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Fall 1: ALK-transloziertes Adenokarzinomn der Lunge

Fall 1

- **39 jähriger Patient Vorstellung aufgrund von Visusminderungen in der Augenklinik (08/2019)**
  Befund einer (amelanotischen) Aderhautmetastase. Staging mit MRT-Schädel und PET-CT

- **09/2019 Verlegung in die Ruhrlandklinik dort Lymphknotenstaging mittels EBUS und histologische Sicherung eines TTF1-positiven Adenokarzinoms**

- **Tumorstadium nach Staging:**
  T3 N3 M1c (BRA, OSS, HEP, ADR, LYM)
  Stadium IVb nach IASLC

- **Nebendiagnosen:**
  Nie-Raucher

Fall 1

- **Molekularpathologie:**

IHC:
ALK: 100% positiv
ROS1: 0% positiv
PD-L1: < 1% TPS

FISH:
Nachweis eines Fusionssignal in 10% der Zellkerne (Schwellenwert 15%)

→ **FISH ALK negativ**

kein Nachweis einer MET-Amplifikation, keine RET-Translokation

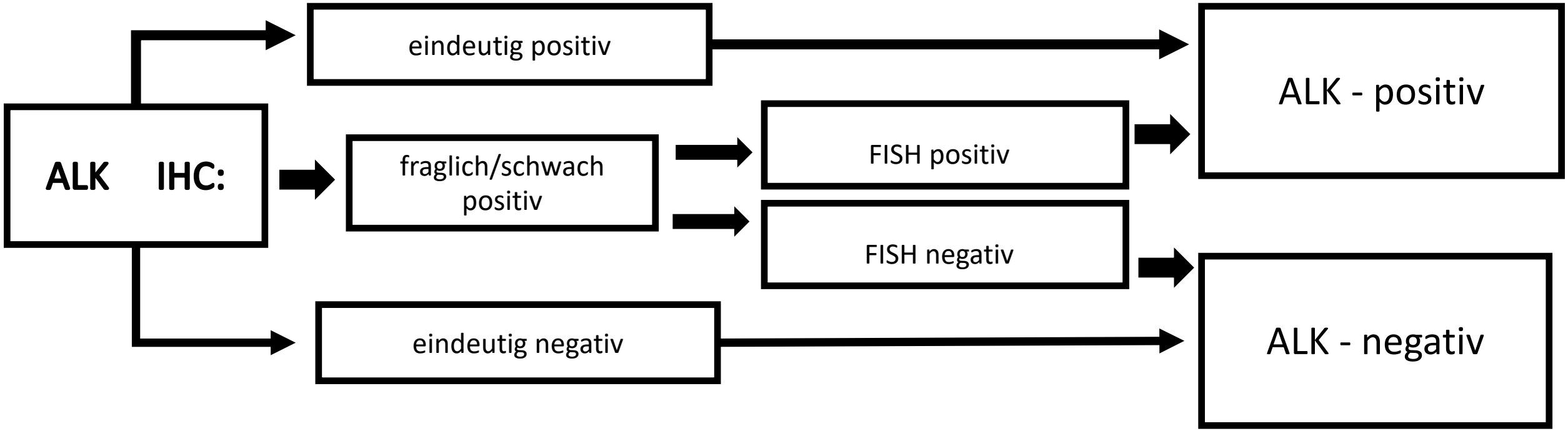
Next Generation Sequencing:
EGFR- und BRAF-Wildtyp

Fall 1

Diskrepanz zwischen Immunhistochemie und FISH!

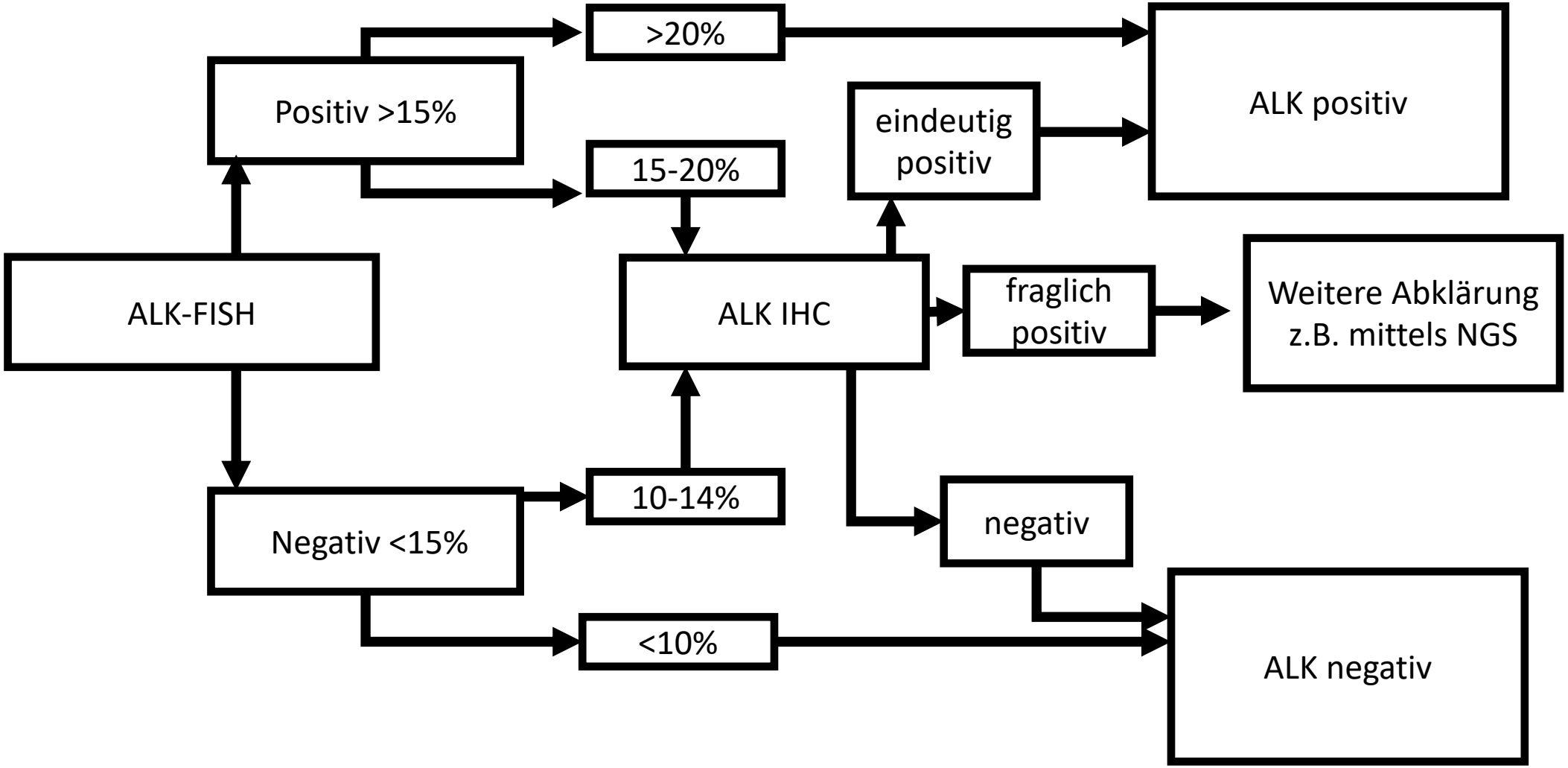
Was nun ??!?

Fall 1:



Modifiziert nach „von Laffert et al.“, DOI http://dx.doi.org/ 10.1055/s-0042-102626;
oder http://dx.doi.org/10.1016/j.lungcan.2016.11.008

Fall 1



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oder http://dx.doi.org/10.1016/j.lungcan.2016.11.008

Fall 1

- **10/2019 Next Generation Sequencing (NGS) Archer Panel mit RNA basierter parallel Sequenzierung.**

  Nachweis einer *therapeutisch adressierbaren EML4-ALK-Inversion* in der RNA-basierten Sequenzierung

- **10/2019 Einleitung einer Therapie mit Alectinib**

Fall 1

Therapieansprechen 1:

CT-Bildgebung mit Ausgangsbefund und Therapieansprechen

09/2019 **11/2019** **07/2020**

Fall 1

Therapieansprechen 2

CT-Bildgebung mit Ausgangsbefund und Therapieansprechen

09/2019 **11/2019** **07/2020**

Fall 1

Therapieansprechen 3

MRT-Bildgebung mit Ausgangsbefund und Therapieansprechen

09/2019 **11/2019** **07/2020**

Wirksamkeit von ALK-Inhibitoren der 2. und 3. Generation im ZNS

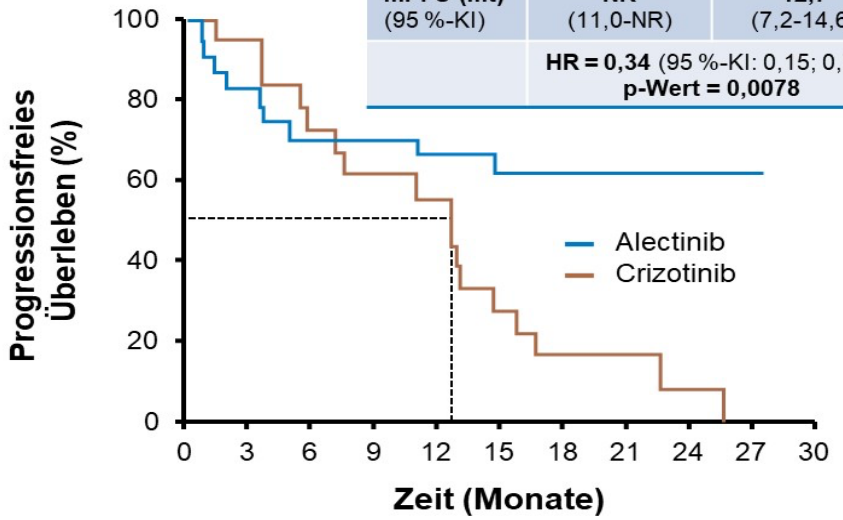
Fall 1: Alectinib

ALEX – PFS je nach ZNS-Radiotherapie

Verzögerte Progression unabhängig von Radiotherapie

Patienten MIT vorausgegangener Radiotherapie

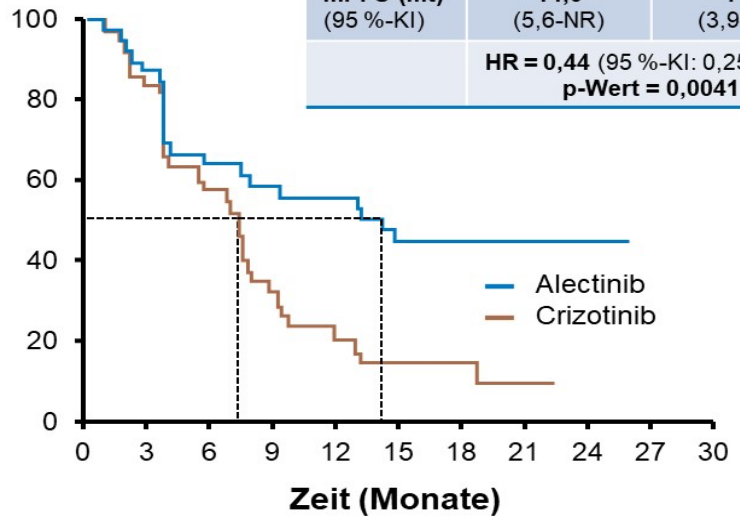
	Alectinib	Crizotinib
mPFS (mt) (95 %-KI)	**NR** (11,0-NR)	**12,7** (7,2-14,6)
	HR = 0,34 (95 %-KI: 0,15; 0,78) **p-Wert = 0,0078**	



No. at Risk										
Crizotinib	21	18	13	11	10	5	2	2	1	
Alectinib	25	20	17	17	16	15	11	3	3	1

Patienten OHNE vorausgegangene Radiotherapie

	Alectinib	Crizotinib
mPFS (mt) (95 %-KI)	**14,0** (5,6-NR)	**7,2** (3,9-8,6)
	HR = 0,44 (95 %-KI: 0,25; 0,78) **p-Wert = 0,0041**	



No. at Risk										
Crizotinib	37	30	20	11	7	4	4	1		
Alectinib	39	34	24	22	20	16	13	7	1	

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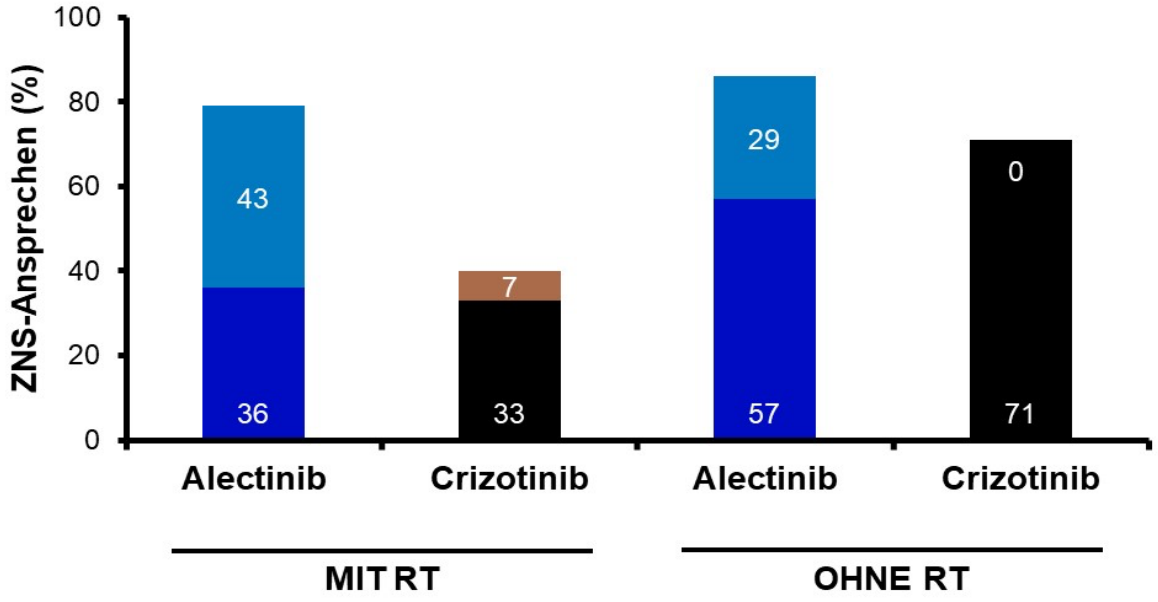
Mod. nach Gadgeel et al. ESMO 2017, Proffered Paper Session – NSCLC, metastatic 2, Abstract No. 12980_PR.

Fall 1: Alectinib

ALEX – ZNS-Ansprechen (Rate und Dauer)

Besseres und längeres Ansprechen unter Alectinib



ZNS-DoR Monate (95%-KI)	Crizotinib	Alectinib
Patienten mit RT	(n=15) **4,6** (1,9–6,8)	(n=14) **17,3** (1,9–NR)
Patienten ohne RT	(n=7) **17,3** (2,1–18,1)	(n=7) **NR** (14,8–NR)

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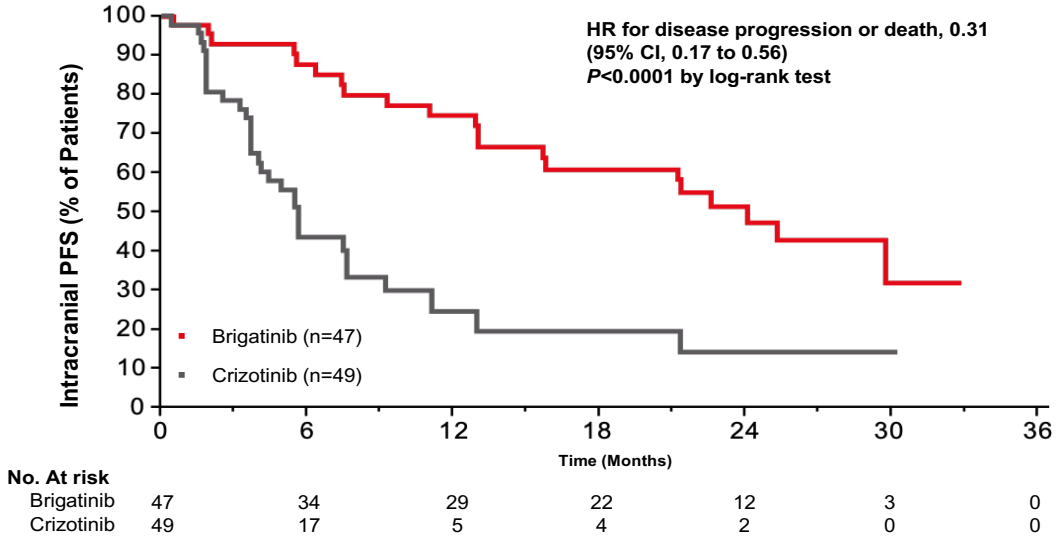
Mod. nach Gadgeel et al. ESMO 2017, Proffered Paper Session – NSCLC, metastatic 2, Abstract No. 12980_PR.

Fall 1: Brigatinib

Intracranial PFS (BIRC) showed a risk reduction of 69% with brigatinib vs crizotinib and confirms the efficacy in overall PFS seen in patients with baseline brain metastases

Only brain lesions were reviewed. Patients are counted as having an event if there was radiological progression, or death, or needed radiotherapy to the brain.

Patients With Any Brain Metastases at Baseline



Treatment	No. (%) Patients With Events		Median Intracranial PFS (95% CI)	2-Year Intracranial PFS, % (95% CI)
	Intracranial progression	Death		
Brigatinib (n=47)	21 (45)[b]	0	24.0 mo (12.9–NR)	48 (30–63)
Crizotinib (n=49)	29 (59)[c]	3 (6)	5.6 mo (3.7–7.5)	15 (5–32)

[a] *Intracranial reviewers are independent from systemic reviewers.* [b] *Includes 1 patient with radiotherapy to the brain.* [c] *Includes 2 patients with radiotherapy to the brain*

Camidge, R, Annals of Oncology (2019) 30 (suppl_9): ix183-ix202. 10.1093/annonc/mdz446 (ESMO Asia 2019)

Fall 1: Brigatinib

Intracranial ORR was high in patients with measurable brain metastases with a long median DoR that was not reached for brigatinib vs 9.2 months for crizotinib[a]

Measurable[b] Brain Metastases at Baseline	Brigatinib n=18	Crizotinib n=23	ORc (95% CI)
Confirmed intracranial ORR, % (95% CI)	78 (52–94)	26 (10–48)	11.67 (2.15–63.27) *P*=0.0014
CR, %	28	0	
PR, %	50	26	
Confirmed and nonconfirmed intracranial ORR, % (95% CI)	78 (52–94)	30 (13–53)	9.22 (1.76–48.43) *P*=0.0036
Median DoR in confirmed responders, mo (95% CI)	NR (5.7–NR)	9.2 (3.9–9.2)	
24-month probability of maintaining response, % (95% CI)	64 (30–85)	(insufficient pts)	
Any Brain Metastases at Baseline	n=47	n=49	
Confirmed intracranial ORR, % (95% CI)	66 (51–79)	16 (7–30)	11.75 (4.19–32.91) *P*<0.0001
CR, %	45	4	
PR, %	21	12	
Confirmed and nonconfirmed intracranial ORR, % (95% CI)	70 (55–83)	20 (10–34)	11.10 (4.06–30.39) *P*<0.0001
Median DoR in confirmed responders, mo (95% CI)	24.0 (16.9–NR)	9.2 (3.9–NR)	
24-month probability of maintaining response, % (95% CI)	55 (32–73)	(insufficient pts)	

[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

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Fall 1: Lorlatinib

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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

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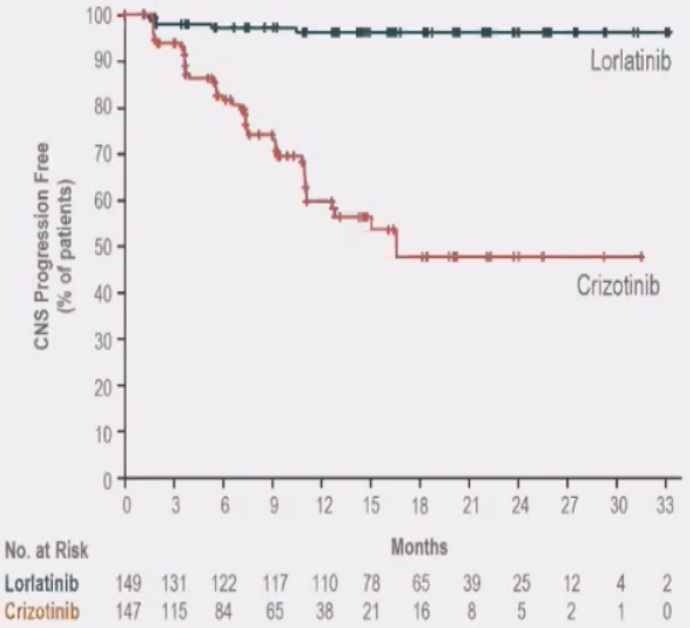
Intracranial Time to Progression by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	5 (3)	45 (31)
Median time to CNS progression, months (95% CI)	NE (NE–NE)	16.6 (11.1-NE)
HR (95% CI) 1-sided P value*	0.07 (0.03-0.17) <0.001	

*By stratified log-rank test.

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; NE, not estimable

Bauer et al., ESMO 2020 #LBA 2

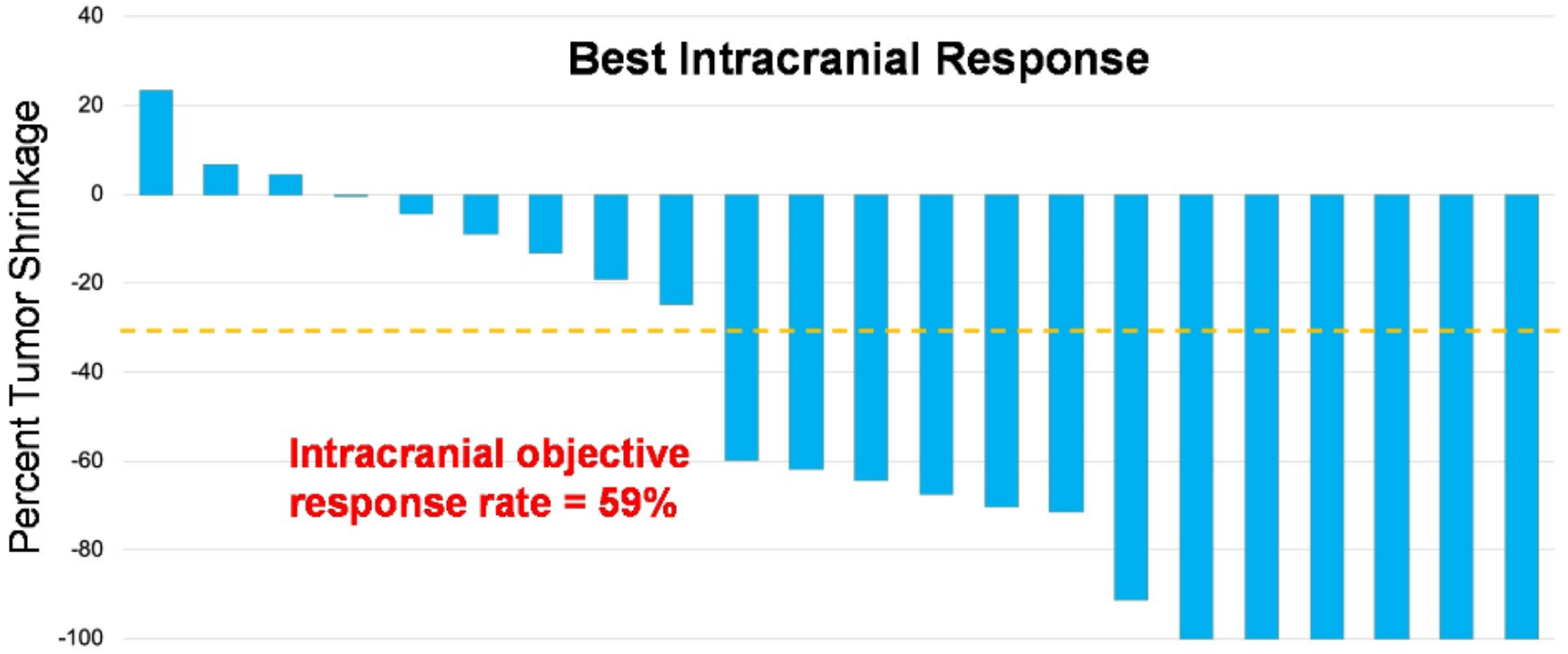
Fall 1: Lorlatinib

Intracranial Response Rate

At 12 weeks, the intracranial disease control rate was 95%

- **3 complete and 10 partial responses**
- **8 patients with stable disease**

3 patients converted from partial to complete intracranial response after 12 weeks



Dagogo-Jack I. et al. ASCO2020 Abs. 9595

Vielen Dank!

Wir danken den Sponsoren