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Editorial Office
World Journal of Clinical Oncology
17th February 2014

Dear Editor,

Name of Journal: World Journal of Clinical Oncology
ESPS Manuscript No: 8492
Title: Advances in Adjuvant Systemic Therapy for Non-Small-Cell Lung Cancer
Authors: David Leong, Rajat Rai, Brandon Nguyen, Andrew Lee, Desmond Yip

Thank you for your prompt review of this manuscript. Please find enclosed the edited manuscript in Word format (file name: 8492-review.docx).

The manuscript has been revised to take into account the suggestions of the reviewers, as follows:

Reviewer 02494535: ***The authors revise extensively and clearly the literature on adjuvant treatment of NSCLC and state the current standard therapy in this setting. I only have minor comments. - They state the importance of stage but do not address the importance of histology. Though the latter is sitll not relevant at the moment for treatment decision in NSCLC it will likely become in the near future. Please address ongoing adjuvant studies as ITACA trial and ERCC1 targeted trial, the latter integrating both histology and biomarker data. - Please address the fact that age is not a contraindication to adjuvant chemotherapy as long as patient is fit, and relevant literature addressing this point.***

We concur with this reviewer's comments. Separate subheadings now address the role of tumour histology and patient age in pages 11-12 and 10-11, respectively. Similarly he ITACA and ERCC1 Targeted trials are covered in pages 17 and 13. In addition, we now include the ongoing TASTE trial which uses ERCC1 expression and EGFR mutation status to optimise adjuvant chemotherapy in the experimental arm, in page 17.

Reviewer 01332768: ***This systematic review for the treatment of Non-SCLC was well written and is ready for publication. Due to the highly aggressive nature of NSCLC and the ineffectiveness of other measures, the adjuvant therapy is a new hope for treatment of this disease. It would be nice if the authors could add some contents to discuss why the mortality of NSCLC was not significantly changed during the past several decades, despite all hard effort***

We have now added a sentence pointing out that long-term survival of NSCLC has not changed much over the last 30 years, in our introduction. A supporting reference accompanies this sentence. A sentence regarding possible explanation has been put in the conclusion.

Whilst we appreciate the need to mention the poor survival from NSCLC and the lack of progress hitherto in this regard, at the same time we feel that it would be unnecessary for this article to elaborate. There are many reasons postulated for this lack of improvement, and if we were to discuss this, the introduction will become disproportionately long. Rather, we hope that the recent advances made in adjuvant therapy, plus further developments in this area, will ultimately contribute to the much-needed improvement in survival for NSCLC in the future.

Reviewer 02493594: ***The paper is well organized and takes considaration state of the art with regard to adjuvant therapy of NSCLC. However, authors should: - Specify the incidence of side effects in the main study - Emphasize the advantage produced by the association cisplatin and vinca alkaloids compared to VP-16 in the study IALT (toxic deaths, dead long period, etc.). Finally, a typing error in the "UFT" section .... [This advantage (ws) was ....]***

Table 2 has been added to the manuscript to list the main acute side-effects of chemotherapy with cisplatin plus vinorelbine, together with their respective incidences. Owing to the heterogeneity of regimens covered across the papers reviewed, it would be impractical to tabulate toxicities to cover *all* the adjuvant studies mentioned. Fortunately the two studies with the best results have both used high-dose cisplatin in conjunction with vinorelbine, and hence we feel that a table describing the toxic effects seen in both studies in detail will provide readers with the most practical information in this regard.

Following this reviewer's comments we went back to the original publication of the IALT study in the *New England Journal of Medicine*, however we could not find any evidence of *"the advantage produced by the association cisplatin and vinca alkaloids compared to VP-16"* as mentioned. Instead fact we found that the paper's conclusions seem contrary to the reviewer's comment, if anything the results are tending to favour VP-16 (etoposide) as illustrated in the Forrest plot taken from the paper, attached.

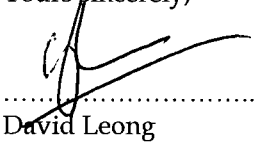
Lastly, the original IALT publication indicates that 7 patients (0.8% of the cohort) died from chemotherapy toxicity, however it did not provide any breakdown to elaborate on this. Toxicities were not compared between the regimens used in this study, either in the original paper or subsequent update, the latter of which has also been referenced in the original manuscript.

The typographic error pointed out by the reviewer in page 7 has been corrected.

All changes to the original manuscript are indicated in red markup using Microsoft Word's Track Changes function. A final check has been performed to ensure that the manuscript now specifically complies with the WCJO's *Instructions to Authors*.

Thank you again for considering the manuscript for publication.

Yours sincerely,



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David Leong

On behalf of all manuscript authors

Attachment: Covariates for survival from IALT trial

Covariate	Chemotherapy Group	Control Group	P Value for Interaction	P Value for Trend
	No. of deaths/No. of patients			
Age			0.46	0.26
<55 yr	141/314	163/316		
55–64 yr	181/355	214/366		
>64 yr	147/263	127/233		
Sex			0.65	—
Male	300/752	417/750		
Female	79/180	87/185		
WHO performance status			0.14	0.21
0	240/505	259/499		
1	186/355	213/372		
2	43/72	32/64		
Type of surgery			0.98	—
Pneumonectomy	182/324	193/324		
Lobectomy or segmentectomy	287/608	311/611		
Tumor stage			0.57	0.32
1	67/169	59/151		
2	282/570	314/603		
3 or 4	120/193	131/181		
Nodal status			0.80	0.56
0	164/423	174/427		
1	144/271	155/267		
2	161/238	175/241		
Stage			0.41	0.21
I	115/333	122/348		
II	123/230	126/222		
III	231/369	256/365		
Histologic type			0.77	—
Squamous cell	205/428	223/444		
Adenocarcinoma	199/386	208/368		
Other	65/118	73/123		
Dose of cisplatin per cycle			0.45	0.63
80 mg/m^2	85/163	93/164		
100 mg/m^2	334/679	360/677		
120 mg/m^2	50/90	51/94		
Drug combined with cisplatin			0.77	—
Vindesine	26/52	26/56		
Vinblastine	62/103	70/102		
Vinorelbine	113/248	128/252		
Etoposide	268/529	280/525		
Planned radiotherapy			0.66	—
No	287/648	303/647		
Yes	182/284	201/288		
Total	469/932	504/935		

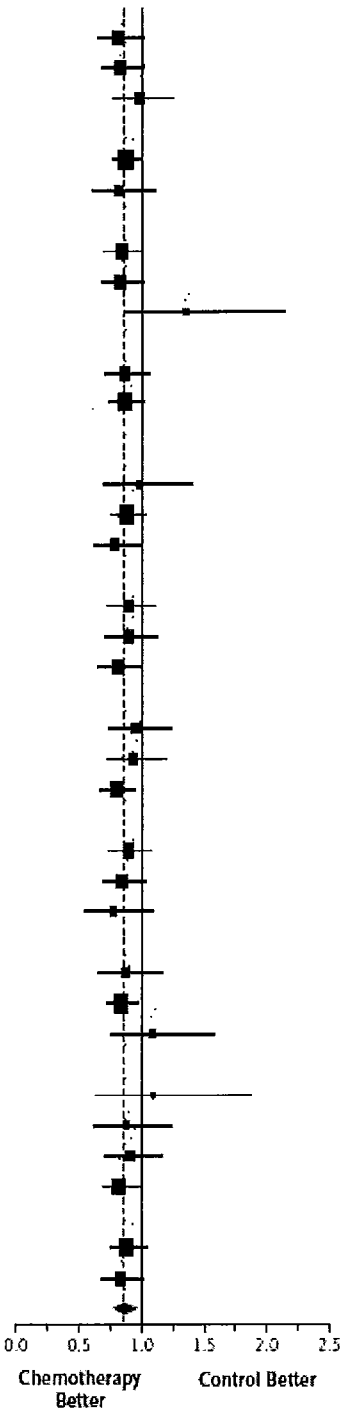

Figure 2. **Hazard Ratios (with 95 Percent Confidence Intervals) for Death in Prespecified Subgroups of Patients in the Chemotherapy Group, as Compared with Patients in the Control Group.**

WHO denotes World Health Organization.