ANTICANCER RESEARCH *34*: 493-502 (2014)

Review

Platinum Drugs and DNA Repair Mechanisms in Lung Cancer

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Abstract. *The standard first-line treatment for around 80% of newly-diagnosed advanced non-small cell lung cancer (NSCLC) is chemotherapy. Currently, patients are allocated to chemotherapy on the basis of clinical conditions, comorbidities and histology. If feasible, platinum-based chemotherapy is considered as the most efficacious option. Due to the heterogeneity in terms of platinum-sensitivity among patients with NSCLC, great efforts have been made in order to identify molecular predictive markers of platinum resistance. Based on the mechanism of action of platinum, several components of DNA repair pathways have been investigated as potential predictive markers. The main DNA repair pathways involved in the repair of platinum-induced DNA damage are nucleotide excision repair and homologous recombination. The most studied potential predictive markers of platinum-sensitivity are Excision Repair Cross Complementing-1 (ERCC1) and Brest Cancer Type-I Susceptibility protein (BRCA1); however, increasing biological knowledge about DNA repair pathways suggests the potential clinical usefulness of integrated analysis of multiple DNA repair components.*

In recent years, considerable improvements have been achieved in the outcomes of patients with advanced non-small cell lung cancer (NSCLC) but the most important progress in the treatment of metastatic disease is related to the discovery of specific molecular alterations functioning as pharmacological targets (1-2). Currently, in the subset of epidermal growth factor receptor (EGFR)-mutated patients, EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib and afatinib have demonstrated clear superiority when compared to standard platinum-based chemotherapy, both in terms of progression-free survival (PFS) and improvement in symptoms and quality of life (3-9). The introduction of EGFR TKIs in the treatment of EGFR-dependent NSCLC has led to considerable increase in overall survival (OS), with medians of over two years for EGFR-mutated patients treated with EGFR TKIs (1, 10).

Another oncogene-addicted subgroup of NSCLC that currently may benefit from targeted therapy is characterized by Anaplastic Lymphoma Kinase (ALK) rearrangements and accounts for 2-7% of patients (11-13).

While translational and clinical research is ongoing to improve non-chemotherapy treatment perspectives, platinum-based chemotherapy remains the best option for more than 80% of patients diagnosed with advanced NSCLC, without substantial differences in efficacy among different chemotherapy combinations. Platinum-based treatment is characterized by great heterogeneity both in terms of efficacy and toxicity. The median PFS of platinum-treated patients ranges between three and seven months and median OS is still less than one year.

The study of molecular predictive markers of platinum sensitivity in lung cancer aims to distinguish those patients who could most benefit from treatment from those who should be tested for alternative treatments, but also to improve prognostic information at diagnosis and to pave the way for consistent improvement in outcomes of NSCLC patients through a customized chemotherapy approach.

Current Status of First-line Treatment of Non-Oncogene-addicted NSCLC

The standard first-line treatment for advanced NSCLC nowadays is a platinum-based doublet containing a third generation agent (14) (Figure 1).

Abbreviations: 53BP1: P53 binding protein 1, BRCA1: breast cancer type 1 susceptibility protein, ERCC1: excision repair cross complementing 1, GG-NER: global-genome nucleotide excision repair, RAP80: receptor protein associated 80, TC-NER: transcription-coupled nucleotide excision repair.

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Key Words: Platinum, DNA repair mechanisms, lung cancer, predictive markers, review.

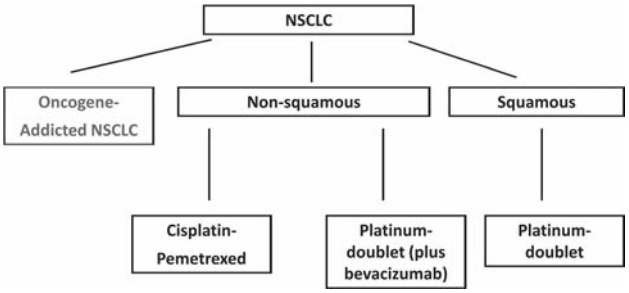

Figure 1. *Simplified model of the current status of first-line treatment for patients affected by advanced non-small cell lung cancer (NSCLC) with good clinical condition at diagnosis.*

In the early years of the 21st century, several phase III trials compared different platinum-based combinations but no substantial differences were seen in efficacy end-points (15-17). The differences between chemotherapy combinations, including gemcitabine, taxanes and vinca alkaloids, were related to the toxicity profile, while all efficacy end-points showed no relevant differences. Across the three trials, the overall response rate (RR) ranged between 17 and 32%, the median PFS between 3.1 and 5.5 months, and the median OS between 7.4 and 9.9 months (15-17).

In addition to comparing different platinum-based combinations, a direct comparison between carboplatin and cisplatin was performed with the aim of optimizing first-line chemotherapy for NSCLC patients. A phase III trial comparing the outcome of patients treated with cisplatin and paclitaxel with that of patients treated with carboplatin and paclitaxel was published in 2002. Although the RR was similar (25 and 28%), the median OS for cisplatin-treated patients was 9.8 months, compared to 8.2 months achieved by the other group (p=0.019). There was no significant difference in quality of life between the two arms (18). This was the first clear evidence of superiority in terms of efficacy for cisplatin *versus* carboplatin. To address the issue, an individual patient data meta-analysis was later carried out, including almost 3,000 patients enrolled in nine clinical trials. Patients treated with cisplatin obtained a statistically superior RR (30 *versus* 24%, p<0.001). In the overall population, carboplatin-treated patients had a tendency for increased risk of death. This became statistically significant when considering non-squamous histology (Hazard ratio (HR)=1.12) and patients treated with third-generation agents (HR=1.11) (19).

More recently, first-line chemotherapy with cisplatin and pemetrexed demonstrated superiority both in terms of PFS and OS when compared to cisplatin and gemcitabine in adenocarcinoma. However, efficacy results were inferior among patients with squamous cell carcinoma (SCC). These conclusions were drawn from pre-planned sub-group analyses of a phase III trial with the primary aim of demonstrating non-inferiority of OS for cisplatin-pemetrexed combinations. While median OS for patients enrolled in the trial was 10.3 months, regardless of the type of chemotherapy administered (cisplatin-gemcitabine or cisplatin-pemetrexed), those patients diagnosed with adenocarcinoma and treated with the pemetrexed combination achieved a median OS of 12.6 months (20).

Another therapeutic option which can improve the outcome of patients with non-oncogene addicted lung non-squamous carcinoma is the addition of bevacizumab, an antibody targeting vascular endothelial growth factor (VEGF), to a platinum-based doublet. A pivotal US phase III randomized trial demonstrated that the addition of bevacizumab to carboplatin and paclitaxel increased the median PFS from 4.5 to 6.2 months and median OS from 10.3 to 12.3 months when compared to the same chemotherapy alone (21). In another European phase III trial, the combination of cisplatin, gemcitabine and bevacizumab led to a statistically significant improvement in PFS when compared to cisplatin and gemcitabine alone: the median PFS of the experimental arm, including the currently used bevacizumab dosage with this chemotherapy, was 6.7 *versus* 6.1 months for the placebo arm (22). A median OS of more than 13 months was recorded in the study population, without statistical improvement conferred by the addition of bevacizumab (23). The exclusion of squamous histology from phase III trials is due to the higher risk of serious hemorrhagic adverse event, highlighted by a phase II trial (24). A recently published meta-analysis included data from more than 2,000 patients enrolled in the two above-mentioned phase III trials of bevacizumab efficacy and other two phase II-trials. The meta-analysis showed a statistically significant reduction of risk of death for patients treated with bevacizumab-combinations (HR=0.9, p<0.03), in addition to confirming the impact on PFS (HR=0.72, p<0.001) (25).

Finally, the combination of three chemotherapy drugs with different mechanisms of action (carboplatin, gemcitabine and paclitaxel) was demonstrated to be feasible in this setting in a phase II-III trial which demonstrated a median OS of 10.8 months *versus* 8.3 months obtained with carboplatin and paclitaxel (26).

The standard first-line treatment for elderly patients is based on the use of a single third-generation agent, on the basis of pivotal phase III trials published in the early years of the 21st century (27-28). More recently, a phase III trial randomized patients older than 70 years old (median age 77 years) to receive a single-agent treatment (gemcitabine or vinorelbine) or carboplatin plus weekly paclitaxel. Despite considerably increased toxicity, the median OS of patients receiving the doublet was significantly increased compared to patients receiving mono-therapy (10.3 *versus* 6.2 months) (29). Prospective phase III clinical trials are ongoing to

evaluate efficacy and safety of other platinum-based doublet in elderly patients with good performance status (PS) at diagnosis (NTCT 01405586; NTCT01656551).

Currently, no molecular predictive marker of platinum-containing chemotherapy efficacy has been approved for clinical use. In addition to PS, age and comorbidities, the only factor routinely taken into account for routine clinical decision-making is histology (Figure 1).

DNA Repair Mechanisms and Platinum

Endogenous and exogenous factors continuously damage cell DNA. For this reason, multiple pathways are normally used to repair the different kinds of DNA damage. Classically, five main DNA repair pathways are described: Nucleotide excision repair (NER), base-excision repair (BER), mismatch repair (MMR), homologous recombination (HRc) and non-homologous end-joining (NHEJ) (Figure 2). Each of these pathways is involved in the repair of different kinds of DNA damage and includes many components which interact to repair DNA lesions and contributing to genome stability. NER is involved in the repair of helix-distorting lesions caused by different agents such as ultraviolet (UV) radiation, tobacco smoke and platinum-based chemotherapeutics. It is subdivided into two sub-pathways, differing in the way they recognize the DNA damage sites and in the target DNA: global-genome (GG)-NER and transcription-coupled (TC)-NER. Oxidative damage to DNA caused by reactive oxygen species (ROS) is repaired by BER. MMR acts to correct replication errors, while defects in MMR capacity, associated with increased risk of solid tumors, are mirrored by so-called microsatellite instability. HRc and NHEJ are involved in repair of DNA double-strand breaks (DSBs) and will be further discussed later in the present review. Examples of endogenous causes of DSBs are stalled replication forks, metabolic stress inducing ROS production and nucleases, whereas exogenous stimulation includes ionizing radiation (IR) and DNA-cross-linking agents (30-31).

Platinum drugs exert their antitumor effect through several mechanisms but the best known and probably the most important is the creation of stable DNA adducts, causing distortions in DNA structure. Mono-functional cisplatin-DNA adducts further lead to the formation of bi-functional intra- and interstrand crosslinks. In cells, cisplatin-DNA adducts are recognized as DNA damage sites and activate cellular mechanisms eventually leading to cell death. Most DNA adducts primarily activate the NER pathway (32), but the repair of interstrand cross-links requires the coordinated action of NER and HRc (33).

While intrastrand crosslinks are the most frequent platinum-induced lesions, interstrand crosslinks are highly cytotoxic since they cause replication and transcription blocks. Stalled replication forks induced by interstrand crosslinks trigger

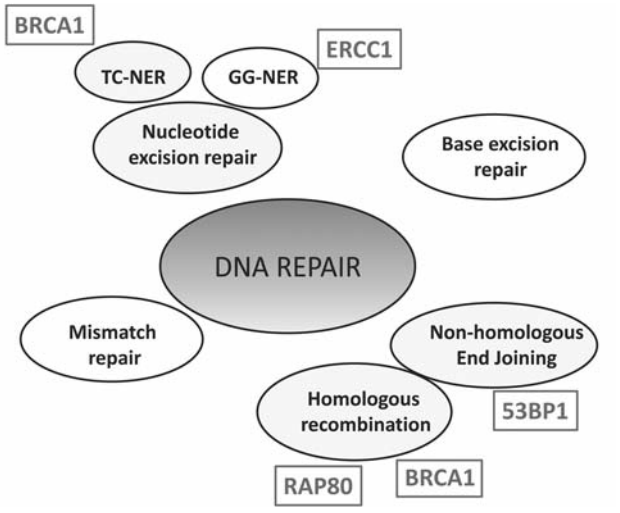

Figure 2. *Main DNA repair pathways and molecular predictive markers of platinum sensitivity. The main kinds of damage induced by platinum on DNA are intra- and interstrand crosslinks requiring nucleotide excision repair (NER) and homologous recombination (HRc) for repair. The main potential predictive markers of platinum resistance discussed in the text are here linked to the main repair pathway in which they are involved.*

repair of DNA damage requiring endonucleases including excision repair cross-complementation group-1 (ERCC1), translesion synthesis polymerases and HRc components (34). A second mechanism of interstrand crosslinks repair occurs in G_0 and G_1 phases of the cell cycle, is thus replication-independent and involves other NER components which recognize and incise interstrand crooslinks and subsequently translesion polymerases polymerase ζ and Rev1 (35-36).

From Biological Knowledge to Molecular Marker Validation: An Update on Clinical Data Concerning Molecular Predictive Markers of Platinum Sensitivity in Lung Cancer

The principal mechanism of action of platinum implies a potential role for DNA repair components in inducing platinum resistance. In parallel, defective DNA repair capacity has been associated with increased sensitivity to platinum-based chemotherapy. In this context, the best studied potential predictive markers of sensitivity to platinum-based chemotherapy are ERCC1 and BRCA1.

ERCC1 is a pivotal component of NER, being involved in the repair of both intra- and interstrand crosslinks. It creates a complex with Xeroderma pigmentosum Factors (XPF) and acts by cleaving the damaged 5'-strand. Many clinical retrospective data are available indicating a predictive role for *ERCC1* expression at mRNA or protein levels in lung cancer. Consistent with the biological rationale, low

expression of *ERCC1* has been correlated with improved outcome to platinum-based chemotherapy (37-39). A recent meta-analysis including data from 836 patients with NSCLC confirmed the association of low *ERCC1*, both at mRNA and at protein levels, with improved RR and median OS to platinum-based chemotherapy (40).

Nevertheless, the prospective validation of the predictive role of ERCC1 in advanced disease has been rather disappointing. The first published phase III prospective trial of customized chemotherapy in lung cancer was coordinated by the Spanish Lung Cancer Group (SLCG) and randomized patients affected by advanced NSCLC to receive standard chemotherapy treatment with cisplatin and docetaxel *versus* customized chemotherapy. In the experimental arm, patients were treated according to mRNA expression levels of *ERCC1*: they received cisplatin and docetaxel in the presence of low *ERCC1* expression and docetaxel/gemcitabine in the presence of high *ERCC1* expression. The primary end-point of the trial was RR and this was reached with statistical significance: an objective response was obtained in 50.3% of patients in the experimental arm and 39.3% of patients in the control arm (p=0.02). Unfortunately, the results were not mirrored by significant improvement in OS (41). More recently, the results of another phase III prospective clinical trial of customized chemotherapy were published (42). In this case, patients in the control arm received carboplatin and gemcitabine, whereas patients in the experimental arm were treated according to the protein expression of ERCC1 and RRM1, that is a subunit of ribonucleotide reductase that represents a cellular target for gemcitabine. High levels of RRM1 have been associated with resistance to gemcitabine (43). Patients whose tumors expressed low levels of both proteins received carboplatin and gemcitabine. When ERCC1 was low but RRM1 high, patients were treated with docetaxel and carboplatin, while docetaxel and vinorelbine was administered in the presence of high levels of both proteins. When comparing outcomes of patients in the two arms, no differences were seen either in terms of OS or PFS (42).

In addition to the lack of clinical prospective validation for ERCC1 in advanced NSCLC, there is still great controversy about the method of evaluating ERCC1, concerning potential differences between mRNA and protein analyses and technical issues about immunohistochemistry evaluation. One of the most famous retrospective studies concerning the predictive role of ERCC1 was published in 2006 and looked at the predictive role of ERCC1 in patients with early-stage NSCLC receiving adjuvant platinum-based chemotherapy. The authors concluded that patients expressing high levels of ERCC1 did not benefit from platinum-based chemotherapy, while reduced risk of death was observed among patients with low or negative ERCC1 treated with adjuvant platinum-based chemotherapy, compared to patients with low/negative ERCC1 who did not receive post-operative chemotherapy (adjusted HR=0.65, p=0.002) (39). Recently, a validation set of patients using the same antibody, targeting ERCC1 (8F1) failed to confirm these results. The authors also re-stained samples from the patients originally analyzed and were not able to confirm the previous findings, suggesting a change in the antibody due to a different batch. Interestingly, a potential biological explanation for the lack of reliability of ERCC1 immunostaining was suggested. The authors demonstrated that only one out of the four isoforms generated by the gene produced a protein able to mediate the repair of platinum-DNA adducts, and none of the 16 antibodies tested was able to distinguish the different protein isoforms (44). On the basis of these results, the phase III clinical trial from the French collaborative intergroup testing the role of customized chemotherapy according to ERCC1 measured at the protein level in the adjuvant setting was abandoned (45).

The BRCA1 protein is a main component of HRc, but is also involved in TC-NER (46). Pre-clinical models demonstrated that BRCA1 is a modulator of cellular response to platinum and anti-microtubule agents. In particular, it confers sensitivity to anti-microtubule agents and resistance to platinum (47-48). The first evidence of a potential predictive role for BRCA1 expression in lung cancer was published in 2004: a retrospective analysis of patients with NSCLC who underwent platinum-based neoadjuvant chemotherapy demonstrated the feasibility of assessing the mRNA expression of *BRCA1* and the association of low *BRCA1* expression with improved OS to platinum-based chemotherapy (49). A phase II prospective trial was later performed and demonstrated the feasibility of *BRCA1* mRNA analysis in clinical setting. *EGFR*-wild-type patients enrolled in the trial were treated according to a customized chemotherapy approach: patients expressing low mRNA levels of *BRCA1* received cisplatin and gemcitabine, patients expressing intermediate levels of the gene were treated with cisplatin and docetaxel, and when *BRCA1* was high they received docetaxel alone. The median OS for the three treatment arms was 11, 9 and 11 months, respectively, thus demonstrating no detrimental effect for patients receiving docetaxel alone according to this customized chemotherapy approach. An exploratory retrospective analysis evaluated levels of mRNA expression of *receptor associated protein 80 (RAP80)* and *ABRAXAS*, genes encoding for proteins collaborating with BRCA1 in HRc, being part of the BRCA1-A complex (50). While the analysis of *ABRAXAS* mRNA demonstrated no predictive value, *RAP80* analysis was able to further sub-classify patients expressing low levels of *BRCA1* and receiving platinum-based chemotherapy. The group of patients expressing low levels of both *BRCA1* and *RAP80* was demonstrated to benefit most from platinum-based treatment, achieving an impressive median PFS of 14 months, with a median OS not

reached (51). On the basis of these results, a prospective phase III trial was planned and interim analyses results were presented at 2013 American Society of Clinical Oncology (ASCO) congress. Patients affected by advanced NSCLC were randomized to receive standard chemotherapy with cisplatin and docetaxel or customized chemotherapy according to the evels of expression of *BRCA1* and *RAP80*. Patients expressing low *RAP80* mRNA and any level of *BRCA1* were treated with gemcitabine and cisplatin, patients with intermediate or high *RAP80* expression and low or intermediate BRCA1 expression received docetaxel and cisplatin, and in the presence of intermediate or high *RAP80* and high *BRCA1* expression docetaxel alone was administered. The primary end-point was PFS. The interim analysis showed no benefit in terms of PFS for patients in the experimental arm and, among these, a detrimental effect was observed for patients receiving docetaxel alone. On the basis of these findings, the phase III trial was closed. However, additional molecular analyses are ongoing to clarify which elements are able to improve the predictive model (52).

New Potential Predictive Markers: Our Experience

On the basis of increasing biological knowledge about DNA repair pathways (53), we hypothesized a predictive role for proteins cooperating with BRCA1 for the repair of double-strand lesions.

For this reason, we selected a population of 115 patients diagnosed with advanced NSCLC (stage IIIB-IV) treated with a platinum-based doublet in the first-line setting. We retrospectively collected clinical data and tumor samples from patients treated with cisplatin and carboplatin plus gemcitabine or pemetrexed. We excluded patients treated with a platinum-based combination including anti-microtubule agents (taxanes and vinca alkaloids), since high levels of expression of *BRCA1* confer resistance to cisplatin and anti-microtubules agents (48). We extracted RNA from paraffin-embedded samples from biopsies previously obtained for diagnosis, according to the protocol (49, 51, 54).

In this study population, we first wanted to confirm the predictive value of the integrated analysis of *BRCA1* and *RAP80* (51). To do so, we considered patients with good PS at diagnosis (PS 0-1 according to Eastern Cooperative Oncology Group scale) and we measured mRNA levels of expression of *BRCA1* and *RAP80* using real-time polymerase chain reaction (PCR) quantitative comparative method, as previously described (49, 51, 54). The results were categorized using tertile values as cut-off points (51). In this way, we subdivided the study population into three groups according to the results of integrated BRCA1-RAP80 analysis. Patients expressing low mRNA levels (less than the lowest tertile value) of the two genes obtained a median PFS of 10 months, while median OS was not reached. Patients expressing high levels of the two genes (greater than the highest tertile value) had median OS of only six months and median PFS of five months. The patients whose tumors expressed other combinations of genes obtained a median OS of 11 months and a median PFS of seven months (55). These results confirmed the data published in 2009 from retrospective analysis of patients enrolled in a phase II prospective trial demonstrating the feasibility of BRCA1-driven customized chemotherapy in the clinical setting (51).

Subsequently, we also tested the hypothesis that components of the pathway of P53 binding protein 1 (53BP1) could have a predictive value in platinum-treated NSCLC patients (56). This idea originated from recent biological knowledge about the role of 53BP1 in repair of DSBs and its interaction with BRCA1 (57-60).

HRc and NHEJ are the main pathways involved in repair of DSBs. HRc acts in an error-free manner, since it uses undamaged homologous sequences of DNA as templates. NHEJ is generally considered an error-prone repair system, since it acts by joining the ends of broken double strands through assembly of a multi-protein complex. DSBs induced by stalled replication forks are repaired mainly by HRc, whereas DSBs caused by IR and nucleases may be repaired by the two pathways (61). The 53BP1 protein has been found to localize at both endogenous and exogenous DSBs sites in a cell-cycle dependent manner, while the phosphorylated forms have been detected only in response to exogenous DSBs (62). BRCA1 and 53BP1 are recruited at DNA damage sites by partially overlapping mechanisms (50), while the complex interplay between BRCA1 and 53BP1 has been investigated in depth in preclinical models (57, 59-60) and has great potential for clinical application. The presence of functional 53BP1 decreases the HRc cell capacity while, by contrast, 53BP1 loss partially restores the BRCA1-null phenotype in preclinical models (57, 59). In the absence of 53BP1, DNA damage response of BRCA1-null cells changes and DNA damage does not induce atassia teleangectasia mutata (ATM)-checkpoint response and G_2 cell-cycle arrest, as when 53BP1 is functional (57). Even though the HRc capacity of BRCA1-null cells is restored by the absence of 53BP1 (57), cells depleted of both BRCA1 and 53BP1 are more sensitive to cisplatin when compared both to wild-type cells and BRCA1-null cells (60). This seems to suggest that DNA interstrand crosslinks may be repaired by a mechanism independent on HRc capacity but involving BRCA1.

On the basis of these molecular data, we decided to test mRNA expression levels of *BRCA1* and other genes encoding for proteins involved in DSB repair and interacting with *BRCA1* and *53BP1*: *Caspase 3, ubiquitin conjugating enzyme 13 (UBC13), ring finger protein 9 (RNF8), RAP80, 53BP1, sumo-conjugatin enzyme 9 (UBC9), multiple myeloma set (MMSET), E3 sumo-protein ligase 4 (PIAS4)* (63).

We analyzed the influence of mRNA expression of each gene on the outcome of the study population, considering this both as a continuous and categorical variable. We categorized mRNA expression levels using the median value as cut-off points.

When we considered the potential predictive value of the expression levels of each gene, none of these significantly affected the outcome of the study population. However, when we analyzed the effect of integrated analysis of *BRCA1* and *53BP1* on the outcome of the study population, a new predictive model emerged. Patients expressing low levels of both *BRCA1* and *53BP1* obtained an impressive median OS of 19.3 (95% confidence interval (CI)=9.8-28.7) months and a median PFS of 10.3 (95% CI=5.4-15.1) months. These results were in sharp contrast with those achieved by patients expressing low levels of BRCA1 but high levels of 53BP1. In this group of patients, median OS and PFS were 8.2 (95% CI=3.2-12.5) months and 5.9 (95% CI=4.4-7.4) months, respectively. The difference was statistically significant with a p value of 0.001 for OS and <0.0001 for PFS (56).

These results indicate that combined analysis of the two genes was able to identify the subgroup of patients with NSCLC who can benefit most from platinum-based chemotherapy, thus considerably improving predictive information given by BRCA1 analysis in isolation.

Conclusion

The study of the DNA repair pathways is extremely interesting from a biological point of view and has great potential clinical application for optimization of the chemotherapy approach to advanced non-oncogene addicted NSCLC. While current available clinical data do not support routine use of molecular predictive markers of platinum sensitivity in lung cancer, recent data suggest that improvement of detection methods and integrated analyses of multiple DNA repair components could pave the way for new perspectives in this field.

Conflicts of Interest

The Authors have no conflicts of interest that are directly relevant to the content of the manuscript.

Acknowledgements

The Authors thank Kate Williams, assistant to Dr. Rosell, for help in revising the language in this manuscript.

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Received August 20, 2013
Revised December 11, 2013
Accepted December 12, 2013