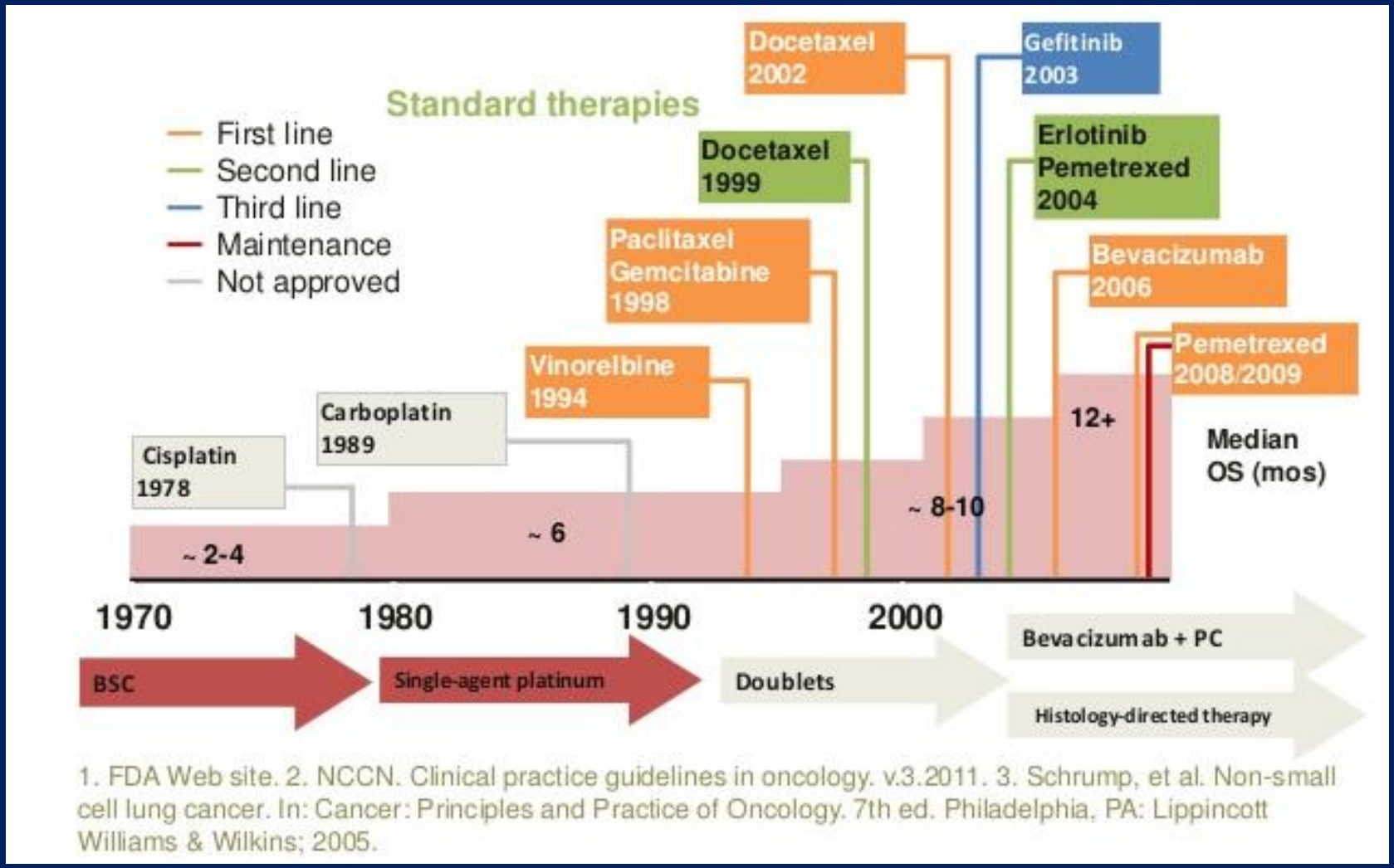
New Drugs in Lung Cancer

In-Jae Oh

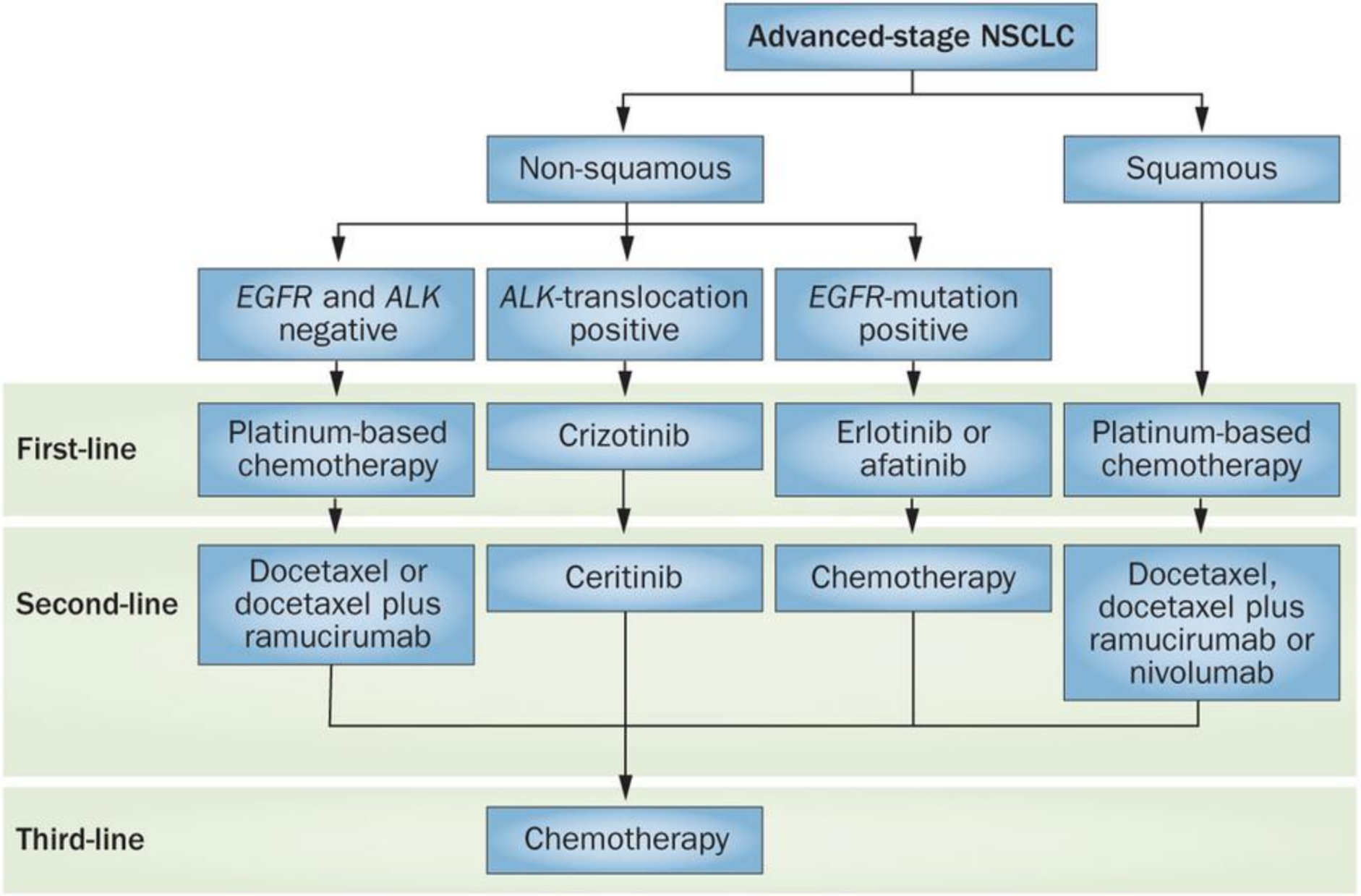
Department of Internal Medicine,

Chonnam National University Hwasun Hospital

History of therapy in advanced NSCLC: FDA approval dates



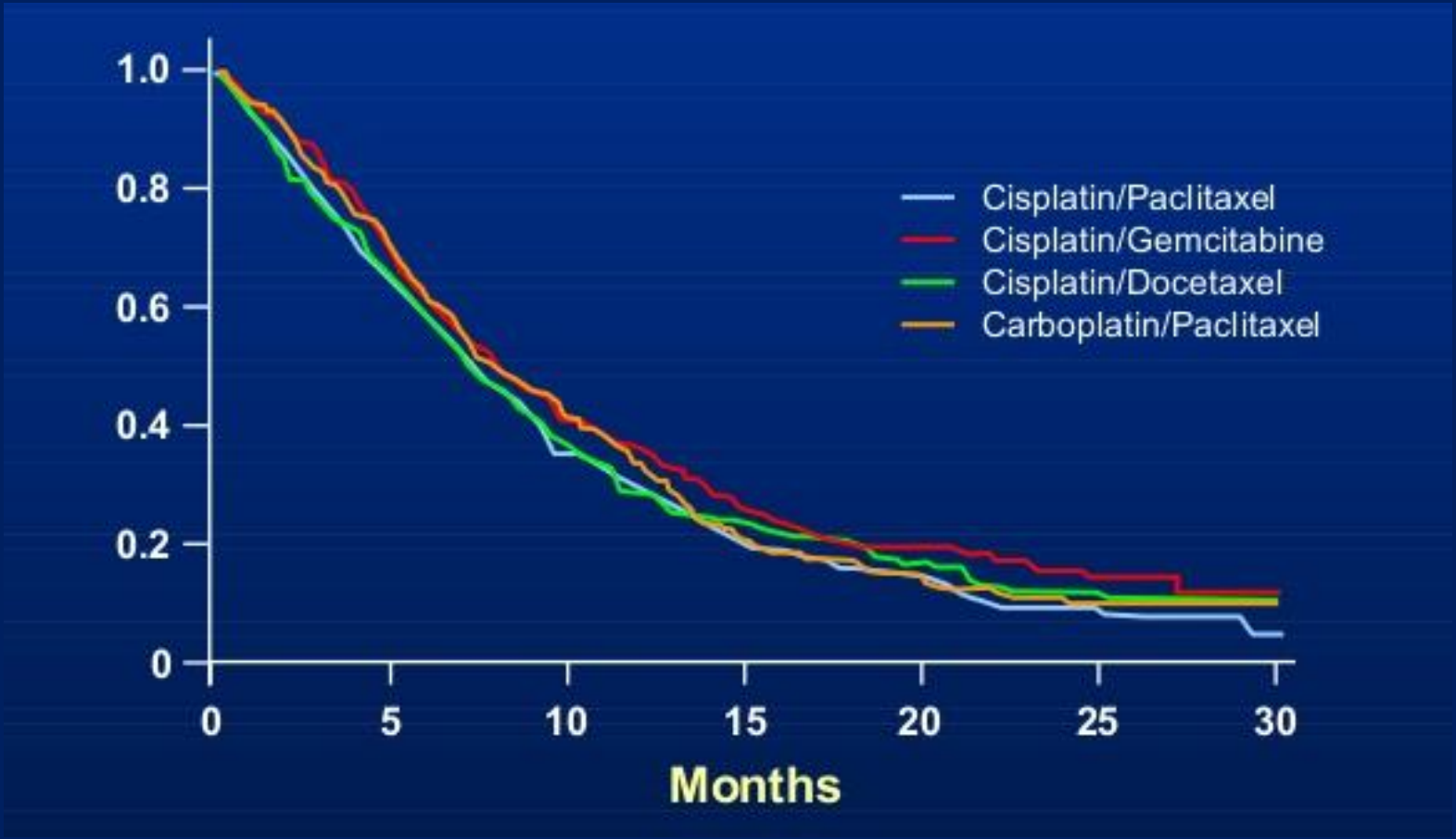
1. FDA Web site. 2. NCCN. Clinical practice guidelines in oncology. v.3.2011. 3. Schrump, et al. Non-small cell lung cancer. In: Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.


Advanced-stage NSCLC
Non-squamous
Squamous
EGFR and ALK negative
ALK-translocation positive
EGFR-mutation positive
First-line
Platinum-based chemotherapy
Crizotinib
Erlotinib or afatinib
Platinum-based chemotherapy
Second-line
Docetaxel or docetaxel plus ramucirumab
Ceritinib
Chemotherapy
Docetaxel, docetaxel plus ramucirumab or nivolumab
Third-line
Chemotherapy

CONTENTS

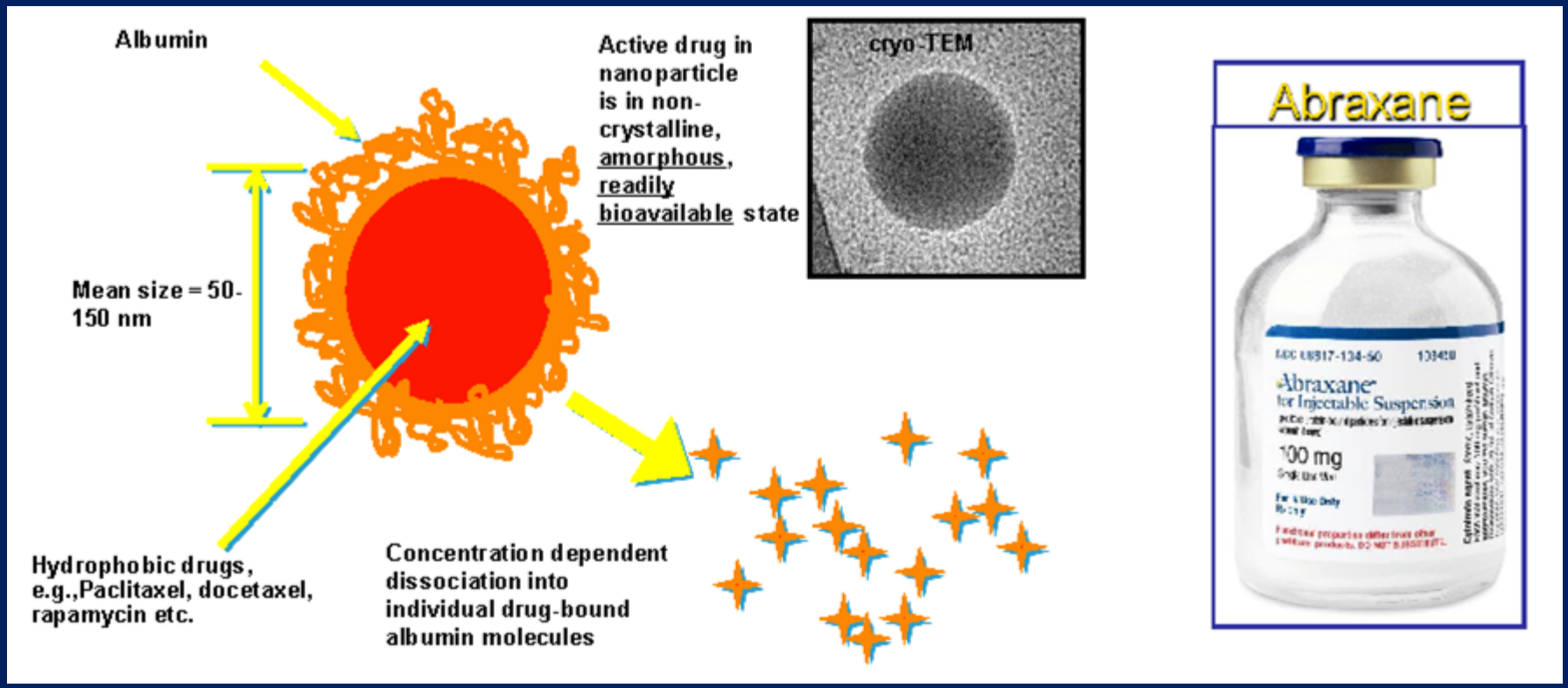
- **Chemotherapy**
  - *nab*-paclitaxel (Abraxane™)
- **Targeted therapy**
  - **EGFR**: Osimertinib (AZD9291, Tagrisso™), HM61713 (BI1482694), Rociletinib (CO-1686)
  - **ALK**: Ceretinib (Zykadia™), Alectinib (Alecensa™)
  - **VEGF**: Ramucirumab (Cyramza™)
- **Immunotherapy**
  - **CTLA4**: Ipilimumab (Yervoy™)
  - **PD1**: Nivolumab (Opdivo™), Pembrolizumab (Keytruda™)

ECOG 1594: All 3rd generation platinum doublets are equivalent



Schiller JH, et al. *N Engl J Med* 2002;346:92-98.

Nanoparticle albumin-bound (nab) platform



*Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication where the standard premedications (ie, dexamethasone, H2-blockers) are contraindicated

NCCN version 4. 2016

Nab-paclitaxel vs Solvent-based Paclitaxel in First-line Chemotherapy

Efficacy Results

Response Rates Based on Independent Radiologic Assessment

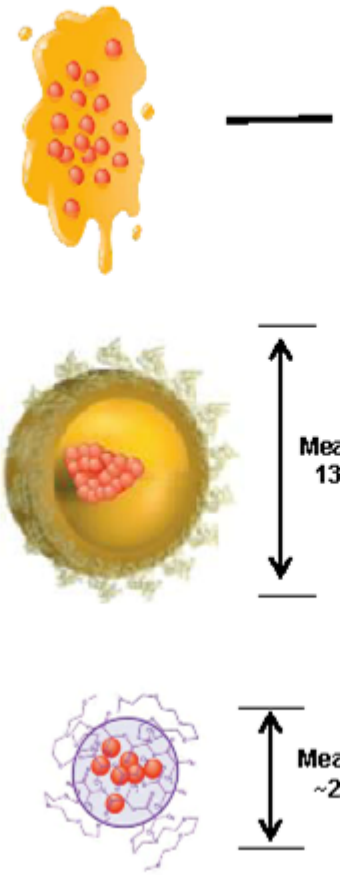
Response Rates	*nab*-PC (%)	Sb-PC (%)
N	**521**	**531**
ORR: ITT	33%	25% (*P* = .005)
ORR: squamous	**41%**	**24%** (*P* < .001)
ORR: nonsquamous	26%	25% (*P* = .808)

Median OS (*nab*-PC vs Sb-PC) = 12.1 vs 11.2 mo, HR 0.922, *P* = .271
Median OS in SCC subgroup = 10.7 vs 9.5 mo, HR 0.890, *P* = .310

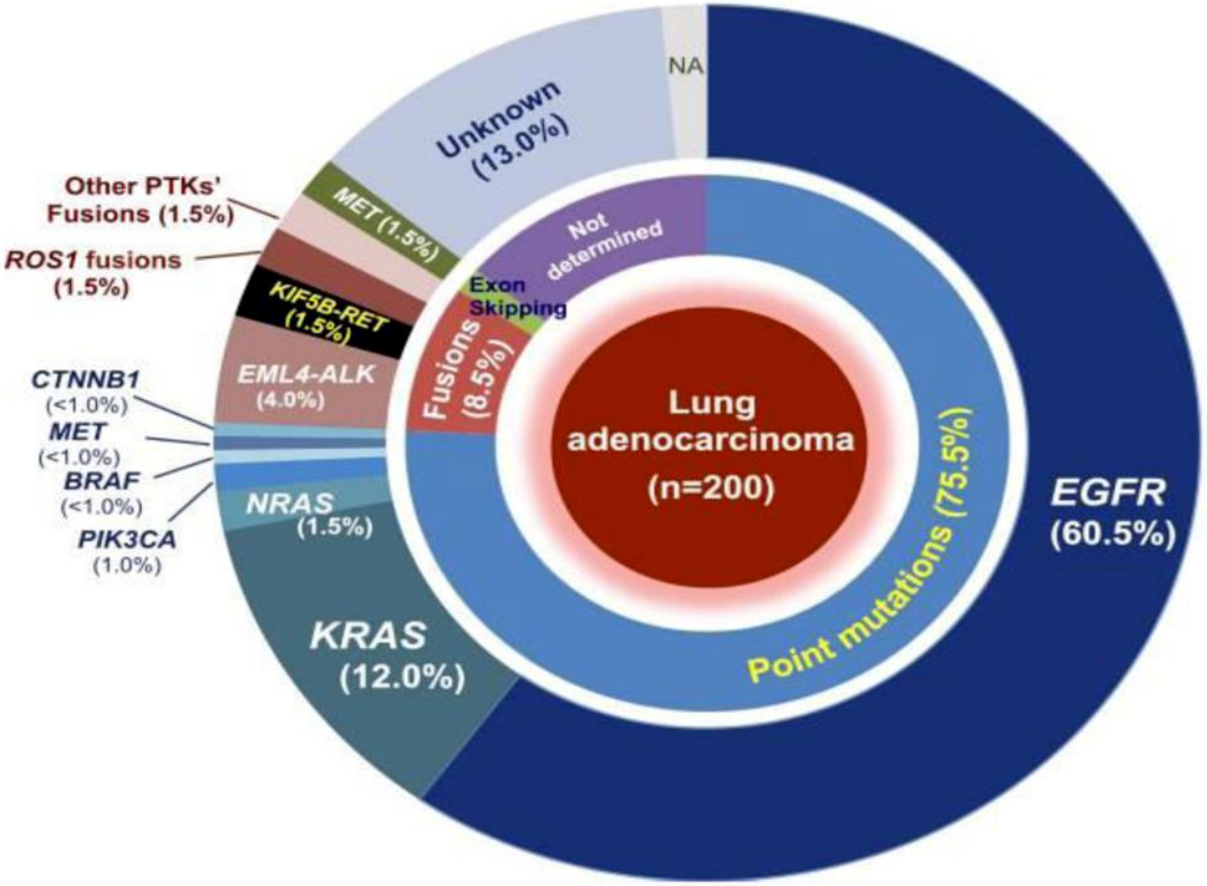
Socinski MA, et al. *J Clin Oncol.* 2012;30:2055-2062.[10]

Next generation paclitaxel therapy

Generation		Formulation	Maximum Tolerated Dose
1st	Taxol® paclitaxel	**Cremophor EL** excipient: Polyoxyethylated castor oil → Hypersensitivity	**175 mg/m²**
		+ 48% dose increase	
2nd	***Abraxane® Albumin-bound*** **paclitaxel***	**Biological** polymer: Donor-derived human serum albumin (HSA) → Virus contamination, Storage issues, Reconstitution issues	**260 mg/m²**
		+ 15-30% dose increase	
3rd	**Genexol-PM®** paclitaxel polymeric micelle	**Chemical** polymer: Poly-lactide and polyethylene glycol diblock copolymer → Not biological, Easy to handle and reconstitute	**>300 mg/m²** (up to 435 mg/m²)



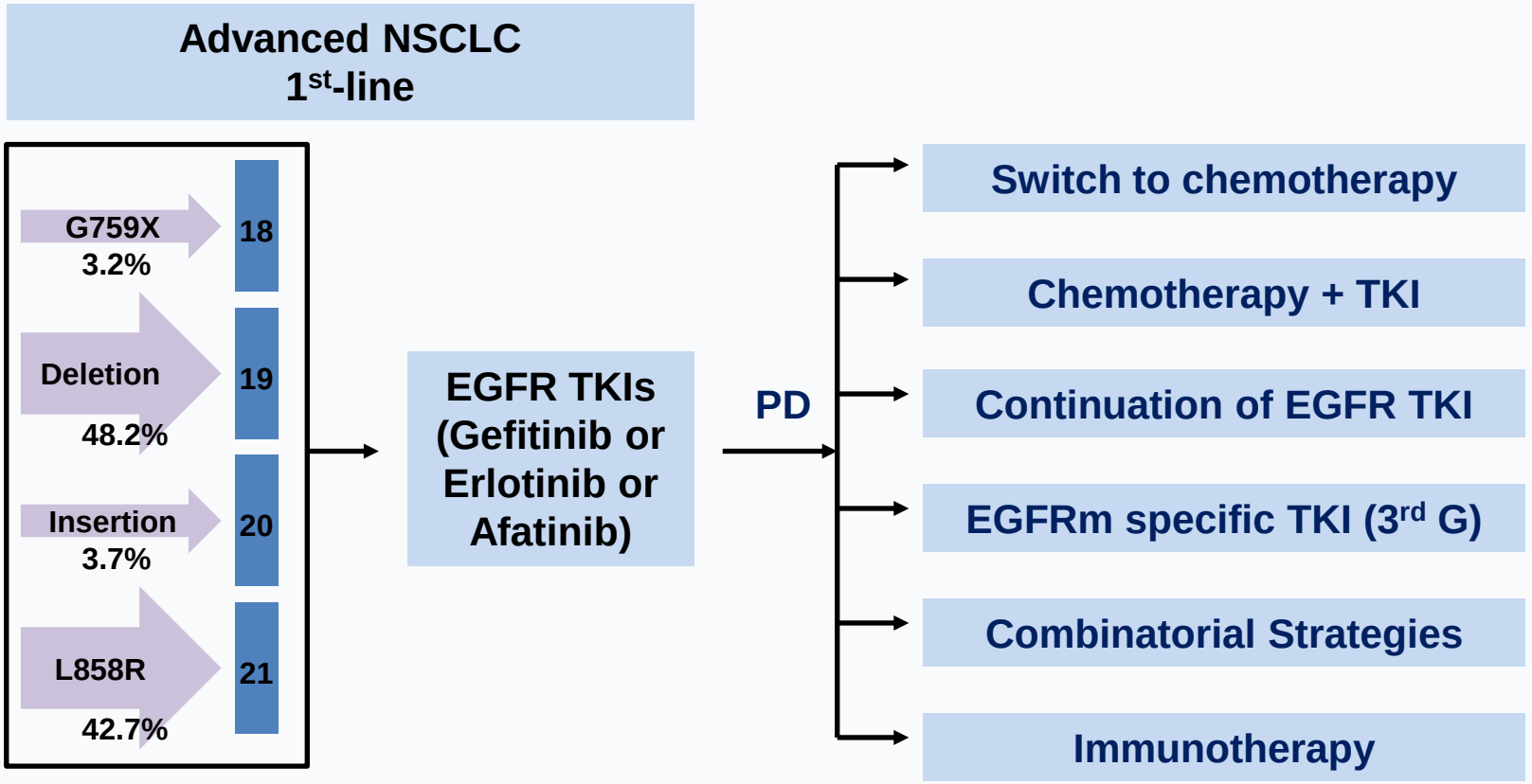
Mutation/Fusion in Korean Adenocarcinoma



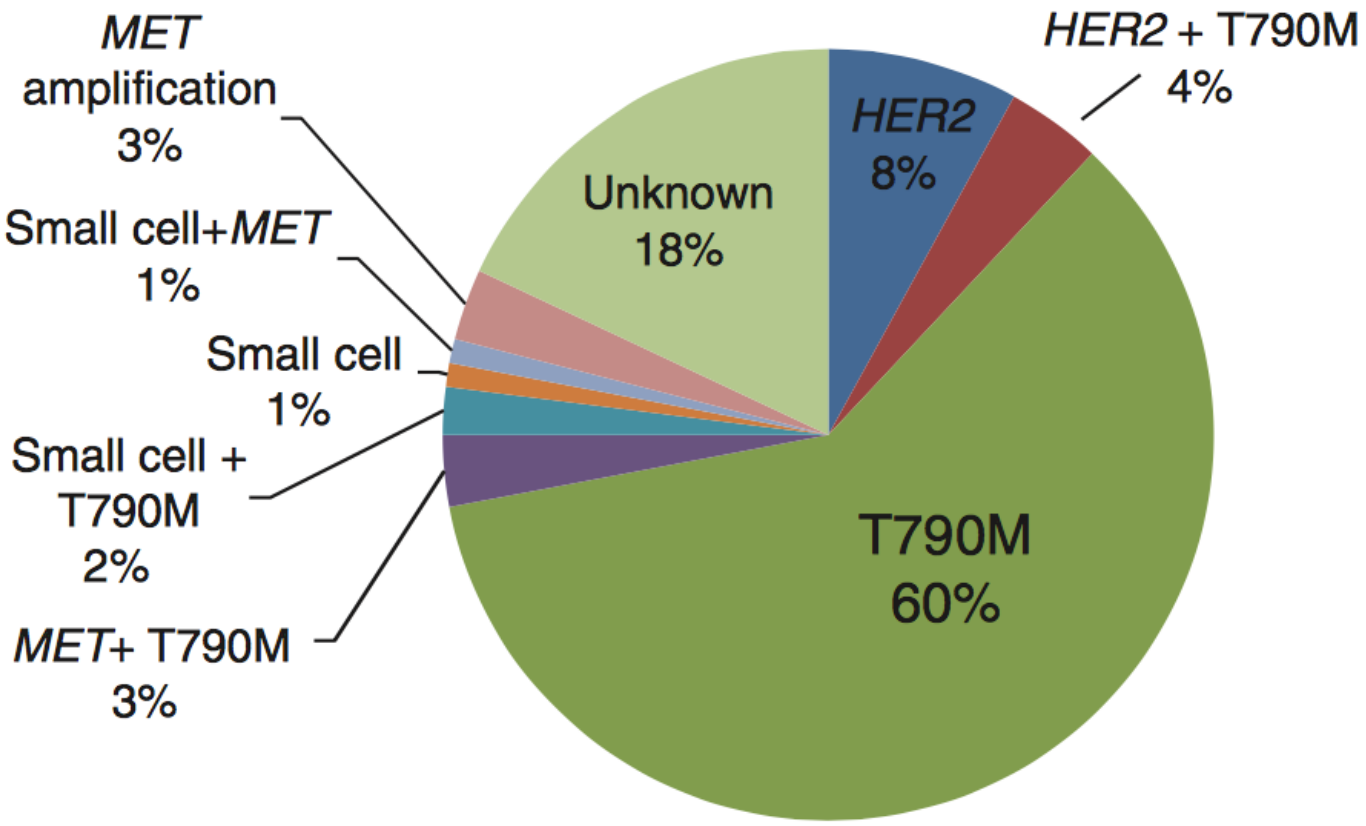
Female: 109 (54.5%)
Never-smoker: 116 (58.0%)

Seo, et al. Genom Res 2012;22:2109-2119

What would be the Mx option at 1st PD?



Acquired or Adaptive Resistance to EGFR TKI

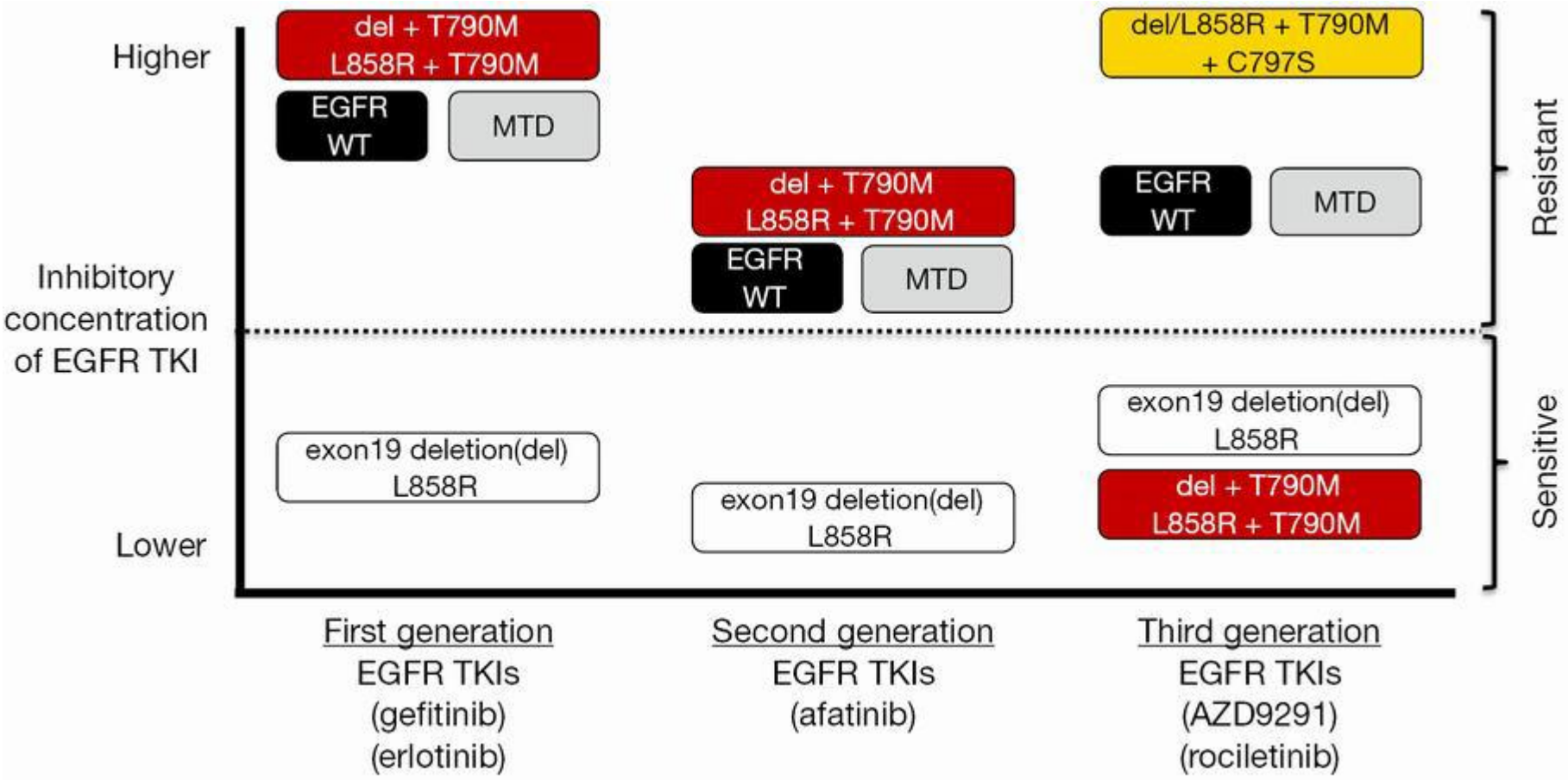


Clin Canc Res 2013;19(8);2240-7

3rd-Generation (Mutant Specific) EGFR TKIs

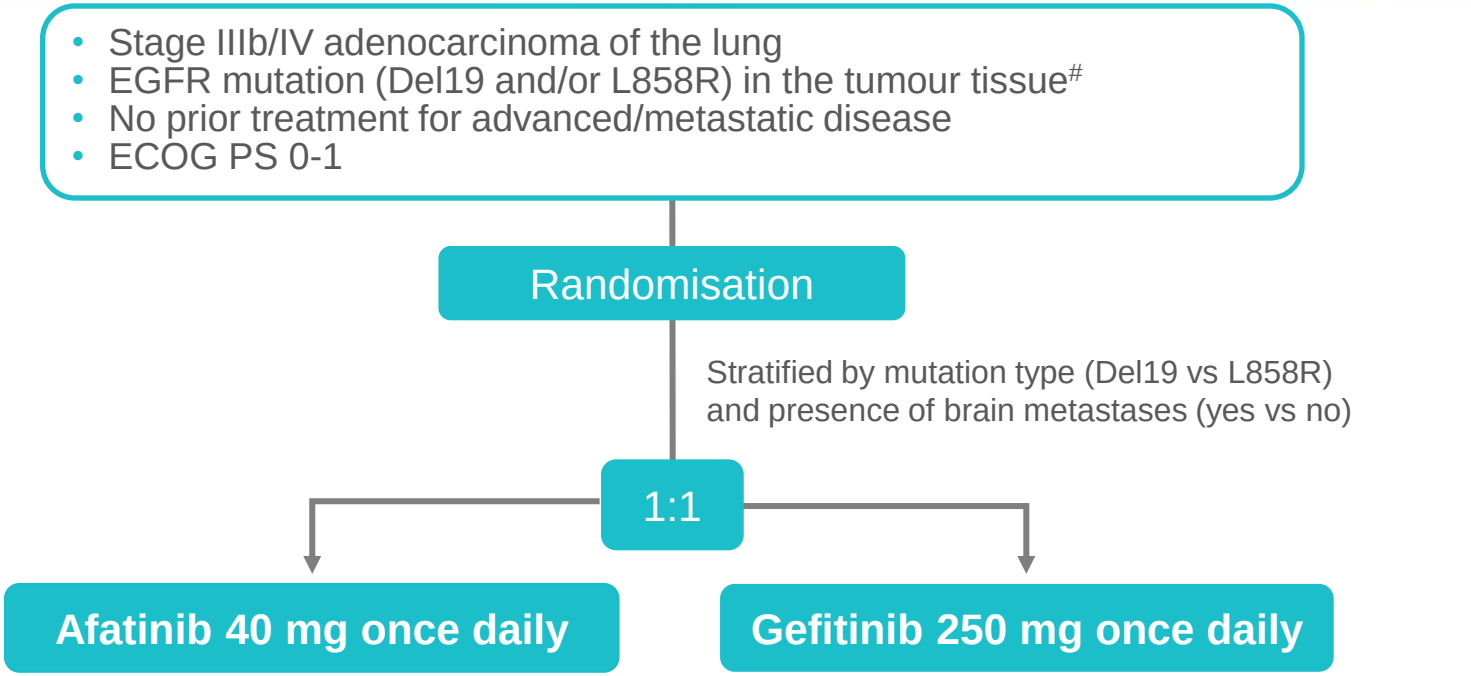
Drug	Target	Reversibility	IC50 (nM)			Company
			EFGR WT	EGFR Mut	EGFR L858R / T790M	
Erlotinib		***Reversible***	***449***	***3.2***	***2253***	
CO-1686	Mutant EGFR	Irreversible	**4275**	7	33	Clovis
AZD9291	Mutant EGFR	Irreversible	**480**	17	15	Astra Zeneca
HM61713	Mutant EGFR	Irreversible	**2225**	9	10	Hanmi

Modified from Thomas Lynch at 2014 ASCO & Christine Lovely at 2015 ASCO Annual Meeting



Transl Lung Cancer Res 2015;4(6):809-815

LUX-Lung 7 - Study Design



Primary endpoints: PFS (independent review)#, **TTF, OS**

Secondary endpoints: ORR, time to and duration of response, duration of disease control, tumour shrinkage, HRQoL, safety

local or central test

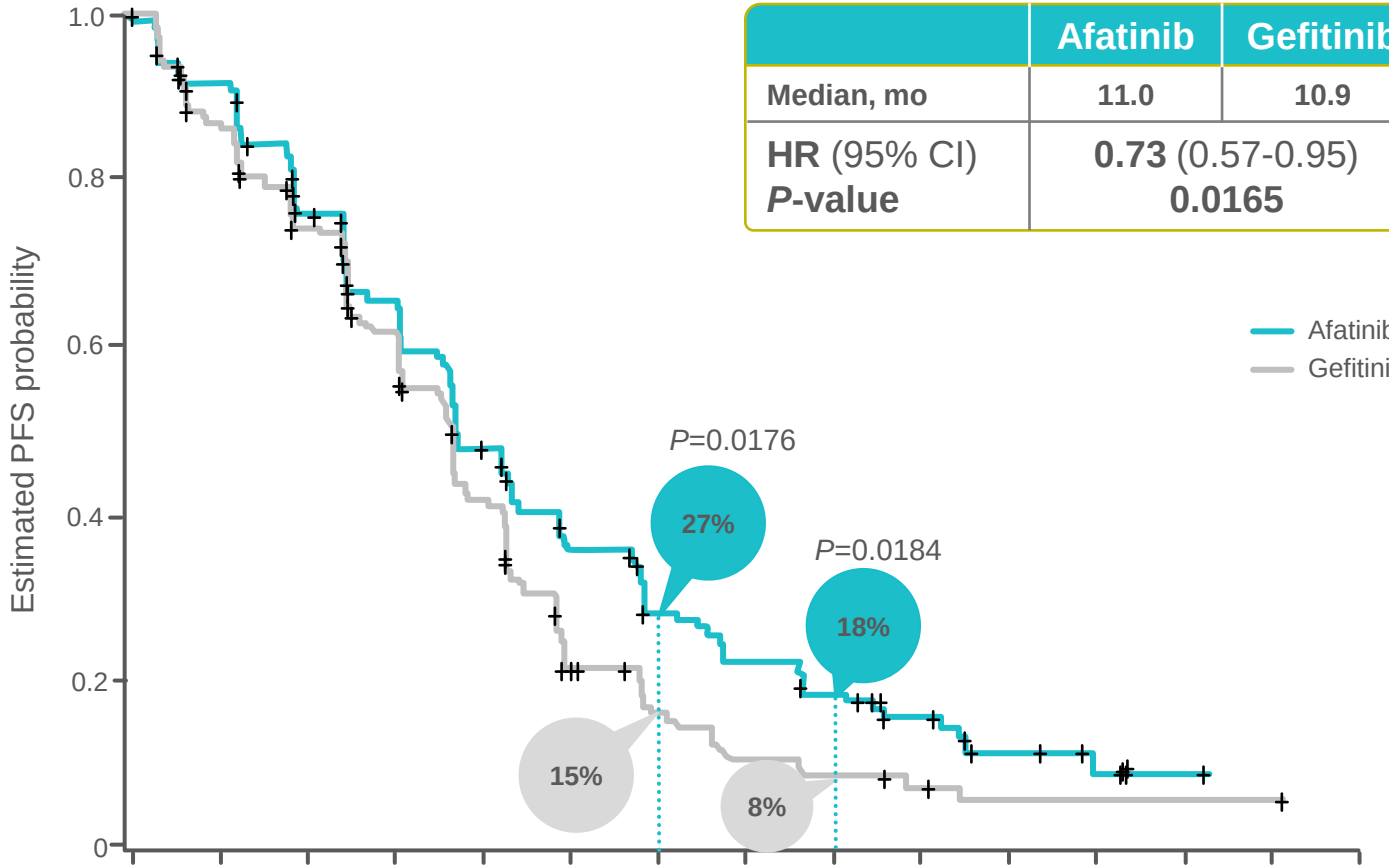
Tumor assessment performed at week 4, 8, every 8 weeks until w64 and every 12 weeks thereafter

Treatment beyond progression allowed if deemed beneficial by investigator.

Park K et al., Ann Oncol, Volume 26, 2015 Supplement 9

PFS by Independent Review

	Afatinib	Gefitinib
Median, mo	11.0	10.9
HR (95% CI) ***P*-value**	**0.73** (0.57-0.95) **0.0165**	



No. at risk:															
Afatinib	160	142	112	94	67	47	34	27	21	13	6	3	1	0	0
Gefitinib	159	132	106	83	52	22	14	9	7	5	3	3	1	1	0

Park K et al., Ann Oncol, Volume 26, 2015 Supplement 9

Clinical Trials of Rociletinib

TIGER-X (Ph 2)

- Single arm – expansion cohorts
- ≥2nd-line mutant EGFR NSCLC, T790M+

TIGER-1 (Ph 2/3)

- Randomized rociletinib vs erlotinib
- 1st-line, treatment-naïve

TIGER-2 (Ph 2)

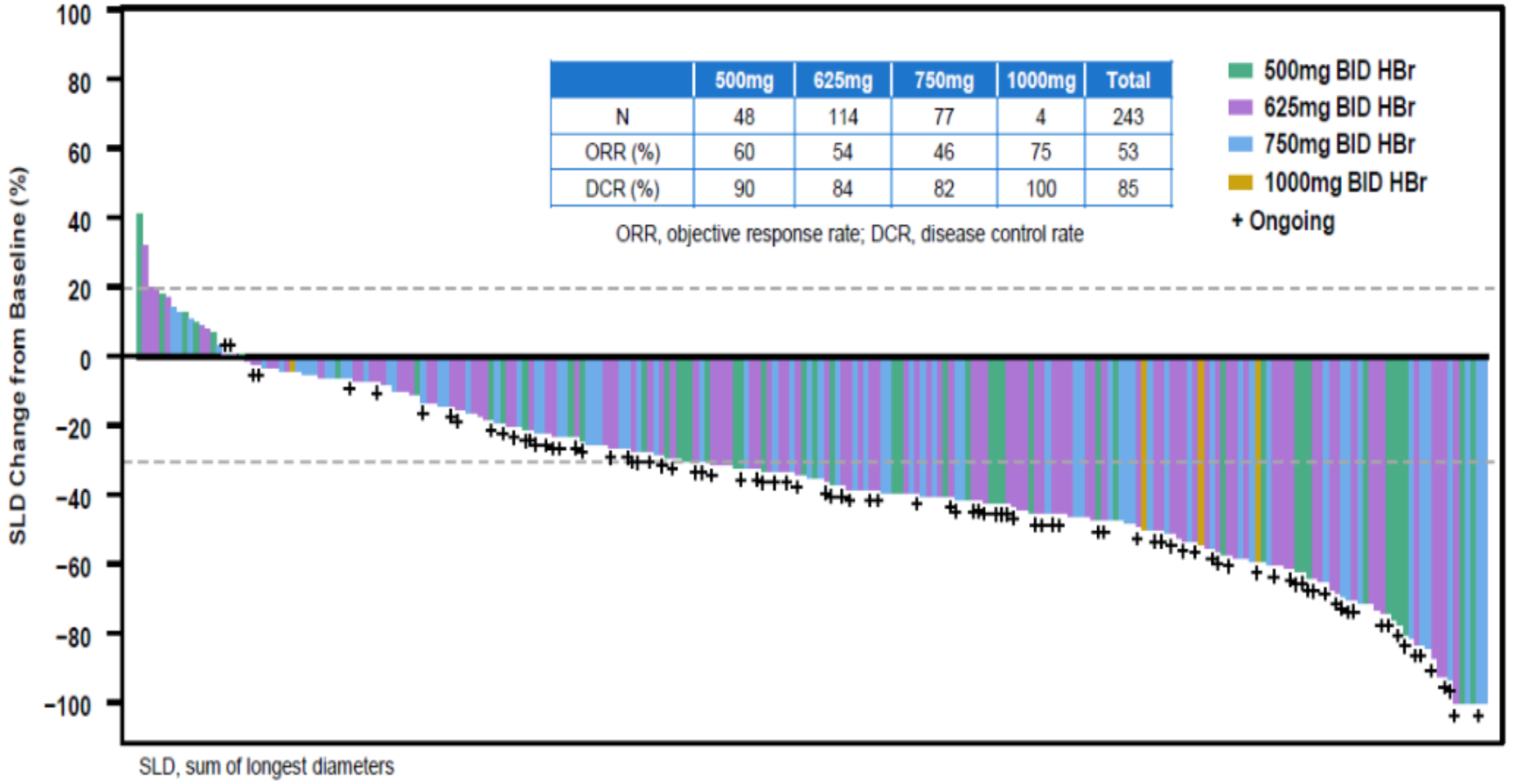
- Single-arm
- 2nd-line mutant EGFR NSCLC, T790M+
- Patients progressing on 1st-line EGFR TKI
- Now adding T790M– cohort

TIGER-3 (Ph 3)

- Randomized rociletinib vs chemotherapy
- >2nd-line mutant EGFR NSCLC, T790M+ and T790M– (sequential analysis)

Soria et al., ENA, 2014

Best Response to Rociletinib (All Doses) in 243 Centrally Confirmed Tissue T790M+ Patients



	500mg	625mg	750mg	1000mg	Total
N	48	114	77	4	243
ORR (%)	60	54	46	75	53
DCR (%)	90	84	82	100	85

ORR, objective response rate; DCR, disease control rate

SLD, sum of longest diameters

Common Treatment-related Adverse Events

Treatment-related adverse events (all grades) seen in >10% of patients, N(%)

AE	Rociletinib dose			
	500mg BID (N=119)	**625mg BID (N=236)**	**750mg BID (N=95)**	**1000mg BID (N=6)**
Hyperglycemia	42(55)	107(45)	56(39)	4(67)
Diarrhea	39(53)	94(40)	28(30)	4(67)
Nausea	23(19)	79(34)	35(37)	3(50)
Fatigue	15(29)	37(30)	21(27)	2(25)
QTc prolongation	16(15)	53(23)	25(16)	3(50)
Decreased appetite	18(15)	38(16)	24(15)	2(33)
Muscle spasm	17(14)	30(15)	20(21)	2(37)
Vomiting	10(8)	38(16)	13(14)	0(0)
Weight loss	12(10)	21(9)	16(17)	2(37)

Grade ¾ treatment-releated adverse Events seen in >10% of patients, N(%)

AE	Rociletinib dose			
	500mg BID (N=119	625mg BID (N=236)	750mg BID (N=95)	1000mg BID (N=6)
Hypergylcemia	20(17)	54(24)	34(36)	2(33)

- No ILD observed in 500mg BID dose group
  - 7/456 cases overall(15%)
  - Rociletinib continuation possible with steroid cover
  - **No fatal ILD** in program
- No paronychia or stomatitis observed; trivial rash
- Grade 3 QTc prolongation at 500mg BID = 2.5%
- Treatment-related AEs leading to drug discontinuation seen in 2.5% of cases at 500mg BID (4% overall)
- **Hyperglycemia** readily managed with oral agents
  - No contraindication for pre-existing diabetic patients

Oncology & Hematology Review 2015;11(2):122–7

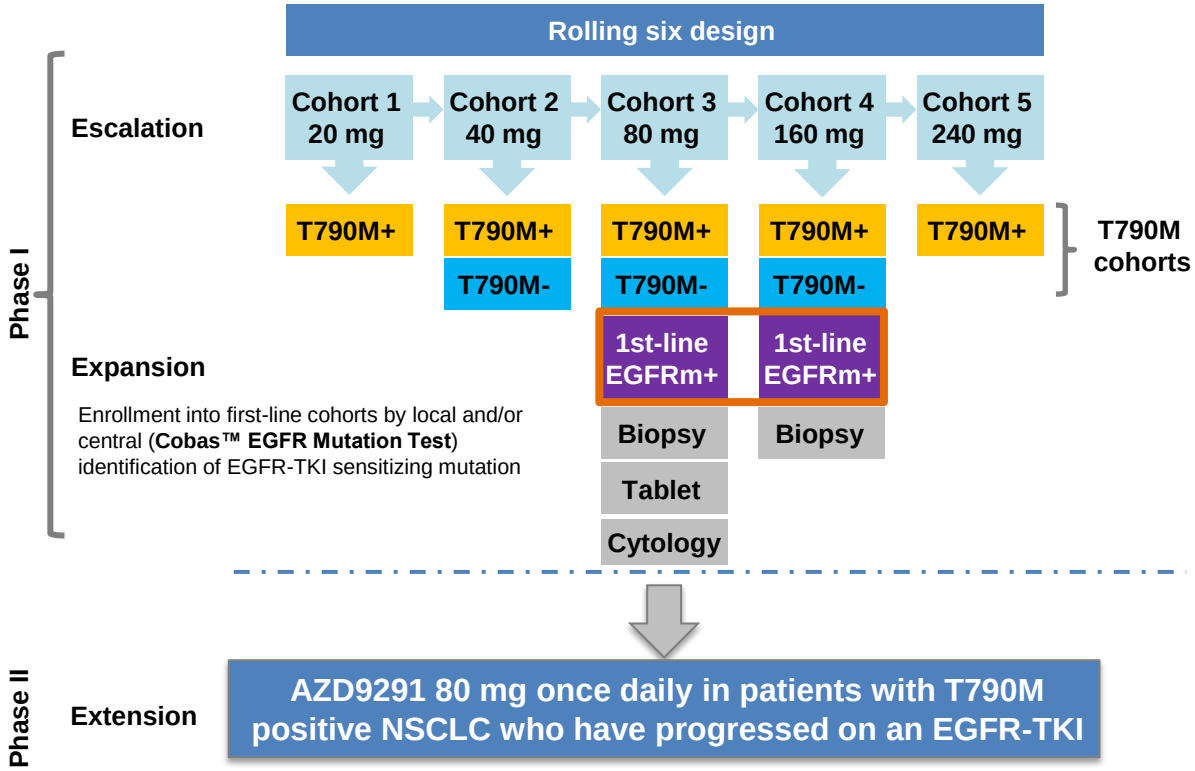
TAGRISSO™ (OSIMERTINIB) (AZD9291) APPROVED BY THE US FDA AS TREATMENT FOR PATIENTS WITH EGFR T790M MUTATION-POSITIVE METASTATIC NON-SMALL CELL LUNG CANCER

One of fastest development programs – from start of clinical trials to approval in just over two and a half years to meet unmet patient need

With objective response rate of 59% and duration of response of 12.4 months, TAGRISSO provides important new option for patients

PR Newswire, (WILMINGTON, Del., November 13, 2015)

AURA Phase I/II global study design



Phase II

Key inclusion criteria:

- Central confirmation of tumor T790M mutation status[b]
- Confirmation of tumor EGFR mutation associated with EGFR-TKI sensitivity (including G719X, exon 19 del, L858R, L861Q)
- Measurable disease at baseline
- WHO performance status 0 or 1
- Acceptable organ function
- Stable asymptomatic brain metastases allowed

Key exclusion criteria:

- Prior history of ILD

Data cut-off: 1 May 2015. [a]Prior therapy for advanced NSCLC not permissible in this cohort; [b]The EGFR T790M mutation status of the patient's tumour was prospectively determined by the designated central laboratory using the cobas™ EGFR Mutation Test (Roche Molecular Systems) using a biopsy sample collected following confirmed disease progression on the most recent treatment regimen. Data from cohorts in grayed out boxes are not included in the analyses reported here. BICR, blinded independent central review; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; RECIST Response Evaluation Criteria In Solid Tumors; WHO PS, World Health Organization Performance Status

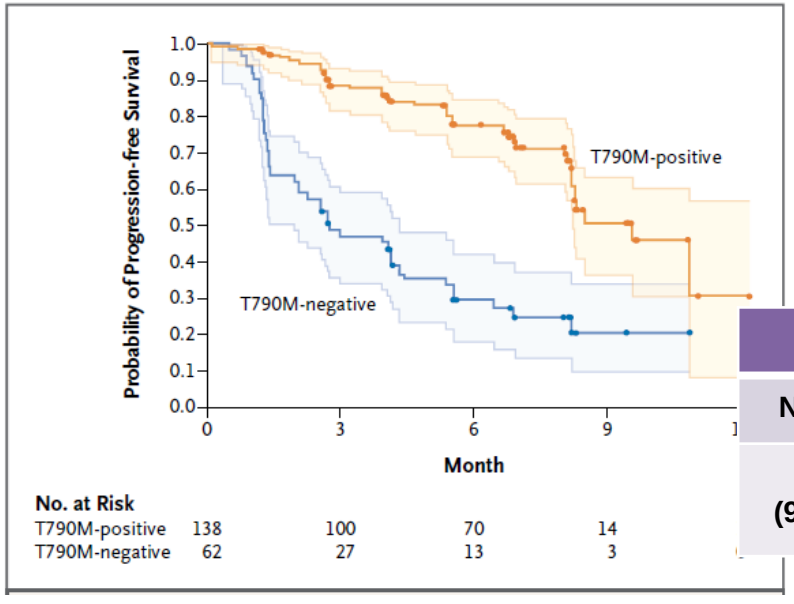
AURA Phase I study

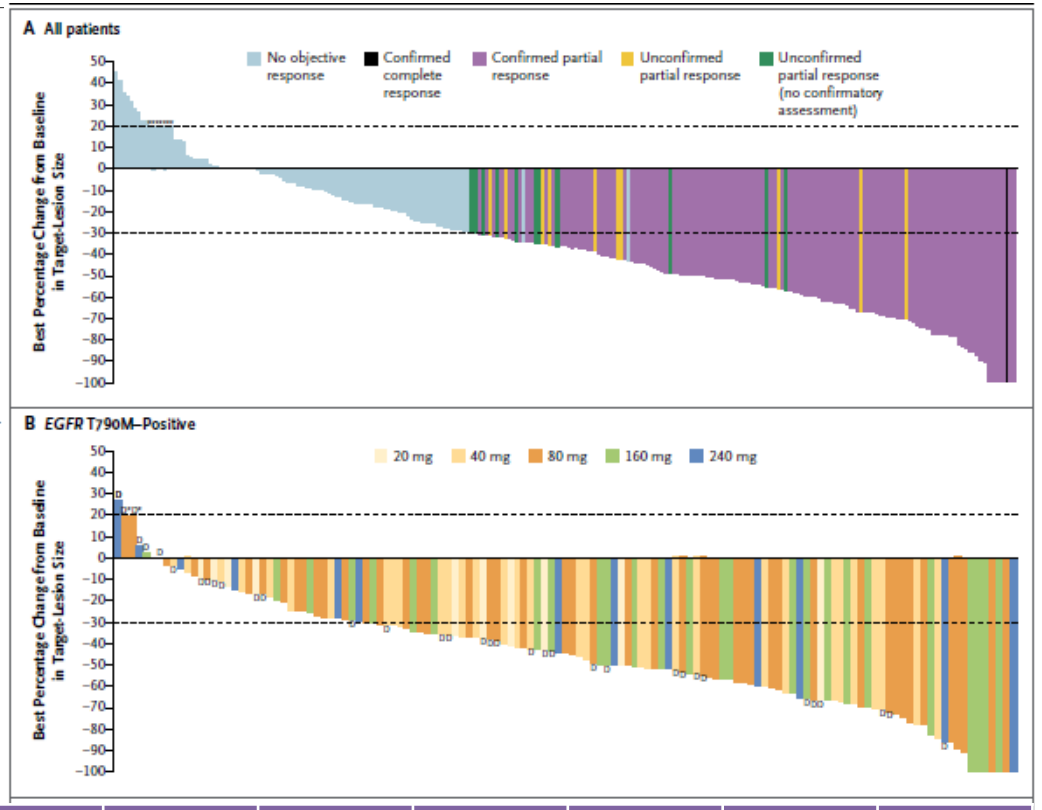
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 30, 2015 VOL. 372 NO. 18

AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., David Planchard, M.D., Ph.D., Yuichiro Ohe, M.D., Suresh S. Ramalingam, M.D., Myung-Ju Ahn, M.D., Ph.D., Sang-We Kim, M.D., Ph.D., Wu-Chou Su, M.D., Leora Horn, M.D., Daniel Haggstrom, M.D., Enriqueta Felip, M.D., Ph.D., Joo-Hang Kim, M.D., Ph.D., Paul Frewer, M.Sc., Mireille Cantarini, M.D., Kathryn H. Brown, Ph.D., Paul A. Dickinson, Ph.D., Serban Ghiorghiu, M.D., and Malcolm Ranson, M.B., Ch.B., Ph.D.



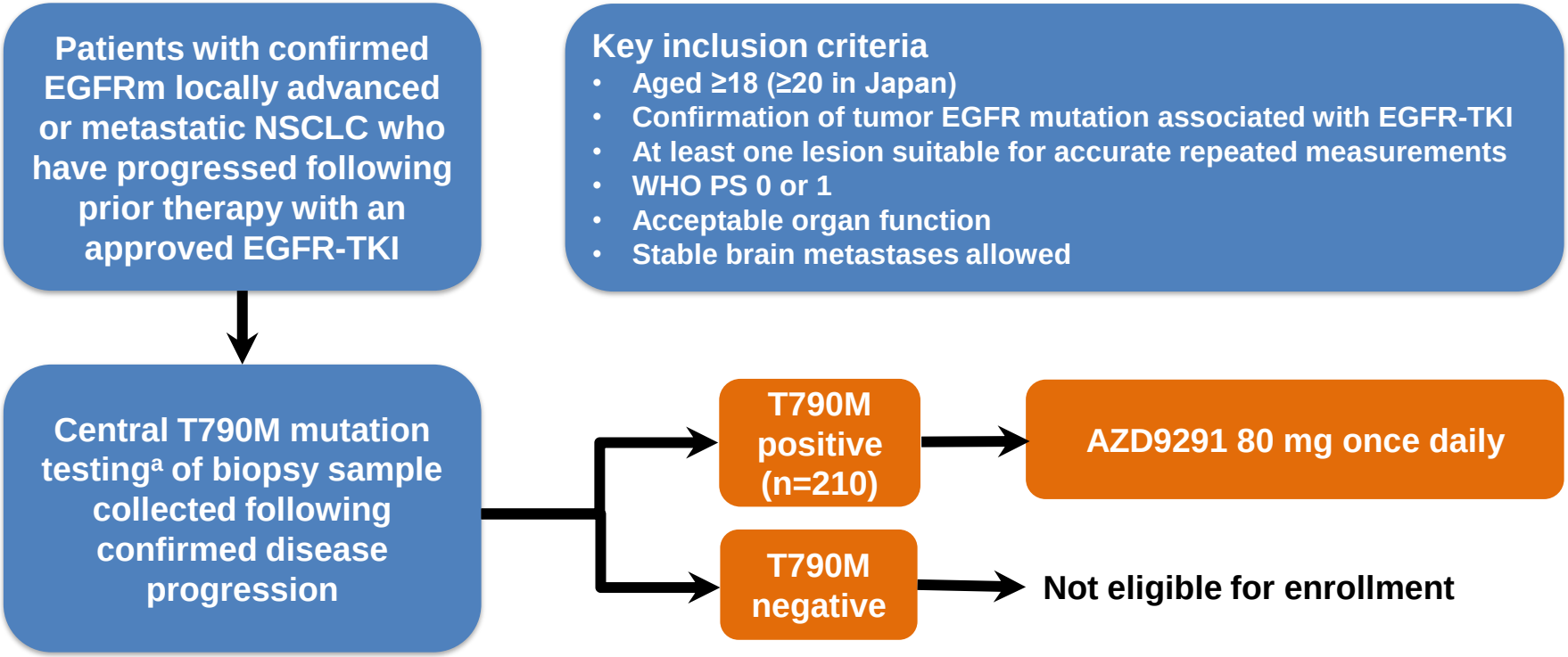


	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

Figure 2. Best Percentage Change in Target-Lesion Size.

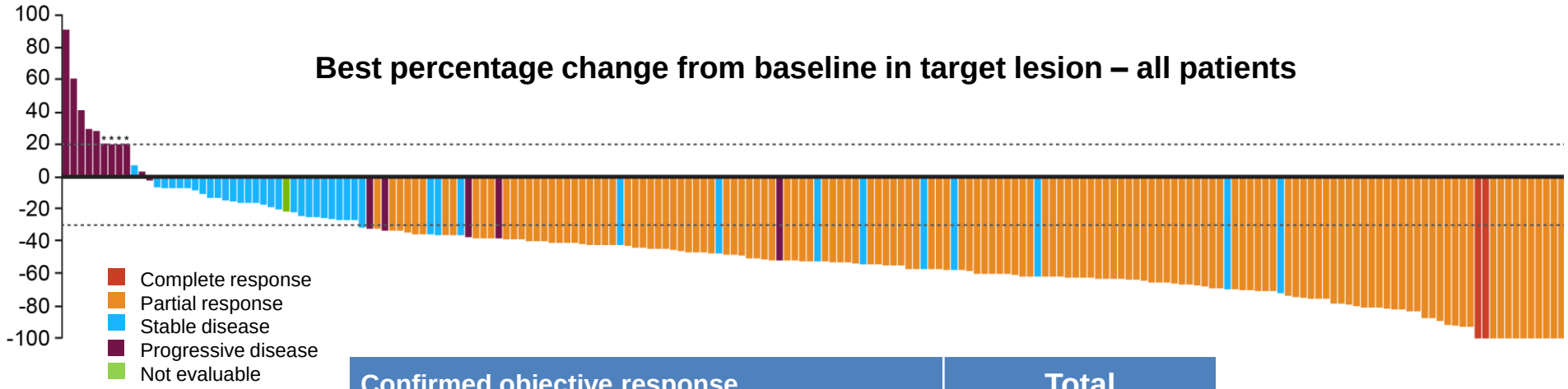
AURA2: Phase II, open-label, single-arm study

Primary objective: to investigate the efficacy of AZD9291 by assessment of ORR (RECIST 1.1 BICR)



[a]The EGFR T790M mutation status of the patient's tumor was prospectively determined by the designated central laboratory using the cobas™ EGFR Mutation Test (Roche Molecular Systems) by biopsy taken after confirmation of disease progression on the most recent treatment regimen. BICR, blinded independent central review; ORR, objective response rate; RECIST Response Evaluation Criteria In Solid Tumors; WHO PS, World Health Organization performance status

Tumor response by independent central review

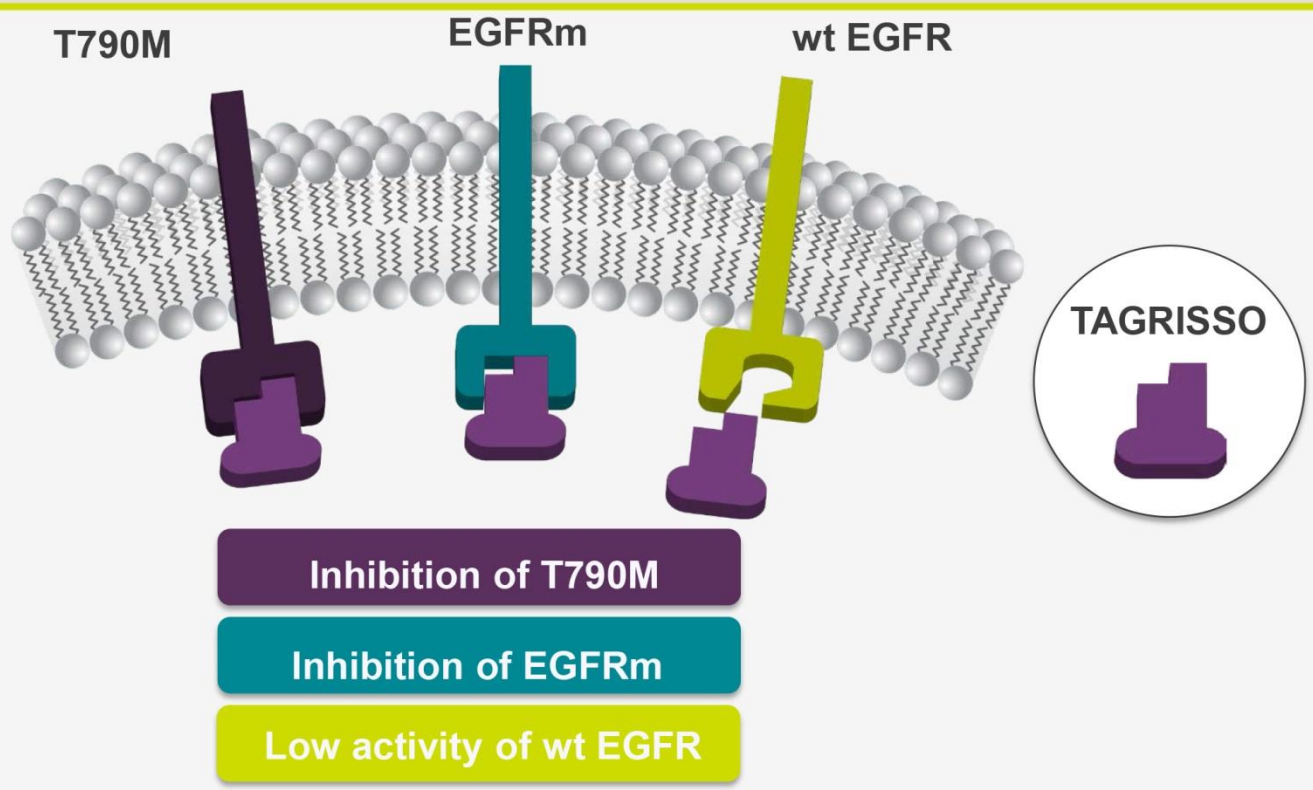


Confirmed objective response	Total
ORR[a] % (95% CI)	71 (64, 77)
Complete response[b], n (%)	2 (1)
Partial response[b], n (%)	139 (70)
Stable disease ≥6 weeks[c], n (%)	41 (21)
Progressive disease, n (%)	15 (8)
DCR, % (95% CI)	92 (87, 95)

NOTE: Investigator assessed ORR was also 71% (95% CI 64, 77)

Data cut-off: 1 May 2015. Population: evaluable for response set (n=199). *Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%; [a]ORR defined as the number (%) of patients with at least 1 visit response of complete response or partial response that was confirmed at least 4 weeks later; [b]Response required confirmation after 4 weeks; [c]Stable disease ≥6 weeks included the RECIST visit window (±7 days). DCR, disease control rate (complete response + partial response + stable disease); ORR, objective response rate

TAGRISSO™ (osimertinib) Is The First Approved Therapy for T790M-Mediated EGFR TKI Resistance[1,2]



EGFRm, EGFR mutant; wt, wild type

1. Cross DA, et al. *Cancer Discov.* 2014;4(9):1046-1061. 2. TAGRISSO [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2015

INDICATION
TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

SELECT SAFETY INFORMATION
- Interstitial Lung Disease (ILD)/Pneumonitis occurred in 3.3% and was fatal in 0.5% of 813 TAGRISSO patients. Withhold TAGRISSO and promptly investigate for ILD in any patient presenting with worsening of respiratory symptoms indicative of ILD (e.g., dyspnea, cough and fever). Permanently discontinue TAGRISSO if ILD is confirmed
- The most common adverse reactions (>20%) observed in TAGRISSO patients were diarrhea (42%), rash (41%), dry skin (31%) and nail toxicity (25%)

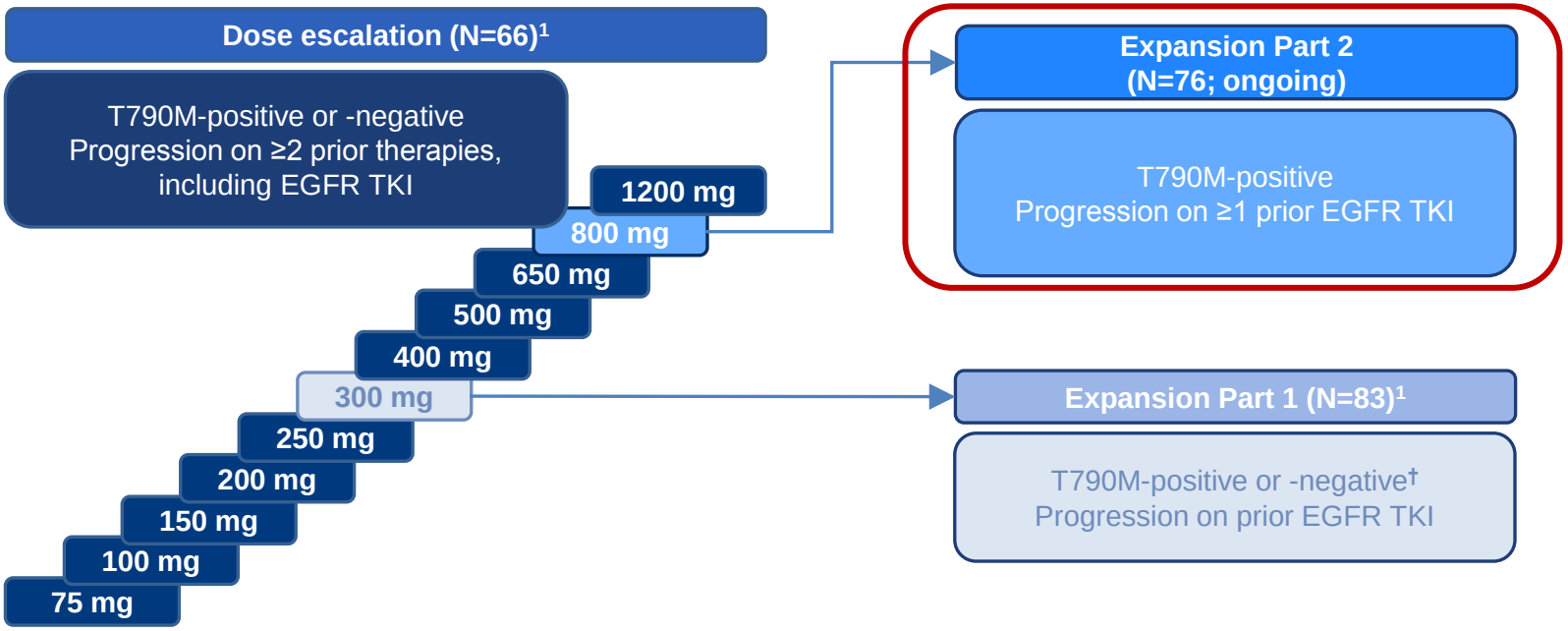
Please see accompanying complete Prescribing Information including Patient Information.

BI1482694/HM61713

Response Rate	HM-61713	CO-1686	AZD-9291	Afatinib+Cetuximab
T790M +	**30%**	58%	64%	32%
T790M -	12%	29%	22%	26%

Any Grade (Gr 3)	Diarrhea	Rash	ILD/SOB*	Hyperglycemia	QTc prolongation
Erlotinib	57%	80%	1%	NR	NR
Afatinib+Cetuximab	71%	97%	NR	NR	NR
CO-1686	23%	4%	NR	55% (22%)	15% (7%)
AZD9291	20%	27%	3%	1%	1%
HM61713	21%	24%	10%*	0%	3%

Results : Expansion Part 2



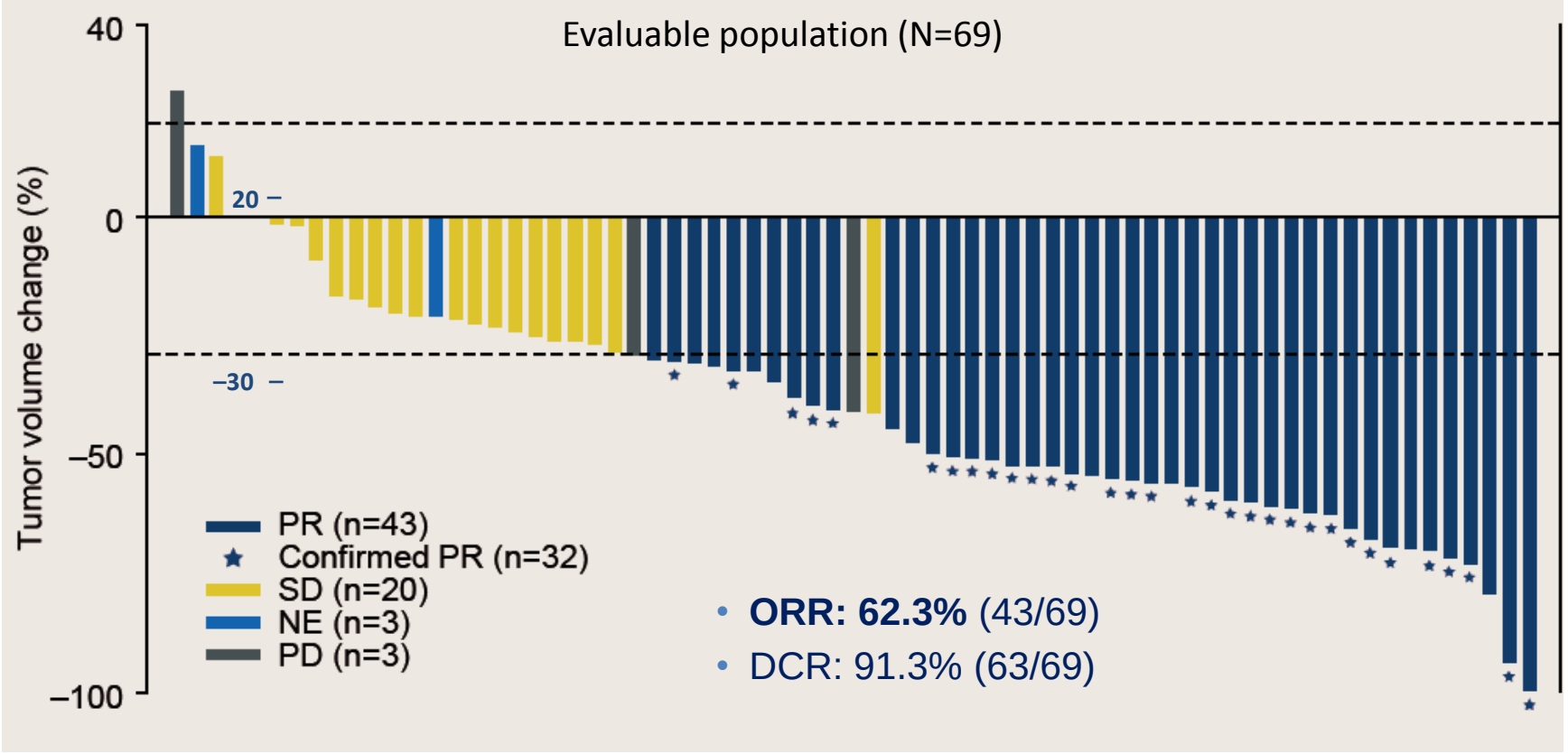
- **Expansion Part 2 (800 mg QD)**
  - ✓ **Primary endpoint: ORR by independent assessment**
  - ✓ **Secondary endpoints included: duration of response, PFS and safety**
- **Data cut-off: 30 June 2015**

†Mandatory biopsy for T790M mutation status required
CNS, central nervous system; ORR, objective response rate; QD, once daily

1. Park K, et al. J Thorac Oncol 2015;33(Suppl. 15): abs 8084

Results : Expansion Part 2

Individual tumor change in target lesions (independent assessment)



PR, partial response

JS Lee, et al. EMSO Asia 2015; abs 425PD

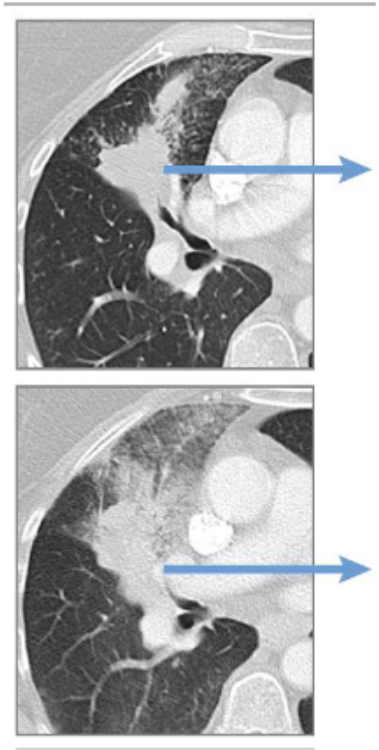
Summary of EMSI

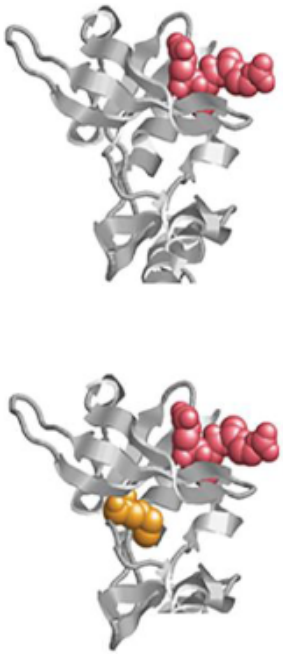
3rd Gen TKIs	RR (%) T790M+	PFS (mos)	Toxicity	DLT	RP2D
Rociletinib (CO-1686)	**58%** (n=244)	8.0/10.3	Hyperglycemia/Nausea/ Fatigue/Diarrhea/QT↑	**Hyperglycemia**	500mg BID
AZD 9291	**61%** (78/127)	~ 9.6	Diarrhea/Rash/Nausea/ Decreased appetite/ Pneumonitis-like events/ QTc ↑	-	**80mg QD** (No DLT)
BI1482694 /HM61713	**62%** (43/69)	NR	Diarrhea/Nausea/ Dry skin/Rash/Pruritus	Abd pain/Diarrhea	**800mg BID**
ASP8273	67% (16/24)	NR	Diarrhea/Nausea/ Vomiting/Hyponatremia/A few rash/ QT↑/ ILD-like events	Diarrhea/Nausea/ Malaise/Colitis/ Biliary tract infect/ Hyponatremia	300mg QD (MTD; 400mg QD)
EGF816	75.5% (40/53)	NR	Rash/Diarrhea/Stomatitis/P ruritus	Rash/Acute kidney injury	NR (as of 2 Feb 2015)

**DLT: dose limiting toxocity, RP2D: recommaned phase 2 dose, ILD: interstitial lung disease*

N Engl J Med 2015;372: 1689, N Engl J Med 2015;372: 1700, PASCO 2015 #8084, PASCO 2015 #8013, PASCO 2015 #8014

Resistance to third generation EGFR TKIs





Pre-Erlotinib
EGFR: exon 19 del 794-750

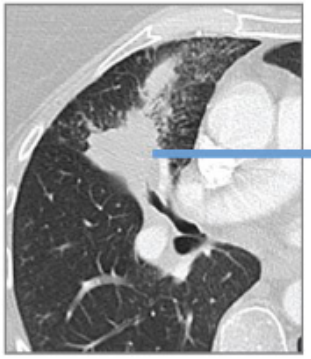
Erlotinib

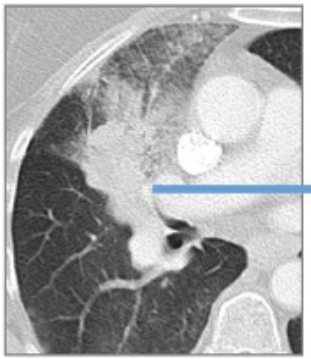
Post-Erlotinib
EGFR: exon 19 del 794-750; **T790M**

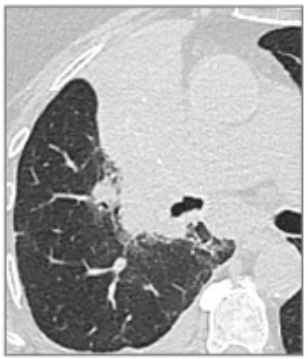
AZD9291

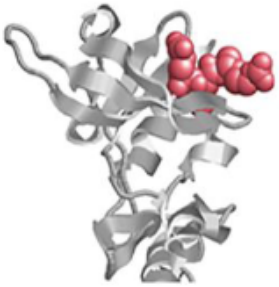
Helena Yu JAMA Oncology 2015

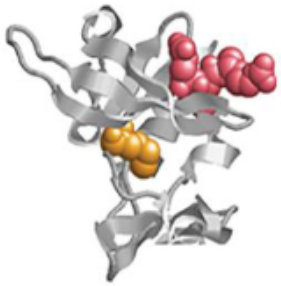
Resistance to third generation EGFR TKIs

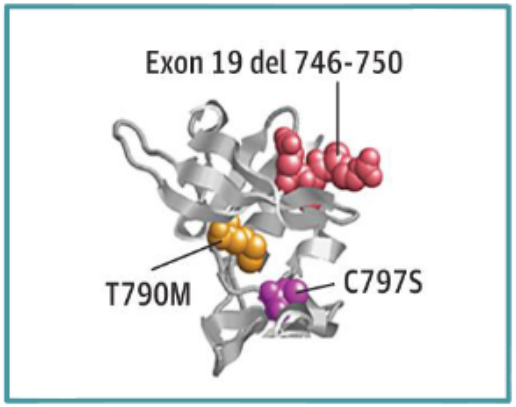












Pre-Erlotinib
EGFR: exon 19 del 794-750

Erlotinib

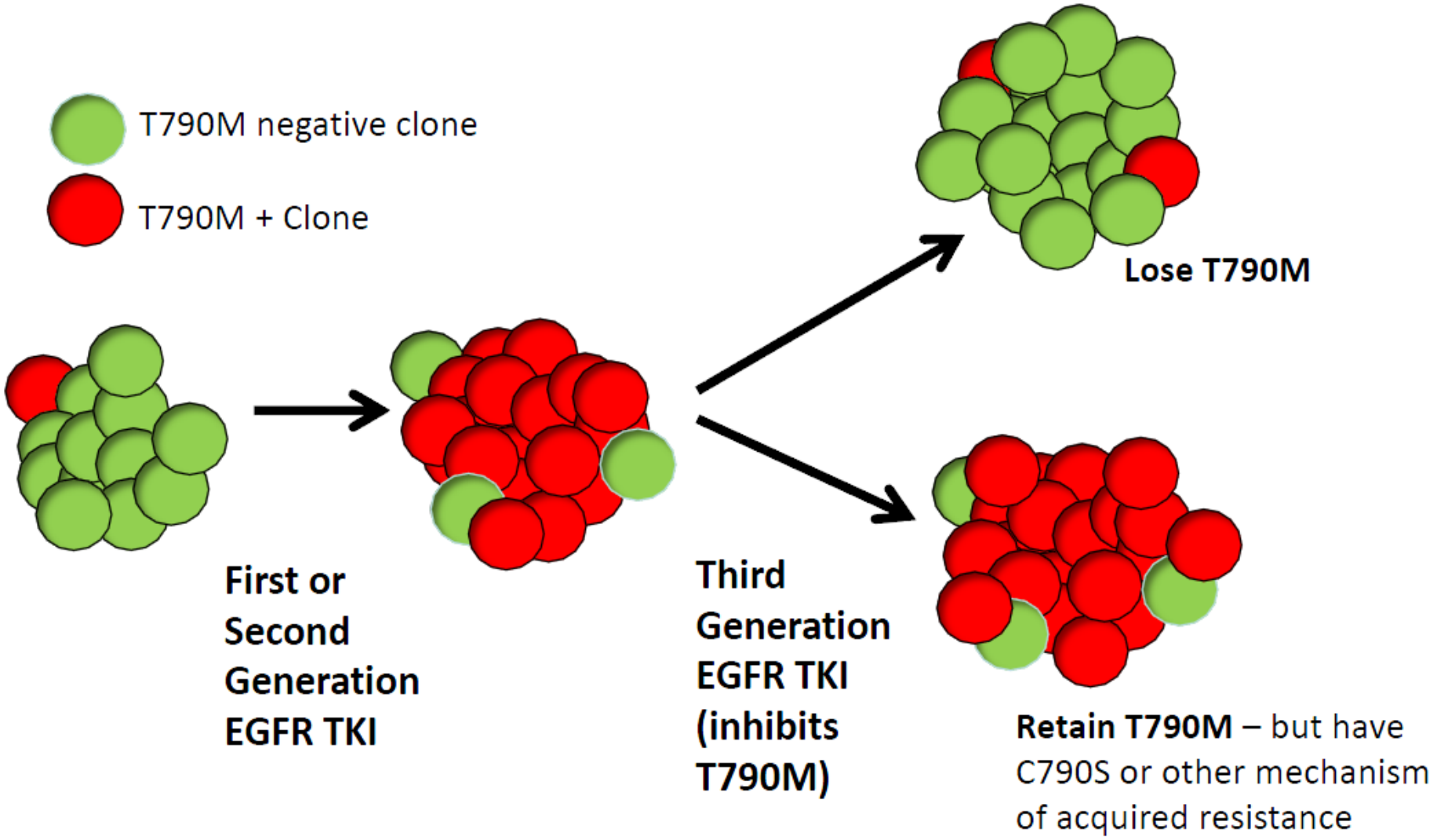
Post-Erlotinib
EGFR: exon 19 del 794-750; **T790M**

AZD9291

Post-AZD9291
EGFR: exon 19 del 794-750; **T790M**
+ C797S

Helena Yu JAMA Oncology 2015

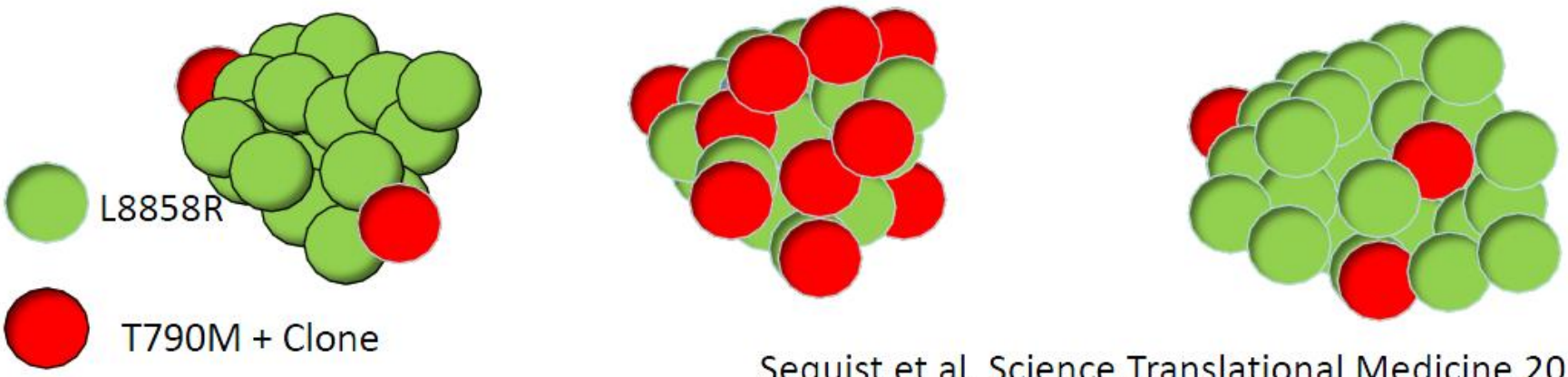
Temporal Heterogeneity of T790M



Modified from Piotrowska Cancer Discovery 2015

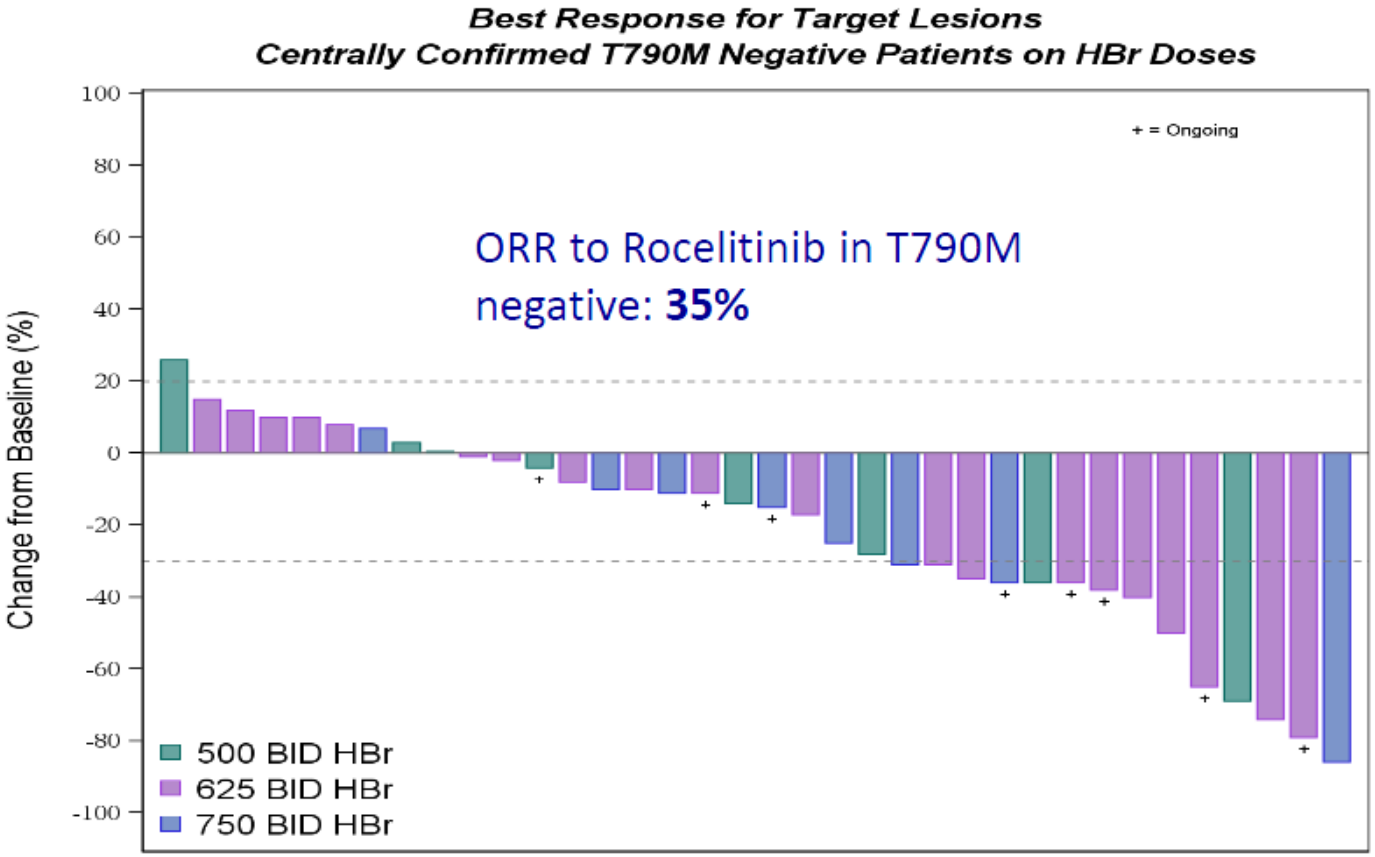
Temporal variation in T790M

Histology	Adeno	Adeno	Adeno
Genotype	L858R TP53	L858R TP53 T790M	L858R TP53
EGFR TKI status	Sensitive	Resistant	Sensitive
Tumor burden			
Treatment	Chemo / Erlotinib	Chemo / Chemo	Erlotinib*
Timeline	2007	2008 / 2009	2010



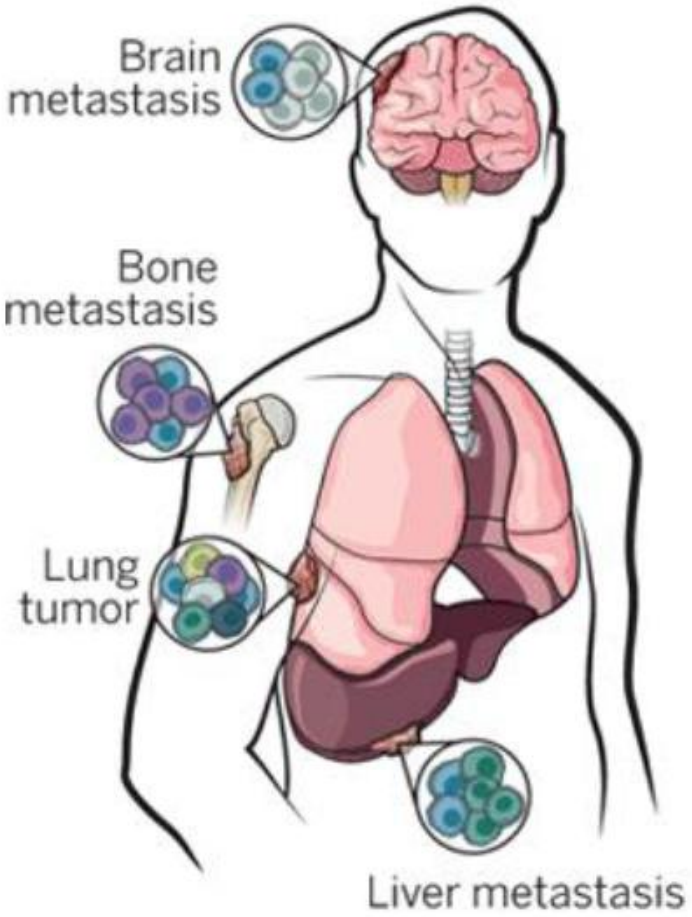
Sequist et al. Science Translational Medicine 2011

Can T790M negative patients benefit from Third generation EGFR TKIs?

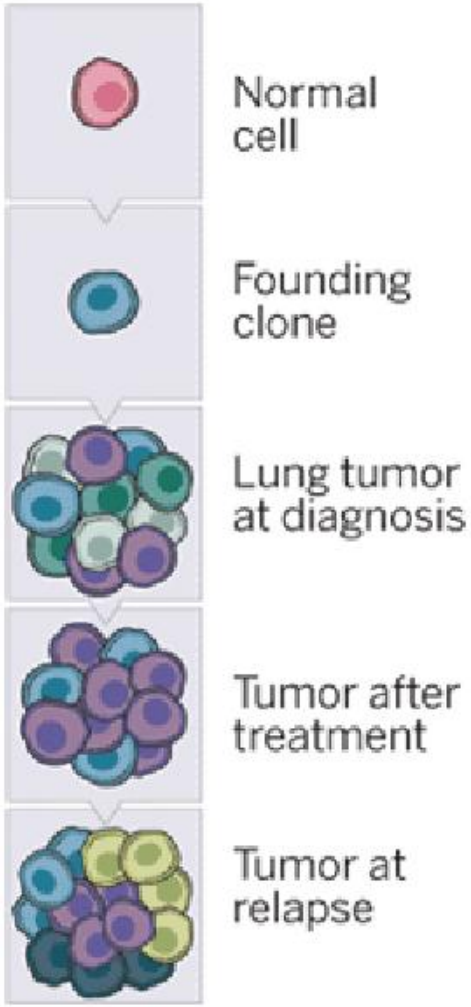


Wakelee Abstract ID: 951, WCLC 2015

Molecular Heterogeneity in NSCLC



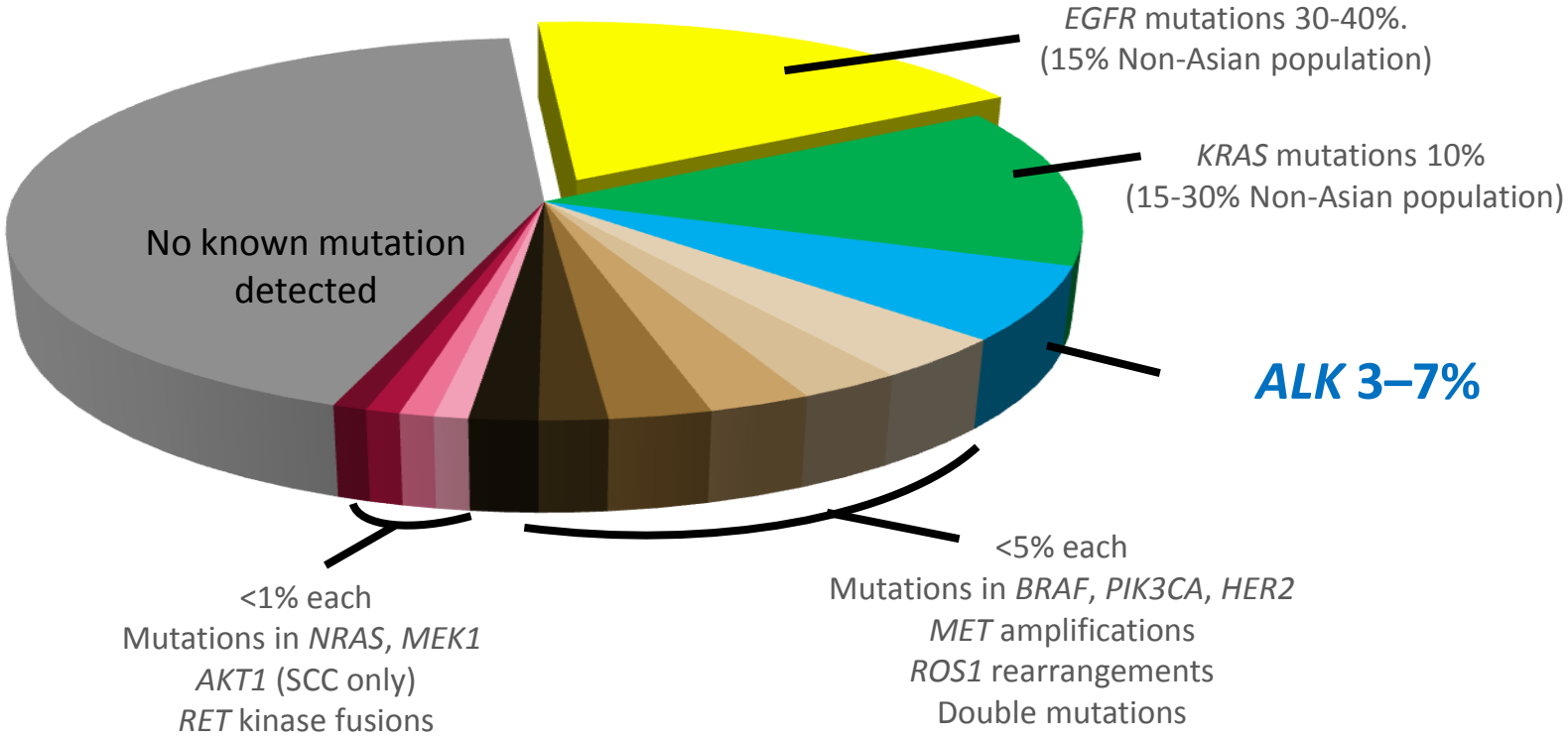
Spatial Heterogeneity



Temporal Heterogeneity

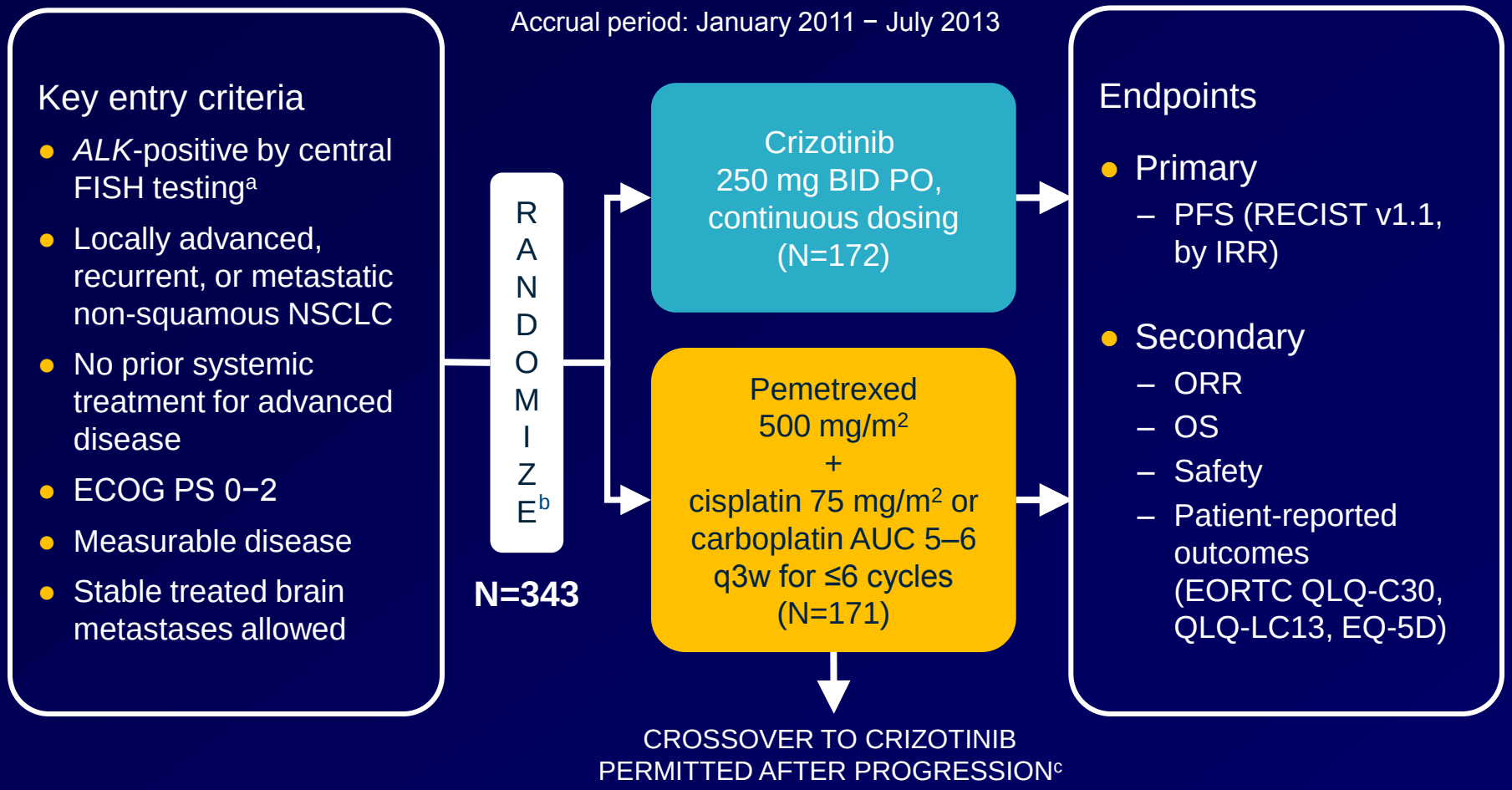
Govindan, Science 2014; De Brouin Science 2014; Zhang Science 2014

Incidence of *ALK* Rearrangements in NSCLC



Kris et al. LCMC 2011 (CRA7506)
Li et al. *J Clin Oncol* 2013
Ohashi K et al. *Clin Cancer Res* 2013; 19(9):2584-91
Pao W, Girard N.*Lancet Oncol* 2011;12(2):175-80
Pao W, Hutchinson KE.*Nat Med* 2012;18(3):349-51

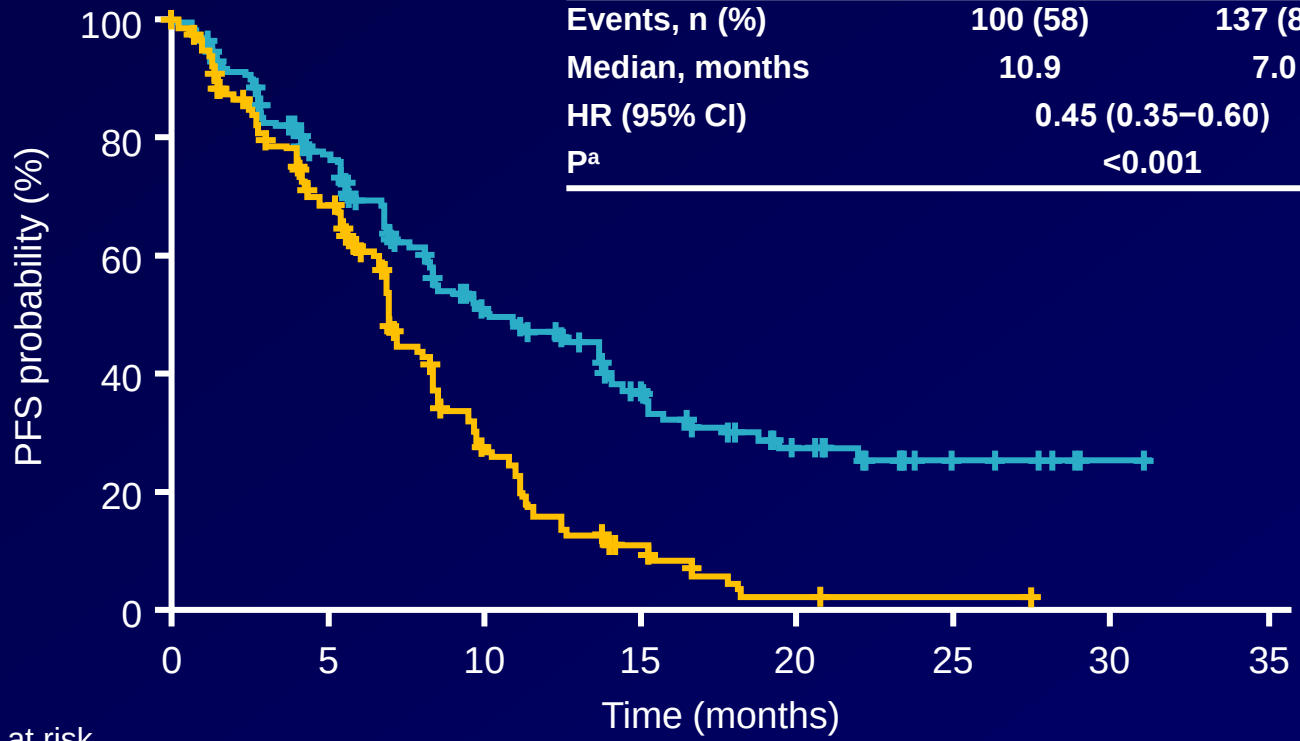
Study Design



[a]*ALK* status determined centrally using Abbott's Vysis ALK Break Apart FISH Probe Kit
[b]Stratification factors: ECOG PS (0/1 vs. 2), Asian vs. non-Asian race, and brain metastases (present vs. absent)
[c]Assessed by IRR

Solomon BJ, et al. N Engl J Med 2014;371:2167–77

Primary Endpoint: PFS by IRR (ITT Population)

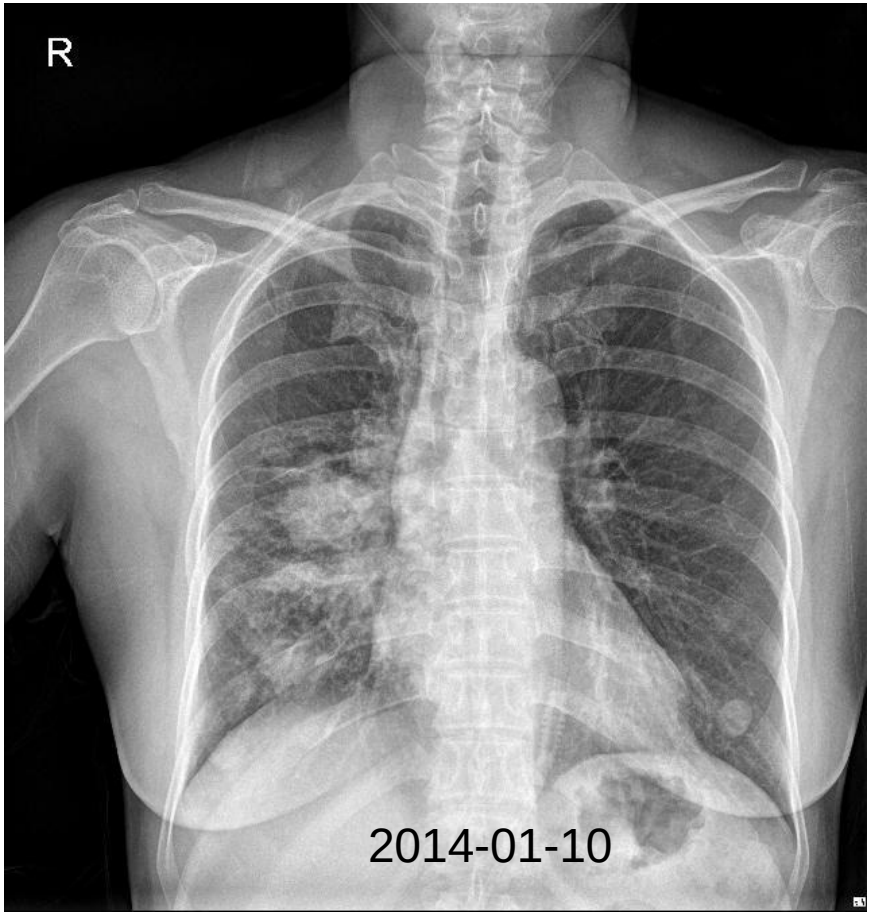


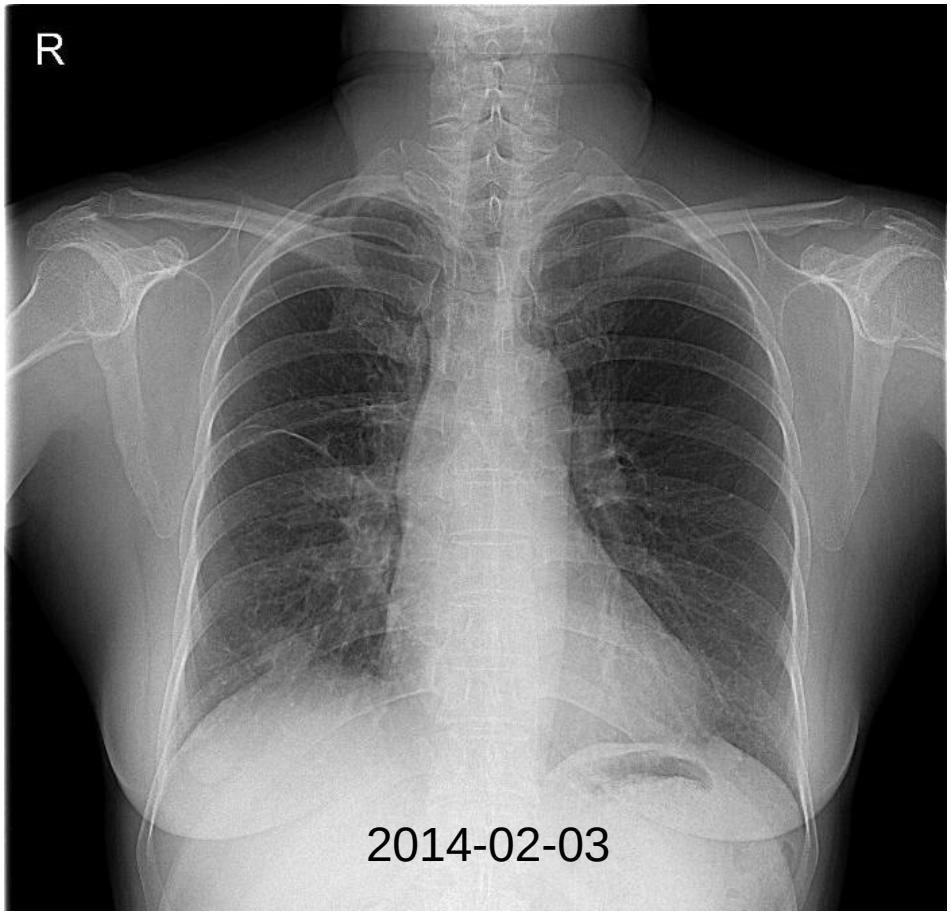
	Crizotinib (N=172)	Chemotherapy (N=171)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	
P[a]	<0.001	

[a]2-sided stratified log-rank test

Solomon BJ, et al. N Engl J Med 2014;371:2167–77

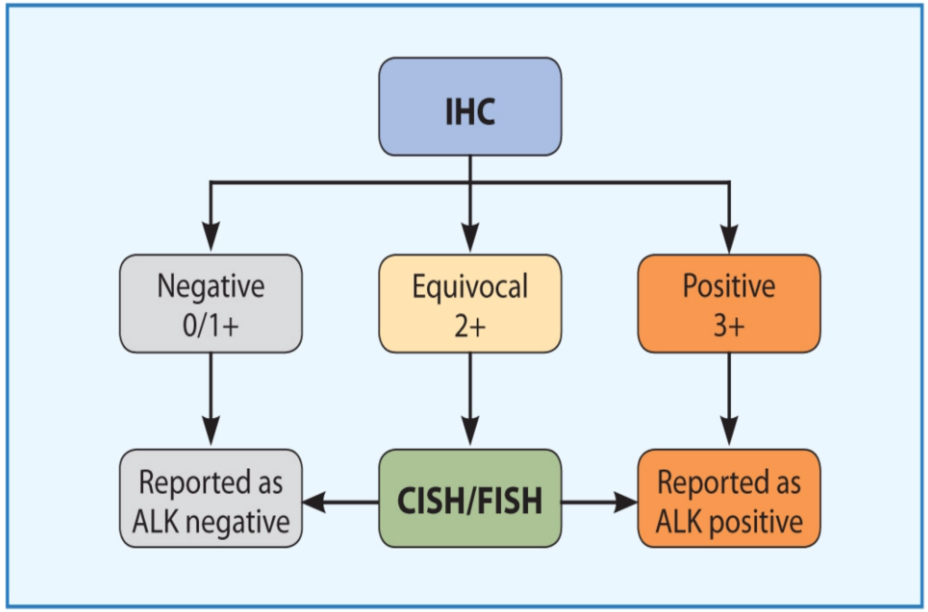
51/F, ADC IV(T3N3M1b)
EGFR PNA: wild, ALK IHC(1+), ALK FISH(+)

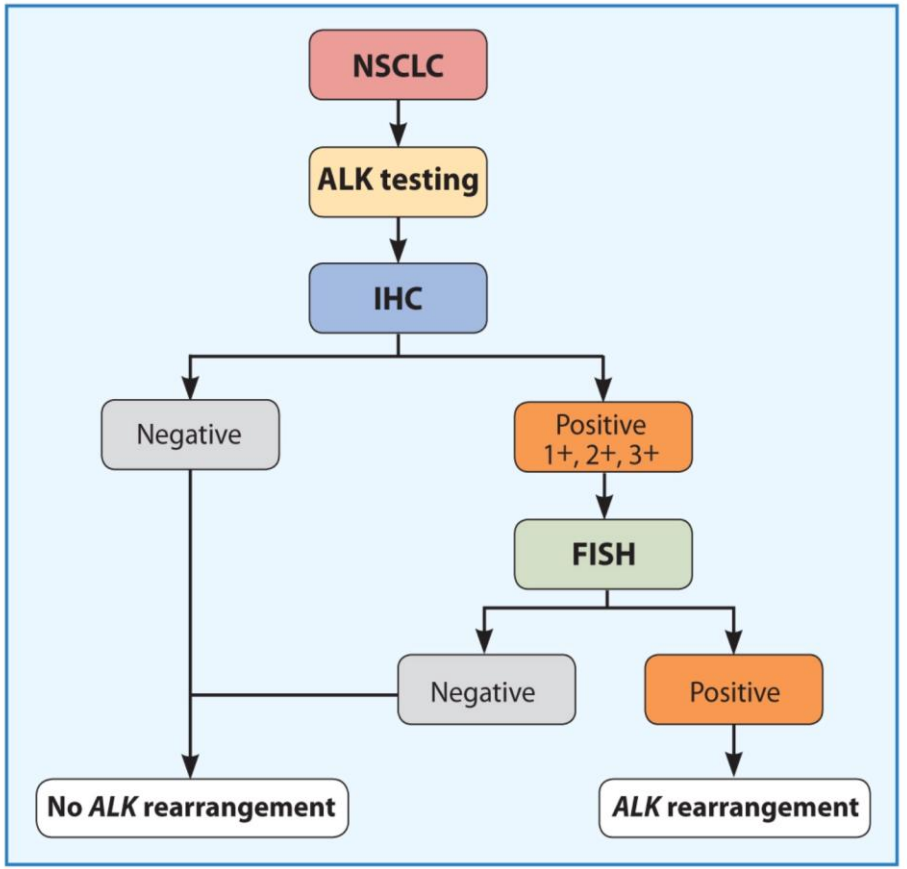




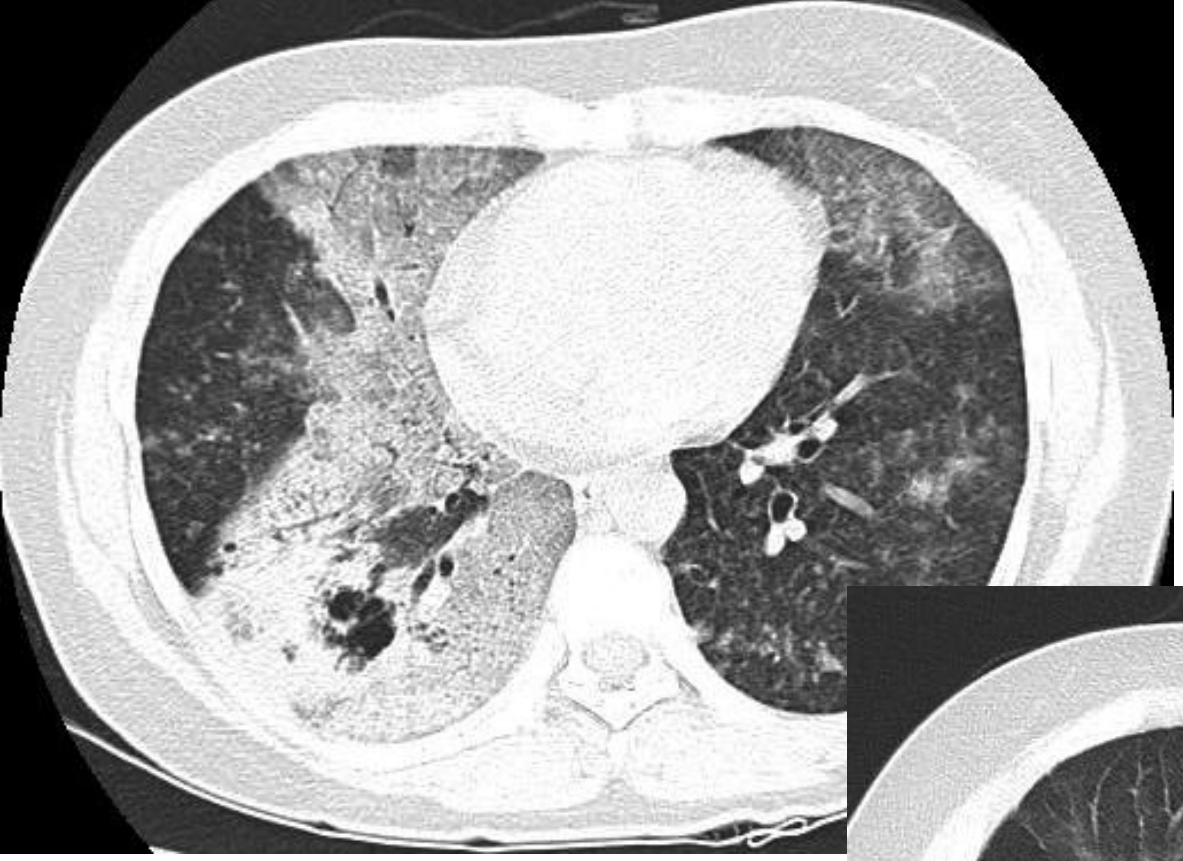
2 weeks after crizotinib

Schematic Algorithm of ALK IHC to predict FISH



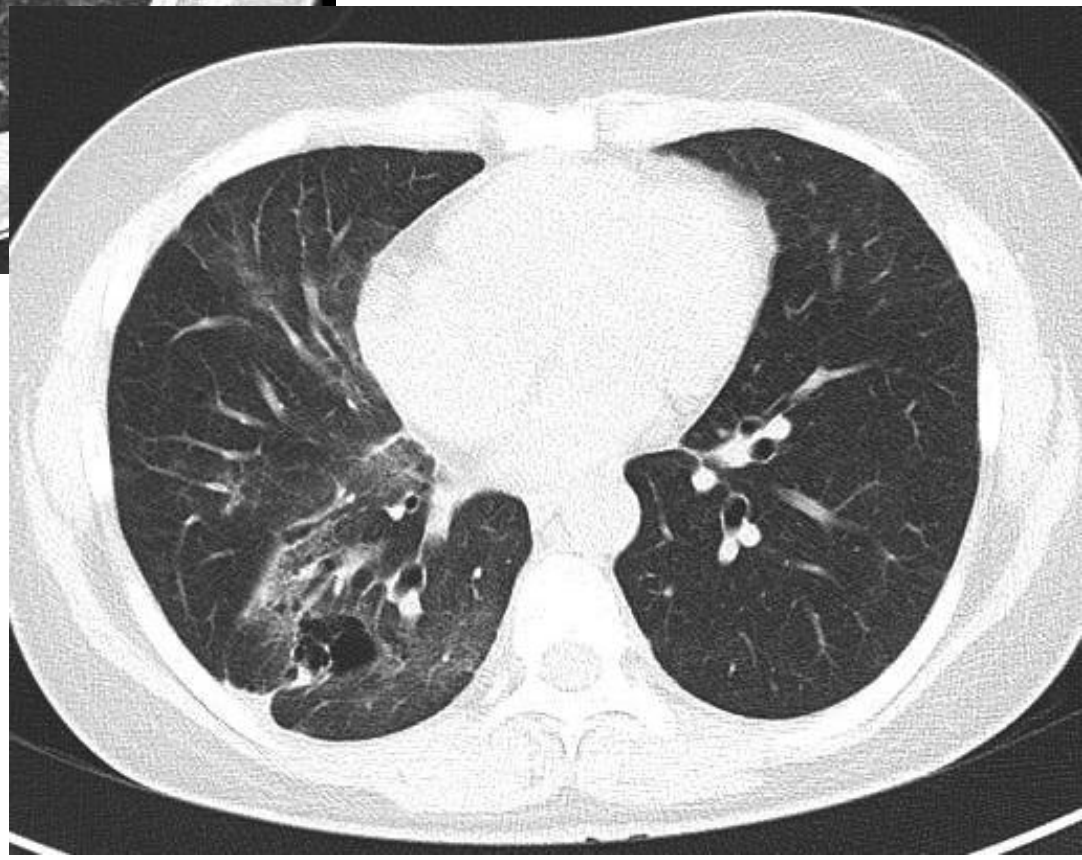


IASLC atlas of ALK testing in Lung cancer



42/F, ADC, T4 N2 M1a

1-AP 2014 6~ 15 1 10x.
2-IRESSA: 2015 1~3
3-Gem: 2015. 3 3x PD



ALK-IHC (-),

ALK-FISH positive

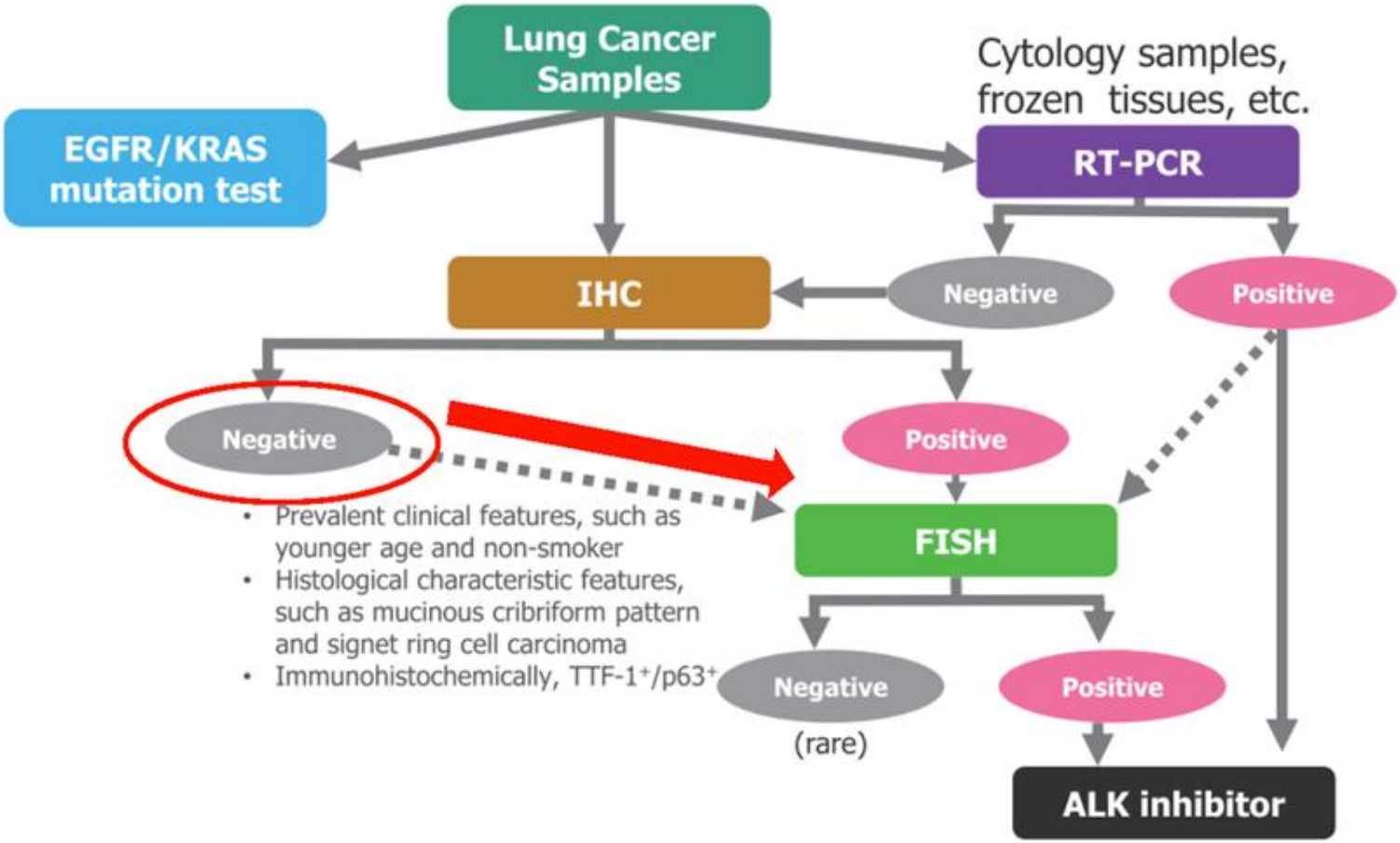
→ 4-Crizotinib
since June 4 2015.

ALK FISH and IHC

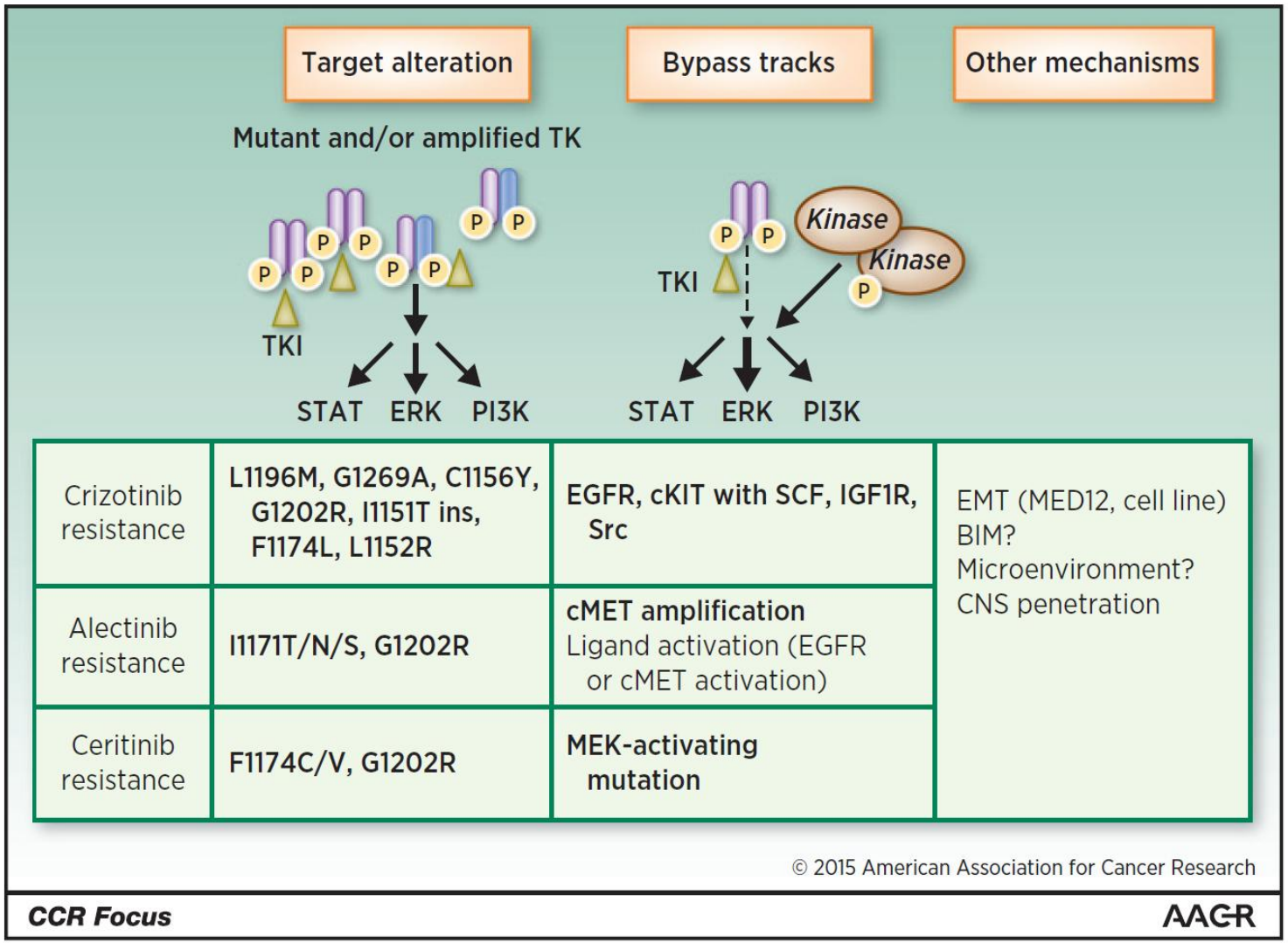
You Cannot Have One without the Other

Yasushi Yatabe, MD, PhD

Journal of Thoracic Oncology® • Volume 10, Number 4, April 2015



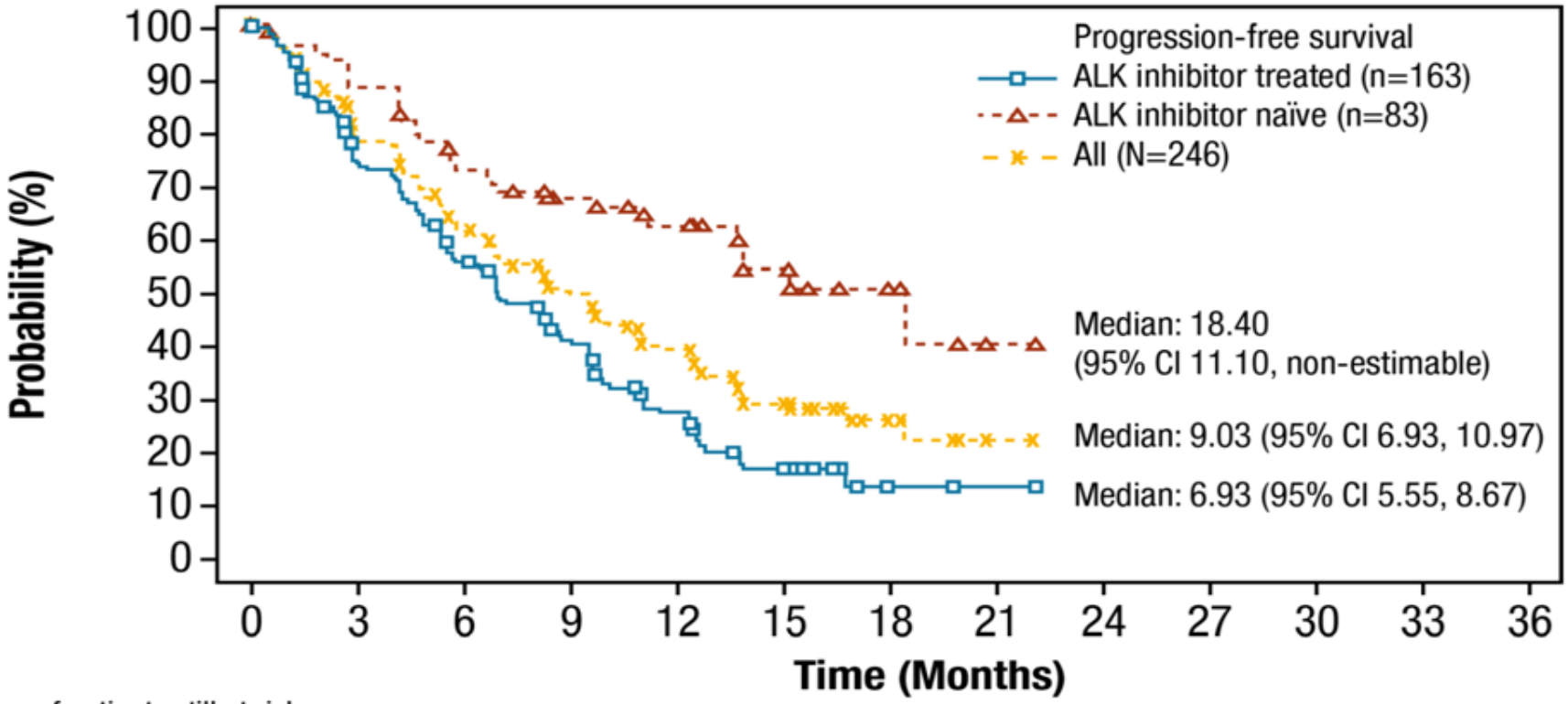
Mechanism of Acquired Resistance to ALK Inhibitors



Crizotinib resistance	L1196M, G1269A, C1156Y, G1202R, I1151T ins, F1174L, L1152R	EGFR, cKIT with SCF, IGF1R, Src	EMT (MED12, cell line) BIM? Microenvironment? CNS penetration
Alectinib resistance	I1171T/N/S, G1202R	cMET amplification Ligand activation (EGFR or cMET activation)	
Ceritinib resistance	F1174C/V, G1202R	MEK-activating mutation	

Katayama R et al. Clin Cancer Res 2015;21(10):2227-2235

Progression-free Survival for ALK+ NSCLC Treated with Ceritinib 750 mg/day



Number of patients still at risk

NSCLC with prior ALKi	163	108	79	52	29	13	2	1	0	0	0	0	0
NSCLC ALKi naïve	83	69	55	43	32	17	6	2	0	0	0	0	0
All NSCLC	246	177	134	95	61	30	8	3	0	0	0	0	0

Summary of Adverse Events for all Patients with ALK+ Disease Treated at Recommended Dose

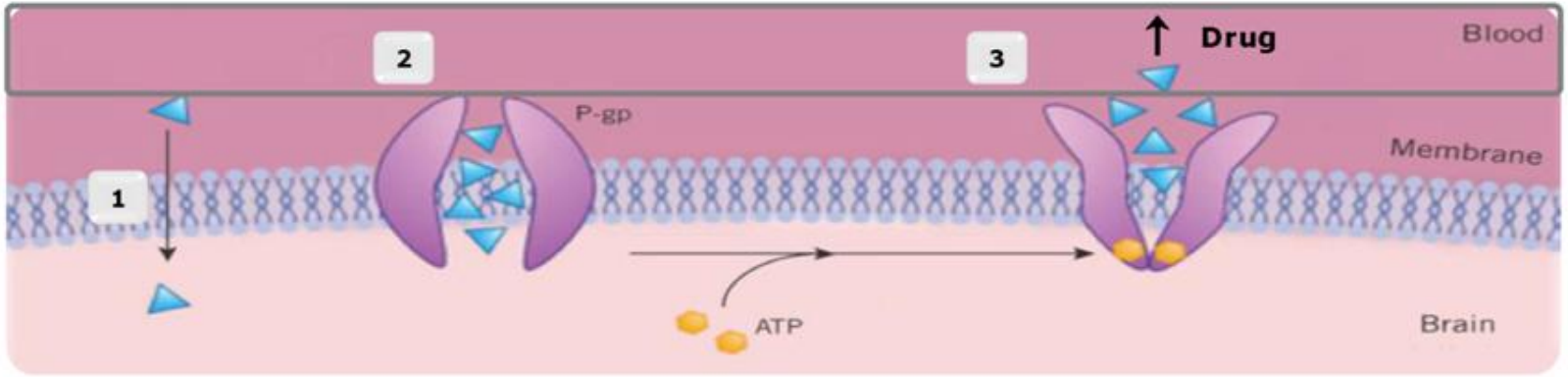
All patients treated with 750 mg (N=255; Includes nine non-NSCLC patients)		
Adverse Events	**All Grades,* n (%)**	**Grade 3/4,* n (%)**
Diarrhoea	221 (86.7)	15 (5.9)
Nausea	211 (82.7)	15 (5.9)
Vomiting	157 (61.6)	12 (4.7)
Fatigue	109 (42.7)	13 (5.1)
Abdominal pain	98 (38.4)	3 (1.2)
Decreased appetite	95 (37.3)	4 (1.6)
Constipation	79 (31.0)	0 (0.0)
Cough	73 (28.6)	0 (0.0)
Dyspnoea	63 (24.7)	11 (4.3)
Abdominal pain, upper	60 (23.5)	2 (0.8)
Weight decreased	46 (18.0)	5 (2.0)
Anaemia	31 (12.2)	13 (5.1)
Pneumonia	25 (9.8)	12 (4.7)
Convulsion	15 (5.9)	8 (3.1)

*AEs shown for >20% for all grades or ≥2% for grades 3/4

Alectinib is not transported out of the brain

The brain is protected by the blood-brain barrier (BBB), a network of tightly connected cells

1. Drugs enter the brain by crossing the blood-brain barrier
2. The drug-efflux-transporter protein P-glycoprotein (P-gp) is expressed at high levels in the brain[1,2]
3. P-gp actively exports drugs back across the BBB into the bloodstream in an ATP-dependent manner[2,3]

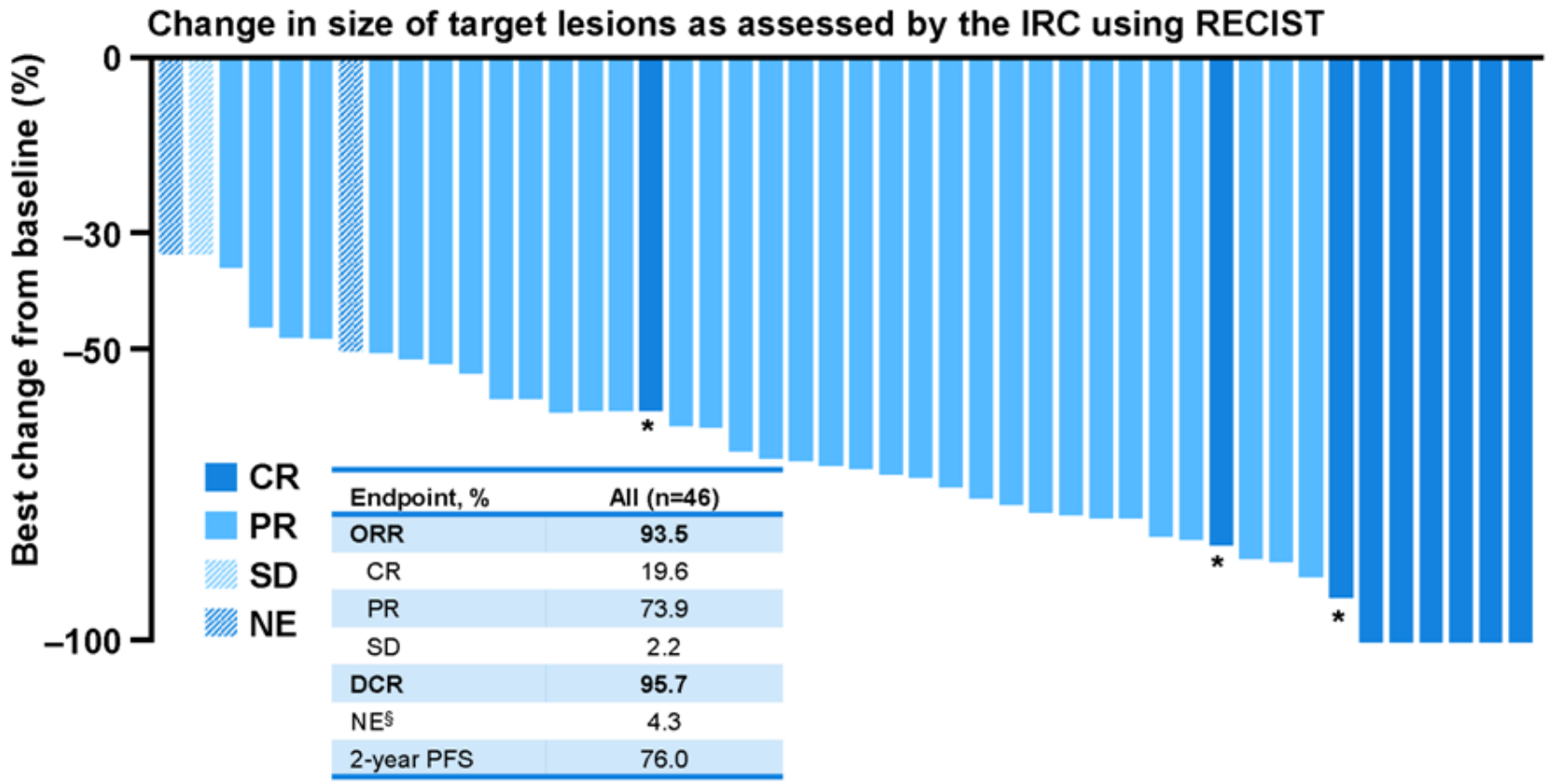


Preclinical data show that alectinib is not a substrate for the drug efflux transporter P-gp[3], and is therefore not actively transported out of the brain

ATP = adenosine triphosphate
BBB = blood-brain barrier; P-gp = P-glycoprotein

1. Thiebaut, et al. Proc Natl Acad Sci 1987; 2. Misra, et al. J Pharm Pharm Sci 2003
3. Kodama, et al. Cancer Chemother Pharmacol 2014

AF-001JP study (phase II portion)
Percentage change in tumour size from baseline by IRC



Endpoint, %	All (n=46)
ORR	**93.5**
CR	19.6
PR	73.9
SD	2.2
DCR	**95.7**
NE§	4.3
2-year PFS	76.0

Data cut-off: 31 Jan 2014
CR = complete response; NE = not evaluated; PR = partial response; SD = stable disease; RECIST = Response Evaluation Criteria in Solid Tumors
*Lymph nodes identified as target lesion for RECIST evaluation
§For best overall response evaluation, one patient withdrew early due to an adverse event (no response data); one patient had investigator-assessed PD not confirmed by the IRC

Tamura, et al. CMSTO 2014

NP28673 study (global)
Median PFS (8.9 months) and DoR (11.2 months)

	Cut-off 18 August 2014	Cut-off 8 January 2015
Progression-free survival (by IRC)	**Median PFS:** **7.5 months** (95% CI 5.9, 11.2) Range 0.6–11.2 months	**Median PFS:** **8.9 months** (95% CI 5.6, 11.3) Range 0.6–16.4 months
Duration of response (by IRC)	**Median DoR:** **9.2 months** (95% CI NE) Range 1.7*–9.2 months	**Median DoR:** **11.2 months** (95% CI 9.6, NE) Range 1.9*–12.7* months
Disease control rate (by IRC)	**DCR = 79.5%** (95% CI 71.3, 86.3)	**DCR = 78.7%** (95% CI 70.6, 85.6)

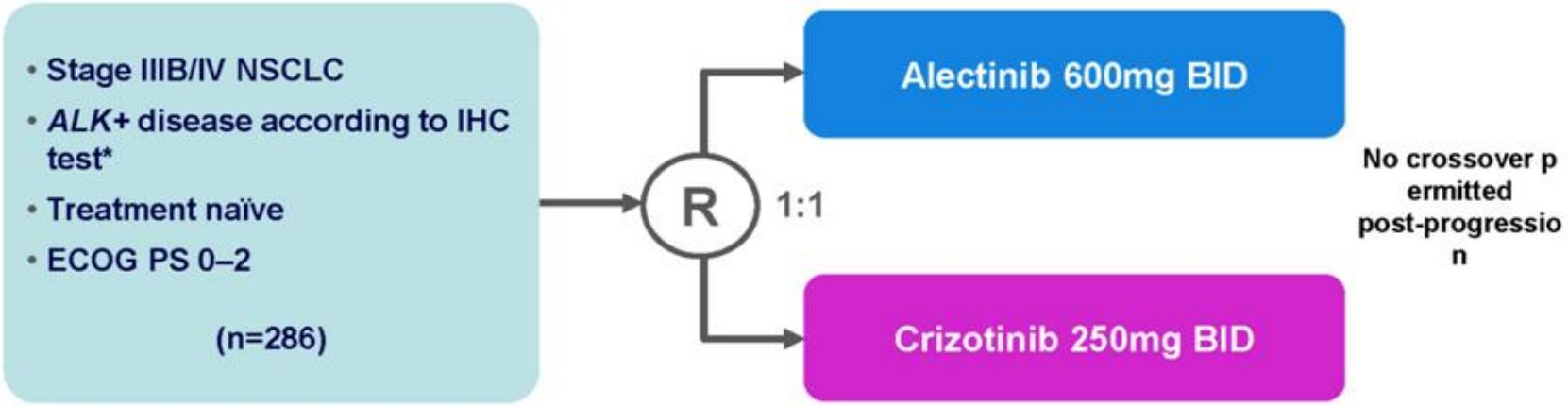
Ou SH, *et al.* ASCO 2015; Abstract 8008 (Oral presentation)
Roche, data on file

NP28673 study (global)
Treatment-related AEs in ≥5% of patients

	Number of patients (%)				
Adverse event	**All events**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Myalgia	23 (17)	19 (14)	3 (2)	1 (1)	0
Constipation	20 (15)	17 (12)	3 (2)	0	0
Fatigue	19 (14)	16 (12)	2 (1)	1 (1)	0
Asthenia	15 (11)	12 (9)	2 (1)	1 (1)	0
AST elevation	14 (10)	11 (8)	1 (1)	1 (1)	1 (1)
ALT elevation	13 (9)	6 (4)	5 (4)	1 (1)	1 (1)
Peripheral oedema	13 (9)	10 (7)	2 (1)	1 (1)	0
Rash	12 (9)	11 (8)	1 (1)	1 (1)	0
Photosensitivity	12 (9)	12 (9)	0	0	0
Bilirubin elevation	11 (8)	2 (1)	7 (5)	2 (1)	0
Nausea	8 (6)	7 (5)	1 (1)	0	0
Dry skin	7 (5)	7 (5)	0	0	0
Diarrhoea	7 (5)	6 (4)	0	1 (1)	0

Ou SH, *et al.* ASCO 2015; Abstract 8008 (Oral presentation)

ALEX: ongoing, phase III study of alectinib versus crizotinib in treatment-naïve patients with *ALK*+ NSCLC



Primary endpoint

- PFS (investigator assessed)

Secondary endpoints

- PFS by IRC
- Time to CNS progression
- ORR
- DoR
- OS
- QoL
- Safety
- PK

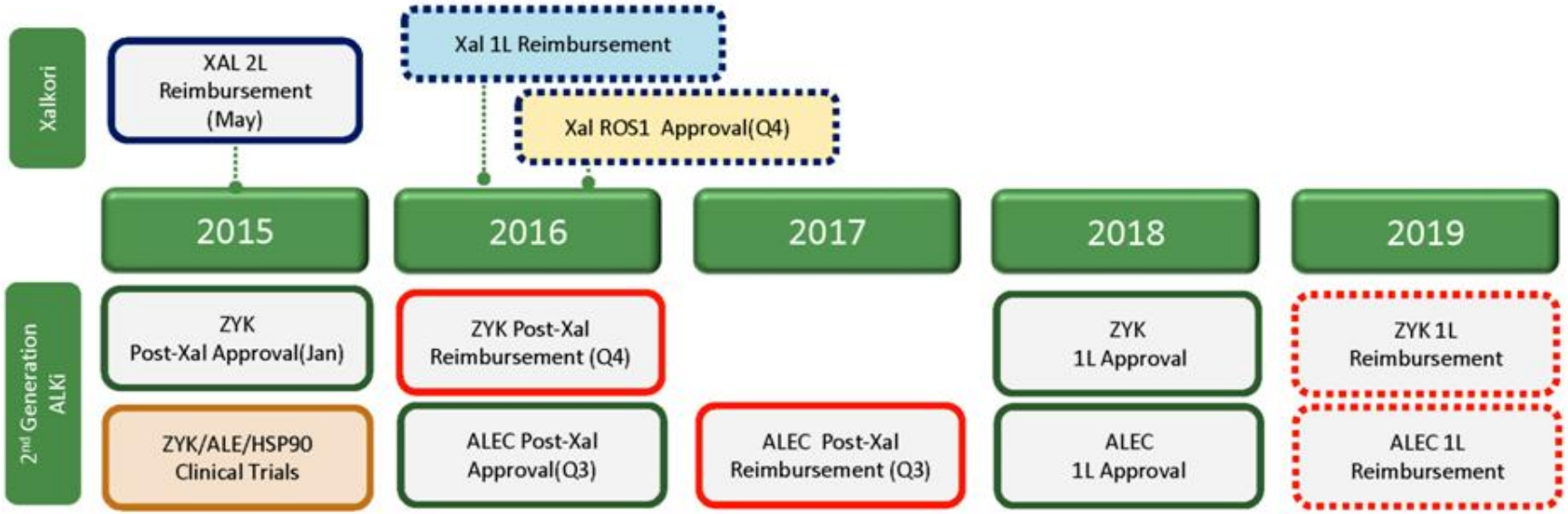
Stratification factors

- ECOG PS (0/1 vs 2)
- Ethnicity (Asian vs non-Asian)
- CNS metastases at baseline (yes vs no)

*IHC test is being developed by Ventana as a companion diagnostic to alectinib
Sufficient tumour tissue is required to test for *ALK*+ disease via IHC and FISH
IHC = immunohistochemistry

BO28984
NCT02075840; Peters, et al. ESMO 2014

2016~2019 Outlook in Korea



ADENOCARCINOMA, LARGE CELL, NSCLC NOS[tt]

FIRST-LINE THERAPY

PS 0-1 → Doublet chemotherapy[ff] (category 1) or Bevacizumab + chemotherapy[ff,uu,vv] (if criteria met)[ww]

PS 2 → Chemotherapy[ff]

PS 3-4 → Best supportive care
See NCCN Guidelines for Palliative Care

→ Tumor response evaluation

Progression →
- PS 0-2 → SUBSEQUENT THERAPY[ff]
  If not already given:
  Systemic immune checkpoint inhibitors (preferred)
  • Nivolumab (category 1) or Pembrolizumab[xx] (category 1)
  or
  Other systemic therapy
  Docetaxel or
  Pemetrexed or
  Erlotinib[yy] or
  Gemcitabine or
  Ramucirumab + docetaxel
  → Progression[ccc]
- PS 3-4 → Erlotinib[zz] or afatinib[zz] or gefitinib[zz] or crizotinib[aaa] (if not already given) or Best supportive care
  See NCCN Guidelines for Palliative Care

Response or stable disease → 4–6 cycles (total) → Tumor response evaluation

Progression → See Subsequent therapy, above

Response or stable disease → Continuation maintenance[ff]
- Bevacizumab (category 1)[uu]
- Pemetrexed (category 1)
- Bevacizumab + pemetrexed[bbb]
- Gemcitabine (category 2B)

or
Switch maintenance[ff] (category 2B)
- Pemetrexed or Erlotinib

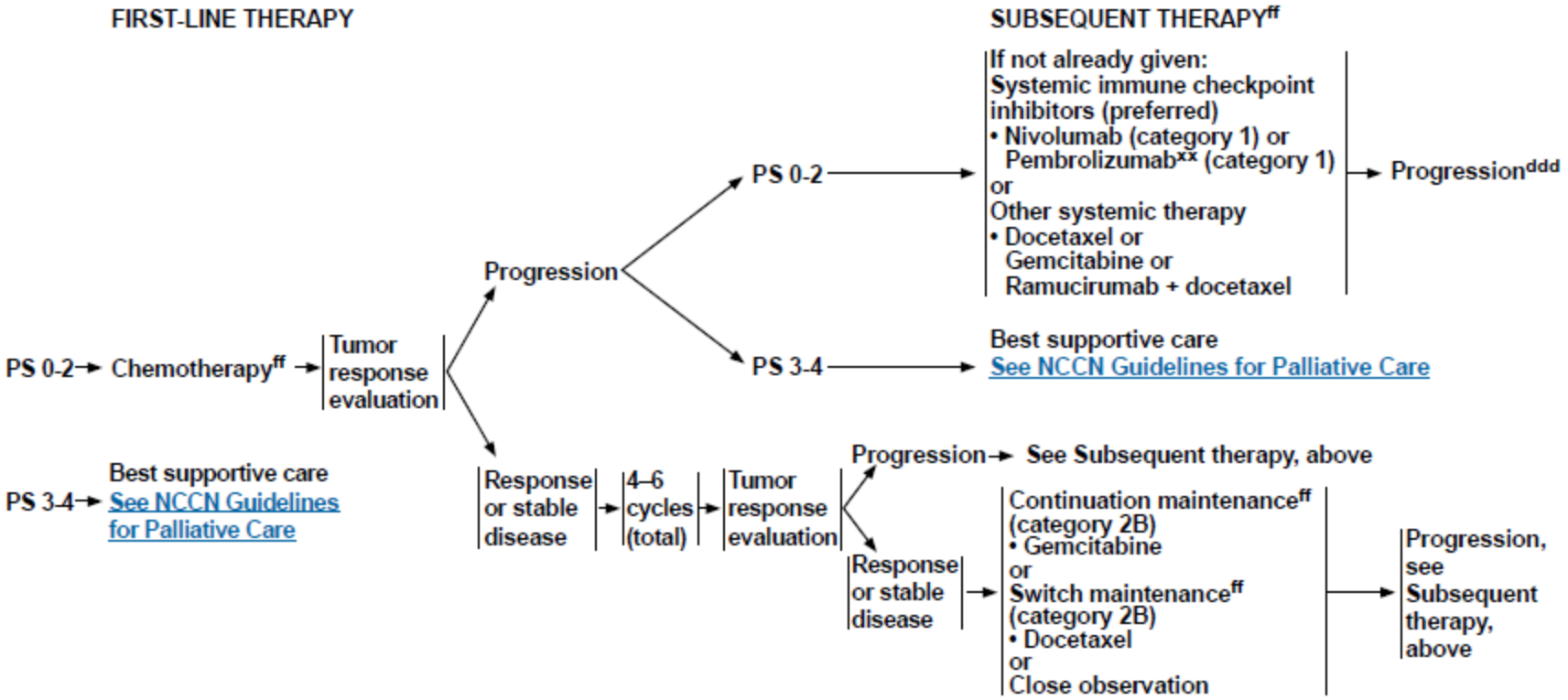
or
Close observation

→ Progression, see Subsequent therapy, above

[ff] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[uu] Bevacizumab should be given until progression.
[vv] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[ww] Criteria for treatment with bevacizumab: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.
[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[yy] Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Lancet Oncol 2014; 15:713-21.
[zz] May be considered for PS 3 and 4 patients with sensitizing EGFR mutations.
[aaa] May be considered for PS 3 and 4 patients if positive for the ALK rearrangement.
[bbb] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.
[ccc] If not already given, options for PS 0-2 include erlotinib, nivolumab, pembrolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

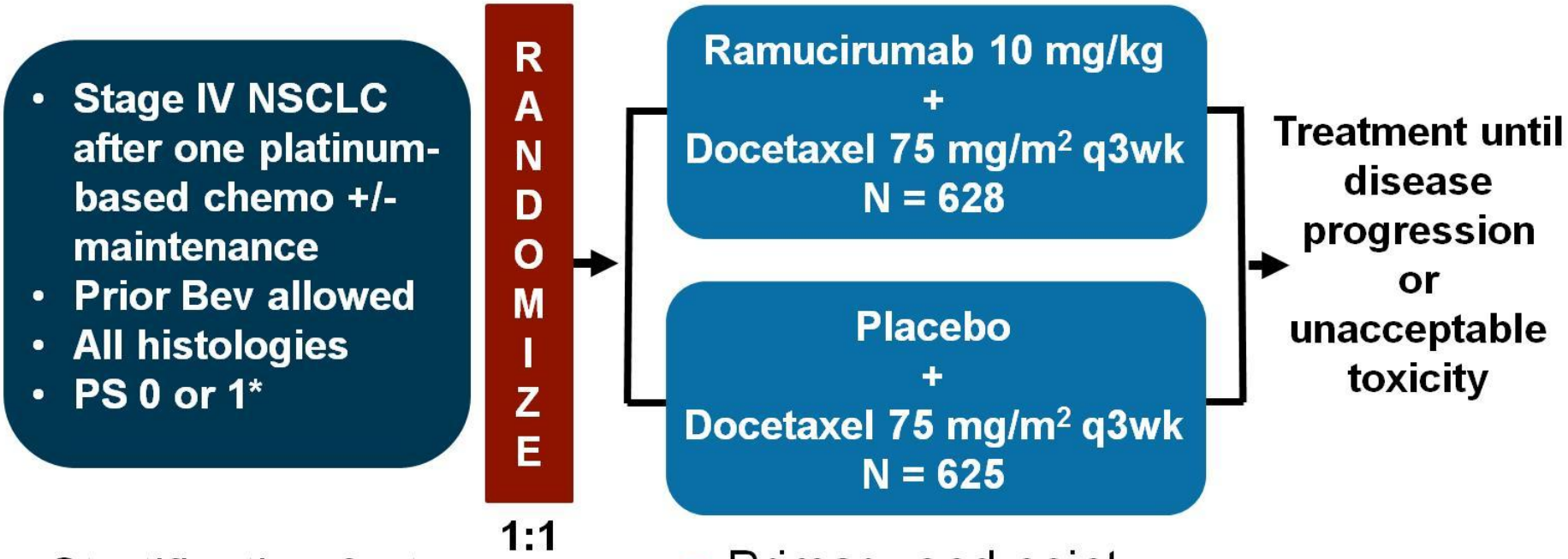
SQUAMOUS CELL CARCINOMA[tt]



[ff] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[ddd] If not already given, options for PS 0-2 include nivolumab, pembrolizumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

REVEL
Study Design



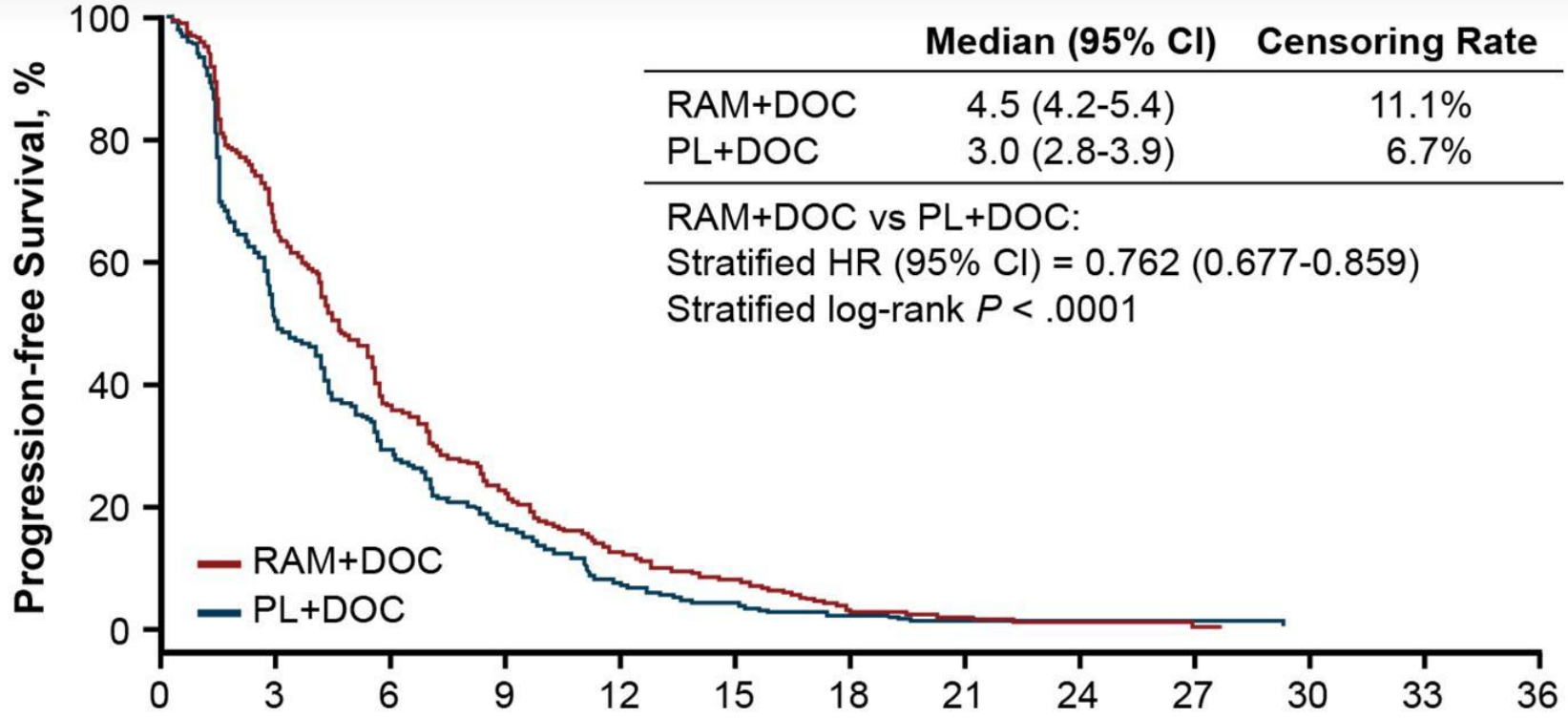
- Stratification factors:
  - ECOG PS 0 vs 1
  - Gender
  - Prior maintenance
  - East-Asia vs ROW

- Primary end point:
  - Overall survival
- Secondary end point:
  - PFS, ORR, safety, patient-reported outcomes

*Baseline characteristics: ~ one-quarter of patients had received prior taxane therapy; PS = 0 in ~ one-third of patients, PS = 1 in ~ two-thirds of patients.

Perol M, et al. *J Clin Oncol*. 2014;32. Abstract LBA8006.[18]

REVEL: PFS



	Median (95% CI)	Censoring Rate
RAM+DOC	4.5 (4.2-5.4)	11.1%
PL+DOC	3.0 (2.8-3.9)	6.7%

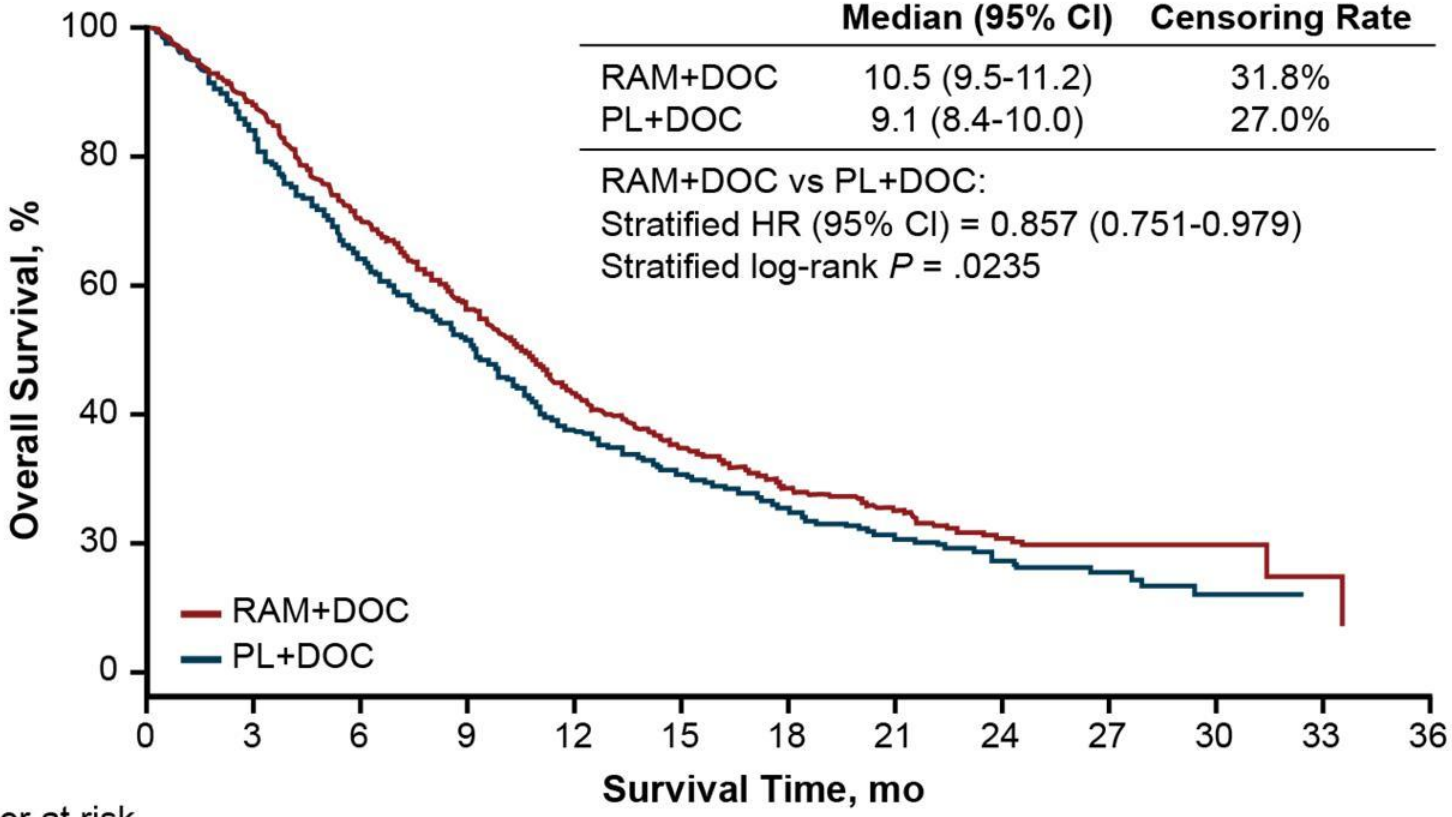
RAM+DOC vs PL+DOC:
Stratified HR (95% CI) = 0.762 (0.677-0.859)
Stratified log-rank $P < .0001$

Number at risk

RAM+DOC	628	383	204	120	59	38	11	7	3	3	0	0	0
PL+DOC	625	301	172	95	37	17	9	4	3	2	0	0	0

Perol M, et al. *J Clin Oncol*. 2014;32. Abstract LBA8006.[18]

REVEL: OS



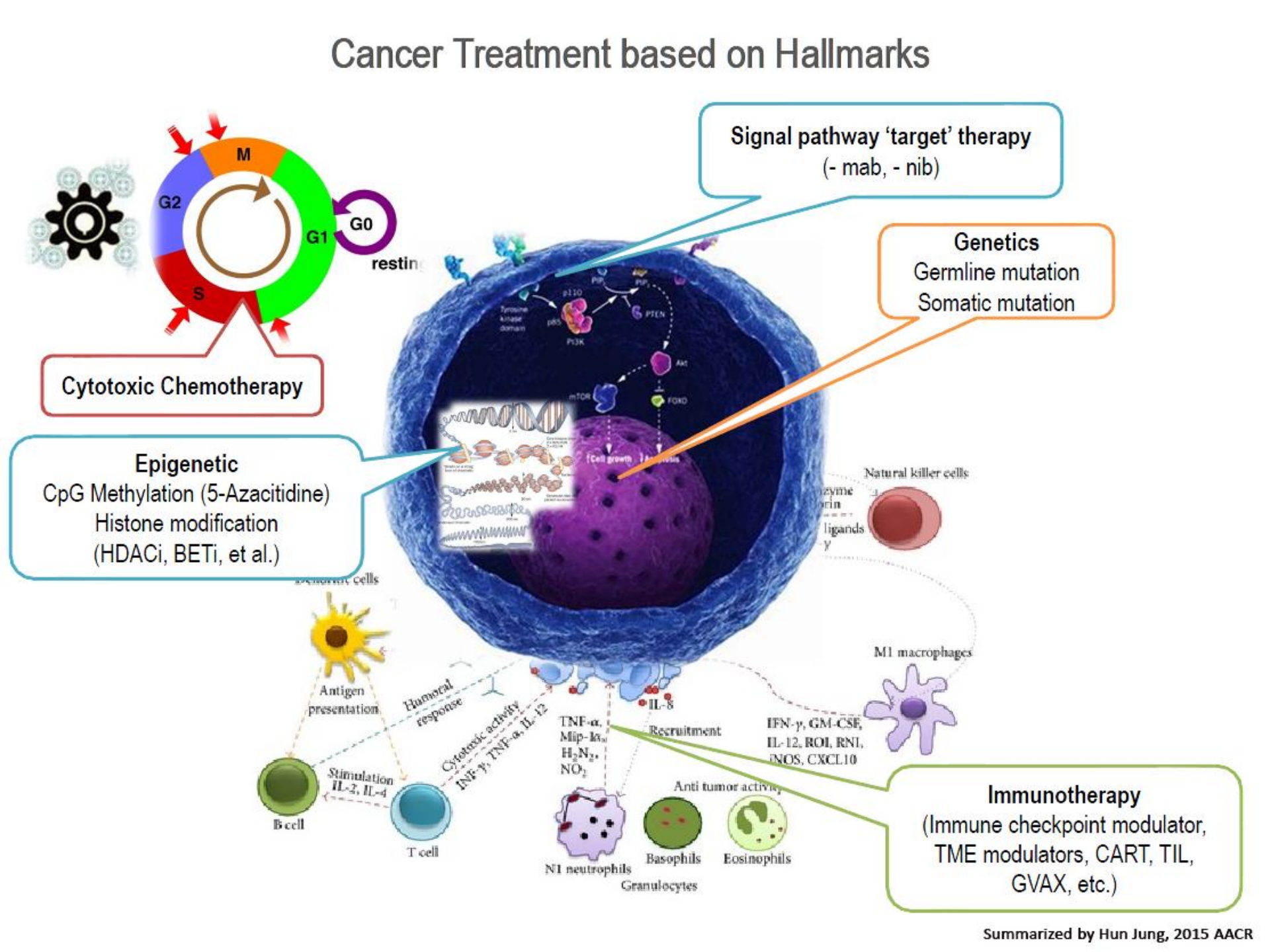
Perol M, et al. *J Clin Oncol*. 2014;32. Abstract LBA8006.[18]

REVEL
Bleeding-related AEs

Adverse Events of Special Interest	RAM + DOC, N = 627			PL + DOC, N = 618		
	Grade 1-2, %	Grade 3-4, %	Grade 5, %	Grade 1-2, %	Grade 3-4, %	Grade 5, %
Bleeding / hemorrhage	26.5	1.1	1.3	12.9	1.0	1.3
Epistaxis	18.2	0.3	0	6.3	0.2	0
GI hemorrhage	0	0	0.2	0	0	0
Hemoptysis	5.1	0.3	0.3	4.5	0.3	0.3
Pulmonary hemorrhage	1.4	0	0.6	1.1	0	0.5

Perol M, et al. *J Clin Oncol*. 2014;32. Abstract LBA8006.[18]

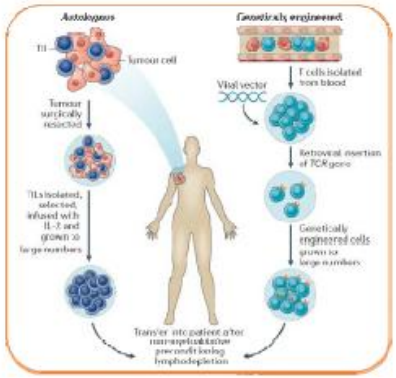
Cancer Treatment based on Hallmarks



Summarized by Hun Jung, 2015 AACR

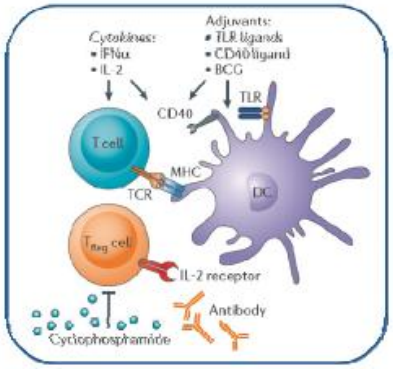
Current status of cancer immunotherapy

Adoptive cell transfer



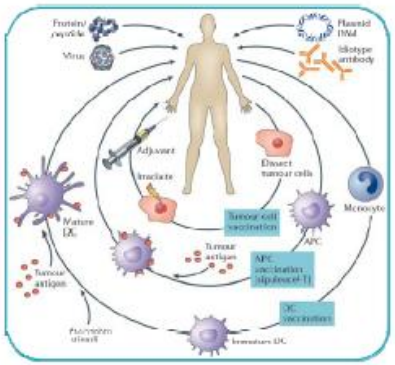
- TILs
- TCR-transfected T cell
- CAR therapy

Non-specific immunotherapy



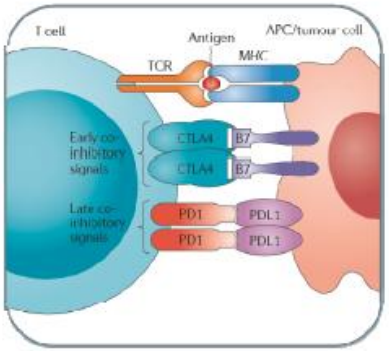
- Cytokines (IL-2, IFN-a)
- CD40 agonist Ab
- TLR agonist

Vaccination strategy



- Sipuleucel-T
- MAGE-3 ASCL
- OncoVEX

Immune checkpoint blockade



- CTLA-4 blocking Ab
- PD-1 blocking Ab

Lesterhuis WJ & Punt CJA. ***Nat Rev Drug Discov*** 2012

T cells during acute vs. chronic environment

Immune Checkpoints

Impaired functionalities
- *cytokine production ↓*
- *cytotoxicity ↓*
- *proliferation ↓*
- *self-renewal ↓*

cytokine receptors

Naive T cells

Immune suppressive chronic environment

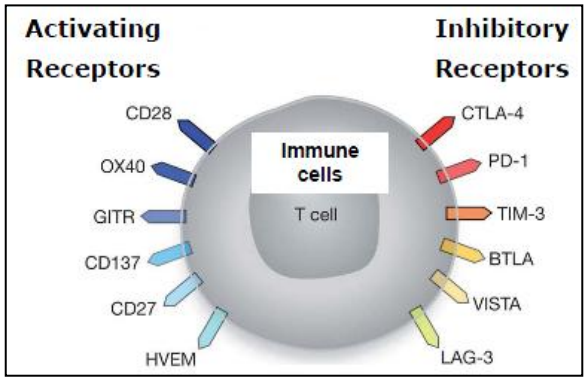
Antigen persistence

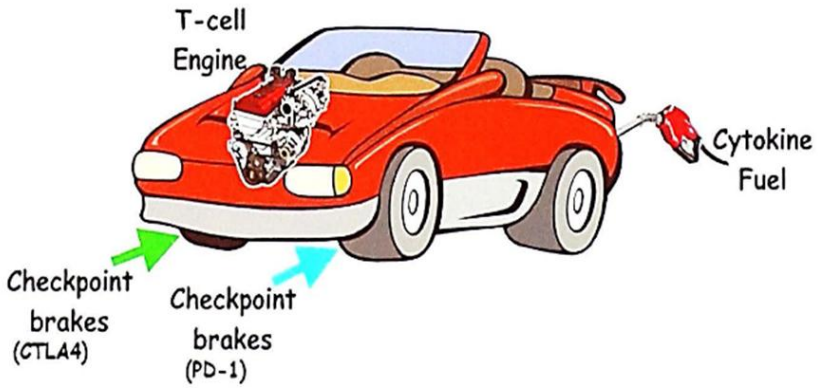
inhibitory receptors

Exhausted T cells

Up-regulation of inhibitory receptors
- *PD-1, TIM-3, CTLA-4, LAG-3, 2B4, CD160*

Down-regulation of cytokine receptors
- *IL-2Rβ, IL-4Rα, IL-7Rα, IL-15Rα*

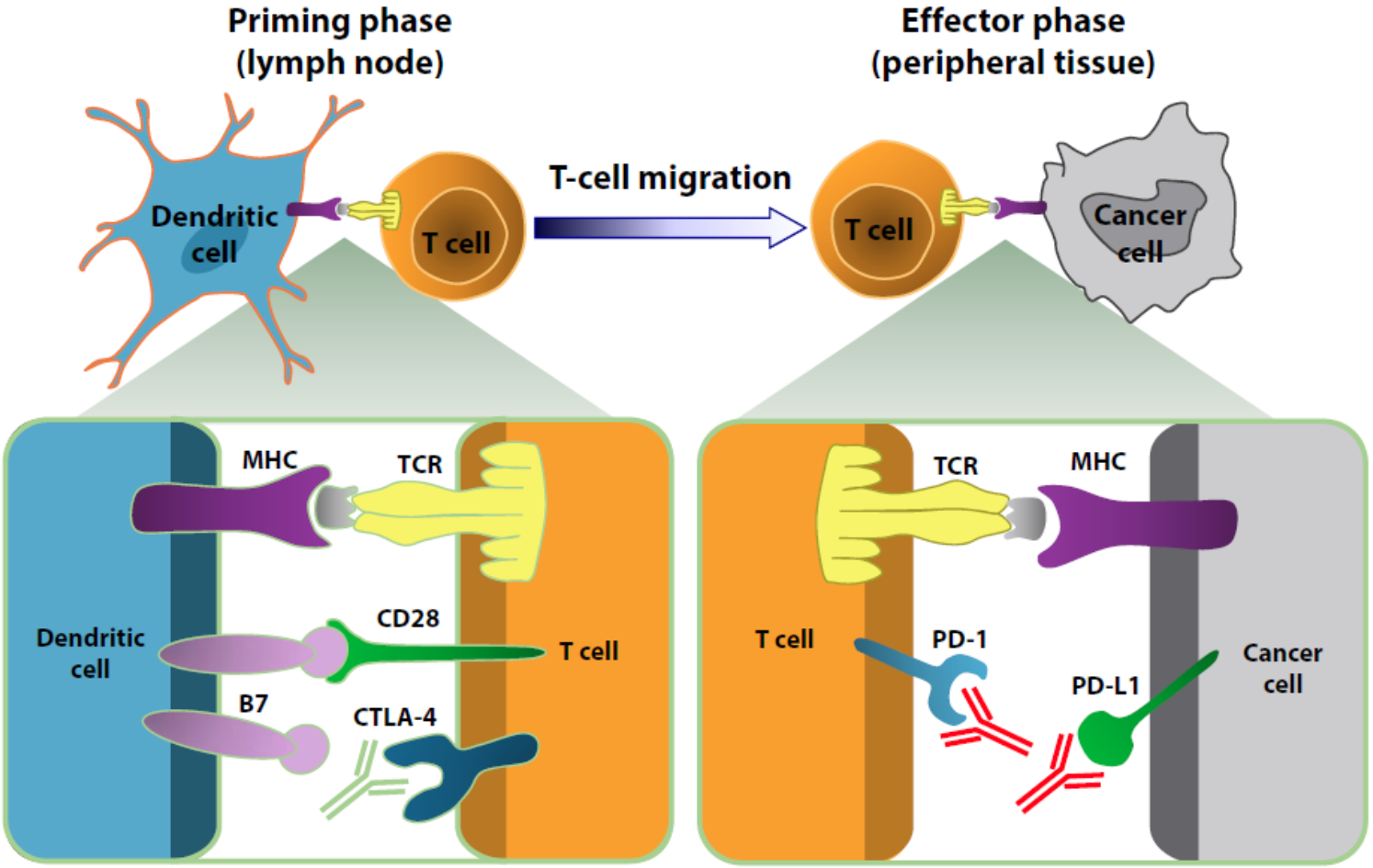




T-regs, MDSC?

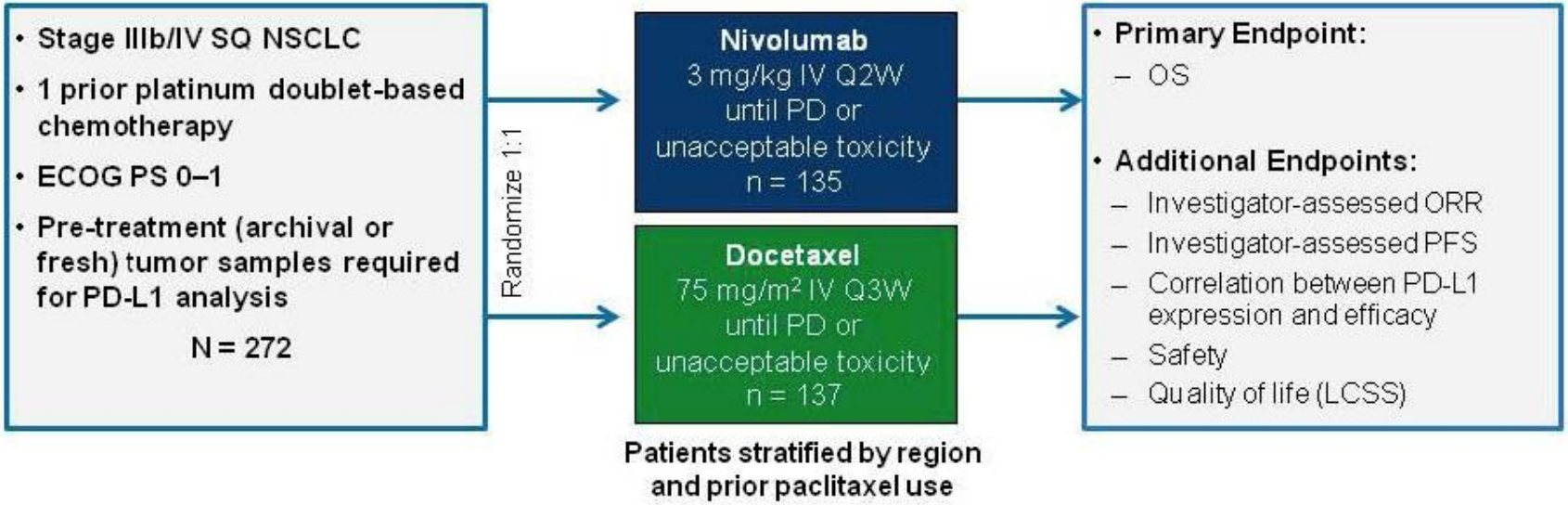
Jin HT *et al.* ***BMB Reports*** 2011 44:217

CTLA-4/B7-1 and PD-1/PD-L1 checkpoint blockade for cancer treatment



Ribas A. ***N Engl J Med*** 2012 366:2517

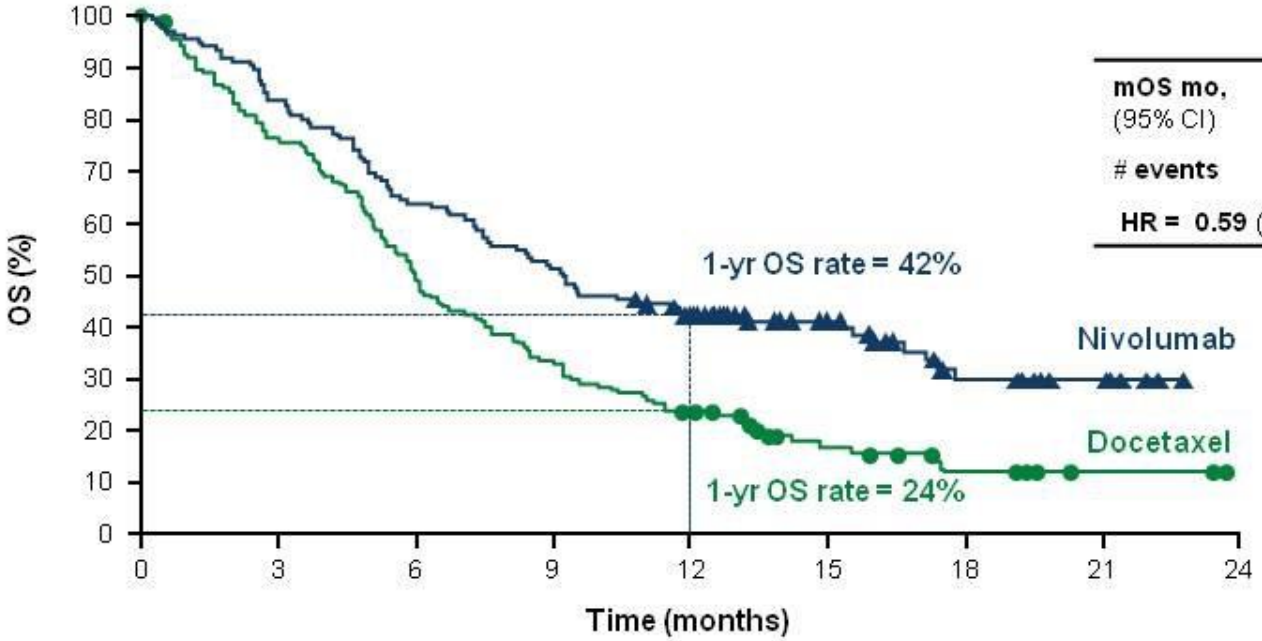
CheckMate 017 (NCT01642004) - Study Design



- One pre-planned interim analysis for OS
- At time of DBL (December 15, 2014), 199 deaths were reported (86% of deaths required for final analysis)
- The boundary for declaring superiority for OS at the pre-planned interim analysis was $P < 0.03$

LCSS = Lung cancer symptom scale

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

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

Symbols represent censored observations

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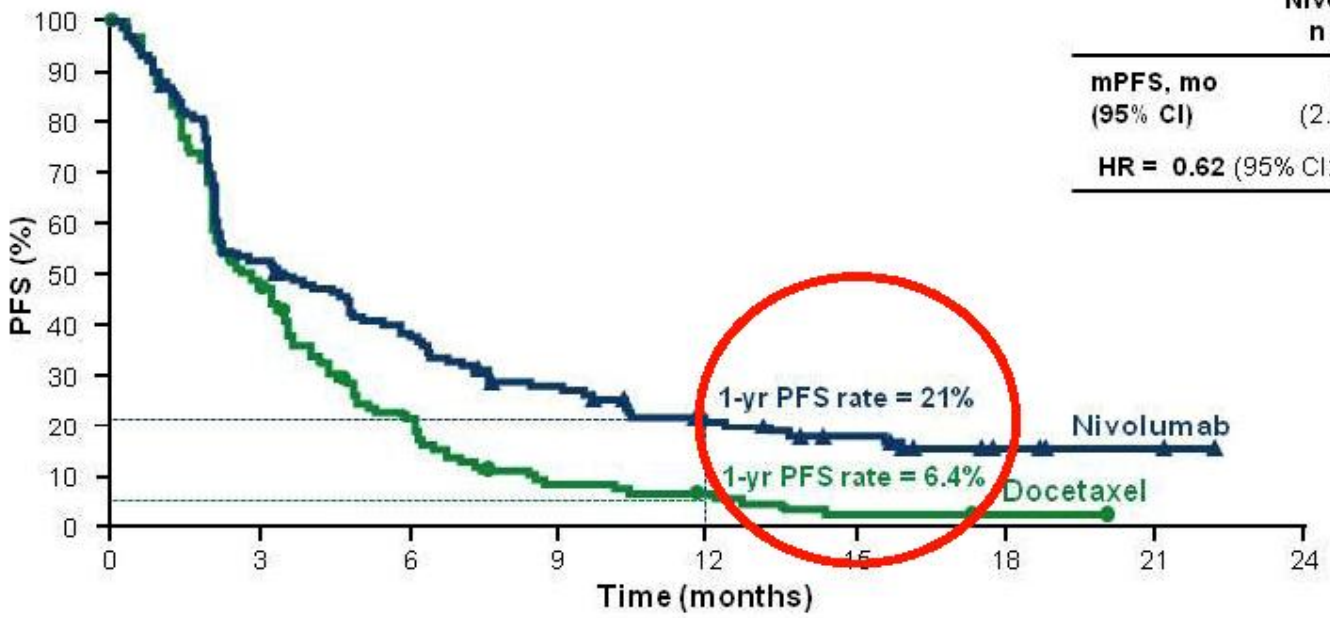
Progression-Free Survival



	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	**3.5** (2.1, 4.9)	**2.8** (2.1, 3.5)

HR = 0.62 (95% CI: 0.47, 0.81); ***P* = 0.0004**

Number of Patients at Risk									
Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

PFS per investigator.

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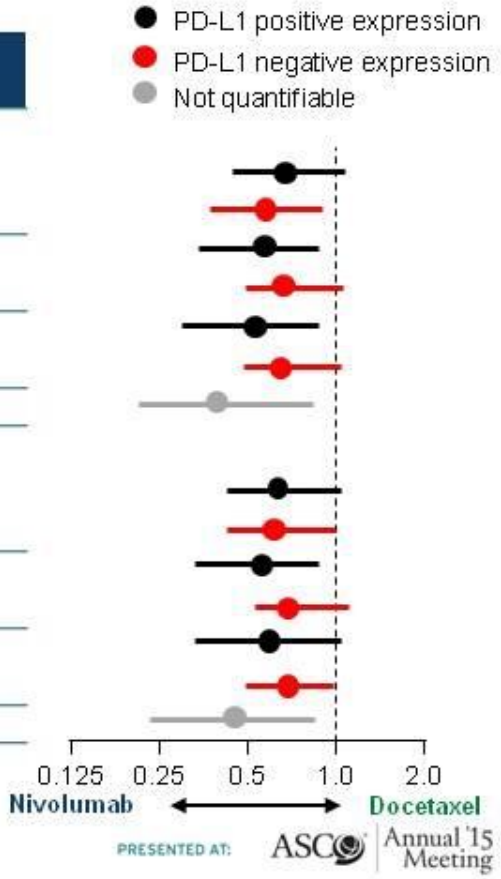
OS and PFS by PD-L1 Expression

- Survival benefit with nivolumab was independent of PD-L1 expression level

PD-L1 expression	Patients, n Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P*-value
OS				
≥1%	63	56	0.69 (0.45, 1.05)	**0.56**
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	**0.47**
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	**0.41**
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	
PFS				
≥1%	63	56	0.67 (0.44, 1.01)	**0.70**
<1%	54	52	0.66 (0.43, 1.00)	
≥5%	42	39	0.54 (0.32, 0.90)	**0.16**
<5%	75	69	0.75 (0.52, 1.08)	
≥10%	36	33	0.58 (0.33, 1.02)	**0.35**
<10%	81	75	0.70 (0.49, 0.99)	
Not quantifiable	18	29	0.45 (0.23, 0.89)	

- PD-L1 expression was measured in pre-treatment tumor biopsies (DAKO automated IHC assay)[15]



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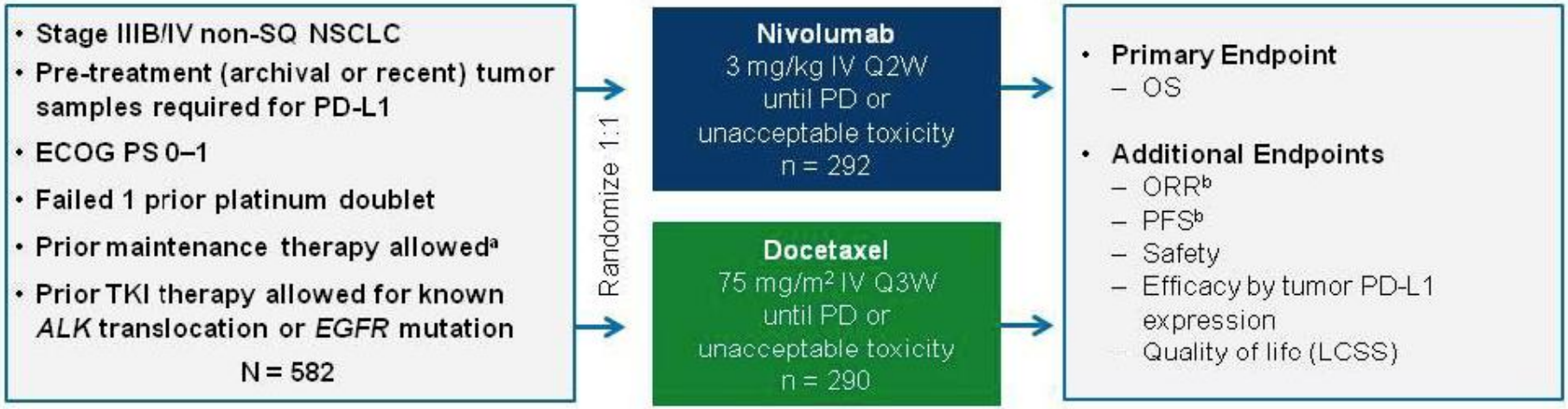
Treatment-related Select AEs

	Nivolumab n = 131		Docetaxel n = 129	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Endocrine, %	4	0	0	0
Hypothyroidism	4	0	0	0
Gastrointestinal, %	8	1	20	2
Diarrhea	8	0	20	2
Colitis	1	1	0	0
Hepatic,[a] %	2	0	2	1
ALT increased	2	0	1	1
AST increased	2	0	1	1
Pulmonary, %	5	1	1[b]	0
Pneumonitis	5	1	0	0
Lung infiltration	1	0	0	0
Interstitial lung disease	0	0	1[b]	0
Renal,[c] %	3	1	2	0
Blood creatinine increased	3	0	2	0
Tubulointerstitial nephritis	1	1	0	0
Skin,[d] %	9	0	9	2
Hypersensitivity/Infusion reaction, %	1	0	2	1
Hypersensitivity	0	0	2	1
Infusion-related reaction	1	0	1	0

- Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention

[a]No cases of increased bilirubin occurred in the nivolumab arm. [b] Grade 5 event. [c]No cases of renal failure were reported in the nivolumab arm. [d] Includes rash, pruritus, erythema, maculopapular rash, skin exfoliation, urticaria and palmar plantar erythrodysasthesia syndrome.

CheckMate 057 (NCT01673867) Study Design



Patients stratified by prior maintenance therapy and line of therapy (second- vs third-line)

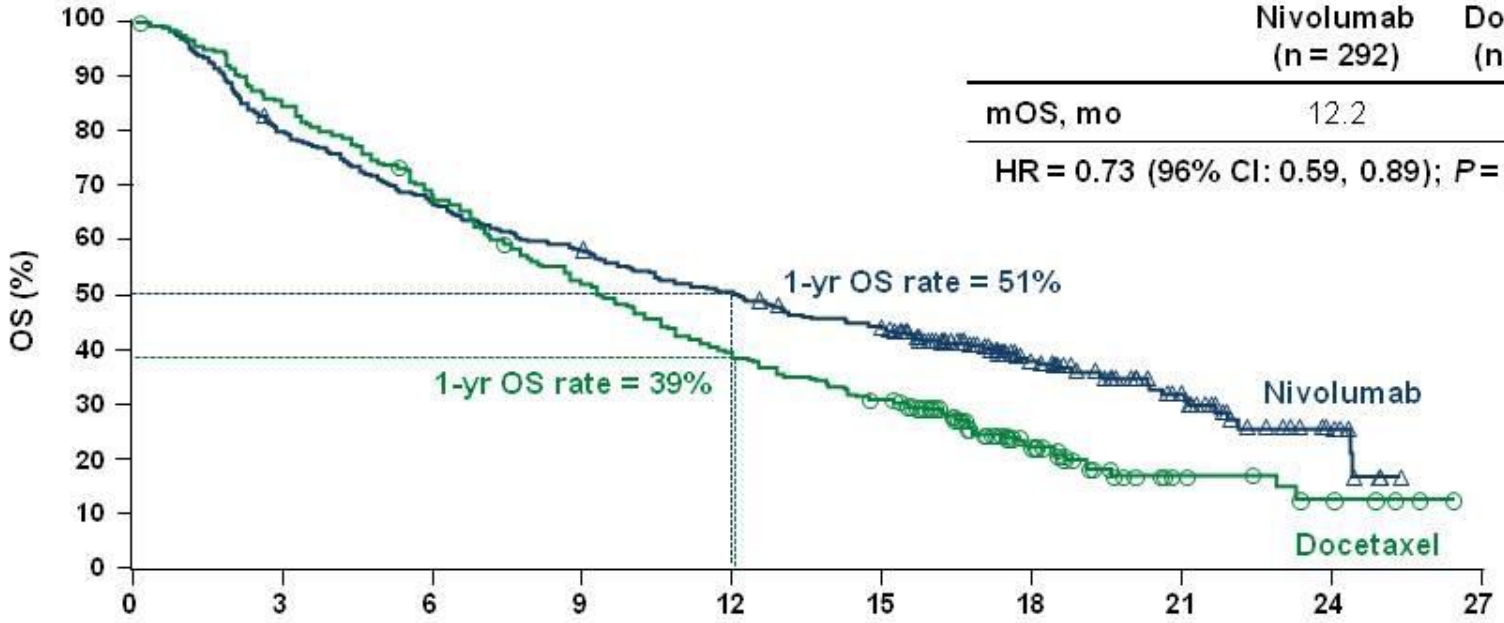
- PD-L1 expression measured using the Dako/BMS automated IHC assay[14,15]
  - Fully validated with analytical performance having met all pre-determined acceptance criteria for sensitivity, specificity, precision, and robustness

[a]Maintenance therapy included pemetrexed, bevacizumab, or erlotinib (not considered a separate line of therapy); [b]Per RECIST v1.1 criteria as determined by the investigator.

Overall Survival

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015



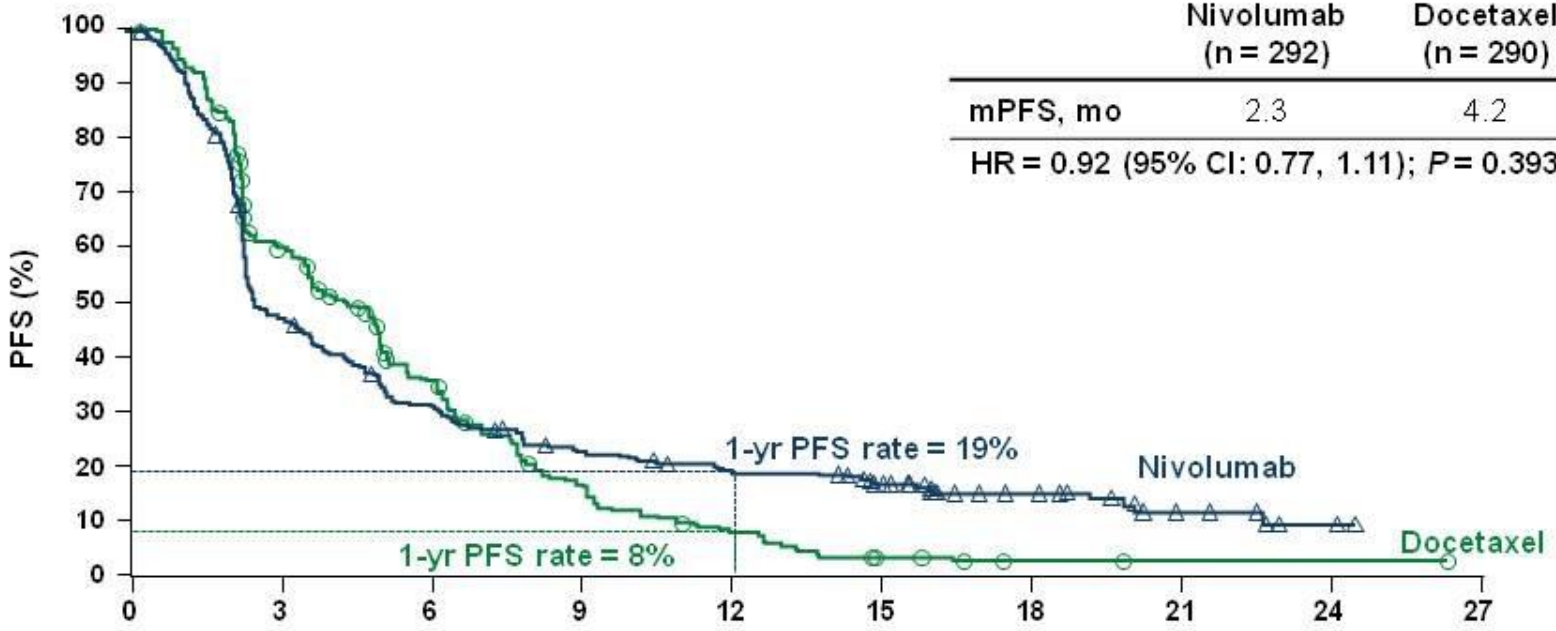
Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Progression-free Survival

	Nivolumab (n = 292)	Docetaxel (n = 290)
mPFS, mo	2.3	4.2

HR = 0.92 (95% CI: 0.77, 1.11); *P* = 0.3932



Number of Patients at Risk										
Nivolumab	292	128	82	58	46	35	17	7	2	0
Docetaxel	290	156	87	38	18	6	2	1	1	0

Symbols represent censored observations.

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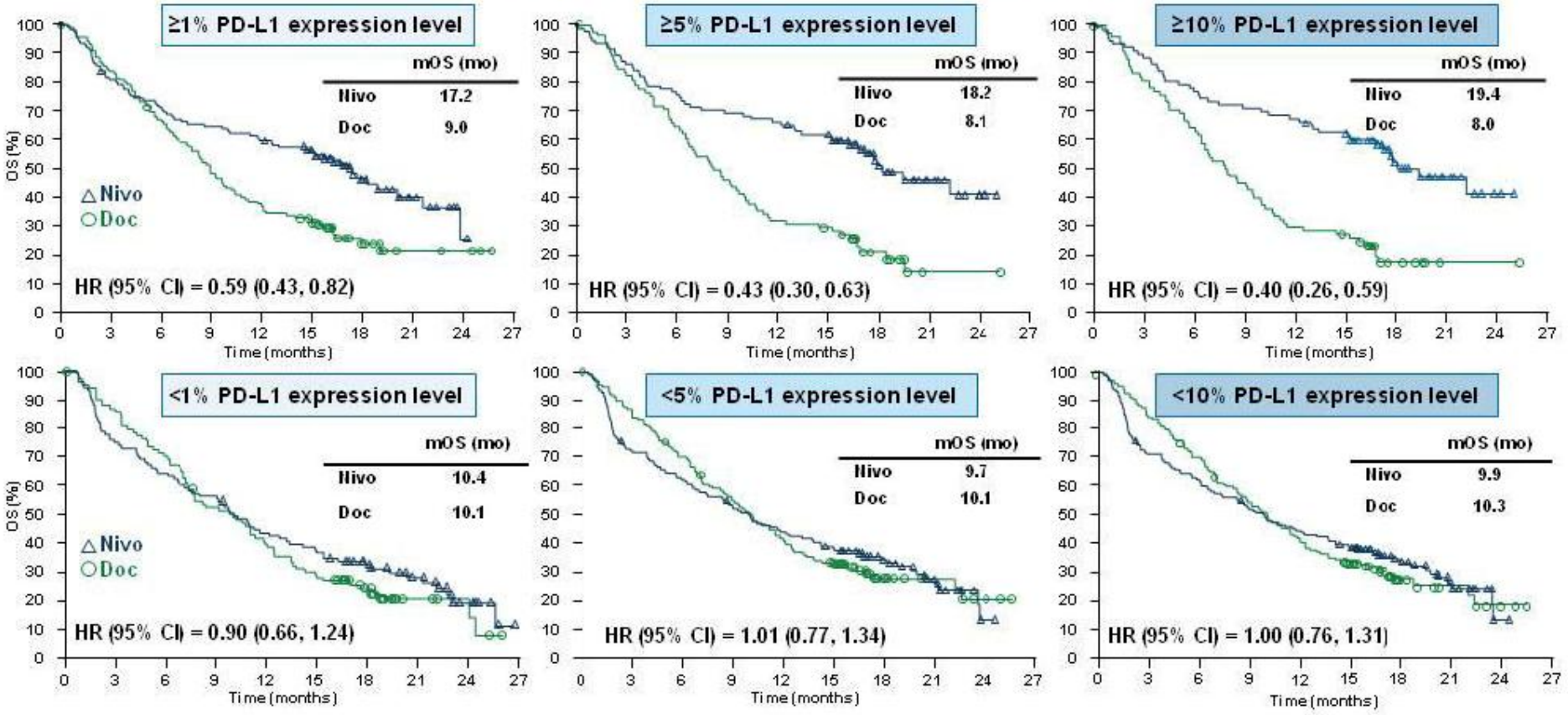
OS by PD-L1 Expression



Symbols represent censored observations.

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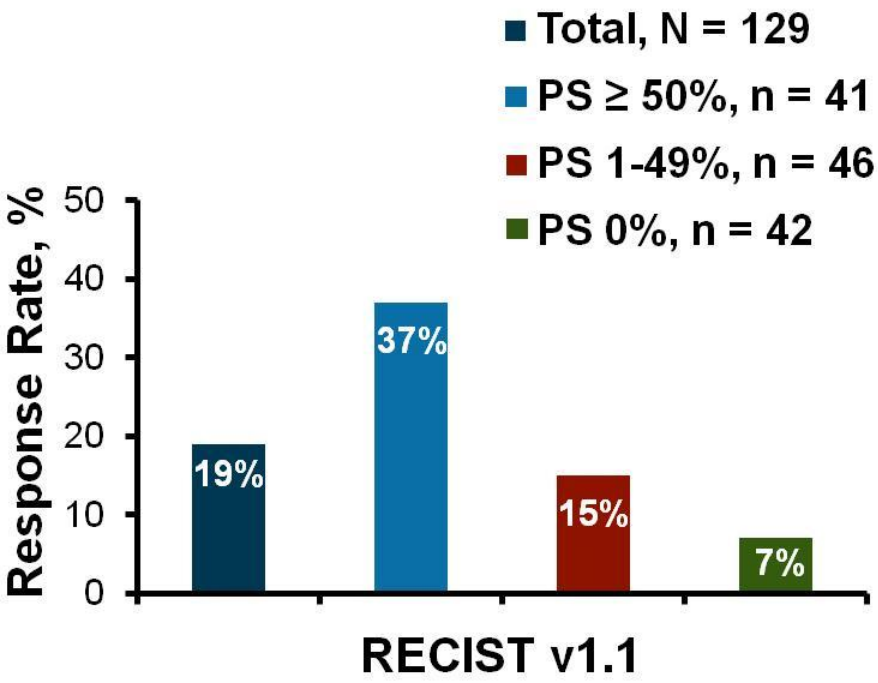
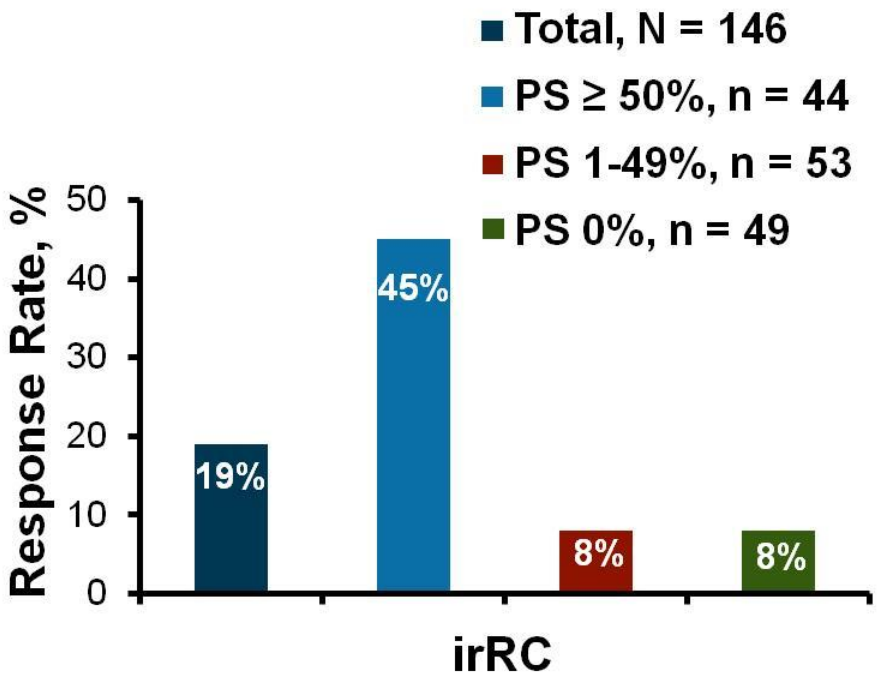
Second line Phase III Trials

Trial	Agent	PD-L1 Status
Checkmate 057	Nivolumab vs. docetaxel (non-squamous)	Not required
Keynote 010	Pembrolizumab vs. docetaxel	PD-L1 positive
OAK	MPDL3280A vs. docetaxel	PD L1 positive
LUNG-MAP	MEDI4736 vs docetaxel	Not required

Relationship Between PD-L1 Tumor Status and Response to MK-3475

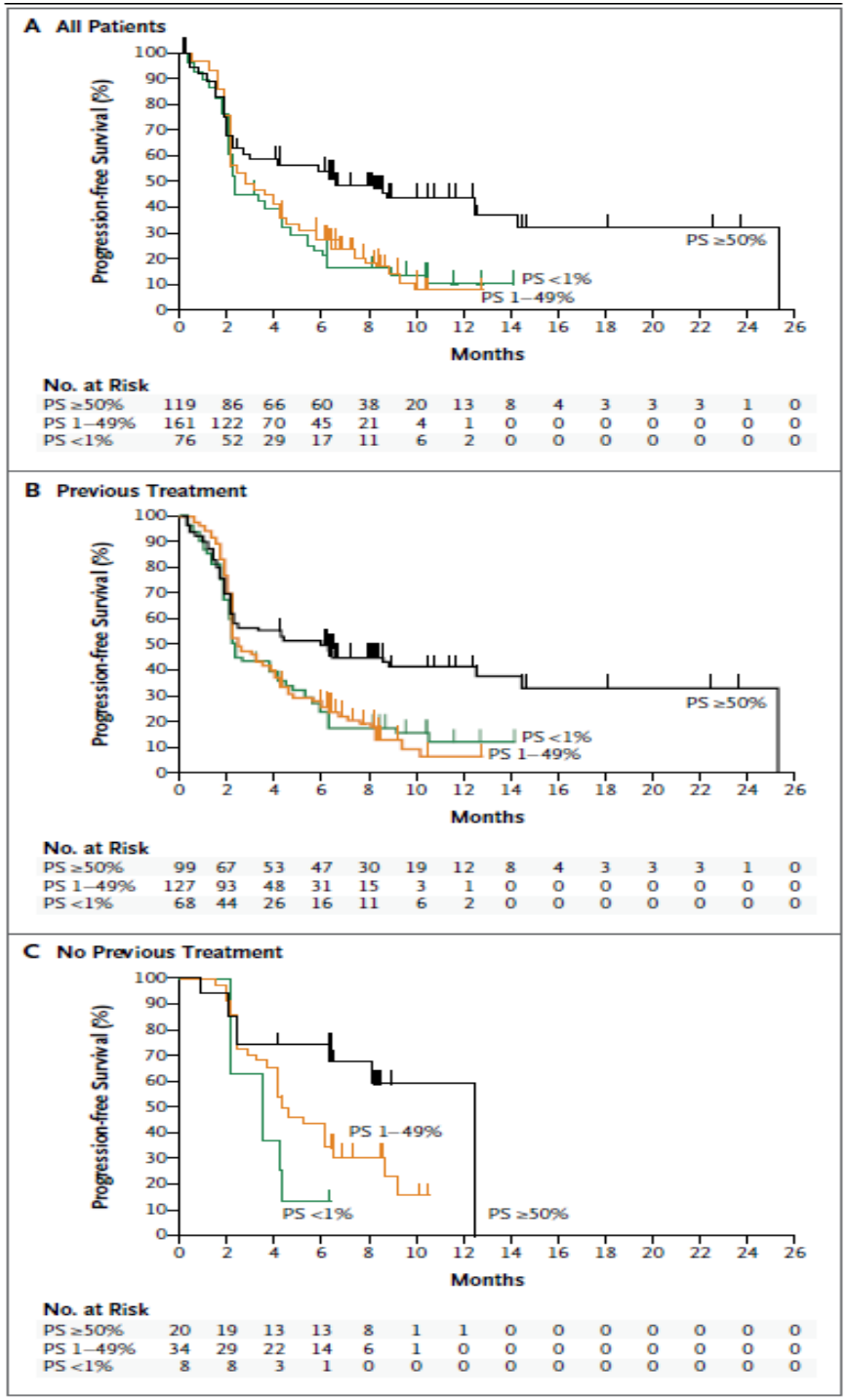
Pretreated Advanced NSCLC

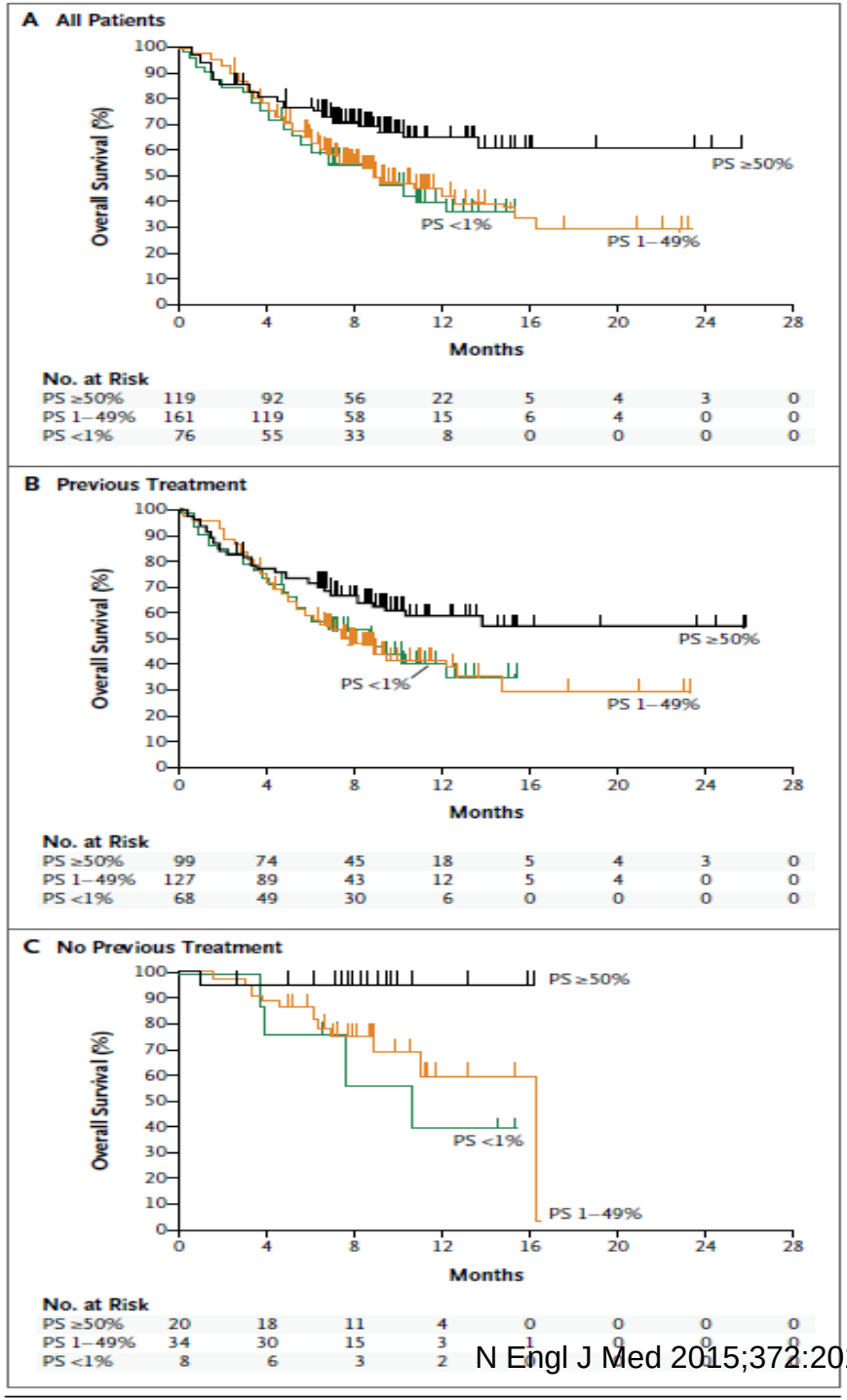




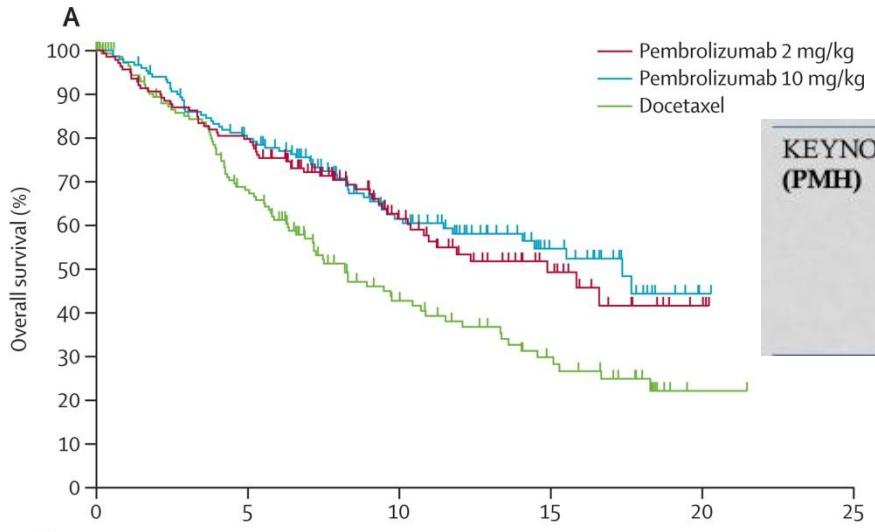
PS = PD-L1 proportion score.

Gandhi L, et al. AACR 2014. Abstract CT105.[37]



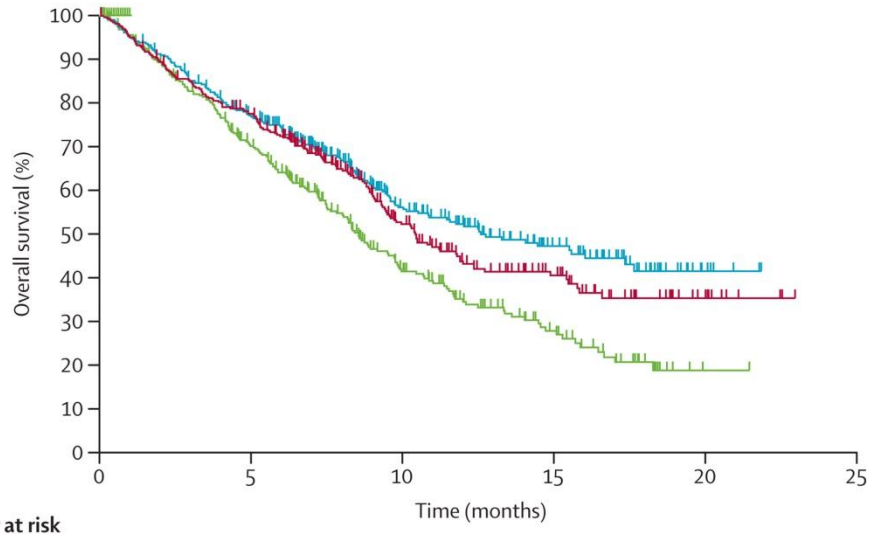


N Engl J Med 2015;372:2018-28



Number at risk

Pembrolizumab 2 mg/kg	139	110	51	20	3	0
Pembrolizumab 10 mg/kg	151	115	60	25	1	0
Docetaxel	152	90	38	19	1	0



Number at risk

Pembrolizumab 2 mg/kg	344	259	115	49	12	0
Pembrolizumab 10 mg/kg	346	255	124	56	6	0
Docetaxel	343	212	79	33	1	0

KEYNOTE-010 **(PMH)**	NSCLC PD-L1(+) tumors who have disease progression after platinum-containing therapy	Phase 2/3	Pembrolizumab: 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks vs. Docetaxel 75 mg/m^2 every 3 weeks

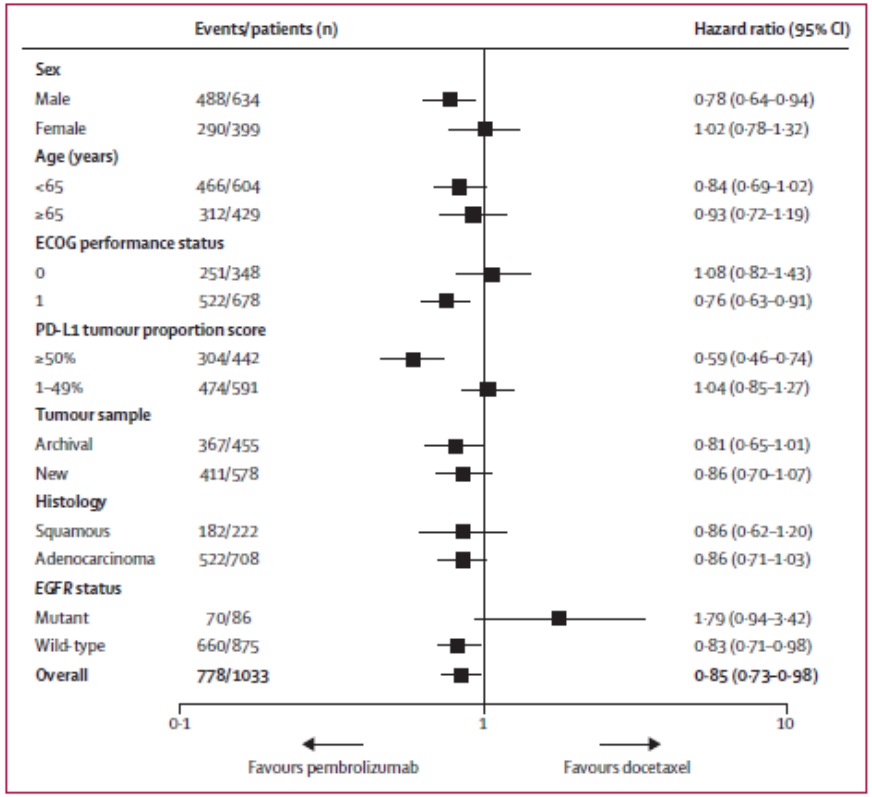


Figure 5: **Subgroup analysis of progression-free survival**
Shows the comparison of the pooled pembrolizumab doses versus docetaxel. ECOG=Eastern Cooperative Oncology Group.

Lancet 2016 Apr 387:1540-1550

POPLAR: A Randomized All-comer Phase II Study

Metastatic or locally advanced NSCLC (2L/3L)
Disease progression on a prior platinum therapy
N = 287

Stratification Factors
- PD-L1 IC expression (0 vs 1 vs 2 vs 3)[a]
- Histology (squamous vs non-squamous)
- Prior chemotherapy regimens (1 vs 2)

R 1:1

Atezolizumab
1200 mg IV q3w
until loss of clinical benefit

Docetaxel
75 mg/m^2 IV q3w
until disease progression

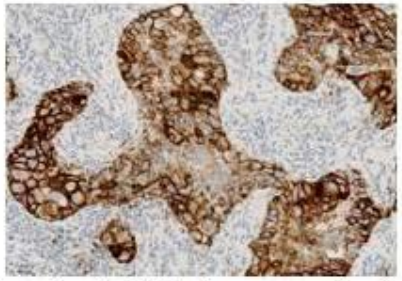
Primary study objective:
- **Estimate OS in PD-L1 selected and ITT populations**

Secondary study objectives:
- Evaluate PFS, ORR and DOR in PD-L1 selected and ITT populations
- Evaluate safety

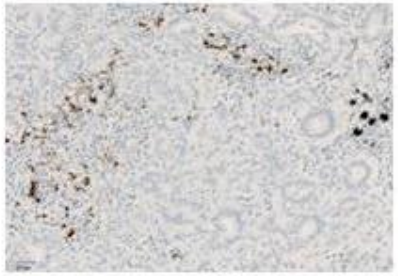
Interim analysis is based on 153 events with a minimum follow-up 10 months

[a]Archival or fresh tissue required for pre-dose testing.

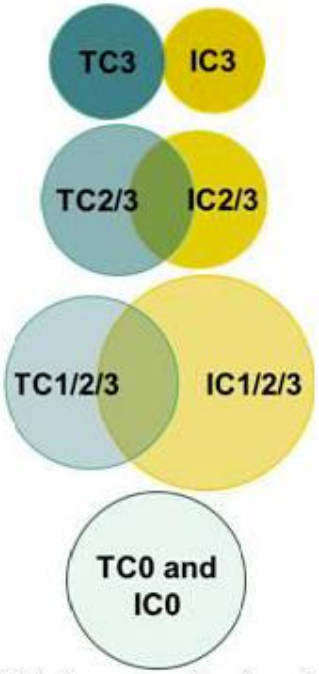
PD-L1 Expression on TC and IC is a Potential Predictive Biomarker for Atezolizumab in NSCLC



Intrinsic PD-L1 expression in tumor cells (TC)



Adaptive PD-L1 expression in tumor-infiltrating immune cells (IC)



PD-L1 expression levels and TC/IC overlap in POPLAR

- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels[a] (Gettinger et al., ASCO 2015)
- PD-L1 expression on TC and IC was independently predictive of response (Horn et al. and Spigel et al., ASCO 2015)

[a]TC scored as percentage of tumor cells and IC scored as percentage of tumor area. **TC3 or IC3** = TC ≥ 50% or IC ≥ 10% PD-L1+; **TC2/3 or IC2/3** = TC or IC ≥ 5% PD-L1+; **TC1/2/3 or IC1/2/3** = TC or IC ≥ 1% PD-L1+; **TC0 and IC0** = TC and IC < 1% PD-L1+, respectively.

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Ongoing Phase III Trials

Trial	Line of Therapy	Agent	PD-L1 Status
CheckMate 026	First	Nivolumab vs. investigator choice chemotherapy	PD-L1 positive
Keynote 042/42	First	Pembrolizumab vs. investigator choice chemotherapy	PD-L1 positive
ARCTIC	Third Line	MEDI4736 vs. Chemotherapy	Not required
PACIFIC	Locally Advanced	Following concurrent chemo-RT vs. placebo	Not required

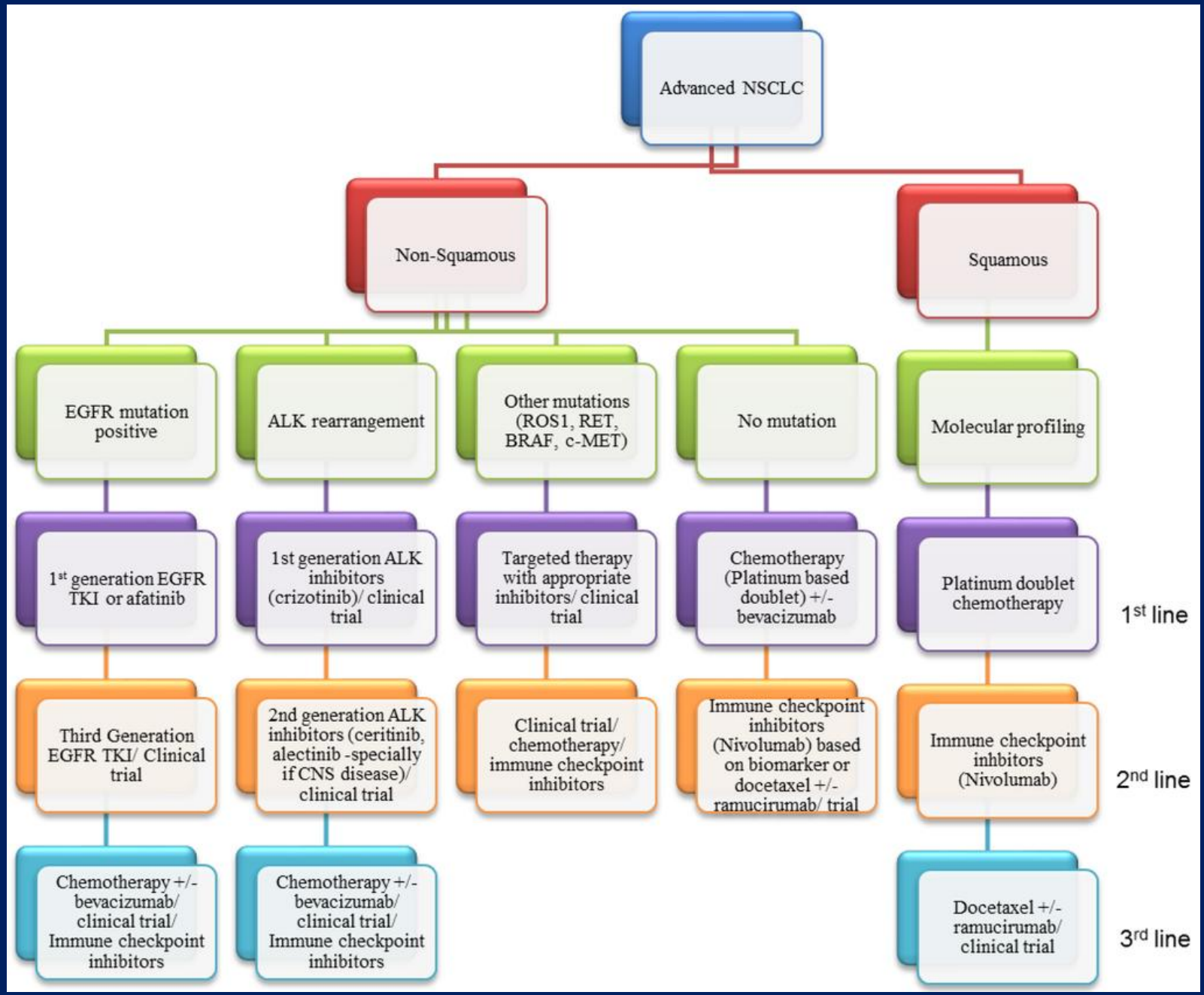
Phase III Trials in Development:

1) Maintenance therapy in advanced NSCLC
2) Adjuvant therapy

Treatment Related Adverse Events

- Fatigue is the most common AE (24%)
- Grade 3-4 AEs are uncommon (6-12.6%)

System	Immune Related Adverse Events
Gastrointestinal	Colitis (Diarrhea, perforation)
Renal	Acute Interstitial Nephritis (Increased serum Creatinine)
Pulmonary	Pneumonitis (dyspnea, cough)
Dermatologic	Dermatitis (Lichenoid/ spongiotic dermatitis, rash), Vitaligo
Hepatic	Hepatitis (elevated LFTs)
Neurologic	Central and Peripheral (Aseptic Meningitis, Guillan-Barre Syndrome, Myasthenia Gravis
Endocrine	Hypophysitis, thyroiditis, adrenal insufficiency
Ocular	Uveitis, Iritis


Advanced NSCLC
Non-Squamous
Squamous
EGFR mutation positive
ALK rearrangement
Other mutations (ROS1, RET, BRAF, c-MET)
No mutation
Molecular profiling
1st generation EGFR TKI or afatinib
1st generation ALK inhibitors (crizotinib)/ clinical trial
Targeted therapy with appropriate inhibitors/ clinical trial
Chemotherapy (Platinum based doublet) +/- bevacizumab
Platinum doublet chemotherapy
1st line
Third Generation EGFR TKI/ Clinical trial
2nd generation ALK inhibitors (ceritinib, alectinib -specially if CNS disease)/ clinical trial
Clinical trial/ chemotherapy/ immune checkpoint inhibitors
Immune checkpoint inhibitors (Nivolumab) based on biomarker or docetaxel +/- ramucirumab/ trial
Immune checkpoint inhbitors (Nivolumab)
2nd line
Chemotherapy +/- bevacizumab/ clinical trial/ Immune checkpoint inhibitors
Chemotherapy +/- bevacizumab/ clinical trial/ Immune checkpoint inhibitors
Docetaxel +/- ramucirumab/ clinical trial
3rd line