



Effect on quality of life of cisplatin added to single-agent chemotherapy as first-line treatment for elderly patients with advanced non-small cell lung cancer: Joint analysis of MILES-3 and MILES-4 randomised phase 3 trials[☆]

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ABSTRACT

Objectives: To evaluate the effect on quality of life (QOL) of the addition of cisplatin to single-agent chemotherapy in the treatment of elderly patients with advanced non-small cell lung cancer (NSCLC) enrolled in two parallel phase 3 trials, MILES-3 and MILES-4.

Patients and methods: Advanced NSCLC pts, > 70 years old, performance status (PS) 0–1, were eligible. Patients were randomly assigned to chemotherapy without or with cisplatin. EORTC QLQ C30 and LC13 questionnaires were planned at baseline, end of cycle 1 and end of cycle 2 in both trials and were used for joint QOL analysis. Trial-specific data including questionnaires at non-shared time-points were used for additional analyses. Intention-to-treat strategy was applied. Analyses were adjusted for baseline QOL, stage, performance status, gender, age, size of centre, trial, histotype and non-platinum companion drug.

Results: Overall, 458/531 pts (86%) answered baseline questionnaire and missing rates over treatment were slightly higher among patients receiving cisplatin. Mean change in sore mouth after cycle 2 was worse with cisplatin ($P = 0.02$). The size of differences between arms was in the small-medium range for peripheral neuropathy and alopecia (0.25 and 0.31 after one and 0.28 and 0.36 after two cycles, respectively) and for nausea/vomiting, sore mouth and dysphagia after two cycles (0.26, 0.38 and 0.25, respectively) always in the direction of worsening with cisplatin. Using a 10% change from baseline as clinically relevant threshold to categorize response, there was no significant difference between the arms. Time to deterioration of sore mouth and alopecia, with progression/death as competitive risk, was shorter with cisplatin (HR 1.72 95%CI 1.02–2.89, $P = 0.04$ and HR 1.84 95%CI 1.09–3.10, $P = 0.02$, respectively).

Conclusion: The addition of cisplatin to single agent chemotherapy worsens sore mouth and alopecia and does not improve any QOL items in elderly patients with advanced NSCLC.

1. Introduction

Chemotherapy remains a cornerstone of advanced lung cancer treatment even after some target based agents have been developed and, more recently, immune checkpoint inhibitors are proving effective. A low rate of patients (about 20%), indeed, is eligible for target based agents, and immune checkpoint inhibitors do actually represent only one possible line of treatment (first or second depending on the drug and the PDL1 expression) and do not yet promise to let chemotherapy disappear from the clinical scenario of lung cancer.

Combination of a platinum compound (cisplatin or carboplatin) with a non platinum agent is a standard approach for adult patients. The same is not true among patients older than 70 years, that represent more than one-third of the lung cancer patient population [1–4].

In fact, in the elderly setting, there is only one prospective trial supporting that carboplatin combined with paclitaxel prolongs survival at the cost of significant toxicity, but with some advantage in QOL [5]. As for cisplatin, the joint analysis of MILES-3 and MILES-4 trials has showed that its addition to single agent gemcitabine or pemetrexed does not significantly prolong overall survival (OS), and only produces a small, not clinically relevant, improvement of progression-free survival (PFS) and response rate [6,7].

Here we report QOL analysis in the MILES-3 and MILES-4 trials, that might eventually affect clinical decision making regarding the use of cisplatin in clinical practice.

2. Patients and methods

MILES-3 and MILES-4 were promoted by the National Cancer Institute (NCI), Napoli, Italy. Full description of the trials, OS, PFS, response rate and toxicity analysis are reported elsewhere [6]. Study conduct was approved by the research ethics boards of all participating institutions, and all patients provided written informed consent to participate. Assessment of QOL was a pre-planned secondary outcome for both trials. The trials were available in public registries with the following codes: MILES-3: ClinicalTrials.gov NCT01405586, EudraCT number 2009-013540-36; MILES-4: ClinicalTrials.gov NCT01656551, EudraCT number 2012-000164-25.

2.1. Study population

Patients aged 70 years or more, with previously untreated, advanced NSCLC with any (MILES-3) or non-squamous (MILES-4) histology, and Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 were eligible.

2.2. Study procedures

Consenting patients completed baseline assessments including QOL evaluation, and were then randomly assigned 1:1 chemotherapy without cisplatin (gemcitabine 1200 mg/m² on days 1 and 8 or pemetrexed 500 mg/m² on day 1, every 3 weeks for 6 cycles) or with cisplatin (60 mg/m² on day 1 plus gemcitabine 1000 mg/m² on days 1 and 8 or plus pemetrexed 500 mg/m² on day 1, every 3 weeks for 6 cycles).

2.3. QOL assessment

The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the lung cancer specific module (EORTC QLQ-LC13) were used to evaluate QOL [8,9]. QOL measurement was planned at baseline (before randomization) and on day 21 of cycle 1 and of cycle 2 in both MILES-3 and MILES-4. Therefore such questionnaires represent the data base for QOL analysis in the joint database. Two further QOL measurements were planned in MILES-3, on day 8 of cycles 1 and 2. Four further QOL measurements were planned in MILES-4, on day 21 of cycles 3, 4, 5 and 6.

The EORTC QLQ-C30 is a 30-item questionnaire composed of 5 multi-item functional subscales (physical, role, emotional, social and cognitive functioning), 3 multi-item symptom scales (fatigue, pain, and emesis), a global health status subscale, and 6 single items to assess financial impact and symptoms (dyspnea, sleep disturbance, appetite, diarrhea, and constipation) during the previous week [8]. The EORTC QLQ-LC13 consists of 13 single items that evaluate specific symptoms of lung cancer [9]. Both questionnaires are designed to be completed by the patient. Scores for multi-item scales are calculated by deriving the mean raw scores of single items and transforming them linearly into scales ranging from 0 to 100. For single items, only linear transformation is performed. For the 5 functional subscales, (physical, role,

emotional, cognitive and social functioning) and global health status, higher values represent better function (i.e. better). For symptom scales, higher values represent greater severity of symptoms (i.e. worse).

2.4. QOL analysis

QOL missing data patterns were described according to the National Cancer Institute of Canada Clinical Trials Group QOL framework under three different scenarios: (a) rate of patients completing baseline and subsequent assessments over the total number of patients enrolled into the trial (defined as the intention-to-treat [ITT] population); (b) rate of patients completing QOL assessments out of those completing the baseline one (defined as the QOL efficacy population); and (c) rate of patients completing QOL assessments out of those expected, therefore excluding those progressed or dead at a date before the date of planned QOL assessment; for this purpose, the expected date was calculated summing to day 1 of cycle 1 the planned interval to all subsequent QOL measurements [10].

Three QOL analysis frames were used.

Mean changes within the two compared groups from baseline to subsequent time points were reported to describe behavior of QOL items. Only patients with available values at baseline and at least one subsequent time point were included in the analysis. A linear regression model adjusted by baseline value, age, gender, PS, stage, size of participating centre, histotype, type of single agent and study was applied to test statistical significance of differences at each time point. No adjustment was applied for multiple comparisons. Clinical relevance of differences after one and two cycles was assessed by calculating the effect size (mean difference between treatment arms/SD in the arm without cisplatin), where values of 0.2, 0.5 and 0.8 correspond to small, medium and large effects, respectively.

Best QOL response from baseline for each domain or symptom was calculated defining a change score of at least 10 points from baseline as clinically relevant [11]. Patients were considered improved if they reported a score ≥ 10 -points better than baseline at any time, and were considered worsened if they reported a score ≥ 10 -points worse than baseline without having improved at any time; those with scores changing less than 10 points from baseline were considered stable. Only patients that had completed the baseline and at least one questionnaire after the baseline one were included. Chi-square test was applied to test statistical significance.

Time-to-deterioration was defined as the time from randomization to QOL deterioration using progression or death as competing events, that prevented the occurrence of QOL assessment. Deterioration of QOL was defined as a worsening of ≥ 10 -points from baseline at any time during QOL assessment, irrespective of any improvement. In the competing risk approach, the different types of events are not considered independent, and subjects who experienced progression or death before documented QOL deterioration were not censored at the time of progression/death. Accordingly, cumulative incidence functions, defined as the probability of deteriorating by the time t , were estimated for each domain and for each arm [12]. Treatments were compared with the Fine & Gray regression model adjusted by baseline item value, age, gender, performance status, stage and stratified by study, histotype and associated drug [13].

All the three QOL analysis frames were applied to the joint database. QOL response analysis was also repeated in the MILES-3 database, because the availability of day 8 questionnaires might in principle increase sensitivity to QOL changes deriving from short term toxicity of cisplatin. Time-to deterioration analysis was also performed in the MILES-4 database, because availability of questionnaires at the end of all subsequent cycles of chemotherapy might increase sensitivity to QOL changes over time.

Table 1
Baseline characteristics and quality of life values by treatment arm in the joint database.

	Without cisplatin (N = 237)		With cisplatin (N = 221)		P
	n	%	n	%	
Study					0.99
MILES3	132	(55.7%)	123	(55.7%)	
MILES4	105	(44.3%)	98	(44.3%)	
Age					0.71
< 75 years	118	(49.8%)	118	(53.4%)	
75-80 years	95	(40.1%)	84	(38.0%)	
> 80 years	24	(10.1%)	19	(8.6%)	
Gender					0.46
Male	189	(79.7%)	170	(76.9%)	
Female	48	(20.3%)	51	(23.1%)	
Performance status					0.65
0	99	(41.8%)	97	(43.9%)	
1	138	(58.2%)	124	(56.1%)	
Histology					0.78
Squamous	68	(28.7%)	66	(29.9%)	
Non-squamous	169	(71.3%)	155	(70.1%)	
Stage					0.56
IIIB	16	(6.8%)	12	(5.4%)	
IV	221	(93.2%)	209	(94.6%)	
Smoking status ^a					0.85
Never smoker	31	(13.1%)	30	(13.7%)	
Former or current smoker	206	(86.9%)	189	(86.3%)	
Mean baseline value (SD)					
Global health status	43.8	(22.3)	44.5	(20.7)	0.70
Physical functioning	74.0	(20.5)	74.5	(20.2)	0.77
Role functioning	74.3	(26.4)	73.9	(26.2)	0.80
Emotional functioning	72.9	(21.6)	71.2	(22.4)	0.42
Cognitive functioning	88.0	(17.3)	88.6	(16.7)	0.71
Social functioning	85.3	(21.7)	84.8	(21.1)	0.71
Fatigue	32.7	(24.3)	33.1	(24.7)	0.91
Nausea/vomiting	4.4	(11.5)	5.4	(13.3)	0.62
Pain	24.7	(26.2)	24.4	(27.2)	0.74
Dyspnoea	27.4	(20.7)	25.2	(19.5)	0.25
Insomnia	27.0	(27.7)	24.0	(27.0)	0.25
Appetite loss	17.6	(22.2)	19.3	(26.8)	0.99
Constipation	18.6	(27.5)	18.4	(26.1)	0.91
Diarrhoea	1.7	(7.3)	3.6	(11.8)	0.40
Financial difficulties	7.6	(17.9)	9.7	(19.8)	0.36
Coughing	34.5	(26.1)	32.7	(27.0)	0.48
Haemoptysis	3.4	(11.4)	4.1	(13.0)	0.78
Sore mouth	3.7	(13.3)	6.0	(17.2)	0.42
Dysphagia	7.1	(17.3)	9.0	(20.8)	0.64
Peripheral neuropathy	7.8	(17.1)	8.7	(19.2)	0.79
Alopecia	2.0	(10.5)	3.9	(15.4)	0.52
Pain in chest	11.9	(22.0)	12.8	(23.0)	0.81
Pain in arm or shoulder	17.0	(25.7)	17.0	(26.5)	0.93
Pain in other parts	74.5	(20.2)	15.5	(24.7)	0.72

^a Smoking information missing in two cases.

3. Results

3.1. Patient disposition and baseline characteristics

Overall, 299 patients were accrued in the MILES-3 and 232 in the MILES-4 trial; therefore, the joint database included 531 patients, 268 assigned chemotherapy without and 263 with cisplatin; of these, 237 (88%) and 221 (84%) completed baseline questionnaires, respectively (Fig. A.1 in Supplementary material). Patients with and without baseline QOL questionnaires were similar (Table A.1 in Supplementary material).

In the joint database, baseline characteristics of patients included in the QOL efficacy population were well balanced between study arms

(Table 1). Median age was 75 years (range 70–85) and 9% of patients were octogenarians. Around one-fifth of patients were female, more than half had an ECOG performance status 1, 71% had non-squamous histology and 13% were never smokers. For all QOL items, baseline values were similar between arms.

3.2. QOL compliance

Compliance with QOL questionnaire completion significantly decreased cycle after cycle, as expected in this poor-prognosis advanced disease setting. Patterns of missing QOL measurements are reported in Fig. A.2 in Supplementary material. In the QOL efficacy population of the joint database, the rate of missing QOL measurements after the baseline was slightly higher in the cisplatin arm. Such a pattern was common in the two trials MILES-3 and MILES-4 for the first two cycles, while it disappeared or slightly reverted in MILES-4 during the later cycles, from the 3rd to the 6th one.

3.3. Mean change analysis

Mean change from baseline analyses revealed a statistically significant difference between the arms only for sore mouth that was worse after cycle 2 ($P = 0.02$) in patients receiving cisplatin (Figs. A.3–A.6 in Supplementary material). Overall, in both arms, physical and role functioning worsened through the first 2 cycles, as well as loss of appetite, fatigue, vomiting and alopecia; some improvements were seen in cough and chest and shoulder pain.

The effect size was between small and medium (ie larger than 0.20 but smaller than 0.50) only for peripheral neuropathy and alopecia (0.25 and 0.31 after one and 0.28 and 0.36 after two cycles, respectively) and for nausea/vomiting, sore mouth and dysphagia after two cycles (0.26, 0.38 and 0.25, respectively) always in the direction of worsening with cisplatin (Table 2).

Table 2
Effect size of differences observed with cisplatin after one and two cycles.

	After one cycle			Effect Size	After two cycles			
	Non-cisplatin		Cisplatin		Non-cisplatin		Cisplatin	
	Mean	SD	Mean		Mean	SD	Mean	
Global health status	42.6	20.38	45.65	0.15	42.08	20.95	44.27	0.10
Physical functioning	73.16	20.13	69.73	−0.17	72.01	21.28	69.42	−0.12
Role functioning	72.7	27.18	71.05	−0.06	72.43	28.44	69.95	−0.09
Emotional functioning	75.31	21.48	75.05	−0.01	75.21	21.98	75.19	0.00
Cognitive functioning	87.57	19.14	86.62	−0.05	87.45	17.43	85.35	−0.12
Social functioning	85.71	20.88	82.59	−0.15	84.88	21	82.06	−0.13
Fatigue	34.33	23.31	38.85	0.19	34.91	23.1	39.14	0.18
Nausea/vomiting	7.23	13.88	8.7	0.11	7.1	12.15	10.23	0.26
Pain	20.9	23.75	22.51	0.07	20.06	22.53	19.95	0.00
Dyspnoea	13.57	9.24	13.11	−0.05	13.67	10.78	14.82	0.11
Insomnia	24.51	26.72	23.35	−0.04	20.78	26.79	21.46	0.03
Appetite loss	20.74	26.05	22.08	0.05	19.96	25.86	18.94	−0.04
Constipation	22.57	28.28	22.08	−0.02	19.75	28.43	21.21	0.05
Diarrhoea	3.7	13.02	4.46	0.06	2.9	12.58	2.78	−0.01
Financial difficulties	9.1	19.41	11.89	0.14	11.11	20.35	12.05	0.05
Coughing	29.28	25.75	27.6	−0.07	25.42	23.49	26.46	0.04
Haemoptysis	2.82	9.92	3.18	0.04	2.08	8.09	2.8	0.09
Sore mouth	5.82	15.23	8.33	0.16	3.54	11.58	7.95	0.38
Dysphagia	6.03	14.6	8.12	0.14	5.7	13.67	9.16	0.25
Peripheral neuropathy	7.76	18.48	12.31	0.25	6.92	15.5	11.2	0.28
Alopecia	3.17	12.46	7.05	0.31	5.63	15.51	11.2	0.36
Pain in chest	9.57	19.88	8.49	−0.05	10.27	19.83	8.65	−0.08
Pain in arm or shoulder	12.41	20.67	14.01	0.08	10.9	21.38	13.59	0.13
Pain in other parts	14.8	24.46	14.44	−0.01	12.66	19.77	14.87	0.11

Bold values indicate an effect size between small and medium.

3.4. Response analysis

QOL response results by treatment arms in the joint database are reported in Table 3. Among all the items, there was no signal of improvement with the addition of cisplatin to single-agent chemotherapy, while alopecia tended to be worse with cisplatin. Such results were confirmed in the analysis of the MILES-3 database, where the rate of patients worsening their report on alopecia was more than triple in the cisplatin arm (Table A.2 in Supplementary material).

3.5. Time-to-deterioration analysis

Time-to-deterioration of sore-mouth (HR 1.72, 95%CI: 1.02–2.89, $P = 0.04$) and alopecia (HR 1.84, 95%CI:1.09–3.10, $P = 0.02$) were significantly shorter in the cisplatin arm (Table 4 and Fig. 1). Such figures were no longer significant in the MILES-4 database with longer observation time, where there was no statistically significant difference for all the items; in this analysis, however, time to deterioration of global QOL tended to be better with cisplatin (HR 0.56, 95% CI 0.31–1.01, $P > 0.05$) (Table A.3 in Supplementary material).

4. Discussion

In the joint analysis of the MILES-3 and MILES-4 trials, and within each separate trial, the addition of cisplatin did not improve any QOL items, whichever the analytic frame, mean change, best response or competitive-risks adjusted time-to-deterioration analysis. However, significant worsening was only seen for two items, sore mouth and alopecia.

The present QOL analysis has several characteristics to highlight. First of all, it was conducted within a randomised design, the best study model to reduce the selection bias and allow proper statistical comparisons. Second, thanks to joining the two trials, the analysis was conducted on a large sample size, with enough statistical power to detect even a small effect size. Third, three different frames were used for analysis, allowing a deep exploration of possible QOL effects, both

Table 3
Best quality of life response by treatment arm in the joint database.

Domain/Item	Without cisplatin (n = 197)			With cisplatin (n = 165)			P
	Improved	Stable	Worse	Improved	Stable	Worse	
Global health status	77 (39.3%)	73 (37.2%)	46 (23.5%)	61 (37.0%)	68 (41.2%)	36 (21.8%)	0.74
Physical functioning	33 (16.8%)	86 (43.7%)	78 (39.6%)	21 (12.7%)	72 (43.6%)	72 (43.6%)	0.52
Role functioning	44 (22.3%)	71 (36.0%)	82 (41.6%)	38 (23.2%)	53 (32.3%)	73 (44.5%)	0.76
Emotional functioning	54 (27.4%)	95 (48.2%)	48 (24.4%)	52 (31.7%)	71 (43.3%)	41 (25.0%)	0.59
Cognitive functioning	48 (24.4%)	97 (49.2%)	52 (26.4%)	35 (21.2%)	83 (50.3%)	47 (28.5%)	0.76
Social functioning	40 (20.3%)	99 (50.3%)	58 (29.4%)	35 (21.2%)	75 (45.5%)	55 (33.3%)	0.64
Fatigue	61 (31.0%)	31 (15.7%)	105 (53.3%)	37 (22.4%)	33 (20.0%)	95 (57.6%)	0.16
Nausea/vomiting	17 (8.6%)	114 (57.9%)	66 (33.5%)	18 (10.9%)	86 (52.1%)	61 (37.0%)	0.52
Pain	58 (29.4%)	69 (35.0%)	70 (35.5%)	50 (30.3%)	58 (35.2%)	57 (34.5%)	0.98
Dyspnoea	37 (19.0%)	120 (61.5%)	38 (19.5%)	27 (16.4%)	100 (60.6%)	38 (23.0%)	0.64
Insomnia	62 (31.5%)	86 (43.7%)	49 (24.9%)	37 (22.4%)	82 (49.7%)	46 (27.9%)	0.16
Appetite loss	29 (14.7%)	101 (51.3%)	67 (34.0%)	32 (19.4%)	82 (49.7%)	51 (30.9%)	0.48
Constipation	34 (17.3%)	105 (53.3%)	58 (29.4%)	32 (19.4%)	81 (49.1%)	52 (31.5%)	0.72
Diarrhoea	9 (4.6%)	165 (84.2%)	22 (11.2%)	13 (7.9%)	136 (82.4%)	16 (9.7%)	0.40
Financial difficulties	18 (9.1%)	146 (74.1%)	33 (16.8%)	13 (7.9%)	115 (70.1%)	36 (22.0%)	0.45
Coughing	59 (30.3%)	100 (51.3%)	36 (18.5%)	52 (31.5%)	83 (50.3%)	30 (18.2%)	0.97
Haemoptysis	12 (6.1%)	178 (90.8%)	6 (3.1%)	13 (7.9%)	140 (84.8%)	12 (7.3%)	0.14
Sore mouth	11 (5.6%)	160 (81.6%)	25 (12.8%)	9 (5.5%)	122 (74.4%)	33 (20.1%)	0.17
Dysphagia	22 (11.3%)	146 (74.9%)	27 (13.8%)	14 (8.5%)	125 (76.2%)	25 (15.2%)	0.67
Peripheral neuropathy	26 (13.3%)	139 (70.9%)	31 (15.8%)	20 (12.1%)	107 (64.8%)	38 (23.0%)	0.22
Alopecia	6 (3.1%)	166 (84.7%)	24 (12.2%)	7 (4.2%)	123 (74.5%)	35 (21.2%)	0.052
Pain in chest	28 (14.4%)	140 (71.8%)	27 (13.8%)	31 (18.8%)	108 (65.5%)	26 (15.8%)	0.40
Pain in arm or shoulder	43 (22.1%)	125 (64.1%)	27 (13.8%)	36 (21.8%)	97 (58.8%)	32 (19.4%)	0.35
Pain in other parts	41 (21.6%)	100 (52.6%)	49 (25.8%)	29 (17.7%)	93 (56.7%)	42 (25.6%)	0.62

Table 4
Time-to-deterioration analysis in the joint database.

Domain/Item	HR ^a	95%CI	p ^b
Global health status	0.88	0.57–1.35	0.55
Physical functioning	1.04	0.75–1.44	0.80
Role functioning	1.00	0.73–1.37	0.99
Emotional functioning	1.03	0.68–1.55	0.91
Cognitive functioning	1.06	0.73–1.54	0.76
Social functioning	0.99	0.69–1.40	0.95
Fatigue	1.10	0.83–1.46	0.50
Nausea/vomiting	1.07	0.76–1.52	0.69
Pain	0.92	0.65–1.31	0.65
Dyspnoea	0.75	0.49–1.13	0.17
Insomnia	1.03	0.68–1.57	0.90
Appetite loss	0.92	0.64–1.33	0.66
Constipation	0.98	0.68–1.43	0.93
Diarrhoea	0.92	0.48–1.76	0.79
Financial difficulties	1.29	0.80–2.07	0.29
Coughing	0.82	0.50–1.36	0.45
Haemoptysis	2.49	0.92–6.76	0.07
Sore mouth	1.72	1.02–2.89	0.04
Dysphagia	1.14	0.66–1.96	0.63
Peripheral neuropathy	1.58	0.97–2.56	0.07
Alopecia	1.84	1.09–3.10	0.02
Pain in chest	1.15	0.66–1.98	0.62
Pain in arm or shoulder	1.43	0.86–2.40	0.17
Pain in other parts	0.86	0.56–1.32	0.50

^a HR of deterioration for patients with cisplatin vs without.

^b P value from Fine & Gray regression model adjusted by baseline item value, age, gender, performance status, stage and stratified by study, histotype and associated drug.

on the short (mean change and best response analysis) and long (time to deterioration analysis) treatment time. Fourth, time-to-deterioration analysis, considering progression and death as competitive risks, allows a proper comprehension of the QOL effect on the ground of the more general treatment effect on disease outcome. Therefore, this QOL analysis was quite sensitive and would be able to find out also a small QOL advantage with the addition of cisplatin. As a consequence, the negative results we actually found may be considered as definitive.

The Intergroupe Francophone de Cancerologie Thoracique reported

QOL analysis of the 0501 trial testing the combination carboplatin/paclitaxel versus single agent gemcitabine or vinorelbine, using the EORTC QLQ-C30 [14]. No significant QOL deterioration was seen with carboplatin/paclitaxel; even, a statistically significant advantage was found in time until definitive deterioration (TUDD) of physical functioning and nausea/vomiting using a 5-point threshold as minimum clinically important difference (MCID), and of fatigue and nausea/vomiting using a 10-point MCID. The analysis was not adjusted for competitive risks and the findings related to nausea/vomiting are counterintuitive given the expected toxicity profile of the drugs. However, interpretation was clearly affected by the positive result of the overall survival analysis, allowing the Authors to define as positive the fact that no QOL worsening was evident and, eventually, some advantage was found. The context is different for MILES-3 and MILES-4, because cisplatin addition does not prolong survival and lack of worsening cannot be considered enough for a positive interpretation of the QOL data. Moreover, we found some worsening with cisplatin in items (sore mouth and alopecia) investigated through the lung cancer specific LC13 questionnaire, which was not used in the 0501 trial.

As a technical point, we believe that the possible impact of the threshold value for MCID should be clarified. Actually, both the 5-point and 10-point thresholds are supported by previous literature [11,15]. Consistently with our strategy in previous NSCLC trials, we planned to use the 10-point threshold that is more challenging in terms of hope for QOL improvement, a goal that should be pursued with a potentially toxic treatment like platinum-containing chemotherapy [2,4,16,17]. The larger threshold, therefore, is more demanding for the experimental arm in analytic frames looking for improvement (ie the best response analysis), while turns to be conservative in favour of the experimental arm in time-to-deterioration analysis; nevertheless, we actually found a significantly shorter TTD for sore mouth and hair loss with the addition of cisplatin, consistent with the expected toxicity profile of the treatment.

5. Conclusions

In conclusion, the QOL analysis of the MILES-3 and MILES-4 studies, combined with the other efficacy data of these trials, confirms that the

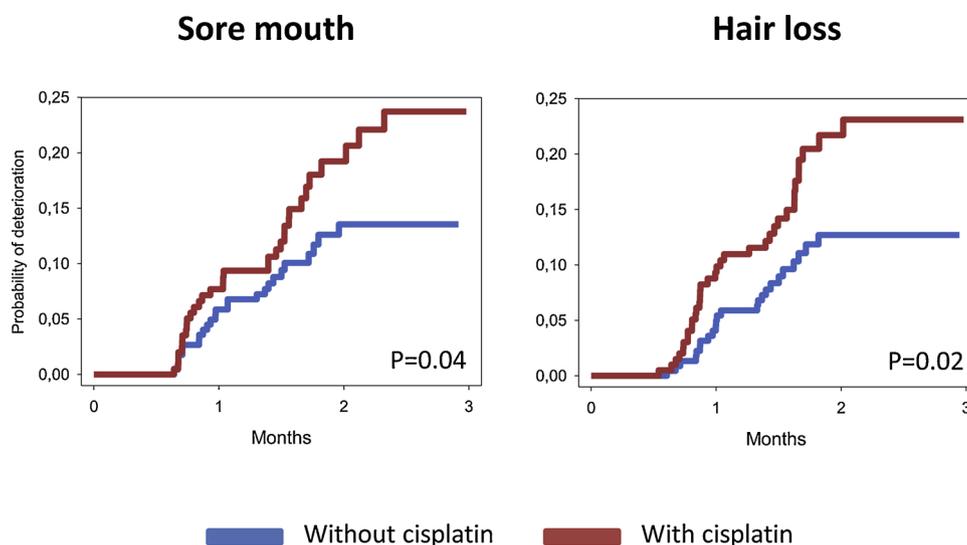


Fig. 1. Significantly different results of time-to-deterioration analysis.

addition of cisplatin to single-agent chemotherapy does not produce any benefit for elderly patients with advanced NSCLC and should no longer be considered among preferred options for first line treatment in clinical practice.

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Conflicts of interest

A.Morabito – Speakers' Bureau: Genentech, Eli Lilly, Pfizer, Boehringer Ingelheim, AstraZeneca, MSD Oncology; M.C. Piccirillo - Honoraria: Merck Sharp & Dohme and Astra Zeneca. Travel, Accommodations, Expenses: Bayer, Roche, Astra Zeneca; P.Maione – None; A.Luciani – None; L.Cavanna – Consulting or Advisory Role: AstraZeneca, Merck; L.Bonanno – None; V.Filipazzi – None; S.Leo – None; S.Cinieri - Speakers' Bureau: Eli Lilly; F.Morgillo – None; M.A.Burgio – None; D.Ferrara – None; F.Rosetti – Travel, Accommodations, Expenses: Bristol-Myers Squibb; R.Bianco – None; F.Artioli – None; D.Cortinovic – None; V.Gebbia – None; V.Fregoni – None; M.Mencoboni – Consulting or Advisory Role: Merck Sharp & Dohme. Travel, Accommodations, Expenses: Roche, Ipsen, Bristol-Myers Squibb; C.Sandomenico – None; A.Rossi – None; A.Montanino – None; A.Manzo – None; G.Rocco – None; L.Arenare – None; G.Daniele – Honoraria: Bayer Schering Pharma; S.Signoriello – None; C.Gallo – None; F.Perrone – Honoraria: Bayer AG, Daiichi Sankyo, Ipsen, AstraZeneca, Bristol-Myers Squibb. Research Funding: Roche (Inst), Bayer AG (Inst). Travel, Accommodations, Expenses: Bayer AG, Daiichi Sankyo; C.Gridelli – Consulting or Advisory Role: Bristol-Myers Squibb, MSD Oncology. Speakers' Bureau: Genentech, MSD Oncology, Bristol-Myers Squibb. Research Funding: Eli Lilly.

Appendix A

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.lungcan.2019.05.009>.

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