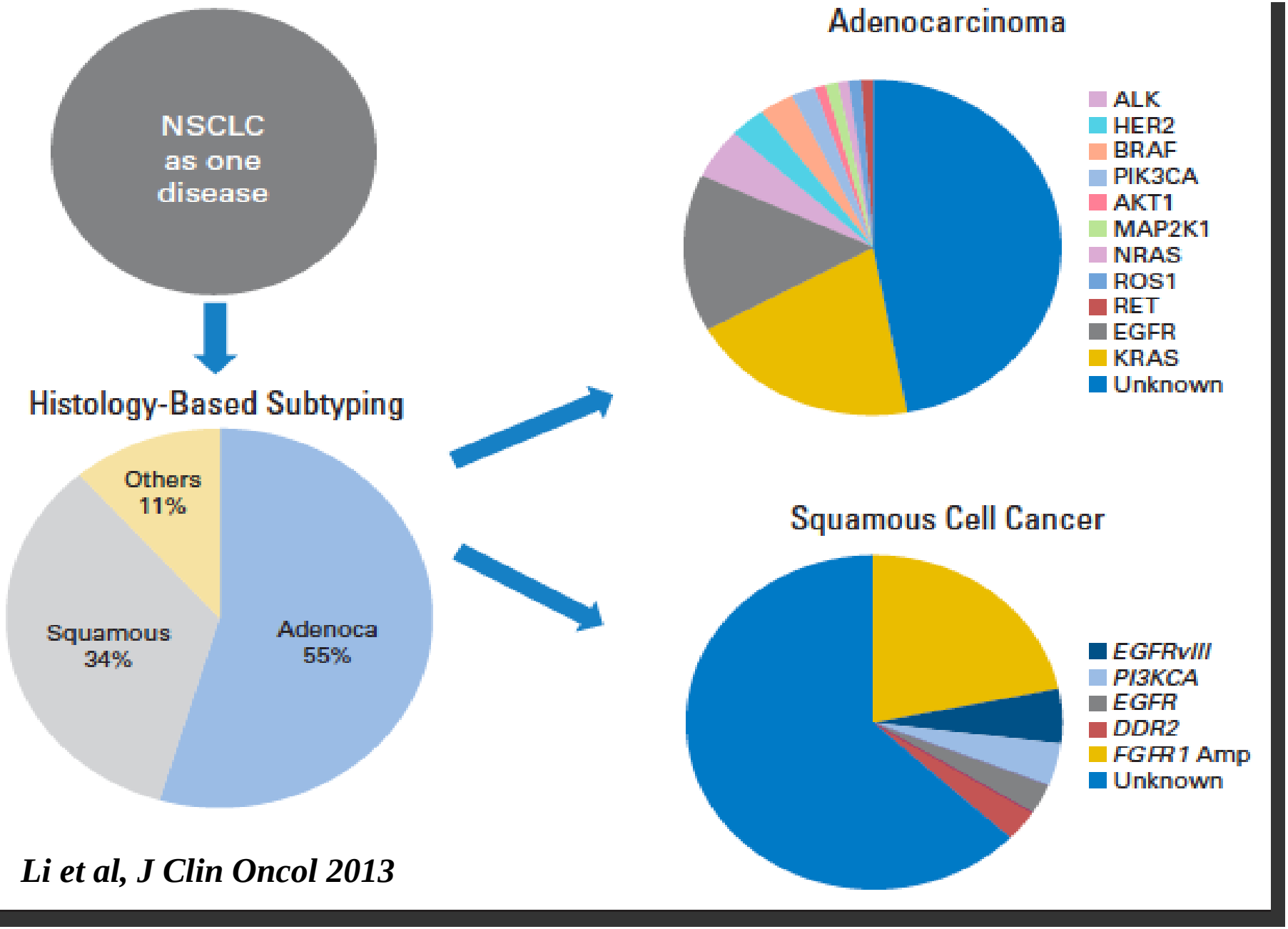
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Martedì dell'Ordine
Ordine dei Medici di Parma, 25.09.2015

Farmaci biologici nelle neoplasie polmonari

Dott. Marcello Tiseo
Oncologia Medica
Coordinatore PDTA Oncologia Toracica
Azienda Ospedaliero-Universitaria Parma



Li et al, J Clin Oncol 2013

Farmaci biologici nel NSCLC

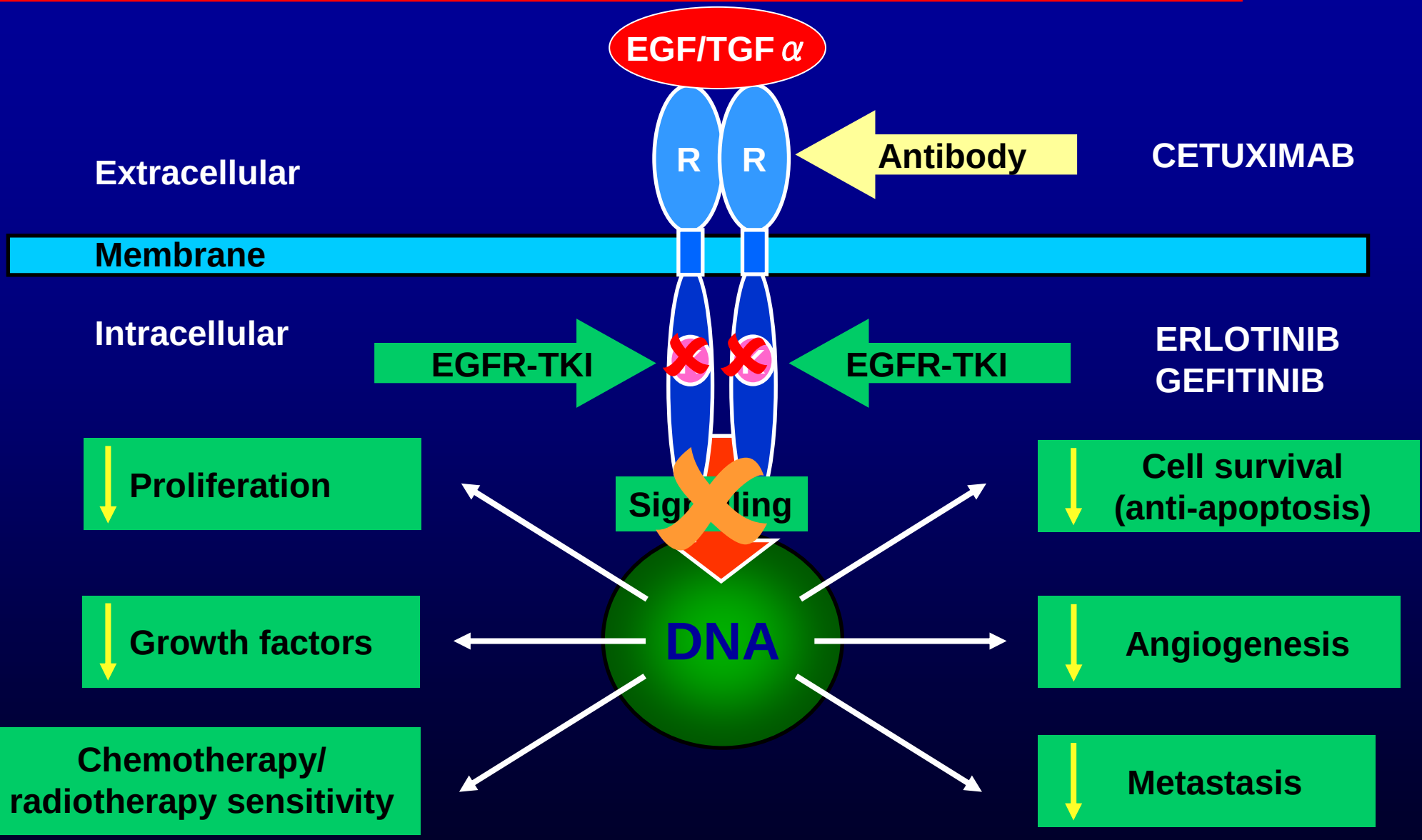
- EGFR-TKIs nei NSCLC EGFR mutati
- ALK-TKIs nei NSCLC ALK positivi
- Altri target molecolari
- Immunoterapia
- Farmaci anti-angiogenetici

Farmaci biologici nel NSCLC

- EGFR-TKIs nei NSCLC EGFR mutati
- ALK-TKIs nei NSCLC ALK positivi
- Altri target molecolari
- Immunoterapia
- Farmaci anti-angiogenetici

EGFR e strategie di inibizione

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma



Baselga et al, Drugs 2000; Baselga et al, J Clin Oncol 2000; Hidalgo et al, J Clin Oncol 2001

Fattori clinici predittivi della risposta a EGFR-TKIs

Group	Response	p value	Study
Female vs Male	19% vs 3%	0.001	IDEAL 2
Japanese vs Caucasian	27.5% vs 10.4%	0.0023	IDEAL 1
Adenocarcinoma vs Others	13% vs 4%	0.046	IDEAL 2
Non-smokers vs Former/current	36% vs 8%	< 0.001	MSKCC

Fukuoka et al, JCO 2003; Kris et al, JAMA 2003; Miller et al, JCO 2003

Fattori biologici predittivi della risposta a Gefitinib

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Characteristics ($n = 91$)	CR + PR n (%)	SD + PD n (%)	p
EGFR gene mutations, $n = 63$			
Mutated	9 (82)	2 (18)	<0.001
Wild-type	5 (10)	47 (90)	
K-ras gene mutations, $n = 63$			
Mutated	0 (0)	7 (100)	0.333
Wild-type	14 (25)	42 (75)	
EGFR FISH, $n = 54$			
Positive	6 (50)	6 (50)	0.016
Negative	6 (14)	36 (86)	
HER2 FISH, $n = 58$			
Positive	2 (18)	9 (82)	1.000
Negative	11 (23)	36 (77)	
EGFR IHC, $n = 59$			
Positive	11 (24)	34 (76)	0.260
Negative	1 (7)	13 (93)	
EGFR intron 1 polymorphism, $n = 76$			
$(CA)_{16}$ genotype	14 (25)	42 (75)	0.211
$(CA)_{else}$ genotype	2 (10)	18 (90)	

Tiseo et al, Lung Cancer 2010

Mutazioni di EGFR

- Mutazioni attivanti con aumento dell'attività recettoriale indipendente dal ligando
- 90% riguardano esoni 19 (delezione) e 21 (LB58R)
- Incidenza globale: 10% caucasici; 30-40% asiatici
- Popolazione: never-smoker o light-smoker
- Più frequenti nel sesso femminile
- Istotipo principale: adenocarcinoma (in particolare BAC non mucinoso)
- Fattore altamente predittivo di risposta agli EGFR-TKIs (in studi retrospettivi e prospettici)

Tiseo et al, Drug Des Devel Ther 2011

IPASS: Study design

Patients

- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB / IV disease

Gefitinib (250 mg / day)

1:1 randomisation

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly#

Endpoints

Primary
- Progression-free survival (non-inferiority)

Secondary
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

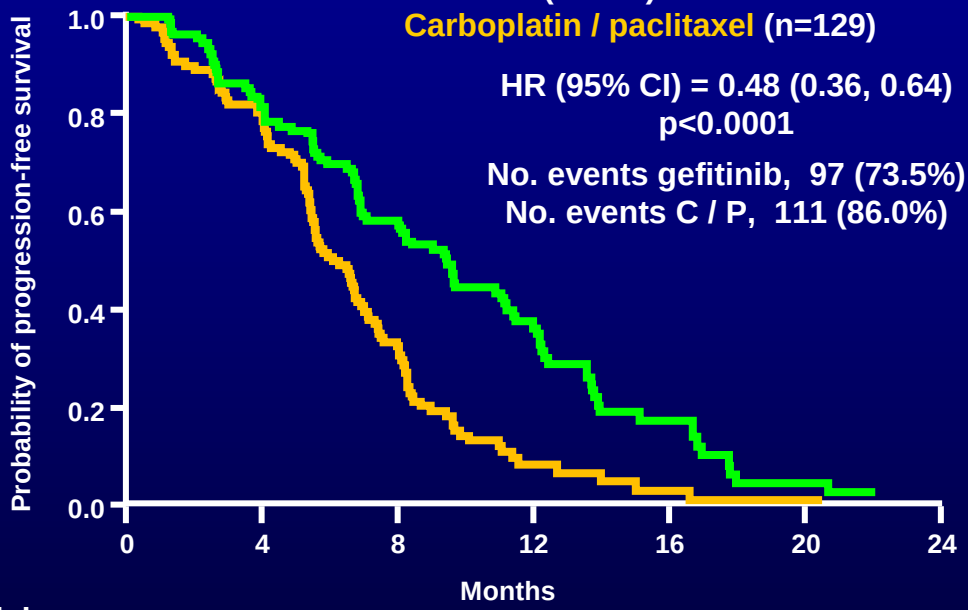
Exploratory
- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

Mok et al, NEJM 2009

Progression-free survival in EGFR mutation positive and negative patients

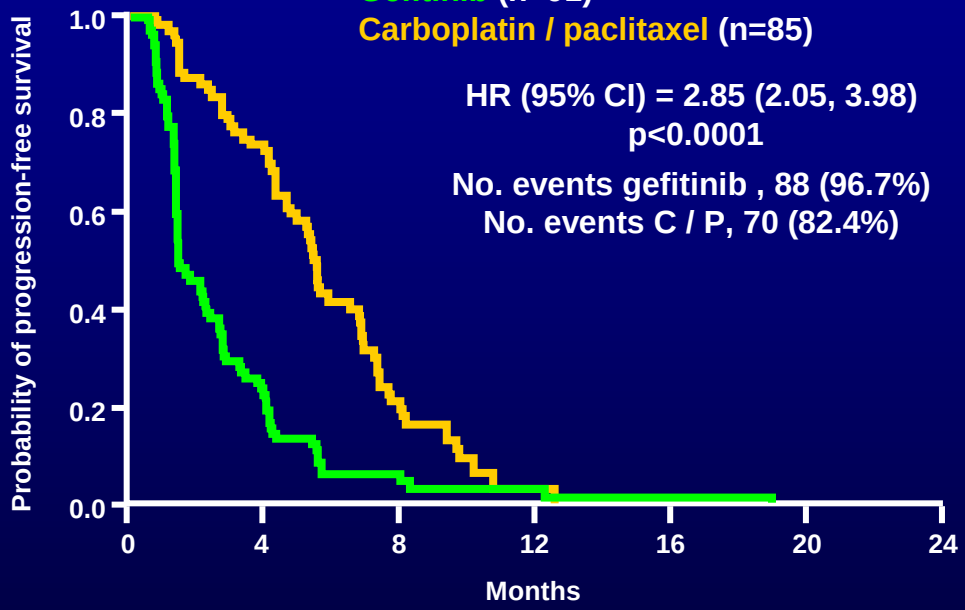
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

EGFR mutation positive



At risk :							
Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

EGFR mutation negative



	91	21	4	2	1	0	0
	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok et al, NEJM 2009

EGFR-TKI vs. CT in I linea in EGFR mutati

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Study	N (EGFR mut+)	RR (%)	Median PFS (Months)	Median OS (Months)

- Tasso di risposte doppio
- PFS doppio
- Effetto rapido, migliore controllo dei sintomi
- Effetto indipendente da età, PS, comorbidità
- Minore tossicità
- Somministrazione orale

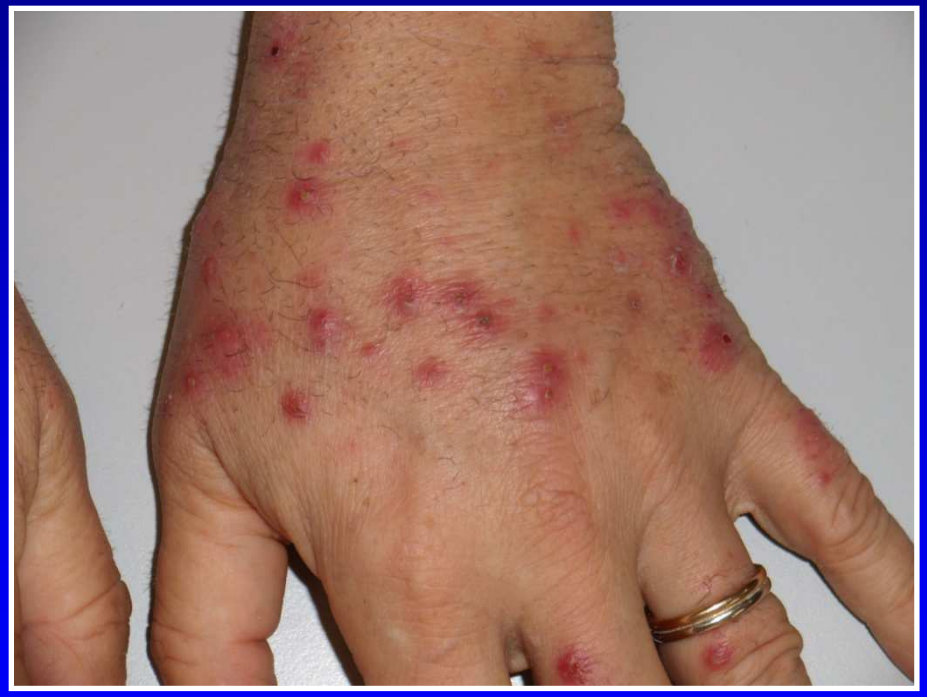
1. Mok TS et al. *N Engl J Med* 2009;361:947–957; 2. Fukuoka M et al. *J Clin Oncol.* 2011;29:2866–2874; 3. Han JY et al. *J Clin Oncol*. 2012;30:1122–1128; 4. Mitsudomi T et al. *Lancet Oncol* 2010;11:121–128; 5. Yoshioka H et al. ASCO 2014 Abstract 8117; 6. Maemondo M, et al. *N Engl J Med* 2010; 24:362:2380–2388; 7. Inoue A et al. *Ann Oncol*. 2013; 24:54–59.; 8. Zhou C et al. *Lancet Oncol*. 2011;12:735–742.; 9. Zhou C et al. ASCO 2012 Abstract 7520; 10. Rosell R et al. *Lancet Oncol*. 2012;13:239–246.; 11. Costa C et al. *Clin Cancer Res.* 2014;20:2001–2010; 12. Sequist LV et al. *J Clin Oncol.* 2013 31:3327–3334; 13. Yang JC-H, et al ASCO 2014 Abstract 8004; 14. Wu YL et al. ASCO 2013 Abstract 8016.

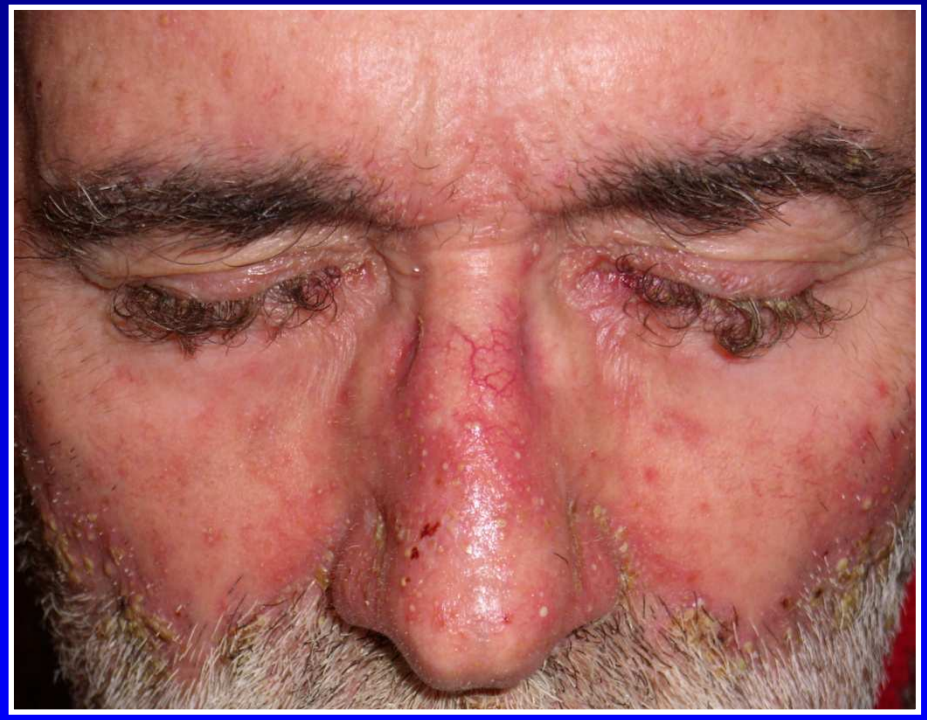
Mutazioni di EGFR e TKIs: stato dell'arte 2015

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

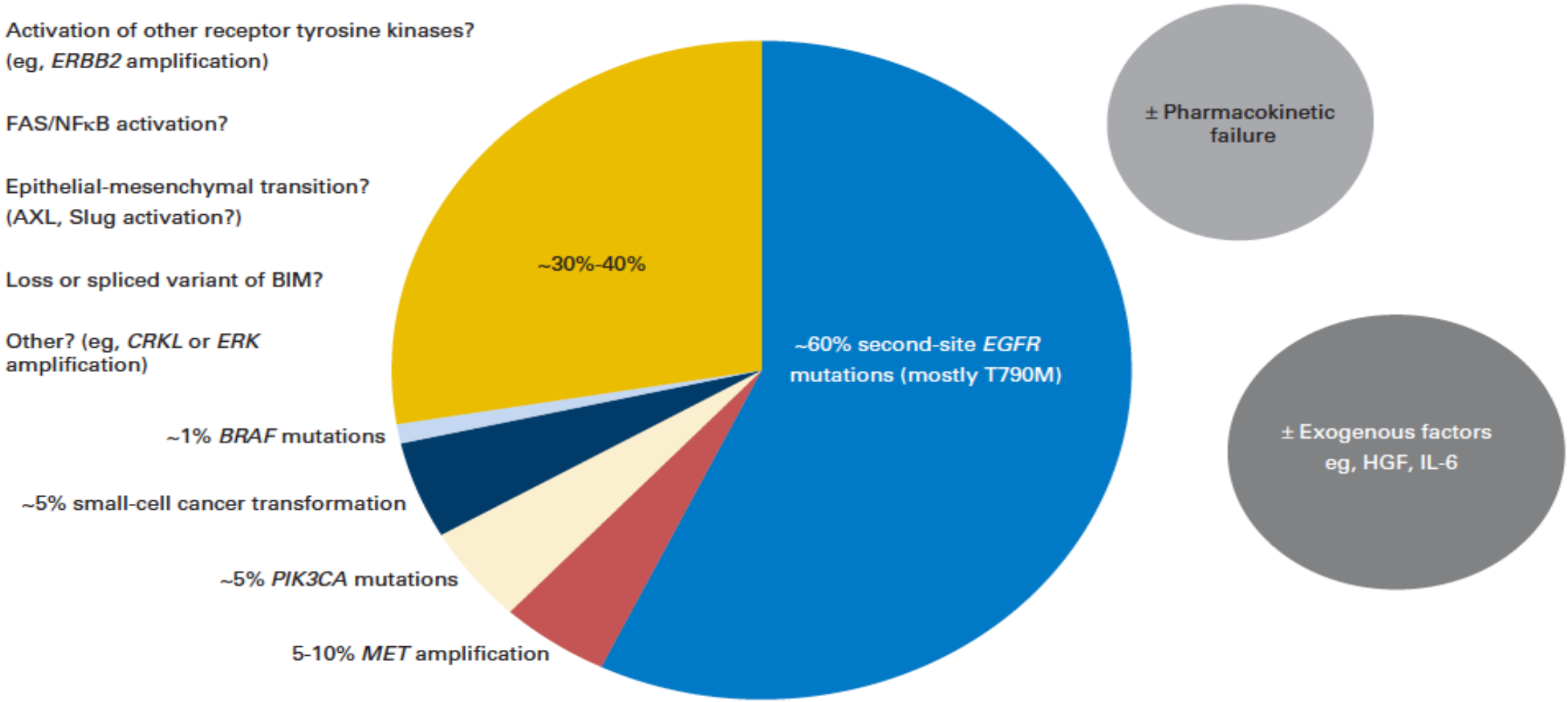
- **Netto impatto in sopravvivenza**: 2-3 anni
- 8 studi random di I linea vs CT
  - TKI > CT in RR (60-70%), PFS (9-13 mesi), QoL
- 3 TKIs in I linea (**Gefitinib, Erlotinib, Afatinib**)
  - non disponibili confronti diretti di fase III
- Efficacia in qualunque linea di terapia
- **Tossicità peculiari** (diarrea e tossicità cutanea)
- **Instaurarsi di resistenza**: differenti meccanismi e diverse potenziali strategie

Tossicità cutanea da EGFR-TKI





Meccanismi di resistenza a EGFR-TKIs



Ohashi et al, J Clin Oncol 2013

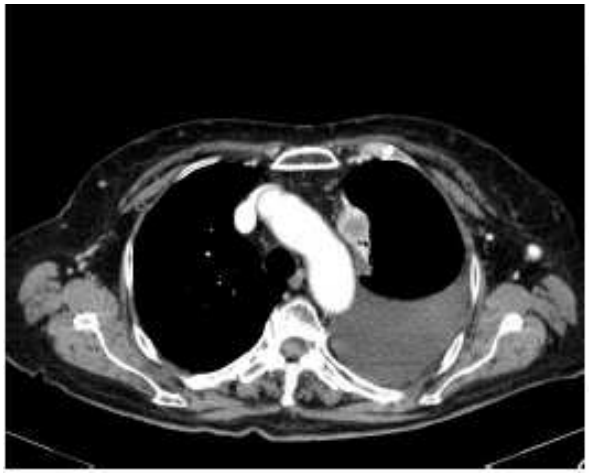
EGFR inibitori di terza generazione

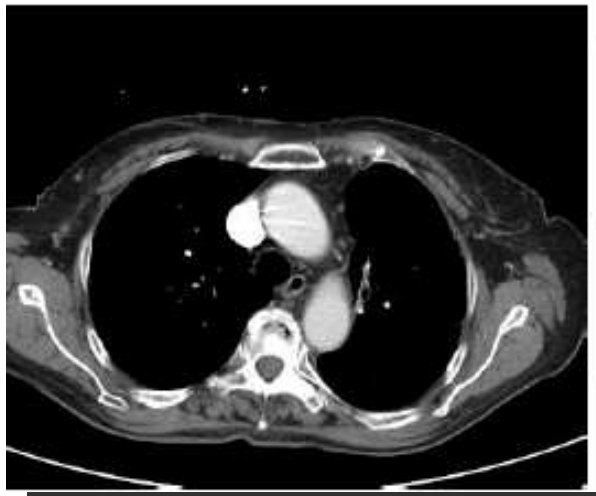
Drug	N	T790M+ RR (%)	T790M- RR (%)	PFS
HM61713[1]	83	29%	12%	4.3 mesi
CO1686[2]	72	59%	29%	13.1mesi T790M+ 5.6 mesi T790M-
AZD9291[3]	127	61%	21%	9.6 mesi T790M+ 2.8 mesi T790M-

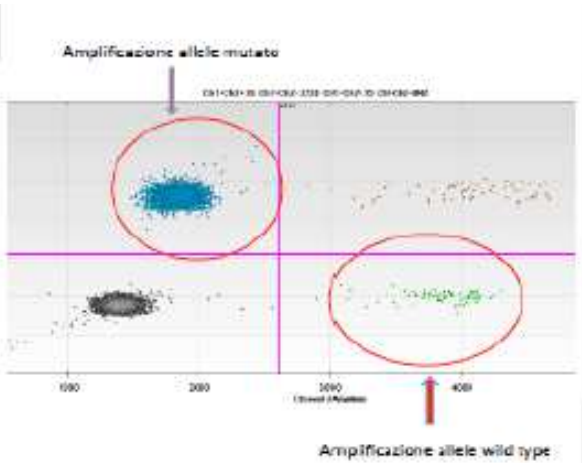
Compounds selectively target EGFR T790M that are 30- to 100-fold more potent against EGFR T790M and up to 100-fold less potent against WT EGFR

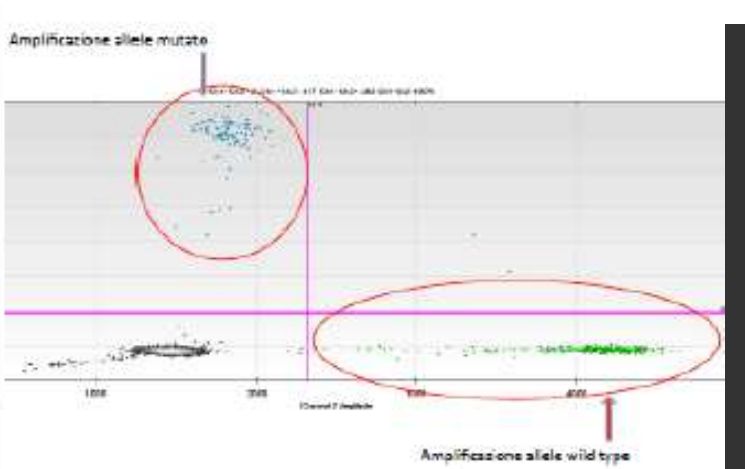
[1]Kim et al, ASCO 2014
[2]Sequist et al, NEJM 2015
[3]Janne et al, NEJM 2015

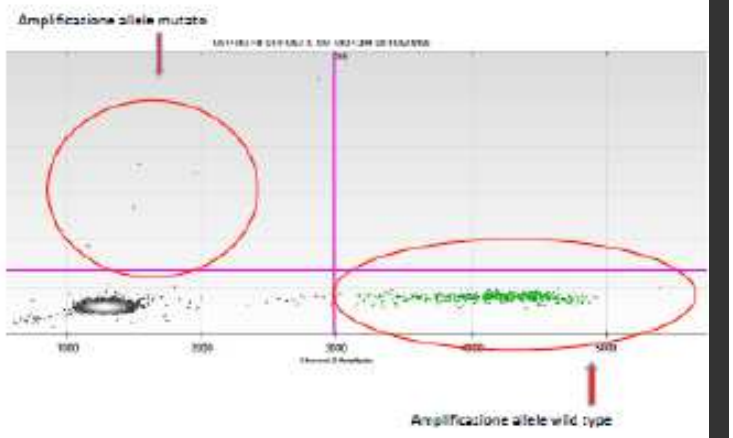
Paziente con ADK EGFR L858R + con T790M, in risposta a AZD9291 (dopo Gefitinib per 2 anni e CT per 6 cicli)











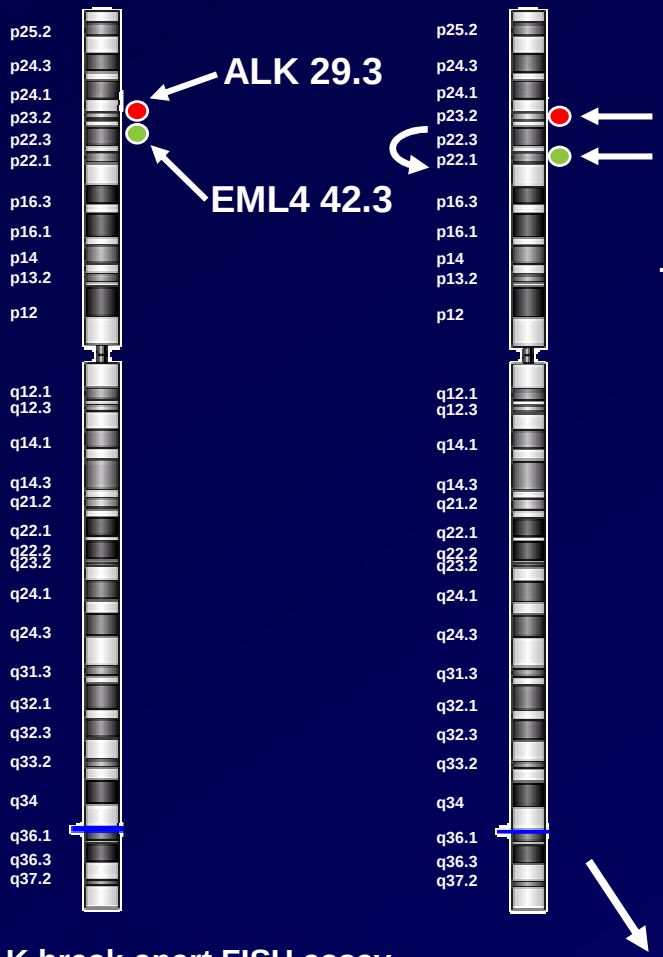
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Farmaci biologici nel NSCLC

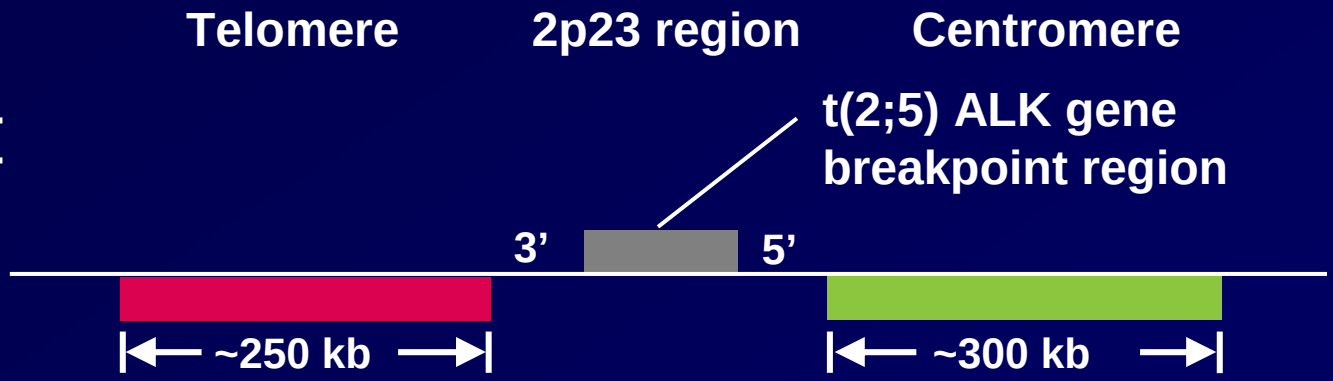
- EGFR-TKIs nei NSCLC EGFR mutati
- ALK-TKIs nei NSCLC ALK positivi
- Altri target molecolari
- Immunoterapia
- Farmaci anti-angiogenetici

FISH Assay for *ALK* Rearrangement

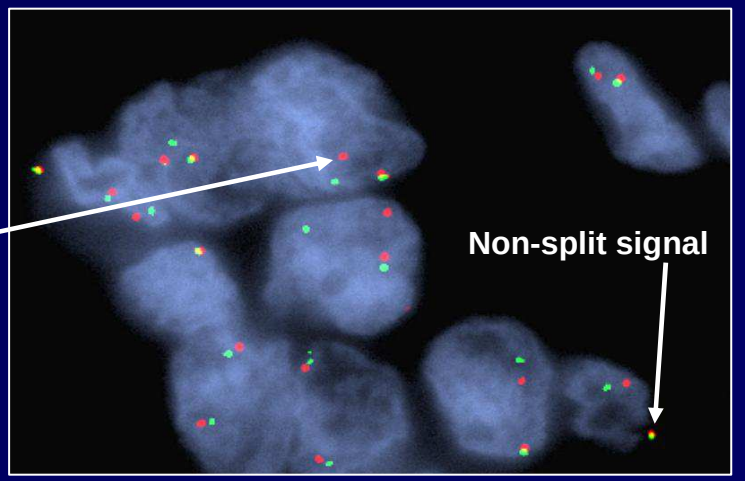
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma



ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]



Break-apart FISH assay for *ALK*-fusion genes[1]



Assay is positive if rearrangements can be detected in ≥15% of cells

FISH = fluorescence in situ hybridization

Shaw AT et al. J Clin Oncol 2009

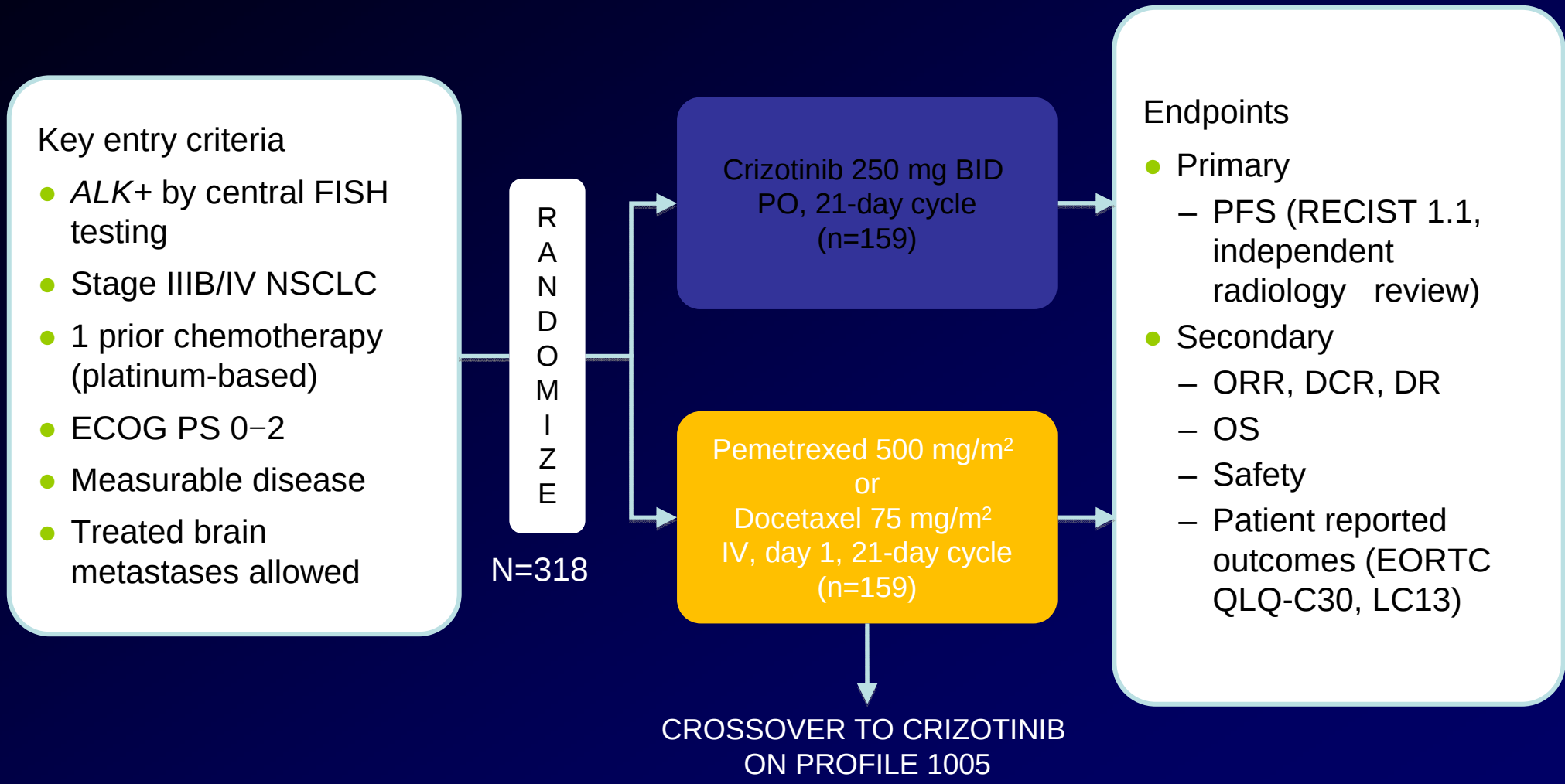
ALK rearrangements: clinico-pathologic characteristics

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

- Global incidence: ~ 5%; + EML4-ALK translocation
- Determination with FISH (and with IHC)
- ++ never-smoker or light-smoker; ++ young pts
- Similar incidence in Caucasians and Asiatic pts
- ++ adenocarcinoma with acinar o solid patterns (in particular signet ring-type cells)
- In general mutually exclusive with EGFR and K-ras mutations
- Factor of EGFR-TKI resistance; data of higher response to pemetrexed

Tiseo et al, Expert Rev Anticancer Ther 2011

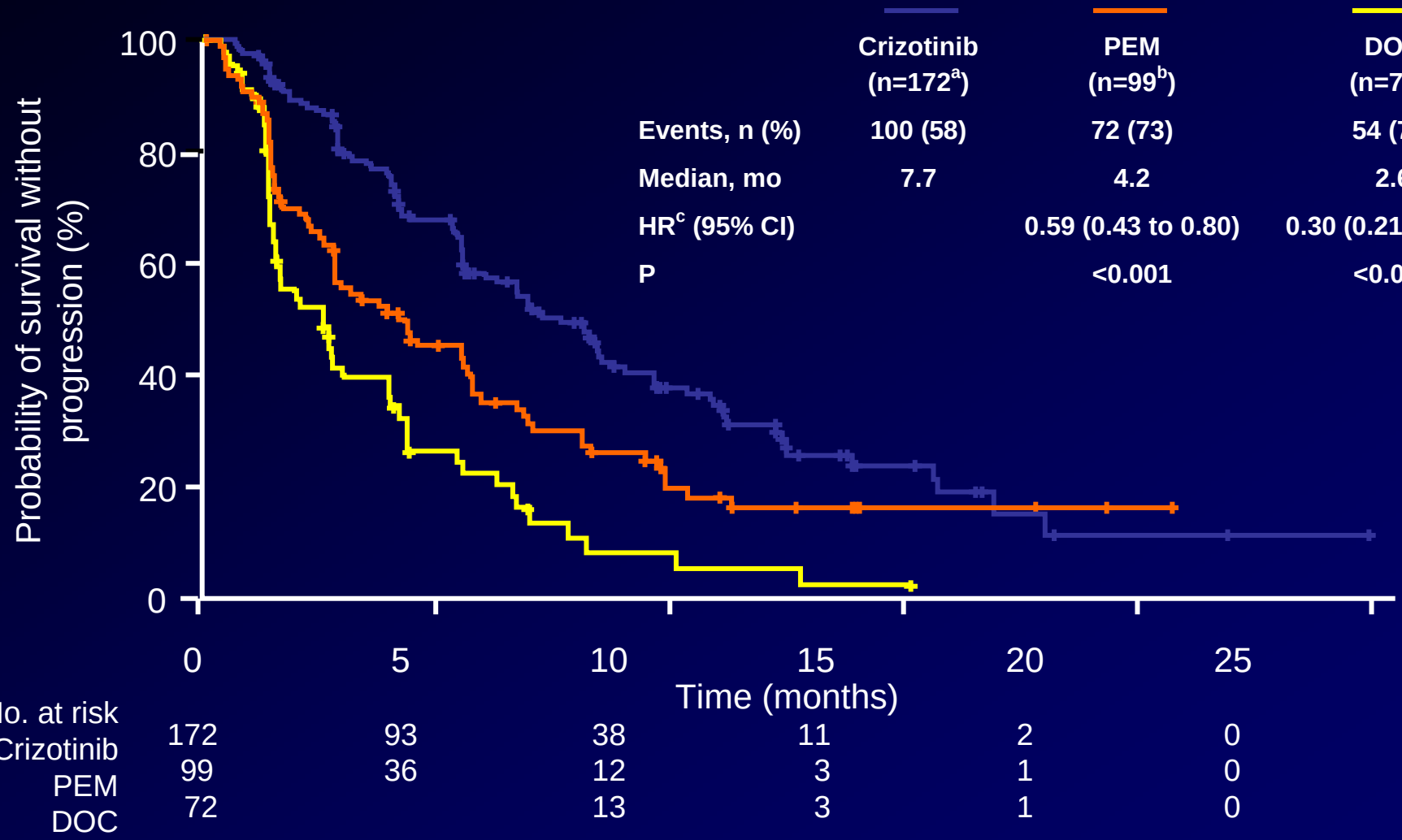
PROFILE 1007: Study Design



[a]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

Shaw et al. NEJM 2013

PFS of Crizotinib vs Pemetrexed or Docetaxel

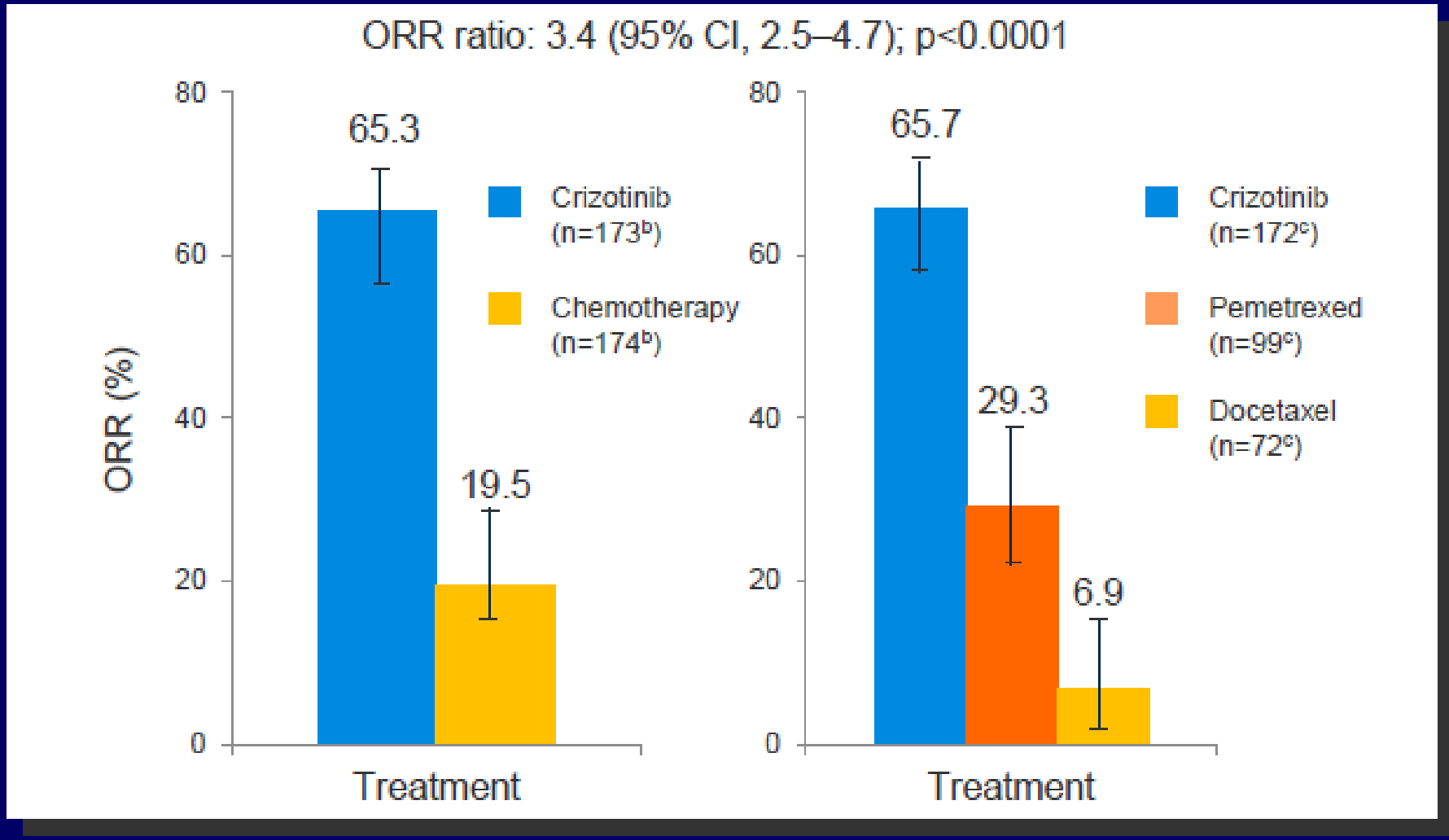


	Crizotinib (n=172[a])	PEM (n=99[b])	DOC (n=72[b])
Events, n (%)	100 (58)	72 (73)	54 (75)
Median, mo	7.7	4.2	2.6
HR[c] (95% CI)		0.59 (0.43 to 0.80)	0.30 (0.21 to 0.43)
P		<0.001	<0.001

[a]Excludes 1 patient who did not receive study treatment; [b]excludes 3 patients in chemotherapy arm who did not receive study treatment; [c]vs crizotinib

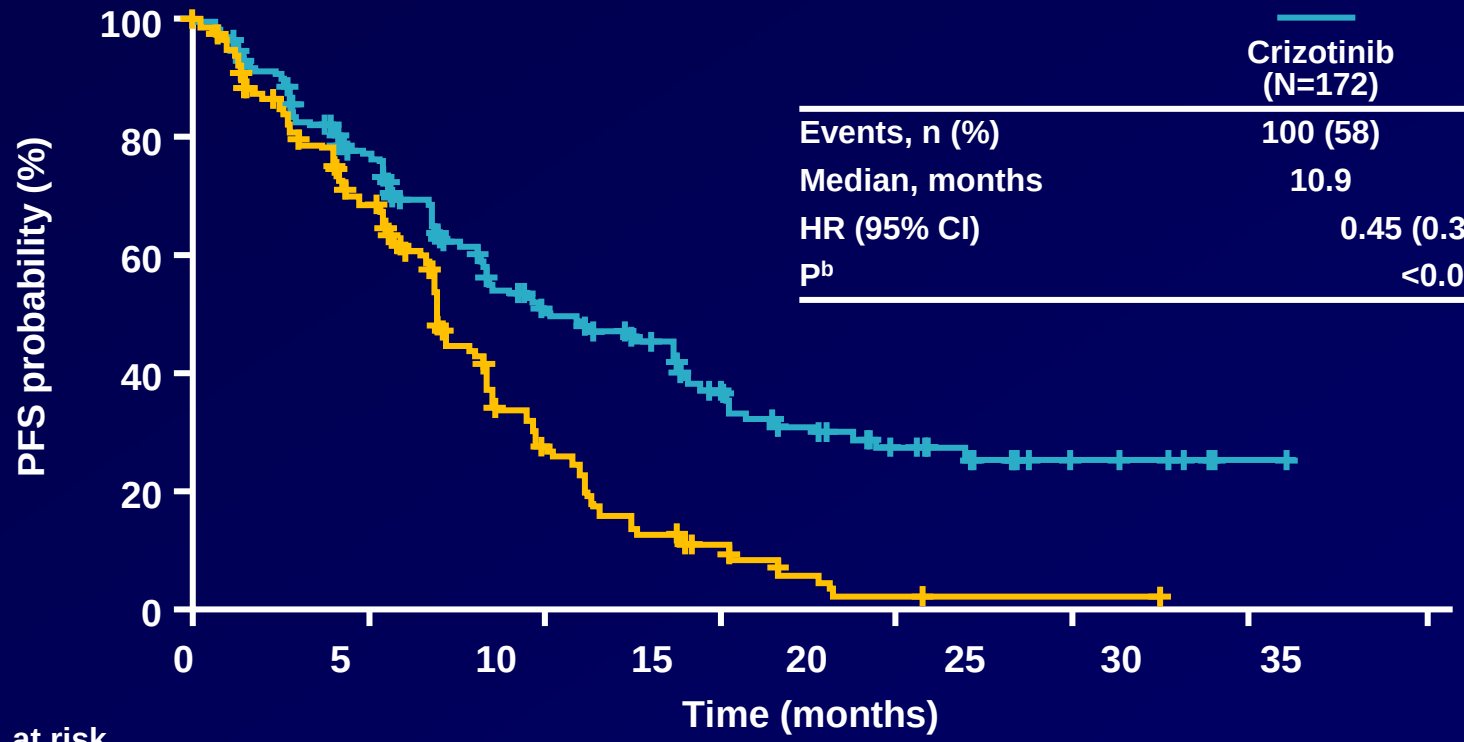
Shaw et al. NEJM 2013

PROFILE 1007: ORR
by independent radiological review (ITT)



Shaw et al. NEJM 2013

PROFILE 1014: Crizotinib Superior to Plat-Pem CT in PFS – 1st line



	Crizotinib (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35–0.60)	
P[b]	<0.0001	

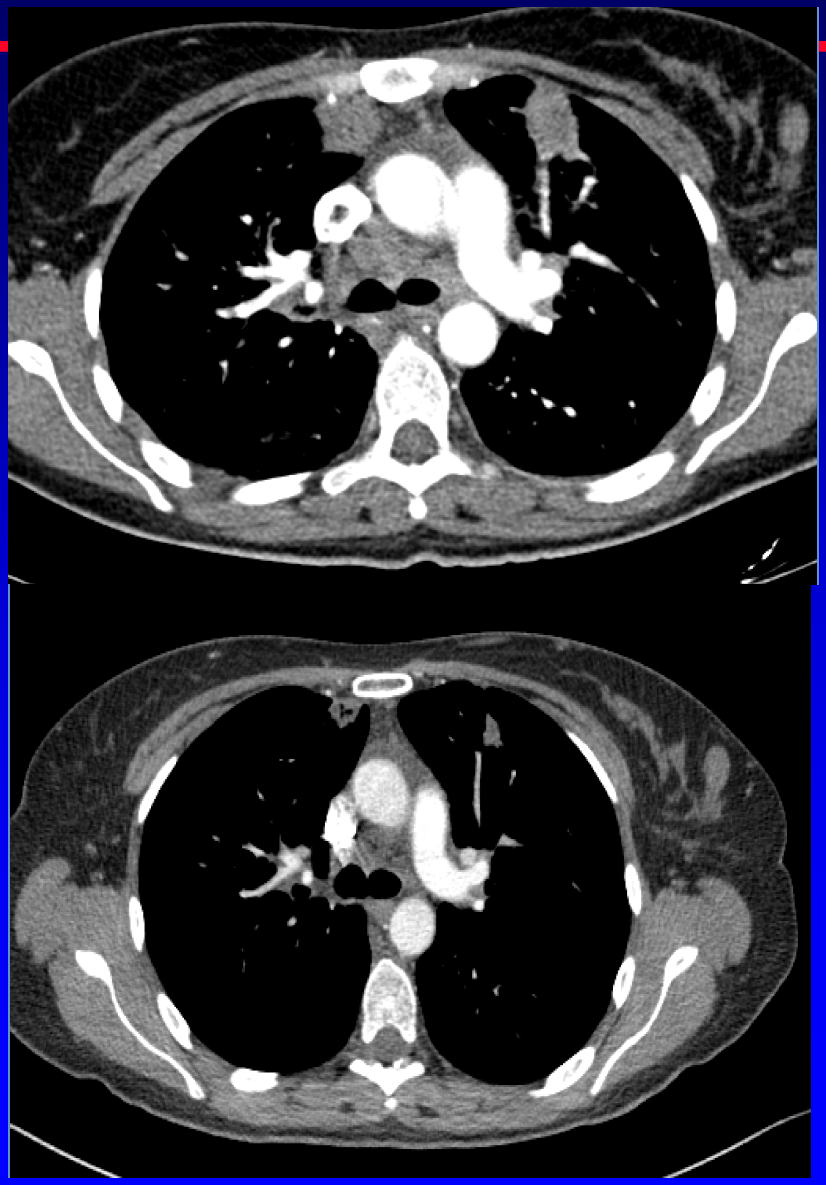
No. at risk								
Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

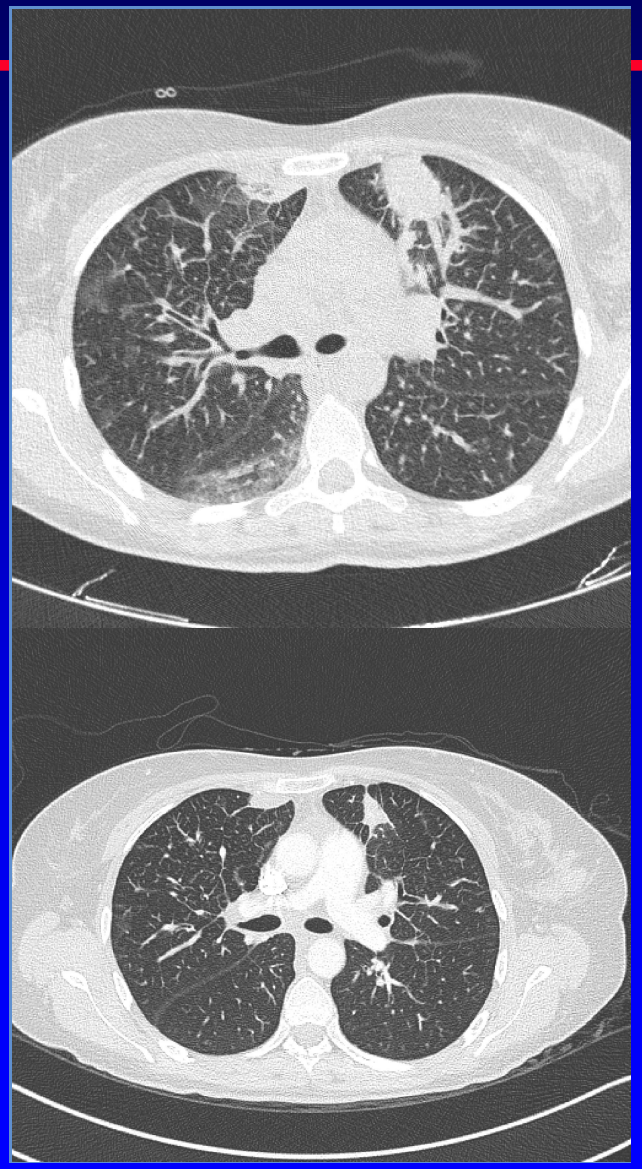
Data cutoff: November 30, 2013
[a]Assessed by IRR
[b]1-sided stratified log-rank test

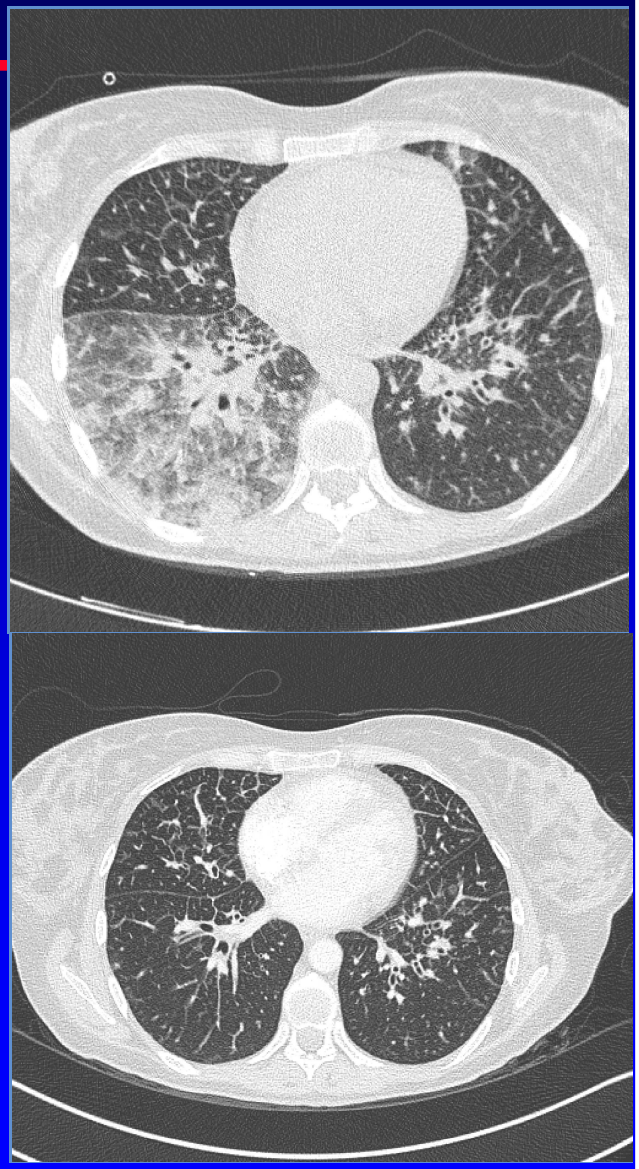
Mok et al, ASCO 2014 and Solomon et al, NEJM 2015

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Risposta dopo 15 giorni con crizotinib







Riarrangiamento di ALK e terapia con Crizotinib

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

- Crizotinib ha dimostrato di superare l'efficacia della CT in seconda e prima linea
- Efficacia in qualunque linea di terapia
- Registrato al momento in seconda linea in Italia
- Tossicità peculiari (per es. disturbi visivi)
- Spesso proseguire oltre la progressione strumentale
- Frequente progressione cerebrale
- Instaurarsi di resistenza dopo circa 9-10 mesi

Crizotinib: most common treatment-related AEs*

Table 1 | Common adverse events attributed to crizotinib

Common treatment-related adverse events*	Proportion of patients affected (%)
Vision disorder‡	62
Nausea	53
Diarrhoea	43
Vomiting	40
Constipation	27
Decreased appetite	19
Oesophageal disorders	11
Oedema	28
Fatigue	20
Dizziness	16
Neuropathy	13
Dysgeusia	12
Rash	10
Increased alanine aminotransferase levels	13

*Treatment-related adverse events (all grades) occuring in ≥10% of patients.[4,5,49,91] ‡Usually involving brief light trails, flashes or image persistence occurring at the edges of the visual field; most commonly, these occur in association with light adaptation.

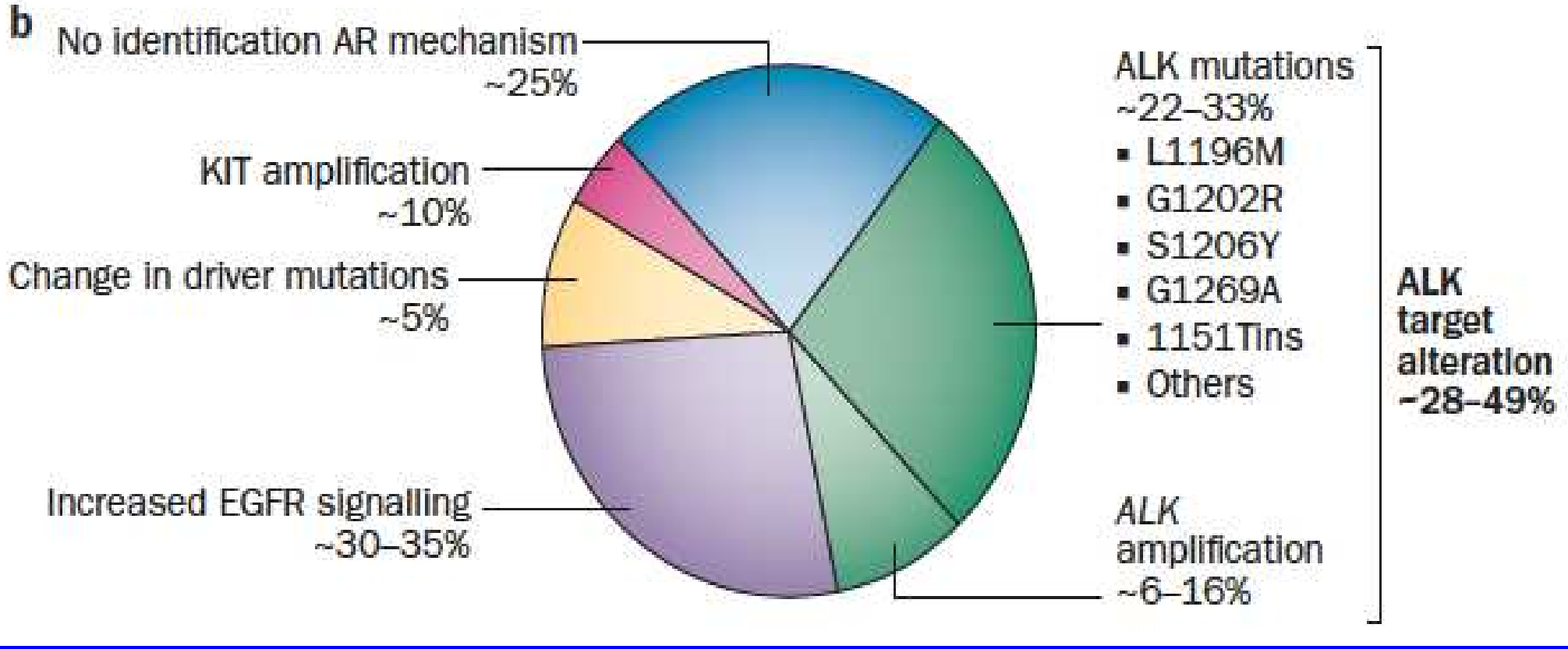
Table 2 | Other adverse events attributed to crizotinib

Characteristic treatment-related adverse events[52,53]	Anticipated frequency
Renal cysts[91]	Rare
Asymptomatic bradycardia	Frequency unknown
Rapid onset low testosterone in men	Common

*AE occurring in ≥ 10% of patients

Camidge & Doebele. Nat. Rev. Clin. Oncol 2012

Resistenza a Crizotinib



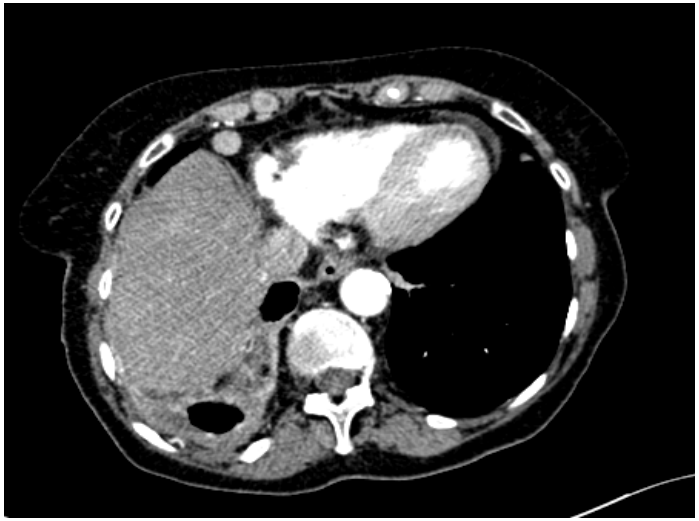
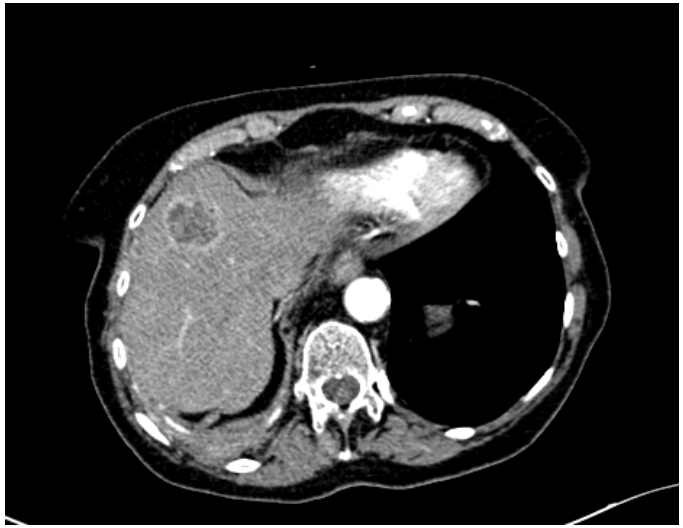
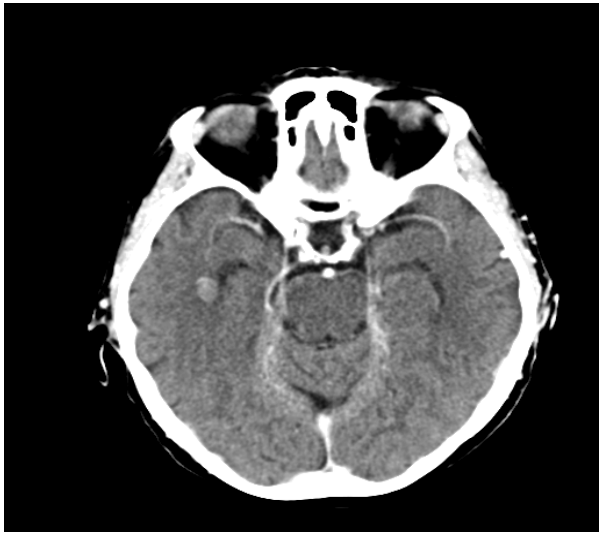
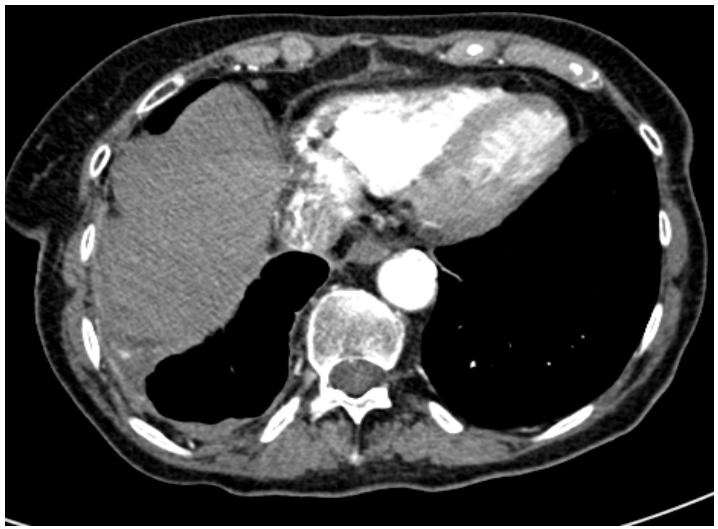
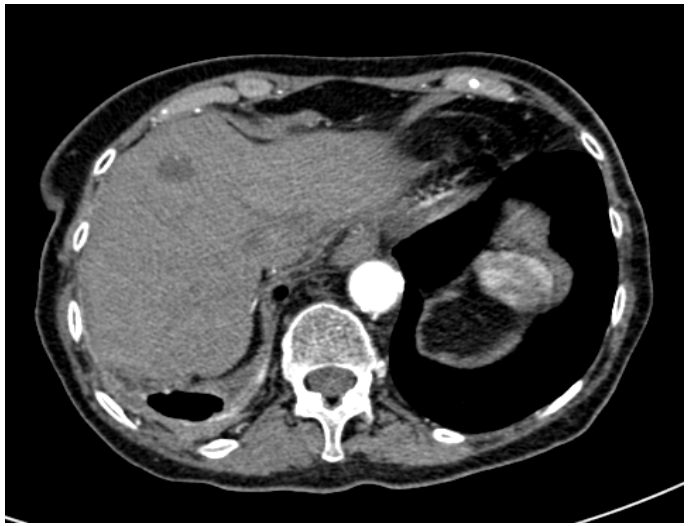
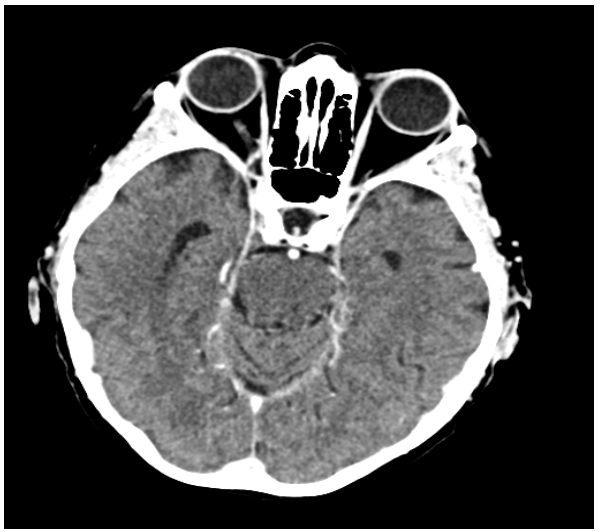
Camidge et al, Nature Reviews 2014

ALK inibitori di seconda generazione

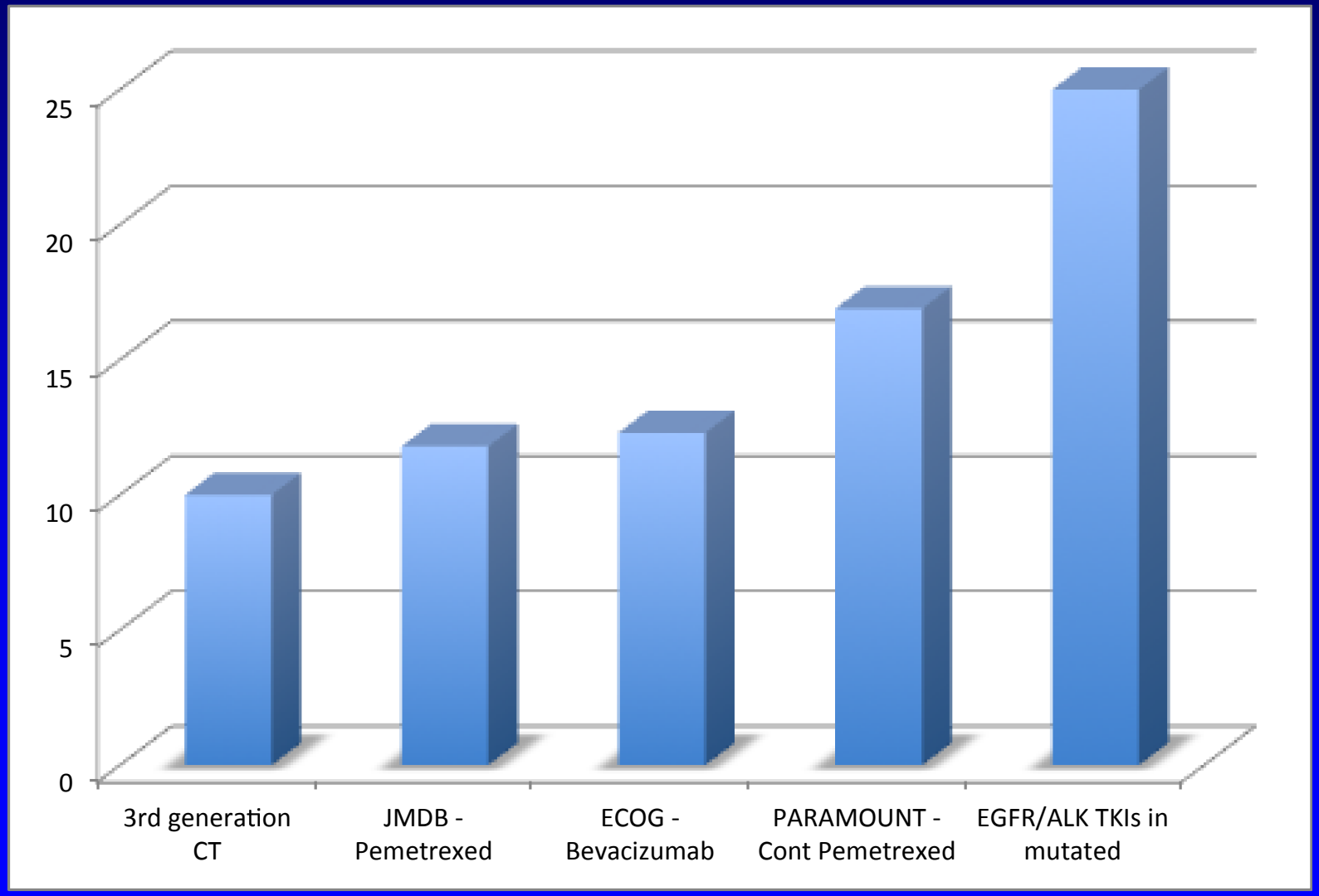
Drug	Company	RR in Crizotinib Naive	RR dopo Crizo	RR Brain mts
LDK378[1] Ceritinib	Novartis	66%	55%	50%
CH5424802 Alectinib	Chugai/Roche	93.5% (43/46)[2]	55%[3]	52%[3]
AP26113[4]	Ariad	100% (7/7)	69%	71%

[1]Kim et al, ASCO 2014
[2]Seto et al, Lancet Oncol 2013
[3]Gadgeel et al, Lancet Oncol 2014
[4]Gettinger et al, ESMO 2014

Paziente con ADK ALK +, in risposta a AP26113 (dopo CT e Crizotinib): malattia metastatica da 3 anni

Novità terapeutiche nel NSCLC: Risultati in OS



EGFR/ALK e terapia con TKIs: considerazioni

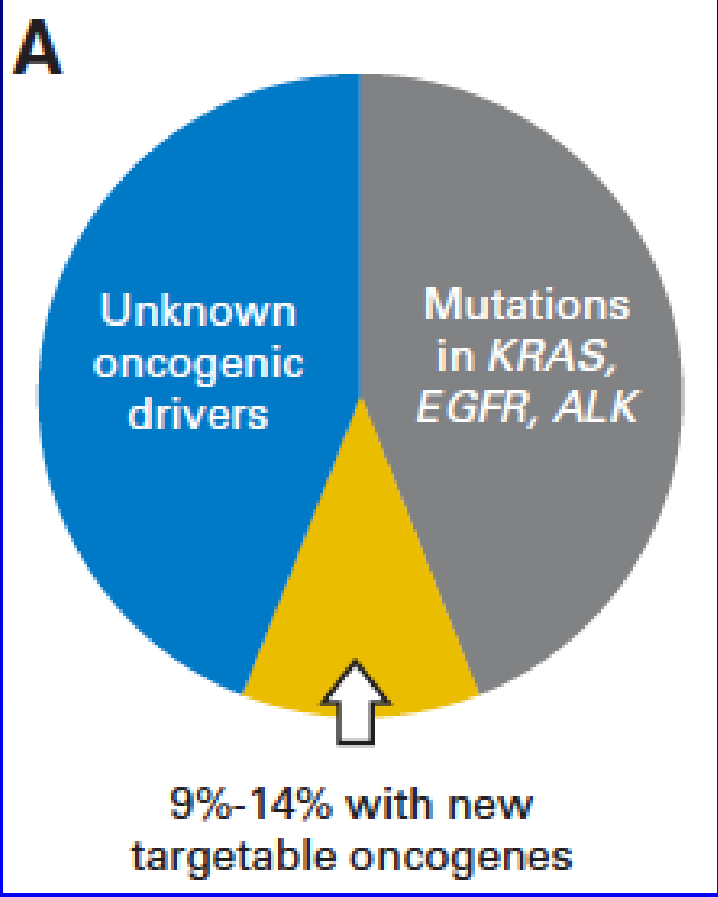
- **EGFR e ALK TKIs sono esempi di terapia "personalizzata" nel NSCLC, che ha dimostrato di superare l'efficacia della CT in pz selezionati e con indice terapeutico migliore**
- **Bassa frequenza delle mutazioni nella popolazione caucasica (EGFR 10-15%, ALK 5%) e tipizzazione non sempre realizzabile**
- **Efficacia comunque a termine (10-12 mesi)**

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

Farmaci biologici nel NSCLC

- EGFR-TKIs nei NSCLC EGFR mutati
- ALK-TKIs nei NSCLC ALK positivi
- Altri target molecolari
- Immunoterapia
- Farmaci anti-angiogenetici

New Targetable Oncogenes in Non–Small-Cell Lung Cancer



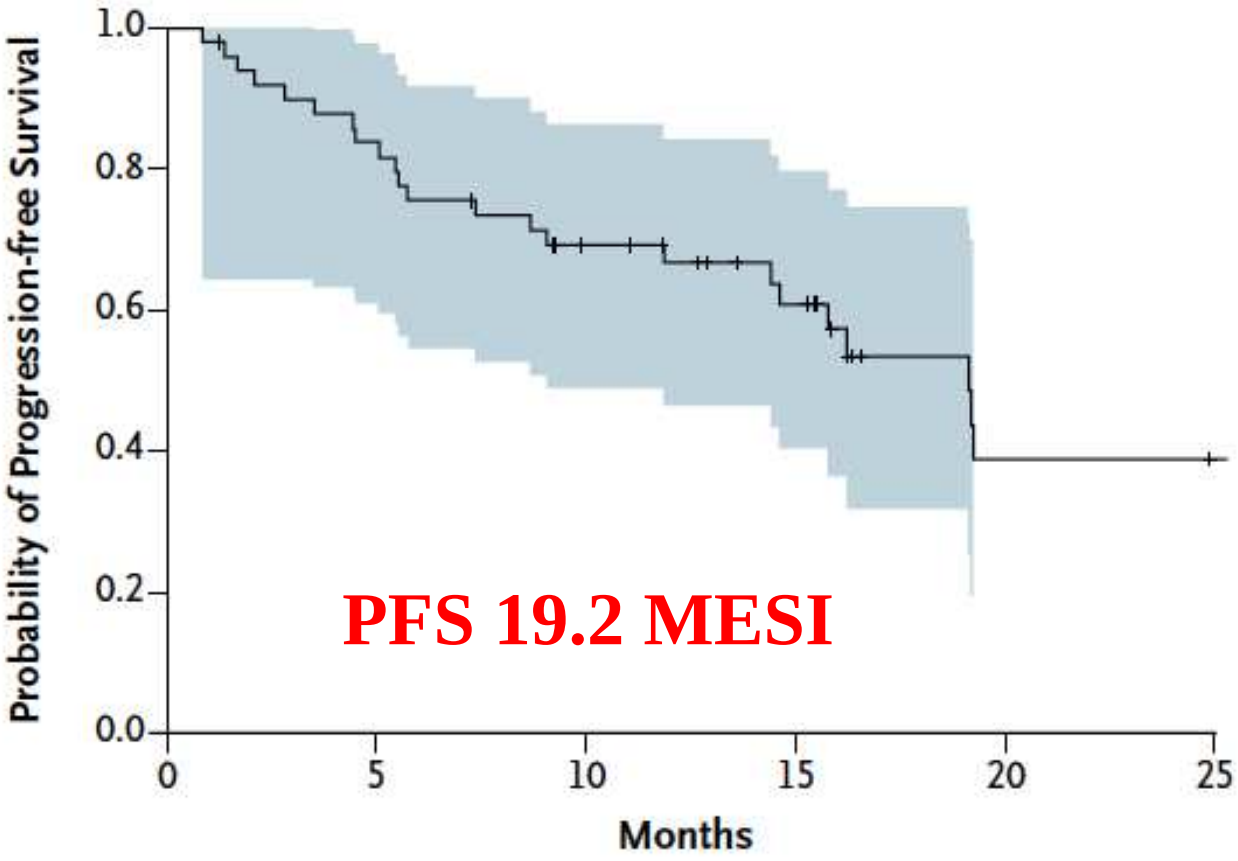
Oxnard and Janne, J Clin Oncol 2013

Table 1. New Targetable Oncogenes in Lung Adenocarcinoma

Oncogenic Target	Prevalence (%)	Reported Clinical Associations	Potential Kinase Inhibitors
HER2 insertions	2.8[9]	Never-smokers[9] Asian race[9] Female sex[9]	Afatinib (BIBW-2992) Neratinib (HKI-272) Dacomitinib (PF-00299804)
BRAF mutations	2 to 4.9[10-12]	Ever-smokers[10] White race[10] V600E: never-smokers[11] V600E: female sex[11]	Vemurafenib GSK2118436
PIK3CA mutations	1.5 to 2.6[12-15]	No association seen[13-15]	GDC-0941 XL147 BKM120
RET rearrangements	1.2[16] 1.9[17•]	Never-smokers[16] Asian race[17]	Vandetanib Sorafenib Sunitinib Cabozantinib (XL184)
ROS1 rearrangements	1.2 to 2.6[16,18]	Never-smokers[18] Asian race[18] Younger age[18]	Crizotinib

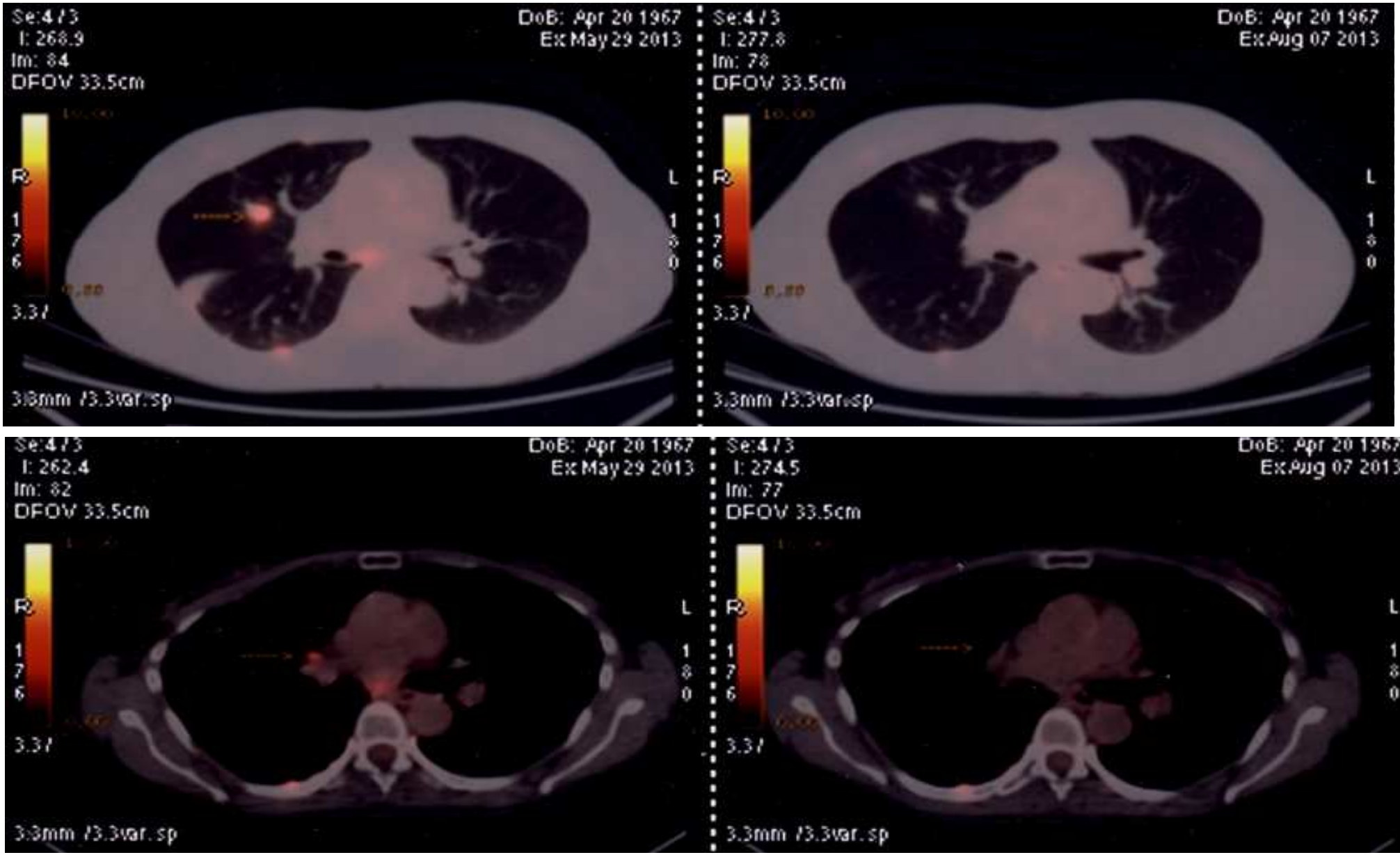
Crizotinib in NSCLC ROS1+ (1-2%)

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma



Shaw et al, N Engl J Med 2014

Paziente di 46 anni con ADK polmonare stadio IV in terza linea con Crizotinib per ROS1+ da 2 anni (metastatica da 4 anni)

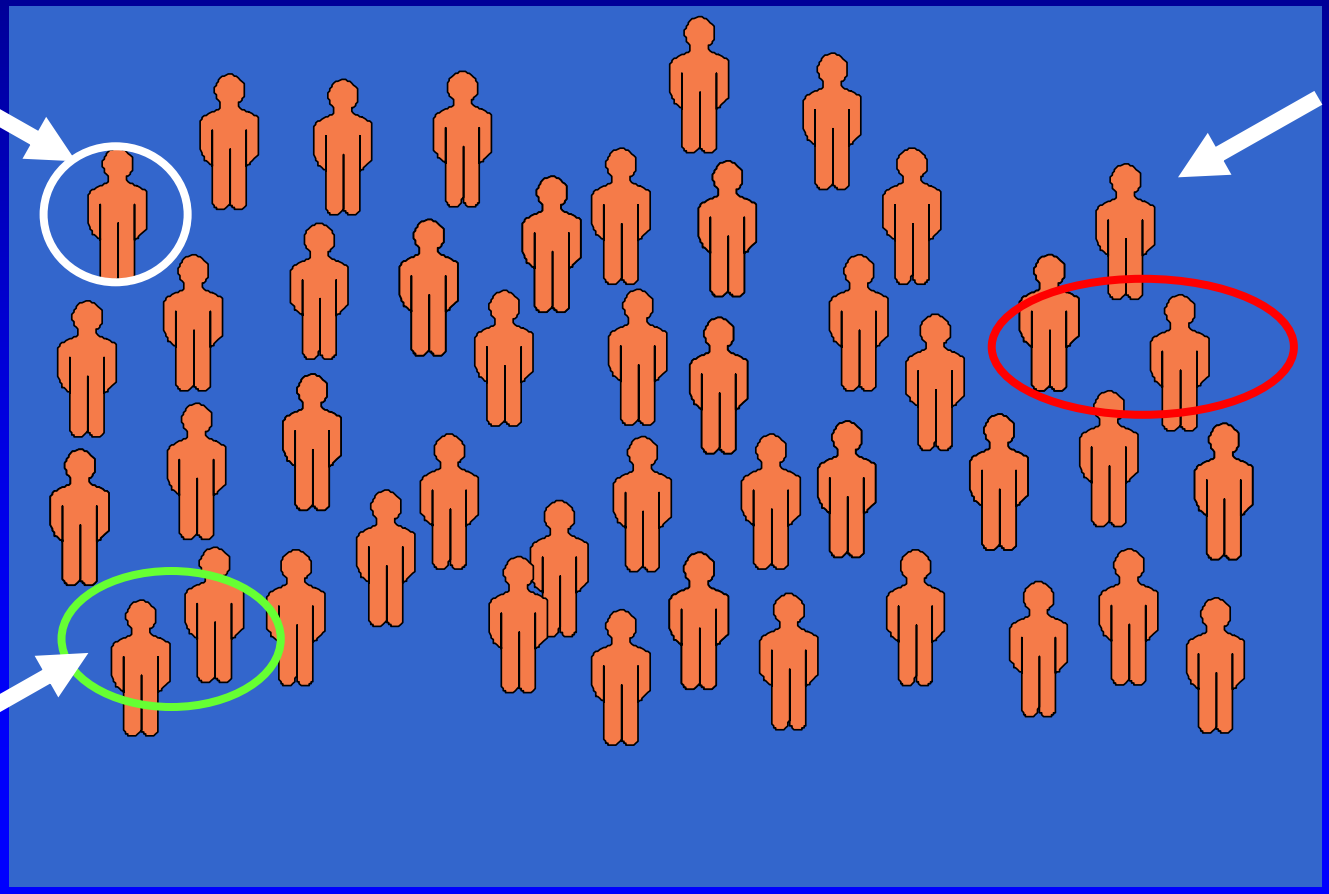


NSCLC con oncogene-addiction

Pazienti con diagnosi di tumore polmonare non a piccole cellule in stadio IV

ROS1 positivo

EGFR mutati

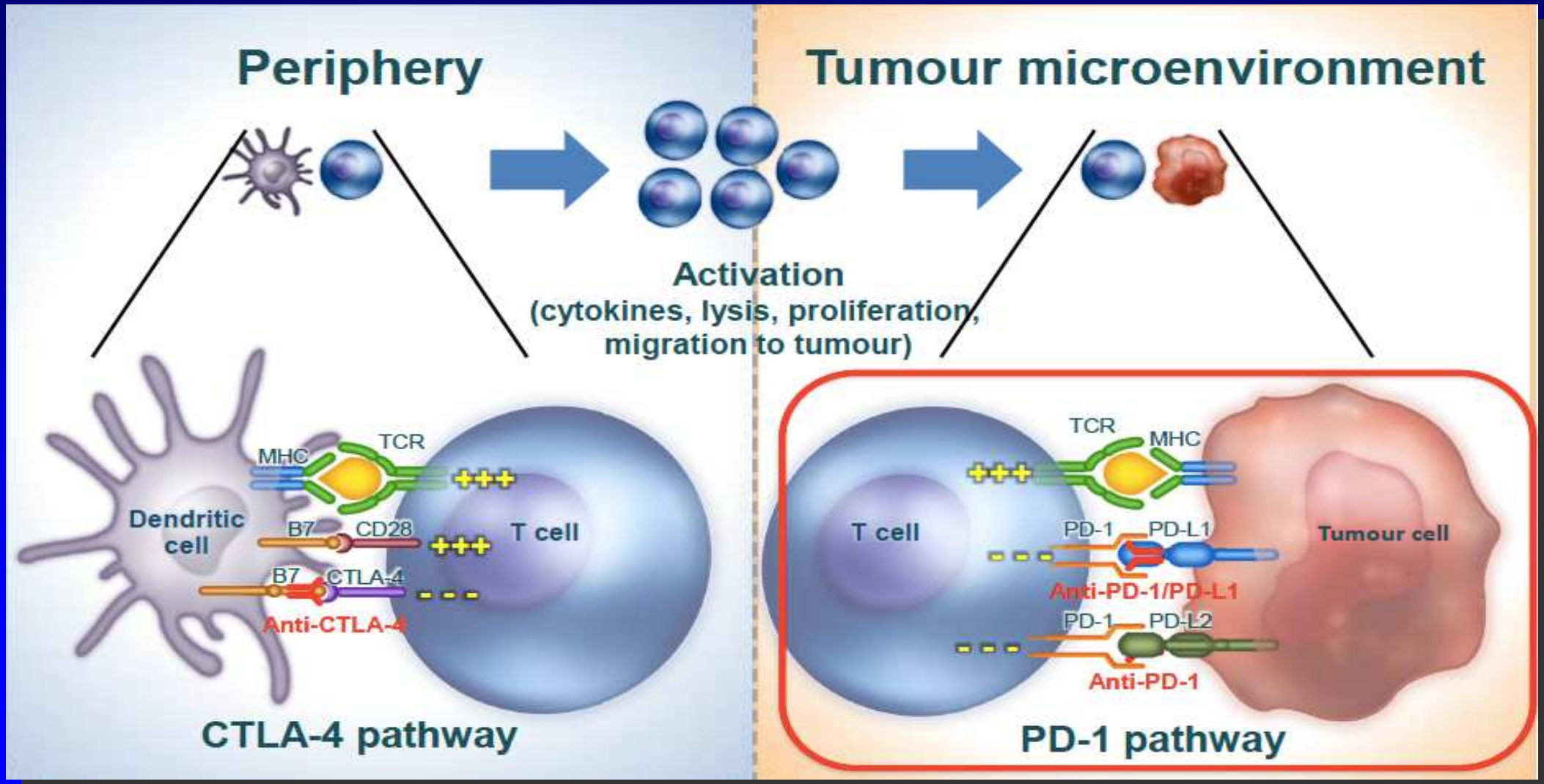


ALK positivi

Farmaci biologici nel NSCLC

- EGFR-TKIs nei NSCLC EGFR mutati
- ALK-TKIs nei NSCLC ALK positivi
- Altri target molecolari
- Immunoterapia
- Farmaci anti-angiogenetici

Immune Checkpoints Pathways

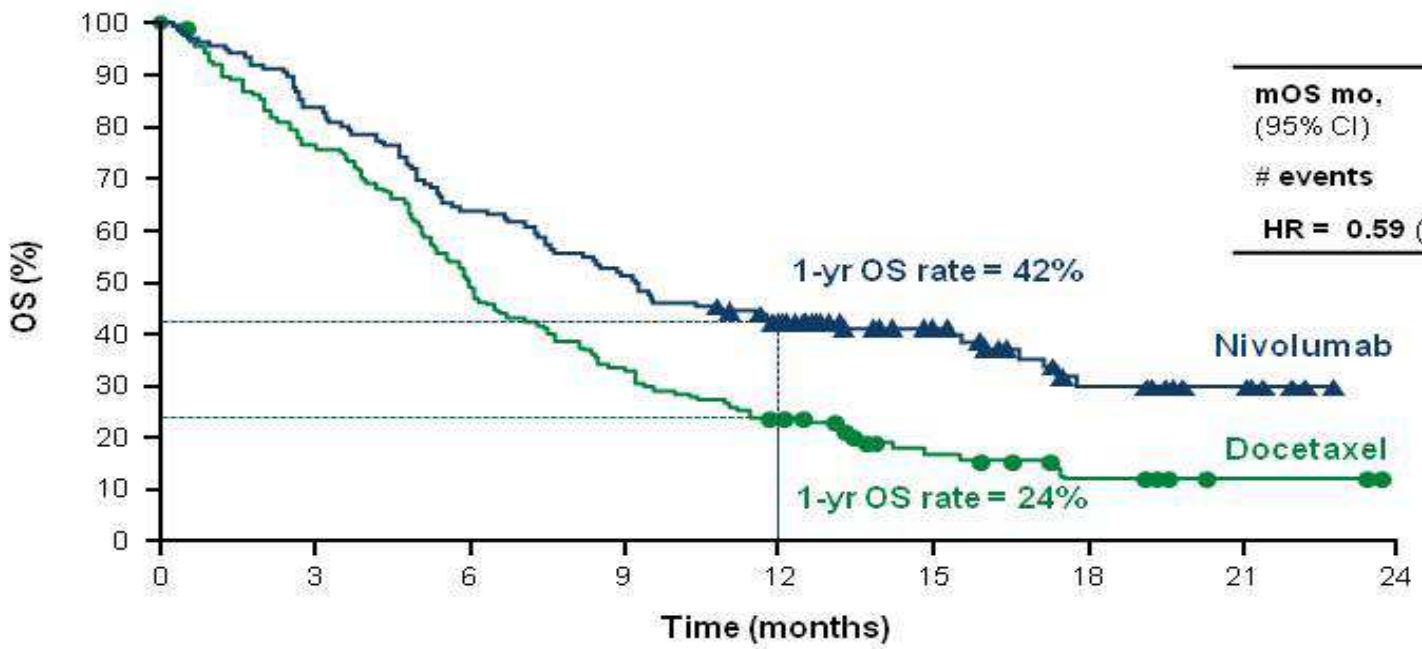


Anti-PD1, Anti-PDL1 in NSCLC: considerazioni

- Agenti attivi in pazienti pretrattati
- Risposte durevoli (anche 2-3 anni)
- Attivi indipendentemente dall'istologia, sembra maggiore in fumatori
- Possibilità di combinazioni con TKI e con CT
- Dati iniziali anche in I linea
- Ruolo dell'espressione PDL-1?
- Studi in corso in vari setting di malattia (adiuvante e malattia localmente avanzata)

NIVOLUMAB vs DOCETAXEL in squamous 2nd line: CheckMate 017

Overall Survival



	Nivolumab n = 135	Docetaxel n = 137
mOS mo, (95% CI)	**9.2** (7.3, 13.3)	**6.0** (5.1, 7.3)
# events	86	113

HR = 0.59 (95% CI: 0.44, 0.79), ***P* = 0.00025**

Number of Patients at Risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

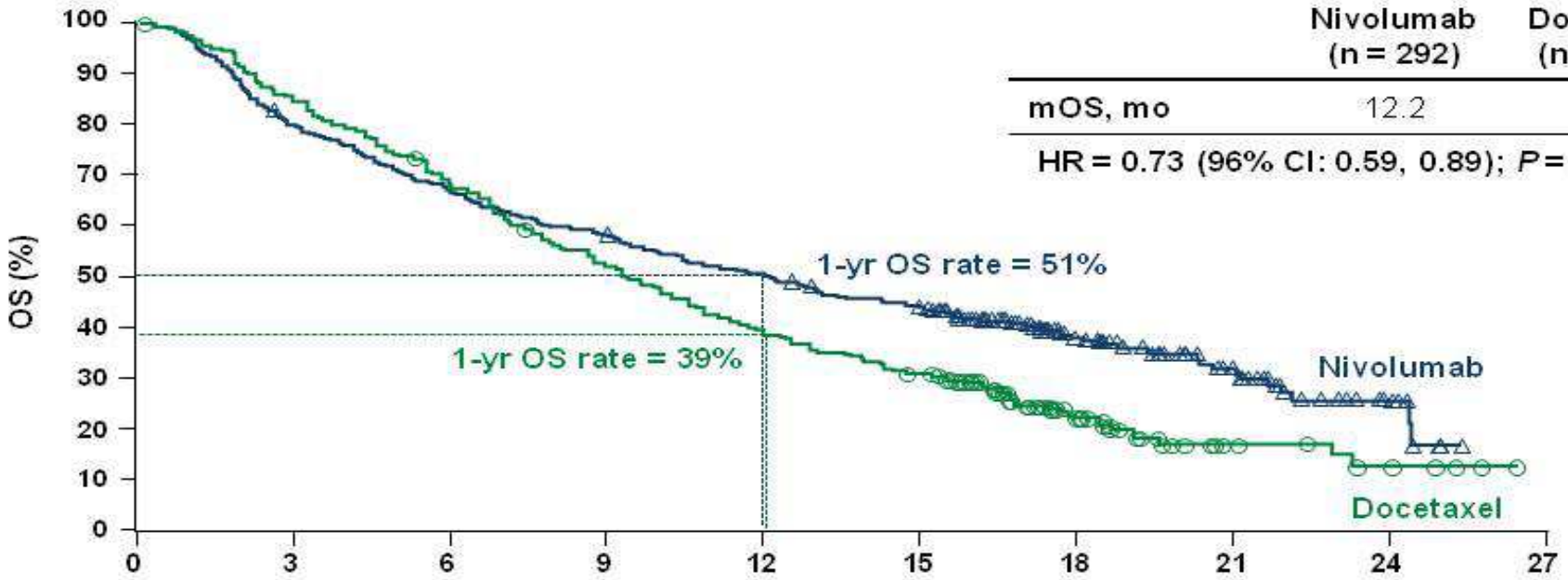
Symbols represent censored observations

PRESENTED AT: ASCO Annual '15 Meeting

Presented By David Spigel at 2015 ASCO Annual Meeting

NIVOLUMAB vs DOCETAXEL in non-squamous 2nd line: CheckMate 057

Overall Survival



	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

PRESENTED AT: ASCO Annual '15 Meeting

NIVO vs DOCETAXEL in non-squamous 2nd line: CheckMate 057

Treatment-related Select AEs

	Nivolumab (n = 287)		Docetaxel (n = 268)	
	Any Grade	Grade 3–4[a]	Any Grade	Grade 3–4[a]
Endocrine, %				
Hypothyroidism	7	0	0	0
Gastrointestinal, %				
Diarrhea	8	1	23	1
Hepatic, %				
ALT increased	3	0	1	<1
AST increased	3	<1	1	0
Pulmonary, %				
Pneumonitis	3	1	<1	<1
Skin, %				
Rash	9	<1	3	0
Pruritus	8	0	1	0
Erythema	1	0	4	0
Hypersensitivity/Infusion reaction, %				
Infusion-related reaction	3	0	3	<1

- Select AEs: AEs with potential immunologic etiology that require frequent monitoring/intervention

Includes events reported in ≥2.5% of patients.

[a]No grade 5 events were reported at DBL;1 grade 5 event for nivolumab was reported post-DBL.

PRESENTED AT: ASCO Annual '15 Meeting

Farmaci biologici nel NSCLC

- EGFR-TKIs nei NSCLC EGFR mutati
- ALK-TKIs nei NSCLC ALK positivi
- Altri target molecolari
- Immunoterapia
- Farmaci anti-angiogenetici

  - **Bevacizumab** combinato alla chemioterapia (poco impiegato)
  - Dati positivi di **Nintedanib** e **Ramucirumab** combinati alla CT
  - **Non esistono fattori predittivi**

Farmaci Biologici nel NSCLC: conclusioni

- **Aumentano le opzioni e le linee terapeutiche** (in generale con migliore profilo di tollerabilità)
- **Più articolata segmentazione dei pazienti**
- Identificazione di specifica popolazione con migliori prognosi e prospettive terapeutiche (**EGFR mutati, ALK positivi, ROS1 positivi, etc**)
- Ricadute nella fase diagnostica con problematiche relative al campione tumorale (quantità e qualità)
- **Importante novità dell'immunoterapia**


SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma
Grazie per l'attenzione
mtiseo@ao.pr.it