ASCO 2014: Promise and Progress in the Treatment of Lung Cancer

EMORY
WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

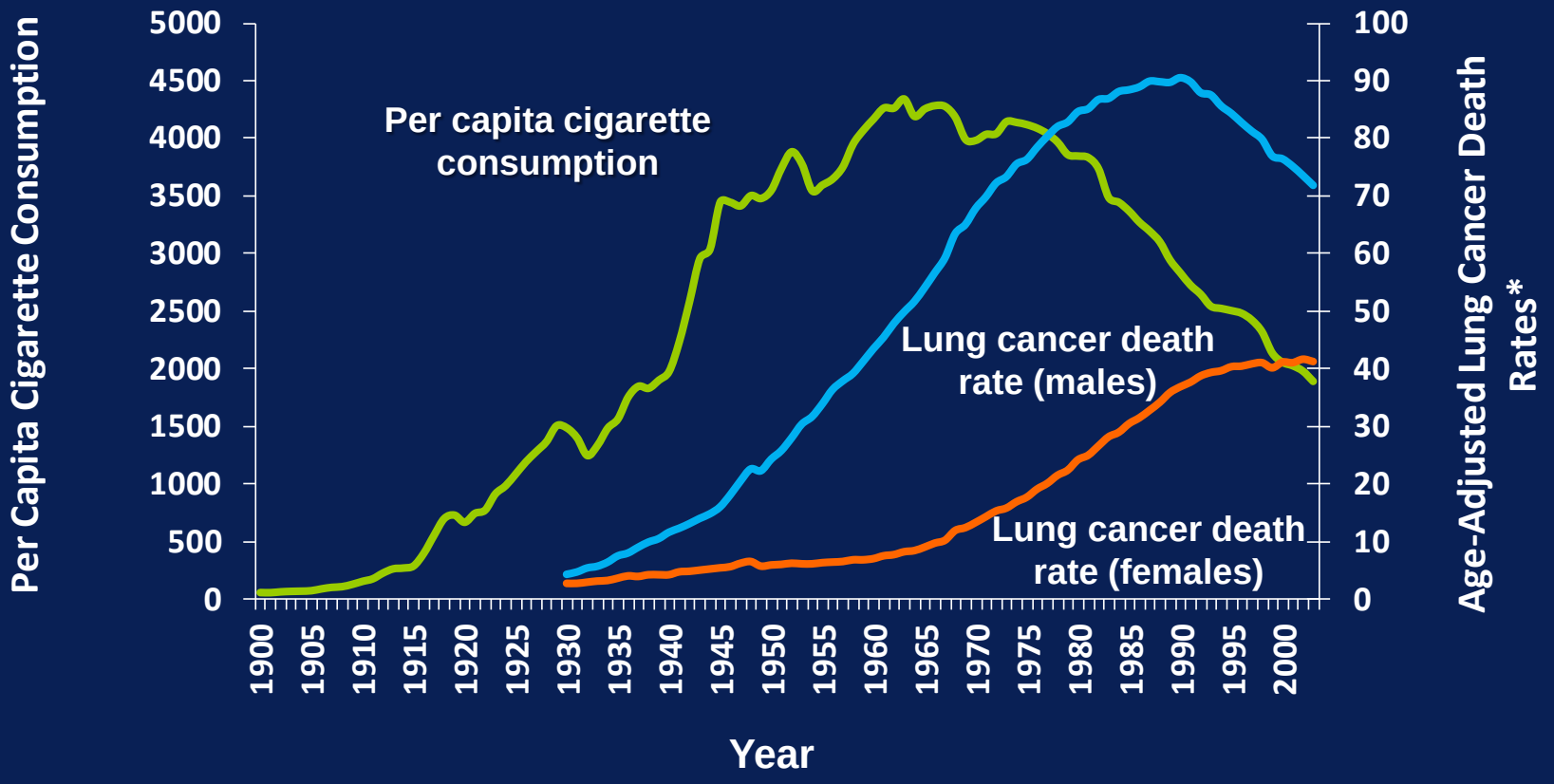
Fadlo Raja Khuri, MD
Professor and Chair
Department of Hematology & Medical Oncology,
Deputy Director
Winship Cancer Institute of Emory University
Roberto C. Goizueta Chair in Cancer Research

September 6, 2014

Educational Objectives

- New roles for targeted therapies for early stage disease?
- Consolidation chemotherapy's last stand in Stage III NSCC?
- Current treatment algorithms for patients with NSCLC with known and unknown driver mutations
- Selecting treatment in patients without an actionable mutation
- Defining the role of prophylactic cranial radiation in small cell lung cancer

The Best Way to Fight Advanced NSCLC Is to Prevent it...Stop Smoking!



*Age-adjusted to 2000 US standard population.

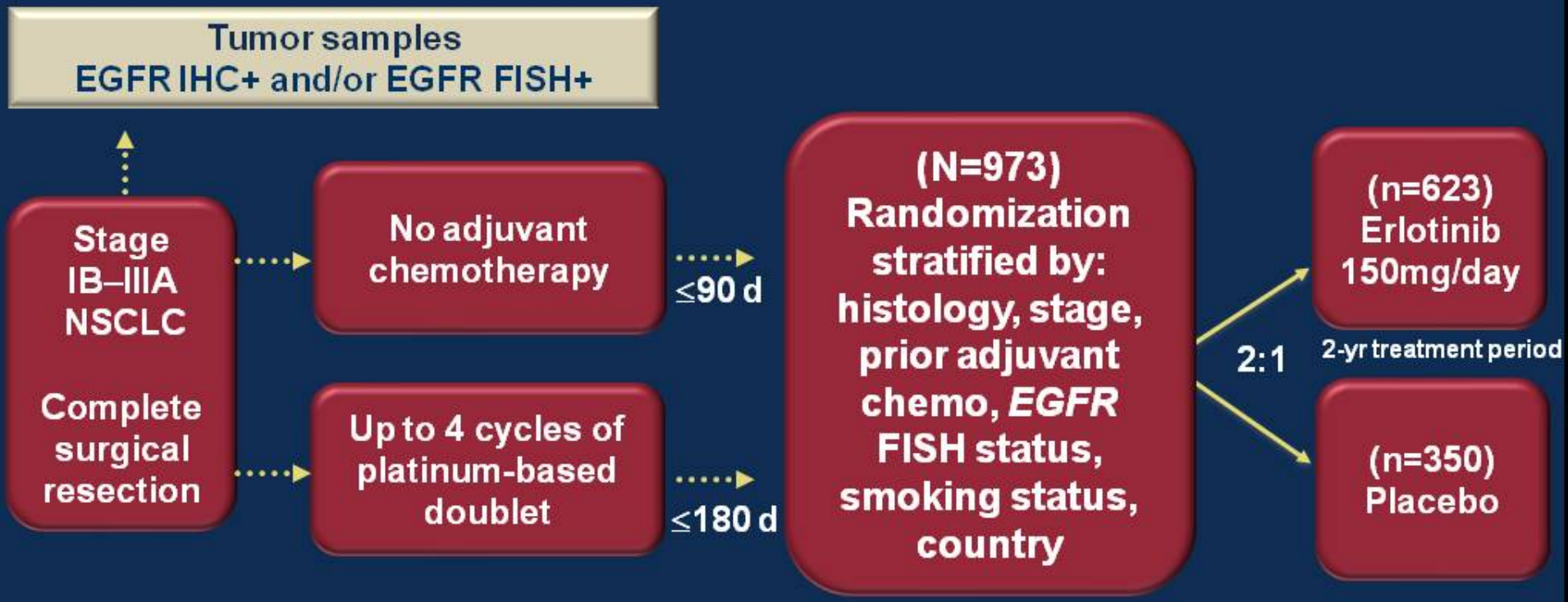
Source: Death rates: US Mortality Public Use Tapes, 1960-2003, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2005. Cigarette consumption: US Department of Agriculture, 1900-2003.

How Much Does Chemotherapy Contribute to Cure in Early Stage NSCLC?

- Stage IB-3%
- Stage II- 10%
- Stage III- 13%

LACE Meta-analysis, Pignon et al, JCO.

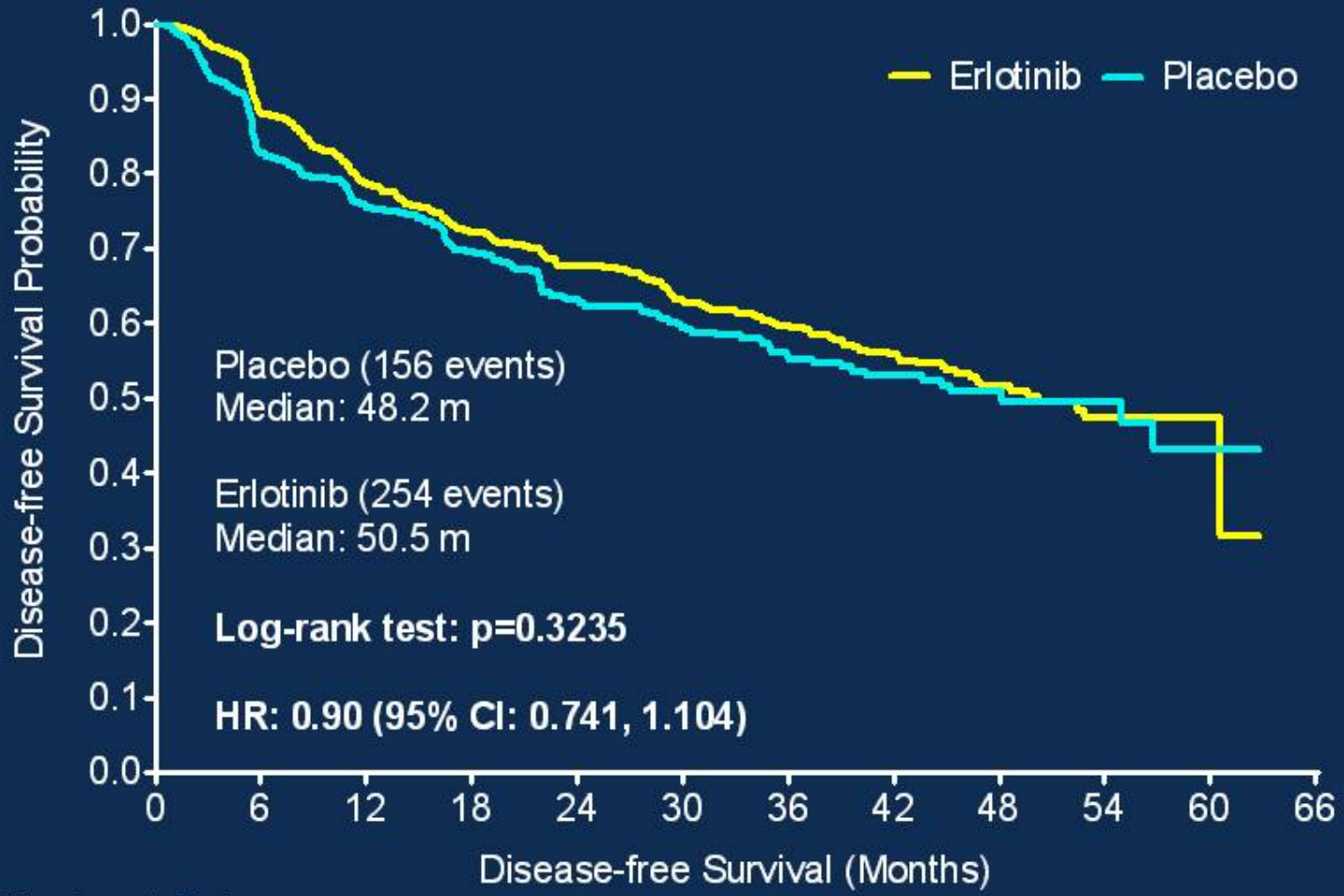
RADIANT Trial Design



- **Radiology assessment:** every 3 months on treatment and yearly during long-term follow up

- **Primary endpoint: DFS**
- **Secondary endpoints: Overall survival (OS); DFS and OS in patients with del19/L858R (*EGFR* M+)**

Disease-free Survival KM Plot



Number at Risk

Placebo	350	280	255	231	198	174	124	83	43	22	1	0
Erlotinib	623	514	451	411	368	320	223	154	82	40	8	0

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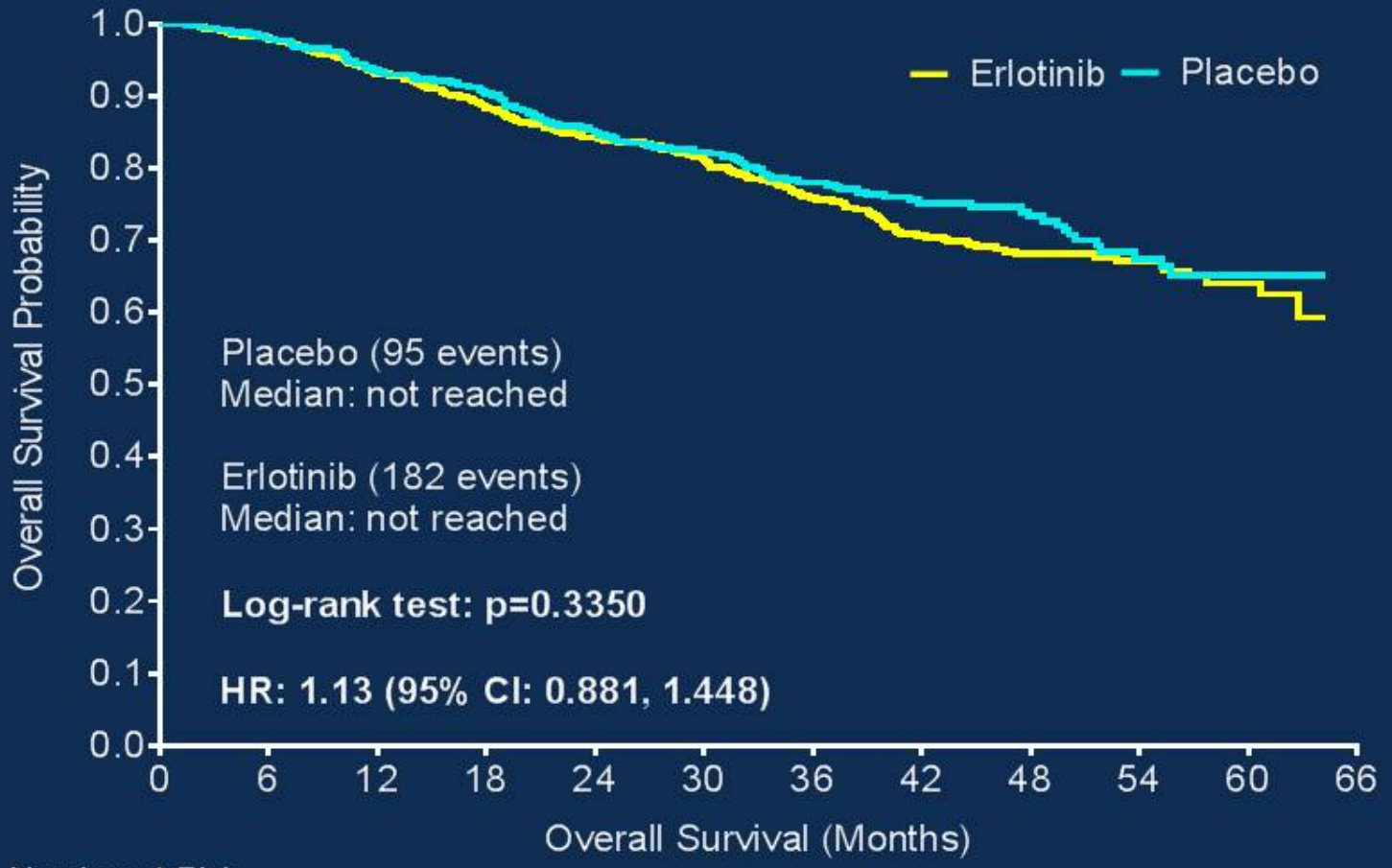
Overall Survival KM Plot



Number at Risk												
Placebo	350	336	318	306	285	274	244	172	119	72	30	0
Erlotinib	623	586	549	519	489	467	412	288	193	118	51	0

Median follow-up duration = 47 months.

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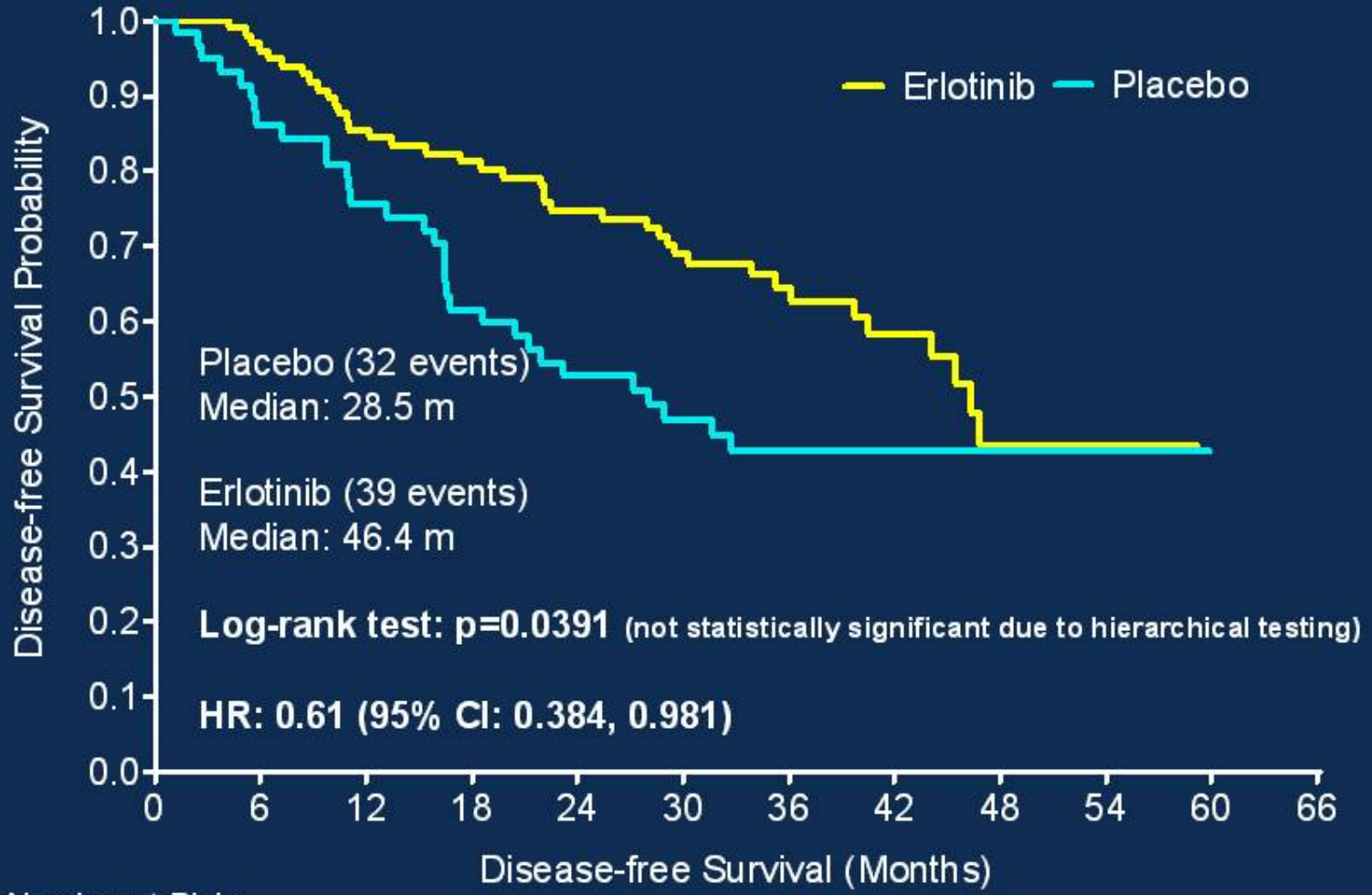
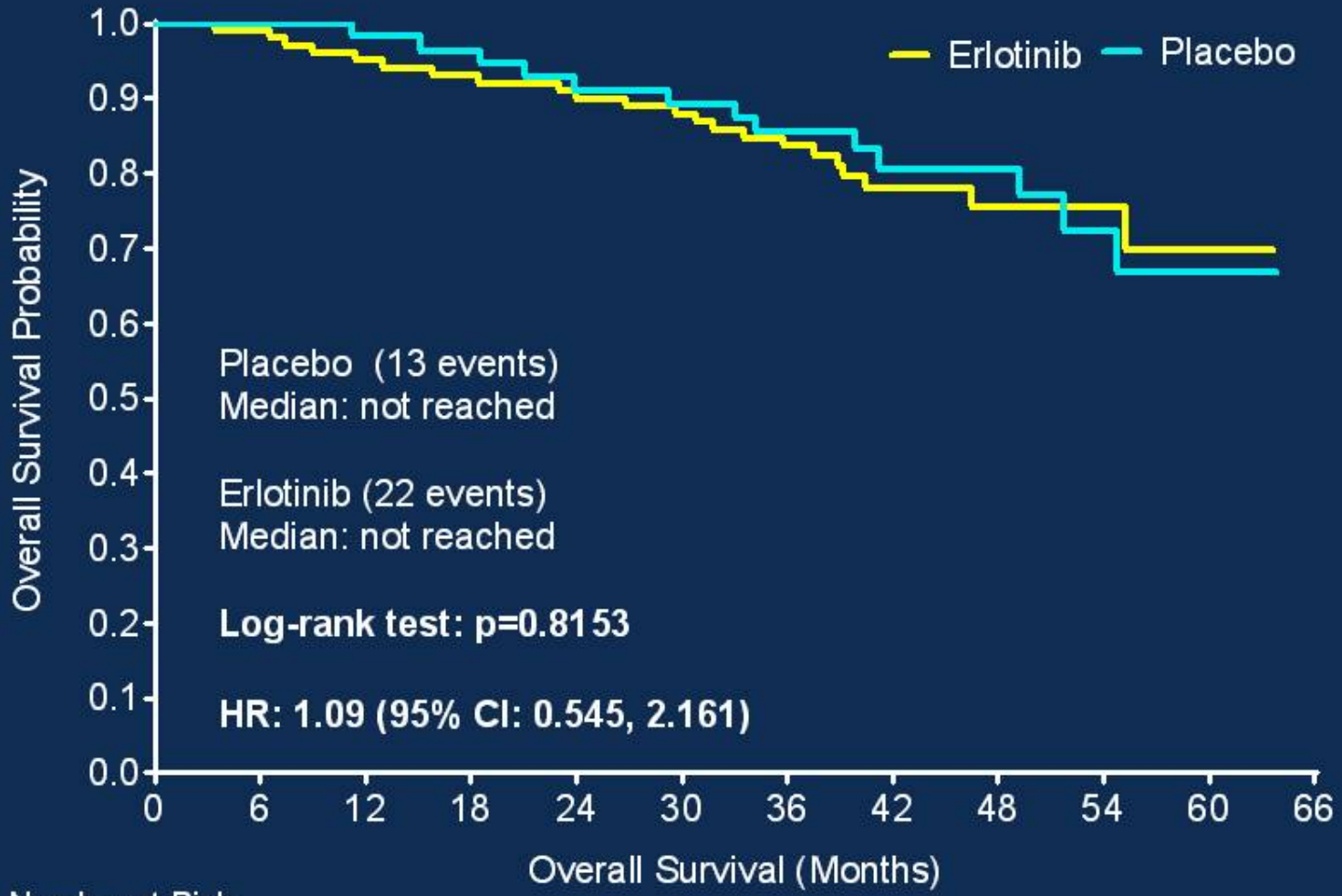
Disease-free Survival: *EGFR* M+



Number at Risk

Placebo	59	49	43	35	30	23	15	12	10	5	0	0
Erlotinib	102	94	80	76	68	56	35	22	10	3	0	0

Overall Survival: *EGFR* M+



Number at Risk

Placebo	59	57	56	53	51	50	41	30	24	14	5	0
Erlotinib	102	100	94	91	88	86	75	43	26	15	7	0

SELECT phase II study

Pennell et al, ASCO 2014, abstract 7514

- Adjuvant Erlotinib in EGFR mutation +
- 76% 2 yr DFS historical control
- 45% stage I, 27% stage II, 28% stage III
- 2/3 received nearly 2 years of therapy

SELECT results

- 2 year DFS was 89%!
  - Stage I: 96%
  - Stage II: 78%
  - Stage III: 91%

- 29 recurred: only 4 during erlotinb
  - Most who recurred off erlotinib, responded when re-challenged

Questions to consider

- What is the meaning of improved DFS in the absence of OS in the adjuvant setting?

- What level of evidence is required?
  - Is this sufficient?
  - Phase III trials?

ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification And Sequencing Trial) Umbrella Protocol Will Screen Patients

Trial Category	A151216 ALCHEMIST	E5412	A081105
Target	Registry/Intervention with biopsy at recurrence	ALK+	EGFR mut
Prevalence	all comers	~5%	~10%
Total Sample Size	**6000 – 8000**	378 (5% inflation)	430 (5% ineligible)
Primary Endpoint	N/A	Overall Survival	Overall Survival
Power	N/A	80%	85%
One-sided α	N/A	0.05	0.05
Hazard Ratio	N/A	0.67	0.67

Doroshow JH. Available at: deainfo.nci.nih/gov/advisory/ncab/164_1213/Doroshow.pdf. Accessed May 14, 2014.

Decision Tree for Adjuvant Therapy for NSCLC: Utilization of Data to positively impact outcomes

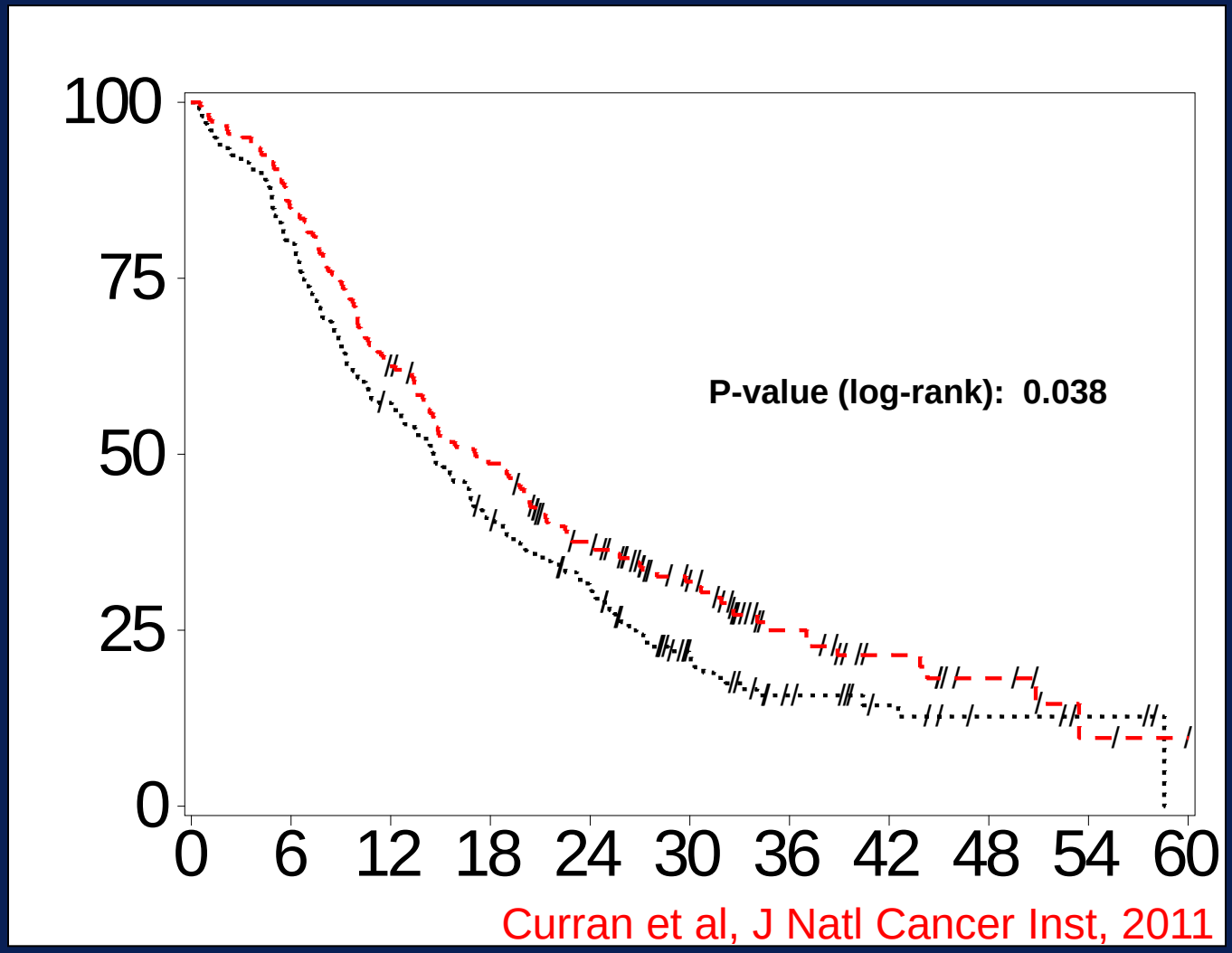
- Personalization of care by histology (pemetrexed and possible bevacizumab) for nonsquamous
- Molecular markers
  - ERCC1, etc, not helpful
  - EGFR and ALK testing critical at the time of surgery
- Support ALCHEMIST by referring and enrolling patients with EGFR and ALK mutation carrying tumors

Locally Advanced NSCLC: Definition

- Stage IIIA
  - Bulky N2 disease
  - Multi-station N2 disease
- Stage IIIB
  - T4 (not including patients with additional nodules in other lobes)
  - N3 disease
  - Supraclavicular lymph node involvement

Approximately 15-20% of NSCLC will fit into the above categories
-150,000 to 200,000 cases each year globally

RTOG 9410: Concurrent vs. Sequential



Curran et al, J Natl Cancer Inst, 2011

HOG LUN 01-24/USO 02-033

ChemoRT

Cisplatin 50 mg/m^2 IV d 1,8,29,36
Etoposide 50 mg/m^2 IV d 1-5 & 29-33
Concurrent RT 59.4 Gy (1.8 Gy/fr)

Stratification Variables:
PS 0-1 vs 2
IIIA vs IIIB
CR vs. non-CR

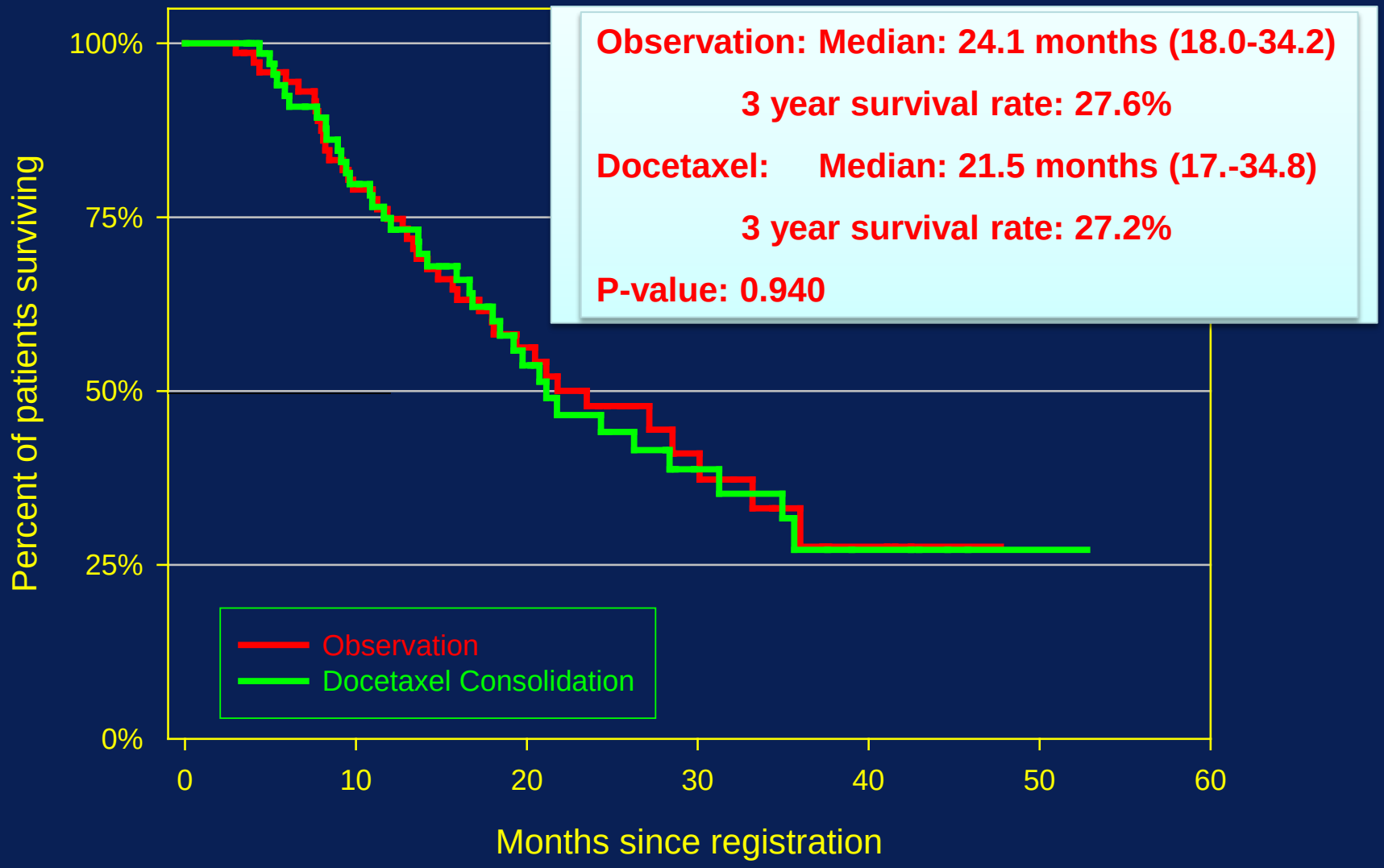
Randomize

Docetaxel 75 mg/m^2 q 3 wk $\times$ 3

Observation

Hanna et al, J Clin Oncol, 2008

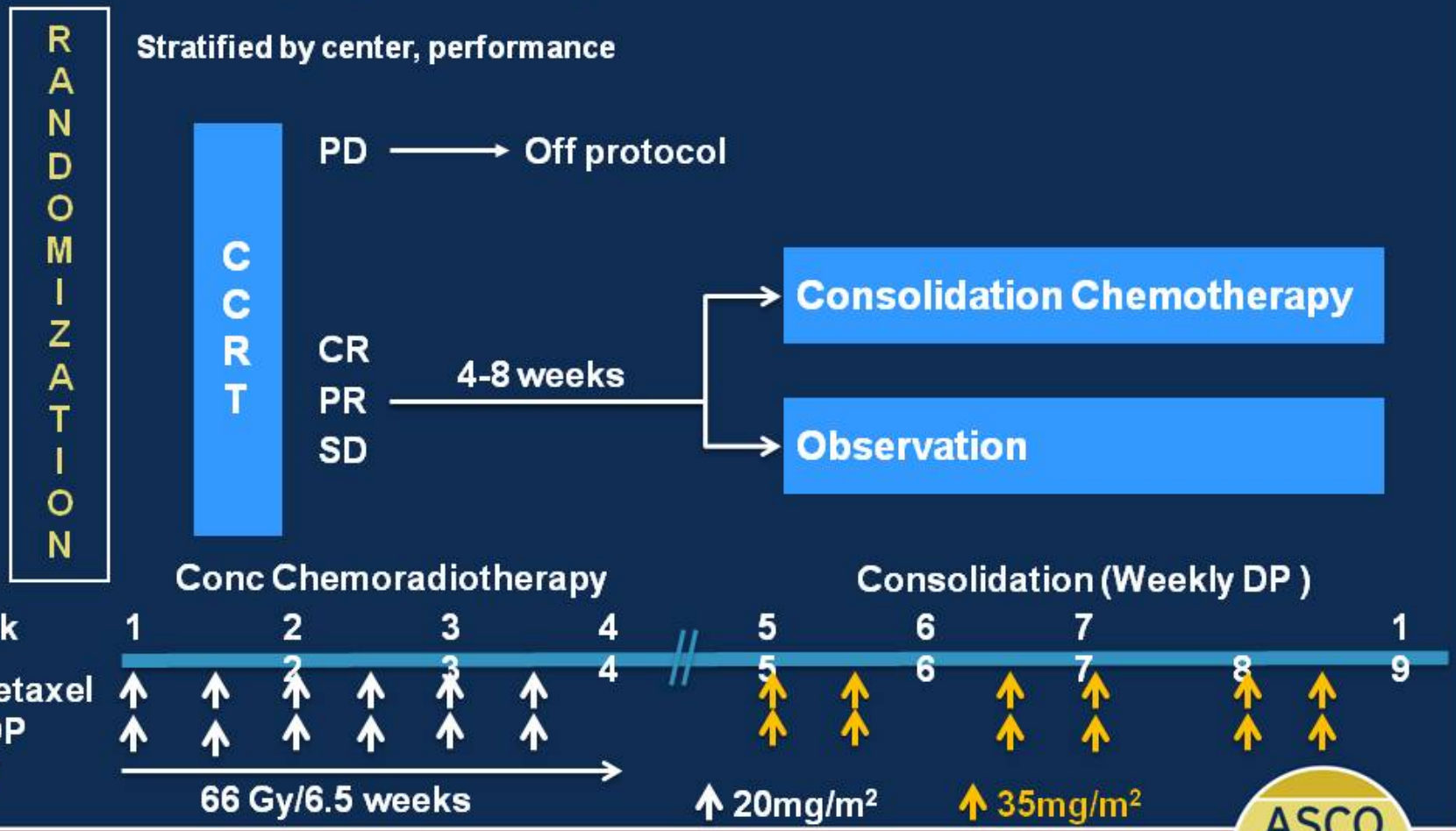
Overall Survival (ITT)
Randomized Patients (n=147)



Study Design

Multinational, phase III randomized trial

Locally Advanced, Inoperable Stage III NSCLC



Presented by: Keunchil Park, M.D., Ph.D.

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Compliance of Consolidation Chemotherapy

		CCRT + Consolidation (n=209)	
		n	%
Cycle 3	Day 8	88	42.1%
	Day 1	4	1.9%
Cycle 2	Day 8	21	10.1%
	Day 1	5	2.4%
Cycle 1	Day 8	15	7.2%
	Day 1	10	4.8%
No consolidation		66	31.6%

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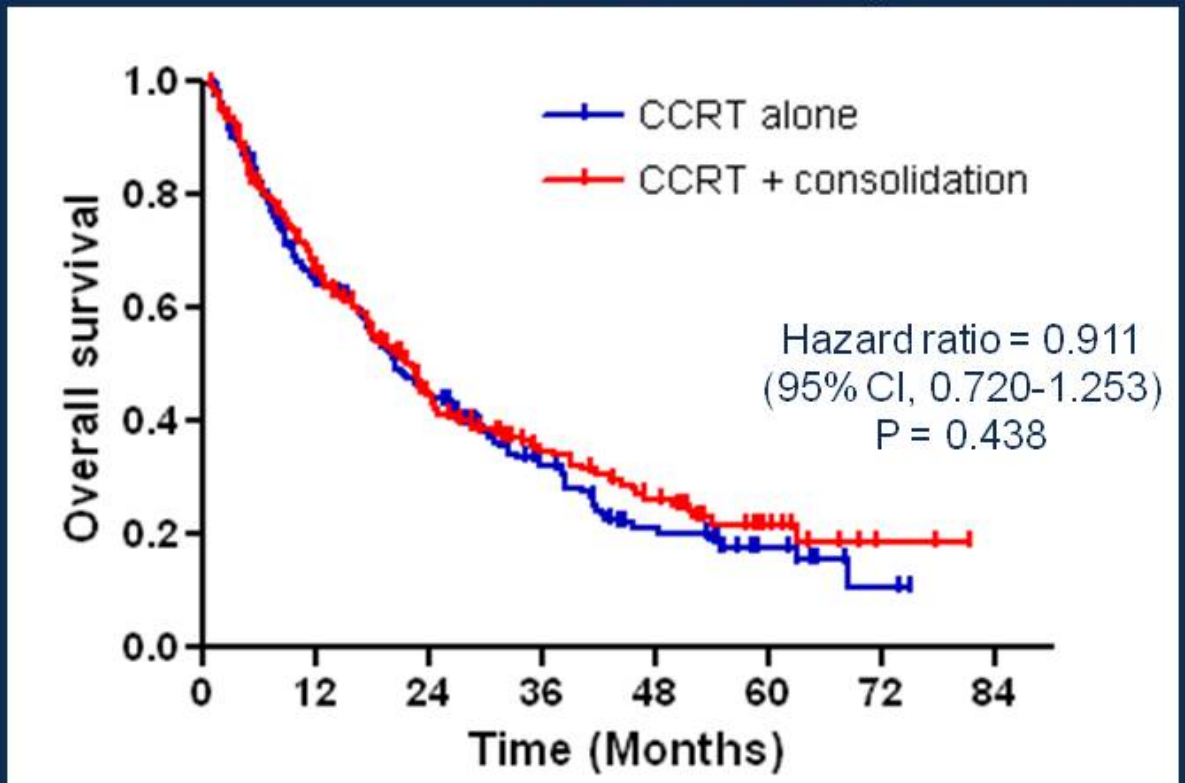
Overall Survival

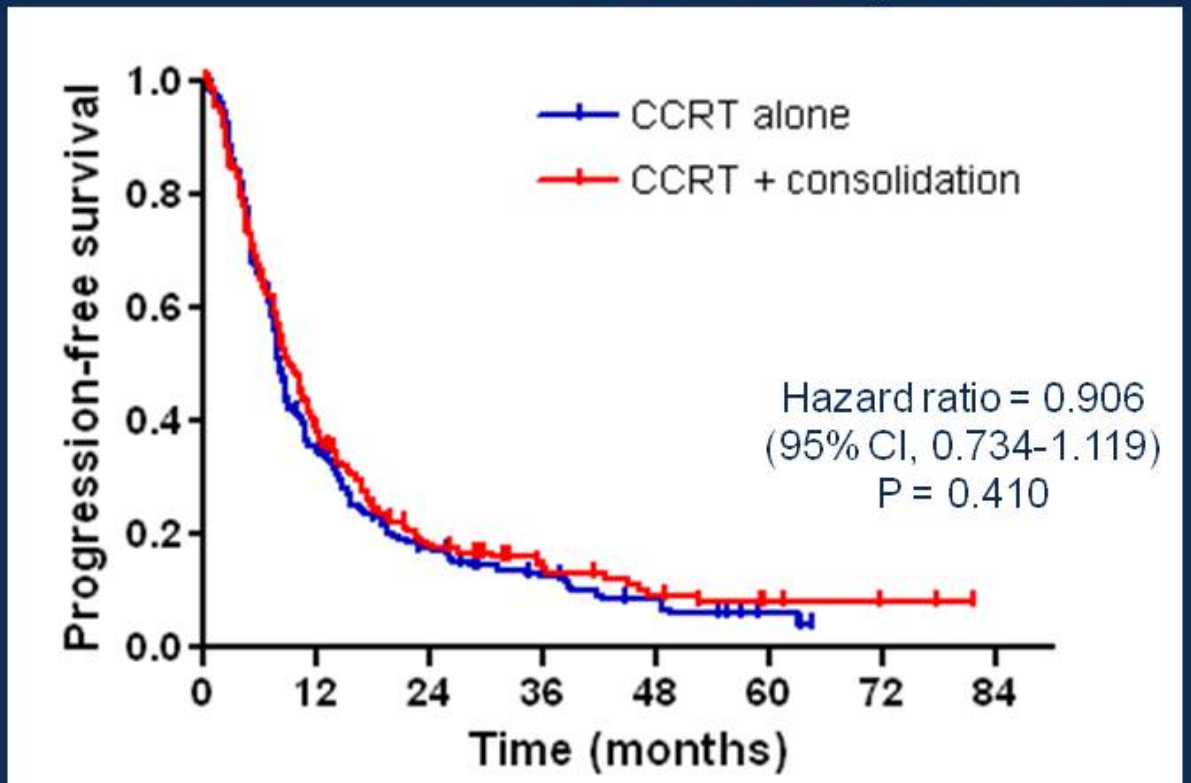
Median follow-up: 50.7 months



	Patients	Events	mOS (95% CI)
CCRT alone	209	145	20.63 (17.58, 26.28)
CCRT + consolidation	211	134	21.78 (17.71, 24.74)

Progression-free Survival

Median follow-up: 50.7 months

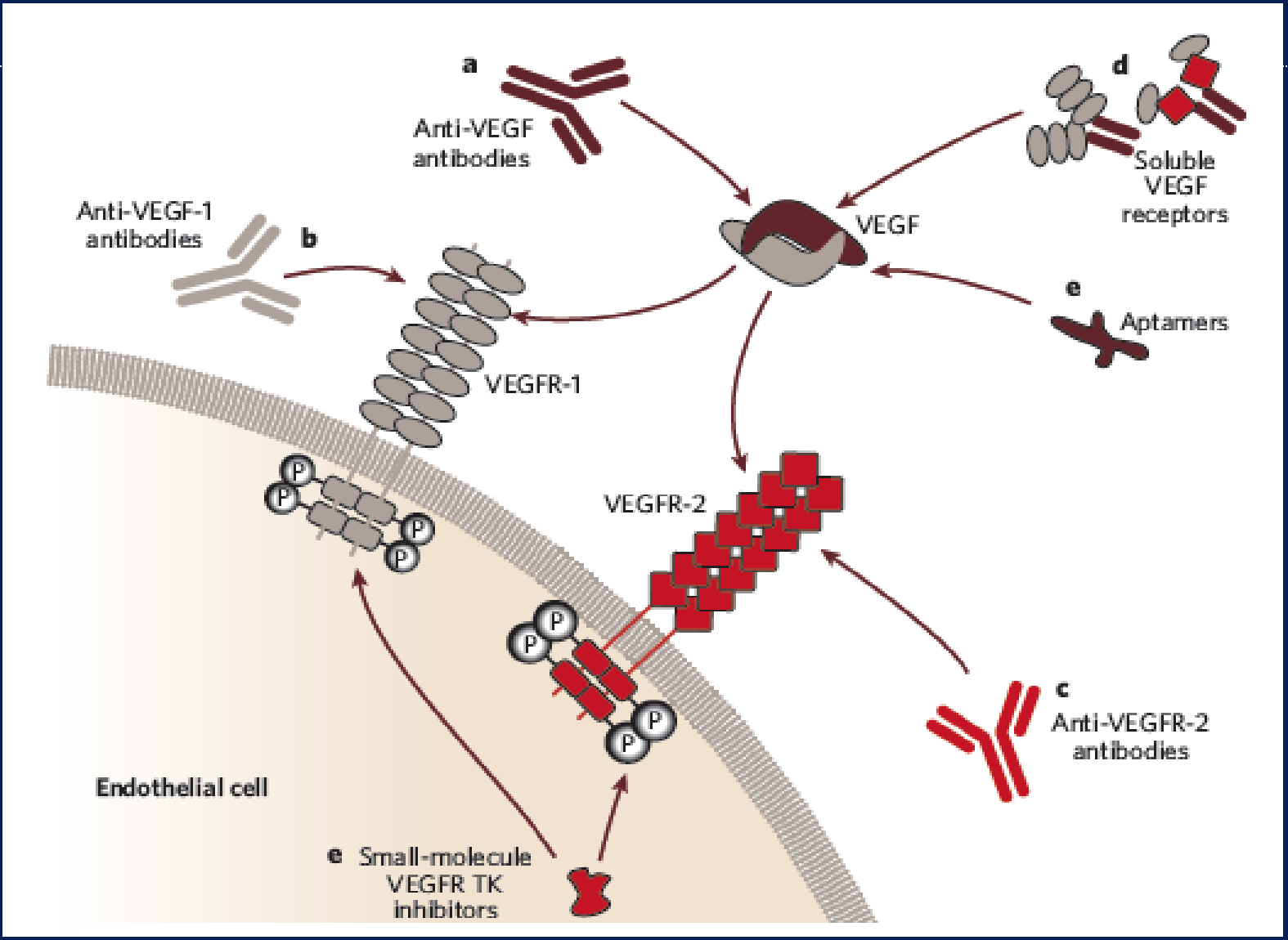


	Patients	Events	mPFS (95% CI)
CCRT alone	209	180	8.05 (7.56, 8.90)
CCRT + consolidation	211	169	9.10 (7.92, 10.94)

Key Chemotherapy Questions in Stage III NSCLC

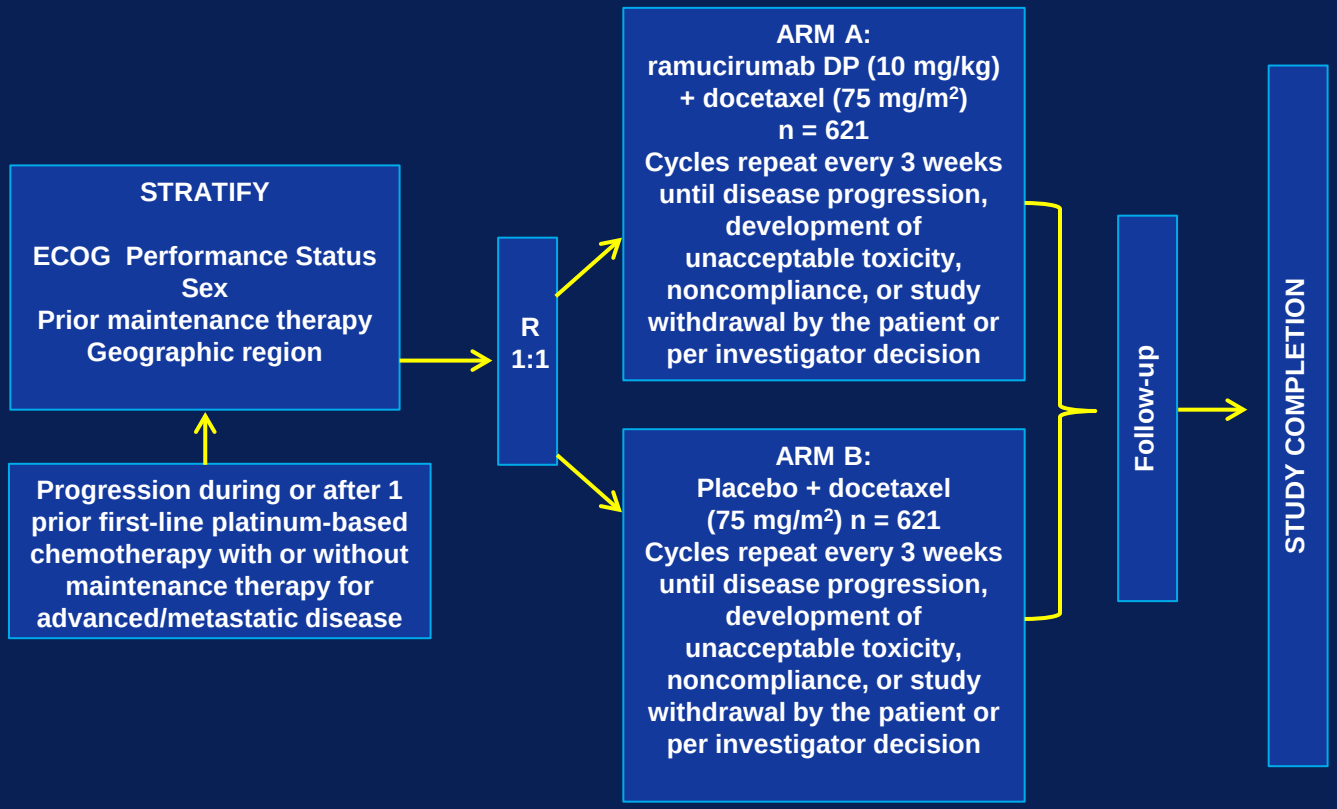
- Is there an optimal drug regimen and cycle number?
- How do we best integrate molecular therapies or immunological approaches?
- How should we advance therapy for marginally resectable stage III disease?
- Can we develop better preclinical models?

VEGF Inhibition



Ferrara N, Nature 2005; 438: 967-974

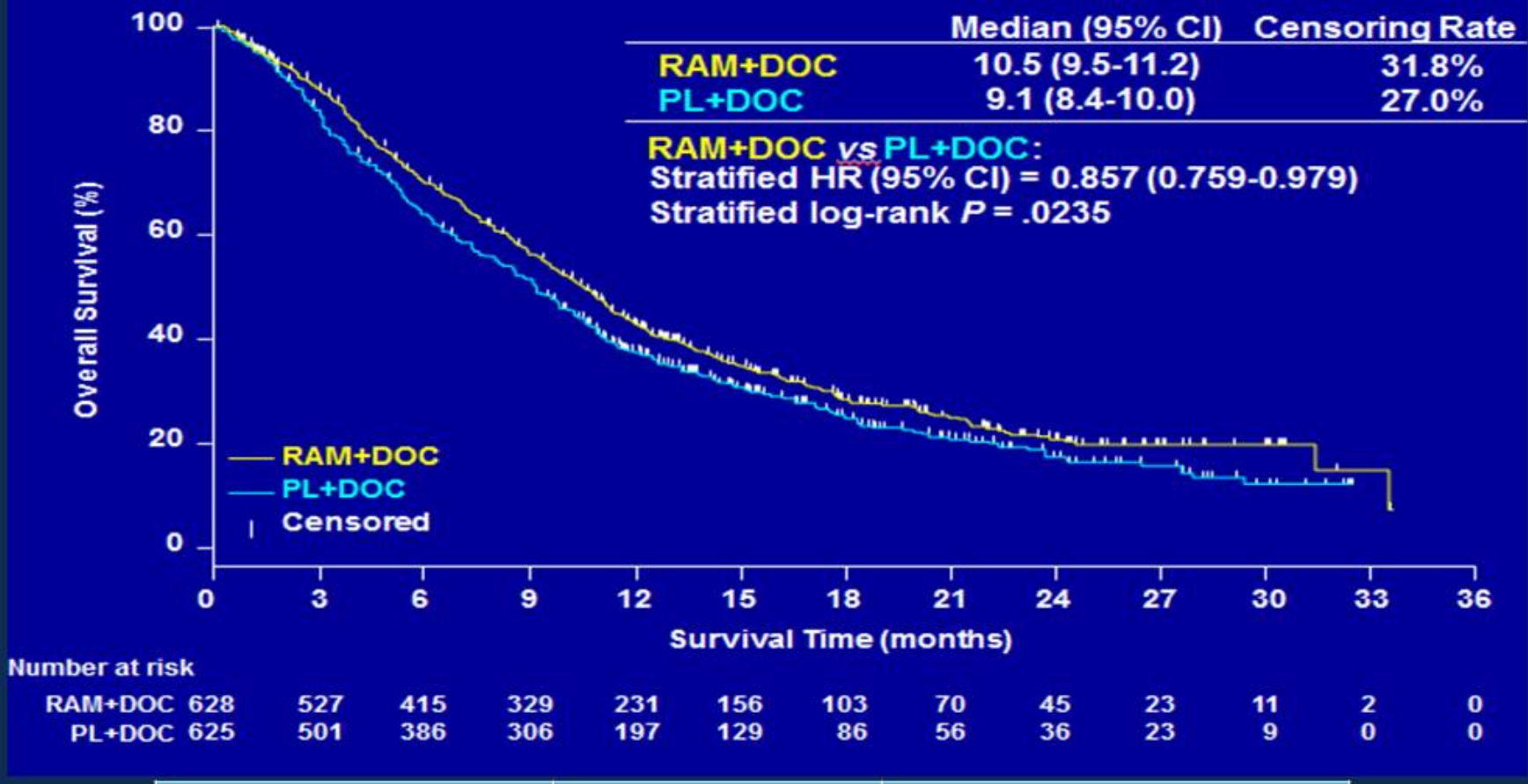
REVEL: Ramucirumab-Human VEGFR-2 ab



Positive per Press Release, 2014
Primary endpoint = OS
Garon EB et al. *Clin Lung Cancer.*2012;13:505-509.

REVEL: Overall Survival

ITT Population



	ORR	Median PFS
RAM + DOC	22.9%	4.5 mo
PL + DOC	13.6% (p<0.001)	3.0 mo (HR 0.76 p<0.0001)

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FIRST LINE THERAPY COMBINING CHEMOTHERAPY WITH AN EGFR ANTIBODY – NECITUMUMAB IN SQUAMOUS NSCLC

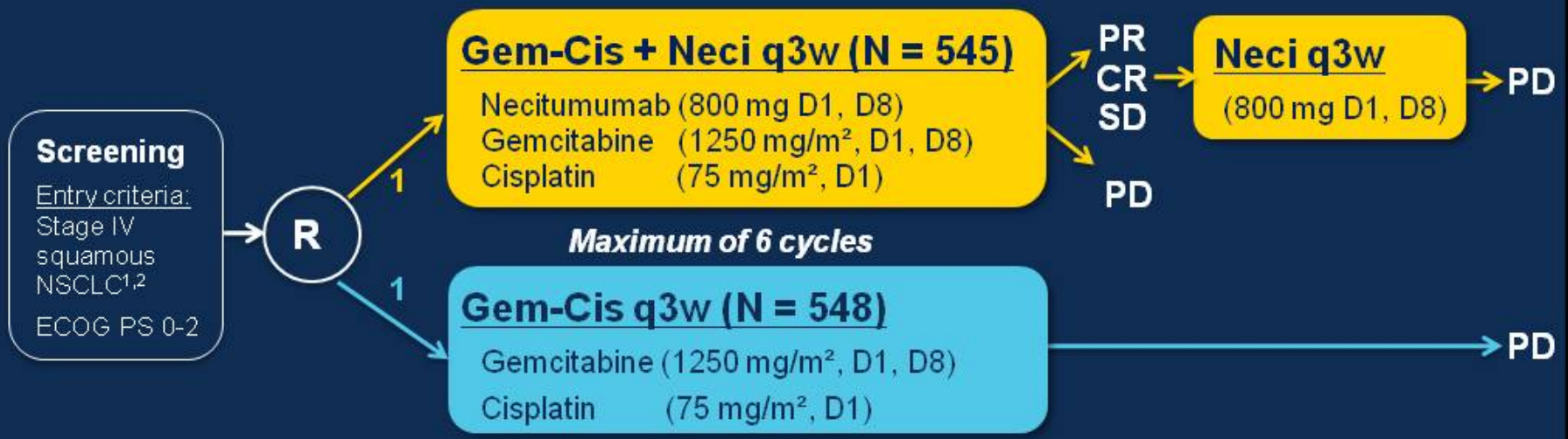
Haven't we been down this road before? i.e. the FLEX trial?

Abstract # 8008 – Thatcher N et al, 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.

Presented by: Julie R. Brahmer, M.D., M.Sc.

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Study Design



Randomization (R) stratified by: ECOG PS (0-1 vs. 2) and geographic region (North America, Europe and Australia; vs. South America, South Africa and India; vs. Eastern Asia)

Patient selection not based on EGFR protein expression

Radiographic tumor assessment (investigator read): at baseline and every 6 weeks until PD

Mandatory tissue collection

[1] AJCC TNM Classification, 7th edition, 2009; [2] UICC TNM Classification of Malignant Tumors, 7th edition, 2009

Presented by: Nick Thatcher

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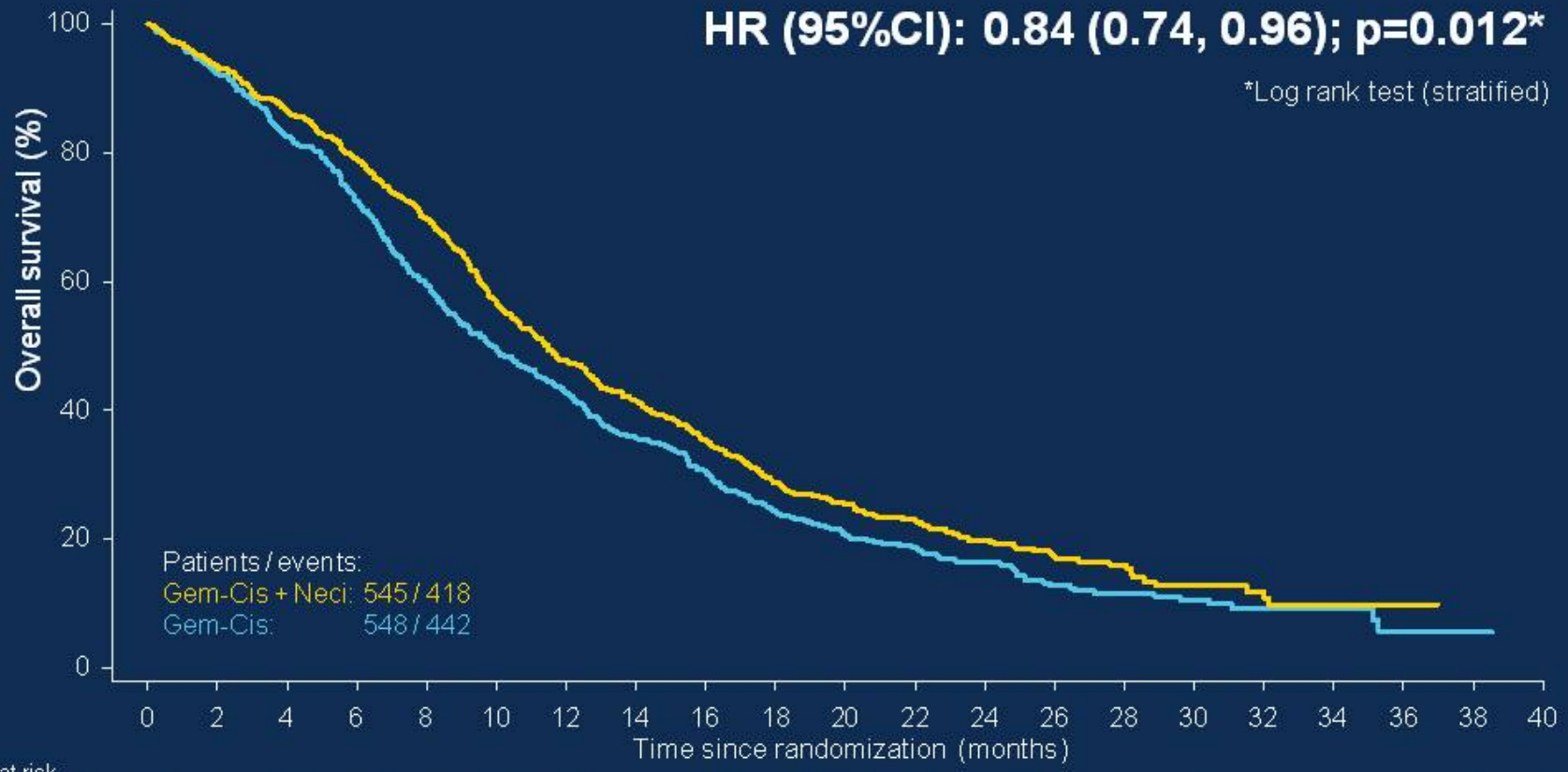
Primary Outcome: Overall Survival (ITT)



No. at risk

Gem-Cis + Neci	545	496	450	407	358	291	243	208	176	130	101	84	61	42	32	20	11	3	3	0	0
Gem-Cis	548	494	435	379	308	254	219	182	153	115	80	63	49	33	27	19	9	7	3	1	0

Presented by: Nick Thatcher

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Progression-Free Survival (ITT)

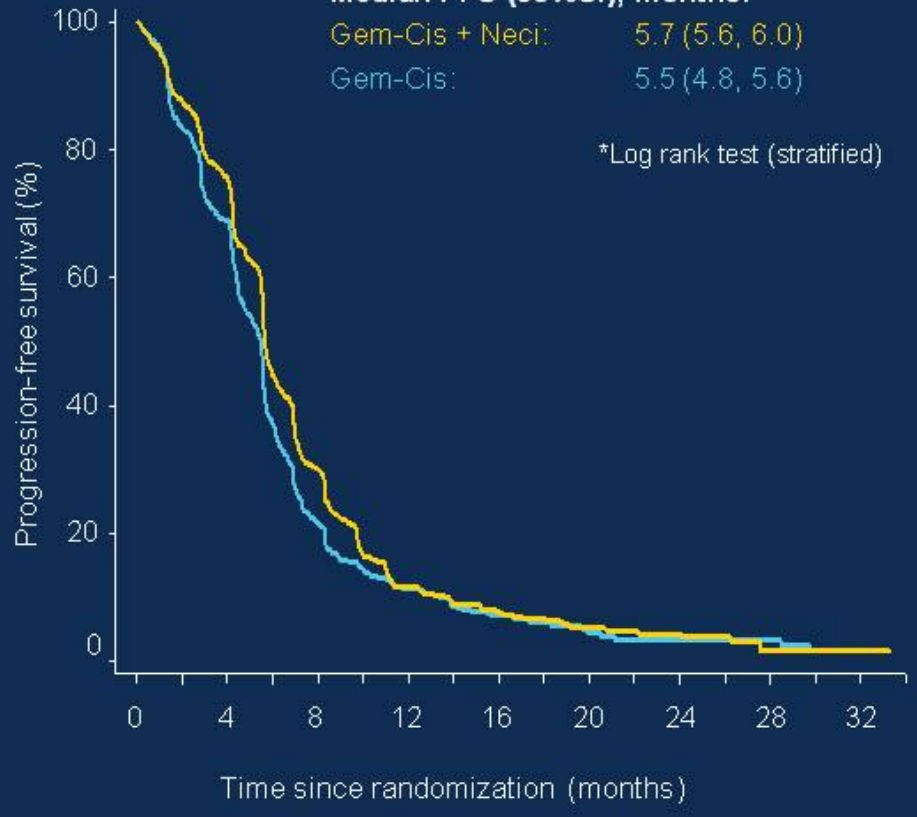
HR (95%CI): 0.85 (0.74, 0.98); p=0.020*

Median PFS (95%CI), months:

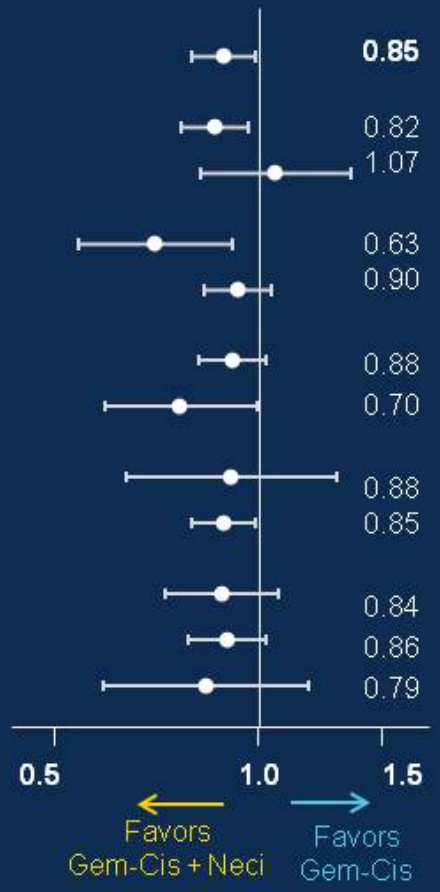
Gem-Cis + Neci: 5.7 (5.6, 6.0)

Gem-Cis: 5.5 (4.8, 5.6)

*Log rank test (stratified)



Hazard ratio



0.85	**ITT population (N=1093)**	
0.82	<70 yrs (N=888)	
1.07	≥70 yrs (N=205)	
0.63	Female (N=185)	
0.90	Male (N=908)	
0.88	Caucasian (N=913)	
0.70	Non-caucasian (N=180)	
0.88	Ex-light & non-smoker (N=97)	
0.85	Smoker (N=995)	
0.84	PS 0 (N=344)	
0.86	PS 1 (N=652)	
0.79	PS 2 (N=96)	

Progression-free survival as assessed by investigators

Presented by: Nick Thatcher

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Is The Glass Half Full or Half Empty?

HALF FULL

- Met its endpoint
- Improvem in multiple subgroups including squamous
- Easier dos compared cetuximab

Is wild type EGFR really a target in NSCLC????

HALF EMPTY

- Modest urvival enefit

ack of iomarker – ts put H core to rest

ASCO Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

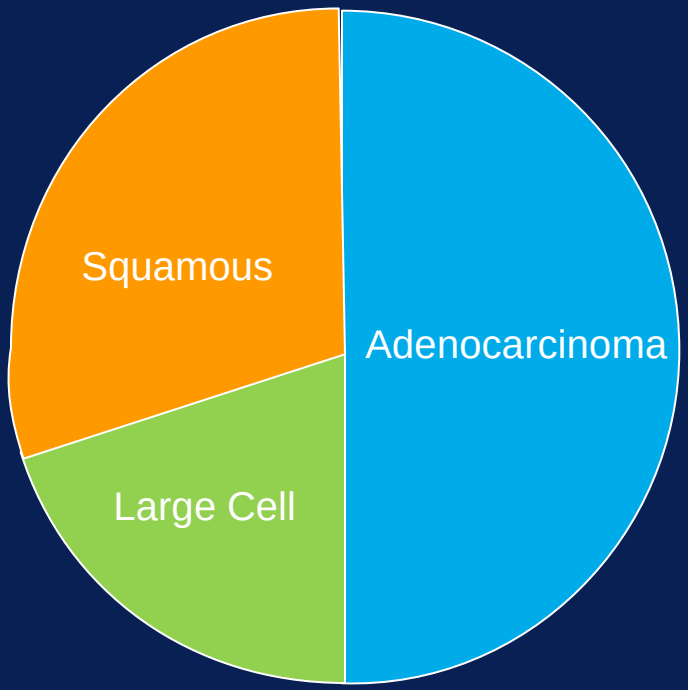
Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

These two phase III trials don't meet these criteria.

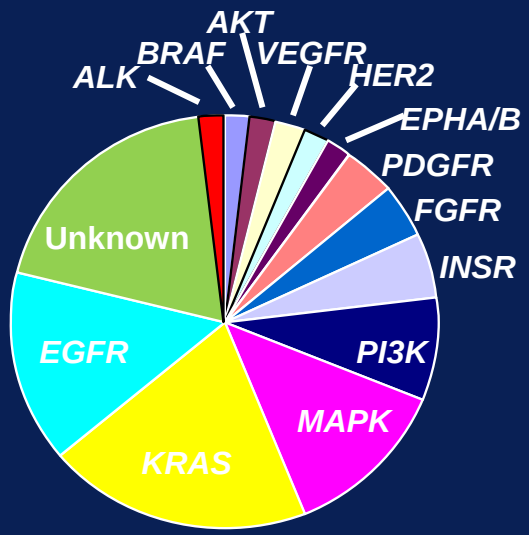
Ellis LM et al JCO 2012

NSCLC Landscape Change - 2014

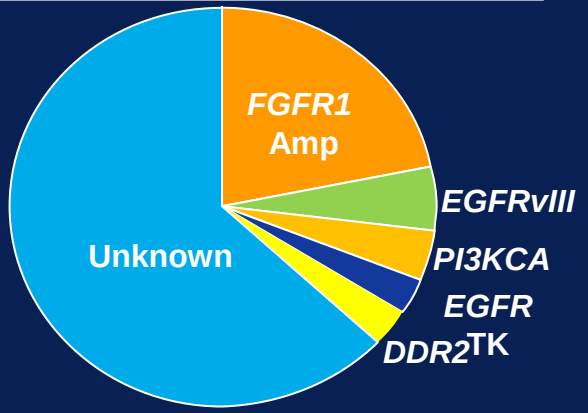
Traditional



Adenocarcinoma



Squamous Cell Carcinoma



Erlotinib +/- Bevacizumab as Second-Line Therapy (BeTa): Subgroup Analysis

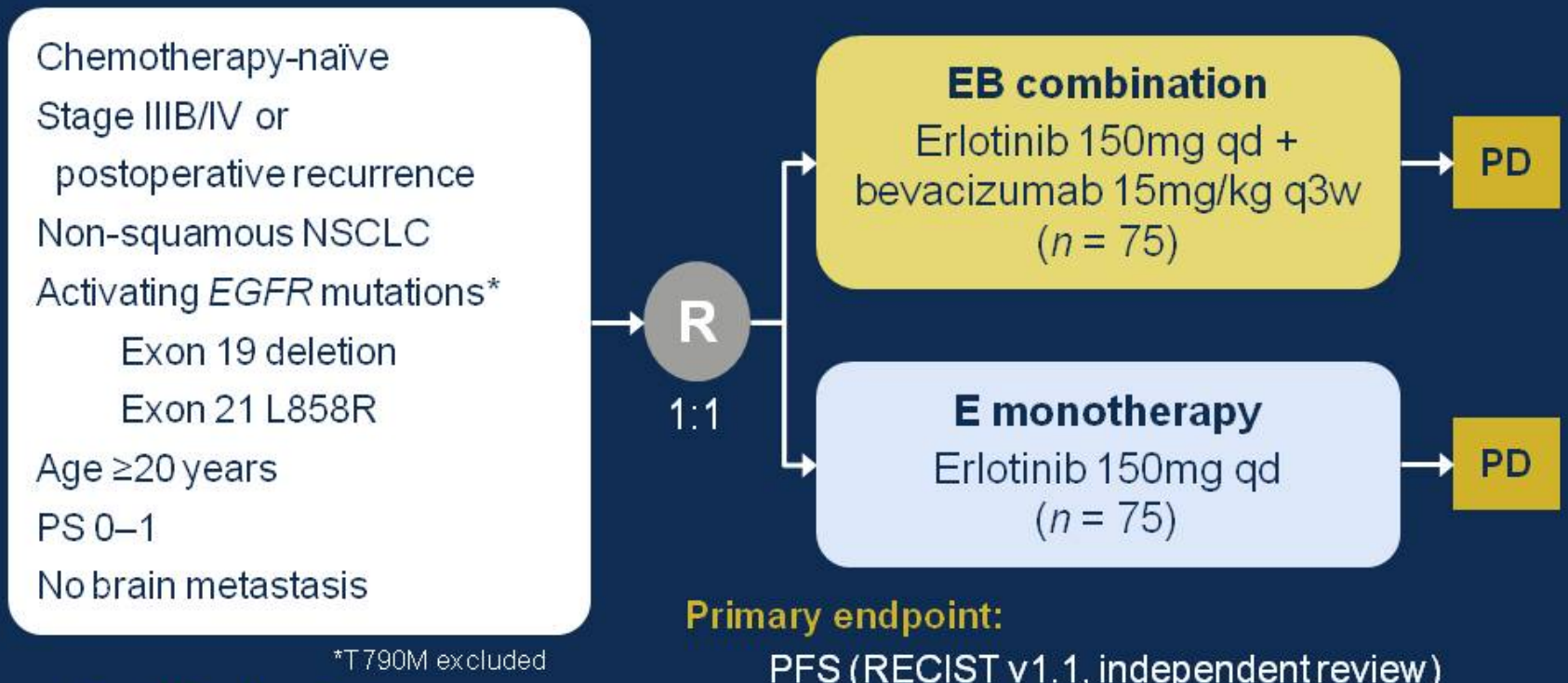
Race							0·0974
White	521	257	9·1 (3·8–19·5)	264	8·2 (3·8–19·9)	1·02 (0·83–1·26)	
Black	54	33	7·9 (3·4–20·2)	21	15·4 (7·4–20·5)	0·72 (0·36–1·43)	
Asian or Pacific islander	41	18	9·9 (3·2–NR)	23	NR (22·6–NR)	0·33 (0·09–1·22)	
Hispanic	18	8	NR (5·8–NR)	10	6·5 (4·3–21·7)	3·55 (0·77–16·49)	
Baseline ECOG score							0·8642
0	250	121	13·9 (7·6–25·1)	129	14·7 (5·8–24·3)	1·04 (0·74–1·46)	
1	342	176	6·7 (2·9–16·1)	166	7·4 (3·6–17·3)	0·93 (0·73–1·20)	
2	43	20	2·4 (1·0–11·0)	23	5·9 (2·3–11·2)	0·92 (0·45–1·85)	
Smoking history							0·0295
Never	67	33	9·2 (4·5–29·3)	34	NR (9·3–NR)	0·44 (0·21–0·94)	
Current or previous	569	284	9·1 (3·7–19·8)	285	8·1 (3·7–19·9)	1·06 (0·87–1·29)	
Histology							0·5349
Other	83	40	11·0 (2·6–17·9)	43	11·8 (4·5–29·5)	0·78 (0·46–1·35)	
Large-cell carcinoma	48	25	6·8 (4·2–20·2)	23	13·3 (5·8–22·5)	0·69 (0·34–1·41)	
Adenocarcinoma	477	235	9·3 (4·0–22·7)	242	9·1 (3·7–20·5)	1·07 (0·85–1·33)	
Squamous-cell carcinoma	28	17	5·1 (3·6–11·8)	11	5·0 (3·8–10·2)	0·91 (0·36–2·33)	
Time since initial diagnosis of NSCLC							0·1838
<6 months	155	78	5·7 (2·1–13·9)	77	4·4 (2·6–9·1)	1·31 (0·91–1·87)	
6–12 months	242	122	9·2 (3·7–19·8)	120	9·2 (4·4–22·2)	0·92 (0·67–1·26)	
>12 months	228	112	11·3 (5·8–23·1)	116	16·0 (6·2–23·7)	0·84 (0·60–1·18)	
Biomarker-defined subgroups of patients							
EGFR mutation status							0·1826
Mutant	30	18	20·2 (16·4–31·1)	12	NR (22·6–NR)	0·44 (0·11–1·67)	
Wild-type	325	152	9·1 (3·8–18·6)	173	8·1 (3·8–17·3)	1·11 (0·86–1·44)	
EGFR FISH status							0·5113

Herbst, Lancet 2011

Presented by: H. Jack West

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Study design



*T790M excluded

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

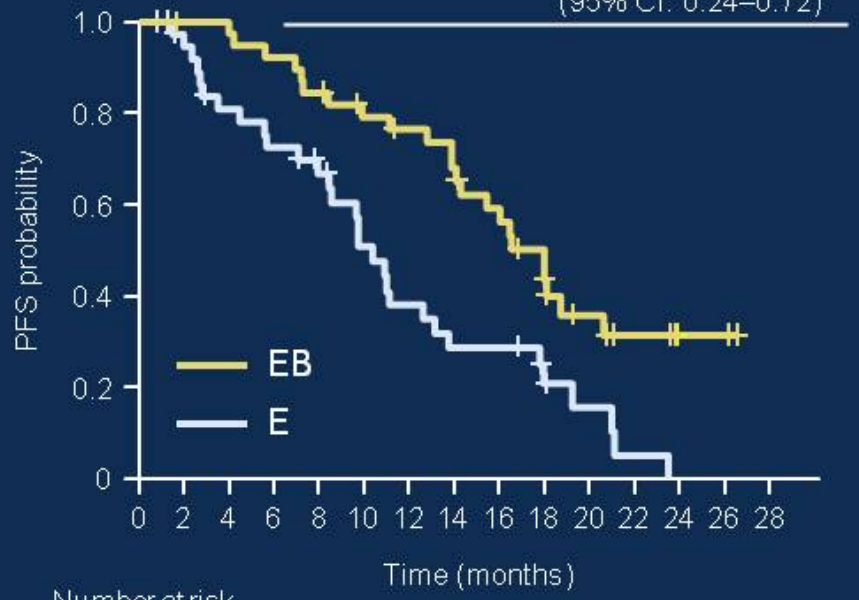
PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Kato: PFS by *EGFR* mutation type

A#8005

Exon 19 deletion

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

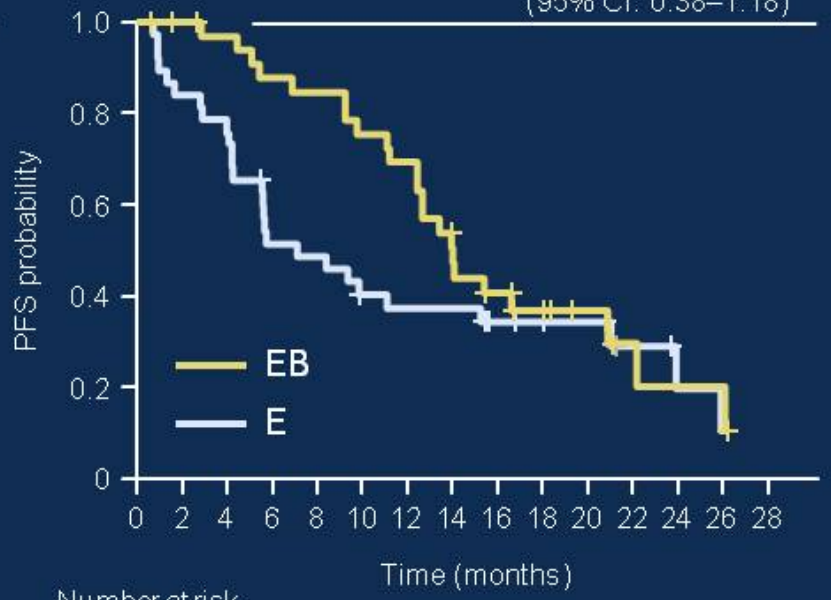


Number at risk

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



Number at risk

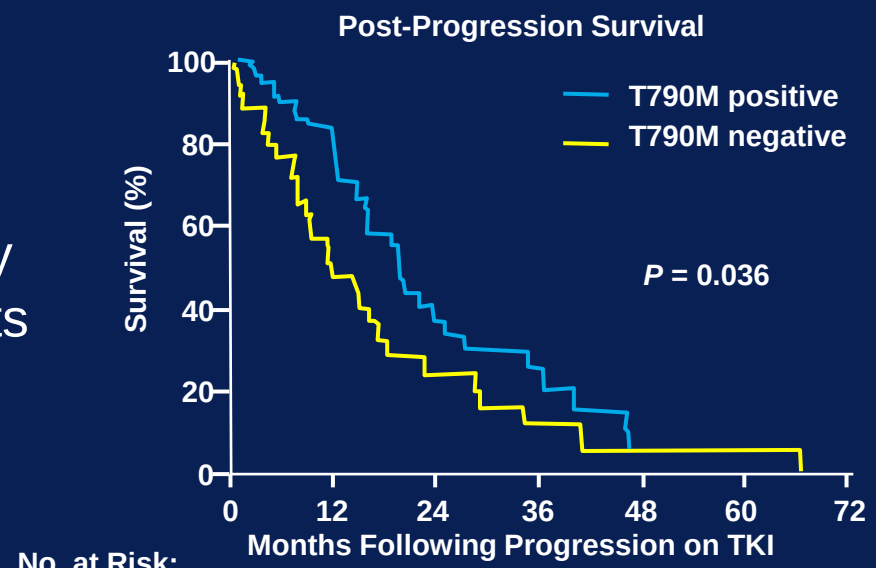
EB	35	33	31	28	27	24	22	14	11	8	5	3	2	2	0
E	37	31	28	18	17	13	12	12	9	7	7	4	2	1	0

Courtesy of: Terufumi Kato

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

T790M in Acquired Resistance

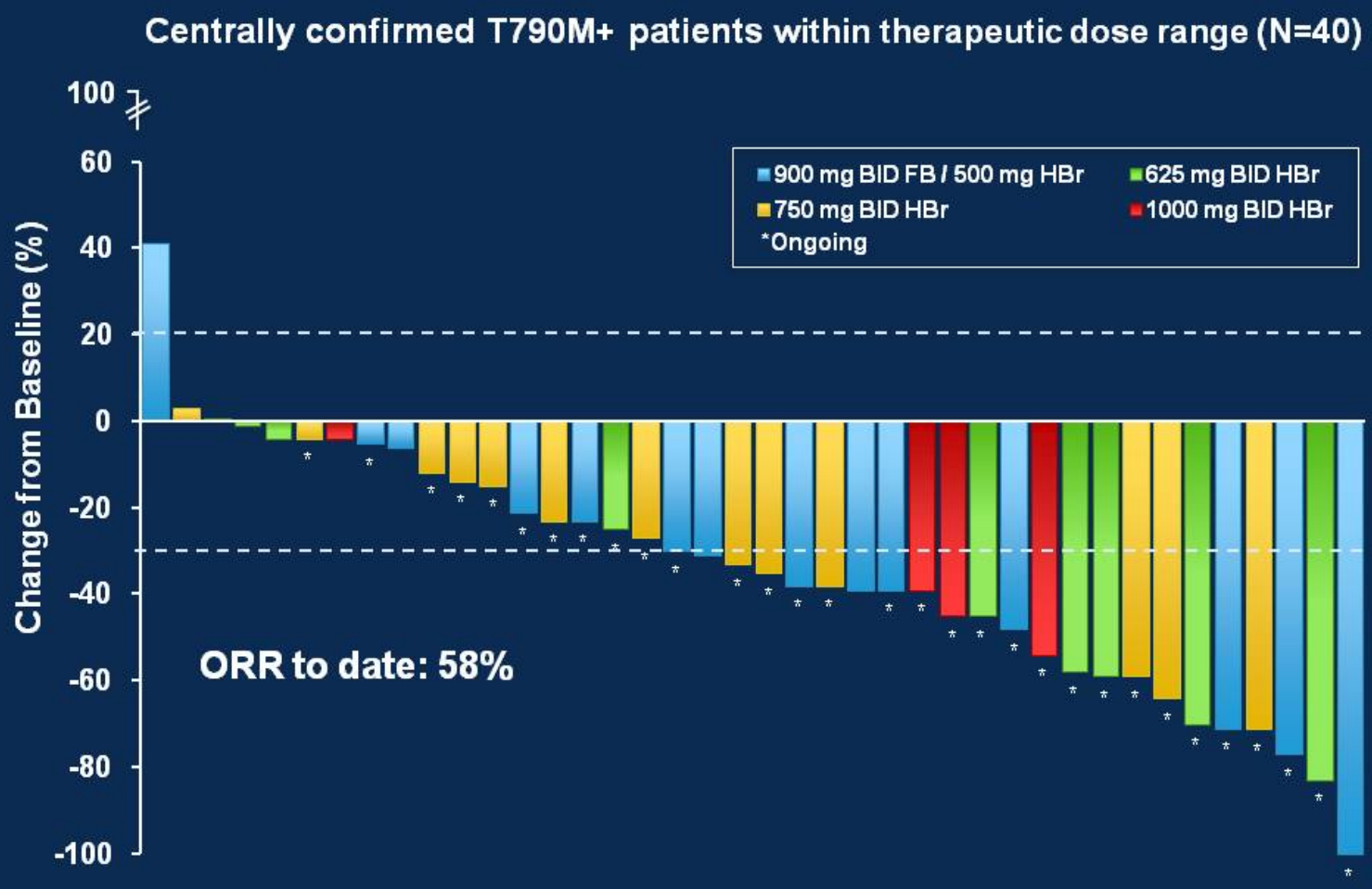
- Acquired exon 20 mutation found in >50% of patients with acquired resistance to EGFR TKI
- Increases relative affinity of mutant EGFR for ATP, may also cause steric hindrance to erlotinib
- More likely to show progression in lungs/pleura
- Less commonly detected in CNS
- Patients with T790M mutation may have better prognosis than patients without T790M



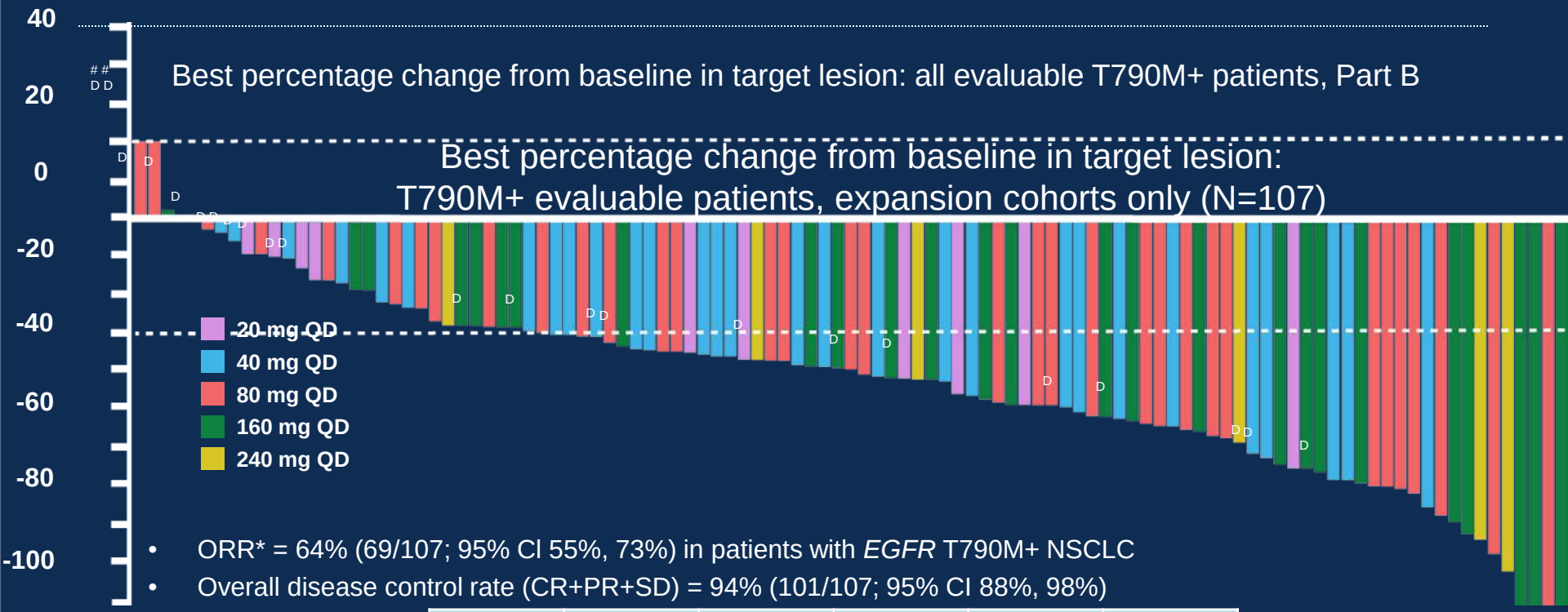
Oxnard GR et al. *Clin Cancer Res*. 2011;17:1616-1622. Permission requested.

CO-1686

Best response in Phase 1 and early Phase 2 expansion cohort patients



AZD9291: Response rate* in central T790M+

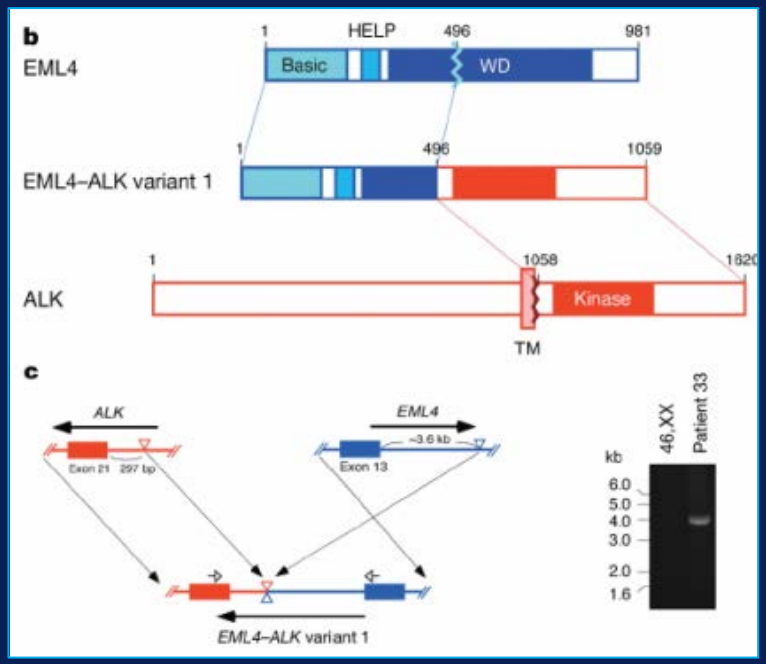


- ORR* = 64% (69/107; 95% CI 55%, 73%) in patients with *EGFR* T790M+ NSCLC
- Overall disease control rate (CR+PR+SD) = 94% (101/107; 95% CI 88%, 98%)

	20 mg	40 mg	80 mg	160 mg	240 mg
N (107)	10	29	34	28	6
ORR	50%	62%	68%	64%	83%

*Includes confirmed responses and responses awaiting confirmation; # represents imputed values.
Population: all dosed central T790M+ patients with a baseline RECIST assessment and an evaluable response (CR/PR, SD or PD), N=107 (from 120 T790M+ patients, 13 patients with a current non-evaluable response are not included).
QD, once daily; central T790M+, T790M positive by central laboratory testing

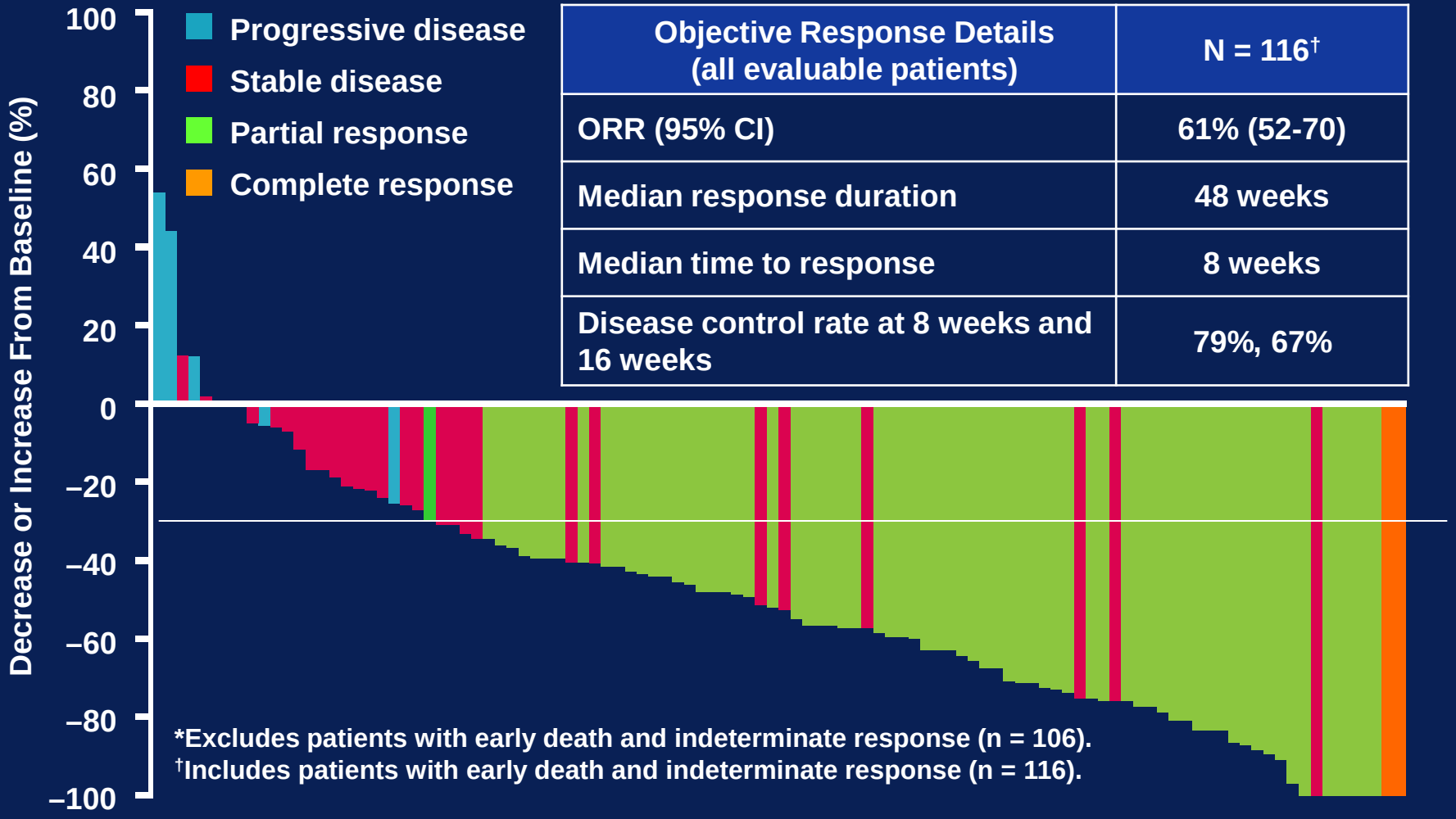
ALK Fusion Gene



- Potent oncogenic activity
- Present in approximately 4% to 5% of NSCLC
- More common in
  - Never smokers
  - Adenocarcinoma
  - Signet-ring morphology

Soda M et al. *Nature.* 2007;448:561-566. Reprinted by permission from Macmillan Publishers Ltd;
Shaw AT et al. *J Clin Oncol*. 2009;27:4247-4253.

Best Percent Change from Baseline in Target Lesions*

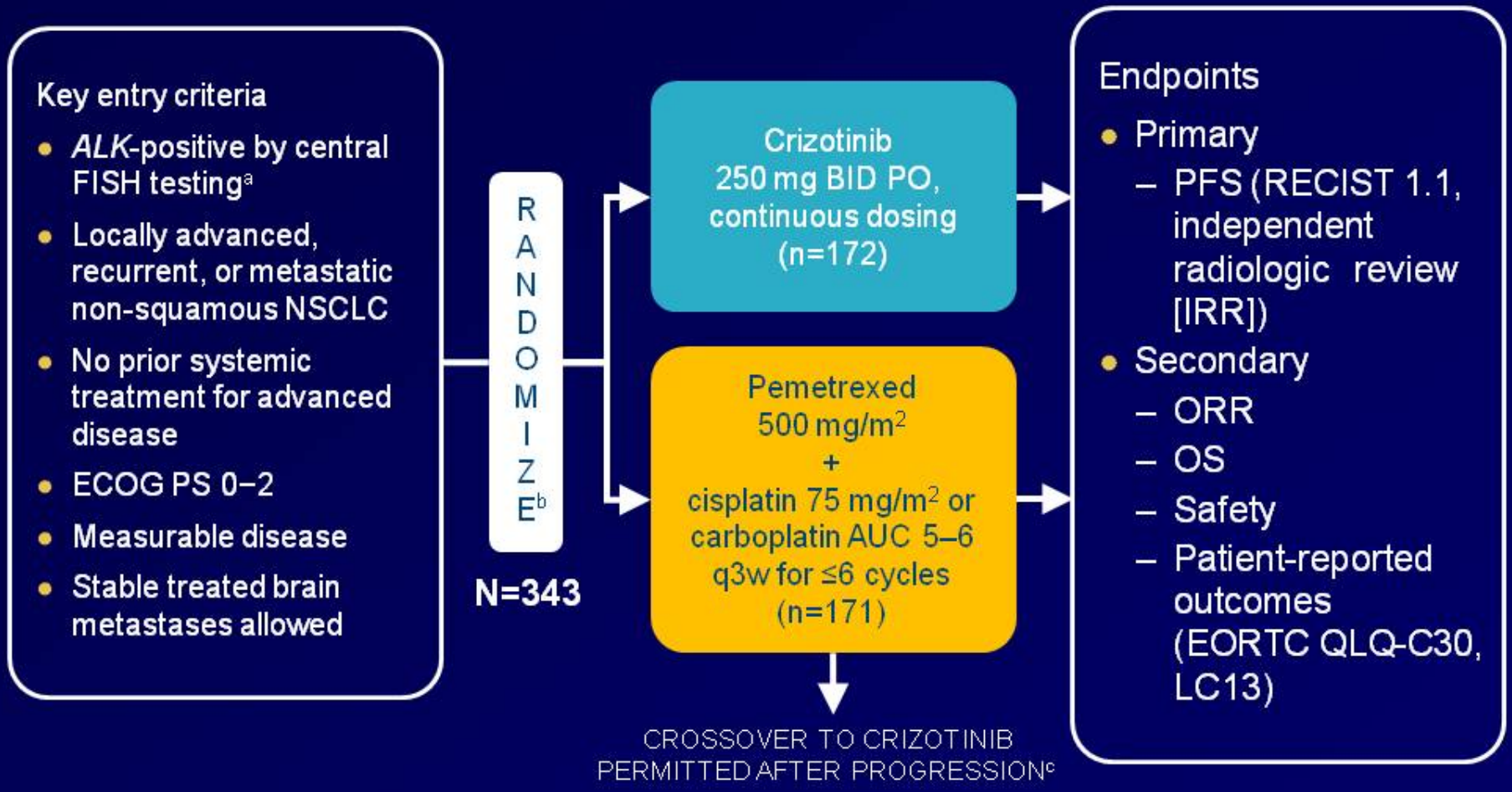


Objective Response Details (all evaluable patients)	N = 116†
ORR (95% CI)	61% (52-70)
Median response duration	48 weeks
Median time to response	8 weeks
Disease control rate at 8 weeks and 16 weeks	79%, 67%

*Excludes patients with early death and indeterminate response (n = 106).
†Includes patients with early death and indeterminate response (n = 116).

Camidge DR et al. ASCO 2011 Annual Meeting.

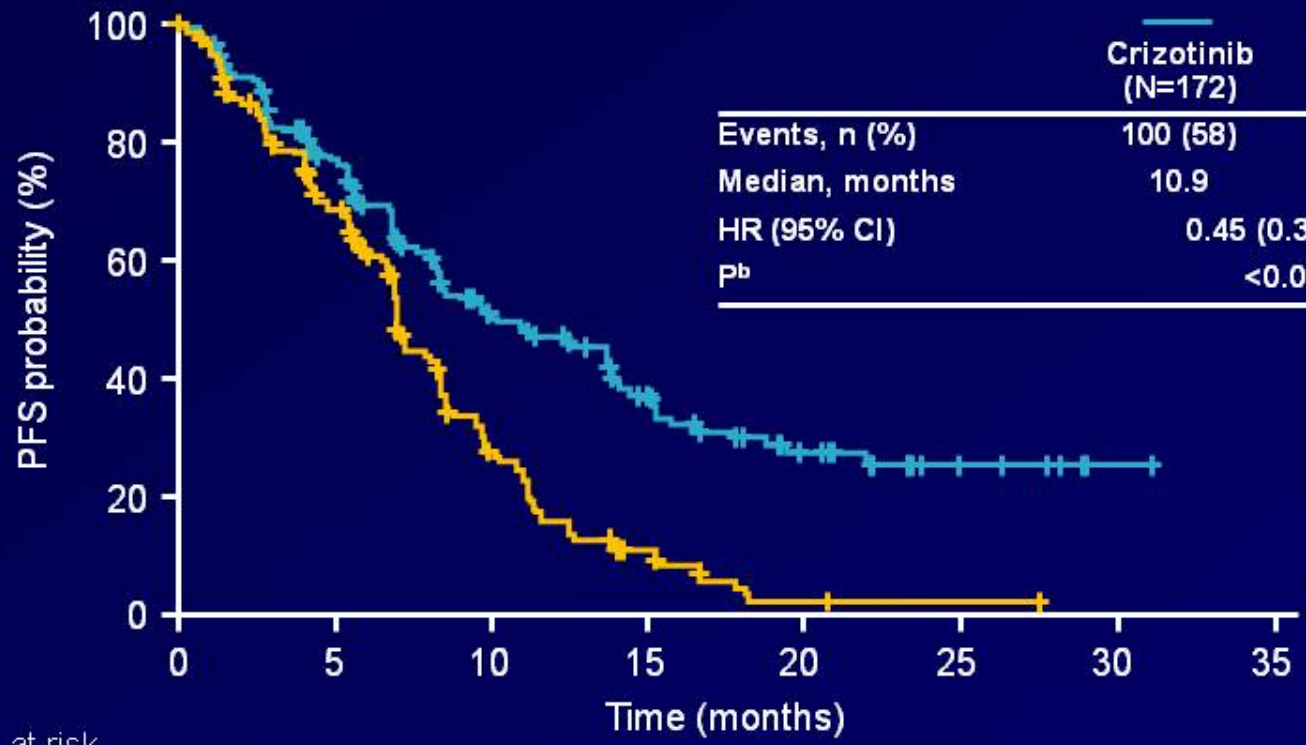
PROFILE 1014 Study Design



[a]*ALK* status determined using standard *ALK* break-apart FISH assay [b]Stratification factors: ECOG PS (0/1 vs. 2), Asian vs. non-Asian race, and brain metastases (present vs. absent)
[c]Assessed by IRR

PROFILE 1014: NCT01154140

Primary Endpoint Met: Crizotinib Superior to Pemetrexed-based Chemotherapy in Prolonging PFS[a]



	Crizotinib (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	
P[b]	<0.0001	

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

Data cutoff: November 30, 2013

[a]Assessed by IRR

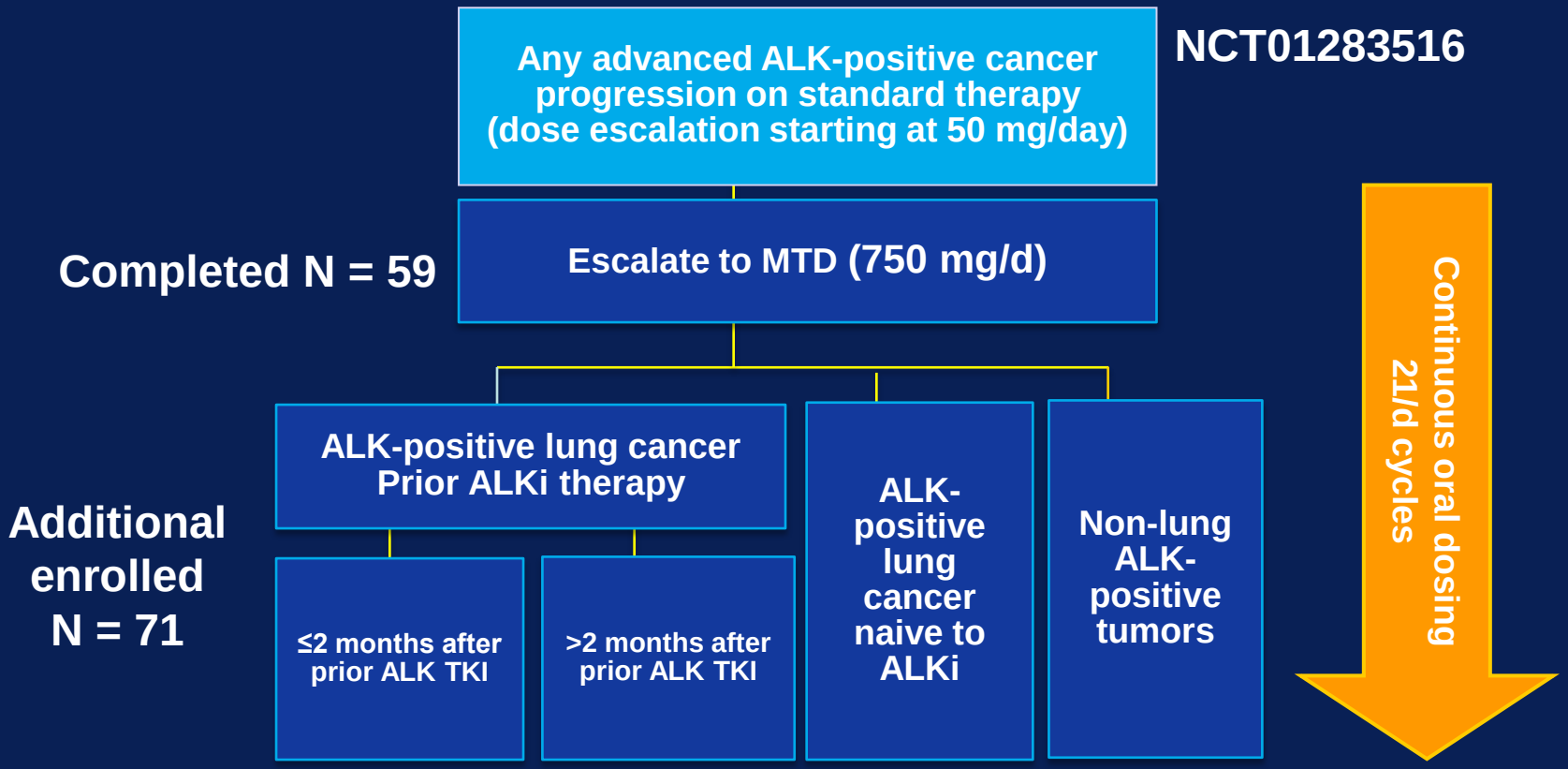
[b]1-sided stratified log-rank test

Ceritinib in Advanced Anaplastic Lymphoma Kinase Rearranged (ALK+) Non-small Cell Lung Cancer (NSCLC) – Results of the ASCEND-1 Trial (#8003)

Dong-Wan Kim,[1] Ranee Mehra,[2] Daniel SW Tan,[3] Enriqueta Felip,[4] Laura QM Chow,[5] D Ross Camidge,[6] Johan Vansteenkiste,[7] Sunil Sharma,[8] Tommaso De Pas,[9] Gregory J Riely,[10] Benjamin J Solomon,[11] Juergen Wolf,[12] Michael Thomas,[13] Martin Schuler,[14] Geoffrey Liu,[15] Armando Santoro,[16] Margarida Geraldes,[17] Anthony L Boral,[18] Alejandro Yovine,[19] Alice T Shaw[20]

[1]Seoul National University Hospital, Seoul, Korea; [2]Fox Chase Cancer Center, Philadelphia, PA; [3]National Cancer Center, Singapore; [4]Vall d'Hebron University, Barcelona, Spain; [5]University of Washington, Seattle, WA; [6]University of Colorado, Denver, CO; [7]University Hospital KU Leuven, Leuven, Belgium; [8]Huntsman Cancer Institute, Salt Lake City, UT; [9]Instituto Europeo di Oncologia, Milan, Italy; [10]Memorial Sloan-Kettering Cancer Center, New York, NY; [11]Peter MacCallum Cancer Center, Melbourne, VIC, Australia; [12]University Hospital Cologne, Cologne, Germany; [13]Thoraxklinik, University of Heidelberg, Translational Lung Research Center Heidelberg, Member of the German Center for Lung Research, Heidelberg, Germany; [14]University Hospital Essen, University Duisburg-Essen, Essen, Germany and German Cancer Consortium, Heidelberg, Germany; [15]Princess Margaret Cancer Center, Toronto, Canada; [16]IRCCS Institute Clinico Humanitas, Milan, Italy; [17]Novartis Pharma, East Hanover, NJ; [18]Novartis Institutes for BioMedical Research, Cambridge, MA; [19]Novartis Pharma AG, Basel, Switzerland; [20]Massachusetts General Hospital, Boston MA

LDK 378: A Potent and Selective ALK Inhibitor

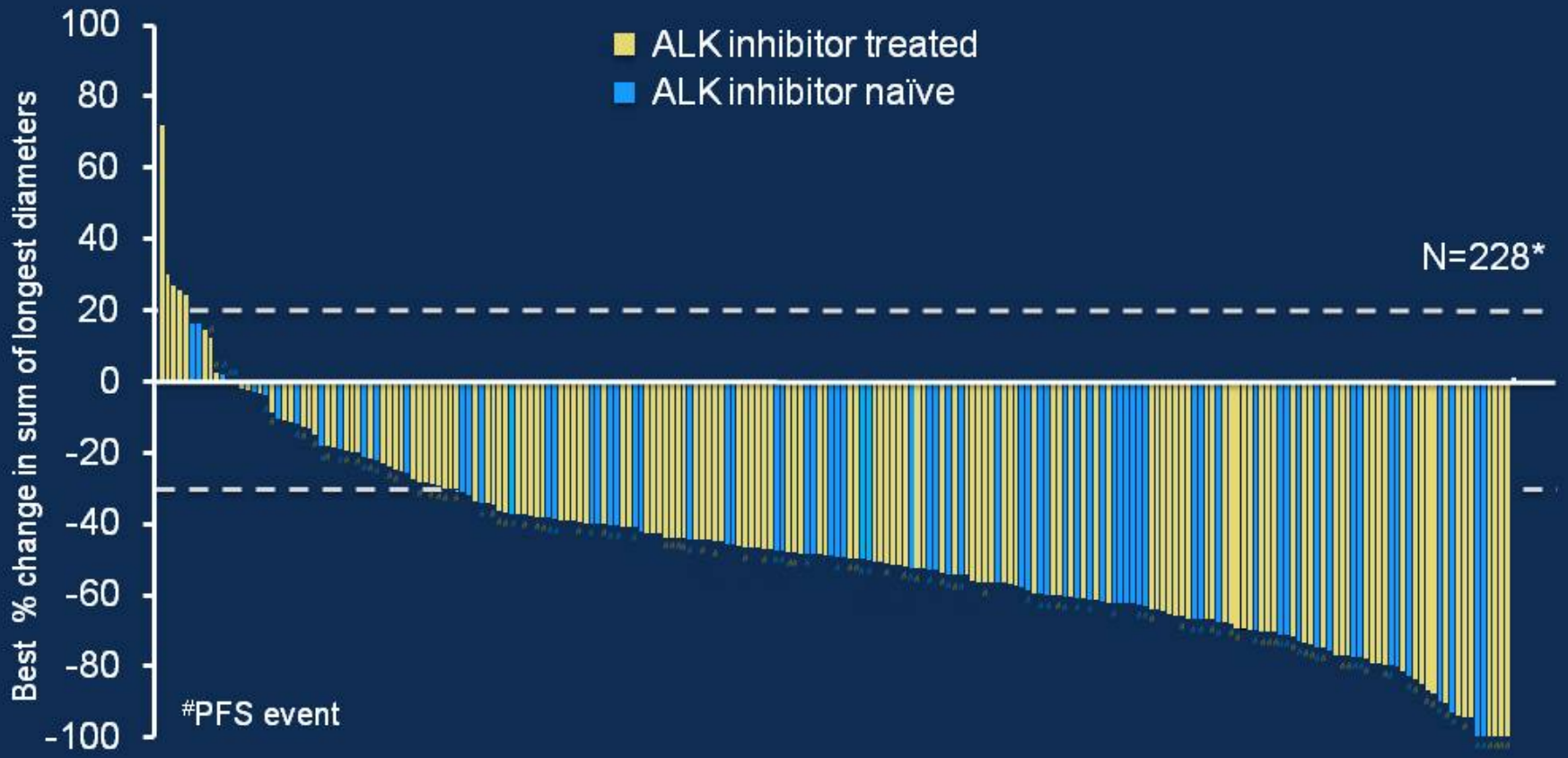


- **Primary objective**: Determination of MTD
- **Secondary objectives**: **Safety**, pharmacokinetics, and preliminary **antitumor activity**

ALKi = ALK inhibitor; MTD = maximum tolerated dose.

Shaw AT et al. ASCO 2013 Annual Meeting. Abstract 8010.

Best Percentage Change from Baseline (NSCLC)

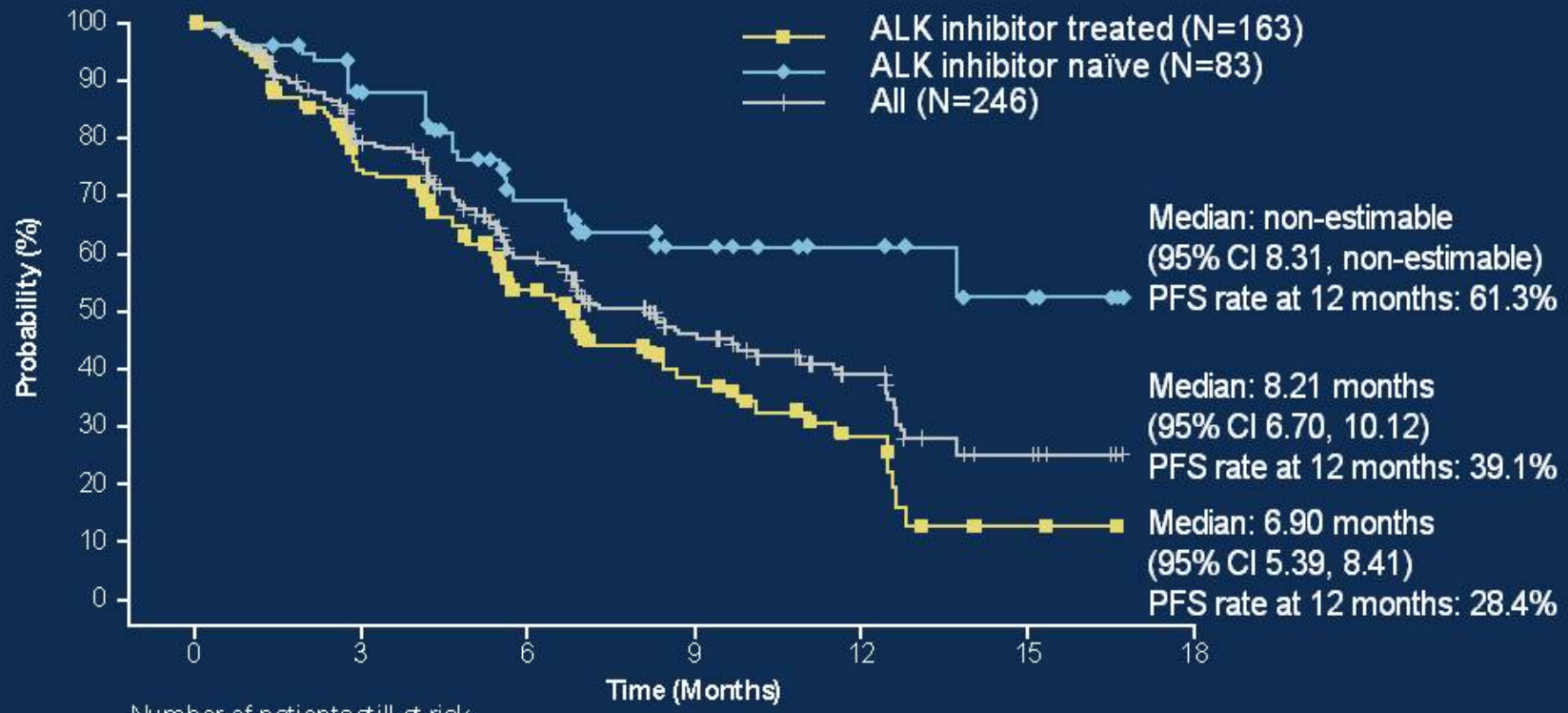


*Patients with measurable disease at baseline and at least 1 post baseline assessment without unknown response for target lesion or overall response

Presented by: Dong-Wan Kim

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Progression-Free Survival in Patients with ALK+ NSCLC



Number of patients still at risk

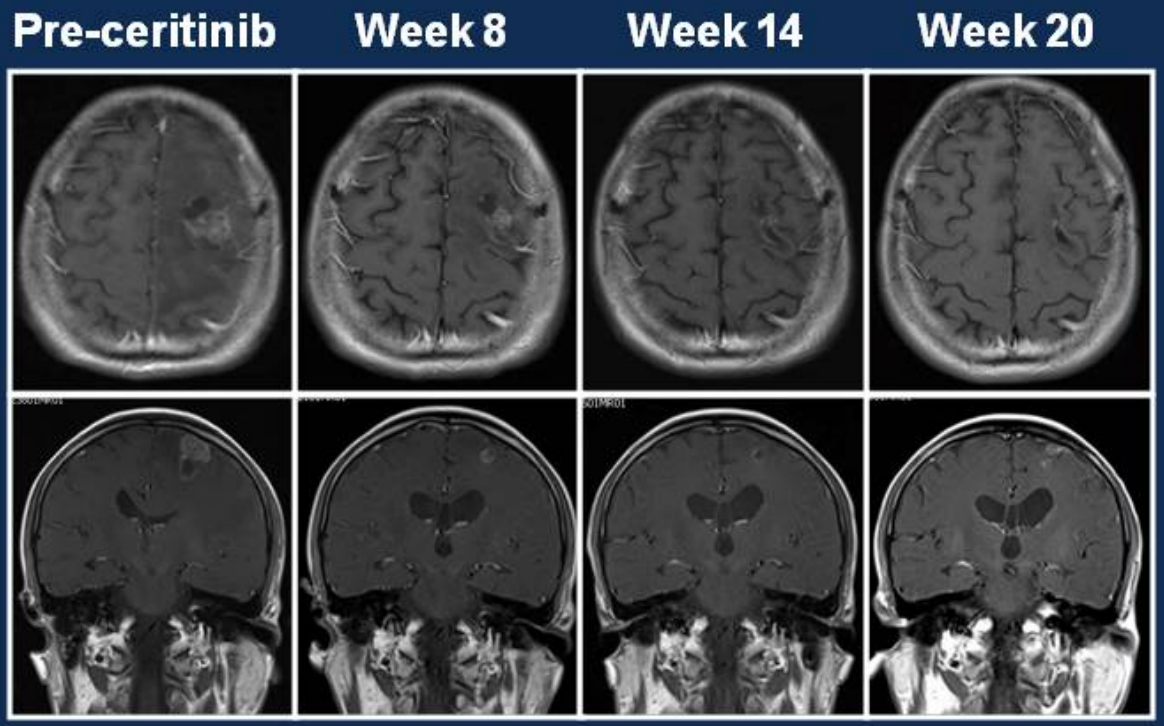
Time (Months)	0	3	6	9	12	15	18
NSCLC with prior ALKi	163	103	58	29	10	2	0
NSCLC ALKi naïve	83	63	38	22	11	5	0
All NSCLC	246	166	96	51	21	7	0

Presented by: Dong-Wan Kim

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Ceritinib Treatment Showed Anti-tumor Activity in the Brain

- 36 year old male patient with lymph node, brain, adrenal, and liver metastases
- Previously treated with radiation therapy, chemotherapy, and progressed on crizotinib



Patient remains on ceritinib 750 mg after 17 months

Figure courtesy of Dr Daniel Tan

Presented by: Dong-Wan Kim

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Toxicity Challenges with Ceritinib

- Greater than with crizotinib
- Dose reduction – 59% (!)
  - Increased ALT/AST, nausea, diarrhea, vomiting
- Discontinuation due to adverse effects – 10%
  - Pneumonia, ILD/pneumonitis, decreased appetite

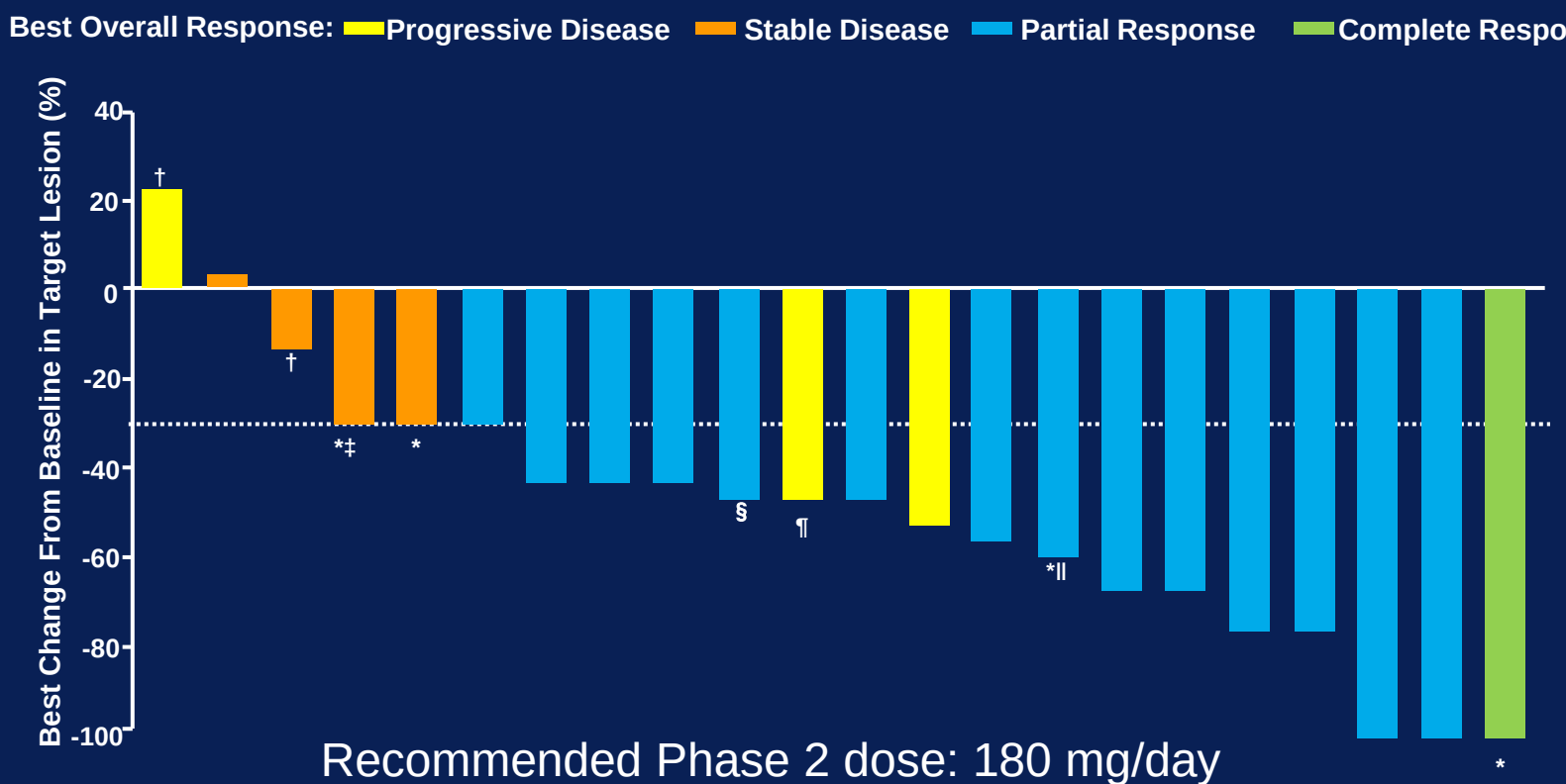
- Oncologists need to know to dose-reduce early
  - 750 mg daily may be more than needed

Kim, A#8003

Presented by: H. Jack West

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

AP26113: Preliminary Anti-Tumor Activity in ALK-Positive Patients



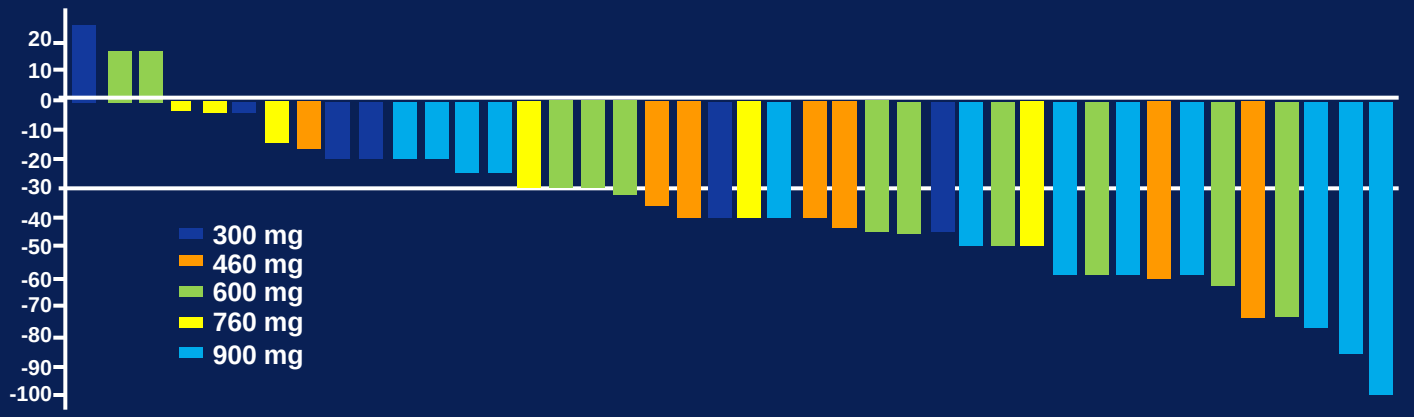
Recommended Phase 2 dose: 180 mg/day
Common AE: Fatigue, nausea, and diarrhea

AE = adverse event

Data as of 17 April 2013. *ALK-TKI naive. †Received prior crizotinib and prior LDK378.
Non-NSCLC diagnoses: ‡neuroendocrine carcinoma; §inflammatory myofibroblastic tumor; ‖ACUP;
¶Patient was PD by RECIST 1.1 due to second primary tumor of melanoma.
Camidge DR et al. ASCO 2013 Annual Meeting. Abstract 8031.

Alectinib in Crizotinib-Resistant ALK-Positive NSCLC

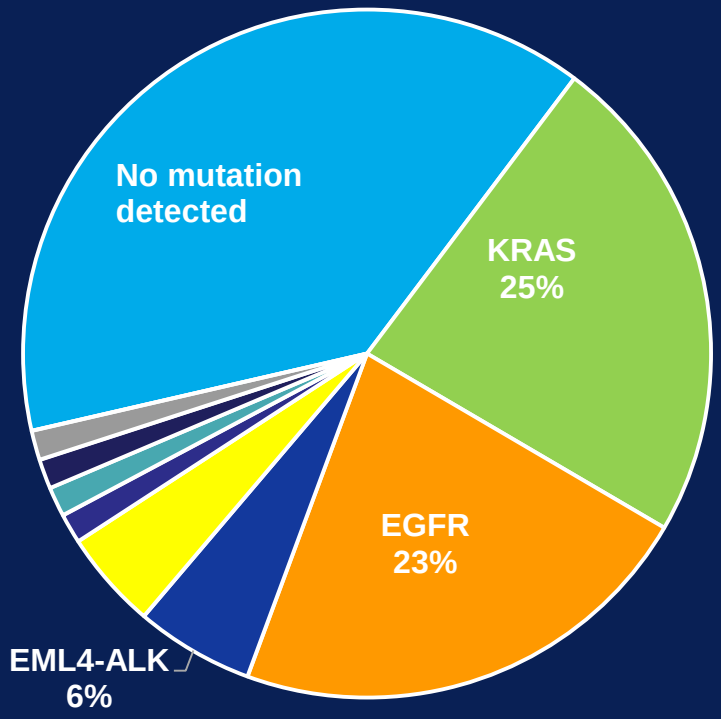
- N = 47 patients
- 70% received ≥2 prior regimens



Objective response rate 60%
Adverse events: Myalgia, fatigue, peripheral edema, elevated CPK, nausea, and photosensitivity (grades 1/2)

Gadgeel S et al. WCLC 2013. Abstract O16.06.

Lung Cancer Mutation Consortium: Incidence of Mutations Detected



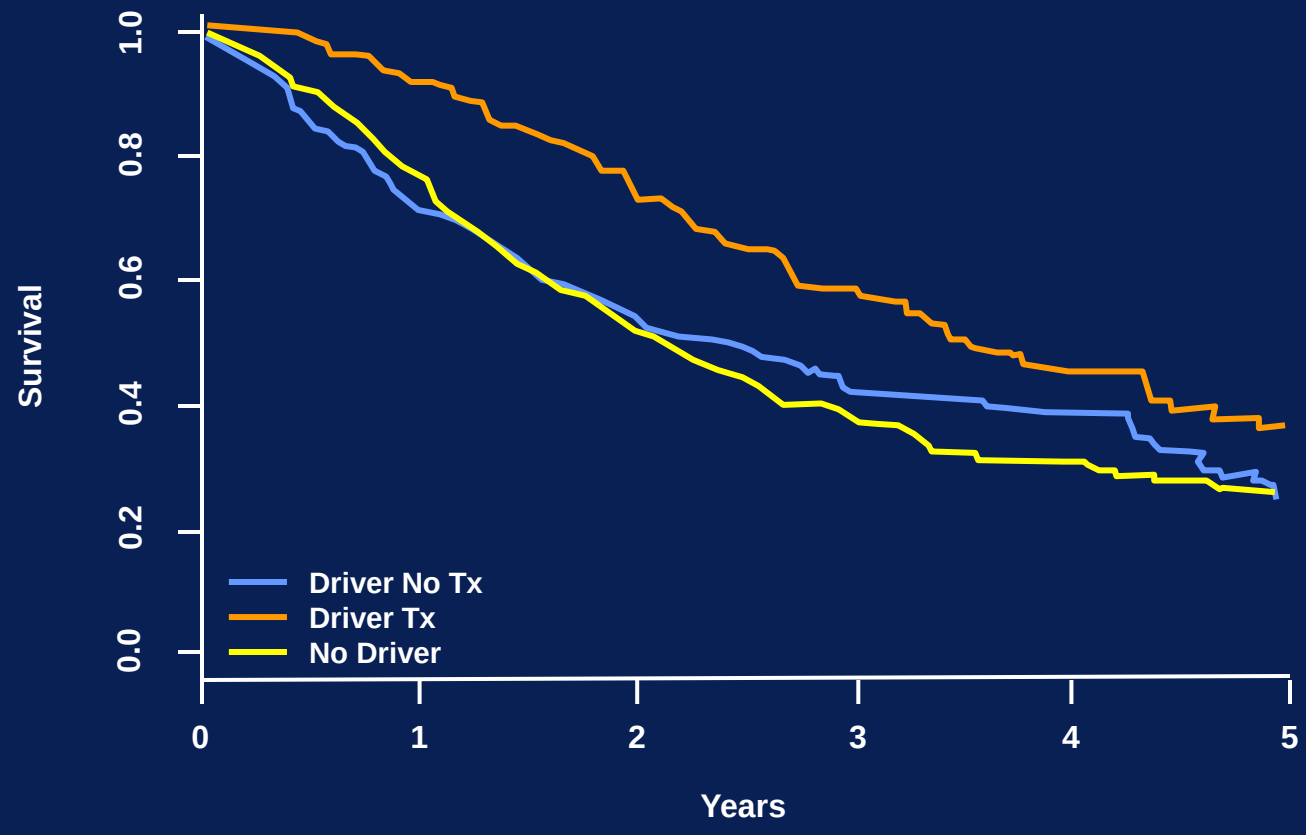
Mutations detected in 60% of tumors tested

EGFR	Erlotinib + OSI 906 (IGF1R) Erlotinib + MM 121 (HER3)
KRAS	Tivantinib + Erlotinib GSK1120212
MET Amplification	
EML4-ALK	Crizotinib
MEK1	GSK1120212
BRAF (V600E)	GSK2118434
BRAF (not V600E)	GSK1120212
HER2	Afatinib
PIK3CA	BKM120
AKT1	

MET = membrane receptor essential for embryonic development and would healing; HER2 = human epidermal growth factor receptor 2; BRAF = human gene that makes a protein called "B-raf"; KRAS = a protein that stimulates signaling pathways downstream from EGFR

Kris MG et al. *JAMA May, 2014*

Lung Cancer Mutation Consortium: Survival by Group



Kris MG et al JAMA May 2014

Crizotinib: selective inhibitor of ALK, MET and ROS

Upstate 102 kinase panel

13 'hits' <100X selective for Met

Cellular selectivity on 10 of 13 relevant hits

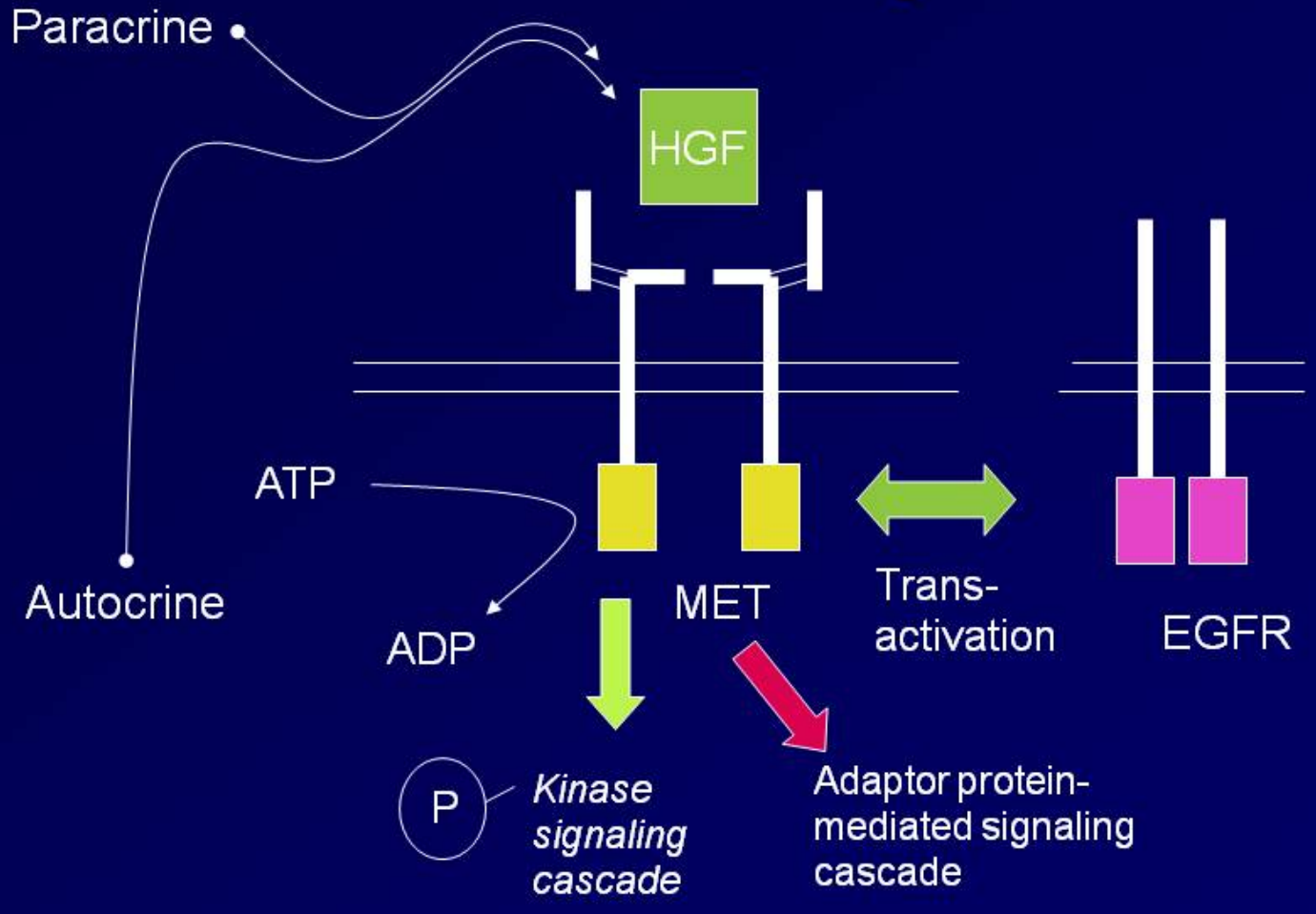
Kinase	IC50 (nM) mean*	Selectivity ratio
Met	8	–
ALK	40–60	5–8X
ROS	55	7X
RON	80	10X
Axl	294	34X
	322	37X
Tie2	448	52X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1000X
VEGFR2	>10,000	>1000X
PDGFRβ	>10,000	>1000X

High probability of ALK, MET and ROS inhibition at clinically relevant doses

*Measured using ELISA capture method

Bang Y, et al. J Clin Oncol 2010;28(suppl):18s (abstr 3)
http://meetinglibrary.asco.org/content/41375?media=vm

MET Pathway

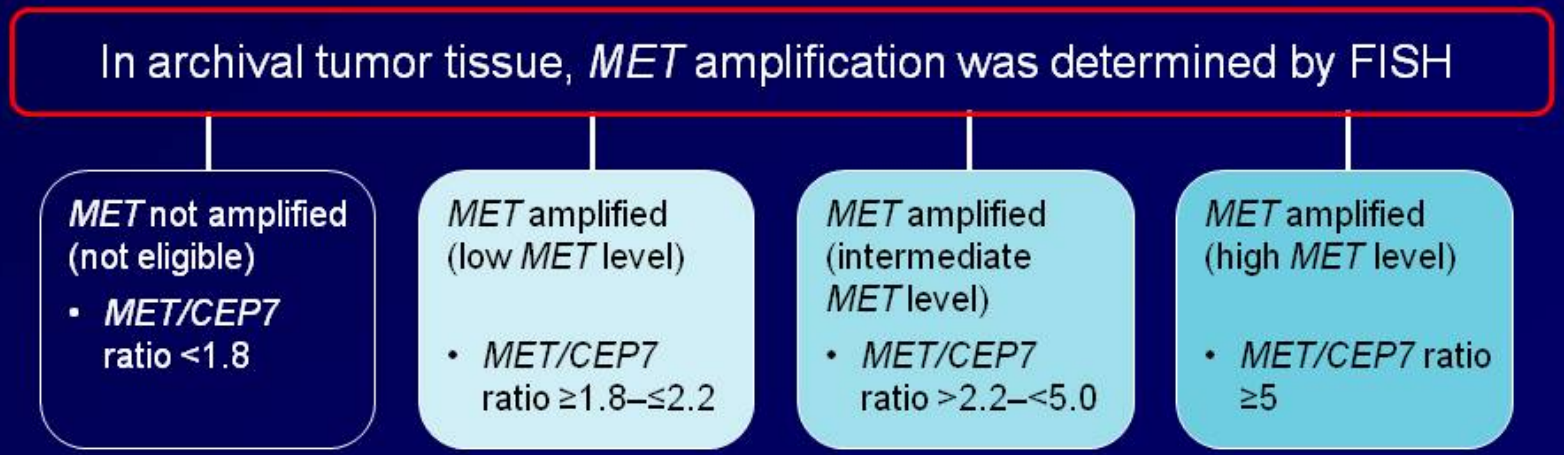


Motogenesis ***Mitogenesis*** ***Angiogenesis*** ***Morphogenesis***

HGF, hepatocyte growth factor/scatter factor

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**



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

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.

Clinical Development of PD-1 Immune Checkpoint Inhibitors

Target	Antibody	Molecule	Development stage
PD-1	Nivolumab-BMS-936558	Fully human IgG4	Phase III
	Pidilizumab CT-011	Humanized IgG1	Phase II multiple tumors
	Pembrolizumab MK-3475	Humanized IgG4	Phase III
PD-L1	BMS-936559 (no longer in development in NSCLC)	Fully human IgG4	Phase I
	MedI-4736	Engineered human IgG1	Phase I
	MPDL-3280A	Engineered human IgG1	Phase III
	MSB0010718C	Human IgG1	Phase I

MK-3475 in First Line Treatment of NSCLC: Initial Signal of Activity from Phase I Trial

- MK-3475: humanized, high affinity, monoclonal IgG4 antibody that exerts dual ligand blockade of the PD-1 pathway
- KEYNOTE-001: ongoing phase I study including patients with advanced NSCLC
- Key First Line Eligibility Criteria
  - EGFR Wild Type and Negative for ALK rearrangement (first 11 could have had)
  - 1% Tumor PD-L1 expression determined centrally from fresh biopsy using prototype IHC assay (22C3 antibody)
- Randomized to 10 mg/kg IV q 2 wks or q 3 wks
- Assessment q 9 weeks using RECIST 1.1 and irRC

Abstract # 8007 – Rizvi N et al, Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lung cancer (NSCLC).

PRESENTED AT:

Antitumor Activity by MK-3475 Dose

MK-3475 Dose	RECIST v1.1, Central Review[a]			irRC, Investigator Review		
	ORR[b]		DCR[b]	ORR[b]		DCR[b]
	n	n (%) [95% CI]	n (%) [95% CI]	n	n (%) [95% CI]	n (%) [95% CI]
Total	42	11 (26%) [14%-42%]	27 (64%) [48%–78%]	45	21 (47%) [32%-62%]	35 (78%) [63%-89%]

- Interim median PFS[c]:
  - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review – 6.75 mo
  - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review - 9.25 mo

- Comparing to classic chemotherapy in the first line setting
- Phase 3 studies
  - Gemcitabine + Cisplatin RR= 22-32%, Median PFS – 5.1 mo
  - Taxol + Carboplatin RR=15-25%, Median PFS – 4.5 mo.
  - Pemetrexed + Cisplatin RR=30%, Median PFS – 4.8 mo. (5.3 mo Nonsquam)

Scagliotti G et al JCO 2002, Schiller J et al NEJM 2002, Sandler A et al NEJM 2006, Scagliotti G et al JCO 2009

ASCO Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

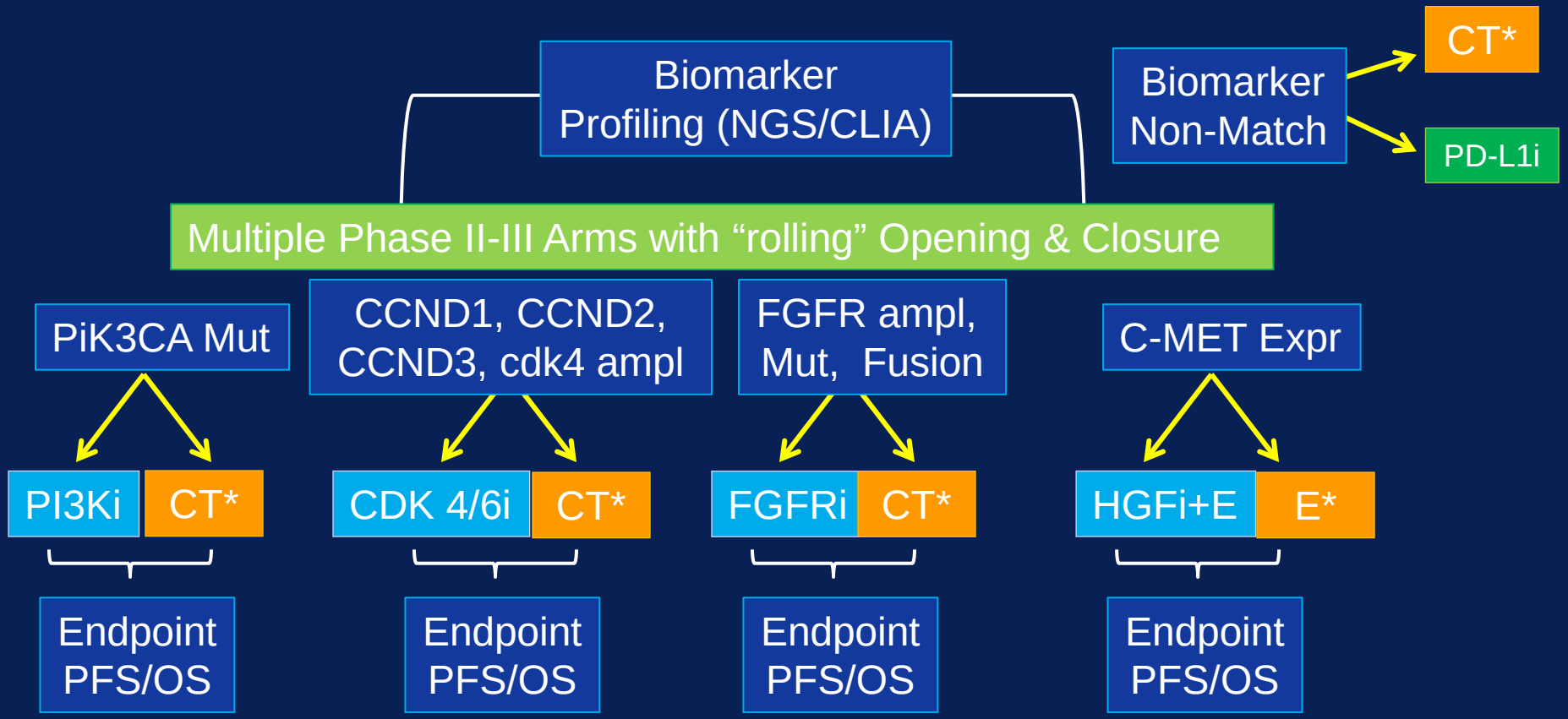
Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

Ellis LM et al JCO 2012

Presented by: Julie R. Brahmer, M.D., M.Sc.

PRESENTED AT: ASCO 50 ANNUAL MEETING SCIENCE & SOCIETY

S1400: MASTER LUNG-1: Squamous Lung Cancer- 2nd Line Therapy



CT = chemotherapy (docetaxel or gemcitabine), E = erlotinib

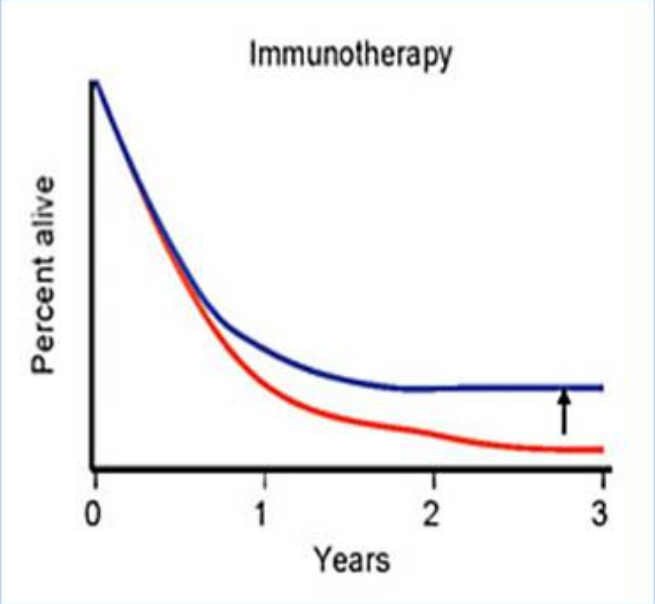
PI: V. Papadimitrakopoulou (SWOG); Steering Committee Chair: R. Herbst (YALE, SWOG); Lung Committee Chair: D. Gandara; Translational Chair: F. Hirsch; Statistical Chair: M. Redman

Decision Tree for the Management of Advanced NSCLC- Utilization of Contemporary Tools

- Personalization of Care by histology (pemetrexed and bevacizumab) for non-squamous
- Molecular markers
  - ERCC1 etc. not helpful
  - 1st line EGFR and ALK testing critical
- Maintenance therapy
  - Switch or continuation pem or erlotinib
- EGFR and ALK 1st, 2nd, 3rd generation drugs on the market or in development

ASCO Perspective: Raising the Bar

But Will These Criteria Take into Account Raising the Tail of the Curve which is where the Power of Immunotherapy Theoretically Lies?

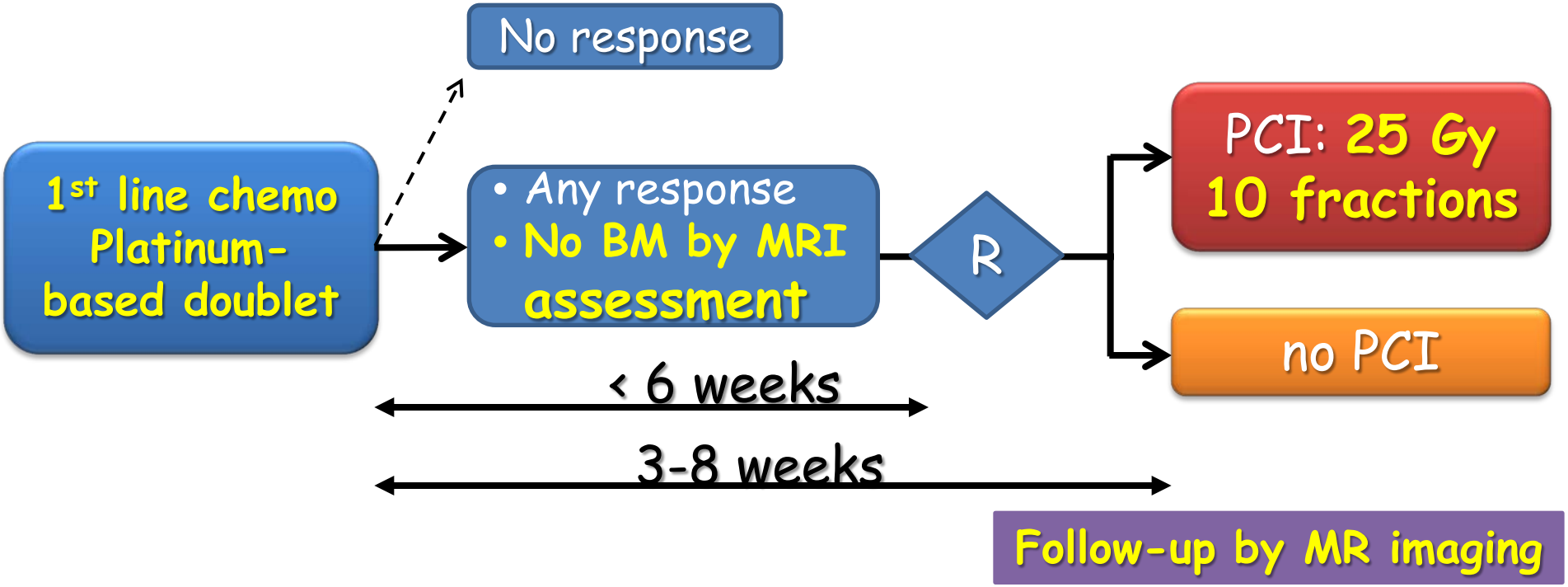


Ellis LM et al JCO 2012

PCI for SCLC: Current Role

- **Well Established Role in LD-SCLC Pts with Response**
- **EORTC Trial (NEJM 2007) Established PCI as Alternative for ED-SCLC Patients: Survival Benefit!**
- **New Toxicity-Mitigating Approaches Under Study**
- **How do these two trials compare?**

Seto et al: Phase III PCI Trial



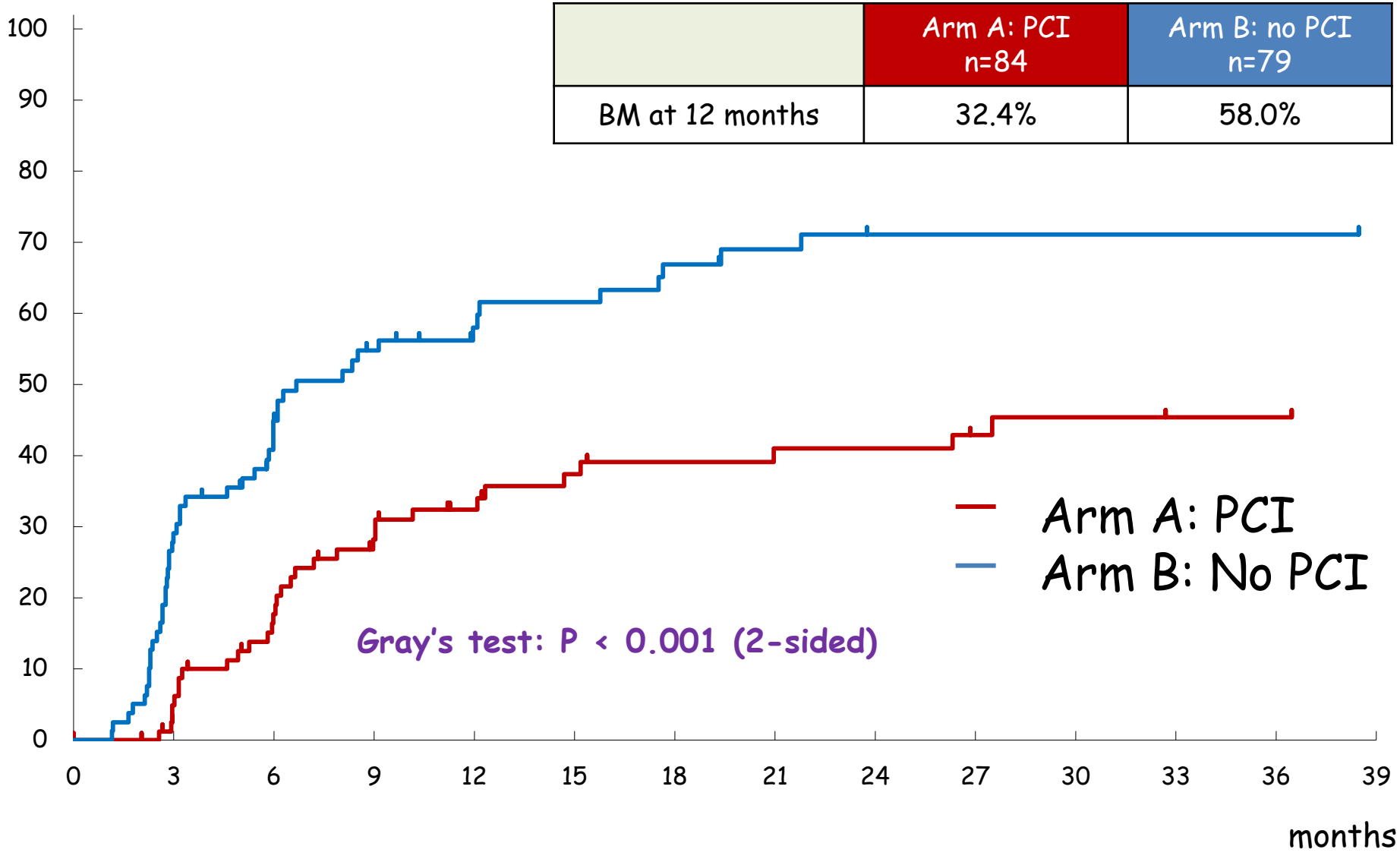
Stratification by Age (70≦ / <70), PS (0-1 / 2), Response (CR / PR+MR), Institutions

Primary endpoint: Overall Survival

Secondary endpoints: Time to BM (evaluated every 3 months)
Progression-Free Survival (PFS)
Safety
Mini Mental State Examination (MMSE)

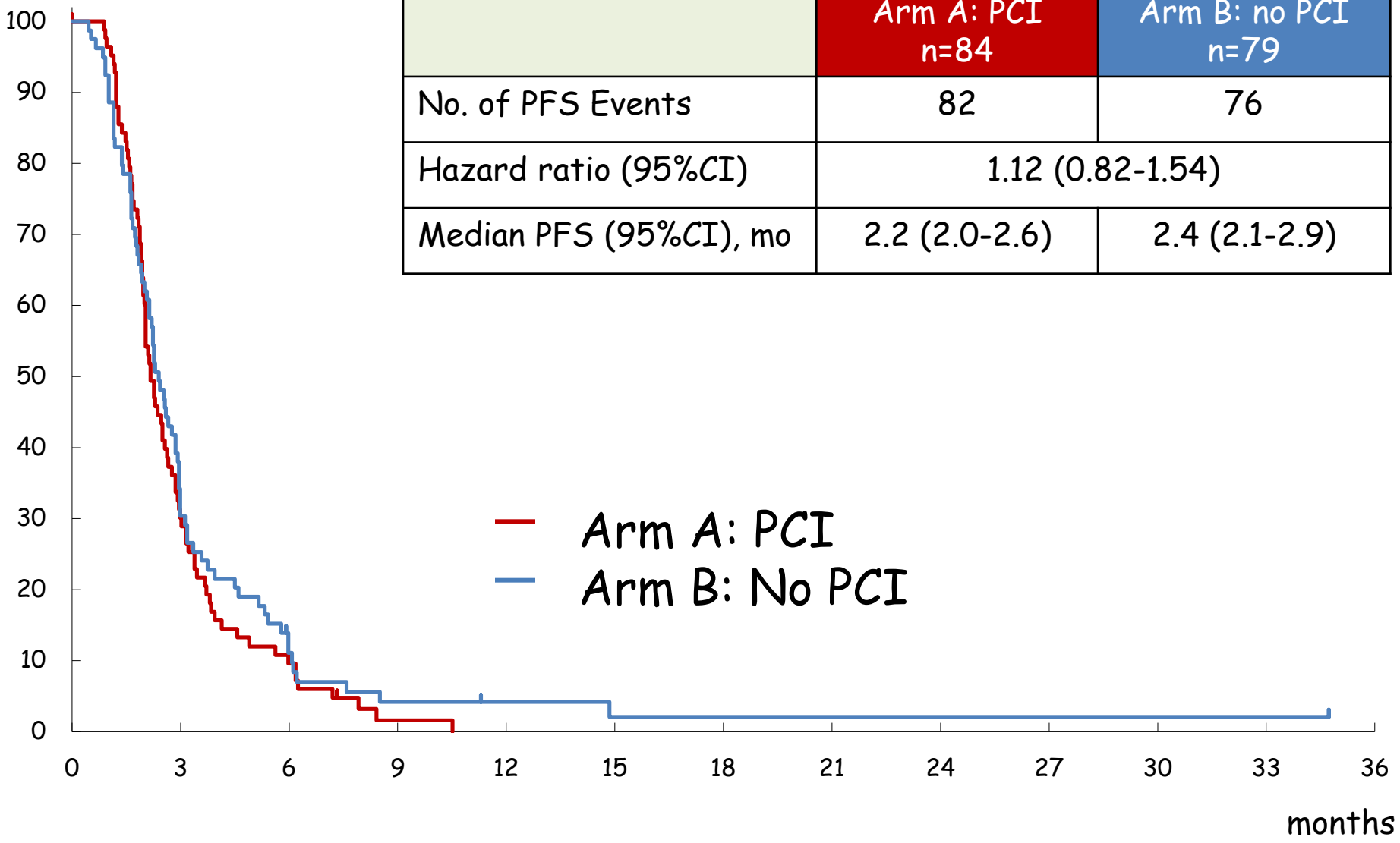
Time to Brain Metastasis (Seto)

	Arm A: PCI n=84	Arm B: no PCI n=79
BM at 12 months	32.4%	58.0%



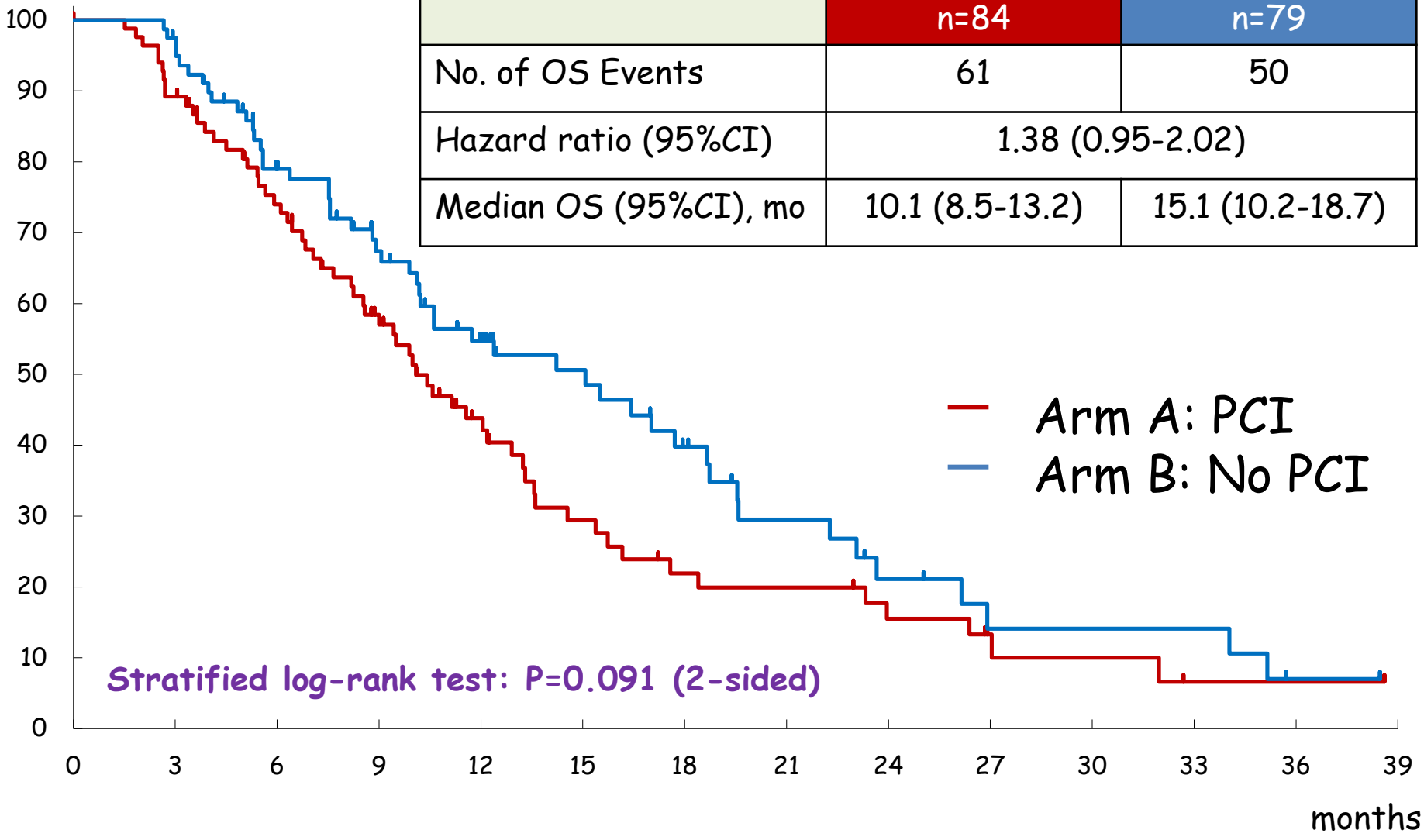
Progression-Free Survival (Seto)

	Arm A: PCI n=84	Arm B: no PCI n=79
No. of PFS Events	82	76
Hazard ratio (95%CI)	1.12 (0.82-1.54)	
Median PFS (95%CI), mo	2.2 (2.0-2.6)	2.4 (2.1-2.9)



Overall Survival (Seto)

	Arm A: PCI n=84	Arm B: no PCI n=79
No. of OS Events	61	50
Hazard ratio (95%CI)	1.38 (0.95-2.02)	
Median OS (95%CI), mo	10.1 (8.5-13.2)	15.1 (10.2-18.7)



EORTC vs Japanese PCI Trials

	EORTC (Slotman)	Japan (Seto)	
# Patients	286 Enrolled	224 of 330 Enrolled	
PCI Dose/Fx	Variable	25 Gy/10 Fractions	
Pre-Enrollment Neuro-Imaging	Not Required	MR Brain Required	
Follow-up Imaging	Not Required	MR Brain Required	
Neuro Function Data	Limited	Limited	

Educational Objectives

- New roles for targeted therapies for early stage disease?
- Consolidation chemotherapy's last stand in Stage III NSCC?
- Current treatment algorithms for patients with NSCLC with known and unknown driver mutations
- Selecting treatment in patients without an actionable mutation
- Defining the role of prophylactic cranial radiation in small cell lung cancer