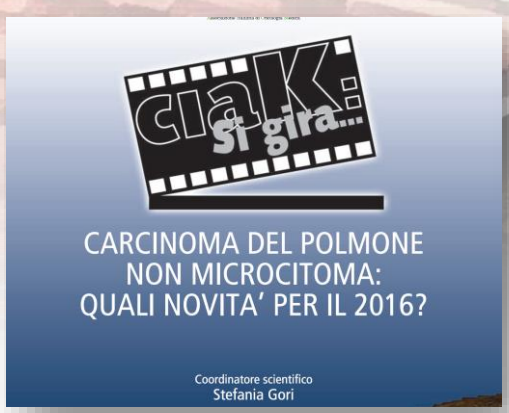


Trattamento del NSCLC avanzato: quale seconda linea nel 2016?

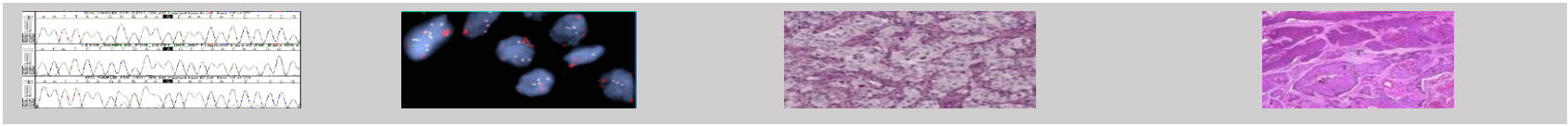
Filippo de Marinis

Thoracic Oncology Division, IEO, Milan, Italy

IEO Istituto Europeo di Oncologia

EBM ALGORITHM IN A-NSCLC THERAPY IN ITALY IN 2015

Stratification for EGFR, ALK and histology



EGFR Mut+

EGFR TKI

UNTIL PD

CTx

ALK+

CTx

Crizotinib

EGFR WT NSq

P/Pem

Pem Maintenance

Erlotinib/ docetaxel

P-based CTx + BEVA

BEVA until PD

Pemetrexed/ docetaxel/ erlotinib

Squamous

P-based doublet

Docetaxel/ erlotinib

Erlotinib

1st Line

Maintenance

2nd Line

3rd Line

ALGHORITM for TREATMENT of EGFR MUT+ve TKI Resistance

NSCLC EGFR Mut+ve responder to TKI

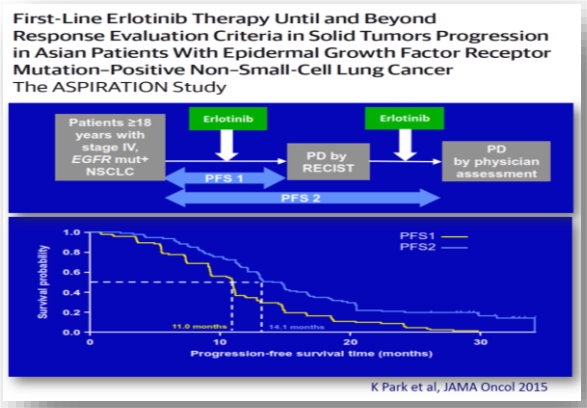
Oligo-Progression

Systemic 1st Progression

Local therapy + continuation of TKI

Systemic PD

Systemic 2nd-line therapy

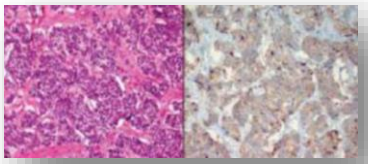


3rd gen. TKI (for T790M+ve)

Targeting the resistant gene (ie. cMET)

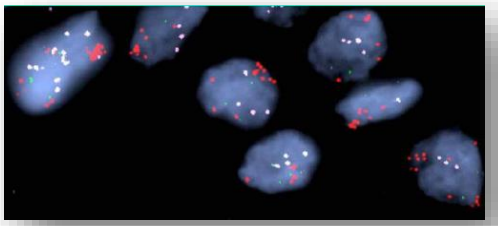
Chemo

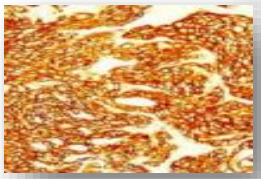
Mechanisms responsible for EGFR-TKI resistance



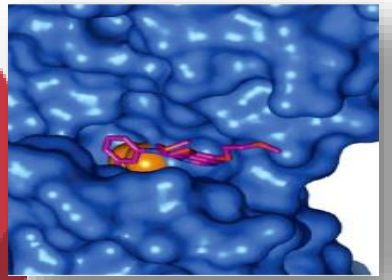
Small-cell transformation (6%)

MET amplification (4%)





HER2 amplification (12%)



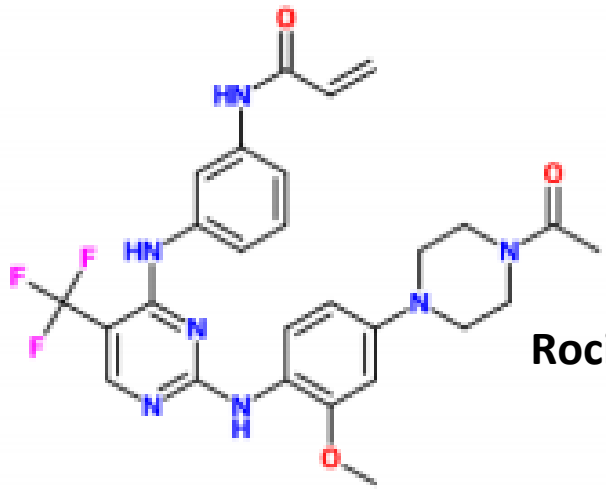
Unknown (18%)*

EGFR^{T790M} and rare second site mutations (60%)

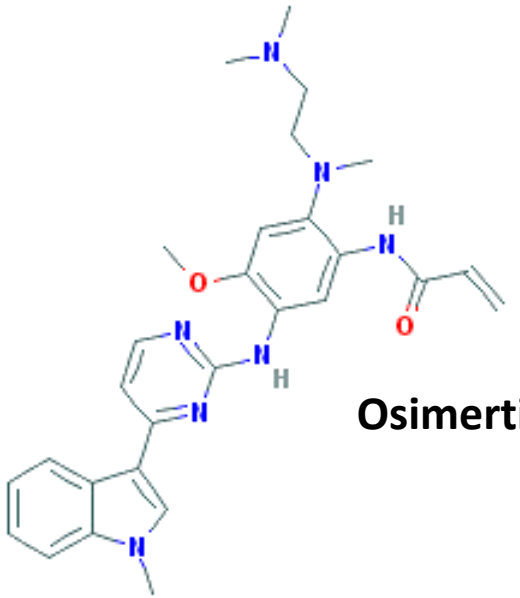
Takezawa et al, Cancer Discovery 2012

THIRD-GENERATION EGFR TKIs: ROCILETINIB (CO-1686) AND OSIMERTINIB (AZD9291)

- **Both drugs are irreversible EGFR TKIs**
- **They selectively inhibit EGFR activating mutations and the dominant acquired T790M resistance mutation**
- **They spare *EGFR* wild-type signalling**



Rociletinib



Osimertinib

TKI = tyrosine kinase inhibitor.

1. TAT congress. Rociletinib (CO-1686), an irreversible EGFR-mutant selective inhibitor. Available at: http://tatcongress.org/wp-content/uploads/2015/03/O10.3-Jean-Charles-Soria.pdf (accessed October 2015). 2. TAT congress. AZD9291 a novel EGFR-TKI that overcomes T790M-mediated resistance in NSCLC. Available at: http://tatcongress.org/wp-content/uploads/2015/03/O10.4-David-Planchard.pdf (accessed October 2015).

AZD9291 – KEY CLINICAL TRIALS

AURA
(NCT01802632)
Available Data

- **Single-arm, dose escalation and expansion (Phase I, completed) and Phase II extension (N=~175)[2]**

Phase I: Safety, tolerability, PK and antitumour activity of ascending doses of AZD9291[2]

Phase II: Assessment of efficacy and tolerability of AZD9291 80 mg QD in T790M NSCLC[2]

AURA 2
(NCT02094261)
Available Data

- **Confirmatory global Phase II – assessment of efficacy and tolerability of AZD9291 80 mg QD in patients with T790M+ NSCLC**

AURA 3
(NCT02151981)
Completed

- **Phase III – AZD9291 vs platinum-based doublet chemotherapy** in second-line patients with T790M+ advanced/metastatic NSCLC who have progressed following prior therapy with an EGFR-TKI

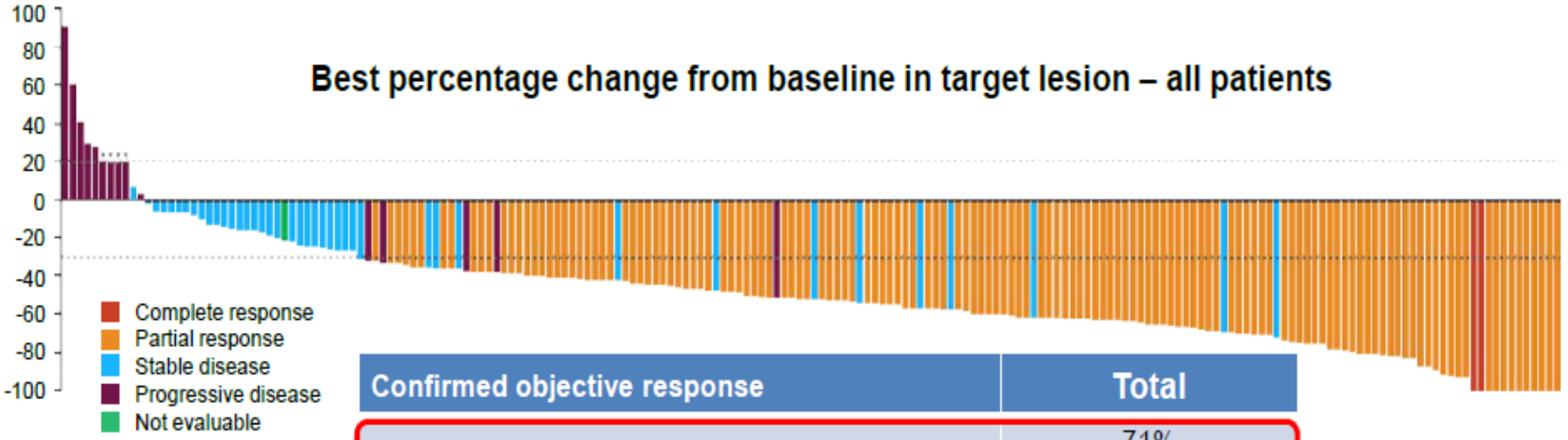
FLAURA
(NCT02296125)
Completed

- **Phase III – AZD9291 vs a Standard of Care EGFR-TKI** as First Line Treatment in Naive Patients With EGFR Mutation Positive, Locally Advanced or Metastatic NSCLC

www.clinicaltrials.gov

AURA PHASE II: AZD9291 TUMOR RESPONSE BY ICR

Tumor response by independent central review



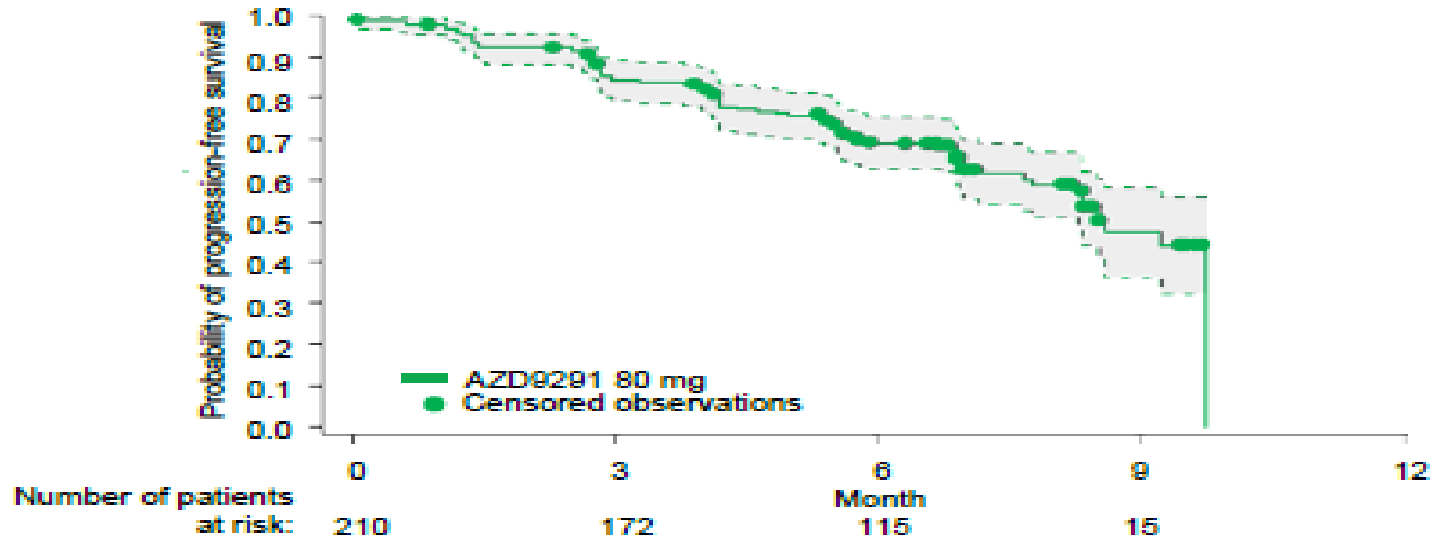
Confirmed objective response	Total
ORR†	71% (95% CI 64, 77)
Complete response,‡ n (%)	2 (1)
Partial response,‡ n (%)	139 (70)
Stable disease ≥6 weeks,§ n (%)	41 (21)
Progressive disease, n (%)	15 (8)
DCR	92% (95% CI 87, 95)

NOTE: Investigator-assessed ORR was also 71% (95% CI 64, 77)
Data cut-off: May 1, 2015. Population: evaluable for response set (n=199). *Represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to disease progression, and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%; †ORR defined as the number (%) of patients with at least one visit response of complete response or partial response that was confirmed at least 4 weeks later; ‡Response required confirmation after 4 weeks; §Stable disease ≥6 weeks included the RECIST visit window (±7 days)
CI, confidence interval; DCR, disease control rate (complete response + partial response + stable disease)

Presented by T Mitsudomi at the World Conference on Lung Cancer 2015. *Journal of Thoracic Oncology* 2015; 10(9, Suppl 2): S320, abstract Mini 16.08

AURA PHASE II: AZD9291 EFFICACY

Progression-free survival* (BICR)



KM-based estimated†	Total§
Median PFS,** months (95% CI)††	8.6 (8.3, 9.7) Maturity: 38%
Remaining alive and progression free, % (95% CI) 6 months 9 months	 70 (63, 76) 48 (36, 58)
Median follow-up for PFS	6.7 months

Data cut-off: May 1, 2015. *Green dotted lines represent 95% CI; †Calculated using the Kaplan-Meier technique; ‡Population: evaluable for response analysis set; §Population: full analysis set (n=210); ¶DoR is the time from the first documentation of complete/partial response (that is subsequently confirmed) until the date of progression or death in the absence of disease progression; **PFS is the time from date of first dosing until the date of objective disease progression or death; ††Median PFS (months) by investigator assessment¶ was NC (95% CI 9.3, NC). Maturity: 37%
DoR, duration of response; KM, Kaplan-Meier; NC, not calculable; PFS, progression-free survival

Presented by T Mitsudomi at the World Conference on Lung Cancer 2015. *Journal of Thoracic Oncology* 2015; 10(9, Suppl 2): S320, abstract Mini 16.08

ASTRIS

Open label, multicentre, real-world treatment study of single-agent AZD9291 for patients with advanced/metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC) who have received prior therapy with an EGFR tyrosine kinase inhibitor (EGFR-TKI)

NSCLC T790M+
EGFR-TKI pre-treated patients

AZD9291
monotherapy 80 mg/d

PRIMARY OBJECTIVE:

to assess the efficacy and safety of single agent AZD9291 in a real-world setting in patients with advanced or metastatic EGFR T790M mutation-positive Non-Small Cell Lung Cancer (NSCLC), who have received prior EGFR-TKI therapy

Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

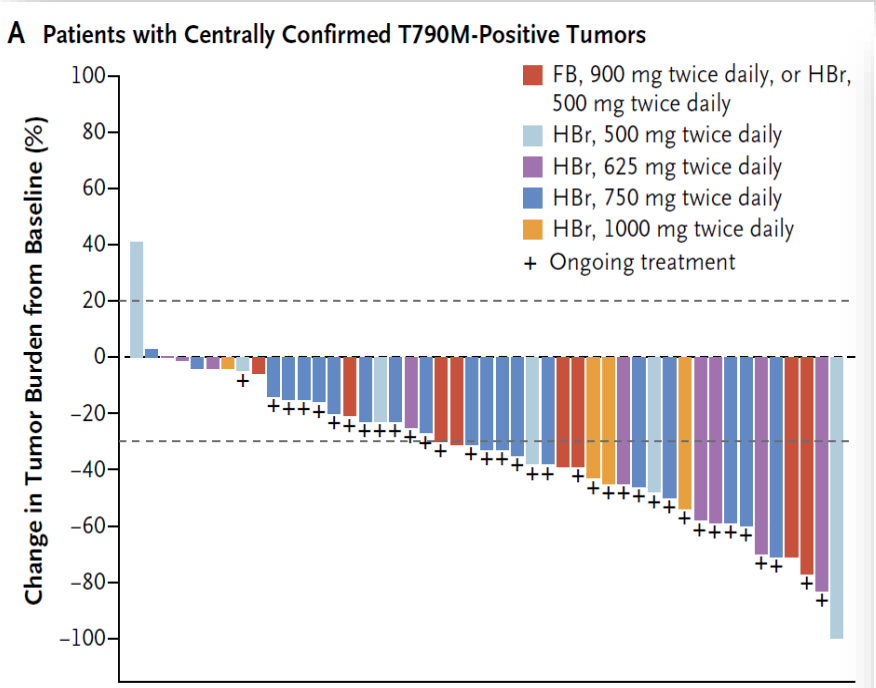
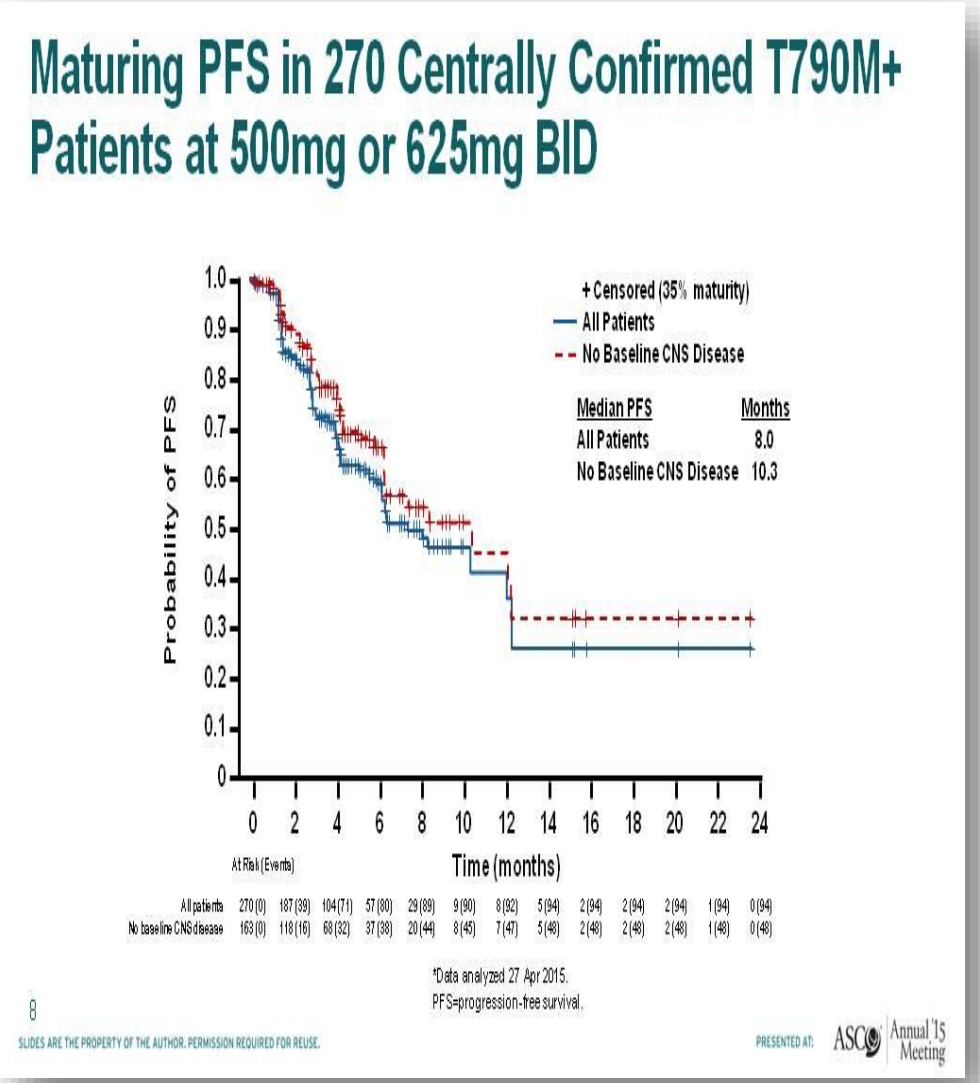


Table 4. Treatment-Related Adverse Events in the 92 Patients Receiving Therapeutic Doses of Rociletinib, According to Event Grade.*

Event	Any Grade	Grade 1	Grade 2	Grade 3
	number (percent)			
Hyperglycemia†	43 (47)	14 (15)	9 (10)	20 (22)
Nausea	32 (35)	16 (17)	14 (15)	2 (2)
Fatigue	22 (24)	9 (10)	9 (10)	4 (4)



LV Sequist, NEJM 2015

ROCILETINIB – KEY CLINICAL TRIALS

TIGER-1 (Ph 2/3)

- Randomized rociletinib vs erlotinib
- 1st-line, treatment-naïve

TIGER-2 (Ph 2)

- Single-arm, 500mg BID going forward
- 2nd-line mutant EGFR NSCLC, T790M+
- Patients progressing on 1st-line EGFR TKI
- Both T790M + and – cohorts

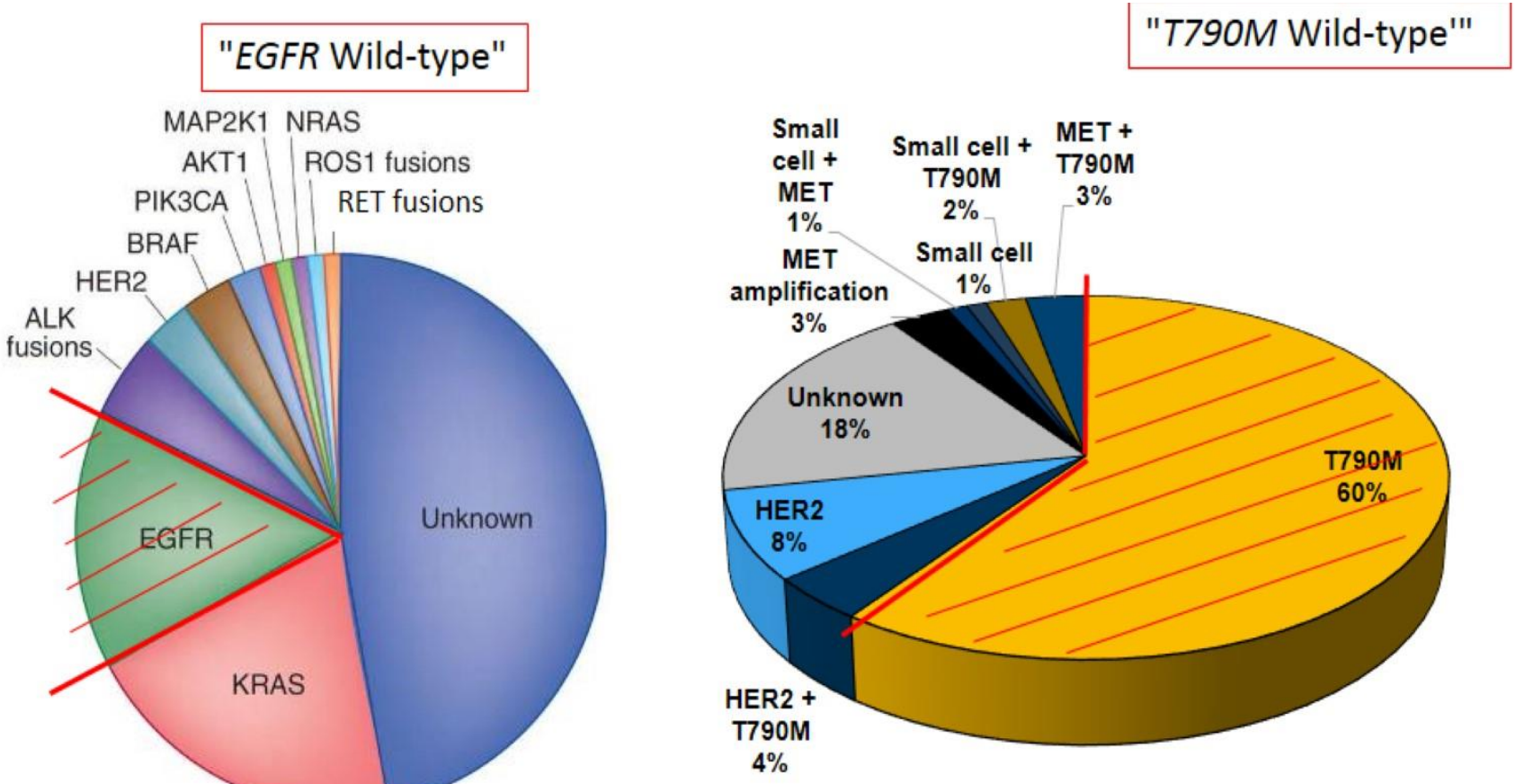
TIGER-3 (Ph 3)

- Randomized rociletinib vs chemotherapy
- >2nd-line mutant EGFR NSCLC, T790M+ and T790M– (sequential analysis)

Combination trials

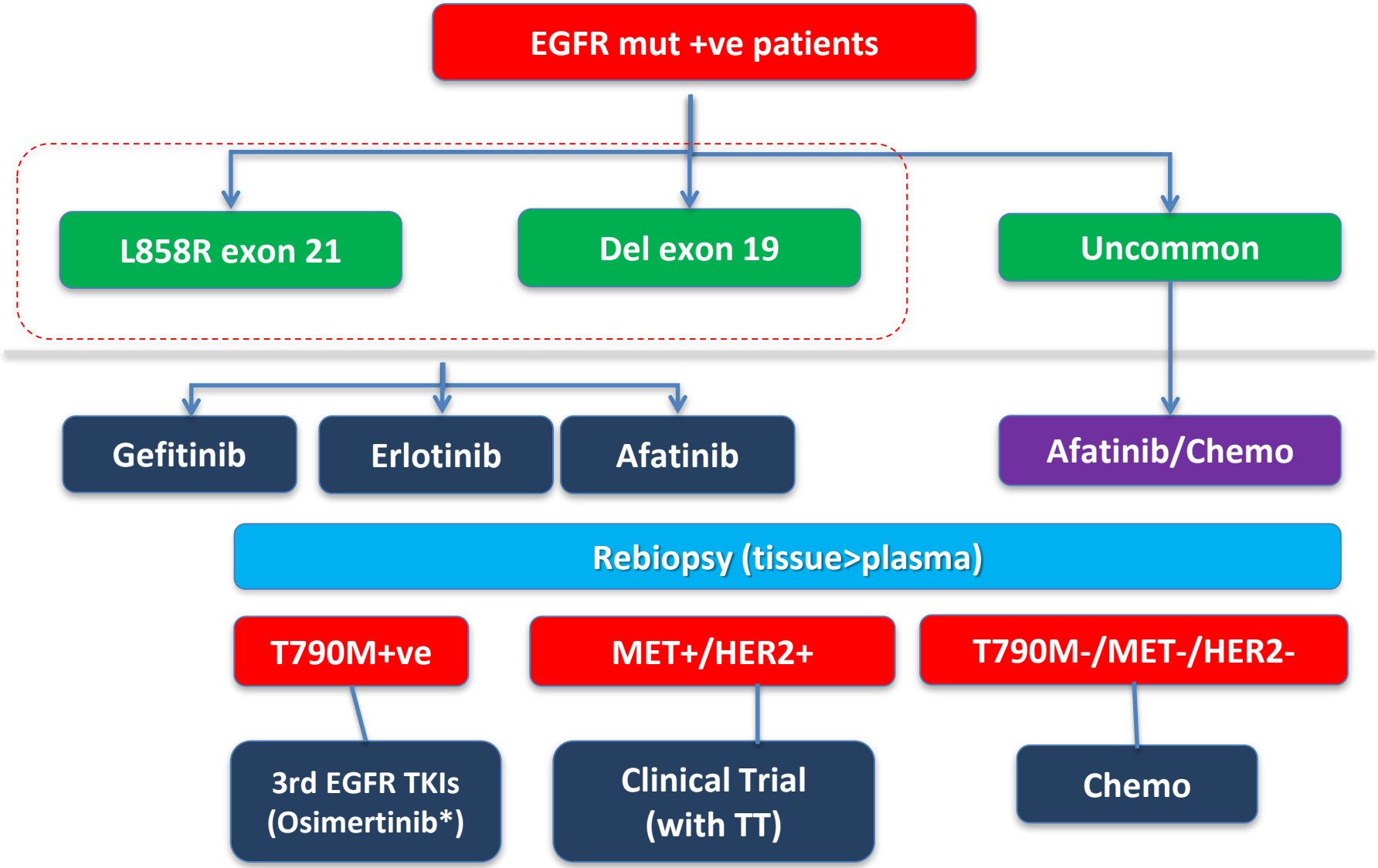
- Checkpoint inhibitors (anti-PD1/PDL1 mAb)
- MEK inhibitor
- VEGF inhibitor
- C-MET inhibitor

FROM EGFR WILD-TYPE TO T790M WILD TYPE



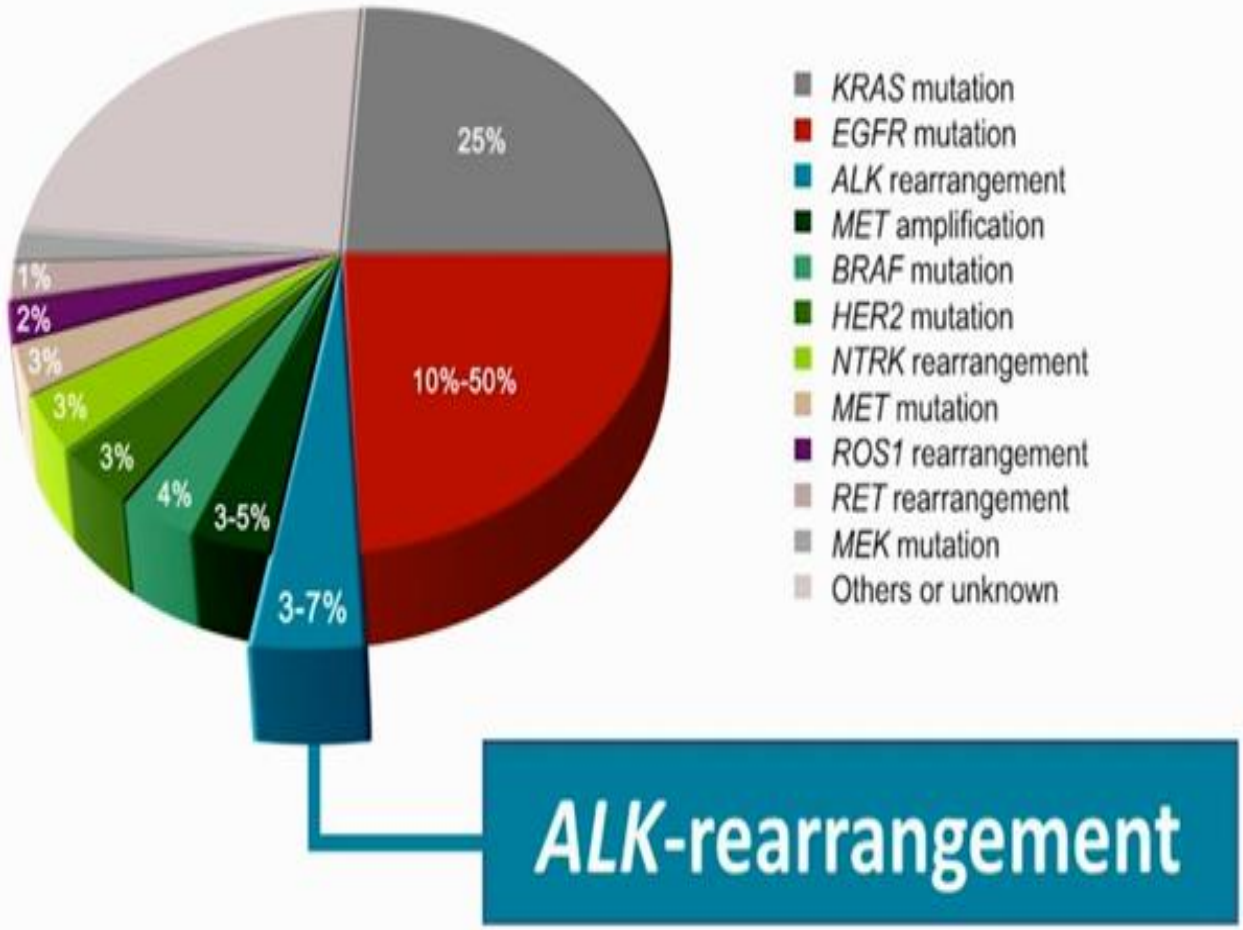
Yu HA, et al. *Clin Cancer Res* 2013;19:2240-2247.

EGFR Mut+ve ALGORITHM



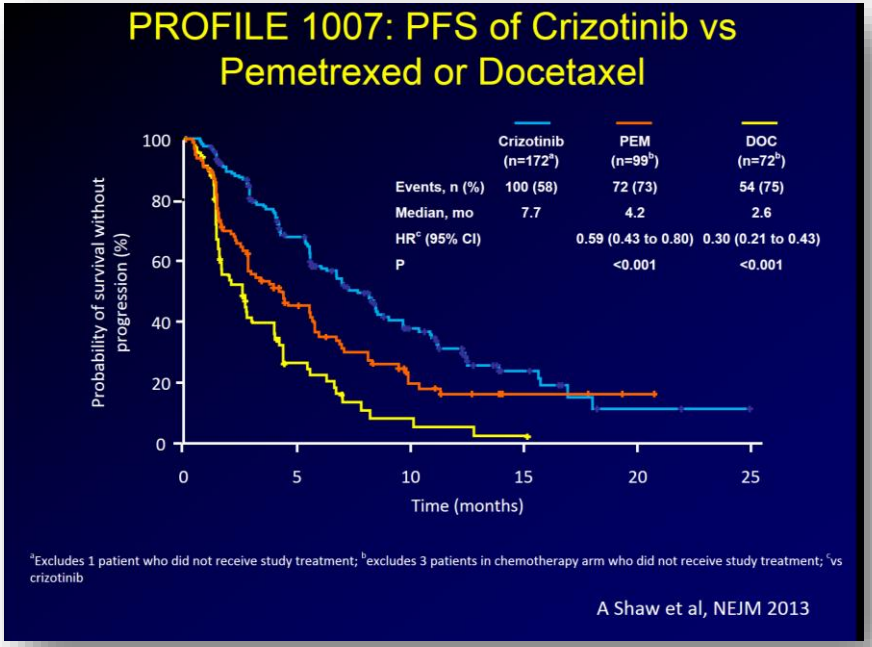
* Not yet reimbursed in Italy)

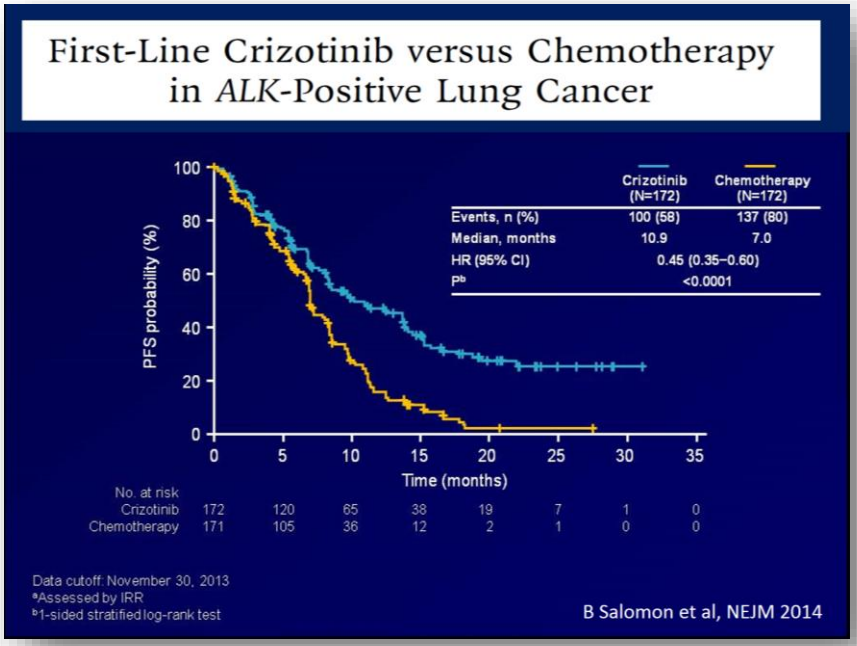
Genetic Alterations in NSCLC: Adenocarcinoma



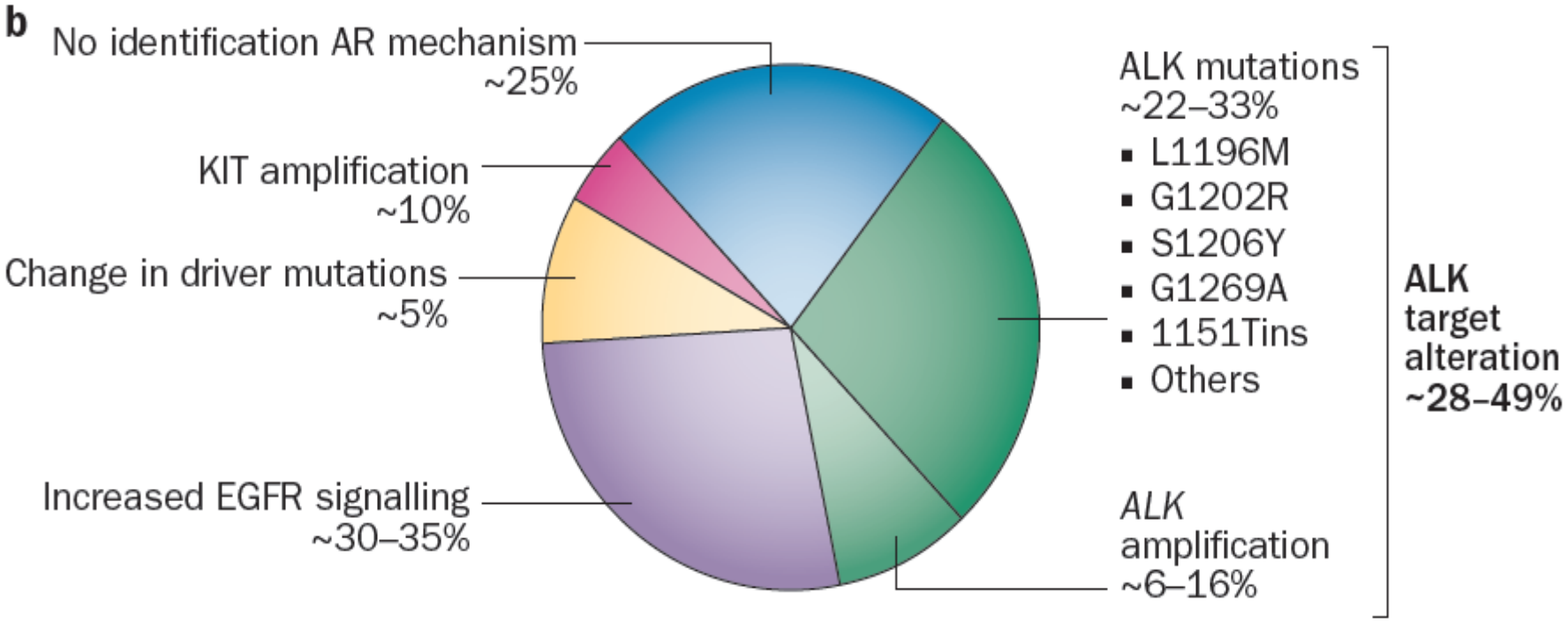
CLINICAL DEVELOPMENT OF CRIZOTINIB FOR ALK+ NSCLC

Study	Phase (planned accrual)	Histology	Line of therapy	Study design	Primary endpoint
PROFILE 1007	III (318 pts)	NSCLC	**2nd**	Pemetrexed or Docetaxel vs Crizotinib	PFS
PROFILE 1014	III (334 pts)	Non-squamous	**1st**	Platinum-Pemetrexed vs Crizotinib	PFS





MOLECULAR MECHANISMS OF ACQUIRED RESISTANCE IN ALK+VE

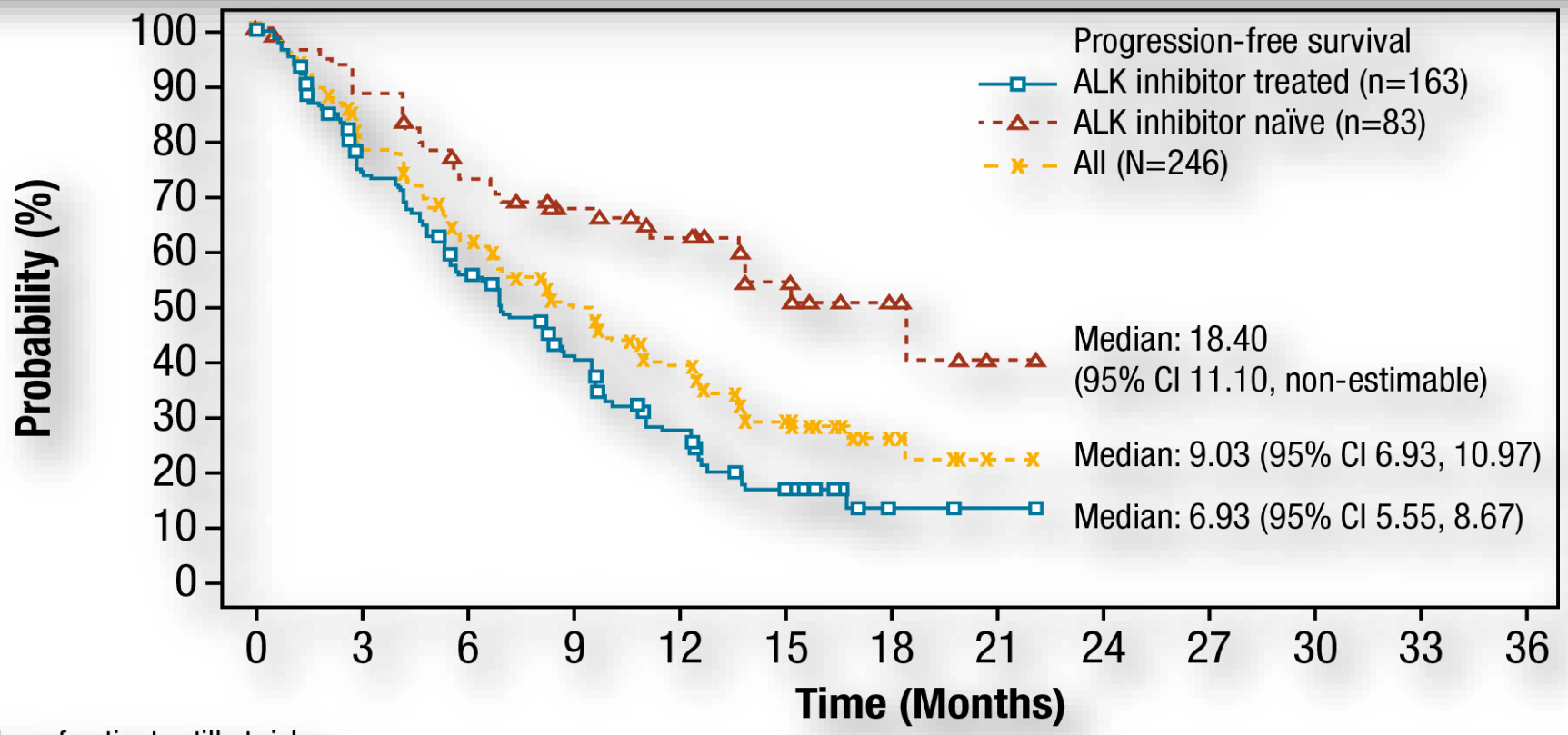


Camidge N Rev Clin Cancer 2014

2nd Generation ALK Inhibitors in Development

Drug	Company	ROS1 Activity	Status	Ongoing Studies	Reference
Ceritinib (LDK378)	**Novartis**	**Yes**	**FDA approved April 2014 EMA approved March 2015**	**Phase 1, Phase 2, Phase 3**	**ASCO 2014 ESMO 2014 NEIM 2014**
Alectinib	Chugai/ Roche	No	Investigational	Phase 3	ASCO 2014, #8103
Brigatinib	Ariad	Yes	Investigational	Phase 1/2	ASCO 2014, #8047
ASP3026	Astellas	Yes	Investigational	Phase 1	ASCO 2014, #2624
X-396	Xcovery	Yes	Investigational	Phase 1	ASCO 2014, #8030
TSR-011	Tesaro	Unk	Investigational	Phase 1/2	Wilcoxen, et al., AACR 2012
NMS-E628	Nerviano	Yes	Investigational	Phase 1	Ardini, et al., AACR 2013
Lorlatinib	Pfizer	Yes	Investigational	Phase 1	ClinicalTrials.gov ID: NCT01970865

Activity and safety of ceritinib in patients with *ALK*-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial

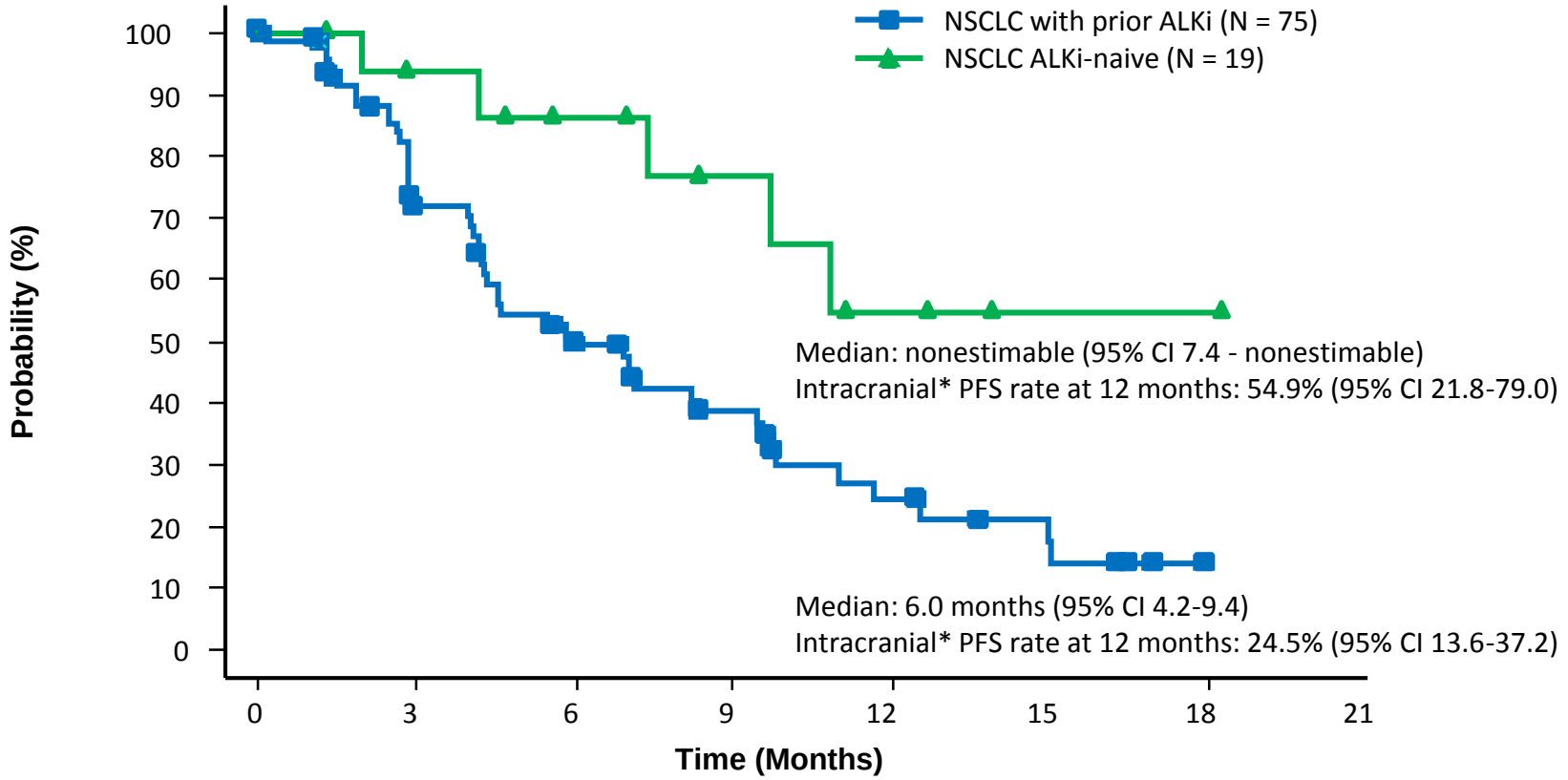


Number of patients still at risk

NSCLC with prior ALKi	163	108	79	52	29	13	2	1	0	0	0	0	0
NSCLC ALKi naïve	83	69	55	43	32	17	6	2	0	0	0	0	0
All NSCLC	246	177	134	95	61	30	8	3	0	0	0	0	0

DW Kim et al, Lancet Oncol 2016

Retrospective Central Analysis of ASCEND-1 Brain Metastases Subset – Intracranial PFS* (Evaluable by MRI/CT)



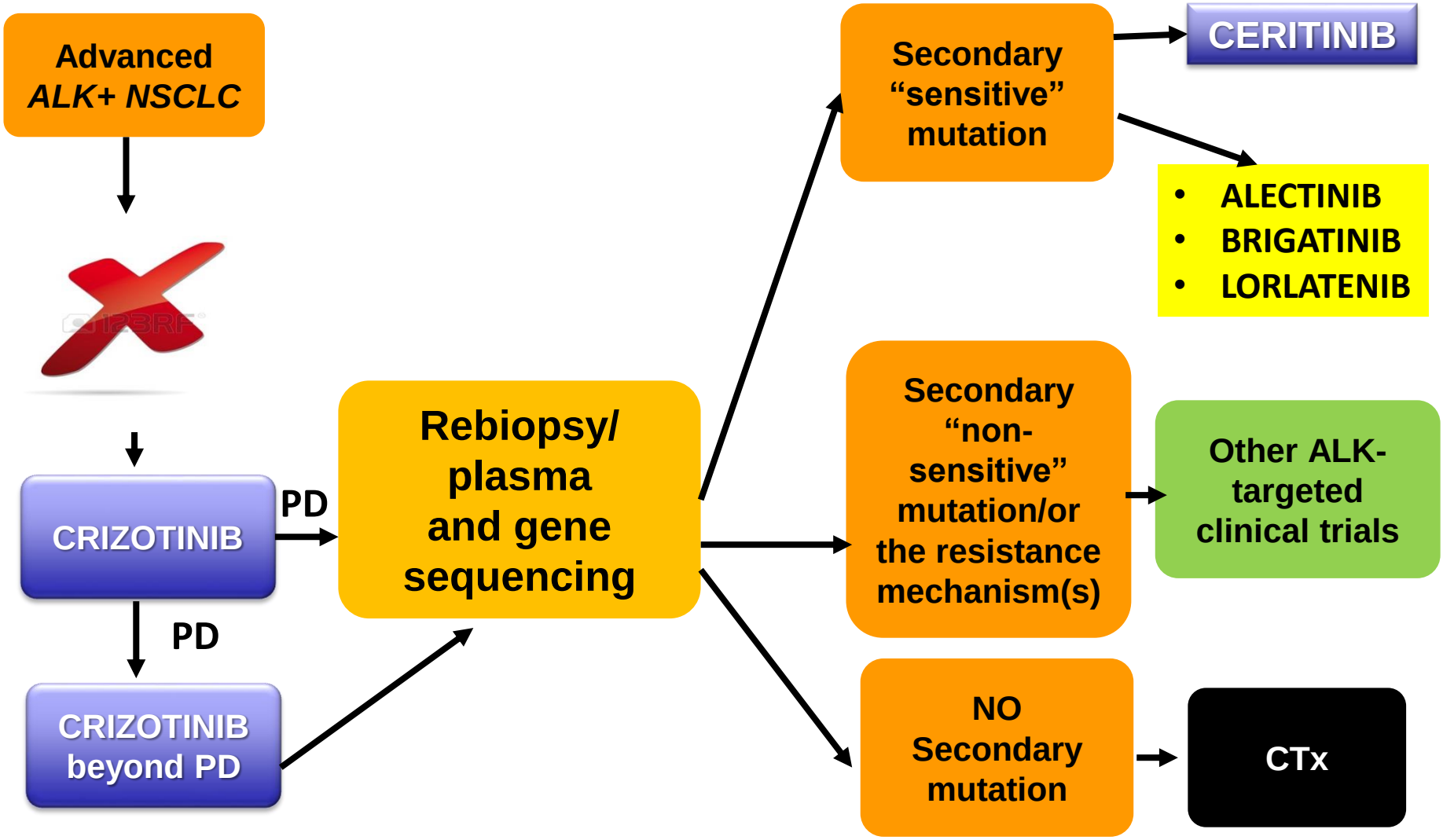
Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21
NSCLC with prior ALKi	75	46	29	20	9	5	0	0
NSCLC ALKi-naive	19	13	10	7	3	1	1	0

*Intracranial PFS calculated as time to progression in brain + deaths due to any cause. Analyses include patients evaluated by MRI (n = 74) and CT (n = 20).

Shaw AT, et al. SNO 2014. Abstract BM-32.

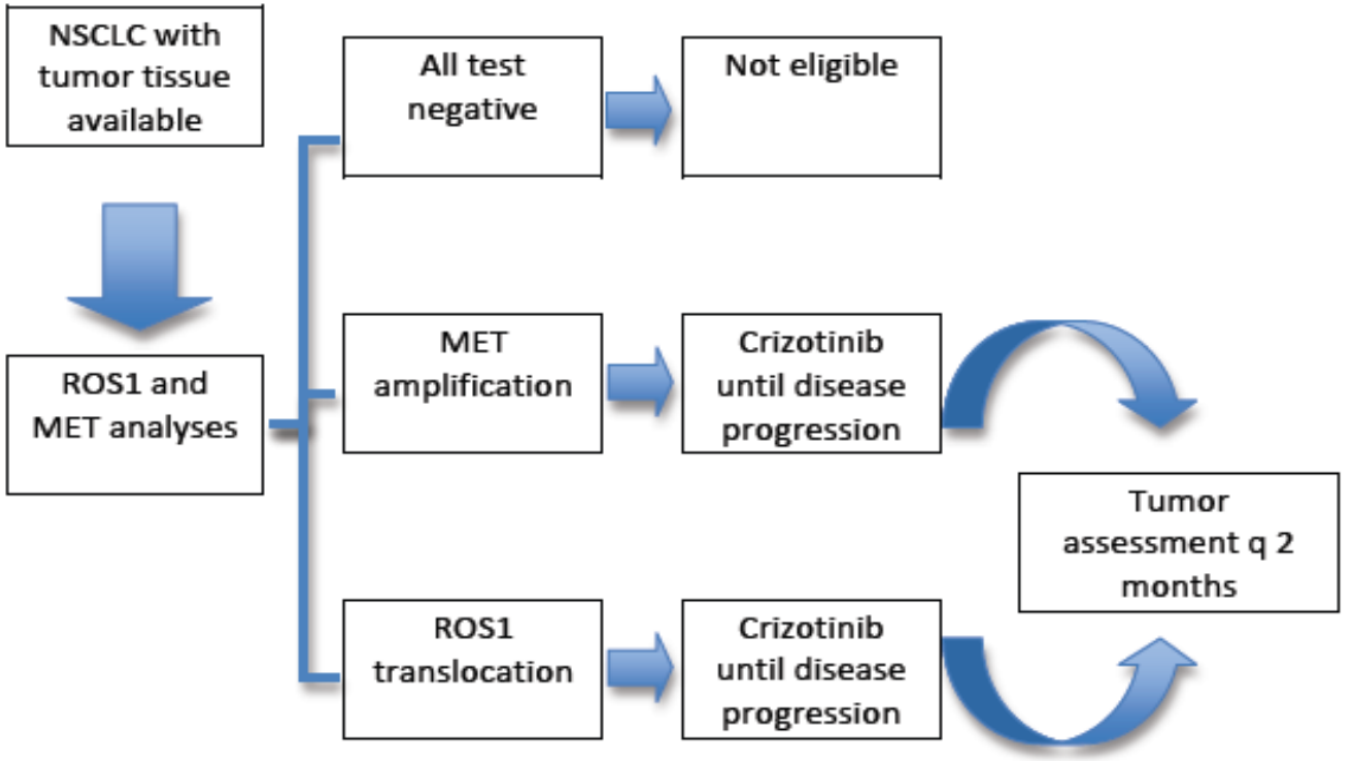
ALK +ve PTS: A POSSIBLE ALGORITHM FOR THE NEXT FUTURE



Modified from Kanaan, et al. Onco Targets Ther 2015

ROS1 and MET in second line

Crizotinib in MET amplified or ROS1 translocated NSCLC: The METROS trial



MET amplification defined as Ratio ≥2 and stratification in ≥2 and <5 versus ≥5

Eudract # 2014-001263-12

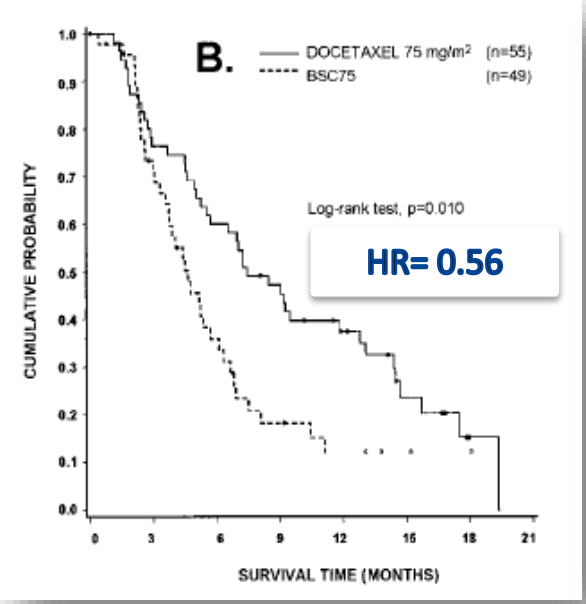
clinical practice guidelines

Annals of Oncology 00: 1–13, 2014

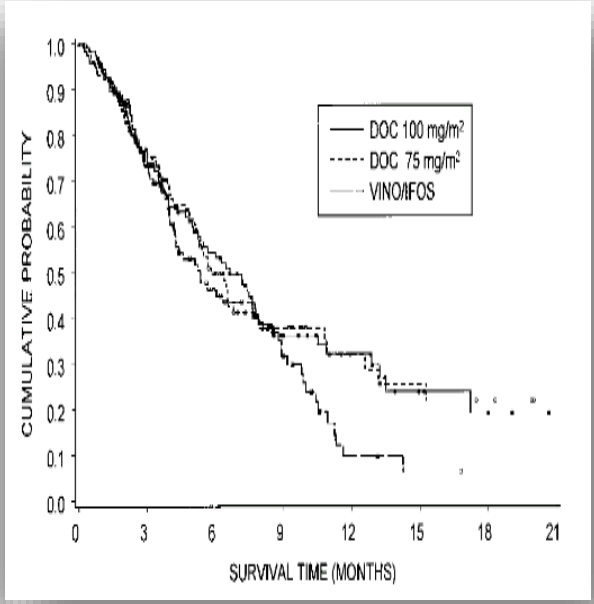
Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

second-line treatment

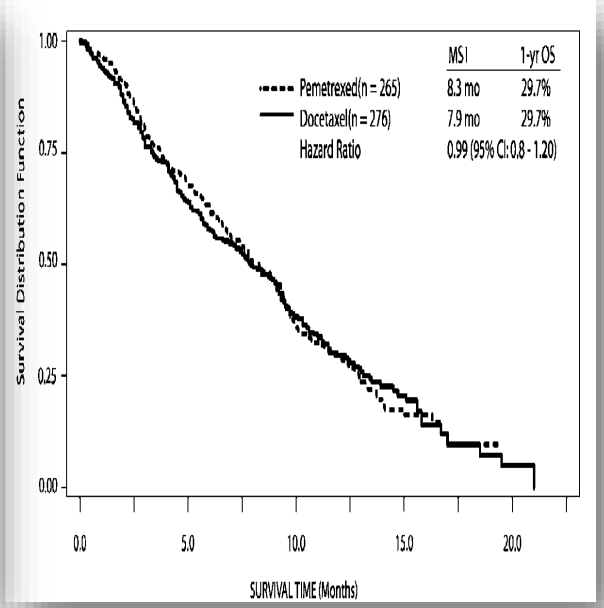
Comparable options in the second line consist of pemetrexed—for non-squamous histology only [51]—or docetaxel [52] [I, B].



F Shepherd et al, TAX 317, JCO 2000



F Fossella et al, TAX 320, JCO 2000



N Hanna et al, JCO 2004

clinical practice guidelines

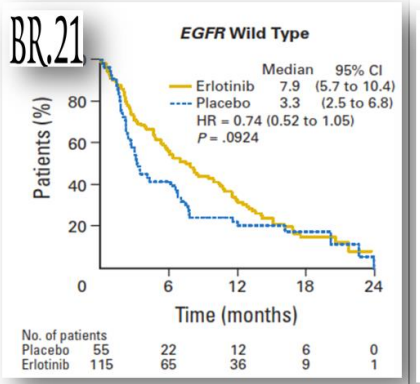
Annals of Oncology 00: 1–13, 2014

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

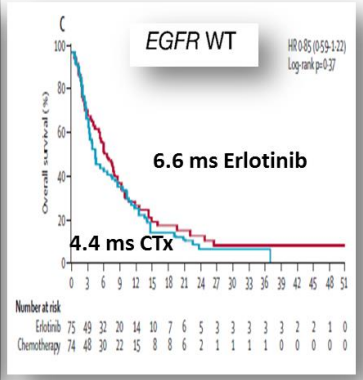
M. Reck[1,2], S. Popat[3,4], N. Reinmuth[1,2], D. De Ruysscher[5], K. M. Kerr[6], S. Peters[7] & on behalf of the ESMO Guidelines Working Group*

second-line treatment

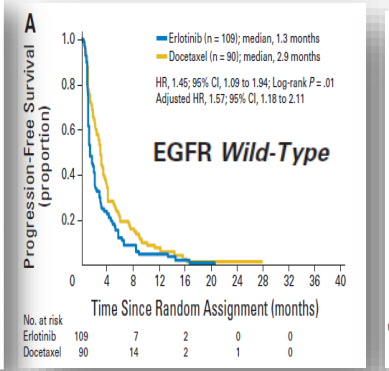
In conclusion, erlotinib represents a potential second-line treatment option in pre-treated patients with undetermined or WT EGFR status [II, B].



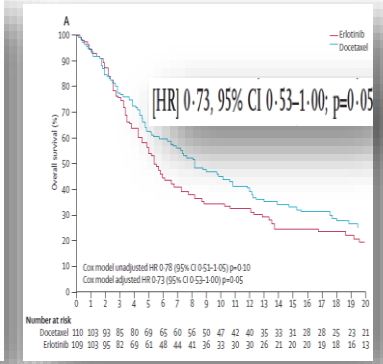
C Zhu et al, JCO 2008



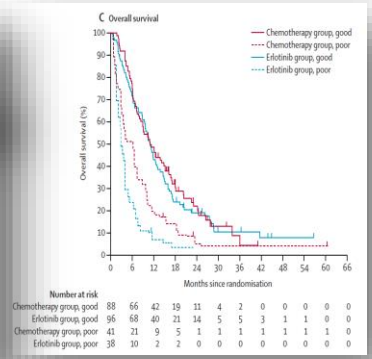
T Ciuleanu et al, Lancet Oncol 2012



T Kawaguchi et al , JCO 2014



M Garassino et al, Lancet 2013



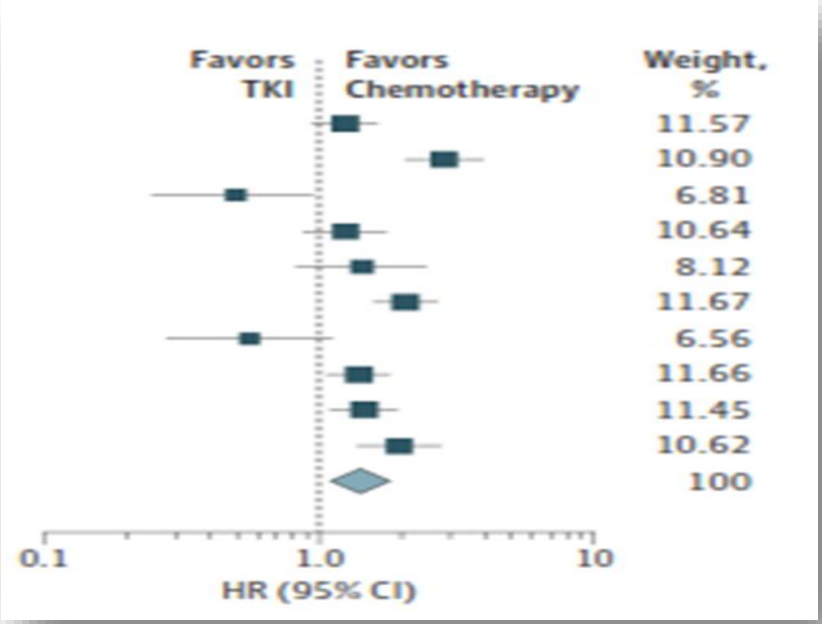
V Gregorc et al, Lancet 2014

Original Investigation

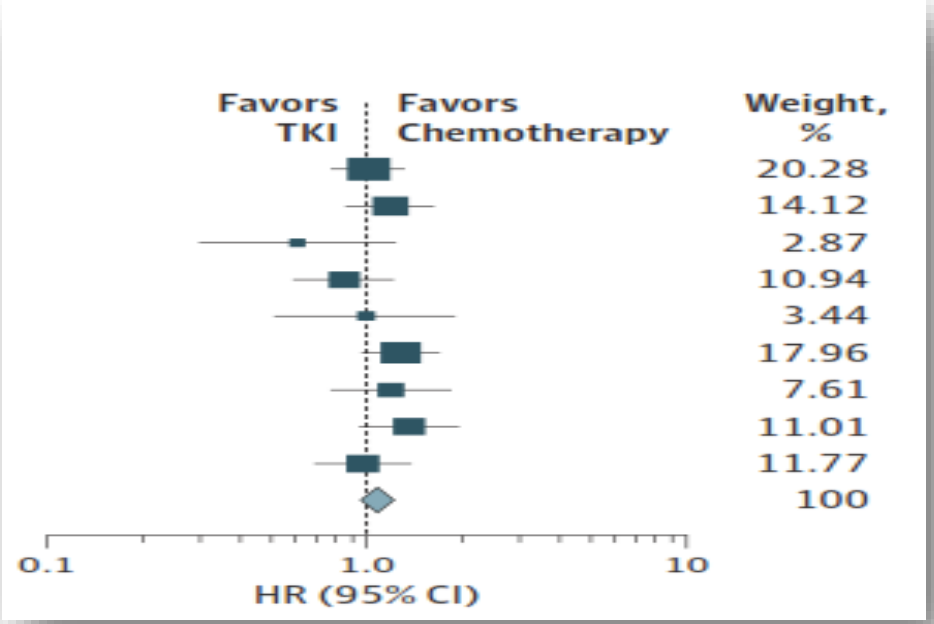
Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors vs Conventional Chemotherapy in Non–Small Cell Lung Cancer Harboring Wild-Type Epidermal Growth Factor Receptor

A Meta-analysis

PFS HR=1.41, p<.001



OS HR=1.08, p=.496

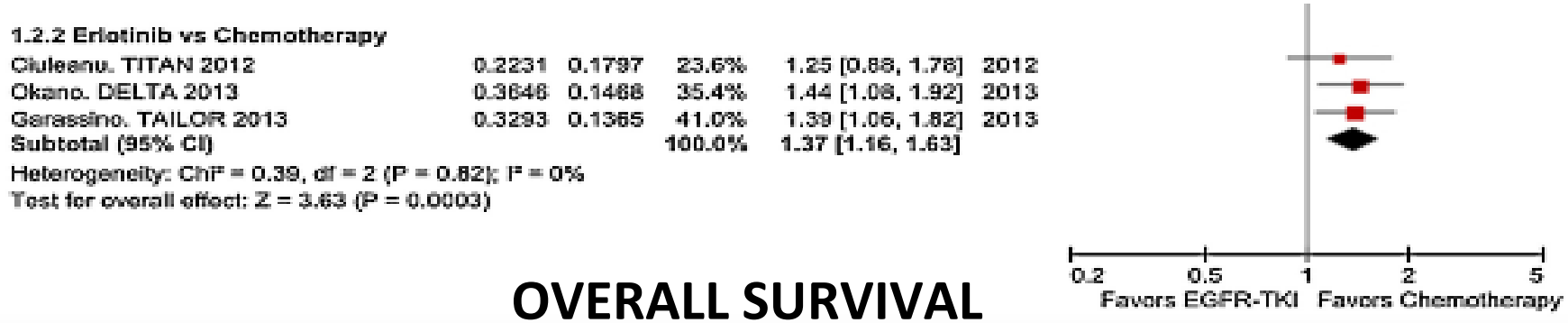


CONCLUSIONS AND RELEVANCE Among patients with advanced NSCLC harboring WT *EGFR*, conventional chemotherapy, compared with first-generation EGFR TKI, was associated with improvement in PFS but not overall survival.

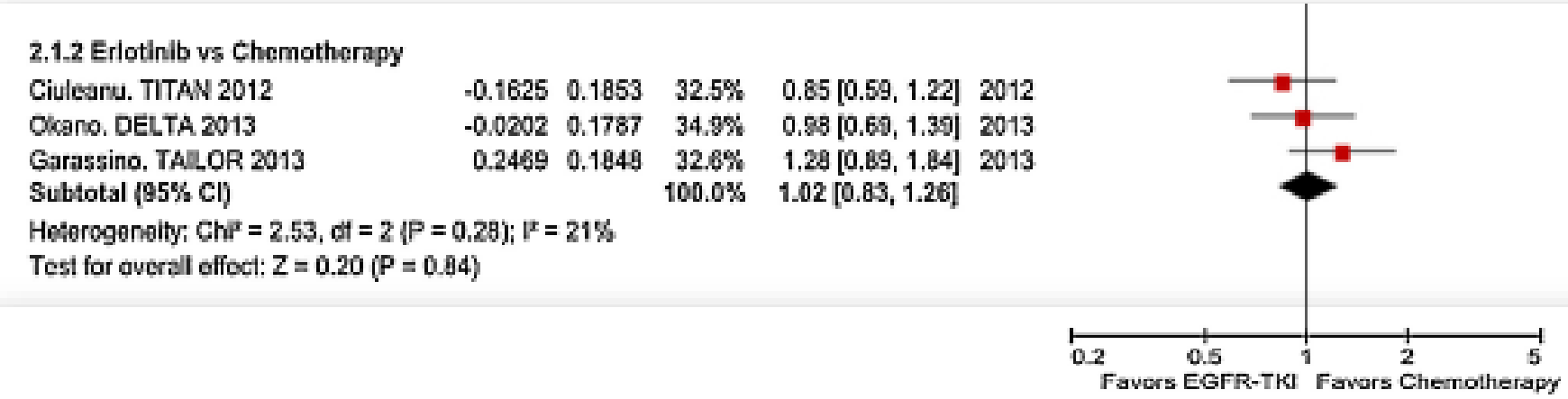
JK Lee et al, JAMA 2014

Efficacy of epidermal growth factor receptor inhibitors versus chemotherapy as second-line treatment in advanced non-small-cell lung cancer with wild-type EGFR: A meta-analysis of randomized controlled clinical trials

PROGRESSION FREE SURVIVAL



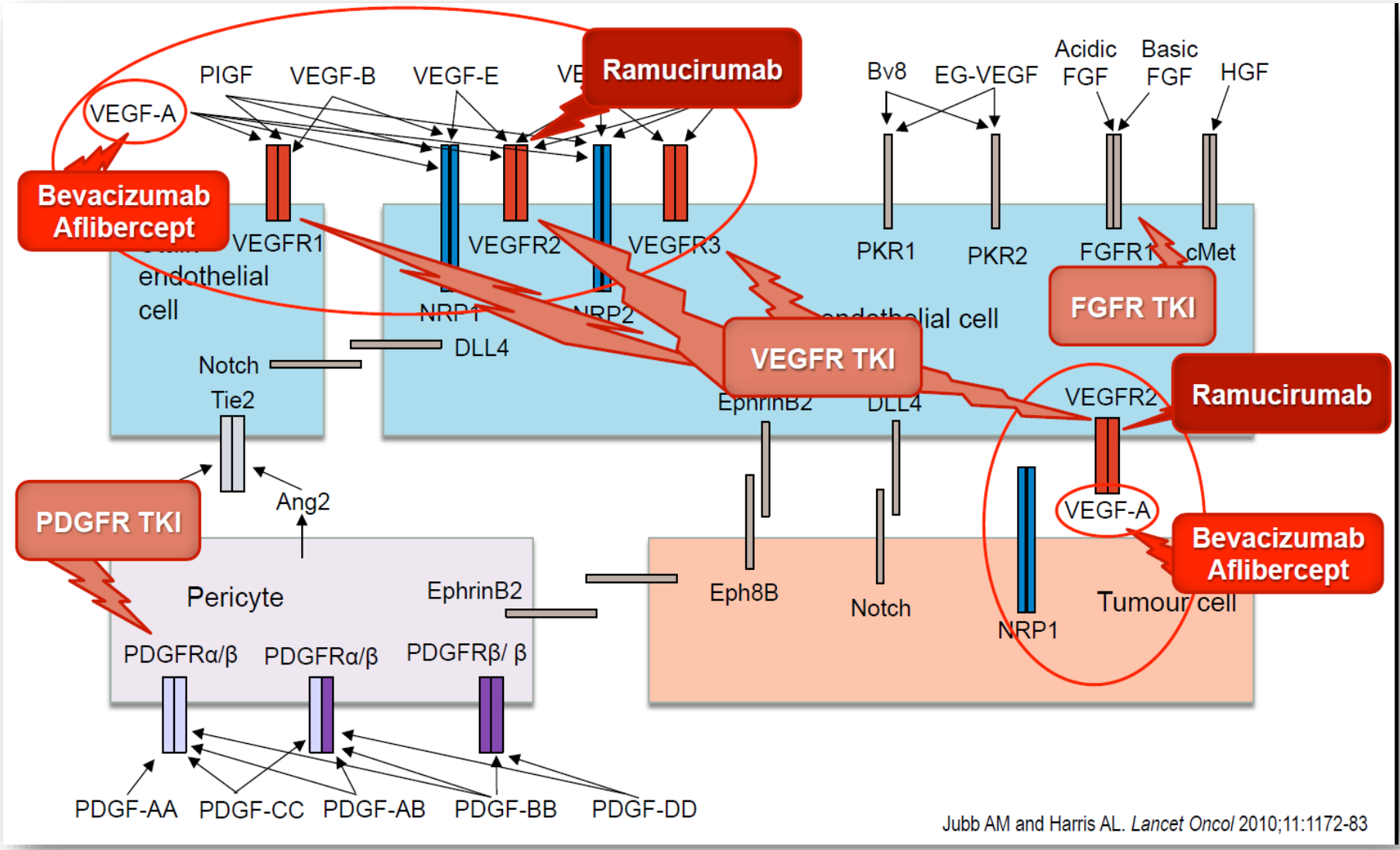
OVERALL SURVIVAL



Conclusions: Chemotherapy improves PFS significantly but not OS, compared with EGFR-TKIs as a second-line treatment in advanced NSCLC with wild-type EGFR.

N Zhao et al, Lung Cancer 2014

How to Target Proangiogenic Ligands and Their Receptors



Jubb AM and Harris AL. *Lancet Oncol* 2010;11:1172-83

REVEL and LUME Lung 1: Studies Design

- Stage IV after 1 platinum-based chemo +/- maintenance
- Prior Bev allowed
- All histologies
- PS 0 or 1
- No major blood vessel invasion, or cavitation

R

1:1

- ECOG PS 0 vs 1
- Gender
- Prior maintenance
- East-Asia vs. ROW

Ramucirumab 10 mg/kg
+
Docetaxel 75 mg/m² q3wks
N=628

Placebo
+
Docetaxel 75 mg/m² q3wks
N=625

Primary endpoint:
OS

Secondary endpoints:
PFS
ORR
Safety
PROs

- Stage IIIB/IV after 1 platinum- based chemo
- Prior Bev allowed
- All histologies
- PS 0 or 1
- No major blood vessel invasion, or cavitation

R

1:1

- ECOG PS 0 vs 1
- Brain mets
- Prior bevacizumab
- Histology

Nintedanib 200 mg x2/j, D2-D21
+ **Docetaxel** 75 mg/m² D1
q3 wks
N=655

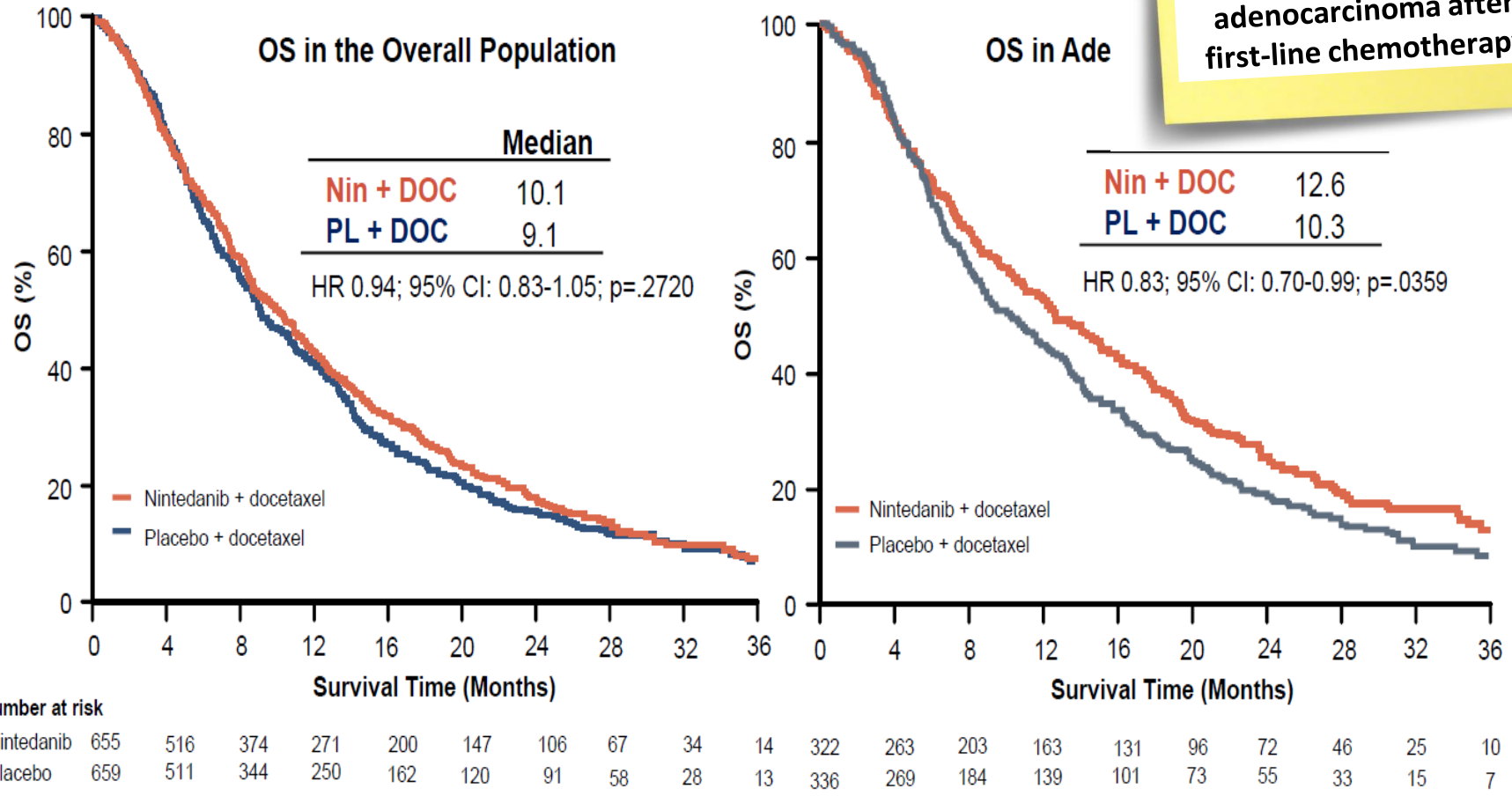
Placebo x 2/j, D2-D21
+ **Docetaxel** 75 mg/m² D1
q3 wks
N=659

Primary endpoint:
PFS
Key secondary endpoint: **OS**
Secondary endpoints:
ORR
Tolerance
QoL

Pérol, ASCO 2014; Garon, Lancet 2014; Reck, Lancet Oncol 2014

Docetaxel plus nintedanib versus docetaxel p
patients with previously treated non-small-
(LUME-Lung 1): a phase 3, double-blind, ran
controlled trial

27 November 2014
Vargatef® (nintedanib) approved in the EU for lung cancer patients with advanced adenocarcinoma after first-line chemotherapy



Kaplan-Meier curves for overall survival at the time of final analysis

M Reck et al, Lancet Oncol 2014

LUME-Columbus Phase III Study: 2-line NSCLC

Key inclusion criteria

- **Stage IIIB/IV NSCLC of adenocarcinoma histology**
- 1 prior treatment line
- ≥1 measurable target lesion
- ECOG PS 0 or 1
- EGFR-mutation negative
- Alk translocation negative

Key exclusion criteria

- Prior VEGFR inhibitors (except bevacizumab) or docetaxel
- Active brain metastases

RANDOMIZE

1 → Nintedanib: 200 mg BID + Docetaxel * → PD

* 75 mg/m² IV, on Day 1 of every 3-week cycle
- No restriction of number of courses

1 → Placebo: 200 mg BID + Docetaxel * → PD

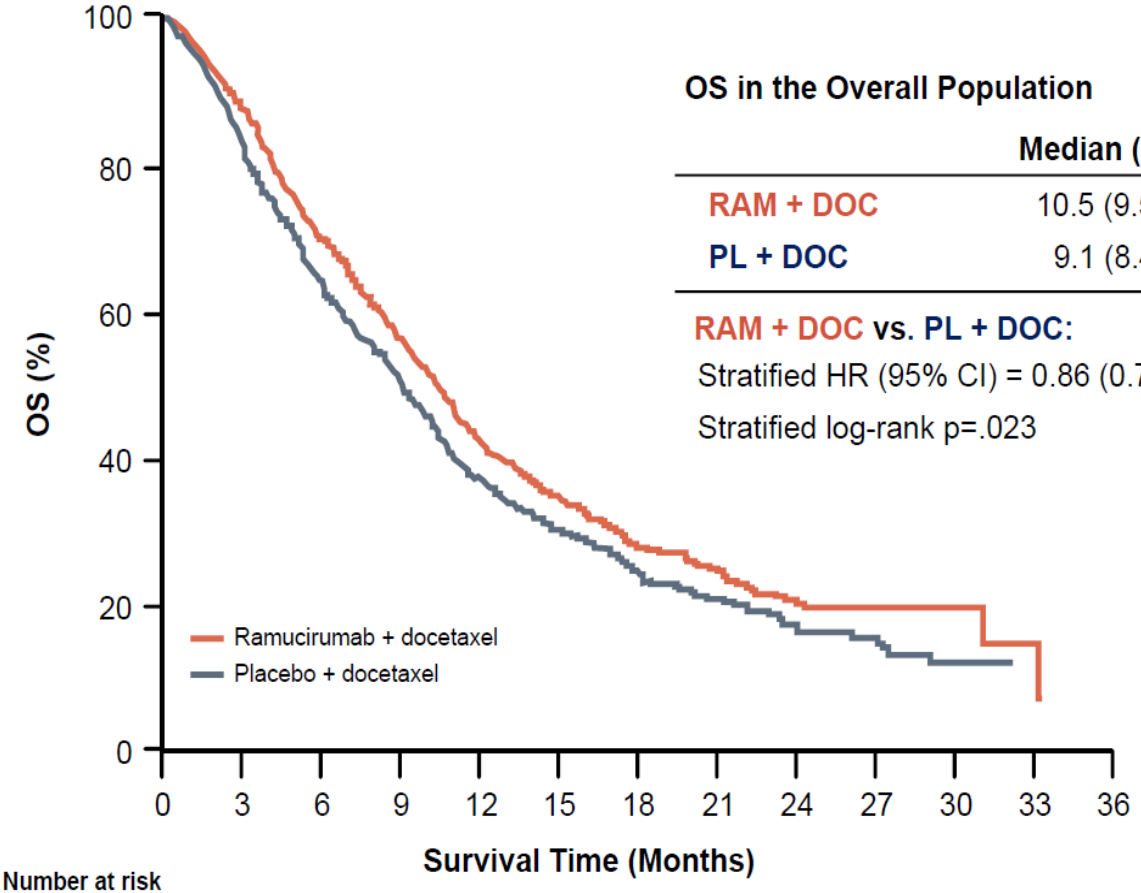
N = 800

Stratification
- Time since start 1st line (<9mo vs. ≥9mo)
- ECOG PS (0 vs. 1)

Co- Primary Endpoints: OS and PFS (by independent review; 6 weeks CT-schedule)
Secondary Endpoints: OR, DC, HRQOL

Study Start Date:	**September 2014**
Accrual	**Completed**
Estimated Primary Completion Date:	**July 2015 (Final data collection date for primary outcome measure)**

Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial



OS in the Overall Population

	Median (95% CI)	Censoring Rate
RAM + DOC	10.5 (9.5-11.2)	31.8%
PL + DOC	9.1 (8.4-10.0)	27.0%

RAM + DOC vs. PL + DOC:

Stratified HR (95% CI) = 0.86 (0.75-0.98)

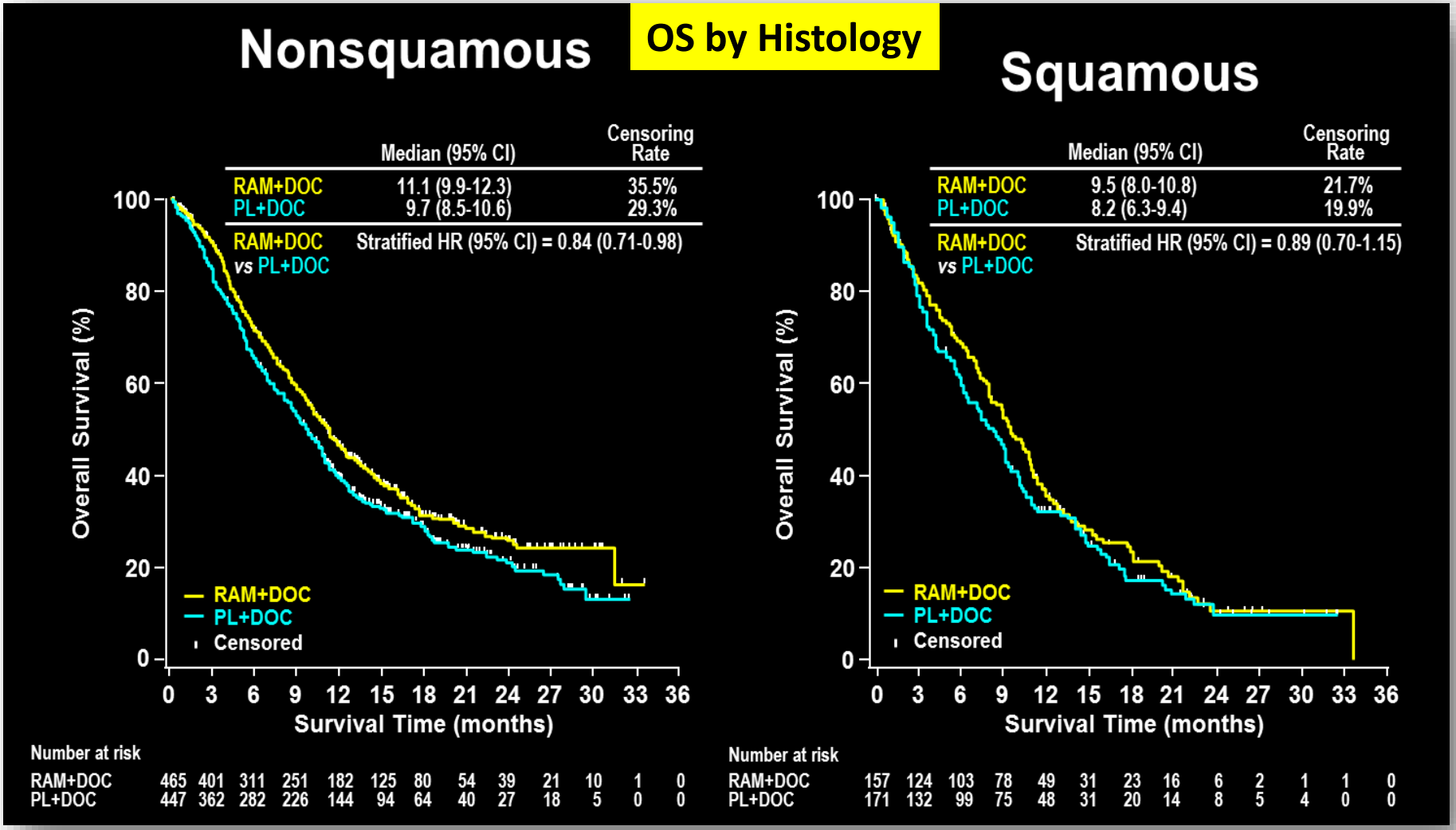
Stratified log-rank p=.023

Number at risk

RAM + DOC	628	527	415	329	231	156	103	70	45	23	11	2	0
PL + DOC	625	501	386	306	197	129	86	56	36	23	9	0	0

EB Garon et al, Lancet Oncol 2014

Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial



EB Garon et al, Lancet Oncol 2014

CROSS-TRIALS COMPARISON of REVEL and LUME 1 ACCORDING to HISTOLOGY

Study	Treatment	Squamous				Non-squamous			
		PFS mos	HR for PFS 95% CI	OS mos	HR for OS 95% CI	PFS mos	HR for PFS 95% CI	OS mos	HR for OS 95% CI
REVEL	Docetaxel + Ramucirumab	4.2°	0.76 0.60-0.96	9.5	0.89 0.70-1.15	4.6°	0.74 0.64-0.86	11.1	0.84 0.71-0.98
	Docetaxel + Placebo	2.7°		8.2		3.7°		9.7	
LUME 1	Docetaxel + Nintedanib	2.9*	0.77 0.62-0.96	8.6	1.01 0.85-1.21	4.0*	0.77 0.62-0.96	12.6	0.83 0.70-0.99
	Docetaxel + Placebo	2.6*		8.7		2.8*		10.3	

°: investigator assessed
*: central review

Garon, Lancet 2014; Reck, Lancet Oncol 2014

Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial

Adverse events occurring in at least 10% of patients or of special interest irrespective of cause

	Ramucirumab plus docetaxel group (n=627)	
	Any grade	Grade ≥3
Treatment-emergent adverse events		
Any	613 (98%)	495 (79%)†
Fatigue	343 (55%)	88 (14%)
Decreased appetite	182 (29%)	14 (2%)
Diarrhoea	199 (32%)	29 (5%)
Nausea	169 (27%)	7 (1%)
Alopecia	162 (26%)	NA
Stomatitis	146 (23%)	27 (4%)
Neuropathy	145 (23%)	17 (3%)
Dyspnoea	138 (22%)	24 (4%)
Cough	133 (21%)	3 (<1%)
Pyrexia	104 (17%))	3 (<1%)
Peripheral oedema	102 (16%)	0
Constipation	101 (16%)	1 (<1%)
Mucosal inflammation	101 (16%)	18 (3%)
Vomiting	87 (14%)	8 (1%)
Lacrimation increased	84 (13%)	1 (<1%)
Myalgia	78 (12%)	4 (1%)
Arthralgia	72 (11%)	7 (1%)
Back pain	71 (11%)	7 (1%)
Abdominal pain	68 (11%)	5 (1%)
Dysgeusia	67 (11%)	NA
Insomnia	67 (11%)	3 (<1%)
Headache	66 (11%)	3 (<1%)

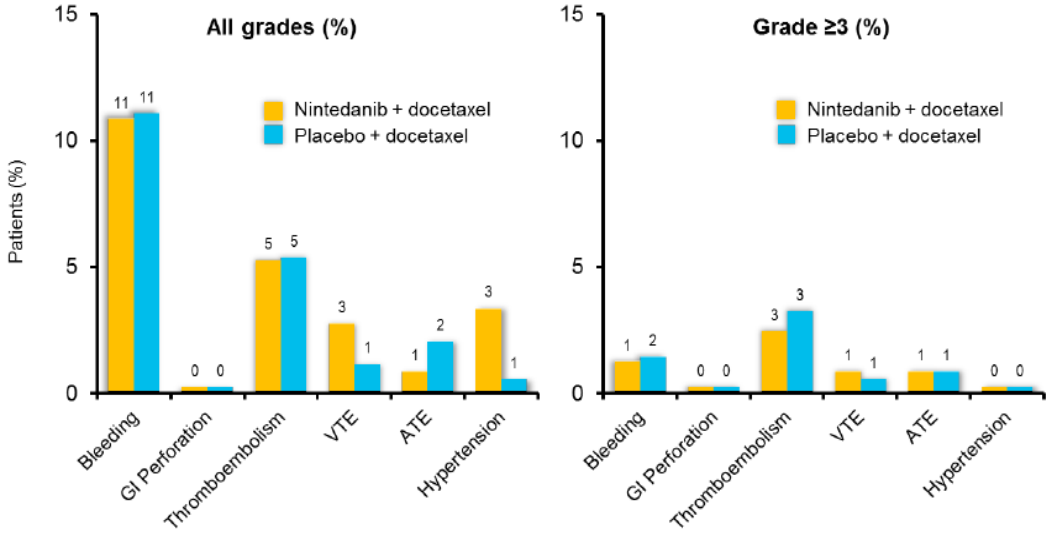
	Ramucirumab plus docetaxel group (n=627)	
	Any grade	Grade ≥3
Treatment-emergent adverse events		
Haematological adverse events		
Neutropenia	345 (55%)	306 (49%)
Leucopenia	134 (21%)	86 (14%)
Anaemia	131 (21%)	18 (3%)
Febrile neutropenia	100 (16%)	100 (16%)
Thrombocytopenia	84 (13%)	18 (3%)
Adverse events of special interest		
Bleeding or haemorrhage	181 (29%)	15 (2%)
Epistaxis	116 (19%)	2 (<1%)
Gastrointestinal haemorrhage	17 (3%)	4 (1%)
Pulmonary haemorrhage	49 (8%)	8 (1%)
Haemoptysis	36 (6%)	4 (1%)
Hypertension	68 (11%)	35 (6%)
Infusion-related reaction	23 (4%)	5 (1%)
Proteinuria	21 (3%)	1 (<1%)
Venous thromboembolic	16 (3%)	11 (2%)
Renal failure	14 (2%)	3 (<1%)
Arterial thromboembolic	10 (2%)	6 (1%)
Congestive heart failure	6 (1%)	5 (1%)
Gastrointestinal perforation	6 (1%)	5 (1%)

EB Garon et al, Lancet Oncol 2014

Nintedanib Plus Docetaxel is Associated With Manageable Additional Risk Compared With Docetaxel

(LUME-Lung 1)

	Nintedanib + Docetaxel (N=652)		Placebo + Docetaxel (N=655)	
AE[a], n (%)	Any Grade	Grade 3 / 4 [5]	Any Grade	Grade 3 / 4 [5]
Diarrhoea	276 (42.3)	42 (6.5) [1 (0.2)]	143 (21.8)	17 (2.6) [0]
Nausea	158 (24.2)	5 (0.8) [0]	118 (18)	6 (0.9) [0]
Increased ALT	186 (28.5)	51 (7.8) [0]	55 (8.4)	6 (0.9) [0]
Increased AST	147 (22.5)	22 (3.4) [0]	43 (6.6)	3 (0.5) [0]
Decreased appetite	145 (22.2)	9 (1.4) [0]	102 (15.6)	7 (1.1) [1 (0.2)]
Vomiting	110 (16.9)	5 (0.8) [0]	61 (9.3)	3 (0.5) [0]



ATE = arterial thromboembolism; GI = gastrointestinal; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VTE = venous thromboembolism

Reck M et al.
Lancet Oncol 2014;15:143-55

Chairmen

F. de Marinis

C. Gridelli

Panelists

F. Ciardiello

L. Crinò

F. de Marinis

J.Y. Douillard

C. Gridelli

F. Griesinger

D. Lambrechts

M. Perol

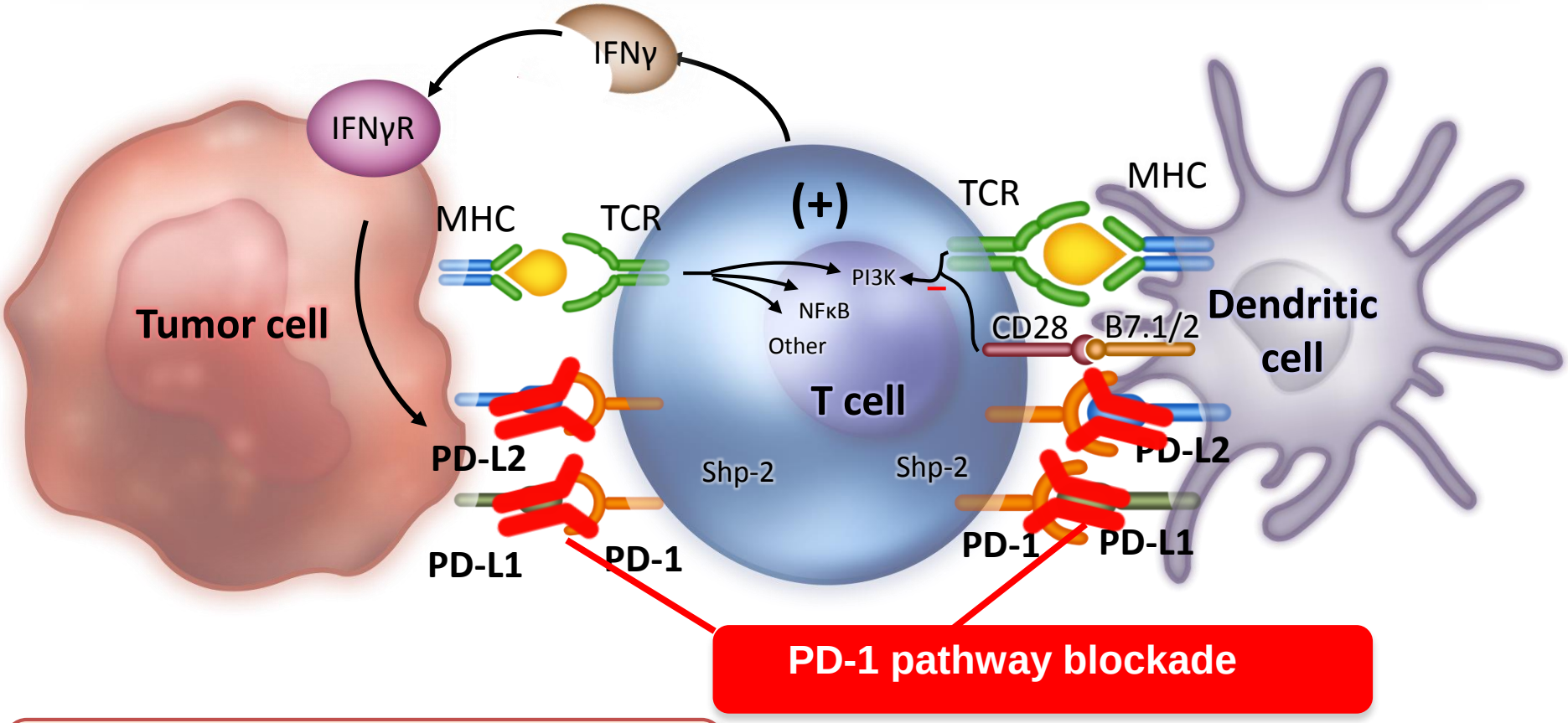
S.Ramalingam

E. Smit

Which selection criteria for antiangiogenetic treatment?

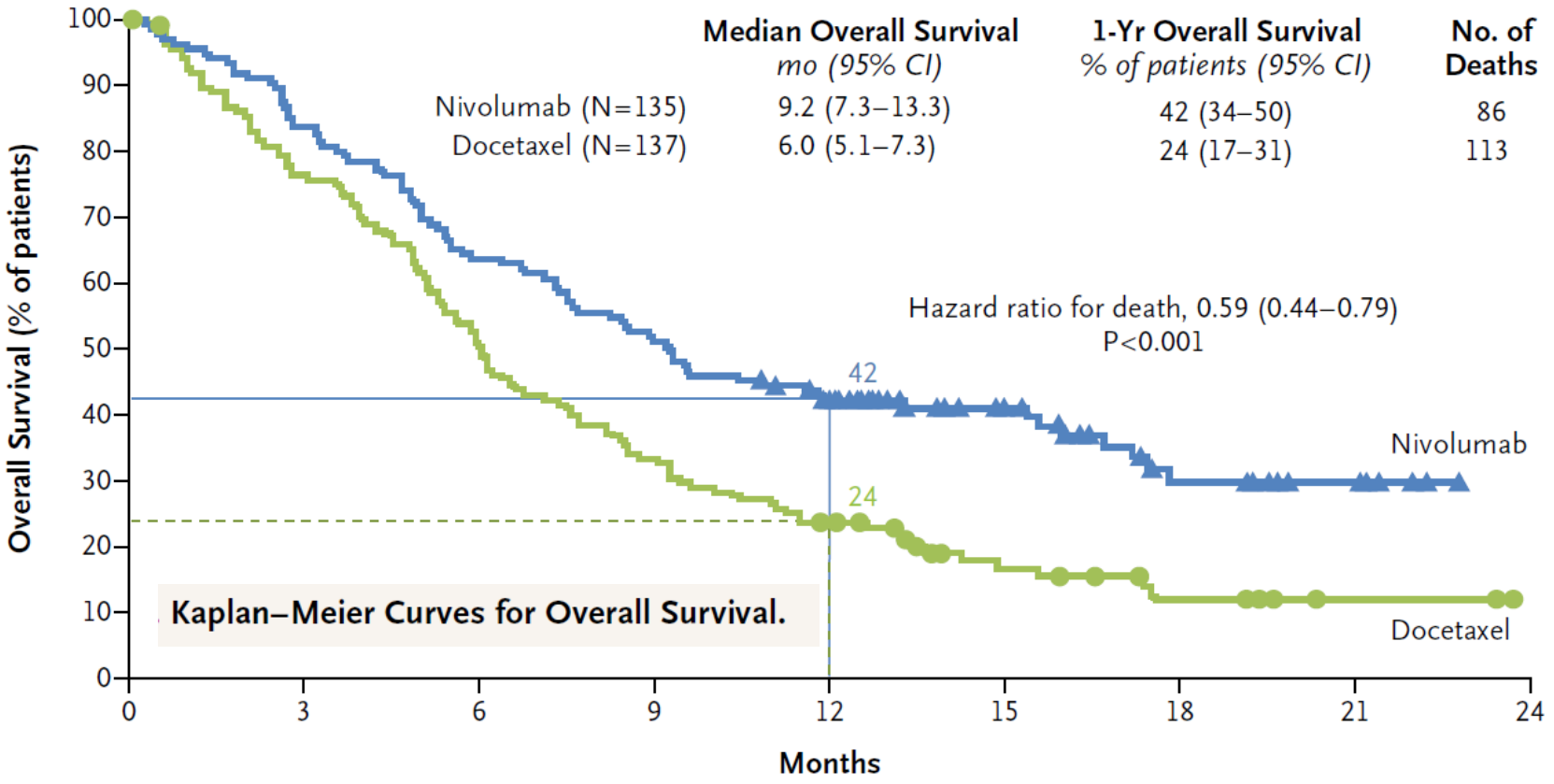
- **Non-squamous**
- **PS 0-1**
- **No serious cardio-vascular comorbidities**
- **No cavitation**
- **No major vessel invasion**
- **No previous hemoptysis**
- **No recent thromboembolic disease or hemorrhage**
- **No severe or uncontrolled hypertension**
- **No recent major surgery (< 4 weeks)**
- **No recent thoracic radiation, including the mediastinum**

IMMUNE CHECKPOINT INHIBITORS IN NSCLC



Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

CheckMate 017 (NCT01642004)



No. at Risk									
Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

Spigel et al, ASCO 2015; Brahmer et al, NEJM 2015

LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

RACCOMANDAZIONI

- Per i pazienti affetti da NSCLC avanzato ad istologia squamosa, il trattamento di seconda linea con nivolumab come agente singolo è raccomandato

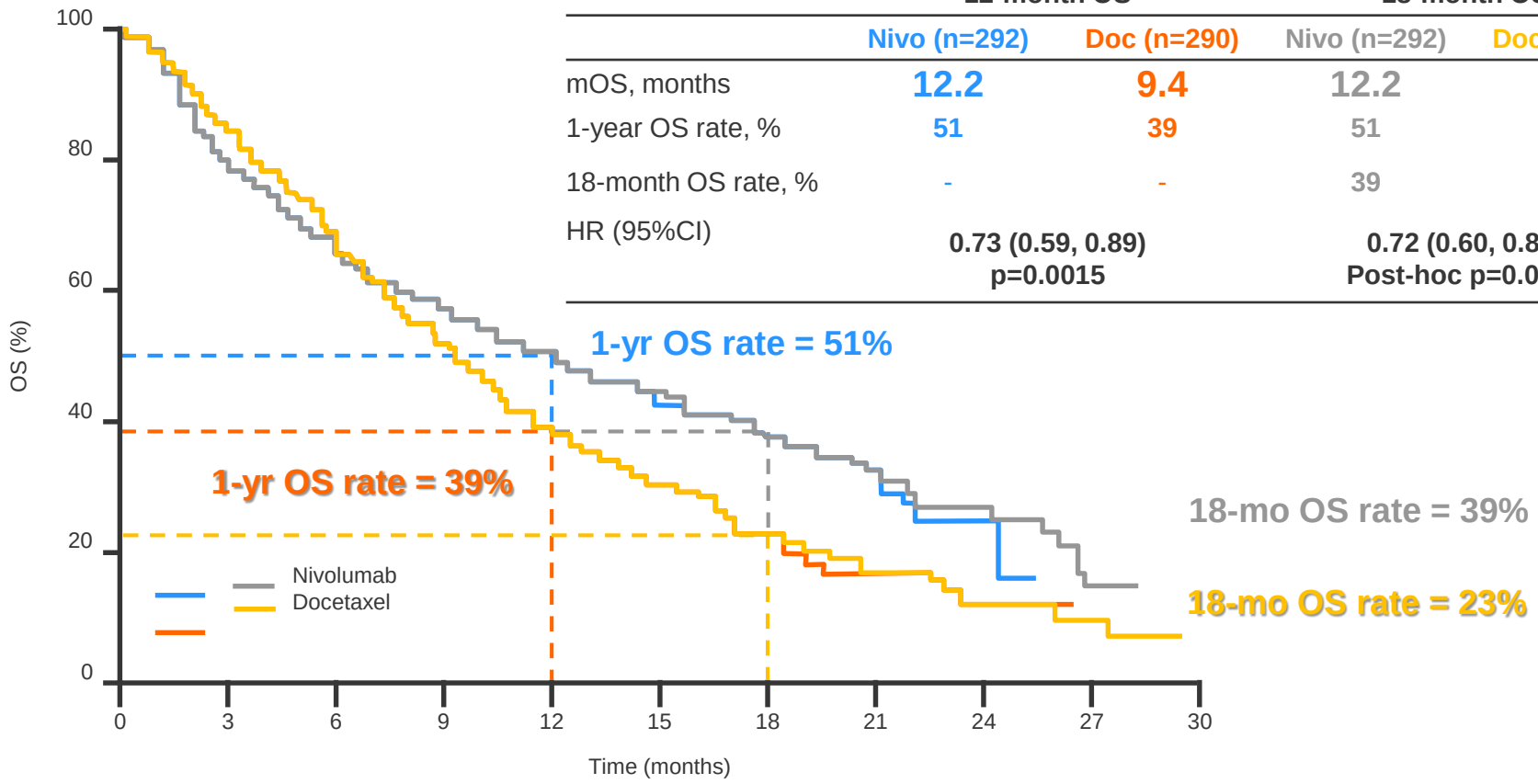
  LIVELLO DI EVIDENZA IB

  GRADO DI RACCOMANDAZIONE A

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

- **CheckMate 057 updatewd Overall Survival**
  - 18-month update showed median survival was unchanged (12.2 months with nivolumab vs. 9.4 months with docetaxel)
  - OS rate at 18 months was higher with nivolumab than docetaxel (39% vs. 23%, HR 0.72 [95%CI 0.60, 0.88]; p=0.0009)

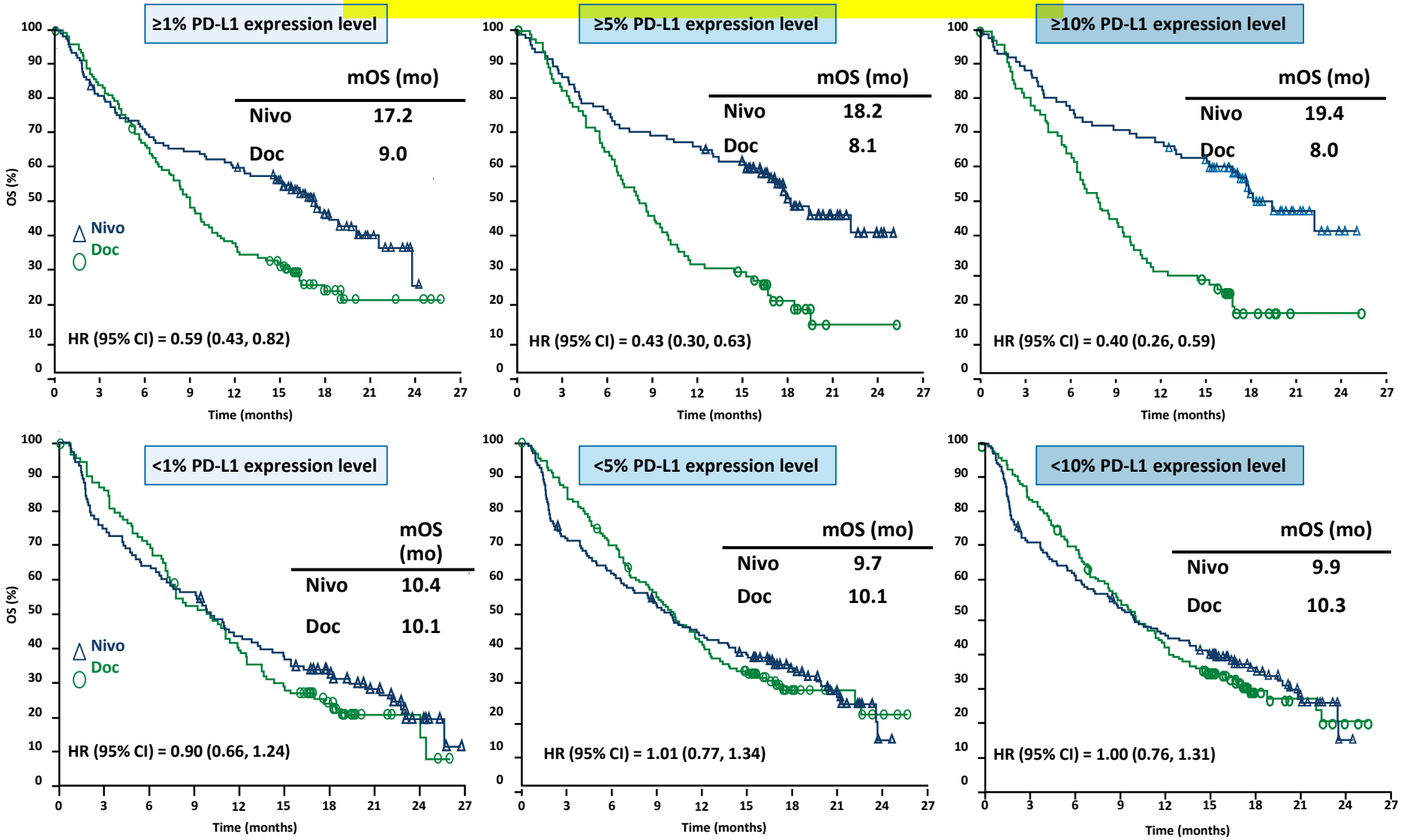
	12-month OS		18-month OS	
	Nivo (n=292)	Doc (n=290)	Nivo (n=292)	Doc (n=290)
mOS, months	12.2	9.4	12.2	9.4
1-year OS rate, %	51	39	51	39
18-month OS rate, %	-	-	39	23
HR (95%CI)	0.73 (0.59, 0.89) p=0.0015		0.72 (0.60, 0.88) Post-hoc p=0.0009	



Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015 Horn et al. Ann Oncol 2015; 26 (suppl 6): abstr 3010

Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer

OS by PD-L1 Expression



Paz-Ares et al, ASCO 2015; Borghaei et al, NEJM 2015

LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

RACCOMANDAZIONI

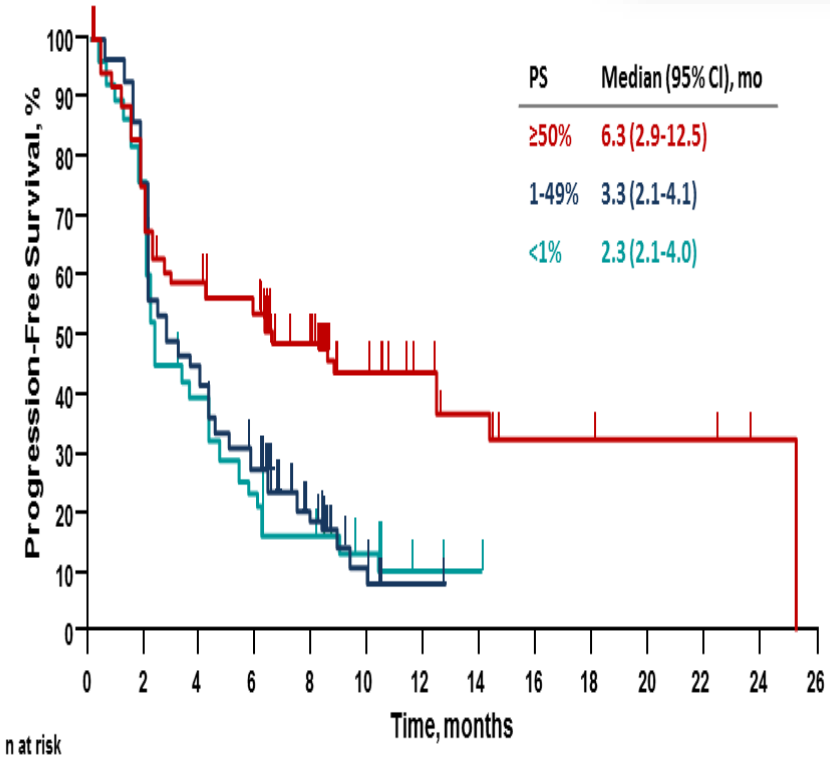
- Per i pazienti affetti da NSCLC avanzato ad istologia non-squamosa, il trattamento di seconda linea con nivolumab come agente singolo è raccomandato. Al momento della stesura delle presenti linee guida, il nivolumab non è ancora registrato in Italia nei pazienti con istologia non-squamosa

  LIVELLO DI EVIDENZA IB

  GRADO DI RACCOMANDAZIONE A

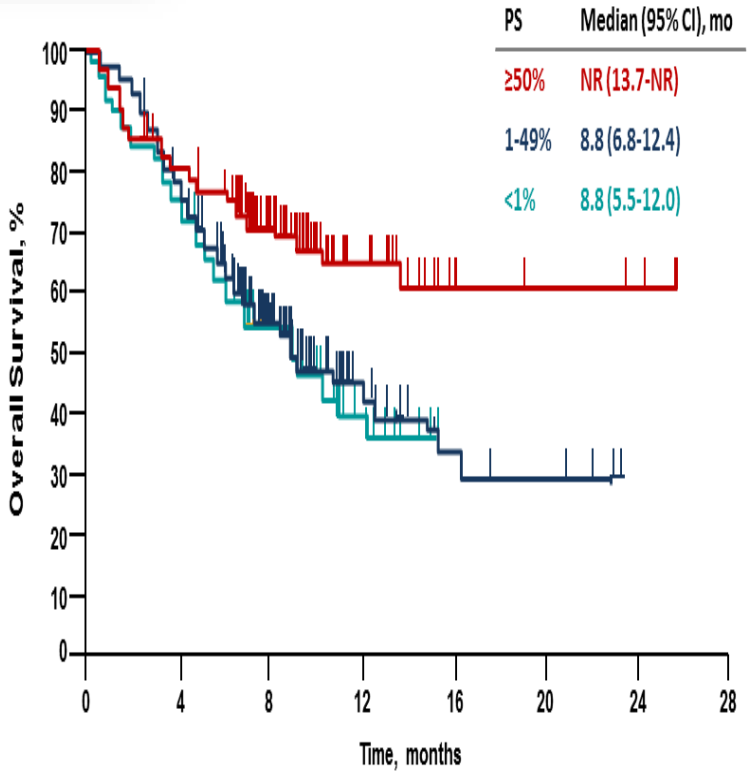
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

KEYNOTE-001 Study



n at risk

PS ≥50%	119	86	66	60	38	20	13	8	4	3	3	3	1	0
PS 1-49%	161	122	70	45	21	4	1	0	0	0	0	0	0	0
PS <1%	76	52	29	17	11	6	2	0	0	0	0	0	0	0



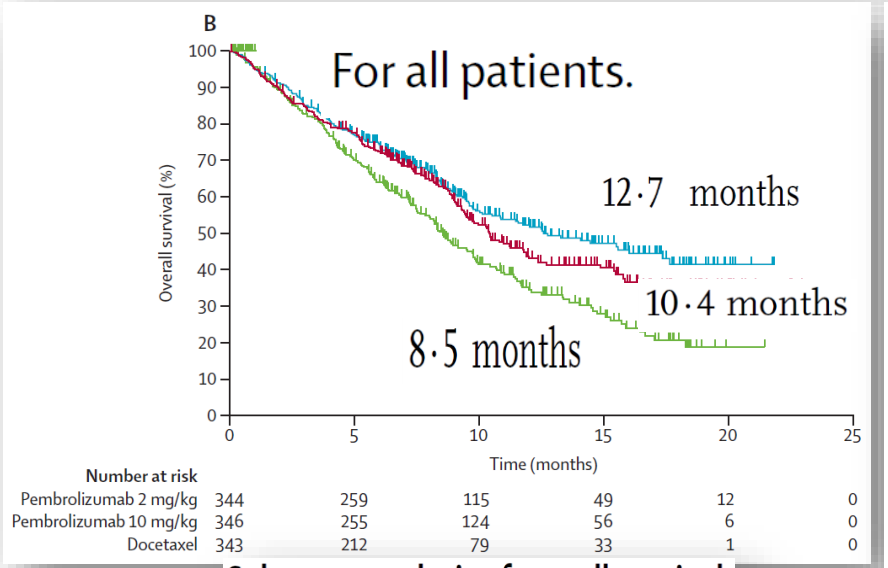
n at risk

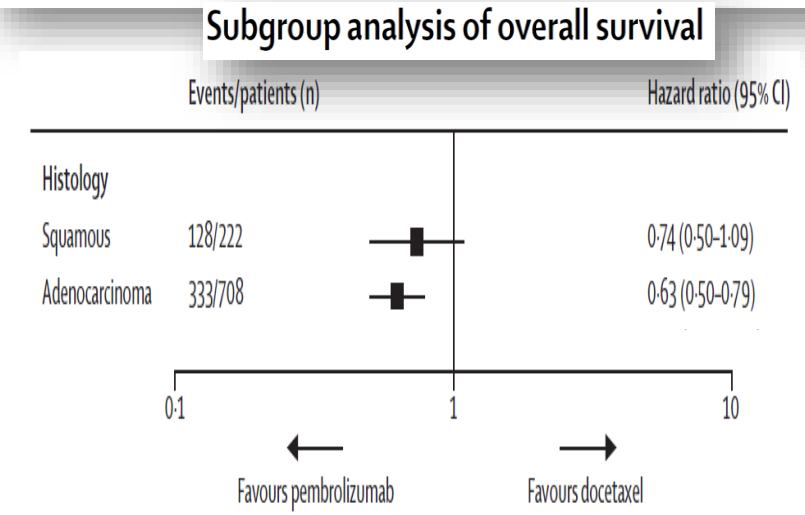
PS ≥50%	119	92	56	22	5	4	3	0
PS 1-49%	161	119	58	15	6	4	0	0
PS <1%	76	55	33	8	0	0	0	0

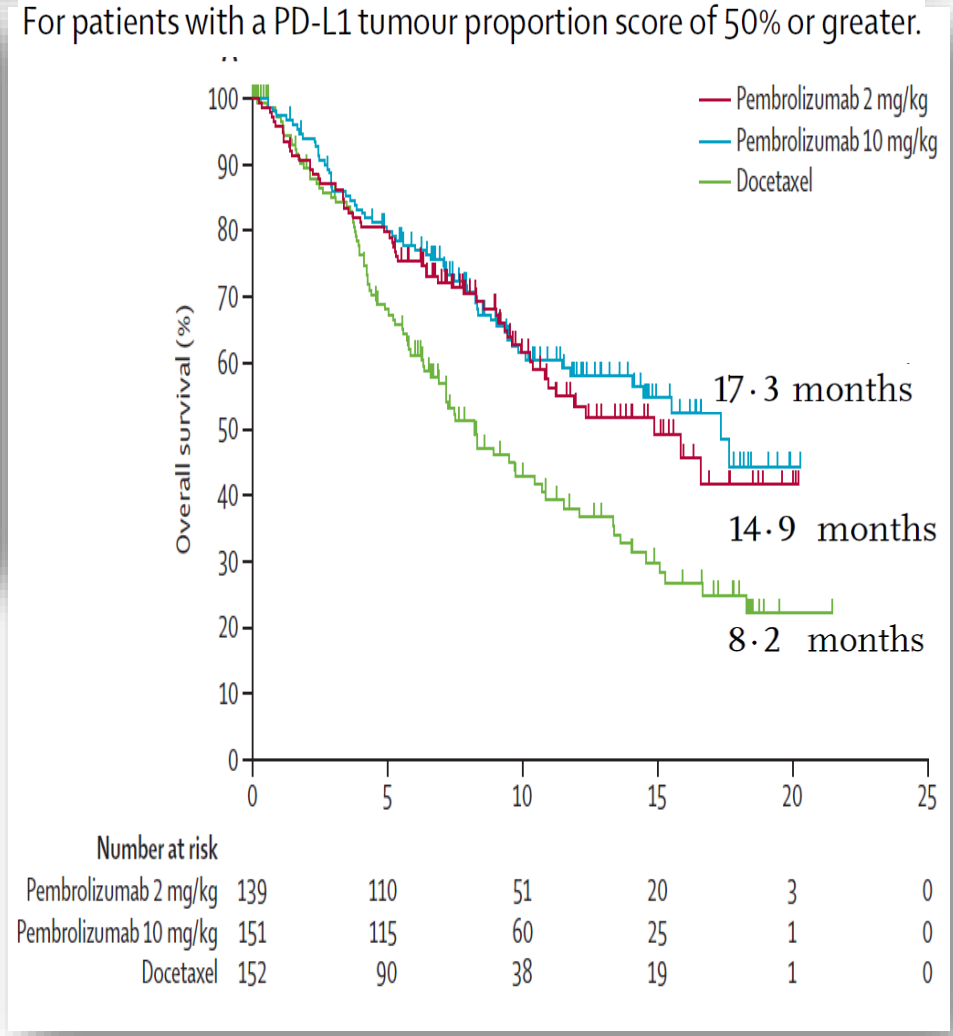
EFFICACY by PD-L1 Expression: ALL CTA-Evaluable Patients

Garon EB et al, *N Engl J Med.* 2015

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







R Herbst et al, Lancet 2016

LINEE GUIDA PER LA GESTIONE INTEGRATA DEL PAZIENTE CON TUMORE POLMONARE

IMMUNOTERAPIA

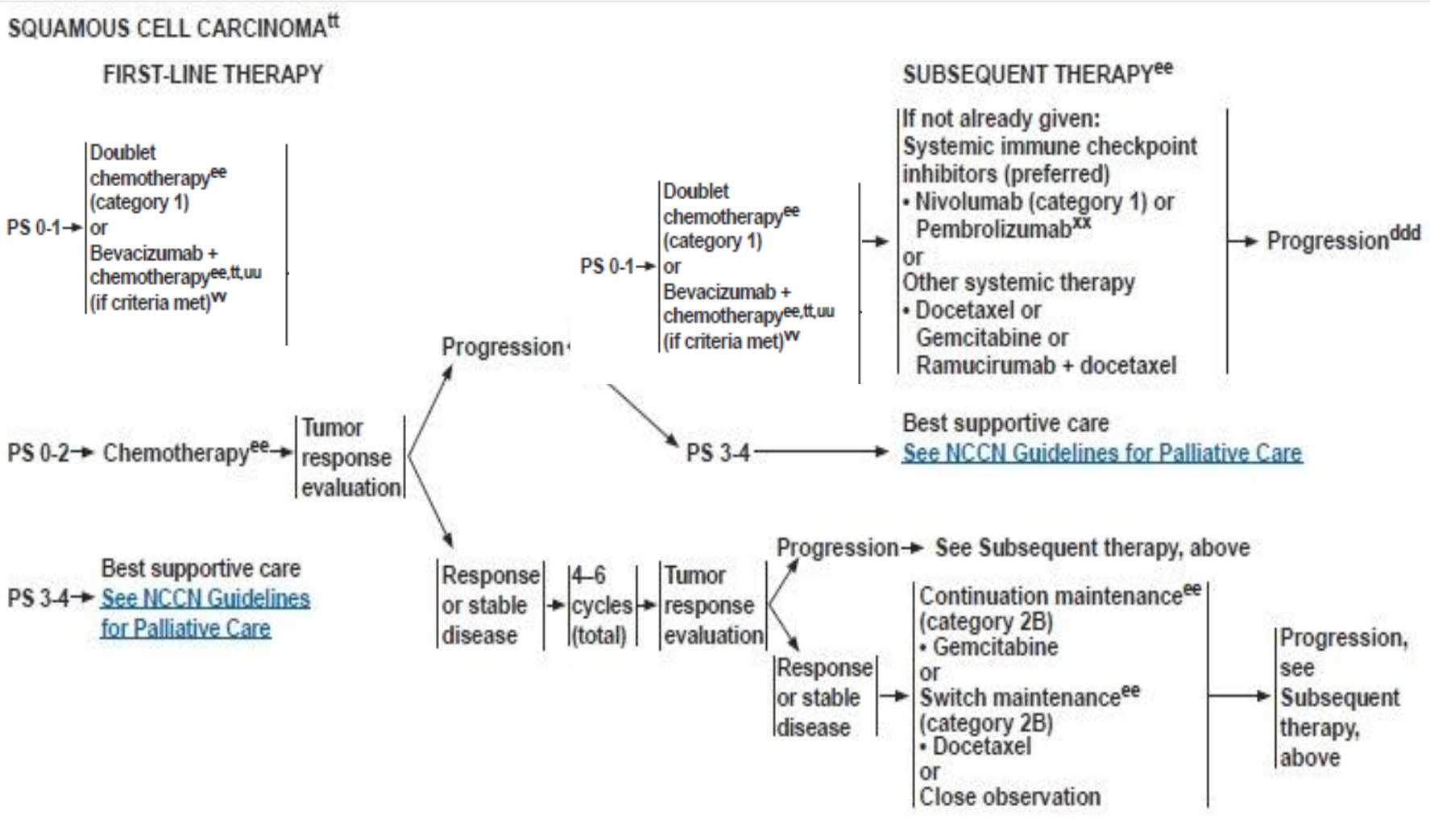
AIOT
ASSOCIAZIONE ITALIANA ONCOLOGIA TORACICA

RACCOMANDAZIONI

- Per i pazienti affetti da NSCLC avanzato, il trattamento di seconda-linea con pembrolizumab come agente singolo è raccomandato solo in presenza di espressione di PD-L1 ≥ 50% determinata con il test PD-L1 IHC 22C3 pharmDx. Al momento della stesura delle presenti linee guida pembrolizumab non è ancora registrato in Italia

  LIVELLO DI EVIDENZA IIA

  GRADO DI RACCOMANDAZIONE B


SQUAMOUS CELL CARCINOMA[tt]
FIRST-LINE THERAPY
SUBSEQUENT THERAPY[ee]
PS 0-1
Doublet chemotherapy[ee] (category 1) or Bevacizumab + chemotherapy[ee,tt,uu] (if criteria met)[vv]
PS 0-2
Chemotherapy[ee]
Tumor response evaluation
Progression
PS 3-4
Best supportive care
See NCCN Guidelines for Palliative Care
Response or stable disease
4–6 cycles (total)
Tumor response evaluation
Progression
See Subsequent therapy, above
Response or stable disease
Continuation maintenance[ee] (category 2B)
• Gemcitabine
or
Switch maintenance[ee] (category 2B)
• Docetaxel
or
Close observation
Progression, see Subsequent therapy, above
PS 0-1
Doublet chemotherapy[ee] (category 1) or Bevacizumab + chemotherapy[ee,tt,uu] (if criteria met)[vv]
If not already given:
Systemic immune checkpoint inhibitors (preferred)
• Nivolumab (category 1) or Pembrolizumab[xx]
or
Other systemic therapy
• Docetaxel or Gemcitabine or Ramucirumab + docetaxel
Progression[ddd]

Second line therapy of squamous cell lung cancer: Comparisons accross recent studies

Nivolumab vs Doc:
9.2 vs 6.0 months; HR 0.62 (0-48-0.81)

Pemetrexed vs Doc
6.2 vs 7.4 months; HR 1.56 (0.8-2.26)

Docetaxel Ramucirumab vs Doc
9.5 *vs* 8.2 months; HR 0.88 (0·69–1.13)

Docetaxel Nintedanib vs Doc
8.6 vs 8.7 months; HR 1.01 (0.85-1.21)

Afatinib vs Erlotinib
7.9 vs 6.8 months; HR 0.81 (0.69-0-95)

The Evolving Role of Nivolumab in Non–Small-Cell Lung Cancer for Second-Line Treatment: A New Cornerstone for Our Treatment Algorithms. Results From an International Experts Panel Meeting of the Italian Association of Thoracic Oncology

Clinical Lung Cancer (2016),

Squamous

Platinum-based chemotherapy
(P-Gemcitabina / P-Paclitaxel)

1st Line

2nd Line

Nivolumab / Pembrolizumab*

3rd Line

Docetaxel ± Ramucirumab

Erlotinib

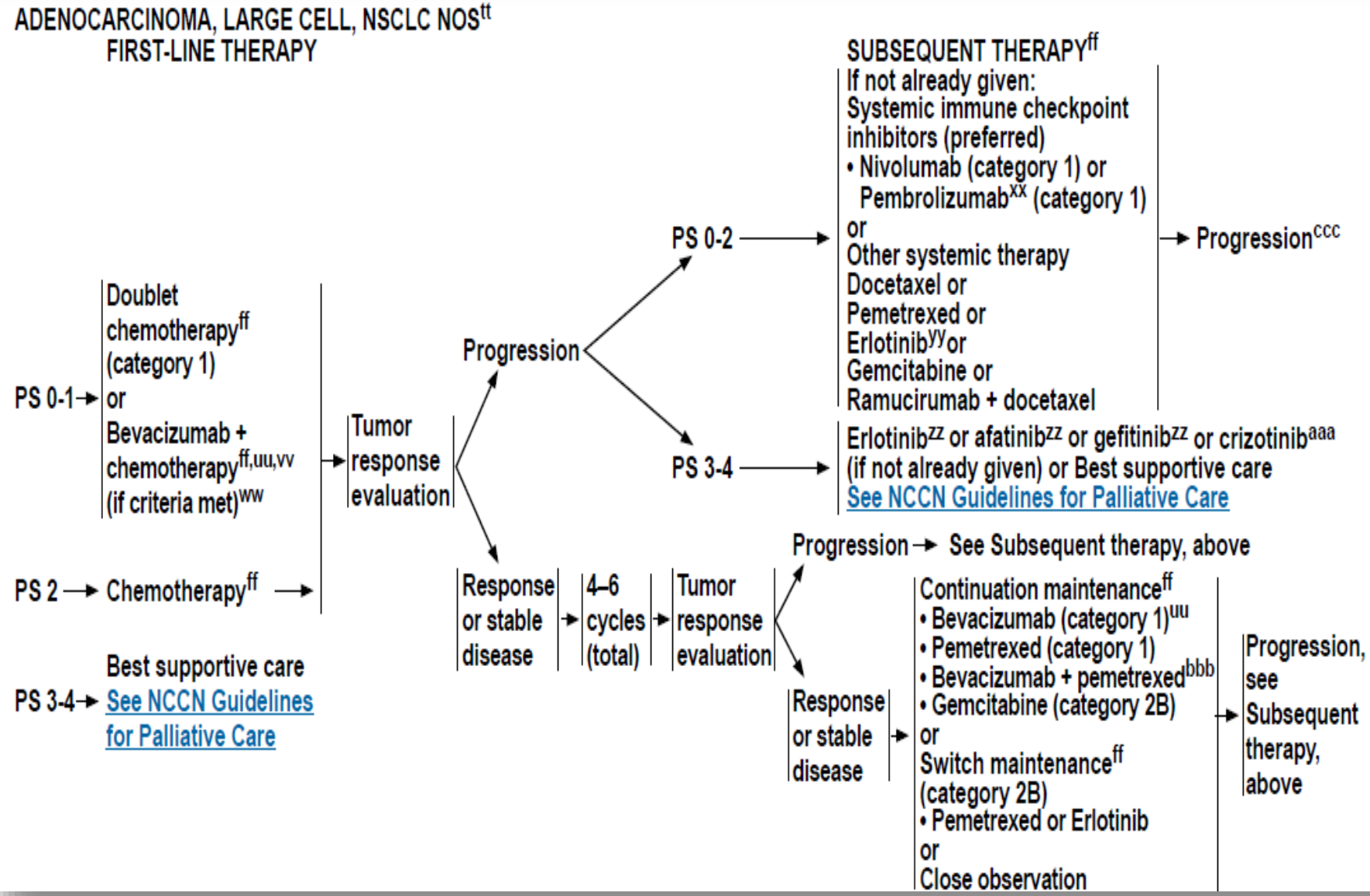
4rd Line

No treatment are approved

Evidence Based Medicine Algorithm

* Only for High PD-L1 positive tumours; not registered in UE
For patients not candidate to Nivolumab/Pembrolizumab, 3rd line chemotherapy should be considered as a 2nd line

Cesare Gridelli,[1] Benjamin Besse,[2] Julie Renee Brahmer,[3] Lucio Crinò,[4] Enriqueta Felip,[5] Filippo de Marinis[6]


ADENOCARCINOMA, LARGE CELL, NSCLC NOS[tt]
FIRST-LINE THERAPY
PS 0-1
Doublet chemotherapy[ff] (category 1) or Bevacizumab + chemotherapy[ff,uu,vv] (if criteria met)[ww]
PS 2
Chemotherapy[ff]
PS 3-4
Best supportive care
See NCCN Guidelines for Palliative Care
Tumor response evaluation
Progression
PS 0-2
SUBSEQUENT THERAPY[ff]
If not already given:
Systemic immune checkpoint inhibitors (preferred)
• Nivolumab (category 1) or Pembrolizumab[xx] (category 1)
or
Other systemic therapy
Docetaxel or
Pemetrexed or
Erlotinib[yy] or
Gemcitabine or
Ramucirumab + docetaxel
Progression[ccc]
PS 3-4
Erlotinib[zz] or afatinib[zz] or gefitinib[zz] or crizotinib[aaa] (if not already given) or Best supportive care
See NCCN Guidelines for Palliative Care
Response or stable disease
4–6 cycles (total)
Tumor response evaluation
Progression
See Subsequent therapy, above
Response or stable disease
Continuation maintenance[ff]
• Bevacizumab (category 1)[uu]
• Pemetrexed (category 1)
• Bevacizumab + pemetrexed[bbb]
• Gemcitabine (category 2B)
or
Switch maintenance[ff] (category 2B)
• Pemetrexed or Erlotinib
or
Close observation
Progression, see Subsequent therapy, above

Second line therapy of non-squamous cell lung cancer: Comparisons accross recent studies

Nivolumab vs Doc:
12.2 vs 9.4 months; HR 0.73 (0-59-0.89)

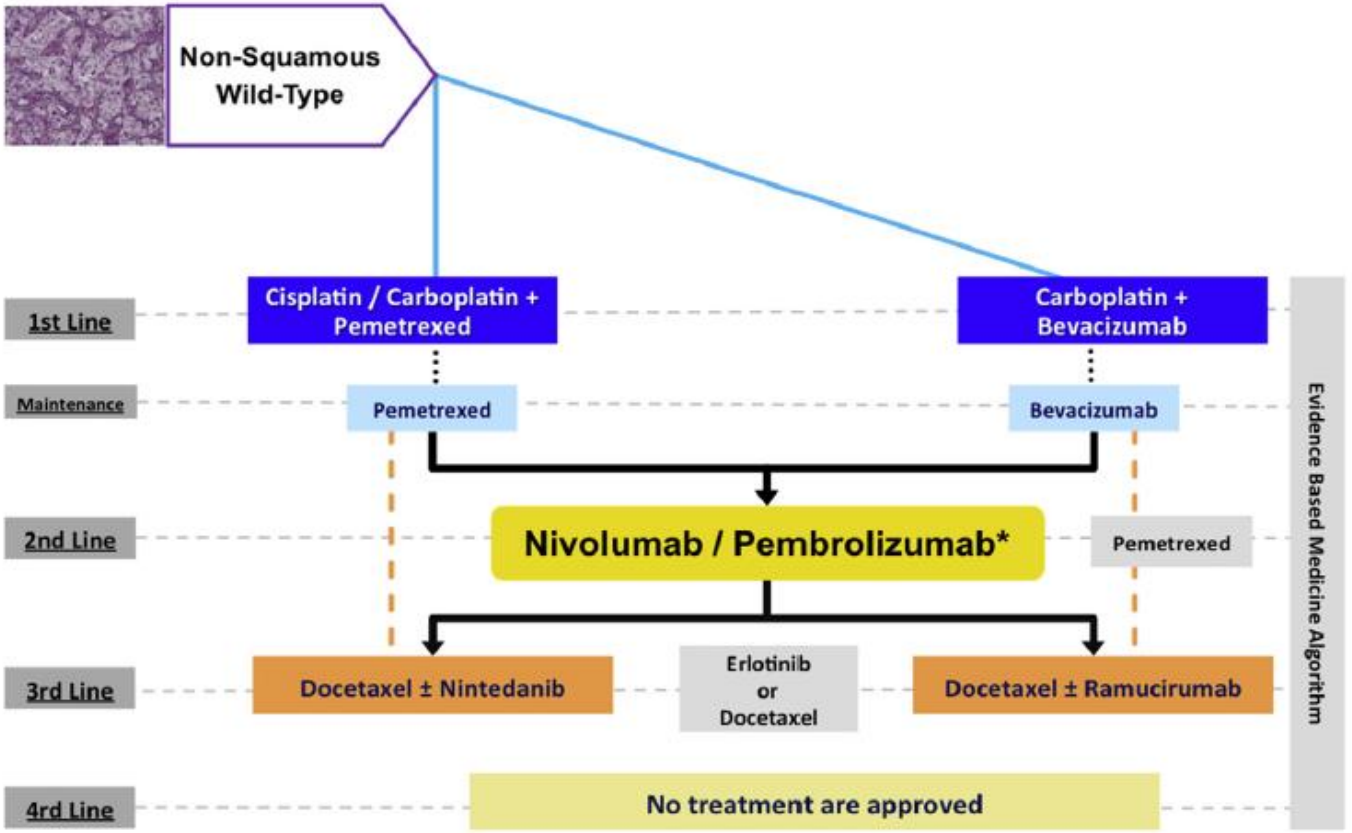
Pemetrexed vs Doc
9.3 vs 8.0 months; HR 0.78 (0.61-1.00)

Docetaxel Ramucirumab vs Doc
11.1 *vs* 9.7 months; HR 0.83 (0.71–0.97)

Docetaxel Nintedanib vs Doc
12.6 vs 10.3 months, HR 0.83 (0.7-0.99)

The Evolving Role of Nivolumab in Non—Small-Cell Lung Cancer for Second-Line Treatment: A New Cornerstone for Our Treatment Algorithms. Results From an International Experts Panel Meeting of the Italian Association of Thoracic Oncology

Clinical Lung Cancer (2016),



* Only for High PD-L1 positive tumours; not registered in UE
For patients not candidate to Nivolumab/Pembrolizumab, 3rd line chemotherapy should be considered as a 2nd line

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Thank You

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