

# Early Response to Platinum-Based First-Line Chemotherapy in Non-small Cell Lung Cancer May Predict Survival

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**Introduction:** Response rates in the palliative treatment of non-small cell lung cancer, with combination platinum-based chemotherapy, vary from 20% to 40%, leaving a large number with either stable or progressive disease. We examined radiographic response after two courses of platinum-based induction chemotherapy to see whether this is an early predictor of outcome.

**Methods:** In this retrospective study, 320 patients with stage III/IV NSCLC were identified who received 4 or more courses of first-line platinum-based chemotherapy and attained partial response (PR) or stable disease (SD).

**Results:** After two courses, 115 patients attained PR and 205 SD. Cox regression analysis shows that response after two courses of chemotherapy remains an independent significant prognostic factor for survival. The 2-year survival for patients attaining PR after two courses ( $n = 115$ ) was 23% compared with 11% ( $n = 205$ ) for those with SD ( $p = 0.002$ ). Patients who achieve an objective response after two courses also have a better symptomatic response ( $p = 0.003$ ) and it was significantly longer ( $p = 0.04$ ). Of the 205 with SD, 51 attained PR with four courses, whereas 154 (48%) remained with SD; there was no difference in survival outcome of these two groups.

**Conclusions:** These data suggest that NSCLC patients who only have SD after two cycles of first-line chemotherapy have poorer survival outcome and less symptomatic benefit than those in PR. Trials looking at change in management at this point are warranted.

**Key Words:** Non-small cell, Early response, Chemotherapy.

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B.S. and M.O. were responsible for the overall conception of the research reported in the paper, the integrity and analysis of the data, and the writing of the manuscript. A.N. was the data manager. S.A. was responsible for the statistical analysis of the data. K.P. was the research nurse involved with the project. B.S., S.P., M.O.B., S.H., and P.P. were the treating physicians involved with the patients.

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Multiple randomized trials have established the standard of care for patients with inoperable locally advanced or metastatic non-small cell lung cancer (NSCLC). Platinum-based combination chemotherapy is the standard treatment, with consistent therapeutic superiority in randomized trials and meta-analyses compared with best supportive care or single-agent platinum.<sup>1,2</sup> Unfortunately, over the past decade, we have seen a plateau in clinical outcome whereby the median survival seldom exceeds 8 to 10 months, 1-year survival rates of 35% to 40% and 2-year survival rates of 10% to 15% at best.<sup>3–6</sup> Attempts to add a third agent to platinum combinations or to extend treatment beyond four to six cycles or to institute non-cross-resistant consolidation has yet to enhance outcome.<sup>7–9</sup> Hence, there is a clear-cut need for either newer treatment approaches with novel agents or optimizing the treatment of these patients with the chemotherapeutic agents that we currently have to attain maximum therapeutic benefit.

It has recently been shown that sequential therapy with a platinum two-drug combination followed by a taxane, when compared with six courses of the same platinum two-drug combination, did not result in a survival benefit. In this trial, patients were switched to receive the taxane after three cycles of the platinum-based chemotherapy.<sup>10</sup> A strategy to improve outcomes from treatment may need to switch patients at an earlier point. This could be reasonable if we have active alternative treatments to offer or treatment dictated by the phenotypic profile. Currently, we assess patients after every two cycles of chemotherapy, so this is the earliest point at which we can get information on response. This retrospective study was an attempt to identify a subset of patients with poor outcome after two courses of first-line platinum-based chemotherapy who warrant investigation of new strategies.

## PATIENTS AND METHODS

### Patients

All patients with histologic or cytologically proven inoperable locally advanced NSCLC suitable only for palliative treatment or metastatic NSCLC who had received platinum-based chemotherapy as first-line treatment were included in the study. Patients received treatment at the Royal Marsden Hospital between August 1987 and August 2004. The criteria to commence chemotherapy were ability to give

signed informed consent to treatment, adequate renal function assessed with chromium-51 (51-Cr) ethylenediaminetetraacetic acid or Cockcroft and Gault calculated glomerular filtration rate, and adequate liver function tests not more than two times normal unless caused by metastatic disease. Patients with serious uncontrolled concomitant illness were considered not eligible to receive chemotherapy.

From a prospectively maintained database, 1041 patients with stage III–IV NSCLC were identified who received platinum-based chemotherapy. Of these, 320 patients received four or more courses of platinum-based chemotherapy as first-line treatment and these patients are analyzed in this paper. The reasons for exclusion for the rest of the patients were as follows: 637 were excluded because they received fewer than four courses, 45 were excluded because their disease progressed or they were unassessable after four courses, and 39 were excluded because their responses were not assessed after two courses. For the 320 patients, responses were assessed after the second and fourth course of chemotherapy with computed tomography scans. Patients attaining either complete response (CR), partial response (PR), or stable disease (SD) were included in the study. All patients provided written informed consent for the treatment received as per local policy.

## Treatment

All the patients received a platinum-based regimen, and this was predominantly MVP (mitomycin C 6 mg/m<sup>2</sup> intravenously [IV] on day 1, vinblastine 6 mg/m<sup>2</sup> (maximum 10 mg) IV on day 1, and cisplatin 50 g/m<sup>2</sup> IV on day 1 or carboplatin if the Cockcroft and Gault calculated glomerular filtration rate was <60; no carboplatin if the Cockcroft and Gault calculated glomerular filtration rate was <30, every 21 days) in the majority of patients. This regimen has been described in detail before.<sup>7</sup> The other regimens used were gemcitabine and carboplatin (gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8; carboplatin area under the curve [AUC] 5), gemcitabine-cisplatin (gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8; cisplatin 80 mg/m<sup>2</sup>), vinorelbine-carboplatin (vinorelbine 25 mg/m<sup>2</sup>, carboplatin AUC5), vinorelbine-cisplatin (vinorelbine 30 mg/m<sup>2</sup>, cisplatin 80 mg/m<sup>2</sup>), Taxol-carboplatin (paclitaxel 175 mg/m<sup>2</sup>, carboplatin AUC5), and mitomycin C, cisplatin, 5-fluorouracil (mitomycin C 9 mg/m<sup>2</sup>, cisplatin 75 mg/m<sup>2</sup>, continuous infusion 5-fluorouracil 200 mg/m<sup>2</sup>/24 hours by ambulatory pump and Hickman line).

## Assessment of Objective Response

Tumor responses were assessed radiographically every two cycles. Designations of CR, PR, no change/SD, and progressive disease (PD) were based on the standardized response definitions established by the World Health Organization.<sup>11</sup> Symptom assessment was done by physicians in the clinic and recorded in the notes; these data were then entered in the database. Each symptom was recorded as “gone–complete resolution/improved–partial resolution/same–no change/worse–progression of symptoms/not assessable.” These responses to individual symptoms were then used to define the overall response as it would be for objective response. This is not a

validated scale but was the same method used for a prospective randomized study comparing three to six courses in this same patient population.<sup>7</sup>

## Statistical Considerations

Patients were divided into three groups depending on their response to chemotherapy after two and four courses (PR after two courses and continued PR after four courses PR2PR4; SD after two courses and PR after four courses SD2PR4; SD after two courses and continued SD after four courses SD2SD4). Differences in demographics and disease characteristics between the groups were assessed by the  $\chi^2$  and Mann-Whitney tests. Overall survival (OS) was measured from the date of first treatment until death. Progression-free survival (PFS) was measured from the date of first treatment until progression or death and was censored at last follow-up. The influence of response after two and four courses on PFS and OS was investigated in a univariate analysis using the Kaplan-Meier<sup>12</sup> method and log-rank statistic<sup>13</sup> and also in a multivariate proportional hazard analysis. Variables included in the multivariate analysis were age, sex, stage of disease, pathology, and performance status. A step-up method was used and variables added at the 0.05 level of significance. The relative risk of death, together with its 95% confidence interval (CI), was calculated for each group. Response after two courses was added to the final model to determine its independent significance. All analyses were done using SPSS and all *p* values were two sided.

## RESULTS

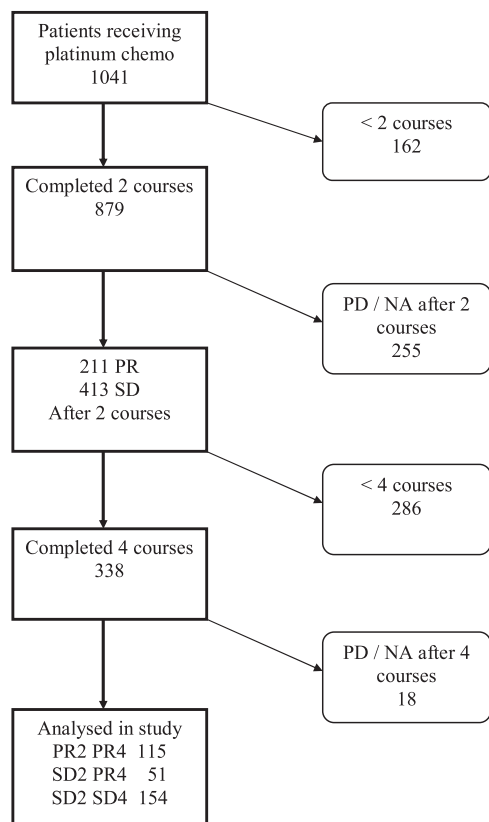
### Patients:

Of 1041 NSCLC patients who had platinum-based chemotherapy, 879 patients received two or more courses (Figure 1). Of these, 624 were responding or had stabilization of disease: 211 (24%) had a PR; 413 (46%) had SD; 338 patients went on to complete four courses of chemotherapy with 320 achieving a response (*n* = 156) or continued stabilization (*n* = 154). These 320 patients are, by definition, a good prognosis group and the subject of this study.

The demography of the 320 patients is summarized in Table 1. The median age of the patients was 60 years (range, 25–82), the majority of the patients had an Eastern Cooperative Oncology Group performance status of 0–1 and had adenocarcinoma. Of the 157 patients with stage III disease, 125 were stage IIIa/stage IIIb (dry) not suitable for radical treatment by virtue of their poor lung function or volume or location of disease. There were 32 (20%) patients with wet stage IIIb disease. Patients were divided into two subgroups for the purpose of the analysis (PR and SD after two courses). There were no statistically significant differences between the two groups apart from more patients with adenocarcinoma in the SD group (*p* = 0.05).

### Treatment Administration

A total of 240 patients received MVP, 16 MCF, 15 vinorelbine-cisplatin, six gemcitabine-cisplatin, 10 Taxol-carboplatin, 14 vinorelbine-carboplatin, and 14 gemcitabine-carboplatin, and five others (platinum-based). The median num-



**FIGURE 1.** Consort diagram of patient denominator. PR, partial response; SD, stable disease; chemo, chemotherapy; NA, not assessed; PD, progressive disease.

ber of cycles of chemotherapy given was five (range, four to eight), with responders receiving more courses in total than those with SD ( $p = 0.01$ ).

### Response Rates

After two courses of platinum-based chemotherapy, 115 of 320 (36%) patients attained a PR and 205 (64%) had SD. After four courses, the patients with a PR continued to have a PR, whereas of the 205 patients with SD, 51 (25%) attained PR with further courses of chemotherapy and 154 (75%) had SD. There was no difference in the outcome of these groups (Figure 2). Subsequently disease progressed in two responders and 12 patients with SD on treatment. Patients who had an objective response after two courses had a significantly better symptomatic response, as shown in Table 2 ( $p = 0.003$ , Mann-Whitney) and also had a longer duration of symptom response. The median duration of symptom response in patients who attained a PR after two courses was 32 weeks (95% CI: 26–39) compared with 23 weeks (95% CI: 18–28) in those with SD after two courses ( $p = 0.04$ ).

### Second-Line or Salvage Treatment

At the time of progression, patients were considered for second-line therapy. Among patients who attained a PR after two courses, 26 of 115 (23%) received second-line therapy compared with 46 of 205 (23%) patients who had attained SD

**TABLE 1.** Patient Characteristics

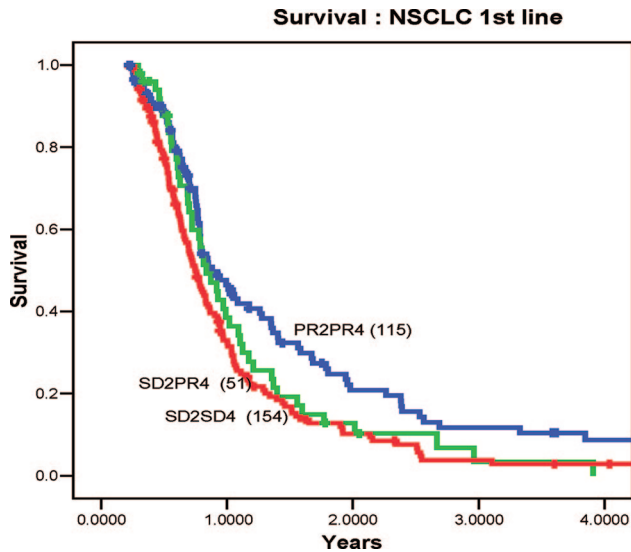
	Response After 2 Courses of Platinum-Based Chemotherapy		<i>p</i>
	PR ( <i>n</i> = 115)	SD ( <i>n</i> = 205)	
Age, yr, median (range)	62 (34–80)	59 (25–82)	0.1
Sex, %			0.8
Male	64	62	
Female	36	38	
Pathology, %			0.05
Adenocarcinoma	44	56	
Squamous cell	40	30	
Large cell	10	10	
Bronchoalveolar	1	2	
Other	5	2	
Stage, %			0.6
III	69	56	
IV	41	44	
PS, %			0.4
0	10	7	
1	69	69	
2	18	19	
3	1	2	
Not known	2	3	
Chemotherapy, %			0.5
MVP	72	77	
Gem/cis/carbo	8	5	
Nav/cis/carbo	12	7	
Other platinum	8	11	
No. of courses, %			1.0
4	43	42	
5	13	16	
6	44	40	
7+	0	2	

PR, partial response; SD, stable disease; PS, performance status; MVP, mitomycin C, vinorelbine, cisplatin or carboplatin; Gem, gemcitabine; cis, cisplatin; carbo, carboplatin; Nav, navelbine.

after two courses. The second-line regimens overall included docetaxel in 12 patients, navelbine based in six, gemcitabine based in four, Iressa in 19, Tarceva in 12, MVP in 11 patients, and other regimens in eight. There was no imbalance in their use between the two groups.

### Survival

The median PFS and OS for this selected group of patients receiving four or more courses of chemotherapy ( $n = 320$ ) were 28 weeks (95% CI: 26–30) and 42 weeks (95% CI: 39–45), respectively. In comparison, the median survival of 304 patients who had stabilization of disease after two courses but are excluded from the current analysis (Figure 1) was 31 weeks. Figure 2 shows the Kaplan-Meier overall survival curves of patients based on response after two courses. The PFS and OS are shown in Table 3 for the two subgroups attaining PR and SD after two courses. The median survival was similar in the two groups (46 weeks versus



**FIGURE 2.** Log rank comparison of overall survival of patients based on response after two courses (PR2PR4: those with a partial response (PR) after two courses who continued to have a PR after four courses; SD2PR4: those with stable disease (SD) after two courses and attained a PR after four courses; SD2SD4: those with SD after two courses who continued to have SD after four courses). NSCLC, non-small cell lung cancer.

**TABLE 2.** Correlation of Symptom Response with Objective Responses

	PR After 2 Courses (n = 115)	SD After 2 Courses (n = 205)	p
Complete resolution of symptoms	29 (25%)	27 (13%)	0.003
Resolution of majority of symptoms	68 (59%)	157 (76%)	
No change in symptomatology	4	12	
Worsening of symptoms	1	2	
Symptomatology not recorded	13	7	

41 weeks), but the curves separated after this point, giving a survival advantage to the responders ( $p = 0.002$ ).

As shown in Table 4, male sex ( $p < 0.001$ ) and stage IV disease ( $p < 0.001$ ) also predicted a worse outcome in the

multivariate analysis. Cox regression analysis shows that after adjusting for other prognostic factors like age, sex, and stage, response after two courses of chemotherapy remains an independently significant prognostic factor for survival. Figure 3 shows OS adjusted for age and sex for patients attaining PR after two courses versus those with SD.

## DISCUSSION

In this study of a subgroup of 320 patients receiving four courses of platinum-based treatment, we were able to show as an independent variable in a Cox multivariate analysis that patients who had responded after two courses of therapy (and who went on to receive four courses) fared better than those with SD after two courses.

Andre et al.<sup>14</sup> showed that for patients with N2 NSCLC who received preoperative chemotherapy, the 3-year event-free survival rate after preoperative chemotherapy was 25% for patients who achieved a CR or a PR and 7% for those who did not ( $p < 0.001$ ), and the 5-year OS rates were 20% and 5%, respectively ( $p < 0.001$ ), suggesting that patients with SD may be considered resistant to chemotherapy and treated in a different manner. Recently, a paper presented at American Society of Clinical Oncology tried to answer the question raised by this study, although the study design was such that patients attaining PR/SD after three courses of chemotherapy were then subsequently randomized to continuation of the same chemotherapy or switched to a taxane.<sup>10</sup> These patients were initially treated with three courses of gemcitabine 1 g/m<sup>2</sup>, ifosfamide 3 g/m<sup>2</sup>, and cisplatin 50 mg/m<sup>2</sup> (GIP) every 3 weeks, and patients with nonprogressing tumor were randomized to three further courses or to three courses of paclitaxel 225 mg/m<sup>2</sup>. The median survival was 14.1 months for the GIP arm and 16.4 months for the GIP-paclitaxel arm ( $p = 0.17$ ). Another phase III trial of induction therapy with four cycles of gemcitabine-carboplatin followed by either delayed or immediate second-line therapy with docetaxel in patients with advanced NSCLC showed that the response rate and clinical benefit rate were higher with immediate use of second-line therapy.<sup>15</sup> In this study, after four cycles of gemcitabine-carboplatin (gemcitabine 1 g/m<sup>2</sup> day 1,8, carboplatin AUC 5 on day 1 every 3 weeks), patients with nonprogressing disease were randomized to immediate docetaxel (75 mg/m<sup>2</sup> on day 1 every 3 weeks) or delayed docetaxel.<sup>15</sup> The survival data have not been presented. Our

**TABLE 3.** Progression-Free Survival and Overall Survival

Survival	All Patients (n = 320)	PR After 2 Courses (n = 115)	SD After 2 Courses (n = 205)
Median PFS, wk (range)	28 (26–30)	32 (29–35)	26 (24–28)
1-yr	18% (95% CI: 13–23)	20% (95% CI: 12–28)	8% (95% CI: 2–13)
2-yr	5% (95% CI: 2–8)	17% (95% CI: 11–22)	4% (95% CI: 1–7)
Median OS, wk (range)	42 (39–45)	46 (34–57)	41 (37–44) <sup>a</sup>
1-yr	39% (95% CI: 33–44)	46% (95% CI: 37–56)	34% (95% CI: 28–41)
2-yr	14% (95% CI: 37–46)	21% (95% CI: 12–30)	11% (95% CI: 6–16)

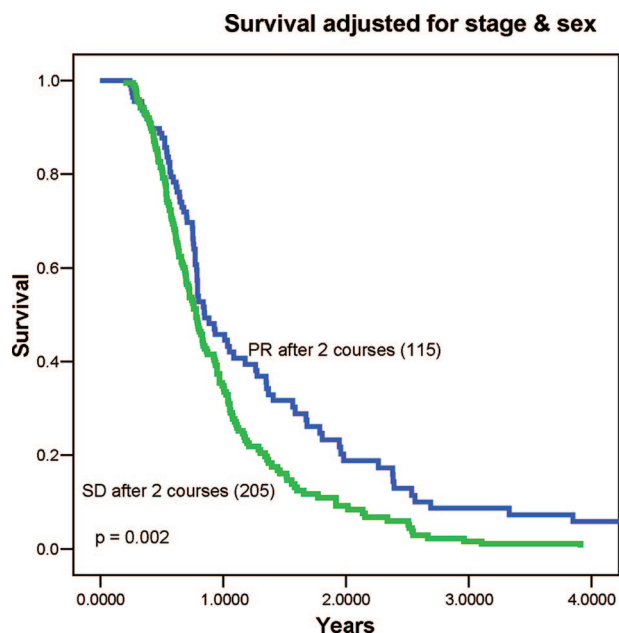
PD, progressive disease; SD, stable disease; PFS, progression-free survival; OS, overall survival; CI, confidence interval.

<sup>a</sup> Those with a PR after two courses have a better OS and PFS than those with SD after two courses (OS,  $p = 0.002$ ; PFS,  $p = 0.03$ ).

**TABLE 4.** Multivariate Analysis

Variable	Adverse Covariate	Relative Risk	95% CI	p
Stage of disease	IV	1.6	1.3–2.1	<0.001
Sex	Male	1.6	1.2–2.1	<0.001
Response after 2 courses	SD	1.5	1.2–2.0	0.002

CI, confidence interval; SD, stable disease.

**FIGURE 3.** Log rank comparison of overall survival adjusted for stage and sex based on response after two courses. PR, partial response; SD, stable disease.

data suggest that these switches in treatment could be proposed as early as after the second cycle of chemotherapy. It is possible that for a group of patients, a noncytotoxic approach or early use of second-line therapy may be better suited compared with sequential salvage chemotherapy.

We have shown that 51 of 205 of our patients with SD after two courses went on to respond after four courses, and disappointingly their outcome was no different in terms of survival and PFS when compared with those who did not respond. This late PR was not as meaningful as the early PR. Our data suggest that patients achieving an early PR have better outcome and that SD after two courses may be the time in a patient's treatment pathway to consider second-line therapy options. It has been shown in cancer treatment that patients with objective tumor responses were more likely to have a better quality of life than those patients where the best overall response was SD or PD.<sup>16</sup>

Current American Society of Clinical Oncology guidelines for unresectable stage III/IV NSCLC recommend four to six courses of chemotherapy with a maximum of four courses in nonresponding patients.<sup>17</sup>

Our study challenges the current norm of continuation of treatment in patients with NSCLC who have stable disease after two cycles of first-line platinum-based chemotherapy, which is currently the standard of care. It may be more important that we individualize treatment for patients with NSCLC to improve outcome. Data from Rosell et al.<sup>18</sup> demonstrated that overexpression of ERCC1 and other nucleotide excision repair enzymes may have an impact on cisplatin resistance. Based on this, an early switch to non-platinum-based regimens might be indicated early on during the treatment pathway for some patients.

Another way forward may be to assess metabolic response (<sup>18</sup>F)fluorodeoxyglucose uptake by using positron emission tomography (PET) within the subgroup of patients who have stable disease after two courses to decide on further continuation of that chemotherapy. This would involve PET for response assessment after completing two cycles of chemotherapy to see whether they have attained a degree of functional response rather than an anatomical response. PET may have a role in better assessment and prediction of response. Preliminary data have been published to indicate that the percentage of [<sup>18</sup>F]fluorodeoxyglucose uptake after one and three courses of induction chemotherapy predicts survival in stage IIIA-N2 patients.<sup>19</sup>

We are aware of the limitations of this study. This is a retrospective study in a selected group of heterogeneously treated patients over a long period who had to be well enough to receive the fourth cycle of chemotherapy. The PFS and the median duration of symptom response in this study is longer because of preselection criteria for these patients to have had already survived progression free for four courses of treatment (approximately 12 weeks). The majority of patients received the triplet regimen MVP, which is not the current standard practice, and only 18.4% patients received the third-generation chemotherapy. However, the treatment was all given in a standard way at a single cancer center with long follow-up. Our data on the 320 patients with SD after two courses includes only those patients who received four courses, but patients appear well balanced for established prognostic factors. This point of intervention, SD after two courses, could become a point when biopsy could be performed again on tumors and phase II development work carried out to help predict a phenotypically or genotypically led treatment.

In conclusion, NSCLC patients with SD after two courses of initial first-line chemotherapy have a poorer outcome than those with a PR and hence should be considered for reassessment possibly with a PET scan and entered into trials of alternative second-line treatment strategies. A prospective randomized trial in a homogeneous group of advanced NSCLC patients with special consideration to salvage treatment is required.

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