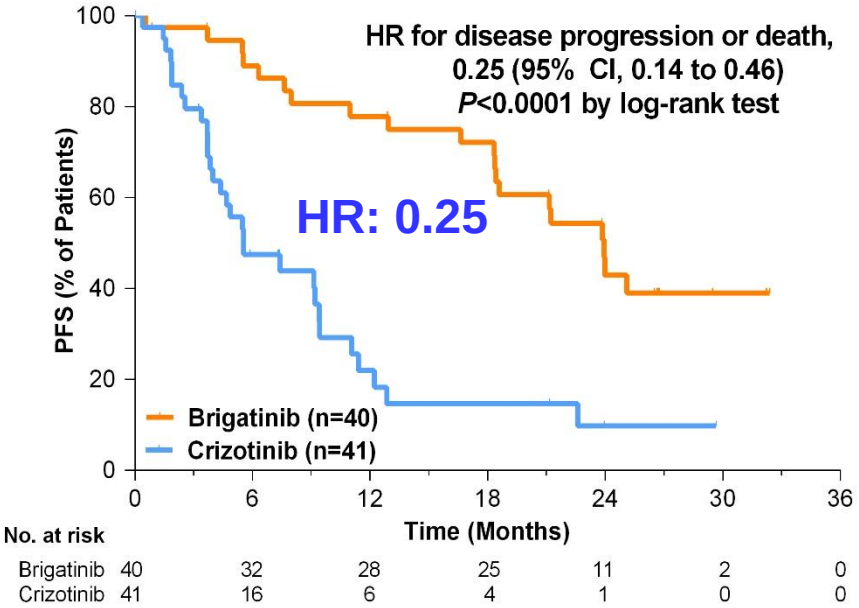
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Brigatinib | 137 | 102 | 88 | 78 | 46 | 4 | 0 |
| Crizotinib | 138 | 82 | 46 | 35 | 14 | 1 | 0 |

| Treatment | No. (%) of Patients With Events | Median PFS (95% CI) | 2-Year PFS, % (95% CI) |
|---|---|---|---|
| Brigatinib (n=137) | 59 (43) | 29.4 mo (21.2–NR) | 56 (46–64) |
| Crizotinib (n=138) | 92 (67) | 9.2 mo (7.4–12.9) | 24 (16–32) |

R. Camidge et al, ESMO Asia 2019

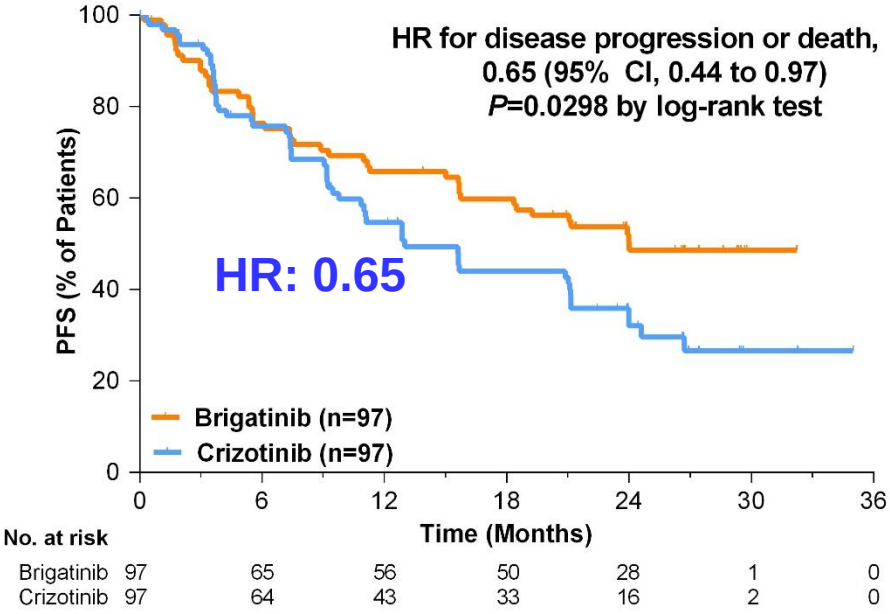
# Updated BIRC-Assessed PFS by Brain Metastases Status at Baseline[a]

## Patients With Any Brain Metastases at Baseline




| Treatment | No. (%) Patients With Events | Median PFS (95% CI) | 2-Year PFS, % (95% CI) |
|---|---|---|---|
| Brigatinib (n=40)[a] | 20 (50) | 24.0 mo (18.4–NR) | 43 (25–59) |
| Crizotinib (n=41)[a] | 30 (73) | 5.6 mo (3.8–9.4) | 10 (2–25) |

## Patients Without Brain Metastases at Baseline

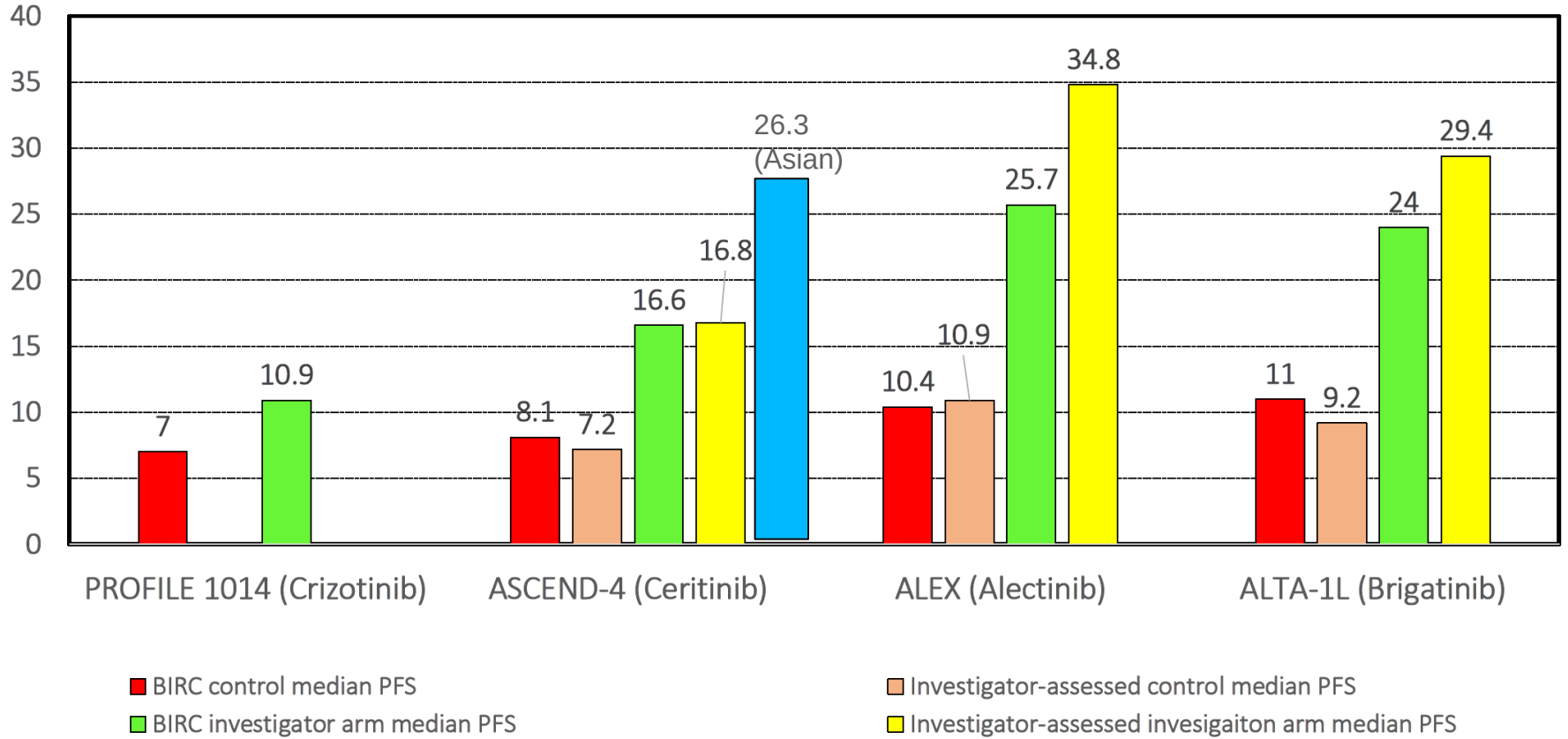



| Treatment | No. (%) Patients With Events | Median PFS (95% CI) | 2-Year PFS, % (95% CI) |
|---|---|---|---|
| Brigatinib (n=97)[a] | 43 (44) | 24.0 mo (15.7–NR) | 50 (39–61) |
| Crizotinib (n=97)[a] | 57 (59) | 13.0 mo (9.5–21.1) | 32 (22–43) |

[a] Per investigator assessment

R. Camidge et al, ESMO Asia 2019

# Comparison of mPFS among phase 3 ALK TKI trials




Solomon et al, NEJM 2014:371,2167-2177; Soria et al, Lancet 2017: 389, 917-929, Peters et al, NEJM 2017: 377,829-838; Camidge et al, NEJM 2018: 379, 2027-2039, Camidge et al, JTO 2019:14, 1233-1243; Camidge et al, ESMO Asia 2019 LBA1

# Safety profiles

| | Crizotinib[1] | Ceritinib[2] | Alectinib[3] | Brigatinib[4] |
|---|---|---|---|---|
| Grade 3+ AEs in ≥5% of patients | ↑ AST/ALT 14%<br>↓ ANC 11% | ↑ ALT 31%<br>↑ GGT 29%<br>↑ ALP 29%<br>↑ AST 17%<br>Diarrhea 5%<br>Vomiting 5% | ↑ ALT 5%<br>↑ AST 5%<br>Anaemia 5% | ↑ CPK 16%<br>↑ Lipase 13%<br>Hypertension 10%<br>↑ Amylase 5% |
| Any Grade AE → Dose Reduction | 21% | (80%)* | 16% | 29% |
| Any Grade AE → Treatment Discontinuation | 12% | 5% | 11% | 12% |

*Dose adjustment or interruption

ASCEND-8[5]: 450mg (fed) vs. 750mg (fasted)
**Equivalent efficacy**
**Less GI toxicity**

[1]Solomon B et al., N Eng J Med (2014); 371:2167-77; [2]Soria, Lancet (2017); 389: 917–929;
[3]Peters, N Engl J Med (2017);377: 829–838; [4]Camidge, N Engl J Med (2018); 379:2027-2039;
[5]Cho et al., J Thor Onc (2019): March 6 - ePub

# Safety profile of ceritinib 750 mg (fasted) in Asian pts similar to that of the overall population and consistent with that of previously reported studies

| Category | Ceritinib 750 mg n=76 | | Chemotherapy n=75 | |
|---|---|---|---|---|
| | All grades n (%) | Grade 3/4 n (%) | All grades n (%) | Grade 3/4 n (%) |
| **AEs** | 76 (100) | 60 (78.9) | 73 (97.3) | 50 (66.7) |
| Suspected to be drug related | 75 (98.7) | 53 (69.7) | 68 (90.7) | 36 (48.0) |
| **Serious AEs** | 29 (38.2) | 25 (32.9) | 22 (29.3) | 18 (24.0) |
| Suspected to be drug related | 18 (23.7) | 16 (21.1) | 13 (17.3) | 10 (13.3) |
| **AEs leading to discontinuation** | 7 (9.2) | 4 (5.3) | 5 (6.7) | 4 (5.3) |
| Suspected to be drug related | 4 (5.3) | 2 (2.6) | 3 (4.0) | 2 (2.7) |
| **AEs requiring dose adjustment** | 51 (67.1) | 33 (43.4) | 19 (25.3) | 19 (25.3) |
| Suspected to be drug related | 50 (65.8) | 33 (43.4) | 18 (24.0) | 18 (24.0) |
| **AEs requiring dose interruption/delay** | 53 (69.7) | 30 (39.5) | 30 (40.0) | 14 (18.7) |
| Suspected to be drug related | 51 (67.1) | 26 (34.2) | 23 (30.7) | 9 (12.0) |
| **AEs requiring dose adjustment or interruption/delay** | 63 (82.9) | 48 (63.2) | 38 (50.7) | 27 (36.0) |
| Suspected to be drug related | 61 (80.3) | 45 (59.2) | 33 (44.0) | 24 (32.0) |
| **AEs requiring additional therapy** | 73 (96.1) | 40 (52.6) | 68 (90.7) | 35 (46.7) |
| Suspected to be drug related | 72 (94.7) | 32 (42.1) | 56 (74.7) | 24 (32.0) |

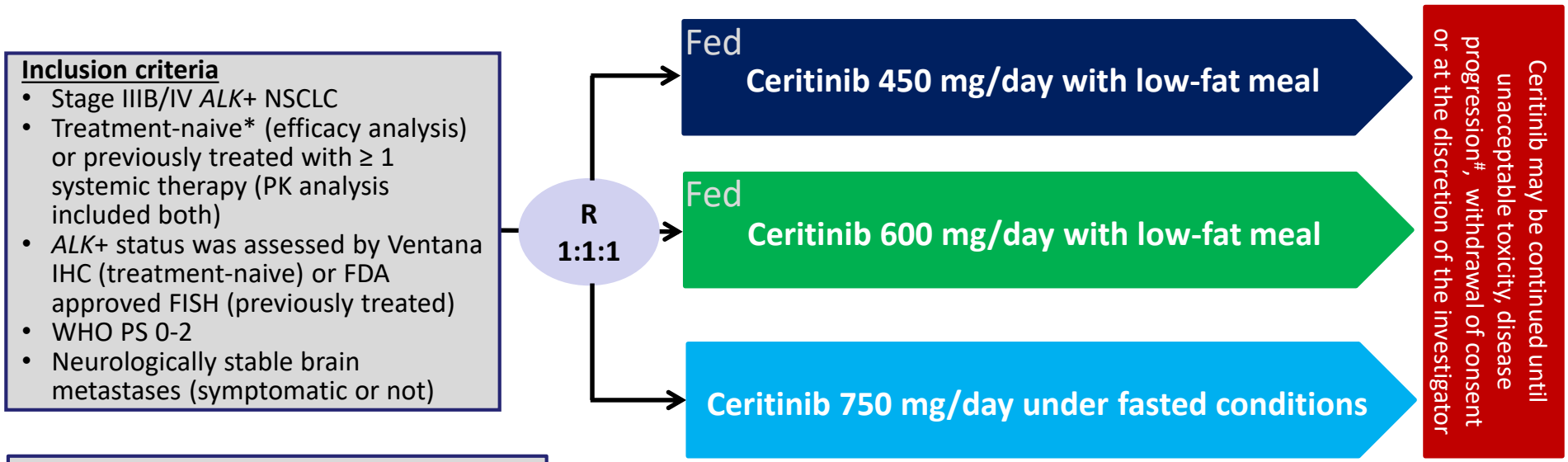
65%

67%

80%

Daniel SW Tan et al, ESMO 2019

# ASCEND-8: Phase 1, Randomized, Global, Open-label, Parallel Design Study (NCT02299505)




**Randomization is stratified by:**
Brain metastases – presence/absence
Prior treatment (applicable only for PK analysis part) – prior crizotinib/crizotinib naive but treated with other systemic therapy/treatment-naive with ALK+ by IHC

*Prior adjuvant or neo adjuvant therapy allowed if relapse occurred >12 months after chemotherapy

#Patients may continue to receive treatment with ceritinib following disease progression, including cases of isolated brain progression if, in the opinion of the investigator, continued treatment provides clinical benefit

FISH, florescence in-situ hybridization; IHC, immunohistochemistry; PK, pharmacokinetics; PS, performance status; WHO, World Health Organization

Cho BC et al, JTO 2017 Cho BC et al, IASLC 2017

# Study Drug Exposure

**The ceritinib 450 mg fed arm presented the highest exposure and RDI and the lowest number of patients with dose reductions among the 3 treatment arms**

| | Ceritinib 450 mg fed (N = 89) | Ceritinib 600 mg fed (N = 86) | Ceritinib 750 mg fasted (N = 90) |
|---|---|---|---|
| Median treatment exposure, weeks (range) | 37.9 (0.1-96.1) | 35.3 (0.4-110.0) | 33.1 (0.3-99.4) |
| Median relative dose intensity, % (range) | 100 (36.6-100) | 85.8 (31.9-100) | 90.2 (41.2-100) |
| Patients with ≥1 dose reduction*, n (%) | **16 (18.0%)** | 50 (58.1%) | 46 (51.1%) |
| Patients with ≥1 dose interruption†, n(%) | 38 (42.7) | 55 (64.0) | 55 (61.1) |

*Patients with one dose reduction: 13 (14.6%) in 450 mg fed arm; 31 (36.0%) in 600 mg fed arm; 26 (28.9%) in 750 mg fasted arm.
†Patients with one dose interruption: 23 (25.8%) in 450mg fed arm; 24 (27.9%) in 600 mg fed arm; 17 (18.9%) in 750 mg fasted arm.
% is calculated by using N as the denominator

RDI, relative dose intensity

Cho BC et al, JTO 2017 Cho BC et al, IASLC 2017 ΔSafety-analysis set

# Overview of GI Toxicities

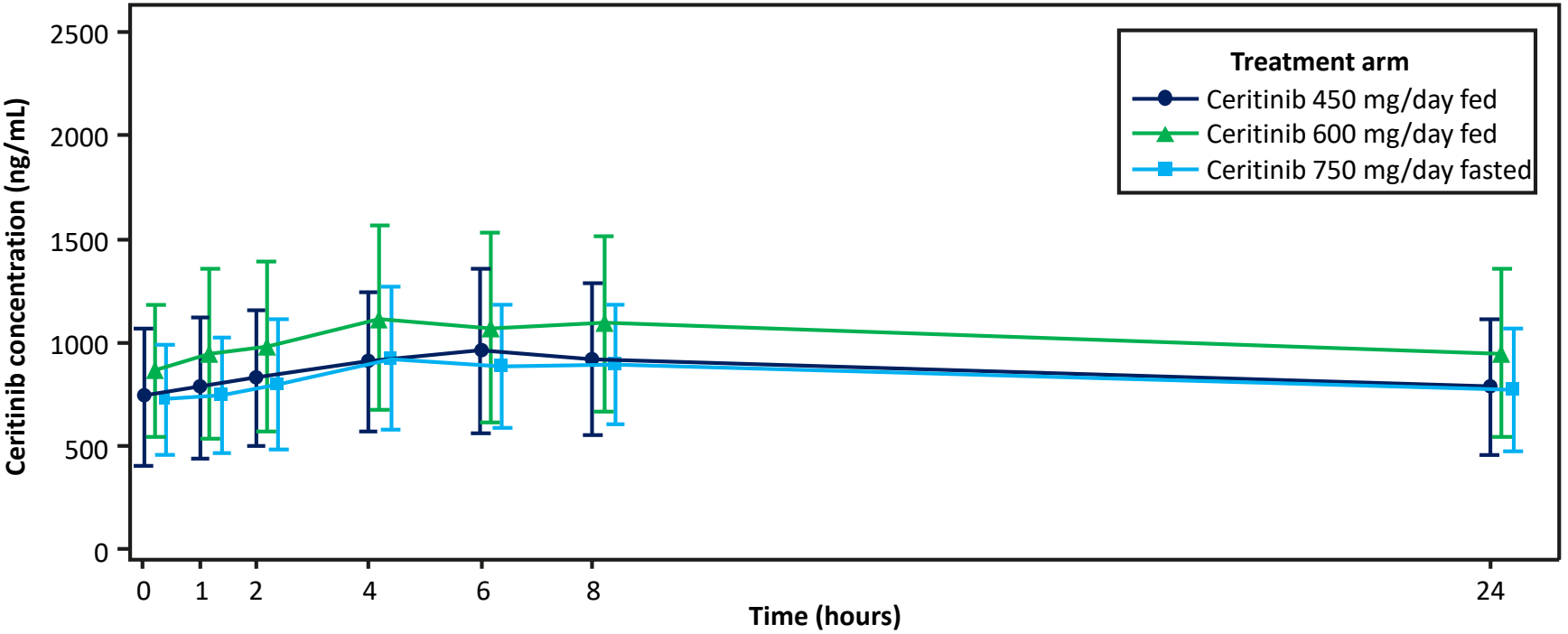
**In the ceritinib 450 mg fed arm GI toxicities were mainly of grade 1; grade 2 events were mostly reduced by half compared to the other arms and there were no grade 3/4 events reported except for 1 AE of diarrhea grade 3**

| | No. of patients (%) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Ceritinib 450 mg fed (N = 89) | | | Ceritinib 600 mg fed (N = 86) | | | Ceritinib 750 mg fasted (N = 90) | | |
| Preferred term | **Grade 1** | **Grade 2** | **Grade 3/4** | Grade 1 | Grade 2 | Grade 3/4 | Grade 1 | Grade 2 | Grade 3/4 |
| **Diarrhea, n (%)** | 41 (46.1) | 8 (9.0) | 1 (1.1) | 38 (44.2) | 13 (15.1) | 2 (2.3) | 43 (47.8) | 18 (20.0) | 7 (7.8) |
| **Nausea, n (%)** | 30 (33.7) | 10 (11.2) | 0 | 30 (34.9) | 13 (15.1) | 5 (5.8) | 28 (31.1) | 12 (13.3) | 5 (5.6) |
| **Vomiting, n (%)** | 27 (30.3) | 4 (4.5) | 0 | 35 (40.7) | 10 (11.6) | 1 (1.2) | 37 (41.1) | 9 (10.0) | 4 (4.4) |

Cho BC et al, JTO 2017 Cho BC et al, IASLC 2017 ΔSafety-analysis set

# Steady-State Pharmacokinetics on Cycle 2 Day 1

**Patients in the 450 mg fed arm demonstrated $AUC_{0–24h}$ and $C_{max}$ values comparable to those of patients in the 750 mg fasted arm** (Cho BC et al. *J Thorac Oncol.* 12(9):1357-1367)




Cho BC et al, JTO 2017 Cho BC et al, IASLC 2017

# ASCEND-8: Phase 1, Efficacy Based on BIRC Assessment

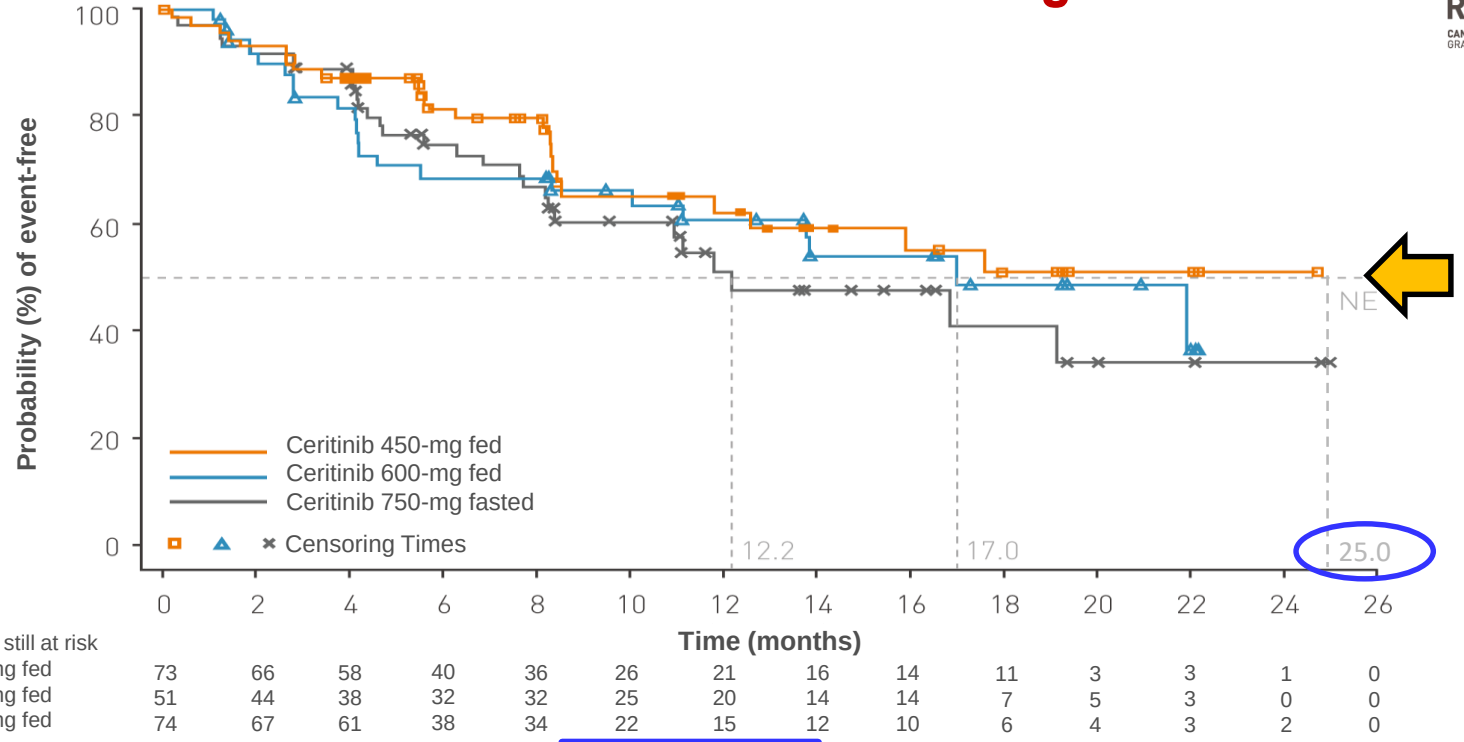
**ORR and DCR are clinically relevant and consistent among the 3 treatment arms. Short TTR is observed in all the 3 treatment arms**

| | Ceritinib 450 mg fed (N = 41) | Ceritinib 600 mg fed (N = 40) | Ceritinib 750 mg fasted (N = 40) |
|---|---|---|---|
| **Overall response rate (CR+PR),** n (%) (95% CI) | **32 (78.0%)** (62.4-89.4) | **30 (75.0%)** (58.8-87.3) | **28 (70.0%)** (53.5-83.4) |
| Complete response (CR) | 1 (2.4) | 0 | 1 (2.5) |
| Partial response (PR) | 31 (75.6) | 30 (75.0) | 27 (67.5) |
| Stable disease (SD) | 6 (14.6) | 7 (17.5) | 8 (20.0) |
| Progressive disease (PD) | 2 (4.9) | 2 (5.0) | 1 (2.5) |
| Unknown* | 1 (2.4) | 1 (2.5) | 3 (7.5) |
| **Disease control rate (CR+PR+SD+non-CR/non-PD),** n (%) (95% CI) | **38 (92.7)** (80.1-98.5) | **37 (92.5)** (79.6-98.4) | **36 (90.0)** (76.3-97.2) |
| Median time to response, weeks (95% CI) | 6.3 (6.0-6.9) | 6.3 (6.1-12.1) | 6.3 (6.0-12.3) |

*Due to no valid post-baseline assessment

Cho BC et al, JTO 2017 Cho BC et al, IASLC 2017 [Δ]Efficacy-analysis set

# 450 mg fed arm demonstrated better PFS than 750 mg fasted arm[Δ]




No. of patients still at risk

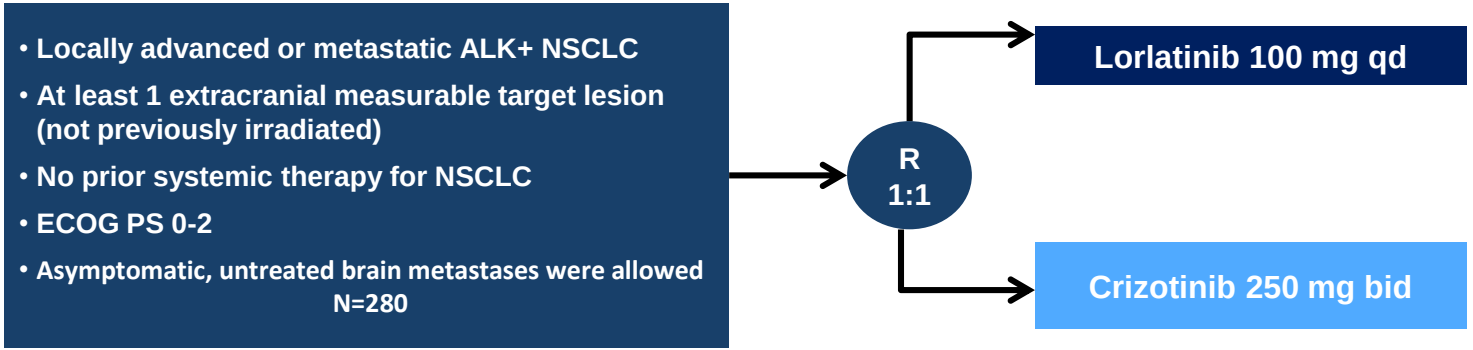
| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ceritinib 450-mg fed | 73 | 66 | 58 | 40 | 36 | 26 | 21 | 16 | 14 | 11 | 3 | 3 | 1 | 0 |
| Ceritinib 600-mg fed | 51 | 44 | 38 | 32 | 32 | 25 | 20 | 14 | 14 | 7 | 5 | 3 | 0 | 0 |
| Ceritinib 750-mg fed | 74 | 67 | 61 | 38 | 34 | 22 | 15 | 12 | 10 | 6 | 4 | 3 | 2 | 0 |

| | Ceritinib 450 mg fed (N = 73) | Ceritinib 600 mg fed (N = 51) | Ceritinib 750 mg fasted (N = 74) |
|---|---|---|---|
| Events, n (%) | 23 (31.5) | 22 (43.1) | 30 (40.5) |
| Patients censored, n (%) | 50 (68.5) | 29 (56.9) | 44 (59.5) |
| Ongoing without event or death | 42 (57.5) | 23 (45.1) | 39 (52.7) |
| Median PFS, months (95%CI) | NE (11.8-NE) | 17.0 (10.1-NE) | 12.2 (8.2-NE) |
| Estimated 18-months event-free probability, % (95%CI) | 50.8 (33.7-65.7) | 48.6 (30.7-64.3) | 40.9 (23.3-57.8) |

[Δ]Efficacy-analysis set; **PFS,** progression free survival; **NE,** no effect

Cho BC, et al. 2018 ESMO LBA59

# CROWN: Phase 3, Randomized, Open-label Study of Lorlatinib vs Crizotinib in 1L ALK+ NSCLC (NCT03052608)




**Primary endpoint**: Blinded independent central review (BICR)–assessed PFS

**Key secondary endpoints**: OS, PFS (Investigator), ORR by BICR and Investigator (per RECIST v1.1), intracranial objective response (BICR), intracranial time to progression, duration of response (BICR), time to tumor response (BICR), clinical benefit response (BICR), PFS2 (Investigator)

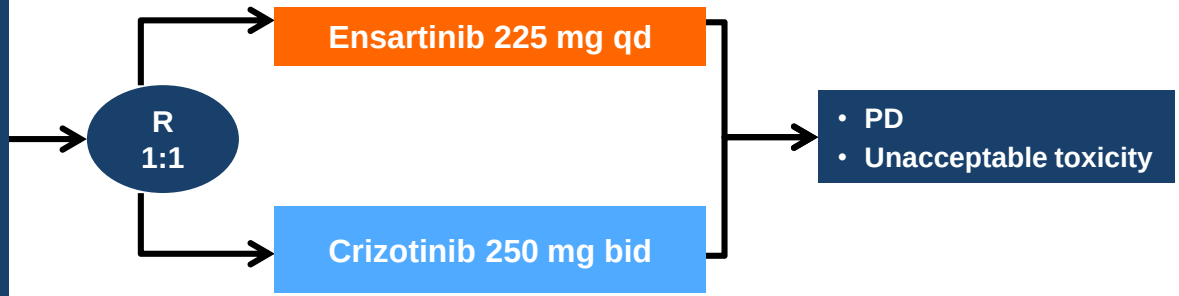
**Recruiting**
**Primary Completion Date: December 31, 2020**

1L, first line; ALK, anaplastic lymphoma kinase; bid, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; qd, every day.
https://clinicaltrials.gov/ct2/show/NCT03052608

# exAlt3: Phase 3, Randomized, Open-label Study of Ensartinib vs Crizotinib in 1L ALK+ NSCLC (NCT02767804)

- Stage IIIB or IV ALK+ NSCLC
  - By FDA-approved assay performed centrally
- At least 1 extracranial measurable target lesion (not previously irradiated)
- ≤1 prior chemotherapy regimen for metastatic disease
- ECOG PS 0-2
- Asymptomatic, untreated brain metastases were allowed

N=290



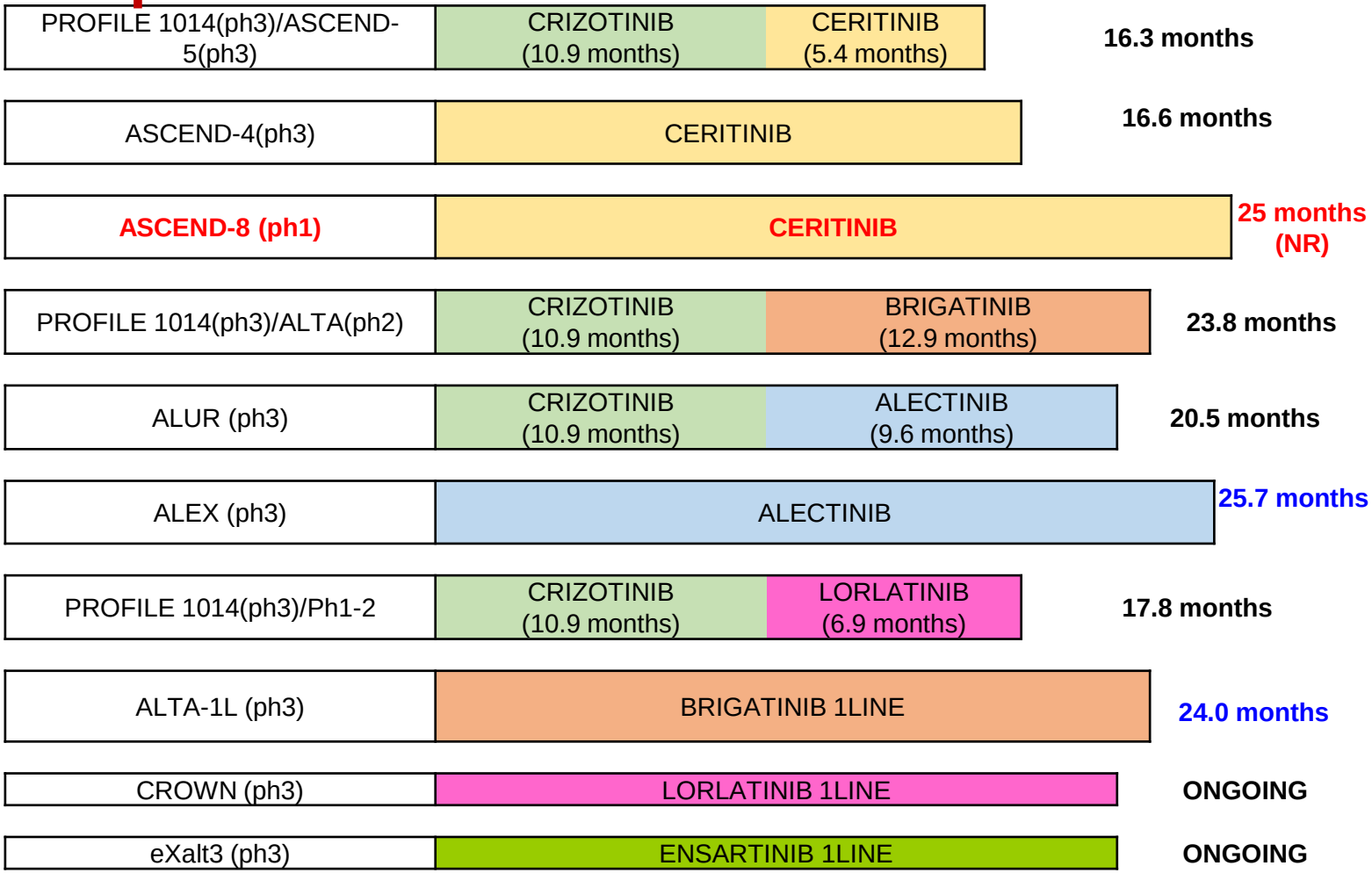

**Primary endpoint**: PFS by independent radiology review (per RECIST v1.1)

**Key secondary endpoints**: OS, ORR (independent radiology review and Investigator), PFS (Investigator), time to response (independent radiology review), duration of response (independent radiology review and Investigator)

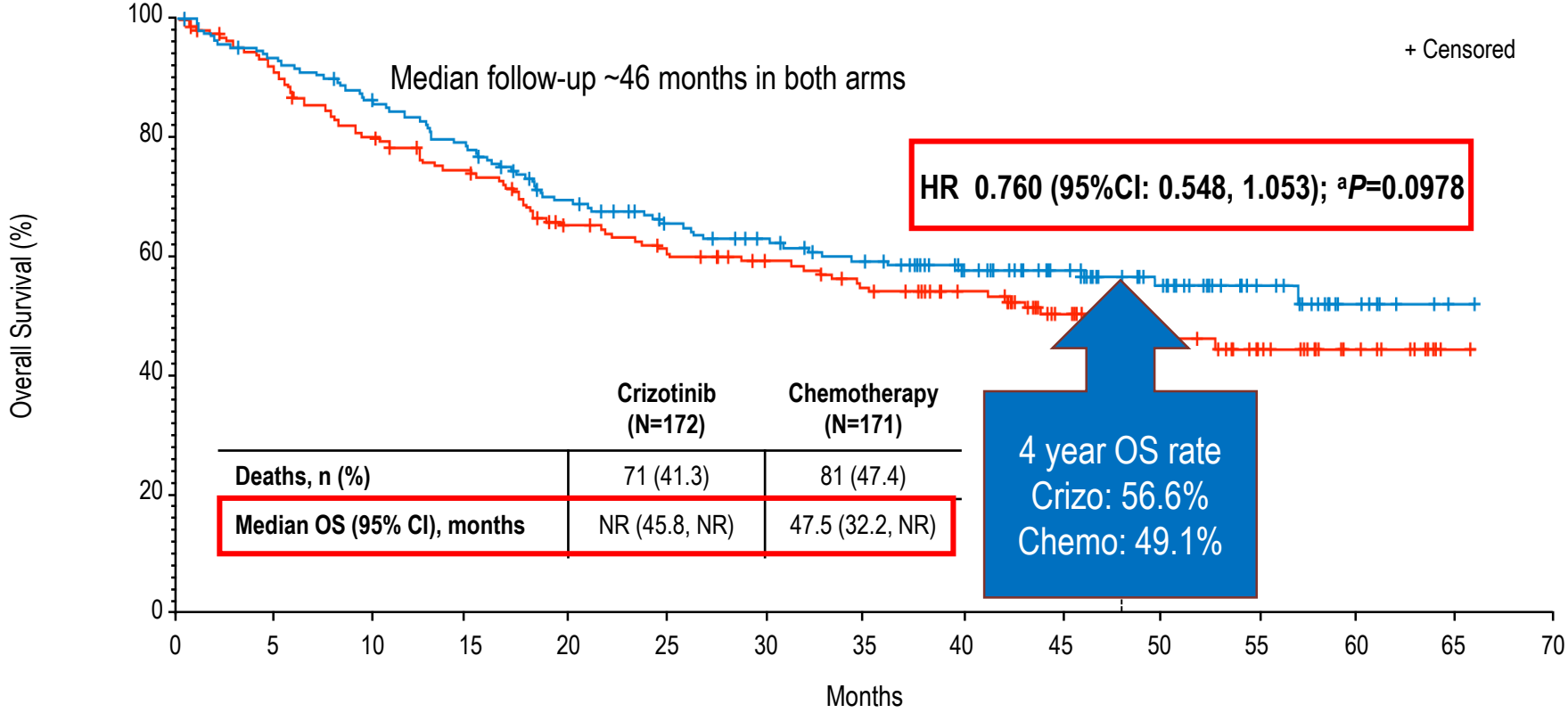
**Active**
**Primary Completion Date: November 4, 218**

1L, first line; ALK, anaplastic lymphoma kinase; bid, twice per day; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; qd, every day.
https://clinicaltrials.gov/ct2/show/NCT03052608

# Best sequence?

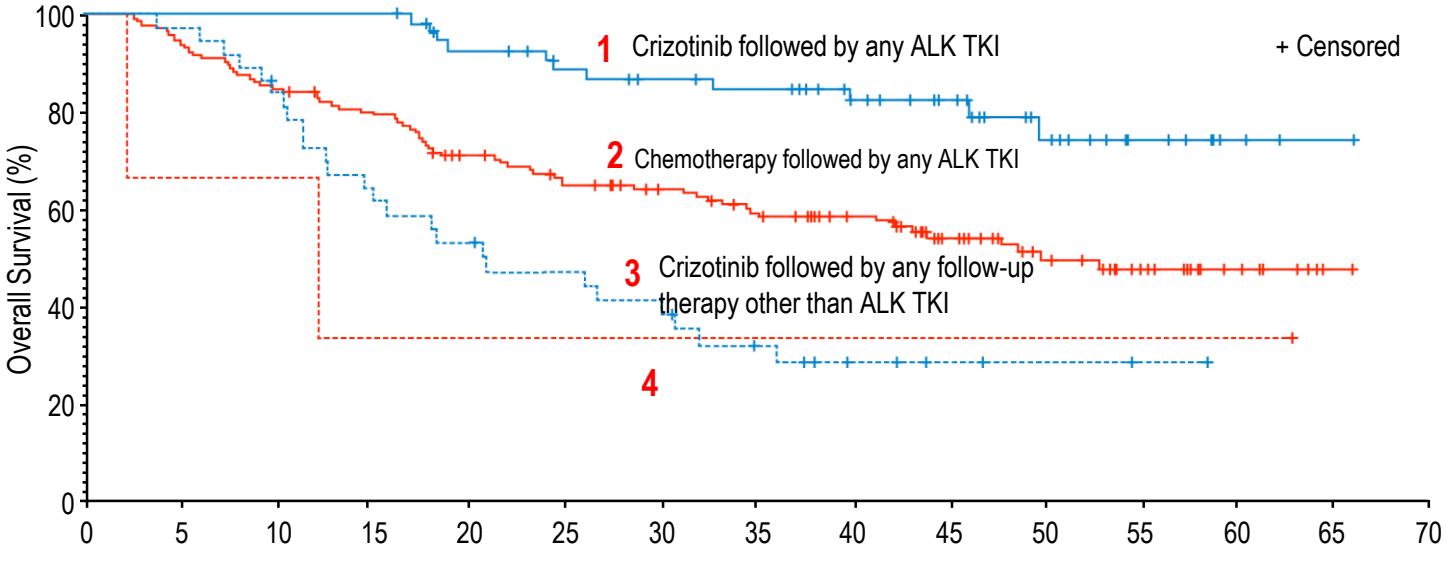


# Updated Results from PROFILE 1014: Final Primary OS Analysis (ITT Population)




T.Mok et al, ASCO 2017, B.J Solomon et al, JCO 2018

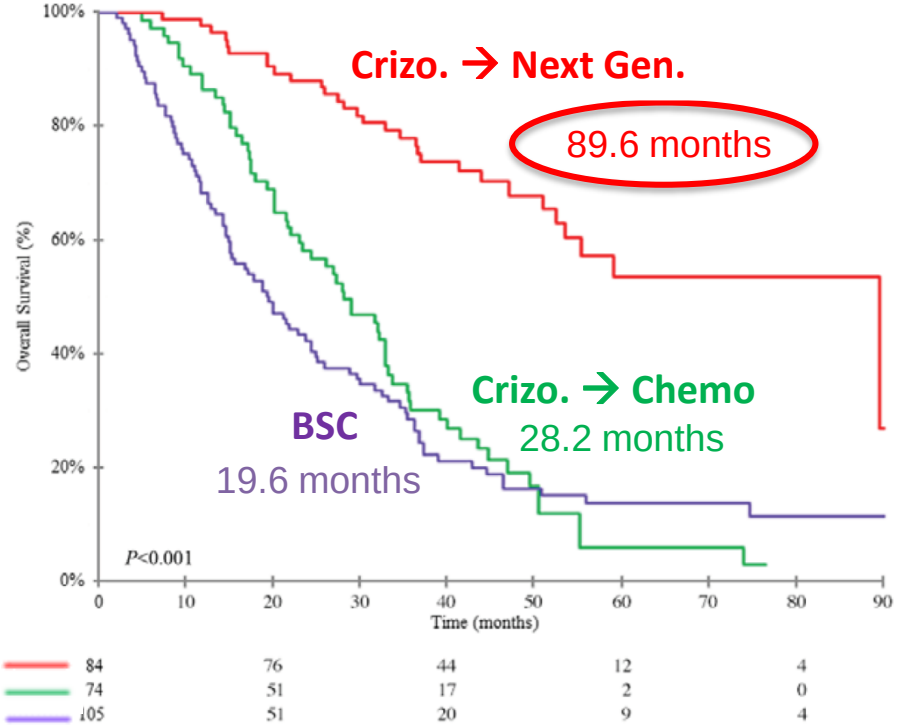
# Impact of Subsequent Therapy on OS: ALK TKI versus Treatment Other Than ALK TKI




| No. at risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Crizotinib followed by any ALK TKI | 57 | 57 | 57 | 57 | 50 | 45 | 42 | 40 | 33 | 25 | 16 | 8 | 3 | 1 | 0 |
| Crizotinib followed by any follow-up therapy other than ALK TKI | 37 | 36 | 30 | 22 | 19 | 16 | 13 | 9 | 5 | 3 | 2 | 1 | 0 | 0 | 0 |
| Chemotherapy followed by any ALK TKI | 145 | 136 | 123 | 113 | 97 | 86 | 79 | 70 | 60 | 43 | 30 | 20 | 10 | 1 | 0 |
| Chemotherapy followed by any follow-up therapy other than ALK TKI | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |

T.Mok et al, ASCO 2017, B.J Solomon et al, JCO 2018

# ALK patients : outstanding OS (French EAP)




## EAP CLINALK

**N=318**

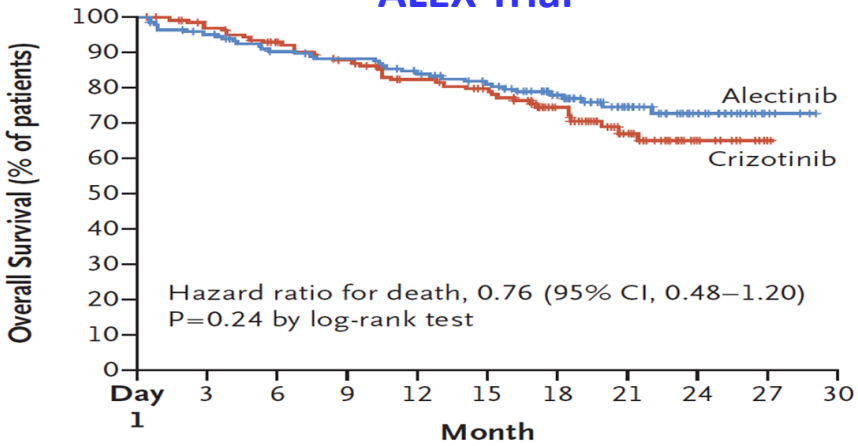
**Crizo→ next gen. TKIs.**

**OS = 7.5 years**

Duruisseaux et al Oncotarget 2017

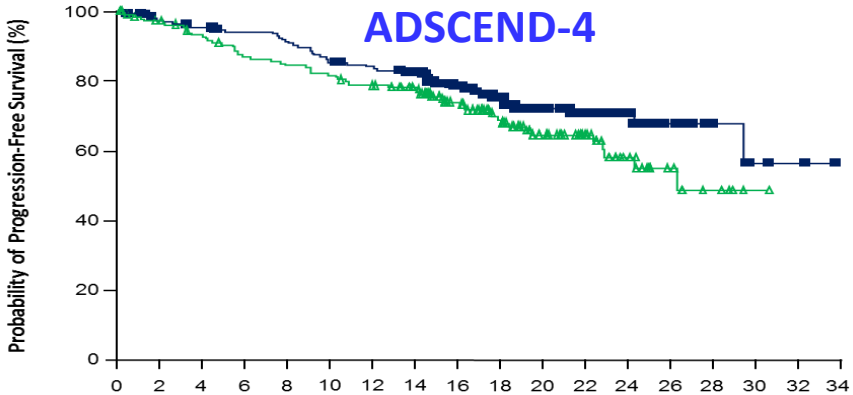
# OS of phase III trials 1st line…

## ALEX Trial

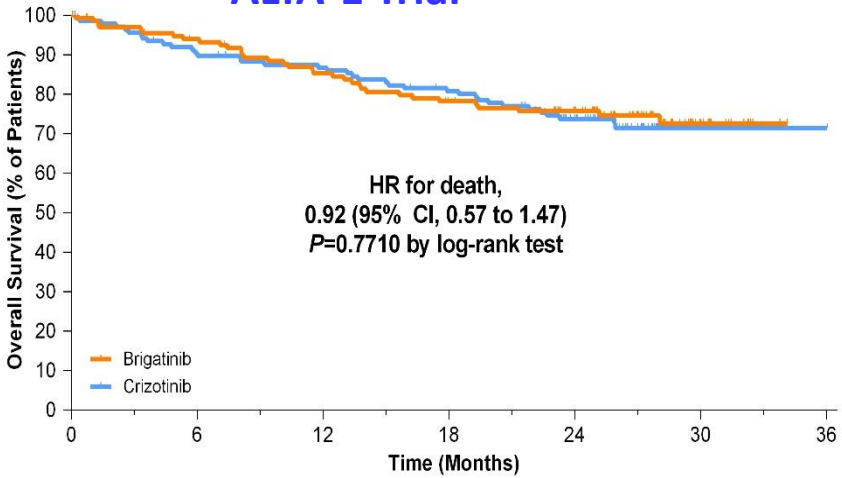



JC Soria et al lancet 2017

## ADSCEND-4




## ALTA-1 Trial



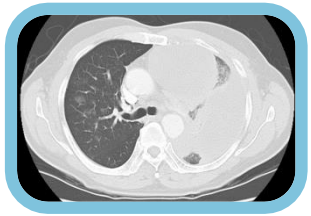

R. Camidge et al, ESMO Asia 2019

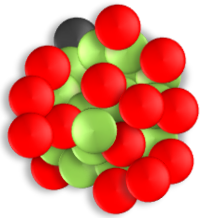
Peters S et al, NEJM 2017

# CHALLENGES TO PRECISION MEDICINE IN NSCLC

## Timing of molecular testing

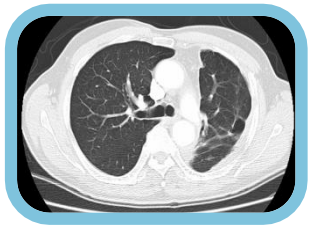
**At diagnosis**

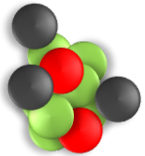




Lung tumor at diagnosis

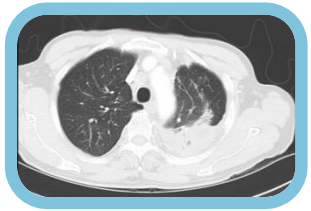
**Therapeutic monitoring?**

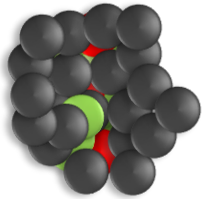




Lung tumor on treatment

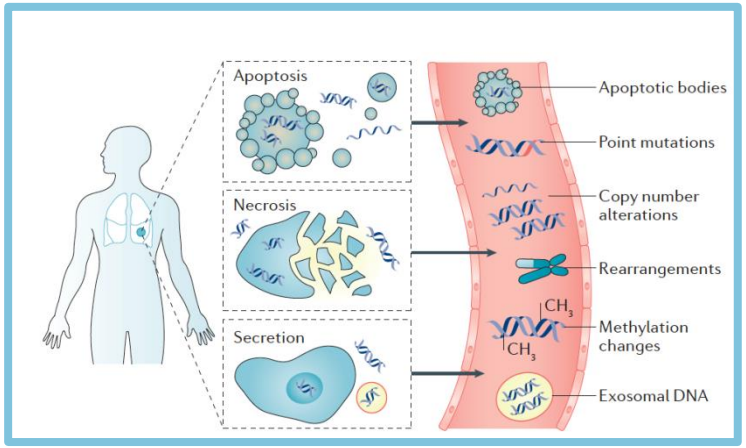
**At relapse**





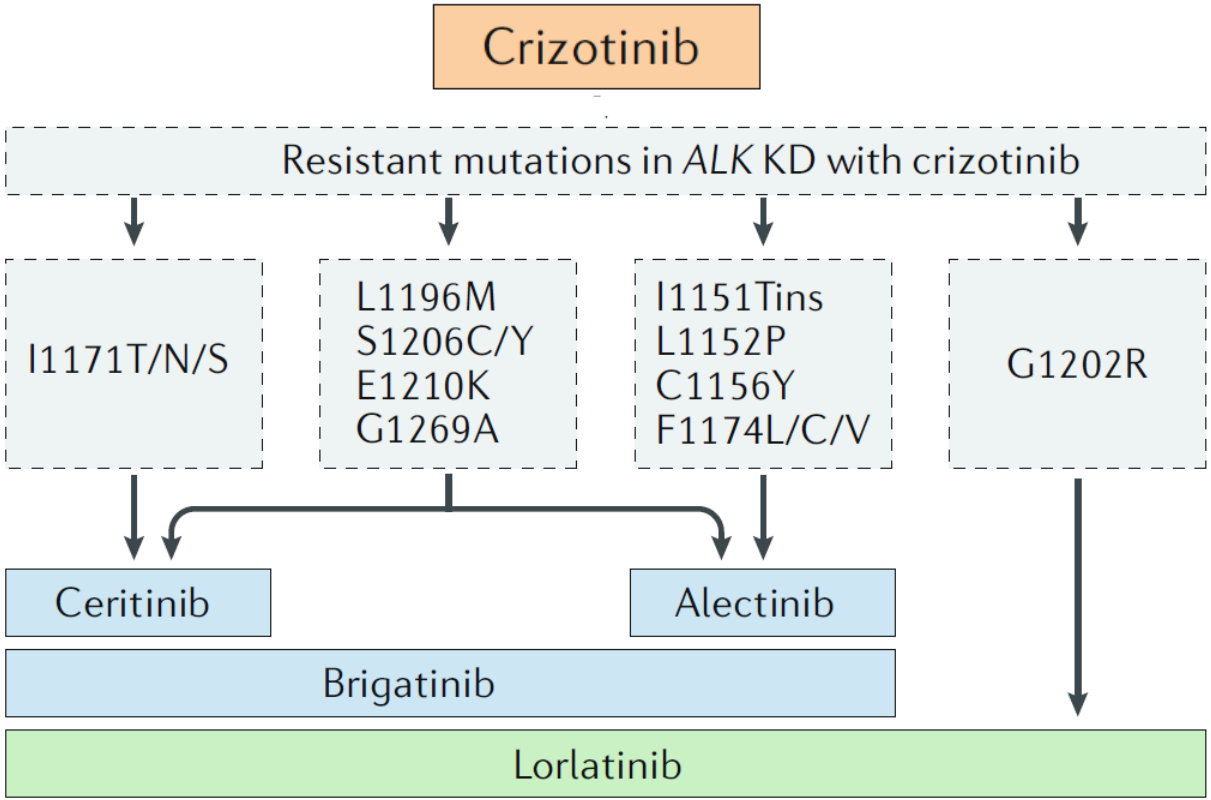
Lung tumor on progression

## Potential role of liquid biopsy



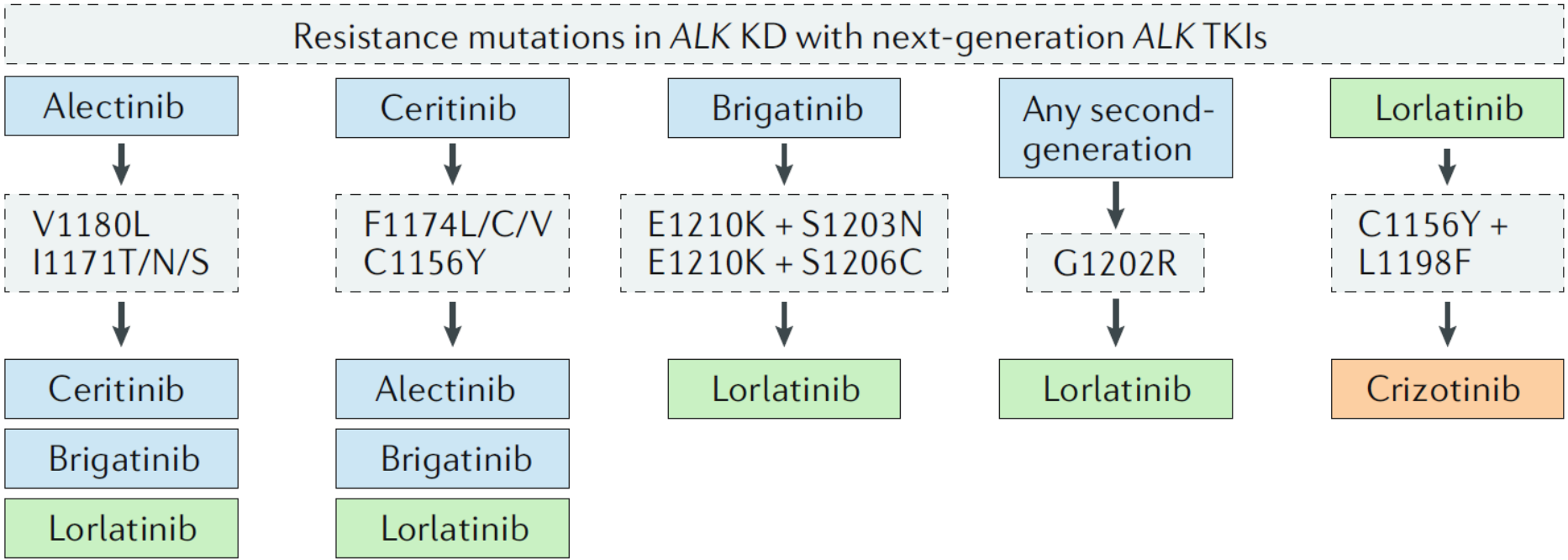

Wan JCM *et al. Nature Rev Cancer* 2017;17:223–238

# Biomarker integration in the management of patients with ALK-NSCLC, post crizotinib




Gonzalo Recondo et al, nature reviews 2018

# Biomarker integration in the management of patients with ALK-NSCLC, 2nd or 3nd generation




Gonzalo Recondo et al, nature reviews 2018

# Best sequence of treatment ?

## 2nd generation AKT TKIs in 1st line as new standard

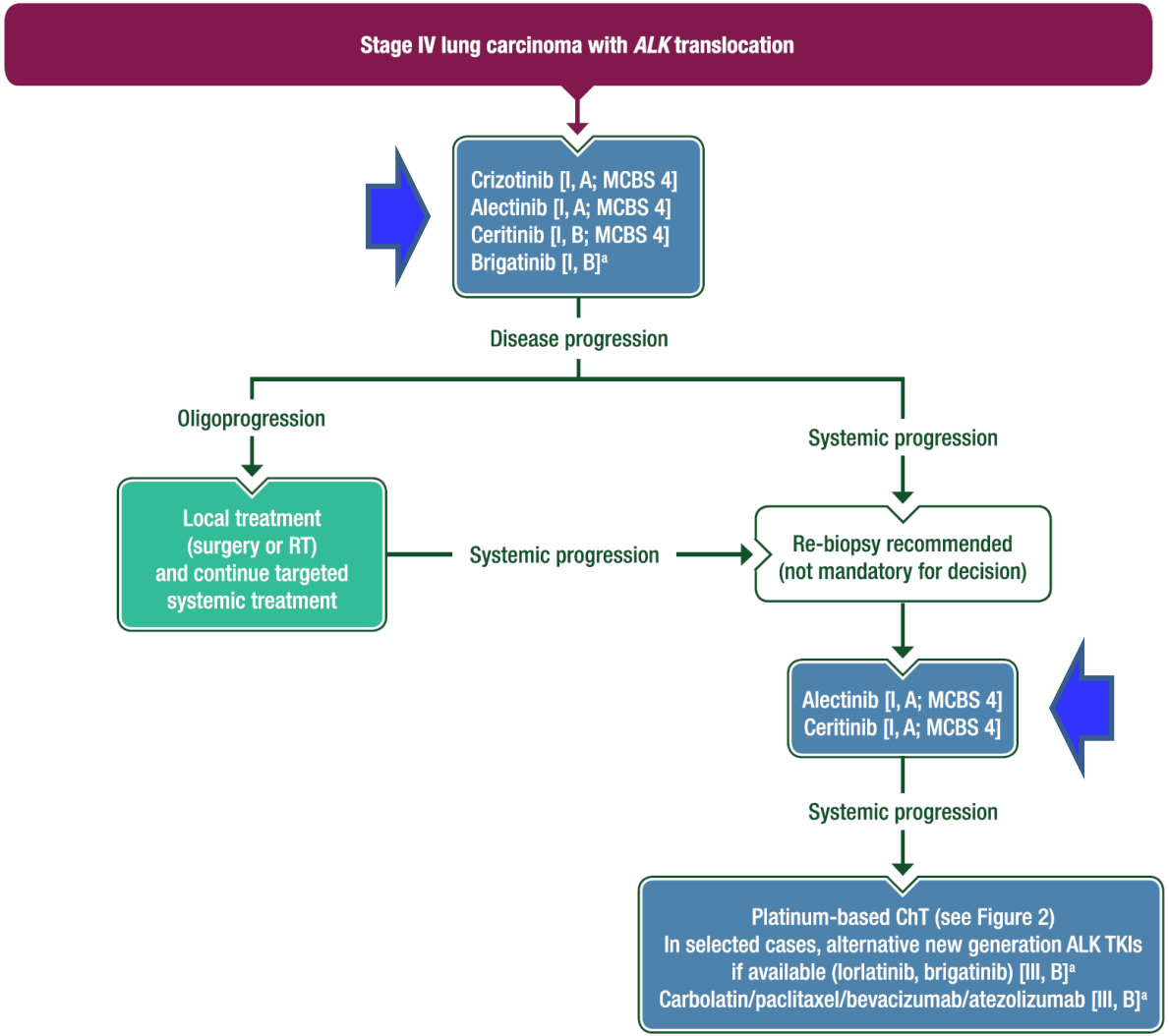
| 1st generation TKI | 2nd generation TKI | 3rd generation TKI |
|---|---|---|
| *crizotinib* | *ceritinib*<br>*alectinib*<br>*brigatinib* | *lorlatinib* |

| 2nd generation TKI | 3rd generation TKI |
|---|---|
| *ceritinib*<br>*alectinib*<br>*brigatinib* | *lorlatinib* |

| | Ceritinib | Alectinib |
|---|---|---|
| **mPFS** | **25-27m**<br>(ASCEND-8 & ASCEND4 Asian group) | **25.7m**<br>(ALEX independent review) |
| **ORR** | **78.1%**(ASCEND-8) | **82.9%**(ALEX) |
| **DCR** | 90.4%(ASCEND-8) | 89.6%(ALEX) |

CLINICAL PRACTICE GUIDELINES

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†




D.Planchard et al, annals of onco 2018

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