Study Protocol of the NVALT25-ELDAPT Trial

Study Protocol of the NVALT25-ELDAPT Trial: Selecting the Optimal Treatment for Older Patients With Stage III Non–small-cell Lung Cancer

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Abstract

Background: Patients aged 75 years or older with stage III non–small-cell lung cancer (NSCLC) are underrepresented in clinical trials, leading to a lack of evidence for selection of the optimal treatment strategy. Information on benefits and harms of concurrent chemoradiotherapy among medically fit elderly patients is largely unknown, and reliable tools are needed to distinguish fit from frail patients for treatment selection. Also, information regarding quality of life during and after treatment is scarce. **Patients and Methods:** This multicenter NVALT25-ELDAPT (Dutch Association of Chest Physicians Trial Number 25 - Elderly with locally advanced Lung cancer: Deciding through geriatric Assessment on the oPtimal Treatment strategy) trial (NCT02284308) consists of a phase III randomized trial in combination with an observational study for all patients who do not participate in the randomized trial. The first aim of this study is to develop a reliable and clinically applicable screening tool to distinguish medically fit from frail patients. All patients ≥ 75 years diagnosed with stage III NSCLC are invited to undergo extensive geriatric assessment (part I). The second aim is to compare treatment tolerance, survival, and quality of life between concurrent and sequential chemoradiotherapy in fit patients (randomized trial, part II). For all patients, overall survival adjusted for quality of life (quality-adjusted survival) is described for each category of fitness and treatment strategy during and after treatment. **Conclusion:** With the results of the NVALT25-ELDAPT trial, treatment selection can be optimized and the best possible outcomes for each individual older patient with stage III NSCLC can be achieved.

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Introduction

Stage III non–small-cell lung cancer (NSCLC) occurs in 35% of patients with lung cancer and comes with poor survival rates.[1] Also, almost 30% of all patients with NSCLC are aged ≥ 75 years.[2] A meta-analysis showed that concurrent chemoradiotherapy (CHRT) results in superior survival (3-year survival of 24%) compared with sequential CHRT (3-year survival of 18%).[3] Based on these results, concurrent CHRT has been recognized as standard treatment for patients with stage III NSCLC and a good performance status.[4] However, the obtained survival gain comes with a significant increase in toxicity.[3,5] With older age, lower rates of treatment with (concurrent) CHRT are seen, from ≥ 50% among those aged 60 to 69 years to 5% among patients aged 80 years or older. Nevertheless, sequential CHRT has been applied more often among older patients in recent years, similar to the proportion of patients solely treated with radiotherapy.[6,7]

Older patients do not often participate in randomized trials, and those included are not representative for the average older patient.[8] Therefore, it remains unclear whether concurrent CHRT is the optimal treatment for older patients with stage III NSCLC as well.

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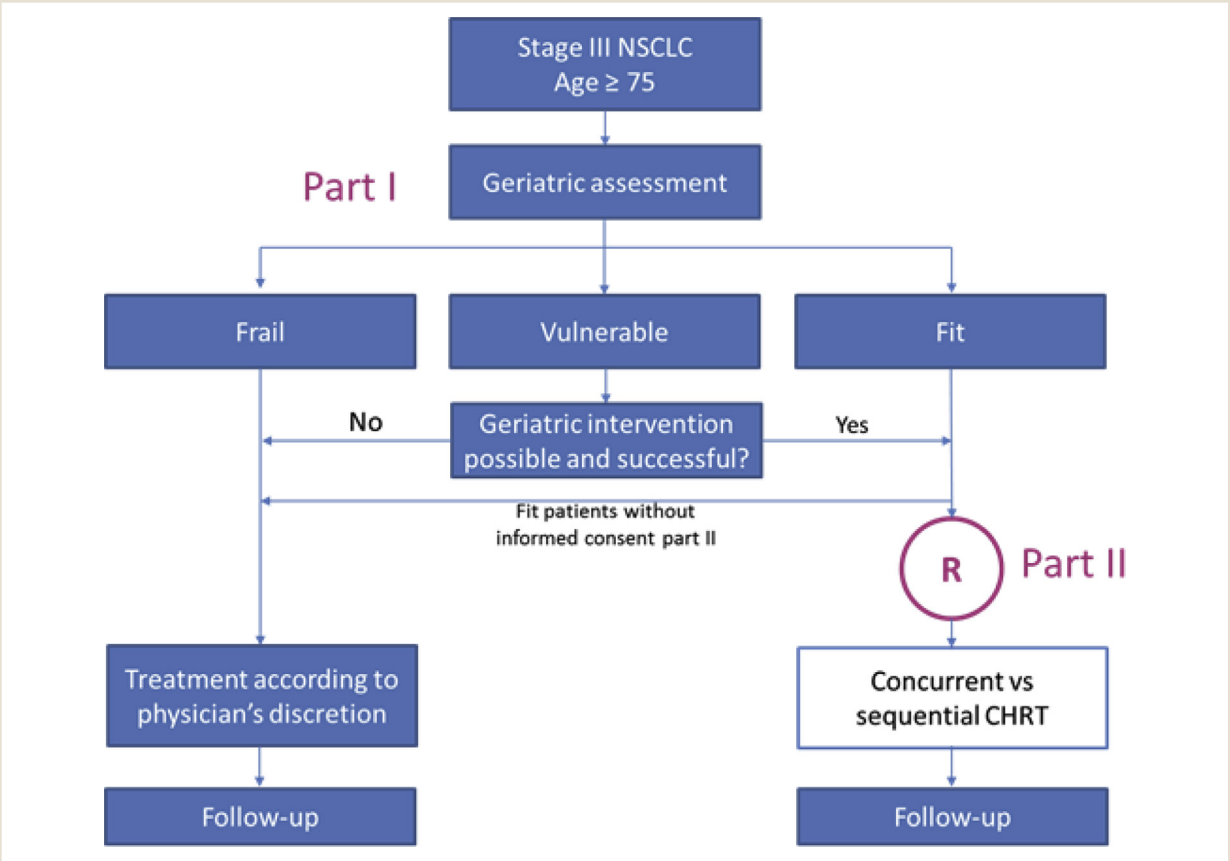
In everyday clinical practice, differences in treatment decisions can emerge from a lack of evidence regarding treatment outcomes within subpopulations. Information about comorbidity, fitness, vulnerability, and effects on treatment choice are currently unknown. The challenge is to properly investigate this older population to make valid statements regarding the most optimal treatment. Extensive geriatric assessment can provide insight into age-related problems and cognitive impairment in case of high-risk treatments among older patients,[9,10] which leads to a more precise estimation of vulnerability and impact of treatment.

Hence, there is an urgent need for research focusing on older patients with lung cancer. Reliable assessment techniques in clinical practice are needed to distinguish patients with good general condition from those who are less fit in order to guide treatment selection.[11] The primary endpoint of the NVALT25-ELDAPT trial (Dutch Association of Chest Physicians Trial Number 25 - Elderly with locally advanced Lung cancer: Deciding through geriatric Assessment on the oPtimal Treatment strategy) is to investigate the added value of concurrent and sequential CHRT among fit older patients is investigated in the randomized part of the study. Furthermore, this trial aims to develop a reliable and clinically applicable instrument to optimize treatment selection and outcomes such as quality-adjusted survival (QAS) and for the individual older patient.

Patients and Methods

A 2-fold study design combining an observational study with a randomized-controlled trial has been chosen for this patient group (Figure 1). All patients aged ≥ 75 years with any subtype of stage III NSCLC are asked to participate in part I of the study: an extensive geriatric assessment with follow-up by questionnaires during and after treatment. Exclusion criteria are surgery or adjuvant chemotherapy for NSCLC in the last year, prior radiotherapy to the ipsilateral thorax or mediastinum, clinical superior vena cava syndrome, or diagnosis of other cancer within the last 3 years (except in situ carcinomas and/or melanoma skin cancer). The geriatric assessment includes domains such as physical fitness and functioning (Short Physical Performance Battery [SPPB, Katz Activities of Daily Living (Katz-ADL), Katz Instrumental Activities of Daily Living (IADL)]), comorbidity (27-item Adult Comorbidity Evaluation [ACE-27]), cognitive functioning (Montreal Cognitive Assessment [MoCa]), anxiety and depression (Hospital Anxiety and Depression Scale [HADS]), nutritional status (Mini Nutritional

Figure 1 Flow Diagram of the NVALT25-ELDAPT Trial Regarding Patient Selection, Geriatric Assessment (Part I), Randomization to CHRT (Part II), and Treatment According to the physician's Discretion



Abbreviations: CHRT = chemoradiotherapy; NSCLC = non–small-cell lung cancer; NVALT25-ELDAPT = Dutch Association of Chest Physicians Trial Number 25 - Elderly with locally advanced Lung cancer: Deciding through geriatric Assessment on the oPtimal Treatment strategy.

Assessment [MNA]), and social situation. Based on these outcomes and predefined cutoff points (Table 1), patients are classified as fit, vulnerable, or frail. Patients are asked to participate in part II of the study when determined fit immediately after geriatric assessment, after reevaluation of the geriatrician, or after geriatric interventions. In part II, fit patients are randomized to concurrent or sequential CHRT. Additional inclusion criteria for part II are forced expiratory volume in 1 second and diffusing capacity of the lungs for carbon monoxide $\geq$ 30% of the age-adjusted normal value, adequate organ function, and absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study. Endpoints of the study are QAS, overall and progression-free survival, overall and lung–cancer-specific quality of life, adverse events, and cost-effectiveness. The primary endpoint of all patients providing informed consent for part I is to assess QAS by EQ-5D and ICEpop CAPability measure for Older people (ICECAP-O) questionnaires. Fit patients additionally receive questionnaires regarding overall, lung–cancer-specific, and elderly-specific quality of life (EQ-5D, ICECAP-O, Core Quality of Life Questionnaire [QLQ-C30/-LC13] and Quality of Life Questionnaire-Elderly Cancer Patients [QLQ-ELD14]) via Data Centre MAASTRO. These questionnaires are sent regularly during treatment until 60 months after treatment. Other endpoints of this study are the development of a clinically applicable geriatric screening instrument, toxicity, and the degree of independence. Patients who are classified as frail receive treatment according to the physician's discretion and patient wishes, including CHRT, radical or palliative radiotherapy, or best supportive care only. Patients classified as vulnerable by geriatric assessment are referred to the geriatrician for additional evaluation. The geriatrician evaluates whether geriatric interventions can optimize the patient sufficiently to undergo CHRT. Patients judged unfit by the geriatrician receive treatment according to the physician's discretion and patient wishes. This also accounts for fit patients who do not provide additional informed consent for part II of the study. The total study duration is 6 years, and patients will be recruited during the first 4 years.

Statistical Analyses

QAS is calculated by summing up the survival times spent with a certain utility score: $QAS = \Sigma((u_1{*}t_1)+(u_2{*}t_2)+ (u_3{*}t_3)+ (u_4{*}t_4)+ (u_5{*}t_5)+ (u_6{*}t_6))$. U_x refers to the utility in each follow-up period, and t_x denotes the time (in years) that the patient is in this health state. Owing to unknown distributions of QAS, non-parametric bootstrapping will be performed (5000 iterations) to obtain reliable estimates of the standard deviation of differences between randomized groups with the associated 95% confidence intervals and *P*-values. To calculate the final sample size for the study, QAS is calculated when 50 patients are included in each treatment arm of the second part of the study. A clinically relevant difference in QAS between the 2 treatment arms has been set at 0.08 (standard error, 0.08) quality-adjusted life years (QALYs).[12] Based on the data collected in the internal pilot trial, the required number of patients for the full phase III randomized trial will be determined using a 2-sided significance level of 5% and a power of at least 80% and preferably 90% (depending on what sample size is practical). Given that QAS is a summation score of health states at different time points, the standard error of this summation score will probably be higher than the standard error of the average clinically relevant difference as described in Pickard et al.[12] With a sample size for the pilot study of 50 patients per arm, a 3.5-fold increase in standard error would still allow to detect a clinically significant difference of 0.08 QALYs. To prevent any bias with regard to the final sample size calculation, this will be performed by another statistician who is not a member of the data monitoring committee. Only the data required for calculation will be provided.

The predictive value of individual elements of the geriatric assessment and physical performance measures (hand grip strength) will be analyzed with respect to QAS, toxicity (any toxicity Common Terminology Criteria for Adverse Events (CTCAE) $\geq$ grade III at any time point), and (non-)completion of treatment. This will be performed for each treatment strategy. Overall and progression-free survival will be plotted in Kaplan-Meier curves. Outcomes of CHRT will be compared using Cox proportional hazards regression analysis with adjustment for treatment arm, age, chemotherapy schedule, and fitness. The hazard ratio, *P*-value and 95% confidence interval for the hazard ratio between treatment arms will be displayed. For patients excluded from part II, associations between patient characteristics and treatment on the one hand and QAS on the other hand will be described. Cost-effectiveness will be calculated by costs per QALYs.

Table 1 Cutoff Points of Extensive Geriatric Assessment and Classification of Fit, Vulnerable, and Frail Older Patients Participating in the NVALT25-ELDAPT Trial

Domain	Affected When
Katz Activities of Daily Living (ADL)	< 5
Katz Instrumental Activities of Daily Living (IADL)	< 10
Montreal Cognitive Assessment (MoCa)	< 26/30
27-item Adult Comorbidity Evaluation (ACE-27)	$\geq$ 3
Hospital Anxiety and Depression Scale (HADS-score)	$\geq$ 8/21
Mini Nutritional Assessment (MNA)	< 24/30

Abbreviation: NVALT25-ELDAPT = Dutch Association of Chest Physicians Trial Number 25 - Elderly with locally advanced Lung cancer: Deciding through geriatric Assessment on the oPtimal Treatment strategy.
Classification based on affected domains: 0-1, fit; 2-3, vulnerable; $\geq$ 4, frail.
Short Physical Performance Battery (SPPB) score: 10-12, fit; 4-9, vulnerable; $\leq$ 3, frail.

Discussion

The results of the combined observational and randomized NVALT25-ELDAPT trial will improve individual treatment choices for older patients with stage III NSCLC by providing the optimal balance between quality of life and survival.

The unique combination of an observational and randomized design contributes to the highly needed evidence regarding treatment selection and (patient relevant) outcomes. In the observational part, information on survival and quality of life can be gained of the entire unselected older population in clinical practice. Through extensive geriatric assessment, insights can be gained in predictive elements for survival, quality of life, and toxicity, which can influence treatment decision-making. The assessment outcomes form the basis for the development of a clinically applicable geriatric screening instrument and enables appropriate treatment selection by choosing those patients who would benefit from intensive treatment with CHRT, and patients who will not. Although most

patients ≥ 75 years with stage III NSCLC are thought to be ineligible for concurrent CHRT in current practice,[13] the use of a geriatric assessment could result in a larger proportion of patients ≥ 75 years treated with CHRT as they could be strengthened by geriatric interventions. Also, geriatric assessment can discover previously undetected signs of vulnerability and impairments. As a result, the proportion of unfit patients or those with impairments will be limited in the randomized part of the study. Nevertheless, higher levels of toxicity from this treatment should be expected compared with clinical practice.[14,15] Therefore, toxicity will be closely monitored by regular contact and measurement times. Until now, the decision whether or not to treat this older patient group with CHRT has been rather subjective, as it is primarily based on the physician's perception and the multidisciplinary tumor board. Despite international recommendations for guidelines, (extensive) geriatric assessment is currently not part of standard care for older patients with NSCLC in most hospitals, and logistic issues could arise when implementing the geriatric assessment between time of diagnosis and start of treatment. Through the randomized part of the study, valuable insights can be gained in treatment with CHRT in fit older patients. Vulnerable patients who qualify for a geriatric intervention in order to improve fitness need a 6-week period to benefit from this intervention, which could delay the start of treatment. This could feel as a drawback for both patients and physicians from following this trajectory. However, the goal of this geriatric intervention is to strengthen the patient in order to undergo a potentially more effective treatment in terms of curative-intent and survival, which will be examined in the randomized part of the study.

Quality of life is an important understudied outcome in patients with stage III NSCLC. In the NVALT25-ELDAPT trial, information regarding quality of life is frequently collected during and after treatment. This puts extra burden on patients next to the tumultuous period of diagnosis and treatment during standard care. However, this burden is considered acceptable as patients are more closely monitored, and important decreases and increases in quality of life during and after treatment can be acted upon. Hereby, an important basis is set regarding quality of life for fit, vulnerable, and frail patients and treatment options. Other important outcomes such as feasibility and safety can be assessed, even as the quality of life during and after (intensive) treatment. Future studies including older cancer patients of other tumor types could adopt these study goals and design as well, and more evidence is built for understudied though growing populations of heterogeneous older cancer patients.

In conclusion, the results of the NVALT25-ELDAPT phase III trial with a combined observational and randomized design will provide insights into optimizing QAS and treatment selection for patients aged ≥ 75 years with stage III NSCLC. Also, a short, effective, and clinically applicable geriatric assessment strategy can be developed for clinical practice. Evidence can be obtained regarding individualized, safe, and cost-effective treatment options for fit and frail patients. Together, the NVALT25-ELDAPT trial will provide highly needed knowledge for treatment selection and outcomes in this increasing but understudied older population with stage III NSCLC.

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Disclosure

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