Trattamento della malattia ALK-positiva

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Carcinoma del polmone: quali novità nel 2023?

Verona – 9 Ott 2023

AGENDA

- ALK-positive advanced NSCLC
  - 1L treatment
  - Molecular stratification
  - Treatment at progression
- ALK in early stage NSCLC

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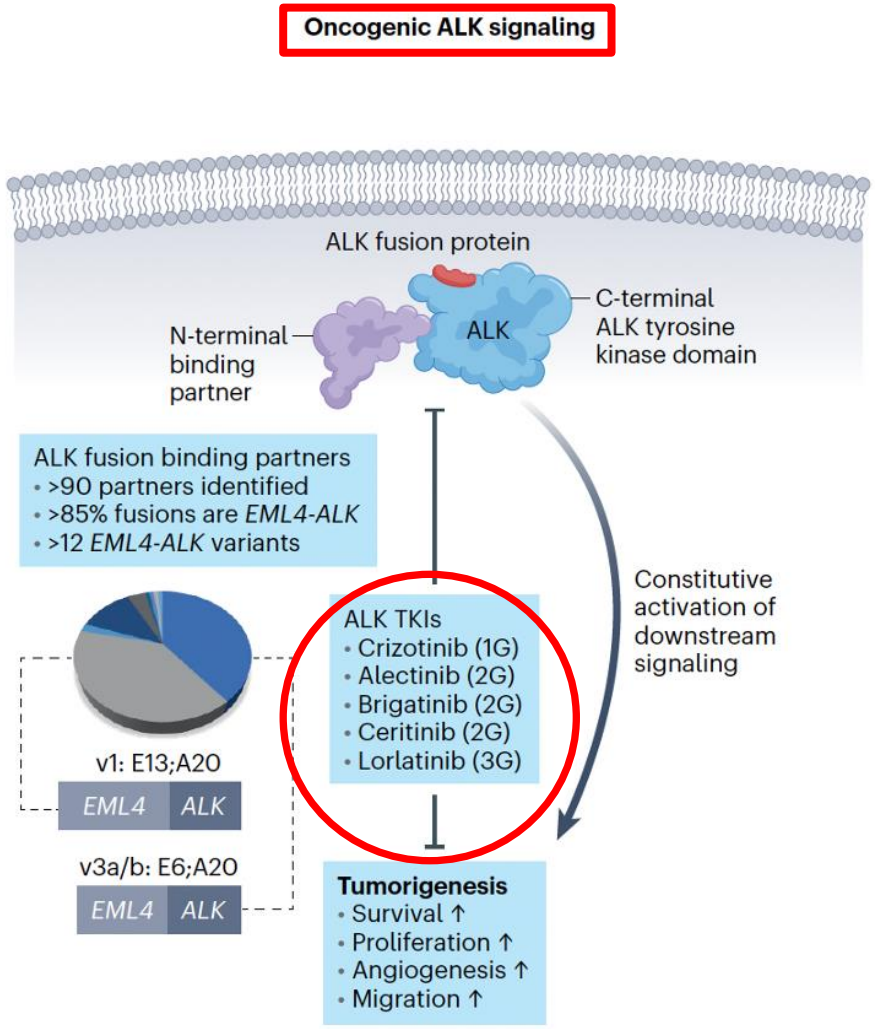
ALK-positive NSCLC

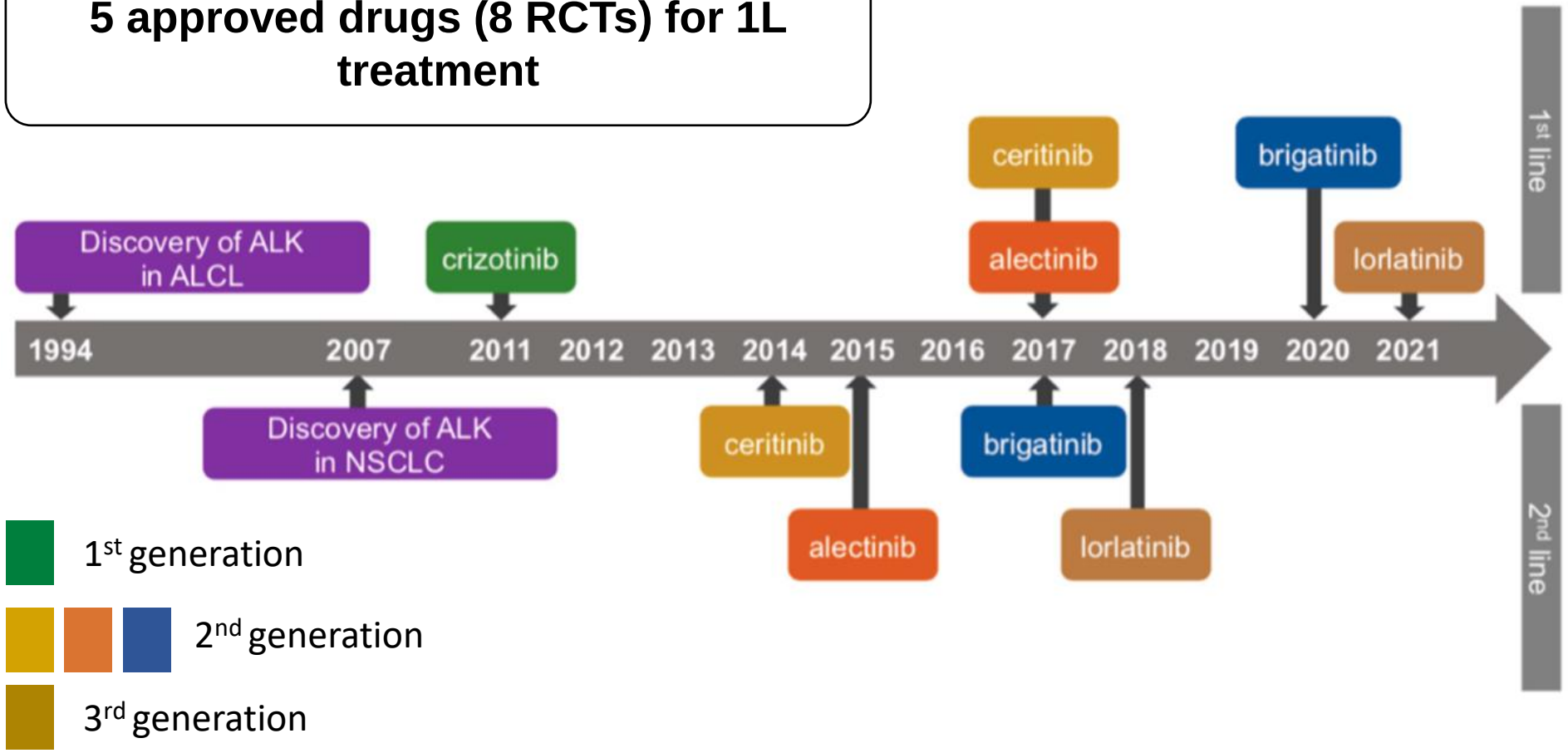
- ALK gene rearrangements found in 3-5% of NSCLCs[1]
- Median age at diagnosis ~ 50 years[2-4]
- Mostly never or light smokers[2]
- Mostly adenocarcinomas[2]
- Brain metastases in 20-40% at diagnosis of advanced disease[5]
- Testing is recommended in all non-squamous NSCLCs and not in patients with confident diagnosis of squamous NSCLC except for[6]:
    - Young (< 50 years)
    - Never/former light/long-time ex-smokers



[1]Chevallier et al. World J Clin Oncol 2021; [2]Shaw et al. J Clin Oncol 2009; [3]Tang et al. Transl Lung Cancer Res 2019; [4]Du et al. Thoracic Cancer 2018; [5]SEER Cancer Stat Facts; [6] Hendriks et al. Ann Oncol. 2023; Schneider et al. Nat Cancer 2023

Evolution of treatment of ALK-positive NSCLC

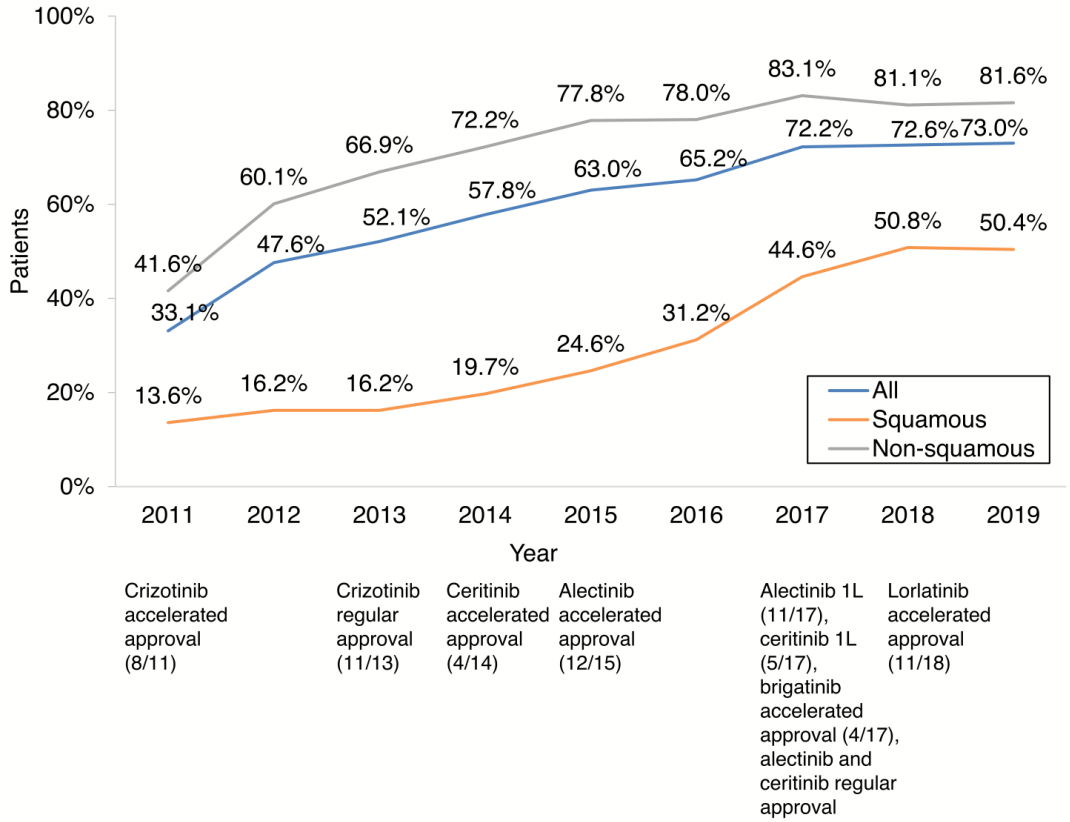
5 approved drugs (8 RCTs) for 1L treatment



Fukui et al. Cancers 2022

ALK testing: U.S. vs Europe

U.S.



Crizotinib accelerated approval (8/11)

Crizotinib regular approval (11/13)

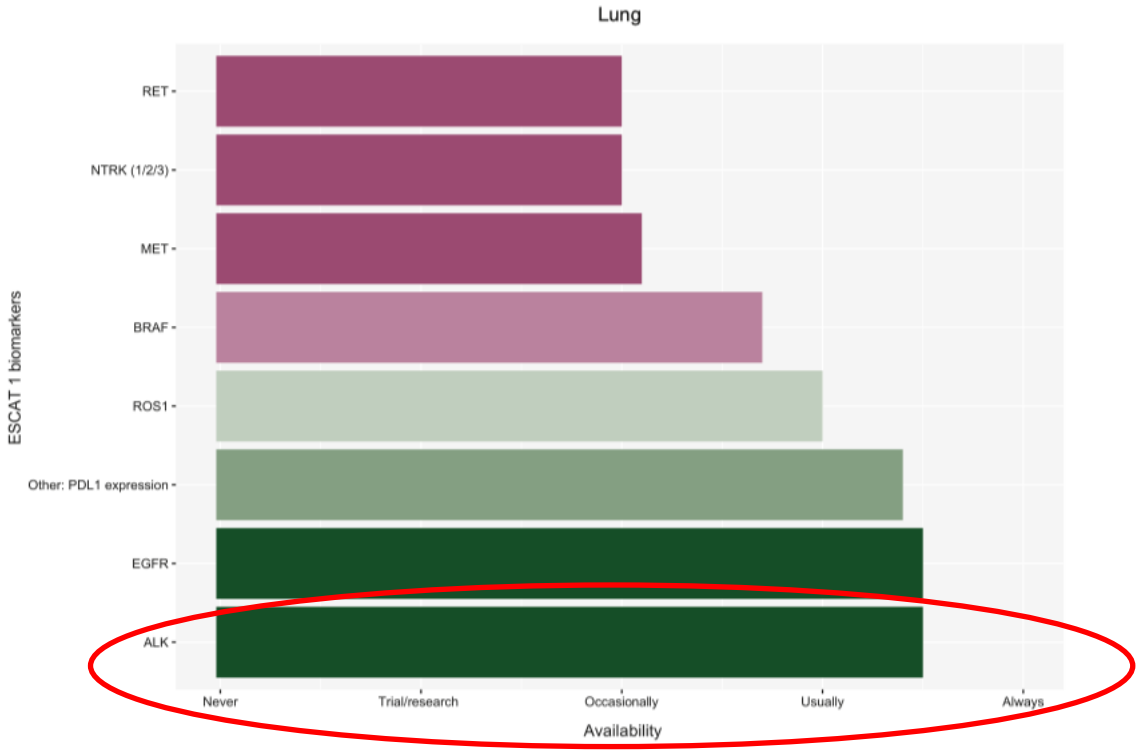
Ceritinib accelerated approval (4/14)

Alectinib accelerated approval (12/15)

Alectinib 1L (11/17), ceritinib 1L (5/17), brigatinib accelerated approval (4/17), alectinib and ceritinib regular approval

Lorlatinib accelerated approval (11/18)

Europe



Electronic survey – 2021

Lin et al. Clin Lung Cancer 2023
Bayle et al. Ann Oncol 2023

ALK-positive NSCLC: type of test

- Detection by FISH remains a standard, but IHC with high-performance ALK antibodies and validated assays may be used for screening [III,A] and has been accepted as an equivalent alternative to FISH for ALK testing[1]
- RNA-based NGS is preferred for identifying an expanding range of fusion genes [III, B][1,2]

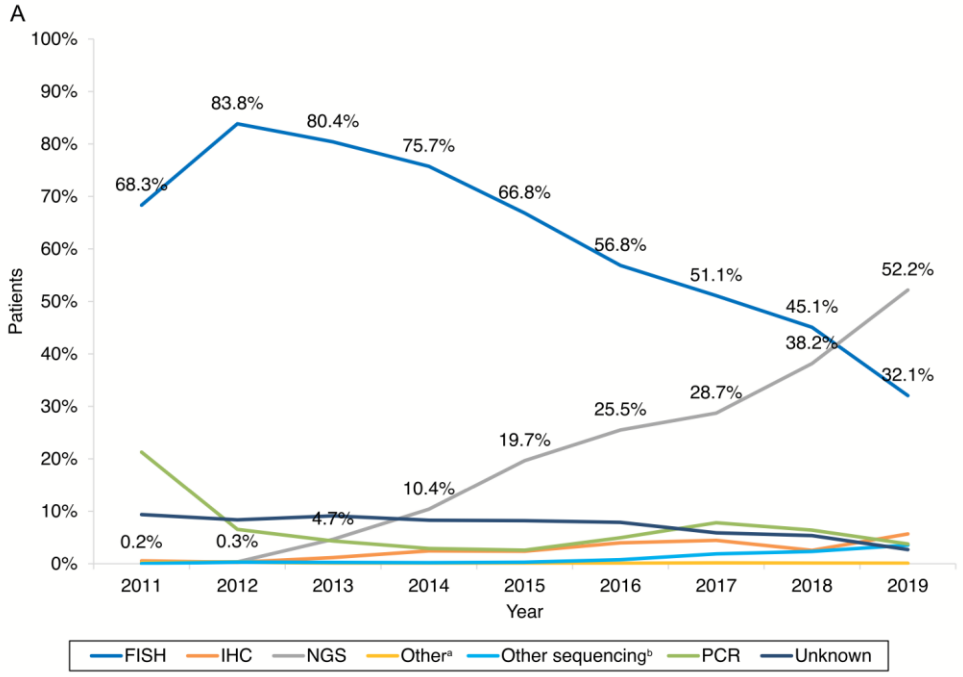
Predictive biomarkers	ESMO guidelines	NCCN guidelines	CAP/IASLC/AMP guidelines	ASCO guidelines	Pan-Asian guidelines
EGFR	●	●	●	●	●
ALK	●	●	●	●	●
ROS1	●	●	●	●	●
BRAF	●	●	●	●	●
PD-L1	●	●	●	●	●
NTRK	●	●	●	●	●

[1] Hendriks et al. Ann Oncol. 2023; [2]Kerr et al. Lung Cancer 2021

Type of ALK test over time: U.S. data

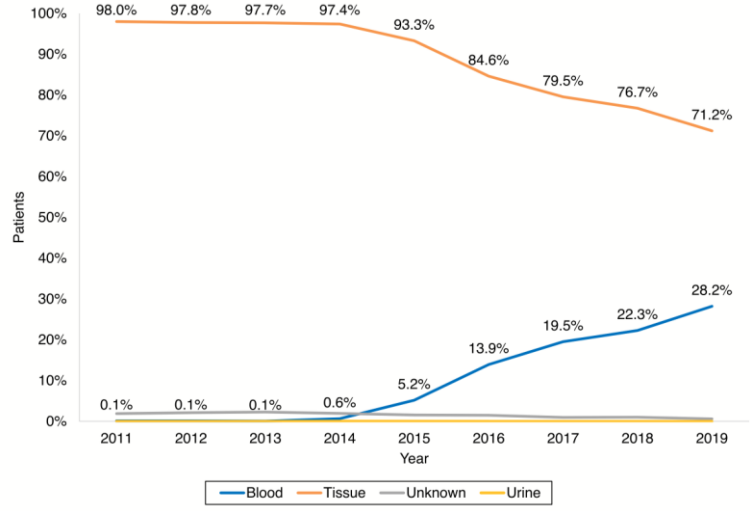
FISH dropped from 68.3% to 32.1%

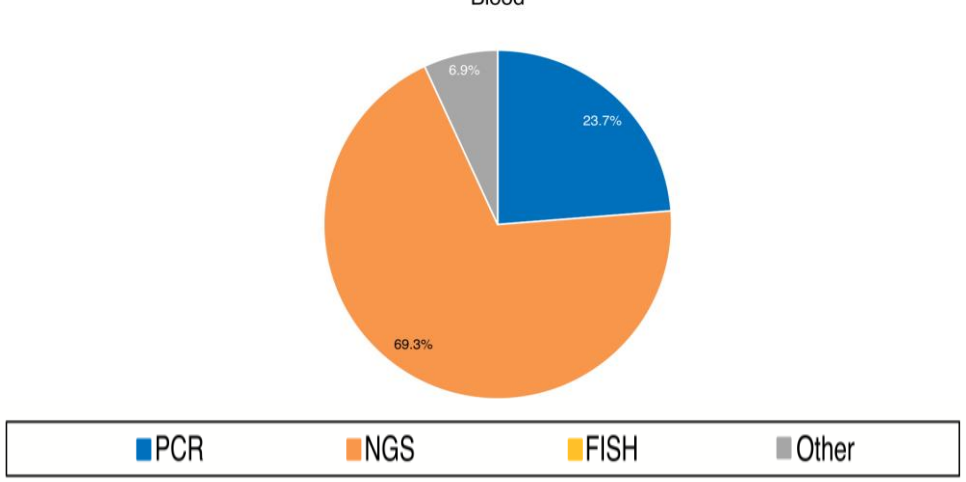
NGS increased from < 1% to 52.2%



Test	Total Advanced Diagnosis to First *ALK*+ Result		
	All (*n* = 983)	Tissue (*n* = 912)	Blood (*n* = 48)
Median (IQR) time (days)	23 (13-43)	22 (13-40.5)	30.5 (17-69)

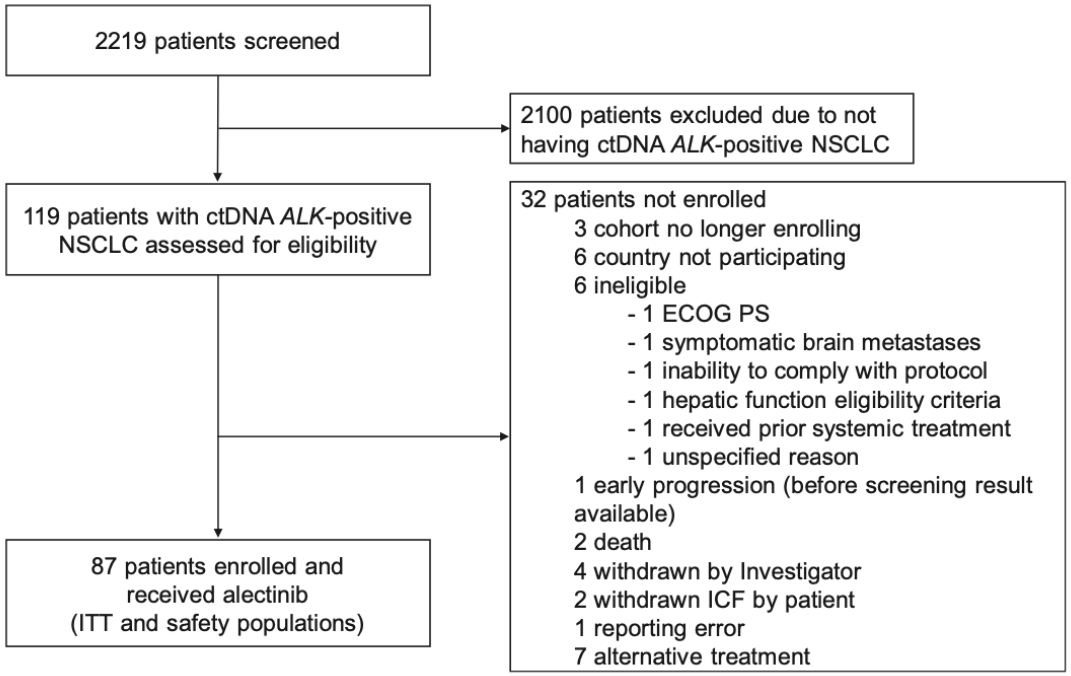
Blood testing increased from 0.1% to 28.2%



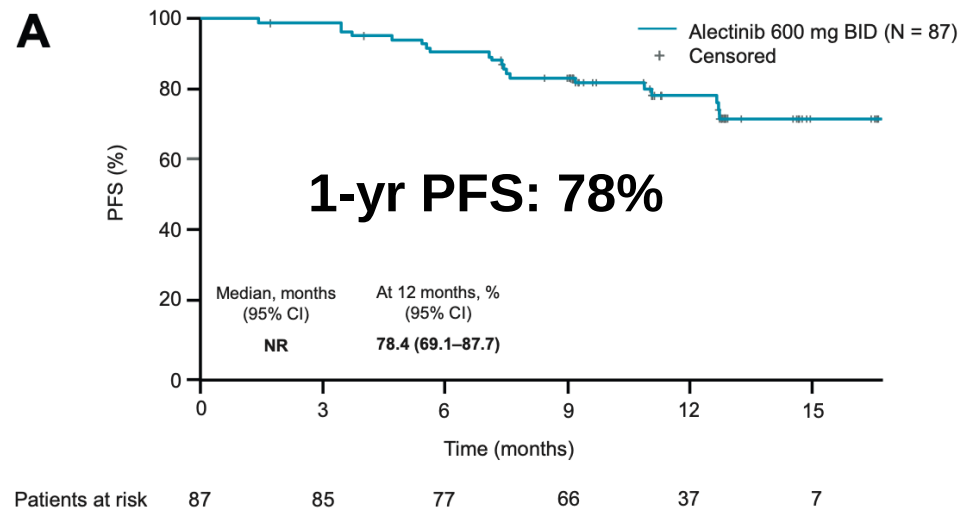


Lin et al. Clin Lung Cancer 2023

Liquid biopsy for ALK testing: BFAST trial



ALK-Positive Cohort	Investigator
Confirmed responders, n (%) 95% CI	**87.4%**



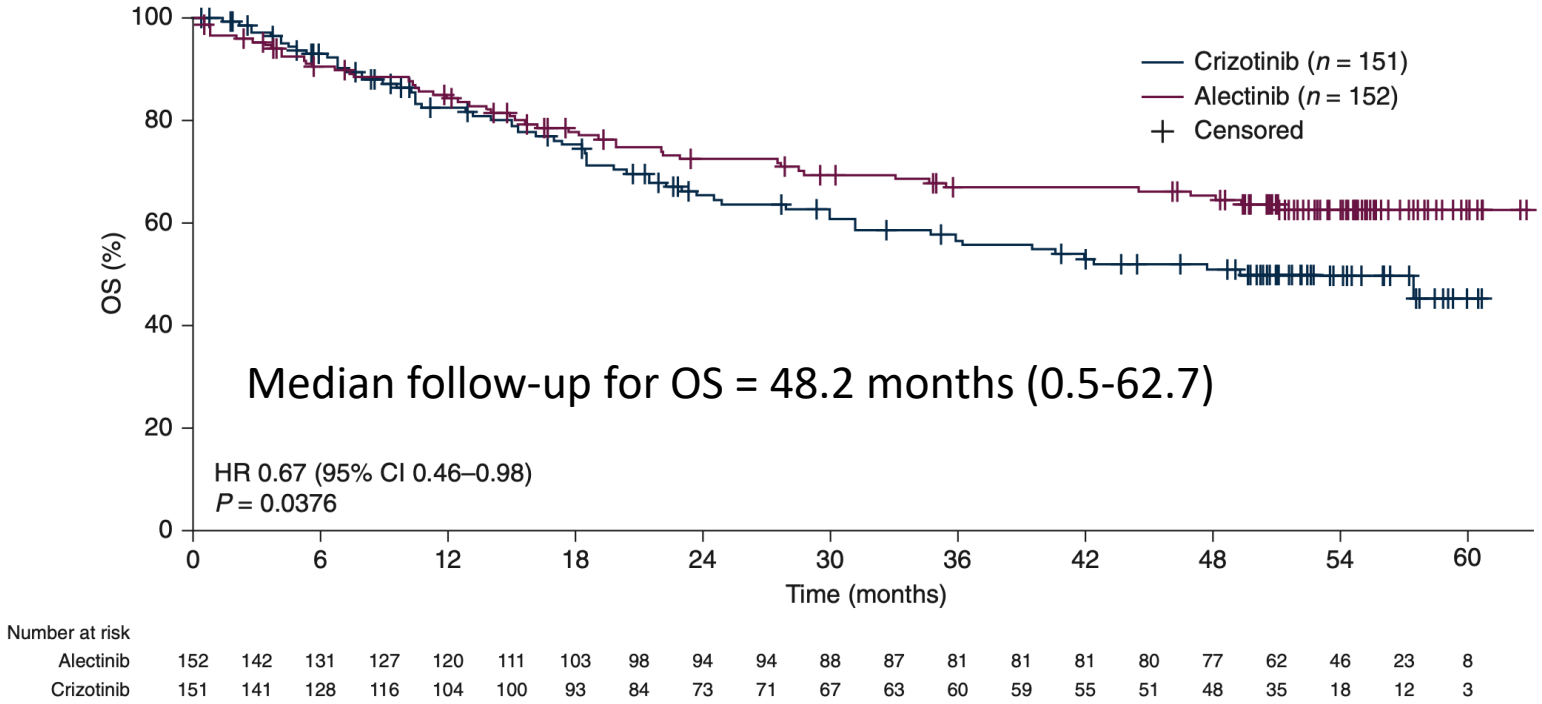
Dziadziuszko et al. J Thorac Oncol 2021

Key randomized trials of 2nd/3rd gen. ALK-TKI vs crizotinib

Study	ALK testing	Prior therapy	Baseline CNS metastases	Primary endpoint	Crossover	ORR	mPFS	mOS
ALEX[1,2] Alectinib (n=152) vs crizotinib (n=151)	IHC; central	Treatment naïve	42% vs 38%	IA PFS	Not allowed	Overall: 83% vs 75.5% IC-ORR: 81% vs 50%	34.8 mos vs 10.9 mos [HR 0.43]	NR vs 57.4 mos [HR 0.67]
ALTA-1L[3,4] Brigatinib (n=137) vs crizotinib (n=138)	Locally approved test	≤1 prior chemo	29% vs 30%	IRC PFS	Allowed	Overall: 74% vs 62% IC-ORR: 78% vs 27%	30.8 mos vs 9.2 mos [HR 0.43]	Not reached for either group
eXalt3[5] Ensartinib (n=201) vs crizotinib (n=201)	Local FDA approved test or central FISH	≤1 prior systemic therapy, but TKI naïve	33% vs 39%	IRC PFS	Not allowed	Overall: 74% vs 64% IC-ORR: 63.6% vs 21.1%	25.8 mos vs 12.7 mos [HR 0.51]	Data immature
CROWN[6,7] Lorlatinib (n=140) vs crizotinib (n=140)	D5F3 IHC	Treatment naïve	26% vs 27%	IRC PFS	Not allowed	Overall: 76% vs 58% IC-ORR: 82% vs 23%	NR vs 9.3 mos [HR 0.28]	Data immature

[1]Peters et al. NEJM 2017; [2]Mok et al. Ann Oncol 2020; [3]Camidge et al. NEJM 2018; [4]Camidge et al. J Thorac Oncol 2021; [5]Horn et al. JAMA Oncol 2021; [6]Shaw et al. NEJM 2020; [7]Solomon et al. Lancet Respir Med 2022

Long life expectancy on ALK-TKIs



At the time of this analysis **34.9%** of pts in the alectinib arm remain on treatment

OS rate, % (95% CI) [patients at risk, *n*]	Alectinib (*N* = 152)
Year 1	84.3 (78.4–90.2) [120]
Year 2	72.5 (65.1–79.9) [94]
Year 3	67.0 (59.1–74.8) [81]
Year 4	65.3 (55.3–73.3) [77]
Year 5	62.5 (54.3–70.8) [8]

Mok et al. Ann Oncol 2020

Is there a best upfront therapy? (1)

Alectinib/brigatinib

- Sequential use of lorlatinib at progression[1]
- Presence of a mature median PFS from both ALEX and ALTA1L trials that conceptualizes their efficacy[3]
- First drugs to receive market authorization for 1L use
- Good CNS penetration (1-year intra-cranial PFS rate in pts without brain mets of 4.8% and 1% for alectinib and brigatinib, respectively) [4,5]

Lorlatinib

- Lorlatinib is poorly active at progression on alectinib/brigatinib(ORR: 38.5-42.9% - median PFS 4.8-5.5 months)[2]
- Cross-trial comparison suggests higher 1- 2- and 3-year PFS vs alectinib/brigatinib[3]
- Excellent CNS penetration (3-year intra-cranial PFS rate in pts without brain mets of 1%)[6]

[1]Not indicated for brigatinib as per EMA/AIFA label; [2]SFelip et al. Ann Oncol 2021; [3]Ou et al. Crit Rev Oncol Hematol 2023; [4]Gadgeel et al., Ann Oncol 2018; [5]Popat et al., Ann Oncol 2018 (abstract); [6]Solomon et al., Lancet Respir 2023

Is there a best upfront therapy? (2)

Always consider:

- No. of pills per day
  - Alectinib: 8 (4 B.I.D.)
  - Brigatinib: 1 Q.D.
  - Lorlatinib 1 Q.D.
- Drug-drug interactions[1]
  - Alectinib: NO dose adjustments with CYP3A inhibitors/inducers
  - Brigatinib: avoid CYP3A inhibitors/inducers
  - Lorlatinib: avoid CYP3A inhibitors/inducers
- Different toxicity profile (grade 3 AEs)[2]
  - Alectinib: anemia 5%, LFT elevation 5%
  - Brigatinib: increase CPK/myalgia 16%, hypertension 10%, increase lipase 13%
  - Lorlatinib: hyperlipidemia up to 20%, weight gain 17%, hypertension 10%, edema 4%, cognitive effect 2%, neuropathy 2%

[1]Boll SIFO 2022; [2]https://dailynews.ascopubs.org/do/debates-treatment-sequencing-alk-rearranged-nsclc-weighing-therapeutic-benefit-versus

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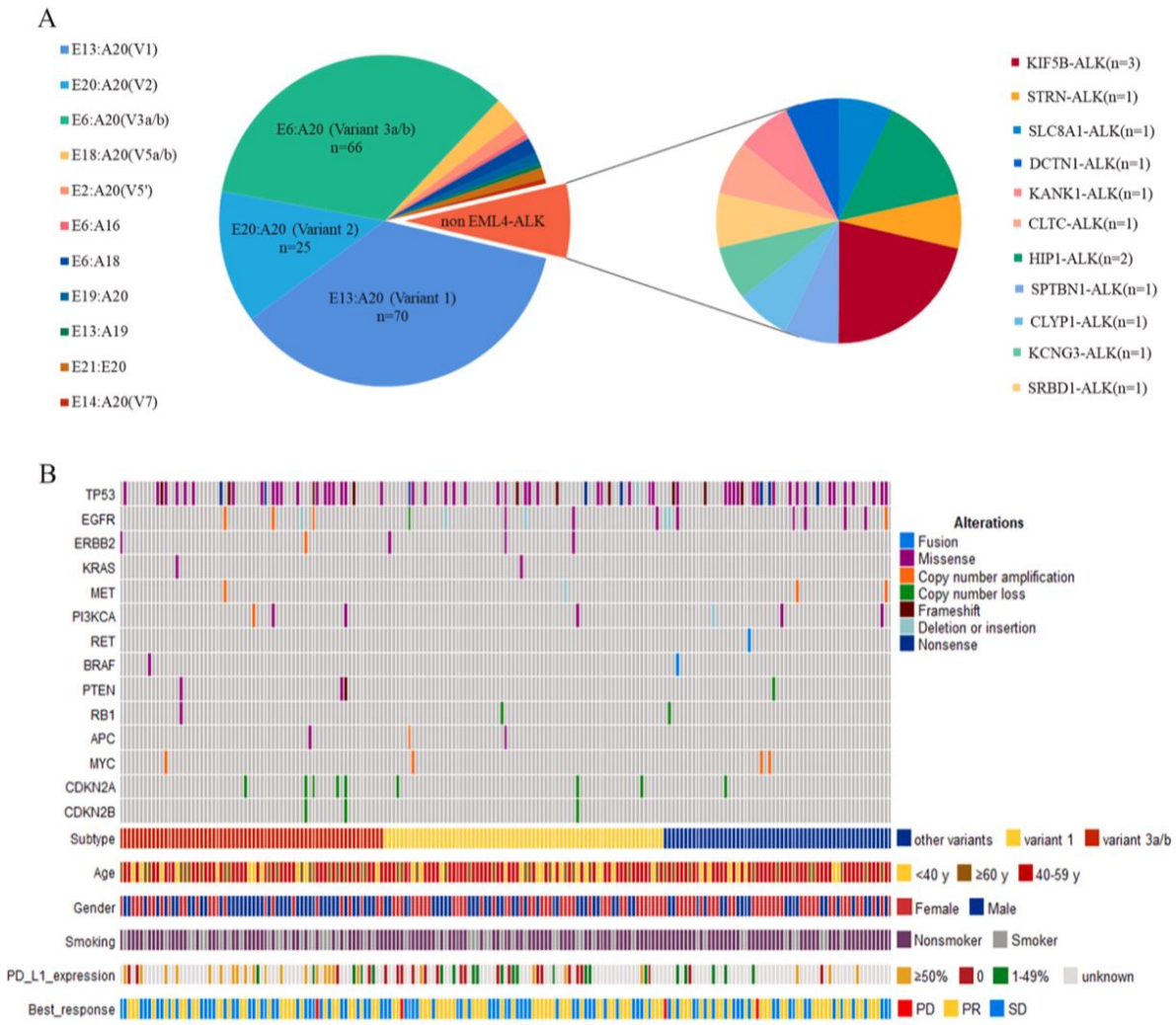
Molecular insights of ALK-positive disease



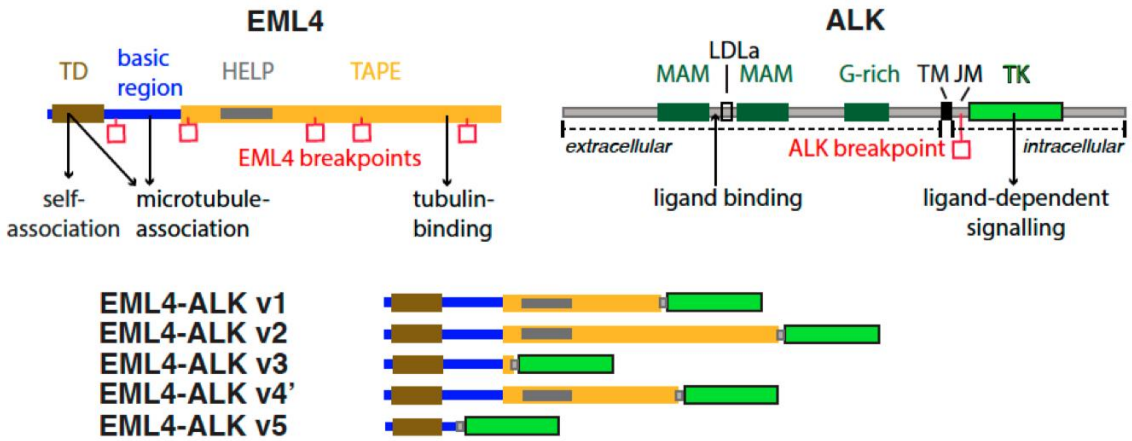
- **~ 90% EML4-ALK fusion variants**
- **~ 10% rare fusion variants**
- **~ 5% multiple ALK fusion variants**
- **Types of EML4-ALK fusion variants:**
  1. *Variant 1(E13:A20)*
  2. *Variant 3a/b (E6:A20)*

  } ~ 75-80%

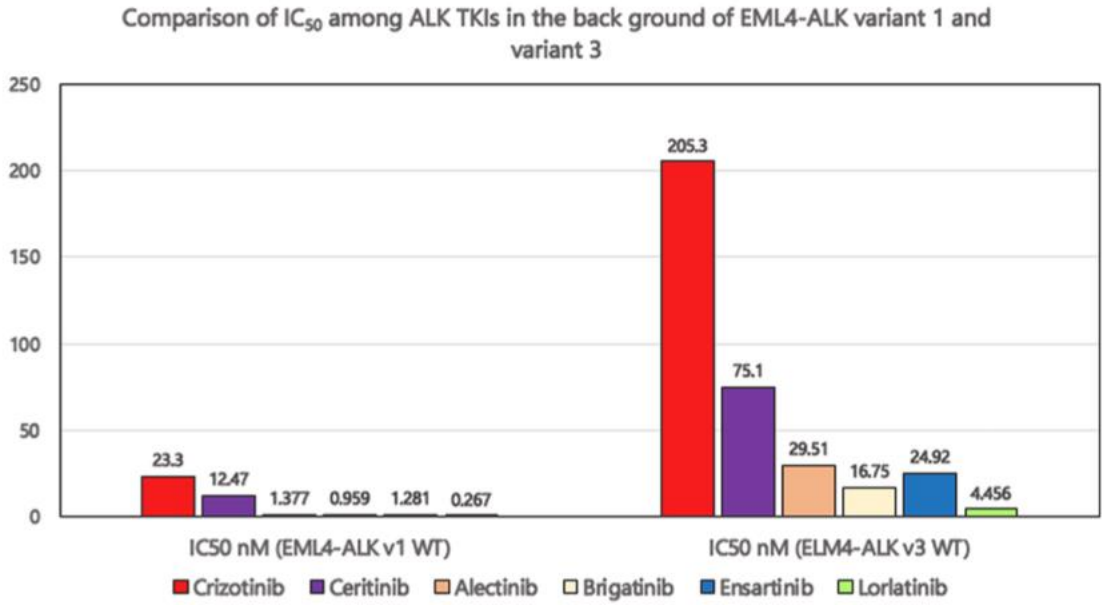
  3. *Variant 2 (E20:A20)*
- **~ 50% concomitant mutations**
  1. *~ 1/3 with TP53 mutations*
- **~ 1/3 with PD-L1 ≥ 50%**

Li et al. Lung Cancer 2022

Does the type of EML4-ALK variant matter?

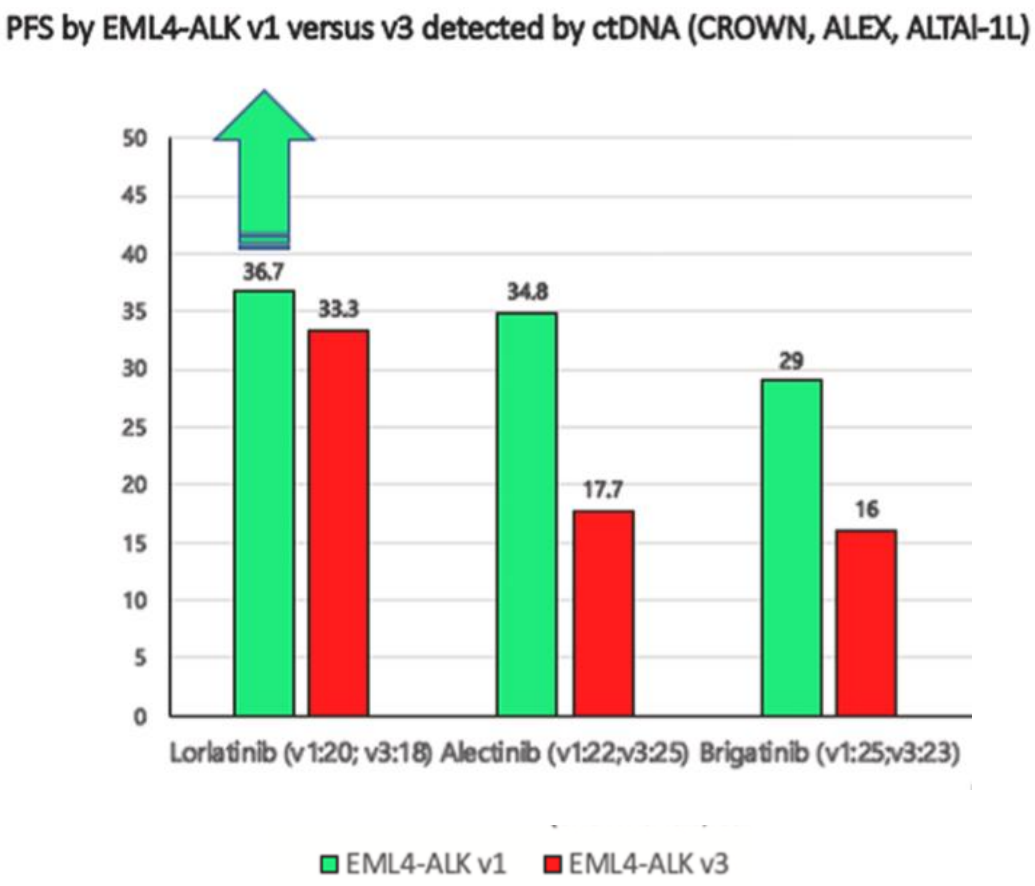


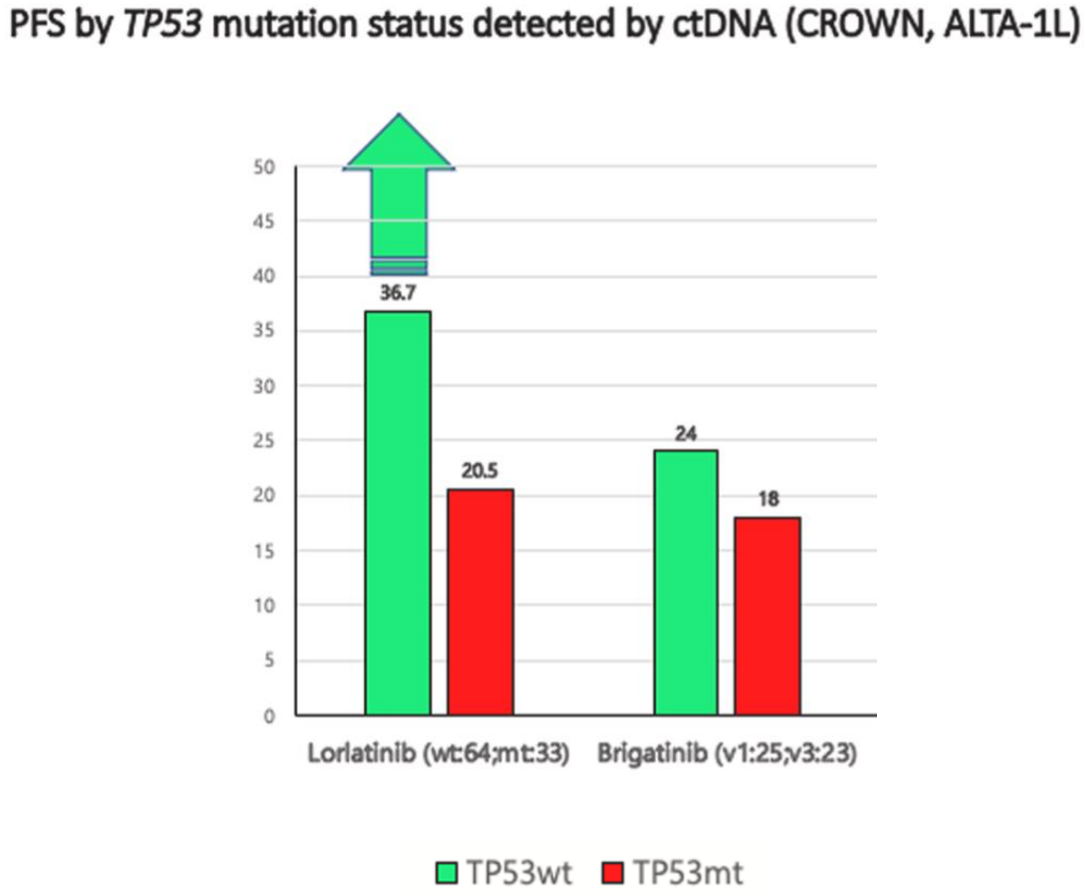
EML4-ALK Variant	Gene Fusion Points	Frequency	TAPE Domain	Inhibitor Sensitivity	Localisation	References
Variant 1	E13; A20	33%	Partial TAPE	ALK- mid HSP90- high	Cytoplasm	[7,15,27,28]
Variant 2	E20; A20	10%	Partial TAPE	ALK- high HSP90- high	Cytoplasm	[7,15,27,28]
Variant 3a/b	E6a; A20	29%	No TAPE	ALK- low HSP90- low	Microtubules, cytoplasm and nucleus	[15,27,28]
Variant 4'	E14; ins11del49A20	3%	Partial TAPE	Not known	Not known	[24,27]
Variant 5a	E2; A20	2%	No TAPE	ALK- low HSP90- low	Cytoplasm	[15,24,27]



Sabir et al. Cancers 2017;
Ou et al. Crit Rev Oncol Hematol 2023

Impact of EML4-ALK variant and *TP53* mut in 1L





Retrospective ctDNA analysis of PFS outcomes according to the EML4-ALK variant 1 and 3 and *TP53* mutational status in ALEX, ALTA 1L and CROWN trials

Ou et al. Crit Rev Oncol Hematol 2023

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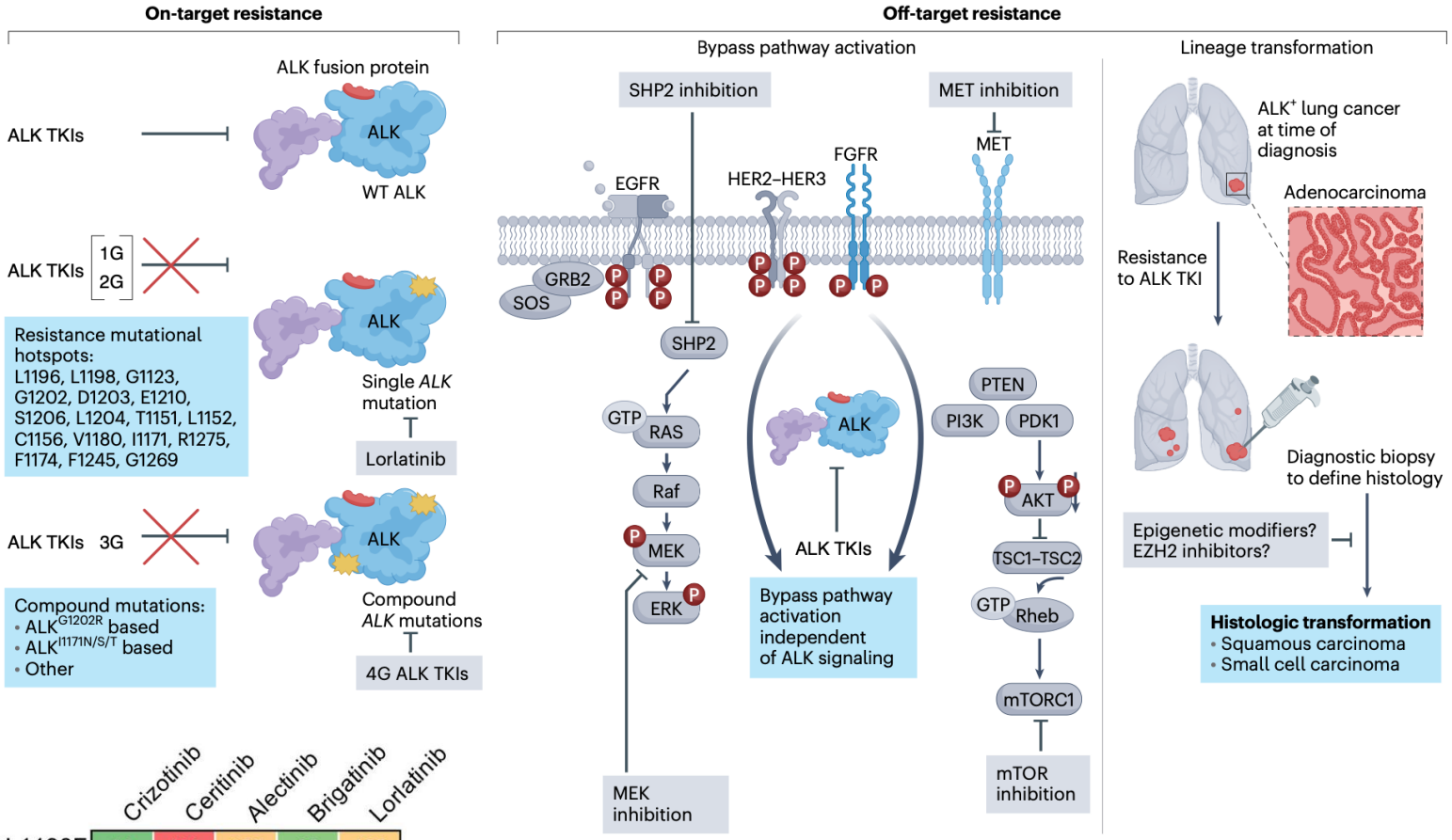
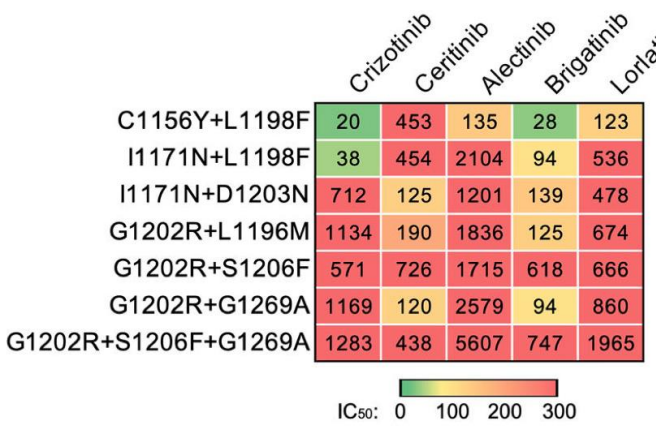
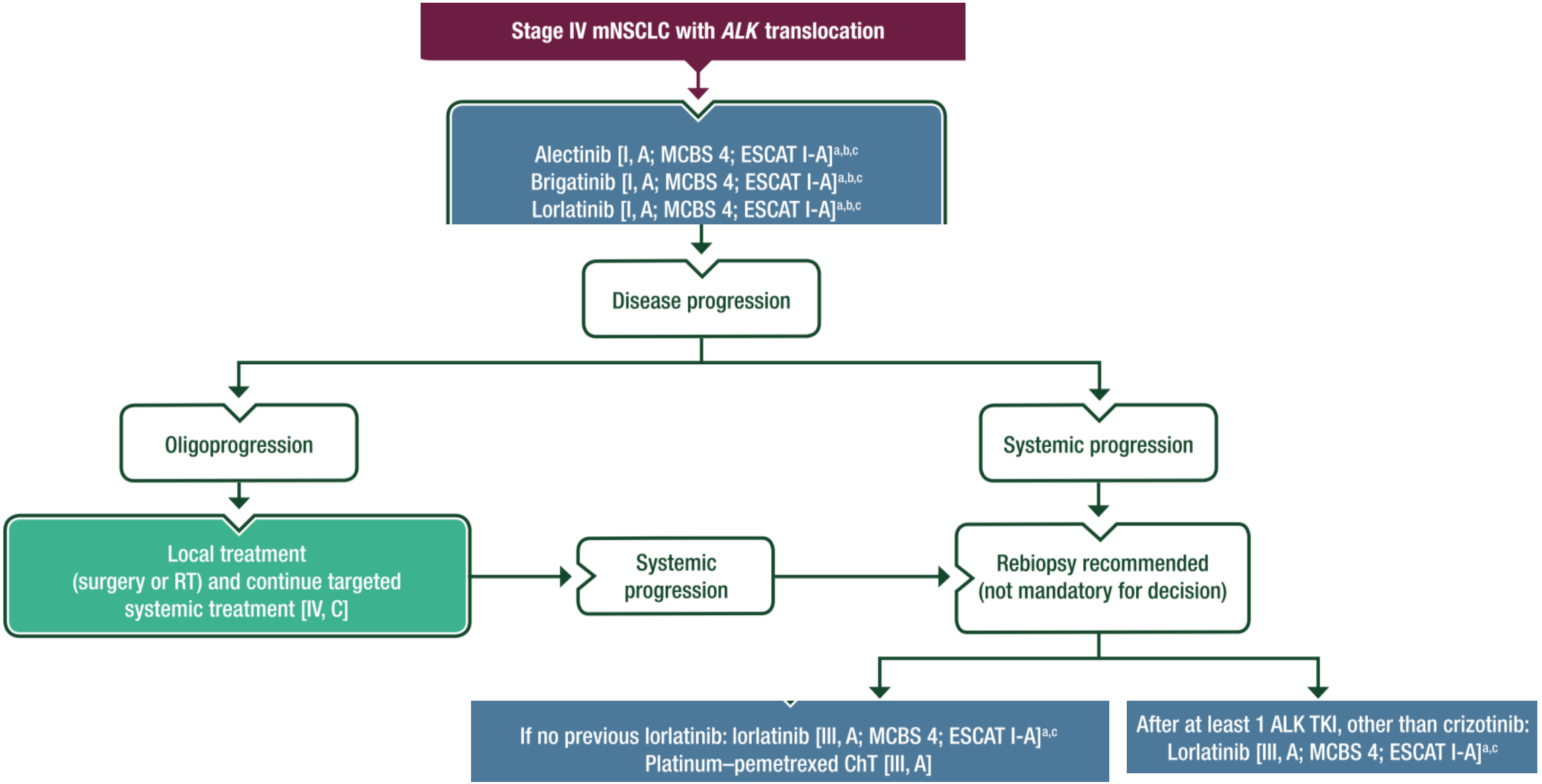
Mechanisms of resistance on an ALK-TKI





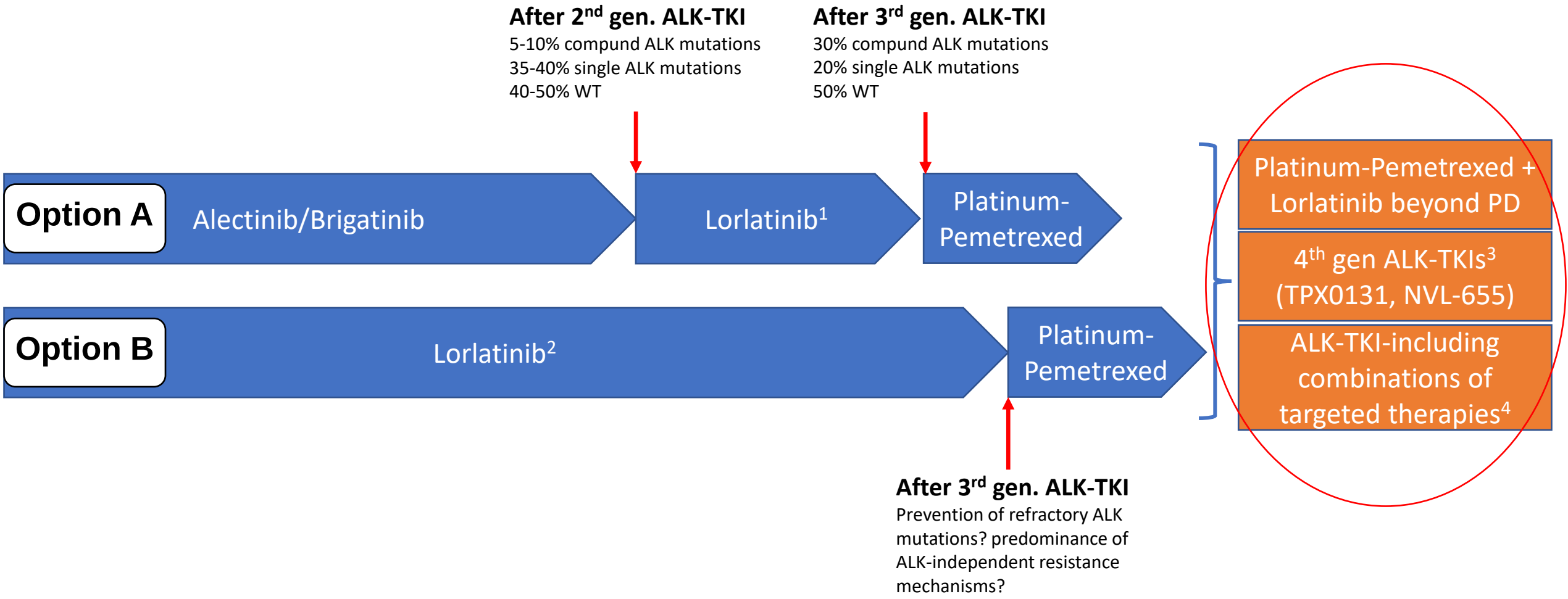
Schneider et al. Nat Cancer 2023;
Shiba-Ishii et al. Nat Cancer 2022

Treatment at progression on 1L ALK-TKI



ESMO guidelines, Ann Oncol 2023

Experimental options at progression



[1]2L Lorlatinib not indicated as per EMA label after brigatinib; [2]Lorlatinib not yet reimbursed in Italy as 1L therapy; [3]NCT04849273, NCT05384626;[4]Reviewed in Schneider et al. Nat Cancer 2023

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ALK testing in resected early-stage candidate to adjuvant atezolizumab

EMA/AIFA indication

Tecentriq as monotherapy is indicated as adjuvant treatment following complete resection and platinum-based chemotherapy for adult patients with NSCLC with a high risk of recurrence whose tumours have PD-L1 expression on ≥50% of tumour cells (TC) and who do not have EGFR mutant or ALK-positive NSCLC.

- ALK
- EGFR
- PD-L1

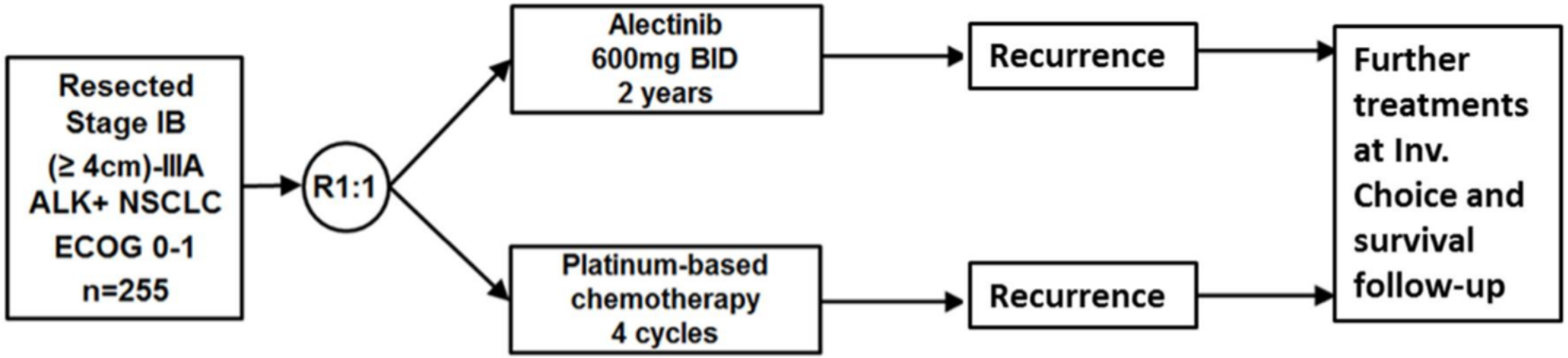
ALK testing in resectable early-stage candidate to neoadjuvant chemo + nivolumab

EMA indication

OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria).

Patients with known EGFR mutations or ALK translocations (testing for EGFR mutations or ALK translocations was not mandatory at study entry) were excluded from the study

ALK-positive resected early stage: ‘ALINA’ trial (NCT03456076)



Primary endpoint: DFS

Secondary endpoint OS

Roche

Roche’s Alecensa delivers unprecedented Phase III results for people with ALK-positive early-stage lung cancer

September 01, 2023 01:00 ET| Source: F. Hoffmann-La Roche Ltd Follow

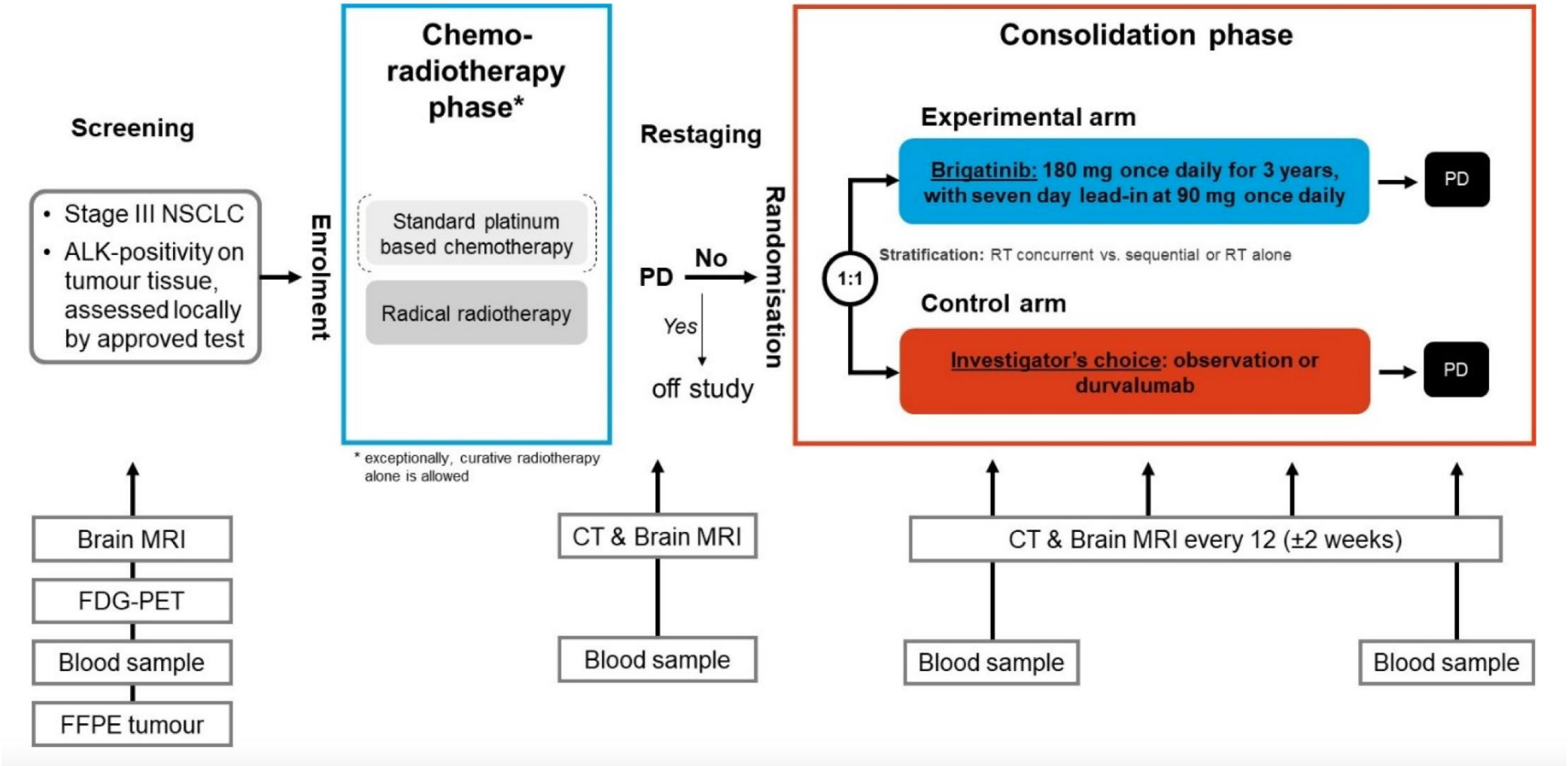
- **ALINA data demonstrate Alecensa reduces disease recurrence in the early setting for people with ALK-positive non-small cell lung cancer (NSCLC), building on its long-established benefit in the advanced setting**

Neoadjuvant trials with alectinib

ALNEO (39), NCT05015010	Phase II; resectable stage III; neoadjuvant alectinib ×8 weeks followed by adjuvant alectinib ×96 weeks	None	mPR	33 patients	Start date: 8/2021; completion date: 5/2026
NAUTIKA1 (43), NCT04302025	Phase II; resectable stage IB-III; neoadjuvant alectinib ×8 weeks followed by adjuvant alectinib ×104 weeks	None	mPR	80 patients	Start date: 3/2020; completion date: 2/2029

table from Chen and Chaft, Transl Lung Cancer Res 2023

Unresectable LA-NSCLC : ETOP ‘BOUNCE’ trial (NCT05718297)



Conclusions

- A sequential 2nd → 3rd generation ALK-TKI treatment can be clearly identified for ALK+ advanced NSCLC
- In selecting 1L treatment, consideration should be given to drug tolerability and convenience in order to guarantee patient adherence
- Among other factors, clinical characteristics and peculiar molecular features (if available) can be taken into account as decision making tools
- ALK testing is gaining relevance in early stage NSCLC as a clinical decision tool

Thanks for your attention

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