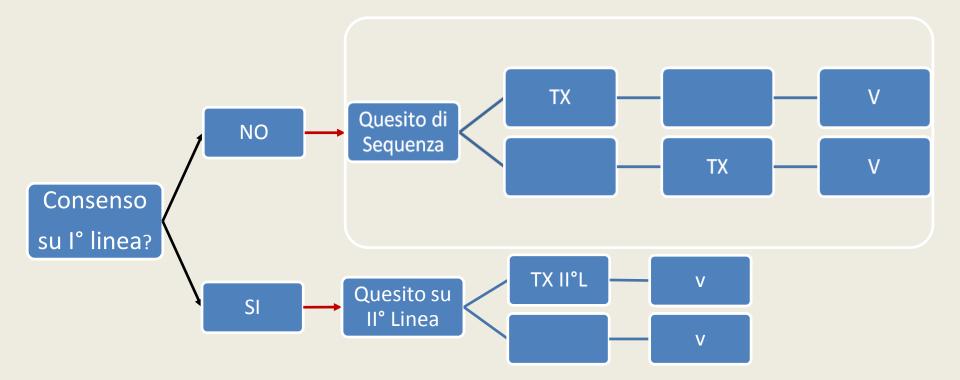


La sequenza terapeutica nel paziente con NSCLC avanzato in base all'istologia e alla caratterizzazione molecolare: Criticità

Valter Torri - Milano



### Possibili disegni per la valutazione della miglior sequenza

# Due scenari

- 1. EGFR mutati
- 2. ALK traslocati

## Scenari considerati



Is there evidence for different effects among EGFR-TKIs? Systematic review and meta-analysis of EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy as first-line treatment for patients harboring EGFR mutations

Eva Regina Haspinger<sup>a</sup>, Francesco Agustoni<sup>a</sup>, Valter Torri<sup>b</sup>, Francesco Gelsomino<sup>a</sup>, Marco Platania<sup>a</sup>, Nicoletta Zilembo<sup>a</sup>, Rosaria Gallucci<sup>a</sup>, Marina Chiara Garassino<sup>a,a</sup>, Michela Cinquini<sup>b</sup> <sup>8</sup> Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy <sup>b</sup> Fondazione IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy Accepted 11 November 2014

Study or Subgroup	log[Hazard Ratio]	SE		Chemotherapy	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% Cl
1.1.1 Gefitinib vs che		9E	Total	Total	AAGIBUR	IV, realized in, 95% Cr	IV, Random, 95% CI
FIRST-SIGNAL		0.3584	28	16	11.8%	0.54 [0.27, 1.09]	
IPASS	-0.73	0.146	10		32.0%	0.48 [0.36, 0.64]	+
NEJSG002	-1.2	0.158	100 Ki2000	10.000	30.2%	0.30 [0.22, 0.41]	
WJT0G3405	-0.71	0.189			26.0%	0.49 [0.34, 0.71]	+
Subtotal (95% CI)	-0.71	0.100	358		100.0%	0.43 [0.32, 0.56]	•
Heterogeneity: Tau <sup>2</sup> =	0.04" Chi <sup>2</sup> = 6.48. df	= 3 (P =	0.090 P = 54%				
Test for overall effect			0.007,1 - 0110				
1.1.2 Erlotinib vs che	motherapy						
EURTAC	-0.99	0.195	86	87	36.2%	0.37 [0.25, 0.54]	+
OPTIMAL	-1.83	0.233			34.6%	0.16 [0.10, 0.25]	
TORCH	-0.51	0.354	19	20	29.1%	0.60 [0.30, 1.20]	
Subtotal (95% CI)	1917.11	1010125	187		100.0%	0.32 [0.16, 0.65]	•
Heterogeneity: Tau* =	0.32; Chi#= 12.26, (	#= 2 (P	= 0.002); I* = 84	%			
Test for overall effect	Z = 3.16 (P = 0.002)	32	0.000				
1.1.3 Afatinib vs cher	motherapy						
LUX-LUNG3	-0.545	0.152	230	115	50.6%	0.58 [0.43, 0.78]	-
LUX-LUNG6	-1.27	0.17	242	122	49.4%	0.28 [0.20, 0.39]	-
Subtotal (95% CI)			472	237	100.0%	0.41 [0.20, 0.82]	•
Heterogeneity: Tau <sup>a</sup> =	0.24; Chi <sup>a</sup> = 10.11, 0	f=1 (P	= 0.001); l <sup>2</sup> = 90	%			
Test for overall effect	Z= 2.49 (P = 0.01)	S093307-S					
							0.005 0.1 1 10 200
Test for subgroup diff	ferences: Chi <sup>p</sup> = 0.55	, df = 2 (	P = 0.76) (P = 09	5			Favours TKI-Inhibitors Favours Chemotherapy

### EGFR mutati - I° linea



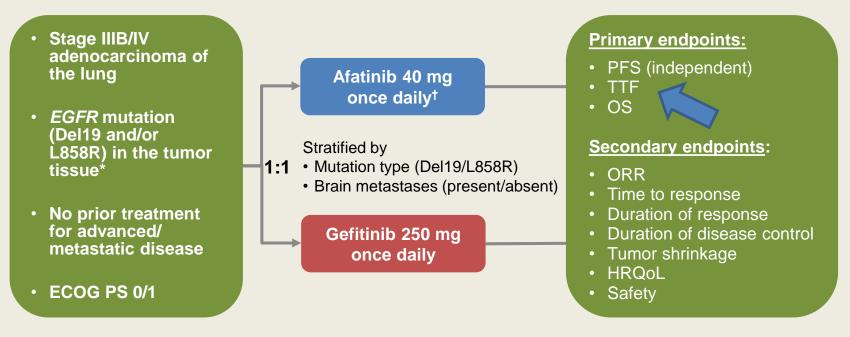
Oncology Hematology heceperating Gamme Oncology

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Overall results of comparisons between TKIs and chemotherapy (CT) and overall results of indirect comparisons among TKIs.											
Outcome	Gefitinib versus Afatinib (ind. comp.)	Conclusion	Erlotinib versus Afatinib (ind. comp.)	Conclusion	Gefitinib versus Erlotinib (ind. comp.)	Conclusion					
Progression-free survival Hazard ratio (HR) (95% CI)	HR = 1.05 (0.61, 1.81)	No difference	HR = 0.78 (0.39, 1.55)	No difference	HR = 1.34 (0.63, 2.86)	No difference					
Progression-free survival (exon 19 deletion) Hazard ratio (HR) (95% CI)	HR = 1.67 (1.05, 2.64)	Afatinib better	HR = 0.83 (0.35, 2.01)	No difference	HR = 2.00 (0.83, 4.80)	No difference					
Progression-free survival (L858R mutation) Hazard ratio (HR) (95% CI)	HR = 1.08 (0.45, 2.60)	No difference	HR = 0.78 (0.26, 2.32)	No difference	HR = 1.39 (0.62, 3.16)	No difference					
Overall survival Hazard ratio (HR) (95% CI)	HR = 0.91 (0.65, 1.26)	No difference	HR = 1.10 (0.74, 1.64)	No difference	HR = 0.90 (0.68, 1.19)	No difference					
Objective response rate Risk ratio (RR) (95% CI)	RR=0.91 (0.67, 1.23)	No difference	RR = 0.94 (0.65, 1.35)	No difference	RR = 0.96 (0.69, 1.34)	No difference					
Diarrhea Risk ratio (RR) (95% CI)	RR = 0.29 (0.20, 0.41)	Gefitinib better	RR = 0.36 (0.25, 0.54)	Erlotinib better	RR = 0.80 (0.63, 1.01)	No difference					
Rash Risk ratio (RR) (95% CI)	RR = 0.41 (0.25, 0.65)	Gefitinib better	RR = 0.41 (0.25, 0.66)	Erlotinib better	RR = 1.00 (0.82, 1.22)	No difference					

## EGFR mutati - I° linea



- Treatment beyond progression allowed if deemed beneficial by investigator
- RECIST assessment performed at Weeks 4, 8 and every 8 weeks thereafter until Week 64, and every 12 weeks thereafter

\*Central or local test <sup>†</sup>Dose modification to 50, 30, 20 mg permitted in line with prescribing information

Park K, et al. ESMO Asia, Oral Presentation (Abstract N° LBA2 PR)

### Lux-lung 7: Study Design

- Afatinib significantly improved PFS of patients with *EGFR*m+ NSCLC relative to gefitinib. Results are consistent across subgroups
- Afatinib treatment was associated with a significant improvement in response rate and TTF
- The improvement in efficacy was observed in both Del19 and L858R populations
- OS data immature (current HR: 0.87, 95%CI: 0.66–1.15)
- AEs in both groups were consistent with previous experience, and were manageable leading to equally low rates of treatment discontinuation
- LUX-Lung 7 confirms the benefit of irreversible ErbB blockade with afatinib over reversible EGFR inhibition with gefitinib in treatment of *EGFR*m+ NSCLC

Park K, et al. ESMO Asia, Oral Presentation (Abstract N° LBA2 PR)

## Lux-lung 7: Conclusion

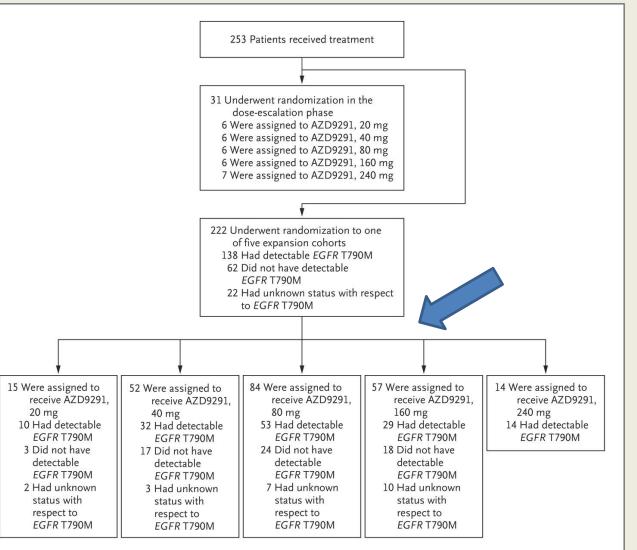
ESTABLISHED IN 1812

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#### AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

APRIL 30, 2015

Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., David Planchard, M.D., Ph.D., Yuichiro Ohe, M.D., Suresh S. Ramalingam, M.D., Myung-Ju Ahn, M.D., Ph.D., Sang-We Kim, M.D., Ph.D., Vu-Chou Su, M.D., Leora Horn, M.D., Daniel Haggstrom, M.D., Enriqueta Felip, M.D., Ph.D., Joo-Hang Kim, M.D., Ph.D., Paul Frever, M.Sc., Mireille Cantarini, M.D., Kathryn H. Brown, Ph.D., Paul A. Dickinson, Ph.D., Serban Ghiorghiu, M.D., and Malcolm Ranson, M.B., Ch.B., Ph.D.



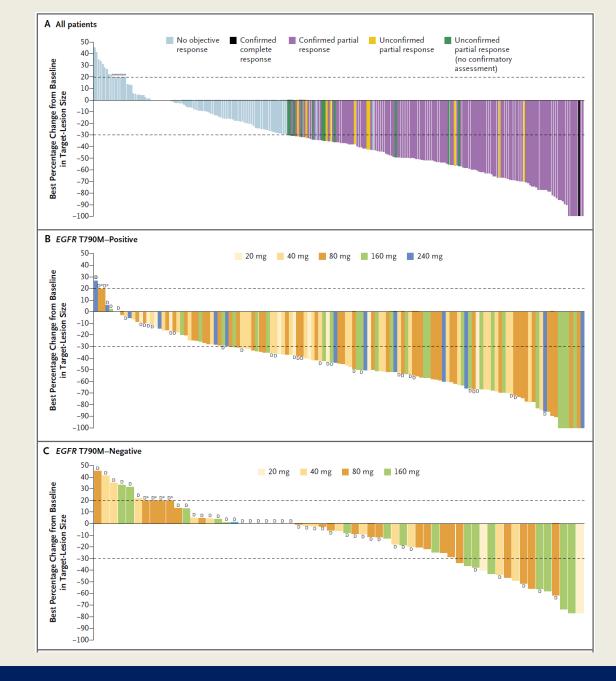
### EGFR Mutati - II<sup>®</sup> Linea

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### EGFR Mutati - II° Linea

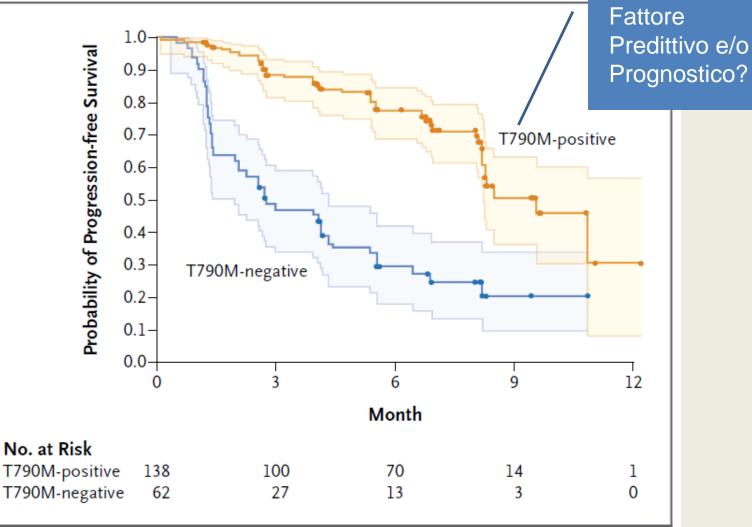
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## EGFR Mutati - II° Linea

# II° Linea

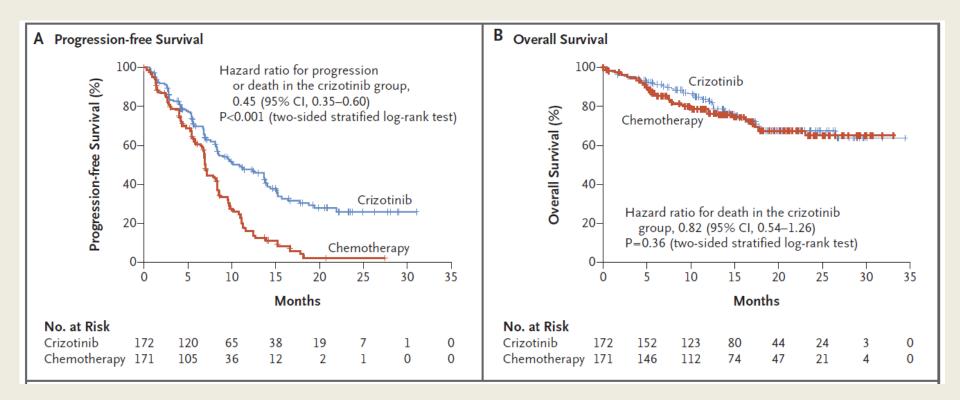
- AURA2
  - Open Label Study in NSCLC after Previous EGFR TKI Therapy in EGFR and T790M Mutation Positive Tumors. [I°EP: PFS]
- AURA3
  - Multicenter, phase III, open-label study comparing the efficacy of AZD9291 with platinum-based chemotherapy (CT) as second- line treatment in patients with progressing advanced/ metastatic T790M positive NSCLC, with documented EGFR mutations, who have received prior EGFR-TKI therapy.
    [I°EP: PFS]
- l° Linea
- FLAURA
  - Randomized, phase III study called comparing AZD9291, vs. gefitinib or erlotinib in treatment-naïve patients with advanced NSCLC showing EGFR-TKI sensitizing mutations. [I°EP: PFS]

## EGFR Mutati - sviluppi futuri

ORIGINAL ARTICLE

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

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators\*

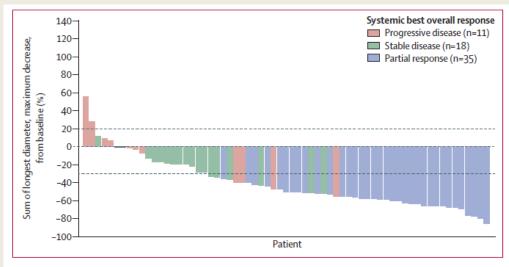


### ALK Mutati – I° Linea

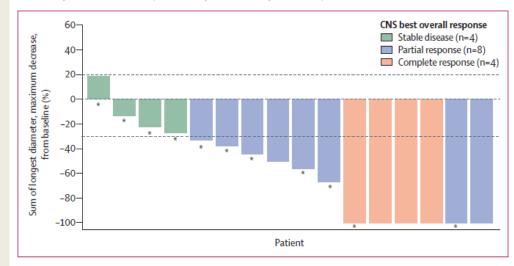
#### Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial

Alice T Shaw, Leena Gandhi, Shirish Gadgeel, Gregory J Riely, Jeremy Cetnar, Howard West, D Ross Carnidge, Mark A Socinski, Alberto Chiappori, Tarek Mekhail, Bo H Chao, Hossein Borghaei, Kathryn A Gold, Ali Zeaiter, Walter Bordogna, Bogdana Balas, Oscar Puig, Volkmar Henschel, Sai-Hong Ignatius Ou, on behalf of the study investigators\*

Lancet Oncol 2016; 17: 234-42







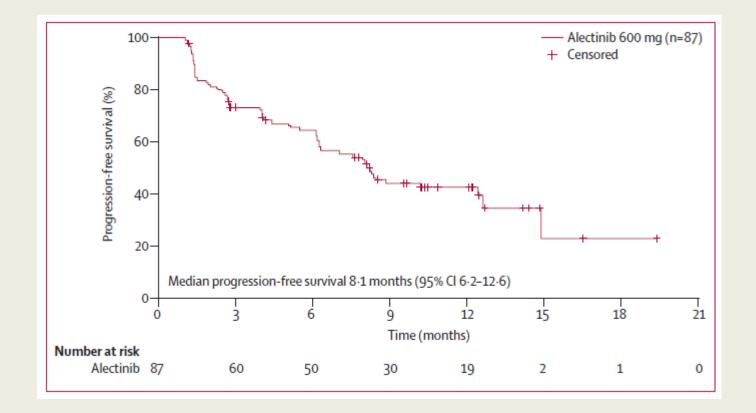
Waterfall plot of best overall CNS response at the updated analysis

### ALK Mutati – II° Linea

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