Tossicità dei TKI nel trattamento del NSCLC

Laura Tonda
Ospedale San Giovanni Bosco

TKI tollerati meglio della CT?

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 [a], Francesco Agustoni [a], Valter Torri [b], Francesco Gelsomino [a], Marco Platania [a], Nicoletta Zilembo [a], Rosaria Gallucci [a], Marina Chiara Garassino [a,*], Michela Cinquini [b]

9 RCTs which involved globally 1.774 *EGFR*-mutated patients

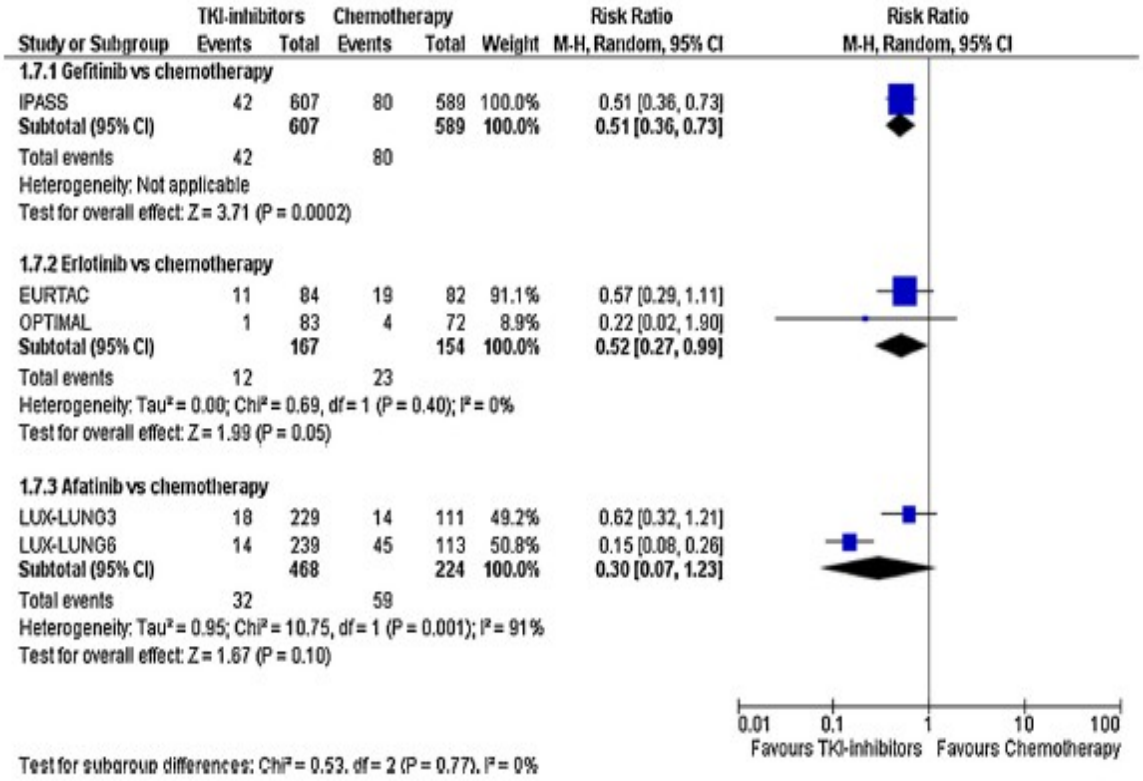
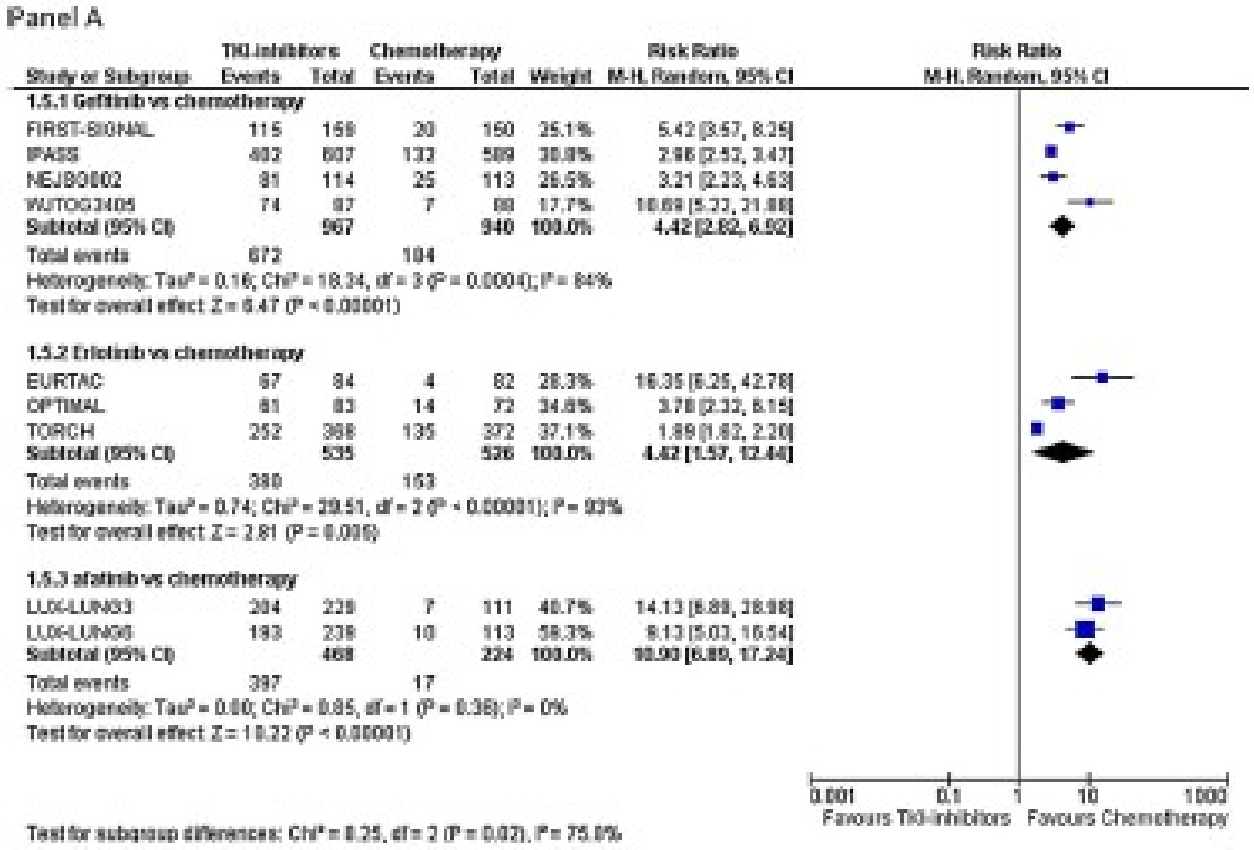
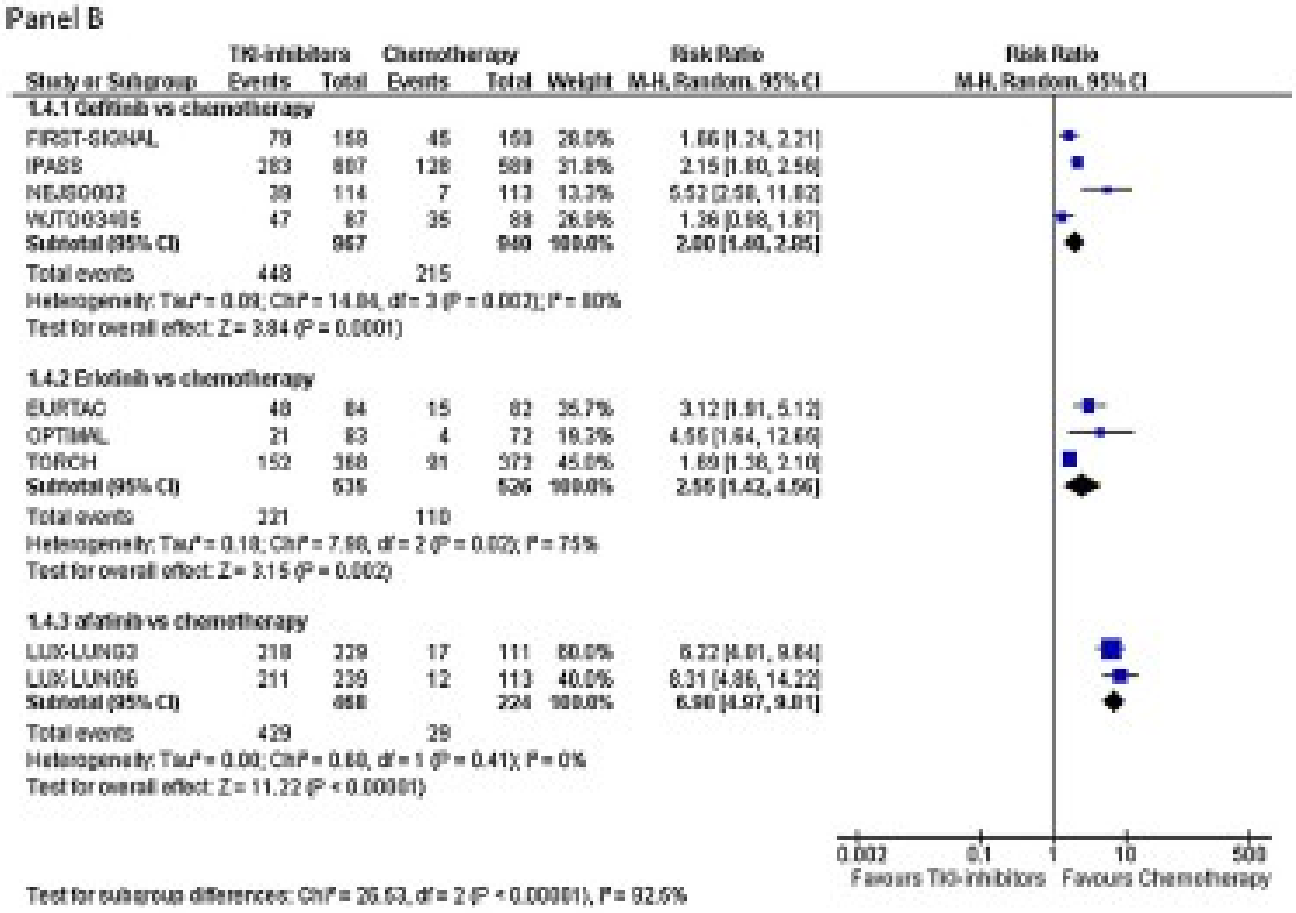


Fig. 7. Forest-plot for treatment discontinuation.

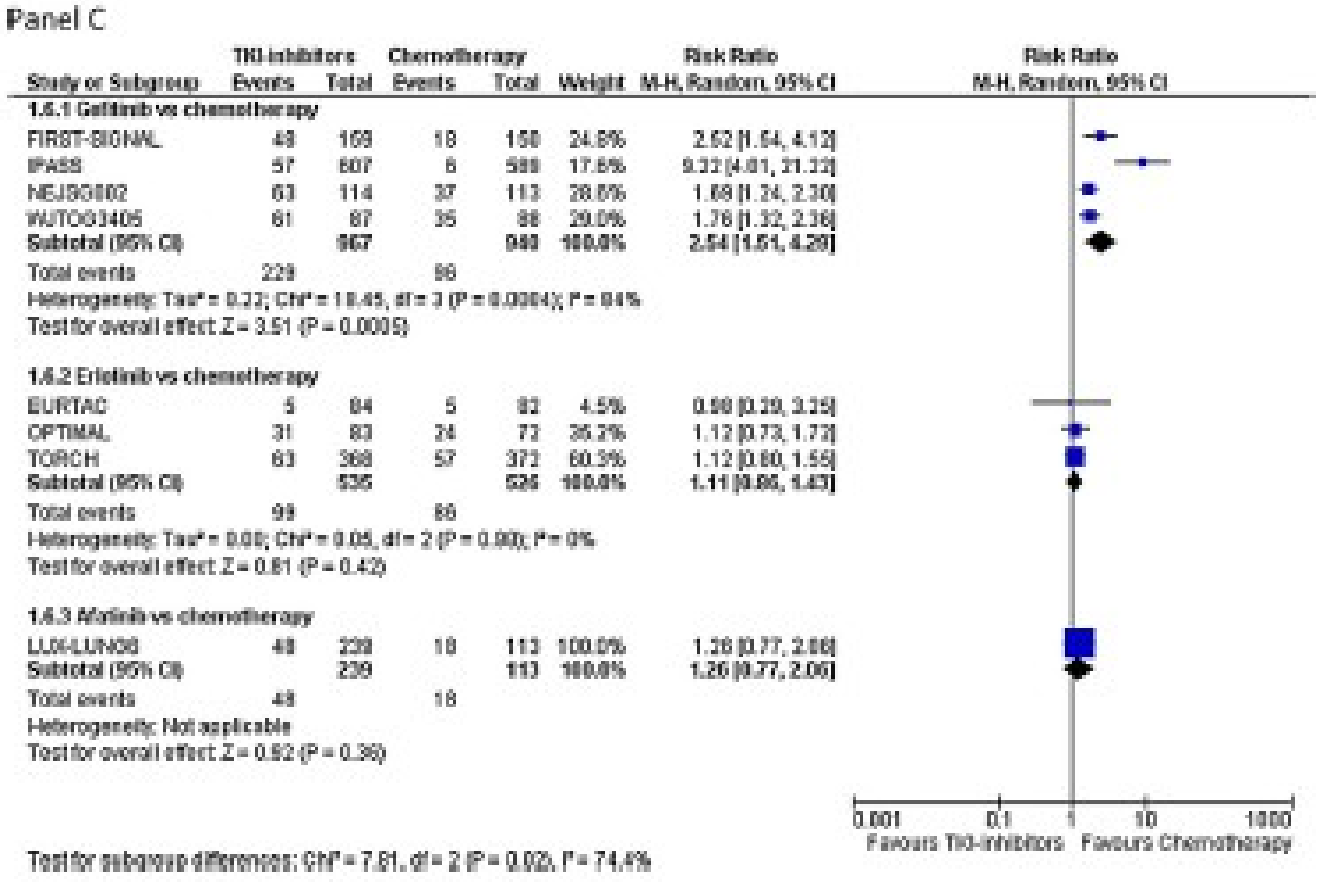
Tossicità cute ed annessi



Diarrea


Panel B
TKI-inhibitors
Chemotherapy
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 Gefitinib vs chemotherapy
FIRST-SIGNAL 79 159 45 159 28.0% 1.86 [1.24, 2.21]
IPASS 263 607 128 589 31.8% 2.15 [1.80, 2.56]
NEJ002 39 114 7 113 13.3% 5.52 [2.58, 11.82]
WJTOG3405 47 87 35 88 26.9% 1.36 [0.98, 1.87]
Subtotal (95% CI) 967 949 100.0% 2.00 [1.48, 2.85]
Total events 448 215
Heterogeneity: Tau² = 0.09; Chi² = 14.84, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 3.84 (P = 0.0001)
1.4.2 Erlotinib vs chemotherapy
EURTAC 48 84 15 82 35.7% 3.12 [1.91, 5.12]
OPTIMAL 21 83 4 72 19.3% 4.55 [1.64, 12.60]
TORCH 152 368 91 373 45.0% 1.69 [1.36, 2.10]
Subtotal (95% CI) 535 526 100.0% 2.55 [1.42, 4.56]
Total events 321 110
Heterogeneity: Tau² = 0.18; Chi² = 7.66, df = 2 (P = 0.02); I² = 75%
Test for overall effect: Z = 3.15 (P = 0.002)
1.4.3 afatinib vs chemotherapy
LUX-LUNG3 218 329 17 111 60.0% 6.22 [4.01, 9.64]
LUX-LUNG6 211 339 12 113 40.0% 8.31 [4.86, 14.22]
Subtotal (95% CI) 668 224 100.0% 6.90 [4.97, 9.61]
Total events 429 29
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 11.22 (P < 0.00001)
Test for subgroup differences: Chi² = 26.63, df = 2 (P < 0.00001), I² = 92.5%
0.002
0.1
1
10
500
Favours TKI-inhibitors
Favours Chemotherapy

Incremento transaminasi



Profili di tossicità diversi?

Pooled safety analysis of EGFR-TKI treatment for *EGFR* mutation-positive non-small cell lung cancer

Masayuki Takeda [a], Isamu Okamoto [b,*], Kazuhiko Nakagawa [a]

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[b] Center for Clinical and Translational Research, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

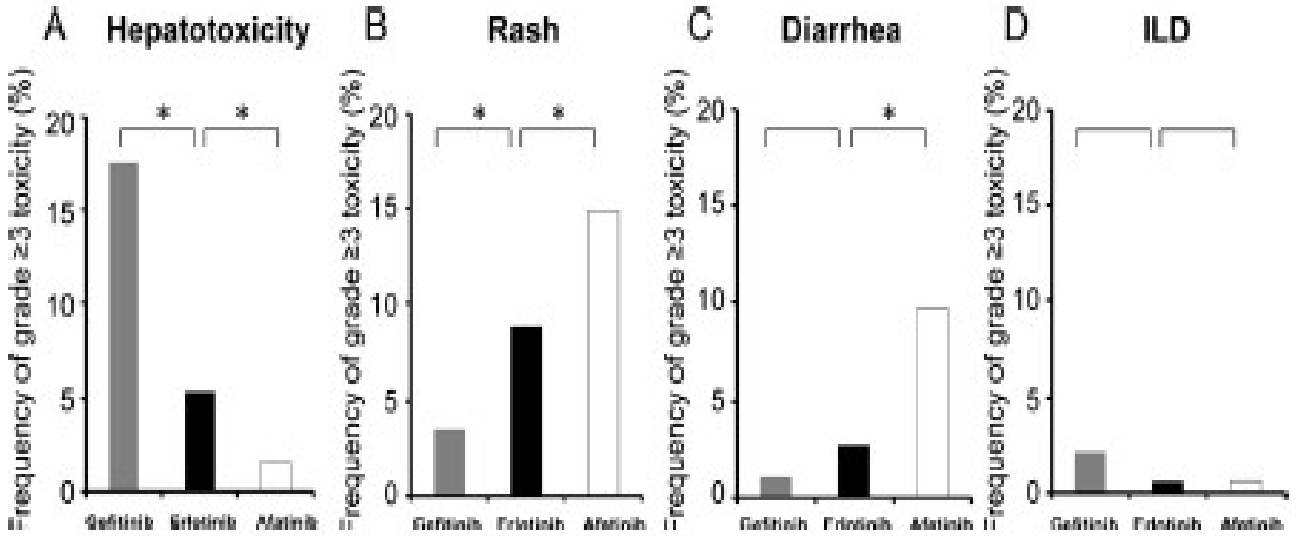


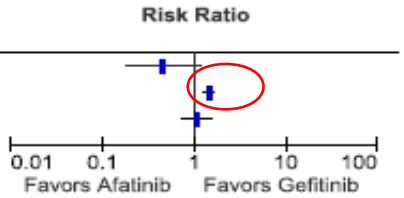
Fig. 2. Frequency of AEs of grade ≥3 including hepatotoxicity (A), rash (B), diarrhea (C), and ILD (D) according to type of EGFR-TKI. Asterisks indicate statistically significant differences.

Esiste un TKI preferibile per minor tossicità ?

Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced *EGFR*-Mutated Non-Small Cell Lung Cancer

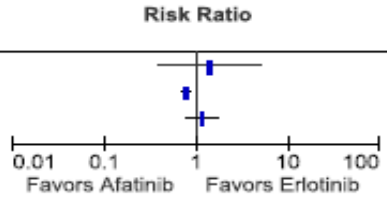
Pei Ni Ding, MBBChir,[a,b] Sarah J. Lord, MSc,[a,c] Val Gebski, MStat,[a] Matthew Links, PhD,[d] Victoria Bray, PhD,[b] Richard J. Gralla, MD,[e] James Chih-Hsin Yang, PhD,[f] Chee Khoon Lee, PhD[a,d,*]

Toxicity outcome	Afatinib Events	Afatinib Total	Gefitinib Events	Gefitinib Total	Risk Ratio [95% CI]
(i) Toxic death	5	468	28	1204	0.46 [0.18, 1.18]
(ii) Grade 3/4 Adverse events	197	468	325	1117	1.45 [1.26, 1.66]
(iii) Treatment discontinuation	39	468	81	1045	1.08 [0.75, 1.55]



B Afatinib vs Erlotinib

Toxicity outcome	Afatinib Events	Afatinib Total	Erlotinib Events	Erlotinib Total	Risk Ratio [95% CI]
(i) Toxic death	5	468	4	529	1.41 [0.38, 5.23]
(ii) Grade 3/4 Adverse events	197	468	436	806	0.78 [0.69, 0.88]
(iii) Treatment discontinuation	39	468	58	806	1.16 [0.78, 1.71]



C Gefitinib vs Erlotinib

Toxicity outcome	Gefitinib Events	Gefitinib Total	Erlotinib Events	Erlotinib Total	Risk Ratio [95% CI]
(i) Toxic death	28	1204	4	529	3.08 [1.08, 8.72]
(ii) Grade 3/4 Adverse events	325	1117	436	806	0.54 [0.48, 0.60]
(iii) Treatment discontinuation	81	1045	58	806	1.08 [0.78, 1.49]

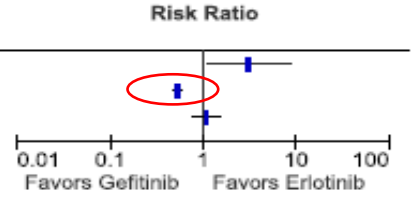


Figure 2. Forest plot showing pooled risk ratio for (*i*) toxic death, (*ii*) grade 3 and 4 adverse events, and (*iii*) discontinuation of treatment because of adverse events with (*A*) afatinib versus with gefitinib, (*B*) afatinib versus with erlotinib, and (*C*) gefitinib versus with erlotinib. The risk ratio for each adverse event is represented by the square, and the horizontal line crossing the square represents the 95% confidence interval (CI).

Pooled safety analysis of EGFR-TKI treatment for *EGFR* mutation-positive non-small cell lung cancer

Masayuki Takeda [a], Isamu Okamoto [b,*], Kazuhiko Nakagawa [a]

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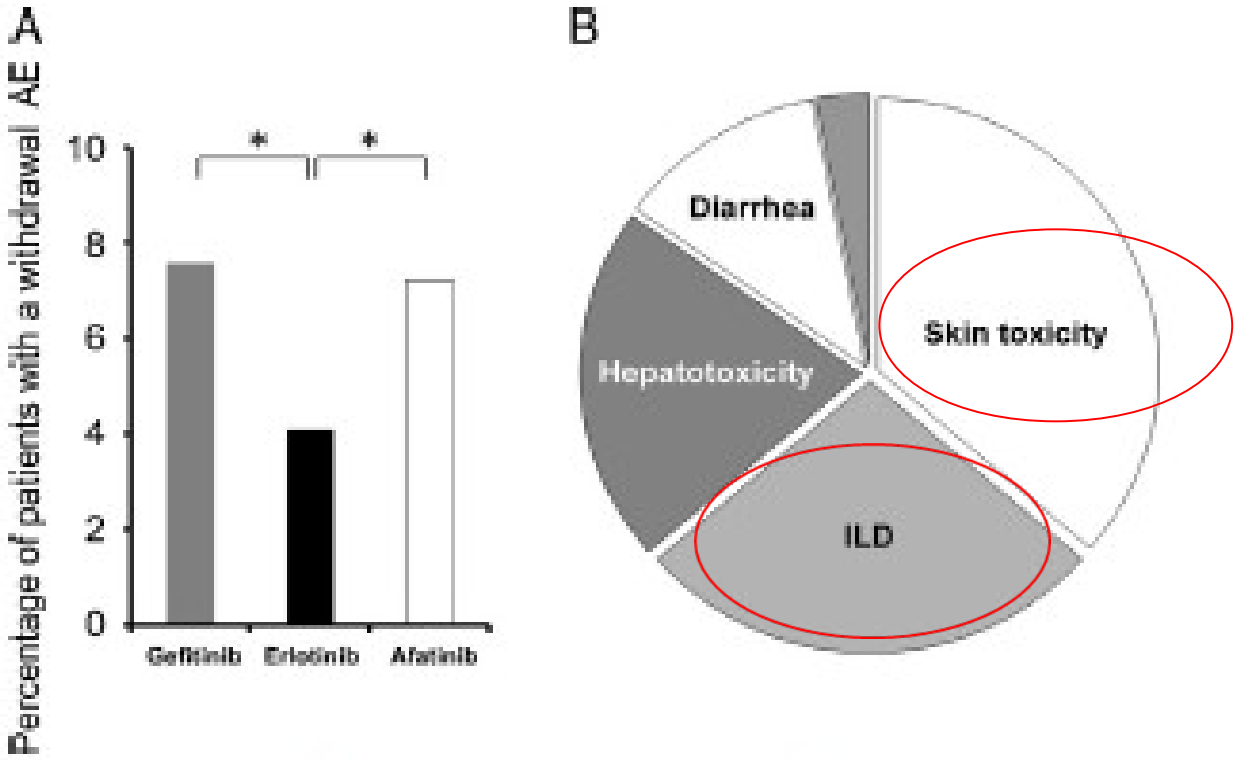
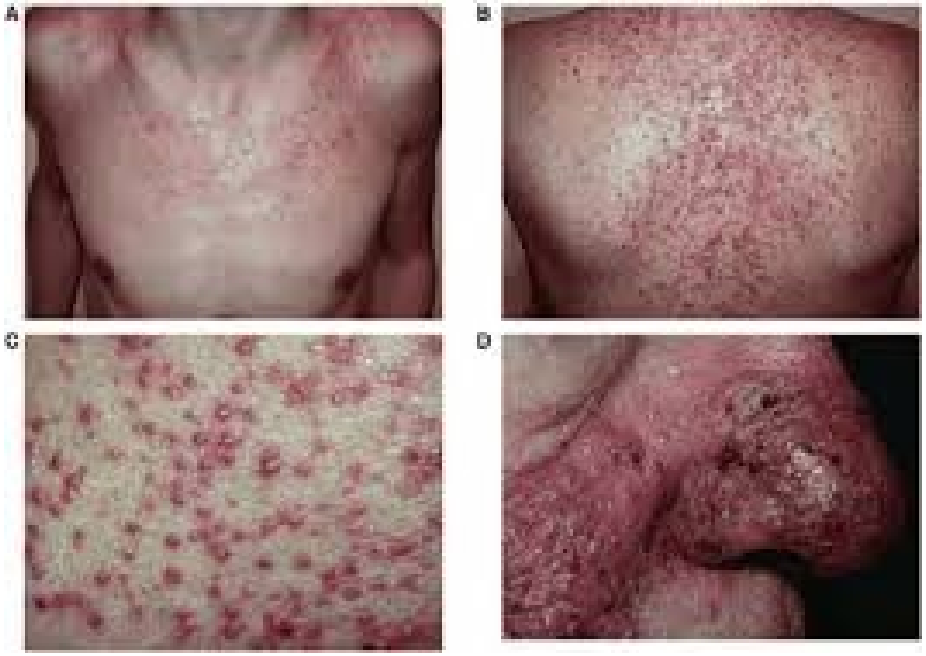
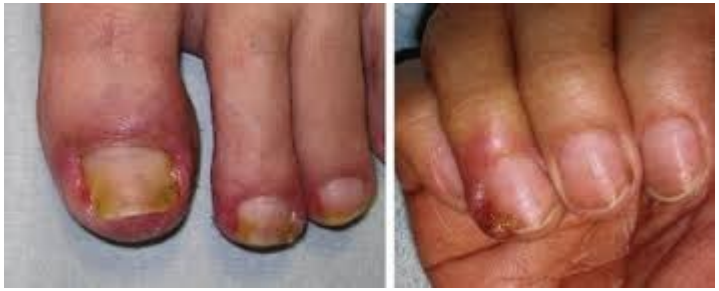


Fig. 4. Frequency of withdrawal AEs according to type of EGFR-TKI (A) and AEs responsible for discontinuation of EGFR-TKI treatment (B). Asterisks indicate statistically significant differences.


A
B
C
D



I protocolli di trattamento degli effetti collaterali da TKI sono efficaci ?

Management of Nonhematologic Toxicities Associated With Different EGFR-TKIs in Advanced NSCLC: A Comparison Analysis

Antonio Passaro,[1] Massimo Di Maio,[2] Ester Del Signore,[1] Bruno Gori,[3] Filippo de Marinis[1]

Table 1 Incidence of EGFR-TKI-Related Dermatologic AEs

Erlotinib 150 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	28 (48%)	1 (2%)	24 (41%)	3 (6%)	34 (58%)
2	14 (24%)	12 (20%)	1 (2%)	1 (2%)	10 (16%)
3	6 (11%)	5 (9%)	1 (2%)	0%	1 (2%)
4	0.0%	0%	0%	0%	0.0%
Gefitinib 250 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	26 (53%)	1 (2%)	25 (51%)	0 (0.0%)	31 (63%)
2	6 (12%)	5 (10%)	1 (2%)	0 (0.0%)	1 (2%)
3	1 (2%)	1 (2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Afatinib 40 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	19 (37%)	2 (4%)	16 (31%)	1 (2%)	25 (50%)
2	20 (39%)	8 (16%)	11 (22%)	1 (2%)	18 (35%)
3	10 (20%)	8 (16%)	2 (4%)	0 (0.0)	3 (6%)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AEs = adverse events; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

Management of Nonhematologic Toxicities Associated With Different EGFR-TKIs in Advanced NSCLC: A Comparison Analysis

Antonio Passaro,[1] Massimo Di Maio,[2] Ester Del Signore,[1] Bruno Gori,[3] Filippo de Marinis[1]

Table 3 Incidence of EGFR-TKI-Related Mucositis or Stomatitis

Erlotinib 150 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	7 (12.5%)	5 (9%)	2 (3.5%)	0 (0.0)	3 (3.5%)
2	1 (2%)	1 (2%)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gefitinib 250 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	6 (12%)	4 (8%)	2 (4%)	0 (0.0%)	2 (4%)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0%)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Afatinib 40 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	8 (14%)	6 (10%)	2 (3.5%)	0 (0.0)	3 (5%)
2	2 (3.5%)	2 (3.5%)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviation: EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

Management of Nonhematologic Toxicities Associated With Different EGFR-TKIs in Advanced NSCLC: A Comparison Analysis

Antonio Passaro,[1] Massimo Di Maio,[2] Ester Del Signore,[1] Bruno Gori,[3] Filippo de Marinis[1]

Table 2 Incidence of EGFR-TKI-Related Diarrhea

Erlotinib 150 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	27 (46%)	24 (42%)	3 (1, 2%)	0 (0.0)	3 (1, 2%)
2	20 (10%)	20 (10%)	0 (0.0)	0 (0.0)	0 (0.0)
3	4 (2%)	4 (2%)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gefitinib 250 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	14 (27%)	14 (27%)	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Afatinib 40 mg daily					
Initial Assessment		Last Assessment			Definitive Grade
Grade	n (%)	Lower	Equal	Worse	
1	22 (47%)	19 (37%)	3 (6%)	0 (0.0)	1 (2%)
2	12 (23%)	12 (23%)	0 (0.0)	0 (0.0)	0 (0.0)
3	7 (14%)	7 (14%)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviation: EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor.

Popolazioni speciali: anziani

Efficacy and safety of erlotinib in elderly patients in the phase IV POLARSTAR surveillance study of Japanese patients with non-small-cell lung cancer

Hiroshige Yoshioka[a,*], Kiyoshi Komuta[b], Fumio Imamura[c], Shoji Kudoh[d], Akihiro Seki[e], Masahiro Fukuoka[f]

- The incidence of hematologic and non hematologic toxicity was comparable between older and younger patients.
- The incidence of ILD was similar between age groups and was comparable with that previously reported in Japanese patients
- there was no significant deterioration of erlotinib tolerability in elderly patients, compared with younger patients

Lung Cancer 86 (2014) 201–206

Are TKIs favourable for the elderly with non-small-cell lung cancer?

Sabrina Rossi[1], Ettore D'Argento[1], Giovanni Schinzari[1], Vincenzo Dadduzio[1],

- The most frequent adverse events were rash,diarrhea and fatigue.
- There was no treatment-related death both in younger and older population and only few adverse events of grade 3/4, comparable in the two groups.
- There was a trend toward a more frequent and severe cutaneous rash between elderly patients (50% of all grades) than in younger population (40% of all grades), but the difference is not statistically significant.
- However, five elderly pts required dose reduction for treatment-related rash, six patients had a dose delay for diarrhea and one patient experienced interstitial lung disease, but there was no treatment interruption due to serious adverse event.

Oncotarget, Vol. 7, No. 30

Popolazioni speciali: IRC

Renal effects of targeted anticancer therapies

Camillo Porta, Laura Cosmai, Maurizio Gallieni, Paolo Pedrazzoli and Fabio Malberti

Table 1 | Renal toxicities of targeted anticancer targeted agents and management indications

Drug	Patients with renal function impairment included in pivotal trial	Renal excretion	Most-frequent renal AEs	Dose reduction required?		
				Patients with mild to moderate CKD*	Patients with severe CKD‡	Patients receiving dialysis
Gefitinib	No	<4%	Electrolyte disorders	No	No (no data)	No
Erlotinib	No	<9%	Electrolyte disorders	No	No (no data)	No
Afatinib	No	<5%	Electrolyte disorders	No	No (no data)	No (no data)
Gefitinib	Fluid retention		Incidence of 6.6% for all grades[164]			
	AKI and nephrotic syndrome		One case of AKI[165] and another of nephrotic syndrome (possibly due to an immunoallergic reaction) secondary to drug administration[166] have been reported			
Afatinib	Hypokalaemia		Incidence of 34% for all grades and 3% for grade 3–4[167]			
	Renal impairment and renal failure		Indicated as common AEs in the drug data sheet without further information			

Abbreviations: AE, adverse event; AKI, acute kidney injury; RR, relative risk.

Di cosa preoccuparci quando prescriviamo un TKI ?

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[a], Francesco Agustoni[a], Valter Torri[b], Francesco Gelsomino[a], Marco Platania[a], Nicoletta Zilembo[a], Rosaria Gallucci[a], Marina Chiara Garassino[a,*], Michela Cinquini[b]

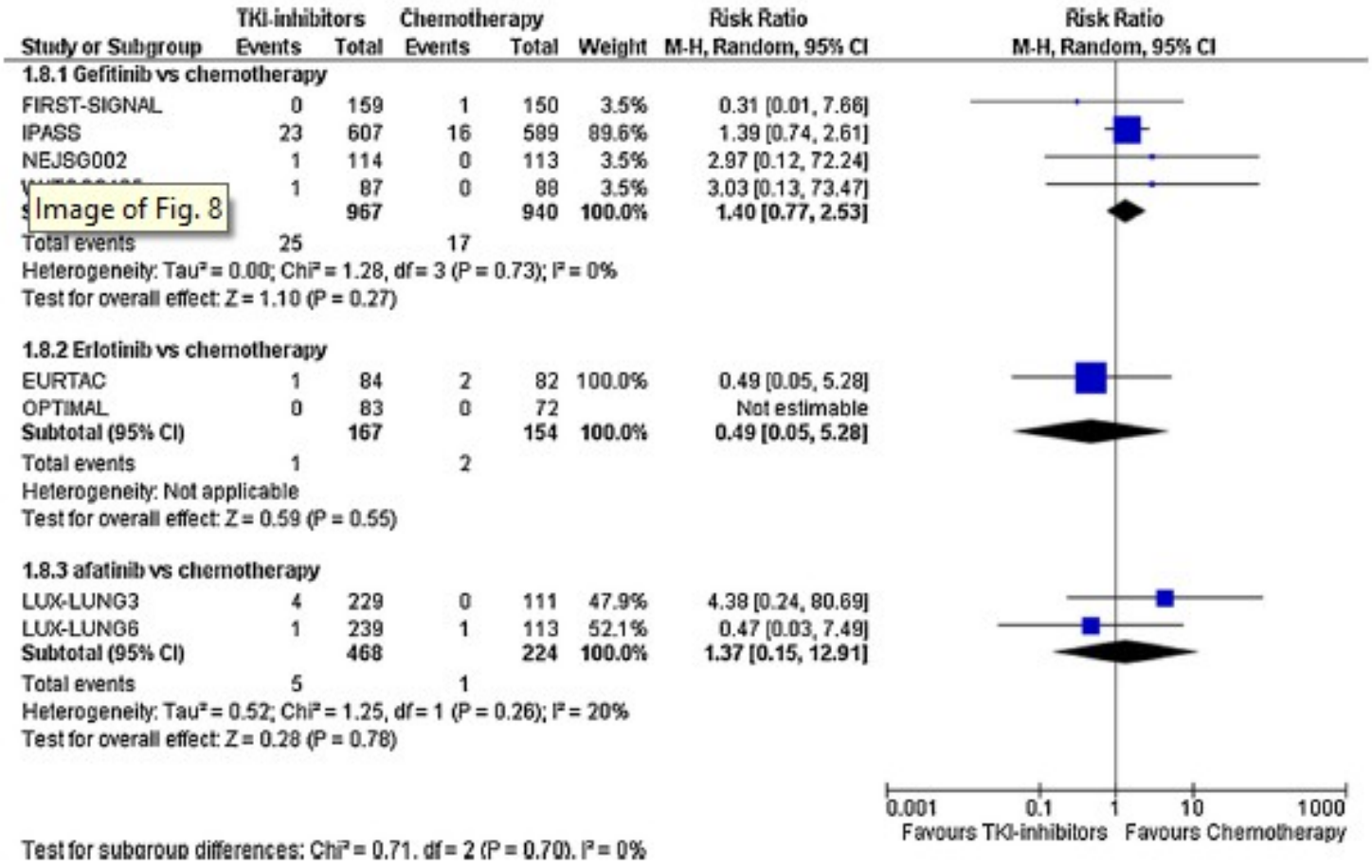


Fig. 8. Forest plot for treatment related deaths.

Morti tossiche

Risk of Treatment-Related Toxicities from EGFR Tyrosine Kinase Inhibitors: A Meta-analysis of Clinical Trials of Gefitinib, Erlotinib, and Afatinib in Advanced *EGFR*-Mutated Non-Small Cell Lung Cancer

Pei Ni Ding, MBBChir,[a,b] Sarah J. Lord, MSc,[a,c] Val Gebski, MStat,[a] Matthew Links, PhD,[d] Victoria Bray, PhD,[b] Richard J. Gralla, MD,[e] James Chih-Hsin Yang, PhD,[f] Chee Khoon Lee, PhD[a,d,*]

- Fifteen trials (with a total of 2201 patients) reported toxic death events and 37 cases (1.7%) were identified.
- The risk for toxic death was 2.3% with gefitinib (95% CI:1.6%–3.4%), 0.8% with erlotinib (95% CI: 0.2%–1.9%), and 1.1% with afatinib (95% CI: 0.4%–2.5%).
- Of the 17 reported causes of death, the most frequent cause of toxic death was **pneumonitis** (65%).

Journal of Thoracic Oncology Vol. 12 No. 4: 633-643

Tossicità polmonare da TKI

Maggior fattore di rischio: etnicità
4-6% asiatici vs 0,3-0,5% altre etnie

Predictive Factors for Interstitial Lung Disease, Antitumor Response, and Survival in Non–Small-Cell Lung Cancer Patients Treated With Gefitinib

Masahiko Ando, Isamu Okamoto, Nobuyuki Yamamoto, Koji Takeda, Kenji Tamura, Takashi Seto, Yutaka Ariyoshi, and Masahiro Fukuoka

Among 1,671 patients with known smoking status, the prevalence of ILD ranged from

0.4% in women with no history of smoking

to 6.6%in men with a history of smoking

Variable	Total No. of Patients	ILD: Patients With ILD No.	ILD: Patients With ILD %	*P*
Age, years				
< 70	1,047	39	3.7	.446
≥ 70	672	30	4.5	
Sex				
Female	631	6	1.0	< .001
Male	1,088	63	5.8	
Smoking status				
No smoking history	658	5	0.8	< .001
Positive smoking history	1,013	63	6.2	
Histology				
Adenocarcinoma	1,294	47	3.6	.130
Others	414	22	5.3	
Disease stage				
Metastatic	1,313	59	4.5	.069
Nonmetastatic	406	10	2.5	
Performance status				
0-1	1,161	44	3.8	.664
2	336	14	4.2	
3-4	216	11	5.1	
Previous chest surgery				
Yes	528	15	2.8	.093
No	1,181	54	4.6	
Previous thoracic RT				
Yes	472	18	3.8	.767
No	1,235	51	4.1	
Previous chemotherapy				
Yes	1,356	57	4.2	.440
No	363	12	3.3	
Coincidence of IP				
Yes	36	5	13.9	.013*
No	1,683	64	3.8	

J Clin Oncol 24:2549-2556. © 2006

Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer

Akihiko Gemma,[1,19] Shoji Kudoh,[2,18] Masahiko Ando,[3,18] Yuichiro Ohe,[4,18] Kazuhiko Nakagawa,[5,18] Takeshi Johkoh,[6,18,19] Naoya Yamazaki,[7,18] Hiroaki Arakawa,[8,19] Yoshikazu Inoue,[9,19] Masahito Ebina,[10,19] Masahiko Kusumoto,[11,19] Kazuyoshi Kuwano,[12,19] Fumikazu Sakai,[13,19] Hiroyuki Taniguchi,[14,19] Yuh Fukuda,[15,19] Akihiro Seki,[16] Tadashi Ishii[16] and Masahiro Fukuoka[17,18]

- Studio osservazionale retrospettivo su ca 10.000 pazienti
- End point primario la incidenza di ILD e la identificazione dei fattori di rischio

Cancer Sci | December 2014 | vol. 105 | no. 12

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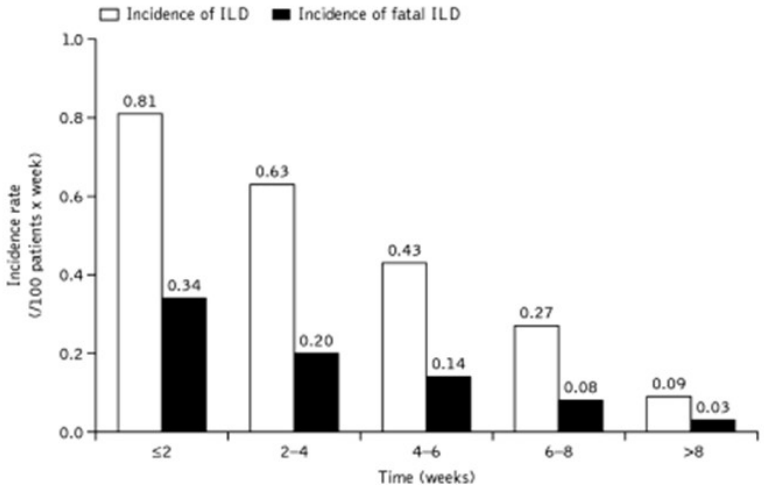
Multivariate analysis						
Concurrent/previous ILD	No	Yes	55.3796	<0.0001	3.187	2.349–4.325
Smoking history	No	Yes	34.1327	<0.0001	2.246	1.712–2.946
Concurrent/previous emphysema or COPD	No	Yes	20.704	<0.0001	1.860	1.424–2.431
Period from initial NSCLC diagnosis to the start of treatment	<360 days	≥360 days	19.3818	<0.0001	0.581	0.456–0.740
Concurrent/previous lung infection	No	Yes	6.5905	0.0103	1.550	1.109–2.165
ECOG PS	0–1	2–4	8.9467	0.0028	1.431	1.131–1.809
History of gefitinib treatment	No	Yes	5.3133	0.0212	0.729	0.557–0.954
Number of chemotherapy regimens†	–	–†	10.4136	0.0013	1.121	1.046–1.201



Final safety and efficacy of erlotinib in the phase 4 POLARSTAR surveillance study of 10 708 Japanese patients with non-small-cell lung cancer

Akihiko Gemma,[1,19] Shoji Kudoh,[2,18] Masahiko Ando,[3,18] Yuichiro Ohe,[4,18] Kazuhiko Nakagawa,[5,18] Takeshi Johkoh,[6,18,19] Naoya Yamazaki,[7,18] Hiroaki Arakawa,[8,19] Yoshikazu Inoue,[9,19] Masahito Ebina,[10,19] Masahiko Kusumoto,[11,19] Kazuyoshi Kuwano,[12,19] Fumikazu Sakai,[13,19] Hiroyuki Taniguchi,[14,19] Yuh Fukuda,[15,19] Akihiro Seki,[16] Tadashi Ishii[16] and Masahiro Fukuoka[17,18]

Table 4. Interstitial lung disease (ILD) poor prognosis risk factors from the final analysis results for Post-Launch All-patient-Registration Surveillance in Tarceva®-treated non-small-cell lung cancer patients (POLARSTAR)

Risk factors for ILD-related death	Criterion variable	Evaluation variable	X^2 value	*P*-value	OR	95% CI
ECOG PS 2–4	0–1	2–4	9.974	0.0016	2.45	1.41–4.27
≤50% normal lung area	>50	≤50	8.896	0.0029	3.12	1.48–6.58
Concomitant honeycombing	No	Yes	5.414	0.02	6.67	1.35–32.94

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

Clinica dell' ILD da TKI

Tempo di insorgenza: In genere entro i primi 30-60 giorni di trattamento

Sintomatologia aspecifica: tosse stizzosa, dispnea, febbricola

Il 50% dei pazienti con alterazioni TC suggestive per ILD sono asintomatici

Quadro radiologico aspecifico

R/O infezioni e PD neoplastica

Trattamento basato su sospensione del farmaco, steroidi ad alte dosi e terapia di supporto

Mortalità 20-35 %

E’ possibile ridurre il rischio di ILD?

- Selezione dei pazienti (fumatori,pz con evidenza clinica o radiologica di COPD)
- Condivisione con il paziente dei rischi e dei benefici correlati all'utilizzo del TKI nelle situazioni di aumentato rischio di tossicità
- Educazione del paziente (immediata segnalazione della comparsa di nuovi sintomi respiratori)
- Precoce valutazione radiologica dei pazienti con modificazione della sintomatologia respiratoria
- Collaborazione con specialisti d'organo e radiologi per una corretta valutazione diagnostica

Rechallenge dopo ILD?

Cancer Chemother Pharmacol. 2017 Apr;79(4):705-710. doi: 10.1007/s00280-017-3261-5. Epub 2017 Mar 3.

Outcome in advanced non-small cell lung cancer patients with successful rechallenge after recovery from epidermal growth factor receptor tyrosine kinase inhibitor-induced interstitial lung disease.

Kashiwabara K[1], Semba H[2], Fujii S[2], Tsumura S[2].

- Il rechallenge, dopo risoluzione clinica e radiologica, e con terapia steroidea cronica associata, può essere in alcuni casi effettuato.
- I pazienti sottoposti a rechallenge hanno avuto un DFS superiore a quelli che non hanno più effettuato trattamenti con TKI

Osimertinib

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*

the most commonly reported adverse events were
diarrhea 41%
rash 34%
dry skin 23%
paronychia 22%

Interstitial lung disease–like adverse events were reported in 10 patients (4%) in the osimertinib group (nine events of grade 1 or 2 in severity and one death)

A prolongation in the QT interval was recorded in 10 patients (4%) in the osimertinib group all events of grade 1 or 2 in severity except for one grade 3 event (.)

Osimertinib was associated with a lower rate of adverse events leading to permanent discontinuation than was platinum–pemetrexed (in19 patients [7%] and 14 patients [10%], respectively).

Fatal adverse events were reported in 4 patients in the osimertinib group (respiratory failure in 2, pneumonitis in 1, and ischemic stroke in1).
One fatal adverse event of hypovolemic shockwas reported in the platinum–pemetrexed group.

Tossicità da ALK-i

Managing treatment–related adverse events associated with Alk inhibitors

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N. Letarte BPharm MSc BCOP†

TABLE 1 All grades of treatment-related adverse events seen in at least 10% of patients in PROFILE 1001[8], PROFILE 1005[9], and PROFILE 1007[10]

Adverse event	*Occurrence (%) in*					
	PROFILE 1001 (n=149)		*PROFILE 1005 (n=901)*		*PROFILE 1007 (n=172)*	
	All grades	*Grade 3 or 4*	*All grades*	*Grade 3 or 4*	*All grades*	*Grade 3 or 4*
Visual effects	64	0	52	<1	60	0
Nausea	56	<1	47	<1	55	1
Diarrhea	50	0	41	1	60	0
Vomiting	39	<1	39	<1	47	1
Peripheral edema	30	0	23	<1	31	0
Constipation	28	<1	28	<1	42	2
Dizziness	21	0	11	0	22	1
Decreased appetite	16	0	19	<1	27	2
Fatigue	16	1	18	2	27	2
Increased ALT	12	4	16	4	NR[a]	NR[a]
Dysgeusia	11	0	17	0	26	0
Increased AST	10	3	12	1	NR[a]	NR[a]

[a] Reported as cluster term "elevated aminotransferase levels," the all-grade occurrence was 38%, and the grade 3 or 4 occurrence was 16%.
ALT = alanine aminotransferase; NR = not reported; AST = aspartate aminotransferase.

TABLE II Recommended monitoring for patients on crizotinib[16]

Toxicity	*Baseline testing*	*Ongoing monitoring*
Hepatotoxicity	AST, ALT, ALP, bilirubin	Every 2 weeks during the first 2 months, then monthly and as clinically indicated More frequent testing for grade 2, 3, or 4 elevation
Hematologic effects	Complete blood count and differential	Monthly and as clinically indicated More frequently if grade 3 or 4 abnormalities observed, or if fever or infection occurs
Cardiac (QTc prolongation and bradycardia)	Concomitant medication list, physical exam (heart rate and blood pressure), electrocardiogram, electrolytes	Concomitant medication list Physical exam (heart rate and blood pressure) Periodic monitoring for patients at risk for abnormalities with electrocardiogram and electrolytes
Ophthalmologic	None	If persistent or severe symptoms, consider ophthalmologic evaluation
Pneumonitis	None	As clinically indicated by symptoms and imaging
Hypogonadism	In men: serum testosterone	If symptomatic: serum testosterone

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase.