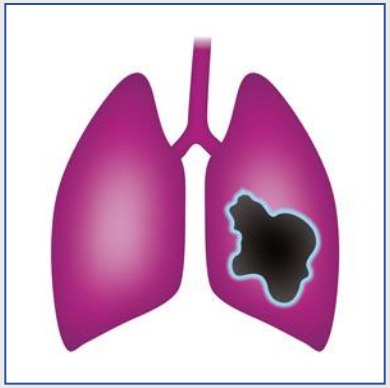
Pneumo Update Europe 2017

9-10 June, Vienna

Oncology



Johan Vansteenkiste, Belgium

Content

1. Oligometastatic NSCLC
2. Advanced NSCLC (stage IV)
    a) Oncogene-driven NSCLC
    b) Immunotherapy for NSCLC
    c) Immunotherapy combinations

3. Other thoracic tumors

+ ASCO Late-Breaking News

Oligometastatic NSCLC

Oligometastatic NSCLC

Distinct cohorts

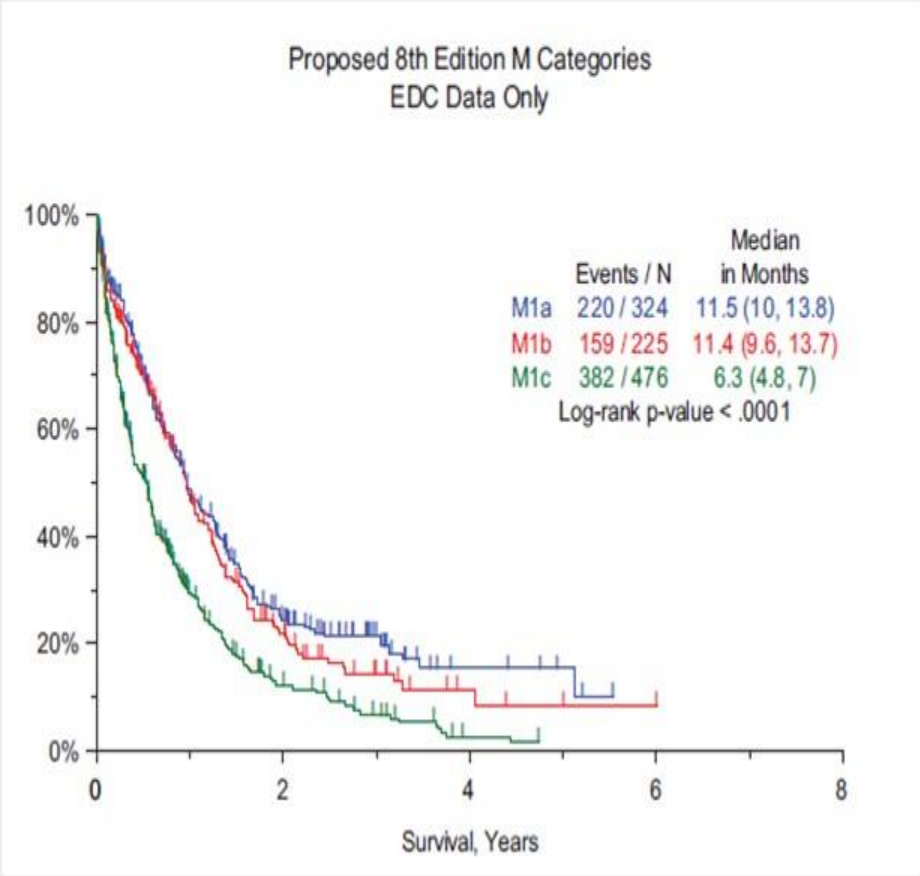
- 'oligometastases' = diagnosed with oligometastatic disease
- 'oligorecurrence' = relapsed oligometastatic disease
- 'oligoprogression' = status after cytoreductive therapy

→ cohorts probably have different prognoses

Oligometastatic NSCLC

First appearance in TNM 8 staging system

- M1a: intrathoracic only
- M1b: single extrathoracic metastasis
- M1c: multiple extrathoracic metastasis



Eberhardt et al. J Thorac Oncol 10:1515-1522, 2015

Oligometastatic NSCLC

Treatment

- Large number of small retrospective series
- A few prospective (non randomized) series published
- Recommendations: few, e.g. ACCP 2013, ESMO 2016, …

> ESMO 2016: Stage IV patients with one to three synchronous metastases at diagnosis may experience long-term DFS following systemic therapy and radical local treatment (high-dose radiotherapy or surgery) [III, B]. Because of limited evidence, inclusion in clinical trials is preferred.

- "To be decided at multidisciplinary tumor board (MTB)…"

Novello et al, Ann Oncol 27 Suppl 5: v1-v27, 2016

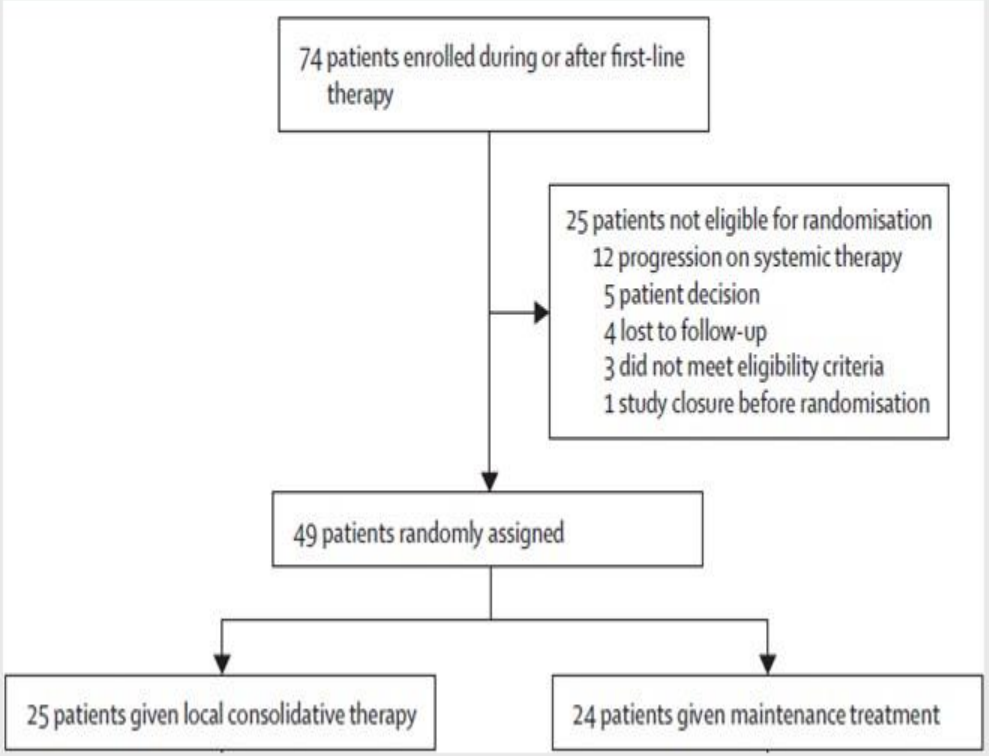
Oligometastatic NSCLC
> ph2 multi-center randomized trial

Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study

Daniel R Gomez, George R Blumenschein Jr, J Jack Lee, Mike Hernandez, Rong Ye, D Ross Camidge, Robert C Doebele, Ferdinandos Skoulidis, Laurie E Gaspar, Don L Gibbons, Jose A Karam, Brian D Kavanagh, Chad Tang, Ritsuko Komaki, Alexander V Louie, David A Palma, Anne S Tsao, Boris Sepesi, William N William, Jianjun Zhang, Qiuling Shi, Xin Shelley Wang, Stephen G Swisher*, John V Heymach*

74 patients

- ≤3 metastatic lesions
- No disease progression after 1L systemic therapy
- PS 0 – 2

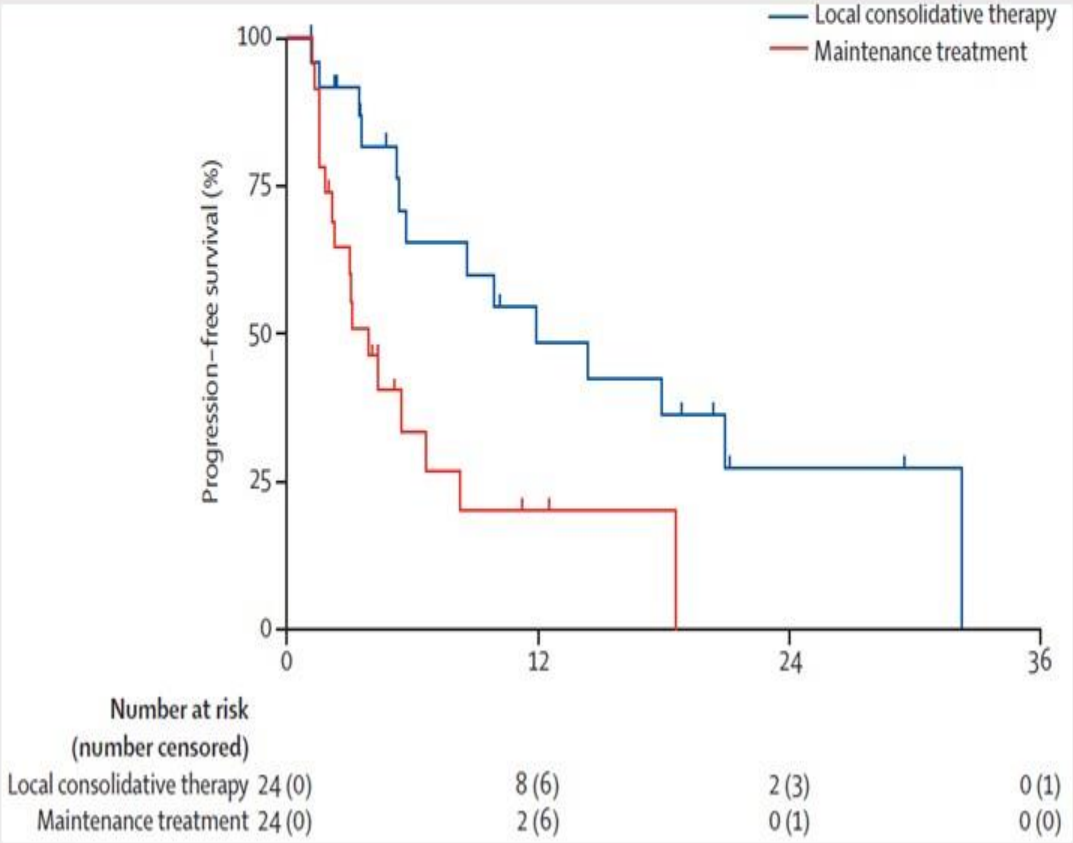


= radiotherapy or resection of all lesions
Subsequent maintenance treatment (could be observation only)

= maintenance treatment alone (could be observation only)

Gomez et al., Lancet Oncol 17;1672-1682.2016

Oligometastatic NSCLC
> ph2 multi-center randomized trial



Gomez et al., Lancet Oncol 17;1672-1682.2016

Take-Home Message

Oligometastatic NSCLC

- Selected patients with potential for long-term DFS or cure
- This selection remains ill-defined
  - Often ≤3 extrathoracic metastatic sites
- Ongoing clinical research
  - Retrospective -> non-randomized prospective -> small but exciting ph2 RCT -> ongoing ph3 RCTs

Advanced NSCLC

a) Oncogene-driven NSCLC
b) Immunotherapy for NSCLC
c) Immunotherapy combinations

+ ASCO Late-Breaking News

What did I tell you last year?

> *stage IV NSCLC innovations*

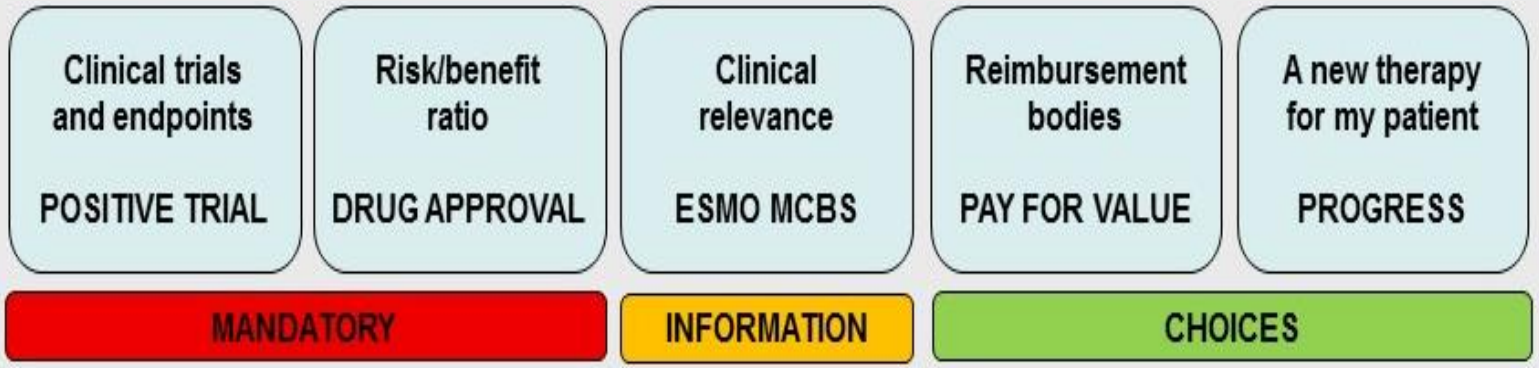
Over the last 10 years,
we have seen more treatment innovations
than in the 50 years before

A new therapy
for my patient

PROGRESS

What did I tell you last year?

> stage IV NSCLC innovations



Stage IV NSCLC: recent Pneumo Updates: 2015-2016

Oncogene-driven NSCLC		Acronym	Comparator	1° endpoint	HR	EMA approval
>EGFR mut+ (10-12%)						
2015	Osimertinib for T790M resistance	AURA 3	Doublet chemo	PFS	0.30	02/2016
>ALK+ (3-4%)						
2015	Crizotinib 1L therapy	PROFILE 1014	Doublet chemo	PFS	0.45	01/2016
2015	Ceritinib for crizotinib resistance	ASCEND 5	Single chemo	PFS	0.49	06/2015
Non-oncogene driven NSCLC 1L						
2016	Necitumumab added to Cis-Gemcitabine (EGFR IHC+)	SQUIRE	Cis-Gemcitabine	OS	0.79	02/2016
Non-oncogene driven NSCLC 2L/3L						
2015	Ramucirumab added to Docetaxel	REVEL	Docetaxel	OS	0.86	11/2015
2015	Nintedanib added to Docetaxel	LUME-LUNG1	Docetaxel	PFS	0.79	01/2015
Immunotherapy						
2015	Nivolumab 2L	CHECKMATE 017	Docetaxel	OS	0.62	12/2015
2015	Nivolumab 2L	CHECKMATE 057	Docetaxel	OS	0.73	02/2016
2016	Pembrolizumab 2L/3L (PD-L1 >1%)	KEYNOTE 010	Docetaxel	OS	0.71	08/2016

adeno

nsclc

squam

Stage IV NSCLC: Pneumo Update 2017

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2017	Alectinib for crizotinib resistance (phase 2 data)	-	-	ORR	-	04/2017
2017	Ceritinib 1L therapy	ASCEND 4	Doublet chemo	PFS	0.55	NA
2017	Alectinib 1L therapy (Japan only)	J-ALEX	Crizotinib	PFS	0.34	NA
>ROS1+ NSCLC (1-2%)						
2017	Crizotinib (phase 2 data)	-	-	ORR	-	08/2016
>BRAF+ NSCLC (0.5-1%)						
2017	Trametinib+Dafrafenib (phase 2 data)	-	-	ORR	-	(02/2017)
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2017	Atezolizumab 2L/3L	OAK	Docetaxel	OS	0.73	pending
2017	Pembrolizumab 1L (PD-L1 >50%)	KEYNOTE 024	Doublet chemo	PFS	0.50	03/2017
2017	Nivolumab 1L (PD-L1 >5%)	CHECKMATE 026	Doublet chemo	PFS	1.15	NA

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nsclc

squam

Stage IV NSCLC: Pneumo Update 2017

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2017	Pembrolizumab 1L (PD-L1 >50%)	KEYNOTE 024	Doublet chemo	PFS	0.50	03/2017
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nsclc

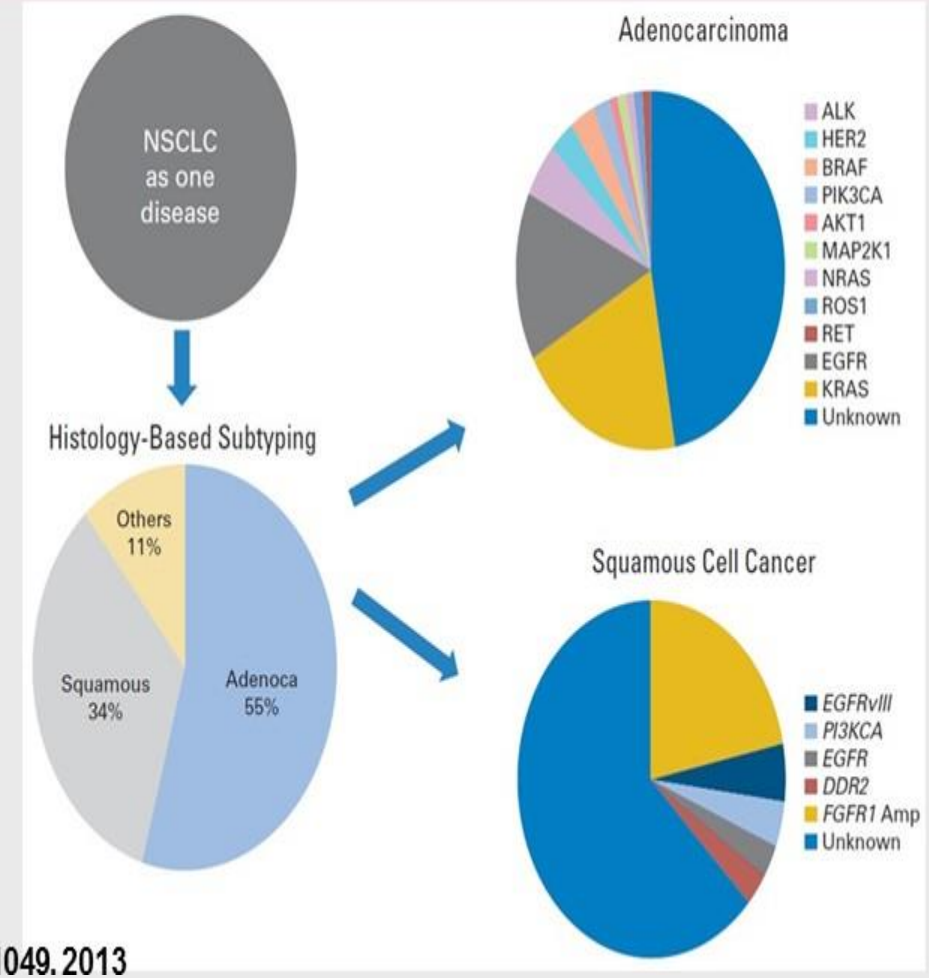
squam

Advanced NSCLC

Onco-gene-driven NSCLC

Stage IV NSCLC

Genetic aberrations in NSCLC



Increasingly druggable

Not druggable

Li et al. J Clin Oncol 31:1039-1049. 2013

Stage IV NSCLC

EGFR-mut+ adenocarcinoma

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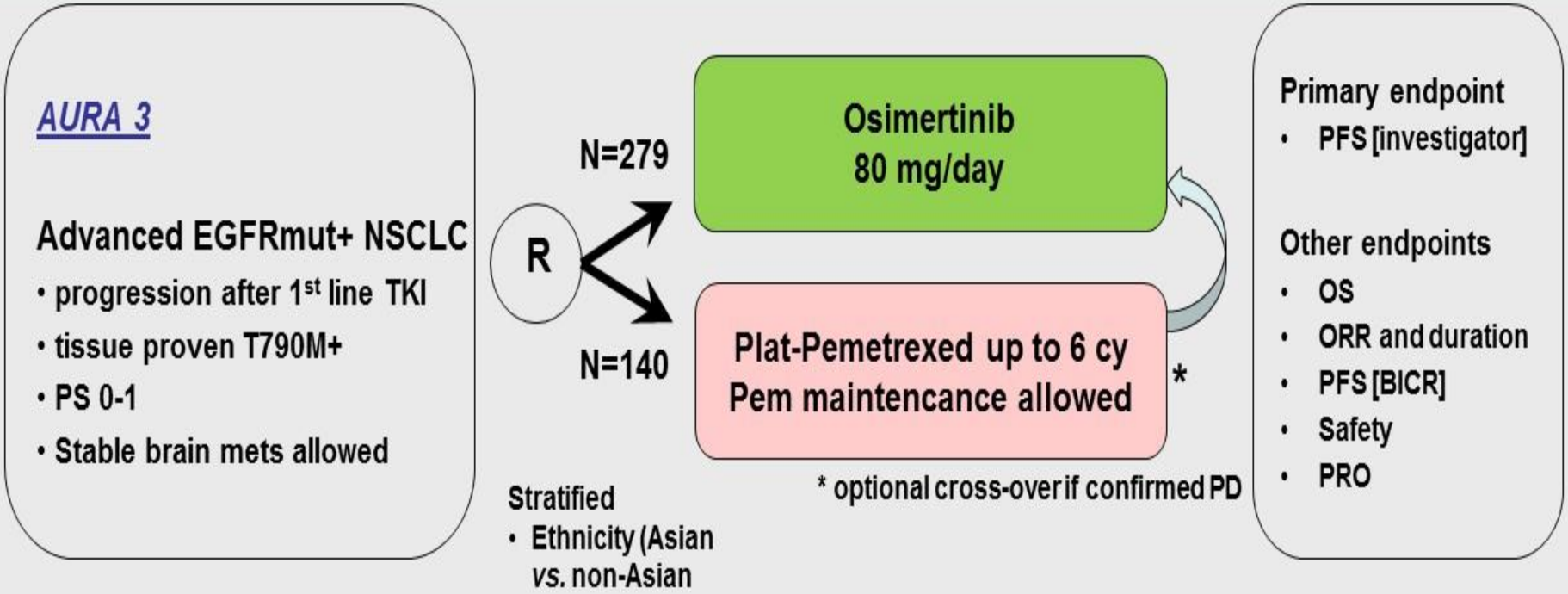
Stage IV NSCLC

Ph3 study: Osimertinib in T790M-based resistance



Papadimitrakopoulou et al, WCLC 2016 and Mok et al, N Engl J Med 376:629-640, 2017

Stage IV NSCLC

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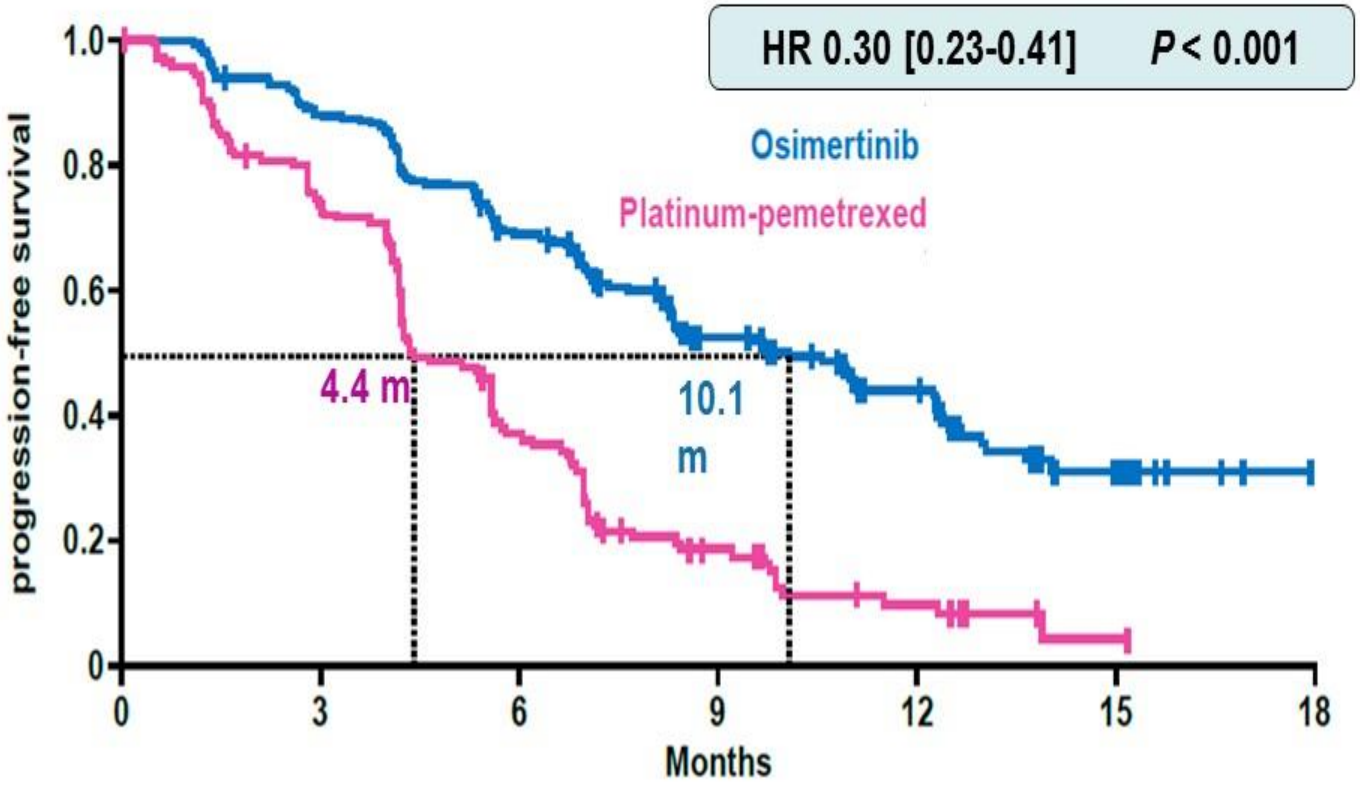


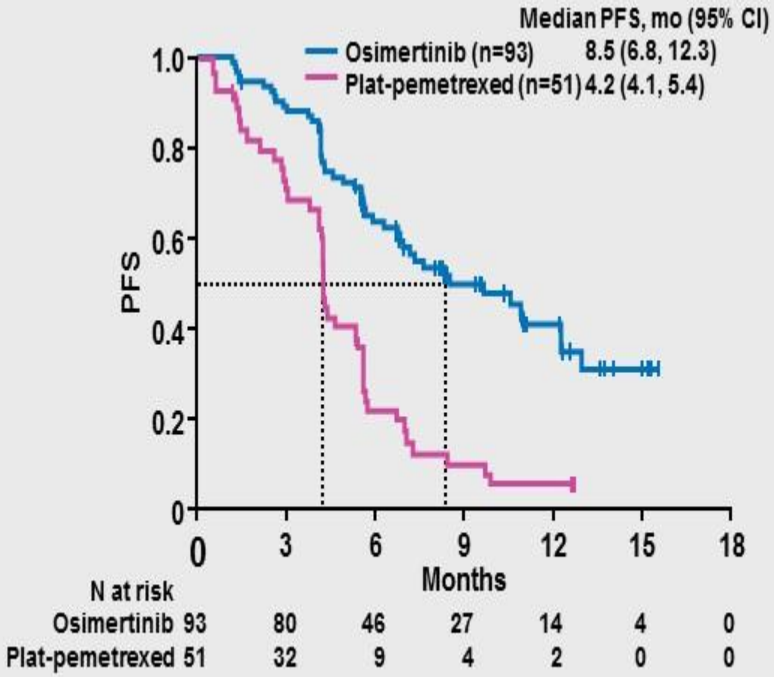
Papadimitrakopoulou et al, WCLC 2016 and Mok et al, N Engl J Med 376:629-640, 2017

Stage IV NSCLC

Ph3 study: Osimertinib in T790M-based resistance

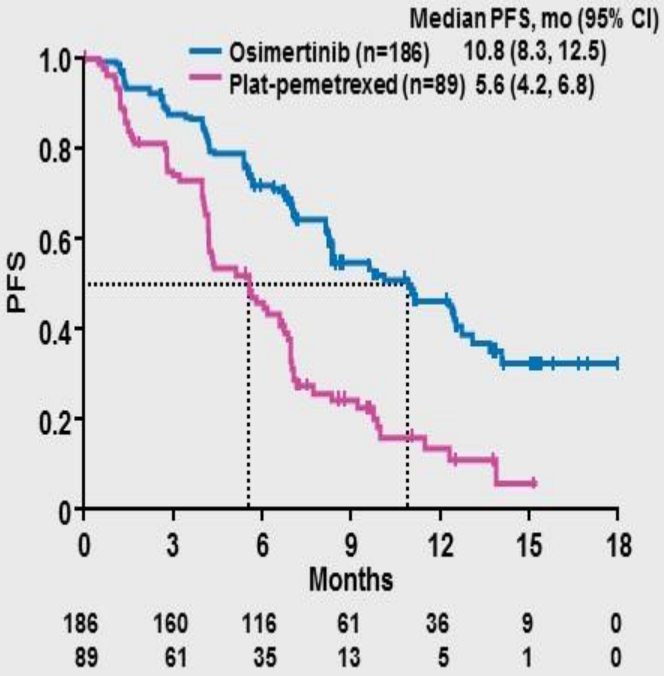
With CNS metastases

HR 0.32 [0.21-0.49]



Without CNS metastases

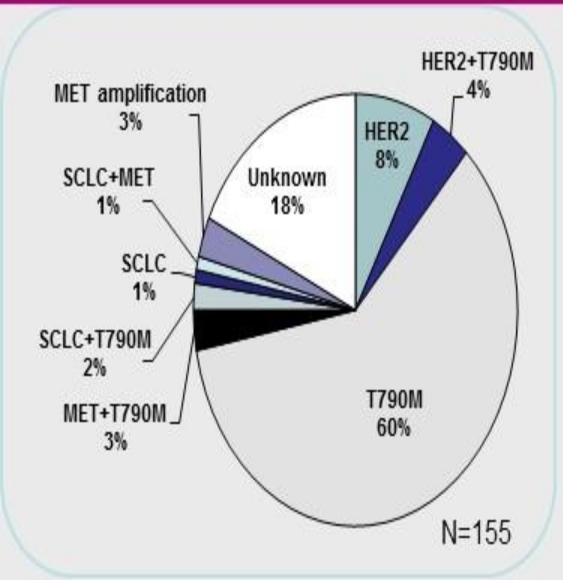
HR 0.40 [0.29-0.55]

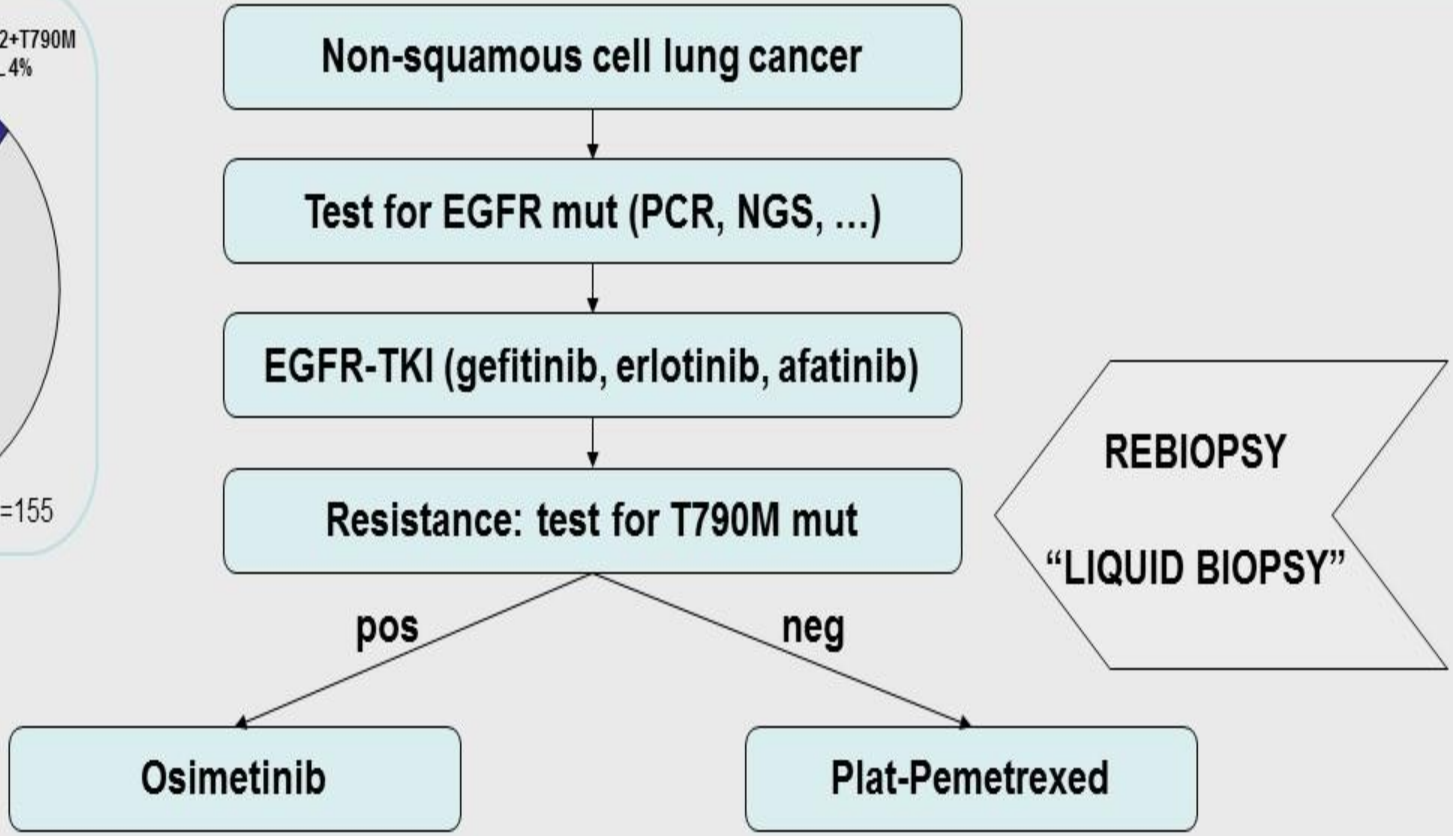


Papadimitrakopoulou et al, WCLC 2016 and Mok et al, N Engl J Med 376:629-640, 2017

Stage IV NSCLC

EGFR-mut+ adenocarcinoma





Yu et al. Clin Cancer Res 18:2240-2247, 2013
Cross et al. Cancer Discov 4:1046-1061, 2014

Stage IV NSCLC

Circulating tumor DNA (ctDNA, liquid biopsy)

- **Highly fragmented DNA**, typically 160-180 bp (shed via apoptosis and necrosis)
- **Short half-life**: ≈ 2 hours
- **Often low quantity**, normal DNA contamination is a major issue
- **Sensitiviy of tests:**

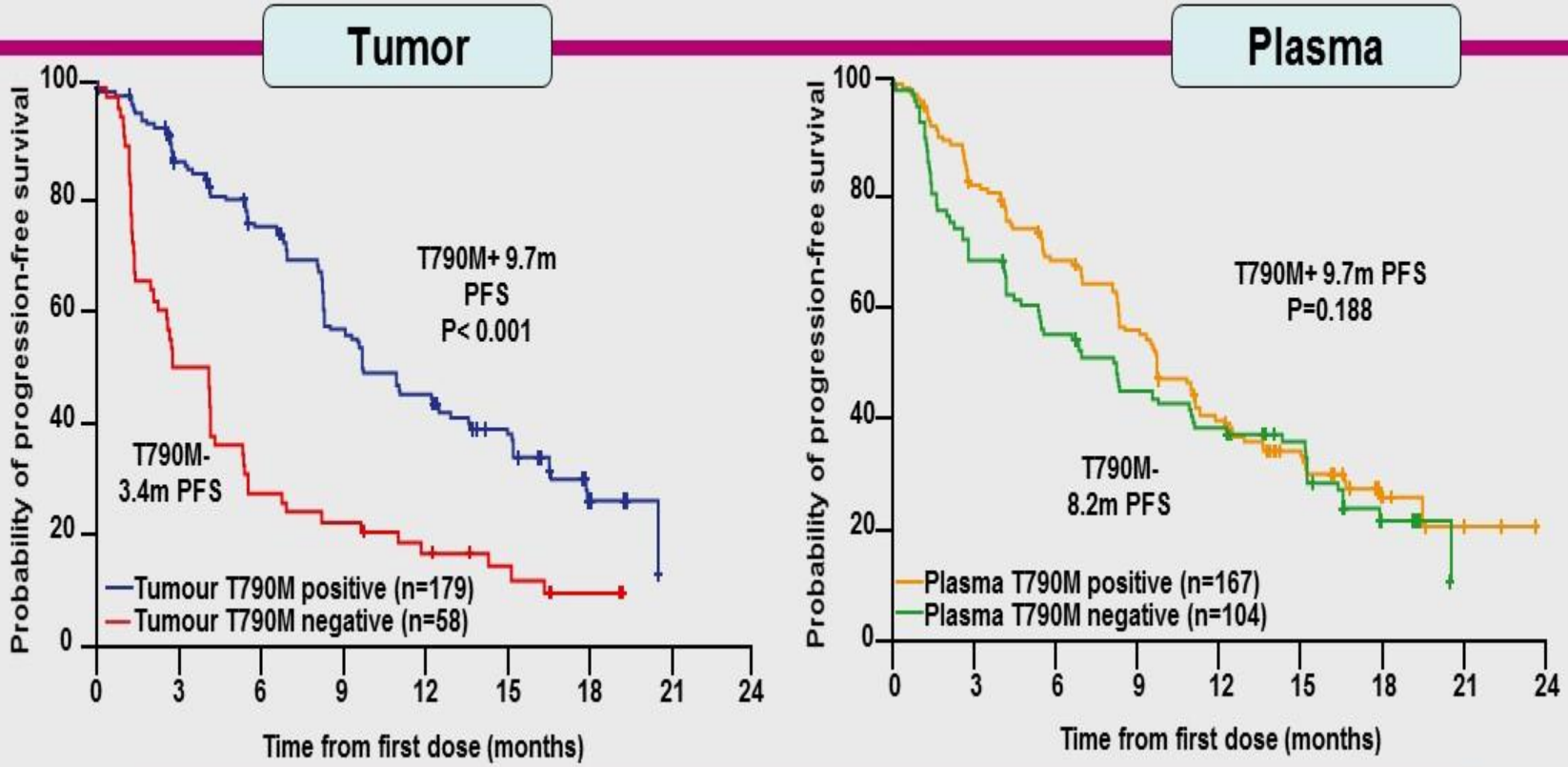
ctDNA method	Study	Exon19 del	L858R	T790M
COBAS	Karlovich 2016 (n=99/95)	73%		64%
ddPCR	Sacher 2016 (n=180/60)	82%	74%	77%
BEAMing dPCR	Oxnard 2016 (n=216)	82%	86%	70%

➢ ctDNA testing: specific requirements for sampling and lab methods

Haber et al. Cancer Discov 650-661, 2014
Pantel et al. Cancer Res 73:6384-6388, 2013
Karlovich et al. Clin Cancer Res 22:2386-2395, 2016
Sacher et al. JAMA Oncol 2:1014-1022, 2016
Oxnard G et al. J Clin Oncol 34:3375-3382, 2016

Stage IV NSCLC

ctDNA: data from Osimertinib ph1 study



1. If ctDNA T790M positive: same benefit from treatment as biopsy positive
2. ctDNA T790M negative is a mix of true and false negatives (variable shed of tumour DNA into blood)

Oxnard G et al. J Clin Oncol 34:3375-3382, 2016

Stage IV NSCLC

Oncogene-driven adenocarcinoma

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2017	Trametinib+Dafrafenib (phase 2 data)	-	-	ORR	-	(02/2017)

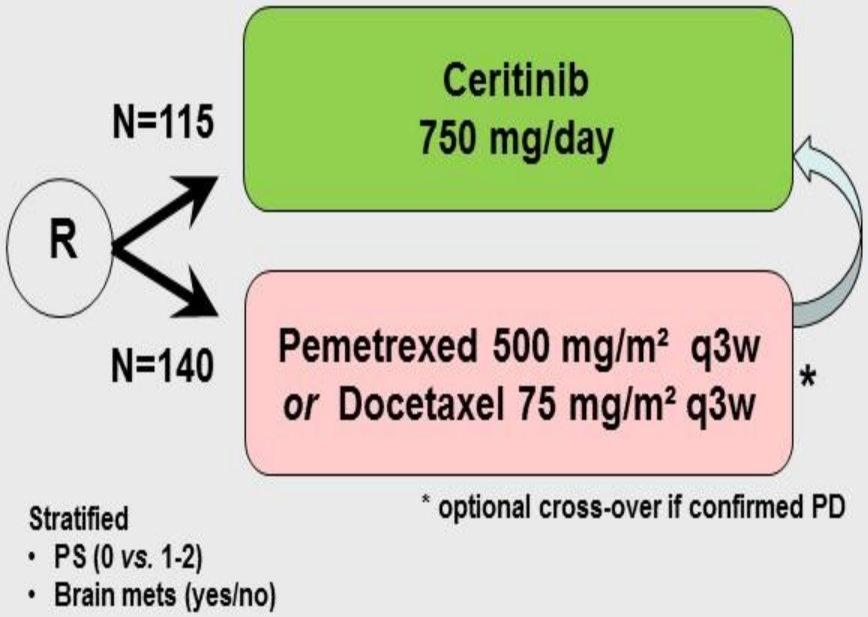
Stage IV NSCLC

Ph3 study: Ceritinib in relapsed ALK+ NSCLC

ASCEND 5

Advanced ALK+ NSCLC

- Prior crizotinib
- 1 or 2 prior chemotherapies
- Progressive disease
- PS 0-2
- Measurable disease
- Stable brain mets allowed



Primary endpoint

- PFS [BIRC]

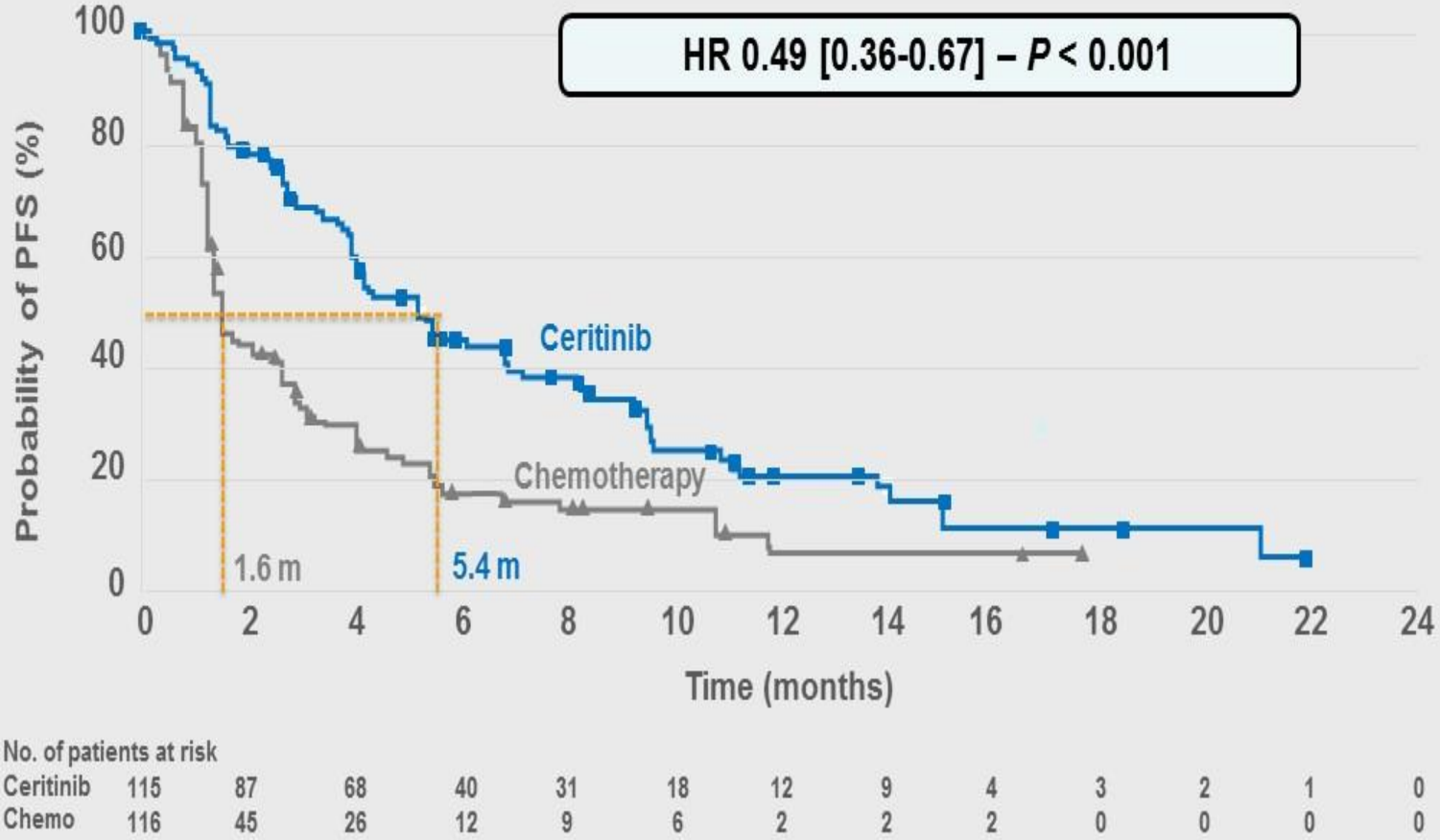
Other endpoints

- OS
- PFS [investigator]
- ORR and duration
- Intracranial efficacy
- Safety
- PRO

Scagliotti et al, ESMO LBA 42, 2016

Stage IV NSCLC

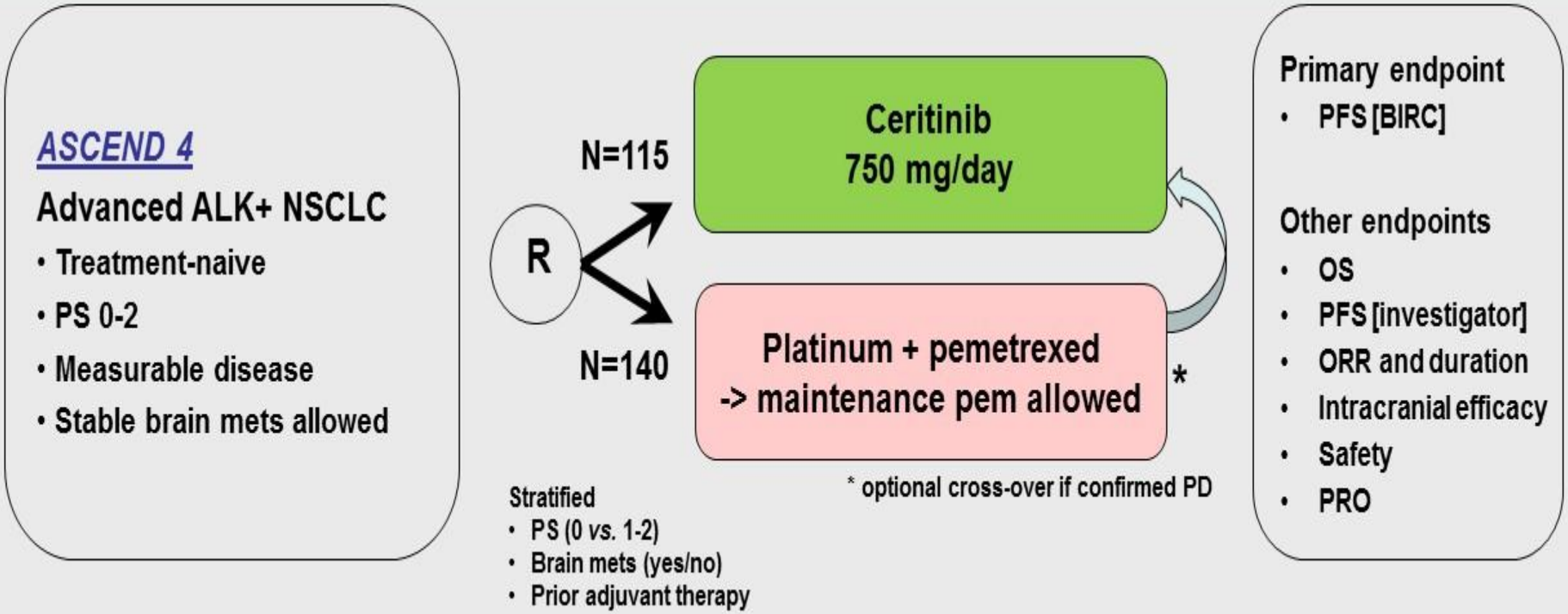
Ph3 study: Ceritinib in relapsed ALK+ NSCLC



Scagliotti et al, ESMO LBA 42, 2016

Stage IV NSCLC

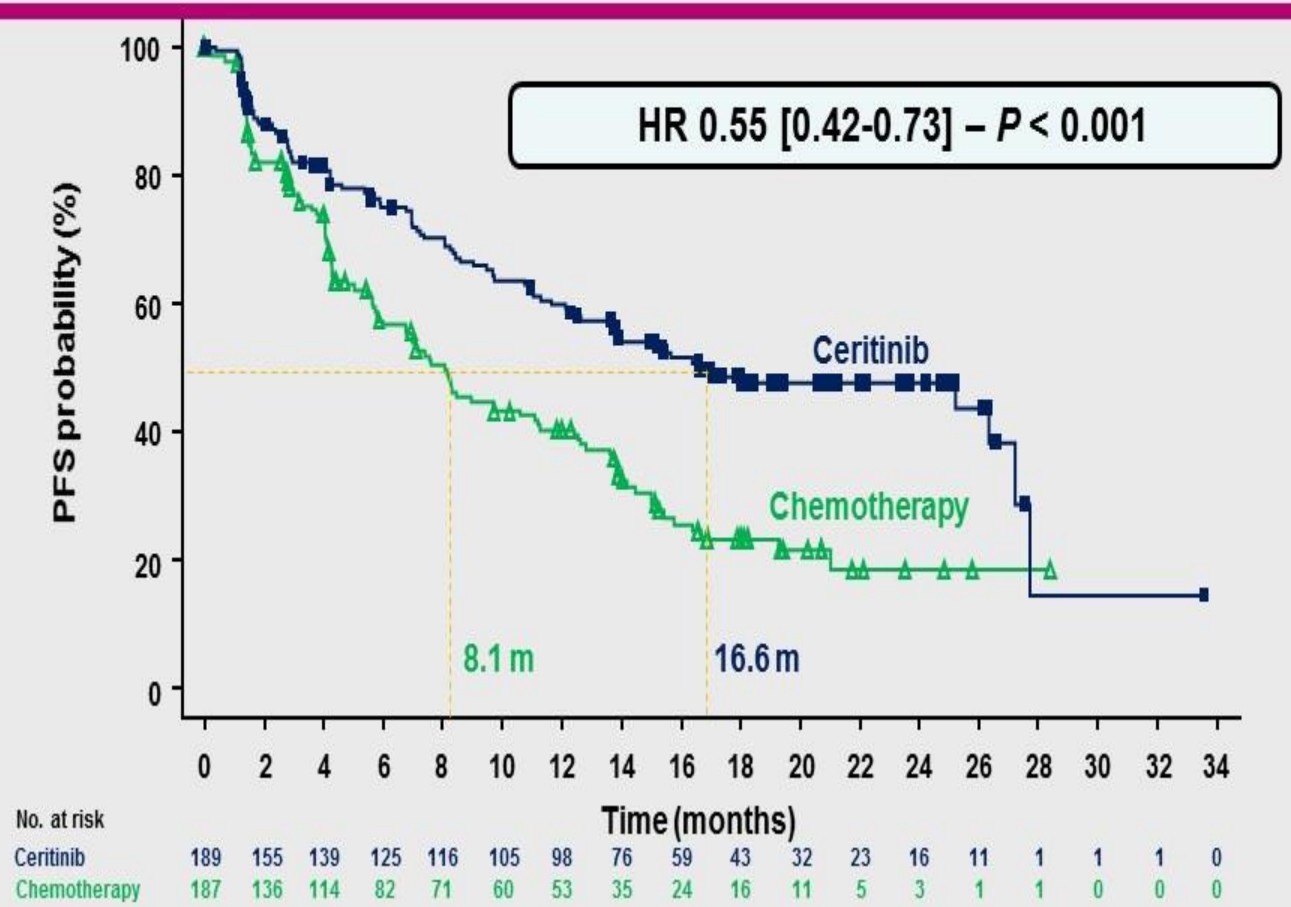
Ph3 study: Ceritinib in untreated ALK+ NSCLC



De Castro et al. WCLC Abstract PL.03, 2016
Soria et al. Lancet 389:917-929, 2017

Stage IV NSCLC

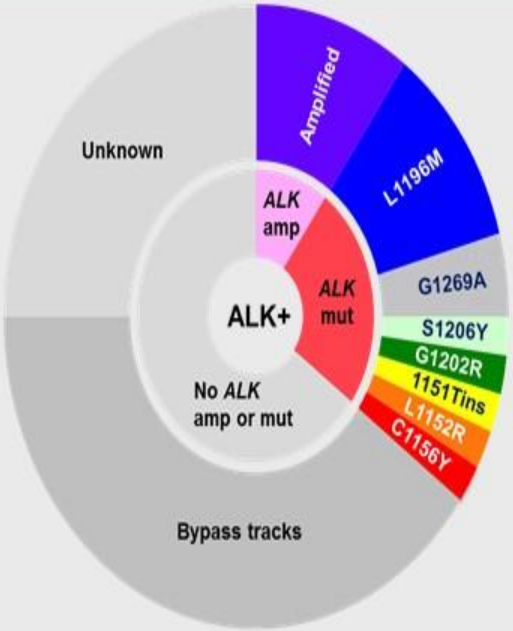
Ph3 study: Ceritinib in untreated ALK+ NSCLC

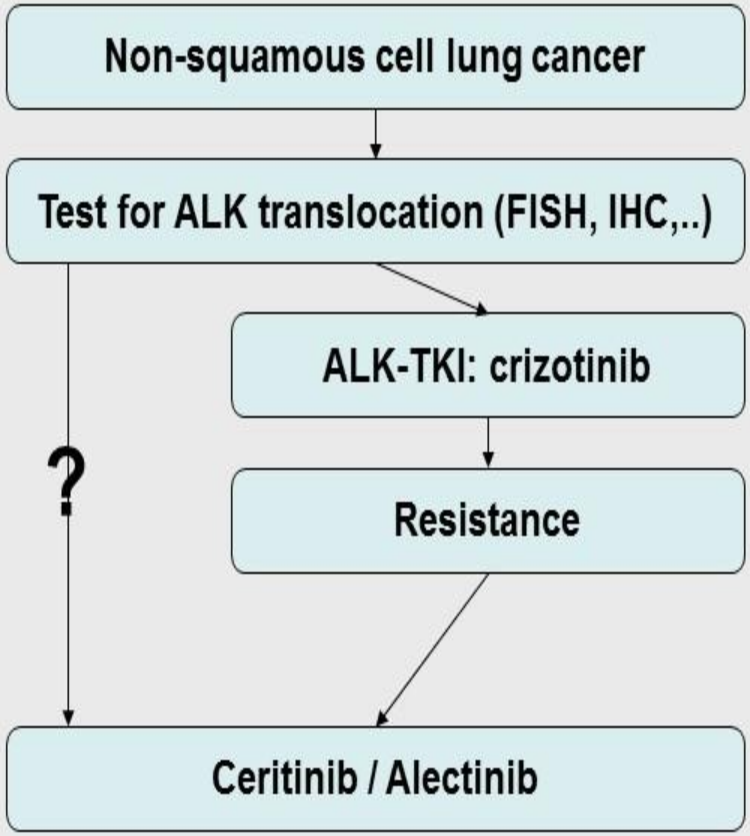


De Castro et al. WCLC Abstract PL.03, 2016
Soria et al. Lancet 389:917-929, 2017

Stage IV NSCLC

ALK+ adenocarcinoma





REBIOPSY

CAN BE DONE

Yu et al. Clin Cancer Res 18:2240-2247, 2013
Cross et al. Cancer Discov 4:1046-1061, 2014

ASCO 2017
Late Breaking News

Alectinib vs crizotinib in treatment-naïve advanced *ALK*+ NSCLC: primary results of the global phase III ALEX study (LBA9008)

Alice Shaw[1], Solange Peters[2], Tony Mok[3], Shirish M. Gadgeel[4], Jin Seok Ahn[5], Sai-Hong Ignatius Ou[6], Maurice Perol[7], Rafal Dziadziuszko[8], Dong-Wan Kim[9], Rafael Rosell[10], Ali Zeaiter[11], Ting Liu[11], Sophie Golding[11], Bogdana Balas[11], Johannes Noe[11], Peter N. Morcos[12], and D. Ross Camidge[13] on behalf of the ALEX investigators

1. Massachusetts General Hospital, Boston, MA, USA; 2. Lausanne University Hospital, Switzerland; 3. Chinese University of Hong Kong, Hong Kong; 4. Karmanos Cancer Institute/Wayne State University, Detroit, MI, USA; 5. Sungkyunkwan University School of Medicine, Seoul, South Korea; 6.Chao Family Comprehensive Cancer Center, University of California, Irvine School of Medicine, Orange, CA, USA; 7. Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France; 8. Department of Oncology and Radiotherapy, Medical University of Gdansk, Gdansk, Poland; 9. Seoul National University Hospital, Seoul, South Korea; 10. Catalan Institute of Oncology, Barcelona, Spain; 11. F. Hoffmann-La Roche Ltd, Basel, Switzerland; 12. Roche Innovation Center, New York, USA; 13. University of Colorado, Denver, CO, USA

Shaw et al Journal of Clinical Oncology 35; 18 suppl

Stage IV NSCLC - *Ph3 study*

Alectinib vs. Crizotinib in untreated ALK+ NSCLC

-----ASCO 2017-----
Late Breaking News

ALEX

Advanced stage NSCLC

- ALK+ (central IHC testing)
- No prior treatment
- PS 0-2
- Asymptomatic brain mets allowed

R

N=152 → **Alectinib 600 mg BID**

N=151 → **Crizotinib 250 mg BID**

No cross-over per protocol

Stratified

- PS (0-1/2)
- Origin (Asian/nonAsian)
- Brain mets (yes/no)

Primary endpoint

- PFS by investigator

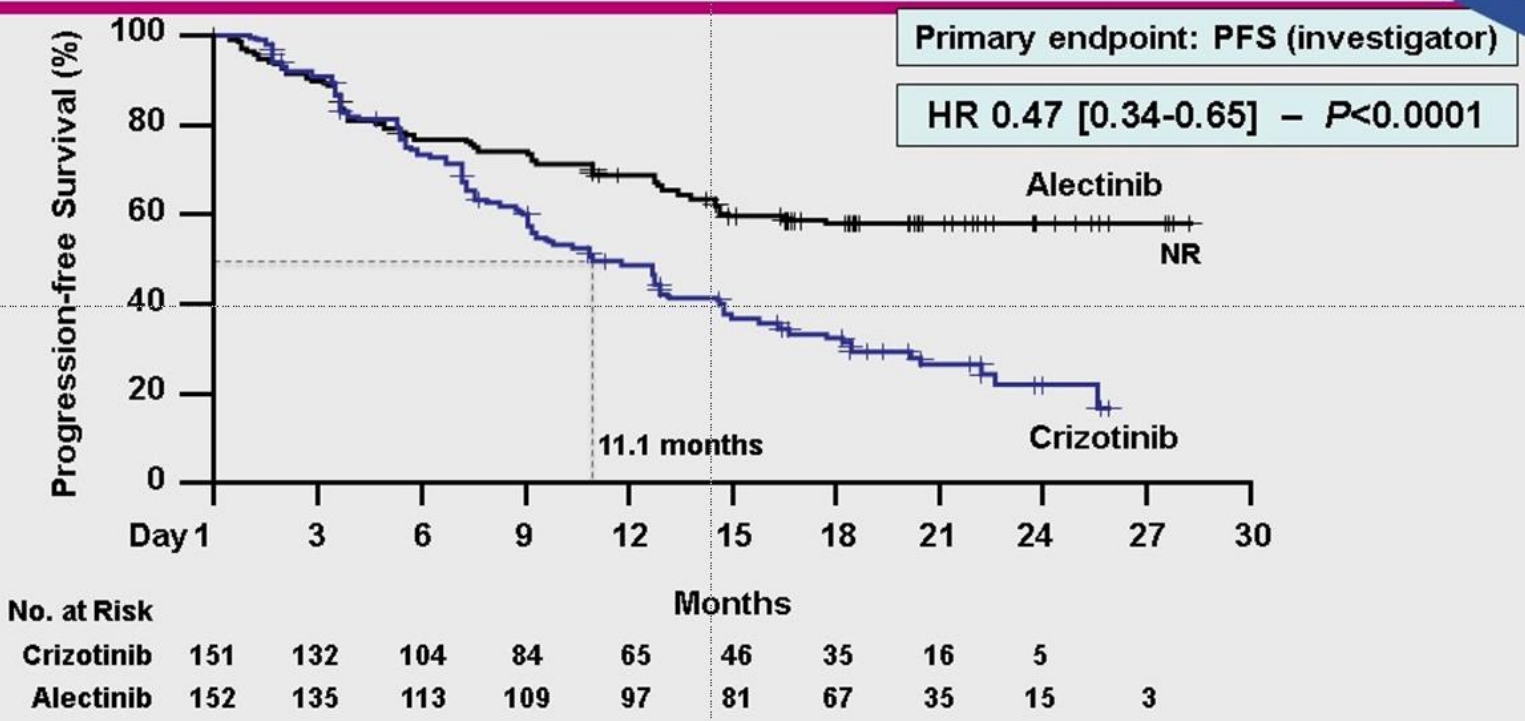
Other endpoints

- PFS by BIRC
- Time to CNS PD
- ORR - DoR
- OS
- Safety
- PRO

Shaw et al Journal of Clinical Oncology 35; 18 suppl

Stage IV NSCLC - *Ph3 study*

Alectinib vs. Crizotinib in untreated ALK+ NSCLC



Shaw et al Journal of Clinical Oncology 35; 18 suppl

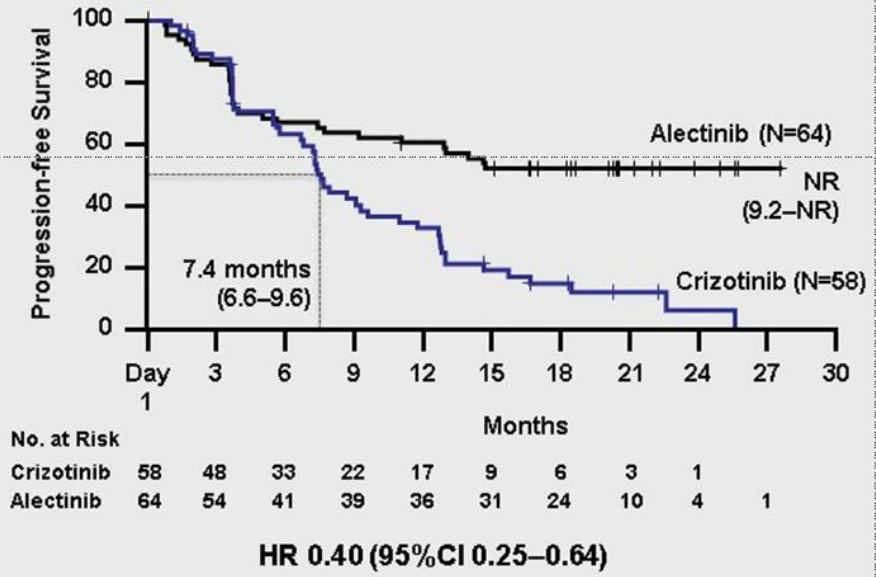
Stage IV NSCLC - *Ph3 study*

Alectinib vs. Crizotinib in untreated ALK+ NSCLC

-----ASCO 2017-------
Late Breaking News

PFS ≈ baseline brain mets

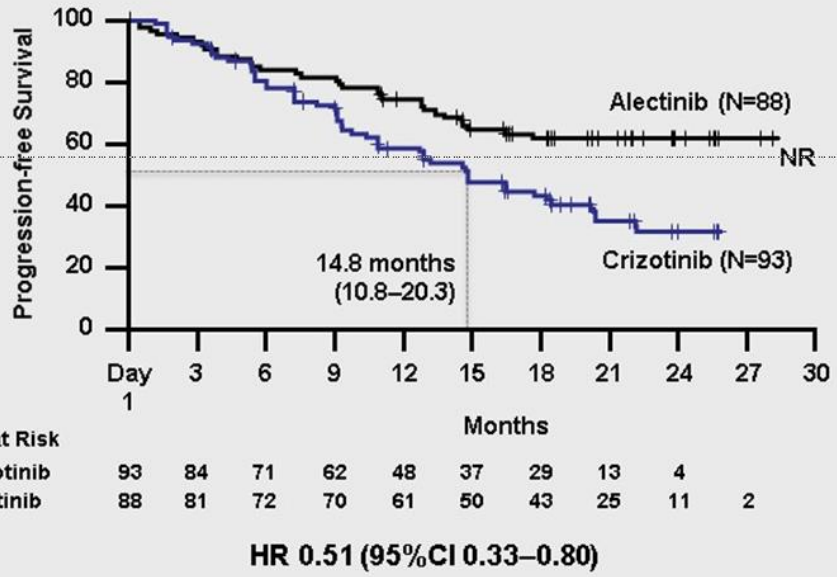
Patients with CNS metastases at baseline



No. at Risk										
Crizotinib	58	48	33	22	17	9	6	3	1	
Alectinib	64	54	41	39	36	31	24	10	4	1

HR 0.40 (95%CI 0.25–0.64)

Patients without CNS metastases at baseline



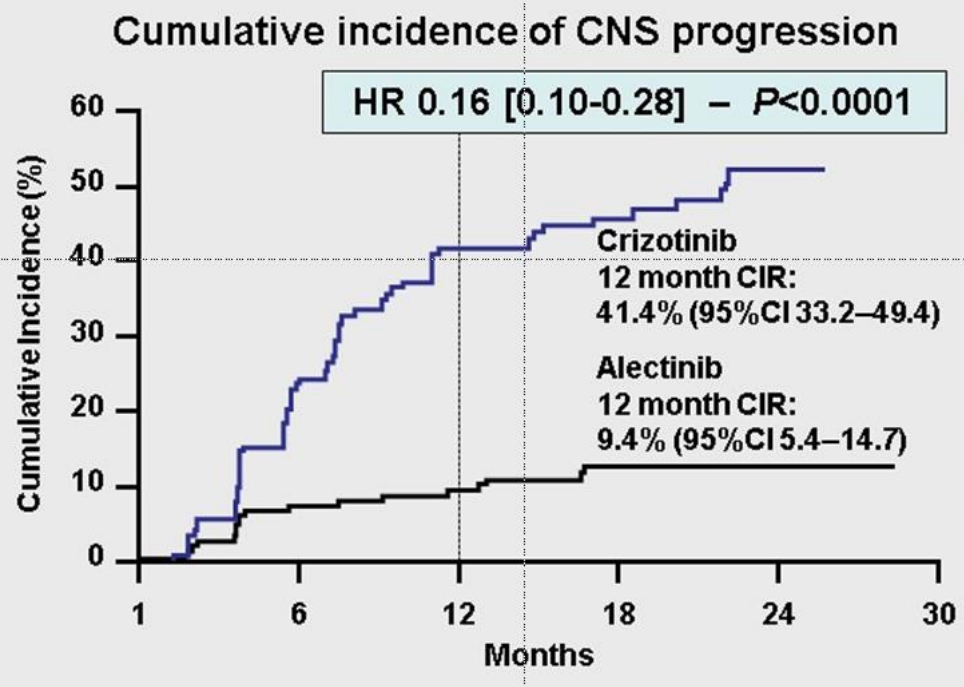
No. at Risk										
Crizotinib	93	84	71	62	48	37	29	13	4	
Alectinib	88	81	72	70	61	50	43	25	11	2

HR 0.51 (95%CI 0.33–0.80)

Shaw et al Journal of Clinical Oncology 35; 18 suppl

Stage IV NSCLC - *Ph3 study*

Alectinib vs. Crizotinib in untreated ALK+ NSCLC



Shaw et al Journal of Clinical Oncology 35; 18 suppl

Stage IV NSCLC - *Ph3 study*

Alectinib vs. Crizotinib in untreated ALK+ NSCLC

- First global RCT comparing next- versus first-generation ALK TKI in 1st line therapy

- Alectinib, in comparison to crizotinib:
  - Significantly prolonged PFS (HR 0.47, 95%CI 0.34-0.65)
  - Significantly improved intracranial ORR (81% *vs.* 50%)
  - Significantly delayed time to CNS progression (HR 0.16 [0.10-0.28] – *P*<0.0001)
  - Had a more favorable safety profile

- Alectinib may become a new standard for previously untreated advanced *ALK*+ NSCLC

Shaw et al Journal of Clinical Oncology 35; 18 suppl

Stage IV NSCLC

Oncogene-driven adenocarcinoma

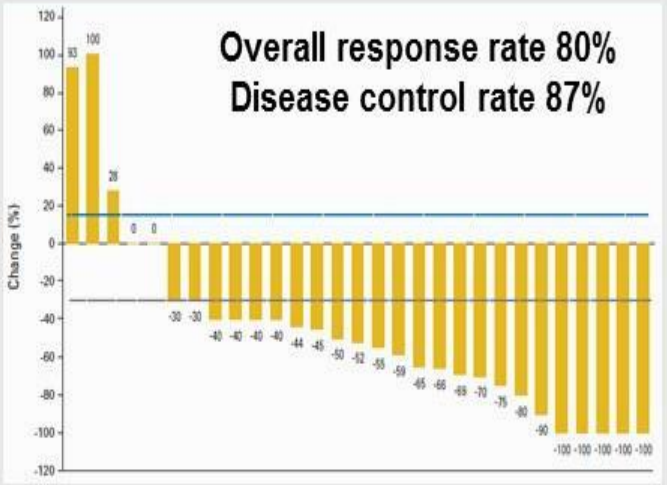
Oncogene-driven NSCLC		Acronym	Comparator	1° endpoint	HR	EMA approval
>EGFR mut+ (10-12%)						
2015	Osimertinib for T790M resistance	AURA 3	Doublet chemo	PFS	0.30	02/2016
>ALK+ (3-4%)						
2015	Crizotinib 1L therapy	PROFILE 1014	Doublet chemo	PFS	0.45	01/2016
2015	Ceritinib for crizotinib resistance	ASCEND 5	Single chemo	PFS	0.49	06/2015
2017	Alectinib for crizotinib resistance (phase 2 data)	-	-	ORR	-	(12/2016)
2017	Ceritinib 1L therapy	ASCEND 4	Doublet chemo	PFS	0.55	NA
2017	Alectinib 1L therapy (Japan only)	J-ALEX	Crizotinib	PFS	0.34	NA
>ROS1+ NSCLC (1-2%)						
2017	Crizotinib (phase 2 data)	-	-	ORR	-	08/2016
>BRAF+ NSCLC (0.5-1%)						
2017	Trametinib+Dafrafenib (phase 2 data)	-	-	ORR	-	(02/2017)

Stage IV NSCLC

Rare oncogene drivers

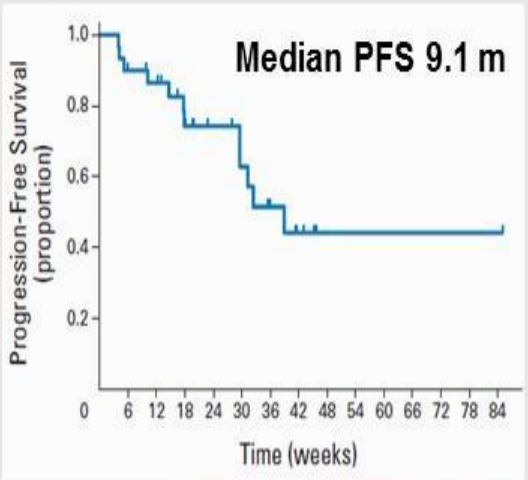
Crizotinib Therapy for Advanced Lung Adenocarcinoma and a *ROS1* Rearrangement: Results From the EUROS1 Cohort

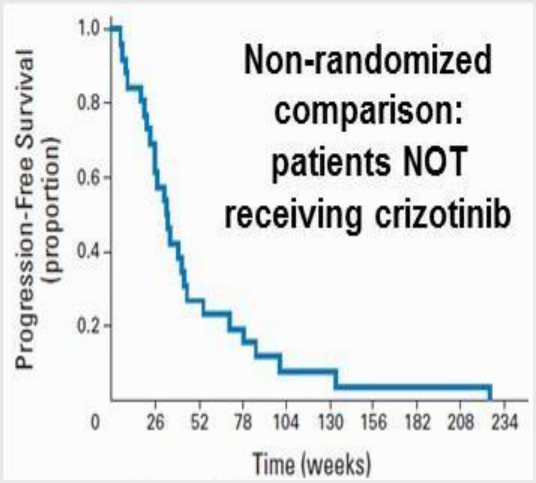
Julien Mazières, Gérard Zalcman, Lucio Crinò, Pamela Biondani, Fabrice Barlesi, Thomas Filleron, Anne-Marie C. Dingemans, Hervé Léna, Isabelle Monnet, Sacha I. Rothschild, Federico Cappuzzo, Benjamin Besse, Luc Thiberville, Damien Rouvière, Rafal Dziadziuszko, Egbert F. Smit, Jurgen Wolf, Christian Spirig, Nicolas Pecuchet, Frauke Leenders, Johannes M. Heuckmann, Joachim Diebold, Julie D. Milia, Roman K. Thomas, and Oliver Gautschi



***ROS1* tumors**

- All adenocarcinoma
- Median age 50.5
- Females 64.5%
- Never-smoker 71%





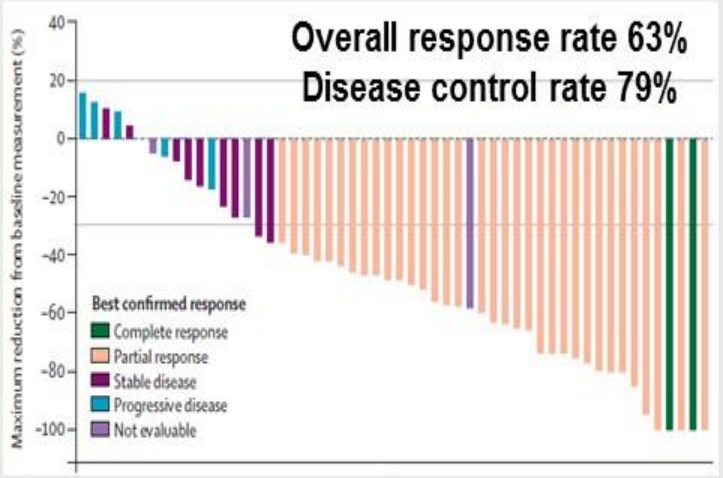
Mazieres et al. J Clin Oncol 33:992-999, 2015

Stage IV NSCLC

Rare oncogene drivers

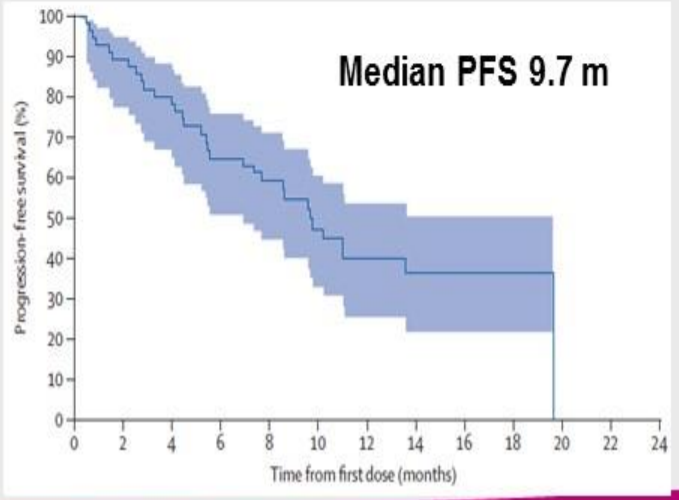
Dabrafenib plus trametinib in patients with previously treated *BRAF*^{V600E}-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, Tae Min Kim, Julien Mazieres, Silvia Novello, James R Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson



***BRAF* tumors**

- All but 2 adenocarcinoma
- Median age 64
- Females 49%
- Never-smoker 28%



Planchard et al, Lancet Oncol 17:984-993, 2016

Take-Home Message

Oncogene-driven NSCLC

- Several generations of TKI for *EGFR*mut+ and *ALK*+ tumors
  - Optimal sequences still to be defined

- Emerging treatments for rare oncogene drivers (*ROS1*, *BRAF*)
  - Drugs registered based on response rates in ph2 trials
  - Others to come (*MET, RET, HER2*, …)

Advanced NSCLC

NSCLC immunotherapy

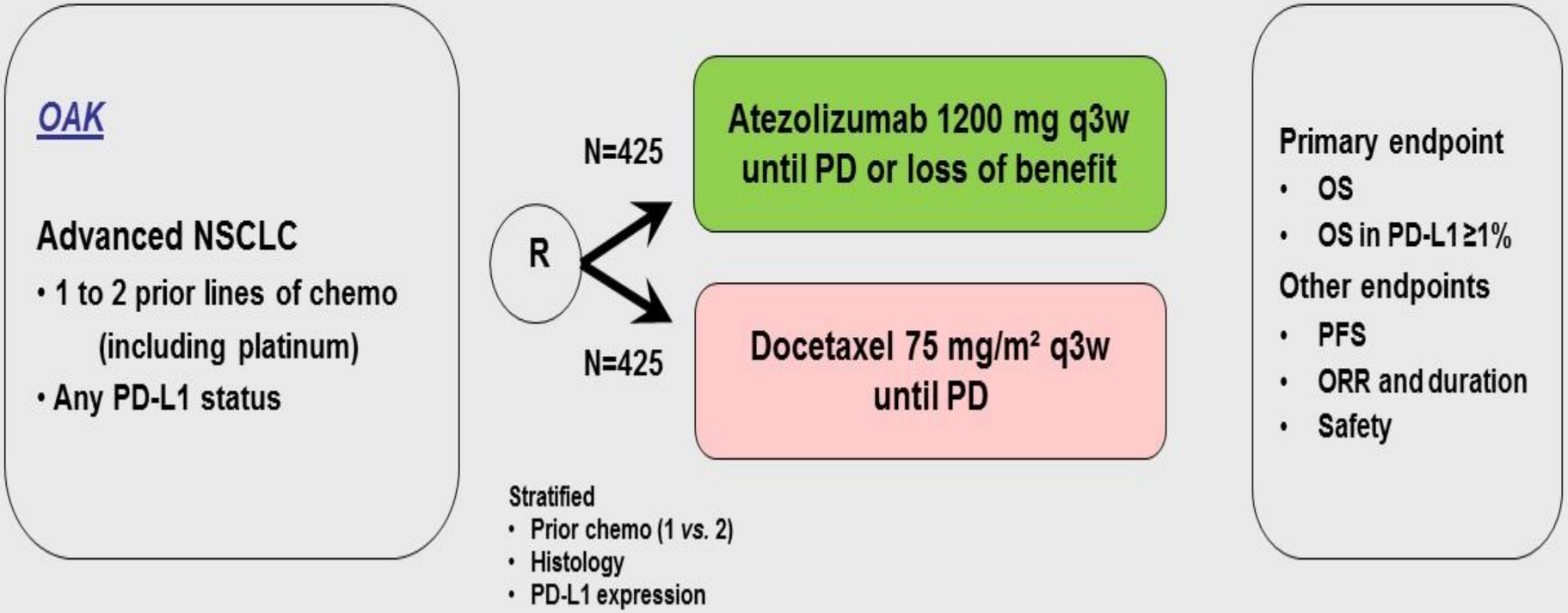
Stage IV NSCLC

Anti-PD-1 / PD-L1 immunotherapy

Immunotherapy						
2015	Nivolumab 2L	CHECKMATE 017	Docetaxel	OS	0.62	12/2015
2015	Nivolumab 2L	CHECKMATE 057	Docetaxel	OS	0.73	02/2016
2016	Pembrolizumab 2L/3L (PD-L1 >1%)	KEYNOTE 010	Docetaxel	OS	0.71	08/2016
2017	Atezolizumab 2L/3L	OAK	Docetaxel	OS	0.73	pending
2017	Pembrolizumab 1L (PD-L1 >50%)	KEYNOTE 024	Doublet chemo	PFS	0.50	03/2017
2017	Nivolumab 1L (PD-L1 >5%)	CHECKMATE 026	Doublet chemo	PFS	1.15	NA

Stage IV NSCLC immunotherapy

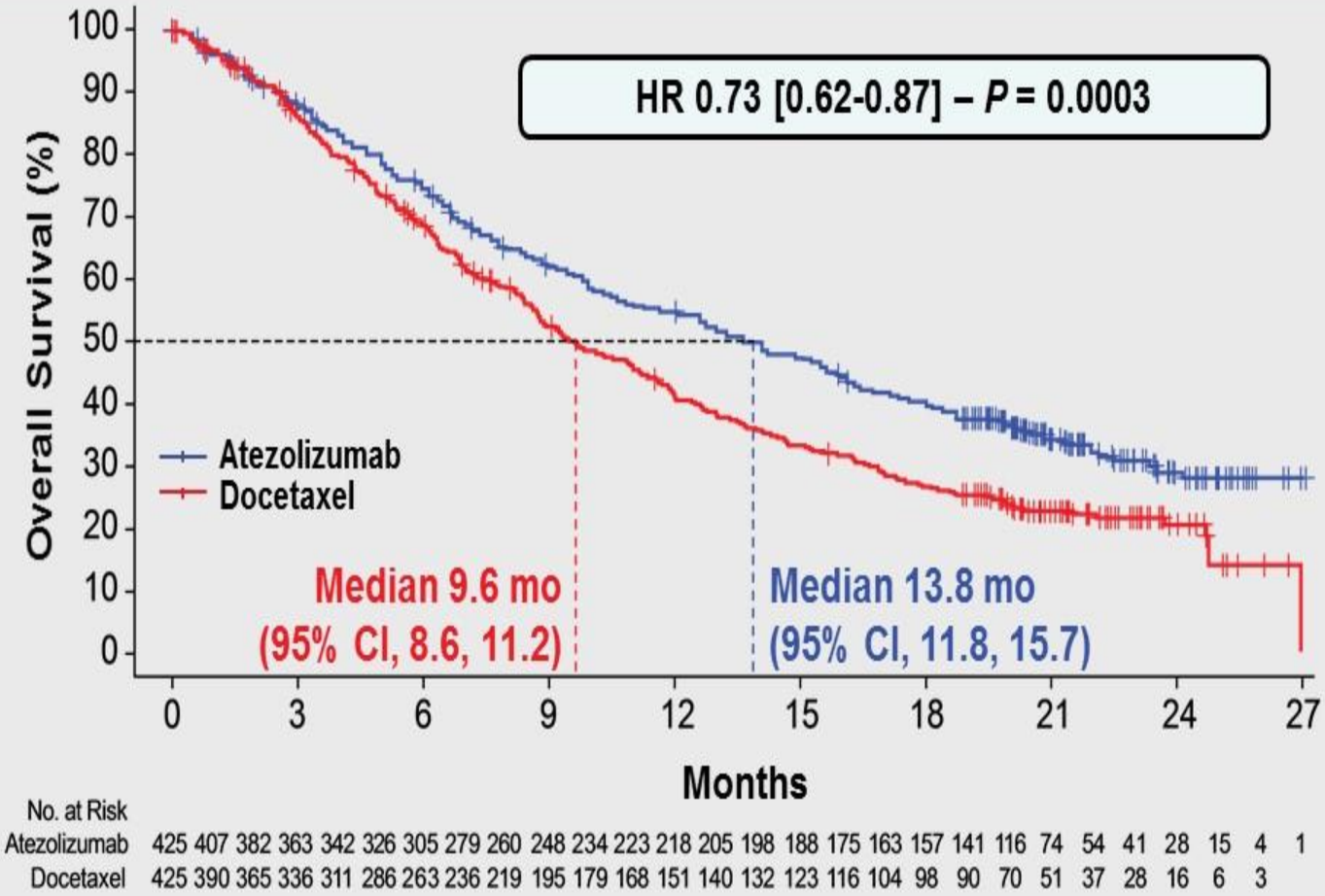
Ph3 study: Atezolizumab in relapsed NSCLC



Barlesi et al, ESMO 2016
Rittmeyer et al, Lancet 389:255-265, 2017

Stage IV NSCLC immunotherapy

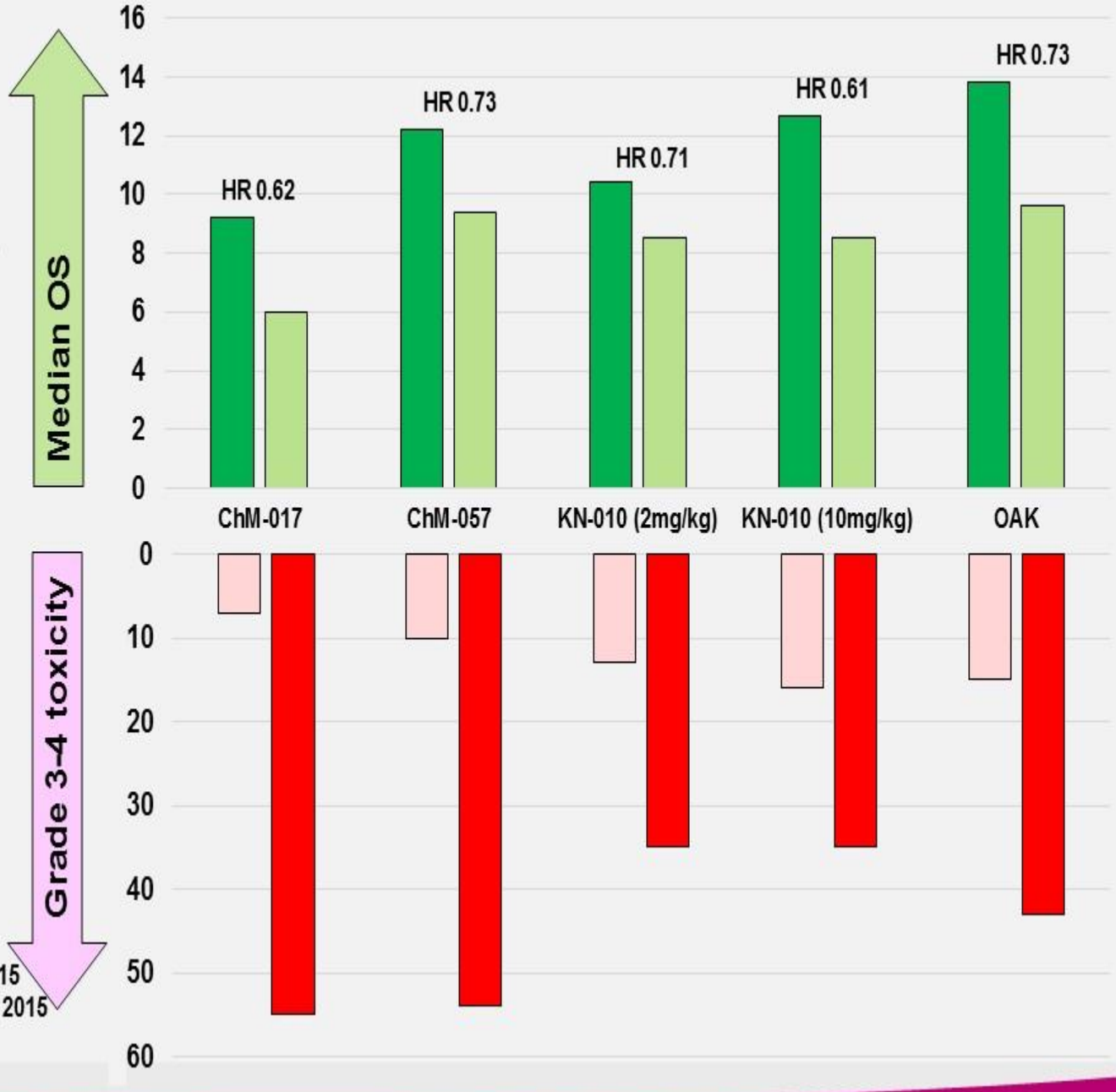
Ph3 study: Atezolizumab in relapsed NSCLC



Barlesi et al, ESMO 2016
Rittmeyer et al, Lancet 389:255-265, 2017

Four phase 3 trials in relapsing NSCLC: CPI *vs.* docetaxel

- Checkmate 017
  - 100% SQ
- Checkmate 057
  - 100% NSQ
- Keynote 010
  - 21% SQ 70% NSQ
- OAK
  - 26% SQ 74% NSQ



Brahmer et al, N Engl J Med 373:123-135, 2015
Borghaei et al, N Engl J Med 373:1627-1639, 2015
Herbst et al, Lancet 387:1540-150, 2016
Barlesi et al, ESMO 2016

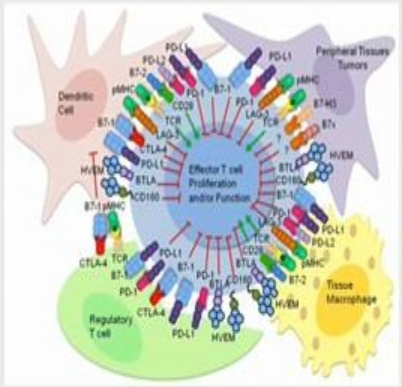
NSCLC immunotherapy

Is PD-L1 a biomarker?

- **EGFRmut ≈ EGFR-TKI**
  - Related to tumor only
  - "Simple" mechanism

  - Yes/No phenomenon

- **PD-L1 IHC ≈ anti-PD-1/PD-L1**
  - Related to tumor & environment
  - Complex mechanism



  - Gradual phenomenon

Landmark biomarker

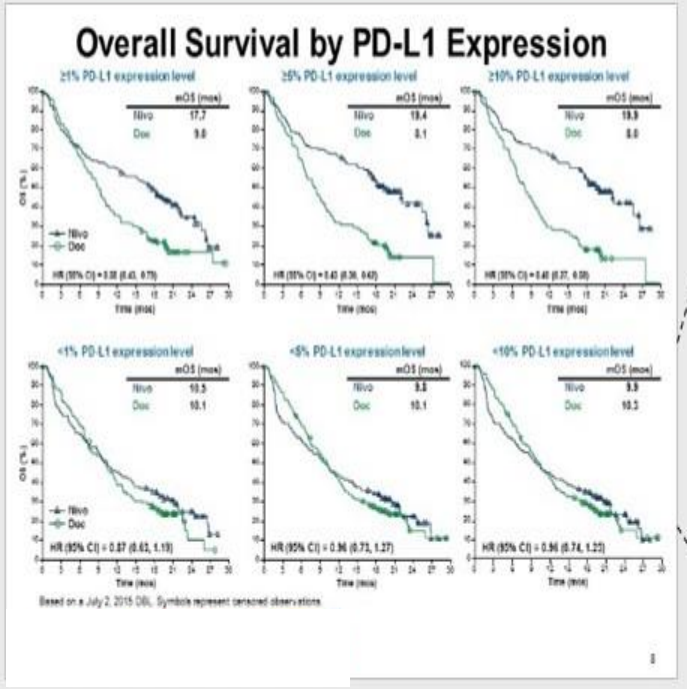
?

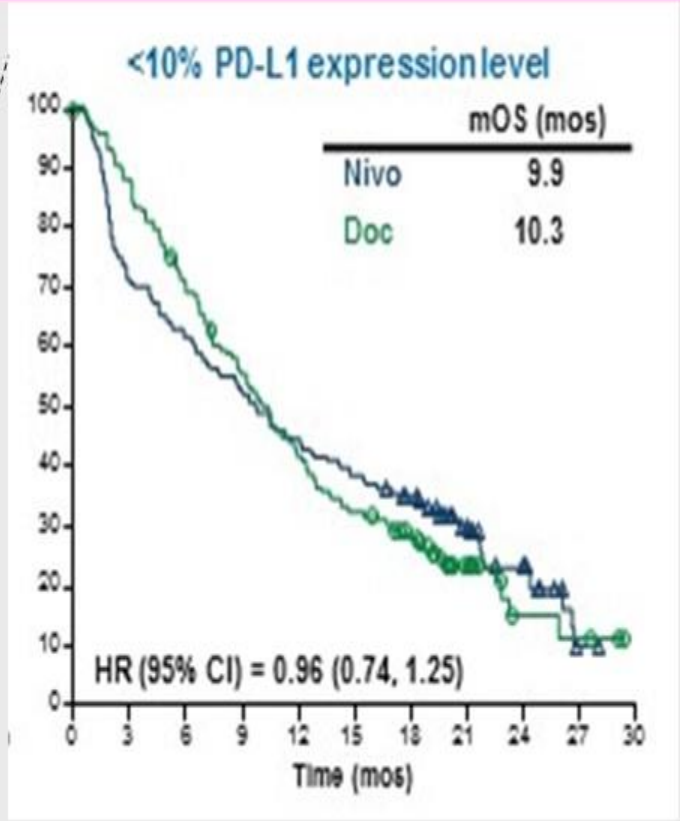
Allison et al, JAMA 314:1113-1114, 2015

NSCLC immunotherapy

PD-L1 biomarker: nivolumab

Nivolumab Ph3 [CheckMate-057



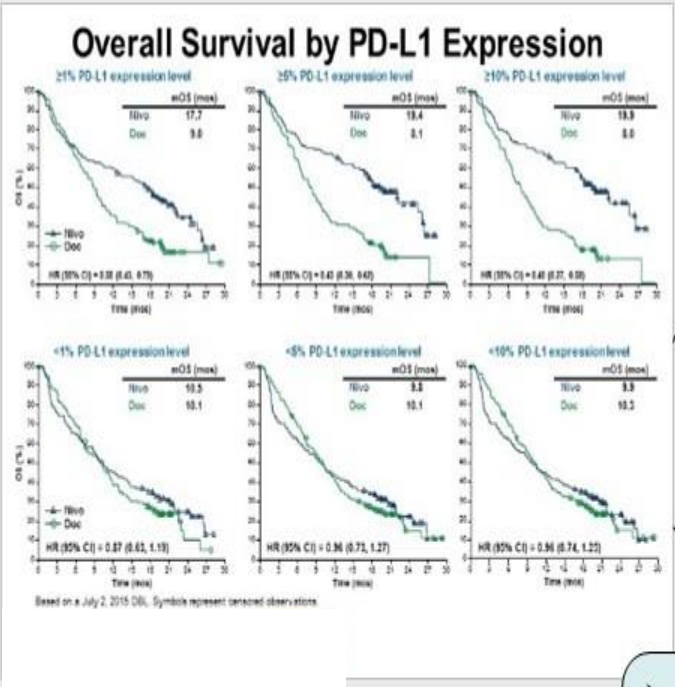


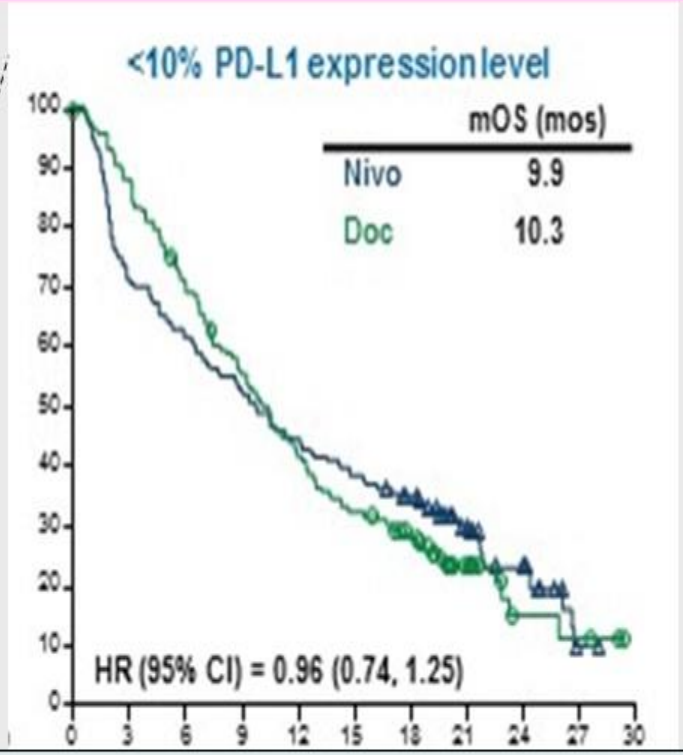
Horn et al, **ESMO-ASIA 2015**

NSCLC immunotherapy

PD-L1 biomarker: nivolumab

Nivolumab Ph3 [CheckMate-057





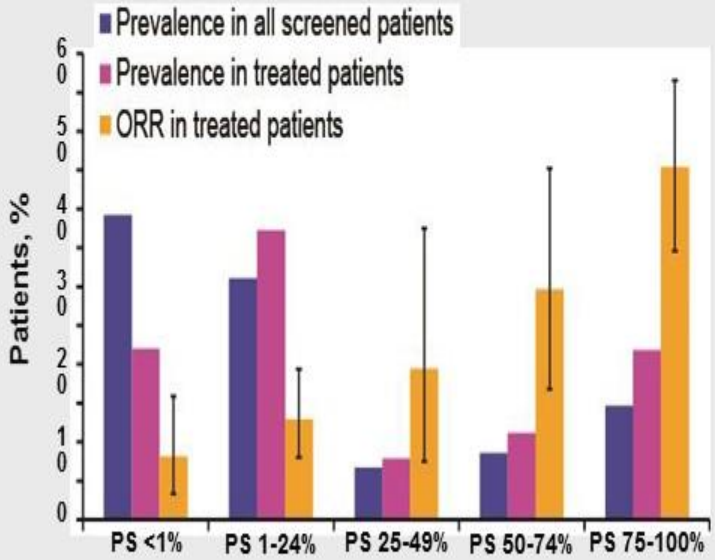
- In 290 patients
  - OS is the same with nivolumab and docetaxel [HR 0.96]
  - Cross-over: patients initially do better with docetaxel

Horn et al, **ESMO-ASIA 2015**

NSCLC immunotherapy

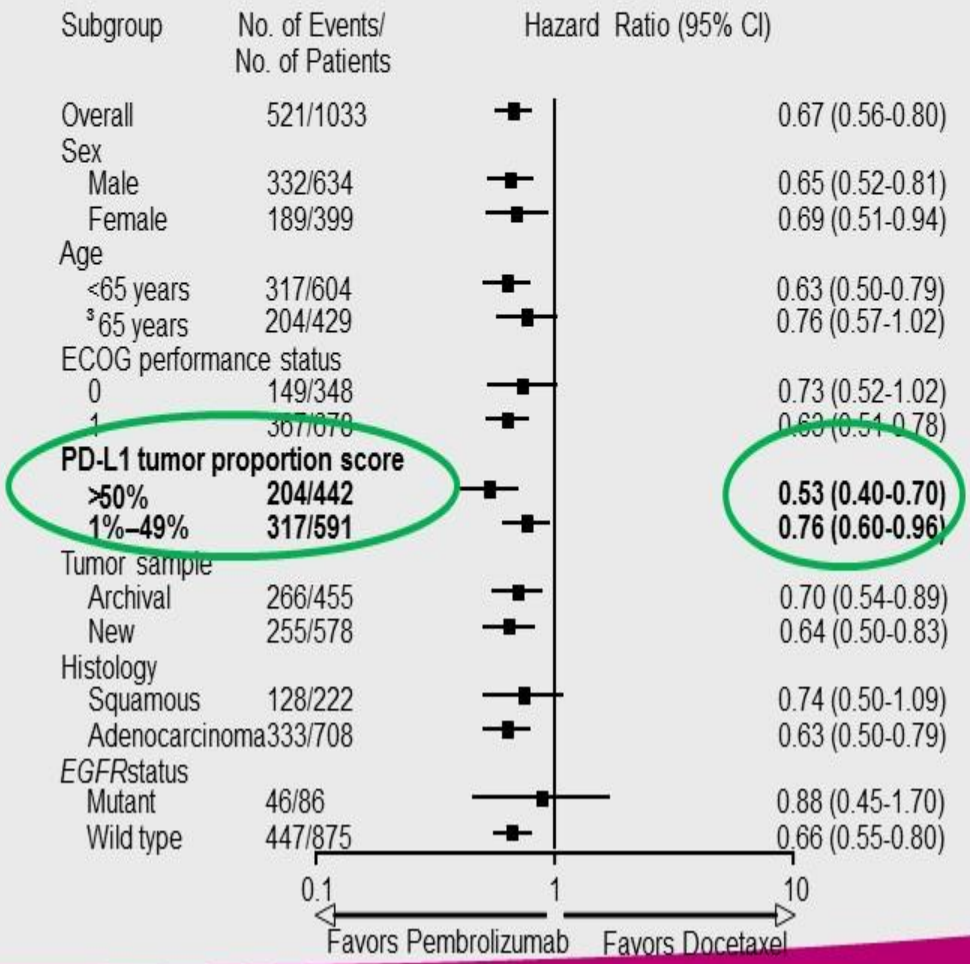
PD-L1 biomarker: pembrolizumab

Pembrolizumab Ph1 [Keynote-001]



<1%	1-24%	25-49%	50-74%	75-100%

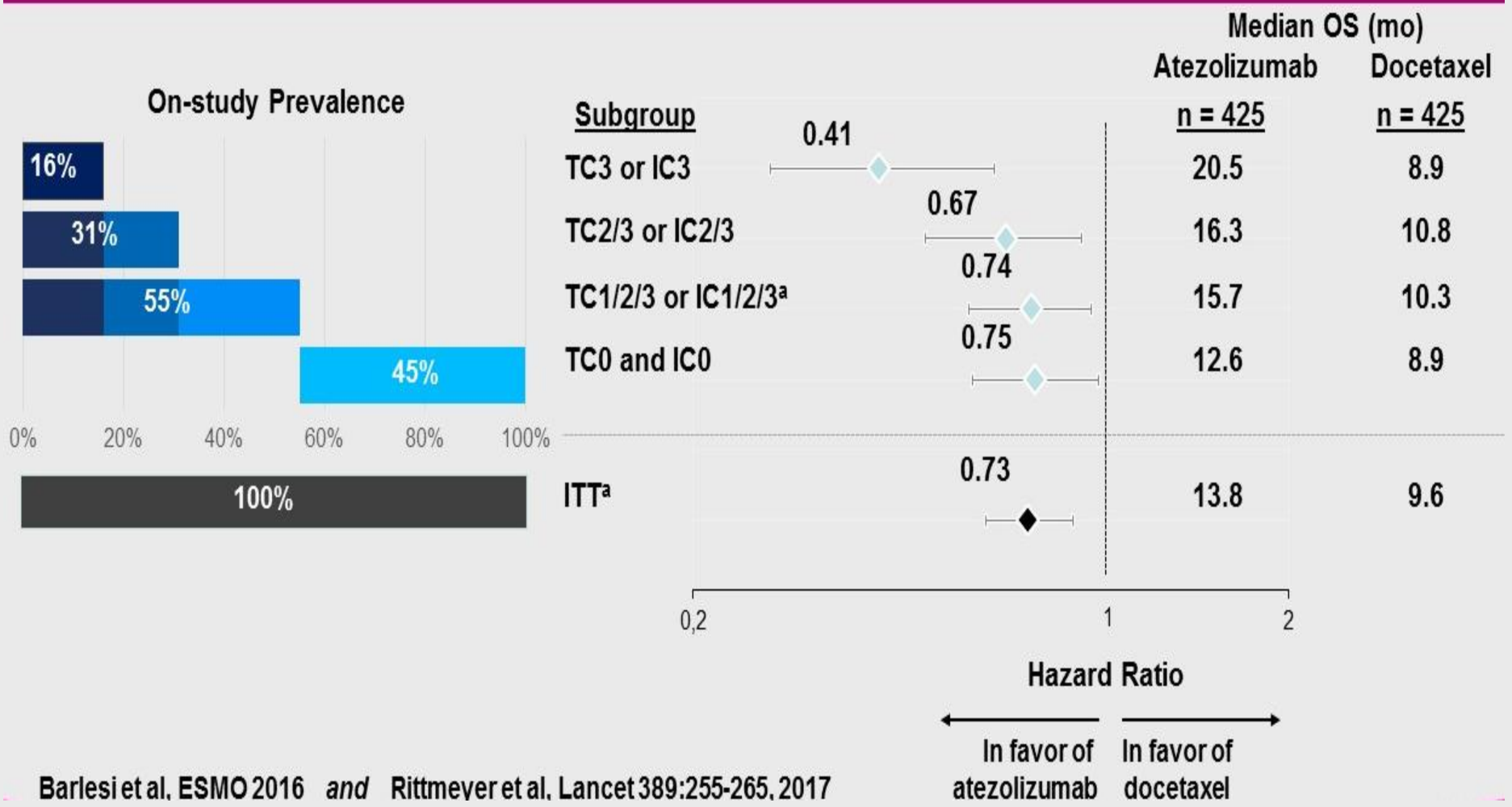
Pembrolizumab Ph3 [Keynote-010]



Garon et al, N Engl J Med 372:2018-2028, 2015 Suppl Material

NSCLC immunotherapy

PD-L1 biomarker: atezolizumab



Barlesi et al. ESMO 2016 *and* Rittmeyer et al. Lancet 389:255-265, 2017

NSCLC immunotherapy

PD-L1 biomarker

YES
PD-L1 IHC is an 'enrichment' biomarker !

Likelihood of response to anti-PD-1/PD-L1

Prefer chemo or TKI

Combination treatment strategies

Anti-PD-1/PD-L1 single agent

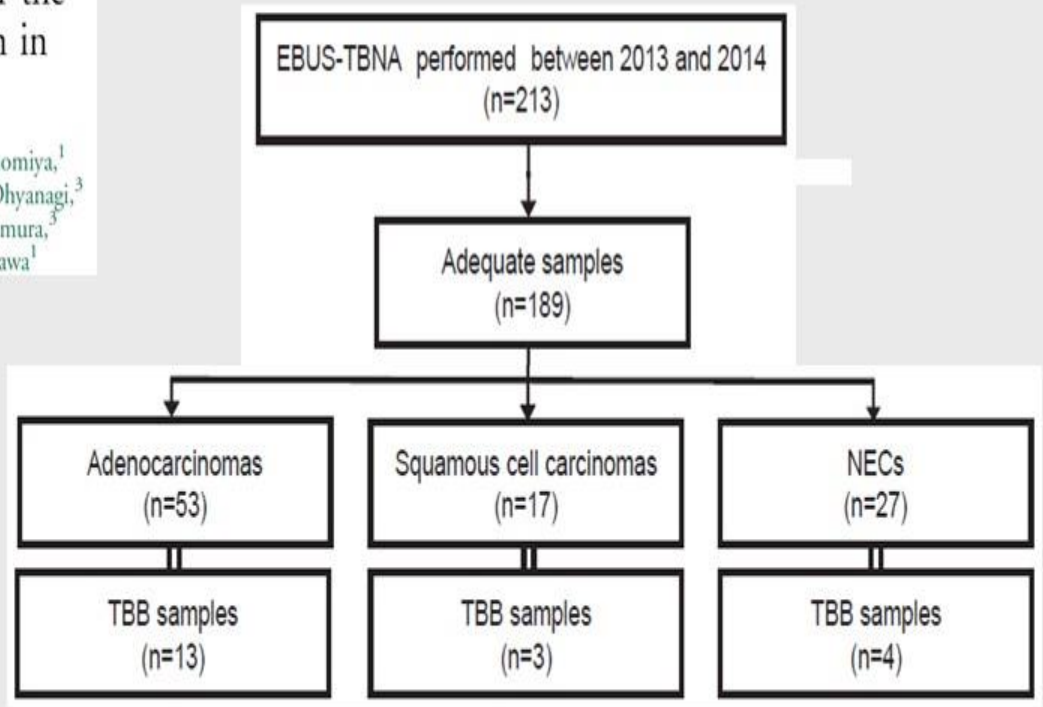
BUT
- Biopsy only
- Multitude of diagnostic tests

NSCLC immunotherapy

PD-L1 biomarker: biopsy only?

EBUS-TBNA as a Promising Method for the Evaluation of Tumor PD-L1 Expression in Lung Cancer

Rie Sakakibara,[1,2] Kentaro Inamura,[1] Yuichi Tambo,[3] Hironori Ninomiya,[1] Satoru Kitazono,[3] Noriko Yanagitani,[3] Atsushi Horiike,[3] Fumiyoshi Ohyanagi,[3] Yosuke Matsuura,[3] Masayuki Nakao,[3] Mingyon Mun,[3] Sakae Okumura,[3] Naohiko Inase,[2] Makoto Nishio,[3] Noriko Motoi,[1,4] Yuichi Ishikawa[1]

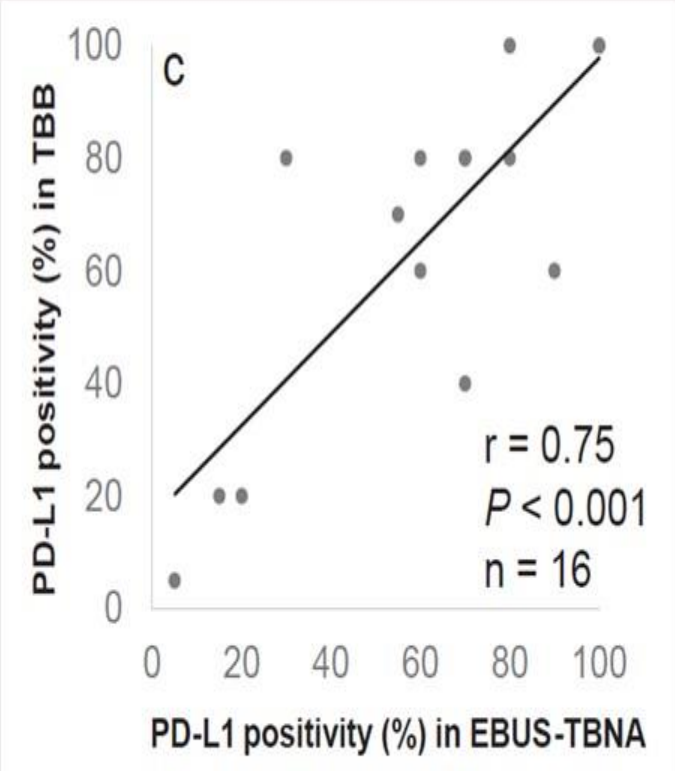


Sakakibara. Clin Lung Cancer. in press 2017

NSCLC immunotherapy

PD-L1 biomarker: biopsy only?

	EBUS-TBNA (n = 97)[a]	TBB (n = 20)[a]	*P*
Total number			
<100	1	1	<.001
100-1000	21	10	
1000-2000	12	7	
>2000	63	2	
Median (IQR)	1149 (379-3334)	510 (218-1085)	
Crush rate, %			
0-5	59	6	<.001
5-50	38	10	
>50	0	4	



Sakakibara. Clin Lung Cancer. in press 2017

NSCLC immunotherapy

PD-L1 biomarker: which test? Blueprint study

PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project

Fred R. Hirsch, MD, PhD,[a,b,*] Abigail McElhinny, PhD,[c] Dave Stanforth, MBA,[d] James Ranger-Moore, PhD,[e] Malinka Jansson, MA,[d] Karina Kulangara, PhD,[d] William Richardson, BA,[e] Penny Towne, BS, MBA,[e] Debra Hanks, MD,[d] Bharathi Vennapusa, MD,[e] Amita Mistry, MD,[e] Rasika Kalamegham, PhD,[f,g] Steve Averbuch, MD,[h] James Novotny, PhD,[h] Eric Rubin, MD,[i] Kenneth Emancipator, MD,[i] Ian McCaffery, PhD,[j,k] J. Andrew Williams, PhD,[j] Jill Walker, PhD,[i] John Longshore, PhD,[m] Ming Sound Tsao, MD,[n] Keith M. Kerr, MB, FRCPath[o]

Agent	Test
Pembrolizumab	Dako 22C3
Nivolumab	Dako 28-8
Atezolizumab	Ventana SP142
Durvalumab	Ventana SP263

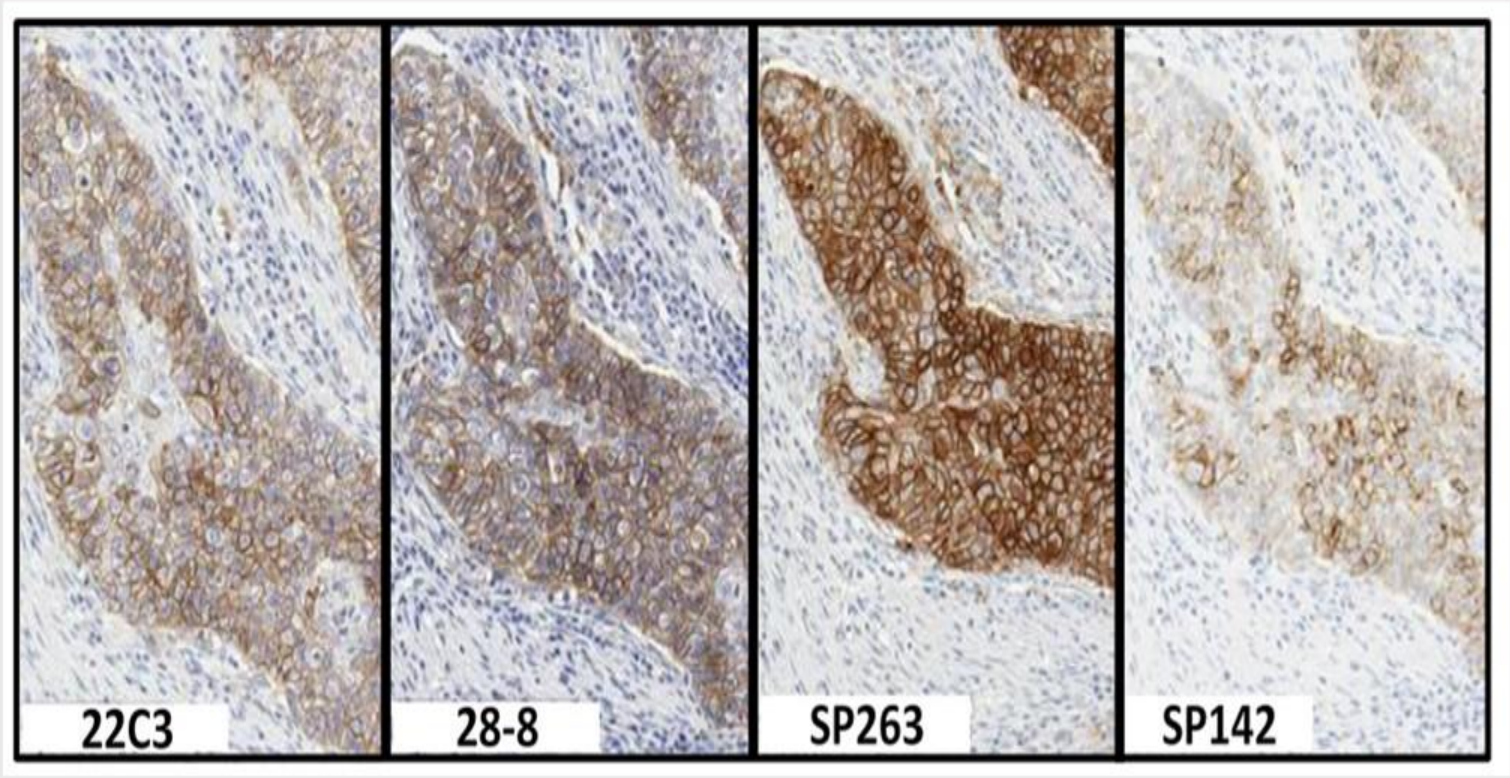
39 NSCLC tumors

- Stained with four PD-L1 IHC assays (22C3, 28-8, SP142, and SP263)
- 3 experts independently evaluated the % of tumor and immune cells staining positive at any intensity
- Clinical diagnostic performance was assessed through comparisons of patient classification above and below a selected expression cut-off and by agreement using various combinations of assays and cut-offs.

Hirsch et al, AACR 2016 *and* J Thorac Oncol 12:208-222, 2017

NSCLC immunotherapy

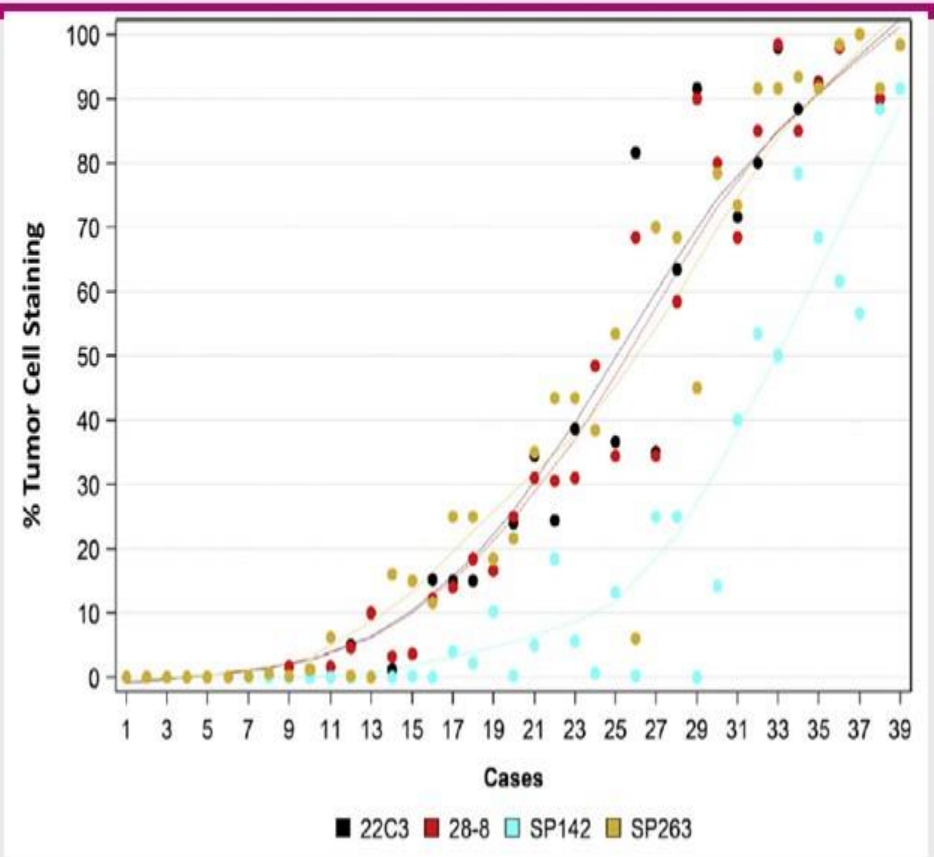
PD-L1 biomarker: which test? Blueprint study

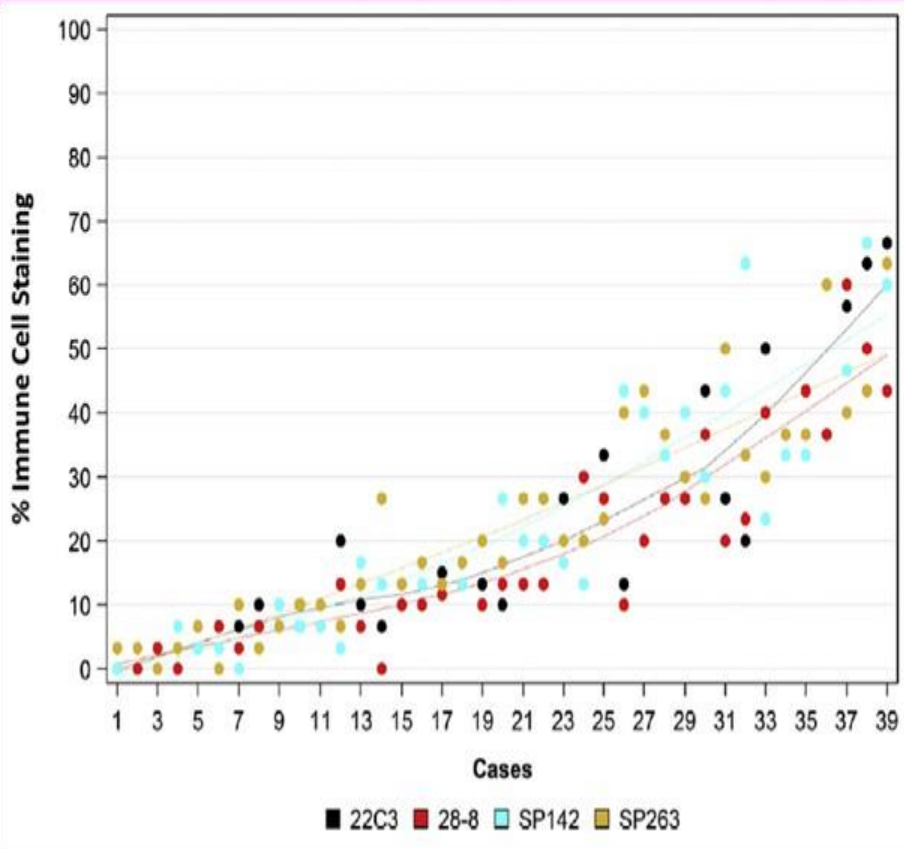


Hirsch et al, AACR 2016 *and* J Thorac Oncol 12:208-222, 2017

NSCLC immunotherapy

PD-L1 biomarker: which test? Blueprint study





Hirsch et al, AACR 2016 *and* J Thorac Oncol 12:208-222, 2017

Take-Home Message

NSCLC immunotherapy (1)

- Established strategies in NSCLC 2L therapy
  - Anti PD-1 (nivolumab; pembrolizumab) / Anti-PD-L1 (atezolizumab)
  - Response: up to about 20%, durable, and translated in remarkable long-term survivals
  - Toxicity: overall less than chemotherapy, but beware of specific immune-related AEs
- PD-L1
  - Established enrichment biomarker
  - Sample type: biopsy established – others to be validated
  - Methodological issues: 3 of 4 assays are close to one another

Stage IV NSCLC

Anti-PD-1 / PD-L1 immunotherapy

Immunotherapy						
2015	Nivolumab 2L	CHECKMATE 017	Docetaxel	OS	0.62	12/2015
2015	Nivolumab 2L	CHECKMATE 057	Docetaxel	OS	0.73	02/2016
2016	Pembrolizumab 2L/3L (PD-L1 >1%)	KEYNOTE 010	Docetaxel	OS	0.71	08/2016
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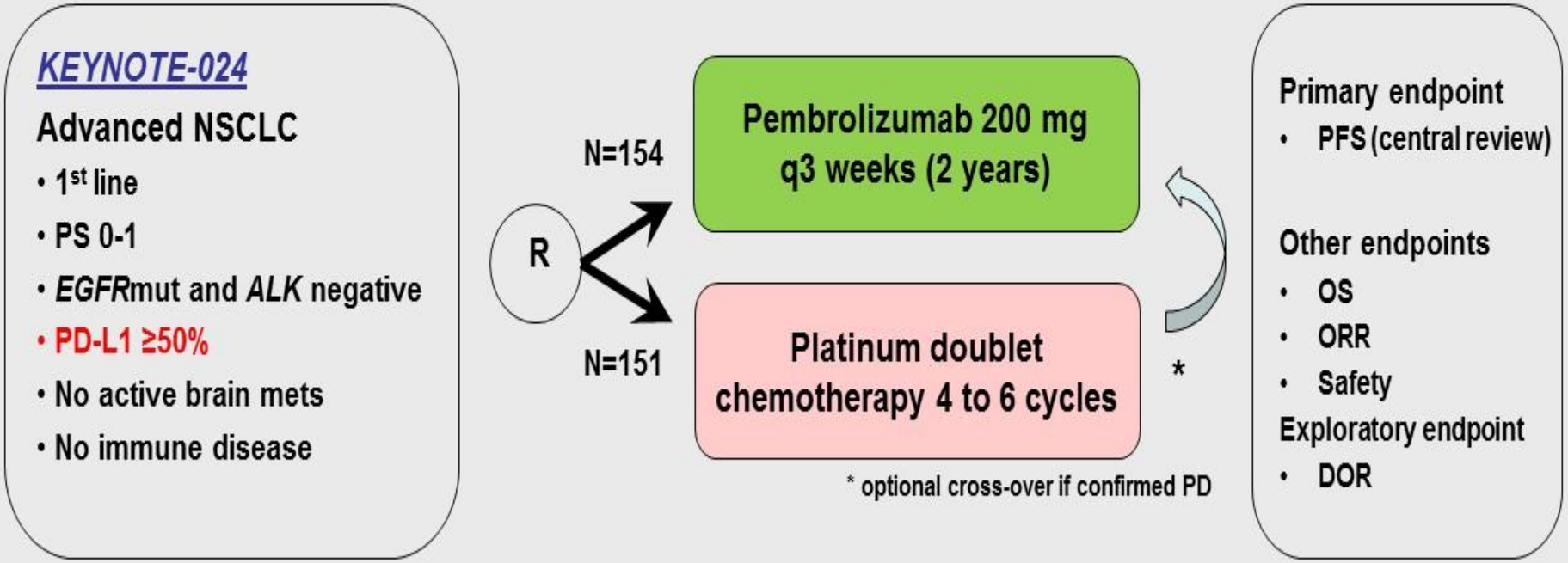
2017	Pembrolizumab 1L (PD-L1 >50%)	KEYNOTE 024	Doublet chemo	PFS	0.50	03/2017
2017	Nivolumab 1L (PD-L1 >5%)	CHECKMATE 026	Doublet chemo	PFS	1.15	NA

NSCLC immunotherapy

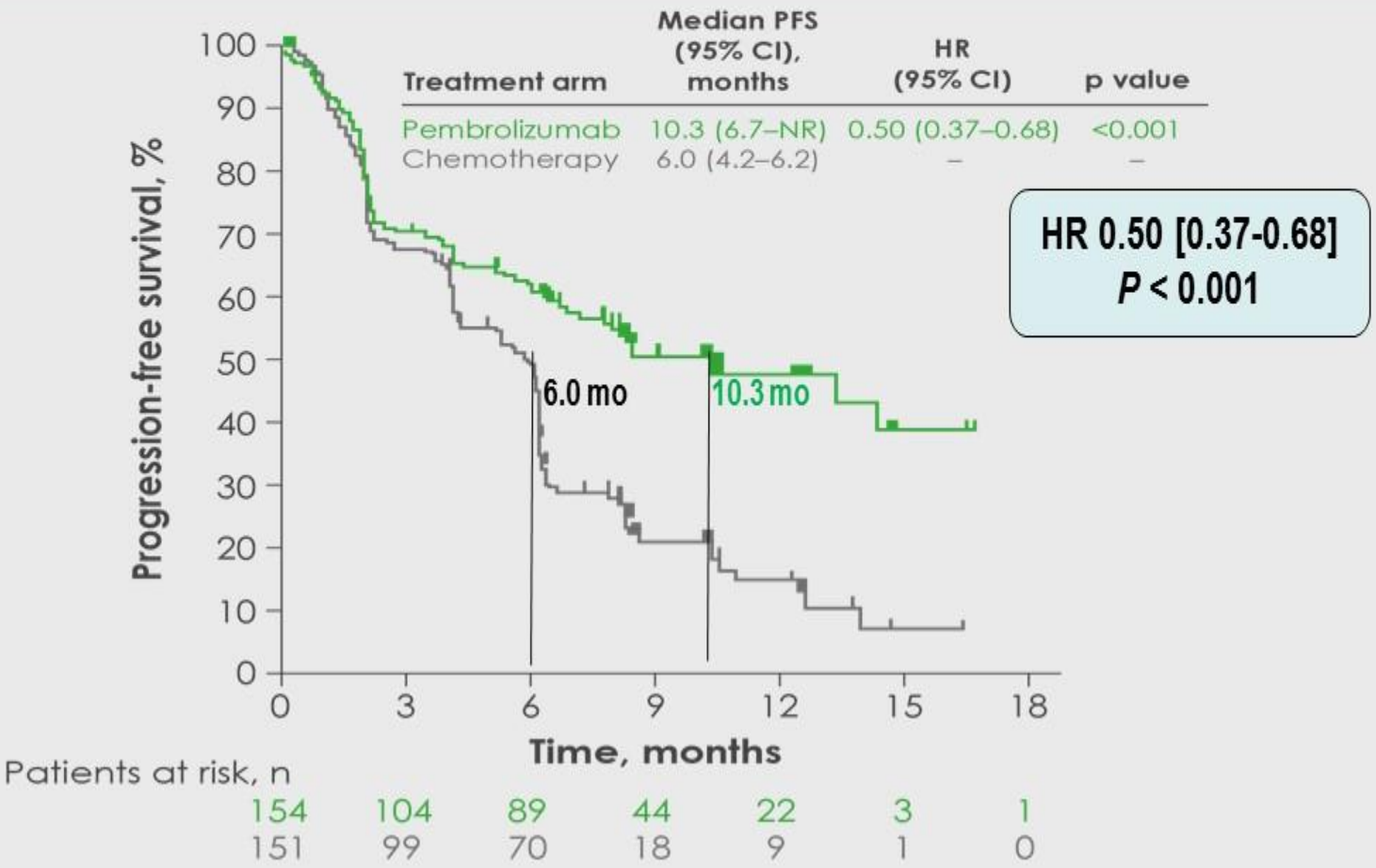
Ph3 study: Pembrolizumab 1L therapy



Reck et al, ESMO 2016 *and* N Engl J Med 375:1823-1833, 2016

NSCLC immunotherapy

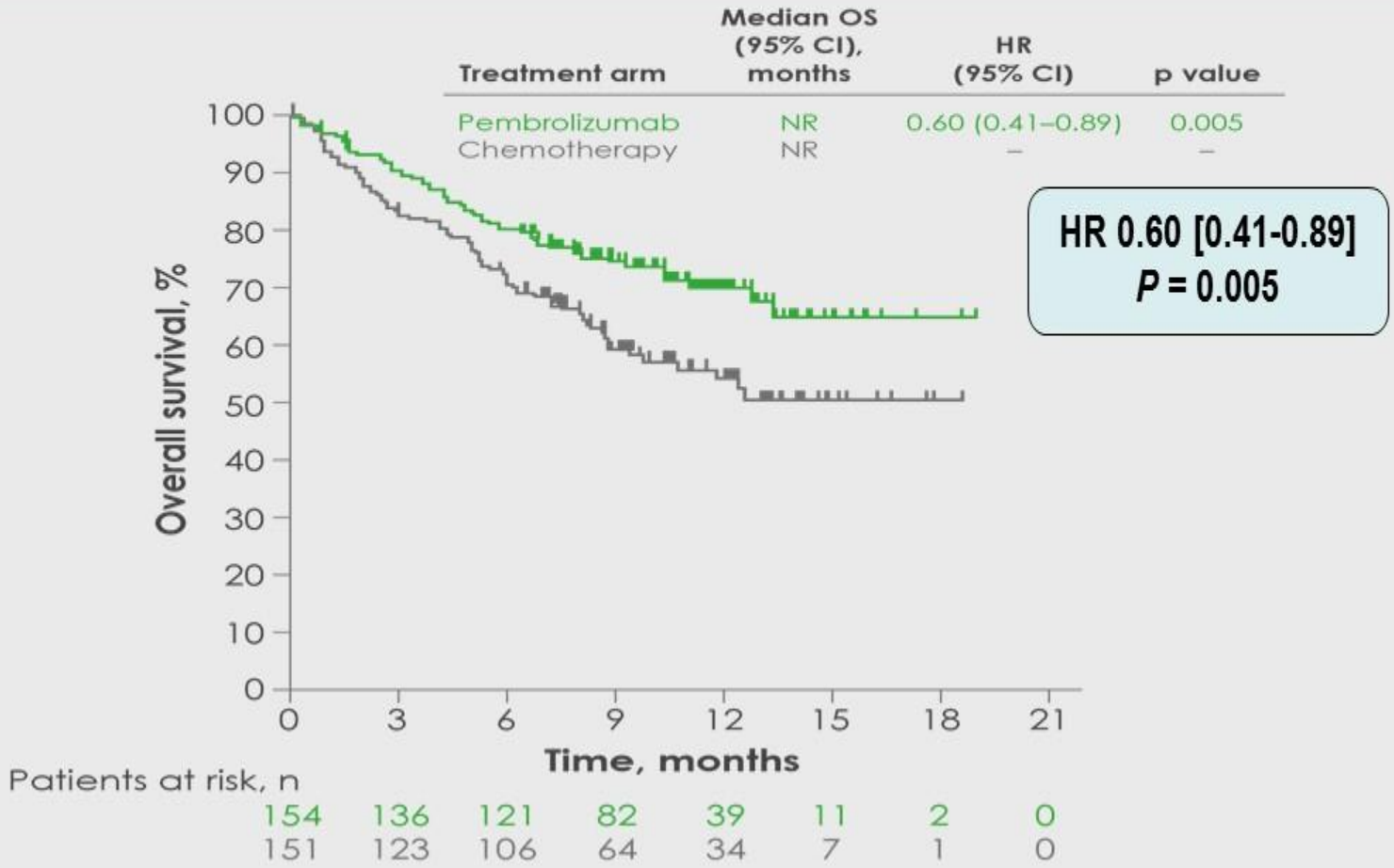
Ph3 study: Pembrolizumab 1L therapy



Reck et al, ESMO 2016 *and* N Engl J Med 375:1823-1833, 2016

NSCLC immunotherapy

Ph3 study: Pembrolizumab 1L therapy



Reck et al, ESMO 2016 *and* N Engl J Med 375:1823-1833, 2016

NSCLC immunotherapy

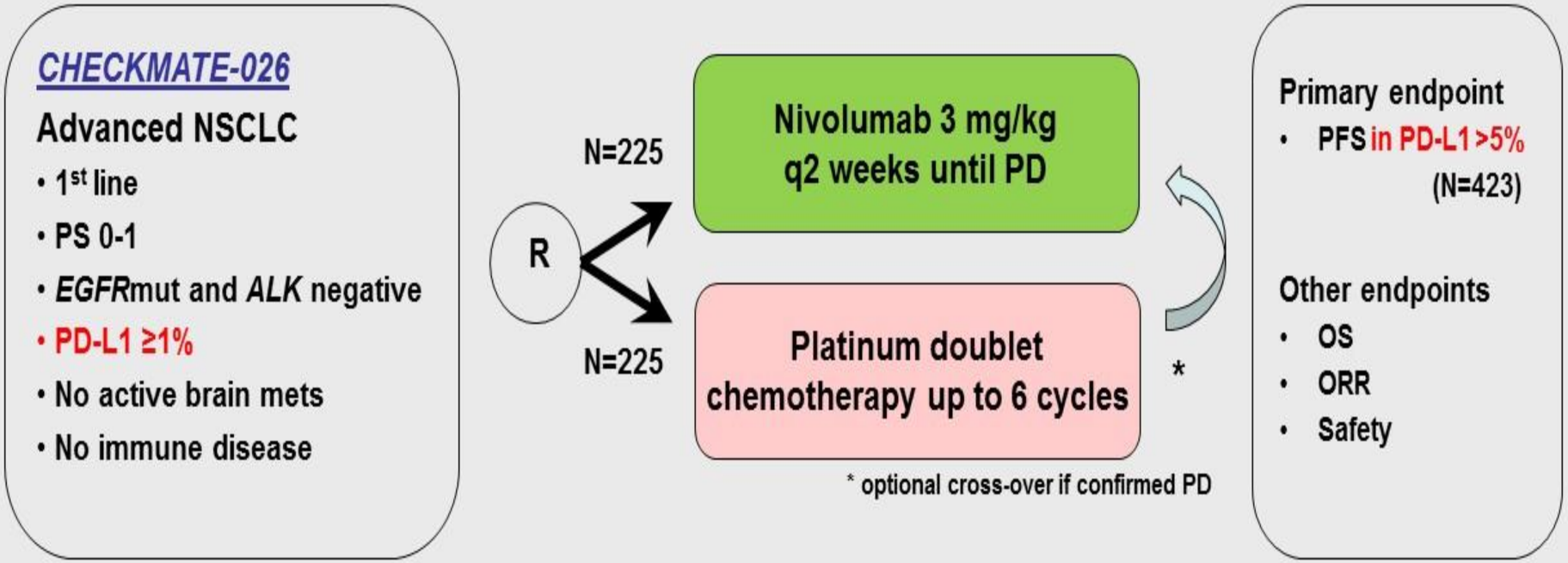
Ph3 study: Pembrolizumab 1L therapy

	Pembrolizumab (n=154)		Chemotherapy (n=150)	
Median duration of treatment (range)	7.0 months (1 day–18.7 months)		3.5 months (1 day–16.8 months)	
Treatment-related AEs, %	Any grade	Grade 3–5	Any grade	Grade 3–5
Any	73	27	90	53
Serious	21	19	21	19
Leading to discontinuation	7	5	11	6
Leading to death	0.6	0.6	2	2

Reck et al, ESMO 2016 *and* N Engl J Med 375:1823-1833, 2016

NSCLC immunotherapy

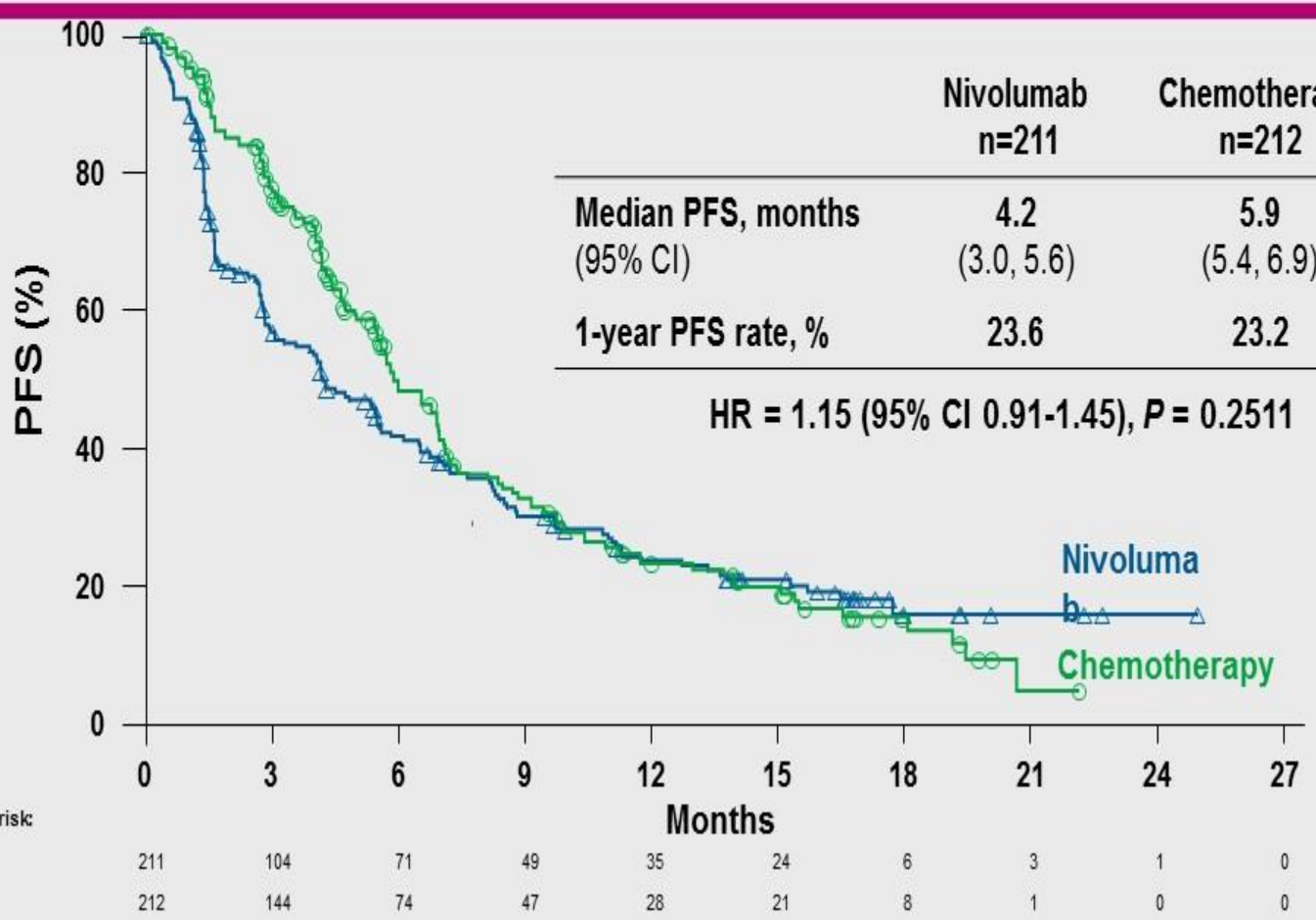
Ph3 study: Nivolumab 1L therapy



Socinski et al, ESMO 2016

NSCLC immunotherapy

Ph3 study: Nivolumab 1L therapy



	Nivolumab n=211	Chemotherapy n=212
Median PFS, months (95% CI)	4.2 (3.0, 5.6)	5.9 (5.4, 6.9)
1-year PFS rate, %	23.6	23.2

HR = 1.15 (95% CI 0.91-1.45), *P* = 0.2511

Socinski et al, ESMO 2016

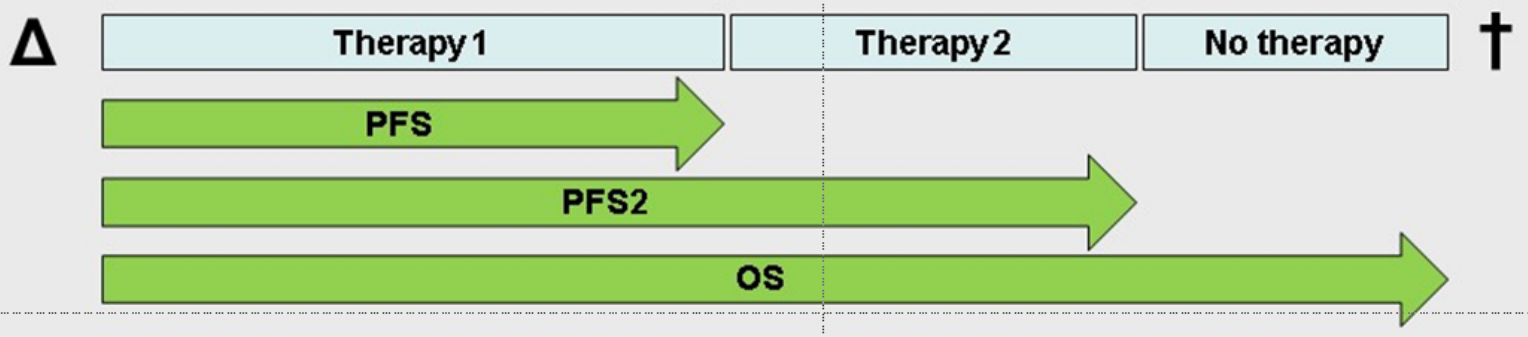
Take-Home Message

NSCLC immunotherapy (2)

- Now established strategy in NSCLC 1L therapy
- Pembrolizumab in tumors with ≥50% PD-L1 expression
- Results of nivolumab disappointing
  - Different populations?
  - Different accuracy of biomarker?
  - Threshold used for biomarker?
  - Different drug?
  - … ?

NSCLC immunotherapy

A new treatment paradigm



ASCO 2017
Late Breaking News

Progression After the Next Line of T… (PFS2) and Updated OS Among Patients With Advanced NSCLC and PD-L1 TPS ≥50% Enrolled in KEYNOTE-024

Julie R. Brahmer,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Melanie A. Leiby,[14] Jessica McLean,[14] Yue Shentu,[14] Reshma Rangwala,[14*] Martin Reck[15]

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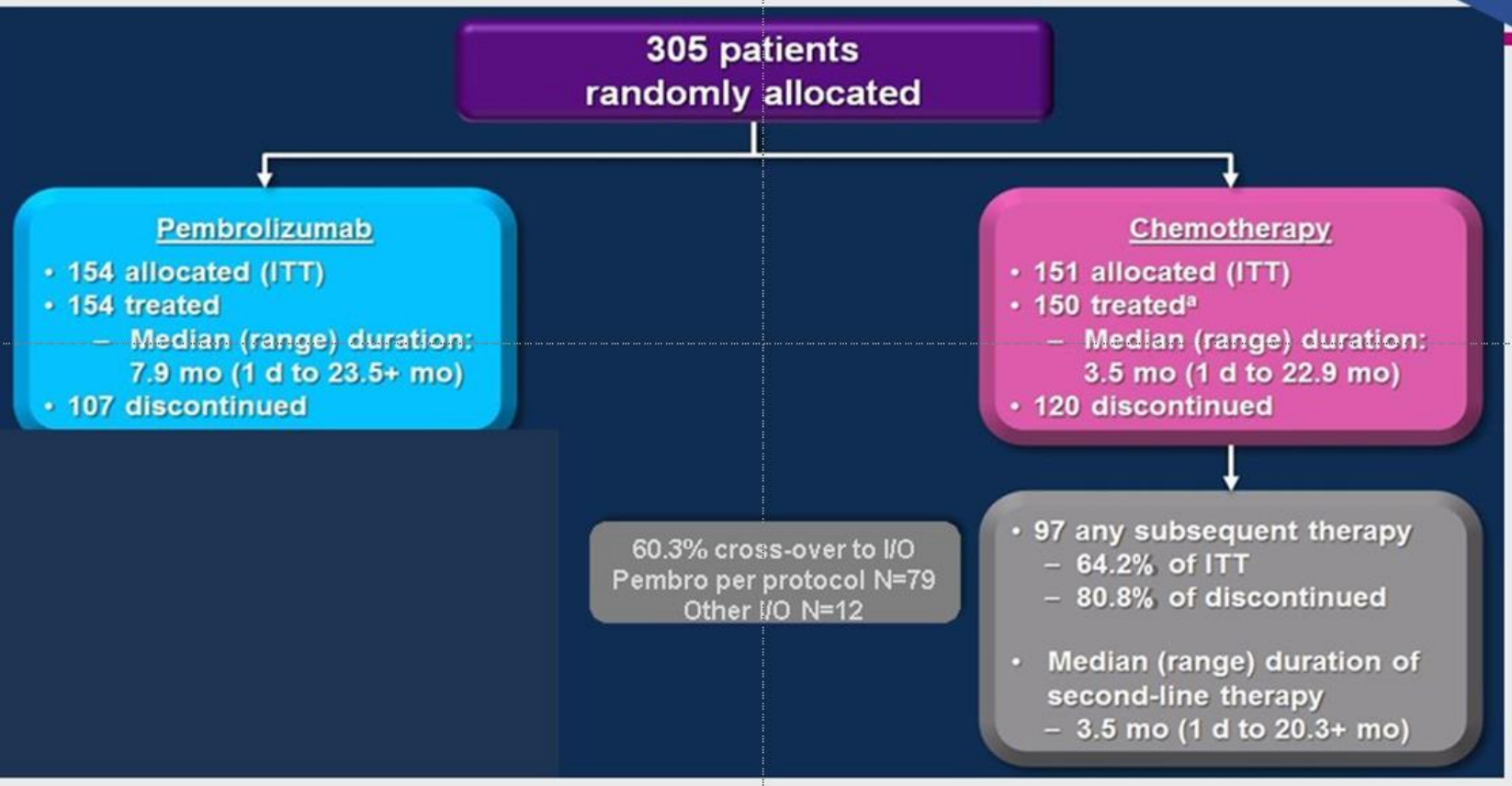
Brahmer et al, J Clin Oncol 35, 2017 (suppl; abstr 9000)

NSCLC immunotherapy

Ph3 study: Pembrolizumab 1L therapy

-------ASCO 2017-------
Late Breaking News



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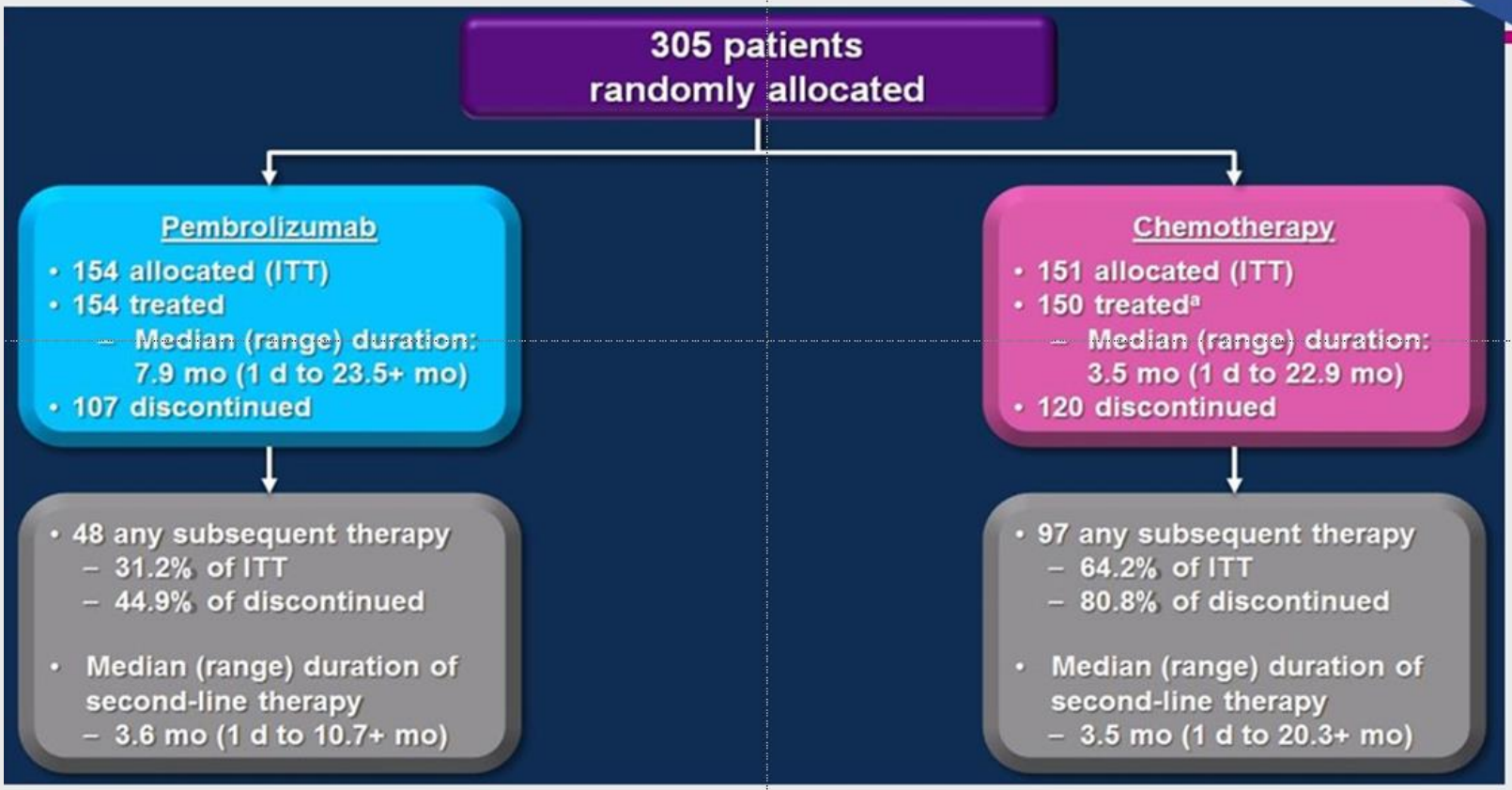

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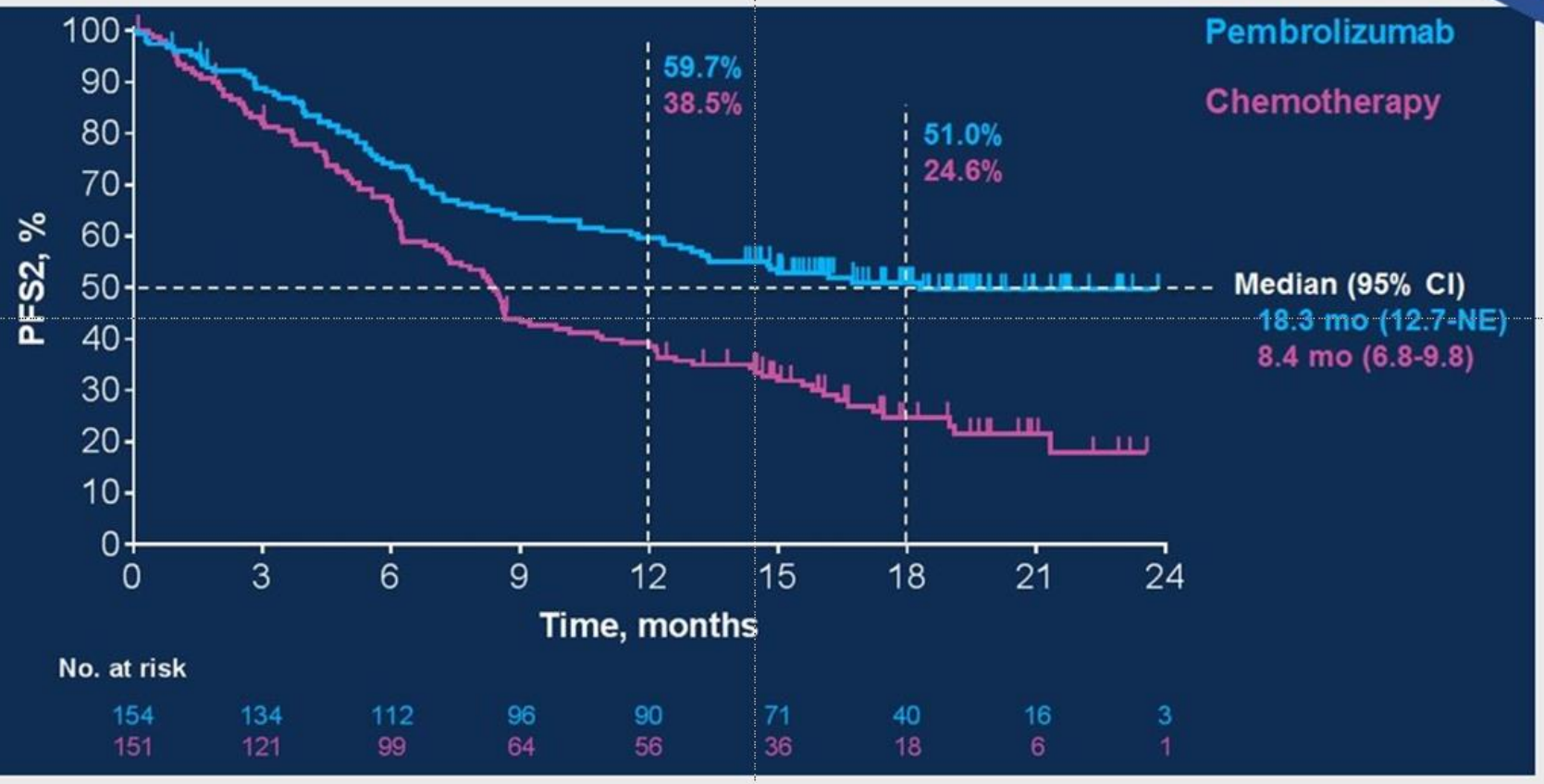

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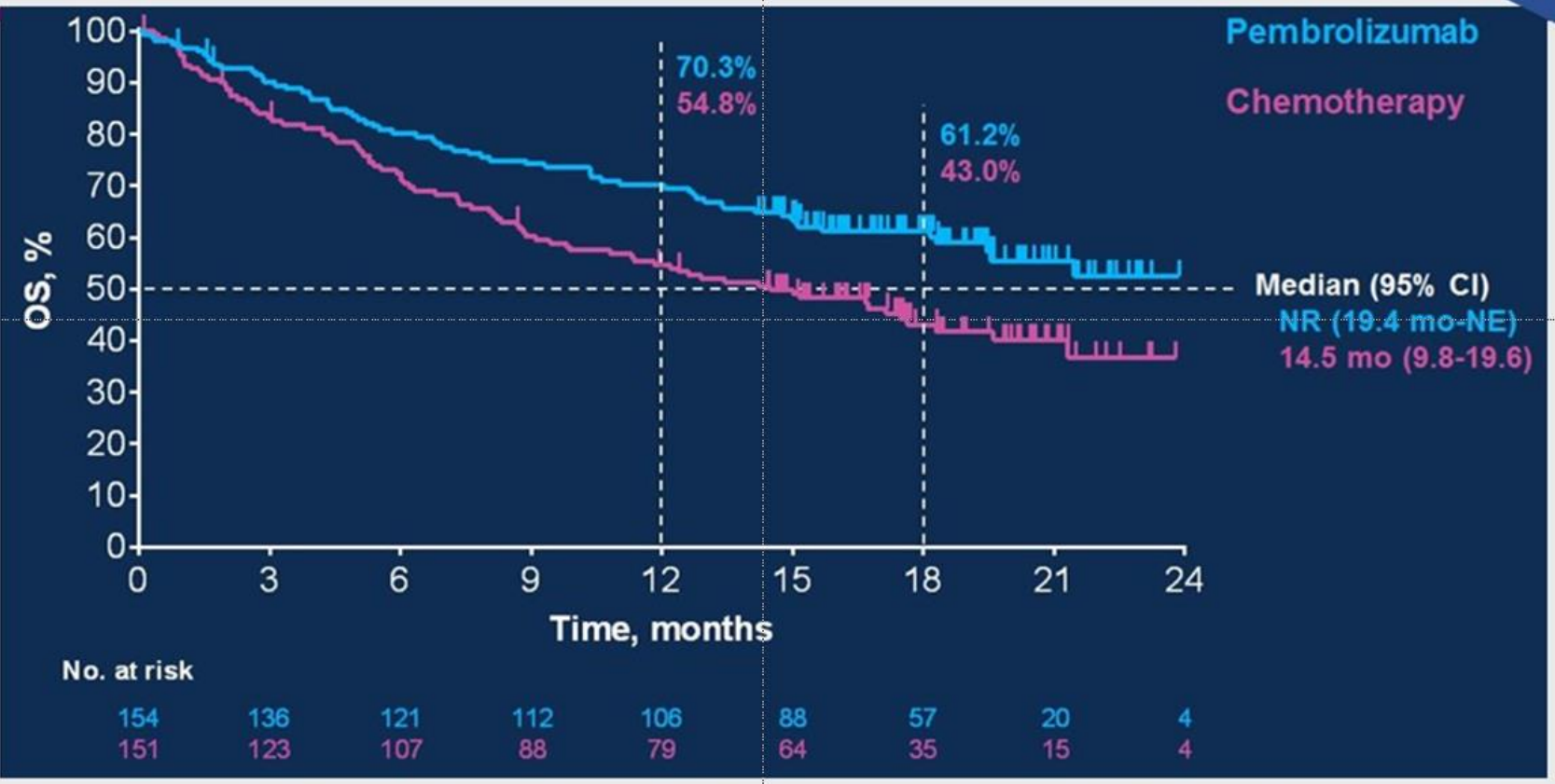

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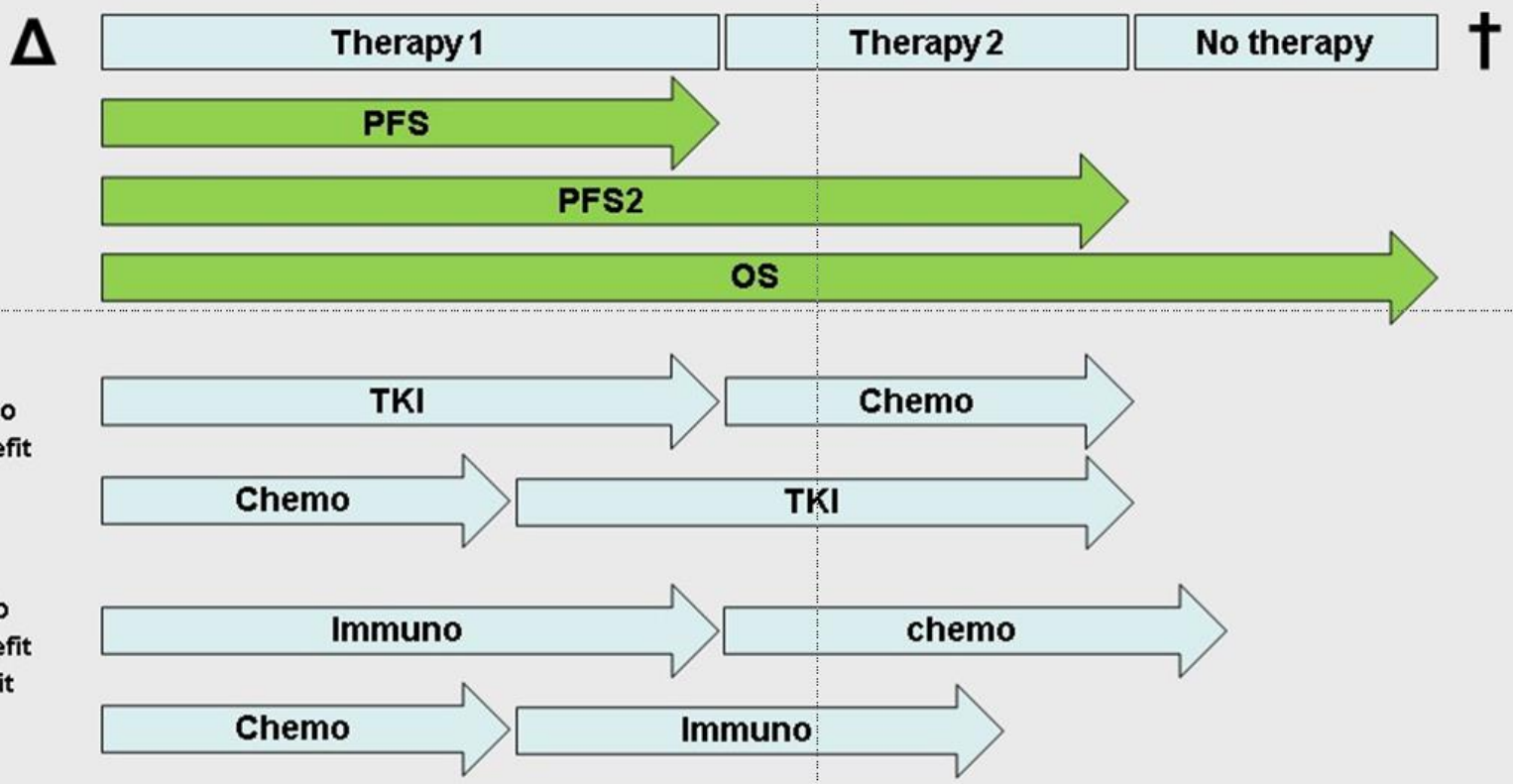
NSCLC immunotherapy

A new treatment paradigm

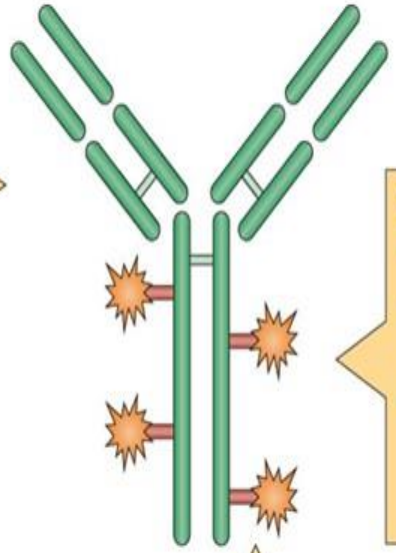


Other thoracic tumors

SCLC

Antibody-drug conjugate therapy

Antibody
- Maintains characteristics when linked to the requisite number of cytotoxic molecules via linker
- Targeted at a well-characterized antigen
- Targeted at an antigen found only on target cells
- Targeted at an antigen that is not downregulated on Ab binding
- Minimal non-specific binding



Cytotoxic agent
- Non-immunogenic
- Non-toxic (dormant or inactive) during circulation in the blood
- Highly potent in small quantities such that two to four molecules are sufficient

Linker
- Stable to ensure ADC remains intact until it reaches target
- Does not alter the Ab characteristics (pharmacokinetics)
- Ensures that the cytotoxic agent is functional once at target site

Zolot et al, Nat Rev Drug Discovery 12: 259-260, 2013

SCLC

Ph1 study with antibody-drug conjugate therapy

Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study

Charles M Rudin, M Catherine Pietanza, Todd M Bauer, Neal Ready, Daniel Morgensztern, Bonnie S Glisson, Lauren A Byers, Melissa L Johnson, Howard A Burris III, Francisco Robert, Tae H Han, Sheila Bheddah, Noah Theiss, Sky Watson, Deepan Mathur, Bharathi Vennapusa, Hany Zayed, Satwant Lally, Donald K Strickland, Ramaswamy Govindan, Scott J Dylla, Stanford L Peng, David R Spigel, for the SCRX16-001 investigators*

Rovalpituzumab tesirine

- Antibody against delta-like protein 3 (DLL3), novel target expressed in more than 80% of SCLC
- Linked to tesirine (potent antitumor agent with favorable hydrophobicity and improved conjugation characteristics)

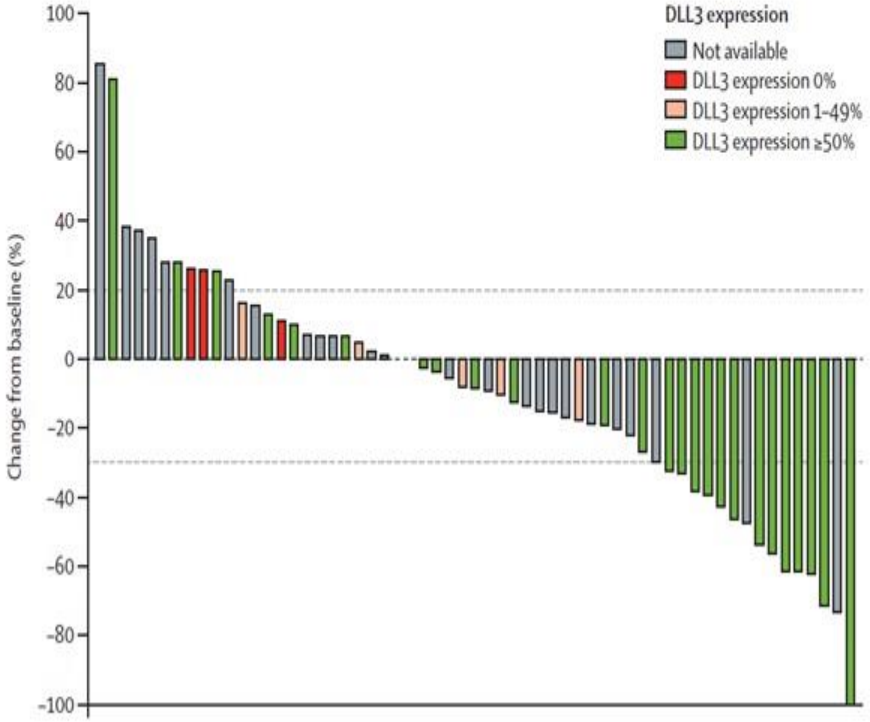
SCLC patients progressing after ≥1 chemotherapies

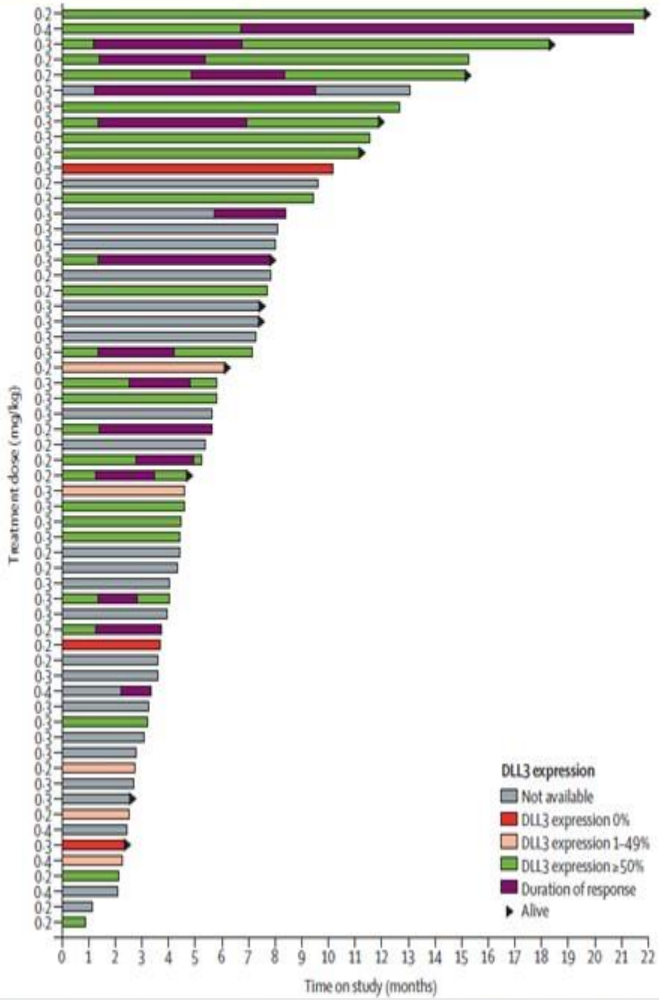
- Response: 11/60 (18%) assessable patients
- Response in tumors with high DLL3 expression (≥50% tumor cells): 10/26 (38%)
- Grade 3-4 side-effects: thrombocytopenia (11%), pleural effusion (8%), and increased lipase (7%)

Rudin et al, Lancet Oncol 18:42-51, 2017

SCLC

Antibody-drug conjugate therapy





Rudin et al, Lancet Oncol 18:42-51, 2017

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