

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of:

TA181; Pemetrexed for the first-line treatment of non-small-cell lung cancer,

TA190; Pemetrexed for the maintenance treatment of non-small-cell lung cancer,

TA192; Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer,

TA227; Erlotinib monotherapy for maintenance treatment of non-small-cell lung cancer,

TA258; Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer

Final recommendation post consultation

The guidance in TA181, TA190, TA192, TA227 and TA258 should be transferred to the 'static guidance list'. TA192 and TA258 should be flagged for further consideration of a review when the results of the LUX Lung 7 trial are available, currently anticipated to be in 2015. Should the clinical guideline for lung cancer (CG121) be updated, then these appraisals will be re-considered for review and removal from the static list.

1. Background

TA181 was published in September 2009. TA190 and TA192 were published in July 2010. TA227 was published in June 2011. TA258 was published in June 2012.

At the GE meeting of 30 September 2014 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance in TA181, TA190, TA192, TA227 and TA258 should be transferred to the 'static guidance list'. TA192 and TA258 should be flagged for further consideration of a review when the results of the LUX Lung 7 trial are available, currently anticipated to be in 2015. That we consult on this proposal.

3. Rationale for selecting this proposal

An independent Health Technology Assessment report has been published on first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer undertaken by the Liverpool Reviews and Implementation Group. The results were supportive of the evidence considered in the appraisal of pemetrexed (TA181), and provided updated results for the evidence considered in the appraisal of gefitinib (TA192).

Generic formulations have become available for gemcitabine, the comparator in TA181, which would be likely to impact on the cost-effectiveness of first-line pemetrexed, and therefore the current recommendation. However, the patent for pemetrexed is anticipated to expire shortly after any review would be undertaken. There is therefore limited value in undertaking a review of TA181, and it is appropriate for the guidance to be transferred to the 'static list'. There has been no new evidence identified which would impact on the recommendations in TA190 and TA227, and therefore it is appropriate to transfer the guidance to the 'static list'.

Since the publication of TA192 and TA258, tyrosine kinase inhibitors (TKIs) targeted specifically for EGFR-TK mutation-positive tumours have become established clinical practice. There is an ongoing clinical trial (LUX-lung 7 trial) comparing gefitinib with afatinib (another TKI which has recently been recommended by NICE). It is therefore considered appropriate to transfer TA192 and TA258 to the 'static guidance list', flagged for further consideration of a review when the results of the LUX-lung 7 trial report.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

<p>Respondent: British Thoracic Oncology Group</p> <p>Response to proposal: No objection</p> <p>BTOG does not have any objection for these existing guidance to move to the static list.</p>	<p>Comment from Technology Appraisals</p> <p>Comments noted. No action required.</p>
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<p>Respondent: Lilly</p> <p>Response to proposal: Agree</p> <p>We welcome the proposal to move the NICE TA181 and TA190 to the static list of technologies. We are not aware of any new clinical evidence which would suggest that a review of these appraisals would be beneficial.</p> <p>Please note the compound pemetrexed is protected by a supplementary protection certificate based on a compound patent. The supplementary protection certificate will expire in December 2015. There is, also, a UK patent to the vitamin dosage regimen for Alimta (expiring in 2021) which is the subject of pending litigation in the UK. See pages 18 and 19 of the attachment; Eli Lilly and Company's 10Q of Quarter 3 20141.</p> <p>As a point of clarification we would highlight that:</p> <ul style="list-style-type: none"> - deterministic incremental cost effectiveness ratios presented in the LRIG Report (20132) for pemetrexed/cisplatin were £26,175 when British National Formulary prices were employed and £37,608 when the Electronic Market Information Tool prices were used. The GE proposal paper quotes the conclusions of the LRIG report but does not clarify the 	<p>Comment from Technology Appraisals</p> <p>Comments noted.</p> <p>It is noted that there is pending litigation about the vitamin dosage regimen for pemetrexed, which may impact on the timing of the availability of generic pemetrexed. However, it is also noted that the most recent decision by the English High Court was that the patent for the vitamin dosage regimen for pemetrexed would not be infringed by the production of generic pemetrexed. Therefore, the current expected date from which generic pemetrexed should be made available in England, December 2015 (that is, the end date of the pemetrexed patent), is still valid at this time.</p> <p>The proposal paper is intended to provide a summary of the key evidence that may impact on the recommendations of the</p>
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<p>method used to reach these conclusions, which are based on the results of the probabilistic sensitivity analysis.</p> <p>References:</p> <ol style="list-style-type: none"> 1. Eli Lilly and Company Form 10Q. For The Quarter Ended September 30, 2014, available at https://investor.lilly.com/secfiling.cfm?filingID=59478-14-169 2. Brown T MG, Bagust A, Boland A, Oyee J, Tudur-Smith C, Blundell M, Lai M, Martin Saborido C, Greenhalgh J, Dundar Y, Dickson R,. Clinical and cost effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. Health Technology Assessment 2013;17(31) http://www.journalslibrary.nihr.ac.uk/hta/volume-17/issue-31#chapters/3 	<p>appraisals in this review. As such, it does not describe all studies in detail.</p>
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<p>Respondent: Pierre Fabre</p> <p>Response to proposal: Disagree (comments relate to TA181)</p> <p>Our recommendations relate to TA181: Pemetrexed for the first line treatment of NSCLC (published September 2009)</p> <p><i>Regarding the cost-effectiveness of pemetrexed with cisplatin</i></p> <p>Generic gemcitabine became available shortly after TA181 was issued. If, as the guidance recommended a re-review of the cost-effectiveness of pemetrexed-cisplatin had been undertaken at that time, the cost-effectiveness of pemetrexed-cisplatin would have been compromised and Lilly may have been asked to provide a patient access scheme (PAS), potentially saving the NHS a substantial sum over the past 5 years.</p> <p>Lilly have been successful in prolonging the patent cover for pemetrexed in the US and, we believe, are continuing to pursue patent extension in Europe despite initial failure. In light of this we would recommend that the cost-effectiveness of pemetrexed-cisplatin should proceed as intended.</p> <p>The recently published NAVo trial (Bennouna J et al 2014)¹ suggests that there may be valid</p>	<p>Comment from Technology Appraisals</p> <p>Comments noted. The aim of the proposal paper is to consider any evidence that has become available after the publication of the appraisals which may impact on the current recommendations.</p> <p>It is noted that there is pending litigation about the vitamin dosage regimen for pemetrexed, which may impact on the timing of the availability of generic pemetrexed. However, it is also noted that</p>
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alternatives to pemetrexed-cisplatin that could be included in any future cost-effectiveness evaluation of treatments of patients with non-squamous NSCLC.

the most recent decision by the English High Court was that the patent for the vitamin dosage regimen for pemetrexed would not be infringed by the production of generic pemetrexed. Therefore, the current expected date from which generic pemetrexed should be made available in England, December 2015 (that is, the end date of the pemetrexed patent), is still valid at this time. In addition, following the positive recommendation for pemetrexed in TA181, it has become a standard treatment option in England for the first line treatment of non-small cell lung cancer, replacing the standard of care comparator at the time of the original appraisal (gemcitabine plus cisplatin). Therefore, there is little value in undertaking a review of this appraisal at this time. Consultees are able to notify NICE at any time about significant new evidence influencing the clinical and cost effectiveness of the technologies included in this review, and new evidence can trigger a review of existing guidance irrespective of whether the guidance is on the static list.

Regarding pemetrexed-cisplatin as a 'standard of care'

NCE Guidance on first line pemetrexed-cisplatin which was based primarily on the results of

Pemetrexed has a marketing authorisation

a comparison of pemetrexed-cisplatin and gemcitabine-cisplatin, (Scagliotti GV et al2008)² recommends pemetrexed cisplatin as an option for first line treatment of patients with locally advanced or metastatic NSCLC only if the histology has been confirmed as adenocarcinoma or large-cell carcinoma. In the proposal paper presented to the Institute's Guidance Executive it is stated that since the positive recommendation in TA181 pemetrexed in combination with cisplatin has become the standard of care in first line NSCLC.

SACT data (<http://www.chemodataset.nhs.uk/home> - (Slides 44-45))³ clearly shows that the majority of pemetrexed is used not with cisplatin, but with carboplatin:

Top Regimens by Diagnostic Group: Lung (NSCLC) July 2013 to June 2014

- Carboplatin + pemetrexed: 2,498 cycles
- Cisplatin + pemetrexed: 2,028 cycles

Pemetrexed with carboplatin is therefore the accepted 'standard of care' in England but is neither licensed nor recommended by NICE, and is clearly being funded by NHS England.

Pemetrexed with carboplatin has been investigated in several large randomised first line studies (two of which are cited in your references) and has consistently failed to demonstrate an overall survival benefit in a population of patients with non-squamous histology when compared to third generation carboplatin combinations:

Study	n	Parameter	Pemetrexed arm	Comparator arm	p
Gronberg 2009 ⁴	248/ 436		Pemetrexed-carboplatin	Gemcitabine-carboplatin	
		Overall survival in non-squamous subgroup	7.8m	7.5m	.77
Rodrigues-Pereira 2011 ⁵	211		Pemetrexed-carboplatin	Docetaxel-carboplatin	
		Overall survival	14.9m	14.7m	.933

in combination with cisplatin for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology. NICE is only able to appraise a technology within its marketing authorisation.

Patel 2012 ⁶ (POINTBREAK)	939		Pemetrexed-carboplatin with pem+bev maintenance	Paclitaxel-carboplatin with bev maintenance	
		Overall survival*	12.6m	13.4m	.949
Zinner 2013 ⁷ (PRONOUNCE)	361		Pemetrexed-carboplatin with pem maintenance	Paclitaxel-carboplatin with bev maintenance	
		Overall survival	10.5m	11.7m	.615

In a recent letter to the Journal of Clinical Oncology following publication of the PARAMOUNT trial, Dr Nevin Murray of the University of British Columbia stated that since the publication of the results of the Scagliotti trial, “All prospective trials testing pemetrexed superiority for nonsquamous NSCLC have failed to confirm the hypothesis” (Murray N. J Clin Oncol 2014)⁸.

We would recommend, in light of the perceived NICE/NHS England endorsement of pemetrexed-carboplatin that the cost-effectiveness of pemetrexed with carboplatin be evaluated by NICE.

References:

1. Bannouna J et al. *Clin Lung Cancer* 2014; 15: 258-265
2. Scagliotti GV et al. *J Clin Oncol* 2008; 26: 3543- 3551
3. <http://www.chemodataset.nhs.uk/home> (Slides 44-45)
4. Gronberg BH et al. *J Clin Oncol* 2009; 27: 3217-3224
5. Rodrigues-Pereira J et al. *J Thorac Oncol* 2011; 6: 1907-1914
6. Patel J et al. *J Thorac Oncol* 2012; 7 (9 Suppl 4): S336
7. Zinner R et al. *J Clin Oncol* 2013; 31 (18 Proc ASCO Suppl): LBA8003 and ASCO presentation
8. Murray N. *J Clin Oncol* 2014; 32: 482-483

<p>Respondent: National Cancer Research Institute; Royal College of Physicians; Royal College of Radiologists; Association of Cancer Physicians</p> <p>Response to proposal: Agree</p> <p>The NCRI/RCP/RCR/ACP are content for the above NICE guidance to move to the static list.</p>	<p>Comment from Technology Appraisals</p> <p>Comments noted. No action required.</p>
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<p>Respondent: Roche Products</p> <p>Response to proposal: No objection</p> <p>Roche has no objections or further comment in regard to moving of these TAGs to the static list.</p>	<p>Comment from Technology Appraisals</p> <p>Comments noted. No action required.</p>
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Paper signed off by: Helen Knight, 27/11/2014

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