Προβλεπτικοί Βιοδείκτες στον Καρκίνο του Πνεύμονα: Παρόν και Μέλλον

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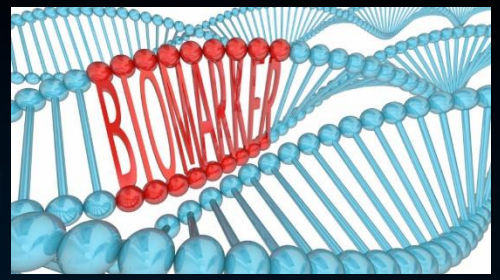
Γ.Ν.Ν.Θ.Α. «Η Σωτηρία»

Τι είναι οι Βιοδείκτες



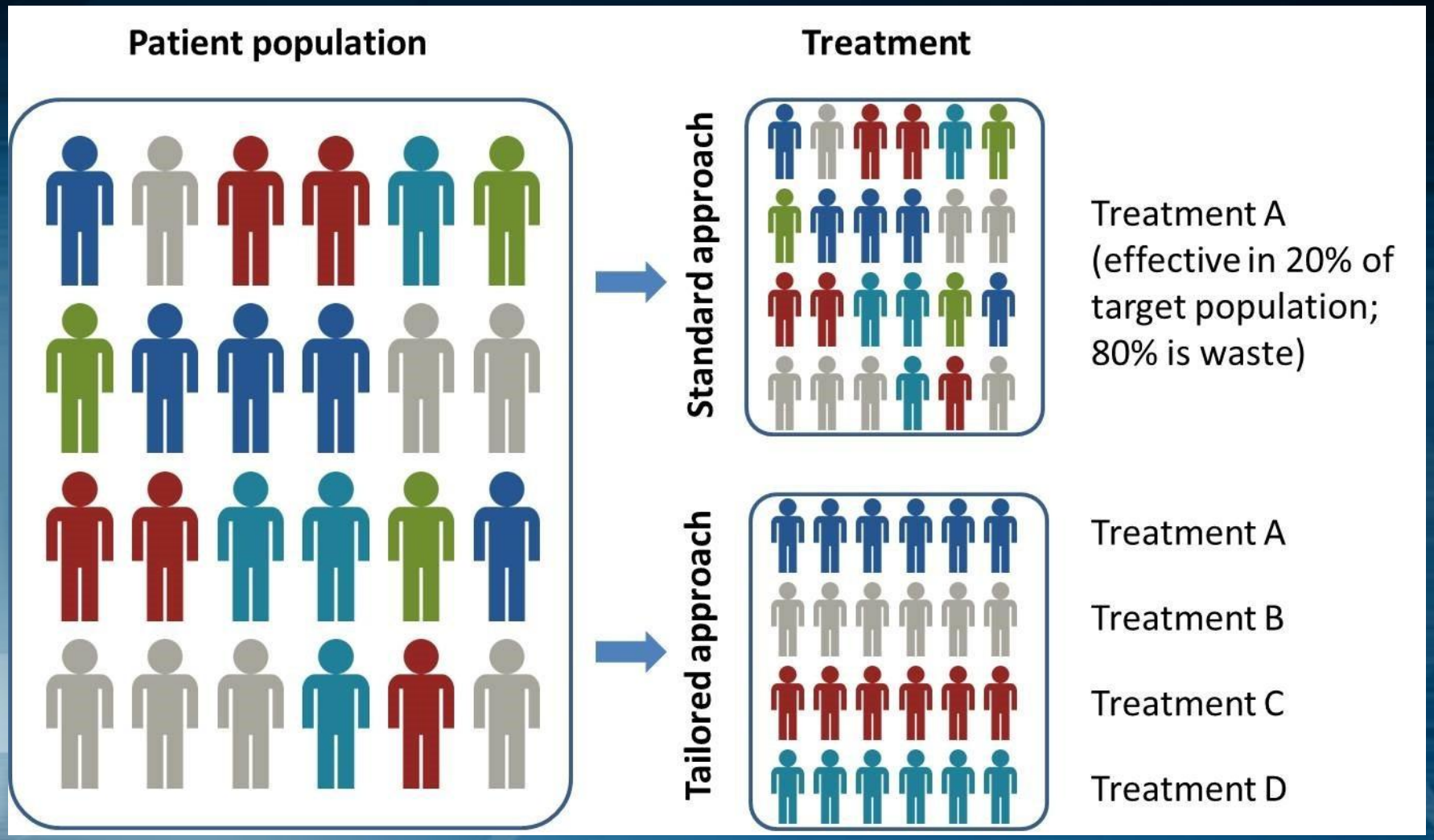
- A BIOMARKER : is any characteristic that can be measured and that gives an indication of the biological state of the patient or their tumor.

- PROGNOSTIC BIOMARKERS : provide information about disease outcome and the pace of progression regardless of treatment

- PREDICTIVE BIOMARKERS : indicate whether a particular treatment is likely to provide a clinical benefit for a patient.

An Update on Predictive Biomarkers for Treatment Selection in Non-Small Cell Lung Cancer
Tamkin Ahmadzada , Steven Kao Glen Reid Michael Boyer Annabelle Mahar and Wendy A. Cooper
J. Clin. Med. **2018**, 7, 153; doi:10.3390/jcm7060153

Γιατί χρειαζόμαστε Βιοδείκτες



Προβλεπτικοί Βιοδείκτες

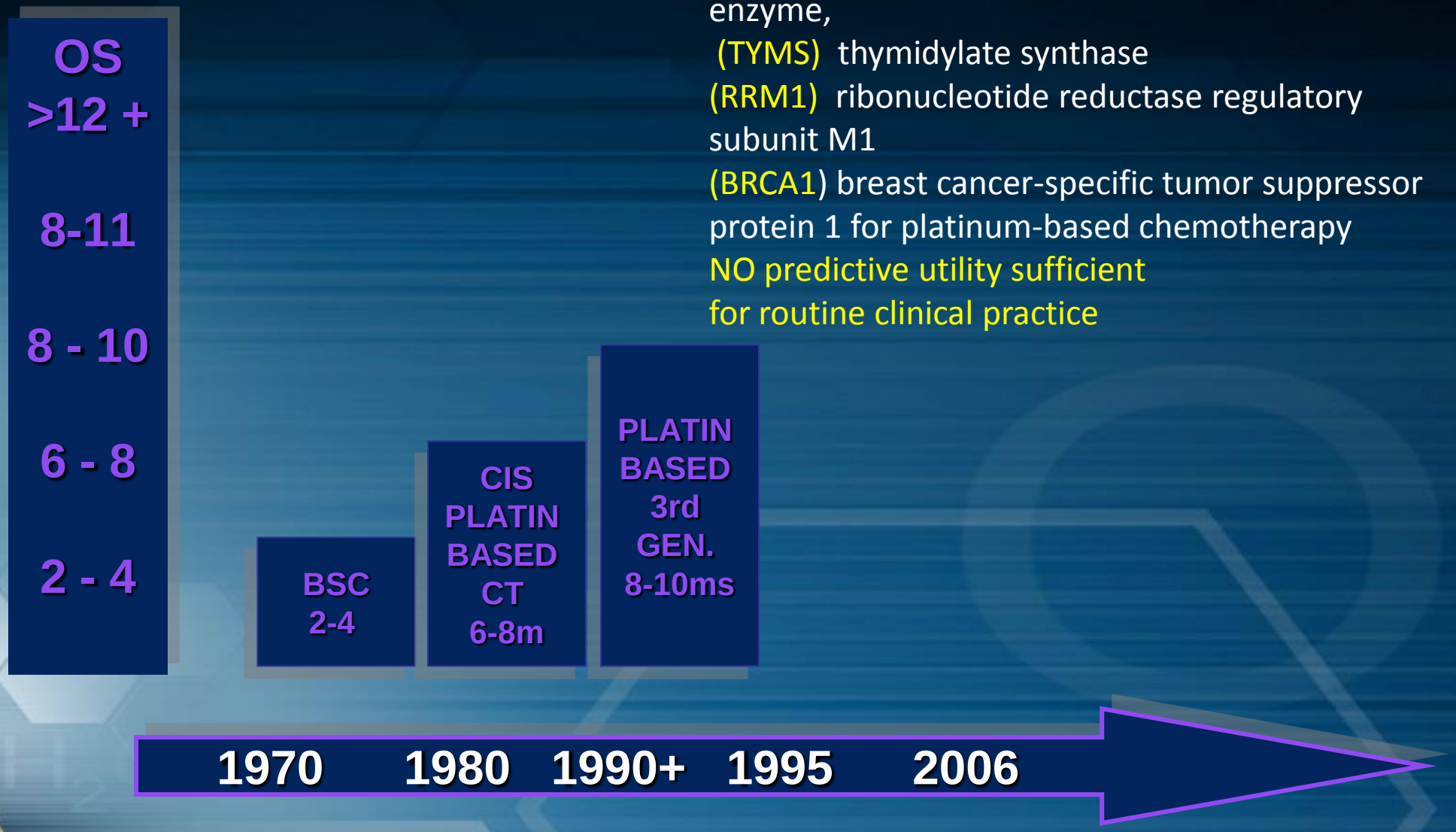
- Προβλέπουν την ανταπόκριση στη θεραπεία
- Μειώνουν το κόστος
- Μειώνουν την τοξικότητα μιας αναποτελεσματικής θεραπείας

- Ο βιοδείκτης πρέπει να είναι:
- Ακριβής
- Φθηνός
- Αναπαραγώγιμος
- Εύκολη δειγματοληψία με ελάχιστα επεμβατική τεχνική

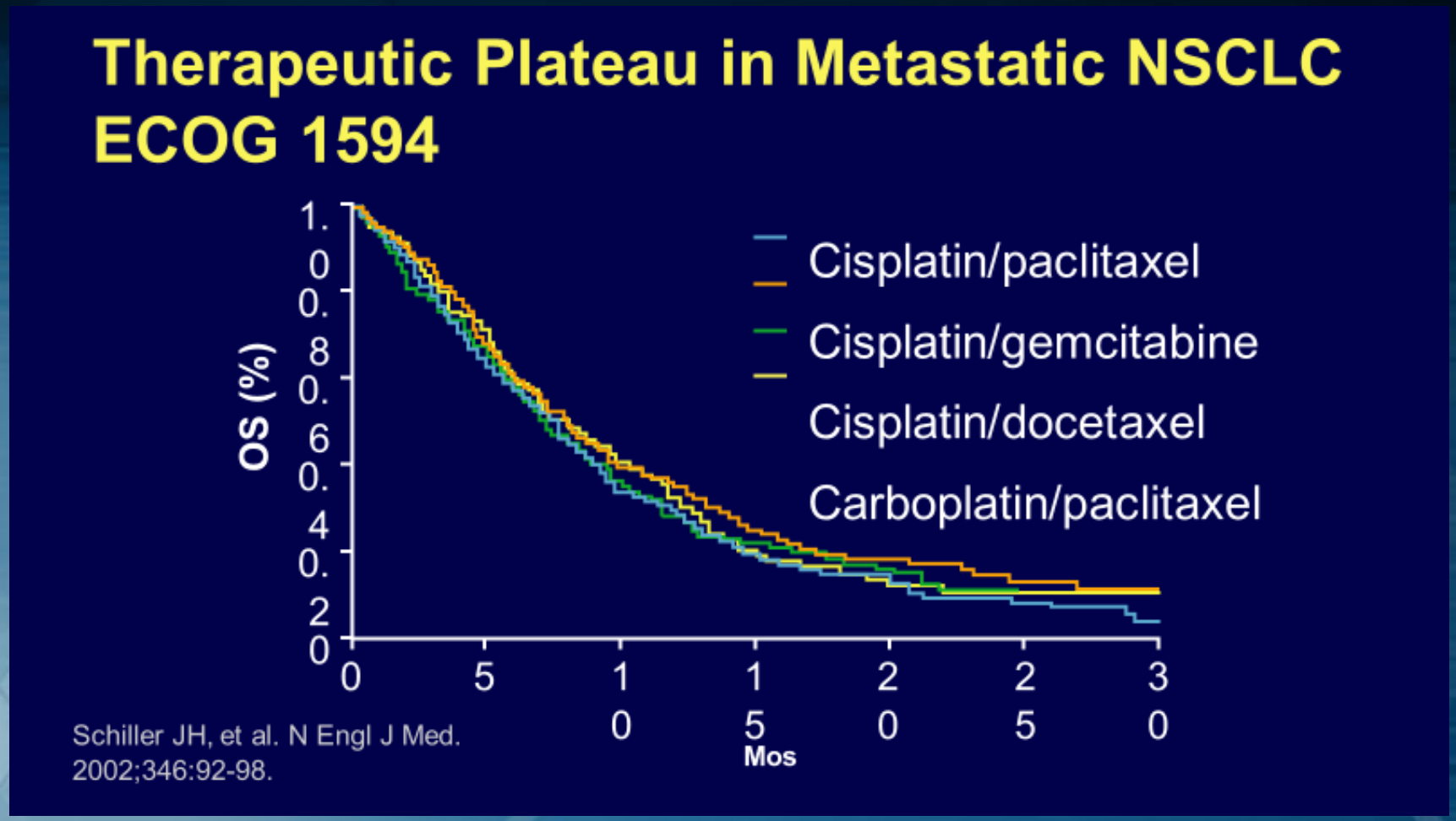
An Update on Predictive Biomarkers for Treatment Selection in Non-Small Cell Lung Cancer
Tamkin Ahmadzada , Steven Kao Glen Reid Michael Boyer Annabelle Mahar and Wendy A. Cooper J. Clin. Med. **2018**, 7, 153; doi:10.3390/jcm7060153

Ιστολογικός τύπος σαν δείκτης

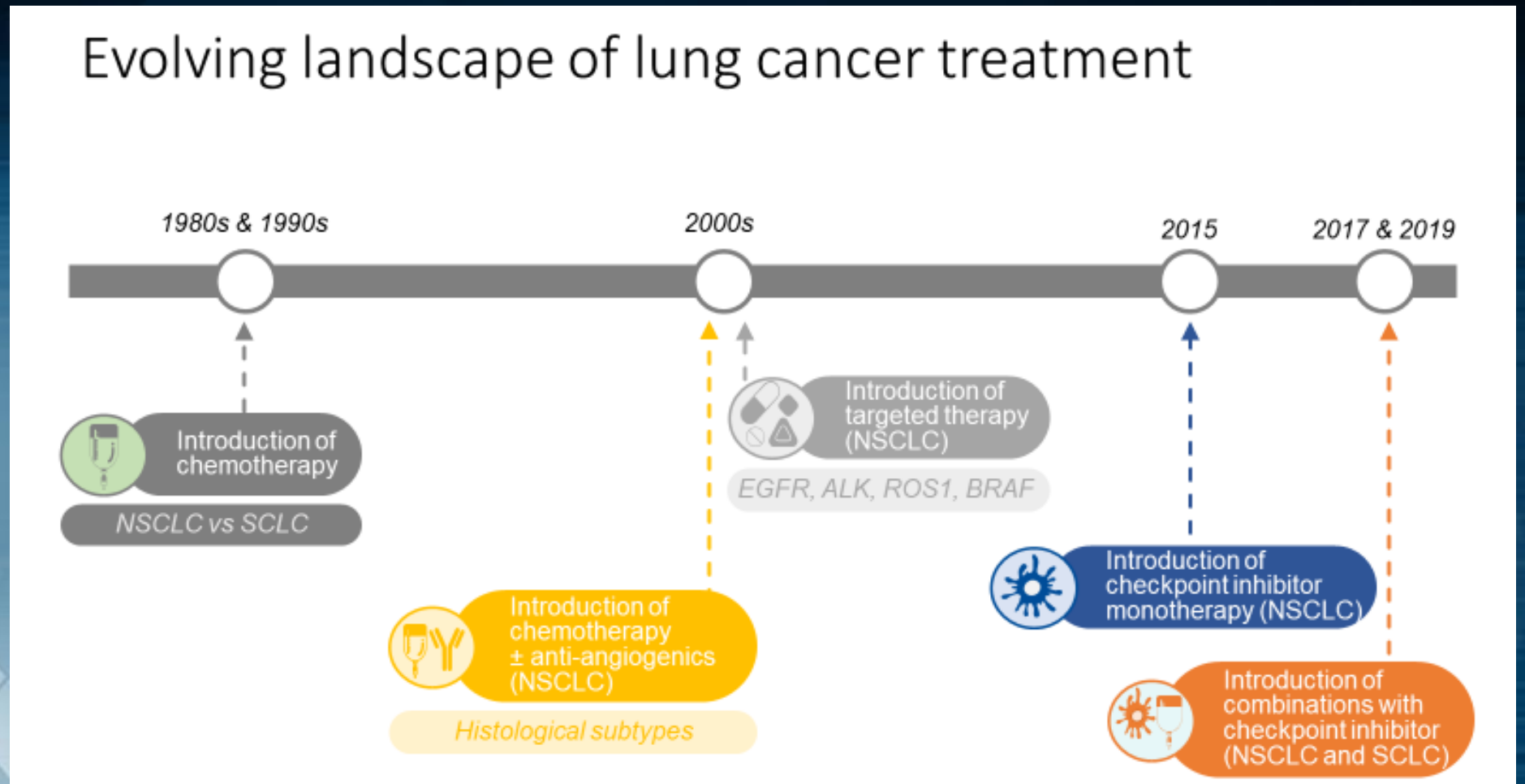
(ERCC1) Excision repair cross-complement group 1 enzyme,
(TYMS) thymidylate synthase
(RRM1) ribonucleotide reductase regulatory subunit M1
(BRCA1) breast cancer-specific tumor suppressor protein 1 for platinum-based chemotherapy
NO predictive utility sufficient
for routine clinical practice



Ιστολογικός τύπος σαν δείκτης

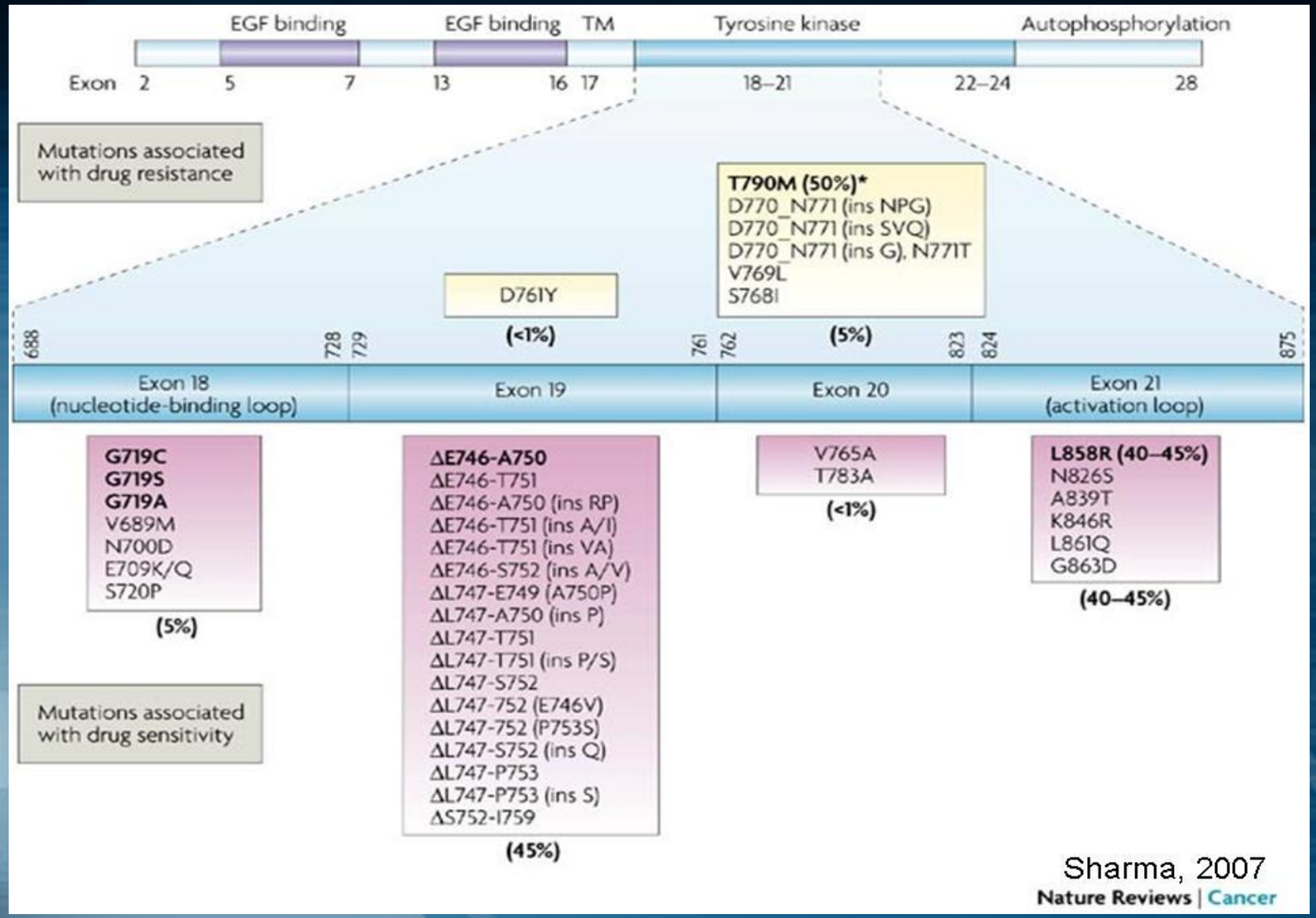


ΜΕΤΑΛΛΑΞΕΙΣ ΣΑΝ ΔΕΙΚΤΕΣ ΘΕΡΑΠΕΙΑΣ



Bunn, Semin Oncol 1989; Bunn, et al. Clin Cancer Res 1998; Scagliotti, et al. J Clin Oncol 2002; Sandler, et al. N Engl J Med 2006 Shepherd, et al. N Engl J Med 2005; Brahmer, et al. N Engl J Med 2015; Horn, et al. N Engl J Med 2018

ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR



ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR

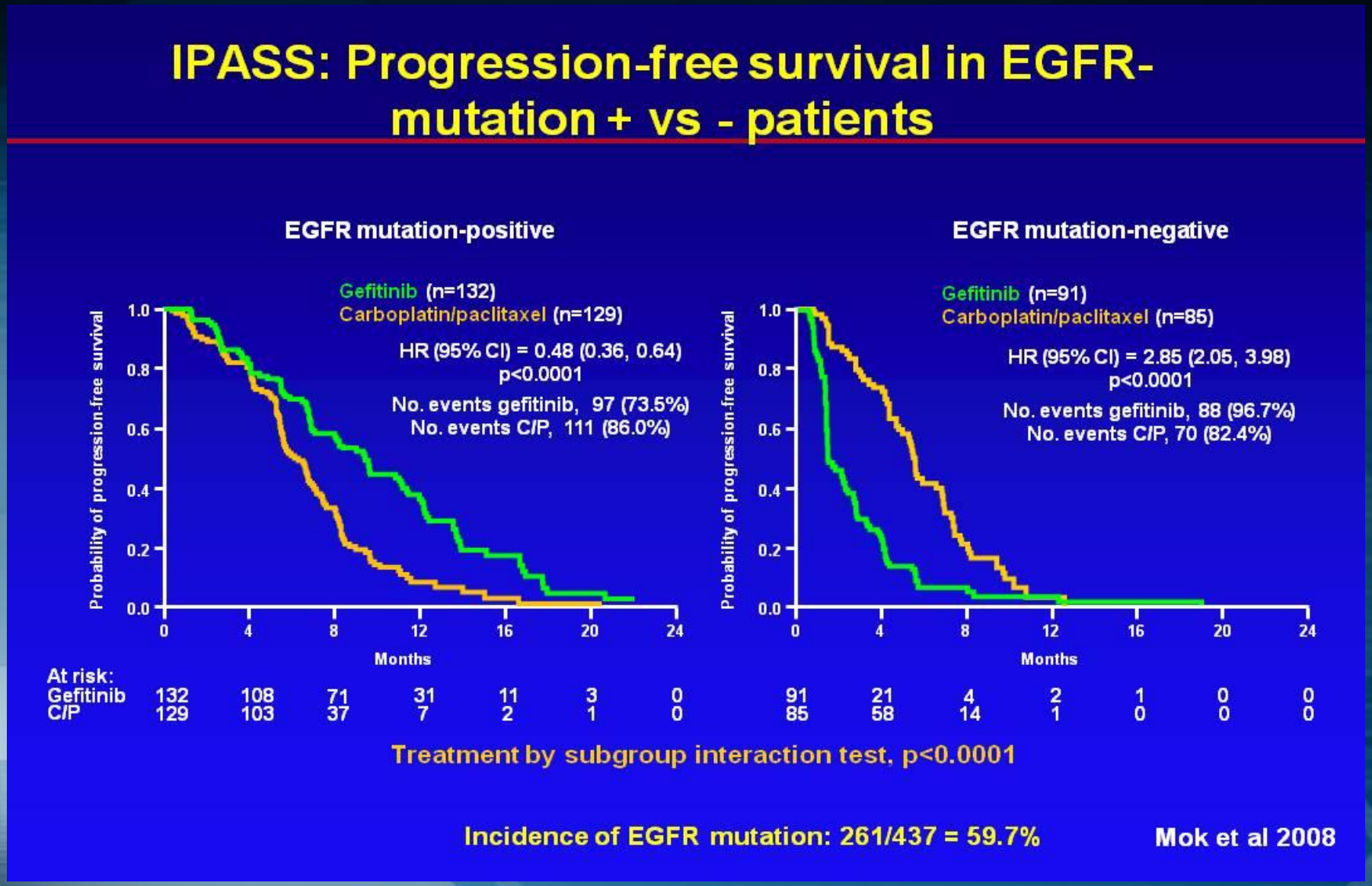
- Ασιατική φυλή
- Γυναικείο φύλο
- Μη καπνιστική ή ελαφρά καπνιστική συνήθεια
- Αδενοκαρκίνωμα
- Εγκεκριμένη, στοχευμένη θεραπεία (αναστολείς τυροσινικής κινάσης, Tyrosine Kinase Inhibitors, TKIs)
- Exon 19 deletion, L858R exon 21 καλύτερη ανταπόκριση
- Προβλεπτική αξία (δείκτης αποτελεσματικότητας θεραπείας)

ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR

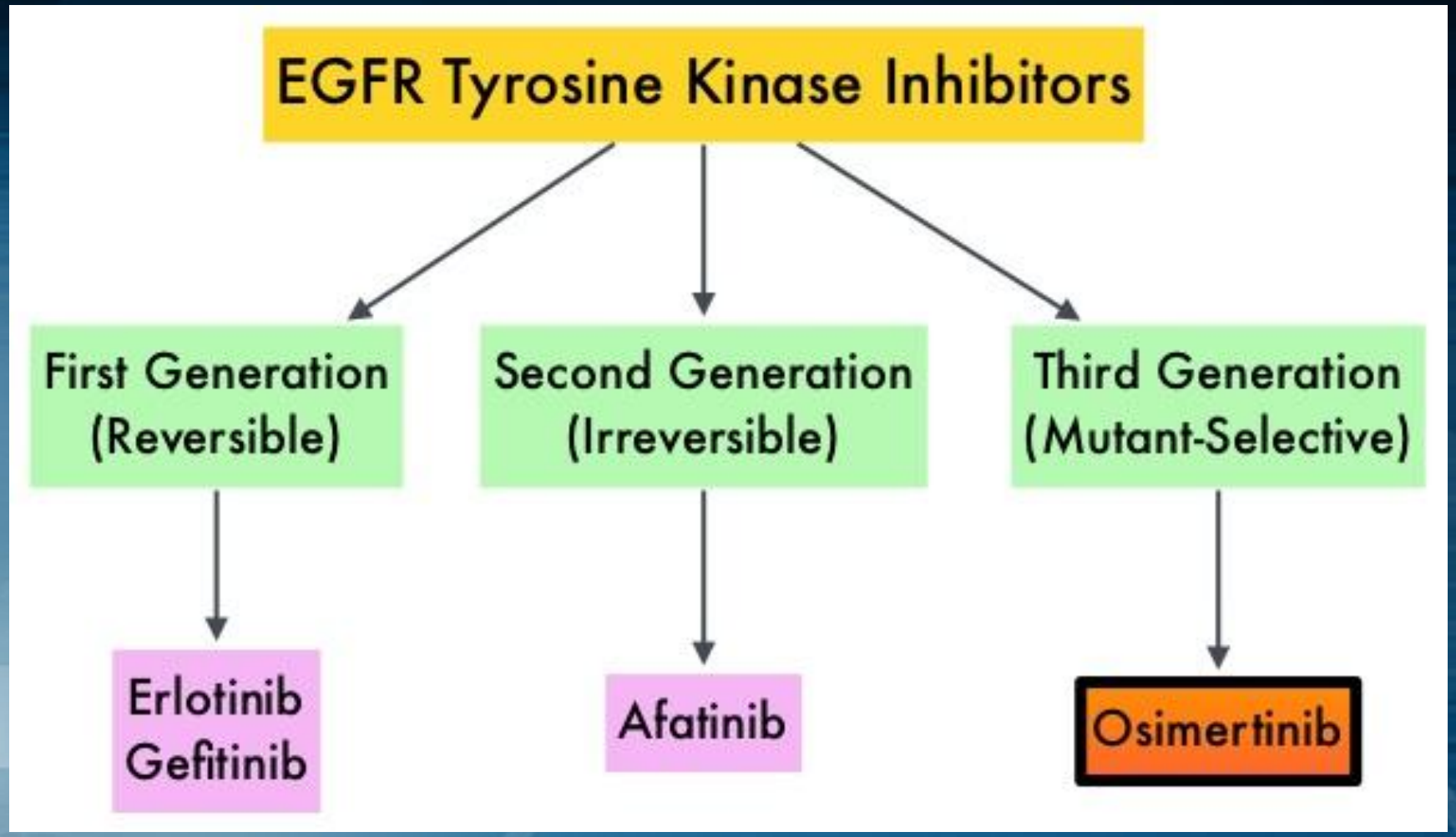
Median progression-free survival (PFS) in clinical trials for patients with *EGFR* mutation–positive advanced non–small cell lung cancer (NSCLC) treated with EGFR-TKIs.

Regimen	Trials	Median PFS (Months)	References
Gefitinib	WJTOG3405, NEJ002, LUX-Lung 7, ARCHER 1050	9.2–10.9	[4,5,10,11]
Erlotinib	EURTAC, OPTIMAL, NEJ026	10.4–13.3	[6,7,12]
Afatinib	LUX-Lung 3, LUX-Lung 6, LUX-Lung 7	11.0–11.1	[8,9,10]
Dacomitinib	ARCHER 1050	14.7	[11]
Erlotinib + Bevacizumab	NEJ026	16.9	[12]
Osimertinib (second line)	AURA3	10.1	[13]
Osimertinib (first line)	FLAURA	18.9	[14]

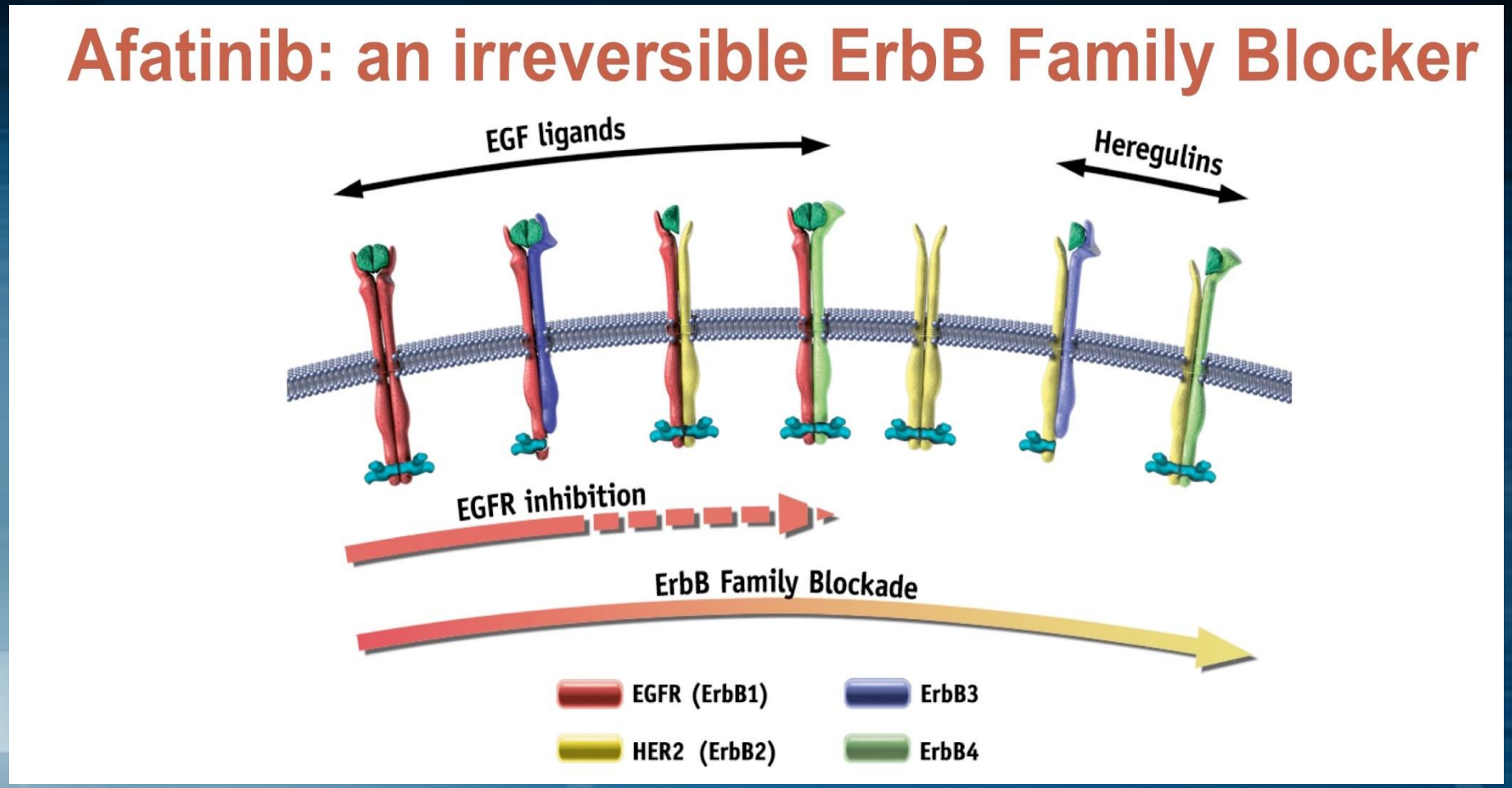
ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR



ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR

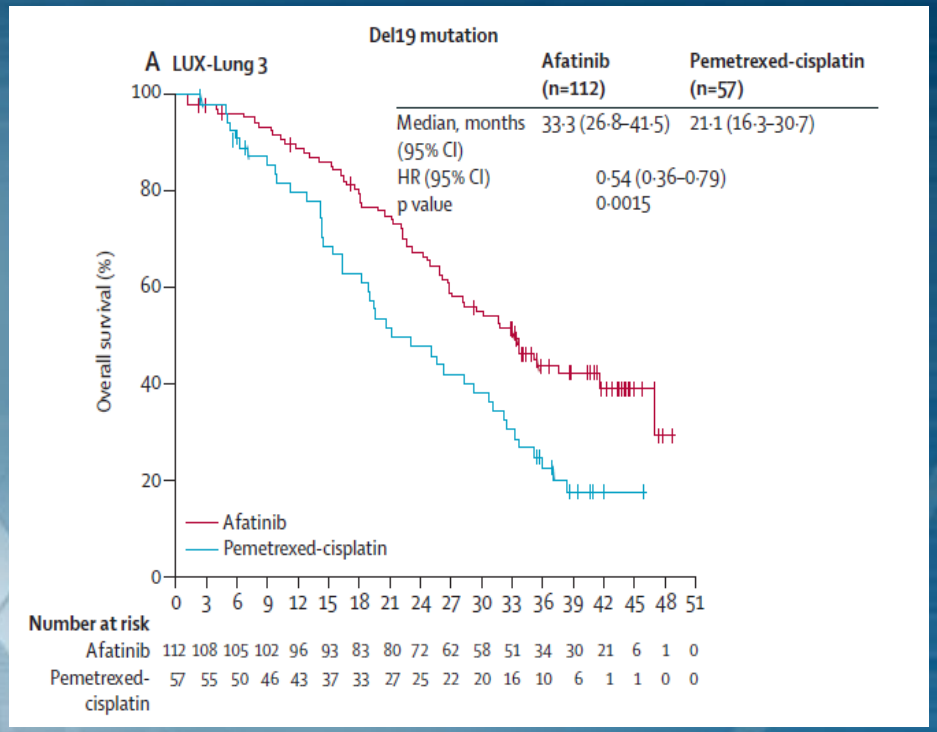


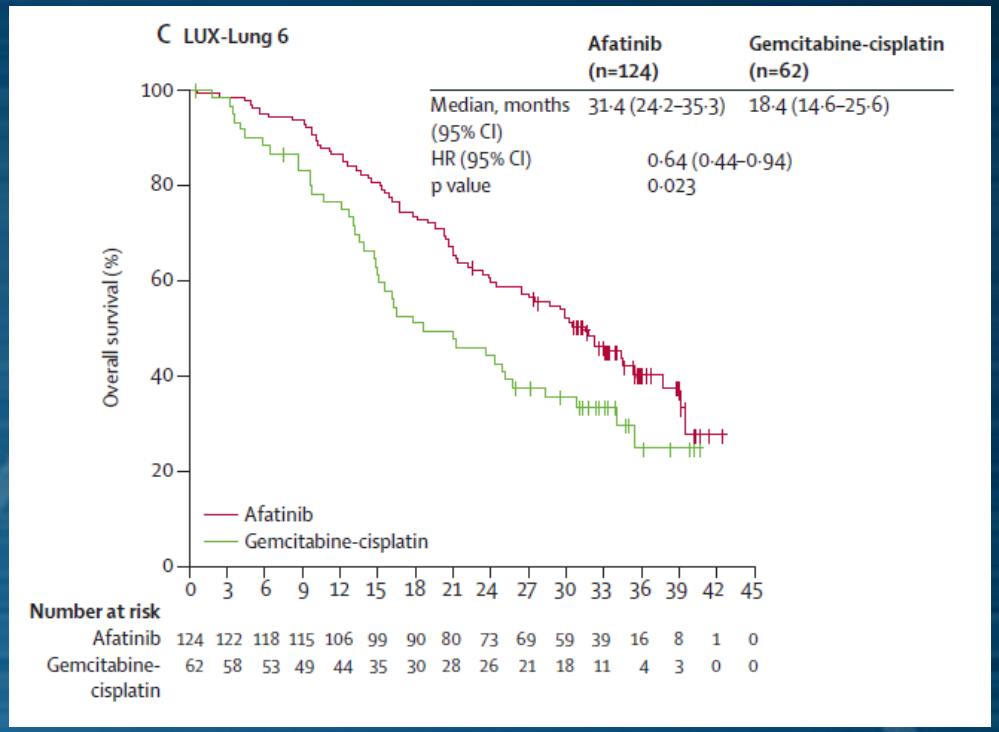
ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR



ΜΕΤΑΛΛΑΞΕΙΣ ΤΟΥ EGFR

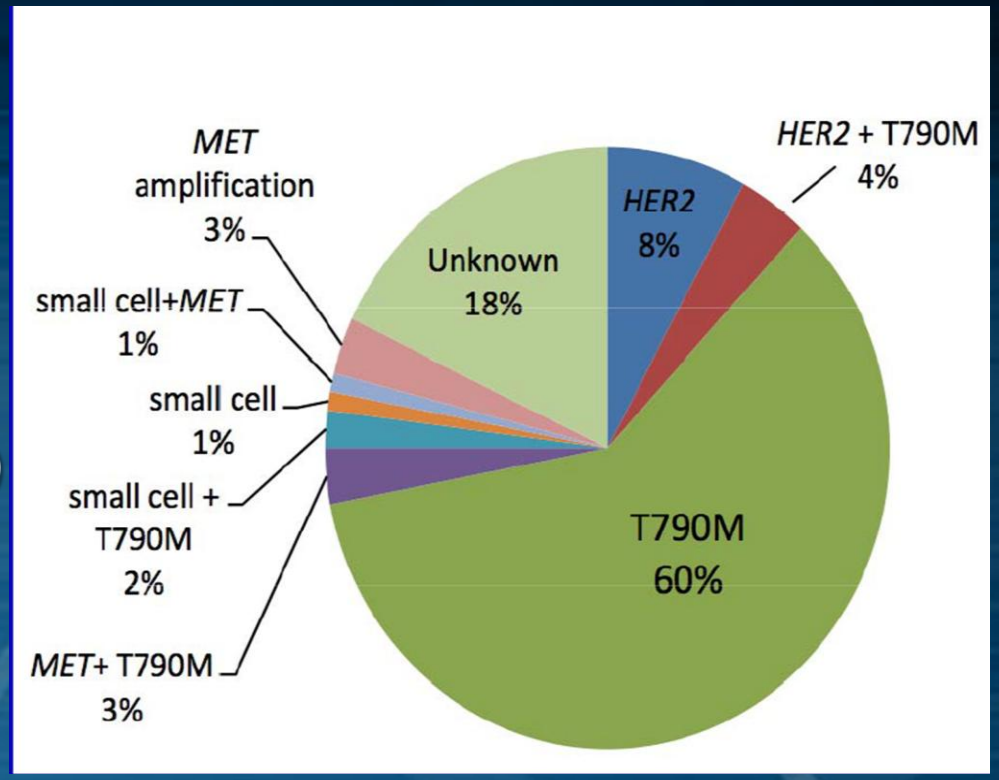
- DELL 19





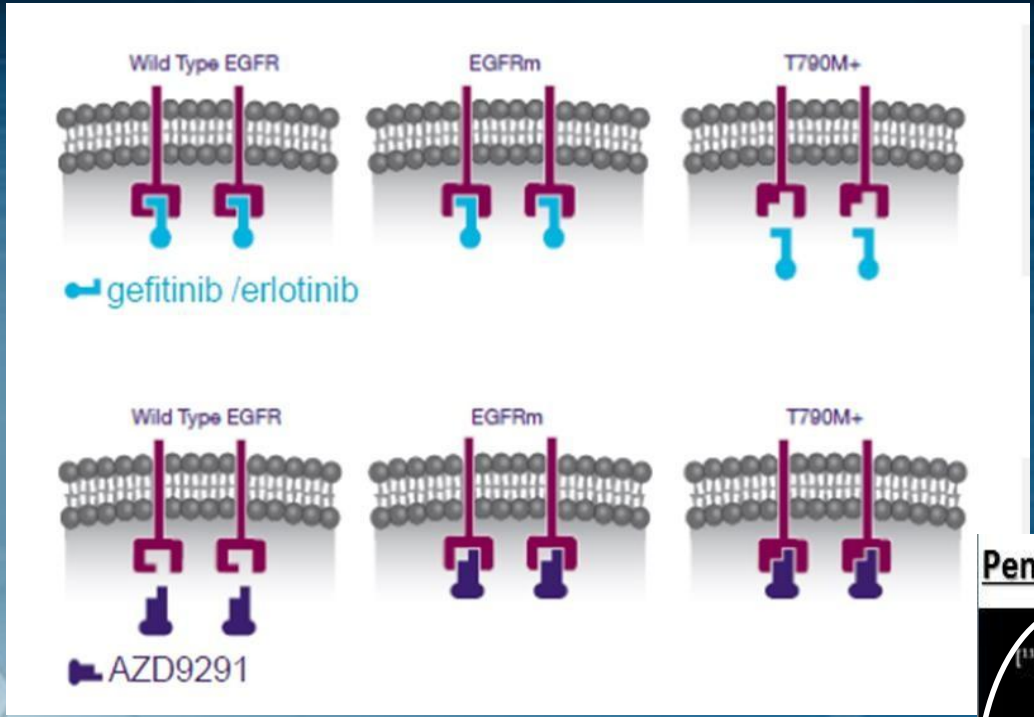
Μηχανισμοί αντίστασης στους TKI'S

- EGFR exon 20 insertions(4%)
- T790M (50%)
- Activation PI3K/AKT (5%)
- IGF1R Pathway
- Activation NFkB
- Met Amplification (4%)
- Histological transformation SCLC (14%)
- PTEN mutation
- PIK3CA mutation
- Her2 Amplification
- MAPK1 amplification
- BRAF mutation
- Loss of activating EGFR mutant gene



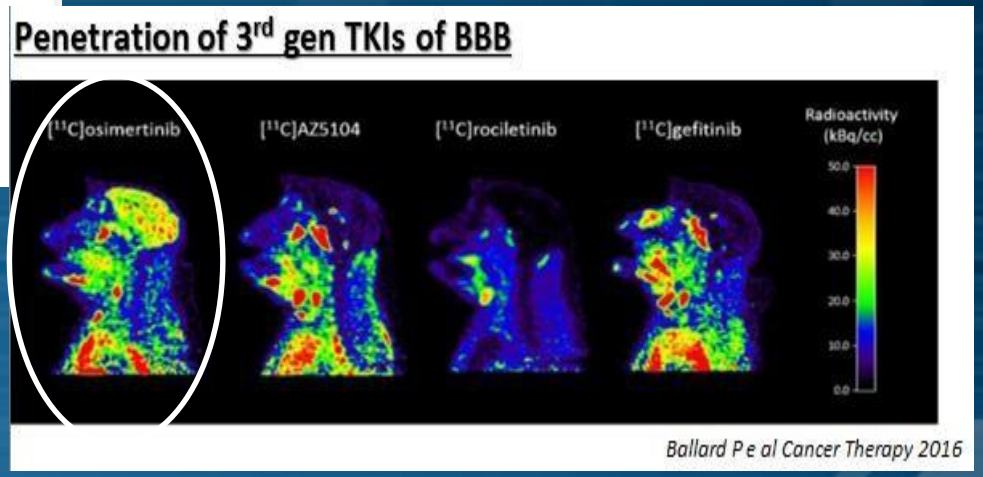
3ης ΓΕΝΙΑΣ TKI'S

Overcome Resistance with next-generation TKIs



Osimertinib

- Increased potency to EGFRT790M
- Potential to sustain longer efficacy
- Reduced toxicity
- CNS penetration



3ης ΓΕΝΙΑΣ TKI'S

FLAURA DOUBLE-BLIND STUDY DESIGN

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years (≥20 years in Japan)
- WHO performance status 0 / 1
- Ex19del / L858R (enrolment by local or central EGFR testing)
- No prior systemic anticancer / EGFR-TKI therapy
- Stable CNS metastases allowed

→ Stratification by **mutation status** (Ex19del / L858R) and **race** (Asian / non-Asian)

→ **Randomised 1:1**

- **Osimertinib** (80 mg p.o. qd) (n=279)
- Comparator EGFR-TKI **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

→ RECIST 1.1 assessment every 6 weeks until objective progressive disease. Following the primary PFS analysis, progression events by RECIST 1.1 were no longer centrally collected

Crossover was allowed for patients in the **comparator EGFR-TKI** arm, who could receive open-label osimertinib upon central confirmation of progression* and T790M positivity

OS was a key secondary endpoint

- Final OS analysis planned for when approximately 318 death events had occurred
- For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required
  - Alpha spend for interim OS analysis was 0.0015
- At data cut-off, 61 patients (22%) in the osimertinib arm and 13 patients (5%) in the comparator arm were ongoing study treatment

BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

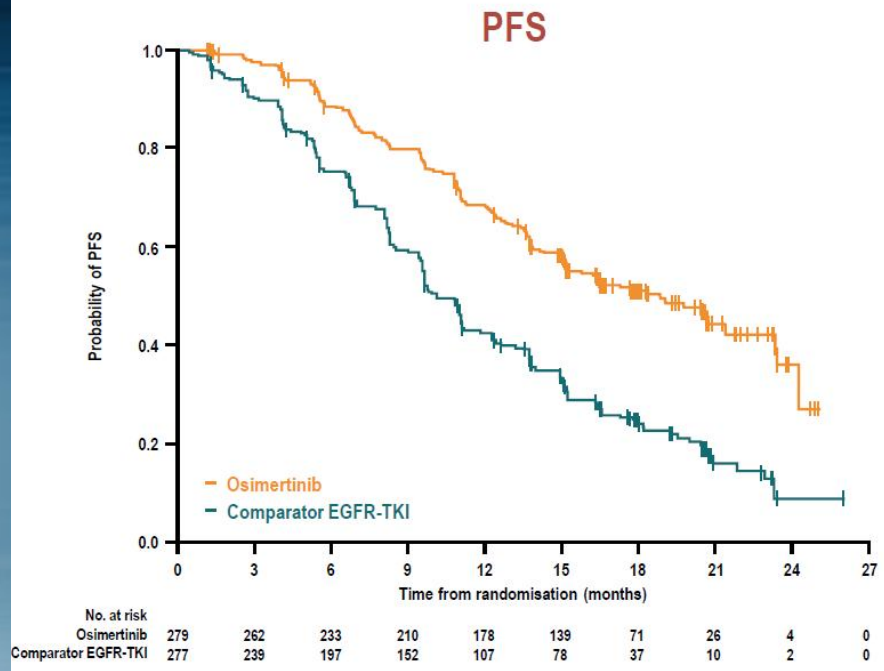
Soria et al. N Engl J Med 2018;378:113-25

*By investigator assessment if disease progression occurred after the primary analysis data cut-off

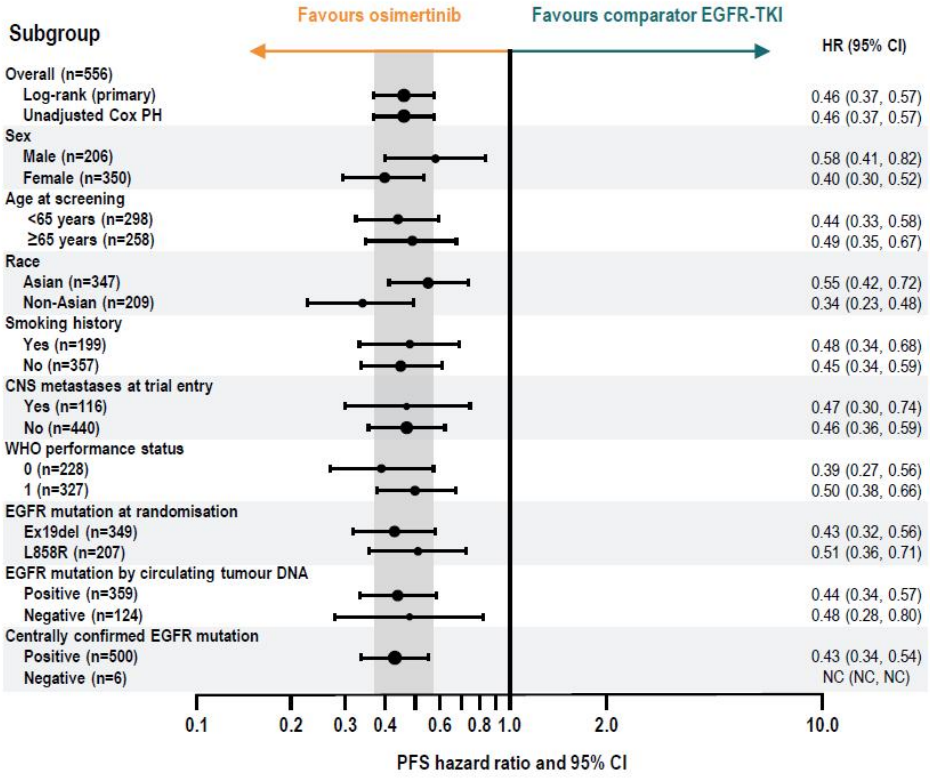
p.o., orally; qd, once daily; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; WHO, World Health Organization

3ης ΓΕΝΙΑΣ TKI'S

PRIMARY ANALYSIS: PROGRESSION-FREE SURVIVAL



	Median PFS, months (95% CI)	HR (95% CI)
Osimertinib	18.9 (15.2, 21.4)	0.46 (0.37, 0.57); p<0.001
Comparator EGFR-TKI	10.2 (9.6, 11.1)	



BARCELONA 2019 ESMO congress

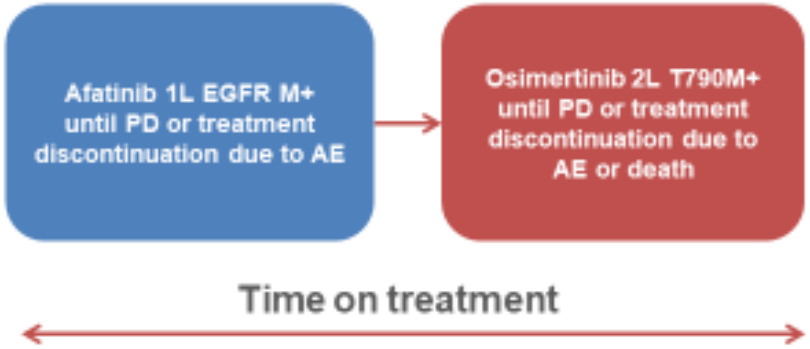
Data cut-off: 12 June 2017

Soria et al. N Engl J Med 2018;378:113-25

CI, confidence interval; ctDNA, circulating tumour DNA; NC, not calculable; PH, proportional-hazards

GioTag: Study objectives and design

- Stage IIIb/IV NSCLC
- Common EGFR mutation (Del19/L858R)
- Afatinib 1st-line
- Osimertinib in 2nd-line for T790M+ disease
- Data were collected only in patients who started osimertinib 10 months prior to data entry*
- Treatment with osimertinib within an EAP/CUP or regular clinical practice



Data collection: From Q1 to Q2, 2018 (retrospective chart review)

Final results: Q2, 2018; final study report: Q3, 2018; publication available

Primary objective

Time on treatment with afatinib as first-line therapy in EGFRM+ NSCLC followed by osimertinib in case the T790M resistance mutation was developed in real-world setting. Time on treatment is defined from the start of the first-line treatment until the end of the second-line treatment.

Secondary objective:

To collect data on acquired resistance mechanism to osimertinib.

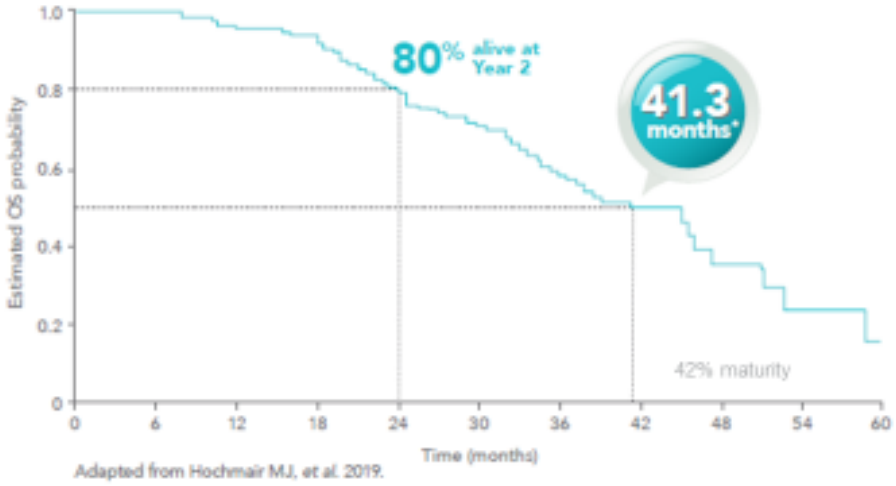
*The threshold of ≥10 months was chosen to avoid early censoring and enable collection of mature data. This threshold does not differentiate between ongoing or discontinued osimertinib treatment. There was no threshold for afatinib.
EAP = expanded access programme; CUP = compassionate use programme.

https://clinicaltrials.gov/ct2/show/NCT03370770. Hochmair M et al. *Future Oncol.* 2018 Oct 19; doi:10.2217/fon-2018-0711

GioTag Study UPDATE

APRIL 2019

Overall population



Adapted from Hochmair MJ, et al. 2019.

Median OS

41.3 months

(90% CI: 36.8 – 46.3)

At time of analysis, the total number of events was 85

At Year 2, 80% of patients treated with the sequence of GIOTRIF® followed by osimertinib were **still alive**

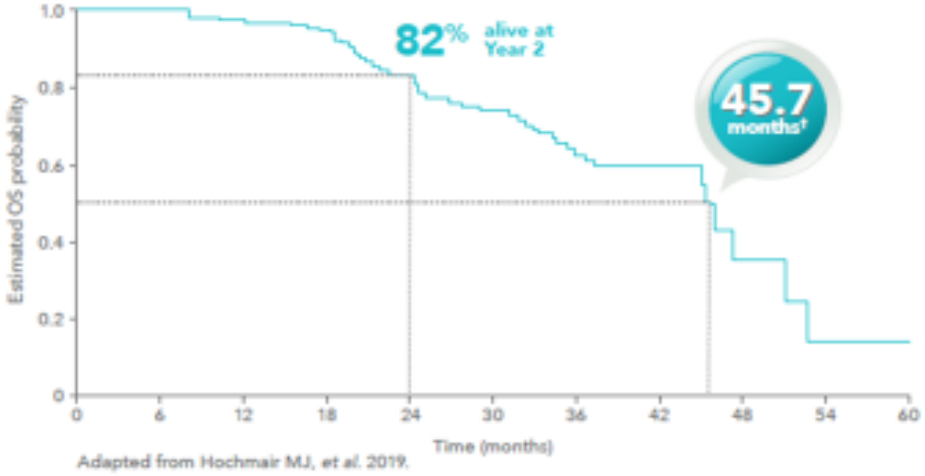
- **Median time on treatment** with GIOTRIF® followed by osimertinib was **28.1 months**

Hochmair M et al. Future Oncol. 2019

GioTag Study UPDATE

APRIL 2019

Patients with Del19



Adapted from Hochmair MJ, et al. 2019.

Median OS

45.7 months

(90% CI: 45.3 – 51.5)

At time of analysis, the total number of events was 58

At Year 2, 82% of patients treated with the sequence of GIOTRIF® followed by osimertinib were **still alive**

- **Median time on treatment** with GIOTRIF® followed by osimertinib was **30.6 months**

Hochmair M et al. Future Oncol. 2019

IASLC
2019 World Conference on Lung Cancer
September 7-10, 2019 | Barcelona, Spain

22-24 months for T790M +ve

1st or 2nd gen TKI up to 12-14 mos → 3rd gen TKI 10 mos

17-19 months for T790M -ve

1st or 2nd gen TKI up to 12-14 mos → Chemo 5 mos

24 months

Osimertinib as the 1st line treatment 19 mos → Chemo 5 mos

Waiting for FLAURA OS result

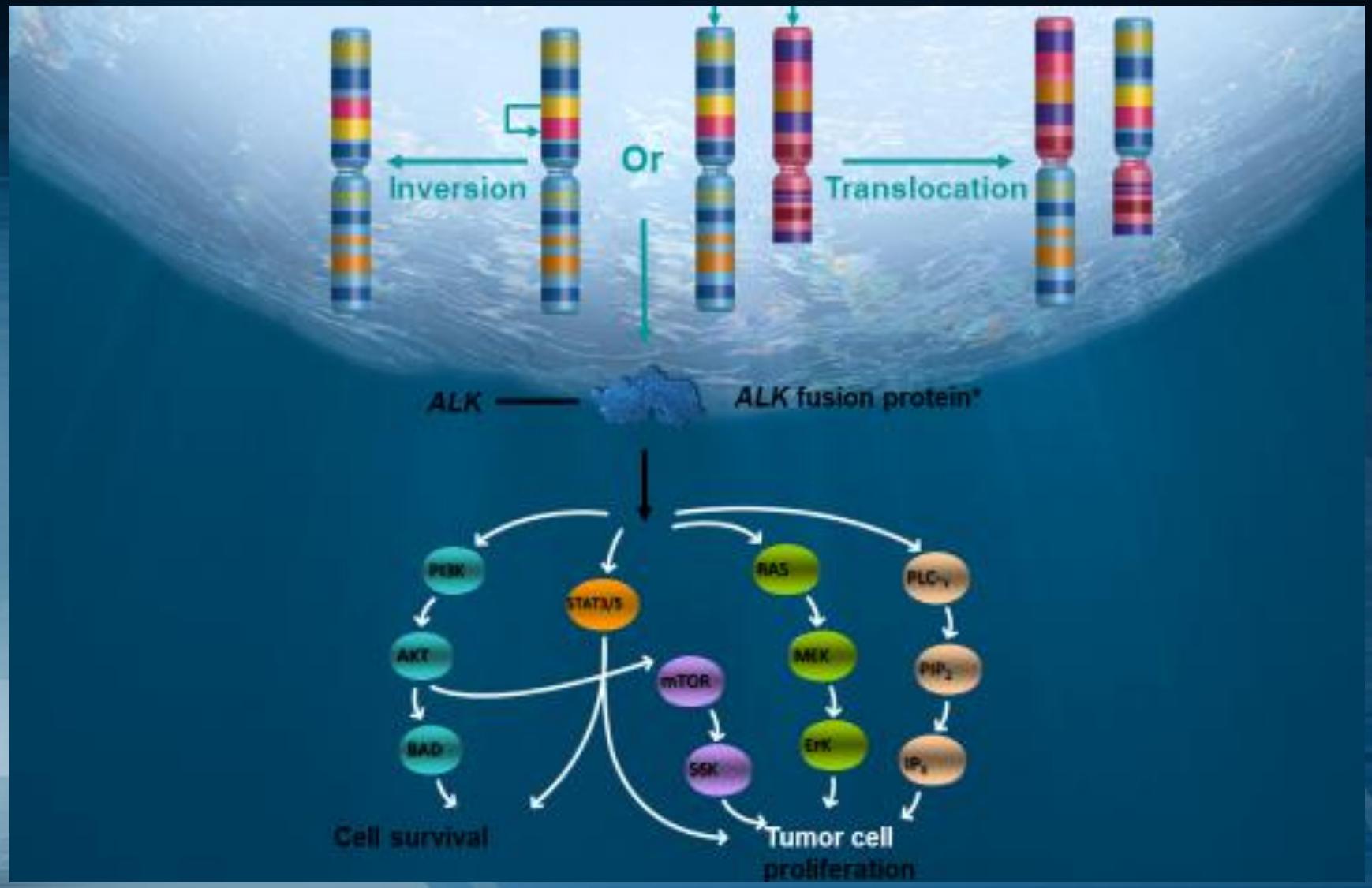
26-31 months, AE ?? Rate of T790M +ve ??, CNS efficacy ??

Combination 1st gen TKI and chemotherapy 16-21 months → 3rd gen TKI 10 mos

26-29 months, AE ?? Rate of T790M +ve ??, CNS efficacy ??

Combination 1st gen TKI and Antiangiogenesis 16-19 mos → 3rd gen TKI 10 mos

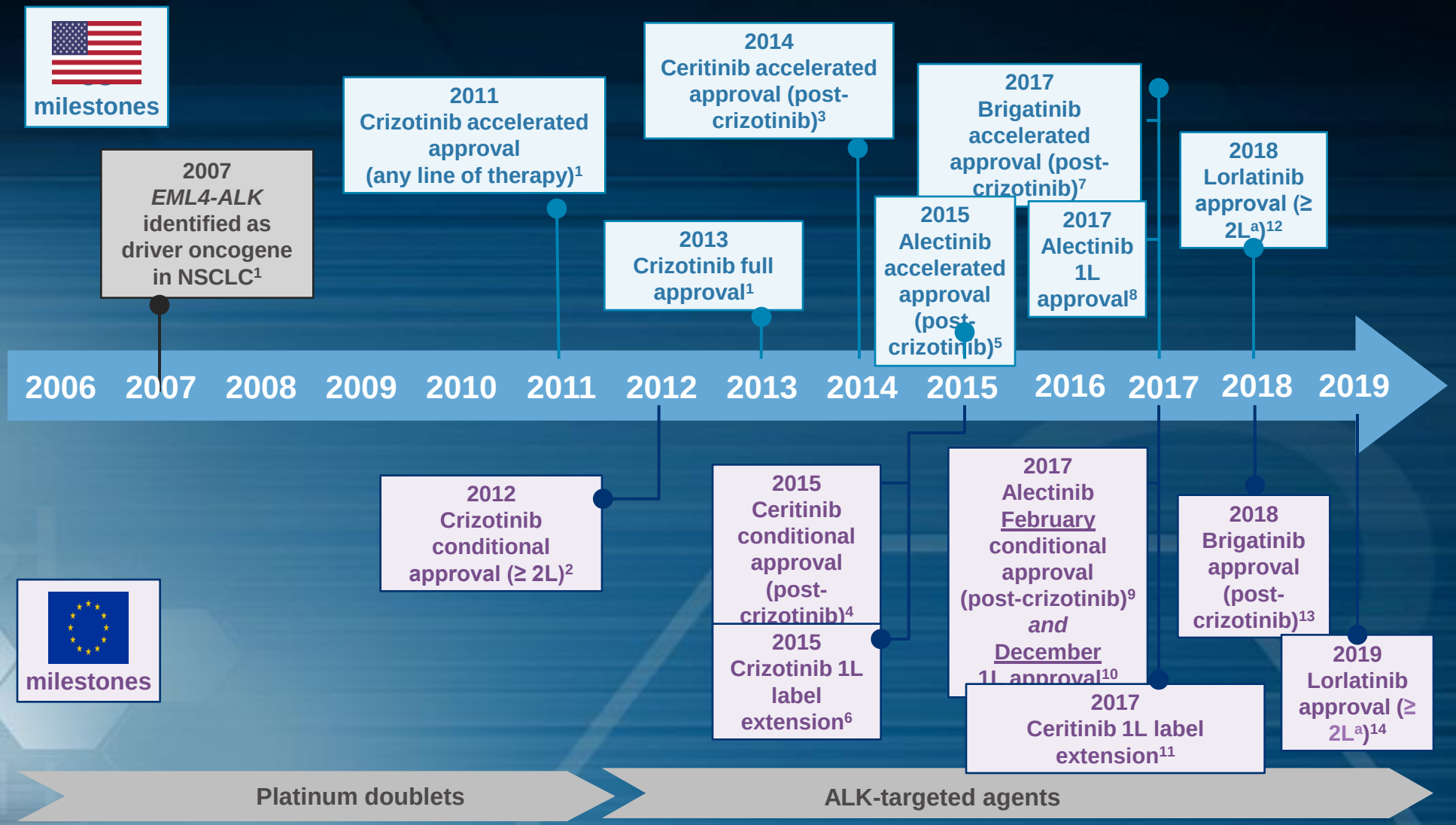
EML4-ALK


Inversion
Or
Translocation
ALK
ALK fusion protein*
PERK
STAT3/5
RAS
PLCγ
AKT
mTOR
MEK
PIP2
BAD
S6K
ErK
IP3
Cell survival
Tumor cell
proliferation

EML4-ALK

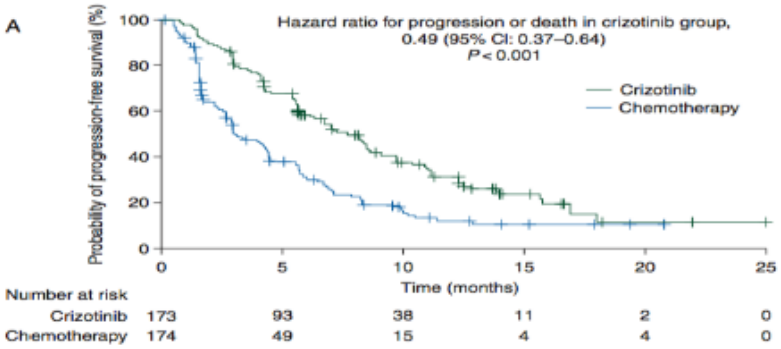
- Ασιάτες και Καυκάσιοι
- Και στα δύο φύλα
- Αδενοκαρκίνωμα
- Μη καπνιστική ή ελαφρά καπνιστική συνήθεια
- Εγκεκριμένη στοχευμένη θεραπεία (TKIς)
- Προβλεπτική αξία (δείκτης αποτελεσματικότητας θεραπείας)

Historical Overview of ALK+ NSCLC Therapeutic Options: Focus on ALK Inhibitors



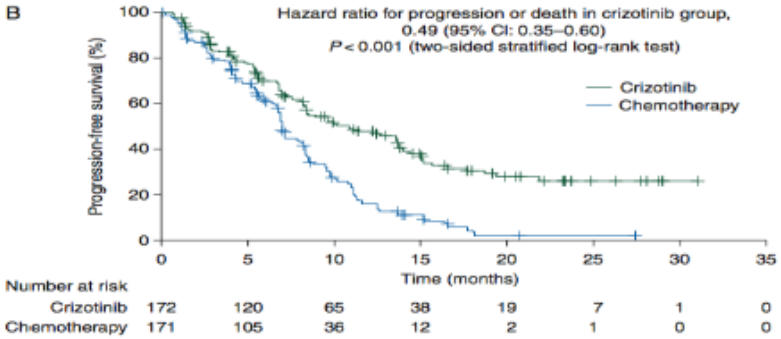
Phase III Trials
of the first ALK/TKI Crizotinib *vs* Chemotherapy

PROFILE 1007
Shaw et al.
NEJM 2013
(2nd line)



Response Rate
65 vs 20%

PROFILE 1014
Solomon et al
NEJM 2014
(1st line)

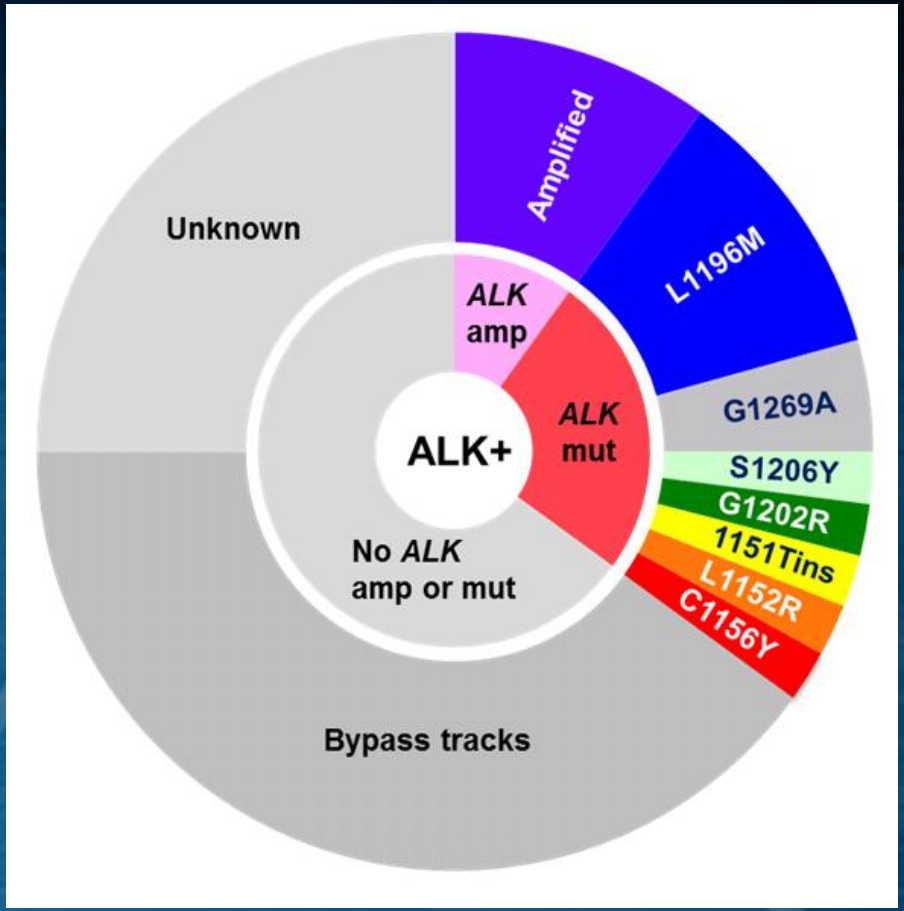


Response Rate
74 vs 45%

Blackhall & Cappuzzo Ann Oncol Supp 3 2016

Acquired Resistance in *ALK*+ NSCLC

- Most patients develop resistance to crizotinib[1,2]
  - Usually within 1–2 years
  - CNS relapses are common[3]
- Mechanisms of resistance are diverse[1,2]
  - *ALK* resistance mutations
  - Alternative signaling pathways



amp, amplification; CNS, central nervous system; mut, mutation

1. Katayama R, et al. Sci Transl Med 2012;4:120ra17;
2. 2. Doebele RC, et al. Clin Cancer Res 2012;18:1472–1482;
3. 3. Takeda M, et al. J Thorac Oncol 2013;8:654–657.

Mutational sensitivity of established and investigational ALK TKIs

Cellular ALK phosphorylation mean IC_{50} (nmol/L)					
Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Gainor JF et al., *Cancer Discov* 2016.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

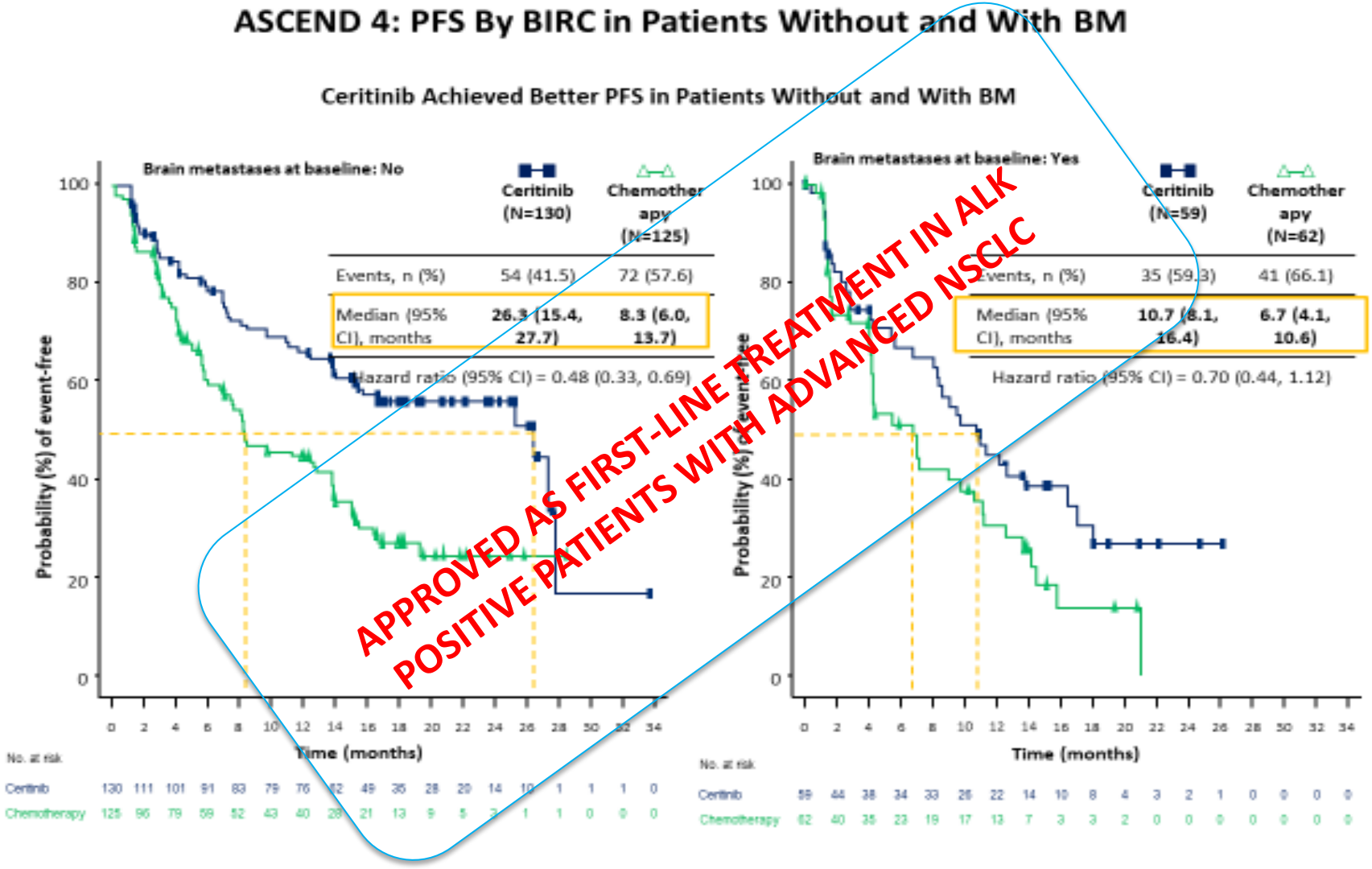
Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

ASCEND-1, 2 and 3: Progression-Free Survival and Duration of Response

	ASCEND-1	ASCEND-1	ASCEND-2	ASCEND-1	ASCEND-3
		ALKi pre-treated		ALKi Naive	
	n=246	n=163	n=140	n=83	n=124
PFS, median (mo)	**9.03**	**6.93**	7.2 (5.4, 9.0)	**18.4**	11.1 (9.3, NE)
12-month PFS	39.1%	28.4%		61.3%	
DOR, median (mo)	9.72	8.25	9.7 (5.6, 12.9)	17.02	9.3 (9.1, NE)

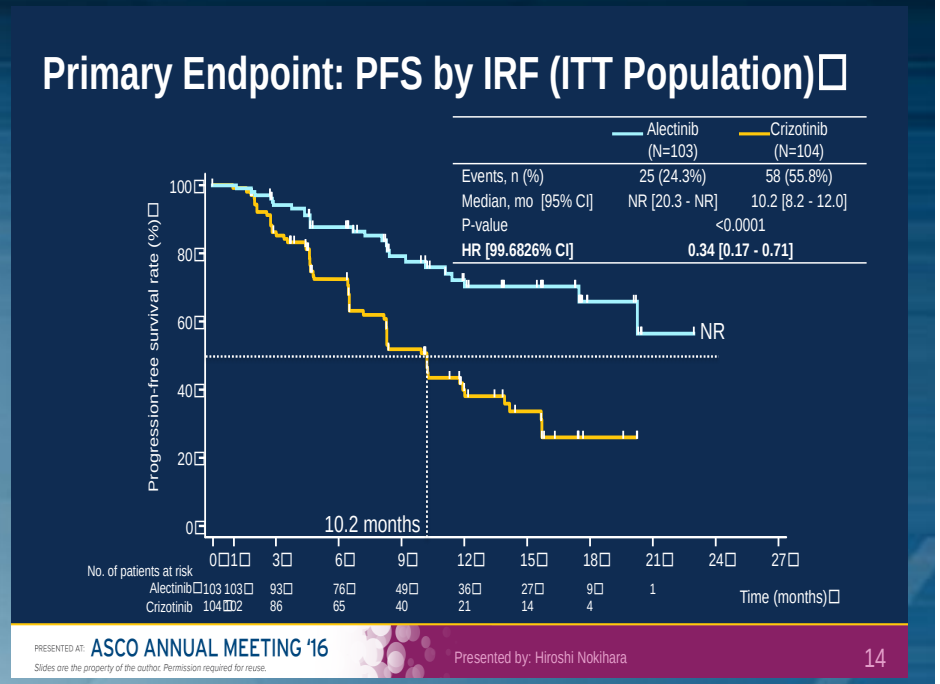
CERITINIB WITH AND WITHOUT BRAIN METS



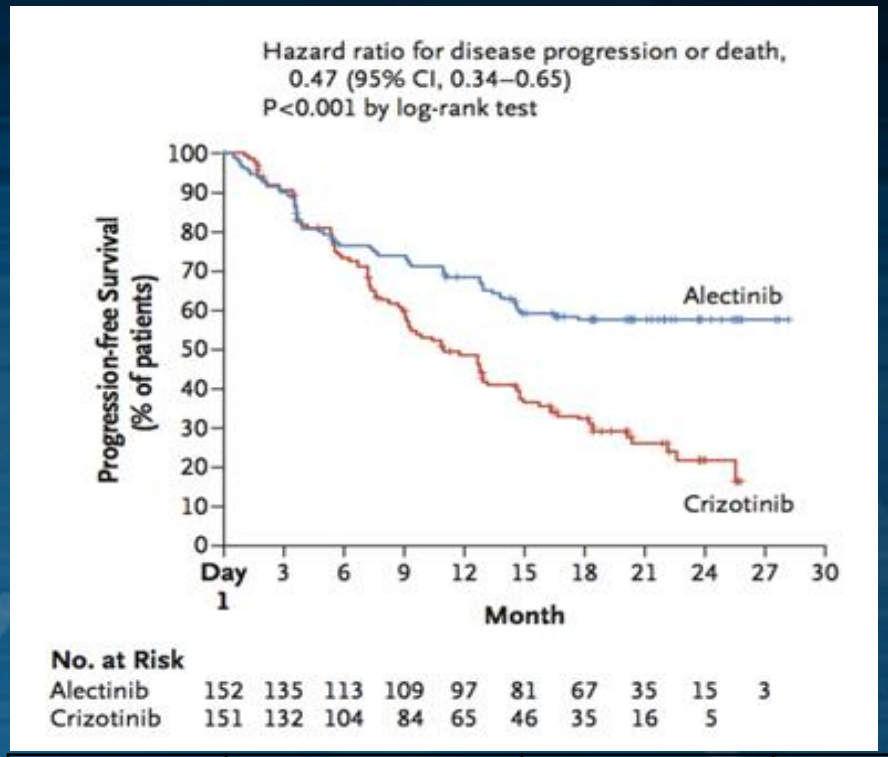
PL03: G de Castro et al. IASLC 17th WCLC, Vienna, December 2016

ALECTINIB

J-ALEX TRIAL
Hida The Lancet 2017



ALEX TRIAL
Peters NEJM 2017



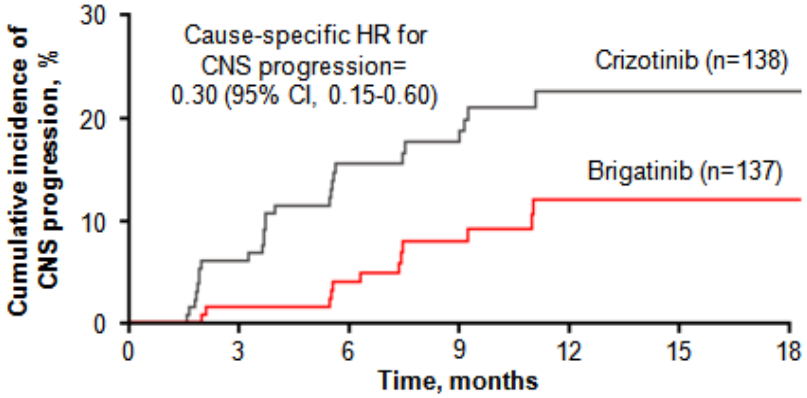
J-ALEX	PFS [95% CI]	HR (95%CI)	ORR
Alectinib	**NR** (20.3,NR)	**0.34** (0.17,0.71)	91.6%
Crizotinib	**10.2** (8.2,12.0)		78.9%

ALEX	PFS [95% CI]	HR (95%CI)	ORR
Alectinib	**25.7** (19.9,NR)	**0.5** (0.36,0.70)	82.9%
Crizotinib	**10.4** (7.7,14.6)		75.5%

BRIGATINIB

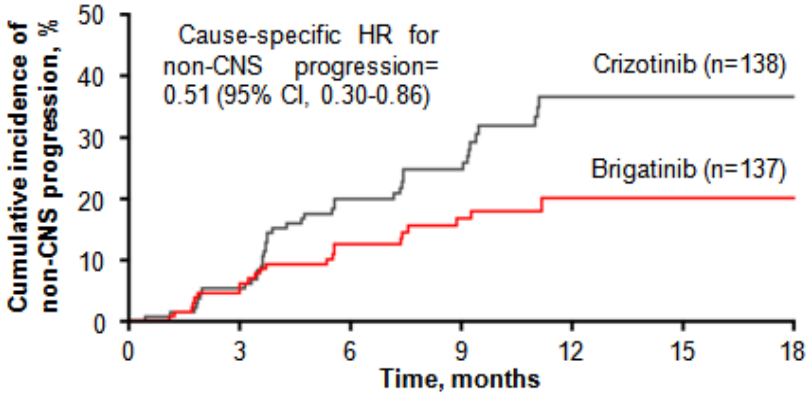
First-line brigatinib (ALTA-1L): CNS and non-CNS efficacy, competing risk analysis

Cumulative incidence of CNS progression without prior systemic progression



Time to CNS progression (without prior systemic progression), ITT population	Brigatinib (n=137)	Crizotinib (n=138)
Cumulative incidence rate, % (95% CI)		
6 months	4.0 (1.5-8.5)	15.5 (9.9-22.3)
12 months	**12.0 (6.4-19.5)**	**22.6 (15.2-31.0)**
Cause-specific HR (95% CI)	0.30 (0.15-0.60); *P*<0.001[a]	

Cumulative incidence of non-CNS progression without prior CNS progression

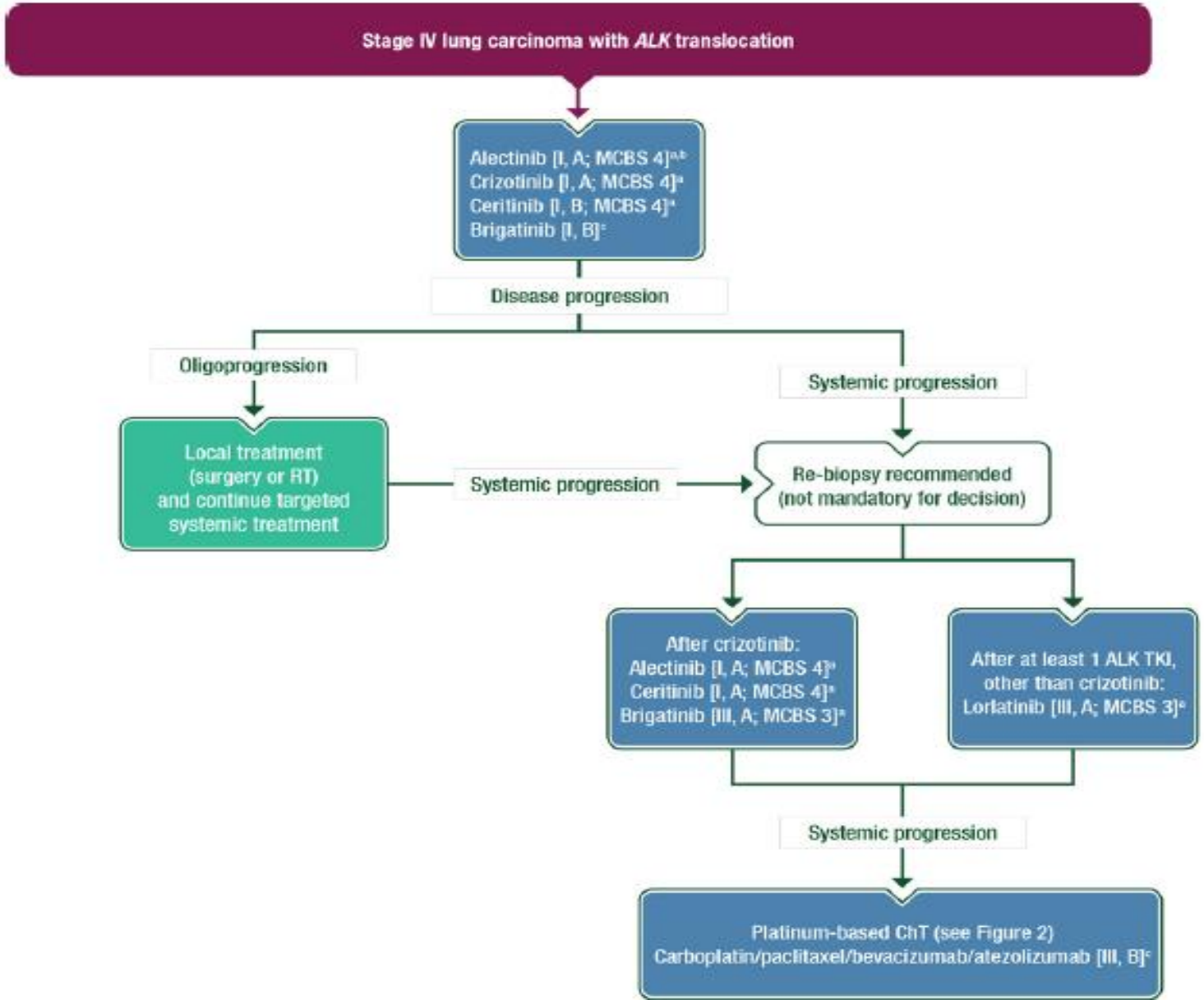


Time to non-CNS progression (without prior CNS progression), ITT population	Brigatinib (n=137)	Crizotinib (n=138)
Cumulative incidence rate, % (95% CI)		
6 months	12.6 (7.6-19.1)	20.0 (13.6-27.3)
12 months	**20.2 (12.8-28.9)**	**36.8 (27.2-46.5)**
Cause-specific HR (95% CI)	0.51 (0.30-0.86); *P*=0.017[a]	

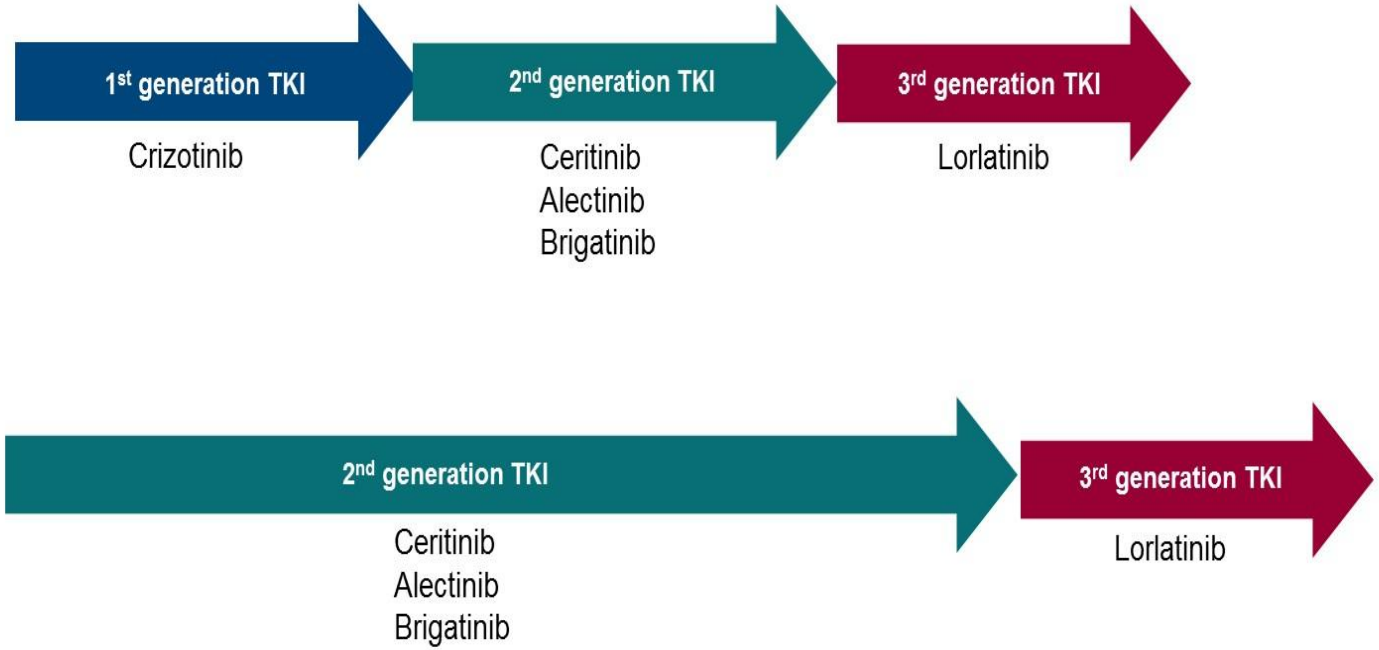
Brigatinib is not approved in the first-line setting.

As of the first interim analysis (data cutoff: February 19, 2018). Median follow-up was 11 months with brigatinib and 9.3 months with crizotinib. [a]Log-rank test.
CNS, central nervous system; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat.
Popat S, et al. Poster. ESMO. 2018 (abstr LBA58).

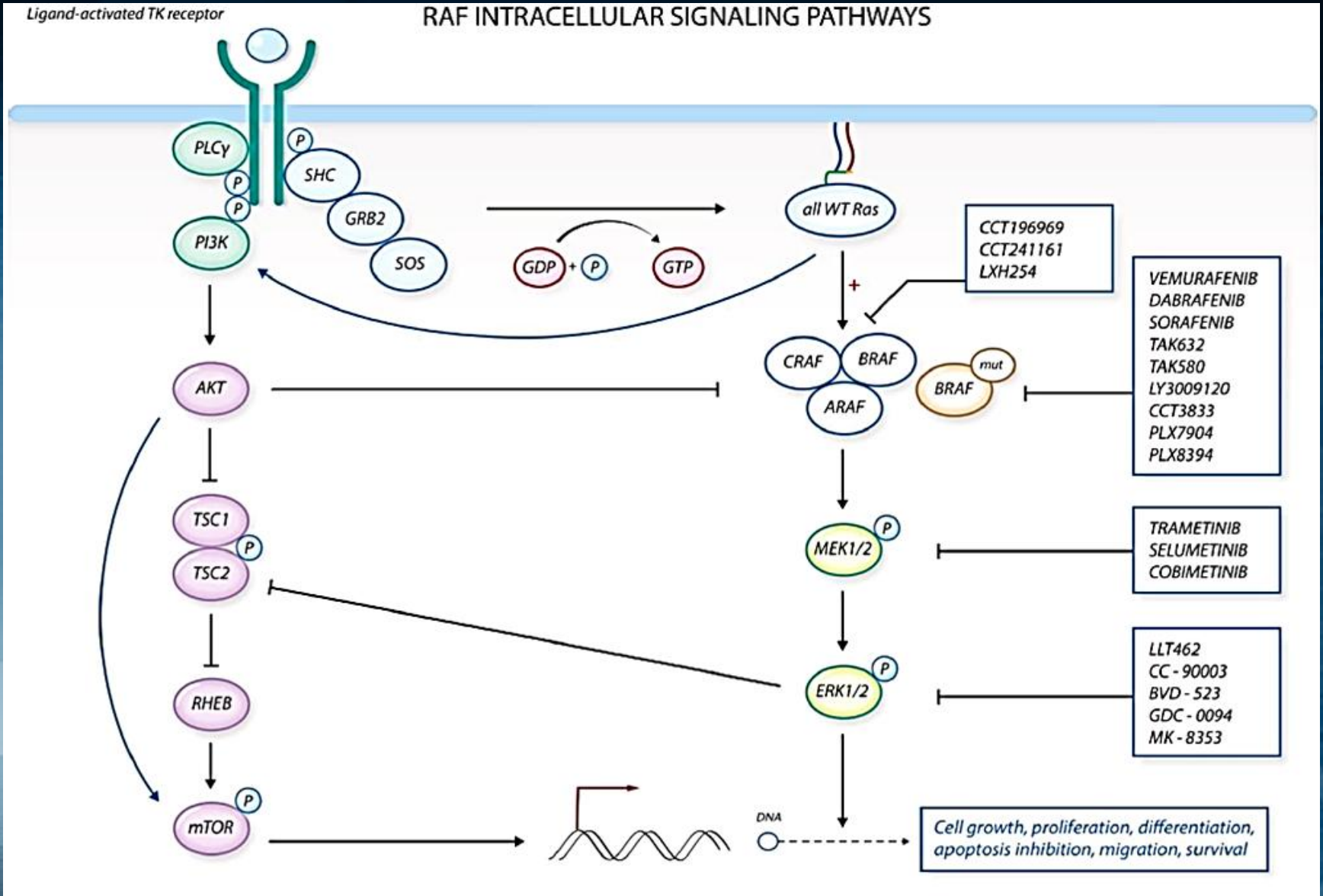
Figure 5. Treatment algorithm for stage IV lung carcinoma with ALK translocation.



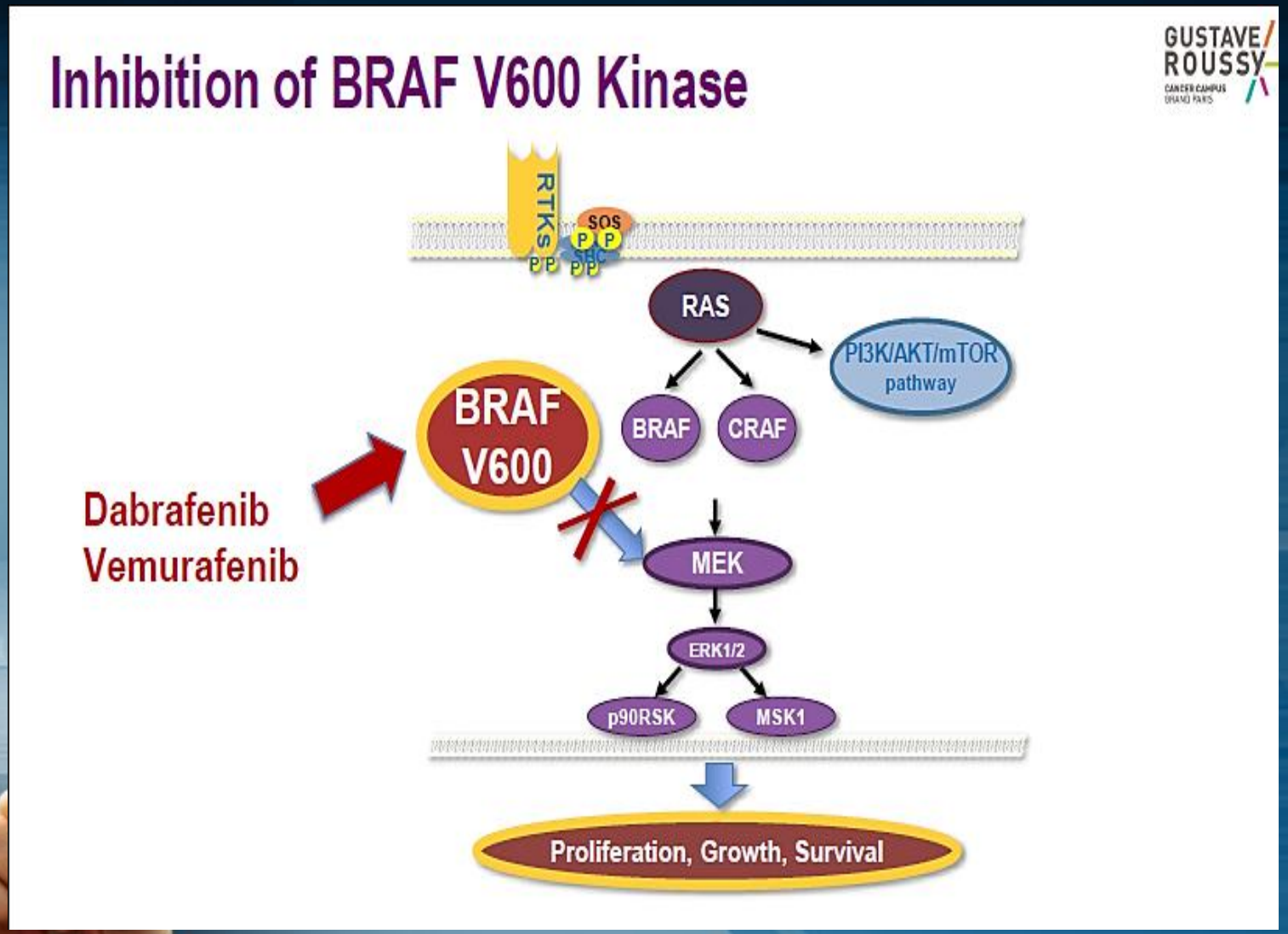
Evolving Treatment Paradigms in ALK+ Lung Cancer



BRAF MUTATIONS

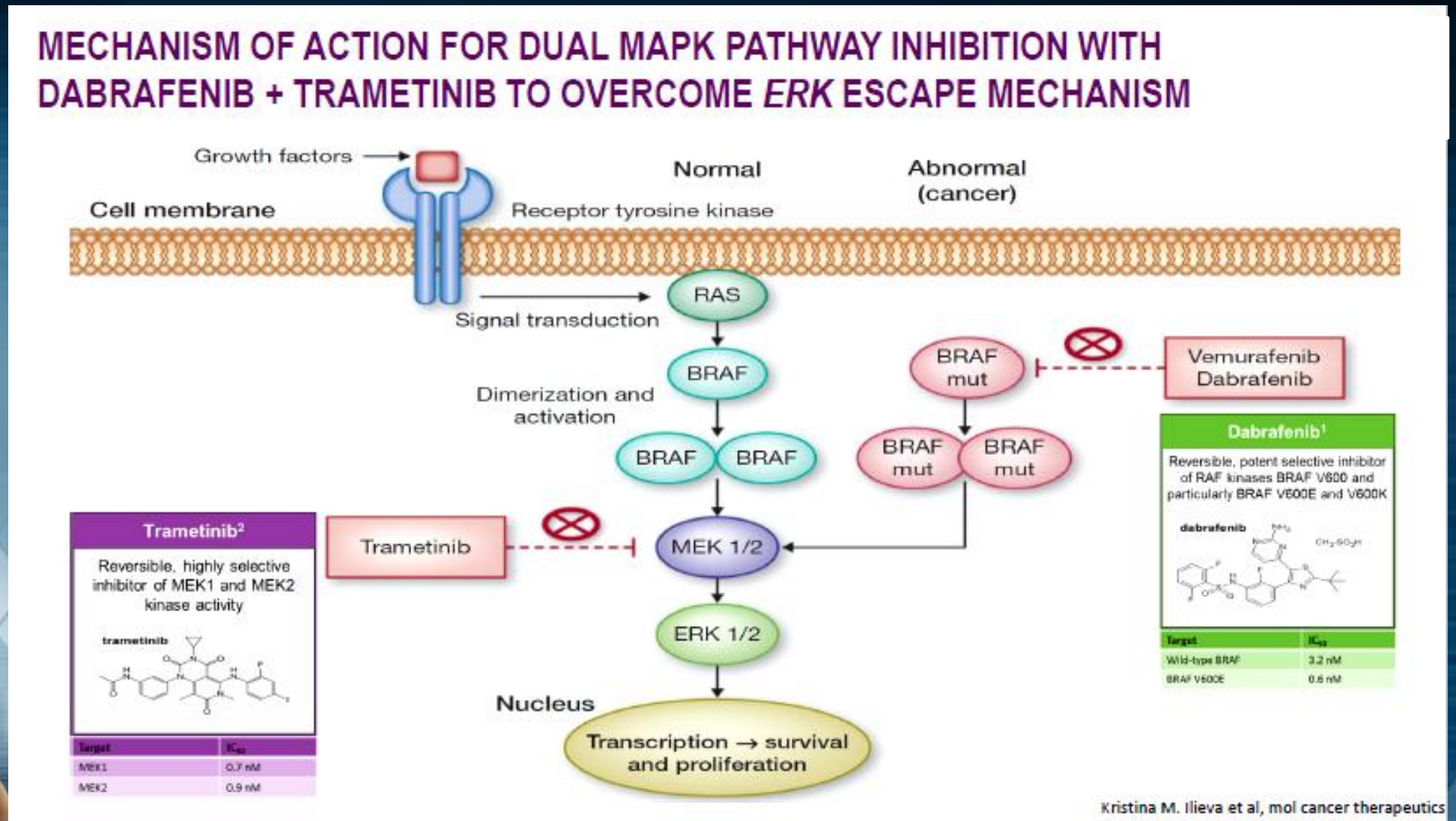


BRAF MUTATIONS



- **V600 mutated BRAF** constitutively activates MEK ERK path
- **Non-V600 mutations** either increase or impair BRAF kinase activity
- Impaired BRAF kinases can still activate the ERK pathway in a CRAF-dependent manner

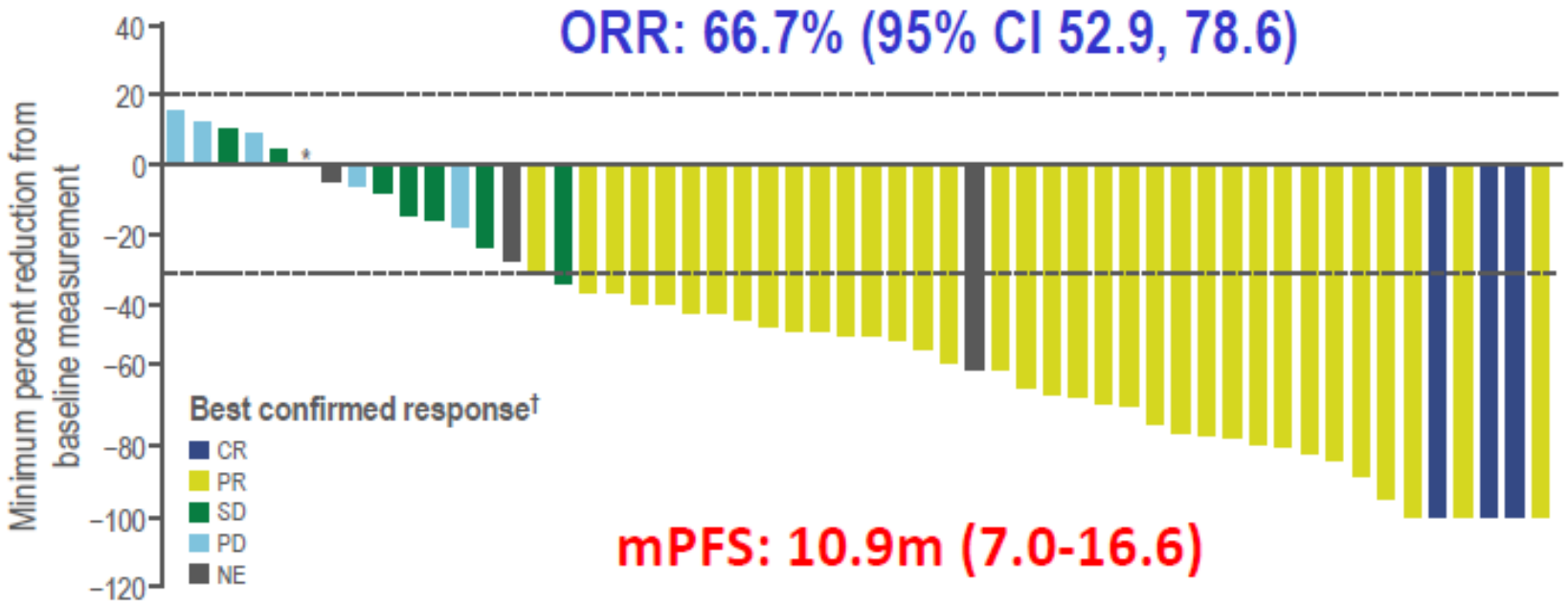
DABRAFENIB + TRAMETINIB



DABRAFENIB + TRAMETINIB 2ND LINE

BRF113928 STUDY : MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 2ND LINE

Cohort B



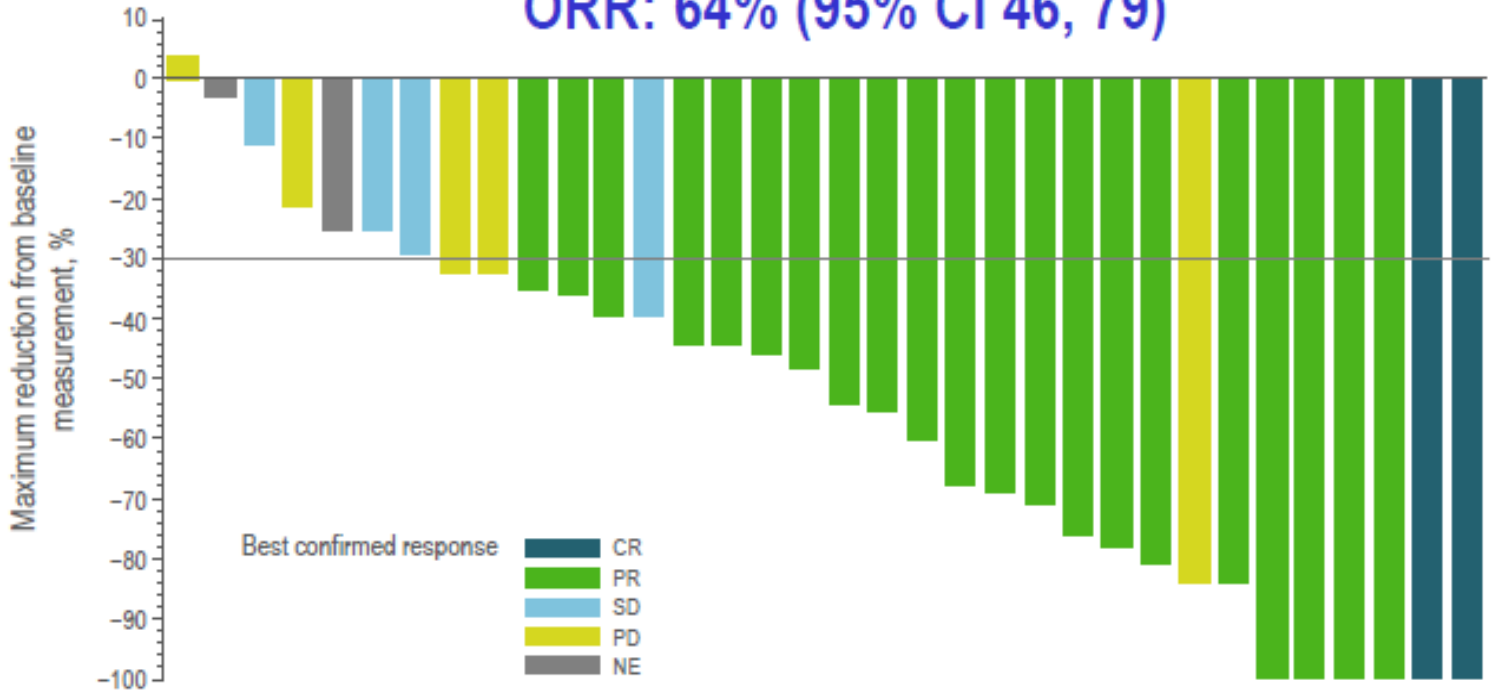
Planchard D *et al. Lancet Oncol* 2016;17:984–993;
Planchard D *et al. J Clin Oncol* 2017;35(Suppl):Abst 9075

DABRAFENIB + TRAMETINIB 1ND LINE

BRF113928 STUDY : MAXIMUM CHANGE IN TARGET LESION BY BEST CONFIRMED RESPONSE WITH DABRAFENIB + TRAMETINIB IN 1ST LINE

Cohort C

ORR: 64% (95% CI 46, 79)

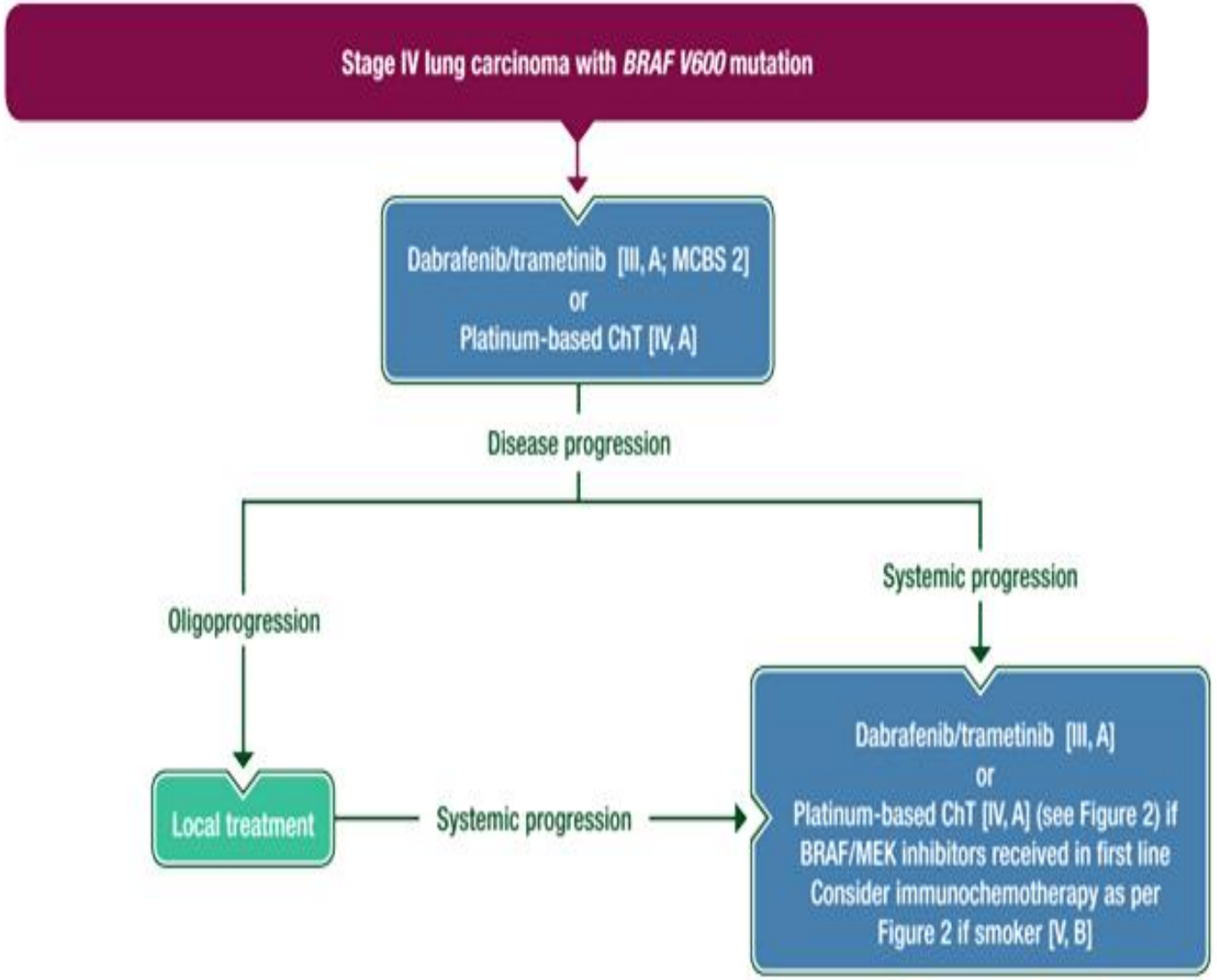


The mOS was 24.6 months, 51% achieved a 2-yr survival

mPFS: 10.2m (6.9-16.7)

Planchard D *et al. Lancet Oncol* 2017;18:1307–1316

Treatment algorithm for stage IV lung carcinoma with BRAF V600 mutation, ESMO Clinical Practice Guidelines, September 2019



NTRK- ROS1

- *ROS1* as a target in NSCLC
- Crizotinib FDA approved for *ROS1+* NSCLC in 2016[8]
  - ORR=72%
  - Median PFS=19 months
  - No intracranial activity data
  - Ceritinib
  - Lorlatinib
  - Entrectinib

Entrectinib

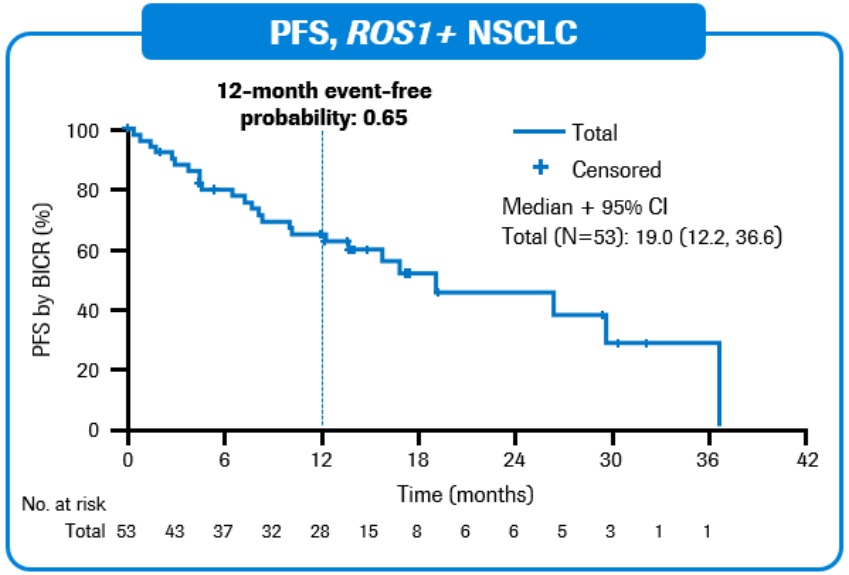
Entrectinib is an oral, potent and selective ROS1 / NTRK / ALK tyrosine kinase inhibitor that is CNS active[1,2]

Designed to cross the blood-brain barrier (BBB), with demonstrated clinical activity in primary brain tumours and secondary CNS metastases

83% intracranial ORR in *ROS1+* NSCLC patients

Intracranial response	Measurable lesions (n=6)	Measurable and non-measurable lesions (n=7)
CNS responders	5/6	5/7
IC ORR (95% CI)	**83.3% (35.9–99.6)**	**71.4% (29.0–96.3)**

Entrectinib



PFS was assessed in 23 patients who had CNS disease at baseline per investigator assessment

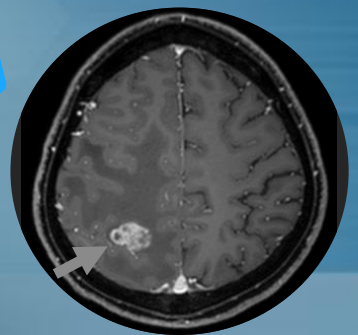
	Total N=53	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts with event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
PD, n	20	8	12
Death, n	5	3	2
Time to event (months) **Median** (95% CI)	**19.0** (12.2, 36.6)	**13.6** (4.5, NE)	**26.3** (15.7, 36.6)

In patients with no CNS disease at baseline, median PFS was > 2 years

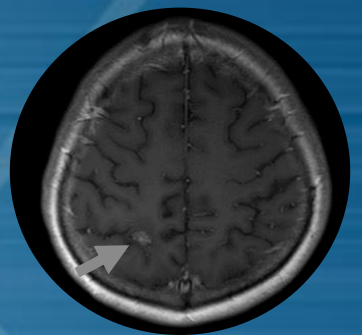
PFS data confirm the high level of disease control and durability of responses obtained with entrectinib

53-year-old female with *ROS1*+ NSCLC

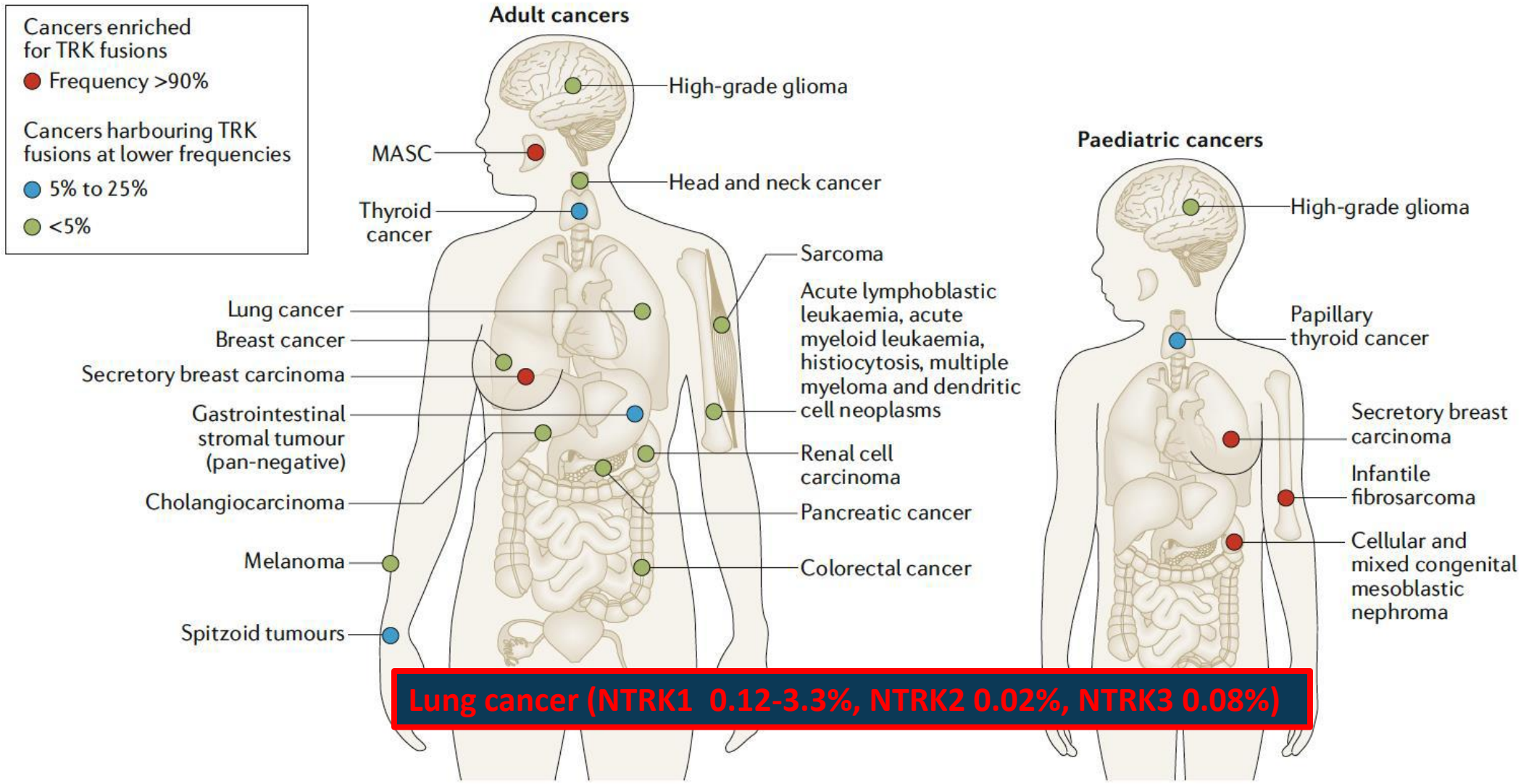
Baseline



Cycle 2

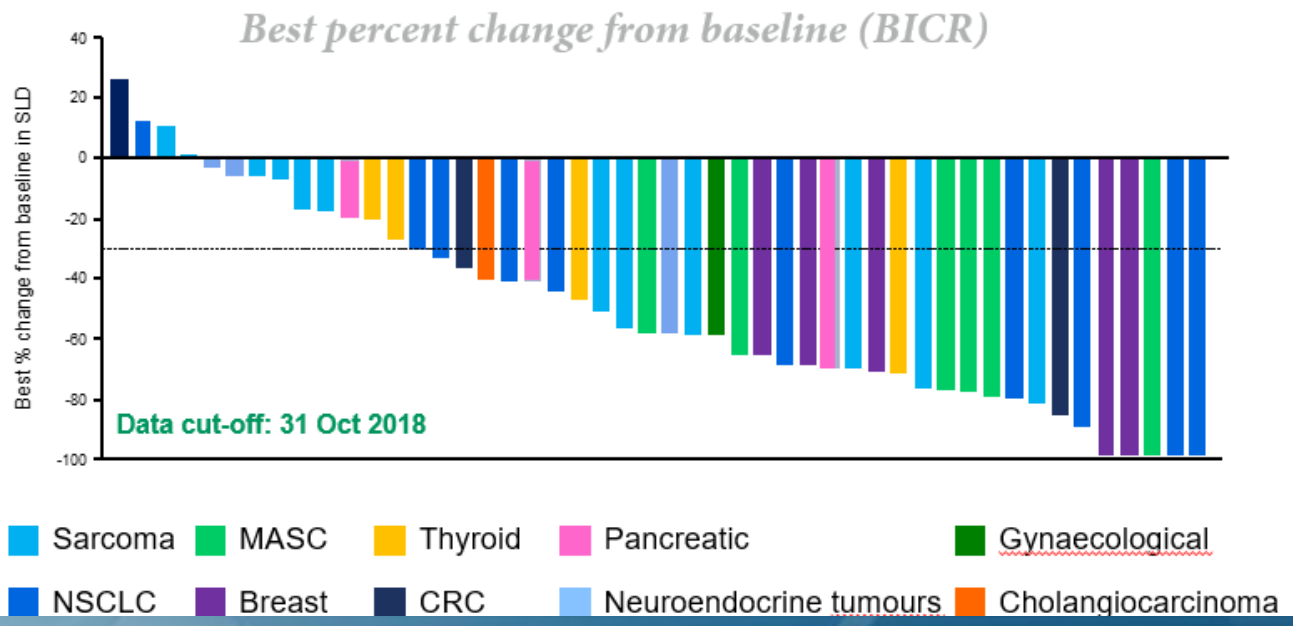


Distribution and frequency of NTRK fusions in adult and paediatrictumours



Lung cancer (NTRK1 0.12-3.3%, NTRK2 0.02%, NTRK3 0.08%)

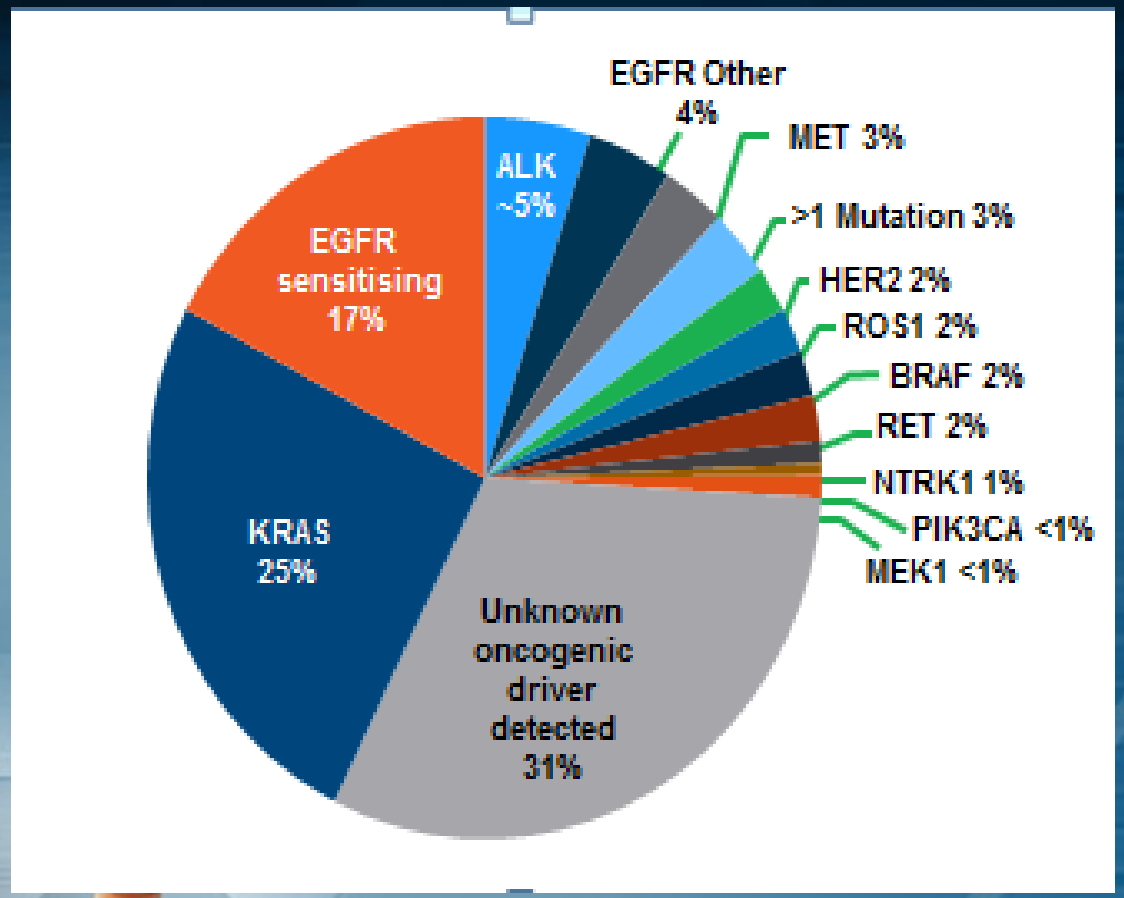
Entrectinib



Total (BICR assessed) (N=54)	May 2018 cut off	Oct 2018 cut off
Responders (n)	31	32
ORR, %	57.4	59.3
CR, %	7.4	7.4
PR, %	50.0	51.9
Clinical benefit rate*	64.8	64.8

Demetri, et al. ESMO 2018; Doebele, et al. AACR 2019; Rolfo et al. ESMO 2019

Today's and Tomorrow's Targeted therapies



EGFR sensitising

- Erlotinib
- Erlotinib +bevacizumab
- Erlotinib +Necitumumab
- Gefitinib
- Afatinib
- Osimertinib

ALK

- Alectinib
- Crizotinib
- Ceritinib
- Lorlatinib
- Brigatinib
- Ensartinib

ROS1

- Crizotinib
- Ceritinib
- Lorlatinib
- Entrectinib
- DS-6051b

BRAF (V600E)

- Dabrafenib+Tram etinib

NTRK1

- Entrectinib
- Larotrectinib

RET

- Cabozantinib
- Apatinib
- Vandetanib
- Ponatinib
- Lenvatinib
- BLU-667

MET

- Crizotinib
- Cabozantinib

HER2

- Trastuzumab
- Trastuzumab emtansine
- Pertuzumab
- Afatinib
- Dacomitinib

KRAS

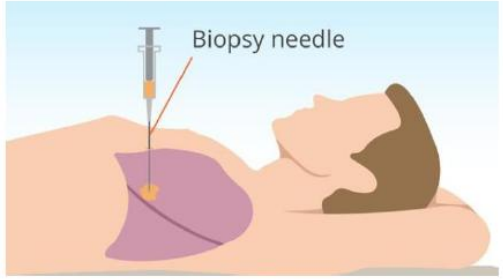
- AMG 510

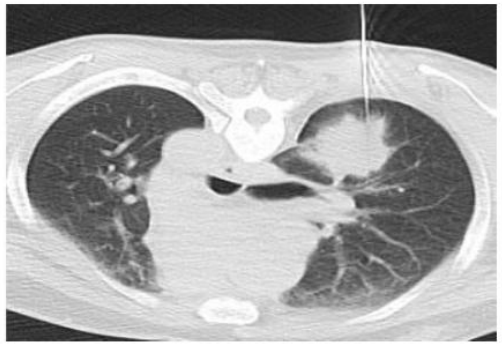
ΝΕΑ ΒΙΟΨΙΑ

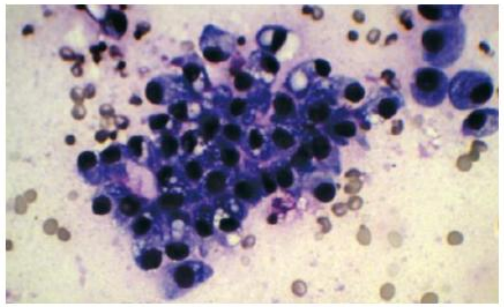
TUMOUR TISSUE BIOPSIES

Tumour tissue is current gold-standard for molecular analysis, **but**:

- Involve invasive medical procedure which can be difficult and expensive (biopsy)
- Can be obtained long time prior to analysis (initial surgical resection) so miss tumour evolution
- Can be limited amounts of material available for molecular analysis as required for pathology and PD-L1 IHC etc.
- Which lesion to analyse in metastatic disease?
- Collection of serial biopsies for analysis are extremely rare making analysis of mechanisms of resistance difficult to investigate







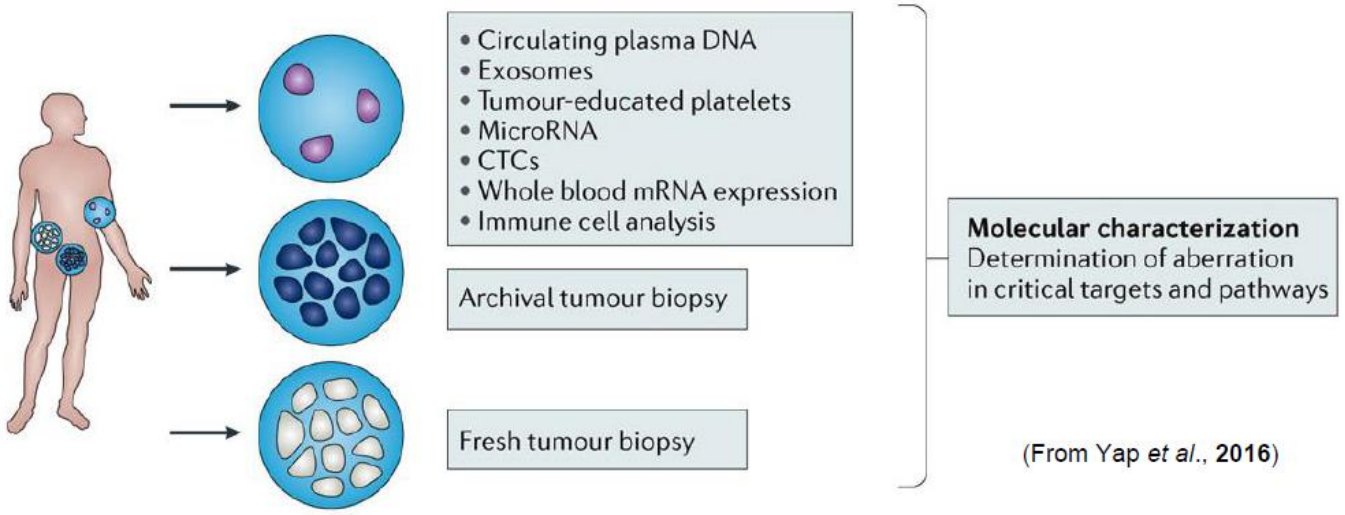
BARCELONA 2019 ESMO congress

ΥΓΡΗ ΒΙΟΨΙΑ

THE NEED FOR A 'LIQUID BIOPSY'

Blood sampling is a non-invasive, inexpensive, routine clinical method

- Enables 'real-time' monitoring of tumour status
- Enables longitudinal sampling to monitor tumour response and resistance
- Provides 'global' picture of metastatic disease



(From Yap *et al.*, **2016**)

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ΠΛΕΟΝΕΚΤΗΜΑΤΑ ΥΓΡΗΣ ΒΙΟΨΙΑΣ

- DNA από το συνολο του όγκου αποφυγη του προβλήματος της ετερογένειας
- Μη επεμβατική, καλά ανεκτή , χωρις επιπλοκές
- Εκτιμά μεταλλάξεις στη διάγνωση και την εμφάνιση αντοχής
- Οι μεταλλάξεις που ανιχνεύονται με υγρή βιοψία εμφανίζουν πολύ καλή ανταπόκριση στην προσαρμογή της θεραπείας

ΠΛΕΟΝΕΚΤΗΜΑΤΑ ΥΓΡΗΣ ΒΙΟΨΙΑΣ

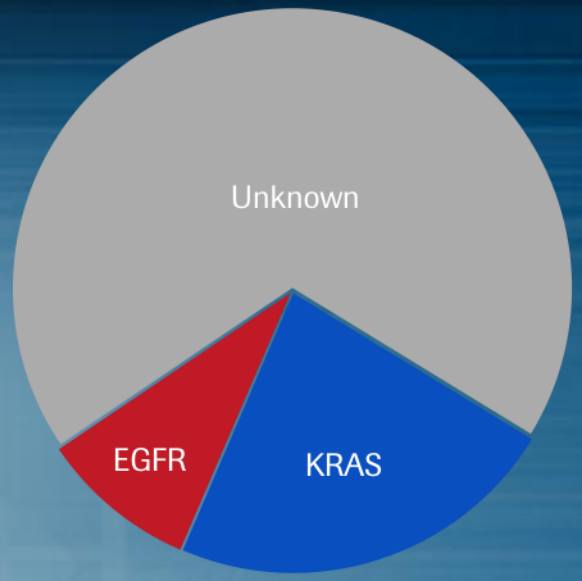
- Μπορεί να επαναλαμβάνεται ανά διαστήματα και να ανιχνεύσει μεταλλάξεις και αντοχή στη θεραπεία πολύ πριν την ακτινολογική εμφάνιση
- Μπορεί να μετρήσει TMB μεσω NGS
- **ΚΥΡΙΟ ΜΕΙΟΝΕΚΤΗΜΑ:**

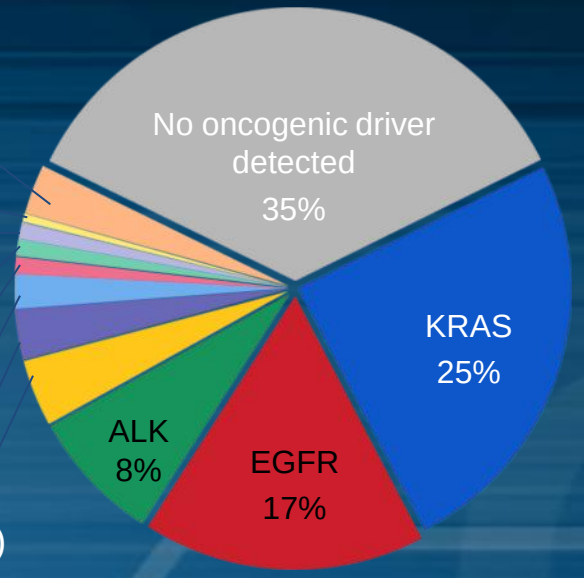
  ΧΑΜΗΛΗ ΑΡΝΗΤΙΚΗ ΠΡΟΓΝΩΣΤΙΚΗ ΑΞΙΑ

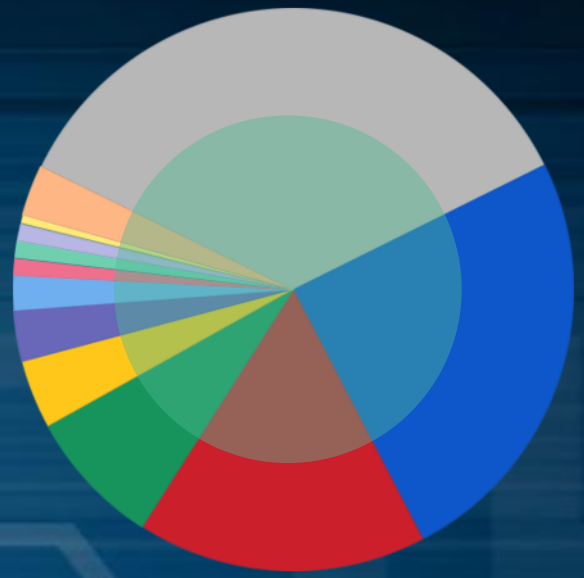
ONCOLOGY IS BECOMING MORE COMPLEX

INCREASING AMOUNT OF DATA NEEDED TO DIAGNOSE/TREAT

Complexity







Classification of lung adenocarcinomas

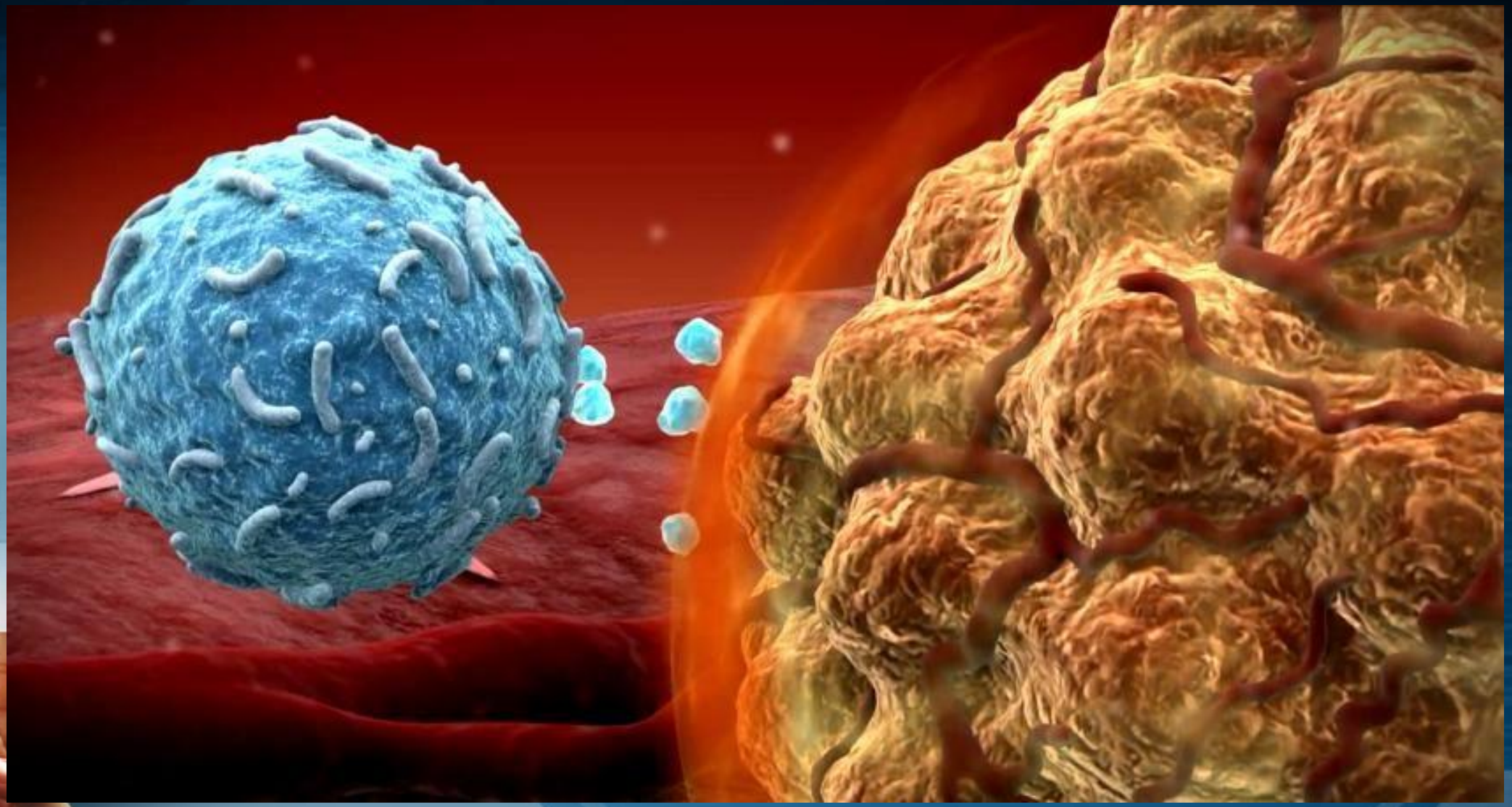
PD-L1 positive

2004 → **2014** → **Today**

References: Pao W and Girard N. New driver mutations in non-small-cell lung cancer. *Lancet Oncol* 2011; Feb;12(2):175-80.

Johnson B, *et al*. *A multicenter effort to identify driver mutations and employ targeted therapy in patients with lung adenocarcinomas: The Lung Cancer Mutation Consortium (LCMC).* ASCO 2013. [Online]. http://meetinglibrary.asco.org/content/111918-132

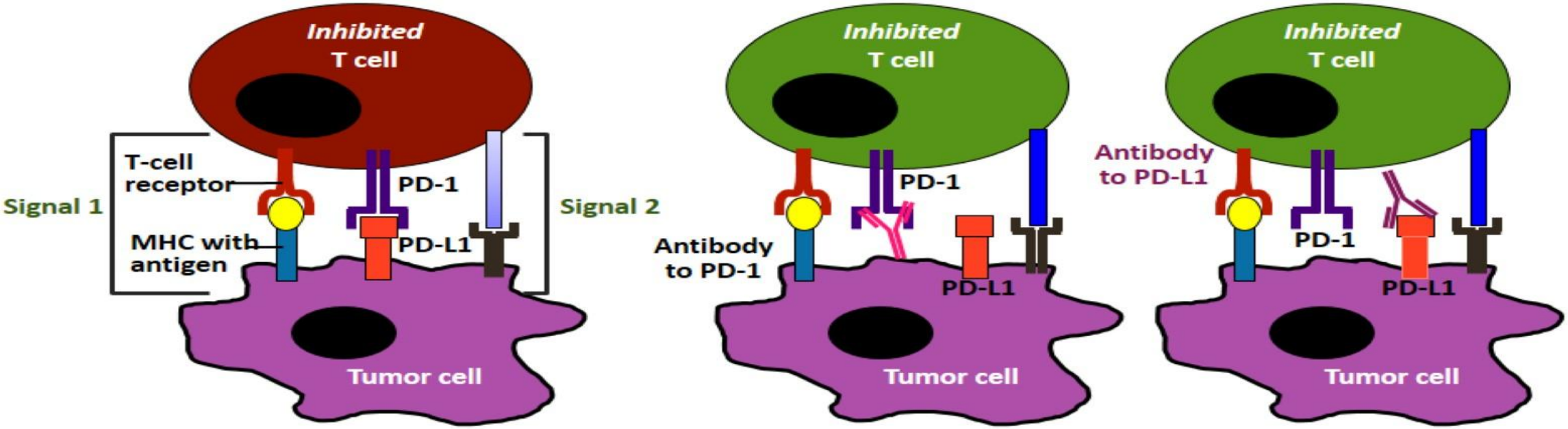
IMMUNOTHERAPY ERA



PD-1/PD-L1 in the Immune Response

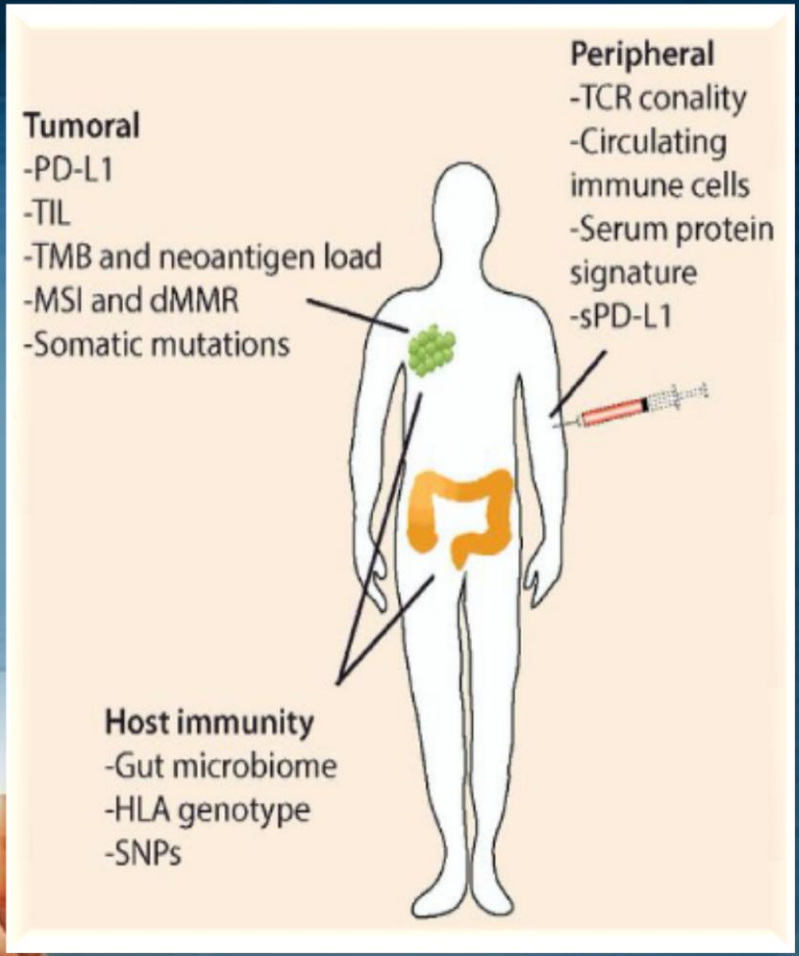
Binding of PD-L1 to PD-1 receptor downregulates T-cell effector functions

Antibody-mediated blockage of the binding of PD-L1 protein to PD-1 receptor restores T-cell effector functions



Sznol M, Chen L. *Clin Cancer Res.* 2013;19:1021-1034.

Immuno-Oncology in NSCLC



Biomarkers are needed because…

Not all patients respond to and benefit from these treatments

- Enrich the treatment population for benefit
- Benefit is relative to standard of care

Avoidance of harm?

- There are toxicities from these drugs
- Is there a subgroup of patients who fair worse on I-O treatment
- Alternative treatment would be better

Financial Burden

PD L1 immunohistochemistry

- The only validated predictive biomarker of ICI efficacy

- Continuous biomarker- higher PD L1 expression levels
  higher chance of clinical benefit

- 4 distinct patterns of PD L1 according to expression on TCs or on ICs

1. TC only
2. IC only
3. TC and IC
4. neither TC nor IC

ORIGINAL ARTICLE

BLUEPRINT 2 PROJECT

IASLC

PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project

Ming Sound Tsao, MD,[a] Keith M. Kerr, MD,[b] Mark Kockx, MD, PhD,[c]
Mary-Beth Beasley, MD,[d] Alain C. Borczuk, MD,[e] Johan Botling, MD,[f]
Lukas Bubendorf, MD,[g] Lucian Chirieac, MD,[h] Gang Chen, MD,[i]
Teh-Ying Chou, MD, PhD,[j] Jin-Haeng Chung, MD, PhD,[k] Sanja Dacic, MD, PhD,[l]
Sylvie Lantuejoul, MD,[m] Mari Mino-Kenudson, MD,[n] Andre L. Moreira, MD,[o]
Andrew G. Nicholson, DM,[p] Masayuki Noguchi, MD, PhD,[q] Giuseppe Pelosi, MD,[r]
Claudia Poleri, MD,[s] Prudence A. Russell, MD,[t] Jennifer Sauter, MD,[u]
Erik Thunnissen, MD, PhD,[v] Ignacio Wistuba, MD, PhD,[w] Hui Yu, MD, PhD,[x]
Murry W. Wynes, PhD,[y] Melania Pintilie, MSc,[z] Yasushi Yatabe, MD, PhD,[aa]
Fred R. Hirsch, MD, PhD[x,y,*]

Summary of PD-L1 monoclonal antibodies and technical aspects for evaluation and agencies' approvals in NSCLC

PD-L1 mAb clone	Ab host species	Automated platform	Checkpoint inhibitor (target)	PD-L1 scoring	Definition of positivity (cutoffs)	FDA status	EMA status	Indication	Cutoffs for indications
22C3	Mouse	Dako (Autostainer Link 48)	Pembrolizumab (PD-1)	TC	TC ⩾1% (minimum of 100 TC)	Companion	CE mark	Second and first-line NSCLC	⩾1% second line ⩾50% first line
28-8	Rabbit	Dako (Autostainer Link 48)	Nivolumab (PD-1)	TC	TC ⩾1% (minimum of 100 TC)	Complementary	CE mark	Second-line NSCLC	All comers
SP142	Rabbit	Ventana (BenchMark ULTRA)	Atezolizumab (PD-L1)	TC, IC	TC ⩾50% or IC ⩾10% (minimum of 50 TC with associated stroma)	Complementary	CE mark	Second-line NSCLC	All comers
SP263	Rabbit	Ventana (BenchMark ULTRA)	Durvalumab (PD-L1)	TC	TC ⩾25% (minimum of 100 TC)	FDA approval only for urothelial carcinoma	CE mark for nivolumab and pembrolizumab in NSCLC and durvalumab in urothelial carcinoma	Locally advanced NSCLC	All comers
73-10	Rabbit	Dako	Avelumab (PD-L1)	TC	TC ⩾1% (minimum	FDA approval	NA	NA	NA

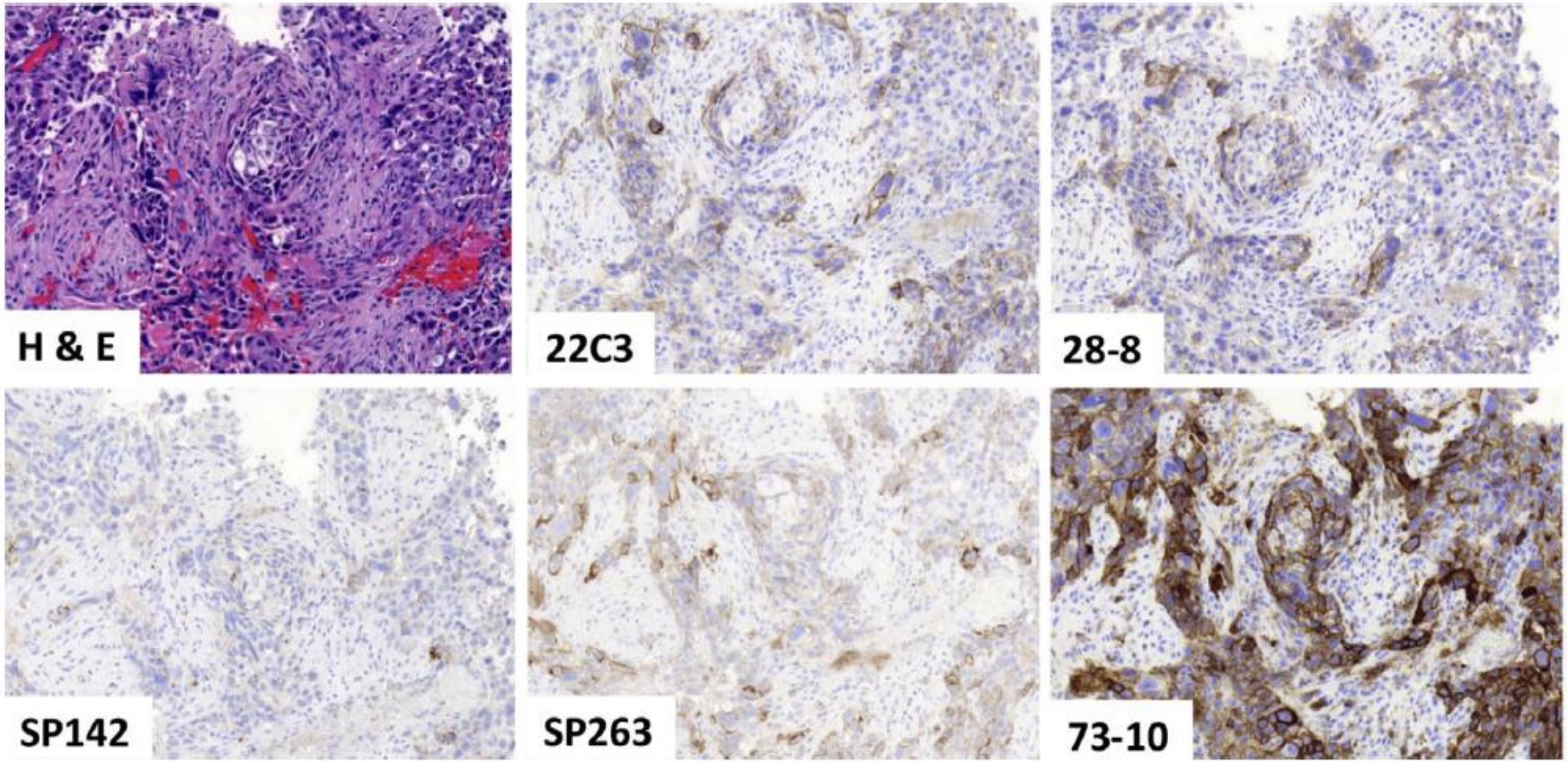
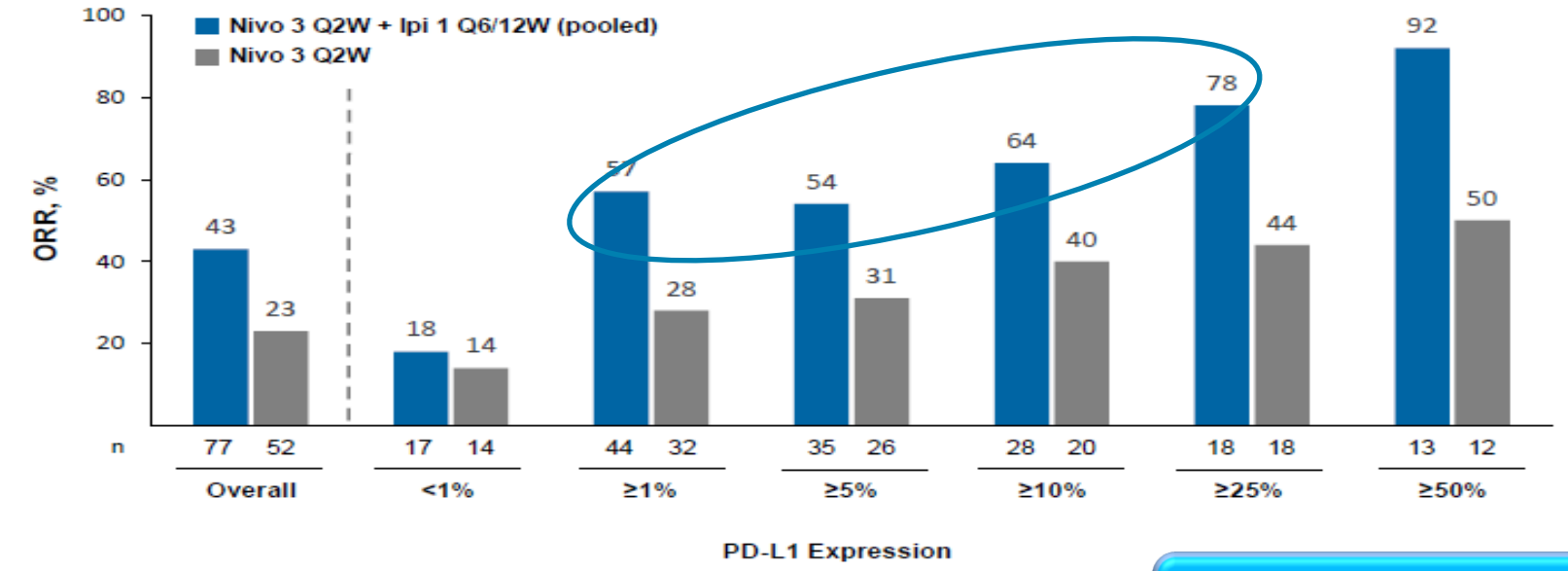


Figure 3. A representative case comparing the programmed death ligand 1 staining on the basis of the five assays.

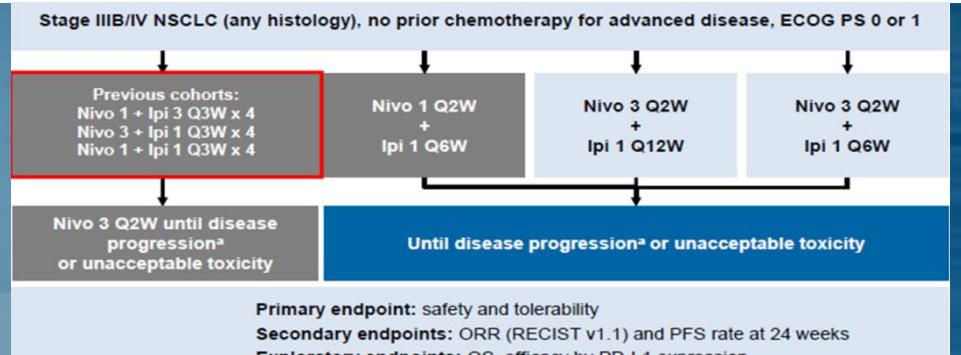
Phase I Check Mate 012: *Nivo* Plus *Ipi* in 1st Line NSCLC



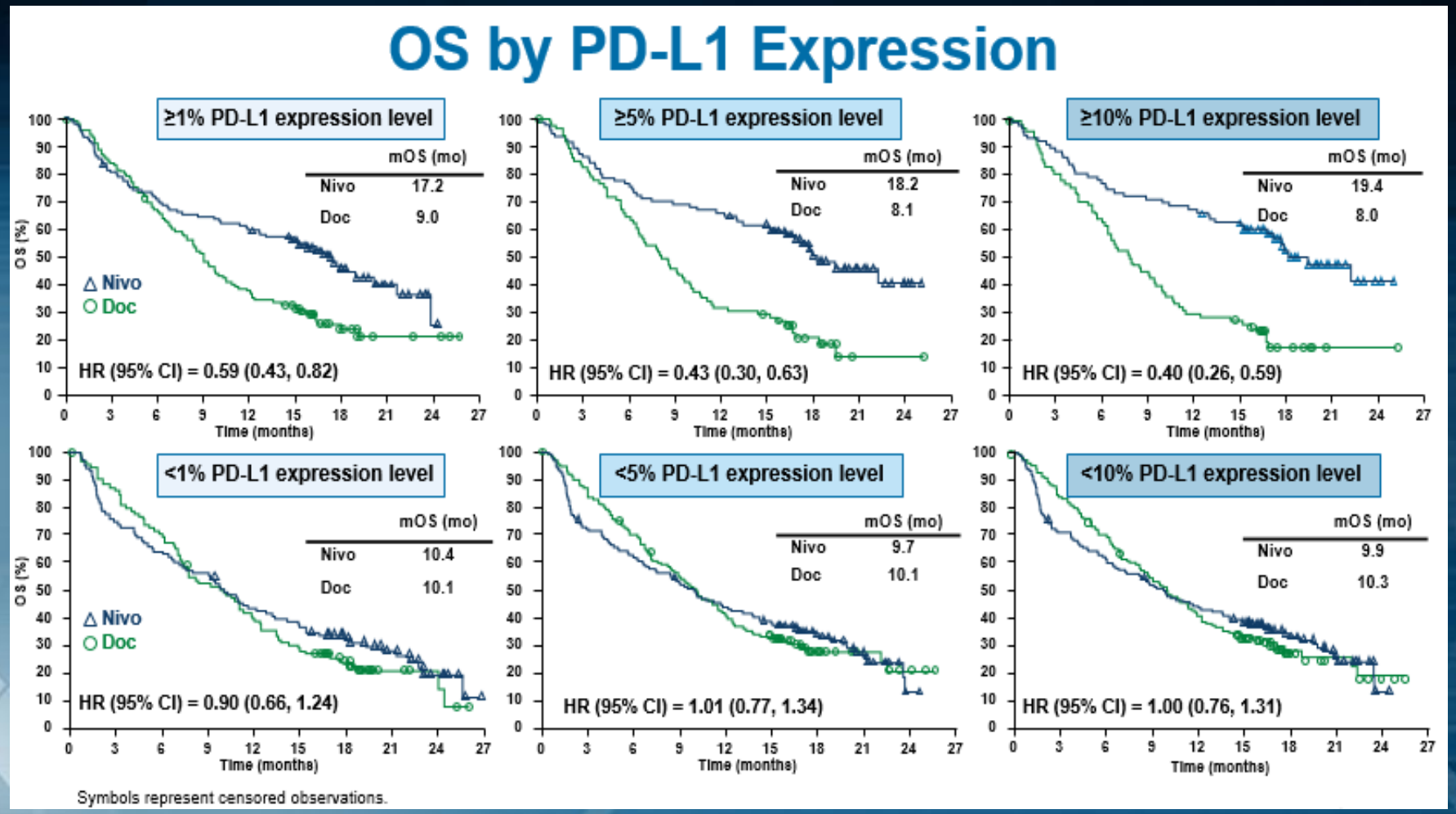
Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock

Efficacy Across All Tumor PD-L1 expression Levels

Hellman MD, et al. *J Clin Oncol.* 2016;34(suppl): Abstract 3001.



CheckMate 057: Nivo vs. Doc in advanced Non-Squamous NSCLC: OS by PD-L1 Expression



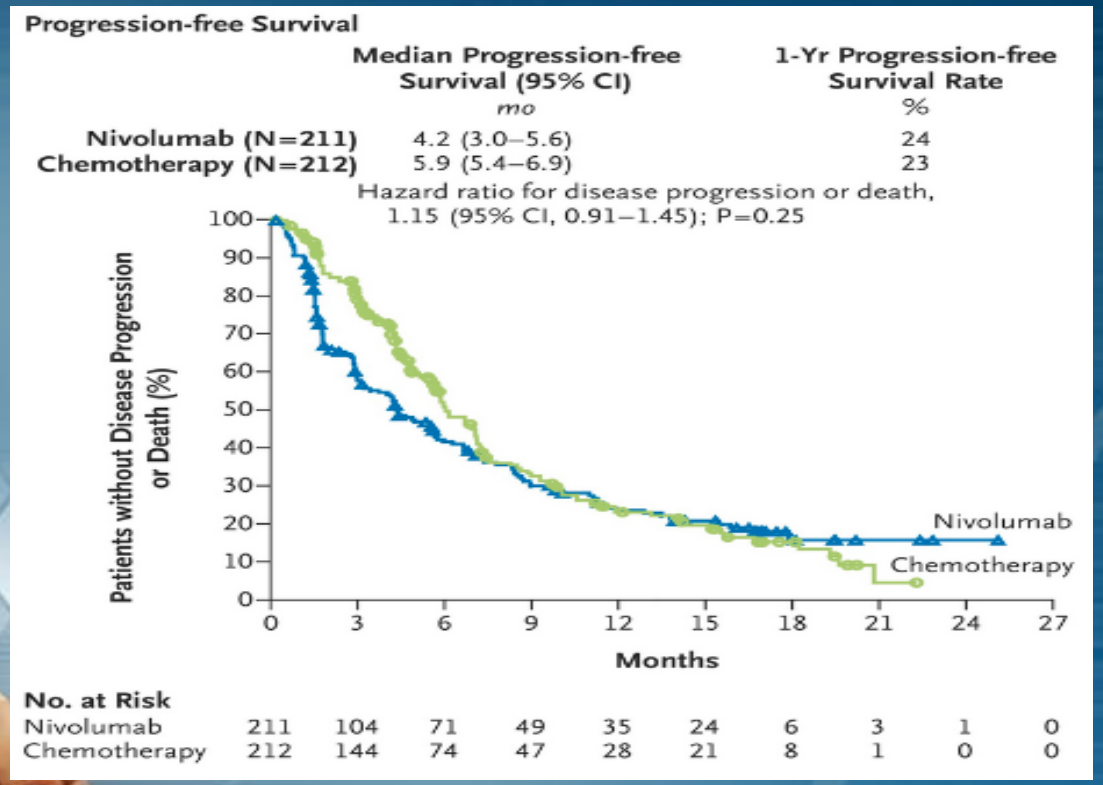
OS benefit correlates with PD-L1 expression in this Non-SQ trial.

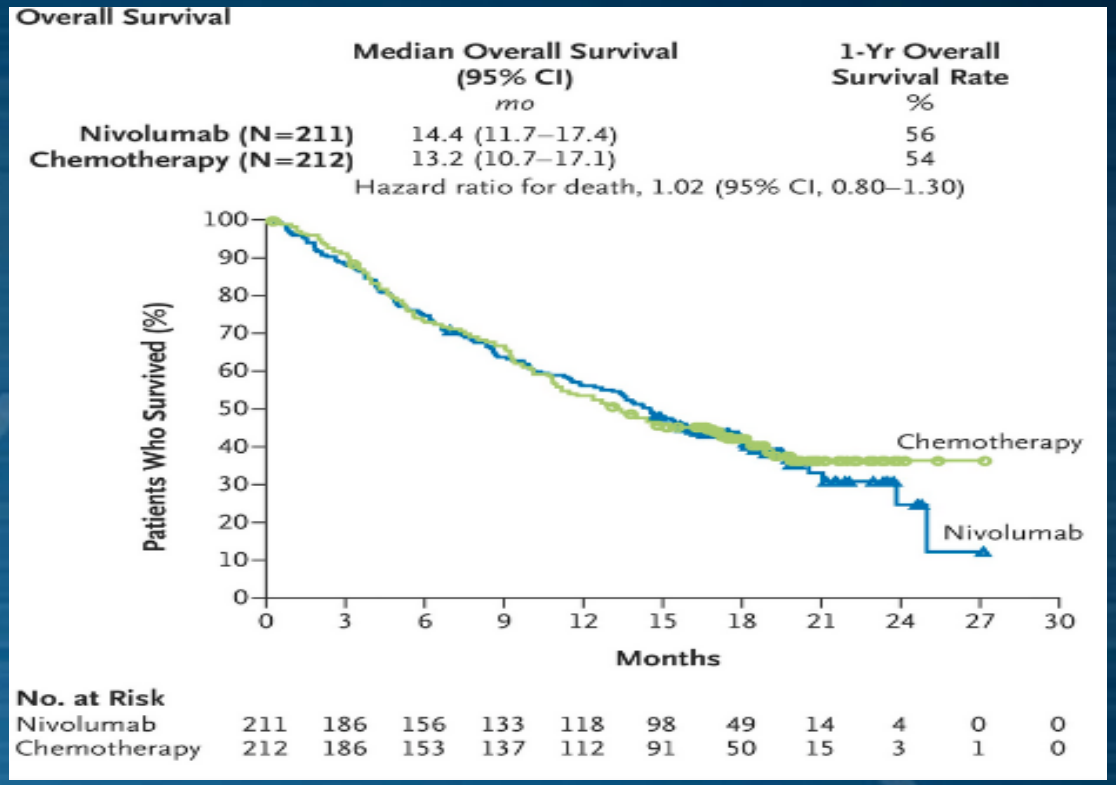
Paz--Ares et al. ASCO 2015, LBA109.

First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer CheckMate 026

The NEW ENGLAND JOURNAL of MEDICINE

- Progression-free Survival and Overall Survival among Patients with a Programmed Death Ligand 1 Expression Level of 5% or More.





5-Year Long-Term Overall Survival for Patients With Advanced NSCLC Treated With Pembrolizumab: Results From KEYNOTE-001

Edward B. Garon,[1] Matthew D. Hellmann,[2] Enric Carcereny,[3] Natasha B. Leighl,[4] Myung-Ju Ahn,[5] Joseph Paul Eder,[6] Ani S. Balmanoukian,[7] Charu Aggarwal,[8] Leora Horn,[9] Amita Patnaik,[10] Matthew Gubens,[11] Suresh S. Ramalingam,[12] Enriqueta Felip,[13] Cathie Scalzo,[14] Erin Jensen,[14] Debra A. Kush, [14] Rina Hui[15]

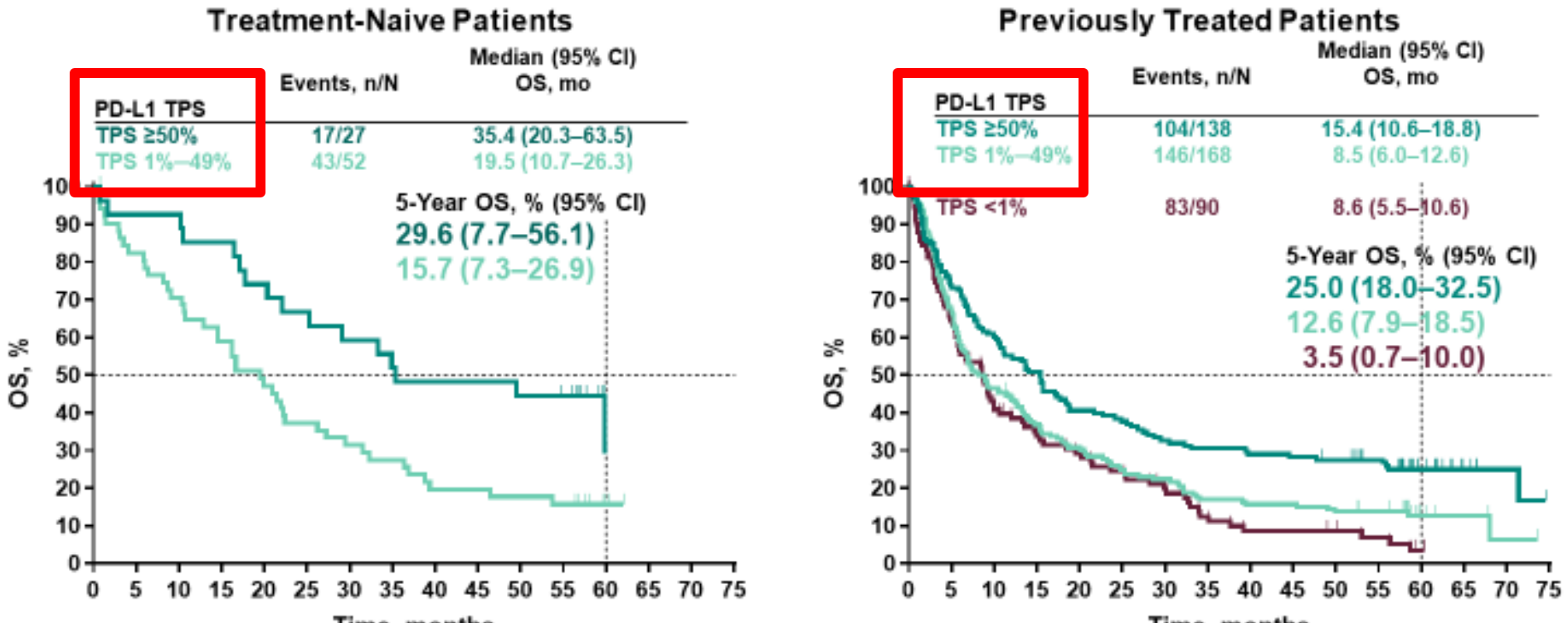
- [1]David Geffen School of Medicine at the University of California, Los Angeles, Santa Monica, CA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Catalan Institute of Oncology Badalona, Badalona, Spain; [4]Princess Margaret Cancer Centre, Toronto, ON, Canada; [5]Samsung Medical Center, Seoul, South Korea; [6]Yale University, New Haven, CT, USA; [7]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [8]Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA, USA; [9]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [10]South Texas Accelerated Research Therapeutics, San Antonio, TX, USA; [11]University of California, San Francisco, San Francisco, CA, USA; [12]Winship Cancer Institute of Emory University, Atlanta, GA, USA; [13]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [14]Merck & Co., Inc., Kenilworth, NJ, USA; [15]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia

5-Year Long-Term Overall Survival for Patients With Advanced NSCLC Treated With Pembrolizumab:

Results From KEYNOTE-001

Overall Survival

By PD-L1 Tumor Proportion Score (TPS)



n, number of patients who died; N, number of patients in the subgroup; OS, overall survival; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.
[a]PD-L1 TPS <1% group not presented because of small patient numbers (n = 12).

KEYNOTE 189

Gandhi KN189
AACR 2018

KEYNOTE-189 Study Design (NCT02578680)

Key Eligibility Criteria

- Untreated stage IV nonsquamous NSCLC
- No sensitizing *EGFR* or *ALK* alteration
- ECOG PS 0 or 1
- Provision of a sample for PD-L1 assessment
- No symptomatic brain metastases
- No pneumonitis requiring systemic steroids

Stratification Factors

- PD-L1 expression (TPS[a] <1% vs ≥1%)
- Platinum (cisplatin vs carboplatin)
- Smoking history (never vs former/current)

R (2:1)

N = 410

Pembrolizumab 200 mg + Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 OR Cisplatin 75 mg/m^2 Q3W for 4 cycles

Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m^2 Q3W

N = 206

Placebo (normal saline) + Pemetrexed 500 mg/m^2 + Carboplatin AUC 5 OR Cisplatin 75 mg/m^2 Q3W for 4 cycles

Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m^2 Q3W

PD[b]

Pembrolizumab 200 mg Q3W for up to 35 cycles

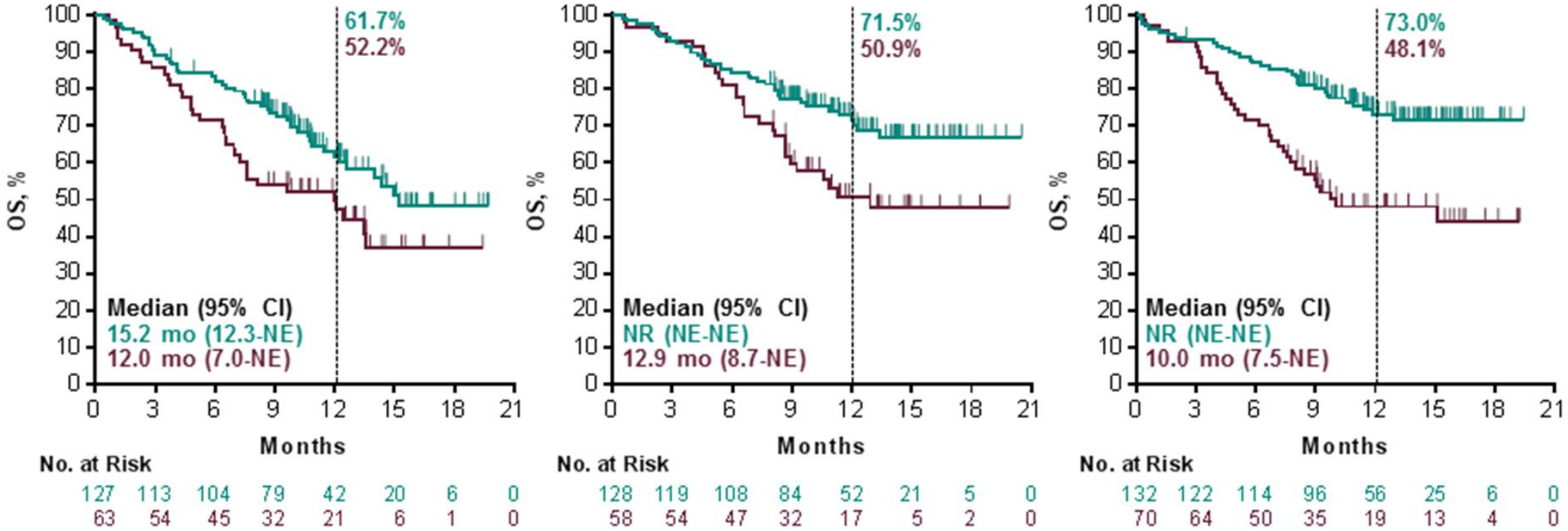
[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

KEYNOTE 189

Gandhi KN189
AACR 2018

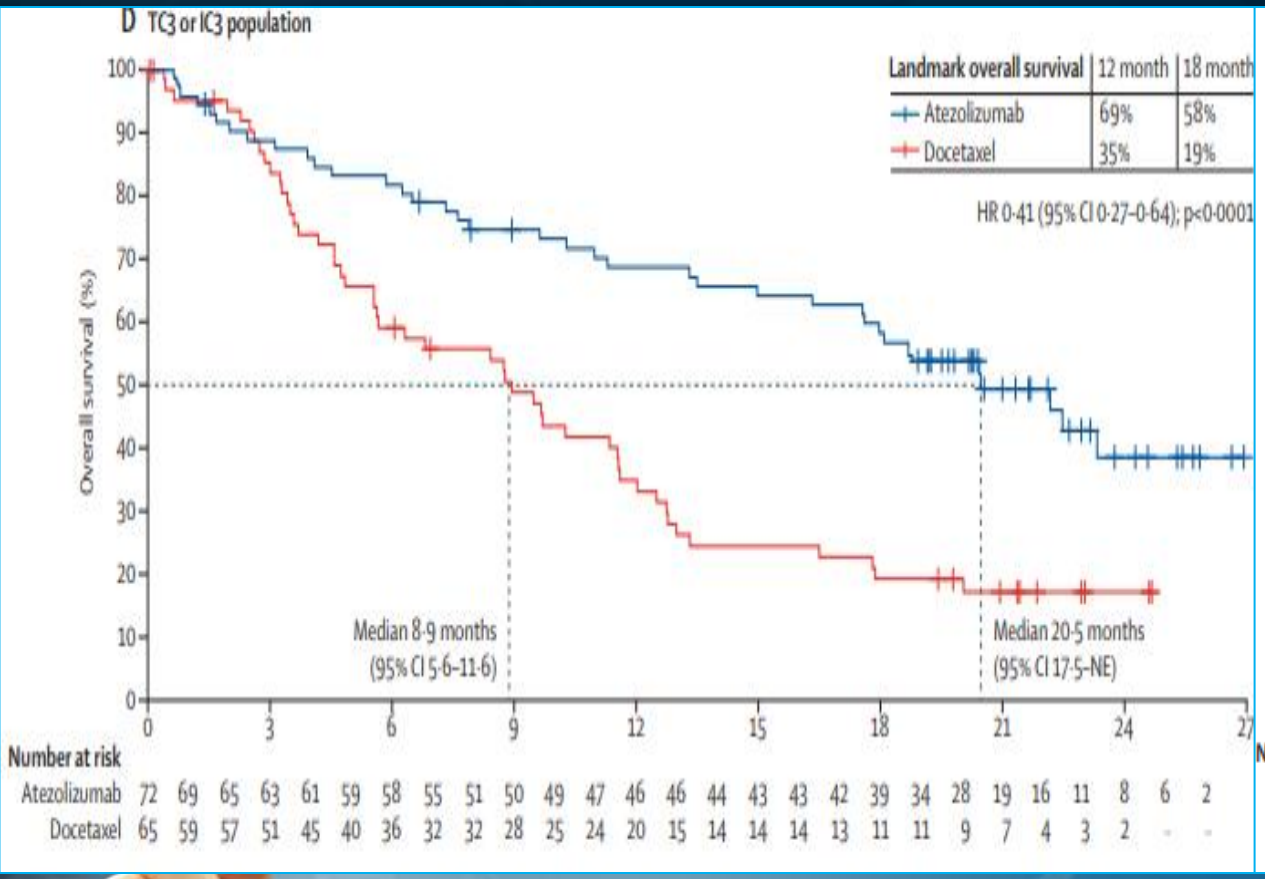
Overall Survival by PD-L1 TPS

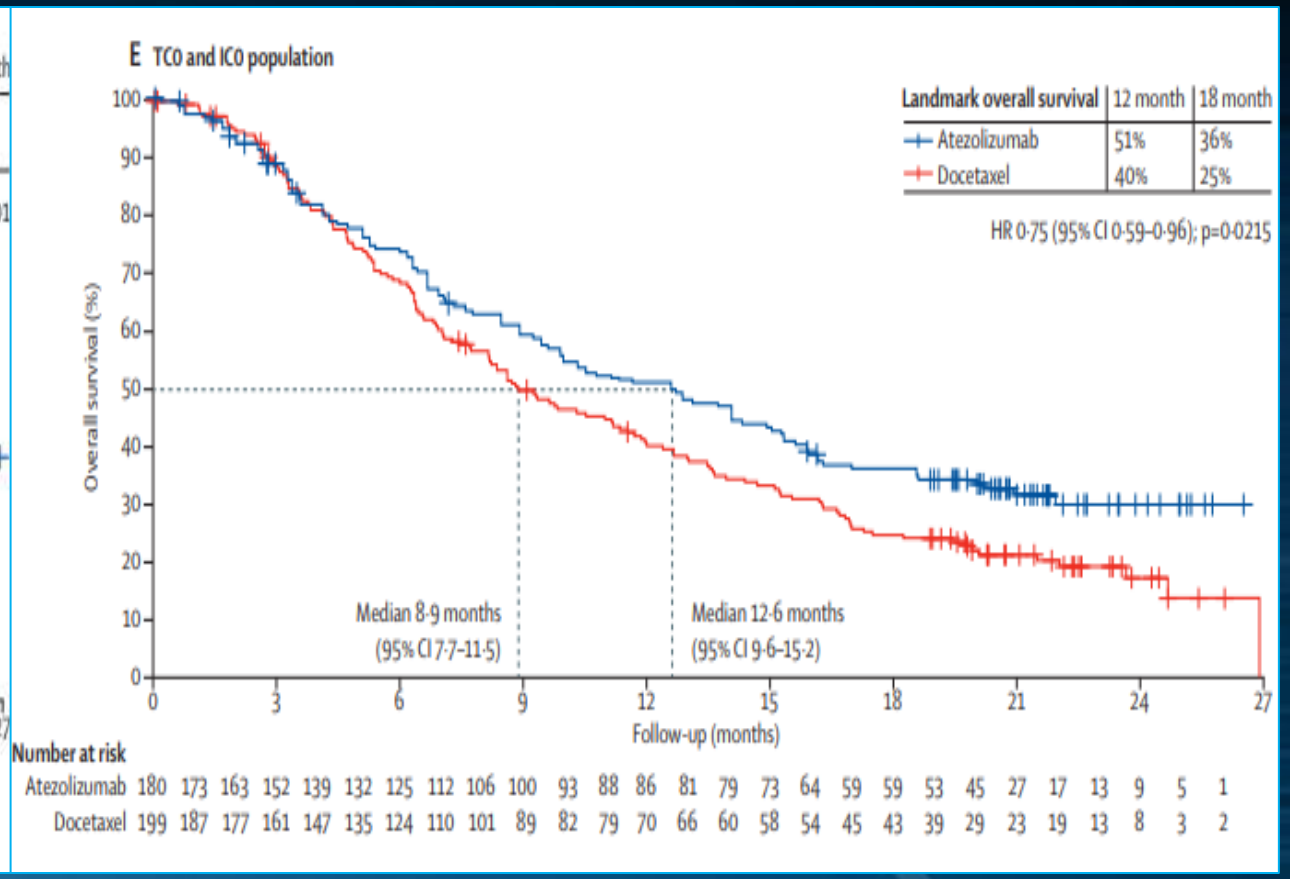
	TPS <1% Events	HR (95% CI)	P[a]	TPS 1-49% Events	HR (95% CI)	P[a]	TPS ≥50% Events	HR (95% CI)	P[a]
Pembro/Pem/Plat	38.6%	0.59	0.0095	28.9%	0.55	0.0081	25.8%	0.42	0.0001
Placebo/Pem/Plat	55.6%	(0.38-0.92)		48.3%	(0.34-0.90)		51.4%	(0.26-0.68)	



[a]Nominal and one-sided. Data cutoff date: Nov 8, 2017.

Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial

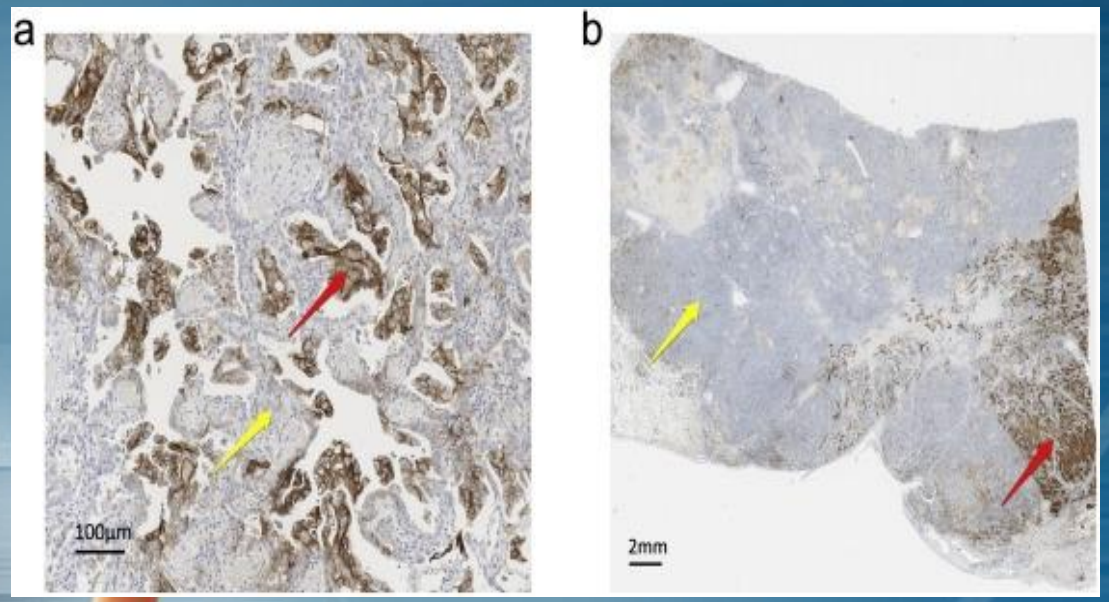




PD-L1

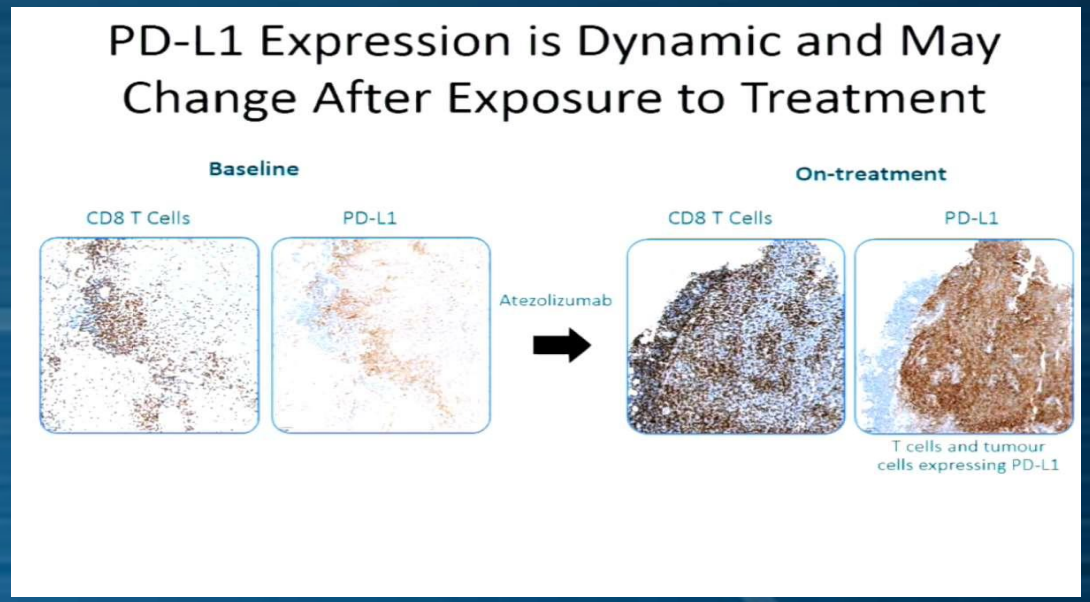
Θετική συσχέτιση με την ανταπόκριση στη θεραπεία με αναστολείς PD-1/PD-L1 σε όλες τις μελέτες

Ετερογένεια έκφρασης



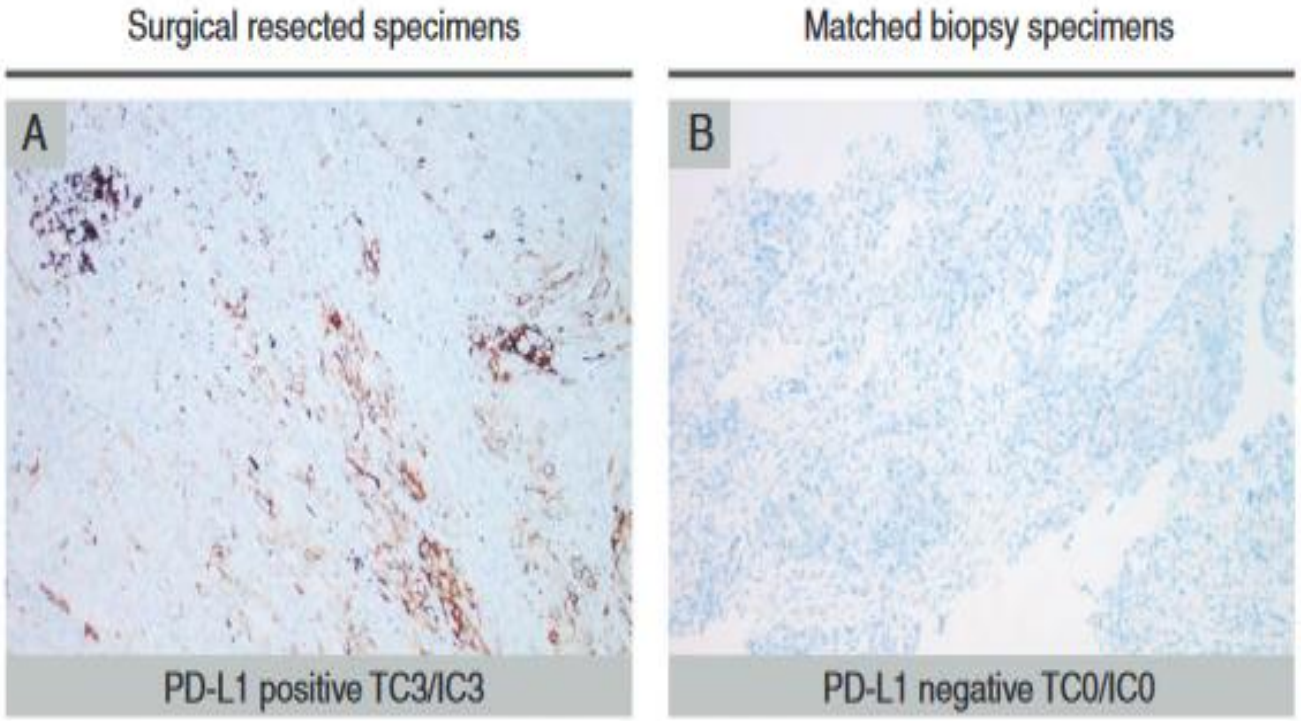
Haragan et al. Lung cancer 2019

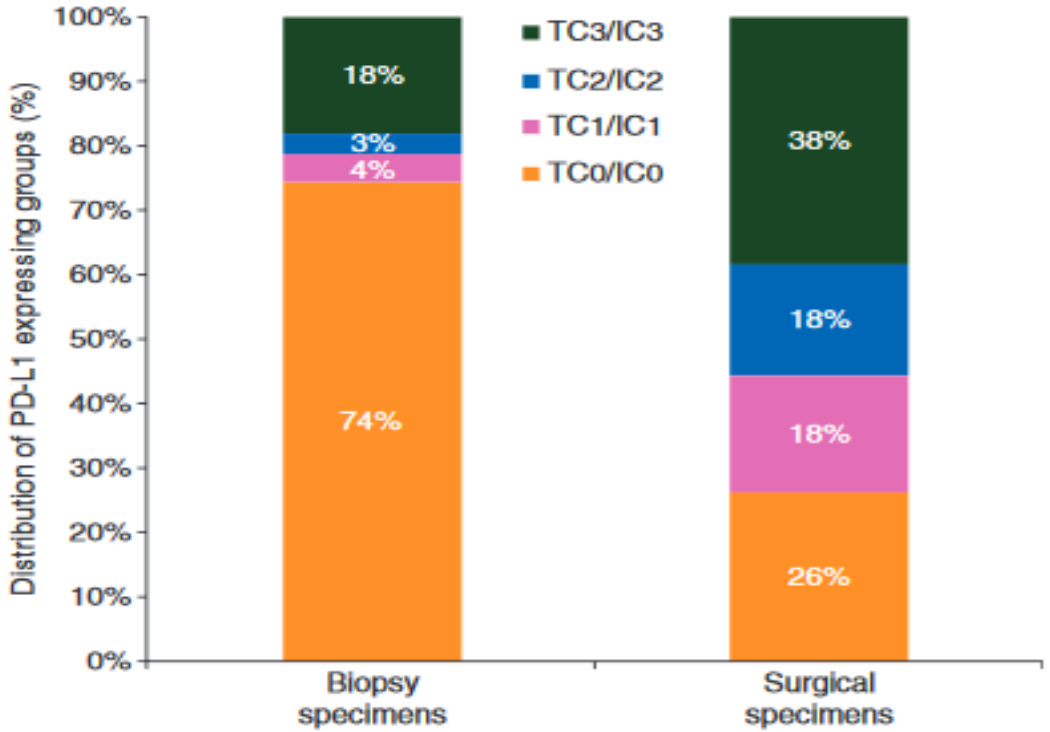
Δυναμική έκφραση



Powderly et al. ASCO 2013

Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies

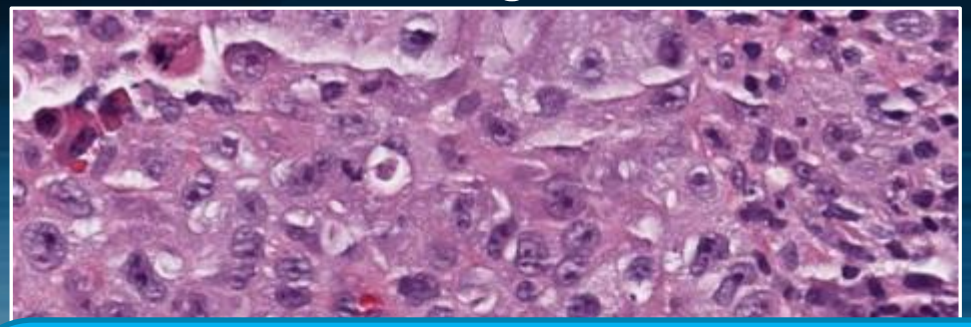




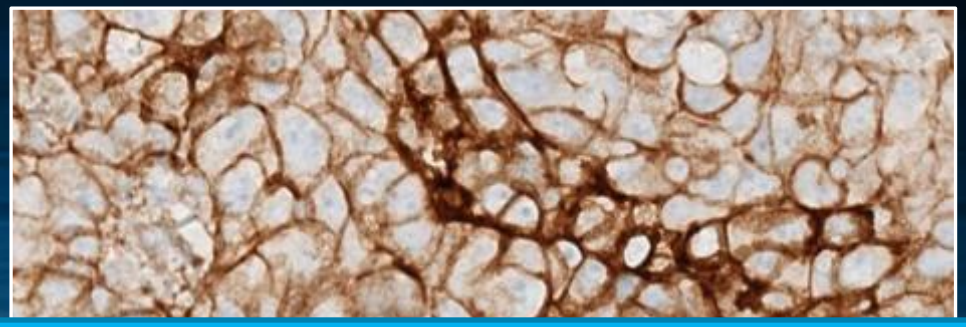
M. Ilie1, E. Long-Mira et al.Annals of Oncology27: 147–153, 2016doi:10.1093/annonc/mdv489Published online 19 October 201

PD-L1–Positive NSCLC: Only Membrane Staining Is Positive

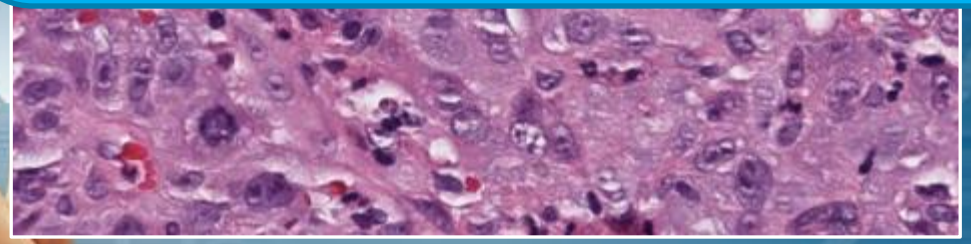
H&E Staining of NSCLC

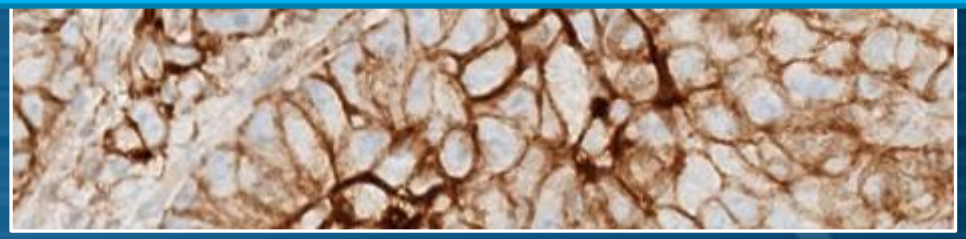


Membrane PD-L1 Staining of NSCLC



- ΖΩΝΤΑΝΟΣ ΙΣΤΟΣ
- ΌΧΙ ΕΚΦΥΛΙΣΜΕΝΑ ΚΥΤΤΑΡΑ



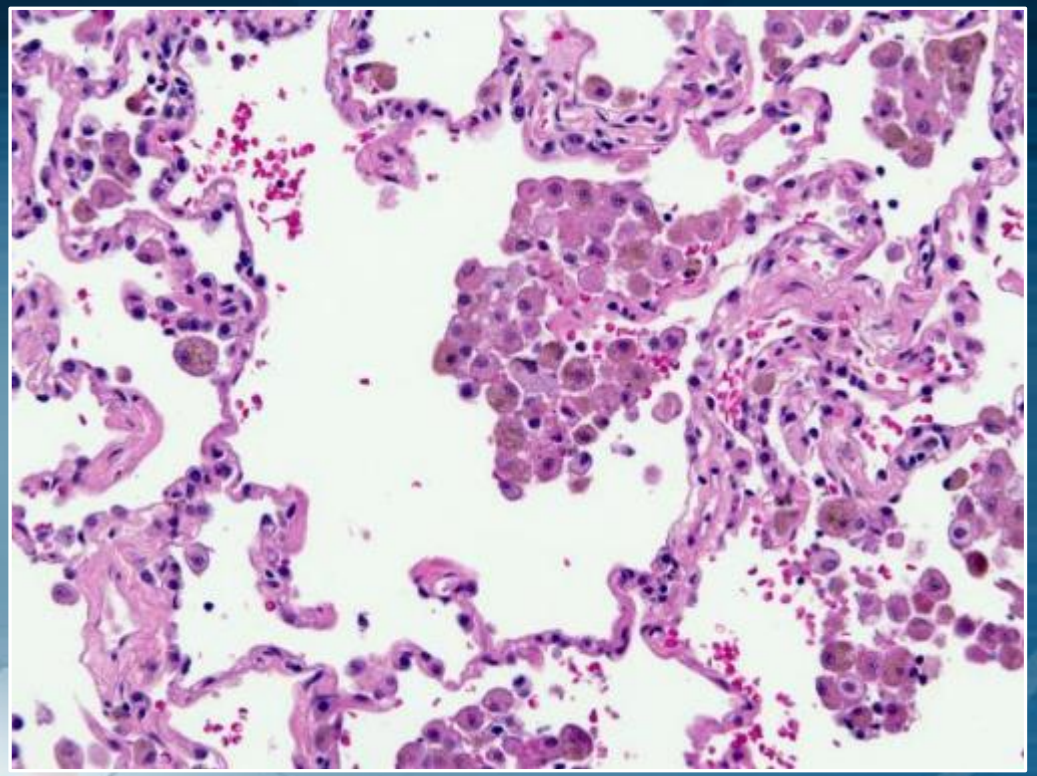


Images provided courtesy of Sanjay Mukhopadhyay, MD. Cleveland Clinic.

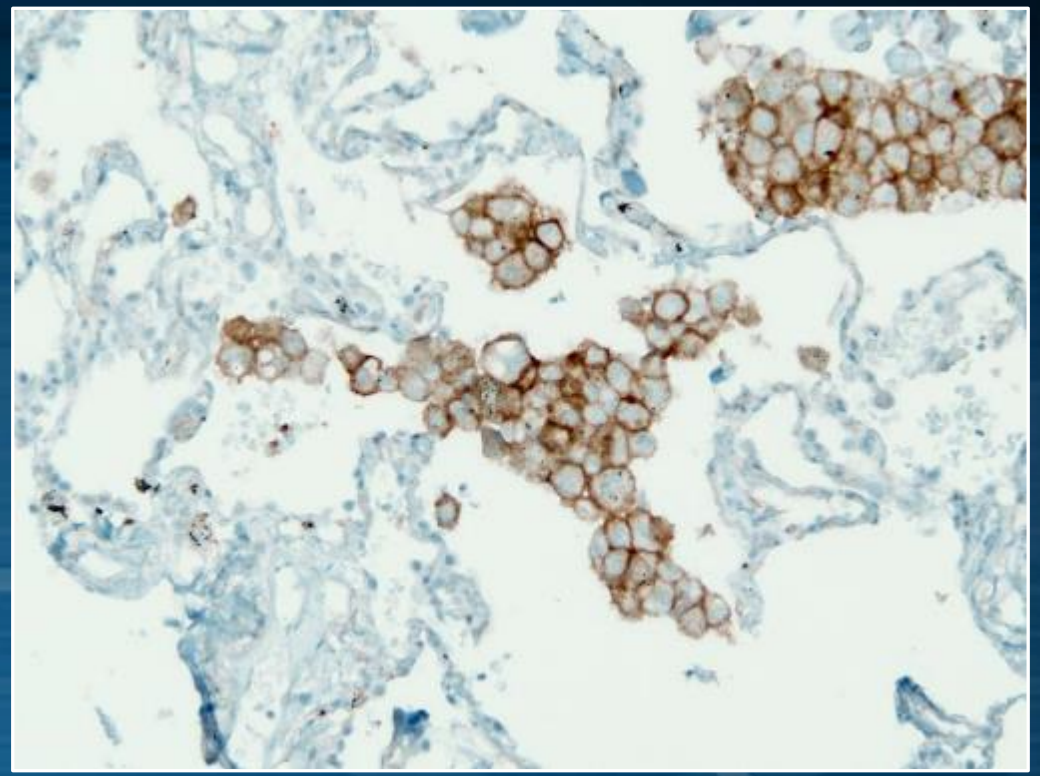
Slide credit: clinicaloptions.com

PD-L1–Positive NSCLC: Macrophages Are Positive for PD-L1

Macrophages (H&E)



Macrophages (PD-L1 Staining)

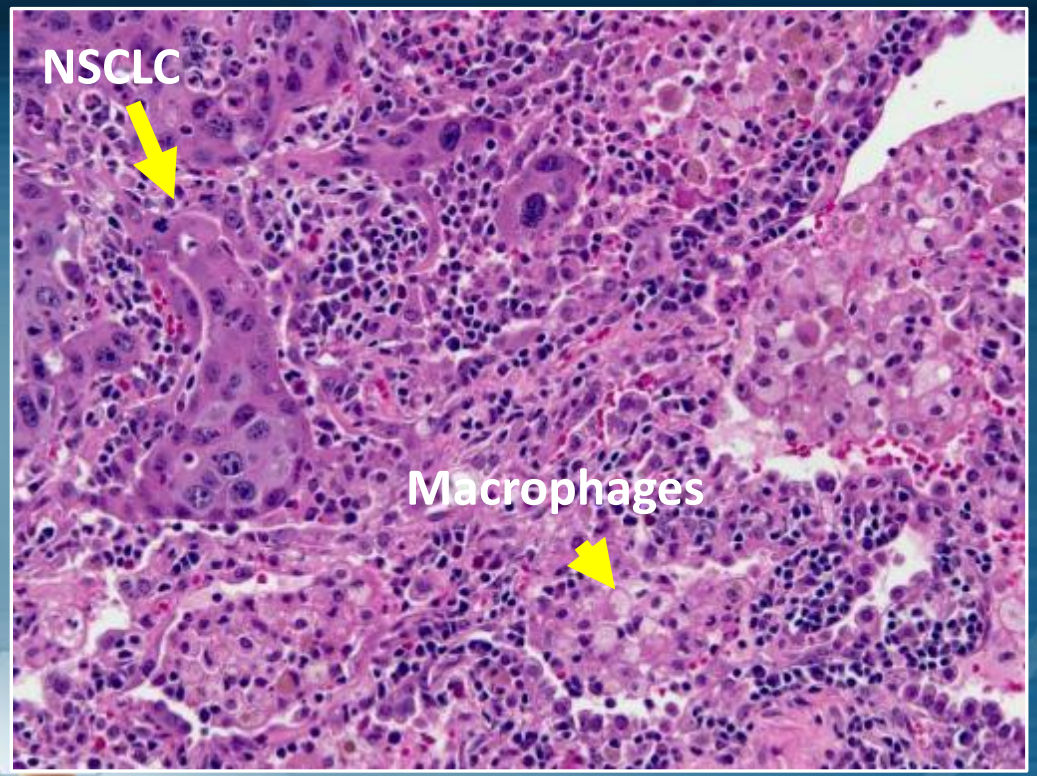


Images provided courtesy of Sanjay Mukhopadhyay, MD. Cleveland Clinic.

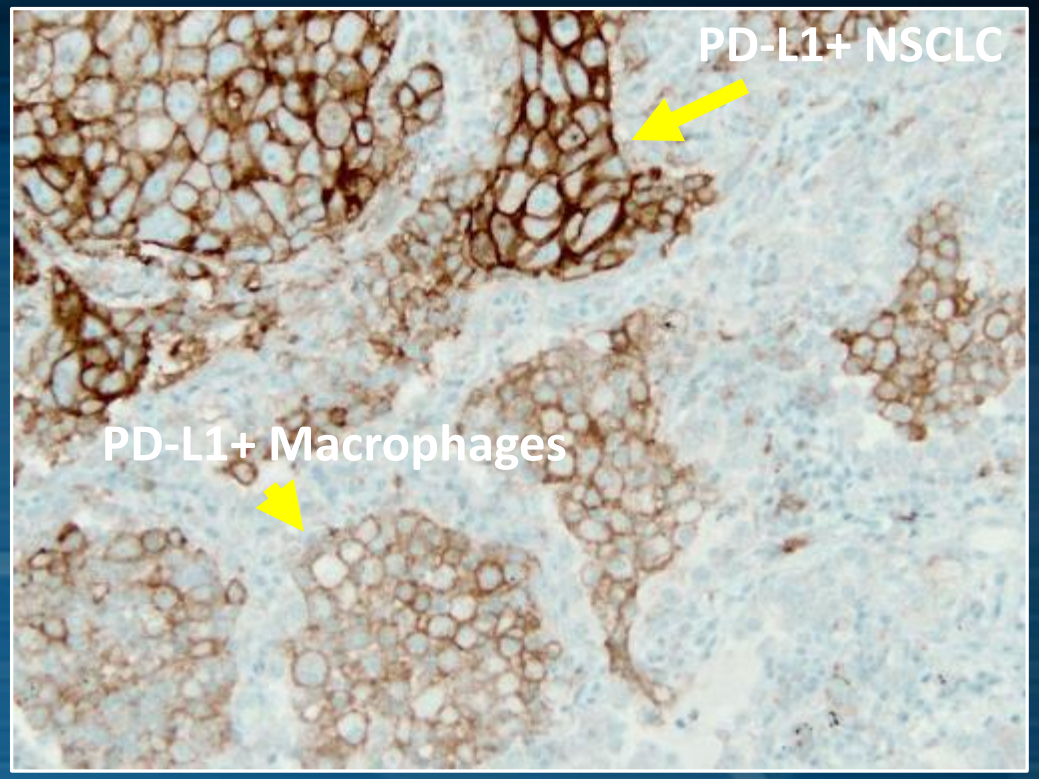
Slide credit: clinicaloptions.com

PD-L1–Positive NSCLC: Macrophages Are Positive for PD-L1

NSCLC and Macrophages (H&E)



NSCLC and Macrophages (PD-L1 Staining)



22C3 PLATFORM

Images provided courtesy of Sanjay Mukhopadhyay, MD. Cleveland Clinic.

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Potential explanations why PD-l1 expression might not predict benefit from PD-1 or PD-l1 inhibition

Hypothesis

PD-L1 expression apparently not necessary

Evidence

PD-L1 absent by IHC but clinical benefit seen from inhibition of PD-1 or PD-L1

Potential explanations

- Spatial and/or temporal variability in PD-L1 expression within tumour (sampling error)
- Incomplete sensitivity of IHC in the detection of PD-L1, with variation between assays (false-negative result)
- PD-L2, the alternative ligand for PD-1, could provide a bypass mechanism for immunosuppression, leading to responses of PD-L1– tumours to anti-PD-1 antibodies, although in theory , not to anti-PD-L1 antibodies

Nature Reviews | Clinical Oncology *D. Ross Camidge1*, Robert C. Doebele1 and Keith M. Kerr* https://doi.org/10.1038/s41571-019-0173-9

Potential explanations why PD-l1 expression might not predict benefit from PD-1 or PD-l1 inhibition

Hypothesis

PD-L1 expression apparently not sufficient

Evidence

PD-L1 present by IHC but no clinical benefit from inhibition of PD-1 or PD-L1

Potential explanations

- Elevation in PD-L1 expression for reasons other than in response to a primed immune attack (for example, intrinsic induction in some oncogene-addicted NSCLCs)
- Engagement of other immune checkpoints in addition to the PD-1–PD-L1 axis and/or immune suppression or deficiencies with different causes
- The measured extent of PD-L1 positivity (a continuous variable) might be insufficient for a response to PD-1 or PD-L1 inhibition, reflecting substantial heterogeneity in the underlying tumour biology (including neoantigen profiles and mechanisms of immune escape

Nature Reviews | Clinical Oncology *D. Ross Camidge1*, Robert C. Doebele1 and Keith M. Kerr* https://doi.org/10.1038/s41571-019-0173-9

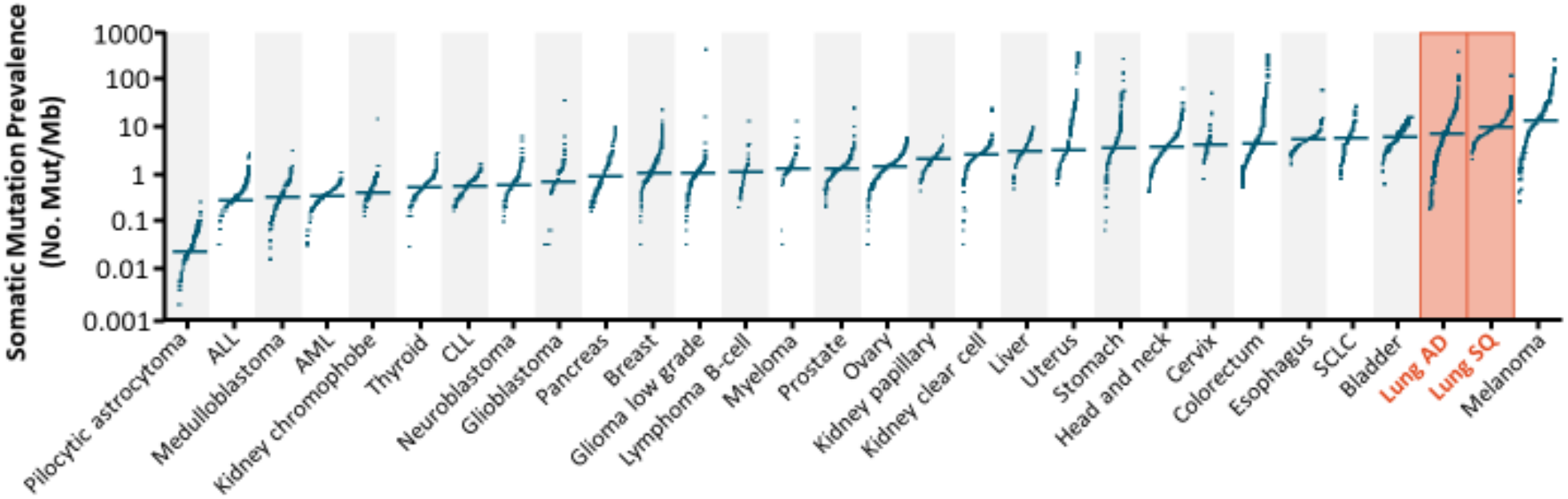
Tumor Mutation Burden TMB

- The sum of somatic (exonic) mutations in a tumor specimen
- Metric system: mutations per Megabase
- Synonyms:

- Συνολικό φορτίο μεταλλάξεων

Tumor Mutation Burden TMB

Prevalence of Somatic Mutations Across Tumor Types

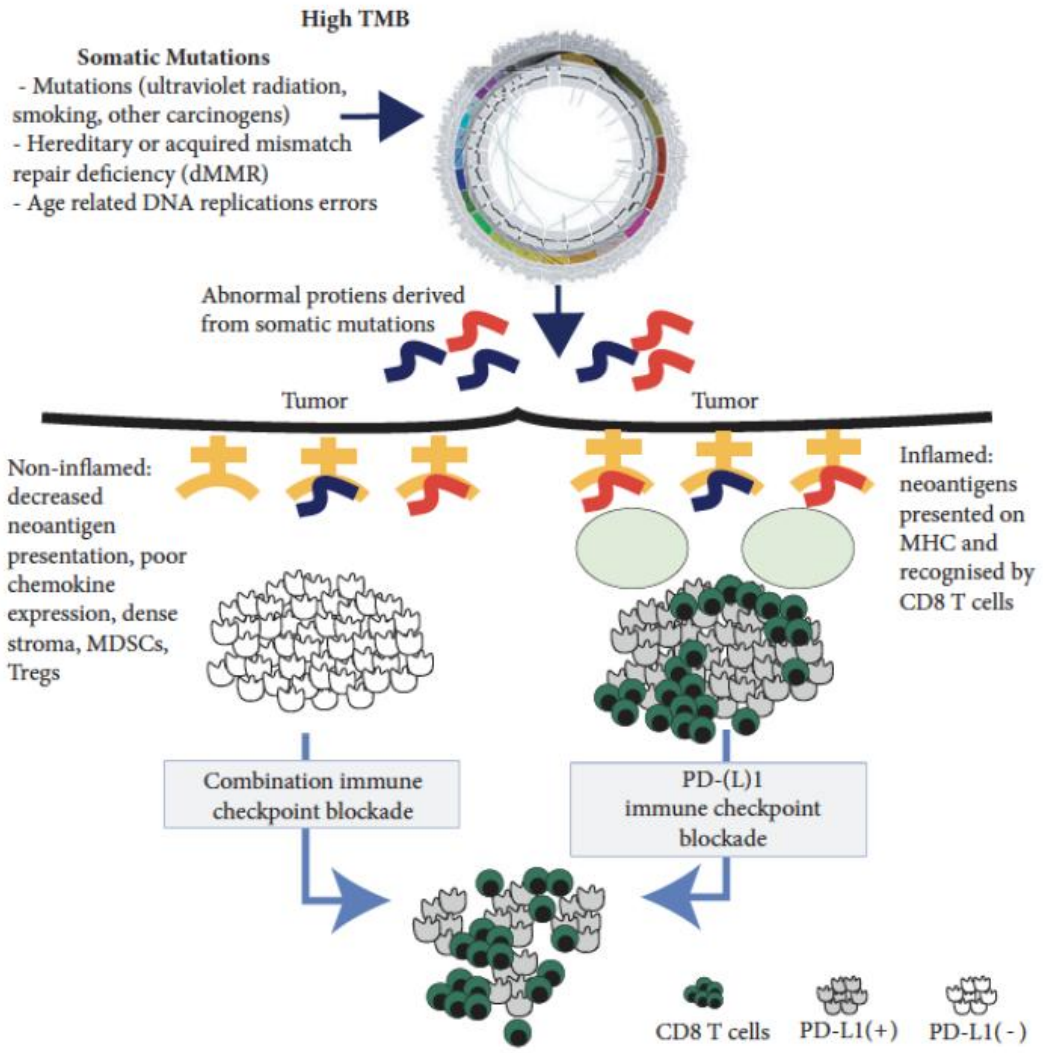


- NSCLC has among the highest prevalence of somatic mutations: 0.1-100 Mut/Mb

Alexandrov. Nature. 2013;500:415. Lawrence. Nature. 2013;499:214.

Slide credit: clinicaloptions.com

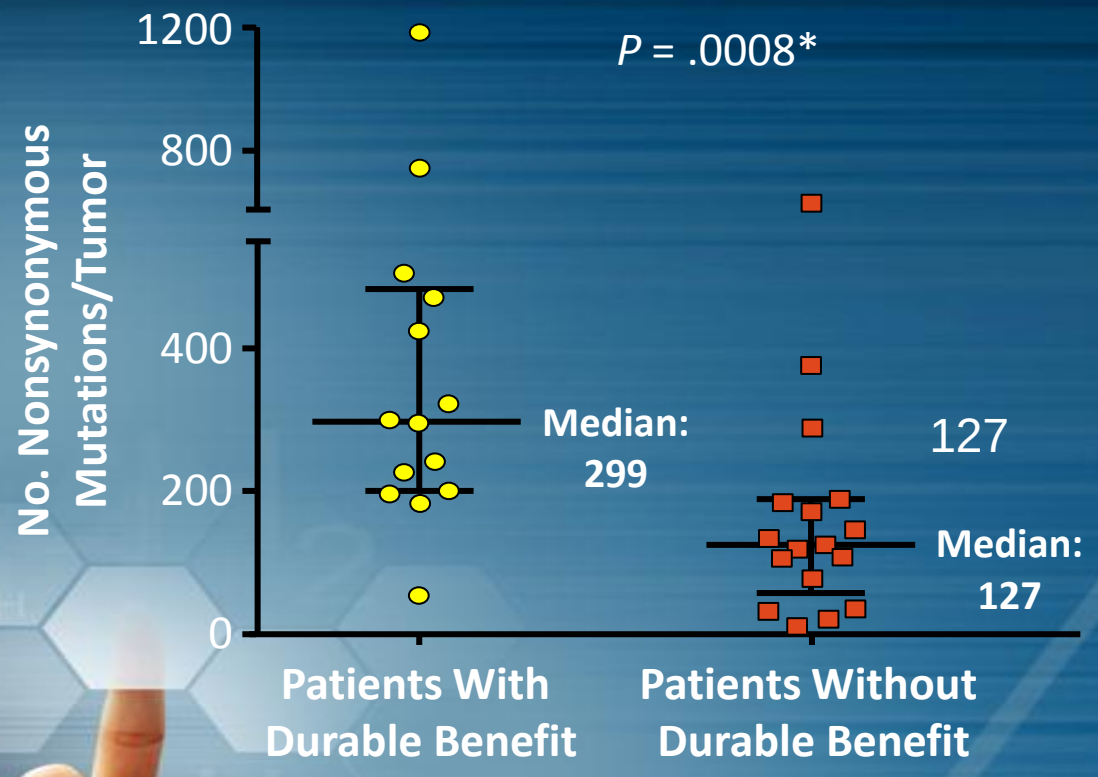
Connection between TMB, neoantigens and immunotherapy



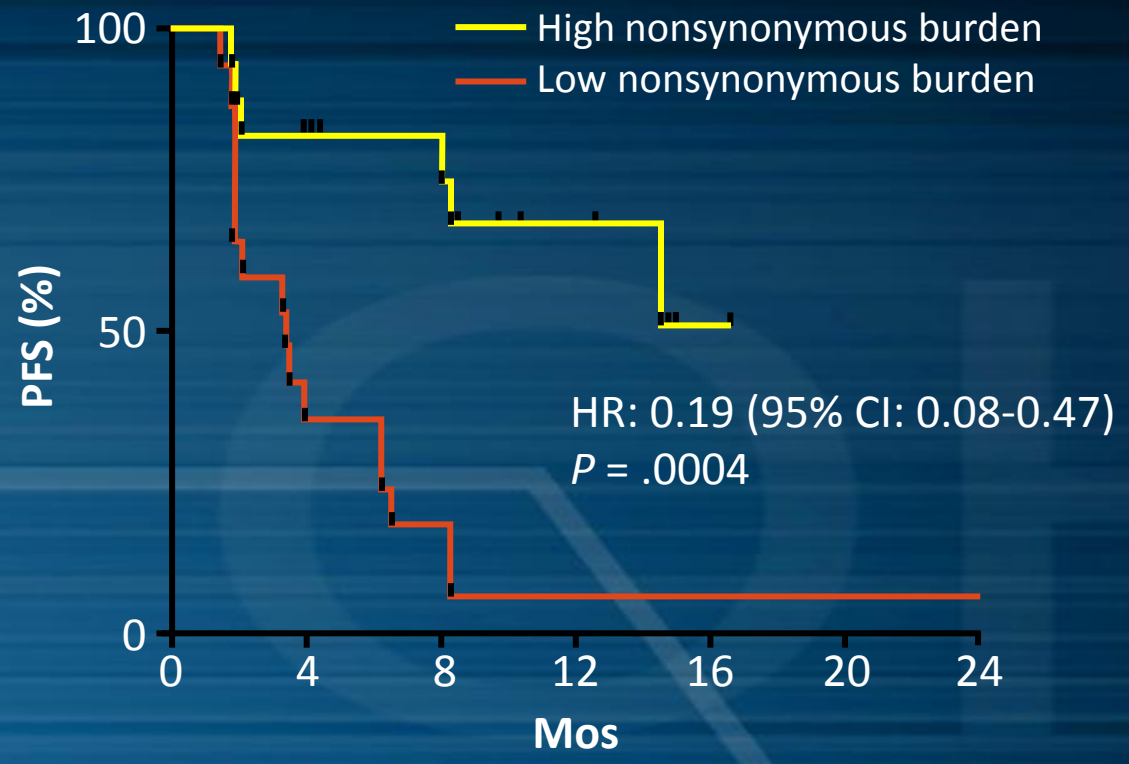
Chan et al. Ann Oncol 2019

Tumor Mutation Burden and ICI Efficacy in NSCLC

Nonsynonymous Mutation Burden by Durable Benefit With IO for Entire Set of Sequenced Tumors



PFS by Nonsynonymous Mutation Burden for Entire Set of Sequenced Tumors



*By Mann-Whitney test.

Rizvi. Science. 2015;348:124.

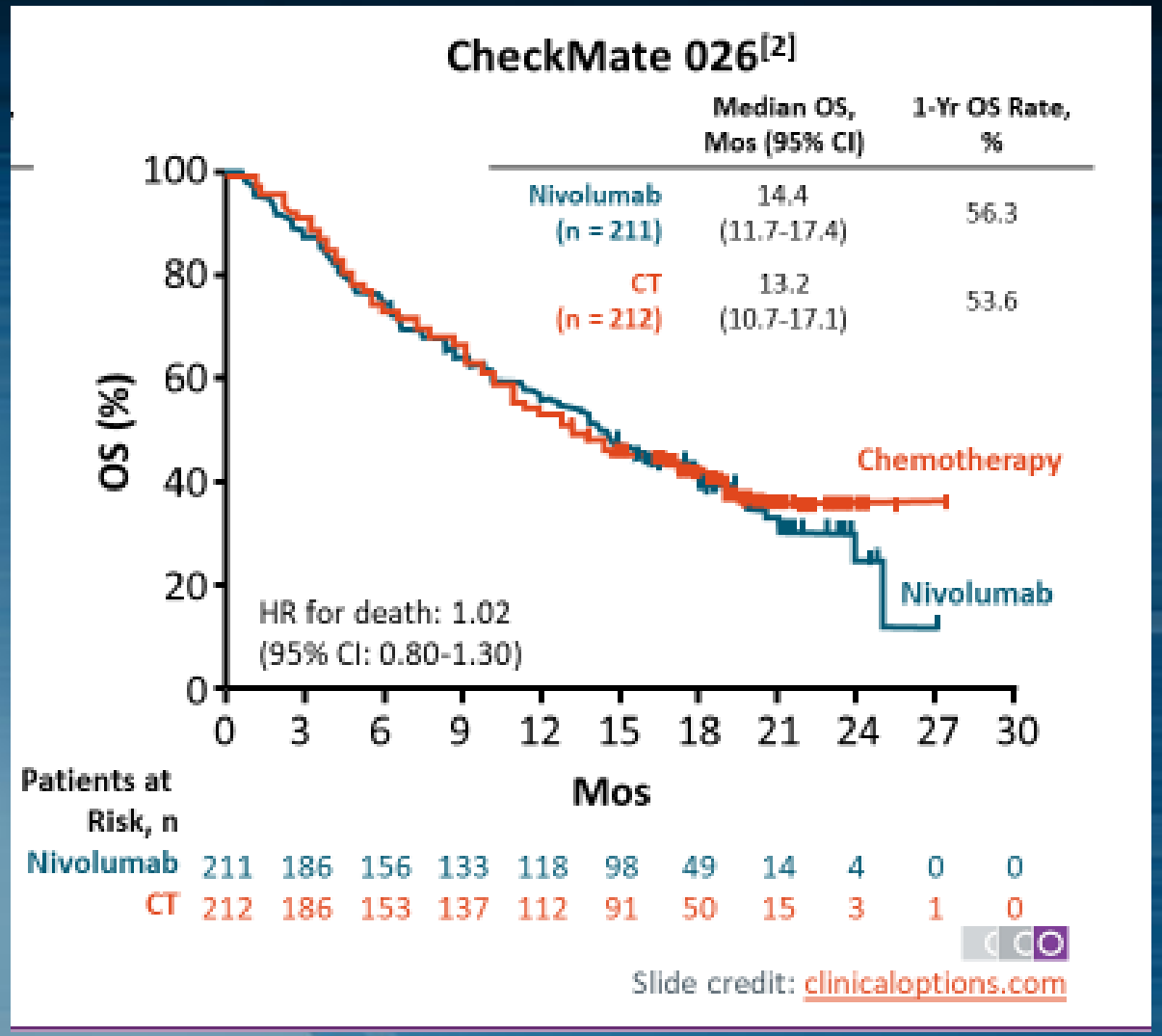
Slide credit: clinicaloptions.com

Selected studies on TMB analysis in lung cancer patients

Drug trial	Study type	Pts, n	Patient population	TMB method & cutoff (high *vs.* low)	Clinical outcomes	Author year
Pembrolizumab	Retrospective	16 (D); 18 (V)^	Advanced NSCLC	WES: high: ≥178 nonsynonymous mutations	In both discovery and validation cohorts, higher TMB was associated with better objective responses, durable clinical benefits and PFS	Rizvi NA, 2015 (10)
Nivolumab CheckMate 026	Exploratory retrospective analysis of phase III study	312	Stage IV or recurrent NSCLC with PD-L1 ≥1%; first line	WES: high TMB >243; low TMB <100 mutations	High TMB pts: PFS 9.7 *vs.* 5.8 months (HR 0.62; 95% CI, 0.38 to 1.00) and ORR (46.8% *vs.* 28.3%) compared to chemotherapy	Peters S, 2017 (11)
Nivolumab & ipilimumab CheckMate 012	Phase I	75	Advanced NSCLC	WES: high TMB > median, 158 mutations; low TMB ≤ median	ORR, DCB, PFS were superior in pts with high TMB *vs.* low TMB (ORR 51% *vs.* 13%, P=0.0005; DCB 65% *vs.* 34%, P=0.011; PFS HR 0.41)	Hellmann MD, 2018 (12)
Nivolumab + ipilimumab part of CheckMate 227	Part of phase III study	299	Stage IV or recurrent NSCLC; first line	FoundationOne CDx assay; high TMB: ≥10 mutations/Mb	PFS was significantly longer with 1st-line nivolumab + ipilimumab than chmo among pts with high TMB (mPFS: 7.2 *vs.* 5.5 months, HR 0.58, P<0.001)	Hellmann MD, 2018 (9)
Nivolumab + ipilimumab CheckMate 568	Phase II	288	Stage IV NSCLC; first line	FoundationOne CDx assay; high TMB: ≥10 Mut/Mb	ORR was >40% in TMB high patients	Ramalingam SS, 2018 (13)
Nivolumab ± ipilimumab CheckMate 032	Exploratory	211	Advanced SCLC	WES: TMB was grouped by tertiles: low, 0 to	In pts with TMB high *vs.* TMB low receiving Nivo + Ipi: ORR: 46.2%	Hellmann MD, 2018 (14)
PD-1 or PD-L1 inhibitors	Retrospective	240	Advanced NSCLC	Targeted NGS using MSK-IMPACT TMB was grouped into percentiles: high TMB >50%	More disease control and longer PFS for pts with TMB >50th percentile *vs.* pts with TMB <50th percentile	Rizvi H, 2018 (15)
Atezolizumab POPLAR & OAK	Retrospective	211 (D); 583 (V)*	Second-line or higher patients with advanced NSCLC	Blood-based TMB; bTMB ≥16 was selected for confirmatory; analysis	In both test (POPLAR) and validation (OAK) cohorts, bTMB reproducibly identified patients who derived an increased PFS benefit from atezolizumab	Gandara DR, 2018 (16)

Mariam Alexander J Thorac Dis. 2018 Nov; 10(Suppl 33): S3994–S3998.

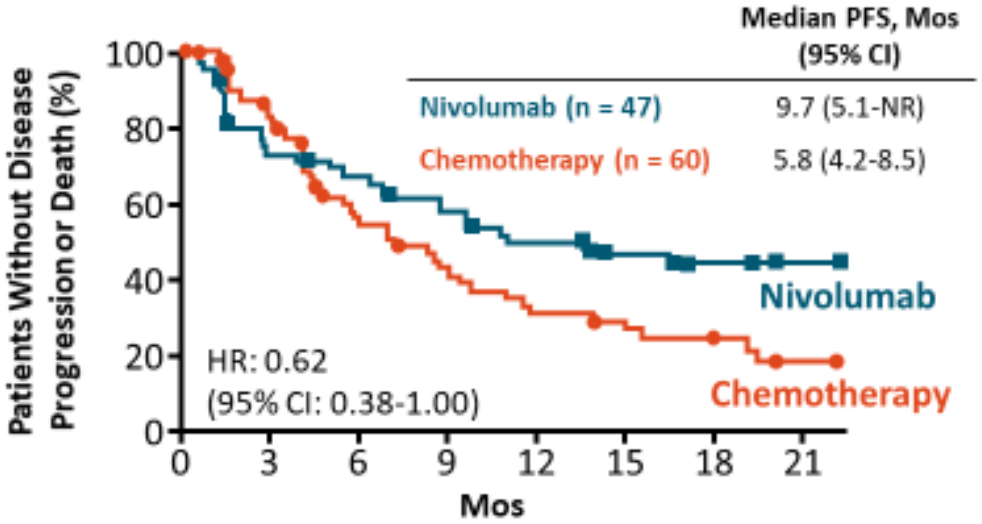
Frontline Protocols: OS With Single-Agent Immunotherapy in Advanced NSCLC



TMB as Selection Tool

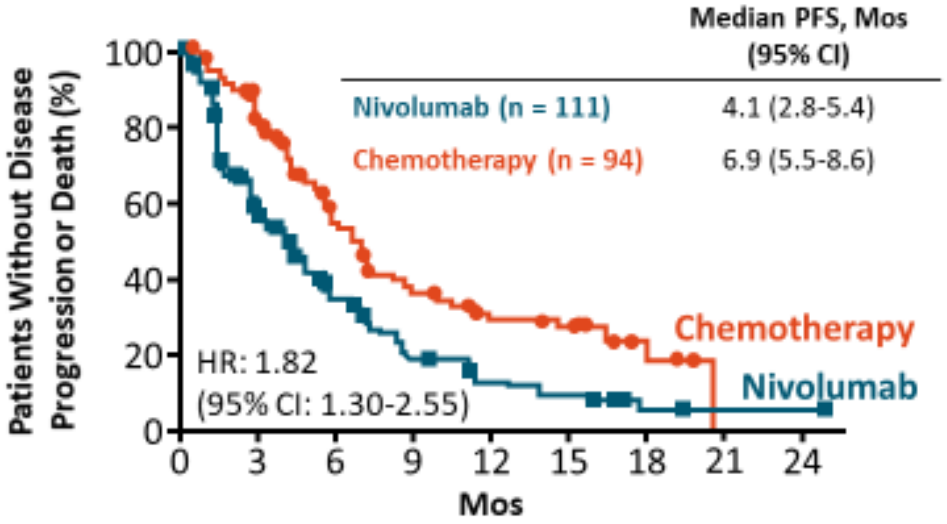
CheckMate 026: TMB as Selection Tool

Survival in Patients With High TMB: Nivolumab Better



Patients at Risk, n								
Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Survival in Patients With Low/Medium TMB: Chemo Better



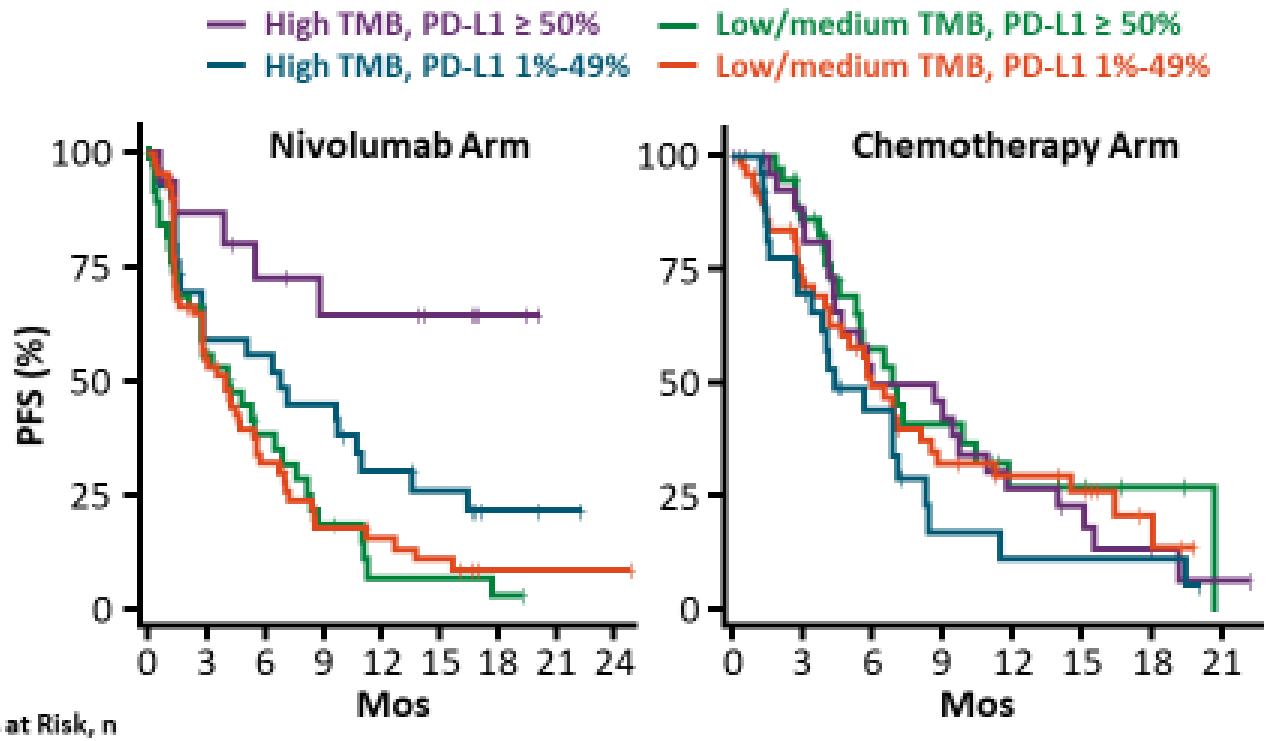
Patients at Risk, n									
Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

Carbone. NEJM. 2017;376:2415.

Slide credit: clinicaloptions.com

CheckMate 026: PFS by TMB Subgroup and PD-L1 Expression With Nivolumab in First-line NSCLC

- Exploratory analysis of patients from phase III CheckMate 026 evaluating single-agent nivolumab vs CT for advanced NSCLC
- Patients with high TMB/ high PD-L1 had best outcomes with nivolumab
- Trend toward patients with high TMB/int PD-L1 doing better than those with low/int TMB/high PD-L1



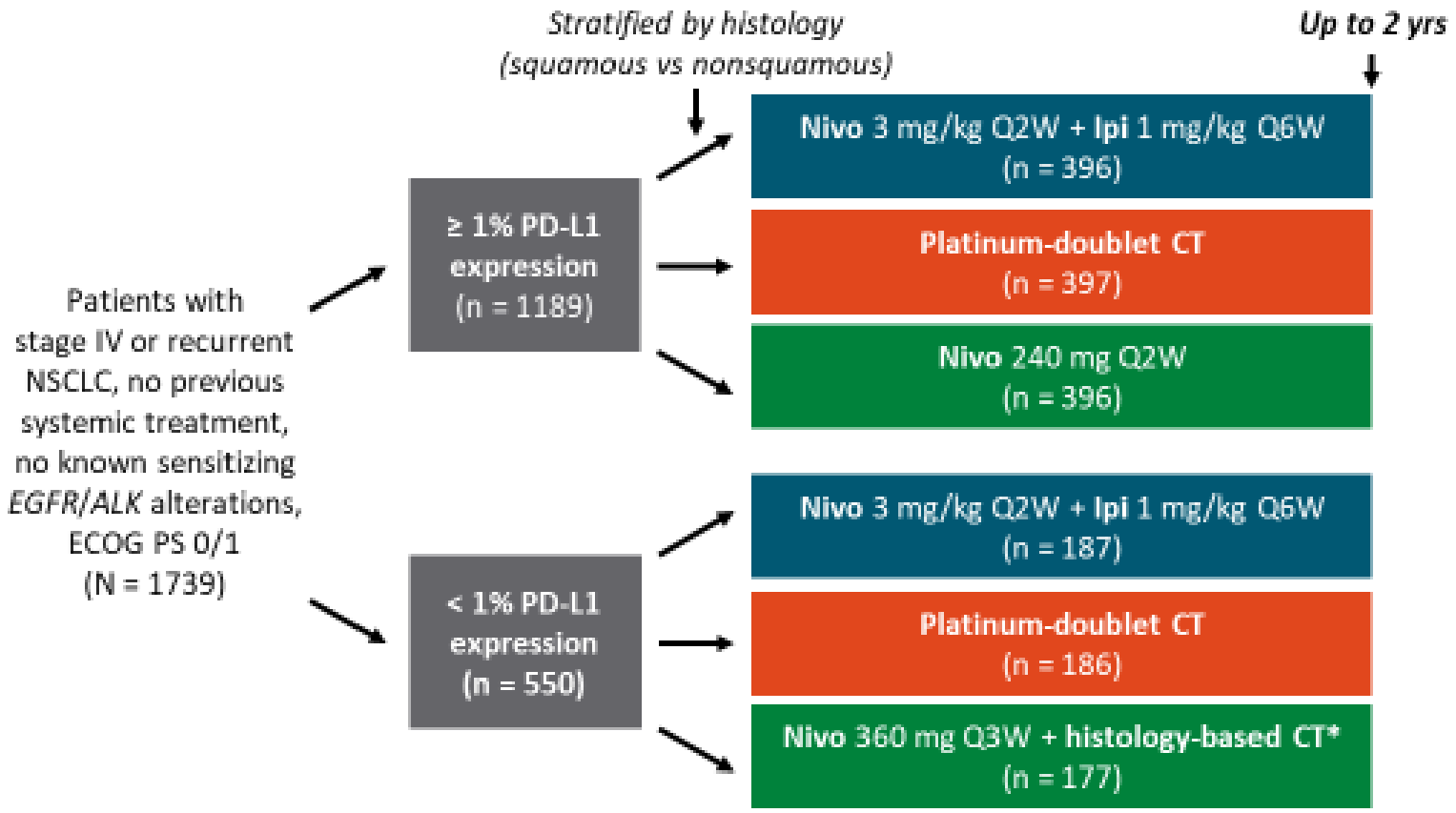
Patients at Risk, n																
High TMB, PD-L1 ≥ 50%	16	13	10	8	8	6	2	0	0	32	24	13	12	7	5	2	1
High TMB, PD-L1 1%-49%	31	17	16	13	8	6	2	1	0	28	18	9	3	2	2	2	0
Low/medium TMB, PD-L1 ≥ 50%	41	21	12	6	2	2	1	0	0	41	30	14	10	5	4	2	0
Low/medium TMB, PD-L1 1%-49%	70	33	18	9	7	5	1	1	1	53	35	23	13	10	8	3	0

Peters. AACR 2017. Abstr CT082.

Slide credit: clinicaloptions.com

CheckMate 227: First-line Nivolumab + Low-Dose Ipilimumab for Advanced NSCLC

- Randomized, open-label, multipart phase III trial

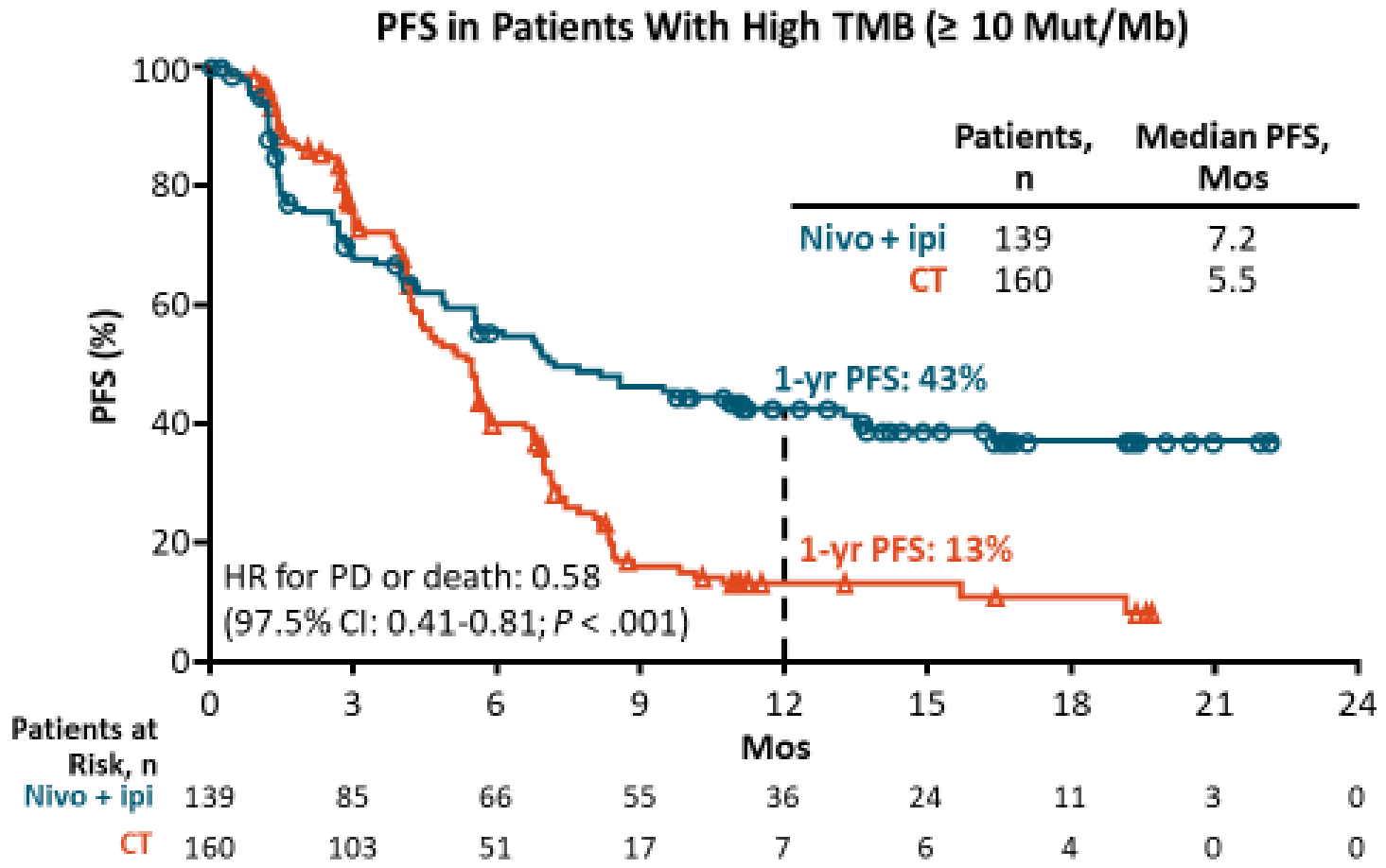


- **Coprimary endpoints for nivolumab + ipilimumab vs CT:**
  - **OS in patients with ≥ 1% PD-L1 expression**
  - **PFS in high TMB population**
- Secondary endpoints: PFS and OS for nivolumab + CT vs CT in patients with PD-L1 < 1%; OS for nivolumab vs CT in patients with PD-L1 ≥ 50%

Peters. ESMO 2019. Abstr LBA4_PR. Hellmann. NEJM. 2019;[Epub]. Hellmann. NEJM. 2018;378:2093.

Slide credit: clinicaloptions.com

CheckMate 227: PFS With Nivolumab + Ipilimumab by TMB

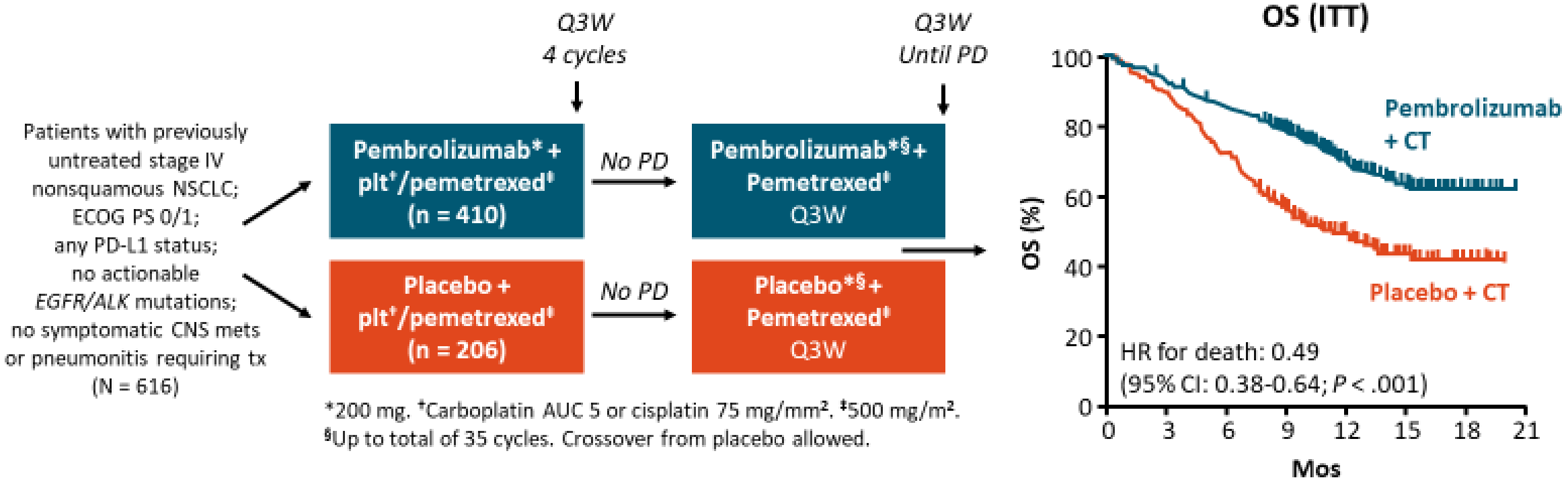


In patients with TMB < 10 Mut/Mb treated with nivo + ipi vs CT, the HR was 1.07 (95% CI: 0.84-1.35; $P = .0018$).

Hellmann. AACR 2018. Abstr CT077.

Slide credit: clinicaloptions.com

KEYNOTE-189: First-line Pembrolizumab + CT vs Placebo + CT in Stage IV Nonsquamous NSCLC

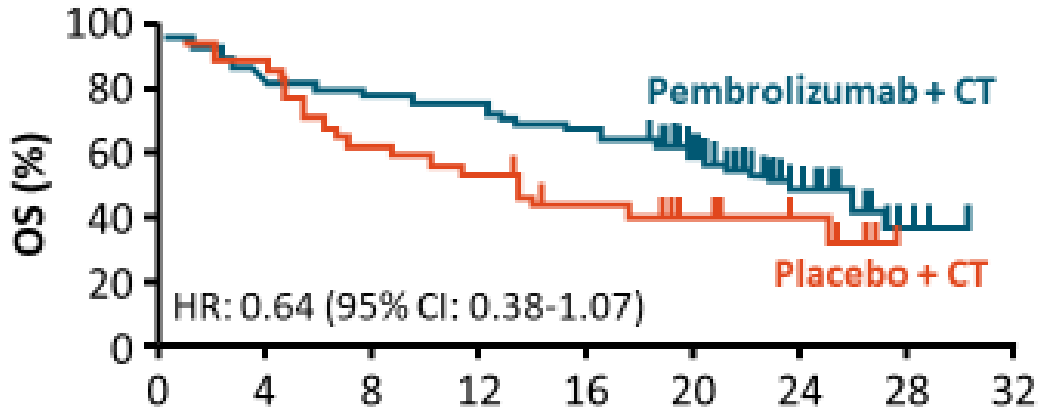


*200 mg. †Carboplatin AUC 5 or cisplatin 75 mg/mm². ‡500 mg/m². §Up to total of 35 cycles. Crossover from placebo allowed.

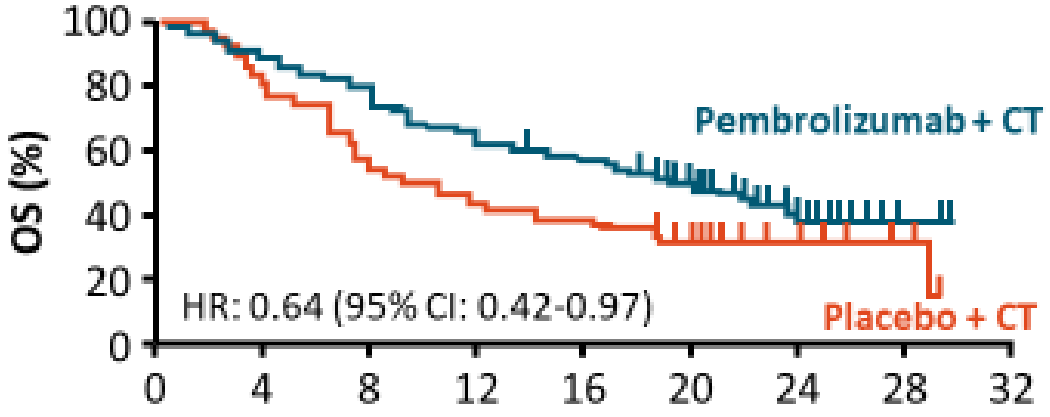
Gandhi. NEJM. 2018;378:2078.

Slide credit: clinicaloptions.com

KEYNOTE-189: Tissue TMB Analysis by WES



Patients at Risk, n									
Pembro + CT	100	83	78	74	67	44	19	4	0
Pbo + CT	34	30	21	18	13	9	5	0	0



Patients at Risk, n									
Pembro + CT	107	96	86	68	61	45	16	2	0
Pbo + CT	52	43	29	24	21	15	7	3	0

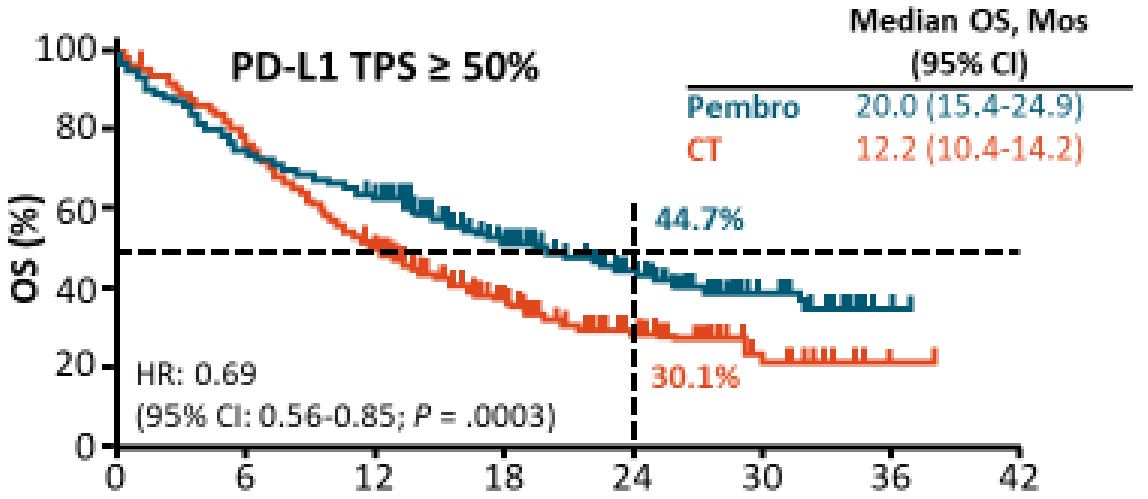
Garassino. WCLC 2019. Abstr OA04.06

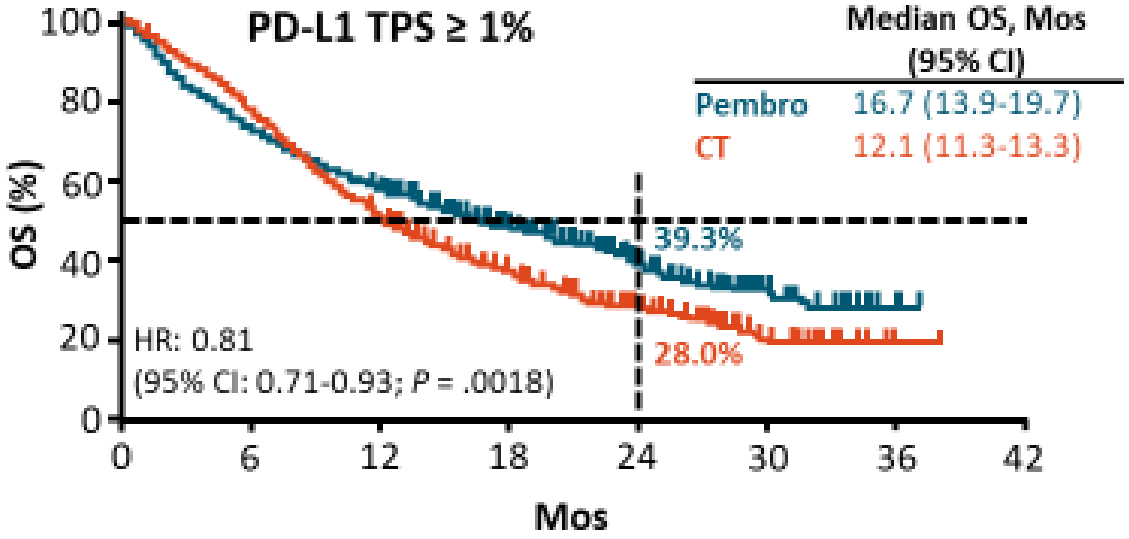
KEYNOTE-042: First-line Pembrolizumab vs CT for Advanced NSCLC With PD-L1 TPS ≥ 1%

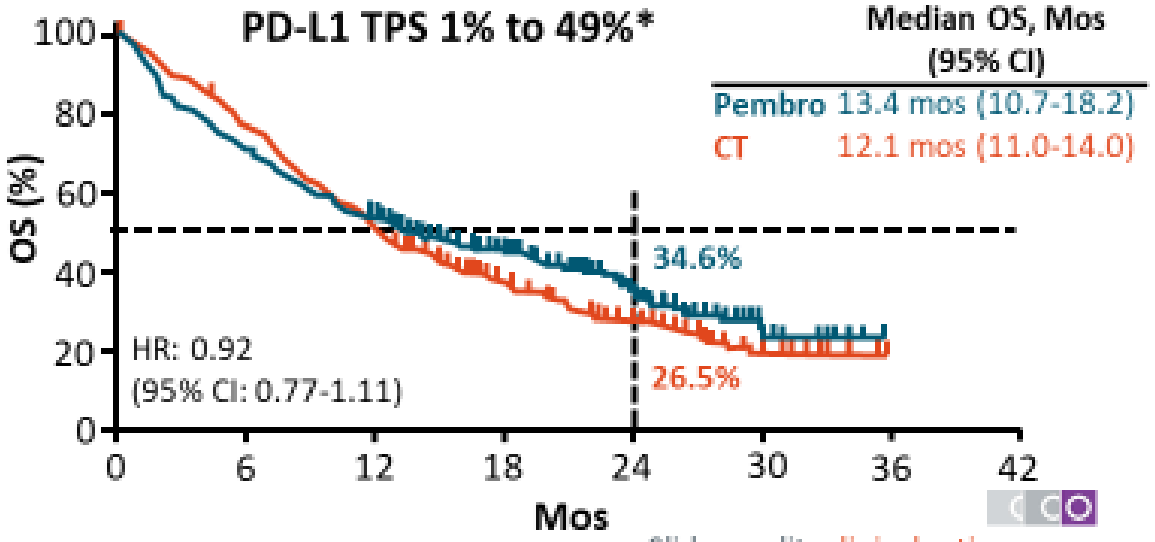
Patients with untreated stage IV NSCLC (any histology); ECOG PS 0/1; PD-L1 TPS ≥ 1%; no actionable *EGFR/ALK* mutations; no untreated CNS metastases or Pneumonitis requiring tx (N = 1274)

Pembrolizumab 200 mg IV Q3W for up to 35 cycles/2 yrs (n = 637)

Chemotherapy† (histology based) for up to 6 cycles (n = 637)







Mok. Lancet. 2019;393:1819.

*Exploratory analysis; no alpha allocated to this comparison.

Slide credit: clinicaloptions.com

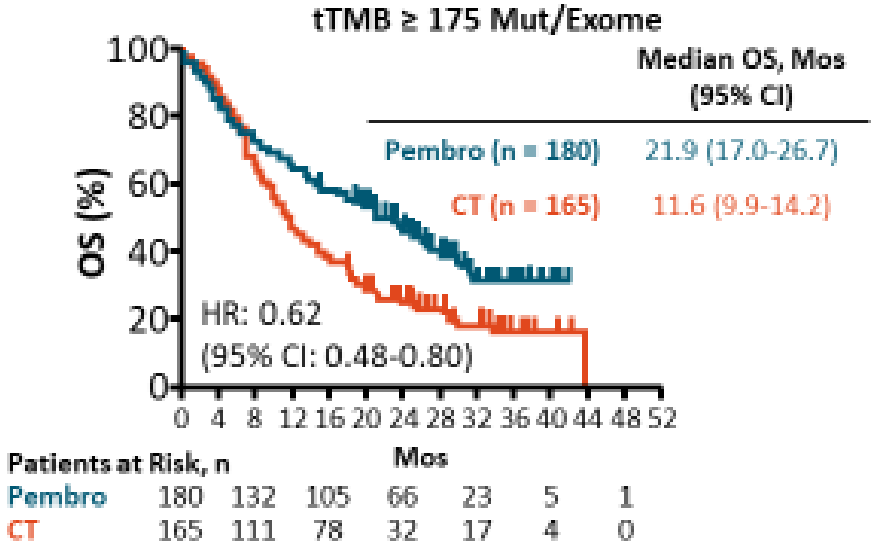
KEYNOTE-042: Analysis of tTMB by WES

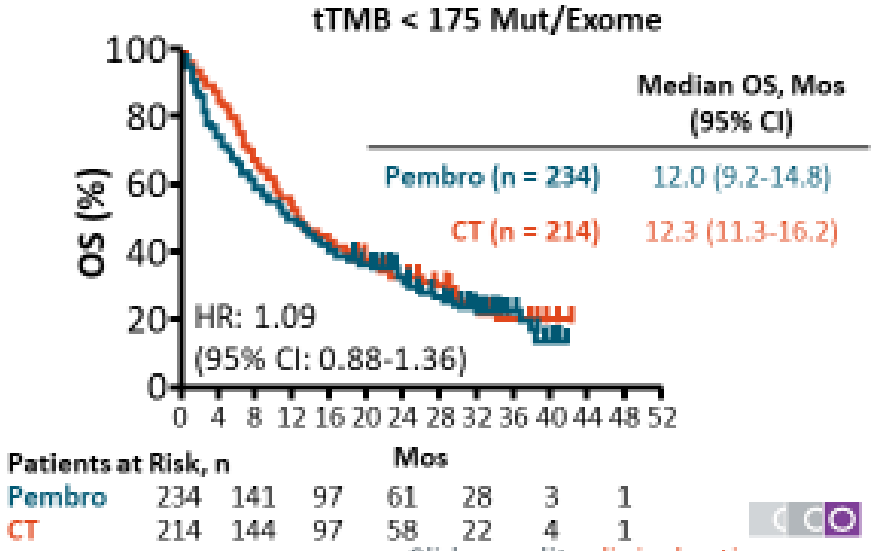
Association of tTMB With Efficacy

Nominal *P* Value	Pembrolizumab (n = 164)	Chemotherapy (n = 89)
OS	< .001 (1-sided*)	.060 (2-sided†‡)
PFS	< .001 (1-sided*)	.174 (2-sided†)
ORR	< .001 (1-sided*)	.035 (2-sided†‡)

*P values are 1-sided because the a priori hypothesis was that tTMB was positively associated with improved outcomes. †P values are 2-sided because there was no a priori hypothesis. TMB was assessed as a continuous log-10 transformed variable. ‡TMB showed negative direction of association with OS and PFS with chemotherapy.

- tTMB associated with outcomes for pembrolizumab as a continuous variable but not with chemotherapy
  - Based on α = 0.05 significance level and AUROC analysis

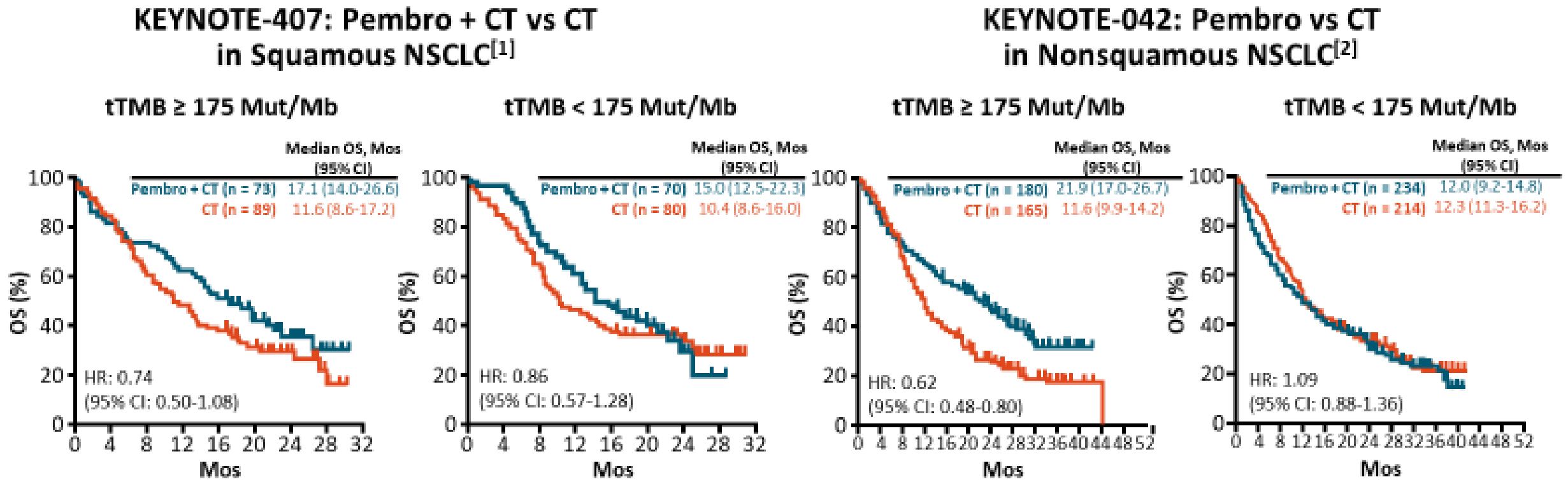




Herbst. ESMO 2019. Abstr LBA79. Adapted from Gandara. ESMO Lung Cancer Summit 2019.

Slide credit: clinicaloptions.com

Summary of tTMB by WES in Trials of CPI Monotherapy vs CPI + CT: New Data From ESMO 2019



In analyses of the KEYNOTE trials, tTMB consistently associated with efficacy of pembrolizumab as monotherapy (KN-010, -042) but NOT when combined with chemotherapy (KN-021, -189, -407)

1. Paz-Ares. ESMO 2019. Abstr LBA80. 2. Herbst. ESMO 2019. Abstr LBA79

MYSTIC: First-line Durvalumab ± Tremelimumab vs Chemotherapy in Metastatic NSCLC

- Multicenter, global, open-label, randomized phase III clinical trial

Stratified by TC PD-L1 expression (< 25% vs ≥ 25%), histology

Patients with stage IV NSCLC; all comers (ie, any PD-L1 status); no actionable *EGFR/ALK* mutations; ECOG PS 0/1; no prior immunotherapy or chemotherapy (N = 1118)

→ **Durvalumab** 20 mg/kg Q4W until PD (n = 374)

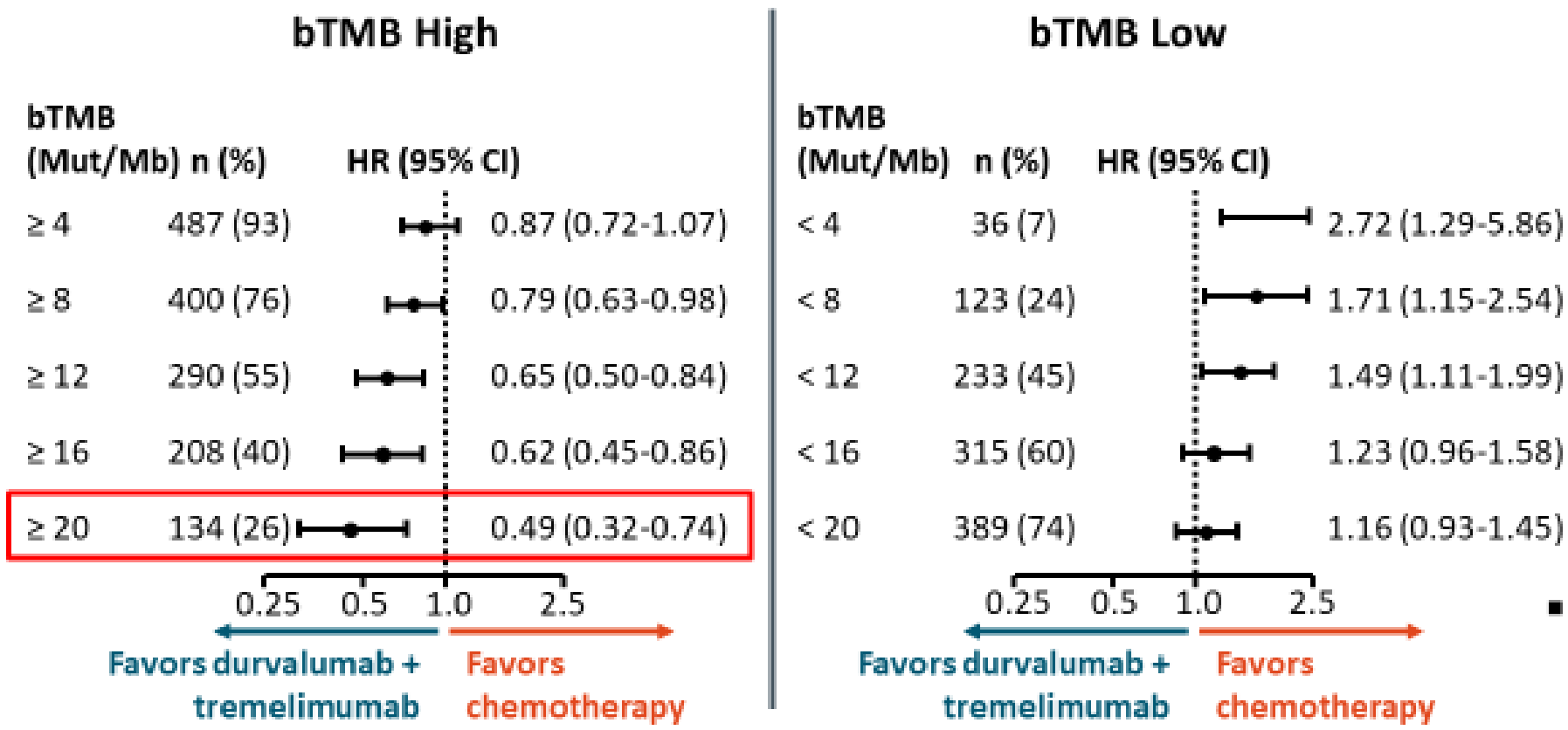
→ **Durvalumab** 20 mg/kg Q4W until PD + **Tremelimumab** 1 mg/kg Q4W x ≤ 4 doses (n = 372)

→ **Platinum-based chemotherapy*** for ≤ 8 cycles (n = 372)

*Squamous: Paclitaxel/carboplatin OR gemcitabine/cisplatin or carboplatin. Nonsquamous: Pemetrexed/cisplatin or carboplatin.

- Primary endpoints (in PD-L1 ≥ 25%): OS (D vs CT; D+T vs CT), PFS (D+T vs CT)
- Key exploratory endpoints: OS by bTMB and tTMB

MYSTIC: OS Across bTMB Cutoffs



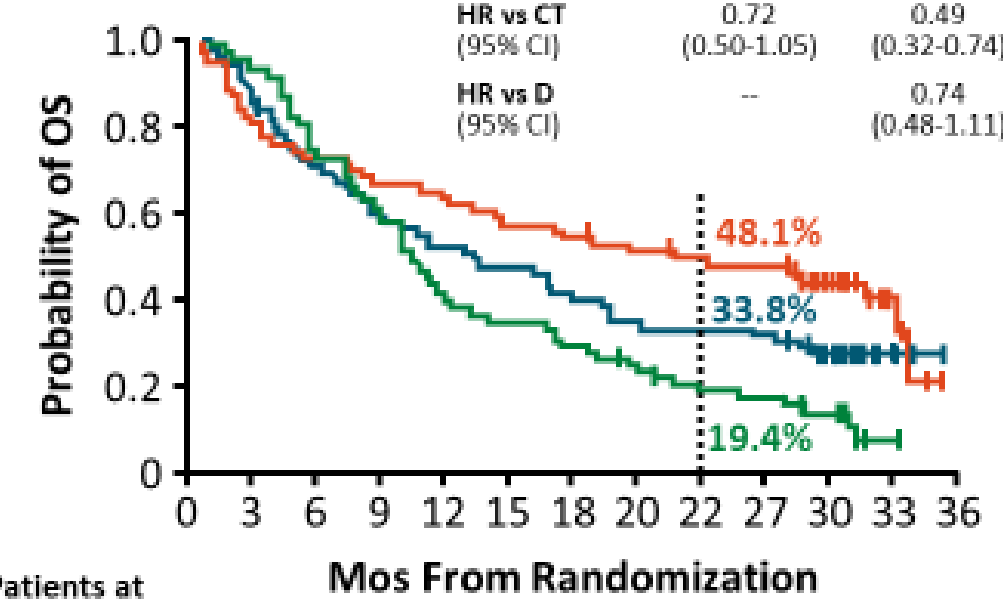
- bTMB determined by GuardantOMNI sequencing
  - 500-gene panel (1.0 Mb DNA footprint; coding regions only)
  - bTMB algorithm incorporates somatic single-nt variants and indels; accounts for low tumor shedding or low ctDNA input
- Large bTMB dataset included baseline samples from 809 patients (72.4% of ITT) in MYSTIC trial

Rizvi. ASCO 2019. Abstr 9016.

MYSTIC: OS by bTMB

bTMB ≥ 20 Mut/Mb

	D (n = 77)	D + T (n = 64)	CT (n = 70)
Median OS, mos (95% CI)	12.6 (7.8-18.6)	21.9 (11.4-32.8)	10.0 (8.1-11.7)
HR vs CT (95% CI)	0.72 (0.50-1.05)	0.49 (0.32-0.74)	--
HR vs D (95% CI)	--	0.74 (0.48-1.11)	--

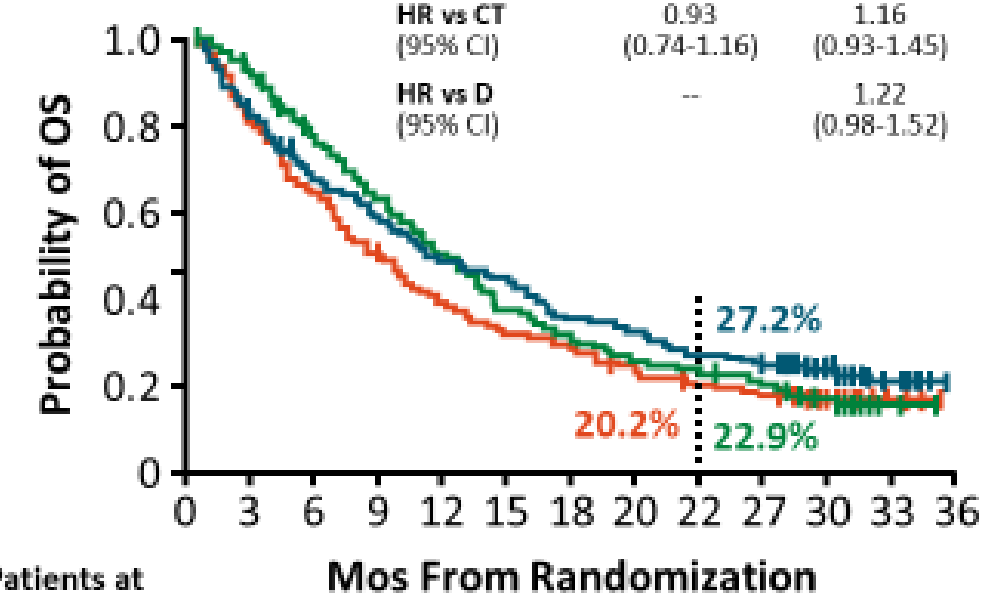


Patients at Risk, n

D	77	64	53	44	39	35	30	25	25	23	10	1	0
D + T	64	50	47	43	40	37	35	32	29	29	14	2	0
CT	70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB < 20 Mut/Mb

	D (n = 209)	D + T (n = 204)	CT (n = 185)
Median OS, mos (95% CI)	11.0 (8.9-14.9)	8.5 (6.7-9.8)	11.6 (9.6-13.1)
HR vs CT (95% CI)	0.93 (0.74-1.16)	1.16 (0.93-1.45)	--
HR vs D (95% CI)	--	1.22 (0.98-1.52)	--



Patients at Risk, n

D	209	167	134	114	98	86	72	63	55	49	21	8	0
D + T	204	161	129	98	75	65	55	45	39	35	18	4	0
CT	185	162	135	110	89	68	53	45	41	34	17	1	0

Peters. AACR 2019. Abstr CT074.

TMB in NSCLC: Summary to Date

- Unclear clinical role for TMB given lack of FDA-approved therapy for TMB-high NSCLC to date
- Multiple issues with TMB
  - Standardization across assays (tumor normal vs tumor only, genomic coverage)
    - Efforts ongoing to address standardization of TMB calculation and reporting
    - ➢ Appropriate cutoff
  - Tissue input requirements
    - ➢ Tissue vs cfDNA
    - ➢ Tissue heterogeneity and tumor purity
  - Expensive and slower test than IHC
    - However, forces clinicians to wait for driver mutation results before treating with anti–PD-1 therapy

ΜΟΡΙΑΚΟΙ ΔΕΙΚΤΕΣ ΑΝΤΑΠΟΚΡΙΣΗΣ ΣΤΗΝ ΑΝΟΣΟΘΕΡΑΠΕΙΑ

- STK11/LKB1
- KEAP1

STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant Lung Adenocarcinoma

Cohort	Foundation Medicine (FM)	Stand Up To Cancer (SU2C)			Checkmate-057 (CM-057)	MDACC (PD-L1 ≥ 1%)
		MDACC	MSKCC	DFCI/MGH		
N	924 (346 *KRAS*^{MUT})	174				
		62	56	56	44	66
Nivolumab	NA		146		24	16
Pembrolizumab	NA		19		NA	40
Atezolizumab	NA		0		NA	5
anti-PD(L)-1 + anti-CTLA4	NA		9		NA	3
Docetaxel	NA		NA		20	NA
Other	NA		NA		NA	2[a]

[a]One patient with *STK11/LKB1*-mutant tumor was treated with nivolumab and NKTR-214 (CD122-based agonist) and one patient with *STK11/LKB1* wild-type tumor was treated with pembrolizumab and OX40 agonist.

r M. Szabo[3], Vitazka[3], el[12], nny[14], po[1], Villalobos[17], Jiang[22,23], t A. Miller[2],

STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant LUAC

Inactivation of *STK11* by mutational or nonmutational mechanisms is associated with an inert or "cold" tumor immune microenvironment, with reduced density of infiltrating cytotoxic CD8 + T lymphocytes in both human tumors and genetically engineered murine models

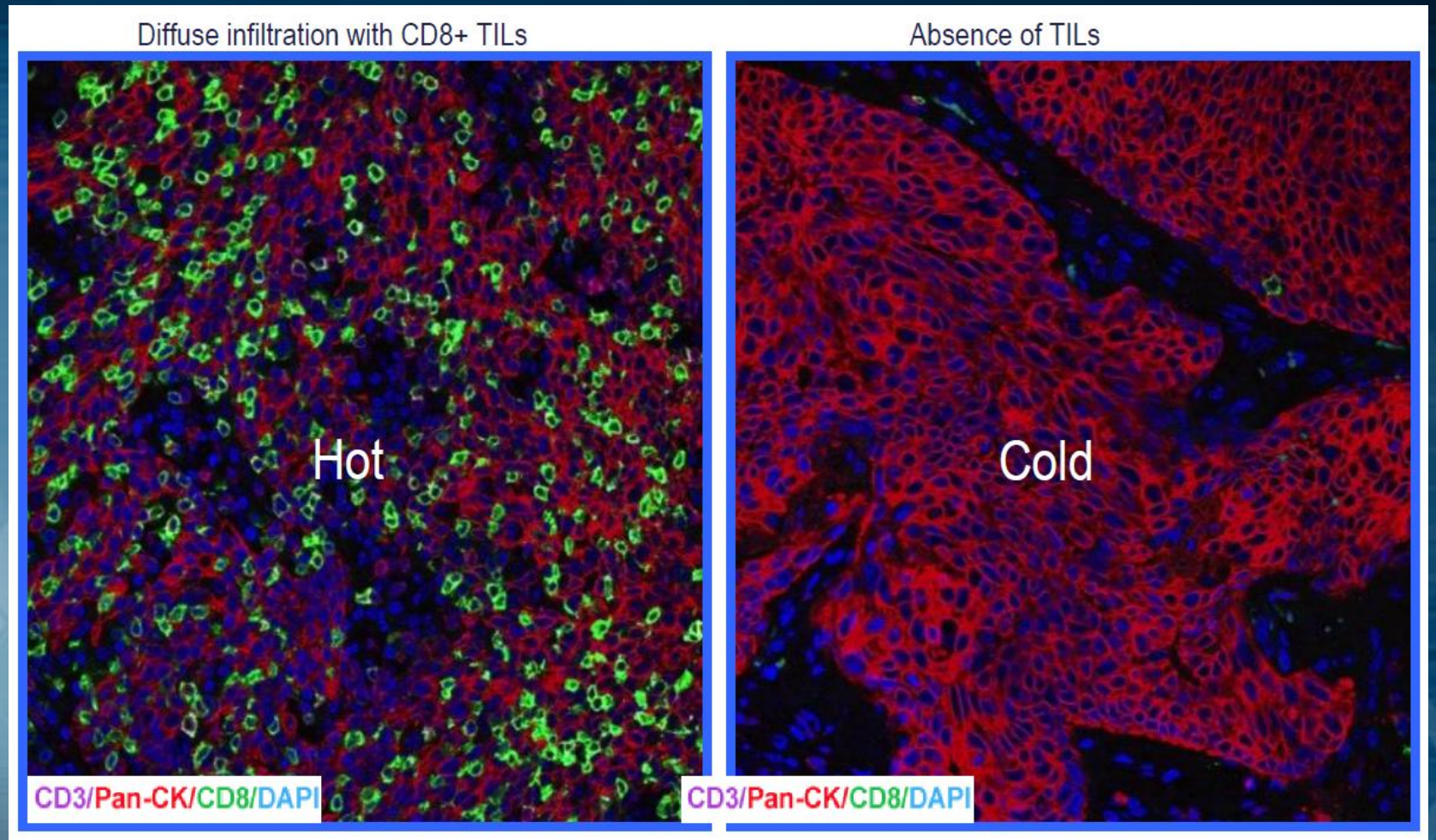
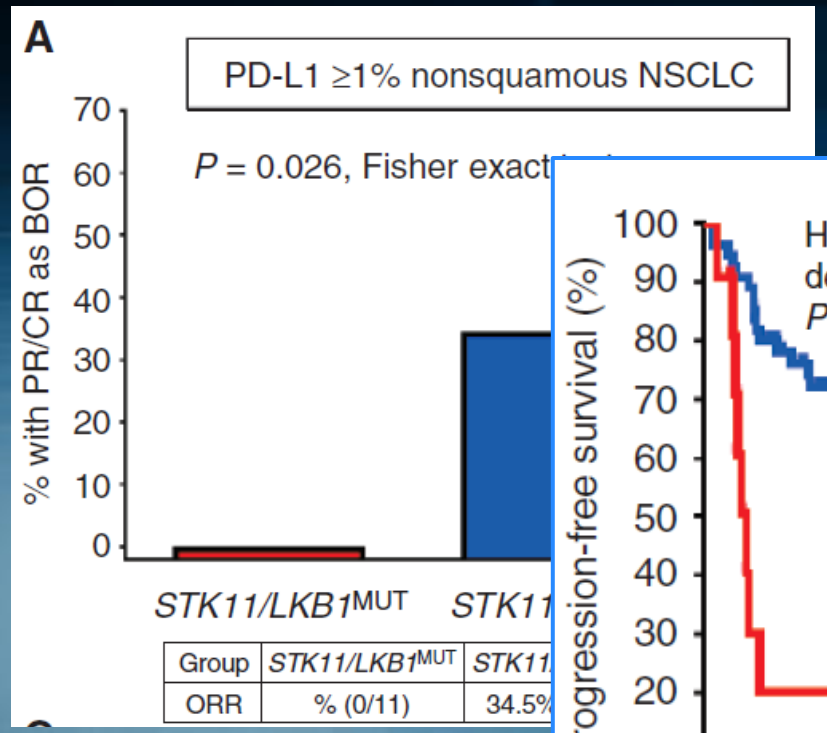
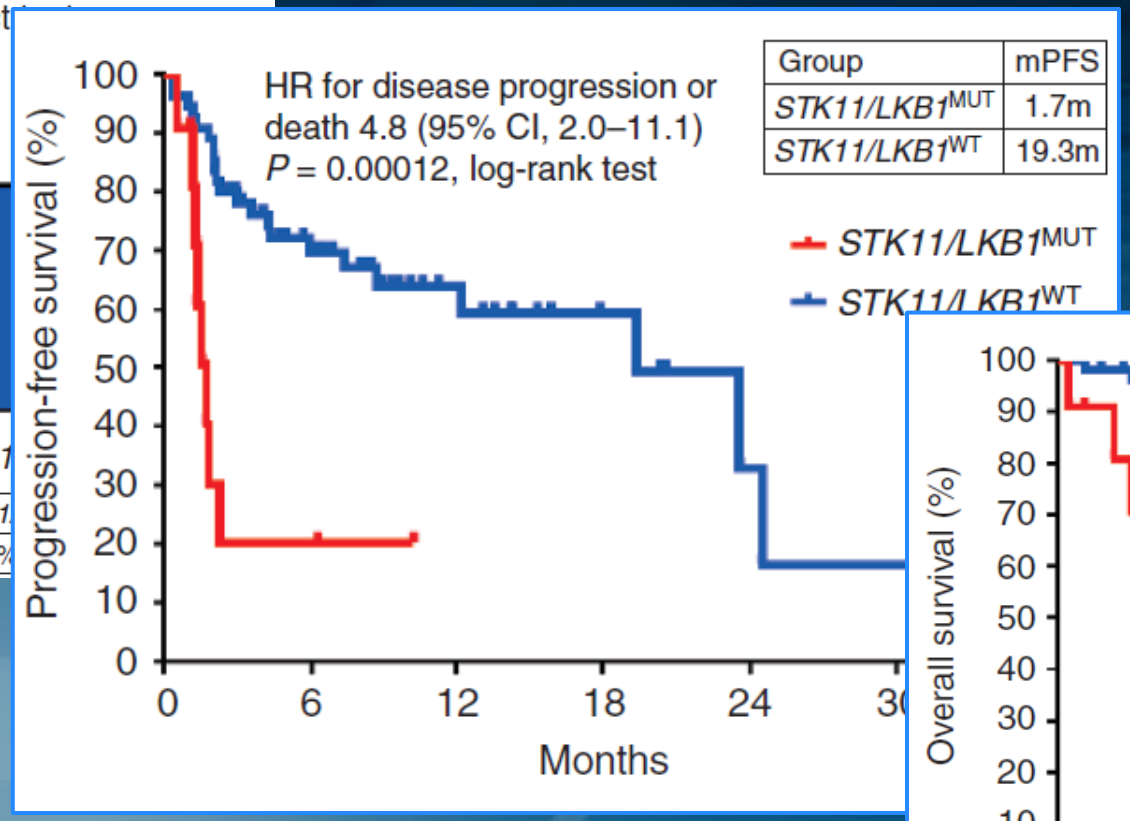
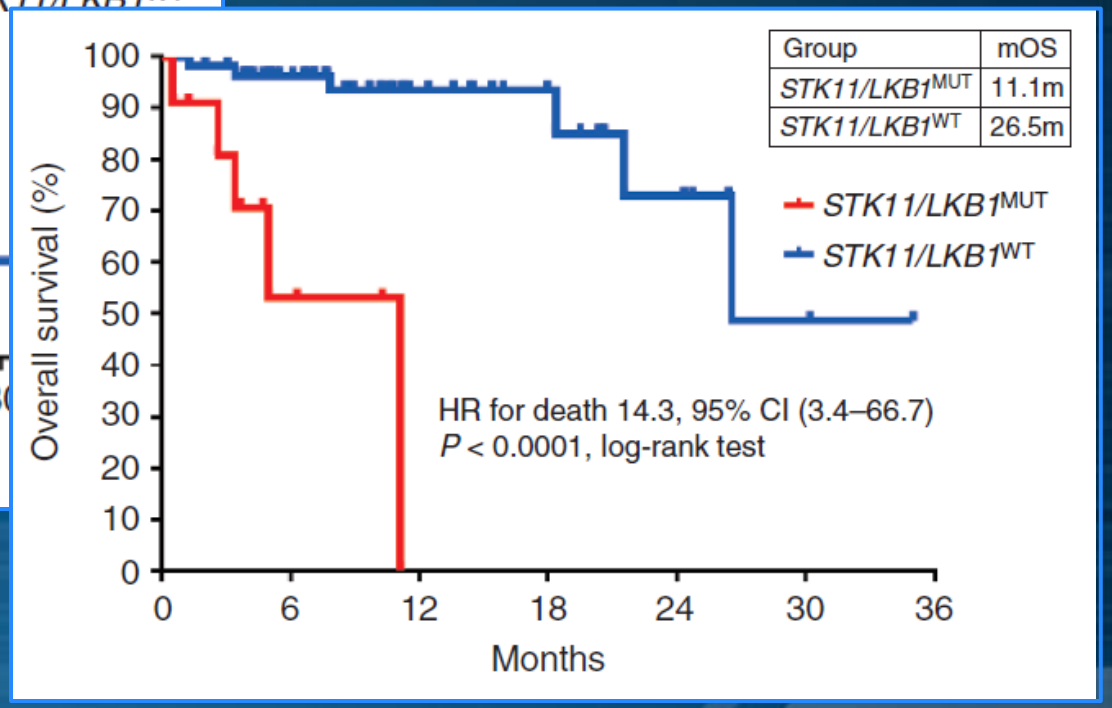


IMAGE
Keck et al., ClinCancRes 2014

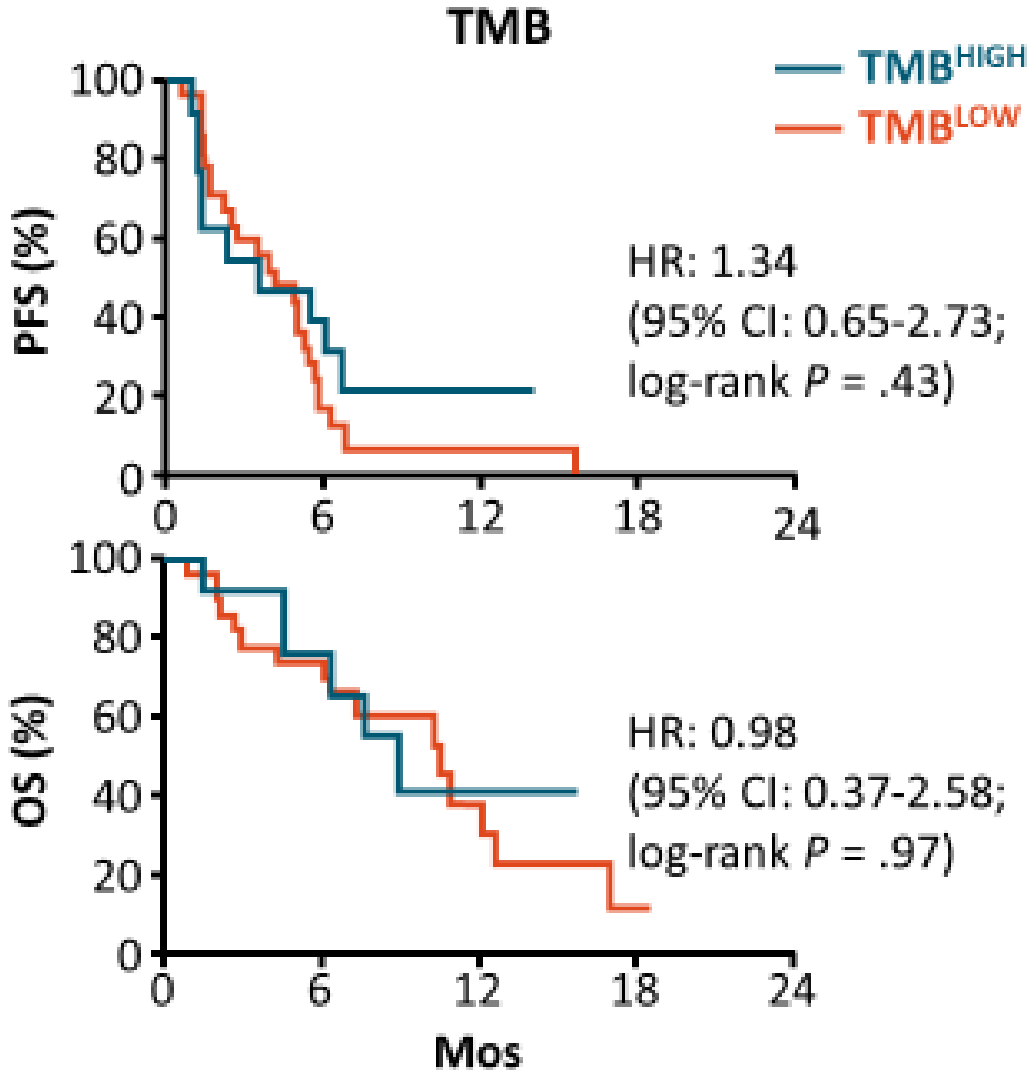
STK11/LKB1 Mutations and PD-1 Inhibitor Resistance in *KRAS*-Mutant LUAC

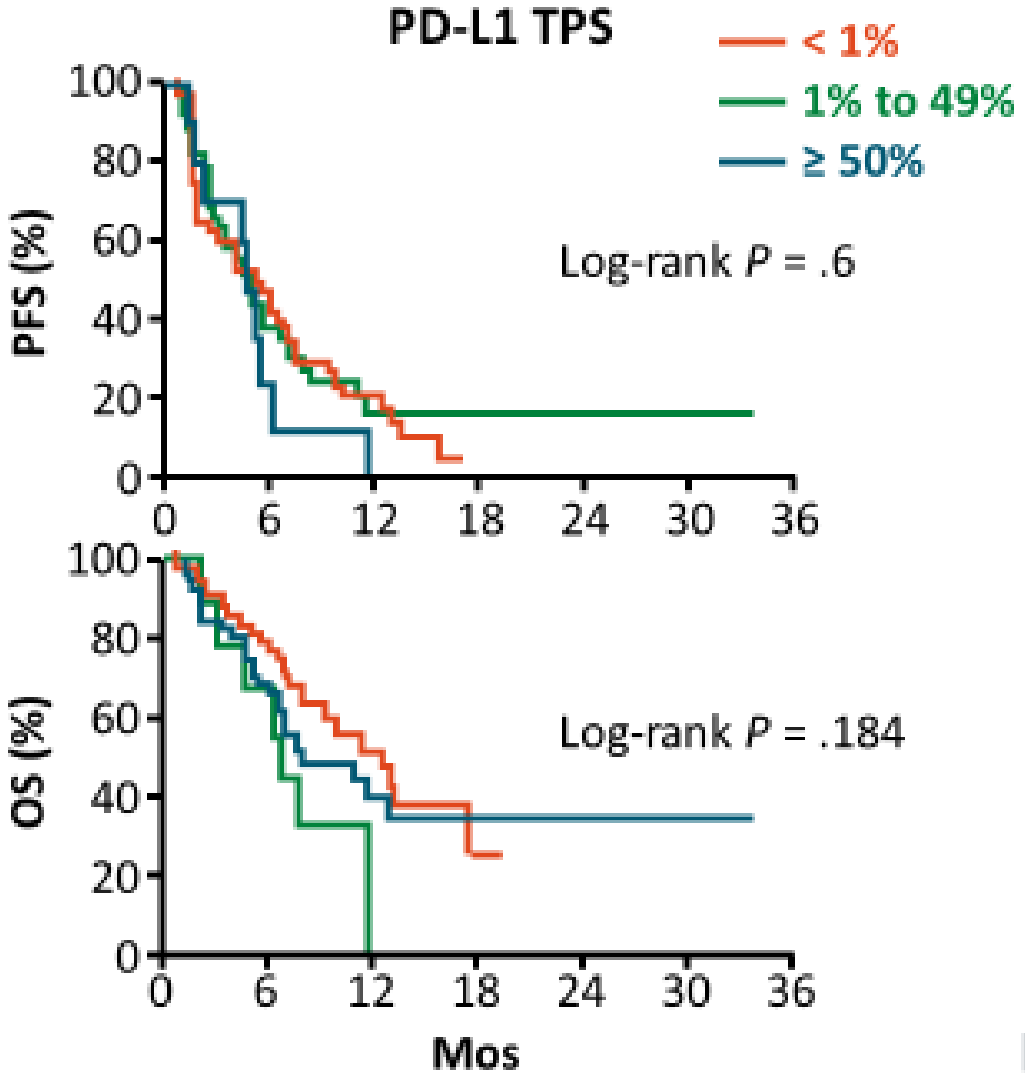






TMB and PD-L1 Independent of Clinical Outcomes With Pembro + CT in *STK11*^{MUT} and/or *KEAP1*^{MUT} Nonsq NSCLC



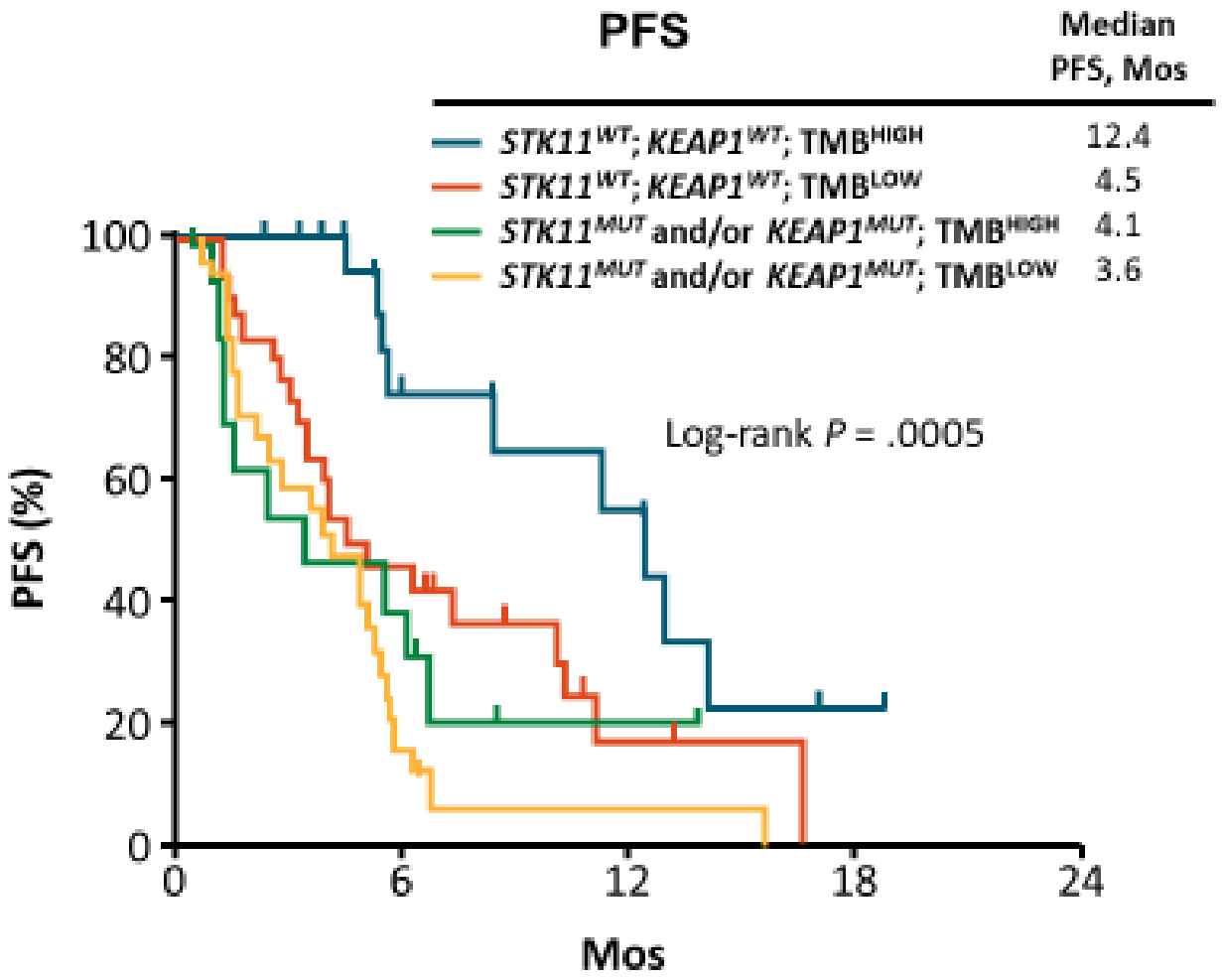


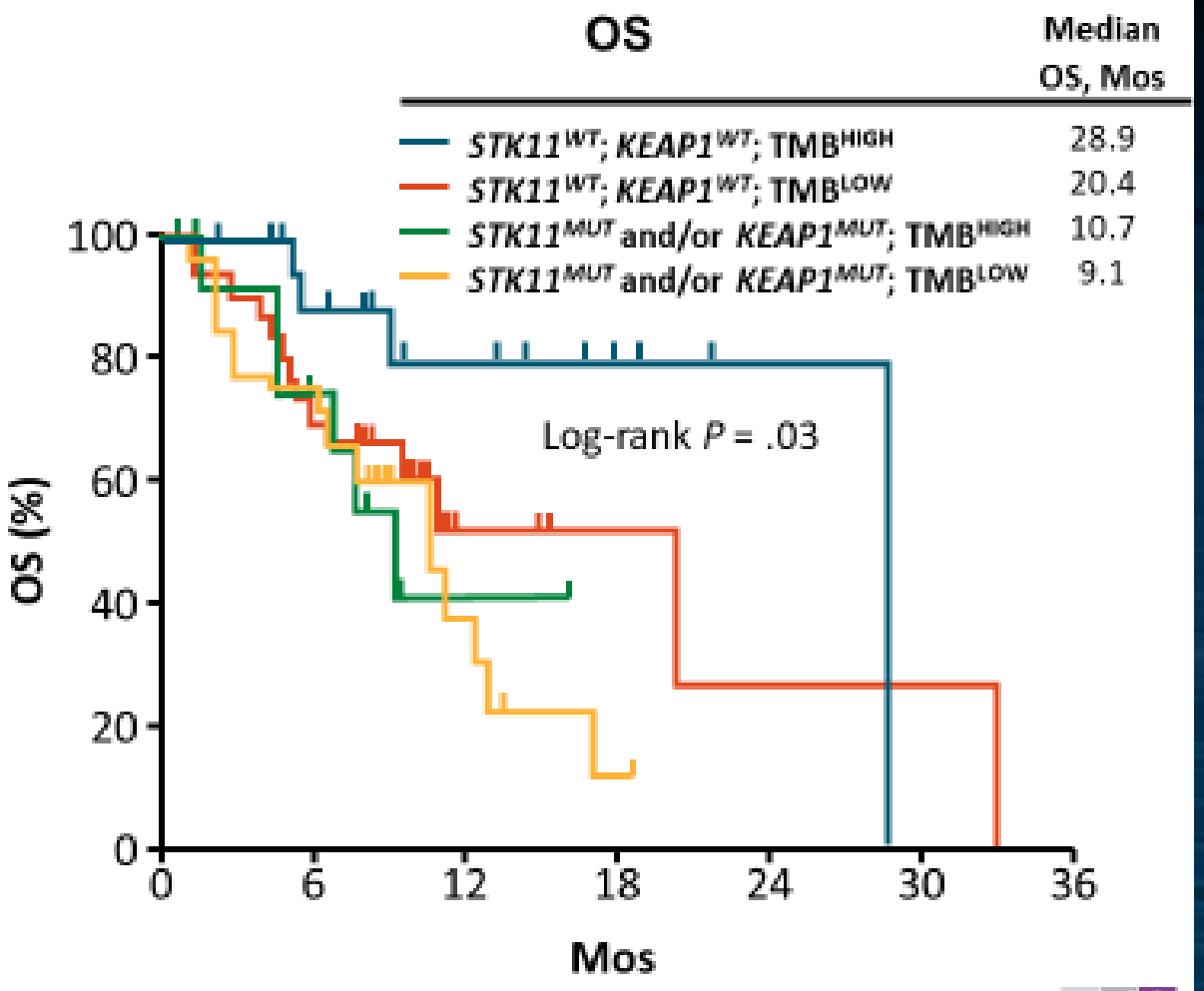
Skoulidis. ASCO 2019. Abstr 102.

CT: carboplatin or cisplatin/paclitaxel.

Slide credit: clinicaloptions.com

Integration of *STK11* and *KEAP1* Genomic Alterations With TMB and Other Biomarkers: Toward a Composite Panel?





Skoulidis. ASCO 2019. Abstr 102.

Slide credit: clinicaloptions.com

Treatment Algorithm for Patients With Advanced-Stage NSCLC and PS 0/1 as of 2014

	Nonsquamous		Squamous
	Oncogene Driven	Nononcogene Driven	All
First Line	TKI (targeted therapy) *EGFR* mutant *ALK* translocation	Chemo doublet ± bevacizumab	Chemo doublet
First Line Maintenance		Pemetrexed or bevacizumab	Chemo
		or Erlotinib	or Erlotinib
Second Line	Chemo ± TKI	Chemo	Chemo
	Next-generation TKI	or Erlotinib	or Erlotinib
Third Line	Chemo	Chemo	Chemo
		or Erlotinib	or Erlotinib

Adapted from Gandara. Clin Lung Cancer. 2017;8:124

Treatment Algorithm for Patients With Advanced-Stage NSCLC and PS 0-1 as of October 2019

	Nonsquamous			Squamous	
	Oncogene Driven	PD-L1+	PD-L1-	PD-L1+	PD-L1-
First Line	TKI (targeted therapy) EGFR, ALK, ROS1 TKIs	Pembro ± chemo or atezo-bev-chemo	Pembro-chemo or atezo-bev-chemo	Pembro ± chemo or atezo-chemo	Pembro-chemo or atezo-chemo
First Line Maintenance	EGFR, ALK, ROS1 TKIs	Pembro-pemetrexed or atezo-bev	Pembro-pemetrexed or atezo-bev	Pembro or atezo	Pembro or atezo
Second Line	Next-generation EGFR/ALK TKIs Other TKIs	Nivo or pembro or atezo	Nivo or pembro or atezo	Nivo or pembro or atezo	Nivo or pembro or atezo
		Docetaxel (± antiangiogenic)	Docetaxel (± anti-angiogenic)	Docetaxel (± antiangiogenic)	Docetaxel (± antiangiogenic)
		Chemo	Chemo	Chemo	Chemo
Second/Third Line	Third-generation TKI or chemo doublet	Chemo	Chemo	Chemo	Chemo
				Afatinib	Afatinib

Adapted from Gandara. Clin Lung Cancer. 2017;8:124.

Immunotherapy Treatment Algorithm for NSCLC in 2019

	Squamous	Nonsquamous	
PD-L1 ≥ 50%	Pembrolizumab or Pembrolizumab + CT	Pembrolizumab or Pembrolizumab + CT	Atezolizumab + Carboplatin/Pemetrexed + Bevacizumab
PD-L1 ≥ 1-49%	Pembrolizumab + Carboplatin/Paclitaxel or nab-Paclitaxel	Pembrolizumab + Carboplatin/Pemetrexed	
PD-L1 < 1%	Pembrolizumab + Carboplatin/Paclitaxel or nab-Paclitaxel	Pembrolizumab + Carboplatin/Pemetrexed *-or-* Chemotherapy Alone	

- Where does TMB fit in, if anywhere?

ΣΥΜΠΕΡΑΣΜΑΤΑ

- Προβλεπτικοί βιοδείκτες (θετικοί – αρνητικοί) είναι πλέον απαραίτητοι
- Σε καρκίνο πνεύμονα προχωρημένου σταδίου
- NCCN GUIDELINES v 1.2020 : EGFR – EML4-ALK – ROS 1- BRAF – PDL1
- + Broader molecular profiling (NGS + NTRK DETECTION)
- Ρόλος του TMB ????
- Συνδυασμός βιοδεικτών (θετικών – αρνητικών) → Καλύτερη επιλογή ασθενών