

National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG109 Pemetrexed plus cisplatin | Advice Document v1.0 | July 2023

Pemetrexed in combination with cisplatin as adjuvant treatment for patients with completely resected stage IIA to IIIA non-squamous, non-small-cell lung cancer.^{A, B}

NCMAG Decision | off-label use is **supported**

This advice applies only in the context of the NHSScotland national framework contract, delivering the cost-effectiveness results upon which the decision was based, or a national framework contract or list price that is equivalent or lower.

The generic product available at the lowest acquisition cost should be prescribed.

^A NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

^BAs per TNM v8

Decision rationale

After consideration of all the available evidence regarding the benefits and risks, the Council were satisfied that the case had been made for the clinical and cost effectiveness of pemetrexed in combination with cisplatin.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	Clinicians treating lung cancer groups from across NHSScotland regional cancer networks.
Medicine Names	Pemetrexed plus cisplatin
Cancer type	Non-squamous, non-small-cell lung cancer (NSCLC)
Proposed off-label use ^B	Adjuvant treatment for patients with completely resected stage IIA to IIIA nonsquamous NSCLC.
Medicine Details	<u>Form</u> : Intravenous (IV)

	<p><u>Dose:</u> pemetrexed 500mg/m² body surface area (BSA) IV every 3 weeks for 4 cycles (plus supportive medicines) and cisplatin 75mg/m² BSA IV on day one, every 3 weeks (one cycle) for 4 cycles.</p>
<p>Advice Eligibility Criteria</p>	<ul style="list-style-type: none"> • Stage IIA to IIIA nonsquamous non small cell lung cancer. • Complete surgical resection (R0 resection). • Performance status 0 or 1.

^B pemetrexed has marketing authorisation as a single agent or in combination for:

- First line treatment of unresectable malignant pleural mesothelioma.
- The first line treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology.
- Maintenance treatment of locally advanced or metastatic NSCLC other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.
- Second line treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology.

1. Current Management Context

Non-Small Cell Lung Cancer incidence, prognosis and symptoms.

Lung cancer is the most common type of cancer in Scotland with 5,476 diagnoses of lung cancer in 2021¹. There are two main types of lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Approximately 85% of all lung cancers are NSCLC, of which approximately 70% are non-squamous^{2, 3}. The median age of diagnosis for NSCLC is reported as 73 years of age⁴.

About 20% of lung cancers are diagnosed as stage I, 7% as stage II, 20% as stage III, 46% as stage IV with 6% unknown stage. The 5-year survival rates for stages I, II, and III diseases are reported as 63%, 41%, and 16%, respectively⁵. Symptoms of lung cancer include cough, bloody sputum, chest pain, fatigue and weight loss.

Guidelines supporting adjuvant chemotherapy

Adjuvant chemotherapy has been shown to offer a survival benefit over observation for NSCLC⁶. Both SIGN and NICE recommend post-operative platinum chemotherapy in patients with completely resected NSCLC (stage II to IIIA disease)^{7, 8}.

Both the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) recommend that adjuvant chemotherapy should be offered to patients with resected stage IIB and IIIA NSCLC and can be considered for patients with stage IIA (T2bN0) resected primary tumours larger than 4 cm⁹. ESMO considers cisplatin and vinorelbine as the most studied regimen, but alternatives like cisplatin in combination with gemcitabine, or docetaxel or pemetrexed are also possible alternatives.

Recent changes to the treatment landscape

Patients whose Programmed death-ligand 1 (PDL-1) tumour expression is greater than 50% are eligible for immunotherapy if they have not progressed on adjuvant platinum-based chemotherapy¹⁰. In patients with the specific epidermal growth factor receptor (EGFR) exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations then osimertinib is an option post-surgery with or without adjuvant chemotherapy¹¹.

Pharmacology of pemetrexed

Pemetrexed is a cytotoxic drug that targets multiple pathways involved in folate synthesis. Folate is essential for both protein and DNA synthesis. Inhibition of these processes results in cancer cell death. Co-administration of Vitamin B12 and low-dose folic acid is required to minimise side effects.

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were pemetrexed, 'non-small-cell lung cancer', adjuvant, resected and non-squamous. No filters were applied to limit the

retrieval by study type. Titles and abstracts were screened by one reviewer with decisions cross-checked (~10% of titles) with another reviewer. The included publications were critically appraised using the Cochrane risk of bias 2.0 tool.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

Evidence comparing pemetrexed plus cisplatin versus vinorelbine plus cisplatin

The key evidence relevant to the proposal using pemetrexed in combination with cisplatin in patients with completely resected pathologic stage II-IIIa non-squamous NSCLC comes from the 'Japan Intergroup Trial of Pemetrexed Adjuvant Chemotherapy for Completely Resected Non-squamous NSCLC' (JIPANG¹²) study and the 'Trial on Refinement of Early-Stage NSCLC Adjuvant Chemotherapy' (TREAT¹³) study.

JIPANG is a phase III randomised, multicentre, open-label study conducted at 50 institutions in Japan¹², while TREAT is a phase II randomised, multicentre, open label study at 16 sites across Germany and Belgium¹³. The JIPANG study includes patients with completely resected pathologic stage II-IIIa non-squamous NSCLC (Union for International Cancer Control TNM classification, version 7)¹²; the TREAT study included a wider population than JIPANG, including patients with stage IB and with squamous pathologies¹³ (Union for International Cancer Control TNM classification, version 6). The TNM IB disease classification underwent a change from version 6 to version 7 resulting in more patients being staged as IIA rather than IB under TNM version 6.

The JIPANG study included patients (n=784) aged 20-75 years with ECOG performance status of 0 or 1, and adequate haematologic and organ function¹². The TREAT study included patients (n=132) aged 18-75 years, with a Karnofsky Performance Status 80% or greater or ECOG 0 or 1¹². Patients in both trials were randomly assigned to receive IV vinorelbine (25 mg/m² BSA, days 1 and 8) plus cisplatin (80 mg/m² BSA, day 1) (vinorelbine regimen) or pemetrexed (500 mg/m² of body surface area (BSA), day 1) plus cisplatin (75 mg/m² BSA, day 1) (pemetrexed regimen)^{12, 13}.

The primary endpoint in JIPANG was initially overall survival (OS), however this was changed during the study to recurrence-free survival (RFS) (time from randomisation to disease recurrence or death, whichever occurred first), due to too few deaths to evaluate survival at follow-up¹². The primary endpoint in the TREAT study is the clinical feasibility rate (dose limiting toxicity is not observed, no non-acceptance by the patient leading to premature withdrawal, and no death due to cancer or cancer therapy); time to treatment failure and RFS are considered as secondary outcomes in the TREAT study¹³. Recurrence-free survival is considered an appropriate outcome in the adjuvant settings after definitive surgery and where survival may be prolonged.

In the JIPANG study, patient characteristics were well balanced, the majority of patients had adenocarcinoma histology (752 [96%] of 784 eligible patients). The median age of patients receiving the vinorelbine regimen was 65 years old (IQR; 58 to 69) and 64 years old (IQR; 57 to 67) for patients receiving the pemetrexed regimen. In JIPANG approximately 34% of study patients were reported as stage IIA and approximately 52% as stage IIIA¹². The TREAT study included both squamous (43%) and

non-squamous (57%) histology, TREAT provided baseline characteristics for the overall populations, which were well balanced, however, they did not take into consideration the histological subtype. In TREAT 37% of patients were reported as stage IB with the majority being stage IIB (46%)¹³.

Following an updated median follow-up of 72.2 months (IQR, 71.3 to 77.0 months), presented at ESMO congress 2022, the JIPANG study, failed to show superiority for the pemetrexed regimen, however there was similar efficacy between the treatment arms for the primary outcome. Disease recurrence or death was reported in 236 patients (60%) assigned to vinorelbine regimen and 220 patients (56%) assigned to pemetrexed regimen. Median RFS was similar; 37.5 months for vinorelbine regimen and 43.4 months for pemetrexed regimen (HR [95%CI] 0.95 [0.79 to 1.14]). Overall survival data are immature with approximately 30% of patients in each treatment arm having died at the time of analysis (Table 1)¹⁴.

Similar to the JIPANG study, the TREAT study, with a mean follow up of 34.1 months (range 1.2 to 58.3) found similar 3-year RFS (60% vinorelbine versus 59% pemetrexed). There were also similar death rates for both treatment arms (vinorelbine regimen 26% versus pemetrexed regimen 27%). Overall survival did not differ between the groups with similar 3-year survival rates reported between treatment arms (Table 1)¹³.

Table 1: Results of key studies

	JIPANG ¹²		TREAT ¹³	
	Cisplatin vinorelbine	Cisplatin pemetrexed	Cisplatin vinorelbine	Cisplatin pemetrexed
Feasibility Rate	-	-	75%	95%
RFS Median (95% CI)	37.5 (29 to 53)	43.4 (29 to 60)	-	-
RFS HR (95% CI)	0.95 (0.79 to 1.14)		-	
Median OS	NR	NR	59 months	-
3Y OS (95% CI)	84% (80 to 87)	87% (83 to 90)	77%	75%
5Y OS (95% CI)	76% (71 to 80)	75% (70 to 79)		
3Y RFS (95% CI)	51% (50 to 75)	52% (47 to 56)	60%	59%
5Y RFS (95% CI)	43% (38 to 48)	45% (40 to 50)		

Key: CI= confidence interval, NR= not reached, OS= overall survival, RFS= relapse free survival

Subgroup analyses in the JIPANG study, from an earlier follow up of 45.2 months included sex, age, pathologic stage, histology, EGFR mutation and performance status, which were broadly consistent with the results for RFS in the overall study group. However, subgroup comparisons are less robust and need to be interpreted with caution, particularly those based on very small sample size¹². In the TREAT study, consistent efficacy was found in OS and RFS across subgroups for stage Ib or histology subtypes.

Patient reported outcomes

Patient-reported outcomes including quality-of-life were not evaluated in any of the studies.

Safety evidence

In the JIPANG study the rate of completion of the planned four cycles of treatment was 73% for the vinorelbine regimen and 88% for the pemetrexed regimen¹². The rates of grade 3 or higher AE were 89% for the vinorelbine regimen and 47% for the pemetrexed regimen arms. The following grade 3 to 4

toxicities were reported more frequently for the vinorelbine regimen: febrile neutropenia (12% v 0.3%), neutropenia (81% v 23%), and anaemia (9.3% v 2.8%)¹². In TREAT the median number of cycles completed was greater in the pemetrexed regimen (3.6 cycles) compared to the vinorelbine regimen (2.7 cycles). There was a higher proportion of patients with grade 3/4 haematologic toxicity in the vinorelbine regimen (78%) compared to the pemetrexed regimen (10%). Similar to the JIPANG study, increased grade 3/4 haematologic toxicities were seen for the vinorelbine regimen versus the pemetrexed regimen: neutropenia (69% versus 9%), febrile neutropenia (8% versus 1%) and anaemia (1% versus 0%)¹³.

Quality assessment of clinical evidence

The key evidence from the JIPANG and TREAT studies were phase III and II respectively, both were randomised, multicentre open label studies. Overall, the included studies were assessed to have low risk of bias (RoB). Randomisation was completed using automated systems, thus limiting the risk of selection bias. In addition, as both trials used an open label design, they are at risk of outcome detection bias for subjective outcomes.

Clinical effectiveness considerations

Two studies concluded there is similar efficacy in relapse-free survival between the pemetrexed and vinorelbine regimens.

The JIPANG study found similar efficacy in five-year RFS between the vinorelbine and pemetrexed regimens (43% versus 45%). Additionally, the TREAT study found similar efficacy for 3-year RFS between the vinorelbine and pemetrexed regimens (60% versus 59%).

Median OS has not been reached in either arm in the JIPANG study. The 5-year OS rate was high, at 75.6% for vinorelbine and 75.0% for pemetrexed. It should be noted that the survival rate for lung cancer is generally higher in Japan compared to the UK¹⁵.

Pemetrexed is associated with fewer side effects, less hospital visits and a higher completion rate than the vinorelbine regimen.

In the JIPANG study, the rates of grade 3 or higher adverse events (AE) were 89% for the vinorelbine regimen and 47% for the pemetrexed regimen arms. Febrile neutropenia, which necessitates hospital admission, occurred in 12% of the vinorelbine arm and only 0.3% in the pemetrexed arm. The TREAT study also reported higher rates of AE in the vinorelbine arm. Quality-of-life data were not captured in either the JIPANG or TREAT studies. However, the lower rates of significant AE observed in the pemetrexed arm suggest that pemetrexed is likely to be associated with a better quality-of-life.

Additionally, the pemetrexed regimen requires one fewer day-case or clinic visit for treatment administration in each 21-day cycle compared to the vinorelbine regimen.

In the JIPANG study, the rate of completion of the planned cycles was higher (88%) for the pemetrexed regimen versus the vinorelbine regimen (73%). In the TREAT study, the clinical feasibility rate was higher for the pemetrexed regimen (95%) versus the vinorelbine regimen (75%).

JIPANG is likely generalisable to patients treated in Scotland.

The proposed patient population is performance status 0 to 1 with aligns to the JIPANG study. The median age of patients in the JIPANG study was 65 years¹². The median age was not provided in the smaller TREAT study¹³. The median age of NSCLC diagnosis in England is 73 years; there are no readily available age data in Scotland. However, only 41% of patients in Scotland receive Systemic Anti-Cancer Therapy (SACT) for NSCLC¹⁸. The proposal suggests that treatment should only be offered to patients where a 5% improvement in absolute OS is expected. Typically, these would be patients who are younger, have fewer co-morbidities and better performance status. JIPANG did not find a statistical difference in RFS or OS between vinorelbine and pemetrexed regimens for patients ≥ 70 or < 70 years of age¹². Taken together this suggests that the age of patients in the JIPANG study is likely generalisable to those treated in Scotland.

There is no direct evidence for pemetrexed regimen efficacy in Stage IIA disease with tumour size >4 cm ≤ 5 cm.

The classification system for lung cancer has changed over time and is different now than when patients were recruited to the JIPANG and TREAT studies. As a result, the group of patients with Stage IIA disease and tumour size between 4 and 5cm is not represented in the clinical trials. However, The TREAT study (which included squamous cell patients) found no statistical difference in RFS or OS for patients with TNM v6 stage IB disease whose tumour size was either less than 4 cm or greater than or equal to 4 cm. Whilst not direct evidence, this provides some reassurance that the JIPANG and TREAT study results may be generalisable to patients with stage IIA disease and a tumour size larger than 4cm.

There is uncertainty on the generalisability of subsequent treatments to the Scottish population.

Neither JIPANG nor TREAT provided detail on subsequent treatments, or whether these were balanced between both arms. Treatment at relapse may vary between Japan, Belgium, and Germany. Access to different regimens, compared to Scotland, may have affected OS results. This may reduce the generalisability of the results to Scottish practice.

4. Patient group summary

Two patient group partner statements were received from the Roy Castle Lung Foundation and the Scottish Lung Cancer Nurse Forum, the key points are summarised below:

- Non-small cell lung cancer can have a significant impact on patients' quality of life.
- There is increased patient interest in adjuvant treatment options offered as evidenced by an increase in calls to helplines.
- The introduction of the pemetrexed regimen may reduce clinic visits and have a more tolerable adverse event profile.
- **In summary** | non-small cell lung cancer can place a significant burden on patients and their families' quality of life, therefore it is important to have a range of highly effective treatments available, and the patient groups state that the pemetrexed regimen may provide a more tolerable option to current therapy and improve patient outcomes and quality of life.

5. Benefit-risk balance

This proposal is for off-label use of pemetrexed in combination with cisplatin for completely resected non-squamous early-stage NSCLC. Two randomised controlled trials, one phase III and one phase II, comparing the pemetrexed regimen with the current standard of care, vinorelbine regimen, report similar efficacy for relapse free and overall survival. Compared with the current standard of care vinorelbine regimen, the pemetrexed regimen was associated with fewer AE (in JIPANG grade 3 or higher AEs were 47% versus 89%), a higher completion rate (88% versus 73%), fewer routine hospital visits for administration and likely fewer unplanned admissions for management of AEs compared to vinorelbine. The evidence is likely generalisable to the proposed Scottish population.

6. Council Review | Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were satisfied with the clinical effectiveness case for pemetrexed plus cisplatin in the proposed population.

7. Economic Evidence Review Summary

Economic Overview

Type of economic evaluation

No published economic evaluations were identified in the literature search. Based on the similar treatment efficacy demonstrated in the key JIPANG study, and the TREAT study, a de-novo cost minimisation analysis was performed ^{12, 13}.

Population, intervention, comparator and outcomes

The population was fully resected non-squamous NSCLC (stages IIA– IIIA) patients. The intervention was pemetrexed (500mg/m² BSA, day 1) and cisplatin (75mg/m² BSA, day 1). The comparators were IV vinorelbine (25mg/m² BSA days 1 and 8) and cisplatin (80mg/m² BSA day 1), and oral vinorelbine (60mg/m² BSA days 1 and 8) and cisplatin (80mg/m² BSA day 1). All treatments were administered in 3-week cycles for a total of 4 cycles. As a cost-minimisation analysis was performed, quality-adjusted life-years (QALYS) were not required in the analysis. Adverse events for febrile neutropenia, neutropenia and anaemia were included as these were identified as statistically significant in the JIPANG study¹² and are likely to lead to hospitalisation costs.

Costs

The cost-minimisation analysis included medicine acquisition, administration and AE costs. Both intravenous and oral methods of administration were considered for vinorelbine. Cost results were calculated for the total treatment duration of 4 cycles. A 1.8m² BSA was assumed. Due to the short treatment durations, costs were not discounted.

Key results

These results include medicine acquisition, administration and AE costs.

IV vinorelbine: Compared to IV vinorelbine and cisplatin, pemetrexed and cisplatin was estimated to lead to cost-increases of £221 (BNF list prices) per patient. When using national framework prices, the pemetrexed regimen was estimated to produce per patient cost savings.

Oral vinorelbine: Compared to oral vinorelbine and cisplatin, pemetrexed and cisplatin was estimated to lead to cost-increases of £1,690 (BNF list prices) per patient. When using national framework prices, the pemetrexed regimen was estimated to produce per patient cost savings.

Cost-effectiveness considerations

Generalisability of results

The dosing of the vinorelbine and cisplatin regimens was consistent with NHSScotland SACT protocols. Pemetrexed and cisplatin dosing was consistent with the proposed use.

NHSScotland national framework contract prices were considered in confidence.

Limitations

There were no published economic evaluations comparing the treatment regimens. Due to this, there is uncertainty in the conclusions of this analysis, as there are no cost-effectiveness or cost-minimisation analysis results available for comparative framing.

The de-novo cost-minimisation analysis was based on an assumption of similar treatment efficacy of the pemetrexed and vinorelbine regimens, as reported in JIPANG and TREAT. If long-term outcomes showed divergence, the conclusions drawn from the de-novo analysis would be increasingly limited.

There were no quality-of-life data to support the use of a cost-minimisation analysis, as these were not collected in either the JIPANG or TREAT studies. However, both studies highlighted improved AE profiles for the pemetrexed regimen compared to the IV vinorelbine regimen, providing indicative evidence that quality-of-life may be improved with the pemetrexed regimen.

The key JIPANG study reported completion rates for the two regimens (88% for pemetrexed and cisplatin; 73% for IV vinorelbine and cisplatin)¹². If generalisable to practice, the higher rate of completion for pemetrexed and cisplatin would likely increase costs beyond those reported in the key results. If applying these completion rates, the pemetrexed regimen would lead to cost increases of £1,256 (BNF list prices) (cost savings using national framework prices) per patient compared to the vinorelbine (IV) regimen, and lead to cost increases of £2,326 (BNF list prices) (cost savings using national framework prices) per patient compared to the vinorelbine (oral) regimen.

Summary

The cost-minimisation analysis provided suitably robust results of relevance to the proposal. These are likely to be generalisable to NHSScotland. The outlined limitations should be considered when interpreting the results.

8. Council review | Cost-effectiveness evaluation

After considering all the available evidence, the Council were satisfied that the case for cost effectiveness had been made for the generic product based on NHSScotland national framework contract pricing.

9. Service Impact

The pemetrexed regimen results in a 50% reduction in clinic visits and blood sampling (four less clinic reviews and four less blood samples) per patient compared to the vinorelbine regimen. Trial and Scottish audit data suggest that completion rates are approximately 15% higher with the pemetrexed regimen, however even when these increased visits are accounted for, pemetrexed is associated with substantially fewer visits for treatment administration than vinorelbine regimens. The pemetrexed regimen is associated with less toxicity, particularly febrile neutropenia, which would normally require hospital admission for intravenous antibiotics.

10. Budget Impact

NCMAG is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the national framework contract pricing.

11. Acknowledgements

NCMAG would like to acknowledge the patient group partners, the Roy Castle Lung Foundation and The Scottish Lung Cancer Nurses Forum for their valuable input.

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by