EUROPEAN JOURNAL OF CANCER 46 (2010) 735–743

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: A prognostic score from individual data of nine randomised trials ☆

Massimo Di Maio [a], *Nicola Lama* [b], *Alessandro Morabito* [a], *Egbert F. Smit* [c], *Vassilis Georgoulias* [d], *Koji Takeda* [e], *Elisabeth Quoix* [f], *Dora Hatzidaki* [d], *Floris M. Wachters* [g], *Vittorio Gebbia* [h], *Chun-Ming Tsai* [i], *Carlos Camps* [j], *Wolfgang Schuette* [k], *Paolo Chiodini* [b], *Maria Carmela Piccirillo* [a], *Francesco Perrone* [a], *Ciro Gallo* [b], *Cesare Gridelli* [l,*]

[a] *Clinical Trials Unit, National Cancer Institute, Napoli, Italy*
[b] *Department of Medicine and Public Health, Second University of Napoli, Italy*
[c] *Department of Pulmonary Diseases, Vrije Universiteit Medical Centre, Amsterdam, The Netherlands*
[d] *Department of Medical Oncology, University General Hospital, Heraklion, Crete, Greece*
[e] *Department of Clinical Oncology, Osaka City General Hospital, Osaka, Japan*
[f] *Service de Pneumologie, Nouvel Hopital Civil, Strasbourg, France*
[g] *Department of Pulmonology, University Medical Center, Groningen, The Netherlands*
[h] *La Maddalena Hospital, University of Palermo, Italy*
[i] *Section of Thoracic Oncology, Chest Department, Taipei Veterans General Hospital, Shih-Pai, Taipei, Taiwan*
[j] *Consorcio Hospital General Universitario, Valencia, Spain*
[k] *Martha-Maria Hospital Halle-Doelau, Halle, Germany*
[l] *Division of Medical Oncology, "S. Giuseppe Moscati" Hospital, 83100 Avellino, Italy*

ARTICLE INFO

Article history:
Received 11 September 2009
Received in revised form 1 December 2009
Accepted 3 December 2009
Available online 4 January 2010

Keywords:
Non-small-cell lung cancer
Second-line treatment
Prognostic factors
Prognostic score
Pooled analysis

ABSTRACT

Purpose: Knowledge of prognostic factors for advanced non-small-cell lung cancer (NSCLC) patients eligible for second-line treatment is scarce. The aim of this study was to assess the prognostic role of a number of routinely collected clinical variables and to provide a summary index to discriminate patients according to probability of survival.

Methods: Individual data from nine randomised trials of second-line treatment in advanced NSCLC were analysed. Primary end-point was overall survival (OS). Cox model, stratified by trial, was used for multivariate analyses, and a prognostic index was provided and validated according to an internal/external procedure.

Results: Out of 1239 patients, 1197 patients (97%) had complete information. Median OS was 7.4 months. At multivariate analysis, prognosis was significantly influenced by gender (worse in males), performance status (PS), tumour histology (worse in squamous and other histology *versus* adenocarcinoma), stage (worse in IV *versus* IIIB), type of previous treatment (worse for patients pretreated with platinum) and response to first-line (worse for patients

☆ This work was presented in part at the 45th Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 29–June 2, 2009 (Lung Cancer – Metastatic General Poster Session, abstract 8082).

* *Corresponding author:* Tel.: +39 0825 203574; fax: +39 0825 203556.
E-mail address: cgridelli@libero.it (C. Gridelli).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.12.013

not obtaining objective response). Prognostic score values ranges from 0 to 14. When three categories were derived, median overall survival values were equal to 11.6, 7.5 and 3.0 months for best (<5), intermediate (5-9) and worst (>9) category, respectively.
Conclusion: Prognosis of patients eligible for second-line treatment of advanced NSCLC is significantly conditioned by gender, PS, histology, stage, previous use of platinum and response to first-line. A prognostic score was derived that discriminates well subjects with a relatively more favourable prognosis and those with very short life expectancy.

1. Introduction

Patients who experience disease progression during or after first-line treatment for advanced non-small-cell lung cancer (NSCLC) have a limited life expectancy. The aims of second-line treatment are palliation of symptoms, benefit in quality of life and prolongation of survival. However, the impact of treatment on the natural history of the disease is modest. Until 10 years ago, there was actually no high-level evidence supporting the efficacy of second-line treatment, although chemotherapy was often offered to patients in good clinical conditions. In recent years, the efficacy of several drugs in the second-line setting has been demonstrated in phase III trials, and second-line treatment is now a standard of care.[1]

Due to the availability of new drugs approved for second- and third-line treatment of advanced NSCLC, the length of time spent by patients receiving active anti-cancer treatment has recently increased. However, many patients with advanced NSCLC who receive second-line treatment are near the end of life. In a retrospective review of patients treated for advanced NSCLC in a community oncology setting, nearly half of the patients had received chemotherapy in the last month of life, and one patient out of five received treatment in the last 2 weeks.[2] This can be partially explained by the increased demand for additional treatment by patients and their relatives, who are unable to recognise the futility of further therapy and the inevitability of death from progressive NSCLC. However, it may also be due to physicians' inability to correctly predict life expectancy, and this emphasises the importance of correctly identifying prognostic factors for patients who are potentially eligible to receive second-line treatment.

While the prognostic factors of patients receiving first-line chemotherapy have been extensively described, much less information is available about the prognostic factors in patients who are candidates to further treatment after first-line failure. Prognostic factors are not necessarily predictive of treatment efficacy, but their identification may help the treating physician in determining the likelihood of clinical benefit of further therapy and in identifying patients with a very limited life expectancy.[3] Furthermore, a better definition of prognostic factors in the second-line setting would be important when planning and interpreting the results of future clinical trials in advanced NSCLC.

The aim of our study was to evaluate the prognostic role of baseline patient characteristics (age, gender, performance status [PS]), tumour characteristics (histology, stage) and characteristics of first-line treatment (use of platinum, best response obtained) in patients with advanced NSCLC eligible for second-line treatment, and to produce a summary prognostic index. With this objective, we analysed individual patient data (IPD) of patients enrolled in nine randomised trials conducted in the setting of second-line treatment.

2. Patients and methods

Data used for this analysis had been previously collected for two IPD meta-analyses of randomised trials performed in the setting of second-line treatment of advanced NSCLC.[4,5] The first meta-analysis collected data of five trials[6–10] by comparing weekly *versus* every 3 week administration of docetaxel.[4] The second meta-analysis collected data of six trials[11–16] by comparing single-agent *versus* doublet chemotherapy.[5]

Out of 11 trials potentially available, 2 trials[8,10] were excluded from this analysis of prognostic factors because of missing information on one or more variables.

The variables considered in this analysis can be divided into patient characteristics (age, gender and PS), tumour characteristics (stage and histology) and characteristics of first-line treatment (use of platinum-based chemotherapy and best objective response).

2.1. *Statistical analysis*

Only patients with complete information on study variables were included in the analysis.

The primary end-point was overall survival (OS), defined as the time between the date of randomisation and the date of death, or the last date of follow-up for censored patients.

In order to describe the impact of baseline characteristics on OS, survival curves were drawn with the Kaplan–Meier product limit method. Statistical analysis was performed by using the Cox proportional hazards model, stratified by trial, including age (older than 70 *versus* younger), gender (male *versus* female), PS (1 *versus* 0; 2 *versus* 0), histology (squamous *versus* adenocarcinoma; other histology *versus* adenocarcinoma), tumour stage (IV *versus* III B), type of first-line (platinum-based *versus* other) and objective response to first-line (no *versus* yes) as covariates. The proportional hazard assumption was tested using graphical methods and was adequately met for all analyses. Results are reported as hazard ratio (HR) of death with 95% confidence intervals (CI). Two-tailed *p* values were determined with the use of a likelihood-ratio test, and values less than 0.05 were considered statistically significant.

The log-hazard rates obtained from the Cox model were used to derive weighting factors of a prognostic index, aimed to identify differential risks of death. Coefficients estimates were 'normalised' dividing by the smallest one and rounding the resulting ratios to the nearest integer value. The concordance C-index statistic proposed by Pencina *et al.*[17] was adopted as a measure of discriminating power allowing for stratification as proposed by the Fibrinogen Studies Collaboration.[18] Possible overfitting bias was assessed by using the internal–external cross-validation (IECV) approach[19] on the C-Index statistic.

Analyses were performed with S-PLUS software (S-PLUS 6.1 Professional, release 1; Insightful Corporation, Seattle, WA, USA).

3. Results

3.1. Patients characteristics

Details about treatment arms, period of accrual and number of patients of the 9 trials are reported in Table 1. Out of 1239 patients, 1197 (97%) had complete information about prognostic factors and were included in this analysis. Their baseline characteristics are depicted in Table 2. Median age was 61 years (range 26–84). The majority of the patients were males (77.7%) and had a good PS (0 or 1 in 87.1%) As expected, there was a significant association between gender and tumour histology: tumours were squamous in 37% of males compared to 14% of females, while adenocarcinomas were more common among women than men (64% and 43%, respectively). Women were younger than men: median age was 58 and 62 years, respectively. There were no gender-related differences in terms of baseline PS.

Most patients had previously received a first-line platinum-based treatment (84.3%). This was obviously driven by inclusion criteria of the trials: previous platinum-based treatment was actually mandatory in six trials,[7,10,11,14–16] not mandatory in four trials,[6,8,9,13] while one trial was dedicated to patients not previously treated with platinum.[12] Overall, 44% of patients had obtained objective response to first-line treatment: this proportion varied significantly in the different trials ranging from 32% to 63%. The higher proportion of responders was recorded in the Japanese trial (61%), and in the Dutch trial that selected patients progressing more than 3 months after completion of first-line platinum-based chemotherapy (63%).[15,16]

3.2. Outcome and prognostic factors

Overall, 956 deaths were recorded (80%), with median OS in the whole population equal to 7.4 months. Six-month survival was 57.9%, and 1-year survival was 29.3%.

Table 1 – Trials included in the analysis.

First author (reference)	Treatment arms	Accrual (years)	Number of patients	
			Randomised	Eligible for analysis of prognostic factors
Gridelli[6]	Arm 1: Docetaxel 75 mg/m^2 every 3 weeks Arm 2: Docetaxel 33.3 mg/m^2 weekly for 6 weeks, then 2 weeks of rest	2000–2002	220	220
Gervais[7]	Arm 1: Docetaxel 75 mg/m^2 every 3 weeks Arm 2: Docetaxel 40 mg/m^2 weekly for 6 weeks, then 2 weeks of rest	2000–2001	125	125
Lai[9]	Arm 1: Docetaxel 66 mg/m^2 every 3 weeks Arm 2: Docetaxel 33 mg/m^2 weekly for 2 weeks, then 1 week of rest	1999–2002	47	47
Georgoulias[11]	Arm 1: Irinotecan 300 mg/m^2 day 1 every 3 weeks Arm 2: Gemcitabine 1000 mg/m^2 day 1 and 8 + irinotecan 300 mg/m^2 day 8 every 3 weeks	1999–2001	147	134
Georgoulias[12]	Arm 1: Cisplatin 80 mg/m^2 day 1 every 3 weeks Arm 2: Cisplatin 80 mg/m^2 day 8 + irinotecan 110 mg/m^2 day 1, 100 mg/m^2 day 8 every 3 weeks	1999–2002	139	118
Wachters[13]	Arm 1: Docetaxel 75 mg/m^2 day 1 every 3 weeks Arm 2: Docetaxel 60 mg/m^2 day 1 + irinotecan 200 mg/m^2 day 1 every 3 weeks	2000–2003	108	103
Gebbia[14]	Arm 1: Docetaxel 33.3 mg/m^2 day 1, 8, 15 every 4 weeks Arm 2: Docetaxel 30 mg/m^2 day 1, 8, 15 every 4 weeks + gemcitabine 800 mg/m^2 (or vinorelbine 20 mg/m^2) day 1, 8 every 4 weeks Arm 3: Docetaxel 30 mg/m^2 day 1, 8, 15 every 4 weeks + capecitabine 1300 mg/m^2 days 5–18 every 4 weeks	2005–2006	84	84
Takeda[15]	Arm 1: Docetaxel 60 mg/m^2 day 1 every 3 weeks Arm 2: Docetaxel 60 mg/m^2 day 8 + gemcitabine 800 mg/m^2 day 1, 8 every 3 weeks	2002–2003	130	128
Smit[16]	Arm 1: Pemetrexed 500 mg/m^2 day 1 every 3 weeks Arm 2: Pemetrexed 500 mg/m^2 day 1 every 3 weeks + carboplatin AUC5 day 1 every 3 weeks	2005–2007	240	238

Table 2 – Characteristics of the patients eligible for the analysis (*n* = 1197).

Age, n (%)		
Median, years (range)	61	(26–84)
Younger than 70 years	988	(82.5%)
Older than 70 years	209	(17.5%)
Gender, n (%)		
Male	930	(77.7%)
Female	267	(22.3%)
Performance status, n (%)		
0	334	(27.9%)
1	709	(59.2%)
2	154	(12.9%)
Tumour stage, n (%)		
IIIB	213	(17.8%)
IV	984	(82.2%)
Histologic type, n (%)		
Squamous	380	(31.7%)
Adenocarcinoma	568	(47.5%)
Other	249	(20.8%)
Type of first-line treatment, n (%)		
Platin-based	1009	(84.3%)
Other	188	(15.7%)
Objective response to 1st line, n (%)		
Yes	527	(44.0%)
No	670	(56.0%)

Kaplan–Meier curves of OS according to baseline patient characteristics (age, gender and PS) are shown in Fig. 1. Kaplan–Meier curves of OS according to tumour characteristics (stage and histology) and characteristics of previous treatment (type of chemotherapy and objective response) are reported in Fig. 2.

In the Cox model stratified by trial, all the covariates were independently prognostic, with the exception of age. Prognosis was worse in males than in females, with a HR of death 1.23 (95% CI 1.04–1.45). As compared with PS 0 patients, HR was 1.36 (95% CI 1.16–1.59) for PS 1 patients and 3.01 (95% CI 2.41–3.76) for PS 2 patients. Compared to patients with adenocarcinoma, risk of death was higher for subjects with both squamous tumours (HR 1.18, 95% CI 1.01–1.38) and other histology (HR 1.49, 95% CI 1.26–1.77). Stage IV was associated with a worse prognosis compared to stage IIIB (HR 1.28, 95% CI 1.07–1.53). Both type of previous treatment and response obtained with first-line were predictive of prognosis: HR of death was 1.49 (95%CI 1.14–1.93) for patients who had received platinum-based first-line chemotherapy, and 1.25 (95% CI 1.10–1.44) for those who had not achieved an objective response. Results of multivariate analysis are summarised in Table 3.

3.3. *Prognostic index*

All the covariates showing independent prognostic role in the Cox model were included in the prognostic index. Table 4

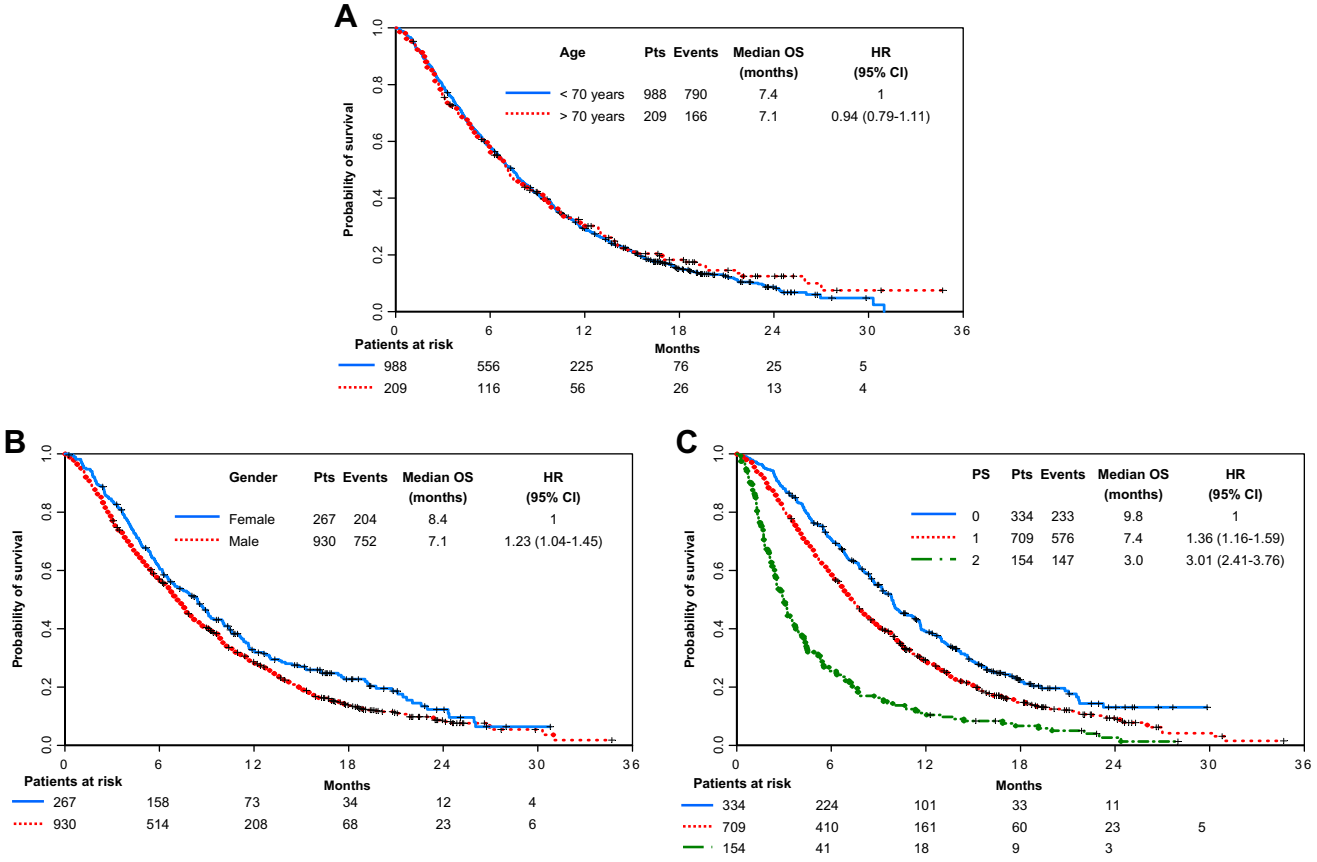

Fig. 1 – Kaplan–Meier curves of overall survival (OS) according to patient characteristics (panel A: age; panel B: gender; and panel C: performance status). HR: Hazard ratio from multivariate analysis.

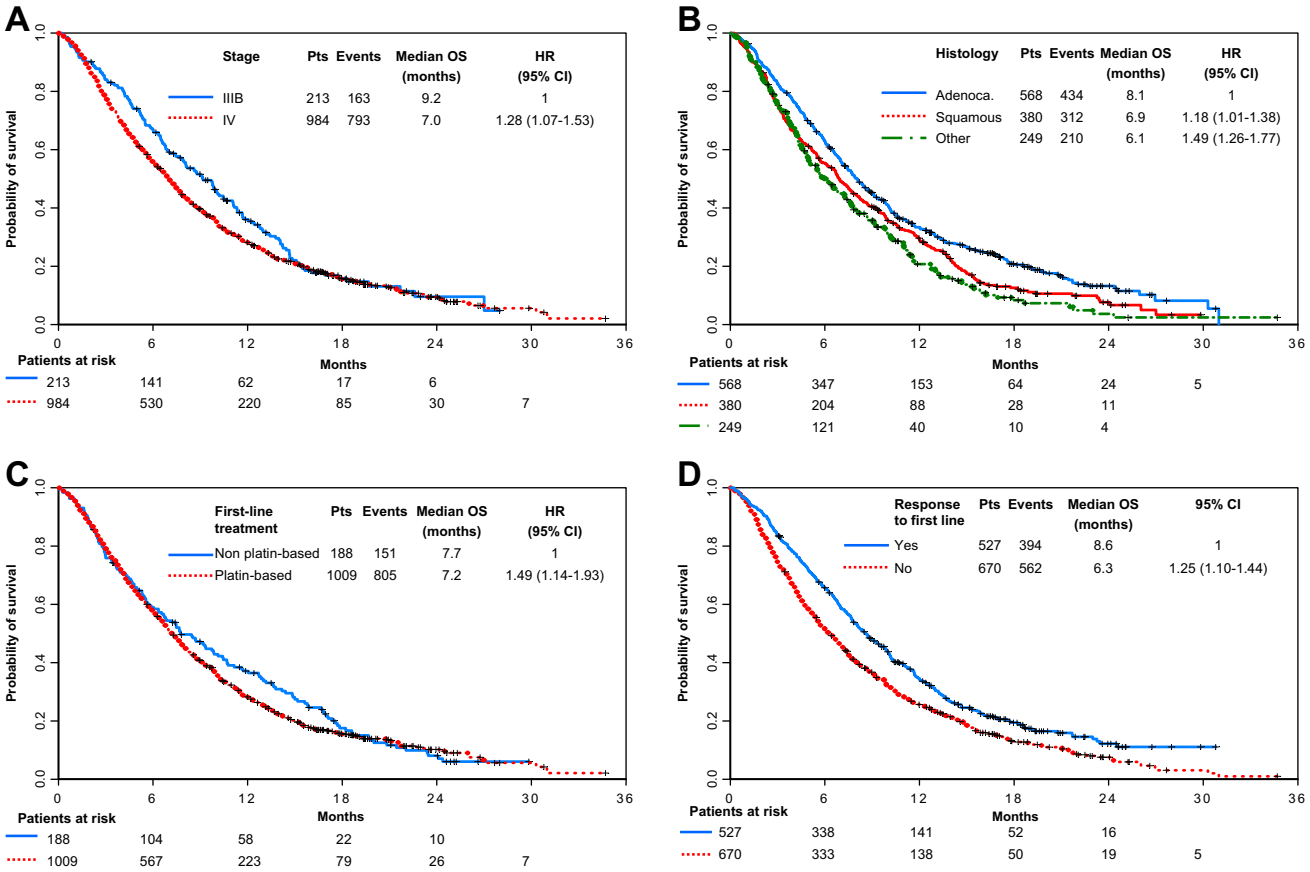

Fig. 2 – Kaplan–Meier curves of overall survival according to tumour characteristics (panel A: tumour stage and panel B: histology) and according to characteristics of first-line treatment (panel C: use of platinum and panel D: objective response). HR: Hazard ratio from multivariate analysis.

Table 3 – Multivariate analysis: Cox model (*n* = 1197).

Covariate	Hazard ratio of death	95% confidence limits	*P*-value[a]
Age			
≫70 *versus* <70 years	0.94	0.79–1.11	0.400
Gender			
Male *versus* female	1.23	1.04–1.45	0.013
Performance status			<0.001
1 *versus* 0	1.36	1.16–1.59	
2 *versus* 0	3.01	2.41–3.76	
Tumor stage			
IV *versus* IIIb	1.28	1.07–1.53	0.006
Histologic type			<0.001
Squamous *versus* adeno	1.18	1.01–1.38	
Other *versus* adeno	1.49	1.26–1.77	
Type of first-line			
Platin-based *versus* other	1.49	1.14–1.93	0.003
Objective response to first-line			
No *versus* yes	1.25	1.10–1.44	0.001

a *P*-values were determined with the use of a likelihood-ratio test. Cox model was stratified by trial.

shows the scores based on the HRs in the Cox model. The C-index was estimated to be 0.626 (CI: 0.605, 0.647) and 0.643 (CI: 0.619, 0.667) for the Cox model and the prognostic index, respectively.

Table 4 – Definition of the scoring system.[a]

	Points			
	0	1	2	7
Gender	Female	Male		
Performance Status	0		1	2
Tumour stage	IIIb	IV		
Histologic type	Adenocarcinoma	Squamous	Other	
Type of first-line	Without platinum		Platin-based	
Objective response to first –line	Yes	No		

a The coefficients estimates (i.e. the logarithm of hazard ratios) were 'normalised' by dividing by the smallest one and rounding the resulting ratios to the nearest integer value.

The possible overfitting biases estimated by the IECV approach[19] were approximately equal to 1.8% and 1.9% for the Cox model and the score, respectively, and were both not statistically significant suggesting that generalisability of the score is well supported by the data.

The outcome of patients according to the prognostic score is shown by dividing patients into three categories. Cutoffs were chosen at approximately equal distance along the range of values: <5 (best), 5–9 (intermediate) and >9 (worst). Such three-category score exhibited a C-index estimate equal to 0.706 (CI: 0.67, 0.741). The associated overall raw survival estimates are depicted in Fig. 3. Median survival was 11.6, 7.5 and 3.0 months for the best, intermediate and worst category, respectively.

Kaplan–Meier curves of overall survival according to three risk categories in the nine analysed trials are reported in Fig. 4.

4. Discussion

This prognostic analysis was conducted in 1197 patients receiving second-line chemotherapy for advanced NSCLC and showed that PS, gender, histology, stage, use of a platinum-based first-line and best response to previous chemotherapy are independent prognostic factors. All these variables are easily collected being part of the minimum baseline evaluation for patients candidate to second-line treatment in clinical practice.

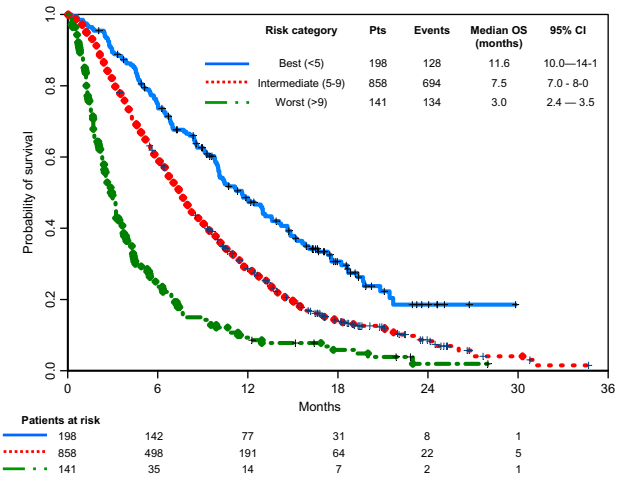

Fig. 3 – Kaplan–Meier curves of overall survival according to three risk categories based on the prognostic score.

Although the trials considered in our analysis are necessarily only a fraction of all the trials conducted in this setting, to our knowledge this is the largest database of patients receiving second-line chemotherapy for advanced NSCLC. Importantly, all patients were enrolled in randomised trials, and information about baseline characteristics and outcome was collected prospectively. We recognise that treatments received were heterogeneous among the different trials, but the two meta-analyses showed no significant difference in efficacy between treatment arms (weekly *versus* every-3-week docetaxel[4] and single-agent *versus* combination chemotherapy[5]), and the Cox model was stratified by trial.

There are several interesting points that deserve some comment.

Interestingly, most of the characteristics with prognostic role are similar to the ones influencing the outcome in first-line treatment. First of all, similarly to what is commonly described in first-line treatment, PS shows a very strong association with outcome of these patients. Life expectancy of subjects who fail first-line therapy appears to be largely dependent on their clinical condition at the beginning of second-line. In our series, despite the potential positive selection bias due to eligibility for a clinical trial, median survival of PS 2 patients was lower than 3 months compared to that of PS 1 patients and PS 0 patients which was more than 7 months and nearly 10 months, respectively. In our model, PS 2 is by far the worst prognostic characteristic, and it is relevant that only patients with PS 2 (7 points) can totalise a prognostic score higher than 9, which is the worst category. Patients with PS 2 are unfit, but are generally considered candidates for further treatment in clinical practice. Little evidence has been produced on the efficacy of second-line chemotherapy compared to best supportive care in poor PS patients, and PS 2 patients probably derive a modest absolute benefit, if any, from treatment. The BR.21 trial compared erlotinib *versus* placebo as second- or third-line in patients considered to be no longer eligible for chemotherapy showing a significant improvement in overall survival with erlotinib.[20] According to subgroup analysis, the benefit associated with erlotinib appears similar in unfit patients (PS 2 or 3) compared to that in patients with better PS, and there was no evidence of significant interaction between treatment efficacy and PS.[20] Although this may suggest avoiding chemotherapy and preferring biologic agents in these patients, in a randomised trial by comparing docetaxel

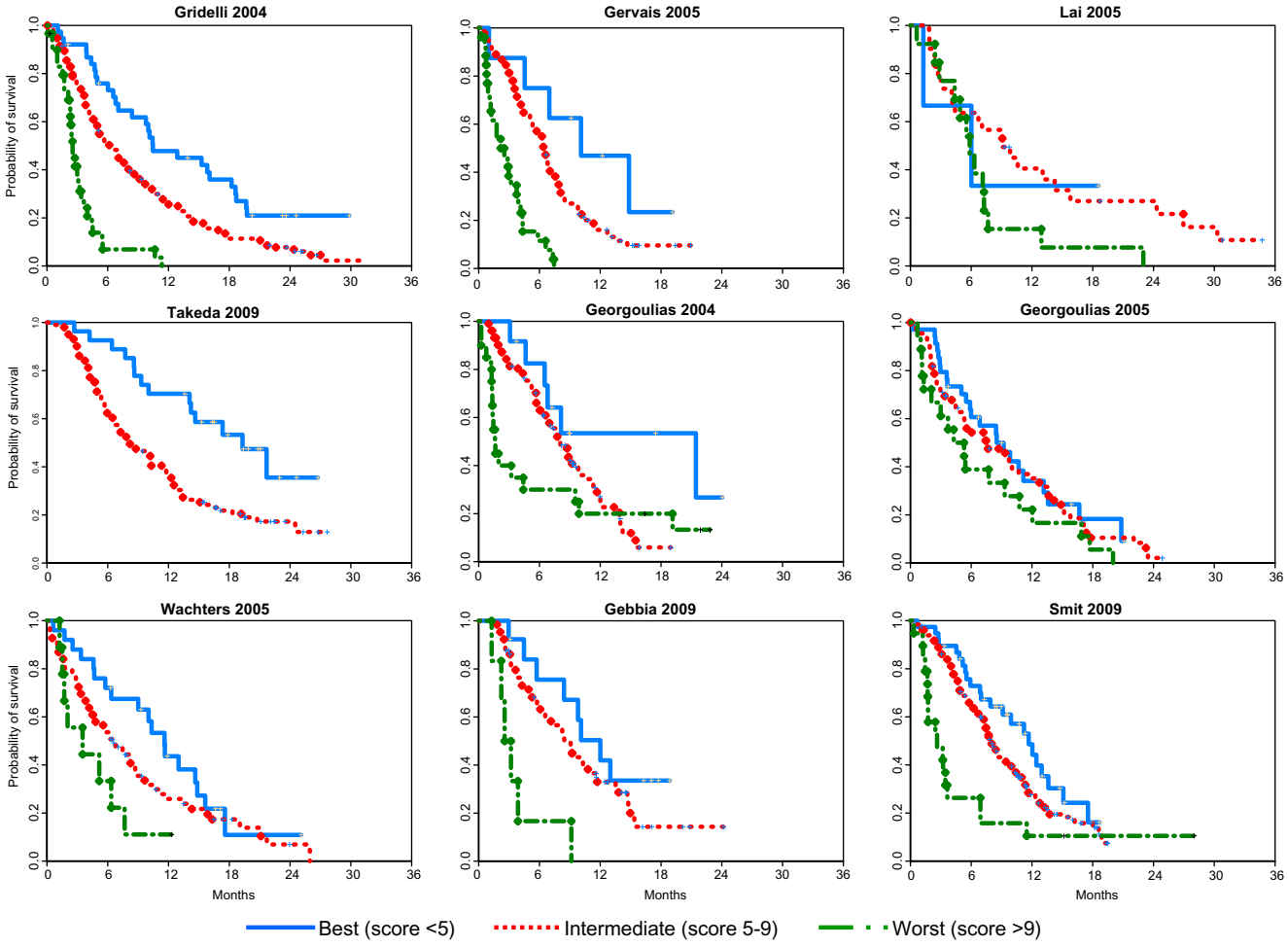

Fig. 4 – Kaplan–Meier curves of overall survival according to three risk categories based on the prognostic score in each of the nine trials considered in the analysis.

with gefitinib, as second-line treatment, there was actually no evidence of better outcome with the biologic agent compared to chemotherapy in PS subgroups.[21] The decision about second-line treatment for patients with poor PS should be based on careful evaluation of the expected toxicity profile considering that the absolute benefit in terms of survival is probably modest.

Treatment of advanced NSCLC has been traditionally independent from histologic subtypes. Recently, this concept has been destabilised by some evidence suggesting differential efficacy of pemetrexed according to tumour histology, both in first- and second-line setting.[22,23] Despite adenocarcinoma being associated with a higher chance of obtaining objective response with Epidermal Growth Factor Receptor (EGFR) inhibitors, tumour histology did not show a significant predictive role for efficacy of erlotinib compared to that of placebo in the BR.21 trial,[20] and there was no significant interaction between treatment and histology in the INTEREST trial comparing gefitinib to docetaxel.[21] Of course, due to trials design, our data cannot explore the predictive role of histology, but the present analysis shows that histotype, besides the suggested predictive role, has some prognostic impact on survival. Similar data have been recently presented in chemotherapy-naïve patients, where adenocarcinoma was associated with a 3-month advantage in overall survival compared to squamous tumours.[24] In our series, compared to adenocarcinoma, prognosis appears to be slightly worse for squamous tumours, and worse for other histotypes (large cell, mixed and undifferentiated) that are currently pooled together with adenocarcinoma, under the definition of non-squamous tumours.

In our analysis, prognosis was significantly better for female patients. Median overall survival was 8.4 months in women, and 7.1 months in men. This gender difference is consistent with a number of previous publications, at various stages of disease.[25,26] In this series, adenocarcinoma was indeed more common in women than in men. However, the significant prognostic impact of gender at multivariate analysis shows that the better outcome of female patients is not explained – at least not entirely – with the difference in terms of histotype.

We found that two characteristics of previous treatment were independently associated with prognosis: use of platinum-based first-line chemotherapy and best response obtained with first-line treatment. In particular, patients who had previously received platinum-based chemotherapy show a worse prognosis compared to patients who have not received platinum compounds. We can argue that the margin of further benefit associated with treatment appears to be

smaller for those patients who have already received the best first-line option. However, this information can be considered relatively less important, because platinum-based combination is currently accepted as standard first-line treatment, and the number of fit patients eligible for second-line who have not previously received platinum is really negligible. More interestingly, patients obtaining objective response during first-line treatment also show a significantly better prognosis when they experience progression and become eligible for second-line treatment. Median overall survival was 8.6 months for first-line responders and 6.3 months for non-responders. We did not collect information about time elapsed since first-line treatment, but this variable is strictly linked to best response, because patients progressing during first-line are obviously those with a shorter interval between first- and second-line, and responders are those with a longer treatment-free interval.

To our knowledge, there are only few previously published studies about prognostic factors in patients receiving second-line chemotherapy for advanced NSCLC. Bonomi and colleagues described the prognostic factors in patients enrolled in a phase III trial that compared docetaxel with paclitaxel poliglumex as second-line treatment.[27] In that analysis, the following factors were significantly associated with shorter survival at multivariate analysis: poor PS, male gender, low haemoglobin, high LDH level, poor Lung Cancer Symptom score, presence of extra-thoracic metastases and short interval between first-line and second-line. Weiss and colleagues retrospectively reviewed data of the trial that compared pemetrexed to docetaxel as second-line chemotherapy.[28] On multivariate analysis, gender, stage at diagnosis, PS and best response to first-line therapy significantly influenced overall survival. In the attempt of developing a prognostic index for patients treated with erlotinib in the setting of BR.21 trial, 10 factors were significantly associated with overall survival: smoking history, PS, weight loss, anaemia, lactic dehydrogenase, response to prior chemotherapy, time from diagnosis, number of prior regimens, *EGFR* copy and ethnicity.[29] Unfortunately, our database cannot test several factors identified in these studies, in particular smoking history and laboratory values, because information about these parameters was not collected.

In recent years, many efforts have been made to identify predictive factors of efficacy of different drugs. Our analysis was not intended to address this topic, because the trials considered in the analysis did not directly compare the drugs currently available for clinical practice (docetaxel and pemetrexed) and did not consider at all the role of targeted agents. However, before clinical or molecular characteristics are included in guidelines for selecting patients for specific treatments, it is important that the prognostic effects of these factors are clearly distinguished from their potential ability to predict a differential clinical benefit from the specific treatment.[30]

A better definition of prognostic factors and the availability of a prognostic score in the second-line setting can be useful for both clinical practice and clinical research. In clinical research, it will help interpreting the outcomes of future trials. In particular, future randomised trials may take into account, when designing the trial and analysing the data, the distribution of specific prognostic factors between two treatment arms or the distribution of risk categories according to prognostic score. Our data clearly imply that two equally effective drugs can produce very different results if patient population is unbalanced, for example, in terms of PS or responders to first-line. Critical use of a prognostic score would also assist in the optimal selection of patients for second-line trials, avoiding the enrolment of patients with very short life expectancy, who have negligible chance of benefit from treatments. Of course, this is also true for decision-making in clinical practice, where a better understanding of factors conditioning life expectancy of patients could greatly help a careful consideration of risks and benefits associated with treatment. Our prognostic score allows to separate the patients quite effectively on survival identifying a subgroup with a relatively more favourable prognosis and another with a very short life expectancy. Although the IECV procedure we adopted[19] suggested that generalisability should be high, predictive ability of the prognostic index should be thoroughly validated in independent data sets.

Conflict of interest statement

None declared.

REFERENCES

1. Gridelli C, Ardizzoni A, Ciardiello F, et al. Second-line treatment of advanced non-small cell lung cancer. *J Thorac Oncol* 2008;**3**:430–40.
2. Murillo JR, Koeller J. Chemotherapy given near the end of life by community oncologists for advanced non-small-cell lung cancer. *Oncologist* 2006;**11**:1095–9.
3. Stinchcombe TE, Socinski MA. Considerations for second-line therapy of non-small cell lung cancer. *Oncologist* 2008;**13**(Suppl 1):28–36.
4. Di Maio M, Perrone F, Chiodini P, et al. Individual patient data meta-analysis of docetaxel administered once every 3 weeks compared with once every week second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2007;**25**:1377–82.
5. Di Maio M, Chiodini P, Georgoulias V, et al. Meta-analysis of single-agent chemotherapy compared with combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer. *J Clin Oncol* 2009;**27**:1836–43.
6. Gridelli C, Gallo C, Di Maio M, et al. A randomised clinical trial of two docetaxel regimens (weekly vs 3 week) in the second-line treatment of non-small-cell lung cancer. The DISTAL 01 study. *Br J Cancer* 2004;**91**:1996–2004.
7. Gervais R, Ducolone A, Breton JL, et al. Phase II randomised trial comparing docetaxel given every 3 weeks with weekly schedule as second-line therapy in patients with advanced non-small-cell lung cancer (NSCLC). *Ann Oncol* 2005;**16**:90–6.
8. Schuette W, Nagel S, Blankenburg T, et al. Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. *J Clin Oncol* 2005;**23**:8389–95.
9. Lai CL, Tsai CM, Chiu CH, et al. Phase II randomized trial of tri-weekly versus day 1 and 8 weekly docetaxel as a second-line treatment of advanced non-small cell lung cancer. *Jpn J Clin Oncol* 2005;**35**:700–6.

10. Camps C, Massuti B, Jimenez A, et al. Randomized phase III study of 3-weekly versus weekly docetaxel in pretreated advanced non-small-cell lung cancer: a Spanish Lung Cancer Group trial. *Ann Oncol* 2006;**17**:467–72.
11. Georgoulias V, Kouroussis C, Agelidou A, et al. Irinotecan plus gemcitabine vs irinotecan for the second-line treatment of patients with advanced non-small-cell lung cancer pretreated with docetaxel and cisplatin: a multicentre, randomised, phase II study. *Br J Cancer* 2004;**91**:482–8.
12. Georgoulias V, Agelidou A, Syrigos K, et al. Second-line treatment with irinotecan plus cisplatin vs cisplatin of patients with advanced non-small-cell lung cancer pretreated with taxanes and gemcitabine: a multicenter randomised phase II study. *Br J Cancer* 2005;**93**:763–9.
13. Wachters FM, Groen HJ, Biesma B, et al. A randomised phase II trial of docetaxel vs docetaxel and irinotecan in patients with stage IIIb-IV non-small-cell lung cancer who failed first-line treatment. *Br J Cancer* 2005;**92**:15–20.
14. Gebbia V, Gridelli C, Verusio C, et al. Weekly docetaxel vs. docetaxel-based combination chemotherapy as second-line treatment of advanced non-small-cell lung cancer patients. The DISTAL-2 randomized trial. *Lung cancer* 2009;**63**:251–8.
15. Takeda K, Negoro S, Tamura T, et al. Phase III trial of docetaxel plus gemcitabine versus docetaxel in second-line treatment for non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG0104). *Ann Oncol* 2009;**20**:835–41.
16. Smit EF, Burgers SA, Biesma B, et al. Randomized phase II and pharmacogenetic study of pemetrexed compared with pemetrexed plus carboplatin in pretreated patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2009;**27**:2038–45.
17. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med* 2004;**23**:2109–23.
18. Fibrinogen Studies Collaboration. Measures to assess the prognostic ability of the stratified Cox proportional hazards model. *Stat Med* 2009;**28**:389–411.
19. Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 2004;**23**:907–26.
20. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small cell lung cancer. *New Engl J Med* 2005;**353**:123–32.
21. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated (INTEREST): a randomized phase III trial. *Lancet* 2008;**372**:1809–18.
22. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist* 2009;**14**:253–63.
23. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;**374**:1432–40.
24. Pirker R, Rodrigues-Pereira J, Szczesna A, et al. Prognostic factors in advanced NSCLC: experience from the FLEX trial. *J Clin Oncol* 2009;**27**:15s [suppl; abstr 8083].
25. Radzikowska E, Głaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. *Ann Oncol* 2002;**13**:1087–93.
26. Fu JB, Kau TY, Severson RK, Kalemkerian GP. Lung cancer in women: analysis of the national Surveillance, Epidemiology, and End Results database. *Chest* 2005;**127**:768–77.
27. Bonomi P, Langer C, O'Brien M, et al. Analysis of prognostic factors in patients with advanced relapsed/refractory NSCLC: Cox regression analysis of a randomized phase III trial comparing docetaxel and paclitaxel poliglumex (PPX). *J Clin Oncol* 2006;**24**(18 suppl):374s.
28. Weiss GJ, Rosell R, Fossella F, et al. The impact of induction chemotherapy on the outcome of second-line therapy with pemetrexed or docetaxel in patients with advanced non-small-cell lung cancer. *Ann Oncol* 2007;**18**:453–60.
29. Florescu M, Hasan B, Seymour L, Ding K, Shepherd FANational Cancer Institute of Canada Clinical Trials Group. A clinical prognostic index for patients treated with erlotinib in National Cancer Institute of Canada Clinical Trials Group study BR.21. *J Thorac Oncol* 2008;**3**:590–8.
30. Clark GM. Prognostic factors versus predictive factors: examples from a clinical trial of erlotinib. *Mol Oncol* 2008;**1**:406–12.