ALK+ NSCLC: Choosing Between 1st Line ALK TKIs (and Overview of Resistance Mechanisms)

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Objectives

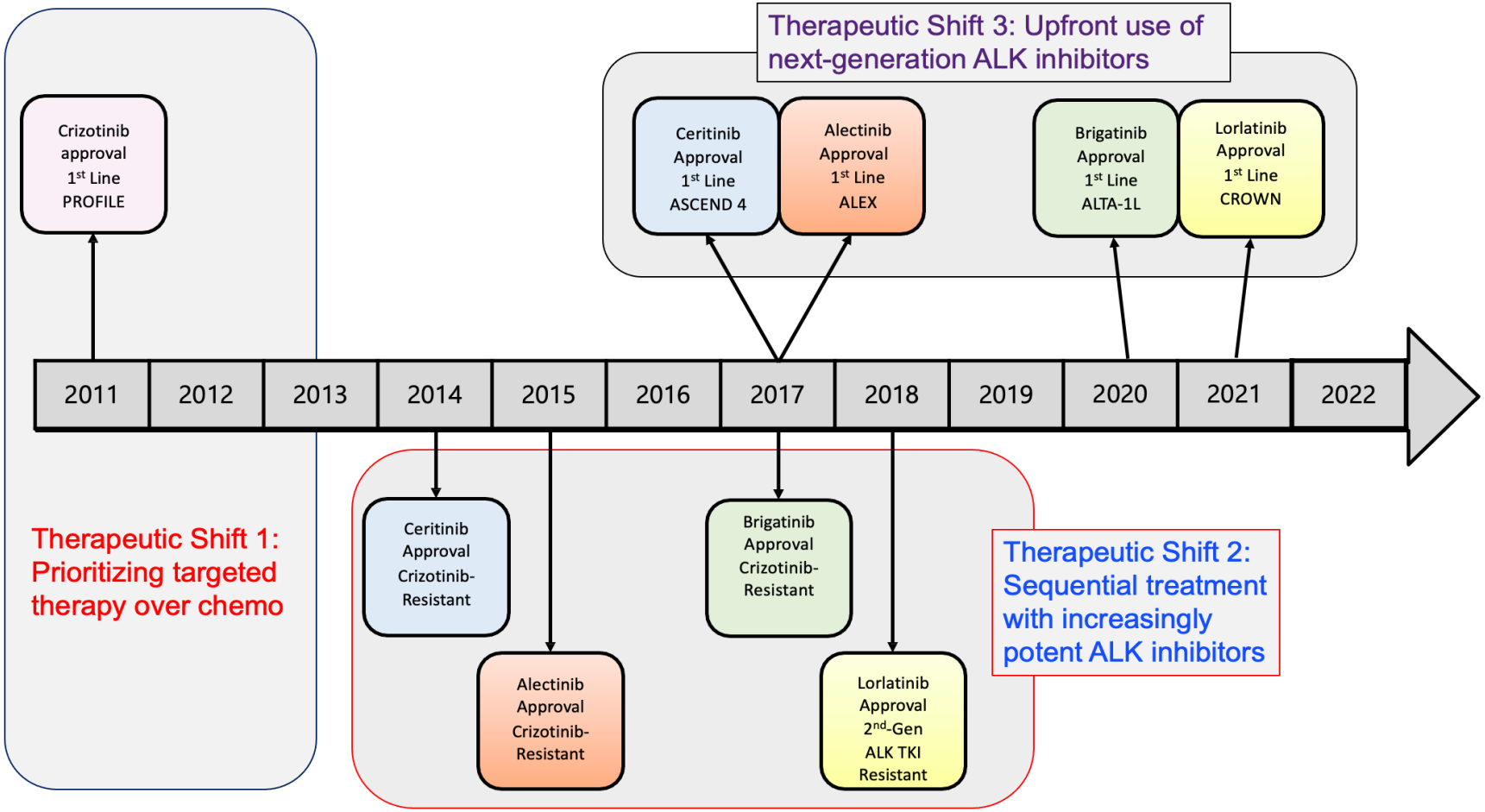
- Summarize safety & efficacy of next-generation TKIs in the 1st line
- Discuss disease and patient factors that may influence selection of 1st line ALK TKI
- Provide an overview of mechanisms of resistance to ALK TKIs
- Review activity of next-generation ALK TKIs after progression on other next-generation ALK TKIs (i.e., sequential therapy)

Background: *ALK*-Rearranged (ALK+) NSCLC

- ALK+ NSCLC occurs in 3-7% of NSCLC
- Enriched in adenocarcinoma histology and among younger pts
- Sensitive to therapeutic targeting with ALK TKIs
- CNS involvement is common
  - 30% of pts at diagnosis
  - >50% of pts during disease course

ALK TKI	1st Generation	2nd Generation	3rd Generation
Crizotinib	✓	✗	✗
Ceritinib	✗	✓	✗
Alectinib	✗	✓	✗
Brigatinib	✗	✓	✗
Lorlatinib	✗	✗	✓

Evolution of the Treatment Paradigm



Factors to Consider:

- Efficacy
- Intracranial Activity
- Tolerability
- Access
- Cost
- Comorbidities
- ?Next-Line Options
- ?Molecular factors

Modification of slide originally created by Ignatius Ou, MD

Patient Case #1

A man in his 60s presents with neck and shoulder pain refractory to outpatient management

- He has no smoking history.
- MRI spine demonstrates bone and intramedullary lesions. A destructive lesion is seen on shoulder imaging.
- Staging studies demonstrate extensive intracranial (asymptomatic) and extracranial disease.
- Biopsy of an adrenal metastasis confirms lung adenocarcinoma.
- Molecular testing reveals an *EML4-ALK* rearrangement.

Patient Case #2

A woman in her 20s presents with persistent cough

- She has no smoking history. She has severe bipolar disorder.
- Imaging demonstrates a lung mass, mediastinal lymphadenopathy, and osseous metastases.
- Brain MRI is within normal limits.
- Biopsy of a bone lesion is consistent with lung adenocarcinoma harboring an *EML4-ALK* rearrangement.

Efficacy of Next-Generation ALK TKIs in 1st Line

ALK TKI	Vs.	# of patients	ORR (%) *Investigator Assessed	Median PFS Independent Review	PFS rate @ 3 years
Ceritinib ASCEND-4[1]	Chemo	376	72.5 vs 26.7	16.6 vs 8.1	---
Alectinib ALEX[2]	Crizotinib	303	*82.9 vs 75.5	25.7 vs 10.4 (HR 0.50)	46%
Brigatinib ALTA-1L[3]	Crizotinib	275	74 vs 62	24.0 vs 11.1 (HR 0.48)	43%
Lorlatinib CROWN[4,5]	Crizotinib	296	76 vs 58	NR vs 9.3 (HR 0.27)	64%

[1]Soria Lancet 2017, [2]Mok Ann of Onc 2020, [3]Camidge JTO 2021, [4]Shaw NEJM 2020, [5]Solomon Lancet Resp Med 2022
ORR: objective response rate, PFS: progression-free survival

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CNS Efficacy of Next-Gen ALK TKIs in the 1st Line

ALK TKI	Intracranial ORR (Measurable Baseline Mets)	CNS CR Rate (Measurable Baseline Mets)	Cumulative Incidence of CNS PD @ 1yr (Brain Mets)	Cumulative Incidence of CNS PD @ 1yr (No Brain Mets)	CNS PFS rate @ 3 years (All pts)
Alectinib ALEX[1]	81%	38%	16%	4.6%	---
Brigatinib ALTA-1L[2]	78%	28%	---	---	57%
Lorlatinib CROWN[3,4]	83%	71%	7%	1%	92%

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CR: complete response; ORR: objective response rate; TKI: tyrosine kinase inhibitor, PD: progression; PFS: progression-free survival

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Sequential Treatment with Next-Gen ALK TKIs

ALK TKI	Study n=	ORR (%)	PFS (Months)	Notes
Ceritinib[1]	**ASCEND-9** n=20	25%	3.7	Prior alectinib
Brigatinib[2]	**ALTA-2** n=103	26.2%	3.8	Prior alectinib ORR: 29.1% Prior Ceritinib ORR: 11.8%
Lorlatinib[3]	**NCT01970865** n=139	39.6%	6.6	Following ≥1 2nd-gen ALK TKI
Lorlatinib[4] (CNS-only PD)	**NCT02927340** n=23	59% (CNS)	24.6 (CNS)	87% had prior alectinib or brigatinib

[1]Hida Cancer Sci 2018, [2]Ou JTO 2022, [3]Felip Annals of Oncology 2021, [4]Dagogo-Jack JCO Precision Oncology 2022,
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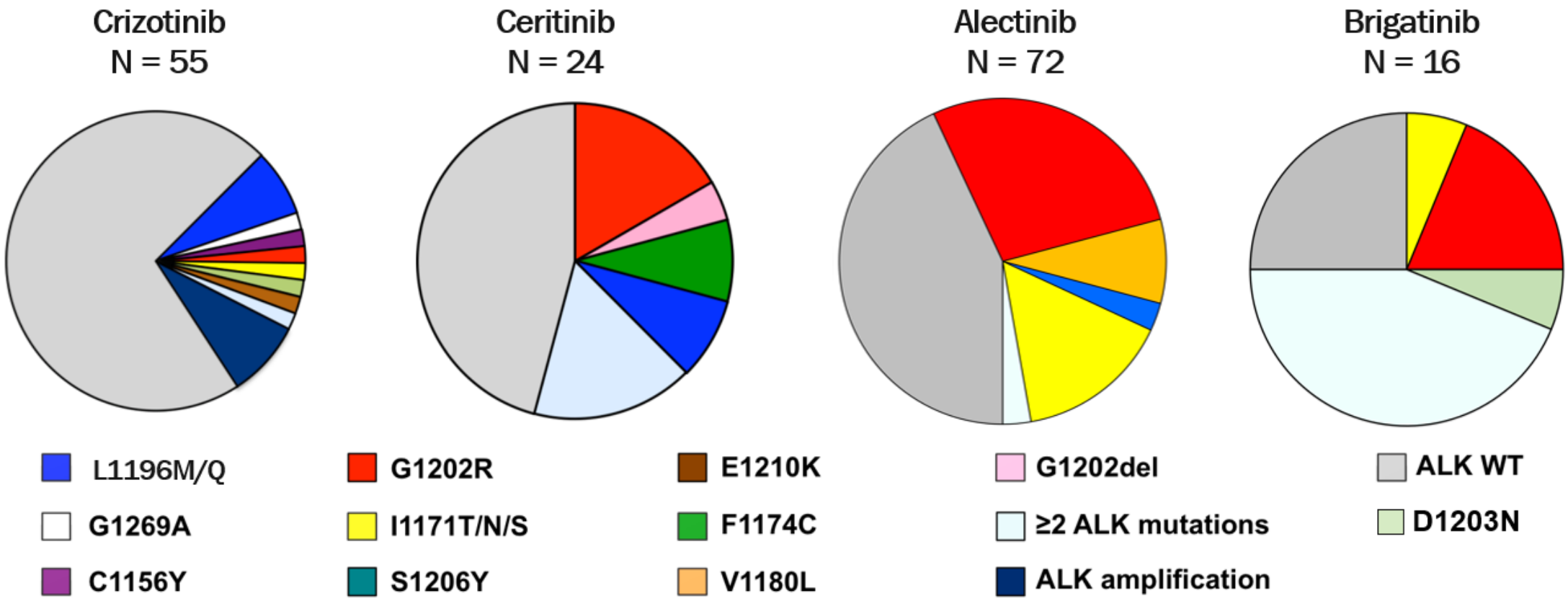
ALK-Dependent Resistance to ALK TKIs



WT, wild type.
Updated from: a. Gainor JF, et al. Cancer Discov. 2016;6:1118-1133

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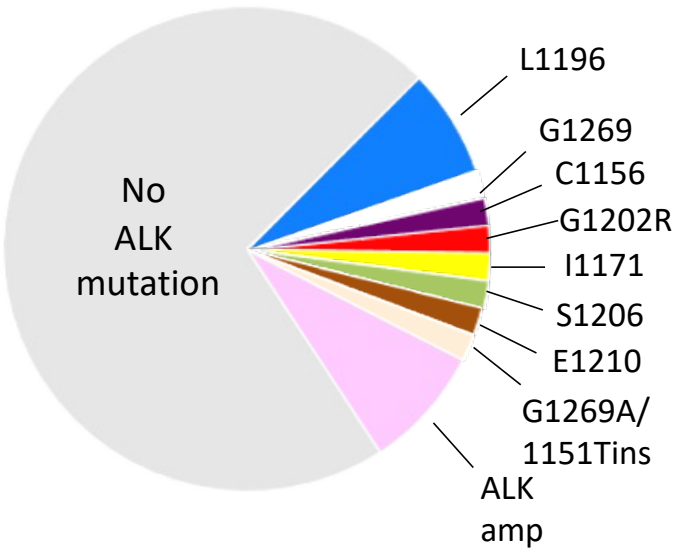
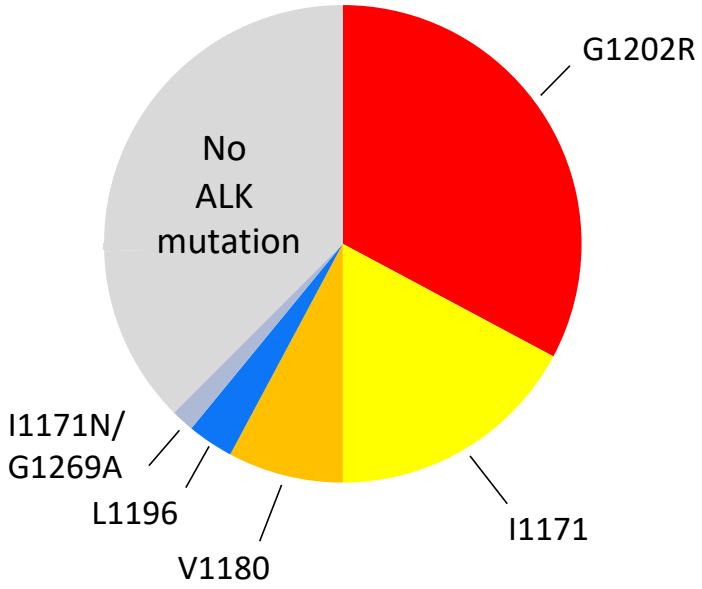
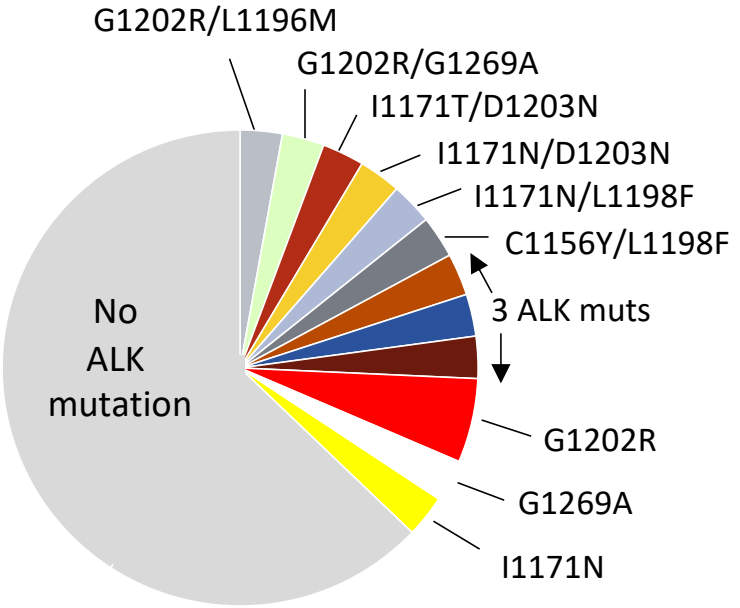






Crizotinib → 2nd-gen TKI → Lorlatinib

Spectrum of Activity of Distinct ALK TKIs

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

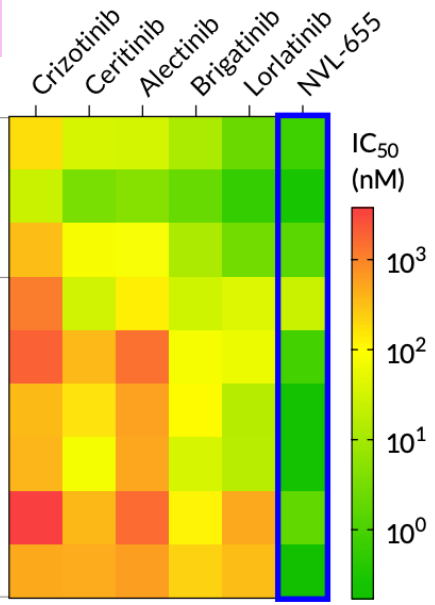
$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

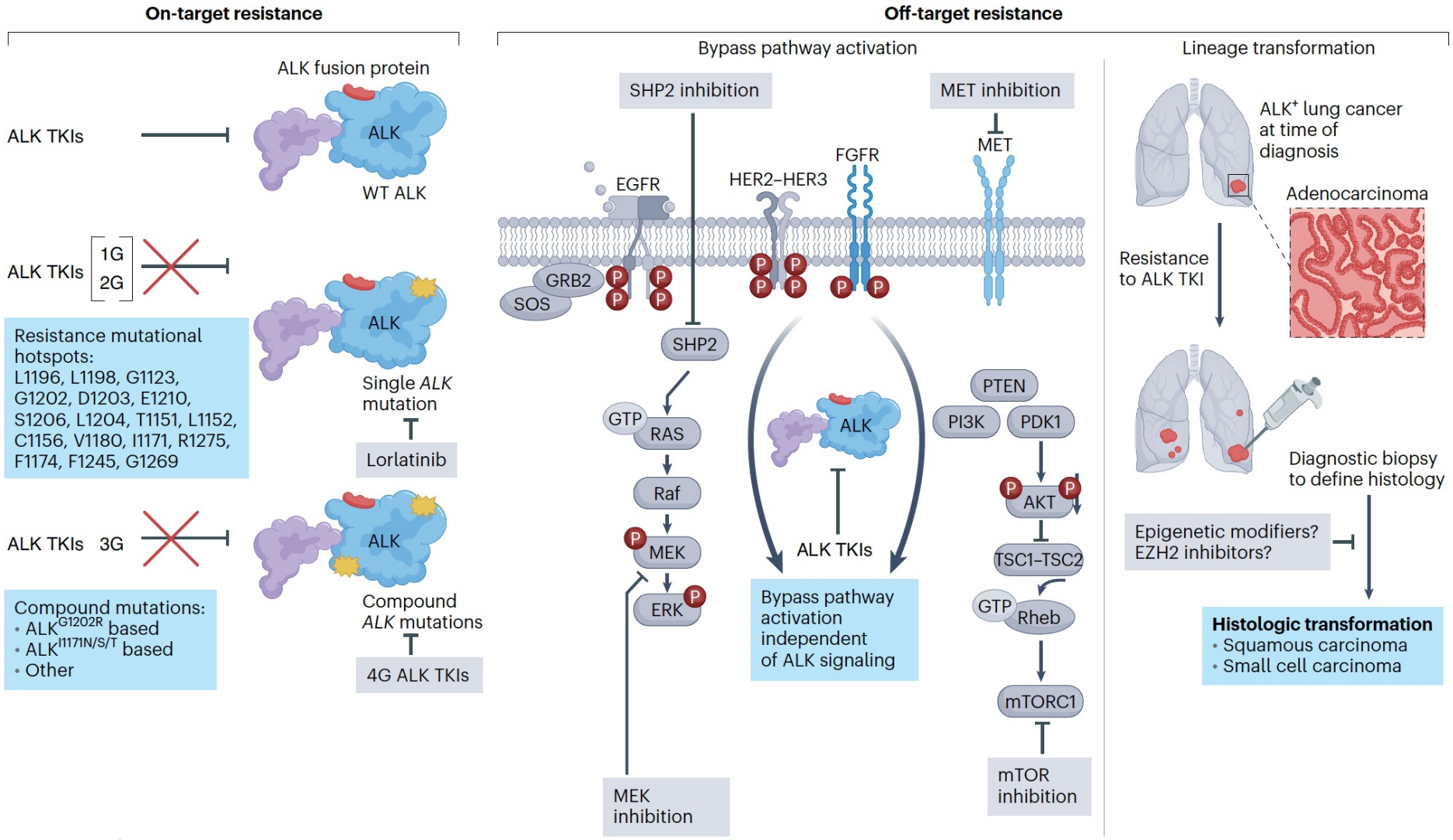
NVL-655: Fourth-Generation ALK TKI

	PDC	Fusion	Mutation	TKI resistance
TREATMENT-NAÏVE	MGH048-1	EML4-ALK v1	–	–
	MGH064-1	EML4-ALK v2	–	–
	MGH026-1	EML4-ALK v3	–	–
TREATMENT-RELAPSED	MGH045-1	EML4-ALK v1	L1196M	Crizotinib
	MGH953-4	EML4-ALK v3	G1202R	Alectinib
	YU-1077	EML4-ALK v3	G1202R	Alectinib*
	MGH9037-2	EML4-ALK v3	G1202R	Brigatinib
	MGH953-7	EML4-ALK v3	G1202R/L1196M	Lorlatinib
	MR448re	EML4-ALK v3	G1202R/T1151M	Lorlatinib



Gainor Cancer Discovery 2016, Lee AACR 2023

Resistance to ALK Targeted Therapy is Complex



Schneider Nature Cancer 2023

Toxicity Profile of Next-Generation ALK TKIs

ALK TKI	AEs requiring dose reduction	AEs requiring discontinuation	Key Adverse Events (Frequency %)
Alectinib (ALEX)	**Alectinib** = 20% **Crizotinib** = 20%	**Alectinib** = 15% **Crizotinib** = 15%	Edema (17%) Myalgia (16%) Bilirubin ↑ (15%) Alanine aminotransferase ↑ (15%)
Brigatinib (ALTA-1L)	**Brigatinib** = 38% **Crizotinib** = 25%	**Brigatinib** = 13% **Crizotinib** = 9%	CPK ↑ (39%) Nausea (26%) Alanine aminotransferase ↑ (19%) Lipase ↑ (19%) ILD/Pneumonitis (5%)
Lorlatinib (CROWN)	**Lorlatinib** = 22% **Crizotinib** = 15%	**Lorlatinib** = 7% **Crizotinib** = 10%	Cholesterol ↑ (70%), Triglyceride ↑ (64%) Edema (55%), Weight ↑ (38%), Neuropathy (34%), Cognitive effects (21%) Mood effects (16%), Speech effects (10-15%)

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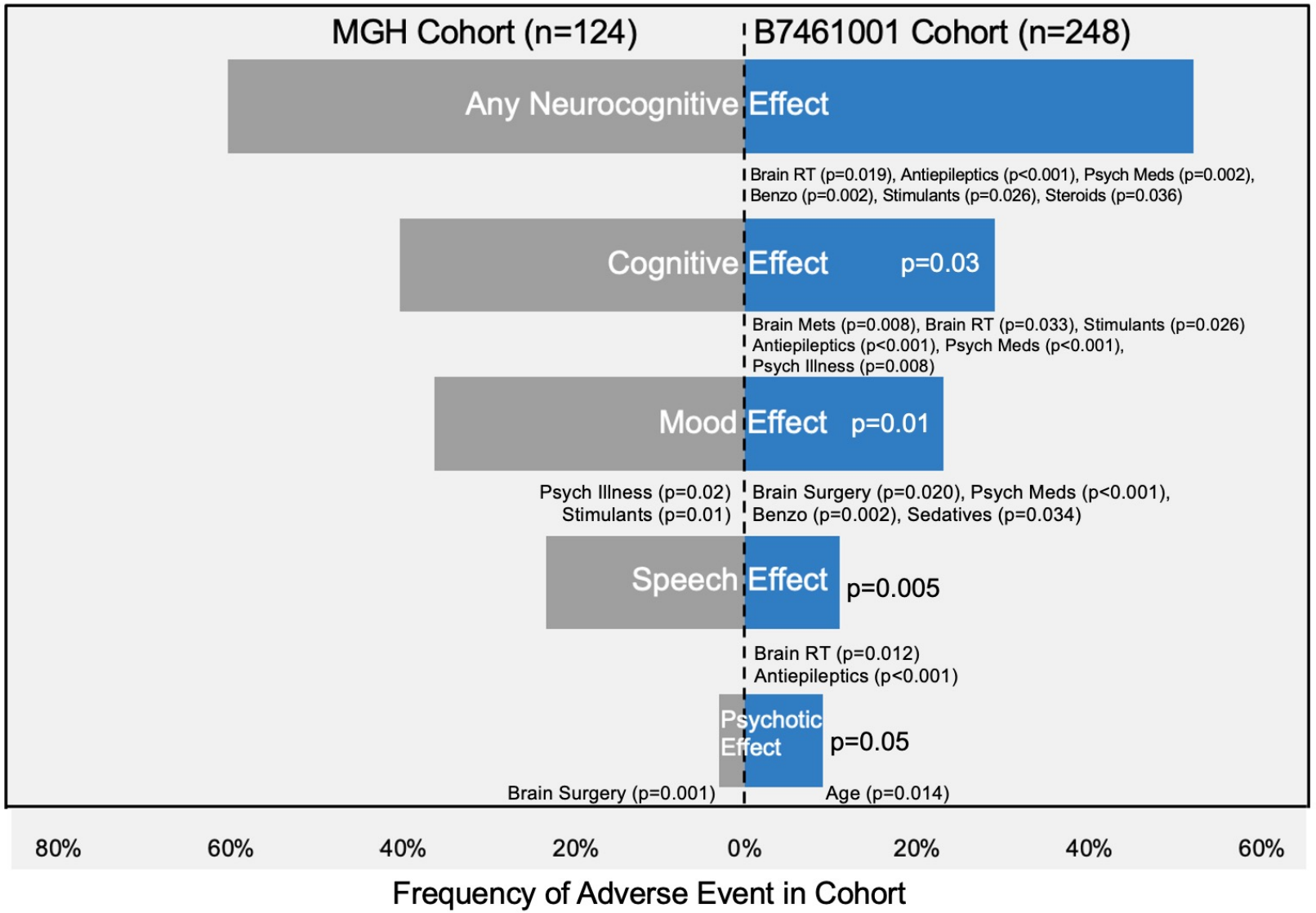
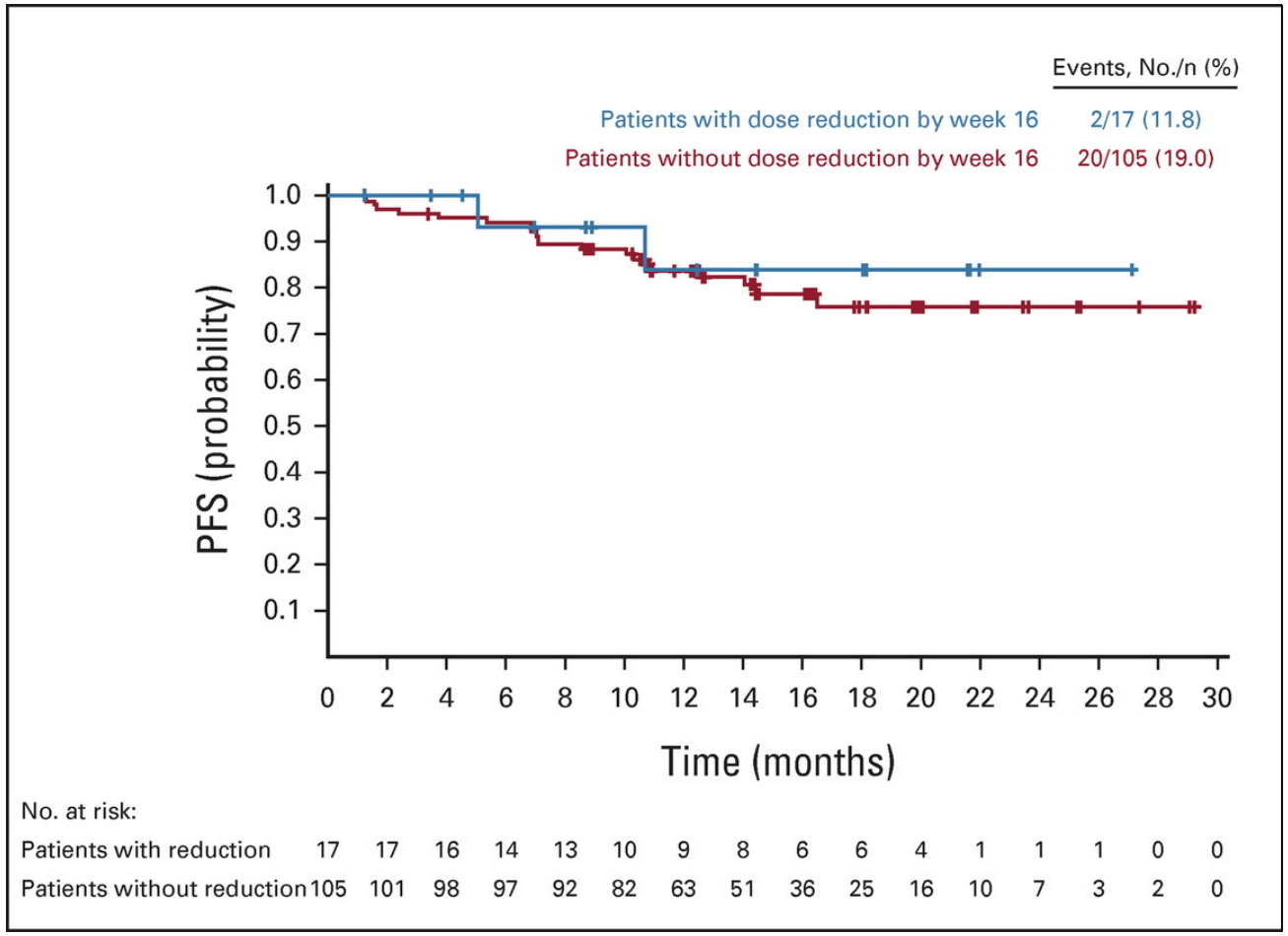
Factors Associated with Neurocognitive Toxicity



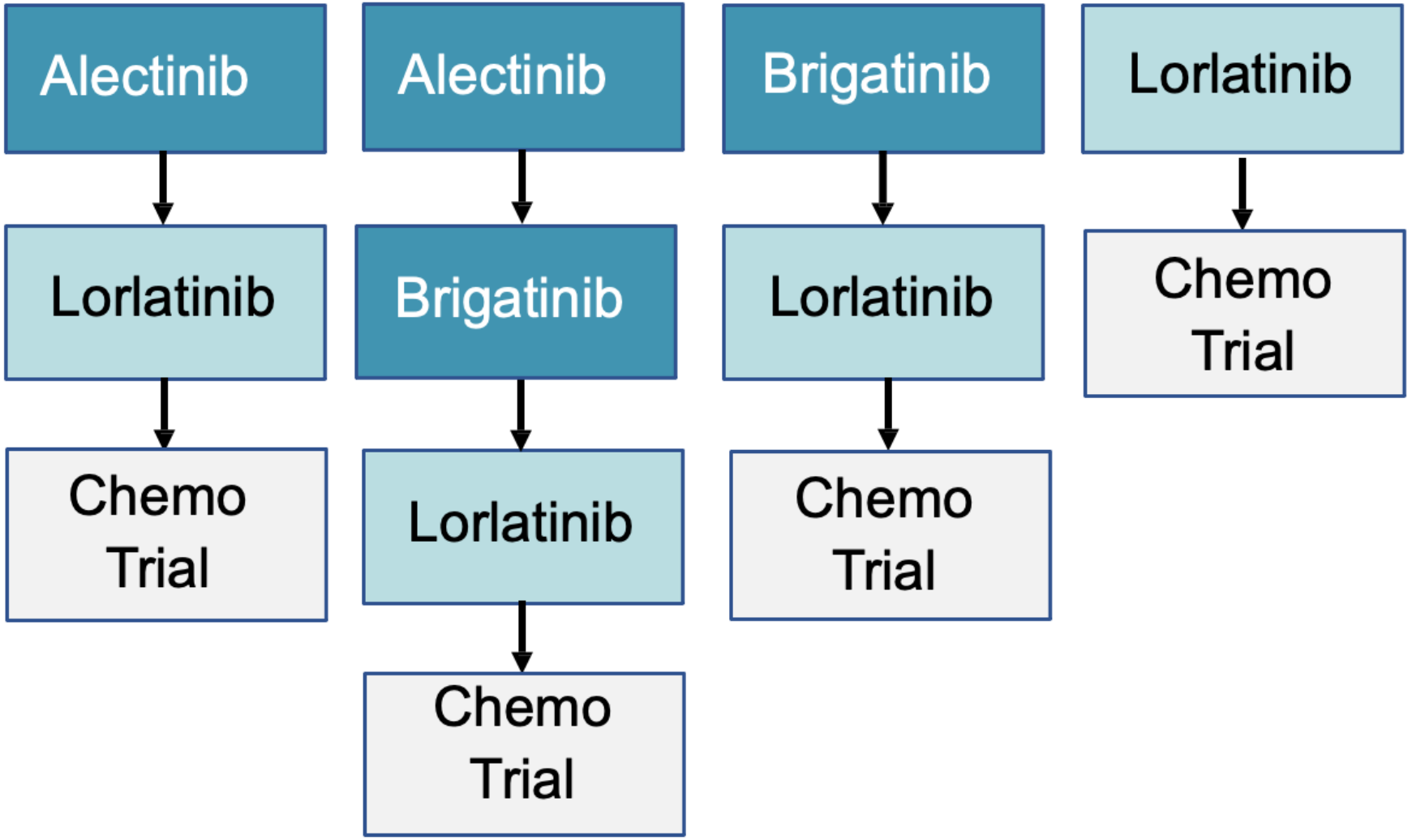
Dagogo-Jack JTO 2022

Dose Reduction Does not Compromise Efficacy: CROWN (Lorlatinib in 1st Line)



Solomon JCO 2022

Management of ALK+ NSCLC in 2023



Back to Patients #1 and #2: What Did I Choose?

A man in his 60s presents with neck and shoulder pain refractory to outpatient management

- Imaging demonstrates extensive intracranial (asymptomatic) and extracranial disease, including a humeral metastasis.
- He was initiated on lorlatinib as 1st line treatment without brain radiation.
- He has required a dose reduction to 75 mg.

A woman in her 20s with severe bipolar disorder presents with persistent cough

- Imaging demonstrates a lung mass, mediastinal lymphadenopathy, and osseous metastases without brain metastases.
- She was initiated on alectinib as 1st line treatment.

Conclusions

- Several next-generation ALK TKIs have significant systemic and intracranial activity in untreated metastatic ALK+ NSCLC.
- Most patients will only benefit from 1-2 of the FDA-approved TKIs.
- The toxicity profiles differ for the distinct ALK TKIs, potentially influencing treatment selection.
- Efficacy can be maintained despite dose reduction!