- NARLAL –
- Navelbine And Radiotherapy in Locally Advanced Lung cancer -

Induction chemotherapy with Carboplatin and Navelbine Oral® followed by concomitant Navelbine Oral® and irradiation in local-regionally advanced non-small cell lung cancer. A randomized phase II study.

Version 1.24 - 19.3.2009

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1. Background

1.1 Concurrent chemo-radiotherapy

Lung cancer is the major cause of cancer-related death in Europe and North America. About 75% to 80% of lung cancer is non-small-cell cancer (NSCLC) with approximately 40% of patients presenting with locally advanced disease. In patients with no malignant pleural effusions, the treatment options have been irradiation up to 60-70 Gy against the primary lung tumor and lymph nodes in mediastinum resulting in a median survival of 6 to 11 months and 5 years survival of 5%. The treatment have until recently consisted of irradiation of the tumor bed and areas around with high risk of relapse. The treatment has now being optimized by giving chemotherapy either before irradiation or concomitant with radiation or both. The irradiation technique have been improved by introduction of 3D-CT-scan based planning technique, and the prognosis have been somewhat improved. Data from Odense shows a 5 year survival rate of 16% at 5 years (1). The treatment of choice for locally advanced NSCLC is radiotherapy combined with chemotherapy since trials using inductions chemotherapy and/or concomitant chemotherapy have demonstrated increased median survivals to 13-15 months with a 5 years survival of 10-20%. The rationale for using of inductions chemotherapy has been to reduce the treatment volume by reducing the tumor burden and to eradicate micro-metastases.

A significant problem in the treatment of local advanced NSCLC is a high rate of local failure of up to 45% without distant metastases after irradiation. In 200 patients with NSCLC stage III treated in Odense the 1 year survival was 61%. 112 of these had received a platinum based induction chemotherapy regimen, and 3 had concomitant therapy with Taxotere. The local failure free survival was 70% 9 months after start of irradiation and 43 % after one year (unpublished data).

Concomitant chemotherapy and radiation has been demonstrated by Furuse et al. (2) and in the RTOG 9410 study (3) to be superior to sequential chemo-radiation. In these 2 studies the 3 year survival increased from 15% to 22% and from 22% to 28%, respectively. In a French study reported in 2005 (4) the 3 year survival increased from 19% to 25% by the use of concomitant chemotherapy and radiation compared with sequential use of chemotherapy and radiotherapy although the difference in this study was not statistically significant.

The chemotherapy used in these studies to combine with radiation have been Cisplatin plus a 2nd generation drugs like Vinblastine, Vindesine, Etoposide, and Mitomycin, and is to be expected that the use of a 3rd generation drug concurrently with radiotherapy may add to the chance of obtaining local control but also to the toxicity.

1.2 Radiation and Vinorelbine in NSCLC

Vinorelbine (Navelbine) is a semi-synthetic vinca alkaloid that is currently used in the treatment of NSCLC and as adjuvant treatment after surgery of NSCLC. Vinca alkaloids appear to exert their antitumor activity by binding to tubulin with high affinity. Two types of tubulin, alpha and beta, exist as dimers that polymerize to form microtubules, of which many cellular structures, including the mitotic spindle, are constituted. The cellular functions of microtubules include neurotrans-mission and mitosis. Vinca alkaloids are cell cycle–specific agents that arrest mitosis by interfering with microtubule assembly and inducing depolarization of microtubules. Like other vinca alkaloids, Vinorelbine may also interfere with amino acid, cyclic adenosine monophosphate (cAMP), and glutathione metabolism; with calmodulin-dependent calcium-transport–adenosinetriphosphatase activity; with cellular respiration; and with nucleic acid and lipid biosynthesis.

There is a prolonged terminal phase due to relatively slow efflux of Vinorelbine from peripheral compartments, which results in a long terminal-phase half-life, with average value ranging from 27.7 to 43.6 hours.

Vinorelbine is highly distributed in lung tissue, with the disposition rate being slower in tumor tissue than in healthy parenchyma. In a study of 13 patients all patients, but two, the Vinorelbine concentrations were lower in tumors than in healthy lung tissue. The median tumor/healthy tissue ratio were 0.09 (range 0.06 to 1.3) at 1 hour increasing to 0.55 (range 0.18 to 1.1) at 3 hour (5). This ratio increased between the 1-hour sampling time and the 3-hour time point as a consequence of a more than 5 fold increased concentration of Vinorelbine in the tumor.

Vinorelbine has been produced as an oral formulation in soft gelatine capsules. At therapeutic doses the absolute bioavailability is close to 40% with an inter-individuel variability in drug exposure independent of the routes of administration (6). Oral Vinorelbine is rapidly absorbed with a T_{max} 14 ± 7 hours. Analyses thus demonstrated bioequivalence between 80 mg/m^2 oral and 30 mg/m^2 i.v., and between 60 mg/m^2 oral and 25 mg/m^2 i.v.

Studies with radiation and Vinorelbine plus a platinum compound:
Vinorelbine is a strong radiation sensitizer in *in vitro* systems (7). The studies showed that Vinorelbine can potentiate the antitumor effects of radiation and that the potentiation is cell cycle-dependent, with the maximal effect being obtained when the cells are in the G_2 phase of the cell cycle. Masters et al. published a phase I study of Vinorelbine, Cisplatin, and concomitant thoracic radiation in the treatment of advanced chest malignancies (8). The radiation dose was 60 Gy in 30 fractions (F), and the MTD of Vinorelbine was found to be 15 mg/m^2 i.v. administered day 1, 8, 22, and 29 together with Cisplatin 80 mg/m^2 i.v. day 1 and 22. No information was given on the timing between radiation and Vinorelbine on the days of the Vinorelbine administration. The dose limiting toxicity was grade 4 esophagitis which appeared in 1/9 patients at the MTD level. However, at the same level another patient experienced a grade 4 pneumonia which the investigators did not relate to the concurrent therapy.

In a subsequent randomized phase II study Vokes continued to use a dose of Cisplatin 80 mg/m^2 every day 1 and 22 together with Vinorelbine 15 mg/m^2 day 1, 8, 22 and 29 concurrent with 66 Gy/33 F (9). In 55 patients, esophagitis grade 3 was seen in 13% and grade 4 was seen in 12%. Dyspnoe grade 3 was seen in 10% and grade 4+ was seen in another 10% of the patient with one patients dying of treatment-related respiratory failure. Another patient was reported with ARDS (acute respiratory distress syndrome). In this study more grade 4 pulmonary toxicity was seen compared with patients receiving concurrent Gemcitabine and Cisplatin. On the other hand, they did not experience a higher frequency of grade 3-4 esophagitis. No information was given on the timing between radiation and Vinorelbine on the days of the Vinorelbine administration. The radiation technique used in the Masters and Vokes studies did not include 3-D conformal radiotherapy and use of Cobalt machines was allowed. This may have lead to a higher the frequency of especially pneumonitis.

From a similar study of 18 patients using Cisplatin 60 mg/m^2 day 1 every 4 weeks, Sekine et al. recommended a dose of Vinorelbine 20 mg/m^2 i.v. day 1 and 8 every 4 weeks given for two cycles concurrent with 60 Gy/ 30 F (10). In this study the radiotherapy started day 2 and a split of 4 days was introduced before the second cycle of chemotherapy. Only the day 8 vinorelbine in each cycle was administered the same day as radiotherapy. In this study no cases of grade 3-4 esophagitis or pulmonary toxicity was observed.

In retrospective study of 73 patients using Cisplatin 80 mg/m^2 day 1 combined with Vinorelbine 20 mg/m^2 i.v. day 1 and 8 every 4 weeks, Naito et al reported 7% grade 3 + 4 toxicity including one toxic death due pulmonary toxicity (11). Esophagitis grade 3 was reported in 4% of the cases.

In retrospective study of 66 high risk patients (PS 2-3, age >70, weight loss or severe comorbidity) using Cisplatin 20 mg/m^2 or Carboplatin 70 mg/m^2 day 1-5 and day 29 -33 combined with weekly Vinorelbine 12.5 mg/m^2 i.v., Semrau et al reported 5% grade 3-4 esophagitis and 3%

grade pneumonitis (12). One case of a tracheal-esophageal fistula was observed, and one patient died with no identifiable cause of death. In the study conventional fractional radiotherapy was used to an equivalent dose of 66 Gy in 35 fractions. 94% completed the radiation schedule.

Winterhalder using 60 Gy in 30-33 F together with daily administered Cisplatin 6 mg/m^2 and weekly Vinorelbine 15 mg/m^2 reported 18% grade 3 esophagitis. Non-neutropenic infections, mainly pulmonary infection, was seen in 35% of the patients, but the authors did not comment on possible lung toxicity (13).

Zatloukal reported a randomized trial of Cisplatin and Vinorelbine given before (sequentially) or concurrently with 60 Gy/30 F (14). Altogether 102 patients were enrolled in the trial. The doses were Cisplatin 80 mg/m^2 day 1 and Vinorelbine 12.5 mg/m^2 i.v. on days 1, 8, 15 of a 28-day cycle repeated once when used concurrently with radiotherapy. An improved survival was seen in the concurrent arm (p=0.025). The median survival was 16.6 months compared with 12.9 months in the sequential arm. The 1 year survival 69% vs. 53%, the 2 year survival 34% vs. 14% and the 3 year survival 19% vs. 10%. An increased frequency of Esophagitis grade 3-4 was also noted, 18% vs. 4% while no excess pneumonitis grade 3-4 was found (1% vs. 4%).

Hirose reported a phase II study of 26 patients with unresected stage III NSCLC. The dose of Vinorelbine i.v. was 20 mg/m^2 day 1 and 8, the dose of Cisplatin 40 mg/m^2 day 1 and 8 administered every 3 week (15). Esophagitis grade 3 was observed in 8% of the patients, and Pneumonitis grade 3-4 was observed in 8%. No information on the timing between Vinorelbine and the radiation were given.

Cardenal et al. reported preliminary data from a randomized phase II trial of sequential versus concurrent Carboplatin and Vinorelbine with 60 Gy /30 F (16). 38 patients participated in the concurrent arm. In this the dose of Vinorelbine was 15 mg/m^2 day 1, 8, 22 and 29. The concurrent dose of Carboplatin was AUC 2.5 the same days. Esophagitis grade 3-4 was observed in 3%, and 8% reported grade 3-4 dyspnoe. In the sequential arm the figures was 0% and 14%. The median survival was 14 months in the concurrent arm compared with 8 months in the sequential arm.

Beckmann reported a phase I study of oral Vinorelbine and Cisplatin concurrent with radiotherapy 66 Gy /33 F (17). He tested 3 levels of oral Vinorelbine 40, 50, and 60 mg/m^2 Vinorelbine orally day 1, 8, 15, 29, 36 and 43. Cisplatin 20 mg/m^2 was given i.v. on days 1-4 and 29-32. Radiotherapy was delivered 1-2 hours after drug administration. The dose limiting toxicity was esophagitis. 3 of 5 patients developed early grade 3 esophagitis with the 3rd dose level. The recommended dose of Vinorelbine oral for phase II study was therefore given to 50 mg/m^2 administered 6 out 7 weeks together with radiation.

Krzakowski et al. reported data from a phase II study of 54 patients with unresected stage III NSCLC (18). After two cycles of neoadjuvant chemotherapy Cisplatin and oral Vinorelbine, 47 of the patients received oral Navelbine and Cisplatin i.v. concurrent with 66 Gy /33 F. The dose of Navelbine oral during radiotherapy was 40 mg/m^2 day 1 and 8 every 3 weeks for 2 cycles concurrent with Cisplatin 80 mg/m^2. No grade 3 or 4 esophagitis or pulmonary toxicity was reported. The overall response rate was 54% in 52 evaluable patients from the intention to treat population. The median survival was reported to 23.4 months, one and two year overall survival 74% and 48%. Only 2 patients (4%) experienced dysphagia grad 3, and only one case of late pulmonary fibrosis (2%) was reported.

Studies with radiation and Vinorelbine alone:

In a small Italian phase I study 9 patients had either 4 mg/m^2 or 5 mg/m2 5 days a week for 5 days together with radiation 55 Gy / 30 F (19). The MTD was determined to 4 mg/m^2 due to hematological toxicity of higher doses. Altogether 2/9 (22%) grade 3 esophagitis was seen, and 1/3 of patient treated with 5 mg/m^2 experienced grade 4 dyspnoe.

Garst reported a phase II trial of 3 times a weekly dosing of Vinorelbine 5 mg/m^2 administered concurrent with 66 Gy / 33 F (20). 36 patients were enrolled. Five patients (14%) experienced esophagitis grade 3, and 1 patient (3%) pneumonitis grade 3. No information was given on the timing between Vinorelbine and the radiotherapy.

Schwarzenberger reported the use of weekly oral Vinorelbine and palliative radiation 5 Gy in two fractions 6 hours apart once per week x 12 weeks in a phase I/II trial (21). The Vinorelbine was administered in the morning on the days of the radiation. The recommended dose was Vinorelbine 60 mg/m^2. No esophagitis or pneumonitis was reported. Only 12% of the patients received the planned dose of radiation.

In a phase I study Krzakowski reported the maximum tolerated weekly dose of oral Vinorelbine to 130 mg administered as 50 mg day 1, 40 mg day 3, and 40 mg day 5 every week together with 60 Gy/ 30 F (22). The oral Vinorelbine was given 2 hours prior to the radiation. No grade 3 or worse dysphagia and no pulmonary toxicity were reported. An update of the study has found the recommended dose to be 50 mg 3 times weekly.

Most of these studies are small. The occurrence of pneumonitis which should be regarded as the potentially most serous side effect, and esophagitis which may be very troublesome too, differs widely across the studies. In some cases this is probably due inadequate follow-up, but an explanation may be addition of platinum in most of the reports but not in all, and may be differences in the radiation technique. 3D-conformal radiation will lower the risk of pneumonitis and esophagitis and explain the rather high doses of oral Vinorelbine that Krzakowski found to be safe without observing significant degrees of pneumonitis and esophagitis. In many cases the studies does not supply information on the timing with the radiation. Based on this study, 3 weekly fixed doses of 50 mg seems to be safe with regard to pneumonitis with a radiation dose 60 Gy in 30 fractions, and a radiation dose of 66 Gy in 33 F may also be safe with regard to pneumonitis while esophagitis may constitute a problem.

No incidence of spinal cord injury has been reported. The radiation dose to the spinal cord has been reported to be in the range of 40 to 49 Gy in 2 Gy fractions.

Table 1: Doses of Vinorelbine used concurrently with conventional radiation of 55 Gy or more

Author	Year	No. pts.	Recommended dose of Vinorelbine	Route	Other drug	Radiation dose	Approx. equiv. weekly dose[3]) of oral Navelbine
Masters (8)	1998	37	15 mg/m^2 x4	i.v.	Cisplatin	60 Gy/30F/6w	25 mg/m^2 [1])
Gridelli (19)	2000	8	4 mg/m^2 /x5 x5	i.v.	*none*	55 Gy/30F/6w	42 mg/m^2 [1])
Garst (20) [*])	2001	36	5 mg/m^2 x3 x7	i.v.	*none*	66 Gy/33F/6.5w	38 mg/m^2 [1])
Vokes (9)	2002	55	15 mg/m^2 x4	i.v.	Cisplatin	66 Gy/33F/6.5w	25 mg/m^2 [1])
Zatloukal (14) [**])	2004	52	12.5 mg/m^2 x4	i.v.	Cisplatin	60 Gy/30F/6w	21 mg/m^2 [1])
Winterhalder (13)	2004	17	15 mg/m^2 x6	i.v.	Cisplatin	60 Gy/30-33F/6w	38 mg/m^2 [1])
Sekine (10)	2004	18	20 mg/m^2 x4	i.v.	Cisplatin	60 Gy/30F/6w	33 mg/m^2 [1])
Schwarzenberger (21) [*])	2005	32	60 mg/m^2 weekly	p.o.	*none*	60 Gy/24F/12w	60 mg/m^2
Hirose (15)	2006	26	20 mg/m^2 x4	i.v.	Cisplatin	60 Gy/30 F/6w	33 mg/m^2 [1])
Cardenal (16) [**])	2006	39	15 mg/m^2 x4	i.v.	Carboplatin	60 Gy/	21 mg/m^2 [1])
Beckmann (17)	2006	22	50 mg/m^2 x6	p.o.	Cisplatin	66 Gy/33F/7w	42 mg/m^2
Semrau (12)	2007	66	12.5 mg/m^2 x6	i.v.	Cis- / Carbo.	66 Gy/35F/7w	31 mg/m^2 [1])
Krzakowski (22) [**])	2007	15	50 + 40 +40 mg x6	p.o.	*none*	60 Gy/30F/6w	65 mg/m^2 [2])
Krzakowski (18)	2007	47	40 mg/m^2 x4	p.o.	Cisplatin	66 Gy/33F/6w	27 mg/m^2
Naito (11)	2008	73	20 mg/m^2 x4	p.o.	Cisplatin	60 Gy/30F/6w	33 mg/m^2

([*] Abstract only ([**] Abstract / poster
([1] Assuming a bioavailability of 40% of oral Navelbine ([2] Assuming a body surface of 2.0 m^2 ([3] The dose of Navelbine was calculated as an average weekly dose for all weeks of the radiation

All the above studies have used conventional fractionation schedules of radiotherapy. In a phase II study by Reguart accelerated, hyperfractionated radiotherapy was used in 37 patients with locally advanced radiotherapy 61.4 Gy given in a 23 day of 1.8 Gy fractions to a large field and a concomitant boost of 0.88 Gy in 5 weeks (23). The radiotherapy flanked before and after by two cycles of Cisplatin and Gemcitabine. The treatment was quite toxic with 30% grade 3-4 esophagitis and two toxic deaths. One incidence of esophageal stricture was observed. However, no cases of pneumonitis were observed.

1.3 Dose-effect of radiation in concomitant chemo-radiation

While a dose-response relationship has been established for survival and symptom control in palliative thoracic radiotherapy of NSCLC (24), only a few studies exists that examine the dose-effect of different doses in curatively intended radiotherapy of NSCLC. In a study recruiting patients in the 70'ties, a dose-response relation ship in 3 year survival was found between dose schedules of 40 Gy /20 F, 50 Gy /25 F to 60 Gy /30 F being 6%, 10%, and 15% (25). However, the difference disappeared at 5 years. A dose–response relation was also found in the local failure rate ranging from 58% to 35%. In the more modern CHART study, two different fractionation schedules were compared (26): a hyperfractionated, accelerated scheme of 54 Gy /36 F administered 3 fractions a day in 12 consecutive days (CHART), and 60 Gy /30 F administered 1 fraction a day 5 days a week for 6 weeks (conventional 60 Gy). The CHART regimen was superior to the conventional 60 Gy scheme, the 3 year survival being 20% and 13%. In a comparable study of the head and neck the CHART regimen was comparable to 66 Gy /33 F, and this is an indirect indication of a dose-response relationship exists in curative intended radiotherapy, but in no way a proof. No randomised studies of radiation dose-response in concurrent chemo-radiation of NSCLC have been published so far.

2. Objectives of the study

The objective of this trial is to test a convenient chemotherapy schedule with an oral formulation of radio-sensitizing Navelbine in concurrent chemo-radiotherapy in radical treatment of inoperable locally advanced non small cell lung cancer (stage IIB-IIIB) with radiotherapy. The trial is a randomized phase II study with two doses of radiotherapy. The primary objective of the study is examine the combination of Navelbine oral 150 mg of Vinorelbine administered in 3 weekly doses a week for 6-6½ weeks concomitant with curatively intended irradiation to 60 Gy (2 Gy x 30, 5 F á weeks) or 66 Gy (2 Gy x 33, 5 F á week) starting 3 weeks after two cycles of inductions chemotherapy with Navelbine oral and Carboplatin.

Primary endpoint:

- Local failure free survival at 9 months after start of radiotherapy

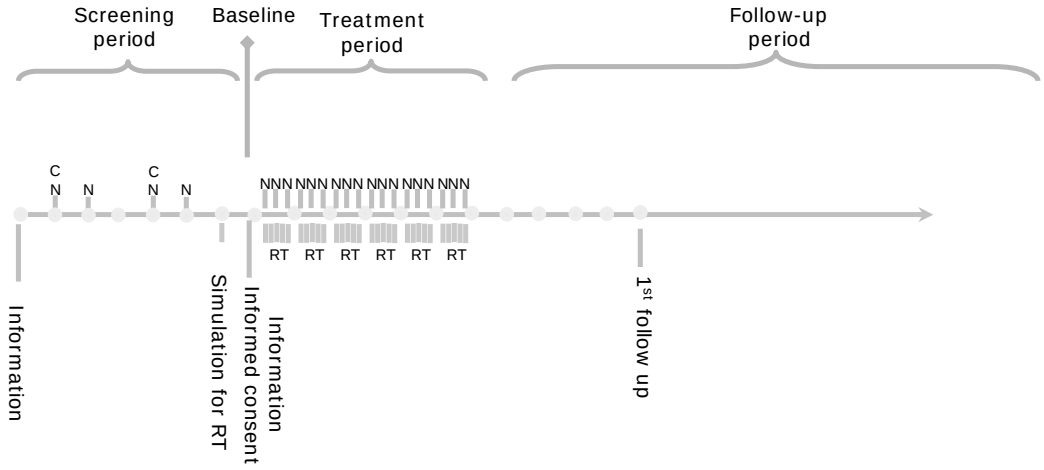
Secondary endpoints

- Toxicity
- Local tumour control
- Overall response rate (CR + PR)
- Local tumour control at 9 months evaluated by PET-CT
- Overall survival
- Disease free survival
- Late toxicity

3. Study design and dosing regimen

3.1 Study design

This study is an open label randomized multi-centre phase II trial in patients with inoperable locally advanced stage IIB –IIIB Non Small Cell Lung Cancer who fulfils the general criteria for curatively intended irradiation. The treatment plan consists of two courses of inductions chemotherapy followed of concomitant therapy chemo-radiotherapy 3 weeks after day 1 of the last induction chemotherapy has been given. The patients will be included in the study after completing the induction chemotherapy. Randomization will take place only if an acceptable dose plan can be obtained.



Figur 1: The time line in the study

3.2 Dosing regimen

Inductions chemotherapy: Two cycles of Navelbine oral and Carboplatin i.v. The doses of Navelbine oral is 60 mg/m^2 day 1 and 8 in the first cycle of 3 weeks, and 80 mg/m^2 day 1 and 8 during cycle 2 in case no hematological toxicity grade 4 occurs. The dose of Carboplatin is AUC 5 day 1 every three week. AUC may be calculated from serum creatinine, age, gender and weight (Cockroft-Calvert formulation), or be measured by urine creatinine clearance or by chrome EDTA clearance measurements.

Concomitant chemo-radiotherapy: Navelbine oral 50 mg 3 times a week administered the evening of Sundays, Tuesdays and Thursdays until the radiotherapy is finished. Drug accountability will be registered according to Good Clinical Practice (GCP). The radiotherapy is administrated 5 days a week.

3.3 Interruption or discontinuation of Navelbine in the individual patient.

Toxicity grading will be according to the CTC version 3.0. Following dose adjustment for drug-related toxicity is recommended: The oral Navelbine administration will be stopped for the individual patient in case of any toxicity grade 3 or worse occurs during radiotherapy. The radiotherapy should be continued. The administration of Navelbine may be resumed if the level of toxicity has decreased to grade 2 or better. For management of radiation complication during therapy see section 8.3

4. Planning of radiotherapy

The planning technique is based on ICRU62 recommendations and the DOLG 2009 criteria. The planning may, however, make use of 4-D scans, and that will influence the margins, se below. Radiation may start 2-5 weeks after last dose of chemotherapy – 2 weeks are preferable.

4.1 Target volumes

GTV comprise the tumor as seen on the planning CT scan (the size after chemotherapy) plus any pathological lymph node during time before start of radiotherapy even if they have disappeared after induction chemotherapy.

CTV encompass the GTV plus the following margins: 1.0 cm in the mediastinum and 0.5 cm in lung tissue. The margins are modified if the CTV is close to the large vessels, bones, trachea or the thoracic wall, then the anatomic structures constitute the demarcation of the CTV as long as no invasion is seen in the surrounding tissue. For a primary in the lung, not involving the hilar region or the mediastinum, the CTV should not be expanded into the mediastinum. For lymph nodes not invading lung tissue, the CRV should not be expanded into healthy lung tissue.

No elective radiation will be used to unaffected lymph nodes.

ITV: If the treatment is based on a standard 3D CT scan without 4D planning, the following margins are used: CTV + 0.5 cm. ITV should be set to zero towards columna, apex and contralateral lung.

If a 4D CT scan is used for the treatment planning, it is allowed to create patient specific margins. In that case the treatment plan should be carried out on the mid-ventilation phase as described by Wolthaus et al. (27). The size of the margin related to the respiration shall be calculated as described by Van Herk et al. (28).

PTV margins should be based on experience related to type of fixation used in the clinic. If patient specific margins are to be used, a study of the size of PTV margin has to be performed at the institution. For the patient specific margins, the size of the PTV margin has to be calculated based on the same formalism as for the ITV (28). For patient specific margins it is important that ITV and PTV margins are not added linearly but as the square-root of the sum of the squares. Thus it might be beneficial to expand directly from CTV to PTV, so that the ITV is contained in the PTV, since most planning systems only supports linear addition of margins. If patient specific margins are applied, it is important to report the size of the margin (appendix 4).

4.2 Doses to organs at risk

The dose to the lungs, spinal cord, heart, and esophagus must be reported. In the treatment of lung cancer with combination treatments, the dose the constraints to the organs at risk are given as:

1. Both lungs must be outlined: $V_{20} \leq 40\%$ i.e. a maximum of 40% of the lungs (outside the GTV) may receive a dose exceeding 20 Gy or more.
2. The spinal cord must be outlined as the spinal canal: The dose must not exceed 45 Gy.
3. The whole of the heart must be outlined: $V_{50} \leq 20\%$.
4. Esophagus through out the thorax: 66 Gy as a maximum dose

5. Study population

The study population is patients with inoperable NSCLC stage IIB - IIIB without pleural effusion suitable for curatively intended irradiation.

5.1 Inclusion criteria

Patients must meet *all* of the following inclusion criteria to be eligible for participation in this program.

- Age ≥18 years
- Patients with histologically or cytologically documented diagnosis of locally advanced NSCLC stage IIB to IIIB without pleural effusion.
- Performance status 0-1 on the ECOG scale.
- Weight loss ≤10% during the last 6 months
- Adequate lung function measured as FEV1 ≥1.0.
- Neutrophile count ≥1.5 x 10^9/L and platelet count ≥100 x 10^9/L.
- Serum bilirubin ≤1.5 upper limit of normal (ULN).
- ALAT ≤2 x ULN
- Able to comply with study and follow-up procedures
- Patients with reproductive potential must use effective contraception.
- Written (signed) informed consent to participate in the study.

5.2 Exclusion criteria

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study:

- Any unstable systemic disease (including active infection, unstable angina, congestive heart failure, severe hepatic, renal, or metabolic disease).
- Any other active malignancies within 5 years (except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer).
- Prior chemotherapy for lung cancer, including neo- and adjuvant chemotherapy.
- Inability to take oral medication, or requirement of intravenous alimentation
- Active peptic ulcer disease.
- Nursing mothers.

5.3 Monitoring during therapy

The patient is informed about the possibility of being included in the study before induction chemotherapy, but the administration is part of the standard neoadjuvant chemotherapy at the institution, and the patients cannot be included in the study before a plan has been worked out showing that curatively intended radiation is possible, and informed consent has been obtained (Fig. 1).

	Screening	Baseline	Treatment Period Timing	Day 30-45 after stop of treatment
Informed Consent	-	x	-	-
Demographics	x	-	-	-
Medical history	x	-	-	-
Physical examination	x	x	Weekly	x
Body weight	x	x	Weekly	x
Laboratory[1]	x	x	Weekly	x
ECG	x	x	-	x
Lung function test FEV_1/FVC	x[2]	x	-	x
Lung CO diffusion test	-	x	-	-
CT scan thorax and upper abdomen	x	x	-	x
Tumor measurements	x	21 days	-	x
PET-CT[3]	x	x	-	x
CT scan brain[4]	-	x[4]	-	-
Performance status	x	x	Weekly	x
Side effects[5]	-		Recorded weekly	x
Study drug [6] compliance	-	x	Recorded weekly	x
Smoking status	x	x	Recorded weekly	x

([1] Hematology: Hemoglobin, WBC, neutrophile count, and platelet count, to be done weekly or more often as clinically indicated). Biochemistry: Alkaline phosphatase, S-bilirubin, S-creatinine, ALAT (SGPT), LDH. Only laboratory abnormalities linked to unexpected clinical symptoms will be documented in the CRF.
([2] Optional
([3] CT scans, PET CT scans per institutional standards. EBUS or mediastinoscopy may be accepted as mediastinal evaluation if PET-CT is not available
([4] If no PET-CT available
([5] Side effects to be recorded according to CTC version 3.0
([6] Pharmacy log

5.4 Follow-up

The patients will be followed until 5 years after the start of radiotherapy or to recurrent disease according to the follow-up schedule. After discontinuation in the study the patient will be followed according to local standard

Follow up (+/- 1 months after start of RT)	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30, 36, 42, 48, 54, 60**
Medical history	x	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x	x
Laboratory[1]	x	x	x	-	x	-	x	-
ECG	-	x	-	-	-	-	-	-
Lung function tests FEV_1/FVC	x	x	x	x[2]	x	x[2]	x	x
Lung CO diffusion test	-	x	-	-	-	-	x	-
Weight	x	x	x	x	x	x	x	x
CT scan thorax /upper abdomen	x	x	x	x	x	x	x	x
Tumor measurements[3]	x	x	x	x	x	x	x	-
PET-CT[4]	-	x	-	-	-	-	-	-
Performance Status	x	x	x	x	x	x	x	x
Smoking status	x	x	x	x	x	x	x	x
Side effects[5]	x	x	x	x	x	x	x	x

([1] Hematology: Hemoglobin, WBC, granulocytes and platelet count. Biochemistry: Alkaline phosphatase, S-bilirubin, S-creatinine, ALAT (SGPT), LDH. Only laboratory abnormalities linked to unexpected clinical symptoms will be documented in the CRF

([2] Optional

([3] RECIST criteria (appendix 2)

([4] PET CT scans if available at the institution

([5] Radiation sequelae.

5.5 Tumor response criteria.

Although PET-CT is allowed, the tumor response will be evaluated according to RECIST-criteria (version 1.1) by CT-scans of thorax and upper abdomen (29). Suspected recurrent tumor locally or regionally should verified by biopsy if appropriate.

6. Criteria for efficiency and data-analysis

6.1 Statistical considerations

All calculations will be performed on the basis of intention to treat. 2 sided tests will be performed. Level of type 1 error is 5%.

6.2 Sample size calculation

The observed local failure free survival rate after 9 months after initiation of radiation was 70% among 200 patients treated in Odense for NSCLC stage IIB-IIIAB. The study will be designed to find local recurrence free survival of 80% at 9 months after initiation of radiation equivalent to about 6-7 months after finishing radiotherapy. A rate of 80% would be clinical interesting, and should be included in the confidence interval of the phase II trial at a power of 90%. This requires 57 patients to be included in each arm of the phase II trial, at total 114 patients.

6.3 Interim analysis

An interim analysis to evaluate toxicity will be performed after patient number 20 has completed radiotherapy and has one month of follow-up. An independent interim analysis committee will be

appointed to the task. The study will stopped if the rate of grade 4 pneumonitis or esophagitis exceeds 15% in one arm of the study, or unexpected severe toxicity appears at any time.

6.4 Expected time frame of study

The study is expected to recruit patients during a 2-year period starting q2 2009 and ending q2 2011. Analyses of results will be performed 9 months after last patient has been included, and results will be reported. Further analyses may be performed 5 years after last patient has been included. Each site is expected to include between 5-25 patients.

6.5 Data management

Data from all included patients will be reported. Every year during the time of inclusion of patients to the study and the next 3 year period safety data will be reported to the authorities. After final analyses of the study the data will stored for 15 years from inclusion of last patient in study. The data will be available for the authorities at all times.

7. Administration of drugs

The drugs used during the induction period are not regarded as part of the study drugs. The Navelbine used in the study after the induction period in connection with radiotherapy will be labelled to each patient, and the records of batch numbers for each patient will be kept at pharmacy for 15 years.

7.1 Navelbine

Soft gelatin capsules of 20, 30 or 80 mg. In the induction phase, the Navelbine is administrated as 60 mg/m^2 orally day 1 and 8 for one cycle. In absence of grade 3 and 4 hematological toxicity, the dose of Navelbine will be increased to 80 mg/m^2 during cycle 2. During radiation Navelbine is administered three times weekly on evenings of Sundays, Tuesdays, and Thursdays in a fixed dose of 50 mg. It is recommended that the patients have a light meal together with the capsules to avoid irritation of the stomach mucosa.

7.2 Carboplatin

Carboplatin is administered in the induction phase i.v. day 1 in each cycle. The dose is estimated after AUC 5 (Calvert's formula). The renal function (GFR) may be estimated by ^{51}Cr-EDTA, urine creatinine clearance rate, or calculated after Cockroft-Gault formulation

8. Adverse events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

Information to be collected includes event description, time of onset, clinician's assessment of grade, relationship to study product (assessed only by those with the training and authority to make a diagnosis), seriousness, action taken with study drug, outcome, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. All AEs

must be reported on CRF to Sponsor in order to record them for a final report to the Danish Medicines Agency.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

8.1 Serious adverse events (SAEs)

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol defined surveillance
- Life-threatening event (defined as a patient at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalisation or prolongation of existing hospitalisation during the period of protocol defined surveillance with the exception of treatment-related enteritis or fatigue, leucopenia, thrombocytopenia or hospitalization due to treatment administration or other elective measures
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalisation, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

In this study unexpected and related SAEs are defined as adverse reactions with at least a possible relationship to study therapy that are not consistent with the approved summary of product characteristics (SPC) and which to their nature are serious. The SPC is available at: www.emea.europa.eu

Abnormal laboratory values and clinical adverse events will be reported as SAEs if they are graded higher than 3 on the CTC v3.0.

All SAEs will be: recorded on the appropriate SAE CRF, followed through resolution by the investigator, reviewed and evaluated by the Medical Monitor.

Any adverse event that is considered SERIOUS must be reported within one working day (IMMEDIATELY) by the investigator to the Sponsor. Sponsor must make sure that information on all suspected unexpected serious adverse reactions (SUSARs) which are fatal or life-threatening are reported as soon as possible and within 7 days to the Danish Medicines Agency after sponsor has received knowledge himself (if applicable also to local health authorities as per national regulations). All other SURSARs must be reported to Danish Medicines Agency within 15 days. All related and unexpected SAEs are also immediately reportable to Pierre Fabre as expedited reports.

Consultant Regulatory Affairs, Pierre Fabre Pharma Norden AB
Fax: +46 8 625 33 55. Tel: +46 8 625 33 50

Not immediately reportable SAE:
Progression or deterioration of the malignancy under study (including new metastatic lesions and death due to disease progression) will be part of the efficacy assessment and should NOT be reported as AE/SAE. *Signs* and *symptoms* clearly associated with the malignancy under study should NOT be reported as AE/SAE unless:

- Newly emergent (i.e. not present at baseline) and association with the underlying malignancy and old/new metastatic lesions is unclear
- If the investigator attributed deterioration of malignancy-associated signs and symptoms directly to the study drug
- Should there be any uncertainty regarding the attribution of the malignancy under study to an AE, it should be reported as an AE or a SAE accordingly.

8.2 Expected adverse effect

The adverse effect occurring after treatment should be treated according to the department standard operating procedure.
Vinorelbine: Hematological toxicity (neutropenia, thrombocytopenia, anemia), constipation, paraesthesia, nausea, fatigue
Carboplatin: Hematological toxicity (neutropenia, thrombocytopenia, anemia)
Irradiation: The toxicity of irradiation of NSCLC is determined of the dose and treatment volume of organs at risk. These may be as followed:

Organs at risk	Acute (1-12 weeks)	Late >3 months
Lung[1]	Pneumonitis (cough, dyspnoe, fever)	Fibrosis (cough, dyspnoe)
Esophagus[2]	Swallowing difficulties, pain	Stenosis (swallowing difficulties)
Heart	Pericarditis[4]	Fibrosis
Skin	Edema, skin rash	Fibrosis, telangiectasier
Spinal cord	Lhermitte sign[3]	Radiation myelitis[4] (neurological deficits)

([1] The risk of acute pneumonitis may increase in irradiation when Navelbine is combined with concomitant chemo-radiation. The risk of pneumonitis increases with the V_{20} of the lung. The symptoms may develop before stop of irradiation. The treatment in the case of pneumonitis is steroid ± antibiotics.
([2] Occurrence of esophagitis is connected to treatment volume and concomitant therapy.
([3] Lhermitte sign is a transient self-limiting symptom of radiation impact on the cervical spinal cord.
([4]Pericarditis and radiation myelitis: no cases of these side effects are expected in this study.

8.3 Management of hematological side effects

In case of grade 4 neutropenia or thrombocytopenia, the administration of Navelbine will be paused until the toxicity has decreased to grade 2 or better. The radiotherapy may continue.

8.4 Management of radiation complications during radiotherapy

In case of grade 3 or worse esophagitis or pneumonitis, the administration of Vinorelbine will be terminated for that patient.

8.5 Management of radiation complications after radiotherapy

In case of increasing dyspnoe during radiation or within 3 months after cessation of radiation, pneumonitis must be suspected. Treatment with steroids is recommended e.g. prednisolone 25-50 mg or higher doses if necessary administered as 1-2 daily doses. Since infection is difficult to rule out, it is recommended to start treatment with antibiotics. Since tumor progression, myocardial infarction, and tromboembolic conditions may occur in these patients, ECG and appropriate biochemistry should be obtained. CT-scan or ECCO of the heart may be necessary.

9. Ethical consideration

Patients with locally advanced NSCLC lung cancer have a very poor long-time survival as only about 15% of the patients are alive 5 years after curatively intended radiotherapy (1). A major cause of these poor results is lack of local control of the tumor after radiotherapy. Another problem in the treatment of locally advanced NSCLC is occurrence of toxicity. There is therefore an urgent need to develop treatment that increases local control without increasing toxicity to an unacceptable level. The current study is designed to do that. The protocol fulfils the Helsinki II declaration and the national requirement to studies of patients with a cancer disease. The patients will be fully informed about the aspects of the treatment and risk included in participating. Informed consent will be obtained after sufficient time of reflection has been given.

10. Study conduct and economy

The study is investigator initiated and will be conducted according to the ICH-CGP guidelines and according to regulatory requirements. Olfred Hansen is the principal investigator (sponsor). The study is part of the Danish Center for Interventional, Research in Radiation Oncology (CIRRO), protocol CIRRO IP020109. The patients will be recruited among patient referred for treatment at each participating center. Financial support of 8,500 DKK per patient included to carry out the study will be applied from the company Pierre-Fabre and which manufactures Navelbine oral. This support is to compensate the additional time used by the staff, primarily by research nurses, who help with registration of effects and side effects of the treatment, and the amount will be paid to the research unit at the oncology centers. There is no economical befit for neither the department, the investigators in the study, nor the staff.

11. Publication

The study will be published in an international journal despite the result. The first draft of the manuscript will be prepared by Olfred Hansen. Other members of the protocol committee will be authors if the institutions they represent include patients. Any other center including 3 patients or more will be offered authorship according to the Vancouver rules of authorship.

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13. Appendixes

Appendix 1: Performance status

Eastern Cooperative Oncology Group (Zubrod-ECOG)[1,2]	
Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.	1
Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self care, confirmed to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	4

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Appendix 2: Objective Response Criteria (RECIST)

Complete Response: Disappearance of all clinical and radiological evidence of tumor (both *target* and *nontarget*) including normalization of elevated tumor markers at baseline, if documented. The patient must be free of all tumor-related symptoms. Complete Response must be confirmed at a second tumor assessment not less than 28 days apart from the assessment at which CR was observed.

Partial Response: At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. Partial Response must be confirmed at a second tumor assessment not less than 28 days apart from the assessment at which PR was observed.

Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Stable disease must be documented to be present at least 28 days from the start of the therapy. There may be no appearance of new lesions for this category.

Progressive Disease: At least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of nontarget lesions may be accepted as evidence of disease progression.

Appendix 3: Monitoring and data capture

Study conduct and monitoring will be done according to GCP. The monitoring will be performed by the GCP unit at Odense University Hospital together with the GCP units at participating centers.

Appendix 4: Dose calculation, treatment margins and reporting of the treatment plan

1. Planning

Energy for treatment is 6-10 MV. If available the treatment plans should be calculated using models that in an approximate way consider changes in lateral electron transport (e.g. Pinnacle/CC, Eclipse/AAA, OMP/CC and XiO/Super) (30).

2. Margins

The planning margins needed to ensure dose coverage of a tumour depends strongly on the imaging equipment used for planning of the treatment and as well as the imaging equipment used during the treatment. New emerging technique (e.g. 4D CT and Cone Beam CT) will soon make it possible individualise the margins for each patient. However, these techniques are not standard clinical practice yet thus each institution can choose between two different sets of margins 1) standard margins 2) individual margins. Each institution shall report which of the two sets of margins they are using. For the individual margins all patient specific value of Σ and σ shall be reported for each patient (all institution specific values of Σ and σ is only to be reported for the first patient)

2.1 *Standard margins*

Refer to protocol §4.1.

2.2 *Individual margins*

GTV and CTV as for standard margins (refer to protocol §4.1).

ITV and PTV is combined to one volume based on the margin formula by (28) Herk et al.

PTV: The PTV is the CTV plus a margin of M as defined below:

$$M = 2.5\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

where Σ and σ is the standard deviation of the systematic and random uncertainty, respectively. σ_p is a measure for the shape of the penumbra of the total dose distribution. The β-value is a constant related to the isodose level which should cover the target. For coverage of the target by 95% of the prescribed dose the value of β is 1.64 (for details see (28)). Since M depends on σ_p, M depends on the field arrangement as this can influence the shape of the penumbra of the overall treatment plan. However, the exact value of σ_p is not very critical since the margin recipe do only depend weakly on this value. Typical value of σ_p is 6-7 mm in the lung region (31).

Both Σ and σ is a combination of all the uncertainties involved in the treatment process which can be divided in tumour delineation (no random component), intra-fractional tumour uncertainty and inter-fractional tumour uncertainty.

$$\Sigma^2 = \Sigma_{delineation}^2 + \Sigma_{intrafractional}^2 + \Sigma_{interfractional}^2$$

$$\sigma^2 = \sigma_{intrafractional}^2 + \sigma_{interfractional}^2$$

The idea of using patient specific margins is to minimize the margins as much as possible for the individual patient. To achieve this goal a number of the above mentioned uncertainties needed to be assessed in the specific institution. Below is a brief description of each uncertainty. For some of the components typical values are given, however these needs to be validated at each institution. It should also be stressed that residual errors will always persist, thus for some of the uncertainties a lower bound of the value is given.

$\Sigma_{delineation}$: Difficult to measure, a value of 2 mm shall be used for a 4D planning CT (31). The uncertainty is larger for a 3D CT due to distortion of the tumour.
$\Sigma_{intrafractional}$: For standard 3D planning CT equal to $\sigma_{intrafractional.}$ Using 4D CT planning can be based on the mid-ventilation phase (32). For planning using the mid-ventilation phase $\Sigma_{intrafractional}$ is very close to zero. However, a residual error will always exist, thus a value of 1 mm is to be used.
$\sigma_{intrafractional}$: Is to be measured in a 4D CT as the standard deviation of the tumour position in each respiration. A lower bound of 1 mm is to be applied for $\sigma_{intrafractional}$.

The values of $\Sigma_{interfractional}$ and $\sigma_{interfractional}$ need to be assessed in each individual institution.
The inter-fractional uncertainty depends strongly on the imaging technique used during the treatment. Especially it is important whether the imaging is based on the bony anatomy or on the soft tumour tissue.

If the imaging technique is based on bony landmarks the inter-fractional uncertainty needs to include the movement of the tumour relative to the bony structure ($\Sigma^2_{intrafractional} = \Sigma^2_{baseline} + \Sigma^2_{setupbony}$ and $\sigma^2_{intrafractional} = \sigma^2_{baseline} + \sigma^2_{setupbony}$). Typical value of $\Sigma_{baseline}$ and $\sigma_{baseline}$ is 2-4 mm and 2 mm, respectively (31).

If the imaging is based on the soft tumour tissue the inter-fractional component do not contain two component, but is just the setup uncertainty relative to the soft tissue. Typical values of $\Sigma_{interfractional}$ and $\sigma_{interfractional}$ are about 1 mm (31, 33).

In Sonke et al (31) there is a graph (fig. 5) showing an example of the overall CTV to PTV margin in their institution. It is seen that the margin do not dependent strongly on the respiration amplitude. This does not indicate that it is possible to just apply a large value of the respiration movement and then disregard 4D CT for treatment planning. The data in Sonke et al. is based on the assumption that the treatment planning is performed in the mid-ventilation phase which is only possible if a 4D CT is used for treatment planning.

It is important to stress that all the above mentioned typical values is only a guideline for the approximate size of the individual parameters. All the values need to be validated at the local institution before use.

3. Reporting of the treatment plan

Reporting of the physical properties of the treatment plan is based on DICOM RT. All plans will be collected in a database such that whey will be available to all institutions.

The database will be hosted at Odense University Hospitals and will be available as a service on on a closed net dedicated for transfer of patient data on secure lines.

All data is reported in DICOM RT such that each institution by a simple operation can export al available instead of using time to extract a few key values of the DVH's

After upload of the treatment plan (CT images, point, regions of interest, dose and plan) the DVH data will be extracted and added to a common database.

Names of Regions of interest (ROI):
In order to obtain usable information from the DICOM RT plans it is important that regions which might be of scientific interest are named in the same way for all patients within each institution. Thus each institution should report a list of their naming convention such that their DVH structures can be recognised automatically. The list of ROI names should consist of the following regions:

Left Lung (suggestion LeftLung)

Right Lung (suggestion RightLung)
Heart (suggestion Heart)
The spinal canal (suggestion Medulla)
Esophagus (suggestion Esophagus)
Gross tumour volume (suggestion GTV or if more than one GTV1, GTV2, …)
Clinical target volume (suggestion CTV or if more than one CTV1, CTV2,…)
Internal target volume (suggestion ITV or if more than one ITV1, ITV2,…)
Planning target volume (suggestion PTV or if more than one PTV1, PTV2,…)

It is important to be consistent in the names of ROI. However, misunderstanding will occur thus each institution should also forward an e-mail on the person to contact if interpretation of the ROI name is not feasible.