16 Aprile 2019

Advances in Non-small Lung Cancer

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Percentages of new cancer cases and cancer deaths worldwide in 2018

Incidence

1. **Lung** — 11.6% of all new cases — 2.094 million
2. **Breast** — 11.6% of all new cases — 2.089 million
3. **Colorectal** — 10.2% of all new cases — 1.8 million
4. **Prostate** — 7.1% of all new cases — 1.3 million
5. **Stomach** — 5.7% of all new cases — 1.0 million

For both sexes, all cancers for all ages, worldwide in 2018

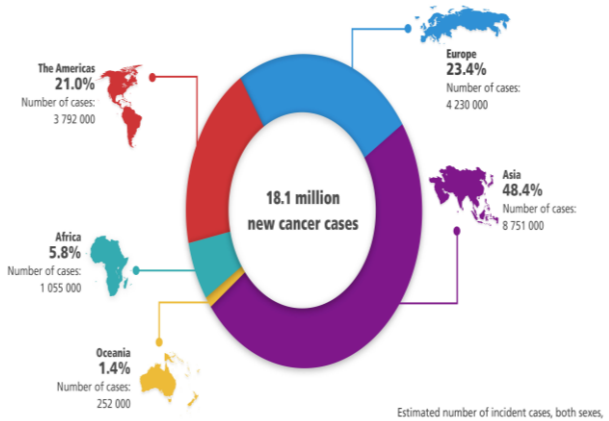
Mortality

1. **Lung** — 18.4% of all cancer deaths — 1.8 million
2. **Colorectal** — 9.2% of all cancer deaths — 881 000
3. **Stomach** — 8.2% of all cancer deaths — 783 000
4. **Liver** — 8.2% of all cancer deaths — 782 000
5. **Breast** — 6.6% of all cancer deaths — 627 000

For both sexes, all cancers for all ages, worldwide in 2018

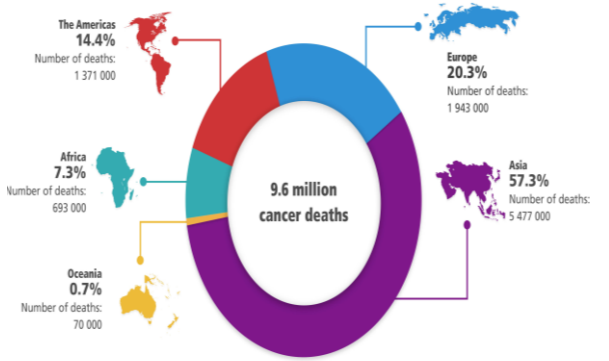
Data source: GLOBOCAN 2018
Available at Global Cancer Observatory (http://gco.iarc.fr/)
© International Agency for Research on Cancer 2018

Global cancer incidence

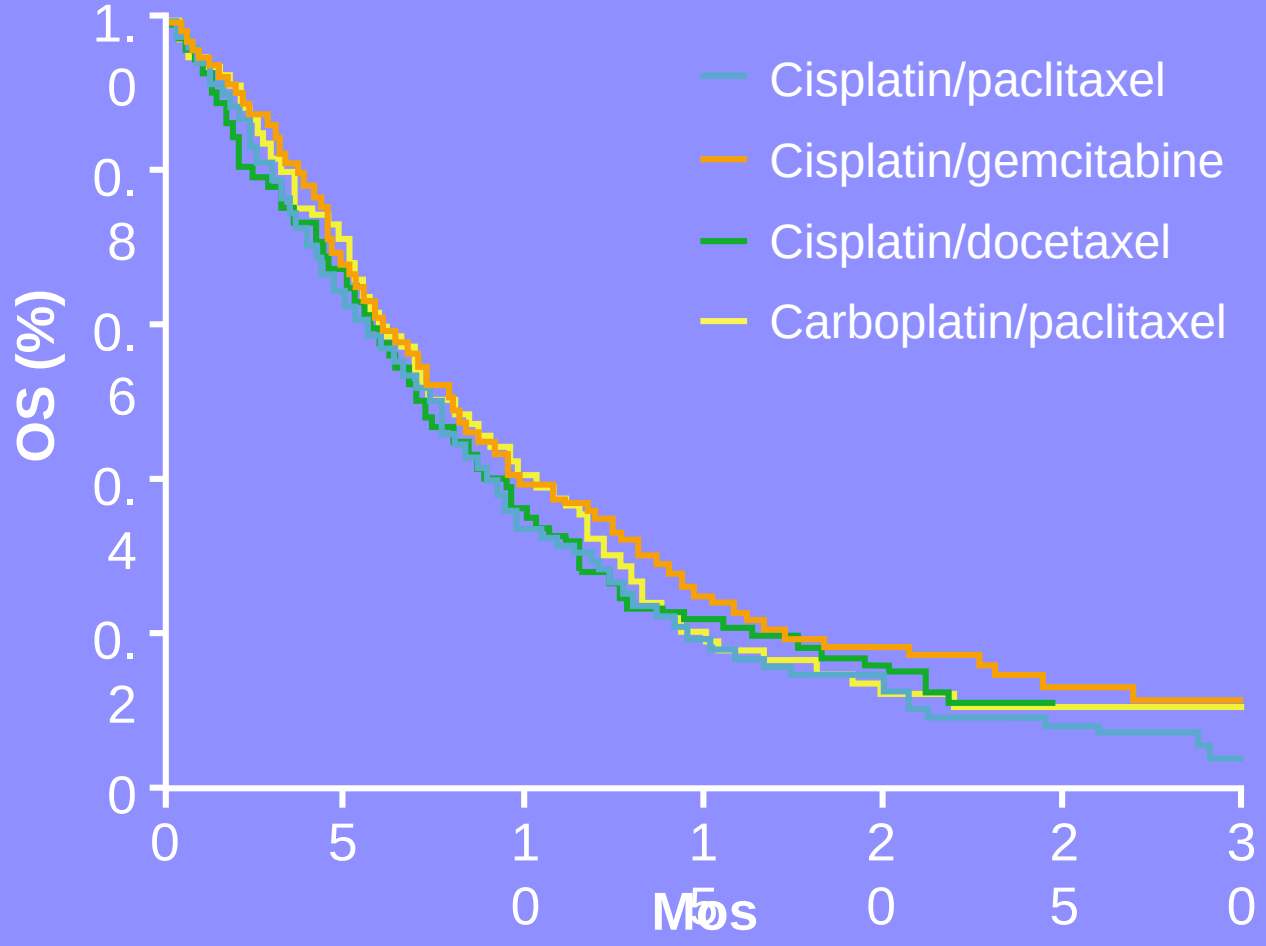


Estimated number of incident cases, both sexes, all cancers including non-melanoma skin cancer, for all ages, worldwide

Global cancer mortality



Therapeutic Plateau in Metastatic NSCLC
ECOG 1594



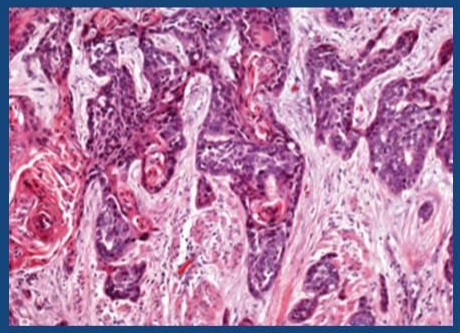
Schiller JH, et al. N Engl J Med. 2002;346:92-98.

Slide credit: clinicaloptions.com

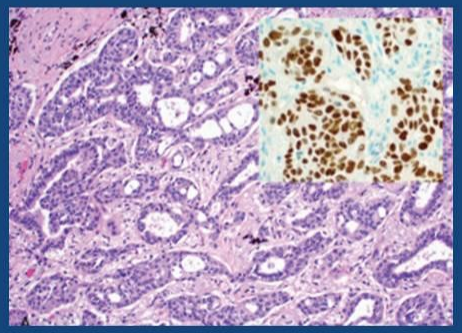
How do we describe lung cancer in 2018?

Histology

Squamous | Non-Squamous



Squamous Cell Carcinoma



Adenocarcinoma

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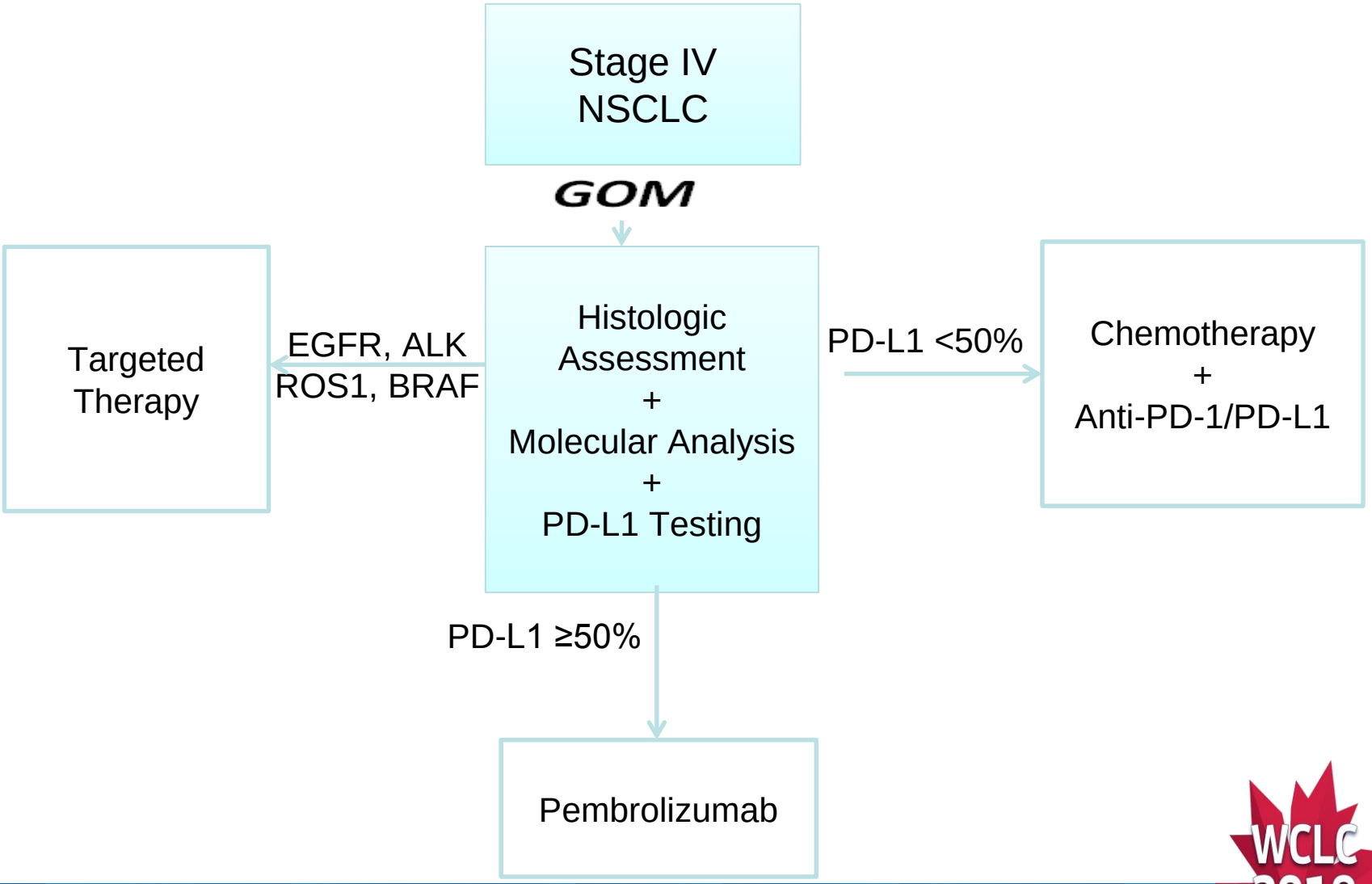
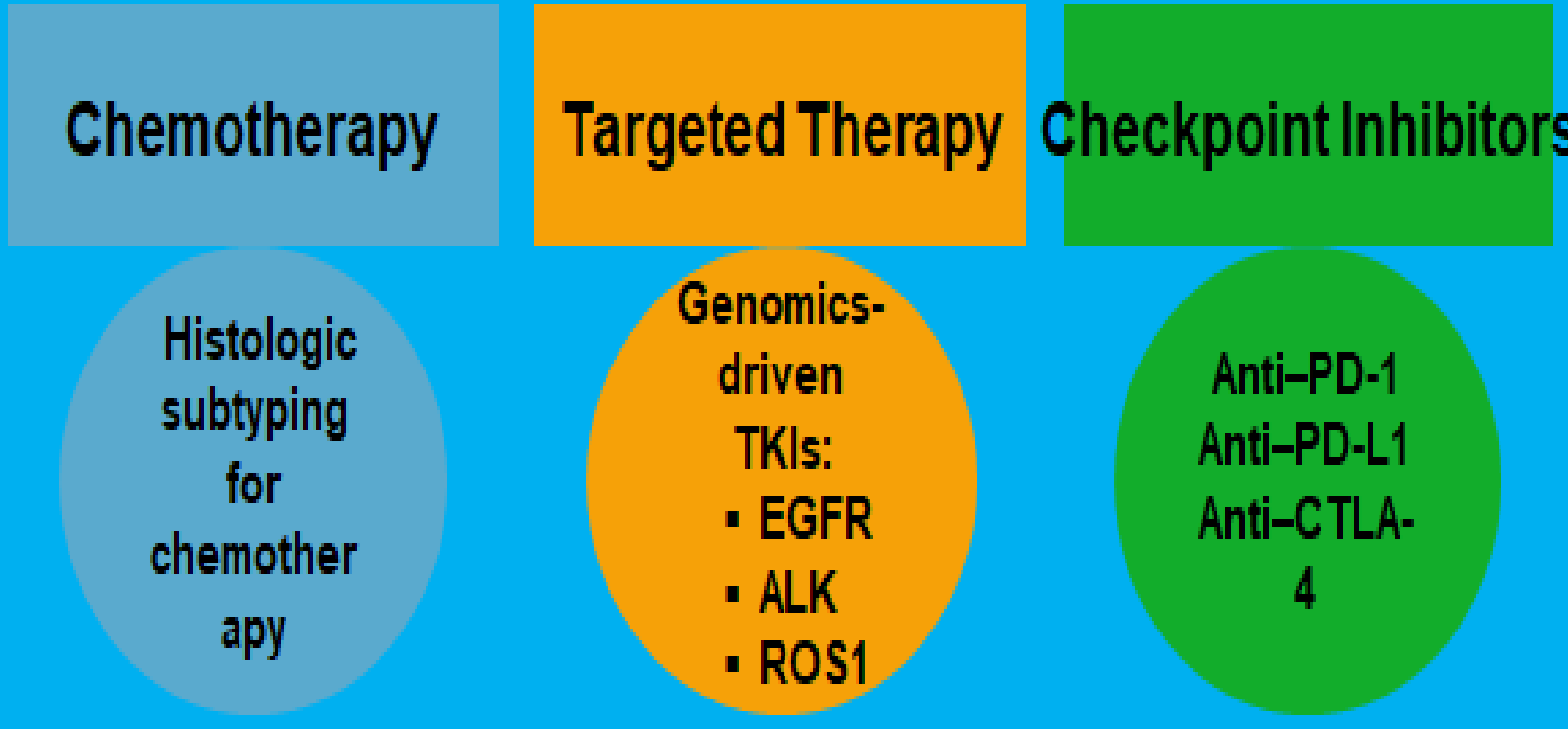
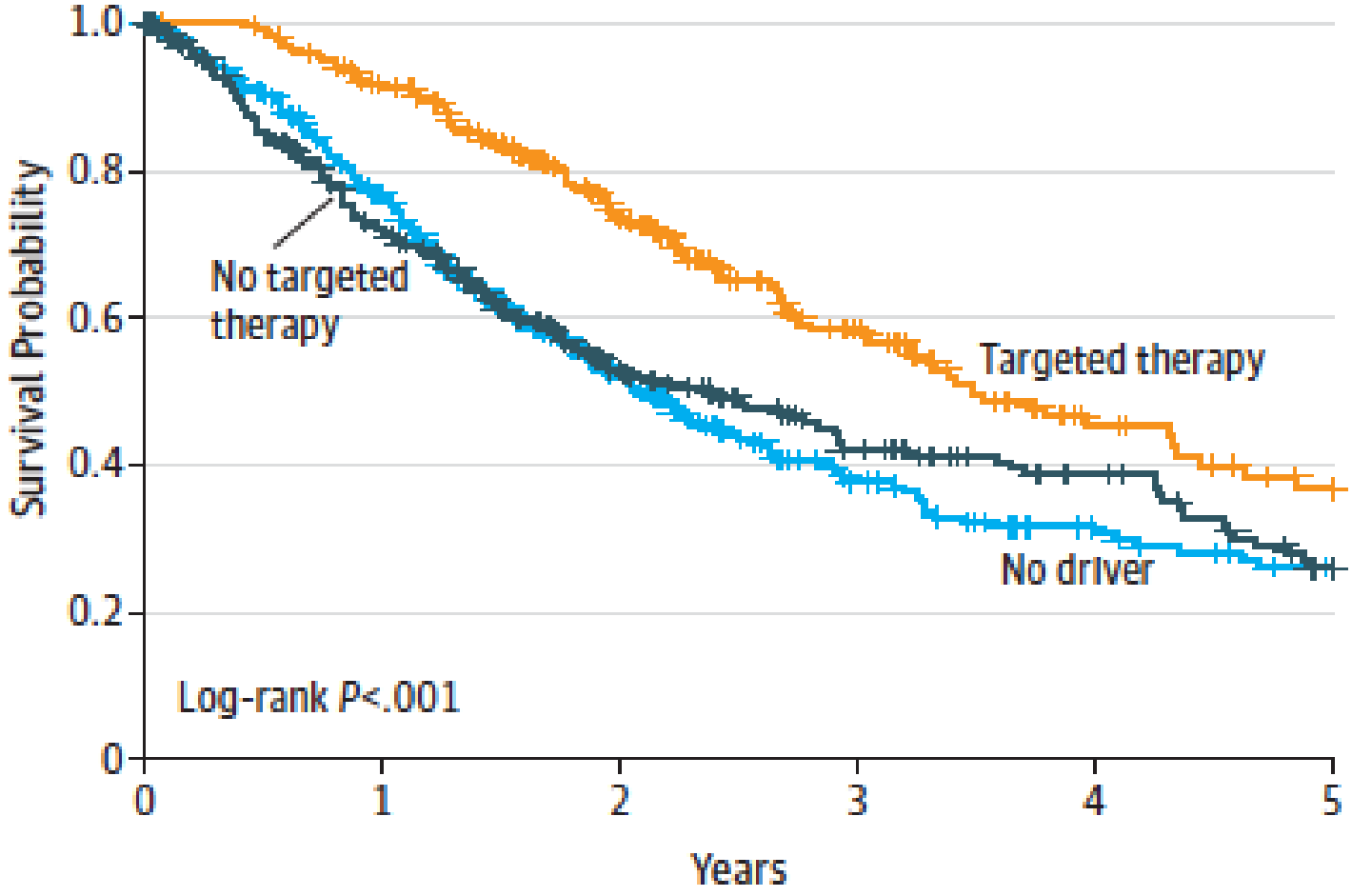

Stage IV NSCLC
GOM
Histologic Assessment + Molecular Analysis + PD-L1 Testing
EGFR, ALK ROS1, BRAF
Targeted Therapy
PD-L1 <50%
Chemotherapy + Anti-PD-1/PD-L1
PD-L1 ≥50%
Pembrolizumab

What Tools Can Facilitate Personalized Therapy in Advanced-Stage NSCLC?



Multiplex Assays of Oncogenic Drivers in Lung Cancer



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

EGFR-TKIs in *EGFR*$^{mut+}$ NSCLC

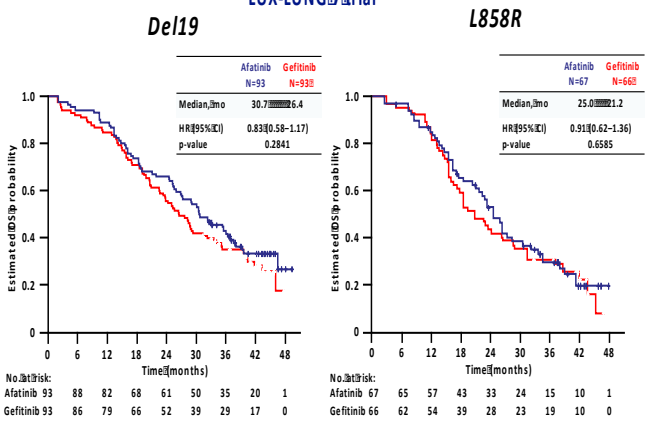
1: Ten studies demonstrated superiority over standard CT

Study	#	Treatment	RR%	PFS		OS	
				mPFS (mos)	HR P-value	mOS (mos)	HR P-value
IPASS* (Mok et al. 2009)	97	Gefitinib	71.2	9.5	0.48	21.6	1.00
	111	CBDCA+PTXL	47.3	6.3	<0.0001	21.9	0.99
First SIGNAL* (Han et al 2012)	159	Gefitinib	84.6	8.0	0.54	27.2	1.04
	150	CDDP+GEM	37.5	6.3	0.008	25.6	NR
WJTOG 3405 (Mitsudomi et al 2010)	88	Gefitinib	62.1	9.2	0.48	34.8	1.25
	89	CDDP+DTXT	32.2	6.3	<0.001	37.3	NR
NEJ002 (Maemondo 2010)	114	Gefitinib	73.7	10.4	0.36	27.7	0.89
	114	CBDCA+PTXL	30.7	5.5	<0.001	26.6	0.48
OPTIMAL (Zhou et al 2011)	82	Erlotinib	83.0	13.1	0.16	22.6	1.06
	72	CBDCA+GEM	36.0	4.6	<0.0001	28.8	0.68
EURTAC (Rosell et al. 2012)	84	Erlotinib	54.5	9.4	0.34	19.3	1.04
	82	Platinum Doublet	10.5	5.2	<0.0001	19.5	0.87
ENSURE (Wu et al. 2013)	110	Erlotinib	68.2	11.1	0.43	NR	NR
	107	CDDP+GEM	39.3	5.7	<0.0001	NR	NR
LUX Lung 3 (Sequist et al 2013)	230	Afatinib	56.0	11.1	0.58	16.6	1.12
	115	CDDP+PEM	23.0	6.9	0.001	14.8	0.60
LUX Lung 6 (Wu et al 2014)	242	Afatinib	66.9	11.0	0.28	22.1	0.95
	122	CDDP+GEM	23.0	5.6	<0.0001	22.2	0.76
Patil VM (2017)	145	Gefitinib	63.5	8.4	0.66	18.0	0.78
(Indian Trial)	145	CBDCA+PEM§	45.3	5.6	<0.001	22.6	0.133

2: Three drugs very similar in efficacy

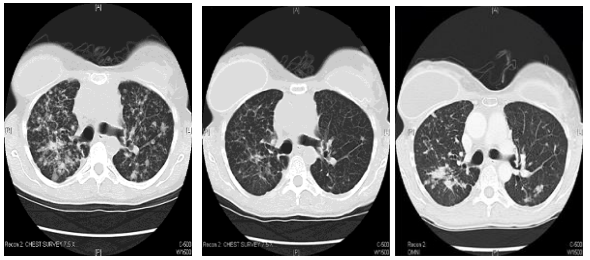
Overall survival according to the type of *EGFR* mutation

LUX-LUNG 7 Trial



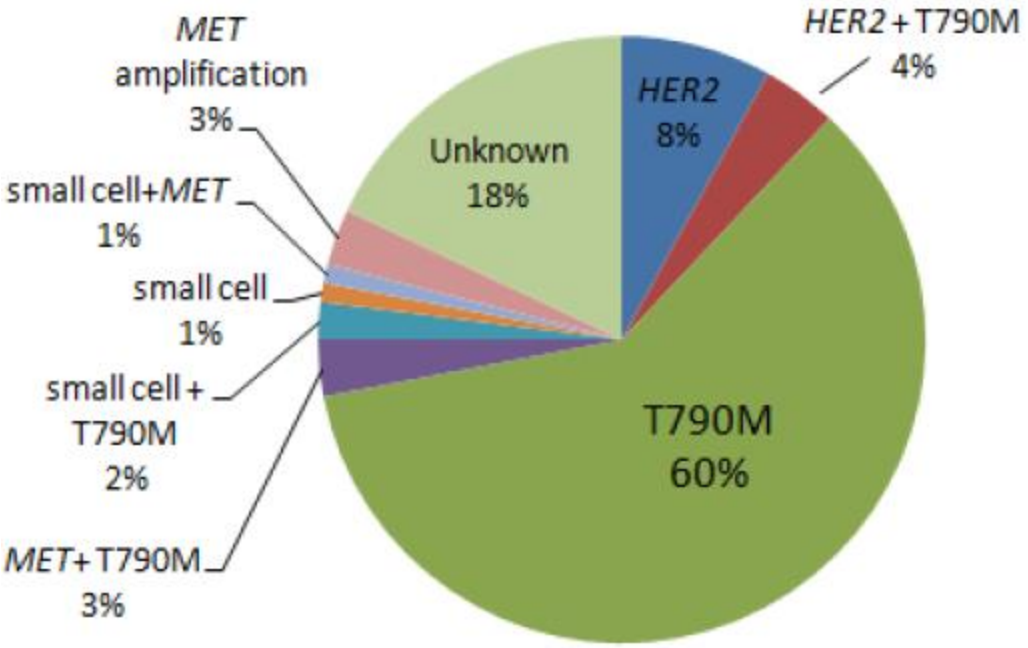
3: Limited PFS and acquired resistance

EGFR^{mut+} or *ALK*+ NSCLC → *Targeted Therapy* → Progression (acquired resistance)



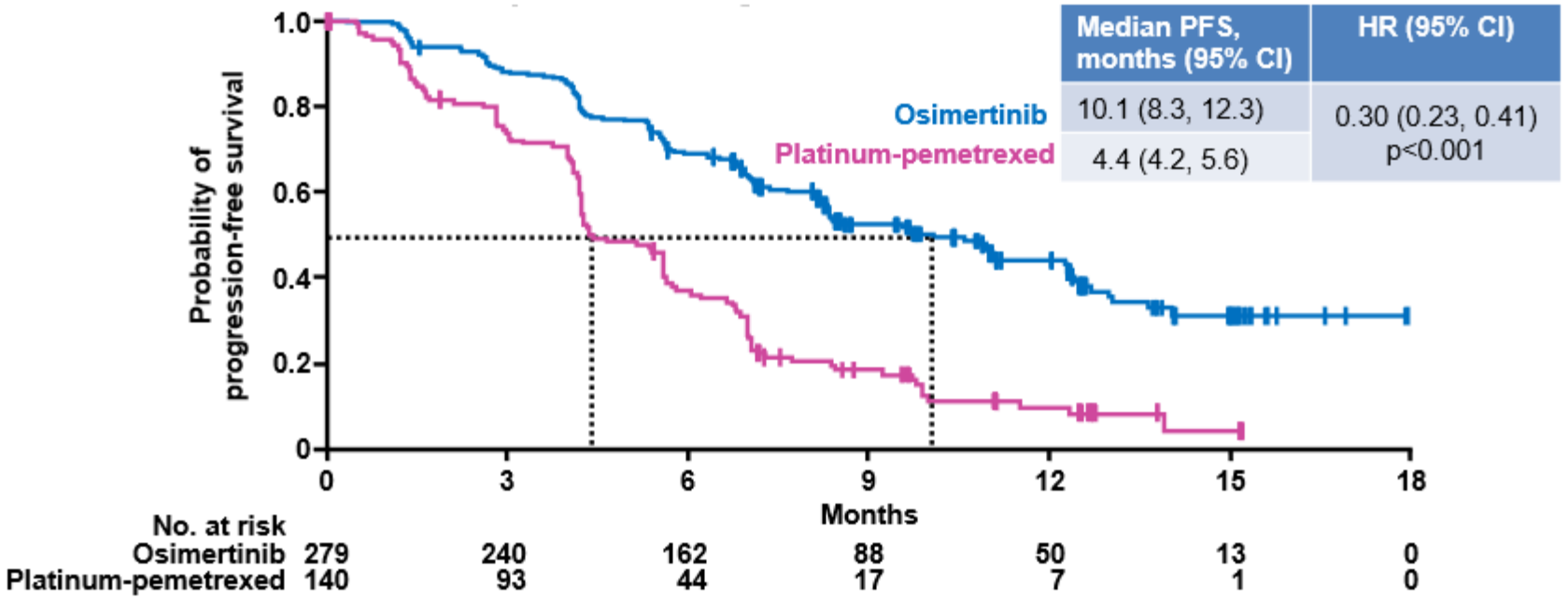
Baseline | Tumor regression (RR up to 90%) | Progression (median 9–13 months)

Mechanisms of resistance to first gen EGFR TKIs



Sequist et al., *Sci Transl Med* 2011 ; Yu et al., *Clin Cancer Res* 2013
(and many other pie bakers)

AURA3 primary endpoint: PFS by investigator assessment

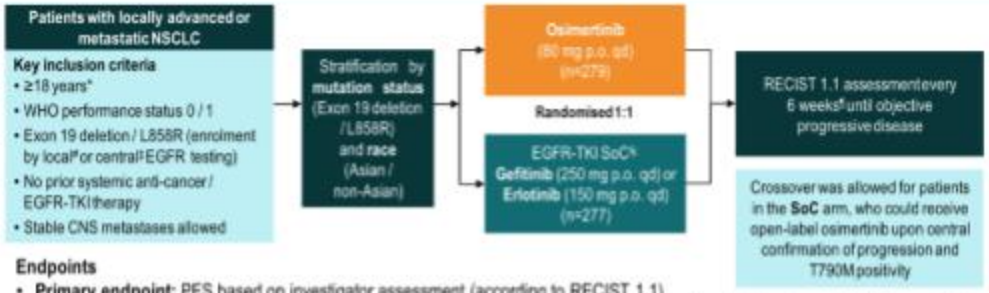


	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	10.1 (8.3, 12.3)	0.30 (0.23, 0.41) p<0.001
Platinum-pemetrexed	4.4 (4.2, 5.6)	

- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death; calculated using the Kaplan-Meier approach. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

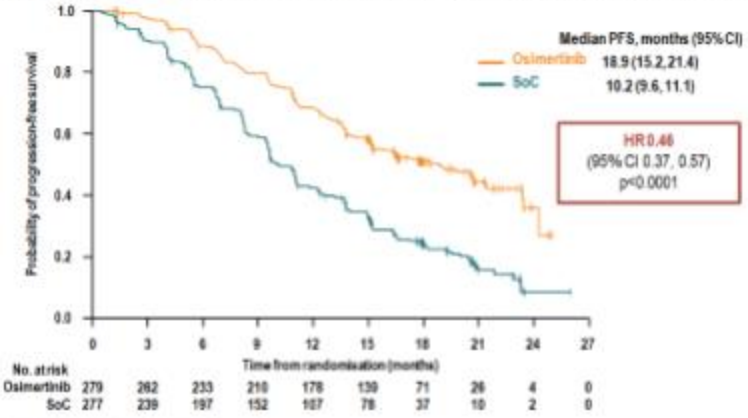
FLAURA trial: survival outcomes



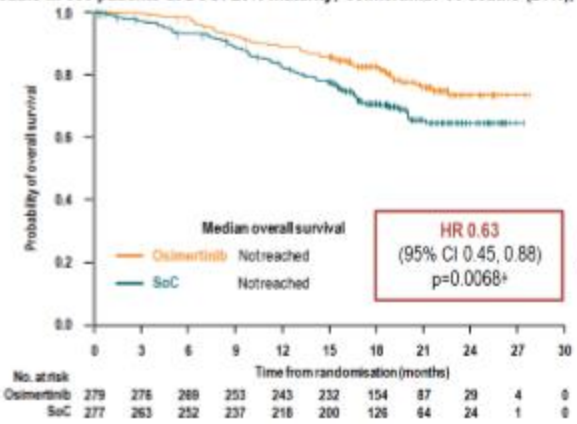
Endpoints

- **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

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

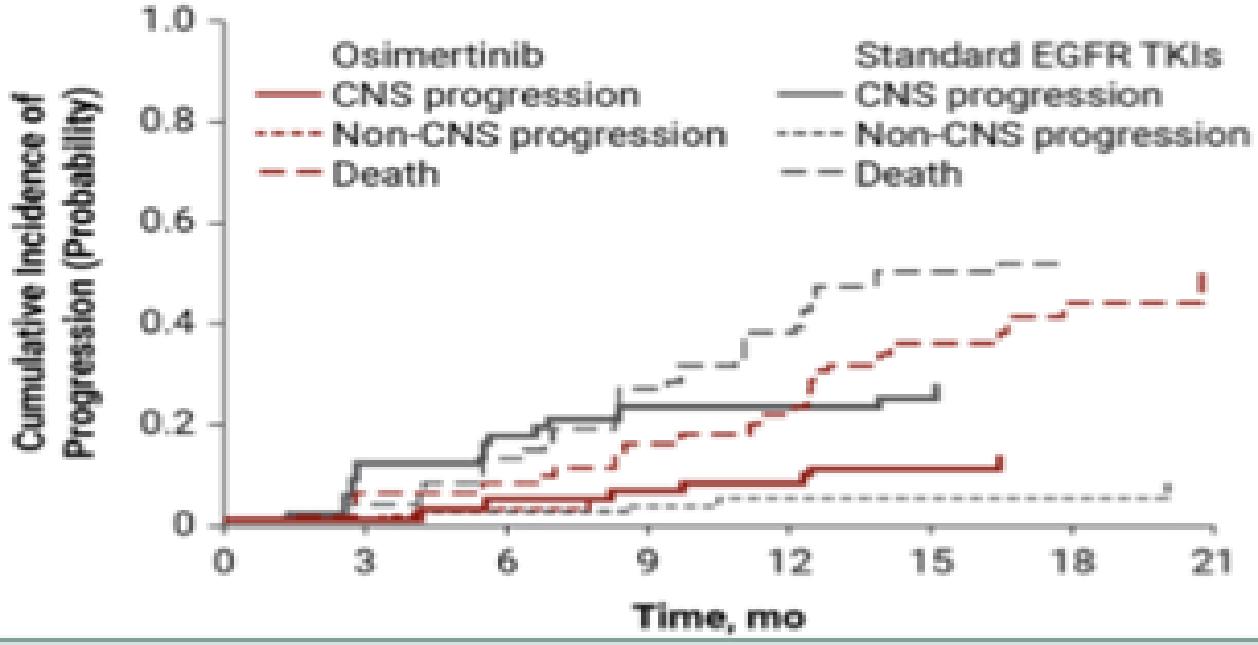


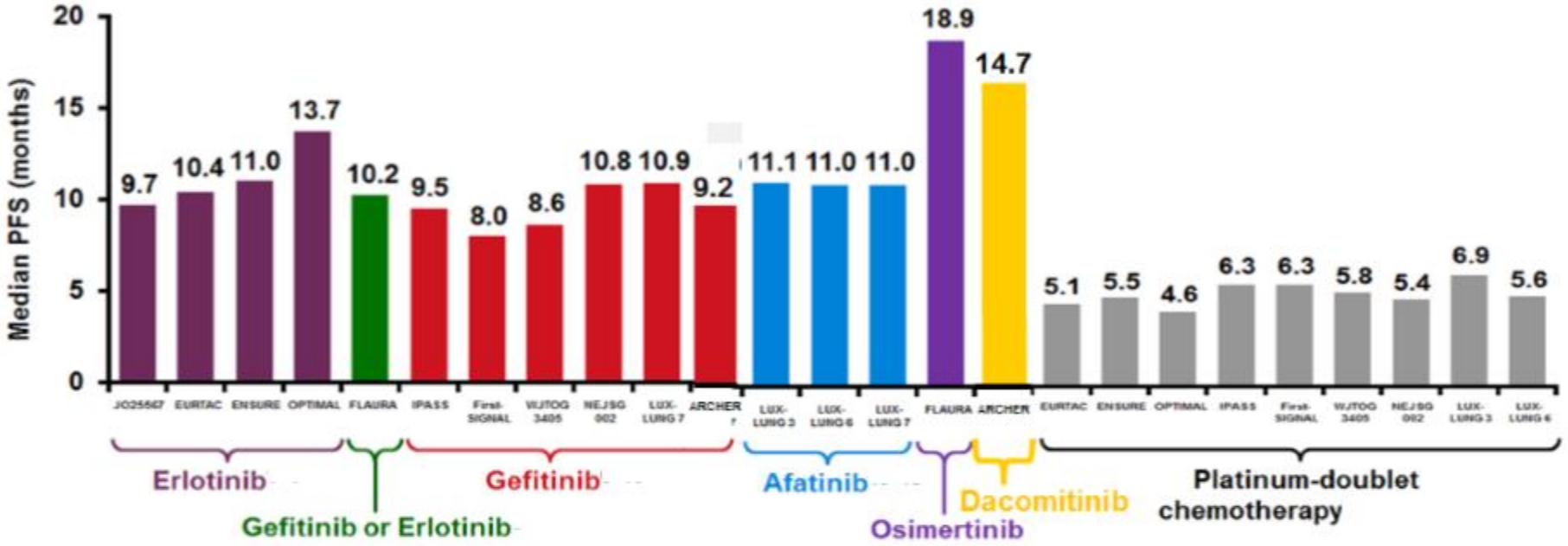
141 deaths in 556 patients at DCO: 25% maturity; osimertinib: 58 deaths (21%), SoC: 83 deaths (30%)



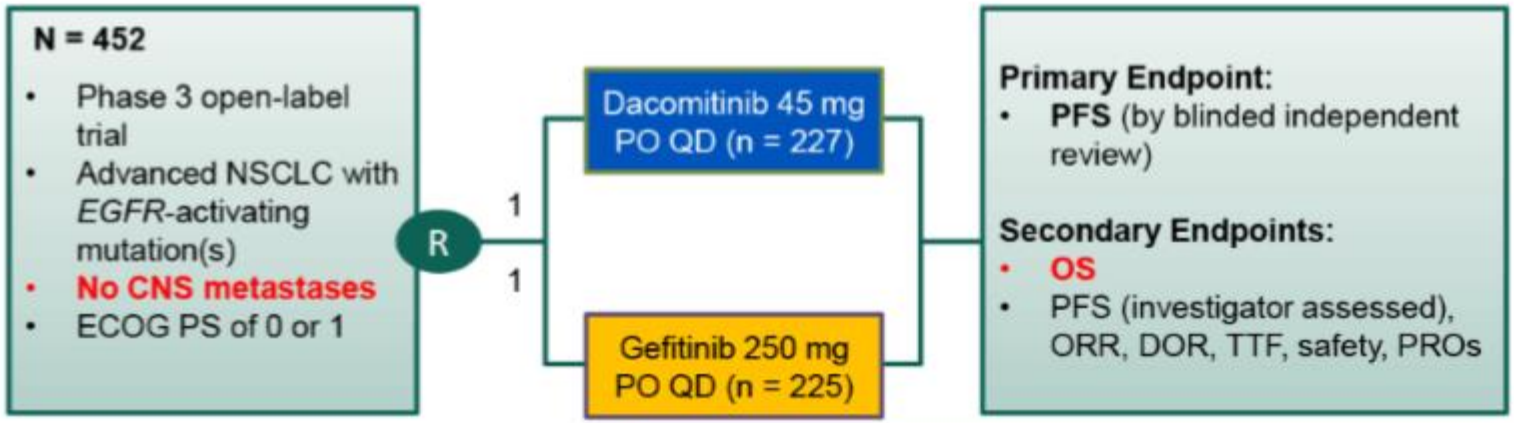
†A p-value of <0.0015 was required for statistical significance at current maturity

CUMULATIVER INCIDENCE OF CNS PROGRESSION WITH OSI VS SOC




Median PFS (months)
20
15
10
5
0
9.7
10.4
11.0
13.7
10.2
9.5
8.0
8.6
10.8
10.9
9.2
11.1
11.0
11.0
18.9
14.7
5.1
5.5
4.6
6.3
6.3
5.8
5.4
6.9
5.6
JO25567
EURTAC
ENSURE
OPTIMAL
FLAURA
IPASS
First-SIGNAL
WJTOG 3405
NEJSG 002
LUX-LUNG 7
ARCHER
LUX-LUNG 3
LUX-LUNG 6
LUX-LUNG 7
FLAURA
ARCHER
EURTAC
ENSURE
OPTIMAL
IPASS
First-SIGNAL
WJTOG 3405
NEJSG 002
LUX-LUNG 3
LUX-LUNG 6
Erlotinib
Gefitinib or Erlotinib
Gefitinib
Afatinib
Osimertinib
Dacomitinib
Platinum-doublet chemotherapy

ARCHER 1050: Study Design

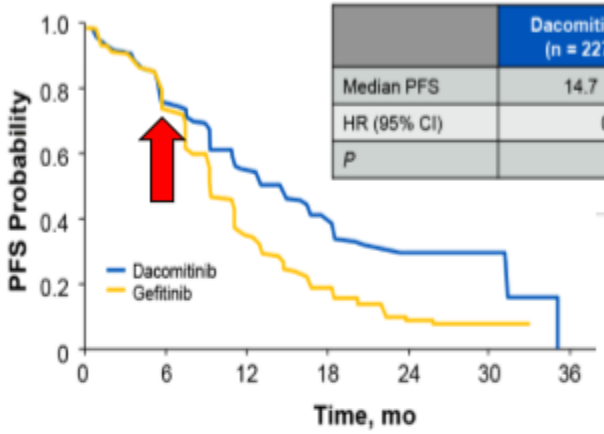


Stratified by:
- Race (including Asian vs non-Asian)
- *EGFR* mutation type (exon 19 vs 21)

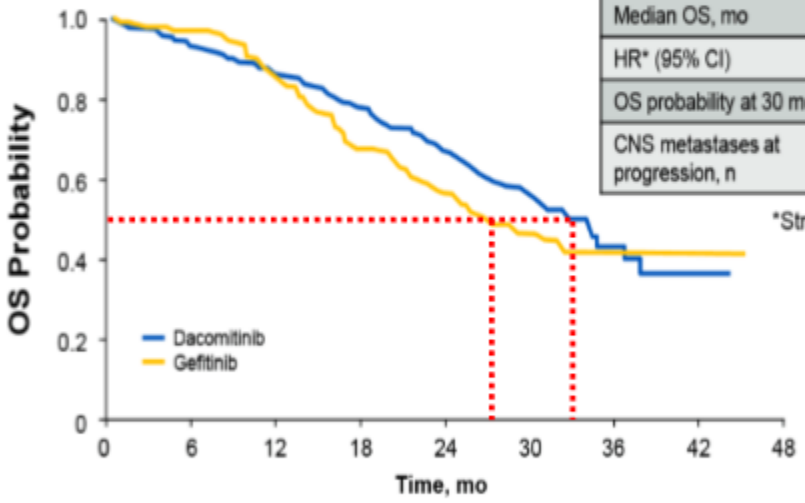
The US FDA has approved dacomitinib for the front-line treatment of patients with metastatic NSCLC with *EGFR* exon 19 deletion or exon 21 L858R substitution mutations

Wu Y-L et al. *Lancet Oncol.* 2017;18:1454-1466.
Mok T et al. ASCO 2018. Presentation 9004.

ARCHER 1050: survival outcomes (PFS & OS)



	Dacomitinib (n = 227)	Gefitinib (n = 225)
Median PFS	14.7	9.2
HR (95% CI)	0.59 (0.47-0.74)	
P	< .0001	



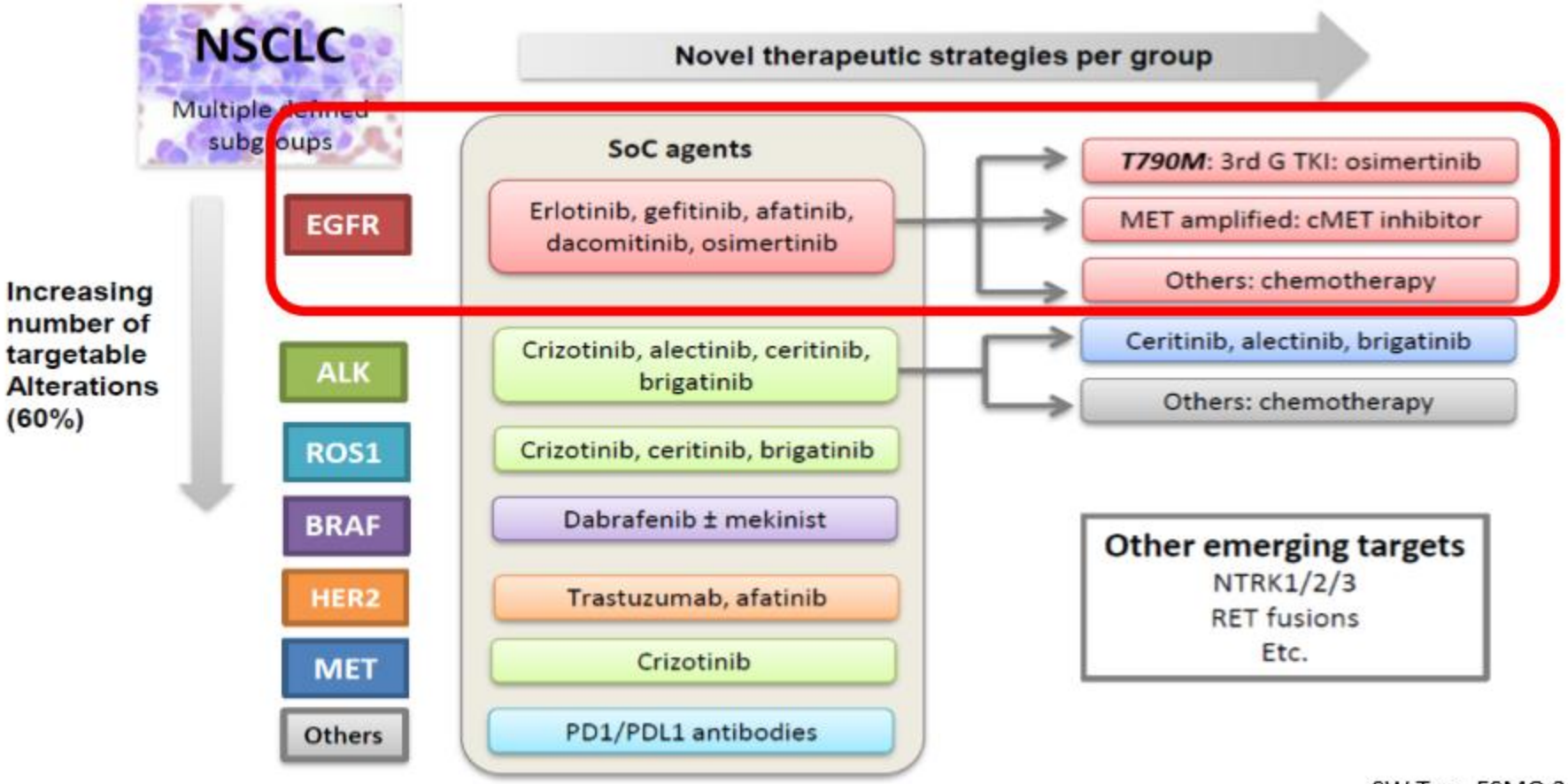
	Dacomitinib (n = 227)	Gefitinib (n = 225)
Median OS, mo	34.1	26.8
HR* (95% CI)	0.760 (0.582-0.993)	
OS probability at 30 mo, %	56.2	46.3
CNS metastases at progression, n	1	11

*Stratified analysis.

Wu Y-L et al. *Lancet Oncol*. 2017;18:1454-1466.
Mok T et al. ASCO 2018. Presentation 9004.

Resistance mechanisms to dacomitinib and subsequent therapy on ARCHER 1050

Oncogenic drivers and target therapies in NSCLC



SW Tan , ESMO 2018

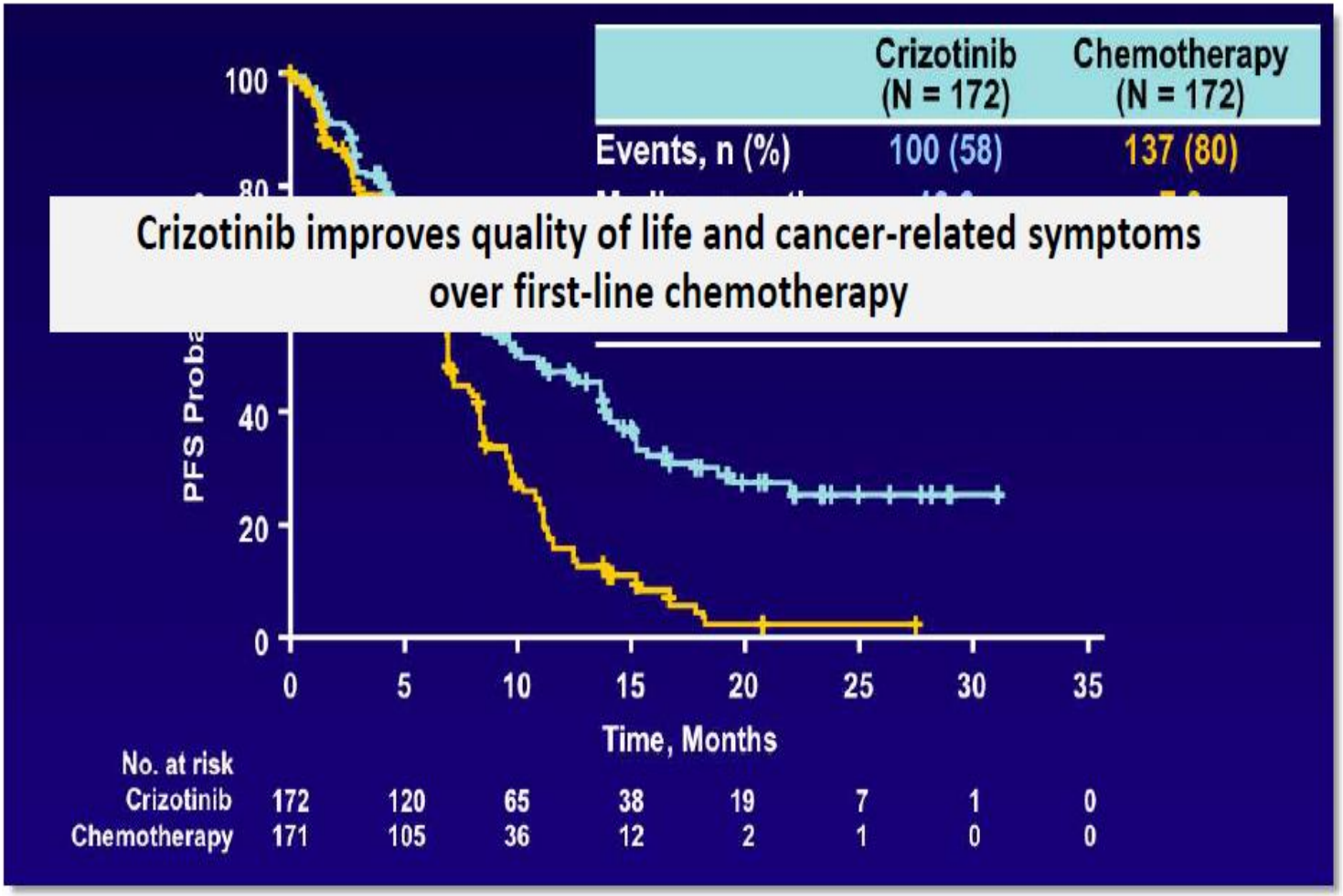
Clinical and Pathologic Characteristics

- 2%–5% of NSCLC patients have *ALK* gene rearrangements[a]
- Higher prevalence in patients who have the following characteristics[a]:
  - ADC histology
  - Never/light smoking history
  - Younger than *ALK*-negative NSCLC patients
- Pleural and pericardial effusion and brain metastases more common[b]

a. Scarpino S, et al. *Lung Cancer.* 2016;97:95-98.
b. Gobbini E, et al. *Lung Cancer.* 2017;111:30-37.

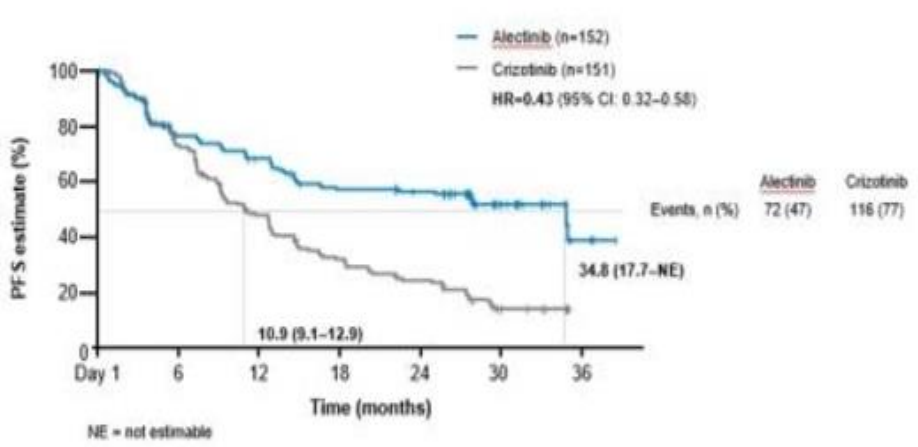
PROFILE 1014

PFS primary endpoint

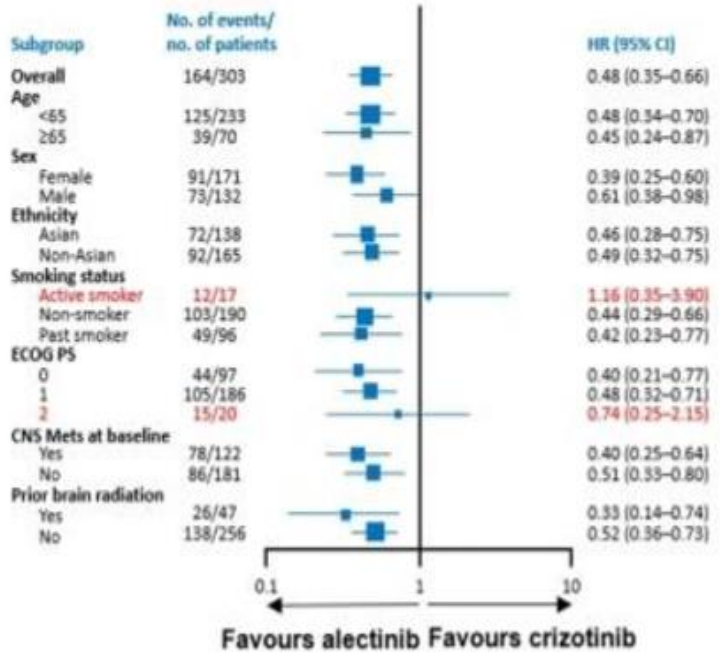


Solomon NEJM 2014

ALEX: updated investigator-assessed PFS

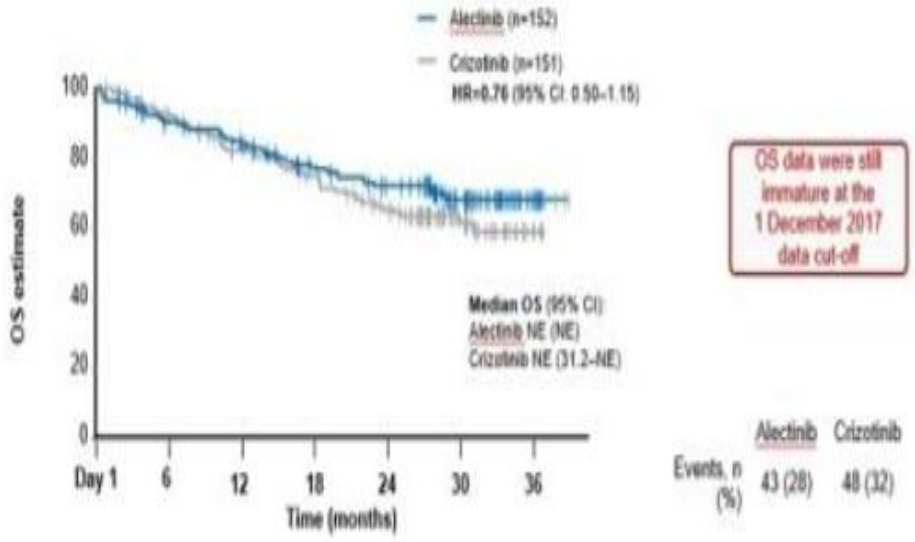


These updated data demonstrate that investigator-assessed PFS was prolonged with alectinib versus crizotinib (median PFS 34.8 months vs 10.9 months)



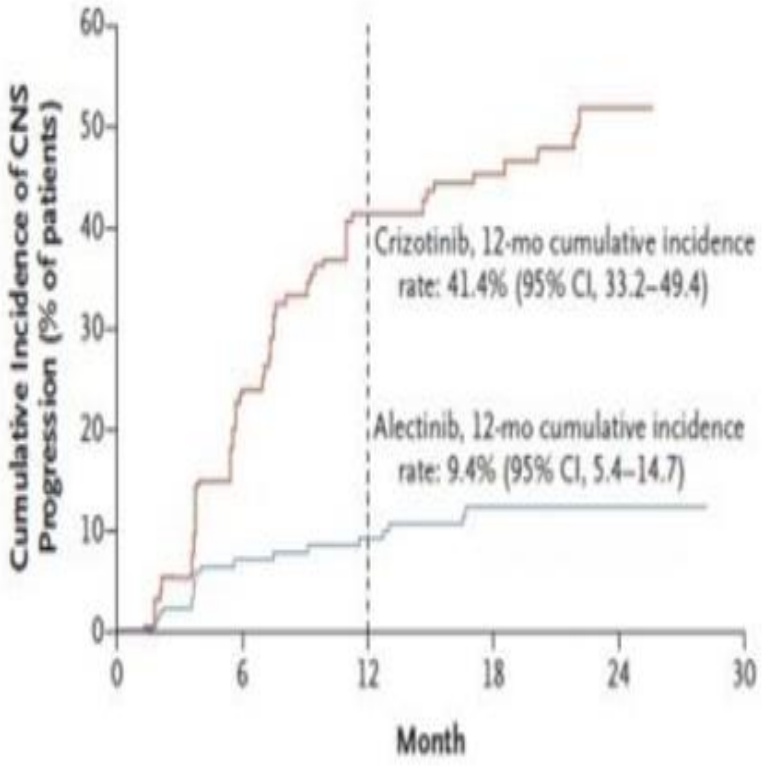
Camidge R, ASCO 2018

ALEX: updated OS and brain mets



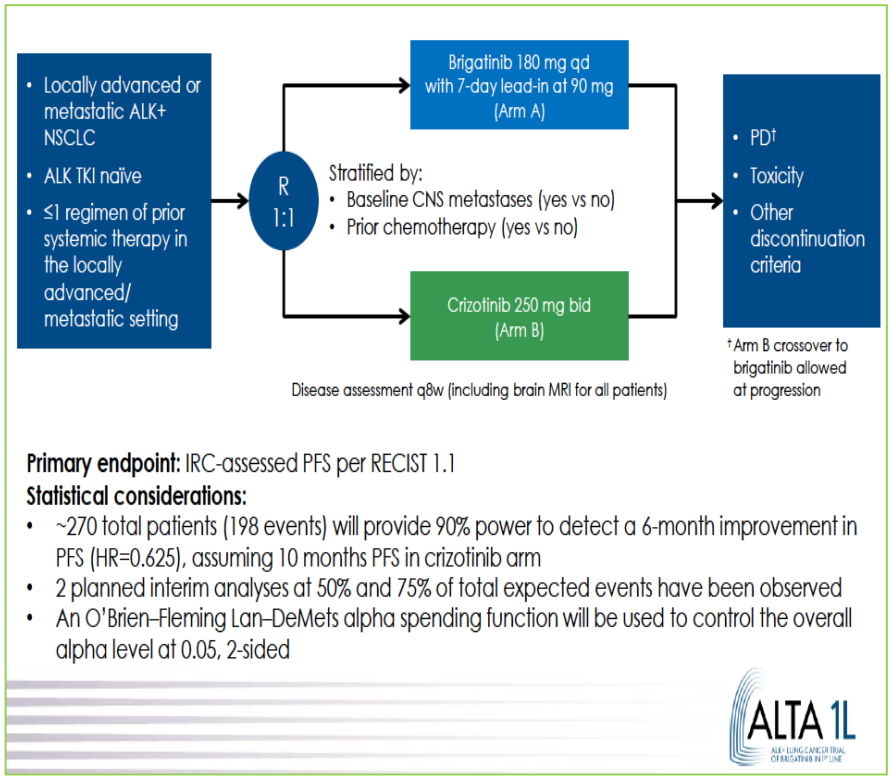
OS data were still immature at the 1 December 2017 data cut-off

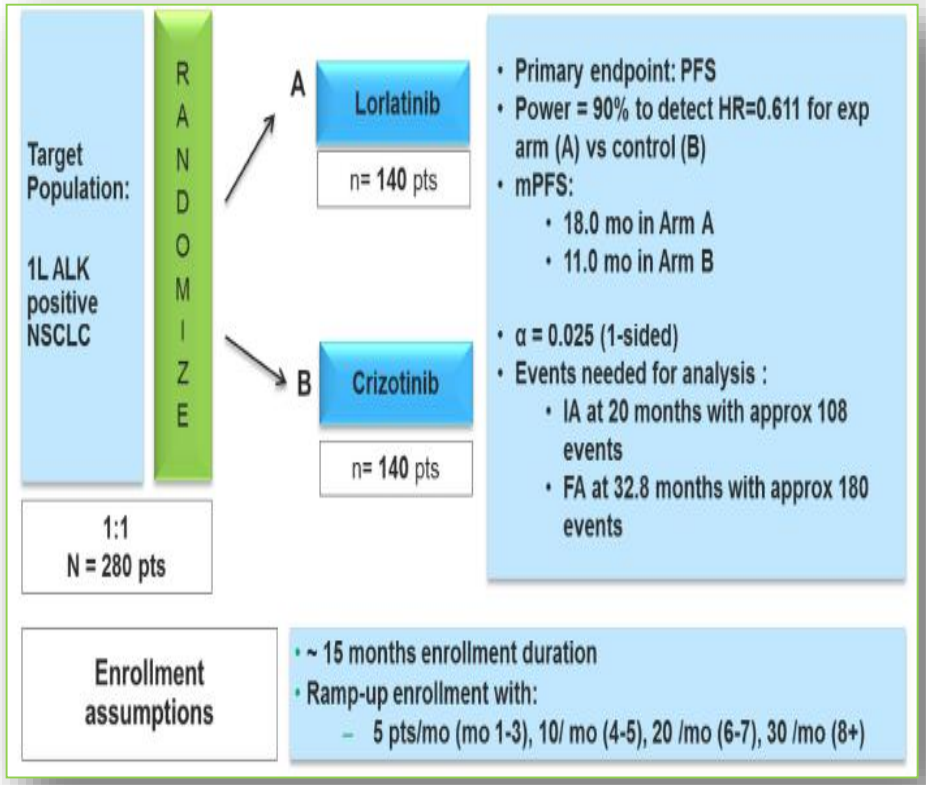
At the updated data cut-off 91, deaths had occurred in the ITT population; 43 (28%) alectinib arm and 48 (32%) crizotinib arm. The HR for OS was 0.76 (95% CI: 0.50–1.15) and median OS was still not estimable in either arm



Updated data cut-off (1 December 2017)

Head to Head: ongoing and coming soon





1L Treatment of ALK+ NSCLC

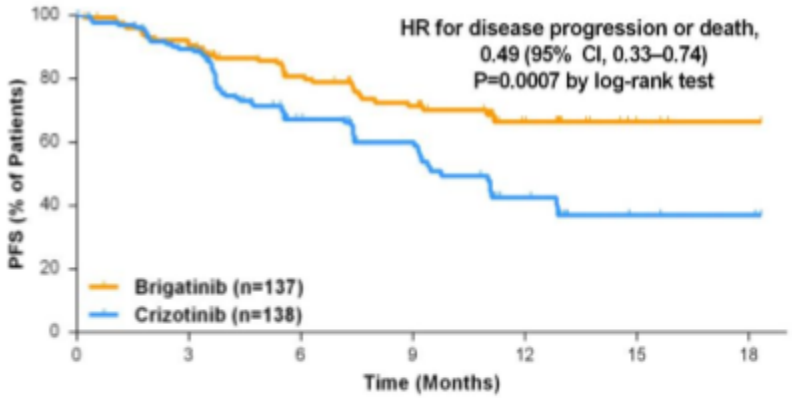
Crizotinib

Ceritinib

Alectinib*

*NCCN Guidelines preferred

ALTA-1L Camidge et al. WCLC 2018



Brigatinib

MUNICH 2018 ESMO congress

Non fumatore-> Driver (TT «risarcimento!»)

E per il fumatore?

Immunoterapia «consolatoria»?

American Association for Cancer Research (AACR) 2017 Annual Meeting

Nivolumab Quadruples 5-Year Survival in NSCLC

WASHINGTON – The longest follow-up to date on patients treated with nivolumab (*Opdivo*, Bristol-Myers Squibb) for advanced non-small cell lung cancer (NSCLC) shows a 16% 5-year overall survival (OS) rate, according to new results presented here at the American Association for Cancer Research annual meeting.

The new data come from the phase 1b CA209-003 study, which is the first trial of any programmed death-1 (PD-1) immune checkpoint inhibitor in lung cancer.

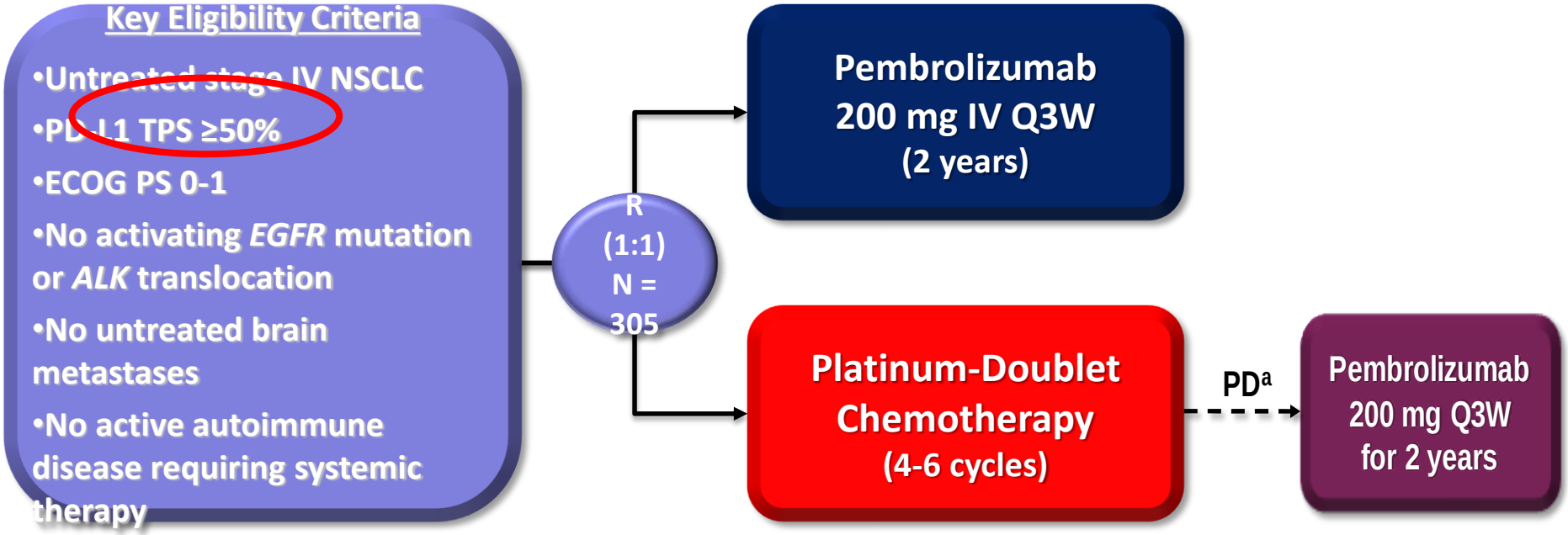
Published Phase III Trials of PD-1/PD-L1 Agents in 2nd-Line NSCLC

Immuno Agent	Trial	Histology	N	Drug Comparison	Primary Endpoint	Outcome
NIVOLUMAB	CHECKMATE 017 [1]	Squamous NSCLC	272 100% 2nd line	vs Docetaxel	OS	Positive HR 0.62 (95% CI, 0.44 to 0.79) p<0.001
	CHECKMATE 057 [2]	Non Squamous NSCLC	582 88% 2nd line	vs Docetaxel	OS	Positive HR 0.73 (96% CI, 0.59 to 0.89) p=0.002
PEMBROLIZUMAB*	KEYNOTE 010 [3]	NSCLC PDL-1 >1%	1034 69% 2nd line	vs Docetaxel	OS	Positive HR 0·71 (95% CI, 0·58–0·88) p=0·0008
ATEZOLIZUMAB * 2mg/kg	OAK [4]	NSCLC	850 75% 2nd line	vs Docetaxel	OS	Positive HR 0·73 (95% CI 0·62–0·87 p=0·0003

[1] Brahmer et al, NEJM 205; [2] Borghaei et al, NEJM 205; [3] Herbst et al, Lancet 2016; [4] Ryttmeier et al, Lancet 2017

Earthquake in Lung Cancer: Immunotherapy First-Line

KEYNOTE 024 study design



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

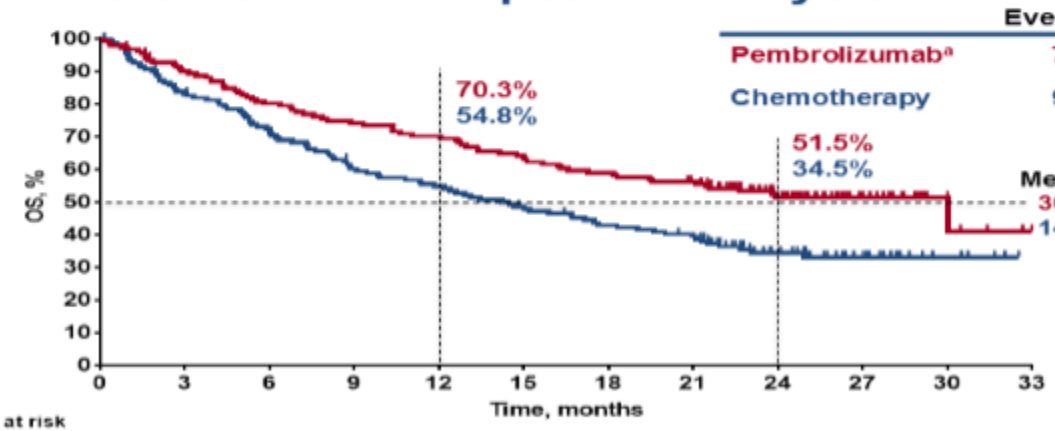
Exploratory: DOR

[a]To be eligible for crossover, progressive disease (PD) had to be confirmed by blinded, independent central radiology review and all safety criteria had to be met.

Reck M, et al. NEJM 2016

Brahmer WCLC 2017

Overall Survival: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab[a]	73	0.63 (0.47–0.86) *P* = 0.002[b]
Chemotherapy	96	

Median (95% CI)
30.0 mo (18.3 mo–NR)
14.2 mo (9.8 mo–19.0 mo)

[a]Effective cross over rate from chemotherapy to anti-PD-L1 therapy, 62.3% (82 patients crossed over to pembrolizumab during the study and 12 received anti-PD-L1 therapy outside of cross over). [b]Nominal *P* value. NR, not reached.
Data cutoff: July 10, 2017.

Immunotherapy

Chemotherapy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

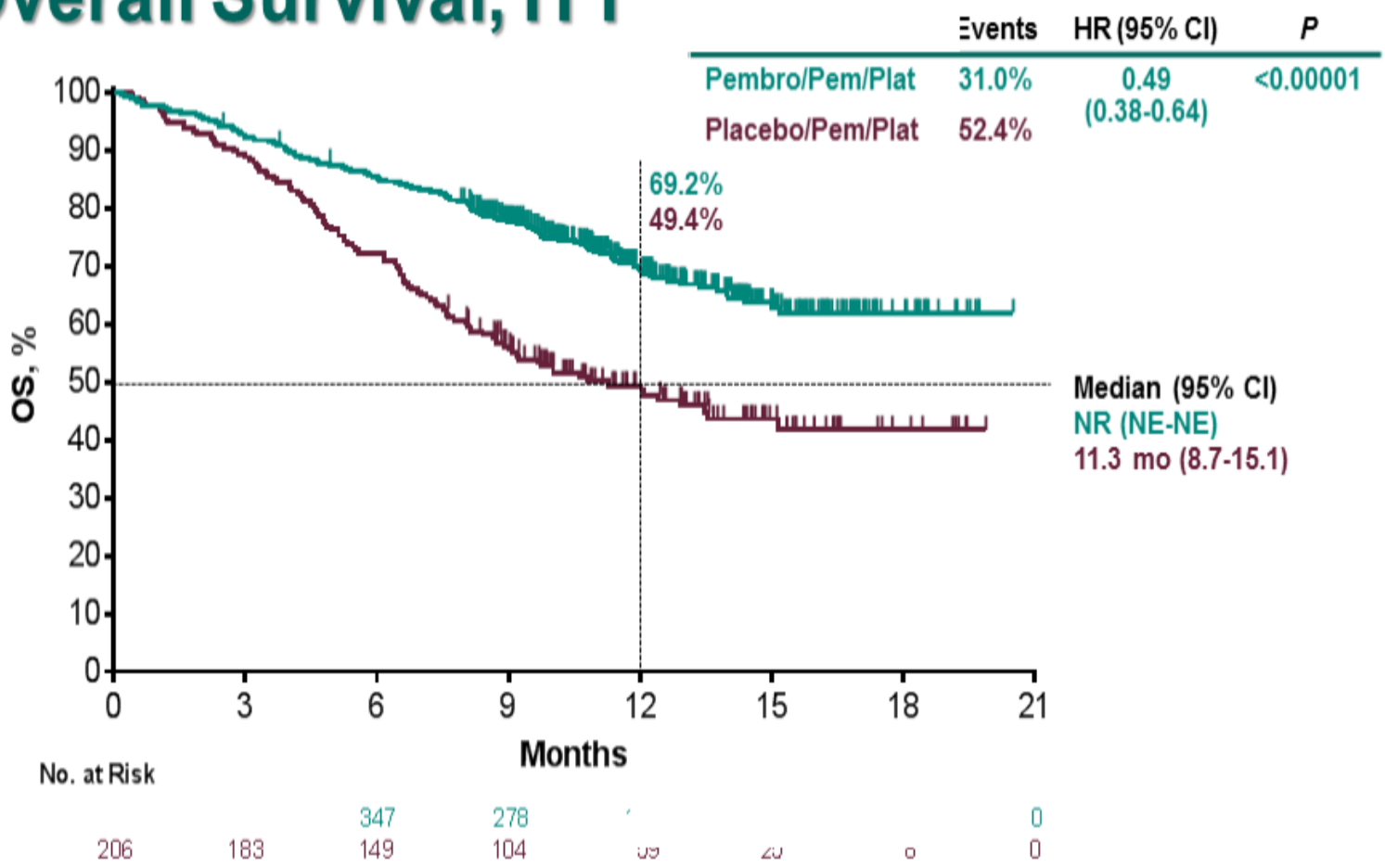
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

Platin/Pem ± Pembrolizumab in Non-SCC NSCLC
KeyNote 189 Trial

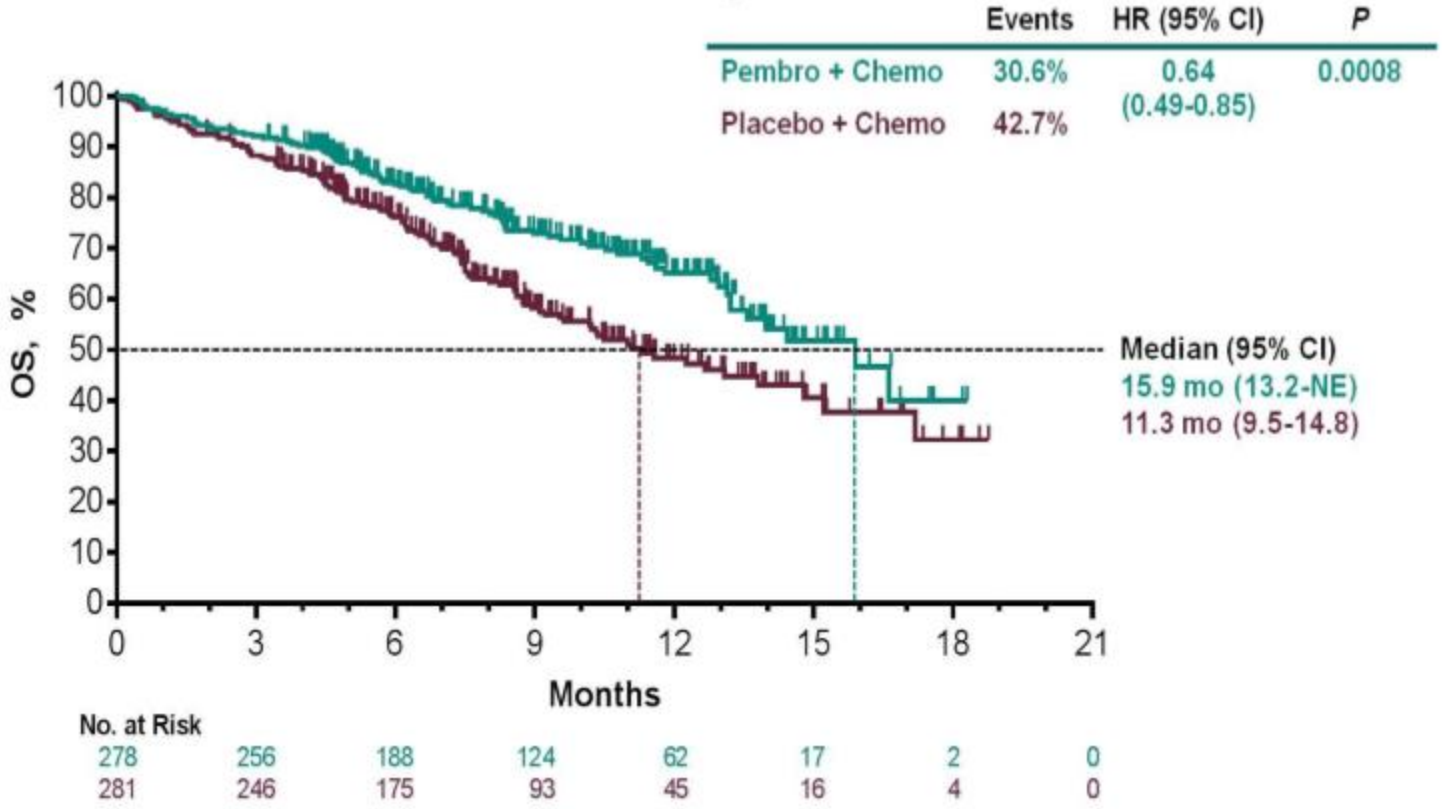
Gandhi KN189
AACR 2018

Overall Survival, ITT



Chemo ± Pembrolizumab in SCC NSCLC
KeyNote 407 Trial

Overall Survival at IA2, ITT

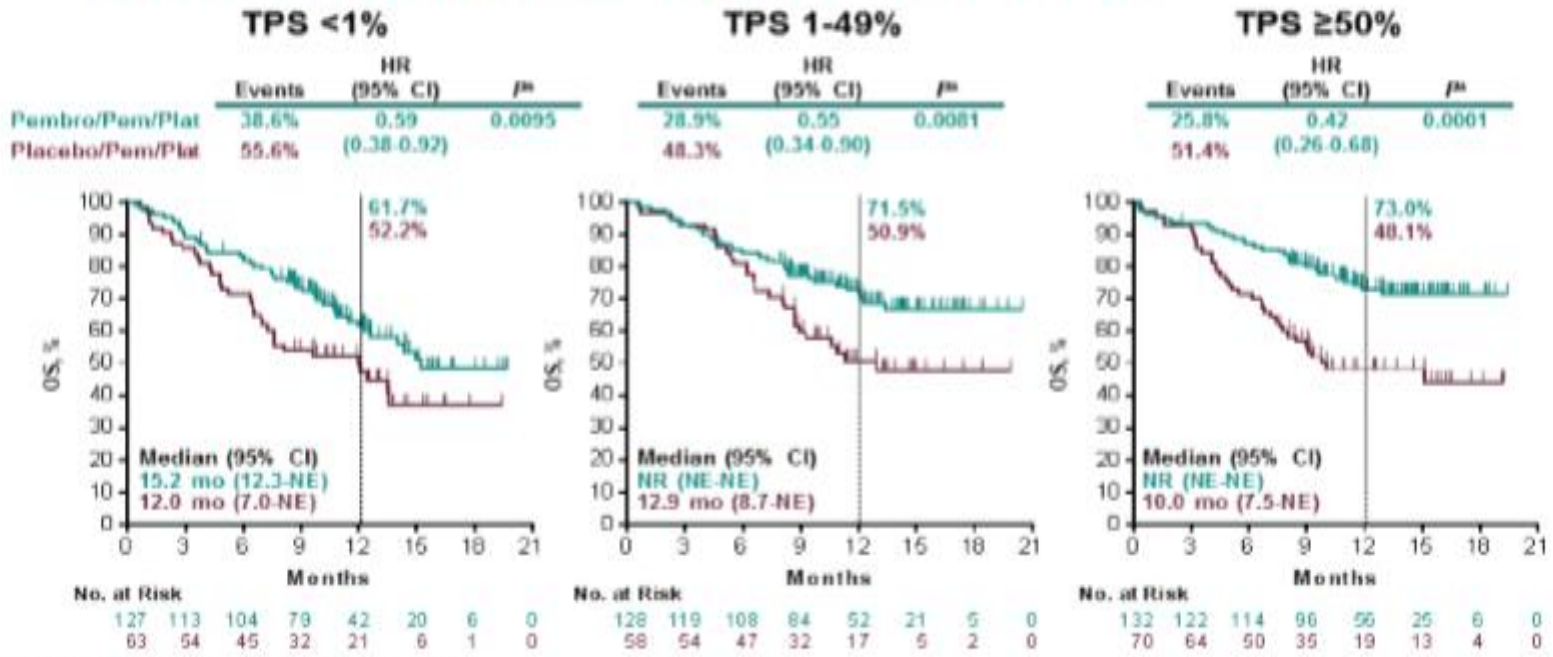


Data cutoff date: Apr 3, 2018.

Platin/Pem ± Pembrolizumab in Non-SCC NSCLC
KeyNote 189 Trial
Benefit according to PD-L1 expression

Gandhi KN189
AACR 2018

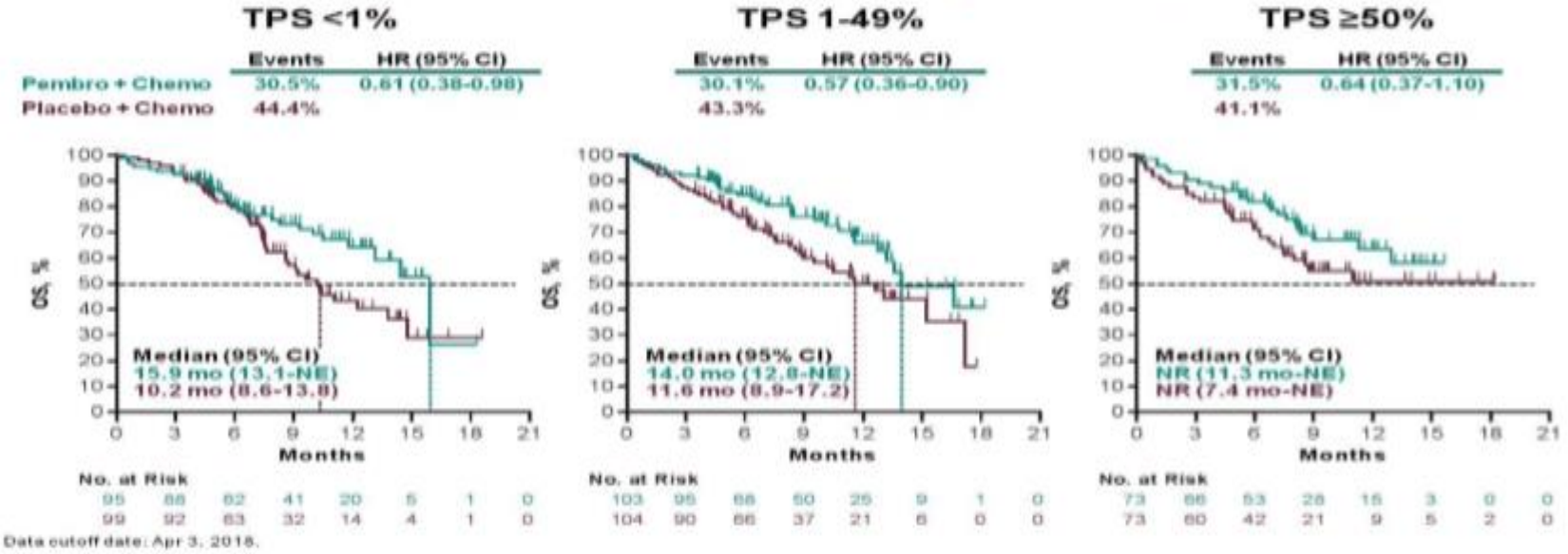
Overall Survival by PD-L1 TPS



*Nominal and one-sided. Data cutoff date: Nov 8, 2017.

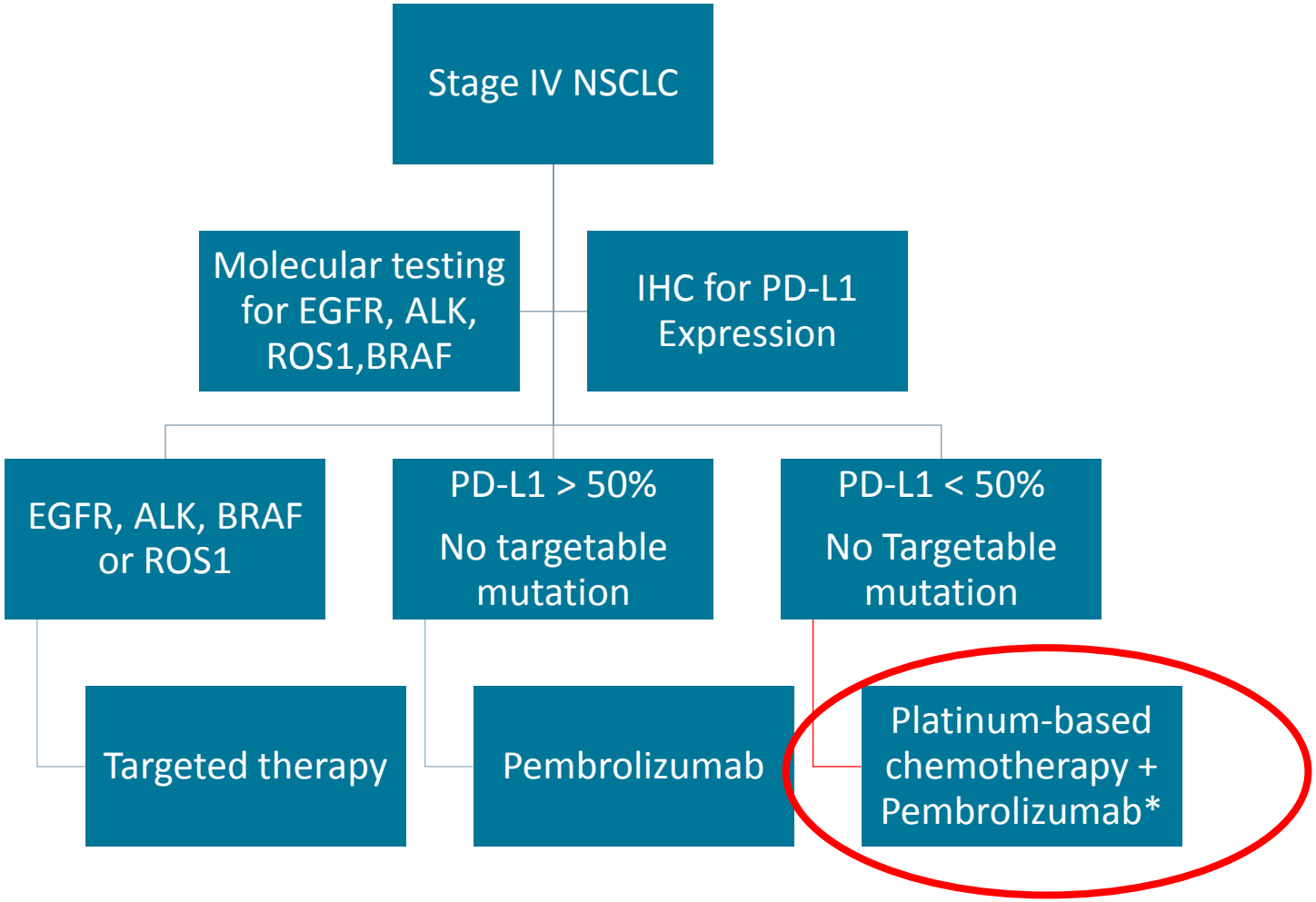
Chemo ± Pembrolizumab in SCC NSCLC
KeyNote 407 Trial – Benefit by PD-L1 expression

Overall Survival at IA2 by PD-L1 TPS



Data cutoff date: Apr 3, 2018.

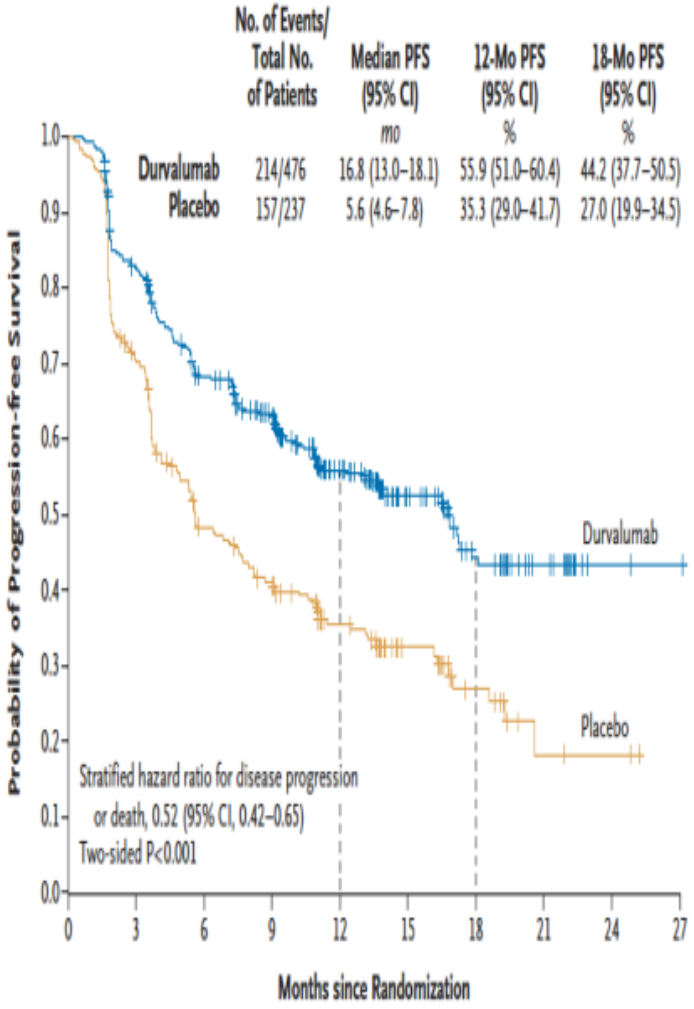
Present Treatment Algorithm for Stage 4 NSCLC

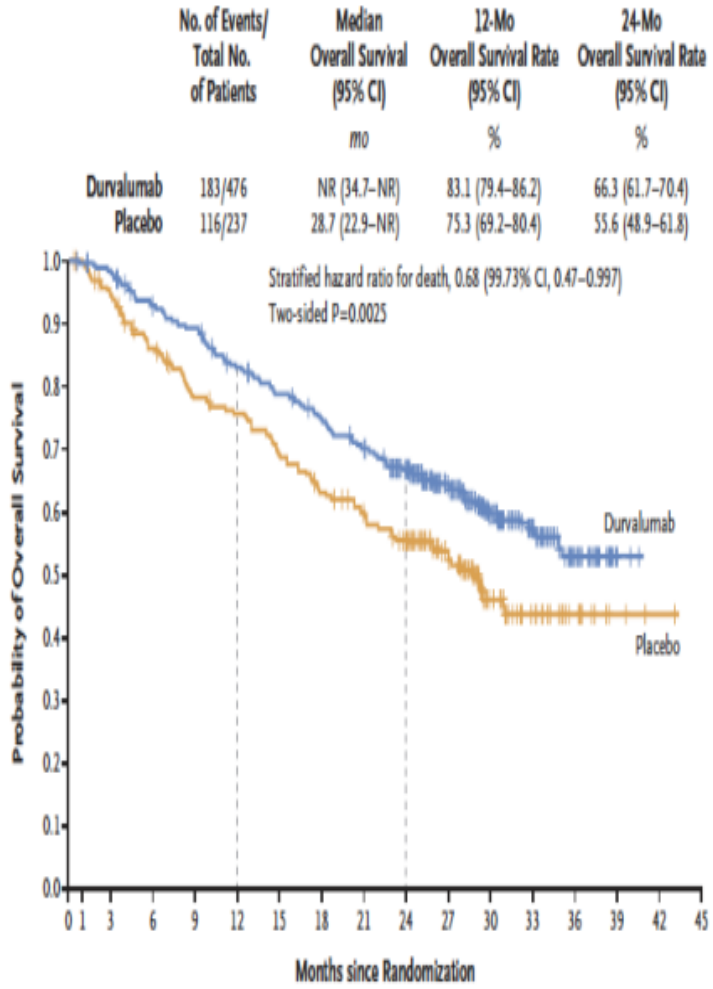


TSUNAMI IN LUNG CANCER: Immunotherapy

stage III

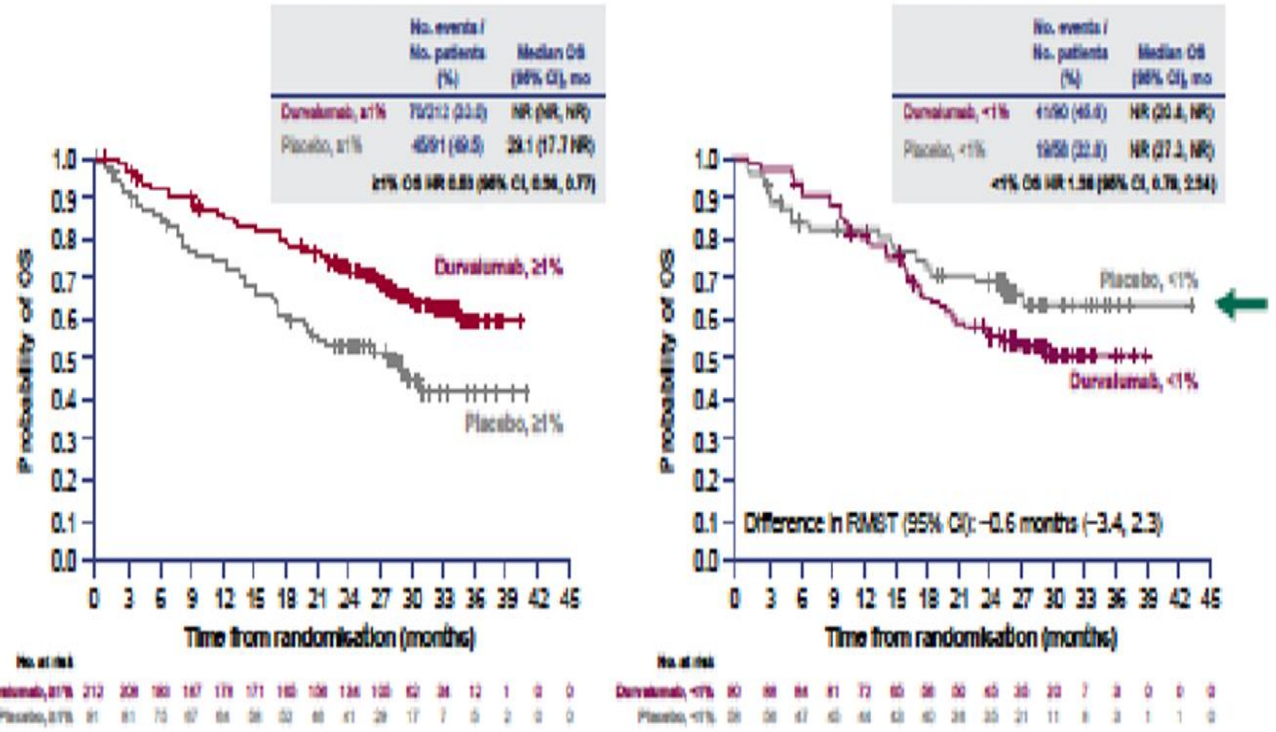
Stage III: PACIFIC TRIAL
PFS and OS





Stage III: PACIFIC TRIAL
OS by PD-L1

OS by PD-L1 TC ≥1% and <1%



- In the PD-L1 TC <1% subgroup, the number of events are low and overall the subgroup is small
- Imbalances in baseline characteristics

RMST, restricted mean survival time

How Do We Decide Which Therapy Is Right For The Patient?

Biomarkers – Tumor – Tumor mutation burden (TMB), neoantigen,TAA, PD-L1, TIL, microenvironment

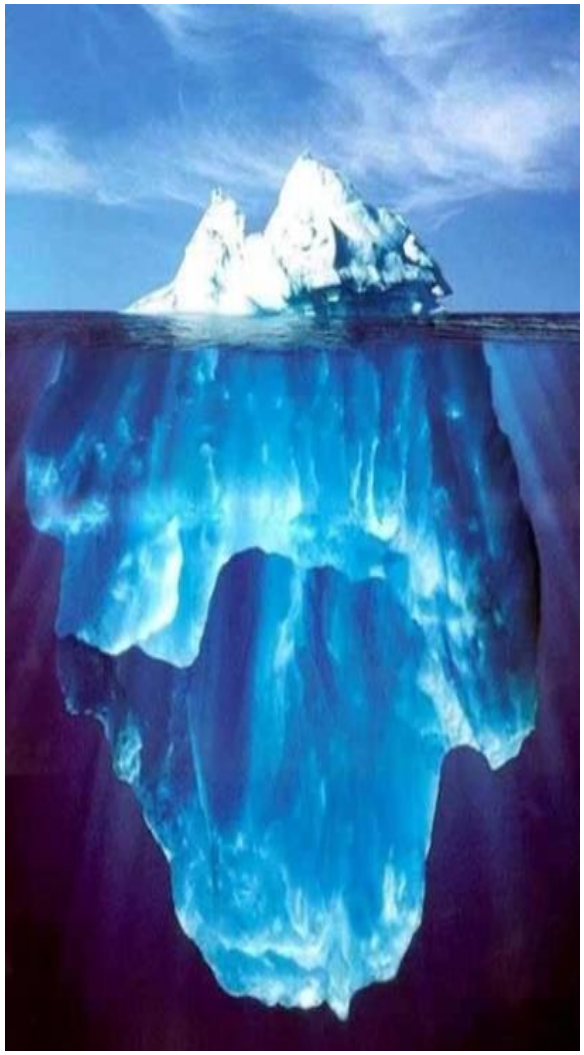
- PD-L1, T
  problem

We are just scratching the surface

Biomarkers – Blood – cfDNA (TMB), soluble cytokines

Microbiome – Gut

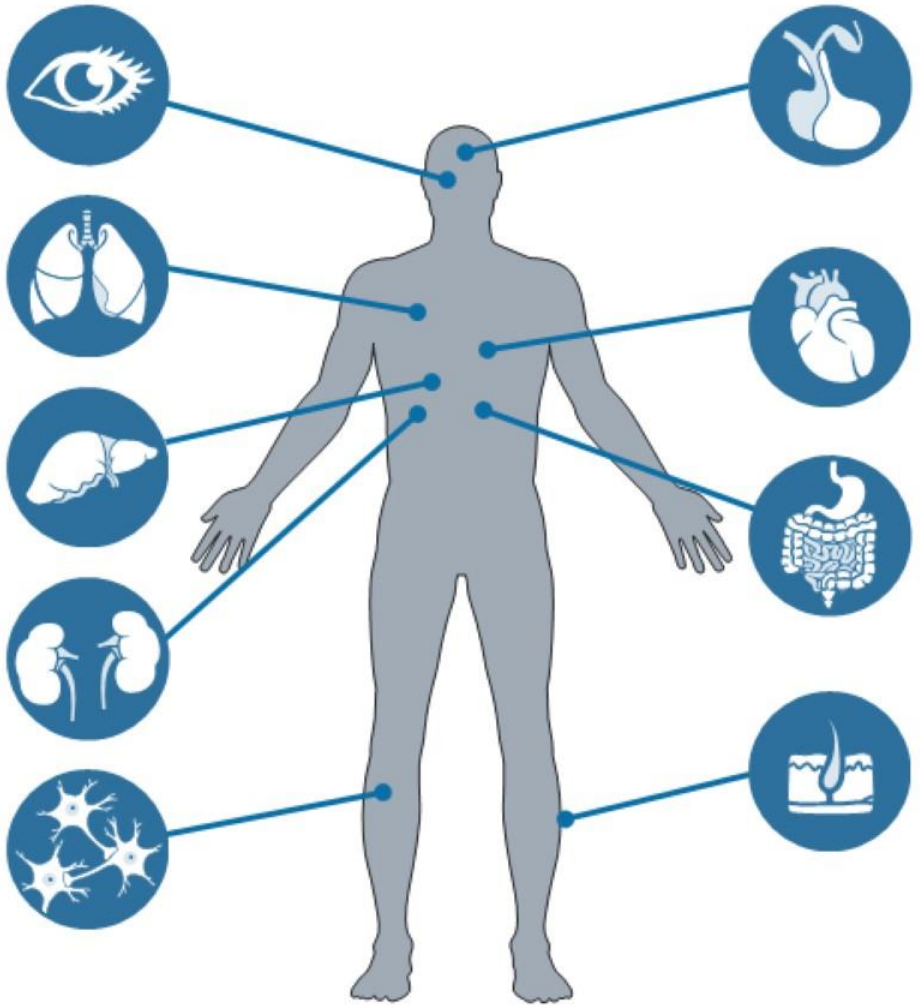
Don’t Give UP!!!!!!




TIME
SPECIAL INVESTIGATION
WHY YOUR DRUGS COST SO MUCH
WHO'S TO BLAME
WHAT WE CAN DO ABOUT IT

Safety of Checkpoint Inhibitors

Immunotherapy Is Associated With Immune-Mediated AEs



Eye
Uveitis
Iritis

Pulmonary
Pneumonitis
Interstitial lung disease
Acute interstitial pneumonitis

Hepatic
Hepatitis, autoimmune

Renal
Nephritis, autoimmune
Renal failure

Neurologic
Autoimmune neuropathy
Demyelinating polyneuropathy
Guillain-Barré
Myasthenia gravis-like syndrome

Endocrine
Hypothyroidism
Hyperthyroidism
Adrenal insufficiency
Hypophysitis

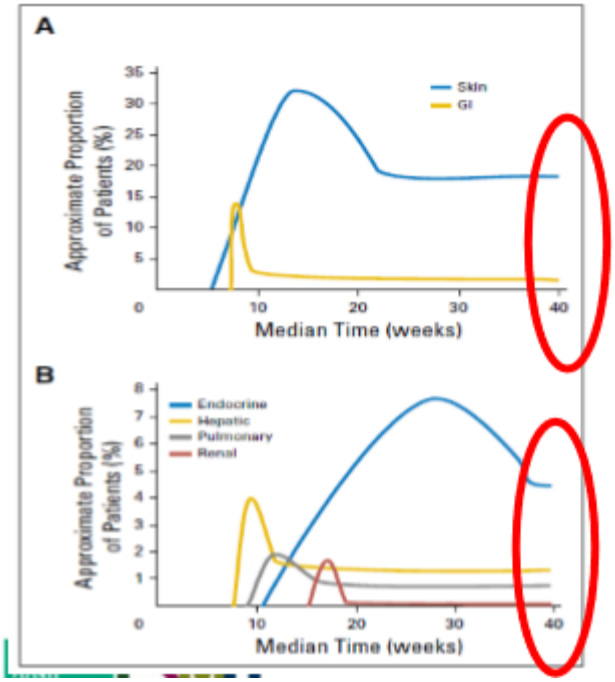
Cardiac
Myocarditis
Cardiomyopathy

Gastrointestinal
Colitis
Enterocolitis
Necrotizing colitis
GI perforation

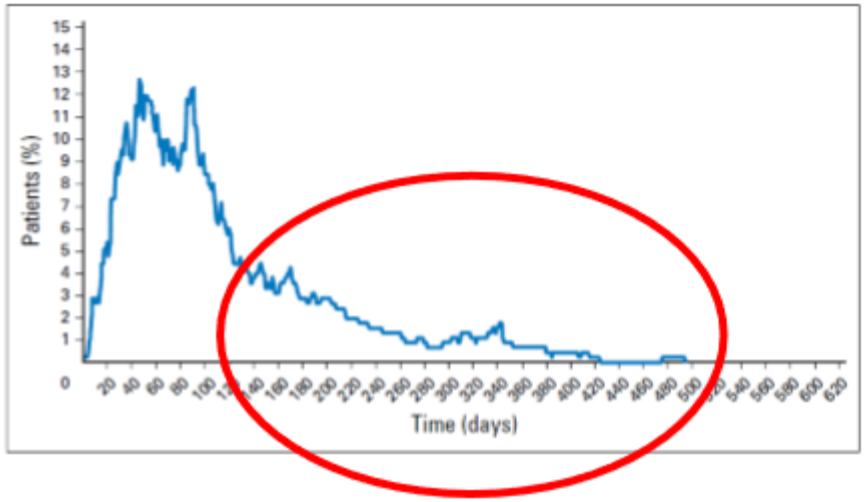
Skin
Dermatitis exfoliative
Erythema multiforme
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Vitiligo
Alopecia

Adverse Events following immune checkpoint blockade are NOT restricted to the first 3 months after onset

TR-AEs of any grade over time
in melanoma pts treated by anti-PDx alone



Grade 3/4 TR-AEs over time
in melanoma pts treated by anti-PDx + anti-CTLA4



Weber, J Clin Oncol 2017
Sznol, J Clin Oncol 2017

Science That Matters

- A lot needs to be done to
  - Define new targets
  - Better select patients
  - Convert responses to cures
- This will only happen through better science!