AGGIORNAMENTO SULLE PATOLOGIE POLMONARI: IL TRATTAMENTO DEL CARCINOMA DEL POLMONE NON A PICCOLE CELLULE

Palmanova (UD), 24 maggio 2017

Trattamenti orali con inibitori delle tirosin chinasi: efficacia e interazioni

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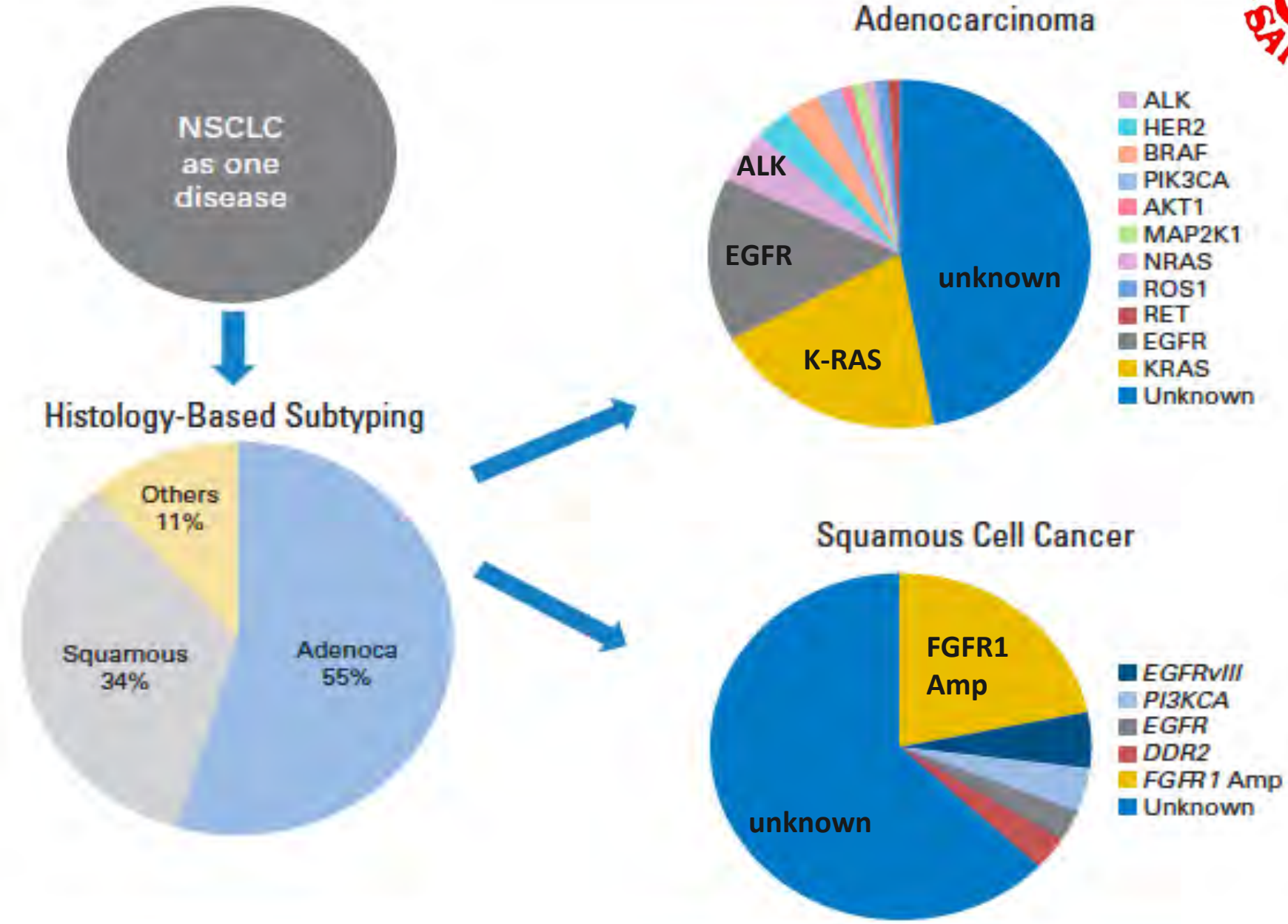
Oncologia CRO Pordenone

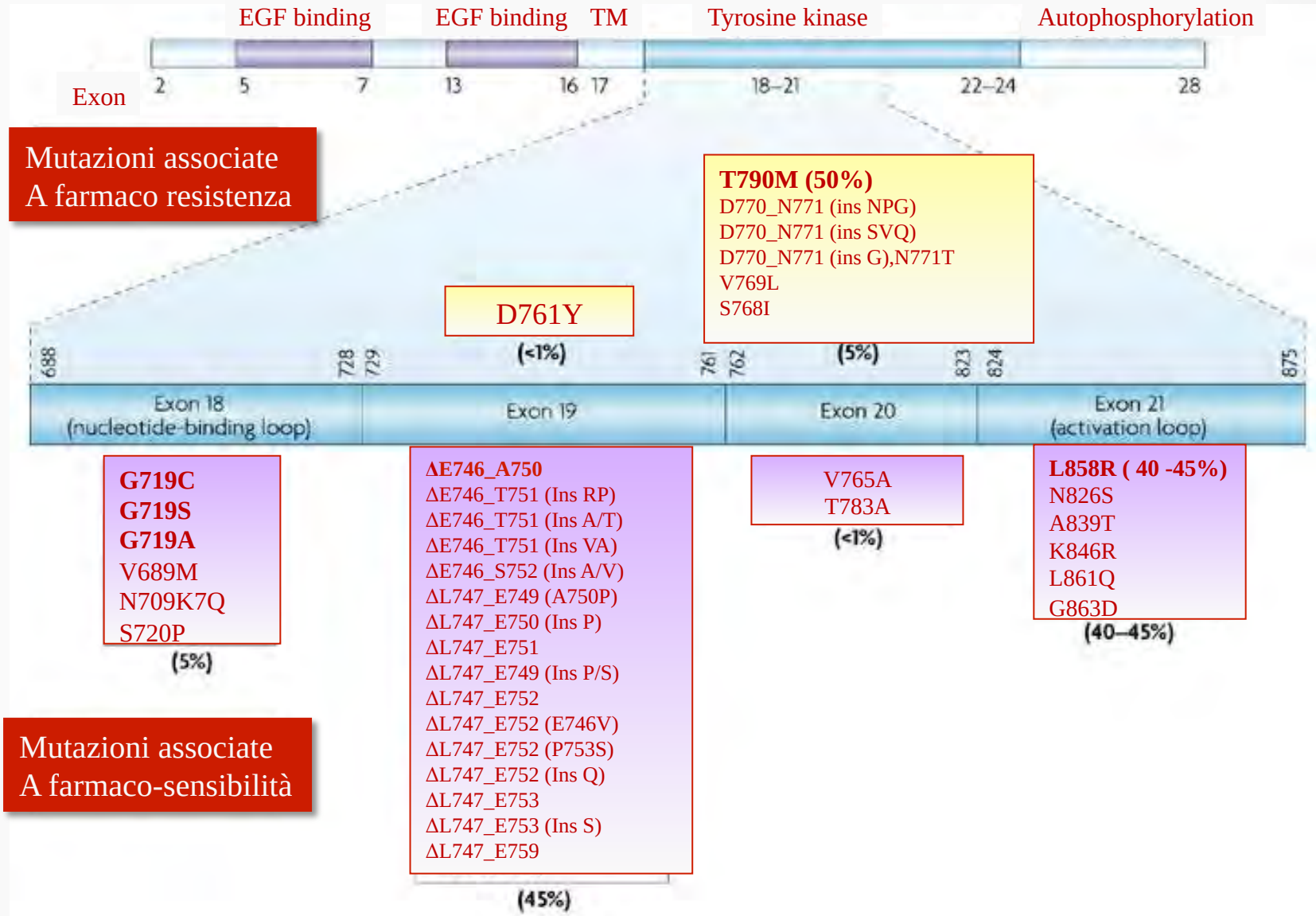
AGENDA

- INIBITORI TKI DI EGFR
  - ✓ 1° linea
  - ✓ 2° linea
  - ✓ Interazioni
- INIBITORI TKI DI ALK
  - ✓ 1° linea
  - ✓ Linee successive
  - ✓ Interazioni

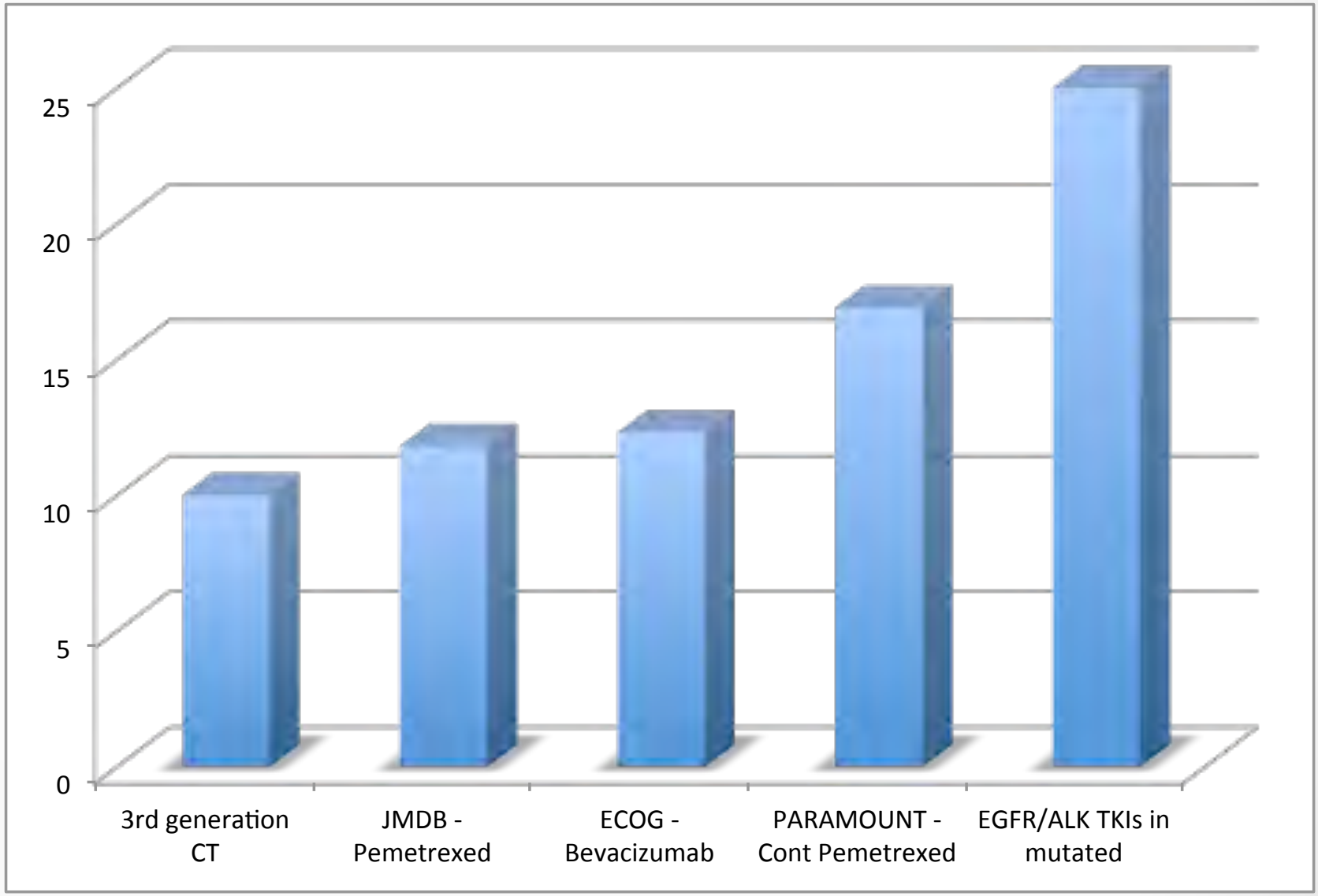
Introduzione



Le mutazioni di EGFR: hot-spots



Novità terapeutiche nel NSCLC: Risultati in OS

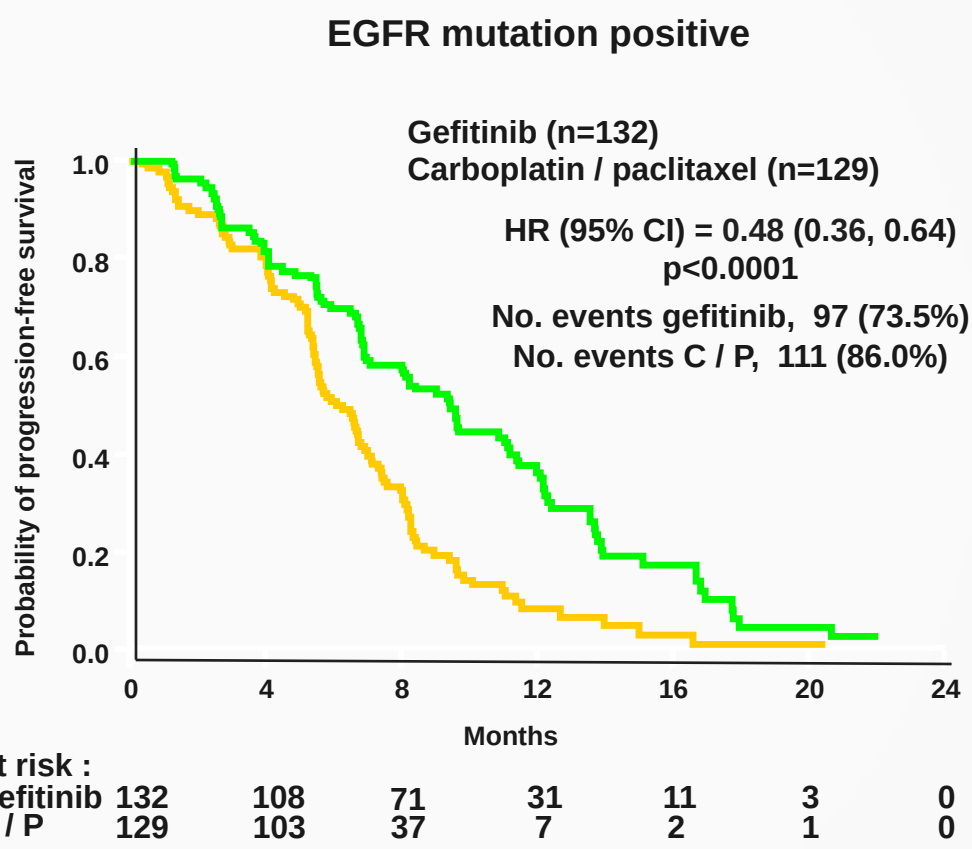


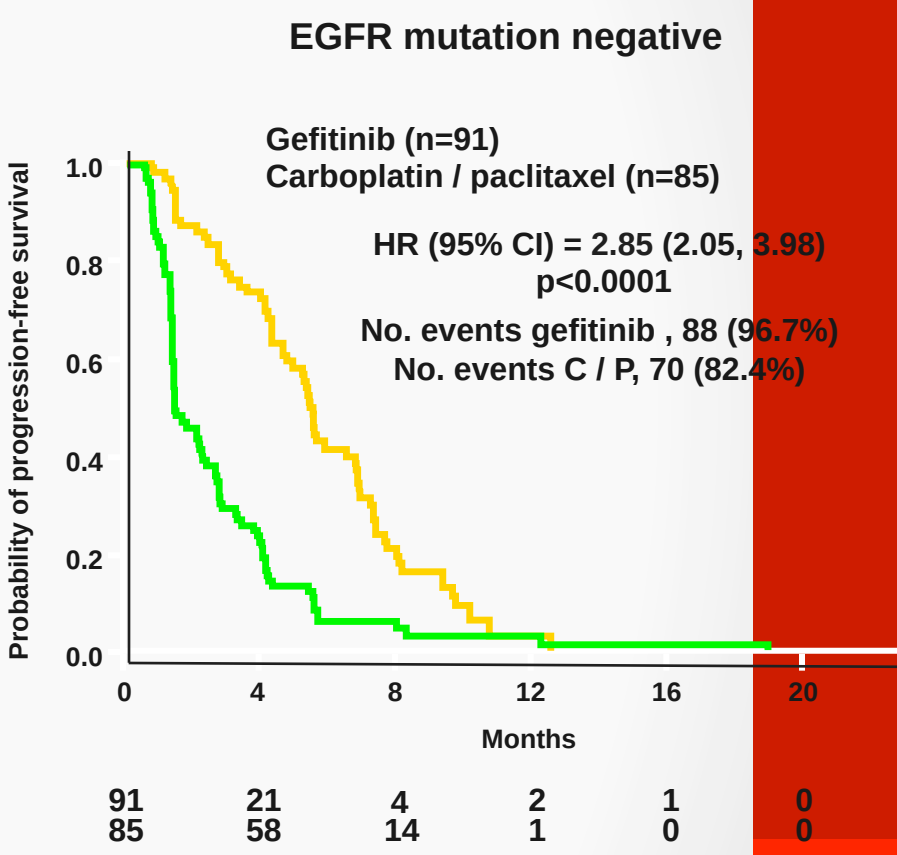
EGFR gene mutations

- Activating mutations with ligand independent receptor activity
- 90% in exons 19 (deletion) and 21 (LB58R)
- Global incidence: 10% caucasians; 30-40% Asiatic pts
- ++ never-smoker or light-smoker
- More frequent in female sex
- ++ adenocarcinoma (in particular BAC non mucinous)
- Predictive factor of EGFR-TKIs, gefitinib (IRESSA®), erlotinib (TARCEVA®), afatinib (GIOTRIF®)

Tiseo et al, Drug Des Devel Ther 2011

PFS in EGFR mut + and – patients





Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok et al, NEJM 2009

Randomized, 1° line studies in NSCLC with EGFR mutation

Trial	EGFR TKI	n	EGFR mutation	Response rate (%)	PFS (months)	OS (months)
IPASS	Gefitinib	1217	261	71 vs. 47 p<0.001	9.5 vs. 6.3 HR=0.48 (0.36–0.64)	21.6 vs. 21.9 HR=1.0 (0.76–1.33)
First-SIGNAL	Gefitinib	309	42	85 vs. 38 p=0.002	8.0 vs. 6.3 HR=0.544 (0.27–1.10)	27.2 vs. 25.6 HR=1.04 (0.50–2.18)
NEJ002	Gefitinib	224	224	74 vs. 31 p<0.001	10.8 vs. 5.4 HR=0.30 (0.22–0.41)	30.5 vs. 23.6
WJTOG-3405	Gefitinib	172	172	62 vs. 32 p<0.0001	9.6 vs. 6.6 HR=0.52 (0.38–0.72)	35.5 vs. 38.8 HR=1.185 (0.76–1.83)
OPTIMAL	Erlotinib	154	154	83 vs. 36 p<0.0001	13.7 vs. 4.6 HR=0.16 (0.10–0.26)	22.7 vs. 28.9 HR=1.04 (0.69–1.58)
EURTAC	Erlotinib	173	173	58 vs. 15	9.7 vs. 5.2 HR=0.37 (0.25–0.54)	19.3 vs. 19.5 HR=1.04 (0.65–1.68)
LUX-Lung 3	Afatinib*	345	345	56 vs. 23 p<0.001	11.1 vs. 6.0, HR=0.58 (0.43–0.78)	–
LUX-Lung 6	Afatinib*	364	364	67 vs. 23 p<0.0001	11.0 vs. 5.6, HR=0.28 (0.20–0.39)	–

*Afatinib is an investigational compound and is not yet approved. Its safety and efficacy have not yet been fully established. Mok T, et al. N Engl J Med 2009;361:947–57; Fukuoka M, et al. J Clin Oncol 2011;29:2866–74; Han J-Y, et al. J Clin Oncol 2012;10:1122–8; Maemondo M, et al. N Engl J Med 2010;362:2380–98; Mitsudomi T, et al. Lancet Oncol 2010;11:121–8; Mitsudomi T, et al. J Clin Oncol 2012;30(Suppl.): Abstract 7521; Zhou C, et al. Lancet Oncol 2011;12:735–42; Zhou C, et al. J Clin Oncol 2012;30(Suppl.): Abstract 7520; Rosell R, et al. Lancet Oncol 2012;13:239–46; Yang JC, et al. J Clin Oncol 2012;30:(suppl; abstr LBA7500); Wu Y-L, et al. J Clin Oncol 2012;31(Suppl.): Abstract 8016.

Elementi a favore dell'EGFR-TKI in prima linea

- Tasso di risposte doppio
- PFS doppio (~ 9-12 mesi)
- Effetto rapido, migliore controllo dei sintomi
- Effetto indipendente da età, PS, comorbidità
- Minore tossicità
- Somministrazione orale
- Rischio di non arrivare alla 2ª linea iniziando con la chemioterapia

Test EGFR su DNA circolante

	Plasma 1 *EGFR* mutation status (*n*)		
	Positive	Negative	Total
Adjusted baseline tumour *EGFR* mutation status, *n*			
Positive	69	36	105
Negative	1	546	547
Total	70	582	652
Specificity	547	99.8	99.0–100.0
PPV	70	98.6	92.3–100.0
NPV	582	93.8	91.5–95.6

For the comparison of tumour and plasma data, the tumour DNA mutation status was adjusted for the mutations analysed in cfDNA from plasma (i.e. for exon 19 deletions, L858R point mutations and T790M point mutations only). Abbreviations: cfDNA = circulating free tumour DNA; CI, confidence interval; *EGFR* = epidermal growth factor receptor; PPV = positive predictive value; NPV = negative predictive value.

Quando si considera l'uso di IRESSA come trattamento per il NSCLC localmente avanzato o metastatico, è importante che la presenza della mutazione dell'EGFR del tessuto tumorale sia cercata per tutti i pazienti. Se un campione del tumore non è valutabile, allora può essere utilizzato il DNA tumorale circolante (ctDNA) ottenuto da un campione di sangue (plasma).

Devono essere usati solo test robusti, affidabili e sensibili con utilità dimostrata per la determinazione dello stato di mutazione dell'EGFR sul tessuto tumorale o ctDNA, questo al fine di evitare risultati falsi negativi o falsi positivi (vedere paragrafo 5.1).

Douillard et al, Br J Cancer 2013

Quale EGFR-TKI in EGFR mutati ? Indicazioni AIFA

Gefitinib (IRESSA)
Indicato in qualunque linea in EGFR mutati

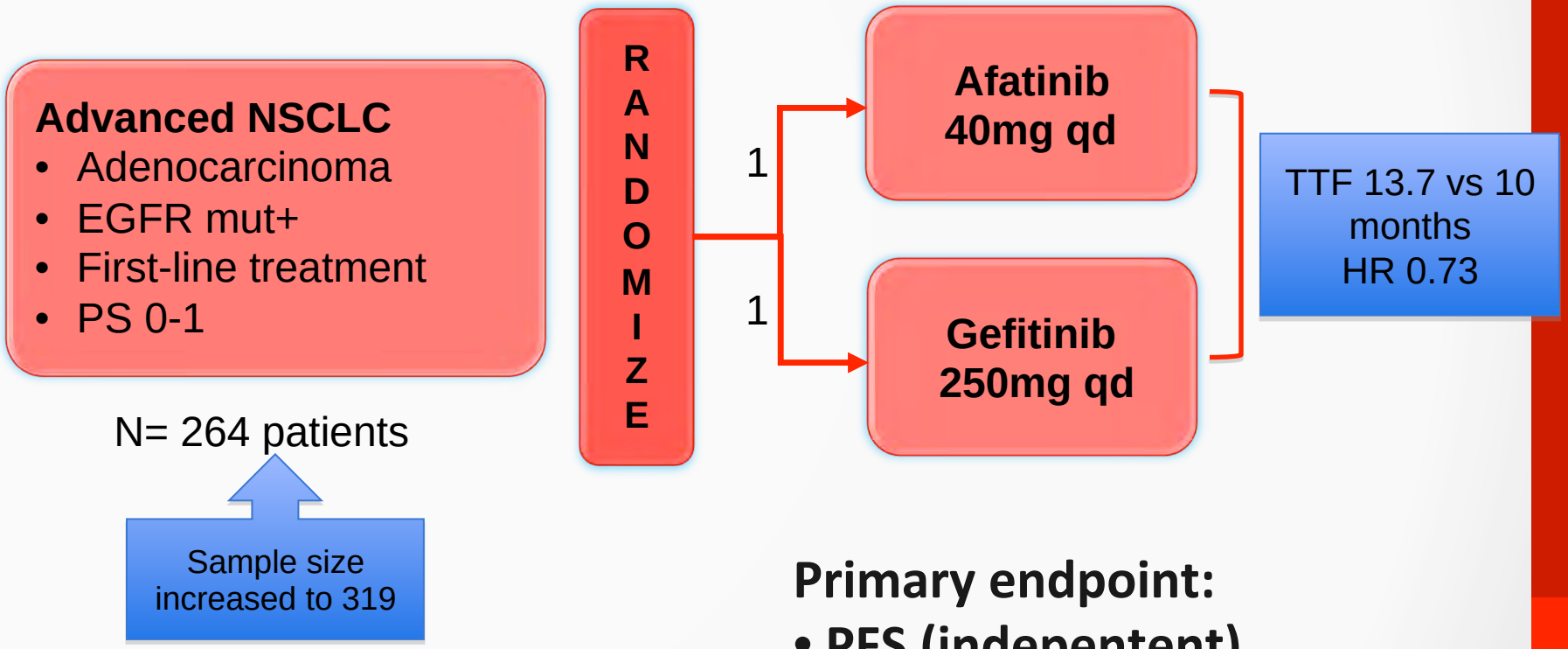
Erlotinib (TARCEVA)
Indicato in I linea negli EGFR mutati; II-III linea indipendentemente da EGFR

Afatinib (GIOTRIF)
Indicato in I linea negli EGFR mutati

Confronto indiretto tossicità ≥ G3

Trial	Molecola	Rash G≥ 3 (%)	Diarrea G≥ 3 (%)	Nausea/ vomito G≥ 3 (%)	Paronichia G≥ 3 (%)
IPASS	Gefitinib	3	4	<1	<1
First Signal	Gefitinib	0	4	0	3
NEJ002	Gefitinib	5	1	1	3
WJTOG3405	Gefitinib	3	1	1	1
OPTIMAL	Erlotinib	2	1	0	0
EUROTAC	Erlotinib	13	5	NR	NR
LUX-Lung 3	Afatinib	16	14	4	11
LUX-Lung 6	Afatinib	15	5	1	0
Lux-Lung 7	Afatinib vs Gefitinib	9 vs 3	13 vs 1	0 vs 1	2 vs 1

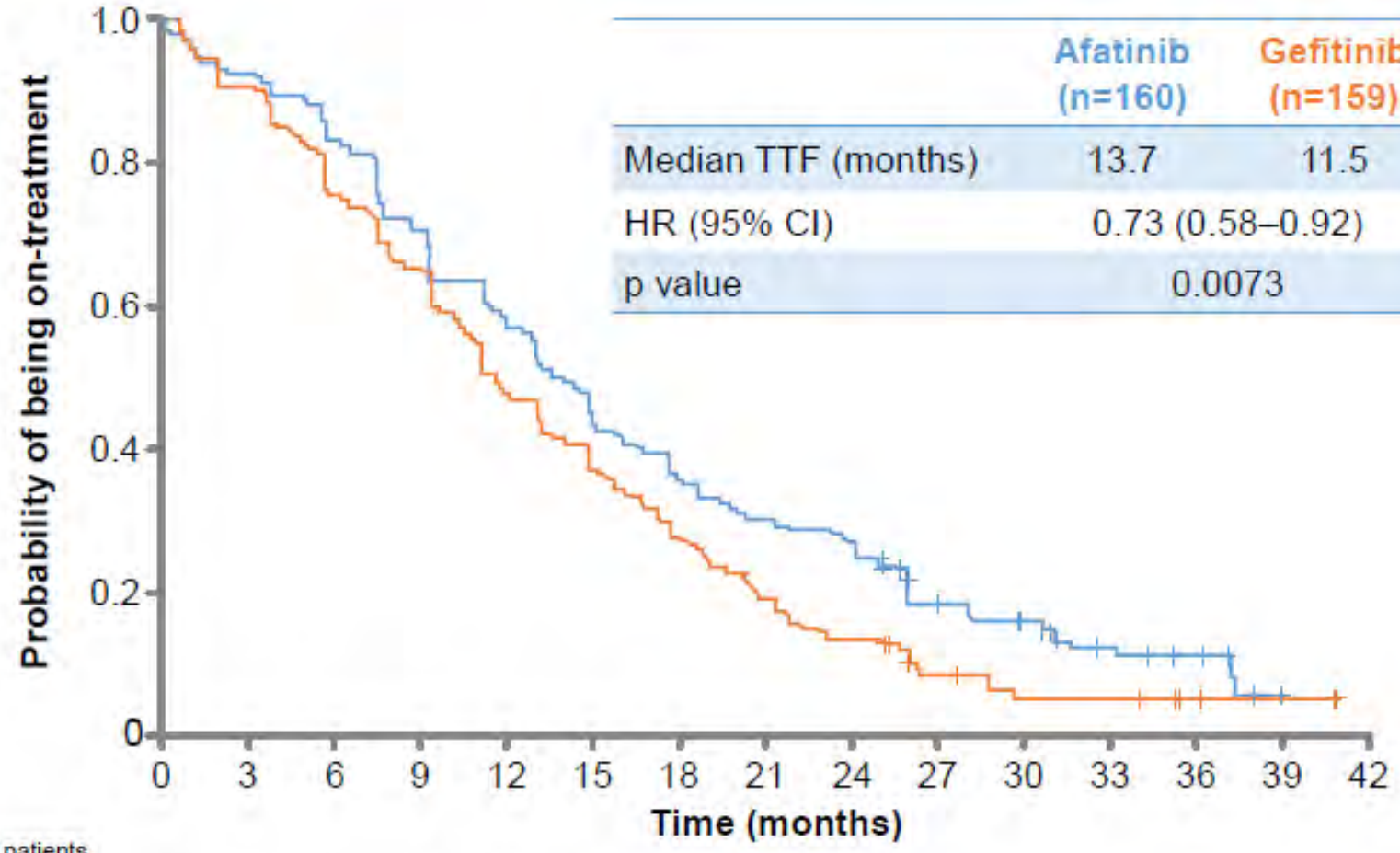
Comparazione diretta: LUX Lung 7, randomizzato fase IIb



Primary endpoint:

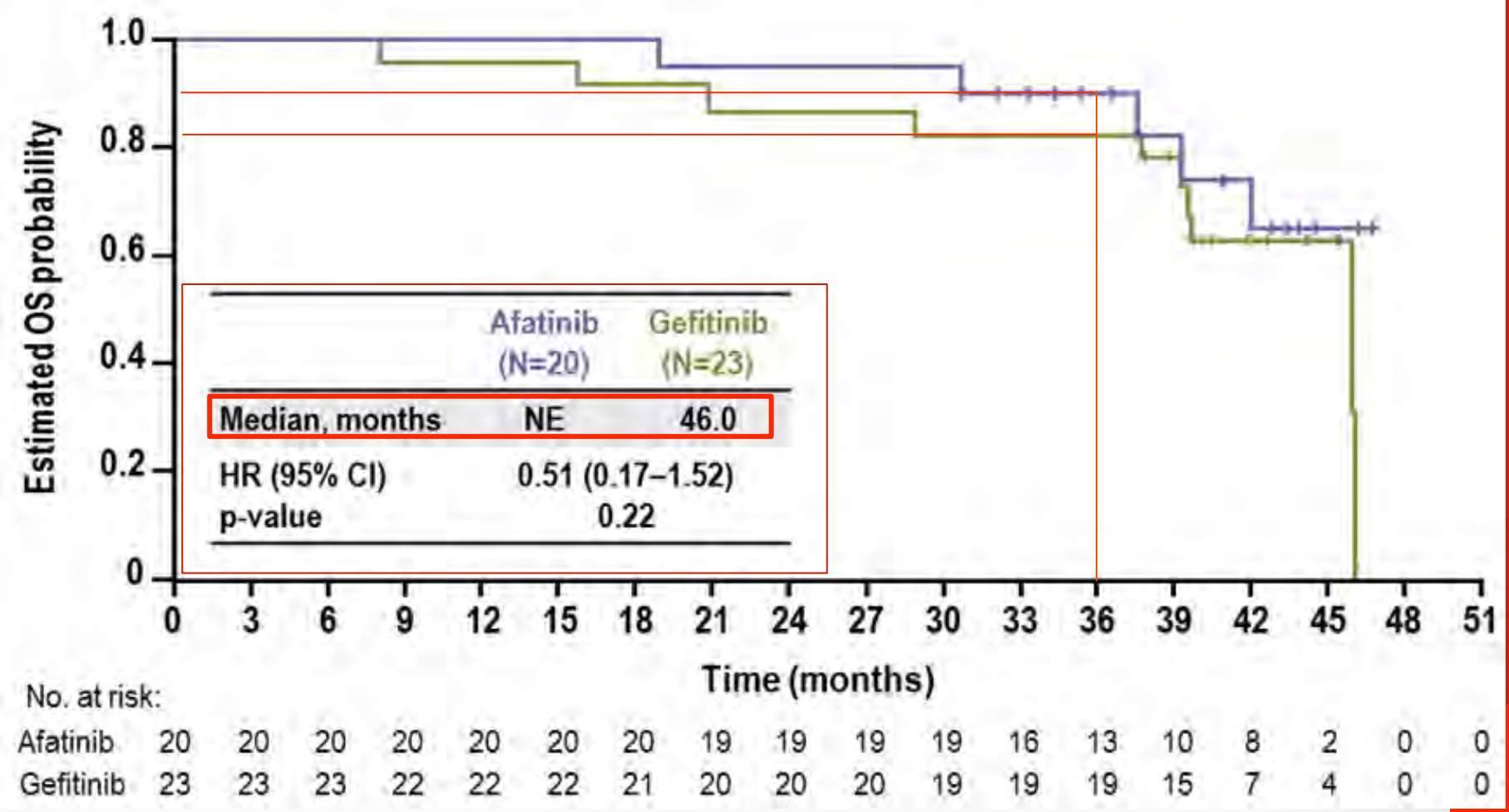
- **PFS (indepentent)**
- **TTF**
- **OS**

LUX Lung 7
Time to treatment failure



	Afatinib (n=160)	Gefitinib (n=159)
Median TTF (months)	13.7	11.5
HR (95% CI)	0.73 (0.58–0.92)	
p value	0.0073	

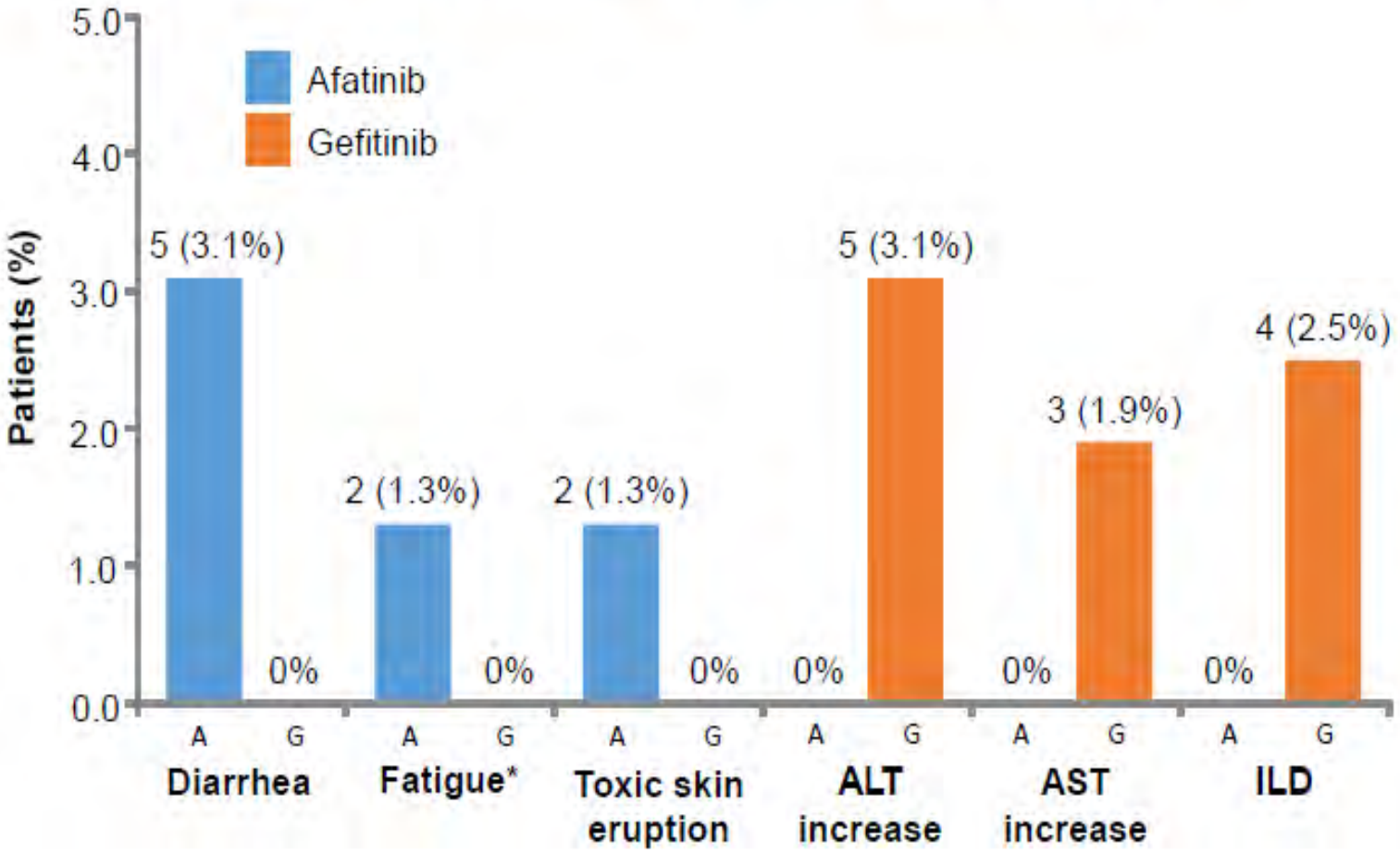
LL7; OS in patients treated with a subsequent 3rd-Gen EGFR TKI



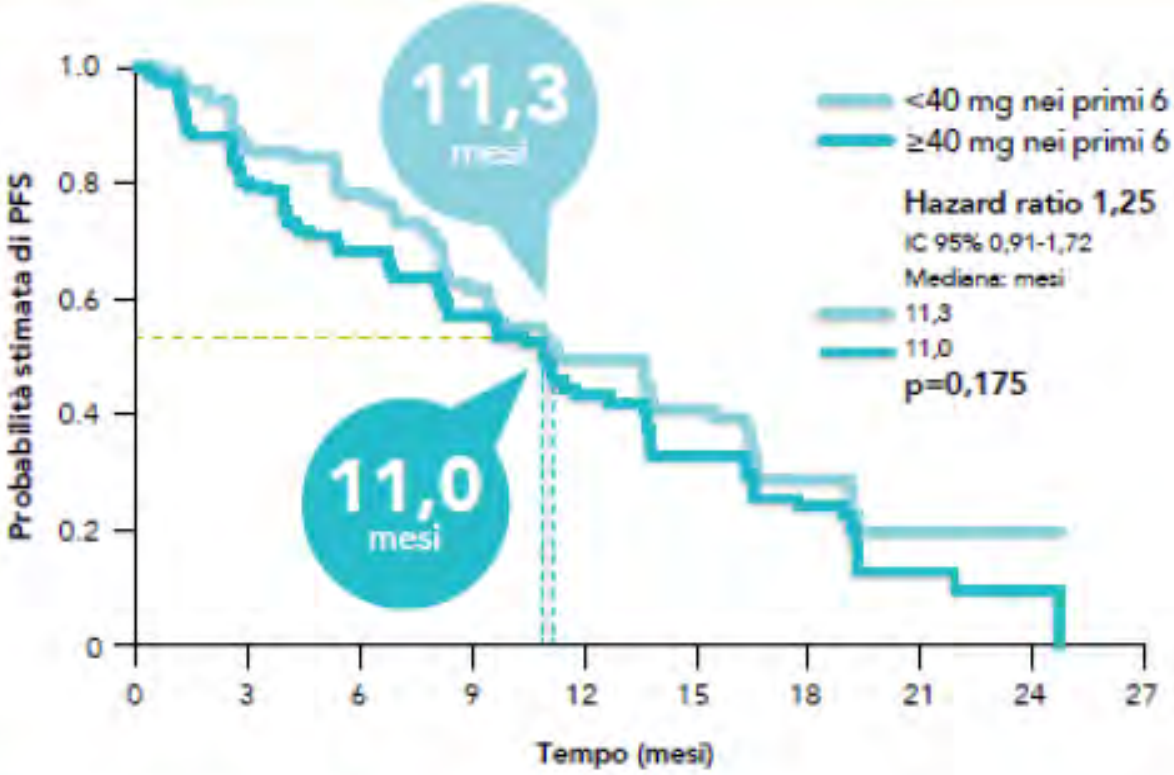
COPENHAGEN 2016 ESMO congress

Luis Paz-Ares et al. ESMO 2016

Drug-related AEs leading to discontinuation in > 1 pts



L'efficacia dei pz trattati con Giotrif non varia se si scala la dose per la comparsa di effetti collaterali



Riproduzione da Fig. 4 da 19

La PFS mediana è risultata simile nei pazienti con riduzione della dose di afatinib nei primi 6 mesi e in quelli rimasti con afatinib 40 mg OD[19]

EGFR-TKI in 1° linea EFFICACIA: conclusioni

- **Necessario ricercare le mutazioni di EGFR (in nonSQ): tessuto, citologia o biopsia liquida**
- **Il trattamento di I linea dei pazienti EGFR mutati dovrebbe essere con TKI**
- **La scelta del TKI dovrebbe considerare le caratteristiche che differenziano i 3 agenti registrati**
- **Prospettive future di terapie di combinazione o con TKI di terza generazione**

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Algoritmo dopo PD a EGFR TKIs

PD dopo TKI in I^ linea

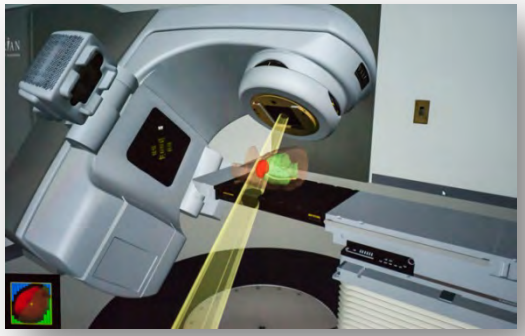
Oligo-PD

PD-Sistemica

Terapia locoregionale+ continuazione di TKI

PD sistemica

2^ linea trattamento sistemico

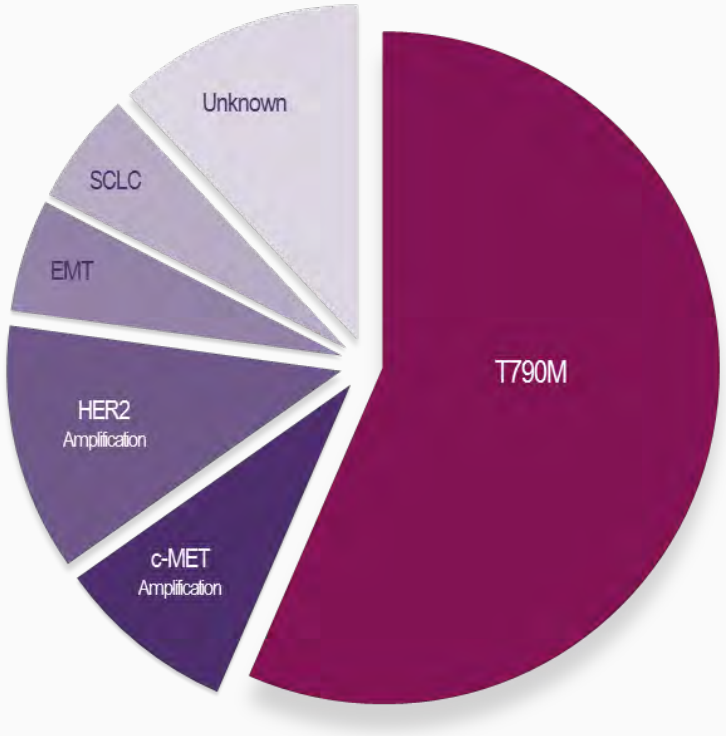


TKI di 3^ gen (for T790M)

Targeting del gene resistente

Chemiotp

Meccanismi di resistenza ad EGFR-TKIs



I principali meccanismi di resistenza acquisita a EGFR-TKIs che sono stati identificati e si possono classificare nei seguenti[1]:

1. Mutazione di T790M (più comune)

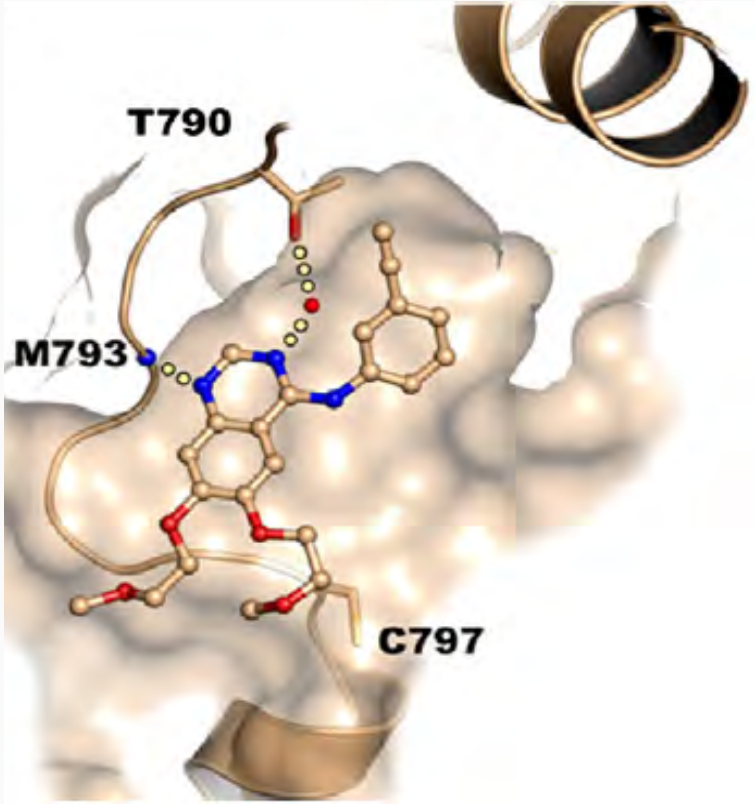
2. Attivazione di vie di segnale Alternative

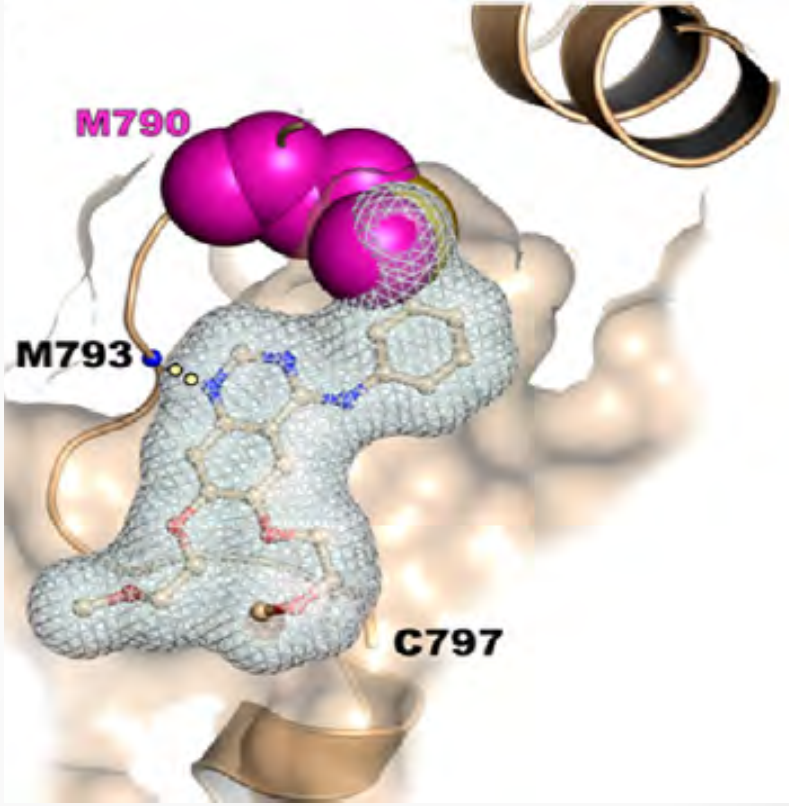
3. Trasformazione fenotipica

1.Cortot AB, Jänne PA. Eur Respir Rev 2014; 23:356–366.

Sostituzione T790M su esone 20

Treonine (~116 A) ⟶ Metionine (~163 A)

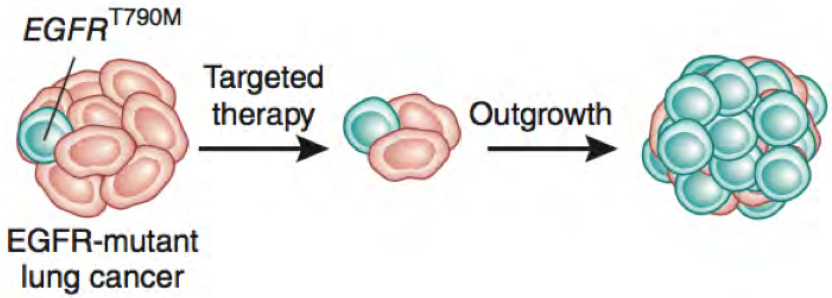




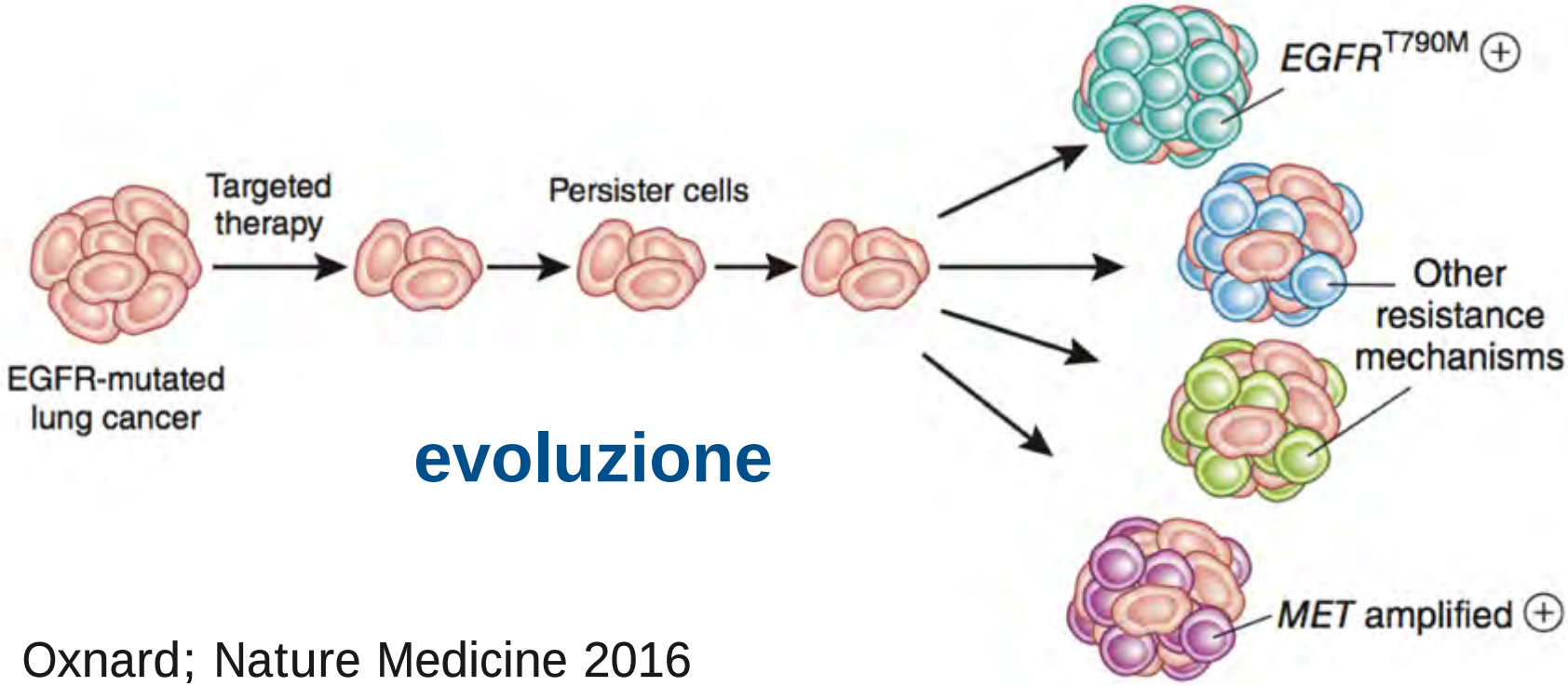
Cambiamento strutturale del sito ATP per un ingombro sterico maggiore della metionina rispetto alla treonina

Michalczyk A et al. Bioorg Med Chem. 2008 Apr 1;16(7):3482-8.

T790M: pre-esistenza vs evoluzione



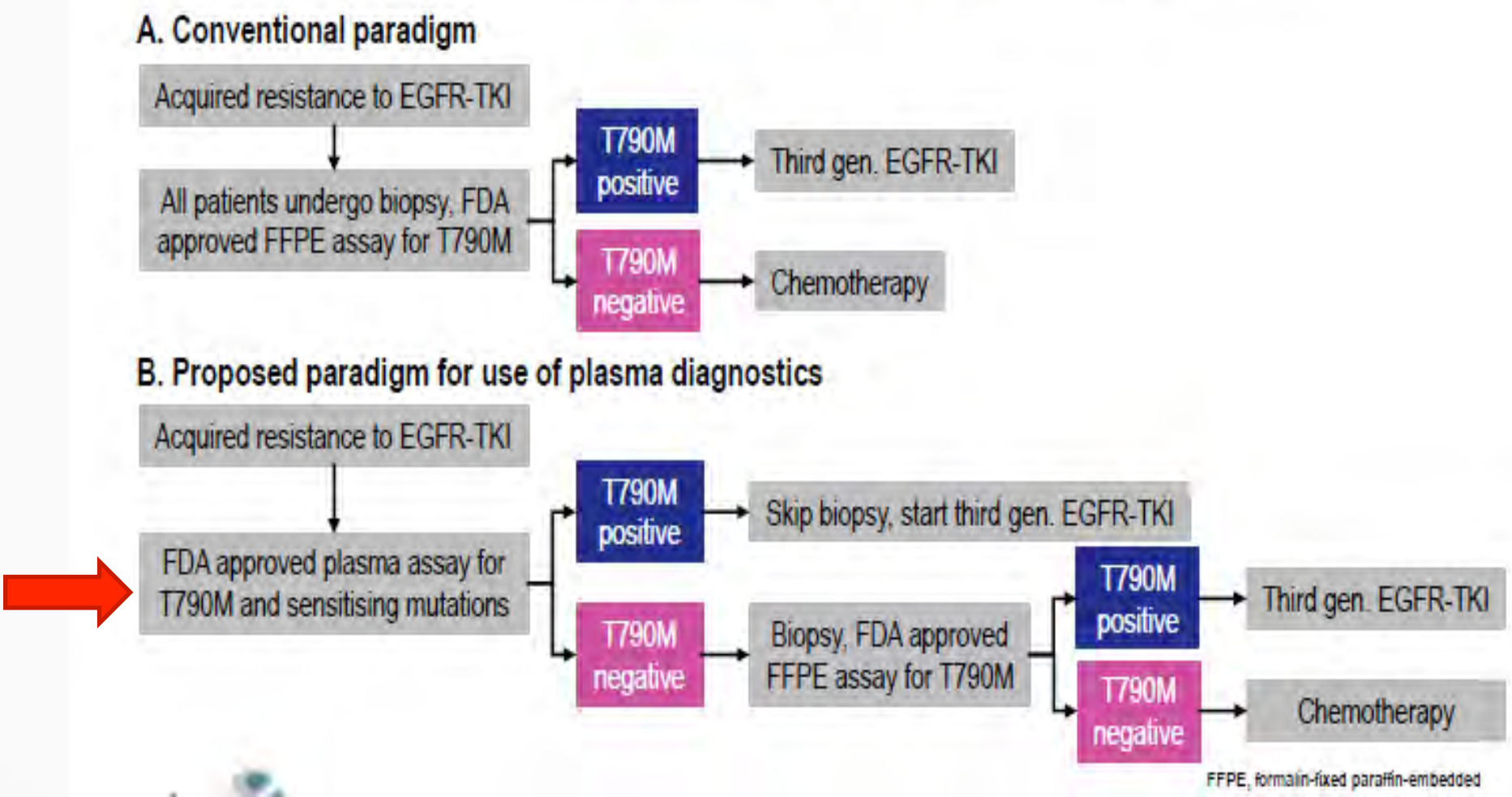
pre-esistenza



evoluzione

Oxnard; Nature Medicine 2016

Valutazione T790M: plasma o tessuto ?

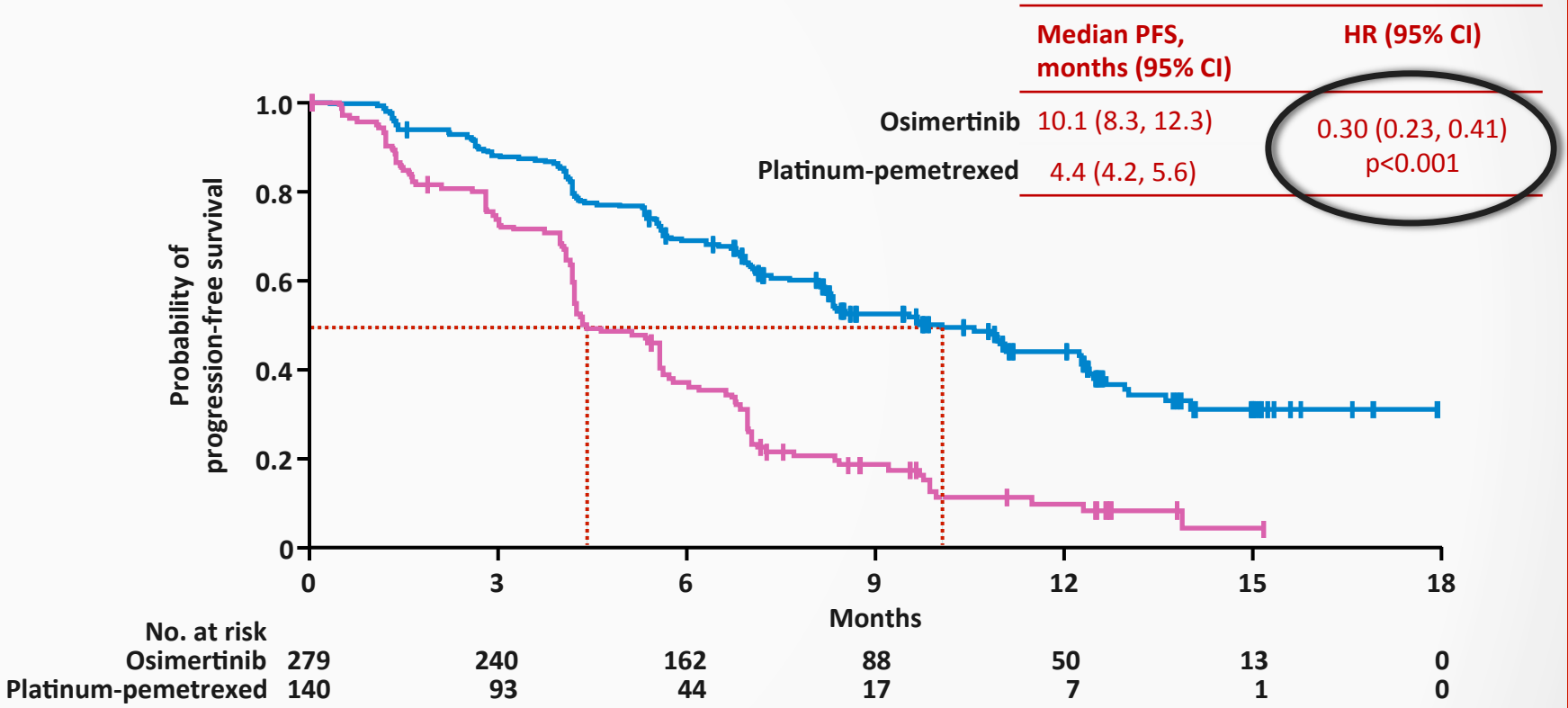


elcc

EUROPEAN LUNG CANCER CONFERENCE 2016

Presented by Geoffrey R Oxnard at the 6th IASLC/ESMO European Lung Cancer Conference, 13–16 April 2016, Geneva, Switzerland; Abstract 1350 PR.

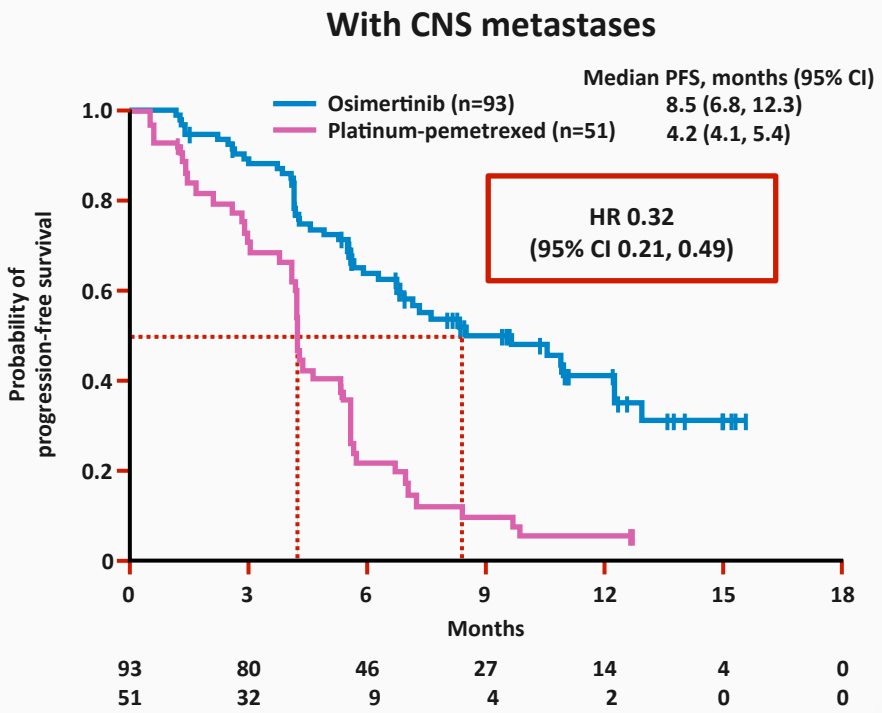
AURA 3 primary endpoint: PFS

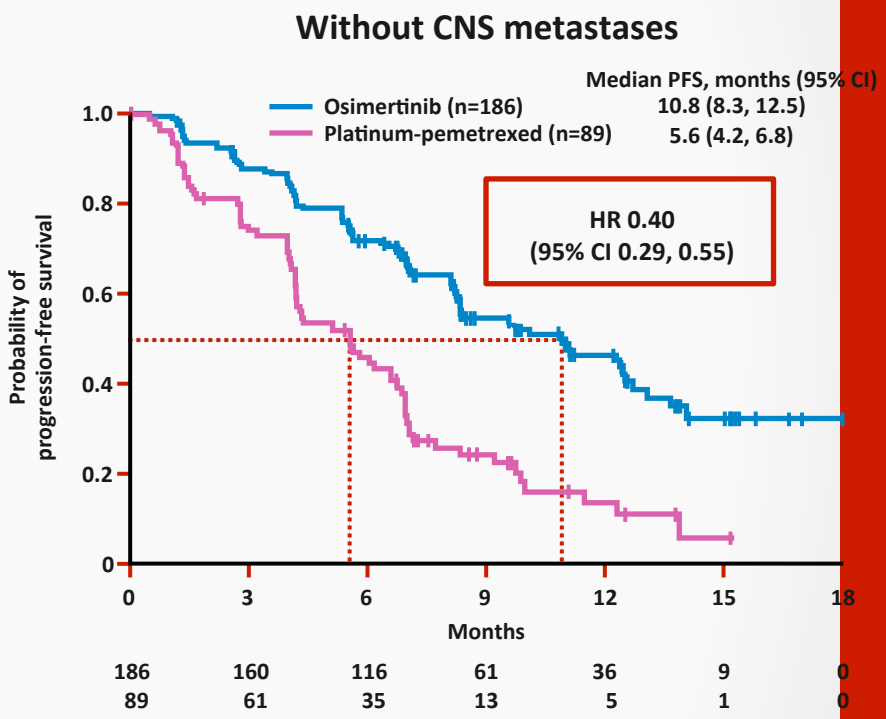


- Analysis of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; median PFS 11.0 vs 4.2 months.

Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data; CI, confidence interval

PFS benefit in AURA 3 with CNS metastases at baseline





Population: intent-to-treat
Progression-free survival defined as time from randomisation until date of objective disease progression or death. Progression included deaths in the absence of RECIST progression.
Tick marks indicate censored data. CNS metastases determined programmatically from baseline data of CNS lesion site, medical history, and/or surgery, and/or radiotherapy.

AURA 3 Safety Summary

AE any*, n (%)	Osimertinib (n=279)	Platinum-pemetrexed (n=136)
Any AE	273 (98)	135 (99)
Any AE Grade ≥3	63 (23)	64 (47)
Any AE leading to death	4 (1)	1 (1)
Any serious AE	50 (18)	35 (26)
Any AE leading to discontinuation	19 (7)	14 (10)
AE, possibly causally related[#], n (%)		
Any AE	231 (83)	121 (89)
Any AE Grade ≥3	16 (6)	46 (34)
Any AE leading to death	1 (<1)	1 (1)
Any serious AE	8 (3)	17 (13)
Any AE leading to discontinuation	10 (4)	12 (9)

Population: safety analysis set (all patients who received at least one dose of study drug and for whom post-dose data were available)
*Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; [#]As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication; AE, adverse event

Mok T. NEJM 2016

EGFR-TKI in 2° linea EFFICACIA: conclusioni

- **Ricercare attentamente la mutazione di resistenza T790M (biopsia liquida -> biopsia tissutale)**
- **Osimertinib (TAGRISSO®): ottima PFS in 2° linea (efficacia simile a quella ottenuta nei pazienti naïve).**
- **In corso fase III in prima linea vs CT (FLAURA)**
- **Da definire la miglior sequenza terapeutica**

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EGFR-TKI e FUMO

- In pazienti fumatori i parametri farmacocinetici (AUC e Cmax) sono più bassi per erlotinib (ma anche per gefitinib)

- Aumentare il dosaggio ??

Hamilton M, et al. Clin Cancer Res. 2006 Apr 1;12(7 Pt 1):2166-71.

EGFR-TKI e terapie NON convenzionali

- "Complementary Medicine is **Used Together With** Conventional Medicine."
- "Alternative Medicine is **Used in Place of** Conventional Medicine."

- 1997 establishment of **National Center of Complementary and Alternative Medicine (NCCAM)** within the NIH
- 1998 establishment of **Office of Cancer Complementary and Alternative medicine (OCCAM)** within the NCI

Alternative Medical Systems	**Ayurveda, Chinese, Native American, Aboriginal, African, Middle Eastern, Tibetan, Central and South American cultures, Homeopathy, Naturopathy**
Mind-Body Interventions	**cognitive-behavioral approaches, meditation, hypnosis, dance, music, art therapy, prayer, mental healing**
Biological Based Therapies	**dietary supplements, herbs, orthomolecular (varying concentrations of chemicals, such as, magnesium, melatonin, and mega-doses of vitamins), individual biological therapies (use of laetrile, shark cartilage, bee pollen).**
Manipulative And Body-Based Methods	**chiropractic, osteopathic manipulation, massage**
Energy Therapies	**Qi gong, Reiki, therapeutic touch, bioelectromagnetic-based therapies (pulsed fields, magnetic fields, or alternating current or direct current fields)**

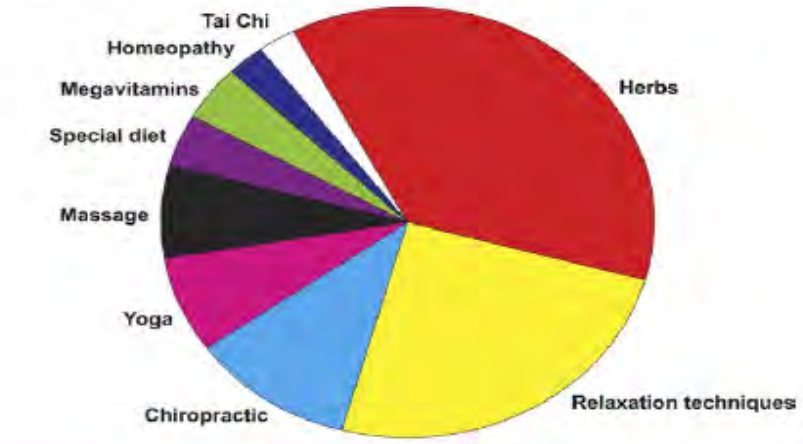


Figure 2 Types of Complementary and Alternative Medicine Used by U.S. Consumers

Data from Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997–2002. Altern Ther Health Med 2005;11:42–9.

As Defined by NCCAM

EGFR-TKI e terapie NON convenzionali

Tossicità indirette

Tabella 2. *CAM e interazioni con agenti antitumorali*[19,20,34,35]

Meccanismo dell'interazione	agenti antitumorali	
Tè verde	Inibizione citocromo P450	Antracicline e taxani, bortezomib
Gingko Biloba	Inibizione CYP3A4 e CYP2C19	Molti chemioterapici e EGFR-TKI
Echinacea	Induzione CYP3A4	Molti chemioterapici e EGFR-TKI
Soia	Fitoestrogeni	Tamoxifene
Ginseng	Inibizione CYP3A4	Molti chemioterapici e EGFR-TKI
Erba di san Giovanni	Induzione molti citocromi	Tutti gli agenti chemioterapici
Essiac	Inibizione CYP3A4	Molti chemioterapici
Vischio	Inibizione CYP3A4	Molti chemioterapici
Liquirizia	Inibizione CYP3A4	Molti chemioterapici

L' Hypericum (= Erba di S. Giovanni) è controindicato in associazione con gli EGFR-TKi

- Poiché induttore di molti citocromi tra cui il CYP3A4.
- Aumenta il metabolismo dei TKI diminuendo conseguentemente le concentrazioni plasmatiche -> riduzione efficacia del trattamento con TKI ?

Vedi schede tecniche di:

- Gefitinib
- Erlotinib
- Afatinib

I rimedi a base di erbe potrebbero ridurre l'efficacia del EGFR-TKIs

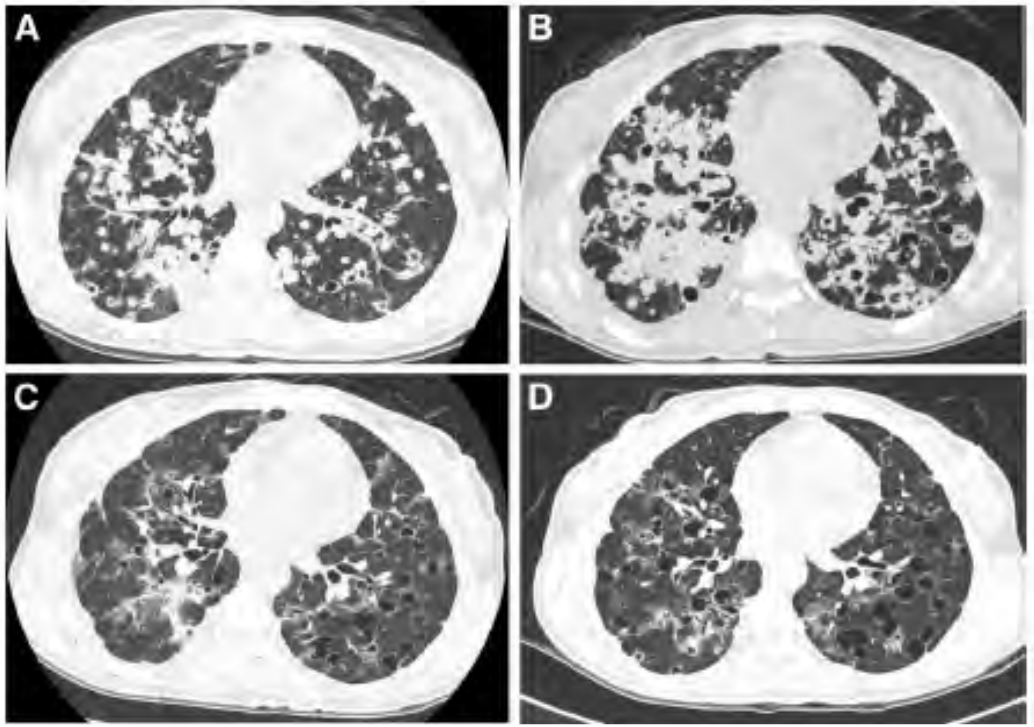
LETTERS TO THE EDITOR

Drug Interaction Between Complementary Herbal Medicines and Gefitinib

- Patient did not inform his physician
- Multiple mixture of herbal medicines (ginseng, mushrooms and selenium)

BASALE

1° RIVAL a 9w



DOPO 4w di SOSPENSIONE ERBE

FOLLOW UP a 30w

Sung-Wook H. JTO Aug 2008

Ginseng, GinKo, Echinacea, Kava potrebbero interagire con EGFR-TKIs

Herb-Drug Interactions

Table 7. Specific Herbal Remedies to Discourage and Avoid During Chemotherapy

Herb	Concurrent Chemotherapy/Condition (suspected effect)
Garlic	Avoid with decarbazine (CYP2E1 inhibition); caution with other concurrent chemotherapy (inconclusive data)
Ginkgo	Caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids (CYP3A4 and CYP2C19 inhibition); discourage with alkylating agents, antitumor antibiotics, and platinum analogues (free-radical scavenging)
Echinacea	Avoid with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and vinca alkaloids (CYP3A4 induction)
Soy	Avoid with tamoxifen (antagonism of tumor growth inhibition), and treatment of patients with estrogen-receptor positive breast cancer and endometrial cancer (stimulation of tumor growth)
Saw palmetto	No significant interactions expected
Ginseng	Caution with camptothecins, cyclophosphamide, EGFR-TK inhibitors, epipodophyllotoxins, taxanes, and Vinca alkaloids (CYP3A4 inhibition); discourage in patients with estrogen-receptor positive breast cancer and endometrial cancer (stimulation of tumor growth)
St. John's wort	Avoid with all concurrent chemotherapy (CYP2B6, CYP2C9, CYP2C19, CYP2E1, CYP3A4, and P-glycoprotein induction)

ENZIMI COINVOLTI NEL METABOLISMO DEGLI INIBITORI TIROSINCHINASICI DI EGFR ORALI[A]

Farmaco	Metabolizzato dagli enzimi CYP								Può inibire[a]				Può indurre[a]	
	3A4	3A5	2D6	1A1	1A2	1B1	2C8	2C9						
Gefitinib	+++	++	+++	++	+			-	CYP2C19 (w)	CYP2D6 (w)	UGT1A9	BRCP		
Erlotinib	+++	+++	+	+	++	+	+	+	CYP3A4 (m)	CYP2C8 (m)	CYP1A1 (s)	UGT1A1 (s)	CYP1A1	CYP1A2
Afatinib	-	-	-	-	-	-	-	-	-	-			-	-
Dacomitinib	++		++					+	CYP2D6 (s)					

La medicina tradizionale cinese potrebbe aumentare l'efficacia degli EGFR-TKIs

• Systematic Review

Traditional Chinese medicinal herbs combined with epidermal growth factor receptor tyrosine kinase inhibitor for advanced non-small cell lung cancer: a systematic review and meta-analysis

Zhong-liang Liu[1*], Wei-rong Zhu[2*], Wen-chao Zhou[3], Hai-feng Ying[2], Lan Zheng[2], Yuan-biao Guo[2], Jing-xian Chen[2], Xiao-heng Shen[2]

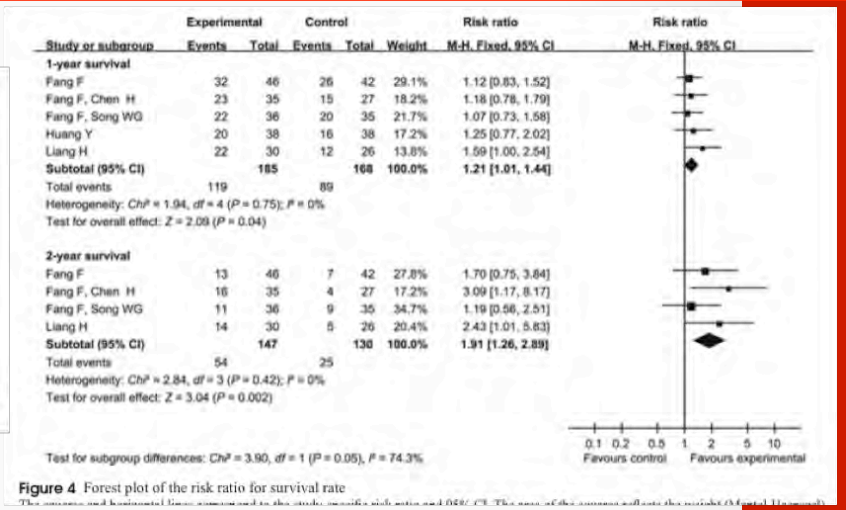


Figure 4 Forest plot of the risk ratio for survival rate

STUDY PROTOCOL Open Access

Fuzheng Kang'ai decoction combined with gefitinib in advanced non-small cell lung cancer patients with epidermal growth factor receptor mutations: study protocol for a randomized controlled trial

Xiao-Bing Yang, Wan-yin Wu*, Shun-qin Long, Hong Deng, Zong-Qi Pan, Wen-Feng He, Yu-Shu Zhou, Gui-Ya Liao, Qiu-Ping Li, Shu-Jing Xiao and Jiao-Zhi Cai

Yang et al. Trials (2015) 16:146

The FZKA granules will consist of *Pseudostellaria heterophylla (Miq.) Pax ex Pax et Hoffm. (Taizishen)* 30 g, *Atractylodes macrocephala Koidz. (Baizhu)* 15 g, *Astragalus membranaceus (Fisch.) Bge. (Huangqi)* 30 g, *Oldenlandia diffusa (Willd.) Roxb. (Baihuasheshecao)* 30 g, *Solanum nigrum L. (Longkui)* 30 g, *Salvia chinensis Benth (Shijianchun)* 30 g, *Cremastra appendiculata (D. Don) Makino (Shancigu)* 30 g, *Coix lachrymal-jobi L. (Yiyiren)* 30 g, *Akebia quinata (Thunb.) Decne (Bayuezha)* 30 g, *Rubus parviflolius L. (Shepaole)* 30 g, *Curcuma kwangsiensis S.G. Lee et C.F. Liang (Ezhu)* 15 g, and *Glycyrrhiza uralensis Fisch. (Gancao)* 10 g [19].

EGFR-TKI e terapie NON convenzionali

- Lack of regulatory oversight
- Lack of quality control
- Lack of knowledge of herb-drug intercation
- Underreporting of adverse drug reaction
- Safe, effective care requires awareness of all your patients' use of herbal supplements and knowledge of their potential interactions with anticancer drugs
- Include all medications when reviewing your patients' meds before their procedure.

EGFR-TKI ed alimenti

TKI sono lipofilici quindi il cibo ha una forte influenza sul loro assorbimento aumentando la loro bio-disponibilità

- Vantaggio: minore dose per ottenere la stessa bio-equivalenza rispetto all'assunzione digiuno

- Svantaggio: notevole variabilità dei contenuti di grassi nei vari pasti -> notevole variabilità nella farmaco cinetica

Somministrazione a digiuno più sicura nella popolazione generale

Assunzione con cibo “high fat”

- Erlotinib: incrementa AUC (33-66%)
- Gefitinib: incrementa AUC ma NON significativo clinicamente
- Afatinib: riduce AUC (39%)
- Osimertinib: AUC sembrerebbe NON essere influenzata significativamente da cibo e PPI

Peters S. et al. Cancer Treat Rev. 2014 Sep;40(8):917-26

IL POMPELMO

IL POMPELMO

- Furanocoumarine (bergamottine) contenute nel succo e buccia di pompelmo sono metabolizzate dal CYP3A4 e legano in maniera covalente l'enzima causandone inattivazione irreversibile soprattutto a livello intestinale ma anche epatico sino alla sintesi de novo dell'enzima.
- Conseguente incremento dell' AUC e della C max

- Singole dose di 200-250 ml di succo o intero frutto sono sufficienti a causare questa interazione
- Inibizione massima nelle prime ore assunzione della bevanda o frutto
- Dopo 10 ore effetto 50% del massimo
- Dopo 24 ore effetto 25 % del massimo

VOLUME 34 · NUMBER 12 · APRIL 20, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Influence of the Acidic Beverage Cola on the Absorption of Erlotinib in Patients With Non–Small-Cell Lung Cancer

Roelof W.F. van Leeuwen, Robert Peric, Koen G.A.M. Hussaarts, Emma Kienhuis, Nikki S. IJzerman, Peter de Bruijn, Cor van der Leest, Henk Codrington, Jeroen S. Kloover, Bronno van der Holt, Joachim G. Aerts, Teun van Gelder, and Ron H.J. Mathijssen

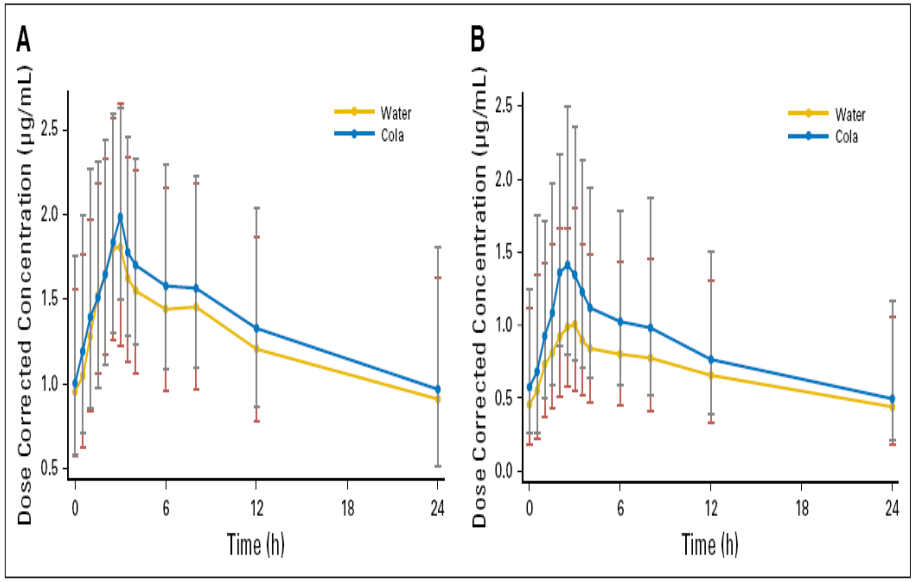


Fig 2. Pharmacokinetic profile. Geometric mean dose corrected concentration *v* time profiles are shown for erlotinib alone administered with water or cola (treatment group A, n = 14) and erlotinib + esomeprazole with water or cola (treatment group B, n = 14).

	Gefitinib	Erlotinib	Afatinib	Suggerimenti
PPI	↓ AUC (50%)	↓ AUC (50%)		TKI dopo 12h da PPI
Anti-H2 o antiacidi	↓ AUC (50%)	↓ AUC (33%)		TKI (E) 2h prima o 6-10h dopo antiH2-antiacido
Induttori CYP3A4 (es. CMP,fenobarbital, rifampicina, iperico)	↓ AUC (>50%)	↓ AUC (> 50%)	↓ AUC (possibile)	Associazione da evitare
Warfarin	↑ INR	↑ INR (rilev. Clinica ?)		Dosare INR più freq
Inibitori CYP3A4 (es. Verapamil)	↑ AUC	↑ AUC (rilev. Clinica ?)		↓ 50 mg E se tox
Statine		↑ Rischio miopatia/ rabdomiolisi		Se ↑ CPK sospendere statine
Induttori glicoproteina P (es. rifampicina)			↓ AUC	↑ A di 10 mg
Inibitori glicoproteina P (es. ritonavir, chetoconazolo, eritromicina)	↑ AUC	↑ AUC (?)	↑ AUC	TKI a 6-12h da inib. P-GP ↓ A di 10 mg se tox

Peters S. et al. Cancer Treat Rev. 2014 Sep;40(8):917-26

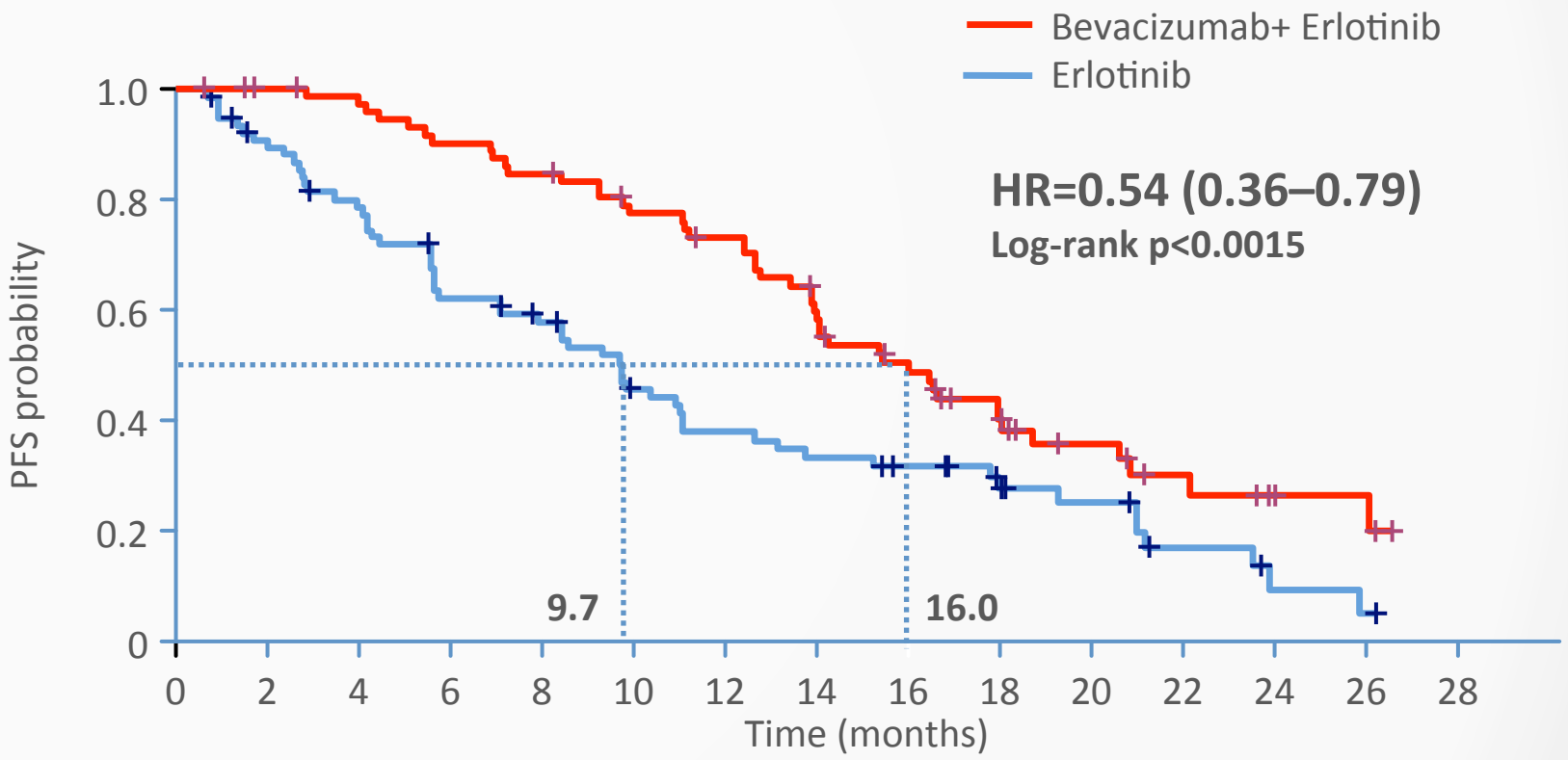
EGFR-TKI ed IMMUNOTERAPIA

- 2 studi con Durvalumab + Osimertinib (fas III Caural e fase I Tatoon) chiusi per aumento di incidenza di interstiziopatie polmonari (ILD)
- 1 studio con anti PDL-1 + EGF616 sospeso per aumento ILD e tossicità cutanea (TEN)
- Un case report di ILD indotta da Osimertinib assunto dopo la sospensione di un anticorpo anti-PDL1

Mamesaya N. et al. Invest New Drugs 2016, Case Report

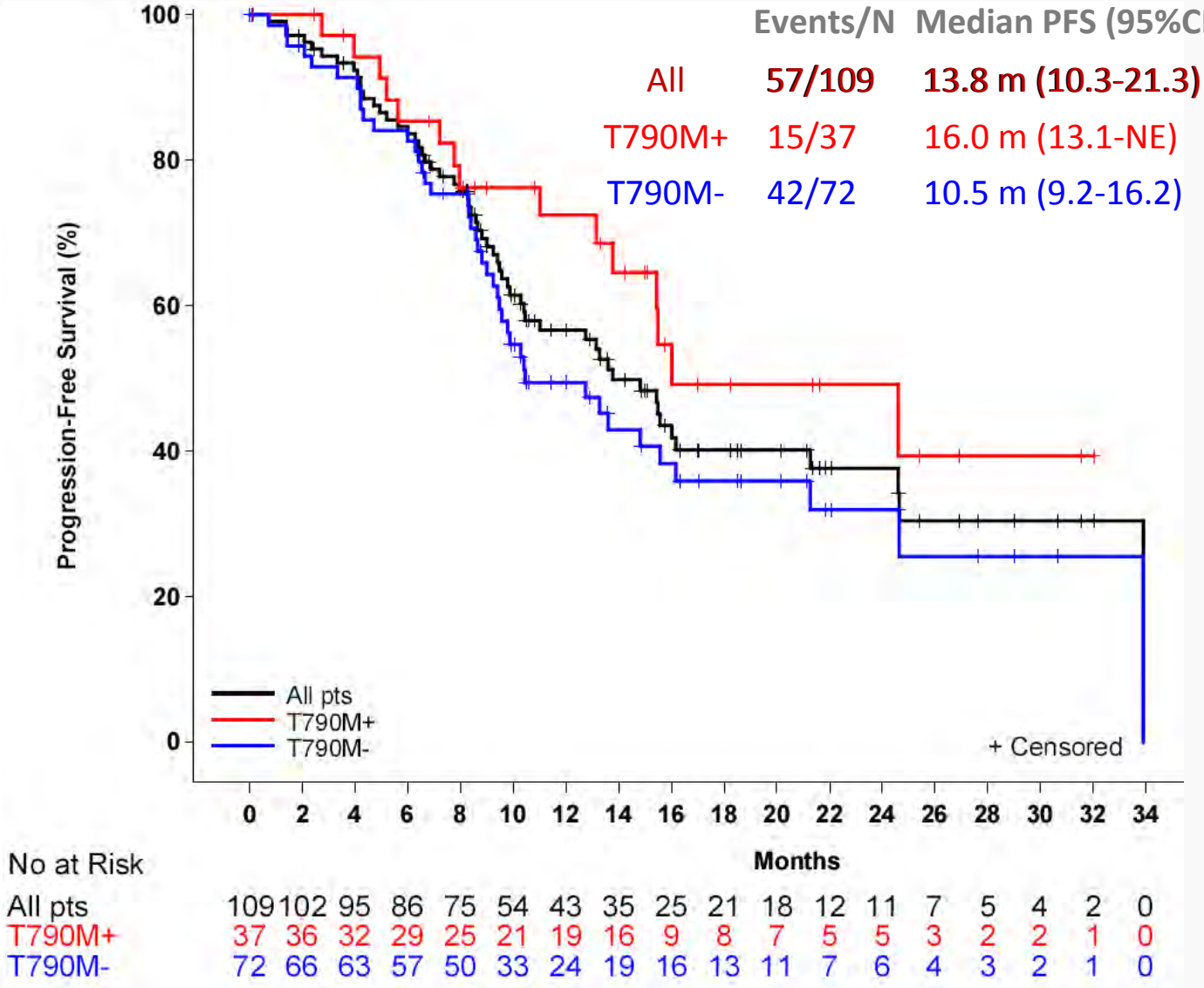
EGFR TKIs e ANTIANGIOGENICI

JO25567: PFS by independent review



Adapted from Seto T, et al. Lancet Oncol. 2014; 15(11): 1236-44.

BELIEF: PFS by T790M mutation



	Events/N	Median PFS (95%CI)	12m PFS (95%CI)
All	**57/109**	**13.8 m (10.3-21.3)**	56.7% (46.0-66.0)
T790M+	15/37	16.0 m (13.1-NE)	72.4% (53.4-84.7)
T790M-	42/72	10.5 m (9.2-16.2)	49.4% (36.6-61.0)

No at Risk

All pts	109	102	95	86	75	54	43	35	25	21	18	12	11	7	5	4	2	0
T790M+	37	36	32	29	25	21	19	16	9	8	7	5	5	3	2	2	1	0
T790M-	72	66	63	57	50	33	24	19	16	13	11	7	6	4	3	2	1	0

ONGOING phase III trials

Eligibility
- **Stage IIIB/IV NSCLC, chemo-naïve**
- ***Acitivating EGFR* mutation**
- **ECOG PS 0–2**
- **Bevacizumab-eligible**

BEVERLY TRIAL

1:1

Erlotinib 150mg

Bevacizumab 15mg/kg + Erlotinib 150mg

- Primary endpoint: PFS
- Co-primary endpoint: IA-PFS e BICR-PFS
- Secondary endpoints: OS, QoL, BICR-ORR, IA-ORR, safety
- Exploratory endpoint: usefulness of **liquid biopsy** at baseline and FW

Eligibility
- **Stage IV NSCLC, chemo-naïve**
- ***Acitivating EGFR* mutation ; NO T790M**
- **ECOG PS 0–2**
- **NO brain metastasis**
- **Ramucirumab-eligible**

RELAY TRIAL

1:1

Erlotinib 150mg

Ramucirumab 10mg/kg 2w + Erlotinib 150mg

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DCR, DoR, **PK and immunogenicity of RAM**, QoL, safety

EMA

28 April 2016

Bevacizumab, in combination with erlotinib, is indicated for first-line treatment of advanced non-squamous NSCLC with EGFR activating mutations

Indicazione NON ancora presente in ITALIA !!!

Quale EGFR-TKI in EGFR mutati ? Differenze

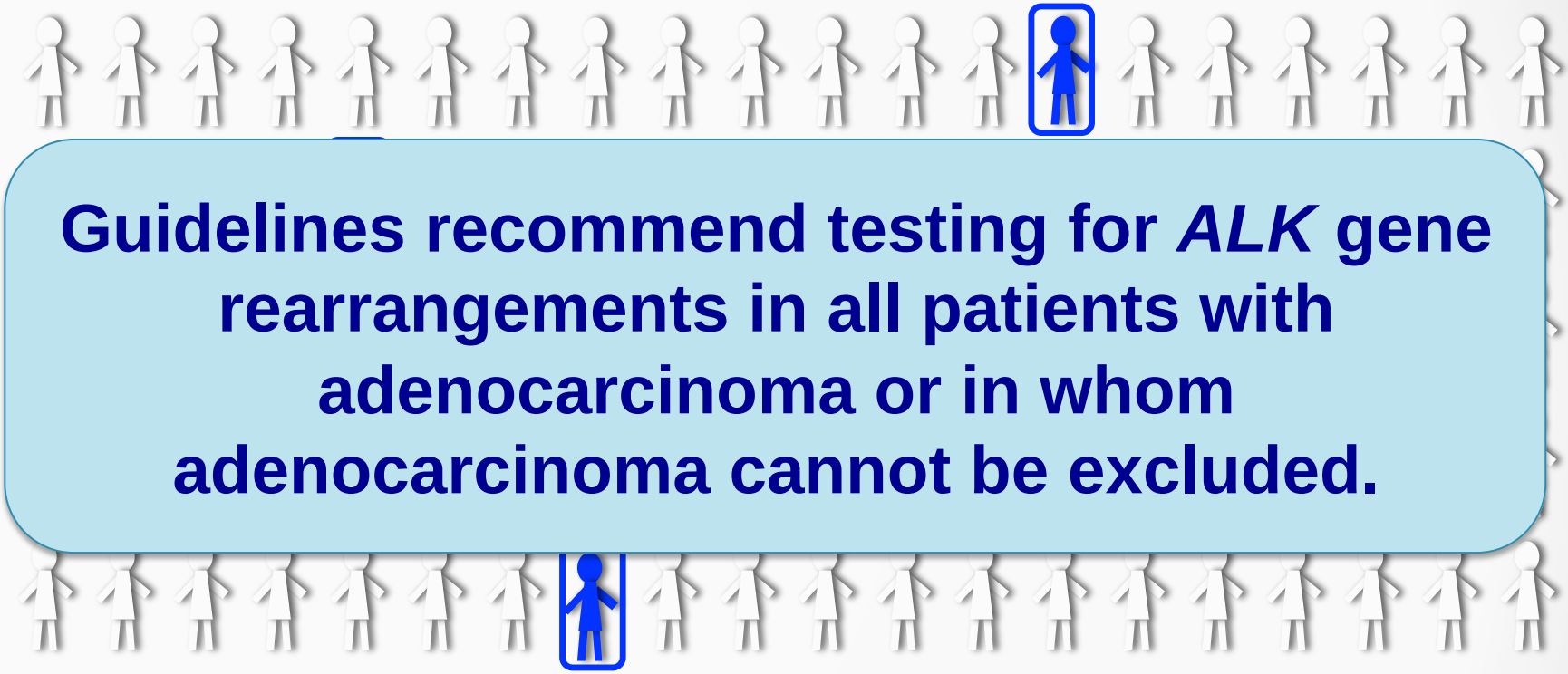
	GEFITINIB	ERLOTINIB	AFATINIB
Efficacia	++	++	+++
Tossicità	+++	++	+
Dosaggi	+ (250)	++ (150, 100)	+++ (40, 30, 20)
Esperienza d'uso	+++	++	+
Linea di terapia	qualunque	qualunque (non pretrattati TKI)	I linea
Drug-interaction	+	+	++
Costo (solo farmaco)	+	++	+++

AGENDA

- INIBITORI TKI DI EGFR
  - ✓ 1° linea
  - ✓ 2° linea
  - ✓ Interazioni

- INIBITORI TKI DI ALK
  - ✓ **1° linea**
  - ✓ **Linee successive**
  - ✓ Interazioni

ALK positive NSCLC



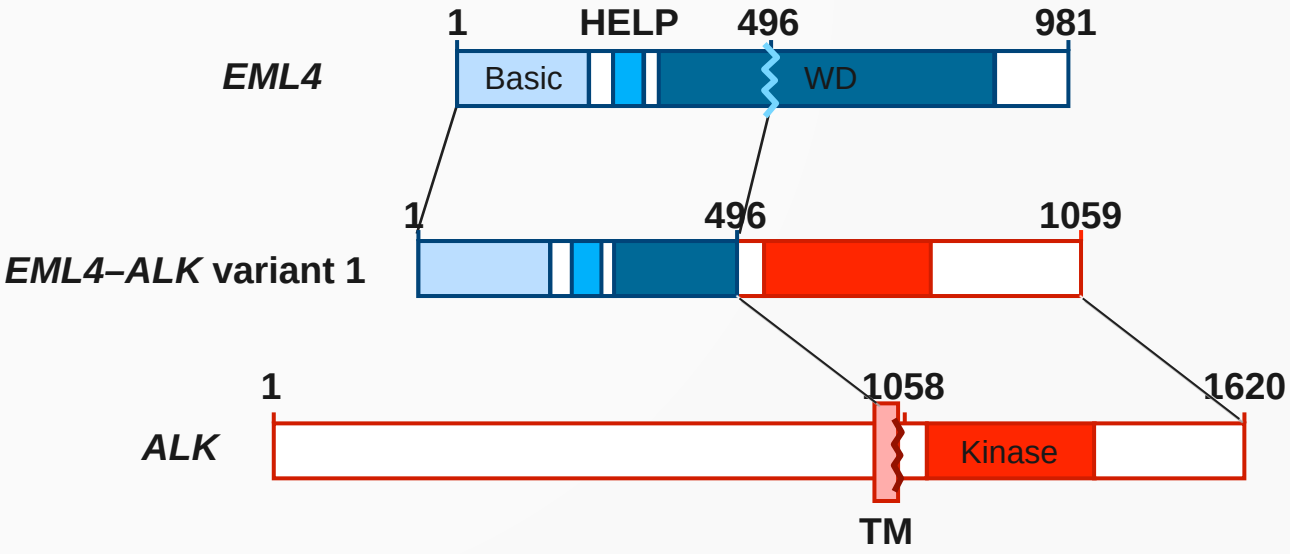
Guidelines recommend testing for *ALK* gene rearrangements in all patients with adenocarcinoma or in whom adenocarcinoma cannot be excluded.

ALK Rearrangements

- **3-5% of NSCLC**
- Adenocarcinoma
- Younger patients
- Never smokers

Discovery of the EML4-ALK Fusion in NSCLC

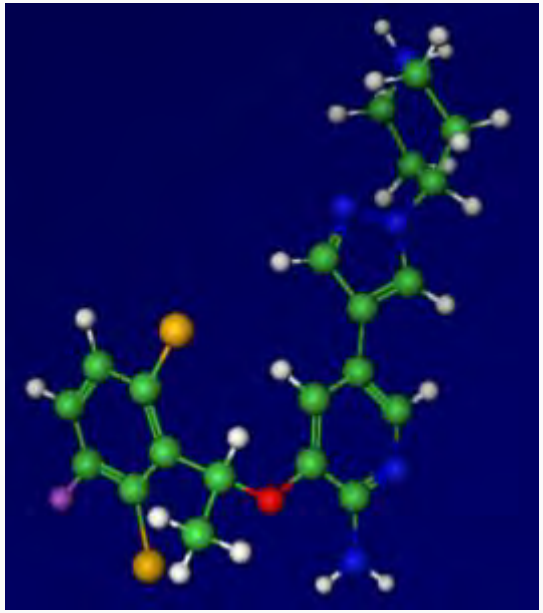
- Initially reported in 2007 as a result of an inversion in chromosome 2p, which results in the fusion of the N-terminal portion of the echinoderm microtubule-associated protein-like 4 (*EML4*) with the kinase domain of *ALK*



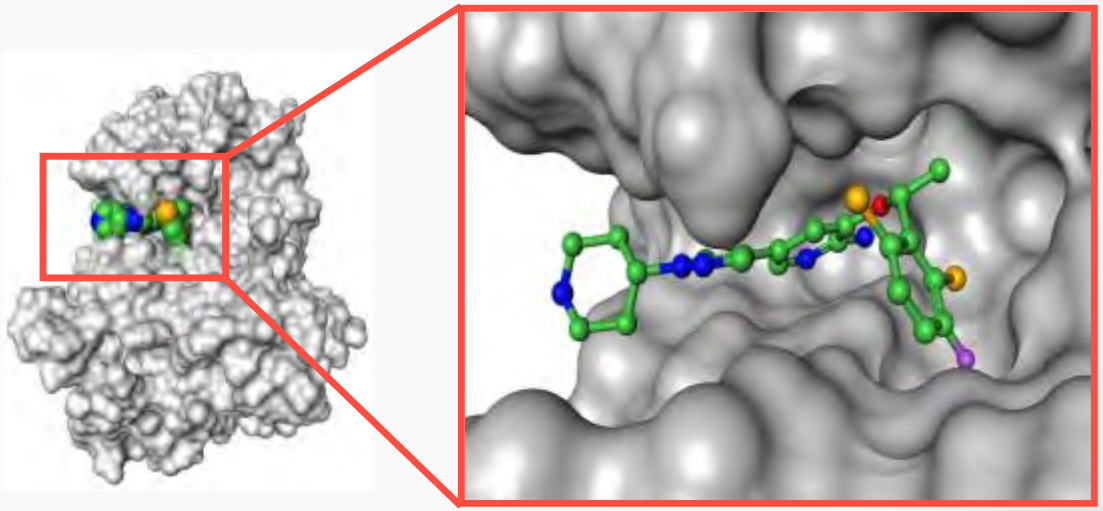
Soda M, et al. Nature 2007;448:561–7

Crizotinib: Overview

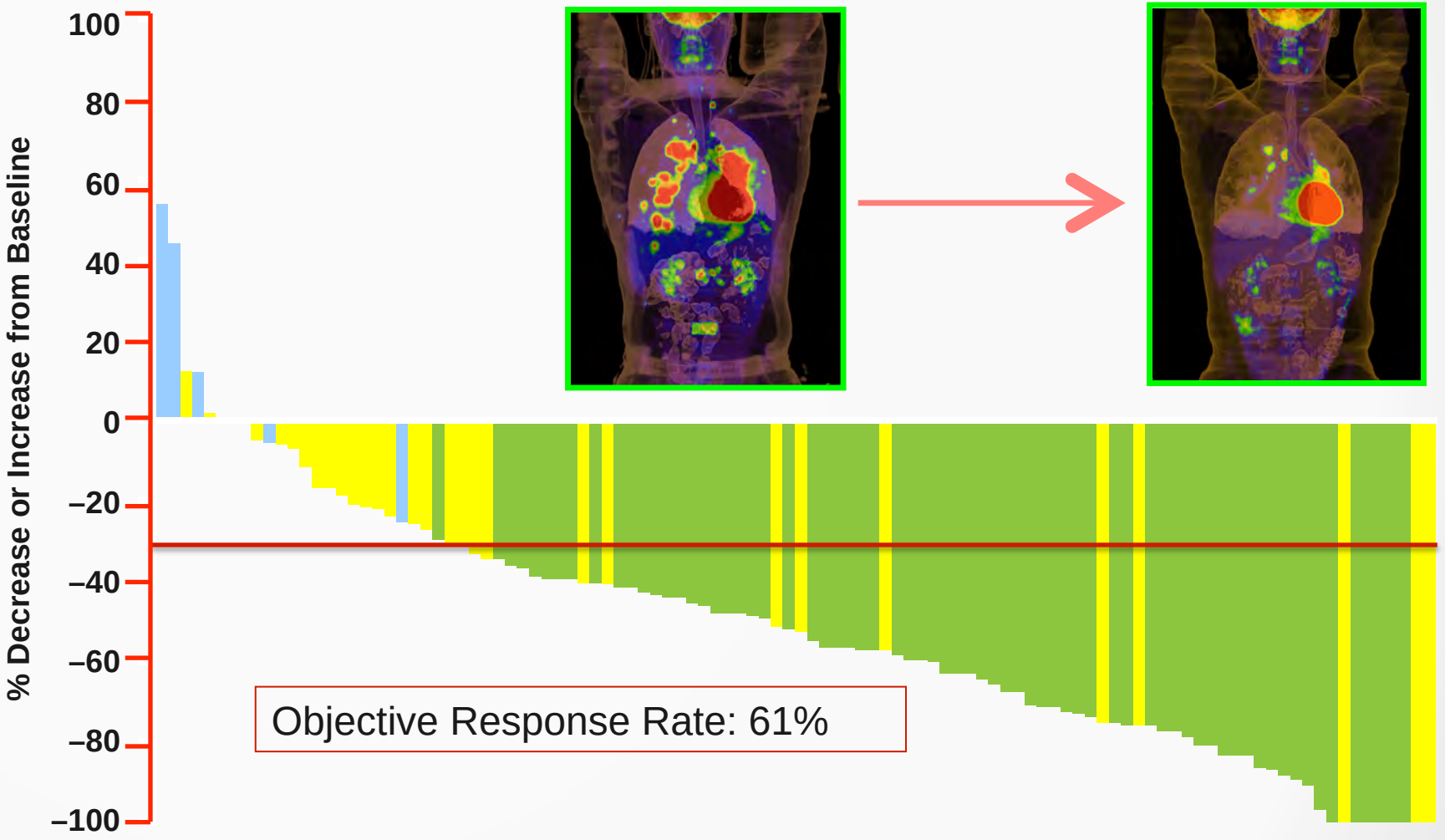
- Formulary name: PF-02341066
- Generic name: Crizotinib
- Trade name: **XALKORI™**
- Chemical formula: $C_{21}H_{22}Cl_2FN_5O$
- Mechanism of action: Competitive ATP inhibitor
- Main targets: ALK, c-Met, ROS
- AIFA approved 1st line for ALK-positive NSCLC on March 2017



Crizotinib in the ALK ATP binding pocket

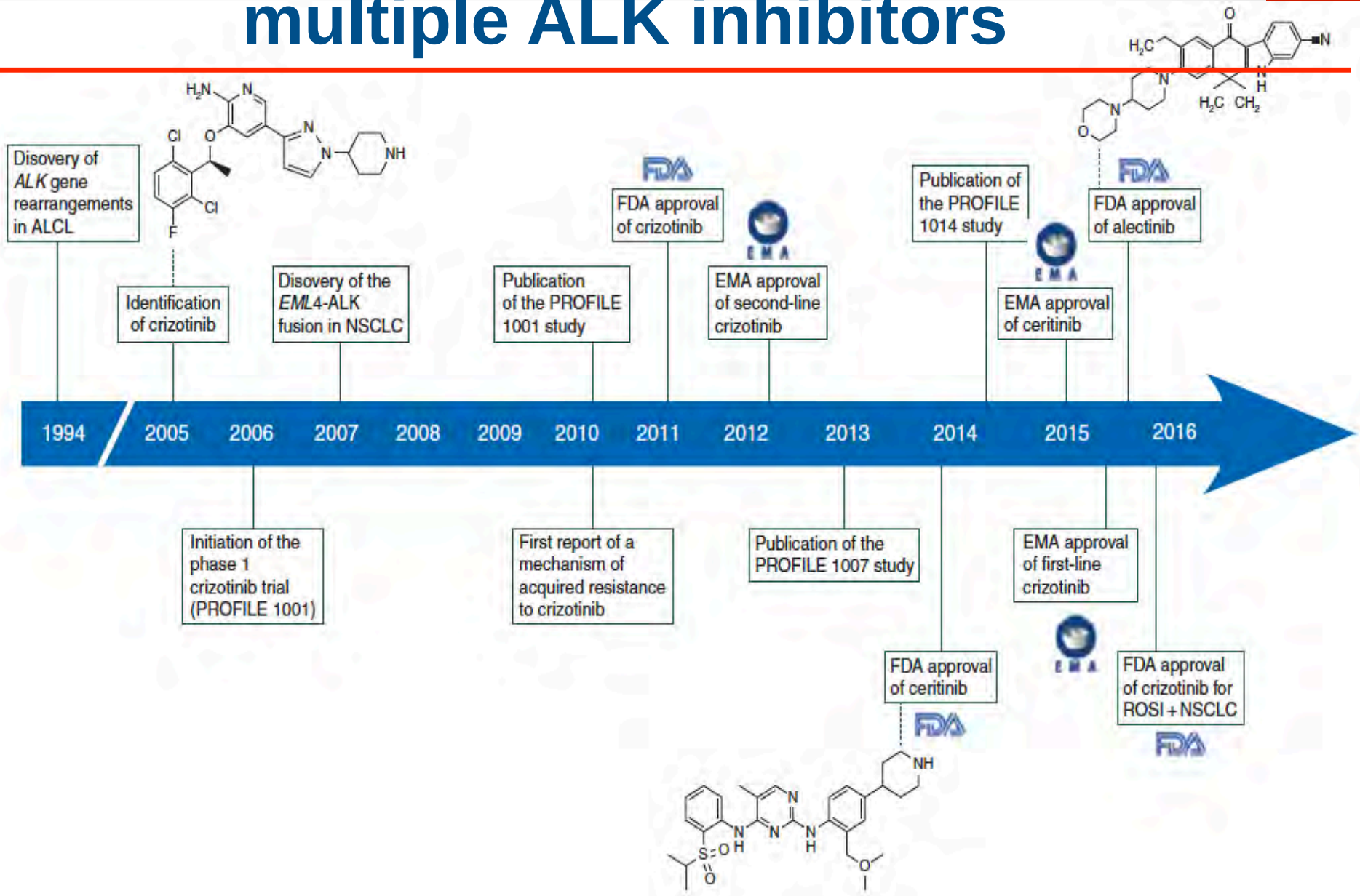


ALK+ NSCLC are sensitive to crizotinib



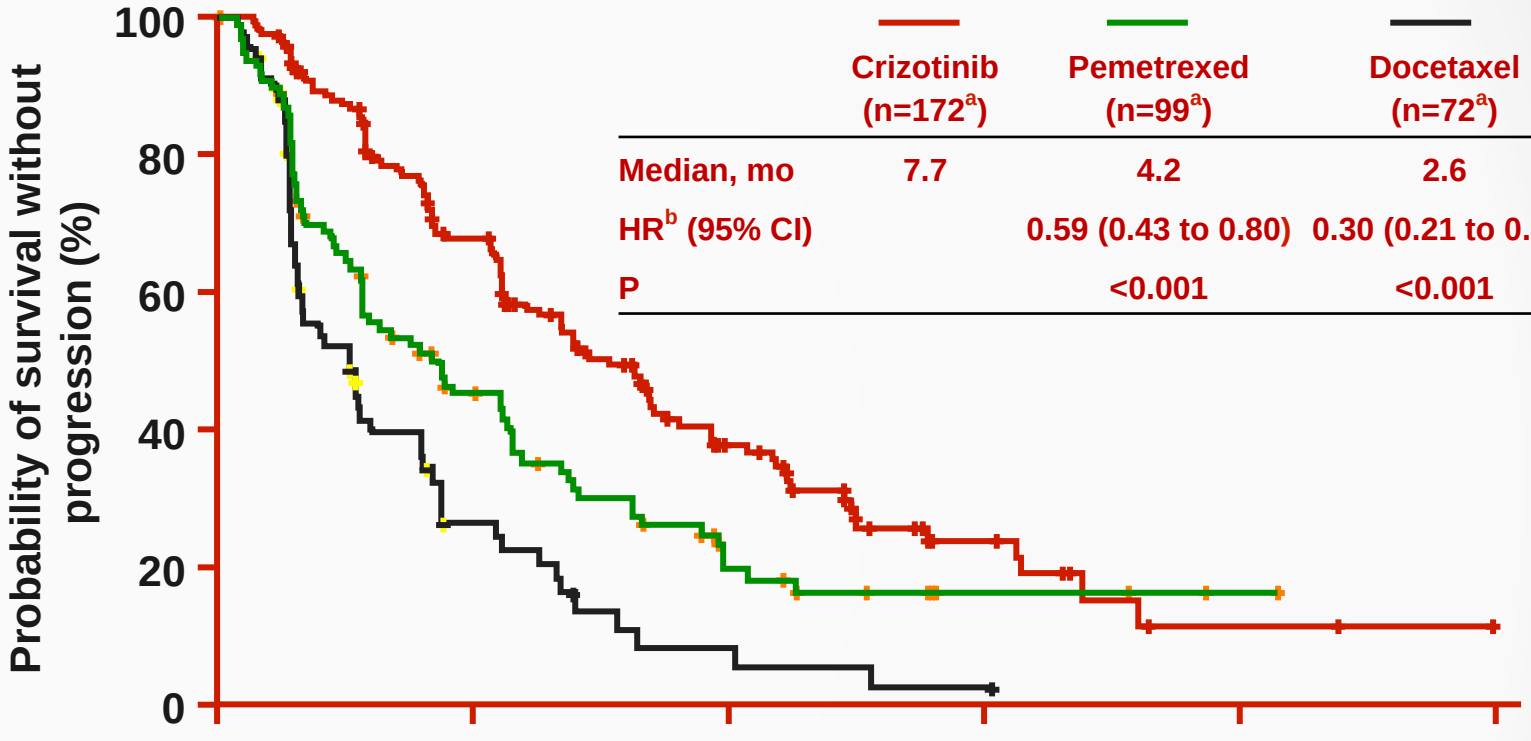
Kwak NEJM 2010; Camidge Lancet Oncology 2012

Rapid clinical development of multiple ALK inhibitors



Solomon & Soria *Ann Oncol* 2016;27:suppl3:iii1-iii3

PROFILE 1007 PFS crizotinib vs PEM vs TXT in pretreated (CHT) pts



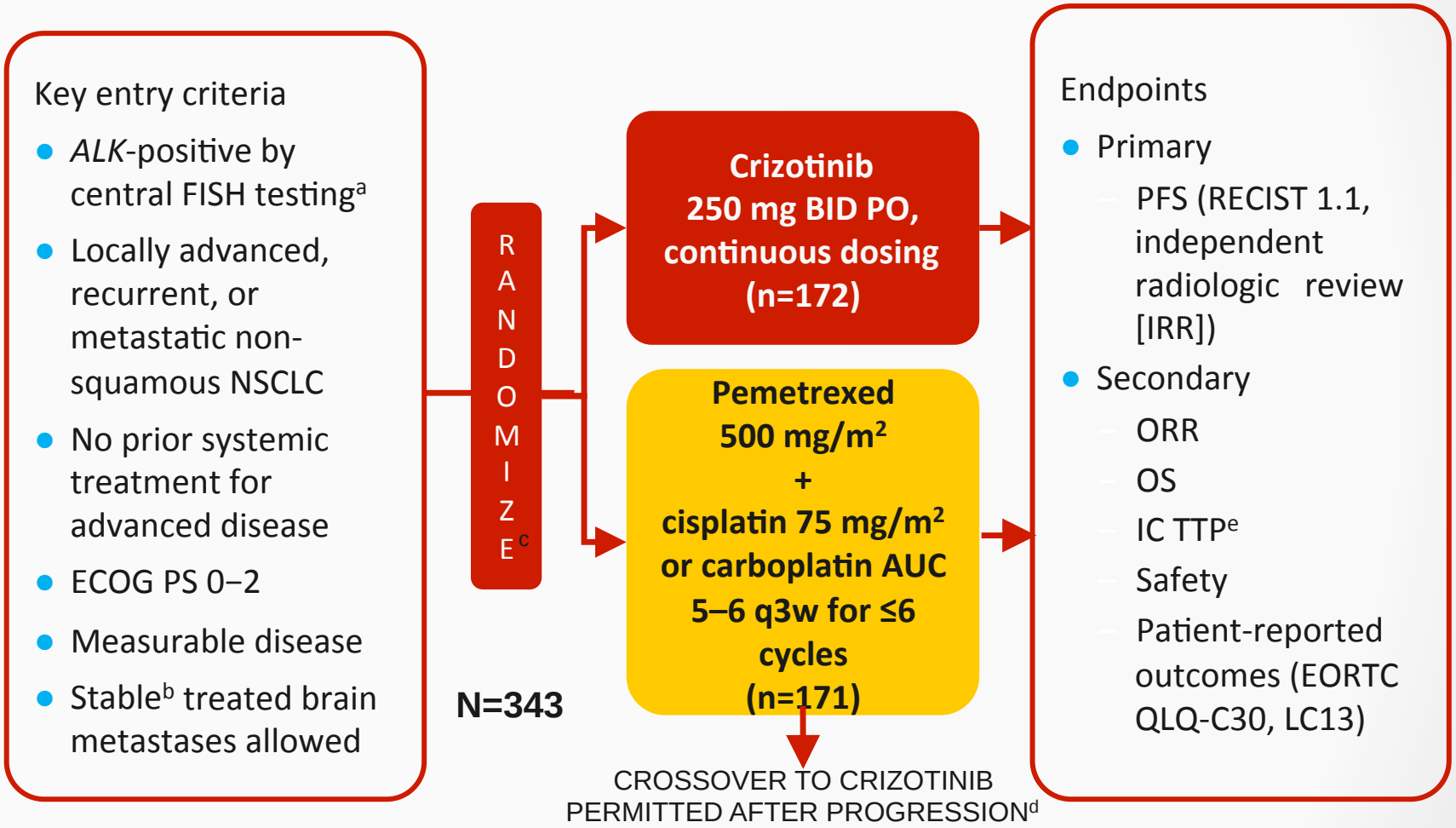
	Crizotinib (n=172[a])	Pemetrexed (n=99[a])	Docetaxel (n=72[a])
Median, mo	7.7	4.2	2.6
HR[b] (95% CI)		0.59 (0.43 to 0.80)	0.30 (0.21 to 0.43)
P		<0.001	<0.001

No. at risk						
Crizotinib	172	93	38	11	2	0
Pemetrexed	99	36	2	3	1	0
Docetaxel	72	13	3	1	0	

Overall response rate = 65.3% in Crizotinib arm and 19.5% in Chemotherapy arm arm

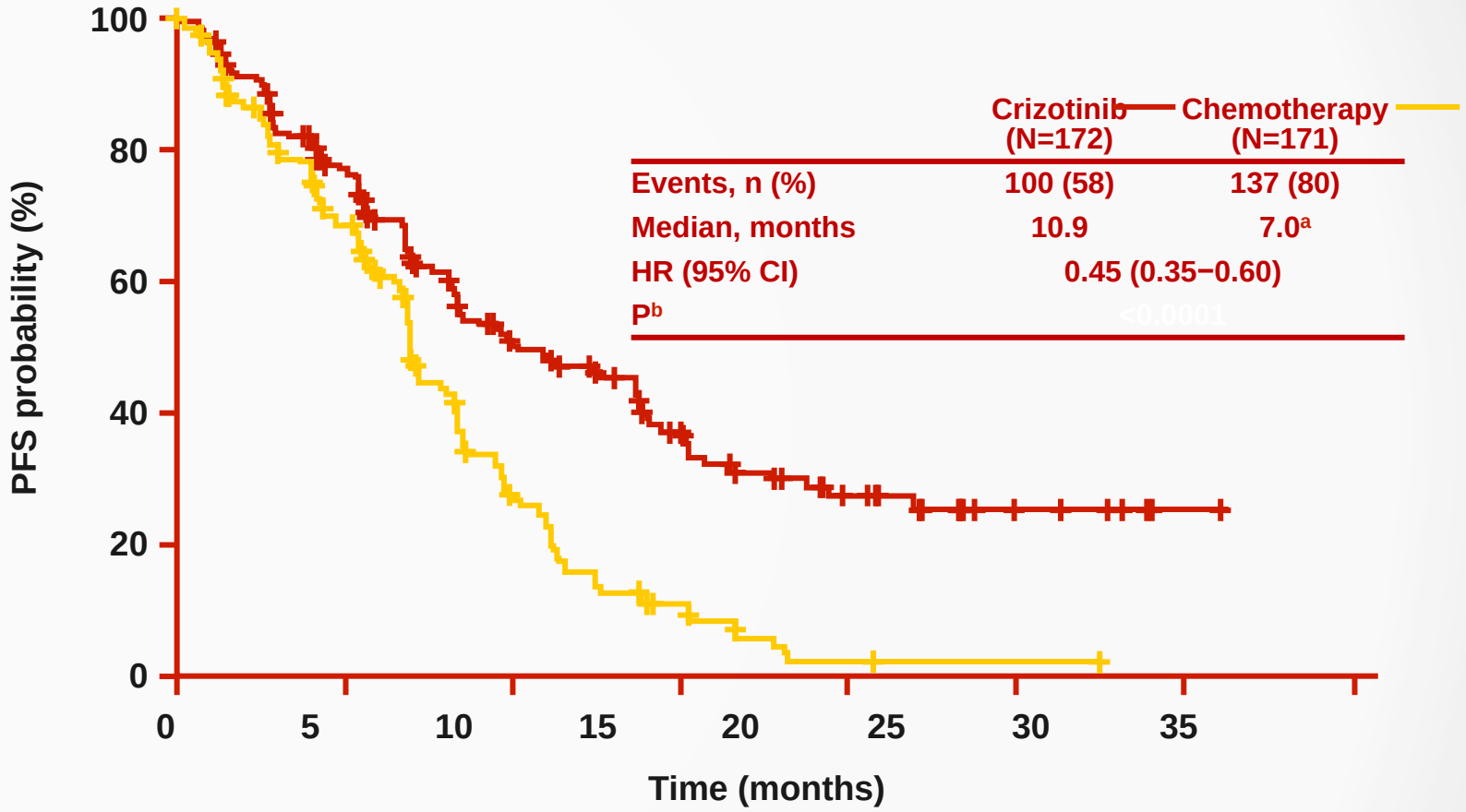
Shaw AT, et al. N Engl J Med 2013;368:2385–94

PROFILE 1014: randomized open-label Phase III trial, 1° line crizotinib



Solomon, Mok *et al.* NEJM 2014

PROFILE 1014: PFS crizotinib vs platinum-pemetrexed in untreated pts



- ORR: crizotinib 74% vs chemotherapy 45% p<0.0001
- Improved lung cancer related symptoms and quality of life with crizotinib vs chemotherapy

Solomon, Mok *et al.* NEJM 2014

PROFILE 1014: AEs

AE	n (%)			
	Crizotinib (N=171)		Chemotherapy (N=169)[b]	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Higher frequency (≥5% absolute difference) in crizotinib arm				
Vision disorder[c]	122 (71)	1 (1)	24 (14)	0
Diarrhea	105 (61)	4 (2)	29 (17)	1 (1)
Edema[c]	83 (49)	1 (1)	22 (13)	1 (1)
Vomiting	78 (46)	3 (2)	68 (40)	6 (4)
Constipation	74 (43)	3 (2)	53 (31)	0
Elevated transaminases[c]	61 (36)	24 (14)	22 (13)	4 (2)
Upper respiratory infection[c]	55 (32)	0	21 (12)	1 (1)
Abdominal pain[c]	45 (26)	0	20 (12)	0
Dysgeusia	45 (26)	0	11 (7)	0
Headache	37 (22)	2 (1)	25 (15)	0
Pyrexia	32 (19)	0	19 (11)	1 (1)
Dizziness[c]	31 (18)	0	18 (11)	2 (1)
Pain in extremity	27 (16)	0	12 (7)	0
Higher frequency (≥5% absolute difference) in chemotherapy arm				
Nausea	95 (56)	2 (1)	103 (61)	3 (2)
Decreased appetite	51 (30)	4 (2)	59 (35)	1 (1)
Fatigue	49 (29)	5 (3)	65 (38)	4 (2)
Neutropenia[c]	36 (21)	19 (11)	51 (30)	26 (15)
Stomatitis[c]	24 (14)	1 (1)	34 (20)	2 (1)
Asthenia	22 (13)	0	42 (25)	2 (1)
Anemia[c]	15 (9)	0	54 (32)	15 (9)
Leukopenia[c]	12 (7)	3 (2)	26 (15)	9 (5)
Thrombocytopenia[c]	2 (1)	0	31 (18)	11 (7)

[a]In any group and with ≥5% absolute difference between treatment groups; not adjusted for differential treatment duration.
[b]Only includes events before crossover to crizotinib.
[c]Clustered term comprising AEs that represent similar clinical symptoms/syndromes.

Solomon, Mok *et al.* NEJM 2014

Efficacy of crizotinib: 1° vs 2° Line

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFI[illegible]	[illegible]OFILE 1014[4] (N=172)
Phase	I	II	III	III
Line of therapy	Any line	2[nd] [illegible]d	2[nd] line	1[st] line
ORR	61%	60%	65%	74%
PFS, median (mos)		8.1	7.7	10.9
Survival probabilit[illegible] mos	75%	NA	70%	84%

Crizotinib: the standard of care in first line !!

[1]Camidge et al., Lancet Onc, 2012
[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM, 2013
[4]Solomon et al., NEJM 2014