Systemic Treatment of Metastatic Lung Cancer: Times are changing

Barbara Melosky, MD

Objectives

- Review how targeted therapies are used
- Discuss when/what pathological testing should be done
- Explore the present and future role for immunotherapy
- Highlight toxicities: How do you treat

Conflict of Interest

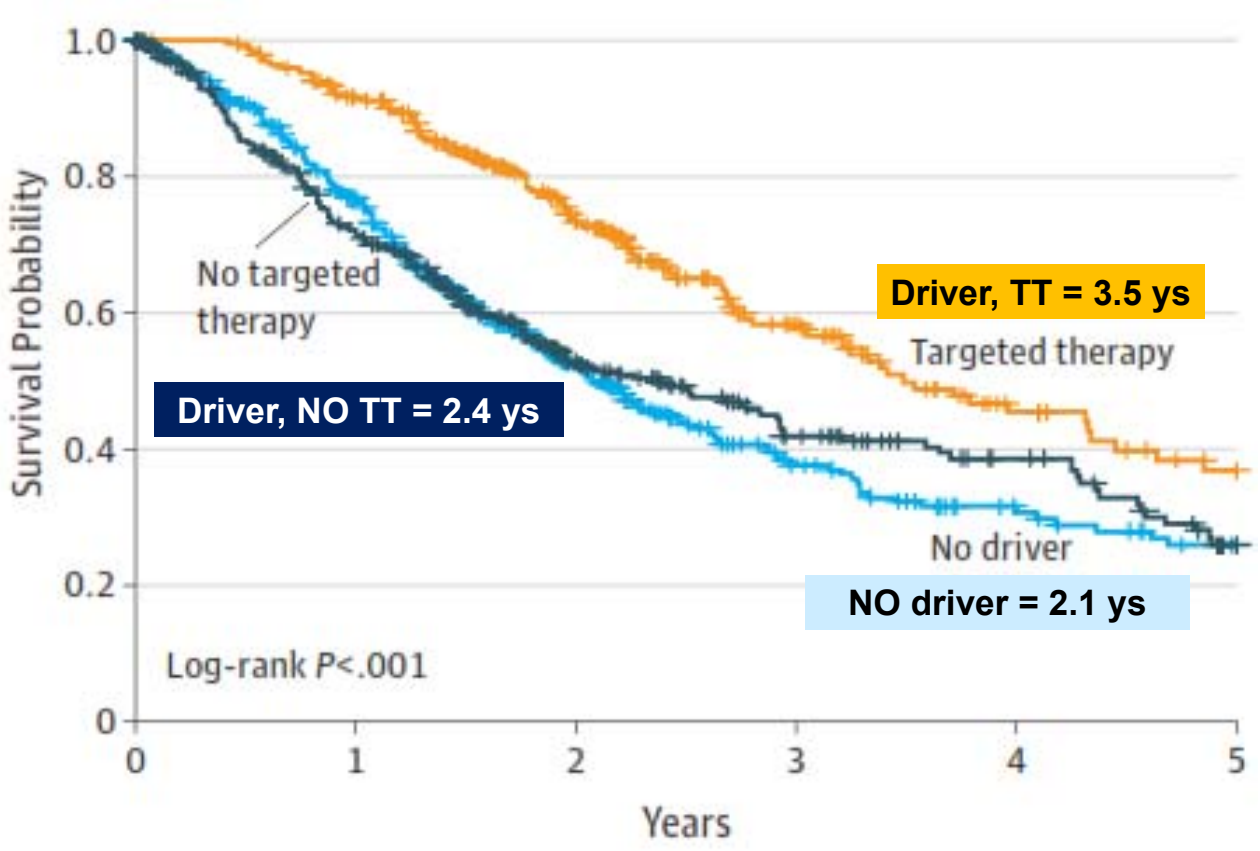
- Advisory Board:
  - Lilly, Astra Zeneca, Boehringer Ingelheim, Merck, BMS, Novartis, Roche, Pfizer

Conflict in My Life

Current Treatment: First Thing We Do Identify a Driver Mutation!

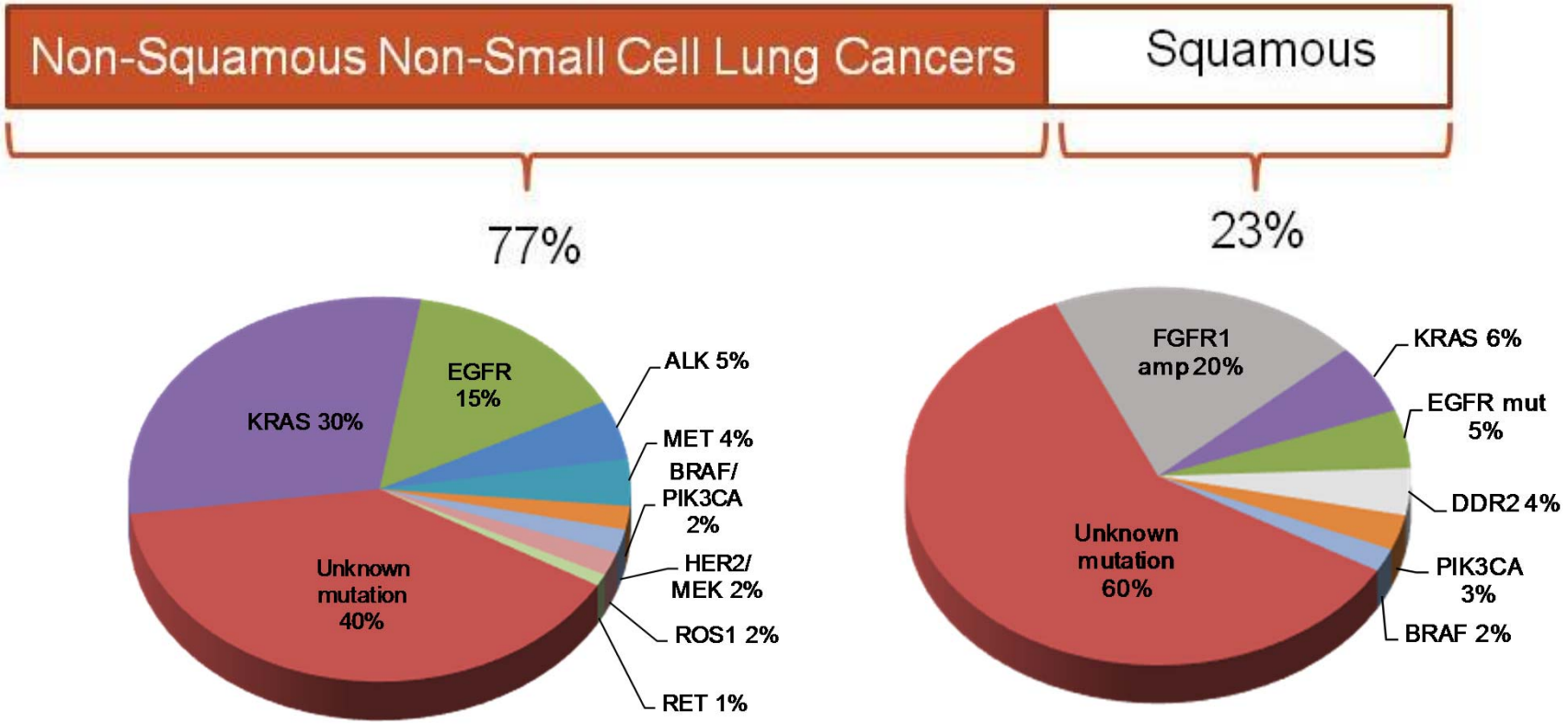
- EGFR
- ALK
- RARE MUTATIONS:
  - ROS, BRAF, HER 2, RET, MET

Using Multiplexed Assays of Oncogenic Drivers in Lung Cancers to Select Targeted Drugs



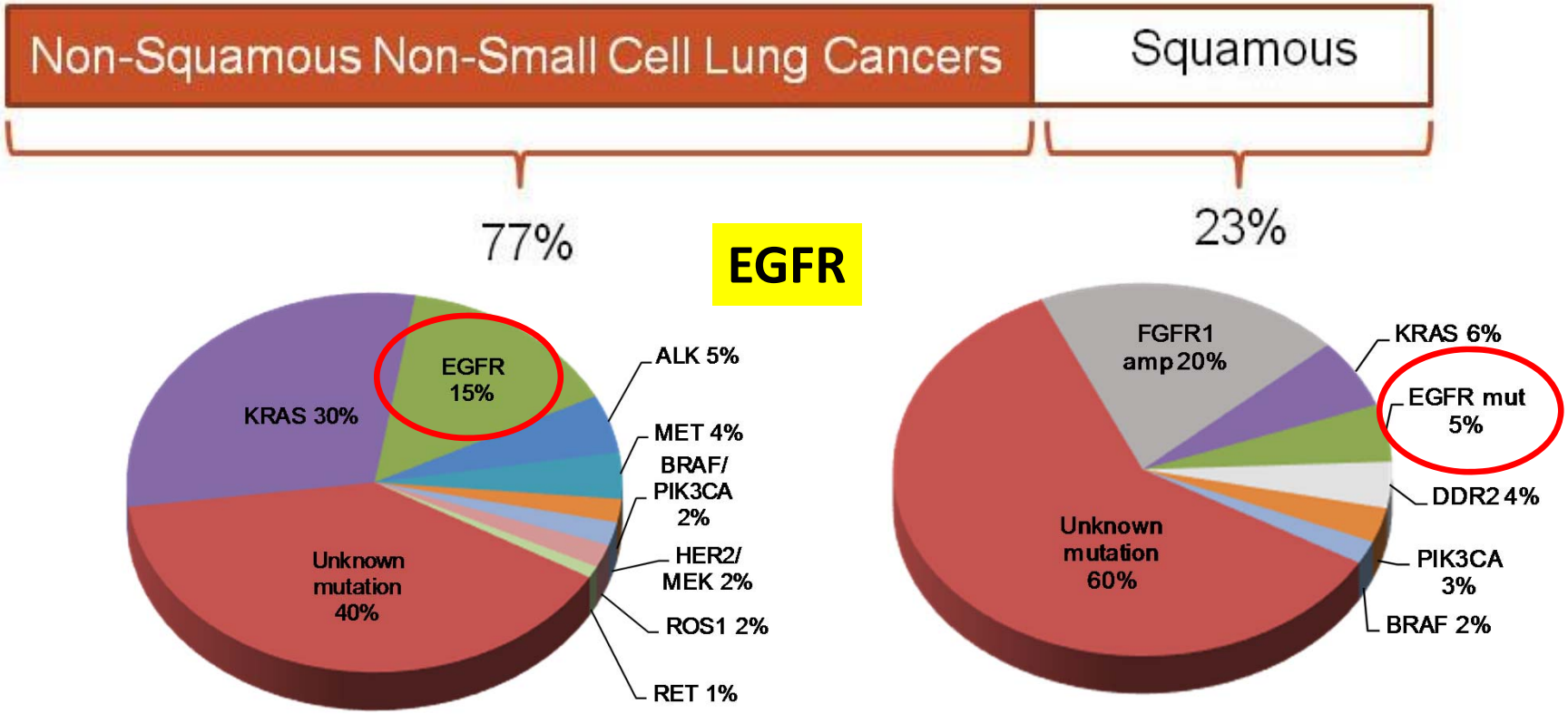
Kris et al. *JAMA*. 2014;311:1998.

Non-Small Cell Lung Cancers – 2016



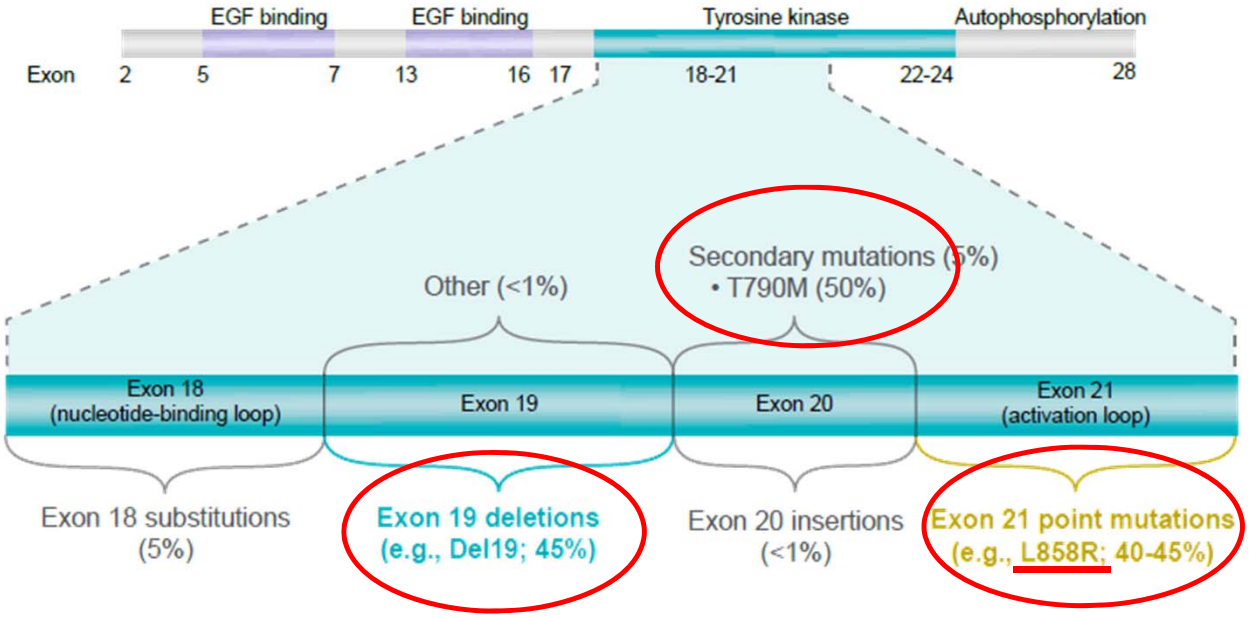
MSKCC data

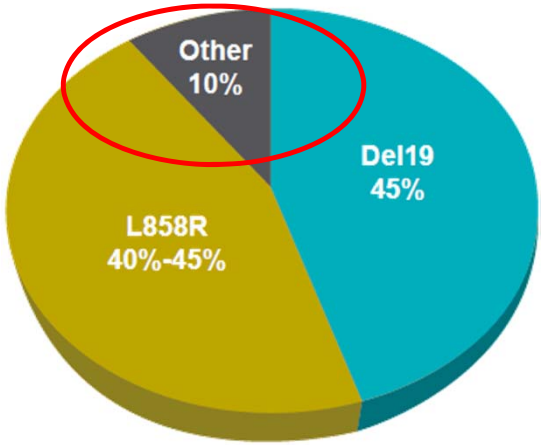
Non-Small Cell Lung Cancers – 2016



MSKCC data

Del19 and L858R: Most Common Mutations in the Tyrosine Kinase Domain of EGFR in NSCLC[1]

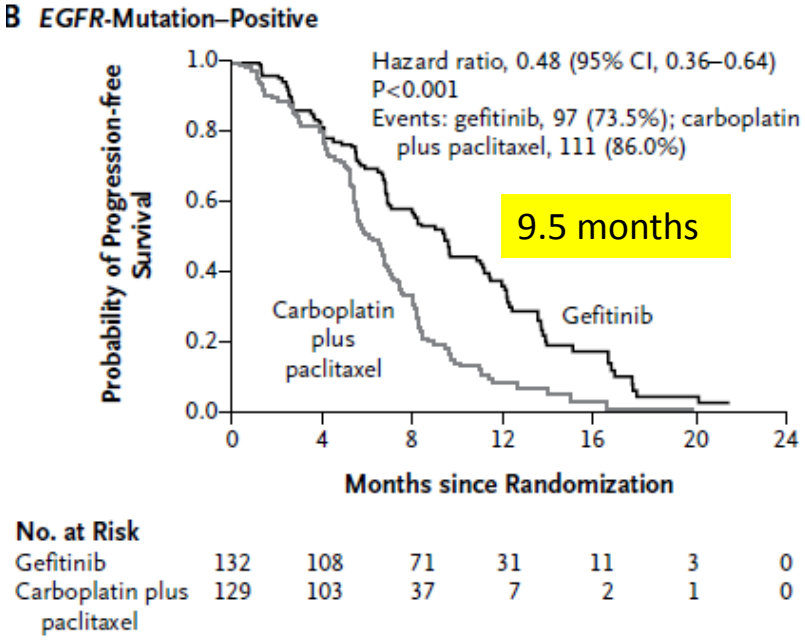




Del19 = exon 19 deletions; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; L858R = exon 21 L858R point mutation; NSCLC = non-small cell lung cancer.

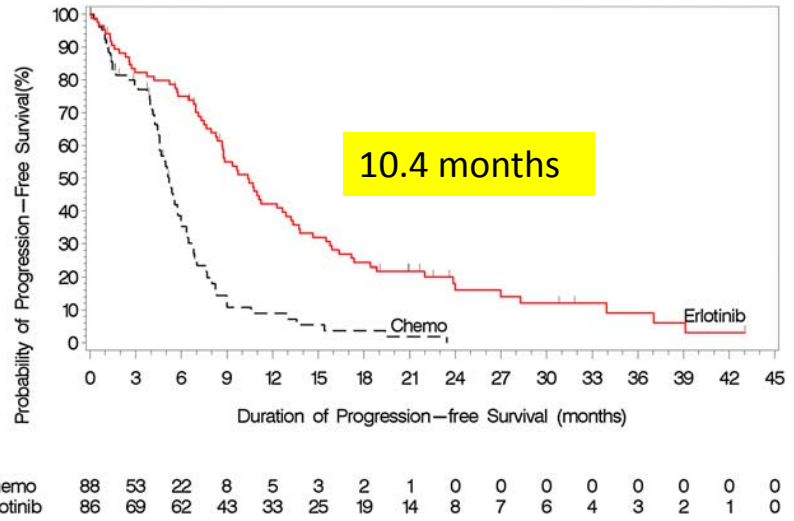
1. Sharma et al. *Nat Rev Cancer.* 2007;7:169.

IPASS: PFS



- Gefitinib: 9.5 months
- Chemotherapy: 6.3 months
  - HR 0.48, 95% CI 0.36-0.64; *P*<0.001

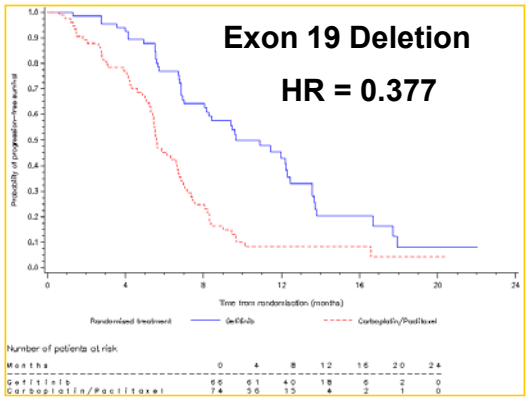
EURTAC: PFS

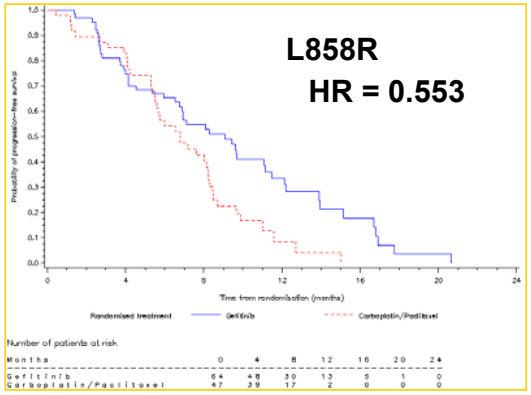


- Erlotinib: 10.4 months
- Chemotherapy: 5.2 months
  - HR 0.34, 95% CI 0.23, 0.49; *P*<0.001

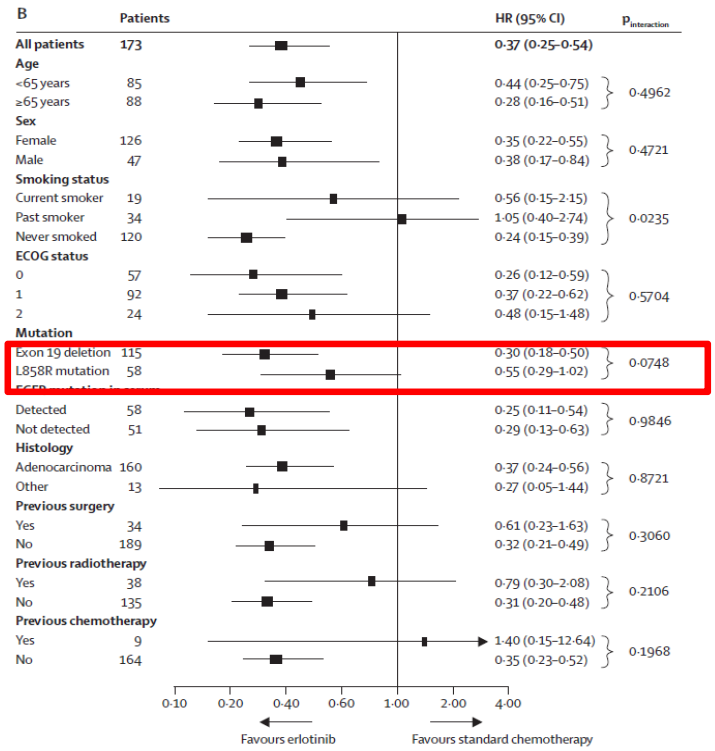
Mok et al. *N Engl J Med.* 2009;361:947.

IPASS: PFS





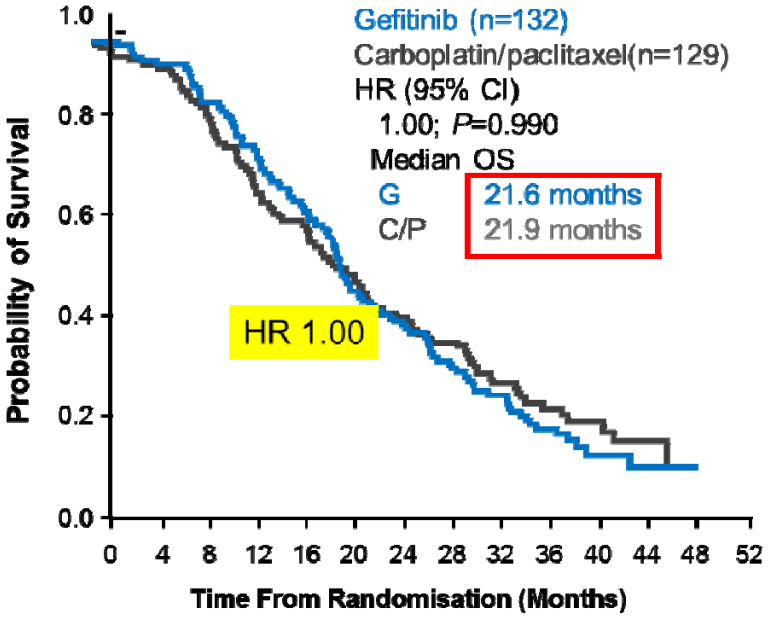
EURTAC: PFS



Sub-group analyses of progression-free survival in the intention-to-treat population[2]

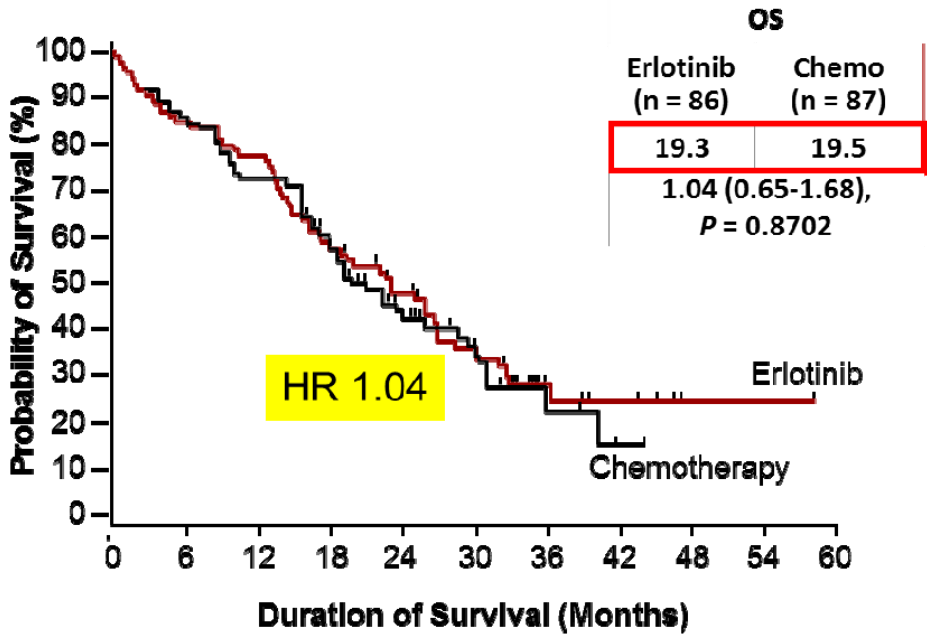
1. Khozin S et al. *Oncologist*. 2014;19:774; 2. Rosell R et al. *Lancet Oncol*. 2012;13:239.

IPASS: OS EGFR Mutation +



Fukuoka M et al. *JCO*. 2011;29:2866-2874.

EURTAC Overall Survival

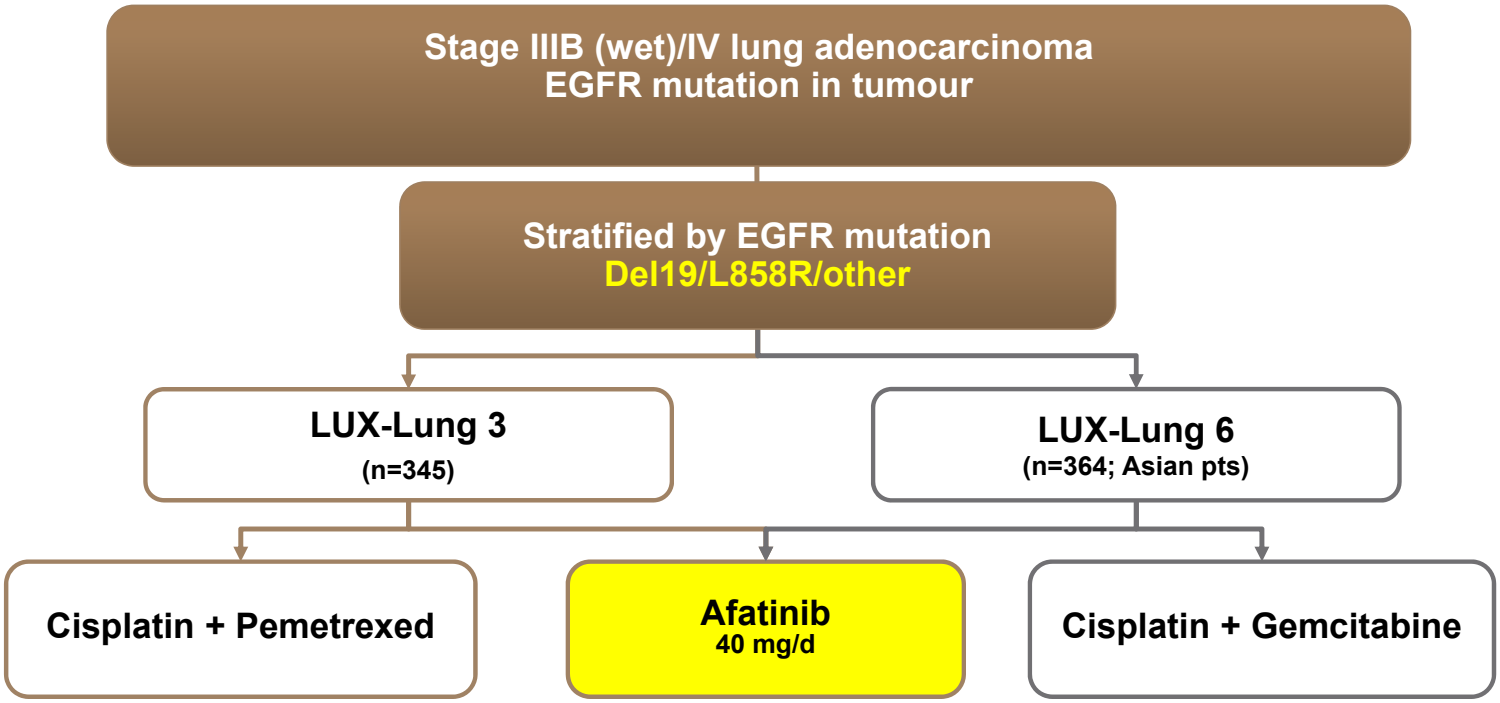


Khozin S, et al. *Oncologist*. 2014;19:774-779.

EGFR TKI First- and Second-Generation

Agent	Reversibility	Targets (IC_{50}, nM)*
Gefitinib	Reversible	EGFR (3) HER2 (1830)
Erlotinib (First-Generation)	Reversible	EGFR (0.5) HER2 (512)
Dacomitinib	**Irreversible**	**EGFR (6) HER2 (46) HER4 (74)**
Afatinib (Second-Generation)	Irreversible	EGFR (0.5) HER2 (14) HER4 (1.0)

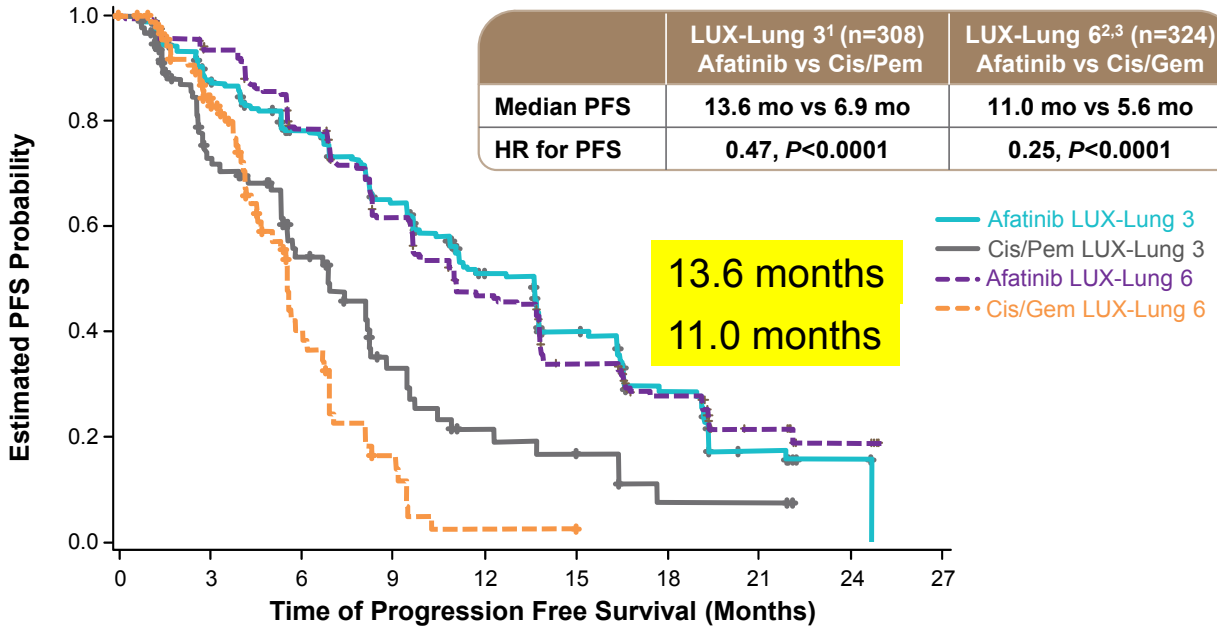
Afatinib: LUX-Lung 3 and LUX-Lung 6



LUX-Lung 3 and LUX-Lung 6:PFS

Patients with common mutations

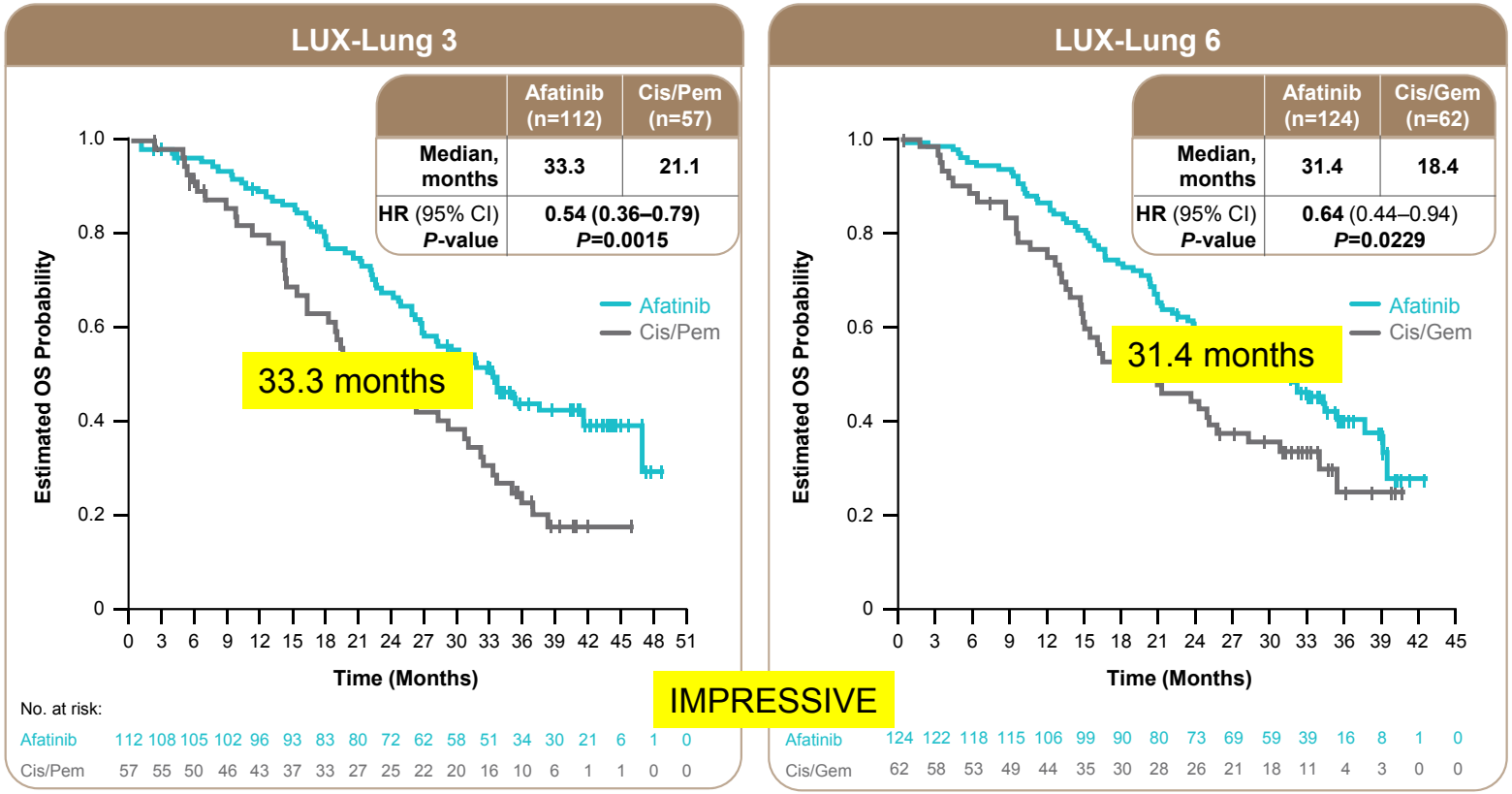
	LUX-Lung 3[1] (n=308) Afatinib vs Cis/Pem	LUX-Lung 6[2,3] (n=324) Afatinib vs Cis/Gem
Median PFS	13.6 mo vs 6.9 mo	11.0 mo vs 5.6 mo
HR for PFS	0.47, *P*<0.0001	0.25, *P*<0.0001



1. Sequist et al. *J Clin Oncol*. 2013;31:3327; 2. Wu et al. *Lancet Oncol*. 2014;15:213; 3. Data on file. Boehringer Ingelheim.

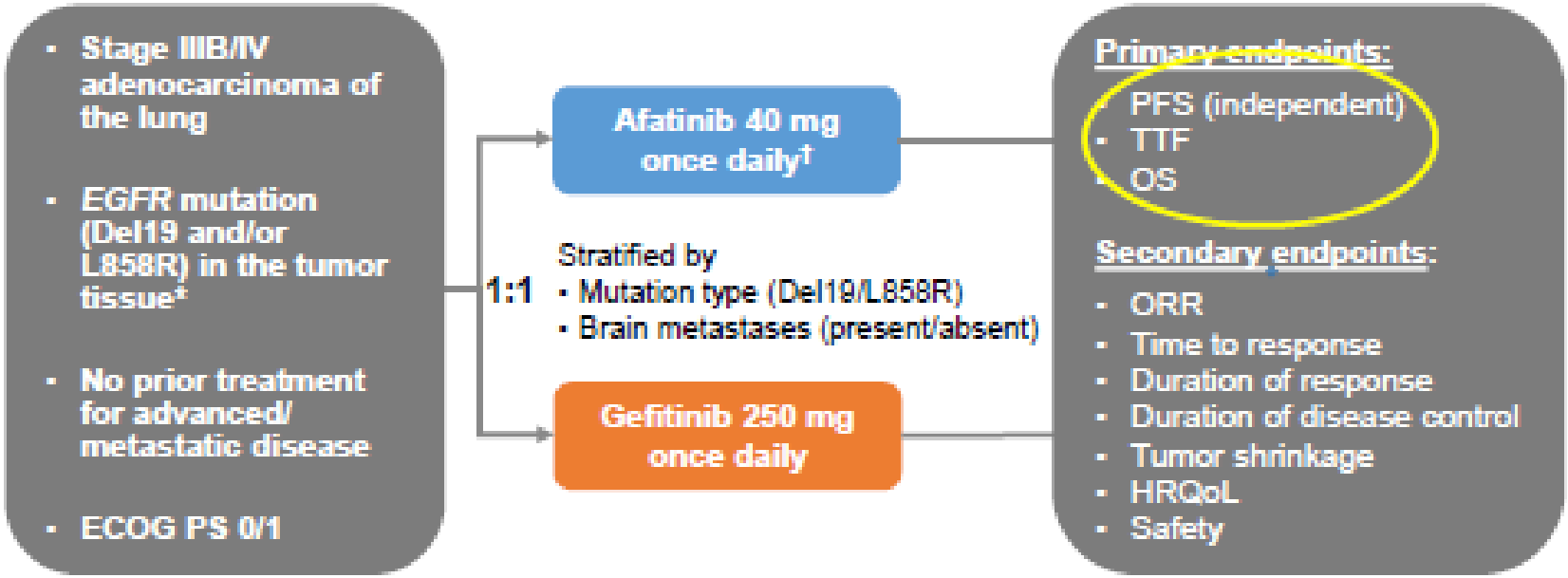
PRESPECIFIED ENDPOINT

LUX-Lung 3 and LUX-Lung 6: OS in Del19 Subgroup



Yang et al. *Lancet Oncol*. 2015;16:141-151.

LUX-Lung 7



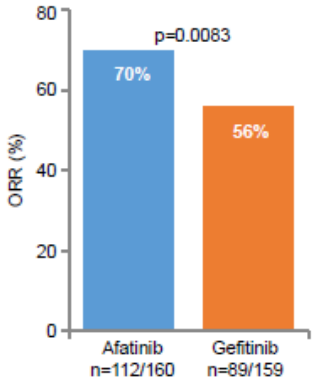
- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

*.

ESMO ASIA 2015

LUX-Lung 7: PFS

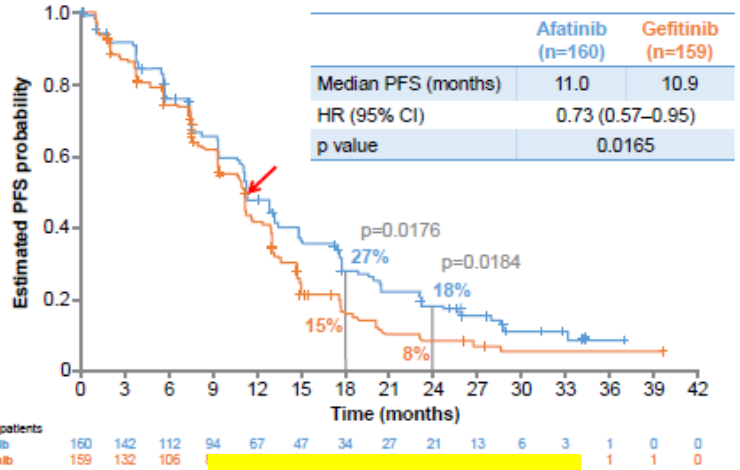
Objective response and duration of response (independent review)



	Afatinib (n=112)	Gefitinib (n=89)
Median DoR (months)	10 .1	8.4
95% CI	(7.8–11.1)	(7.4–10.9)

ORR 70% vs 56%

PFS by independent review



	Afatinib (n=160)	Gefitinib (n=159)
Median PFS (months)	11.0	10.9
HR (95% CI)	0.73 (0.57–0.95)	
p value	0.0165	

HR 0.73 *P*=0.0165

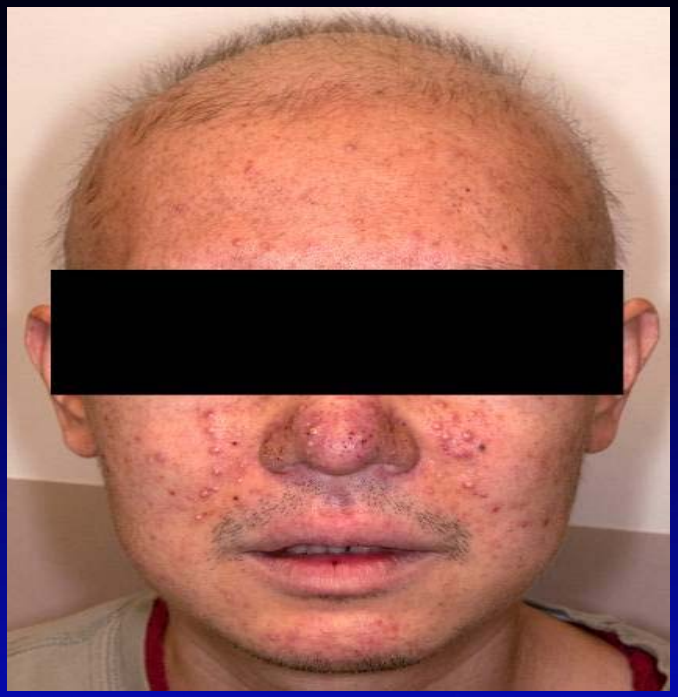
Not All TKIs Are Created Equal – LUX7 Side Effects

	Afatinib (n=160)		Gefitinib (n=159)	
AE category, %	**All**	**Grade 3**	**All**	**Grade 3**
Diarrhea	90.0	11.9†	61.0	1.3
Rash/acne*	88.8	9.4	81.1	3.1
Stomatitis*	64.4	4.4	23.9	-
Paronychia*	55.6	1.9	17.0	0.6
Dry skin	32.5	-	37.1	-
Pruritus	23.1	-	22.6	-
Fatigue*	20.6	5.6	14.5	-
Decreased appetite	16.3	0.6	11.9	-
Nausea	No case of ILD.	1.3	13.8	4 case of ILD. -
Alopecia	10.6	-	15.1	-
Vomiting	10.6	-	3.8	0.6
ALT increased	9.4	-	23.9	7.5‡
AST increased	6.3	-	20.8	2.5

*Grouped terms of AEs

Park et al. ESMO Asia, 2015.

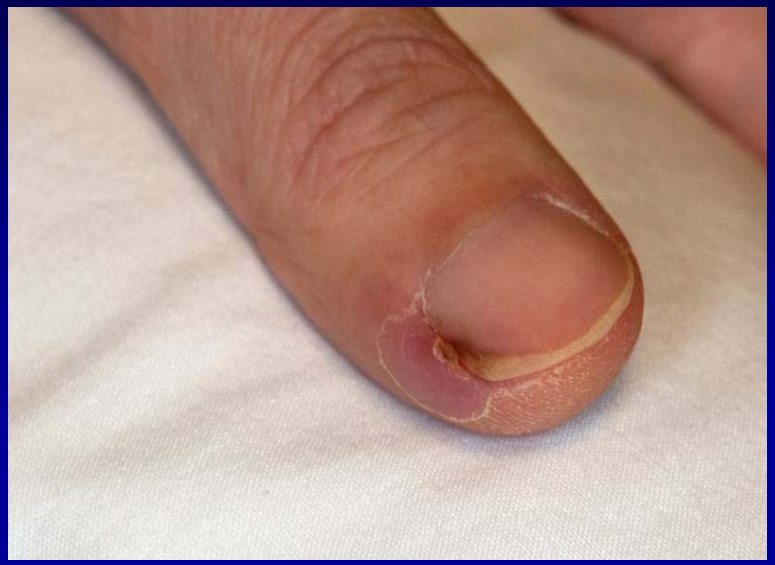
AFATINIB



Rash

Clindamycin 2% Hydrocotisone 2% cream

Minocycline 100 mg bid for 4 weeks



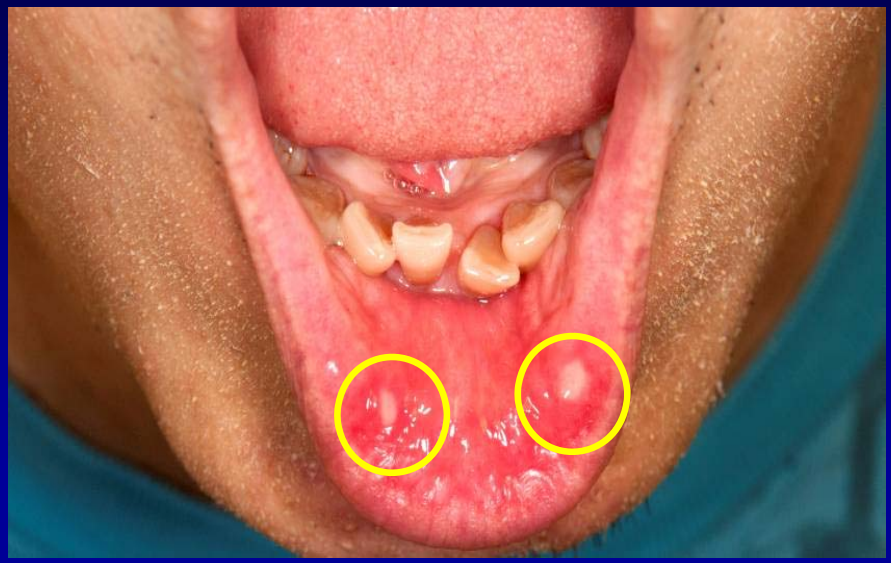
Paronychia

Bethamethasone Valerate

Apply bid to nail bed

M: 60g Rx 3

Liquid bandaid



Mucositis

Kenalog Orobase 0.1%

Apply bid to mouth

M: 1 bottle Rx 3

PROPHYLACTIC MINOCYCLINE

PanCanadian Rash Trial with EGFR Inhibitors

Optimal treatment of rash secondary to erlotinib

Barbara Melosky, Helen Anderson, Ron Burkes, Quincy Chu, Desiree Hao, Vincent Ho, Cheryl Ho, Wendy Lam, Christopher Lee, Natasha Leighl, Nevin Murray, Sophie Sun, Robert Winston, Janessa Laskin

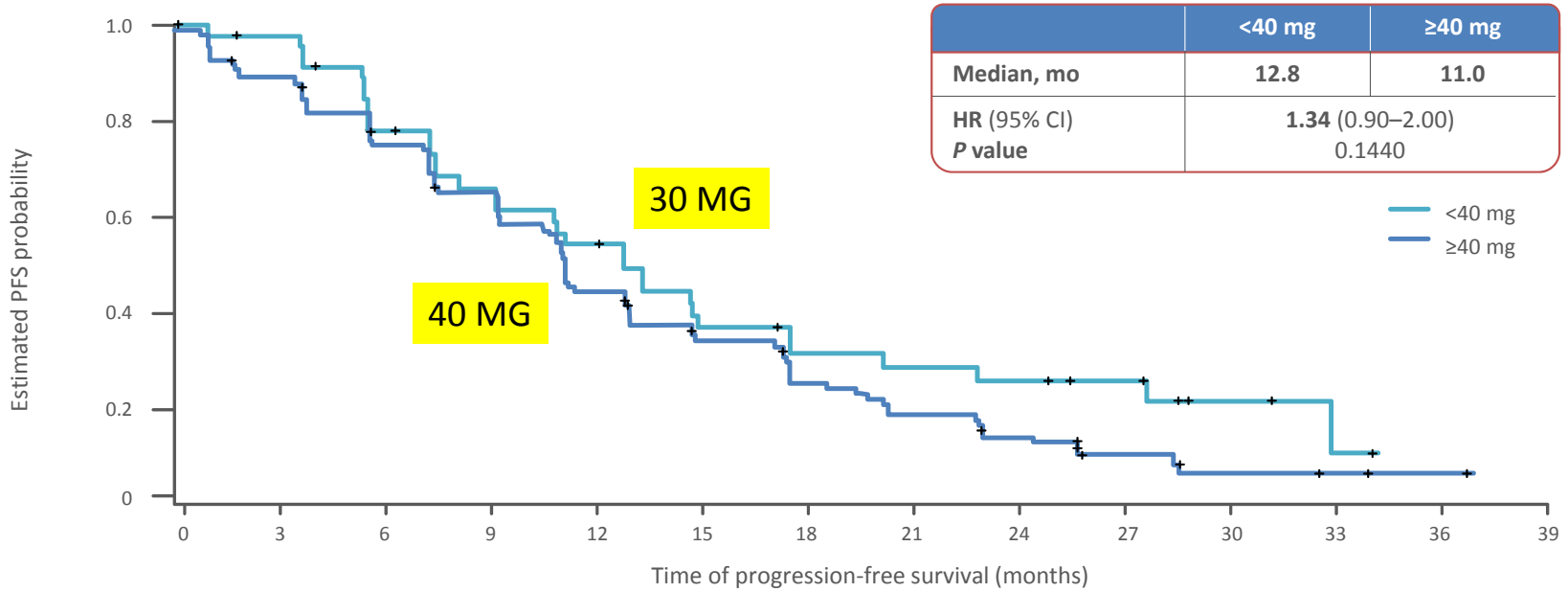
JCO March 2016

Incidence of Rash and Time to Severe Grade 3 Rash

	Incidence of any rash n (%)	Incidence of Grade 3 rash n (%)	P value	Mean (days) to Grade 3 rash onset	P value
ARM 1 (N=50) Prophylactic	84%	9.5%	P = 0.034 Arm 1 vs 3	17.4	P = 0.0147
ARM 2 (N=50)	84%	14.3%	P= 0.065 Arm 2 vs 3	13.3	
Arm 3 (N=50)	82%	34.1%		12	

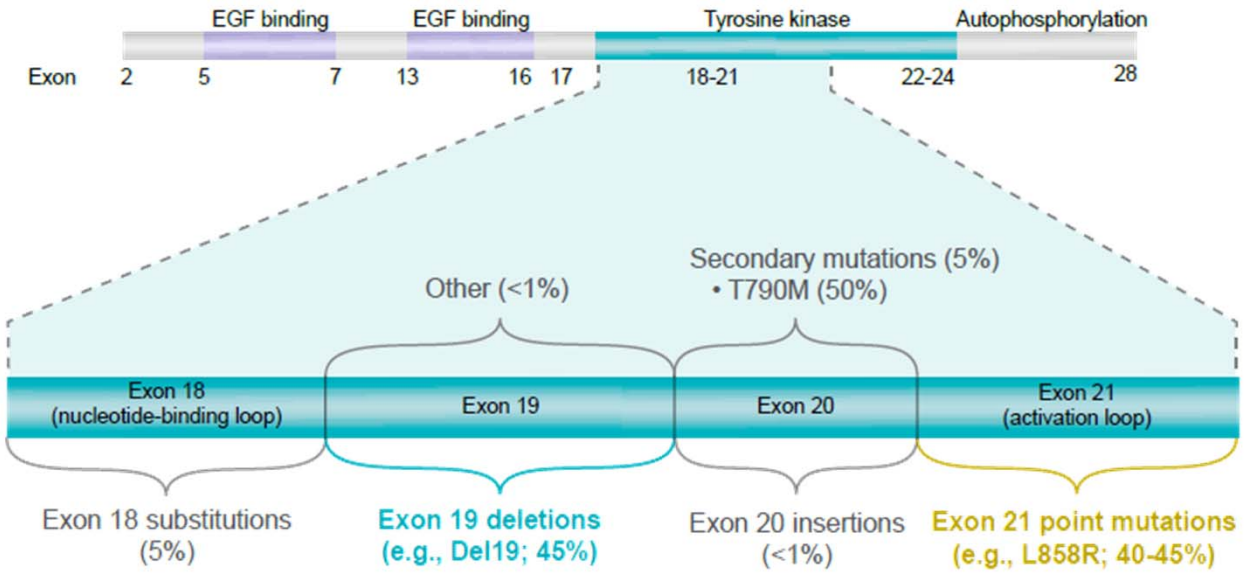
JCO March 2016

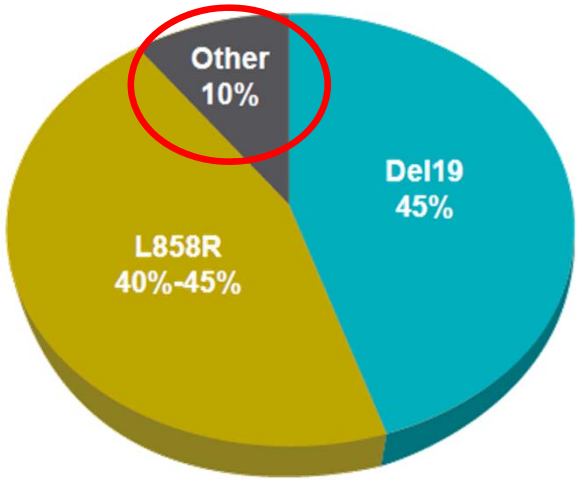
LUX-Lung 7:
Impact of Afatinib Dose Modification on PFS



	<40 mg	≥40 mg
Median, mo	**12.8**	**11.0**
HR (95% CI)	**1.34** (0.90–2.00)	
***P* value**	0.1440	

Del19 and L858R: Most Common Mutations in the Tyrosine Kinase Domain of EGFR in NSCLC[1]



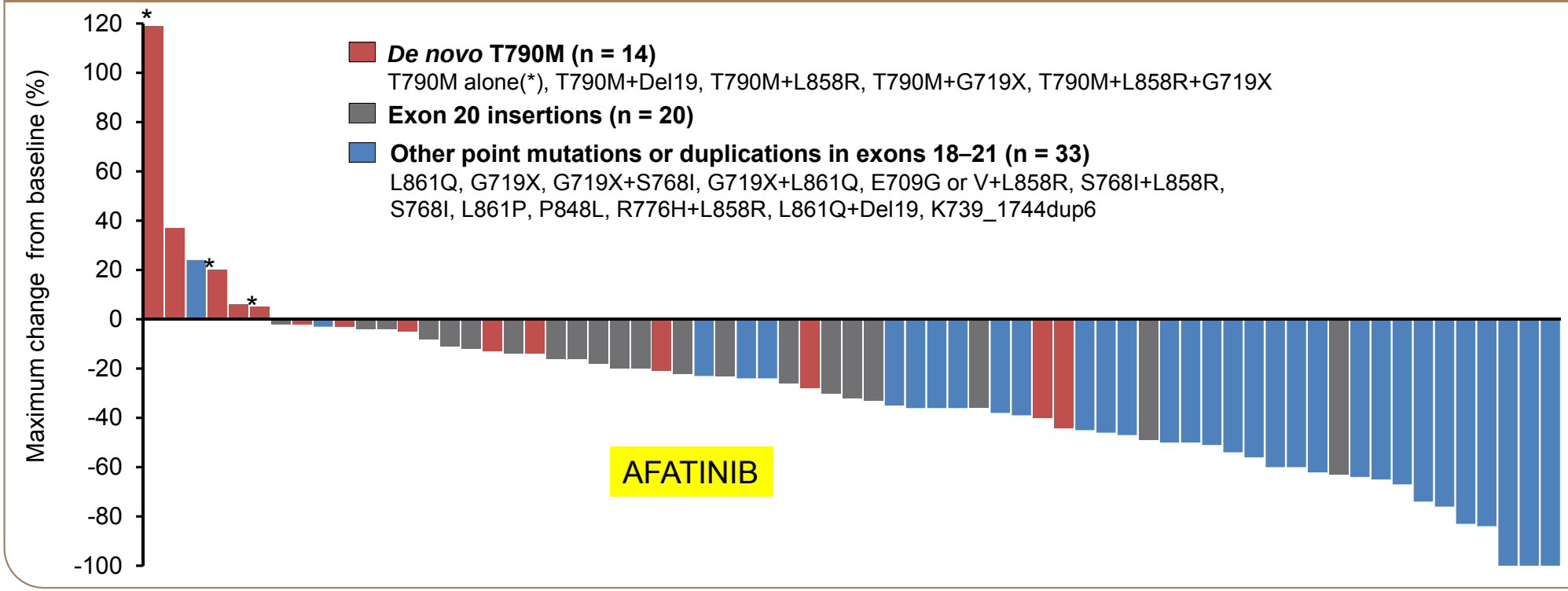


Del19 = exon 19 deletions; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; L858R = exon 21 L858R point mutation; NSCLC = non-small cell lung cancer.

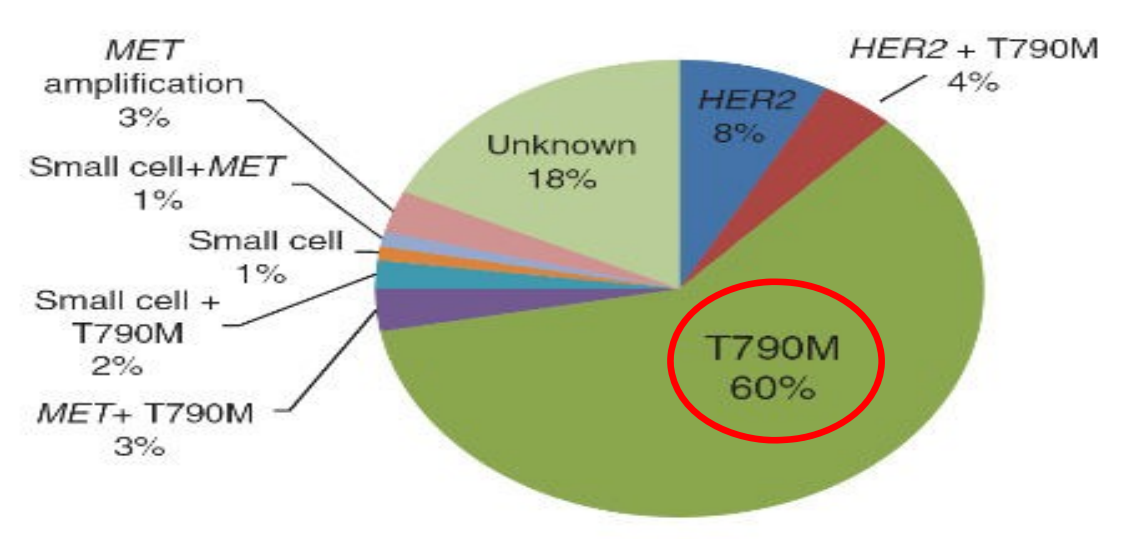
1. Sharma et al. *Nat Rev Cancer.* 2007;7:169.

LUX-Lung 2, 3, & 6: AFATINIB
Uncommon Mutations[a]

Tumour Shrinkage in Uncommon Mutations (independent review)



Molecular Mechanisms of Acquired Resistance to EGFR TKI (N = 155)



Yu H, et al. *Clin Cancer Res*. 2013;19(8):2240-2247.

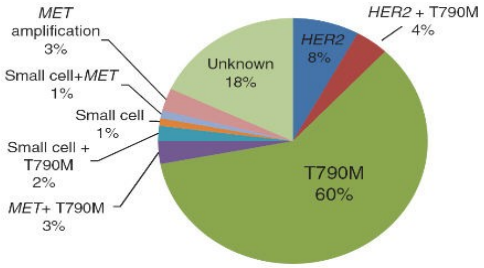
First-, Second-, and Third-Generation EGFR TKIs

Agent		Reversibility	Targets (IC_{50}, nM)
Gefitinib	First-Generation	Reversible	EGFR (3) HER2 (1830)
Erlotinib		Reversible	EGFR (0.5) HER2 (512)
Dacomitinib	Second-Generation	Irreversible	EGFR (6) HER2 (46) HER4 (74)
Afatinib		Irreversible	EGFR (0.5) HER2 (14) HER4 (1.0)
Osimertinib	Third-Generation		TARGET T790
Olmutinib			EGFR (9)

ELCC Geneva 2016

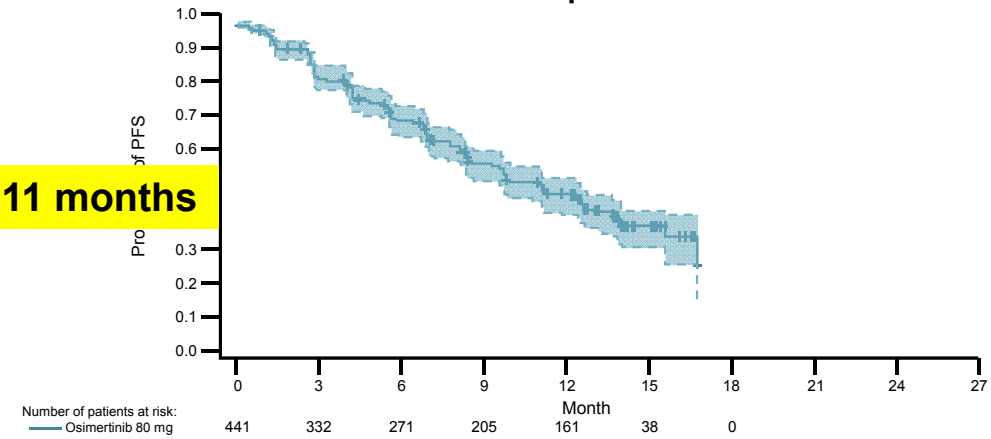
OSIMERTINIB

PFS AURA Trial – 2nd-Line Aquired T790 M+

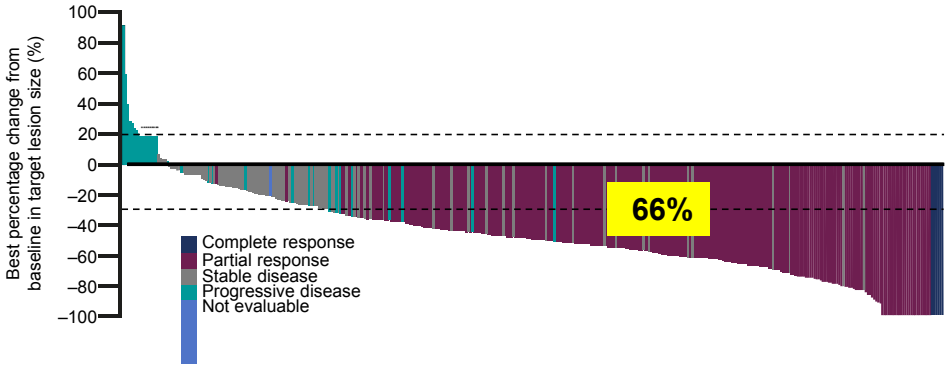


PFS 11 months

AURA pooled Ph II



AURA pooled Ph II



Yang JCH, et al. ELCC 2016; Abstract LBA2_PR.

Causally Related AEs: AURA Ph I

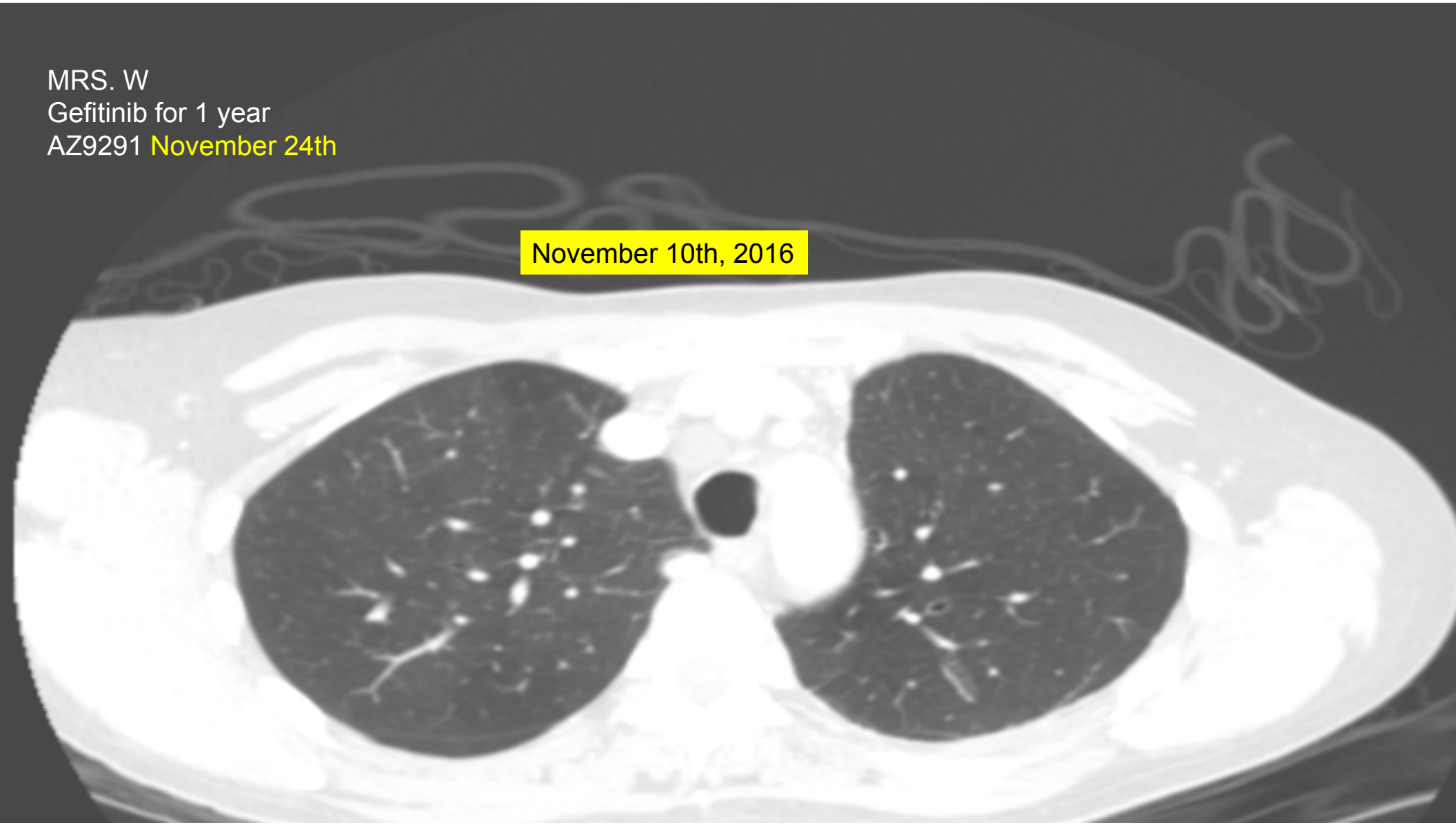
Causally-related AEs occurring in ≥15% of patients overall, n (%)	AURA Ph I (80 mg) N=63*			
	Grade 1	Grade 2	Grade ≥3	Any grade
Rash (grouped terms)	21 (33)	2 (3)	0	23 (37)
Diarrhoea	16 (25)	3 (5)	1 (2)	22 (35)†
Paronychia (grouped terms)	11 (18)	6 (10)	1 (2)	18 (29)
Dry skin (grouped terms)	11 (18)	3 (5)		
Fatigue	9 (14)	0	0	10 (16)‡
Select AEs				
ILD (grouped terms)#	0	0	1 (2)	1 (2)
Hyperglycaemia	0	0	0	0
QT prolongation	0	0	1 (2)	1 (2)

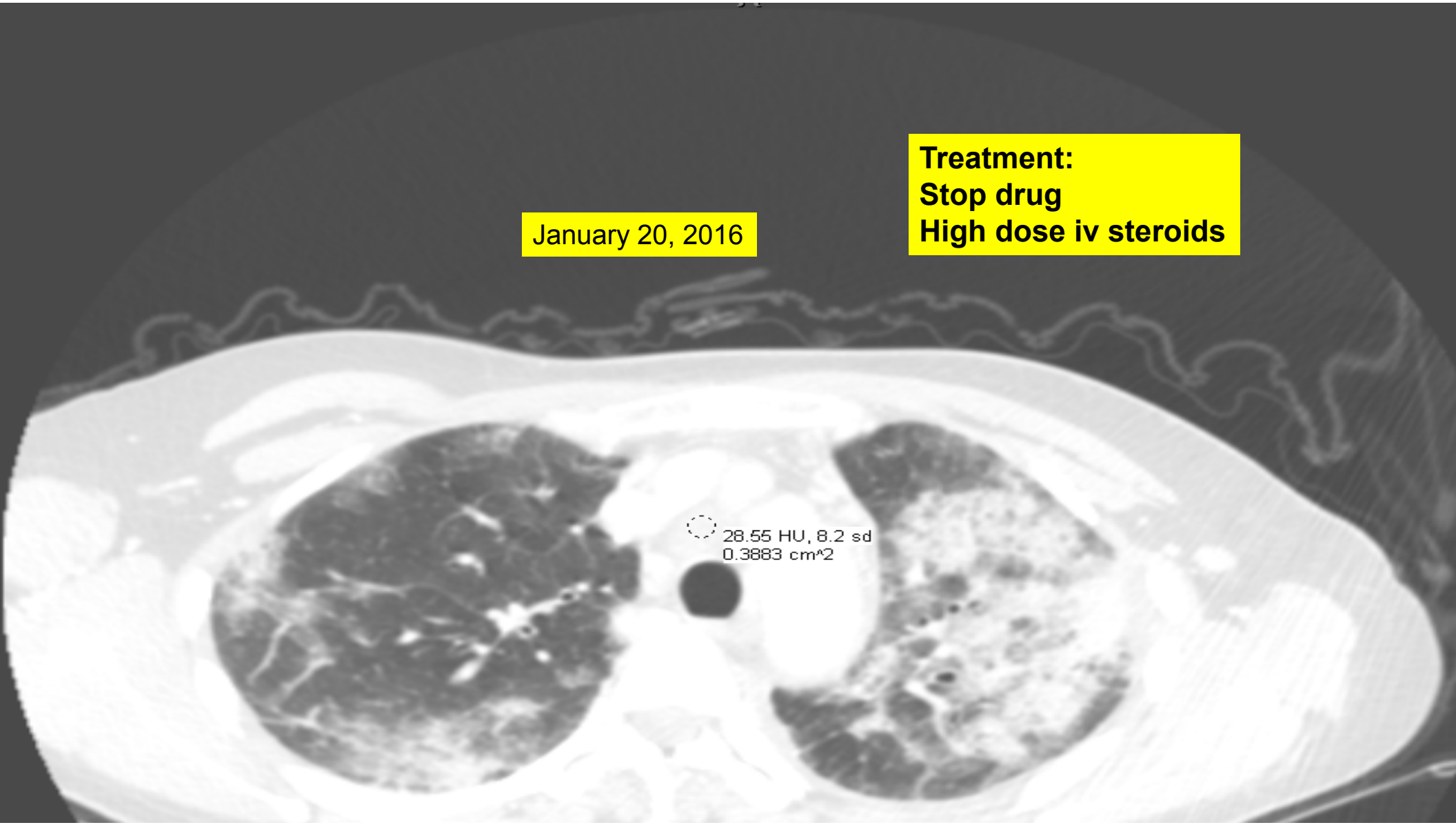
NO RASH or DIARRHEA

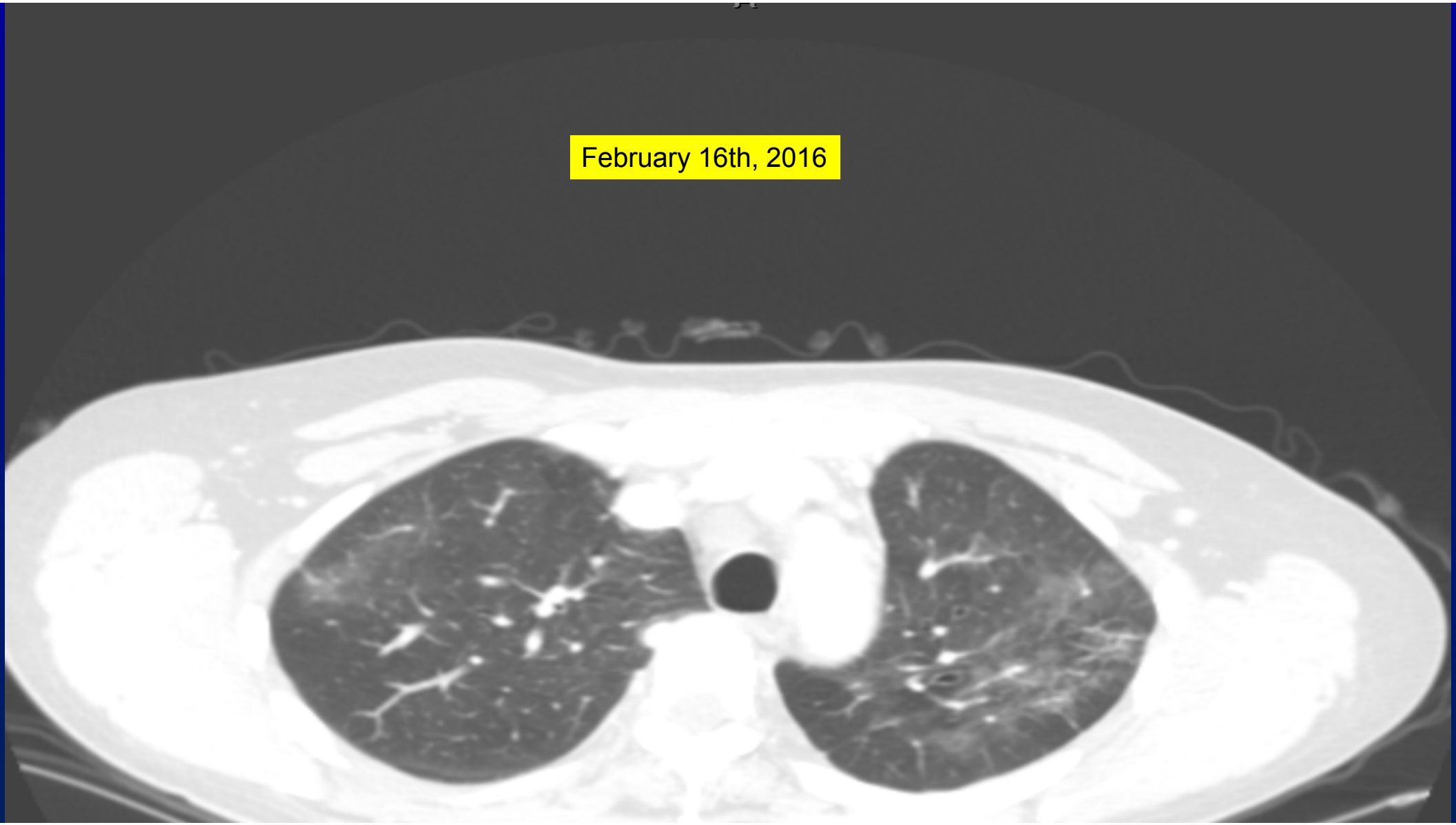
ILD 2.9 %
35/1200 pts

Grade 1	9
Grade 2	6
Grade 3,4	16
Grade 5	4

Yang JCH, et al. ELCC 2016; Abstract LBA2_PR.


MRS. W
Gefitinib for 1 year
AZ9291 November 24th
November 10th, 2016


January 20, 2016
Treatment:
Stop drug
High dose iv steroids
28.55 HU, 8.2 sd
0.3883 cm^2


February 16th, 2016

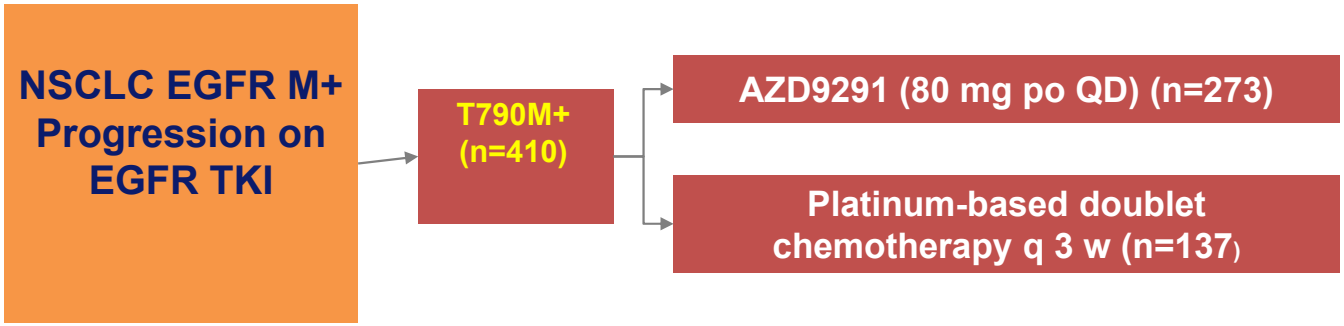
JULY 18th 2016

AURA3 Study Design

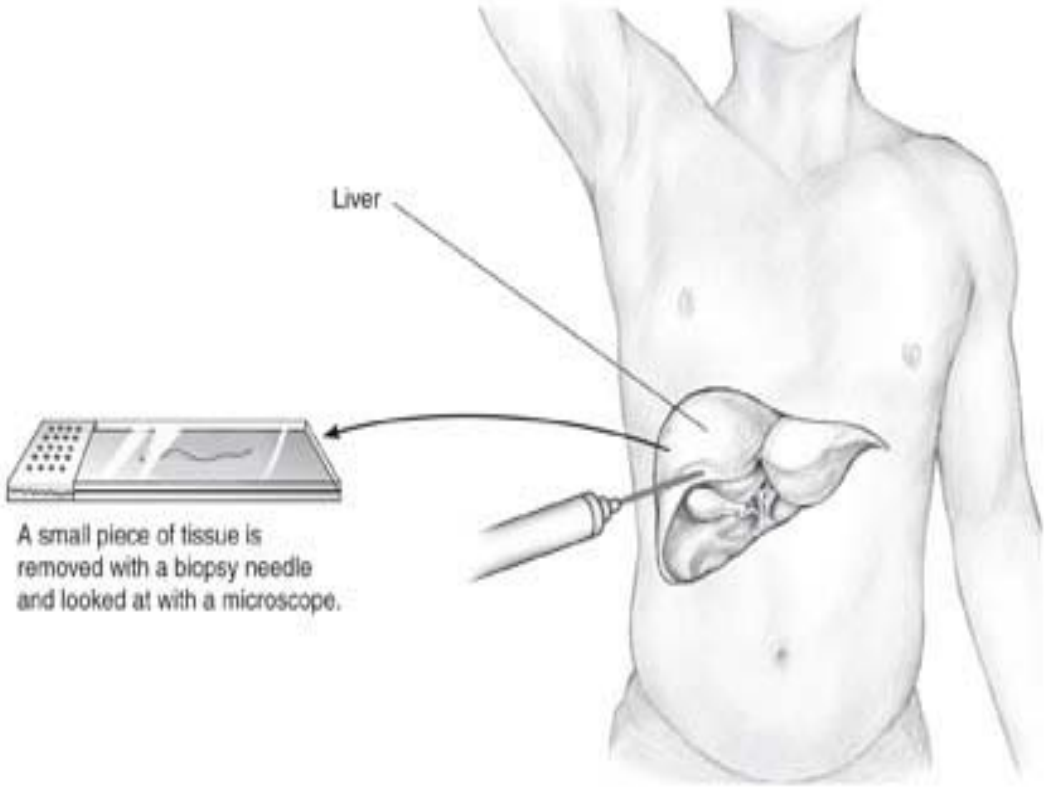
- A Phase III, open-label, randomised study of 410 patients

POSITIVE TRIAL: PFS

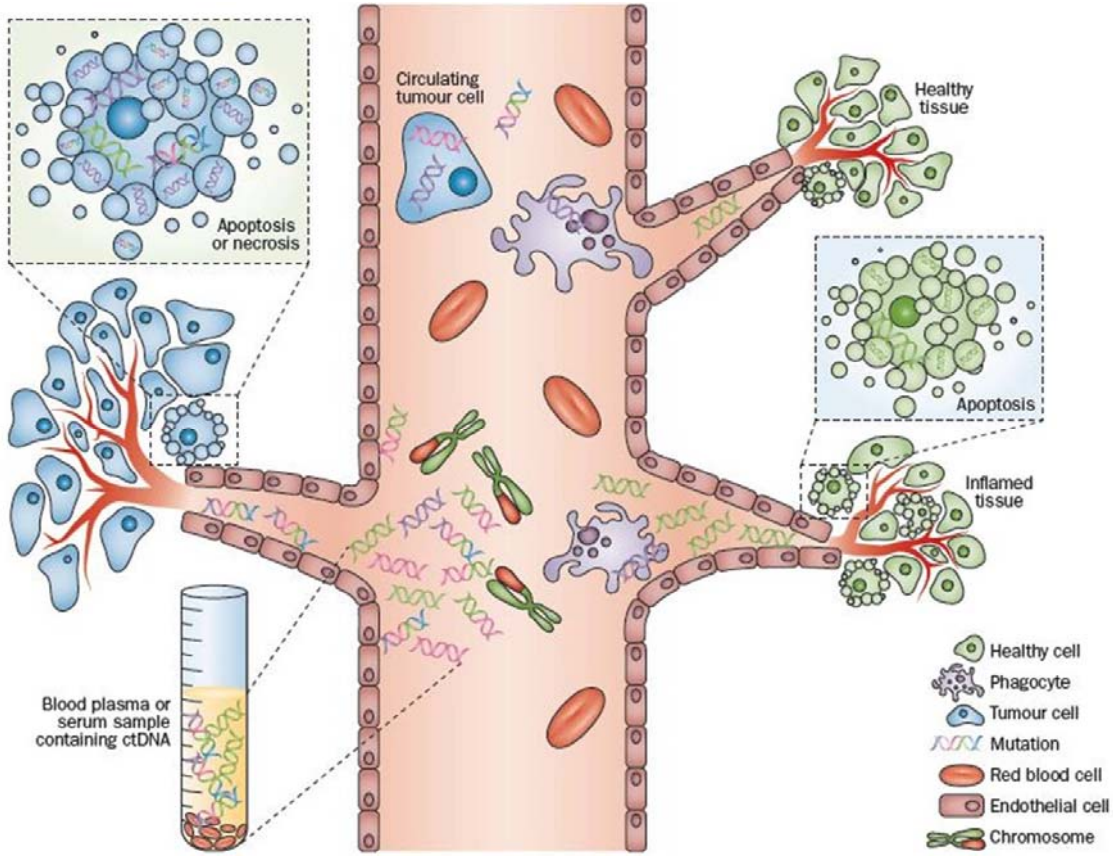
World Lung Vienna 2016



T790 Biopsy: Biopsy the tumor



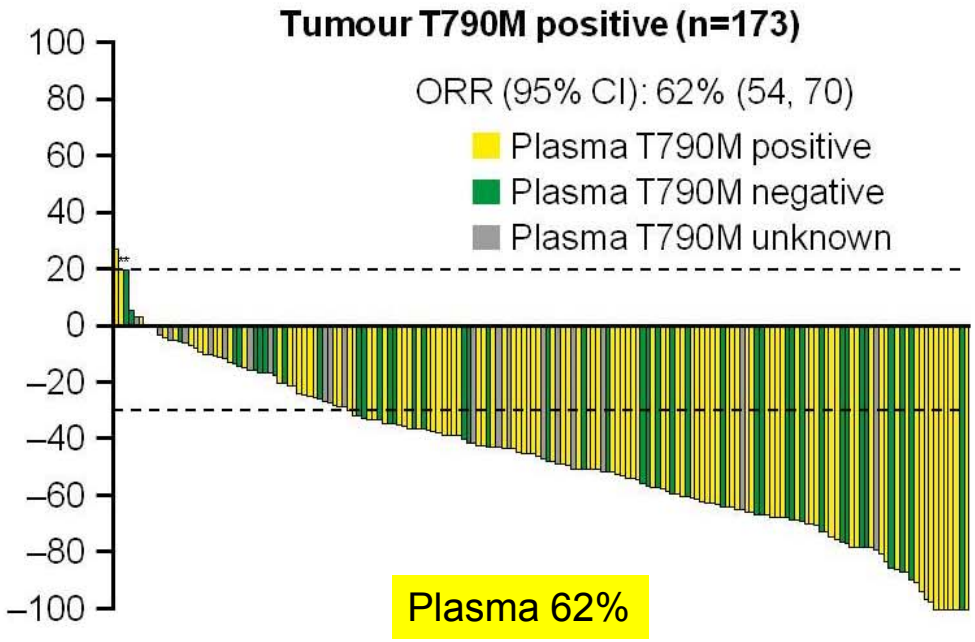
Can We Find EGGR T790M From the Blood?

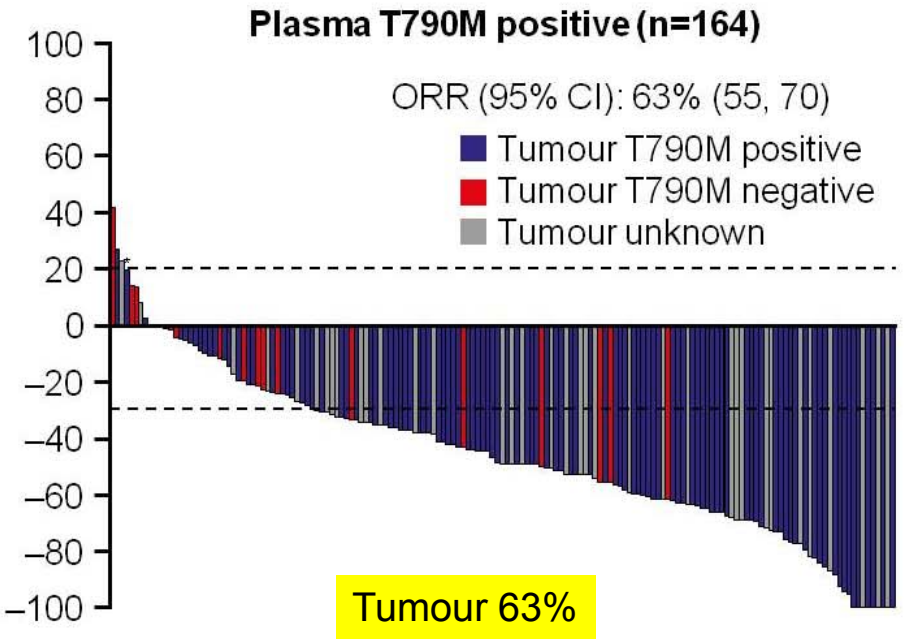


Crowley et al. *Nat Rev Clin Oncol*. 2013;10:472.

ELCC Geneva 2016

High ORR in Patients With Tumour or Plasma-Positive T790M Patients Treated With Osimertinib

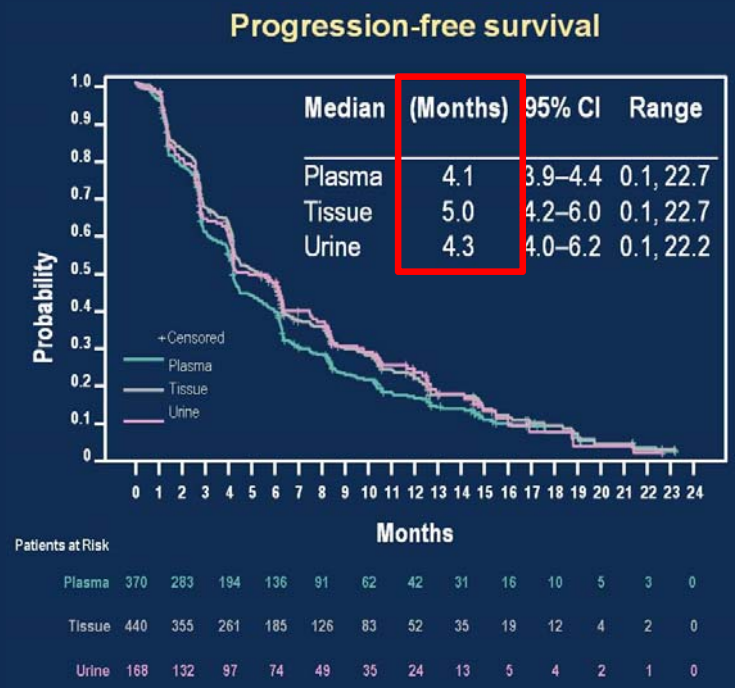




Oxnard et al. ELCC 2016.

ASCO 2016 Investigator-assessed Confirmed Response Rate and PFS are Similar in T790M Patients by Plasma, Tissue, and Urine Test

Sample Type	n	Objective Response Rate* % (95% confidence interval)
Tissue	443	33.9 (29.5–38.5)
Plasma	374	32.1 (27.4–37.1)
Urine	169	36.7 (29.4–44.4)

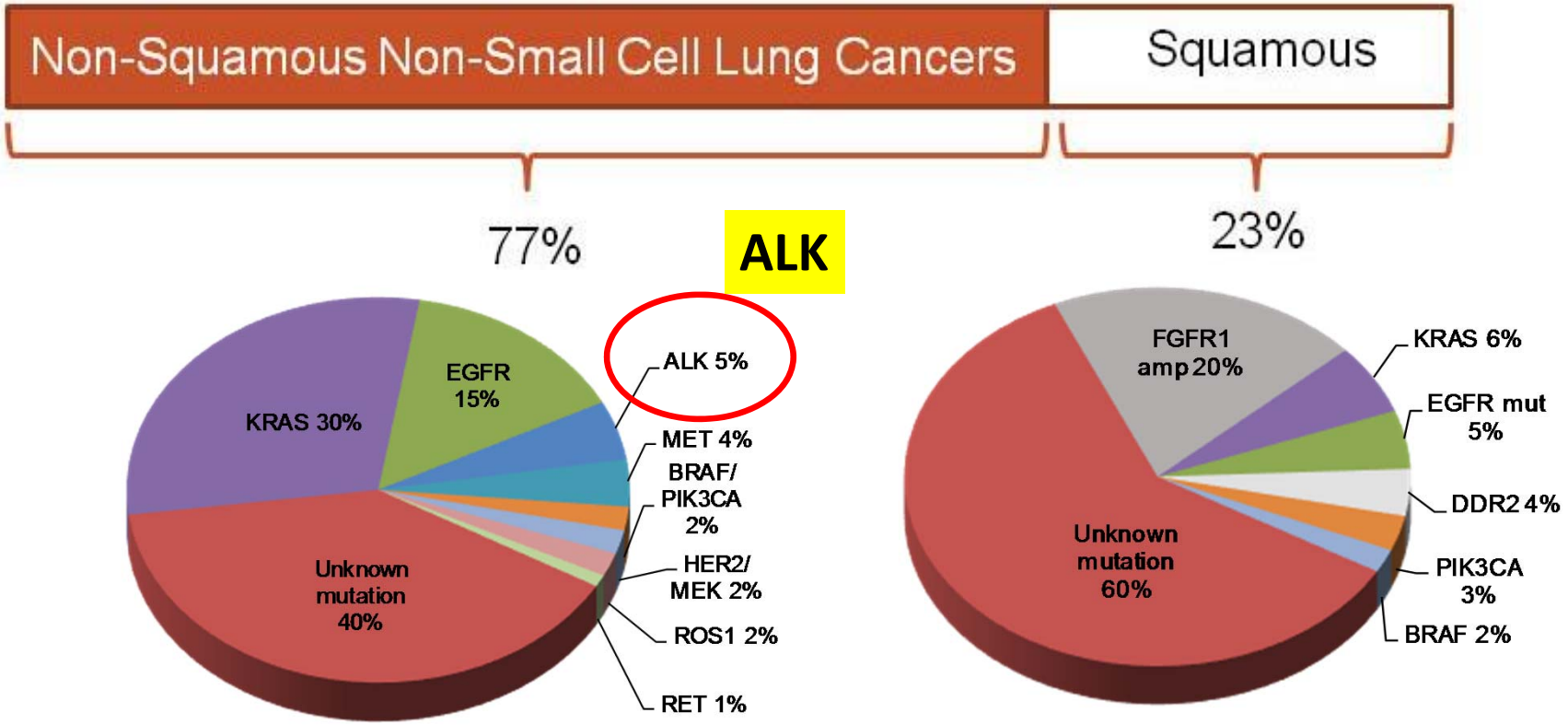


Urine T790M: The Ultimate Liquid Biopsy!

Summary: EGFR

- Current:
  - First line: Gefitinib/ Afatinib
- Recent Advances:
  - LUX Lung 7 Afatinib
  - Osimertinb Aura Trial 2nd Line T790M+: PFS 11 months
  - T790: Plasma may be as accurate as tumor
  - T790: Urine may be accurate

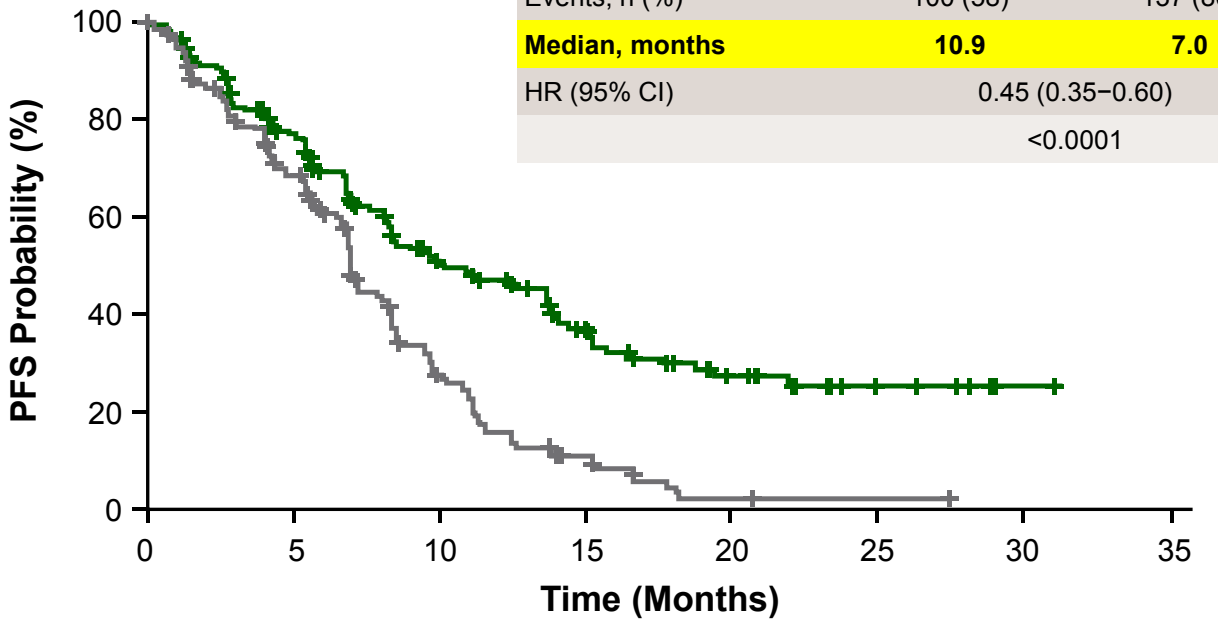
Non-Small Cell Lung Cancers – 2015



MSKCC data

PROFILE 1014:
First-line Crizotinib vs Pem/Cis PFS

	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)	
	<0.0001	



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

Adverse Events

	Crizotinib (n=172), n (%)		Chemotherapy (n=171), n (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Vision disorder	103 (60)	0 (0)	16 (9)	0 (0)
Diarrhea	103 (60)	0 (0)	33 (19)	1 (1)
Nausea	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting	80 (47)	2 (1)	30 (18)	0 (0)
Constipation	73 (42)	4 (2)	39 (23)	0 (0)
Elevated transaminases	66 (38)	27 (16)	25 (15)	4 (2)
Edema	54 (31)	0 (0)	27 (16)	0 (0)
Upper respiratory infection	44 (26)	0 (0)	22 (13)	1 (1)
Dysgeusia	44 (26)	0 (0)	16 (9)	0 (0)
Dizziness	37 (22)	1 (1)	14 (8)	0 (0)
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Alopecia	14 (8)	0 (0)	35 (21)	0 (0)
Dyspnea	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0 (0)	29 (17)	0 (0)

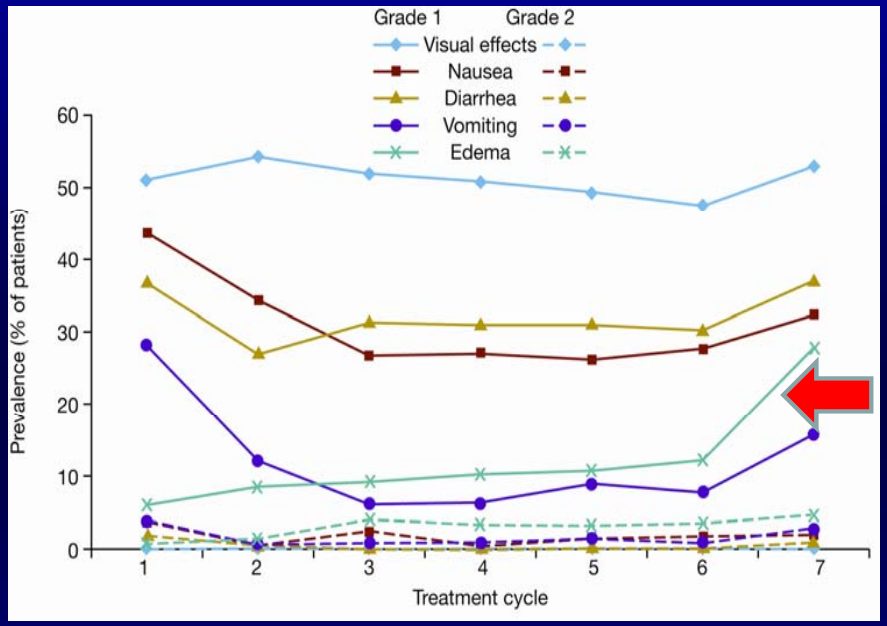
Characteristic Visual Effects with Crizotinib

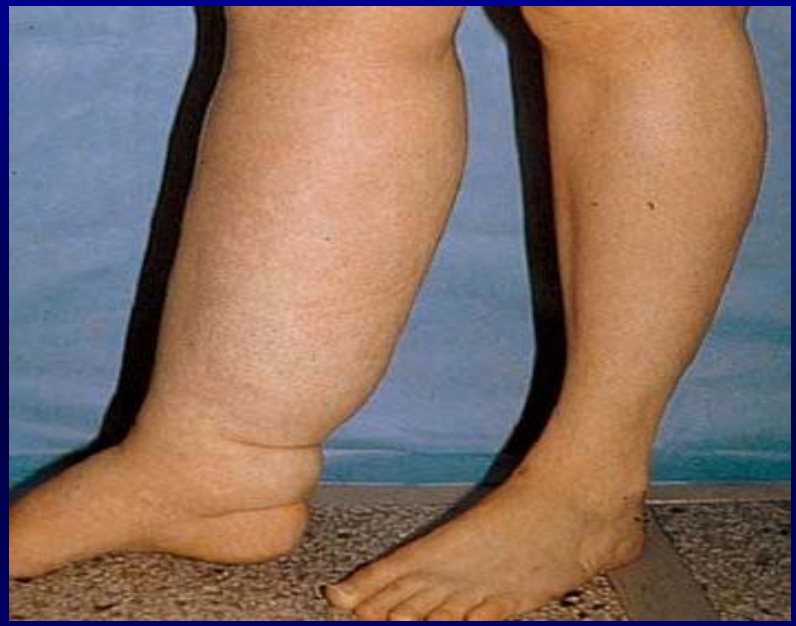
- 'Trails' from lights in peripheral vision in low light conditions (e.g. dawn and dusk)[1]

- Overlapping shadows or after-images[2]

- **At edges of vision in low light conditions:**
  - **Image persistence**
  - **Flashes of light, which do not appear to be connected to a real light source**
  - **Flipped registration from high contrast images (e.g. stripes)**

1. Camidge DR, et al. J Clin Oncol 2011;29(Suppl): Abstract 2501
2. Solomon B, et al. ECCO-ESMO 2011: Abstract 3030

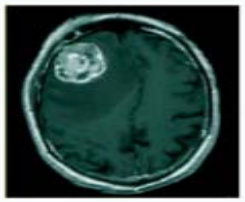

Grade 1
Grade 2
Visual effects
Nausea
Diarrhea
Vomiting
Edema
Prevalence (% of patients)
60
50
40
30
20
10
0
1
2
3
4
5
6
7
Treatment cycle



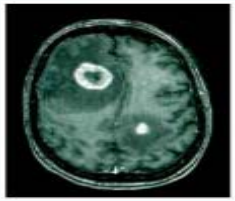
CNS Sanctuary

- Brain metastases

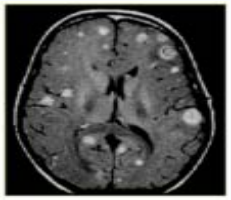
MRI Detection of BMs



Solitary lesion



Oligometastases

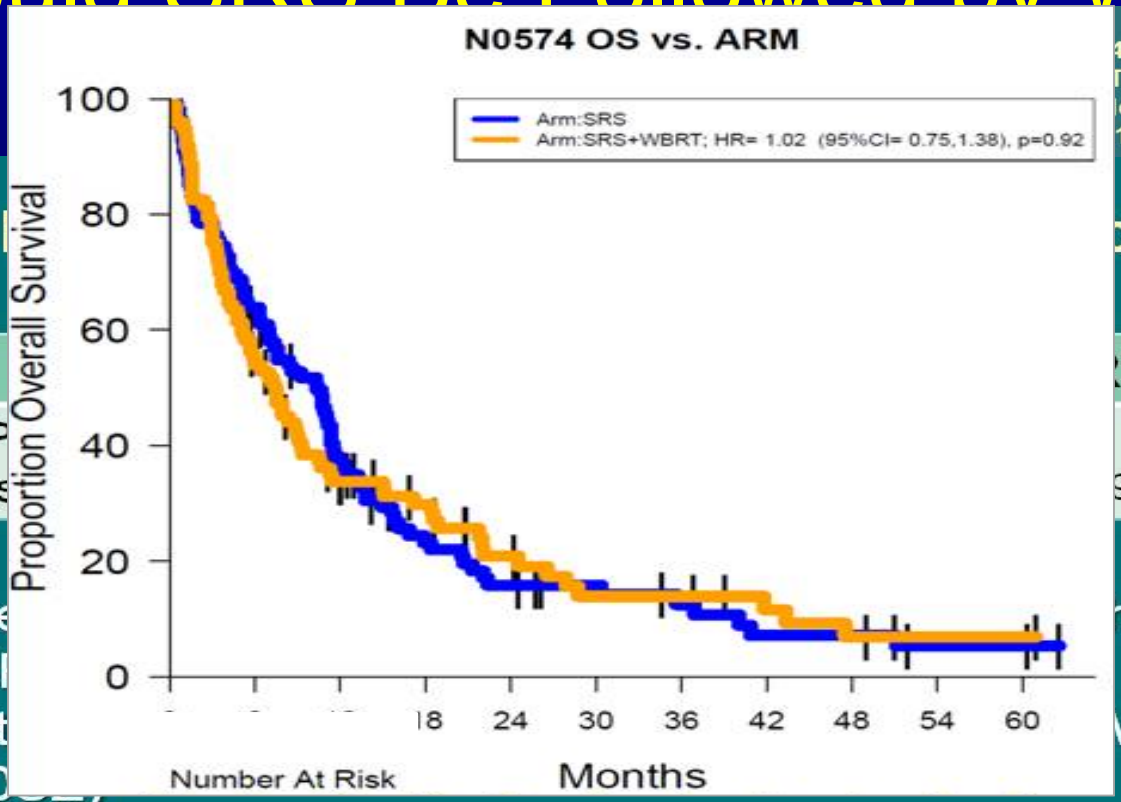


Multiple BMs

1. Costa et al. *J Clin Oncol*. 2015;33:1881]. 2. Hu et al. *Cancer*. 2006;106:1998. 3. Rangachari et al. *Lung Cancer*. 2015;88:108.4. Goodgame and Ramaswamy. http://www.cancernetwork.com/lung-cancer/content/article/10165/1146761. Accessed April 28, 2015. 5. Dziadziuszko and Jassem. *J Thorac Oncol*. 2013;8:1465.

ASCO 2015 Plenary Session

Should SRS Be Followed by WBRT?



4 (Alliance): A Phase III
Trial of Whole Brain Radiation
dition to Radiosurgery in
1 to 3 Brain Metastases

Primary …**on at 3 mos**

	…RT	P-value
Cognitive P… at 3 months	…97.7)	0.0007

- Decline… …n the addition of WBI…
- Persist… …VBRT 97.9%, p = 0.0…

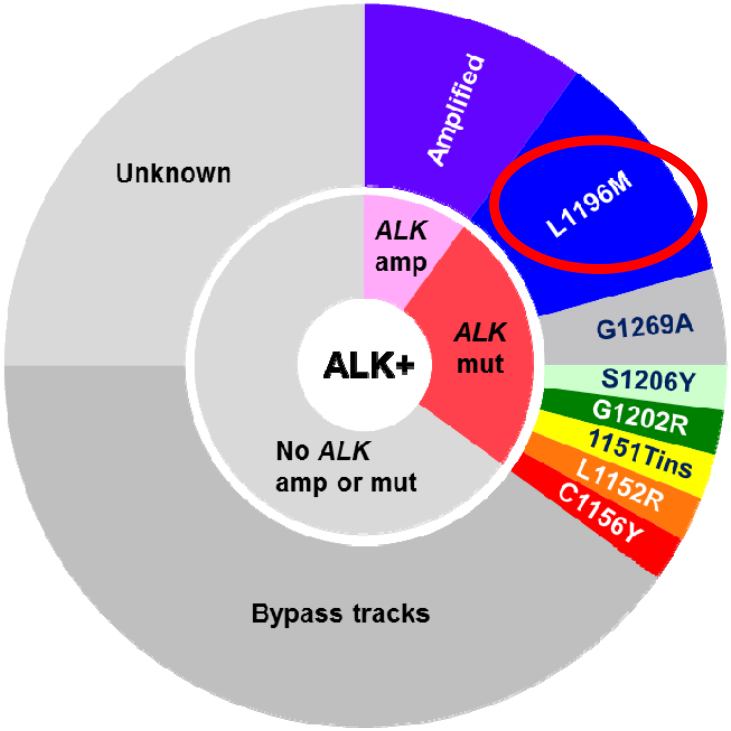
Presented by: Paul Brown, MD

PRESENTED AT: ASCO Annual '15 Meeting

Brown PD, et al. *J Clin Oncol* 33, 2015 (suppl, abstr LBA4).

Acquired Resistance in ALK+ NSCLC

- Most patients develop resistance to crizotinib
  - Usually within 1-2 years
  - CNS relapses are common
- Mechanisms of resistance are diverse
  - ALK resistance mutations
  - Alternative signaling pathways
    - EGFR activation/mutation
    - *c-KIT* amplification, *KRAS* mutation

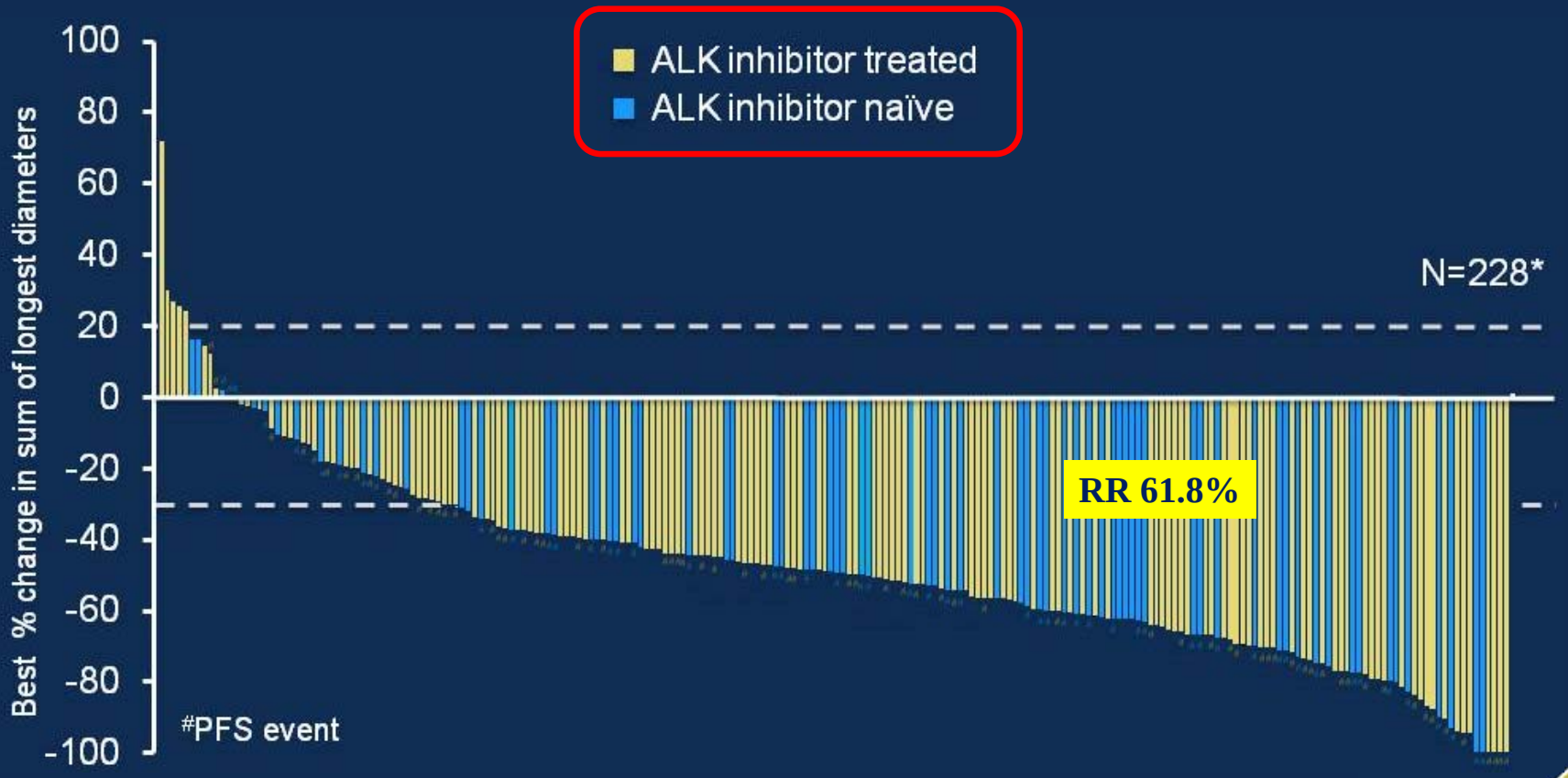


Profile of Second-/Third-Generation ALK Inhibitors

Drug	Company	Activity Against L1196M	Other Kinases Inhibited	Clinical Stage
Crizotinib	Pfizer	No	MET, ROS1	Approved
Ceritinib	Novartis	Yes	ROS1, IGFR1	Approved
Alectinib	Chugai/Roche	Yes	RET	Phase III
Brigatinib	Ariad	Yes	ROS1, EGFR	Phase II
ASP3026	Astellas	Yes	ROS1	Discontinued
Entrectinib	Ignyta	Unknown	ROS1, TRK1/2/3	Phase II
X-396	Xcovery	Yes	ROS1	Phase I/II
TSR-011	Tesaro	Yes	TRK1/2/3	Phase I/II
PF-06463922	Pfizer	Yes	ROS1	Phase I/II

CERITINIB

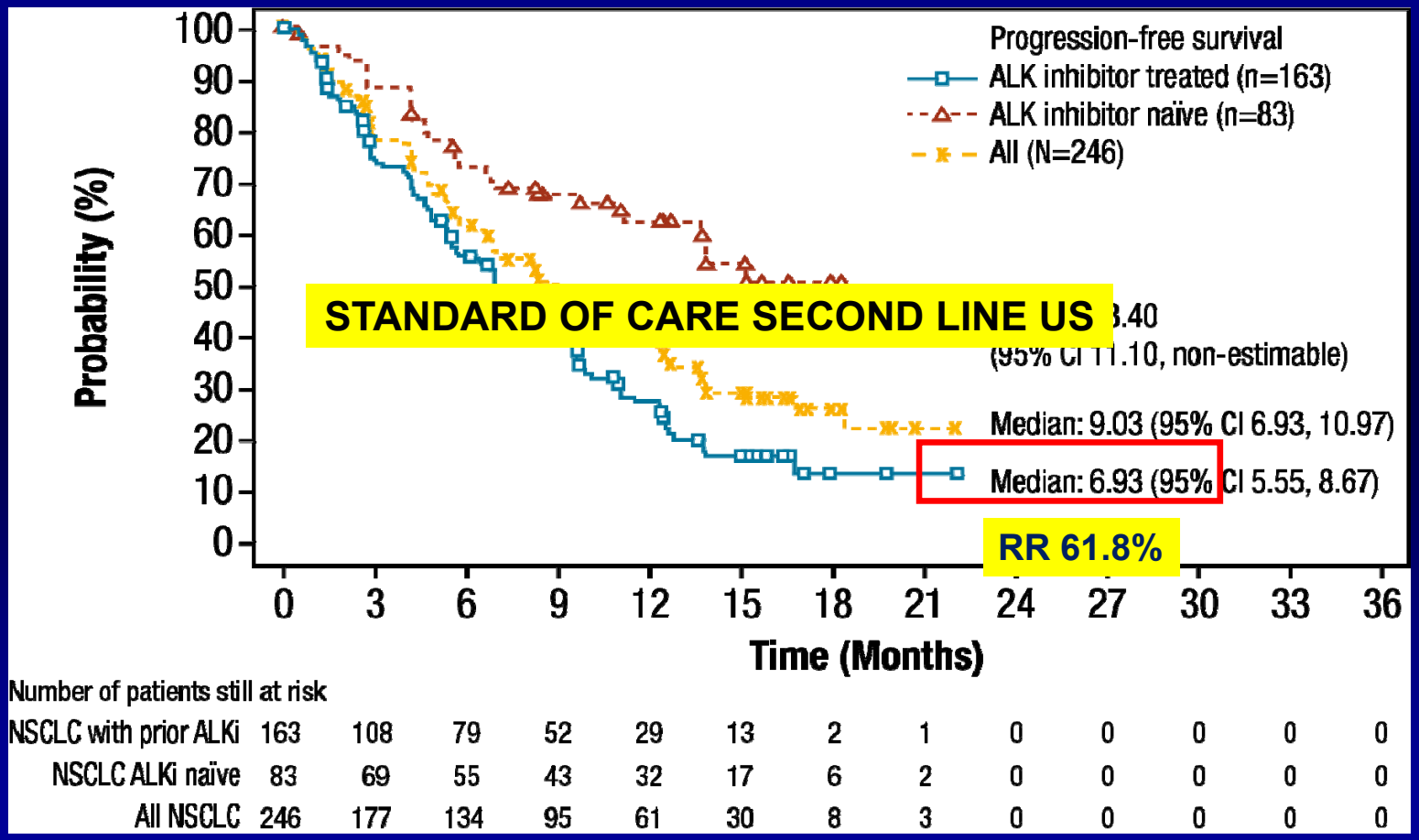
Best Percentage Change from Baseline (NSCLC)



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

ESMO 2014

ASCEND 1: PFS



ASCO 2015

Results Adverse Events

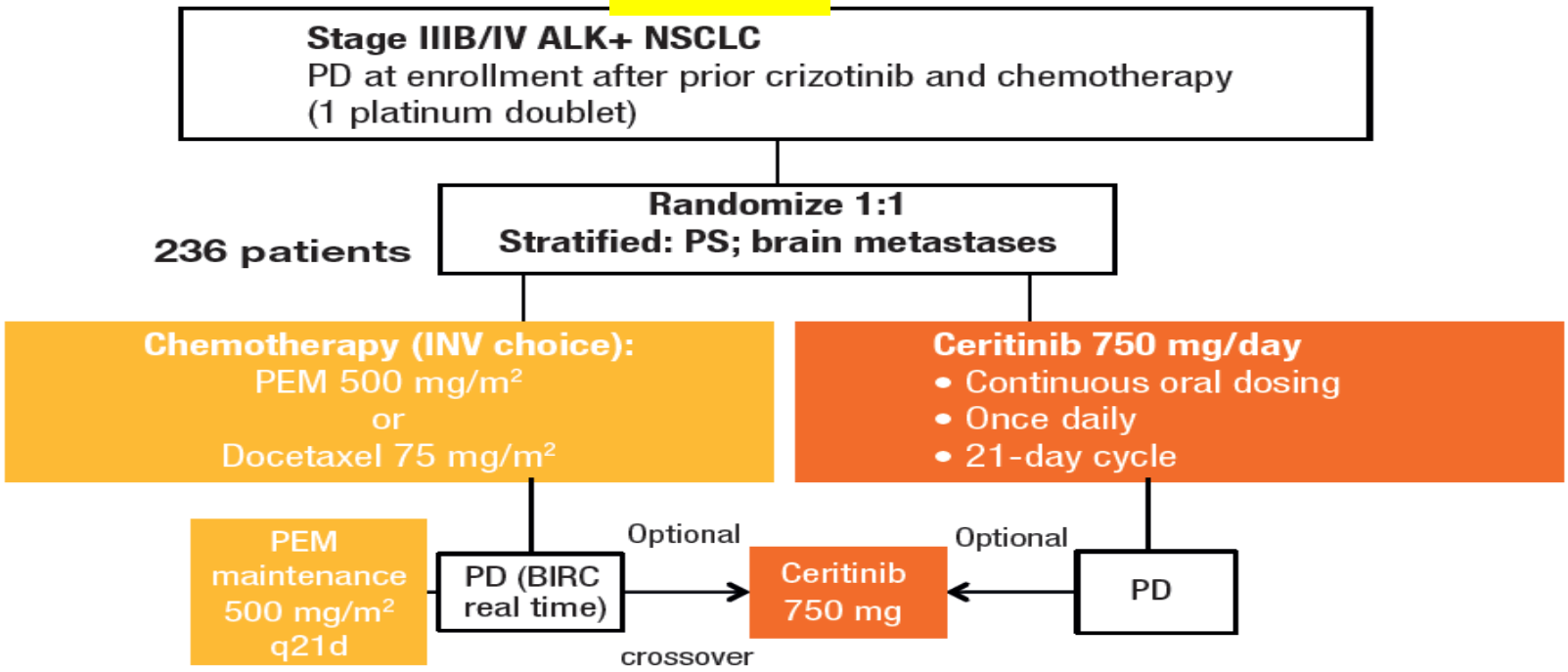
	All Grades, n (%)	Grade 3/4, n (%)
Nausea	114 (81.4)	9 (6.4)
Diarrhea	112 (80.0)	9 (6.4)
Vomiting	88 (62.9)	6 (4.3)
Alanine aminotransferase increased	61 (43.6)	24 (17.1)
Decreased appetite	57 (40.7)	5 (3.6)
Fatigue	51 (36.4)	9 (6.4)
Weight decreased	48 (34.3)	6 (4.3)
Aspartate aminotransferase increased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

41.4% patients required dose adjustment or interruption

ESMO 2016

ASCEND-5

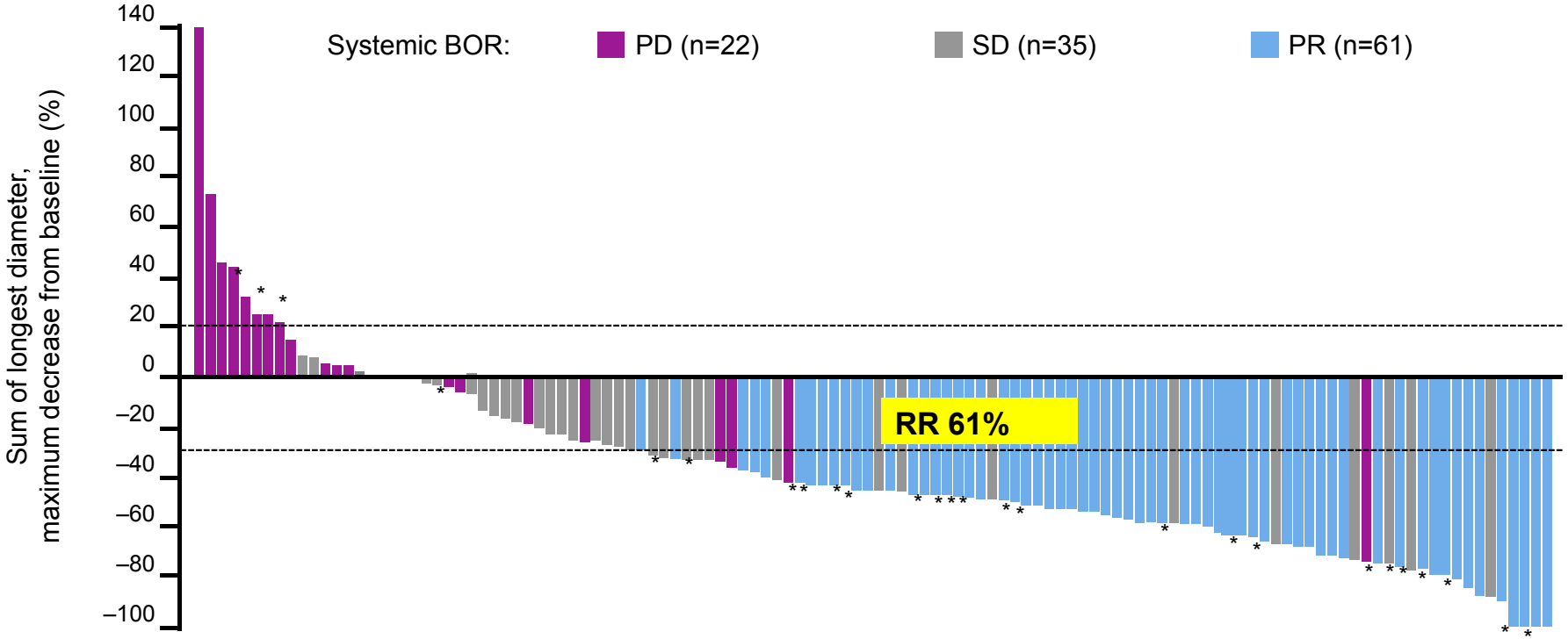
Third Line



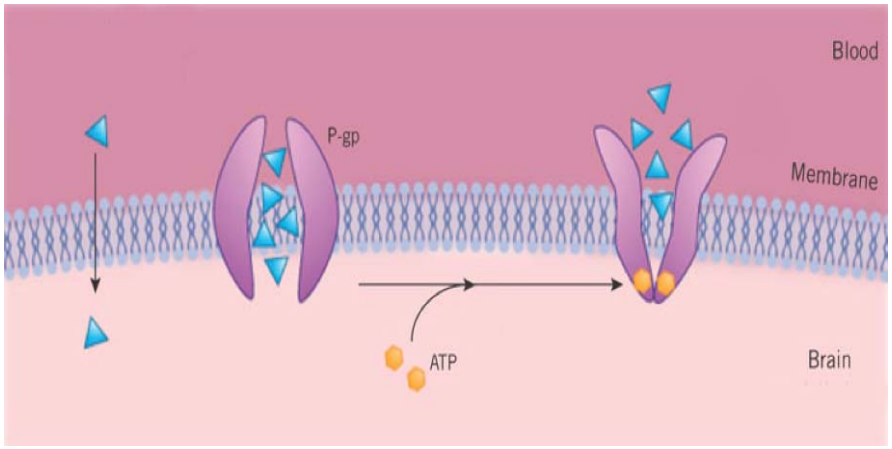
Shaw et al. *Ann Oncol* 2014;25:iv426 (Abstract 1332TIP); www.clinicaltrials.gov (NCT01828112)

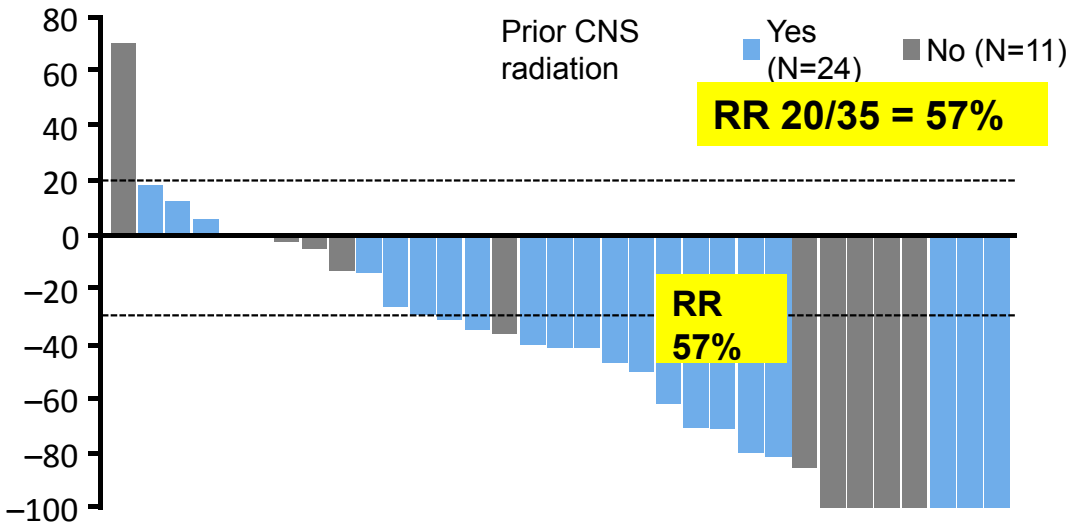
Busine

Alectinib in Patients with Crizotinib-resistant *ALK*+ NSCLC Phase II



Alectinib in Patients With Measurable CNS Metastases





Crizotinib and ceritinib are P-gp substrates; alectinib is not

Updated analysis cut-off 8 Jan 2015.
CNS = central nervous system.
Adapted from: Ou et al. ASCO 2015.

Reported Grade 3/4 Adverse Events With Alectinib

AE of any cause in ≥10% patients, n (%)	All	Grade 1	Grade 2	Grade 3	Grade 4
Constipation	45 (33)	39 (28)	6 (4)	0	0
Fatigue	36 (26)	26 (19)	8 (6)	2 (1)	0
Peripheral edema	34 (25)	27 (20)	6 (4)	1 (1)	0
Myalgia	31 (23)	25 (18)	5 (4)	1 (1)	0
Asthenia	25 (18)	16 (12)	8 (6)	1 (1)	0
Headache	22 (16)	16 (12)	4 (3)	2 (1)	0
Cough	19 (14)	15 (11)	4 (3)	0	0
Dyspnea	18 (13)	8 (6)	5 (4)	4 (3)	0*
Nausea	16 (12)	13 (9)	3 (2)	0	0
AST elevation	16 (12)	13 (9)	1 (1)	1 (1)	1 (1)
Rash	16 (12)	15 (11)	1 (1)	0	0
Vomiting	15 (11)	10 (7)	4 (3)	1 (1)	0
Diarrhea	14 (10)	10 (7)	3 (2)	1 (1)	0
ALT elevation	14 (10)	7 (5)	5 (4)	1 (1)	1 (1)

*One patient had a grade 5 event, unrelated to treatment.

AE = adverse event; ALT= serum glutamic-pyruvic transaminase (enzyme); AST = serum glutamic-oxaloacetic transaminase (enzyme).

Adapted from: Ou et al. ASCO 2015.

FEB 10th 2016

TOKYO, February 10, 2016 - Chugai Pharmaceutical

JALEX Study

Alectinib vs Crizotinib

A phase III study **Japan** *ALK positive* NSCLC **stopped early**

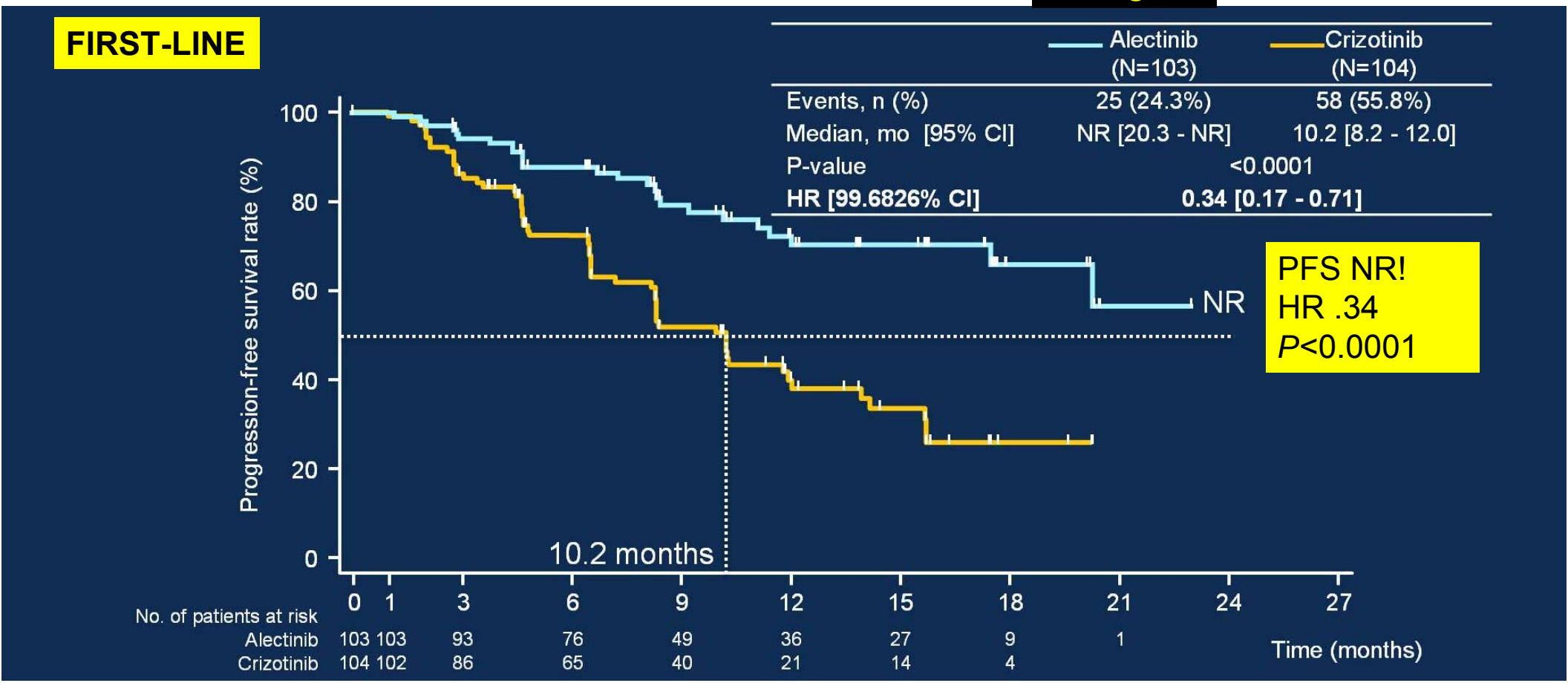
PFS **superior** when treated with Alectinib

ASCO 2016

Primary Endpoint: PFS

300 mg bid

FIRST-LINE



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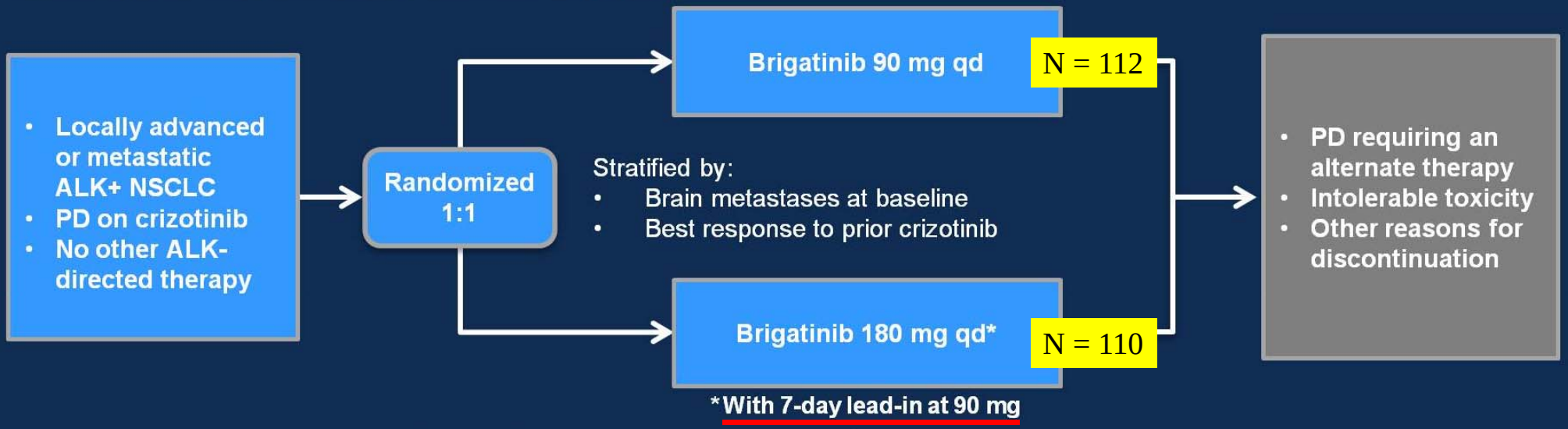
ALTA: Brigatinib Second Line

A phase 2, open-label, multicenter, international study (NCT02094573)

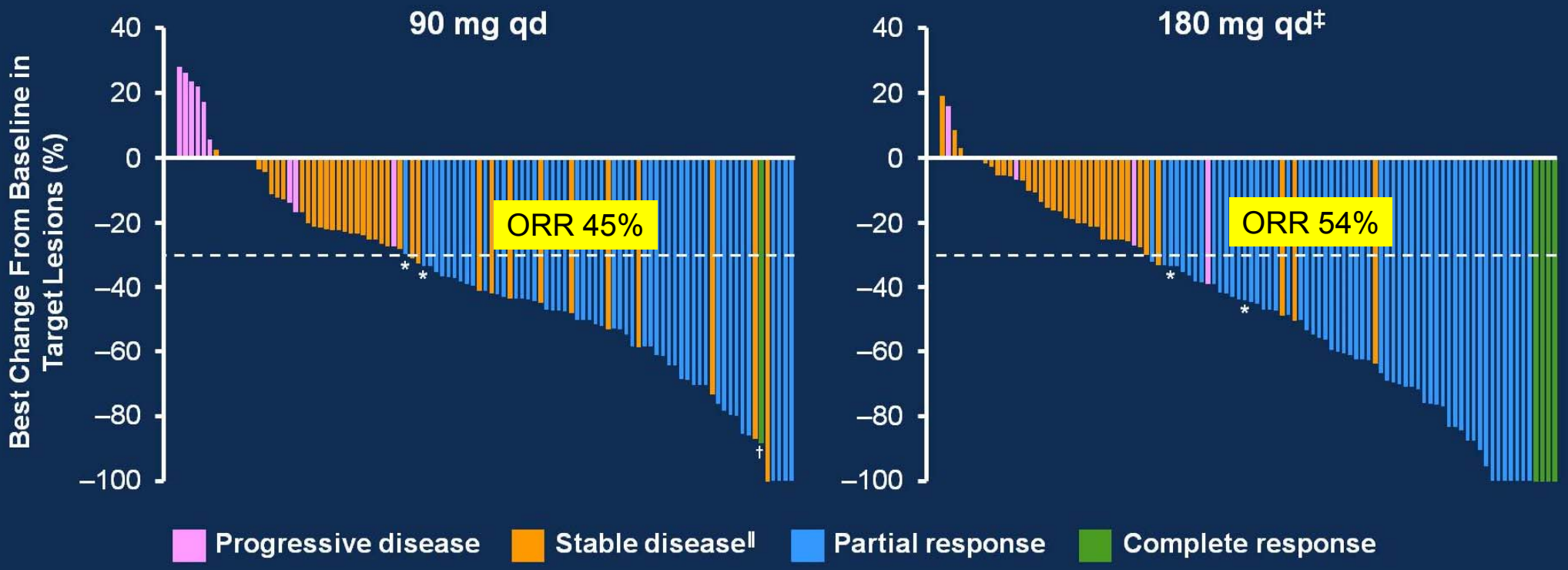


Primary Endpoint: Confirmed ORR per RECIST v1.1 (assessed by investigator)

Key Secondary Endpoints: Confirmed ORR (assessed by an IRC), CNS response (IRC-assessed intracranial ORR and PFS in patients with active brain metastases†), duration of response, PFS, OS, safety, and tolerability

Randomized phase 2 design not intended for statistical comparisons between arms; however, post hoc comparisons were performed on PFS and OS to support dose selection

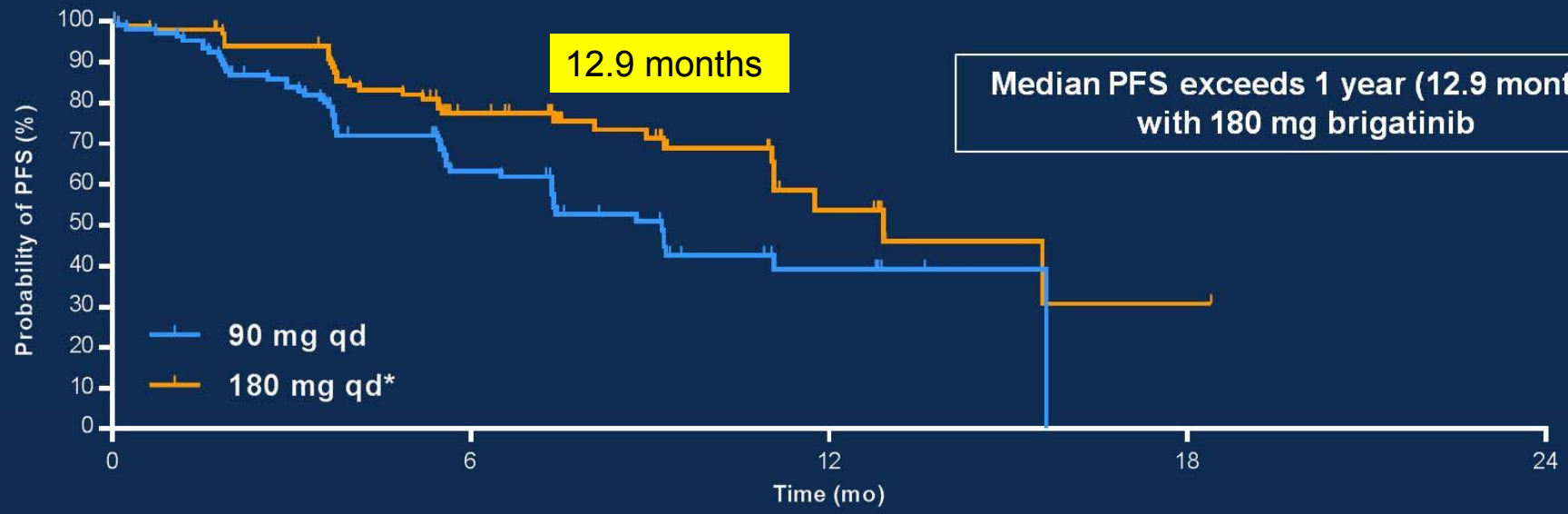
Brigatinib Antitumour Activity by Arm



Dotted line at –30% indicates threshold for partial response per RECIST v1.1
*Single response awaiting confirmation
†Patient had a lymph node target lesion which resolved to <10 mm shortest diameter (CR per RECIST v1.1)
‡180 mg qd with 7-day lead-in at 90 mg
‖Category includes single responses that were not confirmed

Data as of February 29, 2016

PFS by Arm



	Events / Total (%)	1-Year PFS Probability, % (95% CI)	Median PFS (95% CI)	Hazard Ratio (95% CI)†
90 mg qd	50/112 (45)	39 (27–52)	9.2 months (7.4–15.6)	0.55 (0.35–0.86)
180 mg qd*	31/110 (28)	54 (37–68)	12.9 months (11.1–not reached)	

*180 mg qd with 7-day lead-in at 90 mg

† Study was not designed to compare treatment arms statistically; however, post hoc comparisons were performed to support dose selection

Data as of February 29, 2016

Second-Generation ALK Inhibitors

	Ceritinib[1] N= 163	Alectinib[2] N=138	Brigatinib[3] N = 110
Design/ Assessment	Phase I/II Investigator/BIRC	Phase 2 BIRC	Phase 2 Investigator
PS 2	12%	9%	8%
Brain Mets	60%	61%	67%
Previous Rx	56% (≥ 3 prior)	80% (≥ 2 prior)	74% (≥ 2 prior)
ORR	56% (49-64)	50% (41 – 59)	54% (43-65)
CNS Response	36%* N = 28	57% N = 35	67% N = 12
Median PFS	6.9 m (5.6 – 8.7) 6.9	8.9 (5.6-11.3) 8.9	12.9 (11.1- NR) 12.9

* Retrospective Assessment

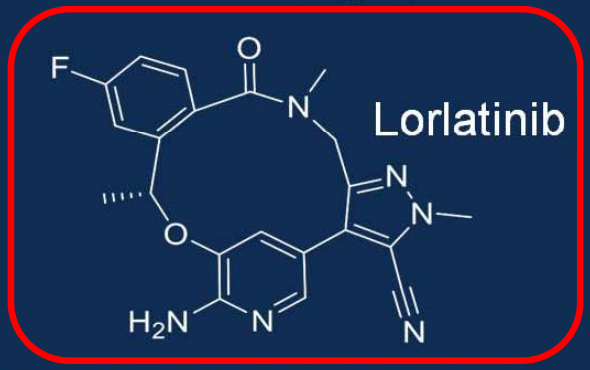
1. Kim,Lancet Oncol,2016
2. Ou, JCO 2016
3. Kim, ASCO 2016

ASCO 2016

THIRD GENERATION ALK INHIBITOR

Lorlatinib – a Next-Generation ALK/ROS1 Inhibitor

- Resistance to ALK TKIs can develop through secondary mutations in the ALK kinase domain[1–3]
  - Secondary mutations have been observed in ~25% of patients with resistance to crizotinib[3,4]
- Similarly, a subset of patients appear to develop acquired resistance to crizotinib through point mutations in the ROS1 kinase domain[4–6]
- Using structure-based design, lorlatinib was identified as a novel macrocyclic ALK inhibitor with broad-spectrum ALK potency and CNS penetration[1]
- Lorlatinib is also a potent inhibitor of ROS1[2]



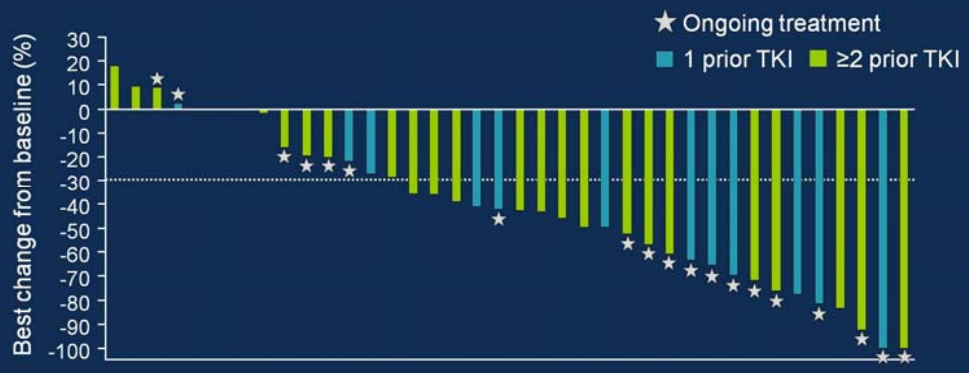
ALK, anaplastic lymphoma kinase; ROS1, c-ros oncogene 1; TKI, tyrosine kinase inhibitor

1. Johnson TW, et al. *J Med Chem* 2014;57:4720-44
2. Katayama R, et al. *Sci Transl Med* 2012;4:120ra17
3. Doebele RC, et al. *Clin Cancer Res* 2012;18:1472-82
4. Zou HY, et al. *PNAS* 2015;112:3493-8
5. Awad MM, et al. *N Engl J Med* 2013;368:2395-401
6. Song A, et al. *Clin Cancer Res* 2015;21:2379-87

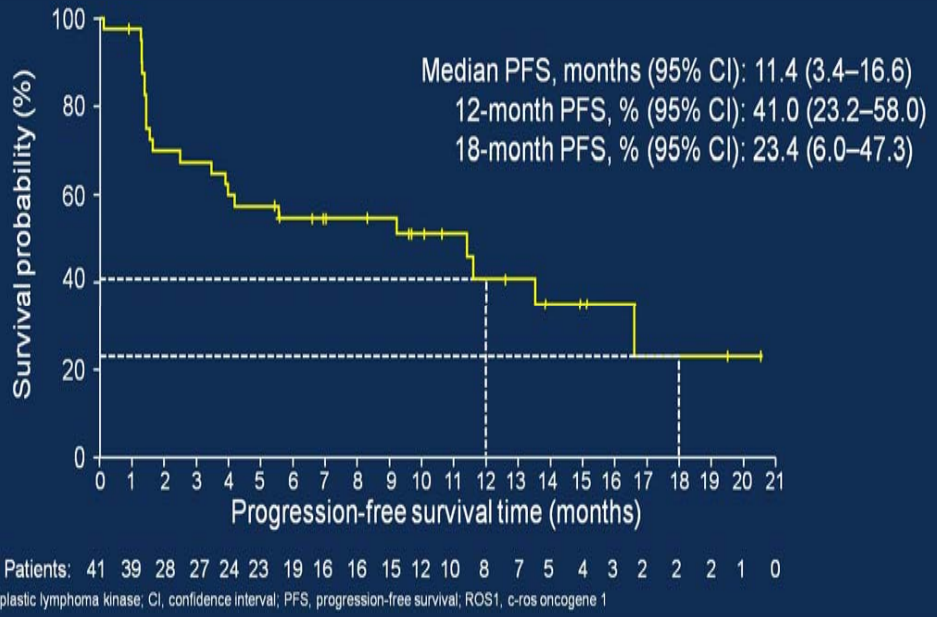
ASCO 2016

Clinical Activity: LORLATINIB ALK+ Patients

ORR 46%



PFS 11.4 months



ALK, anaplastic lymphoma kinase; CI, confidence interval; PFS, progression-free survival; ROS1, c-ros oncogene 1

ASCO 2016

eatment-Related Adverse Events in ≥15% of Patients Treated at t

LORLATINIB

	Lorlatinib 100 mg QD (n=17)				
Adverse event , n (%)	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	16 (94)	2 (12)	9 (53)	5 (30)	0
Hypercholesterolemia*	14 (82) 82%	5 (29)	7 (41)	2 (12)	0
Peripheral edema	9 (53)	6 (35)	3 (18)	0	0
Hypertriglyceridemia**	7 (41) 41%	3 (18)	2 (12)	2 (12)	0
Slow speech	3 (18)	3 (18)	0	0	0

*Includes the preferred terms hypercholesterolemia and total cholesterol increased
**Includes the preferred terms hypertriglyceridemia and blood triglycerides increased
Other Grade 3 events included lipase increased and delirium

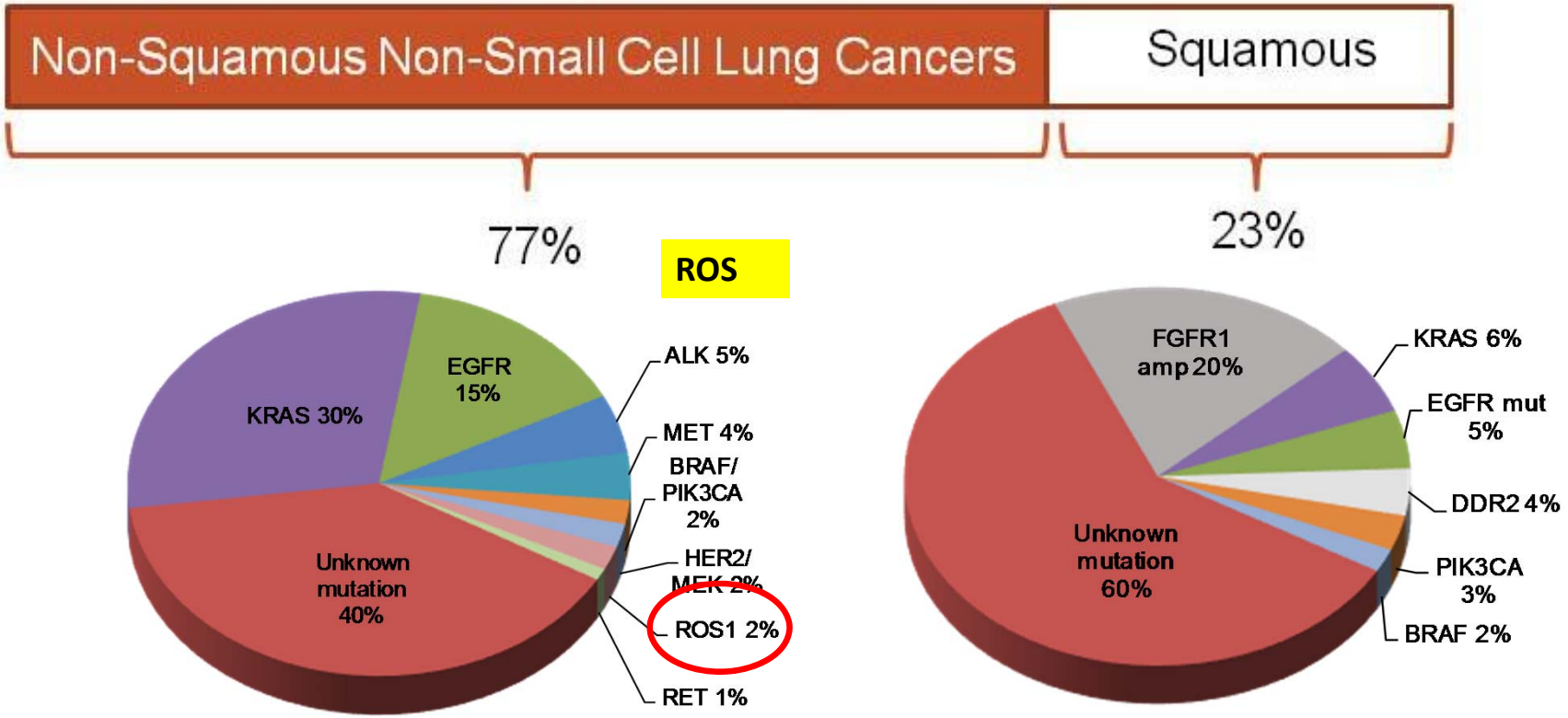
AE, adverse event; QD, once daily; RP2D, recommended phase II dose

Summary: ALK

- Current:
  - First Line: Crizotinib
  - Second Line: Ceritinib/ Alectinib
- Recent Advances:
  - First Line: Japan Alectinib
  - Second Line: Brigatinib
  - Third Line: Lorlatinib

RARE MUTATIONS

Non-Small Cell Lung Cancers – 2015

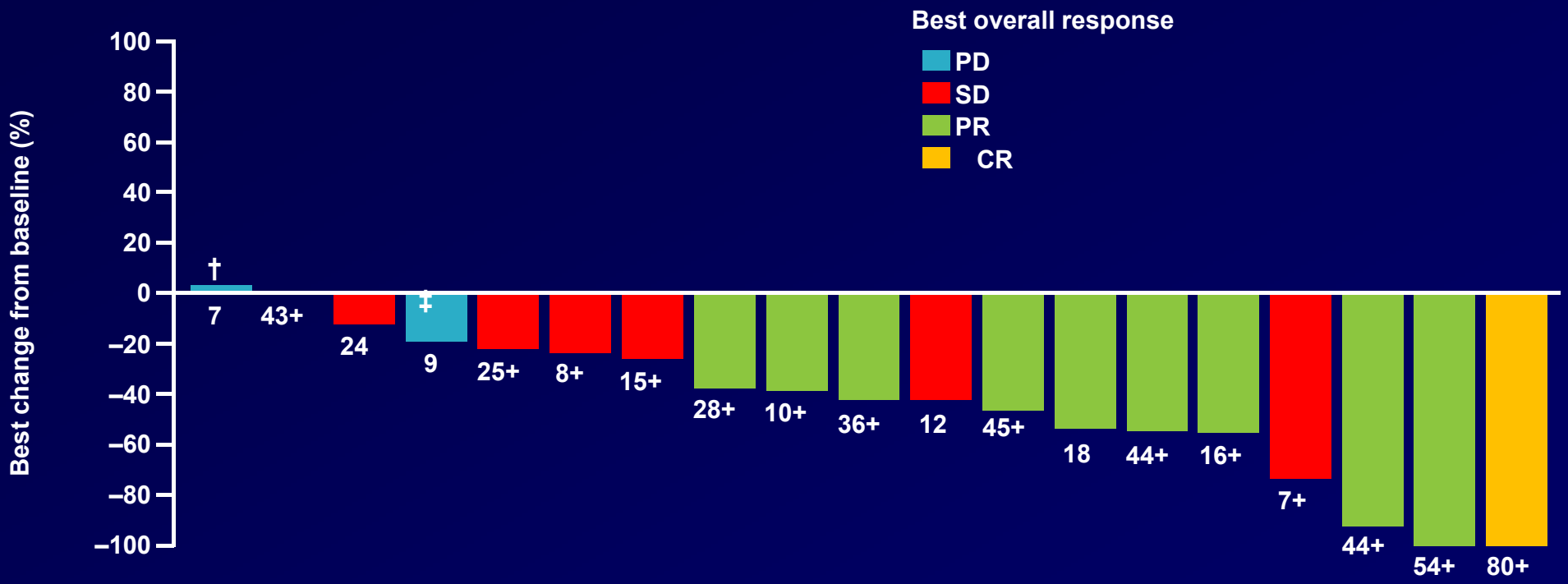


MSKCC data

PRESENTED AT: ASCO Annual '15 Meeting

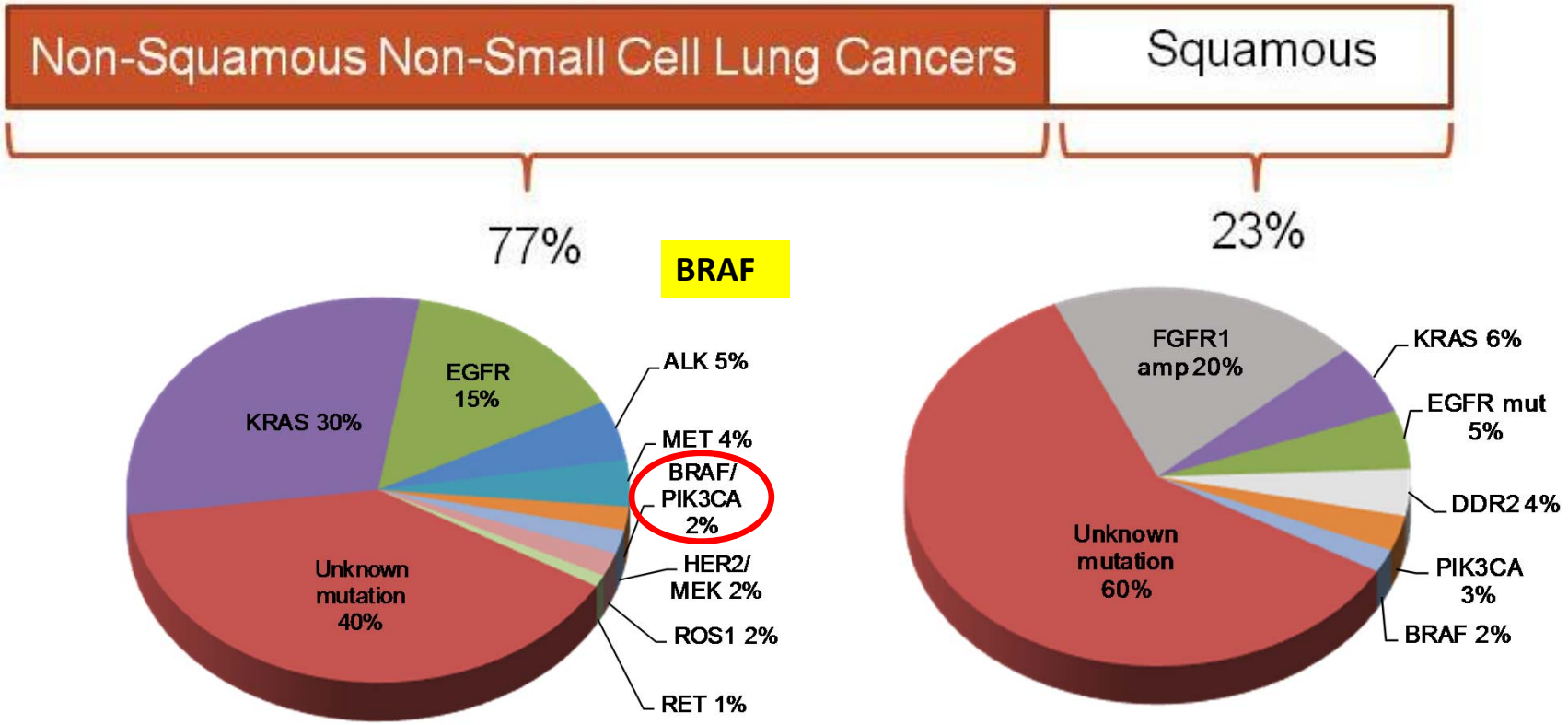
Response in Patients with Advanced ROS1+ NSCLC

Crizotinib



RARE MUTATIONS

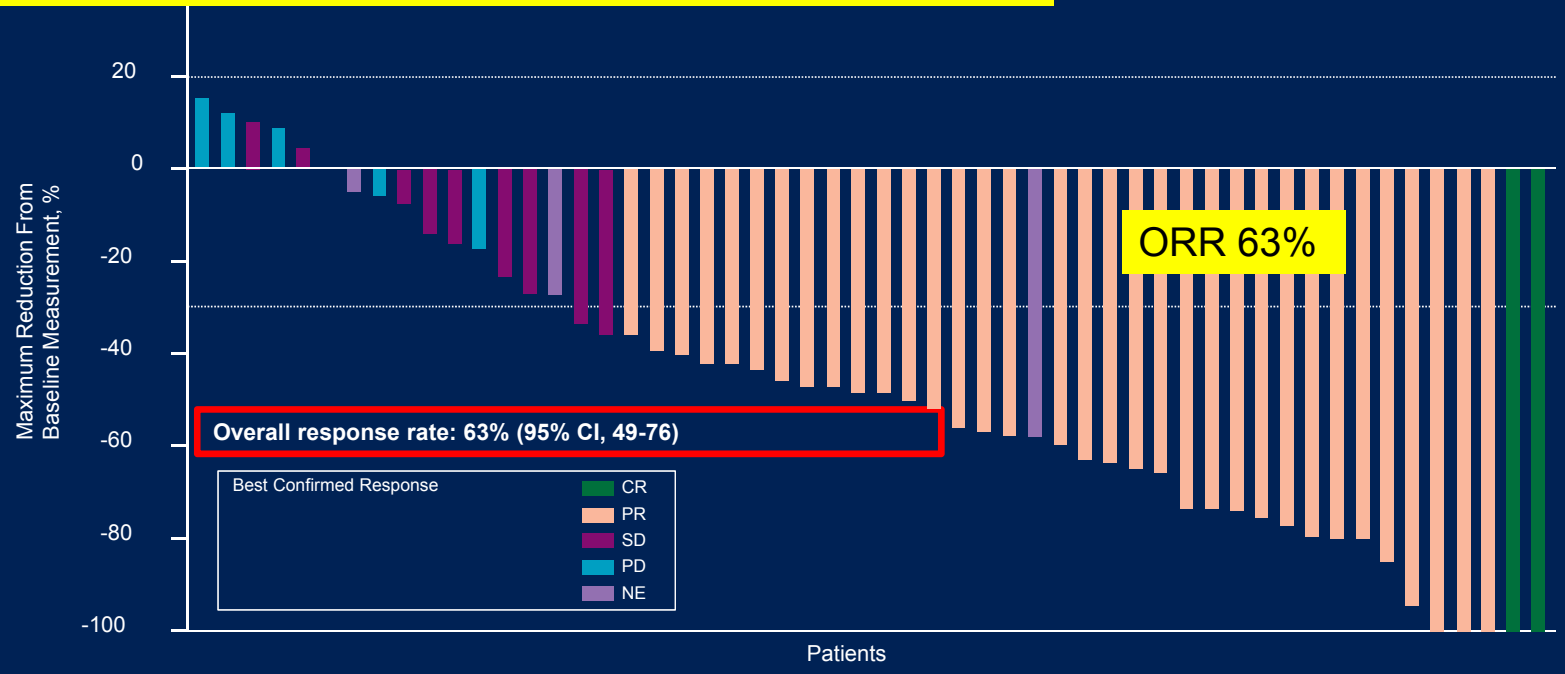
Non-Small Cell Lung Cancers – 2015



MSKCC data

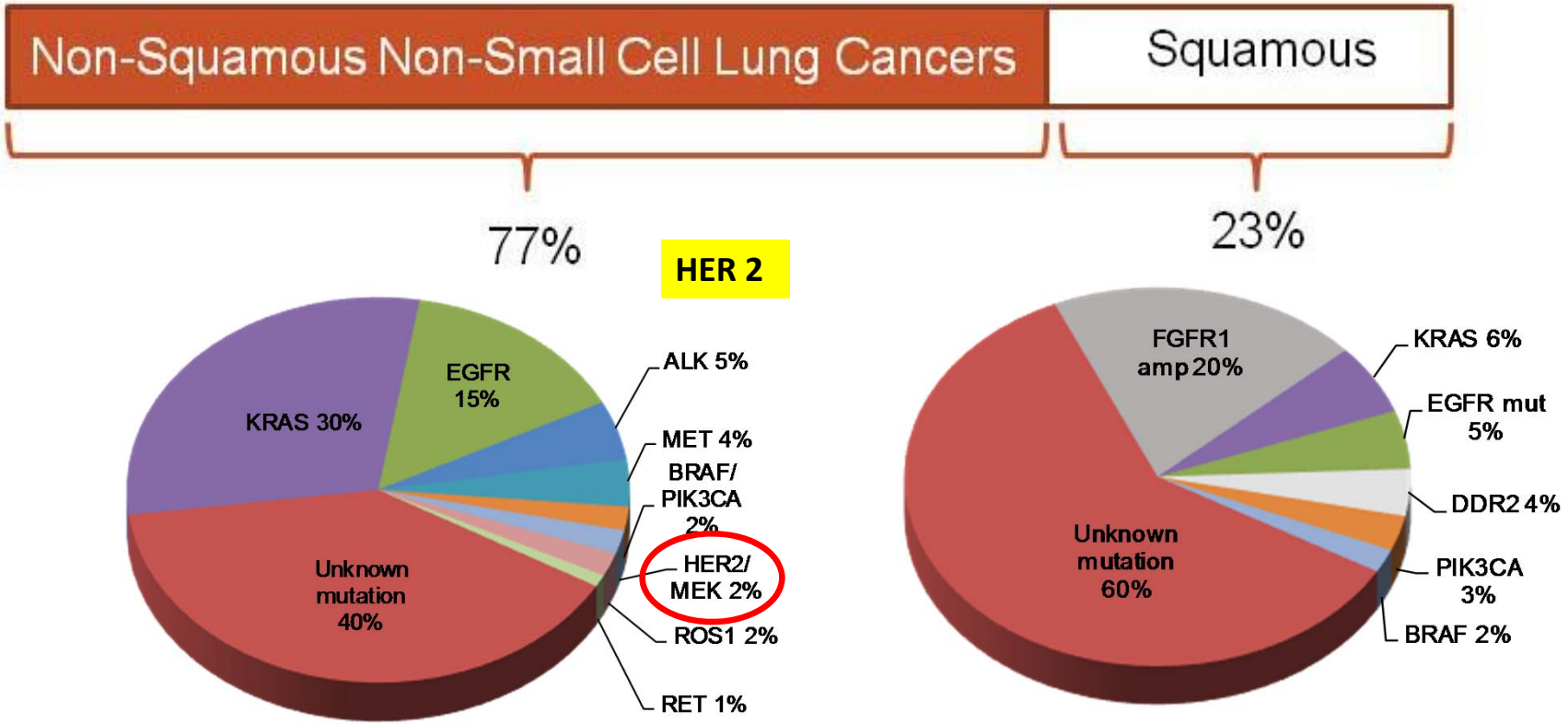
ximum Change in Target Lesion by Best Investigator-Assessed Confirmed Response

BRAF V600: Dabrafenib and Trametinib
ORR 63% PFS 8.6 months



Not Evaluable (NE) patients did not have a follow-up scan required for confirmation.

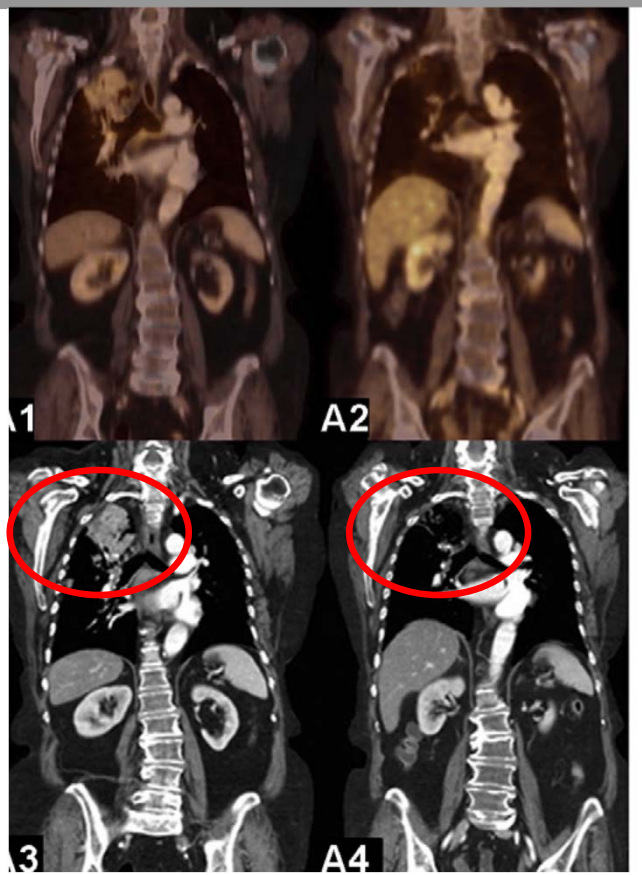
Non-Small Cell Lung Cancers – 2015



MSKCC data

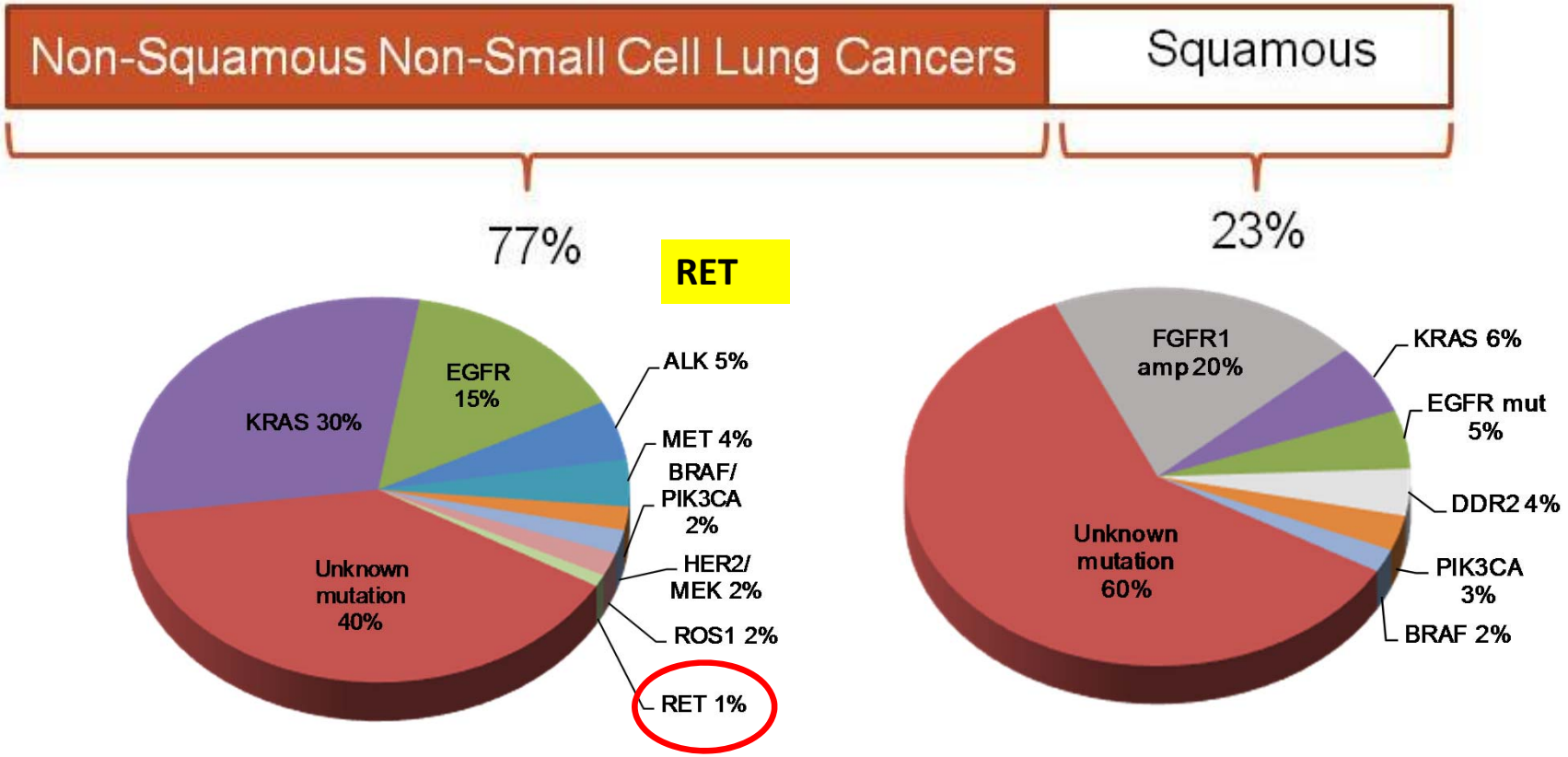
AFATINIB: HER2 Lung Cancer

- HER2/*neu* mutations in 2 – 4% of lung adenocarcinomas
- More frequent in female, non-smokers and patients of Asian origin



Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu.
De Grèvea et al. *Lung Cancer*. 2012;76:123.

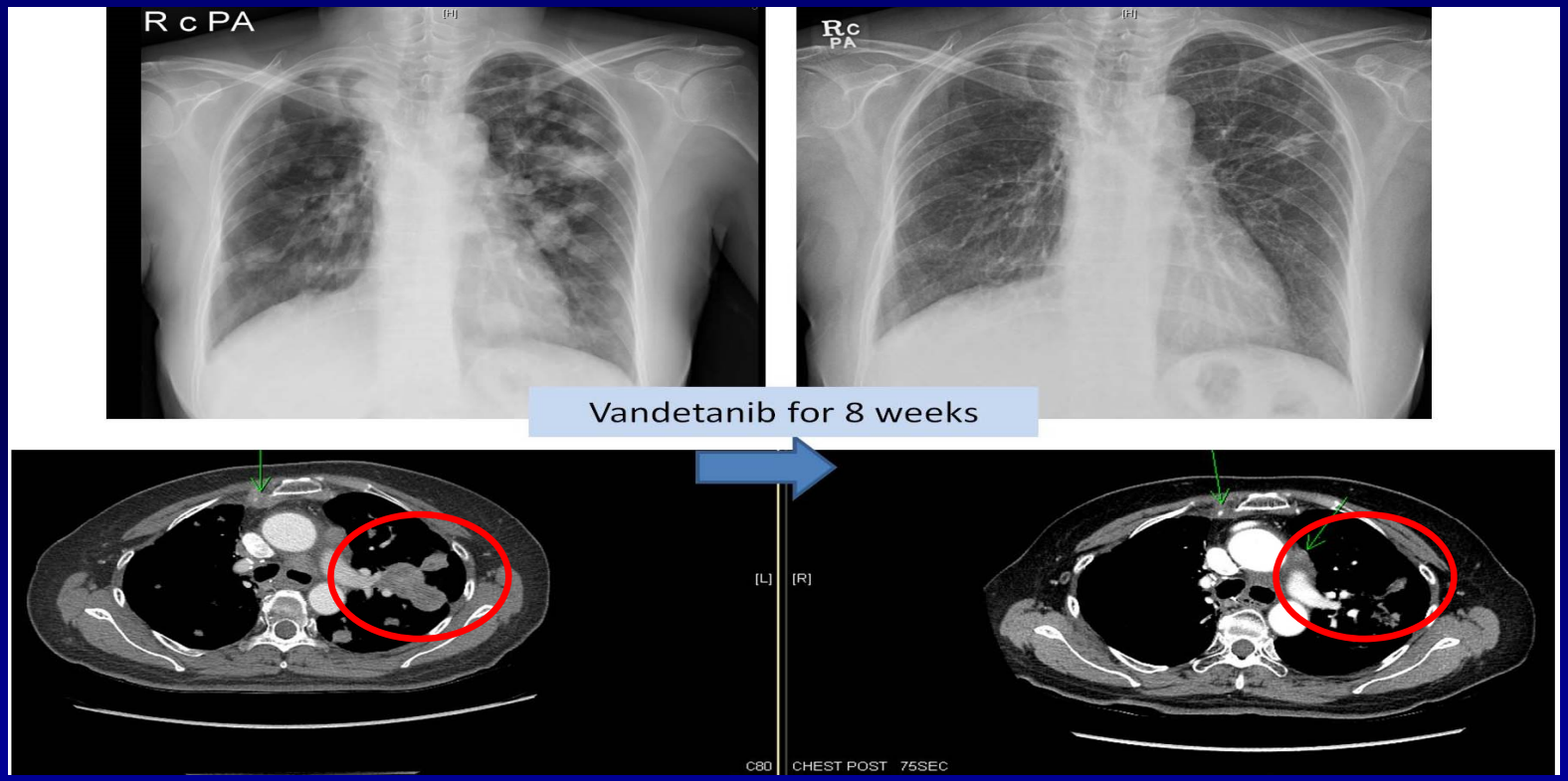
Non-Small Cell Lung Cancers – 2015



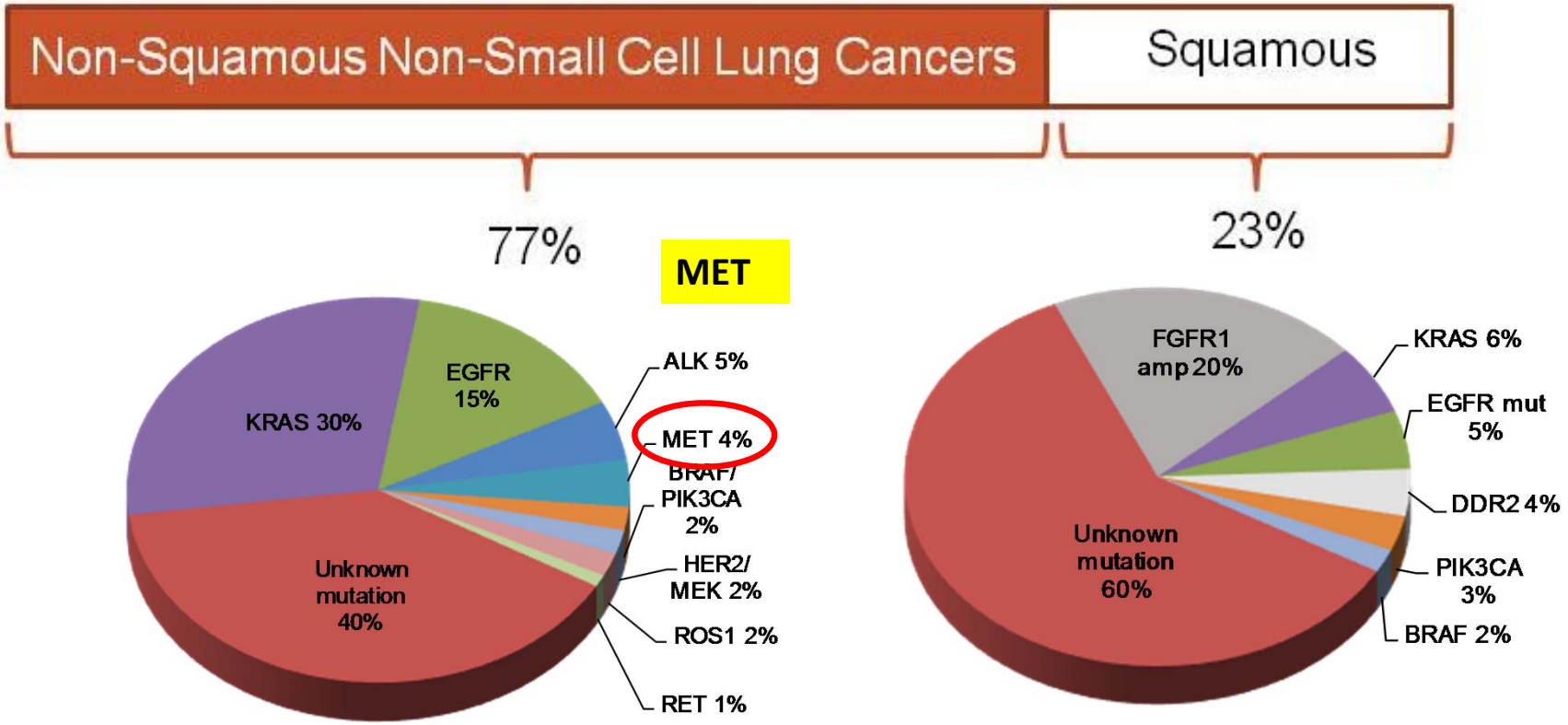
MSKCC data

ASCO 2016

Vandetanib 18 Patients
ORR 17% SD 28%
Se-Hoon Lee et al



Non-Small Cell Lung Cancers – 2015



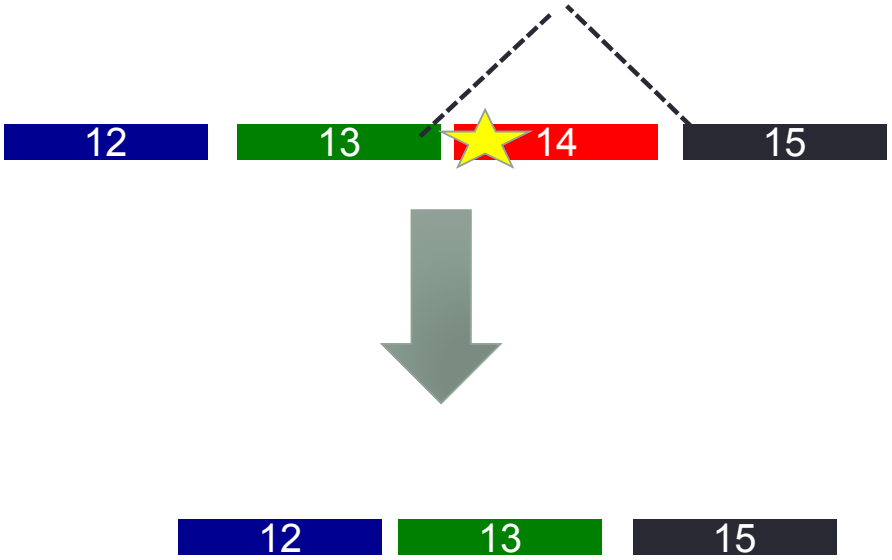
MSKCC data

RESEARCH BRIEF

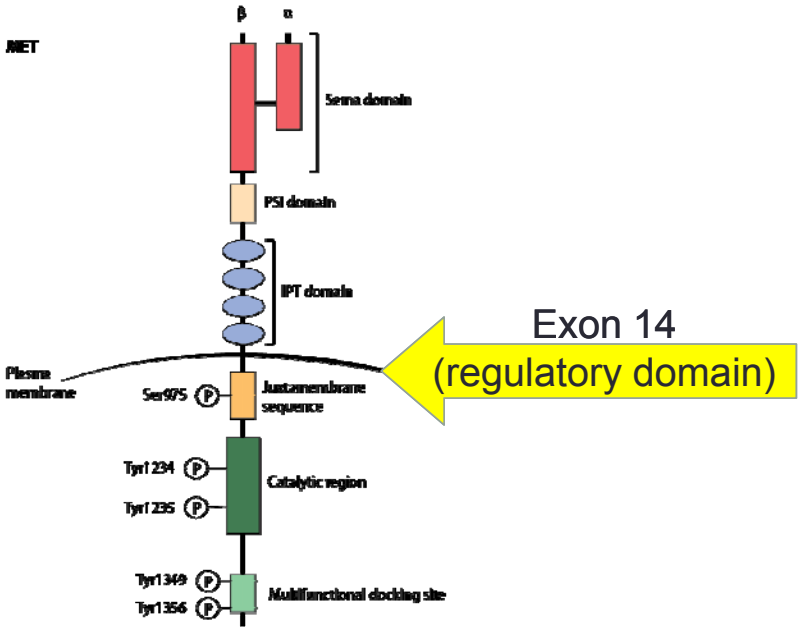
Response to MET Inhibitors in Patients with Stage IV Lung Adenocarcinomas Harboring *MET* Mutations Causing Exon 14 Skipping AC

Paul K. Paik[1,2], Alexander Drilon[1,2], Pang-Dian Fan[3], Helena Yu[1,2], Natasha Rekhtman[3], Michelle S. Ginsberg[4], Laetitia Borsu[3], Nikolaus Schultz[5,6], Michael F. Berger[2,3,5], Charles M. Rudin[1,2], and Marc Ladanyi[3,5]

CANCER DISCOVERY AUGUST 2015

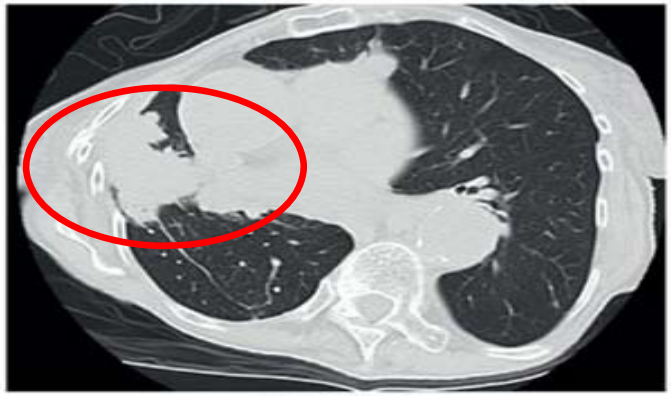


MET X14 Skipped

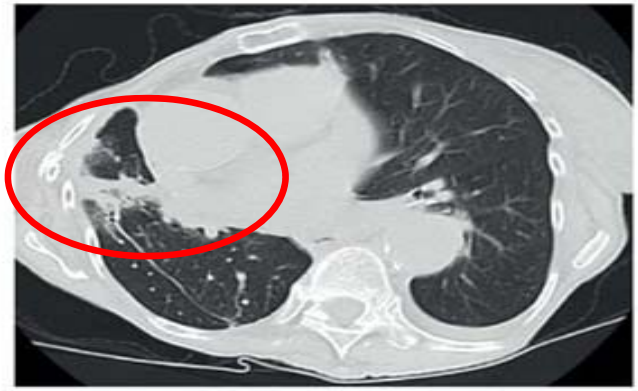


CRIZOTINIB

E



Baseline

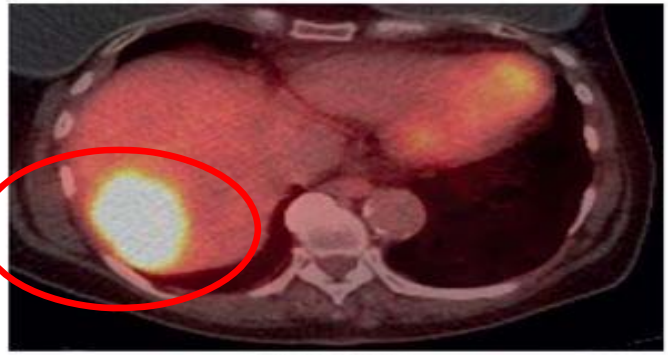


8-week follow-up crizotinib

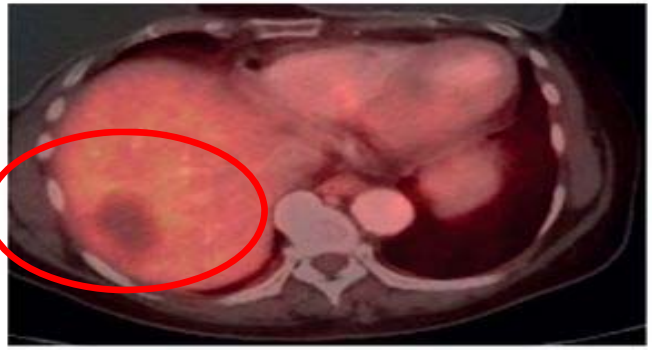
Patient 7

CABOZATINIB

A



Baseline

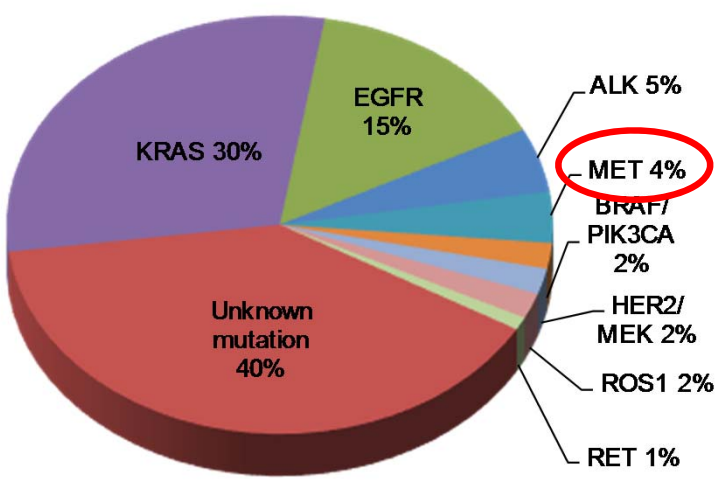


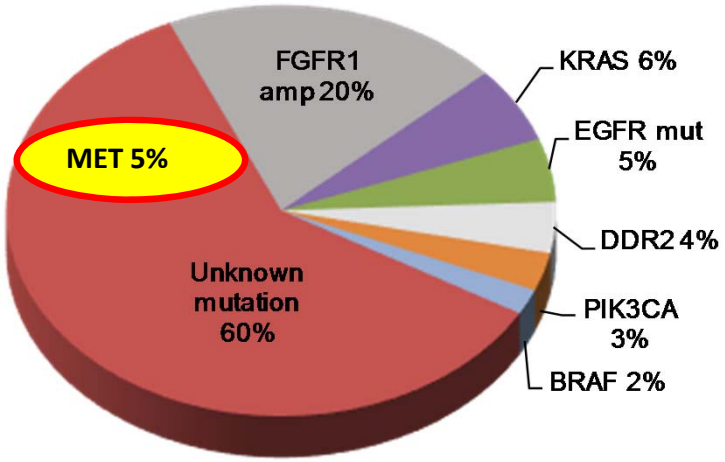
4-week follow-up cabozantinib

Patient 2

Non-Small Cell Lung Cancers – 2015

CMET: EXON 14 Skipping 5% both Non-Squamous and Squamous





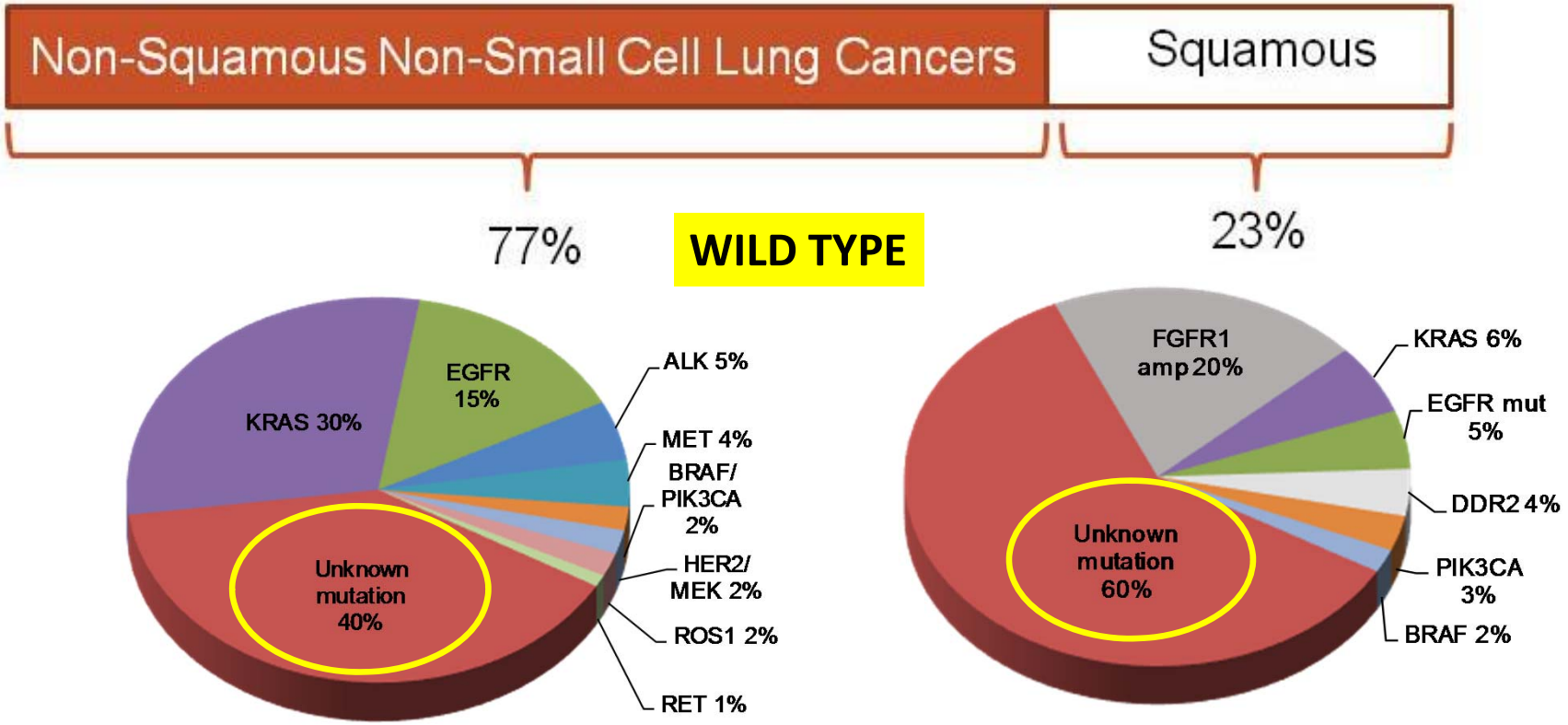
MSKCC data

PRESENTED AT: ASCO Annual '15 Meeting

Summary: RARE MUTATION

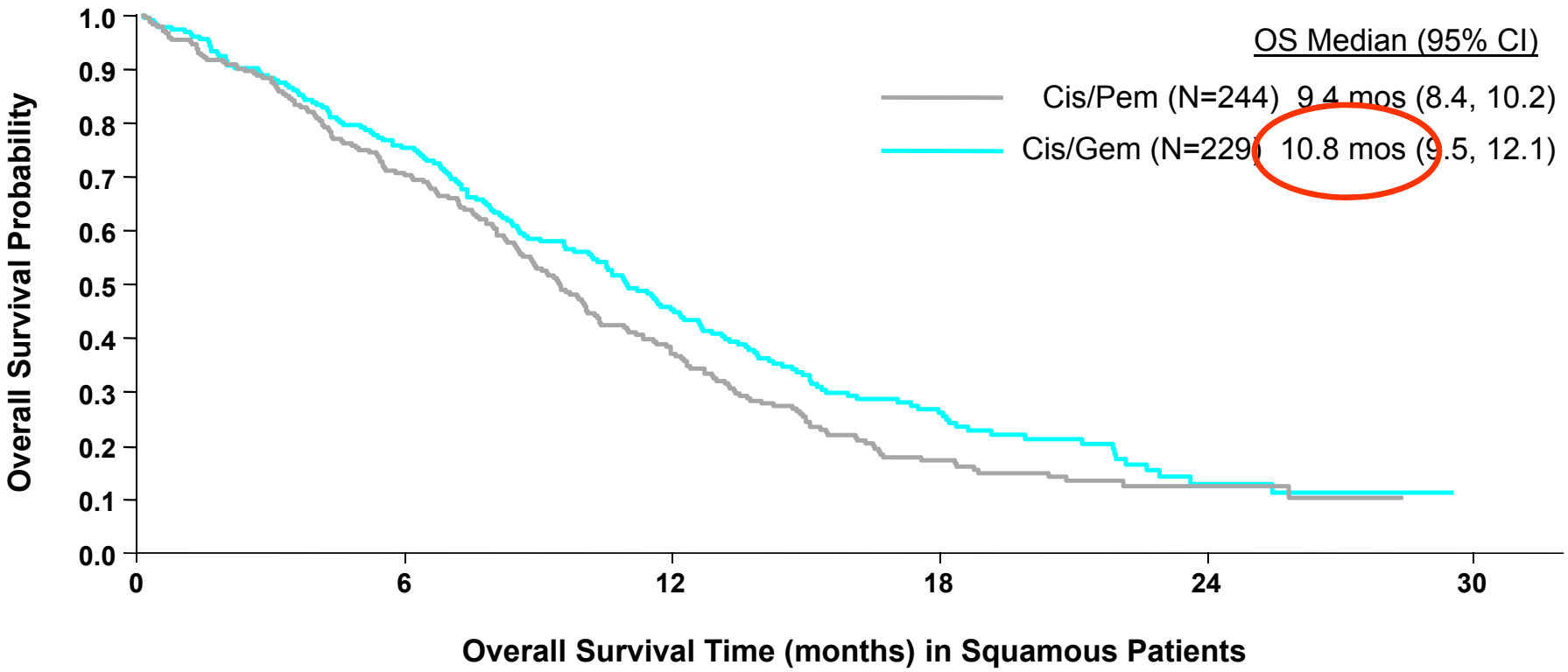
- ROS (1%)
  - Crizotinib
- BRAF (2%)
  - Dabrafenib and Trametinib
- HER 2 (2%)
  - Afatinib
- RET (1%)
  - Vandetinib
- CMET EXON 14 Slice (5% and Squamous)
  - Cabozatinib/Crizotinib

Non-Small Cell Lung Cancers – 2015



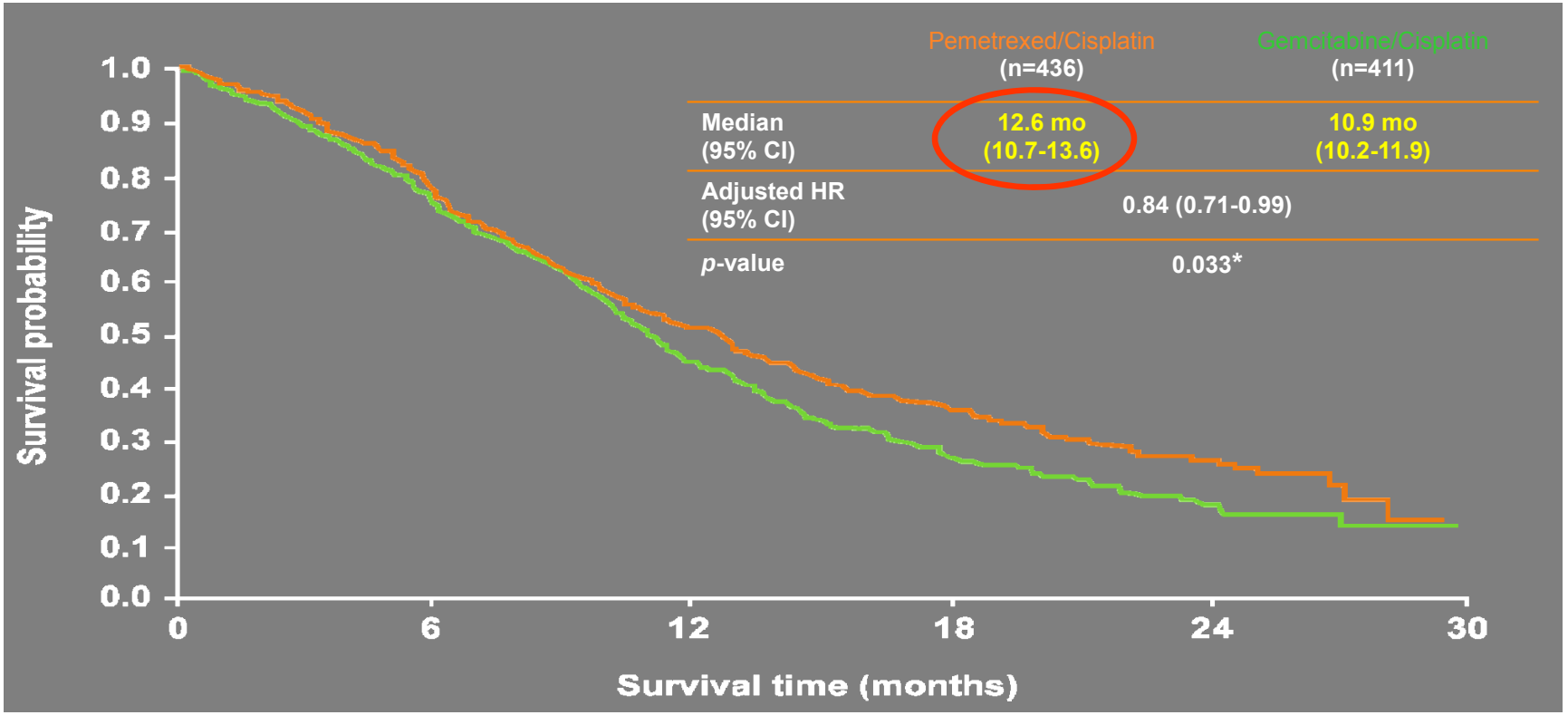
MSKCC data

Overall Survival in Squamous Cell Carcinoma



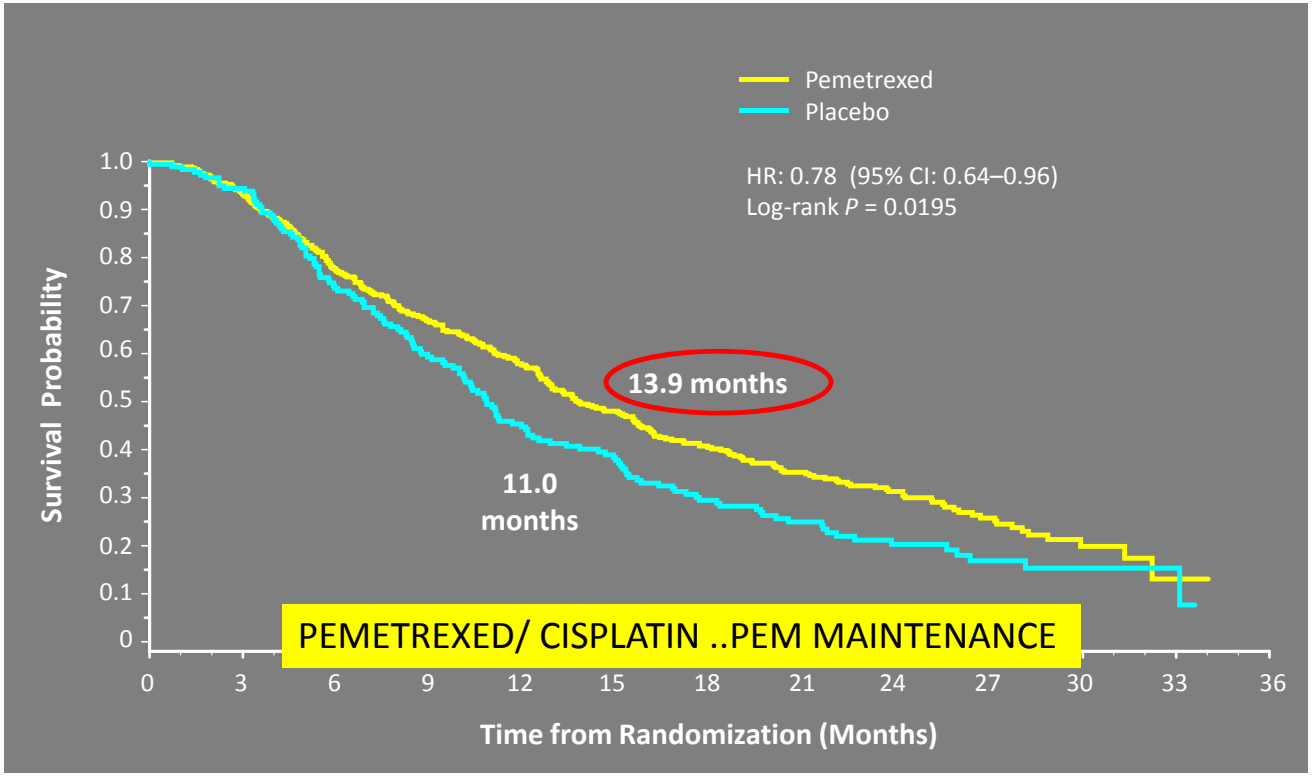
Scagliotti et al. *J Clin Oncol*. 2008;26:3543.

Overall Survival in Adenocarcinoma



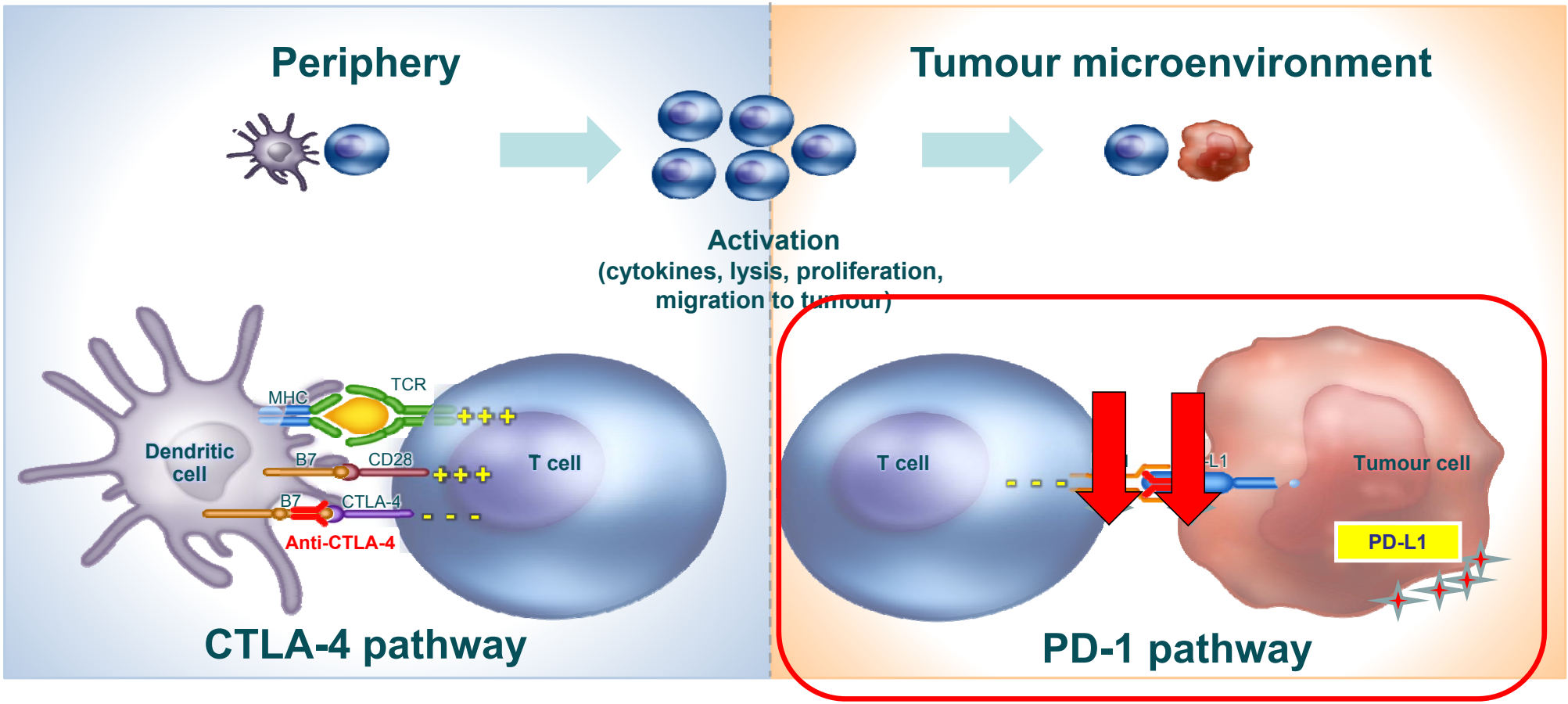
Scagliotti et al. *J Clin Oncol*. 2008;26:3543.

ASCO 2012
PARAMOUNT: Overall Survival



Immunotherapy

Targeting PD-1 Pathways



Wolchock et al. *J Clin Oncol.* 2013;31(suppl): abstr 9012.

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

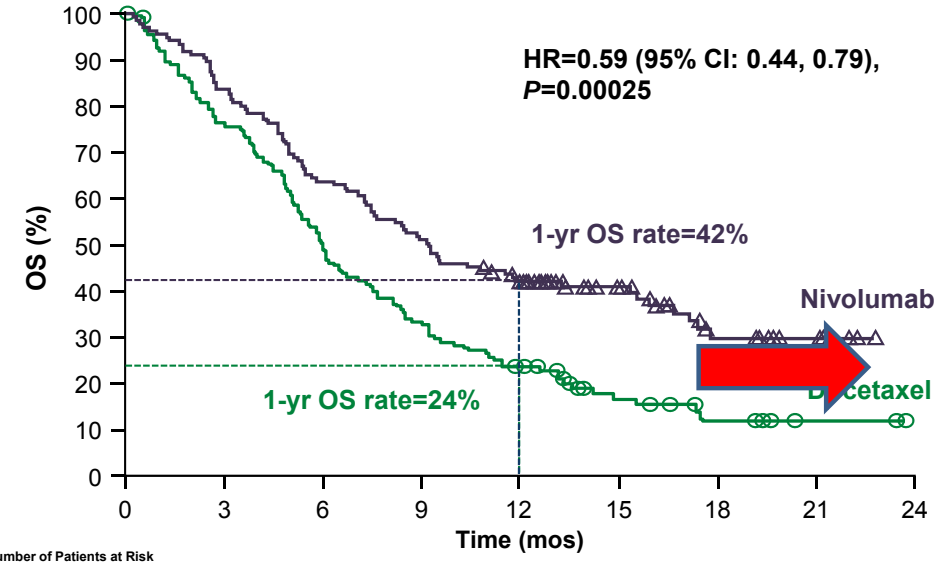
Target	Agent	Molecule	Company	Development
PD-1 **Opdivo**	Nivolumab	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II, III multiple tumors
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	Pembrolizumab	Humanized IgG4 mAb	Merck	Phase I-II
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
PD-L1	Avelumab	Fully human IgG4 mAb	EMD Serono	Phase I
	Durvalumab	Engineered human IgG1 mAb	Astra Zeneca	Phase I
	Atezolizumab	Engineered human IgG1 mAb	Roche	Phase I-II

Adapted from Dr. J. Brahmer ASCO 2013

PRESENTED AT: ASCO Annual '13 Meeting

Overall Survival

CheckMate 017
SQ NSCLC[4]

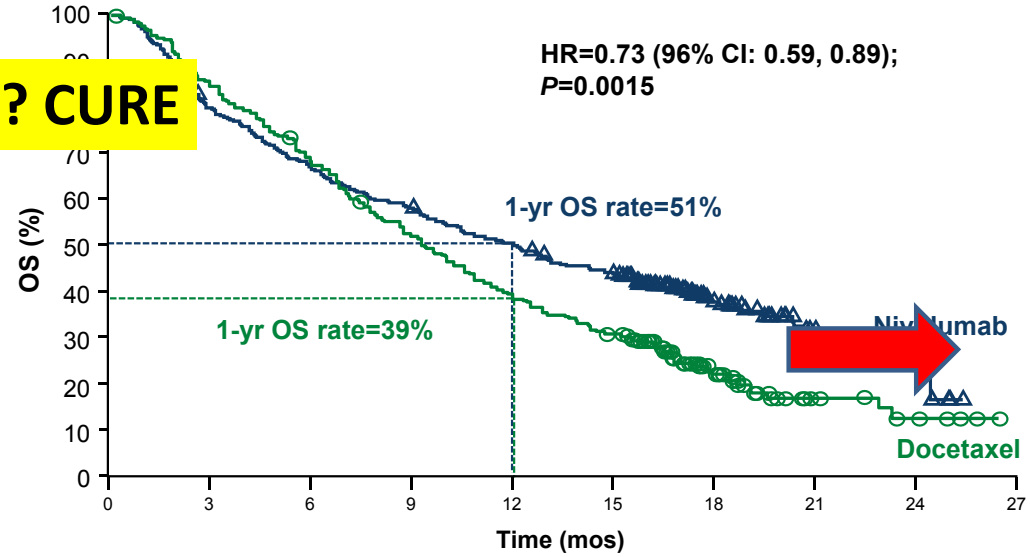


Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

CheckMate 057
Non-SQ NSCLC[5]

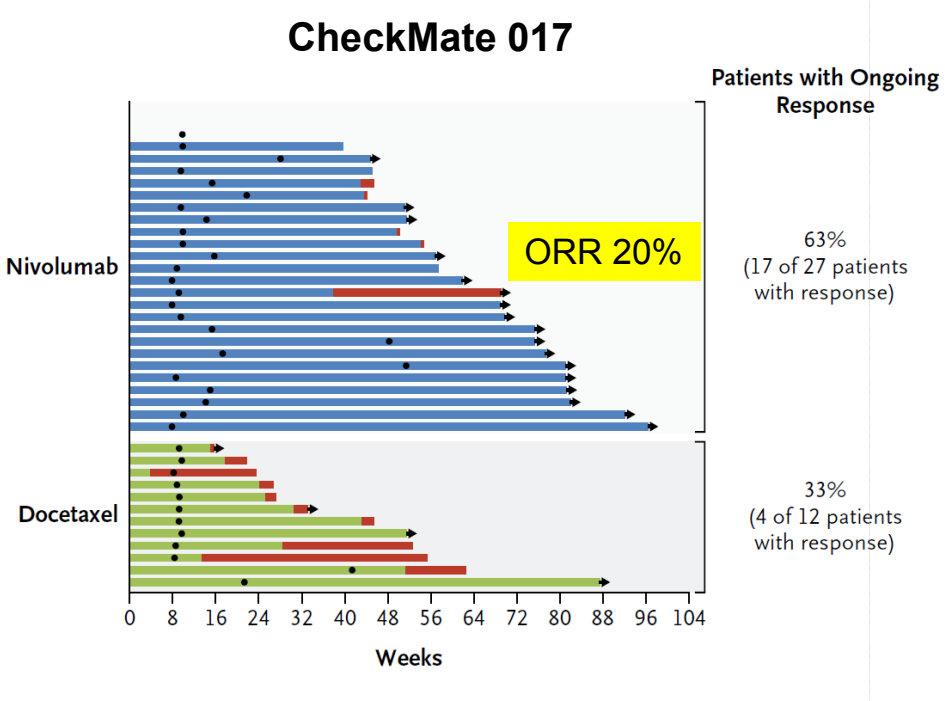
? CURE

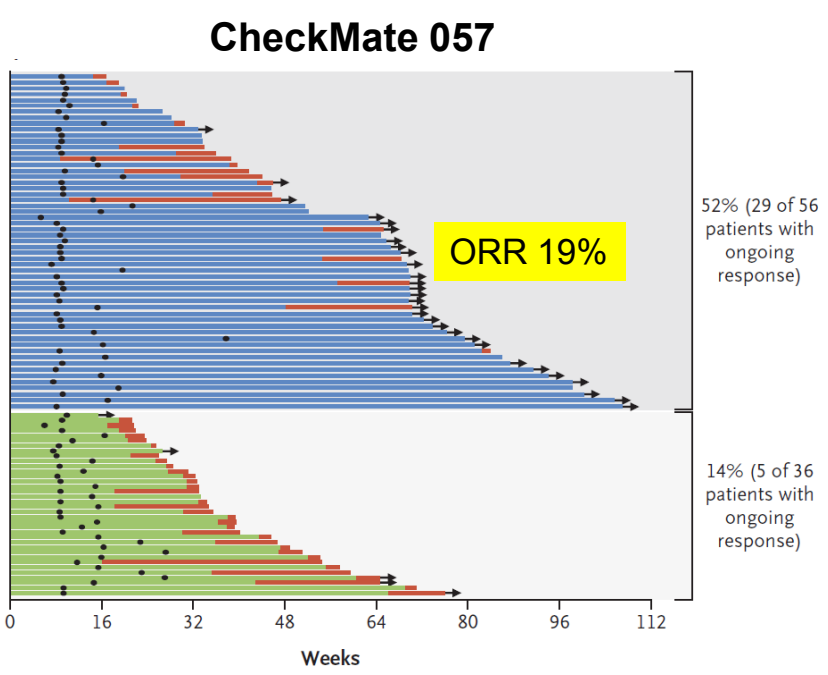


	292	232	194	169	146	123	62	32	9	0
	290	244	194	150	111	88	34	10	5	0

Previously presented at ASCO 2015 (Abstracts 8009 and LBA109).

ORR CheckMate 017 & 057





Horn et al. ECC 2015; Reckamp et al. World Lung Conference 2015.

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

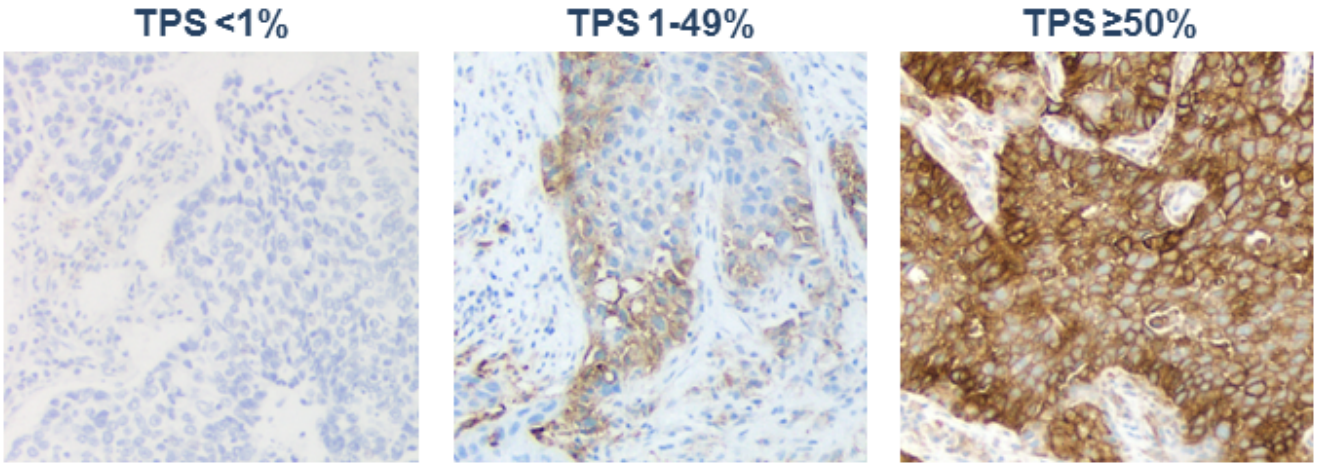
Target	Agent	Molecule	Company	Development
PD-1	Nivolumab-BMS-936558	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II, III multiple tumors
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	Keytruda Pembrolizumab	Humanized IgG4 mAb	Merck	Phase I-II
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
PD-L1	Avelumab	Fully human IgG4 mAb	EMD Serono	Phase I
	Durvalumab	Engineered human IgG1 mAb	MedImmune	Phase I
	Atezolizumab	Engineered human IgG1 mAb	Genentech	Phase I-II

Adapted from Dr. J. Brahmer ASCO 2013

PRESENTED AT: ASCO Annual '13 Meeting

Association of PD-L1 Expression With Efficacy

- Assessed in purposefully collected tumor samples by a clinical-trial IHC assay (Dako) with the 22C3 antibody (Merck)
- Samples scored as the percentage of tumor cells with membranous PD-L1 staining—tumor proportion score, or TPS

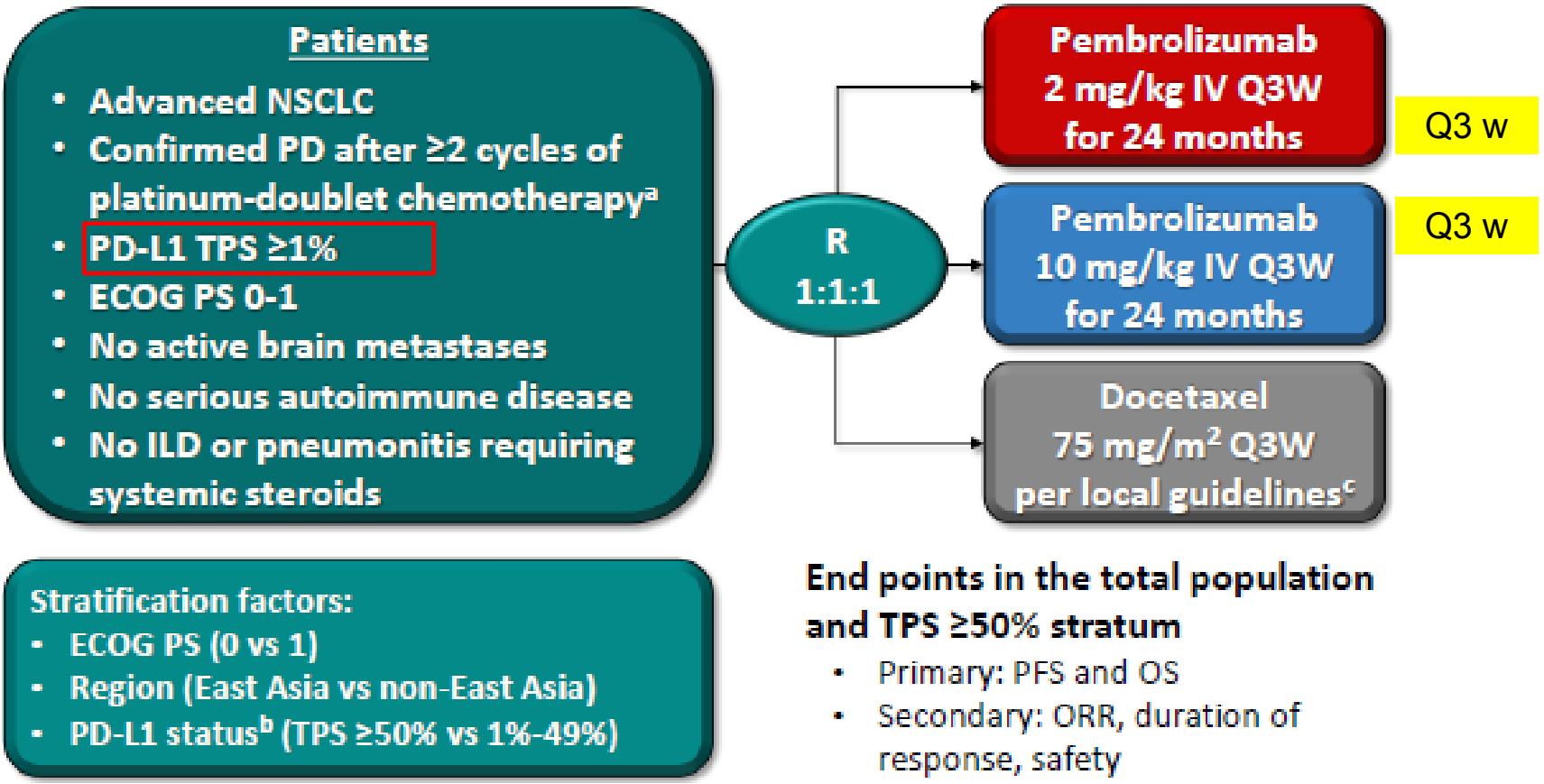


Images originally presented at the AACR 2015 Annual Meeting by Edward B. Garon. Presented with permission of E.B. Garon.

35% <1%, 40% 1-49% 25% >50%

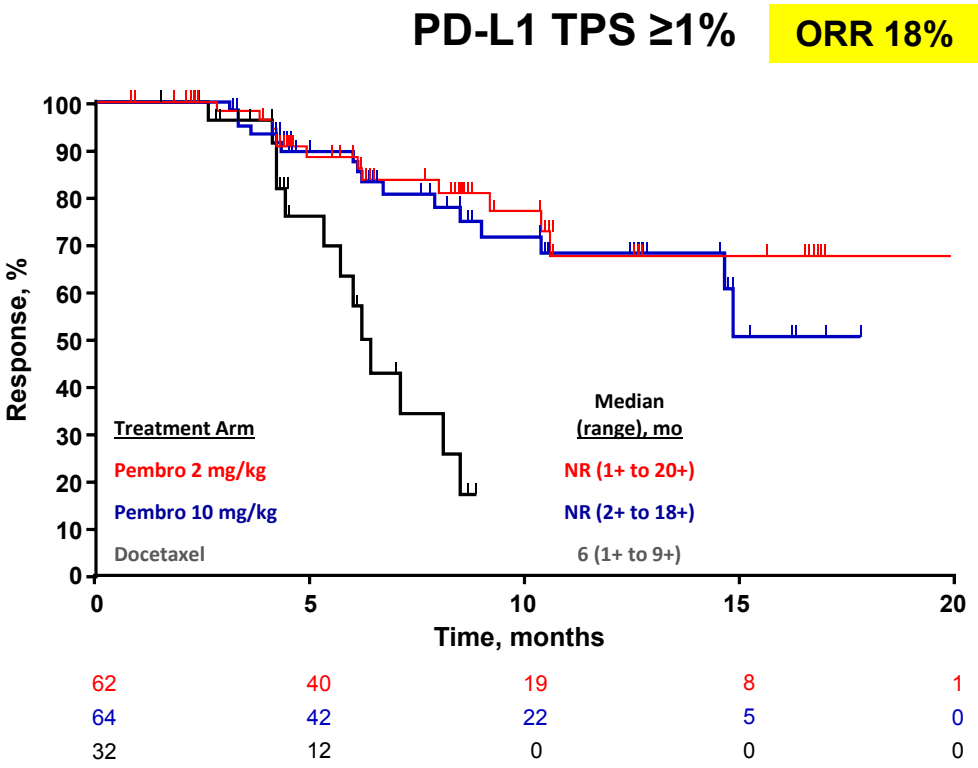
ESMO ASIA 2015

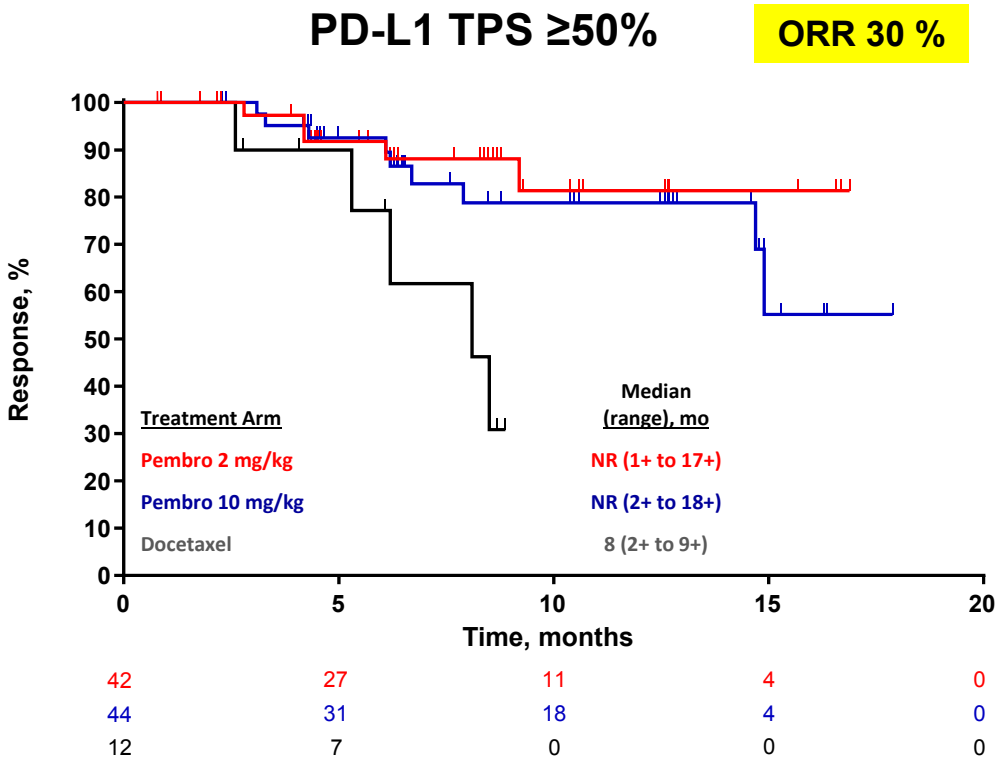
Keynote 010



Herbst et al. ESMO Asia. LBA3.

Duration of Response

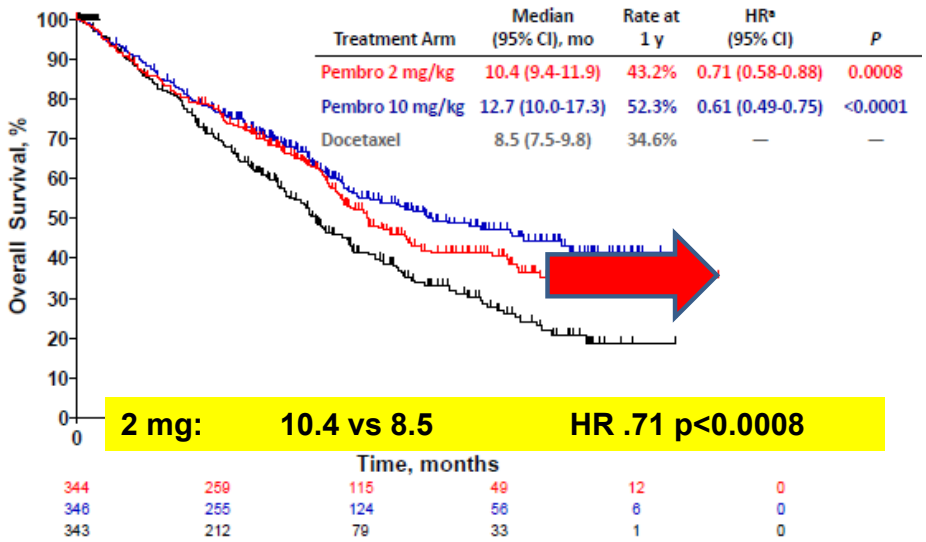




Herbst et al. ESMO Asia 2015.

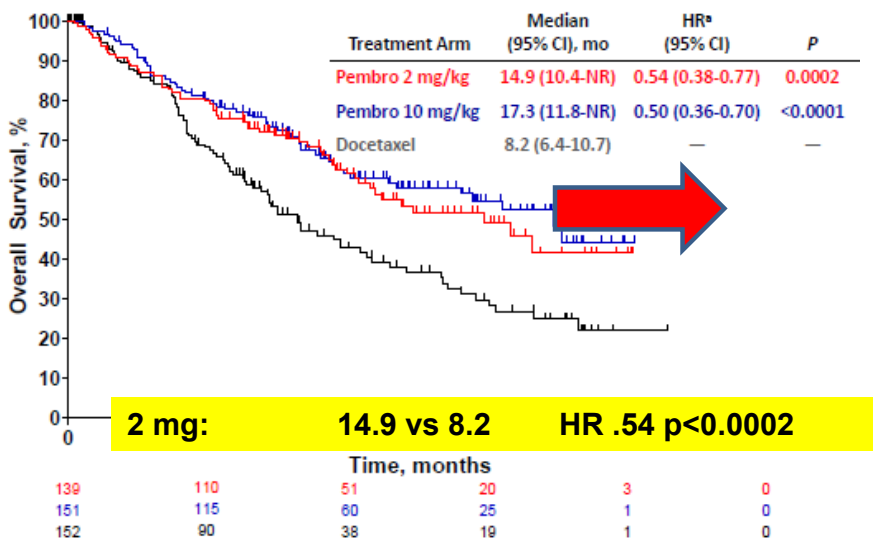
Keynote 010: Overall Survival

OS, PD-L1 TPS ≥1% (Total Population)



2 mg: 10.4 vs 8.5 HR .71 p<0.0008

OS, PD-L1 TPS ≥50% Stratum



2 mg: 14.9 vs 8.2 HR .54 p<0.0002

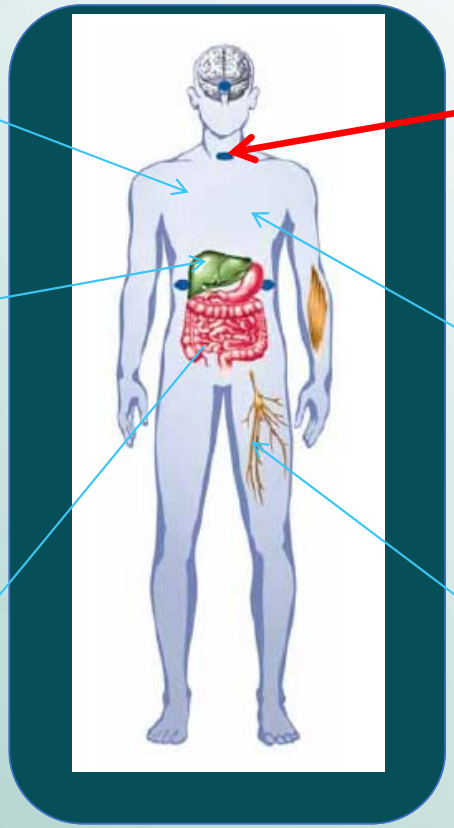
Herbst et al. ESMO Asia. LBA3.

irAEs Immune Therapy

Skin
- Skin rash or pruritus

Hepatic
- Abnormal LFTs (eg, AST, ALT, total bilirubin)

Gastrointestinal (GI)
- Diarrhea
- Bloody stool
- Fever
- Constipation (rarely)



Endocrine
- Hypophysitis (headache,visual changes, weakness)
- Thyroiditis with hyper/hypothryroidism

Pulmonary
- Pneumonitis*

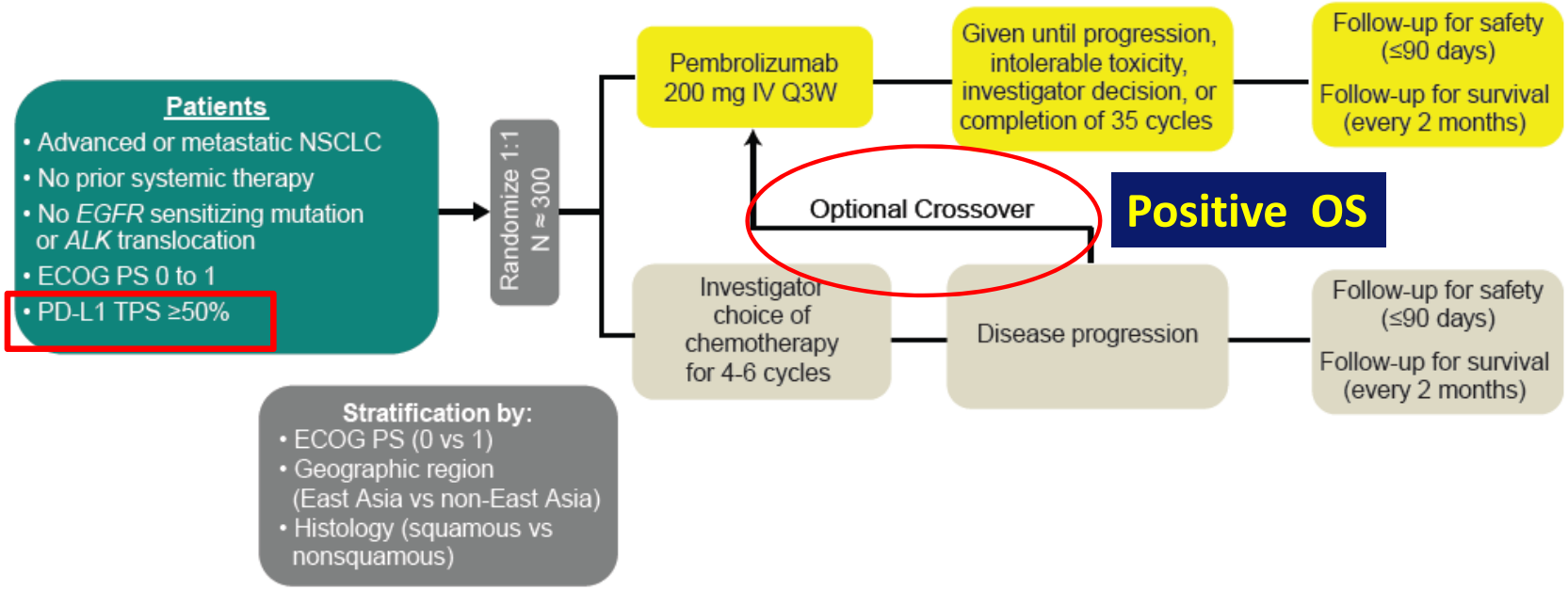
Neurologic
- Sensory or motor neuropathy
- Myositis
- Cerebral vasculitis
- Demyelination, central/peripheral

If not detected early, may result in more serious immune-mediated side effects.


DAILY NEWS
EXTRA!
EXTRA!

FIRST-LINE PEMBROLIZUMAB

KEYNOTE-024: A Randomised Open-Label Phase III Trial of Pembrolizumab Versus Platinum Based Chemotherapy in 1L Subjects With PD-L1 Strong Metastatic Non-Small Cell Lung Cancer (NCT02142738)



Positive PFS
To be presented ESMO Copenhagen October 2016

Brahmer et al. WCLC 2015.

FIRST-LINE NIVOLUMAB

CHECKMATE-026: A Randomised Open-Label Phase III Trial of Nivolumab Versus Investigator's Choice Chemotherapy in 1L Subjects With Stage IV or Recurrent PD-L1+ NSCLC (NCT02142738)

- Advanced NSCLC
- No prior systemic therapy
- No sensitizing EGFR or ALK mutations or brain mets
- ECOG PS 0 or 1
- PD-L1 ≥5%

Nivolumab

Investigator Choice Chemotherapy

Primary objective:
PFS in PD-L1+ patients (with strong expression)

Secondary objective:
ORR, PFS in all PD-L1+ patients

BREAKING NEWS: Trial did not meet primary endpoint

Negative PFS
To be presented ESMO Copenhagen October 2016

Brahmer et al. WCLC 2015.

Summary: Immunotherapy

- Current
  - Second Line Nivolumab 3 mg/kg q 2 w
  - Second Line PDL1 >1% Pembrolizumab 2 mg/kg q 3 w
- Advances
  - First Line PDL1 > 50% Pembrolizumab 200 mg q 3 w

State of the Art NSCLC 2016

- **Look for a Driver Mutation**
  - EGFR
    - Gefitinib, afatinib
    - 3rd generation osimertinib
  - ALK
    - Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
- **Wildtype**
    - Chemotherapy Never Forget
- **Immune checkpoint inhibitors**
  - Evolving PDL1 biomarker

Conclusion

Systemic Treatment of Metastatic Lung Cancer: Times are changing

Making Lung Cancer a Chronic Disease

Canadian Lung Cancer Conference 2017

Vancouver February 9,10th , 2017

www.clcco.ca