

# Precision Medicine in advanced NSCLC – Tissue is the issue

Alona Zer, MD

Head, Thoracic Oncology Service  
Davidoff Cancer Center  
Rabin Medical Center  
Tel Aviv University



# Disclosures

- Research support - BMS
- Advisory board – Lilly, AZ
- Honoraria – Lilly, Novartis, BMS, Roche, MSD

This session sponsored by AstraZeneca

The presented material reflects my point of view only

# אפידמיולוגיה

Estimated New Cases\*

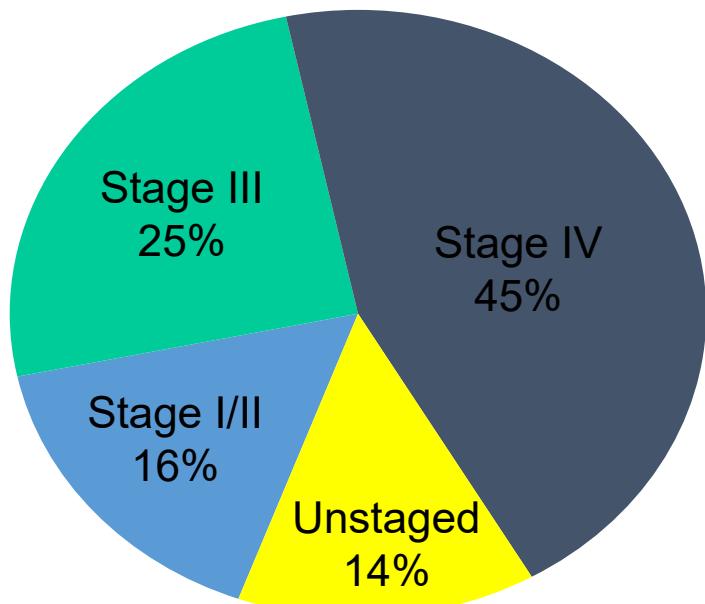
	Males	Females		
Prostate	233,000	27%	Breast	232,670 29%
Lung & bronchus	116,000	14%	Lung & bronchus	108,210 13%
Colorectum	71,830	8%	Colorectum	65,000 8%
Urinary bladder	56,390	7%	Uterine corpus	52,630 6%
Melanoma of the skin	43,890	5%	Thyroid	47,790 6%
Kidney & renal pelvis	39,140	5%	Non-Hodgkin lymphoma	32,530 4%
Non-Hodgkin lymphoma	38,270	4%	Melanoma of the skin	32,210 4%
Oral cavity & pharynx	30,220	4%	Kidney & renal pelvis	24,780 3%
Leukemia	30,100	4%	Pancreas	22,890 3%
Liver & intrahepatic bile duct	24,600	3%	Leukemia	22,280 3%
All Sites	855,220	100%	All Sites	810,320 100%

Estimated Deaths

	Males	Females		
Lung & bronchus	86,930	28%	Lung & bronchus	72,330 26%
Prostate	29,480	10%	Breast	40,000 15%
Colorectum	26,270	8%	Colorectum	24,040 9%
Pancreas	20,170	7%	Pancreas	19,420 7%
Liver & intrahepatic bile duct	15,870	5%	Ovary	14,270 5%
Leukemia	14,040	5%	Leukemia	10,050 4%
Esophagus	12,450	4%	Uterine corpus	8,590 3%
Urinary bladder	11,170	4%	Non-Hodgkin lymphoma	8,520 3%
Non-Hodgkin lymphoma	10,470	3%	Liver & intrahepatic bile duct	7,130 3%
Kidney & renal pelvis	8,900	3%	Brain & other nervous system	6,230 2%
All Sites	310,010	100%	All Sites	275,710 100%

- אחד הסרטנים היוטר שכיחים
- סיבת המוות מס' 1 סרטן
- 2 מיליון - אובחנו עם סרטן ריאה בעולם בשנת 2015
- 1.5 מיליון – מתו הסרטן ריאה ב-2015

## 프로그램וזה

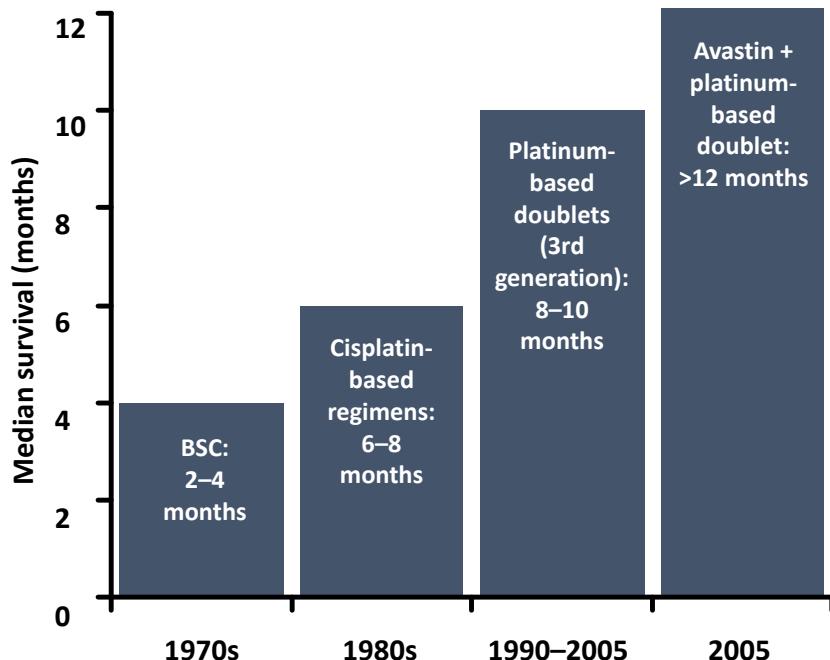


התפלגות שלב המחלת באבחון – SEER DATABASE

- תלואה בשלב המחלת
- בארה"ב רק 18% מהמאבחנים חיים כעבור 5 שנים ( $5y\text{ OS}=18\%$ )
- מבין החולים עם מחלת גורותית –  
 $5y\text{ OS}=4\%$

# Prognosis Stage IV NSCLC – 1970-2010

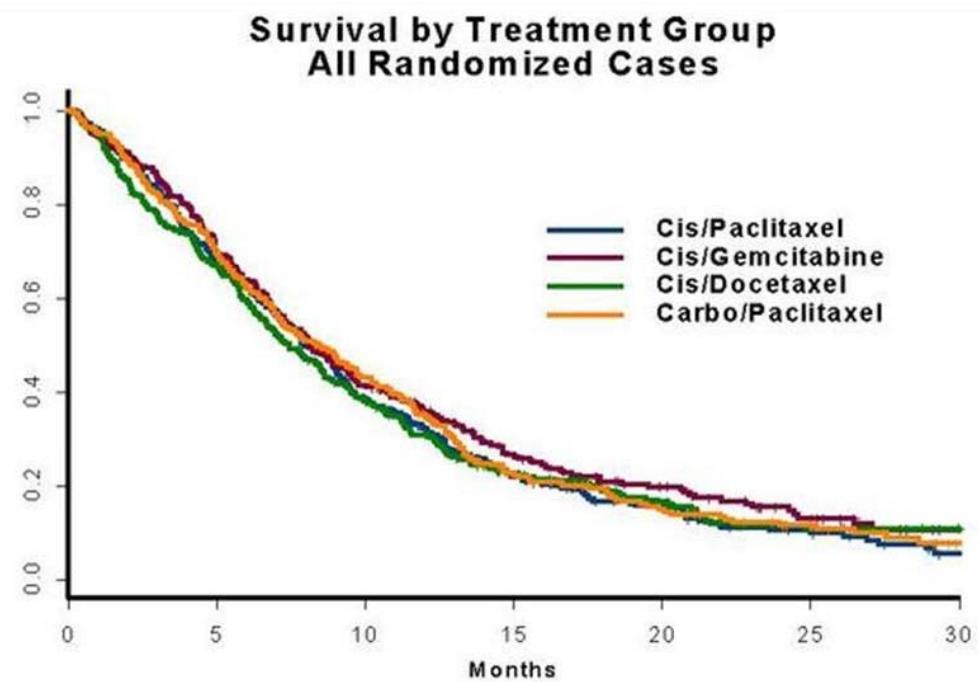
ECOG 1594 OS by Tx group



**Median survival: 12 months ; ORR 25-40%**

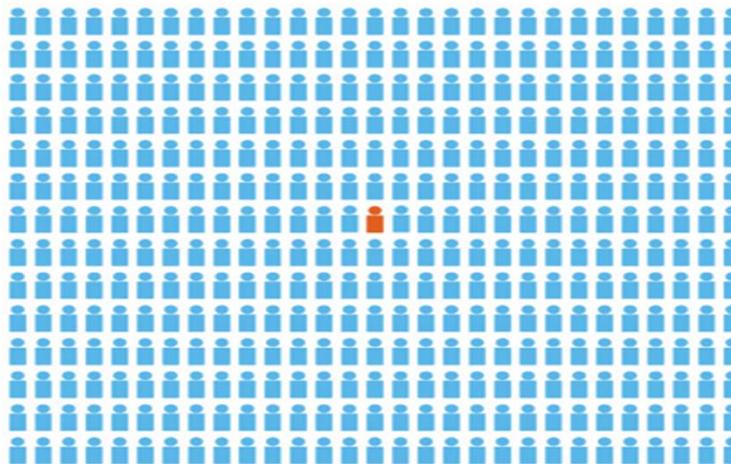
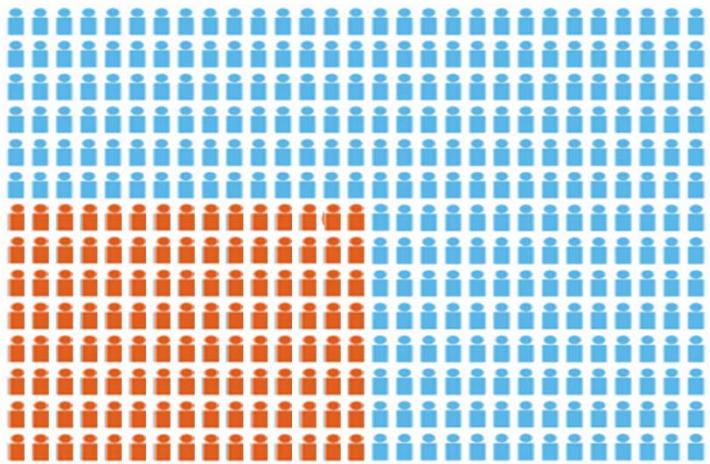
Socinski MA, et al. J Clin Oncol. 2012. Schiller et al, NEJM 2012.

Paz-Ares LG, et al. J Clin Oncol. 2013.



**Platinum-whatever for everyone**

**CURRENT STATE**



- Personalized medicine
- Precision medicine
- Targeted therapy

**Personalized Medicine** (see also **Precision Medicine**) refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not". This term is now widely used, including in advertisements for commercial products, and it is sometimes misinterpreted as implying that unique treatments can be designed for each individual. For this reason, the Committee thinks that the term "precision medicine" is preferable to "personalized medicine" to convey the meaning intended in this report.

## ד"ר – זה מתאים לי?

רפואה מותאמת אישית

מכון ויצמן גייס תרומות בהיקף  
520 מיליון דולר, להקמת מרכז  
לאומי לרפואה מותאמת אישית  
על-שם ננסי וסטיבן גראנד

11.11.2013 | מחלות, רפואיות וטיפולים, רפואיות מותאמת אישית



המרכז ישרת את כל הקוילט המחבר בישראל בתחום  
מדעי-החיים והביו-רפואה

רפואיות מותאמת אישית | y net



## "להפוך את הסרטן לסקירת"

## בריאות ואיכות חיים

מפענה הבדיקות • כאבי ראש • כאבי גב • שאיפות גדולות • דוקטור, אני רק שאלתך • הטיפ היומי •

סרטן ריאיה: רפואיות מותאמת אישית - לא  
תופעות לוואי



# Precision medicine equation

X =

biomarker (drugable target) + test/essay + drug

?

Efficacy

Efficacy

Availability

Availability

Cost

Cost

# Precision medicine equation

biomarker (drugable target) + test/essay + drug

Efficacy

Efficacy

Availability

Availability

Cost

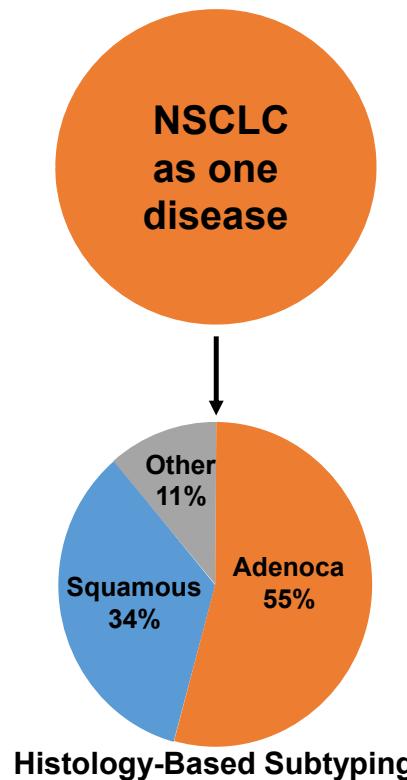
Cost

ER

IHC

Tamoxi

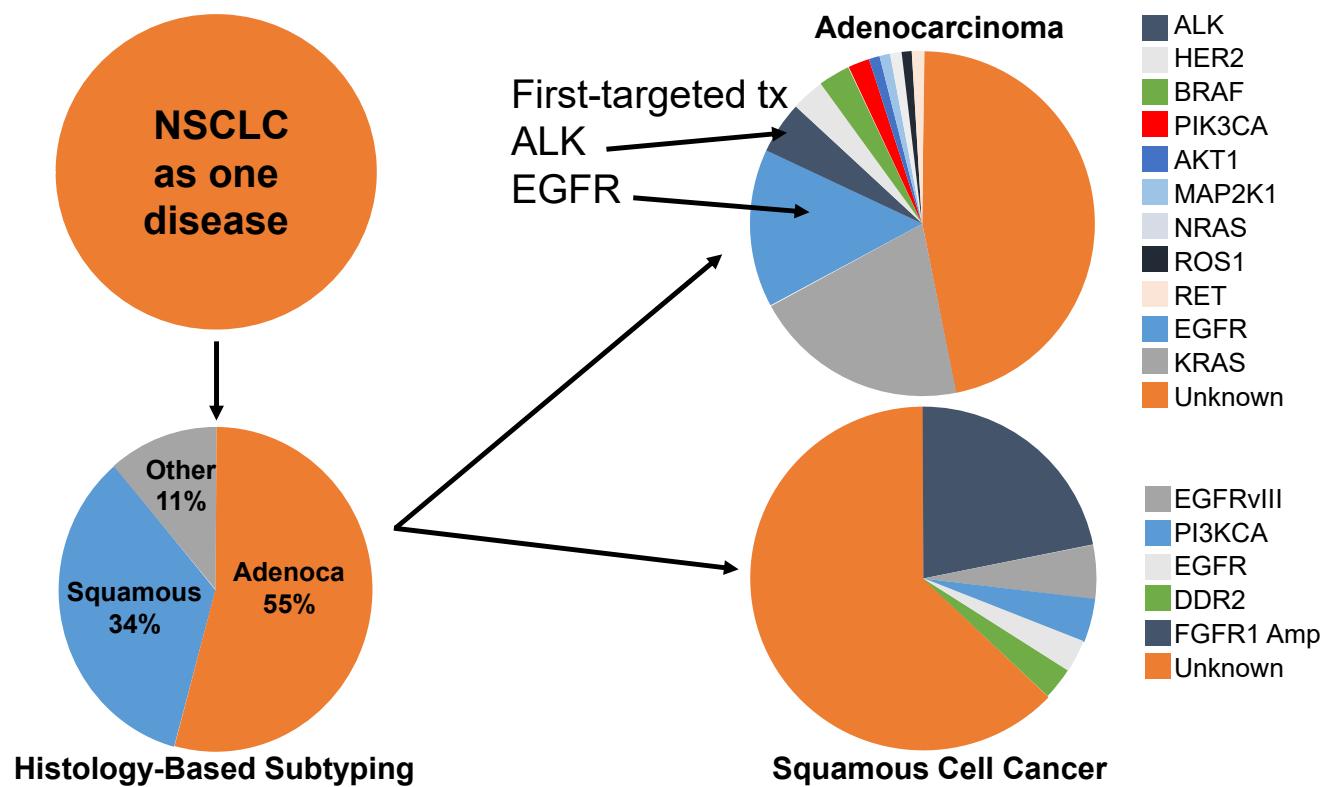
# Evolution of NSCLC Subtyping – Step 1 - Histology



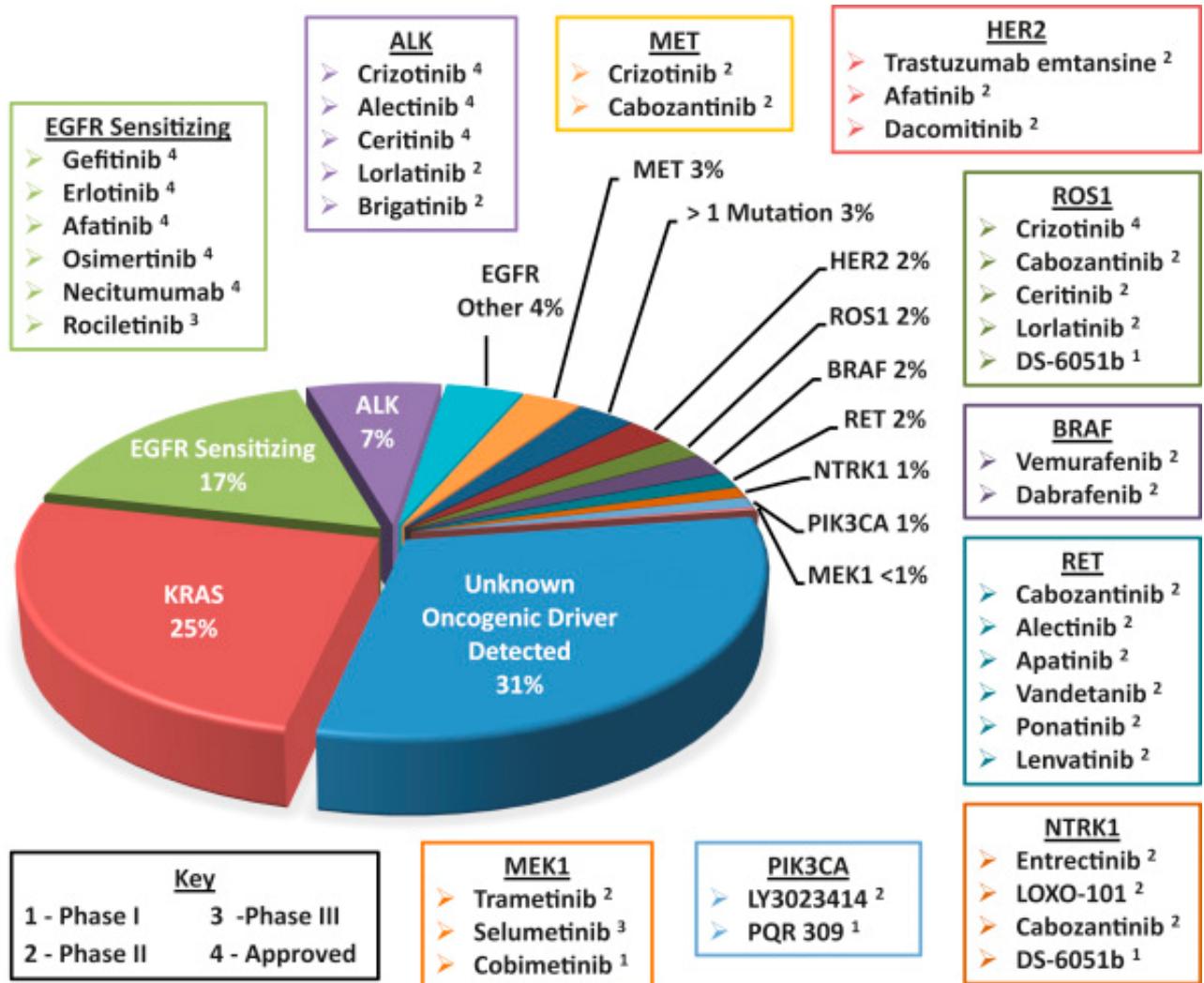
Survival	Pemetrexed + Cisplatin (n = 862)	Gemcitabine + Cisplatin (n = 863)	HR (95% CI)	P Value
Median OS, mos	10.3	10.3	0.94 (0.84-1.05)	Noninferior
Adenocarcinoma (N = 847)	<b>12.6</b>	<b>10.9</b>	0.84 (0.71-0.99)	.03
Large-cell carcinoma (N = 153)	10.4	6.7	0.67 (0.48-0.96)	.03
Squamous cell carcinoma (N = 473)	<b>9.4</b>	<b>10.8</b>	1.23 (1.00-1.51)	.05

Scagliotti GV, et al. J Clin Oncol. 2008;26:3543-3551.

# Evolution of NSCLC Subtyping – Step 2 - Molecular-Defined Subsets

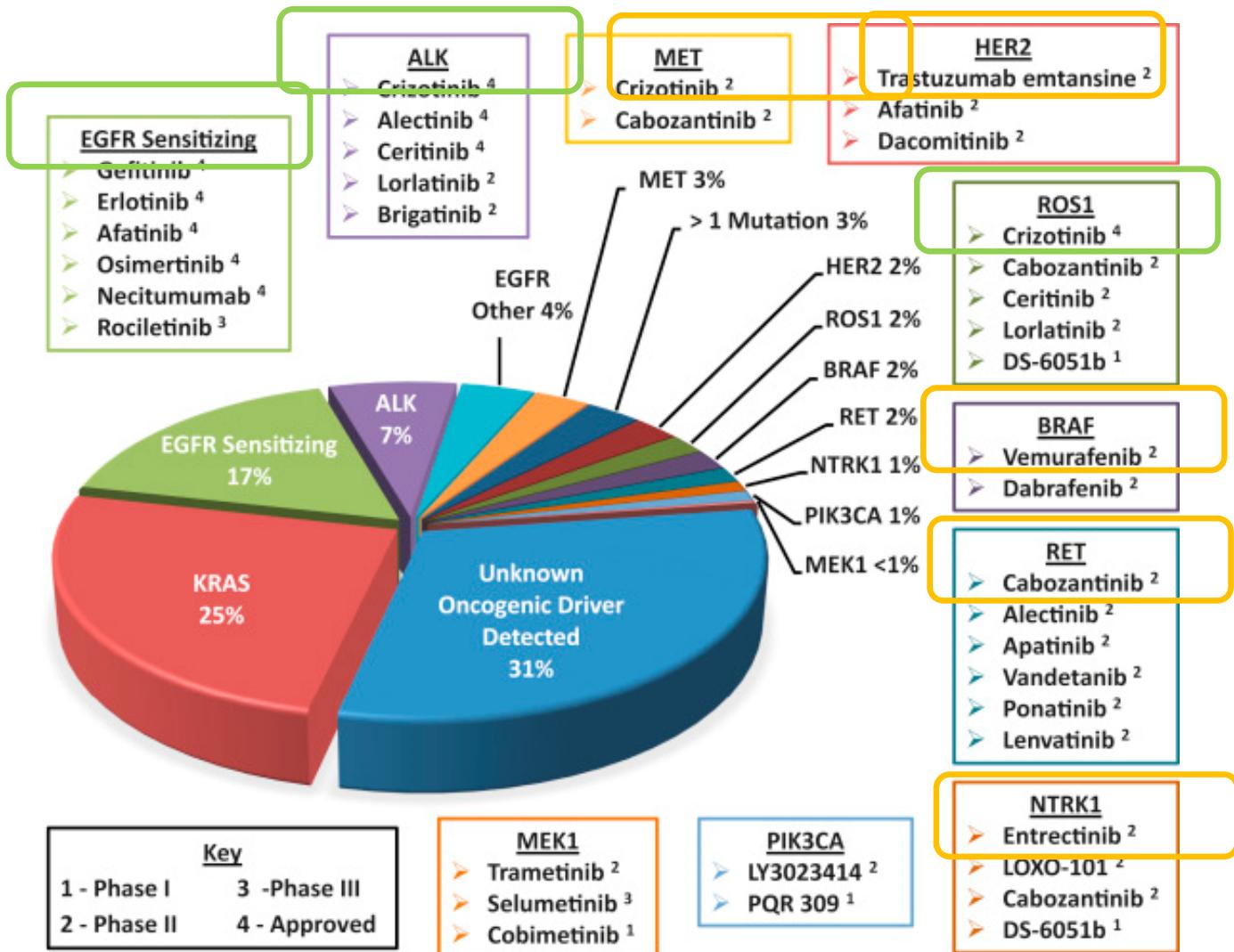


- Methods of detection?
- Are they drugable?
- What is the data to support targeted treatment efficacy?
- Are those drugs available outside a clinical trial?



Adapted from Lung Cancer Mutation Consortium and Journal of Thoracic Oncology 2016)

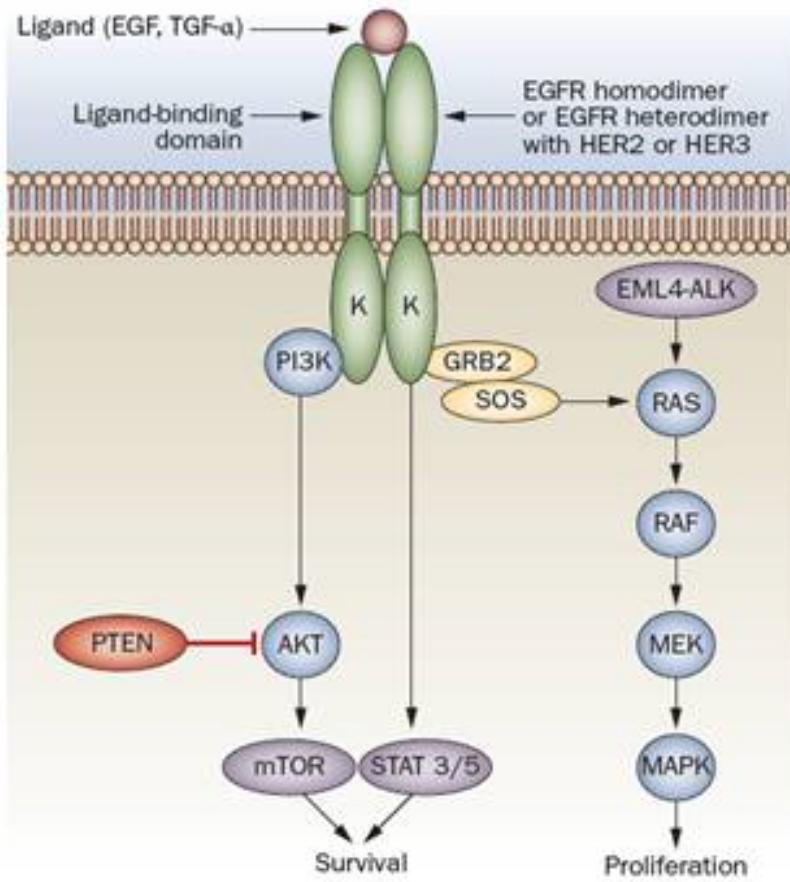
- Methods of detection?
- Are they drugable?
- What is the data to support targeted treatment efficacy?
- Are those drugs available outside a clinical trial?



Adapted from Lung Cancer Mutation Consortium and Journal of Thoracic Oncology 2016)

# EGFR

- EGFR is overexpressed in many malignancies
- *EGFR* mutations activate PI3K/mTOR and MAPK pathways
- *EGFR* mutations are present in 10%-30% of NSCLC (adenocarcinomas)
- *EGFR* mutations predict response to EGFR TKIs



<https://www.youtube.com/watch?v=5pMguzuSP1c>

# TKIs - פעילות חוותי הטירוזין קינאז

## 1<sup>st</sup> Gen EGFR TKIs:

Gefitinib (Iressa)



Erlotinib (Tarceva)

## 2<sup>nd</sup> Gen EGFR TKIs:

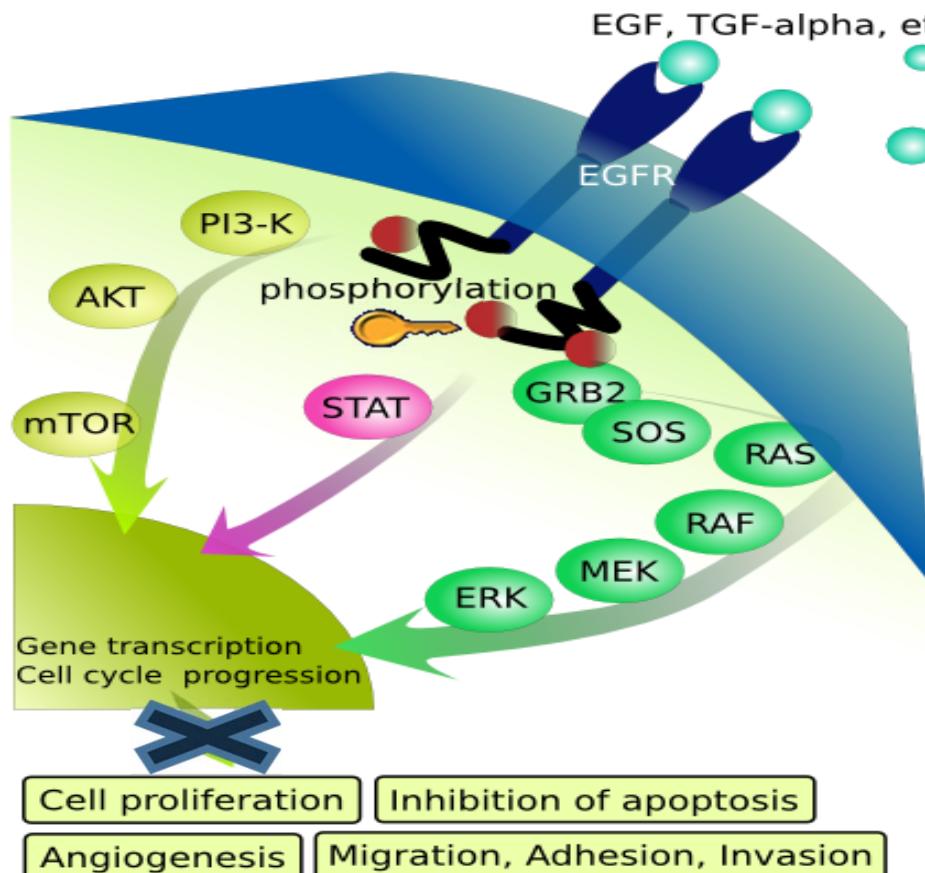
Afatinib (Giotrif)



Dacomitinib

Neratinib

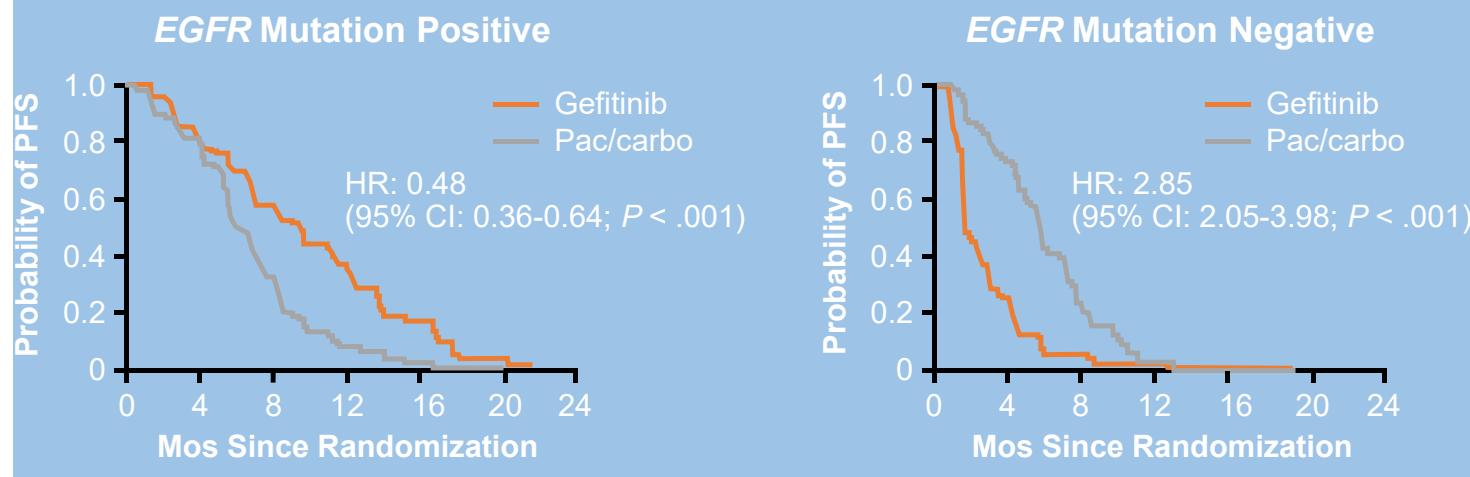
התוצאה -  
אפקטואיזו של  
הטה.



תרופות תוך תאיות  
מוקדות חוסמות  
פוטורילציה של טירוזין  
קינאז ומעכבות את  
מעבר הסיגナル.

# IPASS: Gefitinib vs Paclitaxel/Carbo in NSCLC: PFS by *EGFR* Status

- Randomized phase III trial; previously untreated pts with advanced NSCLC (N = 1217)
- PFS: Gefitinib superior to carboplatin/paclitaxel in ITT population
- ***EGFR* mutations** strongly predicted PFS (and tumor response) to first-line gefitinib vs carboplatin/paclitaxel



Mok TS, et al. N Engl J Med. 2009;361:947-957.

# First-line Treatment With EGFR TKIs vs Chemotherapy in *EGFR*-Mutated NSCLC

Study	Treatment	N	Median PFS, Mos	Median OS, Mos
Maemondo <sup>[1]</sup>	Gefitinib vs carboplatin/paclitaxel	230	10.8 vs 5.4 (P < .001)	<b>30.5 vs 23.6</b> (P = .31)
Mitsudomi <sup>[2,3]</sup>	Gefitinib vs cisplatin/docetaxel	172	9.2 vs 6.3 (P < .0001)	<b>35.5 vs 38.8</b> (HR: 1.19)
OPTIMAL <sup>[4,5]</sup>	Erlotinib vs carboplatin/gemcitabine	165	13.1 vs 4.6 (P < .0001)	<b>22.8 vs 27.2</b> (HR: 1.19)
EURTAC <sup>[6]</sup>	Erlotinib vs platinum-based chemotherapy	174	9.7 vs 5.2 (P < .0001)	<b>19.3 vs 19.5</b> (P = .87)
LUX-Lung 3 <sup>[7,8]</sup>	Afatinib vs cisplatin/pemetrexed	345	11.1 vs 6.9 (P = .001)	<b>28.2 vs 28.2</b> (P = .39)
LUX-Lung 6 <sup>[8,9]</sup>	Afatinib vs cisplatin/gemcitabine	364	11.0 vs 5.6 (P < .0001)	<b>23.1 vs 23.5</b> (P = .61)

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 al. ASCO 2012. Abstract 7521.

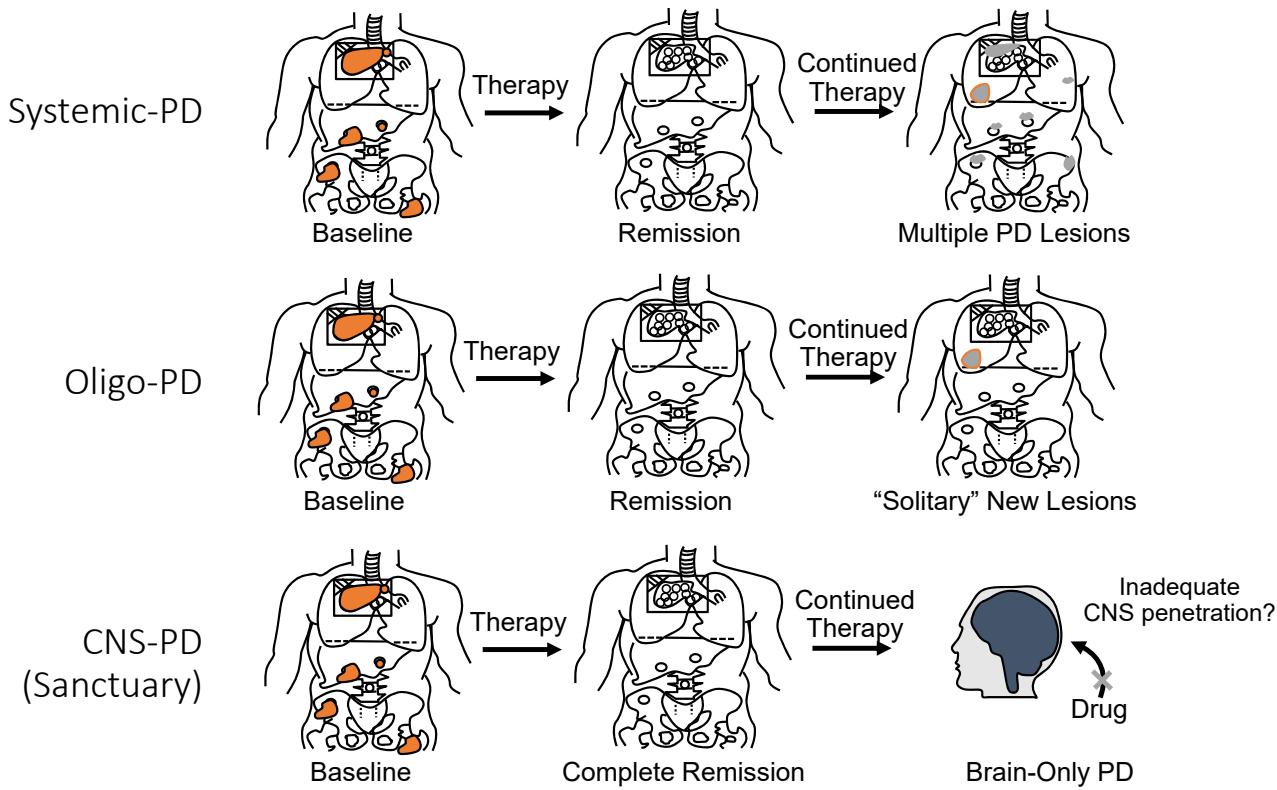
4. Zhou C, et al. Lancet Oncol. 2011;12:735-742. 5. Zhou C, et al. Ann Oncol. 2015;26:1877-1883. 6. Rosell R, et al. Lancet Oncol. 2012;13:239-246. 7. Sequist LV, et al. J Clin Oncol. 2013;31:3327-3334. 8. Yang JC, et al. Lancet Oncol. 2015;16:141-151. 9. Wu YL, et al. Lancet Oncol. 2014;15:213-222.

## רעילות של ZIKV

- פריחה – דמוית אקנה , בעיקר על הפנים והגו העליון 60-70% .
- שלשול - 50% .
- יובש בעור , גרד.
- אנוקרסיה.
- חולשה.
- בחילות והקאות.
- שינויים בציפוריוניים.
- הפרעה באנזימי כבד.



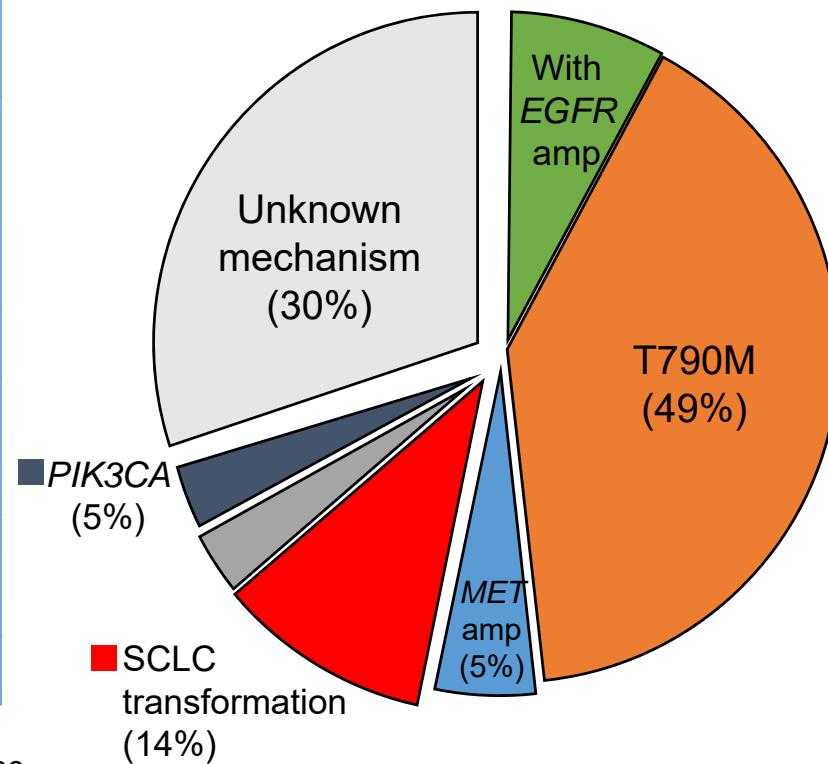
# Acquired Resistance to Targeted TKIs: PD Subtype Influences Clinical Practice



Gandara DR, et al. Clin Lung Cancer. 2014;15:1-6.

# Repeat Biopsies for Pts With NSCLC and Acquired Resistance to EGFR inhibitors

Observed Resistance Mechanisms	N = 37
T790M (total)	21
+ EGFR amp	4
+ beta-catenin	2
+ APC	1
MET amplification	2
PIK3CA	3
SCLC transformation	5
Epithelial-mesenchymal transition	2
No changes identified	8

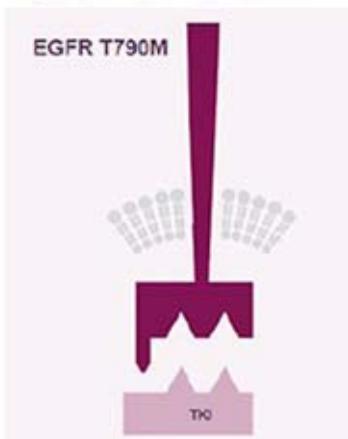


Sequist LV, et al. Sci Trans Med. 2011;3:75ra26.

First- and second-generation TKIs bind the EGFR and block signalling.



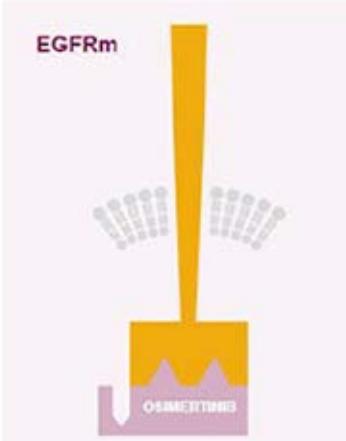
The EGFR develops a T790M mutation so that the TKI can no longer bind and block the EGFR.



Osimertinib can bind EGFR and block signalling in the presence of both mutations.



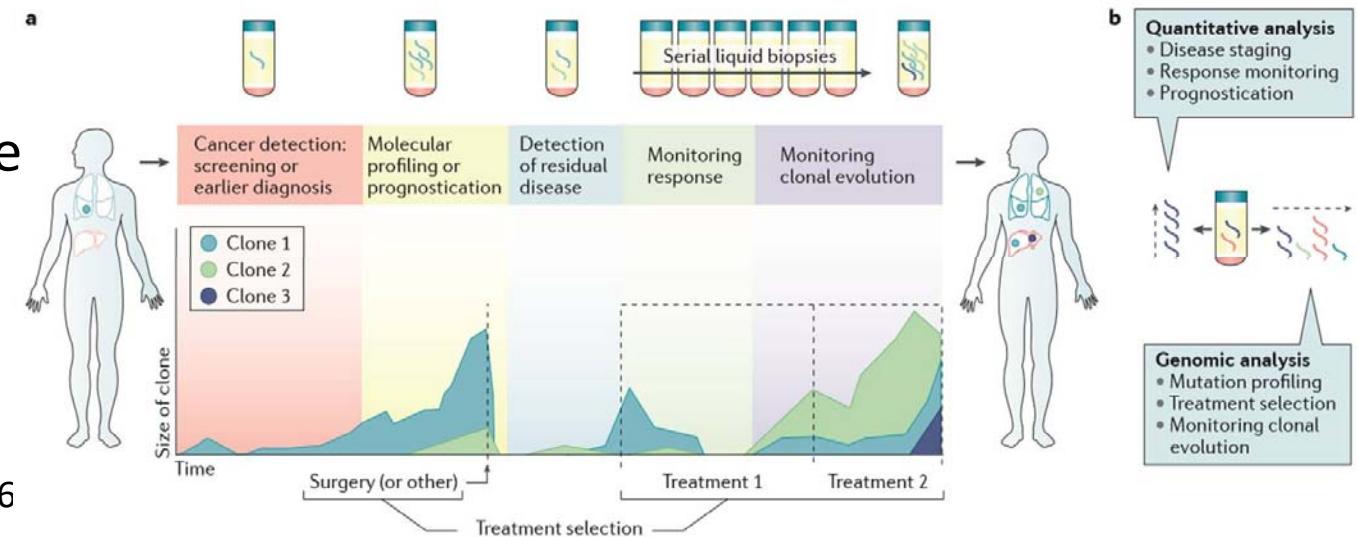
Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) designed to selectively target both the sensitising epidermal growth factor receptor (EGFR) mutation and the T790M resistance mutation in non-small cell lung cancer. Osimertinib therefore inhibits these mutated EGFRs to a greater extent than wild-type (non-mutant) EGFRs. Wild-type inhibition has been associated with high rates of adverse events such as rash and diarrhoea.



# Circulating Tumor DNA

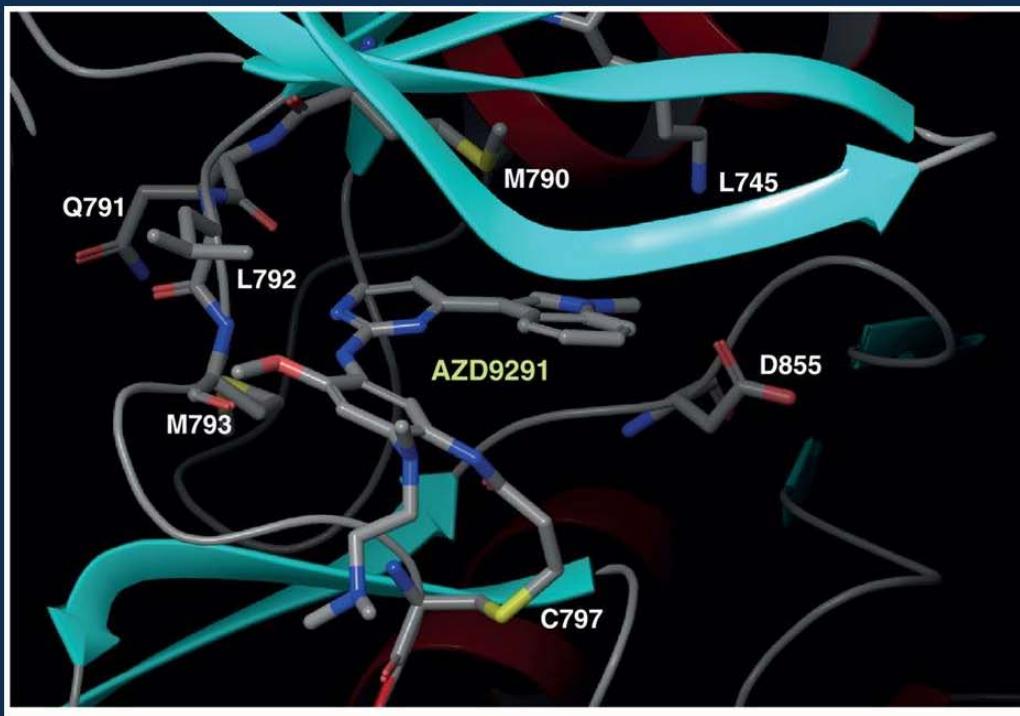
- Tumors continually shed DNA into the circulation
- ctDNA analysis (liquid biopsy or blood sample)
  - Can provide the genetic landscape of all cancerous lesions (primary and metastases)
  - Opportunity to systematically track genomic evolution
  - Potential utility in inaccessible lesions and bone-only tumor

- Sensitivity 60-80%\*
- Negative results require additional testing



\* Oxnard, JTO 2016 ; Normanno JTO 2016

# Mutant-selective EGFR TKIs were designed to overcome the T790M resistance mutation



Depicted is AZD9291 (osimertinib) covalently bound to EGFR T790M via Cys797

# Osimertinib (Tagrisso)

- **Osimertinib is indicated in Israel for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.**
  - Approval based on AURA and AURA2 single-arm phase II studies of osimertinib in advanced/metastatic NSCLC with EGFR T790M
  - Companion diagnostic test for EGFR mutation also approved



	Erlotinib	Gefitinib	Afatinib	Osimertinib
Generation:	1st	1st	2nd	3rd
Irreversible?	No	No	Yes	Yes
Mutant-selective?	No	No	No	Yes
Large “therapeutic window”?	No	No	No	Yes

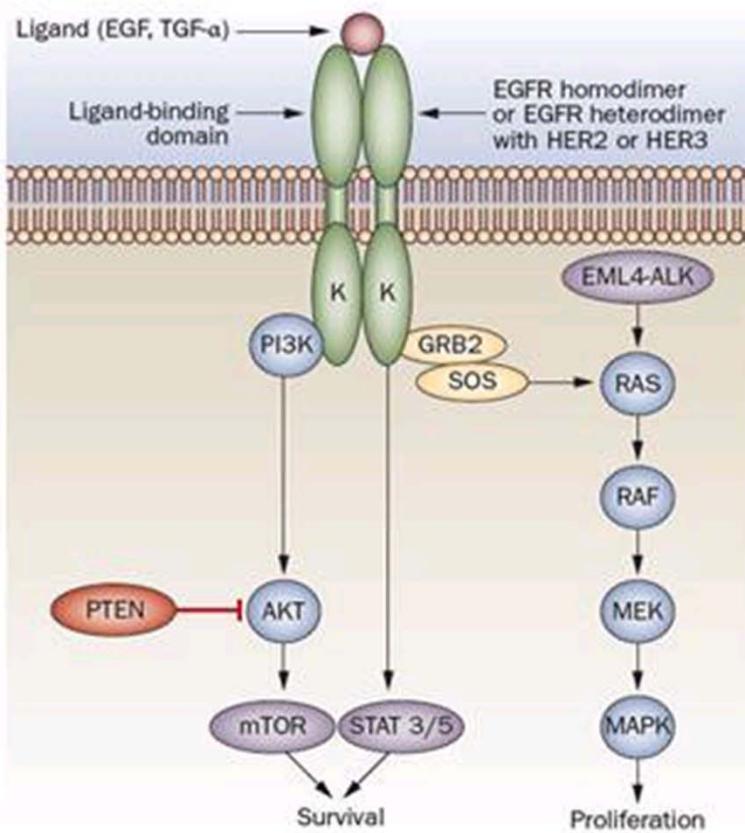
# Third Generation EGFR TKIs

Agent	N	RR, % T790M-	RR, % T790M+	PFS, mos	Toxicity
Osimertinib <sup>[1]</sup>	253	21	61	~ 8.2	Diarrhea
Rociletinib <sup>[2,3]</sup>	130	29 (17)	59 (45)	13.1 (6.1)	Hyperglycemia
Olmutinib <sup>[4]</sup>	62	NR	55	NR	Dyspnea/rash
EGF816 <sup>[5]</sup>	53	—	60	NR	Rash
ASP8273 <sup>[6]</sup>	47	~ 33	61	NR	Hyponatremia/ diarrhea

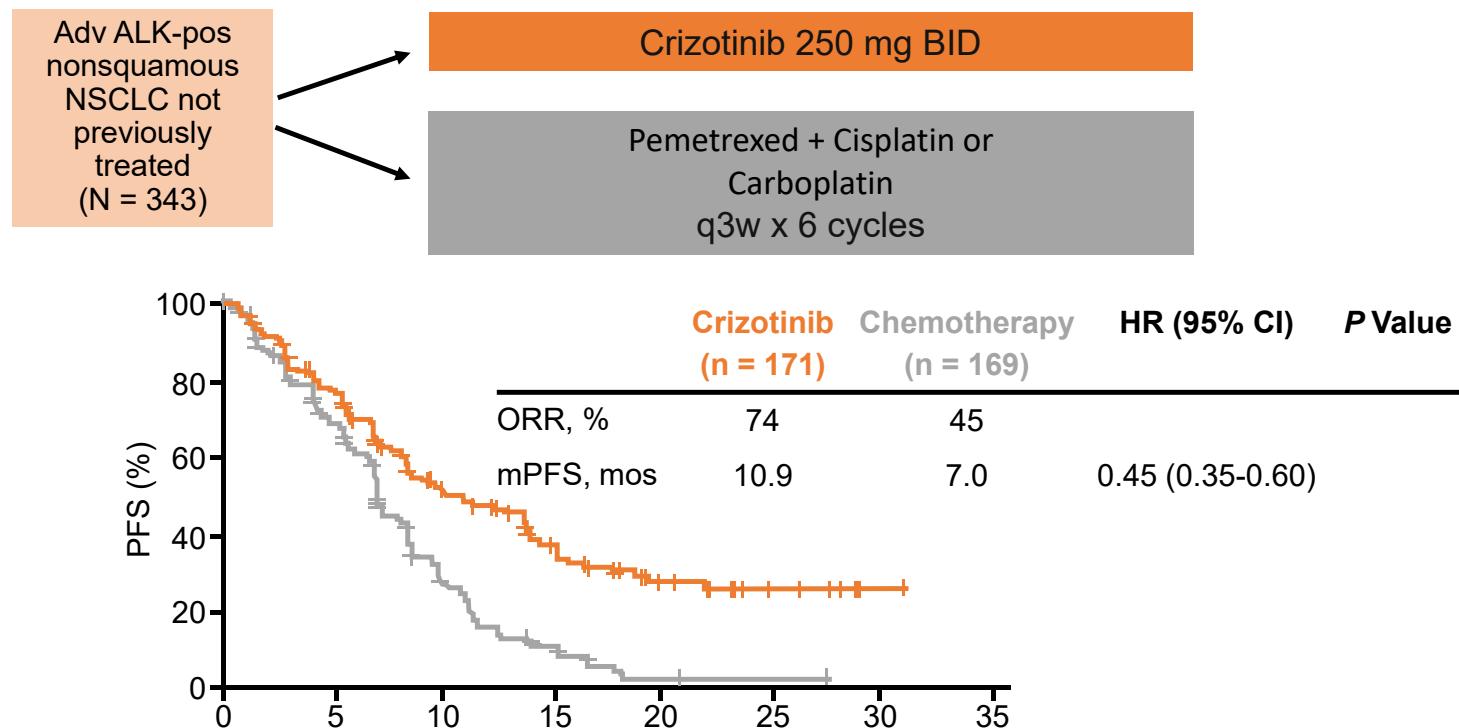
1. Jänne PA, et al. N Engl J Med. 2015;372:1689-1699. 2. Sequist LV, et al. N Engl J Med. 2015;372:1700-1709. 3. Sequist LV, et al. N Engl J Med. 2016;374:2296-2297. 4. Park K, et al. ASCO 2015. Abstract 8084. 5. Tan DS, et al. ASCO 2015. Abstract 8013. 6. Goto Y, et al. ASCO 2015. Abstract 8014.

# EML4-ALK

- *EML4-ALK* fusion leads to activation of MAPK pathway
- In NSCLC ranges from 3%-7%
- In younger patients, adenocarcinomas, non-smokers
- Associated with wt*EGFR*, wt*KRAS* and resistance to *EGFR* TKIs



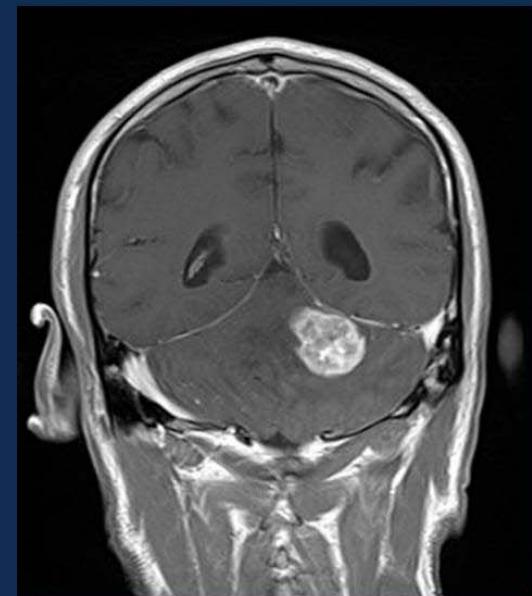
# PROFILE 1014: Crizotinib vs Pemetrexed/Platinum in Advanced Untreated NSCLC



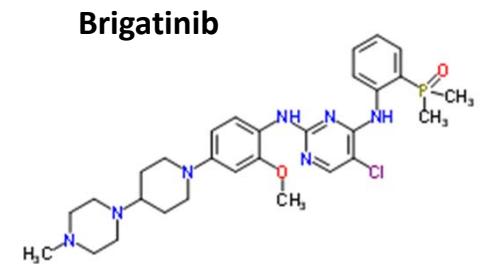
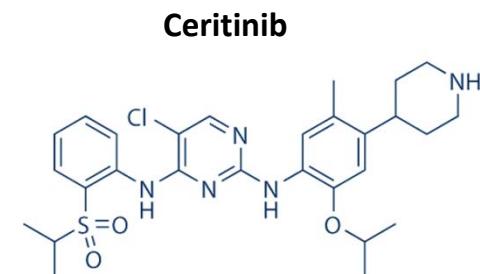
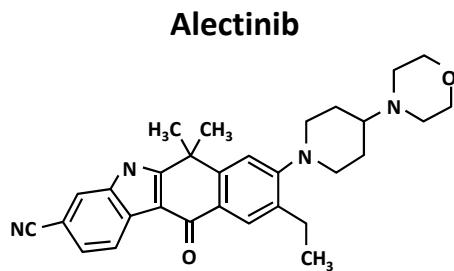
Solomon BJ, et al. N Engl J Med. 2014;371:2167-2177. Mok T, et al. ASCO 2014. Abstract 8002.

## CNS: A Sanctuary Site

- ~30-40% of ALK+ patients have CNS metastases at initial diagnosis.
- CNS is among the most common sites of relapse on crizotinib.
- Among crizotinib-resistant patients entering trials of next-generation ALK inhibitors, rates of CNS metastases approach 60%.

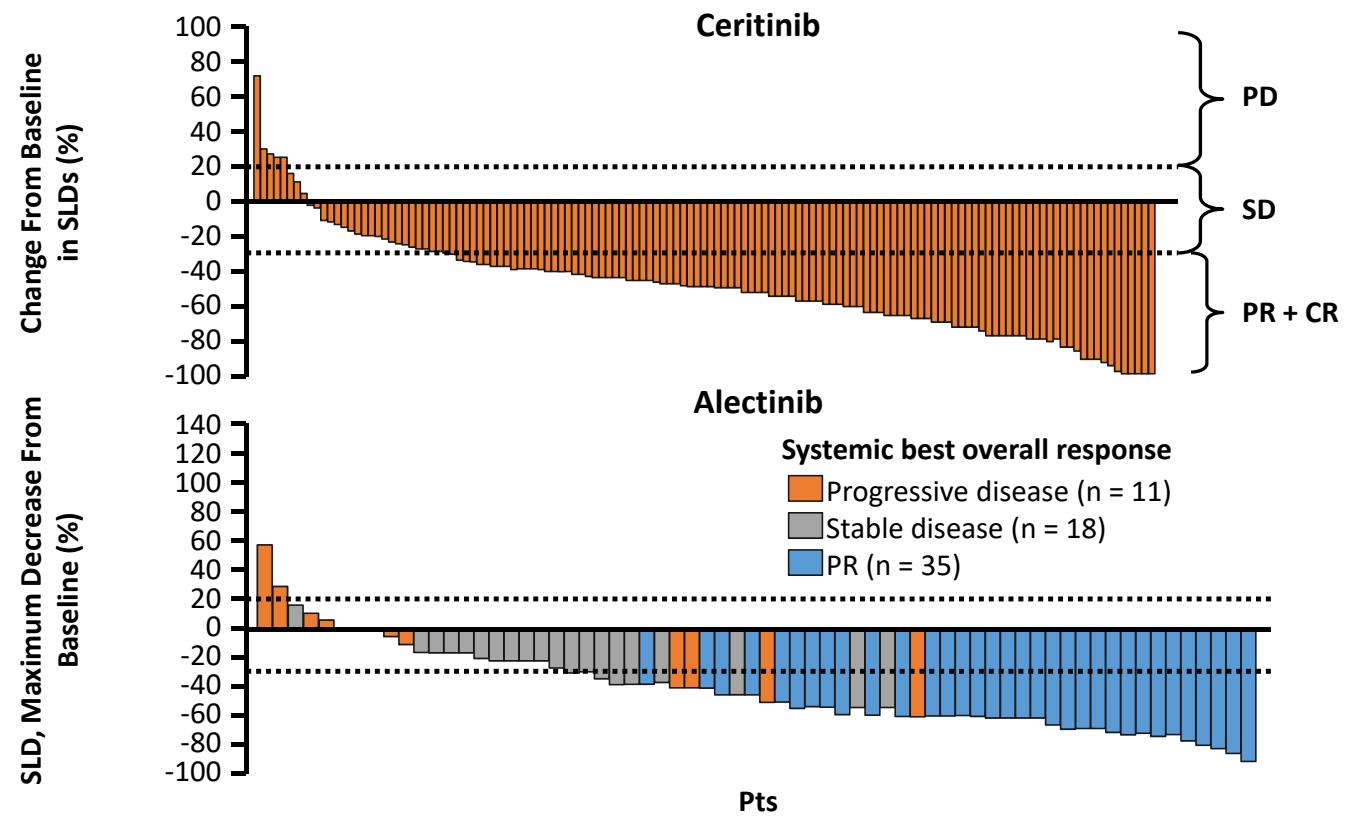


# Crizotinib resistance and new drugs



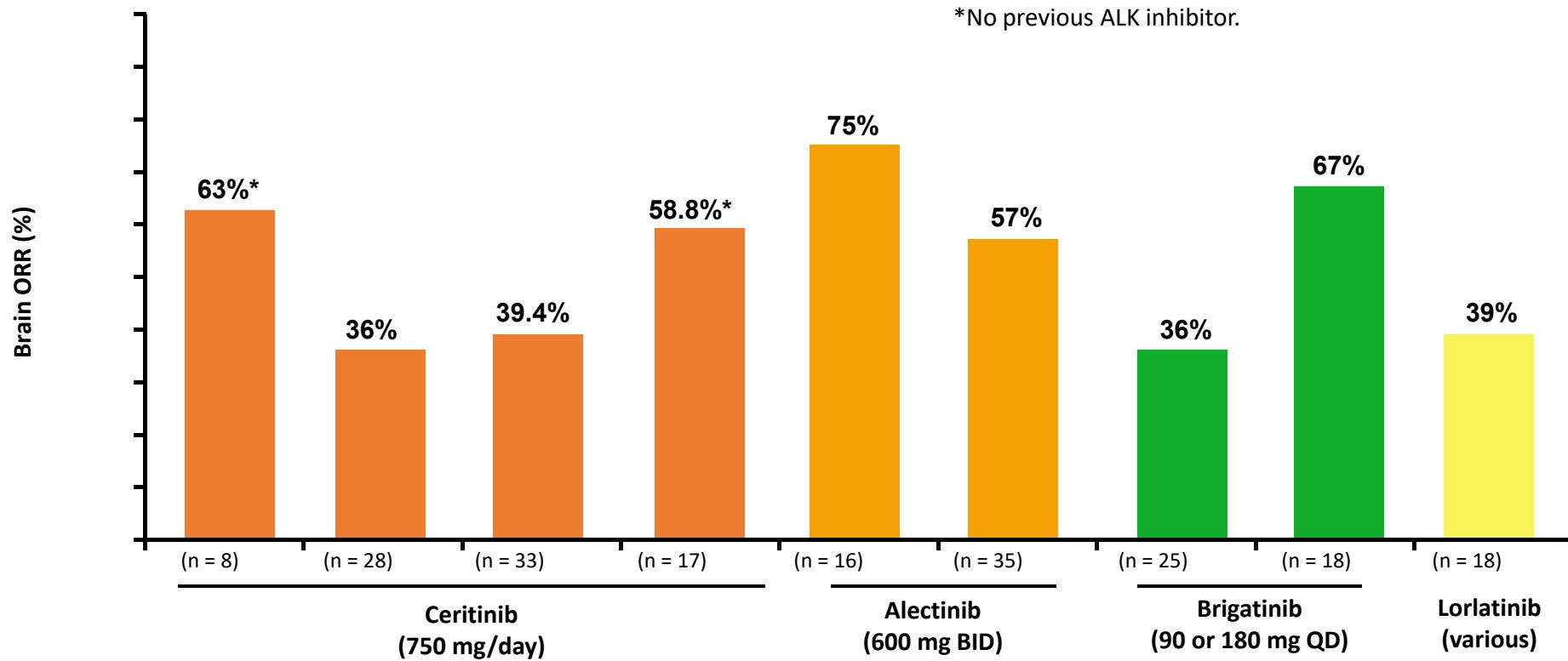
# Response to Ceritinib or Alectinib in Previously Treated ALK-Positive NSCLC

- Ceritinib (2014) and alectinib (2015) approved for pts with ALK-positive, metastatic NSCLC with disease progression on or who are intolerant to crizotinib



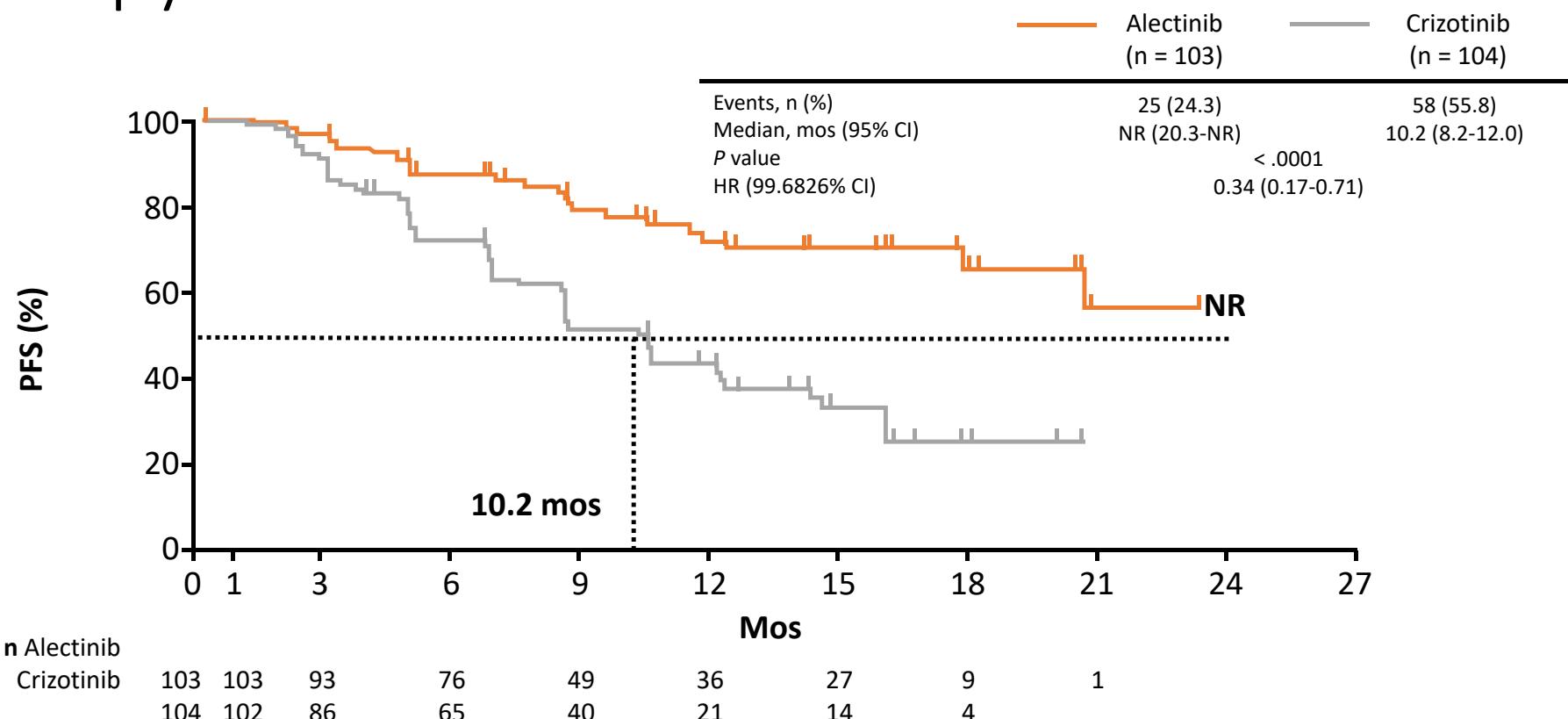
Kim DW, et al. Lancet Oncol. 2016;17:452-63. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. Ou SH, et al. J Clin Oncol. 2016;34:661-668.

# Second-Generation ALK Inhibitor CNS Activity



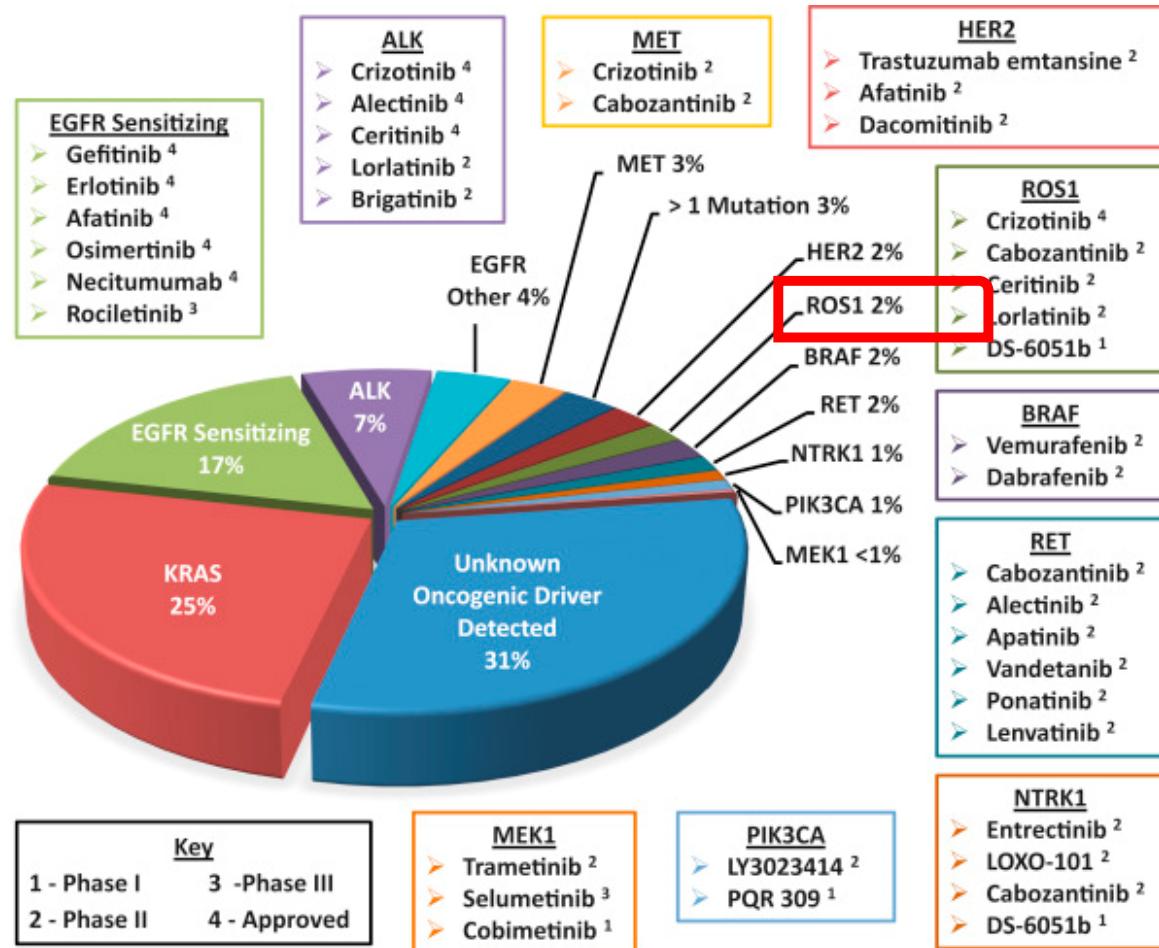
Kim D-W, et al. Lancet Oncol. 2016;17:452-463. Mok T, et al. ASCO 2015. Abstract 8059. Felip E, et al. ASCO 2015. Abstract 8060. Shaw AT, et al. Lancet Oncol. 2016;17:234-242. Ou S, et al. J Clin Oncol. 2016;34:661-668. 5. Kim D-W, et al. ASCO 2016. Abstract 9007. Solomon BJ, et al. ASCO 2016. Abstract 9009.

# J-ALEX: Alectinib Vs Crizotinib as First-line Therapy for ALK-Positive NSCLC



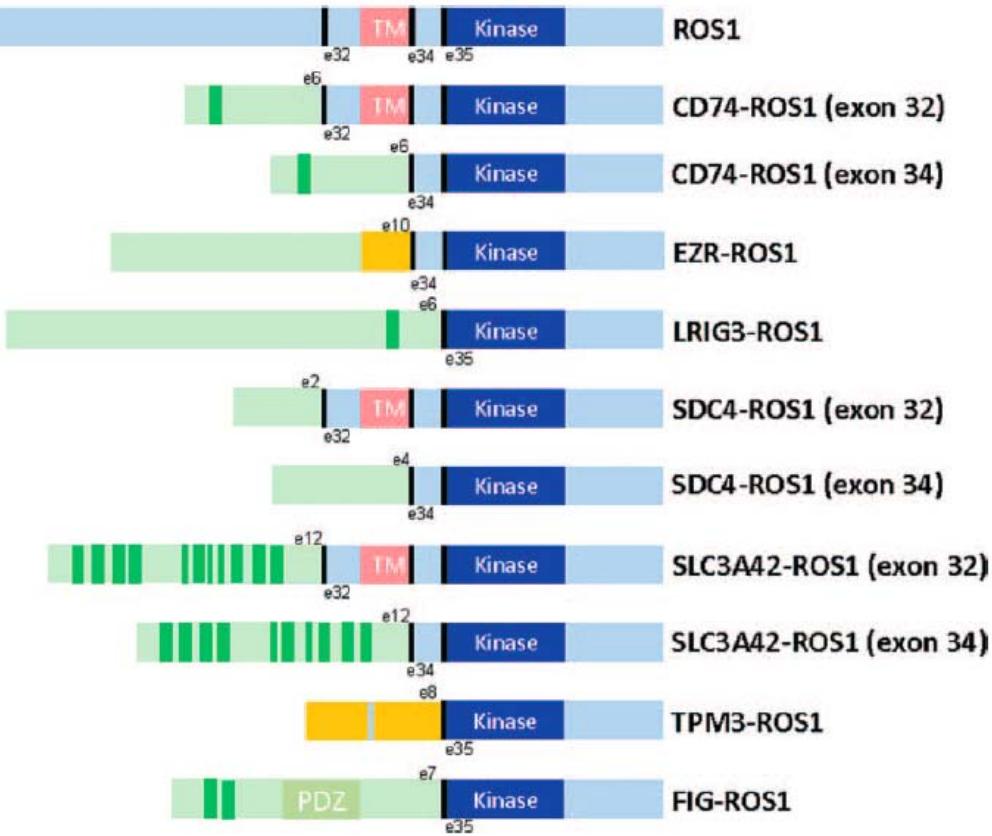
Nokihara H, et al. ASCO 2016. Abstract 9007.

# ROS1



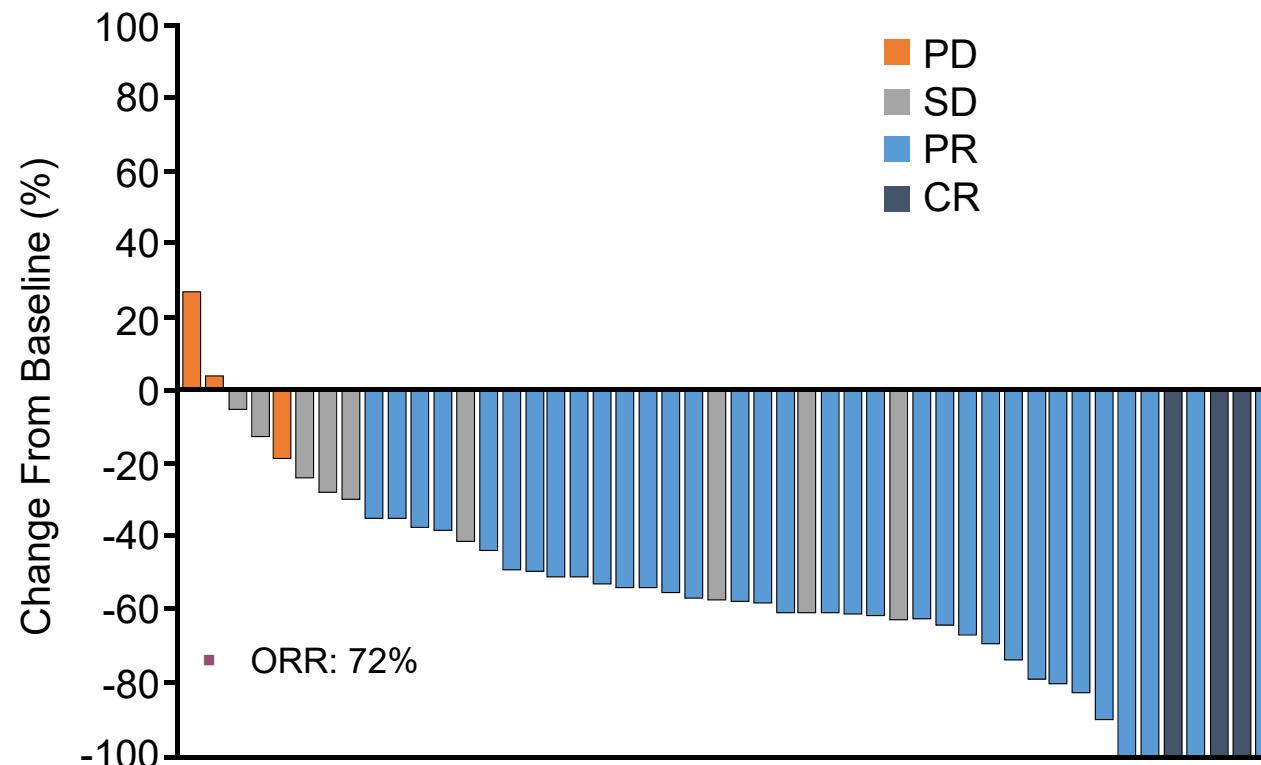
# ROS 1 Fusion Gene Variants

- Most common in younger pts, never-smokers, adenocarcinoma, high grade histology
- Frequency: ~2% of all adenocarcinomas
- Several variants identified with different activation mechanisms; clinical significance unknown
- Testing: FISH (> 15% cells with split signal in 50 nuclei scored)
  - ROS PCR, IHC?
  - NGS



Chin LP, et al J Thorac Oncol 2012

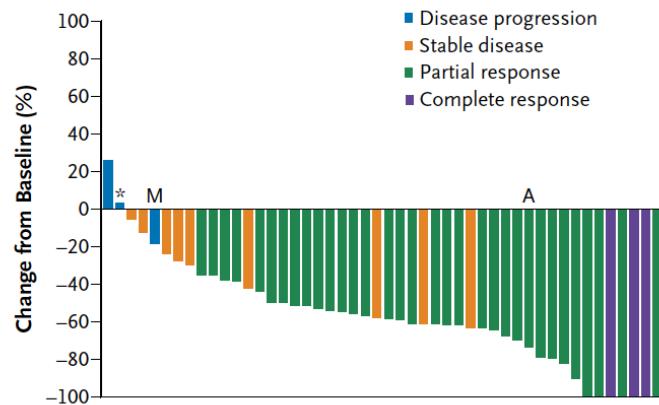
# Activity of Crizotinib in Pts With *ROS1* Fusions: Best Overall Response



Shaw AT, et al. N Engl J Med. 2014;371:1963-1971.

# ROS1 inhibition with crizotinib

A Best Response

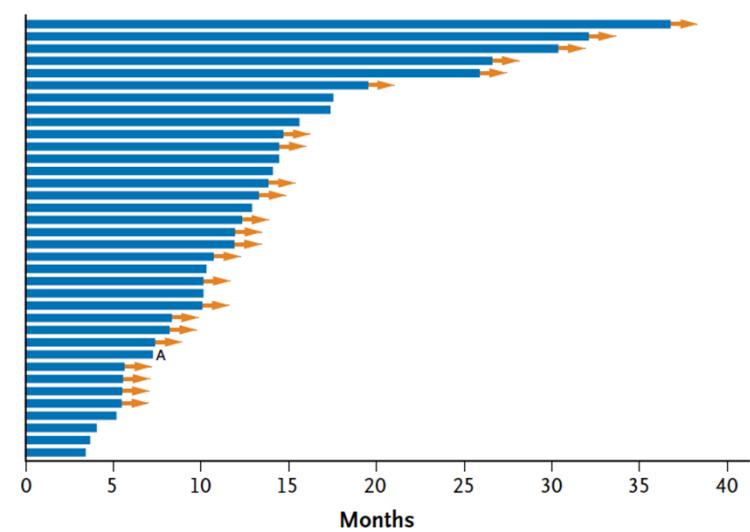


ORR = 72%

- **ORR: 72%**
- **Med duration of response: 17.6 mos**
- **Median PFS: 19.2 mos**
- **Safety profile similar to previously**

Median PFS = 19.2 mos.

Duration of Response



Shaw et al., NEJM 2014

 U.S. Department of Health and Human Services

**FDA** U.S. Food and Drug Administration  
Protecting and Promoting Your Health

A to Z Index | Follow FDA | En Español

Search FDA 

☰ Home Food Drugs Medical Devices Radiation-Emitting Products Vaccines, Blood & Biologics Animal & Veterinary Cosmetics Tobacco Products

## Drugs

Home > Drugs > Drug Approvals and Databases > Approved Drugs

**Approved Drugs**

Hematology/Oncology (Cancer) Approvals & Safety Notifications

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

# FDA Approves Crizotinib Capsules



[!\[\]\(38104251b2aca9c3c8f42bea1a6a1f52\_img.jpg\) SHARE](#) [!\[\]\(4d99ad480a97d1a281e4641fc37dff3d\_img.jpg\) TWEET](#) [!\[\]\(b827c33808e314a093d99e493df4d45e\_img.jpg\) LINKEDIN](#) [!\[\]\(7477d6cf2671ce3dbd18488a95b31d76\_img.jpg\) PIN IT](#) [!\[\]\(93fcffa74c45c69bf1266faf97281dd7\_img.jpg\) EMAIL](#) [!\[\]\(50a681b27458e55e3720ed39fa5d7f4c\_img.jpg\) PRINT](#)

On March 11, 2016, the U. S. Food and Drug Administration approved crizotinib capsules (Xalkori, Pfizer, Inc.) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. Crizotinib was first approved in 2011 for the treatment of patients whose tumors are anaplastic lymphoma kinase (ALK)-positive.

The current approval was based on a multicenter, single-arm trial in patients with metastatic ROS1 rearrangement-positive NSCLC. All patients received crizotinib 250 mg orally twice daily. The efficacy outcome measures were objective response rate (ORR) according to RECIST v1.0 as evaluated by an independent radiology review (IRR) and as evaluated by the investigators. Duration of response (DoR) was an additional outcome measure.

The trial enrolled 50 patients with an age range of 25-77 years whose tumors were prospectively determined to be ROS1-positive by fluorescence in situ hybridization (FISH; 96%) or reverse transcription polymerase chain reaction (RT-PCR; 4%) clinical trial assays. The ORR by IRR was 66% (95% CI: 51%, 79%) with a median DoR of 18 months. The ORR according to investigators was 72% (95% CI: 58%, 84%).

# Tissue is the issue

IHC (ALK, PD-L1)  
FISH (ALK, ROS1,  
MET, RET)  
PCR (EGFR,  
HER2, BRAF,  
MET, RET)  
Hot Spot NGS

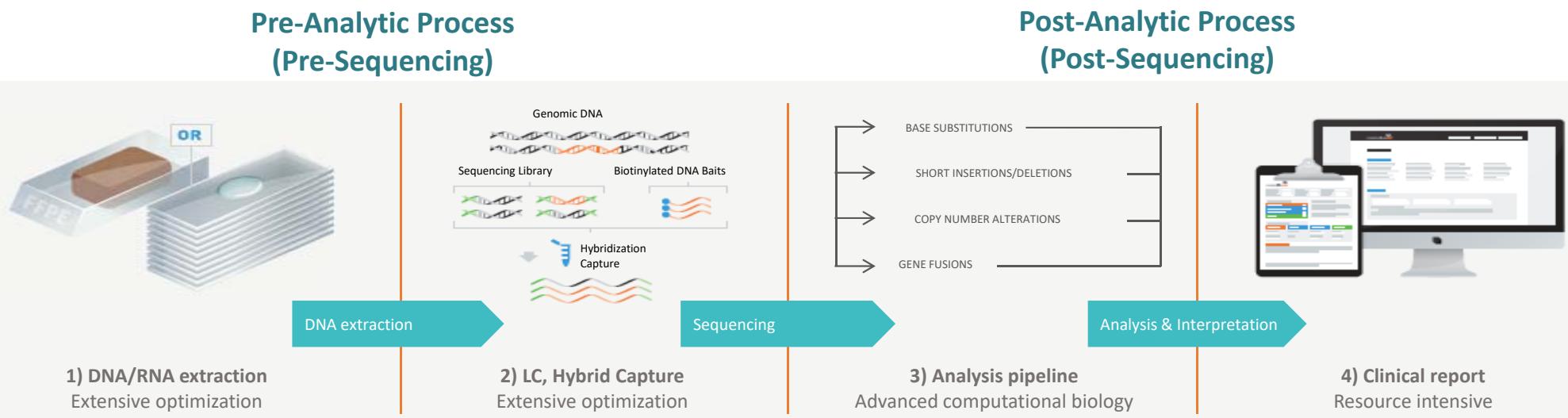
## Problem

- Time consuming
- Small tissue samples
- Cost
- Sensitivity

## Solutions

- Multiplex genotyping
- NGS

# Hybrid Capture NGS



# Precision Medicine for IO

## Immunosurveillance

The diagram illustrates the process of immunosurveillance. It begins with a DC (dendritic cell) presenting tumor antigens (red dots) via MHC (Major Histocompatibility Complex) molecules to a resting T cell. The T cell then undergoes T-cell clonal expansion, becoming an activated T cell. The activated T cell uses its TCR (T-cell receptor) to recognize the MHC-antigen complex and binds to the B7 molecule on the DC via its CD28 receptor. The activated T cell releases perforin and granzyme, which kill the tumor cell. Cytokines (IL-2) are also released to support the activated T cell. A lymph node is shown on the right where these cells are likely to be present.

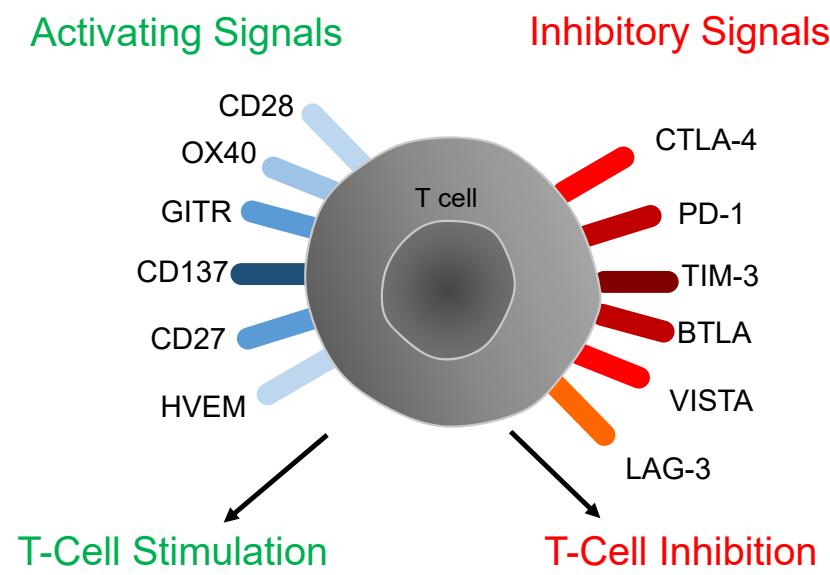
### Innate Immunity

- Nonspecific
- First line of defense
- WBCs (natural killer cells, neutrophils)
- Activation of adaptive immunity

### Adaptive Immunity

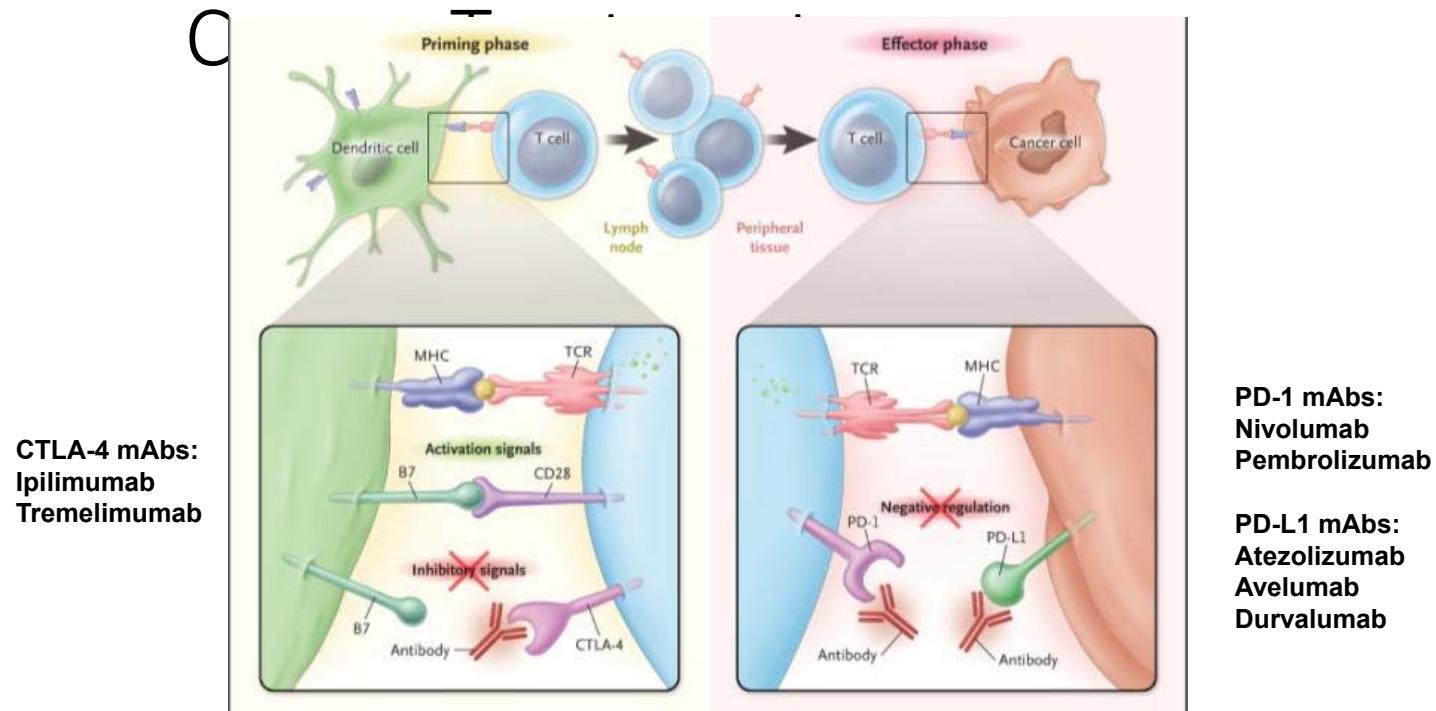
- Specific target recognition
- Slower to develop
- Ab or cell mediated
- Memory
  - Faster, stronger subsequent responses

# T-Cell Response: Second Signal to Accelerate or Brake

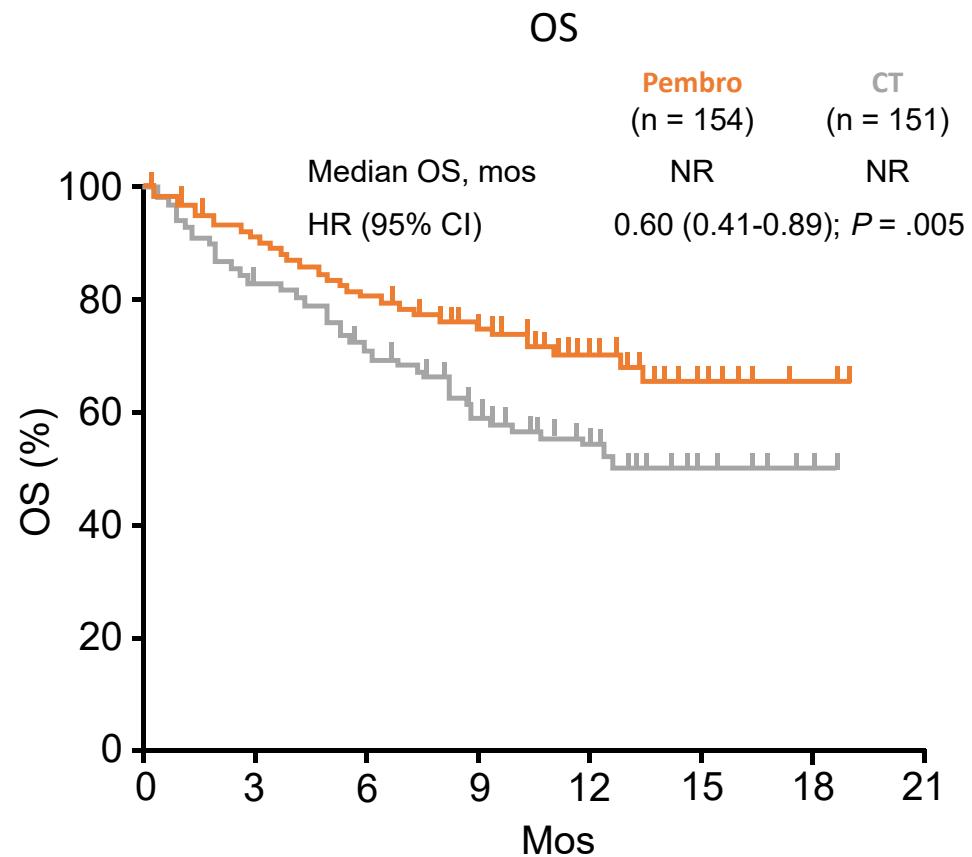
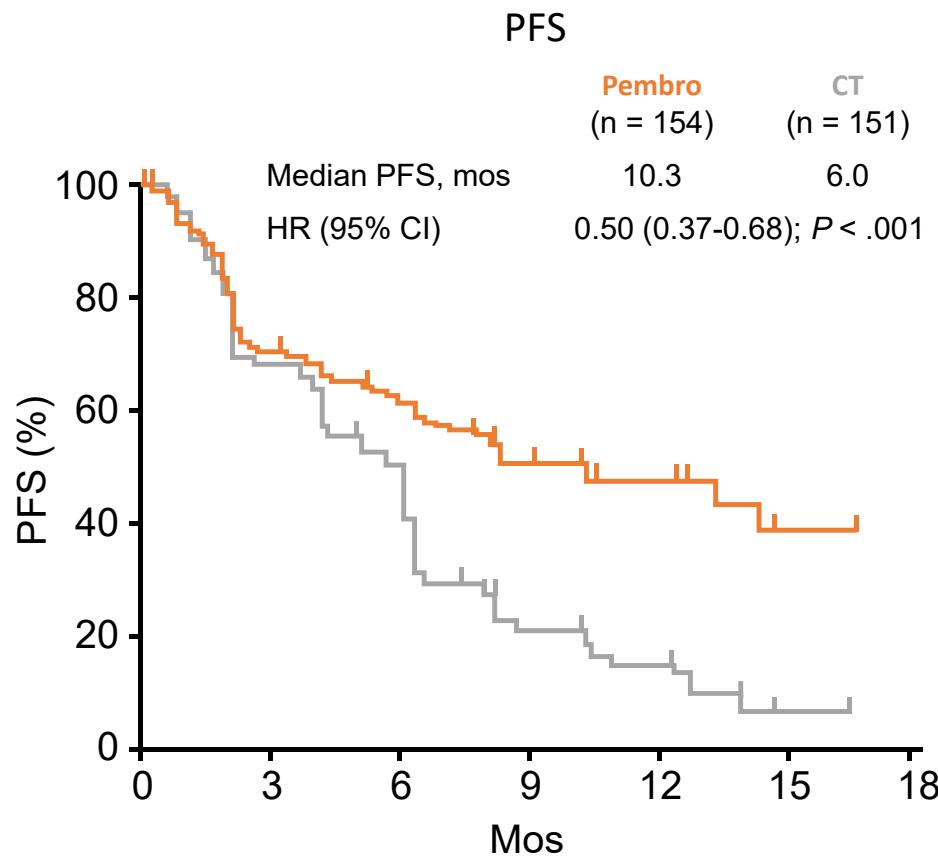


Mellman I, et al. Nature. 2011;480:480-489.

# CTLA-4 and PD-1/PD-L1 Checkpoint Blockade for



# KEYNOTE-024: Survival Outcomes



# Challenges with tumor PD-L1 expression

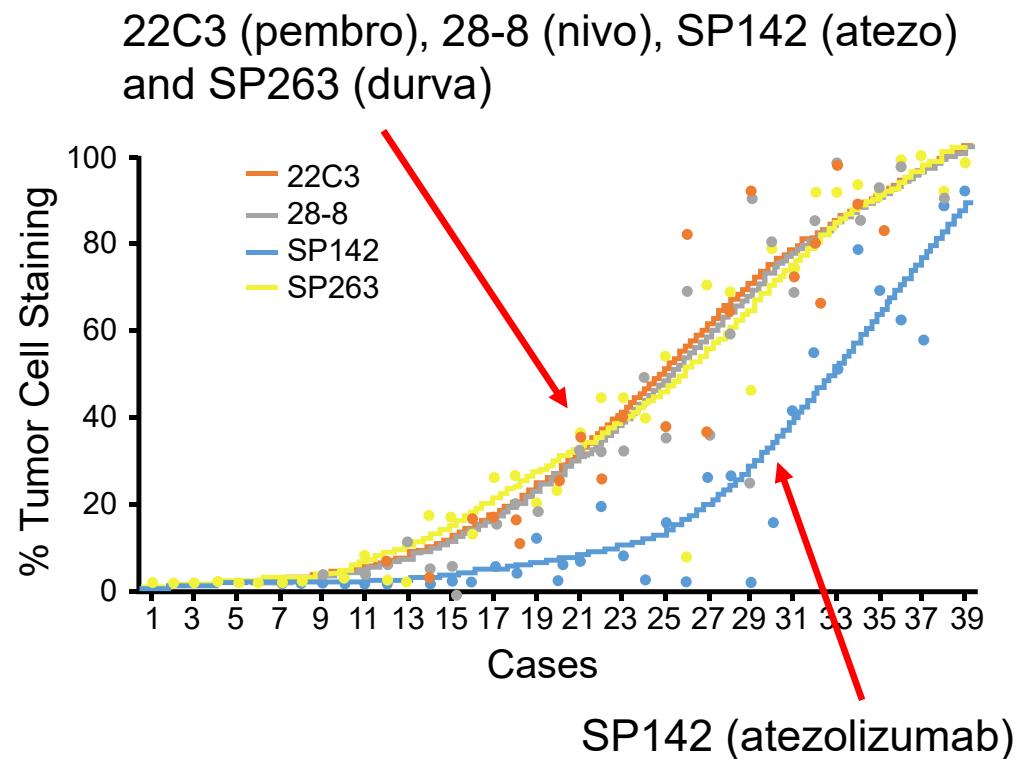
Table 1. PD-L1 Assay Systems Used in the Blueprint Project

Agent	Nivolumab	Pembrolizumab	Atezolizumab	Durvalumab
Primary antibody clone used in the assay system	28-8 (Dako)	22C3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Interpretive scoring	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane Infiltrating immune cells	Tumor cell membrane
Instrument and detection systems required	EnVision Flex on AutostainerLink 48	EnVision Flex on AutostainerLink 48	OptiView detection and amplification on Benchmark ULTRA	OptiView detection on Benchmark ULTRA
Therapeutic developer	Bristol-Myers Squibb	Merck	Genentech	AstraZeneca

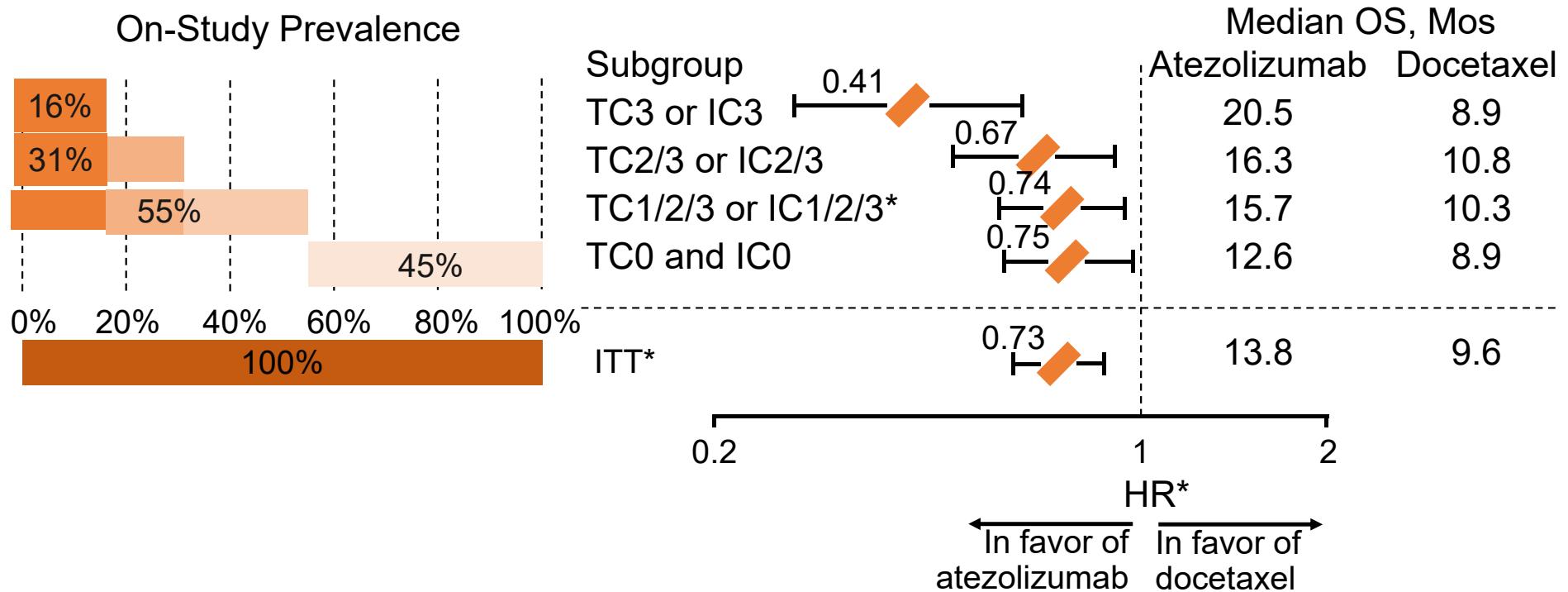
PD-L1, programmed death ligand 1.

# Blueprint PD-L1 IHC Assay Comparison Project: Phase 1

- Analytical comparison of % tumor cell staining (tumor proportion score), by case (n = 39), for each assay
- Data points represent the mean score from 3 pathologists for each assay on each case
- Superimposed lines/points indicate identical TPS values
- No clinical diagnostic cutoff applied
- Conclusion: 3 of 4 assays are analytically similar for tumor cell staining



# OAK: OS by PD-L1 Expression

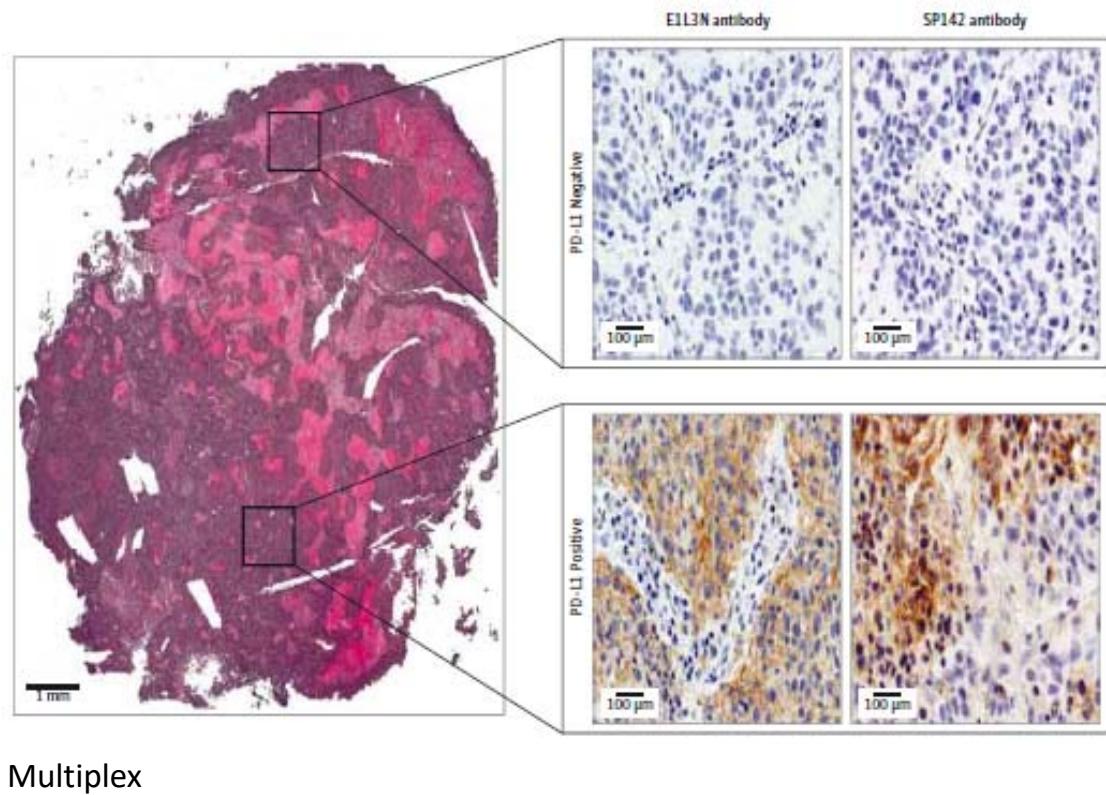


Rittmeyer A, et al. Lancet. 2017

## Tumor PD-L1 Heterogeneity

-Discordant expression frequency ~25%

Not yet validated on cytology specimens

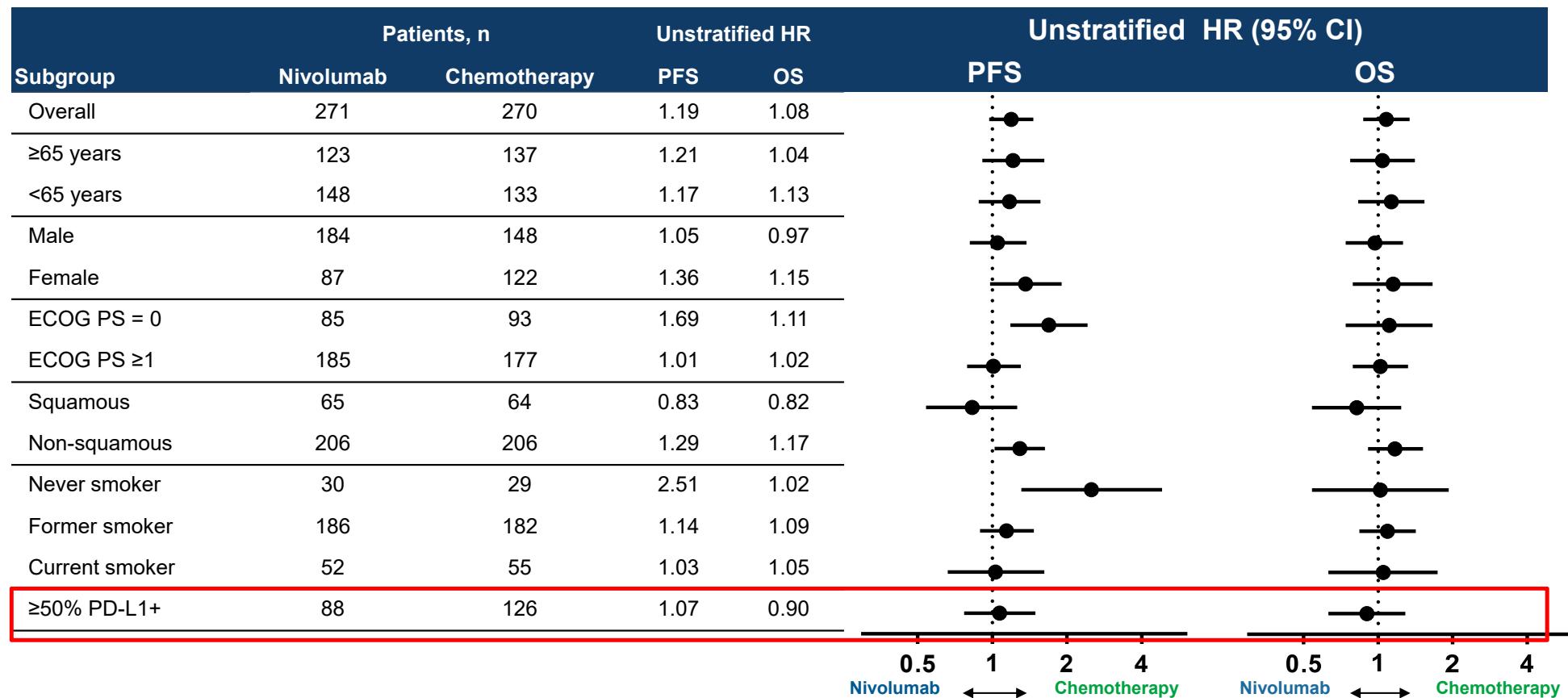


Multiplex

# Challenges with tumor PD-L1 expression

- Diagnostic PD-L1 immunohistochemistry assays vary, with each pharmaceutical company utilizing its own test.
- While all such companies consider PD-L1 expression on tumor cells when defining “PD-L1 positivity,” only one, ATEZO, additionally considers PD-L1 expression on tumor-infiltrating immune cells.
- Different thresholds of PD-L1 positivity, ranging between 1 and 50 percent, have been used in trials when correlating response or survival.
- There can be considerable PD-L1 heterogeneity within tumors and between tumor sites, which may not be accurately accounted for in small tumor biopsy specimens.
- Tumor PD-L1 expression may change over time and after systemic and local therapies; archived tumor samples may not be ideal in determining current PD-L1 tumor status.
- Responses to PD-1 axis inhibitor therapy have been seen in 5 to 20 percent of patients with reported PD-L1-negative tumors across trials.

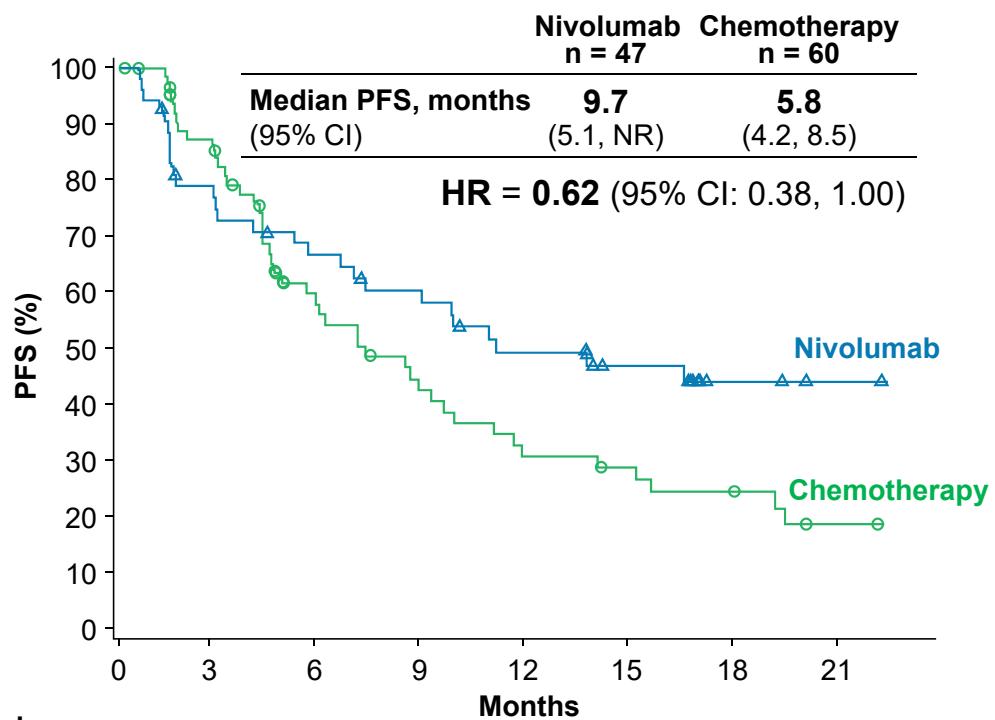
# PFS and OS Subgroup Analyses CheckMate 026: Nivolumab vs Chemotherapy in First-line NSCLC



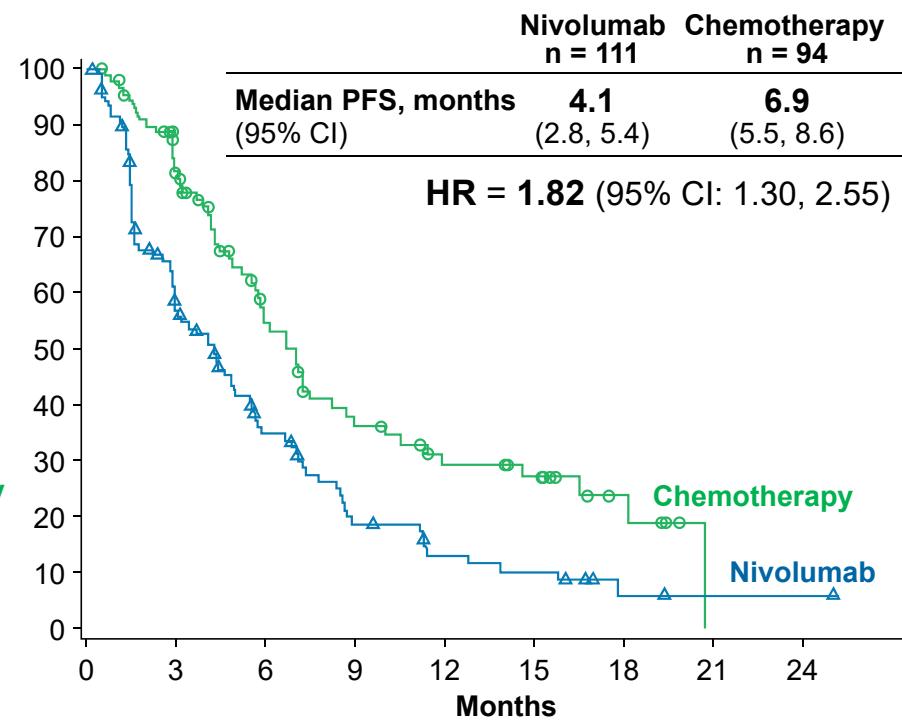
## PFS by Tumor Mutation Burden Subgroup

CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

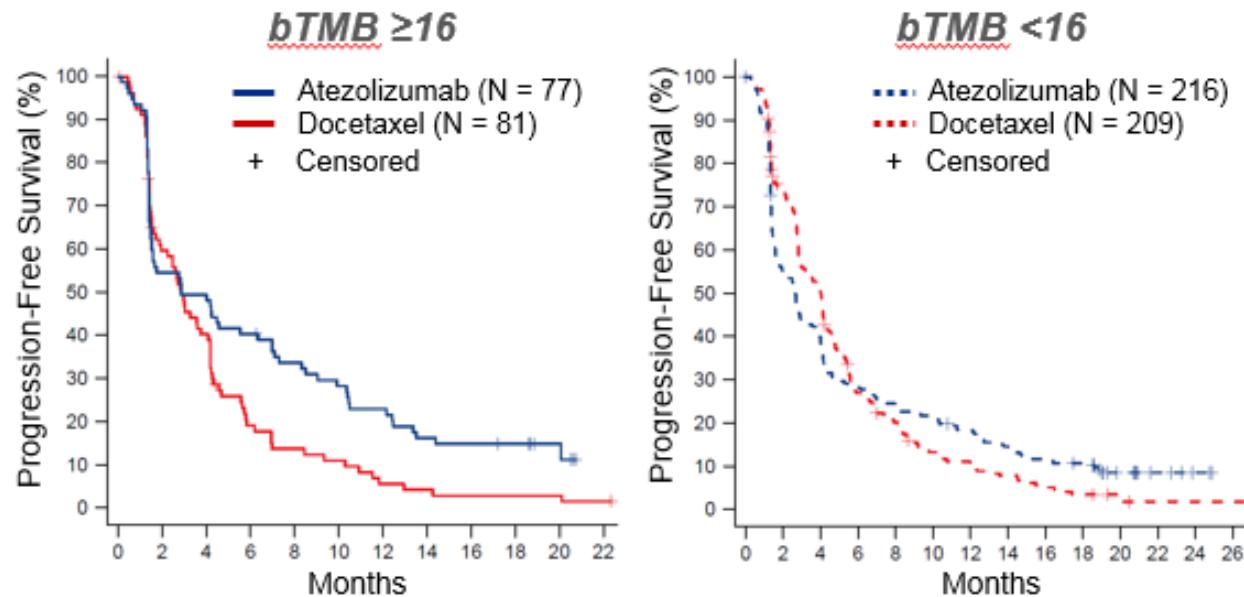
### High TMB



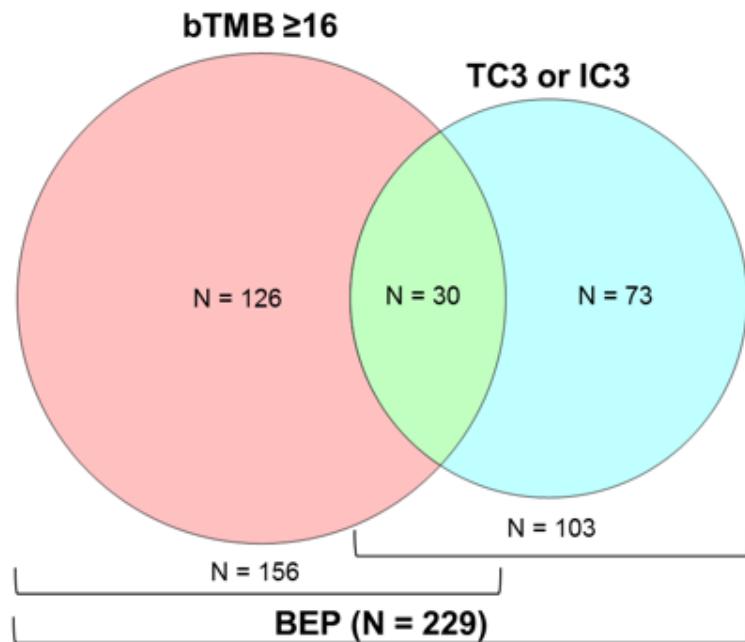
### Low/medium TMB



# OAK: PFS benefit in blood TMB subgroups



# OAK: blood TMB and PD-L1 of the tumor



	PFS HR (95% CI)	OS HR (95% CI)
bTMB $\geq 16$	0.64 (0.46, 0.91)	0.64 (0.44, 0.93)
TC3 or IC3	0.62 (0.41, 0.93)	0.44 (0.27, 0.71)
bTMB $\geq 16$ and TC3 or IC3	0.38 (0.17, 0.85)	0.23 (0.09, 0.58)

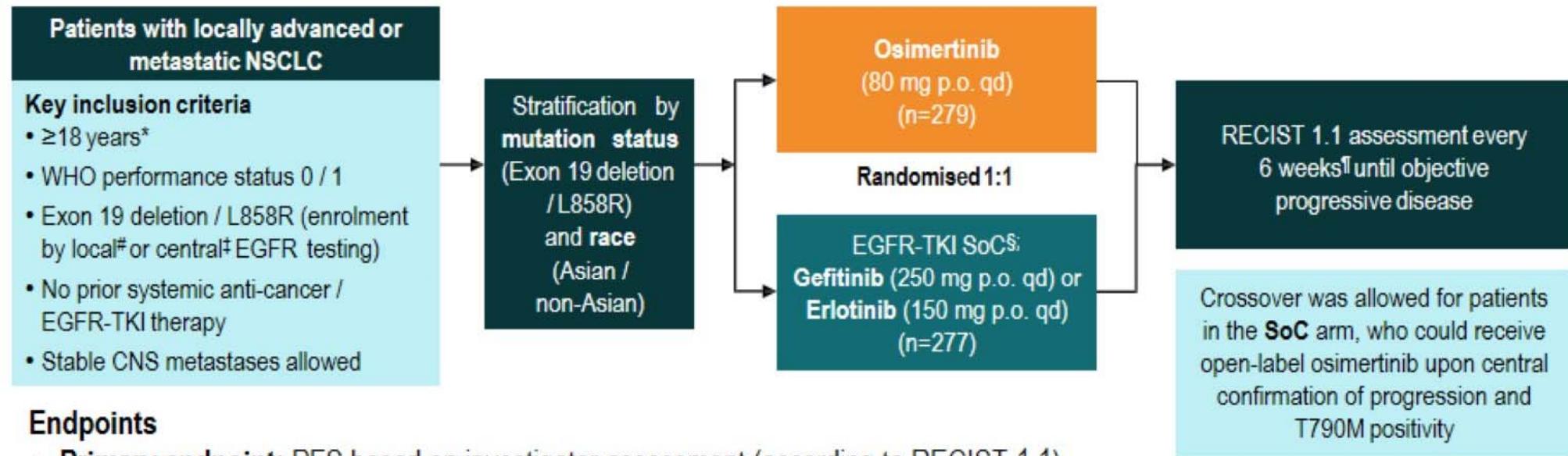
# Thank you

Alona Zer, MD

[alonaz@clalit.org.il](mailto:alonaz@clalit.org.il)



## FLAURA DOUBLE-BLIND STUDY DESIGN



### Endpoints

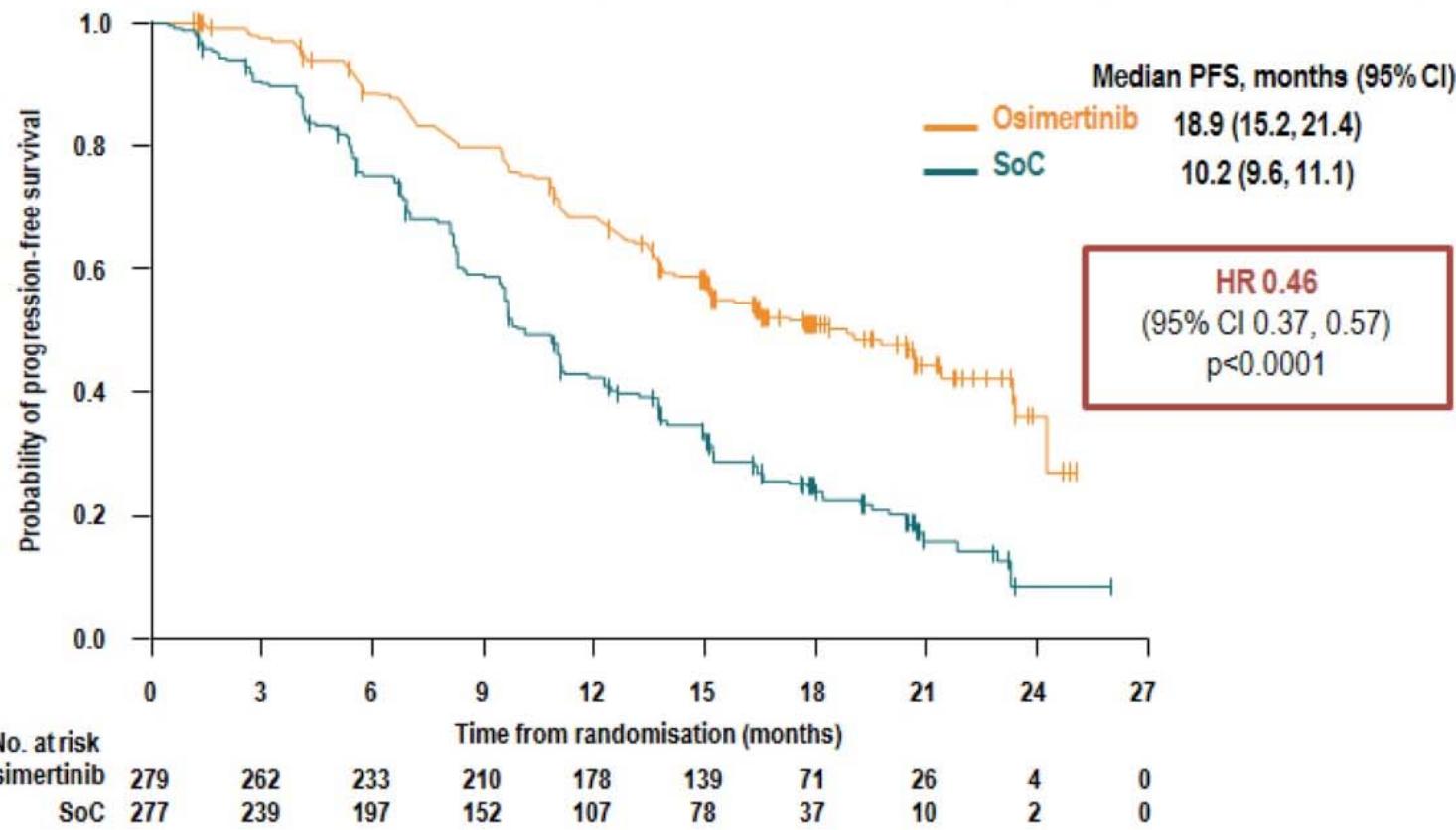
- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

FLAURA data cut-off: 12 June 2017; NCT02296125

\*≥20 years in Japan; <sup>#</sup>With central laboratory assessment performed for sensitivity; <sup>\$</sup>cobas EGFR Mutation Test (Roche Molecular Systems); <sup>†</sup>Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; <sup>†</sup>Every 12 weeks after 18 months CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

## PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)



FLAURA data cut-off: 12 June 2017

Tick marks indicate censored data;

CI, confidence interval; DCO, data cut-off; HR, hazard ratio; SoC, standard-of-care; PFS, progression-free survival

Reason for progression	Known/treated CNS metastases at trial entry		No known/treated CNS metastases at trial entry	
	Osimertinib (n=53)	Standard EGFR-TKI (n=63)	Osimertinib (n=226)	Standard EGFR-TKI (n=214)
Number (percent)				
Total number of progression events	29 (55)	53 (84)	107 (47)	153 (71)
Number of patients with progression due to death*	4 (8)	4 (6)	7 (3)	10 (5)
Number of patients with CNS progression*	10 (19)	27 (43)	7 (3)	15 (7)
Progression in CNS only	3 (6)	10 (16)	4 (2)	12 (6)
New lesions only	3 (6)	9 (14)	4 (2)	12 (6)
Non-target lesions only	0	0	0	0
New and non-target lesions	0	1 (2)	0	0
Progression in CNS and non-CNS	7 (13)	17 (27)	3 (1)	3 (1)
New lesions only	0	0	1 (<1)	0
Non-target lesions only	4 (8)	6 (10)	0	0
New and non-target lesions	3 (6)	4 (6)	2 (1)	2 (1)
New and target lesions	0	2 (3)	0	1 (<1)
Target lesions and non-target lesions	0	1 (2)	0	0
New, target and non-target lesions	0	4 (6)	0	0
Number of patients with non-CNS progression only*	15 (28)	22 (35)	93 (41)	128 (60)

## ALL CAUSALITY ADVERSE EVENTS\* ( $\geq 15\%$ OF PATIENTS)

Median duration of exposure: osimertinib: 16.2 months (range 0.1 to 27.4), SoC: 11.5 months (range 0 to 26.2)

AEs by preferred term, n (%)	Osimertinib (n=279)					SoC (n=277)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	161(58)	120(43)	35(13)	6(2)	0	159(57)*	116(42)	35(13)	6(2)	0
Dry skin	88(32)	76(27)	11(4)	1(<1)	0	90(32)	70(25)	17(6)	3(1)	0
Paronychia	81(29)	37(13)	43(15)	1(<1)	0	80(29)	46(17)	32(12)	2(1)	0
Stomatitis	80(29)	65(23)	13(5)	1(<1)	1(<1)	56(20)	47(17)	8(3)	1(<1)	0
Dermatitis acneiform	71(25)	61(22)	10(4)	0	0	134(48)	71(26)	50(18)	13(5)	0
Decreased appetite	56(20)	27(10)	22(8)	7(3)	0	51(18)	24(9)	22(8)	5(2)	0
Pruritis	48(17)	40(14)	7(3)	1(<1)	0	43(16)	30(11)	13(5)	0	0
Cough	46(16)	34(12)	12(4)	0	0	42(15)	25(9)	16(6)	1(<1)	0
Constipation	42(15)	33(12)	9(3)	0	0	35(13)	28(10)	7(3)	0	0
AST increased	26(9)	18(6)	6(2)	2(1)	0	68(25)	38(14)	18(6)	12(4)	0
ALT increased	18(6)	11(4)	6(2)	1(<1)	0	75(27)	31(11)	19(7)	21(8)	4(1)

FLAURA data cut-off: 12 June 2017. Grade 3 QTc prolongation based on collected digital ECGs values were recorded for 3 patients in the osimertinib arm and 2 patients in the SoC arm

\*In the SoC arm there was one patient with Grade missing and one patient with Grade 5 diarrhoea

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SoC, standard-of-care