# A Phase I Dose Escalation Study of Cisplatin, Pemetrexed and Radiotherapy for Inoperable Stage III Non-Small Cell Lung Cancer.

No registrations found.

| | |
|---|---|
| **Ethical review** | Positive opinion |
| **Status** | Recruiting |
| **Health condition type** | - |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON22825

**Source**
Nationaal Trial Register

**Brief title**
A Phase I Dose Escalation Study of Cisplatin, Pemetrexed and Radiotherapy for Inoperable Stage III Non-Small Cell Lung Cancer

**Health condition**

NSCLC, inoperable stage III

### Sponsors and support

**Primary sponsor:** ErasmusMC Rotterdam, afdeling Longziekten
**Source(s) of monetary or material Support:** Eli Lilly

### Intervention

### Outcome measures

**Primary outcome**

The primary objective of this study is to determine the maximum tolerated dose of pemetrexed, cisplatin and radical involved-field radiotherapy in the treatment of patients with unresectable Stage III NSCLC. Two MTD's will be determined:

1. MTD of pemetrexed and cisplatin in combination with conventional radiotherapy .

2. MTD of pemetrexed and cisplatin with hypofractionated radiotherapy.

**Secondary outcome**

The secondary objectives of this study are the following:

1. the incidence and nature of acute toxicities.

2. the incidence and nature of delayed toxicity at 3-6-12 months after final radiotherapy treatment

3. objective tumour response

4. progression free survival

5. overall survival

# Study description

**Background summary**

Summary EMC 05/121 A Phase I Dose Escalation Study of Cisplatin, Pemetrexed and Radiotherapy for Inoperable Stage III Non-Small Cell Lung Cancer

Overall study design

This open-label, non-randomised Phase I study is designed to determine the maximum tolerated dose of cisplatin, pemetrexed and thoracic radiotherapy that can safely be administered to patients with unresectable Stage III NSCLC who have received no prior chemotherapy.

Treatment schedule

All patients will receive one cycle of pemetrexed 500 mg/m2 and cisplatin 80 mg/m2 (standard systemic dose) before concurrent radiotherapy starts. One cycle is 3 weeks. Patients should have recovered fully from the first cycle of chemotherapy before they

continue with the concurrent chemo radiation part.
Patients will be entered in cohorts of three.

The first cohort of patients will receive three-weekly infusions of pemetrexed at a dose of 400 mg/m2 and cisplatin 60 mg/m2 which will be administered on the morning of Day 1 of the second course of chemotherapy. Radiotherapy will be administered 2 hours after the chemotherapy administration, at an initial dose of 66 Gy in 33 fractions over 45 days. Each agent will be escalated independently, to allow further cohorts to be treated while allowing at least 6 weeks after the completion of radiotherapy to assess acute toxicity. At any dose level, before escalation of the dose of that agent, all 3 patients treated in the previous cohort in which that agent was escalated, or in cohort 1, must have completed the entire 6 weeks of treatment and have been assessed for acute toxicity 6 weeks after completing radiotherapy. In case of grade 4 dose-limiting toxicity no further treatment or escalation is allowed. If 1 patient experiences a grade 3 dose-limiting toxicity, a further 3 patients will be treated at that dose level. If no patients in the second trio experience a dose-limiting toxicity, dose escalation may continue. If one additional instance of dose-limiting toxicity occurs (total 2 of 6 patients within one cohort), dose escalation will be stopped and the cohort will be expanded to 9 patients. If no more than 3 of 9 patients experience DLT the MTD is confirmed.

Inclusion criteria

1.Histologically or cytologically confirmed diagnosis (bronchial brushings and washings or CT-guided fine needle aspiration) of NSCLC, stage III which is not amenable to surgical resection

2. Unidimensional or bidimensional disease on CT scan of the chest. Measurable tumour and/or nodal mass not exceeding 6 cm in largest diameter.

3. Received no prior chemotherapy or radiation therapy.

4. Performance Status 0-1 on the WHO Scale (Appendix A)

5. Estimated life expectancy of at least 24 weeks.

6. Patient compliance and geographic proximity that allow adequate follow-up.

7. Adequate bone marrow reserve: White blood count (WBC) ³ 3.0 ´ 109/L, platelets ³ 100 ´ 109/L, haemoglobin ³ 6 mmol/L (³ 9.6g/dl )

8. Adequate respiratory function: Forced expiratory volume in 1 second (FEV1) ³1.0 L/s (>30%) and transfer factor for carbon monoxide (DLCO) ³ 40% of predicted.

9. Age ³18 years.

10. Written informed consent from patients.

11. Effective use of contraception for both males and females if appropriate during and for 3 months after end of study.

Exclusion criteria

1. Evidence of active infection at the discretion of the investigator.

2. Inadequate liver function: bilirubin >1.5 times normal or ALT or AST >3 times normal.

3. Inadequate renal function: calculated creatinine clearance using Cockcroft-Gault formula of < 60 ml/min.

4. Clinical significant hypercalcemia

5. Evidence of extrathoracic metastases/ Stage IIIB with supraclavicular lymph nodes.

6. Uncontrolled superior vena cava syndrome, uncontrolled haemoptysis, or other situations which make complete staging or treatment planning impossible.

7. Pleural effusion with positive cytology.

8. Pregnancy. (excluded by dipstick or serum test)

9. Breast feeding.

10. Serious concomitant systemic disorder incompatible with the study.

11. Second primary malignancy (except in situ carcinoma of the cervix or adequately treated non-melanomatous skin cancer ), unless off treatment and in remission for greater than 5 years.

12. Use of any investigational agent in the month before enrollment into the study.

13. Any co-morbid pulmonary disease that may put the patient at risk of toxicity: specifically interstitial lung disease (fibrosis) and serious chronic pulmonary disease.

14. Patients who are unable to interrupt aspirin, other nonsteroidal anti-inflammatory drugs for a 5-day period starting 2 days before administration of pemetrexed (8-day period for long acting agents such as piroxicam). Patients that cannot be treated with folic acid and vitamin B12 and dexamethasone.

15. Presence of clinically detectable (by physical examination) third-space fluid collections, for example ascites or pleural effusions that cannot be controlled by drainage or other procedures prior to the study entry.

16. Use of Growth factors

## Study objective

The optimal management of locoregionally advanced NSCLC is evolving. Multimodality treatment is rapidly becoming the most common approach to stage III NSCLC. ASCO guidelines recommend initial chemotherapy (platinum-based, 2 or 3 cycles) combined with radiotherapy in patients with adequate performance status and lung function.

For patients with inoperable stage III disease, concomitant chemoradiotherapy1, appears to provide an additional survival advantage. Although no single drug combination has been established as best, nor has the optimum radiation dose been defined. Pemetrexed is a new agent with promising activity in NSCLC and with potential radiosensitising activity. 11-12 Pemetrexed has activity as single agent in NSCLC and in combination therapy. The combination of Cisplatinum and Pemetrexed has been explored in Phase I, II and III settings. A Phase I trial of Pemetrexed with radiation has been explored. 39 Radiosensitising activity of Pemetrexed in vitro, its activity in combination with Cisplatinum provide the rationale for combining radiotherapy and pemetrexed in a phase I trial.

Attempts at radiation dose escalation in patients with stage III disease have not succeeded in escalating significantly beyond 66 Gy 24-26,40. However this has been in 1.8-2.25 Gy fractions given over 6-7 weeks, and overall treatment time is also known to be a significant factor in determining radiation response in many tumours.

In this study we propose to investigate independent dose escalation of all 3 agents – of the chemotherapeutic agents cisplatin and pemetrexed in conventional fashion, and of the radiotherapy by shortening overall treatment time.

## Intervention

All patients will receive one cycle of pemetrexed 500 mg/m2 and cisplatin 80 mg/m2 (standard systemic dose) before concurrent radiotherapy starts. One cycle is 3 weeks. Patients should have recovered fully from the first cycle of chemotherapy before they continue with the concurrent chemo radiation part.

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patient experiences a grade 3 dose-limiting toxicity, a further 3 patients will be treated at that dose level. If no patients in the second trio experience a dose-limiting toxicity, dose escalation may continue. If one additional instance of dose-limiting toxicity occurs (total 2 of 6 patients within one cohort), dose escalation will be stopped and the cohort will be expanded to 9 patients. If no more than 3 of 9 patients experience DLT the MTD is confirmed.

# Contacts

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# Eligibility criteria

## Inclusion criteria

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5. Evidence of extrathoracic metastases/ Stage IIIB with supraclavicular lymph nodes.

6. Uncontrolled superior vena cava syndrome, haemoptysis causing a decrease of blood hemoglobin of ³1 g/L (³0.062 mmol/L) in 24 hours, or other situations which make complete staging or treatment planning impossible.

7. Pleural effusion with positive cytology.

8. Pregnancy.

9. Breast feeding.

10. Serious concomitant systemic disorder incompatible with the study.

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16. Use of Growth factors

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Crossover |
| Masking: | Open (masking not used) |
| Control: | N/A , unknown |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 01-03-2006 |
| Enrollment: | 39 |
| Type: | Anticipated |

# Ethics review

Positive opinion

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|---|---|
| Date: | 15-08-2006 |
| Application type: | First submission |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| NTR-new | NL742 |
| NTR-old | NTR752 |
| Other | : N/A |
| ISRCTN | ISRCTN91946477 |

# Study results

**Summary results**
The investigators reserve the right to publish or present the results of this study provided that a copy of the manuscript or abstract is made available to Eli-Lilly for review at least 30 days prior to the expected date of submission. The 30 days period does not begin until receipt of the proposed publication or presentation at Lilly in Indianapolis, Indiana. This will be reviewed promptly and approval will not be withheld unreasonably. The investigators may proceed with the presentation or submission for publication; provided, however, that in the event Lilly has no reasonably belief that prior to such publication or presentation it must take action to protect its intellectual property interests, such as the filing of a patent application claiming an invention or a trademark registration application. We shall either delay such publication or presentation for an additional (60) days or until the foregoing actions have been taken, whichever shall first occur. In case of a difference of opinion between Eli Lilly and the investigators the content of the publication will be discussed in order to find a solution which satisfies both parties. We will assist Lilly in obtaining reprints of our publications resulting from the Study.
The names on the authorship list will be given according to the participation in the design and writing of the protocol as well as the accrual of patients in each site. The study will only be published once the study is completed and finalised. First authorship has been assigned to Drs.V. Surmont, Erasmus MC Rotterdam, if she provide the manuscript.