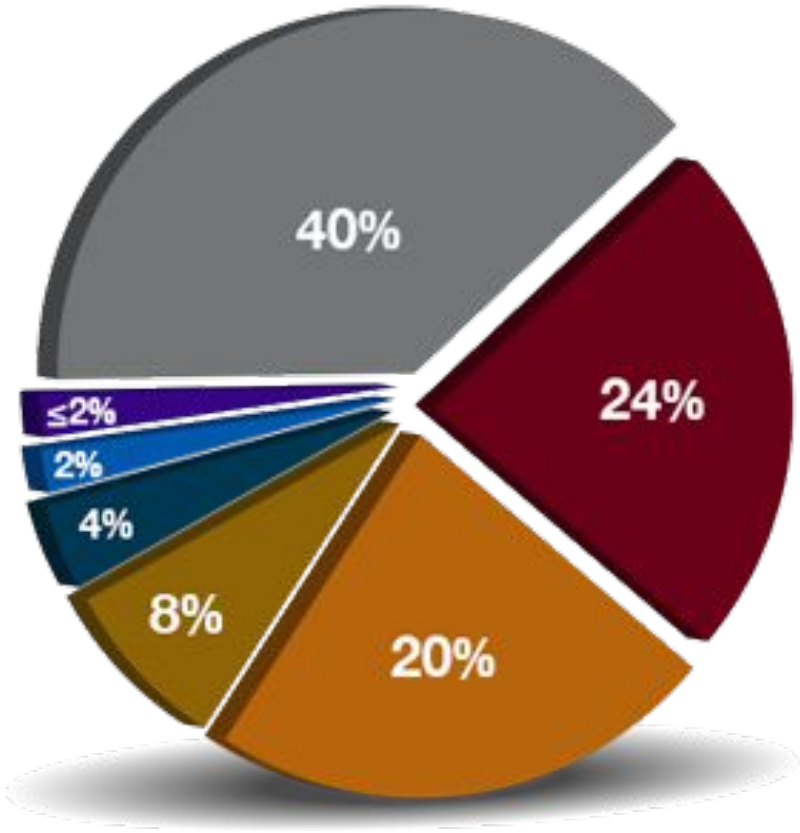
NSCLC Highlights from ASCO 2014

"Beyond the single pathway"

Christian Rolfo

Driver Mutations in NSCLC

LCMC[4]



- Unknown
- KRAS
- EGFR†
- ALK†
- MET amplifications
- BRAF or PIK3CA
- HER2, MEK1, NRAS, or AKT1

*95% of molecular lesions were mutually exclusive.
†Biomarker with predictive and prognostic value.

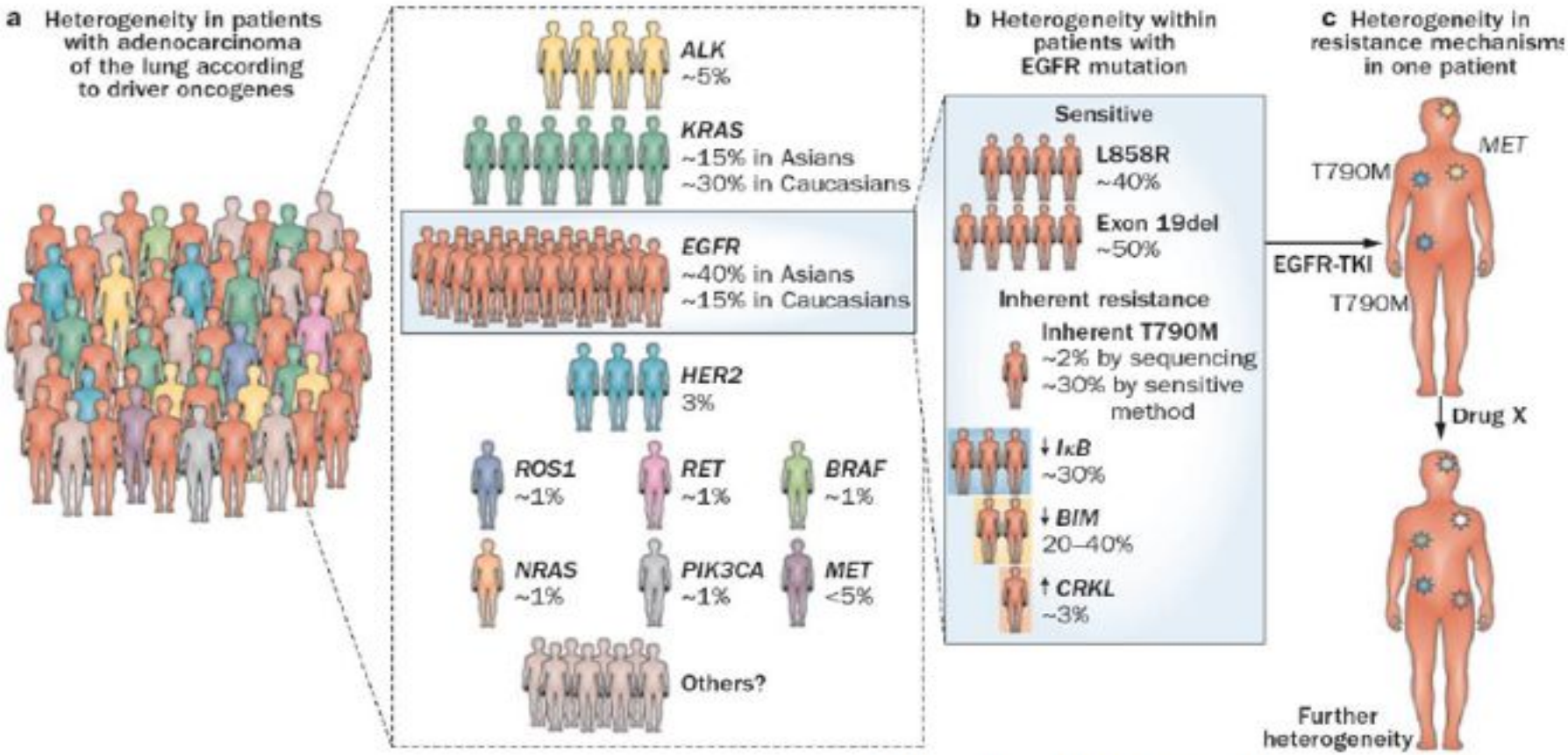
Commons Driver Mutations

- **ALK**
- **EGFR**

There are really news??

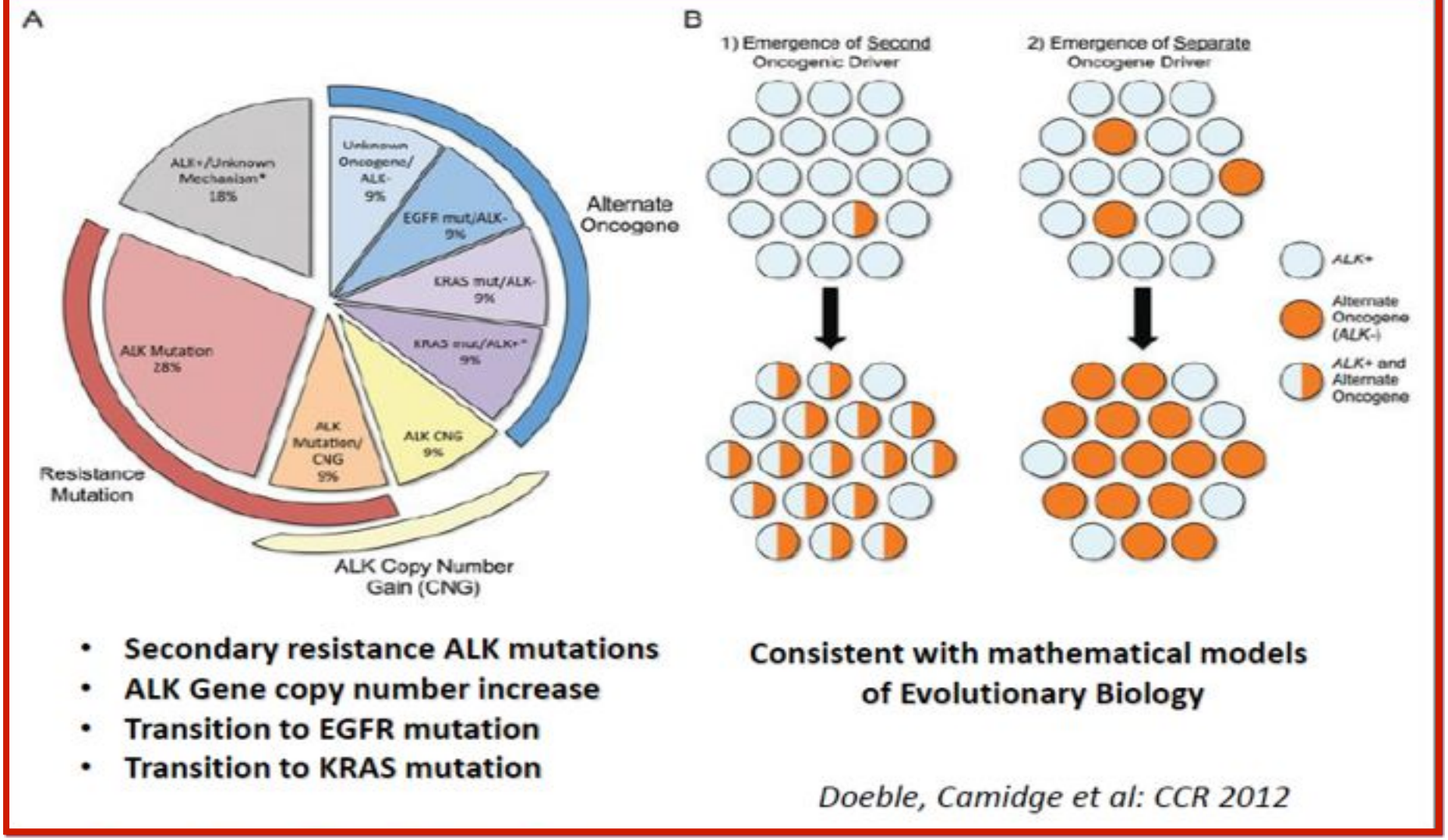
The efficacy of target therapy is affected by…

TUMOR HETEROGENEITY



Mitsudomi Nat Rev Clin Oncol 2013

ALK-Resistance Mechanisms after Crizotinib



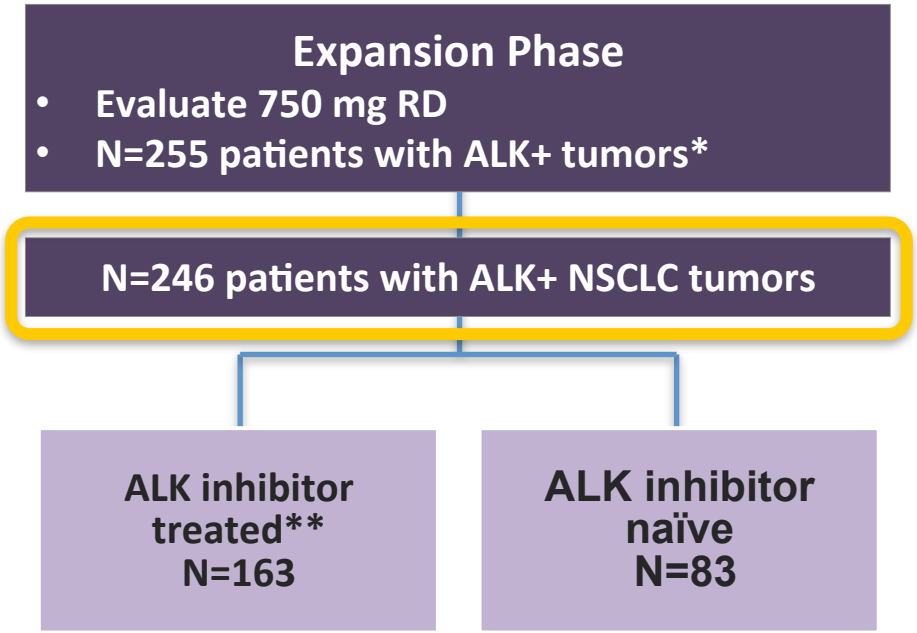
- Secondary resistance ALK mutations
- ALK Gene copy number increase
- Transition to EGFR mutation
- Transition to KRAS mutation

Consistent with mathematical models of Evolutionary Biology

Doeble, Camidge et al: CCR 2012

Ceritinib: ASCEND-1 Study Design

Global pivotal phase 1 trial including 20 centers across 11 countries[1]



Recruitment closed July 2013

- 31 October 2013 data cut-off used for current analysis
- Study ongoing

*9 ALK+ patients had cancers other than NSCLC

**All received crizotinib and 5 also received alectinib

Key Objectives: to determine anti-tumor efficacy and safety of ceritinib

Dose escalation phase (n=59) closed May 2012 with RD of 750 mg/day

[1]Shaw A *et al. NEJM* 2014;370(13):1189–1197

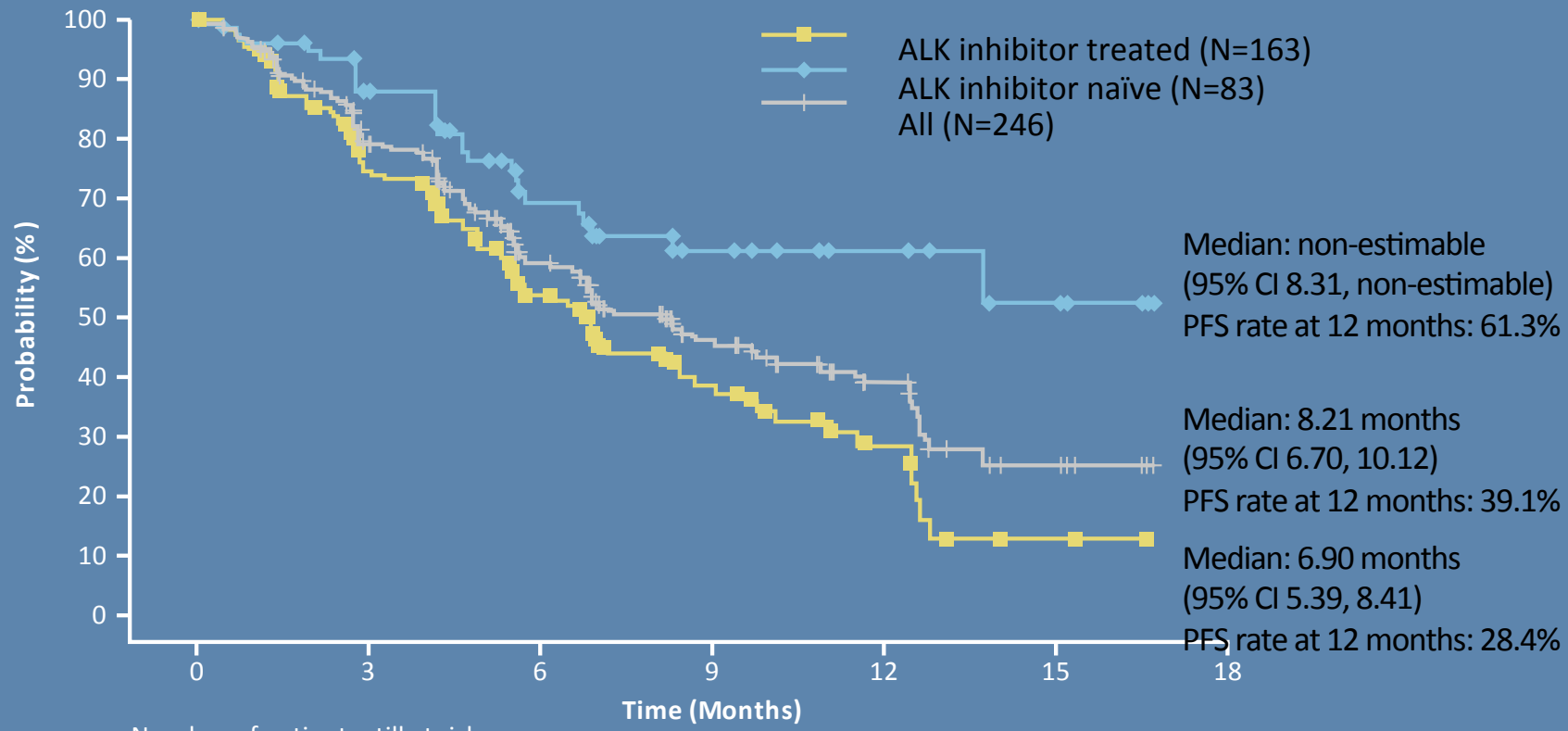
ALKi: ALK inhibitor; RD: recommended dose

Overall Response Rate in ALK+ NSCLC Patients Treated with Ceritinib (750 mg daily)

Efficacy Parameter (RECIST 1.0)	ALK inhibitor treated (N=163)	ALK inhibitor naïve (N=83)	All (N=246)
Complete Response (CR), n (%)	2 (1.2)	1 (1.2)	3 (1.2)
Partial response (PR), n (%)	87 (53.4)	54 (65.1)	141 (57.3)
Stable Disease (SD), n (%)	32 (19.6)	19 (22.9)	51 (20.7)
Progressive Disease (PD), n (%)	16 (9.8)	0	16 (6.5)
Unknown*, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
Overall Response Rate (ORR), n (%) [95% CI]	89 (54.6) [46.6, 62.4]	55 (66.3) [55.1, 76.3]	144 (58.5) [52.1, 64.8]

*No post-baseline assessment done, or the post-baseline assessment had overall response that was not CR, PR, SD or PD

Progression-Free Survival in Patients with ALK+ NSCLC



Median: non-estimable
(95% CI 8.31, non-estimable)
PFS rate at 12 months: 61.3%

Median: 8.21 months
(95% CI 6.70, 10.12)
PFS rate at 12 months: 39.1%

Median: 6.90 months
(95% CI 5.39, 8.41)
PFS rate at 12 months: 28.4%

Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18
NSCLC with prior ALKi	163	103	58	29	10	2	0
NSCLC ALKi naïve	83	63	38	22	11	5	0
All NSCLC	246	166	96	51	21	7	0

Presented by: Dong-Wan Kim

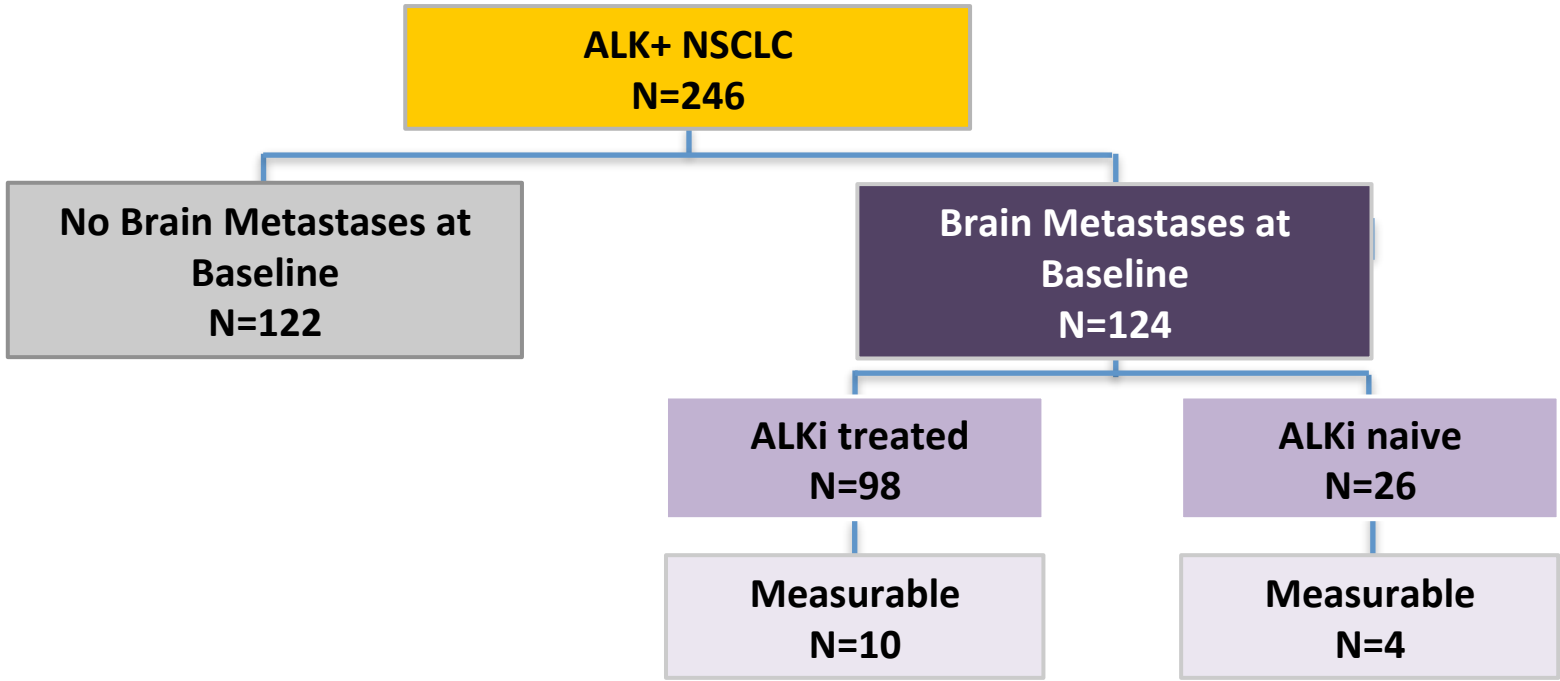
Adverse Events & Laboratory Abnormalities Regardless of Study Drug Relationship

All patients treated with 750 mg (N=255; includes 9 non-NSCLC patients)		
Most common adverse events (AE)	**All grades* (%)**	**Grade 3/4* (%)**
Diarrhea	86	6
Nausea	80	4
Vomiting	60	4
Abdominal pain	54	2
Constipation	29	0
Fatigue	52	5
Decreased appetite	34	1
Interstitial lung disease (ILD)/pneumonitis	4	3
Key Laboratory abnormalities	**All grades* (%)**	**Grade 3/4* (%)**
Hemoglobin decreased	84	5
Alanine transaminase (ALT) increased	80	27
Aspartate transaminase (AST) increased	75	13
Creatinine increased	58	2
Glucose increased	49	13
Phosphate decreased	36	7
Lipase increased	28	10

QTc prolongation >60ms occurred in 3% of pts. 1 pt at 700mg had QTc >500 ms.

Efficacy of Ceritinib in Patients with Brain Metastases

Subset analysis of patients with clinically and neurologically stable brain metastases at baseline



Measurable brain metastases:

- Investigator identified, measured using RECIST 1.0; longest diameter 10 mm or more
- Either not previously radiated, or if previously radiated lesion has grown after irradiation

Overall Response to Ceritinib in Patients with Brain Metastases at Baseline

Efficacy Parameter	ALK inhibitor treated	ALK inhibitor naïve	All patients
Patients with Brain Metastases	**N=98**	**N=26**	**N=124**
ORR, n (%) (95% CI)	49 (50.0%) [39.7, 60.3]	18 (69.2%) [48.2, 85.7]	67 (54.0%) [44.9, 63.0]
DOR, median (months) (95% CI)	6.93 [4.80, 8.54]	NE [5.52, NE]	7.00 [5.45, 9.69]
6 month DOR (%) (95% CI)	53.1% [36.5, 67.1]	65.9% [35.4, 84.5]	56.3% [41.9, 68.4]
PFS, median (months) (95% CI)	6.70 [4.86, 8.38]	8.31 [4.63, NE]	6.90 [5.39, 8.38]
6 month PFS (%) (95% CI)	52.3% [40.9, 62.5]	65.6% [42.7, 81.2]	55.1% [45.0, 64.1]

CI, confidence interval; ORR, overall response rate; DOR, duration of response; PFS, progression-free survival; NE, non-estimable

Overall Intracranial Response Rate for Patients with Measurable Brain Metastases at Baseline

Best Overall Response n (%)	ALK inhibitor treated N=10	ALK inhibitor naïve N=4	All patients N=14
Complete response	0	1	1
Partial response	4	2	6
Stable disease	3	0	3
Progressive disease	0	0	0
Unknown	3	1	4
OIRR [95% CI]	4 (40.0) [12.2, 73.8]	3 (75.0) [19.4, 99.4]	7 (50.0) [23.0, 77.0]

CI, confidence interval; OIRR, overall intracranial response rate

Ceritinib : Conclusions

- A high rate of durable responses and prolonged PFS were seen in both ALKi treated and ALKi naïve patients
  - In ALKi naïve patients, the median DOR and PFS have not been reached
- In all patients, the most common AEs were nausea, vomiting, and diarrhea and most were grade 1 or 2
- In the subset of patients with baseline brain metastases, ceritinib also demonstrated a high rate of durable responses and prolonged PFS in both ALKi treated and ALKi naïve patients
- Ceritinib treatment showed activity in brain metastases

Commons Driver Mutations

- ALK
- **EGFR**

There are really news??

May be….

Was more promising in others trials!

8018: Randomized, double-blinded study of **dacomitinib**, an irreversible pan-human epidermal growth factor receptor (HER) inhibitor, versus erlotinib for second-line/third-line therapy of locally advanced/metastatic non-small cell lung cancer (**ARCHER 1009**)

- **Study design**
  - Interim analysis of a randomised, placebo-controlled phase III study of dacomitinib 45 mg/day or erlotinib 150 mg/day in patients with advanced NSCLC
  - Primary endpoint: PFS; secondary endpoints: OS and best overall response
- **Key results**
  - **878 patients** were enrolled, median age 63 years; 64% male; 76% Caucasian; 90% ECOG PS 0/1; 69% adenocarcinoma; 18% never smokers
  - **Median PFS was 2.6 months in both the dacomitinib and erlotinib groups**, with HR 0.941 (95% CI 0.802, 1.104; p=0.229) across all patient population and HR 1.022 (95% CI 0.834, 1.253; p=0.587) in ***KRAS* wild-type patients**
- **Conclusion**
  - **Dacomitinib was not superior to erlotinib in pretreated patients with advanced NSCLC**
  - Data from the *EGFR* mutation-positive subset will be reported when mature

Ramalingam et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8018)

Bevacizumab and Erlotinib combination

Old friends:
Not really new combination!

Bevacizumab

- Anti-VEGF monoclonal antibody
- Normalize tumor blood vessels
- Improving drug delivery, increasing treatment efficacy

Bevacizumab and Erlotinib

- Simultaneous inhibition of VEGF/EGFR pathways
- Leading to synergistic anti-tumor activity[1]

BeTa Lung Trial

- 2nd line, phase III
- Bevacizumab/Erlotinib combination to Erlotinib monotherapy
- EGFR mutation positive subgroup: OS improved
- HR=0.44 (95% CI: 0.11–1.67)[2]

[1]van Cruijsen, et al. Int J Cancer 2005; [2]Herbst, et al. Lancet 2011, *AACR 2009* LB-131

Erlotinib plus bevacizumab versus erlotinib alone as first-line treatment for advanced *EGFR* mutation-positive non-squamous non-small-cell lung cancer: an open-label, randomized trial

Study design

Chemotherapy-naïve

Stage IIIB/IV or

postoperative recurrence

Non-squamous NSCLC

Activating *EGFR* mutations*

Exon 19 deletion

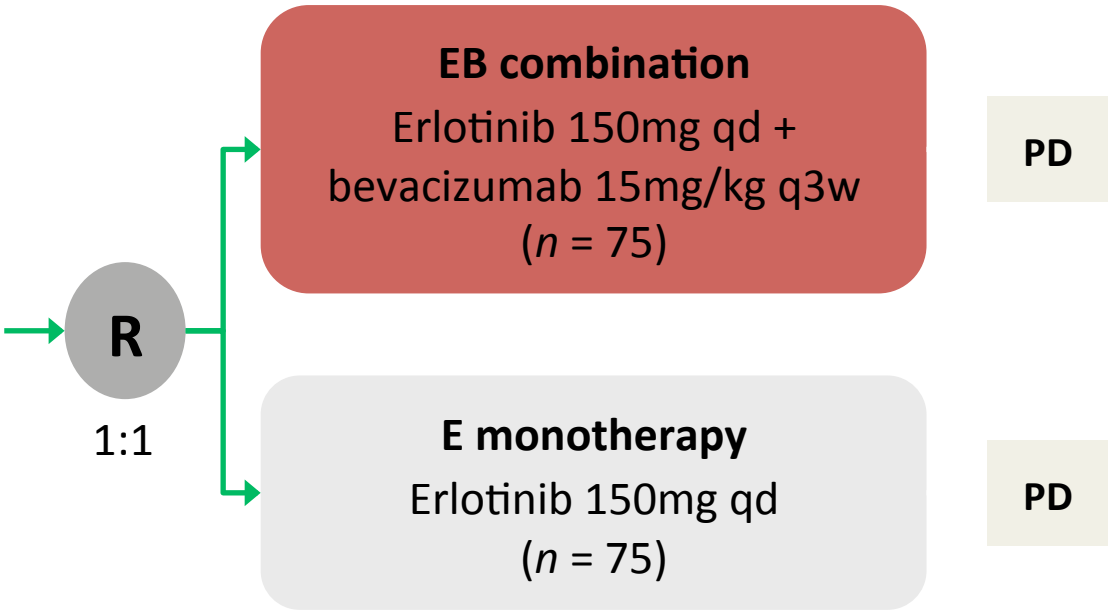
Exon 21 L858R

*T790M excluded

Age ≥20 years

PS 0–1

No brain metastasis



Stratification factors:
sex, smoking status,
clinical stage,
EGFR mutation type

Primary endpoint: PFS (RECIST v1.1, independent review)

Secondary endpoints: OS, tumor response, QoL, safety

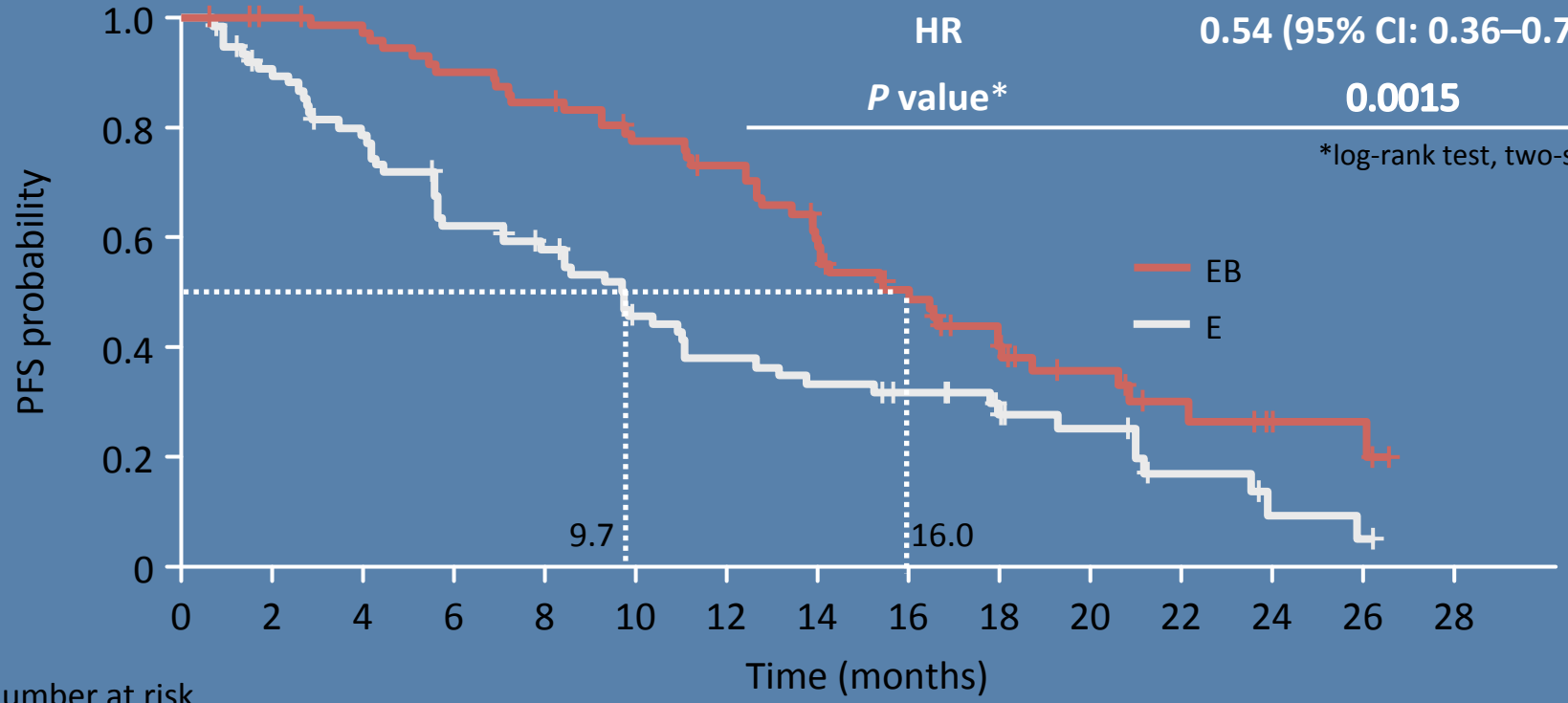
Exploratory endpoint: biomarker assessment

Presented by: Terufumi Kato

Primary endpoint: PFS by independent review

	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*log-rank test, two-sided



Number at risk

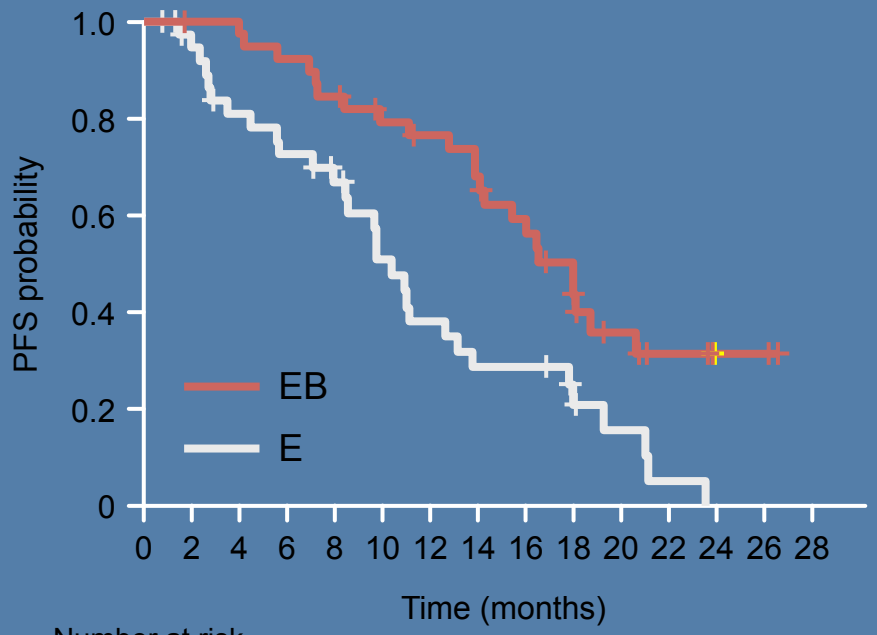
EB	75	72	69	64	60	53	49	38	30	20	13	8	4	4	0
E	77	66	57	44	39	29	24	21	18	12	10	5	2	1	0

Presented by: Terufumi Kato

PFS by *EGFR* mutation type

Exon 19 deletion

	EB	E
Median (months)	18.0	10.3
HR	0.41 (95% CI: 0.24–0.72)	

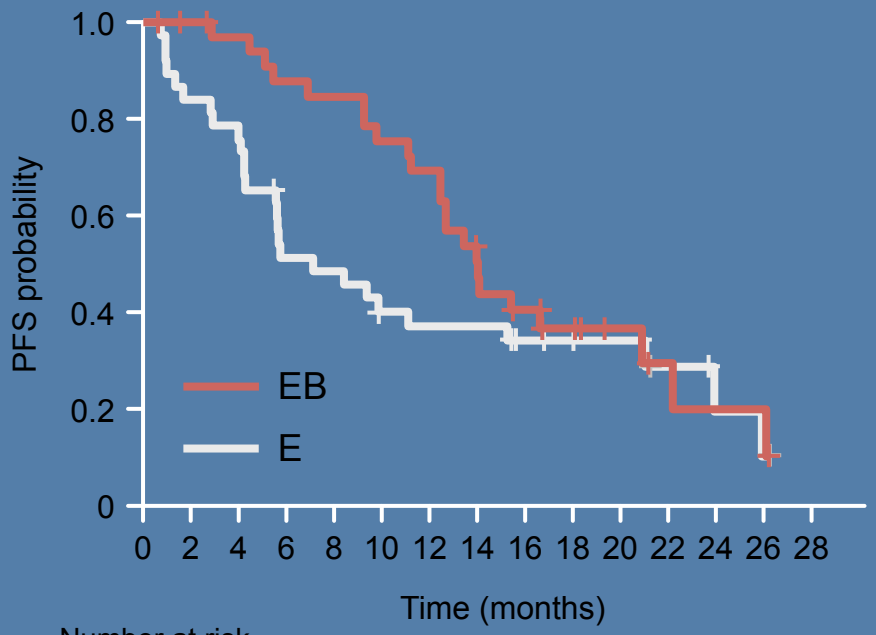


Number at risk

EB	40	39	38	36	33	29	27	24	19	12	8	5	2	2	0
E	40	35	29	26	22	16	12	9	9	5	3	1	0	0	0

Exon 21 L858R

	EB	E
Median (months)	13.9	7.1
HR	0.67 (95% CI: 0.38–1.18)	



Number at risk

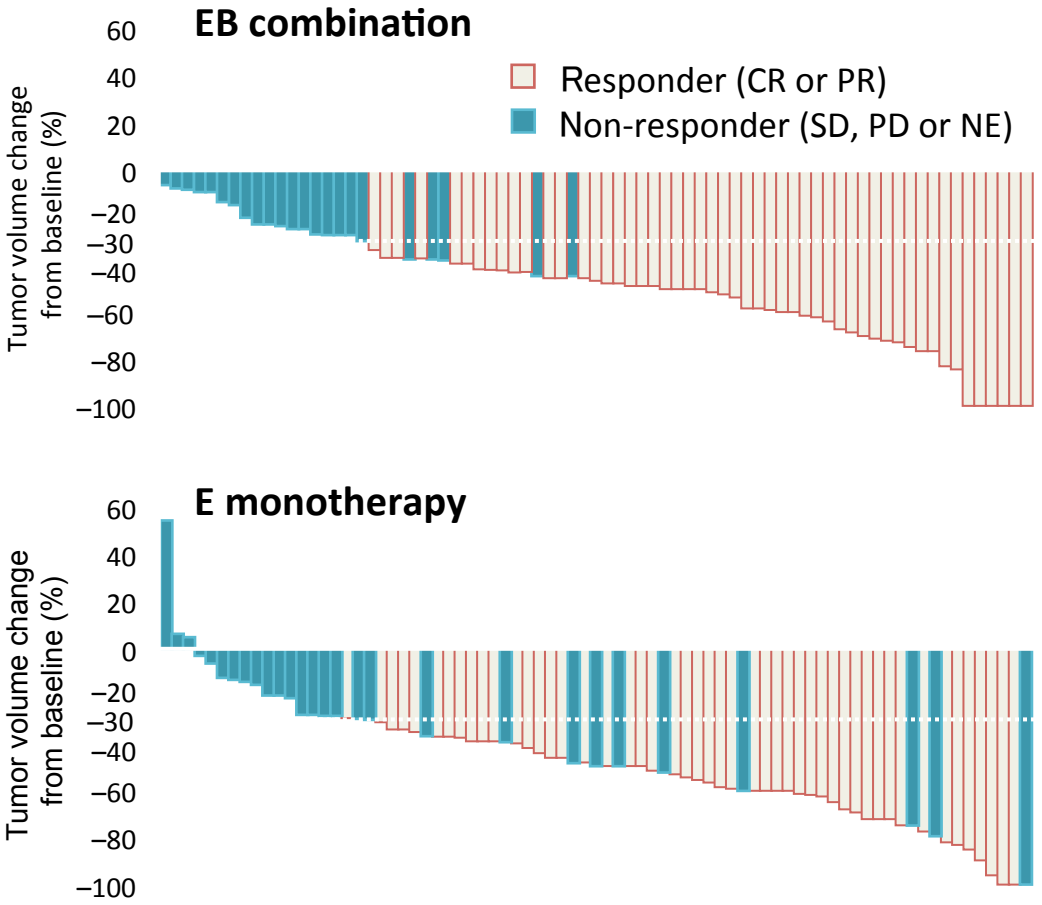
EB	35	33	31	28	27	24	22	14	11	8	5	3	2	2	0
E	37	31	28	18	17	13	12	12	9	7	7	4	2	1	0

Presented by: Terufumi Kato

Objective tumor response

	EB (*n* = 75)	E (*n* = 77)	*P value
CR	3 (4%)	1 (1%)	–
PR	49 (65%)	48 (62%)	–
SD	22 (29%)	19 (25%)	–
PD	0 (0%)	6 (8%)	–
NE	1 (1%)	3 (4%)	–
ORR	69%	64%	0.4951
DCR	99%	88%	0.0177

*Fisher's exact test



Median duration of response: 13.3 months with EB vs 9.3 months with E

Presented by: Terufumi Kato

Bevacizumab and Erlotinib combination: Summary

- JO25567 is the first prospective randomized trial to investigate erlotinib plus bevacizumab as first-line treatment in patients with *EGFR* mutation-positive NSCLC
- Bevacizumab added to erlotinib demonstrated a significant, clinically relevant prolongation of median PFS to 16.0 months compared to 9.7 months with erlotinib alone
- ORR was 69% and DCR was 99% in the combination arm
- No new safety signals were identified
- Addition of bevacizumab did not significantly impact QoL
- OS data are still immature

We already knew!

8009: Clinical activity of the mutant-selective *EGFR* inhibitor **AZD9291** in patients (pts) with EGFR inhibitor–resistant non-small cell lung cancer (NSCLC)

- **Study design**
  - Phase I dose-escalation study of AZD9291 at doses of 20–240 mg qd in patients with *EGFR* mutation-positive NSCLC and acquired resistance to EGFR TKIs
- **Key results**
  - To date, 31 and 201 patients have been enrolled to the escalation and expansion studies (median age 61/60 years; 65%/62% female; 71%/63% Asian), respectively
  - **Overall response rate** (confirmed+unconfirmed) to date are as follows:
    - 53% (95% CI 46%, 60%) among all evaluable patients
    - **64% (95% CI 55%, 73%) in *EGFR* T790 mutation-positive patients**
    - 22% (95% CI 12%, 36%) in *EGFR* T790 mutation-negative patients
  - **The overall DCR (CR+PR+SD) in *EGFR* T790 mutation-positive patients was 94%**
  - No dose-limiting toxicities were observed
- **Conclusions**
  - AZD9291 has robust efficacy and is well tolerated in patients with *EGFR* mutation-positive NSCLC and acquired resistance to EGFR TKIs

Janne et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8009)

We already knew!

8010: First-in-human evaluation of **CO-1686**, an irreversible, highly selective tyrosine kinase inhibitor of mutations of EGFR (activating and T790M)

Sequist et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8010)

- **Study design**
  - Dose-finding study of CO-1686 free-base (up to 900 mg bid) and CO-1686 hydrobromide salt (HBr; 500–1000 mg bid) among patients who had a tumour biopsy in screening for central EGFR genotyping

- **Key results**
  - **72 patients** with median age of 59 years; 75% female; 14% Asian
  - **Objective response rate to date of 58% among T790 mutation-positive patients (n=40)**
  - Median PFS has not yet been reached, but current estimate **exceeds 12 months**

- **Conclusions**
  - CO-1686 shows promising efficacy in patients with T790 EGFR-mutant NSCLC
  - CO-1686 HBr delivered higher exposures than free-base and was equally well tolerated

That are really News! small molecule

8011: Clinical activity and safety of **HM61713**, an EGFR-mutant **selective inhibitor**, in advanced non-small cell lung cancer (NSCLC) patients (pts) with EGFR mutations who had received EGFR tyrosine kinase inhibitors (TKIs)

- **Study design**
  - Phase I dose-escalation study of HM61713 at 300 mg qd (up to 500 mg/day so far) assigned to treatment arm according to time since EGFR TKI (Arm A: <4 weeks; Arm B: ≥4 weeks)
- **Key results**
  - 83 patients enrolled to date
  - Treatment-related AEs were mostly grade 1/2; those occurring in ≥10% were: nausea, skin exfoliation, headache, rash, decreased appetite, diarrhoea, pruritus, constipation, dry skin, vomiting, productive cough, upper abdominal pain, cough, dyspepsia and dyspnoea
  - **Disease control rate was 61.9% and 73.2% in Arm A and B, respectively**
- **Conclusions**
  - HM61713 showed good safety profile and promising anti-tumour activity in patients with EGFR-mutated NSCLC who failed to respond to EGFR TKIs, especially in patients with T790M mutation

Kim et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8011

Dual Inhibition More news!

8014: Phase II trial of **XL184 (cabozantinib) plus erlotinib** in patients (pts) with advanced EGFR-mutant non-small cell lung cancer (NSCLC) with progressive disease (PD) on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy: A California Cancer Consortium phase II trial (NCI 9303)

small molecule inhibits multiple tyrosine kinases, including RET, MET, and VEGFr2

- **Study design**
  - Single-arm study of cabozantinib 40 mg/day + erlotinib 150 mg/day on a 28-day cycle in patients with progressive disease on an EGFR TKI immediately prior to enrolment
  - **Primary endpoint: response rate** (proportion of patients with ≥30% increase in tumour doubling time); secondary endpoints: PFS, OS and safety
- **Key results**
  - **37 patients** have been treated, median age 64.6 years; 62% female; 51% ECOG PS 0
  - **Tumour growth rate reduction of ≥30% was achieved in 85% of patients**
  - **Diarrhoea (11/37, 30%)** was the most common grade 3 AE; 4 patients had grade 4 AEs: 1 increased serum amylase, 2 patients increased lipase and 1 patient nausea/vomiting
- **Conclusion**
  - Combination of erlotinib and cabozantinib demonstrates anti-tumour activity in patients with *EGFR* mutation-positive NSCLC and progressive disease on EGFR TKI

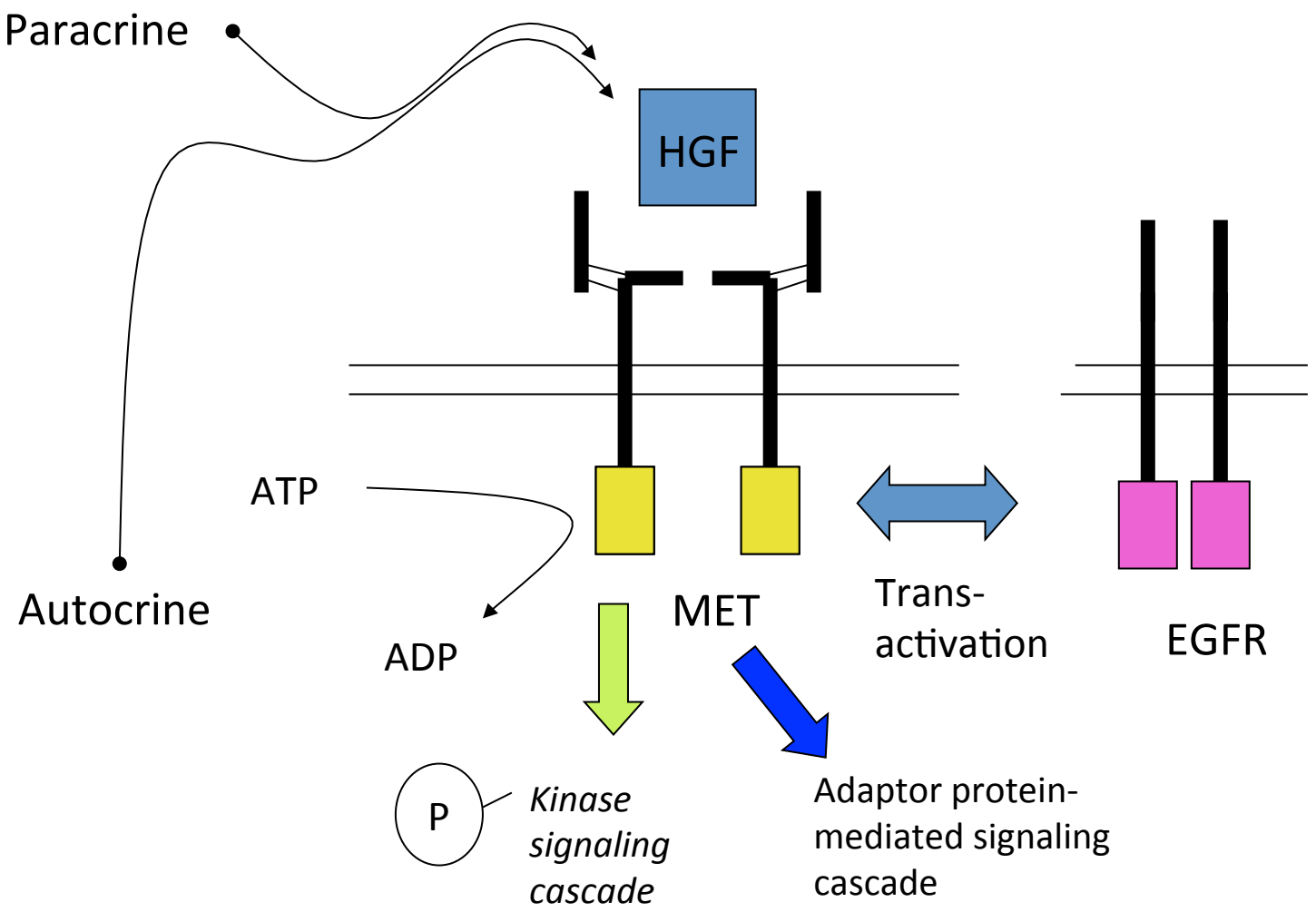
Reckamp et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8014)

New Potential "Druggable" Targets

- **Old friends:**
  c-MET
  BRAF
- **New entries (not really)**
  PD1/PDL1 inhibitors
  CDK inhibitor
  ARAF mutations
  FGFR1

There are really news!

MET Pathway



Motogenesis ***Mitogenesis*** ***Angiogenesis*** ***Morphogenesis***

scatter factor

Various mechanisms of MET activation are implicated in cancer pathogenesis

- **HGF and its receptor MET commonly expressed (by IHC)[1]**
  25–75% of NSCLC
- ***MET* gene point mutations identified in:[1]**
  - PRCC (hereditary, 100%; sporadic ~13%; 95% trisomy 7)
  - **NSCLC (8%)**
  - SCLC (13%)
  - H&N (27%)
  - Ovarian (4%)
  - GBM (9%)
  - Gastric (1%)
- *MET* gene copy number increase/amplification:
  - CRC (9% in advanced cases; 18% in liver metastases),[2] glioma (22%),[3] gastric (10%)[1]
  - **~7% of NSCLC cases[4]**
- **Separate from *MET* as a primary driver, *MET* amplification is reported in 5–20% of lung cancer patients with acquired resistance to EGFR inhibitors[4–6]**

scatter factor;
IHC, immunohistochemistry;
PRCC, papillary renal cell carcinoma

1. Christensen JG, et al. Cancer Lett 2005;225:1–26
2. Fischer U, et al. Genes Chromosomes Cancer 1995;12:63–65
3. Zeng ZS, et al. Cancer Lett 2008;265:258–269
4. Cappuzzo F, et al. Ann Oncol 2009;20:298–304
5. Engelman JA, et al. Science 2007;316:1039–1043
6. Menis J, et al. Transl Lung Cancer Res 2013;2:23–39

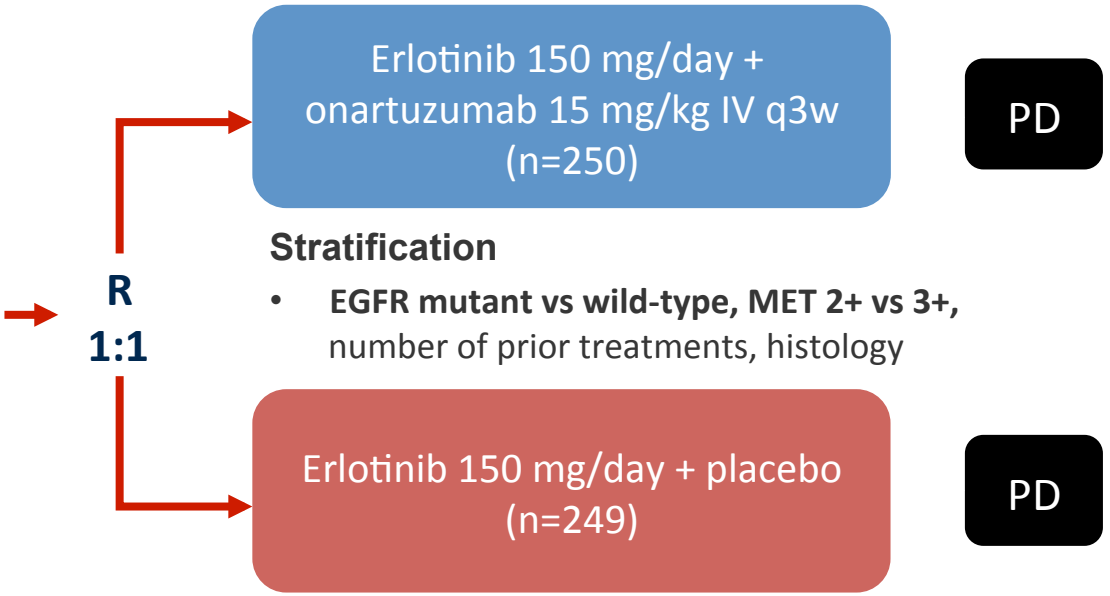
Old friend
Why is negative??

8000: **Onartuzumab plus erlotinib versus erlotinib** in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial

Key patient inclusion criteria

- Stage IIIB/IV NSCLC
- **MET-positive (2+ or 3+)**
- 1 prior platinum-based treatment
- ECOG PS 0–1

(n=490)



Primary endpoint

- OS

Secondary endpoints

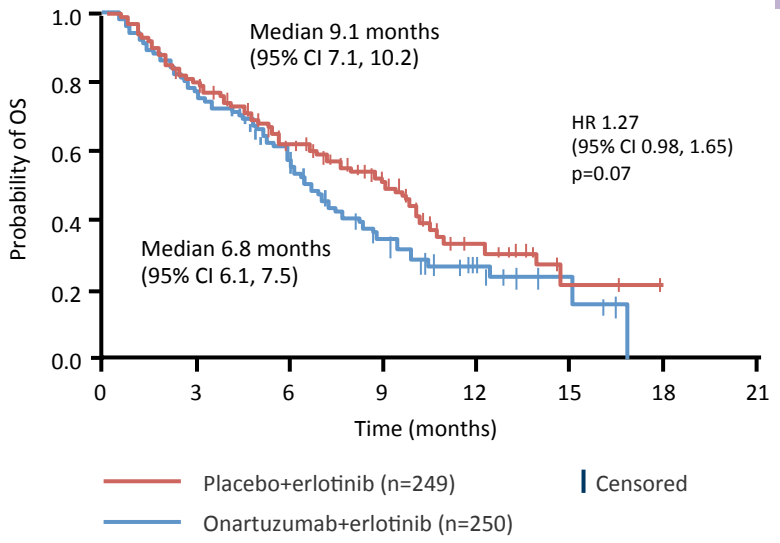
- PFS, ORR, QoL, safety and PK

Spigel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8000)

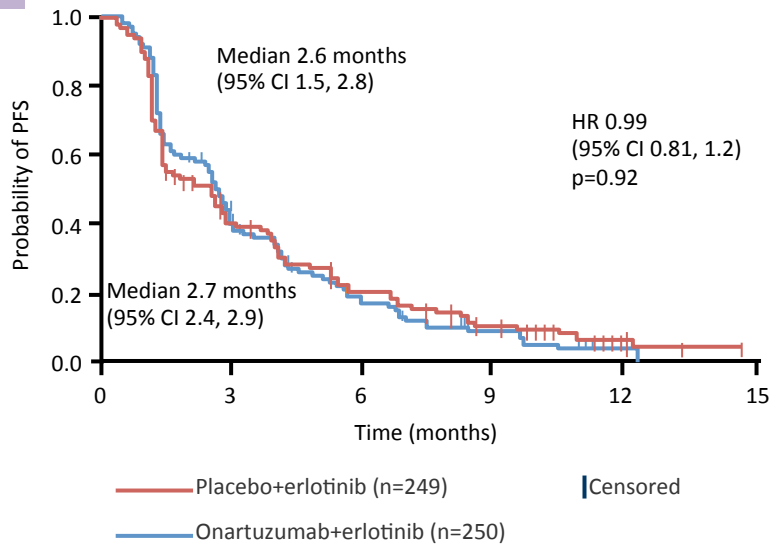
8000: **Onartuzumab plus erlotinib versus erlotinib** in previously treated stage IIIb or IV NSCLC: Results from the pivotal phase III randomized, multicenter, placebo-controlled METLung (OAM4971g) global trial – Spigel DR et al

- **Key results**
  - An independent committee recommended to stop the trial for futility

OS



PFS



Conclusions

Addition of onartuzumab did not confer any benefit on survival in patients with MET-positive 2/3L NSCLC regardless of *MET* FISH or *EGFR* mutation status

ORR 8.8% placebo+erlotinib vs. 6.4% onartuzumab+erlotinib

Spigel et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8000)

We rget??

***MET*- ov**

***MET*- Amplification**

SCHOOL OF MEDICINE
Division of Medical Oncology
UNIVERSITY OF COLORADO ANSCHUTZ MEDICAL CAMPUS

MET is amplified in a subset of lung cancers

MET amplification level categories: Expected frequencies

MET/CEP7 ratio	Number of specimens	MET amplification classification	% of total
<1.8	741		92.6%
≥1.8–≤2.2	29	Low	3.6%
>2.2–<5.0	24	Intermediate	3.0%
≥5.0	6	High	0.8%
Total	800		100.0%

- 800 consecutive NSCLC samples tested at Colorado Molecular Correlates Lab from 2009 to 2012.
- Detailed demographic data not available. Samples were unselected with respect to other biomarker status, but may have been enriched for adenocarcinoma, never smokers, young age, and female, based on time period of testing.

Garcia L, University of Colorado, personal communication

Patient eligibility: NSCLC *MET* amplification cohort

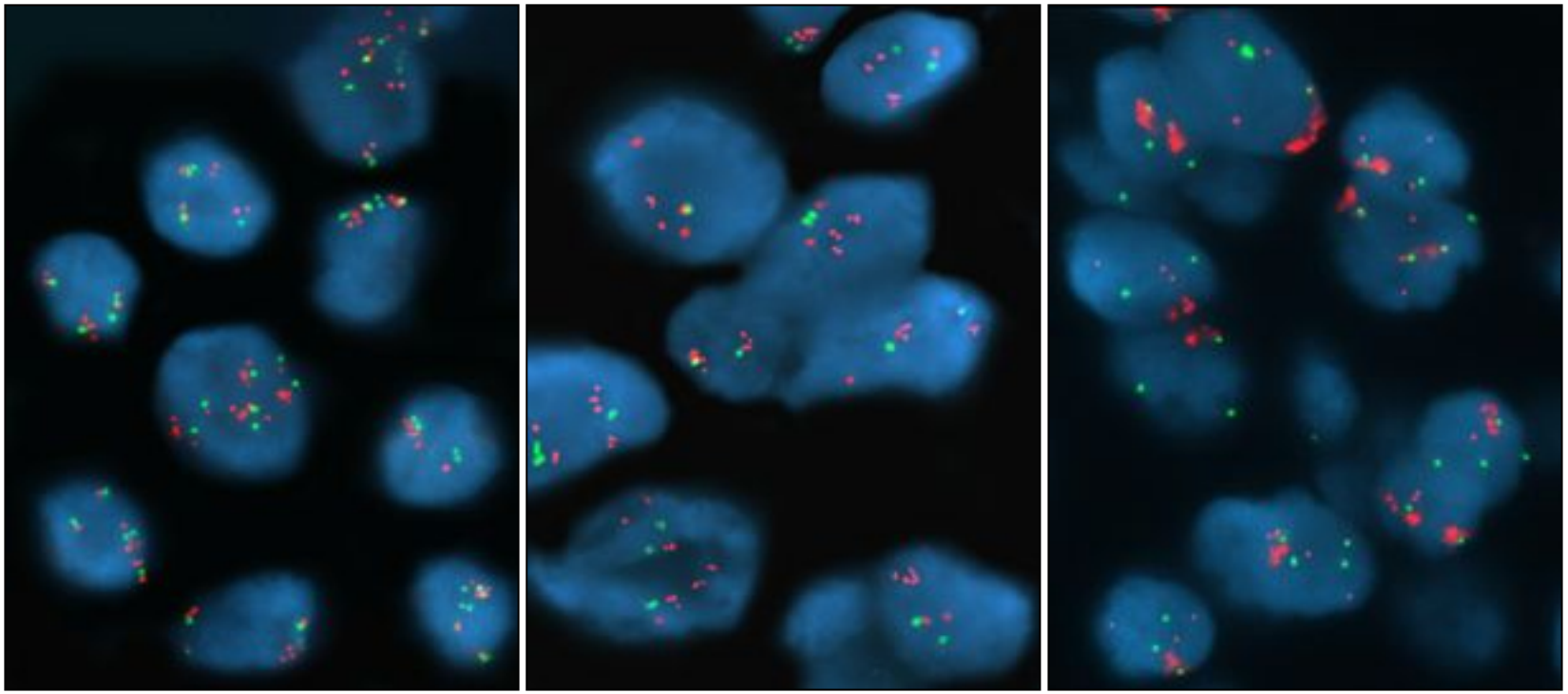
- Patients (≥18 years) had histologically confirmed advanced NSCLC, and
  - measurable disease per RECIST v1.0
  - adequate organ function
  - resolution of acute toxic effects of prior therapies or surgical procedures (CTCAE Grade ≤1)
  - received no prior MET- or HGF-targeted therapies

In archival tumor tissue, *MET* amplification was determined by FISH

MET not amplified (not eligible)	*MET* amplified (low *MET* level)	*MET* amplified (intermediate *MET* level)	*MET* amplified (high *MET* level)
• *MET/CEP7* ratio <1.8	• *MET/CEP7* ratio ≥1.8–≤2.2	• *MET/CEP7* ratio >2.2–<5.0	• *MET/CEP7* ratio ≥5

CEP7, chromosome 7 centromere signal; CTCAE, Common Toxicity Criteria for Adverse Events
FISH, fluorescence in-situ hybridization; RECIST, Response Evaluation Criteria In Solid Tumors

MET amplification cohorts determined by FISH



Low *MET* level	Intermediate *MET* level	High *MET* level
MET/CEP7 ratio ≥1.8–≤2.2	*MET/CEP7* ratio >2.2–<5.0	*MET/CEP7* ratio ≥5
Mean MET cell: 9.0	**Mean MET cell: 7.0**	**Mean MET cell: 15.7**
Mean CEP 7 cell: 4.7	Mean CEP 7 cell: 2.1	Mean CEP 7 cell: 2.8
Ratio: 1.9	**Ratio: 3.3**	**Ratio: 5.6**

Study status and patient disposition

- Data snapshot: 15 April 2014

	MET-amplified patients			
	Low *MET*, n=2	Intermediate *MET*, n=6	High *MET*, n=6	Total N=14[a]
Patients ongoing at data snapshot, n (%)	**0**	**3 (50)**	**2 (33)**	**5 (36)**
Reasons for discontinuation, n (%)				
Progressive disease	**2 (100)**	**2 (33)**	**4 (67)**	**8 (57)**
Adverse event	**0**	**1[b] (17)**	**0**	**1 (6)**
Median duration of treatment, weeks (range)	**6 (4–8)**	**13 (8–56)**	**52 (16–203)**	**17 (4–203)**

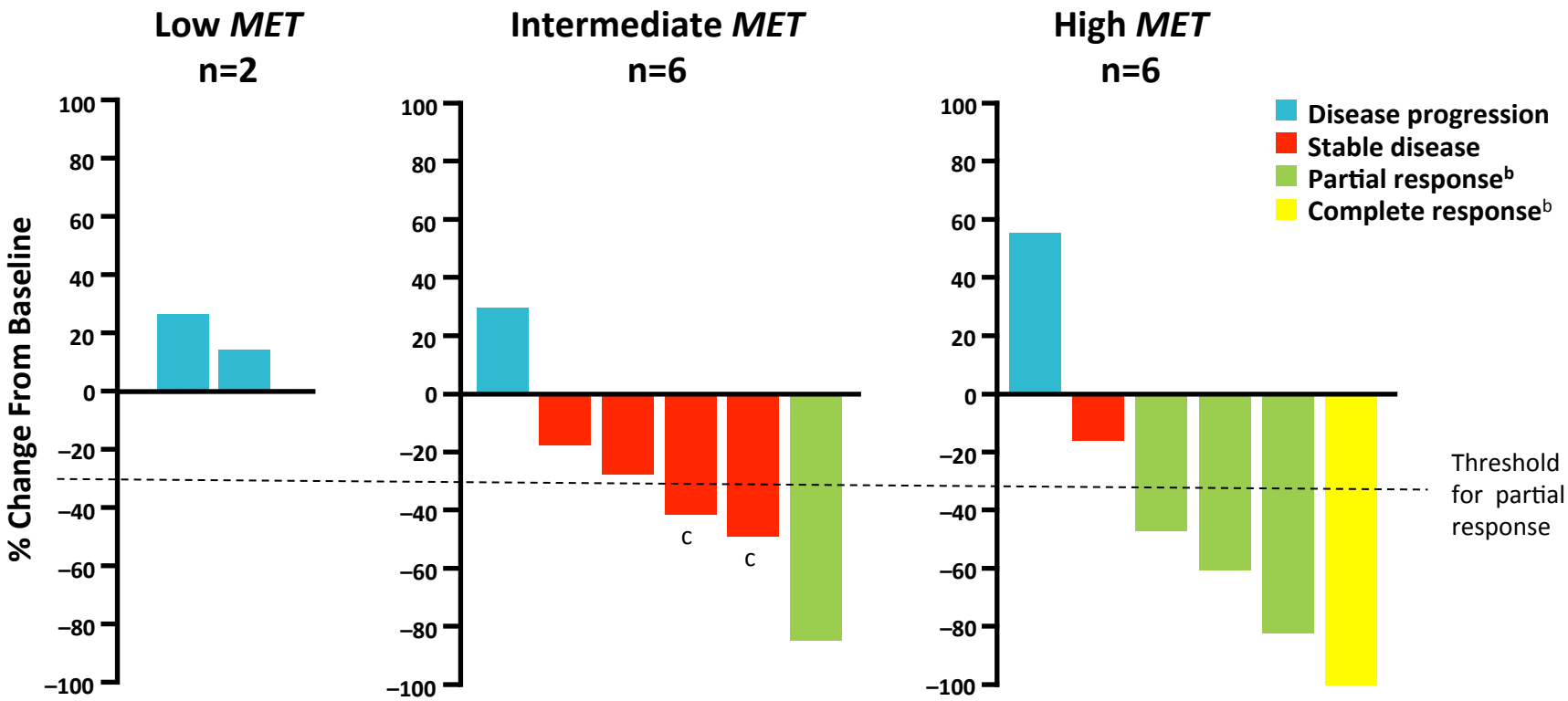
- **There were 7 deaths at the time of data snapshot (low *MET*, 2; intermediate *MET*, 2; high *MET*, 3)**
  - **All were due to disease progression and occurred >28 days after the last dose of study medication**

[a]Three additional subjects enrolled into the *MET*-amplified NSCLC cohort were subsequently confirmed not to meet eligibility criteria (*MET/CEP7* ratio was below the lower *MET* level category and 1 patient had a *MET* mutation); they were not included in the efficacy analysis.

[b]Patient had grade 4 pneumonia and septic shock, which was not attributed to crizotinib.

Tumor Shrinkage Seen in Intermediate and High *MET* Cohorts

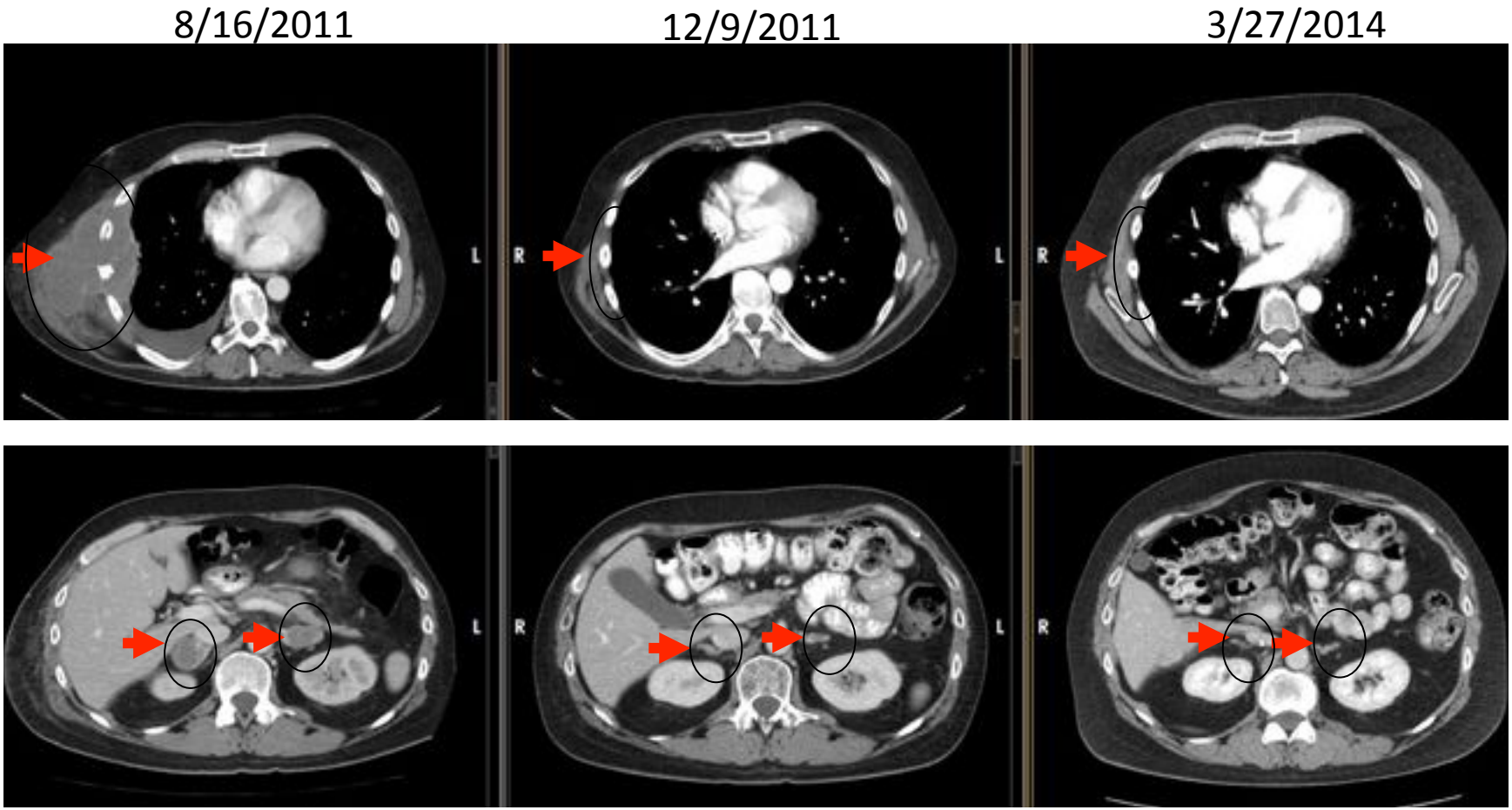
Best percent change from baseline in target tumor lesions[a] by patient



[a]Confirmed objective responses.
[b]Based on investigator assessment.
[c]Two patients in the intermediate *MET* group had an unconfirmed PR that was not confirmed in a second assessment.

Partial response in a patient with high *MET* amplification[a]

Duration of response: 31+ months



[a]MET/CEP7 ratio: >5

Images: G. Shapiro DFCI

Objective response rate[a]

	Low *MET*, n=2	Intermediate *MET*, n=6	High *MET*, n=6
ORR, % (95% CI)[b]	0 (0–84)	17 (0–64)	67 (22–96)
Best response, n (%)			
Complete response	0	0	1 (17)
Partial response	0	1 (17)	3 (50)
Stable disease	0	4 (67)	1 (17)
Objective progression	2 (100)	1 (17)	1 (17)
Median duration of response, weeks (range)[c]	–	16	73.6 (24.1–128.0)
Duration of stable disease, n (%)[d]			
0–<3 months	–	3 (75)	0
3–<6 months	–	1 (25)	1 (100)

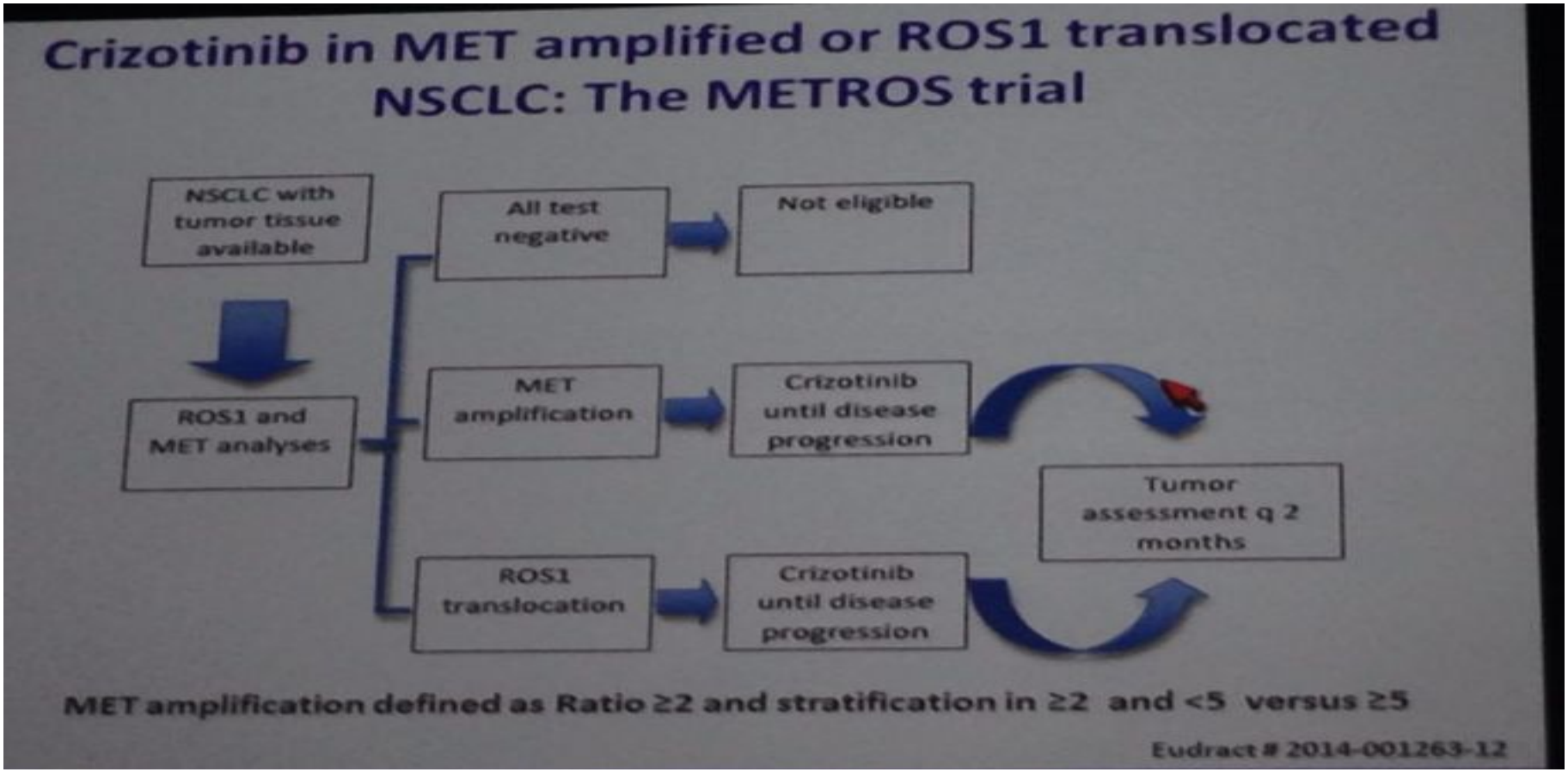
[a]RECIST v1.0, based on investigator assessment.
[b]Complete response + partial response; CI based on exact F distribution.
[c]Descriptive statistics are presented based on all responders
[d]Among patients with stable disease as best overall response.

ORR, objective response rate.

Conclusions: Crizotinib in MET amplified

- *MET*-amplified disease may represent a novel targetable molecular subtype of NSCLC, notably with a smoking history
- Evidence of clinical activity (extended stabilization or tumor shrinkage) from crizotinib was observed in patients with both intermediate and high *MET*-amplified NSCLC
- These findings warrant further study of crizotinib in patients with *MET*-amplified advanced NSCLC
- Exploration of the optimal *MET/CEP7* ratio associated with clinical benefit for crizotinib treatment is ongoing

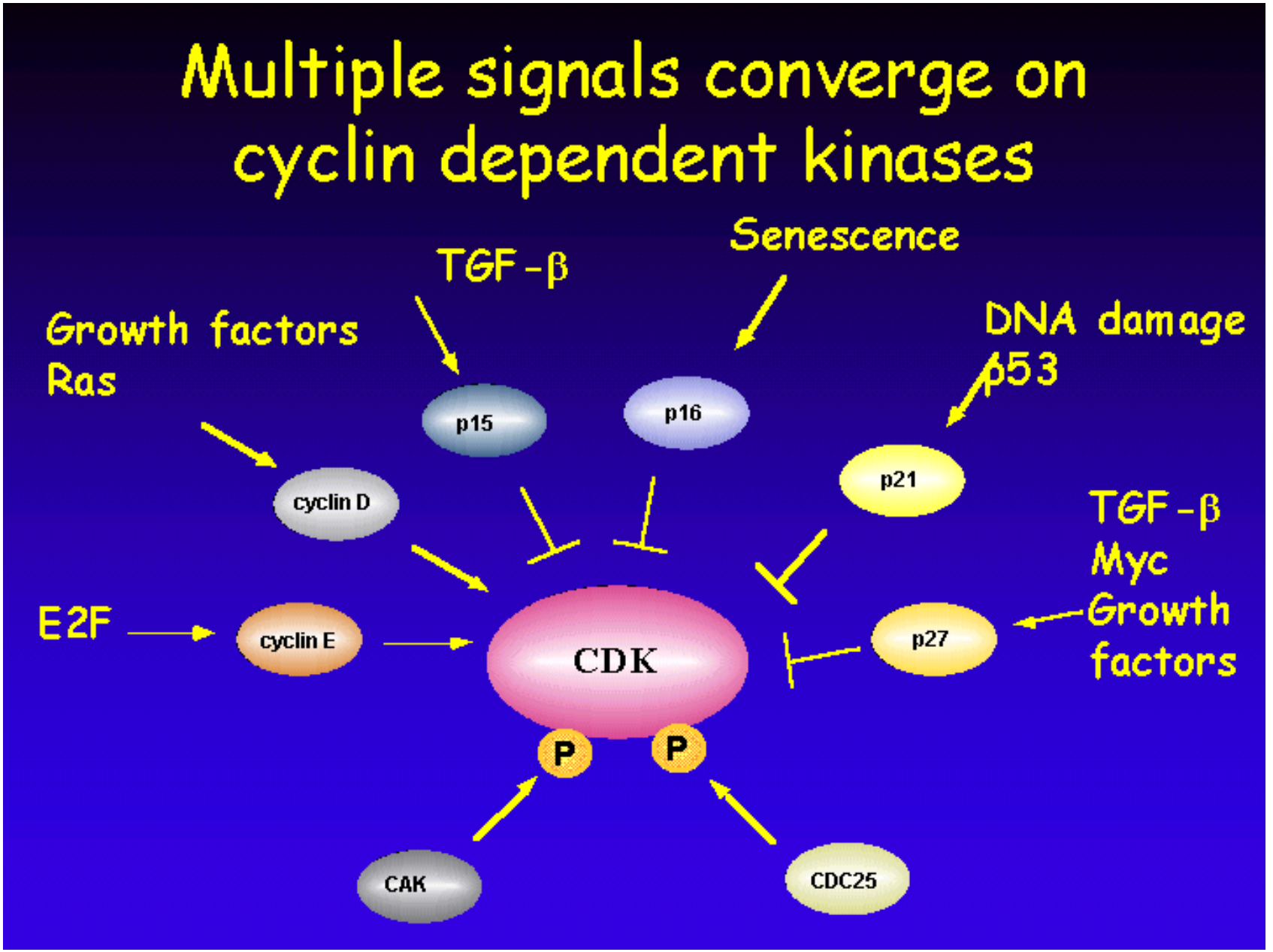
New trials design…



New Potential "Druggable" Targets

- **Old friends:**
  - c-MET
  - BRAF
- **New entries (not really)**
  - PD1/PDL1 inhibitors
  - CDK inhibitor
  - ARAF mutations
  - FGFR1
  - EGFR (IHC)

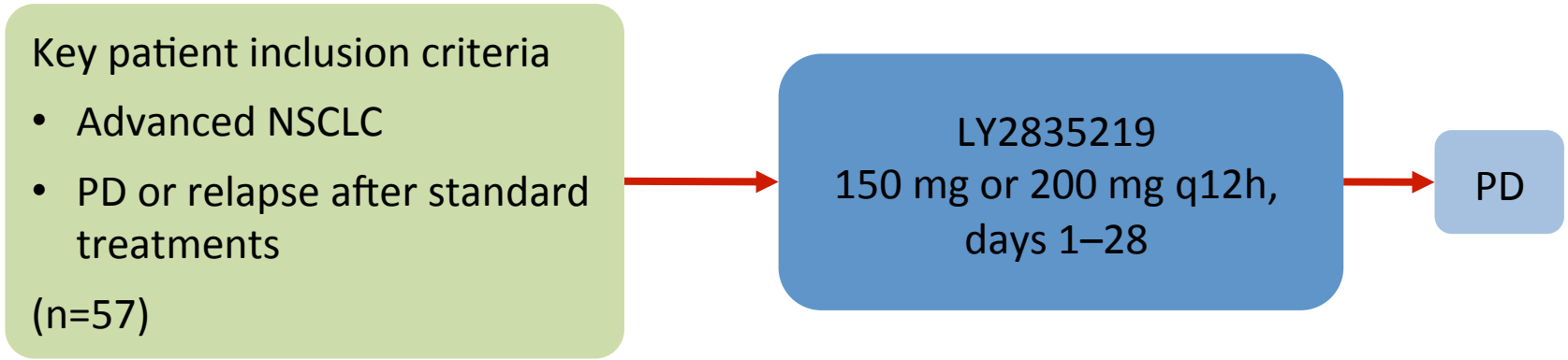
There are really news!


Multiple signals converge on cyclin dependent kinases
TGF-β
Senescence
Growth factors
Ras
DNA damage
p53
p15
p16
p21
cyclin D
TGF-β
Myc
Growth factors
E2F
cyclin E
CDK
p27
P
P
CAK
CDC25

NEW drug for an adult target!

8026: Clinical activity of **LY2835219 (ABEMACICLIB)**, **a novel cell cycle inhibitor selective for CDK4 and CDK6**, in patients with non-small cell lung cancer – Goldman JW et al

- **Study objective**
  - To investigate the efficacy and safety of the cell cycle inhibitor, LY2835219 (abemaciclib), in patients with advanced NSCLC and other solid tumours



Primary endpoint

- Safety

Secondary endpoints

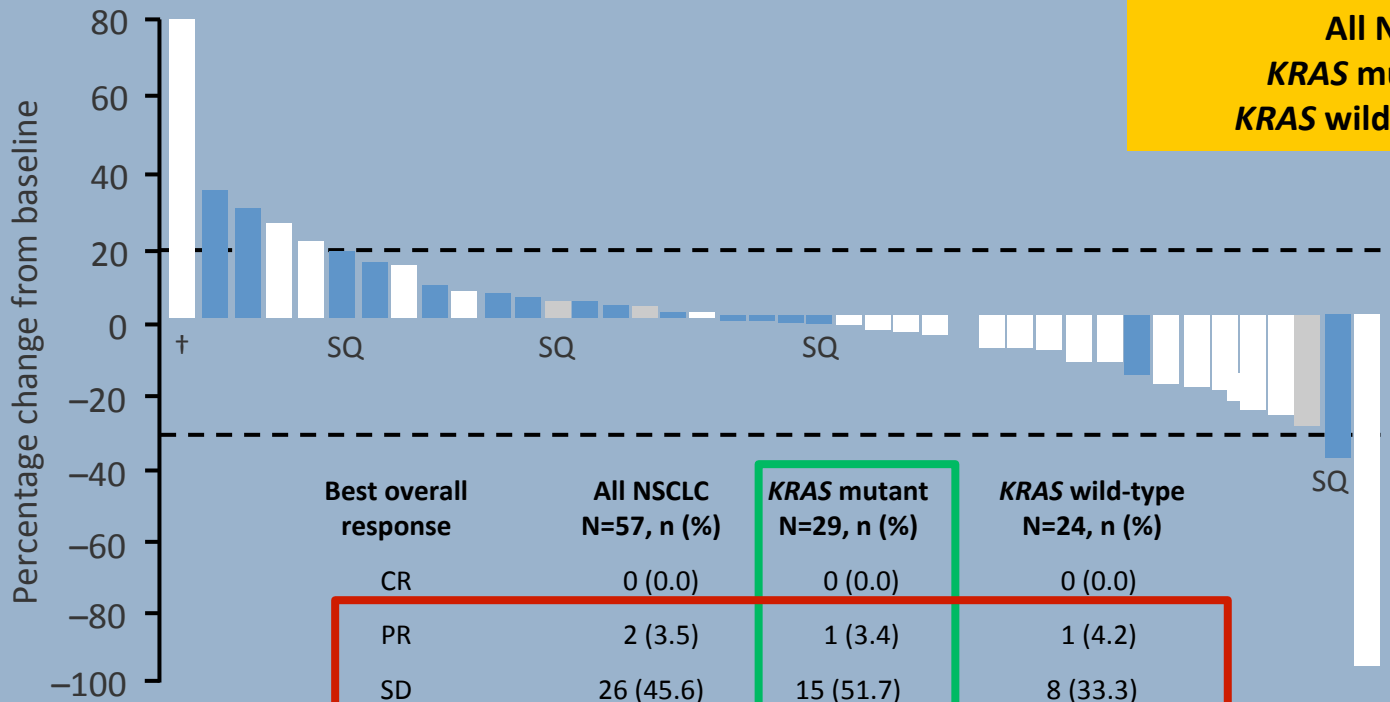
- Anti-tumour activity, pharmacodynamics and predictive biomarkers

Goldman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8026)

8026: Clinical activity of **LY2835219, a novel cell cycle inhibitor selective for CDK4 and CDK6**, in patients with non-small cell lung cancer – Goldman JW et al

- **Key results**

Disease control rate (CR + PR + SD)
All NSCLC (n=57) 49.1%
***KRAS* mutant (n=29) 55.2%**
***KRAS* wild-type (n=24) 37.5%**



Best overall response	All NSCLC N=57, n (%)	*KRAS* mutant N=29, n (%)	*KRAS* wild-type N=24, n (%)
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	2 (3.5)	1 (3.4)	1 (4.2)
SD	26 (45.6)	15 (51.7)	8 (33.3)
PD	14 (24.6)	7 (24.1)	7 (29.2)
Not evaluable	15 (26.3)	6 (20.7)	8 (33.3)

- **Conclusions**
  - LY2835219 demonstrated anti-tumour activity in advanced NSCLC, **particularly in *KRAS* mutation-positive disease**
  - LY2835219 had an acceptable safety profile

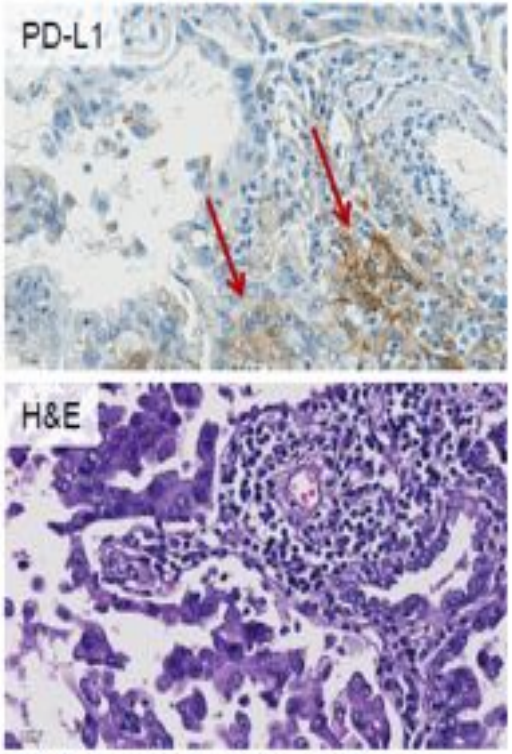
Goldman et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8026)

PD-L1 is Broadly Expressed in NSCLC

Positive PD-L1 staining in NSCLC

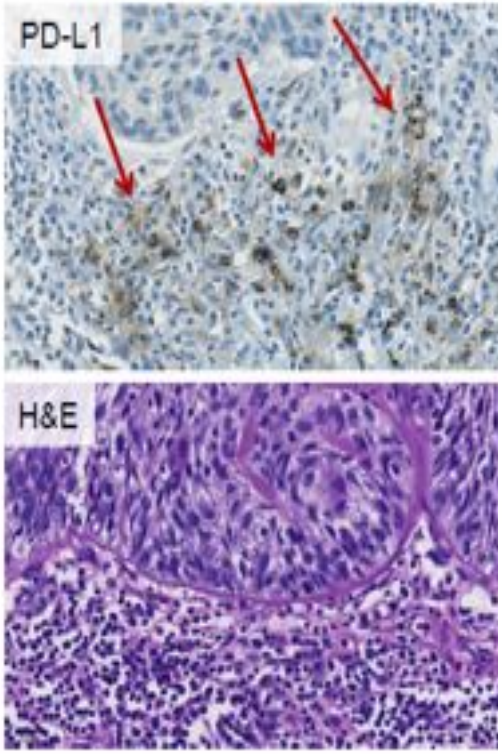
Adenocarcinoma

Prevalence of PD-L1 ≈ 45%



Squamous cell carcinoma

Prevalence of PD-L1 ≈ 50%



Koeppen H. and Kowanetz M., Genentech
Proprietary Genentech/Roche PD-L1 IHC

Tumor Type	Estimated PD-L1 Prevalence (≈ %)*
NSCLC (SCC)	50%
NSCLC (adeno)	45%
Colon	45%
Melanoma	40%
Renal	20%

Nearly all human tumors include a subset that expresses PD-L1

High sensitivity and specificity in FFPE samples

Fashion in Oncology!

Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis

- **Study design**
  - Phase Ib study in which patients received nivolumab (1, 3 or 10 mg/kg) q2w for up to 96 weeks
  - PD-L1 tumour cell membrane expression was measured in archival specimens
- **Key results**
  - Overall, 129 subjects were treated with nivolumab across the three doses
  - At the 3 mg/kg dose (n=37) **median OS was 14.9 months**, **1- and 2-year OS rates were 56% and 45%**, respectively, **objective response rate was 24%**
  - For patients with PD-L1**(+)** and **(–)** tumours, median OS was **7.8** (95% CI 5.6, 21.7) and **10.5** (5.2, 21.2) months, respectively
  - The most common grade 3–4 treatment-related AE was fatigue (3%)
- **Conclusion**
  - Nivolumab continues to demonstrate an encouraging survival profile

Brahmer et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8112^)

Predictive/ prognostic Biomarker value?

First-line nivolumab (anti-PD-1; BMS-936558, ONO-4538) monotherapy in advanced NSCLC: Safety, efficacy, and correlation of outcomes with PD-L1 status – Gettinger SN et al

- **Study design**
  - Interim results of phase I study of nivolumab 3 mg/kg q2w in CT-naïve patients with squamous or non-squamous advanced NSCLC
  - Primary endpoint: safety and tolerability; secondary endpoints: objective response rate and PFS
- **Key results**
  - Five grade 3/4 treatment-related AEs occurred in 4 patients (20%; AST or ALT elevations, hyperglycaemia, rash and cardiac failure)
  - **Objective response rate was 30% overall**
    - Response at first assessment (11 weeks) was observed in 5 of 6 (83%) patients
    - Response was 50% in patients with PD-L1 expression**; no responses were observed in patients without PD-L1 expression**
- **Conclusion**
  - Nivolumab was associated with early durable responses in patients with advanced and PD-L1 expression

Gettinger et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8024)

More Fashion in Oncology!

Immuno check point Combine therapies

Nivolumab & Ipilimumab

Nivolumab plus erlotinib

Nivolumab with platinum-based doublet chemotherapy

More Fashion in Oncology!

Nivolumab (anti-PD-1; BMS-936558, ONO-4538) and ipilimumab in first-line NSCLC: Interim phase I results

- **Study design**
  - Interim results from a phase I study in which CT-naïve patients with **squamous or non-squamous advanced NSCLC received the following first-line** regimen q3w for 4 cycles followed by nivolumab 3 mg/kg q2w: 1) nivolumab 1 mg/kg + ipilimumab 3 mg/kg or 2) nivolumab 3 mg/kg + ipilimumab 1 mg/kg
  - Primary endpoint: safety and tolerability; secondary endpoints: objective response rate and PFS
- **Key results**
  - Grade 3/4 treatment-related AEs occurred in 24 of 49 patients (49%)
  - Among patients with **squamous NSCLC**, objective response rate was better in the higher nivolumab dose group (33% vs 11% with low-dose nivolumab); this was also higher than in the non-squamous groups (both 13%)
  - Other outcomes were similar between patients with or without PD-L1 expression
- **Conclusion**
  - These interim data suggest that a nivolumab+ipilimumab immunotherapy regimen is feasible and active in patients with advanced NSCLC, **regardless of PD-L1 expression status**

Antonia et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8023)

More Fashion in Oncology!

Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC) – Antonia SJ et al

- **Study design**
  - Updated analysis of a phase I study of first-line nivolumab plus PT-DC in CT-naïve patients
  - Based on histology patients were assigned to 4 cycles of one of four treatment arms:
    1) nivolumab 10 mg/kg q3w + gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2 (sq)
    2) nivolumab 10 mg/kg IV q3w + pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 (non-sq)
    3) nivolumab 5 mg/kg q3w + paclitaxel 200 mg/m^2 + carboplatin AUC6 (sq + non-sq)
    4) nivolumab 10 mg/kg q3w + paclitaxel 200 mg/m^2 + carboplatin AUC6 (sq + non-sq)
- **Key results**
  - Overall 56 patients were treated across 4 arms with median age of 64 years; 54% female; 96% stage IV
  - No DLTs were seen during the first 6 weeks of treatment
  - **Objective response rate was 33–47%** over up to 10 months of follow-up and was similar between treatment arms
  - **Median OS was 51–83 weeks; 1-year OS rates were 50–87%**
  - 45% of patients reported grade 3–4 treatment-related AEs
- **Conclusion**
  - Nivolumab plus PT-DC demonstrated anti-tumour activity with encouraging 1-year OS

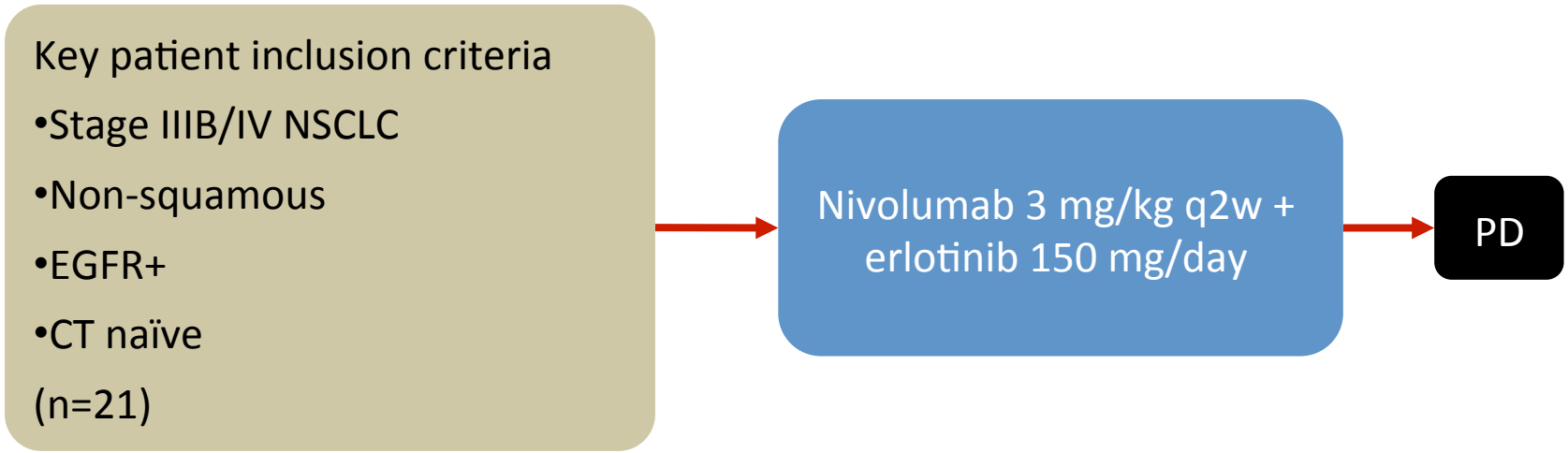
DLT, dose-limiting toxicity; non-sq, non-squamous;
PT-DC, platinum-based doublet CT; sq, squamous

Antonia et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8113)

More Fashion in Oncology!

Safety and response with **nivolumab** (anti-PD-1; BMS-936558, ONO-4538) **plus erlotinib** in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC

- **Study objective**
  - To evaluate the safety and efficacy of nivolumab added to erlotinib in patients with advanced NSCLC and EGFR mutations



Primary endpoint

- Safety and tolerability

Secondary endpoints

- Objective response rate and PFS at 24 weeks

Rizvi et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8022)

8022: Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC

- **Key results**
  - Grade 3 treatment-related AEs occurred in 24% of patients (no grade 4 reported)
  - Objective response rate was 19% (PR in 3 of 20 patients treated previously with erlotinib and 1 of 1 patient with no prior erlotinib)
  - Survival outcomes among all patients are shown in the table

	Nivolumab+erlotinib (n=21)
PFS	
PFS rate (95% CI) at 24 weeks, %	51 (28, 70)
Median (range) PFS, weeks	**29.4 (4.6, 81.7+)**
OS	
1-year OS rate (95% CI), %	**73 (46, 88)**
Median (range) OS, weeks	NR (10.7+, 86.9+)

- **Conclusion**
  - Nivolumab in combination with erlotinib may provide durable clinical benefit in *EGFR* mutation-positive advanced NSCLC, with evidence of activity at TKI resistance

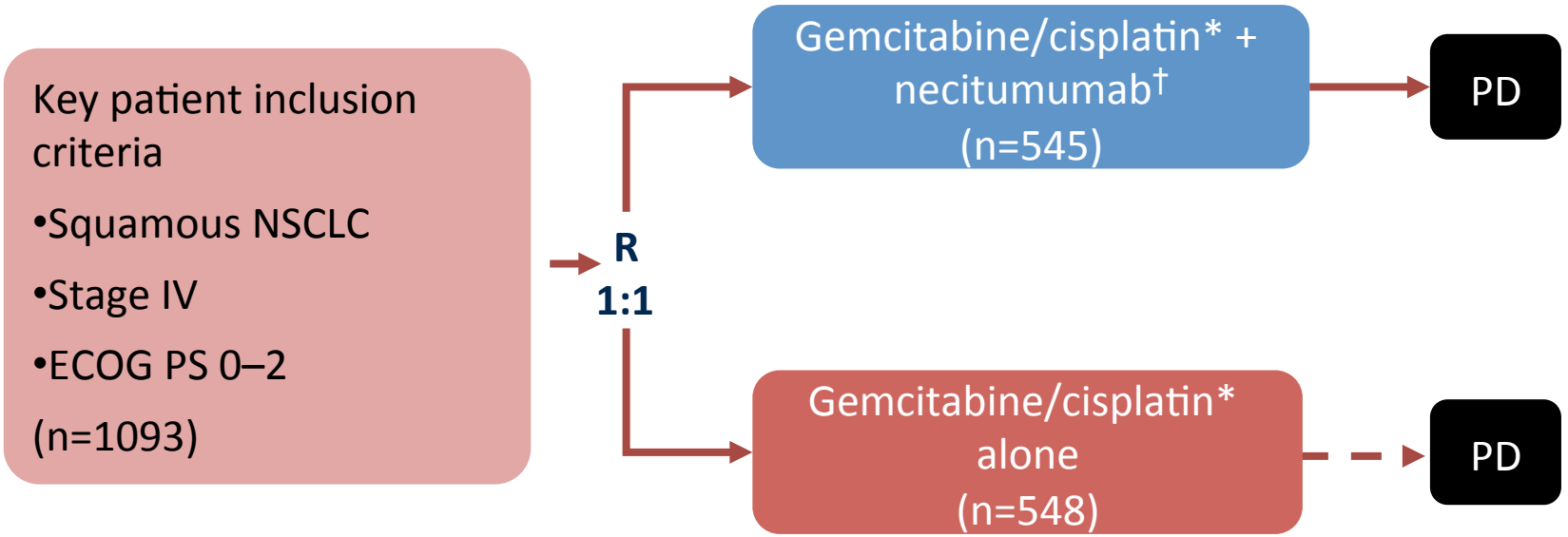
Rizvi et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8022)

fully human IgG1 MoAb targeting EGFR
Other FLEX???

A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus **necitumumab** (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC)

Study objective

– To compare gemcitabine/cisplatin+necitumumab with gemcitabine/cisplatin alone as first-line treatment in patients with squamous NSCLC



Primary endpoint

- OS

Secondary endpoints

- PFS, objective response rate and safety

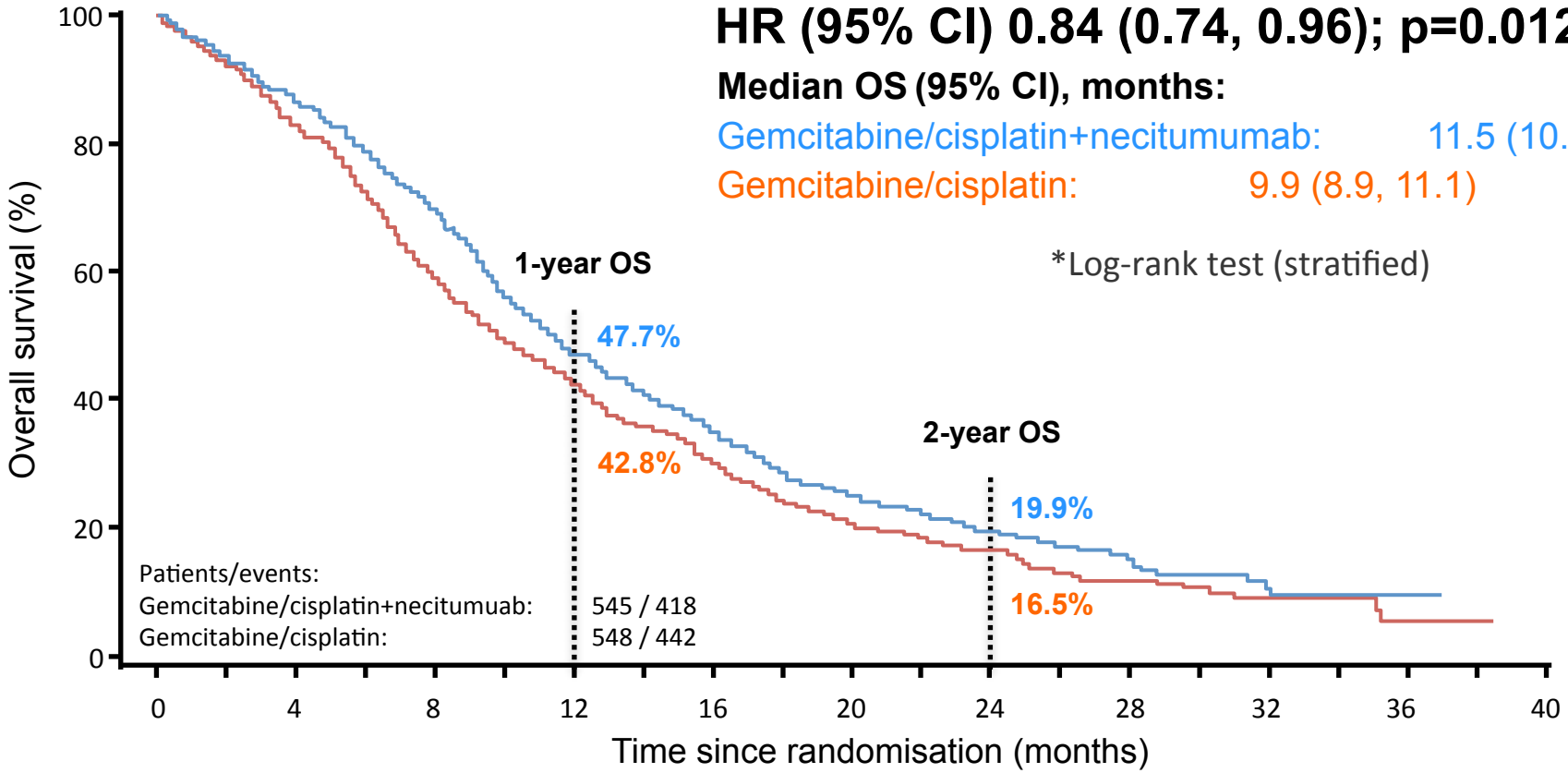
*Gemcitabine 1250 mg/m² IV days 1 and 8, cisplatin 75 mg/m² IV day 1; †800 mg IV days 1 and 8

Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)

8008^: A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC) – Thatcher N et al

- **Key results**

OS



HR (95% CI) 0.84 (0.74, 0.96); p=0.012*

Median OS (95% CI), months:

Gemcitabine/cisplatin+necitumumab: 11.5 (10.4, 12.6)

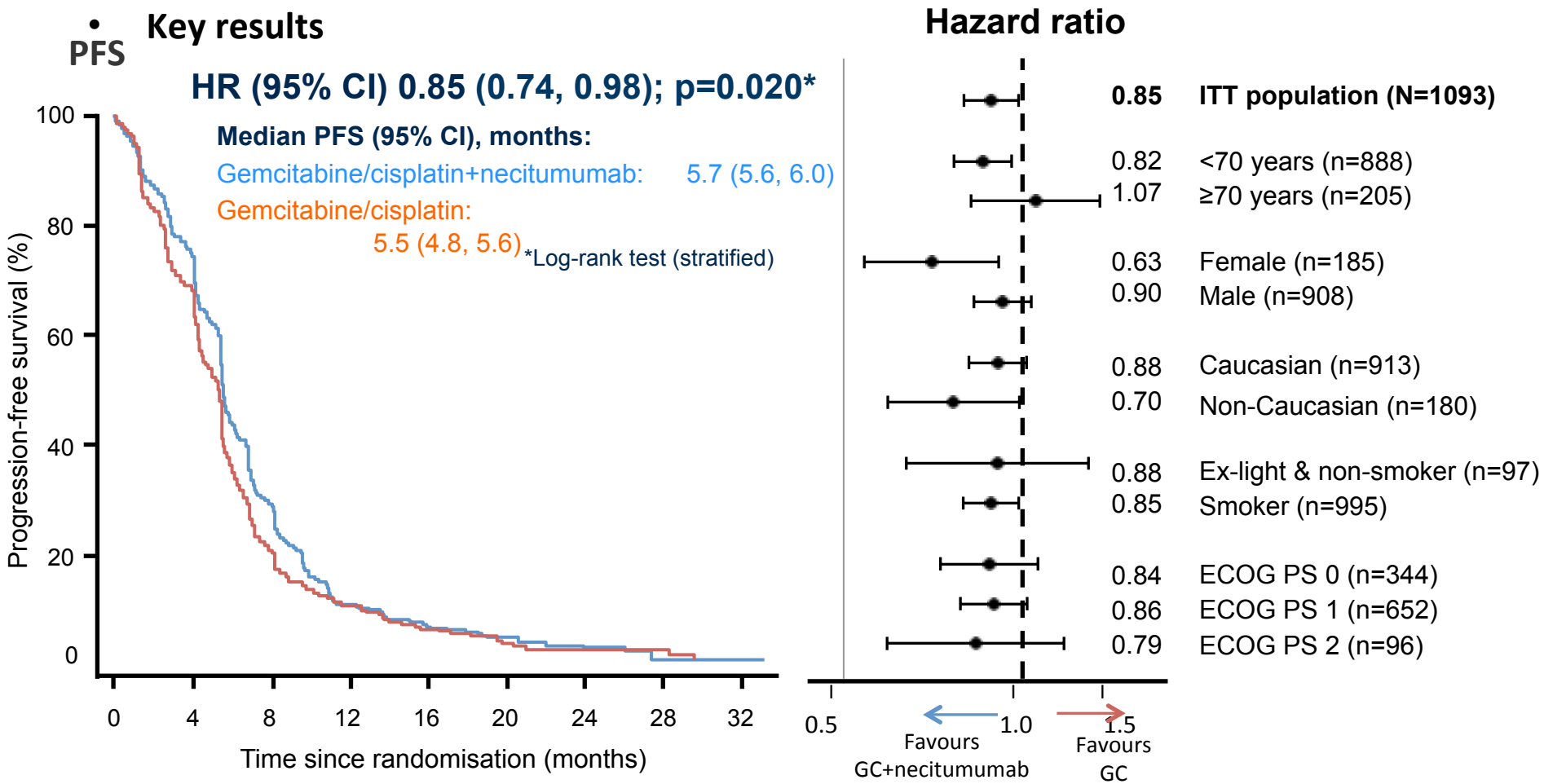
Gemcitabine/cisplatin: 9.9 (8.9, 11.1)

*Log-rank test (stratified)

Follow-up time (median): Gemcitabine/cisplatin+necitumumab: 25.2 months; gemcitabine/cisplatin: 24.8 months

Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)

8008^: A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC) – Thatcher N et al



Progression-free survival as assessed by investigators

Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)

A randomized, multicenter, open-label, phase III study of gemcitabine-cisplatin (GC) chemotherapy plus necitumumab (IMC-11F8/LY3012211) versus GC alone in the first-line treatment of patients (pts) with stage IV squamous non-small cell lung cancer (sq-NSCLC) – Thatcher N et al

- **Conclusions**
  - SQUIRE is the largest randomised phase III trial of first-line treatment for metastatic squamous NSCLC
  - The study met its primary endpoint by showing a statistically significant improvement in OS
  - Results were consistent across endpoints and pre-specified subgroups, including patients with ECOG PS 2

Statistically significant, but is it clinically relevant?

- six-day (0.2-month) improvement in median progression-free survival
- subgroup not to show a survival benefit was the group of patients who were 70 years or older.
- Response Rate: 31% versus 29%, p=0.400
- Unfortunately, in an exploratory analysis presented for the SQUIRE study, the H-score was not predictive for necitumumab activity

Thatcher et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8008^)

Targeting FGFR1-amplified

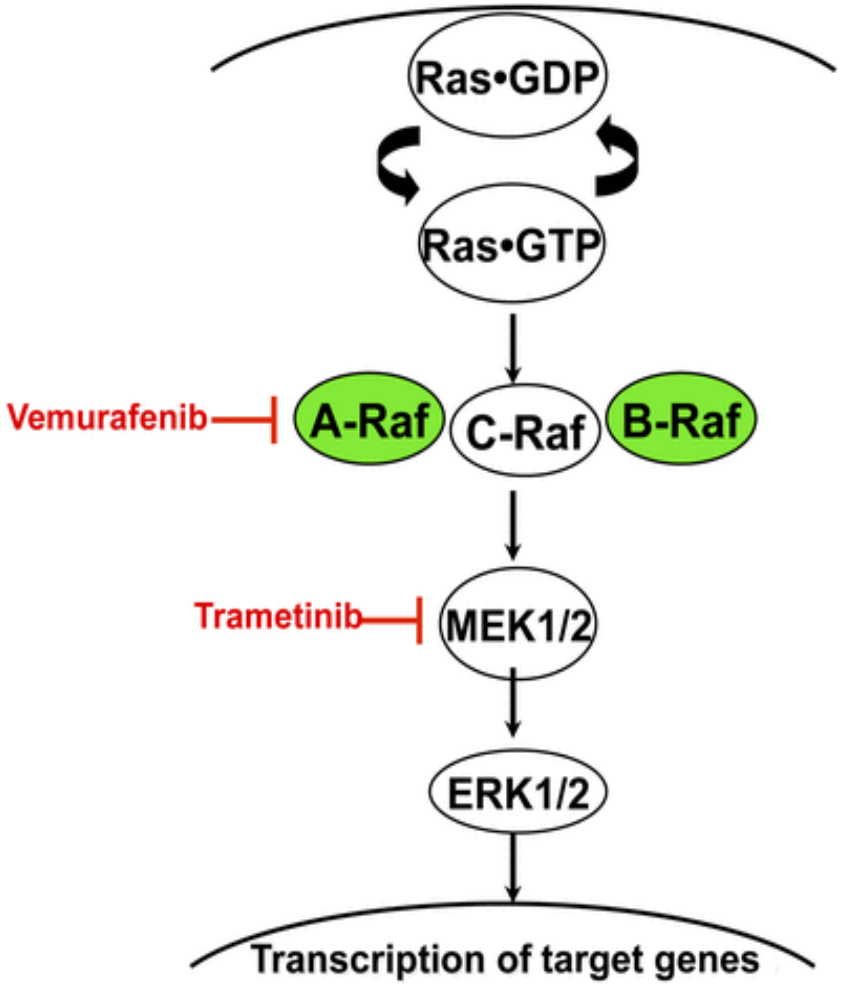
Targeting FGFR1-amplified lung squamous cell carcinoma with the selective pan-FGFR inhibitor BGJ398

- **Study design**
  - Subgroup analysis of phase I dose-escalation study of patients with *FGFR1*-amplified advanced or metastatic lung squamous cell carcinoma treated with BGJ398 5–150 mg/day in 28-day cycles who had progressed following at least one line of therapy
- **Key results**
  - 26 patients were treated at the maximum tolerated dose of 150 mg/day (n=3), 125 mg/day (n=21) or 100 mg/day (n=2)
  - Of the 26 patients receiving ≥100 mg/day, 4 patients achieved PR; 9 patients had SD, 6 patients had PD and status was unknown in 7 patients
  - AEs were manageable and reversible
- **Conclusion**
  - This molecular targeted therapy shows evidence of activity supporting further development of BGJ398 in *FGFR1*-amplified lung squamous cell carcinoma

FGFR, fibroblast growth factor receptors

Nogova et al. J Clin Oncol 2014; 32 (suppl 5; abstr 8034)

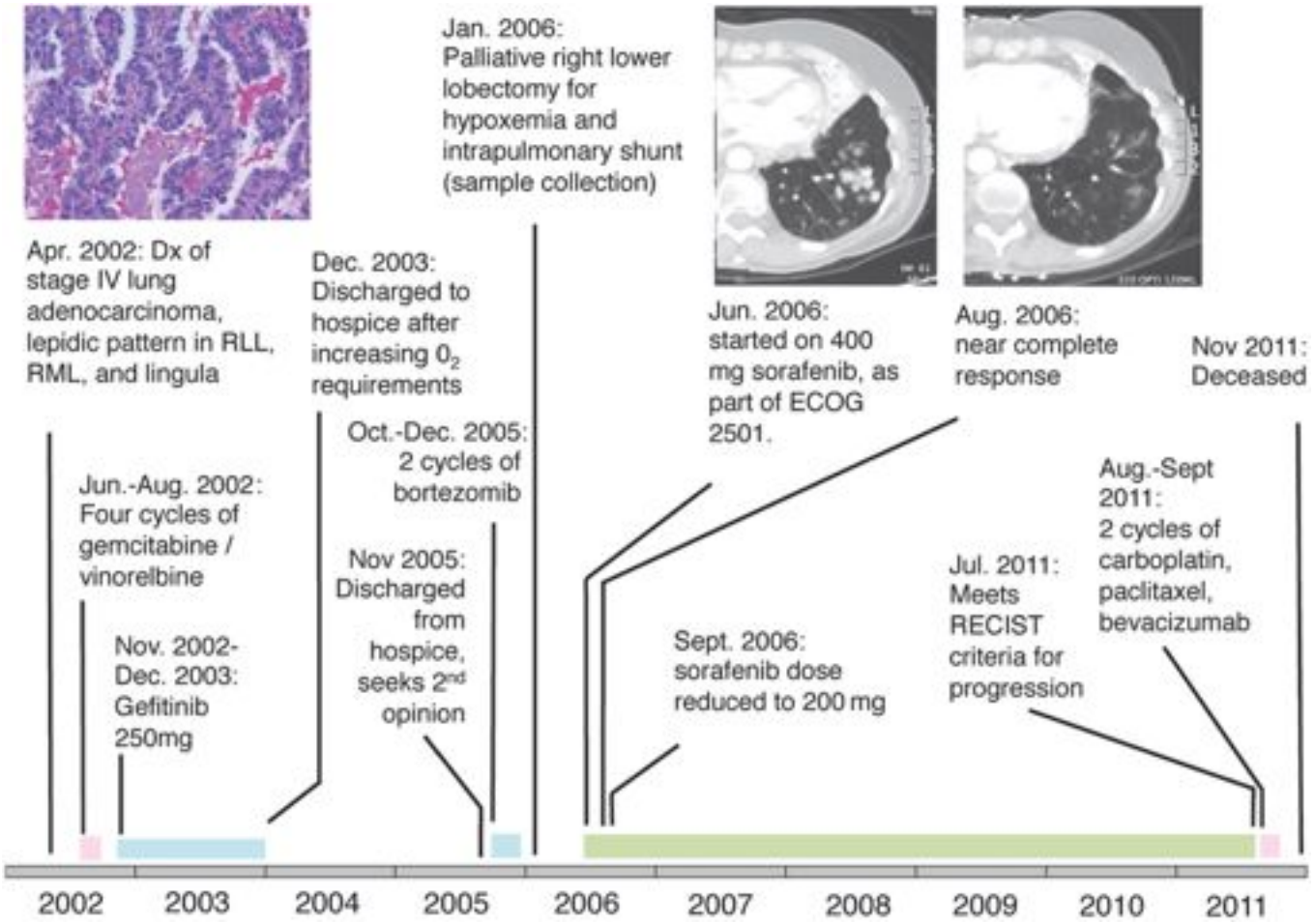
A new target?? ARAF Mutations



Additional mutations affecting this residue of ARAF and a nearby residue in the related kinase RAF1 were demonstrated across 1% of an independent cohort of lung adenocarcinoma cases.

Imielinski et al, J Clin Invest. 2014 Apr 1;124(4):1582-6.

Oncogenic and sorafenib-sensitive *ARAF mutations in lung adenocarcinoma*



Araujo,Amann, Imielinski et al, abstr 11034

Take home messages

- Beyond the estabilished targets in lung cancer (EGFR; ALK, etc) there are many emerging targets:
  - ROS, ARAF, FGFR, etc
- In a significant proportion of NSCLC, a single oncogenic driver cannot be identified
- Targeting pathways may be effective in moleculary defined subsets of patients.
- Dual / multiple pathway inhibition is part of the answer?
- Trial design must be updated!.


BEDANKT
VOOR UW
AANDACHT, ZIJN
ER NOG
VRAGEN?