Il trattamento del NSCLC metastatico *ALK*+

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Caso clinico n.2

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Clinical case

- 35-year-old lady, with a 15 pack/year smoking history and no relevant comorbidities
- August 2012: Onset of dysphonia; a CT scan shows a 2 cm lesion in the left lower lobe, N2 for multiple lymph node stations, M1b for multiple liver, bony (osteosclerotic) and brain (> 5) lesions → stage IV
- 7 September 2012: Trans-bronchial needle ago-biopsy shows adenocarcinoma and confirms N2 status
- 19 September 2012: *EGFR* status results to be wild type

What's next?

1. Start platinum-based chemotherapy
2. Start platinum-based chemotherapy and look for *ALK* rearrangement
3. WBRT followed by platinum-based chemotherapy
4. Look for *ALK* rearrangement and wait for the result. If positive enroll the patient in a front-line study of chemotherapy vs. crizotinib (PROFILE 1014)

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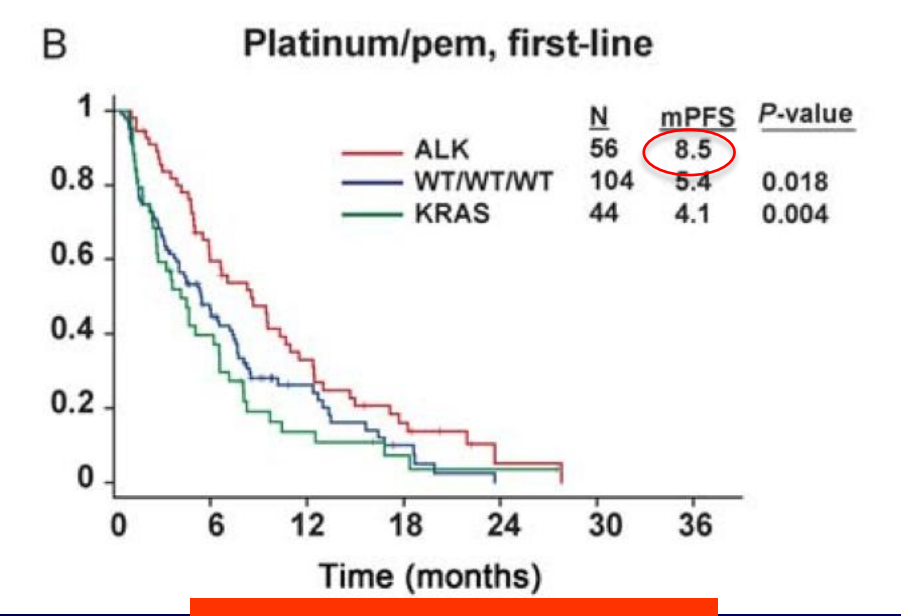
- 24 September 2012: The patient starts i.v. Cisplatin 75 mg/m^2 + Pemetrexed 500 mg/m^2 every 21 days
- Following three cycles of chemotherapy a CT scan shows partial response with complete response in the CNS
- The specimen that was sent for *ALK* testing turns out to be *ALK*-positive

What's next?

1. Continue cisplatin/pemetrexed up to 6 cycles
2. Stop chemotherapy and start crizotinib (compassionate use) as maintenance treatment

Platinum/pemetrexed is highly active in *ALK*-positive patients



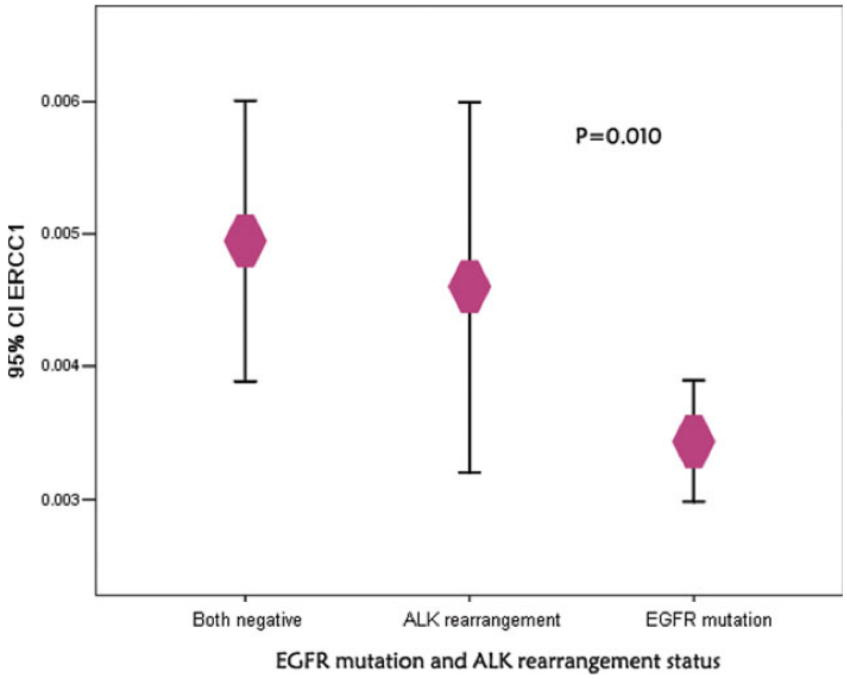
Shaw et al. Ann Oncol 2013

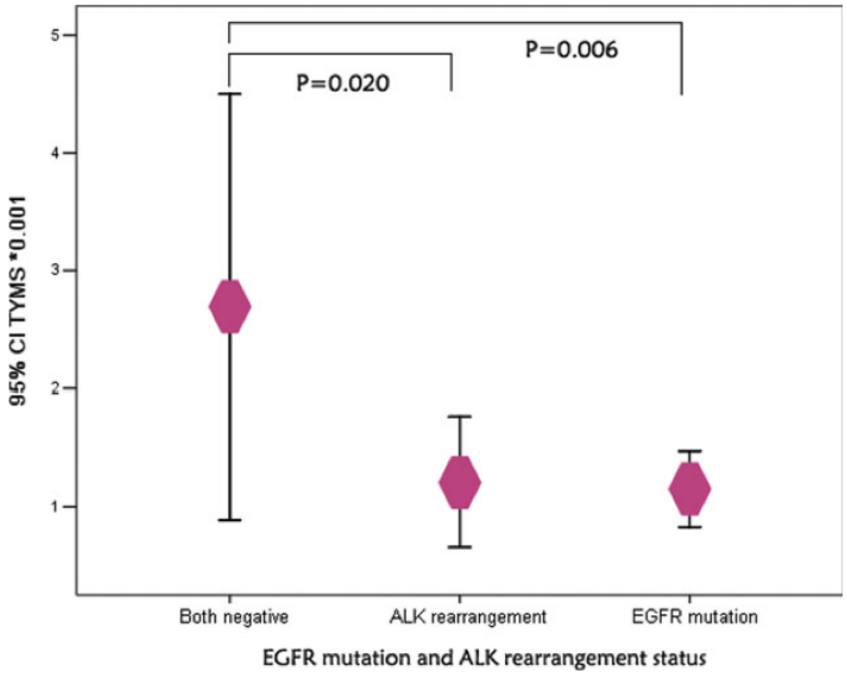
Gefitinib	mPFS
Carbo/Tax (IPASS)	6.3
Carbo/Tax (NEJ002)	5.4
Cis/Doc (WJTOG 3405)	6.3
Cis/Gem (First-SIGNAL)	6.3

Erlotinib	mPFS
Cis or Carbo/Gem or Doc (EURTAC)	5.2
Carbo/Gem (OPTIMAL)	4.6

Afatinib	mPFS
Cis/Pem (LUX-Lung 3)	6.7
Cis/Gem (LUX-Lung-6)	5.6

ERCC1 and TYMS expression according to genotype

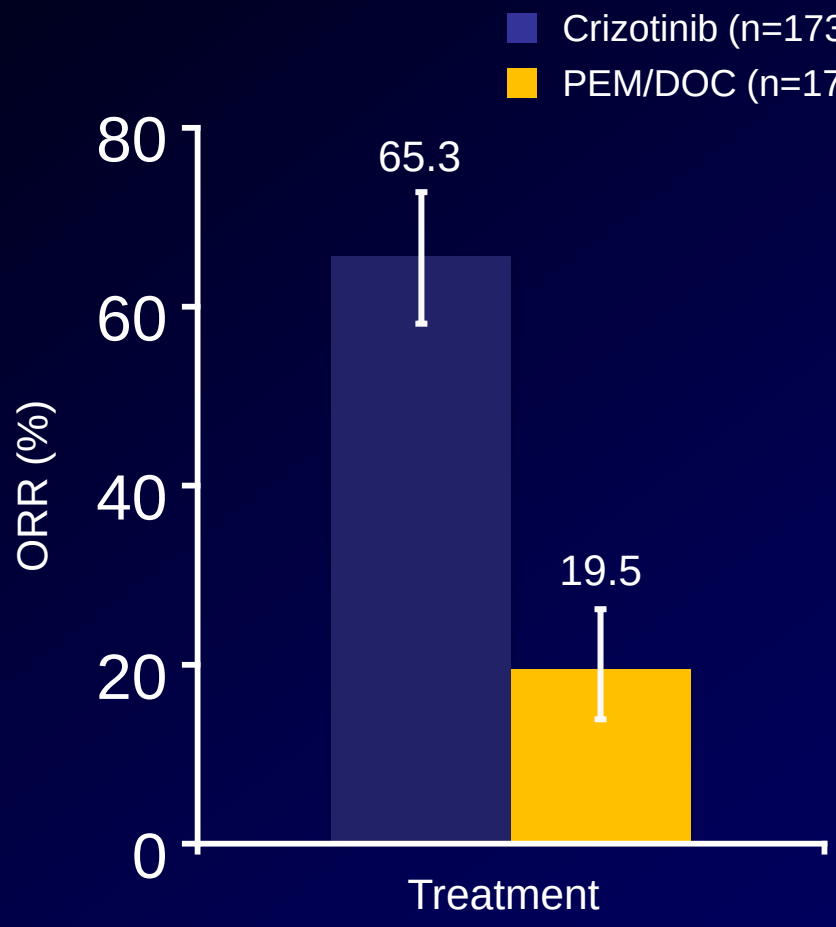


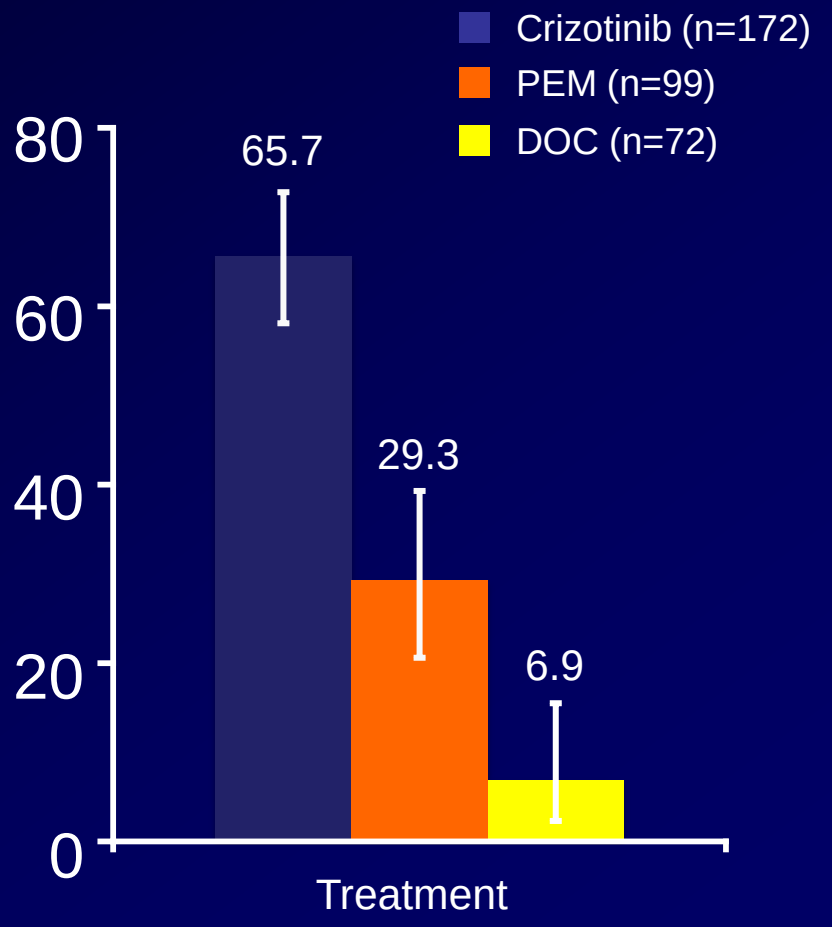


Ren et al. Cancer 2012

PROFILE 1007:
ORR[a] by Independent Radiologic Review

ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.001





[a]RECIST v1.1

Shaw et al. ESMO 2012

Prior pemetrexed exposure leaves unaltered the chances of responding to Crizotinib

Best Response Data (Evaluable Patients) According to RECIST 1.1 criteria[a]

Patient Cohort	CR	PR	SD	PD	ORR
PEM-CRIZ: Pemetrexed (n = 9)	1 (11)	5 (55)	2 (22)	1 (11)	6 (66)
PEM-CRIZ: Crizotinib (n = 19)	1 (5)	15 (79)	3 (16)	0 (0)	16 (84)
CRIZ-PEM: Pemetrexed (n = 4)	1 (25)	2 (50)	0 (0)	1 (25)	3 (75)
CRIZ-PEM: Crizotinib (n = 3)	0 (0)	2 (66)	1 (33)	0 (0)	2 (66)

Data are presented as n (%).
Abbreviations: ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
[a]Data not analyzed statistically because of small sample sizes.

Berge et al. Clin Lung Cancer 2013

What's next?

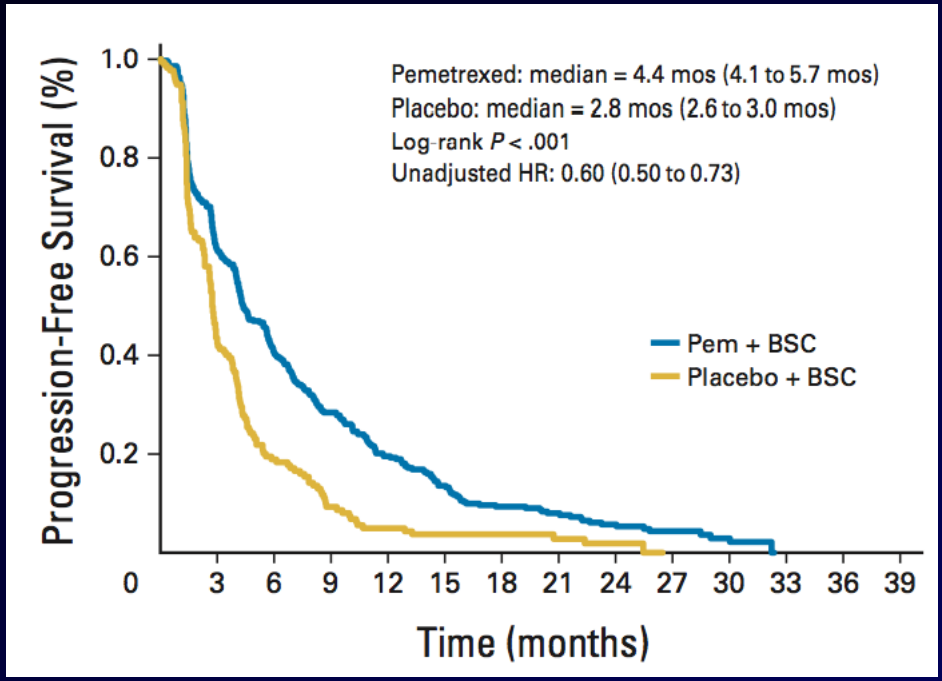
1. Continue cisplatin/pemetrexed up to 6 cycles
2. Stop chemotherapy and start crizotinib (compassionate use) as maintenance treatment

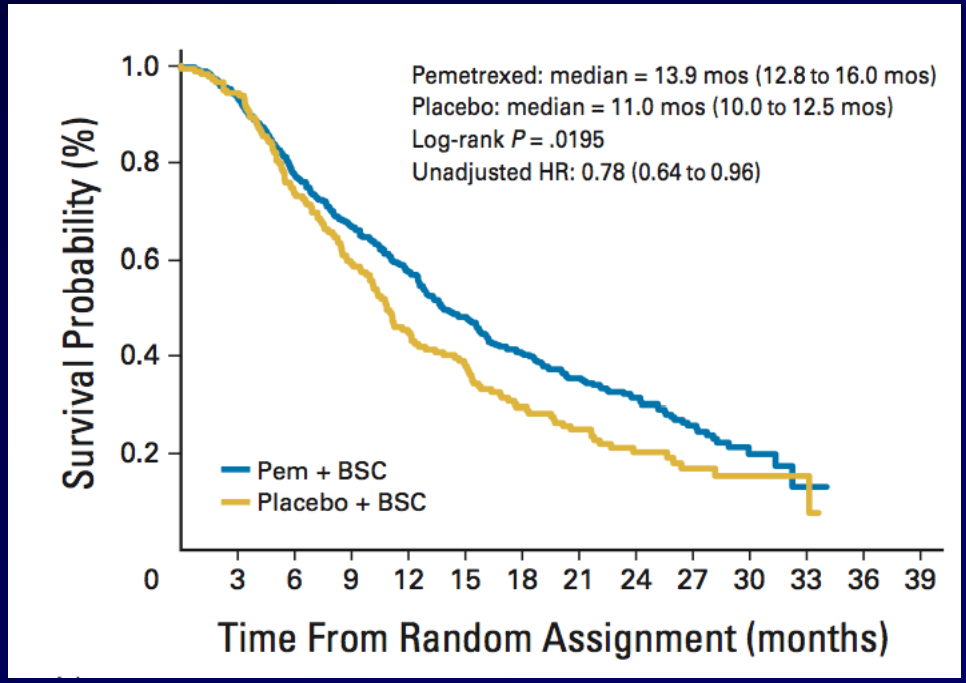
- 20 February 2013: Following six cycles a CT scan confirms partial response and complete response in the CNS

What's next?

1. Continue with Pemetrexed maintenance
2. Continue with crizotinib (compassionate use) as maintenance treatment
3. Stop chemotherapy and start follow-up with crizotinib treatment reserved at disease progression

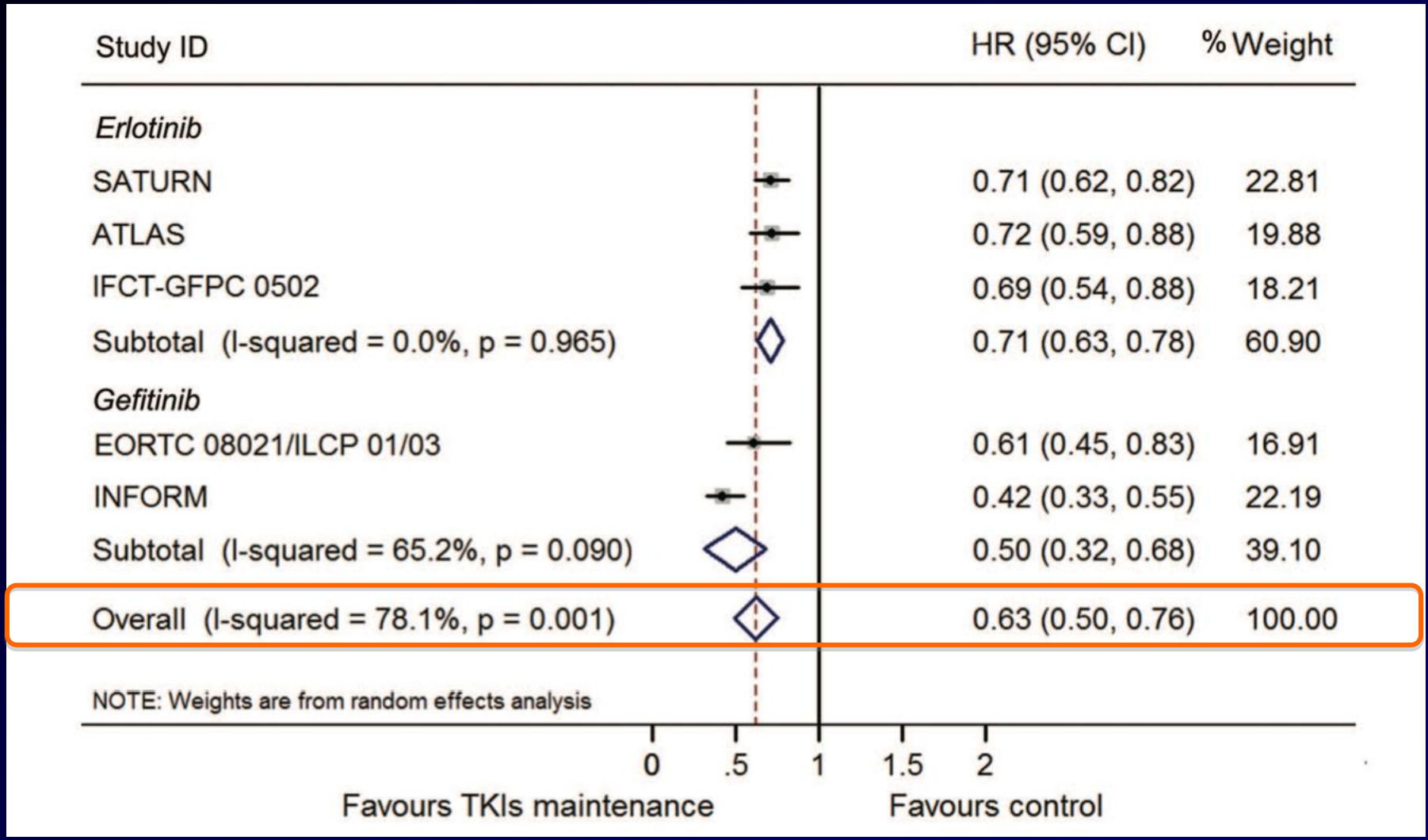
PARAMOUNT trial





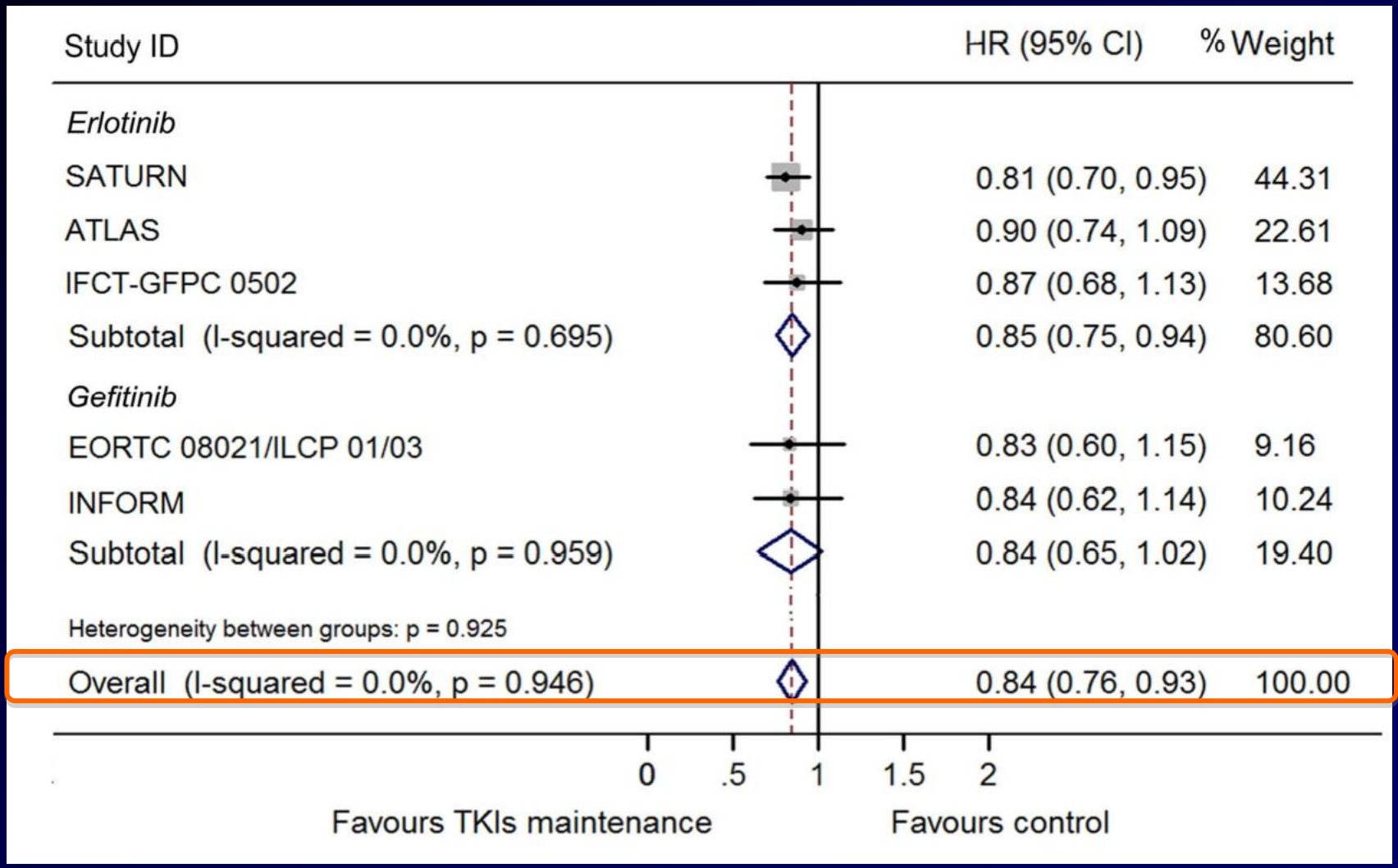
Paz-Ares et al. J Clin Oncol 2013

Meta-analysis of HR for PFS with an EGFR-TKI as maintenance



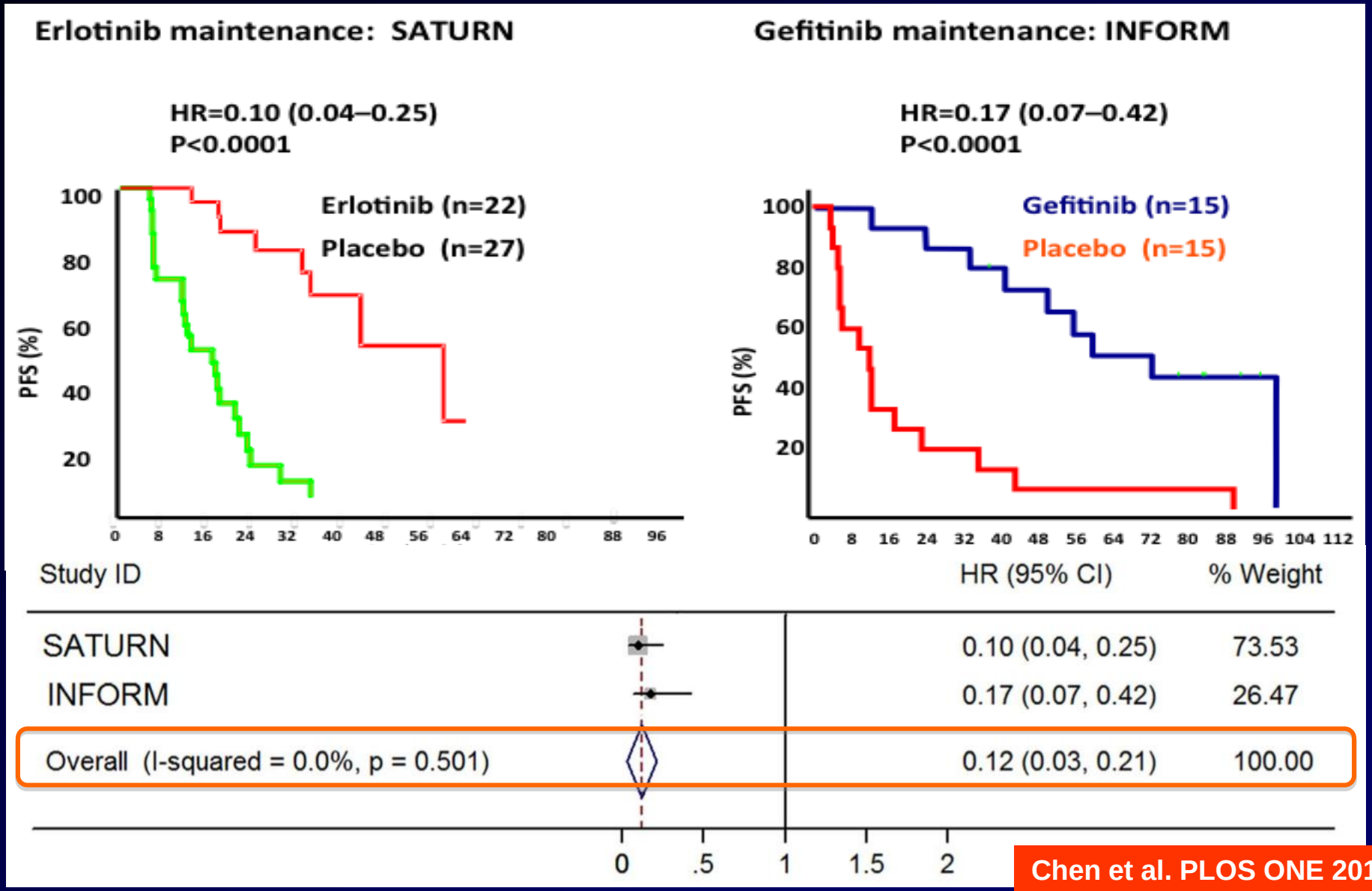
Chen et al. PLOS ONE 2013

Meta-analysis of HR for OS with an EGFR-TKI as maintenance



Chen et al. PLOS ONE 2013

EGFR-TKI maintenance in molecularly selected patients



Chen et al. PLOS ONE 2013

What's next?

1. Continue with Pemetrexed maintenance
2. Continue with crizotinib (compassionate use) as maintenance treatment
3. Stop chemotherapy and start follow-up with crizotinib treatment reserved at disease progression

Primary resistance to crizotinib

- 15 May 2013: Clinico-radiological CNS progression (confusional state); a CT scan shows extracranial disease progression at multiple sites
- 13→ 20/6/13: WBRT (20 Gy in 5 fractions)

What's next?

1. Switch to second-line chemotherapy (e.g. docetaxel)
2. Enroll the patient in a trial with a 2nd generation ALK-TKI (LDK-378) available for patients pretreated with chemotherapy and crizotinib

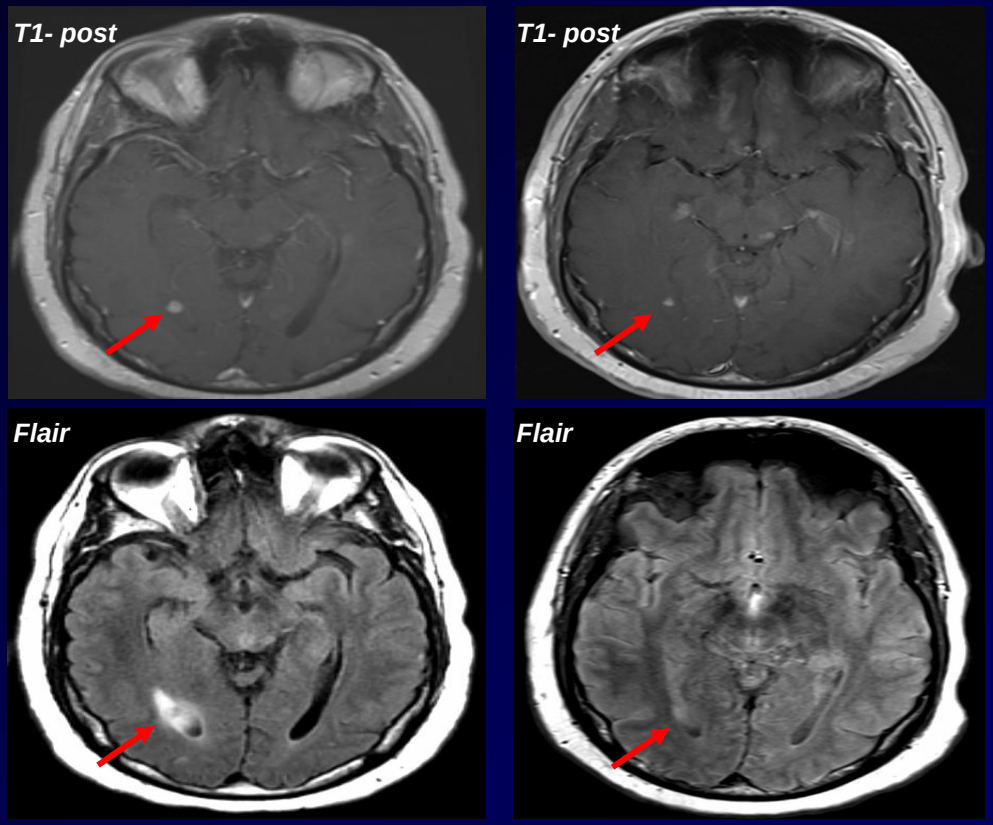
2nd generation ALK-TKIs in clinical development

Drug	Inhibition of secondary L1196M 'gatekeeper' mutation	Company	Clinical stage
LDK378	Yes	Novartis	Phase II/III
AP-26113	Yes	Ariad	Phase I/II
Alectinib	Yes	Roche/Chugai	Phase I/II
TSR-011	Yes	Tesaro	Phase I
NMS-E628	Yes	Nerviano Medical	Phase I
ASP-3026	Yes	Astellas	Phase I
X-376 and -396	Yes	Xcovery	Phase I
CEP-28122	Yes	Cephalon	Preclinical

Activity of 2nd generation ALK-TKIs: crizotinib-naïve vs. crizotinib-refractory

Author	Drug	RR Crizotinib-naïve N (%)	RR following Crizotinib N (%)
Shaw, ASCO 2013	LDK378	21/35 (60)	45/79 (57)
Camidge, IASLC 2013	AP26113	3/3 (100)	19/31 (61)
Nakagawa, ASCO 2013 (Japan)	Alectinib	43/46 (93.5)	-
Gadgeel, IASLC 2013	Alectinib	-	47 (54.5)

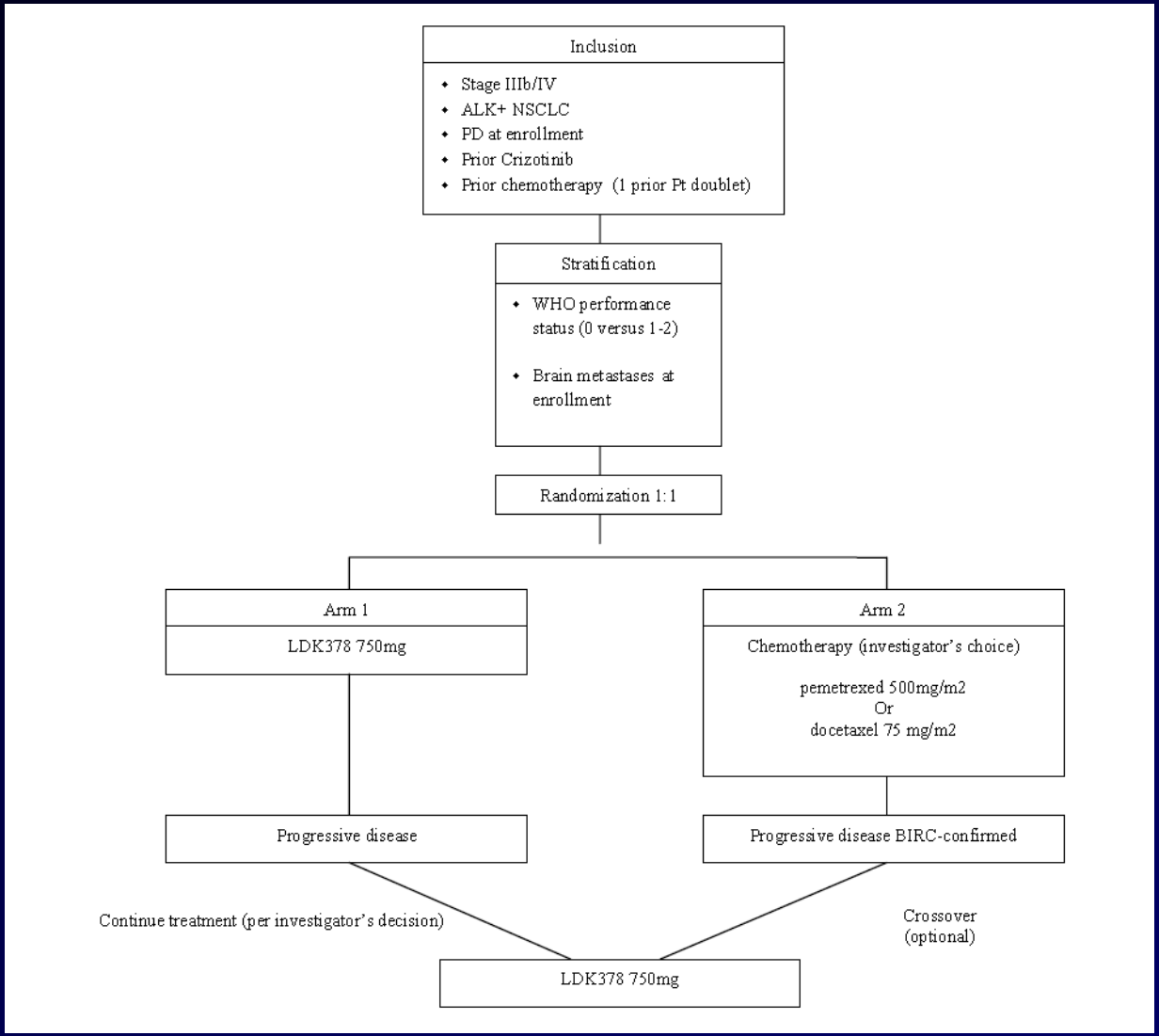
Anti-tumor activity of LDK-378 in the CNS



Baseline **After 6 weeks of LDK378**

Shaw et al. ASCO 2013

Post-crizotinib: 2nd generation ALK-TKI or chemotherapy?



NCT01828112

What's next?

1. Switch to second-line chemotherapy (e.g. docetaxel)
2. Enroll the patient in a trial with a 2nd generation ALK-TKI (LDK-378)

- 4 July 2013: Start of LDK-378 at 750 mg/die
- 29 August 2013: Dose reduction to 450 mg following GI toxicity (nausea/vomiting refractory to standard anti-emetics)
- 19 September 2013: A CT scan shows partial response at extra-cranial measurable lesions. Partial response in the brain is also present
- 28 November 2013: A CT scan confirms extra-cranial response but shows PD in the CNS. LDK-378 is continued
- 9 January 2014: Deterioration of clinical conditions. A MRI of the brain is compatible with meningeal carcinomatosis. LDK-378 is discontinued
- 23 February 2014: Death of the patient

Discussion

1. What is the best first-line for *ALK*-positive NSCLCs?
2. What is the role for crizotinib maintenance in *ALK*-positive patients following induction chemotherapy?
3. Post-chemotherapy and crizotinib: chemotherapy or 2nd ALK-TKI?
4. CNS as significant cause of morbidity/mortality in *ALK*-positive patients. How to increase drug effectiveness in the CNS?

Discussion

1. What is the best first-line for *ALK*-positive NSCLCs? (Profile 1014, NCT01828099)
2. What is the role for crizotinib maintenance in *ALK*-positive patients following induction chemotherapy? we will never know
3. Post-chemotherapy and crizotinib: chemotherapy or 2nd ALK-TKI? Indirect evidence suggests 2nd ALK-TKI
4. CNS as significant cause of morbidity/mortality in *ALK*-positive patients. How to increase drug effectiveness in the CNS? New molecules needed

Thanks for your attention

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