



Chemotherapy versus erlotinib as second-line treatment in patients with advanced non-small cell lung cancer and wild-type epidermal growth factor receptor: an individual patient data (IPD) analysis

Marina Chiara Garassino,¹ Tomoya Kawaguchi,² Vanesa Gregorc,³ Eliana Rulli,⁴ Masahiko Ando,⁵ Silvia Marsoni,⁶ Shun-ichi Isa,⁷ Silvia Novello,⁸ Gabriella Farina,⁹ Sandro Barni,¹⁰ Valter Torri,⁴ Michela Cinquini⁴

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For numbered affiliations see end of article.

Correspondence to
Dr Michela Cinquini; michela.cinquini@marionegri.it

ABSTRACT

The efficacy of second-line treatment in patients with epidermal growth factor receptor (EGFR) wild-type tumours is still debatable. We assessed the efficacy of a standard second-line chemotherapy compared with erlotinib in an individual patient data approach for meta-analysis. The primary endpoint was overall survival (OS), and secondary endpoint was progression-free survival (PFS). Both were compared by log-rank test. The 'restricted mean survival time' (RMST) was estimated in each study and the difference in mean survival time up to the last available time point was calculated. The Cox proportional hazards model was used on survival analyses to provide HRs, to adjust for confounding variables and to test possible interaction with selected factors. Three randomised trials comparing chemotherapy versus erlotinib were analysed, including 587 randomised patients. Overall, 74% of patients included in the original trials were considered. 464 deaths and 570 progressions or deaths were observed. Compared with erlotinib, chemotherapy was associated to a decreased risk of progression (29%; HR: 0.71, 95% CI: 0.60 to 0.84, $p < 0.0001$;) but with no statistical significant reduction in OS (HR: 0.89, 95% CI: 0.74 to 1.06; $p < 0.20$). No heterogeneity was found in both analyses. Patients treated with chemotherapy gained an absolute 1.5 and 1.6 months, respectively, in PFS and lifetime (RMST 95% CI: PFS 0.49 to 2.44; OS 95% CI: -1.04 to 4.25). These results showed that patients without a constitutively activated EGFR had better PFS with chemotherapy rather than with erlotinib while no statistical difference was observed in OS.

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 80% of cases. Most patients presented with advanced disease at the time of diagnosis, with an estimated median overall survival (OS) inferior to 10 months.¹

In 2004, two classes of somatic activating mutations were described, for the first time, in the tyrosine kinase (TK) domain of the epidermal growth factor receptor gene (EGFR) in patients with advanced NSCLC. In vitro experiments showed that these molecular alterations determine the ligand independent activation of the EGFR pathway, thus making tumour cells sensitive to the small molecule epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), gefitinib.² This finding has opened a new era in the treatment of lung cancer.

Thanks to the technological advances, several molecular alterations, amenable of targeted inhibition, have been discovered in NSCLC, particularly in the subgroup of patients with adenocarcinoma,³ substantially improving the first-line treatment options for metastatic lung cancer. Currently, patients who carry EGFR activating mutations or translocations in the anaplastic lymphoma kinase gene are treated upfront with their specific inhibitor, while chemotherapy remains the standard therapeutic choice for wild-type (WT) patients. While this distinction appears clear in first-line setting, for patients with EGFR WT or for individuals with undetermined mutation status, data from literature did not show a definite superiority of standard second-line chemotherapy regimens (docetaxel or pemetrexed) over TKIs. In the past years, several studies have been conducted, comparing EGFR-TKIs (erlotinib or gefitinib) to second-line chemotherapy in

patients with NSCLC, independently of the EGFR genotype or focusing on WT patients only.⁴

Currently, for the treatment of patients with advanced NSCLC in the second-line setting regardless their mutational status, US Food and Drug Administration (FDA) approved, other than docetaxel and pemetrexed, the EGFR-TKI erlotinib, even though its role seems not to be appropriate for WT patients. This issue has been shown by several systematic reviews with meta-analysis that tried to pool together the aggregated data derived from these studies, just concluding that WT patients are not suitable for TKIs option.⁴⁻⁶

This came to an end when, in 2016, the FDA modified the indication for erlotinib (or treatment of NSCLC limiting its use to patients whose tumours have specific EGFR mutations).

Nevertheless, it is of great importance to obtain all the information needed even from those trial reporting results from subgroups. Possible imbalances between arms might be managed by appropriate analyses.

We tried in contacting all authors of relevant studies with the aim at performing an individual patient data (IPD) meta-analysis that could improve the quality of data and the type of analyses and produce more reliable results.

We also identified factors that might affect the effect of erlotinib on OS and provide an unique opportunity to shed light on this important topic. The study allows for a deeper analysis of the pooled data of these three studies, adding the information that, based on the available markers and clinical factors, there is no subgroup of patients with WT NSCLC who can take advantages from a therapy based on erlotinib.

MATERIALS AND METHODS

Identification of eligible trials

On January 2015, we performed a comprehensive search to identify all phase III randomised trials comparing chemotherapy over erlotinib in second line.

We searched PubMed, Embase and the Cochrane Library for papers published until January 2015 with the following keywords: “erlotinib”, “TKI”, “lung neoplasms”, “NSCLC” and “Randomized Controlled Trial”.

We also searched the proceedings of the most important international meetings (American Society of Clinical Oncology, European Society of Medical Oncology, European Cancer Conference and World Conference on Lung Cancer) from 2005 onwards until January 2015.

Studies had to be closed to patient accrual and have at least one survival outcome (OS, progression-free survival (PFS)) to be included.

Studies were excluded if the percentage of genotyped patients was less than 50% to better generalise the results.

Data collection and database quality

For all patients enrolled, we requested individual data to the authors of each identified trial. Before we did the

pooled analyses, we checked the data from each individual study and verified them for coherence with the original publications, and we discussed any discrepancies with the authors. Database quality was good for all the eligible studies. Data for survival analyses, and possible prognostic or predictive factors for all randomised patients were required and provided following an ‘ad hoc’ case report form.

Adverse events were not analysed because this issue is not related to subgroups only but it is a general aspect that affects the entire population.

Statistical analysis

The analyses were performed on all randomised patients meeting the inclusion criteria, according to the intention-to-treat principle. OS was defined as the time from randomisation until death. Patients still alive were censored at the date of last follow-up. PFS was defined as the time from randomisation until progression or death whichever occurred first. Patients alive without disease progression were censored at the date of last follow-up.

As primary analysis, OS and PFS curves were estimated by the Kaplan-Meier technique, and the null hypothesis of no difference between the two arms was assessed using the log-rank test stratified by trial. The Cox proportional hazards model was used on both survival analyses to provide an estimate of the HR, to adjust for confounding variables and to test possible interaction with selected factors.

As secondary analysis, the ‘restricted mean survival time’ (RMST), a model-free and censoring-independent parameter to quantify the treatment difference, was estimated in each singular study, and the difference between arms in mean survival time up to the last available time point were calculated. When the proportional hazards assumption is not valid, the standard maximum partial likelihood estimator of the HR approximates a parameter which is difficult, if not impossible, to interpret as the treatment contrast. Therefore, it is highly desirable to consider an estimable, model-free and censoring-independent parameter to quantify the treatment difference.^{7,8}

This approach returns an easily interpretable, clinically meaningful summary of the survival function in the presence of censoring. The RMST is the average of all potential event times measured up to a time point t^* , which can be estimated consistently by the area under the Kaplan-Meier curve over $[0; t^*]$.

For the pooled analysis, 1 year for PFS and 2 years for OS were used as last available time point mean and SD of RMST were the effect measure used for meta-analysis.

For all pooled analyses, the inverse variance method was used for weighting the results of each trial. A random effect model was considered because an a priori heterogeneity among studies was thought and a χ^2 heterogeneity tests was used to test it. We also calculated the I^2 statistic to measure inconsistency among trials.

If there were sufficient data available, we investigated whether any observed treatment effect was consistent or not across well-defined patient subgroups. These analyses were carried out on all trials and were stratified by trial. Then subgroup analyses were done within treatment categories identified as race, sex, histology and smoking status and K-ras mutation status.

χ^2 tests for interaction or trend was used to test whether there was any evidence that types of patients benefit from chemotherapy.

All statistical analyses were carried out using SAS V.9.4 with a significant level of 0.05; all meta-analyses were performed with RevMan 5.3.⁹

RESULTS

Overall 7 out of 133 studies were found to meet eligible criteria for randomised comparison of chemotherapy versus erlotinib in second-line treatments for NSCLC^{10–16} for which we contacted corresponding authors. The studies of Lee¹³ and Li¹⁶ were excluded because of phase II studies. No data were available for the study HORG¹⁴ and TITAN¹⁵ because authors never answered to our request.

The analysis of the three remaining studies included all 587 patients randomised into the trials (number of erlotinib/chemotherapy: all 303/284; TAILOR¹⁰ 109/110; DELTA¹² 109/90; PROSE¹¹ 85/84); overall, 74% of patients included in the trials were considered (TAILOR 219/222: 99%; DELTA 199/301: 66%; PROSE 169/302: 62%).

Table 1 describes the characteristics of evaluated patients per study group.

Overall, a good balancing of baseline characteristics was achieved between treatments. Analysis across studies showed that DELTA study had a proportion of male higher than the TAILOR and PROSE, and a lower proportion of smokers.

TAILOR had as primary objective whether patients with EGFR WT could benefit from treatment with docetaxel or erlotinib. DELTA, in which an Asian population was enrolled, wanted to show the superiority of erlotinib over docetaxel in second-third line, in patients not selected for EGFR mutation status. PROSE, had a different conception yet, as it wanted to demonstrate that a proteomic signature could select patients either for chemotherapy or erlotinib. Moreover, in both DELTA and PROSE studies, a subgroup analysis, testing the interaction between

Table 1 Baseline characteristics of included studies

	TAILOR		ERL		PROSE		ERL		DELTA		ERL	
	Chemo: 110		Erl: 109		Chemo: 84		Erl: 85		Chemo: 90		Erl: 109	
	n	%	n	%	n	%	n	%	n	%	n	%
Age median (minimum–maximum)	65 (33–81)		64 (39–78)		64 (42–77)		67 (47–81)		67 (36–85)		66 (37–82)	
Gender												
Male	73	66.4	77	70.6	60	71.4	59	69.4	68	75.6	85	78.0
Female	37	33.6	32	29.4	24	28.6	26	30.6	22	24.4	24	22.0
Smoke habits												
Never smoker	30	27.3	19	17.4	7	8.3	9	10.6	14	15.6	22	20.2
Ex smoker	52	47.3	55	50.5	51	60.7	54	63.5	68	75.6	82	75.2
Current smoker	28	25.5	35	32.1	26	31.0	22	25.9	8	8.9	5	4.6
Histology												
Squamous	21	19.1	25	22.9	12	14.3	21	24.7	19	21.1	22	20.2
Adenocarcinoma	74	67.3	69	63.3	58	69.0	50	58.8	58	64.4	72	66.1
Bronchioloalveolar	2	1.8	3	2.8	1	1.2	2	2.4	NA	NA	NA	NA
Large cell	2	1.8	NA	NA	4	4.8	6	7.1	4	4.4	7	6.4
Mixed	1	0.9	1	0.9	NA	NA	NA	NA	NA	NA	NA	NA
Other	6	5.5	8	7.3	7	8.3	5	5.9	9	10.0	8	7.3
Not known	4	3.6	3	2.8	2	2.4	1	1.2	NA	NA	NA	NA
Performance status												
0	53	48.2	52	47.7	43	51.2	46	54.1	38	42.2	52	47.7
1	50	45.4	48	44.0	36	42.9	34	40.0	49	54.5	52	47.7
2	7	6.4	9	8.3	5	5.9	5	5.9	3	3.3	5	4.6

Chemo, chemotherapy; Erl, erlotinib; NA, not applicable.

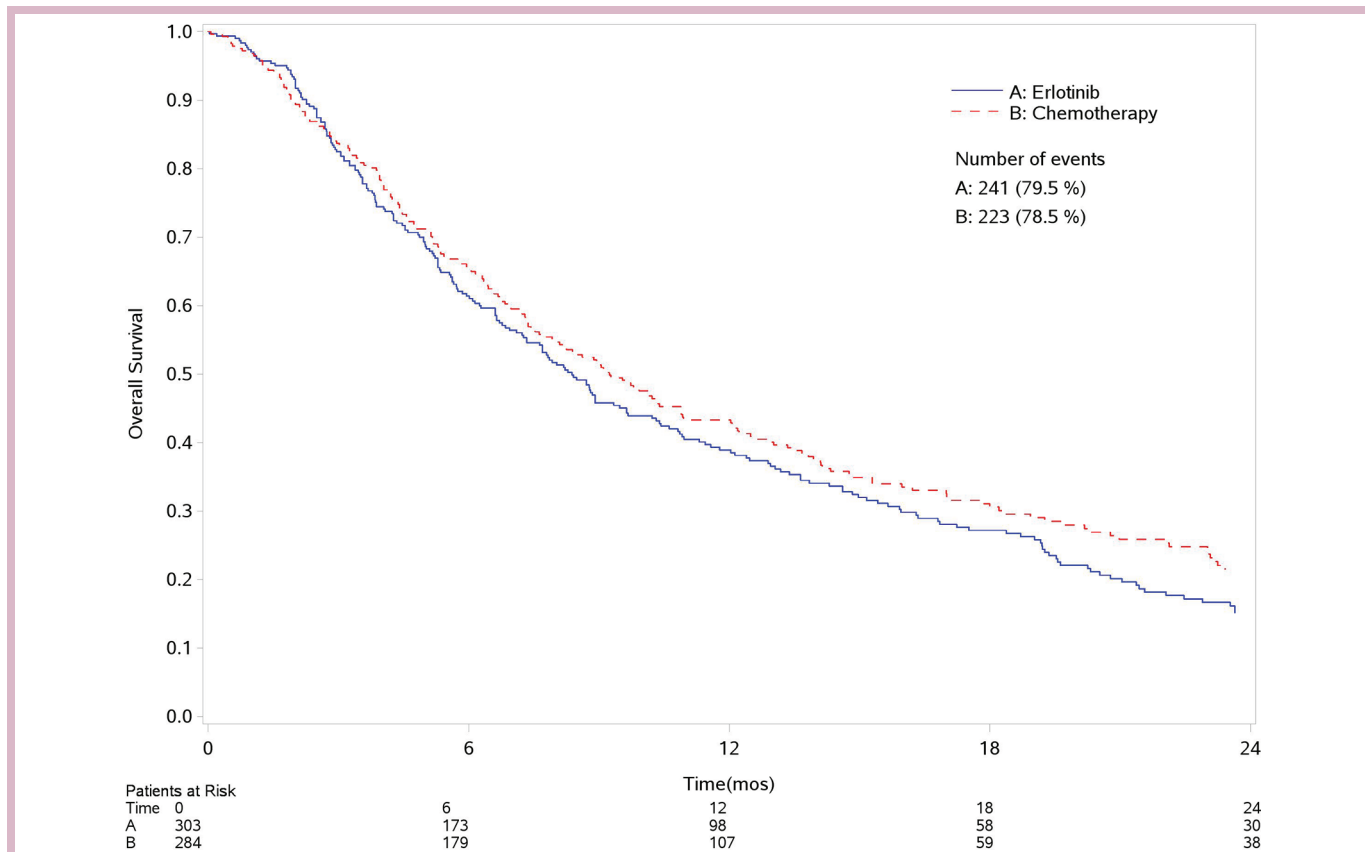


Figure 1 Overall survival. Kaplan-Meier curve. mos, months.

EGFR mutations and treatment, was preplanned, and the majority of the enrolled patients was EGFR WT.

In TAILOR and DELTA, only patients with histological diagnosis were enrolled, while PROSE allowed to enter also patients with cytological diagnosis. Furthermore, in both TAILOR and PROSE, the CT scan evaluation was performed every 8 weeks, while in DELTA, the radiological assessment was performed every month for the first 4 months, and then every 2 months. Moreover, while in TAILOR and PROSE, docetaxel was administered at the dose of 75 mg/m² every 21 days or at 35 mg/m² on days 1, 8, 15, every 28 days, patients enrolled in DELTA received 60 mg/m² every 21 days. Finally, while tumour samples from patients enrolled in TAILOR and DELTA were analysed according to the Sanger method, those from patients recruited in DELTA were genotyped by a highly sensitive PCR method, the PCR-invader method, peptide nucleic acid-locked nucleic acid PCR clamp method.

PFS and overall survival analysis

Figure 1 and figure 2 report the survival curves for OS and PFS, respectively. Four hundred and sixty-four deaths and 570 progressions or deaths were observed. Compared with erlotinib, chemotherapy was associated to a decreased risk of progression (29%) but with no reduction in OS (HR-PFS: 0.71, 95% CI: 0.60 to 0.84, $p < 0.0001$; HR-OS: 0.89, 95% CI: 0.74 to 1.06; $p < 0.2$, figure 3A,C). No heterogeneity was found in both analyses.

Patients treated with chemotherapy gained an absolute 1.5 and 1.6 months, respectively, in progression-free survival and lifetime (RMST 95% CI: PFS 0.49 to 2.44; OS 95% CI: -1.04 to 4.25).

In this case, we found a moderate heterogeneity (36% and 47%, respectively, for PFS and OS) likely because this type of analysis is affected by extreme values (figure 3B,D).

OS results were confirmed after adjustment by age, gender, smoking habit, performance status, histotype and K-RAS (HR-OS: 0.87, 95% CI: 0.72 to 1.04; $p < 0.137$) (table 2).

Among the factors evaluated for possible prognostic effect on survival, only gender (female) and performance status (0) were found to be associated to a better prognosis (table 2). No factors resulted associated to a differential effect of therapy (figure 4).

DISCUSSION

In the last years, the question about treating EGFR WT NSCLC patients with erlotinib has been the focus of much debate.

When TAILOR, DELTA and PROSE were designed, the predictive role of EGFR activating mutations was not yet clear, and the therapeutic options in second-line setting were weak, based only on single agent chemotherapy or erlotinib, but with any criteria to select population.

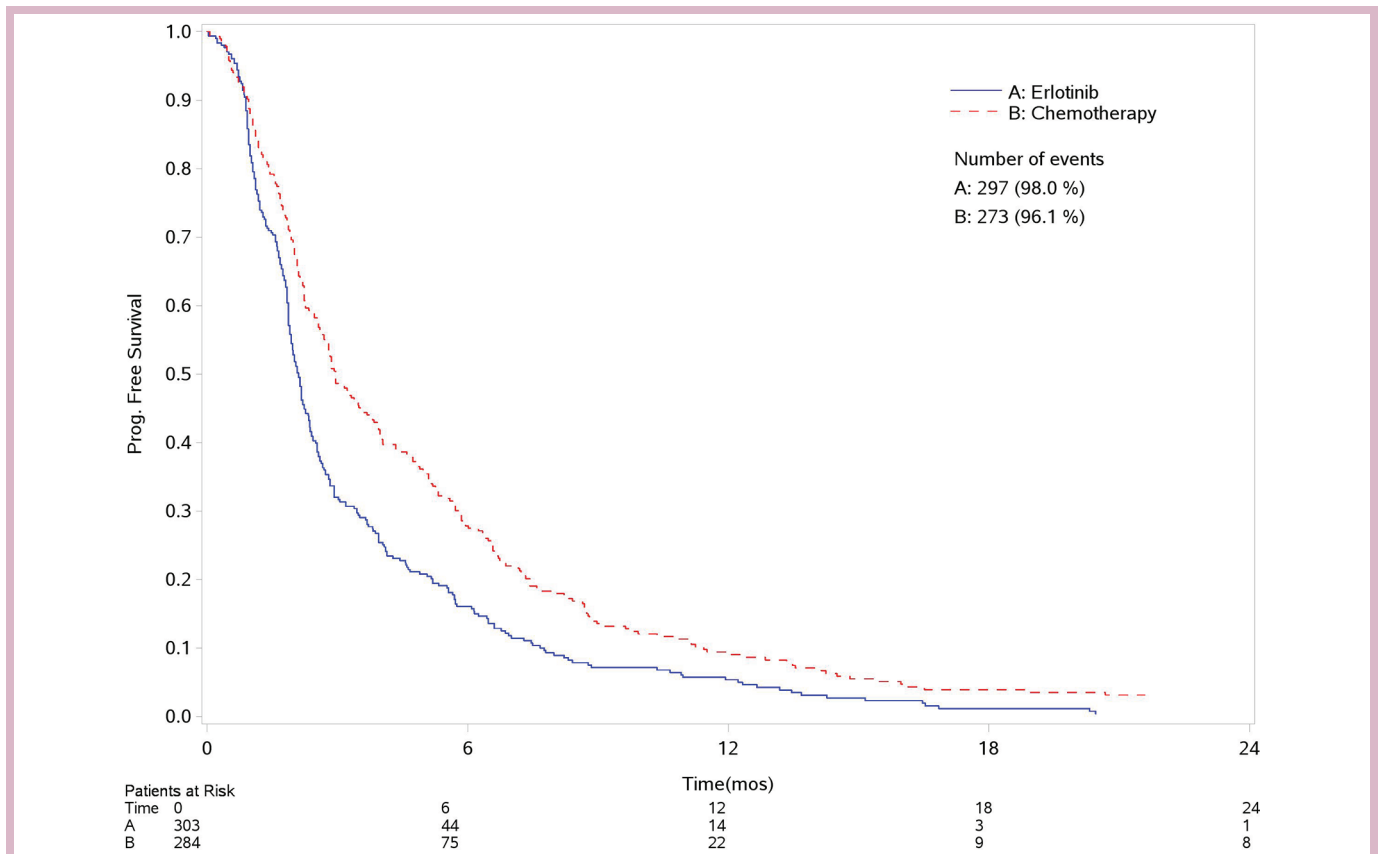


Figure 2 Progression-free survival. Kaplan-Meier curve. mos, months.

With the aim to compare the efficacy of standard second-line chemotherapy and erlotinib in EGFR WT NSCLC patients, we performed this IPD analysis. The three studies selected, although from different rational and objectives, shared the same study design. Despite these differences, results were similar, being the PFS in favour of chemotherapy in EGFR WT patients. Unfortunately, only results from TAILOR showed a longer OS in the chemotherapy arm. It is important to emphasise that TAILOR did not allow the cross-over treatment in further lines and that only taxane naive patients were included, while PROSE and DELTA allowed previous taxane therapy. Furthermore, pemetrexed was an option for the second-line chemotherapy only in the PROSE study. These differences are potentially responsible of differing results of these three trials, even though these aspects did not reflect in heterogeneity when data were analysed using the common method.

Heterogeneity appears when results are presented as mean difference. This may be due to the fact that the effect measure suffers from extreme values.

The strength of this meta-analysis is that the results give us a more accurate estimate of the benefit of chemotherapy compared with erlotinib.

Having all the raw data allowed for a very sensitive analysis of factors potentially associated to survival. Based on this analysis, we can conclude that there is no evidence of predictive role of investigated factors, and only

performance status and gender results to be associated with prognosis. This was already the primary endpoint of PROSE trial with the hypothesis of demonstrating the existence of a significant interaction between the proteomic test and the treatment. Unfortunately, this was the only trial with such a design.

The weakness lies in the fact that not all trials with the required characteristics were included in this analysis because on one hand we did not receive answer from all the contacted authors, but on the other hand we arbitrary chose a minimum percentage of genotyped patients (>50%) to be included in the analysis.

A generalisation of these results is not easy to achieve even because patient characteristics among studies differed remarkably, that is, in the PROSE study there were considerable number of squamous and KRAS mutated patients; DELTA has a totally Asian population, while the others Caucasian.

Is this meta-analysis enough to say that no longer erlotinib should not be given in patients with EGFR WT? Since all three studies show that even a small percentage of patients despite the absence of EGFR mutations will benefit from erlotinib, research should focus on this question. One hypothesis is to evaluate if they are EGFR mutated patients and the Sanger's sequencing is not enough sensitive to recognise them or if they are patients with other alterations that somehow also activate the EGFR pathway. For instance, EGFR-kinase domain duplication

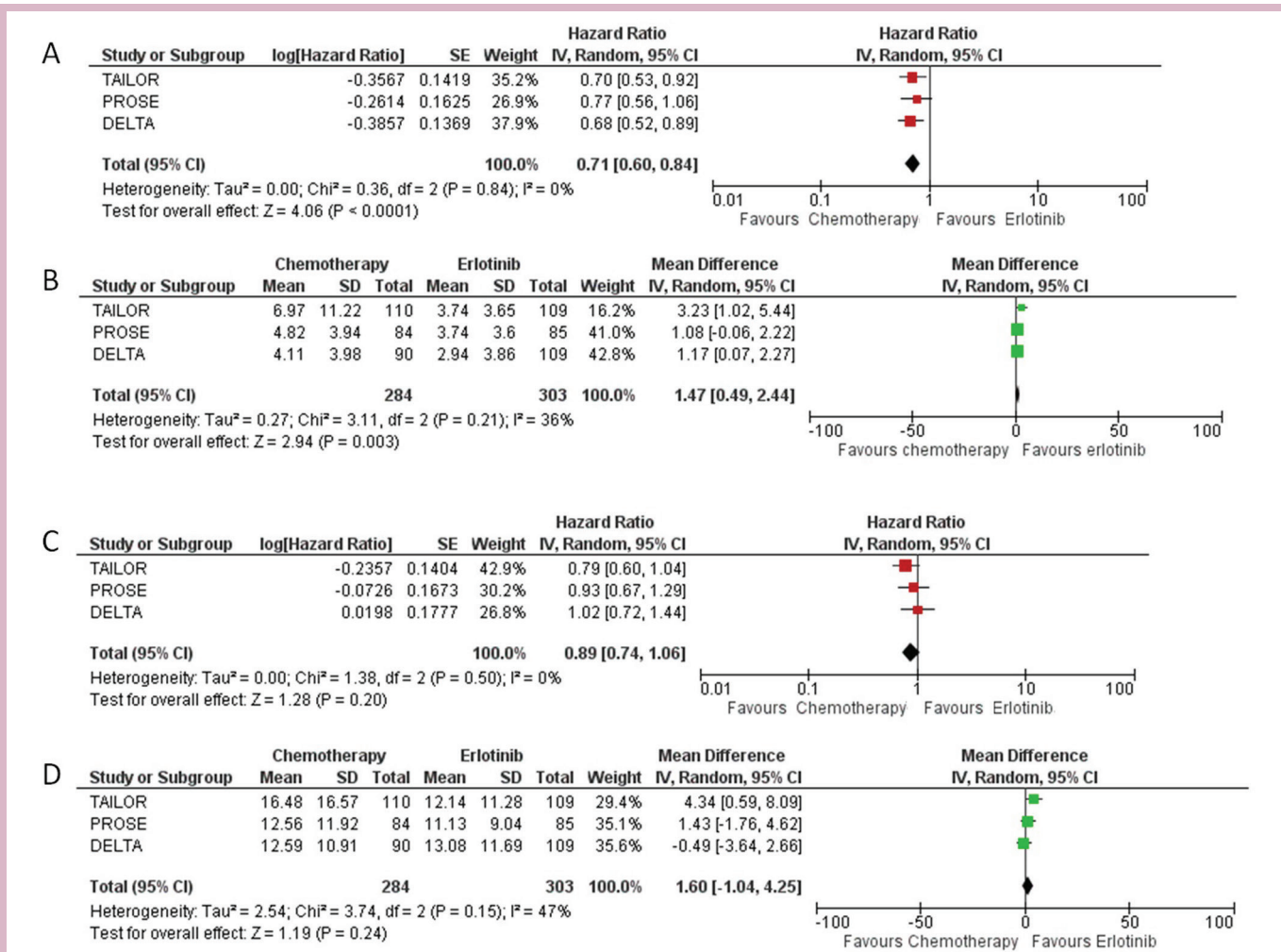


Figure 3 Forest plot of combined HRs for progression-free survival (A); forest plot of combined difference in mean (RMSD) for progression-free survival (B); forest plot of combined HRs for overall survival (C); forest plot of combined difference in mean (RMSD) for overall survival (D). IV, inverse of variance; RMSD, root-mean-square deviation.

(KDD) recently was identified and documented that a patient with metastatic lung adenocarcinoma harbouring the EGFR-KDD derived significant antitumour response from treatment with the EGFR inhibitor afatinib. However, we are confident that in patients with good

Eastern Cooperative Oncology Group performance status and able to tolerate chemotherapy in second line, based on these findings, a chemotherapeutic treatment should be preferred before using EGFR-TKI. Another key question is whether all this discussion will end with the new

Table 2 Multivariable analysis of prognostic factors for overall survival

Factor	Ref. Level	HR	95% CI	P values	
Treatment	Chemotherapy	Erlotinib	0.87	0.72 to 1.04	0.137
Age (years)	Continuous		1.00	0.99 to 1.01	0.690
Gender	Female	Male	0.73	0.58 to 0.93	0.011
Smoke habits	Former	Current	1.08	0.85 to 1.36	0.643
	Never		0.95	0.68 to 1.34	
Histology	Non-squamous	Squamous	0.87	0.69 to 1.11	0.258
Performance status	>0	0	1.74	1.49 to 2.03	<0.001
K-ras*	Mutated	Non-mutated	1.28	0.99 to 1.65	0.066

Analysis is stratified by study.

*Evaluated only in TAILOR and PROSE trials.

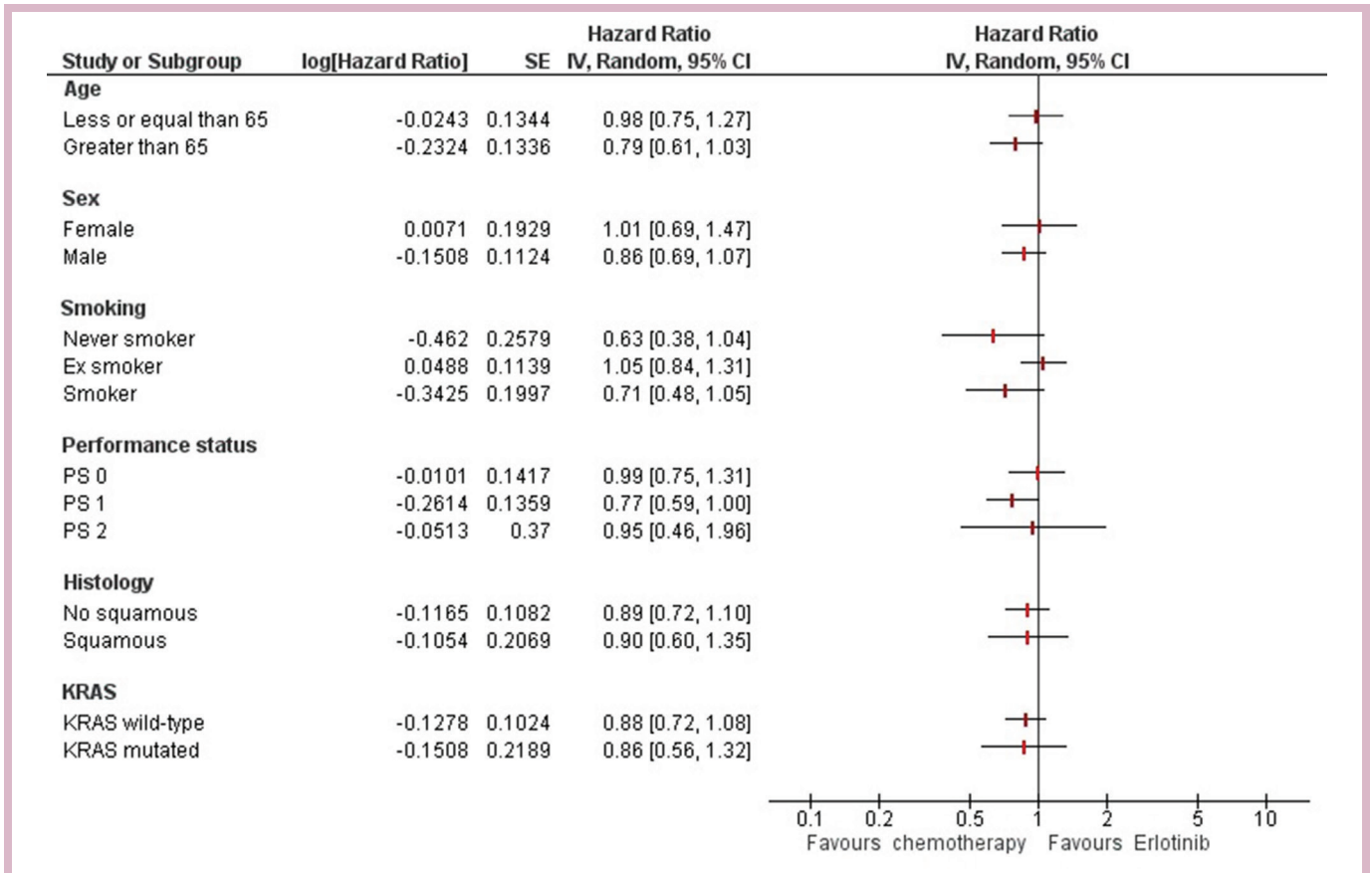


Figure 4 Factors associated to differential treatment effect for overall survival. IV, inverse of variance; PS, performance status.

arrival of immunotherapy and combination of docetaxel with nintedanib or ramucirumab? The answer is no. In fact, it is already clear that the innovative therapies are not applicable for all patients. Therefore, it is possible that the treatment of the lung cancer in the future will have a therapeutic algorithm much more complex than now. Patients will be tested for a much greater number of alterations including all the new discovered activating mutations. In principle, it is possible that for most activating mutations there will be their specific correspondent inhibitor. A fraction of patients who do not have an activating mutation will be candidate for this promising new class of drugs targeting the immune checkpoints and the remaining ones still for chemotherapy alone or in combination with new agents.

The future is very promising with many treatment options unimaginable when TAILOR, DELTA and PROSE had been drawn, but the old chemotherapy remains a part of therapeutic choices alone or in combination. We currently have much more therapeutic opportunities, and the appropriate question is what are the considerations that must be included in decision process to propose the best therapeutic option for the single patient. The therapeutic choice will not only be defined by promising survival outcomes of the novel therapeutic approaches, but it will be determined by patients' comorbidities,

biomolecular and radiological tumour characteristics and by overall patients' preference.

Author affiliations

- ¹Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy
- ²Osaka City University, Graduate School of Medicine, Osaka, Japan
- ³Ospedale San Raffaele Scientific Institute, Vimodrone, Italy
- ⁴Oncology Department, IRCCS-Mario Negri Institute for Pharmacological Research, Milano, Italy
- ⁵Center for Advanced Medicine and Clinical Research, Nagoya University Hospital, Nagoya, Japan
- ⁶Istituto di Candiolo, Fondazione del Piemonte per l'Oncologia-IRCCS, Candiolo, Italy
- ⁷National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan
- ⁸Azienda Ospedaliero-Universitaria S. Luigi Gonzaga, Orbassano, Italy
- ⁹O.U. Medical Oncology, A.O. Fatebenefratelli e Oftalmico, Milan, Italy
- ¹⁰Division of Oncology, Azienda Ospedaliera Treviglio, Treviglio, Italy

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