Nuovi farmaci nel tumore del polmone:

razionale biologico, tossicità ed efficacia

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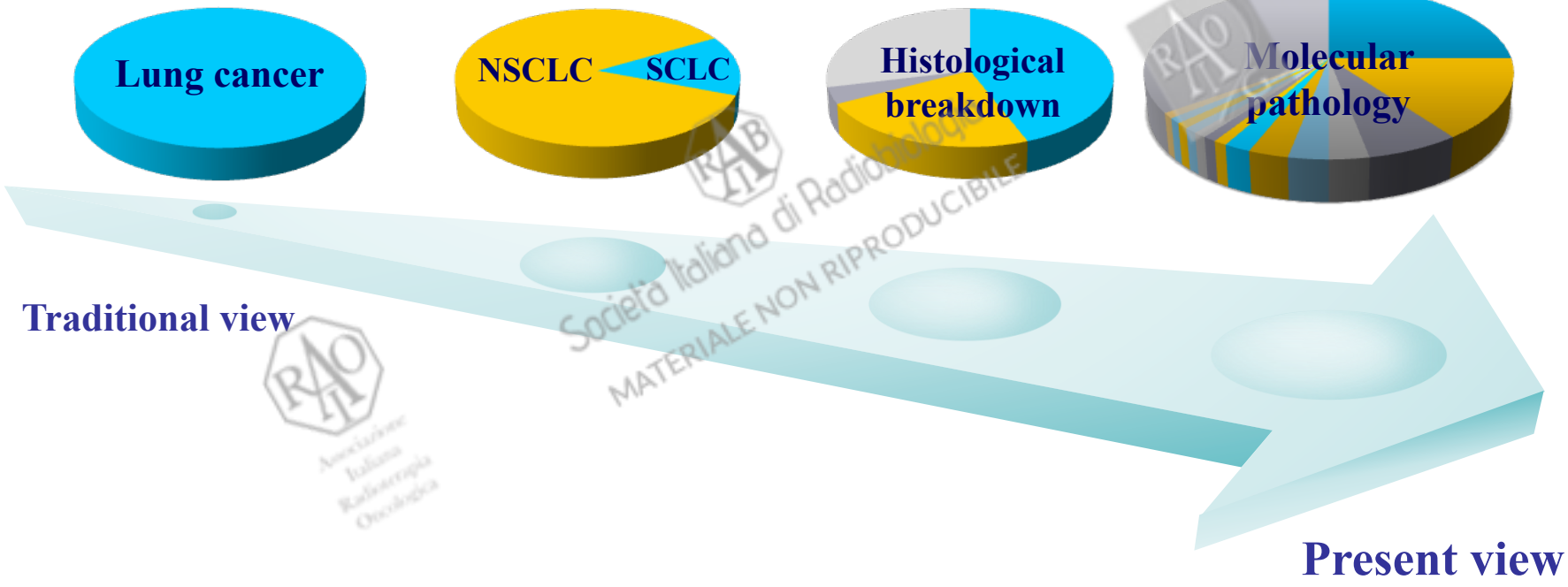
Shifting from an empiric to a customized approach



Adapted from Pao W et al. Lancet Oncol. 2011

Strategies to improve treatment effectiveness

Target Treatments according to:

- Tumor histology (squamous vs non-squamous)
- Epidermal Growth Factor Receptor
- ALK mutations
- Immune checkpoints

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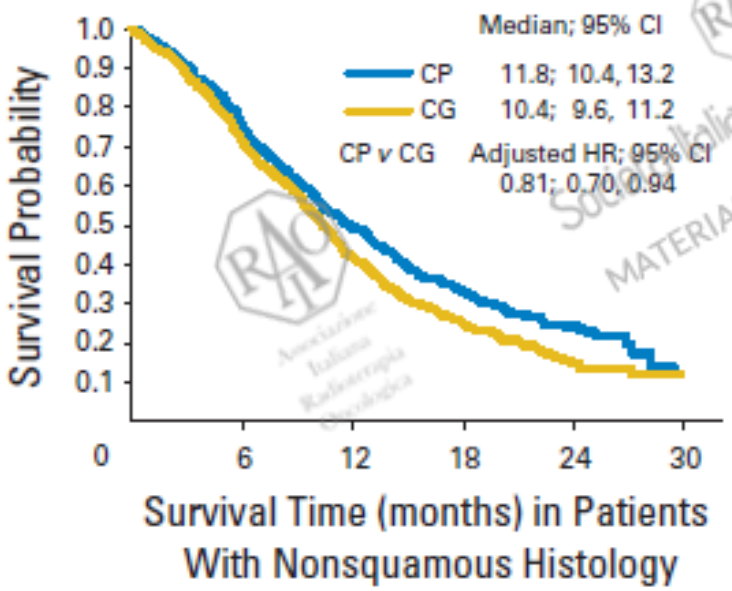
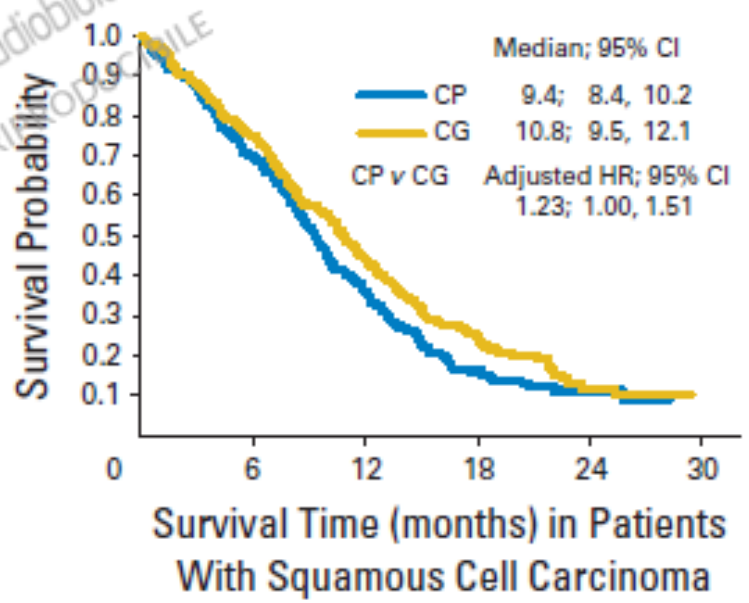
Role of Histology in Patient Selection

Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naive Patients With Advanced-Stage Non–Small-Cell Lung Cancer





Scagliotti GV, J Clin Oncol 2008; 20;26(21):3543-51

Worse outcomes for Squamous NSCLC compared to Adenocarcinoma

Epidemiological overall survival data:
better for adenocarcinoma, worse for squamous tumors

SEER Database 129.337 patients

Period	1-year OS / 2-yr OS			HR; *P* value
	All (N=129.337)	**ADC** (n=53.300)	**SQ** (n=22.944)	
1990–1993	13.2 / 4.6	15.5 / 5.4	13.5 / 4.3	0.990; $p = 0.62$
1994–1997	14.1 / 4.9	16.1 / 5.7	14.3 / 4.9	1.007; $p = 0.72$
1998–2001	17.2 / 6.5	20.4 / 7.9	17.1 / 6.4	0.997; $p = 0.85$
2002–2005	**19.3 / 7.8**	**23.3 / 9.9**	**19.9 / 7.2**	**1.033; $p = 0.02$**

Adapted from Morgensztern DJ et al. J Thorac Oncol. 2009

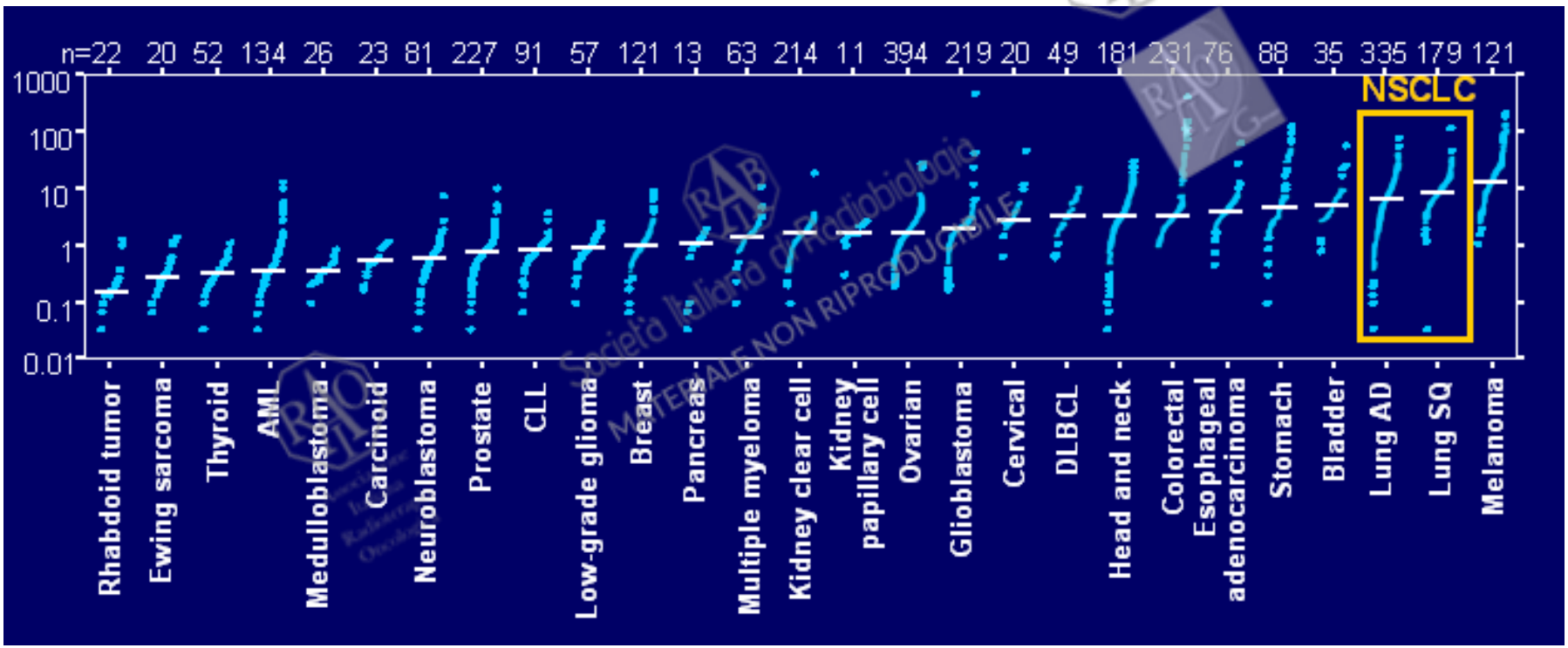
Strategies to improve treatment effectiveness

Target Treatments according to:

- Tumor histology (squamous vs non-squamous)
- Epidermal Growth Factor Receptor
- ALK mutations
- Immune checkpoints

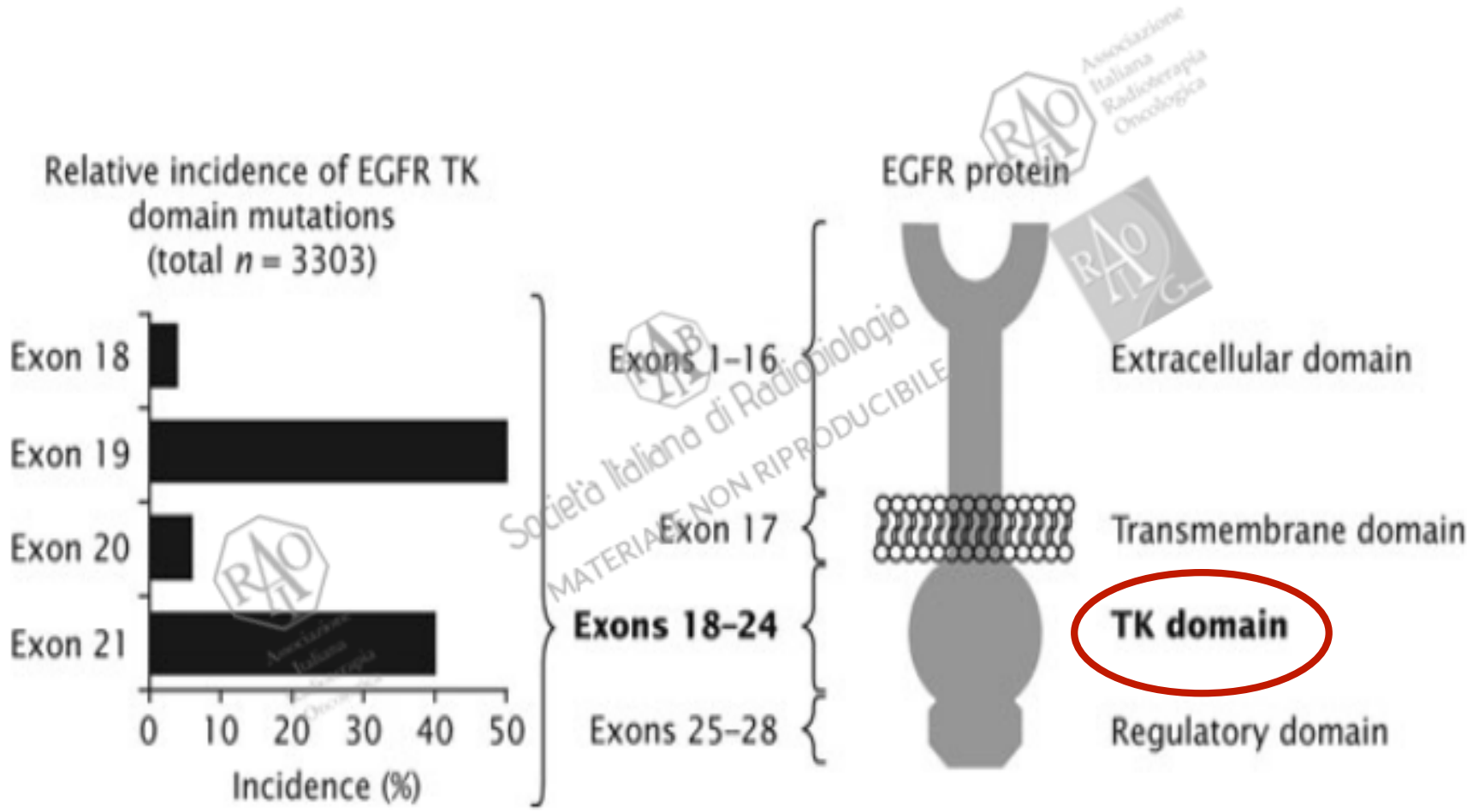
Lung cancer has a high rate of somatic mutations

Mutation frequencies observed in cancers



Adapted from Lawrence MS et al. Nature 2013

EGFR-mutated NSCLC is a distinct disease

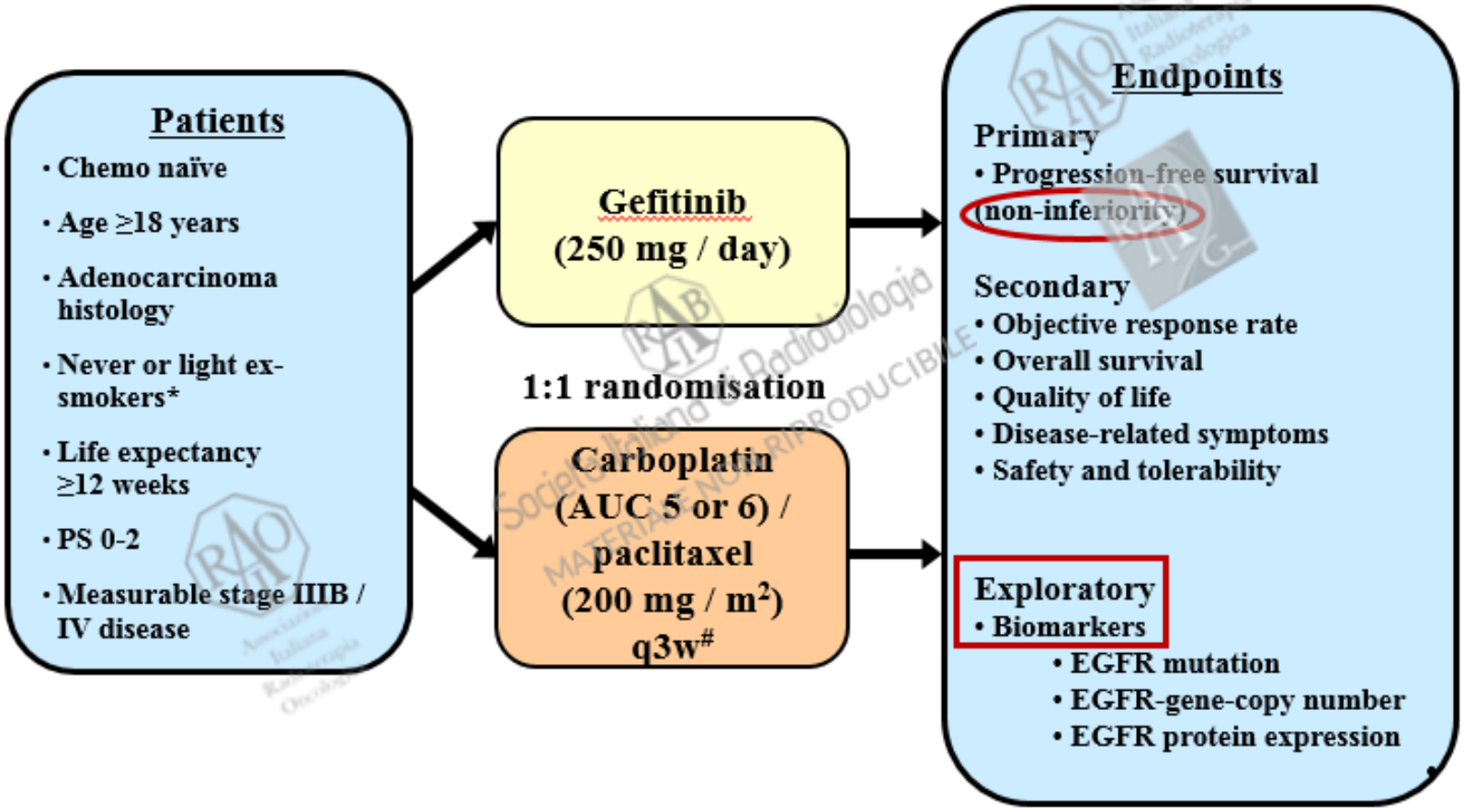


Paz Ares L, J Cell Mol Med 2010;11:2693-2694

Phase III Clinical Trials of TKI vs Platinum-Doublet CT as First-Line Therapy for Advanced *EGFR*-Mutated NSCLC

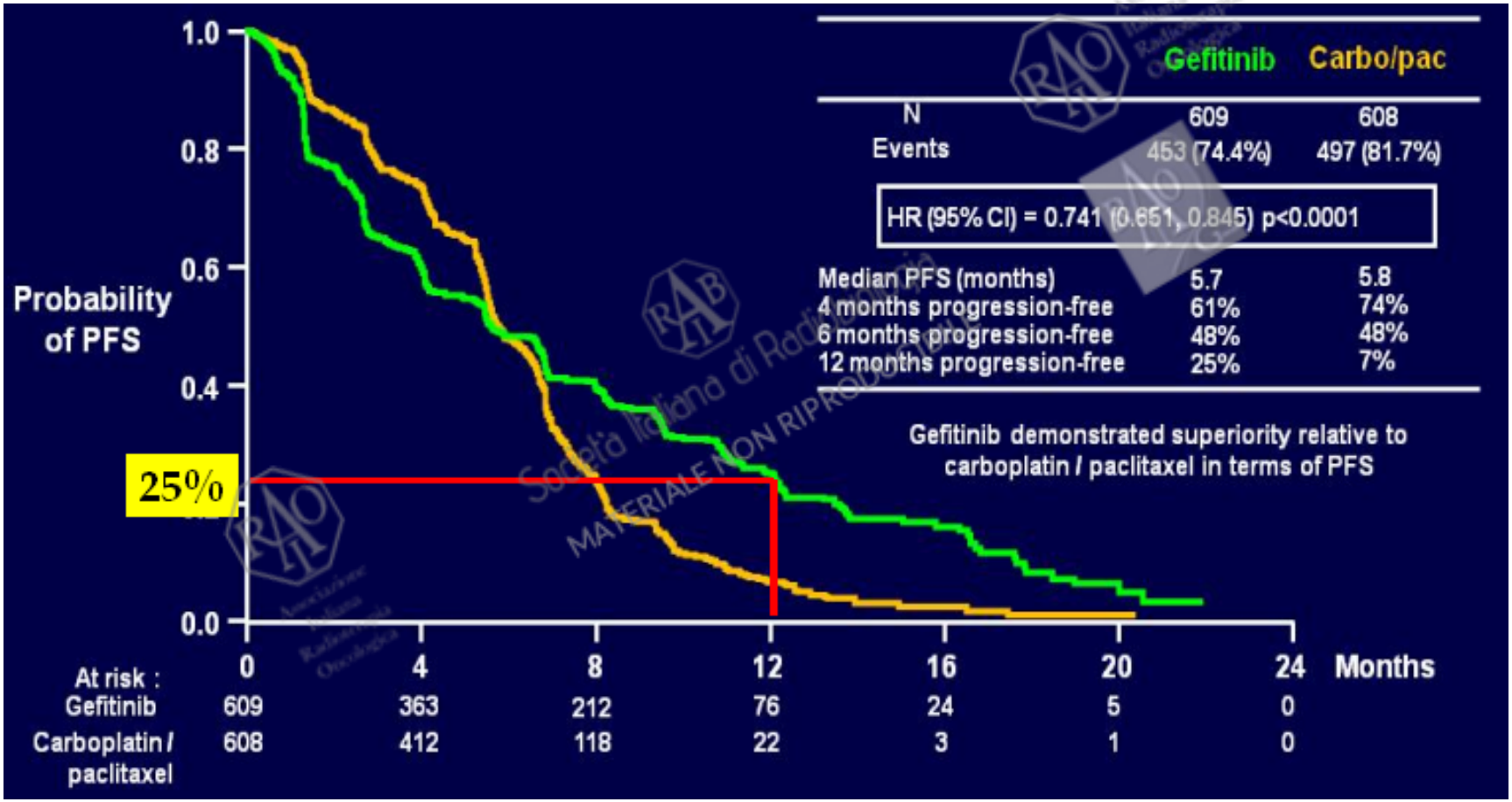
Trial	Patients	Treatment	ORR	P	PFS (mos)	HR (P)	OS (mos)	HR (P)
IPASS	437	Gefitinib	94/132 (71.2%)	<0.001	9.5	0.48 (<0.001)	21.6	1 (0.99)
		Carboplatin-paclitaxel	61/129 (47.3%)		6.3		21.9	
WJTOG 3405	177	Gefitinib	36/58 (62.1%)	<0.001	9.2	0.49 (<0.001)	30.9	1.64 (0.21)
		Cisplatin-docetaxel	19/59 (32.2%)		6.3		NRea	
NEJ 002	230	Gefitinib	84/114 (73.7%)	<0.001	10.8	0.30 (<0.001)	30.5	NR (0.31)
		Carboplatin-paclitaxel	35/114 (30.7%)		5.4		23.6	
OPTIMAL	154	Erlotinib	68/82 (83%)	<0.001	13.1	0.16 (<0.001)	22.6	1.06 (0.68)
		Carboplatin-gemcitabine	26/72 (36%)		4.6		28.8	
EURTAC	173	Erlotinib	50/86 (58%)	<0.001	9.7	0.37 (<0.001)	19.3	1.04 (0.87)
		Platinum-doublet	13/87 (15%)		5.2		19.5	
LUX-Lung3	345	Afatinib	NR/NR (56%)	0.001	11.1	0.58 (<0.001)	NRea 16.6 (25th percentile)	1.12 (0.60)
		Cisplatin-pemetrexed	NR/NR (23%)		6.9		NRea 14.8 (25th percentile)	

IPASS (Iressa Pan-ASia Study)



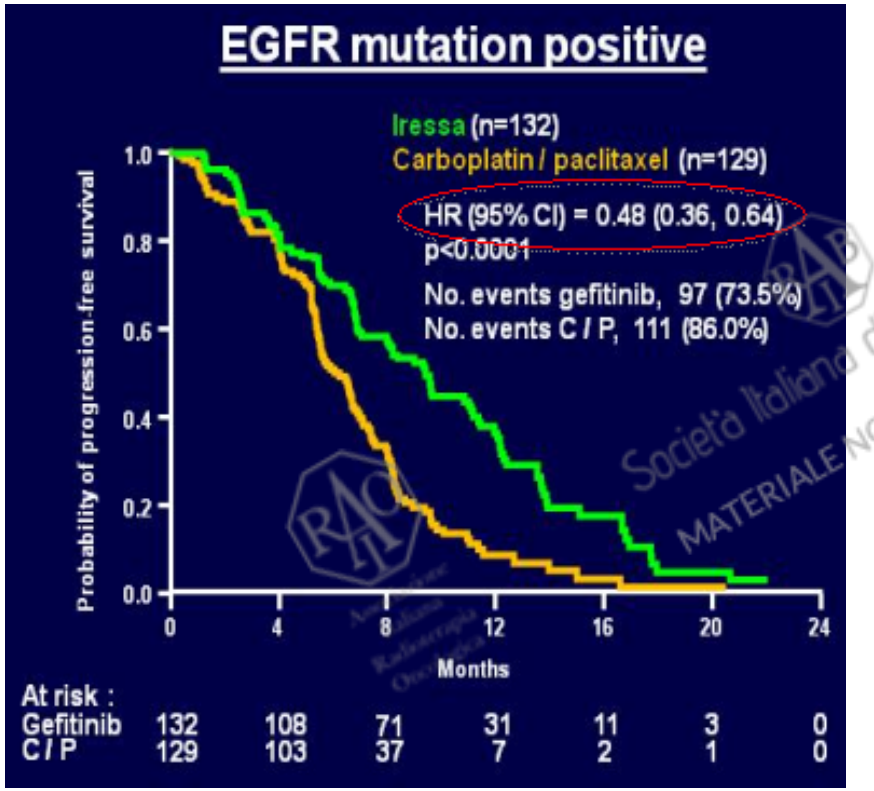
Mok TS, N Eng J Med 2009; 361:947-957

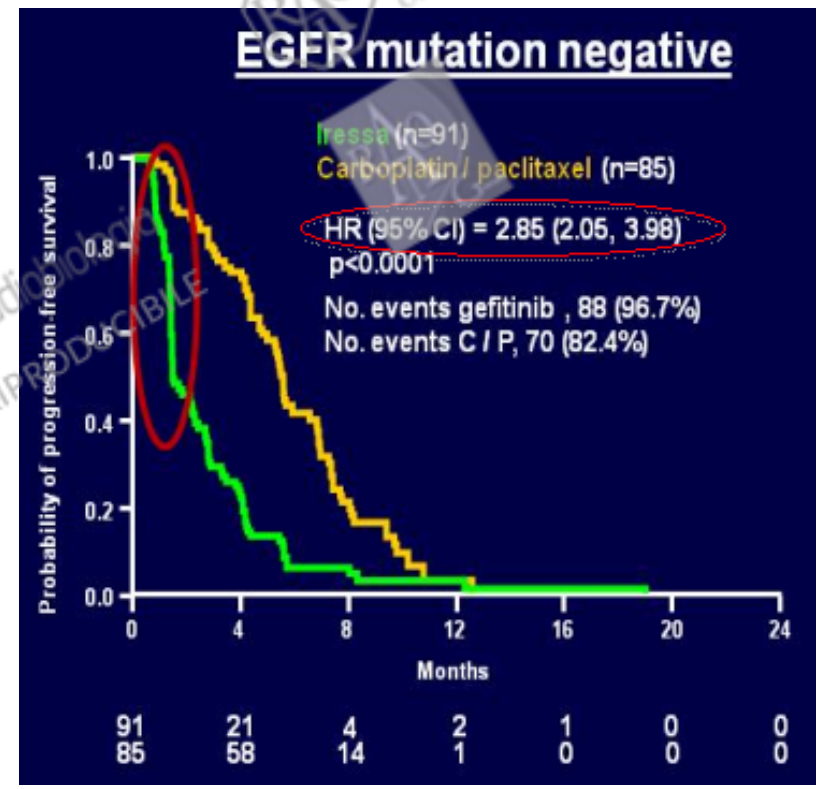
IPASS: Progression-Free Survival



Mok TS, N Eng J Med 2009; 361:947-957

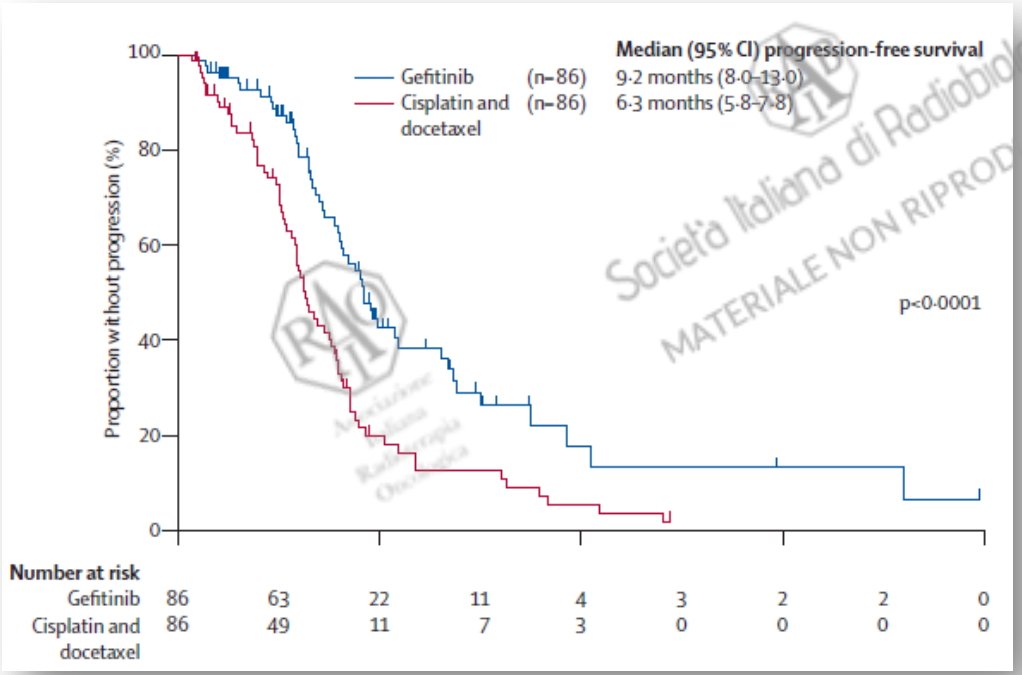
IPASS: PFS by EGFR mutation status





Mok TS, N Eng J Med 2009; 361:947-957

Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial



172 chemotherapy-naive patients

	Gefitinib (n=87)		Cisplatin plus docetaxel (n=88)	
	All	CTC grade ≥3	All	CTC grade ≥3
Non-haematological toxicity				
Rash*	74	2	7	0
AST*	61	14	17	1
ALT*	61	24	35	2
Dry skin*	47	0	3	0
Diarrhoea	47	1	35	0
Fatigue*	34	2	73	2
Paronychia*	28	1	1	0
Stomatitis	19	0	13	0
Nausea*	15	1	83	3
Constipation*	14	0	39	0
Alopecia*	8	0	67	0
Sensory disturbance*	7	1	23	0
Haematological toxicity				
Leucocytopenia*	13	0	82	43
Thrombocytopenia*	12	0	29	0
Neutropenia*	7	0	81	74
Anaemia*	33	0	79	15

Mitsudomi T, Lancet Oncology 2010; 11(2):121-8

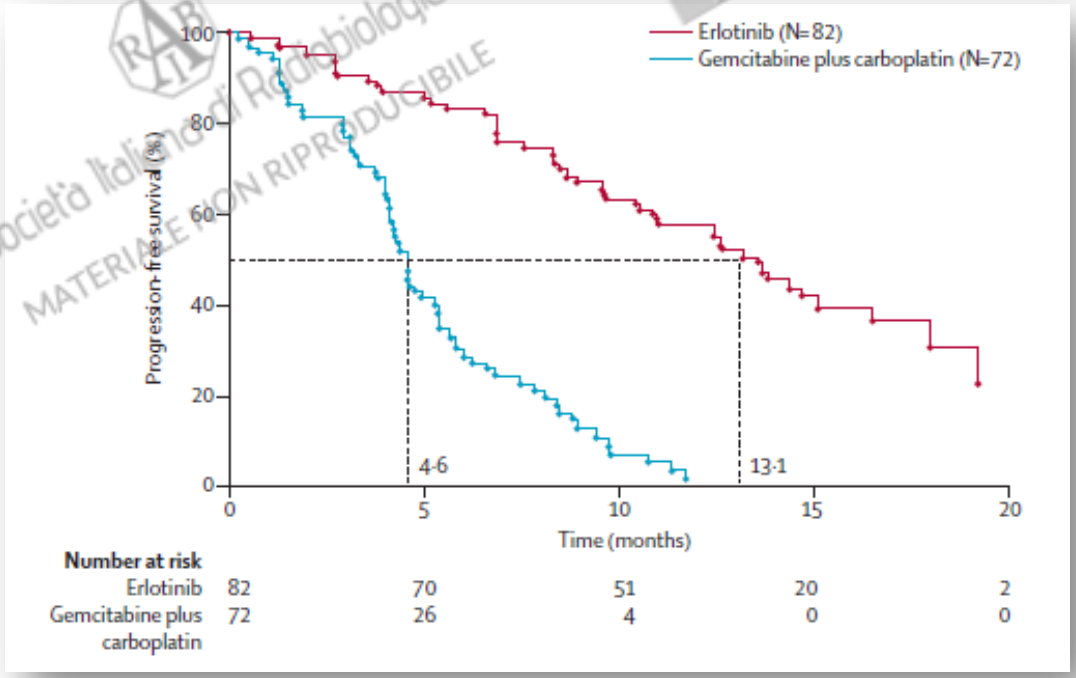
Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study

Caicun Zhou, Yi-Long Wu*, Gongyan Chen, Jifeng Feng, Xiao-Qing Liu, Changli Wang, Shucai Zhang, Jie Wang, Songwen Zhou, Shengxiang Ren, Shun Lu, Li Zhang†, Chengping Hu, Chunhong Hu, Yi Luo, Lei Chen, Ming Ye, Jianan Huang, Xiuyi Zhi, Yiping Zhang, Qingyu Xiu, Jun Ma, Li Zhang‡, Changxuan You*

154 patients

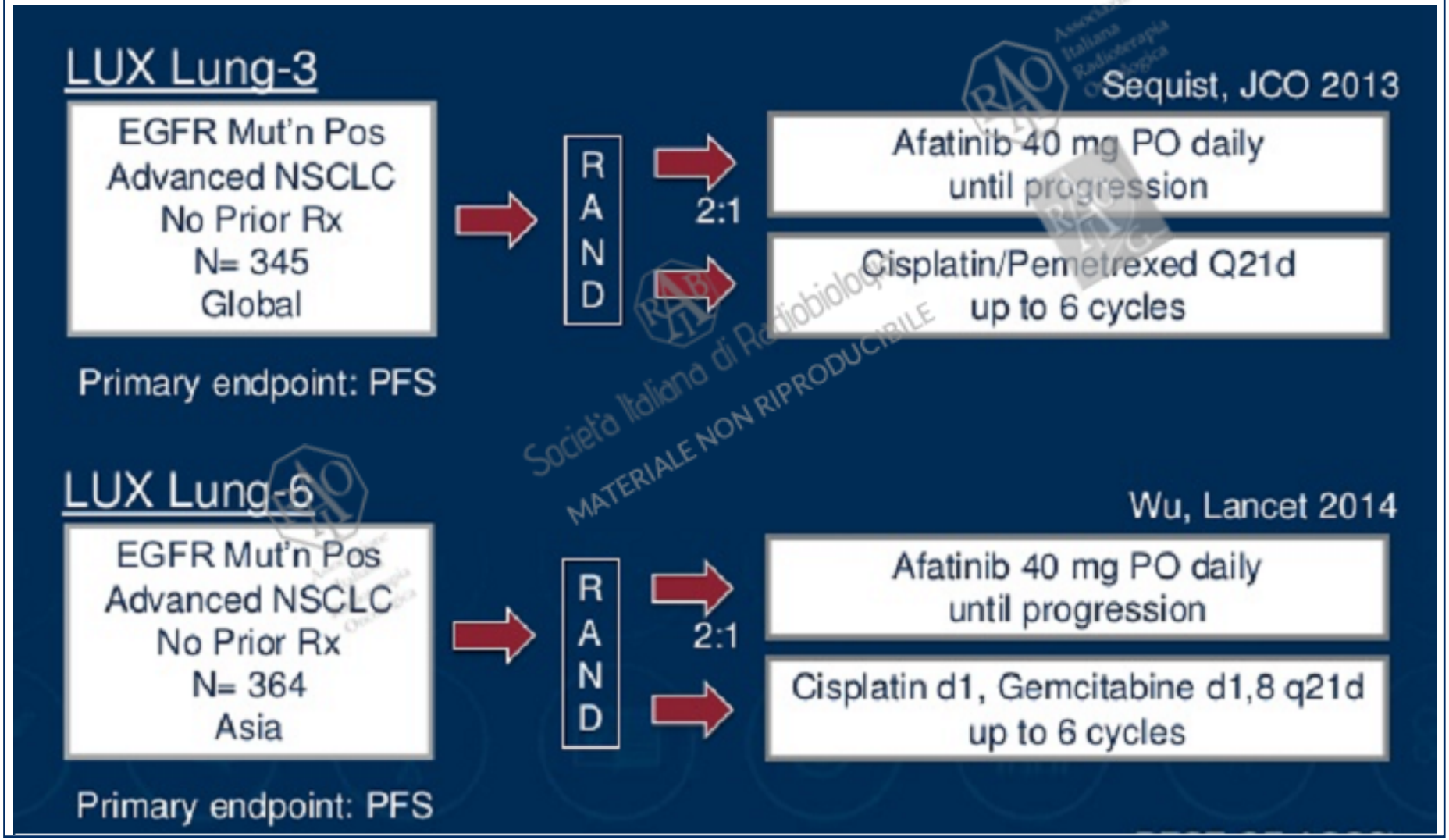
HR 0.16 (95% CI: 0.10-0.26)

p < 0.0001

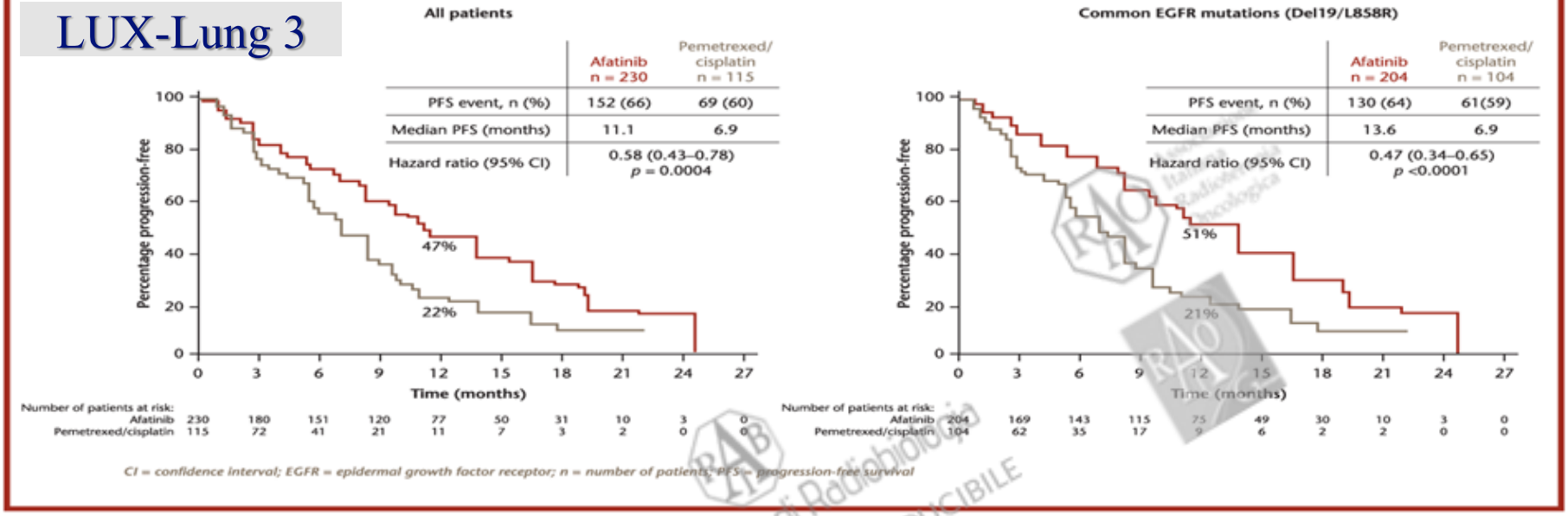


Lancet Oncol 2011; 12:735-42

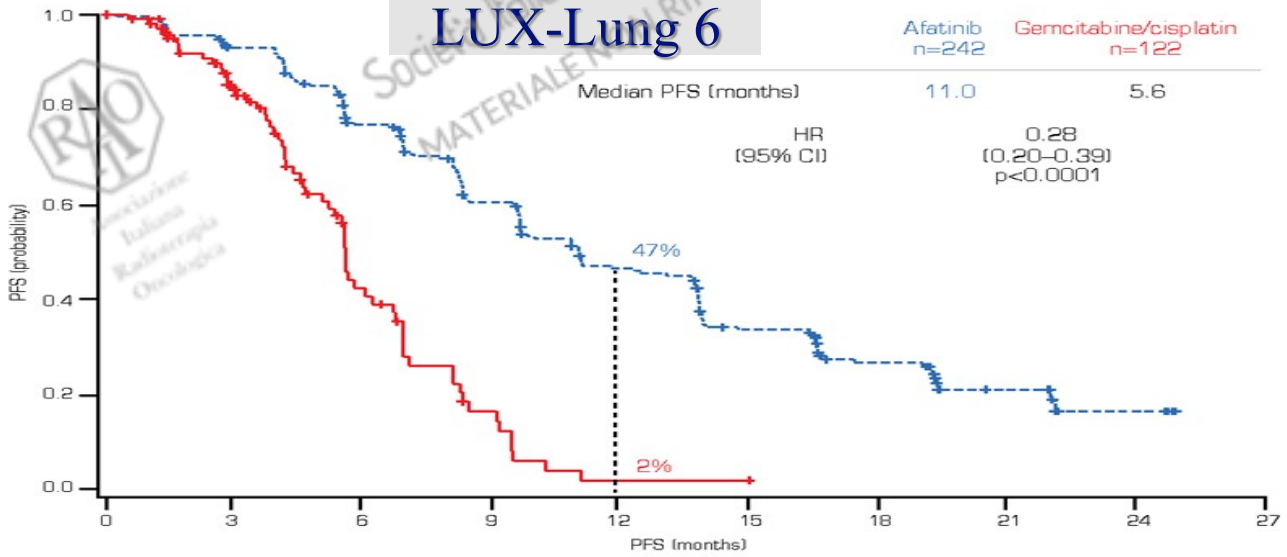
LUX Lung-3, LUX Lung-6 Trials



LUX-Lung 3



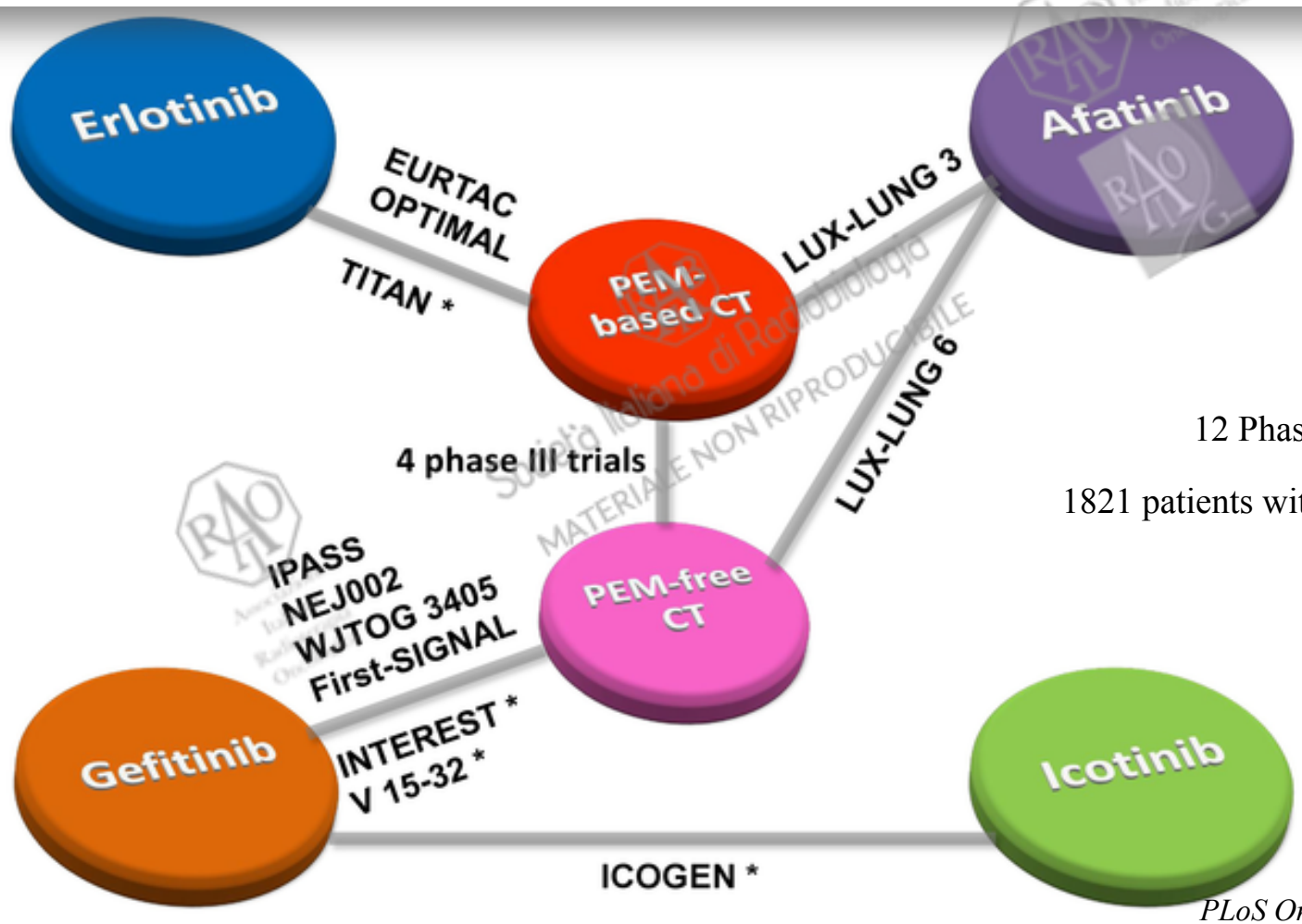
LUX-Lung 6



Grade ≥3 toxicity indirect comparison

Toxicity	Gefitinib				Erlotinib			Afatinib	
	NEJ 002 n=114	IPASS n=607	First-SIGNAL n=159	WJTOG 3405 n=87	OPTIMAL n=83	EURTAC n=84	ENSURE n=110	LUX-Lung 3 n=229	LUX-Lung 6 n=239
Rash	71.0 (5.3)	66.2 (3.1)	72.3 (1.3)	74 (2)	75 (2)	80 (13)	67.3 (6.4)	99.1 (16.2)	80.8 (14.6)
Diarrhoea	34.2 (0.9)	46.6 (3.8)	NR	47(1)	26 (1)	57 (5)	40.9 (1.8)	96.2 (14.4)	88.3 (5.4)
Fatigue	10.5 (2.6)	16.8 (0.3)	28.3 (0.6)	34 (2)	5 (0)	57 (6)	NR	17.5 (1.3)	10.0 (0.4)
Anorexia	NR	21.9 (1.5)	44.7 (0)	NR	NR	NR	NR	20.5 (3.1)	10.0 (1.3)
Stomatitis	NR	17.0 (0.2)	NR	19 (0)	14 (1)	NR	NR	72.1 (8.7)	51.9 (5.4)
Paronychia	NR	13.5 (0.3)	NR	28 (1)	4 (0)	NR	NR	56.8 (11.4)	32.6 (0)
Vomiting	NR	12.9 (0.2)	NR	NR	1 (0)	NR	NR	17.0 (3.1)	9.6 (0.8)

Network Meta-Analysis of Erlotinib, Gefitinib, Afatinib and Icotinib in Patients with Advanced Non-Small-Cell Lung Cancer Harboring EGFR Mutations

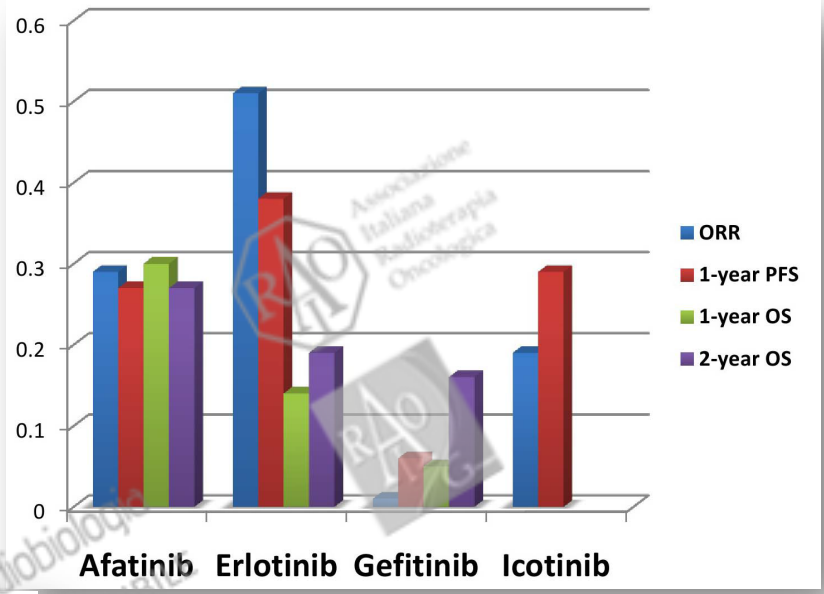


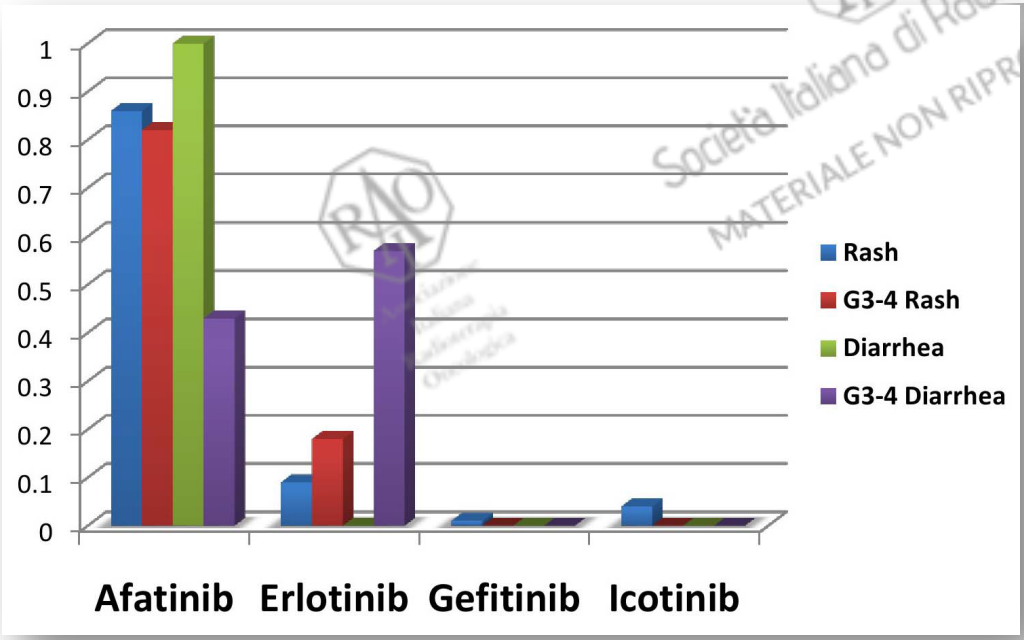
12 Phase III RCTs

1821 patients with EGFR mutation

PLoS One. 2014; 9(2):e85245

Erlotinib, gefitinib, afatinib and icotinib shared equivalent efficacy but presented different efficacy-toxicity pattern for EGFR-mutated patients.

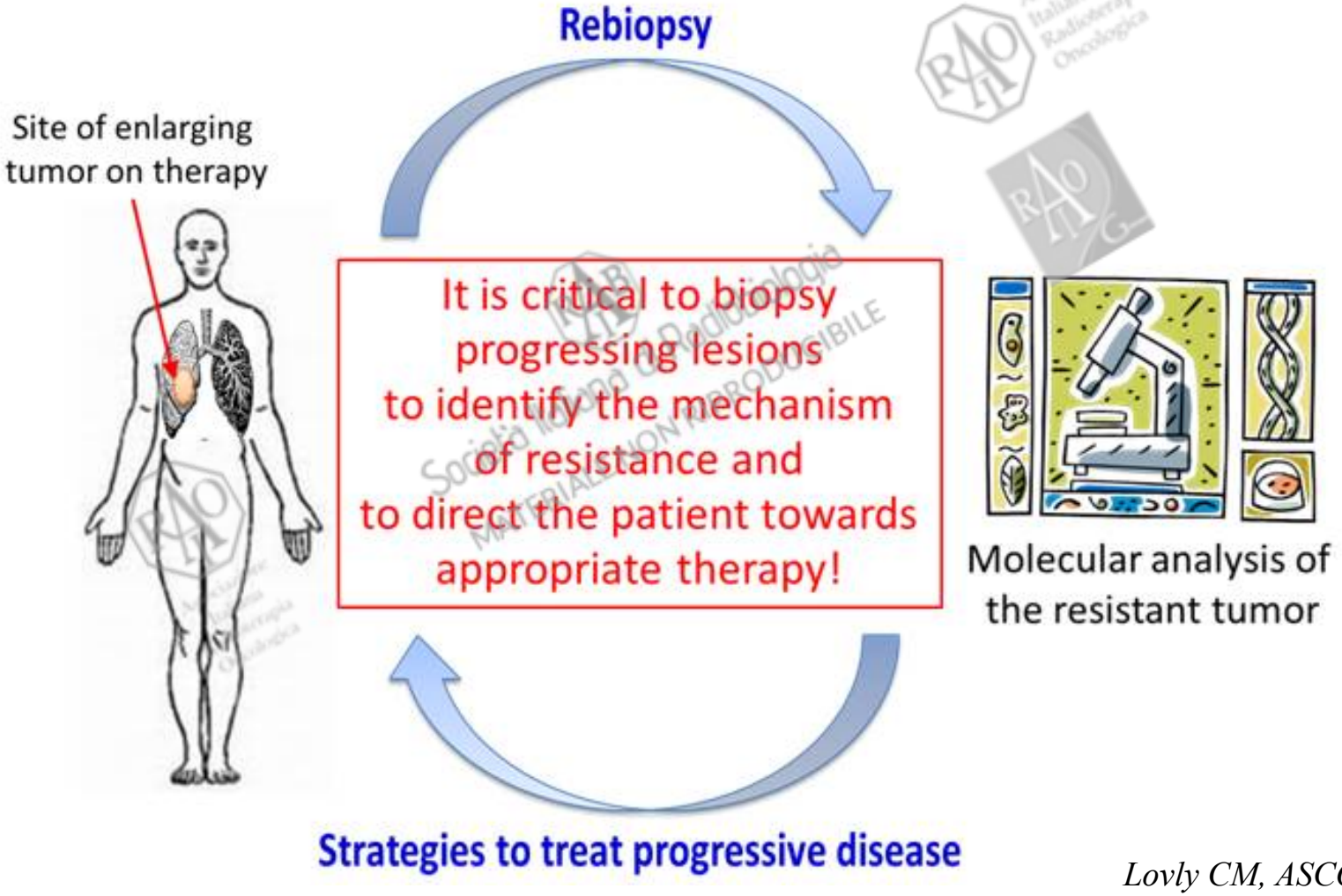




Erlotinib and afatinib revealed potentially better efficacy but significant higher toxicities compared with gefitinib and icotinib.

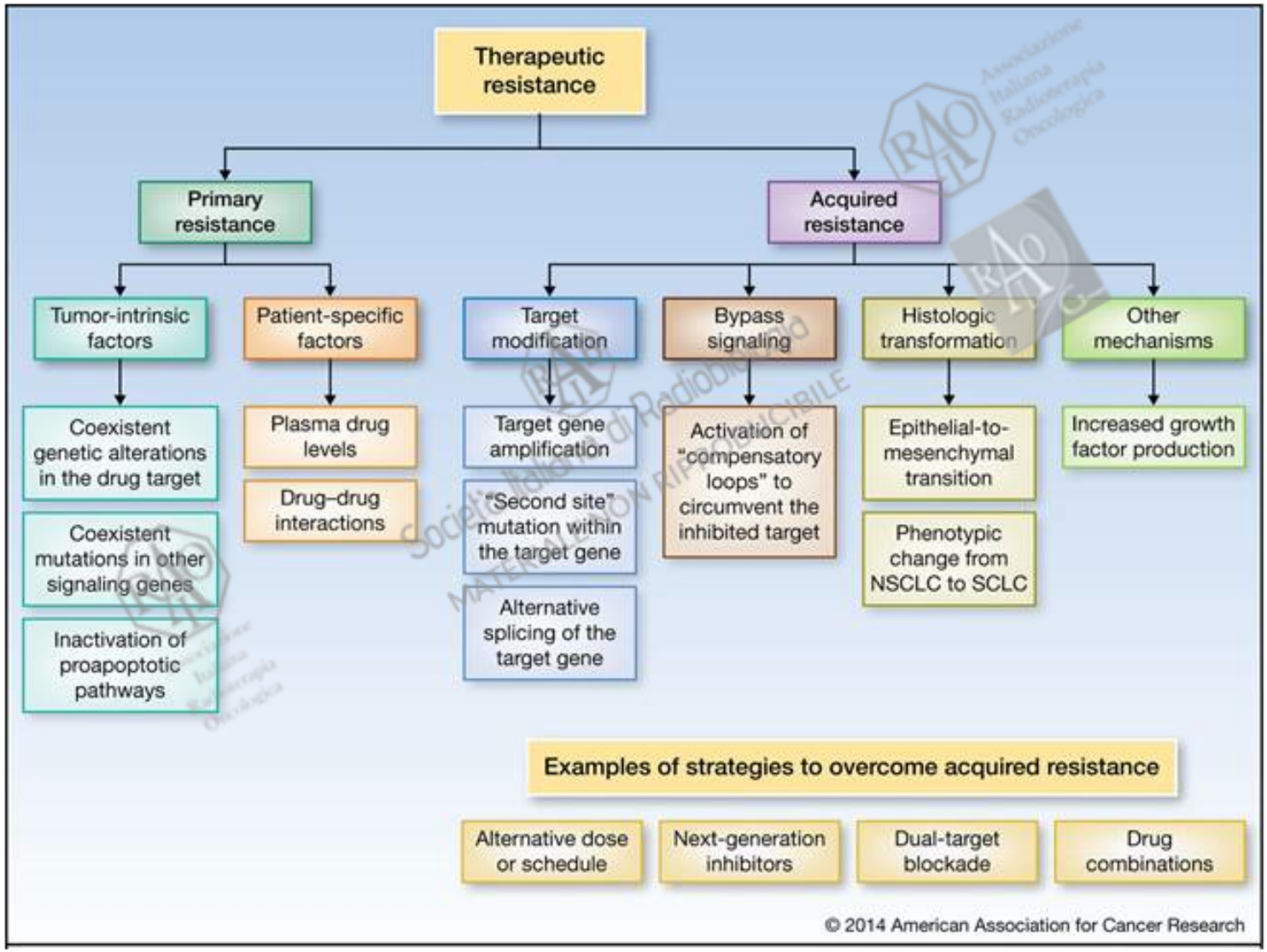
PLoS One. 2014; 9(2):e85245

Understanding and overcoming acquired resistance during target therapies



Lovly CM, ASCO 2015

Mechanisms of resistance to TKi



Half of patients treated with EGFR TKIs progress due to T790M mutations in EGFR

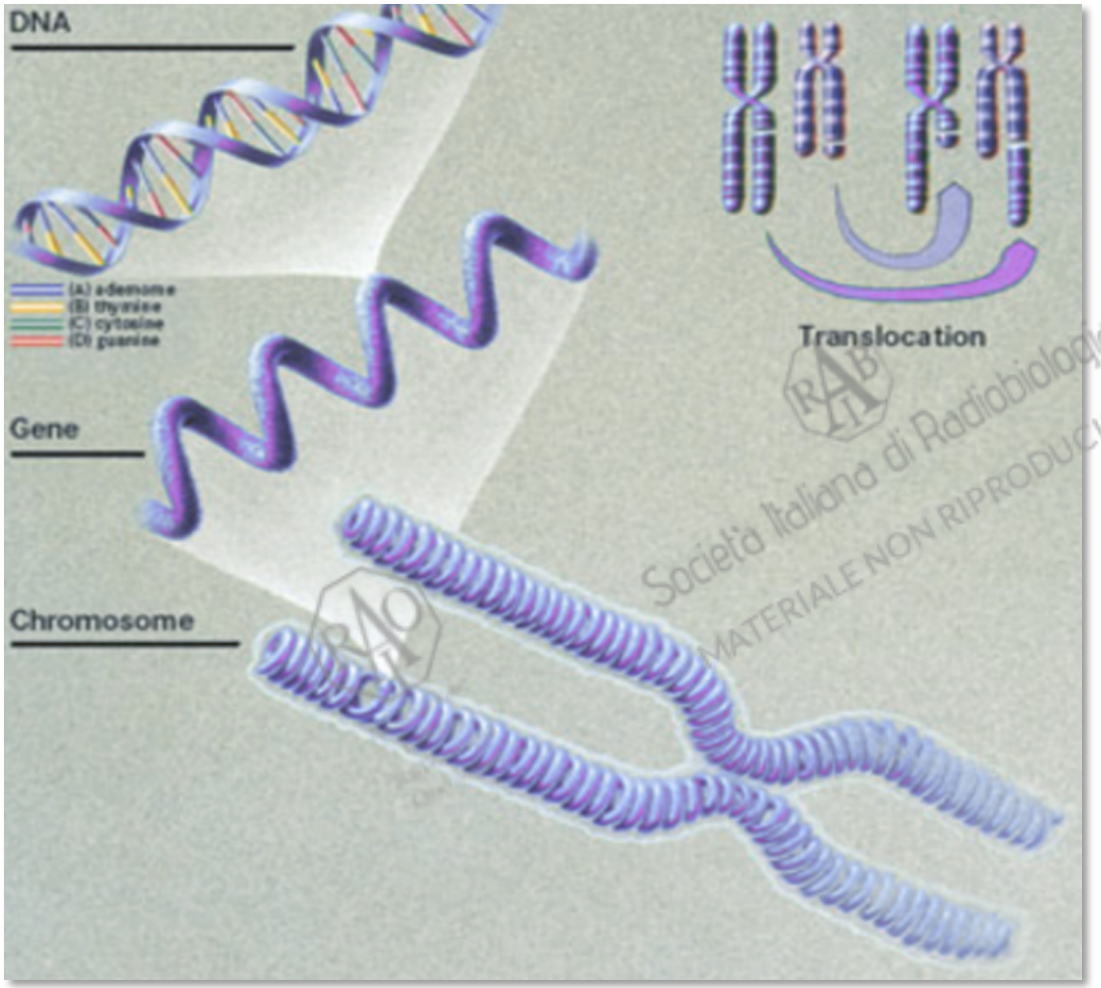
Chen X, Lung Cancer 2013; 81(2):155-61

Strategies to improve treatment effectiveness

Target Treatments according to:

- Tumor histology (squamous vs non-squamous)
- Epidermal Growth Factor Receptor
- ALK mutations
- Immune checkpoints

ALK Rearrangement in Cancer

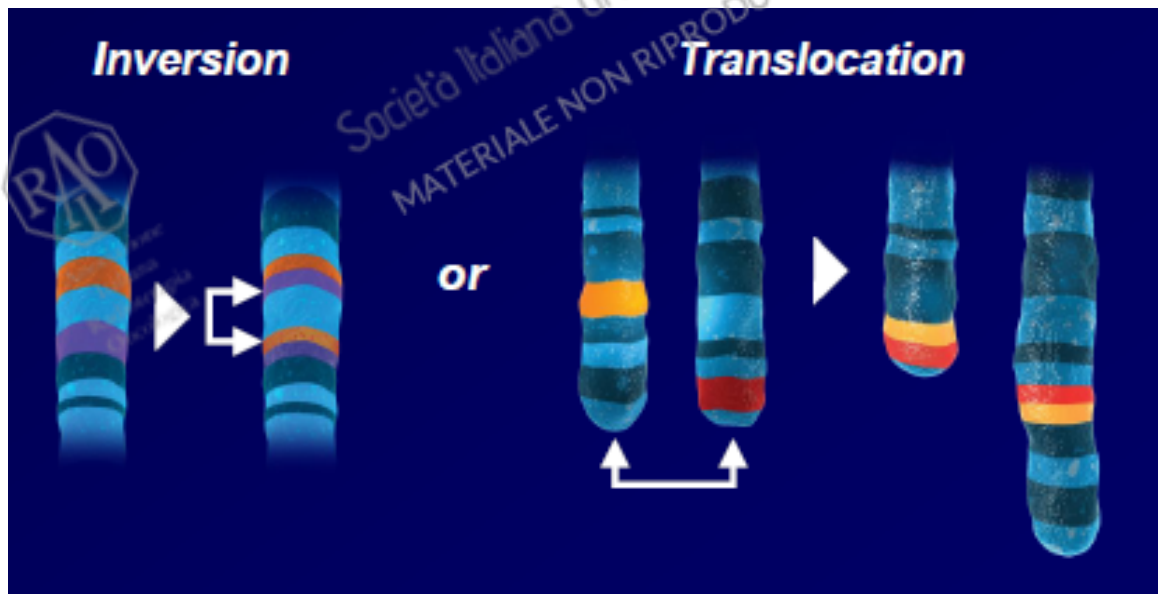


- Chromosomal translocation most common ALK abnormality in cancer
- Rearrangement of genetic info when parts of one chromosome break off and fuse with another, or flip around (inversion)
- Results in new gene and expression of **fusion protein**

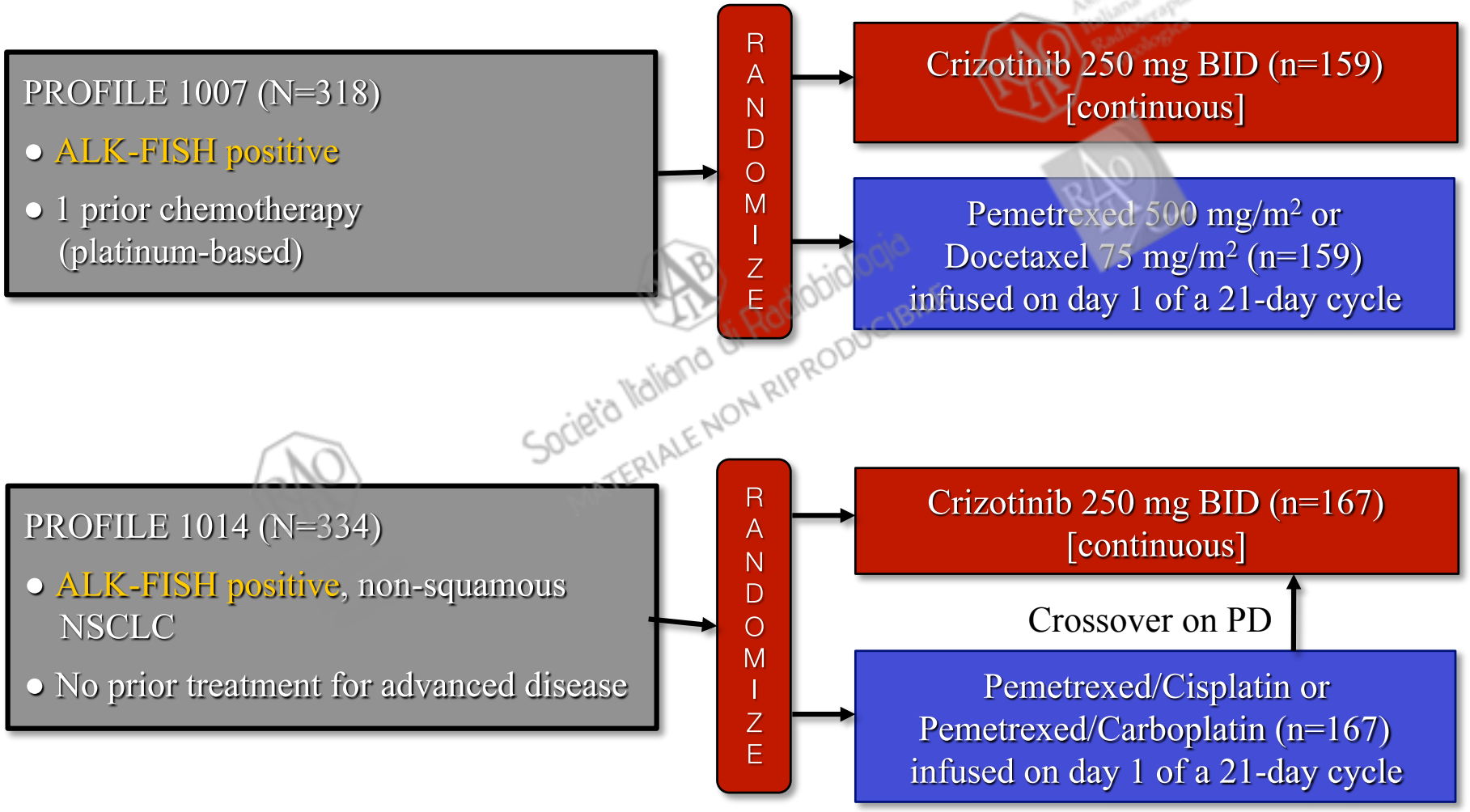
Adapted from Cancer Genome Atlas, National Cancer Institute

ALK Rearrangement in NSCLC

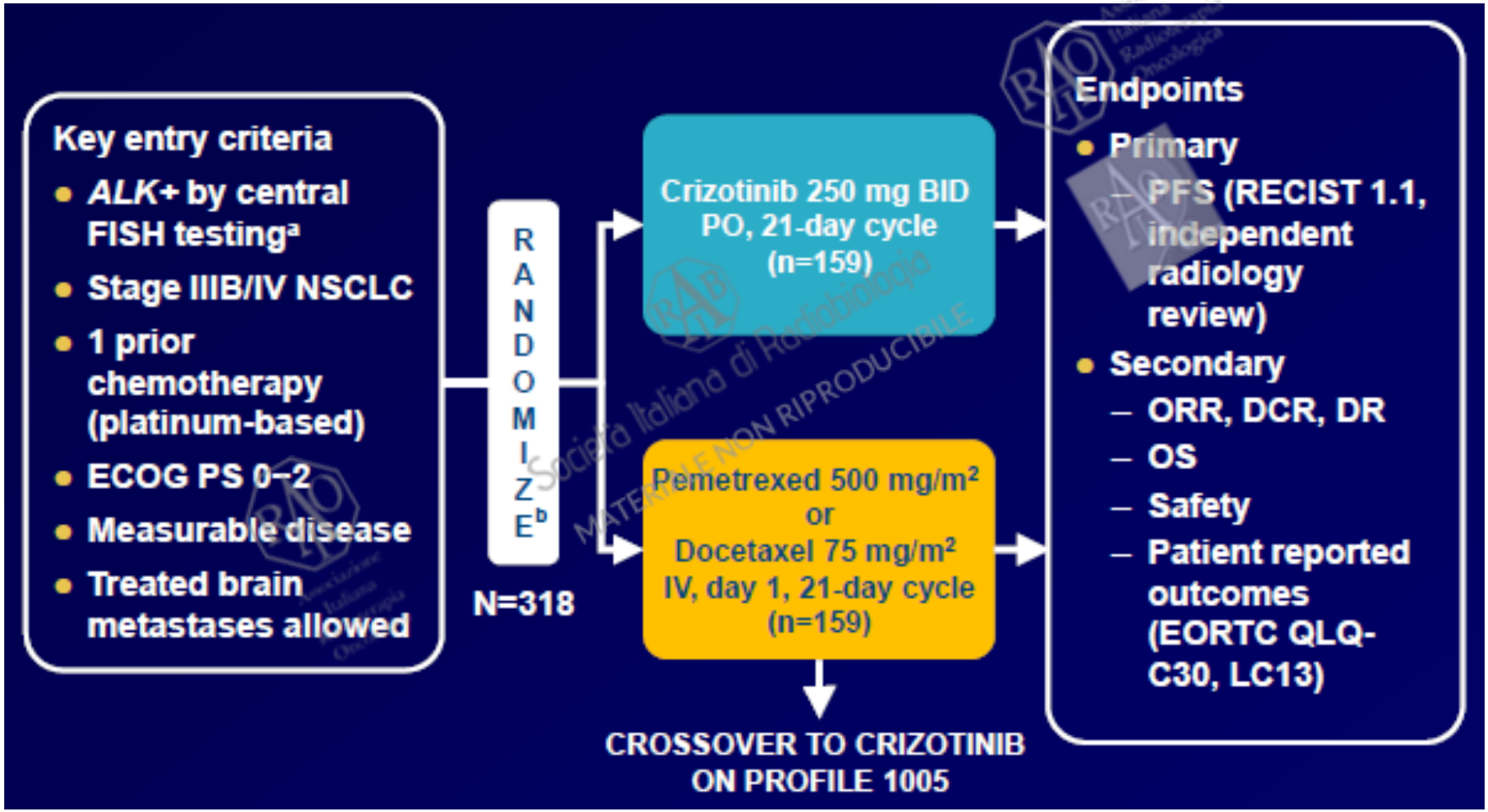
- ALK (anaplastic lymphoma kinase) is a tyrosine kinase target in several different cancers, including NSCLC
- In NSCLC, ALK is activated by chromosomal rearrangement, leading to constitutive kinase activation and oncogene addiction



Randomized trials of crizotinib in *ALK*+ NSCLC



PROFILE 1007 : Study Design



PROFILE 1007 NCT00932893

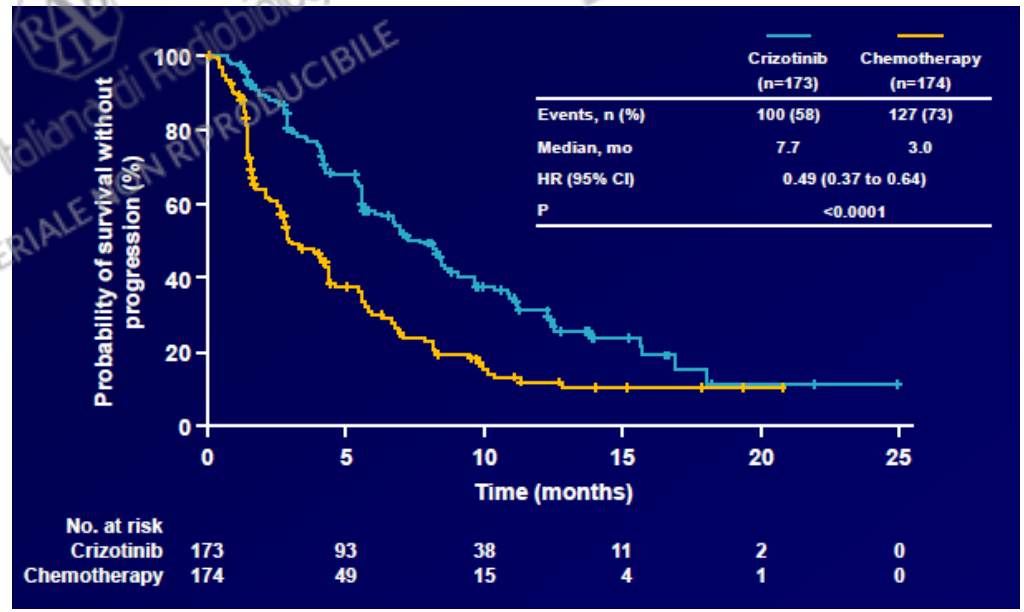
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

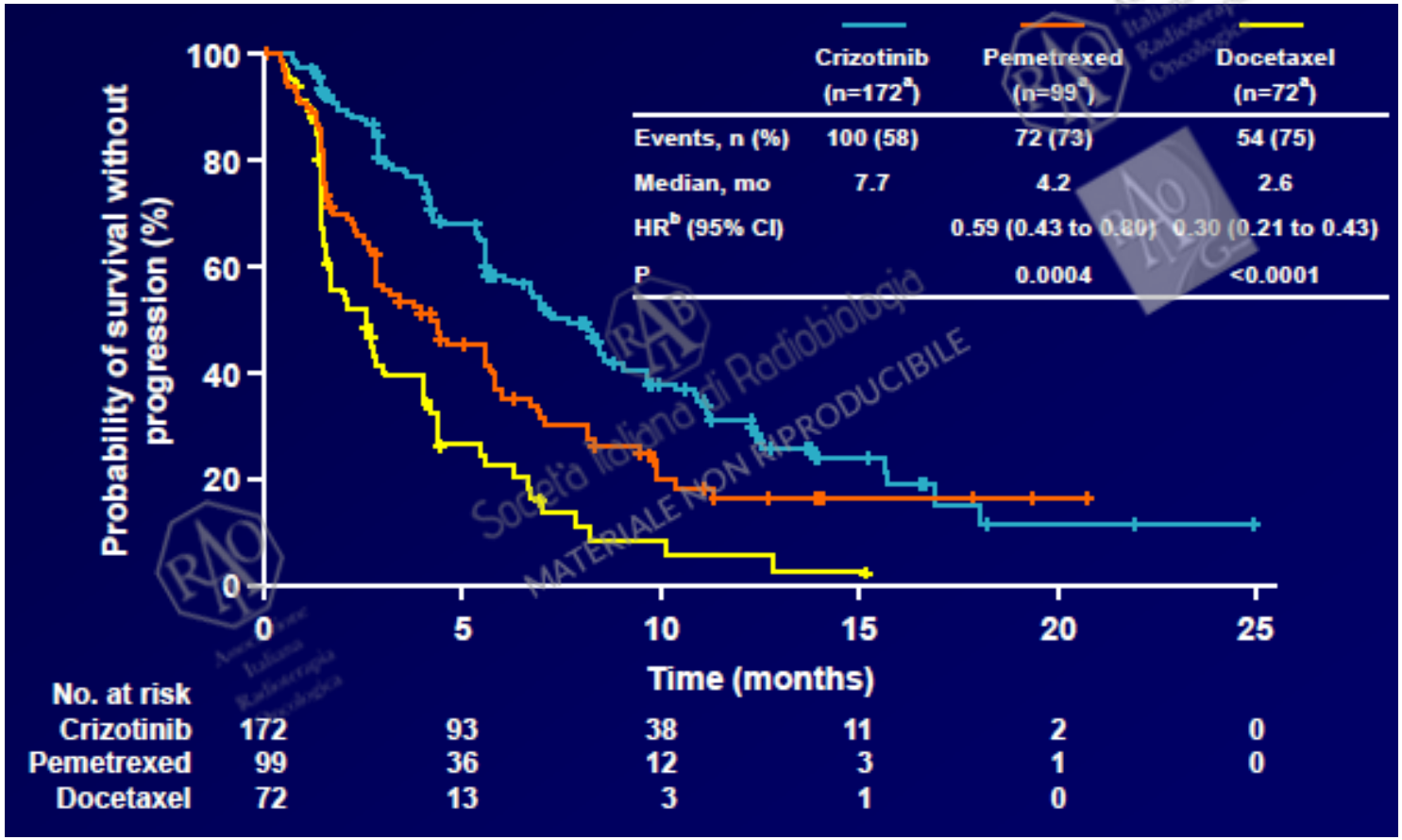
Accrual period:
February 2010 – February 2012

Primary Endpoint: PFS



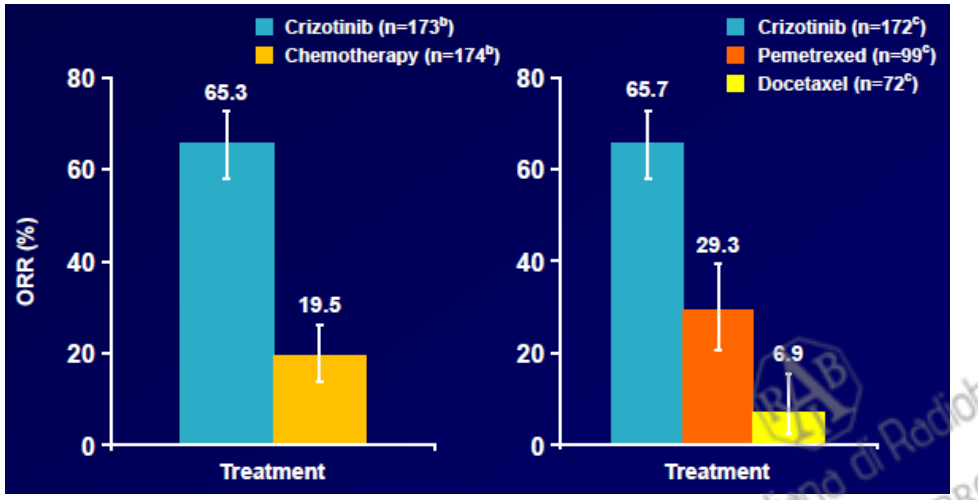
Shaw AT, N Engl J Med 2013; 368: 2385-94

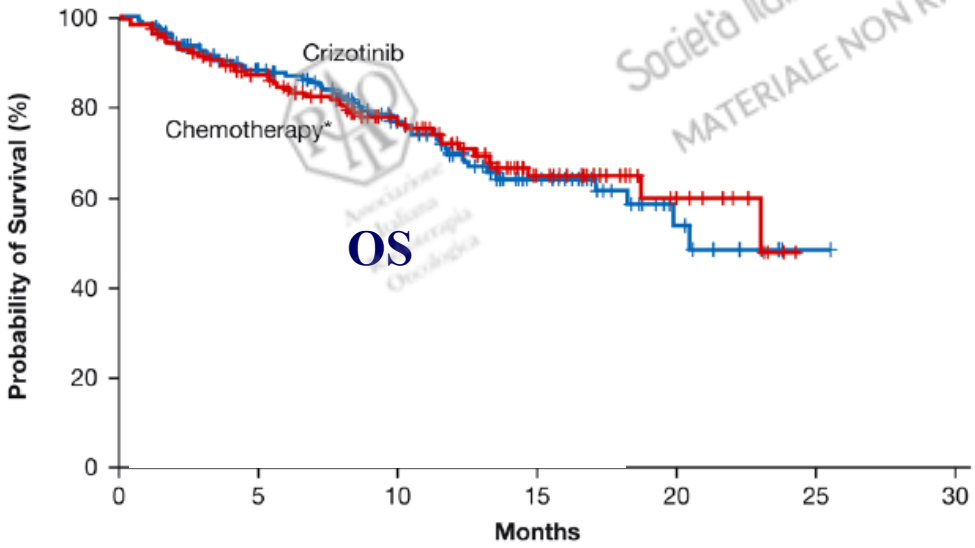
PFS of Crizotinib vs Pemetrexed or Docetaxel



Shaw AT, N Engl J Med 2013; 368: 2385-94

Secondary Endpoints: ORR and OS





ORR ratio: 3.4 (95% CI: 2.5 to 4.7);

p< 0.0001

Median OS: 20.3 vs 22.8 months

HR: 1.02 (95% CI: 0.68 to 1.54);

p= 0.54

Shaw AT, N Engl J Med 2013; 368: 2385-94

Adverse Events of Any Cause

Adverse Event	Crizotinib (N=172)		Chemotherapy (N=171)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Vision disorder†‡	103 (60)	0	16 (9)	0
Diarrhea	103 (60)	0	33 (19)	1 (1)
Nausea§	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting§	80 (47)	2 (1)	30 (18)	0
Constipation	73 (42)	4 (2)	39 (23)	0
Elevated aminotransferase levels†	66 (38)	27 (16)¶	25 (15)	4 (2)
Edema†	54 (31)	0	27 (16)	0
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Upper respiratory infection†	44 (26)	0	22 (13)	1 (<1)
Dysgeusia	44 (26)	0	16 (9)	0
Dizziness†	37 (22)	1 (1)	14 (8)	0
Dyspnea†‖	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0	29 (17)	0
Alopecia	14 (8)	0	35 (20)	0

Common AE associated with Crizotinib were visual disorders, gastrointestinal side effects and eleveted liver aminotransferase levels

Shaw AT, N Engl J Med 2013; 368: 2385-94

Grade 3 or 4 AE of Any Cause in >3% of patients

Adverse Events	Crizotinib (N=172)	Chemotherapy (N=171)
	number of patients (percent)	
Incidence higher in crizotinib arm		
Elevated transaminases*	27 (16)	4 (2)
Pulmonary embolism*	9 (5)	3 (2)
Dyspnea*	7 (4)	5 (3)
Pneumonia	6 (4)	3 (2)
Hypokalemia	6 (4)	0
Electrocardiogram QTc prolonged	6 (4)	0†
Incidence higher in chemotherapy arm		
Neutropenia*	23 (13)	33 (19)
Febrile neutropenia	1 (1)	16 (9)
Anemia*	4 (2)	9 (5)
White blood cells decreased	2 (1)	8 (5)
Fatigue	4 (2)	7 (4)

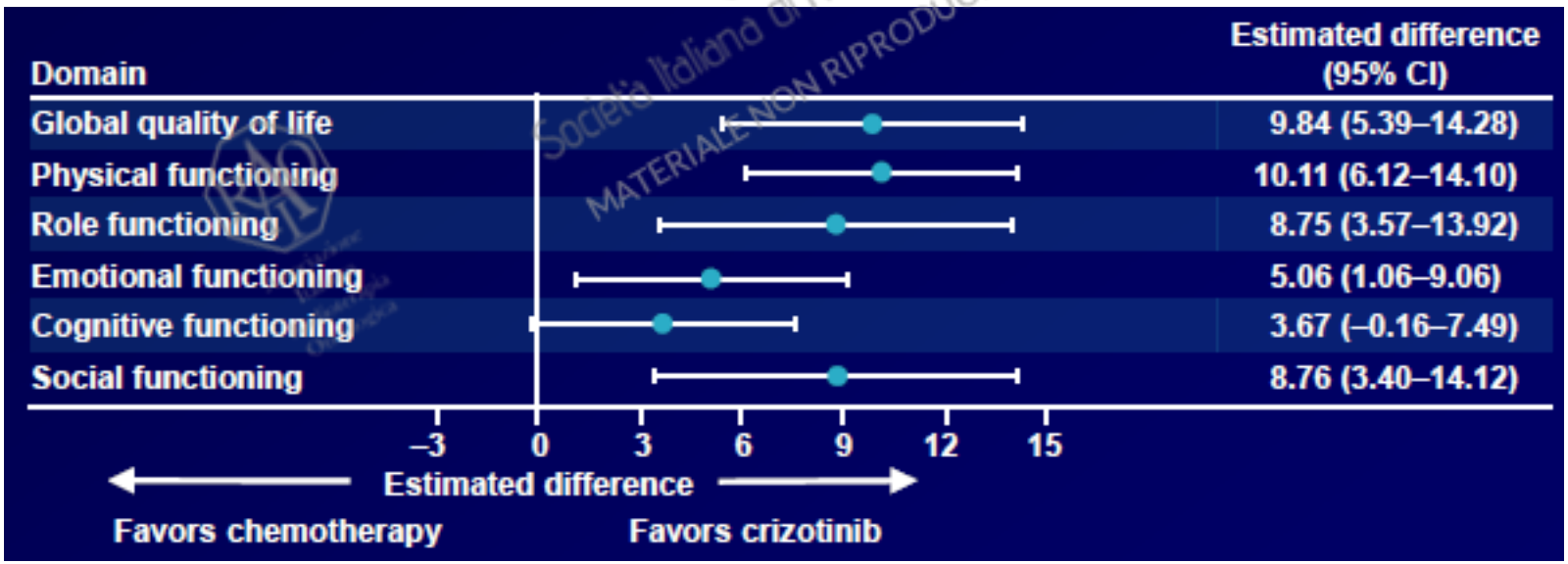
Shaw AT, N Engl J Med 2013; 368: 2385-94

Patient Reported Outcomes

Symptoms and Quality of Life

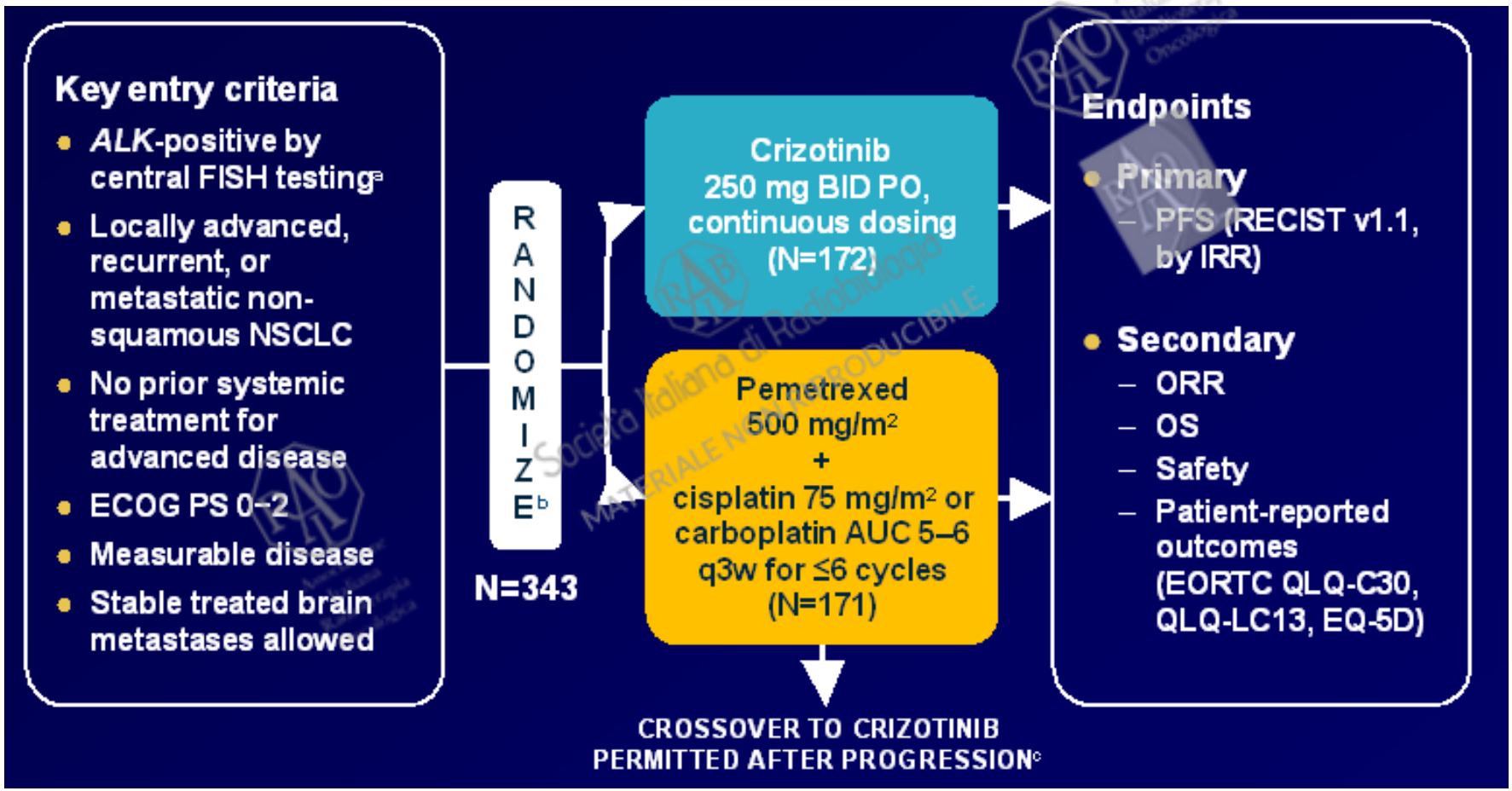
Symptoms: Greater improvement from baseline in cough, dyspnea, fatigue, alopecia, insomnia, and pain with Crizotinib (all p<0.0001)

Quality of life: Greater improvement from baseline in global quality of life in patients treated with Crizotinib (p<0.0001)



Shaw AT, N Engl J Med 2013; 368: 2385-94

PROFILE 1014 : Study Design



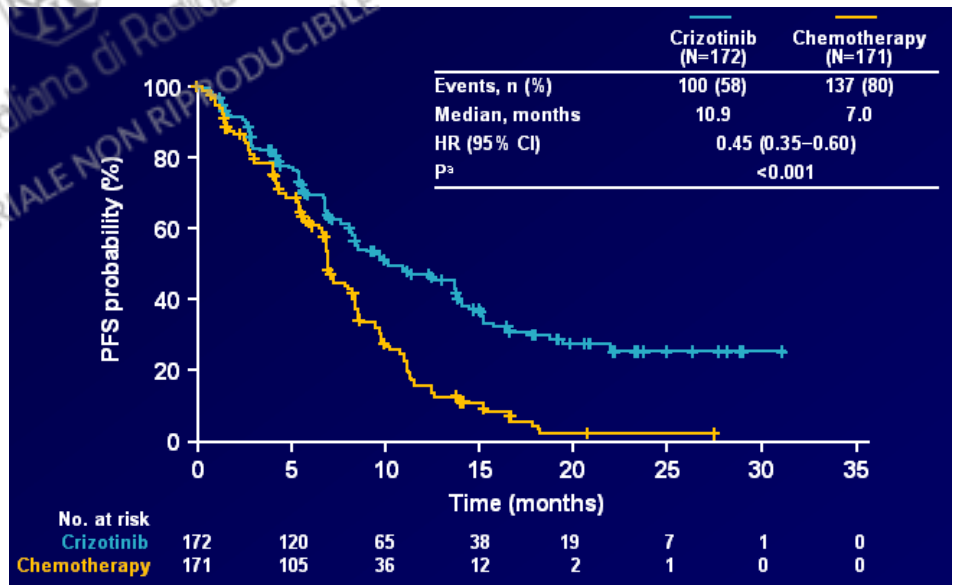
Solomon BJ, N Engl J Med 2014; 371:2167-77

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

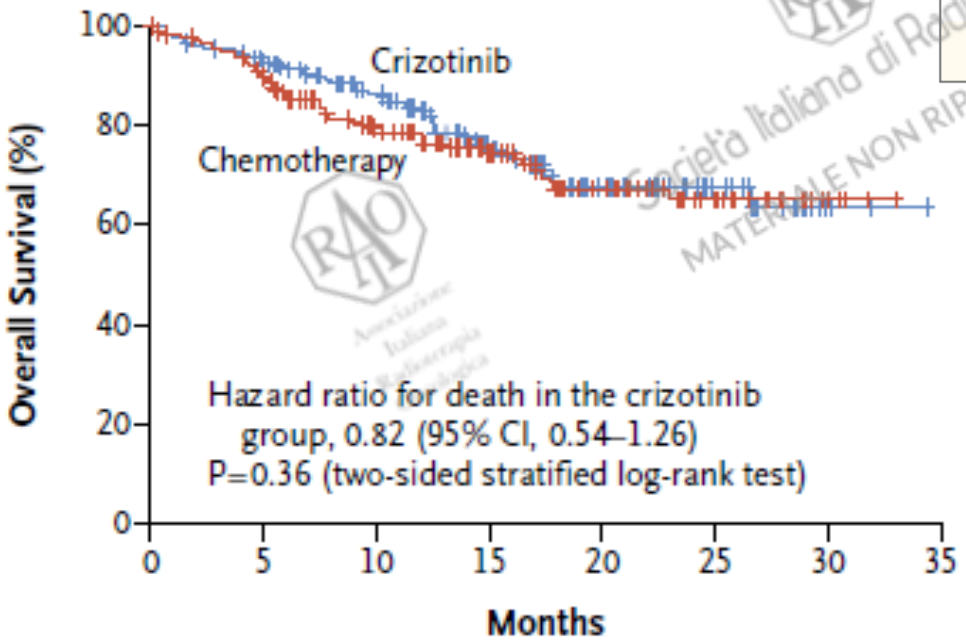
Primary Endpoint: PFS



Solomon BJ, N Engl J Med 2014; 371:2167-77

Response to Treatment

Response	Crizotinib (N=172)	Chemotherapy (N=171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)
Time to response — mo§		
Median	1.4	2.8
Range	0.6–9.5	1.2–8.5
Duration of response — mo¶		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

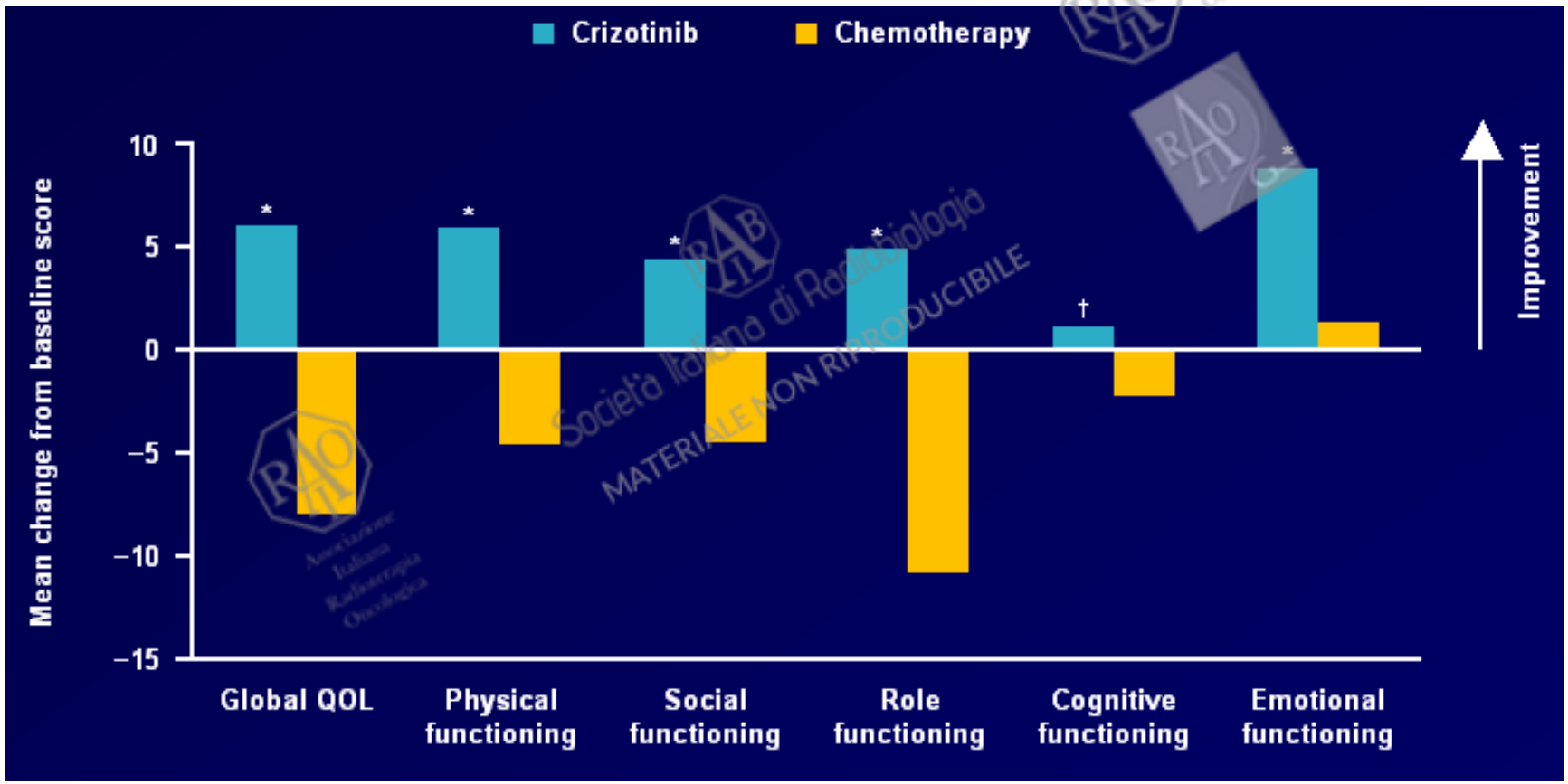


Overall Survival

Solomon BJ, N Engl J Med 2014; 371:2167-77

Patient Reported Outcomes

Global QoL and Functioning Domains (QLQ-C30)



Solomon BJ, N Engl J Med 2014; 371:2167-77

Mechanisms of Crizotinib resistance

Resistance Mechanisms	Patients N=69 (percent)
Secondary mutations in ALK kinase domain	20 (29)
L1196M	9
G1269A	7[a]
C1156Y	2
S1206Y	1
1151Tins	1
L1152R	1
G1202R	1
Amplification of rearranged ALK locus	6[b] (9)
No secondary ALK mutation or amplification	44 (64)

Choi YL et al, Katayama R et al, Doebele RC et al, Sasaki T et al, Gainor JF et al, Kim S et al, Huang D et al, Costa DB et al.

Multicenter Phase II Study of Whole-Body and Intracranial Activity With Ceritinib in Patients With *ALK*-Rearranged Non–Small-Cell Lung Cancer Previously Treated With Chemotherapy and Crizotinib: Results From ASCEND-2

140 patients enrolled

- Two or more prior lines of antineoplastic therapy, including platinum-based chemotherapy;
- all patients had experienced progression during crizotinib treatment.

Investigator-Assessed Intracranial Responses in Patients With Target Brain Lesions at Study Entry

Best overall response	No. (%) of Patients With Target Brain Lesions at Study Entry (n = 20)
CR	2 (10.0)
PR	7 (35.0)
SD	7 (35.0)
PD	3 (15.0)
UNK	1 (5.0)
OIRR*	9 (45.0)
IDCR*	16 (80.0)

Patients who experience progression in the brain during crizotinib treatment may benefit from subsequent treatment with an alternative ALK-targeted therapeutic.

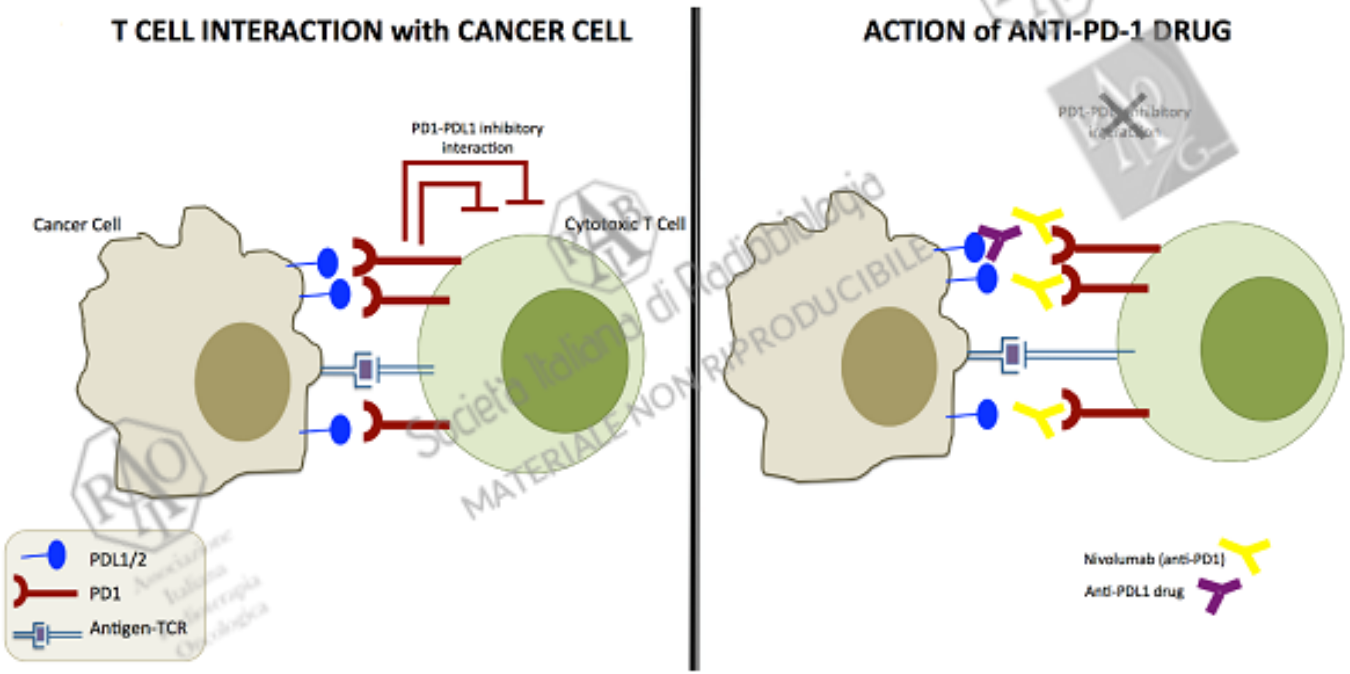
Crinò L, J Clin Oncol 2016; 34:2866-2873

Strategies to improve treatment effectiveness

Target Treatments according to:

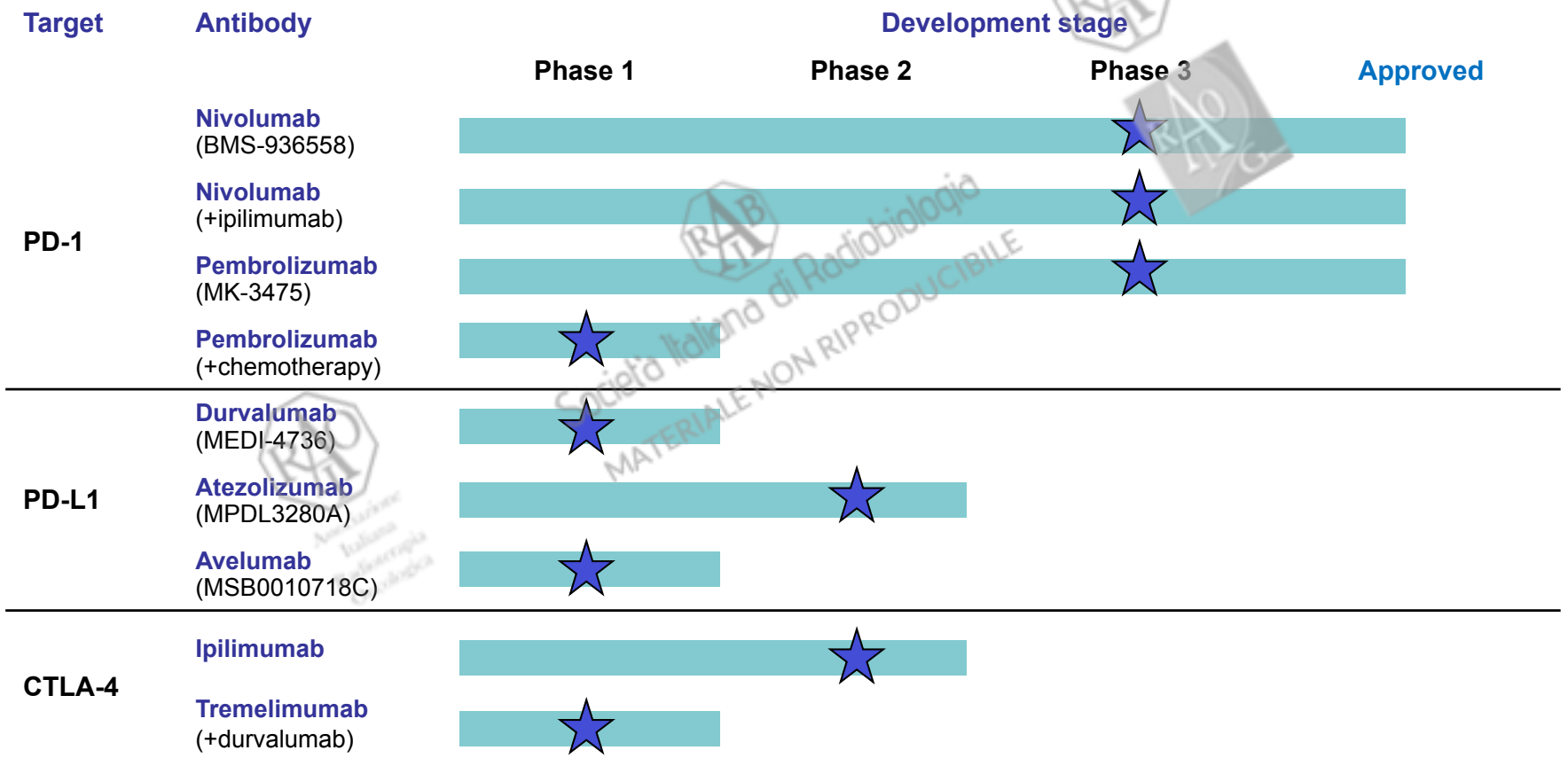
- Tumor histology (squamous vs non-squamous)
- Epidermal Growth Factor Receptor
- ALK mutations
- Immune checkpoints

Immunotherapy checkpoint inhibitors: the New Players in the NSCLC space



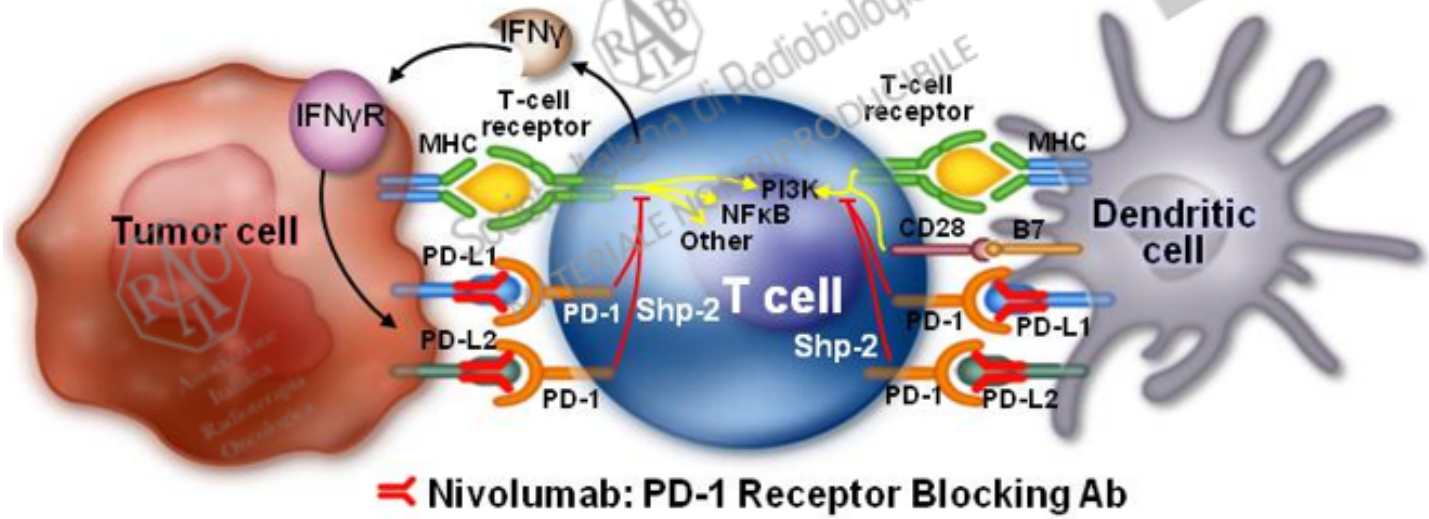
Checkpoint inhibitors: tumors express "checkpoint" proteins on their cell surface to escape detection from the immune system; targeted inhibition towards these receptors enhances T cell response towards the tumor

Immune checkpoint inhibitors in NSCLC



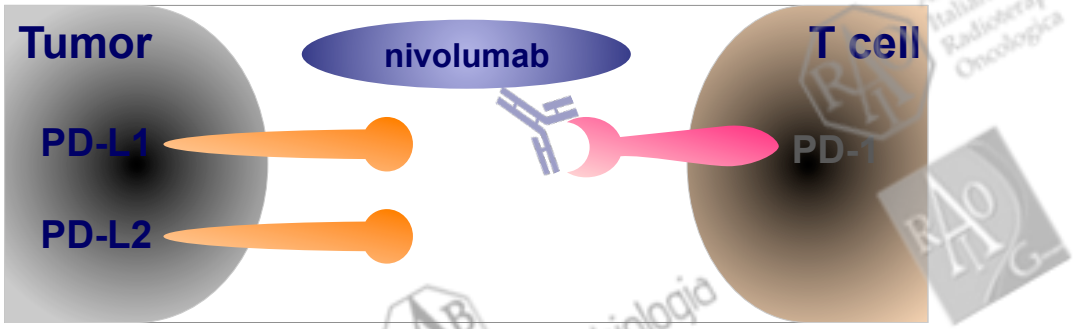
Nivolumab: mechanism of action

- PD-1 expression on tumor-infiltrating lymhocytes is associated with decreased cytokine production and effector function
- Nivolumab binds PD-1 receptors on T cells and disrupts negative signaling triggered by PD-L1/PD-L2 to restore T-cell antitumor function



Pardoll DM, Nat Rev Cancer 2012; 12(4):252-64

PD-L1 expression as a Potential Biomarker



- ✓ Expression of PD-L1 on tumor-infiltrating immune cells or tumor cells may potentially be used as a biomarker to predict anti-tumor response to PD-1 / PD-L1 inhibitors

- ✓ Several clinical trials are assessing the role of PD-L1 expression on the clinical activity of PD-1 / PD-L1 inhibitors to determine if higher expression correlates definitively with increased clinical activity.

Nivolumab

Approved for metastatic squamous and non-squamous NSCLC and progression on and after platinum-based chemotherapy

Efficacy Outcomes With Nivolumab

	ORR, %	mPFS, mo	mOS, mo	1-Year Survival, %	2-Year Survival, %*[d]
CheckMate 017 (squamous)					
Nivo (n = 131)	20	3.5	9.2	42	23
Doce (n = 129)	9	2.8	6.0	24	8
CheckMate 057 (non-squamous)					
Nivo (n = 287)	19	2.3	12.2	51	29
Doce (n = 268)	12	4.2	9.4	39	16

Brahmer J, N Engl J Med 2015; 373:123-135
Borghaei H, N Engl J Med 2015; 373:1627-2639
Borghaei H, J Clin Oncol 2016; 34(suppl):Abstract 9025

Pembrolizumab

- Metastatic NSCLC tumors that express PD-L1 and progression on or after platinum-based chemotherapy
- Studies performed with 2 or 10 mg/kg (doses similar with regards to toxicity and efficacy)

Efficacy Outcomes From KEYNOTE-010

	Overall		≥ 50% PD-L1	
Outcome	Pembro* n = 345	Doce n = 343	Pembro* n = 139	Doce n = 152
ORR, %	18	9	30	8
mOS, mo	10.4	8.5	14.9	8.2
1-year OS, %	43.2	34.6		
mPFS, mo	3.9	4.0	5	4.1

Herbst RS, Lancet 2016; 387:1540-1550

Toxicity with checkpoint inhibitors

	CheckMate 017		CheckMate 057		KEYNOTE-010	
TRAE, %	Nivo n = 131	Doce n = 129	Nivo n = 287	Doce n = 268	Pembro* n = 339	Doce n = 309
Any event	58	86	69	88	63	81
Any grade 3-4	7	55	10	54	13†	35†
Fatigue	16	33	16	29	14	25
Decreased appetite	11	19	10	16	14	16
Asthenia	10	14	10	18		
Nausea	9	23	12	26	11	15
Diarrhea	8	20	8	23	7	18
Pneumonitis	5	0	3	< 1	5	2
Rash	4	6	9	3	9	5
Hypothyroidism	4	0	7	0	8	< 1
Hyperthyroidism					4	1

Key points regarding Toxicity

- Toxicity with checkpoint inhibitors is different than with standard chemotherapy
- Side effects are potentially time sensitive
  - Pneumonitis onset can be rapid
  - Diarrhea or colitis could be an issue
- Presentation of side effects can be subtle
  - Examples include insidious fatigue, decreased appetite, and endocrinopathies
  - Monitor TSH monthly for hyperthyroidism and hypothyroidism

Concluding Remarks

- There are now many options for patients with lung cancer
- Recent advances in the understanding of NSCLC biology have revealed a number of 'targetable' alterations that underlie cancer growth and survival in specific patients subgroups.
- Checkpoint inhibitors have a favorable toxicity profile
- Multiple combinations with checkpoint inhibitors and chemotherapy are currently being pursued and the results are eagerly waited.