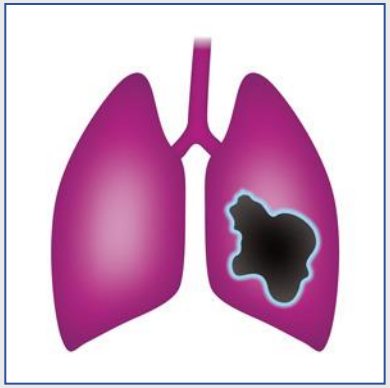
Pneumo Update Europe 2016

24-25 June, Prague

Oncology



Johan Vansteenkiste, Belgium

Leuven Lung Cancer Group
University Hospitals KU Leuven

Content

1. New staging system
2. Early stage NSCLC (stage I-II-some IIIA)
3. Locally advanced NSCLC (stage III)
4. Advanced NSCLC (stage IV)
    1. New targeted therapies for squamous cell lung cancer
    2. Immunotherapy
5. SCLC and mesothelioma (speaker's corner)

+ ASCO Late Breaking News

New staging system (TNM 8)

State of the Art

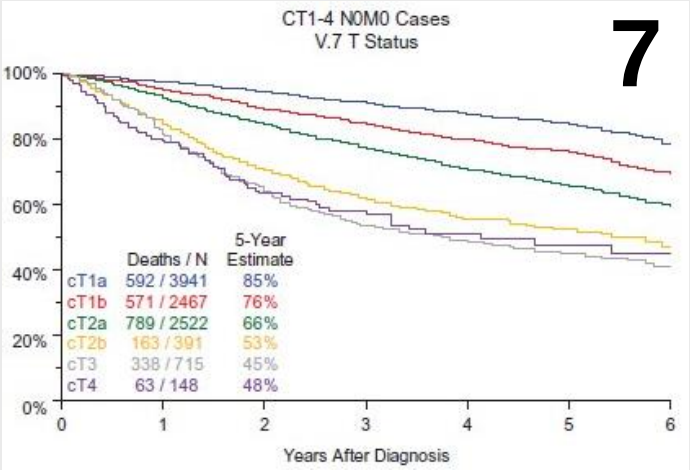
Introducing the changes …

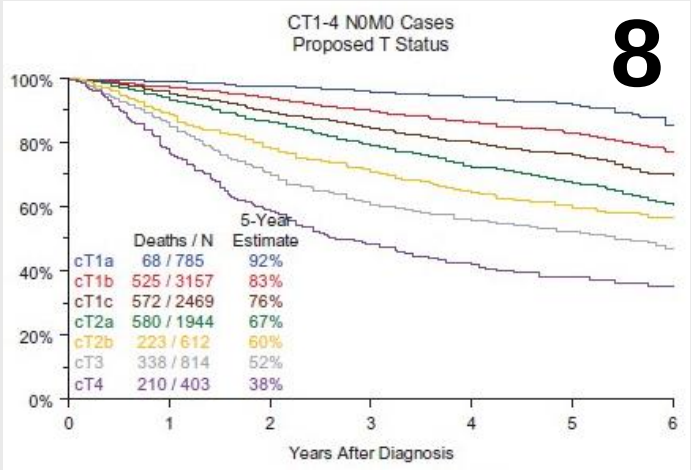
<u>TNM 7 is our current staging system (since 01/01/2010)</u>

- **Revision to TNM 8 based on enlarged retrospective dataset and relatively small prospective dataset**

- **Main changes**
  - **Further refinement of T categories**
  - **Same N categories, but ideas for a change in next revision**
  - **Change in M categories to reflect “oligometastatic disease“**
  - **New TNM categories**
  - **Additional guidance on “blank spaces“**

TNM 8 staging system
T factor





T1 subdivision : T1a (≤1 cm), T1b (>1 to ≤2 cm), T1c (>2 to ≤3 cm)

T2 subdivision: T2a (>3 to ≤4 cm), T2b (>4 to ≤5 cm)

Reclassify 5 to 7 cm as T3, and >7 cm as T4

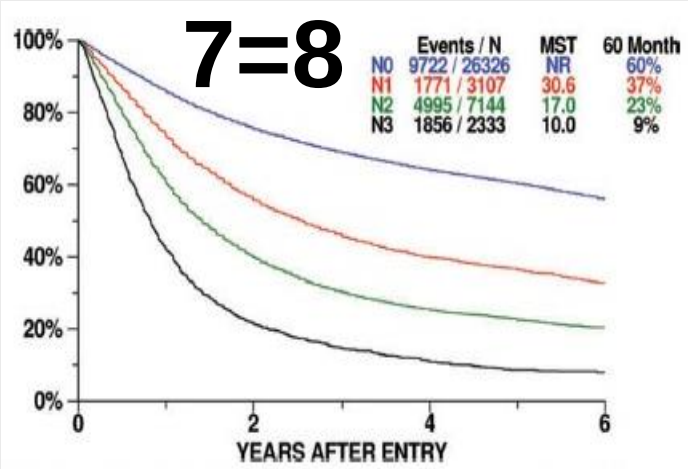
Reclassify main bronchus as T2 regardless of distance from carina

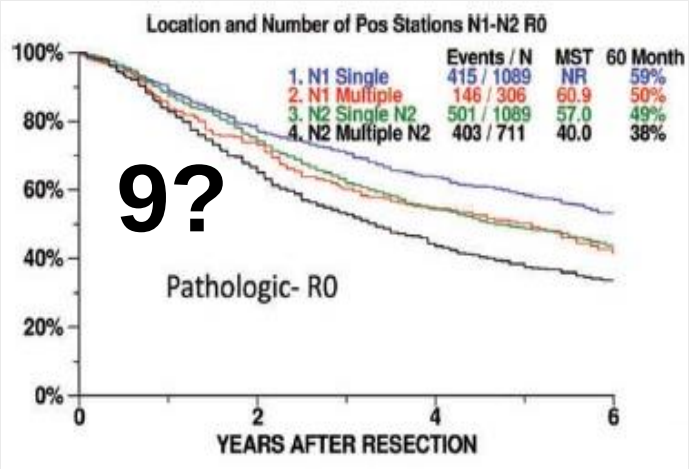
Reclassify both partial and total atelectasis/pneumonitis as T2

Reclassify diaphragm invasion as T4

Rami-Porta et al, J Thorac Oncol 10: 990-1003, 2015

TNM 8 staging system
N factor





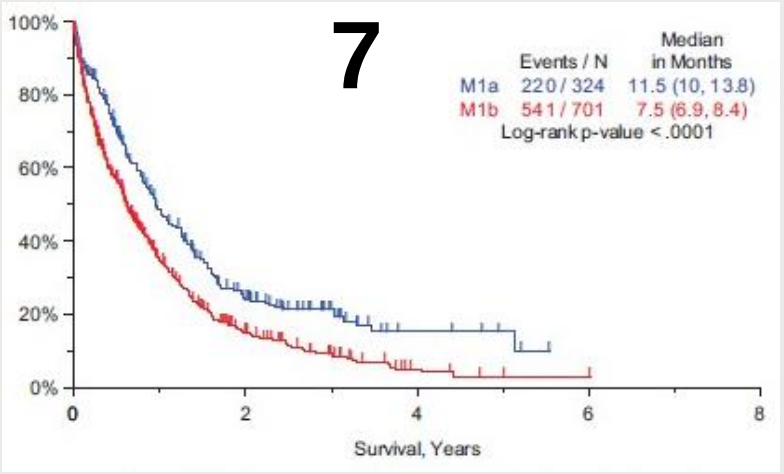
NO changes

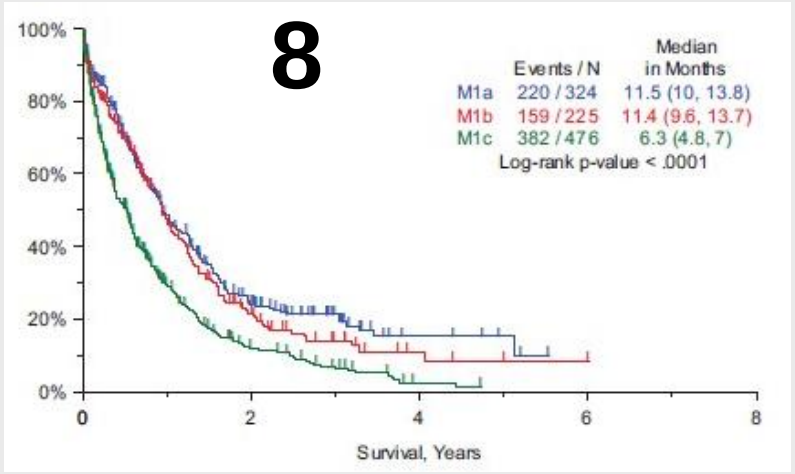
BUT : suggestions for prospective data to feed TNM 9

Asamura et al, J Thorac Oncol 10: 1675–1684, 2015

TNM 8 staging system

M factor





M1a: pleural/pericardial effusions, contralateral lung nodules, pleural nodules

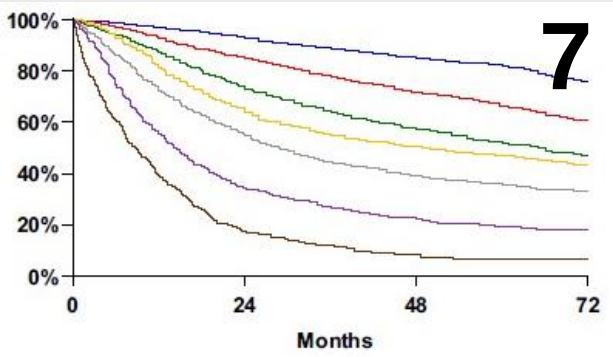
M1b: single metastatic lesions in a single distant organ

M1c: multiple lesions in a single organ or multiple lesions in multiple organs

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

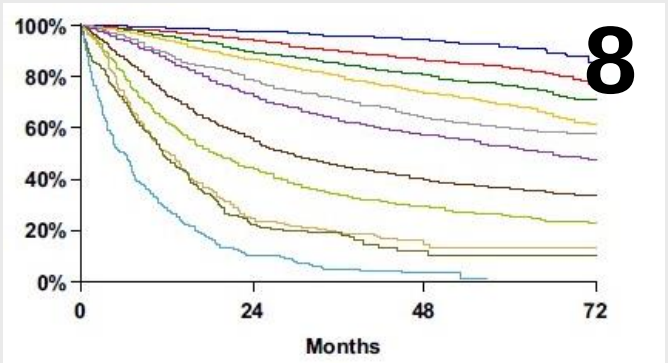
TNM 8 staging system

New categories



7th Ed.	Events / N	MST	24 Month	60 Month
IA	1119 / 6303	NR	93%	82%
IB	768 / 2492	NR	85%	66%
IIA	424 / 1008	66.0	74%	52%
IIB	382 / 824	49.0	64%	47%
IIIA	2139 / 3344	29.0	55%	36%
IIIB	2101 / 2624	14.1	34%	19%
IV	664 / 882	8.8	17%	6%

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a-c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a-c	N2	M0
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a-c	N3	M0
	T2a-b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

Goldstraw et al, J Thorac Oncol 11: 39-51, 2016

TNM 8 staging system

Guidance in blank spaces

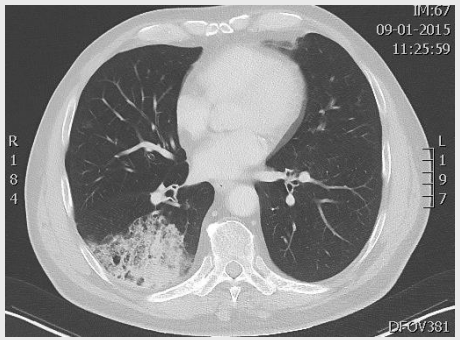
Part-solid nodules [1]

cT*	CT image on HRCT						
	Solid part	0	0 cm	≤0.5 cm†	0.6-1.0 cm†	1.1-2.0 cm†	2.1-3.0 cm†
	Total tumor size including GG	≤0.5 cm	0.6-3.0 cm	≤3.0 cm††	0..6-3.0 cm††	1.1-3.0 cm††	2.1-3.0 cm††
	Pathologic Differential Diagnosis	AAH‡ , AIS, MIA	AIS, MIA, LPA	MIA, LPA, AIS	LPA, Invasive AD, MIA	LPA, Invasive AD	Invasive AD
	Clinical Stage*		cTis	cT1mi	cT1a	cT1b	cT1c

Separate tumor nodules [2]

Multiple pulmonary sites[3]

Multiple GGO nodules or lepidic features or pneumonic-type lesions [4]



1 Travis et al, J Thorac Oncol in press 2016 (DOI: 10.1016/j.jtho.2016.03.025)
2 Detterbeck et al, J Thorac Oncol in press 2016 (DOI: 10.1016/j.jtho.2015.12.114)
3 Detterbeck et al, J Thorac Oncol in press 2016 (DOI: 10.1016/j.jtho.2016.01.024)
4 Detterbeck et al, J Thorac Oncol in press 2016 (DOI: 10.1016/j.jtho.2015.12.113)

Take-Home Message

TNM 8 staging system

- **Further refinement of T-factor, mostly relevant for surgical patients**
- **No change in N-factor**
- **Overall shifts in staging table not relevant for majority of the patients (advanced IIIB/IV)**
  - **M1b (between M1a and M1c) to reflect changing concepts on “oligometastic disease”**
- **Clarification in difficult areas**

Early stage NSCLC (st I-II-IIIA)

State of the Art

What did I tell you last year?

Local treatment for early stage NSCLC

- **Functionally inoperable patients**
  - **SABR the preferred RT approach (<4 cm, location dependent)**
- **Borderline operable patients**
  - **equipoise between SABR and sublobar resections (role MTB)**
  - **ph3 comparative RCTs are ongoing**
- **Fit patients**
  - **anatomical resection (≥ lobectomy) remains the standard**
  - **for low-volume tumours (T1), ph3 RCTs examine the place of sublobar resection and SABR in this setting**

Vansteenkiste et al, Ann Oncol 24 Suppl 6: vi89-vi98, 2013

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. Vansteenkiste[1], D. De Ruysscher[2], W. E. E. Eberhardt[3], E. Lim[4], S. Senan[5], E. Felip[6] & S. Peters[7], on behalf of the ESMO Guidelines Working Group*

State of the Art

Progress in stage IV is not translated in early stages

Anatomical resection	**1/ Improve local therapy ?**	• **Recruitment failure of RCTs with SABR [1]** ➢ **Lobectomy remains standard**
Adjuvant chemo for stage II-IIIA	**2/ Improve chemotherapy?**	• **Failure of pharmocogenetics (ASCO 2015) [2]** ➢ **Cis-vinorelbine remains most studied regimen**
	3/ Targeted therapy ?	• **Failure of gefitinib / erlotinib / bevacizumab [3,4, 5]** ➢ **Targeted agents remain investigational**
	3/ Immuno-therapy ?	• **Failure of MAGE-A3 vaccination (ESMO 2014) [6]** ➢ **Anti-PD-1/PD-L1 ? Ongoing!**

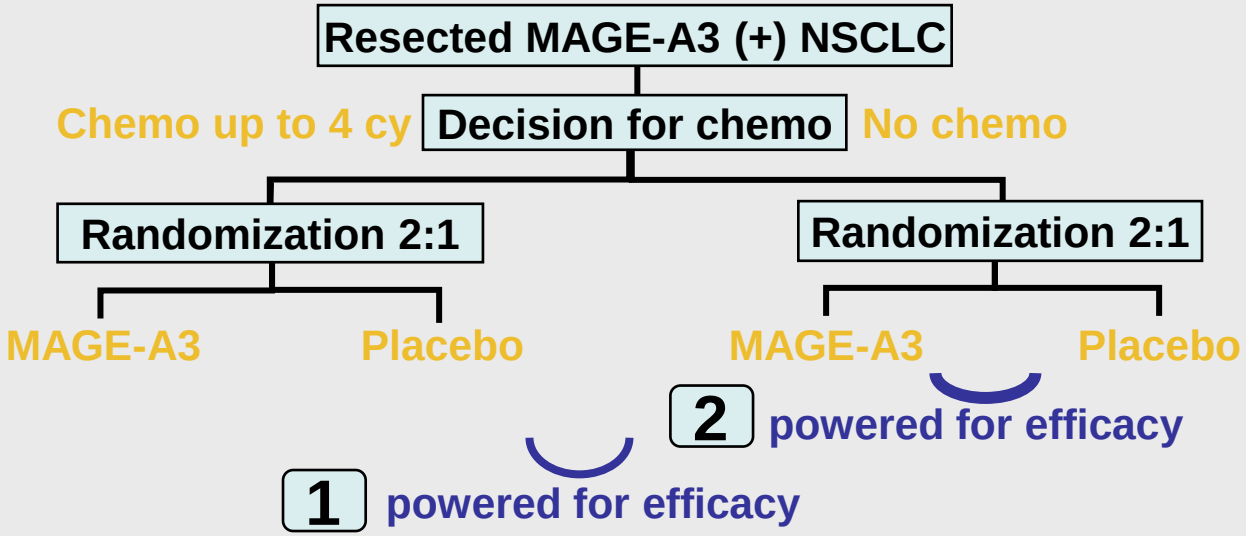
1 Chang et al, Lancet Oncol 16:630-637, 2015
2 Massuti et al, ASCO 2015
3 Goss et al, ASCO 2010 and J Clin Oncol 31:3320-3326, 2013
4 Kelly et al, ASCO 2014 and J Clin Oncol 33:4007-4014, 2015
5 Wakelee et al, WCLC 2015
6 Vansteenkiste et al, ESMO 2014 and Lancet Oncol online April 28, 2016

The good news

Contemporary multidisciplinary care is progress

MAGE-A3 as Adjuvant Non-Small Cell LunG CanceR ImmunoTherapy

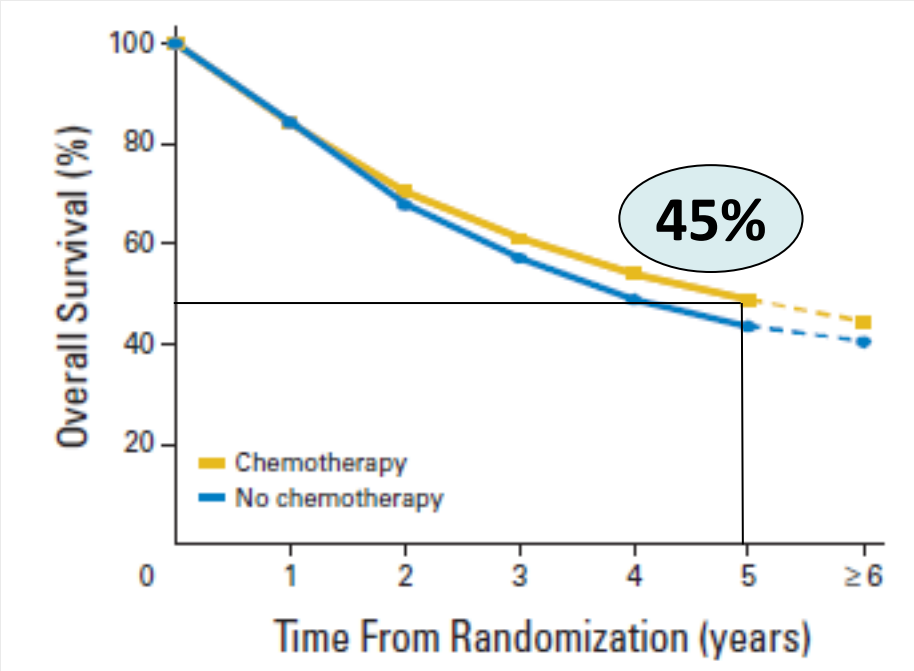
- **worldwide multicenter, randomized, double-blind, placebo-controlled ph3 trial**
- **N=13,849 screened -> N=2312 patients randomized**
- **primary endpoint: disease-free survival**

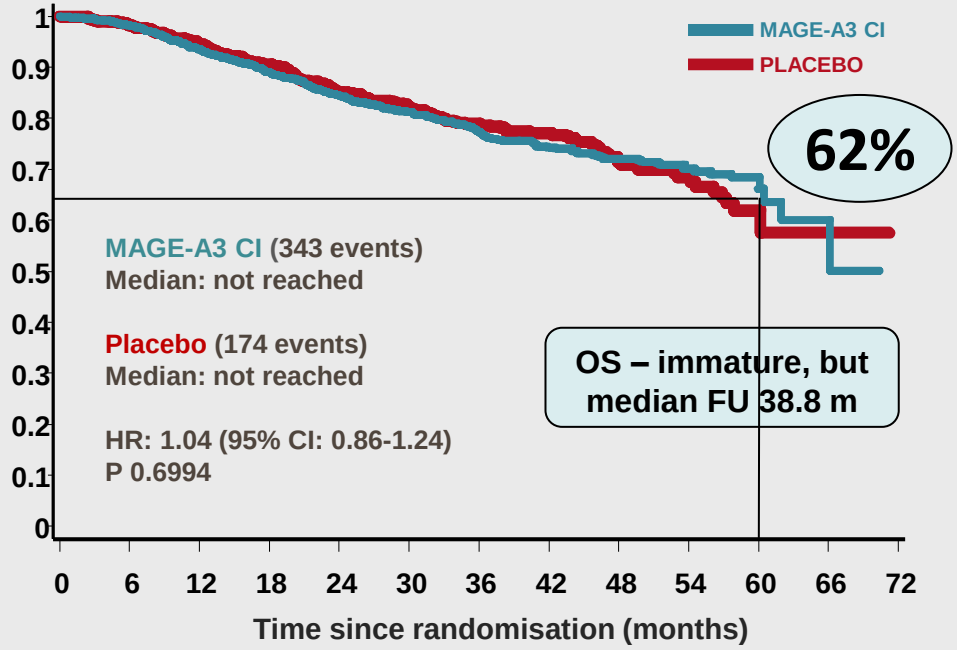


Clinicaltrials.gov NCT00480025

The good news

Contemporary multidisciplinary care is progress





Meta-analysis of studies in the interval 1995-2005

Pignon et al, J Clin Oncol 26:3552-3559, 2008

Large prospective database on contemporary early-stage NSCLC treatment

Vansteenkiste et al, Lancet Oncol online April 28, 2016

Locally advanced NSCLC (st III)

State of the Art

What did I tell you last year?

Stage III NSCLC

- **Concurrent chemoradiotherapy is the preferred approach**
  - **Radiotherapy 60-66 Gy**
- **In less fit patients, sequential therapy may be preferred**
- **In the current state of knowledge**
  - **Chemotherapy: cis-etoposide, cis-vinorelbine, cis-pemetrexed for non-squamous NSCLC, carbo-paclitaxel if cis-intolerant**
  - **Targeted therapy: molecular analyses and use of targeted agents remain investigational**
  - **Immunotherapy: vaccination with current technology (MUC1) has failed, studies with checkpoint inhibitors are ongoing**

Vansteenkiste et al, Ann Oncol 24 Suppl 6: vi89-vi98, 2013

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. Vansteenkiste[1], D. De Ruysscher[2], W. E. E. Eberhardt[3], E. Lim[4], S. Senan[5], E. Felip[6] & S. Peters[7], on behalf of the ESMO Guidelines Working Group*

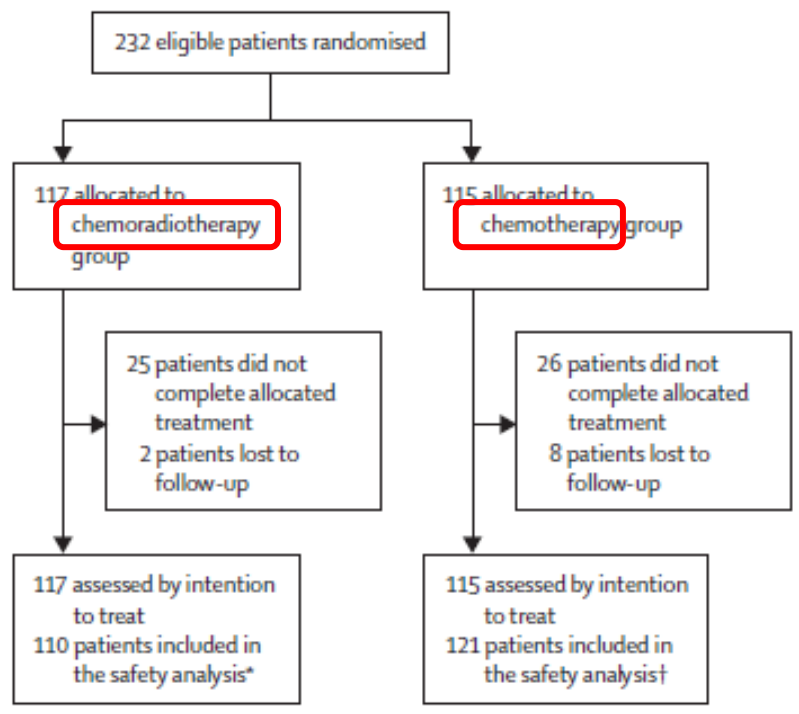
The good news

Studies try to define how to tailor therapy

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group

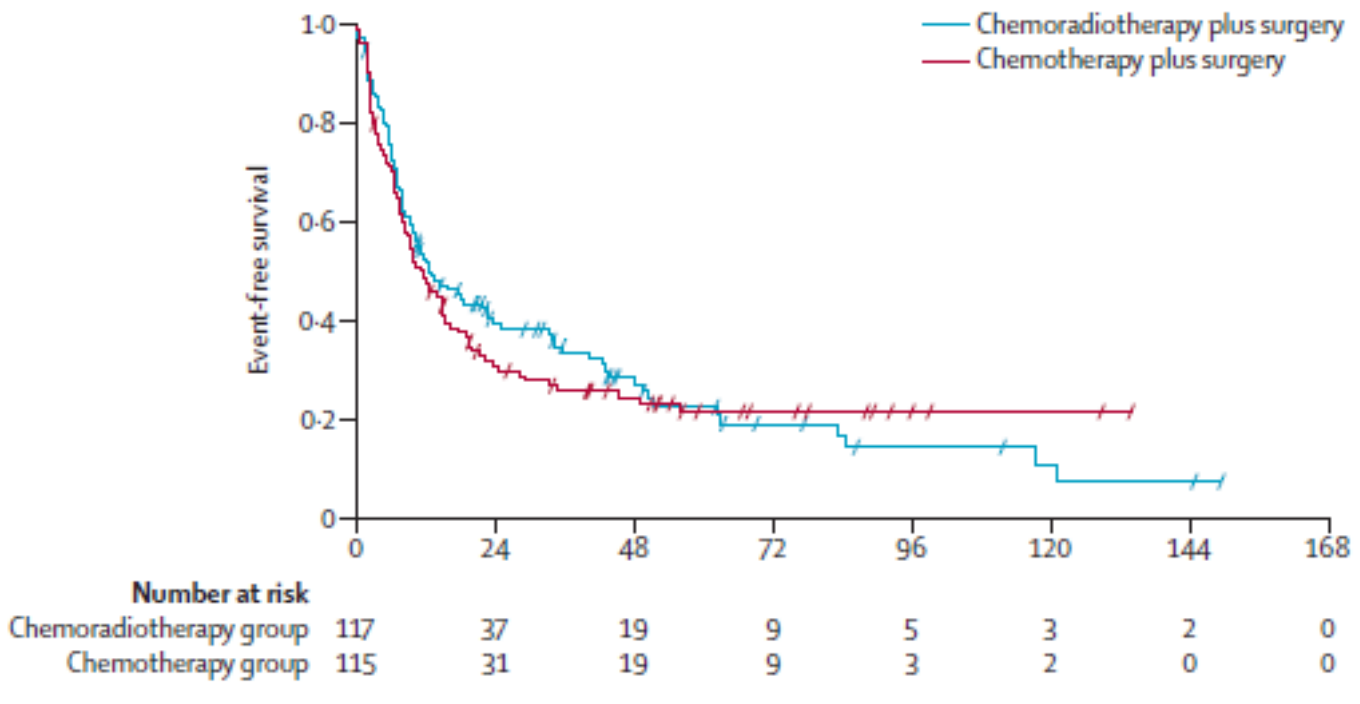
Background: **One of the standard options in the treatment of stage IIIA/N2 NSCLC is neoadjuvant chemotherapy and surgery. We did a randomised trial to investigate whether the addition of neoadjuvant radiotherapy improves outcomes**



Pless et al, Lancet 386: 1049-1056, 2015

The good news

Studies try to define how to tailor therapy



- **Radiotherapy did not add benefit to induction chemotherapy followed by surgery**
- **We suggest that one definitive local treatment modality combined with neoadjuvant chemotherapy is adequate to treat resectable stage IIIA-N2 NSCLC**

Pless et al, Lancet 386: 1049-1056, 2015

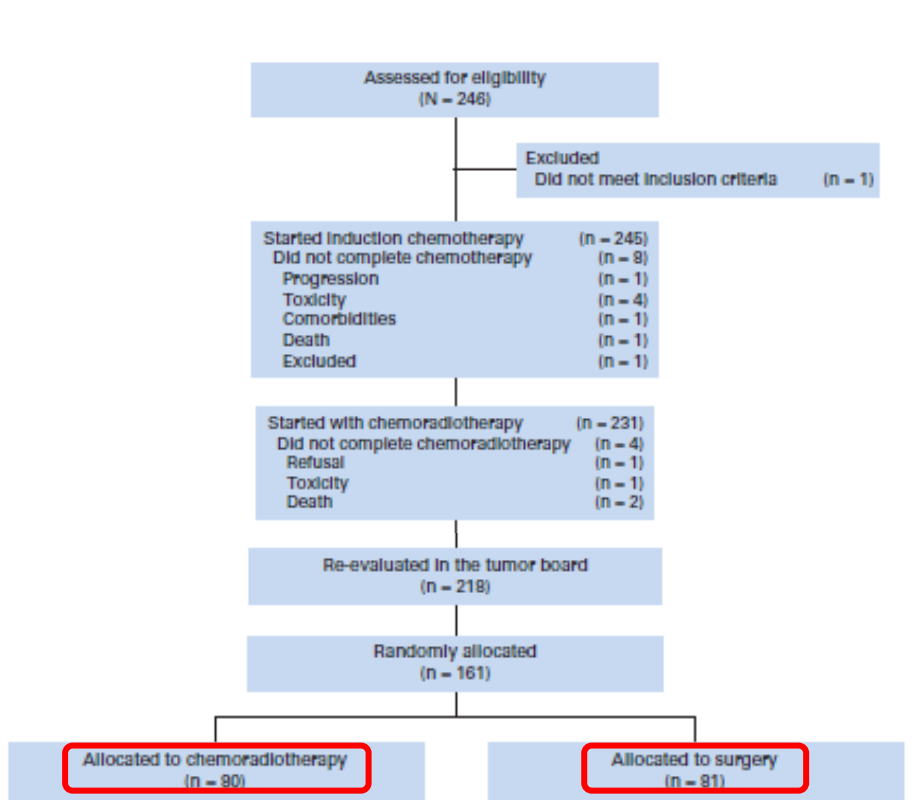
The good news

Studies try to define how to tailor therapy

Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non–Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)

Wilfried Ernst Erich Eberhardt, Christoph Pöttgen, Thomas Christoph Gauler, Godehard Friedel, Stefanie Veit, Vanessa Heinrich, Stefan Welter, Wilfried Budach, Werner Spengler, Martin Kimmich, Berthold Fischer, Heinz Schmidberger, Dirk De Ruysscher, Claus Belka, Sebastian Cordes, Rodrigo Hepp, Diana Lütke-Brintrup, Nils Lehmann, Martin Schuler, Karl-Heinz Jöckel, Georgios Stamatis, and Martin Stuschke

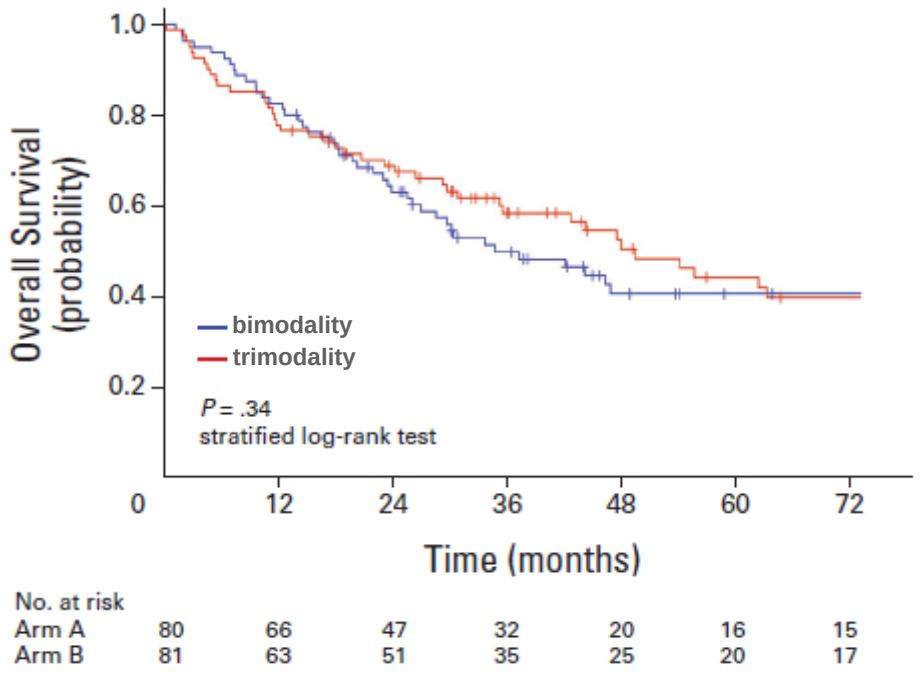
Purpose: **Concurrent chemoradiotherapy with or without surgery are options for stage IIIA-N2 NSCLC… Here, we compared surgery with definitive chemoradiotherapy in resectable stage III disease after induction**



Eberhardt et al, J Clin Oncol 33: 4194-4201, 2015

The good news

Studies try to define how to tailor therapy

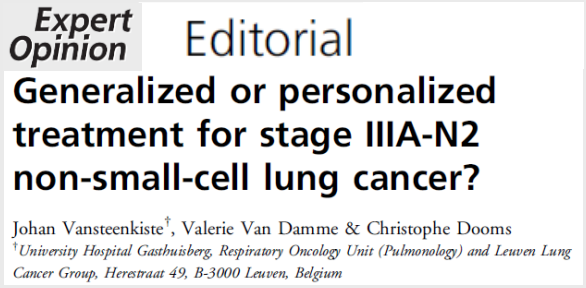


- **The 5-year OS rates in randomly assigned patients with resectable stage III NSCLC were excellent with both treatments**
- **Both are acceptable strategies for this good-prognosis group**

Eberhardt et al, J Clin Oncol 33: 4194-4201, 2015

The good news

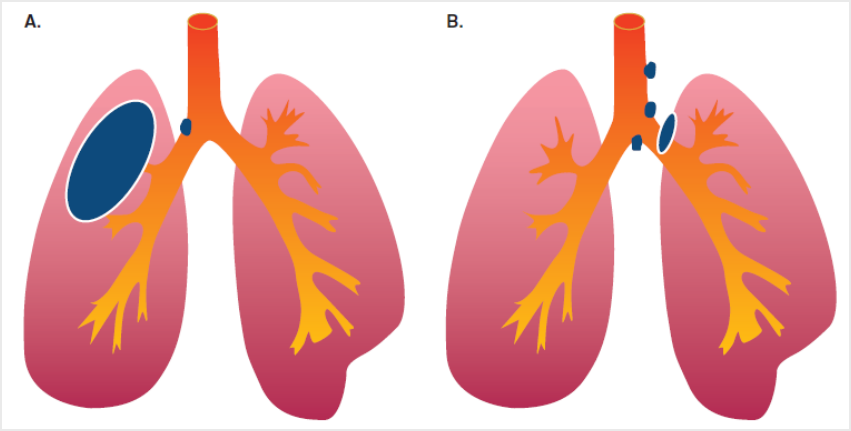
Studies confirm that stage IIIA-N2 therapy should be tailored


Expert Opinion

Editorial

Generalized or personalized treatment for stage IIIA-N2 non-small-cell lung cancer?

Johan Vansteenkiste†, Valerie Van Damme & Christophe Dooms
†*University Hospital Gasthuisberg, Respiratory Oncology Unit (Pulmonology) and Leuven Lung Cancer Group, Herestraat 49, B-3000 Leuven, Belgium*



- **All stage IIIA-N2 RCTs lack sufficient power**
- **Meta-analysis does not solve this, as the disease, trials, and local expertise are heterogeneous**

- **"Those best situated to decide on the optimum treatment for stage IIIA-N2 NSCLC are teams of staff experienced in multimodal treatment, including pulmonologists, medical oncologists, thoracic surgeons, and radiation oncologists. They should discuss each individual's case on the basis of the specific risk profile, according to thoracic tumor board criteria**

Vansteenkiste et al, Exp Opin Pharmacother 11: 1605-1609, 2010
Eberhardt et al, Lancet 386: 1018-1020, 2015

Take-Home Message

Non-metastatic NSCLC

- **Apart from guideline adherence, judgement and treatment in an experienced multidisciplinary environment is crucial**

High Procedure Volume Is Strongly Associated With Improved Survival After Lung Cancer Surgery

Margreet Lüchtenborg, Sharma P. Riaz, Victoria H. Coupland, Eric Lim, Erik Jakobsen, Mark Krasnik, Richard Page, Michael J. Lind, Michael D. Peake, and Henrik Møller

Multidisciplinary Treatment for Stage IIIA Non-Small Cell Lung Cancer: Does Institution Type Matter?

Pamela Samson, MD, Aalok Patel, BS, Traves D. Crabtree, MD, Daniel Morgensztern, MD, Cliff G. Robinson, MD, Graham A. Colditz, MD, PhD, Saiama Waqar, MD, Daniel Kreisel, MD, A. Sasha Krupnick, MD, G. Alexander Patterson, MD, Stephen Broderick, MD, Bryan F. Meyers, MD, MPH, and Varun Puri, MD, MSCI

Patients Selected for Definitive Concurrent Chemoradiation at High-volume Facilities Achieve Improved Survival in Stage III Non–Small-Cell Lung Cancer

Elyn H. Wang, BS, Charles E. Rutter, MD, Christopher D. Corso, MD, PhD, Roy H. Decker, MD, PhD, Lynn D. Wilson, MD, MPH, Anthony W. Kim, MD, James B. Yu, MD, MHS, and Henry S. Park, MD, MPH

- **Stage IIIA NSCLC patients undergoing resection at academic centers had lower 30-day mortality and increased overall survival compared with patients treated at community centers, possibly due to higher patient volume**

Lüchtenborg et al, J Clin Oncol 31: 3141-3146, 2013
Samson et al, Ann Thorac Surg 100: 1773-1779, 2015
Wang et al, J Thorac Oncol 10: 937-943, 2015

Advanced NSCLC (st IV)

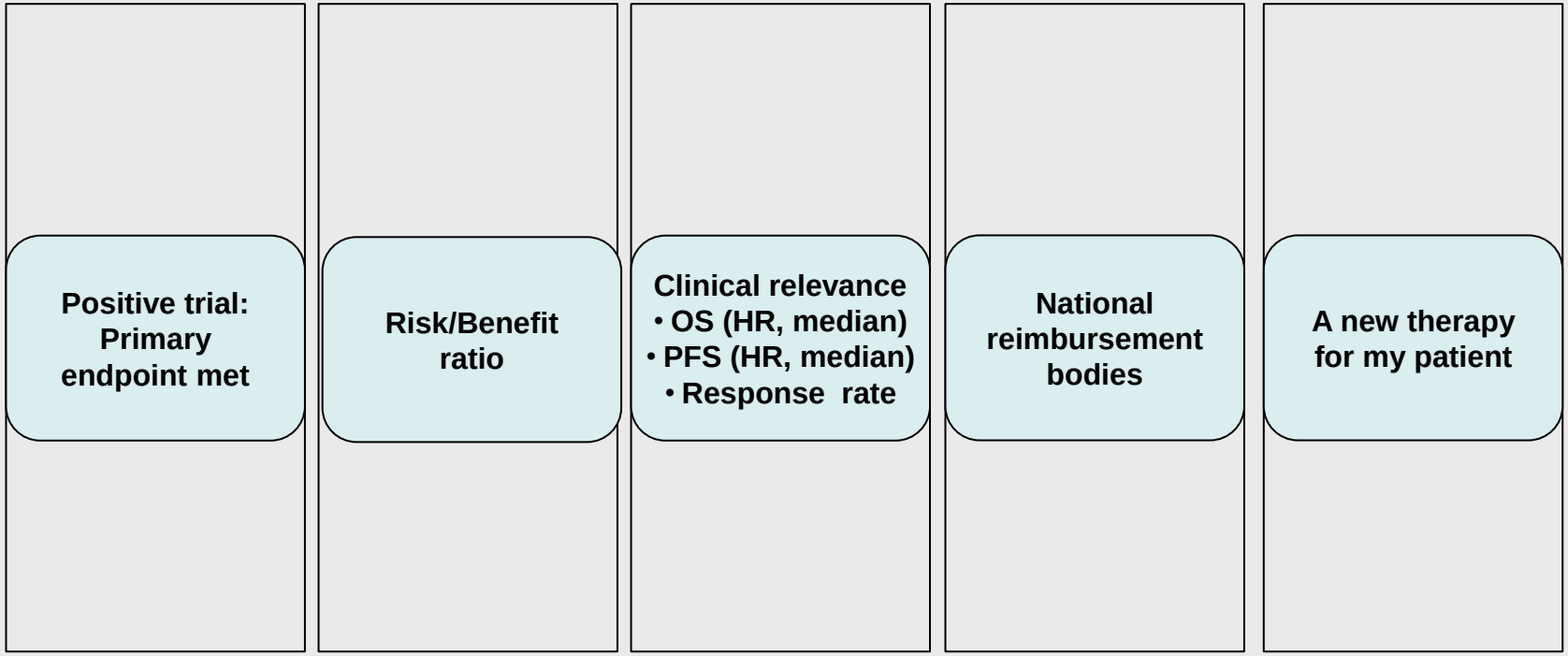
- New targeted therapies for squamous cell lung cancer
- Immunotherapy

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

What did I tell you last year?
> *stage IV NSCLC innovations*



What did I tell you last year?
> *stage IV NSCLC*

- **EGFR mut+ NSCLC (adeno)**
  - **3rd gen EGFR-TKI osimertinib active for T790M resistance**
- **ALK+ NSCLC (adeno)**
  - **Crizotinib: superior PFS results compared to chemo 1L**
  - **2nd gen ALK-TKI ceritinib active for crizotinib resistance**
- **1L therapy (squamous)**
  - **Necitumumab added to cis-gemcitabine better OS**
- **2L therapy**
  - **Docetaxel + ramucirumab better OS than doce alone (all)**
  - **Nivolumab better OS than docetaxel (squamous)**
  - **Nivolumab better OS than docetaxel (adeno)**
  - **Pembrolizumab better OS than docetaxel (PD-L1+)**
  - **Afatinib better OS than erlotinib (squamous)**

What did I tell you last year?
> *stage IV NSCLC*

- **EGFR mut+ NSCLC (adeno)** — EMA approval
  - **3rd gen EGFR-TKI osimertinib active for T790M resistance** — 02/2016
- **ALK+ NSCLC (adeno)**
  - **Crizotinib: superior PFS results compared to chemo 1L** — 01/2016
  - **2nd gen ALK-TKI ceritinib active for crizotinib resistance** — 06/2015
- **1L therapy (squamous)**
  - **Necitumumab added to cis-gemcitabine better OS**
- **2L therapy**
  - **Docetaxel + ramucirumab better OS than doce alone (all)** — 11/2015
  - **Nivolumab better OS than docetaxel (squamous)** — 12/2015
  - **Nivolumab better OS than docetaxel (adeno)** — 02/2016 CHMP
  - **Pembrolizumab better OS than docetaxel (PD-L1+)**
  - **Afatinib better OS than erlotinib (squamous)**

What is new?
> *stage IV NSCLC*

	EMA approval
• EGFR mut+ NSCLC (adeno)	
– 3rd gen EGFR-TKI osimertinib active for T790M resistance	02/2016
• ALK+ NSCLC (adeno)	
– Crizotinib: superior PFS results compared to chemo 1L	01/2016
– 2nd gen ALK-TKI ceritinib active for crizotinib resistance	06/2015
• **1L therapy (squamous)**	
– **Necitumumab added to cis-gemcitabine better OS**	02/2016
• **2L therapy**	
– Docetaxel + ramucirumab better OS than doce alone (all)	11/2015
– Nivolumab better OS than docetaxel (squamous)	12/2015
– Nivolumab better OS than docetaxel (adeno)	02/2016 CHMP
– **Pembrolizumab better OS than docetaxel (PD-L1+)**	ongoing
– **Afatinib better OS than erlotinib (squamous)**	02/2016 CHMP

Squamous cell lung cancer
> *necitumumab 1L (anti-EGFR MoAb)*

Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial

*Nick Thatcher, Fred R Hirsch, Alexander V Luft, Aleksandra Szczesna, Tudor E Ciuleanu, Mircea Dediu, Rodryg Ramlau, Rinat K Galiulin, Beatrix Bálint, György Losonczy, Andrzej Kazarnowicz, Keunchil Park, Christian Schumann, Martin Reck, Henrik Depenbrock, Shivani Nanda, Anamarija Kruljac-Letunic, Raffael Kurek, Luis Paz-Ares, Mark A Socinski, for the SQUIRE investigators**

SQUIRE

Advanced squamous LC
- **1st line**
- **PS 0-2**

R

N=545

Cis-Gem + Necitumumab q3w
-> Necitumumab MT until PD

N=548

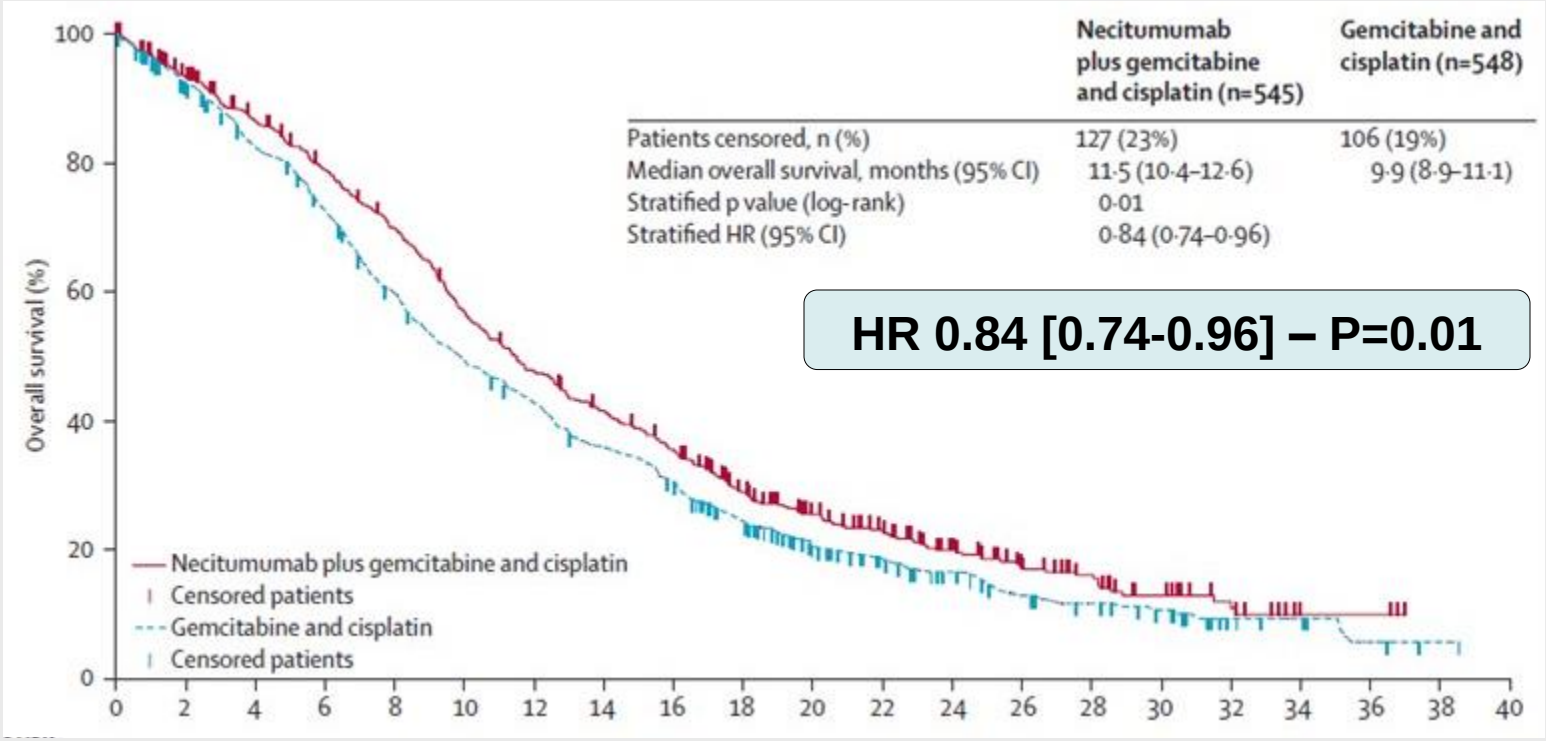
Cis-Gem q3w
up to 6 cy

Stratified PS (0-1 *vs.* 2), region

Cisplatin 75 mg/m² d1
Gemcitabine 1250 mg/m² day 1+8
Necitumumab 800 mg d1+8

Thatcher et al, Lancet Oncol 16:763-774, 2015

Squamous cell lung cancer
> *necitumumab 1L: OS*



Thatcher et al, Lancet Oncol 16:763-774, 2015

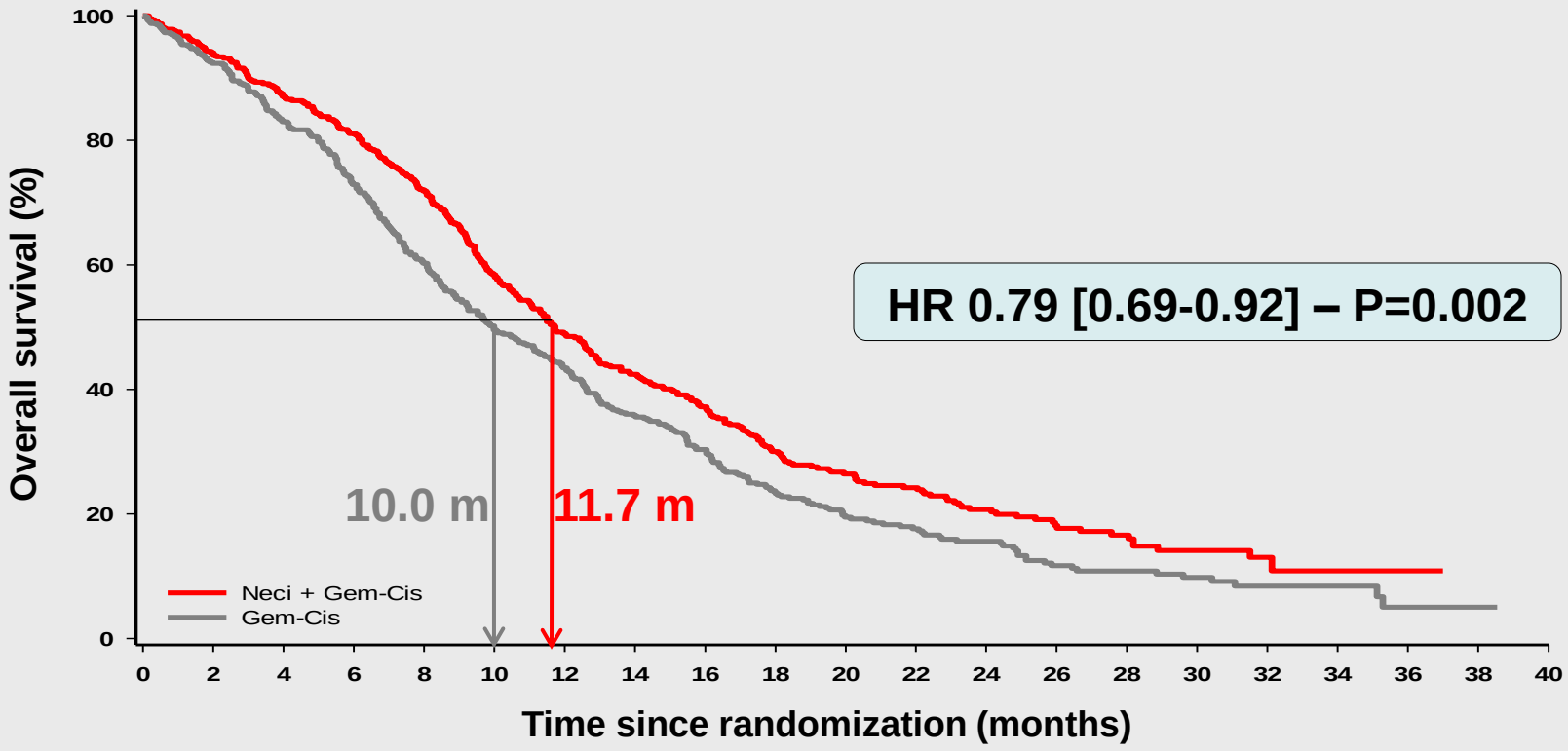
Squamous cell lung cancer
> *necitumumab 1L: safety*

	Necitumumab plus gemcitabine and cisplatin (n=538)				Gemcitabine and cisplatin (n=541)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Neutropenia	104 (19%)	97 (18%)	34 (6%)	0	99 (18%)	106 (20%)	43 (8%)	0
Febrile neutropenia	2 (<1%)	3 (<1%)	1 (<1%)	0	1 (<1%)	6 (1%)	1 (<1%)	0
Anaemia	168 (31%)	55 (10%)	2 (<1%)	0	189 (35%)	56 (10%)	3 (<1%)	0
Thrombocytopenia	62 (12%)	38 (7%)	17 (3%)	0	88 (16%)	35 (6%)	23 (4%)	0
Diarrhoea	75 (14%)	9 (2%)	0	0	53 (10%)	6 (1%)	2 (<1%)	0
Fatigue	190 (35%)	38 (7%)	1 (<1%)	0	192 (35%)	36 (7%)	2 (<1%)	0
Hypomagnesaemia	118 (22%)	37 (7%)	13 (2%)	0	79 (15%)	6 (1%)	0	0
Skin reactions	380 (71%)	44 (8%)	0	0	61 (11%)	3 (<1%)	0	0
Rash	372 (69%)	38 (7%)	0	0	53 (10%)	2 (<1%)	0	0
Hypersensitivity/infusion-related reaction	6 (1%)	2 (<1%)	0	0	11 (2%)	0	0	0
Conjunctivitis	38 (7%)	2 (<1%)	0	0	12 (2%)	0	0	0
Interstitial lung disease (pneumonitis)	3 (<1%)	1 (<1%)	0	1 (<1%)	1 (<1%)	3 (<1%)	0	0
Arterial thromboembolic events	8 (1%)	13 (2%)	5 (<1%)	3 (<1%)	10 (2%)	8 (1%)	2 (<1%)	1 (<1%)
Venous thromboembolic events	22 (4%)	19 (4%)	7 (1%)	1 (<1%)	15 (3%)	5 (<1%)	8 (1%)	1 (<1%)

Thatcher et al, Lancet Oncol 16:763-774, 2015

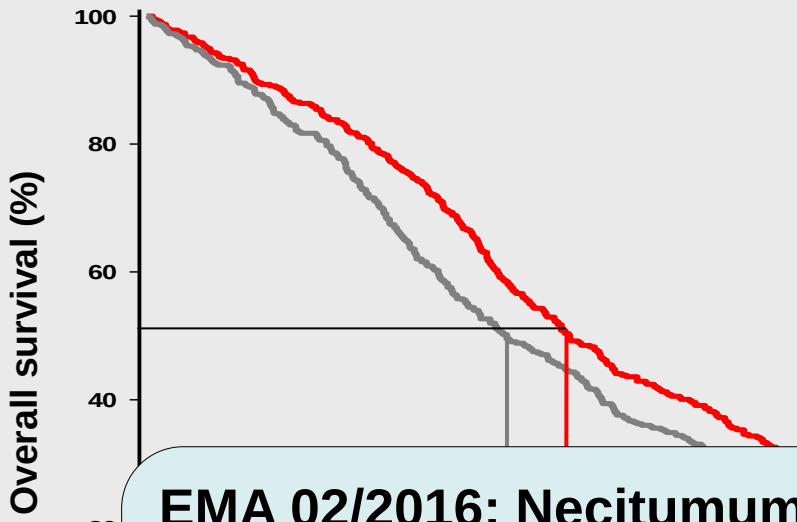
Squamous cell lung cancer

> *necitumumab: OS in EGFR protein+ tumors*



Paz Ares et al, ELCC 2016

Squamous cell lung cancer
> *necitumumab: OS in EGFR protein+ tumors*



HR 0.79 [0.69-0.92] – P=0.002

EMA 02/2016: Necitumumab in combination with cisplatin and gemcitabine chemotherapy is indicated for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) expressing squamous NSCLC who have not received prior chemotherapy for this condition.

Paz Ares et al, ELCC 2016

Squamous cell lung cancer
> *afatinib 2L (2nd gen EGFR-TKI)*

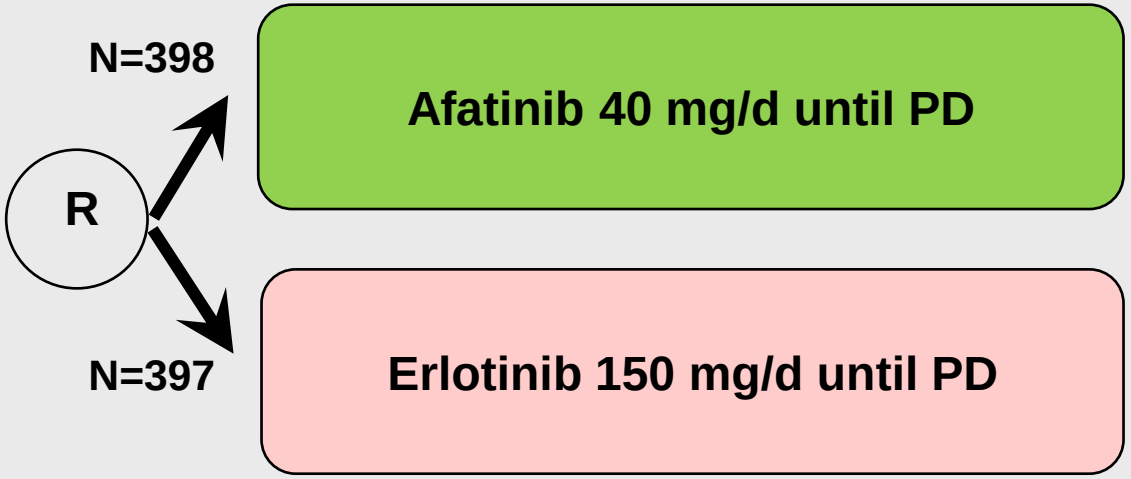
Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial

Jean-Charles Soria, Enriqueta Felip, Manuel Cobo, Shun Lu, Konstantinos Syrigos, Ki Hyeong Lee, Erdem Göker, Vassilis Georgoulias, Wei Li, Dolores Isla, Salih Z Guclu, Alessandro Morabito, Young J Min, Andrea Ardizzoni, Shirish M Gadgeel, Bushi Wang, Vikram K Chand, Glenwood D Goss, for the LUX-Lung 8 Investigators

LUX-Lung 8

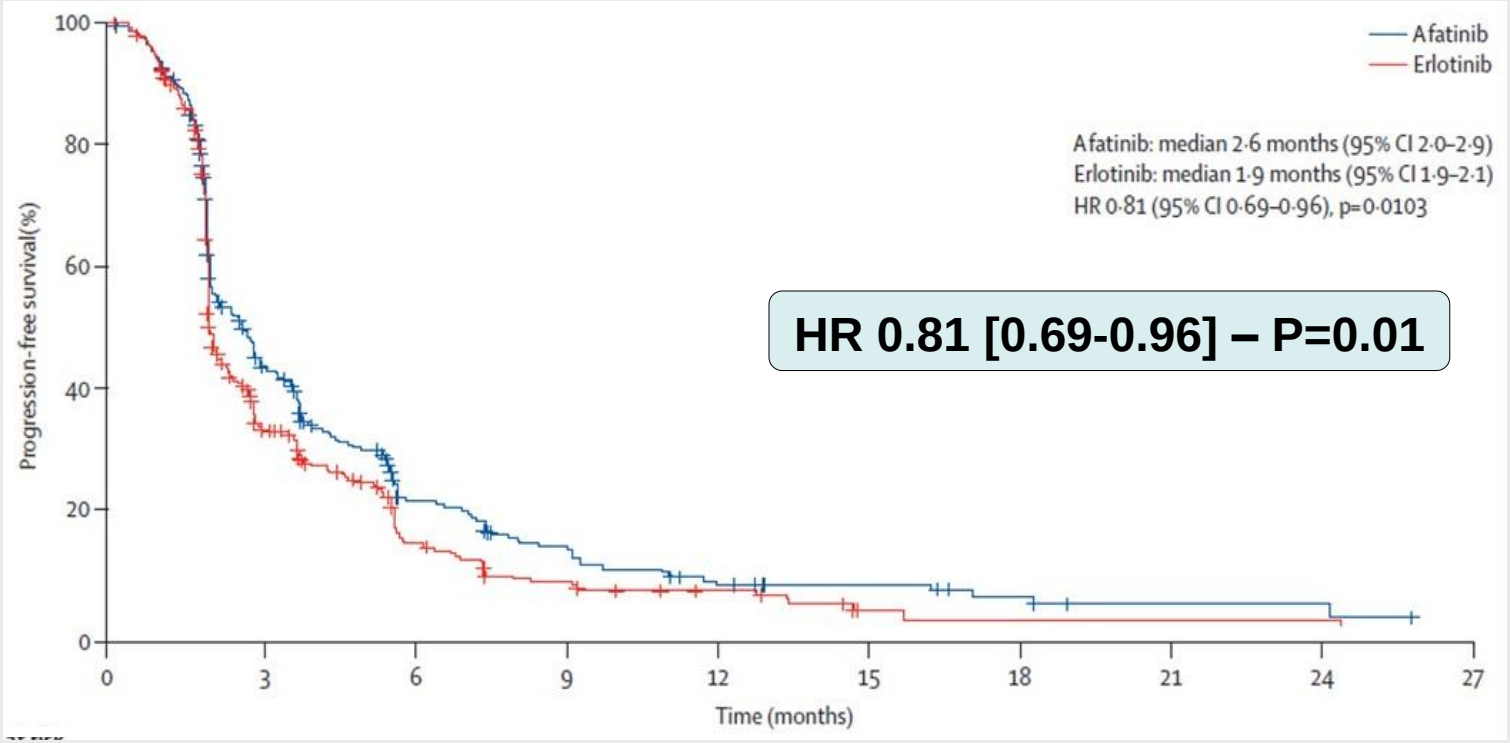
Advanced squamous LC

- **2nd line: PD after platinum-based chemotherapy**
- **PS 0-1**



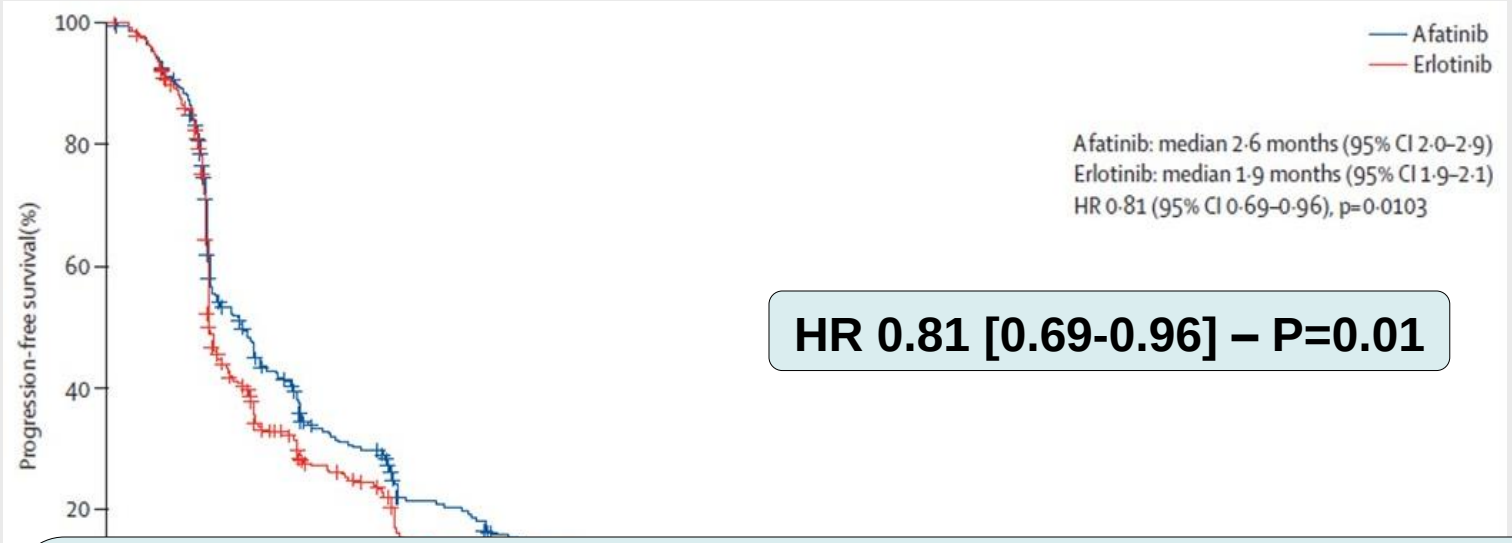
Soria et al, Lancet Oncol 16:897-9074, 2015

Squamous cell lung cancer
> *afatinib 2L (2nd gen EGFR-TKI)*



Soria et al, Lancet Oncol 16:897-9074, 2015

Squamous cell lung cancer
> *afatinib 2L (2nd gen EGFR-TKI)*



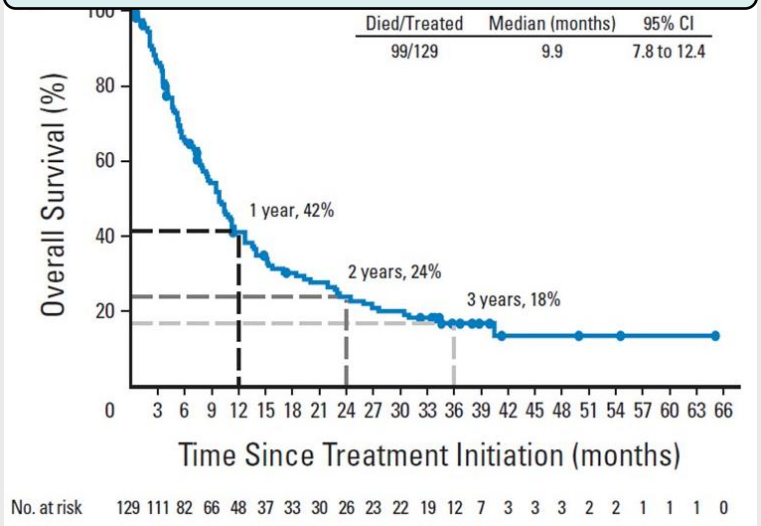
HR 0.81 [0.69-0.96] – P=0.01

CHMP 02/2016: Giotrif as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

Soria et al, Lancet Oncol 16:897-9074, 2015

Immunotherapy
> *PD-1/PD-L1 checkpoint inhibitors*

Recruitment started 04/2009



The race for the antibody

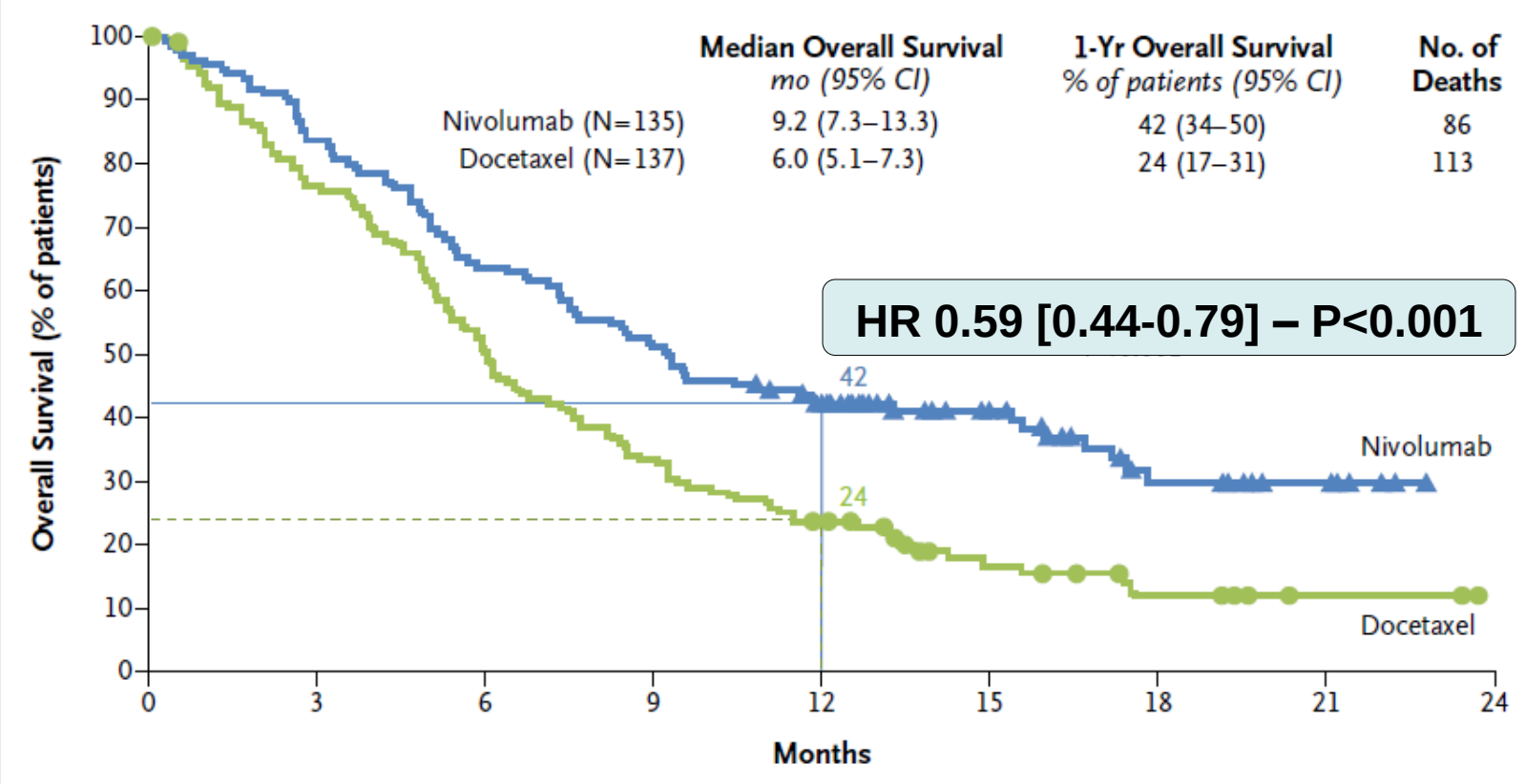
- **PD-1**
  - **nivolumab**
  - **pembrolizumab**
- **PD-L1**
  - **atezolizumab (MPDL3280A)**
  - **durvalumab (MEDI4736)**
  - **avelumab (MSB0010718C)**
- **…**

Gettinger et al, J Clin Oncol 33:2004-2009, 2015

Immunotherapy:

> *ph3 nivolumab in relapsed SQ-NSCLC*

------ASCO 2015------



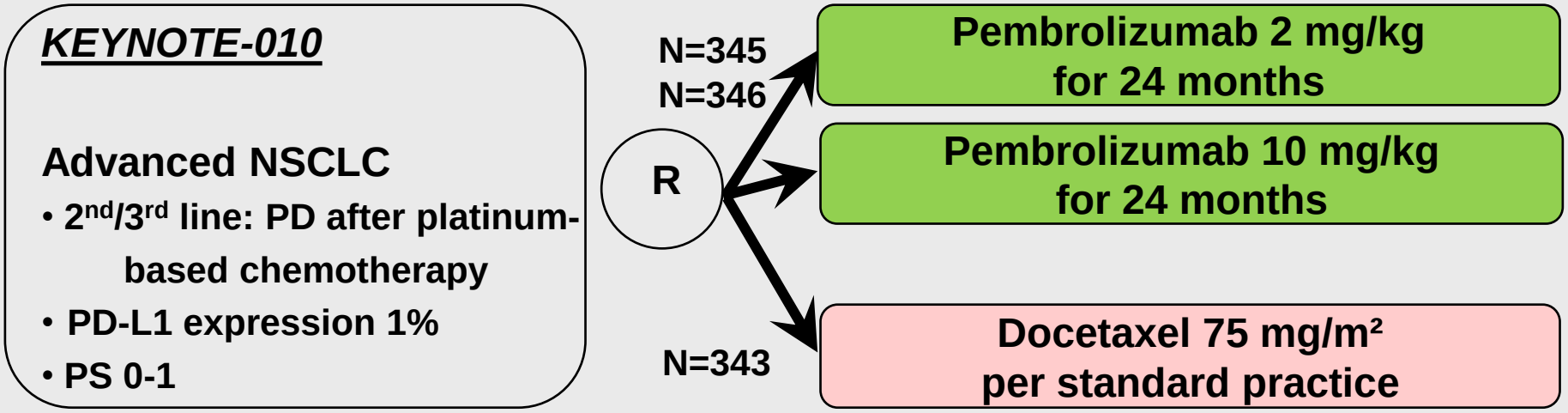
Benefit not significantly driven by PD-L1 biomarker

Spigel et al, ASCO 2015 *and* Brahmer et al, N Engl J Med 373: 123-135, 2015

Immunotherapy
> *ph3 pembrolizumab in relapsed NSCLC*

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial

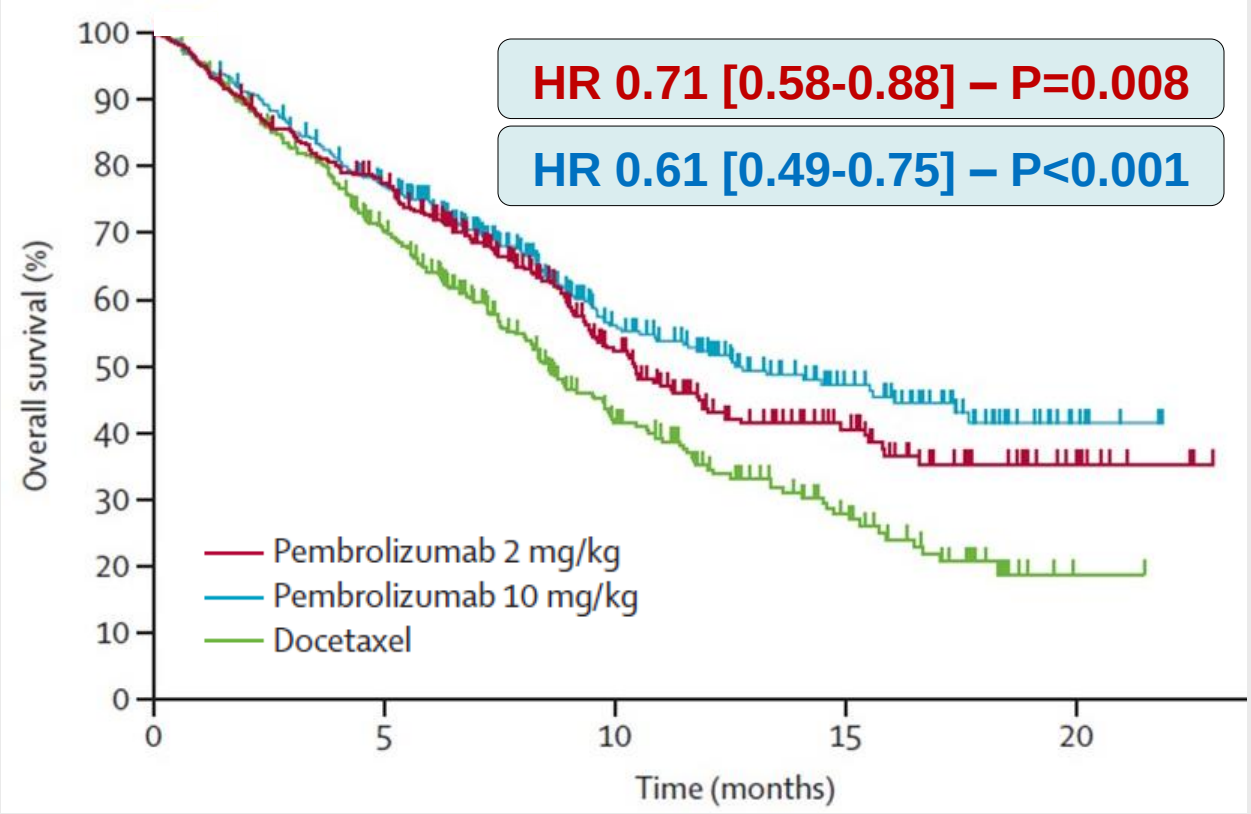
Roy S Herbst, Paul Baas, Dong-Wan Kim, Enriqueta Felip, José L Pérez-Gracia, Ji-Youn Han, Julian Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J Fidler, Gilberto de Castro Jr, Marcelo Garrido, Gregory M Lubiniecki, Yue Shentu, Ellie Im, Marisa Dolled-Filhart, Edward B Garon



Stratified PD-L1 1-49% *vs.* 50-100%

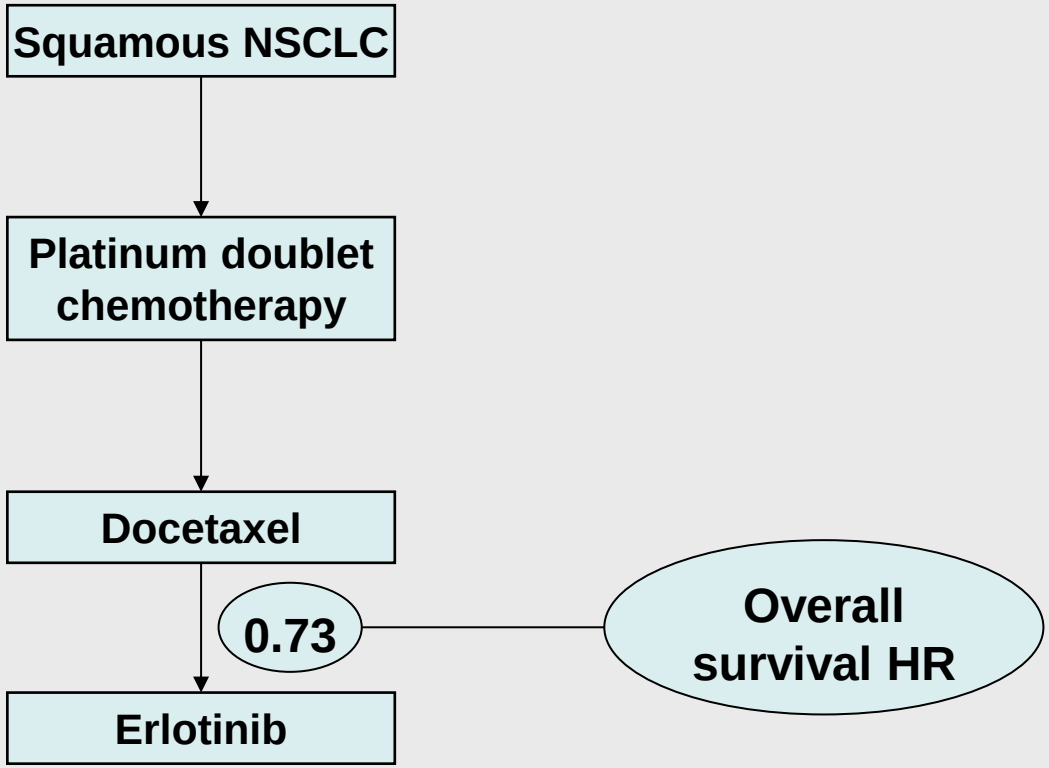
Herbst et al, Lancet 387: 1540-1550, 2016

Immunotherapy
> *ph3 pembrolizumab in relapsed NSCLC*

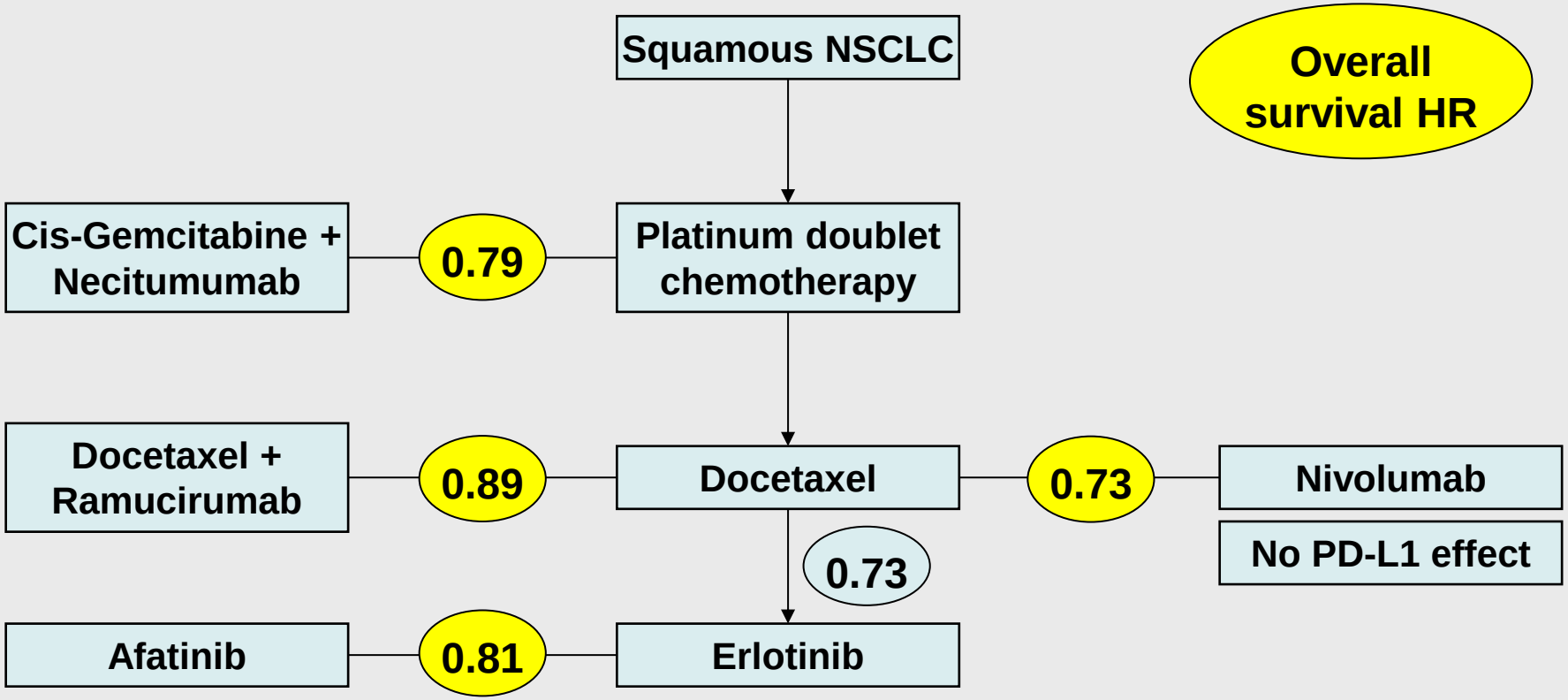


Herbst et al, Lancet 387: 1540-1550, 2016

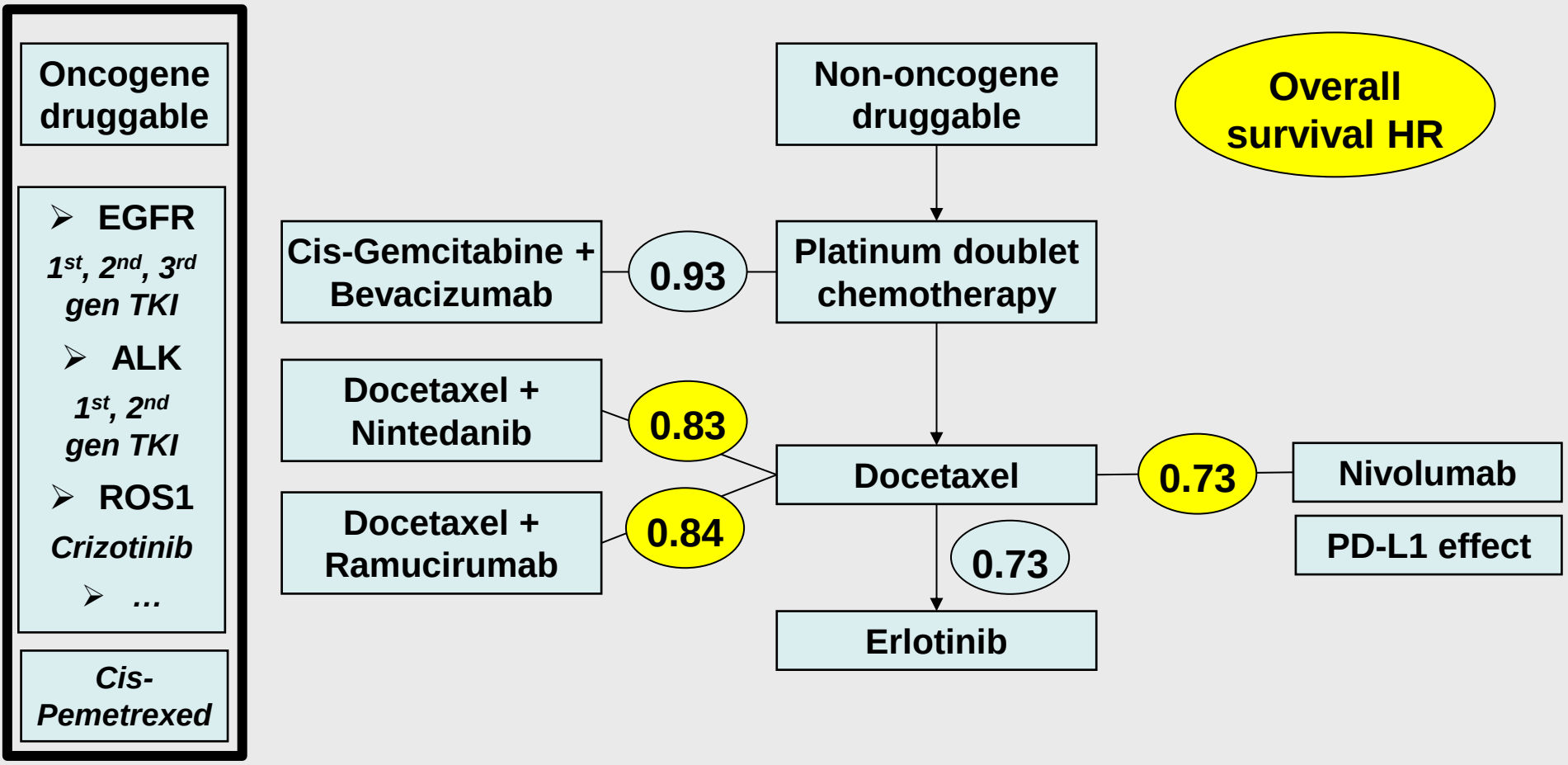
Squamous cell lung cancer
> *treatment innovations*



Squamous cell lung cancer
> *treatment innovations*



Lung adenocarcinoma
> *treatment innovations*



NSCLC immunotherapy
> *PD-L1 biomarker*

- **EGFRmut ≈ EGFR-TKI**
  - **Related to tumor only**
  - **“Simple” mechanism**
  - **Yes/No phenomenon**

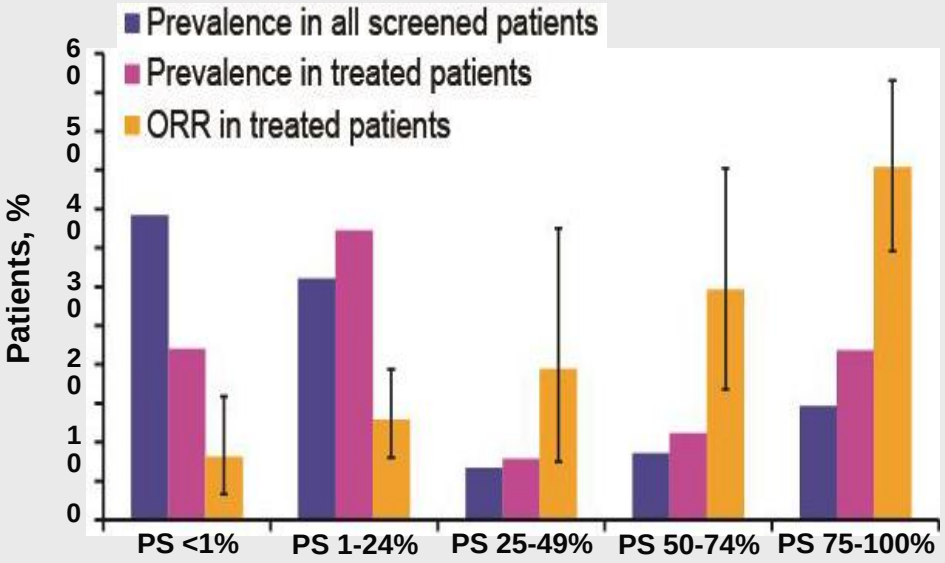
Landmark biomarker

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

?

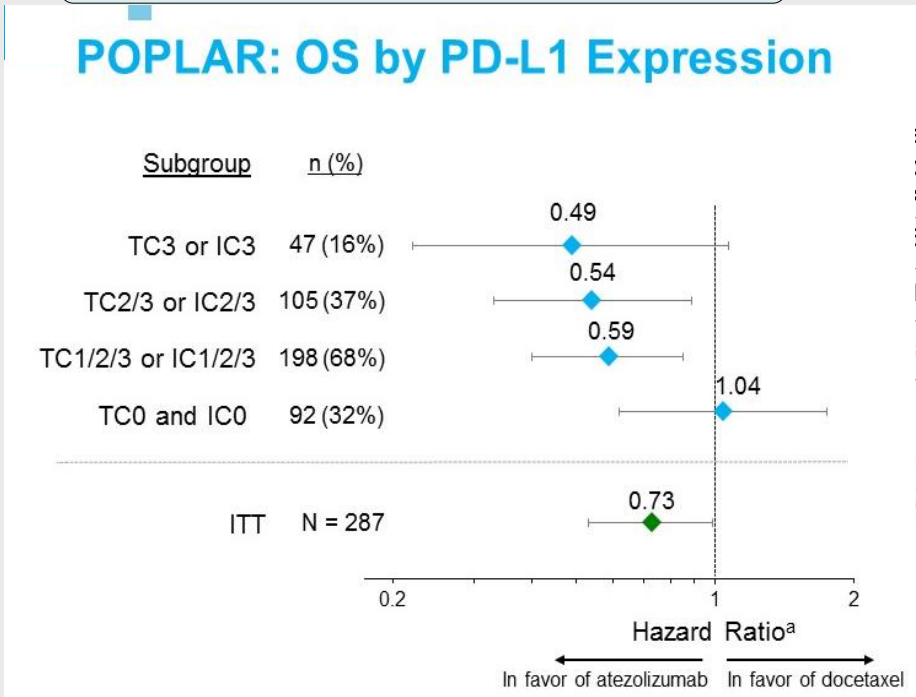
NSCLC immunotherapy
> *PD-L1 biomarker*

Pembrolizumab Ph1 [Keynote-00]



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

Atezolizumab Ph2R [POPLAR]

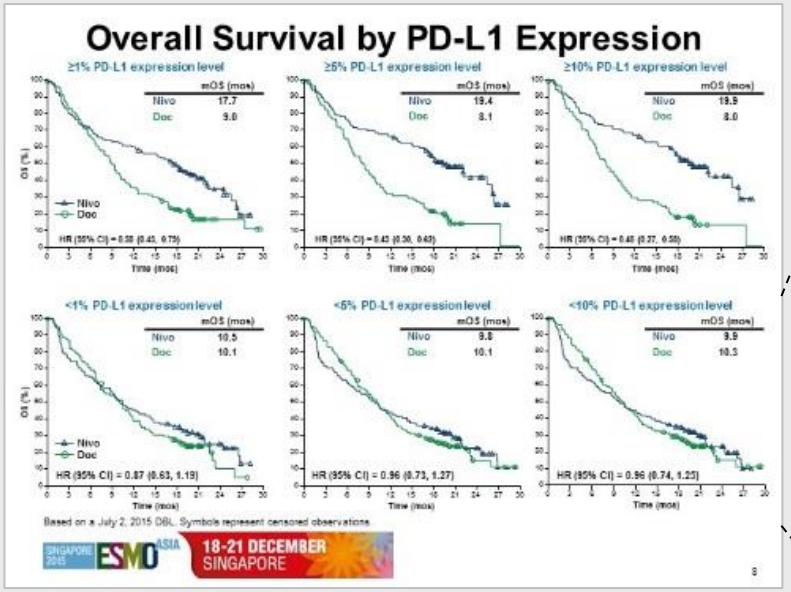


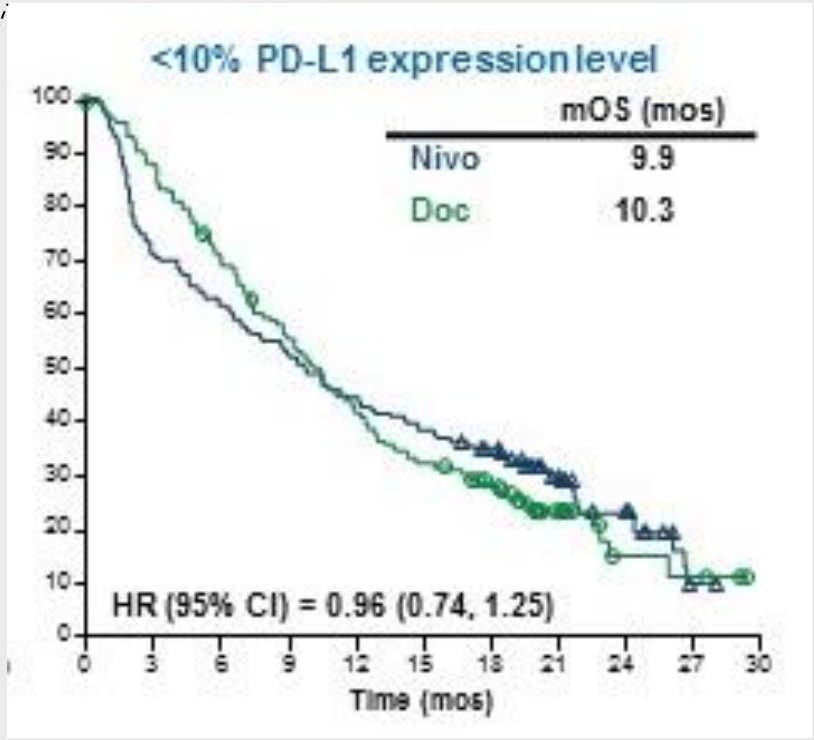
IHC 0 (TC <1%)	IHC 1 (TC 1-4%)	IHC 2 (TC 5-49%)	IHC 3 (TC ≥50%)

Garon et al, N Engl J Med 372:2018-2028, 2015 Suppl Material
Vansteenkiste et al, ESMO 2015 *and* Fehrenbacher et al, Lancet Mar 9, 2016

NSCLC immunotherapy
> *PD-L1 biomarker*

Nivolumab Ph3 [CheckMate-057

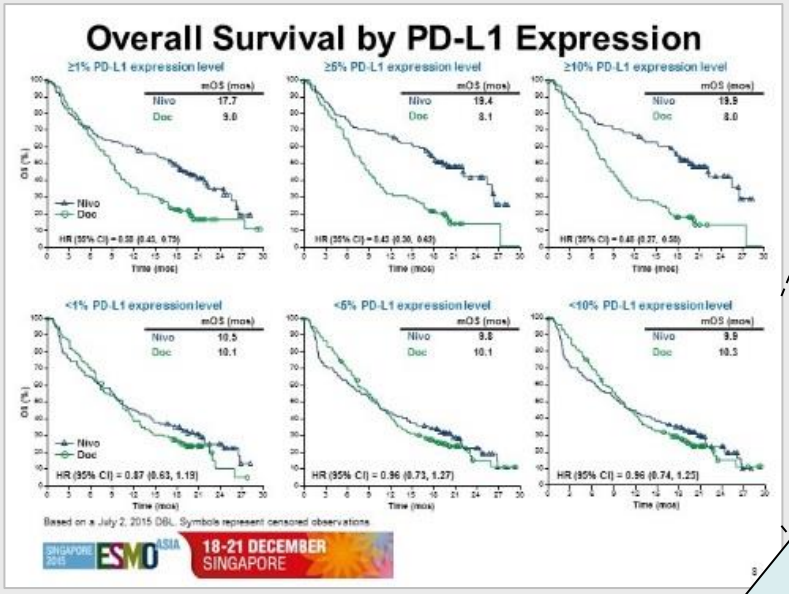


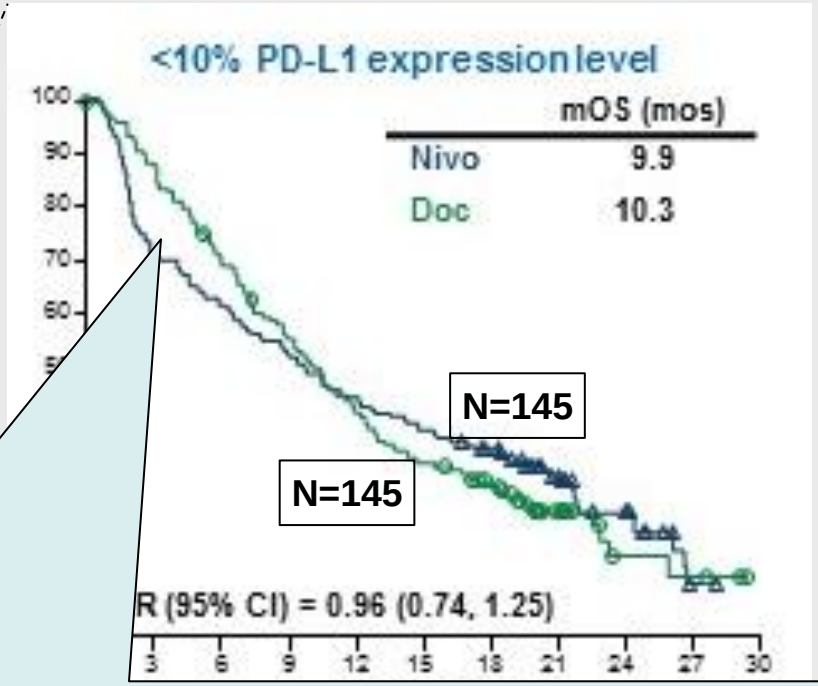


Horn et al, ESMO-ASIA 2015

NSCLC immunotherapy
> *PD-L1 biomarker*

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

Take-Home Message

Stage IV NSCLC

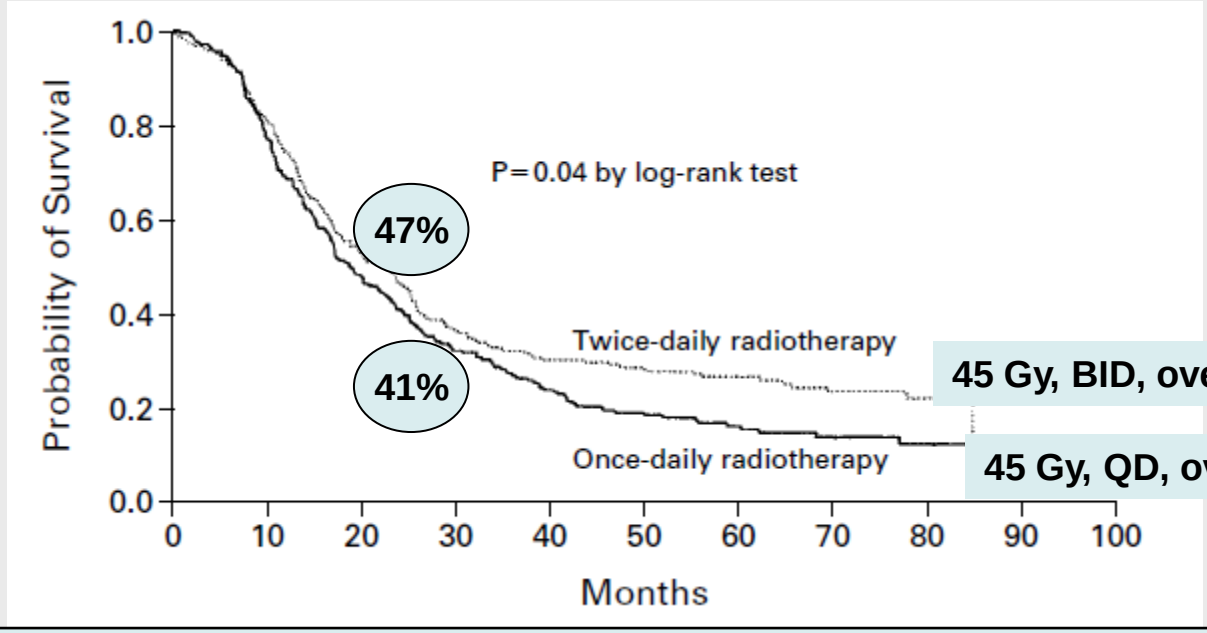
- New treatment options for patients with squamous LC
- Ongoing molecular evolution
  - Number of druggable oncogenes (EGFR, ALK, ROS1, …)
  - Generations of TKIs
- Immunotherapy revolutionizes NSCLC therapy
  - Nivolumab for 2nd line squamous LC
  - Other settings: results oriented by PD-L1 biomarker, amongst other new 2nd line treatment choices

Stage I-III SCLC
Unresectable mesothelioma

SCLC

> *radiotherapy for stage I-III*

TWICE-DAILY COMPARED WITH ONCE-DAILY THORACIC RADIOTHERAPY IN LIMITED SMALL-CELL LUNG CANCER TREATED CONCURRENTLY WITH CISPLATIN AND ETOPOSIDE



45 Gy, BID, over 3 weeks

45 Gy, QD, over 5 weeks

- **Despite these findings, QD radiotherapy (45 to 50 Gy) remained widespread for logistic and other reasons**

Turrisi et al, N Engl J Med 340:265-271, 1999

SCLC
> *radiotherapy for stage I-III*

CONVERT

Stage I-III SCLC

- **PS 0-1**
- **No pleural effusion**
- **Acceptable RT volume**

Stratified: cycle number (4 vs 6), center

R

N=292

Cisplatin-etoposide 4 (to 6) cycles + RT* 45 Gy in 30 fr BID (19 days)

N=290

Cisplatin-etoposide 4 (to 6) cycles + RT* 66 Gy in 33 fr QD (45 days)

*RT started on d1 of cycle 2

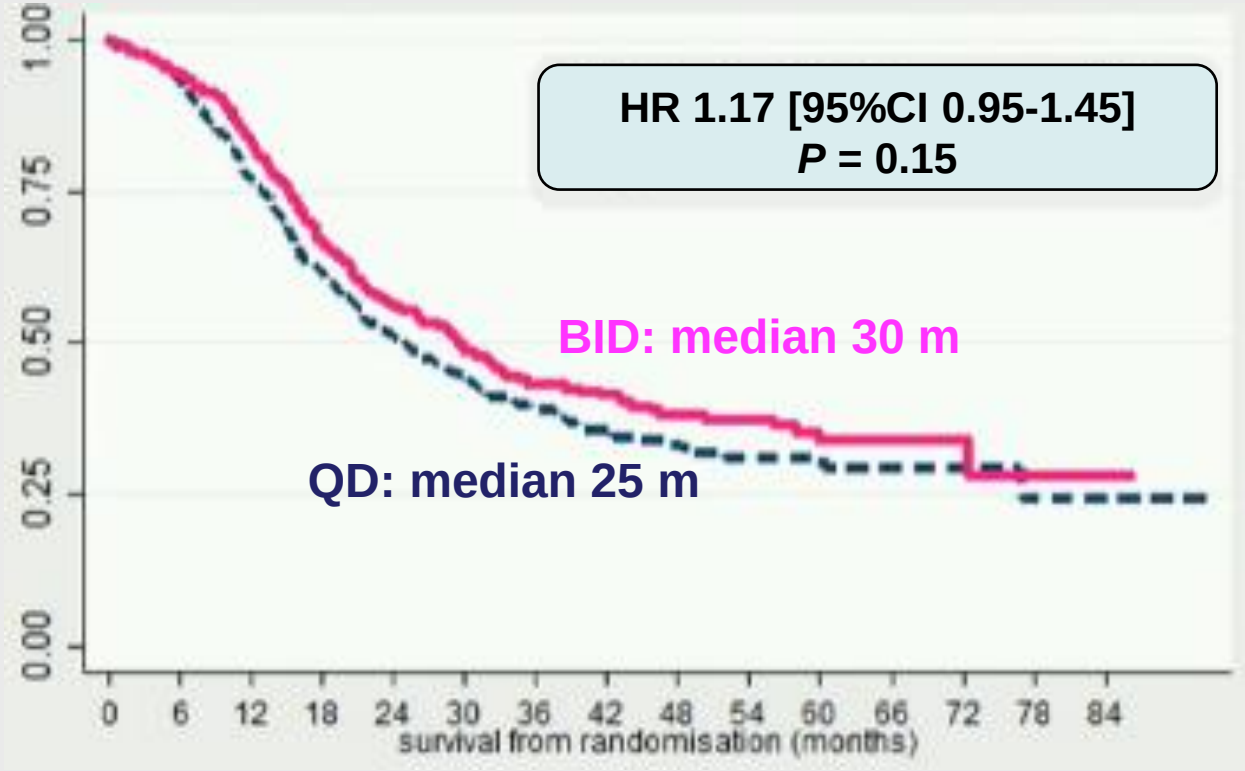
*All stable/responding patients had PCI

Primary endpoint: OS at 2 years

Faivre-Finn et al, ASCO 2016

SCLC

> *radiotherapy for stage I-III*



➢ **2-year OS: 56% (BID) *vs.* 51% (QD)**

Faivre-Finn et al, ASCO 2016

SCLC
> *radiotherapy for stage I-III*

- **Excellent OS in both arms**
  - **Modern RT techniques & quality control**
  - **PET in 70% of the patients**
- **Toxicity lower than expected**
  - **Modern RT techniques & quality control**
- **66 Gy OD did not result in superior OS**
  - **Both regimens are acceptable practice for stage I-III SCLC**

Faivre-Finn et al, ASCO 2016

Mesothelioma
> *anti-CTLA4 immunotherapy*

DETERMINE

Malignant mesothelioma

- **one/two prior regimens (including platinum)**
- **PS 0-1**
- **Measurable disease**

N=382

R

N=189

Tremelimumab 40 mg/kg i.v. q4w x7, then q12w

Placebo same schedule

Stratified: pleural vs. peritoneal, 2nd vs 3rd line, EORTC risk score

Primary endpoint: OS

Other endpoints: PFS, RR, DCR, safety

Kindler et al, ASCO 2016

Mesothelioma
> *anti-CTLA4 immunotherapy*

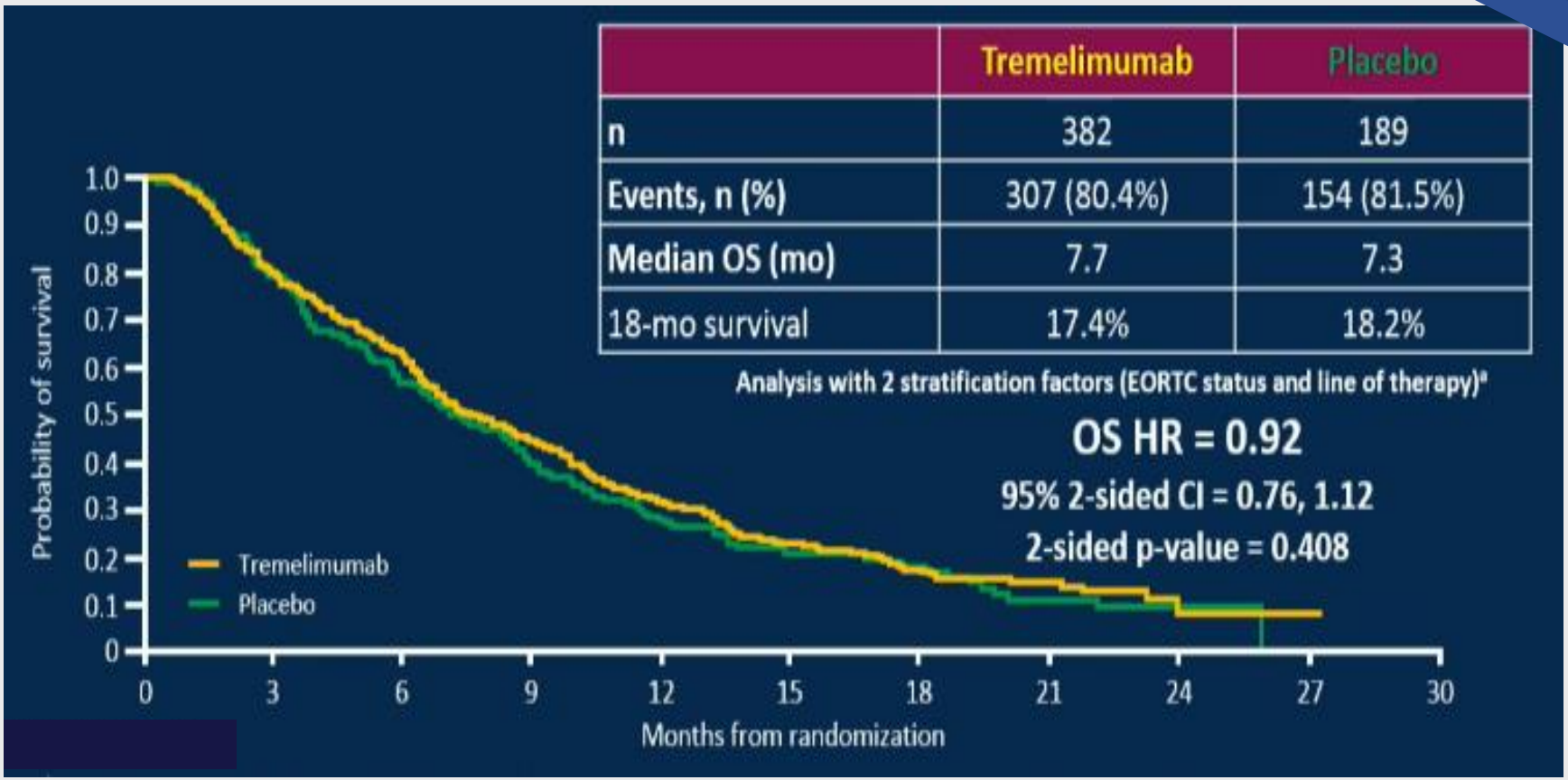
	Tremelimumab	Placebo
n	382	189
Events, n (%)	307 (80.4%)	154 (81.5%)
Median OS (mo)	7.7	7.3
18-mo survival	17.4%	18.2%

Analysis with 2 stratification factors (EORTC status and line of therapy)[a]

OS HR = 0.92

95% 2-sided CI = 0.76, 1.12

2-sided p-value = 0.408



Kindler et al, ASCO 2016

Mesothelioma
> *anti-CTLA4 immunotherapy*

-----ASCO 2016-----
Late Breaking News

- **The anti-CTLA4 immunotherapy with tremelimumab did not improve OS compared to placebo in pre-treated mesothelioma**
- **Rapid accrual underscores the unmet need in this patient group**
- **Combining anti-CTLA4 and anti-PD-1/PD-L1 strategies are the next development step**

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