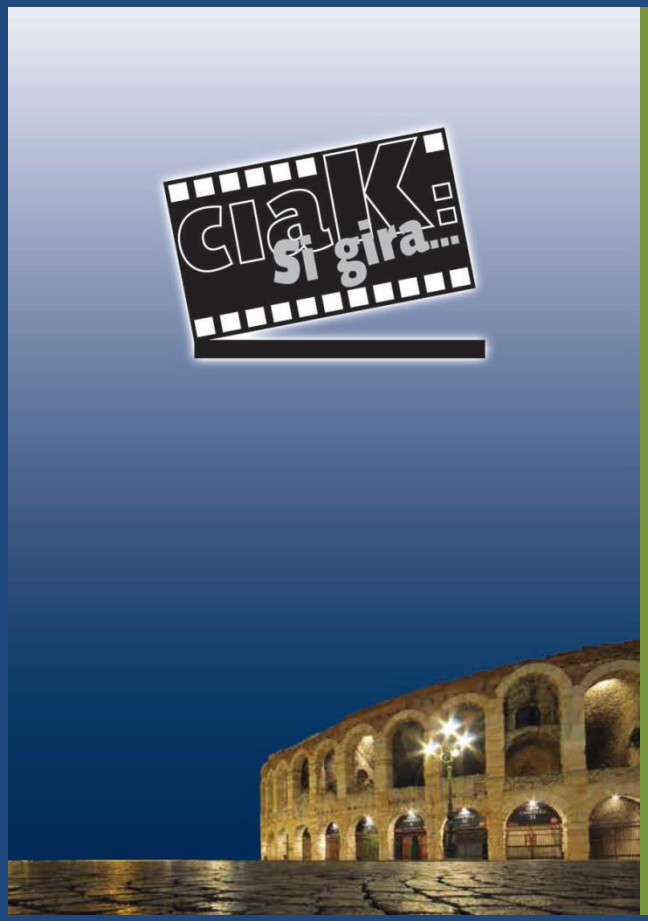


La sequenza terapeutica nel paziente con NSCLC avanzato in base ~~all'istologia e~~ alla caratterizzazione molecolare: Impatto sulla pratica clinica?

GRUPPO A

Luca Toschi (former Vanesa Gregorc)


Vino
Rosso Rubino
Brillante
SALBANELLO
ITALIA
Le Uve
Cabernet e
Malbech

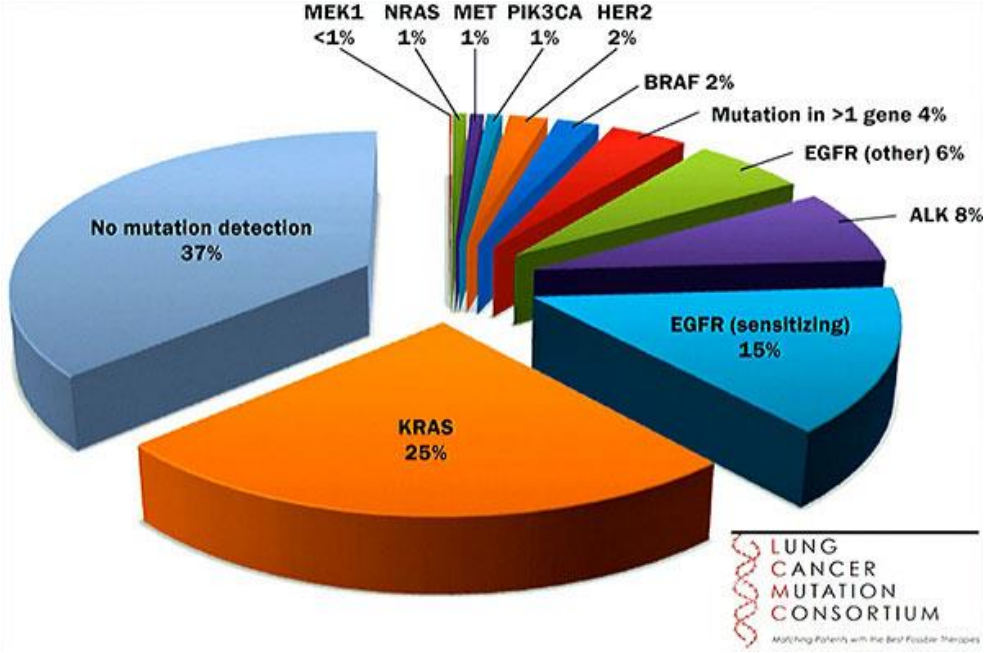
Who are *oncogene addicted* NSCLC patients?

Lung Cancer Consortium Mutation

- 16 US cancer centers

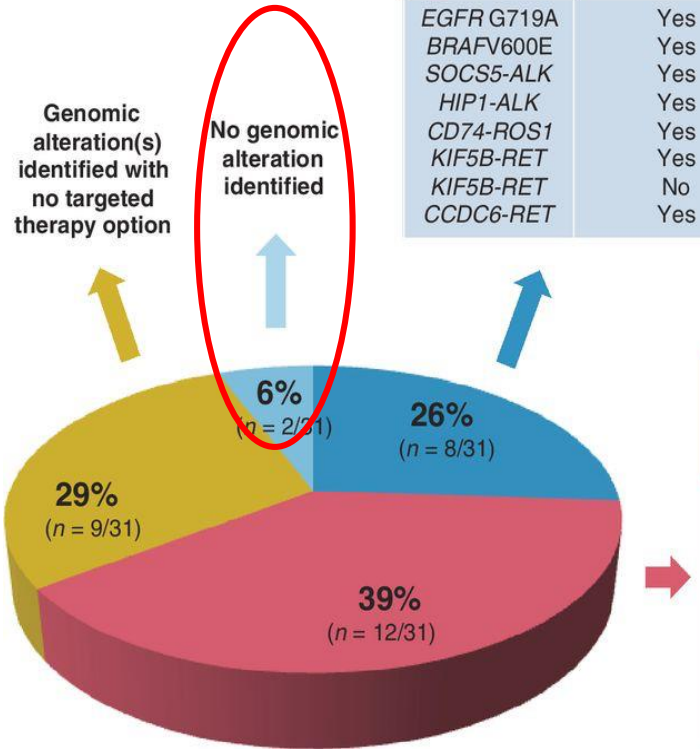
- Test 10 driver mutations in 1007 lung adenocarcinomas

- 63%: oncogenic driver



NGS in never/light smokers with lung ADC with negative non-NGS tests

Genomic alteration with targeted therapy in NCCN guidelines	Tumor from same procedure as tumor subjected to non-NGS testing	Patient's clinical course
EGFR G719A	Yes	Recently started erlotinib, response evaluation pending
*BRAF*V600E	Yes	Subsequently passed away
SOCS5-ALK	Yes	**Disease shrinkage (<30%) with crizotinib**
HIP1-ALK	Yes	**Partial response to crizotinib**
CD74-ROS1	Yes	Recently started crizotinib, response evaluation pending
KIF5B-RET	Yes	**Partial response to cabozantinib**
KIF5B-RET	No	**Disease shrinkage (<30%) with cabozantinib**
CCDC6-RET	Yes	Candidate for cabozantinib after progression on chemotherapy



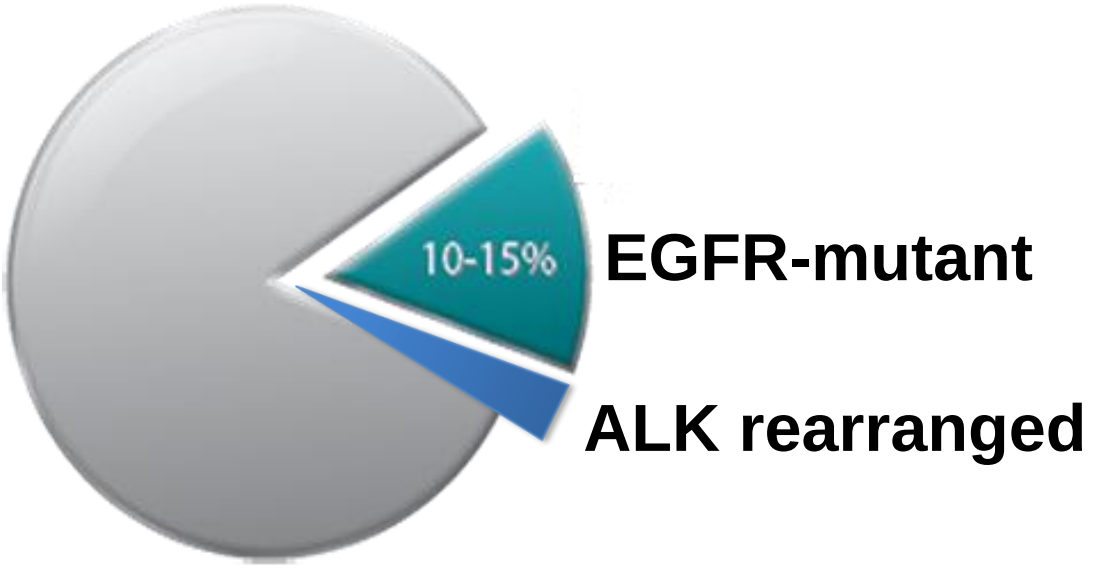
Genomic alteration with targeted agent available on or off a clinical trial	Targeted therapeutic (clinicaltrials.gov number) with potential activity available at institution
CDKN2A loss	CDK4/6 inhibitor (NCT01237236)
EGFR L747P	erlotinib, afatinib
EGFR exon 18 del (*n* = 2)	pan-ERBB inhibitor (NCT01858389)
EGFR exon 20 ins	pan-ERBB inhibitor (NCT01858389)
ERBB2 L755F	pan-ERBB/mTOR inhibitor (NCT01953926)
FGFR1 T141R	FGFR inhibitor (NCT01948297)
KRAS G12C	ERK inhibitor (NCT01781429)
KRAS Q61H	ERK inhibitor (NCT01781429)
MDM2 amp (*n* = 3)	MDM2 inhibitor (NCT01877382)

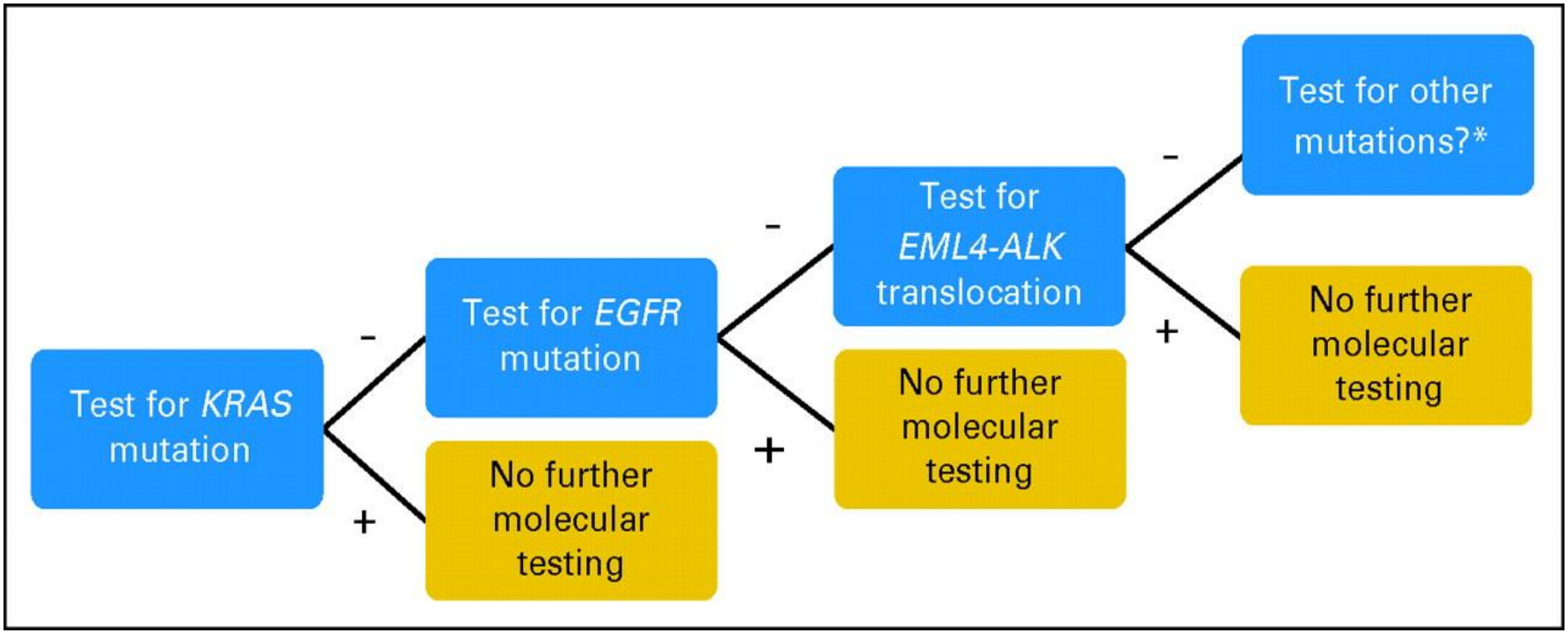
- coding exons of **287** cancer-related genes
- introns of **19** frequently rearranged genes

Drilon, CCR 2015

Today

Who are *oncogene addicted* NSCLC *in clinical practice?*





Horn L, et al. J Clin Oncol, 27 (26):4232-5, 2009

6 patients with concomitant *EGFR* mutation and *EML4-ALK* translocation

- 1.6 % of the overall population
- 13.6% of *EGFR-mutated* patients
- 18.8% of patients with *EML4-ALK* translocation

- 1.1 % of the overall population
- 6.8% of *EGFR-mutated* patients
- 3.2% of *KRAS-mutated* patients

7 patients with concomitant *EML4-ALK* translocation and *KRAS* mutation

- 2.5 % of the overall population
- 29.2% of patients with *EML4-ALK* translocation
- 3.2% of *KRAS-mutated* patients

NSCLC EGFR-mutato

La prima linea è definita?

- EGFR TKI: prima scelta rispetto a CT

1st line: EGFR-TKIs vs CT

Author	Study	N (EGFR mut. +)	EGFR-TKI	ORR	Median PFS*
Mok	IPASS	261	Gefitinib	71.2% vs. 47.3%	9.8 vs. 6.4 months
Lee	First-SIGNAL	42	Gefitinib	84.6% vs. 37.5%	8.4 vs. 6.7 months
Mitsudomi	WJTOG 3405	177	Gefitinib	62.1% vs. 32.2%	9.2 vs. 6.3 months
Maemondo	NEJGSG002	228	Gefitinib	73.7% vs. 30.7%	10.8 vs. 5.4 months
Zhou	OPTIMAL	154	Erlotinib	83% vs. 36%	13.1 vs. 4.6 months
Rosell	EURTAC	175	Erlotinib	58% vs. 15%	9.7 vs. 5.2 months
Yang	LUX-Lung 3	345	Afatinib	56.1% vs. 22.6%	11.1 vs. 6.9 months
Wu	LUX-Lung 6	364	Afatinib	66.9% vs 23.0%	11.0 vs 5.6 months

*Primary endpoint

NSCLC EGFR-mutato

La prima linea è definita?

- EGFR TKI: prima scelta rispetto a CT

Quale TKI scegliere?

- ECOG PS, eta', interazioni farmacologiche
- Dubbi: tipo di mutazione; mutazioni non comuni
- Criticità: aspetti metodologici

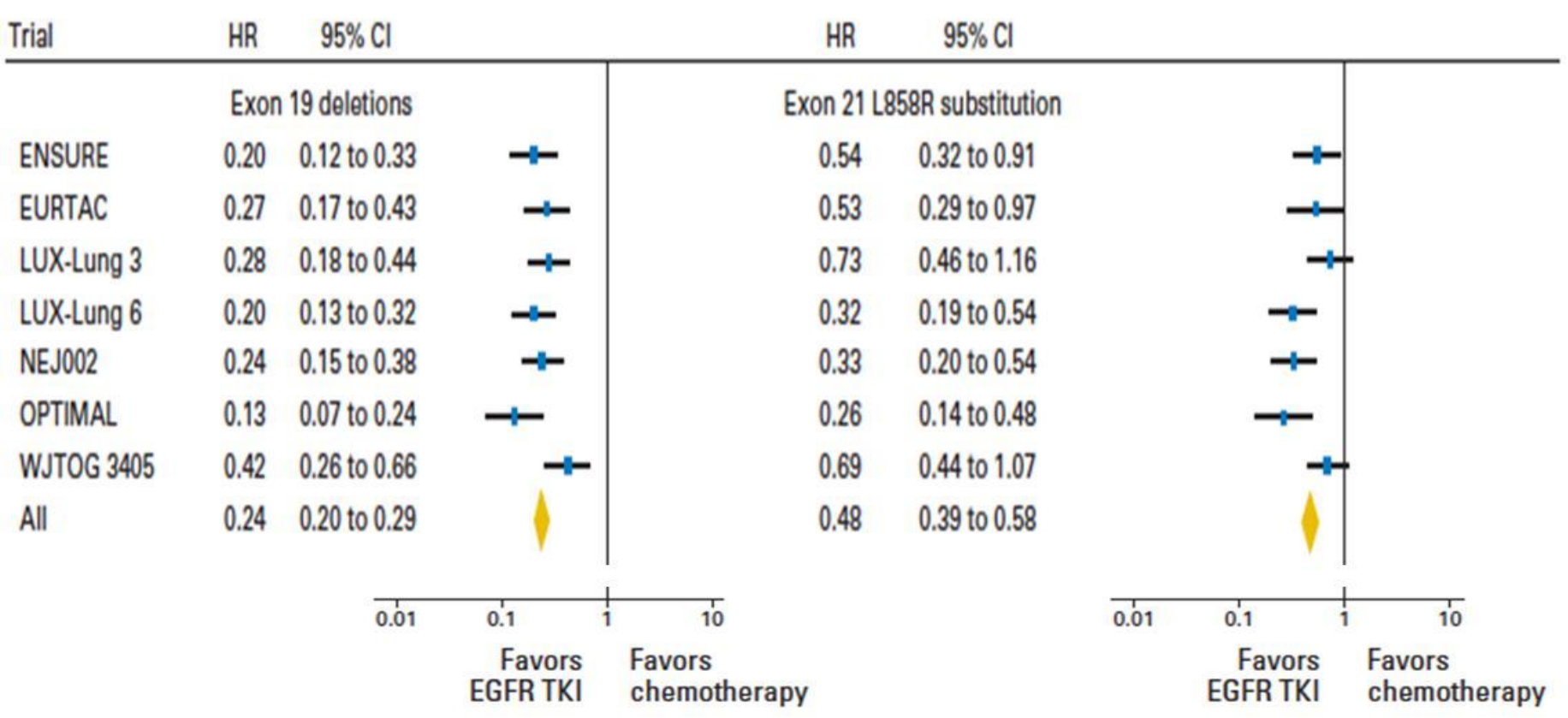
Toxicity with EGFR TKIs

	Gefitinib				Erlotinib		Afatinib	
	IPASS* [48] n = 607	First SIGNAL* [49] n = 159	WJTOG 3405 [50] n = 87	NEJ002 [51] n = 114	OPTIMAL [52] n = 83	EURTAC [53] n = 84	LUX-Lung 3 [54] n = 230	LUX-Lung 6 [55] n = 239
Rash	66.2 (3.1)	72.4 (29.3)	85.0 (2.3)	71.0 (5.3)	73.0 (2)	79.7 (13.0)	89.1 (16.2)	80.8 (14.2)
Diarrhoea	46.6 (3.8)	49.7 (2.5)	54.0 (1.1)	34.2 (0.9)	25.0 (1)	57.1 (5)	95.2 (14.4)	88.3 (5.4)
Fatigue	16.8 (0.3)	28.3 (10.0)	39 (2.2)	10.5 (2.6)	5.0 (0)	57.1 (0)	17.5 (1.3)	10 (0.4)
Anorexia	21.9 (1.5)	44.6 (13.8)	NR	14.9 (5.3)	NR	31 (0)	20.5 (3.1)	10 (1.3)
Stomatitis	17.0 (0.2)	40.2 (1.9)	21.8 (0)	NR	13.0 (1)	NR	72.1 (8.7)	51.9 (5.4)
Paronychia	13.5 (0.3)	NR	32.1 (1.1)	NR	4.0 (0)	NR	56.8 (11.4)	32.6 (0)
Vomiting	12.9 (0.2)	18.9 (0)	NR	NR	1.0 (0)	NR	17.0 (3.1)	9.6 (0.8)

*Shown data include all patients treated with gefitinib
Data are reported as percentage of AEs of any grade and, in parenthesis, of grade 3

Landi L , Expert Opin Pharmacother 2014

PFS with TKIs better for del19 than L858R



Del19 HR: 0.24

p for interaction < 0.001

L858R HR: 0.48

Lee et al. JCO 2015

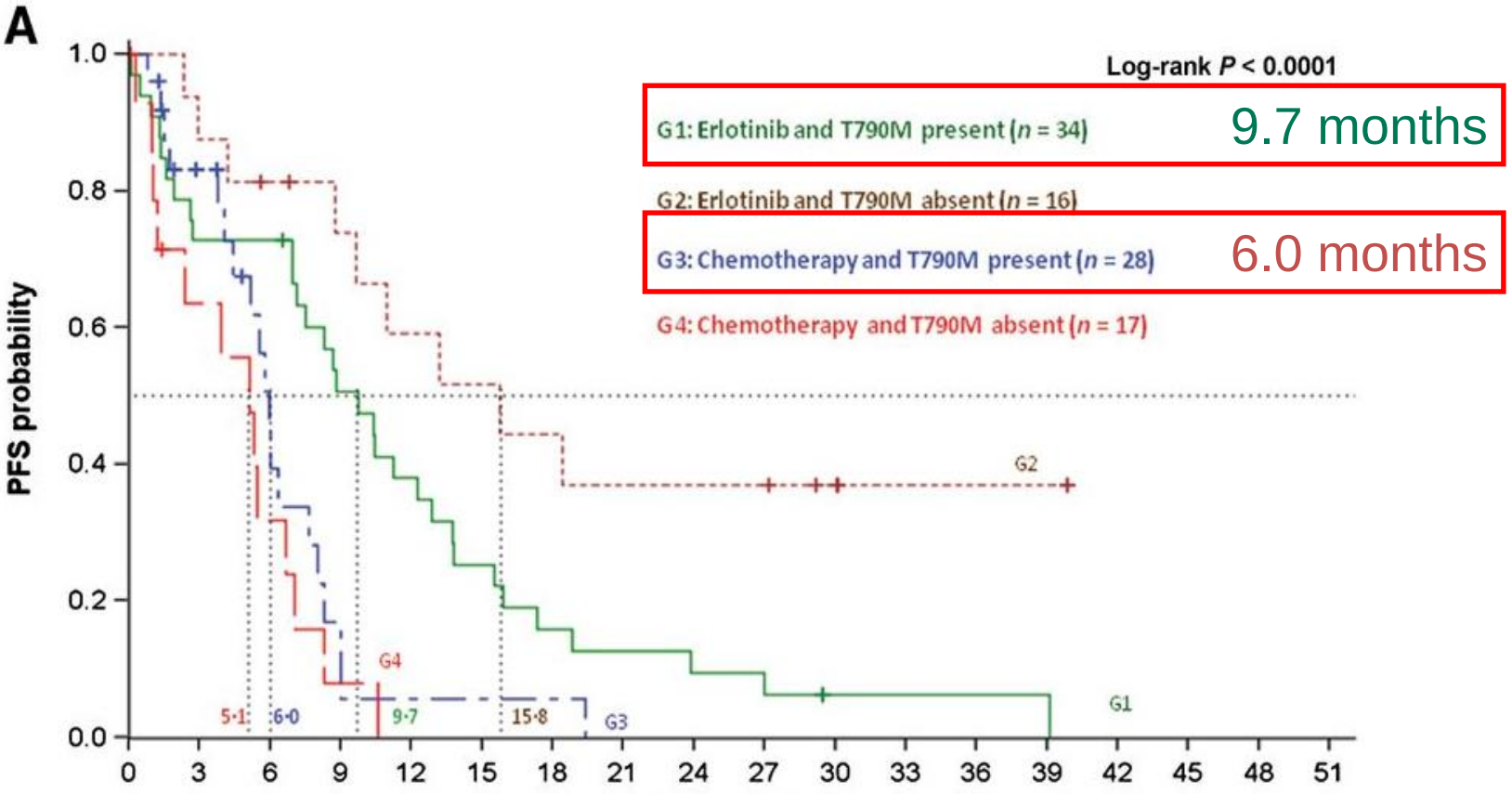
Afatinib activity in uncommon mutations

L861Q (ex 21) G719 (ex 18) S768I (ex 20) other	T790M alone or in combination	Exon 20 insertions
RR 27% PFS 10.7	RR 2% PFS 2.9	RR 2% PFS 2.7

Yang et al. Lancet Oncol 2015

EURTAC: PFS according to T790M and treatment

T790M detected in **65.2%** of patient
(detection threshold **1/5000**)



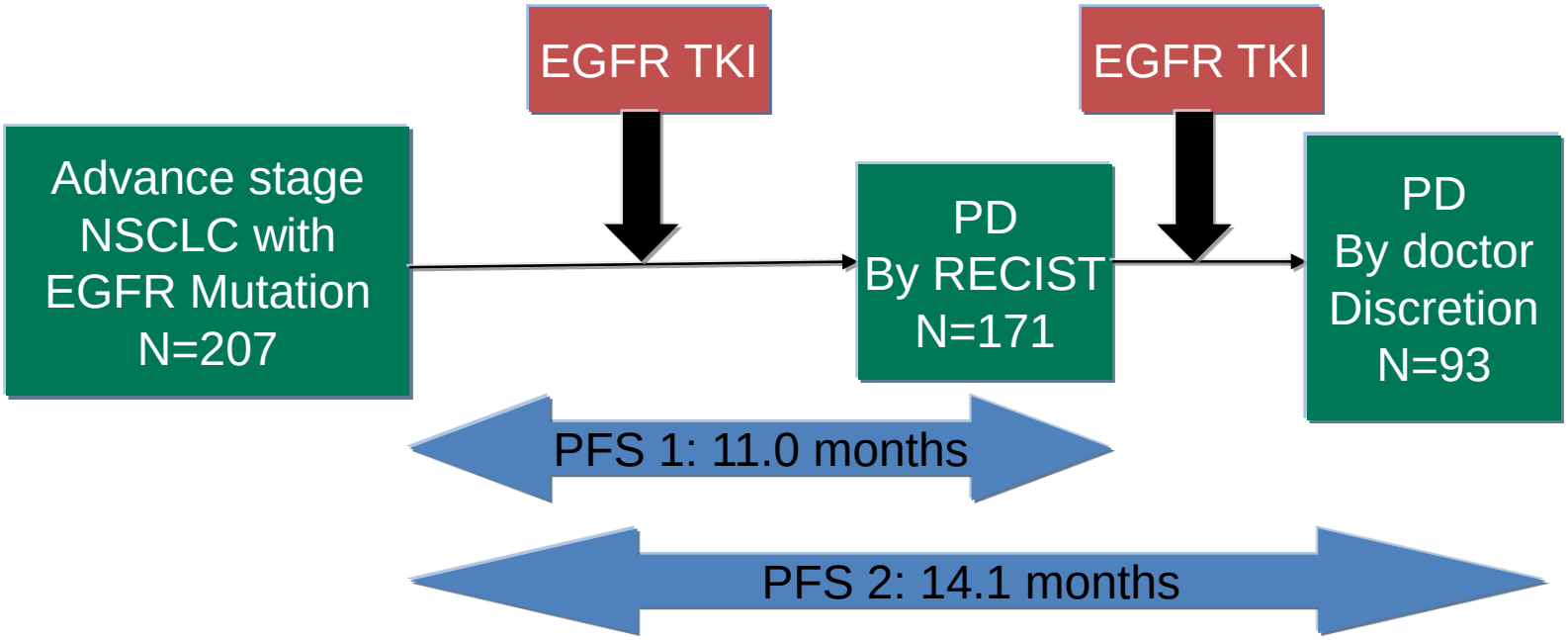
Costa et al. Clinical Cancer Research 2014

NSCLC EGFR-mutato alla progressione

Opportunità di trattamento ma numerose criticità

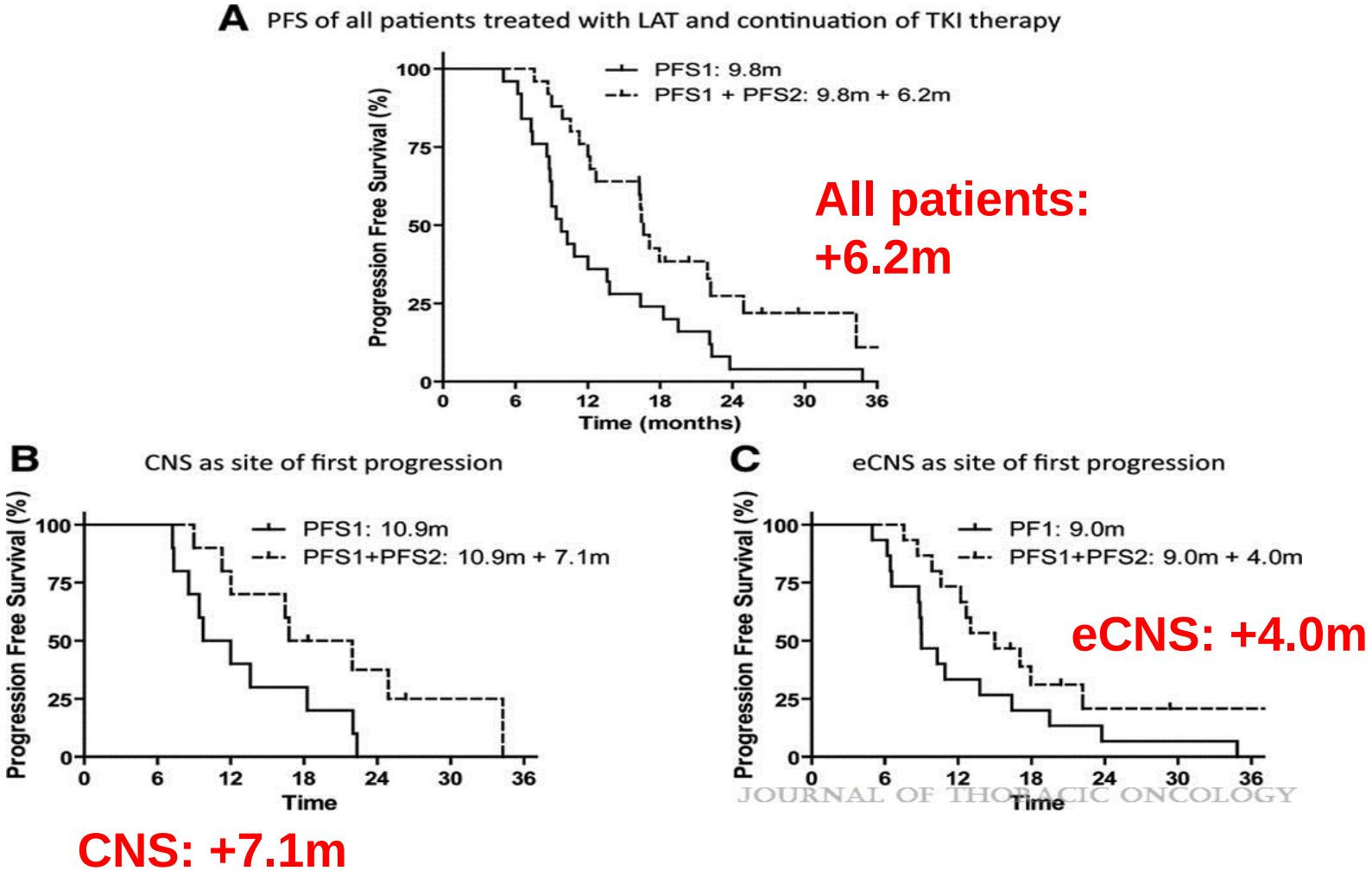
- Definizione di PD (radiologica, clinica?): quando switch?

ASPIRATION: erlotinib beyond PD



Park et al.ESMO 2014

PFS benefit in oligoprogressive EGFR+/ALK+ patients continuing TKI + local therapy (n=65)



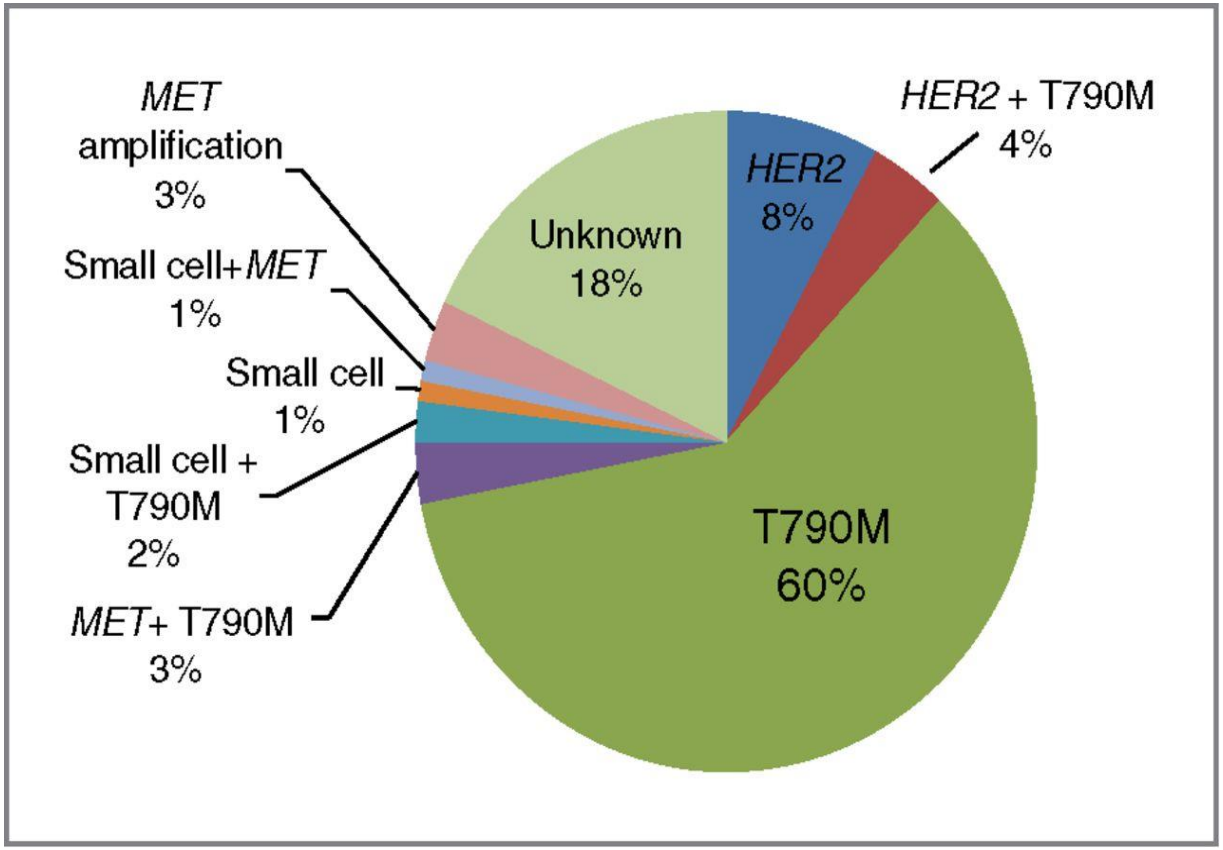
Weickhardt et al. JTO 7: 1807-1814, 2012

NSCLC EGFR-mutato alla progressione

Opportunità di trattamento ma numerose criticità

- Definizione di PD (radiologica, clinica?): quando switch?
- Identificazione T790M (tessuto vs sangue)

Rebiopsy in 155 pts with acquired resistance to gefitinib or erlotinib



Yu et al. Clin Cancer Res 2013

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 11

The mechanism of acquired resistance to irreversible EGFR tyrosine kinase inhibitor-afatinib in lung adenocarcinoma patients

Shang-Gin Wu[1,2], Yi-Nan Liu[3], Meng-Feng Tsai[4], Yih-Leong Chang[5], Chong-Jen Yu[2,3], Pan-Chyr Yang[2,3], James Chih-Hsin Yang[6], Yueh-Feng Wen[7], Jin-Yuan Shih[2,3]

Results: Forty-two patients had tissue specimens taken after acquiring resistance to afatinib. The sensitizing *EGFR* mutation were all consistent between pre- and post-afatinib tissues. Twenty patients (47.6%) had acquired T790M mutation. T790M rate was not different between first-generation EGFR TKI-naïve patients (50%) and first-generation EGFR TKI-treated patients (46.4%) ($p = 0.827$). No clinical characteristics or *EGFR* mutation types were associated with the development of acquired T790M. No other second-site *EGFR* mutations were detected. There were no small cell or squamous cell lung cancer transformation. Other genetic mutations were not identified in *PIK3CA*, *BRAF*, *HER2*, *KRAS*, *NRAS*, *MEK1*, *AKT2*, *LKB1* and *JAK2*.

Wu et al. Oncotarget 2016

Rebiopsy

Feasibility and clinical impact of re-biopsy in advanced non small-cell lung cancer: A prospective multicenter study in a real-world setting (GFPC study 12-01)

Christos Chouaid[a], Cecile Dujon[b], Pascal Do[c], Isabelle Monnet[d], Anne Madroszyk[e], Herve Le Caer[f], Jean Bernard Auliac[g], Henri Berard[h], Pascal Thomas[i], Herve Lena[j], Gilles Robinet[k], Nathalie Baize[l], Acya Bizieux-Thaminy[m], Gislaine Fraboulet[n], Chrystele Locher[o], Jacques Le Treut[p], Stephane Hominal[q], Alain Vergnenegre[r,*]

- **N=100 advanced NSCLC with indication for rebiopsy**
- **Rebiopsy not possible in 19.5% of cases**
- **Inadequate sample in 25.6% of cases**
- **Rebiopsy useful for guiding treatment in 30.4% (25/82)**
- **Complications were infrequent**

Lung Cancer 2014

NSCLC EGFR-mutato alla progressione

Opportunità di trattamento ma numerose criticità

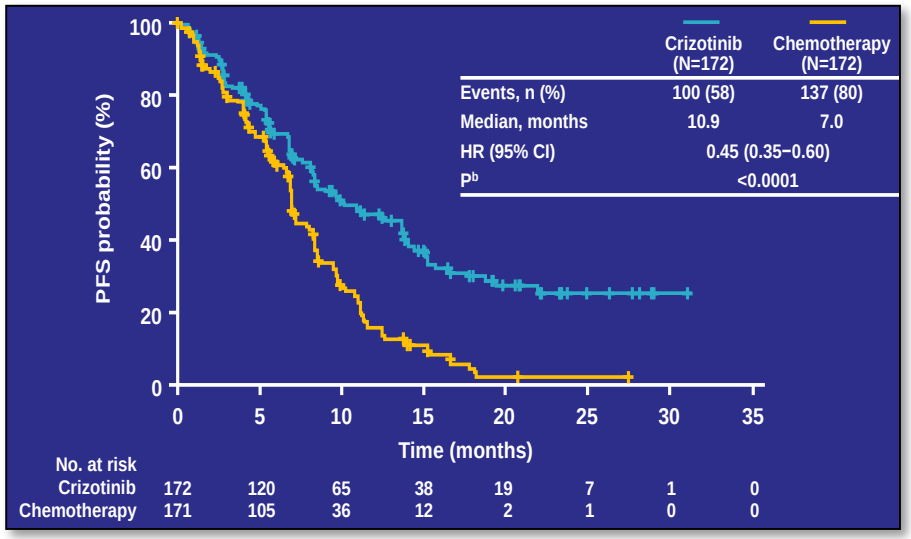
- Definizione di PD (radiologica, clinica?): quando switch?
- Identificazione T790M (tessuto vs sangue)
- Disponibilità del farmaco
- Approvazione basata su fase I
- Gestione T790M-negativi: locoregional, CT

NSCLC ALK-traslocato

Crizotinib Superior to Standard Chemotherapy

1st Line therapy

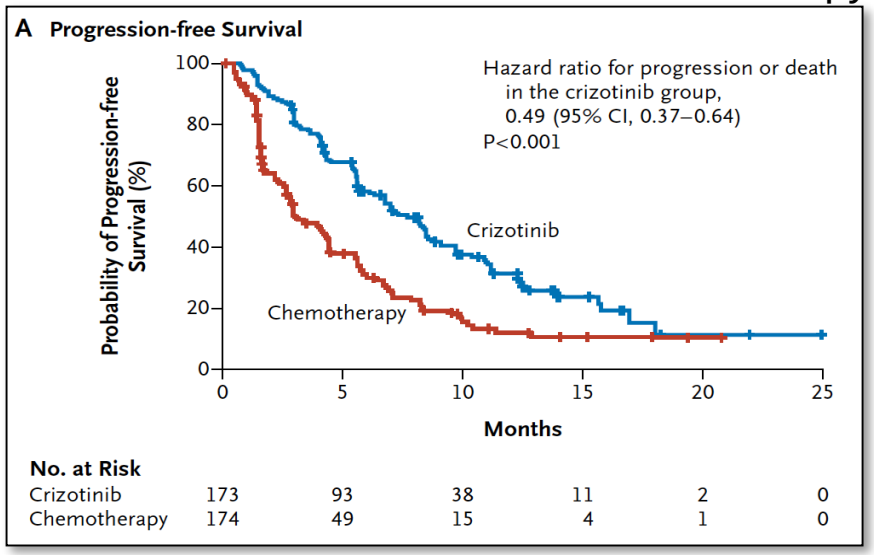
Profile 1014: Crizotinib vs. Platinum/Pemetrexed



ORR: Crizotinib 74% vs. Chemo 45%

2nd Line therapy

Profile 1007: Crizotinib vs. Chemotherapy



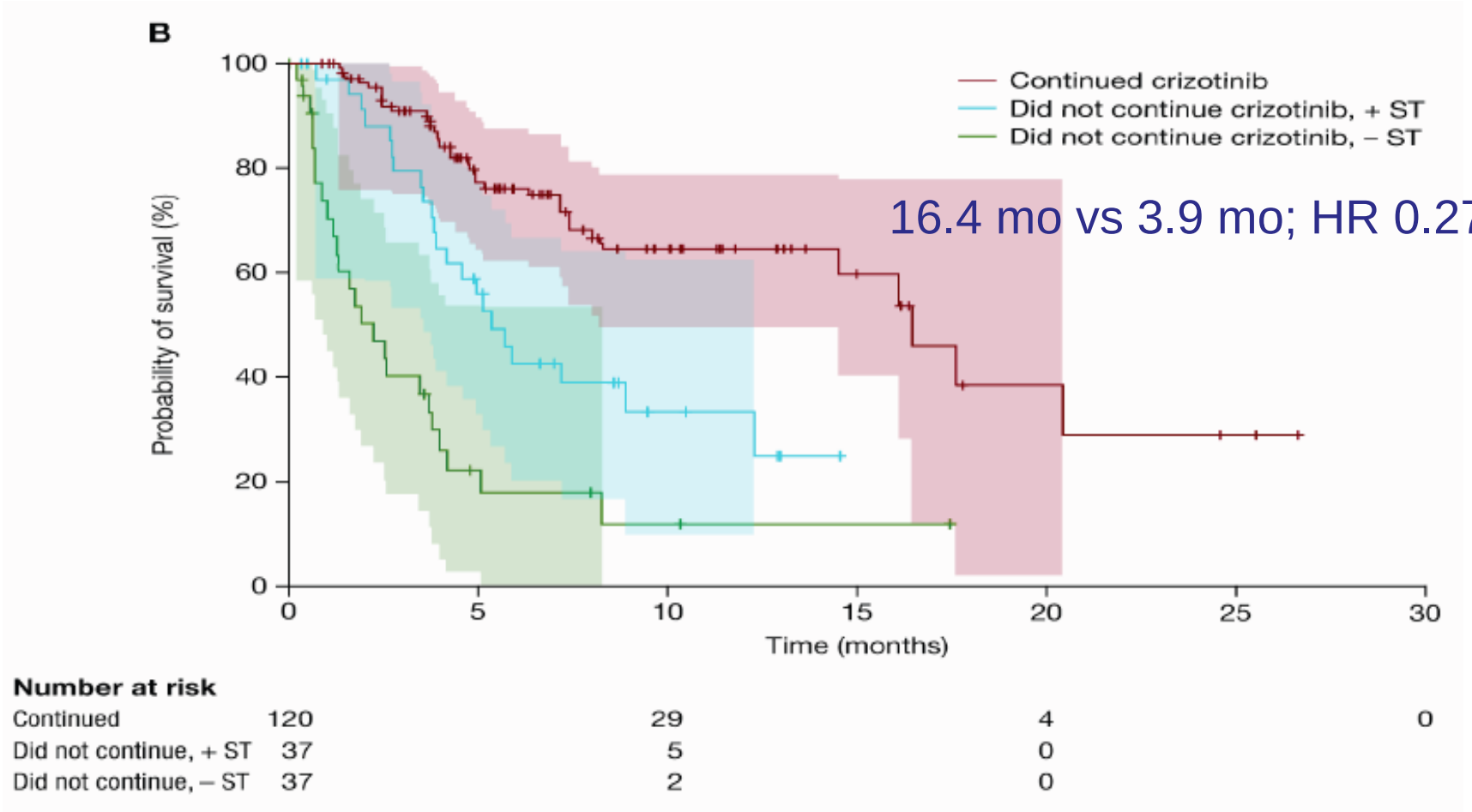
ORR: Crizotinib 65% vs. Chemo 20%

Solomon et at, NEJM 2014
Shaw et al., NEJM 2013

NSCLC ALK-traslocato

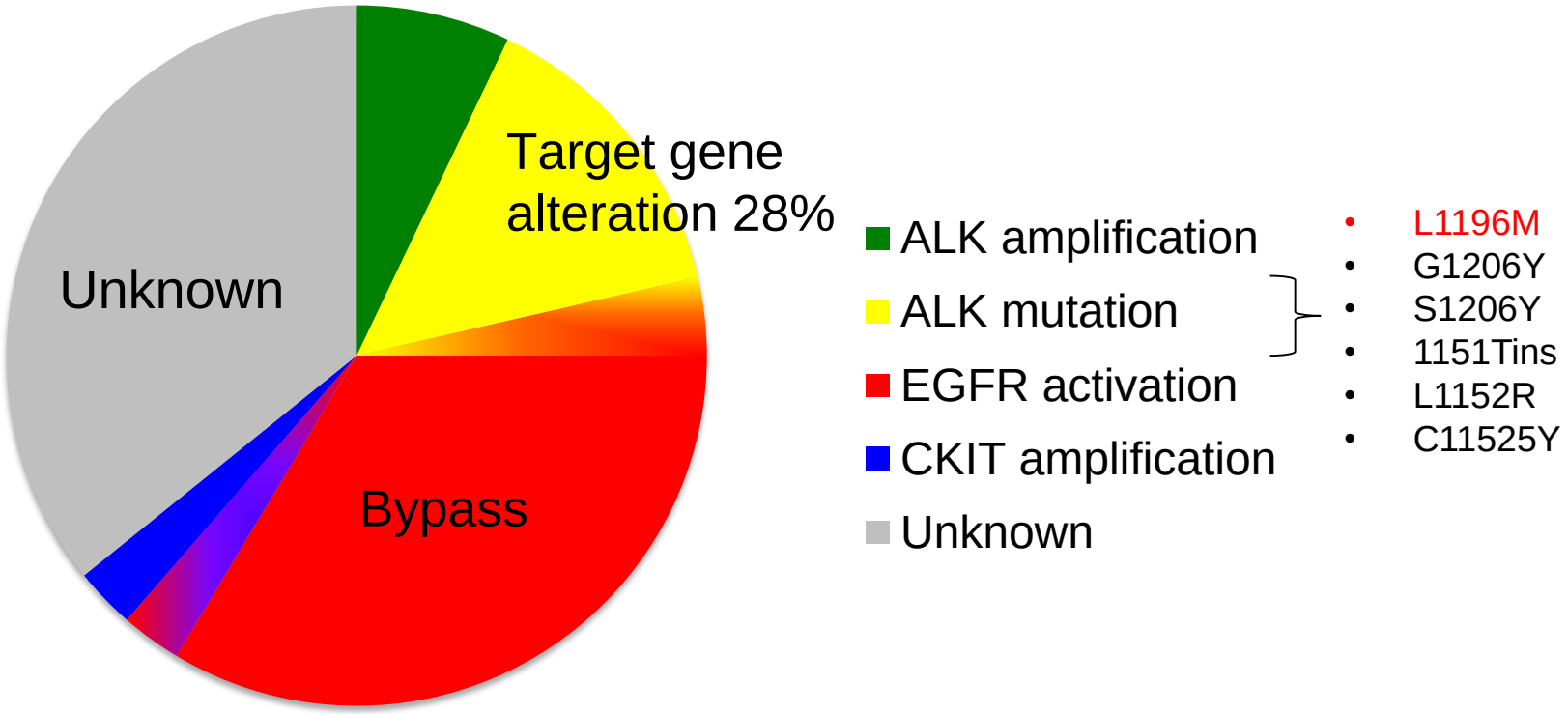
- La prima linea è definita?
  - Idealmente SI, praticamente NO: CT
- Seconda linea: crizotinib
  - Praticamente SI, idealmente NO
- Terza linea
  - Definizione di PD (radiologica, clinica?): quando switch?

Crizotinib Beyond Progression



Ou et al; Ann Oncol 2014

Several Mechanisms of Crizotinib Resistance



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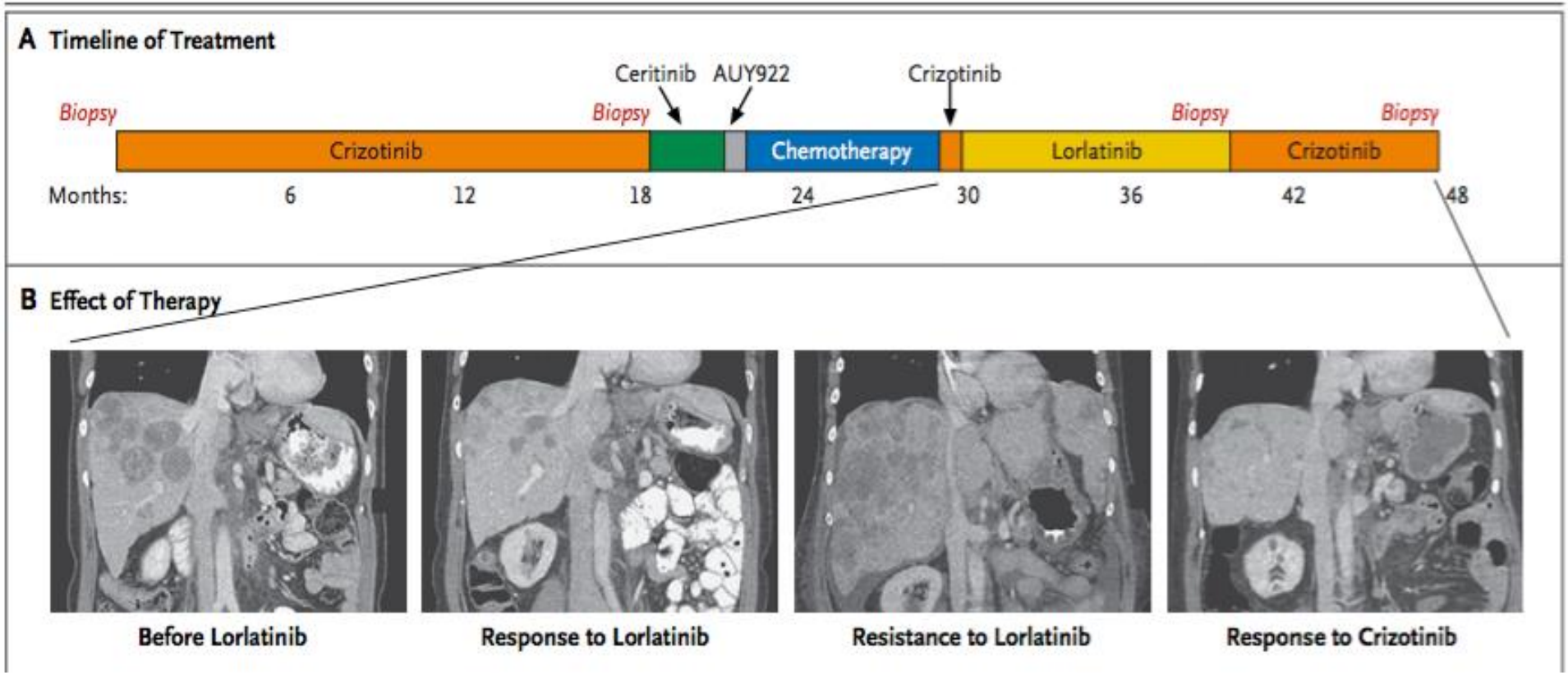
  - No ruolo per la rebiopsia nella pratica clinica ma futuri sviluppi possibili

Acquired resistance to ALK inhibitors: a dynamic process

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Resensitization to Crizotinib by the



NSCLC ALK-traslocato

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  - No ruolo per la rebiopsia nella pratica clinica ma futuri sviluppi possibili
  - Ceritinib EAP
  - Clinical trial

ALK TKI	Sponsor	ROS1 Activity	Status	Ongoing Studies	Reference
Ceritinib	Novartis	Yes	FDA approved (29 Apr 2014)	Phase 3	Shaw et al., NEJM 2014; Kim et al., ASCO 2014
Alectinib	Roche	No	FDA approved (11 Dec 2015)	Phase 3 Expanded access	Seto et al., Lancet Onc 2013; Gadgeel et al., Lancet Onc 2014
AP26113	Ariad	Yes	Investigational	Phase 2	Gettinger et al., ASCO 2014
X-396	Xcovery	Yes	Investigational	Phase 1	Horn et al., ASCO 2014
TSR-011	Tesaro	Unk	Investigational	Phase 1/2	Weiss et al., WCLC 2013
Entrectinib	Ignyta	Yes	Investigational	Phase 1	De Braud et al., ASCO 2014
CEP-37440	Teva	Unk	Investigational	Phase 1	NCT01922752
Lorlatinib	Pfizer	Yes	Investigational	Phase 1/2	Zou et al., EORTC-AACR-NCI 2013

NSCLC ALK-traslocato

- La prima linea è definita?
  - Idealmente si, praticamente no: CT
- Seconda linea: crizotinib
  - Praticamente si, idealmente no
- Terza linea
  - Definizione di PD (radiologica, clinica?): quando switch?
  - No ruolo per la rebiopsia nella pratica clinica ma futuri sviluppi possibili
  - Ceritinib EAP
  - Clinical trial
- Metastasi cerebrali: timing RT?

Grazie