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Discussion: Abstracts #4380, 4390, 4400, 4410

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Disclosures

- Honoraria
  - Boehringer Ingelheim, Pfizer
- Consultant
  - Boehringer Ingelheim, Pfizer

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ALK rearrangements in NSCLC

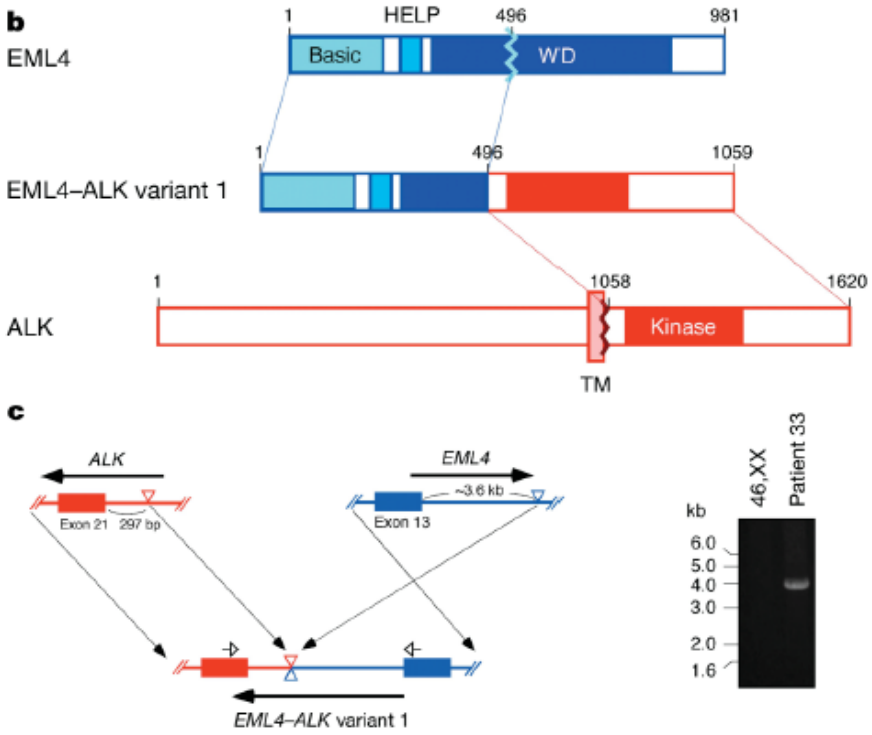
Vol 448|2 August 2007|doi:10.1038/nature05945 nature

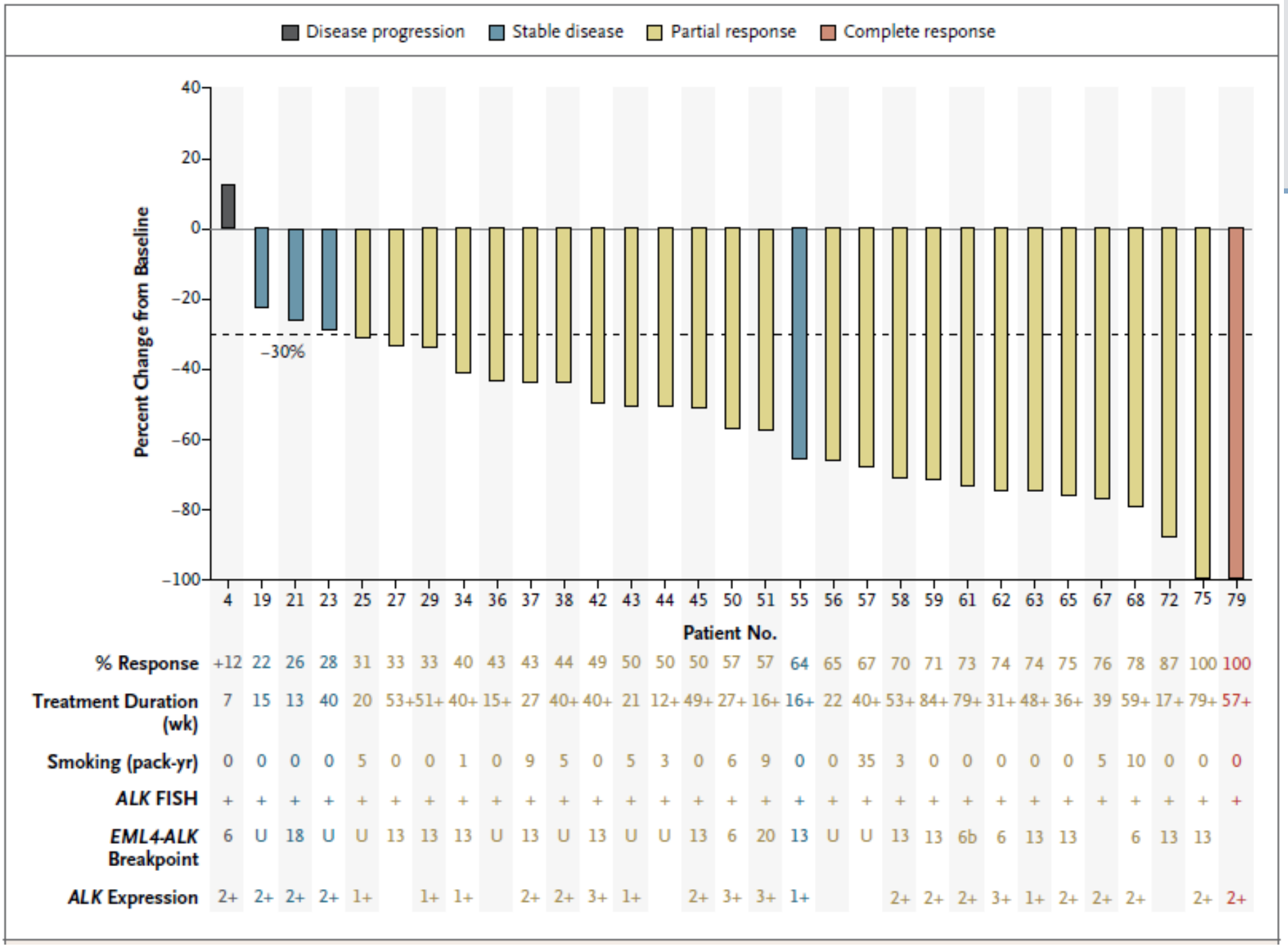
ARTICLES

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

Identified from cDNA screening library from 62yr male smoker adenocarcinoma




Disease progression
Stable disease
Partial response
Complete response
Percent Change from Baseline
40
20
0
−20
−40
−60
−80
−100
−30%
4 19 21 23 25 27 29 34 36 37 38 42 43 44 45 50 51 55 56 57 58 59 61 62 63 65 67 68 72 75 79
Patient No.
% Response +12 22 26 28 31 33 33 40 43 43 44 49 50 50 50 57 57 64 65 67 70 71 73 74 74 75 76 78 87 100 100
Treatment Duration (wk) 7 15 13 40 20 53+ 51+ 40+ 15+ 27 40+ 40+ 21 12+ 49+ 27+ 16+ 16+ 22 40+ 53+ 84+ 79+ 31+ 48+ 36+ 39 59+ 17+ 79+ 57+
Smoking (pack-yr) 0 0 0 0 5 0 0 1 0 9 5 0 5 3 0 6 9 0 0 35 3 0 0 0 0 0 5 10 0 0 0
ALK FISH +
EML4-ALK Breakpoint 6 U 18 U U 13 13 13 U 13 U 13 U U 13 6 20 13 U U 13 13 6b 6 13 13 6 13 13
ALK Expression 2+ 2+ 2+ 2+ 1+ 1+ 1+ 2+ 2+ 3+ 1+ 2+ 3+ 3+ 1+ 2+ 2+ 2+ 3+ 1+ 2+ 2+ 2+ 2+ 2+

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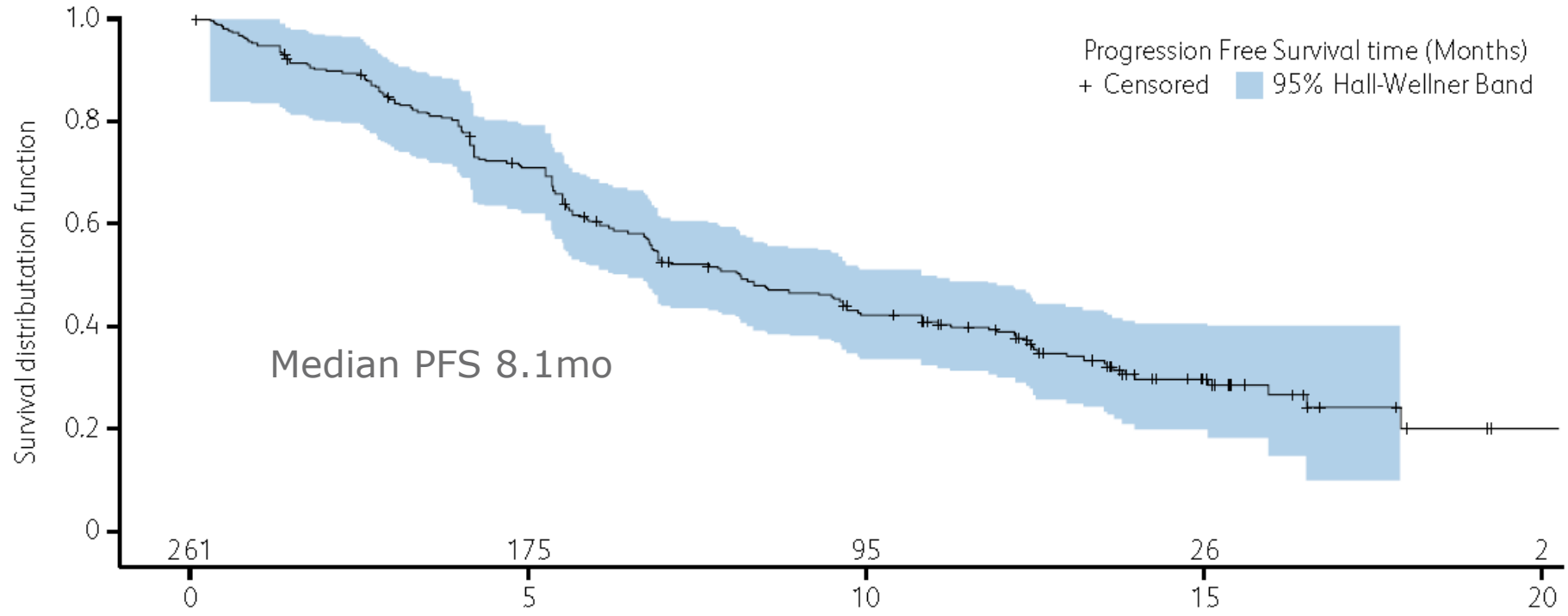
PROFILE 1005; single arm phase 2, crizotinib, ALK FISH+

Figure 2. Kaplan–Meier plot showing progression-free survival in the mature population.



target lesions.

*Three patients not eligible due to prior adjuvant treatment only.

Kim et al. ASCO 2012

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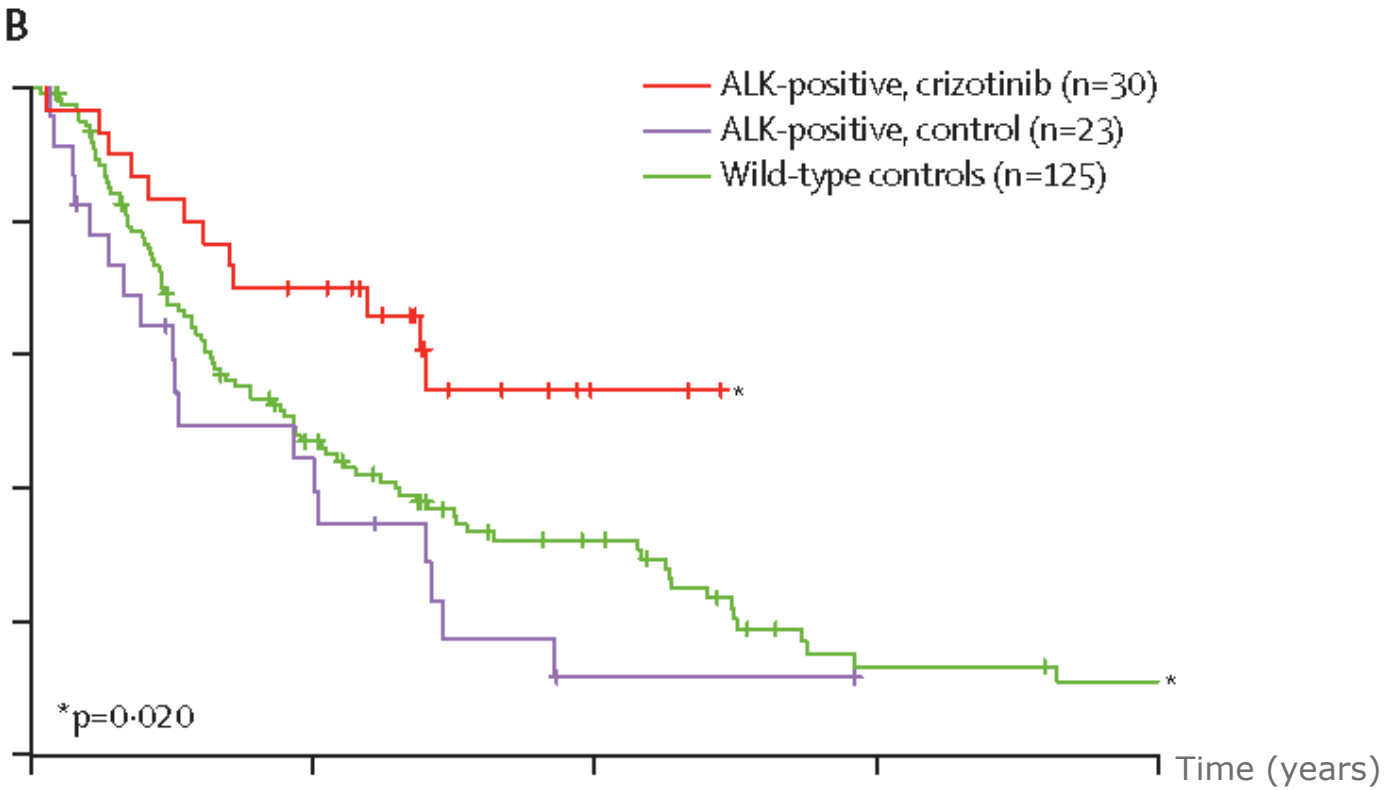
Retrospective OS survival analysis



Number at risk					
ALK crizotinib	30	20	3	0	0
ALK controls	23	9	1	0	0
Wild-type controls	125	50	24	7	5

Shaw Lancet Oncol 2011

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Crizotinib toxicities: PROFILE 1005

Table 3. Treatment-related AEs in ≥10% of patients.

	Crizotinib 250 mg (mature population) (n=261) n (%)		Crizotinib 250 mg (overall population) (N=901) N (%)	
Adverse event	All grade	Grade 3/4	All grade	Grade 3/4
Any AE	245 (93.9)	76 (29.0)	827 (91.8)	220 (24.4)
Nausea	148 (56.7)	1 (0.4)	423 (46.9)	7 (0.8)
Vomiting	116 (44.4)	2 (0.8)	352 (39.1)	7 (0.8)
Vision disorder*	154 (59.0)	0 (0)	468 (51.9)	1 (0.1)
Diarrhea	106 (40.6)	2 (0.8)	369 (41.0)	9 (1.0)
Constipation	86 (33.0)	0 (0)	249 (27.6)	1 (0.1)
Peripheral edema	72 (27.6)	0 (0)	211 (23.4)	3 (0.3)
Fatigue	64 (24.5)	4 (1.5)	163 (18.1)	18 (1.9)
Decreased appetite	59 (22.6)	0 (0)	167 (18.5)	2 (0.2)
Alanine aminotransferase increased	45 (17.2)	19 (7.2)	146 (16.2)	36 (3.9)
Dysguesia	43 (16.5)	0 (0)	149 (16.5)	0 (0)
Dizziness	40 (15.3)	0 (0)	95 (10.5)	0 (0)
Neutropenia	36 (13.8)	22 (8.4)	84 (9.3)	50 (5.5)
Aspartate aminotransferase increased	33 (12.6)	5 (1.9)	106 (11.8)	12 (1.3)

*Includes visual impairment, photopsia, vision blurred, vitreous floaters, photophobia and diplopia.

Kim et al. ASCO 2012

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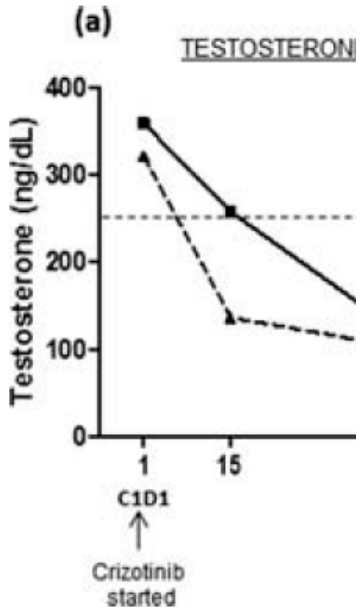
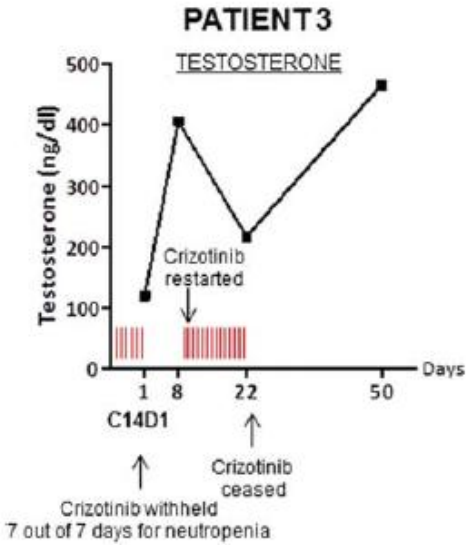
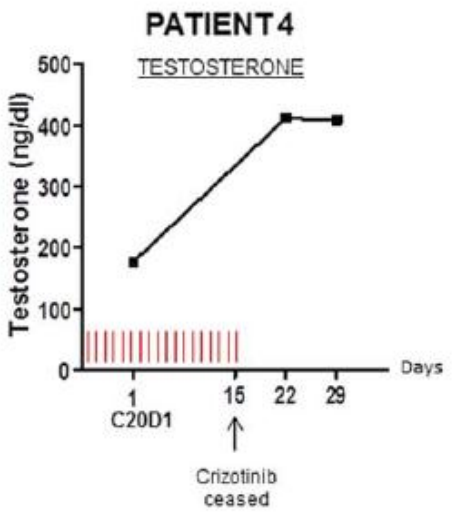
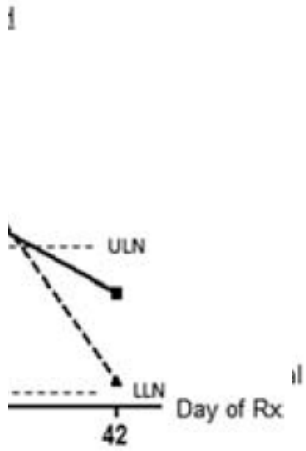
Clinical Issues: Hypogonadism

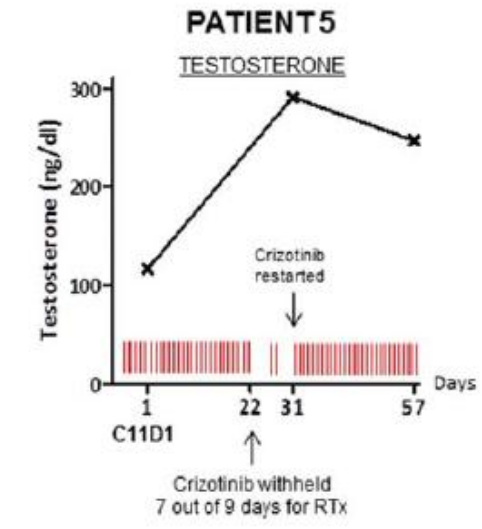
Testosterone leve
(<241ng/dl) in:

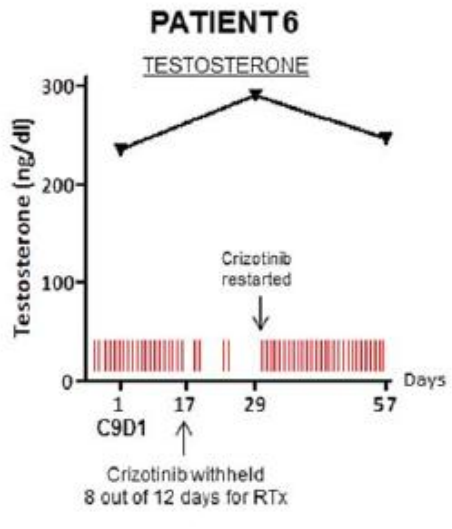












Weickhardt et al. Cancer (*2012*)

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Crizotinib resistance mechanisms: ALK dominant

Table 1. *ALK* FISH comparison before and after crizotinib on evaluable patients

	Pre-crizotinib			Post-crizotinib				
Patient no.	*ALK* FISH% cells positive	*ALK* FISH pattern[a]	Abnormal *ALK* copy number/cell[b]	*ALK* FISH	*ALK* FISH% cells positive	ALK FISH pattern[a]	Abnormal *ALK* copy number/cell[b]	*ALK* change
4	78%	sR	1.2 sR	Positive	90%	sR	1.5 sR	Same
5	37%	split	0.4sR,sG	Positive	51%	split	0.5 sR,sG	Same
6	86%	split	0.8 sR,sG	Positive	70%	split	0.8 sR,sG	Same
7	28%	split	0.3 sR,sG	Positive	82%	split	1.5 sR,sG	**CNG**
8	48%	split	0.5 sR,sG	Positive	66%	split	2.2 sR,sG	**CNG**
9a	80%	sR	1.2sR	**Negative**	2%	NA		**Loss**
9b				Positive	56%	sR	0.9 sR	Same
10[c]	28%	mix	0.3 sR, 0.2 sG	Positive	30%	mix	0.3 sR, 0.2 sG	Same
11	48%	split	0.5 sR,sG	Positive	56%	split	0.7 sR,sG	Same
12	26%	split	0.3 sR,sG	**Negative**	8%	NA		**Loss**
13[c]	60%	split	0.6 sR, sG	Positive	48%	split	0.6 sR, sG	Same
14	68%	sR	1.2 sR	Positive	92%	sR	1.5 sR	Same

NOTE: Bold text denotes a significant result related to the mechanism of resistance.

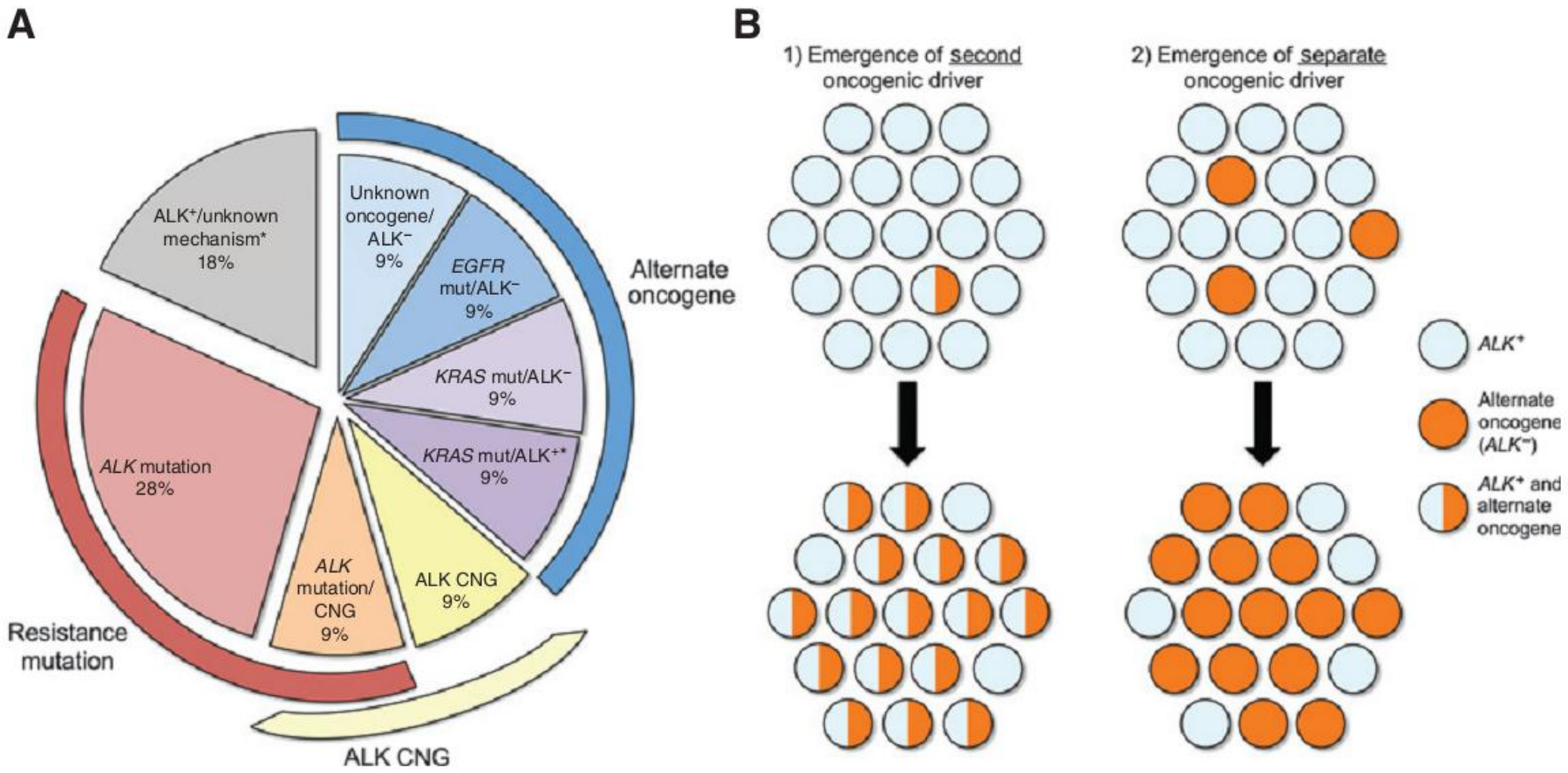
[a]sR, single red; sG, single green; split, split red/green; mix, split red/green and single red.

[b]Rounded to the nearest tenth decimal.

[c]Patients with intrinsic resistance.

Choi NEJM 2010; Camidge 2012 Nat Rev Clin Oncol 2012; Doebele Clin Canc Res 2012

Crizotinib resistance mechanisms: ALK non-dominant



Doebele Clin Canc Res 2012

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Unanswered questions for Target (ALK)-directed therapy

1. Can other therapies improve (crizotinib) efficacy?

2. Can other therapies improve (crizotinib) toxicity?

3. What therapies should be given on acquired (crizotinib/EGFR-TKI) resistance?

4. Which therapy minimizes primary (ALK) therapy-resistance?

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Future directions in Target (ALK)-directed therapy

Anaplastic lymphoma kinase (ALK) inhibitor	Pfizer	Crizotinib NA PF-02341066	Dual small molecule ATP-competitive inhibitor	ALK, c-Met, ROS
	Novartis	NA NA LDK378	Small molecule inhibitor	ALK
	Astellas	NA NA ASP3026	Small molecule inhibitor	ALK
Heat shock protein (HSP)-90 inhibitors	Synta Pharmaceuticals	Ganetespib NA STA-9090	Small molecule inhibitor (nongeldanamycin)	HSP-90
	Novartis	NA NA AUY922	Isoxazole-based compound (nongeldanamycin)	HSP90
	Bristol-Myers Squibb/Kosan Biosciences	Alvespimycin NA KOS-1022/17-DMAG	Benzoquinone antineoplastic antibiotic	HSP-90
	Bristol-Myers Squibb/Kosan Biosciences	Tanespimycin NA KOS-953/17-AAG	Benzoquinone antineoplastic antibiotic	HSP-90

JTO 2011 Santa Monica suppl

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AUY922 Phase 2 data: ALK+

Study Design

NCT01124864

► Prev

► Prior

AUY922 70 mg/m^2
KRAS-activating mutation
n=28

AUY
EGF

Primary endpoint – effic
1. Response (CR or PF
Secondary endpoints

Null hypo
Alternative hypothesis (efficacious

CR, complete response; OS, overall survival; PFS,
TKI, tyrosine kinase inhibitor; WHO PS, World He

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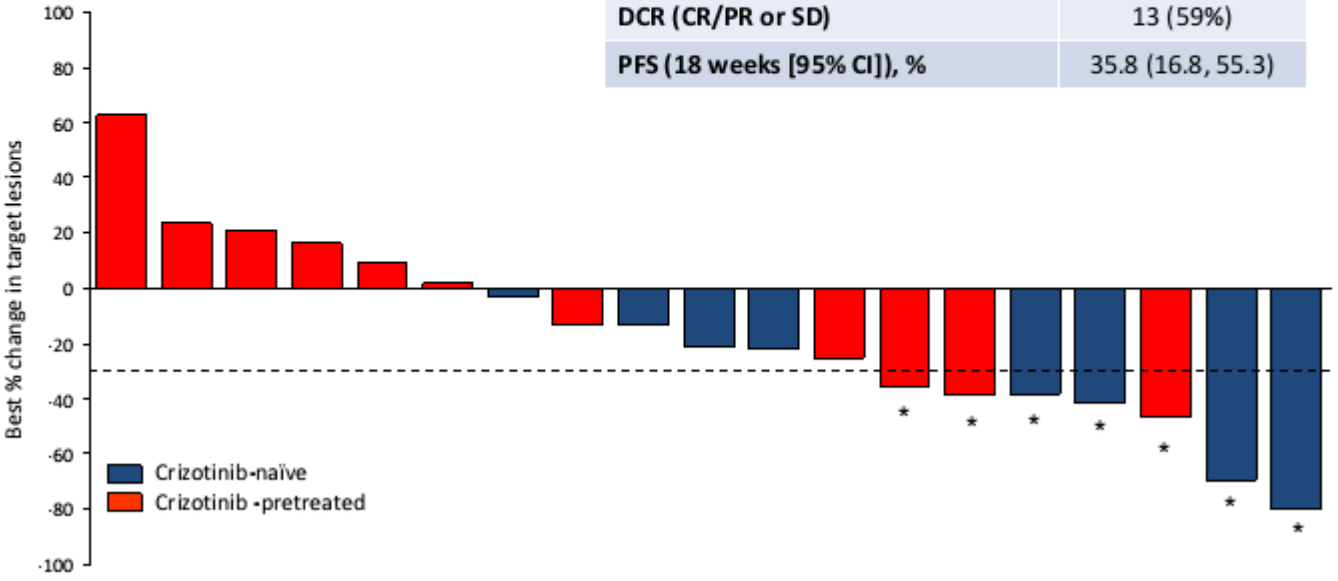
Best CT Response: ALK+ Stratum Patients (n=19†/22)

ALK+ (n=22)	
ORR (any PR)	7 (32%)
DCR (CR/PR or SD)	13 (59%)
PFS (18 weeks [95% CI]), %	35.8 (16.8, 55.3)



*Confirmed responses; †Patients with at least one post-baseline scan.

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AUY922 Phase 2 data: EGFR M+ relapsed after EGFR-TKI

LUX 1 Afatinib

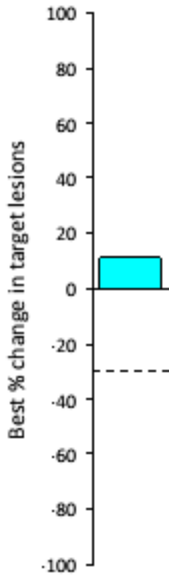
Best CT Response: *EGFR*-mutant P

EGFR T

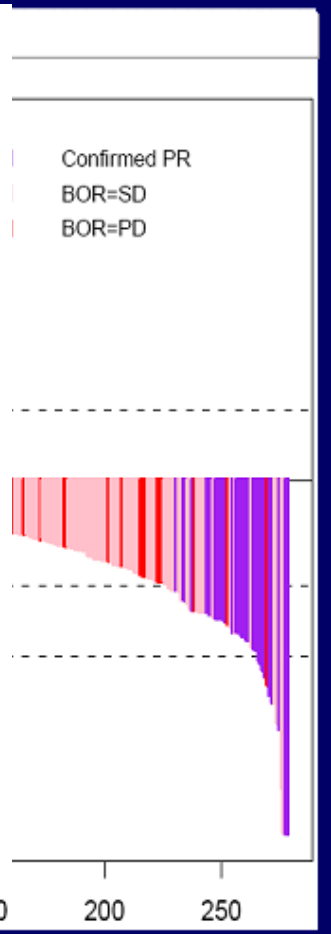
Adverse Events (All Grades, >10% and Grade 3/4) Suspected as Study Drug-Related

Adverse event (AE, all grades)	All grades (N=121)	Grade 3 and 4 (N=121)
Eye disorders*	89 (74)	8 (7)
Diarrhea	82 (68)	7 (6)
Nausea	47 (39)	0 (0)
Asthenia	35 (29)	4 (3)
Vomiting	31 (26)	2 (2)
Fatigue	25 (21)	5 (4)

AEs by preferred term unless otherwise indicated
*System organ class



- Most AEs were Grade 1 or 2
  - Reversible mainly Grade 1 and 2 eye disorders were most commonly photopsia and visual impairment (both 20%)



Stable disease for ≥8 weeks	198 (51%)	194 (50%)
Disease control (partial response+stable disease) for ≥8 weeks	227 (58%)§	236 (61%)§

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Miller Lancet Oncol 2012

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AP26113 first in human data

AP26113 Phase 1/2 Study

Adver

Preferred term (AE
Nausea
Fatigue
Diarrhea
Pain in extremity
Vomiting
Abdominal pain
Constipation
Decreased appetite
Muscle spasms
Peripheral edema
Pneumonia

Ora
30
dai

AP26113 Phase 1/2 Study
Preliminary Anti-Tumor Activity

Mutation Status History	Patients Evaluable for Response[a] N	Partial Response N
ALK+ (translocation)	11[b] (60, 90, 90, 90, 120, 180, 180, 180, 180, 240, 240 mg)	8 (60 , 90, 90, 90, 180, 180, 240, 240 mg)
Crizotinib-resistant	9	6
Crizotinib-naive	2	2
EGFRm (7 T790M by history)	11[c] (60, 60, 90, 120, 120, 120, 120, 180, 180, 180, 240 mg)	1 (120 mg)
EGFR TKI-resistant	9[d]	1
EGFR TKI-naive	2	0
Neither ALK nor EGFRm	5 (30, 30, 30, 90, 120 mg)	0

7

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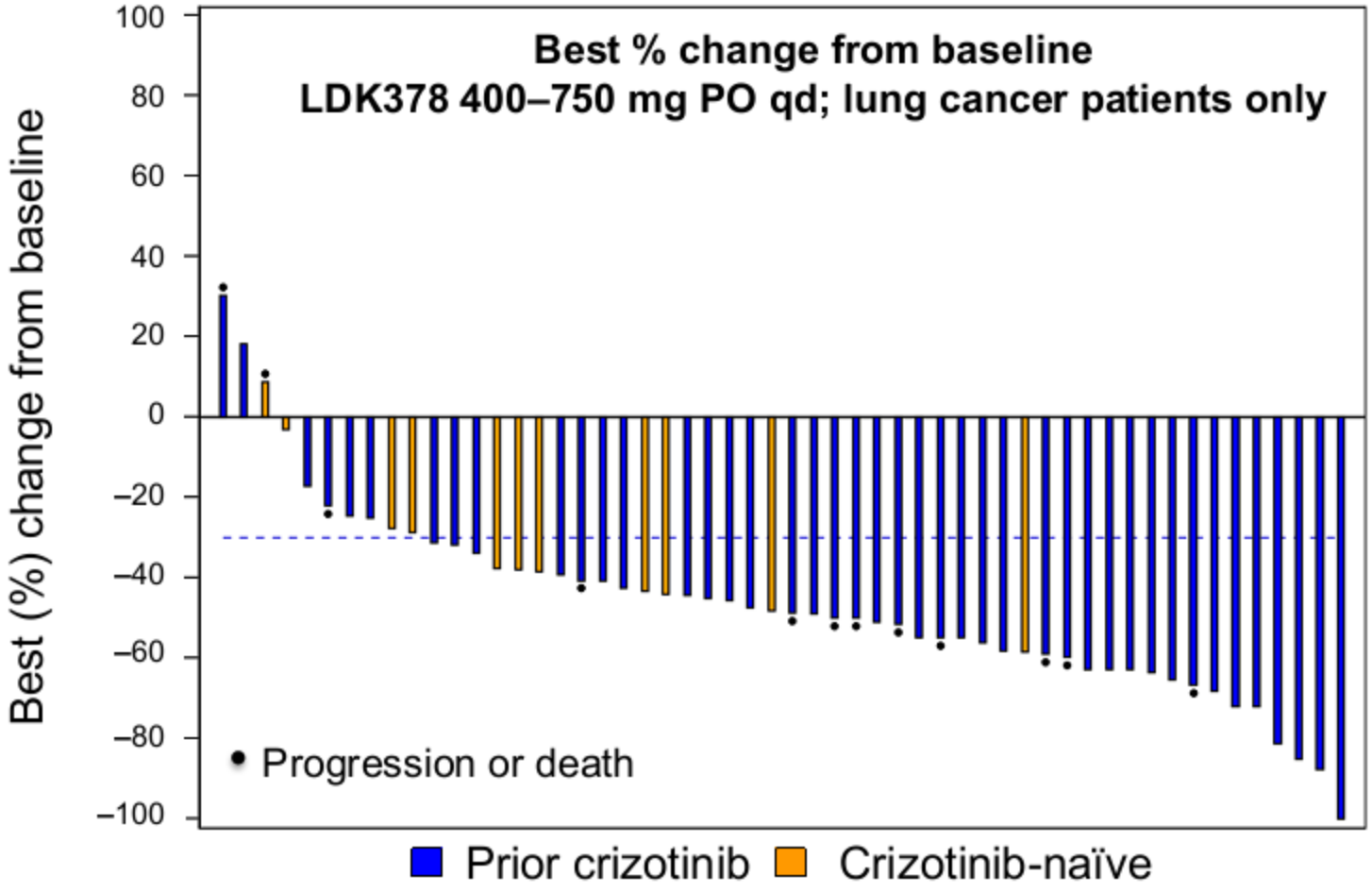
Marked activity of LDK378 in advanced ALK+ NSCLC



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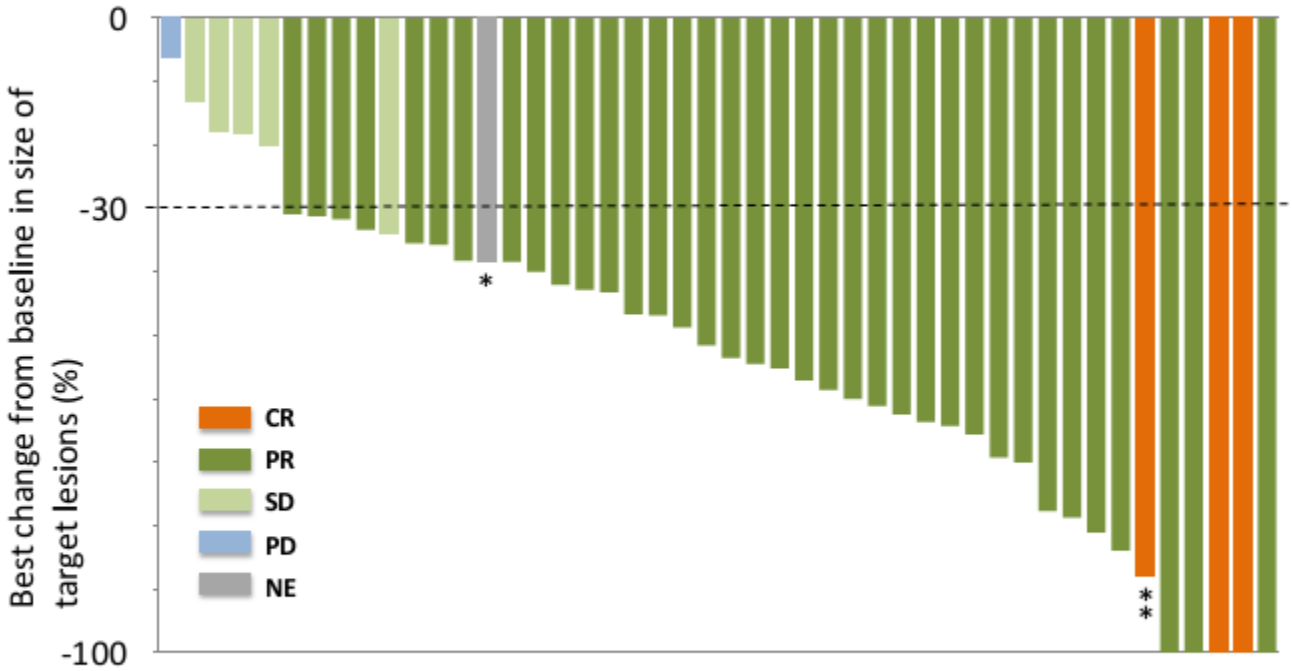
CH5424802 Interim data

Treatment related AEs

Body system	Adverse
Visual disorder	vision blu
	visual imp
	vitreous haemorrh
Gastrointestinal disorder	Nausea
	Diarrhea
	Vomiting

Visual disorders were r

A waterfall plot of tumor shrinkage



N=46, investigator assessment

*Indeterminate response by early stopping due to safety reasons
**Per RECIST 1.1, percent change from baseline for subjects with response of CR can be less than 100% when lymph nodes are identified as target lesions.

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www.esmo2012.org

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Unanswered questions for Target (ALK)-directed therapy

1. Ca
2. Ca
3. Wh /EGFR-TKI) res
4. Wh ce?

OPTIONS

POTENTIAL FUTURE OPTIONS

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HIGHER EDUCATION FUNDING COUNCIL FOR ENGLAND hefce

Acknowledgements

Imperial College,
National Heart and Lung Institute

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Lung Unit

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