Pemetrexed as maintenance therapy for advanced, non-squamous, non-small cell lung cancer (NSCLC)

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Norwegian Knowledge Centre for the Health Services

Background: About 2 600 new cases of lung cancer are diagnosed each year in Norway, of which 80% are classified as non-small cell lung cancer (NSCLC). Of these, about 75% have locally advanced or metastatic disease at the time of diagnosis. Palliative chemotherapy is the standard treatment for patients in NSCLC stages IIIB-IV who cannot receive curative treatment and whose performance status is good (PS 0-2). The five-year survival rate for patients in these stages is low at about 1%. • Pemetrexed disodium (Alimta®) has marketing authorisation in Norway for the maintenance treatment of locally advanced or metastatic NSCLC other than pre-dominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. • This health technology assessment (HTA) includes a systematic review of the efficacy and safety of pemetrexed given in addition to best supportive care for the maintenance treatment of patients with NSCLC. It also incorporates an economic evaluation of this intervention compared to a strategy of watchful waiting plus best supportive care. **Main findings:** • One clinical trial

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(continued from page one) was included in the systematic review, the quality and risk of bias of which was assessed to be moderate and low, respectively. The rate of adverse events associated with pemetrexed was low. • In a sub-group analysis of the non-squamous patient population, the pemetrexed group showed an improved median overall survival compared to the placebo group of 5.2 months (15.5 months vs. 10.3 months, HR 0.70 CI 0.56 to 0.88). • The economic analysis was based on a Markov model with a time-horizon of six years. The analysis resulted in a cost per quality-adjusted life year and life year gained of approximately NOK 770 000 and NOK 425 000, respectively. • Whether maintenance treatment with pemetrexed compared to watchful waiting is to be considered cost-effective depends on whether the threshold of NOK 500 000 is applied to QALYs gained, in which case it most likely is not, or life years gained, in which case it most likely is. • The results are associated with uncertainty as they are based on the efficacy data of a sub-population analysis from only one clinical trial.

Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, June, 2012

Key messages

About 2 600 new cases of lung cancer are diagnosed each year in Norway, of which 80% are classified as non-small cell lung cancer (NSCLC). Of these, about 75% have locally advanced or metastatic disease at the time of diagnosis. Palliative chemotherapy is the standard treatment for patients in NSCLC stages IIIB-IV who cannot receive curative treatment and whose performance status is good (PS 0-2). The five-year survival rate for patients in these stages is low at about 1%.

Pemetrexed disodium (Alimta®) has marketing authorisation in Norway for the 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.

This health technology assessment (HTA) includes a systematic review of the efficacy and safety of pemetrexed given in addition to best supportive care for the maintenance treatment of patients with NSCLC. It also incorporates an economic evaluation of this intervention compared to a strategy of watchful waiting plus best supportive care.

- One clinical trial was included in the systematic review, the quality and risk of bias of which was assessed to be moderate and low, respectively. The rate of adverse events associated with pemetrexed was low.
- In a sub-group analysis of the non-squamous patient population, the pemetrexed group showed an improved median overall survival compared to the placebo group of 5.2 months (15.5 months vs. 10.3 months, HR 0.70 CI 0.56 to 0.88).
- The economic analysis was based on a Markov model with a time-horizon of six years. The analysis resulted in a cost per quality-adjusted life year and life year gained of approximately NOK 770 000 and NOK 425 000, respectively.
- |Whether maintenance treatment with pemetrexed compared to watchful waiting is to be considered cost-effective depends on whether the threshold of NOK 500 000 is applied to QALYs gained, in which case it most likely is not, or life years gained, in which case it most likely is.
- The results are associated with uncertainty as they are based on the efficacy data of a sub-population analysis from only one clinical trial.

Executive summary

BACKGROUND

Lung cancer is one of the most common cancers in the world and is one of the leading causes of cancer mortality In Norway, the disease is the second most common cancer among men and the third among women. About 2 600 new cases of lung cancer are diagnosed each year in Norway of which approximately 80% of lung cancer cases are classified as non-small cell lung cancer (NSCLC). Of these, about 75% have locally advanced or metastatic disease at the time of diagnosis. The main types of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell carcinoma. Although NSCLCs are associated with cigarette smoking in about 90% of patients, adenocarcinomas may also be found in patients who have never smoked. Patients in early and localized stages of NSCLC can be cured by surgery, often in combination with chemotherapy and sometimes radiotherapy. There are patients with local advanced NSCLC (stages IIIA and IIIB) who may receive curative treatment. Resection surgery may be appropriate for a few (stage IIIA) and curative radiotherapy for others (stage IIIB). Poor lung function, large tumour volume, poor performance status and other factors serve to explain why many patients are not candidates for curative treatment. Such patients are offered palliative chemotherapy and/or palliative radiotherapy. Palliative chemotherapy is the standard treatment for patients in stages IIIB-IV who cannot receive curative treatment and whose performance status is good (PS 0-2). The five-year survival rate for these patients is low at about 1%.

Pemetrexed disodium (Alimta®) has marketing authorisation in Norway for the 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. It is estimated that approximately 100-200 patients will be eligible for maintenance treatment with pemetrexed in Norway annually

EVALUATION OF CLINICAL DOCUMENTATION

We performed a systematic search for literature in the following databases:
- The Cochrane Library; CENTRAL, NHS EED
- Centre for Reviews and Dissemination (CRD); NHS EED

- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to present
- EMBASE (Ovid) 1980 to present

Inclusion criteria
Population: Patients with non small cell lung cancer (NSCLC)
Comparator: Watchful waiting, standard care
Outcomes: Overall survival, progression free survival, disease control rate, adverse events and quality of life.

Two reviewers independently identified studies for inclusion and assessed the quality of the documentation. We identified 395 titles in the search for literature. Of, these, 13 titles were found to be potentially relevant and full text copies were reviewed. Finally, only one study was found that met the pre-specified inclusion criteria. The included study was a phase III multicentre, double-blinded randomized controlled trial (JMEN study) published by Ciuleanu *et al.* 2009. The study investigated the clinical usefulness of maintenance treatment with pemetrexed compared to best supportive care for locally advanced or metastatic NSCLC. We assessed the risk of bias in the study as low. Median progression-free survival was significantly longer with pemetrexed (4.3 months) compared with placebo (2.6 months), HR 0.50 (CI 0.42 to 0.61, P <0.0001). Safety data demonstrated that patients in the pemetrexed group had statistically significantly higher rates of grade 3 and 4 toxicity. Both fatigue and neutropenia were higher in the pemetrexed group, and more patients in the pemetrexed group received transfusions and erythropoiesis stimulating agents. No pemetrexed-related deaths occurred. Generally, pemetrexed was well tolerated.

In a subgroup analysis of the 326 patients with non-squamous NSCLC who received pemetrexed and the 156 patients with non-squamous NSCLC who received placebo, the median progression-free survival was significantly longer with pemetrexed (4.7 months) compared with placebo (2.6 months), HR 0.47 (CI 0.37-0.6). The pemetrexed group showed an improved median overall survival compared to the placebo group of 5.2 months (15.5 months vs. 10.3 months, HR 0.70 (CI 0.56 to 0.88). The safety profile of pemetrexed recorded within histological subgroups was consistent with the safety profile noted for the overall study population. The quality-assessment tool GRADE was used to assess the quality of the evidence for each outcome, which was determined to be of a moderate quality (with the exception of the adverse events data), meaning that we have moderate confidence in the results.

ECONOMIC EVALUATION

We performed a cost-utility analysis (CUA) in which relevant costs and effects were expressed in Norwegian kroner (NOK) in 2011-prices and quality-adjusted life years gained (QALYs) respectively. Effects were also calculated in the form of life years

gained (LYG). The analysis was carried out from a health care provider perspective and both costs and effects were discounted at an annual discount rate of 4% according to Norwegian guidelines. We designed a model of the Markov type, with a six-year time horizon and a cycle length of three weeks. Efficacy data in the form of time-to-event data for overall and progression-free survival for patients with non-squamous NSCLC were provided by Eli Lilly, the proprietor company. Costs were estimated on the basis of Norwegian sources.

In the absence of an explicit threshold value for cost-effective interventions in Norway, we used NOK 500 000 per QALY gained as a threshold value since it has been suggested by the Norwegian Directorate of Health as a possible temporary estimate The results indicate that pemetrexed + BSC is associated with an incremental cost of approximately 190 000 NOK , 0.25 QALYs gained and 0.44 life years gained compared to BSC alone for an average patient. The ICER for a QALY gained was thus approximately NOK 770 000 which is clearly above the NOK 500 000 threshold mentioned above. There is no recommended threshold level with regard to cost per life year gained in the health sector in Norway. If the NOK 500 000 were to apply, the ICER for a life year gained of approximately 425 000 would be within the acceptable range. Sensitivity analyses showed that even though there is a great deal of uncertainty regarding health related quality of life data and the cost of best supportive care, these variables had only a marginal impact on the results. The results were most sensitive to variation in efficacy in terms of overall survival and in the cost of pemetrexed.

CONCLUSION

Maintenance treatment with pemetrexed and best supportive care seems to be well tolerated, and leads to an increase in median overall and progression-free survival compared to a regimen of BSC alone, especially in non-squamous NSCLC. Compared to a strategy of watchful waiting and best supportive care, the intervention involves a cost per quality-adjusted life year gained and life year gained of approximately NOK 770 000 and NOK 425 000, respectively. Whether the maintenance treatment with pemetrexed compared to watchful waiting is to be considered cost-effective depends on whether the threshold of NOK 500 000 is applied to QALYs gained, in which case it most likely is not, or life years gained in which case it most likely is.

The results are associated with uncertainty as they are based on the efficacy data of a sub-population analysis from only one clinical trial.

Hovedfunn

Omtrent 2 600 nye tilfeller av lungekreft blir diagnostisert hvert år i Norge, hvorav 80 % blir klassifisert som ikke-småcellet (NSCLC). Av disse får 75 % påvist lokalavansert eller metastatisk sykdom ved diagnosetidspunktet. Det finnes pasienter med lokalavansert sykdom (stadium IIIA og IIIB) som kan motta kurativ behandling. Imidlertid er lindrende cellegiftbehandling vanligst for pasienter i stadium IIIB-IV som ikke kan motta kurativ behandling men som har en god tilstand målt som "performance status". Femårsoverlevelse for denne gruppen er lav, på omtrent 1 %. Pemetrexed disodium (Alimta®) har markedsføringstillatelse for vedlikeholdsbehandling av lokalavansert eller metastatisk NSCLC av typen ikke-plateepitel (ikke-skvamøs) cellehistologi hos pasienter hvis sykdom ikke har forverret seg umiddelbart etter forstelinjebehandling med platineumbasert kjemoterapi.

Denne HTA-rapporten omfatter en systematisk oversikt av litteratur om effekt og sikkerhet knyttet til bruk av pemetrexed sammen med støttebehandling som vedlikeholdsbehandling for pasienter med ikke-plateepitel NCSCLC. Den inneholder også en økonomisk evaluering av dette tiltaket sammenlignet med en strategi der kun støttebehandling blir gitt før pasientene gis andrelinjebehandling.

- En klinisk studie ble inkludert i den systematiske oversikten, der kvaliteten på utfallsmålene ble vurdert til å være moderate og risikoen for systematiske skjevheter lav. Forekomsten av bivirkninger knyttet til pemetrexed var lav.
- I en subgruppeanalyse av pasientene uten plateepitelkarsinom (pasienter med ikke-plateepitel NSCLC) viste pemetrexed-gruppen en bedring i median total overlevelse i forhold til placebogruppen på 5.2 måneder (15,5 måneder vs. 10,3 måneder, HR 0.70 CI 0.56 to 0.88).
- Den økonomiske analysen var basert på en Markov modell med en tidshorisont på seks år. Analysens resulterte i en kostnad per vunnet QALY og leveår på henholdsvis NOK 770 000 og NOK 425 000.
- Hvorvidt vedlikeholdsbehandling med pemetrexed og støttebehandling sammenlignet med støttebehandling alene kan regnes som kostnadseffektivt avhenger av om terskelen på NOK 500 000 skal gjelde for vunne kvalitetsjusterte leveår – som innebærer at den mest sannsynligvis ikke er det – eller vunne leveår, som tilsier at den mest sannsynligvis er det.
- Resultatene må tolkes med forsiktighet siden de er basert på en subgruppeanalyse fra kun en klinisk studie.

Sammendrag

BAKGRUNN

Lungekreft er en av de mest vanlige krefttypene i verden og er den ledende årsak til kreftdødelighet i Norge Sykdommen er den nest mest vanlige krefttypen blant menn og den tredje mest vanlige blant kvinner. Omtrent 2 600 nye tilfeller av lungekreft blir diagnostisert i Norge hvert år, hvorav ca. 80 % blir klassifisert som ikke-småcellet (non-small cell lung cancer NSCLC). Av disse har omtrent 75 % lokalavansert eller metastatisk sykdom ved diagnosetidspunktet. Hovedtypene av NSCLC er plateepitelkarsinom (skvamøs karsinom). adenokarsinom og storcellet karsinom. Selv om NSCLC er forbundet med røyking i omtrent 90 % av tilfellene kan en finne adenokarsiomer hos pasienter som aldri har røykt. Pasienter i tidlig eller lokalt stadium av NSCLC kan bli kurert med kirurgi, ofte i kombinasjon med kjemoterapi og av og til strålig. Det finnes også pasienter med lokalavanasert NSCLC (stadium IIIA og IIIB) som kan motta kurativ behandling. Reseksjonskirurgi kan være aktuelt for noen få pasienter (stadium IIIA) og kurativ strålebehandling for andre (stadium IIIB). Svekket lungefunksjon, stort tumorvolum, dårlig performance status og andre faktorer er med på å forklare hvorfor mange pasienter ikke er kandidater for kurativ behandling. Slike pasienter blir tilbudt palliativ kjemoterapi og/eller palliativ stråling. Palliativ kjemoterapi er den vanligste behandlingen for pasienter I stadium IIIB-IV som ikke kan motta kurativ behandling og hvis pasientens tilstand (performance status) er god (0-2). Femårsoverlevelsesrate for disse pasientene er lav, på rundt 1 %.

Pemetrexed disodium (Alimta®) har markedsføringstillatelse for vedlikeholdsbehandling av lokalavansert eller metastatisk NSCLC av typen ikke-plateepitel (ikke-skvamøs) cellehistologi hos pasienter hvis sykdom ikke har forverret seg umiddelbart etter forstelinjebehandling med platineumbasert kjemoterapi. Det anslås at mellom 100 og 200 pasienter kan være aktuelle for denne type behandling med pemetrexed i Norge hvert år.

EVALUERING AV KLINISK DOKUMENTASJON

Vi utførte et systematisk søk etter litteratur I følgende databaser:

- The Cochrane Library; CENTRAL, NHS EED
- Centre for Reviews and Dissemination (CRD); NHS EED
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to present
- EMBASE (Ovid) 1980 to present

Inklusjonskriterier

Populasjon: Pasienter med ikke-småcellet lungekreft (non small cell lung cancer, NSCLC)

Intervensjon: Vedlikeholdsbehandling med pemetrexed

Komparator: "Watchful waiting" (ekspektans), standardbehandling

Utfall: Total overlevelse, progresjonsfri overlevelse, sykdomskontrollrate, bivirkninger og livskvalitet.

To forskere identifiserte studier uavhengig av hverandre og vurderte kvaliteten på dokumentasjonen. Vi identifiserte 395 titler i litteratursøket. Av disse ble 13 titler vurdert til å være potensielt relevante slik at fulltekstversjoner ble gjennomgått. Til slutt viste det seg at det bare en studie som tilfredstilte inklusjonskriteriene. Dette var fase III multisenter, dobbeltblind, randomisert kontrollert studie (JMEN studien) publisert av Ciuleanu *et al.* 2009. Studien undersøkte den kliniske nytten av vedlikeholdsbehandling med pemetrexed og støttebehandling (best supportive care, BSC) sammenlignet med støttebehandling alene for lokalavansert eller metastatisk NSCLC. Vi vurderte risikoen for systematiske skjevheter I studien som lav. Median progresjonsfri overlevelse var signifikant lenger med pemetrexed (4,3 måneder) sammenlignet med placebo (2,6 måneder), HR 0,50 (KI 0,42 til 0.61, P <0.0001). Sikkerhetsdata viste at pasienter I pemetrexed-gruppen hadde statistisk signifikante høyere forekomster av 3. og 4. grads bivirkninger. Både fatigue (slapphet) og nøytropeni forekom relativt oftere i pemetrexed-gruppen, og relativt flere pasienter mottok erytropoiese-stimulerende legemidler. Ingen pemetrexed-relaterte dødsfall ble observert. Generelt var pemetrexed godt tolerert.

I en subgruppeanalyse av de 326 pasientene med ikke-plateepitel NSCLC som fikk pemetrexed og de 156 pasientene med ikke-plateepitel NSCLC som fikk placebo var median progresjonsfri overlevelse signifikant lenger med pemetrexed (4,7 måneder)sammenlignet med placebo (2,6 måneder), HR 0.47 (CI 0.37-0.6), P <0.00001). Pemetrexed-gruppen viste en forbedring i median total overlevelse i forhold til placebogruppen på 5,2 måneder (15,5 måneder vs. 10.3 måneder, HR 0.70 CI 0.56 to 0.88.) Sikkerhetsprofilen til pemetrexed innenfor denne histologiske subgruppen var konsistent med profilen til hele populasjonen. Kvalitetsvurderingsverktøyet GRADE ble brukt til å vurdere kvaliteten til evidensen knyttet til hvert enkelt utfall. Resultatene av vurderingen var at effektutfallene ble vurdert til å være av moderat kvalitet og sikkerhetsutfallene ble vurdert til å være av lav kvalitet.

ØKONOMISK EVALUERING

Vi utførte en cost-utility analyse (kostnad per QALY analyse) der relevante kostnader og effekt ble uttrykt i henholdsvis norske kroner i 2011-priser og vunne kvalitetsjusterte leveår (QALYs). Effekt ble I tillegg beregnet I form av vunne leveår. Analysen ble utført fra et helsetjenesteperspektiv og både kostnader og effekter ble diskontert med en årlig rate på 4 % i tråd med norske retningslinjer. Vi konstruerte en Markov modell med en tidshorisont på 6 år og sykluser på 3 uker. Effektdata i form av "tid-til-hendelse" data for total og progresjonsfri overlevelse for pasienter med ikke-plateepitel NSCLC pasienter ble utlevert fra Eli Lilly, firmaet som innehar markedsføringstillatelsen for pemetrexed. Kostnader ble beregnet på grunnlag av norske kilder. I mangel av en eksplisitt uttrykt terskelverdi for kostnadseffektivitet i Norge anvendte vi NOK 500 000 per vunnet QALY da denne verdien har blitt foreslått av Helsedirektoratet som et midlertidig anslag.

Våre resultater viser at behandling med pemetrexed + støttebehandling (BSC) for en gjennomsnittspasient innebærer en merkostnad på omtrent 190 000 NOK, 0,25 vunne QALYs og 0, 44 vunne leveår i forhold til behandling med BSC alene. Kostnadseffektivitetsbrøken (ICER) for en vunnet QALY var dermed på NOK 770 000 som er klart høyere enn den foreslåtte terskelverdien på NOK 500 000 nevnt ovenfor. Det synes ikke å finnes noen anbefalt terskelverdi md hensyn til vunne leveår i norsk helsesektor. Dersom man anvender den samme grensen på NOK 500 000 vil kostnadseffektivitetsbrøken for vunne leveår (ICER) på omtrent NOK 425 000 være innenfor det akseptable området. Sensitivitetsanalyser viste at selv om det er en god el usikkerhet knyttet til livskvalitetsdata og kostnader knyttet til støttebehandling (BSC) har disse variablene bare en marginal innflytelse på resultatet. Resultatene var mest følsomme med hensyn til variasjon i effektdata målt som totaloverlevelse samt kostnadene knyttet til innkjøp og administrasjon av pemetrexed.

KONLUSJON

Vedlikeholdsbehandling med pemetrexed og støttebehandling (BSC) synes å være godt tolerert og fører til en økning i median total og progresjonsfri overlevelse sammenlignet med et regime av støttebehandling alene for pasienter med ikke-plateepitel NSCLC. En slik behandling innebærer en kostnad per vunnet QALY og vunnet leveår på henholdsvis omtrent NOK 770 000 og NOK 425 000. Hvorvidt vedlikeholdsbehandling med pemetrexed og støttebehandling sammenlignet med støttebehandling alene kan regnes som kostnadseffektivt avhenger av om terskelen på NOK 500 000 skal gjelde for kvalitetsjusterte leveår – som innebærer at den mest sannsynligvis ikke er det - eller leveår, som tilsier at den mest sannsynligvis er det. Resultatene må tolkes med forsiktighet siden de er basert på en subgruppeanalyse fra kun en klinisk studie.

Glossary and abbreviations

Disease control rate	The disease control rate is the sum of complete responses (CR) + partial responses (PR) + stable disease (SD).
Hazard rate	The probability per time unit that a case that has survived to the beginning of the respective interval will fail in that interval.
Hazard ratio	In a trial, the hazard ratio is the hazard rate of the intervention group divided by the hazard rate of the control group
HR	Hazard ratio (see above)
ICER	**Incremental cost-effectiveness ratio**. The ratio of the difference in costs between two alternative health technologies to the difference in effectiveness between these two technologies. $$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$
CI	**Confidence interval.** A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true mean effect lies. Wider intervals indicate lower precision; narrow intervals, greater precision.
CUA	**Cost-utility analysis.** An economic evaluation where health consequences are measured in **QALYs**.
Meta-analysis	Statistical analysis that involves pooling data from several separate but similar studies and using the pooled data to test the effectiveness of the results.
NHB	**Net Health Benefit.** In a decision-making process, a positive NHB suggests that the intervention represents good value for money $$NHB = \Delta E - \frac{\Delta C}{\lambda}$$
NMB	**Net Monetary Benefit.** In a decision-making process, a positive NMB suggests that the intervention represents good value for money. $$NMB = \lambda \cdot \Delta E - \Delta C$$

Non-squamous NSCLC	Adenocarcinoma, large cell carcinoma and NSCLCs with indeterminate histology
NSCLC	Non-small cell lung cancer
Odds	The odds of an event happening is defined as the probability that an event will occur, expressed as a proportion of the probability that the event will not occur.
OR	**Odds ratio.** The ratio of the odds of an outcome in one treatment group divided by the odds of the same outcome in a different treatment group.
PSA	**Probabilistic sensitivity analysis.** An analysis of the uncertainty related to all parameters in a decision analytic model. Typically performed by Monte Carlo simulation, hence by drawing values from probability distributions for all parameters simultaneously
QALY	**Quality-adjusted life-year.** A measure of health outcomes that combines quantity and quality of life by assigning to each year of life a weight from 1 (perfect health) to 0 (state judged equivalent to death) dependent on the individual's health related quality of life during that year
RCT	**Randomised controlled trial.** An experiment in which investigators use randomisation to allocate participants into the groups that are being compared This design allows assessment of the relative effects of interventions.
RR	**Relative risk / risk ratio.** The relative risk is the absolute risk (AR) in the intervention group divided by the AR in the control group. It is to be distinguished from odds ratio (OR) which is the ratio of events over non-events in the intervention group over the ratio of events over non-events in the control group.
SR	**Systematic review.** A review in which specified and appropriate methods have been used to identify, appraise, and summarise studies addressing a defined question. It can, but need not, involve meta-analysis.
Statistically significant	Means that the findings of a study are unlikely to have arisen because of chance. Significance at the commonly cited 5% level ($P < 0.05$) means that the observed difference or greater difference would occur by chance in only 1/20 similar cases. Where the word "significant" or "significance" is used without qualification in the text, it is being used in this statistical sense.
WTP (λ)	**Willingness to pay**. A pre-specified limit of what society is willing to pay for a given health unit (e.g. QALY or life year). In Norway it is common to use NOK 500 000 per QALY or life year in economic evaluations.

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Preface

This health technology assessment (HTA), of maintenance treatment with pemetrexed for patients with advanced non-small cell lung cancer (NSCLC), was commissioned by the Norwegian Directorate of Health in October 2010. A health economic model based on the evidence of efficacy and safety was to be developed in order to calculate the cost per quality-adjusted life year and life year gained of this treatment option compared to a strategy of watchful waiting followed by second line treatment. The results were intended to support the decision of whether maintenance treatment with pemetrexed should be incorporated into the treatment guidelines for patients with non-small cell lung cancer in Norway.

Espen Movik was lead reviewer for the health economic evaluation and Lene K. Juvet led the clinical evaluation.

The project group consisted of

- Espen Movik, researcher
- Lene K. Juvet, senior researcher
- Vida Hamidi, senior researcher
- Ingvil von Mehren Sæterdal, senior researcher
- Ingrid Harboe, research librarian
- Marianne Klemp, research director

Internal peer reviewers were:
- Åse Skår, senior researcher, oncologist
- Torbjørn Wisløff, senior researcher, health economist

External peer reviewers were:
- Sverre Sörenson, Associate Professor and Pulmonary Physician, University of Linköping
- Eline Aas, senior researcher and health economist, University of Oslo

The aim of this report is to support well-informed decisions in health care and to improve the quality of health services. The evidence should be considered together with other relevant issues such as clinical experience and patient preferences.

15 Preface

Gro Jamtvedt	Marianne Klemp	Lene K. Juvet	Espen Movik
Executive director	*Research director*	*Lead reviewer, clinical evaluation*	*Lead health economist*

Objectives

The primary objective of the project was to carry out an HTA with a health economic analysis of maintenance treatment with pemetrexed and best supportive care of patients with advanced non-squamous non-small cell lung cancer (NSCLC). Employing a Markov model, costs per quality-adjusted life year and life year gained were calculated compared to a strategy of watchful waiting with best supportive care followed by second-line treatment. A systematic review of the safety and efficacy of pemetrexed for this indication was also to be conducted.

Background

NON-SMALL CELL LUNG CANCER

Lung cancer is one of the most common cancers in the world and is one of the leading causes of cancer mortality Approximately 15% of all cases of lung cancer are classified as small-cell-carcinomas and 80% as non-small cell lung cancer (NSCLC) (1;2). About 75% of patients with NSCLC have locally advanced or metastatic disease at the time of diagnosis (3). The main types of NSCLC are squamous cell carcinoma, adenocarcinoma and large cell carcinoma. The latter two categories are often, along with indeterminate types of NSCLC, referred to as non-squamous NSCLC. The relative incidence of adenocarcinoma has risen dramatically during the last decades, and there has been a corresponding decrease in the incidence of other types of NSCLC and SCLC. Although NSCLCs are associated with cigarette smoking in about 90% of patients, adenocarcinomas may also be found in patients who have never smoked (4). Patients in early and localized stages of NSCLC can be cured by surgery, often in combination with chemotherapy and sometimes radiotherapy. Unfortunately, patients are often in an advanced stage of disease when diagnosed and resection rates are low. Evidence of lower postoperative mortality and slightly increased survival has been reported (5;6).

In Norway, lung cancer is the second most common cancer among men and the third among women. About 2 600 – 2 700 new cases of lung cancer are diagnosed each year in Norway, of which 80% (7) are non-small cell lung cancer[1].The incidence of lung cancer is increasing, particularly amongst women where the annual increase is about 5%. Five-year survival is reported to be up to 65% for patients with NSCLC in stage I (1). There are patients with local advanced NSCLC (stages IIIA and IIIB) who may receive curative treatment. Resection surgery may be appropriate for a few patients (stage IIIA), but curative treatment mainly comprises chemotherapy and radiotherapy (stage IIIB). Poor lung function, large tumour volume, poor performance status and other factors serve to explain why many patients are not candidates for curative treatment. Such patients are offered palliative chemotherapy and/or palliative radiotherapy. Palliative chemotherapy is the standard treatment for patients in stages IIIB-IV who cannot receive curative treatment and whose perform-

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[1] "According to Sverre Sörenson, the proportion of NSCLC cases is similar in Norway and Sweden. (Of 25 000 cases of lung cancer recorded in Sweden in the period 2002-2009, approx. 15% are small—cell, 80 % non-small-cell and the remaining 5% cannot be sufficiently characterized."

ance status is good (0-2). The five-year survival rate for patients in these stages is low at about 1% (1).

Treatment of advanced or metastatic non-small-cell lung cancer

There are different treatment options available for advanced or metastatic NSCLC (stage IIIB / IV) including radiation, chemotherapy and targeted drug therapies (8). Platinum agents (cisplatin or carboplatin) are the drugs of choice for first-line chemotherapy for younger patients in good condition, usually in combination with gemcitabine, vinorelbine, paclitaxel, docetaxel or pemetrexed (only in non-squamous NSCLC). The non-platinum agents can also be used as monotherapy, either as second-line treatment upon progression on first-line treatment, or as an option for older patients (>65 years) or for patients in a reduced condition. In Norway first-line chemotherapy usually takes the form of carboplatin combined with vinorelbine if it is tolerated (9).

Patients with NSCLC who experience tumour progression during or after primary palliative chemotherapy and who have an acceptable performance status may be offered second-line treatment with other anticancer drugs. Three agents have been approved for second line therapy in metastatic NSCLC; docetaxel, pemetrexed and erlotinib. Whenever possible, the therapy should be individualized based upon molecular and histological features of the tumour. In Norway, second line therapy will be considered upon disease progression. If the patient has received chemotherapy previously, monotherapy with docetaxel, pemetrexed (if non-squamous cell carcinoma), erlotinib or gefitinib (if EGFR mutations) may be given, or the patient may, if it is feasible, be included in a new drug trial (9). The response rate in second line chemotherapy is generally about 10% (9). Erlotinib or gefitinib may be given as third-line treatment to selected patients with a good performance status (0-2). Those with performance status 3 and 4 are often managed with best supportive care alone (9).

The role of maintenance therapy, either with one or more chemotherapy agents or with a molecularly targeted agent, is still not clear. Options for maintenance therapy can be to: Continue the initial combination chemotherapy regimen, continue only one of the agents or introduce a new agent as "maintenance" (4). Favourable outcomes have been reported after addition of pemetrexed following standard first-line platinum-based combination chemotherapy (10). The eligible population has been defined as patients with advanced or metastatic (stage III and IV) NSCLC, whose disease has not progressed following treatment with platinum-based, first-line chemotherapy.

The technology

Pemetrexed disodium (Alimta®) is an anti-folate agent that works by disrupting folate-dependent metabolic processes that are essential for cancer replication and

survival (11).Pemetrexed is approved in combination with cisplatin for first-line treatment of malignant pleural mesothelioma, as a single agent for second-line treatment of advanced non-squamous NSCLC, and in combination with cisplatin for first-line therapy of advanced non-squamous NSCLC (10). Pemetrexed also has marketing authorization for maintenance treatment of locally advanced or metastatic non-small-cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. The marketing authorisation states that the first–line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel (a platinum doublet is platinum-based chemotherapy plus one other drug (11). In practice, it is also likely that patients on vinorelbine will qualify for maintenance treatment with pemetrexed (7).

Estimated number of patients eligible for maintenance treatment with pemetrexed in Norway

In 2009, 2 648 new cases of lung cancer were diagnosed in Norway (12). Approximately 80% of patients with lung cancer are estimated to have NSCLC (approx. 2 100). Every year, almost 1,800 of patients with NSCLC are estimated, at the point of diagnosis, to have advanced or metastatic cancer (stage III or IV). About 70% of these patients (1,300 patients) will receive chemotherapy as first-line treatment. It is further assumed that of those surviving after four cycles of first-line chemotherapy; 75-80% will be in remission or have a stable disease. Of these 800 patients, 600 patients will have non-squamous NSCLC. Sverre Sörenson estimates - on the basis of trial data and clinical experience - that fewer than 300 patients will be eligible and motivated for maintenance treatment in Norway (7). For some patients, erlotinib will be an appropriate alternative which means that the probable number of patients that would be treated with pemetrexed is somewhere between 100 and 200 per year. Calculating the potential number of patients eligible for pemetrexed maintenance treatment annually employing the method used by NICE and Norwegian incidence figures yields the same results (13).

CHOICE OF OUTCOMES IN THIS REPORT

We identified overall survival (OS), progression-free survival (PFS), health related quality of life (HRQoL), response rates and rates of serious adverse events (AEs) as key outcomes.

INTRODUCTION TO HEALTH TECHNOLOGY ASSESSMENTS (HTA)

The basis of an HTA is a systematic review and evaluation of scientific literature on efficacy and safety of different interventions or diagnostics. An HTA also includes

economic evaluations and often a discussion regarding ethical, social, legal and organisational aspects depending on the question under evaluation.

This HTA consists of a systematic review of efficacy and safety and an economic evaluation.

INTRODUCTION TO ECONOMIC EVALUATIONS OF HEALTH CARE PROGRAMMES

The basic task of any economic evaluation is to identify, measure, value and compare costs and consequences of different interventions(14). Hence, the results of economic evaluations can be expressed as incremental cost-effectiveness ratios (ICERs), which are calculated as the ratio of the difference in costs between two options over the difference in effectiveness

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

If the incremental costs of an intervention are negative and the incremental effects are positive, an intervention is said to be dominant (more effective and less costly) compared with another intervention. Likewise, positive incremental costs and negative incremental effects result in interventions being dominated (less effective and more costly). In both these circumstances, the ICER is negative and the economic evaluation has a simple conclusion. Otherwise, the ICER is positive and the conclusion depends on the maximum cost-effectiveness ratio one is willing to accept. Spending in the health care sector and in society in general, is restricted by scarce resources, which means that economic evaluations are tools that may assist in prioritisation and maximisation of benefits within a limited budget. For an economic evaluation to be meaningful in a decision making process, the positive ICER must be judged with regard to a ceiling – also known as a threshold - ratio that reflects the decision maker's maximum willingness to pay (WTP) for a health gain. The decision rule for an economic evaluation can therefore be expressed as:

$$\frac{\Delta C}{\Delta E} \leq \lambda$$

where λ equals WTP. The rule means that if the ICER of an intervention is below the ceiling or threshold ratio, introducing the intervention represents good value for money. Because ICERs have poor statistical properties, they are often rearranged to express either net monetary benefit (NMB) or net health benefit (NHB), which yield the following decision rules:

$$NMB : \lambda \cdot \Delta E - \Delta C \geq 0$$

$$NHB: \Delta E - \frac{\Delta C}{\lambda} \geq 0$$

An intervention can in other words be considered cost-effective if it yields a positive NHB or NMB (15).

Economic evaluations are often based on decision models (such as decision trees, Markov models etc) that calculate results based on various input parameters in the model. There are always uncertainties related to the values of these parameters, making sensitivity analyses an important feature of any economic evaluation. In short, sensitivity analysis illustrates how much the results vary when model parameters are being changed. Sensitivity analyses can be performed in many ways, with one-way or two-way sensitivity analysis being common approaches. These entail changing, respectively one or two model-parameters at a time while all the other model-parameters are held constant, in order to see how much impact the variation in these parameters has on the results. One-way sensitivity analyses are often presented as tornado-diagrams, which are intended to identify and illustrate the model-parameters that have the highest impact on the results. It is however, important to remember that one-way sensitivity analyses do not take all the decision uncertainty into account.

Another important kind of sensitivity analysis is referred to as probabilistic sensitivity analysis (PSA), where uncertainties in many model-parameters are taken into account simultaneously. The basic approach in PSA is to assign appropriate probability distributions to the model-parameters, which makes it possible to replace the "fixed" values of the parameters by values generated by random draws from the distributions. Doing this repeatedly, with a definite number of iterations, makes it possible to estimate probabilities of alternative interventions being cost-effective subject to different ceiling values of WTP. PSA is often presented as scatter plots, which show point estimates of the ICER for all iterations in the cost-effectiveness plane, and also by cost-effectiveness acceptability curves (CEACs), that show the probability of the alternatives being cost-effective subject to changing values of WTP.

PSA may also be used to generate expected value of perfect information (EVPI) results which provide information about the societal value of having more accurate information about the input parameters. This may subsequently be used to inform on which parameters it would be most useful to obtain new and improved data. The ranking of EVPI for different parameters is dependent on the threshold willingness to pay. If EVPI is to be compared between different patient groups, the ranking is also dependent on the number of patients in each group. In short, making a model probabilistic means that it is possible to estimate the uncertainty in the decision of implementing alternative interventions, and also provides the opportunity of estimating the value of collecting additional information from new research.

PRIORITY SETTING CRITERIA

According to Norwegian policy documents (15;16), a treatment should be prioritised if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

The policy documents mentioned above give no guidance as to what constitutes a "reasonable" relationship between costs and effectiveness. The Directorate of Health however, has recently recommended a preliminary estimate of NOK 500 000 per statistical life year in full health (17). However, there exists no academic consensus regarding this threshold value, nor has it been subject to a political process, and it can therefore be regarded as nothing more than a tentative suggestion.

Evaluation of clinical documentation

METHODS

Literature search

The research librarian Ingrid Harboe planned and executed all systematic searches in collaboration with the project manager and members of the project group. We searched electronic databases for randomized controlled trials, economic evaluation and ongoing clinical trials. We used a filter for randomized controlled trials and a filter for economic evaluations.

The searches were performed on 17th February 2011. We used Ovid MEDLINE, EMBASE (Ovid), the Cochrane Library and the Centre for Reviews and Dissemination databases when searching for randomized controlled trials and economic evaluation. We used the WHO ICTRP search portal and ClinicalTrials.gov when we searched for ongoing clinical trials. We used a combination of keywords and text words relating to the populations and the relevant drugs. The terms used were adapted to the different databases, full search strategies are shown in appendix 1.

We also hand searched the reference list of included systematic reviews and NIHR Health Technology Assessment programme (http://www.hta.ac.uk/) and INAHTA (http://www.inahta.org) for other published HTA reports). Finally, the pharmaceutical company Eli Lilly, which has the marketing authorization for the pharmaceutical assessed in this HTA report, were presented with the identified randomized controlled trials and additional abstract, and invited to submit further relevant literature to the scope of this project.

We performed a systematic search for literature in the following databases:
- The Cochrane Library; CENTRAL, NHS EED
- Centre for Reviews and Dissemination (CRD); NHS EED
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1950 to present
- EMBASE (Ovid) 1980 to present

Inclusion criteria

Population: Patients with non small cell lung cancer (NSCLC)
Intervention: Maintenance treatment with pemetrexed
Comparator: Watchful waiting, standard care
Study design: Randomized controlled trials

Outcomes: Primary

Overall survival
Progression free survival
Disease control rate
Adverse Events (specify?)
Quality of Life

On the basis of retrieved data from the systematic review as well as - to the extent it was available – relevant Norwegian data on quality of life, costs, treatment practices and survival, we developed a health economic model of the Markov-type. 'Population, intervention, comparator and outcomes were as follows:

Population: Patients with non-small cell lung cancer (NSCLC), non-squamous, and that is not progressing under first-line chemotherapy.
Intervention: Maintenance treatment with pemetrexed,
Comparator: Expectant Follow-up and then second line chemotherapy at progression, if possible.
Outcome: The cost per gained quality adjusted life year (QALY) and cost per life year gained

Languages: No limitations in languages during the search, but we only included articles in English, articles with English abstract or articles in Scandinavian.

Selection of articles

Two persons (LKJ and IS) independently inspected all citations generated by the search to identify potentially relevant articles based on title and/or abstract. Full text versions were obtained for articles appearing to meet the inclusion criteria or in cases where sufficient information was not available to make a decision. Two persons (LKJ and IS) independently assessed whether the article was relevant or not according to our list of inclusion criteria. Disagreements were resolved by discussion or by consulting a third party.

Articles meeting the predefined inclusion criteria were assessed for quality according to risk of bias for randomized controlled trials (18). All assessments were per-

formed and agreed upon by two persons (LKJ and IS). Final assessments are available in appendix 2.

Data analysis

Data were extracted from the randomized controlled trial and presented as they appear in the articles. Our analyses of efficacy were performed on the population of 663 randomly assigned patients according to the principle of "intention-to-treat".

Grading the quality of evidence

Two persons (LKJ and IS) assessed the overall documentation for each outcome using GRADE (Grading of Recommendations, Assessment, Development and Evaluation, www.gradeworkinggroup.org). The method used involves an evaluation of study type, risk of bias, consistency between trials, directness (in how similar the population, intervention, and outcomes are between the trials and the objectives of this report), precision of the effect estimates and publication bias. Finally the overall quality will be categorized as high, moderate, low or very low.

GRADE gives the following definition of the different classes of evidence:

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

RESULTS

We identified 395 titles in the search for literature. Of these, 13 titles were found to be potentially relevant and full text copies were reviewed. Finally, one study met our pre-specified inclusion criteria (fig. 1).

Flow chart of identified literature and process until included studies:
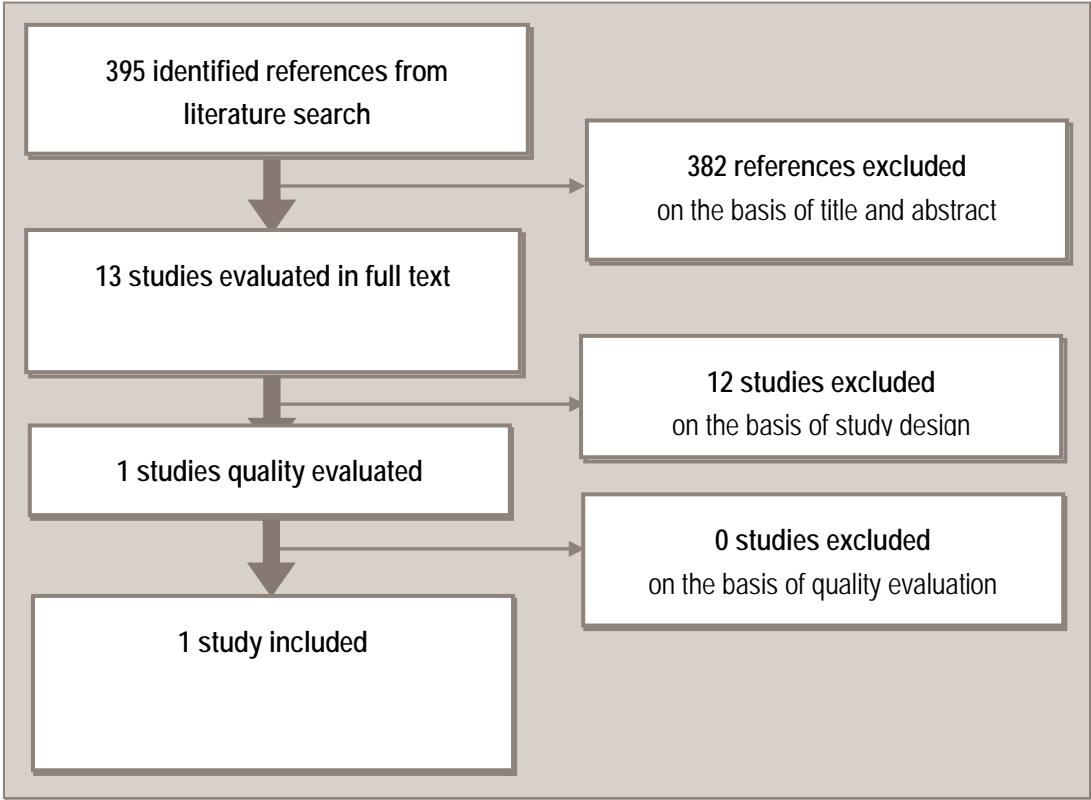
Figure 1 *Flowchart of identification of documentation.*

Description of the included study

The included study was a phase III multicentre, double-blinded randomized controlled study (a.k.a. the JMEN study) by Ciuleanu *et al.* 2009 (10). The study investigated the clinical usefulness of maintenance treatment with pemetrexed compared to standard care for locally advanced or metastatic NSCLC. We assessed the risk of bias in the study as low (see table 1 and Appendix 2).

Table 1: Included RCT on the clinical usefulness of maintenance treatment with pemetrexed for NSCLC.

Study	Design	N	Country	Outcome	Risk of bias
Ciuleanu 2009	Randomized controlled trial	663	Multicentre study	Progression free survival, overall survival, disease control rate, adverse effects	Low risk of bias for all outcomes

Efficacy of maintenance treatment with pemetrexed compared to placebo in NSCLC patients according to the JMEN-study (10)

Pemetrexed is given to patients who have not progressed after first-line treatment (four rounds of platinum-based combination therapy). The effect of maintenance treatment of pemetrexed is based on a phase III multicenter, double-blinded randomized controlled trial (JMEN study) (10). The study included 663 patients with advanced or metastatic NSCLC (EOCG status 0-1) who had not progressed after first-line treatment with a platinum-based combination therapy (cisplatin or carboplatin combined with paclitaxel, docetaxel or gemcitabine, but not with vinorelbine). The intervention group included 441 patients who received pemetrexed and standard follow-up (best supportive care; BSC). The control group included 222 patients who received placebo and standard follow-up. Patients and the study team were all masked to the treatment assignment. The medicine was given every three weeks as an intravenous infusion. The dose of pemetrexed was 500 mg/m². The infusion lasted 10 minutes. To minimize side effects of pemetrexed, patients were given corticosteroid (dexamethasone), folic acid and vitamin B12 injections. This was also given to the placebo group. Median progression-free survival was significantly longer with pemetrexed (4.3 months) compared with placebo (2.6 months), HR 0.50 (CI 0.42 to 0.61, P <0.0001) (table 2) (10). We evaluated the quality of the documentation to be moderate for PFS and OS and low for the adverse events outcomes (Table 2).

Table 2. Key results of the JMEN study (10).

End point	Pemetrexed (n=441)	Placebo (n=222)	HR (95% CI) or RR (95% CI)	p-value	Quality of the evidence (GRADE)
Progression free survival (months) median	4.3	2.6	HR = 0.50 (0.42-0.61)	<0.0001	**Moderate** ⊕⊕OO[1]
Overall survival (months) median	13.4	10.6	HR = 0.79 (0.65-0.95)	0.012	**Moderate** ⊕⊕OO[1]
Drug related grade three or four toxicity(%)	70 (16 %)	9 (4 %)	RR = 0.88 (0.84 – 0.92)	<0.0001	**Low** ⊕OOO[1,2]
Fatigue All grades (%)	108 (24 %)	23 (10 %)	RR = 0.84 (0.79 – 0.90)	0.001	**Low** ⊕OOO[1,2]
Neutropenia All grades (%)	26 (6 %)	0 (0 %)	RR = 0.95 (0.92 – 0.97)	0.006	**Low** ⊕OOO[1,2]

CI, confidence interval; CR, complete response; HR, hazard ratio; RR; relative risk, PFS,

progression-free survival; PR, partial response; SD, stable disease.

[1.] Only one study

[2.] Few events (total number of event are less than 300)

HR was based on many timepoints estimated on Cox analysis.

RR was based on time point (6 month).

No data for health-related quality of life was reported[2] (10) . Safety data demonstrated that patients in the pemetrexed group had statistically significantly higher rates of grade 3 and 4 toxicity. Both fatigue and neutropenia were higher in the pemetrexed group, and   more patients in the pemetrexed group received transfusions and erythropoiesis- stimulating agents. No pemetrexed-related deaths occurred. Treatment discontinuation due to drug-related toxic effects was higher in the pemetrexed group (21 patients (21%) than in the placebo group (3 patients (1%). The incidence of admission to hospital due to drug-related effects was also higher, but the overall rates of these events were low (10). Generally pemetrexed was well tolerated. We evaluated the overall quality of the documentation to be low for adverse events outcomes, which means that we have **limited confidence with the results.**

Table 3. Key results of the JMEN study subgroup (non-squamous population) (10).

End point	Pemetrexed (n=325)	Placebo (n=156)	HR (95% CI)	p-value	Quality of the evidence (GRADE)
Progression free survival (months) median	4.5	2.6	0.44 (CI 0·36–0·55)	<0.0001	Moderate $\oplus\oplus OO^{1}$
Progression free survival (months) median*	4.4	1.8	0.47 (CI 0·37–0·60)	<0.0001	Moderate $\oplus\oplus OO^{1}$
Overall survival (months) median	15.5	10.3	0.70 (0.56-0.88)	0.002	Moderate $\oplus\oplus OO^{1}$
Survival rate 1 year (%)	60	42	0.70		
Survival rate 2 year (%)	28	22	0.79		

CI, confidence interval; CR, complete response; HR, hazard ration; PFS, progression-

[2] However, HRQoL data (LCSS) were published separately in an article published later, see Discussion section.

free survival; PR, partial response; SD, stable disease.

[1.] Only one study

* PFS data from independent, central review of scans available from 581 randomly
assigned patients

Economic Evaluation

The objective of the economic evaluation was to compare the effectiveness and costs of pemetrexed (Alimta®) as maintenance treatment for patients with non-squamous non-small cell lung cancer, more specifically for patients in advanced stages IIIB and IV who have not progressed after completion of four cycles of platinum-based induction therapy.

METHODS

General

We performed a cost-utility analysis (CUA) where relevant costs and effects were expressed in Norwegian kroner (NOK) in 2011-prices and quality-adjusted life years (QALYs) respectively. Effects were also calculated in the form of life years gained (LYG). The analysis was carried out from a health care provider perspective and both costs and effects were discounted at an annual discount rate of 4% according to Norwegian guidelines (19).

The results were expressed in terms of ICERs, and conclusions with regard to cost-effectiveness were made on a threshold value for a willingness to pay (WTP) of NOK 500 000 per QALY gained. In the absence of an explicit threshold value for cost-effective interventions in Norway, we used NOK 500 000 per QALY gained as a threshold value since it has been suggested by the Norwegian Directory of Health as a possible temporary estimate (17) (see discussion earlier in this report).

Uncertainties in model parameters were handled by performing one-way (tornado diagram) and probabilistic sensitivity analyses.

Model structure

The model compares two strategies; pemetrexed plus best supportive care (PEM+BSC) and best supportive care alone[3] (BSC alone). Patients enter the model

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[3] In practice "watchful waiting" + BSC

after having received 4 cycles of first-line platinum-based chemotherapy and are assumed to be stable on this therapy.

The model is of the Markov type, in which a cohort of patients is followed over a given period of time. The time horizon, which in this case is 6 years, is divided into a number of intervals of equal length known as cycles. The cycle length is three weeks, reflecting the time intervals at which pemetrexed infusions are administered. The total number of cycles in the model is thus 104.

In each cycle, patients are assigned to one, and only one, of a number of mutually exclusive pre-defined states and may upon completion of the cycle transfer to another state or remain in the same state, depending on so-called transition probabilities. Each state is associated with specific outcomes and costs.

The states in our model are as follows:

Progression-free: In the PEM+BSC arm, the patient is given an infusion of pemetrexed 500 mg/m² every third week, i.e. once every cycle plus best supportive care (see main text for definition). In the "BSC alone" arm, the patient is only given BSC.

Progressed: It is assumed that all surviving patients ,in both arms, move on to second-line treatment with either an infusion of docetaxel 75 mg/m² every third week or erlotinib orally every day (tablets, 150 mg x 21 days per cycle) while receiving BSC. Second -line treatment in both arms is given for up to four cycles, after which any remaining patients transfer to the palliative state.

Palliative: Here patients are assumed to only receive BSC and palliative care (see main text for definition), either at home or in hospital.

Dead: Final state. No costs or effects are accumulated in this state.

A graphical representation of the model is shown in the figure below:
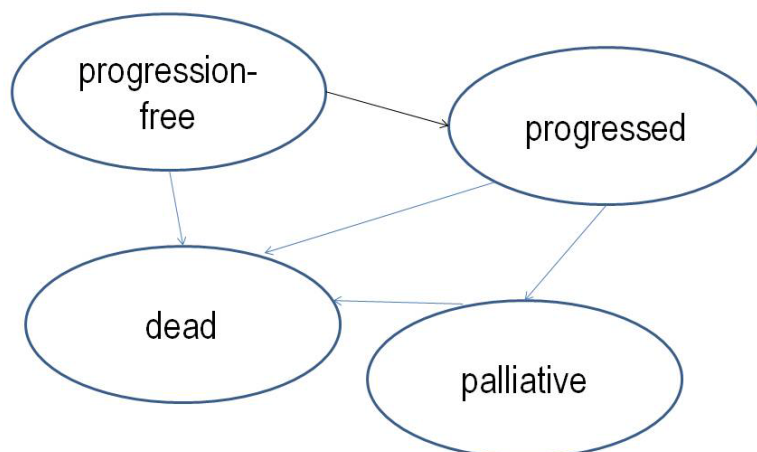
Figure 2 Model structure

At the beginning of the model, all patients are in the "progression-free" state. The probability of transferring to another state or remaining in the same state is determined by effectiveness data for the non-squamous patient sub-group from the JMEN study (shown in figure 3 in Ciuleanu *et al.* 2009 (10)). In the progressed state, patients may be given second line treatment (docetaxel/erlotinib) for up to 12 weeks (4 cycles). Subsequently, only BSC/palliative care is given, a more specific description of which will be provided later. Patients may die in the progression-free, progressed and palliative states.

Model Parameters

The sources for, and methods used to derive, model parameters are described below:

Epidemiology
Ideally, we should have applied the measure of efficacy from the clinical trial (the hazard ratio) to Norwegian epidemiological data. However, no such data matching the patient population in question was found. A survival study of Norwegian NSCLC patients was identified (20), but the results of this study was not broken down by subgroups which could match the patient population in the JMEN clinical trial with regard to performance status, histology and number of cycles of chemotherapy received. Data for the model's comparator has therefore been drawn from the control arm of the JMEN trial.

Clinical efficacy

Efficacy data was taken from the hazard ratio results for overall (OS) and progression-free survival (PFS) for the non-squamous sub-population in the JMEN trial (10) as seen in table 3. These ratios were in the model multiplied by the OS and PFS hazard rates of the control (BSC alone) arm as described below.

The OS and PFS survival curves are shown in the study's figure 3. The corresponding time-to-event (failure) data were provided by Eli Lilly Norway and used to construct hazard rates for OS and PFS in the control arm. The OS and PFS time-to-event data were entered into SPSS (21) where non-linear regression was employed to construct exponential hazard functions which was in turn used to calculate transition probabilities. Hazard rates were assumed to be constant over time.

The hazard rate 0.0643 was calculated for overall survival for the placebo+BSC arm. This rate was multiplied by the hazard ratio from the JMEN trial of 0·70 (CI 0·56–0·88) (see Clinical Evaluation chapter, table 3) (10) to find the hazard rate for the intervention arm, 0.0450. The hazard rates for progression-free survival were estimated in a similar fashion to be 0.3260 and 0.1532 for the control and intervention arms respectively, using the PFS hazard ratio from the JMEN trial (non-squamous patients) of 0·47 (CI 0·37–0·60)) (see Clinical Evaluation chapter, table 3 (10). For the distributions around the hazard ratios used in the probabilistic sensitivity analysis, consult Appendix 7.

Based on the hazard rates above, three-week transition probabilities were calculated using the rate-to-probability formula provided by Briggs *et al.* (22)

$p = 1 - \exp(-rt)$

where p=probability, r=hazard rate and t=time (3 weeks=0.693 months)

The hazard rates and corresponding transition probabilities are shown in table 4 below:

Table 4: Hazard rates and transition probabilities

	Hazard rate	Transition prob*
Overall survival BSC	0,0643	0,0435
Overall survival PEM+BSC	0,0450	0,0307
Progression-free survival, BSC	0,3260	0,2020
Progression-free survival, PEM+BSC	0,1532	0,1006

*The transition probabilities represent the probability per cycle of moving to the states "dead" (overall survival and "progressed" (progression-free survival).

Costs

Given that the analysis was performed from a third party payer perspective, only direct costs were calculated. This did not involve a comprehensive costing exercise where all costs associated with treatment of NSCLC were identified. Rather, we tried to identify what we assumed would be the most important factors affecting the difference in resource use in treatment scenarios with and without pemetrexed. These were drug costs, staff costs and costs related to hospitalisation and treatment of adverse events. Costs associated with best supportive care and palliative care have obviously been incorporated, albeit in a somewhat simplistic manner. The reason for this is that we assume these costs to be fairly similar in both treatment strategies, although the lengths of time in which they are given may differ. To assess the potential impact on the results, the levels of BSC and palliative care costs have hence been varied in the sensitivity analyses.

Drug costs

The cost per cycle of pemetrexed is NOK 24 300, and was taken from the Norwegian National Pharmacological Cancer Treatment Registry (Oncolex). The cost includes the price of a 500 mg/m^2 for an average patient with a body surface of 1.73 m^2 and includes preparation costs in the hospital pharmacy and premedication costs, but not staff costs[4]. Second line treatment in both arms involves either docetaxel (i.v. infusion) every third week or a daily erlotinib tablet. The costs per cycle for the former were estimated to be NOK 6 100 in Oncolex, whereas the latter, NOK 15 518, was estimated on the basis of the Norwegian Medicine Agency's price database (see appendix 4 for details). The respective fractions of docetaxel and erlotinib use in second line treatment is uncertain, and therefore varied in the probabilistic sensitivity analysis (PSA) in a normal distribution, (mean 50%, std. dev=35.36%). This uncertainty will not only pertain to second line drug costs, but also to staff time (specialist nurse time) since the former is given in hospital while the latter is taken at home.

Specialist nurse costs

The costs of specialist nurses involved in administering i.v. chemotherapy were calculated based on the time required for chemotherapy in each drug regimen included in the model. The mean cost per hour, including social expenses and overhead costs, was estimated to be NOK 391 (see appendix 4 for details). Costs associated with other types of staff and administration are assumed to be similar for both model arms, while the costs of oncologist consultations are assumed to be covered in the total costs of best supportive care. Means specialist nurse time per cycle is assumed to be 1.5 hours for both maintenance (pemetrexed) and second-line (docetaxel) treatment, which includes time for premedication, i,v. infusion, administration and

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[4] For further details (in Norwegian) see the Oncolex website at:
http://oncolex.no/en/NRMB/Spoersmaal%20og%20svar.aspx

monitoring. The cost mean specialist nurse cost per cycle for pemetrexed is esti-mated to be NOK 586. Taking into account the distribution among the two drugs used as second-line treatment, the mean specialist nurse cost per cycle for second-line treatment is estimated to be NOK 293.

Costs associated with" best supportive care"
The JMEN trial compared a regimen of maintenance treatment with pemetrexed+ best supportive care with one of best supportive care alone. In Ciuleanu *et al.* 2009 (10), no description of what BSC actually involves in terms of resource use is pro-vided. Lilly's submission to NICE (23) however, based on the trial states that:

> " BSC was defined as treatment without a specific antineoplastic regimen and treatment was ad-ministered as considered appropriate by the prescribing physician. Acceptable BSC therapies in-cluded, but were not limited to antibiotics, antiemetics, thoracentesis, pleurodesis, blood trans-fusions, and/or nutritional support. Best supportive care specifically excluded anticancer sur-gery, immunotherapy, radiotherapy, anticancer hormonal therapy, and systemic chemotherapy in which the goal would be to either eradicate or slow the progression of the study disease."
> (p. 26)

Nevertheless, there is neither a description in the article, nor in Lilly's submission referred to above as to the extent of resource use involved in such treatment. More-over, since the treatment of some of the conditions (nausea, for example) mentioned above is handled in the adverse events part of the model, we have employed a very simplistic definition of BSC:

In the progression-free and progressed state, BSC is simply defined as a visit to an oncologist on average once per every second cycle (the distribution for this variable is presented in appendices 4 and 8). In the palliative state, the definition is ex-panded to include the risk of hospitalization, the cost of which was assumed to be a flat per diem rate of 1 600 NOK which was taken from a study by Nieder *et al.* 2010 (24) This study measured the resource use associated with the last two years of life of patients with metastatic brain cancer in a hospital in Northern Norway. Since the figure may be perceived to be somewhat low, it has been varied in the one-way sensi-tivity analysis (tornado diagram).

The costs per cycle for BSC are shown in the table below. Details of the calculations of BSC costs for the progression-free, progressed and palliative states are given in appendix 4, and variable distributions are also presented in Appendix 7. We have also assumed that there may be a reduction in BSC costs in the range of 0%-50% while on chemotherapy, which is accounted for in Appendix 4.

Table 5: Mean costs of best supportive care per cycle per state

State	Mean cost per cycle, NOK
Progression-free and progressed	425
Palliative	460

Adverse events

Three types of grade III/IV adverse events have been included in the model. These are anaemia, neutropenia and nausea/vomiting[5]. Since Ciuleanu *et al.* 2009 (10) does not report the occurrence of adverse events for the non-squamous patient group separately, the data on the occurrence of these events have been drawn from an abstract based on 38-month data from the JMEN trial reported in the submission to NICE (23) and are shown in the table below.

Table 6: 38-month and cycle probabilities of adverse events, non-squamous patients

Adverse event	38-m prob PEM+BSC, %	38-m prob BSC, %	cycle prob* PEM+BSC	cycle prob* BSC
Anaemia	2.5	0	0.00046	0.00000
Neutropenia	2.8	0	0.00052	0.00000
Nausea	0.6	0.6	0.00011	0.00011
Vomiting	0.3	0	0.00005	0.00000
Nausea/vomiting combined	0.9	0.6	0.00016	0.00011

*calculated using the rates to probability formula in Briggs *et al.* (22)

The costs of treating adverse events have been drawn from two Norwegian reports on cancer patents on chemotherapy, Pike *et al.* 2008 (25) (nausea/vomiting) and Möller *et al.* 2011 (26) (anaemia and neutropenia) and are shown in the table below. Details of the calculations are provided in appendix 4. The reduction in quality of life associated with adverse events is addressed in the next section.

Table 7: Costs per cycle associated with adverse events

	Costs per cycle, NOK
Neutropenia (mean grades 3 and 4)	7 496
Nausea/vomiting	1 748
Anaemia	8 457

---

[5] Adverse events have not been included in the progressed (second-line treatment) or palliative states in the model, as they are deemed to be similar in both treatment groups.

Hospitalisations due to transfusions

According to Lilly's submission to NICE (23) (p.53) significantly higher percentages of patients in the pemetrexed arm required transfusions (9.5% vs 5.9%, respectively, p=0.003).

Table 8: 38-month and cycle probabilities of transfusion-related hospitalisations

Hospitalisations	38-m prob PEM+BSC, %	38-m prob BSC, %	cycle prob PEM+BSC*	cycle prob BSC*
Transfusions	9,5	5,9	0,00181	0,00111

*calculated using the rates to probability formula in Briggs *et al.* (22)

The average cost of transfusion-related hospitalisation, NOK3 743 was estimated using the DRG weight 816R (27) of 0.0102 multiplied by the 2011-unit price of 36 698.

Health related quality of life

It is recommended that preference-based health-related quality of life measures should be used in economic evaluations (14). However, no such data is reported in the JMEN-trial. We have identified studies of Norwegian patients with NSCLC incorporating HRQoL, such as those by Helbekkmo *et al.* 2009 (28) and Grønberg *et al.* 2005 (29). These studies both reported outcomes in terms of the cancer-specific HRQoL scale EORTC QLQ-C30. Even though it has been shown (30) that mapping from QLQ-C30 to preference-based measures such as EQ-5D may be feasible, there is still insufficient data for this to be relevant in our case.

Even if it was arguably not an ideal approach, we found that the best available option was to use preference-based HRQoL data from a UK-study of lung cancer patients from 2008, Nafees *et al.* (31) . In this study, preference-based utility weights for health states associated with metastatic NSCLC were elicited from a sample of the UK public using the standard gamble method. The mean values and standard errors of the utility weights used in our model are shown in the table below.

Table 9: Quality of life data

	Utility weight	Standard error
Progression-free state	0.65	0.022
Progressed state	0.47	0.022
Palliative state	0.47	0.022
Adverse events: anaemia	-0.07	0.018
neutropenia	-0.09	0.015
nausea/vomiting*	-0.05	0.016

*assumed to last for a maximum 5 days in a 21-day cycle, all other adverse events assumed to last for full cycle

Due to there being significant uncertainty associated with the use of these weights in a Norwegian context, and the fact that we have used the same weights in two states, we have assessed their significance with regard to results in expected value of perfect information (EVPI) analysis. Moreover, there may be caveats associated with the use of utility weights in cancer (32) and their potential to reach "full health" is severely constrained . We therefore also present results with regard to life year gained.

RESULTS

Incremental Cost-effectiveness Estimates

The results, presented in table 10 below, show that for an average patient pemetrexed + BSC is associated with an incremental cost of approximately NOK190 000 and 0.25 QALYs gained compared to BSC alone. The ICER is thus approximately NOK770 000, which is clearly above the NOK500 000 threshold discussed earlier in this chapter. The net health benefit is therefore negative given this threshold level.

Table 10: The expected total costs and QALYs for the alternative interventions

Intervention	Costs (NOK)	Incremental Cost, NOK	Effects (QALY)	Incremental Effect	ICER, NOK	NHB
BSC alone	46 542		0.67			
PEM+BSC	235 692	189 150	0.91	0.25	767 301	-0.13

We have also estimated the effects in terms of life years gained. There is no recommended threshold level with regard to cost per life year gained in Norway. Hypothetically – if the NOK 500 000 were to apply, the ICER of approximately 425 000 would be within the acceptable range and the net health benefit would be positive.

Table 11: The expected total costs and life years for the alternative interventions

Intervention	Costs (NOK)	Incremental Cost	Effects (LYG)	Incremental Effect	ICER	NHB
BSC alone	46 542		1,32			
PEM+BSC	235 692	189 150	1,76	0,44	425 145	0,06

Sensitivity analyses

One-way sensitivity analysis (Tornado diagram)

A tornado diagram illustrates the impact of a series of one way sensitivity analyses, *i.e.* one parameter is changed at a time. The bars are ordered according to the impact each parameter change has on the ICER. The ordering of the parameters is sensitive to the upper and lower values chosen for the different variables. As shown in the figure below the results are most sensitive to the hazard ratio with regard to overall survival. The variation within the confidence interval from the JMEN trial leads to a variation in the ICER between NOK 500 000 and NOK 1.7 million. Reducing the cost of pemetrexed and its administration by 20% brings the ICER down to approximately NOK 600 000. However, none of the changes in the parameters within the ranges specified here will bring the ICER below the assumed willingness to pay threshold per QALY of NOK 500 000. See Appendix 6 for further details.

**Tornado Diagram at
PEM+BSC v. BSC only**

⊠ hazard ratio overall survival: 0,56 to 0,88
⊞ QoL palliative state: 0,3 to 0,5
▨ hazard ratio progression-free survival: 0,37 to 0,60
◫ pem drug cost per average patient per cycle including premedication: 19440 to 24300
☐ QoL progression-free state: 0,6 to 0,8
■ discount rate (whole number): 0 to 4
⊠ PEM time spent per cycle, Specialist Nurse, hours: 0 to 2
⊞ Specialist nurse, salary per month, NOK: 30758, to 46137
▨ QoL progression state: 0,4 to 0,6
◫ cost of BSC per cycle: 142 to 849
⊟ QoL Anemia: 0 to 0,1472
▨ cAnemia: 4229 to 16914
⊠ QoL_Neutropenia: 0 to 0,17946
⊞ cost of treating nausea/vomiting: 874 to 3496

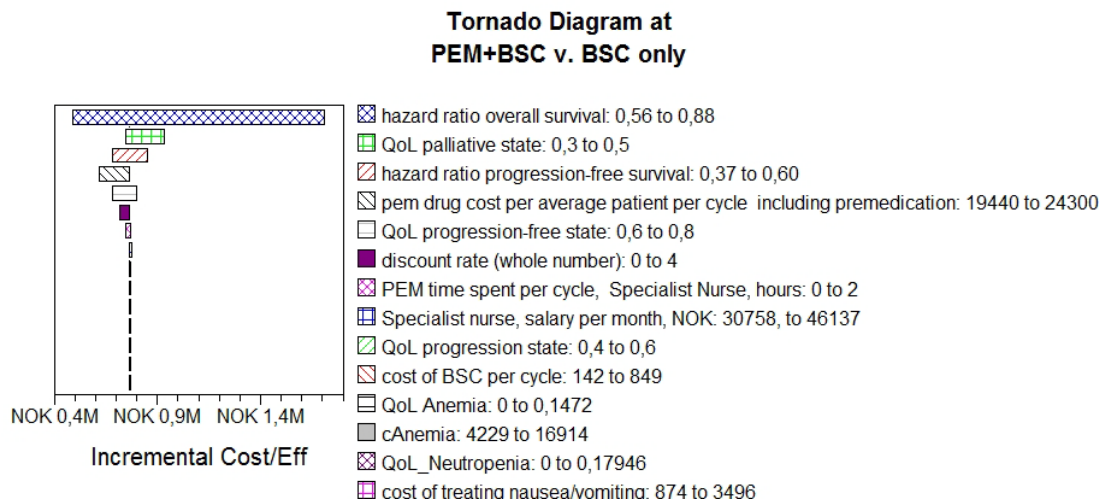NOK 0,4M   NOK 0,9M   NOK 1,4M
Incremental Cost/Eff

Figure 3 Tornado diagram

Probabilistic sensitivity analysis

We performed a Monte Carlo simulation with 1000 draws from all distributions which showed that pemetrexed + BSC is cost-effective subject to a WTP of NOK 500 000 per QALY in only 3% of cases, as seen in the figure below.
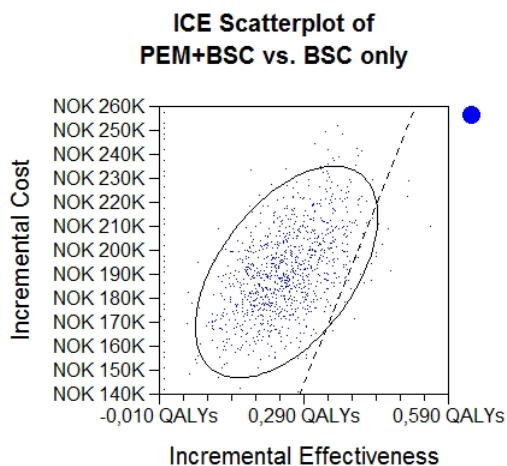
Figure 4 Incremental cost-effectiveness scatter plot

The cost-effectiveness acceptability curve in figure 4 shows that a strategy of BSC alone is more likely to be cost effective up to a WTP level of 770 000 per QALY, whereas the PEM+BSC strategy is more likely to be cost-effective at WTP levels higher than that. This corresponds well with the ICER of 770 000 which is based on the expectation of incremental costs and incremental effects.
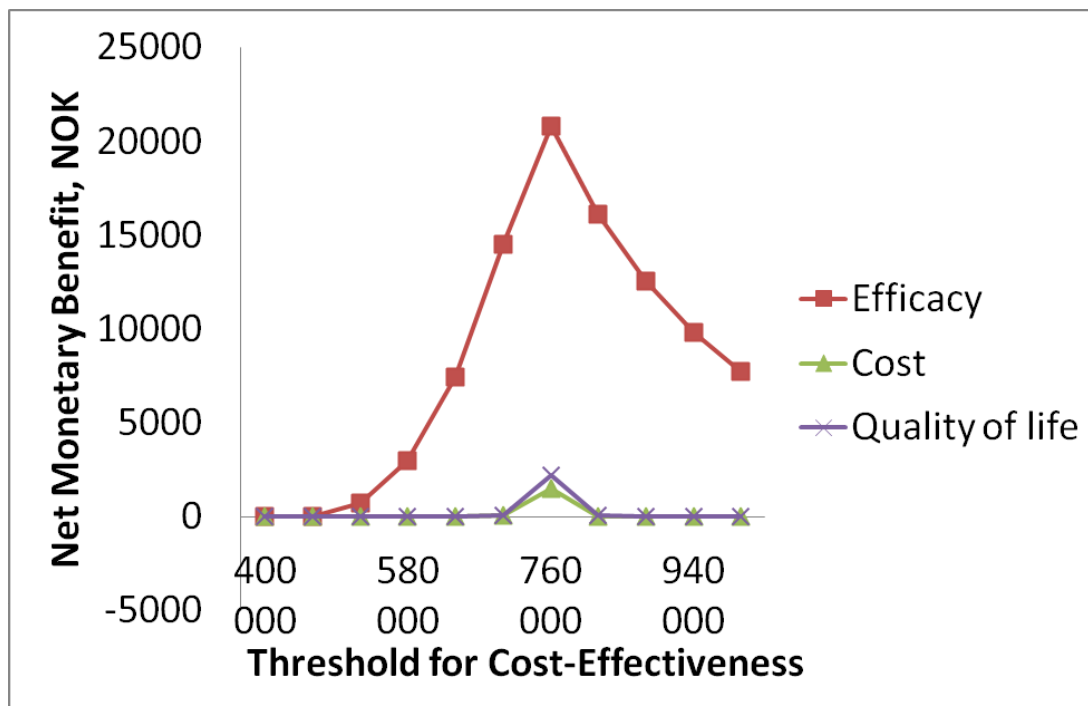
A value of information analysis was conducted with 100 x 100 trials in order to generate expected value of perfect information (EVPI). This plots the potential loss in net monetary benefit if the "wrong" decision is made against the cost-effectiveness

threshold (willingness to pay for an extra QALY) (22). The "wrong" decision implies choosing the intervention(s) which is not cost-effective for a given threshold-level, the probability of which can be reduced if the uncertainty surrounding underlying variables is also reduced. Groups of variables were analysed at a time in order to see which group had the most impact on results. The figure below shows that the EVPI values are generally low, but if new research is to be undertaken then it seems that efficacy data has the biggest potential to reduce decision uncertainty.
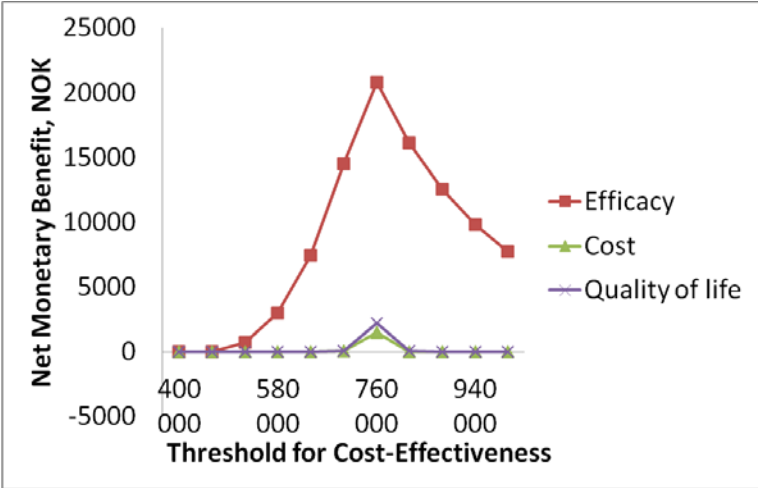

Figure 5 Expected value of perfect information

Discussion

In this HTA, we have systematically reviewed and summarized a randomized controlled trial of maintenance treatment with pemetrexed + best supportive care compared with best supportive care in patients with non-small cell lung cancer, with regard to efficacy and safety. Further, we have performed an economic evaluation to examine the cost-effectiveness of this intervention in a Norwegian setting.

SUMMARY OF RESULTS

In the JMEN trial's subgroup analysis with non-squamous NSCLC patients, the median progression-free survival was significantly longer in the pemetrexed group (4.7 months) than in the placebo group (2.6 months), HR 0.45 (CI 0.35-0-59, P <0.00001). This was also the case with regard to median overall survival, with a difference of 5.2 months in favour of pemetrexed (15.5 months vs. 10.3 months, HR 0.70 CI 0.56 to 0.88). The results of the economic evaluation based on these efficacy data as well as Norwegian data on costs, adverse events and hospitalisations, are ICERs of approximately NOK770 000 and NOK427 000 per QALY and life year gained respectively.

Health-related quality of life

As mentioned in the evaluation of the clinical documentation, Ciuleanu *et al.* (10) did not report any health related quality of life data. However, such data were recorded in the JMEN trial using the Lung Cancer Symptom Scale (LCSS) and reported recently in Belani *et al.* (33). Although the LCSS is not preference-based and could therefore not be used in the economic evaluation, the Belani study does provide interesting background information. HRQoL was according to the study similar between treatment groups. The only significant differences between the pemetrexed and placebo groups with regard to time to worsening on the LCSS were associated with pain (HR 0.76, 95% CI 0.59-0.99; p=0.041) and haemoptysis (HR 0.58, 95% CI 0.34-0.97; p=0.038). Baseline LCSS scores were low, indicating a relatively high HRQoL for patients who had not experienced disease progression following first-line treatment.

QUALITY OF DOCUMENTATION/MODEL

Using GRADE, we evaluated the quality of the efficacy data to be moderate and we found that the study had a low risk of bias, which means that we are **moderately confident with the results**. As for the economic evaluation, the sensitivity analyses show that the results were robust to changes in key variables. However, the external validity of the efficacy data with regard to the Norwegian patient population is limited since the JMEN trial only included patients with PS 0 or 1 whereas 40% of Norwegian NSCLC patients will have a performance status of 2-4 (28). The effect of chemotherapy on HRQoL is likely to differ depending on performance status (28).

OUR RESULTS COMPARED TO OTHER FINDINGS/OTHER REVIEWS OR RESULTS

In the reassessment of Lilly's economic evaluation submitted to NICE, the ICER per QALY gained was estimated to be GBP 47 000 (11), approximately NOK 439 000 which is much lower than the results presented here. The cost per cycle of procuring and administering pemetrexed were approximately 74% higher in our context than in the UK setting at the time of publication. The Lilly submission also included a QALY gain which was 0.02 points higher than our estimate (0.27 vs 0.25). The estimates of life years gained were fairly similar. In a US study by Klein *et al.* from 2010, which was also based on the JMEN trial, compared maintenance treatment with pemetrexed and BSC to "observation" (watchful waiting) and BSC. They found a cost per life year gained in the non-squamous patient group of USD122 371 (approx NOK715 000), but figures per QALY were not presented. The fact that there exist few economic evaluations and clinical trials available makes it difficult to draw any meaningful comparisons with our results.

Conclusions

NEED FOR FURTHER RESEARCH

This health technology assessment is based on only one clinical trial, and efficacy data in the economic analysis was taken from a subgroup of that trial. The trial may not represent Norwegian clinical practice very well, and it may therefore be advantageous to undertake clinical studies in Norway where the efficacy of pemetrexed for maintenance treatment in NSCLC patients is examined. Since there is also a lack of appropriate, preference-based quality of life data in this field, such outcomes should be included in future studies.

IMPLICATIONS FOR PRACTICE

Maintenance treatment with pemetrexed seems to be well tolerated, and leads to an increase in median overall and progression-free survival compared to a regimen of BSC alone, especially in non-squamous NSCLC. Whether the maintenance treatment with pemetrexed compared to watchful waiting is to be considered cost-effective depends on whether the threshold of NOK 500 000 is applied to QALYs gained in which case it most likely is not, or life years gained in which case it most likely is. We have not examined the cost-effectiveness of pemetrexed used in other treatment contexts.

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xls+%22VEDLEGG+5A+TIL+ISF-
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Appendices

APPENDIX 1: SEARCH STRATEGIES

Database: EMBASE, Ovid MEDLINE(R)

1   pemetrexed/
2   pemetrexed.mp.
3   or/1-2
4   lung non small cell cancer/ use emez [Embase]
5   Carcinoma, Non-Small-Cell Lung/ use prmz [Medline]
6   (non small cell lung adj (cancer or carcinoma)).tw.
7   or/4-6
8   3 and 7
9   8 use emez [Embase]
10 8 use prmz [Medline]
11 limit 9 to "treatment (2 or more terms high specificity)"
12 limit 10 to "therapy (specificity)"
13 11 or 12 [RCT]
14 "Cost Benefit Analysis"/ use emez [Embase]
15 Cost-Benefit Analysis/ use prmz [Medline]
16 "Cost Effectiveness Analysis"/ use emez [Embase]
17 "Cost Minimization Analysis"/ use emez [Embase]
18 "Cost Utility Analysis"/ use emez [Embase]
19 (cost* adj2 (benefit* or effective* or minim* or utilit*)).tw.
20 cba.tw.
21 cea.tw.
22 cua.tw.
23 Economic Evaluation/ use emez [Embase]
24 Economics, Medical/ use prmz [Medline]
25 Health economics/
26 (health economic? or economic evaluation?).tw.
27 Pharmacoeconomics/
28 Economics, Pharmaceutical/ use prmz [Medline]
29 (pharmacoeconomic? or (pharmac* adj economic?)).tw.
30 Technology Assessment, Biomedical/ use prmz [Medline]
31 technology assessment?.tw.
32 or/14-31 [Filter: Cost effect./-utility]
33 9 and 32
34 10 and 32
35 33 or 34 [Embase or Medline: Econ. eval]

Database: Cochrane Library

Results: Clinical Trials [56] | Economic Evaluations [4]

#1 MeSH descriptor Carcinoma, Non-Small-Cell Lung, this term only

#2 (non small cell lung carcinoma):ti,ab,kw

#3 (non small cell lung cancer):ti,ab,kw

#4 (non small cell lung neoplasm):ti,ab,kw

#5 (#1 OR #2 OR #3 OR #4)

#6 pemetrexed:ti,ab,kw

#7 (#5 AND #6)

Database: CRD

NHS EED (10)

# 1	MeSH Carcinoma, Non-Small-Cell Lung EXPLODE 1
# 2	"Non-Small-Cell Lung Carcinoma"
# 3	"Non-Small Cell Lung cancer"
# 4	"Non-Small Cell Lung neoplasm"
# 5	#1 or #2 or #3 or #4
# 6	pemetrexed
# 7	#5 and #6

APPENDIX 2: RISK OF BIAS

Study	Ciuleanu 2009	
Adequate sequence generation	"A computerised, interactive, voice-activated response system (IVRS) at a central location controlled random assignment for all study sites."	Yes
Allocation concealment	The investigator provided the necessary information to the unmasked pharmacist or designee who called the IVRS to obtain the patient's treatment assignment. Patients and the study team were all masked to the treatment assigned.	Yes
Blinding of participants, personnel and outcome assessors **– progression free survival and overall survival**	Blinding of participants and key study personnel were ensured. To preserve the masking of the patient and the personnel involved in patient assessments or data collection, an unmasked third party, such as a pharmacist, was designated.	Yes
Incomplete outcome data addressed **– all outcomes**	Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups *Figure 1:* Trial profile includes reasons for loss to follow-up	Yes
Free of selective report-	The study protocol is available and all of the study's pre-	Yes

ing – all outcomes	specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way. The primary endpoint of progression-free survival and the secondary endpoint of overall survival were analysed by intention to treat. "This study is registered with ClinicalTrials.gov, number NCT0010280"	
Free of other bias	This study appears to be free of other sources of bias. Funded by Eli Lily, and conflict of interest has been claimed in the study.	Yes

Short form:

Study	Ciuleanu 2009
Adequate sequence generation	Yes
Allocation concealment	Yes
Blinding of participants, personnel and outcome assessors – progression free survival	Yes
Blinding of participants, personnel and outcome assessors – overall survival	Yes
Incomplete outcome data addressed – all outcomes	Yes
Free of selective reporting – all outcomes	Yes
Free of other bias	Yes
Overall conclusion	Low risk of bias

APPENDIX 3: GRADE EVIDENCE PROFILE

Author(s): LKJ, IS
Date: 2011-12-20
Question: Should Maintenance pemetrexed vs best suppotive care be used in NSCLC?
Settings: hospital
Bibliography: Ciuleanu et al. Lancet 2009

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Maintenance pemetrexed	Best suppotive care	Relative (95% CI)	Absolute	Quality	Importance
		Quality assessment					No of patients		Effect			
Progression free survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/441 (0%)[3]	0/222 (0%)[3]	HR 0.50 (0.42 to 0.61)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Overall survival												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	_[3]	-	HR 0.79 (0.65 to 0.95)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Drug related toxic effects (grade III or IV) (assessed with: 6 month)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[2]	none	70/441 (15.9%)	12/222 (5.4%)	RR 0.88 (0.84 to 0.92)	6 fewer per 1000 (from 4 fewer to 9 fewer)	⊕⊕OO LOW	IMPORTANT
Neutropenia (all grades) (assessed with: 6 month)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[2]	none	26/441 (5.9%)	0/222 (0%)	RR 0.95 (092 to 0.97)	-	⊕⊕OO LOW	IMPORTANT
Fatigue (all grades) (assessed with: 6 month)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	[4]	serious[2]	none	108/441 (24.5%)	23/222 (10.4%)	RR 0.84 (0.79 to 0.90)	17 fewer per 1000 (from 10 fewer to 22 fewer)		IMPORTANT
Progression free survival (non-squamous population)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	serious	serious[2]	none	0/325 (0%)	0/156 (0%)	HR 0.44 (0.36 to 0.55)	-	⊕⊕OO LOW	CRITICAL
								0%		-		
Overall survival (non-sqaumous population)												
1[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/325 (0%)	0/156 (0%)	HR 0.70 (0.56 to 0.88)	-	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		

[1] Ciuleanu T 2009

[2] Only one study.

[3] Numbers at not available when estimate is HR

[4] Few events

APPENDIX 4: COSTS

Drug costs

Drug dosage regimens and premedication specifications have been taken from The Norwegian National Pharmacological Cacner Treatment Registry (Oncolex)
All retail prices from Norwegian Medicines Agency, as reported in Norwegian Pharmaco Catalogue of Medicines in May 2011 (inclusive of VAT).

Pemetrexed
The cost per cycle of NOK 24 300 has been taken from the price quoted for pemetrexed 500 mg/m2 for NSCLC in Oncolex per November 2011 , which includes premedication and preparation at the hospital pharmacy. The price is based on an average patient body surface of 1.73m2.

Second line treatment

Second line treatment in both arms involves either docetaxel (i.v. infusion) OR erlotinib tablets, the costs of which are estimated as follows:

Docetaxel:
Based on the above source, the price of docetaxel 75 mg/m2 per cycle including premedication is: NOK 6 100

Erlotinib
One 150 mg tablet per day (21 day cycle)
Cost per 30 tablets= NOK 22 168.60
21 tablets @ NOK 738.95= NOK 15 518

The respective fractions of docetaxel and erlotinib use in second line treatment is uncertain, and therefore varied in the PSA in a normal distribution, (mean 50%, std. dev=35.36%). This will not only pertain to drug costs, but also to staff time since the former is given in hospital while the latter is taken at home.

Staff costs

Staff costs per cycle are dependent on the time allocated per patient per cycle, which is in turn to some extent determined by the drug administered in the cycle. For example, pemetrexed and docetaxel have to be given as i.v. infusions, whereas erlotinib is taken as a tablet at home. Visits to the hospital for monitoring purposes and best supportive care will nevertheless be necessary regardless of which drug regimen the patient is on. Such costs are however incorporated in the calculation of best supportive care costs (see separate section further down).

The costs of specialist nurses involved in administering the i.v. chemotherapy courses have been incorporated were calculated on the basis of hourly wage rates and the time (depending on drug regime) allocated per patient per cycle for chemotherapy. Costs associated with other types of staff and administration are assumed to be similar for both model arms, while the costs of oncologist consultations are assumed to be covered in the total costs of best supportive care (see below). The mean salary per month for specialist nurses was multiplied by 1.4 to account for social expenses. A gamma distribution with a standard error of 1.515was used in the probabilistic sensitivity analysis, based on the distribution of older salary figures by years of experience from the Norwegian Nurses Organisation[6] . It was not possible to find a source that could be used to calculate overhead costs as a percentage of specialist nurse salaries. We have therefore varied an overhead cost factor in a probabilistic sensitivity analysis between 1,25 and 1.5 (mean 1.375) (see Appendix 7).

Mean salary specialist nurse per month: NOK 30 758
Mean number of standard.* working hours: 152
Mean cost per hour: NOK 203
   Incl. social expenses (x 1.4) : NOK 284
   incl. overhead costs (x 1,375) NOK 391

*not including overtime and extra shifts), 35-hour week

Best supportive care costs

The costs of best supportive care in the different states in the model are shown in table A1 and are calculated as follows:

Progression-free and progressed states

In the progression-free and progressed states, non-hospitalised patients are assumed to require an outpatient consultation every 6-9 weeks (every second to third cycle), which implies a mean number of consultations per cycle of 0.42 (for distribution see Appendix 7). We also assumed that there may be a reduction in the need for BSC while on active chemotherapy. This has been incorporated into the model by reducing the BSC costs by a factor of 0 to 0,5 (mean 0,25) for patients on pemetrexed as first-line treatment and for all patients on second-line treatment (see Appendix 7 for distribution).

Palliative state

In the palliative state, we assume that no chemotherapy is given and that BSC costs rise due to an expected increase in the rate of hospitalisation. Of the total lifetime in the palliative state covered in the study Nieder *et al.* 2010 (121 days)., the percent-

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[6] Statistics 2010, table 0810

age of days spent n a nursing home and hospital was 4% and 8% respectively. A 121-day probability of 12% of spending time in either a nursing home or a hospital) translates into a three-week or cycle probability of 0,021942 and a mean additional cost in the palliative cycle of NOK 35. (See formula from Briggs' *et al.* 2006 in the main text).

Table A1: Costs of best supportive care per cycle

Specification	
DRG unit price, NOK	36 968
DRG weight 904C outpatient consultation, tumour in the lungs	0,026
DRG-weighted price per consultation, NOK	961
Plus patient co-payment, NOK	307
Total cost per consultation, NOK	1 268
Estimated mean number of consultations per cycle	0,42
Mean costs per cycle, progression-free/progressed states, when not on chemotherapy, NOK	533
Estimated reduced mean proportion of BSC costs when on active chemotherapy (distribution from 1 to 0,5)	0,75
Mean costs per cycle, progression-free/progressed states, when on chemotherapy, NOK	399
Additional mean costs per cycle in palliative state (no chemotherapy)	35
Total mean costs per cycle, palliative state (no che-motherapy)	568

Costs of treating adverse events

The cost of treating nausea/vomiting, i.e. an emetic episode, has been taken from the report by Pike *et al.* 2008 (25) which describes the resource use involved in such treatment in Norway in 2007. All patients are assumed to receive suppositories of 4x20 mg metoclopramide. Since this is a grade 3 or 4 toxicity, it further assumed that all patients are given additional treatment in the outpatient clinic (the cost of which was estimated by Pike *et al.* to be NOK 750 in 2007-prices) and furthermore that 10% are admitted to hospital (also estimated by Pike *et al.* to be 8 277 NOK per

episode, see table below). The total cost of treating an emetic episode in 2010-prices is thus estimated to be NOK 1 748.

Table A2: Cost of an emetic episode

Specification	2007-prices, NOK	2011-prices, NOK
Cost per outpatient consultation	750	823
Assume 10% hospital admissions (at NOK 9 101 per admission)	828	910
Cost of 4 x 20 mg metoclopramide		34
Estimated cost per antiemetic episode		1 767

The costs of managing cases of anaemia and neutropenia were taken from a cost-effectiveness study by Möller *et al.* 2011, which based its adverse events costs on a survey of Norwegian and Swedish clinical experts:

> This survey provided the frequency and type of laboratory and disease monitoring, as
> well as the treatment and location of care for treatment related
> AEs within the Norwegian context. Costs for these
> events were taken from official Norwegian price lists, physician
> fees, and the Norwegian DRG database" Möller 2011, p. 694

The costs of managing anaemia and neutropenia were differentiated by grade and we have therefore used the mean estimate in our model, as shown in the table below.

Table A3: Cost of treating anaemia and neutropenia

Adverse event	Grade 3	Grade 4	Mean
Anaemia	8 457	8 457	8 457
Neutropenia	5 770	9 222	7 496

APPENDIX 5: MODEL STRUCTURE
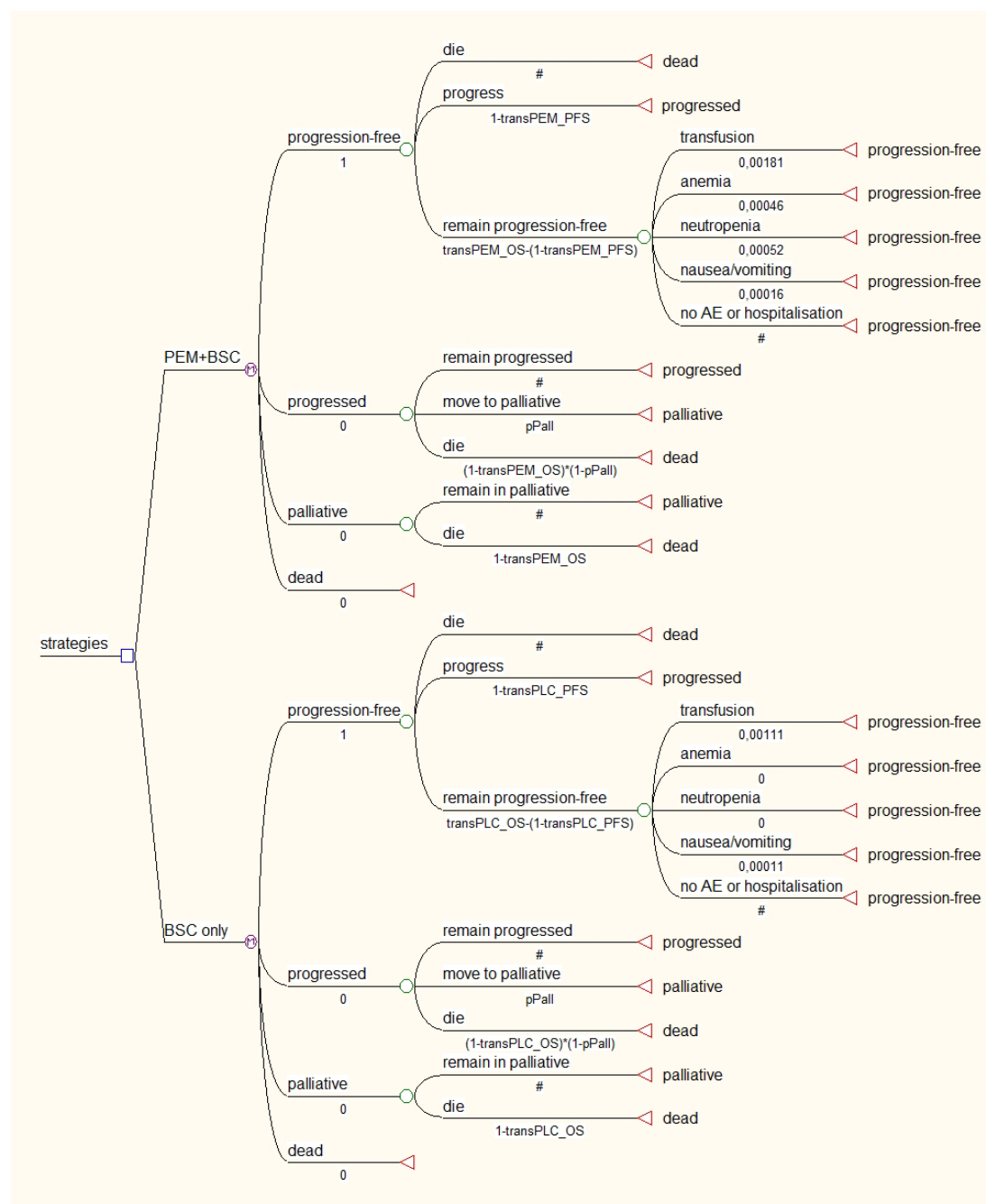
APPENDIX 6: TORNADO DIAGRAM REPORT

Variable	Low EV	High EV	Low Input	High Input
	NOK	NOK		
pem drug cost per average patient per cycle including premedication	619K	768K	19440	24300
	NOK	NOK		
PEM time spent per cycle, Specialist Nurse, hours	750K	774K	0	2
	NOK	NOK		
Specialist nurse, salary per hour, NOK	764K	786K	300	800
	NOK	NOK		
costs of managing neutropenia	768K	768K	3748	14992
	NOK	NOK		
cAnaemia	768K	768K	4229	16914
	NOK	NOK		
cost of treating nausea/vomiting	768K	768K	874	3496

APPENDIX 7: DISTRIBUTIONS

Description	Parameters/Info
Specialist Nurse, salary per month, NOK	Gamma, alpha = (30758^2)/(1515^2), lambda = 30758/(1515^2); Expected value: 30758
distr hazard ratio overall survival	Log-Normal, u (mean of logs) = -0,356674944, sigma (std dev of logs) = 0,115304446; Expected value: 0,704668791
distr hazard ratio progression free survival	Log-Normal, u (mean of logs) = -0,755022584, sigma (std dev of logs) = 0,123325391; Expected value: 0,473587775
share of docetaxel in second line treatment	Normal, Mean = 50, Std Dev = 35,36; Expected value: 50
distr overhead cost factor	Gamma, alpha = (1,375^2)/(0,176776695^2), lambda = 1,375/(0,176776695^2); Expected value: 1,375
distr QoL progression-free state	Beta, Real-numbered parameters, alpha = ((0,6532^2)*(1-0,6532)/(0,02223^2)), beta = (0,6532*(1-0,6532)/(0,02223^2))-((0,6532^2)*(1-0,6532)/(0,02223^2)); Expected value: 0,6532
distr QoL progression	Beta, Real-numbered parameters, alpha = ((0,4734^2)*(1-0,4734)/(0,02169^2)), beta = (0,4734*(1-0,4734)/(0,02169^2))-((0,4734^2)*(1-0,4734)/(0,02169^2)); Expected value: 0,4734
distr QoL palliative state	Beta, Real-numbered parameters, alpha = ((0,4734^2)*(1-0,4734)/(0,02169^2)), beta = (0,4734*(1-0,4734)/(0,02169^2))-((0,4734^2)*(1-0,4734)/(0,02169^2)); Expected value: 0,4734
distr QoL Nausea	Beta, Real-numbered parameters, alpha = ((0,011433333^2)*(1-0,011433333)/(0,0039^2)), beta = (0,011433333*(1-0,011433333)/(0,0039^2))-((0,011433333^2)*(1-0,011433333)/(0,0039^2)); Expected value: 0,011433333
distr QoL Anemia	Beta, Real-numbered parameters, alpha = ((0,07346^2)*(1-0,07346)/(0,01849^2)), beta = (0,07346*(1-0,07346)/(0,01849^2))-((0,07346^2)*(1-0,07346)/(0,01849^2)); Expected value: 0,07346
distr QoL Neutropenia	Beta, Real-numbered parameters, alpha = ((0,08973^2)*(1-0,08973)/(0,01543^2)), beta = (0,08973*(1-0,08973)/(0,01543^2))-((0,08973^2)*(1-0,08973)/(0,01543^2)); Expected value: 0,08973
distr hazard rate OS PLC	Log-Normal, u (mean of logs) = -2,748872196, sigma (std dev of logs) = 0,015949364; Expected value: 0,064008141
distr hazard rate PFS placebo	Log-Normal, u (mean of logs) = -1,120857898, sigma (std dev of logs) = 0,008729231; Expected value: 0,326012421

distr cost BSC	Gamma, alpha = (425^2)/(425^2), lambda = 425/(425^2); Expected value: 425
distr hospitalisations and nursing home stays in palliative state	Gamma, alpha = (0,022^2)/(0,081^2), lambda = 0,022/(0,081^2); Expected value: 0,022
proportional reduction of BSC while on chemotherapy	Beta, Real-numbered parameters, alpha = ((0,75^2)*(1-0,75)/(0,353553391^2)), beta = (0,75*(1-0,75)/(0,353553391^2))-((0,75^2)*(1-0,75)/(0,353553391^2)); Expected value: 0,75