Survival and Quality of Life in the Treatment of Patients with Non-Small Cell Lung Cancer

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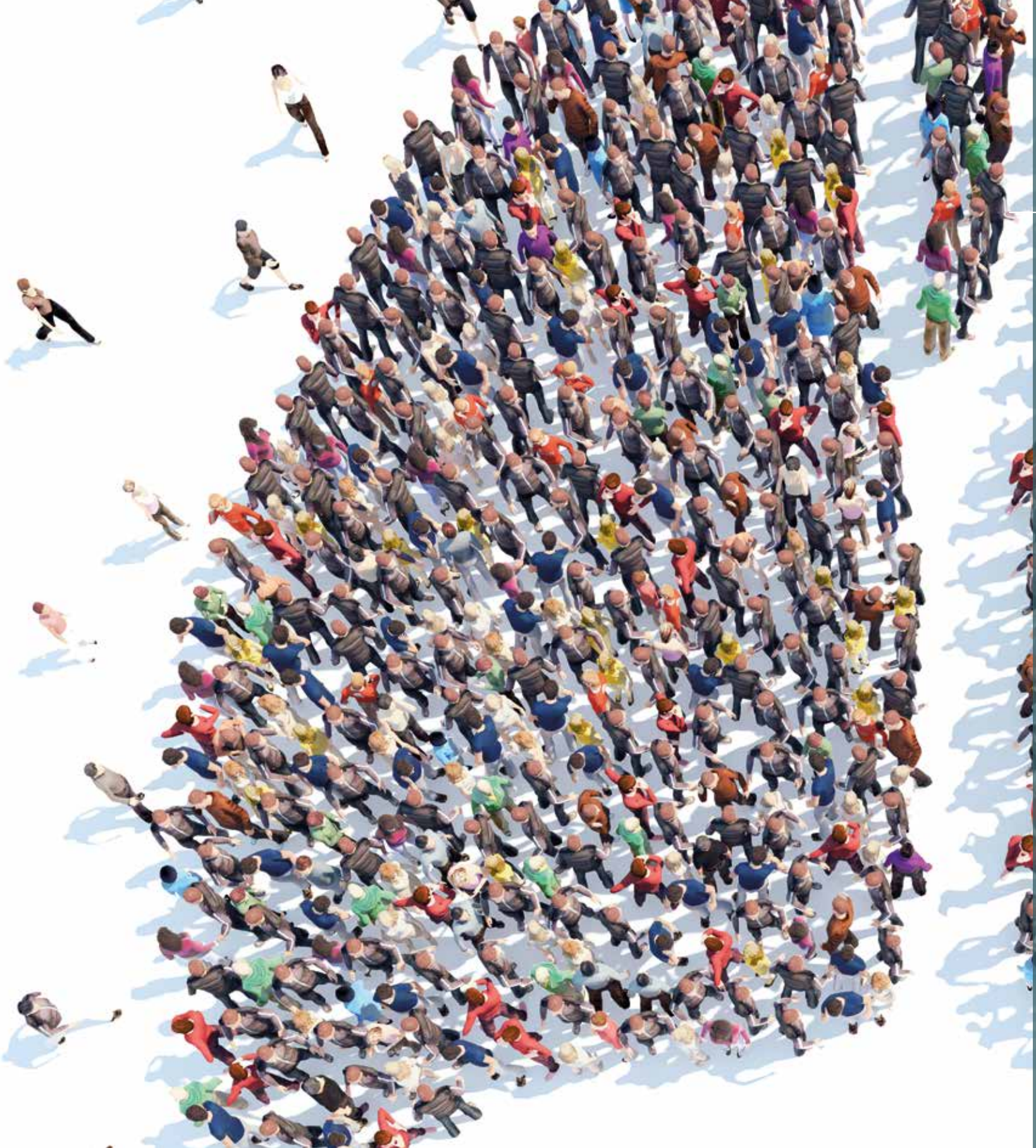

CHAPTER 1

General introduction

GENERAL INTRODUCTION

This thesis focuses on the treatment of advanced stage non-small cell lung cancer (NSCLC) as administered in real-life clinical practice. Background information pertaining to NSCLC will be elucidated, alongside an outline detailing specific subgroups of patients for whom active anti-tumor treatment may deviate from the standard approach applied to the majority of NSCLC patients. Furthermore, the discussion will delve into the merits of real-world studies and underscore the importance of quality of life (QoL) considerations within the context of cancer treatment.

GENERAL BACKGROUND OF LUNG CANCER

Lung cancer is the second most diagnosed malignancy worldwide in both men and women, following prostate and breast cancer respectively. More than 2.2 million patients receive a diagnosis of lung cancer annually. It is the leading cause of cancer deaths, with an estimated 1.8 million deaths (18% of all cancer related deaths) recorded in 2020, worldwide.[1]

In the Netherlands, lung cancer ranks as the third most diagnosed malignancy in both sexes, following prostate, breast, and skin (excluding basal cell carcinoma) cancer, with an incidence of proximately 14,000 new patients each year. The annual death rate from lung cancer stands at approximately 10,000 patients, rendering it the leading cause of cancer related deaths.[2,3] While the incidence is notably higher among men, there has been a concerning rise in incidence among female patients over the last decades, attributed to the increase of self-inflicted smoking habits among women. Moreover, these figures are expected to escalate in the forthcoming decade due to an ageing population, characterized by increased frailty, coupled with historical exposure to elevated, albeit now diminishing, concentrations of air pollution from various sources. Consequently, the burgeoning impact of lung cancer on local healthcare facilities is increasing, necessitating substantial resources for treatment and care, while significantly affecting QoL for affected individuals.[4]

Within the total cohort of patients with lung cancer, non-small cell lung cancer (NSCLC) comprises the majority, constituting approximately 68% of cases, while small cell lung cancer (SCLC) accounts for 12%. The remaining 20% of cases are attributed to less common subtypes or are diagnosed solely based on clinical features without histopathological confirmation. The latter scenario is more prevalent among elderly and/or frail patients.[2]

Tobacco smoking is considered as the primary contributing factor to the onset of lung cancer across all major histopathological subtypes. Persistent smokers face a staggering 20-50 times higher risk of developing lung cancer compared to individuals who have never smoked, with this risk decreasing in former smokers.[5] However, it's essential to recognize that not all tobacco exposition is voluntary; exposure to second-hand smoking during childhood or adulthood significantly elevates the lifetime risk of lung cancer.

Another important contributor to lung cancer risk is air pollution. Long-term exposure to particulates with an aerodynamic diameter ≤10μm (PM_{10}) and nitrogen dioxide (NO_2) has been associated with lung cancer mortality in the Dutch population ≥30 years of age.[6]

While there may be genetic implications, genome-wide association studies reveal substantial heterogeneity across histological subtypes (such as SCLC, adenocarcinoma, squamous cell carcinoma) and ethnicities (such as European versus Asian). This complexity suggests a multifaceted biological interplay between ancestry and various environmental factors, including smoking and air pollution, leading to diverse oncogenic mechanisms.[7] Furthermore, the interaction between smoking status and air pollution extends to dietary and other lifestyle factors, the precise effects of which remain unclear at present.[8]

For the staging of lung cancer, the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) employ a stage classification system, utilizing data provided by the International Association for the Study of Lung Cancer (IASLC). This system is universally applied, ensuring consistency in staging practices globally, and undergoes periodically refinement to align with advancements in the treatment modalities. The current eighth edition of this staging system was implemented in clinical practice as of January 2017 and serves as the basis for staging assessment in this thesis.[9] The forthcoming update (ninth edition) is anticipated to be introduced in early 2025.[10]

The disease staging process for lung cancer involves evaluating three primary characteristics: T(umor), which considers the size or extent of local invasion; N(ode), which assesses regional lymph node involvement; and M(etastasis), which examines the presence of distant metastases, whether intra- or extra thoracic. Each component is categorized into subgroups (e.g. T0-4, N0-3, M0-1c), with higher numbers indicating a greater extent of the disease. Collectively, these TNM factors are utilized to assign patients into staging groups, ranging from stage I (localized disease without lymph node involvement) to IV (metastasized disease).[9]

Regrettably, in 2019 48% of all Dutch NSCLC patients were diagnosed at stage IV, compared to 20%, 8%, and 24% for stages I, II, and III, respectively. The overall survival (OS) rates for Dutch patients with NSCLC between 2015-2019, irrespective of treatment were 53% at 1 year and 26% at 5 years. However, OS rates significantly declined when assessed per stage. For instance, the 1- and 5-year OS rates for patients diagnosed with stage I disease were 93% and 67%, respectively, in stark contrast to 29% and 8% for those with stage IV disease.[2]

DISEASE SPECIFIC SUBGROUPS

Over the past decade, the treatment landscape for patients with stage IV NSCLC has changed dramatically. Previously, treatment strategies primarily relied on chemotherapy often guided by histopathology (squamous versus non-squamous carcinoma). Currently, the approach encompasses a diverse array of systemic therapies, contingent upon molecular tumor characteristics. Initially, all stage IV NSCLC patients should be screened for actionable molecular alterations, such as mutations in KRAS, EGFR, BRAF, HER2, and MET or fusions of ALK, ROS1, RET, NTRK1-3, and NRG1, to have insights regarding targeted therapy options (Table 1.1).[11–13] These molecular findings should then be combined with testing for PDL1 expression. In patients with high PDL1 scores (>50%) without actionable targets, checkpoint inhibition is possible. If PDL1 score is lower chemotherapy is added.[14] Beside actionable targets, other mutations result in inactivation in tumor suppressor genes, such as

STK11 and KEAP1, are also associated with lack of immunotherapy efficacy.[11,15,16] In the Netherlands, a list of clinical necessary molecular tests has been adopted and approved by the different stakeholders in August 2023 and adapted several times in 2024.[17] The incidence of driver mutations is varying across the globe, with a higher incidence of EGFR mutations in Asia compared to Europe (47% versus 15%) and KRAS being more common in Europe (26% versus 11%).[18,19] Table 1.1 summarizes the real-world OS of patients with a targetable mutation, with treatment with target therapy provided by general care or from clinical trials.

Table 1.1 Incidence, commonly available drugs in general care in the Netherlands, and real-world median overall survival for patients with stage IV (mutated) NSCLC.

	Incidence (%)[20,21]	Available drugs[17]	Median OS (months (95% CI))
Wildtype[22]	44.9	Chemo- and/or immunotherapy	16.8 (N/A)
KRAS (G12C)[23]	33.0 (13.0)	Sotorasib	16.8 (12.7-22.3)
EGFR (common)[24]	11.0	Erlotinib (+ramucirumab or bevacizumab), gefitinib, afatinib, osimertinib, dacomitinib, amivantamab (2nd line Ex20 only)	22.8 (21.1-24.8)
EGFR (Ex20)[25]			17.0 (11.2-19.5)
EGFR (other) [26]			12.2 (9.4-15.0)
BRAF[27]	4.0	Dabrafenib + trametinib	56.5 (13.4-89.1)
ALK[28]	2.0	Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	48.0 (12.9-83.0)
MET ex14 skipping[29]	2.0	Tepotinib	27.1 (18.0-29.7)
ROS1[30]	0.6	Crizotinib	24.3 (12.1-NR)
RET[31]	0.5	Selpercatinib	34.3 (N/A)
NTRK[32] *	0.2	Entrectinib, larotrectinib	41.5 (30.9-NR)

* As no real-world data is available, RCT data is shown

In patients with an EGFR mutation, it is notable that approximately 90% of these mutations consist of deletions in exon 19 (Ex19del) or a single point mutation in exon 21 (L858R). Extensive research has shown that these common mutations correlate with better outcomes compared to other, uncommon EGFR mutations.[26] Furthermore, there is evidence suggesting that patients with Ex19del exhibit a superior OS compared to those with L858R mutations. This discrepancy in prognosis may stem from disparities in the biological behavior induced by the structure of the mutation itself, potentially resulting in a more aggressive phenotype. Alternatively, it could reflect variations in the effectiveness of TKI treatments across different mutation types.[33,34]

Treatment with EGFR-TKIs became available starting in 2004, with the introduction of the first-generation TKIs erlotinib and gefitinib as treatment for unselected NSCLC patients. Initial trials failed to show a significant OS advantage with these agents. However, after the discovery of the EGFR mutation as an active driver of tumor proliferation, a clear survival benefit was shown.[35,36] Whereas both erlotinib and gefitinib bind reversibly to the EGFR receptor, the second generation TKI afatinib binds irreversibly. Despite the difference in

binding mechanism, direct comparison in the LUX LUNG 7 trial did not reveal any disparity in OS between both generations TKI.[37] By the end of 2019, the third-generation EGFR-TKI osimertinib emerged as superior to first-generation TKIs in patients harboring common Ex19del and L858R mutations in the FLAURA trial. Subsequently, osimertinib was implemented as first-line treatment in the Netherlands.[38] However, although the progression-free survival (PFS) favored osimertinib, OS rates showed only borderline significant (hazard ratio (HR) 0.46 (95% confidence interval (CI) 0.37-0.57) and HR 0.80 (95% CI 0.64-1.00), respectively). In addition, superior OS was observed only in patients with an Ex19del mutation (HR 0.68 (95% CI 0.51-0.90)), with no significant difference noted among those with L858R mutations (HR 1.00 (95% CI 0.71-1.40)).[39]

To enhance the efficacy of the first generation EGFR TKI, two phase III studies analyzed the effects of concurrent gefitinib with carboplatin plus pemetrexed versus gefitinib alone as first-line treatment, showing superior PFS and OS in patients with Ex19del but not in those with L858R mutations.[40,41] However, a significant concern regarding this concurrent approach arose from preclinical data, indicating potential interference between EGFR TKIs and chemotherapy in EGFR mutated NSCLC. Preclinical evidence suggests that the cell cycle phase effects of chemotherapy may be attenuated by EGFR TKIs, owing to cell cycle arrest induced by the latter.[42] However, when administered sequentially, considering biological availability and half-life, the treatment effects of pemetrexed and erlotinib may exhibit synergy, potentially leading to even greater enhancement of PFS and OS compared to those demonstrated in these concurrent trials.[43]

Randomized clinical trials (RCTs) are characterized by clear in- and exclusion criteria resulting in a homogenous study population. However, a notable limitation of RCTs is their tendency to enroll younger and healthier patients from the overall patient pool.[44,45] While this approach allows for the measurement of clean biological and clinical effect without confounding factors, it does not fully represent the diversity encountered in daily clinical practice. Clinicians frequently encounter patients who do not meet the strict criteria set by RCTs. For example, patients with (active) brain metastasis, a common occurrence in NSCLC, are often excluded from RCTs.[46] Real-world studies, in contrast, encompass the full heterogeneity of patient groups encountered in clinical practice. However, they are plagued by inherent methodological challenges. Being observational and often retrospective in nature, these studies may suffer from inadequate structuring of data collection or incomplete recording of key variables, thus compromising the reliability and validity of their findings.[47]

Studies have demonstrated that the OS of patients without a targetable mutation treated with first line chemo- or immunotherapy in the real-world setting is significantly shorter than that of patients included in clinical trials. Conversely, the real-world OS outcomes of patients with EGFR-mutated NSCLC treated with first line EGFR TKIs shows heterogeneity when compared to findings from clinical trials.[48–50] The results of real-world studies present conflicting results when comparing different types of EGFR mutations or different EGFR-TKIs such as erlotinib, gefitinib and afatinib. Notably, there is a scarcity of studies including osimertinib, particularly among patients with brain metastasis.[51–54]

PATIENT SPECIFIC SUBGROUPS

When assessing treatment options for patients, the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) Scale is commonly used to gauge a patient's functional capacity, encompassing their ability to care for themself, engage in daily activities, and manage physical functioning. Adopted by the World Health Organization (WHO), the ECOG PS scale comprises five grades scale, ranging from 0 (fully active) to 5 (deceased). A PS status of 1 indicated restricted physical activity but the patient is able to carry out light work, while PS 2 signifies ambulatory status and self-care capability, yet unable to carry out any work activities for up to 50% of waking hours. Patients with PS 3 exhibit limited self-care and spent over 50% of waking hours bedridden or confined to a chair, whereas those with PS 4 are completely disabled.55 Patients with a targetable mutation can be treated even with a PS of 3-4, given the mild toxicity profile of TKI and high overall response rates, which typically manifest rapidly.[11] In contrast, patients with stage IV NSCLC without a targetable mutation and with PS 0-1 are eligible for immunotherapy with or without chemotherapy. In those with high PDL-1 expression and low tumor burden, immunotherapy alone may be considered. However, patients with PS 3-4 typically receive best supportive care (BSC).[14] Patients with PS 2 are often excluded from randomized clinical trials (RCT) due to their poorer outcomes and increased toxicity compared with those with PS 0-1. Therefore, newer anticancer agents, such as immunotherapy, are reserved for those with PS 0-1, with chemotherapy being the primarily recommendation for patients with PS 2.[14,56,57] There is no clear preferred chemotherapy regimen, European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) clinical guidelines suggest both platinum doublet chemotherapy and non-platinum monotherapy as a possible treatment option.[14,58]

Given that lung cancer predominantly affects older individuals (with 69% of Dutch NSCLC patients being at least 65 years old at the time of diagnosis) and considering the ageing population in the Netherlands, it is expected that the number of patients aging >75 years will double in the coming years. This demographic shift suggests that there will be a substantial increase in the number of patients with higher rates of comorbidities and diminished performance and health status, indicating a sizeable population of frail patients. Therefore, it is imperative to establish clear treatment strategies for these patients. This may involve conducting RCTs including frail patients and those with PS 2 or utilizing retrospective real-world data. As the use of electronic health records is rapidly increasing, larger databases are becoming available, facilitating the feasibility of such endeavors.

In the last years, there has been a shifting focus in cancer care towards optimizing QoL as an important outcome measure. There is a growing need for data that delve into the various domains of QoL, including physical, social, emotional, functional aspects, as well as the decisions patients make regarding their treatment.[59,60] This shift is significant is because, for patients, the impact of treatment on their active life expectancy may just as crucial as extending their overall lifespan.[61] The advent of immunotherapy and target therapy has brought about a notable change in long-term survivorship for certain patient subgroups. For instance, in patients with stage IV NSCLC historically treated with chemotherapy, the 5-year OS rate was approximately 5%. However, in the immunotherapy arm of the KEYNOTE-024 trial (comparing first line pembrolizumab versus platinum chemotherapy in patients with PDL1 >50%), this rate increased to 32%.[9,62] Similar improvements have been observed in patients with EGFR-mutated NSCLC, with a 3- and 5 year OS rate of 41% and 22%, respectively.[63] Nevertheless, the occurrence of relatively low-grade adverse events associated with immunotherapy or TKIs over an extend period of time could potentially lead to physical disabilities, resulting in a decline of QoL. Despite this, treatment is often continued for prolonged periods due to favorable treatment responses and prolonged overall survival.[64] As the group of long-term surviving cancer patients continues to grow, it becomes increasingly vital to gain better understanding of influence of long-term treatment and survival on QoL and other aspects of cancer survivorship. This knowledge will be crucial in informing treatment decisions and optimizing the overall well-being of cancer survivors.

SCOPE OF THIS THESIS

The overarching objective of this thesis is to identify advancements in cancer care for patients with stage IV NSCLC, with a focus on assessing long-term OS, treatment toxicity, and QoL. This research will particularly concentrate on patients with EGFR-mutated stage IV NSCLC, as well as those without an EGFR mutation with poor performance (PS 2).

In **Chapter 2,** we postulate that the real-world outcomes of Dutch patients with advanced EGFR-mutated NSCLC, undergoing first-line TKI treatment, are akin to those reported in other European real-world studies but fall short when compared to Asian series. This discrepancy arises from variations in the incidence of various EGFR mutations and the efficacy of TKI as observed in clinical trials worldwide. In a retrospective study we will utilize data extracted from the Netherlands Cancer Registry (NCR), offering nationwide real-world data on patient and disease characteristics. Additionally, this chapter will summarize all available series reporting OS for patients with EGFR mutated NSCLC, primarily treated with TKI.

In **chapter 3** we will further explore the real-world OS of Dutch patients with advanced EGFR-mutated NSCLC harboring an EGFR Ex19del or L858R mutation. We hypothesize that the introduction of the third generation EGFR TKI osimertinib in 2018 improved the real-world OS compared to treatment with first- and second generation TKI. The influence of mutation type and the presence of brain metastasis at baseline on survival benefit are also assessed using data from the NCR.

In **chapter 4** we present the results of the phase III NVALT17 trial, which examines the efficacy of intercalated erlotinib with chemotherapy compared to erlotinib monotherapy in untreated patients with advanced EGFR-mutated NSCLC. The study hypothesized that this combinations regime may offer superior outcomes in terms of response rate, PFS, OS, and toxicity.

In **chapter 5**, the focus shifts to describing the overall QoL, treatment satisfaction, and motives of a real-world population of long-term survivors (more than three years after diagnosis) with stage IV EGFR-mutated NSCLC. The study aims to understand the unique challenges and perceived health care experiences of this group through general questionnaires and semi-structured interviews covering various aspects of their cancer journey.

Chapter 6 involves a systemic review (part A) assessing first-line therapies for advanced NSCLC in patients with PS 2 without a targetable mutation or with unknown mutation status. The study aims to compare platinum doublet therapy with non-platinum monotherapy in terms of OS, PFS, and toxicity/adverse events using Cochrane's method. In part B, we highlight important caveats in a recent study assessing immunotherapy in patients with PS 2.

Chapter 7 summarizes the main findings of this thesis and provides insights into future perspectives and directions for further research in this field.

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CHAPTER 2

Nationwide real-world cohort study of first-line tyrosine kinase inhibitor treatment in epidermal growth factor receptor-mutated non-small cell lung cancer

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ABSTRACT

Background

Only a few randomized trials directly compared the relative efficacy of tyrosine kinase inhibitors (TKI) in patients with advanced epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) and most trials comprised selected series from Asian populations. Therefore, the aim of this study was to assess OS of advanced EGFR mutated NSCLC in a large White population and to evaluate variation between different TKIs and identify predictors of survival.

Patients and methods

Information about clinical characteristics, treatment and survival for 873 patients with stage IV EGFR+ NSCLC, diagnosed from 2015 through 2017, was derived from the Netherlands Cancer Registry. Overall survival was evaluated by actuarial analysis and multivariable Cox regression. Prognostic factors are reported as hazard ratios (HR) and 95% confidence intervals (CI).

Results

A total of 596 (68%) patients received first-line treatment with regular TKIs providing a median survival of 20.2 months. 45% of patients were 70 years and older and 54% of patients had distant metastasis in multiple organs. In the multivariate analysis, survival was significantly worse for men, higher age, poorer performance and >=3 organs with metastasis. Compared to erlotinib, overall survival was worse for gefitinib users (adjusted HR 1.30, 95% CI 1.02-1.64), predominantly in patients with brain metastasis.

Conclusion

Dutch patients with EGFR mutated NSCLC who received first-line treatment with regular TKIs have a median OS of 20.2 months in a nationwide real-world cohort. In patients with brain metastasis, erlotinib showed superior results compared to gefitinib and was similar to afatinib.

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the most common cause of cancer related death worldwide, despite the rapid development of new therapies.[1] For NSCLC harboring an epidermal growth factor receptor (EGFR) mutation, first (erlotinib, gefitinib) and second generation (afatinib, dacomitinib) tyrosine kinase inhibitors (TKI) resulted in a significant higher response rate and prolonged progression free survival (PFS) in randomized clinical trials compared to standard chemotherapy, but overall survival (OS) did not differ.[2] Recently, the third generation EGFR TKI osimertinib was registered as first line treatment of EGFR mutated NSCLC, which showed a prolonged OS compared to standard TKIs.[3]

Direct head-to-head comparisons of the different first- and second-generation EGFR TKIs are scarce. A meta-analysis which summarized direct analysis between gefitinib and erlotinib showed no difference in OS. Also, the OS in the subgroup of patients with cerebral metastasis (6 studies, 303 patients) did not differ between treatments with erlotinib or gefitinib as these drugs hardly pass the blood-brain barrier.[4] As first line treatment, a direct comparison between gefitinib and afatinib showed no difference in OS and PFS, except for a small long responder subgroup. In patients with cerebral metastasis, this study showed no OS differences.[5] Another study reviewed results in patients with uncommon EGFR mutations and concluded that afatinib tends to perform better than first generation TKIs.[6] This was also found in a large retrospective Canadian population based study.[7]

While it is clear that TKIs are effective in treatment of EGFR mutated NSCLC, when extrapolating data from clinical trials to our (mainly White[8]) patients a number of difficulties arise. The incidence of EGFR mutations differs across the globe, with a higher rate in Asians (47%) than in patients from the United States (22%) and Europe (15%).[9] Moreover, the relative frequency of various EGFR mutations (exons 18 through 21) tends to vary across continents.[10,11] Most trials evaluating EGFR TKIs were performed in Asia.[2] Only a few studies were performed in a European cohort, showing that treatment with TKIs improved PFS, but could be more effective in Asian populations.[12,13]

A second limitation is that results from clinical trials cannot be directly extrapolated to a general population, as outcomes are generally assessed in a highly selected population of relatively fit and younger patients or excluding patients with (symptomatic) brain metastasis.[14,15] A recent study by Cramer et al. shows that survival in real-world surveys is nearly one-quarter shorter than for patients in clinical trials.[16]

Therefore, the primary aim of this study was to assess contemporary overall survival of Dutch patients (mostly White population) with stage IV EGFR mutated NSCLC in order to compare the outcome with international real -world series. The secondary aim was to identify predictors of survival as age, performance score, type of TKI and disease characteristics such as the location of metastasis.

PATIENTS AND METHODS

Data and procedures

This is a retrospective, non-interventional, population-based study from the Netherlands. The Netherlands have a population of 17 million inhabitants, mainly White and including approximately 6% from Asian descent.[8] All patients diagnosed with any type of cancer are registered in the Netherlands Cancer Registry (NCR). A standardized dataset is collected from patient records consisting of basic patient and disease characteristics, including histology, TNM stage, WHO Performance Score (PS), site(s) of metastasis and type of first line treatment. Information on overall survival is obtained by annual linkage with the population registry. Data on treatment response, progression, second line treatment and cause of death is not available.

From the NCR, we selected all patients diagnosed between January 1, 2015 and December 31, 2017, with stage IV NSCLC and having an EGFR mutation, excluding patients with complex multiple mutations (e.g. EGFR + KRAS). Information on EGFR mutation subtypes and EGFR testing procedure was not available. Prior evaluation of pathology reports revealed that 79% of patients with advanced non-squamous NSCLC had been tested for EGFR in 2015.[17]

The primary endpoint of this study was OS, calculated from the day of starting TKI, with follow up until February 1st, 2019. For the overview of general characteristics, OS was calculated from the day of diagnosis.

For the evaluation of the primary endpoint, the analysis was restricted to the patients who received primary treatment with then regularly available TKIs (gefitinib, erlotinib or afatinib). Patients treated with experimental agents (including osimertinib at that time) or for whom type of TKI was not recorded were excluded from the main analysis.

Considering its retrospective and non-interventional nature, this study does not require approval from an accredited medical ethics committee (MEC) or the Central Committee on Research involving Human Subjects (CCMO). However, the study has been reviewed and approved by the Privacy Review Board of the NCR (application number K19.125).

Literature search

For comparing our results to other real-world observational studies, a global review of literature was performed using a combination of the following general keywords in PubMed: “lung cancer”, “EGFR”, “real world” and/or “observational”.

Statistical analysis

Categorical variables were tabulated and reported as proportions. Associations between categorical variables were tested for significance with the chi-square test.

The Kaplan-Meier method was used to estimate median and two-year OS, including 95% confidence intervals (CI). For patients treated by regular first line TKI, prognostic factors were assessed by multivariable Cox regression and results are reported as hazard ratios with 95% CI. Variation between TKIs was additionally assessed after stratification by organ of metastasis, controlling for gender, age, WHO PS, histology and number of metastatic organs in multivariable Cox regression. To allow comparison with trial series, variation between TKIs was also assessed after exclusion of patients with brain metastasis. A p-value of <5% was considered as significant.

RESULTS

From 2015 through 2017, 873 patients were diagnosed with stage IV NSCLC and an EGFR mutation. General patient characteristics are shown in table 2.1. The majority of patients were female (65%) and 45% were aged 70 years or older. In 590 (68% of all) patients a PS was recorded, with a PS of 0-1 in 482 (82%) patients. Median time between diagnosis and start of TKI treatment was 25 days. In five patients, start of TKI treatment was not recorded but imputed at 25 days.

Most patients (70%) received first line treatment with a TKI, whereas 141 (16%) patients received first line chemotherapy and 123 (14%) received other treatment or best supportive care (BSC) only. Most common type of TKI was erlotinib (n=320), whilst 177 patients received gefitinib and 99 afatinib. 12 patients were treated with another or unknown type of TKI as first line therapy and were therefore excluded. Use of afatinib was increasing during the study period.

Median survival from day of diagnosis was 20,2 months (95% CI 17,8-23,2) for patients treated with a regular available TKI as first line treatment (n=596), 21,2 months (95% CI 18,6-24,5) for patients treated with any TKI (n=608) and 18,5 months (95% CI 15,5-21,1) for patients treated with first line chemotherapy (n=142). For patients receiving BSC only, with or without palliative radiotherapy on the primary tumor or metastatic sites, median survival was only 2,7 months (95% CI 2,0-3,8).

Fourteen patients (2,3%) died within 30 days. Survival was favorable for patients who were female, of younger age (<80 years) and those with a better PS (table 2.2). Survival was inferior for patients with non-adenocarcinoma histology and those with 3 or more organs affected with distant metastasis. In comparison with erlotinib, survival for gefitinib (HR 1,30, 95% CI 1,02-1,64) was inferior according to multivariable analysis, whilst results for afatinib did not differ (HR=1,24, 95% CI 0,91-1,68). Two-year survival for gefitinib, erlotinib and afatinib was 43% (95% CI 35-51), 47% (41-52) and 43% (31-54), respectively (figure 2.1).

Table 2.1 General characteristics of 873 patients with EGFR-mutation

		N	%	Median OS* (months)	95% CI
Gender	Men	304	34,8	15,7	13,1-18,3
	Women	569	65,2	18,2	15,9-20,5
Age	18-59	198	22,7	22,0	17,8-27,7
	60-69	281	32,2	17,8	15,3-20,0
	70-79	282	32,3	17,2	14,1-20,4
	80+	112	12,8	7,4	4,8-11,3
WHO PS	0	251	28,8	23,9	20,8-27,7
	1	231	26,4	17,8	15,1-20,4
	2+	108	12,4	7,0	4,3-11,1
	Not specified	283	32,4	13,3	11,3-15,9
Histology	Adenocarcinoma	790	90,5	17,9	16,1-19,6
	Other	83	9,5	10,0	6,5-15,2
Number of	1	401	45,9	19,8	16,9-24,7
metastatic	2	256	29,3	20,1	16,6-22,7
organs	3+	216	25,7	10,4	8,5-12,5
First line	TKI	608	69,8	21,2	18,6-24,5
treatment	Chemotherapy	142	16,1	18,5	15,5-21,2
	Other/BSC	123	14,1	2,7	2,0-3,8

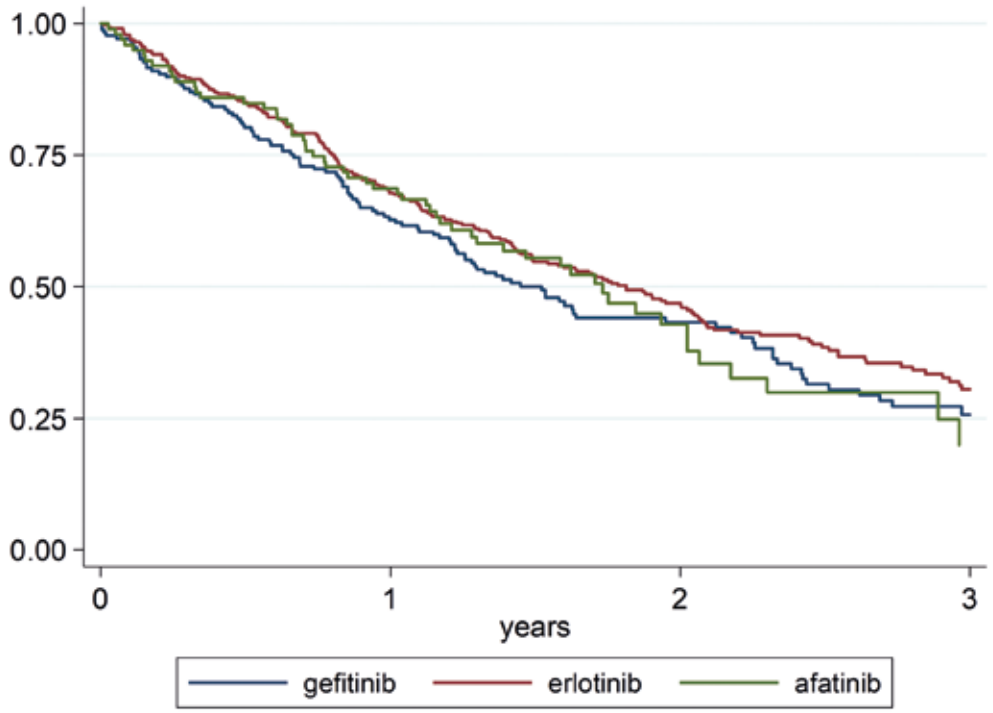
OS = overall survival, CI = confidence interval, WHO PS = WHO performance score, TKI = Tyrosine Kinase Inhibitor, BSC = Best supportive care * = calculated from date of diagnosis

Table 2.2 Prognostic factors for overall survival calculated from start of treatment in patients treated with first line TKI according to multivariable analysis. (N=596)

		N	Median OS (95% CI) (months)	HR	95% CI
Gender	Men	200	17,6 (14,8-20,5)	1	-
	Women	396	22,5 (19,0-26,1)	0.76	0.61-0.95
Age	18-59	145	24,3 (19,7-28,9)	1	-
	60-69	181	18,4 (15,6-24,3)	1.26	0.95-1.69
	70-79	204	20,8 (15,7-27,0)	1.29	0.97-1.71
	80+	66	14,5 (8,8-19,5)	2.00	1.40-2.88
WHO PS	0	186	24,8 (21,0-31,6)	1	-
	1	155	19,6 (16,1-24,3)	1.24	0.94-1.65
	2+	69	12,5 (8,5-20,2)	1.67	1.17-2.39
	NS	186	16,1 (13,2-23,2)	1.42	1.08-1.86
Histology	Adeno	553	20,8 (18,3-24,1)	1	-
	Other	43	11,5 (6,0-21,8)	1.47	1.01-2.14
Number of	1	265	24,5 (19,7-27,8)	1	-
metastatic	2	187	21,8 (19,0-29,0)	1.16	0.90-1.49
organs	3+	144	12,5 (10,3-16,7)	1.98	1.53-2.56
TKI Type	Erlotinib	320	21,8 (17,9-24,7)	1	-
	Gefitinib	177	18,3 (14,7-25,5)	1.30	1.02-1.64
	Afatinib	99	20,8 (15,4-24,3)	1.24	0.91-1.68

HR = Hazard ratio, OS = overall survival , CI = confidence interval, WHO PS = WHO performance score
TKI = Tyrosine Kinase Inhibitor, BSC = Best supportive care

Figure 2.1 Overall survival for patients with stage IV NSCLC and EGFR-mutation, stratified by type of TKI



TKI preference was not significantly associated with organ or number of metastasis at baseline and is mainly determined by institutional preference and year of diagnosis. At baseline, bone metastasis was the most frequent site of metastasis (54%) while brain metastasis was diagnosed in 19% (table 2.3). Variation in OS between TKIs was most prominent for patients with brain metastasis, showing median survival of 14.5 months (95% CI 9.5-19.4), 15.0 months (95% CI 6.5-not reached) and 26.1 months (95% CI 18.6-37.1) for gefitinib, afatinib and erlotinib, respectively. Compared with erlotinib, gefitinib tends to perform worse (adjusted HR 1.30 (95% CI 1.02-1.64)), most prominent in patients with brain metastasis (adjusted HR 2.50 (95% CI 1.33-4.71)). Statistical significance was also reached in patients with bone and lung metastasis (table 2.4). After exclusion of patients with brain metastasis and controlling for the other parameters, overall survival result for erlotinib were no longer superior in the multivariate analysis (HR 1.14, 95% CI 0.88-1.48) suggesting that patients with brain metastasis were clinical responsible for this variation in efficacy.

Table 2.3 Association between type of EGFR TKI and organ of metastasis at baseline

	N	Erlotinib	Gefitinib	Afatinib	p-value
Overall	596	320 (53.7)	177 (29.7)	99 (16.6)	
Adrenal	63	36 (57.1)	17 (27.0)	10 (15.9)	0.84
Bone	322	182 (56.5)	92 (28.6)	48 (14.9)	0.28
Brain	112	65 (58.0)	29 (25.9)	18 (16.1)	0.55
Liver	116	67 (57.8)	29 (25.0)	20 (17.2)	0.46
Lung	185	96 (51.9)	54 (29.2)	35 (18.9)	0.59
Pleural	216	109 (50.5)	71 (32.9)	36 (16.7)	0.41

Table 2.4 Prognostic impact of type of TKI, adjusted for other prognostic factors in multivariable analysis, stratified by organ of metastasis

	Erlotinib	Gefitinib		Afatinib		p-value
	reference	HR	95% CI	HR	95% CI	
Overall		1.30	1.02-1.64	1.24	0.91-1.68	0.08
Adrenal	0.82	0.35-1.94		1.00	0.35-2.84	0.89
Bone	1.54	1.13-2.11		1.51	1.01-2.27	0.01
Brain	2.50	1.33-4.71		1.72	0.82-3.65	0.01
Liver	1.33	0.75-2.37		1.63	0.81-3.29	0.32
Lung	1.96	1.23-3.14		1.57	0.90-2.74	0.02
Pleural	0.85	0.58-1.25		0.65	0.37-1.15	0.29

HR = Hazard ratio, CI = confidence interval
* = controlling for gender, age, WHO PS, histology and number of metastatic organs

DISCUSSION

The present study reported the real-world treatment patterns and outcomes of patients with NSCLC harboring EGFR mutations in the Netherlands. A total of 596 patients received first-line treatment with regular TKIs with a median survival of 20.2 months. Survival was significantly worse for men, higher age, poorer PS and ≥ 3 organs with metastasis. Compared to erlotinib, we observed a poorer adjusted survival for gefitinib users, especially when diagnosed with brain metastasis at baseline.

To our knowledge, this study is the largest European real-world cohort of patients with advanced NSCLC with an EGFR mutation evaluating first line TKI treatment (table 2.5) and the first to report data from an entire country as this registry includes the data of all Dutch hospitals.

Compared to other large real-world observational studies (table 2.5) our study is similar regarding the number of female patients and median age. Also, the median OS is comparable to most other European studies. The Asian studies tended to show a better OS which is comparable to the clinical trials which are also mainly performed in Asia.[2] The real-world results of TKIs are inferior to those reported in clinical trials, probable because of less favorable patient characteristics such as a higher age or lower PS.[16]

One explanation for the difference in OS between European and Asian populations could be the variation in EGFR mutation subtype distributions. A number of studies showed a trend that patients with exon 19 deletions performed better than patients with a mutation in exon 21.[18] The latter occurs more often in European patients, next to a higher occurrence of non-sensitizing mutation of exon 20 and other rare mutations at baseline.[19,20] Another hypothesis would be that Asian patients respond better to TKI treatment due to other, still unknown biological differences.

As already known, in our study, higher age, male gender, poorer PS and ≥ 3 organs with metastasis were identified as negative predictors of survival.[20] Although the number of distant metastasis and involved organs is becoming more important in staging and subsequent survival according to the TNM 8th edition, this issue is often not routinely assessed in trial series. Also, these patients are often excluded from clinical trials.

Against expectations, we observed that patients treated with erlotinib had a superior survival compared to patients treated with gefitinib and not statistically different to afatinib. This difference disappeared when the patients with brain metastasis were excluded from the analysis with control for other factors, suggesting that this subgroup is clinical responsible for this difference. In a pooled analysis with 303 patients from 6 studies, OS was similar between patients treated with gefitinib or erlotinib.[4] There are no prospective trials directly comparing different TKI's in patients with brain metastasis. However, there is evidence of a better blood-brain barrier passage of erlotinib.[21] Our findings could be biased by residual confounding, parameters not included in the multivariate analysis (e.g. WHO PS was missing in 31% of all cases and information about symptomatology of brain metastasis is unknown). Also, information about (exon-)specific EGFR mutation type is lacking and choice of TKI could be mutation specific, for example afatinib in uncommon mutations.[6,7]

Table 2.5 Selected review of real-world series reporting overall survival for patients with EGFR-mutation, primarily treated with TKI

First author	Origin	N	Female %	Age (median)	Treatment	Survival (months)
Asia						
Fujiwara [26]	Japan	147	65	75	Gefitinib	27.3 (CI NS)
			61	72	Erlotinib	29.3 (CI NS)
Inoue [20] **/**	Japan	1104	65	67	Gefitinib	28.5 (26.4 - 31.0)
Okamoto[27]						
Yao [28]	Taiwan	226	65	65	Gefitinib	26.9 (21.2 - 32.5)
Shi [29]	China	463	54	62	Not stated	15 (13.1 - 16.9)
Xu [30]	China	141	61	63	Erlotinib /	30.7 (28.4 - 32.9)
					Gefitinib /	
					Icotinib	
Europe / North America						
Arriola [31]	Spain	187	62	71	Total	17.2 (13.5 - 21.4)
					Gefitinib	16.7 (12.4 - 20.1)
					Erlotinib	23.7 (15.2 - 31.5)
Remon [32]	Spain	318	100	65	Gefitinib /	23.0 (19.8 - 26.2)
					Erlotinib	
Schuette	Germany	334	63	--	Any TKI	17.2 (15.1 - 19.8)
[11,19]						
Li [33]	USA	593	68	69	Afatinib	20.7 (16.2 - 35.1)
		87			Erlotinib	23.2 (21.2 - 24.9)
Lau [7]	Canada	412	67	68	1st generation	25,0 (23,1 – 27,5)
		70	62	63	Afatinib	39,0 (25,6 – 48,8)
Gijtenbeek	NL	596	65	68	Total	20,2 (17.8 - 23.2)
(this study)					Gefitinib	18,3 (14,7 - 25,5)
					Erlotinib	21,7 (17,9 - 24,7)
					Afatinib	20,8 (15,4 - 24,3)

CI = confidence interval, NS = not significant, TKI = tyrosine kinase inhibitor, NL = The Netherlands

When assessing the quality of the now presented data, it is important to consider that in this study period, 79% of all Dutch patients with non-squamous NSCLC had been tested for EGFR which is equal to high compared to other countries, ranging 43-85%.[17,22,23] Many patients received first line chemotherapy as they were participating in the NVALT 17 trial (EudraCT Number: 2013-004303-39, no published results) comparing first line monotherapy erlotinib versus 4 cycles of cisplatin / pemetrexed / erlotinib with subsequent maintenance pemetrexed / erlotinib in EGFR mutated NSCLC. Also, several patients started with chemotherapy before definitive assessment of EGFR status was performed to decrease treatment delay. Median OS was similar between patients who received a first line TKI compared with those who started with chemotherapy. Former studies comparing TKI with chemotherapy did not find a significant difference in OS, often attributed to crossover.[12]

As this is a cohort derived from a national registry, we were able to create a large study population without inclusion bias as we included all stage IV NSCLC and only excluded patients with co-occurring mutations. As our patients are included from all hospitals in the country (e.g. general, teaching, and university medical centers) we do not expect selection bias of TKI prescription by hospital type. But, as this is a retrospective registry, our dataset is limited to key data only and information on therapy response and subsequent treatment is lacking. Second line treatment could vary between hospitals thereby causing bias when comparing the different first line TKIs.

For patients diagnosed during 2015-2017, second line osimertinib may have been used. Osimertinib has recently been approved by the European Medicines Agency (EMA) and soon will become first-line treatment for patients with EGFR mutated NSCLC. Osimertinib penetrates the blood-brain barrier, prolongs survival and has comparatively mild side effects. This will change the standard EGFR TKI treatment in patients with EGFR mutations in favor of osimertinib. However, this practice change will lead to new resistance mutations as tumor escape to TKI treatment.[24] These new mutations show in vitro response to first or second generation TKIs.[25] The future of the EGFR TKI development will involve evaluations of the patterns of distant metastasis after osimertinib, the spectrum of resistance mutations and the role of local treatments for oligometastatic disease. Novel EGFR TKIs will be developed along the novel mutations that will be found. However, osimertinib will not be approved or reimbursed in all countries in the world and therefore these data can help in guiding which TKI is the best treatment option.

CONCLUSION

In this Dutch nationwide population study OS in patients with EGFR mutated NSCLC treated with a first-line, first or second generation TKI was median 20.2 months which is comparable with other European population-based studies but lower than that of Asian population-based studies. Higher age, male gender, poorer PS and >=3 organs with metastasis were associated with shorter survival. In patients with brain metastasis, erlotinib showed superior results compared to gefitinib and was similar to afatinib.

CLINICAL PRACTICE POINTS

The incidence of EGFR mutations differs across the globe with a much higher incidence in Asia. Therefore, only a few studies evaluating EGFR TKIs were performed in small European cohorts. Although TKI treatment shows a prolonged PFS, there is no benefit on overall survival. A limited number of European population-based studies showed inferior survival of European patients compared to Asian patients.

The present large cohort study reported the real-world treatment patterns and outcomes of mainly White patients with NSCLC harboring EGFR mutations in the Netherlands. We conform the results of smaller cohorts and found that overall survival is comparable with other European population-based studies but lower than that of Asian population-based studies. We found that survival was significantly worse for men and patients with higher age, poorer PS and >=3 organs with metastasis. Compared to erlotinib, we observed a poorer adjusted survival for gefitinib users, especially when diagnosed with brain metastasis at baseline.

The now observed differences in outcomes between the different first- and second-generation line TKI's suggests that future EGFR TKI development will have to involve evaluations of the treatment response patterns of distant metastasis and the spectrum of resistance mutations. The now found differences in response remain important when in the future multiple third-line EGFR TKI's become available.

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CHAPTER 3

Overall survival in advanced epidermal growth factor receptor mutated non-small cell lung cancer using different tyrosine kinase inhibitors in The Netherlands: A retrospective, nationwide registry study

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for studies published up to August 2022, using the terms "osimertinib AND observational AND overall survival", restricted to English articles, resulting in 37 articles. These studies mainly focused on second line treatment, real world series without first line osimertinib, sequencing of EGFR TKI, and reported only progression free survival of first line treatment with osimertinib, due to limited follow up with recent adaption to first line osimertinib for EGFR mutated NSCLC. For first-line osimertinib the real-world overall survival (OS) in mutation subgroups remains unknown.

Added value of this study

This is one of the largest cohorts from Western Europe reporting real-world treatment effects of EGFR TKI on OS, including first line osimertinib, stratifying between patients with del19 or L858R mutation.

Implications of all the available evidence

Based on real-world evidence from our large, nationwide cohort, we showed that individual patient characteristics may be of influence on treatment choice, as we did not observe differences in OS between first-, second-, en third-generation EGFR TKI.

ABSTRACT

Background

Clinical guidelines advise osimertinib as preferred first line treatment for advanced epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC) with deletions in exon 19 (del19) or exon 21 L858R mutation. However, for first-line osimertinib the real world overall survival (OS) in mutation subgroups remains unknown. Therefore, the aim of this study was to evaluate the real-world OS of those patients treated with different generations of EGFR- tyrosine kinase inhibitors (TKI), and to identify predictors of survival.

Methods

Using real-world data from the Dutch nationwide Cancer registry (NCR) we assessed patients diagnosed with stage IV NSCLC with del19 or L858R mutation between January 1, 2015, and December 31, 2020, primarily treated with then regularly available TKIs (including osimertinib).

Findings

Between January 1, 2015, and December 31, 2020, 57592 patients were included in the NCR. Within this cohort we identified 1109 patients, 654 (59%) with del19 and 455 (41%) with L858R mutations, respectively; 230 (21%) patients were diagnosed with baseline brain metastasis (BM). Patients were treated with gefitinib (19%), erlotinib (42%), afatinib (15%) or osimertinib (24%). Median OS was superior for del19 vs L858R (28.4 months (95% CI 25.6-30.6) versus 17.7 months (95% CI 16.1-19.5), p<0.001. In multivariable analysis, no difference in survival was observed between various TKIs in both groups. Only in the subgroup of patients with del19 and baseline BM, a benefit was observed for treatment with osimertinib.

Interpretation

In this nationwide real-world cohort, survival of Dutch patients with advanced NSCLC and an EGFR del19 mutation was superior versus those harboring an L858R mutation. Osimertinib performed only better as first-line treatment in patients with del19 and BM.

INTRODUCTION

In patients with advanced non-small cell lung cancer (NSCLC), the presence of a common epidermal growth factor receptor (EGFR) mutation is prognostically favorable as these patients have a superior overall survival (OS) compared with patients with wild type EGFR status.[1] Treatment with first- and second-generation tyrosine kinase inhibitors (TKIs) showed superior results regarding progression free survival (PFS) compared to chemotherapy in both clinical trials as well as real world data, wheras OS was similar, probably due to cross-over in later treatment lines.[2,3] Third-generation TKI have been compared to first- and second-generation TKIs mainly in clinical trials.[4–7]

The most frequent detected mutations in EGFR are deletions in exon 19 (del19) and a single point mutation in exon 21 (L858R), together they account for 90% of EGFR mutations. It has been demonstrated that these common mutations are associated with better outcomes than uncommon EGFR mutations.[8,9]

Randomized trials comparing first- and second-generation EGFR TKI with chemotherapy as first-line therapy concluded that treatment with TKI significantly prolonged OS, in which the benefit was more pronounced for patients with del19 mutations compared to those with L858R mutations.[10,11]. This difference in OS between the two groups could mean either a different prognosis due to the structure of the mutation itself leading to a more aggressive biological behavior or be reflective of differences in efficacy of the used TKI for each mutation type.[12] Resistance to targeted therapy due to genetic alterations, cell lineage plasticity, and the tumor microenvironment is different between del19 and L858R mutations.[13] When the first- and second-generation TKI gefitinib and afatinib were compared directly in the LUX-lung 7 trial, OS did not differ between patients with del19 or L858R mutations, suggesting that both generations of TKI perform equally in patients within these common mutations.[14] The third-generation EGFR TKI osimertinib was compared directly to the first-generation TKI erlotinib or gefitinib in the FLAURA study. In a post hoc analysis, a superior OS in patients with del19 treated with osimertinib was found, with a hazard rate (HR) of 0.68 (95% confidence interval (CI) 0.51 – 0.90), compared to a HR of 1.00 (95% CI 0.71 – 1.40) in patients with L858R mutation.[15]

The incidence of brain metastases (BM) is higher in patients with EGFR mutations compared to wild-type EGFR.[16] Whereas the penetration of earlier generation TKI through the blood brain barrier is limited, the biological availability of osimertinib in the brain is better, showing a prolonged time to cerebral progression in patients with BM at start of treatment, although the efficacy on OS in the FLAURA trial was equal between patients with or baseline without BM (screening was not mandated).[15,17–19]

Whereas RCTs are the gold standard for evidence-based medicine, they are often not representative for clinical practice due to selection and exclusion criteria.[20] On the other hand, real-world studies are prone to bias but may provide information about patient groups that are underrepresented in RCTs (poor performance status, elderly, BM) and can have sufficient sample size to allow subgroup analyses.[21]

At the end of 2019, as the third-generation EGFR TKI osimertinib was found superior compared to earlier generation TKI's in clinical trials, osimertinib was implemented as first line treatment in the Netherlands.[4] Till date, there is limited real-world evidence that supports the benefit of osimertinib on OS found in clinical trials. Therefore, the aim of this study was to evaluate whether the introduction of osimertinib improved the OS of Dutch patients with advanced NSCLC harboring an EGFR del19 or L858R mutation compared to treatment with earlier-generation EGFR TKIs and whether the survival benefit was influenced by mutation type and the presence of baseline BM.

METHODS

All patients diagnosed with any type of cancer are registered in the Netherlands Cancer Registry (NCR). A standardized real-world dataset is collected from patient records consisting of basic patient and disease characteristics, including histology, TNM stage, World Health Organization (WHO) performance score (PS), site(s) of metastasis, and type of first-line treatment. Information on OS is obtained by annual linkage with the population registry. Data on treatment response, progression of disease, coexisting mutations such as TP53 and STK11, second-line treatment, and cause of death are not available. Mutation analyses were predominantly performed with Next Generation Sequencing (83%).[22]

From the NCR, we assessed patients diagnosed with stage IV NSCLC with del19 or L858R mutation between January 1, 2015, and December 31, 2020, primarily treated with then regularly available TKIs (including osimertinib). The primary endpoint of this study was OS, calculated from the day of starting TKI, with follow up until February 1, 2022.

Considering its observational nature, this study did not require approval from an accredited medical ethics committee (MEC) or the Central Committee on Research involving Human Subjects (CCMO). However, the study has been reviewed and approved by the Privacy Review Board of the NCR (application number K21.320).

Statistical analyses were performed using StataSE 17. Patient characteristics were summarized using descriptive statistics and variation in the proportion of EGFR subtypes was assessed with chi-square tests. Survival was estimated by the Kaplan-Meier method and variation between subgroups was assessed with log-rank tests. The prognostic contribution of type of mutation and type of TKI was assessed by multivariable Cox regression and represented by HR and 95% confidence intervals (95% CI). The proportional hazard assumption was tested using log-log plots and independent prognostic factors have been determined using the backwards selection method. The final model included age, WHO PS, and number of organs with metastasis as significant covariates. A p-value of <5% was considered as significant. A subgroup analysis was performed for patients with known baseline BM.

RESULTS

The Netherlands has a population of about 17 million inhabitants, mainly white and including approximately 6% inhabitants from Asian descent.[23] In the period 2015-2020, a total of 57592 patients were diagnosed with NSCLC and registered in the NCR. We assessed 1109 patients with a median age of 68 years (interquartile range (IQR) 60-75) including

68% women. Baseline brain imaging (comprising MRI in 86%) was performed in 400 (36%) patients, diagnosing 230 (58%) patients with BM. Median time from diagnosis to start of TKI was 23 days. Before start of TKI, local treatment of these metastases was performed in 74 of 230 (32%) patients, 66 with radiotherapy (Stereotactic Body Radio Therapy (SBRT) or Whole Brain Radio Therapy (WBRT)), 4 with surgery and 4 with combined modality. The use of upfront local treatment for BM decreased sharply after 2018, from 44% to 19%.
In patients with BM treated with osimertinib, local treatment of BM was performed in 17% of cases compared with 39% in patients treated with other TKIs. The use of osimertinib increased with time from 3% in 2018 to 18% in 2019 and 94% of all prescribed first line EGFR TKI in 2020.

With respect to type of mutation, 654 (59%) patients had an EGFR del19 and 455 (41%) L858R mutation (Table 3.1). Patient characteristics were similar between the two mutations except for WHO PS 2 or higher, which was more frequent in patients with del19 (15.0% vs 8.1%).

At the time of data cutoff, 70% of patients had deceased (41% in the osimertinib subgroup versus 79% in the other TKI group). Median follow-up was 28 months for the whole series and 17 months for patients treated with osimertinib.

The median OS was 22..8 months (95% CI 21.1-24.8) while three- and five-year survival rates were 31% (95%CI 28-34) and 12% (95%CI 10-15), respectively. Survival decreased with increasing age and poorer PS (Table 3.2). Survival was better for patients with stage M1A and those with less than 3 organs affected by metastases compared to more advanced disease. Survival of patients with del19 was significantly superior than for L858R, median OS 28.4 (95% CI 25.6-30.6) versus 17.7 months (95% CI 16.1-19.5), p<0.001 (Figure 3.1). The presence of baseline BM had no significant impact on survival, with a three-year survival rates of 27% vs. 32%, p=0.20. In patients with BM, local treatment did not influence survival, with three-year survival rates of 28% versus 26% (p=0.70), respectively.

Table 3.1 Patient characteristics (n total=1109)

		Del19		L858R		p-value
		N	%	N	%	
Age	18-59	165	25·2	96	21·1	0·07
	60-69	209	32·0	140	30·8	
	70-79	212	32·4	150	33·0	
	80+	68	10·4	69	15·2	
Gender	Men	218	33·3	137	30·1	0·26
	Women	436	66·7	318	69·9	
Histology	Adenocarcinoma	616	94·2	419	92·1	0·17
	Large NOS	38	5·8	36	7·9	
TKI	Gefitinib	115	17·6	98	21·5	0·10
	Erlotinib	269	41·1	201	44·2	
	Afatinib	103	15·8	58	12·8	
	Osimertinib	167	25·5	98	21·5	
WHO PS	0	241	36·9	165	36·3	0·003
	1	177	27·1	152	33·4	
	2+	98	15·0	37	8·1	
	Unknown	138	21·1	101	22·2	
TNM M	1A	179	27·4	110	24·2	0·23
	1B/C	475	72·6	345	75·8	
Period	2015-2017	266	42·2	202	44·4	0·22
	2018-2020	388	57·8	253	55·6	
Brain	Yes	137	21·0	93	20·4	0·84
metastases	No	517	79·1	362	79·6	
Number of	1	285	43·6	215	47·3	0·39
metastatic	2	207	31·7	128	28·1	
organs	3+	162	24·8	112	24·6	
PD-L1	0	195	29·8	127	27·9	0·79
	1-49	110	16·8	72	16·4	
	50+	72	11·0	56	11·5	
	Unknown	277	42·4	200	44·0	

TKI: tyrosine kinase inhibitor, WHO PS: World Health Organization performance score.

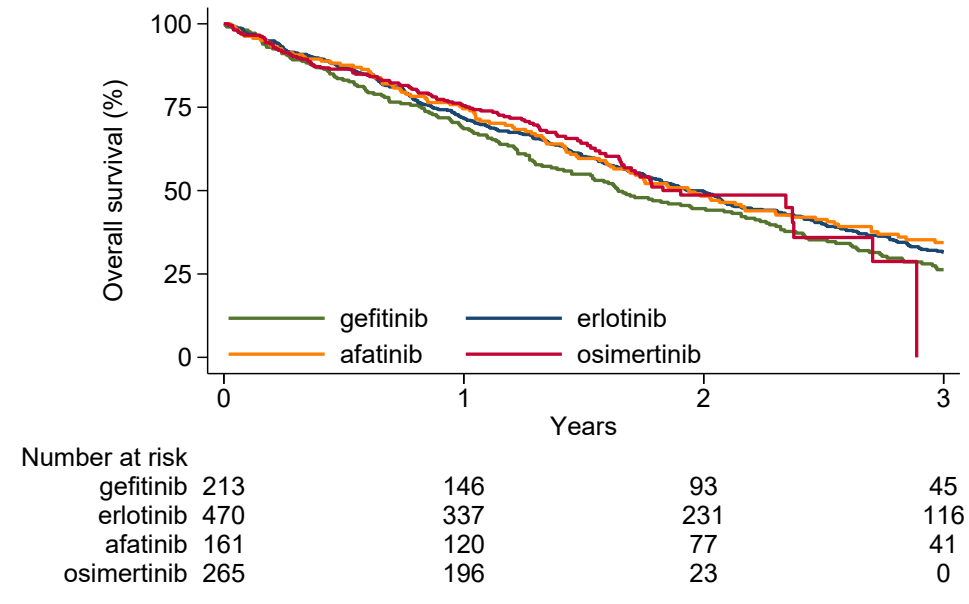
Table 3.2 Overall survival (median and 3-year) by subgroups

		n	Median (months)	3-Year (%)	p-value
Age	18-59	261	25·9	35	<0·001
	60-69	349	24·7	33	
	70-79	362	21·8	31	
	80+	137	16·9	18	
Gender	Men	355	20·6	27	0·15
	Women	754	24·4	33	
Histology	Adeno	1035	23·2	31	0·24
	Large NOS	74	19·2	26	
TKI	Gefitinib	213	19·7	26	0·29
	Erlotinib	470	23·2	32	
	Afatinib	161	23·3	34	
	Osimertinib	265	22·8	-	
WHO PS	0	406	26·8	34	<0·001
	1	329	23·2	32	
	2+	135	13·1	16	
	Unknown	239	21·2	32	
TNM M	1A	289	28·5	41	<0·001
	1B/C	820	21·2	27	
Period	2015-2017	468	21·0	29	0·10
	2018-2020	641	24·1	32	
Brain	Yes	230	21·0	27	0·20
metastases	No	879	23·3	32	
Number of	1	500	26·4	37	<0·001
metastatic	2	335	24·0	31	
organs	3+	274	17·7	18	
Mutation	Del19	654	28·4	37	<0·001
	L858R	455	17·7	22	
PD-L1	0	322	27·6	37	0·07
	1-49	182	21·8	25	
	50+	128	20·8	32	
	Unknown	477	21·2	29	

TKI: tyrosine kinase inhibitor, WHO PS: World Health Organization performance score.

Figure 3.1 Overall survival by type of mutation in patients with stage IV EGFR mutated NSCLC, treated with first line TKI

Figure 3.2 Overall survival by type of TKI in patients with stage IV EGFR mutated NSCLC treated with first line TKI



Univariable analysis did not show a significant difference in OS between the various TKIs (Table 3.2 and figure 3.2). Age, WHO PS and number of organs affected by metastases were identified as independent prognostic factors in multivariable analysis. When controlling for these factors in multivariable analysis, again no difference in survival was observed between the individual TKIs (Table 3.3). In the subgroup of patients with BM and del19, a benefit was observed for treatment with osimertinib while survival was significantly worse for gefitinib in patients with BM and L858R. Subgroup analysis in patients with BM treated with osimertinib confirmed a significant difference in survival between del19 and L858R (Figure 3.3).

DISCUSSION

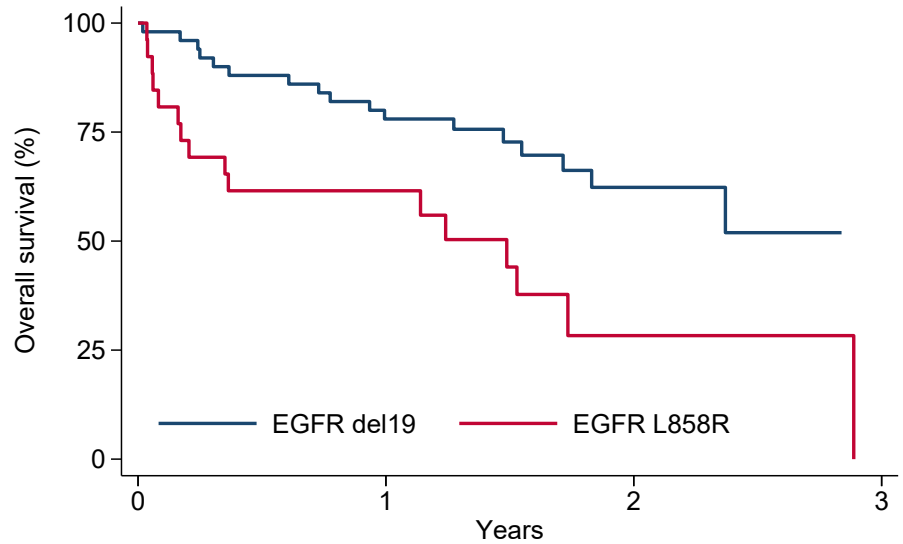
In this Dutch nationwide real-world cohort, we confirmed the previously described superior OS for patients with an EGFR del19 versus an L858R mutation.[11] OS benefit for patients treated with the third-generation TKI osimertinib as first line therapy was not different compared with first- and second-generation TKI. However, subgroup analysis revealed a benefit of osimertinib in patients with del19 and baseline BM, suggesting that the efficacy of the various TKIs may vary depending on tumor characteristics.

Table 3.3 Prognostic impact of type of TKI, stratified by type of EGFR mutation, controlling for age, WHO performance score and number of metastatic organs involved.

	TKI	Del19			L858R		
		n	HR	95%CI	n	HR	95%CI
Overall	Erlotinib	115	1	-	98	1	-
	Gefitinib	269	1·11	0·86-1·42	201	1·12	0·86-1·45
	Afatinib	103	1·00	0·76-1·32	58	1·20	0·87-1·66
	Osimertinib	167	0·82	0·60-1·12	98	1·02	0·73-1·41
Brain	Erlotinib	60	1	-	36	1	-
metastasis	Gefitinib	17	0·96	0·49-1·87	18	1·99*	1·05-3·76
	Afatinib	13	0·87	0·41-1·85	13	1·71	0·83-3·52
	Osimertinib	50	0·54*	0·30-0·99	26	1·60	0·80-3·20

TKI: tyrosine kinase inhibitor; HR: Hazard ratio; CI: Confidence interval; *: p.value<0.05

Figure 3.3 Overall survival by type of mutation in patients with stage IV EGFR mutated NSCLC and brain metastases, who received first-line treatment with osimertinib



Similar findings were observed in the FLAURA trial, in which first-line osimertinib was compared with the first-generation TKIs gefitinib and erlotinib. Overall a major PFS benefit (HR 0.46 (95% CI 0.37-0.57)) was found, but with a borderline significant OS benefit (HR 0.80 (95% CI 0.64-1.00)). Subgroup analysis suggested that this OS benefit was restricted to del19 patients (HR 0.68 (95% CI 0.51–0.90)), no OS benefit was observed among L858R patients (HR 1.00 (95% CI 0.71–1.40)).[15] Furthermore, in the FLAURA trial only an OS benefit was found for non-Asian patients (HR 0.54 (95% CI 0.38–0.77). In contrast to our results, no advantage with osimertinib was found for patients with baseline BM (HR 0.83 (95%CI 0.53–1.30)). Pursuing this approach, we also stratified the OS analyses by type of mutation but did not find significant variation between the individual TKIs in our mainly white population. However, despite including more than 1000 patients, the confidence intervals are relatively wide as osimertinib was only introduced in recent years and follow-up for patients treated with osimertinib was relatively short. Second-line treatment with osimertinib after first- or second-generation TKI was available during the study period for patients with T790M resistance and may have diluted the comparison. A concurrent study reported that 42% of Dutch patients with EGFR mutated NSCLC were diagnosed with resistance mutations upon progression, and that 75% of patients receiving second-line therapy were treated with a TKI.[22] However, other, smaller real-world studies evaluating the introduction of first line osimertinib also failed to find an OS benefit and this may reflect

the poor results of second-line treatment after progression on osimertinib.[24,25] Regrettably, information on date and type of progression and type of second-line treatment was not available within the Netherlands Cancer Registry.

Subgroup analysis of patients with BM suggests that OS does vary between TKIs, depending on the type of EGFR mutation. Gefitinib and erlotinib are almost identical in chemical structure, but some substituents are different, and this may have consequences in selective binding. The chemical structure of afatinib and osimertinib differs significantly from first-generation agents.[26] Also, the pharmacokinetics of the agents are different, with respect to the area under the drug plasma concentration–time curve and maximum drug concentration at steady state, and the influence of smoking status, drug interactions and negative influence of acid-suppressant therapies. Of the agents reported here, osimertinib is least affected by these factors.[27]

Whereas gefitinib and erlotinib bind competitively and reversibly to the ATP-binding site of the EGFR tyrosine kinase domain, afatinib and osimertinib form irreversible covalent bonds to the ATP-binding site, hereby irreversibly blocking activation. Osimertinib is also capable of targeting the T790M mutation and its metabolites penetrate the blood brain barrier better than previous generation TKIs.[27] These factors suggest that osimertinib has superior pharmacokinetic properties compared to gefitinib, erlotinib and afatinib, especially for patients with BM. However, in our study this was only confirmed for patients with a del19 mutation, but the relatively small number of patients limit clinical application of these findings.

Several studies suggest that BM of patients with del19 are biologically different from those in L858R patients. Takano et al. reported that BM in patients with L858R are spread differently within the brain, as they are located more often closer to the brain surface and located in the caudate, cerebellum, and temporal lobe compared to del19.[28] Sekine et al. found that patients with del19 were more prone to miliary BM compared to L858R patients.[29] Moreover, CNS progression appears to be earlier in L858R patients than del19 patients.[30]

Over the years, cranial radiotherapy is increasingly deferred when there is an option to treat patients with TKI that may cross the blood brain barrier. However, for patients with L858R mutation and BM, a retrospective Chinese study analyzing 61 patients showed that median OS was significantly better (29.2 versus 18.8 months) if osimertinib was combined with cranial radiotherapy.[31] This can also be suggested from our data as, although the number of patients was low, 40% of patients with L858R and BM died within 4 months, the minority of these patients received local treatment for their BM before start of systemic treatment. It is not clear whether these patients died from neurological progression (i.e. no CNS response), or that there was a high need to immediately starting TKI to control extracranial disease, but without success. RCTs evaluating osimertinib versus osimertinib plus stereotactic radiotherapy are currently under investigation.[32,33] Another treatment option for these patients might be dose escalation to 160mg daily. This strategy was analyzed in the phase I BLOOM trial as upfront treatment (n=41) and in a recent retrospective multicenter study after progressive disease on regular dose of 80mg (n=105). Only minor toxicity was observed with 160mg, but efficacy with escalating the dose from 80 to 160mg was limited, and prospective trials evaluating a dose escalation strategy are absent.[34,35]

Real-world studies about the treatment and survival of EGFR mutated NSCLC have their pros and cons.[20] Data were derived from a national registry and included octogenarians (12%) and patients with performance status 2 or higher (12%). BM were diagnosed in 21% of patients and the real prevalence may even be higher as only 36% of patients received brain imaging before treatment start. To our knowledge, this is one of the largest cohort studies from Western Europe reporting real-world treatment effects of first-, second- and third-generation TKI, stratifying between patients with del19 or L858R mutation. However, due to its retrospective design, we did not have information about method of testing, clinical information on therapy response (e.g., response rate or PFS), treatment duration, toxicity, resistance mechanisms, subsequent treatments and data on quality of life, thus lacking the details of data from RCT's. However, we provided results that are more generalizable to the average patient in Europe. Also, multiplicity should be taken in account for our subgroup analysis. For a proper interpretation of OS findings, the availability and use of second-line treatment should have been incorporated. As a second-line treatment, osimertinib was formally approved for patients with EGFR T790M mutation in 2017 but it may have been available earlier in clinical trials or early access programs. As a first-line treatment, osimertinib was made available through an expanded access program as of 2019 and got reimbursed in the Netherlands in 2020.

As we did not observe a clear survival benefit for patients treated with first line osimertinib, this study challenges the current guideline with respect to appropriate sequencing of TKI and other treatment options. Of note, as the median follow-up of osimertinib treated patients is still limited in this study, it might be possible that there are more long-term survivors on osimertinib compared to previous generation TKI. Approximately half of the patients treated with first- or second-generation TKI can be treated with osimertinib upon progression due to an acquired T790M mutation. Notably, there appears to be no difference in the occurrence of the T790M co-mutation between del19 and L858R patients.[36] For these patients, the quality of life may be preserved for a longer period, as those treated with upfront osimertinib mainly rely on cytotoxic chemotherapy upon progression, with decreased treatment time on TKI.[37] When analyzing the toxicity profiles of osimertinib and erlotinib/gefitinib in the FLAURA trial, patients treated with osimertinib experienced less grade ≥3 adverse events than those treated with first-generation TKI, however, these rates become equal with expanded follow up.[4,15] In a network meta-analysis performed by Holleman et al, gefitinib, erlotinib, and osimertinib were associated with fewer toxicities compared to afatinib, whereas the increased toxicity of afatinib was also shown in the large retrospective study by Pluzanski et al.[38,39] However, data on any grade toxicity and quality of life and more specific BM related quality of life over multiple treatment lines is lacking.

Combination therapy with other anti-cancer drugs is currently investigated. Preclinical data showed that L858R is correlated with a higher expression of vascular endothelial growth factor (VEGF) compared to del19.[40] And whereas patients with del19 profit more from TKI monotherapy compared to those with an L858R mutation, the addition of the VEGF inhibitor ramucirumab to erlotinib treatment in the RELAY trial seems to be more effective in L858R in terms of PFS, equalizing the difference with del19 patients. Although the OS data from that trial are still immature, a hypothesis-generating trend to a better OS was observed in L858R patients treated with erlotinib plus ramucirumab.[41,42] This was also observed in the ARTEMIS-CTONG1591 trial comparing erlotinib plus bevacizumab

with monotherapy erlotinib. In addition, in this trial a potential benefit was found for the patients with baseline BM, as the effect of the combination therapy is approaching statistical significancy albeit with immature OS data (HR 0.62 (95%CI 0.38 - 1.01)).[43] However, for these combination regimens, a comparison with osimertinib is not available in first line and in second line no superiority for osimertinib plus bevacizumab versus monotherapy osimertinib was shown.[44] Also, the effect might be affected by for example baseline TP53 co-mutation or smoking status.[42,45] Another study showed that addition of chemotherapy to gefitinib enhanced OS in patients with del19, whereas this was not significant for L858R, at cost of a higher rate of grade ≥ 3 treatment-related adverse events.[46] The results of the addition of immune checkpoint inhibition to TKI treatment are disappointing.[47] Currently, platinum and pemetrexed added to concurrent osimertinib is being evaluated in the first-line setting in the FLAURA2 (ClinicalTrials.gov Identifier: NCT04035486) and TAKUMI (UMIN000024438) trials.[48] Next, although a phase 2 trial recently failed to show benefit of addition of bevacizumab to osimertinib, it is still under investigation (ClinicalTrials.gov Identifier: NCT04181060).[49,50] These trials may lead to new treatment options and sequences, but due to the heterogeneity of the patient population and evolving options for biomolecular testing, optimal treatment for specific subgroups cannot readily be evaluated.

CONCLUSION

Dutch patients with stage IV EGFR mutated NSCLC harboring a del19 mutation have superior OS compared to patients with a L858R mutation. A survival benefit of the introduction of first line treatment with osimertinib was observed for a subgroup of patients with del19 and BM as compared to other TKI, but not for other subgroups. This finding needs to be substantiated in larger real-world populations.

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CHAPTER 4

Randomised controlled trial of first-line tyrosine-kinase inhibitor (TKI) versus intercalated TKI with chemotherapy forEGFR-mutated nonsmall cell lung cancer

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ABSTRACT

Introduction

Previous studies have shown interference between epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and chemotherapy in the cell cycle, thus reducing efficacy. In this randomised controlled trial we investigated whether intercalated erlotinib with chemotherapy was superior compared to erlotinib alone in untreated advanced EGFR-mutated nonsmall cell lung cancer (NSCLC).

Materials and methods

Treatment-naïve patients with an activating EGFR mutation, ECOG performance score of 0–3 and adequate organ function were randomly assigned 1:1 to either four cycles of cisplatinpemetrexed with intercalated erlotinib (day 2–16 out of 21 days per cycle) followed by pemetrexed and erlotinib maintenance (CPE) or erlotinib monotherapy. The primary endpoint was progression-free survival (PFS). Secondary end-points were overall survival, objective response rate (ORR) and toxicity.

Results

Between April 2014 and September 2016, 22 patients were randomised equally into both arms; the study was stopped due to slow accrual. Median follow-up was 64 months. Median PFS was 8.8 months (95% CI 4.2–18.8) for CPE and 10.3 months (95% CI 7.1–15.5; hazard ratio (HR) 0.78, 95% CI 0.32–1.91) for erlotinib monotherapy; when compensating for number of days receiving erlotinib, PFS of the CPE arm was superior (HR 0.32, 95% CI 0.10–1.01; p=0.02). ORR was 64% for CPE versus 55% for erlotinib monotherapy. Median overall survival was 30.9 months (95% CI 18.5–61.9 months) for CPE compared to 17.2 months (95% CI 11.5–45.5 months) for erlotinib monotherapy (HR 0.66, 95% CI 0.27–1.65 months). Patients treated with CPE had higher rates of treatment-related fatigue, anorexia, weight loss and renal toxicity.

Conclusion

Intercalating erlotinib with cisplatin-pemetrexed provides a longer PFS compared to erlotinib alone in EGFR-mutated NSCLC at the expense of more toxicity.

INTRODUCTION

Since 2004, efforts to combine epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) and chemotherapy in patients with advanced nonsmall cell lung cancer (NSCLC) have been explored, starting with unselected NSCLC patients. Four randomised phase III studies failed to improve outcome of combinations versus chemotherapy alone[1–4]. However, it was more important to study the role of adding chemotherapy to the treatment with an EGFR TKI in EGFR-mutated NSCLC patients. CHENG and co-workers[5, 6] showed improved progression-free survival (PFS) in the combined arm in a randomised phase II study enrolling Asian EGFR-mutated advanced NSCLC patients treated with gefitinib plus pemetrexed versus gefitinib alone. However, gefitinib/pemetrexed patients had more toxicity compared to gefitinib alone. In 2020, NORONHA et al.[7] and HOSOMI et al.[8] reported in phase III studies superior PFS and overall survival for concurrent gefitinib and carboplatin plus pemetrexed versus gefitinib alone as first-line treatment. This suggests that the combination of chemotherapy and TKI treatment overcomes early EGFR resistance mechanisms that emerge when using EGFR TKI alone. Of note, in these studies, only 15% and 22% of all patients received subsequent treatment with osimertinib, respectively.

Although concurrent use of TKI and chemotherapy is shown to be superior in PFS and overall survival, one of the concerns is the interference between EGFR TKI and chemotherapy in EGFR-mutated advanced NSCLC, which came from pre-clinical data where G1 cell cycle arrest due to EGFR TKI reduces the cell cycle dependent phase of chemotherapy[9]. However, when administered sequentially with respect to biological availability and half-life, the treatment effects of pemetrexed and erlotinib are synergic[10]. Therefore, to enhance the treatment effect by avoiding such interfering effects, we designed a randomised phase III trial to demonstrate the superiority of first-line treatment with cisplatin+pemetrexed with intercalated erlotinib (CPE) for days 2–16 in a 3-week cycle compared to continuous erlotinib monotherapy in patients with advanced EGFR-mutated NSCLC, in terms of PFS, overall survival, objective response rate (ORR) and toxicity.

MATERIAL AND METHODS

Study design

The NVALT-17 trial is a multicentre randomised controlled trial in patients with EGFR- mutated advanced NSCLC, who have been randomised in equally to either CPE or erlotinib monotherapy. Patients were enrolled from eight study centres in the Netherlands, and treatment was assigned by participating centre by means of a minimisation technique stratifying for ECOG performance status (0–1 versus 2–3) and activating EGFR mutation. Clinical data were entered into a web-based electronic data capture system, hosted at the NVALT data centre using the ALEA system. The study was approved by the central medical ethical committee of the University Medical Centre Groningen (nr. 2013/457); all patients gave informed consent before registration.

Eligibility criteria

Treatment-naïve patients with histologically or cytologically confirmed NSCLC having a documented activating EGFR mutation in exon 18, 19 or 21; aged >18 years; a performance status of 0–3; and adequate bone marrow, hepatic and renal function were enrolled. Estimated life expectancy should be >12 weeks.

Patients who were poor medical risks because of nonmalignant disease or those with active uncontrolled infection were ineligible, as were patients with symptomatic brain metastases unless local therapy was completed, and systemic corticosteroids had been discontinued ≥2 weeks before enrolment. Concomitant treatment with any other experimental drug or potent CYP3A4 inhibitor was not allowed. Patients with concurrent or previous malignancy were excluded, except for cervical carcinoma in situ, treated basal cell carcinoma, superficial bladder tumours or any cancer curatively treated >2 years prior to study entry. Patients known to be positive for HIV or chronic hepatitis B/C were not eligible.

Study procedures

Baseline evaluations were history including comorbidity, physical examination, blood counts, liver and renal function test and blood chemistry, electrocardiography, computed tomography (CT) of the chest and abdomen, positron emission tomography or bone scan. Subsequent CT scan evaluations were performed every 6 weeks. Tumour response was assessed according to Response Evaluation Criteria in Solid Tumors 1.1 criteria.

Treatment protocol

Patients were randomised to four cycles of cisplatin 75 mg·m−2 and pemetrexed 500 mg·m−2 plus intercalated (day 2–16) erlotinib 150 mg every 3 weeks followed by maintenance pemetrexed plus erlotinib (CPE) or daily erlotinib 150 mg (E) alone until disease progression. For comparability, both arms received folic acid 0.5 mg daily and vitamin B12 1000 µg intramuscular once every 6–9 weeks until disease progression.

All adverse events were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0). At the start of each cycle, absolute neutrophil count had to be $\geq 1.5\times10^9$ cells·L^{-1} and platelets $\geq 100\times10^9$ cells·L^{-1}. If applicable, chemotherapy dose was adjusted based on platelet ($<50\times10^9$ cells·L^{-1}) and neutrophil nadir counts ($<0.5\times10^9$ cells·L^{-1}) from the preceding cycle of therapy and maintained for subsequent cycles. In case of neurosensory toxicity grade ≥2 or creatinine clearance ≥60 mL·min^{-1}, cisplatin dose was reduced. In the event of grade 3 diarrhoea, the study therapy was not administered until resolved. For other nonhaematological effects CTCAE grade ≥3 (except alopecia, mucositis), the drug was held until resolution to less than or equal to the baseline value before proceeding. Treatment restarted at a 25% dose reduction if deemed appropriate by the treating physician.

Dose reduction for erlotinib (100 or 50 mg daily) took place whenever toxicity was noted during the study. Within 2 weeks following a dose reduction, erlotinib-related toxicity must have improved by at least one CTCAE grade and be CTCAE grade ≤2, otherwise further dose reduction by one level was required.

Study treatment was discontinued if a cycle was delayed for >2 weeks; erlotinib therapy was not restarted unless chemotherapy was postponed definitely. Replacement of cisplatin by carboplatin in case of oto-, neuro- or renal toxicity was allowed.

Outcomes

The primary end-point was PFS, defined as the time of random assignment to disease recurrence or death, whatever came first. Secondary end-points included overall survival, 6-month and 1-year overall survival rate, ORR, toxicity, symptoms and general health status. Overall survival was measured from the date of randomisation to the date of death. Duration of tumour response was measured from the date of the first objective status assessment of a complete or partial response to the date of progression of disease or death from any cause. All time to event end-points were analysed using the Kaplan–Meier method. Toxicity was recorded according to CTCAE (version 4.0).

Statistical analysis

The primary objective was to compare PFS between the CPE and erlotinib monotherapy study arms. Cox proportional hazard regression was used to compare PFS between arms both univariately followed by adjustment for the duration of erlotinib treatment. Descriptive statistics were used for patient characteristics. For toxicities occurring in >10% of patients, Fisher's exact test was used to compare the two arms.

A sample size of 75 subjects per arm was calculated, as an increase in median PFS from 10 to 17 months was estimated, which required a total of 150 eligible patients, with an inclusion rate of 50 patients per year. It was estimated that after 1 year of follow-up, 112 events would be observed, providing 80% power to detect the specified increase in PFS at the 95% confidence level.

RESULTS

Basic characteristics

150 patients had been scheduled to be enrolled during a 5-year period starting April 2014. However, the trial was terminated prematurely in 2017 due to slow enrolment. During this period, only 22 patients were enrolled in the study, with 11 patients assigned to each arm. The last patient was included on 12 September, 2016. Median follow-up time was 64 months; the most recent follow-up took place in August 2021.

Basic characteristics at baseline were well balanced between the groups. Median age was 64 years (interquartile range (IQR) 59–68 years); 55% were female. All patients had advanced disease and adenocarcinoma histology. 64% of patients had an exon 19 deletion and 23% had an exon 21 L858R mutation (table 4.1). In the CPE arm, median treatment length was 291 days (range 21–1031 days), compared to 324 days (range 57–932 days) in the er-

lotinib monotherapy arm. The median number of days of receiving erlotinib was 219 (range 14–994) in the CPE arm compared to 324 (range 53–918) in the erlotinib monotherapy arm. At time of disease progression, five patients from each arm underwent a re-biopsy. In the CPE arm, one patient acquired a T790M mutation, compared to two patients in the erlotinib monotherapy arm.

Table 4.1 Baseline patient characteristics

	CPE	E	All
Number of patients	11	11	22
Age (median (IQR))	60 (58 - 64)	67 (62 - 68)	64 (59-68)
Male gender (n (%))	5 (45)	5 (45)	10 (45)
Performance score			
0 (n (%))	8 (73)	7 (64)	15 (68)
1 (n (%))	3 (27)	4 (36)	7 (32)
Smoking			
Never smoker (n (%))	6 (55)	2 (18)	8 (36)
Former smoker (n (%))	5 (45)	5 (45)	10 (45)
Current smoker (n (%))	0 (0)	4 (36)	4 (18)
Pack years (median (IQR))	15 (9 - 15)	14 (6 - 19)	
Stage IV (n (%))	11 (100)	11 (100)	22 (100)
Non-squamous (n (%))	11 (100)	11 (100)	22 (100)
Type of EGFR mutation			
Exon 19 deletion	7 (64)	7 (64)	14 (64)
L858R	2 (18)	3 (27)	5 (23)
Others	2 (18)	1 (9)	3 (13)

E: erlotinib, CPE: cisplatin-pemetrexed-erlotinib, IQR: interquartile range

Table 4.2 Outcome measures by treatment arm

	CPE		E		
		95% CI		95% CI	HR (95% CI)
Randomized (n)	11		11		
PFS (median)	8.8	4.2 - 18.8	10.3	7.1 - 15.5	0.78 (0.32 - 1.91)
OS (median)	30.9	18.5 - 61.9	17.2	11.5 - 45.5	0.66 (0.27 - 1.65)
1-year OS (%)	81.8	48.2 - 97.7	72.7	39.0 – 94.0	
ORR (%)	64	31 - 89	55	23 - 83	
CR (n (%))	1 (9)		1 (9)		
PR (n (%))	6 (54)		5 (46)		
SD (n (%))	4 (36)		5 (46)		
Duration of response (median)	10.8	7.3 – 31.2	8.0	5.5 - 8.7	0.43 (0.12 - 1.47)

* after compensating for numbers of days receiving erlotinib HR 0.32 (95% CI 0.10–1.01; p=0.05).
E: erlotinib, CPE: cisplatin-pemetrexed-erlotinib, CI: confidence interval, HR: hazard ratio, PFS: progression free survival, OS: overall survival, ORR: overall response rate, CR: complete response, PR: partial response, SD: stable disease, NR: not reached

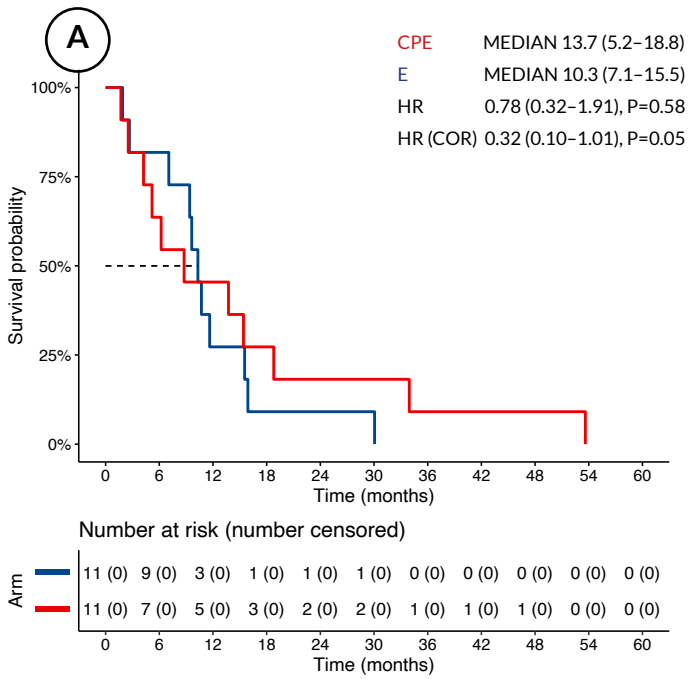
Tumour response and survival

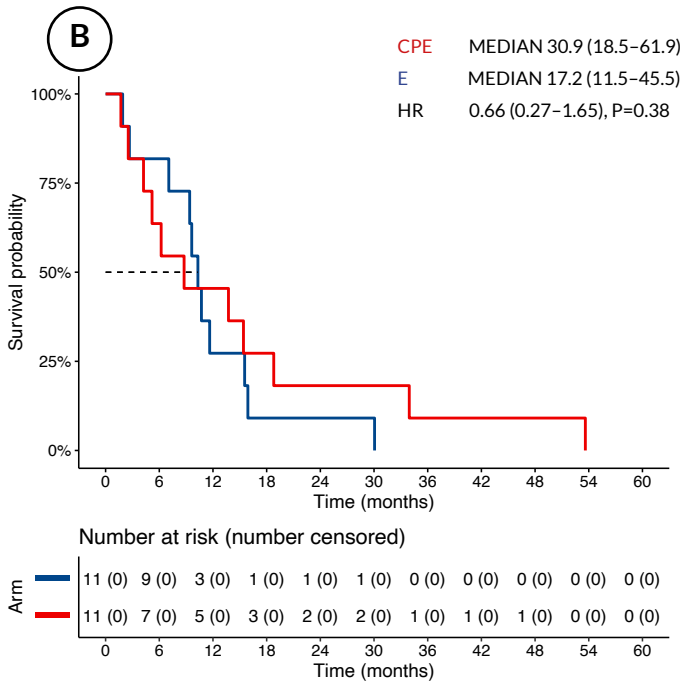
ORR and duration of tumour response were not different between both arms: in the CPE arm the ORR was 64% (seven out of 11); time to best response was 49 days (IQR 44–90 days), with a median duration of response of 10.8 months. In the erlotinib monotherapy arm, 55% (six out of 11) of patients responded to therapy, with a median response duration of 8 months. The median time to best response was 68 days (IQR 47–148 days). The main end-points are summarised in table 4.2.

PFS in patients treated with CPE was 8.8 months (95% CI 4.2–18.8 months) compared to 10.3 months (95% CI 7.1–15.5 months) in those treated with erlotinib monotherapy (unstratified hazard ratio (HR) 0.78, 95% CI 0.32–1.91; p=0.58) (figure 4.1a). With compensation for the number of days receiving erlotinib, the PFS advantage of the CPE over the erlotinib monotherapy arm became more pronounced (HR 0.32, 95% CI 0.10–1.01; p=0.05).

Median overall survival for CPE and erlotinib monotherapy was 30.9 months (95% CI 18.5–61.9 months) versus 17.2 months (95% CI 11.5–45.5 months; HR 0.66, 95% CI 0.27–1.65; p=0.38), with a 1-year survival rate of 82% (95% CI 48–98%) for CPE versus 73% (95% CI 39–94%) for erlotinib monotherapy (figure 4.1b).

Figure 4.1A Progression-free survival and **Figure 4.1B** overall survival in months by treatment arm





Data are presented with 95% CI. CPE: cisplatin-pemetrexed-erlotinib; E: erlotinib; HR: hazard ratio; cor: corrected.

Safety outcomes

Treatment-related adverse events occurred more often in the CPE group (58 versus 37 events), with a numerically higher frequency of patients reporting treatment-related fatigue (45% versus 18%; p=0.36), weight loss (18% versus 0%; p=0.48) and renal toxicity (27% versus 0%; p=0.21), while anorexia was significantly increased in the combination arm (55% versus 0%; p=0.01 (supplementary material Table 4.1A). In addition, the number of reported grade 3 and 4 treatment-related adverse events was higher in the CPE arm (11 versus 1). There was one grade 5 adverse event in a patient treated with CPE (epileptic seizures, not treatment-related). An overview of treatment-related adverse events occurring in ≥10% of patients or grade ≥3 is shown in table 4.3.

Of the patients treated with CPE, six (55%) completed all four cycles of cisplatin therapy; one additional patient was switched to carboplatin and completed four cycles with combination chemotherapy. Therapy delays (six times in four patients) and dose reductions of cisplatin or pemetrexed (three patients) were more common in this group. Treatment interruptions for intercalated erlotinib occurred in three patients and dose reductions occurred five times in three patients. However, in the erlotinib monotherapy arm no patient discontinued therapy because of toxicity; there were four treatment interruptions in three patients and dose reduction occurred twice in one patient.

DISCUSSION

In this study comparing alternating erlotinib with chemotherapy to exclude interfering effects between both treatments versus erlotinib alone, we found that PFS and overall survival were numerically better for patients treated with the combination therapy. When stratifying for type of EGFR mutation and days receiving erlotinib, PFS was clearly prolonged. The main objection for patients to participate in this study was the availability of TKI monotherapy as a less intensive and toxic treatment regimen.

The improvement in PFS of almost 4 months was observed in only 22 patients and despite the fact that only 55% of the patients tolerated treatment well enough to complete the four cycles of chemotherapy as intended. Combined administration of chemotherapy and EGFR TKI seems promising and the treatment effects are better compared to TKI monotherapy. In two other phase III studies comparing concurrent chemotherapy and EGFR TKI regimens to EGFR TKI monotherapy, significant improvements in PFS of 8 and 9 months (pooled HR 0.50, 95% CI 0.43–0.58) were observed, while HR in our study was 0.62 (95% CI 0.25–1.57)[7,8]. HR was even lower when correcting for days of erlotinib use, indicating a clinical effect of the combination treatment or intercalation of erlotinib with chemotherapy.

Theoretically, intercalated use of EGFR TKI next to chemotherapy might be more effective in the initial treatment phase in comparison with concurrent use. Pre-clinical studies showed that TKI arrest tumour cells in a cell cycle phase that protects them from cell cycle specific cytotoxic agents such as pemetrexed, reducing the activity of the chemotherapy[10].

Table 4.3 Number of treatment-related adverse events with incidence ≥10% or grade ≥3

	All grades		≥ grade 3	
	CPE	**E**	**CPE**	**E**
Abdominal pain	1	1	0	0
Alopecia	2	0	0	0
Anemia	1	0	0	0
Anorexia	6	0	1	0
Diarrhea	3	1	1	0
Dry skin	5	4	0	0
Dry eyes	0	1	0	0
Fatigue	5	2	1	0
Hypocalcemia	1	0	1	0
Hypomagnesemia	1	0	1	0
Mucositis	1	0	1	0
Nail infection	1	6	0	0
Nausea	2	1	1	0
Neutropenia	1	0	1	0
Pruritus	1	1	0	1
Rash	6	8	1	0
Renal toxicity	3	0	2	0
Weight loss	2	0	0	0

E: erlotinib, CPE: cisplatin-pemetrexed-erlotinib

WU et al.[11] showed that combined use of pemetrexed and gefitinib had antagonistic effects in gefitinib-sensitive NSCLC cells, while synergistically inhibiting the growth of gefitinib-resistant NSCLC cells. LI et al.[10] showed a synergistic effect when pemetrexed was administered ≥8 h before erlotinib. This effect may be an indication that the interaction between EGFR TKI and chemotherapy is a clinical meaningful issue that may enlarge the already positive survival outcome of randomised concurrent studies. This NVALT-17 study tried to overcome this interfering mechanism by its intercalated design, with administration of erlotinib starting the day after chemotherapy was completed until day 16, to ensure that erlotinib plasma levels were decreased by approximately four half-lives to prevent interaction between erlotinib and pemetrexed[10, 12].

Patients with EGFR-mutated NSCLC will develop disease progression due to acquired TKI resistance. The most common mechanism of acquired resistance to first- and second-generation TKIs is the acquisition of a secondary EGFR mutation, T790M[13]. It is not known if the combination of first-generation TKI with chemotherapy will lead to different resistance mechanisms. Previous trials did not report resistance mechanisms and the number of patients in this study with known acquisition of T790M is too small to draw any conclusion. Osimertinib and newer TKI will induce different resistant mechanisms, both EGFR-dependent and -independent[14].

We reported a higher rate of treatment-related toxicity among patients treated with CPE compared to erlotinib monotherapy. CPE showed not only the typical skin, fatigue and gastrointestinal toxicity, but also seems to result in a higher rate of patients with renal toxicity (three patients, of whom two had grade 3 toxicity) compared with previous trials assessing chemotherapy combined with EGFR TKI. HOSOMI et al.[8] reported that 25.3% of all patients treated with chemotherapy+TKI experienced creatinine elevation, all grade 1-2. NORONHA et al.[7] reported 32 (19.5%) patients with renal dysfunction grade ≥3, of whom 10 had grade 3 dysfunction. The higher rate of renal toxicity in our trial could be due to the use of cisplatin, as in both referenced studies carboplatin was administered. The perceived treatment toxicity compared with TKI monotherapy was one of the major reasons for limited enrolment. As monotherapy TKI was already the most appropriate first-line therapy, we assume that many patients choose this proven effective and less-toxic treatment, reflecting that individual patient goals extend beyond maximal life expectancy and that for some patients the impact of treatment on other goals such as quality of life may be as important as extension of life itself [15, 16].

To our knowledge, this is the first phase III trial reporting on intercalated use of TKI next to chemotherapy in selected EGFR patients and our results do support further exploration of combination treatment of EGFR TKI with other anticancer therapies. However, until a direct head-to-head comparison in a combined chemotherapy approach exists, it remains unclear which treatment regimen, concurrent or intercalated use with which TKI, is most beneficial. Whereas the different-generation TKI may have different effects in subgroups, the switch to upfront treatment with the third-generation EGFR TKI osimertinib will raise the question whether previous results can be improved with osimertinib combination therapies [17]. A phase II trial evaluating combined osimertinib with carboplatin and pemetrexed showed no overall survival or PFS advantage in progressive pre-treated patients with a T790M mutation compared to osimertinib alone[18]. Phase III trials on first-line osimertinib with or

without bevacizumab (ClinicalTrials.gov identifier NCT04181060) and osimertinib with or without chemotherapy (FLAURA2/ ClinicalTrials.gov identifier NCT04035486) are ongoing [19–21]. Future results will show whether early elimination of resistance clones is more effective with intercalation versus the concurrent approach.

CONCLUSION

Although the results should be interpreted with caution, since the trial was ended prematurely and as a consequence was underpowered, the addition of chemotherapy to EGFR TKI treatment in an intercalated regimen led to a longer PFS, not statistically different compared to concurrent regimens. Therefore, this study supports the hypothesis that CPE has a longer PFS than erlotinib monotherapy, but the combination of intercalated erlotinib with cisplatin and pemetrexed is not favourable over erlotinib alone, due to toxicity. The results encourage further research combining chemotherapy with upcoming next-generation EGFR treatments.

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CHAPTER 4
SUPPLEMENTAL MATERIALS

Table 4.1A Adverse events that were deemed possibly, probably or certainly related to treatment

	All grades			Grades 3-4			Grade 5		
	Erlo 11	CPE 11	All 22	Erlo 11	CPE 11	All 22	Erlo 11	CPE 11	All 22
Alopecia	0	2	2	0	0	0	0	0	0
Anemia	0	1	1	0	0	0	0	0	0
Anorexia	0	6	6	0	1	1	0	0	0
Diarrhea	1	3	4	0	1	1	0	0	0
Dry mucous	0	1	1	0	0	0	0	0	0
Dry skin	4	5	9	0	0	0	0	0	0
Eye disorders: blepharitis	1	1	2	0	0	0	0	0	0
Eye disorders: blurred vision	0	1	1	0	0	0	0	0	0
Eye disorders: burning eyes	0	1	1	0	0	0	0	0	0
Eye disorders: dry eyes	1	0	1	0	0	0	0	0	0
Eye disorders: teary eyes	0	1	1	0	0	0	0	0	0
Fatigue	2	5	7	0	1	1	0	0	0
Fissures	1	0	1	0	0	0	0	0	0
Folliculitis	0	1	1	0	0	0	0	0	0
Hemorrhage: nos	1	0	1	0	0	0	0	0	0
Hypocalcemia	0	1	1	0	1	1	0	0	0
Hypomagnesemia	0	1	1	0	1	1	0	0	0
Infection: eye	1	0	1	0	0	0	0	0	0
Infection: eyelids	1	0	1	0	0	0	0	0	0
Infection: nail infection	1	0	1	0	0	0	0	0	0
Infection: nails	6	1	7	0	0	0	0	0	0
Malaise	0	1	1	0	0	0	0	0	0
Menopausal/Stopped mentruating	0	1	1	0	0	0	0	0	0
Mouth ulcers	0	1	1	0	0	0	0	0	0
Mucositis: nose	0	1	1	0	1	1	0	0	0
Mucositis: oral	0	1	1	0	0	0	0	0	0
Nausa	1	2	3	0	1	1	0	0	0
Neutrophil count decreased	0	1	1	0	1	1	0	0	0
Pain: abdominal	1	1	2	0	0	0	0	0	0
Pain: nails	1	0	1	0	0	0	0	0	0
Pain: skin	1	0	1	0	0	0	0	0	0
Peripheral sensoral neuropathy	0	2	2	0	0	0	0	0	0
Pimpels	1	0	1	0	0	0	0	0	0
Pimpels and redness under eyelids	0	1	1	0	0	0	0	0	0
Pruritis	1	1	2	1	0	1	0	0	0
Rash	1	1	2	0	0	0	0	0	0
Rash acneiform	8	6	14	0	1	1	0	0	0
Renal disorders: real insufficiency	0	3	3	0	2	2	0	0	0
Skin disorders: gorges	1	0	1	0	0	0	0	0	0
Skin peels	0	1	1	0	0	0	0	0	0
Thickened skin	1	0	1	0	0	0	0	0	0
WBC decreased	0	1	1	0	0	0	0	0	0
Weight loss	0	2	2	0	0	0	0	0	0

CHAPTER 5

Functioning and Quality of Life in Long-Term Survivors with EGFR-Mutated stage IV Non-Small Cell Lung Cancer; a mixed-methods study

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ABSTRACT

Objective

A small subgroup of patients with advanced NSCLC harboring an activating mutation in the epidermal growth factor receptor gene (EGFR+) survives more than 3 years. There is little information about how these patients appreciate their gain in survival time. Therefore, the aim of this study was to assess overall quality of life (QoL) and treatment satisfaction from a real-world population of long-term survivors with advanced EGFR+ NSCLC.

Materials and methods

This is a multicenter mixed methods observational cohort study, including all patients within the Northern-Netherlands diagnosed with advanced stage EGFR+ NSCLC, diagnosed before January 1, 2019, alive at the start of the study in July 2021. We assessed QoL and treatment satisfaction using questionnaires (EORTC QLQ-C30, LC13, EQ-5D, CTSQ) and semi-structured interviews.

Results

Of 11 identified patients, 10 were eligible. Median duration of TKI administration was 40 months (range 31-94). General QoL was fairly high, with a median QLQ-C30 global health status of 75.0 and median EQ-5D VAS of 72.5. Patients were very satisfied with therapy (median CTSQ score 91.1). Patients perceived their terminal disease as chronic disease and long-term TKI treatment was tolerated well. Symptoms with a mean score of >25.0 on QLQ C30 /LC13 questionnaires (fatigue, pain, neuropathy) were different from those reported in the interviews (alopecia, nail, and skin problems). Patients with symptoms from brain or bone metastases reported inferior performance.

Conclusion

Long-term survivors of EGFR+ NSCLC tolerate long-term TKI treatment well and are satisfied with therapy. The validated questionnaires originate from the chemotherapy era and are less appropriate for assessing performance following long-term EGFR treatment.

INTRODUCTION

Annually, about 6.000 patients are diagnosed with metastatic non-small cell lung cancer (NSCLC) in the Netherlands and those numbers are still increasing.[1,2] In 2006, tyrosine kinase inhibitors (TKI) gefitinib and erlotinib were approved as second or third line of therapy in an unselected patient population. The discovery that activating mutations in the EGFR gene caused the superior tumor response and survival, led to approval of EGFR TKI as first line therapy in the subgroup of patients with advanced stage EGFR mutated NSCLC.[3,4] This increased the median survival up to 20.2 months with a 15% five year overall survival (OS) rate in this group, compared to only 8.8 months and < 5% in the total group of patients with advanced stage NSCLC, respectively.[5–7]

Treatment toxicity is generally measured using the Common Terminology Criteria for Adverse Events (CTCAE) ranging from mild (Grade 1) to life threatening (Grade 4). The administration of chemotherapy has traditionally been associated with relatively short periods, wherein grade 1-2 side effects were historically deemed of lesser significance. However, in the context of treatment with TKI, the therapeutic regimen often extends over a larger treatment period owing to more favorable responses and prolonged overall survival. It is hypothesized that the persistence and accumulation of low-grade side effects over an extended timeframe may contribute to a gradual deterioration in QoL.

There is only limited information reporting how patients experience the time gained with TKIs, in terms of QoL and treatment satisfacion.[8] In the leading clinical trials comparing chemotherapy with TKI, quality of life (QoL) was measured as a secondary endpoint, but usually limited to a few months of follow-up. During this short period, QoL of patients treated with chemotherapy improved for a small group, while the QoL of patients treated with TKIs improved significantly for the majority.[9,10]

Moreover, the commonly used QoL-questionnaires (e.g. the European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30) or the Functional Assessment of Cancer Therapy - General (FACT-G)) may not be adequate. These questionnaires were designed and validated for patients treated with chemotherapy and measure treatment effects on symptoms and functional status, including items that are less relevant when assessing QoL in long-term cancer survivors treated with TKI and not covering functional and psychosocial items relevant for them.[11] Also, the questionnaires do not cover less quantifiable areas as, for example, life goals, treatment expectations and survivor guilt.[12] Patients who survive longer than their initial prognosis experience specific QoL challenges reclaiming their pre-cancer life but still facing a terminal prognosis. To get better insight in long-term QoL, qualitative research by interviews to understand concepts, opinions, or experiences, can be useful as it allows exploring the psychosocial and contextual aspects of the disease and captures the patients' complexities and context of experience.[13,14]

Therefore, we designed this mixed-methods study in a real-world population of long-term surviving patients with advanced stage EGFR-mutated NSCLC, using traditional QoL instruments and qualitative research for assessing their overall QoL, treatment satisfaction, long term side effects and treatment goals.

METHODS

This study is a regional multicenter mixed methods observational cohort study among long term survivors of advanced stage EGFR mutated NSCLC in the Northern Netherlands. In the Netherlands, approximately 13.000 patients are diagnosed with any stage NSCLC each year. Of those, approximately 10% will have a treatment relationship with one of the hospitals in the Northern Netherlands, including an average of 40 patients per year with advanced stage EGFR mutated NSCLC.

This study was approved by the medical ethical committee of the Medical Center Leeuwarden (nWMO 2020 0088).

Study procedure

We extracted a list of all patients with advanced stage EGFR mutated NSCLC who were still alive after 30 months or more after diagnosis and living in the Northern region of the Netherlands from the Netherlands Cancer Registry (NCR). The extraction was performed on July 1st, 2021. As patients are only registered in the NCR at diagnosis, an additional search was performed in the local hospital systems using the same parameters to identify patients who progressed from earlier stages of disease. We contacted the patients after consultation with their local care provider. Patients receiving end-of-live support or those unable to understand and complete protocol requirements, instructions, questionnaires, and the interview, were excluded.

After obtaining informed consent for study participation, all enrolled patients were asked to complete four questionnaires. Following this, patients were invited for a one-hour semi-structured interview, conducted by a clinical psychologist (MB). The interviews were seamlessly integrated into regular clinic visit or conducted either at the patients' residence or through video connection, based on individual patient preferences. Basic patient and disease characteristics were documented through an exhaustive review of patient medical records (RG).

Instruments

We used four questionnaires, the EuroQol five-dimensional questionnaire (EQ-5D-5L), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire with the Lung Cancer Module (EORTC QLQ-C30 + LC13), the Cancer Therapy Satisfaction Questionnaire (CTSQ) and the Outcome Prioritization Tool (OPT). Except for the OPT, all questionnaires are regularly used in landmark trials with EGFR TKI and validated in Dutch.[15]

The EQ-5D-5L is a widely used questionnaire developed to assess QoL in a general population, consisting of 5 questions each scoring one dimension: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with 5 possible answers (levels) per dimension. The scores on each dimension are summarized using a calculated index value, which reflects how good or bad a health state is ranging from 0 (dead) to 1 (full healthy). Negative values are considered worse than dead. In a sixth question, patients evaluated their overall health status using a visual analogue scale (VAS) ranging from 0 (bad) to 100 (excellent) (EQ-VAS).16,17

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) a widely used questionnaire developed to assess the QoL of cancer patients, consists of 30 general questions regarding QoL. It is scored using nine multi-item scales: five functioning scales (physical, role, cognitive, emotional, and social), one global QOL scale, and three symptom scales (fatigue, pain, and nausea/vomiting). In addition, six single item symptom measures are used (dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties). This general questionnaire was supplemented with the Lung Cancer Module (EORTC QLQ-LC13) to assess specific lung cancer related domains of QoL (13 questions) using both multi- and single-item measures of lung cancer-associated symptoms (dyspnea, coughing, hemoptysis, or pain) and side-effects (sore mouth, dysphagia, peripheral neuropathy, or alopecia). The score ranges from 0 to 10, where a high score for a functional scale or global health status represents a high level of functioning or QoL whereas a high score for a symptom scale or item represents a high level of symptomatology / problems.[18,19]

The Cancer Therapy Satisfaction Questionnaire (CTSQ) is a 16-item questionnaire measuring three domains related to patients' satisfaction with cancer therapy (oral or intravenous chemo- or biological therapy): expectations of therapy (ET), feelings about side effects (FSE) and satisfaction with therapy (SWT), ranging from 0 to 100, with a higher score representing a better outcome on each domain.[20,21]

The Outcome Prioritization Tool (OPT) consists of four visual analogue scales ranging from 0 (not important) to 100 (very important), covering four general treatment goals: prolongation of life, staying independent, relief or reduction of pain and reduction of other symptoms.[22] The different goals are ranked according to the trade-off principle that they cannot be equally important.

Interview

A recorded semi-structured interview was conducted regarding the patient's cancer journey, treatment objectives, decision making and quality of life, encompassing self-care, daily activities, physical aspects (such as lung cancer symptoms and side effects), psychological, emotional, and relational issues. The interviews were transcribed, and the items discussed were broken down to core themes and coded using Atlas.it version 9 by two authors (RG and MB).

Statistical analysis

Basic characteristics and questionnaire data were summarized using SPSS version 27. Due to the low number of patients and to cover for skewed data the various questionnaire scores are described with means with standard deviations (SD) and median values with ranges. The low sample size did not allow to perform any intergroup comparison or relationship analysis.

RESULTS

Study population

Eleven patients met the inclusion criteria, but one patient received end-of-life support and was therefore excluded. All ten patients agreed to participate in the study and completed the questionnaires and a subsequent semi-structured interview.

The study population consisted of four males and six women diagnosed between 33 and 137 months before study enrollment (median 41.5 months), still under treatment in seven hospitals. Three patients were diagnosed previously with local disease and had been treated with surgery, of which two also had received adjuvant chemotherapy. Seven patients were diagnosed directly with advanced stage disease, including one with brain metastases. Furthermore, three additional patients developed brain metastasis during the course of the disease. All patients started TKI treatment as first line systemic treatment for advanced stage or recurrent disease and received TKI treatment for a median time of 40 months (range 31-94). At time of the study, three of them were still on first-line treatment with afatinib and five were currently receiving osimertinib (Table 5.1).

Table 5.1 General characteristics of long-term EGFR TKI users

Number of patients		10
Age	Mean (SD)	69 (10)
	Median (range)	72 (45 – 81)
Male n (%)		4 (40)
Mutation type	Exon 19 (del)	6 (60)
	Exon 20	1 (10)
	Exon 20 + exon 18	1 (10)
	Exon 21 (L858R)	2 (20)
Survival time (months)	Mean (SD)	53 (31.5)
	Median (range)	42 (33 – 137)
Treatment line n (%)	First	3 (30)
	Second	3 (30)
	Third	4 (40)
Current treatment n (%)	Erlotinib	1 (10)
	Afatinib	3 (30)
	Osimertinib	5 (50)
	Chemoimmunotherapy	1 (10)
Time on TKI (months)	Mean (SD)	47 (19.3)
	Median (range)	40 (31 – 96)

TKI: tyrosine kinase inhibitor; SD: standard deviation

Table 5.2 Questionnaire results (n=10)

	Mean (SD)	**Median (range)**
QLQ-C30		
Global health status	65.0 (28.5)	75.0 (16.7 - 100)
Functioning scores		
Physical	77.0 (19.9)	80.0 (46.7 - 100)
Role	66.7 (37.7)	75.0 (0 - 100)
Emotional	78.3 (21.9)	79.2 (50 - 100)
Cognitive	75.0 (21.2)	83.3 (33.3 - 100)
Social	81.5 (24.2)	83.3 (33.3 - 100)
EQ-5D		
Index score	0.79 (0.23)	0.85 (0.28 - 1.00)
VAS	67.6 (18.4)	72.5 (35 - 90)
CTSQ		
Expectations of therapy (ET)	52.2 (28.9)	57.5 (0 - 100)
Feelings about side effects (FSE)	71.9 (15.7)	68.8 (50 - 100)
Satisfaction with therapy (SWT)	88.2 (10.7)	91.1 (71.4 - 100)
OPT	**n (%)**	
Live longer	6 (66.7)	
Reduce pain	2 (22.2)	
Other (not specified)	1 (11.1)	

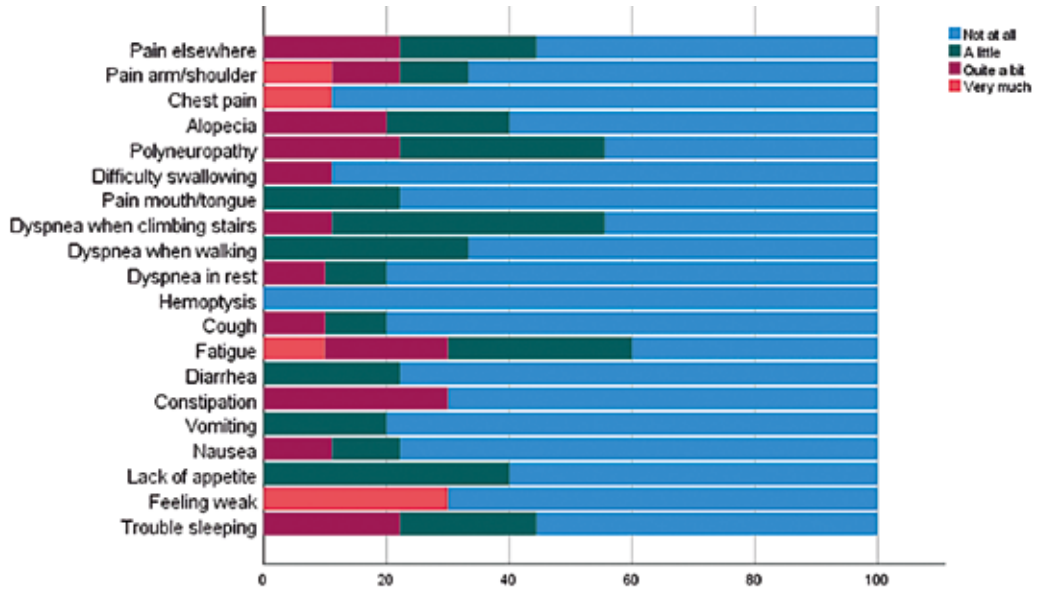
SD: standard deviation; VAS: Visual Analogue Score; CTSQ: cancer treatment satisfaction questionnaire

Quantitative analysis

All main questionnaire scores are summarized and displayed in table 5.2. One patient was not able to complete all the questionnaires. Some patients found the questionnaires to lengthy and certain questions challenging to comprehend.

General QoL and treatment satisfaction was reported as relatively well with a mean and median QLQ-C30 global health status of 65.0 and 75.0 (range 16.7 – 100), corresponding with the EQ-5D-5L index score of mean 0.79 and median 0.85 (range 0.28 – 1.00) and EQ-VAS score of 67.6 and median of 72.5 (range 35 – 90), respectively. The patients were overall satisfied with therapy (median 91.1 (range 71.4 - 100)) with a positive view about the impact of side effects (median 68.8 (range 50 – 100)). Fatigue, pain, dyspnea, polyneuropathy, and sleeping difficulties were reported by more than four out of ten participants by questionnaire (figure 5.1). The primary treatment objective of most patients (66.7%) was to extend their lifespan.

Figure 5.1 Reported severity of symptoms and side effects as measured by QLQ-C30 and QLQ-LC13



Qualitative analysis

The period surrounding the primary diagnosis was regarded as a rollercoaster experience by patients, attributed to the multitude of diagnostic procedures initially undertaken and subsequent long waiting times (noted by five out of ten patients). Interestingly, this aspect was not mentioned by the three patients who had recurrent disease. The presence of the EGFR mutation and subsequent initiation of TKI treatment were perceived as positive news (even called a miracle) by all patients. The treatment and the associated prolonged life expectancy led to a perceptual shift in six out of ten patients regarding their outlook for the future. What was initially perceived as a life-threatening disease with imminent mortality transformed into a chronic condition.

When starting treatment, shared decision making was not a major issue for our patients. Frequently, patients consistently adhered to their physicians' recommendations, emphasizing trust in their expertise and belief that the healthcare provider possessed the knowledge to determine the most effective treatment for their individual case.

All patients reported an acceptable rate and grade of side effects. Reported side effects were related to skin (7/10), hair (2/10), nail (2/10), gastro-intestinal (3/10), or bladder (3/10) problems. Patients noted that the questionnaires provided did not sufficiently address the prevalent side effects associated with EGFR TKI treatment. It was reported that the side effects of afatinib were considered worse compared to those of first or third generation TKI. Two patients contributed comparisons of TKI treatment with previous adjuvant chemotherapy and palliative chemo-immunotherapy after TKI progression and reported significant deterioration of QOL due to the toxicity of these treatments.

Physical functioning mainly depended on the symptoms patients perceived. Patients with symptoms from brain (three) or bone metastases (one) reported a higher impact on their daily activities, resulting in poorer performance. The majority (eight out of ten) could continue daily life, however, symptoms such as fatigue resulted in a limitation of daily activities. These limitations tended to increase over the course of the disease. Only three patients were of working age when diagnosed, resulting in termination of working life in two patients due to lung cancer symptoms whereas one patient maintained his working life partially for some time.

None of the participants was suffering from significant mental problems directly attributed to the disease or treatment. Some reported that the symptoms caused by, for example, brain or bone metastases led to substantial impairment. Dealing with these issues occasionally triggered feelings of desperation or fear, particularly when symptoms proved challenging to treat. Next, their diagnosis led to diminished confidence in their body. New or persistent symptoms often contributed to the fear of disease progression. On the other hand, disease progression often did not enhance symptoms and was only identified by radiological imaging (four out of ten), performed every three months, except for one patient who was checked once yearly. At that time, anxiety will arise as patients must wait several days between the scan and the appointment with their physician. Survivor guilt was discussed with the participants but was not reported as an issue by any of our patients.

Of the nine patients cohabiting with a partner, four reported that their partners exhibited a greater degree of emotional imbalance compared to the patients themselves, but all were able to cope with this together without difficulties. Some patients engaged in open discussion with outsiders about the challenges they perceived, while others chose to keep such matters more private, about equally divided in our group. Notably, this behavior appeared not linked to the suspected coping strategies of the individual patients. During the initial stages of their cancer journey, people were paying attention and were more supportive to the patients. In the later stages the situation normalized, and the level of attention waned.

DISCUSSION

As the overall survival is increasing in advanced NSCLC due to better therapeutic options, the importance of data on long-term cancer survivorship and QoL will increase. In this exploratory observational study analyzing both quantitatively and qualitatively assessed QoL of ten patients with EGFR mutated NSCLC, and surviving a least 33 months after diagnosis, long-term treatment tolerance and satisfaction with TKIs was reported well, with bone and brain metastasis leading to worser symptoms and lower QoL.

The EORTC QLQ-C30 and QLQ-LC13 questionnaires are well established and widely used in advanced NSCLC treatment trials, including those assessing the efficacy of EGFR TKI.[15,23] From the FLAURA trial, mean QLQ-C30 global health status and functional scales at baseline are comparable to our patients. Also, the most reported symptoms in our study were fatigue, pain, dyspnea, polyneuropathy, and sleeping difficulties. This was also shown in the FLAURA trial, although they report a higher number of other symptoms, which may be related to our small sample size.[15] When comparing the EQ-5D index score to other study cohorts, it is shown that our patients do relatively well. In 2010, Grutters et al. analyzed this score in Dutch lung cancer survivors at least 1 year after treatment, and they reported a mean index score of 0.74, while we found a mean index score of 0.79.24 In the healthy, general population, this index score is 0.78, reflecting the well performance of our patients.[25] Our patients were satisfied with their therapies, as shown by the satisfaction with treatment and the feelings about side effects scores of the CTSQ questionnaire. These were equivalent to those in both arms of the FLAURA trial, where these questionnaires were completed two months after start of therapy (unpublished data, available from https://clinicaltrials.gov/). The expectation of therapy-score was lower in our study group (52 versus approximately 75), which can be explained by the fact that the patients in the FLAURA had just started therapy. Cheung et al validated the Dutch CTSQ in a study group of 55 patients, treated with platinum doublet chemotherapy. They found an almost comparable ET score (56 versus 52), but a lower FSE (72 vs 52) and SWT (88 vs 80). Most patients (6/9) reported that their primary treatment goal was prolongation of life. This is higher than reported in other studies, explained by the long-term efficacy of EGFR TKI treatment.[22] The questionnaire scores suggest that our patients performed well, are satisfied with treatment, and maintained QoL for more than three years of therapy.

From the semi-structured interviews, we learned that there is a preference for brevity in the questionnaires. The QLQ-C30 and LC13 consist of 43 questions. However, as the QLQ-LC13 is recently updated as QLQ-LC29, 16 more questions were added to the list. Whereas only a single question may be applicable to our TKI treated patients, most questions do not cover the symptoms and side effects these patients experience. We have learned that our two patients who had received chemotherapy during their cancer journey experienced treatment with TKI considerably better compared to chemotherapy. Living over a long period of time with lung cancer can be challenging. Although side effects and symptoms can be relatively mild, the disease is presented as chronic disease. But as the survival of lung cancer used to be short, these patients are sometimes not recognized as patients with chronic disease and therefore, for example, cannot benefit from paramedical resources such as physiotherapy due to health insurance issues.

Patients with EGFR mutated NSCLC are more susceptible to developing brain metastasis during the course of the disease compared to patients with EGFR wildtype.[26] In our study group one out of ten patients was diagnosed with brain metastases at baseline and three out of ten patients developed brain metastasis during the course of the disease. This progression and the associated treatment with radiotherapy led to a deterioration of quality of life in these patients. Routine imaging of the brain is not recommended by clinical guidelines at start of TKI and during follow-up but should be considered to detect the brain metastasis in an earlier phase.[27] In the Netherlands, this is currently common practice in centers with large experience with TKI treatment. Clinically, asymptomatic brain metastasis will be treated with upfront TKI, as the penetration of osimertinib through the blood-brain barrier is superior to that of first- and second-generation TKI.28 Studies evaluating combination of radiotherapy with osimertinib treatment are ongoing.[29,30]

As the sample size of our study is limited, no firm conclusions can be drawn. However, we included a real-world population and all patients approached agreed to participate, resulting in a heterogeneous group ranging from young male to elderly female patients. The experiences made during this study and its findings can be used for extending this project over the Netherlands, to improve care for these patients. We used the same general QoL questionnaires also applied in recent trials to enhance comparability and showed that they did not cover the reported side effects of EGFR TKI treatment as they were discussed in the interviews.[15] With this data, specific PROMS for chronic lung cancer patients should be developed, rather than using generic lung cancer questionnaires in regular follow up. This also applies to, for example, long-term surviving patients harboring an anaplastic lymphoma kinase (ALK) rearrangement, or patients treated with checkpoint inhibitors. The EORTC QLQ-SURV11, a general questionnaire focusing on cancer survivors currently being internationally validated in a phase IV study, could be used as a starting point.[31] Additional assessment of a larger study group of long- surviving patients with EGFR mutated NSCLC will allow the development of a questionnaire with focus on this group.

CONCLUSION

Long-term survivors of EGFR lung cancer tolerate treatment relatively well and are satisfied with TKI therapy. Most clinical health issues are due to the presence of especially brain and bone metastasis, causing more severe symptoms. Traditional questionnaires (QLQ-C30 and LC13) are deficient to measure quality of life properly and supplementary interviews can be used to detect additional health issues in an earlier phase.

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CHAPTER 6

Best first-line therapy for people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status

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ABSTRACT

Rationale

Most people who are newly diagnosed with non-small cell lung cancer (NSCLC) have advanced disease. For these people, survival is determined by various patient- and tumor-related factors, of which the performance status (PS) is the most important prognostic factor. People with PS 0 or 1 are usually treated with systemic therapies, whereas people with PS 3 or 4 most often receive supportive care. However, treatment for people with PS 2 without a targetable mutation remains unclear. Historically, people with a PS 2 cancer are frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity. We aim to address this knowledge gap, as this group of people represents a significant proportion (20% to 30%) of the total population with newly diagnosed lung cancer.

Objectives

To identify the best first-line therapy for advanced lung cancer in people with performance status 2 without a targetable mutation or with an unknown mutation status.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 17 June 2022.

Eligibility criteria

We included randomized controlled trials (RCTs) that compared di)erent chemotherapy (with or without angiogenesis inhibitor) or immunotherapy regimens, specifically designed for people with PS 2 only or studies including a subgroup of these people.

Synthesis methods

We used standard Cochrane methods. Our primary outcomes were 1. overall survival (OS), 2. health-related quality of life (HRQoL), and 3. toxicity/adverse events. Our secondary outcomes were 4. tumor response rate,5. progression-free survival, and 6. survival rates at six and 12 months' treatment. We used GRADE to assess certainty of evidence for each outcome.

Synthesis of results

We included 22 trials in this review and identified one ongoing trial. Twenty studies compared chemotherapy with different regimens, of which 11 compared non-platinum therapy (monotherapy or doublet) versus platinum doublet. We found no studies comparing best supportive care with chemotherapy and only two abstracts analyzing chemotherapy versus immunotherapy.

We found that platinum doublet therapy showed superior OS compared to non-platinum therapy (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.57 to 0.78; 7 trials, 697 participants; moderate-certainty evidence). There were no di)erences in six-month survival rates (risk ratio [RR] 1.00, 95% CI 0.72 to 1.41; 6 trials, 632 participants; moderate-certainty evidence), whereas 12-month survival rates were improved for treatment with platinum doublet therapy (RR 0.92, 95% CI 0.87 to 0.97; 11 trials, 1567 participants; moderate-certainty evidence). PFS and tumor response rate were also better for people treated with platinum doublet therapy, with moderate-certainty evidence (PFS: HR 0.57, 95% CI 0.42 to 0.77; 5 trials, 487 participants; tumor response rate: RR 2.25, 95% CI 1.67 to 3.05; 9 trials, 964 participants).

When analyzing toxicity rates, we found that platinum doublet therapy increased grade 3 to 5 hematologic toxicities, all with low-certainty evidence (anemia: RR 1.98, 95% CI 1.00 to 3.92; neutropenia: RR 2.75, 95% CI 1.30 to 5.82; thrombocytopenia: RR 3.96, 95% CI 1.73 to 9.06; all 8 trials, 935 participants).

Only four trials reported HRQoL data; however, the methodology was different per trial and we were unable to perform a meta-analysis.

Although evidence is limited, there were no diff)erences in 12-month survival rates or tumor response rates between carboplatin and cisplatin regimens. With an indirect comparison, carboplatin seemed to have better 12-month survival rates than cisplatin compared to non-platinum therapy.

The assessment of the efficacy of immunotherapy in people with PS 2 was limited. There might be a place for single-agent immunotherapy, but the data provided by the included studies did not encourage the use of double-agent immunotherapy.

Authors' conclusions

This review showed that as a first-line treatment for people with PS 2 with advanced NSCLC, platinum doublet therapy seems to be preferred over non-platinum therapy, with a higher response rate, PFS, and OS. Although the risk for grade 3 to 5 hematologic toxicity is higher, these events are often relatively mild and easy to treat. Since trials using checkpoint inhibitors in people with PS 2 are scarce, we identified an important knowledge gap regarding their role in people with advanced NSCLC and PS 2.

PLAIN LANGUAGE SUMMARY

Best therapy for people with advanced non-small cell lung cancer who have not been treated without a targetable mutation and moderately impaired performance status

Key messages

- The preferred chemotherapy for people with moderately impaired performance status (PS) with advanced non-small cell lung cancer (NSCLC) and that have never received any treatment before should contain two medicines, one of which is a platinum-based medicine.
- Although the risk for bone marrow damage is higher with a platinum-based medicine, these events are often relatively mild and easy to treat.
- We were unable to assess the effects of immunotherapy on moderately impaired people.

What is non-small cell lung cancer?

Lung cancer is the most frequent cause of cancer-related death worldwide and NSCLC is the most common subtype. At the time of diagnosis, the disease has already spread in more than half of all cases. In the tumors of a minority of people diagnosed with NSCLC that has spread to other parts of the body specific mutations can be found, which are treated distinct from the majority of people without such mutations.

How can non-small cell lung cancer be treated?

NSCLC can only be treated with life-prolonging medicines such as chemotherapy (a medicine used to destroy cancer cells) or immunotherapy (a medicine that boosts the person's immune system and helps the body find and destroy cancer cells). Selecting the best treatment depends on the health condition of the person. That condition is determined using a scale from 0 (no symptoms) to 5 (dead). There is no discussion on the treatment of relatively fit people (scoring 0 or 1), as they often tolerate these treatments relatively well. People with a low health condition (scoring 3 or 4) receive only supportive care in most cases. However, although representing 20% to 30% of all people, the best treatment for moderately impaired people (PS 2) is not clear, as they often do not participate in trials.

What did we want to find out?

Our objective was to investigate the best therapy for people with advanced NSCLC without a specific mutation with PS 2.

What did we do?

We searched medical databases for clinical trials comparing treatments for advanced NSCLC with best supportive care or other treatments.

What did we find?

We found 22 trials; 20 compared different types of chemotherapy and two compared chemotherapy versus immunotherapy.

Main results

People treated with chemotherapy regimens using two medicines, including a platinum-based medicine, had longer survival than people treated with chemotherapies without a platinum-based medicine. However, these people did have more side effects, especially with a negative influence on the bone marrow (matter found in the center of bones), resulting in a temporary lack of red and white blood cells, and platelets. The few studies that analyzed health-related quality of life all used different methods of measurement. We found no difference in quality of life when we looked at those studies individually. We found two partly published trials studying immunotherapy, which found no survival benefit compared to chemotherapy.

What are the limitations of the evidence?

We are moderately confident in our results that chemotherapies with a platinum-based medicine increases survival. We are also moderately confident in the evidence evaluating the time to progression of disease because in all included studies, both investigators and trial participants were fully aware of which treatment the participants received. This might lead to substantial bias. In addition, we have little confidence in the evidence regarding toxicities because the evidence is based on a small number of studies with conflicting outcomes.

How up to date is this evidence?

The evidence is up to date to 17 June 2022.

SUMMARY OF FINDINGS

Platinum doublet compared to non-platinum therapy for people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status

Patient or population: people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status
Setting: –
Intervention: platinum doublet
Comparison: non-platinum therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-platinum therapy	Risk with platinum doublet				
Overall survival	**Study population**		**HR 0.67** (0.57 to 0.78)	697 (7 RCTs)	⨁⨁⨁⊖ **Moderate**[a]	Platinum doublet increases overall survival.
	Not applicable					
12-month survival rates	**Study population**		**RR 0.92** (0.87 to 0.97)	1567 (11 RCTs)	⨁⨁⨁⊖ **Moderate**[a]	Platinum doublet increases 12 months survival rates.
	824 per 1000	767 per 1000 (726 to 808)				
Progression-free survival	**Study population**		**HR 0.57** (0.42 to 0.77)	487 (5 RCTs)	⨁⨁⨁⊖ **Moderate**[a]	Platinum doublet likely increases progression-free survival.
	Not applicable					
Tumor response rate	**Study population**		**RR 2.25** (1.67 to 3.05)	964 (9 RCTs)	⨁⨁⨁⊖ **Moderate**[a]	Platinum doublet likely increases tumor response rate.
	103 per 1000	231 per 1000 (172 to 314)				
Toxicity – anemia grade 3–5	**Study population**		**RR 1.98** (1.00 to 3.92)	935 (8 RCTs)	⨁⨁⊖⊖ **Low**[a,b]	Platinum doublet may result in an increase of anemia grade 3–5.
	63 per 1000	126 per 1000 (63 to 249)				
Toxicity – neutropenia grade 3–5	**Study population**		**RR 2.75** (1.30 to 5.82)	935 (8 RCTs)	⨁⨁⊖⊖ **Low**[a,b]	Platinum doublet may result in an increase of neutropenia grade 3–5.
	123 per 1000	337 per 1000 (159 to 714)				
Toxicity – thrombocytopenia grade 3–5	**Study population**		**RR 3.96** (1.73 to 9.06)	935 (8 RCTs)	⨁⨁⊖⊖ **Low**[a,b]	Platinum doublet may result in an increase of thrombocytopenia grade 3–5.
	30 per 1000	117 per 1000 (51 to 268)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level. All studies were open-label and, therefore, considered high risk for outcome bias and allocation concealment was unclear.
[b] Downgraded one level due to high heterogeneity.

BACKGROUND

Description of the condition

Lung cancer is the most frequent cause of cancer-related death worldwide, diagnosed in over 2.2 million people annually[1]. Non-small cell lung cancer (NSCLC) accounts for 75% of all cases. At the time of diagnosis, more than 50% of people already have advanced disease and can be treated only with palliative systemic therapies or best supportive care (BSC)[2]. Unfortunately, despite these therapies, survival rates remained poor, with a median survival of 8.8 months for people with Stage IV disease[3]. More recently, after the introduction of checkpoint inhibitors and targeted therapies, the prognosis of selected patients improved [4, 5, 6]. However besides tumor stage and driver mutation status, survival is determined by various patient- and tumor-related factors (e.g. smoking status, age, gender, performance status [PS], histologic characteristics), of which PS is the most important prognostic factor [7].

The two most commonly used PSs are the Karnofsky Performance Status (KPS) and the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS). These scores correlate strongly, although the ECOG PS shows better predictive performance[8], and has been adopted by the World Health Organization (WHO)[9]. The ECOG PS is a five-grade scale: 0 - fully active, able to carry on all predisease activities without restriction; 1 - restriced in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature; 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; 3 – capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 – completely disabled, cannot carry on any self-care, totally confined to bed or chair; and 5 – dead.

Evidence is clear that people with known molecular targets (e.g. epidermal growth factor receptor [EGFR] mutation, anaplastic lymphoma kinase [ALK] rearrangement or fusion) should be treated with targeted therapy, regardless of PS[10, 11, 12, 13, 14]. People with PS of 0 or 1 are usually treated with systemic therapies such as platinum-based doublet chemotherapy or checkpoint inhibitors (or both), whereas people with PS of 3 or 4 most often receive supportive care (except for patients eligible for target therapy). However, treatment for people with PS 2 without a targetable mutation remains unclear[11]. Historically, people with a PS of 2 were included in clinical trials[15]. However, in the last decades they were frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity compared with people with a PS of 0 or 1[16, 17, 18, 19, 20, 21]. As a consequence, trial populations often fail to represent the real-world population of people with lung cancer, as 20% to 30% of all newly diagnosed people with advanced NSCLC present with PS 2[22, 23]. Due to developments over time and real-world evidence, study protocols are slowly migrating to re-include people with PS 2 (Lee 2022[24, 25]; Lena 2022[26]). Also, subsets of people with PS 2 can be distinguished in clinical practice: those who were in poor health due to comorbidities and developed lung cancer; those whose PS is (in part) a result of their lung cancer; and those who fall into both groups. Most trials do not distinguish between these groups.

Description of the intervention and how it might work

To identify the best first-line treatment for people with advanced NSCLC with PS of 2 and non-targetable or unknown mutation status, we included trials assessing chemotherapy (platinum doublet-based regimens, single or combination cytotoxic agents), immunotherapy (anti-programmed cell death protein 1 [PD-1] or programmed death-ligand [PD-L1]/cytotoxic T lymphocyte-associated antigen 4 [CTLA-4]), vascular endothelial growth factor (VEGF) inhibitors, and BSC.

Regardless of PS, a variety of single cytotoxic agents and combination regimens have been evaluated for the treatment of NSCLC. In 1995, the Non-Small Cell Lung Cancer Collaborative Group published a meta-analysis showing the benefits of chemotherapy added to BSC for overall survival (OS)[27, 28]. In 2008, a subsequent add-on meta-analysis by the same group showed overall improvement in one-year survival of 9% (from 20% to 29%), representing an absolute increase in median survival of 1.5 months (hazard ratio [HR] 0.77, 95% confidence interval [CI] 0.71 to 0.83). The most commonly studied groups of agents are vinca alkaloid or etoposide with or without platinum agents as single- or doublet-agent regimens[29]. Regimens using combinations of cytotoxic agents containing platinum agents show better results than those with single-agent treatment and BSC[30]. Guidelines, therefore, recommend standard first-line chemotherapy consisting of a platinum doublet regimen[11, 14]. To date, the most commonly used agents are cisplatin or carboplatin plus docetaxel; gemcitabine; paclitaxel; vinorelbine; and pemetrexed. Adding bevacizumab to first-line chemotherapy regimens showed additional absolute survival of 26 days[31].

In recent years, immunotherapy has emerged as a novel treatment. Since 2015, multiple immune checkpoint inhibitors (e.g. nivolumab and pembrolizumab [both PD-1 inhibitors] and atezolizumab [PD-L1 inhibitor]) have been approved by the US Food and Drug Administration (FDA) for the treatment of advanced lung cancer and have become standard therapies in first-line or second-line (or both) settings for people with advanced disease. Compared to current chemotherapy regimens, these immune checkpoint inhibitors lead to better progression-free survival (PFS) and one-year survival along with improved quality of life (QoL)[16, 32, 33]. Results of studies combining chemotherapy and immunotherapy have been published[34]. Therapies combining different types of immunotherapy such as ipilimumab, a CTLA-4 inhibitor, and nivolumab, are now being introduced as an addition to current regimens of chemotherapy or immunotherapy (or both)[35].

Currently used cytotoxic agents can be divided into four groups.

- Alkylating agents (platinum agents [cisplatin and carboplatin]): these agents cause cross-linking of DNA, thereby inhibiting DNA repair or synthesis (or both).
- Antimetabolites (pyrimidine analogues [gemcitabine], folate antagonists [pemetrexed]): agents that interfere with DNA synthesis by disrupting processes essential to cell replication.
- Antimicrotubule agents (taxanes [docetaxel, paclitaxel] and vinca alkaloids [vinorelbine]): agents that block cell division by inhibiting formation or disassembly of microtubules.
- Topoisomerase inhibitors (i.e. epipodophyllotoxins [etoposide]): agents that create DNA strand breaks and block DNA unwinding.

Bevacizumab is a monoclonal antibody that targets VEGF, thereby inhibiting angiogenesis. Immune checkpoint inhibitors (anti PD-1/L1, CTLA-4) affect the function of the immune system by stimulating or inhibiting regulatory feedback signaling of T cells, leading to a T-cell response to tumor cells.

Why it is important to do this review

We identified a gap in the current overview literature about the best first-line treatment for people with advanced NSCLC with PS 2 and non-targetable or unknown mutation status. Guidelines from the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) do not provide definitive answers[11, 14]. We aimed to address this knowledge gap, as this group of people represents a significant proportion (20% to 30%) of the total population with newly diagnosed lung cancer.

OBJECTIVES

To identify the best first-line therapy for advanced lung cancer in people with performance status 2 without a targetable mutation or with unknown mutation status.

METHODS

There are two differences in methodology between protocol and review[36]. We did not perform any subgroup analyses due to a lack of data. We chose to present the sensitivity analysis in line in the results section instead of a predefined table.

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) reporting at least one subset analysis of people with PS 2, with or without blinding. We excluded cross-over studies.

Types of participants

People aged 18 years and older who had not received previous therapy for pathologically confirmed Stage IIIB, IIIC, or IV NSCLC (Eighth Edition of TNM [tumor-node-metastasis] in Lung Cancer[3] or corresponding stages from previous editions) and with an ECOG PS of 2 or equivalent. Participants were considered for palliative systemic therapy only. We included people regardless of their histology (e.g. squamous, non-squamous). We excluded people with confirmed targetable and treated mutations (e.g. EGFR, BRAF, ALK, MET, ROS1).

Types of interventions

We included all types of chemotherapy and checkpoint-inhibiting immunotherapy. Chemotherapy was defined as cytotoxic drugs, for example (but not limited to), cisplatin, carboplatin, paclitaxel, pemetrexed, gemcitabine, vinorelbine, irinotecan, or docetaxel. Checkpoint-inhibiting immunotherapy was defined as drugs that targeted T-cell suppressive pathways, for example, nivolumab, pembrolizumab (anti-PD-1), atezolizumab, durvalumab (anti-PD-L1), and ipilimumab (anti-CTLA-4). Other antitumor treatments such as bevacizumab (angiogenesis inhibitor) were allowed and categorized as subgroups.

We investigated the following comparisons.

- Chemotherapy versus BSC
- Chemotherapy versus chemotherapy
- Chemotherapy versus immunotherapy
- Chemotherapy plus immunotherapy versus chemotherapy or immunotherapy
- Immunotherapy versus BSC
- Immunotherapy versus immunotherapy
- Interventions named above with the same intervention plus bevacizumab

Outcome measures

Critical outcomes

- Overall survival (OS), defined as time from start of treatment until death by any cause
- Health-related quality of life (HRQoL), measured via validated international scales
- Toxicity/adverse events (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 to 5, and Patient Reported Outcomes [PRO]-CTCAE if reported)[37]

Important outcomes

- Tumor response rate, defined as the percentage of people whose cancer shrank or disappeared after treatment based on the Response Evaluation Criteria in Solid Tumors (RECIST 1.1)[38], or in cases of immunotherapy as reported via iRECIST criteria[39]
- Progression-free survival (PFS), defined as time from randomization until disease progression
- Survival rates at specified time points (six and 12 months), defined as time from start of treatment until death by any cause

Search methods for identification of studies

Electronic searches

We conducted searches in the following electronic databases from inception to 17 June 2022.

- Cochrane Lung Cancer Group Trials Register
- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (Supplementary material Table 6AS.1)
- MEDLINE, accessed via PubMed (Supplementary material Table 6AS.2)
- Embase, accessed via Elsevier (Supplementary material Table 6AS.3)

We applied no restriction on the language of publication.

The Information Specialists of the Cochrane Lung Cancer Group designed the search strategies.

We searched all databases using both controlled vocabulary (namely, medical subject headings [MeSH] in MEDLINE and Emtree in Embase) and a wide range of free-text terms. We performed the MEDLINE search using the Cochrane highly sensitive search strategy and the precision-maximizing version (2008 version), as described in the Cochrane Handbook for Systematic Reviews of Interventions (Section 6.4.11.1, and detailed in Box 6.4.b)[40].

Searching other resources

We used the following additional resources to identify studies eligible for inclusion.

- Reference lists of included trials
- Meeting abstracts of conferences of the ASCO from 2016 to 13 September 2022
- Meeting abstracts of conferences of the ESMO from 2016 to 13 September 2022
- Meeting abstracts of conferences of the International Association for the Study of Lung Cancer (IASLC) from 2016 to 13 September 2022
- Clinical trials registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu) from 2016 to 17 June 2022

Data collection and analysis

Selection of studies

We transferred all retrieved titles and abstracts to a reference manager database[41], and excluded duplicates. Two review authors (RG and WG) independently selected studies for review that meet inclusion criteria, based on titles and abstracts, and obtained the full-text of potentially relevant references. We discussed any disagreements to achieve consensus. If there was no consensus, we consulted a third review author (BV). Where appropriate, we corresponded with investigators to clarify study eligibility or to obtain raw data. If a study population combined multiple PS groups (e.g. PS 0 to 2), we included the whole group. Where possi-ble, we recalculated KPS and WHO PSs as ECOG PSs to enhance comparability. We documented reasons for exclusion at the full-text stage in the online version of this Cochrane review.

Data extraction and management

Two review authors (RG and WG) independently extracted and documented characteristics and outcome data from the included studies using an electronic data collection form. If we identified multiple published reports for an included study, we collected data on separate data collection forms and combined them after extraction. One review author (RG) transferred data to the Review Manager 5 [42], and a second review author (WG) checked the data. In cases of disagreement, we consulted a third review author (BV) to reach consensus.
We extracted the following data.

- Author, year of publication, journal of origin, funding source
- Methods (inclusion and exclusion criteria; type of analysis – intention-to-treat [ITT] or per-protocol [PP]; endpoints [with time points]; characteristics used to define subgroups)
- Participants (total number, baseline characteristics [if available: age, sex, smoking status, PS, histology, mutation status, stage, country, ethnicity])
- Intervention (agents used and control intervention)
- Outcomes (results on primary and secondary endpoints)

Risk of bias assessment in included studies

We assessed the following types of bias using the Cochrane RoB 1 tool (as reported in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Intervention[40]).

- Selection bias (sequence generation, allocation concealment)
- Performance bias (blinding of participants and personnel)
- Detection bias (blinding of outcome assessment)
- Attrition bias (incomplete outcome assessment)
- Reporting bias (selective outcome reporting)
- Other sources of bias (as identified during analysis)

We rated each domain of the tool at 'low', 'high', or 'unclear' risk of bias at study level and for each outcome where possible. We supported the rating of each domain with a brief description.

Measures of treatment effect

We used the following measures of treatment effect.

- For time-to-event data, we used hazard ratio (HR) and 95% confidence interval (CI), if possible. We also presented median survival and six- or 12-month survival if applicable.
- For dichotomous outcomes, we used risk ratio (RR) and 95% CI, if possible.
- For continuous outcomes, we used mean difference (MD) where studies used the same scale or standardized mean difference (SMD) where studies used difference scales, if possible.

Unit of analysis issues

We did not include trials using a non-standard design. For studies with more than one intervention arm, we analyzed these groups separately.

Dealing with missing data

If data were missing, we tried to contact the corresponding author of that study to obtain these results. If data were missing to such an extent that the study could not be included in the analysis, we reported this.

Reporting bias assessment

We used funnel plots to assess small-study effects as publication bias if at least 10 studies were included in the analyses. We visually inspected these plots and considered publication bias as one of several possible explanations when we observed asymmetry, and we conducted further exploration.

Synthesis methods

When we identified a sufficient number of studies with a low degree of heterogeneity (I^2 of 30% or less or $P \geq 0.1$ on the Chi^2 test), we conducted a meta-analysis using the fixed-effect model. If there was substantial heterogeneity (I^2 greater than 30% or $P \leq 0.1$ on the Chi^2 test), we conducted a meta-analysis using a random-effects model. For dichotomous outcomes, we pooled (calculated) RRs for an event or property. For time-to-event data, we pooled HRs.
If we were unable to conduct a meta-analysis, we summarized the results narratively and use appropriate tables and images.
We assessed the degree of heterogeneity using I^2 statistics and considered a significance of heterogeneity test (Chi^2 test). An I^2 value greater than 30% or a low P value on the Chi^2 test ($P < 0.1$) was considered to represent at least moderate heterogeneity.

Investigation of heterogeneity and subgroup analysis

We considered the following factors as potential predictors of heterogeneity and planned a subgroup analysis to evaluate the effects of interventions in the following groups, if there were sufficient data.

- Histology (squamous or non-squamous)

- PD-L1 status (tumor proportion score (TPS) less than 1%, 1% to 49%, 50% or greater)
- People aged less than 70 years or 70 years or greater
- Presence or absence of central nervous system metastasis
- Chemotherapy monotherapy versus doublet (post-hoc)

Sensitivity analysis

When we identified issues suitable for sensitivity analysis, we performed this analysis. When there were sufficient trials, we excluded trials with potentially high risk of bias, with the exception of blinding. If we performed a sensitivity analysis, we reported this by producing a summary table.

Certainty of the evidence assessment

We created a summary of findings table to report the following outcomes.

- OS
- HRQoL
- Toxicity/adverse events
- Tumor response rate
- PFS
- Survival rates

When creating the summary of findings table, we applied the GRADE approach as suggested in Chapters 11 and 12 of the Cochrane Handbook for Systematic Reviews of Interventions [40] and used GRADEpro GDT software[43] .

RESULTS

Description of studies

Results of the search

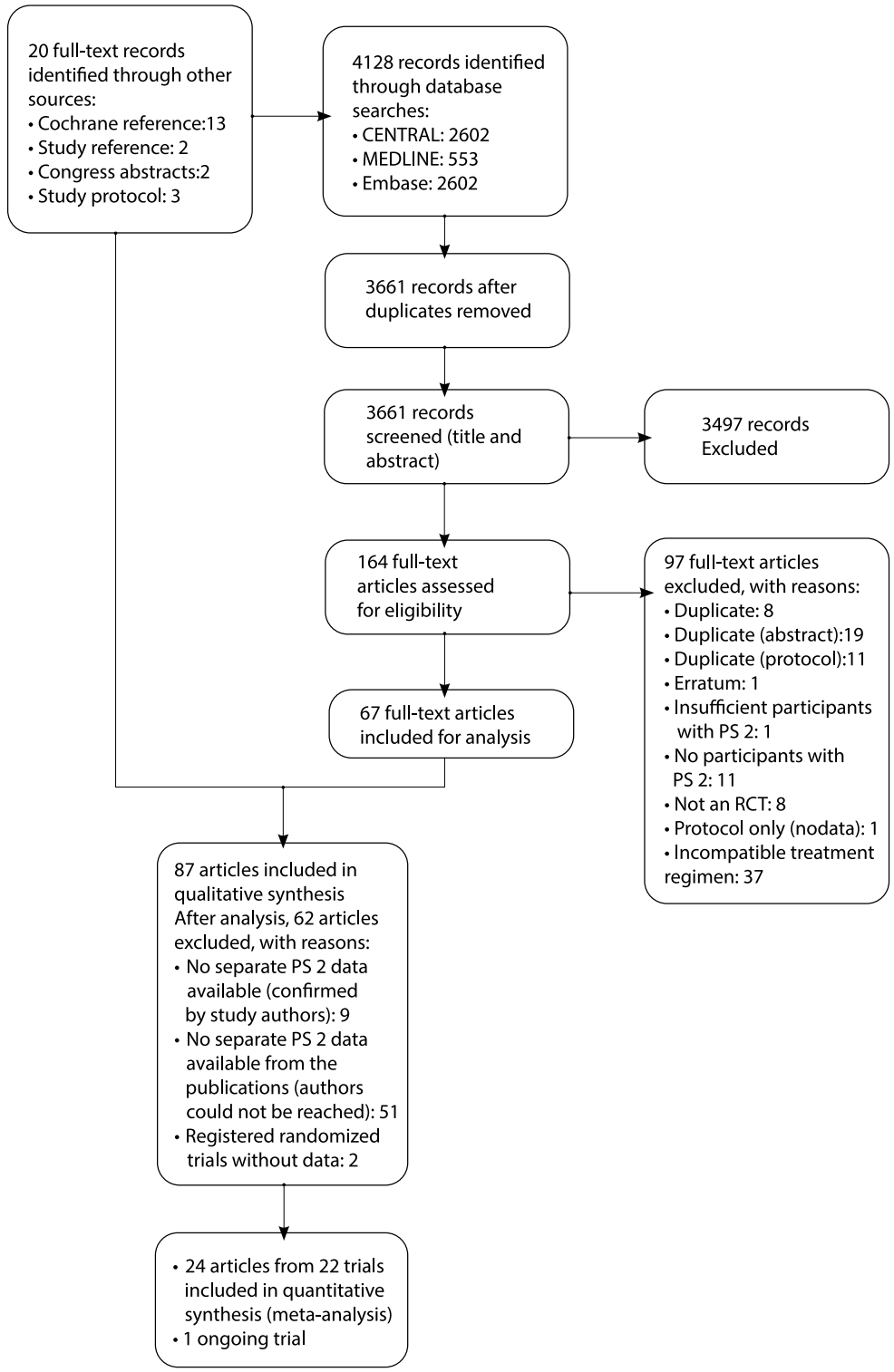
We identified 4128 records (2602 from CENTRAL, 553 from MEDLINE, and 973 from Embase), which reduced to 3661 after the removal of duplicates.

Initial screening of titles and abstracts excluded 3538 manuscripts, resulting in 164 manuscripts requiring full-text analysis (Figure 6A.1). Of these, 67 were eligible, 20 manuscripts were added by additional sources. After exclusion of 62 articles for various reasons (see Excluded studies), we included 22 trials in this systematic review (Flotten 2012 [44] ; Gridelli 2007[45]; Gronberg 2009[46]; Hainsworth 2007[47]; Karampeazis 2011[48]; Kosmidis 2007[49]; Kosmidis 2012[50]; Langer 2007[51]; Le Chevalier 2001[52, 53]; Lee 2022; Lena 2022; Lilenbaum 2005[54]; Morabito 2013[55]; Morere 2010[56, 57]; Quoix 2011[58]; Reynolds 2009[59]; Saito 2012[60]; Schuette 2017[61]; Spigel 2018[62]; Sweeney 2001[63, 64]; Yadav 2021[65]; Zukin 2013[66]). One trial was still ongoing (NCT02581943[67]).

Except for two trials presented as congress abstract only (Lee 2022; Lena 2022), all other studies compared chemotherapy with different regimens, of which 11 compared non-platinum therapy versus platinum doublet. There were no studies comparing BSC with chemotherapy.

Of those 20 chemotherapy trials, nine were designed especially for or reported outcomes of people with PS 2 only, of which six compared non-platinum therapy versus platinum

Figure 6A.1 Prisma flow diagram



doublet (Kosmidis 2007; Morabito 2013; Reynolds 2009; Saito 2012; Spigel 2018; Zukin 2013). The other three trials used various non-comparable chemotherapy regimens (Kosmidis 2012; Langer 2007; Sweeney 2001).

We obtained full subgroup data from five studies (Flotten 2012; Gronberg 2009; Morere 2010; Quoix 2011; Yadav 2021). We were unable to obtain additional data from the six other studies and only incomplete subgroup data were available (Gridelli 2007; Hainsworth 2007; Karampeazis 2011; Le Chevalier 2001; Lilenbaum 2005; Schuette 2017). We did not identify any imbalances in recruitment of people with PS 2 between treatment arms, in any included study (Table 6A.1; Table 6A.2).

INCLUDED STUDIES

Chemotherapy versus chemotherapy

Non-platinum therapy versus platinum doublet regimens

We included 11 trials in this subgroup, involving 1244 people with PS 2. Nine trials compared non-platinum monotherapy with a platinum doublet regimen (Kosmidis 2007; Le Chevalier 2001; Lilenbaum 2005; Morabito 2013; Quoix 2011; Reynolds 2009; Schuette 2017; Spigel 2018; Zukin 2013), and two trials used non-platinum doublet therapy (Flotten 2012; Saito 2012). The data of these studies are summarized and analyzed in Table 6A.1 and Table 6A.3.

Flotten 2012 conducted an open-label, randomized, multicenter phase III trial in Norway comparing treatment with oral vinorelbine 60 mg/m^2 and gemcitabine 1000 mg/m^2 versus carboplatin area under the curve (AUC) 5 and vinorelbine in people with PS 0 to 2. A total of 444 participants were randomized, stratified by WHO PS 0 or 1 versus 2, Stage IIIB versus IV, and age under 75 years versus 75 years or older, including 111 people with PS 2. The primary endpoint was OS; secondary endpoints were QoL, toxicity, and use of palliative radiation therapy. The study was not designed to assess response rates or time to progression (TTP). The study authors provided additional data on the PS 2 subgroup upon request.

Kosmidis 2007 evaluated single-agent gemcitabine 1250 mg/m^2 versus carboplatin AUC 3 and gemcitabine in 90 participants with PS 2 only in a prospective randomized phase II trial in Greece. Their primary outcome was clinical benefit, based on three measures: Lung Cancer Symptom Scale (LCSS), which consists of six symptoms (dyspnea, cough, hemoptysis, fatigue, anorexia, and pain); general feeling (very good, good, or poor); and the participant's weight. Secondary outcomes were OS, PFS, and toxicity. We contacted the study authors for additional information; however, this was no longer available.

Le Chevalier 2001 reported the long-term analysis of survival in a European multicenter randomized phase III study [68], comparing cisplatin 120 mg/m^2 and vinorelbine 30 mg/m^2 (on days one and 29, then every six weeks) to cisplatin and vindesine 3 mg/m^2 (on days one and 29, then every six weeks) and vinorelbine 30 mg/m^2 weekly alone. A total of 612 participants were randomized, stratified by center and stage; 121 people had PS 2. Their primary endpoint was OS, with response rate and tolerance as secondary endpoints. Not all our endpoints regarding participants with PS 2 could be retrieved from the publication, and we were unable to retrieve additional data.

Table 6A.1 Non-platinum therapy versus platinum doublet: used regimens per study

Study	Number of people with PS 2	Cycle length (days)	Non-platinum regimen	Platinum regimen	Duration
Flotten 2012	55/56	21	1. Vinorelbine capsules 60 mg/m^2 2. Gemcitabine 1000 mg/m^2 on days 1 and 8	1. Vinorelbine capsules 60 mg/m^2 on day 1 and 8 2. Carboplatin AUC 5 on day 1	NR
Kosmidis 2007	47/43	28	Gemcitabine 1250 mg/m^2 on days 1 and 14	1. Gemcitabine 1250 mg/m^2 2. Carboplatin AUC 3 on day 1 and 14	Gemcitabine: 0.5 hours Carboplatin: 1 hours
Le Chevalier 2001	46/(42 or 33)	N/A	Vinorelbine 30 mg/m^2 weekly	1. Vinorelbine 30 mg/m^2 weekly 2. Cisplatin 120 mg/m^2 on days 1 and 29 and then every 6 weeks *or* 1. Vindesine 3 mg/m^2 weekly for 6 weeks and then every 6 weeks 2. Cisplatin 120 mg/m^2 on days 1 and 29 and then every 6 weeks	Vinorelbine: 20 minutes Vindesine: push Cisplatin: 1 hour
Lilenbaum 2005	50/49	21	Paclitaxel 225 mg/m^2 on day 1	1. Paclitaxel 225 mg/m^2 on day 1 2. Carboplatin AUC 6	Paclitaxel: 3 hours Carboplatin: 30 minutes
Morabito 2013	28/28	21	Gemcitabine 1200 mg/m^2 on days 1 and 8	1. Gemcitabine 1000 mg/m^2 on days 1 and 8 2. Cisplatin 60 mg/m^2 on day 1	Gemcitabine: 30 minutes Cisplatin: NR
Quoix 2011	62/61	21/28	Vinorelbine 25 mg/m^2 on days 1 and 8 *or*	1. Paclitaxel 90 mg/m^2 on days 1, 8, and 15	NR

Table 6A.1 Non-platinum therapy versus platinum doublet: used regimens per study (continued)

			Gemcitabine 1150 mg/m² on days 1 and 8	2. Carboplatin AUC 6 on day 1	
Reynolds 2009	85/85	21	Gemcitabine 1250 mg/m² on days 1 and 8	1. Gemcitabine 1000 mg/m² on days 1 and 8 2. Carboplatin AUC 5 on day 1	NR
Saito 2012	43/41	21	1. Vinorelbine 25 mg/m² on days 1 and 8 2. Gemcitabine 1000 mg/m² on days 1 and 8	1. Paclitaxel 200 mg/m² on day 1 2. Carboplatin AUC 6 on day 1	Paclitaxel: 3 hours Carboplatin: 1 hour Vinorelbine: 6–10 minutes Gemcitabine: 30 minutes
Schuette 2017	6/7	21	1. Pemetrexed 500 mg/m² on day 1 2. Bevacizumab 7.5 mg/kg on day 1	1. Pemetrexed 500 mg/m² on day 1 2. Carboplatin AUC 5 on day 1 3. Bevacizumab 7.5 mg/kg on day 1	Pemetrexed: 10 minutes Carboplatin: 30–60 minutes Bevacizumab: 90–30[a]
Spigel 2018	63/61	21	1. Pemetrexed 500 mg/m² on day 1 2. Bevacizumab 15 mg/kg on day 1	1. Pemetrexed 500 mg/m² on day 1 2. Carboplatin AUC 5 on day 1 3. Bevacizumab 15 mg/kg on day 1	NR
Zukin 2013	102/103	21	Pemetrexed 500 mg/m² on day 1	1. Pemetrexed 500 mg/m² on day 1 2. Carboplatin AUC 5 on day 1	NR

AUC: area under the curve; PS: performance score, NR: not reported, N/A: not applicable.
[a]The first bevacizumab treatment was administered as an intravenous infusion over 90 minutes after chemotherapy. If the first infusion was well tolerated, the second infusion was given over 60 minutes and all subsequent infusions over 30 minutes.

Lilenbaum 2005 (CALGB 9730) analyzed the effect of single-agent paclitaxel 225 mg/m² versus combination therapy of carboplatin AUC 6 and paclitaxel in a US population. Randomization was stratified by stage, PS (0 or 1 versus 2), and age (under 70 years versus 70 years or older) and the primary endpoint was OS. Secondary endpoints were PFS and response rate, not defined according to RECIST. A total of 99/561 (18%) randomized participants had a PS of 2. Not all data of participants with PS 2 were reported and we were unable to retrieve additional data.

Morabito 2013 (NCT00526643) performed an open-label randomized multicenter phase III study in Italy dedicated to people with PS 2 younger than 70 years, comparing gemcitabine 1200 mg/m² monotherapy with cisplatin 60 mg/m² and gemcitabine. Randomization was stratified by gender, center, and stage (IIIB versus IV). The primary outcome was OS and the secondary outcomes were PFS, response, toxicity, and QoL. A total of 57 participants were randomized. This publication reported all our endpoints.

Quoix 2011 (IFCT-0501) included 451 participants aged 70 years or older in an open-label multicenter randomized phase III trial from France, comparing carboplatin AUC 6 and weekly paclitaxel 90 mg/m² with monotherapy (vinorelbine 25 mg/m² or gemcitabine 1150 mg/m²). Randomization was performed centrally and stratified participants by center, PS (0 or 1 versus 2), stage (III versus IV), and age (80 years or younger versus older than 80 years). The study was designed with an estimate of 520 required participants, but in view of the highly positive results of the second interim analysis, the independent data monitoring committee recommended that participant recruitment be stopped after the inclusion of 451 participants, containing 123 people with PS 2. As only the HR of OS of people with PS 2 was reported, we contacted the Intergroupe Francophone de Cancérologie Thoracique (IFCT) to obtain additional information and received a full analysis of the PS 2 subgroup data.

Fiteni 2016 published QoL data; however, they did not report the QoL data of people with PS 2 separately. We were unable to retrieve additional data.

Reynolds 2009 evaluated the efficacy of gemcitabine 1250 mg/m² versus carboplatin AUC 5 and gemcitabine 1000 mg/m² in people with PS 2, primarily on OS and secondarily on PFS, response rate, and two biomarkers. They randomized 170 of the targeted 220 people to both arms, but as participant accrual was 50% of the expected rate, the trial was terminated prematurely. Not all data of participants with PS 2 were reported and we were unable to retrieve additional data. The biomarker data provided were beyond the scope of this meta-analysis.

Saito 2012 investigated the one-year survival rate of people with PS 2 treated with carboplatin AUC 6 and paclitaxel 200 mg/m² compared to those treated with vinorelbine 25 mg/m² and gemcitabine 1000 mg/m². Secondary endpoints were response rate, PFS, symptom improvement, and toxicity. After randomization with disease stage (IIIB versus IV) and bodyweight loss in the previous six months (less than 5% versus 5% or greater) as stratification factors, 84 people were assessable for analysis. Not all the endpoints of this meta-analysis were reported, but we were unable to retrieve additional data.

Schuette 2017 compared pemetrexed 500 mg/m^2 and bevacizumab 7.5 mg/kg with carboplatin AUC 5, pemetrexed, and bevacizumab for at least four to a maximum of six cycles, in an open-label, multicenter, randomized phase III study from Germany. The primary outcome was PFS, and secondary outcomes were OS, objective response rate, and safety profile.
A total of 271 participants were randomized without stratification by PS, containing only 13 participants with PS 2 (six and seven per arm). In the total study group, a higher rate of people discontinued the study due to adverse events with platinum therapy compared to the non-platinum arm. Also, in the platinum arm, reduction of study medication occurred twice as often. Not all endpoints were reported for participants with PS 2 only and we were unable to retrieve additional data.

Spigel 2018 performed an open-label, multicenter, randomized phase II trial in the US, dedicated to participants with PS 2. They compared three arms, pemetrexed 500 mg/m^2; pemetrexed and bevacizumab 15 mg/kg; and pemetrexed, bevacizumab, and carboplatin AUC 5, with PFS as their primary outcome and objective response rate (ORR), TTP, OS, and six- to 12-month survival as secondary outcomes. They included 172 participants; 48 in the pemetrexed arm, 63 in the pemetrexed and bevacizumab arm, and 61 in the pemetrexed, bevacizumab, and carboplatin arm, after randomization stratified by age (under 75 years versus 75 years or older) and albumin (less than 3.5 g/dL versus 3.5 g/dL or greater). During the trial, inclusion in the single-agent pemetrexed arm was discontinued after publication of the study performed by Zukin 2013. In our analysis, we decided to compare pemetrexed plus bevacizumab with pemetrexed plus bevacizumab plus carboplatin. We did not include the pemetrexed alone arm. This publication reported almost all our endpoints and could be supplemented using data published in NCT00892710.

Zukin 2013 performed a trial dedicated to people with PS 2 only. They studied the effect of single-agent pemetrexed 500 mg/m^2 versus carboplatin AUC 5 and pemetrexed on OS, ORR, PFS, and toxicity in an open-label, multicenter, randomized phase III trial in the US and Brazil. A total of 217 participants were randomized, stratified by stage (IIIB versus IV), weight loss (less than 5% versus 5% or greater), and age (under 70 years versus 70 years or older). Best response could not be determined in 34% of the pemetrexed arm versus 23% of the carboplatin and pemetrexed arm. This publication reported all our endpoints.

Other studies

Nine other studies used different treatment regimens. See also Table 6A. 2 for an overview of treatment regimens and outcome measurements.

Gridelli 2007 studied the differences in TTP, ORR, OS, and toxicity between single-agent pemetrexed or sequential pemetrexed plus gemcitabine in a European open-label, multicenter phase II study in elderly people or people with poor PS, ineligible for platinum therapy. A total of 92 participants were randomized, stratified by stage (IIIB versus IV) and PS (0 or 1 versus 2), with 14 participants with PS 2 in the pemetrexed arm and 17 participants with PS 2 in the pemetrexed plus gemcitabine arm. Only aggregated data on OS and PFS were reported for participants with PS 2. We attempted to contact the authors but were unable to retrieve additional data.

Gronberg 2009 conducted an open-label, multicenter phase III trial in Norway. They compared pemetrexed 500 mg/m^2 plus carboplatin AUC 5 with gemcitabine 1000 mg/m^2 plus carboplatin, with HRQoL (European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire [EORTC QLQ-C30]/European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer [EORTC QLQ-LC13]) as the primary outcome. Secondary outcomes were OS and toxicity. Randomization was stratified by PS (0 or 1 versus 2), stage (IIIB versus IV), and age (under 75 years versus 75 years or over). There were 47 (22%) participants with PS 2 in the pemetrexed plus carboplatin arm and 49 (23%) participants with PS 2 in the gemcitabine plus carboplatin arm. As the primary publication of this trial provided the OS analysis in people with PS 2 only, we contacted the study authors and subsequently received all data required for this review.

Hainsworth 2007 performed a multicenter phase III trial in the US, comparing docetaxel 36 mg/m^2 with gemcitabine 800 mg/m^2 plus docetaxel 30 mg/m^2. All drugs were administered on days one, eight, and 15 of a 28-day cycle for a recommended 6 courses of therapy. People included were older than 65 years or poor candidates for platinum therapy due to comorbidity or poor performance. There was no stratification in randomization reported. The primary endpoint was OS, and secondary endpoints were ORR, PFS, and toxicity. Except for OS, there was no full PS 2 analysis. We contacted the study authors, but the data necessary for our analysis were no longer available.

Karampeazis 2011 evaluated OS, ORR, TTP, and safety profile in people aged 65 years or older treated with either docetaxel 38 mg/m^2 or vinorelbine 25 mg/m^2, both administered on days one and eight of a three-week cycle, in an open-label, multicenter, phase III trial from Greece. They randomized 138 participants, stratifying according to PS (0 or 1 versus 2) and stage (IIIB versus IV). Among them were 26 participants with PS 2; 19 treated with docetaxel and six with vinorelbine. The study reported aggregated data on OS and ORR for the subgroup of participants with PS 2. Therefore, we attempted to contact the study authors but were unable to retrieve additional data.

Kosmidis 2012 randomized people to vinorelbine 60 mg/m^2 or paclitaxel 90 mg/m^2 on days one, eight, and 15 of a four-week cycle for a maximum of four cycles. They included people with PS 2 only and were primarily focused on clinical benefits. There was no stratification in randomization provided. Secondary endpoints were ORR, OS, TTP, and toxicity. The total number of participants was estimated to be 92, but due to low accrual, the study was prematurely terminated after randomization of 75 participants. Not all our endpoints could be retrieved from the publication. We contacted the study authors but no further data were available.

Langer 2007 (ECOG 1599) conducted an open-label phase II trial in the US comparing carboplatin AUC 6 plus paclitaxel 200 mg/m^2 with cisplatin 60 mg/m^2 plus gemcitabine 1000 mg/m^2 in participants with PS 2. Stratification factors included weight loss in preceding six months (less than 5% versus 5% or greater) and stage (IIIb versus IV/recurrent). The primary endpoint was one-year survival rate, other endpoints were ORR, PFS, and toxicities. As a result of power calculations based on previous studies, they randomized 103 participants, which proved to be underpowered to detect the reported improvement in one-year OS. As this publication presented almost all our endpoints, we contacted the study authors but were unable to retrieve additional data.

Table 6A.2 Treatment efficacy (response rate, overall survival, progression-free survival, 6-/12-month survival rates) of non-comparable therapies

Study	Study regimens	Number of people with PS 2	Response rate (% [95% CI])	OS (median [95% CI])	PFS (median [95% CI])	6-month OS (%)	12-month OS (%)	HR (95% CI)
Gridelli 2007	1. Pemetrexed + gemcitabine	17	NR	3.9	1.9	NR	NR	—
	2. Pemetrexed	14		1.8	1.3			
Gronberg 2009	1. Carboplatin + pemetrexed	47	NR	4.3 (3.3 to 5.4)	NR	36.2	23.4	For OS: 1.02 (0.25 to 4.22)
	2. Carboplatin + gemcitabine	49		5.1 (3.3 to 7.0)		46.9	20.4	
Hainsworth 2007	1. Docetaxel	57	NR	2.9	NR	NR (graph)	NR (graph)	—
	2. Docetaxel + gemcitabine	65		3.8				
Karampeazis 2011	1. Docetaxel	19	5.3	3.3 (0.2 to 20.6)	NR	NR	NR	—
	2. Vinorelbine	7	11.8	2.8 (0.9 to 40.6)				
Kosmidis 2012	1. Vinorelbine	36	5	3.1 (2.3 to 3.9)	2.1 (1.8 to 2.4)	NR	13.9	—
	2. Paclitaxel	38	13	5.1 (2.7 to 7.9)	2.6 (1.7 to 4.7)		21.0	
Langer 2007	1. Carboplatin + paclitaxel	54	14 (6.4 to 23.4)	6.2 (NR)	3.5 (2.6 to 6.0)	NR	25.5 (13.1 to 38.0)	
	2. Cisplatin + gemcitabine	49	23 (13.1 to 34.4)	6.9 (NR)	3.0 (1.7 to 4.8)		19.6 (8.7 to 30.5)	
Morere 2010	1. Docetaxel	42	7	6.6 (3.5 to 8.3)	2.2 (1.6 to 4.6)	51.8 (31.9 to 68.4)	19.9 (7.3 to 37.0)	OS: 0.89 (0.57 to 1.41
	2. Gemcitabine	42	0	3.1 (2.0 to 6.4)	2.1 (1.3 to 3.1)	37.9 (20.9 to 54.9)	8.4 (1.5 to 23.3)	PFS: 0.66 (0.37 to 1.16
Sweeney 2001	1. Cisplatin + paclitaxel	14	17 (3.4 to 39.6)	7.0 (range 0.5–29)	1.4 (range 0.2–11.7)	NR	19.0	—
	2. Cisplatin + gemcitabine	13	23 (5.5 to 57.2)	7.9 (range 0.4–16.2)	4.6 (range 0.4–14.6)		38.5	
	3. Cisplatin + docetaxel	18	6 (1.0 to 27.3)	2.3 (range 0.2–31)	1.4 (range 0.2–21.4)		10.5	
	4. Carboplatin + paclitaxel	15	13 (1.7 to 40.5)	4.6 (range 0.9–13.3)	1.5 (range 0.5–13.3)		13.3	
Yadav 2021	1. Carboplatin + pemetrexed	23	NR	9.03 (4.06 to 17.63)	3.27 (1.8 to 9.67)	59.1 (36.1 to 76.2)	45.5 (24.4 to 64.3)	OS: 1.11 (0.54 to 2.28
	2. Carboplatin + paclitaxel	21	—	6.66 (2.93 to 20.46)	2.93 (1.6 to 6.4)	61.9 (38.1 to 78.8)	41.67 (20.5 to 61.7)	PFS: 1.21 (0.64 to 2.29

CI: confidence interval; HR: hazard ratio; NR: not reported; OS: overall survival; PFS progression-free survival; PS: Performance Status.

Morere 2010 (IFCT-0301) presented the results of an open-label multicenter, phase II trial from France. People with PS 2 or 3 were randomized to gefitinib, gemcitabine 1250 mg/m^2, or docetaxel 75 mg/m^2, stratifying by PS (2 versus 3) and pathologic diagnosis (adenocarcinoma versus non-adenocarcinoma). They assessed PFS, ORR, OS, and toxicities. The gefitinib arm was not included in this review. A total of 42 participants were randomized: 30 participants with PS 2 received gemcitabine and 28 participants with PS 2 received docetaxel. The study was set up as exploratory, therefore it was underpowered to make definite conclusions. We contacted the IFCT to obtain additional information and received a complete analysis of the PS 2 subgroup.

Sweeney 2001 reported the results of the ECOG 1594 trial, which compared four platinum doublet regimens, cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2, cisplatin 100 mg plus gemcitabine 1000 mg/m^2, cisplatin 75 mg/m^2 plus docetaxel 75 mg/m^2, and carboplatin AUC 6 plus paclitaxel 225 mg/m$^{2.}$ Stratification variables used in randomization were PS (0 or 1 versus 2), weight loss in preceding six months (less than 5% versus 5% or greater), stage (IIIB versus IV/recurrent), and presence or absence of brain metastases. After 66 participants with a PS of 2 had been enrolled, the study design was amended to include only participants with a PS of 0 or 1 because of the high rate of serious adverse events in the people with a PS of 2[20]. A later conclusion was that these events were related to disease progression rather than treatment-related adverse events. This publication reported all our endpoints.

Yadav 2021 performed a single center open-label randomized trial with a superiority design in India. A total of 44 participants were randomized to carboplatin AUC 5 plus pemetrexed 500 mg/m^2 or carboplatin AUC 5 plus paclitaxel 80 mg/m^2, without stratification by any factor. Participants in both treatment arms were allowed to receive maintenance pemetrexed 500 mg/m^2. The primary endpoint was six-month PFS rate, and secondary endpoints were ORR, disease control rates, OS, and toxicity. We contacted the study authors and received a full analysis of the PS 2 subgroup.

Chemotherapy versus immunotherapy

We identified two studies comparing chemotherapy versus immunotherapy.

Lee 2022 designed a global, multicenter, open-label phase III trial for people not eligible for platinum chemotherapy, randomizing participants between single-agent atezolizumab 1200 mg or single-agent non-platinum chemotherapy (vinorelbine or gemcitabine at investigators choice, dose per relevant local guidelines), without reported stratification factors. Most participants were not eligible for any platinum-doublet chemotherapy due to poor PS (ECOG PS 2 or 3), or participants aged 70 years or older with PS 0 or 1 with substantial comorbidities or contraindication(s) for any platinum-doublet chemotherapy. The primary endpoint was OS, and secondary endpoints were OS rates at six, 12, 18 and 24 months; ORR; PFS; duration of response; toxicity; and QoL. Data were presented at the 2022 ESMO congress only, and we were unable to obtain additional data from the authors.

Lena 2022 conduced a randomized phase III trial in France, randomizing participants stratified by age (under 70 years versus 70 years or older), PS (0 or 1 versus 2), and histology (squamous versus non-squamous), to either nivolumab 240 mg every two weeks plus ipilimumab 1 mg/kg every six weeks, or doublet chemotherapy with carboplatin AUC 5 plus pemetrexed 500 mg/m^2 or carboplatin AUC 6 plus paclitaxel 90 mg/m^2, and the possibility to use maintenance with pemetrexed. The primary endpoint was OS, and secondary endpoints were one-year OS, ORR, PFS, safety rate, tolerability rate, and QoL. A preplanned interim analysis carried out after observation of 33% of deaths, out of 174 randomized participants (of planned 242 participants), showed a risk of futility especially for participant with PS 2. This led to a halt in randomization. As this study was only accessed by abstract from the 2022 ASCO annual congress, we were unable to obtain additional data.

Excluded studies

After full-text analysis, we excluded 97 manuscripts as they did not match our inclusion criteria (Figure 6A.1). The main reasons for exclusion were the use of an incompatible treatment regimen (37/97) or duplicate items (38/97).

We excluded 60 studies as they did not provide separate PS 2 data. We attempted to contact study authors, and in nine cases it was confirmed that there was no possibility of obtaining aggregated PS 2 data only (Al-Gizawy 2014[70]; Doebele 2015[71]; Ferry 2017[72]; Giaccone 1998[73]; Kosmidis 1994[74]; Kumar 2015[75]; Perol 2002[76]; Rodrigues-Pereira 2011[77]; Wachters 2003[78]). We could not contact the authors from the other 51 studies, probably because many studies were performed decades ago (Anderson 1985[79]; Anderson 2000[80]; Atagi 2017[81]; Belani 2006[82]; Cartei 1993[83]; Cellerino 1991[84]; Comella 2004[85]; Crino 1990[86]; Crino 1995[87]; Cullen 1999[88]; Danson 2003[89]; ELVIS 1999[90]; Esteban 2006[91]; Fossella 2003[92]; Ganz 1989[93]; Gebbia 2002[94]; Gebbia 2003[95]; Georgoulias 2001[96]; Greco 2007[97]; Gridelli 1996[98]; Gridelli 2003a[99]; Gridelli 2003b[100]; Grigorescu 2002[101]; Helbekkmo 2007[102]; Helsing 1998[103]; Hillerdal 2011[104]; Jang 2017[105]; Jelić 2001[106]; Kaasa 1991[107]; Karampeazis 2017[108]; Leong 2007[109]; Manegold 1997[110]; Masutani 1996[111]; Paccagnella 2006[112]; Quoix 1991[113]; Ranson 2000[114]; Rapp 1988[115]; Rosell 1987[116]; Rosell 2002[117]; Rosso 1990[118]; Roszkowski 2000[119]; Ruckdeschel 1985[120]; Ruckdeschel 1986[121]; Shinkai 1985[122]; Sorensen 2012[123]; Spiro 2004[124]; Stathopoulos 2004[125]; ten Bokkel Huinink 1999[126]; Thongprasert 1999[127]; Veronesi 1988[128]; Woods 1990[129]).

Two trials were registered on Clinicaltrials.gov; however, we were unable to obtain any data (NCT00004887 [130]; NCT01593293[131]).

ONGOING STUDIES

Chemotherapy plus immunotherapy versus immunotherapy

We identified one ongoing clinical trial designed for people with PS 2, randomizing people between single-agent pembrolizumab or pembrolizumab plus paclitaxel plus carboplatin (NCT02581943). Results from this study are expected in 2023.

RISK OF BIAS IN INCLUDED STUDIES

See Figure 6A.2 and Figure 6A.3 for an overview of risk of bias in all included studies.

Flotten 2012, Gridelli 2007, Gronberg 2009, Karampeazis 2011, Langer 2007, Lilenbaum 2005, Morabito 2013, Morere 2010, Quoix 2011, Saito 2012, Yadav 2021, and Zukin 2013 had a low risk of bias for random sequence generation. Hainsworth 2007, Kosmidis 2007, Kosmidis 2012, Le Chevalier 2001, Lee 2022, Lena 2022, Reynolds 2009, Schuette 2017, Spigel 2018, and Sweeney 2001 had an unclear risk of bias for random sequence generation. No studies were at high risk of random sequence generation.

We considered Langer 2007 and Yadav 2021 to have a low risk of bias for allocation concealment. All other included trials were at unclear risk.

Almost all included studies were reported as open-label trials. In Kosmidis 2007, we were unable to retrieve the blinding status of participants and investigators and Saito 2012 provided no information on blinding (it was probably an open-label trial as treatment days between arms were different); therefore, this was at unclear risk of performance blinding.

We considered that an open-label trial is unlikely to influence OS; therefore, we considered this outcome at low risk of detection bias. However, the bias for the other outcomes in terms of PFS, ORR, and toxicity are considered high risk in all but one of the included studies. Le Chevalier 2001 used a panel of at least three experts, who were blinded to the treatment assignment, verified eligibility criteria, staging, and toxicity, and reviewed original x-rays to evaluate response in all cases and it was, therefore, considered at low risk of detection bias.

We classified five studies at high risk for incomplete outcome reporting (Gridelli 2007; Hainsworth 2007; Lee 2022; Lena 2022; Yadav 2021). Gridelli 2007 did change their outcome measures after data analysis as 44/87 included people had censored times for time to progressive disease, whereas only 14/87 people had censored times for PFS, therefore adding PFS as outcome measurement. Next, best overall response was not assessable in 17 (38.6%) versus four (9.3%) of the people and therefore considered as high risk. Kosmidis 2007 had high rates of missing QoL data on the LCSS, which was the primary outcome measure. After enrollment of 102 people, 12 people were not included in the analysis. Two people were excluded from the analysis and 10 people were considered ineligible. Seven people were inadvertently randomized (PS less than 2), two received protocol treatment as second line, and one had another cancer. Two people randomized in the platinum doublet arm received gemcitabine only but were included in the survival analysis. Lee 2022 and Lena 2022 were only reported as congress abstracts and did not provide a full detailed analysis. Yadav 2021 included 180 of planned 362 people before study termination. However, nine people did not start study treatment due to various reasons, four were lost to follow-up, and three switched to target therapy. Next, radiologic response evaluation was not possible in 18 people.

Six studies were classified at unclear risk. Kosmidis 2012 was unable to include all people in the toxicity analysis with an unknown effect. Le Chevalier 2001 was classified at unclear risk, as in the primary study a small number of people were not treated according to protocol but were included in the analysis[68]. Reynolds 2009 and Zukin 2013 did not have data

Figure 6A.2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

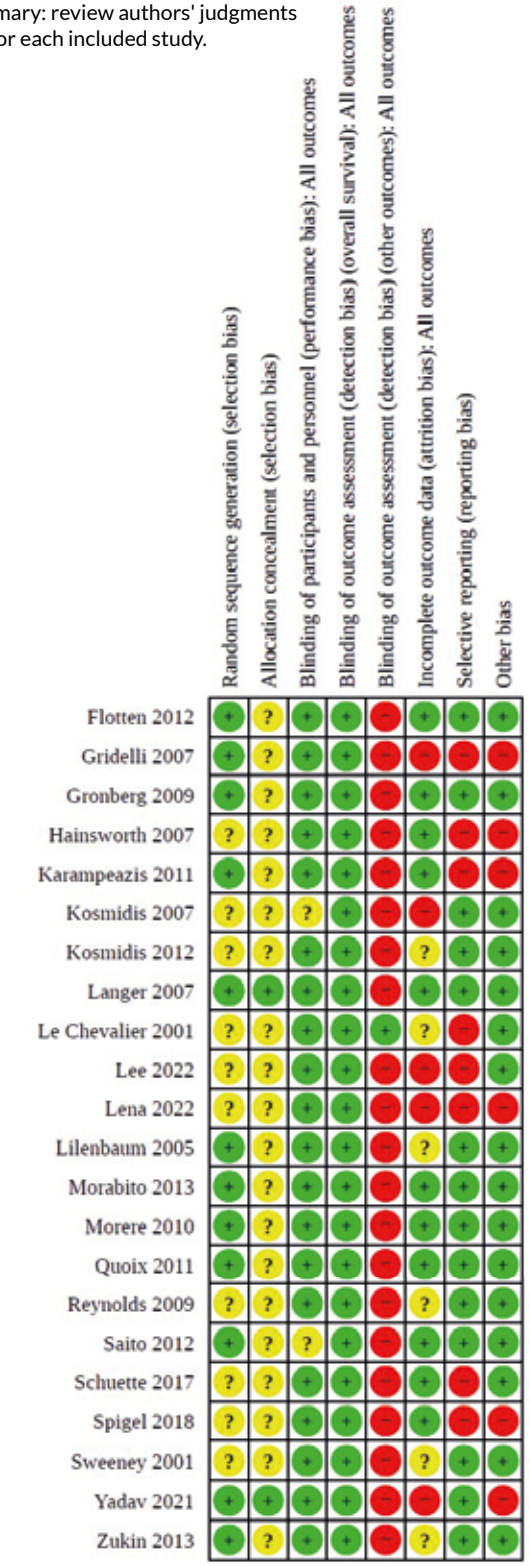
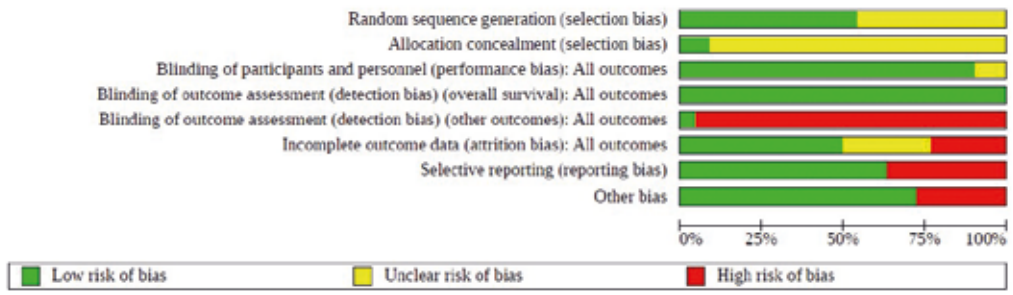


Figure 6A.3 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



available for all people when analyzing response, with unclear risk. Sweeney 2001 was classified at unclear risk for incomplete outcome bias. Accrual of participants with PS 2 was discontinued because of a perception of excess adverse events. Lilenbaum 2005 was considered at unclear risk as 23 (3.9%) participants either withdrew from the study before receiving protocol therapy or were later found to be ineligible.

Flotten 2012, Gronberg 2009, Hainsworth 2007, Karampeazis 2011, Langer 2007, Morabito 2013, Morere 2010, Quoix 2011, Saito 2012, Spigel 2018, and Schuette 2017 were at low risk of attrition bias.

Eight studies were at high risk for reporting bias (Gridelli 2007; Hainsworth 2007; Karampeazis 2011; Le Chevalier 2001; Lee 2022; Lena 2022; Schuette 2017; Spigel 2018).

Gridelli 2007 was considered high risk for selective reporting, as PFS was retrospectively added as an outcome measurement. Hainsworth 2007 did not perform a full separate analysis of participants with PS 2 except for OS, although this group of participants was a different subgroup compared to the PS 0 or 1, elderly group. Karampeazis 2011 did not perform all analyses in participants with PS 2, whereas this was one of the study aims. Le Chevalier 2001 only reported the one-year survival rates of participants with PS 2, the other outcomes were not assessed in participants with PS 2 only. Lee 2022 and Lena 2022 only reported limited data in congress abstracts, not providing all required data for this review. Schuette 2017 did not report all outcomes in participants with PS 2. Also, they provided insufficient information on severity grade of toxicities. Spigel 2018 reported treatment-related toxicities only if the incidence was greater than 10% of at least one study arm, thereby considered at high risk for reporting bias.

The other included studies were considered at low risk for selective reporting, as no evidence of selective reporting bias was found and all outcomes were provided (Flotten 2012; Gronberg 2009; Kosmidis 2007; Kosmidis 2012; Langer 2007; Lilenbaum 2005; Morabito 2013; Morere 2010; Quoix 2011; Reynolds 2009; Saito 2012; Sweeney 2001; Yadav 2021; Zukin 2013).

Table 6A.3 Overall survival and 6-/12-month survival rates for non-platinum therapy versus platinum doublet

		Non-platinum therapy			Platinum doublet				
Study	**Number of people with PS 2**	**Median OS (months) (95% CI)**	**6-month OS (%) (95% CI)**	**12-month OS (%) (95% CI)**	**Median OS (months) (95% CI)**	**6-month OS (%) (95% CI)**	**12-month OS (%) (95% CI)**	**HR (95% CI)**	**P value**
Flotten 2012	55/56	4.0 (NR)	29 (NR)	15 (NR)	4.5 (NR)	43 (NR)	16 (NR)	0.86 (0.59 to 1.25)	0.418
Kosmidis 2007	47/43	4.8 (2.45 to 7.25)	NR	17.8 (NR)	6.7 (2.47 to 10.8)	NR	20 (NR)	0.85 (0.54 to 1.35)	0.49
Le Chevalier 2001	42/33/46	3.9 (NR)	NR	15 (NR)	CisVino: 4.1 (NR)	NR	17 (NR)	NR	NR
					CisVind: 4.1 (NR)	NR	13 (NR)	NR	NR
Lilenbaum 2005	50/49	2.4 (1.9 to 3.6)	NR	10 (4 to 23)	4.7 (3.1 to 6.9)	NR	18 (10 to 33)	0.60 (0.40 to 0.91)	0.016
Morabito 2013	28/28	3.0 (1.9 to 6.3)	21.4 (NR)	7.1 (NR)	5.9 (2.8 to 11.3)	46.4 (NR)	14.2 (NR)	0.52 (0.28 to 0.98)	0.039
Quoix 2011	62/61	3.6 (2.3 to 4.3)	26.7 (16.3 to 38.2)	10.0 (4.1 to 19.1)	6.1 (4.2 to 8.3)	50.9 (37.3 to 62.9)	23.9 (13.7 to 35.6)	0.63 (0.43 to 0.91)	0.006
Reynolds 2009	85/85	5.1 (3.9 to 6.3)	NR	21.2 (NR)	6.7 (4.9 to 10.0)	NR	31.3 (NR)	NR	0.242
Saito 2012	43/41	5.9 (NR)	NR	22.0 (9.3 to 34.6)	6.0 (NR)	NR	27.9 (14.5 to 41.3)	NR	NR
Schuette 2017	6/7	7.0 (0.2 to 11.6)	66.6 (NR)	0 (NR)	3.8 (0.3 to 5.2)	14.3 (NR)	14.3 (NR)	1.48 (0.44 to 5.00)	0.325

Table 6A.3 Overall survival and 6-/12-month survival rates for non-platinum therapy versus platinum doublet (continued)

Spigel 2018	63/61	Pem: 7.7 (3.0 to 11.2)	NR	30 (18 to 43)	8.7 (5.4 to 13.0)	NR	32 (21 to 45)	NR	NR
		PemBev: 8.6 (5.3 to 11.2)	NR	32 (21 to 45)					
Zukin 2013	102/103	5.3 (4.1 to 6.5)	44.9 (NR)	21.9 (NR)	9.3 (7.4 to 11.2)	66.8 (NR)	40.1 (NR)	0.62 (0.46 to 0.83)	0.001
Total	1244 participants								

CI: confidence interval; CisVind: cisplatin + vindesine; CisVino: cisplatin + vinorelbine; HR: hazard ratio; NR: not reported; OS: overall survival; pem: pemetrexed; PemBev: pemetrexed + bevacizumab.

Karampeazis 2011 had a slow accrual rate because of the reluctance of investigators to prescribe chemotherapy in people with a PS of 2, and a further slowdown of accrual occurred after 2006 when[132] reported their randomized trial in elderly people. Because of these reasons, the data monitoring committee decided to close the study after including 138/176 planned participants, resulting in an underpowered study. Due to a change in the standard of care and slow accrual, Yadav 2021 was terminated early after randomizing 180 people while the estimated sample size was 364 (182 in each arm).

While Spigel 2018 was ongoing, a randomized phase 3 trial demonstrated the superiority of platinum doublet (Lilenbaum 2005). As a result, the accrual of people to single-agent pemetrexed (arm one) was stopped, and subsequent randomization (1:1) was continued to arms two and three only.

Hainsworth 2007 included both people with PS 2 or elderly people, however, a separate analysis was not performed and therefore considered at high risk of bias.

Lena 2022 showed partly incorrect data in their congress abstract, therefore considered at high risk of bias.

Gridelli 2007 was at high risk as they performed complete subgroup analysis including both people with PS 2 or elderly people.
All other trials were at low risk of other bias.

SYNTHESIS OF RESULTS

We summarized the effects of interventions in the Summary of findings on page 92, Table 6A.2, and Table 6A.3.

Chemotherapy versus chemotherapy: non-platinum therapy versus platinum doublet regimens

Overall survival

All 11 RCTs included in this analysis evaluated OS as an endpoint (Table 6A.3). However, we excluded four studies from the analysis as they presented no HRs (Le Chevalier 2001; Reynolds 2009; Saito 2012; Spigel 2018).

Meta-analysis of the seven remaining studies included 697 people showed the superiority of platinum doublet therapy over non-platinum therapy with low heterogeneity (HR 0.67, 95% CI 0.57 to 0.78; I^2 = 1%; moderate-certainty evidence; Analysis 1.1; Figure 6A.4). Although there was significant heterogeneity between non-platinum monotherapy and non-platinum doublet subgroups (I^2 = 50.3%), excluding the only study using non-platinum doublet (Flotten 2012) did not influence the pooled results (HR 0.64, 95% CI 0.54 to 0.76; I^2 = 0%). Analyzing only the studies designed for participants with PS 2 (Kosmidis 2007; Morabito 2013; Zukin 2013), and excluding the studies performing PS 2 subgroup analysis (Flotten 2012; Lilenbaum 2005; Quoix 2011; Schuette 2017), did not influence the results (HR 0.66, 95% CI 0.52 to 0.83; I^2 = 0%).

Six- and 12-month survival rates

Of the 11 trials included in this analysis, only six reported six-month survival rates. In contrast, all trials reported 12-month survival rates (Table 6A.3).

There was no difference in six-month survival between treatment regimens (random-effects model; RR 1.00, 95% CI 0.72 to 1.41; I^2 = 76%; moderate-certainty evidence; Analysis 1.2). The reason for heterogeneity was unclear. Exclusion of the only study using non-platinum doublet (Flotten 2012) did not influence the pooled results (RR 1.03, 95% CI 0.64 to 1.63; I^2 = 80%). When including only studies designed especially for participants with PS 2 (Morabito 2013; Spigel 2018; Zukin 2013), heterogeneity decreased and there was a trend towards the superiority of platinum therapy, but did not reach a significance level (RR 0.75, 95% CI 0.53 to 1.04; I^2 = 57%).

In the meta-analysis of 1567 participants from 11 studies, 12-month survival rates were improved with platinum doublet therapy (RR 0.92, 95% CI 0.87 to 0.97; I^2 = 15%; moderate-certainty evidence; Analysis 1.3; Figure 6A.5). However, there was clear subgroup heterogeneity between the non-platinum monotherapy and non-platinum doublet therapy arms (I^2 = 83.9%). The treatment effect of platinum doublet was higher in the subgroup compared with non-platinum monotherapy (RR 0.88, 95% CI 0.82 to 0.94; I^2 = 0%; 9 trials, 1046 participants), whereas there was no difference between treatment arms in the non-platinum doublet subgroup (RR 1.00, 95% CI 0.92 to 1.08; I^2 = 0%; 2 trials, 521 participants). When analyzing only the studies designed for participants with PS 2 (Kosmidis 2007; Morabito 2013; Reynolds 2009; Saito 2012; Spigel 2018; Zukin 2013), and thus excluding those per-

forming PS 2 subgroup analysis (Flotten 2012; Le Chevalier 2001; Lilenbaum 2005; Quoix 2011; Schuette 2017), we found no changes in treatment effect or heterogeneity (HR 0.87, 95% CI 0.80 to 0.95; I^2 = 18%), but there was lower heterogeneity when excluding the only remaining study comparing to non-platinum doublet therapy (Saito 2012) (HR 0.85, 95% CI 0.77 to 0.93; I^2 = 0%).

Progression-free survival

Five trials including 487 participants contributed to the meta-analysis of PFS (Kosmidis 2007; Morabito 2013; Quoix 2011; Schuette 2017; Zukin 2013); all compared platinum doublet to non-platinum monotherapy. PFS of people treated with platinum doublet therapy was superior compared to people treated with non-platinum monotherapy, with substantial heterogeneity (random-effects model; HR 0.57, 95% CI 0.42 to 0.77; I^2 = 48%; moderate-certainty evidence; Analysis 1.4; Figure 6A.6). When analyzing only the studies designed for people with PS 2 (Kosmidis 2007; Morabito 2013; Zukin 2013), there was no change in treatment effect and higher heterogeneity (HR 0.56, 95% CI 0.39 to 0.80; I^2 = 53%). However, when excluding the two studies with a high risk of bias on domains other than blinding (as all studies were open-label) (Kosmidis 2007; Schuette 2017), the heterogeneity disappeared (HR 0.47, 95% CI 0.38 to 0.59; I^2 = 0%).

Tumor response rate

Nine studies including 964 participants found a higher tumor response rate for people treated with platinum therapy (RR 2.25, 95% CI 1.67 to 3.05; I^2 = 9%; moderate-certainty evidence; Analysis 1.5; Figure 6A.7). This did not change after excluding Saito 2012 (RR 2.44, 95% CI 1.75 to 3.39; I^2 = 8%), or when excluding studies evaluating PS 2 subgroups only (RR 2.16, 95% CI 1.49 to 3.14; I^2 = 19%).

Toxicity

Of the 11 included studies in this analysis, three did not report any adverse event analysis in participants with PS 2 only (Le Chevalier 2001; Lilenbaum 2005; Schuette 2017).

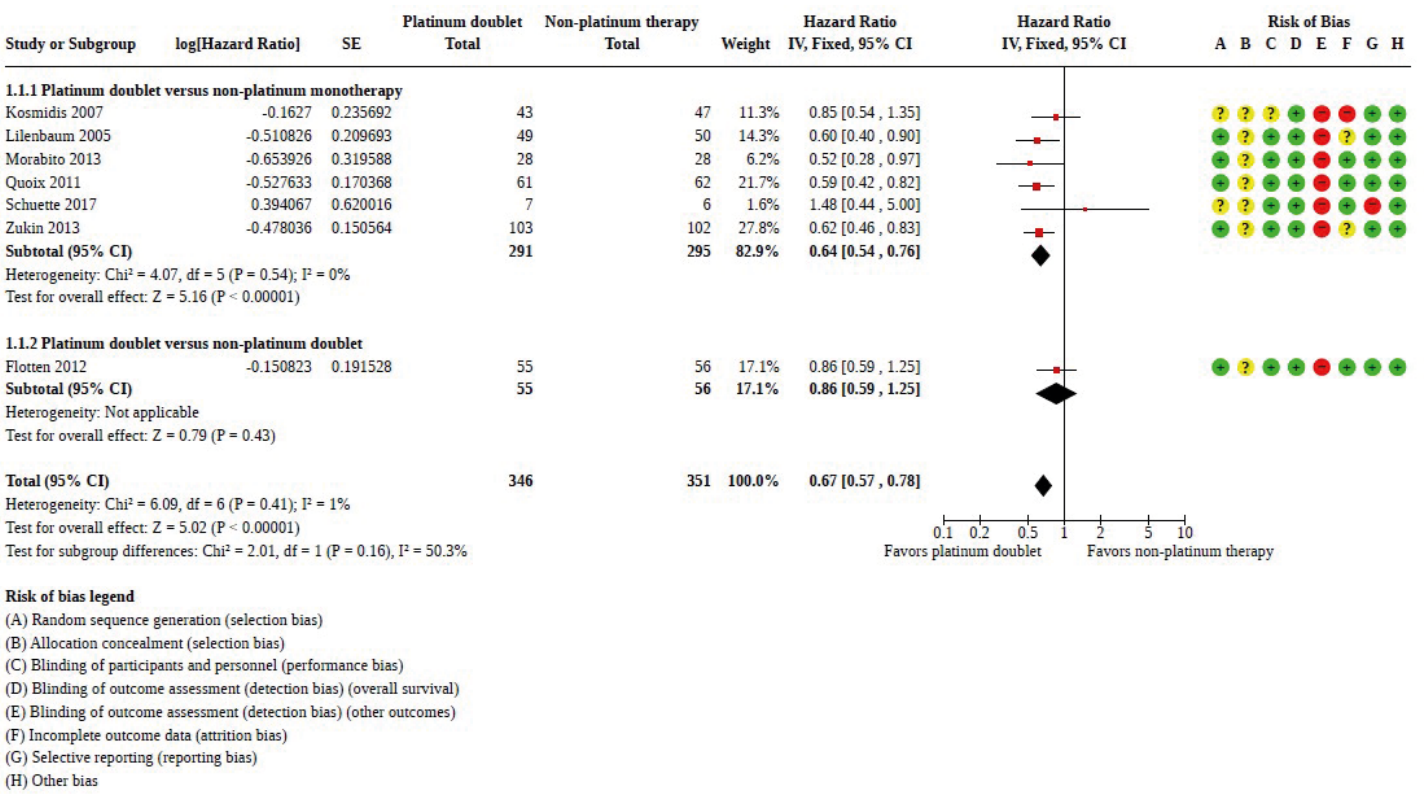
Five studies reported all-grade adverse events (Kosmidis 2007; Morabito 2013; Quoix 2011; Schuette 2017; Spigel 2018), whereas 11 studies reported hematologic adverse events, but there was considerable heterogeneity in the publication of non-hematologic adverse events and, therefore, we were only able to meta-analyze nausea/vomiting, asthenia, and fatigue.

Eight studies reported data for adverse events with grade 3 or higher, with low heterogeneity among the hematologic adverse events and high heterogeneity in reporting of non-hematologic adverse events.
Except for febrile neutropenia (moderate-certainty evidence), all other toxicity outcomes were of low-certainty evidence.

All grades hematologic adverse events

There was no difference in risk of anemia (any grade) (RR 1.13, 95% CI 0.92 to 1.39; I^2 = 28%; 4 studies, 304 participants; Analysis 1.6). However, there was increased risk of any-grade neutropenia and thrombocytopenia in people treated with platinum doublet therapy in a pooled analysis of five studies including 391 participants (neutropenia: RR 2.22, 95% CI 1.58 to 3.11; Analysis 1.7; thrombocytopenia: RR 3.05, 95% CI 2.08 to 4.48; Analysis 1.8).

Figure 6A.4 Forest plot of comparison of platinum doublet versus non-platinum therapy on overall survival



All grades non-hematologic adverse events

There were no differences in risk for nausea/vomiting, asthenia, or fatigue (nausea/vomiting: RR 1.23, 95% CI 0.94 to 1.60; I^2 = 0%; 4 studies, 304 participants; Analysis 1.9; asthenia: RR 1.30, 95% CI 0.92 to 1.85; I^2 = 0%; 3 studies, 250 participants; Analysis 1.10; fatigue: RR 1.16, 95% CI 0.86 to 1.56; I^2 = 0%; 2 studies, 168 participants; Analysis 1.11).

Grade 3 or higher hematologic adverse events

We assessed the risk for grade 3 or higher hematologic adverse events in eight studies including 935 participants (Flotten 2012; Kosmidis 2007; Morabito 2013; Quoix 2011; Reynolds 2009; Saito 2012; Spigel 2018; Zukin 2013). In the pooled analysis, people treated with platinum doublet therapy were at higher risk for severe anemia (random-effects model; RR 1.98, 95% CI 1.00 to 3.92; I^2 = 46%; Analysis 1.12). The high heterogeneity was due to the inclusion of Flotten 2012 and Saito 2012, as they compared to non-platinum doublet therapy. When we excluded these studies, the risk difference was enhanced and there was no heterogeneity (RR 2.78, 95% CI 1.58 to 4.89; I^2 = 0%).

People treated with platinum doublet therapy were at higher risk for severe neutropenia and thrombocytopenia (neutropenia: RR 2.75, 95% CI 1.30 to 5.82; I^2 = 82%; Analysis 1.13; thrombocytopenia: RR 3.96, 95% CI 1.73 to 9.06; I^2 = 42%; Analysis 1.14). When we excluded Flotten 2012 and Saito 2012, the risk differences were increased and there was no heterogeneity (neutropenia: RR 4.31, 95% CI 2.80 to 6.64; I^2 = 0%; Analysis 1.13; thrombocytopenia: RR 7.69, 95% CI 3.74 to 15.80; I^2 = 0%; Analysis 1.14). Seven studies including 821 participants found no difference in the risk for febrile neutropenia (RR 1.63, 95% CI 0.85 to 3.12; I^2 = 27%; Analysis 1.15).

Grade 3 or higher non-hematologic adverse events

There were no differences in risk for grade 3 to 5 nausea/vomiting (RR 2.74, 95% CI 0.83 to 9.04; I^2 = 44%; 7 studies, 850 participants; Analysis 1.16). This did not change after exclusion of the non-platinum doublet studies of Flotten 2012 and Saito 2012 (RR 1.41, 95% CI 0.32 to 6.27; I^2 = 41%). However, when pooling only those two studies, there was a difference (RR 8.72, 95% CI 2.07 to 36.71; I^2 = 0%).

Four studies including 439 participants assessed grade 3 to 5 fatigue. There was no difference between arms (RR 0.81, 95% CI 0.35 to 1.90; I^2 = 62%; Analysis 1.17). Excluding Flotten 2012 did not result in a change. There was no difference in grade 3 to 5 asthenia between arms (RR 2.06, 95% CI 0.97 to 4.38; I^2 = 0%; 2 studies, 237 participants; Analysis 1.18).

Health-related quality of life

Four trials reported HRQoL data. Of those, three were performed in a trial including participants with PS 2 only (Kosmidis 2007; Morabito 2013; Saito 2012). One included participants with PS 2 as a subgroup, and did not report on this subgroup in their primary report but provided the data following our request (Flotten 2012). However, the used methodology was different in each trial and, therefore, we were unable to perform a meta-analysis on these data.

Figure 6A.5 Forest plot of comparison of platinum doublet versus non-platinum therapy on 12 months survival rates

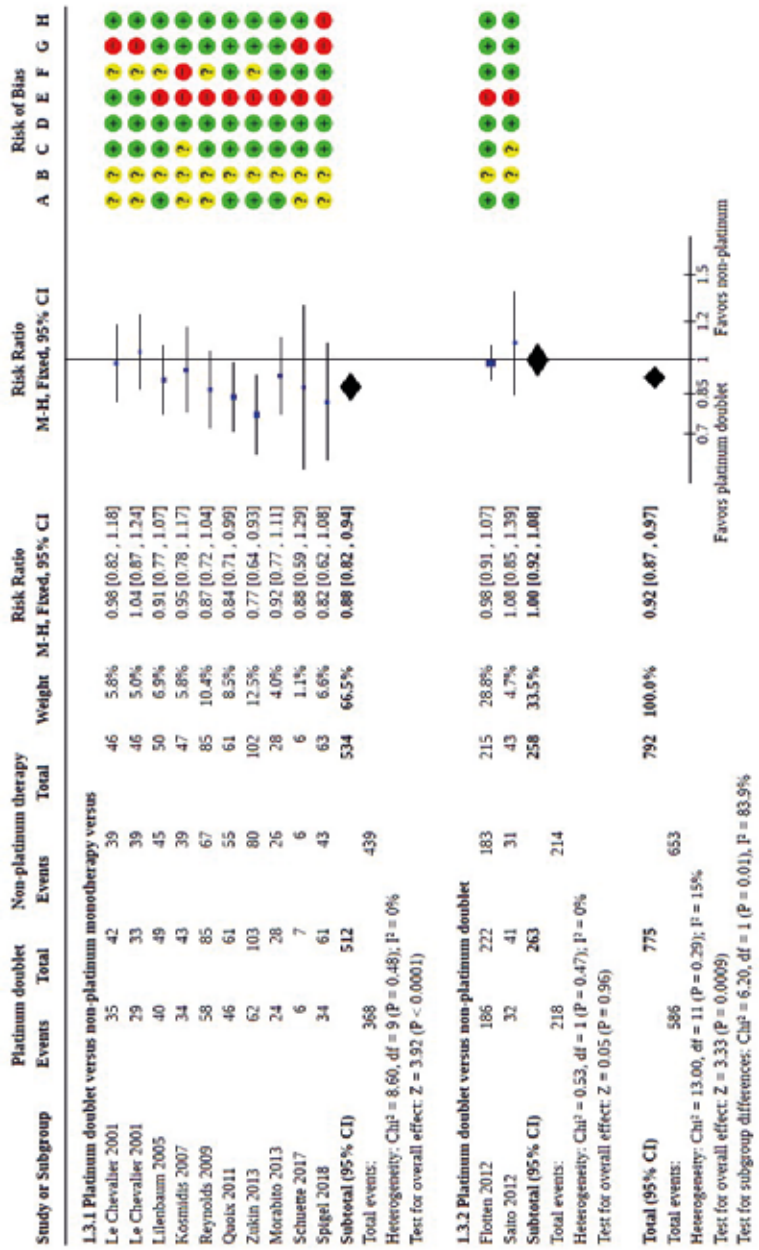
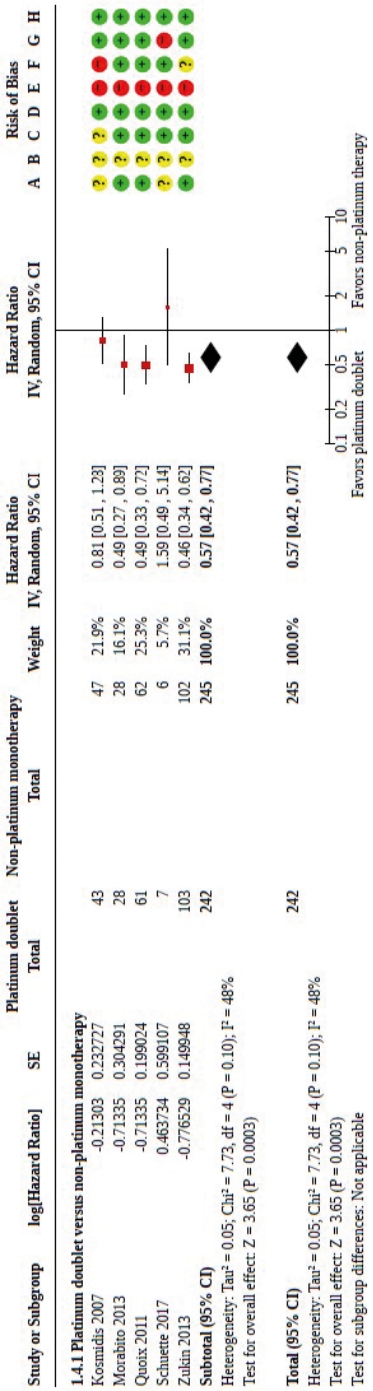


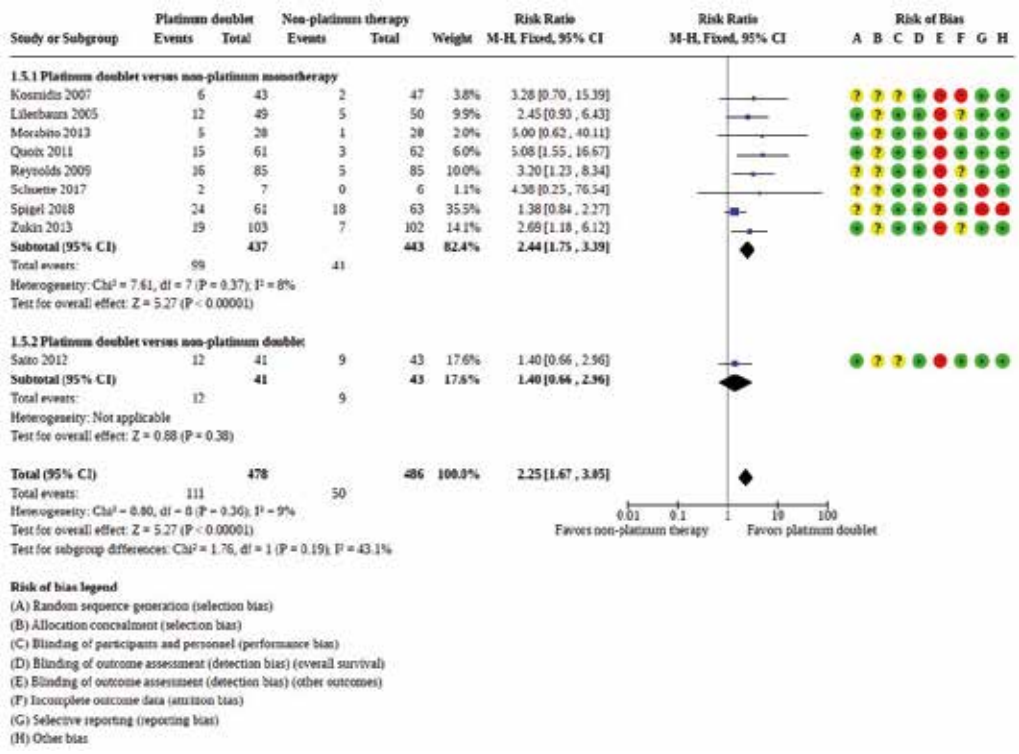
Figure 6A.6 Forest plot of comparison of platinum doublet versus non-platinum therapy on progression free survival



Study or Subgroup	log[Hazard Ratio]	SE	Platinum doublet Total	Non-platinum monotherapy Total	Weight	IV, Random, 95% CI
1.4.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	-0.21303	0.232727	43	47	21.9%	0.81 [0.51 , 1.28]
Morabito 2013	-0.71335	0.304291	28	28	16.1%	0.49 [0.27 , 0.89]
Quoix 2011	-0.71335	0.199024	61	62	25.3%	0.49 [0.33 , 0.72]
Schuette 2017	0.463734	0.599107	7	6	5.7%	1.59 [0.49 , 5.14]
Zukin 2013	-0.776529	0.149948	103	102	31.1%	0.46 [0.34 , 0.62]
Subtotal (95% CI)			242	245	**100.0%**	**0.57 [0.42 , 0.77]**
Heterogeneity: Tau² = 0.05; Chi² = 7.73, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Total (95% CI)			242	245	**100.0%**	**0.57 [0.42 , 0.77]**
Heterogeneity: Tau² = 0.05; Chi² = 7.73, df = 4 (P = 0.10); I² = 48%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Test for subgroup differences: Not applicable						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Figure 6A.7 Forest plot of comparison of platinum doublet versus non-platinum therapy on tumor response rate



Study or Subgroup	Platinum doublet Events	Total	Non-platinum therapy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Platinum doublet versus non-platinum monotherapy						
Kosmidis 2007	6	43	2	47	3.8%	3.28 [0.70 , 15.39]
Lilenbaum 2005	12	49	5	50	9.9%	2.45 [0.93 , 6.43]
Morabito 2013	5	28	1	28	2.0%	5.00 [0.62 , 40.11]
Quoix 2011	15	61	3	62	6.0%	5.08 [1.55 , 16.67]
Reynolds 2009	16	85	5	85	10.0%	3.20 [1.23 , 8.34]
Schuette 2017	2	7	0	6	1.1%	4.38 [0.25 , 76.54]
Spigel 2008	24	61	18	63	35.5%	1.38 [0.84 , 2.27]
Zukin 2013	19	103	7	102	14.1%	2.69 [1.18 , 6.12]
Subtotal (95% CI)		**437**		**443**	**82.4%**	**2.44 [1.75 , 3.39]**
Total events:	99		41			
Heterogeneity: Chi² = 7.61, df = 7 (P = 0.37); I² = 8%						
Test for overall effect: Z = 5.27 (P < 0.00001)						
1.5.2 Platinum doublet versus non-platinum doublet						
Saito 2012	12	41	9	43	17.6%	1.40 [0.66 , 2.96]
Subtotal (95% CI)		**41**		**43**	**17.6%**	**1.40 [0.66 , 2.96]**
Total events:	12		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.88 (P = 0.38)						
Total (95% CI)		**478**		**486**	**100.0%**	**2.25 [1.67 , 3.05]**
Total events:	111		50			
Heterogeneity: Chi² = 0.80, df = 8 (P = 0.36); I² = 9%						
Test for overall effect: Z = 5.27 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.76, df = 1 (P = 0.19), I² = 43.1%						

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias) (overall survival)
(E) Blinding of outcome assessment (detection bias) (other outcomes)
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Flotten 2012 compared the results of the EORTC QLQ-C30 with LC13 lung cancer subscale from baseline to week 17 in people randomized to vinorelbine plus gemcitabine or carboplatin plus vinorelbine. They found no difference between arms in general HRQoL, nausea/vomiting, dyspnea, pain, or fatigue subscales during the study period. A formal calculation analyzing changes overtime was not performed, although numerically, the global QoL score (on a scale from 0 to 100) was not clinically relevant (less than 10 points).

Morabito 2013 also reported the outcomes of the EORTC QLQ-C30 and LC13 subscale; however, they only evaluated QoL on days one and eight of cycles one and two in people randomized to gemcitabine monotherapy or cisplatin plus gemcitabine. There was no evidence of a negative impact of platinum doublet compared to gemcitabine monotherapy in terms of general HRQoL; however, compliance to the questionnaires was low with a 32% completion rate for gemcitabine monotherapy and 46% for platinum doublet.

Kosmidis 2007 used the LCSS to assess clinical benefit after cycles two and four in 90 people randomized to gemcitabine monotherapy or carboplatin plus gemcitabine. Regarding general feeling and symptoms, there was no difference between the two arms at each timepoint, or when compared to baseline values. There was a high rate of missing values, varying per item, ranging from 37% to 93% missing data.

Saito 2012 analyzed disease-related symptoms using the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy – Lung Cancer Subscale (FACT-LCS) at baseline and after cycles one and two in people randomized between carboplatin plus paclitaxel or gemcitabine plus vinorelbine. With a completion rate of 81% at the end of cycle two, there was an improvement of the summed score compared to baseline in both arms, above minimal important difference but no difference between arms.

Chemotherapy versus chemotherapy: carboplatin versus cisplatin therapy

For direct comparison, two studies including 131 participants provided sufficient data for analysis of 12-month survival and tumor response rates (Langer 2007 (PS 2 only); Sweeney 2001 (subgroup analysis)). For comparability, we included only the cisplatin plus gemcitabine arm from Sweeney 2001 in this analysis.

Twelve-month survival rate

There was no difference in 12-month survival rates (random-effects model; RR 1.08, 95% CI 0.73 to 1.60; I^2 = 59%; Analysis 2.1), or in tumor response rate (RR 0.64, 95% CI 0.64 to 1.34; I^2 = 0%; Analysis 2.3).

We also performed an indirect comparison, comparing subgroups. Two studies including 223 participants used cisplatin as the platinum compound (Le Chevalier 2001 (subgroup analysis); Morabito 2013 (PS 2 only)) versus nine trials including 1344 participants using carboplatin (Flotten 2012; Kosmidis 2007; Lilenbaum 2005; Quoix 2011; Reynolds 2009; Saito 2012; Schuette 2017; Spigel 2018; Zukin 2013). In the carboplatin subgroup, 12-month survival rates were better for the carboplatin group compared to the non-platinum group (RR 0.91, 95% CI 0.86 to 0.96; I^2 = 28%), while cisplatin showed no survival benefit (RR 0.98, 95% CI 0.89 to 1.09; I^2 = 0%; Analysis 2.2).

Tumor response rate

There was no difference in tumor response rate (RR 0.64, 95% CI 0.31 to 1.34; I^2 = 0%; Analysis 2.3).

Chemotherapy versus immunotherapy

We included only two trials comparing immunotherapy with chemotherapy (Lee 2022; Lena 2022). Both were published as congress abstract only, providing only limited data and, therefore, we were unable to perform a meta-analysis using these data.

After inclusion of 344 people with PS 2, Lee 2022 found that atezolizumab was not superior to non-platinum chemotherapy (vinorelbine or gemcitabine) on median OS (12-month OS rate: 43.7% with atezolizumab versus 38.6% with non-platinum chemotherapy; HR 0.86, 95% CI 0.67 to 1.10). In a cohort of (estimated) 64 participants with PS 2, Lena 2022 found a median OS of 2.9 months (95% CI 1.4 to 4.8) in people treated with nivolumab plus ipilimumab compared to 6.1 months (95% CI 3.5 to 10.4) in those treated with platinum doublet therapy (P = 0.22). Other endpoints were not specified or reported. There might be an inclusion bias in this trial, as there were fewer participants included with PD-L1 expression of 50% or greater than expected.

DISCUSSION

Summary of main results

Historically, people with a PS of 2 are frequently excluded from (important) clinical trials because of poorer outcomes and increased toxicity compared with people with a PS of 0 or 1[16, 18, 19, 21]. This is reflected in the fact that of 3661 unique screened records, only 67 articles were included in our analysis, whereas only the data of 22 trials were reported or retrieved sufficient to be included in the meta-analysis. These studies included 6759 participants, including only 2395 participants with PS 2 (35.4%). As there was high heterogeneity between treatment regimens, we were only able to perform a full meta-analysis of platinum doublet versus non-platinum therapy.

From the analysis of 11 studies comparing non-platinum therapy versus platinum doublet, we found that the use of platinum doublet therapy resulted in superior OS, 12-month survival rate, PFS, and tumor response rate compared with non-platinum monotherapy. There were no changes in the outcomes when we restricted the analysis to only including studies specifically designed for people with PS 2.

There were no differences in the comparison with platinum doublet versus non-platinum doublet therapy. However, these advantages were associated with a greater risk of grade 3 or 4 adverse events compared to non-platinum therapy for anemia, neutropenia, and thrombocytopenia. There was no difference in risk for febrile neutropenia, neither were there differences in non-hematologic toxicity such as fatigue, asthenia, nausea, and vomiting.
Although evidence was limited, carboplatin seemed to give better 12-month survival rates than cisplatin when compared to non-platinum therapy.

Although checkpoint inhibitors with or without platinum doublet became first-line treatment in people with PS 0 and 1[11, 133], we identified an important knowledge gap as data from randomized trials of its use in people with PS 2 were limited. In this analysis with limited supporting data, whereas use of double-agent immunotherapy is not encouraged in people with PS 2, there might be a place for single-agent immunotherapy.

Limitations of the evidence included in the review

All studies were open-label and therefore considered high risk for outcome bias, except OS. Therefore, we downgraded the certainty of evidence of these outcomes (PFS, response rate, toxicities). Also, due to high heterogeneity, we downgraded the certainty of evidence of the toxicity outcomes, except for febrile neutropenia. Finally, because the number of studies reporting asthenia was sparse, we downgraded the certainty of evidence.

We were unable to include randomized trials comparing chemotherapy with BSC. Although such studies were performed in participants with PS 2, no data were available to date for use in this review as the studies were performed decades ago.

Our analysis included only studies using cytotoxic chemotherapy, with or without the addition of an angiogenesis inhibitor. As there were too many various treatment regimens, we could not specify the effect size by type of cytotoxic agent other than platinum doublet versus non-platinum therapies, and we were unable to select the preferred platinum doublet regimen. People with PS 2 could benefit more from platinum doublet chemotherapy, whereas for people who are ineligible for platinum chemotherapy, non-platinum (mono or doublet) therapies could be beneficial.

The group of people with PS 2 is heterogeneous and the results of our study should be interpreted with caution as the cause of the deterioration of the PS might be due to comorbidity or the disease itself. The latter might benefit more from systemic therapy than the first group [134]. Of note, most included studies were performed before the introduction of immunotherapy and most targeted therapies, therefore PD-L1 status and availability of targetable mutations were not assessed in these people. Also, as the ECOG PS is a subjective score, different healthcare providers may report different PS [135].

There were only two partially published randomized trials using immune checkpoint inhibitors in people with PS 2, showing disappointing results in OS in people treated with immunotherapy compared to chemotherapy. They did not report toxicity rates specified to people with PS 2. As the OS might be similar between single-agent chemotherapy and single-agent immunotherapy, the decision might be based on the adverse events people experience. One prospective phase II trial evaluating first-line immunotherapy in people with PS 2 with advanced NSCLC found that pembrolizumab can be safely administered, with no increase in the risk of immune-related or other toxicities, with OS of 7.9 months (95% CI 2.6 to unlimited) (PePS2 trial,[136]. A virtual International Expert Panel was established in July 2021 with the aim of reviewing the available evidence on the use of immunotherapy in NSCLC people with ECOG PS 2, both in clinical practice and in a research setting. The panelists agreed that, though limited, the available data support the safety of single-agent immunotherapy in NSCLC people with PS 2[137].

Limitations of the review process

This review contains, to our knowledge, the largest dataset on people with advanced NSCLC with PS 2 and first-line therapy. However, a few limitations should be stated.

From a high number of included studies, we were unable to retrieve some data to analyze in our study. In most studies including people with PS 2, the main endpoints were not reported for this subgroup only and were subsequently excluded.

Also, the treatment regimens used in the analysis of platinum doublet versus non-platinum therapy were varied. We were unable to perform an analysis to evaluate each therapy separately due to the limited number of trials.

All included studies were open-label, which enhances detection bias for response rates, PFS, and toxicities. We do not expect that OS and six- and 12-month rates were influenced by this study methodology.

Agreements and disagreements with other studies or reviews

In 1995, the NSCLC Collaborative Group published an analysis comparing chemotherapy with BSC based on individual patient data, including people with PS 2 [27]. This study was later adapted by Cochrane and found a survival benefit of chemotherapy over BSC in people with PS of 2 or greater in a pooled analysis of 2714 people from 16 RCTs, including 594 participants with PS 2 or greater [29]. Whereas they did not suggest a specific treatment regimen and they included a minority of people with PS 3, it is clear that people with declined PS benefit from chemotherapy compared to BSC only.

Vasconcellos 2020 performed a Cochrane Review comparing cisplatin versus carboplatin in combination with a third-generation drug for advanced NSCLC. They showed equivalent OS, 12-month OS, and response rate. Regarding adverse events, carboplatin caused more thrombocytopenia, and cisplatin caused more nausea/vomiting. They did not include a subgroup of participants with PS 2. One Cochrane Review in people with advanced NSCLC aged greater than 70 years without significant comorbidities found that survival increased with platinum combination therapy when compared with non-platinum therapy, with a higher risk of major adverse events [139]. Although the performance of older people is often reduced, this review also did not include a PS 2 subgroup.

The results of this systemic meta-analysis support the recommendations made by ESMO [11] for the treatment of people with PS 2 with advanced NSCLC, based on a meta-analysis performed by Bonte 2015[140]. This review included six RCTs, which are also included in our review.

AUTHORS' CONCLUSIONS

Implications for practice

This review showed that platinum doublet chemotherapy as a first-line treatment for people with performance status (PS) 2 with advanced non-small cell lung cancer (NSCLC) results in a higher response rate, progression-free survival, and overall survival, compared to non-platinum chemotherapy. Although the risk for especially grade 3 or 4 hematologic toxicity is higher, these events are often relatively mild and easy to treat. However, a few studies compared quality of life during the study period and observed no difference between the treatment arms, suggesting that platinum doublet therapy is tolerated well.

We did not find a beneficial effect of cisplatin over carboplatin. However, this analysis should be interpreted with care as the direct comparison of cisplatin with carboplatin contained a small number of people. The assessment of the efficacy of immunotherapy in people with PS 2 is limited. There might be a place for single-agent immunotherapy, but the use of double-agent immunotherapy in people with PS 2 is not encouraged.

Implications for research

Our results showed a significant advantage of platinum doublet therapy over non-platinum therapies. However, many of the included studies were not designed for people with PS 2 only and reported only subgroup analysis, thus lacking power. Only when this population is represented in prospective randomized controlled trials can definitive conclusions be drawn. Presently, the first-line treatment for people with advanced NSCLC without a targetable mutation is immunotherapy or chemo-immunotherapy, stratified by PD-L1 status. As the use of immunotherapy is emerging, people with PS 2 are generally not included in randomized controlled trials[16, 18, 19, 21], and data are not sufficient to create general conclusions. Evidence from non-randomized trials show that people with PS 2 can be treated safely and effectively with immunotherapy or chemo-immunotherapy, but trials performed and published to date do not compare immunotherapy with regimens used in general practice.

Planned subgroups were based on histology (squamous or non-squamous), PD-L1 status, people aged under 70 years or 70 years or over, and the presence or absence of central nervous system metastasis. There were insufficient data to conduct these subgroup analyses, as the included trials did not sufficiently report our outcomes.

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CHAPTER 6A
SUPPLEMENTAL MATERIALS

Table 6AS.1 Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

# 1	MeSH descriptor: [Lung Neoplasms] explode all trees
# 2	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
# 3	lung carcinom*
# 4	lung neoplasm*
# 5	lung cancer*
# 6	nsclc
# 7	non small cell lung
# 8	#1 or #2 or #3 or #4 or #5 or #6 or #7
# 9	advanced
#10	"stage 4"
#11	"stage IV"
#12	metasta*
#13	#9 or #10 or #11 or #12
#14	#8 and #13
#15	PS2
#16	PS of 2
#17	"performance status 2"
#18	performance status of 2
#19	performance status (PS) of 2
#20	#15 or #16 or #17 or #18 or #19
#21	#14 and #20
#22	MeSH descriptor: [Induction Chemotherapy] explode all trees
#23	first line
#24	MeSH descriptor: [Antineoplastic Agents] explode all trees
#25	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
#26	carboplatin
#27	cisplatin
#28	deoxycytidine
#29	erlotinib
#30	gemcitabine
#31	paclitaxel
#32	pemetrexed
#33	platinum based combination
#34	MeSH descriptor: [Taxoids] explode all trees
#35	taxanes
#36	vinblastine
#37	vinorelbine
#38	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
#39	#21 and #38

Table 6AS.2 MEDLINE search strategy

#41	"Search #23 AND #40"
#40	"Search #24 OR #25 OR #26OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39"
#39	"Search vinorelbine[Title/Abstract]"
#38	"Search Vinblastine[MeSH Terms] OR vinblastine[Title/Abstract]"
#37	"Search Taxoids[MeSH Terms] OR taxanes[Title/Abstract]"
#36	"Search platinum based combination[Title/Abstract]"
#35	"Search Pemetrexed[MeSH Terms] OR pemetrexed[Title/Abstract]"
#34	"Search Paclitaxel[MeSH Terms] OR paclitaxel[Title/Abstract]"
#33	"Search gemcitabine[Title/Abstract]"
#32	"Search Erlotinib Hydrochloride[MeSH Terms] OR erlotinib[Title/Abstract]"
#31	"Search docetaxel[Title/Abstract]"
#30	"Search Deoxycytidine[MeSH Terms] OR Deoxycytidine[Title/Abstract]"
#29	"Search Cisplatin[MeSH Terms] OR cisplatin[Title/Abstract]"
#28	"Search Carboplatin[MeSH Terms] OR carboplatin[Title/Abstract]"
#27	"Search Antineoplastic Combined Chemotherapy Protocols[MeSH Terms]"
#26	"Search Antineoplastic Agents[MeSH Terms]"
#25	"Search first line[Title/Abstract]"
#24	"Search Induction chemotherapy[MeSH Terms]"
#23	"Search #19 AND #22"
#22	"Search #20 OR #21"
#21	"Search performance status of 2[Title/Abstract] OR performance status 2[Title/Abstract]"
#20	"Search PS2[Title/Abstract] OR PS 2[Title/Abstract] OR PS of 2[Title/Abstract]"
#19	"Search #13 AND #18"
#18	"Search #14 OR #15 OR #16 OR #17"
#17	"Search metasta*[Title/Abstract]"
#16	"Search Stage IV[Title/Abstract]"
#15	"Search Stage 4[Title/Abstract]"
#14	"Search Advanced[Title/Abstract]"
#13	"Search #1 OR #2 OR #12"
#12	"Search #10 and #11"
#11	"Search #8 OR #9"
#10	"Search #3 OR #4 OR #5 OR #6 OR #7"
# 9	"Search nonsmall cell*[Title/Abstract]"
# 8	"Search non small cell*[Title/Abstract]"
# 7	"Search lung tumour*[Title/Abstract]"
# 6	"Search lung tumor*[Title/Abstract]"
# 5	"Search lung neoplasm*[Title/Abstract]"
# 4	"Search lung carcinoma*[Title/Abstract]"
# 3	"Search lung cancer*[Title/Abstract]"
# 2	"Search nsclc[Title/Abstract]"
# 1	"Search Carcinoma, Non-Small-Cell Lung[MeSH Terms]"

Table 6AS.3 Embase search strategy

#50 #10 AND #15 AND #48 AND #49
#49 #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
#48 #16 OR #17 OR #18 OR #19 OR #20
#47 'navelbine':ab,ti
#46 'vinorelbine':ab,ti
#45 'navelbine'/exp
#44 'vinblastine':ab,ti
#43 'vinblastine'/exp
#42 'taxanes':ab,ti
#41 'taxoid'/exp
#40 'platinum based combination*':ab,ti
#39 'pemetrexed':ab,ti
#38 'pemetrexed'/exp
#37 'paclitaxel':ab,ti
#36 'paclitaxel'/exp
#35 'gemcitabine':ab,ti
#34 'gemcitabine'/exp
#33 'erlotinib':ab,ti
#32 'erlotinib'/exp
#31 'docetaxel':ab,ti
#30 'docetaxel'/exp
#29 'deoxycytidine':ab,ti
#28 'deoxycytidine'/exp
#27 'cisplatin':ab,ti
#26 'cisplatin'/exp
#25 'carboplatin':ab,ti
#24 'carboplatin'/exp
#23 'antineoplastic agent'/exp
#22 'first line':ab,ti
#21 'induction chemotherapy'/exp
#20 'performance status of 2':ab,ti
#19 'performance status 2':ab,ti
#18 'ps of 2':ab,ti
#17 'ps 2':ab,ti
#16 'ps2':ab,ti
#15 #11 OR #12 OR #13 OR #14
#14 'metasta*':ab,ti
#13 'stage iv':ab,ti
#12 'stage 4':ab,ti
#11 'advanced':ab,ti
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
9 'nonsmall cell*':ab,ti
8 'non small cell*':ab,ti
7 'lung tumour*':ab,ti
6 'lung tumor*':ab,ti
5 'lung neoplasm*':ab,ti
4 'lung carcinoma*':ab,ti
3 'lung cancer*':ab,ti
2 'nsclc':ab,ti
1 'non small cell lung cancer'/exp

CHAPTER 6B

Immunotherapy in frail non-small-cell lung cancer patients

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We read the study published by Siow Ming Lee and colleagues[1] with great interest. The authors concluded that atezolizumab monotherapy was associated with better outcomes for patients deemed ineligible for platinum-based chemotherapy. However, the study raised two substantial concerns regarding the heterogeneity of the study population and the single-agent treatment of the control group.

First, the trial combined frail and very frail patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) 2 and 3 with a substantial number of fit (ECOG PS 0–1) older patients. These are three very distinctive groups who respond differently to treatment.[2] There was no difference between immunotherapy or chemotherapy in ECOG 2 (hazard ratio [HR] 0.86, 95% CI 0.67–1.10). The paper even stated that the median overall survival of ECOG PS 2 patients treated with chemotherapy was better than those treated with immunotherapy (9.w7 vs 10.4 months). The question here is whether the benefit of the total group might be driven by the fit older patient ECOG PS 0–1 group.

Second, IPSOS investigators possibly deemed platinum-based therapy unsuitable for patients primarily by their performance score. A 2023 Cochrane review, with IPSOS data included, showed that patients with ECOG PS 2 should be treated with platinum doublet therapy first, not non-platinum monotherapy (HR 0.67 [0.57–0.78]), contrary to its use in this trial.[3] Furthermore, the observed crossing of the survival curve during the first months could be attributed to withholding chemotherapy in a substantial part of the atezolizumab group. Consequently, the findings from this study for patients with ECOG PS 2, should be interpreted with caution.

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CHAPTER 7

Discussion

AIM OF THIS THESIS

This thesis intends to uncover advancements in cancer management for patients diagnosed with stage IV mutated NSCLC, specially delving into long-term OS, treatment-related toxicity, and QoL. It will place particular emphasis on patients afflicted with EGFR-mutated stage IV NSCLC, alongside those lacking EGFR mutations but exhibiting diminished performance status.

MAIN FINDINGS AND THEIR RELATION TO PREVIOUS LITERATURE

Optimizing the role and relevance of observational cohort studies in lung cancer research

When attempting to generalize data from clinical trials to real-world setting, it's crucial to acknowledge several key issues. While first- and second generation TKIs have demonstrated efficacy in treating EGFR-mutated NSCLC, assessing these trials present various difficulties. Firstly, there is a scarcity of randomized trials directly compared to the relative efficacy of different generation TKIs in patients with advanced EGFR-mutated NSCLC.[1,2] Secondly, the incidence and distribution of EGFR mutations vary across continents, with most clinical trials conducted in predominantly Asian populations.[3,4] Thirdly, these clinical trials often involve highly selective populations consisting of relatively fit and younger patients, frequently excluding those with (symptomatic) brain metastasis. Consequently, the outcomes observed may not accurately reflect the heterogeneity present in real-world patient populations.[5] It is noteworthy that a substantial portion (60-70%) of real-world patients may be ineligible for trial participation.[6,7] Exploring alternative study strategies could lead to valuable insights in this patient demographic.

In **chapter 2** we described the results from a real-world study, assessing the overall survival of Dutch patients with advanced EGFR-mutated NSCLC treated with first- or second generation TKI as first line treatment. Our study also compared these outcomes with other international real-world series. The median survival observed was 20.2 months (95% CI 17.8-23.2 months), which aligned with results from most other European observational studies but appeared lower in comparison to Asian populations.[8–10] Factors such as male gender, advanced age, poorer performance status, and the presence of metastases in ≥3 organs were associated with reduced overall survival. Notably, our study revealed poorer survival among gefitinib users, particularly in cases with baseline brain metastases, compared to erlotinib users.

To date, our cohort represents among the largest population-based studies evaluating EGFR TKI in a real-world European population in terms of overall survival. Subsequent smaller European studies have reported similar overall survival results for patients treated with erlotinib, gefitinib and afatinib.[11,12] However, there remains a lack of clear evidence regarding whether first- or second-generation TKI performs better in terms of overall survival among European patients, in both clinical trials and real-world series. A large heterogeneity is seen among the published real-world studies, ranging from single-center to multicenter or national cohorts.[8–12] Besides these data are conflicting with data from large phase III clinical trials. To date, no meta-analysis has combined the data from these studies. Among Asian patients, afatinib tends to outperform gefitinib and erlotinib in both the general population and in patients with baseline brain metastasis, as shown in a networked meta-analysis.[13] However, sensitivity analyses have not revealed a significant difference in overall survival.

The observed inferior performance of gefitinib compared to erlotinib in patients with brain metastasis in our study remains questionable, particularly given the almost identical molecular structure of these drugs and the absence of similar findings in other studies. Therefore, this result might be due to small numbers of patients and confounding parameters as missing data on performance scores and symptomatology of brain metastasis.

As the third-generation EGFR TKI osimertinib was found superior compared to earlier generation TKI's in clinical trials, osimertinib was implemented as first line treatment in the Netherlands at the end of 2019.[1] In **chapter 3**, we further explored the real-world OS of Dutch patients with advanced EGFR-mutated NSCLC, focusing on common mutations (Ex19del or L858R). We evaluated whether the introduction of osimertinib conferred an improved overall survival compared to earlier generation EGFR TKIs and whether this survival benefit was influenced by mutation type and the presence of brain metastasis at baseline. In contrast to our initial expectations, we did not observe a survival benefit for patients treated with upfront osimertinib compared to earlier generations TKIs overall. However, upon conducting subgroup analysis, we observed a benefit of osimertinib specifically in patients with Ex19del and baseline brain metastasis.

Based on our data, it could be debated whether osimertinib should be used as upfront treatment for all patients without brain metastasis. While osimertinib demonstrated superior progression free survival compared to first- and second generation TKIs, its impact on OS remains unclear.[1] This uncertainty may stem from various factors, including dilution of the comparison due to previous second line treatment with osimertinib following erlotinib/gefitinib therapy. Additionally, the OS data from the FLAURA trial were published before a significant proportion of patients had died (58%). Next, subgroup analysis indicated that only non-Asian patients benefit from this drug as compared to Asian patients, despite the latter group comprising 63% of the study population. Moreover, smaller real-world studies conducted both before and after ours have also failed to identify an OS benefit for osimertinib.[14–16] For instance, a recent Chinese prospective, multicenter, observational study encompassing 606 patients adjusted for baseline patient characteristics between the osimertinib and erlotinib/gefitinib groups using propensity score matching, including gender, age, perfomance status, smoking history, family history of tumor, pathology, EGFR mutations, and brain metastases.[17] The study reported median overall survival of 40.5 months (95% CI 27.1–54.0) in the osimertinib group versus 34.3 months (95% CI 30.6–38.0) in the erlotinib/gefitinib group (HR 0.76 (95% CI 0.58–1.00), p=0.045). When assessing both Ex19del and L858R mutation separately, no differences in OS were observed (Ex19del HR 0.85 (95% CI 0.54–1.35) and L858R HR 0.75 (95% CI 0.48–1.18), respectively).[17] These results closely parallel those of the FLAURA trial, indicating only a marginal superiority in OS (HR 0.79 (95% CI 0.63–0.98)), primarily driven by patients with del19.[18] Moreover, osimertinib demonstrates superior blood-brain barrier penetration, leading to a notable 52% decrease in the likelihood of cerebral progression when juxtaposed with erlotinib/gefitinib, encompassing both known and newly developed lesions.[19]

For patients, optimizing life expectancy while minimizing treatment-related side effects is paramount. TKI treatment is generally better tolerated than chemotherapy, making delaying the need for chemotherapy highly beneficial. Next, treatment with monotherapy with immune checkpoint inhibitors is not regularly recommended after TKI failure due to the expected resistance of EGFR mutated NSCLC. Although the combination of chemotherapy and vascular endothelial growth factor (VEFG) inhibitors might be effective after TKI failure, it often comes with increased toxicity. Therefore, conducting next generation sequencing (NGS) might reveal new resistance mutations or pathway aberrations that might be of high value for these patients. A recent study indicates approximately 50% of patients treated with first- and second-generation TKI developed the T790M mutation, with markedly improved overall survival observed after second line treatment with osimertinib (50 months, including first line treatment) compared to other systemic therapies (23 months).[20] Lee et al. reported a median overall survival of 36.7 months (95% CI 30.9 – NR) after initiating second line osimertinib.[21] It is plausible that first-line osimertinib provides a different repertoire of resistance mutations that may cause challenges for subsequent treatments. For now, there is currently no clinical observation to suggest such a disadvantage.

A retrospective analysis using the United States Flatiron Health database showed that the majority of patients who received first line treatment with first- or second generation TKI subsequently received second line therapy with osimertinib. Interestingly, among patients initially treated with osimertinib, a greater variety of second line treatments were reported, with over 30% of patients receiving a platinum-based regimen.[22] Another factor is that patients starting first line TKI treatment may not proceed with second line treatment other than TKI due to various reasons. This is especially common in elderly patients, where the potential impact of alternative therapies, aside from TKI treatment, may be deemed excessively burdersome.[23]

With the findings presented in **Chapter 2** and **Chapter 3**, we have contributed to a better understanding of real-world overall survival of patients with EGFR mutated NSCLC. These studies underscore the importance of considering real-world studies alongside clinical trials, as they offer valuable insights into treatment outcomes in diverse patient populations. Furthermore, our research highlights the impact of individual patient and disease characteristics on treatment decisions, emphasizing the need for personalized approach to patient care. Moreover, our studies provide compelling real-world evidence supporting the timing and sequencing of TKI treatment. By elucidating the outcomes of different treatment regimens in clinical practice settings, we contribute to a more nuanced understanding of optimal treatment strategies for patients with EGFR-mutated NSCLC. Ultimately, these findings serve to inform clinical decision-making and enhance patient care in real-world settings.

Maximizing TKI Therapy: Enhancing Treatment Effectiveness for Long-Term Success

Following the initiation of treatment with TKI, disease progression inevitably occurs at some point, often attributed to new mutations, signal transduction and pathway aberrations, or histopathological transformation. To prolong progression free survival, and potentially overall survival, investigations into combinations with other types of therapy are underway.

In **chapter 4**, we investigated whether intercalated erlotinib with chemotherapy outperformed erlotinib monotherapy in untreated patients with advanced EGFR-mutated NSCLC, in terms of response rate, PFS, OS, and toxicity. Although slow accrual led to the premature termination of the study, mainly due to the availability of less intensive and toxic TKI monotherapy. The limited number of concluded patients revealed a clear benefit in progression-free survival with combination therapy. By targeting EGFR-mutated tumor cells with TKI alongside chemotherapy targeting unselected tumor cells, that the potential synergistic effects of intratumor heterogeneity and dual anti-tumor therapy may contribute to the superiority of combination therapy. Similar benefits have also been observed in other trials combining first generation TKI with platinum doublet chemotherapy.[24,25] These findings suggest that chemotherapy continues to have a role in this patient group, albeit with considerations for balancing survival advantages with toxicity.

Recently, the initial findings of the FLAURA2 landmark trial were published.[26] In this study, treatment-naïve patients with EGFR-mutated (exon 19 deletion or L858R mutation) advanced non–small-cell lung cancer (NSCLC) were randomized between osimertinib with platinum doublet chemotherapy and osimertinib monotherapy. Progression free survival increased from 16.7 months to 25.5 months with the combination therapy (HR 0.62 (95% CI 0.49 – 0.79)), although no significant effect on overall survival yet (HR 0.90 (95% CI 0.65 - 1.24)). Final overall survival results are anticipated in the coming years. It is noteworthy that, akin to our findings in the NVALT17 trial, the combination therapy in the FLAURA2 study, was associated with significant higher toxicity. Planchard et al. showed that in the FLAURA2 trial, the rate of grade 3 or worse treatment-related adverse events increased from 11% with monotherapy to 53% with combination therapy. The rate of serious adverse events related to treatment increased from 5% to 19%. Next, although a better PFS was reported, the overall response rate was similar and there was no increase in overall survival (with limited follow-up). These findings suggest that, although therapy might be more durable if combined, treatment tolerance and long-term quality of life might be better preserved when treated subsequently. This might hinder the adoption of osimertinib in combination with chemotherapy over osimertinib monotherapy as the preferred initial treatment option in clinical guidelines.

In summary, **chapter 4** of this thesis has contributed valuable insights into the potential of combination therapy with TKI and chemotherapy. The results of our trial encourage further research with combinations of chemotherapy with EGFR treatments, to reduce toxicity, by for example alternating therapies instead of concurrent use, or addition only after non-cerebral progression of disease. Also, for the acceptance of more toxic combination therapies, an effect on overall survival should be proven.

Shifting the paradigm towards treating EGFR-mutated NSCLC as a more chronic condition.

The advent of modern therapies such as TKIs and immunotherapy has substantially improved the prognosis of patients with advanced NSCLC, offering them a significant greater opportunity to survive years following diagnosis compared to previous standards of care. Howlader et al conducted a study demonstrating a marked decrease in population-level mortality from NSCLC in the United States between 2013 and 2016, accompanied by significant improvement in survival rates post-diagnosis. They suggested that a reduction in

disease incidence along with treatment advances likely contributed to the observed reduction in mortality during this period.[27]

An analysis of 2-year survival rates among patients with stage IIIB-IV NSCLC in the real world population in the Czech Republic revealed a nearly twofold increase between 2011-12 and 2015-16 (from 24 to 43%).[28] Considering the World Health Organization's (WHO) definition of chronic disease as a condition characterized by long term duration and typically slow progression, it is reasonable to apply this framework to long-surviving NSCLC patients, especially those responding well on immunotherapy or TKI therapy.[29] These patients may effectively manage their condition as a chronic illness, benefiting from ongoing treatment and monitoring to sustain their improved prognosis over an extended period.

In **chapter 5**, we undertook an assessment of the overall quality of life, treatment satisfaction and underlying motives of ten patients diagnosed with advanced EGFR mutated NSCLC, who survived approximately three or more years following their diagnosis. The evaluation employed a mixed method approach, combining validated general questionnaires with semi-structured patient interviews. Our findings revealed that the patients generally tolerated long-term oral TKIs considerably well and expressed satisfaction with their extended TKI therapy. However, it was noted that the primary clinical health issues stemmed from symptoms associated with brain and bone metastases. Importantly, we observed limitations in the utility of the utilized, validated questionnaires, which were originally developed during the chemotherapy era and may not adequately capture the nuances of quality of life following long-term EGFR treatment. Therefore, our study suggests that supplementary interviews should be considered to effectively identify and address additional health issues that may arise during long-term EGFR treatment, particularly in its earlier phase. Such an approach would enable a more comprehensive understanding of the overall well-being and treatment experiences of patients undergoing extended TKI therapy for EGFR mutated NSCLC.

Multiple patient and disease-related factors exert influence on the overall survival of patients with advanced EGFR mutated NSCLC. Among these factors, a superior performance status, limited metastases, and the presence of favorable del19 mutation treated with TKI are associated with enhanced survival outcomes. Conversely, the presence of baseline brain metastasis is deemed as an unfavorable prognostic factor. Notably, despite experiencing prolonged survival, patients with advanced EGFR mutated NSCLC face an elevated risk of developing brain or leptomeningeal metastasis.[30,31] Consequently, tailored treatment strategies are essential, given the significant impact of brain metastasis symptoms on patients' quality of life. Available treatments with such as surgery, whole brain radiotherapy or stereotactic radiosurgery are generally associated with a further decline in QoL. Therefore, achieving enhanced blood-brain barrier penetration of TKIs is imperative.[32] Preclinical comparison of the blood-brain barrier permeability of various generations of TKI using PET imaging in primates demonstrated osimertinib as the sole TKI among demonstrating significant brain penetrance. Subsequent findings from the phase I ODIN-BM study confirmed the high cerebral distribution of the commonly used oral dosage of 80mg daily of osimertinib in treatment-naïve patients, suggesting an adequate penetration of the blood-brain barrier.[33] Furthermore, exploratory analysis comparing the cerebral efficacy of osimertinib versus first generation EGFR TKIs in the FLAURA trial showed superior response rates and CNS PFS favoring of osimertinib.[19] Real-world evidence corroborated excellent response rates on brain metastasis using osimertinib monotherapy, although its impact on overall survival might be limited as shown in **chapter 3** of this thesis.[34] Therefore, for asymptomatic patients, additional radiotherapy following osimertinib may not be necessary, as indicated by retrospective studies.[35–37] However, for symptomatic patients, the necessity for additional treatment remains unknown, given their exclusion from randomized trials. The potential impact of upfront osimertinib treatment on reducing the overall risk of developing brain metastases in treatment-naïve patients remains uncertain.

The utilization of routine MRI for the detection of brain metastasis warrants consideration and may provoke debate within clinical settings. While screening can enable the early detection of asymptomatic brain metastasis in patients with EGFR mutated NSCLC, it also raises concerns regarding potential adverse psychological effects on patients The diagnosis of asymptomatic brain metastasis may precipitate feelings of distress and anxiety, particularly during the initial stages following diagnosis, potentially leading to a decline in overall quality of life.[38] Furthermore, despite the option of treating asymptomatic brain metastasis with TKI alone, patients often receive local therapies such as radiotherapy, with subsequent toxicity due to this irradiation.[39–41] This suggests a potential drawback of routine MRI screening, as it may lead to unnecessary treatments and associated side effects. Conversely, the regular monitoring of known brain metastasis could be beneficial for patients. By closely monitoring these lesions, clinicians may be able to implement local therapies promptly upon disease progression, potentially intervening at an earlier stage than if symptoms were to develop. This approach could mitigate the risk of disease advancement and improve overall patient outcomes. Ultimately, the decision regarding the implementation of routine MRI screening for brain metastasis should carefully weigh the potential benefits of early detection and intervention against the risks of psychological distress and unnecessary treatments. Patient preferences, individual risk profiles, and available resources should all be considered when making such decisions. In the Netherlands, as well as in various other regions worldwide, guidelines and protocols are being updated to include MRI screening for brain metastasis in patients with mutation-positive lung cancer, such as those harboring EGFR mutations. This recommendation aligns with the growing understanding of the impact of brain metastasis on patient outcomes and the availability of targeted therapies that can effectively manage these lesions.

Thus, with **chapter 5** we contribute to the knowledge of long-term survivorship of EGFR mutated NSCLC. Most clinical health issues are due to the presence of brain and bone metastasis, advocating the screening for (asymptomatic) brain metastasis. Current questionnaires are deficient to measure QoL of these patients properly, specific questionnaires should be developed.

Optimizing treatment for lung cancer patients with performance status 2

Till date, prevailing clinical guidelines lack robust evidence regarding the optimal therapeutic approach for patients with stage IV NSCLC and exhibiting a moderate impaired performance status.[42,43] This subset of patients represents a considerable proportion (20% to 30%) of the overall population diagnosed with lung cancer. Hence, it becomes important to delineate the most effective treatment strategies for this cohort, especially for those lacking targetable mutation.

In **chapter 6A**, we reported the outcomes of a Cochrane review, which evaluated the existing evidence regarding the optimal first-line therapy for patients with advanced NSCLC and possessing a performance status of 2, in the absence of a (known) targetable mutation. Our analysis indicated that platinum doublet chemotherapy appears to be preferable for these patients compared to non-platinum chemotherapy, exhibiting superior response rates, progression-free survival, and overall survival. Despite a higher incidence of severe hematologic toxicity associated with platinum doublet chemotherapy, as most included studies used carboplatin, these adverse events are typically transient, relatively mild, and amenable to treatment. While there may be a role for single-agent immunotherapy, the available data did not support the use of double-agent immunotherapy. Trials assessing the efficacy of immunotherapy with checkpoint inhibitors in NSCLC patients with a performance status of 2 are limited, highlighting a notable gap in knowledge regarding their therapeutic role in this specific patient population. Next, available trials might be prone to bias due to their methodology, as shown in **chapter 6B**.

Over the last decades, several reviews and meta-analysis focusing on first-line therapy for patients with advanced lung cancer have been published.[44–47] To date, our review stands as the most comprehensive, encompassing the largest number of published studies and incorporating unpublished data from several trials, thereby enhancing the robustness of the evidence. The findings unequivocally support the notion that patients diagnosed with advanced NSCLC without a driver mutation should receive treatment with platinum doublet chemotherapy, unless contraindicated due to comorbidities. Notably, this recommendation aligns with existing clinical guidelines.[43]

Evidence supporting the safe administration of immunotherapy to patients with PS2 is accumulating. The retrospective PePS2 trial showed that pembrolizumab administration was safe, with no increase in immune-related or other adverse events, while efficacy outcomes were comparable to those observed patients with PS 0 – 1.[48] Subsequent to the publication of our review, several prospective studies evaluating the efficacy and safety of checkpoint inhibitors in patients with PS 2 were published in full paper, including one previous included in our review as a congress abstract.[49–51] Among these, the phase III IPSOS trial compared atezolizumab monotherapy to single-agent non-platinum chemotherapy (vinorelbine oral or intravenous, or gemcitabine intravenous) in patients ineligible for platinum-based chemotherapy, concluding that atezolizumab yielded superior outcomes. However, several caveats should be considered. Firstly, subgroup analysis showed no significant differences in overall survival among patients with PS 2 (HR 0.86 (95% CI 0.67-1.10)). Secondly, the comparison of immunotherapy with single agent non-platinum chemotherapy may not be optimal, given that our review suggested platinum doublet chemotherapy as the preferred treatment in patients with PS 2. Thirdly, survival curves intersected during initial months, potentially attributable to the withholding of chemotherapy in a substantial proportion of the atezolizumab group.[51]

Two phase II studies evaluated durvalumab monotherapy in single-arm studies, enrolling 48 and 50 patients with PS 2, respectively.[49,50] Mark et al. (SAK 19/17 trial) showed a median overall survival of 8.5 months (95% CI 4.4–16.7), which was consistent regardless of PD-L1 expression (< 50% vs. ≥ 50%). Conversely, Shaverdashvili et al. found a median OS of 6 months (95% CI 4–10), with an encouraging survival benefit among patients with PDL1-positive tumors (6 months for TPS 0%, 11 months for TPS 1-49%, and ≥ 50%, respectively). Both trials reported treatment-related adverse events of grade ≥3 in 19% of patients, with one patient succumbing to therapy-related toxicity. Notably, in the SAK 19/17 trial, an interim unplanned safety analysis prompted a protocol amendment to restrict first line durvalumab treatment to patients exhibiting fewer symptoms from the tumor, particularly those with respiratory symptoms, following a high mortality rate observed after the initial 21 patients.[52] These patients might benefit from the preceding or addition of chemotherapy to accelerate treatment response. This might also be reflected in the crossing survival curves in the earlier phases of treatment in the IPSOS trial, although this remains unclear as data on disease symptomology is not reported.[51]

Many trials were excluded from our review due to the absence of PS2 patients or inadequate subgroup analysis. Recently, a multidisciplinary working group comprising the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research encouraged broader inclusion of PS2 patients in clinical trials, especially when treating with more effective and less toxic regimens.[53] However, it is imperative to acknowledge the subjective nature of determining PS, which may vary among observers.[40] Additionally, pursuing this statement, there is a possibility that patients with an actual PS 2 might be categorized as PS 1 in clinical trial setting. This suggests that solely rating PS may not suffice when more effective treatments are available. For instance, integrating assessments of physical functioning through patient-reported outcomes or functional exercise tests could provide additional insights into evaluating patient performance accurately.[40]

The results presented in **Chapter 6** support evidence supporting the utilization of platinum doublet chemotherapy as a viable treatment option for patients diagnosed with advanced-stage NSCLC, provided there are no contraindications for platinum-based chemotherapy. Although evidence supporting the use of checkpoint inhibitors is limited, the data only supports its use when administered as monotherapy. Furthermore, it is advisable that patients with PS2 be actively included in new clinical trials to ensure broader representation and to better understand treatment efficacy and safety in this patient subgroup.

GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis has provided valuable insights into various aspects of regular lung cancer treatment, particularly focusing on patients with impaired performance status or those with advanced stage EGFR mutated NSCLC. The following conclusions can be drawn from the research:

Firstly, the overall survival of patients with advanced EGFR mutated NSCLC in the Dutch population is comparable to that reported in other European population-based studies, but lower compared to studies conducted in Asian populations. Additionally, poorer adjusted survival was observed for gefitinib users compared to erlotinib users, especially among patients with brain metastasis at baseline.

Secondly, Dutch patients with advanced NSCLC harboring an EGFR Ex19del mutation exhibited superior survival compared to those harboring an L858R mutation. Osimertinib demonstrated better performance as first line treatment specifically in patients with Ex-19del mutation and brain metastasis.

Thirdly, intercalated administration of erlotinib with cisplatin/pemetrexed prolonged progression-free survival compared to erlotinib monotherapy. However, the combination treatment was associated with higher toxicity rates.

Fourth, long-term survivors of EGFR mutated NSCLC exhibit tolerance to, and satisfaction with long-term oral TKI therapy. The main clinical health issues observed were attributed to symptoms of brain and bone metastasis. Validated quality of life questionnaires primarily originated from the chemotherapy era and may be less suitable for assessing performance following long-term EGFR treatment.

Finally, for patients with performance status 2 and advanced NSCLC without a targetable mutation, platinum doublet therapy emerges as the preferred option over non-platinum therapy. This approach demonstrated higher response rates, PFS, and OS, despite elevated risk of grade 3 to 5 hematologic toxicity. However, the scarcity of trials investigating, checkpoint inhibitors in these patients underscores a significant knowledge gap regarding their role in the management of advanced NSCLC with PS 2.

Future perspectives

This thesis highlights the imperative for larger, international, real-world patient populations, in addition to randomized trials, to advance our understanding of lung cancer treatment. The development of electronic health records and the increasing availability of data facilitate the development of registries that transcend national borders. Leveraging such data enables more accurate predictions on how to treat patients with maximum efficacy while minimizing the risk of toxicity. Moreover, the analysis of treatment sequencing can be more readily explored outside the confines of rigid randomized clinical trials, allowing for clearer observation of biological effects. Additionally, owing to the infrequent occurrence of various developed resistance mutations, conducting clinical trials to evaluate treatment options for these mutations proves challenging within these populations. Furthermore, the identification of predictors for the development of T790M-associated resistance could potentially restore the role of first or second-generation TKI in the management of advanced EGFR mutated NSCLC. As patient survival prolongs a broader array of drug resistance patterns is expected to emerge, necessitating the utilization of advanced tests such as DNA and RNA sequencing. Emerging technologies such as protein or receptor modeling will predict the most effective drug interventions under such circumstances. Additionally, personalized treatment decisions should take into account response patterns and distant metastasis, especially for brain metastasis. Lastly, it is essential to acknowledge that patients with more impaired performance status are more likely to be included in real-world data, highlighting the importance of considering their specific needs and responses when formulating treatment strategies.

Concluding remarks

In conclusion, this thesis aimed to drive improvements in the care of patients with advanced stage mutated NSCLC, irrespective of EGFR mutation. We showed the value of large-scale real-world studies in assessing the efficacy of TKIs in routine care setting, alongside evaluating treatment-related toxicity and its impact on (long-term) quality of life. It was emphasized that the toxicity profiles of short-term treatments such as chemotherapy (administered over weeks) should be distinguished from the long-term toxicity associated with daily TKI intake (spanning months to years). The assessment of grade 1-2 toxicity over prolonged periods assumes greater importance as treatments become increasingly combined, and patients, particularly those with EGFR mutated NSCLC, are often subjected to extended treatment durations

Furthermore, the thesis advocated for regular evaluation of brain metastasis in long-term lung cancer survivors to facilitate early interventions with stereotactic brain treatment. Additionally, it encourages future research efforts to focus on real-world patient populations and extending the spectrum of patients included in clinical trials. Notably, inclusion of patients with impaired performance status is deemed advantageous, given their substantial represen tation in daily practice. By incorporating these approaches, we aim to optimize patient outcomes and enhance the effectiveness of treatment strategies for advanced NSCLC.

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CHAPTER 8

Summary

In **chapter 2** we conducted a comparative analysis of the efficacy of upfront treatment with erlotinib, gefitinib and afatinib in a real-world population. Our findings revealed that survival outcomes were significantly worse for male patients and older individuals, those with poorer PS, and those with metastases in three or more organs. Among patients without brain metastasis, no significant differences in overall survival were observed among those treated with erlotinib, gefitinib, or afatinib. However, in patients diagnosed with baseline brain metastasis, poorer survival outcomes were noted for gefitinib users particularly when compared to erlotinib.

In **Chapter 3**, we further explored the real-world OS of patients treated with different generations of EGFR- tyrosine kinase inhibitors (TKI), including the third generation TKI osimertinib. Focusing exclusively on patients with a deletion in exon 19 (Ex19del) or an exon 21 L858R mutation, our national cohort of 1100 patients, including 265 patients treated with osimertinib, revealed a survival benefit among patients with an Ex19del mutation compared to those with an L858R mutation. However, no enhanced overall survival was observed among patients treated with upfront osimertinib overall. Notably, a survival benefit for osimertinib treatment was evident in the subgroup of patients with Ex19del and baseline brain metastasis.

In **Chapter 4**, we presented the results of the NVALT17 randomized clinical trial, which compared platinum doublet chemotherapy combined with intercalated erlotinib to treatment with erlotinib alone. Despite the trial being halted due to slow accrual, the limited number of concluded patients demonstrated a clear benefit in progression free survival favoring combination therapy. The results advocate further research into combining chemotherapy with upcoming next-generation EGFR treatments, provided treatment toxicity and quality of life remain manageable.

In **Chapter 5**, we evaluated the overall quality of life, treatment satisfaction, and motives of ten patients with advanced EGFR mutated NSCLC who survived more than three years after diagnosis. Employing a mixed-method approach involving validated general questionnaires and a semi-structured patient interview, we found that patients generally tolerated long-term oral TKIs considerably well and expressed satisfaction with their long-term TKI therapy. However, main clinical health issues persisted due to symptoms of brain and bone metastasis. Notably, we identified deficiencies in validated questionnaires originating from the chemotherapy era, suggesting the need for supplementary interviews to detect additional health issues earlier in the treatment process.

Finally, in **Chapter 6**, we conducted a systemic Cochrane review of the current available evidence regarding the optimal first-line therapy for patients with advanced NSCLC and a performance status of 2, without a targetable mutation or with an unknown mutation status. Our review underscored platinum doublet chemotherapy as the preferred option over non-platinum chemotherapy, giving its higher response rate, progression free survival and overall survival, with an increased but acceptable risk of hematologic toxicity. While single-agent immunotherapy may have a role, data did not encourage the use of double-agent immunotherapy. Notably, trials assessing immunotherapy with checkpoint inhibitors in NSCLC patients with a performance status of 2 were scarce, revealing an important knowledge gap in understanding their role in this patient population.

CHAPTER 9

Nederlandse samenvatting

NEDERLANDSE SAMENVATTING

Dit proefschrift heeft tot doel de behandeling van patiënten met stadium IV NSCLC te analyseren, met een specifieke focus op langetermijnoverleving, behandeling gerelateerde toxiciteit en kwaliteit van leven. De onderzoeken richten zich met name op de subgroep patiënten met stadium IV NSCLC met een EGFR-mutatie, evenals op patiënten zonder EGFR-mutatie maar met een verminderde performance status.

Allereerst hebben we een vergelijkende analyse uitgevoerd naar de effectiviteit van eerstelijnsbehandeling met erlotinib, gefitinib en afatinib in een real-world populatie patiënten met stadium IV NSCLC met een EGFR-mutatie. We vonden dat de overlevingsresultaten significant slechter waren voor mannelijke patiënten, patiënten op leeftijd, met een slechtere PS, en degenen met metastasen in drie of meer organen. Onder patiënten zonder hersenmetastasen werd geen significant verschil in overleving waargenomen tussen degenen die behandeld werden met erlotinib, gefitinib of afatinib. Echter, bij patiënten die bij start van de behandeling al gediagnostiseerd waren met hersenmetastasen, waren de overlevingsresultaten van gefitinib-gebruikers slechter, vooral in vergelijking met erlotinib.

Vervolgens hebben we deze real-world analyse verder uitgebreid, waarbij ook de derde generatie EGFR-remmer osimertinib werd meegenomen, in een populatie uitsluitend bestaand uit patiënten met een deletie in exon 19 (Ex19del) of een exon 21 L858R mutatie. Hieruit bleek dat er een overlevingsvoordeel is van patiënten met een Ex19del in vergelijking met degenen met een L858R mutatie. Opmerkelijk was echter dat er geen verbeterde overleving werd waargenomen bij patiënten die in de eerste lijn behandeld werden met osimertinib in vergelijking met de eerdere generatie EGFR-remmers. Er was wel een overlevingsvoordeel voor osimertinib-behandeling werd aangetoond in de subgroep van patiënten met Ex19del en hersenmetastasen bij start van de therapie.

Om de effectiviteit van EGFR-remmers te vergroten, kan chemotherapie worden toegevoegd aan de behandeling. In de NVALT 17 studie, een Nederlands multicenter, open label, randomized clinical trial en ook onderdeel van dit proefschrift, werd platinum doublet chemo-therapie gecombineerd met geïntercaleerd erlotinib en vergeleken met behandeling met alleen erlotinib. Ondanks dat de studie werd stopgezet vanwege trage inclusie, toonde het ondanks het beperkte aantal patiënten een duidelijk voordeel in progressievrije overleving in het voordeel van combinatie therapie, zonder effect op de langetermijnoverleving, echter met een behoorlijke toename van toxiciteit gerelateerd aan de behandeling. De resultaten pleiten voor verder onderzoek naar het combineren van chemotherapie met aankomende next-generation EGFR-behandelingen, mits de behandelingstoxiciteit en invloed op kwaliteit van leven beheersbaar blijven.

Om te onderzoeken welke invloed EGFR-remmers op de lange termijn hebben, evalueerden we de algehele kwaliteit van leven, behandelingstevredenheid, en behandelmotieven van tien patiënten met gevorderde EGFR gemuteerde NSCLC die meer dan drie jaar overleefden na hun diagnose. Door een benadering met gevalideerde, algemene vragenlijsten over kwaliteit van leven in combinatie met een semigestructureerd patiëntinterview, vonden we dat patiënten over het algemeen EGFR-remmers over een lange periode behoorlijk goed verdroegen en dat ze tevreden waren met deze therapie. De belangrijke gezondheidsproblemen ontstonden door symptomen van hersen- en botmetastasen. Met de beschikbare vragenlijsten konden we niet alle onderzoeksvragen beantwoorden, deze vragenlijsten zijn afkomstig uit het chemotherapie tijdperk, wat pleit voor het ontwikkelen van aanvullende vragenlijsten en gesprekken om tijdens de behandeling met doelgerichte behandelingen en immunotherapie ook tijdig symptomen en bijwerkingen op te kunnen sporen.

Als laatste hebben we in een systematische Cochrane review de beschikbare gegevens samengevat met betrekking tot de optimale eerstelijnstherapie voor patiënten met gevorderde NSCLC en een performance status van 2, zonder een target mutatie of met een onbekende mutatiestatus. Onze review benadrukte het belang van platinumdoublet chemotherapie als de voorkeur boven niet-platinum mono chemotherapie gezien het hogere responspercentage, betere progressievrije overleving en langetermijnoverleving, met een verhoogd maar acceptabel risico op hematologische toxiciteit. Daar waar enkelvoudige immunotherapie een rol kan spelen, is het gebruik dubbele immunotherapie niet aan te bevelen. Opmerkelijk was dat er weinig studies waren die immunotherapie met checkpoint-remmers beoordeelden bij NSCLC-patiënten met een performance status van 2, wat een belangrijke kenniskloof onthulde in het begrijpen van hun rol in deze patiëntengroep. Verder hebben we met collega's in het buitenland brieven uitgewisseld over deze Cochrane en een recente studie die hierover gepubliceerd is, de IPSOS-studie, waarin we schreven over de beperkte kennis die we in de wereld hebben over immunotherapie bij kwetsbare patiënten.

Concluderend, dit proefschrift laat met behulp van real-world onderzoek en een RCT, de effectiviteit van EGFR-remmers zien. Verder onderzochten we toxiciteit gerelateerd aan de therapie en de (soms langdurige) impact daarvan op kwaliteit van leven.
Daarnaast pleit dit proefschrift voor diagnostiek naar hersenmetastasen bij langdurige overlevers om eventuele interventies te vervroegen. Ook wordt toekomstig onderzoek aangemoedigd om zich te richten op de real-world patiëntenpopulatie en opnemen van patiënten met een verminderde performance status in klinische studies.

Appendices

Curriculum vitae

Rolof Gerrit Pieter Gijtenbeek werd op 6 augustus 1986 geboren te 's-Gravenhage.
In 2004 ronde hij zijn VWO op het CSG Comenius te Leeuwarden af en kon aansluitend aan de opleiding geneeskunde beginnen. In mei 2011 was deze opleiding afgerond en startte het werkzame leven als poortarts in het Gemini Ziekenhuis te Den Helder. Na nog een korte periode in 2013 te hebben gewerkt op de IC van het Westfries Gasthuis te Hoorn, begon hij in mei 2013 als ANIOS longziekten bij het Medisch Centrum Leeuwarden.
In december 2013 begon hij aan de opleiding tot longarts in het MCL, met als opleiders dr. A. ten Brinke en dr. B.J.W. Venmans, met als verdieping thoracale oncologie. Begin 2020, vlak voor het begin van de COVID-19 pandemie, was zijn opleiding afgerond en werd hij aangenomen in de Leeuwarder vakgroep van de Maatschap Friese Longartsen. Hier beoefent hij het vak in de breedst mogelijke zin, met als aandachtsgebied longoncologie. Daarnaast heeft hij zich sinds 2016 toegelegd op de ontwikkeling van het lokale EPD EPIC.

Rolof is getrouwd met Chantal Gijtenbeek-Weitenberg, samen hebben ze drie kinderen; Reinout (2014), Carlijn (2018) en Vera (2022).

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Mijn eerste copromotor, Wouter van Geffen. Al snel na de start van mijn wetenschappelijke activiteiten in het MCL werd jij bij mijn onderzoek betrokken. Zonder deze samenwerking was dit proefschrift nooit tot stand gekomen. Met jou als copromotor aan mijn zijde heb ik nooit getwijfeld of dit project kon worden afgerond. De inhoud van dit boekje is dan ook te danken aan jouw enthousiasme en creativiteit. Je gaf alle ruimte om mijn eigen plan te trekken en daarmee ook om mijzelf te ontwikkelen tijdens mijn opleiding en de jaren daarna. Als ik vastliep bij logistieke zaken, analyse van data of tijdens het schrijven, jouw deur stond altijd open voor het krijgen van advies en raad, maar ook voor koffie en ijsjes in de winkelstraat. Dat heb ik altijd enorm gewaardeerd, mijn dank daarvoor! Ik hoop dat wij in de toekomst nog mooie projecten samen kunnen opzetten.

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Mijn wetenschappelijke reis begon al tijdens mijn geneeskundestudie toen ik dankzij Marina Umans in contact kwam met Jorien Kerstjens, om administratieve ondersteuning te bieden bij het Pinkeltje-onderzoek, een grote landelijke studie naar de groei en ontwikkeling van premature kinderen. Dit project vormde de basis voor mijn eerste ervaring met wetenschappelijk onderzoek en legde het fundament voor mijn onderzoeksvaardigheden, die van onschatbare waarde zijn gebleken in mijn verdere ontwikkeling. Deze eerste stappen in de wetenschap hebben uiteindelijk geresulteerd in mijn eerste wetenschappelijke publicatie, over de impact van een RSV infectie bij premature kinderen.

Ik wil Jorien en Elianne Vrijlandt in het bijzonder bedanken voor jullie inhoudelijke begeleiding, evenals alle andere collega's die betrokken waren bij dit project. Jullie tijd, expertise en enthousiasme hebben me laten inzien hoe inspirerend en waardevol onderzoek kan zijn naast het klinische werk. Deze ervaring heeft mij gemotiveerd om de stap naar dit promotietraject te zetten.

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