Doctoral theses at NTNU, 2023:312

Kristin Stokke

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Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
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Department of Clinical and Molecular Medicine

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Trondheim, oktober 2023

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| | |
|---|---|
| ***Navn kandidat:*** | **Kristin Stokke** |
| ***Institutt:*** | **Institutt for klinisk og molekylær medisin (IKOM)** |
| ***Hovedveileder:*** | **Tarje Onsøien Halvorsen** |
| ***Biveiledere:*** | **Bjørn Henning Grønberg**<br>**Marie Søfteland Sandvei**<br>**Marit Slaaen** |
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## Norsk sammendrag

Lungekreft er den vanligste kreftformen i verden og den tredje vanligste i Norge etter tarm- og brystkreft, men det er den kreftsykdommen som tar flest liv både globalt og nasjonalt (1, 2). I 2021 ble det diagnostisert 3499 nye tilfeller i Norge og i 2020 døde 2168 pasienter (3). Lungekreft deles inn i to hovedgrupper; småcellet lungekreft (SCLC) som utgjør omtrent 15% av alle tilfellene, og ikke-småcellet lungekreft (NSCLC) som utgjør resten. Om lag 40% av alle nyoppdagede tilfeller av lungekreft har sykdom med spredning som tradisjonelt har vært vurdert som uhelbredelig.

Fire kurer platinumbasert cellegift har vært standard behandling for pasienter med uhelbredelig NSCLC. Påfølgende vedlikeholdsbehandling med cellegiften pemetrexed har vært foreslått for å øke overlevelsen for pasienter som ikke har plateepitelkarsinom. I dette doktorgradsarbeidet undersøkte vi om umiddelbar oppstart av vedlikeholdsbehandling med pemetrexed etter den platinumbaserte cellegiftbehandlingen, forlenger overlevelsen sammenlignet med observasjon og oppstart av pemetrexed først når tilbakefall påvises. Underveis i studieperioden ble immunterapi tilgjengelig for denne pasientgruppen som medførte at inklusjonen gikk ned og vi fikk færre deltagere enn vi hadde planlagt. Våre resultater indikerer likevel at vedlikeholdsbehandling med pemetrexed er godt tolerert og resulterer i litt bedre sykdomskontroll enn å starte pemetrexed ved progresjon.

Når det gis anbefaling om behandling, vektlegges hovedsakelig krefttype (inkl. evt. undergruppe) og utbredelse, i tillegg til pasientens allmenntilstand. Imidlertid ser vi at det er stor variasjon i behandlingseffekt mellom pasienter. Noen har ikke nytte av behandlingen, som igjen betyr at de ofte opplever unødvendige bivirkninger. Det er derfor stort behov for mer kunnskap om pasienters prognose, og hvordan man best kan tilpasse behandling og behandlingsintensitet til den enkelte pasient.

Kreft, og spesielt lungekreft, er ofte assosiert med inflammasjon (betennelse). Studier viser at ved å ta enkle blodprøver (CRP og albumin) og summere de i en score kalt *Glasgow Prognostic Score* (GPS), kan vi få et mål på prognosen til pasienten. Hvordan GPS utvikler seg over tid og i relasjon til respons på kreftbehandling, er lite undersøkt. Vi fant at GPS målt etter de innledende fire cellegiftkurene ga mer informasjon om prognose enn GPS målt før behandlingen startet.

Studier har vist at fysisk funksjonsnivå kan gi informasjon om prognose. I vår studie ønsket vi å se om tre enkle og ulike mål på fysisk funksjon kan være til nytte når man skal forsøke å identifisere pasienter som har så dårlig prognose at de sannsynligvis ikke har nytte av

cellegiftbehandling. Vi fant at pasientrapportert fysisk funksjon ga informasjon om prognose, mens objektive undersøkelser utført på sykehuset, ikke ga det.

Oppsummert understøtter denne doktorgradsavhandlingen nytten av umiddelbar vedlikeholdsbehandling med pemetrexed for pasienter med uhelbredelig ikke-plateepitel NSCLC. I tillegg har vi vist at det å måle GPS underveis i behandlingen er enkelt og kan gi viktig informasjon om videre prognose, mens enkle tester på fysisk funksjon alene ikke har en slik nytte.

## English summary

Lung cancer is the most common cancer world-wide, the third most common in Norway after colon- and breast cancer, but the most common cause of cancer-related deaths both globally and nationally (1, 2). In 2021, 3499 new cases were diagnosed in Norway and in 2020, 2168 patients died (3). Lung cancer is divided into two main groups; small cell lung cancer (SCLC) which makes up about 15% of all cases, and non-small cell lung cancer (NSCLC) which makes up the rest. About 40% of all newly discovered cases of lung cancer have metastatic disease which has traditionally been considered as an incurable situation.

Four courses of platinum-based chemotherapy have been standard for patients with advanced NSCLC. Immediate maintenance pemetrexed afterwards has been suggested to improve survival among patients with non-squamous NSCLC. This doctoral thesis is based on a national study where the aim was to examine if immediate maintenance pemetrexed after the platinum-based chemotherapy, improves survival compared with observation and starting pemetrexed when progression was detected. The study was preliminary closed when immunotherapy was introduced and became the drug of choice to our patients, but our results underpin that immediate maintenance pemetrexed is more effective than treatment at progression.

When recommending treatment, emphasis is placed on the type of cancer (including subgroups), cancer stage, and the patient's performance status. However, there is a great variation in treatment effect. Some patients do not benefit from the treatment, which means they often experience unnecessary side effects. Therefore, there is a need for more knowledge about the patient's prognosis, how to adapt the treatment and treatment intensity, best for the individual patient.

Cancer, and lung cancer specifically, is often associated with inflammation. Studies show that by measuring simple blood tests (albumin and CRP) summarized in a score called the *Glasgow Prognostic Score (GPS,)* you can get prognostic information about the patient. However, little research has been done on how GPS develops over time and in response to cancer treatment. We found that GPS measured after the initial four chemotherapy coursers had a greater prognostic value than GPS measured before treatment started.

Studies have showed that physical function is associated to the patient's prognosis. In our study we wanted to examine if three simple methods measuring the physical function, could be useful identifying patients who have such a poor prognosis that they are unlikely to benefit from

chemotherapy. Surprisingly, we found that only patient-reported, but not measured, physical function was a prognostic factor.

In summary, this thesis underpins the benefit from immediate maintenance pemetrexed for patients with advanced non-squamous NSCLC. Measuring GPS during treatment is easy and can provide important prognostic information. Simple measures of physical function alone do not have such a clinical value.

# Acknowledgement

The work of this thesis has been carried out at det Department of Clinical and Molecular Medicine. The PhD has been founded by the Liaison Committee between the Central Norway Regional Health Authority (RHA) and the Norwegian University of Science and Technology (NTNU). The clinical study was conducted by the Norwegian Lung Cancer Group (NLCG).

A clinical study could not be done without participants, so first, I want to thank all the patients and their relatives, who were included in the research project. I am grateful, their contribution has been important for me and my research and furthermost, for future patients.

Secondly, I would like to thank my research supervisors, Dr. Tarje Onsøien Halvorsen, professor Bjørn Henning Grønberg, Dr. Marie Søfteland Sandvei and professor Marit Slaaen. Without their assistance and dedicated involvement in every step throughout the process, this thesis would never have been accomplished. I would like to thank you very much for your support and understanding over the past years.

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Thank you!

Trondheim, May 2023

Kristin Stokke

## List of papers

1. **Randomized phase III trial comparing switch-maintenance pemetrexed with observation followed by pemetrexed at progression in advanced NSCLC** Halvorsen TO, Stokke K, Killingberg KT, Raj SX, Sørhaug S, Brustugun OT, Fløtten Ø, Helbekkmo N, Hornslien K, Madebo T, Fluge S, Grønberg BH. Acta Oncol 2020 Vol. 59 Issue 9 Pages 1051-1057

2. **Prognostic Value of Post First-Line Chemotherapy Glasgow Prognostic Score in Advanced Non-Small Cell Lung Cancer** Stokke K, Sandvei MS, Grønberg BH, Slaaen M, Killingberg KT, Halvorsen TO. Clin Med Insights Oncol. 2022;16:11795549221086578

3. **Associations between Measured and Patient-Reported Physical Function and Survival in Advanced NSCLC** Stokke K, Halvorsen TO, Grønberg BH, Saltvedt I, Slaaen M, Kirkevold Ø, Killingberg KT, Sandvei MS. Healthcare. 2022;10(5):922

## Abbreviations

| | |
|---|---|
| ALK | Anaplastic Lymphoma Kinase |
| ANC | Absolute Neutrophile Count |
| AUC | Area Under a Curve |
| BMI | Body Mass Index |
| CCTG | Canadian Cancer Trials Group |
| CI | Confidence Interval |
| CR | Complete Response |
| CT | Computer Tomography |
| ECOG | Eastern Cooperative Oncology Group |
| EGFR | Epidermal growth factor receptor |
| EORTC | European Organization for Research and Treatment of Cancer |
| G-CSF | Granulocyte Colony Stimulating Factor |
| GA | Geriatric Assessment |
| GPS | Glasgow Prognostic Score |
| HR | Hazard Ratio |
| HRQoL | Health Related Quality of Life |
| ICI | Immune Checkpoint Inhibitor |
| NCI | National Cancer Institute of the United States and |
| NLCG | Norwegian Lung Cancer Study Group |
| NSCLC | Non-Small Cell Lung Cancer |
| NTRK | Neurotrophic Tyrosine Receptor Kinase |
| OR | Odds Ratio |
| OS | Overall Survival |
| PD | Progressive Disease |

| | |
|---|---|
| PD-(L)1 | Programmed Cell Death Protein (Ligand) 1 |
| PET | Positron Emission Tomography |
| RFA | Radio Frequency Ablation |
| PFS | Progression Free Survival |
| PO | Per Oral |
| PR | Partial Response |
| PRO(M) | Patient Reported Outcome (Measures) |
| PRPF | Patient Reported Physical Function |
| PS | Performance Status |
| RCT | Randomized Controlled Trial |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| ROS1 | Receptor tyrosine kinase (encoded by the gene ROS1) |
| RT | Radiotherapy |
| SCC | Squamous cell carcinoma |
| SCLC | Small Cell Lung Cancer |
| SD | Stable Disease |
| SBRT | Stereotactic Body Radiotherapy |
| TNM | Tumor, Nodes and Metastasis |
| TS | Thymidylate Synthase |
| TUG | Timed Up and Go |
| ULN | Under Lower Normal |
| WHO PS | World Health Organization Performance Status |
| QoL | Quality of Life |
| QLQ C30 | Quality of Life Core Questionnaire 30 |
| QLQ LC13 | Quality of Life Questionnaire Lung Cancer Modules 13 |

| | |
|---|---|
| 5mWT | 5-meter Walk Test |

# 1 Introduction

Lung cancer is the most common cause of cancer related deaths. There are two main types of lung cancer; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is the most frequent and accounts for approximately 85% of all cases. NSCLC is further divided into several subgroups, where adenocarcinoma and squamous cell carcinoma are the most common. About 40% of lung cancer patients have advanced disease at diagnosis and are not candidates for curative treatment (3). For these patients, prognosis has been very limited, and there is a need for improved treatment. It has been especially important to identify the patients with the poorest prognosis that are unlikely to benefit from potentially toxic systemic cancer therapy.

A combination of carboplatin and vinorelbine was standard first-line treatment in Norway for patients with advanced (stage IIIB and IV) NSCLC in 2014, when the trial which the thesis is based on, was initiated. Two prior studies, the JMEN and the PARAMOUNT trials, had shown that immediate maintenance pemetrexed therapy after induction chemotherapy, improved survival compared with observation followed by salvage chemotherapy. There were, however, some limitations in the study designs, and it was unclear whether patients with poor performance status benefitted from maintenance therapy. Primarily, pemetrexed might be more effective than other drugs in non-squamous NSCLC, and few of the patients in the control arms received pemetrexed at progression in these two studies (4-6).

In addition to stage of disease, the patient's performance status (WHO PS) is the strongest and most important prognostic factor used in treatment decisions for cancer patients. There is a need to improve knowledge on prognostic and predictive factors to identify patients with different prognosis and outcomes from therapy, and to adapt treatment accordingly.

Lung cancer is marked by a high level of systemic inflammation and poor survival (7, 8), and a high proportion of patients have elevated inflammatory markers (8). The Glasgow prognostic score (GPS), based on CRP and albumin, reflects cancer induced inflammation, and is a prognostic factor in many cancers. It is reasonable to believe that the GPS might change in response to effective cancer therapy. However, few have investigated if measuring GPS during or after initial treatment, provide additional information to baseline GPS.

There are indications that poor physical performance reflect the patients' health status (9) and is correlated with survival in cancer patients (10, 11). However, differences in the tests used, variation in patients' characteristics, type of cancer and treatment received, make the results

difficult to compare and interpret. Little is known about whether measuring physical function provides additional prognostic information in advanced NSCLC.

We conducted a randomized multicenter phase III trial including patients with advanced non-squamous NSCLC. Patients who received four courses of a platinum doublet without progression, were randomized to receive either immediate maintenance pemetrexed or observation followed by pemetrexed upon progression.

The main aims of this PhD-project were to:

- Investigate if immediate maintenance pemetrexed was well tolerated and improved survival compared to observation followed by pemetrexed therapy at progression.
- Investigate if GPS changes during first-line chemotherapy, and if GPS measured after treatment provided additional prognostic information to GPS measured before treatment commenced.
- Investigate if simple physical performance measures, timed up and go (TUG) and 5-meter walk test (5mWT), provided predictive and prognostic information, and in case, whether the measures provided more such information than patient-reported physical function (PRPF).

# 2 Background

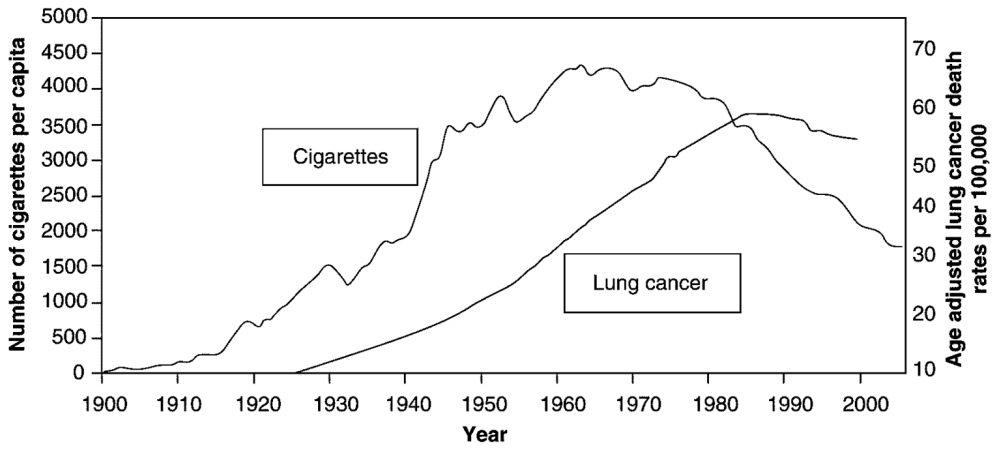
## 2.1 Lung cancer

### *2.1.1 Etiology, epidemiology, and survival*

Lung cancer was uncommon before cigarette smoking became popular during the beginning of the 20th century (Figure 1). The association between tobacco smoking and incidence of lung cancer was documented in 1950 (12). The varying trends in lung cancer incidence by sex reflects the different phases of the smoking epidemic in men and women. Women started smoking later than men and while the proportion of male smokers had declined from the 1960s, the number of daily female smokers peaked in the 1970s and was stable until 2000 (1, 13). In Norway, the prevalence of daily smokers has been reduced from more than 30% in the late 1990s to 8% in 2021 (14). In developing countries, the estimated number of smokers is still close to a billion (15).

Other known causes of lung cancer include passive smoking, radon, asbestos, genetic factors, and pollution. It is believed that pollution will cause a new epidemic of lung cancer in developing countries where air pollution is becoming a major health problem (16, 17).

**Figure 1** Relationship between cigarette consumption and lung cancer deaths over years in the US. Figure copied from (18)



Lung cancer is the most common cancer worldwide with 2.21 million cases annually in 2020 (2). In Norway, lung cancer is the third most common cancer with 3499 new cases in 2021 (10% of all new cases) and the second most common malignancy in men (1786 cases) and women (1713 cases) separately. Median age at diagnosis in both genders is 72 years (3).

For many years, the survival in lung cancer has been poor, but since the early 2000s there has been an improvement (Figure 2- 4). The improvement is present for all stages, but the prognosis for patients with metastatic disease is still limited. Median OS with stage IV disease is right below six months (19). The increase in overall survival is probably partly due to better methods both for diagnosis, classification, and staging, but also due to the introduction of more effective and tolerable therapies. Most important improvements include the introduction of PET CT in staging, endobronchial ultrasound (EBUS), thoracoscopic surgery, stereotactic radiosurgery, targeted therapy, and immunotherapy.

Lung cancer is still the most frequent cause of cancer related deaths worldwide with 1.79 million cases in 2020 (2). In 2020 lung cancer accounted for 20% of the cancer mortality in Norway, with 1162 men and 1006 women dying because of the disease (3). With increasing incidence and improved treatment, the prevalence of lung cancer is increasing rapidly, and has almost doubled from 5335 persons at the end of 2010, to 9936 in 2020 (Figure 2 and 5) (1).

**Figure 2** Incidence, mortality and 5-year survival from lung cancer in Norway (1965-2020). Figure copied from (1)

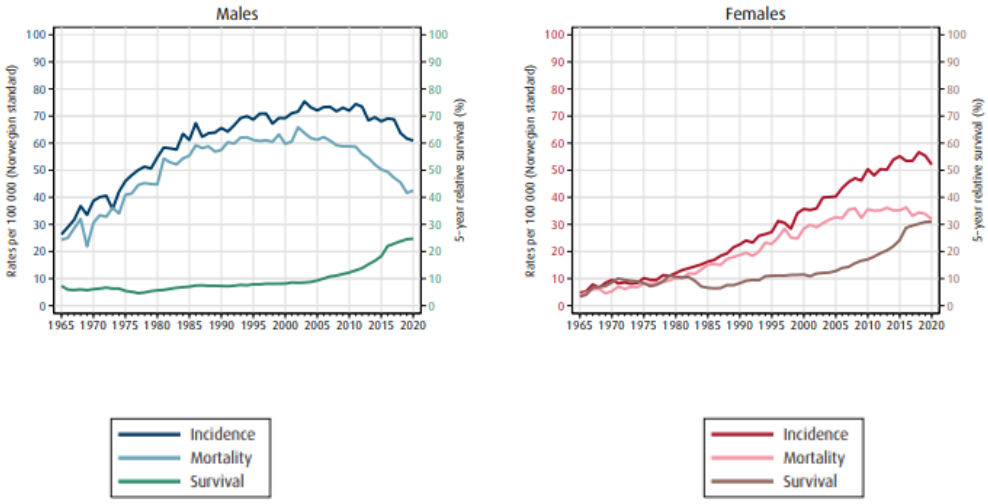


**Figure 3** Survival for all stages of lung cancer. Figure copied from (19)

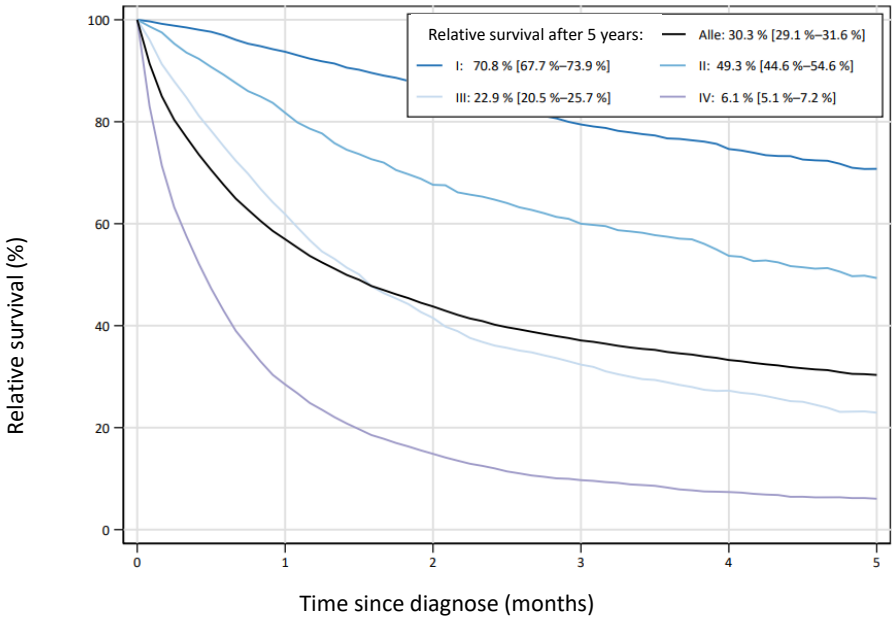



**Figure 4** Relative survival of patients with lung cancer by stage, sex, and year of observation. Figure copied from (20)

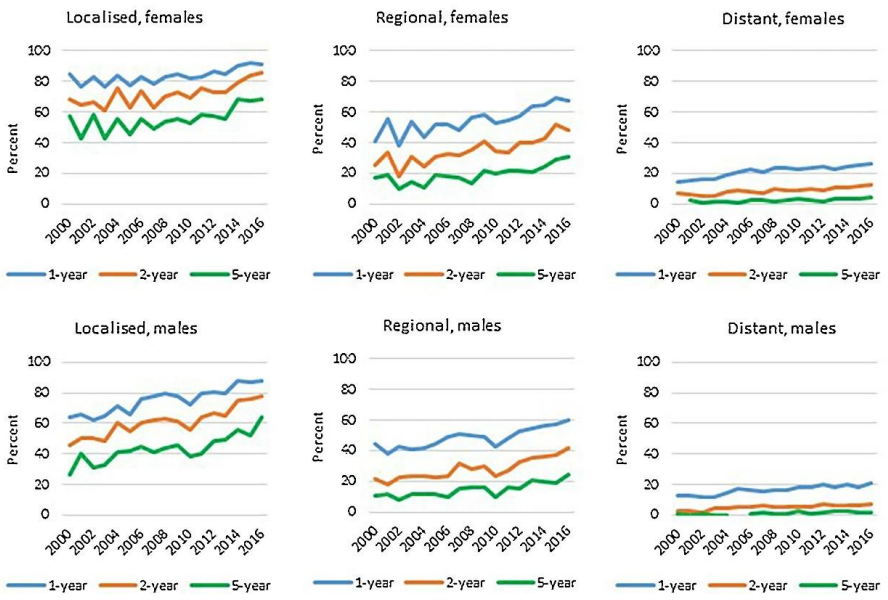
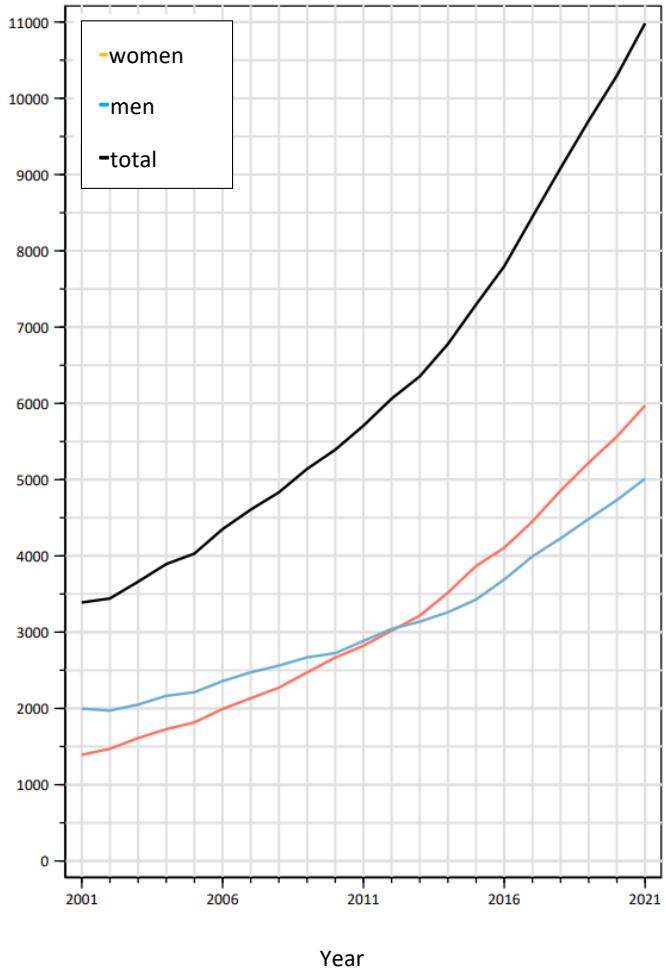


**Figure 5** Prevalence of lung cancer in Norway. Figure copied from (19)




### *2.1.2 Classification of lung cancer*

Lung cancer is divided into two main groups; small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

SCLC account for approximately 15% of all new cases of lung cancer (3). SCLC was described as a separate entity from NSCLC due to a different clinical presentation, where few patients had resectable disease at diagnosis, poor outcomes from surgery, and high response rates from chemotherapy (21). In addition, SCLC had a stronger association to tobacco smoking (>90% of the

cases seen in heavy smokers) than NSCLC (22). Since this thesis is based on a trial of NSCLC, SCLC is not discussed below.

## 2.2 Non-small cell lung cancer (NSCLC)

### *2.2.1 Etiology and epidemiology*

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer and represents about 85% of all cases both worldwide and in Norway. Adenocarcinomas are the most frequent in the Western world (approximately 50% of cases), squamous cell carcinomas (SCC) are the second most frequent (approximately 20%), and large-cell carcinomas account for 10-15% of cases (20). There has been a relative incidence shift from SCC to adenocarcinoma over years, which can be explained by differences in smoking habits, as the use of non-filtered cigarettes has decreased over the last years (23).

### *2.2.2 Symptoms and clinical characteristics*

Lung cancer has no pathognomonic symptoms. Common symptoms include cough, wheezing, and dyspnea, all common symptoms among smokers. An increase in these symptoms in smokers should raise suspicion of underlying lung cancer. Hemoptysis should always lead to investigations (e.g., CT scan) to rule out lung cancer.

Many lung tumors grow slowly and may be large before they give symptoms. The lung cancer cells are often aggressive with a high potential of distant metastasis causing specific symptoms from the affected organs. The five most common sites for metastasis are the lymph nodes, bones, brain, liver, and adrenal glands. Lung cancer may also cause frequent or persistent infections, fatigue, and weight loss, most commonly in metastatic setting. In some cases, lung cancer is diagnosed in asymptomatic patients when a CT scan performed for other reasons reveals the disease. Screening for lung cancer has been debated, with increasing evidence of a benefit in survival (24, 25). At the time, there is no established screening program in Norway, but in 2019 The Norwegian Cancer Society funded an ongoing pilot project at Akershus University Hospital for lung cancer screening in Norway (26).

### *2.2.3 Staging and classification of NSCLC*

Extent of disease is crucial in deciding treatment for lung cancer patients, and all patients should have a CT scan of thorax and upper abdomen. A PET-CT is performed if potentially curative therapy can be offered, since it is a more sensitive and specific imaging technique than CT. MRI of the brain is

recommended if there are symptoms from CNS, for all stage III patients, and stage IV patients eligible for targeted therapy (27).

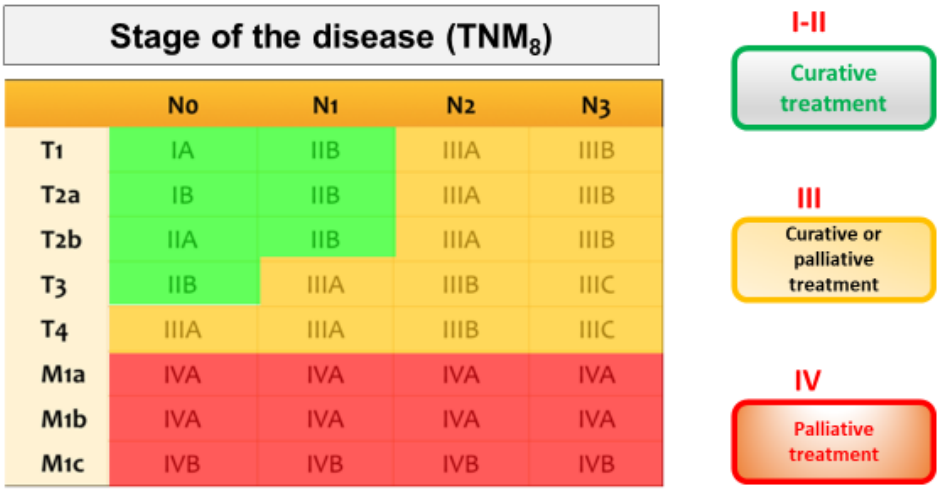
The extent of disease is classified according to the TNM- staging system (28). Briefly, the T descriptor is ranging from 1-4 based on the primary tumor size and invasion of nearby tissue. The N descriptor, ranging from 0-3, is based on presence and location of regional metastatic lymph nodes while the M descriptor denotes presence (1) or absence (0) of distant metastasis (Table 1). Based on the TNM-status, the stage of disease is defined as stage I-IV, where stage IV reflects the most advanced stage with distant metastases and the poorest survival (Figure 6). Criteria for T, N and M descriptors and stage are adjusted at regular revisions to assure optimal separation in survival according to stage, as this is influenced by advances in diagnostic procedures and treatment policy. The most recent edition for lung cancer, is the 8th edition, which was published in 2016 (29).

In 2020, 26.2% of the newly diagnosed lung cancer patients in Norway had stage I, 7.0% stage II, 18.4% stage III and 45.4% stage IV (19).

**Table 1** Description of TNM 8th for lung cancer (28)

| **T (Primary Tumor)** | |
|---|---|
| T0 | No primary tumor |
| Tis | Carcinoma in situ (squamous or adenocarcinoma) |
| T1 | Tumor < 3cm |
| - T1mi | Minimally invasive adenocarcinoma |
| - T1a | Superficial spreading tumor in central airways |
| - T1a | Tumor 1cm |
| - T1b | Tumor > 1 but < 2cm |
| - T1c | Tumor > 2 but < 3cm |
| T2 | Tumor > 3 but < 5 cm or tumor involving: visceral pleura, main bronchus, atelectasis to hilum |
| - T2a | Tumor > 3 but < 4cm |
| - T2b | Tumor > 4 but < 5cm |
| T3 | Tumor > 5 but < 7 cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe |
| T4 | Tumor > 7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe |
| **N (Regional Lymph Nodes)** | |
| N0 | No regional node metastasis |
| N1 | Metastasis in ipsilateral pulmonary or hilar nodes |
| N2 | Metastasis in ipsilateral mediastinal or subcarinal nodes |
| N3 | Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes |
| **M (Distant Metastasis)** | |
| M0 | No distant metastasis |
| M1a | Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe |
| M1b | Single extrathoracic metastasis |
| M1c | Multiple extrathoracic metastases (1 or > 1 organ) |

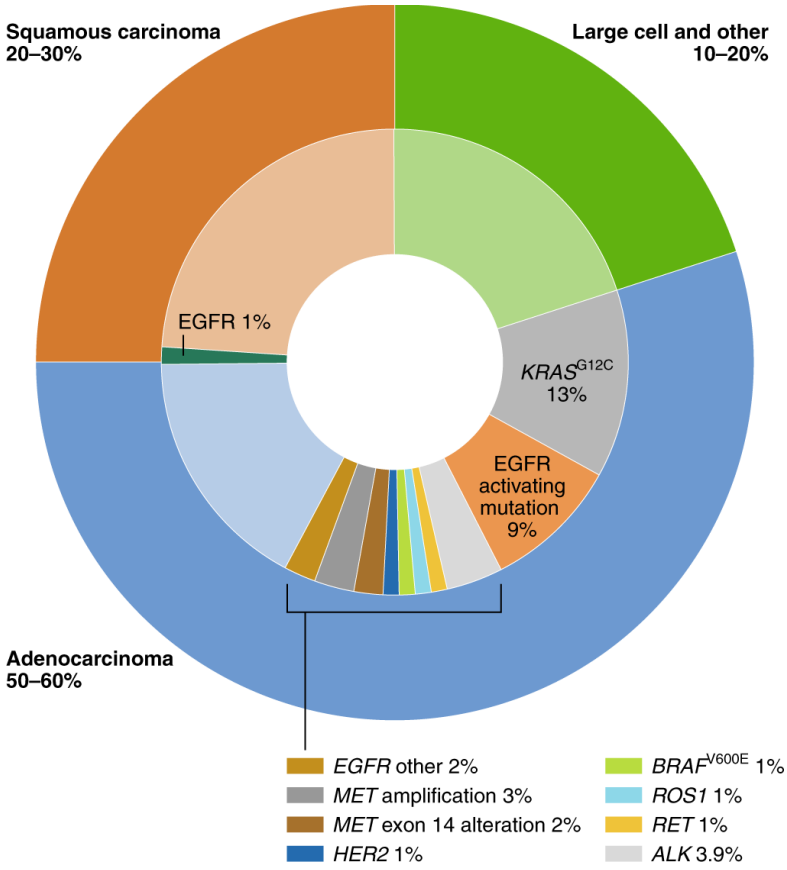
**Figure 6** Definition of stage of lung cancer based on TNM status. Adapted from (28)




The disease is also classified by histology and biomarkers, preferably by analyzing a biopsy, or through a fine needle aspiration cytology (FNAC), or cytology of pleural effusion if it is not possibly to collect a biopsy. The biopsy should be from a lesion with low risk for complications, and from the lesion most crucial to decide the stage of the disease.

All NSCLC samples should be tested for programmed cell death protein (Ligand) 1 (PD-L1) expression, and all patients with non-SCC are routinely tested for epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) rearrangement, ROS proto-oncogene 1 receptor tyrosine kinase (ROS1)- rearrangement, BRAF gene- mutation, and neurotrophic tyrosine receptor kinase (NTRK)- mutation (Figure 7). Next generation sequencing (NGS) is used to examine all the common gene alternations at once.

**Figure 7** Molecular landscape of NSCLC. Figure copied from (30)




### *2.2.4 Treatment of NSCLC*

#### *2.2.4.1 Brief history of treatment of lung cancer and NSCLC*

Milton Anthony performed the first surgical resection for lung cancer in 1821 (31), and the first successful pneumectomy was done by Dr Graham in 1933, which proved that lung cancer was a potentially curable disease (32). Palliative radiotherapy has been used since the 1940s, and radical radiotherapy on inoperable patients, was first attempted in the 1950s (33). In 1948 chemotherapy was introduced in the treatment of lung cancer (34). Cisplatin became an important part of the treatment in the early 1970s (35), and cisplatin-based combination chemotherapy has demonstrated superior survival to best supportive care (BSC) and single agent chemotherapy, and has been regarded the most effective treatment for decades (36).

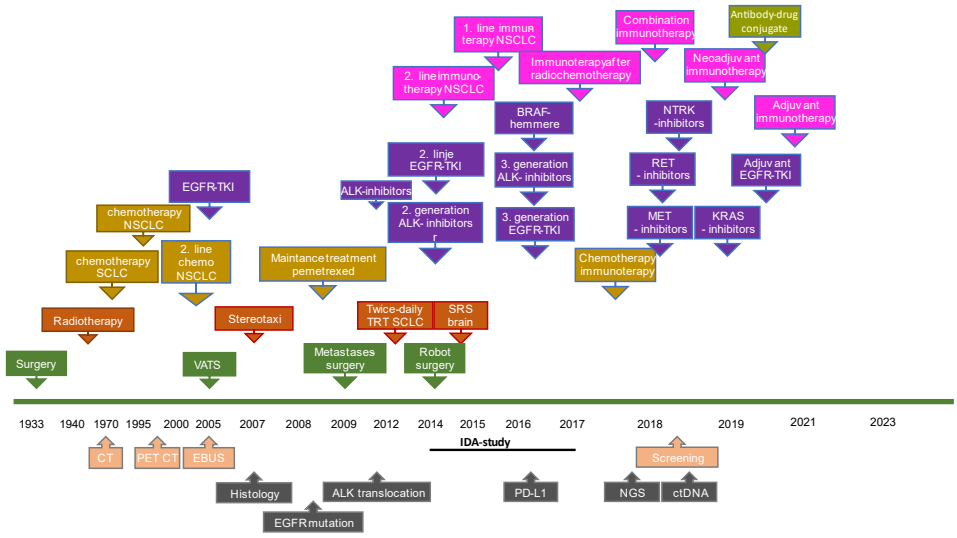
In the late 1990s, several “third-generation” cytotoxic drugs (i.e., vinorelbine, gemcitabine, docetaxel, and paclitaxel) were developed, and combinations of cisplatin and a third-generation drug proved to be more effective first-line regimens than older platinum-doublets (37-39).

The benefit of second-line chemotherapy with docetaxel in patients with advanced NSCLC, was first demonstrated in 2000 (40). The benefit of pemetrexed as second-line treatment in non-SCC patients was shown in 2004 (41). Few patients (<50%) were fit enough to receive second-line therapy at progression, consequently *immediate* maintenance therapy was investigated. Immediate maintenance therapy with docetaxel (42, 43) or gemcitabine (44) was found to be superior to observation followed by second-line therapy when progression was detected. Pemetrexed was preferred as maintenance therapy due to its favorable toxicity profile. Several studies suggested a survival benefit from immediate maintenance pemetrexed compared to BSC (4-6).

The first available targeted therapy for NSCLC, was gefitinib, an EGFR tyrosine kinase inhibitor (EGFR-TKI) (45). Another EGFR-TKI, erlotinib, was the first to demonstrate prolonged survival and improved health related quality of life (HRQoL) compared to BSC as second-/third-line therapy. The number of available targeted therapies is constantly increasing, but still only a small proportion of patients have disease available for targeted therapy (Figure 7).

Immune checkpoint inhibitors (ICI) were introduced in 2015 and were first available for PD-L1-positive patients who relapsed after first line therapy (46-48). Later studies established ICIs as first-line therapy, as monotherapy or in combination with chemotherapy, for all patients with advanced NSCLC (48-52) (Figure 8).

**Figure 8** Development of treatment for advanced NSCLC




### 2.2.4.2 Current recommendation for treatment of NSCLC

Traditionally, a curative treatment strategy has been available for most patients with stage I and II disease, some patients with stage III, but rarely in patients with stage IV disease, though the latter might have changed with the introduction of immunotherapy and more aggressive treatment of (oligo) metastases.

Surgery is the preferred curative treatment modality in patients with stage I, II and III (N0, N1, or single N2) disease. Stereotactic radiosurgery, conventional radiotherapy or chemoradiotherapy plus adjuvant immunotherapy, are alternative curative strategies for inoperable patients, or based on patient preferences. Fit patients with stage IV disease and few (1-4) metastases (oligometastatic disease), may be considered for surgery or radiotherapy of all tumors, in particular patients with a resectable lung tumor and a single brain (53) or adrenal metastasis (54, 55). Treatment of oligometastatic disease results in excellent local control and prolongs survival (56).

Palliative radiotherapy can be offered to relieve or prevent local symptoms, e.g., from brain metastases, painful bone metastasis or tumor compression, in patients with incurable disease.

Systemic therapy is the cornerstone of palliative cancer treatment but can be combined with surgery or radiotherapy in curative intent treatment, either before (neoadjuvant), together (concomitant or sequential) or afterwards (adjuvant).

#### 2.2.4.2.1 Chemotherapy in NSCLC

All chemotherapeutic agents interfere with cell proliferation (the cell cycle) and are thus more likely to influence cancer cells with typically high proliferation rates. Main classes of chemotherapeutic agents are *alkylating agents* which damage DNA directly, *antimetabolites* which substitute normal building blocks for RNA and DNA synthesis, and *plant alkaloids* which inhibit enzymes preparing DNA replication (topoisomerase inhibitors), and cell division (mitotic inhibitors).

Side effects from rapidly proliferating normal tissue are common. E.g., bone marrow suppression is a common side-effect of chemotherapy and may be dose limiting. In addition, some drugs have direct toxic effects on specific organs as well, e.g., platinum may cause toxicity to the heart or kidneys.

While cisplatin is preferred in curative intent treatment, carboplatin is the platinum (alkylating agent) of choice in the treatment of advanced lung cancer. Carboplatin is often better tolerated and has comparable effect to cisplatin (57). In contrast to other chemotherapies where the doses are calculated from the patient's body surface area (based on the weight and height), the doses of carboplatin are individualized based on the patient's renal function and clearance of the drug; the "Calvert Formula". The Calvert formula calculates the total carboplatin dose needed to achieve a given AUC (area under the free carboplatin plasma concentration versus time - curve) while considering the renal function. The carboplatin dose D in mg is:

*Dose = AUC (mg/mL/min) x (GFR in mL/minute + 25)*

Common adverse events include nausea, vomiting, fatigue, and hair loss, while constipation, diarrhea, and loss of appetite are less common. Severe adverse events as nephrotoxicity and ototoxicity may also occur. Anaphylactic-like reactions can occur within minutes of administration.

Vinorelbine is a vinca alkaloid, where the antitumor activity is due to inhibition of mitosis through interaction with tubulin, thus called an "antimicrotubular agent" (58). Common side-effects are nausea or vomiting, a general feeling of weakness (asthenia), and constipation. Less common toxicities are chemotherapy-induced peripheral neuropathy (numbness, intense pain, and hypersensitivity to cold), diarrhea, tiredness, hair loss, and inflammation of the vein into which it was injected (phlebitis).

Pemetrexed is an antimetabolite and induces cell cycle arrest in the G1/S-phase (59). By inhibiting the formation of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of DNA and RNA in cells. Common toxicities include nausea and fatigue. Less common toxicities are vomiting, diarrhea, oral mucositis, skin rash, constipation, and poor appetite.

If the bone marrow suppression is too severe with neutropenia or thrombocytopenia with increased risk for infections or bleedings, the next course is usually postponed, and the chemotherapy doses are adjusted. Granulocyte colony stimulating factor (G-CSF) reduces the risk of neutropenia, often reducing the need for dose reductions, but it is unclear whether the use of G-CSF improve overall treatment outcomes. Other potential toxicities from chemotherapy are furthermost prevented or reduced with administration of glucocorticoids and antiemetics before treatment (60). The frequency and severity of adverse events caused by pemetrexed, are reduced by routinely administration of Vitamin B12 and folic acid in supplementation (61).

The survival benefit from chemotherapy in advanced NSCLC, is limited (62). Typically, objective response is observed in 30-35% of patients, and median OS is around 7 months (63). Treatment beyond 4-6 courses of doublet chemotherapy gives no significant survival benefit and increases the risk for severe toxicity (64), but there is evidence that immediate maintenance mono-chemotherapy (gemcitabine, pemetrexed or docetaxel) improve OS compared to observation in patients with non-progression after the induction doublet chemotherapy (65).

#### 2.2.4.2.2 Targeted therapy in NSCLC

Lung cancer evolves because of a series of mutational events in the lung cells genes. These mutations often play a key role in cancer development (66). It is well known that tobacco smoke, which contains carcinogens as well as high levels of reactive oxygen species, cause genomic alterations (67). Certain somatic mutations, or acquired mutations in oncogenic or tumor promoting genes, are found more frequently in never smokers compared with ever smokers (68-70). Drugs acting specifically on proteins made from these genetic alterations causing cancer, have huge potential for effect.

In Norway, targeted therapy is currently available for EGFR, ALK, ROS1, and NTRK positive NSCLC. Many more targeted therapies are under development, but all are currently not reimbursed at public hospitals (Figure 8).

Most of these targeted therapies are more effective than cytotoxic chemotherapy, but most patients will experience relapse due to acquired resistance due to several mechanisms (71). The resistance might be caused by a single genetic alteration in tumor cells (72). E.g., in EGFR mutated

NSCLC, a T790M mutation is causing resistance in approximately 50% of patients treated with a first- or second-generation EGFR-TKI (73), while a transformation to SCLC is reported in 3-14% (74, 75). Thus, it is important to perform a re-biopsy at time of progression to determine further treatment options.

In general, targeted therapies are better tolerated than chemotherapy. Common side effects include rash, depigmentation, diarrhea, hypertension, hypothyroidism, hepatotoxicity, tiredness, nausea, vomiting, and proteinuria (76). The administration form as tablets is another benefit for the patients.

For patients with advanced NSCLC harboring EGFR or ALK alterations, with the use of EGFR or ALK inhibitors, median survival is more than 3 and 5 years, respectively (77, 78).

#### 2.2.4.2.3 Immunotherapy in NSCLC

There are several main types of immunotherapies used to treat cancer. Most relevant are immune checkpoint inhibitors (ICI), cancer vaccines, Chimeric antigen receptor (CAR) T-cell therapy, cytokines, and immunomodulators. As of today, only ICIs are implemented in the treatment of NSCLC.

Cancer cells differentiate from healthy cells. Due to a high level of antigen presentation on the surface of the healthy cells, the immune system can differentiate cancer cells from normal cells and initiate a cytotoxic response. However, the cancer cells try to avoid this effect by blocking activation of immune cells.

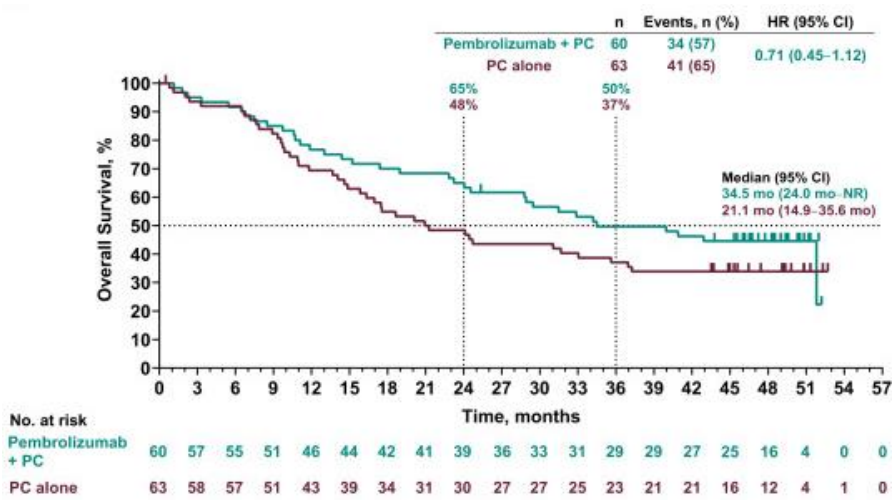
Programmed death-1 (PD-1) is a cell surface receptor on T- (and B-) cells. PD-1 is activated by the engagement of its ligand (PD-L1 or PD-L2). The ligands are expressed on antigen-presenting cells. The receptor and ligand play a central role in regulating the T-cell function, and to prevent autoimmunity. The PD-1 receptor delivers inhibitory checkpoint signals to the activated T-cells upon binding to its ligands. Cancer cells may express PD-L1 to suppress T-cell effector function, causing tumor immune evasion. This suppression can be counteracted by drugs targeting these checkpoints, either PD-1 or PD-L1, called immune checkpoint inhibitors (ICI) (79).

The toxicity profile from immunotherapy differs significantly from chemotherapy and targeted therapy. Immunotherapy is mostly well tolerated but can cause inflammation in any organ. Examples include; lungs (pneumonitis), liver (hepatitis), colon (colitis/diarrhea), skin (rash), or thyroid gland (thyroiditis). Patients might be on immunotherapy for a long time, and side-effects can occur at any point during or after treatment.

For patients with non-squamous advanced NSCLC without targetable mutations, todays treatment recommendation is four courses with pembrolizumab plus carboplatin-pemetrexed followed by maintenance pembrolizumab plus pemetrexed up to two years (27). This is based on several studies, including the KEYNOTE-189 and KEYNOTE-021G studies (49, 80, 81). In KEYNOTE-021G Pemetrexed-carboplatin (PC) combined with pembrolizumab compared to PC alone, showed a significant increase in median OS with 34.5 against 21.1 months in patients with advanced non-squamous NSCLC treated with pembrolizumab (82) (Figure 9).

PD-L1 expression is a predictive marker in cancer immunotherapy (83). Monotherapy with pembrolizumab is considered if the PD-L1 expression is high (>50%) or if there are concerns about the tolerability of chemotherapy (52). Especially when the PD-L1 expression is >75%, the additional effect of chemotherapy is marginal (84).

**Figure 9** OS comparing ICI and chemotherapy with only chemotherapy in advanced NSCLC. Figure copied from (82)




(PC= pemetrexed carboplatin)

### *2.2.5 Follow-up during and after treatment for patients with advanced NCSLC*

There is limited evidence for how often and how long patients should be controlled during and especially after, treatment (55). During treatment, both the treatment effect and the patient's tolerance must be evaluated. The patient's general condition is crucial. It is important to detect relapses while the patients still are fit enough to receive effective palliative therapy. CT scans are the main part of the follow-up and re-biopsies of new lesions are important to select optimal therapy.

For patients not fit for more systemic treatment, follow up should focus on preventing and relieving symptoms.

## 2.3 Evaluation of outcomes in advanced NSCLC

The main objectives for treatment of advanced NSCLC, are to improve survival and health related quality of life (QoL).

In clinical trials that assess novel therapeutic agents, OS is the gold-standard endpoint for establishing clinical benefit. However, since measuring OS can be time consuming, other endpoints are often used, e.g., progression free survival (PFS), time to progression (TTP), response rate (RR), or biological markers measured in blood samples. Evaluation of the negative effects, e.g., toxicity and HRQoL, are equally important to evaluating the impact on disease control.

### *2.3.1 Overall- (OS) and progression free survival (PFS)*

OS is defined as time to death from all causes, while PFS is time to disease progression or death from any cause. PFS could be used as a surrogate endpoint for OS, but it has also an independent value. PFS has some benefits compared to OS as well: PFS measures how long the treatment effect is, and it is not affected by crossover between the treatment arms as OS is. It is valuable to delay the progression of the disease, both due to absence of potential symptoms from a progression, and then less time spent in the hospital. PFS may matter to patients, even if it does not affect their OS. PFS has the advantage that trial completion can be quicker with fewer patients required.

### *2.3.2 Tumor response assessment*

RECIST (Response Evaluation Criteria in Solid Tumors) is mainly used to evaluate treatment response in solid tumors. It is composed of validated and consistent criteria to assess changes in tumor burden (85, 86). According to RECIST, lesions are defined as *target lesions* or *non-target lesions* depending on size and location. Sum of the longest diameter of all target lesions is measured and compared, and response is categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR is defined as disappearance of all target lesions, PR as at least 30% reduction of the sum of the longest diameter of target lesions compared to baseline. SD is defined as neither sufficient shrinkage to qualify as PR nor sufficient increase to qualify as PD. PD is defined as 20% increase in the sum of target lesions compared to baseline. Disease control usually includes both CR, PR, and SD.

### *2.3.3 Toxicity*

Toxicity is usually reported according to The Common Terminology Criteria for Adverse Events (CTCAE) (87). This system rates events according to specific criteria on a scale from 1-5 (1; mild, 2; moderate, 3; severe, 4; life threatening or disabling, 5; death). Toxicity is often reported as "overall toxicity" and divided into hematological toxicity or non-hematological toxicity. If toxicity grade 3-4 occurs, treatment intensity is often adjusted, either as dose reduction, delays, or termination.

### *2.3.4 Patient reported physical function – Health Related Quality of Life (HRQoL) – assessment*

Patient-reported outcome (PRO) is a broad category of health status measures reported by the patients and the instruments used are called patient reported outcome -measures (PROM) (88). A PROM can reflect any aspects of a patient's health.

Quality of life (QoL) is a PRO generally perceived as the overall enjoyment of life and well-being, and is often closely linked to good health and the ability to perform activities of daily living (89). QoL measures are approved by the Food and drug administration (FDA) as an important primary outcome in cancer research (90).

In medical research, we are mostly interested in QoL and the association to health, and thus, the concept of Health related quality of life (HRQoL) has been established; defined as the dimensions of QoL which are most influenced by health and health-care interventions (91). It could be related to World Health Organizations (WHO) definition of health: "A state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" (92). HRQoL includes several domains, which consider the general perception of the patient on the impact of disease or treatment on physical as well as psychological and social aspects of life (88).

PROMs are increasingly used in cancer research (93) and measuring PROs can have several benefits for the patients: e.g., increased satisfaction (94), improved communication between patients and physicians (95), improved symptom control (96), and improved QoL (97). In addition, it is important to have the patient's self-evaluation, since health care professionals tend to overestimate the QoL benefit from treatment, while the side-effects tend to be underestimated (98).

HRQoL should be measured with validated instruments. In lung cancer research, the most commonly used is the European Organization for Research and Treatment of Cancer Core questionnaire (EORTC QLQ) C30 (99, 100), plus the Lung Cancer supplement (LC 13) (101) (Table 3).

EORTC QLQ C30 consist of 30 questions which measures 15 fundamental aspects of HRQoL, and symptoms commonly reported by cancer patients (Table 3). Nine of the aspects are answered by

multi-item scales: Five functional scales (physical, role, emotional, cognitive, and social function); three symptom scales (fatigue, pain, and nausea/vomiting); and one scale for global health/quality of life. Six single item scales assess common symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea), and the perceived financial impact of having a malignant disease. All scales are fourfold: not at all – a little – quite a bit – very much, except the global health/QoL which is sevenfold; specified as 1 (very poor) to 7 (excellent).

LC13 is the lung cancer specific module and consist of 13 questions to evaluate lung cancer specific symptoms: coughing (one item), hemoptysis (one item), dyspnea (three items), treatment side effects (sore mouth, dysphagia, alopecia, peripheral neuropathy; each one item), pain (three items) and pain medication (one item) (Table 3). Dyspnea is the only multi-item scale; the others are single-item scales. All these scales are also four-fold: not at all – a little – quite a bit – very much.

EORTC QLQ LC13 is only validated in combination with the QLQ C30 (101). QLQ LC13 was developed for more than 20 years ago when there were no guidelines for module development. Recently, QLQ LC29 was initiated for a more optimal and relevant assessment of the QoL using the Module Development Manual and by considering the new trends in treatment (102). QLQ LC29 contains a total of 29 items, it retained 12 of the 13 in the LC13 version and added items on relevant and common side-effects as well as a surgical subscale. The updated module is used and perceived as highly relevant by patients with lung cancer (103).

All HRQoL-scores are calculated according to the EORTC scoring manual and transformed to a scale from 0-100 (99-101). Several categories have shown to be prognostic factors for survival (104).

**Table 3** Content of the EORTC QLQ C30 plus LC13

| QLQ | Type of scale | Scale | No. of items | Question no. |
|---|---|---|---|---|
| C30 | Global Health/QoL | Global QoL | 2 | 29, 30 |
| | Functional scales | Physical function | 5 | 1-5 |
| | | Role function | 2 | 6,7 |
| | | Emotional function | 4 | 21-24 |
| | | Cognitive function | 2 | 20,25 |
| | | Social function | 2 | 26,27 |
| | Symptom scales | Fatigue | 3 | 10,12,18 |
| | | Nausea and vomiting | 2 | 14,15 |
| | | Pain | 2 | 9,19 |
| | | Dyspnea | 1 | 8 |
| | | Insomnia | 1 | 11 |
| | | Appetite loss | 1 | 13 |
| | | Constipation | 1 | 16 |
| | | Diarrhea | 1 | 17 |
| | | Financial difficulties | 1 | 28 |
| LC13 | Symptom scales | Dyspnea | 3 | 3-5 |
| | | Coughing | 1 | 1 |
| | | Hemoptysis | 1 | 2 |
| | | Sore mouth | 1 | 6 |
| | | Dysphagia | 1 | 7 |
| | | Peripheral neuropathy | 1 | 8 |
| | | Alopecia | 1 | 9 |
| | | Pain in chest | 1 | 10 |
| | | Pain in arm or shoulder | 1 | 11 |
| | | Pain in other parts | 1 | 12 |

## 2.4 Prognostic and predictive factors in advanced NSCLC

The outcome of a particular disease depends on many factors. They may be clinical, biological, radiological, molecular, and related to the tumor or the patient. A prognostic factor foresees the effect of a disease on outcomes, e.g., survival, while a predictive factor foresees the modifying effect on outcomes from the specific treatment (54). Factors may be both prognostic and predictive.

A number of publications refer to prognostic and predictive factors in lung cancer, and already in 2002 a review reported 150 possible prognostic markers in NSCLC (105), but only a few of them are used in clinical practice.

In NSCLC-patients, disease stage (106), gender (107), performance status (108), smoking status (109), are well known prognostic factors, while it remains unclear whether for example physical function is a true prognostic or predictive factor.

In addition to EGFR-mutations (110), PD-L1 expression (111), ALK-translocations (112), and ROS1-rearrangement (113), are examples of predictive factors that are used to determine treatment in advanced NSCLC.

### *2.4.1 Physical function and functional status*

Physical function may refer to the patient's mobility, strength, endurance, and the ability to perform common activities of daily living (114, 115). It can be reported in many ways, either by the patient himself or by the physicians, and the description may be based on passive objective observations, subjective self-reports, or active performance measurements. Physical performance might be an indicator of general health status since it integrates known and unknown disturbances in multiple organ systems such as heart, lungs, circulatory, and musculoskeletal systems (116).

Generally, in non-cancer patients and especially in elderly, reporting the activity of daily living (ADL) and instrumental activity of daily living (IADL), have been of special interest (117, 118). Physical function measured with different performance tests are frequently used in e.g., preoperative evaluations (119), estimating the fall-tendency (120) and evaluation of the patient's ability to live at home (121) as well.

#### 2.4.1.1 Performance status (PS)

Performance status (PS) is the most established patient-related prognostic factor used in oncology (122). PS grades a patient's performance status by their ability to care for themselves, restrictions in daily activity, and physical ability. It is a strong prognostic determinant of survival (123), and predicts treatment tolerance in cancer patients (124).

Most rate PS according to the World Health Organizations performance status (WHO PS) from 0-5 (125), while the commonly used alternative, the Karnofsky score, rates patients from 0-100 (34) (Table 4).

WHO PS 0-1 patients are considered fit for all therapies, while WHO PS 3-4 are not. Whether patients with a WHO PS 2 should be offered all therapy, is debated. WHO PS 2 patients are often excluded from RCTs, but some studies show that patients with a WHO PS of 2 tend to tolerate treatment poorer and have an inferior survival compared to patients with a WHO PS of 0 to 1 (126). If the WHO PS of 3-4 is disease-related and expected to reverse upon treatment response, treatments that are generally associated with a high degree of effect (e.g., chemotherapy in SCLC) and good tolerance (e.g. EGFR TKIs), can be offered (127).

**Table 4** WHO performance status and Karnofsky score. Figure copied from (128)

| ECOG/WHO score system | Definition | Karnofsly score |
|---|---|---|
| **0** | Fully active, able to carry on all pre-disease activities without restriction | 90-100 |
| **1** | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature | 70-80 |
| **2** | Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours | 50-60 |
| **3** | Capable of only limited self-care, confirmed to bed or chair 50% or more of waking hours | 30-40 |
| **4** | Completely disabled; cannot carry on any self-care; totally confined to bed or chair | 10-20 |
| **5** | Dead | 0 |

ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; PS performance score

#### 2.4.1.2 Performance measurements

Due to increased life expectancy, more elderly people being considered for cancer treatment (129). Elderly patients often have comorbidity and functional or cognitive decline which makes the treatment decisions challenging. In addition, they are often underrepresented in clinical trials (130). But the age itself has shown not to be a useful selection tool for oncologic treatment, and the patients should be treated according to their individual health status. Measuring physical function is an important part of geriatric evaluations and has shown promising results as a prognostic factor in elderly cancer patients (11).

A brief measure reflecting physical function and functional capacity, seems to be useful as a prognostic factor in clinical oncological studies (131-135). Various physical performance measures appear to reflect the health status and to be prognostic for health events (9). Gait-speed (several measures), timed up and go (TUG), short physical performance battery (SPPB) (136), and hand-grip strength, are the most established measures. If the patient has poor physical function, oncologic treatment may result in a vicious cycle of reduced physical activity and deconditioning that has a direct effect on health and survival (116, 137). In addition to an association to survival (138-144), studies of cancer patients show that these performance tests both have associations to treatment-related complications (145, 146), and functional decline (142, 147, 148), at least in older patients (11, 145, 149). The likelihood of spending a greater part of the survival time in a disabled status, is higher if the patient has poor physical performance prior to treatment (150).

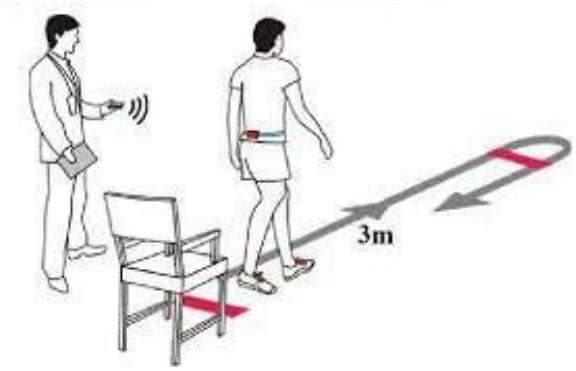
In addition to performance measures, physical function may also be reported by the patients, patient-reported physical function (PRPF).

#### 2.4.1.2.1 Timed- up and go (TUG)

TUG was established in 1986 (151) and modified in 1991 (152) as a test to examine balance in older patients. Later the test has been used in several other settings such as preoperative evaluations (153), estimating fall-tendency (154), and in cancer patients (11).

Patients are asked to stand up from a chair, walk 3 meters (marked on the floor) at a comfortable pace, turn, walk back, and sit down (152). The performance reflects many aspects of the physical function of the patients; gait-speed, strength in the lower limbs and balance. The test result is usually dichotomized, but the cut-off values vary between studies.

**Figure 8** Timed up and go -test. Picture copied from (155)




TUG has shown association to survival (138, 140, 141, 144), complications (146), and functional decline (148) in studies including patients with different types of cancer (lung cancer proportion between 8-100%) receiving different treatment modalities (chemotherapy included), where a poor performance is associated with worse outcome. In a study including only patients with advanced NSCLC treated with chemotherapy, they also found an association to survival in univariable analysis, while multivariable analyses to evaluate the independent value, were not performed (138).

#### 2.4.1.2.3 5-meter walk test (5mWT)

There are many different tests examining walk-speed. The tests vary significantly in length and duration (from 5 meters up to 20 minutes), in the walking speed (fast or normal), and whether the start and stop are flying or not. The pace and cut-off values vary between the studies, and most of

the studies include a heterogenous population of patients, cancer types, and treatments. Despite huge heterogenicity, several studies show that gait speed is associated with important endpoints in studies of cancer patients, as survival and complications (139, 142).

#### 2.4.1.2.4 Patient-reported physical function (PRPF)

PRPF can be measured in different ways. In this thesis we used the compound score of the five items from the EORTC QLQ C30 questionnaire (Appendix A); Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase, 2) Do you have any trouble taking a long walk, 3) Do you have any trouble taking a short walk outside of the house, 4) Do you need to stay in bed or a chair during the day, 5) Do you need help with eating, dressing, washing yourself or using the toilet?" Each item is scored from 0 (not at all) to 4 (very much), summarized and transformed into a scale ranging from 0-100 where higher score indicates better function (99, 100). Previous studies show that PRPF is an independent prognostic factor for survival in cancer patients (140, 156).

### *2.4.2 Inflammation in cancer*

Inflammation is a response triggered by damage to living tissues. The inflammatory response is a defense mechanism to protect from infection and injury. Its purpose is to localize and eliminate the injurious agent and to remove damaged tissue components so that the body can start the healing process. The response consists of changes in blood flow, an increase in permeability of blood vessels, and the migration of fluid, proteins, and leukocytes from the circulation to the site of tissue damage.

A multifactorial network of chemical signals initiates and maintains a host response to heal the afflicted tissue in response to tissue injury. Leukocytes (neutrophils, monocytes, and eosinophils) are activated and migrate from the venous system to sites of damage, and tissue mast cells also have a significant role. These cells produce different immune-modulating agents which both influence the local inflammatory response and cause systemic responses as fever, catabolism of muscles, and shifts the body's protein synthesis towards an inflammatory state (157).

Inflammation can damage the cell's DNA by the altered microenvironment, and initiate cancer, but also promote the tumor growth and spread (158). Already in the middle of 19$^{th}$ century (159), the link between inflammation and cancer was hypothesized, but it was not proved until the early 2000's (160). Now it is well accepted that inflammation is a critical component of cancer development and progression (157, 159, 161, 162). Chronic inflammation can trigger and increase the risk of developing various cancers in predisposed individuals. Such triggers include microbial infections (e.g., Helicobacter pylori infection is associated with gastric cancer and gastric mucosal

lymphoma), autoimmune diseases (e.g., inflammatory bowel disease associated with colon cancer), and inflammatory conditions of unknown origin (e.g., prostatitis associated with prostate cancer). World-wide, underlying inflammation has been estimated to contribute to 15-20% of all deaths from cancer (161). Inflammatory measures have been shown to have prognostic value in many cancers (163), including lung cancer (164).

The association between different inflammatory components measurable in blood samples, and cancer, have been examined (165, 166). C-reactive protein (CPR) is an acute phase protein, and Tumor necrosis factor-alfa (TNF-α), and different interleukins (e.g., IL-1α and β), are examples of cytokines produced in the inflammatory process (167, 168). Inflammatory cancers cause elevated CRP and low albumin (169). CRP is elevated because of several potential reasons: tumor growth may cause tissue inflammation, immune response to an antigen, or cancer cells can increase the production of inflammatory proteins (158). Albumin tends to fall because of an ongoing systemic inflammatory response. This contributes to the progressive loss of these vital protein components of the body with increased degradation and loss of body mass (which is the pool for amino acids) and lower production (inflammatory proteins are preferred instead of albumin) (170).

Lung cancer is marked by high systemic inflammation and poor outcome (7, 8), and a high proportion of patients have elevated inflammatory markers as compared to other cancer types (8). It is reasonable to think that inflammatory markers reflect the cancer activity since lung cancer has high mortality.

#### 2.4.2.1 GPS/mGPS – a systemic inflammatory score

Glasgow Prognostic Score (GPS) is an inflammatory score based on values of CRP and albumin (171), and appears to be a solid prognostic factor among cancer patients including NSCLC patients (8, 172-176), and is the most validated (163). The benefit of GPS is that it is an objective measure, simple, cheap, easily available, and with well standardized thresholds which are internationally recognized.

When scoring GPS, an elevated CRP of >10 mg/L and hypoalbuminemia of <35 mg/L are considered abnormal values. If both values are normal, GPS is 0. If one value is abnormal, GPS is 1, and when both are abnormal, GPS is 2 (Table 5). A higher score is associated with shorter survival (171). Later, a modified version was proposed (mGPS). mGPS differs from the original GPS in that CPR must be abnormal if an abnormal albumin should give effect to the score, which means; an isolated low albumin does not affect the score (Table 5). The mGPS was developed since an isolated abnormal albumin was rarely seen and did not have the same association to survival as in situations where CRP was elevated, both isolated and in combination with low albumin (177). Both GPS and

mGPS have been used in studies afterwards. One study including both operable and non-operable NSCLC patients comparing the scores concluded that GPS was superior to mGPS giving information about cancer patients (178).

**Table 5** The description and difference between of Glasgow prognostic score (GPS) and the modified Glasgow prognostic score (mGPS)

| Description | GPS | mGPS |
|---|---|---|
| **CRP ≤10 mg/l and albumin ≥35 mg/l** | 0 | 0 |
| **CRP ≤10 mg/l and albumin <35 mg/l** | 1 | 0 |
| **CRP >10 mg/l and albumin ≥35 mg/l** | 1 | 1 |
| **CRP >10 mg/l and albumin <35 mg/l** | 2 | 2 |

The prognostic value of GPS has been shown in several studies in cancer patients in general (171, 174-176, 179-181). Primarily, GPS before start of treatment is examined. There are studies which have examined GPS during or after treatment; studies of palliative chemotherapy for colorectal cancer (182), surgery for localized NSCLC (183) and gastric cancer (184), concurrent chemoradiotherapy in advanced head and neck cancer (185), and a study with neo-adjuvant chemotherapy before surgery in esophagogastric cancer (186). Recent studies have also examined the relationship between GPS and OS in patients treated with ICI and found an positive association between GPS at evaluation and survival in patients with advanced NSCLC (187, 188) and renal-cell carcinoma (189).

# 3 Rationale for the project

## 3.1 Need for improved treatment

When the RCT which this thesis is based on, was initiated, chemotherapy was standard therapy for advanced NSCLC without targetable driver mutations. Median overall survival was approximately 7.5 months (63, 190, 191). There was a clear and unmet need for improved treatment. Studies had shown a survival benefit from maintenance therapy immediate after induction platinum-doublet chemotherapy (4-6). However, these studies had some limitations; few patients received pemetrexed at progression in the observation arm, and WHO PS 2 patients were excluded from the trials.

## 3.2 Need for improved prognostic and predictive information

There is a need for improved knowledge on how to identify patients that benefit from treatment and how to individualize the cancer care. Time spent on ineffective treatment and unnecessary toxicity may be avoided, treatment may be changed or discontinued earlier when disease progresses, and patients may receive effective salvage therapy upon relapse before their performance status deteriorates so much that they do not tolerate such therapy. Such tools would promote more individualized therapy.

Lung cancer is a highly inflammatory disease, and GPS measured at baseline is a prognostic factor in patients with advanced NSCLC (8, 172-176). It is reasonable to assume that the inflammation decreases if patients respond to treatment, and that GPS measured during treatment can provide additional prognostic information. Since GPS is an easy, objective, cheap, and universal score and easy to implement, we wanted to examine if this score could be used as a prognostic factor in daily practice.

The patient's physical function is associated with survival in advanced NSCLC patients (131), but the definition of physical function varies between different studies. WHO PS is routinely used as a prognostic factor in daily clinic, but it is unclear how WHO PS and physical performance measures are correlated, and if they give different information about the patients. We wanted to examine if simple physical performance measures as TUG and 5mWT, could be used as prognostic factors, if they give additive prognostic information to WHO PS, and if TUG and 5mWT are better prognostic factors than patient reported physical function (PRPF).

# 4 Aims and research questions

The overall aim for the project was to improve survival for patients with advanced non-squamous NSCLC of all ages and WHO PS 0-2.

## 4.1 Research questions for paper I

- Does immediate maintenance pemetrexed therapy after four courses of induction therapy with carboplatin and vinorelbine, prolong OS or PFS compared with pemetrexed therapy upon progression? Is immediate maintenance pemetrexed well tolerated in this patient group?

## 4.2 Research questions for paper II

- Is GPS measured after four courses of carboplatin and vinorelbine a stronger prognostic factor than GPS measured before start of treatment? Are there any associations between response to chemotherapy and GPS measured before or after therapy?

## 4.3 Research questions for paper III

- Is physical performance measured with TUG or 5mWT prognostic factors for OS or predictive for disease control after four courses of carboplatin and vinorelbine? Are objective measurements stronger prognostic factors than PRPF?

# 5 Material and methods

This thesis is based on a Norwegian randomized phase III multicenter trial by the Norwegian Lung Cancer Study Group (NLCG) (192). Patients were enrolled from May 2014 to September 2017 at 19 hospitals in Norway.

## 5.1 Inclusion and eligibility criteria

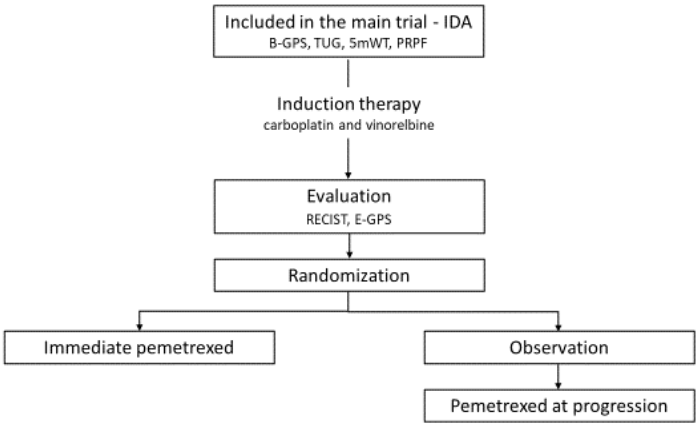
Eligible patients had stage IIIB (ineligible for curative therapy) or IV non-squamous NSCLC without known EGFR-mutation or ALK-translocation and had received no prior systemic therapy for advanced NSCLC. They were at least 18 years old with no upper age limit, in WHO PS 0-2 and had adequate liver, kidney, and bone marrow function. No other serious concomitant systemic disorder which could compromise the patient's ability to complete the study or interfere with the evaluation of the efficacy and safety of the study treatment, were allowed. All patients had a CT scan of thorax and upper abdomen within four weeks of the first course of induction therapy with measurable disease according to RECIST 1.1.

Patients who completed all four courses of induction chemotherapy without disease progression, were eligible for randomization if their WHO PS remained between 0 and 2. They were randomized to immediate maintenance therapy with pemetrexed (maintenance arm) or to observation followed by pemetrexed at progression (observation arm) stratified for WHO PS (0, 1 or 2), response to induction chemotherapy (CR/PR or SD), and the presence of known brain metastases detected before induction therapy (yes or no). All randomized patients were analyzed in paper I.

For the main analyses in paper II, patients who received three or four courses of carboplatin/vinorelbine and had Glasgow prognostic score (GPS) scored both at baseline (B-GPS) and at evaluation (E-GPS), were included. In sensitivity analysis of B-GPS and survival, all patients with B-GPS, independent of number of completed chemotherapy courses, were included.

For paper III, all patients who had completed the physical function tests, TUG and 5mWT, at baseline, independent of treatment and outcome in the study, were included in the analysis.

**Figure 9** Consort all three papers




## 5.2 Study treatment

### *5.2.1 Induction chemotherapy*

Patient were to receive four courses of carboplatin with area under a curve (AUC) 5 (Calvert's formula) intravenously (IV) and vinorelbine 25 mg/m2 IV day 1 and vinorelbine 25 mg/m2 IV or 60 mg/m2 per oral (PO) day 8 every three weeks. A full dose day 1 was administered if absolute neutrophile count (ANC) was ≥1.5 x $10^9$/L and platelets ≥100 x $10^9$/L. Otherwise, the course was postponed one week, and doses reduced by 25%.

The doses of the subsequent courses were adjusted according to nadir values; 25% reduction if ANC was <0.5 x $10^9$/L or platelets <50 x $10^9$/L and reduced by 50% if both occurred. Doses were reduced by 25% in case of any grade 3-4 (CTCAE v4.0) non-hematological toxicity. The vinorelbine dose on day 8 was reduced by 25% if ANC was <1.0 x $10^9$/L or platelets <100 x $10^9$/L and omitted if ANC was <0.5 x $10^9$/L or platelets <50 x $10^9$/L. All dose-reductions were maintained for subsequent courses. Chemotherapy was discontinued and the patient excluded if a course was delayed more than three weeks.

### *5.2.2 Pemetrexed therapy*

All patients were to receive pemetrexed 500 mg/m2 IV every three weeks. The first course was to be administered within 5 weeks after day 1 of the fourth course of induction chemotherapy in the

maintenance arm, and within 2 weeks after progressive disease was detected in the observation arm. Treatment was to be continued until progressive disease or unacceptable toxicity. All patients were given folic acid and vitamin B12 from ≥5 days prior to the first pemetrexed course and until three weeks after the last course.

Blood values were measured on day 1 and 10 (nadir) of every course. A full dose was given if ANC >1.5 x $10^9$/L; platelets ≥100 x $10^9$/L; bilirubin <1.5x under lower normal (ULN); ALAT/ALP ≤3x ULN if there were no known liver metastasis, ≤5x ULN if patients had liver metastases; and creatinine clearance was ≥45 ml/min on day 1. If these criteria were not met, the course was postponed one week, and the dose reduced by 25%. The dose of the next course was reduced by 25% if nadir ANC was <0.5 x $10^9$/L or nadir platelet count was <50 x $10^9$/L, or by 50% if both ANC and platelet count was below this level. If any CTCAE v4.0 grade 3-4 non-hematological toxicity occurred, doses were reduced by 25%. Dose-reductions were maintained for all subsequent courses. Chemotherapy was discontinued if a course was delayed more than three weeks. Granulocyte-colony stimulating factor (G-CSF) was allowed. The therapy should continue until progressive disease according to RECIST 1.1, or discontinuation due to other reasons e.g., toxicity, withdrawal of consent.

### *5.2.3 Radiotherapy*

Palliative radiotherapy was allowed prior to inclusion, but the irradiated lesions were not considered as target lesions for response evaluation according to RECIST. Radiotherapy during the study was allowed for other reasons than progressive disease, i.e., if the patient had painful skeletal metastasis when starting second line pemetrexed. After completion of the study treatment, radiotherapy was administered as recommended by the treating physician.

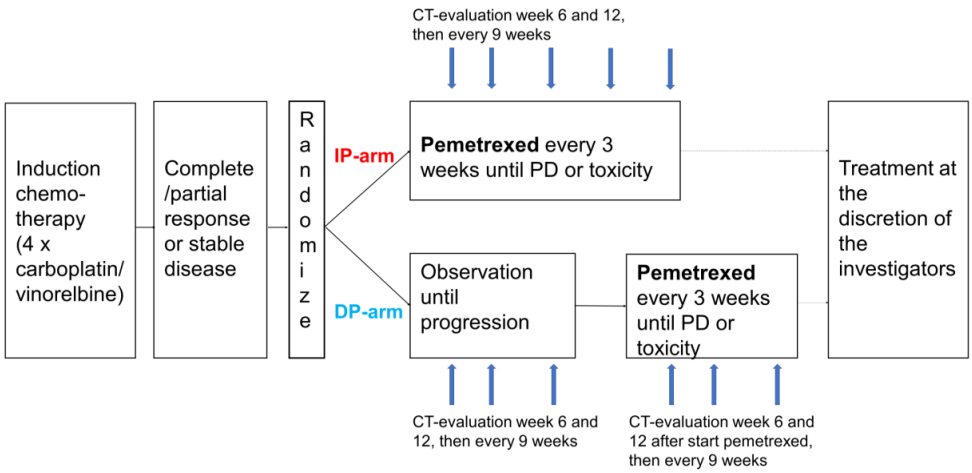
### *5.2.4 Post-study treatment*

Patients who experienced progression during or after study therapy, were to receive further therapy as recommended by the investigators.

## 5.3 Evaluation and follow up

The trial plan is presented in Figure 10. Clinical examination, hematology and creatinine, assessment of WHO PS, and toxicity were performed at all visits. Biochemistry (bilirubin, ALT, LDH, albumin, CRP) was performed at the beginning of every chemotherapy course, both before and after randomization.

**Figure 10** Flow chart – trial design:




*IP-arm* received immediate maintenance pemetrexed

*DP-arm* received delayed maintenance pemetrexed; pemetrexed at time for progression after initial observation

## 5.4 Assessments

### *5.4.1 Response to treatment*

All patients had a CT scan within three weeks after the last course of induction chemotherapy regardless of number of courses administered. All patients receiving pemetrexed had a CT evaluation every six weeks after start of pemetrexed the first 12 weeks, then every nine weeks, corresponding to every third course of pemetrexed (Figure 10). All patients should have a CT scan within three weeks after the last course of pemetrexed.

In the observation arm, all patients should have a CT scan at week six and 12 after randomization, and then every nine weeks until progressive disease according to RECIST 1.1 (Figure 10). If progressive disease was suspected, it should be verified on a CT-scan.

For paper III, disease control after the induction therapy was defined as stable disease (SD), partial response (PR) or complete response (CR) according to RECIST 1.1.

### *5.4.2 Toxicity and treatment completion*

Toxicity was assessed at all visits and reported as present or not (yes/no) during induction therapy and classified according to CTCAE v4.0 during treatment with pemetrexed.

For paper III, treatment completion was assessed in three ways: as the proportion of patients completing all four induction courses, the proportion of patients without any dose reductions of ≥20%, or the proportion without any delays (≥7 days) of induction chemotherapy courses.

### *5.4.3 Health related quality of life (HRQoL)*

HRQoL questionnaires, EORTC QLQ C30 and LC13, were completed at inclusion, evaluation after induction therapy/at randomization, at week six and 12 after randomization, then every ninth week in both arms, and at time at progression after pemetrexed treatment (at discontinuation of the study therapy). The first 60 weeks from inclusion, corresponding to the first 12 months after randomization, was defined as the period of interest.

### *5.4.4 Glasgow Prognostic Score (GPS)*

GPS was calculated at baseline (B-GPS) and at evaluation (E-GPS) after induction therapy, independent of number of courses received.

### *5.4.5 Timed up and go (TUG) and 5-meter walk test (5mWT)*

TUG and 5mWT, were performed at baseline, at evaluation after induction therapy, at week 6, 12, and then every ninth week after randomization in both arms. Measurements at baseline were used in paper III.

When performing TUG, patients were permitted to use routine walking aids and were instructed not to use their arms to stand up. No physical assistance was given. The task was performed three times, and the counting result in seconds was the average of performance two and three.

For the 5mWT, patients started at zero speed at the starting line and timing stopped when the patient crossed the line after five meters. The test was performed at normal speed. Routine walking aids were allowed. The test was performed three times, and the counting result in seconds was the average.

## 5.5 Survival, endpoints, and statistical considerations

Two months improvement in median OS was considered as clinically relevant and sufficient to change practice, based on previous studies on chemotherapy without maintenance therapy. Sample-size estimation was based on WHO PS 0-1 patients since WHO PS 2 patients were not included in the comparable studies. Based on a two-sided alpha of 0.05 and a beta of 0.20, an expected 10% drop-out and 30% ineligible for randomization (191), we needed 623 WHO PS 0-1 patients. Moreover, we estimated that 100 WHO PS 2 patients were included and randomized until the required number of WHO PS 0-1 patients had been accrued. Consequently, we estimated the total sample size to be 765 patients with WHO PS 0-2.

OS was the primary endpoint in the RCT, and in all three papers. Secondary endpoints were PFS, toxicity and HRQoL (Global QoL, physical function, dyspnea, and fatigue) in paper I, response to treatment in paper II, and disease control in paper III.

OS was time until death from any cause or last observation. Starting point was from randomization in paper I and in analysis of E-GPS in paper II, and from inclusion in analysis of B-GPS in paper II and in all analysis in paper III.

PFS was defined as time from randomization until the first date of verified disease progression, or death from any cause. Patients alive without progression, were censored at time of the final survival analysis (18$^{th}$ December 2018).

Follow-up time was defined as time until censoring and estimated using the revers Kaplan Meier method.

Survival was estimated using the Kaplan Meier method and compared using the log rank test (paper I), or the Cox proportional hazard model (paper II and III). The Cox proportional hazard method was used for multivariable survival analyses adjusting for baseline characteristics; age (continuous), gender, stage of disease (III versus IV), performance status (0, 1, 2) in all three papers. In paper I, the multivariable survival analyses were also adjusted for brain metastases and response to induction therapy (CR/PR vs SD). In sensitivity analysis for paper II, multivariable survival models were also adjusted for treatment allocation (no randomization, observation-arm, or maintenance-arm), and whether patients received immunotherapy after the study treatment. In paper III, TUG, 5mWT, and PRPF were entered separately in multivariable analyses, either as continuous or dichotomous variables according to the chosen cut-offs (TUG </≥10 seconds, 5mWT: </≥5 seconds, PRPF </≥73.3). In exploratory analyses, the multivariable survival model for analysis of PRPF was

adjusted for TUG or 5mWT, while another model was adjusted for receipt of ICIs. A HR <1 in all the survival analysis was associated with improved survival.

Pearson's Chi-square test or Fisher's exact test were used for group-wise comparison of categorical data.

All HRQoL-scores were transformed to a scale from 0-100 according to the EORTC scoring manual (99-101).

Distribution of TUG and 5mWT were presented as median and range. As there is no consensus regarding cut-offs for TUG (140, 144, 193) or 5mWT (142, 194), we decided to use 10 seconds (TUG) and 5 seconds (5mWT) for cut-offs separating patients with normal and poor physical function (137, 195). PRPF was presented as mean with 95% confidence interval, but median (73.3) was used to separate patients with normal and poor function in analyses. Scattered plots were used to explore associations between TUG, 5mWT and PRPF and univariable linear regression was used to analyze the strength of any association. Distribution of TUG, 5mWT and PRPF according to baseline WHO PS, were illustrated with bubble plots.

Logistic regression was used for uni- and multivariable analyses of the association between TUG, 5mWT, or PRPF and disease control. An odds ratio (OR) >1 represented improved disease control. TUG, 5mWT, and PRPF were entered separately in multivariable analyses either as continuous or dichotomous variables. In exploratory analyses, multivariable models of PRPF were adjusted for TUG or 5mWT in addition to baseline characteristics (age (continuous), gender, stage of disease (III versus IV), performance status (0, 1, 2)).

A two-sided $p<0.05$ was considered statistically significant in all papers. A difference in mean HRQoL of 10 was considered clinically significant (196). SPSS Version 27.0 (Armonk, NY: IBM Corp) was used for all statistical analyses. Figure 17D-F in paper III was made in RStudio v1.4.

## 5.6 Ethics

The study was approved by the regional committee for Medical Research Ethics, Central Norway, the Norwegian Social Science Data Services and the Norwegian Directorate for Health and social affairs. All patients gave written informed consent, and they could withdraw their consent anytime. The research was conducted according to the Helsinki declaration and principles of Good Clinical Practice (197). ClinicalTrials.gov Identifier: NCT02004184.

# 6 Results

## 6.1 Paper I

### *6.1.1 Patients*

Inclusion into the RCT stopped prematurely due to the introduction of immunotherapy, and only 232 out of the planned 765 patients were included. Of these, 161 (69.4%) completed induction chemotherapy, 106 (45.7%) were randomized and 105 (45.2%) were included in the final analysis; 54 in the maintenance arm, and 51 in the observation arm (Figure 11). Baseline characteristics were balanced between the arms (Table 6).

Median follow up from randomization was 11.1 months (range 1–46) for PFS, and 34 months (range 12–51) for OS. At the time of the final survival analyses (December 2018), 19 patients were alive (13 in the maintenance arm, 6 in the observation arm).

**Figure 11** Consort paper I

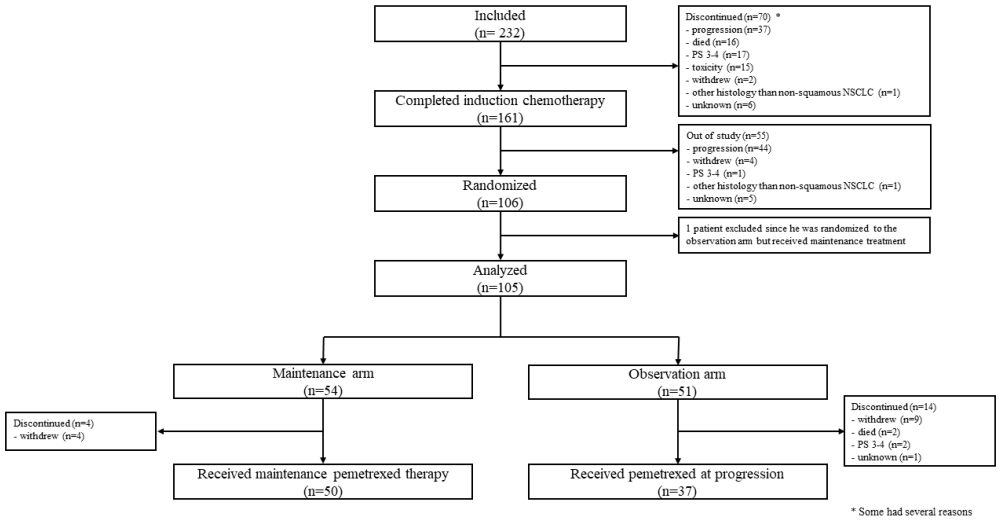


**Table 6** Baseline characteristics

| | | Included patients n=232 | | <4 induction courses n=71 | | 4 induction courses n=161 | | Randomized patients n=105 | | Maintenance arm n=54 | | Observation arm n=51 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | n | % | n | % |
| **Age** | Median (range) | 67 (46-83) | | 66 (47-82) | | 67 (46-83) | | 67 (50-83) | | 68 (50-83) | | 67 (51-83) | |
| | <70 | 152 | 66% | 48 | 68% | 104 | 65% | 67 | 64% | 34 | 63% | 33 | 65% |
| | ≥70 | 80 | 34% | 23 | 32% | 57 | 35% | 38 | 36% | 20 | 37% | 18 | 35% |
| **Gender** | Female | 125 | 54% | 24 | 34% | 83 | 52% | 49 | 47% | 25 | 46% | 24 | 47% |
| | Male | 107 | 46% | 47 | 66% | 78 | 48% | 56 | 53% | 29 | 54% | 27 | 53% |
| **PS** | 0 | 77 | 33% | 18 | 25% | 59 | 37% | 43 | 41% | 21 | 39% | 22 | 43% |
| | 1 | 123 | 53% | 35 | 49% | 88 | 55% | 53 | 50% | 28 | 52% | 25 | 49% |
| | 2 | 32 | 14% | 18 | 25% | 14 | 9% | 9 | 9% | 5 | 9% | 4 | 8% |
| **Stage** | IIIB | 17 | 7% | 5 | 7% | 12 | 8% | 9 | 9% | 6 | 11% | 3 | 6% |
| | IV | 215 | 93% | 66 | 93% | 149 | 92% | 96 | 91% | 48 | 89% | 48 | 94% |
| **Brain** | No | 188 | 81% | 54 | 76% | 134 | 83% | 87 | 83% | 42 | 78% | 45 | 88% |
| **metastases** | Yes | 44 | 19% | 17 | 24% | 27 | 17% | 18 | 17% | 12 | 22% | 6 | 12% |

### *6.1.2 Study therapy*

In the maintenance arm, 50 (93%) patients received immediate pemetrexed. In the observation arm, 37 (73%) patients received pemetrexed at progression (Figure 11). Patients in the maintenance arm received a median of 3.5 courses of pemetrexed (mean 6.5, 95% CI 4.6-8.3, range 1-29), while in the observation arm, patients received a median of 3 courses (mean 4.0, 95% CI 3.0-5.0, range 0-12).

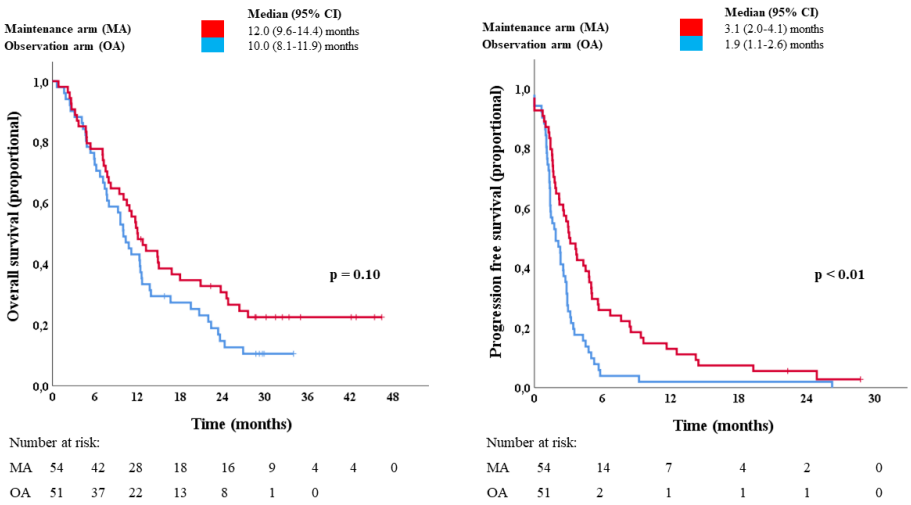
### *6.1.3 Survival*

There was a 2-month improvement in median OS in favor of immediate compared to delayed pemetrexed, but the difference in OS was not statistically significant (maintenance: 12.0 months, 95% CI 9.6-14.4; observation: 10.0 months, 95% CI 8.1-11.9; p=0.10). Patients in the maintenance arm had 1.2 months improved median PFS, and the difference in PFS was statistically significant (maintenance: 3.1 months, 95% CI 2.0-4.1; observation: 1.9 months, 95% CI 1.1-2.6; p<0.01) (Figure 12).

In multivariable analysis, there was a trend towards a statistically significant difference in OS in favor of immediate versus delayed maintenance pemetrexed (HR 0.65, 95% CI 0.42-1.01; p=0.05). The difference in PFS remained statistically significant in multivariable analysis (HR 0.53, 95% CI 0.35-0.80; p<0.01). Stage of disease was an independent negative prognostic factor for PFS (stage IV vs

IIIB; HR 2.96, 95% CI 1.39-6.34; p<0.01). There were no other significant associations between baseline characteristics and PFS or OS.

**Figure 12** Overall survival and progression free survival



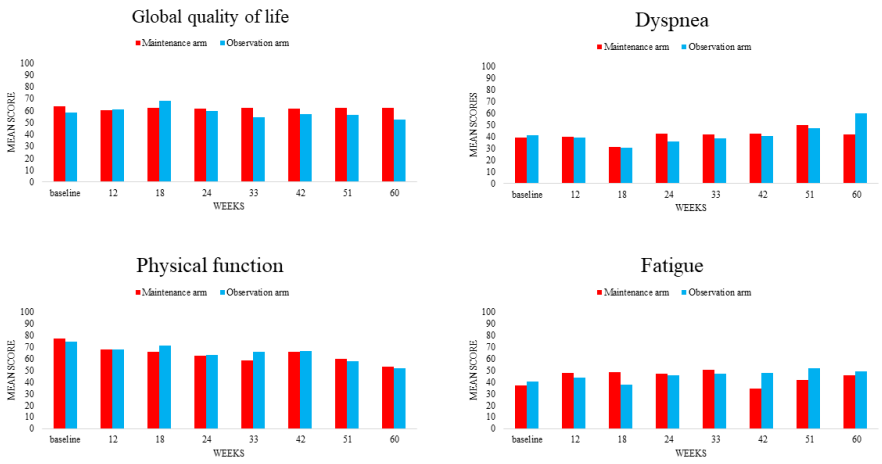

### *6.1.4 Toxicity and Health Related Quality of Life (HRQoL)*

Pemetrexed therapy was well tolerated in both arms. There were no differences in frequency of grade 3-4 pemetrexed toxicity between the treatment arms (maintenance: 62%, observation: 49%; p=0.12) (Figure 13), and there were no clinically relevant differences in global QoL, physical function, dyspnea, or fatigue (figure 14).

**Figure 13** Treatment toxicity according to CTCAE v5.0

| | All patients n=87 | | Maintenancearm n=50 | | Observationarm n=37 | | |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | p |
| **Any grade 3-4 toxicity** | 46 | 56% | 30 | 62% | 16 | 49% | 0.12 |
| **Grade 3-4 hematologicaltoxicity** | 8 | 9% | 4 | 8% | 4 | 11% | 0.65 |
| Anemia | 6 | 7% | 2 | 4% | 4 | 11% | |
| Neutropenia | 1 | 1% | 1 | 2% | - | - | |
| Pancytopenia | 3 | 3% | 1 | 2% | - | - | |
| **Grade 3-4 non-hematologicaltoxicity** | 33 | 38% | 21 | 42% | 11 | 30% | 0.24 |
| Neutropenicinfections | 9 | 10% | 4 | 8% | 2 | 5% | |
| Infectionwithoutneutropenia | 16 | 18% | 8 | 16% | 7 | 19% | |
| Fatigue | 4 | 5% | 2 | 4% | 2 | 5% | |
| Trombocytopenicbleeding | 2 | 2% | 2 | 4% | - | - | |
| Skinrash | 2 | 2% | 2 | 4% | - | - | |
| Nausea | 2 | 2% | 2 | 4% | - | - | |

**Figure 14** Mean HRQoL scores




A higher score on the global QoL represents a better HRQoL, a higher score on the symptom scales is associated with a worse HRQoL. A difference in mean scores of 10 points was considered clinically relevant.

## 6.2 Paper II

### *6.2.1 Patients*

For paper II, 138 of the 232 patients in the RCT (59%) had both B- and E-GPS measured and were available for main analysis. A total of 208 (90%) had measured B-GPS and were included in sensitivity analysis of B-GPS and survival (Figure 15).

**Figure 15** Consort paper II

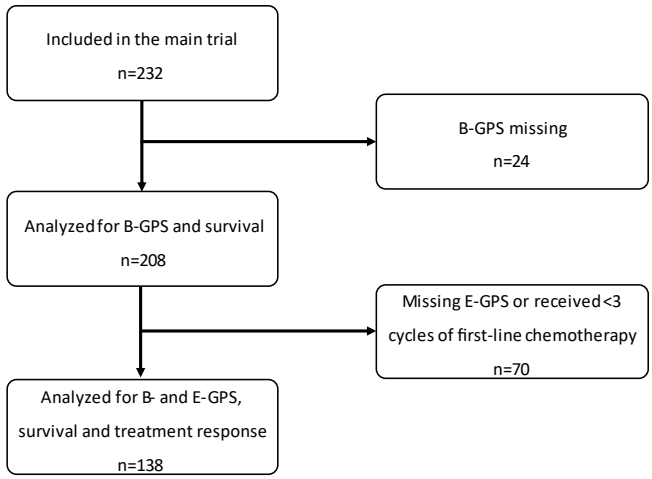


**Table 7** Baseline characteristics of all patients in the main study cohort, n=138

| | | Main study cohort | | GPS at baseline (B-GPS) | | | | | | GPS at evaluation (E-GPS) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n=138 | | B-GPS 0 n=55 | | B-GPS 1 n=53 | | B-GPS 2 n=30 | | E-GPS 0 n=59 | | E-GPS 1 n=50 | | E-GPS 2 n=29 | |
| | | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Age | Median (range) | 67 (47-83) | | 65 (47-83) | | 68 (56-81) | | 66 (50-82) | | 65 (47-81) | | 68 (51-83) | | 66 (50-77) | |
| Sex | Male | 68 | (49) | 30 | (55) | 24 | (45) | 14 | (47) | 26 | (44) | 25 | (50) | 17 | (59) |
| | Female | 70 | (51) | 25 | (45) | 29 | (55) | 16 | (53) | 33 | (56) | 25 | (50) | 12 | (41) |
| Stage | IIIb | 8 | (6) | 3 | (5) | 3 | (6) | 2 | (7) | 6 | (10) | 2 | (4) | - | - |
| | IV | 130 | (94) | 52 | (95) | 50 | (94) | 28 | (93) | 53 | (90) | 48 | (96) | 29 | (100) |
| WHO PS | 0 | 50 | (36) | 28 | (51) | 16 | (30) | 6 | (20) | 26 | (44) | 18 | (36) | 6 | (21) |
| | 1 | 80 | (58) | 24 | (44) | 33 | (62) | 23 | (77) | 30 | (51) | 29 | (58) | 21 | (72) |
| | 2 | 8 | (6) | 3 | (5) | 4 | (8) | 1 | (3) | 3 | (5) | 3 | (6) | 2 | (7) |
| Randomization | No | 58 | (42) | 21 | (38) | 25 | (47) | 12 | (40) | 17 | (29) | 22 | (44) | 19 | (66) |
| | Observation | 38 | (28) | 18 | (33) | 10 | (19) | 10 | (33) | 22 | (38) | 13 | (26) | 3 | (10) |
| | Maintenance | 42 | (30) | 16 | (29) | 18 | (34) | 8 | (27) | 20 | (34) | 15 | (30) | 7 | (24) |
| Received immunotherapy after chemotherapy | No | 102 | (74) | 37 | (67) | 43 | (81) | 22 | (73) | 38 | (64) | 40 | (80) | 24 | (83) |
| | Yes | 36 | (26) | 18 | (33) | 10 | (19) | 8 | (27) | 21 | (36) | 10 | (20) | 5 | (17) |

Among patients analyzed for paper II, 80 (58%) patients had been randomized, 42 in the maintenance and 38 in the observation arm, while 58 were not randomized. A total of 36 patients (26%) received immunotherapy after the study therapy (Table 7).

**Table 8** Baseline characteristics for all patients with B-GPS available, n=208

| | | All patients | | GPS at Baseline (B-GPS) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | n=208 | | B-GPS 0 n=75 | | B-GPS 1 n=90 | | B-GPS 2 n=43 | |
| | | n | (%) | n | (%) | n | (%) | n | (%) |
| Age | Median (range) | 66 (46-83) | | 65 (47-83) | | 68 (53-82) | | 65 (46-83) | |
| Sex | Male | 97 | (47) | 37 | (49) | 40 | (44) | 20 | (47) |
| | Female | 111 | (53) | 38 | (51) | 50 | (56) | 23 | (53) |
| Stage | IIIb | 15 | (7) | 5 | (7) | 8 | (9) | 2 | (5) |
| | IV | 193 | (93) | 70 | (93) | 82 | (91) | 41 | (95) |
| WHO PS | 0 | 67 | (32) | 34 | (45) | 24 | (27) | 9 | (32) |
| | 1 | 113 | (54) | 35 | (47) | 48 | (53) | 30 | (54) |
| | 2 | 28 | (14) | 6 | (8) | 18 | (20) | 4 | (14) |
| Randomization | No | 115 | (55) | 35 | (47) | 57 | (63) | 23 | (53) |
| | Observation arm | 44 | (21) | 22 | (29) | 11 | (12) | 11 | (26) |
| | Maintenance arm | 49 | (24) | 18 | (24) | 22 | (24) | 9 | (21) |
| Received immunotherapy after chemotherapy | No | 165 | (79) | 54 | (72) | 78 | (87) | 33 | (77) |
| | Yes | 43 | (21) | 21 | (28) | 12 | (13) | 10 | (23) |

All baseline characteristics, except the proportion of WHO PS 2 patients, were similar comparing the two cohorts (n=138 vs n=208). The proportion of WHO PS 2 patients was higher in the larger cohort (14% vs 6%) (Table 7 and 8).

### *6.2.2 Overall survival*

#### 6.2.2.1.B-GPS and survival

Overall, median OS was 10.6 months (95% CI: 9.2-11.9) among the 138 patients with B-GPS and E-GPS available. There were no statistically significant differences in OS according to B-GPS in uni- or multivariable analyses (Figure 16 and Table 9).

In sensitivity univariable analysis including all patients with B-GPS (n=208), the difference in survival between patients with B-GPS 1 and 0 reached statistical significance (HR 1.51, 95% CI 1.1-2.1, p=0.01) (Figure 16), and remained significant in multivariable analysis as well (HR 1.42, 95% CI 1.0-2.0, p=0.04) (not shown).

**Figure 16** B-GPS and OS in the main study cohort (n=138) (left) and in all patients with B-GPS (n=208) (right)

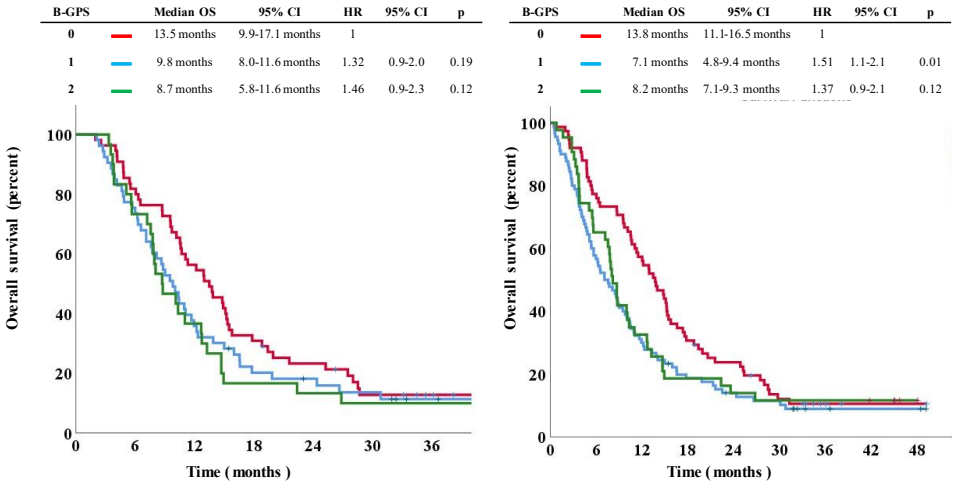


**Table 9** Uni- and multivariable analysis of B-GPS and overall survival in the main study (n=138) cohort*

| | | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | n | HR | 95% CI | p-value | HR | 95% CI | p- value |
| **GPS at baseline (B-GPS)** | **0** | 55 | 1 | | | 1 | | |
| | **1** | 53 | 1.32 | 0.88-1.98 | 0.19 | 1.27 | 0.83-1.93 | 0.27 |
| | **2** | 30 | 1.46 | 0.91-2.34 | 0.12 | 1.29 | 0.77-2.14 | 0.33 |
| **Age (continous)** | | 138 | 1.01 | 0.98-1.03 | 0.60 | 1.00 | 0.97-1.03 | 0.91 |
| **Sex** | **Female** | 70 | 1 | | | 1 | | |
| | **Male** | 68 | 1.14 | 0.80-1.63 | 0.47 | 1.14 | 0.79-1.65 | 0.47 |
| **Disease stage** | **IIIb** | 8 | 1 | | | 1 | | |
| | **IV** | 130 | 1.04 | 0.51-2.13 | 0.92 | 1.03 | 0.50-2.14 | 0.93 |
| **WHO-PS at baseline** | **0** | 50 | 1 | | | 1 | | |
| | **1** | 80 | 1.48 | 1.01-2.18 | 0.05 | 1.40 | 0.92-2.12 | 0.12 |
| | **2** | 8 | 2.67 | 1.25-5.72 | 0.01 | 2.53 | 1.15-5.56 | 0.02 |

** measured from baseline*

### 6.2.2.2 E-GPS and survival

Overall, median OS from evaluation after first-line chemotherapy, was 7.7 months (95% CI 6.3-9.2). A higher E-GPS was significantly associated with shorter survival; HR 1.57 (95% CI 1.04-2.37, p=0.03) for E-GPS 1 as compared to E-GPS 0, and HR 2.77 (95% CI 1.73-4.45, p<0.01) for E-GPS 2 as compared to E-GPS 0 (Figure 17). E-GPS remained a significant prognostic factor in the multivariable analysis, E-GPS 2 versus 0; HR 2.11 (95% CI 1.26-3.57, p<0.02), with a trend towards significance in E-GPS 1 versus 0; HR 1.47 (95% CI 0.96-2.27, p=0.08) (Table 10).

**Figure 17** E-GPS and OS in the main study cohort (n=138)

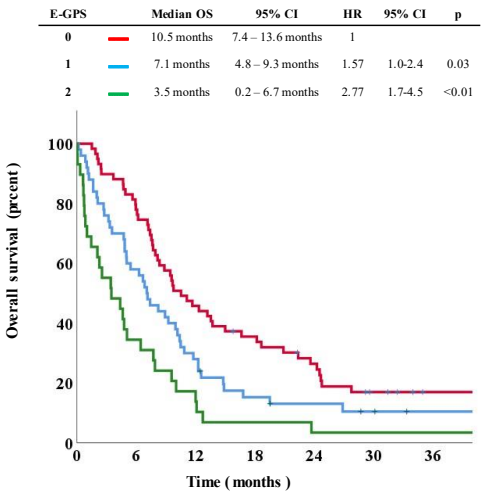



**Table 10** Uni- and multivariable analysis of E-GPS and overall survival in the main study cohort* (n=138)

| | | | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|---|---|
| | | n | HR | 95% CI | p-value | HR | 95% CI | p-value |
| **GPS at evaluation (E-GPS)** | **0** | 59 | 1 | | | 1 | | |
| | **1** | 50 | 1.57 | 1.04– 2.37 | 0.03 | 1.47 | 0.96-2.27 | 0.08 |
| | **2** | 29 | 2.77 | 1.73– 4.45 | <0.01 | 2.11 | 1.26-3.57 | <0.01 |
| **Age (continous)** | | 138 | 1.01 | 0.98– 1.03 | 0.69 | 1.00 | 0.97-1.03 | 0.99 |
| **Sex** | **Female** | 70 | 1 | | | 1 | | |
| | **Male** | 68 | 1.17 | 0.81– 1.66 | 0.42 | 1.25 | 0.86-1.83 | 0.24 |
| **Disease stage** | **IIIb** | 130 | 1 | | | 1 | | |
| | **IV** | 8 | 1.12 | 0.54– 2.29 | 0.76 | 0.84 | 0.40-1.77 | 0.65 |
| **WHO-PS at evaluation**** | **0** | 26 | 1 | | | 1 | | |
| | **1** | 77 | 2.38 | 1.39– 4.01 | <0.01 | 2.14 | 1.23-3.73 | <0.01 |
| | **2** | 21 | 4.75 | 2.46– 9.18 | <0.01 | 4.52 | 2.31-8.82 | <0.01 |
| | **3** | 6 | 26.91 | 9.61– 75.34 | <0.01 | 18.52 | 6.28-54.58 | <0.01 |
| | **4** | 2 | 7.75 | 1.75– 34-32 | <0.01 | 10.71 | 2.28-50-17 | <0.01 |

** measured from the time of evaluation after induction chemotherapy,** missing in 6 patients*

In multivariable sensitivity analyses adjusting for outcomes at evaluation of induction (no randomization/observation/maintenance pemetrexed) and whether patients received

immunotherapy after the study (yes/no), E-GPS, but not B-GPS, remained a significant prognostic factor for overall survival (data not shown).

### *6.2.3 Treatment response*

At evaluation after induction chemotherapy, 38 patients (28%) had a partial response (PR), 48 (35%) had stable disease (SD), 48 (35%) had progressive disease (PD), and four (3%) were not evaluable (Table 11).

B-GPS was not significantly associated with treatment response (p=0.54), whereas E-GPS was (p<0.01). Furthermore, change in GPS was associated with treatment response (p=0.01) (Table 11). Patients with improved GPS were more likely to have responded to treatment (45% achieved PR), than those having stable GPS (26% achieved PR) or worse GPS (Table 11).

**Table 11** GPS and response to first-line chemotherapy in the main study cohort (n=138)

| | | | GPS at baseline (B-GPS) | | | | | | | GPS at evaluation (E-GPS) | | | | | | | Change in GPS | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n=138 | | B-GPS 0 n=55 | | B-GPS 1 n=53 | | B-GPS 2 n=30 | | | E-GPS 0 n=59 | | E-GPS 1 n=50 | | E-GPS 2 n=29 | | | Worsened GPS n=32 | | Stable GPS n=73 | | Improved GPS n=33 | | |
| | n | (%) | n | (%) | n | (%) | n | (%) | p | n | (%) | n | (%) | n | (%) | p | n | (%) | n | (%) | n | (%) | p |
| **Partial response** | 38 | (28) | 16 | (30) | 11 | (21) | 11 | (38) | | 24 | (41) | 10 | (21) | 4 | (14) | | 4 | (13) | 19 | (26) | 15 | (45) | |
| **Stable disease** | 48 | (35) | 20 | (38) | 20 | (38) | 8 | (28) | | 22 | (38) | 19 | (40) | 7 | (25) | | 10 | (32) | 26 | (36) | 12 | (36) | |
| **Progressive disease** | 48 | (35) | 17 | (32) | 21 | (40) | 10 | (34) | 0.54 | 12 | (21) | 19 | (40) | 17 | (61) | <0.01 | 16 | (50) | 27 | (37) | 5 | (15) | 0.01 |
| **Not evaluable** | 4 | (3) | 2 | (1) | 1 | (1) | 1 | (1) | | 1 | (1) | 2 | (1) | 1 | (1) | | 2 | (6) | 1 | (1) | 1 | (3) | |

## 6.3 Paper III

### *6.3.1 Patients*

Two hundred and eight (90%) patients had performed TUG and 5mWT at baseline and were included in this study (Figure 18 and Table 12).

**Figure 18** Patient selection

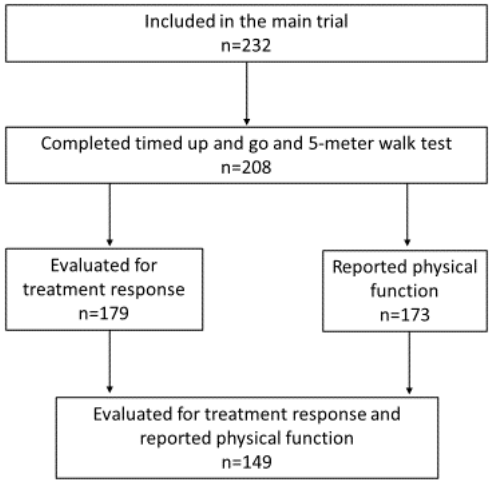



**Table 12** Patient and treatment characteristics

| | | | | TUG | | | | | | 5mWT | | | | | | PRPF | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | < 10 sec | | ≥ 10 sec | | | | < 5 sec | | ≥ 5 sec | | | | ≥ 73.3 | | < 73.3 | | |
| | | n | % | median (range) | n | % | n | % | p | median (range) | n | % | n | % | p | mean (95% CI) | n | % | n | % | P |
| TUG | | 208 | (100%) | 7.8 (0.7-44.2) | 166 | (80%) | 42 | (20%) | | | | | | | | | | | | | |
| 5mWT | | 208 | (100%) | | | | | | | 4.5 (1.8-28.1) | 131 | (63%) | 77 | (37%) | | | | | | | |
| PRPF | | 173 | (83%) | | | | | | | | | | | | | 72.2 (69.375.2) | 100 | (58%) | 73 | (42%) | |
| Age | Median (range) | 67 (46-83) | | | 66 (46-83) | | 69 (55-83) | | 0.03 | | 66 (46-83) | | 69 (51-83) | | 0.03 | | 68 (66-69) | | 66 (65-67) | | 0.17 |
| Sex | Male | 96 | (46%) | 8.0 (2.6-27.4) | 78 | (47%) | 18 | (43%) | | 4.2 (1.8-28.1) | 62 | (47%) | 34 | (44%) | | 75.9 (71.879.9) | 48 | (48%) | 31 | (42%) | |
| | Female | 112 | (54%) | 7.6 (0.7-44.2) | 88 | (53%) | 24 | (57%) | 0.63 | 4.5 (2.0-24.7) | 69 | (53%) | 43 | (56%) | 0.66 | 69.2 (65.073.3) | 52 | (52%) | 42 | (58%) | 0.47 |
| Stage | IIIB | 13 | (6%) | 7.7 (3.6-10.0) | 13 | (15%) | - | - | | 4.2 (2.69.5) | 9 | (7%) | 4 | (5%) | | 83.0 (74.291.8) | 9 | (9%) | 2 | (3%) | |
| | IV | 195 | (94%) | 7.8 (0.7-44.2) | 153 | (85%) | 42 | (100%) | 0.08 | 4.5 (1.8-28.1) | 122 | (93%) | 73 | (95%) | 0.63 | 71.5 (68.474.6) | 91 | (91%) | 71 | (97%) | 0.10 |
| WHO PS | 0 | 66 | (32%) | 7.2 (2.6-19.6) | 58 | (35%) | 8 | (19%) | | 4.4 (1.8-14.0) | 44 | (34%) | 22 | (29%) | | 78.5(72.984.2) | 36 | (36%) | 16 | (22%) | |
| | 1 | 112 | (54%) | 7.8 (0.7-13.5) | 93 | (56%) | 19 | (45%) | | 4.1 (2.1-14.0) | 77 | (59%) | 35 | (45%) | | 72.7 (69.376.2) | 56 | (56%) | 37 | (51%) | |
| | 2 | 30 | (14%) | 10.7 (6.8-44.2) | 15 | (9%) | 15 | (36%) | <0.01 | 6.1 (3.0-28.1) | 10 | (7%) | 20 | (26%) | <0.01 | 58.8 (50.367.3) | 8 | (8%) | 20 | (27%) | <0.01 |
| Completed 4 induction courses | No | 62 | (30%) | 8.2 (0.7-25.9) | 43 | (26%) | 19 | (42%) | | 4.6 (2.5-24.7) | 36 | (27%) | 26 | (34%) | | 67.8 (61.673.9) | 26 | (26%) | 28 | (38%) | |
| | Yes | 146 | (70%) | 7.7 (2.3-44.2) | 123 | (74%) | 23 | (58%) | 0.01 | 4.3 (1.8-28.1) | 95 | (63%) | 51 | (66%) | 0.34 | 74.2 (71.077.5) | 74 | (74%) | 45 | (62%) | 0.08 |
| Randomization | No | 111 | (53%) | 8.2 (0.7-44.2) | 80 | (48%) | 31 | (74%) | | 4.6 (1.8-24.7) | 66 | (50%) | 45 | (58%) | | 69.3 (65.173.6) | 46 | (46%) | 44 | (60%) | |
| | Yes | 97 | (47%) | 7.7 (2.3-27.4) | 86 | (52%) | 11 | (27%) | <0.01 | 4.2 (2.0-28.1) | 65 | (50%) | 32 | (42%) | 0.26 | 75.4 (71.379.4) | 54 | (54%) | 29 | (40%) | 0.06 |
| | Observation | 47 | (23%) | 7.7 (2.9-12.6) | 43 | (26%) | 4 | (10%) | | 4.2 (2.5-11.6) | 30 | (23%) | 17 | (22%) | | 75.2 (68.681.9) | 26 | (26%) | 14 | (19%) | |
| | Maintenance | 50 | (24%) | 7.4 (2.3-27.4) | 43 | (26%) | 7 | (17%) | 0.39 | 4.3 (2.0-28.1) | 35 | (27%) | 15 | (20%) | 0.52 | 75.5 (705-80.5) | 28 | (28%) | 15 | (21%) | 1.00 |
| Post study immunotherapy | No | 163 | (78%) | 7.9 (0.7-44.2) | 126 | (76%) | 37 | (88%) | | 4.5 (1.8-28.1) | 100 | (76%) | 63 | (82%) | | 69.9 (66.673.2) | 72 | (72%) | 64 | (83%) | |
| | Yes | 45 | (22%) | 7.0 (2.3-12.6) | 40 | (24%) | 5 | (12%) | 0.09 | 4.2 (2.1-13.2) | 31 | (24%) | 14 | (18%) | 0.35 | 80.9 (75.086.7) | 28 | (28%) | 9 | (17%) | 0.01 |

*TUG=timed up and go, 5mWT=5m walk test, PRPF=patient reported physical function.*

## *6.3.2 Treatment completion*

A total of 146 (70%) patients received all four induction courses. Patients with TUG <10 seconds (74%) were more likely to complete all courses than those with TUG ≥10 seconds (58%), p=0.01. No

such association was seen between 5mWT (p=0.34) or PRPF (p=0.08) and completion of induction therapy (Table 12).

There were no differences in dose reductions or delays between patients with normal or poor physical function according to TUG, 5mWT or PRPF. Of all patients in this study, 55 (26%) received all four induction courses without any dose reductions or delays, and there were no differences between patients with normal or poor physical function (not shown).

Only 97 (47%) patients were randomized. Patients with a normal physical performance according to TUG were more likely to become randomized (p<0.01), while there were no such association with 5mWT (p=0.26) or PRPF (p=0.06). There were no differences in number of pemetrexed courses received between patients with normal and poor physical function (TUG p=0.90, 5mWT p=0.93, PRPF p=0.62) (not shown).

In total, 114 (55%) of the patients received post-study treatment, with no difference in proportions of patients receiving salvage therapy between those with normal and poor physical function. Only 45 (22%) received ICI-therapy. Patients with a normal PRPF were more likely to receive ICI (p=0.01) compared to those with poor PRPF, while no such associations were observed for TUG or 5mWT (Table 12).

### *6.3.3 Timed up and go (TUG), 5-meter walk test (5mWT), patient reported physical function (PRPF) and their association to gender and disease stage*

Median TUG was 7.8 seconds (range 0.7-44.2 seconds), and median 5mWT was 4.5 seconds (range 1.8-28.1 seconds) (Table 12). There was no difference in TUG or 5mWT between men and women or patients with stage IIIB or IV disease.

Median PRPF score was 73.3 (range 13.3-100) and mean score was 72.2 (95% CI 69.3-75.2) (Table 12). There was no difference in mean PRPF score between men and women, but patients with stage IIIB disease had better mean PRPF score than patients with stage IV.

### *6.3.4 Association between TUG, 5mWT, PRPF and WHO PS*

A worse TUG and 5mWT was significantly associated with lower PRPF, but variation in physical tests only partly explained the variation in PRPF (TUG versus PRPF: $R^2 = 0.11$, p <0.01; 5mWT versus PRPF: $R^2 = 0.10$, p <0.01) (Figure 19D-E). Several patients with good physical function according to TUG or 5mWT reported a low PRPF score. The association between TUG and 5mWT was stronger ($R^2 = 0.23$, $p$ <0.01 (Figure 19F)).

Patients with poor WHO PS had a longer TUG and 5mWT, and patients with a poor WHO PS had a lower mean PRPF score than those with better WHO PS. The variation in TUG or 5mWT among patients with WHO PS 0 or 1 was limited, while a wide range of values were seen among patients with WHO PS 2. Of interest, the variation in PRPF seemed to be independent of WHO PS – as a full range of values were seen among patients with both WHO PS 0, 1 and 2 (Figure 20).

**Figure 19** Physical performance tests and patient reported physical function at baseline

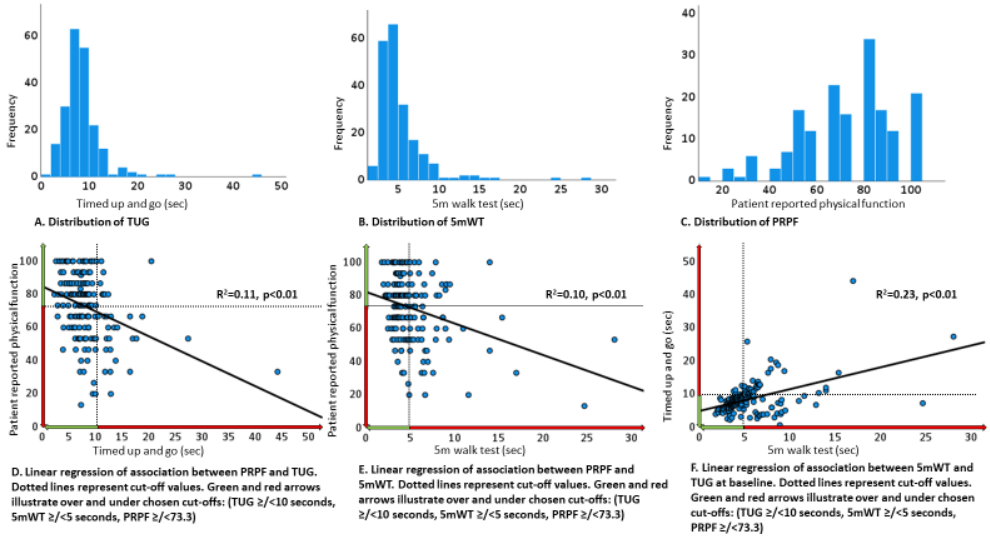
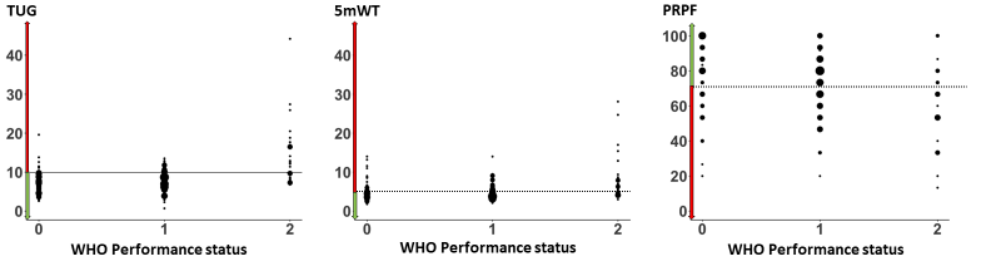



**Figure 20** Associations between WHO performance status and timed up and go, 5-meter walk test and patient-reported physical function




A. Association between WHO PS and TUG at baseline. Point size reflects frequency of observations, ranging 1-6.
Dotted line represents cut-off value. Green and red arrows illustrate over and under chosen cut-offs: (TUG ≥/<10 seconds, 5mWT ≥/<5 seconds, PRPF ≥/<73.3)

B. Association between WHO PS and 5mWT at baseline.
Point size reflects frequency of observations, ranging 1-8
Dotted line represents cut-off value. Green and red arrows illustrate over and under chosen cut-offs: (TUG ≥/<10 seconds, 5mWT ≥/<5 seconds, PRPF ≥/<73.3)

C. Association between WHO PS and PRPF at baseline. Point size reflects frequency of observations, ranging 1-20. Dotted line represents cut-off value. Green and red arrows illustrate over and under chosen cut-offs: (TUG ≥/<10 seconds, 5mWT ≥/<5 seconds, PRPF ≥/<73.3)

### *6.3.5 Overall survival*

Median OS in the whole cohort was 10.0 months (95% CI 8.82-11.18). In univariable models, worse physical function (continuous TUG, 5mWT or PRPF) was associated with poorer survival, however, in multivariable analysis only PRPF remained as an independent prognostic factor (Table 13). In exploratory multivariable analysis adjusting for either TUG (HR 1.01, p=0.05) or 5mWT (HR 1.01, p=0.05) in addition to baseline characteristics in the PRPF-model, PRPF was still a borderline significant prognostic factor. This association disappeared when adjusting for later use of ICI in addition to the baseline characteristics (HR 1.00, p=0.42).

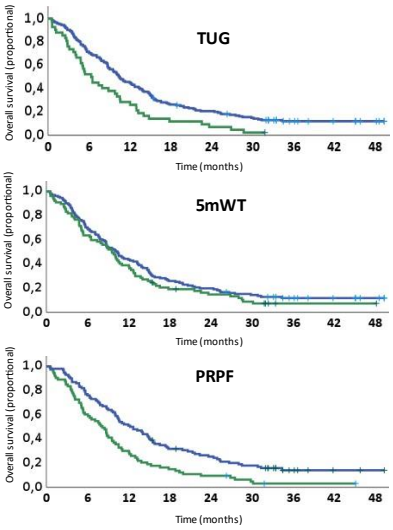
When comparing patients with *normal versus poor* physical function, TUG (p<0.01), but not 5mWT (p=0.21) had a significant association to survival. In multivariable analysis, neither TUG (p=0.07) nor 5mWT (p=0.41) remained significant prognostic factors. In contrast, a normal PRPF was significantly associated with improved survival both in uni- (p<0.01) and multivariable (p<0.01) analyses (Figure 21).

**Table 13** Physical performance as prognostic factor for survival

| | | | | Univariable analysis | | | Multivariable model with TUG | | | Multivariable model with 5mWT | | | Multivariable model with PRPF | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | (%) | HR | 95% CI | p-value | HR | 95% CI | p- value | HR | 95% CI | p- value | HR | 95% CI | p- value |
| TUG* | | 208 | (100%) | 1.05 | 1.02-1.08 | <0.01 | 1.03 | 0.99-1.07 | 0.18 | | | | | | |
| 5mWT* | | 208 | (100%) | 1.05 | 1.01-1.10 | 0.03 | | | | 1.04 | 0.99-1.09 | 0.13 | | | |
| PRPF* | | 173 | (83%) | 1.01 | 1.01-1.02 | <0.01 | | | | | | | 1.01 | 1.00-1.02 | 0.03 |
| Age* | | 208 | (100%) | 1.00 | 0.98-1.02 | 0.94 | 0.99 | 0.97-1.01 | 0.99 | 0.99 | 0.97-1.01 | 0.99 | 0.96 | 0.97-1.02 | 0.67 |
| Sex | Male | 96 | (46%) | 1 | | | 1 | | | 1 | | | 1 | | |
| | Female | 112 | (54%) | 1.13 | 0.84-1.50 | 0.42 | 1.09 | 0.81-1.45 | 0.58 | 1.08 | 0.81-1.45 | 0.61 | 1.06 | 0.76-1.49 | 0.73 |
| Stage of disease | IIIB | 13 | (6%) | 1 | | | 1 | | | 1 | | | 1 | | |
| | IV | 195 | (94%) | 1.55 | 0.86-2.78 | 0.14 | 1.51 | 0.82-2.76 | 0.19 | 1.50 | 0.82-2.74 | 0.19 | 1.21 | 0.65-2.28 | 0.55 |
| WHO PS | 0 | 66 | (32%) | 1 | | | 1 | | | 1 | | | 1 | | |
| | 1 | 112 | (54%) | 1.45 | 1.04-2.02 | 0.03 | 1.51 | 1.07-2.12 | 0.02 | 1.56 | 1.11-2.19 | 0.01 | 1.38 | 0.94-2.02 | 0.10 |
| | 2 | 30 | (14%) | 2.57 | 1.63-4.06 | <0.01 | 2.25 | 1.32-3.83 | <0.01 | 2.44 | 1.51-3.96 | <0.01 | 2.11 | 1.23-3.62 | <0.01 |

** Entered as a continuous variable. TUG=timed up and go, 5mWT= 5-meter walk test, PRPF= Patient reported physical function.*

**Figure 21** Differences in survival according to cutoff values for TUG, 5mWT and PRPF




| | Median OS | 95% CI | HR univariable model | 95% CI | p | HR multivariable model | 95% CI | p |
|---|---|---|---|---|---|---|---|---|
| < 10 sek | 10.4 | 8.6-12.2 | 1 | | | 1 | | |
| ≥ 10 sek | 6.3 | 3.9-8.7 | 1.74 | 1.23-2.47 | <0.01 | 1.43 | 0.97-2.10 | 0.07 |

| | Median OS | 95% CI | HR univariable model | 95% CI | p | HR multivariable model | 95% CI | p |
|---|---|---|---|---|---|---|---|---|
| < 5 sek | 10.4 | 8.4-12.3 | 1 | | | 1 | | |
| ≥ 5 sek | 9.6 | 7.6-11.5 | 1.21 | 0.90-1.63 | 0.21 | 1.14 | 0.84-1.55 | 0.41 |

| | Median OS | 95% CI | HR univariable model | 95% CI | p | HR multivariable model | 95% CI | p |
|---|---|---|---|---|---|---|---|---|
| ≥ median | 12.2 | 8.6-15.6 | 1 | | | 1 | | |
| < median | 8.2 | 6.1-10.2 | 1.80 | 1.31-2.49 | <0.01 | 1.60 | 1.14-2.24 | <0.01 |

*TUG=timed up and go, 5mWT=5m walk test, PRPF=patient reported physical function.*

### *6.3.6 Disease control*

Treatment response was evaluated in 179 (86%) patients. Overall, disease control was achieved in 61% of the patients. TUG, 5mWT or PRPF were not statistically significant predictors for disease control neither in uni- nor multivariable analyses.

# 7 Discussion

This thesis is based on the first trial comparing immediate maintenance pemetrexed to pemetrexed at progression in patients with advanced non-squamous NSCLC, where patients of all ages and WHO PS 0-2 were included. The trial supports that immediate maintenance pemetrexed therapy is well tolerated and improves survival.

Furthermore, this thesis indicates that incorporating GPS score in follow-up may provide clinically important prognostic and predictive information, potentially enabling clinicians to better assess whether to continue, switch, or discontinue cancer therapy.

In contrast to what we hypothesized, measuring physical performance alone does not appear to provide important information when making treatment decisions for this group of patients.

## 7.1 Immediate maintenance pemetrexed in non-squamous NSCLC

We observed a 2.0 month longer median overall survival in patients that received immediate maintenance pemetrexed compared to patients that received pemetrexed at progression. The numeric difference in overall survival was not statistically significant (12 vs 10 months) neither in uni- nor multivariable analysis. However, the 1.2 months (1.9 vs. 3.1 months) improved progression free survival was statistically significant, both in uni- and multivariable analysis adjusting for baseline characteristics (age, gender, stage of disease, and WHO PS). Pemetrexed was well tolerated and there were no differences in toxicity or HRQoL between the two treatment arms.

Two comparable trials, JMEN and PARAMOUNT, compared immediate pemetrexed and best supportive care (BSC) with placebo and BSC, after four cycles of platinum-based induction therapy in advanced NSCLC (4-6). Numerically, the benefit in PFS we observed was similar to these trials (1.2 vs. 1.3–1.9 months), while the survival benefit was smaller (2.0 vs. 2.9–5.2 months). JMEN included all NSCLC histological subtypes, and PARAMOUNT only non-squamous NSCLC. Overall, the survival benefit in JMEN and PARAMOUNT was similar (13.4 vs. 10.6 months and 13.9 vs. 11.0 months respectively), but the survival benefit for non-squamous patients was even higher in JMEN (15.5 vs. 10.3 months). Previous studies have shown that pemetrexed is more effective in non-squamous than in squamous NSCLC and is the reason why only patients with non-squamous tumors were included in our RCT (4).

The small difference in OS between studies may be explained by patient selection. Both the JMEN and PARAMOUNT studies included only patients having WHO PS 0-1. Median age in JMEN was

60 years, with none older than 67.5 years. In PARAMOUNT, median age was 62 years, and only 34% was older than 65 years. In our trial, WHO PS 2 patients accounted for 14% of the included patients, the median age was 67 years, and 34% were ≥70 years. With the lack of WHO PS 2 patients in the two comparable studies, it is reasonable to think that inclusion of WHO PS 2 patients has influenced survival negatively in our trial, compared to the population in JMEN and PARAMOUNT. WHO PS 2 has consistently been found to be a negative prognostic factor for survival among advanced NSCLC patients receiving palliative chemotherapy (198).

In addition to differences in the patient characteristics, there were differences in the induction treatment and in the treatment at progression after randomization. In JMEN, all patients received four cycles of platinum-based induction therapy without pemetrexed before randomization. In PARAMOUNT, all patients received four courses of cisplatin and pemetrexed before randomization. Studies have shown comparable survival from different platinum-doublets, but the tolerance is higher when pemetrexed is used (63, 190, 191). Therefore, we believe the difference in survival between studies is not influenced by differences in induction therapy. The most important difference in treatment between our and JMEN and PARAMOUNT studies, is that in our study everyone was to receive pemetrexed upon progression in the observation arm. Only few patients in the control arms received pemetrexed at progression in JMEN (18%) and in PARAMOUNT (3.9%). Consequently, the survival advantage from immediate maintenance therapy in these studies might have been due to the difference in effectiveness of drugs administered upon relapse in the control arms and not only the timing of treatment. 73% of the patients received pemetrexed at progression in the observation arm in our trial, which might explain the somewhat smaller survival difference than in previous trials.

The survival from immediate maintenance pemetrexed is also evaluated in two other studies, the Pronounce and LVBL studies (199, 200). The survival benefit from immediate maintenance pemetrexed was not the main aim for these two studies. The Pronounce study compared the efficacy and safety of first line pemetrexed-carboplatin followed by maintenance pemetrexed with paclitaxel-carboplatin-bevacizumab followed by maintenance bevacizumab, in patients with advanced non-squamous NSCLC (200). The LVBL-study compared first line pemetrexed-(cis-) carboplatin and immediate maintenance pemetrexed with or without Ramucirumab (VEGF antibody) (199). Both OS and PFS was measured from inclusion in these two studies, which gives approximately three months longer survival comparing to our RCT where OS and PFS were measured from randomization. The median OS in arms comparable to our immediate maintenance pemetrexed arm, were in agree with our results (our study 12.0 months, Pronounce 16.1 months,

JVBL 10.5 months). Similar results were found in analysis of median PFS (our study 3.1 months, Pronounce 4.4 months, JVBL 2.6 months).

**Table 14** Studies of maintenance Pemetrexed in patients with advanced NSCLC

| | Design | Median OS | Median PFS | Discontinnued pemetrexed due to tox | Fatigue | Neutropenia | Anemi |
|---|---|---|---|---|---|---|---|
| JMEN (Ciuleanu) 2009 | RCT double blinded Phase 3 | 15.5 months* | 4.3 months* | 5% | 5% | 3% | 3% |
| Paramount (Paz-Ares) 2012 | RCT double blinded Phase 3 | 13.9 months* | 4.1 months* | 12% | 5% | 6% | 6% |
| Pronounce (Zinner) 2015 | RCT Phase 3 | 16.1 months** | 4.4 months** | | | 25%*** | 18.7*** |
| JVBL (Doebele) 2015 | RCT Phase 2 | 10.5 months** | 5.6 months** | - | 17.4%*** | 18.8%*** | 17.4%*** |
| Winfree 2018 | Real world | 20.6 months** | 9.4 months** | - | - | - | - |
| Nelli 2020 | Real world | 19.6 months** | 8.8 months** | - | - | | |
| Li 2021 | Real world | 30.5 months** | 9.5 months** | - | - | 9% | 0% |

*measured from randomizatin (after receiving 4 courses of a platinum-duplex) **measured from inclusion ***toxicity including the induction period

In parallel with the previous studies (5, 41, 201), immediate maintenance pemetrexed was well tolerated in our study. Few patients experienced grade 3-4 toxicity and there were no treatment related deaths from pemetrexed. Most of the reported adverse events reported in JMEN and PARAMOUNT, were carried over from the induction period with no change in severity from the end of induction. Unfortunately, our study was not designed to evaluate toxicity from induction therapy, and we were not able to examine the relation between induction and maintenance treatment. Maintenance treatment appeared to be well tolerated also by patients >70 years, corroborating previous studies of patients in this age group (202-204).

HRQoL was reported on the same timepoints for all patients, independent of treatment arm. Neither immediate nor delayed maintenance pemetrexed impaired the HRQoL. We focused on global QoL, fatigue, dyspnea, and physical function during the first 60 months after inclusion. In PARAMOUNT and JMEN, HRQoL was reported using different scales than us, EQ-5D (205) and LCC (206) respectively, but there were no overall differences in HRQoL in these studies either (207, 208).

Our study terminated prematurely due to the introduction of ICIs as second-line therapy (49). Since then, there have been no other RCTs on pemetrexed as a single maintenance treatment.

Population-based studies, the most recent published in 2020, have, however, shown survival benefit from immediate maintenance pemetrexed, although smaller than in RCTs (209-211). However, this is expected since population-based studies usually include patients with less favorable prognostic factors than RCTs (e.g., WHO PS) (212) (Table 14).

## 7.2 Identification of prognostic and predictive factors

### *7.2.1 GPS as a prognostic factor*

Several studies have shown that GPS is an independent prognostic factor for numerous cancers, different disease stages, and treatment settings (172-176, 179, 213, 214). Primarily, these studies only measured GPS before start, and not repeated later in the treatment or follow up. In our main study cohort, including patients with GPS measured both at baseline and at evaluation (n=138), B-GPS was not associated to OS. However, this may be due to selection bias, as these patients were fit enough to receive several courses of chemotherapy. Of the 138 patients in our main study cohort, 94% had WHO PS 0-1 at baseline. In the exploratory analysis including all patients with B-GPS available (n=208), a lower B-GPS was associated with improved survival. Of these 208 patients, 84% had WHO PS 0-1. It might be that GPS is a stronger prognostic factor in unselected populations including patients considered unfit for palliative chemotherapy. This agrees with previous studies of B-GPS in patients with advanced NSCLC, where the populations were relatively unselected, both regarding the diseases and patient characteristics (171, 174-176, 179-181, 214). In these studies, the B-GPS categories are often grouped when running the analysis, which limits the prognostic evidence of each of the three GPS values. In addition, not all patients received cancer treatment, and there was great variation in treatment. Treatments in these studies included both radiotherapy against symptomatic lesions e.g., and not only systemic palliative treatment as chemotherapy. In addition, many patients had WHO PS 3-4.

In contrast to B-GPS, GPS measured at evaluation (E-GPS) after at least three courses of a platinum-doublet in the same cohort (n=138), was an independent prognostic factor for survival. We are aware of one study including patients with advanced NSCLC which have examined GPS both before start of treatment and 3-6 months afterwards (174). In this study, B-GPS was associated with OS, but E-GPS was not. However, this study differed in several ways from ours where only a minority (42%) of patients received active cancer treatment, and few (38%) had GPS measured during follow up. The study did not perform separate analysis in the patients with both B- and E-GPS available.

On the other side, there are other studies which corroborate the results of our study: Three small studies (n=24-64) have reported that elevated GPS measured 3 to 6 weeks after initiation of

immune checkpoint inhibitor therapy was associated with poor survival in advanced NSCLC (187, 188), and renal cell carcinoma (189). Other studies have found that elevated GPS after initiation of palliative chemotherapy for colorectal cancer (182), and after surgery for localized NSCLC (183), and gastric cancer (186), was associated with poor prognosis. In addition, a study of patients with advanced head and neck cancer found that GPS after concurrent chemoradiotherapy was associated with recurrence free and overall survival, whereas pretreatment GPS was not (185). Elevated modified GPS (mGPS) after neo-adjuvant chemotherapy before surgery for adenocarcinoma of the esophagogastric junction, was associated with reduced survival, whereas pre-neo-adjuvant mGPS was not (186).

There is evidence that systemic inflammation might influence the tumor microenvironment and reduce the effect from chemotherapy (215). B-GPS was not a predictive factor for treatment response (according to RECIST) in our study, and we are not aware of any study which have examined the association between GPS and treatment response. Change in GPS (from baseline to evaluation) and E-GPS were both significantly associated to treatment response. We are not aware of studies which have assessed E-GPS and response, but neutrophil-to-lymphocyte ratio (NLR) and CRP after targeted therapy or immune checkpoint blockade, were associated with overall response rate in advanced renal cell carcinoma (189, 216, 217). The treatments, settings, and designs are different, but these studies support the hypothesis that E-GPS holds more prognostic information than B-GPS because E-GPS includes information about response to treatment. A possible explanation is that effective systemic therapy reduces the tumor load and thereby the cancer-induced inflammation. However, investigating underlying mechanisms or the association between anti-inflammatory drugs and cancer, was beyond the scope of this thesis.

We are not aware of any prospective studies that has used GPS to guide treatment and follow-up of cancer patients. All available evidence is based on retrospective analysis where GPS is observed and reported retrospectively, as in our study. Measuring GPS is easy, cheap and has many possible advantages for both the health-care system and the patient. It is reasonable to believe that repeated measures of GPS during or after treatment, could give good indications of the treatment response and cancer activity. Repeated measuring of GPS may identify patients at risk of treatment failure or in need of a closer follow up.

Today, more elderly patients receive active cancer treatment than before. The normal aging process and high level of comorbidity make older lung cancer patients more vulnerable to side-effect than younger patients (218). A recent retrospective study of elderly (>70 years) patients with advanced NSCLC treated with platinum-combination chemotherapy, showed that elderly with

pretreatment GPS 0-1 had good tolerability and efficacy compared to those with GPS 2 (219). We planned to examine if GPS could be e useful tool especially in the treatment of the elderly. Due to the limited sample-size, we decided not to do perform this separate analysis.

### *7.2.2 Physical performance as a prognostic factor*

In this study, physical function measured by TUG and 5mWT were not independent prognostic factors for survival, while patient-reported physical function (PRPF) was. Patients with a normal physical function measured by TUG were more likely to complete four courses of induction therapy and thus become randomized, but none of the measures of physical function were significantly associated with achieving disease control after induction chemotherapy.

Studies have shown that several different measures of physical function are associated with overall survival, and we hypothesized that this would be the case in advanced NSCLC patients too. Tests used to measure physical function are primarily different gait-speed-tests, TUG, or Short Physical Performance Battery (SPPB). Physical measurements are often components in a comprehensive geriatric assessment (CGA), including several other domains of the patient's health status and situation (e.g., functional status, cognition, mood, nutritional status, comorbidity, polypharmacy, and social support). In our study, we chose TUG and 5mWT since they do not require a lot of equipment, are easy to perform, and do not require much practicing or time. We cannot rule out that other tests or performing a CGA, may have given useful information.

Several studies have investigated the associations between TUG or gait speed, and OS in patients with cancer, including two recent systematic reviews (Verweji et al. in 2016 and Ezzatvar in 2020); the latter also including a meta-analysis (10, 11). Seven of the studies included in these reviews had patients with NSCLC, with a proportion ranging between 8 - 100% of all patients (138, 140-142, 144, 149, 220). There were numerous differences in the inclusion criteria, both regarding patient characteristics, cancer types and stages, treatments given, and tests used to measure gait-speed. All these differences make the results difficult to interpret and compare across studies. In four of the studies, TUG was analyzed in patients receiving only chemotherapy (138, 140, 141, 144). TUG was found to be an independent prognostic factor in one of the studies (144), but only 28 out of 348 (8%) patients had NSCLC. In studies investigating gait speed, the association with survival is also inconsistent (142, 220-222).

In our study, patients with normal performance in TUG where more likely to complete induction chemotherapy and become randomized than patients with poor performance. An association with treatment completion was not found for 5mWT or PRPF. None of the three

performance measures could separate between those who achieved disease control and those who did not. We are not aware of any other study where the associations between physical function and disease control have been investigated.

Interestingly, neither TUG nor 5mWT held any significant prognostic information for overall survival, while PRPF did. PRPF was an independent prognostic factor for OS as shown in previous reports (140, 156, 223). One reason might be a selection bias due to the eligibility criteria in our trial. Median TUG (7.8 seconds) was lower than in studies of healthy population at the same age (9.0 seconds), and our patients reported relatively high scores for physical function compared to other populations of advanced NSCLC patients (224, 225). There was less variation between the patients' performances in TUG and 5mWT, and most of the performances were in the normal category (TUG 80%, 5mWT 63%). When reporting PRPF, patients compare their current functional level with their previous habitual status. Their reports incorporate involuntary changes in physical function due to their underlying cancer, adding to the evidence showing that patient reports hold strong prognostic information (140, 156, 223). Another reason might be that previous studies have not collected data or adjusted for other important prognostic factors (e.g., WHO PS) in their analyses.

TUG and 5mWT are primarily performance measures used as a part of a comprehensive geriatric assessment (CGA) when the patient population is elderly (>70 years). Only about one third of the included patients in the RCT were ≥70 years. We do not know if the value of performing a CGA including TUG or 5mWT, has the same value in a younger population. In addition, the chosen cut-offs are important. If the chosen endpoint is increased risk of falling, a cut-off TUG >12 seconds is associated to increased risk (226), and a cut-off of >13.5 (~14) seconds is associated with increased mortality (227). If we had used 12 or 14 seconds as the cut-offs of choice, only 4% or 1% of the patients would have been classified as having poor physical performance, respectively. We performed exploratory ROC-analysis to find cut-offs both in TUG and 5mWT, but the analysis did not give any cut-offs that could help discriminate survival better. The fact that our patients were relatively fit may have reduced the prognostic value of these measures of physical performance, and the result may have been different with an older or more vulnerable patient population.

WHO PS is the most established prognostic and predictive factor in clinical oncology. There is considerable interrater variation in scoring WHO PS, especially in patients with significant comorbidity who are previously unknown for the health care personnel who perform the assessment. While assessment of WHO PS is reported by a physician, the score is based on information given from the patient or relatives. The patient and the relatives might have different opinions about the patient's functional status than health care personnel. This may explain why

physicians tend to score WHO PS lower than patients (228). There is an important distinction in the management of patients with WHO PS 0-2 and >2. Patients having WHO PS >2 are mainly not considered candidates for active systemic treatment (126). WHO PS and PRPF are two different methods reporting the patient's function, with different reference point for comparison. In our study, the variation in PRPF seems to be independent of WHO PS – as a full range of values were seen among patients with both WHO PS 0, 1 and 2. In contrast, the variation in TUG or 5mWT among patients with WHO PS 0 or 1 was limited, while a wide range of values were seen among patients with WHO PS 2 (Figure 20). This supports our hypothesis that TUG and 5mWT do not discriminate between patients having good physical function.

The association between the different performance tests is not clear; TUG or 5mWT was significantly associated with worse PRPF, but the variation in PRPF was only partly explained by variation in TUG or 5mWT (Figure 19). TUG and 5mWT had a stronger association to each other. Several patients with normal physical function according to TUG or 5mWT, reported a low PRPF score. A walking test is simple and examining the patients balance and the ability to walk straight forward. TUG is more complex, where the strength in the lower limbs, balance, coordination, and the ability to walk, are all important parts of the test. In exploratory survival analysis of the independent value of PRPF in our study, models including either TUG or 5mWT in addition to baseline characteristics, still showed a significant association between PRPF and OS. Although we could not prove that performing TUG and 5mWT were useful in our study, we still believe that the physical performance and function are important components in the assessment of the patients.

## 7.3 Strengths and limitations

### *7.3.1 Study design*

This thesis is based on a randomized controlled trial (RCT) phase III, which is considered the optimal design for comparing therapies (192). The RCT was open labeled, where both the health providers and the patients were aware of the drug or treatment being given. It was important not to use blinding and placebo-controls due to one of the main aims of the study: timing of intervention with immediate or delayed maintenance pemetrexed. In addition, potential benefits from being randomized to observation and delayed pemetrexed were difficult to measure if they received placebo. It was important to avoid unnecessary hospital visits for administration of placebo among this group of patients with a short life-expectancy.

The prospective design with a well-defined cohort receiving the same treatment, is primarily a strength of the study. This contrasts to most of the comparable studies of GPS and physical

function where both patients' characteristics and treatments varies. On the other side, this might also limit the generalizability of the results.

GPS is based on CRP and albumin. Both components could be influenced by other conditions, e.g., infections, use of steroids, NSAIDs, and malnutrition. We did not collect these data in our trial. Anti-inflammatory treatments, as e.g., dexamethasone, given prior to chemotherapy, enhance efficacy in the treatment of patients with advanced NSCLC (229), and may reduce the cancer-mediated inflammation and confound the analysis. All our patients received dexamethasone as premedication before chemotherapy. The physical performance measurements may also be influences by other conditions which are independent of the cancer disease, e.g., arthrosis in hips, knees and ancles, but we did not collect this data in our trial either.

Although patients received the same first-line treatment, differences in post-study therapy might have influenced the results in all our studies. The availability of ICI therapy varied with time and between hospitals during the study period. The use of ICI may have washed out the difference between the treatment arms in paper I, and the use of ICI may explain the increase in survival. But it could be problematic to include later use of ICI in exploratory multivariable analysis while patients with good response to first-line treatment where more likely to received ICI than non-responders. In paper II, E-GPS seems to be a prognostic factor independent of ICI. In paper III, PRPF which was an independent prognostic factor for survival, did not remain significant when including the use of ICI in exploratory multivariable models.

### *7.3.2 Sample-size*

The trial was closed prematurely in September 2017 when practice was immediately changed, and checkpoint inhibitors became standard treatment for recurrent NSCLC. The small sample size limits the power and external validity of our phase III trial and is the main limitation of this thesis. While we planned to enroll 765 patients to randomize 536, we were only able to include 232 and randomize 105. The planned sample size was relatively large, and we believe that our study is of sufficient size to support the clinical relevance of immediate maintenance pemetrexed. The observed improvement in OS was in range of what we expected as a minimum difference that would lead to routine use of maintenance pemetrexed in Norway. It is reasonable to conclude that immediate maintenance pemetrexed therapy prolongs survival also when all patients on the control arm receive pemetrexed upon progression. The sample size was, however, too low to explore whether the oldest patients or WHO PS 2 patients, benefit from maintenance therapy, which were important reasons for conducting the trial.

The statistical power for study II and III was also limited by the low number of patients in the RCT. However, study II and III are still among the largest of their kind in advanced NSCLC and should be considered hypothesis-generating regardless of their size.

### *7.3.3 Choice of endpoints*

We chose OS as the most important endpoint in the RCT. The strengths of OS is that it is easy to measure, unambiguous, objective, felt to be clinically significant, and is unaffected by the timing of assessment (230). But OS may be influenced by cross-over and later treatment, and studies may need long follow-up if survival is long. However, when the trial was designed, the effect of relapse treatment in this setting was limited, and survival was short. Today, with more effective therapies available, progression free survival (PFS) and time to second progression or death (PFS2), have emerged as more common endpoints.

A benefit with PFS is that it is not influenced by cross-over or later treatment, and the endpoint is reached in shorter time than with OS. However, the evidence of surrogate endpoints for OS in cancer studies, is limited and debated (231). In general, the correlation between PFS and OS is poor, and PSF is mainly not supported as a surrogate endpoint for OS in studies of NSCLC (232). In our study, the increase in PFS was 1.2 month (1.9-3.1 months), which is isolated a minor increase, but in these patients with short life-expectancy, this is not negligible.

In paper III, we used disease control as a secondary endpoint in order to eliminate the potential bias in second line therapy, primarily the use of ICI. Achieving disease control (CR+PR+SD) is associated to better outcome (233).

We decided to limit the number of endpoints for study II and III due to the limited sample size.

### *7.3.4 Selection of patients*

Patients included in a RCT are selected by eligibility criteria. Consequently, the study population might be different from the population seen in daily clinic, which again reduces the generalizability (external validity) of the study results.

B-GPS was measured in 90% of the patients, which is a fairly high proportion. The fact that E-GPS was only available in 66% of the patients who had B-GPS, was a major limitation of study II. The main reasons for the low completion rate at evaluation were death, progression, and poor WHO PS, indicating that those who completed both GPS-assessments were more fit than those who did not.

As previously discussed, this most likely explains why B-GPS was a significant prognostic factor only when these less fit patients were included in the analysis.

For paper III, 90% of the patients had measured physical performance at baseline. We do not have any information why the remaining 24 patients did not. Since the completion rate was high, we do not believe this has significantly influenced the results.

## 7.4 Implication of results

The importance of our results is much more limited today than when the trial was designed. First, immunotherapy replaced pemetrexed as relapse therapy. Later, immunotherapy has become the main first-line treatment of advanced NSCLC. However, studies show that combining immunotherapy and chemotherapy is more effective than immunotherapy alone for most patients, and carboplatin/pemetrexed/pembrolizumab followed by pembrolizumab/pemetrexed maintenance therapy, is currently the standard regimen for non-squamous NSCLC - especially for those without high PD-L1 expression or targetable mutations.

Chemotherapy remains standard first-line therapy for patients who are ineligible for immunotherapy (e.g., patients who have undergone organ transplants or with severe autoimmune disorders).

Although the results are intriguing, study II was too small and explorative in its nature to provide any definitive conclusions, and more research is needed to explore the potential benefit of repeated GPS-measurements. There was no signal of clinical value of measuring only physical function, by TUG and 5mWT, in these patients. But we do not know if the value of the measurements would have been better if they were included in a GA and thereto management (GAM). We believe that our study clearly demonstrates that other approaches should be pursued in future research.

# 8 Conclusion

In patients with non-squamous advanced NSCLC without targetable mutations, we found that:

- Immediate maintenance pemetrexed after induction therapy with a platinum doublet, is well tolerated and improves PFS compared with observation followed by pemetrexed therapy upon progression. There was also a trend towards an overall survival benefit of the magnitude we defined as of clinical relevance when planning the trial (2.0 months).
- Repeated GPS measurements might provide important information about treatment response and prognosis beyond the baseline setting.
- The physical performance tests TUG and 5mWT, do not provide clinically relevant predictive or prognostic information in our study cohort, but our study confirms that baseline patient reported functional status is an independent prognostic factor.

# 9 Future perspectives

Although there have been important improvements in treatment and survival of advanced NSCLC in later years, there is still an unmet need for better therapies. Advanced NSCLC is probably the therapeutic area in which development of targeted therapies has been most successful, and there is a large and increasing focus on personalized therapy, although one might argue that it is individualized according to features of the tumor cells and not the person suffering from cancer.

Due to the availability of many drugs, it is more challenging to predict the optimal sequence and combination for each patient, and it has become increasingly important to evaluate treatment response as early as possible, to avoid that the patients deteriorate too much before relapses are detected.

Maintenance pemetrexed is well accepted as a standard chemotherapy regimen, but the potential for extended use, other than today's recommendations, is probably limited and not a high priority since the main treatments today are immunotherapy and targeted therapy. A solid predictive biomarker would promote more correct use of pemetrexed, and it was hypothesized that tumor thymidylate synthase (TS) level might be such a marker (234). However, a previous Norwegian study, suggested that TS level was a prognostic and not a predictive factor (235). Recent data from the ITACA (International Tailored Chemotherapy Adjuvant) trial, partly supports the conclusion. Treatment decided from the TS level showed a non-statistically significant trend for improved OS in patients where treatment was decided from the TS level (TS-tailored) compared to patients where the treatment was given independent of the TS level (TS-non-tailored) (236). Thus, in terms of safety, the TS-tailored arm was associated with better efficacy/toxicity ratio.

To develop more general tools for adapting treatment and treatment intensity, remains an important goal. Such a universal system would be of great importance. There are still relatively high proportions of patients who do not respond to targeted therapies, and not all tumors with 100% PD-L1 expression respond to immunotherapy either. Thus, the prognosis for many patients remains poor. According to the report from the Norwegian Lung Cancer Registry, median overall survival for stage IV NSCLC has not improved much during the last ten years, but there has been an encouraging improvement for patients in a satisfactory general condition available for targeted therapy or ICI.

Since GPS is easy to measure, studies aiming at validating and expanding the utility of repeated GPS measurement in assisting clinicians in treatment decision, should be possible to perform. The value of GPS in the treatment of and follow-up in cancer patients should be examined in bigger studies, primarily in prospective studies, where the GPS score is the main factor for

deciding further treatment and follow-up. If GPS could supply, or even substitute, some CT-scans in the evaluations, there would be a huge improvement both for the patients, physicians, and the health care system.

The negative results of our study of measuring only physical function, strongly suggest that future research should focus on other methods for assessing patients' overall health. Many patients are at risk of side-effects due to old age and comorbidities. The patient's performance status would remain important in the treatment decisions in the future as well, but other factors reflecting the patient's capacity and treatment tolerance, would be important supplements. There is more and more evidence suggesting that a geriatric assessment (GA), enables clinicians to better individualize cancer therapy for older patients, reducing treatment toxicity without compromising tumor control or survival. A GA and recommended managements (GAM), consist of systematic evaluation of domains with suitable assessment tools where older patients often have deficits, and includes an evaluation of functional status, mobility and risk for falling, cognitive function (237-239), emotional status (depression), nutritional status (240), comorbidity (241, 242), polypharmacy (243), and social support. Performing a GA and adapt the therapy according to the results in elderly (≥70 years), reduces toxicity in patients with advanced NSCLC (244), but it is not clear whether a GAM improves survival yet.

Patient-reported outcomes have over years been seen to be useful as prognostic and predictive factors, also in lung cancer patients treated with immunochemotherapy (245), which underlines the importance of this factor. Facilitating implementation and adaptation should be of highest priority in the future.

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## Appendix A The five items from the EORTC QLQ C30 questionnaire included in the patient-reported physical function (PRPF) score

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌋⌊_⌊_⌋⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌋⌊_⌊_⌋⌊_⌊_⌊_⌋

| | | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|---|
| 1. | Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. | Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. | Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. | Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. | Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

# Appendix B Paper I-III

Paper I

Paper II

# Prognostic Value of Post First-Line Chemotherapy Glasgow Prognostic Score in Advanced Non-Small Cell Lung Cancer

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Kristin Stokke[1,2], Marie Søfteland Sandvei[2,3], Bjørn Henning Grønberg[1,2], Marit Slaaen[4,5], Kristin T Killingberg[1,2] and Tarje O Halvorsen[1,2]

[1]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. [2]The Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. [3]Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), Trondheim, Norway. [4]Research Centre for Age-related Functional Decline and Disease (AFS), Innlandet Hospital Trust HF, Hamar, Norway. [5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

**ABSTRACT**

**BACKGROUND:** The Glasgow prognostic score (GPS) is an established inflammatory prognostic index in cancer patients. Most studies have only measured GPS at baseline (B-GPS). Effective cancer therapy may reduce inflammation, and we investigated whether re-assessing GPS after first-line chemotherapy (E-GPS) provided more prognostic information than B-GPS in a phase III trial of advanced non-squamous non-small cell lung cancer (NSCLC).

**METHODS:** Glasgow prognostic score was assessed before and after carboplatin/vinorelbine chemotherapy. When assessing GPS, C-reactive protein (CRP) ⩾ 10 mg/L and albumin < 35 mg/L are defined as abnormal values. GPS 0: both values normal, GPS 1: one abnormal value, and GPS 2: both values abnormal.

**RESULTS:** Glasgow prognostic score at baseline and E-GPS were available in 138 patients. Median age was 67 years, 51% were women, and 94% had performance status 0-1. B-GPS was not a statistically significant prognostic factor (B-GPS 1 vs 0: hazard ratio [HR] = 1.32, 95% confidence interval [CI] = 0.9-2.0; B-GPS 2 vs 0: HR = 1.46, 95% CI = 0.9-2.3), while E-GPS was (E-GPS 1 vs 0: HR = 1.57, 95% CI = 1.0-2.4; E-GPS 2 vs 0: HR = 2.77, 95% CI = 1.7-4.5). E-GPS was associated with treatment response ($P < .01$), whereas B-GPS was not.

**CONCLUSION:** Glasgow prognostic score at baseline after first-line chemotherapy provided more prognostic information than baseline GPS in patients with advanced non-squamous NSCLC and was associated with treatment response.

**ClinicalTrials.gov Identifier:** NCT02004184.

**KEYWORDS:** Lung cancer, non-small cell lung cancer (NSCLC), prognostic biomarker, chemotherapy, maintenance therapy

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**TYPE:** Original Research Article

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**CORRESPONDING AUTHOR:** Marie Søfteland Sandvei, Department of Public Health and Nursing, Norwegian University of Science and Technology (NTNU), P.O. Box 8905, 7491 Trondheim, Norway. Email: marie.s.sandvei@ntnu.no

## Background

Inflammation plays an essential role in cancer development and progression,[1-3] and the development and maintenance of a systemic inflammatory response has been consistently associated with poorer outcome in both early and advanced disease.[4]

Glasgow prognostic score (GPS) is an inflammatory score based on values of C-reactive protein (CRP) and albumin.[5] Mounting evidence has shown that it is an independent prognostic factor in numerous cancers, different disease stages, and treatment settings.[6-13] An important aspect is that it is objectively assessed, affordable, and easy to implement in clinical practice.

Almost all previous studies have measured GPS only once and mainly before start of treatment (at baseline, "B-GPS").[5-9,11-23] However, GPS is believed to reflect inflammation as an expression of cancer activity, and hence, in patients who respond to cancer treatment, a reduction in inflammation and thereby in GPS is to be expected.[4] Thus, GPS measured after treatment (at evaluation, "E-GPS") might capture the effect of treatment and be a more precise prognostic factor than B-GPS.

Lung cancer is marked by high inflammation and poor survival,[24,25] and a high proportion of patients have elevated GPS as compared with other cancer types.[25] Therefore, in a randomized phase III trial comparing immediate maintenance pemetrexed with pemetrexed at progression in patients with advanced non-squamous non-small cell lung cancer (NSCLC),[26] we measured B-GPS and E-GPS after induction chemotherapy. The aims were to assess whether E-GPS provides better prognostic information than B-GPS and whether there were associations between response to chemotherapy and B-GPS, E-GPS, or change in GPS.

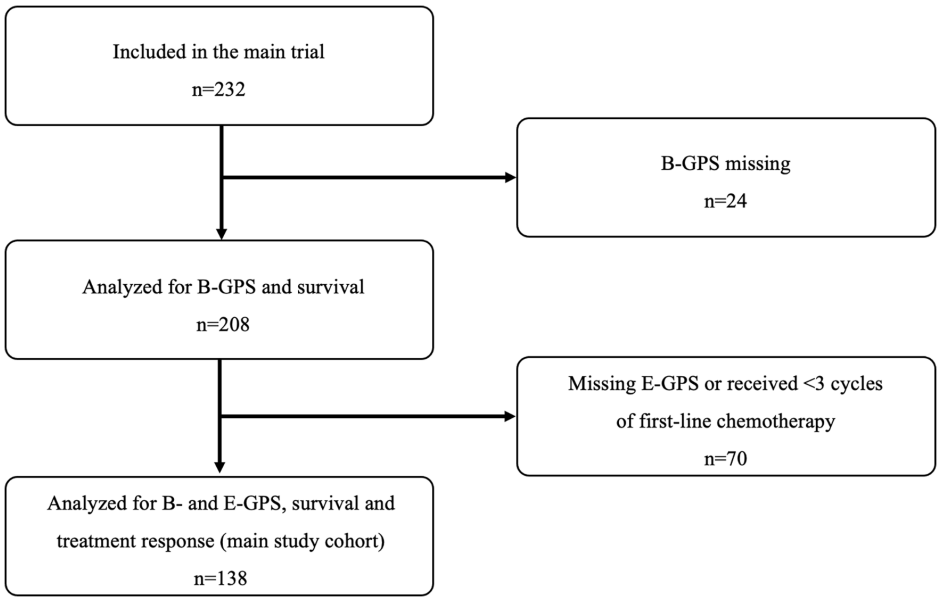


**Figure 1.** Consort flow diagram.

## Methods

### *Approvals*

This open randomized phase III multicenter trial was approved by the Regional Committee for Medical Research Ethics in Central Norway (ID 2013/645, approved on June 17, 2013) and The Norwegian Medicines Agency.

### *Patients*

From May 2014 to September 2017, a total of 232 patients were enrolled at 19 hospitals in Norway. Eligible patients were treatment naïve, had stage IIIB-IV non-squamous NSCLC, no known activating EGFR-mutation or ALK-translocation, WHO performance status (PS) 0-2, and adequate bone marrow/liver/kidney function. Patient were to receive 4 courses of induction chemotherapy with carboplatin AUC 5 (Calvert's formula) IV and vinorelbine 25 mg/m$^2$ IV day 1 and vinorelbine 25 mg/m$^2$ IV or 60 mg/m$^2$ PO day 8, every 3 weeks. Patients who completed 4 courses, had PS 0-2 and non-progression were randomized to immediate maintenance pemetrexed therapy or observation. Pemetrexed was the treatment of choice at progression. Patients who were not randomized were treated according to each hospital's routines. The study closed prematurely when immunotherapy became available in Norway and replaced pemetrexed as standard relapse treatment. In the randomized trial, there was no significant difference in overall survival (OS) ($P$=.10) between treatment arms. Thus, in the present study, all patients were analyzed as one cohort.[26]

For our main analyses, we included patients who received 3 or 4 courses of carboplatin/vinorelbine if GPS was scored both at baseline and evaluation (main study cohort) (Figure 1). In a sensitivity analysis of B-GPS and survival, we included all patients with a B-GPS, independent of number of completed chemotherapy courses (Figure 1).

### *Glasgow prognostic score*

According to the GPS, an elevated CRP of ⩾10 mg/L and hypoalbuminemia of <35 mg/L are considered abnormal values. If both values are normal, GPS is 0. If one value is abnormal, GPS is 1, and when both are abnormal, GPS is 2. A higher score is associated with shorter survival.[5]

Blood samples for assessing GPS were collected within 2 weeks before chemotherapy commenced (B-GPS) and within 3 weeks after the last chemotherapy course was administered (E-GPS).

### *Endpoints*

Overall survival was defined as time from inclusion until death of any cause in the analyses with B-GPS and as time from evaluation after first-line chemotherapy until death of any cause in analyses with E-GPS. Response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[27]

### *Statistical considerations*

Survival was estimated using the Kaplan-Meier method and compared using the Cox proportional hazard model. To assess the prognostic value of B-GPS and E-GPS in our main study cohort, multivariable Cox proportional hazards models for survival were adjusted for sex, age (continuous variable), and stage of

**Table 1.** Patient characteristics of all patients in the main study cohort.

| | | MAIN STUDY COHORT | GPS AT BASELINE (B-GPS) | | | GPS AT EVALUATION (E-GPS) | | |
|---|---|---|---|---|---|---|---|---|
| | | N = 138 | B-GPS 0 N = 55 | B-GPS 1 N = 53 | B-GPS 2 N = 30 | E-GPS 0 N = 59 | E-GPS 1 N = 50 | E-GPS 2 N = 29 |
| | | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) | N (%) |
| Age | Median (range) | 67 (47-83) | 65 (47-83) | 68 (56-81) | 66 (50-82) | 65 (47-81) | 68 (51-83) | 66 (50-77) |
| Sex | Male | 68 (49) | 30 (55) | 24 (45) | 14 (47) | 26 (44) | 25 (50) | 17 (59) |
| | Female | 70 (51) | 25 (45) | 29 (55) | 16 (53) | 33 (56) | 25 (50) | 12 (41) |
| Stage | IIIb | 8 (6) | 3 (5) | 3 (6) | 2 (7) | 6 (10) | 2 (4) | – |
| | IV | 130 (94) | 52 (95) | 50 (94) | 28 (93) | 53 (90) | 48 (96) | 29 (100) |
| WHO PS | 0 | 50 (36) | 28 (51) | 16 (30) | 6 (20) | 26 (44) | 18 (36) | 6 (21) |
| | 1 | 80 (58) | 24 (44) | 33 (62) | 23 (77) | 30 (51) | 29 (58) | 21 (72) |
| | 2 | 8 (6) | 3 (5) | 4 (8) | 1 (3) | 3 (5) | 3 (6) | 2 (7) |
| Randomization | No | 58 (42) | 21 (38) | 25 (47) | 12 (40) | 17 (29) | 22 (44) | 19 (66) |
| | Observation | 38 (28) | 18 (33) | 10 (19) | 10 (33) | 22 (38) | 13 (26) | 3 (10) |
| | Maintenance | 42 (30) | 16 (29) | 18 (34) | 8 (27) | 20 (34) | 15 (30) | 7 (24) |
| Received immunotherapy after chemotherapy | No | 102 (74) | 37 (67) | 43 (81) | 22 (73) | 38 (64) | 40 (80) | 24 (83) |
| | Yes | 36 (26) | 18 (33) | 10 (19) | 8 (27) | 21 (36) | 10 (20) | 5 (17) |

GPS, Glasgow Prognostic Score; WHO PS, WHO Performance Status.

disease (III vs IV). In addition, we adjusted for PS scored at baseline when examining B-GPS, and PS at evaluation in models with E-GPS. Performance status at evaluation was missing for 6 patients who were excluded from multivariable analyses.

As E-GPS was not measured in all patients with a B-GPS, we performed sensitivity survival analyses including all patients with a B-GPS (n = 208) to account for a potential selection bias.

Finally, we performed sensitivity survival analyses in the main study cohort (n = 138), adjusting for randomization (no/observation-arm/maintenance-arm), and whether patients received immunotherapy after chemotherapy, as this has been shown to significantly improve survival in some patients with advanced NSCLC.[28,29]

Associations between B-/E-GPS and response to chemotherapy were compared using Pearson's chi-square test or Fisher's exact test. A 2-sided $P < .05$ was considered statistically significant. SPSS Version 27.0 (Armonk, NY: IBM Corp) was used for all statistical analyses.

## Results

### *Patients*

For 138 (59%) of the 232 patients enrolled in the randomized controlled trial (RCT), both B-GPS and E-GPS were available. These patients were included in the present study as our main study cohort. B-GPS was measured in an additional 70 patients, who were also included in sensitivity analyses, whereas 24 patients had no GPS measures and were excluded altogether (Figure 1).

In our main study cohort, median age was 67 years (range, 47-83), 70 (51%) were women, 130 (94%) had stage IV disease, and 50 (36%), 80 (58%), and 8 (6%) had PS 0, 1, and 2, respectively (Table 1). After completing induction chemotherapy, 80 (58%) of the patients were randomized to immediate maintenance pemetrexed therapy (n = 42) or observation (n = 38). Thirty-six (26%) of the patients received immunotherapy after the study therapy (Table 1). Mean follow-up time was 14.1 months (95% confidence interval [CI] = 12.3-15.9). Eighteen of 138 patients were alive when follow-up was completed.

In our main study cohort, 55 (40%) patients had B-GPS 0, 53 (38%) B-GPS 1, and 30 (22%) B-GPS 2. At evaluation after induction chemotherapy, 59 (43%) patients had E-GPS 0, 50 (36%) E-GPS 1, and 29 (21%) E-GPS 2 (Table 1). Patients with B-GPS 0 were more likely to have PS 0 than patients with B-GPS 1-2. Otherwise, baseline and treatment characteristics were balanced between patients with B-GPS 0, 1, and 2.

Seventy-three patients (53%) had no change in GPS. Thirty-three patients (24%) improved their GPS; 19 (14%) from 1 to 0, 8 (6%) from 2 to 1, and 6 (4%) from 2 to 0. Glasgow prognostic score deteriorated in 32 (23%) patients; 19 (14%) from 0 to 1, 2 (1%) from 0 to 2, and 11 (8%) from 1 to 2.

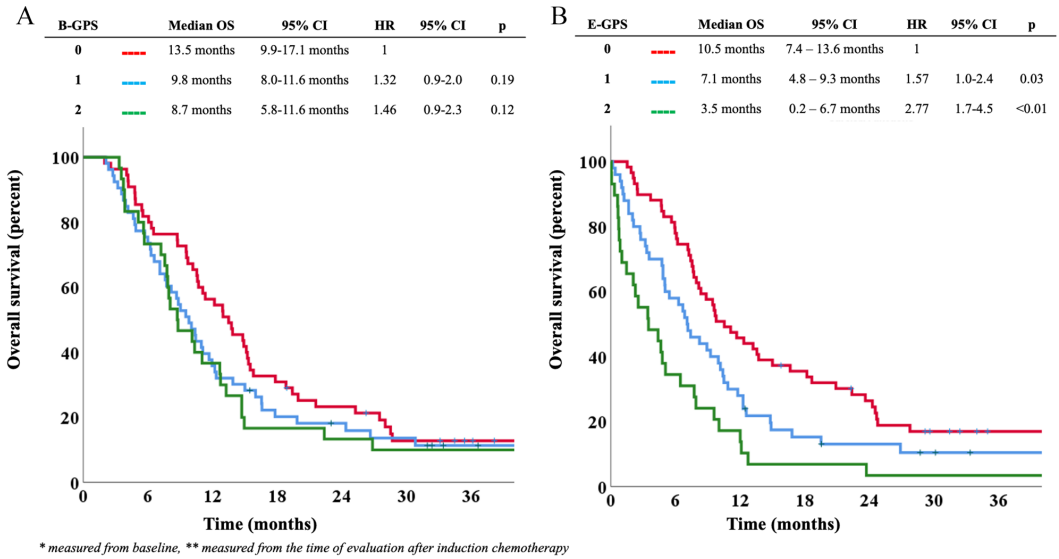


**Figure 2.** (A) B-GPS and overall survival in the main study cohort.* (B) E-GPS and overall survival in the main study cohort.** B-GPS indicates Glasgow Prognostic Score at baseline; CI, confidence interval; E-GPS, Glasgow Prognostic Score at evaluation; HR, hazard ratio; OS, overall survival. *Measured from baseline. **Measured from the time of evaluation after induction chemotherapy.

Baseline characteristics of the 70 patients included in the sensitivity analysis and the 24 excluded patients (Figure 1) were comparable to the characteristics of the main study cohort (Supplementary Table).

### *Overall survival*

*B-GPS and survival.* Overall, median OS was 10.6 months (95% CI: 9.2-11.9) in the main study cohort (n = 138). Patients with B-GPS 0, 1, and 2 had median OS of 13.5 (95% CI: 9.9-17.1) months, 9.8 (95% CI: 8.0-11.6) months, and 8.7 (95% CI: 5.8-11.6) months, respectively (Figure 2A). There were no statistically significant differences in OS according to B-GPS in univariable or multivariable analyses (Figure 2A and Table 2), nor in a post hoc multivariable analysis in which B-GPS 1 and 2 were pooled and compared with B-GPS 0 (hazard ratio [HR] = 1.27, 95% CI: 0.87-1.88, $P = .22$ in multivariable analysis).

Sensitivity survival analysis of all patients with B-GPS measured (n = 208) showed that patients with B-GPS 0, 1, and 2 had median OS of 13.8 (95% CI: 11.1-16.5) months, 7.1 (95% CI: 4.8-9.4) months, and 8.2 (95% CI: 7.1-9.3) months, respectively. For this group, the lower survival in patients with B-GPS 1 compared with B-GPS 0 reached statistical significance (HR = 1.51, 95% CI: 1.1-2.1, $P = .01$) (Supplementary Figure).

In the final sensitivity multivariable survival analysis of the main study cohort (n = 138) adjusting for randomization and whether patients later received immunotherapy, B-GPS was still not a significant prognostic factor (data not shown).

*E-GPS and survival.* Overall, median OS from evaluation after first-line chemotherapy was 7.7 months (95% CI: 6.3-9.2). Patients with E-GPS 0, 1, and 2 had median OS of 10.5 (7.4-13.6) months, 7.1 (4.8-9.3) months, and 3.5 (0.2-6.7) months, respectively. Higher E-GPS was significantly associated with shorter survival time; HR = 1.57 (95% CI: 1.04-2.37, $P = .03$) for E-GPS 1 as compared with E-GPS 0, and HR = 2.77 (95% CI: 1.73-4.45, $P < .01$) for E-GPS 2 as compared with E-GPS 0 (Figure 2B). In the multivariable analysis, the survival difference between E-GPS 2 vs 0 remained statistically significant ($P < .01$), while there was a trend toward a significant difference between E-GPS 1 and 0 patients ($P = .08$) (Table 3).

In the sensitivity multivariable survival analysis adjusting for randomization and whether patients received subsequent immunotherapy, E-GPS but not B-GPS remained a significant prognostic factor (data not shown).

### *GPS and response to induction chemotherapy*

At evaluation after induction chemotherapy, 38 patients (28%) had partial response (PR), 48 (35%) had stable disease (SD), 48 (35%) had progressive disease (PD), and 4 (3%) were not evaluable (Table 4).

B-GPS was not significantly associated with treatment response ($P = .54$), whereas E-GPS was ($P < .01$). Forty-one percent of patients with E-GPS 0 had achieved a PR, while corresponding numbers among patients with E-GPS 1 and E-GPS 2 were 21% and 14%, respectively. Furthermore, change in GPS was associated with treatment response ($P = .01$).

**Table 2.** Univariable and multivariable analyses of B-GPS and overall survival in the main study cohort.[a]

| | | | UNIVARIABLE ANALYSIS | | | MULTIVARIABLE ANALYSIS | | |
|---|---|---|---|---|---|---|---|---|
| | | N | HR | 95% CI | *P*-VALUE | HR | 95% CI | *P*-VALUE |
| GPS at baseline (B-GPS) | 0 | 55 | 1 | | | 1 | | |
| | 1 | 53 | 1.32 | 0.88-1.98 | .19 | 1.27 | 0.83-1.93 | .27 |
| | 2 | 30 | 1.46 | 0.91-2.34 | .12 | 1.29 | 0.77-2.14 | .33 |
| Age (continuous) | | 138 | 1.01 | 0.98-1.03 | .60 | 1.00 | 0.97-1.03 | .91 |
| Sex | Female | 70 | 1 | | | 1 | | |
| | Male | 68 | 1.14 | 0.80-1.63 | .47 | 1.14 | 0.79-1.65 | .47 |
| Disease stage | IIIb | 8 | 1 | | | 1 | | |
| | IV | 130 | 1.04 | 0.51-2.13 | .92 | 1.03 | 0.50-2.14 | .93 |
| WHO-PS at baseline | 0 | 50 | 1 | | | 1 | | |
| | 1 | 80 | 1.48 | 1.01-2.18 | .05 | 1.40 | 0.92-2.12 | .12 |
| | 2 | 8 | 2.67 | 1.25-5.72 | .01 | 2.53 | 1.15-5.56 | .02 |

CI, confidence interval; GPS, Glasgow Prognostic Score; HR, hazard ratio; WHO PS, WHO Performance Status.
[a]Measured from baseline.

**Table 3.** Univariable and multivariable analyses of E-GPS and overall survival in the main study cohort.[a]

| | | | UNIVARIABLE ANALYSIS | | | MULTIVARIABLE ANALYSIS | | |
|---|---|---|---|---|---|---|---|---|
| | | N | HR | 95% CI | *P*-VALUE | HR | 95% CI | *P*-VALUE |
| GPS at evaluation (E-GPS) | 0 | 59 | 1 | | | 1 | | |
| | 1 | 50 | 1.57 | 1.04-2.37 | .03 | 1.47 | 0.96-2.27 | .08 |
| | 2 | 29 | 2.77 | 1.73-4.45 | <.01 | 2.11 | 1.26-3.57 | <.01 |
| Age (continuous) | | 138 | 1.01 | 0.98-1.03 | .69 | 1.00 | 0.97-1.03 | .99 |
| Sex | Female | 70 | 1 | | | 1 | | |
| | Male | 68 | 1.17 | 0.81-1.66 | .42 | 1.25 | 0.86-1.83 | .24 |
| Disease stage | IIIb | 130 | 1 | | | 1 | | |
| | IV | 8 | 1.12 | 0.54-2.29 | .76 | 0.84 | 0.40-1.77 | .65 |
| WHO-PS at evaluation[b] | 0 | 26 | 1 | | | 1 | | |
| | 1 | 77 | 2.38 | 1.39-4.01 | <.01 | 2.14 | 1.23-3.73 | <.01 |
| | 2 | 21 | 4.75 | 2.46-9.18 | <.01 | 4.52 | 2.31-8.82 | <.01 |
| | 3 | 6 | 26.91 | 9.61-75.34 | <.01 | 18.52 | 6.28-54.58 | <.01 |
| | 4 | 2 | 7.75 | 1.75-34.32 | <.01 | 10.71 | 2.28-50.17 | <.01 |

CI, confidence interval; GPS, Glasgow Prognostic Score; HR, hazard ratio; WHO PS, WHO Performance Status.
[a]Measured from the time of evaluation after induction chemotherapy
[b]Missing in 6 patients.

Among patients with improved GPS, 45% had achieved a PR, among those with stable GPS, 26% had a PR, while 13% of those with worse GPS had a PR.

## Discussion

In this study of patients with advanced non-squamous NSCLC, we found that GPS assessed at evaluation after 3 or 4 courses

**Table 4.** B-GPS, E-GPS, and change in GPS and response to first-line chemotherapy in the main study cohort.

| | | GPS AT BASELINE (B-GPS) | | | | GPS AT EVALUATION (E-GPS) | | | | CHANGE IN GPS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N = 138 | B-GPS 0 N = 55 | B-GPS 1 N = 53 | B-GPS 2 N = 30 | | E-GPS 0 N = 59 | E-GPS 1 N = 50 | E-GPS 2 N = 29 | | WORSENED GPS N = 32 | STABLE GPS N = 73 | IMPROVED GPS N = 33 | |
| | N (%) | N (%) | N (%) | N (%) | *P* | N (%) | N (%) | N (%) | *P* | N (%) | N (%) | N (%) | *P* |
| Partial response | 38 (28) | 16 (30) | 11 (21) | 11 (38) | | 24 (41) | 10 (21) | 4 (14) | | 4 (13) | 19 (26) | 15 (45) | |
| Stable disease | 48 (35) | 20 (38) | 20 (38) | 8 (28) | | 22 (38) | 19 (40) | 7 (25) | | 10 (32) | 26 (36) | 12 (36) | |
| Progressive disease | 48 (35) | 17 (32) | 21 (40) | 10 (34) | .54 | 12 (21) | 19 (40) | 17 (61) | <.01 | 16 (50) | 27 (37) | 5 (15) | .01 |
| Not evaluable | 4 (3) | 2 (1) | 1 (1) | 1 (1) | | 1 (1) | 2 (1) | 1 (1) | | 2 (6) | 1 (1) | 1 (3) | |

of first-line platinum-doublet chemotherapy (E-GPS) was prognostic for survival, whereas GPS at baseline (B-GPS) was not. Furthermore, patients with a low E-GPS and those with an improved GPS from baseline until evaluation after chemotherapy had higher response rates to chemotherapy than other patients. There was no significant association between B-GPS and response to chemotherapy.

Studies of the prognostic role of GPS in cancer comprise more than 70 000 patients,[7-9] but only a few have looked at the impact of GPS measured during or after treatment: Three small studies (n = 24-64) reported that elevated GPS measured 3 to 6 weeks after initiation of immune checkpoint inhibitor therapy was associated with poor survival in advanced NSCLC[30,31] and renal cell carcinoma.[32] Others have found that elevated GPS after initiation of palliative chemotherapy for colorectal cancer[33] and after surgery for localized NSCLC[34] and gastric cancer[15] was associated with poor prognosis. A study of patients with advanced head and neck cancer found that GPS after concurrent chemoradiotherapy was associated with recurrence free and overall survival, whereas pretreatment GPS was not.[35] Moreover, elevated modified GPS (mGPS) after neo-adjuvant chemotherapy before surgery for adenocarcinoma of the esophagogastric junction was associated with reduced survival, whereas pre-neo-adjuvant mGPS was not.[16] Overall, these studies corroborate the results of our study. In contrast, Forrest and colleagues studied patients with inoperable NSCLC treated with chemotherapy[11] and found that B-GPS was associated with survival, whereas GPS measured 3 to 6 months after inclusion was not. However, only a minority (42%) of patients received active cancer treatment and a minority (38%) had GPS measured during follow-up.

Most previous studies of NSCLC have found B-GPS to be a prognostic factor,[5,6,10-13,22,23] but many studies have pooled B-GPS categories when running the analyses,[6,8-10,30,36,37] which limits the evidence for the prognostic value of each of the 3 different GPS values. Furthermore, most included relatively unselected populations, only subsets of patients received cancer treatment,[6,11] and many included patients with PS of 3 or 4.[6,11,22,23] Our main analyses only included patients who completed 3 or 4 courses of chemotherapy, and the majority (94%) had a PS of 0 to 1. Thus, it is possible that B-GPS provides less prognostic information in patients who are considered fit for systemic cancer treatment than in less selected cohorts including cancer patients unfit for palliative chemotherapy, because there might be less variation in prognostic/predictive factors including B-GPS. The potential impact of patient selection might explain why there was a statistically significant survival difference between B-GPS 0 and 1 in our expanded cohort (all 208 with a B-GPS), while this was not the case in the main study cohort.

To the best of our knowledge, no studies have assessed E-GPS and response, but neutrophil-to-lymphocyte ratio (NLR) and CRP after targeted therapy or immune checkpoint

blockade were associated with overall response rate in advanced renal cell carcinoma.[32,38,39] Although treatments, settings, and design are different, these studies support the hypothesis that E-GPS holds more prognostic information than B-GPS because it incorporates the treatment effect. A possible explanation, as hypothesized, is that effective systemic therapy reduces the cancer-induced inflammation. On the contrary, systemic inflammation might reduce the effect of chemotherapy, possibly due to influence on tumor microenvironment.[40] However, our study was not designed to investigate underlying mechanisms.

The main limitation of our study is the sample size. Furthermore, we cannot rule out that our results might have been influenced by a selection bias. There were only lab values for assessing E-GPS in 138 of the 232 patients included in the trial, and most common reasons for not measuring E-GPS were death, progression, or poor PS. The time frames for measuring CRP and albumin were generous. There was only a trend toward a statistically significant difference between E-GPS 0 and 1 patients in the multivariable survival analysis ($P = .08$). In sensitivity analyses including all patients with B-GPS measured (n = 208), there was a statistically significant difference in survival between patients with B-GPS 0 and 1, possibly indicating that B-GPS have less prognostic value among cancer patients who tolerate palliative chemotherapy than in less selected populations including patients unfit for such therapy. Finally, GPS might also be influenced by malnutrition and side effects from chemotherapy such as nausea and anorexia, and one study shows that patients with a poor B-GPS experience more toxicity from cancer therapy.[13] Unfortunately, our study was not designed to investigate such complex interactions.

Another limitation of our study is that subsequent treatment differed largely between the participants, especially as immunotherapy was introduced during the study period. However, this is not likely to affect our results, as it would rather be a mediator than a confounder of the association between GPS and OS. And in sensitivity analysis adjusting for group in our original RCT (randomized to pemetrexed maintenance therapy, randomized to observation, or did not meet criteria for randomization) and whether patients received immunotherapy or not, the prognostic value of E-GPS remained stronger than for B-GPS (data not shown). Platinum-doublet chemotherapy alone is no longer standard primary treatment for advanced NSCLC, but our and previous studies have demonstrated associations between E-GPS and response to treatment and survival in patients with several cancers receiving different therapies, indicating that E-GPS reflects treatment effect independently of treatment modality. Finally, CRP and albumin, and thereby GPS, could have been influenced by other factors, ie, infection, inflammation, comorbidity, nutrition, and medication (eg, corticosteroids), but our study was not designed to collect such data. On the contrary, this also applies to most previous studies of GPS.[6,11,23,31-37]

The main strength of our study is that we have investigated a relatively uniform patient population. Furthermore, the differences in survival between the 3 E-GPS categories are relatively large and clinically meaningful and might guide clinicians when planning follow-up intervals of patients, when considering maintenance therapy, or switching ongoing treatment. However, the clinical value of E-GPS and how it should be used needs to be further evaluated, ideally in prospective trials.

## Conclusion

To conclude, we found that E-GPS was a stronger prognostic factor than B-GPS and that E-GPS, but not B-GPS, was significantly associated with response to chemotherapy in patients with advanced non-squamous NSCLC.

## Author Contributions

BHG and TOH conceived and designed the work and acquired data and handled funding and supervision. KS performed the statistical analyses and drafted the manuscript. All authors played an important role in interpreting the results. All authors revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

## ORCID iD

Marie Søfteland Sandvei https://orcid.org/0000-0002-8972-8254

## Supplemental Material

Supplemental material for this article is available online.

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Paper III

*healthcare*

MDPI

*Article*

# Associations between Measured and Patient-Reported Physical Function and Survival in Advanced NSCLC

**Kristin Stokke [1,2,*], Tarje Onsøien Halvorsen [1,2], Bjørn Henning Grønberg [1,2], Ingvild Saltvedt [3,4], Marit Slaaen [5,6], Øyvind Kirkevold [5,7,8], Kristin Toftaker Killingberg [1,2] and Marie Søfteland Sandvei [1,2]**

1 Department of Clinical and Molecular Medicine, NTNU—Norwegian University of Science and Technology, N-7491 Trondheim, Norway; tarje.halvorsen@gmail.com (T.O.H.); bjorn.h.gronberg@gmail.com (B.H.G.); kristin.t.killingberg@ntnu.no (K.T.K.); marie.s.sandvei@ntnu.no (M.S.S.)
2 Department of Oncology, St. Olavs Hospital, Trondheim University Hospital, N-7006 Trondheim, Norway
3 Department of Geriatrics, St. Olavs Hospital, Trondheim University Hospital, N-7006 Trondheim, Norway; ingvild.saltvedt@ntnu.no
4 Department of Neuro Medicine and Movement Science, NTNU—Norwegian University of Science and Technology, N-7491 Trondheim, Norway
5 The Research Centre for Age Related Functional Decline and Diseases, Innlandet Hospital Trust, P.O. Box 68, N-2313 Ottestad, Norway; marit.slaaen@sykehuset-innlandet.no (M.S.); oyvind.kirkevold@aldringoghelse.no (Ø.K.)
6 Institute of Clinical Medicine, University of Oslo, N-0318 Oslo, Norway
7 The Norwegian National Centre for Ageing and Health, Vestfold Hospital Trust, N-3103 Tønsberg, Norway
8 Department of Health Science in Gjøvik, NTNU—Norwegian University of Science and Technology, N-2802 Gjøvik, Norway
* Correspondence: kristin.stokke@ntnu.no; Tel.: +47-95-91-85-97

**Abstract:** Background: There is a lack of tools for selecting patients with advanced lung cancer who benefit the most from systemic treatment. Patient-reported physical function (PRPF) has been identified as a prognostic factor in this setting, but little is known about the prognostic value in advanced non-small-cell lung cancer (NSCLC). The aim of this study was to investigate if measured physical performance was an independent or stronger prognostic factor than PRPF in patients with advanced NSCLC receiving platinum-doublet chemotherapy. Methods: We analyzed patients from a randomized trial comparing immediate and delayed pemetrexed therapy in stage III/IV NSCLC (n = 232) who performed timed up and go (TUG) and 5 m walk test (5 mWT) and reported physical function on the EORTC QLQ-C30 before chemotherapy commenced. Results: Overall, 208 patients performed TUG and 5 mWT and were included in the present study. Poor physical function was significantly associated with poor survival (TUG: HR 1.05, $p < 0.01$, 5 mWT: HR 1.05, $p = 0.03$, PRPF: 1.01, $p < 0.01$), but only PRPF remained an independent prognostic factor in multivariable analyses adjusting for baseline characteristics (HR 1.01, $p = 0.03$). Conclusions: Patient-reported, but not measured, physical performance was an independent prognostic factor for survival in patients with advanced NSCLC receiving platinum-doublet chemotherapy.

**Keywords:** physical performance; timed up and go; 5-meter walk test; advanced NSCLC; chemotherapy; overall survival



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## 1. Introduction

Lung cancer is the third most common cancer and the most common cause of cancer-related deaths [1]. About 40% of patients have advanced disease at the time of diagnosis with limited survival expectancy and are offered palliative, systemic treatment [1]. Immune checkpoint inhibitors (ICI) and targeted therapies have improved survival for patients with advanced non-small-cell lung cancer (NSCLC), but cytotoxic chemotherapy still has a role, alone or combined with ICIs [2]. Even if chemotherapy is usually reserved for patients with a good performance status [3], response rates are moderate, approximately 30–35%, and it would be of great value to identify the patients who benefit the most from such therapy.

There is evidence that patients with poor physical function experience more toxicity from treatment and are consequently less able to complete treatment as planned [4], and several studies have shown that patient-reported physical function (PRPF) is an independent prognostic factor in advanced NSCLC [5,6]. Furthermore, there are indications that lower extremity function reflects patients' health status and is prognostic in patients with cancer [7,8]. Timed up and go (TUG) [9,10] and gait speed are simple yet sensitive measures that have consistently been identified as prognostic factors among patients with cancer [7,8]. However, previous studies have included patients with different cancers, stages of disease, and treatment, and only one study adjusted for other important prognostic factors such as performance status (PS) in the analyses [11]. Consequently, there is limited knowledge of their independent prognostic information, and it is unclear whether these measures provide more clinically relevant prognostic information than PRPF. Additionally, if patients with poor physical function tolerate less systemic therapy, they might achieve less disease control. However, no study has investigated whether there are associations between TUG or gait speed and disease control after chemotherapy.

The aim of this study was to investigate whether TUG and gait speed measured by the 5-meter walk test (5 mWT) were independent prognostic factors, stronger prognostic factors than PRPF, or predictive factors for disease control in patients with advanced NSCLC receiving carboplatin and vinorelbine in a randomized trial of maintenance pemetrexed therapy.

## 2. Materials and Methods

### *2.1. Patients*

From May 2014 to September 2017, 232 patients were enrolled in a randomized controlled trial (RCT) at 19 hospitals in Norway. Eligible patients were treatment naïve, had stage IIIB/IV non-squamous NSCLC (TNM v7), no known activating epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation, World Health Organization Performance Status (WHO PS) 0–2, and adequate bone marrow, liver, and kidney function. Patients who completed four courses of carboplatin/vinorelbine and had WHO PS 0–2 and non-progression were randomized to immediate maintenance pemetrexed therapy or observation followed by pemetrexed at progression. The study closed prematurely due to a stop in patient recruitment when ICI became available in Norway [12].

Patients who received induction chemotherapy and completed TUG and 5 mWT at baseline were analyzed in the present study (Figure 1).

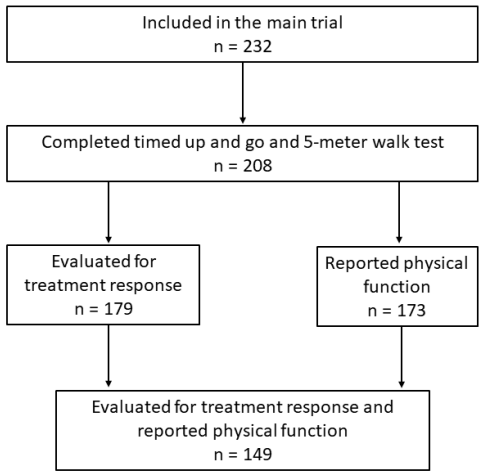


**Figure 1.** Patient selection.

### 2.2. Timed Up and Go Test (TUG)

TUG was performed according to standardized guidelines [9] and registered as the time the patient needed to stand up from a chair, walk 3 m (marked on the floor) at a comfortable pace, turn, walk back, and sit down again. Patients were permitted to use routine walking aids and were instructed not to use their arms to stand up. No physical assistance was given. The task was performed three times, and the average of performances two and three was included in the analyses.

### 2.3. 5-Meter Walk Test (5 mWT)

In the 5 mWT, patients started at zero speed at the starting line, and timing stopped when the patient crossed the line after five meters (marked on the floor). The test was performed at normal speed. Routine walking aids were allowed. The test was performed three times, and the average time of all three performances was included in the analyses [13].

### 2.4. Patient-Reported Physical Function (PRPF)

PRPF was assessed at baseline by the physical functioning scale on the Norwegian version of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30. This score is a compound score of five items: (1) "Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase", (2) "Do you have any trouble taking a long walk", (3) "Do you have any trouble taking a short walk outside of the house", (4) "Do you need to stay in bed or a chair during the day", and (5) "Do you need help with eating, dressing, washing yourself or using the toilet?" Each item is scored from 0 (not at all) to 4 (very much), summarized, and transformed into a scale ranging from 0 to 100, where a higher score indicates better function [14,15].

### 2.5. Treatment Completion and Endpoints

Treatment completion was assessed in three ways: as the proportion of patients completing all four induction courses, the proportion of patients without any dose reductions of $\geq$20%, and the proportion without any delays ($\geq$7 days) of induction chemotherapy courses. We also assessed the proportion of patients who were randomized after completion of induction courses, treatment allocation, and number of pemetrexed courses received, as well as the proportion of patients receiving post-study therapy, especially the use of ICIs.

The primary endpoint was overall survival (OS), defined as the time from inclusion (baseline) to death from any cause. The secondary endpoint was disease control, defined as stable disease (SD), partial response (PR), or complete response (CR) according to the RECIST 1.1 [16] evaluated by CT scan 2–3 weeks after the last induction chemotherapy course.

### 2.6. Statistical Considerations

There was no significant difference in overall survival (OS) ($p = 0.10$) between treatment arms in the main trial, and all patients were analyzed as one cohort in the present study [12].

The distribution of TUG and 5 mWT was presented as median and range. There are no established cut off-values for poor TUG or 5 mWT, but 1 m per second or faster is often defined as normal gait speed [17], and 10 s or less has been considered normal values for TUG in previous reports [6,18]. Thus, we considered patients completing the 5 mWT in 5 s or less and those completing the TUG in 10 s or less as having a normal physical function. PRPF was presented as a mean with a 95% confidence interval. The median value was used to separate patients with normal and poor physical function in our analyses. A difference in mean PRPF of 10 was considered clinically significant [19].

Associations between normal or poor physical function (according to TUG, 5 mWT, PRPF), baseline characteristics, and treatment completion were tested with chi-square and Fischer exact test, while the association with age (continuous) was tested with Student's *t*-test. Scatterplots were used to describe associations between TUG, 5 mWT, and PRPF, and univariable linear regression was used to analyze the strength of any association. The

distribution of TUG, 5 mWT, and PRPF according to baseline WHO PS was illustrated with bubble plots. Treatment completion was compared with chi-square and Fischer exact test between patients with normal and poor physical function, while the number of pemetrexed courses was compared with the Mann–Whitney test.

Overall survival (OS) was estimated using the Kaplan–Meier method and compared using the Cox proportional hazard method in uni- and multivariable models. Logistic regression was used for uni- and multivariable analyses of the associations between TUG, 5 mWT, or PRPF and disease control.

All multivariable models were adjusted for baseline characteristics; sex, age (continuous), stage of disease (III versus IV), and WHO PS (0, 1, and 2). TUG, 5 mWT, and PRPF were entered separately in multivariable analyses both as continuous and dichotomous variables. In exploratory analyses, the multivariable model of PRPF and OS was adjusted for TUG and 5 mWT, respectively, and another model of PRPF and OS was adjusted for receipt of ICIs.

A two-sided $p < 0.05$ was considered statistically significant. SPSS v27 was used for all statistical analyses. Plots were made in SPSS or RStudio v1.4.

### 2.7. Approvals

The RCT was approved by the Regional Committee for Medical Research Ethics in Central Norway and The Norwegian Medicines Agency. ClinicalTrials.gov identifier: NCT02004184.

## 3. Results

### 3.1. Baseline Characteristics

Of the 232 patients included in the RCT, 208 (90%) performed TUG and 5 mWT at baseline and were included in the present study. Among these, the median age was 67 years (range 46–83), 112 (54%) were women, 195 (94%) had stage IV disease, and 66 (32%), 112 (54%), and 30 (14%) had WHO PS 0, 1, and 2, respectively. There were more patients with WHO PS 2 among those with poor physical function according to TUG ($p < 0.01$), 5 mWT ($p < 0.01$), and PRPF ($p < 0.01$) (Table 1).

### 3.2. Treatment Completion

Of 208 patients, 146 (70%) received all four induction courses. Patients with a TUG $\geq$10 s were less likely to complete all four courses ($\geq$10 s: 58%, <10 s: 74%; $p < 0.01$), but there were no associations between 5 mWT ($p = 0.34$) or PRPF ($p = 0.08$) and completion of four courses (Table 1).

In total, 95 (46%) patients had at least one dose reduction, and 72 (35%) patients had at least one chemotherapy course delayed. There were no differences in dose reductions (TUG: $p = 0.77$, 5 mWT: $p = 0.60$, and PRPF: $p = 0.68$) or delays between patients with normal or poor physical function (TUG: $p = 0.17$, 5 mWT: $p = 0.64$, and PRPF: $p = 0.77$).

Of all patients, 55 (26%) received all four induction courses without any dose reductions or delays, and there were no differences between patients with normal or poor physical function (TUG: $p = 0.11$, 5 mWT: $p = 0.44$, PRPF: $p = 0.49$).

Only 97 (47%) were randomized after completion of induction chemotherapy, 50 (24%) to immediate maintenance pemetrexed therapy (median 3 courses, range 0–29), and 47 (23%) to the control arm, of whom 34 (72%) patients received pemetrexed at progression (median 4 courses, range 1–12). Patients with a normal physical function according to TUG were more likely to be randomized ($p < 0.01$), while there were no significant associations with 5 mWT ($p = 0.26$) or PRPF ($p = 0.06$) (Table 1). Allocation to treatment arm was balanced (TUG: $p = 0.39$, 5 mWT: $p = 0.52$, PRPF: $p = 1.00$) and there were no differences in number of pemetrexed courses received between patients with normal or poor physical function (TUG: $p = 0.90$, 5 mWT: $p = 0.93$, PRPF, $p = 0.62$).

**Table 1.** Patient and treatment characteristics.

| | | | | TUG | | | | | | 5 mWT | | | | | | PRPF | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | <10 s | | | ≥10 s | | | <5 s | | | ≥5 s | | | ≥73.3 | | <73.3 | | |
| | | *n* | % | Median (Range) | *n* | % | *n* | % | *p* | Median (Range) | *n* | % | *n* | % | *p* | Mean (95% CI) | *n* | % | *n* | % | *p* |
| **TUG** | | 208 | (100%) | 7.8 (0.7–44.2) | 166 | (80%) | 42 | (20%) | | | | | | | | | | | | | |
| **5 mWT** | | 208 | (100%) | | | | | | | 4.5 (1.8–28.1) | 131 | (63%) | 77 | (37%) | | | | | | | |
| **PRPF** | | 173 | (83%) | | | | | | | | | | | | | 72.2 (69.3–75.2) | 100 | (58%) | 73 | (42%) | |
| **Age** | **Median (range)** | 67 | (46–83) | | 66 | (46–83) | 69 | (55–83) | 0.03 | | 66 | (46–83) | 69 | (51–83) | 0.03 | | 68 | (66–69) | 66 | (65–67) | 0.17 |
| **Sex** | **Male** | 96 | (46%) | 8.0 (2.6–27.4) | 78 | (47%) | 18 | (43%) | | 4.2 (1.8–28.1) | 62 | (47%) | 34 | (44%) | | 75.9 (71.8–79.9) | 48 | (48%) | 31 | (42%) | |
| | **Female** | 112 | (54%) | 7.6 (0.7–44.2) | 88 | (53%) | 24 | (57%) | 0.63 | 4.5 (2.0–24.7) | 69 | (53%) | 43 | (56%) | 0.66 | 69.2 (65.0–73.3) | 52 | (52%) | 42 | (58%) | 0.47 |
| **Stage** | **IIIB** | 13 | (6%) | 7.7 (3.6–10.0) | 13 | (15%) | - | - | | 4.2 (2.6–9.5) | 9 | (7%) | 4 | (5%) | | 83.0 (74.2–91.8) | 9 | (9%) | 2 | (3%) | |
| | **IV** | 195 | (94%) | 7.8 (0.7–44.2) | 153 | (85%) | 42 | (100%) | 0.08 | 4.5 (1.8–28.1) | 122 | (93%) | 73 | (95%) | 0.63 | 71.5 (68.4–74.6) | 91 | (91%) | 71 | (97%) | 0.10 |
| **WHO PS** | **0** | 66 | (32%) | 7.2 (2.6–19.6) | 58 | (35%) | 8 | (19%) | | 4.4 (1.8–14.0) | 44 | (34%) | 22 | (29%) | | 78.5 (72.9–84.2) | 36 | (36%) | 16 | (22%) | |
| | **1** | 112 | (54%) | 7.8 (0.7–13.5) | 93 | (56%) | 19 | (45%) | | 4.1 (2.1–14.0) | 77 | (59%) | 35 | (45%) | | 72.7 (69.3–76.2) | 56 | (56%) | 37 | (51%) | |
| | **2** | 30 | (14%) | 10.7 (6.8–44.2) | 15 | (9%) | 15 | (36%) | <0.01 | 6.1 (3.0–28.1) | 10 | (7%) | 20 | (26%) | <0.01 | 58.8 (50.3–67.3) | 8 | (8%) | 20 | (27%) | <0.01 |
| **Completed 4 induction courses** | **No** | 62 | (30%) | 8.2 (0.7–25.9) | 43 | (26%) | 19 | (42%) | | 4.6 (2.5–24.7) | 36 | (27%) | 26 | (34%) | | 67.8 (61.6–73.9) | 26 | (26%) | 28 | (38%) | |
| | **Yes** | 146 | (70%) | 7.7 (2.3–44.2) | 123 | (74%) | 23 | (58%) | 0.01 | 4.3 (1.8–28.1) | 95 | (63%) | 51 | (66%) | 0.34 | 74.2 (71.0–77.5) | 74 | (74%) | 45 | (62%) | 0.08 |
| **Randomization** | **No** | 111 | (53%) | 8.2 (0.7–44.2) | 80 | (48%) | 31 | (74%) | | 4.6 (1.8–24.7) | 66 | (50%) | 45 | (58%) | | 69.3 (65.1–73.6) | 46 | (46%) | 44 | (60%) | |
| | **Yes** | 97 | (47%) | 7.7 (2.3–27.4) | 86 | (52%) | 11 | (27%) | <0.01 | 4.2 (2.0–28.1) | 65 | (50%) | 32 | (42%) | 0.26 | 75.4 (71.3–79.4) | 54 | (54%) | 29 | (40%) | 0.06 |
| **Post-study immunotherapy** | **-Observation** | 47 | (23%) | 7.7 (2.9–12.6) | 43 | (26%) | 4 | (10%) | | 4.2 (2.5–11.6) | 30 | (23%) | 17 | (22%) | | 75.2 (68.6–81.9) | 26 | (26%) | 14 | (19%) | |
| | **-Maintenance** | 50 | (24%) | 7.4 (2.3–27.4) | 43 | (26%) | 7 | (17%) | 0.39 | 4.3 (2.0–28.1) | 35 | (27%) | 15 | (20%) | 0.52 | 75.5 (70–5–80.5) | 28 | (28%) | 15 | (21%) | 1.00 |
| | **No** | 163 | (78%) | 7.9 (0.7–44.2) | 126 | (76%) | 37 | (88%) | | 4.5 (1.8–28.1) | 100 | (76%) | 63 | (82%) | | 69.9 (66.6–73.2) | 72 | (72%) | 64 | (83%) | |
| | **Yes** | 45 | (22%) | 7.0 (2.3–12.6) | 40 | (24%) | 5 | (12%) | 0.09 | 4.2 (2.1–13.2) | 31 | (24%) | 14 | (18%) | 0.35 | 80.9 (75.0–86.7) | 28 | (28%) | 9 | (17%) | 0.01 |

In total, 114 (55%) of the patients received post-study treatment, of whom 45 (22%) received ICI therapy. There was no difference in proportions of patients receiving salvage therapy between those with normal or poor physical function (TUG: $p = 0.37$, 5 mWT: $p = 0.98$, and PRPF: $p = 0.20$). However, patients with a normal PRPF were more likely to receive an ICI (≥73.3: 28%, <73.3: 17%, $p = 0.01$), while no such associations were observed for TUG ($p = 0.09$) or 5 mWT ($p = 0.35$) (Table 1).

### 3.3. Timed Up and Go (TUG)

The median TUG was 7.8 s (range 0.7–44.2 s). Forty-two (20%) patients had TUG ≥ 10 s. There was no difference between men and women or patients with stage IIIB or IV disease. Patients with a poor WHO PS had a longer TUG: WHO PS 0: median 7.2 s (range 2.6–19.6 s), WHO PS 1: median 7.8 s (range 0.7–13.5 s), and WHO PS 2: median 10.7 s (range 6.8–44.2 s) (Table 1). The association between WHO PS and TUG is illustrated in Figure 2. The largest variation in TUG was observed among patients with WHO PS 2.

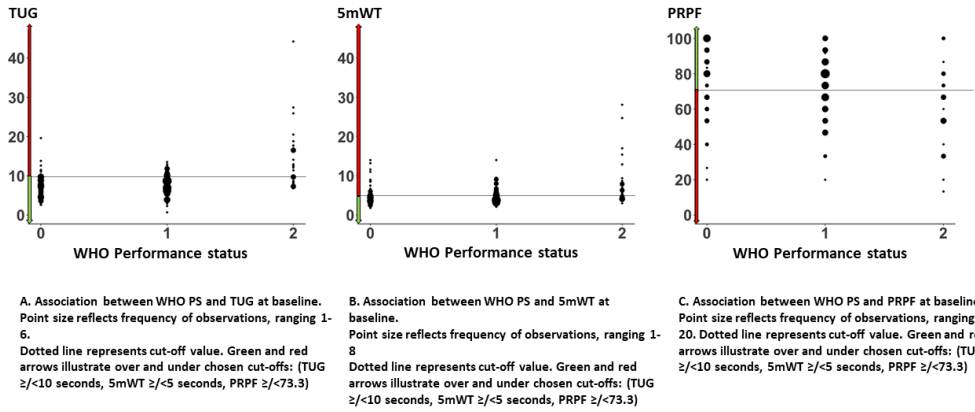


**Figure 2.** Associations between WHO performance status and timed up and go, 5-meter walk test, and patient-reported physical function.

### 3.4. 5-Meter Walk Test (5 mWT)

The median 5 mWT was 4.5 s (range 1.8–28.1 s). Seventy-seven (37%) had 5 mWT ≥ 5 s. There was no difference between men and women or patients with stage IIIB or IV disease. Patients with poor WHO PS had a longer 5 mWT: WHO PS 0: median 4.4 s (range 1.8–14.0 s), WHO PS 1: median 4.1 s (range 2.1–14.0 s), and WHO PS 2: median 6.1 s (range 3.0–28.1 s) (Table 1). The associations between WHO PS and 5 mWT are illustrated in Figure 2B. The largest variation in 5 mWT was observed among patients with WHO PS 2.

### 3.5. Patient-Reported Physical Function (PRPF)

The QLQ C30 was completed at baseline by 173 (83%) patients. The mean PRPF was 72.2 (95% CI 69.3–75.2), and the median was 73.3. There was no significant difference in mean PRPF between men and women, but patients with stage IIIB reported better PRPF than patients with stage IV (83.0 vs. 71.5). Patients with a poor WHO PS had a lower mean PRPF: WHO PS 0: 78.5, WHO PS 1: 72.7, and WHO PS 2: 58.8 (Table 1). The associations between WHO PS and PRPF are illustrated in Figure 2C. There was a large variation in PRPF among patients independent of WHO PS.

### 3.6. Association between TUG, 5 mWT, PRPF, and WHO PS

A worse TUG and 5 mWT was significantly associated with lower PRPF, but variation in physical tests only partly explained the variation in PRPF (TUG versus PRPF: R2 = 0.11, $p < 0.01$; 5 mWT versus PRPF: R2 = 0.10, $p < 0.01$). The association between TUG and

5 mWT was stronger (R2 = 0.23, $p < 0.01$) (Figure 3D–F). Several patients with good physical function according to TUG or 5 mWT reported a low PRPF (Figure 3D,E).

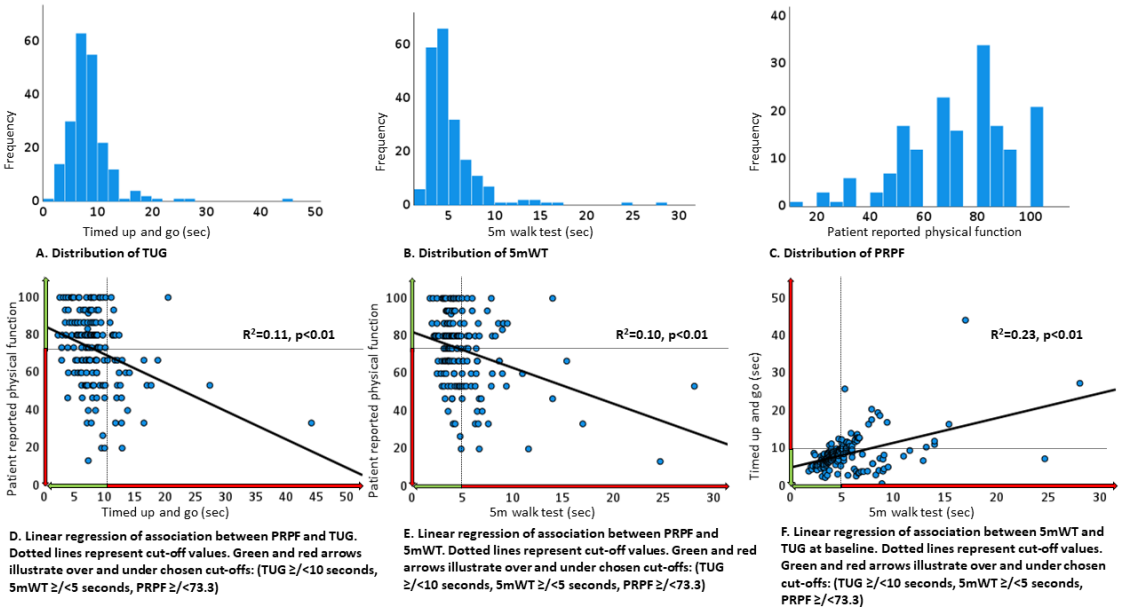


**Figure 3.** Physical performance tests and patient-reported physical function at baseline.

There was less variation in TUG or 5 mWT among patients with WHO PS 0 and 1 than among patients with WHO PS 2, but a wide range of values was observed for all WHO PS categories (Figure 2A,B).

### *3.7. Overall Survival*

Median OS was 10.0 months (95% CI 8.82–11.18) for the whole study population. Median follow up time was 36.2 months (95% CI 33.0–39.3). Neither sex ($p = 0.42$) nor stage of disease ($p = 0.14$) was significantly associated with survival. A poor WHO PS was significantly associated with shorter survival both in uni- and multivariable models (PS 2 vs. 0: $p < 0.01$) (Table 2). When entered as continuous variables in univariable models, poor physical function was associated with shorter survival: TUG: HR 1.05, $p < 0.01$, 5 mWT: HR 1.05, $p = 0.03$, PRPF: HR 1.01, $p < 0.01$. In multivariable analysis, only PRPF remained an independent prognostic factor: TUG: $p = 0.18$, 5 mWT: $p = 0.13$, PRPF: HR 1.01, $p = 0.03$ (Table 2). In exploratory analyses, the association between PRPF and survival reached borderline significance when the multivariable model was adjusted for TUG (HR 1.01, $p = 0.05$) or 5 mWT (HR 1.01, $p = 0.05$), but not when it was adjusted for post-study ICI therapy (HR 1.00, $p = 0.42$).

When patients were categorized as having normal or poor physical function, TUG ($p < 0.01$) but not 5 mWT ($p = 0.21$) was significantly associated with survival. In multivariable analyses, neither TUG ($p = 0.07$) nor 5 mWT ($p = 0.41$) were significantly associated with survival. In contrast, a normal PRPF was significantly associated with improved survival both in uni- (HR 1.80, $p < 0.01$) and multivariable analyses (HR 1.60, $p < 0.01$) (Table 3 and Figure 4).

**Table 2.** Survival analyses.

| | | | | Univariable Analysis | | | Multivariable Model with TUG | | | Multivariable Model with 5 mWT | | | Multivariable Model with PRPF | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | (%) | HR | 95% CI | *p*-Value | HR | 95% CI | *p*-Value | HR | 95% CI | *p*-Value | HR | 95% CI | *p*-Value |
| **TUG *** | | 208 | (100%) | 1.05 | 1.02–1.08 | <0.01 | 1.03 | 0.99–1.07 | 0.18 | | | | | | |
| **5 mWT *** | | 208 | (100%) | 1.05 | 1.01–1.10 | 0.03 | | | | 1.04 | 0.99–1.09 | 0.13 | | | |
| **PRPF *** | | 173 | (83%) | 1.01 | 1.01–1.02 | <0.01 | | | | | | | 1.01 | 1.00–1.02 | 0.03 |
| **Age *** | | 208 | (100%) | 1.00 | 0.98–1.02 | 0.94 | 0.99 | 0.97–1.01 | 0.99 | 0.99 | 0.97–1.01 | 0.99 | 0.96 | 0.97–1.02 | 0.67 |
| **Sex** | **Male** | 96 | (46%) | 1 | | | 1 | | | 1 | | | 1 | | |
| | **Female** | 112 | (54%) | 1.13 | 0.84–1.50 | 0.42 | 1.09 | 0.81–1.45 | 0.58 | 1.08 | 0.81–1.45 | 0.61 | 1.06 | 0.76–1.49 | 0.73 |
| **Stage of disease** | **IIIB** | 13 | (6%) | 1 | | | 1 | | | 1 | | | 1 | | |
| | **IV** | 195 | (94%) | 1.55 | 0.86–2.78 | 0.14 | 1.51 | 0.82–2.76 | 0.19 | 1.50 | 0.82–2.74 | 0.19 | 1.21 | 0.65–2.28 | 0.55 |
| **WHO PS** | **0** | 66 | (32%) | 1 | | | 1 | | | 1 | | | 1 | | |
| | **1** | 112 | (54%) | 1.45 | 1.04–2.02 | 0.03 | 1.51 | 1.07–2.12 | 0.02 | 1.56 | 1.11–2.19 | 0.01 | 1.38 | 0.94–2.02 | 0.10 |
| | **2** | 30 | (14%) | 2.57 | 1.63–4.06 | <0.01 | 2.25 | 1.32–3.83 | <0.01 | 2.44 | 1.51–3.96 | <0.01 | 2.11 | 1.23–3.62 | <0.01 |

* Entered as a continuous variable. TUG—timed up and go; 5 mWT—5-meter walk test; PRPF—patient-reported physical function.

**Table 3.** Differences in survival according to cutoff values for measured and patient-reported physical function.

| | Median OS | 95% CI | HR Univariable Model | 95% CI | *p* | HR Multivariable Model | 95% CI | *p* |
|---|---|---|---|---|---|---|---|---|
| TUG < 10 sek | 10.4 | 8.6–12.2 | 1 | | | 1 | | |
| TUG ≥ 10 sek | 6.3 | 3.9–8.7 | 1.74 | 1.23–2.47 | <0.01 | 1.43 | 0.97–2.10 | 0.07 |
| 5 mWT < 5 sek | 10.4 | 8.4–12.3 | 1 | | | 1 | | |
| 5 mWT ≥ 5 sek | 9.6 | 7.6–11.5 | 1.21 | 0.90–1.63 | 0.21 | 1.14 | 0.84–1.55 | 0.41 |
| PRPF ≥ median | 12.2 | 8.6–15.6 | 1 | | | 1 | | |
| PRPF < median | 8.2 | 6.1–10.2 | 1.8 | 1.31–2.49 | <0.01 | 1.6 | 1.14–2.24 | <0.01 |

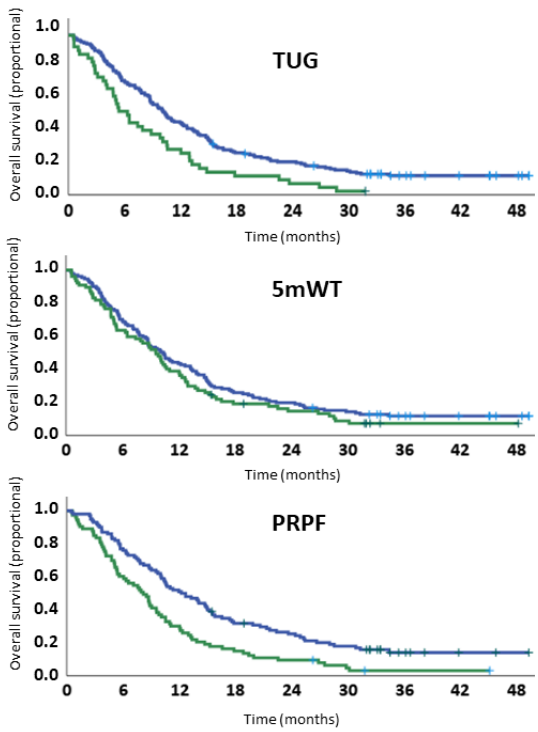


**Figure 4.** Survival curves according to cutoff values for measured and patient-reported physical function.

### 3.8. Disease Control

Treatment response was evaluated in 179 (86%) patients. Overall, disease control was achieved in 109/179 (61%) patients and in 92/149 (62%) patients that completed PRPF at baseline. TUG, 5 mWT, or PRPF were not statistically significant predictors for disease control in uni- (TUG: $p = 0.66$, 5 mWT: $p = 0.36$, and PRPF: $p = 0.94$) or multivariable analyses (TUG: $p = 0.30$, 5 mWT: $p = 0.69$, and PRPF: $p = 0.13$) (Table S1).

## 4. Discussion

In this study of patients included in our trial of maintenance pemetrexed therapy in advanced non-squamous NSCLC, physical function as measured by TUG and 5 mWT were not independent prognostic factors for survival, while patient-reported physical function (PRPF) was. Patients with a good physical function measured by TUG were more likely to complete four courses and thus be randomized, but none of the measures of physical function were significantly associated with achieving disease control at evaluation after induction chemotherapy.

To the best of our knowledge, this is the first study investigating whether the measured physical function is an independent prognostic factor in patients with advanced non-squamous NSCLC receiving palliative platinum-doublet chemotherapy, including analyses adjusting for established prognostic factors, baseline characteristics, and treatment completion.

Several studies have investigated the associations between TUG or gait speed and OS in patients with cancer, including two recent systematic reviews (Verweji et al. in 2016 and Ezzatvar in 2020); the latter also included a meta-analysis [7,8]. Seven of the studies included in these reviews analyzed patients with NSCLC, with a proportion ranging between 8 and 100% [6,11,20–24].

Four of these studies analyzed TUG in patients with advanced NSCLC that received chemotherapy [6,11,20,21]. As in our study, TUG was a prognostic factor for survival in univariable analyses. However, in the only study including multivariable analyses, TUG was also found to be an independent prognostic factor. In contrast to our cohort, only 28 out of 348 patients had NSCLC in that study [11].

In studies investigating gait speed, the association with survival is less consistent [22–25], and gait speed was not an independent prognostic factor in a study (n = 112) in which 24% of patients had lung cancer, 44% stage III-IV disease, and 26% received palliative chemotherapy [24]. However, differences in patient selection and the use of different tests for measuring gait speed make it difficult to compare results across studies. To the best of our knowledge, no previous studies have investigated the associations between TUG, 5 mWT, or PRPF and disease control.

The fact that objectively assessed physical function was not an independent prognostic factor in our study cohort might be explained by a selection bias; all patients were considered fit for palliative chemotherapy in the setting of an RCT. The median age (67 years) and rate of PS 2 (14%) were lower than seen in the daily clinic. Overall, there was little variation in TUG and 5 mWT, and median TUG (7.8 s) was lower than reported in community-dwelling adults of similar age, height, and weight (9.0 s) [26]. Patients in our study reported relatively high physical function compared to other populations with advanced NSCLC [27]. The limited variation and overall good physical function might have limited the chances of detecting clinically relevant associations.

The fact that PRPF was an independent prognostic factor is consistent with previous studies [5,6], and it might be that PRPF better reflects changes in physical function or how the physical function is compared with the patients' former or habitual daily function. Consequently, it may be more sensitive to disease-specific changes and, thus, holds more prognostic information than TUG and 5 mWT. Interestingly, many patients with good physical function according to TUG or 5 mWT reported a poor PRPF, indicating that PRPF includes other aspects than TUG and 5 mWT. Patients with a poor WHO PS were more

likely to report a poor PRPF, but the prognostic information from PRPF was independent of WHO PS in multivariable analyses.

Despite being the largest of its kind, this study is still limited by size. Although patients received the same first-line treatment, differences in post-study therapy might have influenced our results. ICI therapy for advanced NSCLC was introduced in Norway during the enrolment period, and the availability of ICI varied with time and between hospitals. Patients with a normal PRPF were more likely to receive ICI therapy, and fitness for such treatment might explain the improved survival among these patients, supported by the fact that PRPF was no longer an independent prognostic factor when adjusting for the use of ICI in the exploratory multivariable model.

Another possible limitation is that not all patients completed the physical functions tests or reported their physical function. However, we believe that a completion rate for physical tests of 90% is quite good in a multicenter RCT, and patients with missing data did not differ from other patients with respect to age, gender, WHO PS, or disease stage (data not shown). Our results are based on an RCT from the pre-ICI era, but they are still relevant since many patients with advanced NSCLC still receive platinum-doublet chemotherapy, either combined with ICIs in the first-line setting or as salvage therapy.

In conclusion, measuring TUG and 5 mWT did not provide clinically relevant predictive or prognostic information in patients with advanced non-squamous NSCLC receiving platinum-doublet chemotherapy. TUG and 5 mWT held less prognostic information than physical function (PRPF) reported by patients on the EORTC QLQ C30.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/healthcare10050922/s1, Table S1: Physical performance as predictor of disease control.

**Author Contributions:** B.H.G. and T.O.H. conceived and designed the work and acquired data and handled funding and supervision. K.S. performed the statistical analyses and drafted the manuscript. All authors played an important role in interpreting the results. All authors revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** The study was conducted in accordance with the Declaration of Helsinki and approved by the Regional Committee for Medical Research Ethics Central Norway (protocol code 2013/645, date of approval; 1 May 2013).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data that support the finding of this study are available from the corresponding author; KS, upon reasonable request.

**Conflicts of Interest:** The authors declare no conflict of interest.

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