Opzioni terapeutiche nel paziente *ALK*-traslocato

Giulio Metro

S.C. Oncologia Medica – Ospedale Santa Maria della Misericordia, Azienda Ospedaliera di Perugia

"Carcinoma del polmone non microcitoma: quali novità per il 2016"

Verona – 8-9 Apr 2016

ALK “history” in NSCLC: from target discovery to approval of targeted therapy in record time

Target	Year of discovery		Year of correlation with therapeutic efficacy of targeted therapy		Year of approval of targeted therapy (crizotinib)
ALK	2007	3 yrs	2010	1-2 yrs	2011 (FDA) 2012 (EMA)

ALK-targeted therapy: the present

Fusion gene	Frequency	Available in clinical practice
ALK	3-7%	Crizotinib* (FDA, EMA) Ceritinib[1≠] (FDA, EMA) Alectinib[1] (FDA)
ROS1	1-2%	Crizotinib (FDA)

*Available as 2nd line in Italy
[1]For patients refractory or intolerant to crizotinib
≠Available on a compassionate use basis in Italy

Outline

- *Timing of crizotinib*
- *Safety of crizotinib*
- *What after crizotinib?*
- *Brain mets*
- *Ongoing clinical research*

Outline

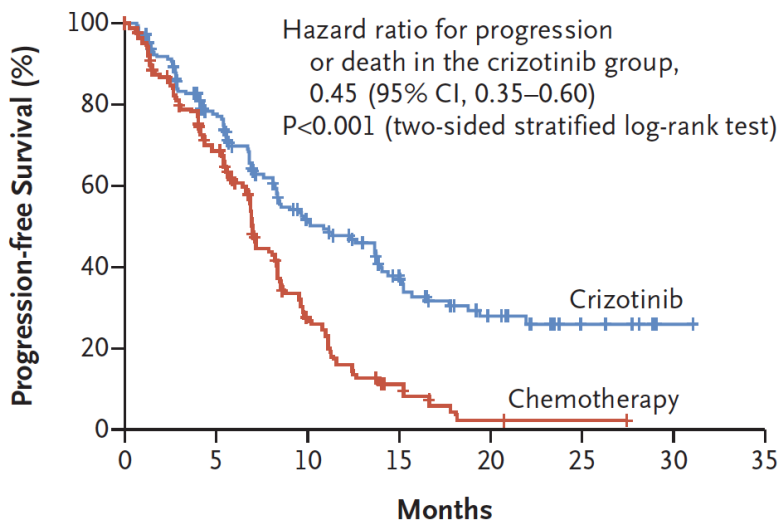
- ***Timing of crizotinib***
- ***Safety of crizotinib***
- ***What after crizotinib?***
- ***Brain mets***
- ***Ongoing clinical research***

Upfront crizotinib: PROFILE 1014

Table 2. Response to Treatment in the Intention-to-Treat Population.*

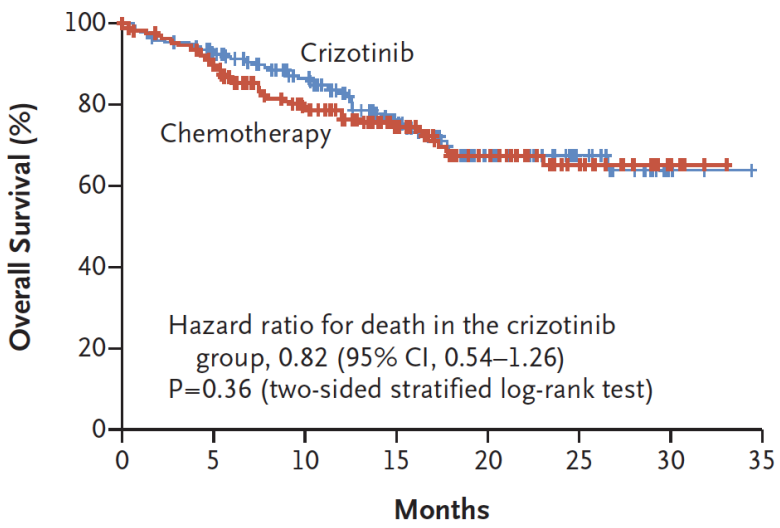
Response	Crizotinib (N = 172)	Chemotherapy (N = 171)
Duration of response — mo ‖		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

A Progression-free Survival



No. at Risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

B Overall Survival



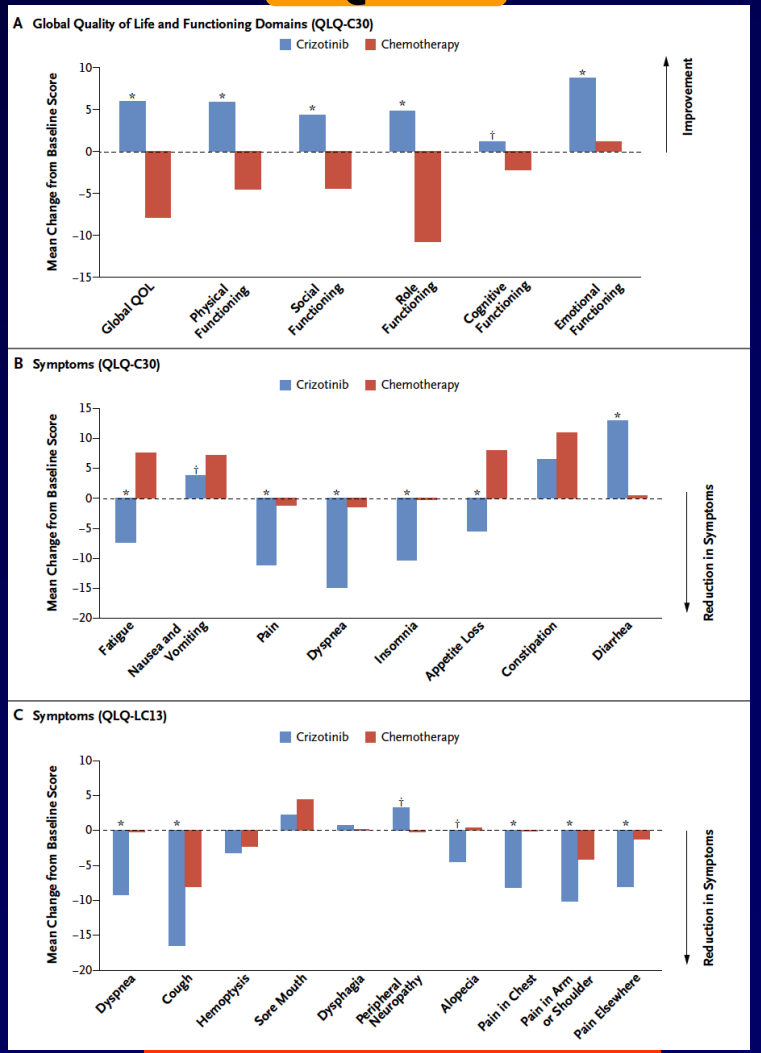
No. at Risk								
Crizotinib	172	152	123	80	44	24	3	0
Chemotherapy	171	146	112	74	47	21	4	0

Solomon et al., NEJM 2014

...issues on OS for PROFILE 1014...

- ***Long post-progression survival*** **makes it difficult to observe significant differences in OS**
- ***Cross-over:***
  - ***86% (114/132) of progressors on the chemo arm received crizotinib***
  - ***14% (18/132) of progressors on the chemo arm did not receive crizotinib***
- ***No OS difference but improvement in quality of life***

QoL



Solomon et al., NEJM 2014

Crizotinib's development program

Study	No. of patients	RR (%)	PFS (mos.)
PROFILE 1001	143	60.8	9.7
PROFILE 1005	261	59.8∞	8.1
PROFILE 1007	173	65*	7.7
PROFILE 1014	172	74*	10.9

∞259 pts evaluable for response
*Independent radiologic review

More active as upfront therapy!

Camidge, et al. Lancet Oncol 2012
Kim, et al. ASCO 2012
Shaw, et al. NEJM 2013
Solomon, et al. NEJM 2014

Outline

- *Timing of crizotinib*
- *Safety of crizotinib*
- *What after crizotinib?*
- *Brain mets*
- *Ongoing clinical research*

Most common AEs (>10%) in PROFILE trials

	PROFILE 1001 [23] n = 82		PROFILE 1005 [25] n = 901*		PROFILE 1007 [26] n = 172		PROFILE 1014 [27] n = 171	
	Any grade n (%)	Grade 3 – 4 n (%)	Any grade n (%)	Grade 3 – 4 n (%)	Any grade n (%)	Grade 3 – 4 n (%)	Any grade n (%)	Grade 3 – 4 n (%)
Nausea	43(52)	1 (1)	423 (46.9)	7 (0.8)	94 (55)	2 (1)	95 (56)	2 (1)
Vomiting	35 (43)	1 (1)	352 (39.1)	7 (0.8)	80 (47)	2 (1)	78 (46)	3 (2)
Diarrhea	38 (46)	1 (1)	369 (41.0)	9(1.0)	103 (60)	0	105 (61)	4 (2)
Visual disorders	34 (41)	0	468 (51.9)	1(0.1)	103 (60)	0	122 (71)	1 (1)
Elevated transaminase levels	9 (11)	1 (1)	252 (27.9)	48(5.3)	66 (38)	27 (16)	61 (36)	24 (14)
Edema	13 (16)	0	211 (23.4)	3(0.3)	54 (31)	0	83 (49)	1 (1)
Fatigue	8 (10)	0	163 (18.1)	18 (1.9)	46 (27)	0	48 (29)	5 (3)
Neutropenia	1 (1)	0	84 (9.3)	50 (5.5)	NR	23 (13)	12 (7)	3 (2)

Landi et al.Expert Opin Pharm 2014

Summary of liver AEs in PROFILE trials

	PROFILE 1001[1] N=149		PROFILE 1005[2] N=901		PROFILE 1007[3] N=172		PROFILE 1014[4] N=171	
	Any Grade N (%)	Gr. 3-4 N (%)	Any Grade N (%)	Gr. 3-4 N (%)	Any Grade N (%)	Gr. 3-4 N (%)	Any Grade N (%)	Gr. 3-4 N (%)
Elevated AST	15 (10)	5 (3)	84 (9.8)	50 (5.5)	66 (38)	27 (16)	61 (36)	24 (14)
Elevated ALT	18 (12)	6 (4)	146 (16.2)	36 (3.9)				
	N (%)							
Dose reduction	6 (0.4)		NR		NR		NR	
Permanent discontinuation	1 (<0.1)		5 (<1)		4 (2.3)		NR	

Camidge, et al. Lancet Oncol 2012
Kim, et al. ASCO 2012
Shaw, et al. NEJM 2013
Solomon, et al. NEJM 2014

Liver AEs: management

Starting dose: crizotinib 250 mg BID

Grade CTCAE	Treatment with crizotinib
Grade 3 or 4 ALT and/or AST elevation with bilirubin levels ≤ grade 1	Withold until grade ≤ 1, then resume ad 250 mg/die and escalate to 200 mg BID if tolerated[∞]
Grade 2, 3 or 4 ALT and/or AST elevation with bilirubin levels > grade 1	Permanent discontinuation

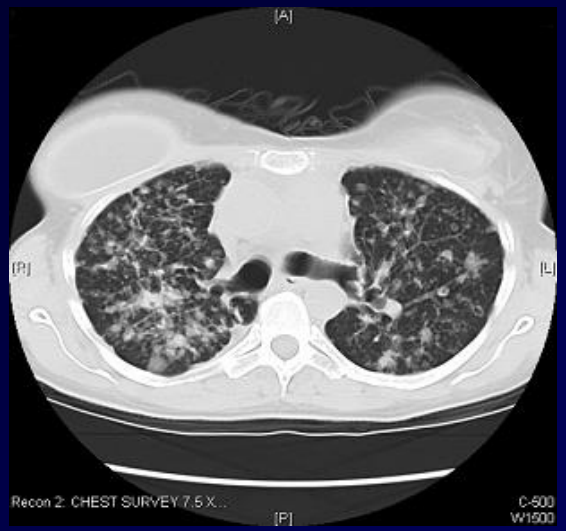
[∞]Permanent discontinuation in case reoccurrence of grade ≥ 3 liver AEs

Liver function tests should be monitored weekly durging the first 2 months and monthly thereafter (or more frequently in case of toxicity grade > 1)

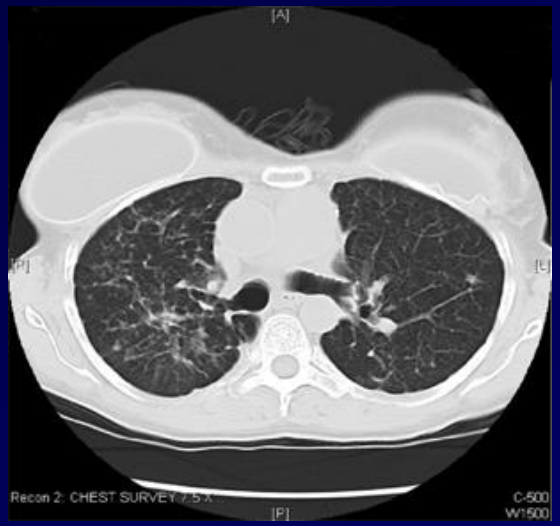
Outline

- *Timing of crizotinib*
- *Safety of crizotinib*
- *What after crizotinib?*
- *Brain mets*
- *Ongoing clinical research*

No cure with crizotinib



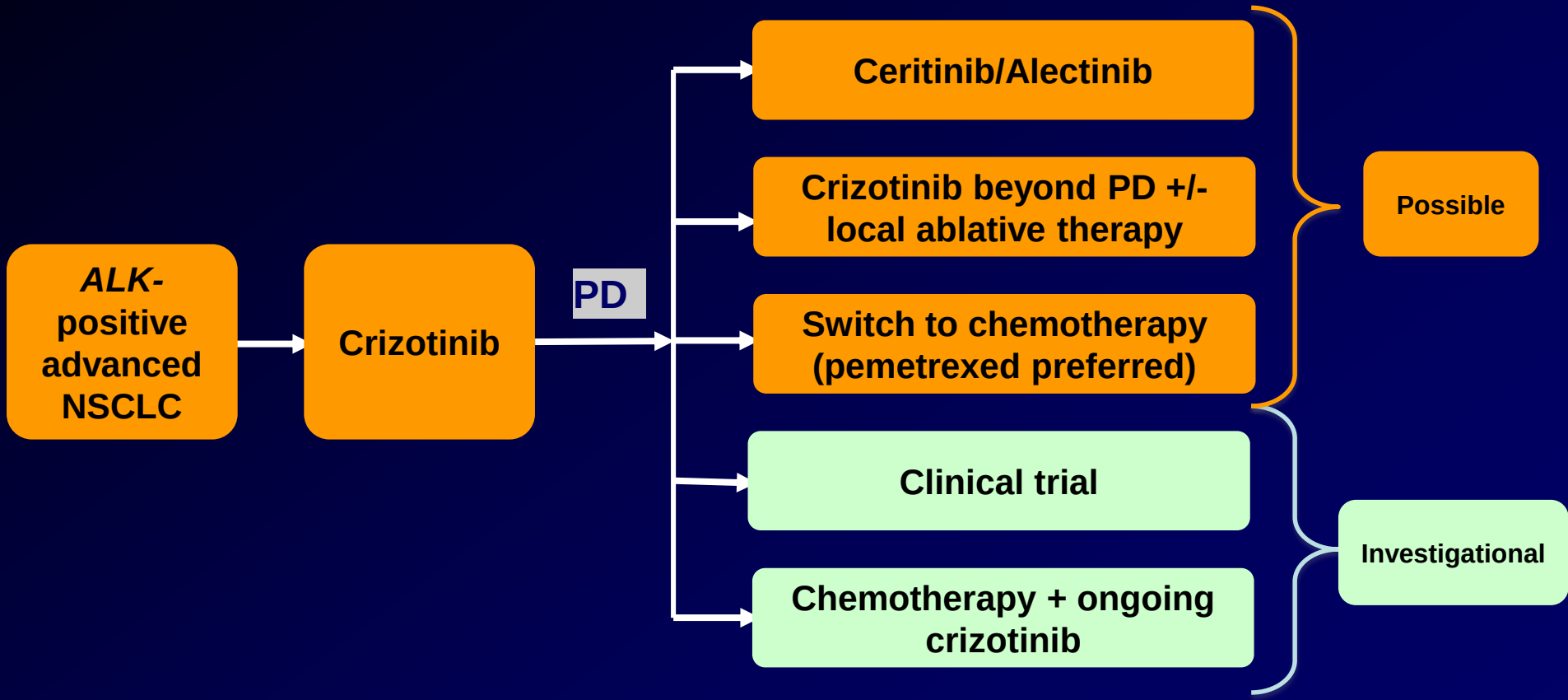
Baseline



Tumor regression

Progression
(median 9 months)

PD on crizotinib: what's next?



Ceritinib development program

- Ceritinib is being evaluated in patients with ALK+ NSCLC in the ASCEND clinical trial program – ASCEND 1 to 5 → enrollment of over 900 patients with ALK+ NSCLC

Study	Phase	Design
(2101, N=304 pts) ASCEND-1	1	Dose-finding study with ceritinib in patients with tumors with genetic abnormalities in ALK
(2201, N=140) ASCEND-2	2	Ceritinib in adult patients with ALK-activated NSCLC previously treated with chemotherapy and crizotinib
(2203, N=124) ASCEND-3	2	Ceritinib in adult patients with ALK-activated NSCLC previously treated with chemotherapy and crizotinib naive
(2301[a] N=348) ASCEND-4	3	Ceritinib vs chemotherapy in previously untreated patients with ALK-rearranged NSCLC
(2303, N=236) ASCEND-5	3	Ceritinib vs standard chemotherapy in adult patients with ALK-rearranged advanced NSCLC who have been treated previously with chemotherapy (platinum doublet) and crizotinib

Include ALKi-naïve patients

Additional clinical experience outside of trials with CUP (>600pts)

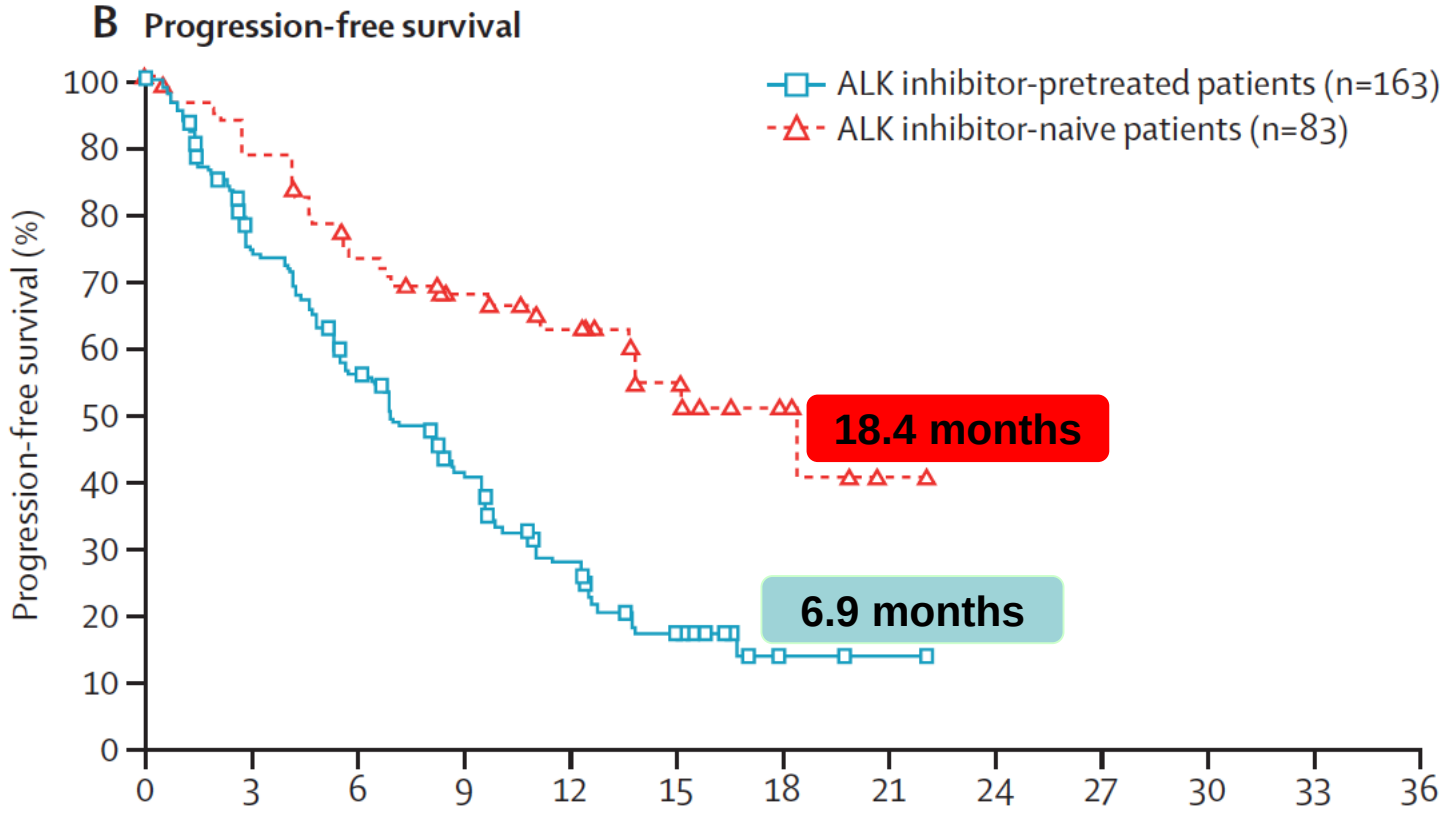
NOVARTIS

Ascend-1: anti-tumor activity of ceritinib

Efficacy Parameter	ALK inhibitor-pretreated N = 163	ALK inhibitor-naïve N = 83
Complete response, n (%)	3 (2)	1 (1)
Partial response, n (%)	89 (55)	59 (71)
Stable disease, n (%)	29 (18)	14 (17)
Progressive disease, n (%)	16 (10)	0
Unknown, n (%)	26 (16)	9 (11)
12-month duration of response	26% (16-36)	64% (49-76)
12-month PFS	27% (20-35)	62% (50-72)
12-month OS	67% (59-74)	83% (72-90)

Kim et al., Lancet Oncol 2016

Ascend-1: PFS on ceritinib



Number at risk

ALK inhibitor-pretreated	163	108	79	52	29	13	2	1	0	0	0	0	0
ALK inhibitor-naive	83	69	55	43	32	17	6	2	0	0	0	0	0

Kim et al., Lancet Oncol 2016

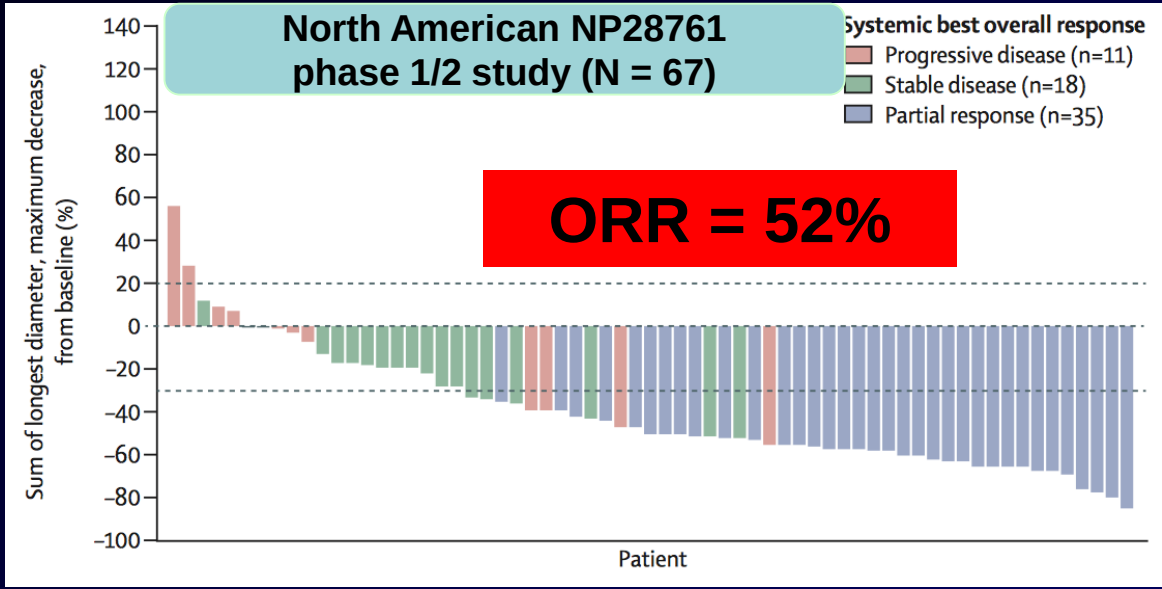
Ascend-2: AEs regardless of relationship to study drug (> 20% for all grades) (N = 140)

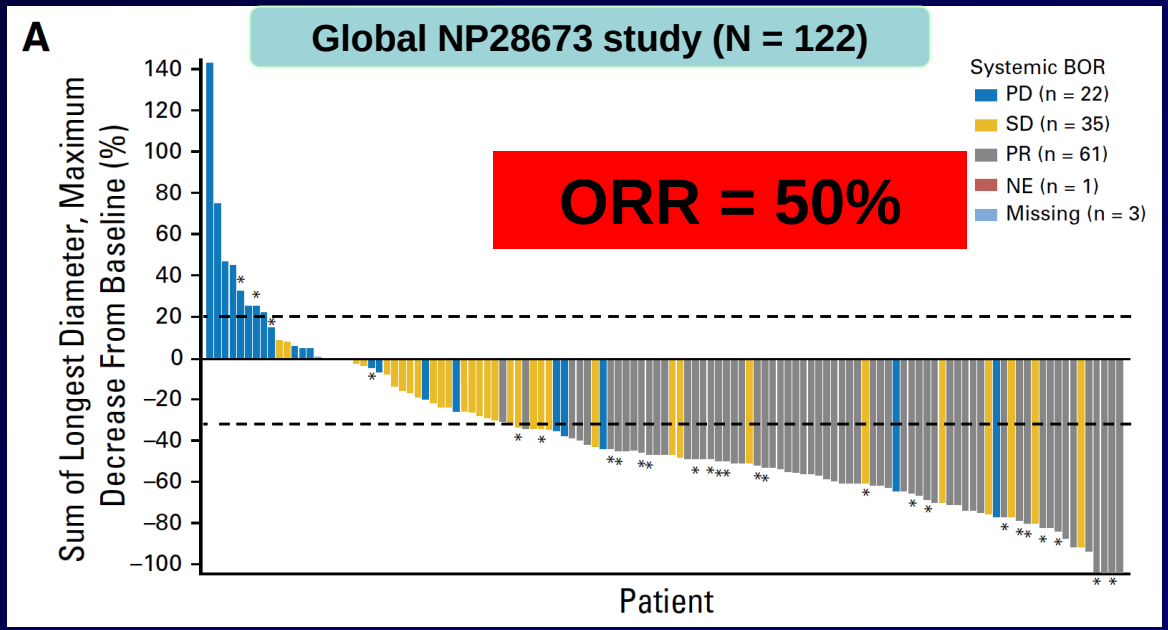
Preferred Term	All Grades, n (%)	Grade 3/4, n (%)
Nausea	114 (81.4)	9 (6.4)
Diarrhea	112 (80.0)	9 (6.4)
Vomiting	88 (62.9)	6 (4.3)
Alanine aminotransferase increased	61 (43.6)	24 (17.1)
Decreased appetite	57 (40.7)	5 (3.6)
Fatigue	51 (36.4)	9 (6.4)
Weight decreased	48 (34.3)	6 (4.3)
Aspartate aminotransferase increased	45 (32.1)	7 (5.0)
Abdominal pain	44 (31.4)	2 (1.4)
Constipation	40 (28.6)	3 (2.1)
Cough	30 (21.4)	0
Pyrexia	29 (20.7)	4 (2.9)
Dyspnea	29 (20.7)	8 (5.7)

Adverse events leading to permanent discontinuation in 7.9% of patients (N = 11)

Mok et al., ASCO 2015

Alectinib: in crizotinib-pretreated patients





Shaw, et al. Lancet Oncol 2016
Ou, et al. J Clin Oncol 2016

PROs ceritinib vs PROs alectinib following crizotinib

PRO ceritinib

- *20 fold more potent than crizotinib against native ALK*
- *Inhibition of IGFR-1 (a possible resistance mechanism)*
- *Active against most of resistance mutations*

PRO alectinib

- *Indirect comparison with ceritinib suggests less toxicity*
- *Alectinib is not a substrate of gp-150, a key efflux protein present at high concentrations in the BBB*
- *Active against most of resistance mutations*

Outline

- *Timing of crizotinib*
- *Safety of crizotinib*
- *What after crizotinib?*
- *Brain mets*
- *Ongoing clinical research*

Crizotinib and BMs from *ALK*+ NSCLC

	Untreated brain metastases (n = 109)			Treated brain metastases (n = 166)		
	# pts	outcome	95% CI	# pts	outcome	95% CI
IC ORR, % (target lesions)	22	18%	5-40	18	33%	13-59
IC DCR at 12 weeks	109	56%	46-66	166	62%	54-70

Intra-cranial failure accounts for appr. 70% of PDs in patients with brain metastases at baseline and 20% of PDs in patients without brain metastases at baseline

Costa, et al. J Clin Oncol 2015

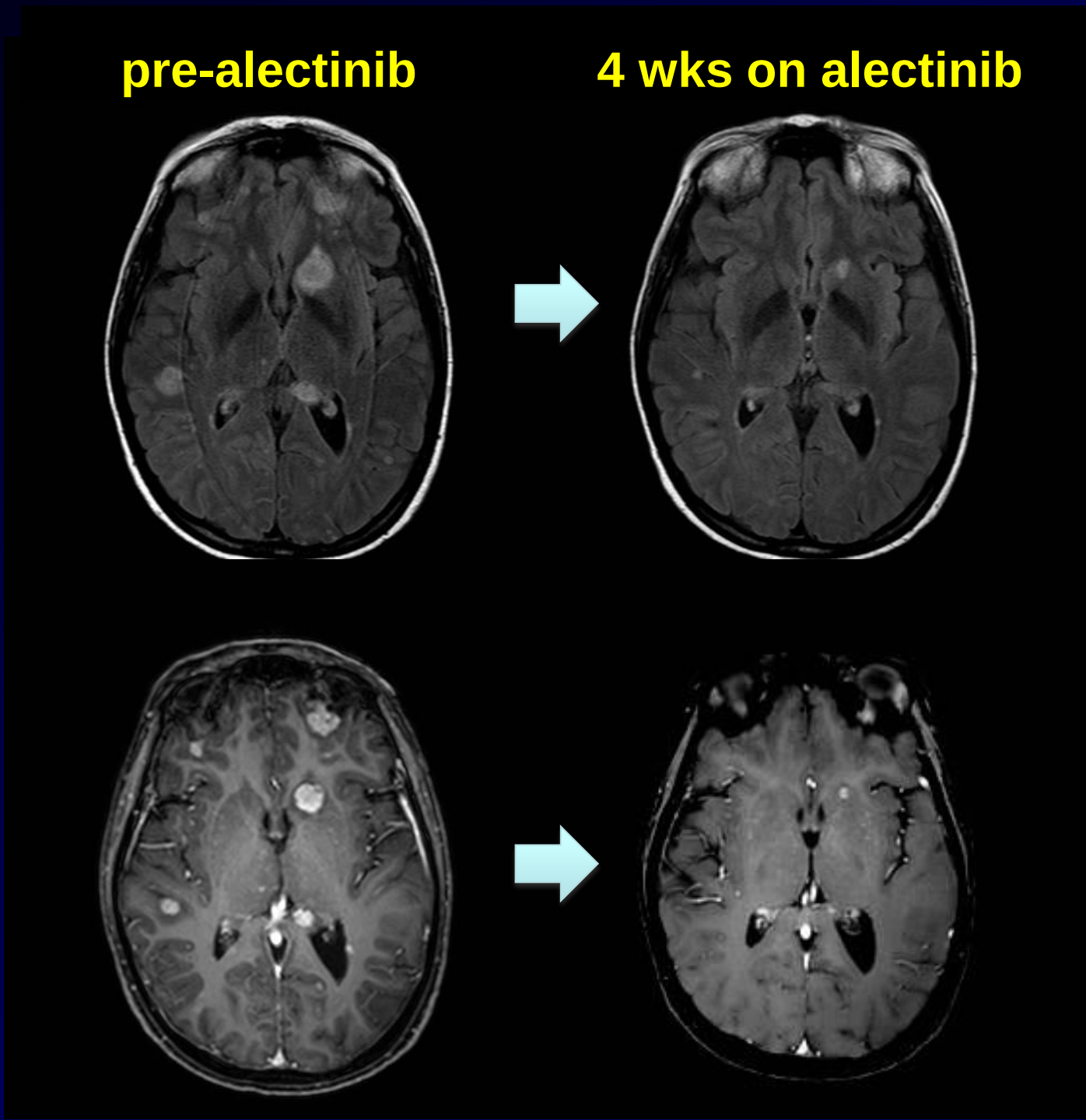
Activity of next-generation ALK-TKIs against CNS mets

Agents (author year)	Brain RR (measurable CNS disease)		Brain RR (measurable and/or non-measurable CNS disease)	
	N	%	N	%
Alectinib (Ou 2016)	20/35	57 %	36/84	42.9%
Alectinib (Shaw 2016)	12/16	75 %	21/52	40%
Ceritinib (Mok 2015)	13/33∞	39.4 %	NR	NR
Ceritinib (Felip 2015)	10/17∞ *	58.8 %	NR	NR
Lorlatinib (Shaw 2015)	5/14 **	33 %	NR	NR
Brigatinib (Camidge 2015)	8/15 **	53 %	19/48	39.5%

∞as BIRC assessed
*ALK-TKI-naïve
**Phase I/II studies; include ALK-TKI-naïve pts; lorlatinib trial include also pts treated with ≥ 1 ALK-TKI

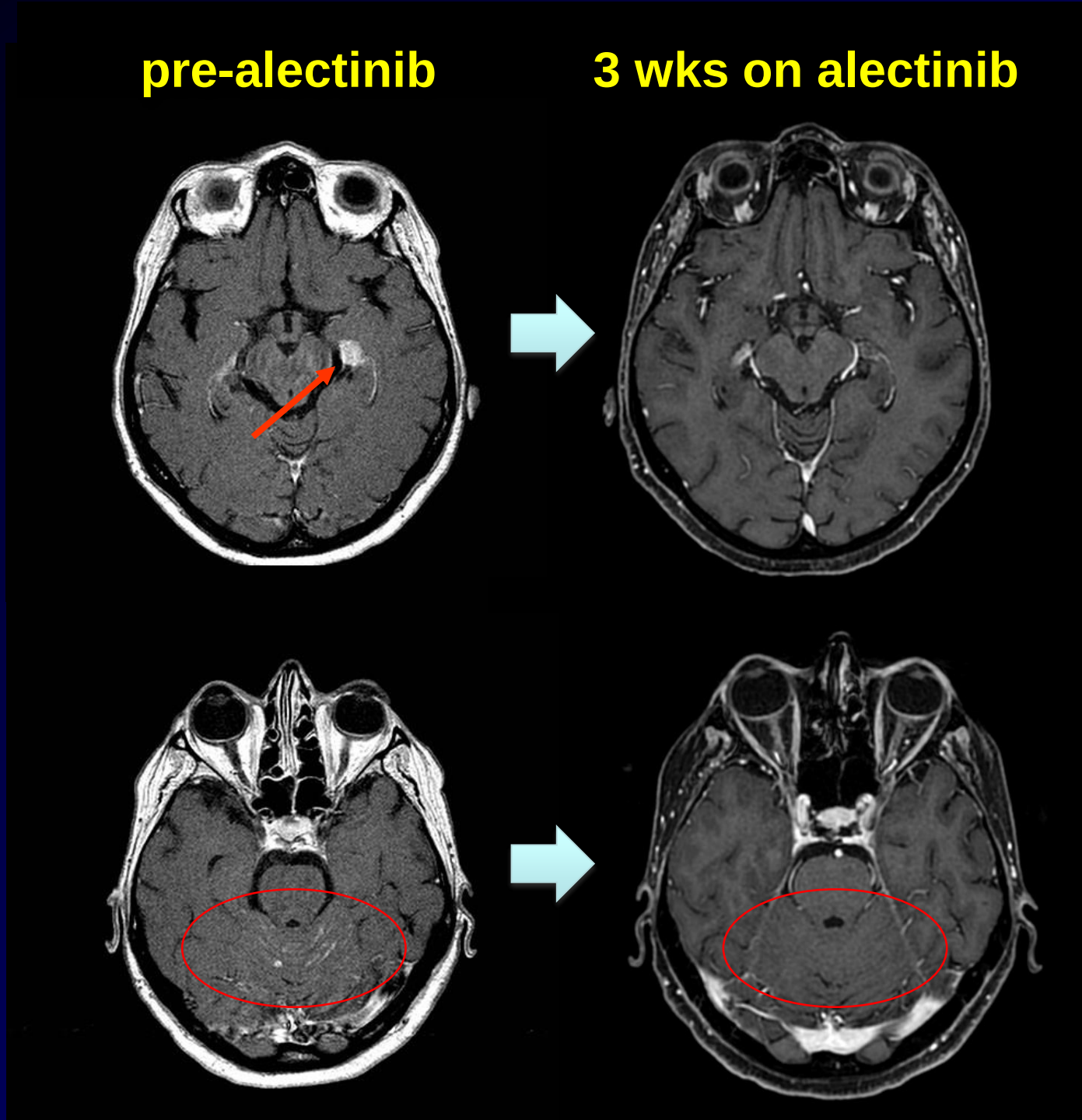
44-year old woman never smoker, stage IV *ALK*+ adenoca., pre-treated with platinum-pemetrexed and then nivolumab; then brain PD treated with WBRT and crizotinib thereafter with SD.

At further isolated CNS progression starts Alectinib 600 mg b.i.d.



46-year old woman never smoker, stage IV *ALK*+ adenoca., 1st line crizotinib with SD

At isolated CNS PD (including LC) starts Alectinib 600 mg b.i.d.



Low CSF penetration rate of both crizotinib and alectinib

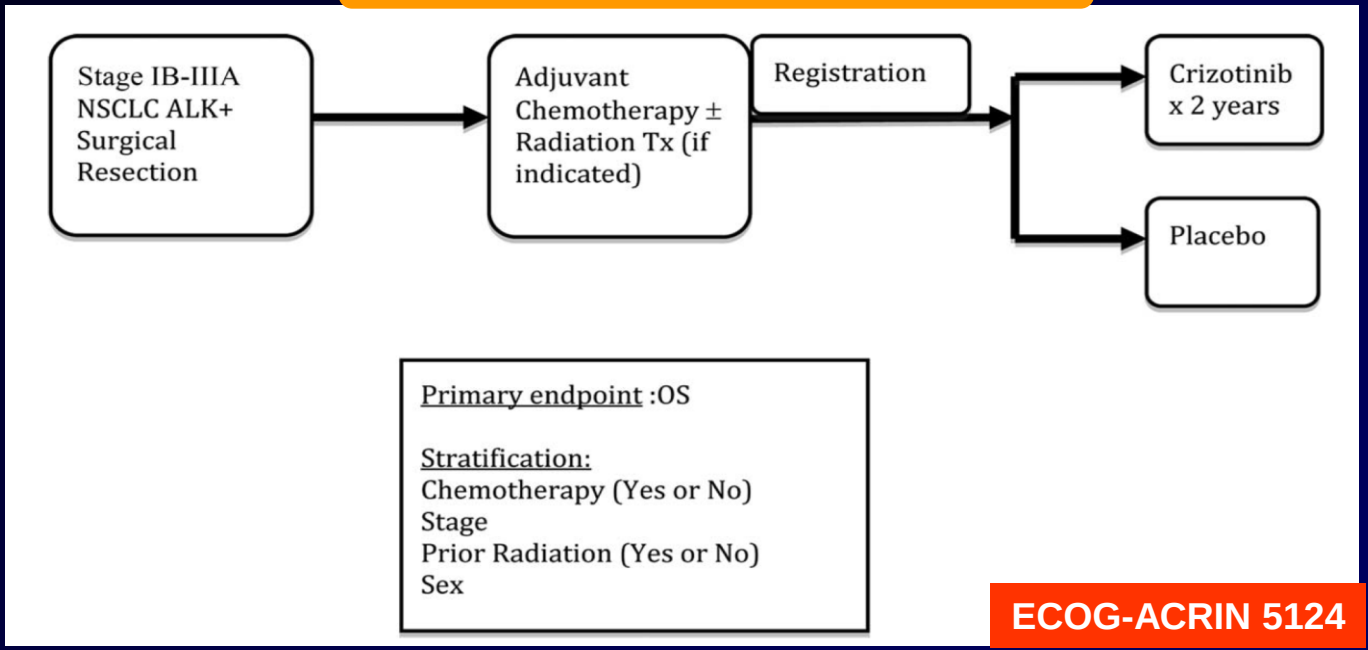
Author	Drug	No. of pts	mean CSF/serum concentration, ng/mL	CSF penetration rate
Costa 2011	Crizotinib	1	0.6/237	0.25%
Metro 2015	Crizotinib	2	0.57/693	0.08%
Gadgeel 2014	Alectinib	5	1.29/NR	NR
Metro (unpl.)	Alectinib	2	1.4/700	0.20%

Outline

- ***Timing of crizotinib***
- ***Safety of crizotinib***
- ***What after crizotinib?***
- ***Brain mets***
- ***Ongoing clinical research***

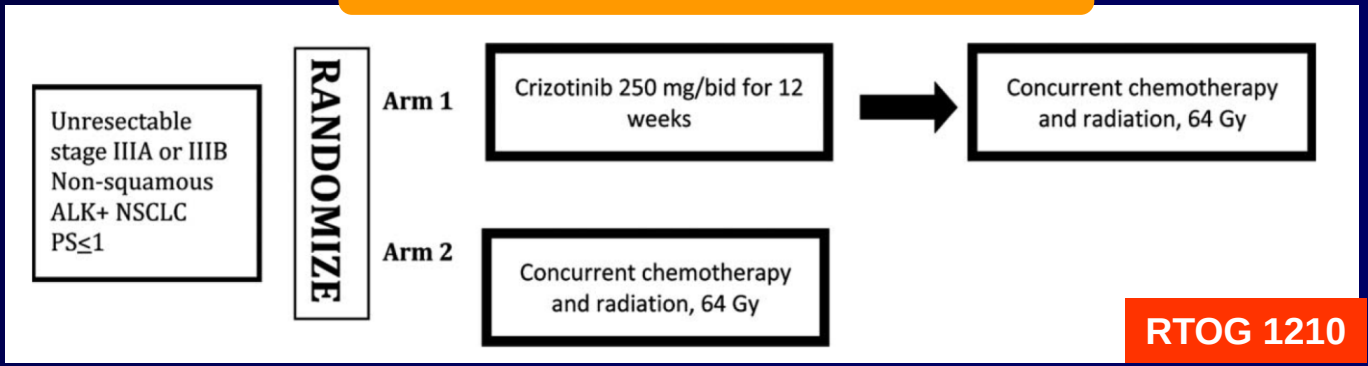
Ongoing crizotinib studies

Adjuvant after surgery



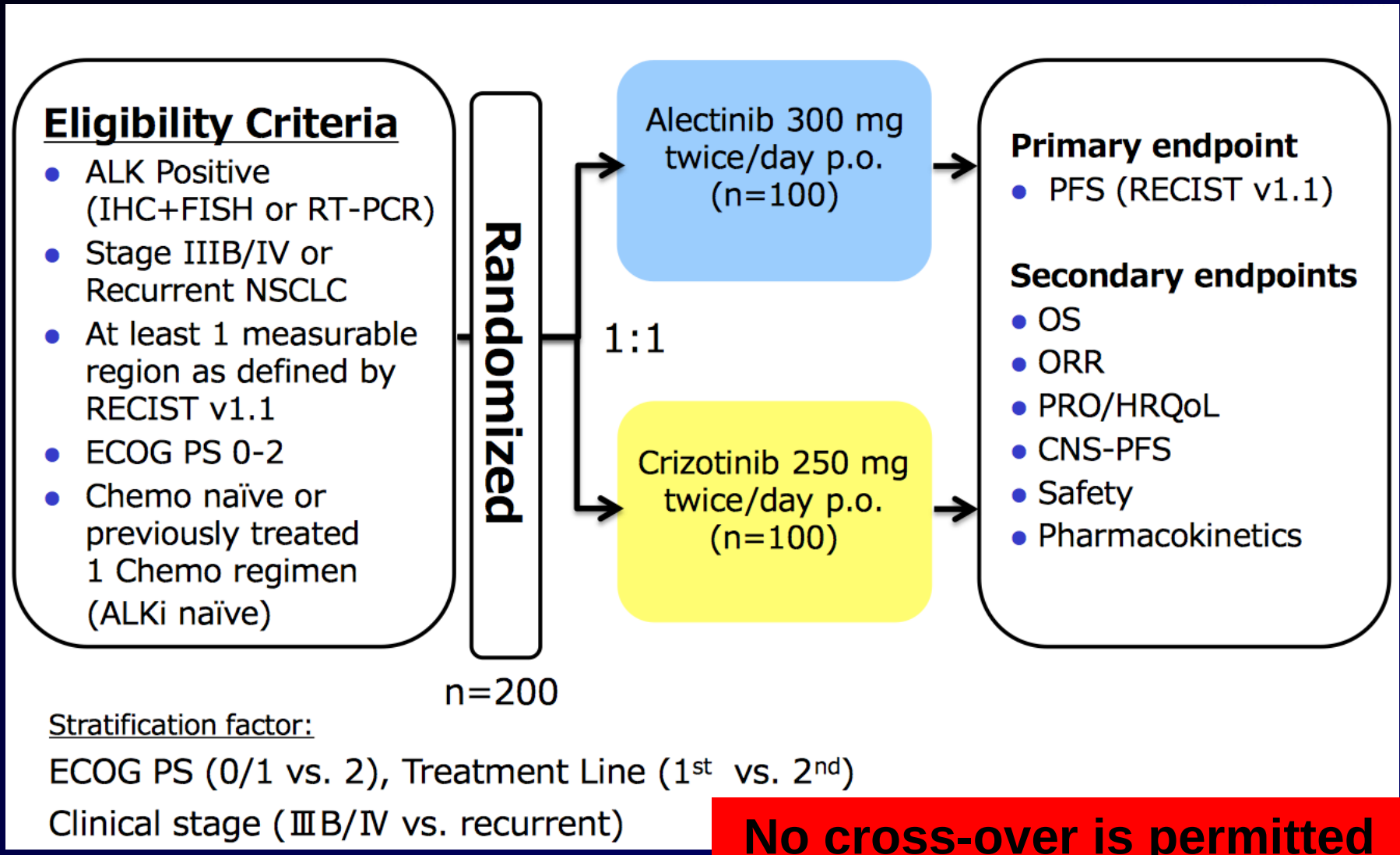
ECOG-ACRIN 5124

In combination with RT



RTOG 1210

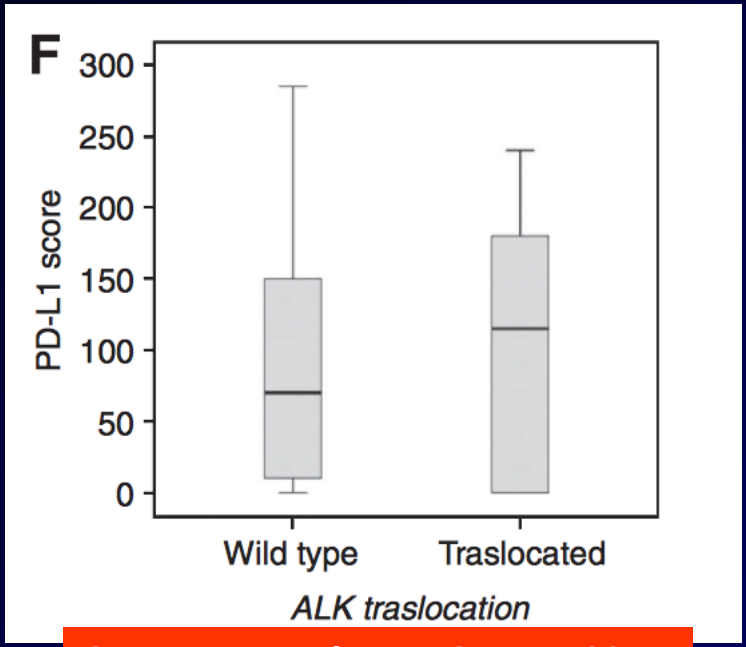
Randomized phase III trial of ALECTINIB vs. CRIZOTINIB (ALEX trial)



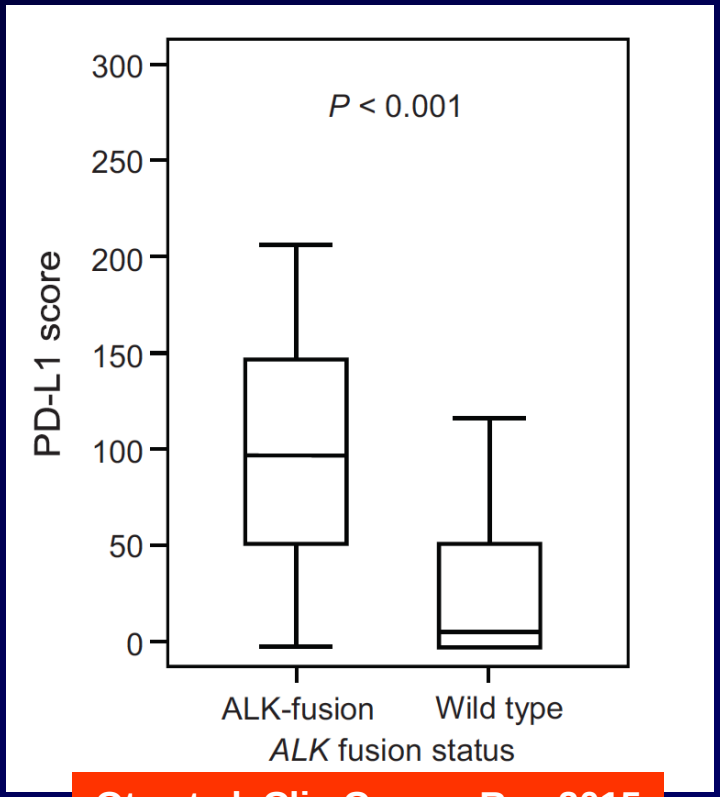
No cross-over is permitted

NCT02075840

ALK-positive NSCLC is significantly associated with PD-L1 expression



Cappuzzo et al. Br J Cancer 2015



Ota et al. Clin Cancer Res 2015

ALK-TKI + immunotherapy: Javelin Lung 102

Patient enrollment is planned to begin in the third quarter of 2016

Target population:
- 1st line *ALK*-positive NSCLC

1:1:1
N = 551 pts

Primary endpoint: PFS (BIRC assessed)

Stratification factor:
- ECOG PS
- Smoking satus

RANDOMIZE

Crizotinib

n = 187 pts

Lorlatinib

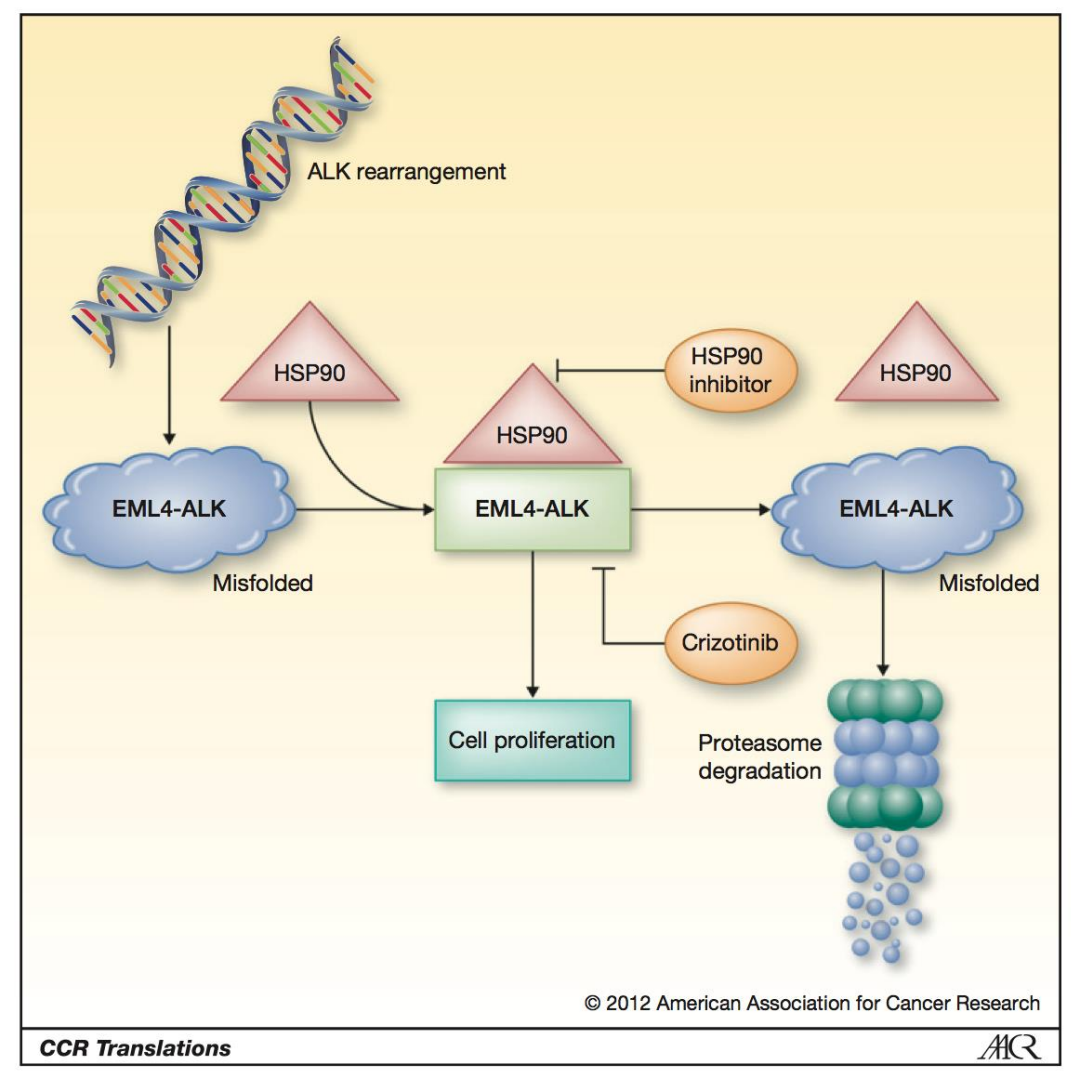
n = 187 pts

Lorlatinib + Avelumab

n = 187 pts

No cross-over is permitted

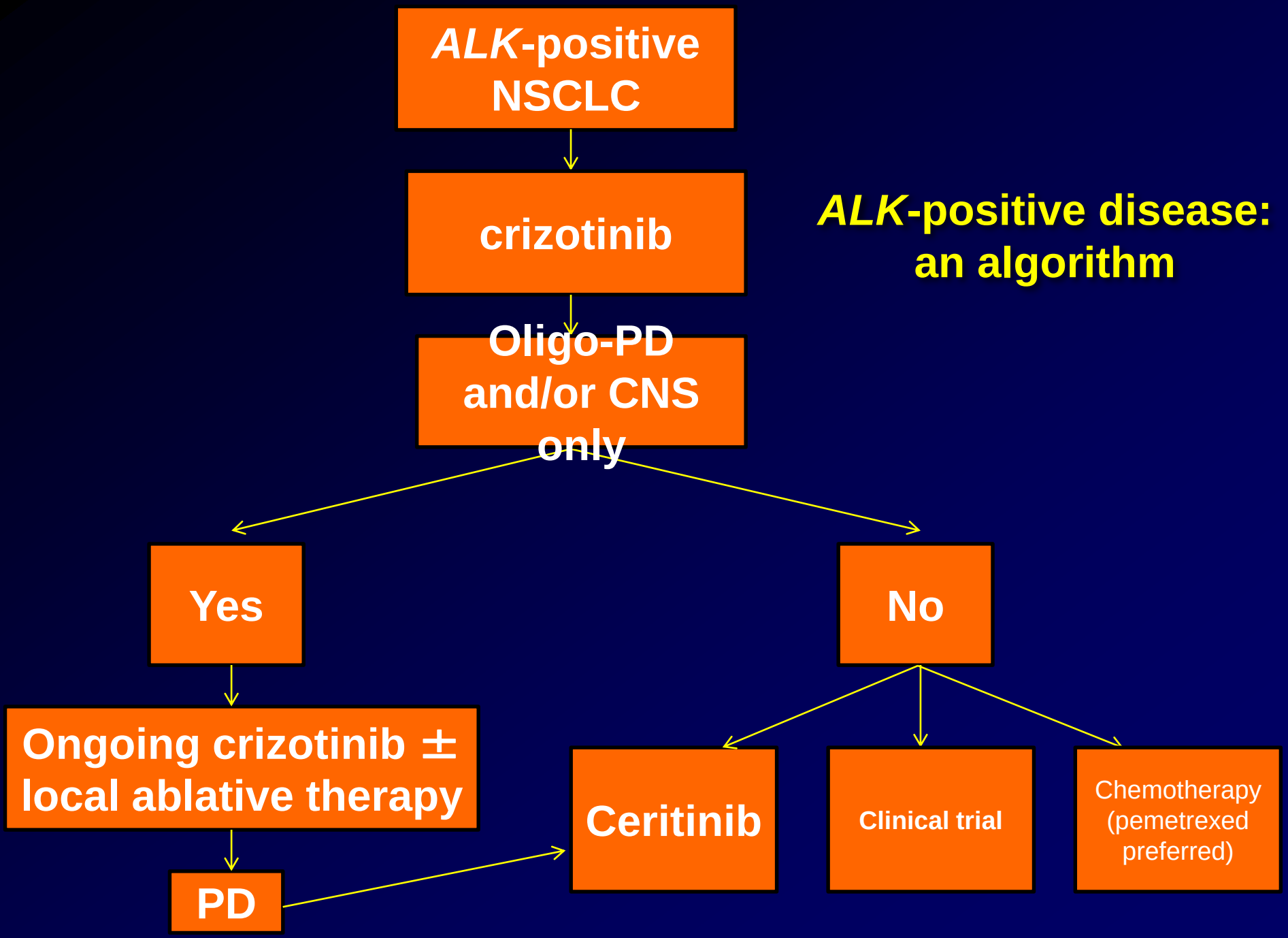
Rationale for dual ALK/Hsp90 inhibition in *ALK*+ advanced NSCLC



From Crystal and Shaw, Clin Cancer Res 2012

Trials of Hsp90-i with or without an ALK-TKI in either ALK-naïve or -resistant *ALK*+ advanced NSCLC

ClinicalTrials.gov Identifier	Regimen	Prior ALK-TKI	Phase	Target accrual
NCT01562015	Ganetespib	No	II	100
NCT01752400	AUY922	Yes (any)	II	20
NCT01712217	Crizotinib + AT13387	No	I	228
	Crizotinib ± AT13387	No	II	
	AT13387 ± Crizotinib	Yes (Crizotinib)	II	
NCT01579994	Crizotinib + Ganetespib	No	I/II	55
NCT01772797	Ceritinib + AUY922	Yes (any)	Ib	142


ALK-positive NSCLC
crizotinib
Oligo-PD and/or CNS only
Yes
No
Ongoing crizotinib ± local ablative therapy
PD
Ceritinib
Clinical trial
Chemotherapy (pemetrexed preferred)
ALK-positive disease: an algorithm

Thanks for your attention

giulio.metro@yahoo.com