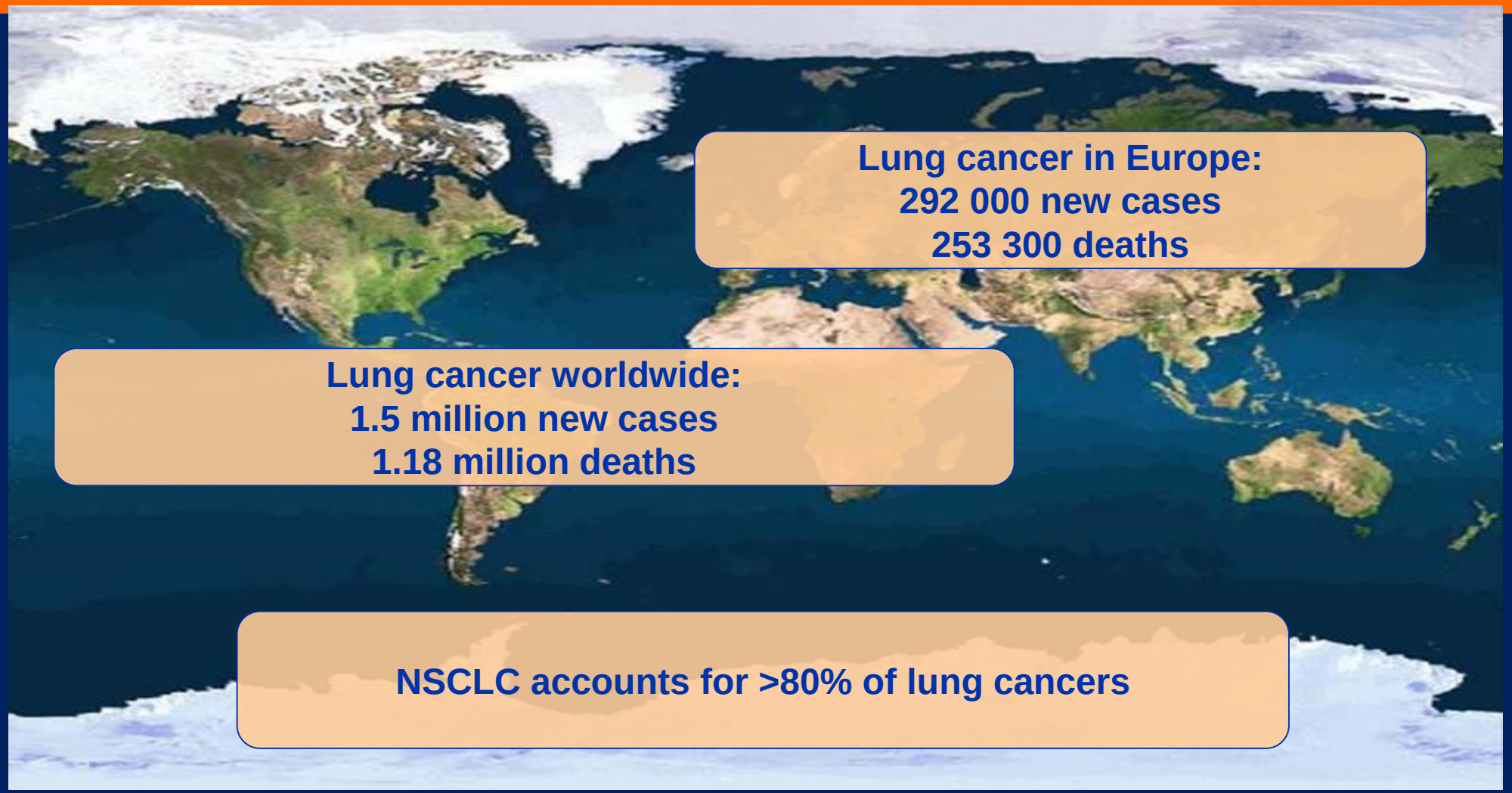
FIRST GENERATION ANTI-EGFR THERAPIES AND RESISTANCE MECHANISMS

Lucio Crinò
IRST IRCCS - Meldola

The burden of NSCLC



Lung cancer in Europe:
292 000 new cases
253 300 deaths

Lung cancer worldwide:
1.5 million new cases
1.18 million deaths

NSCLC accounts for >80% of lung cancers

Parkin D, et al. CA Cancer J Clin 2005;55:74–108; Ferlay J, et al. Ann Oncol 2007;18:581–592

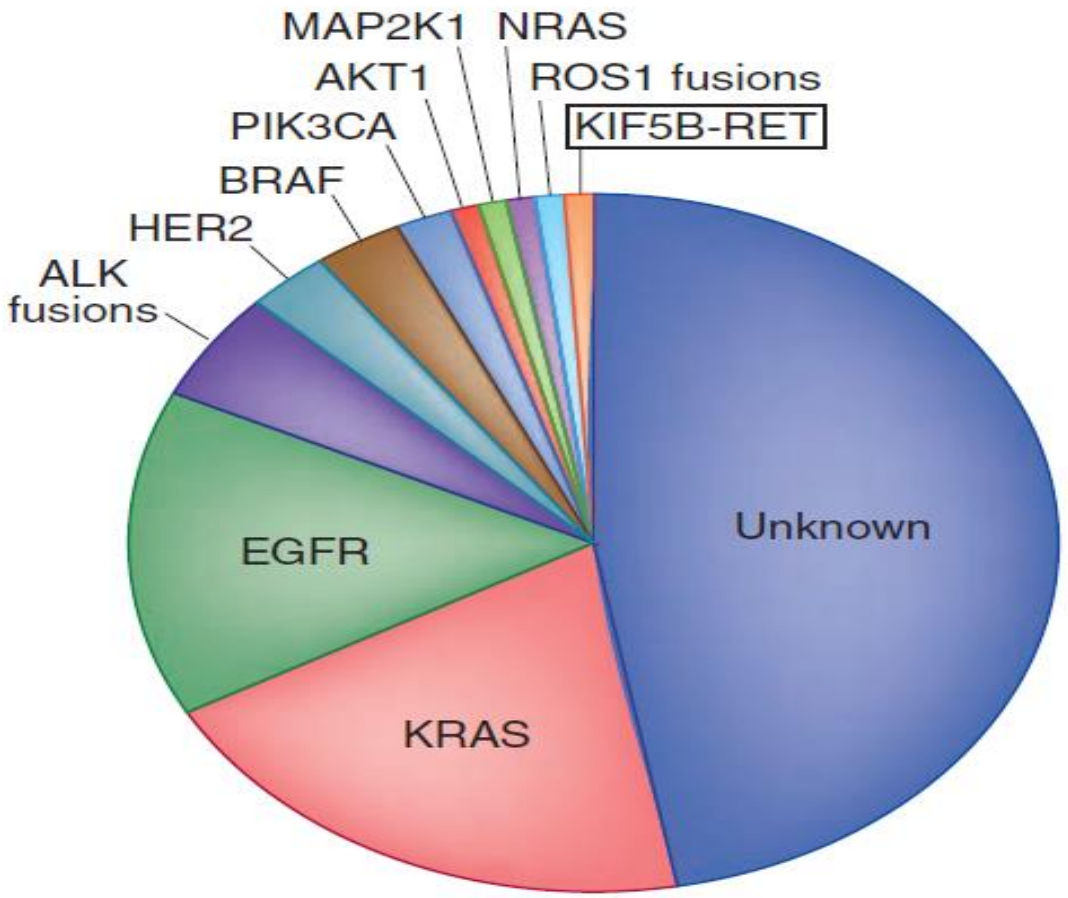
ONCOGENE ADDICTION

Some cancers that contain multiple genetic, epigenetic and chromosomal abnormalities are dependent to one or a few genes for both maintenance of the malignant phenotype and cell survival

- **ERB-B2 in breast cancer**
- **EGFR in NSCLC**
- **EML4-ALK in NSCLC**
- **ROS1 in NSCLC**
- **BRAF in NSCLC and melanoma-KIT in GIST**
- **RET in medullary thyroid cancer**
- **RET in NSCLC**
- **HIF/VEGF in renal cancer**

Weinstein Science, 2002

Molecular subsets of lung adenocarcinoma



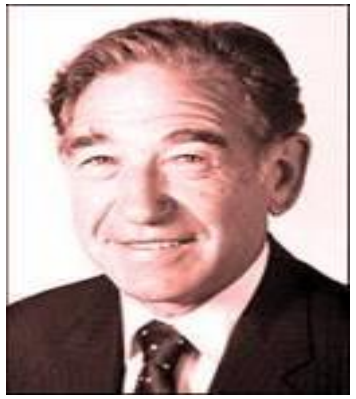
Pao & Hutchinson Nat Med 2012

Pioneers and milestones: evidence that EGFR is important in NSCLC biology

1980

Isolation of human EGF receptor (EGFR) by Stanley Cohen

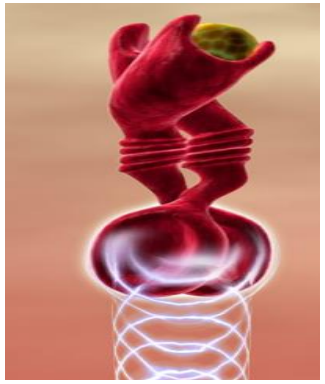
Cohen S, et al. J Biol Chem 1980



1984

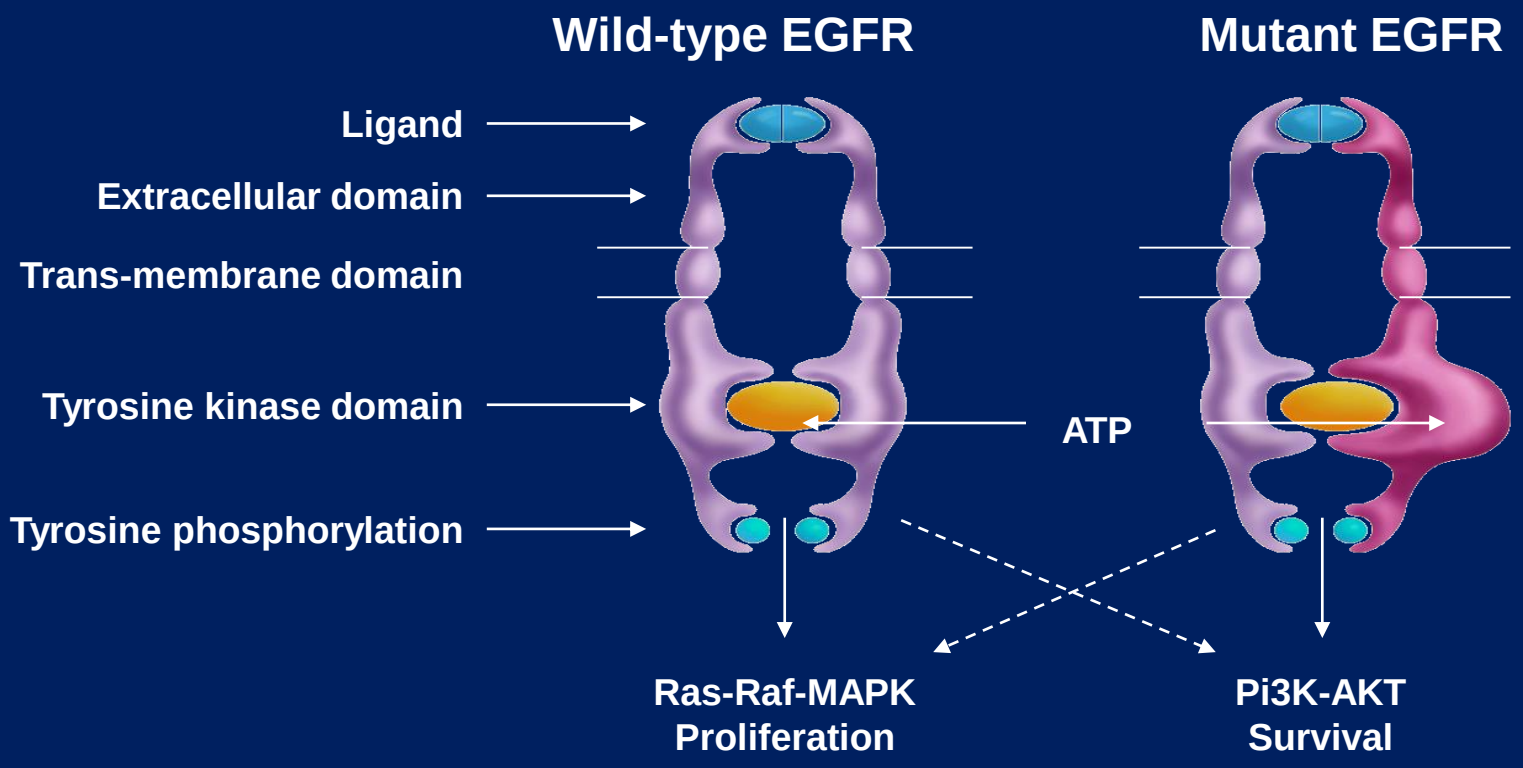
Human EGFR gene cloned and sequenced

Ullrich A, et al. Nature 1984

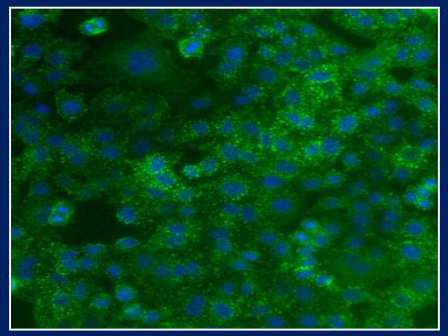


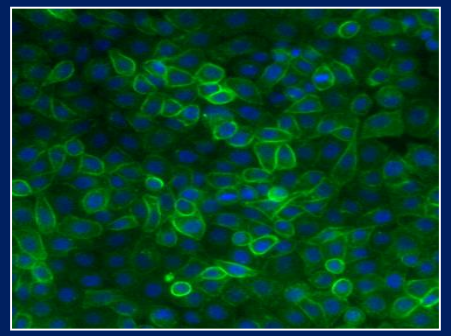
1930 1940 1950 1960 1970 1980 1990 2000 2010

EGFR mutation causes conformational change and increased activation



EGFR internalisation
Degradation / recycling





EGFR signals for longer
at the cell membrane

Arteaga 2006; Gadzar et al 2004; Hendricks et al 2006; Sordella et al 2004

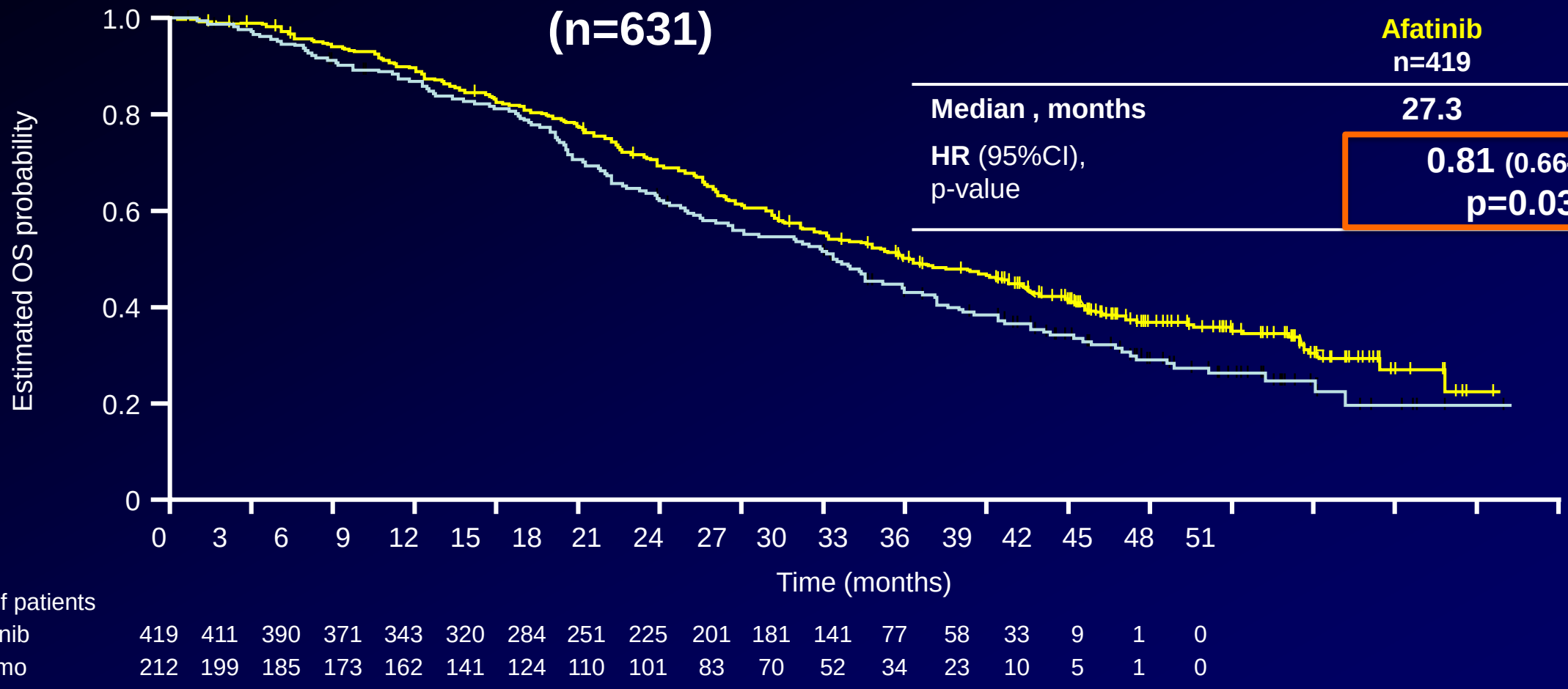
EGFR-TKIs in first-line in EGFR-M+

	Study	Treatment	N	Median PFS, Mos	Median OS, Mos
GEFITINIB	Maemondo[1]	Gefitinib vs carboplatin/ paclitaxel	230	10.8 vs 5.4 (*P* < .001)	30.5 vs 23.6 (*P* = .31)
GEFITINIB	Mitsudomi[2,3]	Gefitinib vs cisplatin/docetaxel	177	9.2 vs 6.3 (*P* < .0001)	HR: 1.19
ERLOTINIB	OPTIMAL[4,5]	Erlotinib vs carboplatin/gemcitabine	165	13.1 vs 4.6 (*P* < .0001)	HR: 1.065
ERLOTINIB	EURTAC[6]	Erlotinib vs platinum-based chemotherapy	174	9.7 vs 5.2 (*P* < .0001)	19.3 vs 19.5 (*P* = .87)
AFATINIB	LUX-Lung 3[7]	Afatanib vs CDDP/pemetrexed	345	11.1 vs 6.9 (*P* = .001)	33.3 vs 21.1 (P=0.0015)
AFATINIB	LUX-Lung 6[8]	Afatinib vs cisplatin/gemcitabine	364	11.0 vs 5.6 (*P* < .0001)	31.4 vs 18.4 (P=0.00229)

1. Maemondo M, et al. N Engl J Med. 2010;362:2380-2388. 2. Mitsudomi T, et al. Lancet Oncol. 2010;11:121-128. 3. Mitsudomi T, et a. ASCO 2012. Abstract 7521. 4. Zhou C, et al. Lancet Oncol. 2011;12:735-742. 5. Zhang C, et al. ASCO 2012. Abstract 7520. 6. Rosell R, et al. Lancet Oncol. 2012;13:239-246. 7. Sequist LV, et al. J Clin Oncol. 2013;31:3327-3334. 8. Wu YL, et al. Lancet Oncol. 2014;15:213-222.

Lux-Lung 3 and 6: combined OS analysis Del19 + L858R

(n=631)



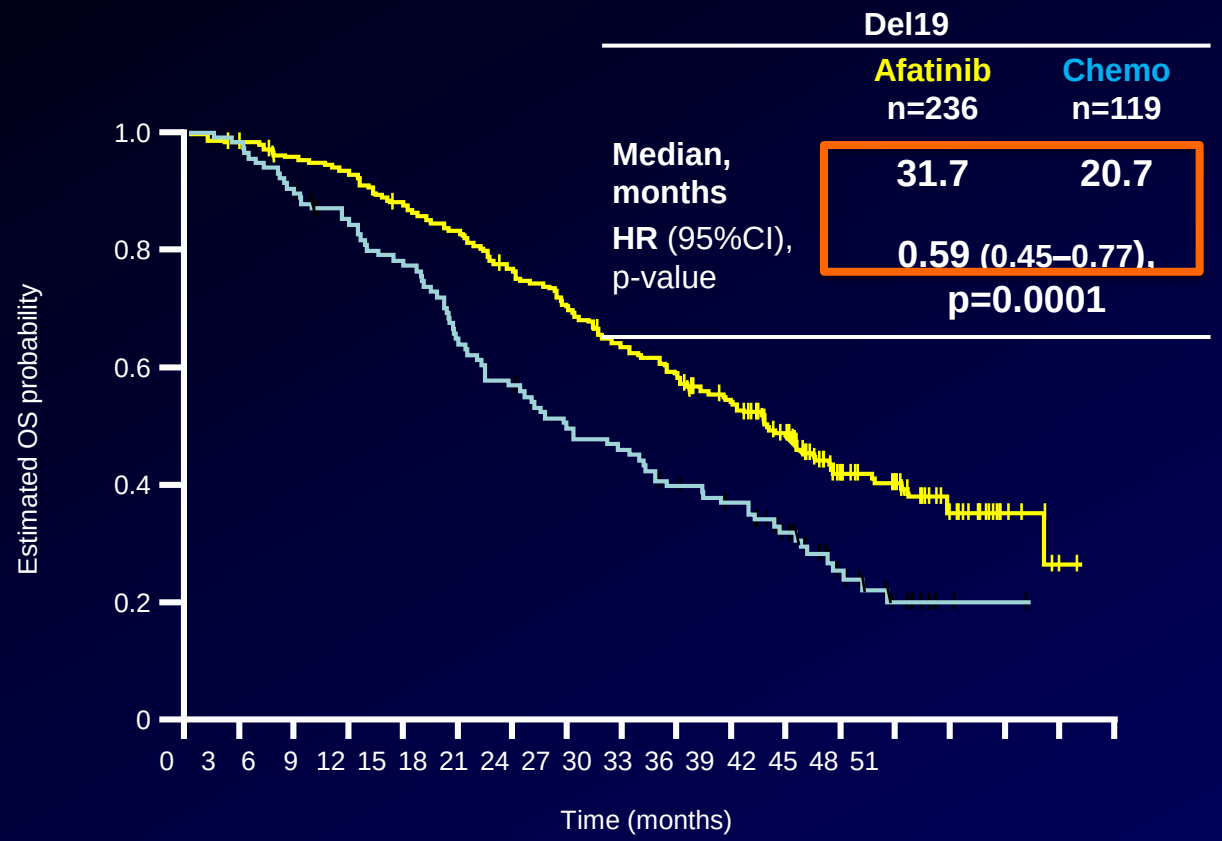
	Afatinib n=419	Chemo n=212
Median , months	**27.3**	**24.3**
HR (95%CI), p-value	**0.81 (0.66–0.99), p=0.0374**	

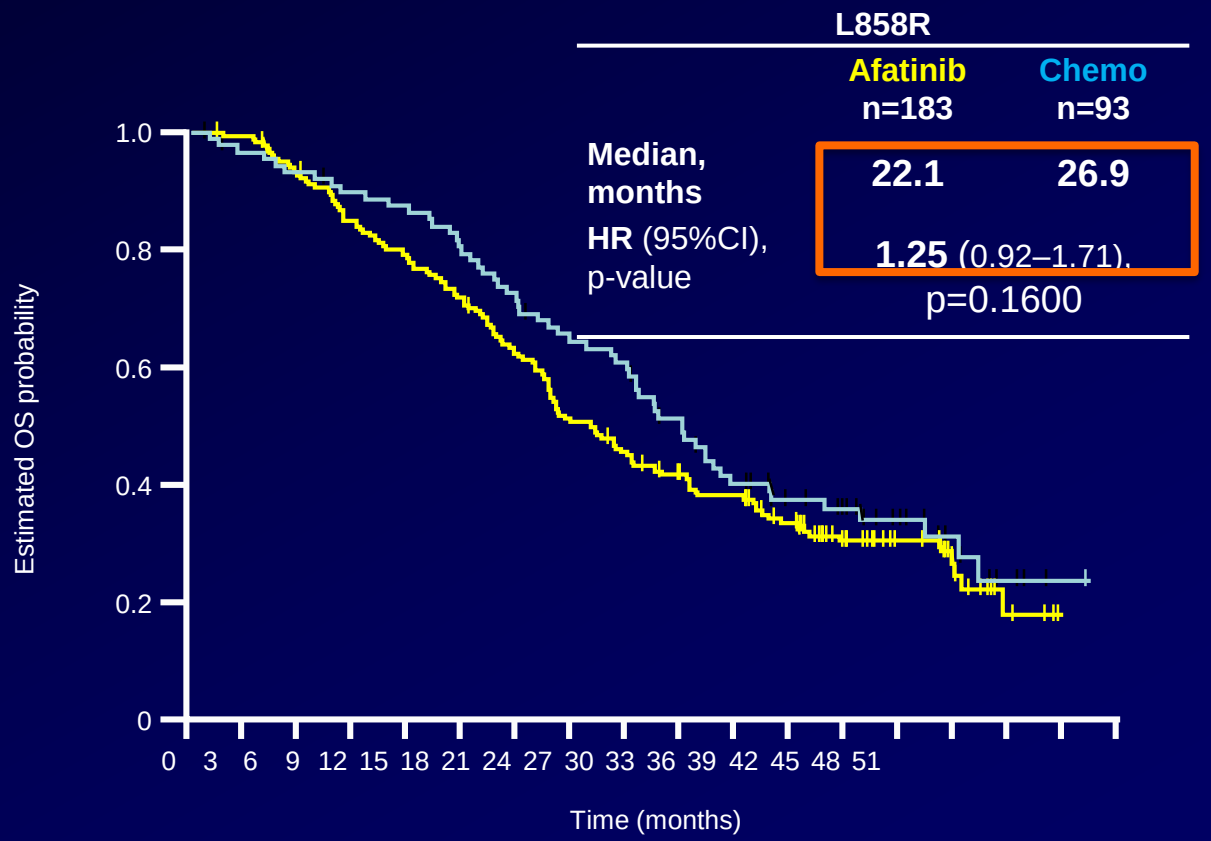
No of patients

Afatinib	419	411	390	371	343	320	284	251	225	201	181	141	77	58	33	9	1	0
Chemo	212	199	185	173	162	141	124	110	101	83	70	52	34	23	10	5	1	0

Median follow-up for OS has been of 36.5 months

1 year OS gain a in Del19
No OS advantage in L858R





No of patients																									
Afatinib	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0							
Chemo	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0							

No of patients																									
Afatinib	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0							
Chemo	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0							

Erlotinib + Bevacizumab in 1st line in EGFR-M+

Chemotherapy-naïve
Stage IIIB/IV or
postoperative recurrence
Non-squamous NSCLC
Activating *EGFR* mutations*
Exon 19 deletion
Exon 21 L858R
Age ≥20 years
PS 0–1
No brain metastasis

*T790M excluded

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

R
1:1

EB combination
Erlotinib 150mg qd +
bevacizumab 15mg/kg q3w
(*n* = 75)

→ PD

E monotherapy
Erlotinib 150mg qd
(*n* = 75)

→ PD

Primary endpoint:
PFS (RECIST v1.1, independent review)
Secondary endpoints:
OS, tumor response, QoL, safety
Exploratory endpoint:
biomarker assessment

Primary endpoint: PFS by independent review

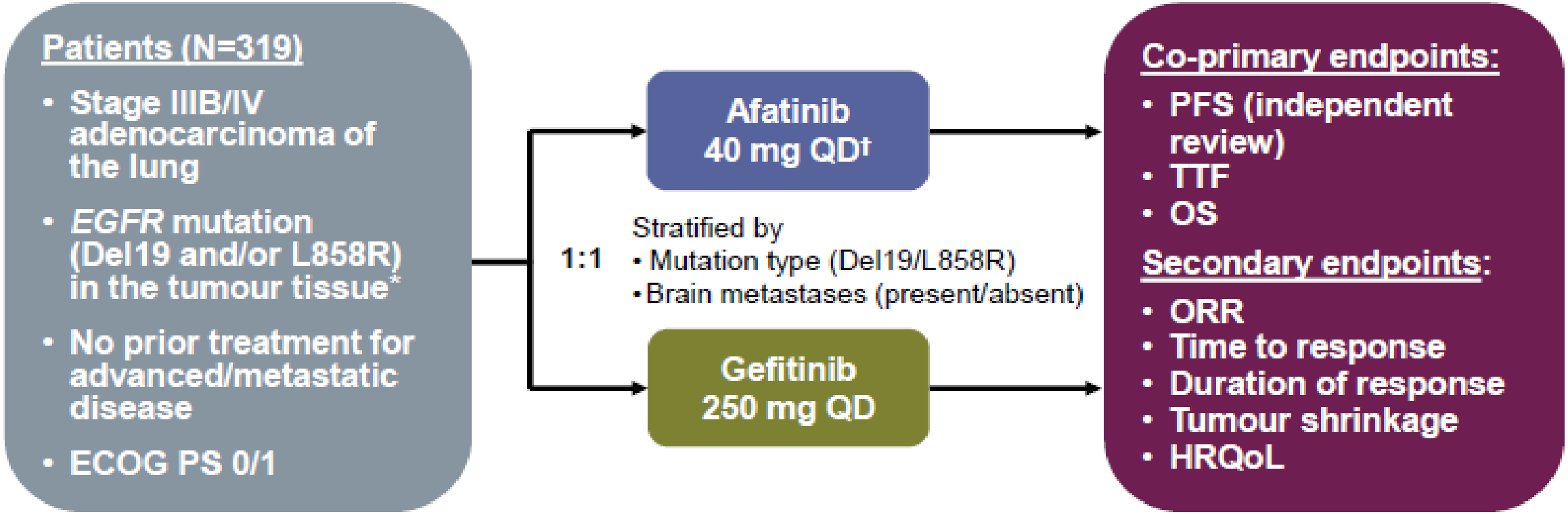
	EB	E
Median (months)	16.0	9.7
HR	0.54 (95% CI: 0.36–0.79)	
P value*	0.0015	

*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

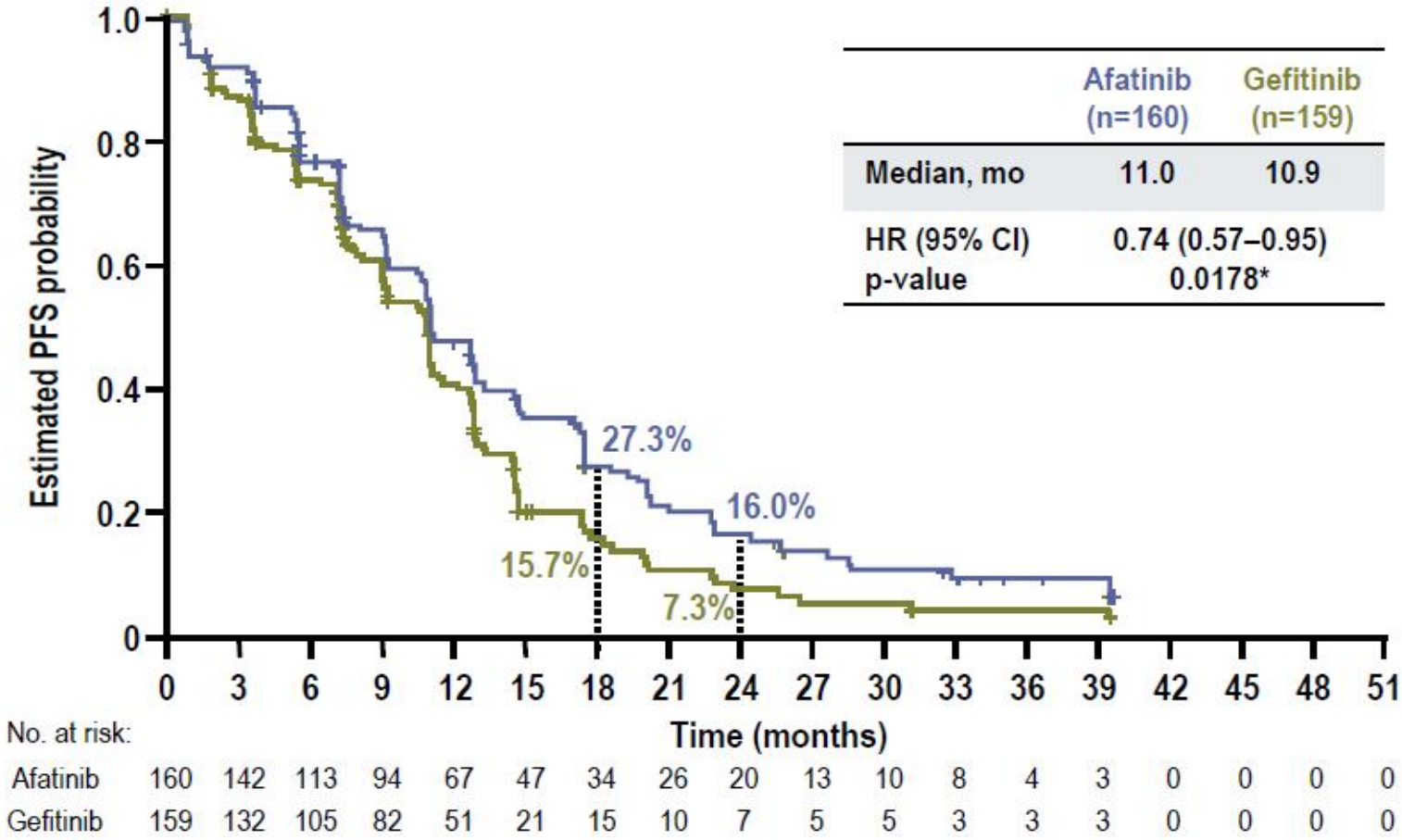
LUX-LUNG 7 STUDY DESIGN



- 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
- Primary PFS analysis conducted after ~250 events; primary OS analysis conducted after ~213 events and ≥32-mo follow-up
- All statistical testing at two-sided 5% alpha level with no adjustment for multiplicity

*Central or local test; †Dose modification to 50, 30, or 20 mg was permitted in line with prescribing information
ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors;

UPDATED PFS (INDEPENDENT REVIEW)

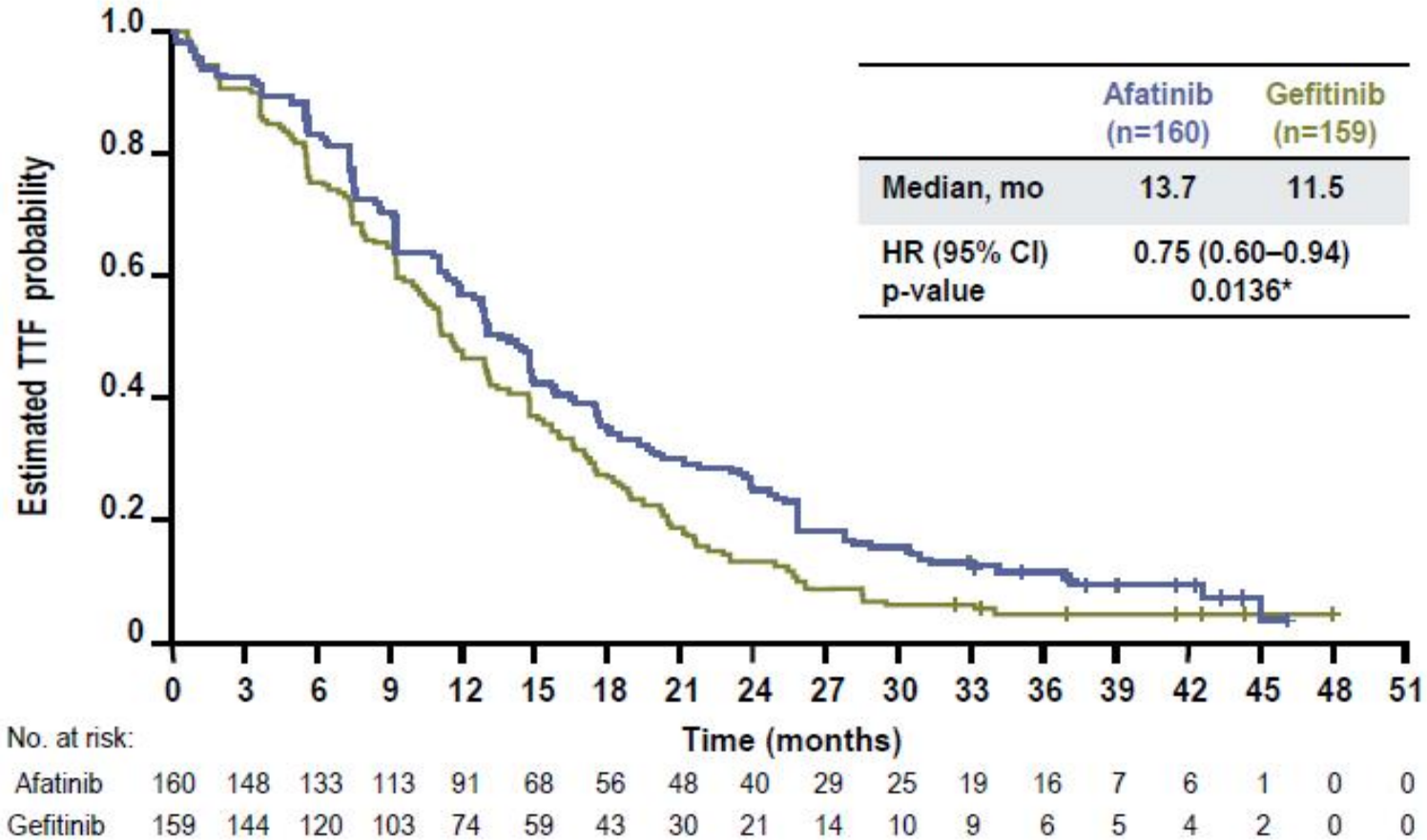


	Afatinib (n=160)	Gefitinib (n=159)
Median, mo	11.0	10.9
HR (95% CI)	0.74 (0.57–0.95)	
p-value	0.0178*	

COPENHAGEN 2016 ESMO congress

*unadjusted

UPDATED TTF

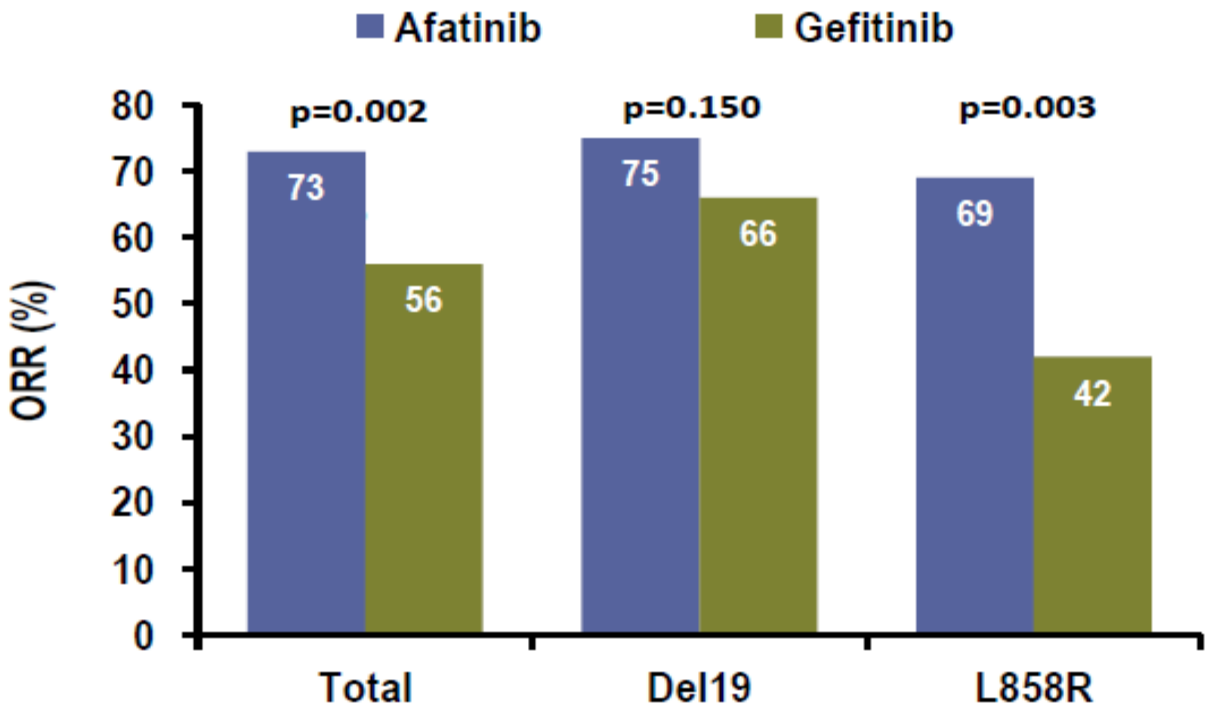


	Afatinib (n=160)	Gefitinib (n=159)
Median, mo	13.7	11.5
HR (95% CI)	0.75 (0.60–0.94)	
p-value	0.0136*	

COPENHAGEN 2016 ESMO congress

*unadjusted

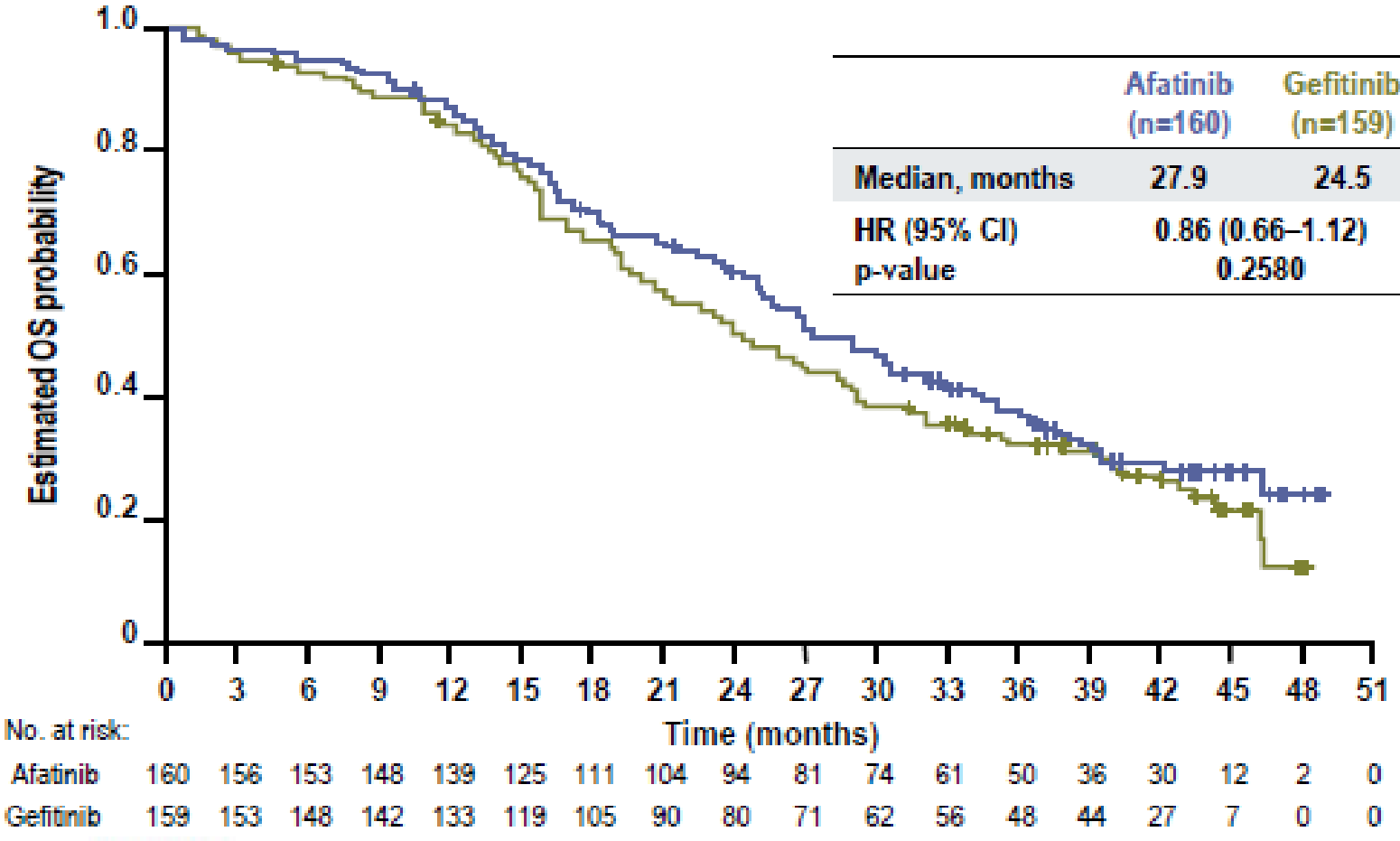
UPDATED TUMOUR RESPONSE



	Afatinib	Gefitinib
Median DoR (months)	10 .1	8.3
95% CI	(8.2–11.1)	(7.3–10.2)

DoR, duration of response

OS (OVERALL POPULATION)



	Afatinib (n=160)	Gefitinib (n=159)
Median, months	27.9	24.5
HR (95% CI)	0.86 (0.66–1.12)	
p-value	0.2580	

- Median follow-up: 42.6 months (as of 08 April 2016)
- Median treatment duration (afatinib vs gefitinib): 13.7 vs 11.5 months

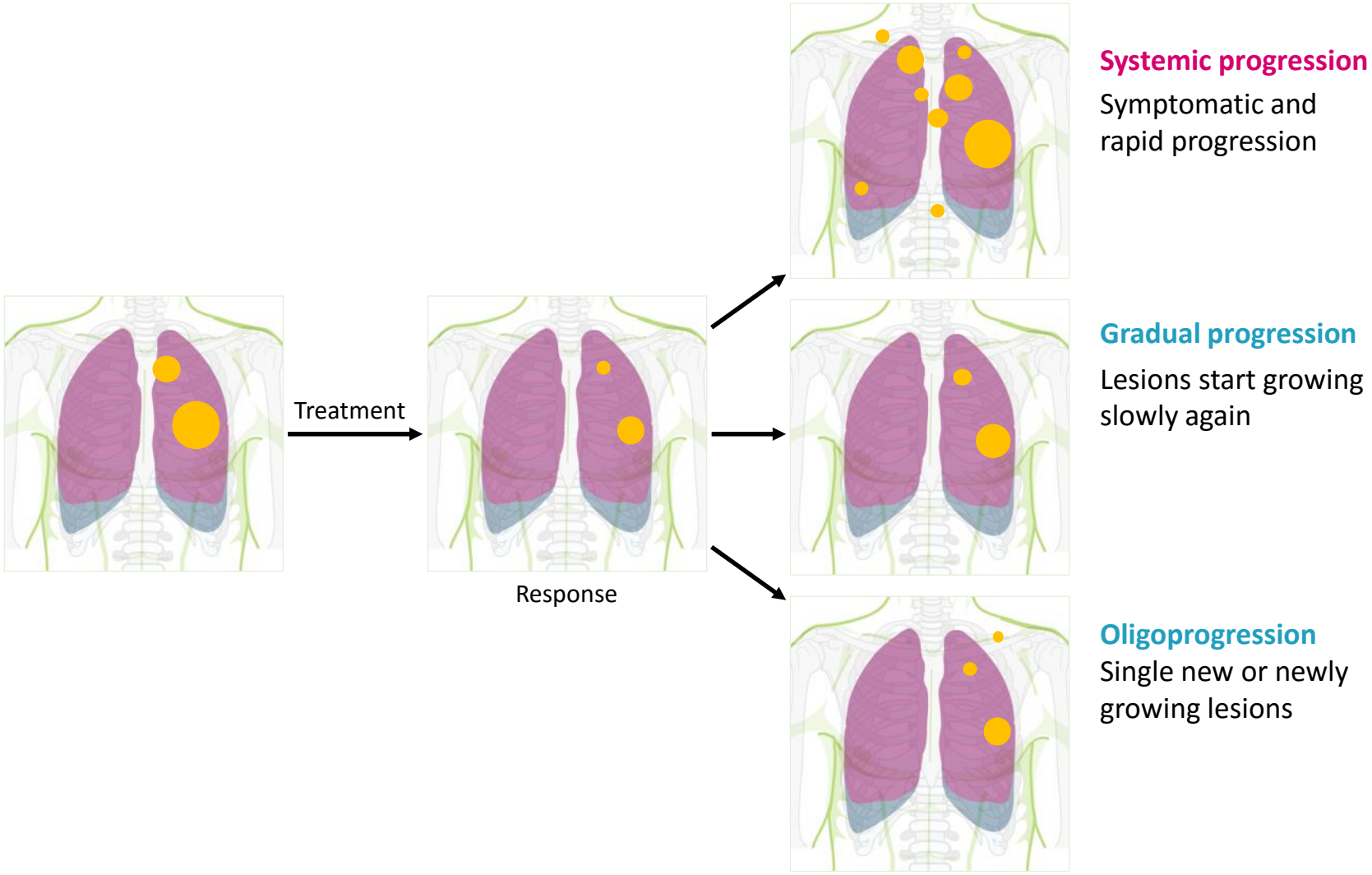
TKIs primary and acquired resistance:

- TKIs are the treatment of choice in any line of metastatic lung adenocarcinomas harboring EGFR mutations or ALK and ROS1 rearrangements
- Response Rate ranges between 60 or 70% implying that 30-40% of the patients present primary resistance
- Activity is limited because complete remissions are below 5% and most of patients relapse in 9-11 months
- Resistance mechanisms are not completely understood and seem to be multiple and independent.

EGFR mut+ lung Adenocarcinoma: what happens after the first line?

1. The awareness that the first line result will not last forever: all patients will progress whatever EGFR-TKI we will use.. 1st-2nd-n° generation!
2. Defining progression by RECIST criteria may lead to premature termination of the EGFR-TKI
3. Clinical presentation at disease progression: «oligoprogressive» vs «widespread» vs «CNS only»
4. Defining the mechanism of resistance
    - Re-biopsy
5. Third generation EGFR-TKIs: OSIMERTINIB and…the others
6. Potential and «Hazards» of liquid biopsy
7. Potential and «Hazards» of combinations

RECIST-defined progression may not reflect general treatment failure



Suggested criteria for considering local Ablative therapy of EGFR mut+ oligoprogressive disease

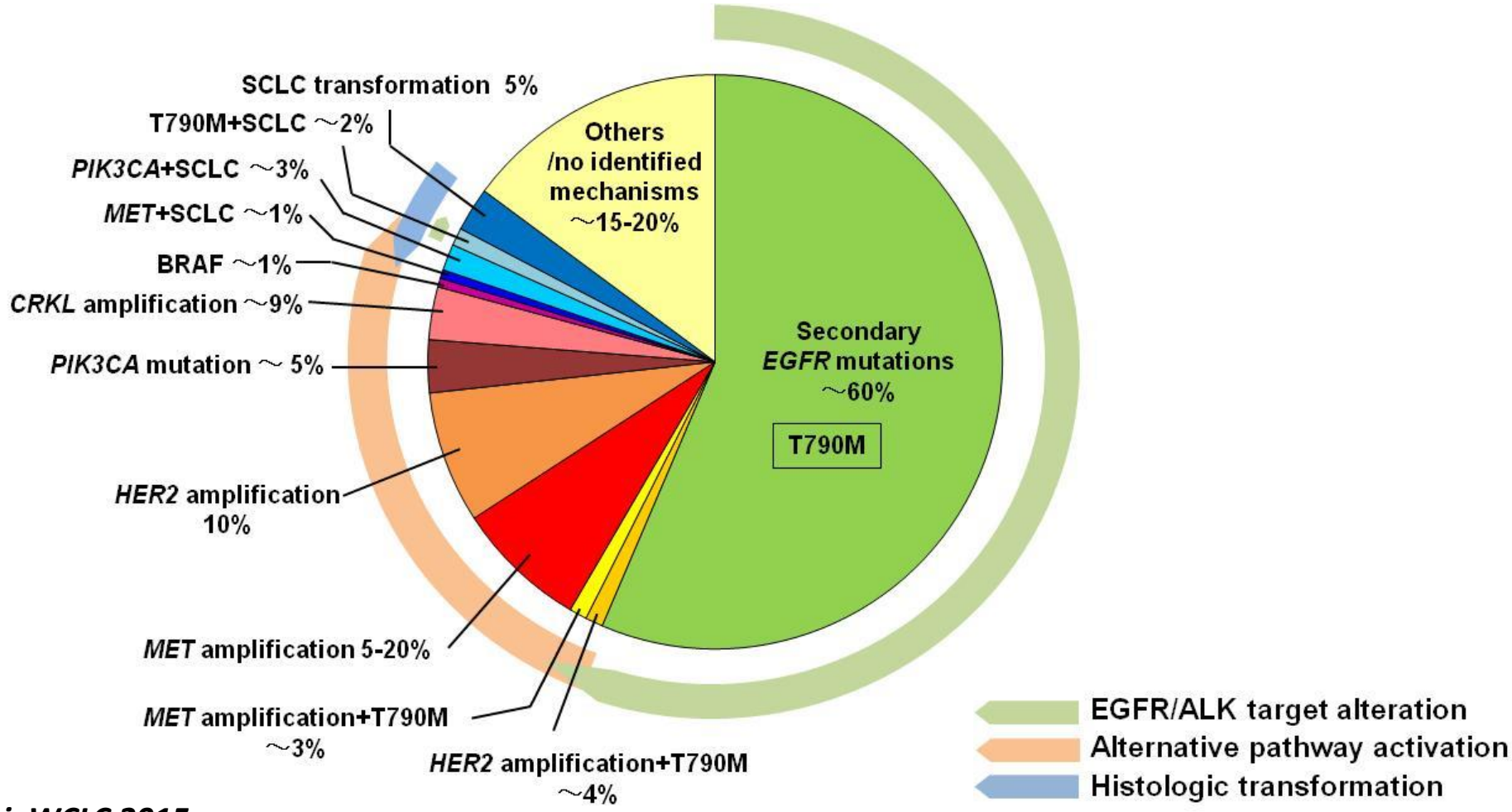
1. *EGFR*-mutant metastatic NSCLC
2. TKI is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as:
CNS progression without leptomeningeal disease amenable to WBRT, SRS, or surgical resection.
4. Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT, or surgical resection.

... today probably we would add

5. whenever a 3rd generation EGFR-TKI is not «easily» available for the patient

Weickhardt et al , JTO 2013

Mechanisms of drug resistance to EGFR TKis

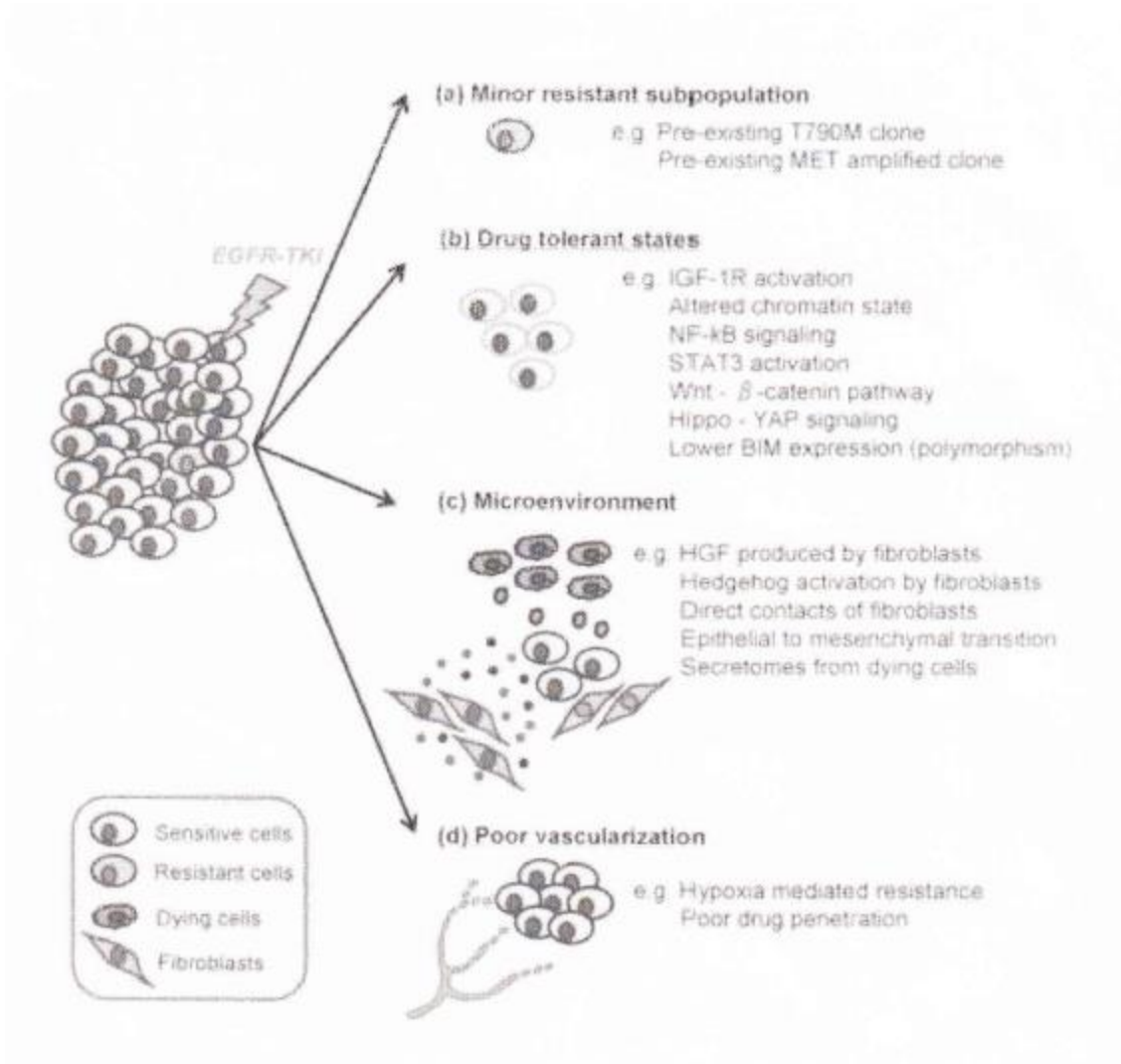


Junko Tanizaki, WCLC 2015

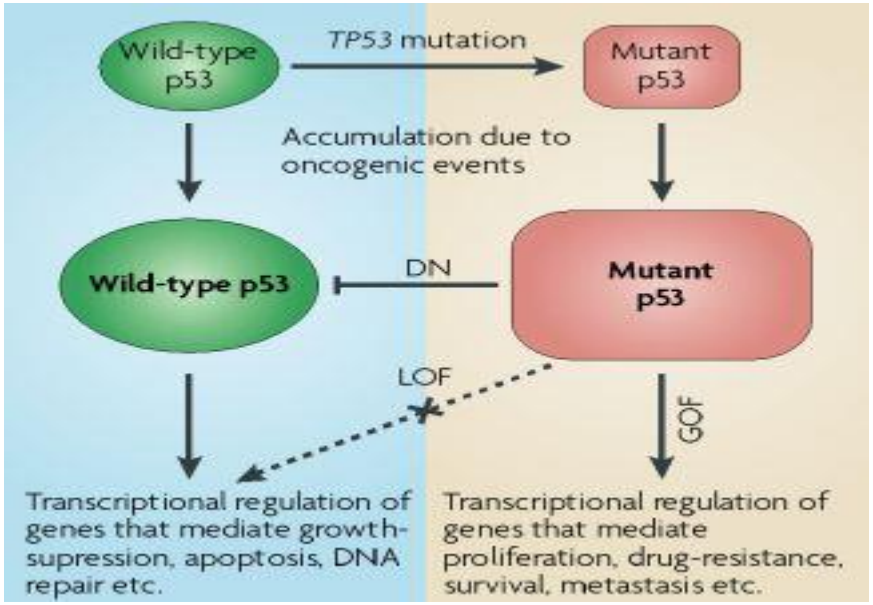
MOLECULAR MECHANISMS OF EARLY PRIMARY RESISTANCE TO EGFR TKI

- Pre-existence of minor resistance subpopulations (T790M or MET amplified clones)
- Reversible drug tolerance state (cell line models)
- Survival signaling from microenvironments (fibroblast or dying cancer cells)
- Poor vascolarization of the tumor

Mechanisms of residual tumor cells against EGFR TKIs



TP53 mutation as potential resistance mechanism to TKIs



***TP53* GOF mutations are able to:**

- Increase tumorigenicity
- Increase growth rate and motility
- Increase metastasis and invasiveness

- Up-regulate the expression of Axl
- Induce the EMT process

} Both implicated in TKIs resistance

Impact of *TP53* Mutations on Outcome in *EGFR*-Mutated Patients Treated with First-Line Tyrosine Kinase Inhibitors

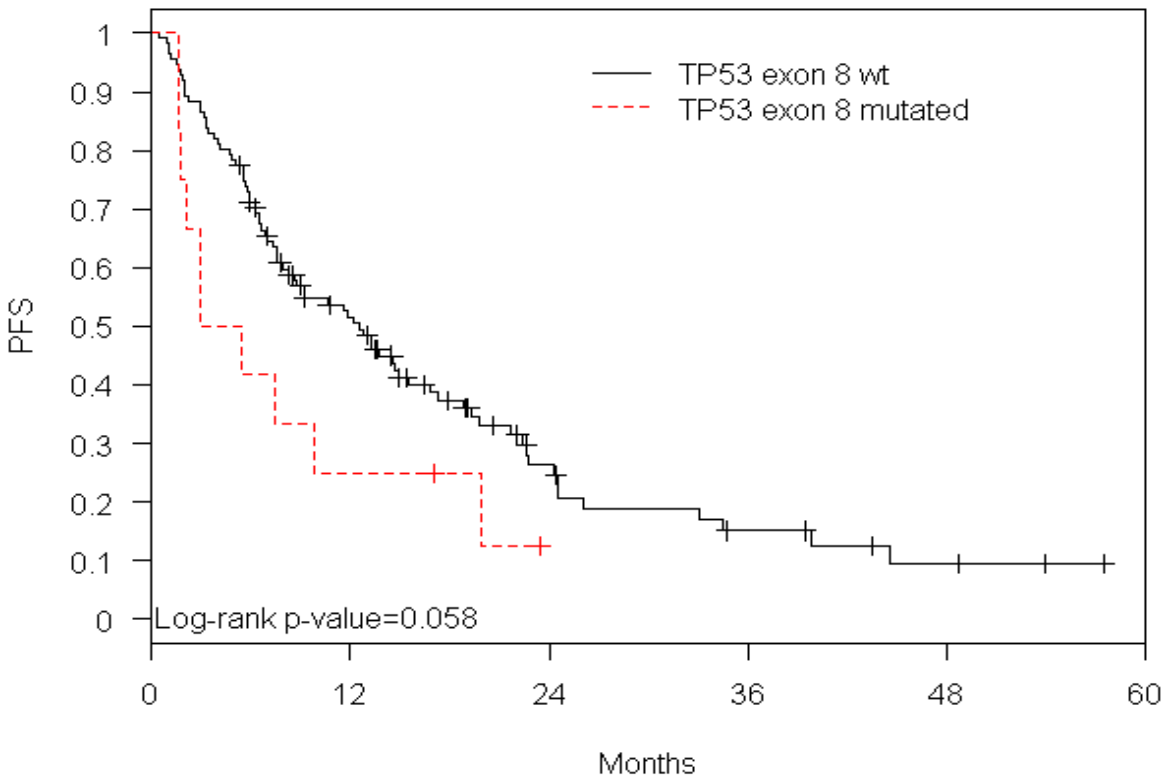
Matteo Canale[1], Elisabetta Petracci[2], Angelo Delmonte[3], Elisa Chiadini[1], Claudio Dazzi[4], Maximilian Papi[5], Laura Capelli[1], Claudia Casanova[4], Nicoletta De Luigi[3], Marita Mariotti[3], Alessandro Gamboni[6], Rita Chiari[7], Chiara Bennati[7], Daniele Calistri[1], Vienna Ludovini[7], Lucio Crinò[7], Dino Amadori[3], Paola Ulivi[1]

Clin Cancer Res. 2016 Oct 25

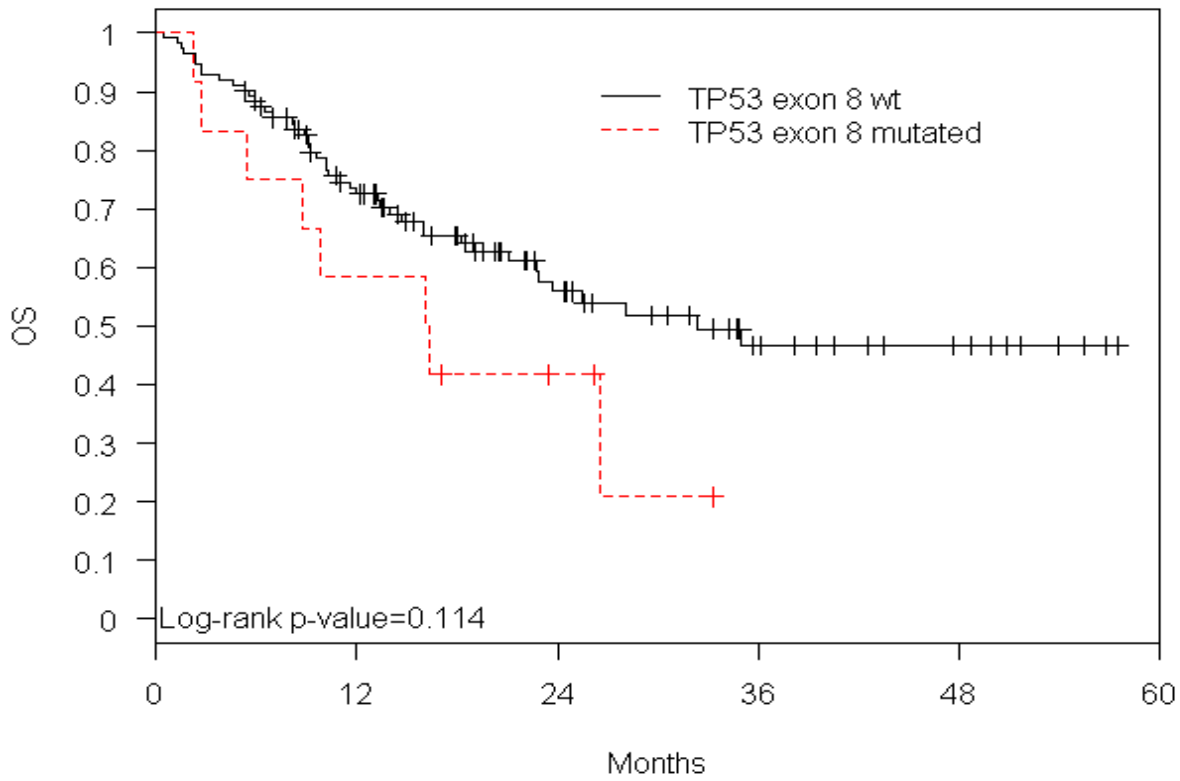
	DCR, n (%)		Unadjusted	
***TP53* mutation**	No (n=22)	Yes (n=101)	RR [95% CI]	P
All mutations				
Wt	10 (11.8)	75 (88.2)	1	0.019
Mut	11 (29.7)	26 (70.3)	3.17 [1.21 - 8.48]	
Exon 8				
Wt	14 (12.7)	96 (87.3)	1	< 0.001
Mut	7 (58.3)	5 (41.7)	9.6 [2.71- 36.63]	

PFS e OS in patients with TP53 exon 8 mutations respect to those exon 8 wt (overall case series)

a

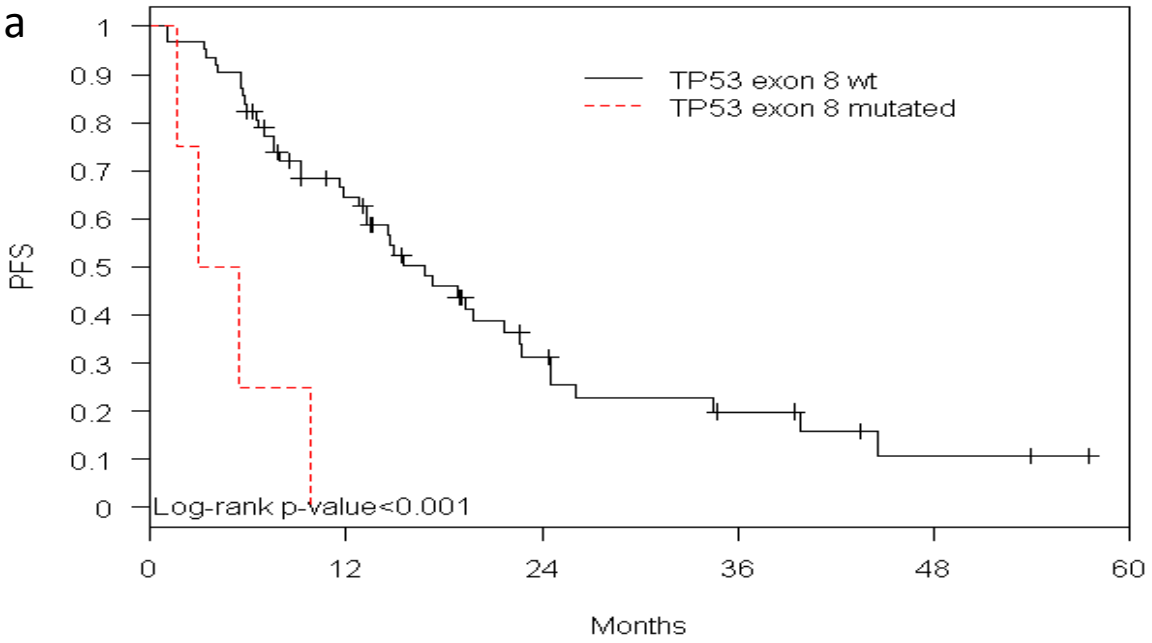


b

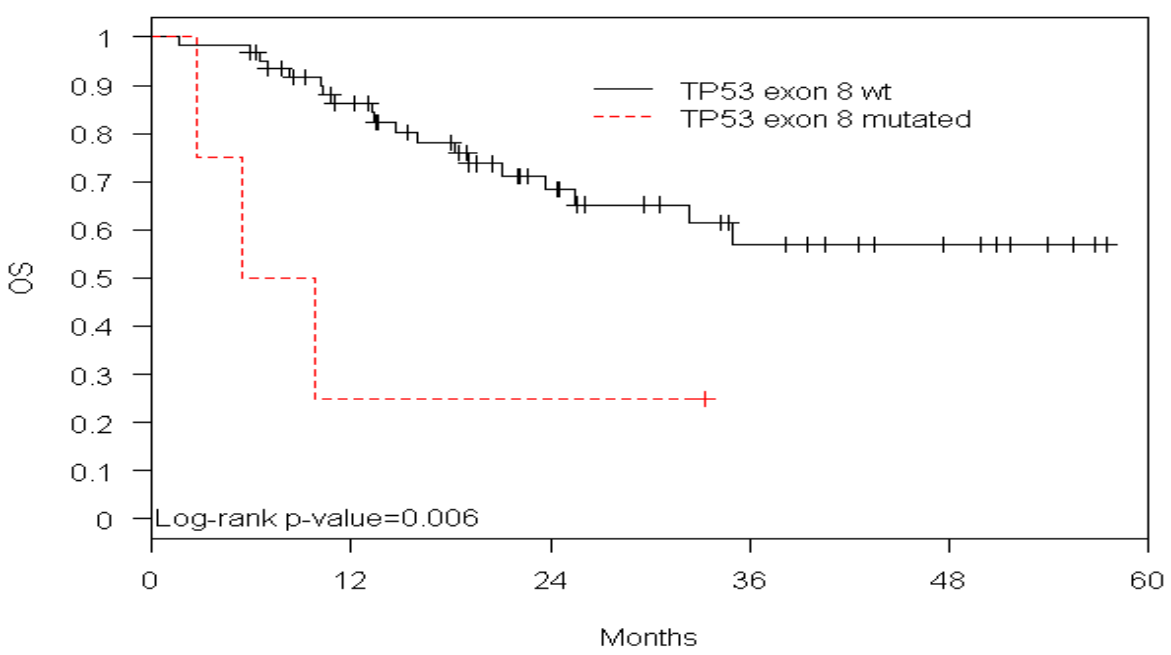


PFS e OS in patients with TP53 exon 8 mutations respect to those exon 8 wt, in the subgroup of patients with EGFR exon 19 deletions

a



b



	PFS		OS	
***TP53* mutation**	HR [95% CI]	p	HR [95% CI]	p
wt	1		1	
mut	1.74 [0.92 – 3.29]	0.086	1.58 [0.64 – 3.87]	0.321
***TP53* exon 8 mutation**				
wt	1	0.006	1	0.013
mut	6.99 [2.34-20.87]		4.75 [1.38-16.29]	

Third generation EGFR-TKIs

Drug	ORR T790M +	ORR T790M -	G 1-2 Diarrhea	G1-2 Rash
AZD9291	65%	22%	20%	27%
CO-1686	58%	-	23%	4%
HM 61713	29%	12%	21%	24%

AURA TRIALS

- **AURA**: Phase 1/2 study in advanced EGFR mut+ NSCLC TKI failure +/- primary resistance mutation T790M
- **AURA2**: Phase 2 study in advanced EGFR mut+ NSCLC TKI failure and primary resistance mutation T790M
- **AURA3**: Phase 3 study in advanced EGFR mut+ NSCLC TKI failure and primary resistance mutation T790M versus chemotherapy
- **FLAURA**: Phase 3 study in advanced EGFR mut+ NSCLC TKI versus gefitinib or erlotinib

TIGER TRIALS

- **TIGER1**: Phase 2/3 randomized registration study in newly-diagnosed advanced NSCLC patients (vs. erlotinib)
- **TIGER2**: Phase 2 registration study in 2nd line T790M+ patients directly progressing on first TKI
- **TIGER3**: Phase 2 registration study in later-line T790M+ patients, progressing on second or later TKI or subsequent chemotherapy
- **TIGER4**: Phase 2 study in 2nd or later-line patients with T790M detected with a blood/plasma assay
- **TIGER5**: Phase 3 randomized confirmatory study in 2nd or later-line patients (vs. chemo)

OSIMERTINIB: The drug

Pharmacodynamics

- ✓ It is an irreversible EGFRTKI, with 200 times greater affinity for EGFR with L858R, Del19 and T790M mutations than wild-type EGFR in vitro
- ✓ Single-dose daily, Cmax reached in 6 h , dose-proportional over the 20–240 mg range
- ✓ Acquired resistance mediated by the EGFR C797S mutation, amplification of HER2, MET or alternative pathways, and histological transformation.

Pharmacokinetics

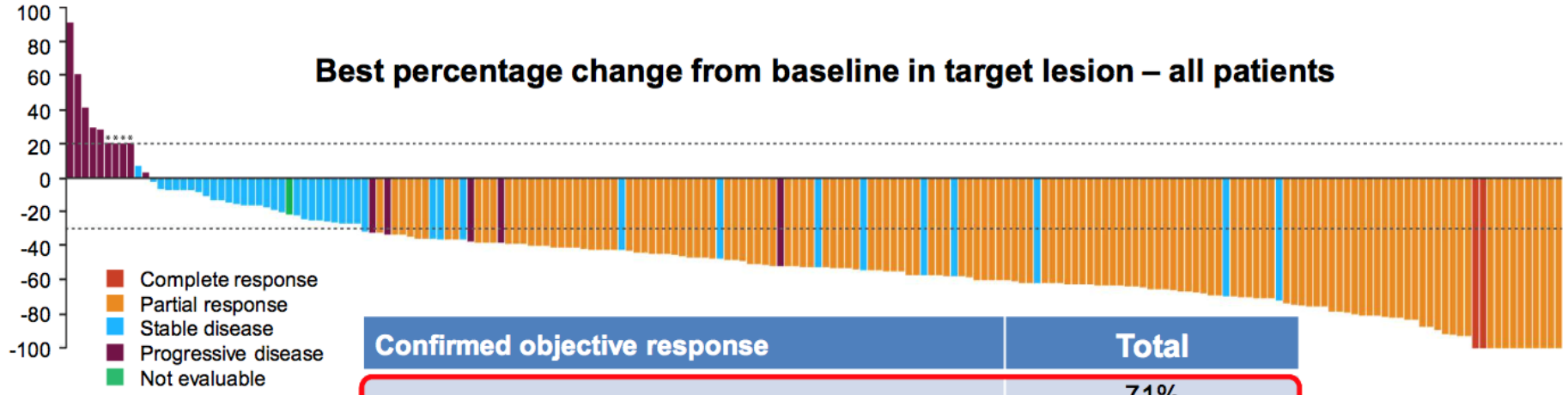
- ✓ In a mouse model distribution to the brain 5- to 25-fold higher in brain tissue than plasma and 10-fold higher than that of gefitinib
- ✓ 80 mg daily is predicted to be sufficient to be effective in EGFRm+ brain metastases.
- ✓ No food effect

Drug Interactions

- ✓ Potential drug interactions with strong CYP3A inhibitors or inducers, and substrates of CYP3A, BCRP or CYP1A2 with narrow therapeutic indices

Data with AZD9291

Tumor response by independent central review

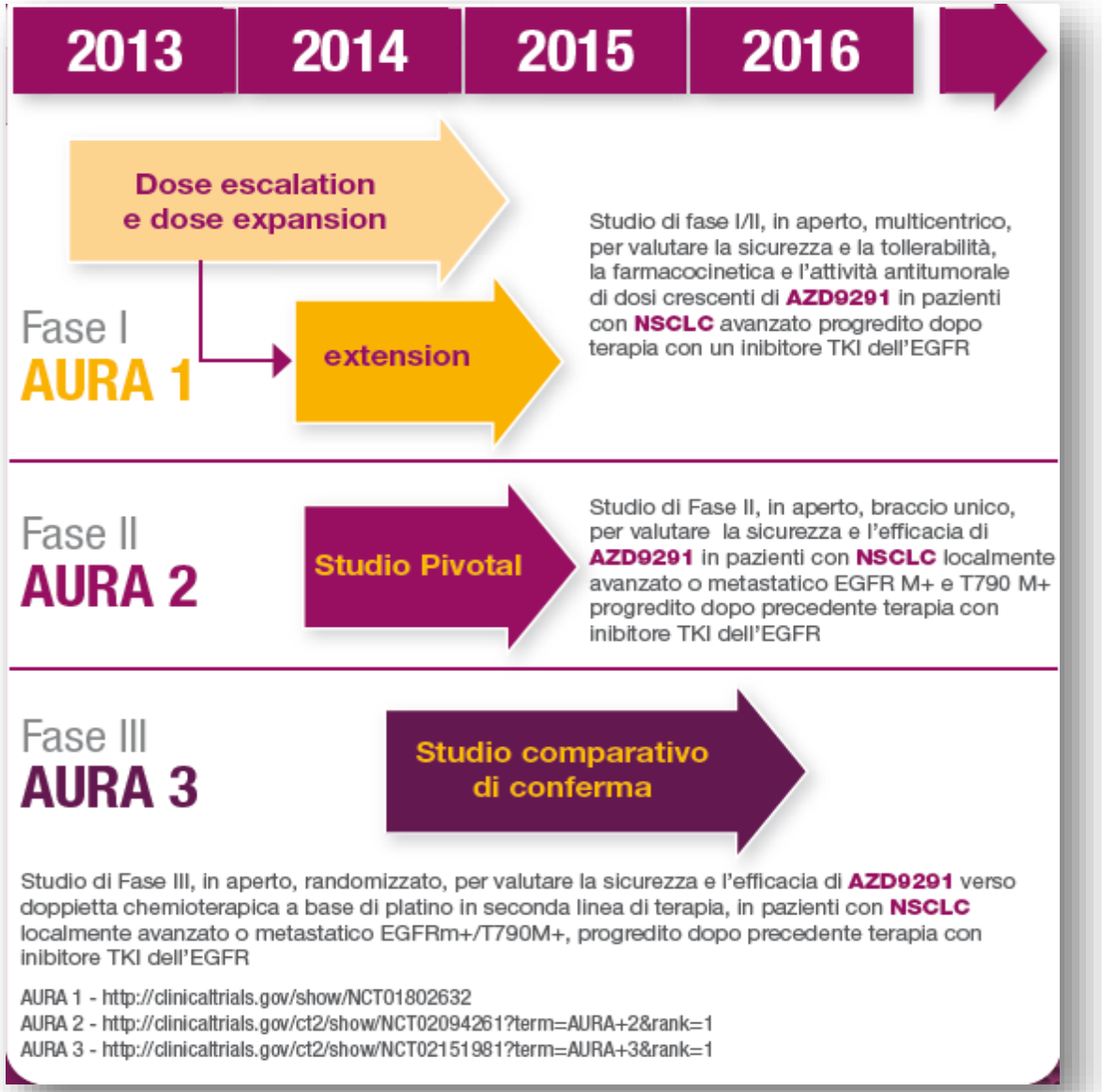


Confirmed objective response	Total
ORR†	71% (95% CI 64, 77)
Complete response,‡ n (%)	2 (1)
Partial response,‡ n (%)	139 (70)
Stable disease ≥6 weeks,§ n (%)	41 (21)
Progressive disease, n (%)	15 (8)
DCR	92% (95% CI 87, 95)

Partial response	20	25	45
Stable disease	8	5	13
Progressive disease	2	0	2

Ramalingam S et al, Mitsudomi T et al, Yang J et al, MINI ORAL 16, WCLC 2015

Osimertinib – Second line or later monotherapy



Consistent data of ORR (60-70%) and DCR (80-90%) across all trials in T790M positive patients!

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

AZD9291 in pre-treated T790M positive advanced NSCLC: AURA2 Phase II study

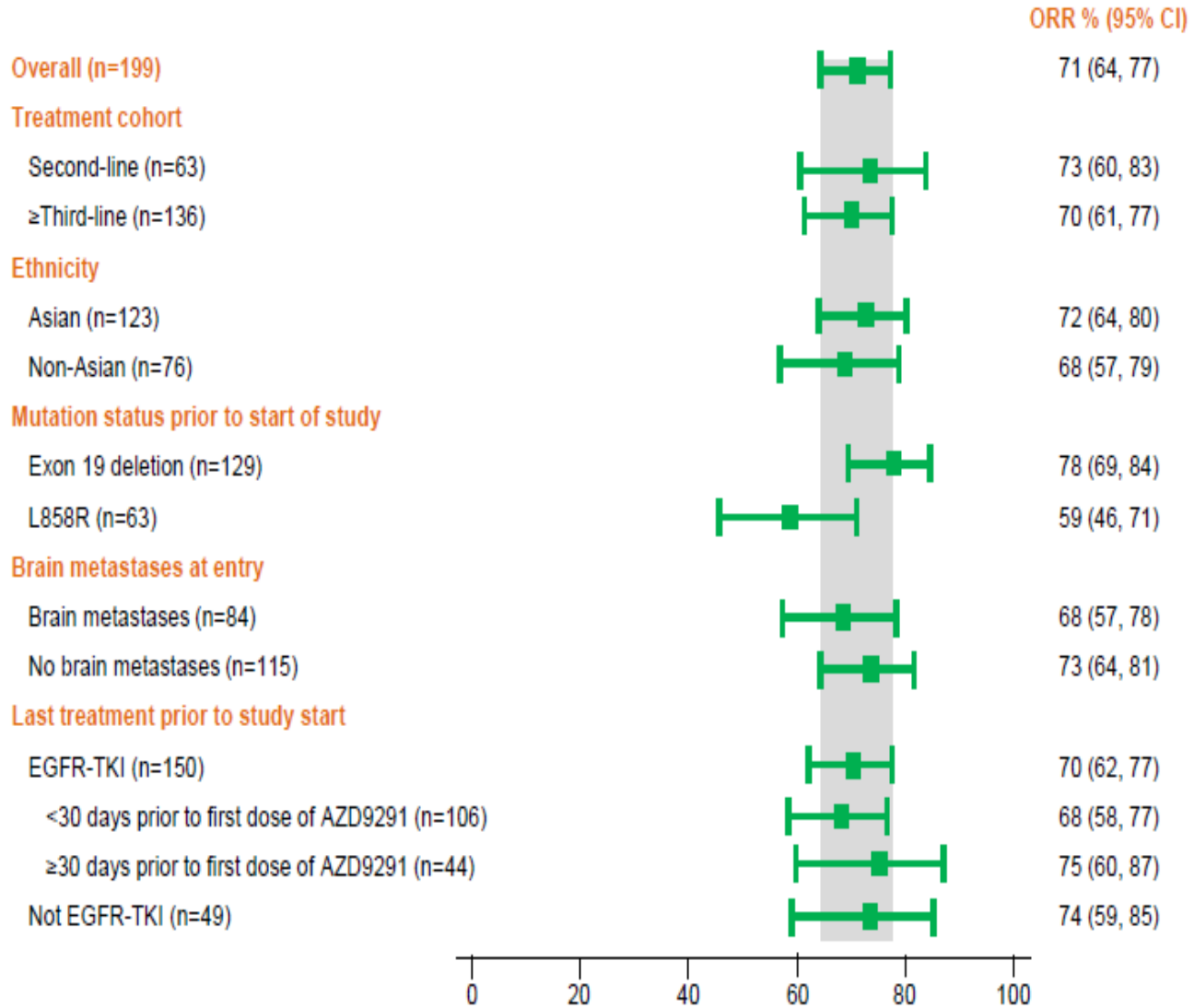
Tetsuya Mitsudomi[1], Chun-Ming Tsai[2], Frances A. Shepherd[3], Lyudmila Bazhenova[4], Jong Seok Lee[5], Gee-Chen Chang[6], Lucio Crino[7], Miyako Satouchi[8], Quincy Chu[9], Rachael Lawrance[10], Mireille Cantarini[10], Serban Ghiorghiu[11], Glenwood Goss[12]

[1]Kinki University Faculty of Medicine, Osaka-Sayama, Japan; [2]Department of Chest Medicine, Taipei-Veterans General Hospital and School of Medicine, National Yang-Ming University, Taipei, Taiwan; [3]Princess Margaret Cancer Centre, Toronto, Canada; [4]Moores Cancer Center, La Jolla, CA, USA; [5]Seoul National University, Bundang Hospital, Seongnam, Republic of Korea; [6]National Yang-Ming University, Taipei, and Taichung Veterans General Hospital, Taichung, Taiwan; [7]Perugia University Medical School, Perugia, Italy; [8]Hyogo Cancer Center, Akashi, Japan; [9]University of Alberta, Cross Cancer Institute, Edmonton, Alberta, Canada; [10]AstraZeneca, Macclesfield, UK; [11]AstraZeneca, Cambridge, UK; [12]The Ottawa Hospital Cancer Centre, Ottawa, Canada

Presented by T Mitsudomi at the World Conference on Lung Cancer 2015
Journal of Thoracic Oncology 2015; 10(9, Suppl 2): S320, abstract Mini 16.08

IASLC 40 YEARS

ORRs across predefined subgroups

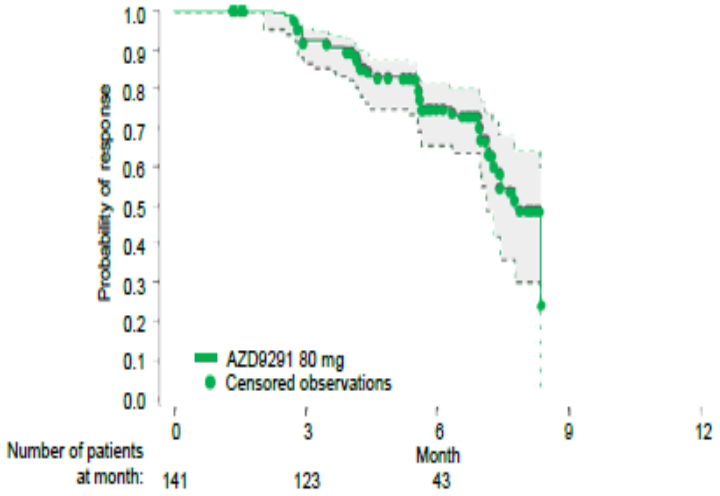


NOTE: Other predefined subgroups were: gender, age at screening (<65, ≥65), duration of most recent EGFR-TKI (<6 months, ≥6 months), smoking status (never, ever), T790M status in baseline plasma sample (circulating tumor DNA), region (North America, Asia, EU, and rest of world)
Data cut-off: May 1, 2015. Population: evaluable for response set (n=199)

Presented by T Mitsudomi at the World Conference on Lung Cancer 2015. *Journal of Thoracic Oncology* 2015; 10(9, Suppl 2): S320, abstract Mini 16.08

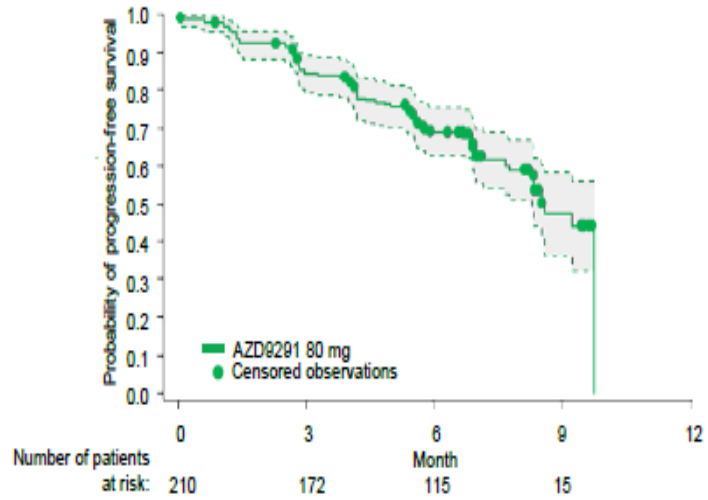
Duration of response and progression-free survival

Duration of response* (BICR)



KM-based estimated†	Total‡
Median DoR,¶ months (95% CI)	7.8 (7.1, NC) Maturity: 27%
Remaining in response, % (95% CI) 6 months 9 months	 75 (65, 82) NC (NC, NC)
Range of DoR, months	1.3–8.4

Progression-free survival* (BICR)



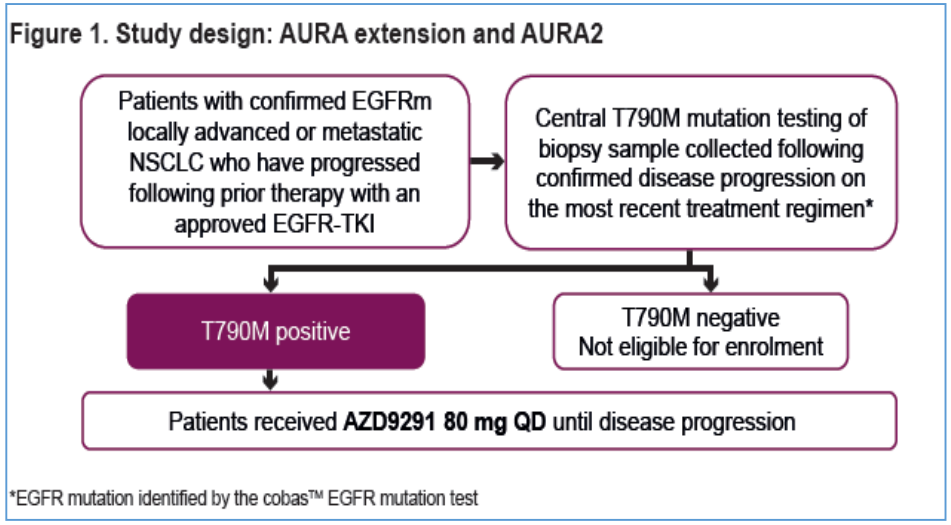
KM-based estimated†	Total§
Median PFS,** months (95% CI)††	8.6 (8.3, 9.7) Maturity: 38%
Remaining alive and progression free, % (95% CI) 6 months 9 months	 70 (63, 76) 48 (36, 58)
Median follow-up for PFS	6.7 months

Data cut-off: May 1, 2015. *Gr… from the first documentation o… date of objective disease prog… DoR, duration of response; KI…

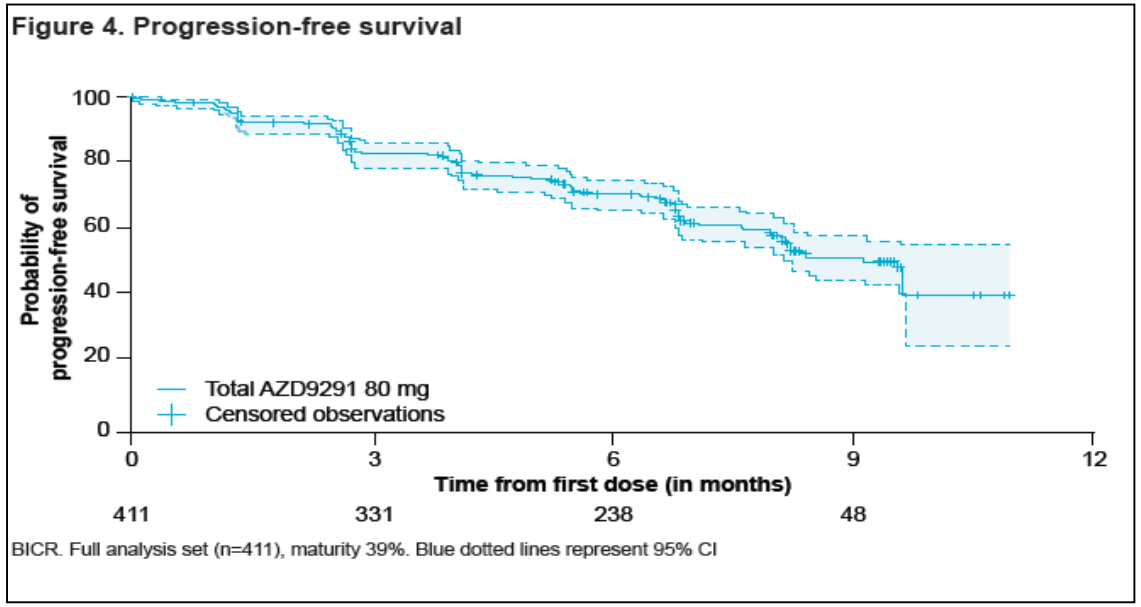
Presented by T Mitsudom…

Median PFS, months (95% CI): 8.6 (8.3,9.7)
Maturity: 38%

AZD9291 in pre-treated patients with T790M positive advanced non small cell lung cancer (NSCLC): pooled analysis from two Phase II studies



411 patients



Median PFS in months:

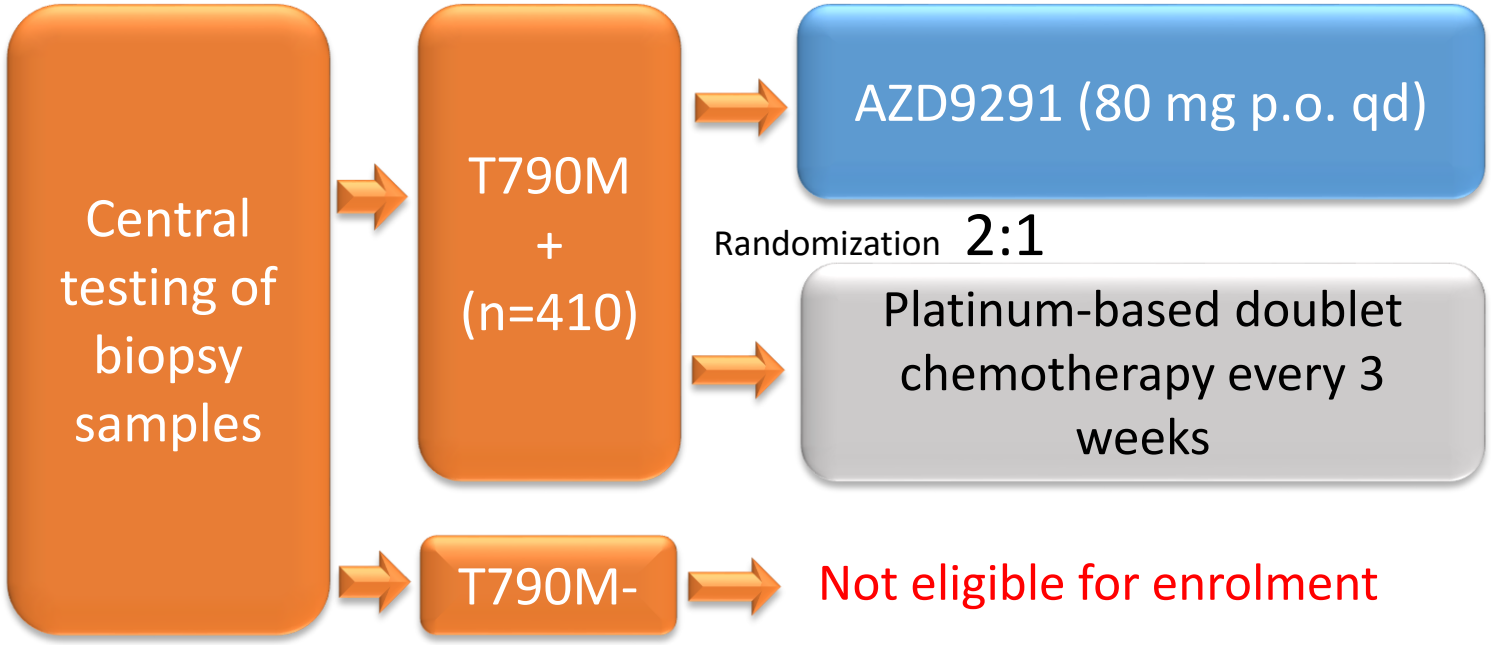
9.7 (95% CI 8.3, NC)

maturity: 39%, full analysis set

Goss et al ESMO 2015

AURA 3 Study Design

A Phase III, open-label, randomised study to assess the safety and efficacy of AZD9291 vs platinum-based doublet chemotherapy in second-line treatment of patients with advanced or metastatic NSCLC who have progressed following treatment with an EGFR-TKI and whose tumours are EGFRm+ and T790M+



Primary end point: PFS

Secondary end points: ORR, DoR, DCR
OS
HRQoL
PK
Safety and tolerability

Clinicaltrial.gov NCT02151981

Enrollment closed

AZD9291 activity in patients with EGFR-mut advanced NSCLC and BRAIN METASTASES: data from Phase II studies

We report exploratory and investigatory results relating to brain metastases of patients enrolled in the AURA extension Phase II component and the AURA 2 Phase II study

Results

Demographics

- As of 1 May 2015, 411 patients were enrolled; 201 in AURA extension, and 210 in AURA2.
- 161 (39%) had documented history of brain metastases at entry across both trials, assessed by medical history (Table 1).
- 50% (206/411) of patients submitted baseline brain scans for BICR.
  - Over half (56%, 90/161) of the patients with history of brain metastases had brain metastases assessed by BICR for response as RECIST NTLs.
- Brain lesions were only assessed as NTLs or NLs by RECIST 1.1.
- At baseline, a higher proportion of ≥third-line patients had brain metastases compared with second-line patients (44% vs 28%).

Ahn et al ESMO 2015

Table 3. RECIST progression events (BICR) by medical history of brain metastases

	Patients with brain metastases (n=161)	Patients without brain metastases (n=250)
RECIST progression	68 (42.2%)	74 (29.6%)
RECIST progression in the brain/CNS	23 (14.3%)	3 (1.2%)
Progression due to NTLs in brain/CNS	13 (8.1%)	0
NLs in the brain/CNS	14 (8.7%)	3 (1.2%)
Death	11 (6.8%)	6 (2.4%)
No progression	82 (50.9%)	170 (68.0%)

BICR, blinded independent central review; CNS, central nervous system; NL, new lesion; NTL, non-target lesion; RECIST, Response Evaluation Criteria In Solid Tumors

- 35% of all patients (142/411) had a RECIST progression event at data cut-off (1 May 2015).
- 18% of these patients (26/142) had progression in the brain: 23 with, and three without history of brain metastases (Table 3).
- More than half (51%, 82/161) of the patients with medical history of brain metastases had not progressed at the time of data cut-off.
- Three patients without brain metastases at baseline experienced RECIST progression due to progression of a new brain lesion.

Ahn et al ESMO 2015

Table 4. Progression-free survival (BICR) by medical history of brain metastases

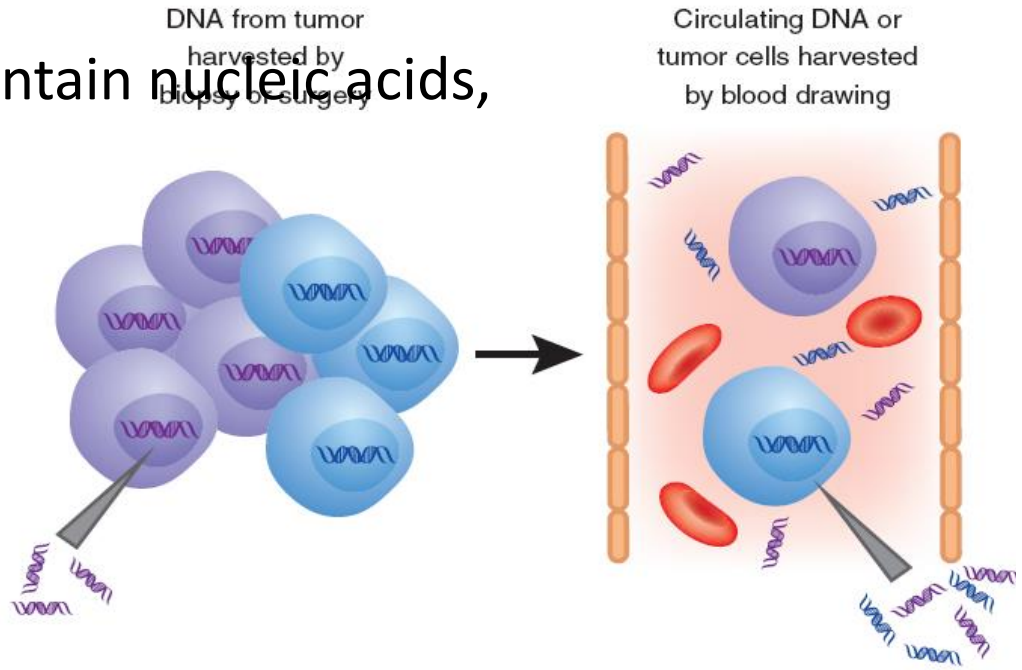
	Patients with brain metastases (n=161)	Patients without brain metastases (n=250)
Total number of events	79	80
Progression-free survival, months		
Median (95% CI)	8.0 (6.9, 8.5)	9.7 (9.7, NC)
Percentage remaining progression free		
3 months (95% CI)	78.5 (71.2, 84.1)	86.2 (81.3, 90.0)
6 months (95% CI)	63.4 (55.3, 70.4)	75.5 (69.7, 80.7)
9 months (95% CI)	36.5 (25.5, 47.5)	61.7 (53.9, 68.5)

BICR, blinded independent central review; CI, confidence interval; NC, not calculated; PFS, progression-free survival
Maturity of PFS data in the full analysis set is 39%; median follow-up for PFS was 6.8 months

Ahn et al ESMO 2015

The potential and “hazards” of liquid biopsies

- ✓ Liquid biopsy comprises a set of blood-based analyses to assess tumor-specific genetic alterations, therapy response, and resistance development.
- ✓ **cfDNA** consists of small fragments of nucleic acids that are not associated with cells or cell fragments.
- ✓ **CTCs** represent intact, viable tumor cells that can be purified from blood.
- ✓ **Exosomes** are extracellular vesicles that contain nucleic acids, proteins, and metabolites.



The potential and "hazards" of liquid biopsies

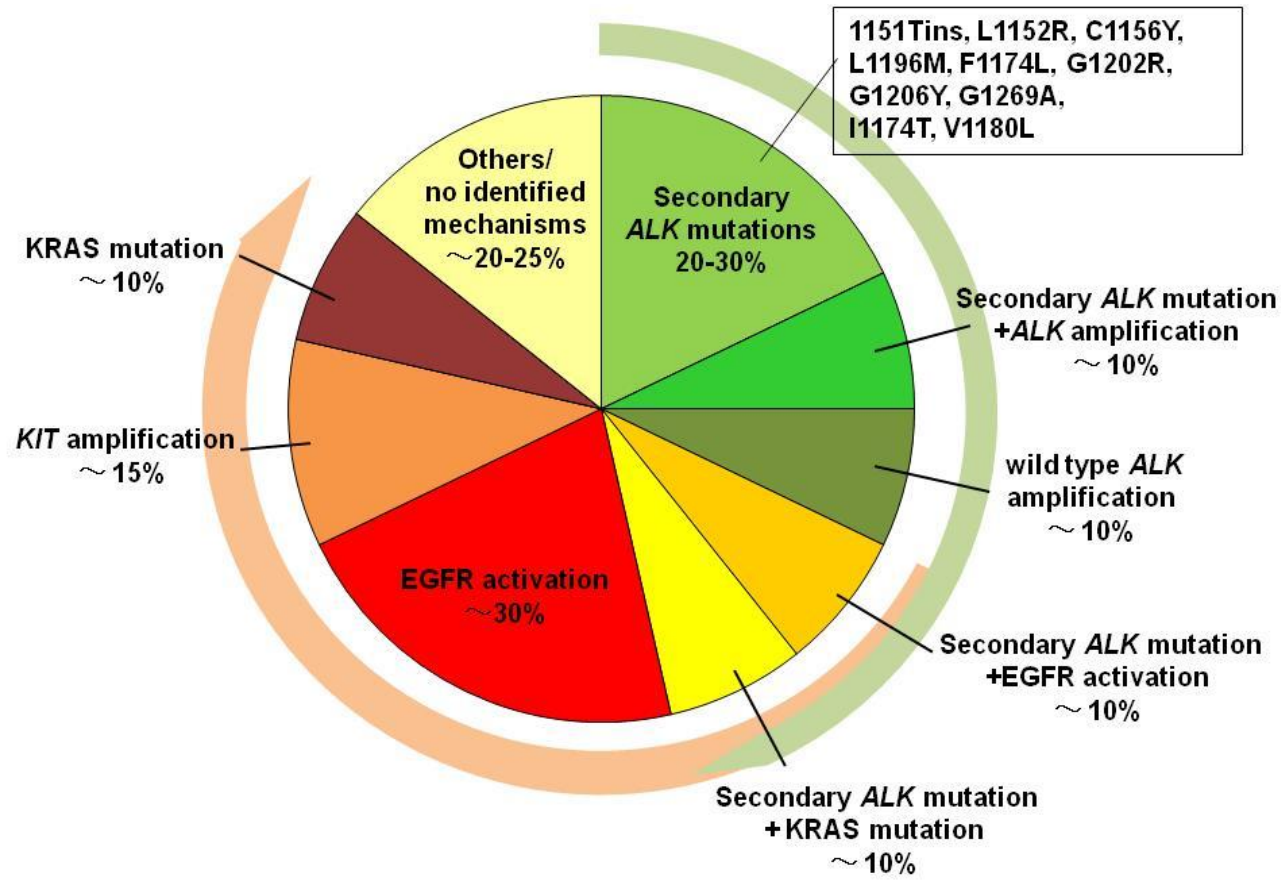
- ✓ **Avoid the need of re-biopsy.**
- ✓ **Monitoring and early identification of emerging changes leading to acquired resistances.**
- ✓ **A very sensitive genotyping assay such as ddPCR can detect EGFR sensitizing and resistance mutations**
- ✓ **Prediction of resistance several weeks (4–14) before radiologic progression**

…..Is liquid biopsy ready for the clinic?

-ALK TKI Resistance

Finding the Cause of Resistance

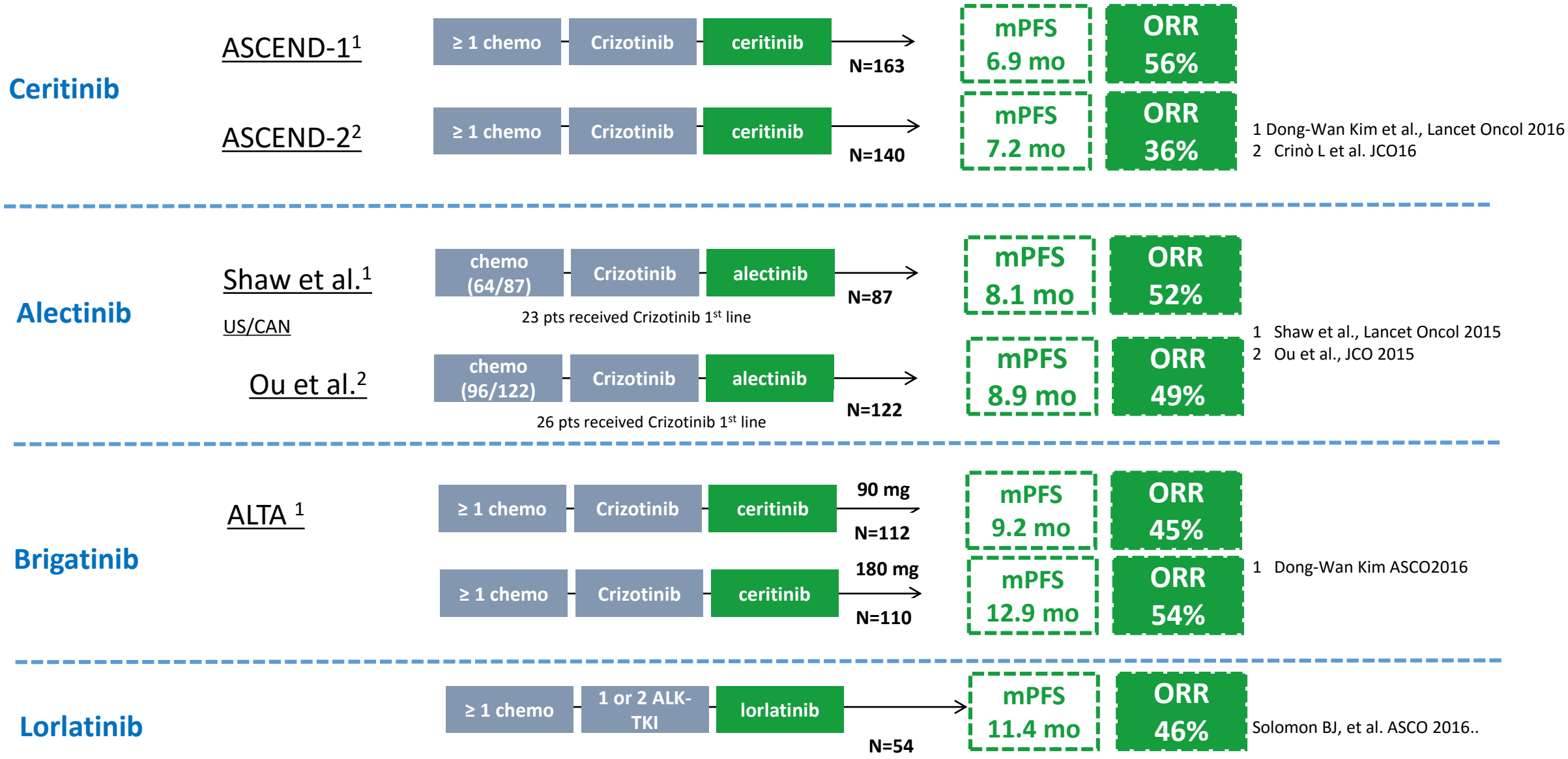
- **Re-biopsy**



ALK rearranged

Junko Tanizaki, WCLC 2015

Next generation ALK-TKIs after Crizotinib: phase I and II clinical trials



Suggested criteria for considering local Ablative therapy of oligoprogressive disease: EGFR mut+ and ALK+

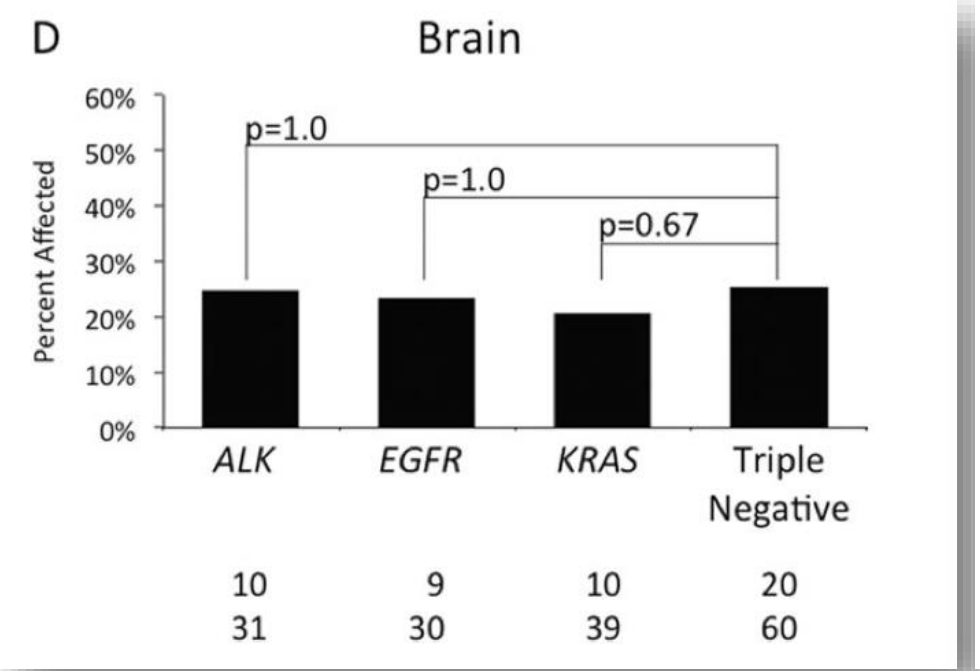
1. *EGFR*-mutant or Alk+ metastatic NSCLC
2. TKI is well tolerated
3. Oligoprogressive disease on TKI therapy, defined as:
CNS progression without leptomeningeal disease amenable to WBRT, SRS, or surgical resection.
4. Progression in ≤ 4 extra-CNS sites amenable to SBRT, XRT, or surgical resection.

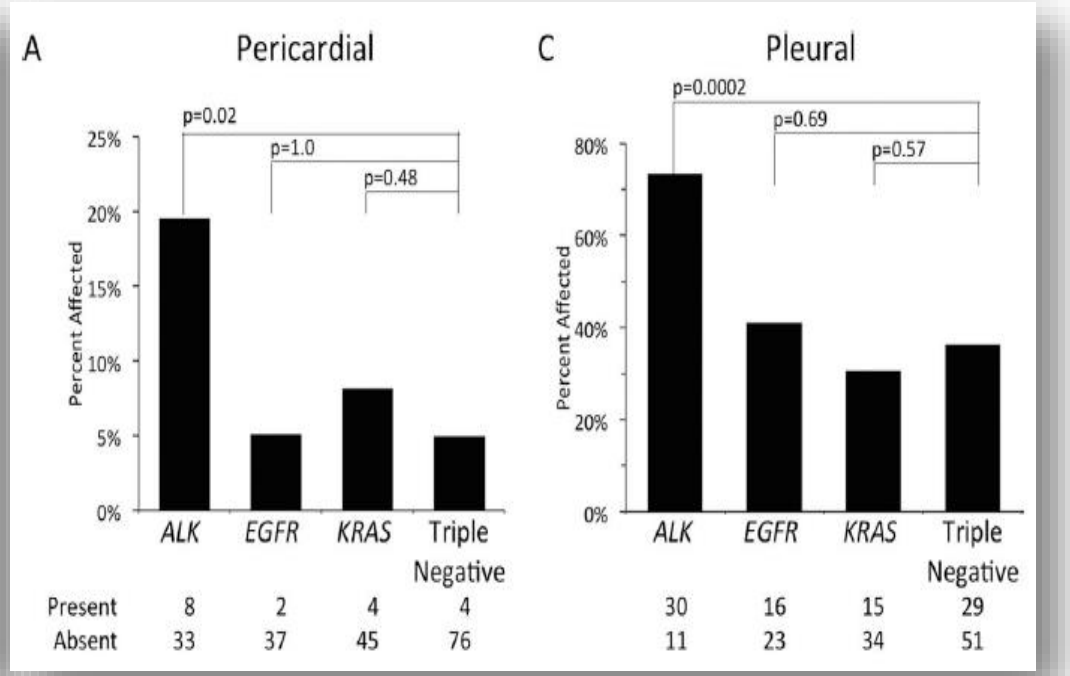
... today probably we would add

5. whenever a next generation EGFR-TKI or ALK-TKI is not «easily» available for the patient
6) Are this concepts appliable to second generation ALK-TKIs???....probably yes

Weickhardt et al , JTO 2013

NSCLC ALK + and Brain mts: Incidence compared with other genotypes?





Doebele et al, Cancer 2012;118(18):4502-11.

Crizotinib and Brain mets: more certainties than doubts!

- Crizotinib, has a very poor penetration rate to the CSF of 0.06-0.26% [1,2]
- However, crizotinib has a well documented clinical activity against BMs (retrospective analysis of PROFILE 1005 and PROFILE 1007) [3] as well as data from PROFILE 1014 [4]
- ***"The CNS is a sanctuary site in ALK positive NSCLC on crizotinib"*** being the first site of progression in 46% of cases, 85% of which lacked coincident systemic progression[1]
- **More frequent intramedullary spinal cord metastasis and leptomeningeal carcinomatosis[2]**
- **High-dose crizotinib for brain mts refractory to standard-dose (500 mg single adm[3]; 600 mg/day[4]; 1000 mg/day[5])**

[1]Costa, et al. JCO 2011; [2]Metro et al, JTO 2015; [3]Costa et al, JCO2015; [4]Solomon et al, NEJM 2014

Crizotinib and BMs from *ALK*+ NSCLC

	Untreated brain metastases (n = 109)			Treated brain metastases (n = 166)		
	# pts	outcome	95% CI	# pts	outcome	95% CI
IC ORR, % (target lesions)	22	18%	5-40	18	33%	13-59
IC DCR at 12 weeks	109	56%	46-66	166	62%	54-70

Intra-cranial failure accounts for appr. 70% of PDs in patients with brain metastases at baseline and 20% of PDs in patients without brain metastases at baseline

Costa, et al. J Clin Oncol 2015

2nd generation ALK-TKIs: active against most but not all secondary mutations

Crizotinib	Ceritinib	AP26113	Alectinib
1151Tins			
L1152R			
C1156Y			
F1174V/L	F1174V/C		
L1196M			
G1202R	G1202R	G1202R	G1202R
D1203N		D1203N	
S1206Y			
G1269A			
			I1171T/N/S
			V1180L

Presented By Alex Adjei at 2015 ASCO Annual Meeting — Alice Shaw

ALK secondary mutations
(L1196M)
(G1269A)
(S1206Y)
(I1171T)

Response expected to 2nd generation ALK TKI
Ceritinib
Alectinib (except I1171T)

ALK secondary mutations
(G1202R)
(F1174C)
(C1156Y)
(L1152R)
(1151Tins)

Resistance to Ceritinib or Alectinib

Lorlatinib (PF-06463922) is a potent and selective3rd generation, CNS penetrant ALK/ROS1 TKI active against all Known ALK and ROS1 Resistance Mutations

Zou HY, et al. *Proc Natl Acad Sci U S A* 2015;112:3493

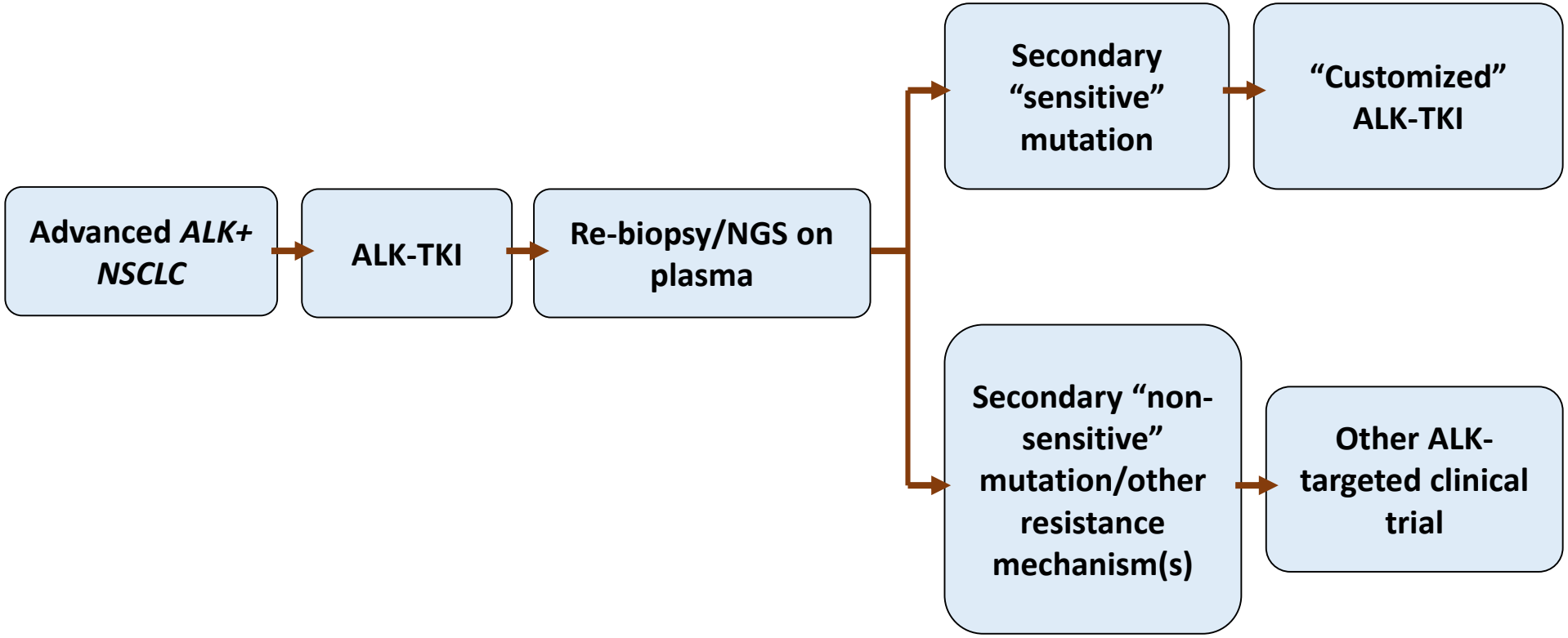
ALK Mutations With Reported Clinical Resistance to ALK Inhibitors

ALK Version	Crizotinib	Ceritinib	Alectinib	Brigatinib
Wild-type				
T1151TIns	X			
L1152R	X	X		
C1156Y	X			
I1171N	X		X	
F1174C		X		
F1174L	X			
F1174V	X	X		
L1196M	X			
G1202R	X	X	X	X
D1203N	X			X
S1206F	X			
S1206Y	X			
G1269A	X			

Kim D-W, et al. ASCO 2016. Abstract 9008.

Slide credit: clinicaloptions.com

PD on an ALK-TKI: a possible algorithm for the future?



Modified from Kanaan, et al. Onco Targets Ther 2015