

## Treatment of advanced non-small cell lung cancer: chemotherapy with or without cisplatin?

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### introduction

The treatment of patients with advanced non-small cell lung cancer (NSCLC) mainly relies on the use of systemic combination chemotherapy (CT). A large meta-analysis of 52 trials has demonstrated that cisplatin-based CT improves patient's survival, quality of life (QoL), tumor-related symptoms, and it is cost-effective when compared to best supportive care [1]. To date there is considerable agreement that the best treatment for non-elderly patients with advanced NSCLC and good performance status (ECOG 0–1) is represented by doublets including a platinum compound in combination with a new third generation drug, such as gemcitabine (GEM), vinorelbine (VNR), paclitaxel (PCT) and docetaxel (DCT) [2, 3]. These regimens are considered equiactive leading to the consideration that there is a wide choice of active treatments rather than a treatment of choice [2–7]. Therefore the oncologists' decision of employing a certain regimen should be based on patients' characteristics, economic costs, expected toxicity, and convenience of administration [7]. Despite significant progresses achieved in the two last decades, the treatment of advanced NSCLC maintains a palliative intent for a significant debate exist among oncologists on patients selection, choice of active drugs, and the real need of using an aggressive regimen in such clinical setting [8]. As a consequence, patients' QoL, toxicity, and drug therapeutic index have become important issues challenging the pivotal role played by cisplatin so far [9].

Cisplatin is traditionally considered a highly emetogenic drug potentially associated with severe asthenia, vestibular damage, and neurological and renal toxicity, and its administration requires a rather complex and time-consuming procedure [10]. The use of full-dose cisplatin is consequently limited to patients with poor performance status [11], age >65–70 years, and those with significant concomitant co-morbidities, such as cardio-respiratory diseases [10]. All the above-mentioned data might explain the relatively low acceptance of cisplatin-based regimens in the daily oncological practice. There is the need of an 'easier' treatment for advanced stage NSCLC further motivated by the use of high-dose cisplatin in the adjuvant treatment of radically resected patients [12]. Therefore the role of cisplatin in advanced NSCLC has been recently challenged [13, 14].

### carboplatin-based regimens

One of the strategies investigated to avoid the use of cisplatin is the substitution of carboplatin for cisplatin since the former is more easily administered with a very low rate of renal and neurological toxicity [13–15]. But are the two drugs truly the same? It should be kept in mind that carboplatin is significantly more toxic to the bone marrow than cisplatin, rendering combination with other myelotoxic drug sometime problematic. Moreover, while the two agents have been shown to be equiactive in ovarian carcinoma, several studies have suggested the inferiority of carboplatin in other malignancies, such as head/neck squamous cell carcinoma and testicular cancer.

Only a small number of randomized trials has specifically addressed the question of equivalence of cisplatin and carboplatin. Data from clinical studies comparing cisplatin-versus carboplatin-based regimens have not been univocal. A large randomized non-inferiority trial compared cisplatin/PCT with carboplatin/PCT [16]. The main end-point was objective response rate (ORR) which was 28% with cisplatin/PCT and 25% with carboplatin/PCT ( $P = \text{NS}$ ). However, median progression-free survival (PFS) and overall survival (OS) in the cisplatin/PCT arm were significantly longer than those reported in the carboplatin/PCT arm: PFS was 4.8 and 3 months ( $P = 0.035$ ), and OS was 9.8 and 8.2 months ( $P = 0.019$ ), respectively. There was no advantage of carboplatin/PCT in terms of tolerance or QoL evaluated with the QLQ-C30 and LC-13 scales. These data in favour of cisplatin were consistent with those reported in a large international randomized trial [17] comparing cisplatin/DCT with carboplatin/CT and cisplatin/VNR reported a significantly superior median OS in the cisplatin/DCT arm (10.9 months). The advantage of cisplatin over carboplatin was not confirmed by another similar randomised trial carried out by the ECOG [4]. This trial compared cisplatin plus PCT given as a 24-h infusion with carboplatin plus PCT given as a 3-h infusion, and cisplatin/GEM as well as cisplatin/DCT. Median OS was 7.8 months in the cisplatin/PCT arm compared with 8.1 months in the carboplatin/PCT arm. The 1-year survival rates were 31% and 34%, and the 2-year survival rates were 10% and 11%, respectively. Tolerability was similar in both arms.

A large literature-based meta-analysis has been recently carried out to determine whether cisplatin and carboplatin are

equally effective in advanced NSCLC [18]. The meta-analysis included eight trials for a total of 2948 patients treated with regimens containing platinum plus a new generation agent. Pooled data analysis showed that ORR was higher in patients treated with cisplatin-based CT but without a statistically significant survival advantage ( $HR=1.050$ ;  $P = 0.515$ ). Subgroup analysis revealed that combination CT consisting of cisplatin plus a new agent yielded an 11% longer survival than carboplatin plus the same new agent ( $HR=1.106$ ;  $P = 0.039$ ). Cisplatin-based CT was more frequently associated with nausea/vomiting than carboplatin which however induced thrombocytopenia was more frequent during carboplatin-based CT. The conclusion was that cisplatin plus a new agent yields a substantial survival advantage compared with carboplatin plus a new agent in patients with advanced NSCLC, although the analysis failed to find any survival difference in an analysis that included both new and old agents.

Overall, it should be stressed that the strength of conclusions reported in this meta-analysis is limited because of the use of abstracted data, and careful interpretation is thus required [19, 20]. More reliable data could certainly come from an individual patients' data meta-analysis of trials specifically addressed to the clinical question [20]. However, to date, the above-reported data suggest that carboplatin and cisplatin are not equiactive and that cisplatin-based doublet regimens should remain the standard therapy for patients with advanced NSCLC with good performance status even if associated with a greater gastrointestinal and neurological toxicity [14, 15]. These statements do not mean that carboplatin has no role in the management of advanced diseases since cisplatin remains a potentially very toxic drug which requires a rather complex hydration protocol, an important anti-emetic therapy and hospitalisation in many cases. Many oncologists feel that toxicity issues are enough to justify the use of carboplatin and that its slightly reduced activity has a very small practical importance. Therefore, accordingly to the ASCO guidelines [2], carboplatin-based regimens are a reasonable and active therapeutic alternative in all patients where the use of cisplatin is not advisable for whichever clinical reason.

## non-platinum regimens

The availability of several active, third-generation drugs has prompted many researchers to design and test new regimens devoid of platinum compounds. Several randomized trials have been carried out to answer the question whether non-platinum combination regimens were as effective or even more active than platinum-based ones. In general, no single study was successful in demonstrating a survival advantage in favour of platinum-based regimens [21–23]. However, in some studies, a trend towards a higher ORR, or PFS or OS was observed in patients treated with platinum-based combinations compared with those treated with cisplatin-devoid regimens [24–27]. One only study has reported that a non-platinum combination regimen was superior to carboplatin-based regimen in terms of ORR, PFS, OS and clinical benefit [29].

Gridelli et al. [24] carried out a trial on 500 patients aimed to assess whether a combination of GEM/VNR could improve QoL, without influencing negatively OS, as compared with

cisplatin plus GEM or VNR. There were no significant differences in global QoL between the two arms, but worse scores for appetite, vomiting, and alopecia were significantly more common in the cisplatin-based regimens. Median survival was 38 vs. 32 weeks and median PFS was 23 vs. 17 weeks in the cisplatin-based arm versus the cisplatin-devoid one, respectively. For the GEM/VNR arm the hazard ratio for death was 1.15 and the hazard ratio for progression was 1.29. Grade 3–4 myelo-suppression, vomiting, alopecia, and ototoxicity were significantly more frequent with cisplatin-based treatment. The authors concluded that global QoL is not improved with the GEM/VNR regimen, although advantages in some components of QoL were apparent. GEM/VNR is less toxic than standard cisplatin-based CT and could be offered to advanced NSCLC patients who express concern about toxicity, but a non-significant slight survival advantage in favour of cisplatin-based chemotherapy was recorded.

Alberola et al. [25] carried out a three-arm phase III randomized trial comparing a cisplatin-based triplet (cisplatin/GEM/VNR) versus a cisplatin-based doublet (cisplatin/GEM  $\times$  6 cycles) versus a non-platinum sequential doublet (GEM/VNR for 3 cycles followed by VNR/ifosfamide for 3 cycles). No differences in median survival or time to progression were observed and toxicity was higher for the triplet and comparable between the doublets.

The EORTC [26] compared the efficacy of cisplatin/PCT versus cisplatin/GEM versus PCT/GEM in 400 patients with OS as the primary end point. Median OS was 8.1, 8.9, and 6.7 months respectively, while ORR were 31.8%, 36.6%, and 27.7%. No statistically or clinically significant differences were observed for secondary end points which included PFS, toxicity, QoL, and costs. The average treatment costs were 25% higher for cisplatin-devoid regimen.

Georgoulis et al. [27] compared the activity and tolerability of DCT/GEM with prophylactic G-CSF and cisplatin/VNR in 413 patients. Median OS was 9.0 and 9.7 months ( $P = 0.965$ ), 1-year survival rate was 34.3% and 40.8%, and ORR was 30% and 39.2% ( $P = 0.053$ ) for DCT/GEM and cisplatin/VNR respectively. Anemia, grade 3–4 neutropenia, febrile neutropenia, and severe nausea/vomiting were statistically more frequent in the cisplatin arm. QoL was improved in patients treated with platinum-devoid regimen but not in those receiving cisplatin. The authors concluded that the two regimens produced comparable OS, but cisplatin-devoid regimen had a better toxicity profile, and could be used in patients who cannot tolerate cisplatin.

The Hellenic Cooperative Oncology Group randomly assigned patients to receive PCT with either carboplatin or GEM [28]. Median and 1-year survival were 10.4 months and 41.7% for the platinum arm, and 9.8 months and 41.4% for the non-platinum arm ( $P = 0.32$ ). Toxicity was mild and similar in both arms and no differences were evident at a retrospective cost analysis.

The GLOB-2 trial [29] compared two VNR-based doublets with carboplatin or with GEM in 316 patients with advanced NSCLC with ORR as the primary endpoint and PFS and OS, tolerance and clinical benefit as secondary ones. The ORR on intent-to-treat was 20.8% in VC and 28% in VG ( $P = 0.15$ ). Median PFS was 3.9 months in VNR/cisplatin arm and

4.4 months in VNR/GEM one ( $P = 0.18$ ). Median OS was significantly longer ( $P = 0.01$ ) for VNR/GEM then for VNR/cisplatin with 1-year survival rate of 48.9% and 34.4%, respectively. Tolerance and clinical benefit were better in the carboplatin-devoid arm. Conclusions stated that platinum-devoid regimen was associated with higher ORR, longer median OS and better toxicity profile than carboplatin-based combination.

A very recent, large literature-based meta-analysis was carried out to compare ORR, 1-year survival rates, and side-effects of platinum-based versus non-platinum-based given as first-line therapy [30]. Thirty-seven randomized phase II and III trials, for a total of 7,633 patients, were included in the analysis. ORR rate was significantly higher with platinum-containing regimens with a 62% increase in the odds ratio for response was attributable to platinum-based regimens (OR 1.62;  $P < 0.0001$ ). The 1-year survival rate was increased by 5% with platinum-based regimens (34% vs. 29%; OR, 1.21;  $P = 0.0003$ ), but this statistical advantage disappeared when platinum regimens were compared to non-platinum-based ones including third-generation drugs (OR=1.11;  $P = 0.17$ ). Overall, toxicity was generally higher for platinum-based regimens. In particular hematologic side-effects, renal toxicity and nausea/vomiting were significantly more frequent in platinum-based regimens, while there was no difference for neurotoxicity, febrile neutropenia rate, or toxic death rate.

At the last ASCO meeting another literature-based meta-analysis [31] of trial randomizing a platinum-based chemotherapy versus a doublet non-platinum-based including at least one third-generation drug was presented. A statistical heterogeneity was detected, related to the studies that used triplets as the standard arms. The heterogeneity disappeared when the analysis was restricted to the study that used well-recognized platinum-based doublets as standard and the conclusion was for a significant reduction in risk of death for platinum-containing regimen.

The value of these literature-based meta-analysis is limited by the lack of individual patients' data and for this reason overall survival could not be correctly assessed [20].

An important issue is toxicity profile. Overall, platinum-devoid regimens showed a more favourable toxicity profile than platinum-based ones. However, these data are not univocal since two large trials failed to show any significant differences in terms of toxicity between the platinum-based and platinum-devoid regimens [26, 28], and another study reported only qualitative differences [32]. QoL analysis did not show significant differences in patients' global health status [14, 15, 17]. Some studies showed that cisplatin-based regimens were more cost-effective as compared to the non-platinum regimens [26], while one trial proved there was no difference between the two regimens [28]. Non-platinum-based regimens are not significantly different from the platinum-based combinations at least in terms of OS. However, the reported studies are not powered to address the question of equivalence of the two combinations. One such study testing the survival equivalence of non-platinum-based and platinum-based therapy has reported an interim analysis showing no statistical survival advantage for platinum- or non-platinum based therapy [33].

A separate issue is the treatment of patients with ECOG PS 2 and/or elderly advanced NSCLC patients. MILES trial [34] randomized elderly (>70 years) patients to receive non-platinum chemotherapy. The combination of GEM and VNR was compared to the two single drugs with no survival advantage and more toxicity in the combination arm. The same results were obtained also in the sub-group of PS2 patients. A recent European expert panel [11] indicates a single-agent third generation non-platinum chemotherapy as preferred option in patients with PS 2, although carboplatin-based or low-dose cisplatin-based doublets may represent alternative options.

## future strategies to tailor chemotherapy

In the last years several studies have indicated that gene expression can play a predictive role to tailor chemotherapy in different subgroups of patients. The efficacy of removal of cisplatin DNA adducts by the nucleotide excision repair (NER) system is assumed to be one of the determinants of cisplatin resistance. The excision repair cross-complementing 1 (ERCC1) and ribonucleotide reductase subunit M1 (RRM1) genes are leading components of this system. RRM1 is also a direct target of GEM.

Some retrospective studies explored the correlation between these genes and the clinical outcomes. Rosell [35] analysed ERCC1 and RRM1 mRNA expression in samples obtained from bronchoscopy of advanced NSCLC patients from the over mentioned phase III randomized trial (22bis) comparing a cisplatin-based triplet (cisplatin/GEM/VNR for 6 cycles) versus a cisplatin-based doublet (cisplatin/GEM for 6 cycles) versus a non-platinum sequential doublet (GEM/VNR for 3 cycles followed by VNR/ifosfamide for 3 cycles). In the cisplatin/GEM arm, patients with low RRM1 and ERCC1 mRNA levels had significantly longer median survival than those with higher levels.

Isla [36] studied a single nucleotide polymorphism in ERCC1 (ERCC1 118 C) in peripheral blood lymphocytes of cisplatin/DCT treated advanced NSCLC. Patients homozygous for the ERCC1 118C allele demonstrated a significantly better survival.

Gurubhagavatula [37] demonstrated that an increasing number of variant alleles in RCC1 were associated with a decreased overall survival in advanced NSCLC patients treated with platinum agents (cisplatin or carboplatin). Moreover these polymorphisms independently predicted overall survival even after taking in account stage, PS and chemotherapy regimen.

At the last ASCO meeting Rosell [38] presented the preliminary results of the first prospective phase III randomized trial, to confirm the value of ERCC1 to predict the response to cisplatin. Patients with available tumor biopsy samples were randomized to the control arm (cisplatin/DCT) or to the genotypic arm where chemotherapy was tailored according to levels of ERCC1. Patient with low ERCC1 levels received same platinum chemotherapy of control arm whereas patients with high ERCC1 levels were treated with a non-platinum chemotherapy (DTC/GEM). Lower ERCC1 mRNA levels were correlate to better response to cisplatin-based chemotherapy

(cisplatin-DCT) and there was also a correlation between higher levels of ERCC1 mRNA and better response to non-cisplatin arm (GEM-DCT).

Based on these preliminary results it is probable that, in the future, the platinum versus non-platinum chemotherapy will be chosen in relationship to the genetic determinations of platinum resistance.

## conclusions

NSCLC in the advanced recurrent/metastatic setting essentially remains an incurable disease. In the last decade clinical trials have shown a plateau in survival which is unlikely to be further improved using currently available chemotherapeutic drugs and regimens. New discoveries in therapeutic targets will probably overcome the issue of choosing platinum-based or platinum-devoid regimens. To date in our current clinical practice therapeutic choices should be tailored to individual patients. Treatment decision making should also take into account age, performance status, number and degree of existing co-morbidities, and basal quality of life. Others important parameters should be toxicity profile, expected side-effects, and the cost of treatment.

## references

1. Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomized clinical trials. *Br J Med* 1995; 311: 899–909.
2. Pfister DG, Johnson DH, Azzoli CG et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004; 22: 330–353.
3. Bunn PA. Chemotherapy for advanced non-small cell lung cancer. Who, what, when, why? *J Clin Oncol* 2002; 20 (Suppl. 18): 23s–33s.
4. Schiller JH, Harrington D, Belani CP et al. Comparison of four chemotherapy regimens for advanced non-small cancer. *N Engl J Med* 2002; 346: 92–98.
5. Kelly K, Crowley J, Bunn PA et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. *J Clin Oncol* 2001; 19: 3210–3218.
6. Fossella F, Pereira RJ, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combination versus vinorelbine plus cisplatin for advanced non-small cell lung cancer. The TAX 326 Study Group. *J Clin Oncol* 2003; 21: 3016–3024.
7. Ettinger D, Johnson D. Update. NCCN Small Cell and Non-Small Cell Lung Cancer Clinical Practice Guidelines. *J Natl Compr Canc Netw* 2005; 3 (Suppl 1): S17–S21.
8. Bunn PJ, Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clin Cancer Res* 1998; 5: 1087–1100.
9. Thongprasert S, Sanuganmitra P, Juthapan N. Relationship between quality of life and clinical outcomes in advanced non-small cell lung cancer: best supportive care (BSC) versus BSC plus chemotherapy. *Lung Cancer* 1999; 24: 17–24.
10. Rossi A, Maione P, Gridelli C. Safety profile of platinum-based chemotherapy in the treatment of advanced non-small cell lung cancer in elderly patients. *Exp Opin Drug Saf* 2005; 4: 1051–1067.
11. Gridelli C, Ardizzone A, Le Chevalier T et al. Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel. *Ann Oncol* 2004; 15: 419–426.
12. Winton T, Livingston R, Johnson D et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med* 2005; 352: 2589–2597.
13. Socinski MA: Cytotoxic chemotherapy in advanced non-small cell lung cancer. A review of standard treatment paradigms. *Clin Cancer Res* 2004; 10: 4210S–4214S.
14. Soria JC, Le Chevalier T. Is cisplatin still the best platinum compound in non-small-cell lung cancer? *Ann Oncol* 2002; 13: 1515–1517.
15. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. *J Clin Oncol* 1999; 17: 409–422.
16. Rosell R, Gatzemeier U, Betticher DC et al. Phase III randomised trial comparing paclitaxel/carboplatin versus paclitaxel/cisplatin in patients with advanced non-small-cell lung cancer: a cooperative multinational trial. *Ann Oncol* 2002; 13: 1539–1549.
17. Fossella F, Pereira RJ, von Pawel J et al. Randomized, multinational, phase III study of docetaxel plus platinum combination versus vinorelbine plus cisplatin for advanced non-small cell lung cancer. The TAX 326 Study Group. *J Clin Oncol* 2003; 21: 3016–3024.
18. Hotta K, Matsuo K, Ueoka H et al. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004; 22: 3852–3859.
19. Tiseo M, Boni L, Ardizzone A. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: does cisplatin versus carboplatin make a difference? *J Clin Oncol* 2005; 23: 6276–6277.
20. Piedbois P, Buyse M. Meta-analyses based on abstracted data: a step in the right direction, but only a first step. *J Clin Oncol* 2004; 22: 3839–2841.
21. Bunn PA. Platinums in lung cancer: sufficient or necessary? *J Clin Oncol* 2005; 23: 2882–2883.
22. Androulakis N, Georgoulas V. NSCLC – platinum or not. *Lung Cancer* 2005; 47: 380–383.
23. Schiller JH. Platin or no platin? That is the question. *J Clin Oncol* 2003; 21: 3009–3010.
24. Gridelli C, Gallo C, Shepherd FA et al. Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine for advanced non-small cell lung cancer: a phase III trial of the Italian GEMVIN Investigators and the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2003; 21: 3025–3034.
25. Alberola V, Camps C, Provencio M et al. Cisplatin plus gemcitabine versus a cisplatin-based triplet versus non-platinum sequential doublets in advanced non-small-cell lung cancer: A Spanish Lung Cancer Group Phase III randomized trial. *J Clin Oncol* 2003; 21: 3207–3213.
26. Smit EF, van Meerbeeck JP, Lianes P et al. Three-arm randomized study of two cisplatin based regimens and paclitaxel plus gemcitabine in advanced non small cell lung cancer: a phase III trial of the European organization for research and treatment of cancer. Lung Cancer Group EORTC 08975. *J Clin Oncol* 2003; 21: 3909–3917.
27. Georgoulas V, Ardanavis A, Tsiafaki X et al. Vinorelbine plus cisplatin versus docetaxel plus gemcitabine in advanced non small cell lung cancer: a phase III randomized trial. *J Clin Oncol* 2004; 23: 2937–2945.
28. Kosmidis P, Mylonakis N, Nicolaidis C et al. Paclitaxel plus carboplatin versus gemcitabine plus paclitaxel in advanced non-small cell lung cancer: A phase III randomized trial. *J Clin Oncol* 2002; 20: 3578–3585.
29. Tan EH, Szczesna A, Krzakowski M et al. Randomized study of vinorelbine-gemcitabine versus vinorelbine-carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer* 2005; 49: 233–240.
30. D'Addario G, Pintilie M, Leigh NB et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. *J Clin Oncol* 2005; 23: 2926–2936.
31. Barlesi F, Pujol J, Daurès J. Should chemotherapy for advanced non-small-cell lung cancer (NSCLC) be platinum-based? A literature-based meta-analysis of randomized trial. *Proc Am Soc Clin Oncol* 2005; 23: 673s (Abstr 7213).
32. Yamamoto N, Fukuoka M, Negoro SI et al. Randomized phase II study of docetaxel/cisplatin vs. docetaxel/irinotecan in advanced non-small cell lung cancer: a West Thoracic Oncology Group Study (WJTOG 9803). *Br J Cancer* 2004; 90: 87–92.
33. Rigas JR, Carey M, Cole B et al. Multicenter web-based phase III study to test the survival equivalence of non platinum-based (NPB) vs platinum-based (PB) therapy for advanced non-small cell lung cancer (NSCLC). The Dartmouth NPB

- Chemotherapy Trial (D0112). *Proc Am Soc Clin Oncol* 2004; 23: 631 (Abstr 7071).
34. Gridelli C, Perrone F, Gallo C et al. Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. *J Natl Cancer Inst* 2003; 95: 362–372.
  35. Rosell R, Danenberg KD, Alberola V et al. Ribonucleotide reductase messenger RNA expression and survival in gemcitabine/cisplatin-treated advanced non-small-cell lung cancer patients. *Clin Cancer Res* 2004; 10: 1318–1325.
  36. Isla D, Sarries C, Rosell R et al. Single nucleotide polymorphism and outcome in docetaxel-cisplatin-treated advanced non-small-cell lung cancer. *Ann Oncol* 2004; 15: 1194–1203.
  37. Gurubhagavatula S, Liu G, Park S et al. XDP and XRCC1 genetic polymorphism are prognostic factor in advanced non-small-cell lung cancer patients treated with platinum chemotherapy. *J Clin Oncol* 2004; 22: 2594–2601.
  38. Rosell R, Cobo M, Isla D et al. ERCC1 mRNA-based randomized phase III trial of docetaxel (doc) doublets with cisplatin (cis) or gemcitabine (gem) in stage IV non-small-cell lung cancer (NSCLC) patients (p). *Proc Am Soc Clin Oncol* 2005; 23: 621s (Abstr 7002).