FINAL REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with lung cancer

December 2014

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with lung cancer

Produced by:
Liverpool Reviews and Implementation Group (LR*i*G)
University of Liverpool
Institute of Psychology, Health and Society
Department of Health Services Research
Second Floor
Whelan Building
The Quadrangle
Brownlow Hill
Liverpool
L69 3GB
Tel: +44 (0) 151 794 5067
Fax: +44 (0) 151 794 5821
Email: LRiG@liv.ac.uk

Authors:
Gerlinde Pilkington, Research Assistant (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool

Juliet Hockenhull, Research Fellow (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool

Angela Boland, Associate Director, Liverpool Reviews and Implementation Group, University of Liverpool

Rumona Dickson, Director (LR*i*G), Liverpool Reviews and Implementation Group, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), Liverpool Reviews and Implementation Group, University of Liverpool

Jeremy Braybrooke, Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Marianne Nicolson, Consultant Medical Oncologist, Aberdeen Royal Infirmary

David Gilligan, Consultant Clinical Oncologist, Cambridge University Hospitals and Papworth Hospital, Cambridge

Correspondence to: Professor Rumona Dickson, Director (LR*i*G), Liverpool Reviews and Implementation Group, University of Liverpool, Room 2.06, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Source of funding: This report was commissioned by The National Cancer Equity Initiative (NCEI) and Pharmaceutical Oncology Initiative (POI)

Declared competing interests of the authors: None

This report should be referenced as follows: Pilkington G, Hockenhull J, Boland A, Dickson R, Dundar Y, Braybrooke J, Nicolson M, Gilligan D. Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with lung cancer. LR*i*G, The University of Liverpool, 2014

Contributions of authors:

Gerlinde Pilkington	Project management, data extraction, quality assessment and preparation of report
Juliet Hockenhull	Data extraction, quality assessment and preparation of report
Angela Boland	Preparation of report
Rumona Dickson	Input into all aspects of the review
Yenal Dundar	Development of search strategies
Jeremy Braybrooke	Clinical input into report
Marianne Nicolson	Clinical input into report
David Gilligan	Clinical input into report

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Abbreviations:

ADL	Activities of Daily Living
AE	Adverse event
ALK	Anaplastic lymphoma kinase
BADL	Basic Activities of Daily Living
CALGB	Cancer and Leukemia Group B
CCI	Charlson Comorbidity Index
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
DDI	Delivered dose intensity
EGFR	Epidermal growth factor receptor
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Cancer Questionnaire
EORTC QLQ-LC13	EORTC Quality of Life Cancer Questionnaire Lung Cancer-Specific Module
EQ-5D	EuroQoL – 5D questionnaire
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-L	Functional Assessment of Cancer Therapy-Lung
FFS	Failure-free survival
GDS	Geriatric Depression Scale
HR	Hazard ratio
IADL	Instrumental Activities of Daily Living
IPD	Individual patient data
ITT	Intention to treat
KPS	Karnofsky performance status
LASA	Linear Analogue Self-Assessment
LCSS	Lung Cancer Symptoms Scale
MDI	Median dose intensity
NCEI	The National Cancer Equity Initiative
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NR	Not reported
NSCLC	Non-small cell lung cancer
NTTX	Neurotoxicity and Taxane Toxicity
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
POI	Pharmaceutical Oncology Initiative
PS	Performance status
PSI	Pulmonary symptom improvement
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
SD	Standard deviation
SCLC	Small cell lung cancer
TNM	Tumour, Node, Metastasis (cancer staging system)
TOI (L)	Trial Outcome Index (Lung)
TTF	Time to treatment failure
TTP	Time to disease progression
UFT	Tegafur-uracil
WHO	World Health Organisation

1 EXECUTIVE SUMMARY

1.1 Background

Older people with cancer are less likely to receive radical treatment for their disease, due to comorbidities and/or frailty associated with old age, and uncertainty over the tolerability of chemotherapy treatment in older patients. The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which takes into account fitness, choice and benefit to the individual.

1.2 Aims and objectives

The aim of this review is to systematically review the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat lung cancer in older people.

1.3 Methods

Search strategy

Four electronic databases (MEDLINE, EMBASE, The Cochrane Library and Web Of Knowledge) were searched from January 2000 to May 2013.

Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria were excluded.

Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spreadsheet using a sample of included studies, and adapted to reflect the nature of both randomised controlled trials and observational studies. Data were extracted on study design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer, with disagreements resolved through discussion with a third reviewer where necessary.

Evidence synthesis

Due to the heterogeneity of the included studies and the limited data available, it was not possible or appropriate to perform any statistical analyses. The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

1.4 Results

Electronic searching of databases resulted in 1052 references. Manual de-duplication of references resulted in 955 unique references for screening at stage 1.

Initial screening of titles and abstracts identified 321 references, which were obtained as full-text papers. A total of 211 references (199 studies) met the inclusion criteria at stage 2 and were included in the review. The 199 studies included in the review were divided into six categories, based on study design.

1.5 Conclusions

There is much research into the treatment of older people with lung cancer, but it is of poor quality. There is no consistent definition of ‘older’ or ‘elderly’ and a lack of uniformity in terms of reporting of outcome measures such as tolerability, quality of life and comprehensive geriatric assessment.

Chemotherapy can benefit some older patients and age alone should not be a barrier to access to palliative chemotherapy for the treatment of non-small cell lung cancer and small cell lung cancer, as other factors including fitness, comorbidities and personal choice should be taken into account.

2 BACKGROUND

Older people with cancer are less likely to receive radical treatment. There are a number of reasons for this, including comorbidities and/or frailty associated with older age, and a complex mix of factors affecting patient and/or clinician choice. There is also uncertainty about the tolerability of chemotherapy treatment in older patients. However, not all older people are frail; many have good life expectancy and are in good health overall. There is evidence to suggest that characteristics other than age are not always fully assessed by healthcare professionals when treating older people with cancer, some of whom may be able to tolerate effective treatment.

The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which take into account fitness, choice and benefit to the individual.

Older patients are underrepresented in clinical trials, and study results are not generally applicable to the older population typically seen in routine clinical practice due to the enrolment of fitter and healthier patients. As a result, there are limited data on the efficacy and tolerability of chemotherapy for this patient population.

2.1 Description of health problem

Lung cancer is the most common cancer worldwide. Approximately 1.61 million new cases were diagnosed in 2008, and it is the second most diagnosed cancer in the UK after breast cancer, accounting for 12.9% of all cancer cases. It is also the most common cause of death in the UK. In 2010, 42,000 people in the UK were diagnosed with lung cancer and there were 35,000 registered deaths from lung cancer. The incidence of lung cancer increases with age; 90% of diagnoses during 2009-11 were in those aged >60 years and 40% were in those aged >75 years.[1]

Survival rates from lung cancer are low because the majority (66%) of cases are diagnosed at a late stage when curative treatment is not possible.[2] Other modifying factors for survival from lung cancer include smoking status, general health, sex, ethnicity and cancer treatment. Incidence rates for lung cancer differ between men and women. For men, rates have decreased by more than 45% since the late 1970s, whereas incidence rates for women are still increasing. The outlook for patients in the UK remains poor, with a 1-year survival rate of 27% for women and 30% for men. At 5 years, survival in men and women is 7% and 9% respectively.[2]

The majority (86%) of lung cancers are probably caused by smoking and 3% by passive smoking. Other risk factors include family history, exposure to radon, air pollution and exposure to asbestos.[3]

2.1.1 Lung cancer types and subtypes

Non-small cell lung cancer (NSCLC) accounts for approximately 87% of all lung cancers diagnosed and the remaining 12% are small-cell lung cancers (SCLC).[4]

Non-small cell lung cancer has three main histological subtypes: squamous cell carcinoma (33%), non-squamous cell carcinoma (29%), large cell carcinoma (4%); approximately 36% of patients are listed as being NSCLC 'not-otherwise specified' (NOS).

There are also subtypes based on active mutations of cancer cells, for example anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR).

2.1.2 Disease stage and performance status

The stage of lung cancer at diagnosis reflects the degree of spread of cancer and is crucially important to determine which patients have potentially curative disease and which do not, as this helps to define a patient's prognosis. Most patients will present with advanced disease that is not amenable to curative treatment, and for whom palliative chemotherapy is the only treatment option available.

In NSCLC, staging using the TNM system (Tumour, Node, Metastases) is quite complex. In brief terms, stages I-II indicate early lung cancer and stages III-IV indicate locally advanced or metastatic disease. Staging for SCLC is often simplified to include limited disease, meaning that the cancer is only in one lung or in local lymph nodes and may include pleural effusion. Extensive disease indicates that the cancer is metastatic.

The performance status (PS) indicates the degree of general well-being in a patient. The PS rating may be used when determining fitness for treatment, need for dose adjustment and a patient's supportive care needs. The three main PS scales comprise the World Health Organisation (WHO) PS scale, the Eastern Cooperative Oncology Group (ECOG) PS scale and the Karnofsky PS scale (KPS). A WHO or ECOG rating of 0 indicates that a patient is completely able to look after themselves, and a rating of 4 indicates that a patient requires substantial support. For KPS, a score of 100 indicates good health overall, and 0-10 indicates poor health.

2.1.3 Current treatment options

The treatment options for patients with NSCLC depend on the stage of disease, disease histology, mutations such as EGFR status, PS, comorbidities and patient preferences. For fit patients with early-stage NSCLC (stages I-II and some stage III), curative surgical resection or radical radiotherapy may be an option providing the patient is medically fit. A combination of radiotherapy and chemotherapy may also be an option for patients with stages I-III disease.

In patients with stage III or IV NSCLC and good PS but for whom curative treatment is not an option, palliative radiotherapy or chemotherapy may be offered initially to improve survival, disease control and quality of life (QoL).

For early-stage SCLC without lymph node involvement, surgery may be an option. However, most patients are diagnosed with extensive disease and are treated with chemotherapy and/or radiotherapy.

Increasingly, clinicians have the option to use targeted, or biological, therapy to treat specific subtypes of lung cancer, for example erlotinib or gefitinib for EGFR+ patients, or crizotinib to treat patients who are ALK+.

3 AIMS AND OBJECTIVES

3.1 Objectives

The aim of this review is to systematically consider the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat lung cancer in older people. The review forms part of a larger project, which reports on six types of cancer in older populations: breast, colorectal, lung, renal cell, chronic myeloid leukaemia and non-Hodgkin's lymphoma. The final report will consist of the results of a systematic review of the literature in each of these six clinical areas.

The objectives of this review are to:

- systematically review and summarise the relevant evidence related to clinical effectiveness and tolerability to treatment
- explore the implications of these findings for practice and service provision in order to disseminate accessible information to clinicians
- inform future decisions on research priorities through the identification of gaps and weaknesses in the available evidence.

3.2 Inclusion considerations

The population of interest is older people with lung cancer. There is no agreed definition of 'older': The World Health Organisation[5] states that most countries of the developed world have accepted the chronological age of 65 years as a definition of 'elderly' or 'older', whereas the British Geriatrics Society[6] describes geriatric medicine as being mainly concerned with people aged over 75. We have therefore focussed on published studies that specifically describe their patients or subgroups of patients, as 'older' or 'elderly'. In order to obtain a comprehensive dataset, no restrictions have been made in terms of the stage of disease, tumour histology or the line of treatment.

All forms of chemotherapy (defined as a systemic anti-cancer therapy) have been considered. To ensure that the most recent treatments are included it was decided, in consultation with clinical experts, that targeted biological therapies would also be considered, based on the premise that the two treatment types tend to be considered equally efficacious in clinical practice.

4 METHODS

4.1 Search strategy

Four electronic databases (MEDLINE, EMBASE, The Cochrane Library and Web Of Knowledge) were searched from January 2000 to May 2013, and all references were exported to EndNote® version X4. A comprehensive search strategy was employed and is shown in Appendix 1.

4.2 Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers using the inclusion criteria outlined in Table 1. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria at stage 2 were excluded.

Table 1 Inclusion criteria

Study design	Randomised controlled trials; systematic reviews; cohort studies, including retrospective studies of databases and registries
Patient population	Older people (older as defined by study authors) treated for lung cancer
Interventions	Any chemotherapy (all lines of treatment)
Comparators	• an alternative chemotherapy or • best supportive care
Outcomes	Efficacy outcomes: • overall survival • progression-free survival • response rates Tolerability outcomes: • adverse events • tolerability Other outcomes: • quality of life measures • comprehensive geriatric assessment
Other considerations	Studies that were not elderly-only, but reported subgroup analyses for older people in their abstract were included Only studies published since 2000 in full or with an English language abstract were included

4.2.1 Outcomes

The majority of outcomes presented in this review are commonly used measures of survival or response to treatment; however, 'tolerability' and 'comprehensive geriatric assessment (CGA)' may require further explanation.

Tolerability

In order to determine whether or not older patients can tolerate chemotherapy treatment, it was necessary to gather evidence from a range of outcomes. One measure of tolerability is a patient's adherence to the treatment regimen and/or how much of the treatment was received. Common

measures reported in studies are the mean or median number of cycles delivered per patient, how many people completed the treatment and the relative dose intensity (RDI) of treatment. Therefore, data were extracted from any measure that could be used to determine how much treatment a patient received.

Treatment discontinuations and withdrawals are other measures of how well a patient has tolerated chemotherapy. Therefore, any data relating to discontinuation due to toxicity, withdrawal of consent, disease progression or death were extracted.

Many studies report the number of patients whose dose of treatment was modified or interrupted due to adverse events (AEs), which again is a good measure of how well a treatment is tolerated. Any data that encompassed modifications or interruptions in treatment were extracted.

Randomised controlled trials (RCTs) commonly report AEs, and therefore all reported AEs of grade 3 or higher that occurred in more than 10% of patients in each arm were included in data extraction, together with any information on toxic deaths.

Comprehensive geriatric assessment

Comprehensive geriatric assessment is often carried out to determine an older person's health, both physical and mental, in order to decide on the appropriate treatment pathway for the individual. There are numerous tools used by clinicians, and studies often use CGA to determine eligibility for trials or as an outcome measure to establish how well the patient has responded to treatment in terms of how fit and well they are.

4.3 Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spreadsheet using a sample of included studies, and then adapted to reflect the nature of both RCTs and non-randomised studies. Data were extracted on study design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer, with disagreements resolved through discussion with a third reviewer where necessary.

Included RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance.[7] Data relating to quality assessment were extracted by one reviewer and independently checked for accuracy by a second reviewer. Where necessary, disagreements between reviewers were discussed in consultation with a third reviewer to achieve consensus. Full details of quality assessment criteria are provided in Appendix 2.

No universally accepted standardised quality assessment tool exists for use in non-randomised studies. There are a multitude of non-randomised study designs, and so even where tools exist, applying them

is problematic and of limited value. Due to the nature of the study designs of the included non-randomised studies, it was difficult to extract or compare information in a meaningful and relevant manner. Therefore, we made the pragmatic decision not to quality assess the non-randomised studies.

4.4 Evidence synthesis

Due to the heterogeneity of the included studies and the limited data available, it was not possible or appropriate to perform any statistical analyses. The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

5 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

5.1 Number of studies identified

Electronic searching of databases resulted in 1052 references. Manual de-duplication of references resulted in 955 unique references for screening at stage 1. See Figure 1 for details.

Initial screening of titles and abstracts identified 321 references, which were obtained as full-text papers. A total of 211 references (199 studies) met the inclusion criteria at stage 2 and were included in the review. A list of references that were excluded at stage 2 is presented in Appendix 3. The 199 studies included in the review were divided into six categories, based on study design. Table 2 presents the number of studies in each category and a brief description of the study type.

Table 2: Categorisation of included studies

Study type	Definition	Number of studies
RCTs	RCTs recruiting only patients defined as elderly/older	36
Subgroup analyses of RCTs	Analyses of RCTs from the general population with elderly/older subgroups reported separately	13
Pooled analyses	Published studies that use aggregated subgroup data on elderly/older patients from RCTs	4
Prospective comparative cohorts	Studies that report two or more comparators of a non-randomised trial with an elderly/older population	4
Prospective single cohorts	Studies that report single cohorts of elderly/older patients	95
Retrospective data	Any reports of chemotherapy treatment for elderly/older patients in a defined cohort of patients or from registries of patient outcomes	47
Total		**199**

RCT=randomised controlled trial

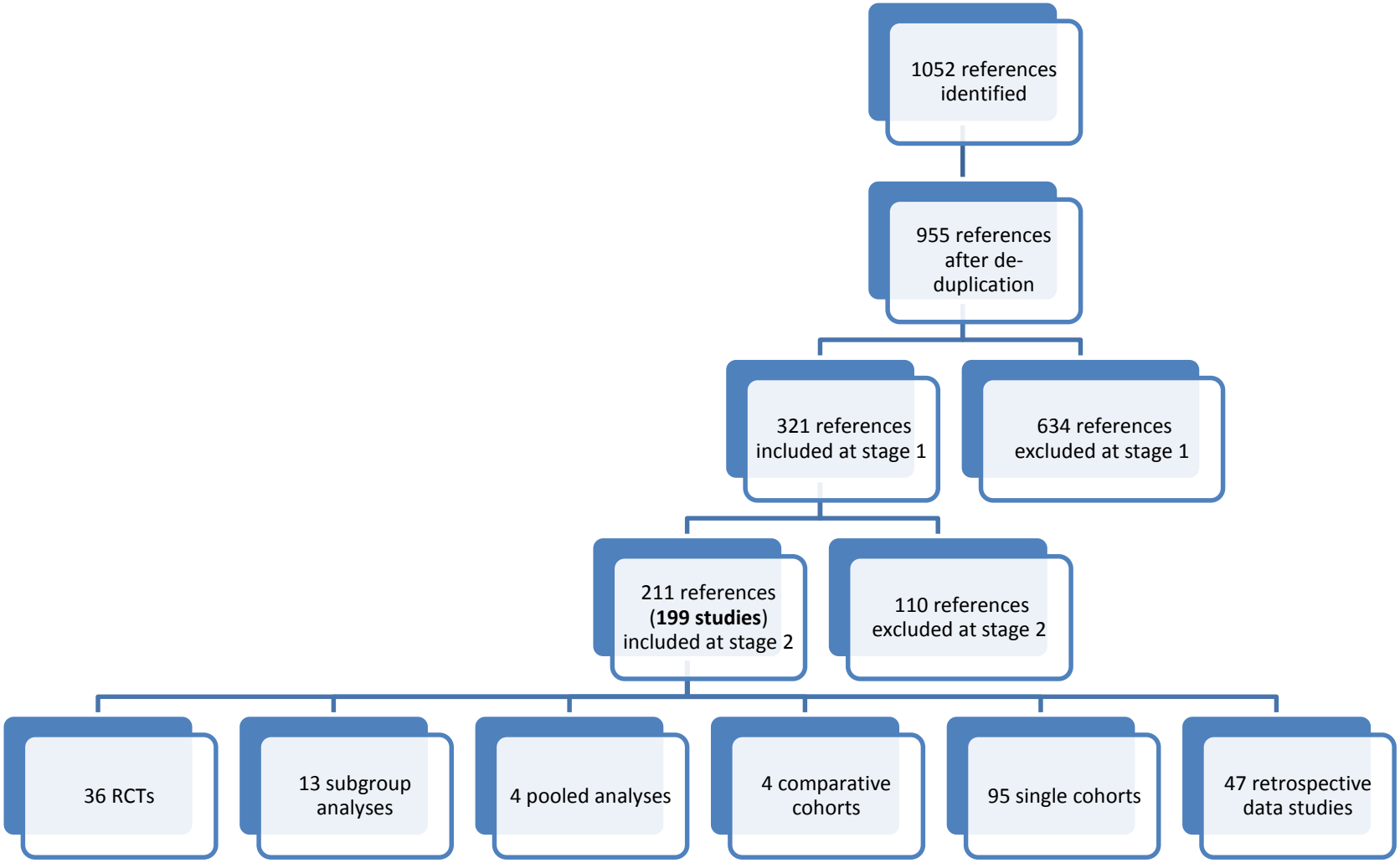

Figure 1 Flow diagram of included studies

6 RANDOMISED CONTROLLED TRIALS

A total of 36 trials[8-48] (reported in 41 publications) were included in the review. Thirty-three trials[9-32,35-48] focussed on populations with NSCLC, and three[8,33,34] focussed on SCLC.

6.1 Quality assessment of randomised controlled trials

Quality assessment of RCTs is presented in Table 3. Studies reported in abstract form only were not quality assessed due to the lack of information presented.[16,26,31,34,42]

Of the included trials, only ten[13,18-20,25,27,28,30,36,43,44,46-48] were assessed as being truly random. Schuette et al[38] was the only trial to report adequate blinding of participants, assessors and administrators. Jatoi et al[24] was reported as a double-blind trial, but details of blinding were not reported. In the remaining trials the blinding procedures were unclear.

Baseline comparability was achieved in all but five trials,[10,11,14,15,25,48] which only partially achieved baseline comparability. All trials presented adequate details regarding the number of participants randomised, and details of baseline characteristics.

It was unclear in five trials[18,19,28,32,37,43,46,47] whether an intention-to-treat (ITT) analysis was performed. Eight trials[17,23,25,32,35,37-39,45,48] did not provide information, or information was unclear, about the statistical powering of the study.

Table 3 Quality assessment of randomised controlled trials

Study	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		Other measures	Intention to treat	Powering
	Truly random	Allocation concealment	Number stated	Baseline presented	Baseline achieved			Assessors	Administrators	Participants	Procedure assessed	>80% in final analysis	Reasons stated			
NSCLC																
Chen 2012[12]	?	?	✓	✓	✓	✓	x	?	?	?	N/A	✓	✓	x	✓	✓
Kusagaya 2012[28]	✓	x	✓	✓	✓	✓	✓	?	?	?	?	✓	?	?	?	✓
LeCaer 2012[41]	?	x	✓	✓	✓	✓	✓	?	?	?	N/A	x	✓	?	✓	✓
Biesma 2011[9]	?	?	✓	✓	✓	✓	?	?	?	?	?	✓	✓	?	✓	✓
Gridelli 2011[21]	?	?	✓	✓	✓	✓	✓	x	?	?	?	✓	✓	?	✓	✓
Karampeazis 2012[25,48]	✓	?	✓	✓	✓/x	✓	✓	?	?	?	?	✓	✓	x	✓	x
LeCaer 2011[29]	?	?	✓	✓	✓	✓	?	?	?	?	N/A	✓	✓	✓	✓	✓
Schuette 2011[38]	?	?	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	?	✓	x
Stinchcombe 2011[40]	?	?	✓	✓	✓	✓	✓	?	?	?	?	x	✓	?	✓	✓
Quoix 2011[36]	✓	✓	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	✓
Spigel 2012[39]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	x
Gridelli 2010[43,46,47]	✓	?	✓	✓	✓	✓	?	?	?	?	?	✓	✓	x	?	✓
Hu 2010[23]	?	?	✓	✓	✓	✓	x	?	?	?	N/A	✓	✓	?	x	?
Jatoi 2010[24]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	✓
Sakakibara 2010[37]	?	?	✓	✓	✓	✓	?	?	?	?	?	✓	✓	?	?	?
Chen 2008[10]	?	?	✓	✓	✓/x	✓	x	?	?	?	?	✓	x	✓	✓	✓
Crino 2008[15]	?	?	✓	✓	✓/x	✓	x	x	x	x	N/A	✓	✓	x	✓	✓
Comella 2007[14]	?	?	✓	✓	✓/x	✓	x	?	?	?	?	✓	✓	x	✓	✓

Study	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		Other measures	Intention to treat	Powering
	Truly random	Allocation concealment	Number stated	Baseline presented	Baseline achieved			Assessors	Administrators	Participants	Procedure assessed	>80% in final analysis	Reasons stated			
Gridelli 2007[18,19]	✓	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	?	✓
Hainsworth 2007[22]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	✓
Leong 2007[30]	✓	?	✓	✓	✓	✓	✓	?	?	?	?	✓	?	x	x	✓
Lilenbaum 2007[32]	?	?	✓	✓	✓	✓	?	?	?	?	?	✓	✓	?	?	?
Chen 2006[11]	?	✓	✓	✓	✓/x	✓	✓	?	?	?	?	?	?	x	✓	✓
Kudoh 2006[27]	✓	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	✓
Quoix 2005[35]	?	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	?
Comella 2004[13]	✓	?	✓	✓	✓	✓	?	?	?	?	?	✓	✓	✓	✓	✓
Gridelli 2003[20]	✓	?	✓	✓	✓	✓	✓	?	?	?	?	✓	✓	x	✓	✓
Frasci 2001[17,45]	?	?	✓	✓	?	✓	✓	?	?	?	?	✓	✓	x	x	?
Gridelli 2001[44]	✓	?	✓	✓	✓	✓	?	✓	?	?	?	✓	✓	x	✓	✓
SCLC																
Okamoto 2007[33]	?	?	✓	✓	✓	✓	✓	?	?	?	N/A	✓	✓	x	✓	✓
Ardizzoni 2005[8]	x	x	✓	✓	✓	✓	x	?	?	?	N/A	✓	✓	x	✓	✓

Items are graded in terms of ✓ yes (item properly addressed), ✕ no (item not properly addressed), ✓/✕ partially (item partially addressed), **?** Unclear/not enough information, or N/A not applicable

6.2 Study characteristics

Study characteristics for the 36 included RCTs[8-48] are presented in Table 4.

6.2.1 Non-small cell lung cancer

There were nine phase III trials,[9,17,20,22,25,27,36,38,44,45,48] 18 phase II trials,[10-12,14,15,18,19,21,26,28-30,32,35,37,39-41,43,46,47] and the phase was unknown in six[13,16,23,24,31,42] trials.[13,16,23,24,31,42] Funding was provided by pharmaceutical companies for 12 of the trials,[9,12,15,18,19,22,29,35,38-41,43,46,47] 16 trials[10,11,13,14,16,17,23,24,26,27,30-32,37,42,44,45] did not report funding and four[20,21,25,36,48] were funded by research grants. Kusagaya et al[28] reported that no funding supported the trial. The majority of trials were relatively small; 17 trials[10,11,14,16,18,19,21,23,24,26,28,29,31,35,37,41-43,46,47] recruited fewer than 100 patients, 13 trials[9,12,13,15,17,25,27,30,32,38-40,44,45,48] recruited between 100 and 300 patients and three trials[20,22,36] randomised more than 300 patients. Gridelli et al[20] was the largest trial with 698 patients.

The definition of 'older' (minimum age for trial eligibility) across the trials varied between 60[23] to ≥76[28] years, and the median age of participants ranged from 71[24] to 79.[28] Consistently, the majority of patients in each trial had a PS of 0-1.

The trials that focussed on NSCLC recruited patients with stage IIIB/IV disease, with the exception of Biesma et al[9] who also included patients with stage IIIA disease. All but six trials compared first-line treatments; LeCaer et al[29] included a mix of first- and second-line treatment, and five trials did not report the line of treatment.[13,16,20,23,24]

6.2.2 Small cell lung cancer

There was one phase III trial,[33] one phase II trial[8] and the phase was unknown in Pu et al.[34] The smallest trial included 71 patients[34] and the largest included 220.[33] Two trials[8,33] were multicentre. Pu et al[34] did not report the study details. One trial[33] reported the funding of the trial, which came from research grants, and the other two trials did not report funding sources.[8,34]

The definition of 'older' was ≥70 across the trials, and the median age ranged between 72[34] and 74.[8,33] The proportion of males in both Pu et al[34] and Okamoto et al[33] was similar at >80%, but the proportions of males reported by Ardizzoni et al[8] were 79% and 96% in the two treatment arms. The trials reported that most patients had an ECOG PS of 0-1. All three trials[8,33,34] focussed on extensive-stage disease.

Table 4 Study characteristics, randomised controlled trials

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
NSCLC						
Chen 2012[12]	Phase II Open-label Taiwan 2007-2008 F. Hoffmann-La Roche, Ltd Funded by Council of the Republic of China Taipei Veterans General Hospital	Chemotherapy naïve Stage IIIB/IV Aged ≥70 years	Oral erlotinib (n=57)	Mean age: 78.1 years Median age: 77 years (70-90) Male: 82.5% ECOG PS: 0=3.5%, 1=77.2%, 2=15.8%, 3=3.5%	Primary: response rate Secondary: DCR, PFS, OS, QoL, tolerability	Erlotinib is highly effective compared with oral vinorelbine in elderly, chemotherapy-naïve, Taiwanese patients with NSCLC. patients with EGFR-mutated disease had better survival than those with EGFR wild-type disease, regardless of the treatment received
			Oral vinorelbine (n=56)	Mean age: 77.8 years Median age: 77 years (70-90) Male: 80.4% ECOG PS: 0=3.6%, 1=69.6%, 2=21.4%, 3=5.4%		
El Shenshawy 2012[16] (abstract only)	NR	Stage IIIB/IV Aged ≥65 years	Paclitaxel plus carboplatin (Overall n=86)	NR	Evaluation of efficacy and safety of treatments and the feasibility of subsequent maintenance therapy vs observation	Efficacy was similar between the weekly regimen and the standard regimen of carboplatin and paclitaxel for elderly patients with advanced NSCLC and may be advantageous based on its favourable tolerability profile
			Paclitaxel plus carboplatin	NR		
Kim 2012[26] (abstract only)	Phase II 2009-2012 Funding NR	Chemotherapy naïve Stage IIIB/IV Aged >65 years	Docetaxel plus cisplatin (n=45)	NR	Primary: safety (proportion of grade 3/4 toxicities)	Docetaxel/cisplatin is similar to gemcitabine/cisplatin in terms of efficacy and toxicity in treatment of elderly patients with poor PS
			Gemcitabine plus cisplatin (n=44)	NR		
Kusagaya 2012[28]	Phase II Multicentre Japan 2008-2011	Chemotherapy naïve Stage IIIB/IV Aged ≥76 years	Bi-weekly Gemcitabine plus carboplatin (n=31)	Median age: 79 years (76-88) Male: 87.1% ECOG PS: 0=12.9%,	Primary: ORR Secondary: DCR, PFS, OS and safety	Bi-weekly gemcitabine and low-dose carboplatin combination chemotherapy showed acceptable efficacy, toxicity, and tolerability in those aged >76 years with

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
	No financial support was provided for this study			1=87.1%		NSCLC. Further investigations with a large population are required to confirm the results
			Gemcitabine monotherapy (n=30)	Median age: 79 years (76-85) Male: 80.0% ECOG PS: 0=43.3%, 1=56.7%		
LeCaer 2012[41]	Phase II Open-label Multicentre France 2006-2010 Supported by an unrestricted educational grant from Roche, Lilly, Sanofi-Aventis and Chugai	Chemotherapy naïve Stage IIIB/IV Aged >65 years	Gemcitabine followed by erlotinib at progression (n=44)	Mean age + SD: 78.2+3.59 years Male: 84.1% PS: 0=25%, 1=45.5%, 2=29.5%	Primary: TTP2 Secondary: OS, TTP1, ORR, DCR, safety and QoL	In vulnerable elderly patients with NSCLC not selected for EGFR expression, both strategies were feasible but had modest efficacy. Further studies are needed to identify elderly patients who should receive palliative care only
			Erlotinib followed by gemcitabine at progression (n=50)	Mean age + SD: 78.2+4.42 years Male: 78% PS: 0=28%, 1=54%, 2=18%		
Spigel 2012[39]	Phase II Open-label Multicentre USA 2007-2009 Supported, in part, by grants from Eli Lilly and Co., Genentech, Inc.	First-line Stage IIIB/IV Aged ≥70 years	Bevacizumab, plus pemetrexed and gemcitabine (n=55)	Median age: 76 years (70–89) Male: 53% ECOG PS: 0=45%, 1=55%	Primary: TTP Secondary: ORR, toxicity, OS	Treatment with pemetrexed/carboplatin/bevacizumab was associated with improved TTP and OS in this elderly population and should be further evaluated. Treatment-related toxicities were expected and usually manageable, although deaths occurred with both regimens
			Bevacizumab, plus pemetrexed and carboplatin (n=55)	Median age: 77 years (70–88) Male: 47% ECOG PS: 0=38%, 1=62%		
Zeng 2012[42] (abstract only)	China	First-line Stage IIIB/IV	Single-agent paclitaxel	Median age: 75 years (70-83)	Primary and secondary: 1 year	The clinical efficacy of paclitaxel liposome plus

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
	2008-2010 Funding NR	Aged >70 years	(n=35)	Male: 65% ECOG PS: 0-1=83%, 2=17%	survival rate, efficacy and toxicity, DCR, PFS	oxaliplatin as a first-line chemotherapy for elderly patients with advanced NSCLC is better than that of the single-agent paclitaxel liposome. It prolongs PFS and is safe for clinical use
			Paclitaxel liposome plus oxaliplatin (n=34)	Median age: 74 years (70-81) Male: 58% ECOG PS: 0-1=71%, 2=29%		
Biesma 2011[9]	Phase III Netherlands 2003-2006 Funded by Eli Lilly, Bristol Myers Squib and Amgen	Stage IIIA/IIIB/IV Chemotherapy naïve Aged >70 years	Carboplatin plus gemcitabine (n=90)	Median age: 74 years (70-87) Male: 78% WHO PS: 0=26%, 1=57%, 2=18%	Primary: QoL Secondary: OS, toxicity	Paclitaxel or gemcitabine added to carboplatin did not have a differential effect on global QoL. CGA was associated with toxic effects in a very limited manner. CGA and QoL items measure one underlying dimension, which is highly prognostic
			Carboplatin plus paclitaxel (n=91)	Median age: 74 years (70-84) Male: 76% WHO PS: 0=34%, 1=51%, 2=15%		
Gridelli 2011[21]	Phase II Multicentre Italy 2007-2009 Funded by Associazione Italiana per la Ricerca sul Cancro, Milan, Italy	First-line Stage IV/IIIB Aged ≥70 years	Sorafenib plus gemcitabine (n=31)	Median age: 74 years (69-82) Male: 65% ECOG PS: 0=39%, 1=55%, 2=6%	Primary: proportion of patients alive at 1 year Secondary: ORR, safety, TTF, OS	The combination of erlotinib and sorafenib was feasible in elderly patients with advanced NSCLC and was associated with a higher 1-year survival rate than the other arm. According to the selection design, this combination warrants further investigation in phase III trials
			Sorafenib plus erlotinib (n=29)	Median age: 76 years (70-86) Male: 59% ECOG PS: 0=14%, 1=86%, 2=0%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Karampeazis 2011[25,48]	Phase III Multicentre Greece 2003-2008 Funded by Cretan Association for Biomedical Research (CABR)	Chemotherapy naïve Stage IIIB/IV Aged ≥65 years	Docetaxel (n=66)	Median age: 75.5 years (66-87) Male: 92.4% ECOG PS: 0=27.3%, 1=43.9%, 2=28.8%	Primary: OS Secondary: ORR, safety profile, TTP	Docetaxel has an efficacy comparable to that of vinorelbine as first-line treatment in elderly patients with NSCLC and has an acceptable toxicity profile. The trial was closed prematurely because of low accrual, thus limiting the strength of the conclusions derived
			Vinorelbine (n=64)	Median age: 77 years (66-87) Male: 93.8% ECOG PS: 0=25.0%, 1=48.4%, 2=26.6%		
LeCaer 2011[29]	Phase II Open-label Multicentre France 2006-2008 Funded by Roche, Lilly, Sanofi-Aventis and Chugai	First-line/second-line Stage IIIB/IV Aged >65 years	Docetaxel plus gemcitabine then 2-week treatment-free period followed by erlotinib (n=48)	Mean age ±SD: 76.0±4.65 years Male: 60.4% PS: 0=46.8%, 1=44.7%, 2=8.5%	Primary: TTP2 Secondary: OS, TTP1, safety, ORR, disease control rate, QoL	These results suggest that weekly docetaxel plus gemcitabine, followed by erlotinib, is a promising treatment for fit elderly patients with NSCLC; the efficacy of the reverse sequence was insufficient to recommend it for EGFR-non-selected patients
			Erlotinib followed by docetaxel plus gemcitabine (n=51)	Mean age ±SD: 75.7±4.11 years Male: 58.8% PS: 0=41.2%, 1=54.9%, 2=3.9%		
Li 2011[31] (abstract only)	China Funding NR	First-line Stage IIIB/IV Aged >70 years	Gemcitabine plus oxaliplatin (n=33)	Median age: 73 years (70-82) Male: 66% PS: 0-1=76%, 2=23%	NR	The clinical efficiency of gemcitabine plus oxaliplatin vs gemcitabine plus cisplatin regimens as first-line chemotherapy for advanced NSCLC in elderly patients was similar, but the toxicity profile of gemcitabine plus oxaliplatin tends to be more tolerable and safer
			Gemcitabine plus cisplatin (n=33)	Median age: 74 years (70-79) Male: 76% PS: 0-1=82%, 2=18%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Quoix 2011[36]	Phase III Open-label Multicentre France 2006-2009 Funded by Intergroupe Francophone de Cancérologie Thoracique; Institut National du Cancer	First-line treatment Stage III/IV Aged >70 years	Monotherapy (vinorelbine or gemcitabine) (n=226)	Median age: 76.9 years (70.1-88.8) Male: 76.1% PS: 0-1=72.4%, 2=27.6%	Primary: OS Secondary: PFS, response rate, toxicity	Despite increased toxic effects, platinum-based doublet chemotherapy was associated with survival benefits compared with vinorelbine or gemcitabine monotherapy in elderly patients with NSCLC. We feel that the current treatment paradigm for these patients should be reconsidered
			Doublet chemotherapy (carboplatin plus paclitaxel) (n=225)	Median age: 77.4 years (70.0-86.3) Male: 71.6% PS: 0-1=72.9%, 2=27.1%		
Schuette 2011[38]	Phase III Double-blind, placebo controlled Multicentre Germany 2004-2008 Supported by Sanofi Aventis	Chemotherapy naïve Stage IIIB/IV Aged ≥65 years	Docetaxel plus carboplatin and levofloxacin prophylaxis (n=95)	Mean age: 70.8 years (62-79) Male: 80.0% ECOG PS: 0=42.1%, 1=49.5%, 2=8.4%	Primary: rate of grade of infection Secondary: toxicity, RR,1-year survival overall infection rate, OS, PFS	Levofloxacin prophylaxis reduces the rate of infection compared with placebo and is well tolerated in elderly patients receiving docetaxel plus carboplatin
			Docetaxel plus carboplatin and placebo (n=92)	Mean age: 70.7 years (59-83) Male: 80.4% ECPG PS: 0=30.4%, 1=60.9%, 2=8.7%		
Stinchcombe 2011[40]	Phase II United States of America 2010-2006 Funded by Genentech	First-line Stage IIIB/IV Aged >70 years	Gemcitabine (n=44)	Median age: 74 years (70-86) Male: 50% ECOG PS: 0=23%, 1=48%, 2=29%	Primary: PFS, OS Secondary: QoL	Erlotinib or erlotinib and gemcitabine do not warrant further investigation in an unselected elderly patient population
			Erlotinib (n=51)	Median age: 76 years (69-86) Male: 47% ECOG PS: 0=14%, 1=57%, 2=27%,		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
				Missing=2%		
			Gemcitabine and erlotinib (n=51)	Median age: 78 years (70-90) Male: 53% ECOG PS: 0=12%, 1=57%, 2=27%, Missing=4%		
Gridelli 2010[43,46,47]	Phase II Multicentre Italy 2005-2006 Funded by Merck-Serono	Stage IIIB/IV First-line Aged ≥70 years	Cetuximab plus gemcitabine (n=29)	Median age: 74.4 years (70-81) Male: 72.4% PS: 0-1=86.2%, 2=13.8%	Primary: survival at 1 year Secondary: OS, PFS, ORR, toxicity	In both groups of patients, sequential strategy cannot be proposed for future trials because of low compliance. Inconsistency of survival outcomes also indicates that concomitant treatment is not a candidate for further testing in unselected elderly and PS 2 NSCLC patients
			Gemcitabine then cetuximab (n=29)	Median age: 73.8 years (70-80) Male: 75.9% PS: 0-1=81.8%, 2=18.2%		
Hu 2010[23]	Open-label Single centre China 2001-2005 Funding NR	Stage IIIB/IV Aged 60-75 years	Shenfu plus vinorelbine (n=25)	Aged 60–69=10 (40%) Aged 70–75=15 (60%) Male: 72.0% ECOG PS: 0-1=32%, 2=68%	Primary: QoL Secondary: efficacy, toxicity	Shenfu injection plus vinorelbine can enhance QoL in elderly NSCLC patients
			Vinorelbine (n=21)	Aged 60–69=11 (52%) Aged 70–7=10 (48%) Male: 76.2% ECOG PS: 0-1=29%, 2=71%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Jatoi 2010[24]	Multicentre Double-blind, placebo controlled USA 2002-2005 Funding NR Terminated early	Metastatic disease Aged ≥65 or aged <65 with PS=2	Infliximab plus docetaxel (n=32)	Median age: 71 years (59-86) Male: 84% ECOG PS: 0=53%, 1=63%, 2=16%	Primary: non-fluid weight gain of ≥10% of baseline weight Secondary: QoL, response rate, AEs	This trial closed early because infliximab did not prevent or palliate cancer-associated weight loss. Infliximab was associated with increased fatigue and inferior global QoL
			Placebo plus docetaxel (n=29)	Median age: 75 years (59-83) Male: 69% ECOG PS: 0=5 (17%), 1=12 (41%), 2=12 (41%)		
Sakakibara 2010[37]	Phase II Multicentre Japan 2004-2007 Funding NR	Stage IIIB/IV or post-operative recurrence Chemotherapy naïve Aged ≥70	Weekly paclitaxel plus carboplatin (n=42)	Median age: 74 years (70-83) Male: 90.5% ECOG PS: 0=50%, 1=50%	Primary: ORR Secondary: PFS, OS toxicity	This is the first randomized study that compares the platinum doublet designed specifically for the elderly. Regarding the safety, the weekly regimen was less toxic than the standard regimen and seems to be preferable for elderly patients with advanced NSCLC
			Standard paclitaxel plus carboplatin (n=40)	Median age: 75 years (70-87) Male: 73.8% ECOG PS: 0=50%, 1=50%		
Chen 2008[10]	Phase II Single centre Taiwan 2005-2006 Funding NR	Chemotherapy naïve Stage IIIB/IV Aged ≥70	Vinorelbine (n=31)	Mean age: 76.5 years (70-82) Male: 77% WHO PS: 1=48%, 2=52%	Primary: response rates, survival, toxicity	Adding cisplatin to vinorelbine treatment is feasible in elderly patients, and has a better response rate and longer median time to disease progression. However, both statistically significantly higher toxicity and no survival advantage for the combination treatment was observed
			Vinorelbine plus cisplatin (n=34)	Mean age: 75.6 years (70-83) Male: 94% WHO PS: 1=52%,		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
				2=48%		
Crino 2008[15]	Phase II Open-label, parallel-group Multicentre International 2004-2005 Funded by AstraZeneca	Chemotherapy naïve Stage IIIB/IV Aged ≥70 years	Gefitinib (n=97)	Median age: 74 years (70-89) Male: 77.3% WHO PS: 0=13.4%, 1=62.9%, 2=23.7%	Primary: PFS Secondary: OS, ORR, QOL, pulmonary symptom improvement, tolerability	There was no statistical difference between gefitinib and vinorelbine in efficacy in chemotherapy-naïve, unselected elderly patients with advanced NSCLC, but there was better tolerability with gefitinib. Individuals who were EGFR FISH-positive benefited more from vinorelbine than from gefitinib; this unexpected finding requires further study
			Vinorelbine (n=99)	Median age: 74 years (70-86) Male: 73.7% WHO PS: 0=21.2%, 1=61.6%, 2=16.2%		
Comella 2007[14]	Phase II Multicentre Italy 2004-2006 Funding NR	Chemotherapy naïve Stage III/IV Aged 70-84	Alternated dose escalation of paclitaxel and gemcitabine (n=51)	Median age: 74 years (70-84) Male: 84% ECOG PS: 0=37%, 1=63%	Primary: FFS Secondary: compliance, toxicity. ORR, PFS, OS	The combination of paclitaxel and gemcitabine has been confirmed in the present study to be safe and active, and could represent a therapeutic option for fit elderly NSCLC patients
			Fixed dose of paclitaxel and gemcitabine (n=47)	Median age: 73 years (70-84) Male: 87% ECOG PS: 0=28%, 1=72%		
Gridelli 2007[18,19]	Phase II Open-label Multicentre Italy 2003-2004 Sponsored by Eli Lilly and Company	First-line Stage IIIB/IV Aged ≥70 years or <70 years (if ineligible for platinum-based chemotherapy because of poor PS or comorbidities)	Pemetrexed (n=44)	Median age: 73 years (58-82) Male: 79.5% ECOG PS: 0=9.1%, 1=59.1%, 2=31.8%	Primary: TTP Secondary: toxicity, ORR, OS	Single-agent pemetrexed and sequential pemetrexed/ gemcitabine have shown moderate activity and are well tolerated as first-line treatments for advanced NSCLC in elderly patients or patients unsuitable for platinum-based combination
			Pemetrexed plus gemcitabine	Median age: 73 years (61-83)		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
			(n=43)	Male: 67.4% ECOG PS: 0=7.0%, 1=53.5%, 2=39.5%		chemotherapy
Hainsworth 2007[22]	Phase III Multicentre 39 centres in the USA 2001-2006 Funded by Sanofi-Aventis and the Minnie Pearl Foundation	First-line Stage IIIB/IV Aged >65 or ECOG PS 2	Docetaxel (n=171)	Median age: 74 years (45-90) Male: 61% ECOG PS: 0=9%, 1=58% 2=33%	Primary: 1-year survival rate Secondary: objective response rates, TTP, toxicities	Treatment with docetaxel/gemcitabine produced a modest improvement in time-to-progression but had no impact on survival when compared with single-agent weekly docetaxel in this group of patients. Results with both regimens were disappointing, particularly in patients with poor PS. Improved treatment for these patients will require the introduction of novel, well-tolerated, targeted agents
			Docetaxel plus gemcitabine (n=174)	Median age: 74 years (47-91) Male: 62% ECOG PS: 0=6%, 1=56%, 2=37%		
Leong 2007[30]	Phase II Singapore 2000-2005 Funding NR	Chemotherapy naïve Stage III/IV Aged ≥70 years	Gemcitabine (n=43)	Median age: 72 years (42-90) Male: 63% ECOG PS: 0=0, 1=32%, 2=18%, 3=49%	Primary: tolerability, ORR, toxicity, QoL Secondary: OS, PFS	There was no significant advantage of any of the treatment arms over the rest. There was benefit seen with improvement of QoL in patients who were able to receive more cycles of chemotherapy
			Vinorelbine (n=45)	Median age: 73 years (47-94) Male: 71% ECOG PS: 0=2%, 1=31%, 2=16%, 3=51%		
			Docetaxel (n=46)	Median age: 72 years (45-79) Male: 67% ECOG PS: 0=2%, 1=30%, 2=26%, 3=41%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Lilenbaum 2007[32]	Phase II Multicentre US 2002-2004 Funding NR	Chemotherapy naïve Stage IIIB/IV Aged >70 or any age if ECOG PS 2	Tri-weekly docetaxel (n=55)	Median age: 75 years (53-86) Male: 58% ECOG PS: 0=9%, 1=40%, 2=51%	Primary: grades 3-4 toxicity Secondary: overall toxicity, response rates, OS, QoL	Weekly docetaxel is associated with less neutropenia and a trend toward improved survival in elderly or PS 2 patients. PS rather than age is the primary determinant of outcome in this population. Octogenarians benefited from weekly docetaxel. Future studies should separate elderly patients from PS 2 patients
			Weekly docetaxel (n=56)	Median age: 75 years (46-86) Male: 57% ECOG PS: 0=11%, 1=36%, 2=54%		
Chen 2006[11]	Phase II Taiwan 2000-2005 Funding NR	Chemotherapy naïve Stage IIIB/IV Aged ≥70 years	Paclitaxel plus carboplatin (n=40)	Mean age: 76 years (70-84) Male: 100% WHO PS: 0=2.5%, 1=50%, 2=47.5%	Primary: peripheral neuropathy Secondary: OS, TTP, response rate	Paclitaxel plus carboplatin or cisplatin treatment is feasible in elderly patients and has similar activity. However, paclitaxel plus carboplatin had less non-haematological toxicity than paclitaxel plus cisplatin
			Paclitaxel plus cisplatin (n=41)	Mean age: 75 years (70-87) Male: 85.4% WHO PS: 0=7.3%, 1=51.2%, 2=41.5%		
Kudoh 2006[27]	Phase III Multicentre Japan 2000-2003 Funding NR	Chemotherapy and radiotherapy naïve Stage IIIB/IV Aged ≥70 years	Docetaxel (n=89)	Median age: 76 years (70-86) Male: 77.5% ECOG PS: 0-1=98.9%, 2=1.1%	Primary: OS, PFS Secondary: QoL, toxicity	Docetaxel improved PFS, response rate, and disease-related symptoms vs vinorelbine. OS was not statistically significantly improved at this time. Docetaxel monotherapy may be considered as an option in the standard treatment of elderly patients with advanced NSCLC
			Vinorelbine (n=91)	Median age: 76 years (70-84) Male: 74.7% ECOG PS: 0-1=93.4%,		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
				2=6.6%		
Quoix 2005[35]	Phase II Multicentre France 1999-2001 Funded by Lilly Oncology	Chemotherapy naïve IIIB/IV Aged 70-90 years	Gemcitabine (4 weeks) (n=42)	Median age: 75 years (71-90) Male: 85.7% KPS: 60-70=19.0%, 80-90=81.0%	Primary: TTF Secondary: OS, ORR, safety	Although both 3- and 4-week gemcitabine regimens were safely and effectively administered in chemotherapy-naïve elderly patients with advanced NSCLC, the 3-week schedule appears to be the more convenient for this population. Although only a phase II study, the 3-week schedule appears to be at least as efficient as the 4-week regimen
			Gemcitabine (3 weeks) (n=39)	Median age: 75 years (70-89) Male: 79.5% KPS: 60-70=28.2%, 80-90=71.8%		
Comella 2004[13]	Multicentre Italy 1999-2003 Funding NR	Stage IIIB/IV Aged >70 years	Gemcitabine (n=68)	Median age: 75 years (49-86) Male: 84% PS: 0-1=72%, 2=28%	Primary: survival Secondary: response rate, toxicity	GT should be considered a reference regimen for elderly NSCLC patients with PS ≤1
			Paclitaxel (n=63)	Median age: 72 years (50-81) Male: 90% PS: 0-1=65%, 2=35%		
			Gemcitabine plus vinorelbine (GV) (n=68)	Median age: 72 years (42-82) Male: 93% PS: 0-1=77%, 2=23%		
			Gemcitabine plus paclitaxel (GT) (n=65)	Median age: 73 (53-83) Male: 91% PS: 0-1=69%, 2=31%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Gridelli 2003[20]	Phase III Open-label Multicentre Italy 1997-2000 Partially supported by Associazione Italiana per la Ricerca sul Cancro (AIRC), Clinical Trials supporting Group (CTPG) and Gruppo Italiano di Oncologia Geriatrica (GIOGER)	Stage IIIB/IV Aged ≥70 years	Vinorelbine (n=233)	Median age: 74 years (63-83) Male: 88% ECOG PS: 0=30%, 1=51%, 2=19%	Primary: OS Secondary: QoL, toxicity	The combination of vinorelbine plus gemcitabine is not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC
			Gemcitabine (n=233)	Median age 74 years (70-86) Male: 83% ECOG PS: 0=29%, 1=53%, 2=18%		
			Vinorelbine plus gemcitabine (n=232)	Median age: 74 years (69-84) Male: 79% ECOG PS: 0=28%, 1=53%, 2=19%		
Frasci 2001[17,45]	Phase III Multicentre Italy 1997-1999 Funding NR	Stage IIIB/IV Chemotherapy naïve Aged ≥70 years	Gemcitabine plus vinorelbine (n=60)	Median age: 75 years (71-83) Male: 88% ECOG PS: 0=18% 1=55% 2=17%	Primary: survival Secondary: toxicity, QoI, ORR	Gemcitabine plus vinorelbine treatment is associated with a significantly better survival than vinorelbine alone in elderly NSCLC patients. The magnitude of the difference justifies the early closure of the study. The regimen is now the SICOG reference regimen in this type of patients
			Vinorelbine (n=60)	Median age: 74 years (71-81) Male: 92% ECOG PS: 0=22%, 1=56%, 2=22%		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Gridelli 2001[44]	Phase III Italy 1996-1997 Funding NR Trial stopped early	Stage IIIB/IV First-line Aged >70 years	BSC (n=78)	Median age: 74 years (70-86) PS: 0=19%, 1=56%, 2=24%	Primary: QoL	While aspects of QoL issues that were directly related to drug toxicity (such as nausea and constipation) were lower in the vinorelbine group, patients who received vinorelbine fared better than controls on measures related to lung cancer symptoms and pain and on social, cognitive, and physical functioning
			BSC plus vinorelbine (n=76)	Median age: 74 years (70-85) PS: 0=18%; 1=58%; 2=24%		
SCLC						
Pu 2013[34] (abstract only)	China Funding NR	First-line Extensive-stage Aged >70 years	Etoposide plus oxaliplatin (EO) (n=35)	Median age: 73 years (70-83) Male: 86% ECOG PS: 0-1=74%, 2=16%	Efficacy and toxicity	The clinical efficiency of EO and EP regimens is similar to the first-line chemotherapy for extensive-stage SCLC in elderly patients. Tolerance of EO regimens is better than in the EP regimens
			Etoposide plus cisplatin (EP) (n=36)	Median age: 72 years (70-79) Male: 81% ECOG PS: 0-1=74%, 2=16%		
Okamoto 2007[33]	Phase III Multicentre Japan 1998-2004 Funded by Grants-in-Aid for Cancer Research and Ministry of Health, Labour, and Welfare	First-line Extensive stage Aged ≥70 years or <70 and PS 3	Carboplatin plus etoposide (CE) (n=110)	Median age: 74 years (56-86) ≥70 years=102 (93%) Male: 86% ECOG PS: 0=74%, 1=19%, 2=7%	Primary: OS Secondary: ORR, PFS, safety, toxicity, compliance	Although the SPE regimen is still considered to be the standard treatment in elderly or poor-risk patients with extensive-disease SCLC, the CE regimen can be an alternative for this population considering the risk–benefit balance
			Cisplatin plus etoposide (SPE) (n=110)	Median age: 73.5 years (55-85) ≥70 years=100 (91%) Male: 89% ECOG PS: 0=74%,		

Study	Study details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
				1=17%, 2=9%		
Ardizzoni 2005[8]	Phase II Multicentre Italy 1997-2001 Funding NR	Extensive stage disease Aged ≥70 years	Attenuated-dose cisplatin plus etoposide (n=28)	Median age: 74 years (70-80) Male: 96% ECOG PS: 0=28%, 1=61%, 2=11%	Primary: therapeutic success Secondary: OS, ORR, toxicity	In elderly patients with SCLC a full-dose cisplatin/etoposide regimen combined with prophylactic lenograstim is active and feasible, while attenuated doses of the same regimen are associated with a poor therapeutic outcome
			Full-dose cisplatin plus etoposide (n=67)	Median age: 73 years (70-79) Male: 79% ECOG PS: 0=28%, 1=60%, 2=12%		

EGFR=epidermal growth factor receptor; DCR=disease control rate; PFS=progression free survival; OS=overall survival; QoL=quality of life; CGA=comprehensive geriatric assessment; AE=adverse event; NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; ORR=objective response rate; TTP=time to progression; TTF=time to treatment failure; FFS=failure-free survival; BSC=best supportive care; SD=standard deviation; PS=performance status; KPS=Karnofsky performance status; ECOG=Eastern Cooperative Oncology Group; WHO=World Health Organisation; FISH=fluorescence in situ hybridisation; NR=not reported; SICOG=Southern Italy Cooperative Oncology Group

6.3 Efficacy evidence

Outcomes of progression-free survival (PFS) or time to disease progression (TTP), overall survival (OS) and objective response rates (ORR) for all RCTs are presented in Table 5. Of the 36 included trials, seven[8,13,17,23,24,26,44,45] did not report PFS/TTP as an outcome measure. Overall survival was reported in 33 trials,[8-22,24,25,27-41,43-48] and ORR in 31 trials.[8-25,27,28,30,32-40,42,44,48]

6.3.1 Non-small cell lung cancer

The lowest reported median PFS was 1.9 months[25,48], and the highest was 10.2 months.[39] Six trials reported statistically significant results: Chen et al[12] reported a statistically significantly longer median PFS for erlotinib versus vinorelbine (4.57 vs 2.53 months; hazard ratio [HR] 0.64, 95% confidence interval [CI] 0.43 to 0.96; p=0.0308); in Kusagaya et al,[28] the median PFS for gemcitabine plus carboplatin versus gemcitabine monotherapy was 3.9 versus 2.4 months (HR 0.46; p<0.02). Kudoh et al[27] compared docetaxel with vinorelbine and reported a PFS of 5.5 versus 3.1 months (p<0.001); Hainsworth et al[22] compared docetaxel with docetaxel plus gemcitabine and achieved a median PFS of 2.9 months (2.0 to 3.6) and 4.8 months (3.9 to 6.2), respectively (p=0.004); Spigel et al[39] compared bevacizumab plus pemetrexed and gemcitabine with bevacizumab plus pemetrexed and carboplatin, and found that the carboplatin-containing arm had a significantly higher median PFS (4.7 months [3.8 to 5.8] versus 10.2 months [6.3 to 12.7]; p=0.0011); and Quoix et al[36] compared monotherapy (PFS 2.8 months [2.6 to 3.7]) with doublet therapy (PFS 6.0 months [5.5 to 6.8]; HR 0.51, 95% CI 0.42 to 0.62; p<0.0001). Overall, 13 trials[9-11,14,16,18-20,27,31,37-39,42] achieved a median PFS/TTP of >3 months in all treatment arms.

The lowest median OS was reported by Lilenbaum et al[32] (3.5 months) and the highest reported OS was 15.5 months.[37] There were two statistically significant results reported: Quoix et al[36] demonstrated a significant OS gain for doublet therapy (10.3months [8.3 to 12.6]) versus monotherapy (6.2 months [5.3 to 7.3]; HR 0.64, 95% CI 0.52 to 0.78; p<0.0001), and Spigel et al reported a higher OS for pemetrexed plus carboplatin and bevacizumab (14.8 months) versus pemetrexed plus gemcitabine and bevacizumab (7.5 months; p=0.0017). Twelve trials[10-12,16,21,27,28,31,36-39] achieved an OS of >10 months in one or more arms.

Objective response rates varied across trials from 3.1%[15] to 55%.[37] Two trials reported statistically significant differences between treatment arms: doublet therapy versus monotherapy (27.1% [95% CI 21.4 to 33.4] vs 10.2% [95% CI 6.6 to 14.9]; p<0.0001) reported by Quoix et al[36] and erlotinib versus vinorelbine (22.8% vs 8.9%; p=0.04) reported in Chen et al.[12]

6.3.2 Small cell lung cancer

The lowest reported PFS was 4.7 months[33,34] for cisplatin plus etoposide, and the highest was 5.5 months for etoposide plus oxaliplatin;[34] however, none of the results were statistically significant.

Overall survival was reported in all three trials,[8,33,34] and ranged from 7.1 months[8] to 10.6 months.[33] Pu et al[34] and Okamoto et al[33] reported 10.5 months and 10.6 months, respectively. None of the results were statistically significant.

Objective response rates were reported in all three trials,[8,33,34] but there were no statistically significant results. Ardizzoni et al[8] reported an ORR of 39.3% (22.1 to 59.3) in the etoposide plus attenuated-dose cisplatin arm, which was much lower than the other ORR results. The highest ORRs were reported by Okamoto et al,[33] with both trial arms reaching an ORR of 73% (63 to 81) for etoposide plus either carboplatin or cisplatin.

Table 5 Survival outcomes, randomised controlled trials

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
NSCLC							
Chen 2012[12]	Erlotinib	4.57	0.64 (0.43 to 0.9601) p=0.0308	11.67	p=0.70	22.8	p=0.04
	Vinorelbine	2.53		9.3		8.9	
El Shenshawy 2012[16] (abstract only)	Paclitaxel plus carboplatin	TTP: 7.0	NR	10.8	NR	42.9	NR
	Paclitaxel plus carboplatin	TTP: 5.6	NR	9.0	NR	31.8	NR
Kusagaya 2012[28]	Gemcitabine plus carboplatin	3.9 (0.5 to 8.5)	0.46 p<0.02	12.6 (3.3 to 38.2)	NR	22.6 (11.4 to 39.8)	NR
	Gemcitabine monotherapy	2.4 (0.5 to 6.7)		15.4 (2.0 to 27.8)	NR	10 (3.5 to 25.6)	NR
LeCaer 2012[41]	Gemcitabine followed by erlotinib	TTP1: 2.5 (2 to 4) TTP2: 4.3 (3 to 6.2)	p=0.58 p=0.55	4.4 (3.1 to 7.2)	p=0.26	NR	NR
	Erlotinib followed by gemcitabine	TTP1: 2.2 (1.8 to 3.8) TTP2: 3.5 (2.9 to 3.8)		4 (3 to 6)		NR	NR
Spigel 2012[39]	Pemetrexed plus gemcitabine and bevacizumab	4.7 (3.8 to 5.8)	p=0.0011	7.5 (5.6 to 11.3)	p=0.0017	35 (23 to 49)	NR
	Pemetrexed plus carboplatin and bevacizumab	10.2 (6.3 to 12.7)		14.8 (10.25 to upper limits not reached)		35 (23 to 49)	NR
Zeng 2012[42] (abstract only)	Paclitaxel liposome	3.5	p=0.024	NR	NR	22.9	p=0.297
	Paclitaxel liposome plus oxaliplatin	5		NR	NR	35.3	
Biesma 2011[9]	Carboplatin plus gemcitabine	4.7 (3.9 to 5.8)	NR	8.6 (7.2 to 10.2)	1.22 (0.89 to 1.69)	27	NR
	Carboplatin plus paclitaxel	4.5 (4.1 to 5.3)	NR	6.9 (5.6 to 10.0)		19	NR
Gridelli 2011[21]	Sorafenib plus gemcitabine	TTF: 1.9 (0.2 to 15)	NR	6.55	NR	6.5 (0.8 to 21.4)	NR
	Sorafenib plus erlotinib	TTF: 2.92 (0.5 to 16)	NR	12.6	NR	10.3 (2.2 to 27.4)	NR
Karampeazis 2011[25,48]	Docetaxel	2.33	p=0.29	6.07	p=0.09	12.1 (4.25 to 20)	p=0.79
	Vinorelbine	1.9		3.87		14.1 (5.55 to 22.58)	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
LeCaer 2011[29]	Docetaxel plus gemcitabine >erlotinib	TTP2: 7.5±3.6 TTP1: 4.7±2	TTP2, p=0.53 TTP1, p=0.53	9.4 (7.6 to 2)	p=0.26	NR	NR
	Erlotinib >doxetaxel plus gemcitabine	TTP2: 5.8±2.2 TTP1: 2.7±1.5		7.1 (5.1 to 9.8)		NR	NR
Li 2011[31] (abstract only)	Gemcitabine plus oxaliplatin	5.5 (4.8 to 5.9)	p=0.565	10.1 (8.5 to 11.4)	p=0.918	NR	NR
	Gemcitabine plus cisplatin	4.1 (1.8 to 6.2)		8.2 (6.8 to 9.4)		NR	NR
Quoix 2011[36]	Monotherapy	2.8 (2.6 to 3.7)	0.51 (0.42 to 0.62) p=<0.0001	6.2 (5.3 to 7.3)	0.64 (0.52 to 0.78) p<0.0001	10.2 (6.6 to 14.9)	p<0.0001
	Doublet chemotherapy	6.0 (5.5 to 6.8)		10.3 (8.3 to 12.6)		27.1 (21.4 to 33.4)	
Schuette 2011[38]	Docetaxel plus carboplatin and levofloxacin prophylaxis	5.4	0.82 (0.60 to 1.13) p=0.22	10	0.83 (0.58 to 1.17) p=0.28	29.5	p=1.0
	Docetaxel plus carboplatin and placebo	3.9		10.3		30.4	
Stinchcombe 2011[40]	Gemcitabine	3.7 (2.3 to 4.7)	NR	6.8 (4.8 to 8.5)	NR	7	NR
	Erlotinib	2.8 (1.4 to 3.4)	NR	5.8 (3.0 to 8.3)	NR	0	NR
	Gemcitabine plus erlotinib	4.1 (2.4 to 5.0)	NR	5.6 (3.5 to 8.4)	NR	21	NR
Gridelli 2010[43,46,47]	Cetuximab plus gemcitabine	2.6 (2 to 4.4)	NR	5.5 (2.8 to 16.8)	NR	NR	NR
	Gemcitabine then cetuximab	3.7 (2 to 4.8)	NR	8.3 (5.3 to 11.5)	NR	NR	NR
Hu 2010[23]	Shenfu plus vinorelbine	NR	NR	NR	NR	14.3	p=0.05
	Vinorelbine	NR	NR	NR	NR	15.0	
Jatoi 2010[24]	Infliximab plus docetaxel	NR	NR	6.2	p=0.88	3.7	p=0.48
	Placebo plus docetaxel	NR	NR	5.6		8.3	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Sakakibara 2010[37]	Weekly paclitaxel plus carboplatin	6.0	NR	14.7	NR	55 (40 to 70)	NR
	Standard paclitaxel plus carboplatin	5.6	NR	15.5	NR	53 (38 to 68)	NR
Chen 2008[10]	Vinorelbine	TTP: 3.1	p=0.0303	12	NR	16.1	p=0.009
	Vinorelbine plus cisplatin	TTP: 5.2		11.3	NR	32.4	
Crino 2008[15]	Gefitinib	2.7	1.19 (0.85 to 1.65) p=0.310	5.9	0.98 (0.66 to 1.47)	3.1 (0.6 to 8.8)	NR
	Vinorelbine	2.9		8.0		5.1 (1.7 to 11.4)	NR
Comella 2007[14]	Alternated dose escalation of paclitaxel plus gemcitabine	5.2 (4.6 to 5.8)	p=0.363	9.7 (5.0 to 14.2)	p=0.708	25 (14 to 40)	p=0.343
	Fixed dose paclitaxel plus gemcitabine	5.1 (3.7 to 6.5)		9.6 (5.3 to 14.1)		26 (14 to 40)	
Gridelli 2007[18,19]	Pemetrexed	TTP: 4.5 (3 to 9.3) PFS: 3.3 (2 to 4.4)	NR	4.7	NR	4.5 (0.6 to 15.5)	NR
	Pemetrexed plus gemcitabine	TTP: 4.1 (1.7 to 5.8) PFS: 3.3 (1.7 to 4.1)	NR	5.4	NR	11.6 (3.9 to 25.1)	NR
Hainsworth 2007[22]	Docetaxel	2.9 (2.0 to 3.6)	p=0.004	5.1	p=0.65	17 (11 to 24)	p=0.1
	Docetaxel plus gemcitabine	4.8 (3.9 to 6.2)		5.5		25 (18 to 34)	
Leong 2007[30]	Gemcitabine	3.42	NR	5.16	NR	16	NR
	Vinorelbine	2.99	NR	6.8	NR	20	NR
	Docetaxel	2.78	NR	5.06	NR	22	NR
Lilenbaum 2007[32]	Tri-weekly docetaxel	TTP: 1.7	p=0.549	3.5	p=0.581	9.1	OR 1.8 (0.4 to 7.8) p=0.452
	Weekly docetaxel	TTP: 2.3		6.7		5.4	NR
Chen 2006[11]	Paclitaxel plus carboplatin	TTP: 6.6	NR	10.3	NR	40 (24.8 to 55.2)	p=0.93
	Paclitaxel plus cisplatin	TTP: 6.9	NR	10.5	NR	39 (24.1 to 53.9)	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Kudoh 2006[27]	Docetaxel	5.5	0.606 (0.45 to 0.816) p<0.001	14.3	0.78 (0.561 to 1.085) p=0.138	22.7 (13.9 to 31.5)	p=0.019
	Vinorelbine	3.1		9.9		9.9 (3.8 to16)	
Quoix 2005[35]	Gemcitabine (4 weeks)	TTP: 2.7 (2.3 to 3.2)	NR	5 (3.6 to 7.5)	NR	14.3	NR
	Gemcitabine (3 weeks)	TTP: 3 (2.1 to 3.7)	NR	6.7 (4.1 to 11.3)	NR	28.2	NR
Comella 2004[13]	Gemcitabine	NR	NR	5.1 (2.2 to 8.0)	NR	18 (9 to 30)	NR
	Paclitaxel	NR		6.4 (4.4 to 8.4)		13 (6 to 24)	NR
	Gemcitabine plus vinorelbine	NR		9.7 (7.9 to 11.5)		23 (13 to 35)	NR
	Gemcitabine plus paclitaxel	NR		9.2 (4.8 to 13.6)		32 (20 to 45)	NR
Gridelli 2003[20]	Vinorelbine	TTP: 4.1 (2.9 to 4.5)	p=0.32 p=0.31	8.2 (6.8 to 10.3)	p=0.93 p=0.69	18 (13 to 23)	p=0.47 p=0.18
	Gemcitabine	TTP: 3.9 (2.9 to 4.3)		6.4 (5.7 to 7.8)		16 (12 to 21)	
	Vinorelbine plus gemcitabine	TTP: 4.3 (3.6 to 4.8)		6.8 (6.2 to 8.2)		21 (16 to 26)	
Frasci 2001[17,45]	Gemcitabine plus vinorelbine	NR	NR	6.68	NR	22 (12 to 34)	NR
	Vinorelbine	NR	NR	4.14	NR	15 (7 to 27)	NR
Gridelli 2001[44]	BSC	NR	NR	4.8 (3.7 to 6.2)	NR	NR	NR
	BCS plus vinorelbine	NR	NR	6.4 (5.3 to 8.04)	NR	19.7 (11.5 to 30.5)	NR
SCLC							
Pu 2013[34] (abstract only)	Etoposide plus oxaliplatin	5.5	p=0.638	10.5	p=0.862	55.9	p=0.894
	Etoposide plus cisplatin	4.7		9.1		54.3	
Okamoto 2007[33]	Carboplatin plus etoposide	5.2	p=0.2	10.6	p=0.54	73 (63 to 81)	NR
	Cisplatin plus etoposide	4.7		9.9		73 (63 to 81)	NR
Ardizzoni 2005[8]	Attenuated-dose cisplatin plus etoposide	NR	NR	7.1	NR	39.3 (22.1 to 59.3)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
	Full-dose cisplatin plus etoposide	NR	NR	9.4	NR	68.7 (56.0 to 79.1)	NR

PFS=progression-free survival; TTP=time to progression; OS=overall survival; BSC=best supportive care; CI=confidence interval; ORR=objective response rate; OR=odds ratio; NR=not reported

[a] Values are PFS, unless otherwise stated

6.4 Tolerability evidence

Outcomes relating to tolerability provided by RCTs are presented in Table 6. All RCTs, except for Zeng et al[42] and Lilenbaum et al,[32] reported at least one outcome of interest.

6.4.1 Non-small cell lung cancer

Treatment completion was a commonly reported outcome in the trials, and was expressed either as a proportion of the planned treatment received, or as a proportion of how many patients completed the planned treatment. Gridelli et al[20] reported that approximately 40% of the planned doses were delivered in each study arm; however, Sakakibara et al[37] reported that 93% of the planned doses were administered overall. Hainsworth et al[22] reported that 11% and 14% of patients in each arm completed treatment. The highest proportion of patients who completed the planned treatment was reported by Biesma et al[9] (64% and 65%). Kusagaya et al[28] reported that 26.6% completed the study in one arm (which is similar to the 26% reported by Gridelli et al[21]) and 71% completed in the comparator arm. Stinchcombe et al[40] reported 59% of patients completed treatment in the gemcitabine arm, however no patients completed treatment in either the erlotinib or erlotinib plus gemcitabine arms. Similar figures for both arms were reported by Schuette et al,[38] with 32% of patients completing the study in the docetaxel plus carboplatin and levofloxacin arm and 34% completing in the docetaxel plus carboplatin and placebo arm. Dose intensity was also commonly reported. The lowest mean dose intensity was reported by LeCaer et al[41] at 46% (second-line), and then varied between the mean dose intensity of 74% in LeCaer et al[29] and 99% in Leong et al.[30]

Schuette et al[38] reported high rates of discontinuations due to disease progression (31%, 44%) and toxicity (25%, 15%), and figures for withdrawal due to patient choice were also relatively high (15% both arms). Karampeazis et al[25,48] reported high figures for withdrawal due to disease progression (34.8%, 38.1%); however, discontinuations due to AEs and patient choice were low (<10%). Similarly, Hainsworth et al[22] and Kudoh et al[27] reported higher rates of discontinuation due to disease progression in all arms, respectively, and high rates of AEs in all arms.

In the majority of trials, rates of reductions or omissions of treatment were similar. However, lower rates were reported in two studies: Karampeazis et al[25,48] reported that dose reductions occurred in 7.7% and 12.9% of cycles, which is similar to the 8.7% and 8.9% reported by Quoix et al.[35] The highest reported dose reductions were reported by Spigel et al[39] (33%, 42%). Dose interruptions were reported in 9.6% and 21.9% of cycles in Crino et al,[15] and 74% of administrations were skipped due to toxicity in Sakakibara et al.[37] Treatment cycles with dose delays varied from 3% in Biesma et al[9] to 47.9% in Crino et al.[15]

There were several grade 3-4 AEs of >10% reported across the trials. Commonly reported haematological AEs were neutropenia, anaemia, thrombocytopenia and leukopenia. Twenty

trials[9,10,14,16,17,20,22,25-30,35,37,38,40,43-48] reported neutropenia, which ranged from 11%[14] to 88%[37] across trials. Neutropenia almost doubled for standard versus weekly paclitaxel plus carboplatin reported in Sakakibara et al, with 41% and 88%, respectively (p<0.0001).[37] Thrombocytopenia was reported in four trials[9,22,31,39] and ranged from 2%[9] to 53%.[9] Seven trials[9,11,27,28,35,38,39] reported leukopenia. Low figures were reported in Quoix et al (12.2%),[35] Chen et al (15%)[11] and Biesma et al (17%)[9] and higher figures were reported in Kudoh et al (52.3%)[27] and Schuette et al (63.2%).[38]

Fatigue was a commonly reported non-haematological AE, and was reported by nine trials.[9,11,21,22,24,26,30,39,43,46,47] Biesma et al[9] reported the lowest rate of 8%, similar to the 13% and 14% reported by Gridelli et al.[21] The highest rates were reported by Kim et al[26] with 36.4% and 40% in each arm, and Jatoi et al[24] also reported a high rate of 38%.

6.4.2 Small cell lung cancer

The tolerability evidence available from published studies of patients with SCLC is not quite as detailed as for NSCLC. Of the three included trials,[8,33,34] two presented information relating to treatment completion, discontinuations or dose modifications,[8,33] and two provided details of grade 3-4 AEs >10%.[33,34]

Okamoto et al[33] reported figures for the proportion of planned doses delivered (80%, 83%), and Ardizzoni et al[8] reported that 75% and 72% of patients completed treatment as per protocol.[8] Dose intensity was 96% and 98% for the two study arms in Ardizzoni et al.[8]

The total percentage of discontinuations in Ardizzoni et al[8] were 25% and 24%, respectively. Discontinuations due to toxicity were relatively low (11%, 8%) in Okamoto et al,[33] and patient refusal was <5%. Dose delays were reported in 41% and 37% in Okamoto et al,[33] and in 18% and 16% of cycles in Ardizzoni et al.[8] Dose reductions were 29% and 10% in Okamoto et al.[33]

Neutropenia was reported by Okamoto et al,[33] with high rates of 90% and 95%, and anaemia was recorded in 25% and 29%. Thrombocytopenia was 14.3% and 11.1% in Pu et al,[34] and 16% and 56% in Okamoto et al.[33] Leukopenia was higher in the Okamoto et al study (54% and 51%) than in the Pu et al study[34] (11% and 16.7% for grade 4 leukopenia).

There were no non-haematological AEs reported in any of the three trials.[8,33,34]

Table 6 Tolerability outcomes, randomised controlled trials

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
NSCLC				
Chen 2012[12]	Erlotinib Median cycles=5	NR	NR	Rash=64.91% Diarrhoea=29.82% Mouth ulceration=14.04%
	Vinorelbine Median cycles=3.5	NR	NR	Decreased appetite=26.32% Diarrhoea=12.28% Vomiting=10.53% Anorexia=10.53%
El Shenshawy 2012[16] (abstract only)	NR	NR	NR	Paclitaxel plus carboplatin Grade 3-4 anemia=23.8% Grade 3-4 neutropenia and febrile neutropenia=14.3%
Kim 2012[26] (abstract only)	NR	NR	NR	Docetaxel plus cisplatin: Total n=27 Anaemia=66.7% Hyponatremia=53.3% Anorexia=53.3% Fatigue=40.0% Death=1 patient
	NR	NR	NR	Gemcitabine plus cisplatin: Total n=21 Neutropenia=15.9% Anaemia=63.6% Anorexia=56.8% Fatigue=36.4% Neutropenia=45.5% Death=1 patient
Kusagaya 2012[28]	Combination therapy: Completed >4=71% Mean dose intensity of carboplatin=93.0% Mean dose intensity of gemcitabine=93.4%	NR	Dose reductions=10 patients	Grade 3: Leukopenia=38.0% Neutropenia=19.4% Anaemia=19.4%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Monotherapy: Completed >4=26.6% Median cycles=4	Most patients in the monotherapy arm withdrew treatment because of disease progression	Dose reductions=9 patients	Grade 3: Leukopenia=30.0% Neutropenia=20.0%
LeCaer 2012[41]	Gemcitabine followed by erlotinib at progression: First-line: Mean dose=65% All eligible patients received at least one dose Mean cycles=2.9 per patient Second-line: Received dose=48% Mean duration=1.7 months	n=44 Non-assessable first-line therapy: Toxicity=2 Death=4 Withdrew before second-line: Death=11 Major toxicity=1 Patient refusal=1 Other=4 Non-assessable second-line therapy: Death=2	NR	First-line grade 3-4: Pulmonary=13.6% Asthenia=11.4%
	Erlotinib followed by gemcitabine at progression: First-line: All eligible patients received at least one dose Mean duration=2 months Second-line: Mean dose=51% Received dose=46% Mean cycles=2.7 per patient	n=50 Non-assessable first-line therapy: Major toxicity=2 Death=5 Withdrew before second-line: Death=10 Patient refusal=1 Major toxicity=3 Loss of sight=1 Progression=1 Other=3 First-line on-going=1 Non-assessable second-line therapy: Death=6	NR	First-line grade 3-4: Asthenia=18% Second-line grade 3-4: Asthenia=21%
Spigel 2012[39]	Pemetrexed plus gemcitabine and bevacizumab Median number of cycles=2.5 cycles (2.5 months; range, 0.5–11months)	NR	Dose reduction=33% Bevacizumab held at least once=51%	Grade 3: Anaemia=20% Leukopenia=31% Neutropenia=24% Dyspnoea=18%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Fatigue=35% Infection=22% Grade 4: Neutropenia=27%
	Pemetrexed plus carboplatin and bevacizumab: Median cycles=6 (4.5 months; range 0.75–9 months)	NR	Dose reduction=42% Bevacizumab held at least once=9%	Grade 3: Leukopenia=25% Neutropenia=35% Thrombocytopenia=22% Fatigue=18% Grade 4: Neutropenia=11%
Biesma 2011[9]	Carboplatin plus gemcitabine: Completed all 4 cycles=64%	Did not start allocated intervention: (n=2) Progressive disease=1 Wrong treatment arm=1 Did not complete four courses: (n=32) Unacceptable toxicity=6 Progressive disease=10 Death=9 Clinical progression=3 Patient refusal=3 Other reasons=1 Died prior to week 18: (n=26)	Per-protocol dose reductions=30% (p<0.001) Dose delays=15% (p=0.008)	Leukopenia=38% Neutropenia=42% Thrombocytopenia=53% Fatigue=17%
	Carboplatin plus paclitaxel: Completed all 4 cycles=65%	Did not start allocated intervention: (n=2) Patient refusal=1 Early death=1 Did not complete four courses: (n=33) Unacceptable toxicity=11 Progressive disease=8 Death=5 Clinical progression=1 Patient refusal=5	Per-protocol dose reductions=9% (p<0.001) Dose delays=3% (p=0.008)	Leukopenia=17% Neutropenia=33% Thrombocytopenia=2% Fatigue=8%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
		Other reasons=3 Died prior to week 18: (n=19)		
Gridelli 2011[21]	Sorafenib plus gemcitabine: Completed the planned six cycles=8/31 Continued with single agent sorafenib=median 20 weeks Overall, 101 courses of chemotherapy were delivered Median cycles per patient=3	Chemotherapy was discontinued earlier than planned in 23 patients (10 patients after one cycle, 5 patients after two cycles, 5 patients after three cycles and 3 patients after five cycles) Discontinued therapy because of AEs=7	Non-compliance=1 AEs=7 Disease progression/death=15 Consent withdrawn=3 Lost to follow-up=0 Interruption >21 days=2 Squamous histology=1 Medical decision=1 Deterioration=1 Gemcitabine administration on day 8 was omitted 17 times because of lack of haematological recovery	Grade 3-4 fatigue=13%
	Sorafenib plus erlotinib: NR	Discontinued therapy because of AEs=6	Non-compliance=2 AEs=6 Disease progression/death=10 Consent withdrawn=1 Lost to follow-up=1 Interruption >21 days=3 Squamous histology=1 Medical decision=0 Deterioration=1	Grade 3-4 fatigue=14% Grade 3-4 diarrhoea=14%
Karampeazis 2011[25,48]	Docetaxel: Dose intensity=95.7% 222 cycles Median cycles=3 (range 1 to 6)	Disease progression=34.8% Early death from disease progression=21.2% Patient refusal=7.6% AEs=1.5% Protocol violation=3.0% Consent withdrawn=2.3%	Delayed=12.0% Dose reduction=7.7%	NR
	Vinorelbine: Dose intensity=96.6% 202 cycles Median cycles=3 (range 1 to 6)	Disease progression=38.1% Early death from disease progression=19.0% Patient refusal=3.2% AEs=4.8% Protocol violation=1.6% Consent withdrawn=3.3%	Delayed=15.0% Dose reduction=12.9%	Neutropenia Grade 3=12.5% Grade 4=17.2%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
LeCaer 2011[29]	Docetaxel plus gemcitabine >erlotinib: Mean number of first-line cycles per patient=1.83 Mean RDI gemcitabine=79% Mean RDI docetaxel=85% Received second-line erlotinib=60.4% Mean duration erlotinib=4.7 months	NR	NR	First-line grade 3-4: Neutropenia=31.3% Second-line grade 3-4: Asthenia=10.0%
	Erlotinib >docetaxel plus gemcitabine Mean number of second-line cycles per patient=1.83 Mean RDI gemcitabine=74% Mean RDI docetaxel=90% Received second-line chemotherapy=47% Mean duration erlotinib=3.1 months	NR	NR	Second-line grade 3-4: Neutropenia=16.6% Asthenia=12.0% Pulmonary=12.0%
Li 2011[31] (abstract only)	NR	NR	NR	Gemcitabine plus oxaliplatin Grade 3-4: Thrombocytopenia=15.2% Anaemia=12.1%
	NR	NR	NR	Gemcitabine plus cisplatin Grade 3-4: Anaemia=33.3%
Quoix 2011[36]	NR	NR	NR	Monotherapy Toxic death=1.3%
	NR	NR	NR	Doublet therapy Toxic death=4.4% Decreased neutrophil count:

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Grade 3=30.9% Grade 4=17.5%
Schuette 2011[38]	Docetaxel plus carboplatin and levofloxacin prophylaxis: Completed study=32% Median cycles=4	n=65 Progression=20 Toxicity=16 Patient wish=10 Other reasons=8 Death=7 Lost to follow-up=2 Toxicity and patient wish=2	NR	>Grade 3: Leukopenia=63.2% Neutropenia=62.0%
	Docetaxel plus carboplatin and placebo: Completed study=34% Median cycle=4	n=61 Progression=27 Toxicity=9 Patient wish=9 Other reasons=8 Death=8 Lost to follow-up=0 Toxicity and patient wish=0	NR	>Grade 3: Leukopenia=52.2% Neutropenia=51.1%
Stinchcombe 2011[40]	Gemcitabine: Completed treatment=59% Median cycles=4 (range 1 to 4) Received second-line erlotinib n=19	n=44 Death=4 Progressive disease=7 Medical illness=3 Consent withdrawn=1	NR	The rate of grade 3 neutropenia was low in all three arms, and no episodes of febrile neutropenia were observed
	Erlotinib: Completed treatment=0 Median cycles=2 (range 1 to 39) Received second-line therapy n=12	n=51 AEs=8 Death=3 Progressive disease=30 Consent withdrawn=2	NR	NR
	Gemcitabine plus erlotinib: Completed treatment=0 Median cycle=4 (range 1 to 9) Received second-line therapy n=9	n=51 AEs=11 Death=2 Progressive disease=26 Medical illness=6 Consent withdrawn=2	NR	NR
Gridelli 2010[43,46,47]	Cetuximab plus gemcitabine Median administrations=8 (range 2-78) Dose intensity=0.82 (range 0.45-1)	Treatment never began=0 Progression=68.9% Toxicity=20.7% Death=6.9% Refusal=3.5%	NR	Grade 3-5: Fatigue=20.7% Skin (any)=13.8%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Gemcitabine then cetuximab Median administrations=8 (range 1-60) Dose intensity=0.93 (range 0.72-1)	Treatment never began=34.5% Progression=44.8% Toxicity=6.9% Death=0 Refusal=13.8%	NR	Grade 3-5: Neutropenia=17.2% Heart general=10.3% Pulmonary=10.3% Fatigue=13.8% Skin (any)=10.3% Folliculitis=10.3%
Hu 2010[23]	Average cycles=3.1	Withdrawals=2 Lost to follow-up=3	NR	NR
Jatoi 2010[24]	NR	Infliximab plus docetaxel: Declined further therapy/suffered SAE=14 Progressive disease=15	NR	Fatigue=22% One treatment-related death
	NR	Placebo plus docetaxel: Declined further therapy/suffered SAE=7 Progressive disease=20	NR	Fatigue=38%
Sakakibara 2010[37]	Standard paclitaxel plus carboplatin: Total cycles=139 Median cycles=3 (range 1-6) Patients with 3 or more cycles=75%	NR	NR	Grade 3-4 neutropenia=41% Grade 3 peripheral neuropathy=0
	Weekly paclitaxel plus carboplatin: Median cycles=3 (range 1-6) Patients with 3 or more cycles=75%	NR	NR	Grade 3-4 neutropenia=88% (p<0.0001) Grade 3 peripheral neuropathy=25% (p=0.018)
	Overall: Planned doses administered=93%	NR	Overall: Administrations skipped due to toxicity=7.4%	NR
Chen 2008[10]	Vinorelbine: Median cycles per patient=4	NR	NR	NR

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Vinorelbine plus cisplatin: Median cycles per patient=4	NR	NR	Neutropenia: Grade 3=26.5% Grade 4=14.7% Toxic death=2.9%
Crino 2008[15]	NR	Gefitinib: AEs=13 Objective disease progression=49 Consent withdrawn=2 Protocol non-compliance=1 Clinical progression=19	Dose interruption because of AEs=9.6%	Any NCI-CTC grade 3-5=41.5% Treatment related grade 3-5=12.8%
	NR	Vinorelbine: AEs=23 Objective disease progression=39 Consent withdrawn=5 Protocol non-compliance=1 Clinical progression=17 Other=6	Dose interruption because of AEs=21.9% Dose delay because of AEs=47.9%	Any NCI-CTC grade 3-5=55.2% Treatment-related grade 3-5=41.7%
Comella 2007[14]	Alternated-dose escalation paclitaxel plus gemcitabine: ≥3 cycles=82% ≥4 cycles=45% ≥5 cycles=39% ≥6 cycles=37%	n=9 Clinical deterioration=5 Consent withdrawn=3 Toxicity=1	Dose escalation: Paclitaxel=41% Gemcitabine=37% Dose reductions or omissions: Cycle 1=10% Cycle 2=23% Cycle 3=24%	Grade 3-4: Neutropenia=14%
	Fixed-dose paclitaxel plus gemcitabine: ≥3 cycles 87% ≥4 cycles 43% ≥5 cycles 38% ≥6 cycles 36%	n=9 Physician's decision=3 Progression=1 Refusal=1 Toxicity=1	Dose reductions or omissions: Cycle 1=13% Cycle 2=30% Cycle 3=22%	Grade 3-4: Neutropenia=11% Vomiting=11%
Gridelli 2007[18,19]	Pemetrexed: Cycles received=163 Median cycles=2.5 Dose intensity=164.8 mg/m² per	Early discontinuations: Lack of efficacy=2 Death=3 AEs unrelated to study drug=4 AEs related to study drug=2	36 delays 5 reductions	NR

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	week (range 95.0-169.5).	Other=1		
	Pemetrexed plus gemcitabine: Cycles received=166 Median cycles=3 Dose intensity=786.7 mg/m² per week (range 384.7-839.3)	Early discontinuations: Death=2 AEs unrelated to study drug=1	33 delays 2 reductions	NR
Hainsworth 2007[22]	Docetaxel: Completed planned 6 cycles=11%	Disease progression (64%) Treatment-related toxicity=15 (9%) Remaining patients=29 were removed from treatment for a variety of reasons (e.g. patient request, intercurrent illness, physician decision)	NR	Grade 3 fatigue=16%
	Docetaxel plus gemcitabine: Completed planned 6 cycles=14%	Disease progression=55% Treatment-related toxicity=13% Remaining patients=31 removed from treatment for a variety of reasons (patient request, intercurrent illness, physician decision)	NR	Neutropenia: Grade 3=11% Grade 4=8% Grade 3 thrombocytopenia=12% Grade 3-4 RBC transfusions=13% Grade 3 fatigue=20%
Leong 2007[30]	Gemcitabine: Received >4 cycles=35% Median RDI=0.99 (range 0.63-1.11)	NR	NR	Grade 3-4: Fatigue=12% Haemoglobin=14%
	Vinorelbine: Received <4 cycles=42% Median RDI=0.92 (range 0.5-1.07)	NR	NR	Grade 3-4: Fatigue=22% Haemoglobin=11% Whole count=22% Neutrophils=36%
	Docetaxel: Received >4 cycles=35% Median RDI=0.99 (range 0.43-1.07)	NR	NR	Grade 3-4: Fatigue=20%
Chen 2006[11]	Paclitaxel plus carboplatin: 152 cycles of carboplatin Median cycles per patient=4	NR	NR	Leukopenia=15% Anaemia=12.5%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Paclitaxel plus cisplatin: 172 cycles of cisplatin Median cycles per patient=4	NR	NR	Fatigue=17.1%
Kudoh 2006[27]	Docetaxel: Received 4 cycles=51.1% Dose intensity=90.7%	Withdrawals due to: Disease progression=19.3% AEs=12.5% Physician's decision=6.8% Protocol violation=3.4% Consent withdrawn=2.3%	NR	Grade 3: Leukopenia=52.3% Neutropenia=26.1% Nausea=10.2% Febrile neutropenia=12.5% Infection=11.4% Grade 4: Neutropenia=56.8%
	Vinorelbine: Received 4 cycles=40.7% Dose intensity=83.1%	Withdrawals due to: Disease progression=35.2% AEs=9.9% Physician's decision=5.5% Protocol violation=3.3%	NR	Grade 3: Leukopenia=35.2% Neutropenia=30.8% Febrile neutropenia=11.0% Infection=13.2% Grade 4: Leukopenia=16.5% Neutropenia=38.5%
Quoix 2005[35]	Gemcitabine (4 weeks): Cycles administered=132 Median cycles=3 (range 1-10)	Treatment discontinued due to AEs=11.9% Death=19.0%	Reduced or omitted administrations=8.7%	Grade 3: Leukopenia=12.2% Neutropenia=12.2%
	Gemcitabine (3 weeks): Cycles administered=169 Median cycles=4 (range 1-9)	Treatment discontinued due to AEs=17.9% Death=10.3%	Reduced or omitted administrations=8.9%	Grade 3: Neutropenia=13.5%
Comella 2004[13]	Gemcitabine: Total cycles=176 Median cycles/patient=3	NR	Dose reductions or omissions: First cycle=37% Second cycle=32% Third cycle=39%	NR
	Paclitaxel: Total cycles=175 Median cycles/patient=3	NR	Dose reductions or omissions: First cycle=18% Second cycle=15% Third cycle=19%	NR
	Gemcitabine plus vinorelbine: Total cycles=233 Median cycles/patient=3	NR	Dose reductions or omissions: First cycle=23% Second cycle=22% Third cycle=13%	NR

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Gemcitabine plus paclitaxel: Total cycles=219 Median cycles/patient=3	NR	Dose reductions or omissions: First cycle=15% Second cycle=11% Third cycle=10%	NR
Gridelli 2003[20]	Vinorelbine: Received planned six cycles=41% (median=11 weeks).	Treatment stopped before sixth cycle: Progressive disease/death=42% Toxicity=7% Other=9%	NR	Grade 3: Neutropenia=14% Grade 4 Neutropenia=11%
	Gemcitabine: Received planned six cycles=39% Median duration=10.3 weeks	Treatment stopped before sixth cycle: Progressive disease/death=46% Toxicity=7% Other=8%	NR	NR
	Vinorelbine plus gemcitabine: Received planned six cycles=38% Median duration=10.0 weeks	Treatment stopped before sixth cycle: Progressive disease/death=39% Toxicity=11% Other=12%	NR	Grade 3: Neutropenia=13%
Frasci 2001[17,45]	Gemcitabine plus vinorelbine: Median delivered dose intensity=78%	Discontinuations due to AE=7	NR	Grade 3-4 neutropenia=38% Toxic death=2
	Vinorelbine: Median delivered dose intensity=81%	Discontinuations due to AE=7	NR	Grade 3-4 neutropenia=28% Toxic death=1
Gridelli 2001[44]	NR	NR	NR	BSC plus vinorelbine: Neutropenia=10%
SCLC				
Pu 2013[34] (abstract only)	NR	NR	NR	Etoposide plus oxaliplatin Grade 3: Leukopenia=22.0% Thrombocytopenia=14.3% Grade 4: Leukopenia=11.1%
	NR	NR	NR	Etoposide plus cisplatin

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Grade 3: Leukopenia=22.2% Thrombocytopenia=11.1% Nausea/vomiting=11.1% Grade 4: Leukopenia=16.7%
Okamoto 2007[33]	Carboplatin plus etoposide: Total delivered courses/projected courses 353/440 (80%)	No change; with two courses=6% Disease progression=11% Toxicity or complications=11% Patient refusal=3% Others=4% Treatment-related death=3%	Dose reduction=32 (29%) Course delay=45 (41%)	Leukopenia=54% Neutropenia=95% Anaemia=29% Thrombocytopenia=56% Hyponatraemia=16%
	Cisplatin plus etoposide: Total delivered courses/projected courses 360/436 (83%)	No change with two courses=5% Disease progression=15% Toxicity or complications=8% Patient refusal=4% Others=1% Treatment-related death=1%	Dose reduction=10% Course delay=37%	Leukopenia=51% Neutropenia=90% Anaemia=25% Thrombocytopenia=16% Hyponatraemia=14%
Ardizzoni 2005[8]	Cisplatin plus etoposide: Median cycles=4 (range 1-8) The median actually delivered RDI for both drugs=96% (range 65%-125%) Completed the treatment as per protocol=75%	Discontinuation=25% Toxicity=3% Disease progression=2% Disease-related early death=2%	Treatment delays and/or dose reductions=18% (due to chemotherapy-related toxicity=14%)	NR
	Cisplatin plus etoposide: Median cycles=4 (range 1-6) The median actually delivered RDI for both drugs=98% (range 13%-125%) Completed the treatment as per protocol=72%	Discontinuation=24% Toxicity=12% Progression=1% Refusal of treatment=2% Myocardial infarction=1%	Treatment delays and/or dose reductions=16% (due to chemotherapy-related toxicity=10%)	NR

AE=adverse event, RDI=relative dose intensity; RBC=red blood cell; BSC=best supportive care; SAE=serious adverse event; NCI=National Cancer Institute; CTC=Common Terminology Criteria
NR=not reported

6.5 Comprehensive geriatric assessment and quality of life

Summary outcomes relating to CGA and QoL reported in RCTs are presented in Table 7, and full outcomes are presented in Appendices 6 and 7. None of the SCLC trials[8,33,34] reported outcomes of interest.

6.5.1 Non-small cell lung cancer

Comprehensive geriatric assessment

Four trials[9,20,29,41] presented different CGA measures. The two LeCaer et al studies[29,41] used three tools as part of the eligibility criteria for the trial. Biesma et al[9] used nine measures and Gridelli et al[20] used two tools as outcome measures, with data being collected during treatment and follow-up.

Three trials[9,29,41] used the Charlson Comorbidity Index (CCI) as part of a complex CGA exercise. Four trials used the Activities of Daily Living (ADL) and the Instrumental Activities of Daily Living (IADL) as geriatric assessment tools.[9,20,29,41]

Quality of life

Sixteen of the included trials[9,10,12,15,17,20,23,24,27,29,30,32,36,40,41,45] measured QoL as an outcome measure, and eight[9,10,20,27,29,30,32,36,41] of those trials reported the proportion of patients who completed the QoL questionnaires during the study period (see Appendix 7).

Across trials there were 15 different QoL measures used: FACT-L (Functional Assessment of Cancer Therapy-Lung);[12,15,32,40] FACT-G (Functional Assessment of Cancer Therapy-General);[24] the Spitzer Index;[29,41] LCSS (Lung Cancer Symptoms Scale);[10,17,29,40,41,45] TOI (Trial Outcome Index);[15,32] TOI-L (Trial Outcome Index-Lung);[40] EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30);[9,20,30,36,44] EORTC QLQ-LC13 (European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Lung Cancer–Specific Module);[9,20,30,36] KPS;[23] PSI (Pulmonary symptom improvement);[15] and Kudoh et al[27] used the Visual Face Scale for global QoL, eight disease-related symptom items derived from the Lung Cancer Working Party, Medical Research Council and the Functional Living Index, Cancer.

Completion of questionnaires was high, with the lowest rate reported by Gridelli et al[20] (59%) and the highest rate by Chen et al[10] (85%) (see Appendix 7).

Table 7 Comprehensive geriatric assessment and quality of life, randomised controlled trials

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Results summary**
Chen 2012[12]	NR	NR	FACT-L questionnaire (subscales: physical well-being, social/family well-being, emotional well-being, functional well-being lung cancer symptom-specific, lung cancer)	Most FACT-L subscales showed no significant change at the end of treatment for both treatment arms, except that patients in the erlotinib arm had significantly better physical well-being than patients in the vinorelbine arm
LeCaer 2012[41]	CCI ADL IADL	Used as eligibility criteria for patient selection	Spitzer Index LCSS	The median global LCSS score, the median symptom score and the global Spitzer score were similar in the two arms and indicated little deterioration of QoL after treatment. These scores did not change significantly during treatment
Biesma 2011[9]	CCI ADL IADL CIRS-G TUG MMSE GDS-15 PANAS GFI	Before start of treatment a CGA was administered by a trained nurse. During treatment and follow-up, a mini-geriatric assessment was carried out on days 1 and 8 of each cycle, at weeks 12, 15 and 18	EORTC QLQ-C30, QLQ-C13	There were no associations between the global QoL and treatment, age, sex, pretreatment weight loss or extent of disease. There were also no significant interactions between QoL scores and treatment
LeCaer 2011[29]	CCI ADL IADL	Used as eligibility criteria for patient selection	Spitzer Index LCSS	The median global LCSS score, the median symptom score and the global Spitzer score were similar in the two arms and showed little deterioration of QoL after treatment
Quoix 2011[36]	NR	NR	EORTC QLQ-C30; QLQ-LC13	At week 6, the global QoL scores were similar but more patients in the monotherapy group had pain and dyspnoea, and more in the doublet chemotherapy group had diarrhoea. At week 18, the global QoL score was similar, but role functioning and fatigue were worse in the doublet chemotherapy group than in the monotherapy

Study	Geriatric assessment		Quality of life	
	Tool(s) used	How tool was used	Tool(s) used	Results summary
Stinchcombe 2011[40]	NR	NR	TOI-L LCSS FACT-L	The best overall health-related QoL response did not differ between treatment arms on the TOI-L (p=0.76), the LCSS (p=0.85), or the FACT-L total score (p=0.57)
Hu 2010[23]	NR	NR	KPS	The QoL was enhanced in both experimental group and control group. However, the difference of KPS after treatment in the experimental group was markedly higher than in the control group (14±10 vs. 8±10, *t*=2.116, p=0.04), improvement rate of QoL was better than in the control group (76.2% vs. 45.0%, $\chi_{2=}$4.188, p=0.041)
Jatoi 2010[24]	NR	NR	FACT-G	The FACT-G showed no clinically or statistically significant differences between groups over time for emotional and social well-being. However, infliximab-/docetaxel-treated patients had lower levels of functional and physical well-being
Chen 2008[10]	NR	NR	LCSS	The results of the completed LCSS showed that there was no statistically significant difference in the scales between the two treatment arms, either after two cycles of treatment or when the patient went off study, and whether scored by the patients
Crino 2008[15]	NR	NR	FACT-L TOI PSI	Overall QoL improvement rates, as assessed by the total FACT-L and TOI scores, were higher with gefitinib than with vinorelbine for FACT-L analyses. The overall improvement rates of the disease-related Lung Cancer Subscale of the FACT-L, and PSI rates were similar with gefitinib and vinorelbine

Study	Geriatric assessment		Quality of life	
	Tool(s) used	How tool was used	Tool(s) used	Results summary
Leong 2007[30]	NR	NR	EORTC QLQ-C30 and QLQ-LC13	The results suggest that the QoL of patients in all three arms improved over the treatment period. In particular, specific symptom scores suggested that there were improvements in the severity of cough and haemoptysis over the treatment period
Lilenbaum 2007[32]	NR	NR	FACT-L TOI	The average change in TOI scores within treatment arms (–2.4 in the every 3 weeks schedule and –2.3 in the weekly schedule) did not exceed the threshold for a minimally important difference. TOI average change from baseline scores did not differ across age or PS groups
Kudoh 2006[27]	NR	NR	Visual Face Scale for global QoL (primary QoL analysis); eight disease-related symptom items (secondary QoL Analysis) derived from the Lung Cancer Working Party, Medical Research Council and the Functional Living Index, Cancer	In terms of global QoL, no significant difference was observed between the two arms. Docetaxel was associated with significantly better improvement in the overall symptom score than vinorelbine. When the eight-symptom scores were analysed separately, the docetaxel arm showed significantly better improvement in anorexia and fatigue than the vinorelbine arm
Gridelli 2003[20]	ADL IADL	Used at baseline and after third and sixth cycles	EORTC QLQ-C30 and QLQ-LC13	There were no statistically significant differences in functional symptom scales between treatment arms
Frasci 2001[17,45]	NR	NR	Modified LCSS	Gemcitabine plus vinorelbine combination was associated with a clear superiority in terms of symptom-control and QoL. The probability of showing an improvement or at least a stabilisation of symptoms at 6 months was almost double in the combination arm vs the vinorelbine alone arm

Study	Geriatric assessment		Quality of life	
	Tool(s) used	How tool was used	Tool(s) used	Results summary
Gridelli 2001[44]	NR	NR	EORTC QLQ-C30	No significant difference was detected between treatments on the scales measuring emotional function, sleep disturbance, appetite loss, diarrhoea, and the financial impact of illness

FACT-L=Functional Assessment of Cancer Therapy for Lung Cancer; FACT-G=Functional Assessment of Cancer Therapy-General; LCSS=Lung Cancer Symptoms Scale; CCI=Charlson Comorbidity Index; ADL=Activities of daily Living; IADL=Instrumental Activities of Daily Living; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire; EORTC QLQ-LC13=EORTC Quality of Life Cancer Questionnaire – Lung Cancer. TOI=Trial Outcome Index; TOI-L=Trial Outcome Index-Lung; KPS=Karnofsky performance status; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; TUG=Timed Up and Go test; MMSE=Mini-Mental State Examination; GDS=Geriatric Depression Scale; PANAS=Positive and Negative Affect Schedule; GFI=Groningen Frailty Indicator; PSI=Pulmonary Symptom Improvement; QoL=quality of life; PS=performance status; NR=not reported

6.6 Summary and discussion

A total of 36 RCTs that enrolled only older or elderly people were included in the review. The large volume of evidence available reflects the fact that lung cancer is a highly prevalent disease. Unfortunately, the majority of trials were relatively small and of poor methodological quality.

Across trials there were more than 25 different chemotherapy regimens. The definition of 'older' (minimum age for entry into a trial) varied from 60 to 75 for NSCLC patients and was ≥70 for all three trials of SCLC patients. Most of the trials enrolled patients with a good PS.

For NSCLC patients, efficacy outcomes were well reported across trials. In terms of PFS/TTP, over one-third of trials achieved a median PFS/TTP of >3 months in each treatment arm, and six[12,22,27,28,36,39] trials reported statistically significant results. Two trials[36,39] reported statistically significant results for OS, and over one third of trials achieved a median OS of more than 10 months in one or more treatment arms. Two trials[12,36] reported statistically significant results for ORR. For patients with SCLC, two trials[33,34] reported PFS, with a median PFS of >3 months across all study arms. Overall survival ranged from 7.1 months[8] to 10.6 months.[33] The lowest ORR was 39.3%[8] and the highest was 73%.[33]

Across all trials, tolerability measures were difficult to compare in any meaningful way due to differences in how measures were reported. The reported outcomes for treatment completion were variable; however, the dose intensity was quite high in the studies that reported it, suggesting that older patients with lung cancer can complete planned chemotherapy treatment. Across trials, figures for treatment discontinuation were similar, with disease progression being the most common reason for discontinuation of treatment. Adverse events were well reported; however, estimates varied greatly and comparisons were difficult.

Four NSCLC trials[9,20,29,41] reported use of CGAs, and 16 trials[9,10,12,15,17,20,23,24,27,29,30,32,36,40,41,44,45] reported QoL measures. None of the SCLC trials reported CGA or QoL data.

Based on the authors' conclusions, chemotherapy is generally effective and tolerable, with acceptable toxicity in older patients with lung cancer. Most trials found no significant differences between chemotherapy regimens, and many recommend further trials in specific populations of older patients to determine which treatment is most suitable for older patients. However, five trials[22,24,29,40,43,46,47] concluded that the regimens used should not be given to older patients due to disappointing efficacy outcomes, low compliance, or associated AEs.

7 SUBGROUP ANALYSES OF RANDOMISED CONTROLLED TRIALS

7.1 Study characteristics

A total of 13 studies[49-63] (reported in 15 publications) reported on subgroup analyses of older patients in RCTs and were included in the review. All studies focussed on patients with NSCLC. Details of study characteristics can be found in Table 8.

The 13 subgroup analyses were conducted on 11 phase III trials,[49,51-53,55-63] one phase II trial,[54] and the phase was unknown in one study.[50] Eight[49-54,56-58,62] of the studies were multicentre, and six were international.[49,50,52,56-59,62]

Trials that reported study dates were conducted between 1997[53] and 2007.[60] Seven studies[51-55,59,60,62] were funded by pharmaceutical companies; however, funding was not reported in six studies.[49,50,56-58,61,63] Only four studies reported that patients were stratified by age at randomisation.[49,50,53,57,58]

All studies focussed on patients with stage IIIB/IV NSCLC except for Gridelli et al[50] and Wheatley-Price et al,[61] which did not report stage-related information. Eight studies[49,52,53,55-58,60,62,63] assessed first-line treatment, one study focussed on second-line treatment,[59] and two studies had mixed lines of treatment.[51,61] One study included maintenance treatment.[50] There were a total of 16 different regimens delivered across the studies; however, six studies used combinations of paclitaxel and carboplatin,[51,53-55,57,58,60] and two used placebo on its own.[50,61]

The definition of 'older' varied from >60[56] to >70,[32,50,51,53-55,57-61,63] and proportions of older patients within trials were as low as 7% (>70),[57,58] and as high as 53% (>70)[60] and 57% (>60).[56]

Table 8 Study characteristics, subgroup analyses of randomised controlled trials

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Socinski 2012[57,58] (abstract only)	Phase III Multicentre International Stratified by age at randomisation	First-line Stage: IIIB/IV Older defined as >70	Nab-paclitaxel plus carboplatin 74/1052 (7%) >70 years Solvent-based paclitaxel plus carboplatin 82/1052 (8%) >70 years	Male: 72%	Primary: efficacy, safety Secondary: ORR, PFS	In elderly patients with advanced NSCLC, nab-paclitaxel as first-line therapy was well tolerated and led to improved ORR and PFS, with significantly longer OS vs solvent-based paclitaxel
Gridelli 2011[50] (abstract only)	Multicentre International Stratified by age at randomisation	Maintenance therapy Older defined as >70 >70=92/539 (17%)	Pemetrexed Placebo	>70 median age: 73 years Male: >70: 66% <70: 56% >70 PS: 0/1=20%/79% <70PS: 0/1=34%/66%	Primary: PFS	The toxicity was manageable and consistent with the known safety profile of pemetrexed in elderly patients
Weissman 2011[60]	Phase III USA 2004-2007 Eli Lilly Stratification NR	Chemotherapy naïve Stage: IIIB/IV Older defined as >70	Gemcitabine plus oxaliplatin >70: 101/191 (52.9%) Paclitaxel plus carboplatin >70: 99/192 (51.6%)	Overall median age: 63 years (36-84) Overall male: 54.5% Overall ECOG PS: 0=55.5%, 1=44.5% Overall median age: 64 years (35-87) Overall male: 56.3% Overall ECOG PS: 0=47.4%. 1=52.6%	Primary: PFS Secondary: tumour ORR, TTF, OS, safety, QoL	PFS, OS, and ORR with gemcitabine plus oxaliplatin were similar to paclitaxel plus carboplatin. Nevertheless, toxicities limit the adoption of this regimen for routine use in advanced NSCLC
Leighl 2010[52,62]	Phase III Multicentre International: Canada, Czech Republic, Germany, Poland and Switzerland	First-line Stage: IIIB/IV or recurrent non-squamous NSCLC Chemotherapy naïve Older defined as >65	Placebo plus cisplatin and gemcitabine >65: 112/1043 (11%) Bevacizumab (7.5 mg) plus cisplatin and gemcitabine	Median age: 68 years Male: 70% PS: 0=43%, 1=57% Median age: 68 Male: 71%	Primary: PFS Secondary: ORR, duration of response, OS, safety	This analysis of the randomised, phase III AVAiL trial shows that bevacizumab-based therapy improves outcomes for elderly patients with NSCLC. Furthermore, bevacizumab-based therapy is well tolerated in elderly

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	2005-2006 Supported by F. Hoffmann-La Roche Ltd Stratification unclear		>65: 89/1043 (9%)	PS: 0=34%, 1=66%		patients
			Bevacizumab (15 mg) plus cisplatin and gemcitabine >65: 103/1043 (9.9%)	Median age: 68 years Male: 69% PS: 0=39%, 1=61%		
Ramalingam 2008[55]	Phase III USA Supported by a grant from Bristol-Myers Squibb Stratification NR	Stage: IIIB/IV (inoperable) First-line Older defined as >70	Weekly paclitaxel plus carboplatin >70: 72/444 (16%)	Median age: 74 years (70-86) Male: 63% ECOG PS: 0/1=90%, 2=8%	Primary: OS Secondary: ORR, TTP	Efficacy was similar between the weekly regimen and the standard regimen of carboplatin and paclitaxel for elderly patients with advanced NSCLC and may be advantageous based on its favourable tolerability profile
			Standard 3-weekly paclitaxel plus carboplatin >70: 64/444 (14%)	Median age: 75 years (70-92) Male: 67% ECOG PS: 0/1=80%, 2=17%		
Ramalingam 2008[63]	Phase III USA Stratification NR	Stage: IIIB/IV First-line Older defined as >70=224/850 (26%)	Paclitaxel plus carboplatin >70: 113 <70: 320	Median age: 74 years >70 male: 66% <70 male: 56% ECOG PS 1: >70: 60% <70: 61%	Primary: OS, toxicity	In elderly NSCLC patients, paclitaxel plus carboplatin and bevacizumab was associated with a higher degree of toxicity, but no obvious improvement in survival compared with paclitaxel plus carboplatin
			Paclitaxel plus carboplatin and bevacizumab >70: 111 <70: 306	Median age: 74 years >70 male: 59% <70 male: 47% ECOG PS 1: >70: 70% <70: 56%		
Wheatley-Price 2008[61]	Phase III Double blind Canada	Second/third-line Older defined as >70	Erlotinib >70: 112 (23%) <70: 376 (77%)	Median age: 62 years(34-87)	Primary: QoL, time to deterioration	Elderly patients treated with erlotinib gain similar survival and QoL benefits as younger

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Not stratified by age at randomisation	>70=162/731 (22%)		>70 male: 68% <70 Male: 64% >70 ECOG PS: 0-1=65%, 2-3=35% ECOG PS: 0-1=66%, 2-3=34%	Secondary: efficacy, toxicity, OS	patients but experience greater toxicity
			Placebo >70: 51 (21%) <70: 192 (79%)	Median age: 59 years (32-89) Male: >70: 63% <70: 67% ECOG PS: >70: 0-1=71%, 2-3=29% <70 0-1=68%, 2-3=32%		
Ramalingam 2006[54]	Phase II Multicentre USA 1998-2000 Supported by a grant from Bristol-Myers Squibb Not stratified by age at randomisation	Stage: IIIB/IV Older defined as ≥70=111/390 (28%)	Paclitaxel (100 mg) and carboplatin (Auc-6 mg) ≥70: 44 <70: 88	Median age: 74 years ≥70 male: 57% <70 male: 60% ECOG PS 2: ≥70: 11% <70: 16%	Primary: OS Secondary: ORR, TTP	The weekly regimen of paclitaxel administered in combination with carboplatin is tolerated well by elderly NSCLC patients and has comparable efficacy with younger patients
			Paclitaxel (100 mg) and carboplatin(Auc-2 mg) ≥70: 34 <70:96	Median age: 74 years ≥70 male: 76% <70 male: 60% ECOG PS 2: ≥70: 29% <70: 8%		
			Paclitaxel (150 mg) and carboplatin (Auc-2 mg) ≥70: 33 <70:95	Median age: 74 years ≥70 male: 64% <70 male: 60% ECOG PS 2: ≥70: 21%		

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
				<70: 13%		
Weiss 2006[59]	Phase III International: USA, Canada and Spain 2001-2002 Supported by a grant from Eli Lilly and Co Not stratified by age at randomisation	Stage: IIIB/IV Second-line Older defined as >70	Docetaxel >70: 39 (14%) <70: 249 (86%)	Median age: >70: 73 years (70-87) <70: 55 years (28-69) Male: >70: 87.1% <70: 73.5% ECOG PS: >70: 0=15.4%, 1=56.4%, 2=20.5% <70: 0=16.9%, 1=68.3%, 2=10.4%	Outcomes: ORR, stable disease rate, TTP,OS	Elderly patient participation was similar to rates observed in the first-line setting. There was no significant difference in outcome or toxicity between elderly and younger patients. For elderly patients with advanced NSCLC and good PS, second-line cytotoxic therapy is appropriate. In this subset, pemetrexed produced a more favourable toxicity profile
			Pemetrexed >70 years: 47 (17%) <70 years: 236 (83%)	Median age: >70: 74 years (70-81) <70: 56 years (22-69) Male: >70: 70.2% <70: 68.2% ECOG PS: >70: 0=21.3%, 1=53.2%, 2=10.6% <70: 0=17.8%, 1=66.5%, 2=10.6%		
Belani 2005[49]	Phase III Multicentre International: 28 countries 1998-2000 Patients stratified by age at randomisation	Chemotherapy naïve Stage: IIIB/IV Older defined as ≥65	Docetaxel plus cisplatin ≥65: 149 <65: 259	Median age: ≥65: 69 years (65–81) <65: 56 years (30–64) male: ≥65: 75% <65: 70% KPS: ≥65: 100%=15%, 80-90%=83%, 70%=2% <65: 100%=17%, 80-90%=79%, 70%=5%	Primary: OS Secondary: toxicity, QoL	First-line docetaxel plus cisplatin chemotherapy showed similar activity in elderly and younger patients with advanced/metastatic NSCLC; elderly patients tolerated docetaxel-platinum well despite experiencing slightly more toxicity than younger patients

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
			Docetaxel plus carboplatin ≥65: 118 <65: 288	Median age: ≥65: 69 years (65–87) <65: 56 years (23–64) Male: ≥65: 76% <65: 70% KPS: ≥65: 100%=15%, 80-90%=82%, 70%=3% <65: 100%=17%, 80-90%=79%, 70%=5%		
			Vinorelbine plus cisplatin ≥65: 134 <65: 270	Median age: ≥65: 68 years (65–80) <65: 56 years (35–64) Male: ≥65: 73% <65: 76% KPS: ≥65: 100%=15%, 80-90%=82%,70%=3% <65: 100%=18%, 80-90%=78%,70%=4%		
Lilenbaum 2005[53]	Phase III Multicentre US 1997-2000 National Cancer Institute (CA31946) Partially supported by Bristol-Myers Squibb Company Stratified by age at randomisation	Chemotherapy-naïve Stage: IIIB/IV Older defined as >70 >70=155/584 (27%)	Paclitaxel	Overall median age: 63 years (31-86) Overall male: 69% Overall ECOG PS: 0-1=82%, 2=18%	Primary: OS Secondary: ORR, FFS, median survival	Combination chemotherapy improves response rate and FFS compared with single-agent therapy, but there was no statistically significant difference in the primary end point of OS. The results in elderly patients were similar to younger patients. PS 2 patients had a superior outcome when treated with combination chemotherapy
			Paclitaxel plus carboplatin	Overall median age: 64 years (39-83) Overall male: 68% Overall ECOG PS: 0-1=83%, 2=17%		

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Hensing 2003[51]	Phase III Multicentre America 1998-2000 Supported by an investigator-initiated grant from Bristol-Myers Squibb Oncology Not stratified by age at randomisation	First-/second-line Stage: IIIB/IV Older defined as >70 >70=67/230 (29%)	Carboplatin and paclitaxel-4 cycles Second-line paclitaxel: 114/230 (50%) <70: 90 (79%) >70: 24 (21%)	Overall mean age: 63 years (31-82) Male: <70: 60% >70: 69% KPS: <70: 90-100=58%, 70-80=42% >70: 90-100=37%, 70-80=63%	Primary: TOI-L QoL Secondary: TOI-NTTX QoL	The current analysis demonstrated that C/P exhibited similar toxicity profiles in patients aged ≥70 years compared with patients <70 years. The survival rates were not different between the two age groups, and there was no difference in progression of QoL outcomes. In fit, elderly patients, C/P represented a reasonable standard regimen
			Carboplatin and paclitaxel-until patients developed disease progression Second-line paclitaxel: 116/230 (50%) <70: 73 (63%) >70: 43 (37%)	Male: <70: 60% >70: 69% KPS: <70: 90-100=58%, 70-80=42% >70: 90-100=37%, 70-80=63%		
Sculier 2002[56]	Phase III Multicentre International: Belgium, France, Greece, Spain and Slovakia 1998-2000 Not stratified by age at randomisation	Chemotherapy naïve Stage: IIIB/IV Older defined as >60	(CCI regimen) Cisplatin and carboplatin combined with ifosfamide <60: 52% >60: 48%	Overall male: 90% KPS: <70=27%. >80=73%	Primary: survival improvement Secondary: impact on response rate, toxicity comparisons	In stage IV NSCLC, treatment with regimens including the new drug gemcitabine were associated with a better but not statistically significantly different observed survival compared with a classical first-generation cisplatin-containing regimen. The non-platinum combination of gemcitabine was as effective as its combination with platinum
			(CCG regimen) Cisplatin and carboplatin combined with gemcitabine <60: 43% >60: 57%	Overall male: 80% KPS: <70=27%, >80=73%		

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
			(IG regimen) Ifosfamide plus gemcitabine <60: 51% >60: 49%	Overall male: 83% KPS: <70=28%, >80=72%		

NSCLC=non-small cell lung cancer; PFS=progression-free survival; OS=overall survival; QoL=quality of life; CGA=comprehensive geriatric assessment; AEs=adverse events; ORR=objective response rate; TTP=time to progression; TTF=time to treatment failure; FFS=failure-free survival; TOI-L=Trial Outcome Index (Lung); NTTX=Neurotoxicity and Taxane Toxicity; KPS=Karnofsky performance status; ECOG= Eastern Cooperative Oncology Group; NR=not reported

7.2 Efficacy evidence

Outcomes relating to PFS/TTP, OS and ORR for all subgroup analyses are presented in Table 9.

Five trials[50,57,58,60,61,63] reported PFS, and four reported TTP.[51,54,55,59] There were no statistically significantly different results when older patients were compared with younger patients; however, across the majority of comparisons of PFS and TTP, older patients achieved a longer median PFS/TTP than younger patients.

Median OS was reported by 11 studies[49,51,53-61,63] and varied from 4.6 months[56] to 19.9 months[57,58] in the older subgroups. Only one OS result was statistically significantly different between the age groups: Socinski et al[57,58] recorded 19.9 months OS for those >70 and 11.4 months for those <70 (HR 0.583; p=0.009) in the nab-paclitaxel plus carboplatin arm.

Seven studies reported data on ORR,[51,52,55-59,62,63] which varied from the lowest ORR of 5%[59] to the highest of 40.3%[52,62] in the older subgroups. There were no statistically significantly different ORR results reported for older versus younger comparisons.

Table 9 Survival outcomes, subgroup analyses of randomised controlled trials

Study	Intervention		Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Socinski 2012[57,58] (abstract only)	Nab-paclitaxel plus carboplatin	>70	8.0	0.687 p=0.134	19.9	0.583 p=0.009	34	p=0.196
		<70	6.0		11.4		32	
	Solvent-based paclitaxel plus carboplatin	>70	6.8	0.903 p=0.256	10.4	0.999 p=0.988	24	p=0.013
		<70	5.8		11.3		25	
Gridelli 2011[50] (abstract only)	Pemetrexed	>70	6.4 (3.3 to NE)	NR	NR	NR	NR	NR
		<70	4.0 (2.9 to 4.2)					
	Placebo	>70	3.0 (1.5 to 4.1)	NR	NR	NR	NR	NR
		<70	2.8 (2.6 to 3.5)					
Weissman 2011[60]	Gemcitabine plus oxaliplatin (GEMOX)	All	4.44	NR	9.90 (7.85 to 11.62)	NR	NR	NR
		>70	5.07		9.35 (6.99 to 15.20)			
		<70	4.37		10.10			
	Paclitaxel plus carboplatin (PCb)	All	4.67	NR	9.24 (8.18 to 10.89)	NR	NR	NR
		>70	5.60		9.8 (6.99 to 14.17)			
		<70	4.34		8.71			
Leighl 2010[52,62]	Placebo plus cisplatin and gemcitabine	>65	NR	NR	NR	NR	29.8	NR
		<65					24.0	
	Bevacizumab (7.5 mg) plus cisplatin and gemcitabine	>65	NR	NR	NR	NR	40.3	NR
		<65					41.1	
	Bevacizumab (15 mg) plus cisplatin and gemcitabine	>65	NR	NR	NR	NR	29.1	NR
		<65					44.5	

Study	Intervention		Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Ramalingam 2008 [55]	Weekly		4.2	NR	8.5	NR	26	p=0.358
	Standard		2.9	NR	7.1	NR	19	
Ramalingam 2008[63]	Paclitaxel plus carboplatin		4.9	0.76 (0.57 to 1.01) p=0.63	12.1		17.3	p=0.67
	Paclitaxel plus carboplatin and bevacizumab		5.9		11.3		28.7	
Wheatley-Price 2008[61]	Erlotinib	≥70	3.0 (1.9 to 3.8)	0.91 (0.73 to 1.13) p=0.38	7.6 (4.9 to 10.4)	1.02 (0.81 to 1.30) p=0.85	NR	NR
		<70	2.1 (1.9 to 2.6)		6.4 (5.4 to 7.7)			
	Placebo	≥70	2.1 (1.8 to 3.4)	0.84 (0.61 to 1.15) p=0.28	5.0 (3.8 to 7.7)	0.81 (0.57 to 1.14) p=0.22	NR	NR
		<70	1.8 (1.8 to 1.9)		4.7 (4.0 to 6.7)			
Ramalingam 2006[54]	Paclitaxel (100 mg) and carboplatin (Auc-6 mg)	≥70	TTP=7.2	NR	11.3	NR	NR	NR
		<70	TTP=6.9		11.2			
	Paclitaxel (100 mg) and carboplatin(Auc-2 mg)	≥70	TTP=5.3	NR	6.0	NR	NR	NR
		<70	TTP=4.2		7.7			
	Paclitaxel (150 mg) and carboplatin (Auc-2 mg)	≥70	TTP=8.6	NR	14.4	NR	NR	NR
		<70	TTP=6.0		9.1			
Weiss 2006[59]	Docetaxel	≥70	TTP=2.9	1.03 (0.83 to 1.26)	7.7	1.02 (0.82 to 1.26)	5.6 vs 9.2	p=0.751
		<70	TTP=3.9		8.0			
	Pemetrexed	≥70	TTP=4.6	0.72 (0.43 to 1.21)	9.5	0.86 (0.53 to 1.42)	5.0	p=0.549
		<70	TTP=3.0		7.8		9.8	
Belani	Docetaxel plus	≥65	NR	NR	12.6 (10.6 to 15.4)	NR	NR	NR

Study	Intervention		Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
2005[49]	cisplatin	<65			11.0 (9.7 to 12.2)			
	Docetaxel plus carboplatin	≥65	NR	NR	9.0 (7.6 to 10.3)	NR	NR	NR
		<65			9.7 (8.7 to 11)			
	Vinorelbine plus cisplatin	≥65	NR	NR	9.9 (8.7 to 12.2)	NR	NR	NR
		<65			10.1 (9 to 11.5)			
Lilenbaum 2005[53]	Paclitaxel		NR	NR	6.7	NR	NR	NR
	Paclitaxel plus carboplatin		NR		8.8		NR	
Hensing 2003[51]	Carboplatin and paclitaxel-4 cycles	>70	First-line TTP=4.8 Second-line TTP=2.4	First-line, p=0.049[b] Second-line, p=0.98	7.8 (6.3 to 9.1)	p=0.65	First-line=20 Second-line=8.3	First-line, p=0.28 Second-line, p=0.53
		<70	First-line TPP=3 Second-line TTP=2.1		7.1 (4.8 to 11.6)		First-line=27 Second-line=7.1	
Sculier 2002[56]	Cisplatin plus carboplatin and ifosfamide	>60	NR	NR	4.6	NR	23 (15 to 32)	p=0.61
		<60			6.0			
	Cisplatin plus carboplatin and gemcitabine	>60	NR	NR	9.0	NR	29 (20 to 39)	
		<60			6.2			
	Ifosfamide plus gemcitabine	>60	NR	NR	6.4	NR	25 (16 to 33)	
		<60			6.9			

PFS=progression-free survival; TTP=time to progression; OS=overall survival; CI=confidence interval; ORR=objective response rate; NR=not reported

[a] Values are PFS, unless otherwise stated

[b] not stated as statistically significant in published paper

7.3 Tolerability evidence

Outcomes relating to tolerability in subgroup analyses of RCTs are presented in Table 10. All studies report on patients with NSCLC.

Three studies made comparisons between older and younger patients in terms of the median number of cycles delivered.[49,51,59] Hensing et al[51] reported that both patients aged <70 and those aged >70 received a median of four cycles in both treatment arms. Weiss et al[59] showed similar figures, with patients <70 in both treatment arms receiving three cycles, and those >70 receiving two and four cycles in the docetaxel and pemetrexed arms, respectively. Belani et al[49] reported that the median number of cycles administered and the mean RDI were similar for patients who were <65 and ≥65 within each treatment group. Three studies[52,57,58,61,62] compared the proportion of planned treatment delivered to older and younger patients. Socinski et al reported that 86%, 89% and 60% of older patients received fewer than six cycles as planned across three different geographical locations.[57,58] Wheatley-Price et al[61] reported that 64% of those aged >70 received >90% of the planned dose compared with 82% of those aged <70, and that the proportion of patients receiving <80% of the planned dose was 29% (>70) compared with 14% (<70). Leighl et al[52,62] found that older patients received fewer cycles than the younger patients across treatment arms.

Seven studies[49,51,55,56,59-61] reported reasons for discontinuations. Wheatley-Price et al[61] reported that the number of patients in the erlotinib group who discontinued treatment due to AEs was statistically significantly higher in those aged >70 (13% and 5%; p=0.003) and so too were treatment-related AEs in this age group (12%, 3%; p=0.003). There were no other statistically significant results reported; however, Weissman et al[60] reported that 70.2% and 62% of older patients in each arm discontinued due to AEs, death or disease progression. Hensing et al[51] noted that in those aged <70, 17% and 47% in the respective treatment arms discontinued due to disease progression compared with 17% and 21%, respectively, in those aged >70. Discontinuations due to toxicity occurred in 4% and 21% of those aged >70 and in 3% and 14% in those aged <70.[51] Weiss et al[59] reported similar figures for discontinuation rates due to progressive disease between age groups (45% for >70 and 52% for <70), and Belani et al[49] reported that in all treatment arms, the figures for discontinuations in the ≥65 group were similar to the whole population in terms of discontinuation due to haematological AEs.

Only one study[61] reported dose modifications, reporting that patients aged >70 were statistically significantly more likely to have prolonged dose interruptions (35%) compared with those aged <70 (18%; p<0.001).

All studies reported data relating to AEs. Socinski et al[57,58] found that rates of AEs were similar in older patients compared with the whole population, and Leighl et al[52,62] also found that AE results

were generally similar across all arms between age groups. Gridelli et al[50] reported that older patients experienced more drug-related AEs than younger patients (21% vs 7%).

Neutropenia was a commonly reported haematological AE. Leighl et al[52,62] reported rates of 33%, 44% and 41% across three arms for patients >65, compared with 35%, 43% and 39% for patients aged <65. Grade 4 neutropenia was slightly higher in those aged >70 (12.1% and 13.6%) compared with 9.5% and 4.5% in those aged <70 across both arms in Ramalingam et al.[54] Weiss et al[59] reported higher rates of neutropenia in the older patients in the pemetrexed arm (12.5% vs 4.0%) whereas younger patients had a higher rate of neutropenia in the docetaxel arm (29.7% vs 41.8%). Neutropenia rates in both older and younger patients were high across all arms in the study by Belani et al[49] (>65: 81.8%, 86.6%, 75.2%; <65: 70.7%, 69.6% and 80.8%, respectively).

Thrombocytopenia was compared between older and younger patients in Leighl et al,[52,62] with rates of 27%, 40% and 38% in older patients compared with 25%, 29% and 24% in younger patients.

Table 10 Tolerability outcomes, subgroup analyses of randomised controlled trials

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Socinski 2012[57,58] (abstract only)	Nab-paclitaxel plus carboplatin Median cycles: North America=5 Japan=4 Russia/Ukraine=6 Proportion of patients receiving <6 cycles: North America=86% Japan=89% Russia/Ukraine=60%	NR	NR	AEs similar in patients 70 years old vs the entire population
Gridelli 2011[50] (abstract only)	NR	NR	NR	Grade 3-4: >70=21% <70=7%
Weissman 2011[60]	A median of four (range: 1–6) cycles of chemotherapy 57/191 patients (29.8%) completed 6 cycles	The study was terminated early following a recommendation by the Independent Data Monitoring Committee, due to AEs.70.2% of patients discontinued treatment due to AEs, disease progression, death	NR	Grade 3-4: Fatigue=34 (18.5%) Dyspnoea=25 (13.6%) Platelet count decreased=22(12.0%) Thrombocytopenia=56 (30.4%) Neutropenia=46 (25.0%)
	A median of four (range: 1–6) cycles of chemotherapy. 73/192 patients (38.0%) completed 6 cycles	62% of patients discontinued treatment due to AEs, disease progression, death	NR	Grade 3-4: Fatigue=24 (12.8%) Neutropenia=78 (41.7%) Leukopenia=22 (11.8%) Peripheral sensory neuropathy=23 (12.3%)
Leighl 2010[52,62]	>65 vs <65 years Placebo plus cisplatin and gemcitabine	NR	NR	Treatment related deaths=6% overall >65 vs <65 Grade >3: Neutropenia=33% vs 35% Thrombocytopenia=27% vs 25% Anaemia=16% vs 13% Venous thromboembolic events=8% vs 7% Vomiting=3% vs 4% Hypertension=<1% vs 3%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	>65 vs <65 years Bevacizumab (7.5 mg) plus cisplatin and gemcitabine: Cisplatin and gemcitabine: (Arms 2+3) >1 cycle=181 vs 479 >4 cycles=143 (79%) vs 387 (81%) Bevacizumab: (Arms 2+3) >1 dose=179 vs 476 >4 doses=131 (73%) vs 375 (79%) Single-agent bevacizumab maintenance from cycle 7=85 (47%) vs 238 (50%)	NR	NR	Treatment related deaths=2% overall Grade >3: Neutropenia=44% vs 43% Thrombocytopenia=40% vs 29% Anaemia=10% vs 13% Venous thromboembolic events=10% vs 7% Vomiting=3% vs 9% Hypertension=8% vs 7%
	>65 vs <65 years Bevacizumab (15 mg) plus cisplatin and gemcitabine: Cisplatin and gemcitabine: (Arms 2+3) >1 cycle=181 vs 479 > 4 cycles= 143 (79%) vs 387 (81%) Bevacizumab: (Arms 2+3) >1 dose=179 vs 476 >4 doses= 131 (73%) vs 375 (79%) Single-agent bevacizumab maintenance from cycle 7=85 (47%) vs 238 (50%)	NR	NR	Treatment related deaths=4% overall Grade >3: Neutropenia=41% vs 39% Thrombocytopenia=38% vs 24% Anaemia=13% vs 12% Venous thromboembolic events=6% vs 7% Vomiting=7% vs 10% Hypertension=7% vs 10%
Ramalingam 2008 [55]	Weekly Median number of cycles=2 Completed all 4 cycles=44%	Discontinued=52 Due to: Toxicity causing >2 week delay=8 Progression=20 Death=5 Patient refusal=5	NR	Neutropenia=17% Anaemia=16% Fatigue=10%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
		Investigator decision=6 Other=8		
	Standard Median number of cycles=3 Completed all 4 cycles=46%	Discontinued=46 Due to: Toxicity causing >2 week delay=3 Progression=20 Death=5 Patient refusal=3 Investigator decision=10 Other=5	NR	Neutropenia=16% Anaemia=6% Fatigue=6%
Ramalingam 2008[63]	NR	NR	NR	Paclitaxel plus carboplatin: Grade 3-4: Fatigue=12.9% Sensory neuropathy=13.8% Treatment related deaths, n=2
	NR	NR	NR	Paclitaxel plus carboplatin and bevacizumab: Grade 3-4: Fatigue=20.2% Treatment related deaths, n=7 (p=0.10)
Wheatley-Price 2008[61]	Erlotinib >70 vs <70 years: >90% of total planned dose=64% vs 82% 80%-90% of total planned dose=6% vs 4% <80% of total planned dose=29% vs 14%	AEs: 13% vs 5% (p=0.003) Treatment-related AEs: 12% vs 3% (p=0.003)	Dose interruptions <7 days: 35% vs 18% (p<0.001)	Diarrhoea: 16% vs 6% (p=0.022)
Ramalingam 2006[54]	Paclitaxel (100 mg) and carboplatin (AUC-6 mg) >70 vs <70 years Cycles=4	NR	NR	Grade 4: Neutropenia=13.6% vs 4.5%
	Paclitaxel (100 mg) and carboplatin (AUC-2 mg) >70 vs <70 years Cycles=4	NR	NR	NR
	Paclitaxel (150 mg) and carboplatin (AUC-2 mg	NR	NR	Grade 3 neuropathy=12.2% vs 12.4%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	>70 vs <70 years Cycles=2			Grade 4 neutropenia=12.1% vs 9.5%
Weiss 2006[59]	Docetaxel >70 vs <70 years: Median cycles=2 (0-11) vs 3 (0-14)	Disease progression: 45% vs 52% Toxicity: 12% vs 7% >70 years Toxicity related discontinuations: 7/39 (18%) (p=0.175)	NR	Neutropenia: 29.7% vs 41.8% Febrile neutropenia: 18.9% vs 11.7%
	Pemetrexed >70 vs <70 years: Median cycles=4 (range, 0-15) vs 3 (range, 0-20)	Disease progression: 45% vs 52% Toxicity: 12% vs 7% >70 years Toxicity related discontinuations: 3/47 (6%) (p=0.175)	NR	Neutropenia: 12.5% vs 4.0% Febrile neutropenia: 2.5% vs 1.8%
Belani 2005[49]	Docetaxel plus cisplatin: ≥65 Median cycles=5 (range, 1-13) Mean RDI=0.93 <65 Median cycles=6 (range, 1-10) Mean RDI=0.94	Fewer elderly patients on the docetaxel-cisplatin (19.5%) and docetaxel-carboplatin (15.3%) arms discontinued treatment owing to an AE than on the vinorelbine-cisplatin arm (32.1%). For all treatment groups, the percentage of patients aged ≥65 years discontinuing treatment due to haematological toxicity mirrored the percentage observed in the full population	NR	Grade 3-4: Age <65 years: Nausea/vomiting=12.8% Asthenia=11.2% Leukopenia=98 (38.3%) Neutropenia=181 (70.7%) Anemia=20 (7.8%) Age >65 years: Nausea/vomiting=11.5% Asthenia=14.2% Neurotoxicity=16.2% Pulmonary=12.2% Infection=11.5% Pain=10.1% Leukopenia=75 (50.7%) Neutropenia=121 (81.8%) Febrile neutropenia=12 (8.1%)
	Docetaxel plus carboplatin ≥65 Median cycles=6 (range 1-9) Mean RDI=0.93 <65	NR	NR	Grade 3-4: Age <65 years: Pulmonary=11.8% Leukopenia=124 (43.5%) Neutropenia=197 (69.6%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Median cycles=6 (range 1-10) Mean RDI=0.93			Age >65 years: Asthenia=13.2% Neurotoxicity=11.4% Pulmonary=17.5% Infection=17.5% Pain=10.5% Leukopenia=73 (64.6%) Neutropenia=97 (86.6%) Anaemia=15 (13.3%)
	Vinorelbine plus cisplatin ≥65 Median cycles=3 (range 1-8) Mean RDI=0.76 <65 Median cycles=4 (range 1-9) Mean RDI=0.79	NR	NR	Grade 3-4: Age <65 years: Nausea/vomiting=17.5% Asthenia=13.1% Neurotoxicity=14.2% Pulmonary=10.1% Leukopenia=143 (53.8%) Neutropenia=215 (80.8%) Anaemia=62 (23.2%) Age >65 years: Nausea/vomiting=25.8% Asthenia=17.2% Neurotoxicity=16.4% Pulmonary=14.1% Infection=10.2% Pain=11.7% Leukopenia=70 (56.0%) Neutropenia=94 (75.2%) Anaemia=32 (25.6%)
Hensing 2003[51]	Carboplatin and paclitaxel-4 cycles: <70 years (163/230) Median cycles=4 (0-19) >70 years (67/230) Median cycles=4 (range,1-11)	<70 years Completed therapy=58% Disease progression=17% Toxicity=3% Patient/physician choice=12% Death=10% >70 years: Completed therapy=46% Disease progression=17%	NR	<70 years (163/230) Grade 3: Neutropenia=24% Grade 4: Neutropenia=14% >70 years (67/230) Grade 3: Neutropenia=19% Grade 4: Neutropenia=16%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
		Toxicity=4% Patient/physician choice=12% Death=21% p=0.55		
	Carboplatin and paclitaxel - until developed disease progression: 163/230 <70 years Median cycles=4 (0-19) 67/230 >70 years Median cycles=4 (1-11)	(116/230) <70 years Completed therapy (Arm A) patients=0% Disease progression=47% Toxicity=14% Patient/physician choice=27% Death=11% >70 years Completed therapy (Arm A) patients=0% Disease progression=21% Toxicity=21% Patient/physician choice=51% Death=7% p=0.017	NR	(163/230) Grade 3 - <70 years Neutropenia=24% Grade 4: Neutropenia=14% (67/230) Grade 3 >70 years: Neutropenia=19% Grade 4: Neutropenia=16% All grades of neutropenia p=0.77
Sculier 2002[56]	Cisplatin and carboplatin combined with ifosfamide: Cycle=4 weeks Duration of response=29 weeks (CI:20-39) p=0.28 Overall treatment median duration=84 days (0-202) Received at least six courses=26 Dose intensity: Cisplatin=14.9 weekly p=0.007 Ifosfamide=1.1 weekly p=0.02 Carboplatin=NS-24.4 weekly p=0.13	Early death due to cancer=8 Toxic death=5 Removal-excess toxicity=3 Death by tumour necrosis=0 Sudden death related to cardiovascular events=3	NR	Leucopenia=52% Thrombopenia=33% Emesis=12% Infection=15% Alopecia=23% Time of analysis=78 deaths
	Cisplatin and carboplatin combined with gemcitabine: Cycle=4 weeks Duration of response= 54 weeks (CI:33-71) p=28 Overall treatment median	Early death due to cancer=4 Toxic death=4 Removal–excess toxicity=3 Death by tumour necrosis=1 Sudden death related to	NR	Leucopenia=48% Thrombopenia=60% Emesis=8% Infection=8% Alopecia=12%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	duration=86 days (28-233) Received at least six courses=26 Dose intensity: Cisplatin=14.6 weekly p=0.007 Carboplatin=NS-21.9 weekly p=0.13 Gemcitabine=NS-0.60 weekly p=0.53	cardiovascular events=4		Time of analysis=72 deaths
	Ifosfamide plus gemcitabine: Cycle=4 weeks Duration of response= 38 weeks (CI:27-50) p=28 Overall treatment median duration=84 days (28-221) Received at least six courses=24 Dose intensity: Ifosfamide=1.04 weekly p=0.02 Gemcitabine=0.58 weekly p=0.53	Early death due to cancer=4 Toxic death=4 Removal–excess toxicity=6 Death by tumour necrosis=0 Sudden death related to cardiovascular events=0	NR	Leucopenia=73% Thrombopenia=17% Emesis=9% Infection=9% Alopecia=28% Time of analysis=73 deaths

AUC=area under the curve; RDI=relative dose intensity; AE=adverse event; CI=confidence interval; NR=not reported

7.4 Comprehensive geriatric assessment and quality of life

Outcomes relating to CGA and QoL reported in subgroup analyses of RCTs are presented in Table 11. None of the studies reported the use of any CGA tools, and only three studies[51,60,61] reported QoL data.

Three studies[51,60,61] reported QoL, using seven measures: FACT-L,[51,60] TOI,[60] TOI-L,[51] EORTC QLQ-C30 and EORTC QLQ-C13,[61] and two subscales relating to neurotoxicity and taxane toxicity, FACT-NTTX (Neurotoxicity and Taxane Toxicity)[51] and TOI-NTTX.[51] One study[51] reported that questionnaire completion rates were similar between older and younger patients (see Appendix 7 for details).

Table 11 Comprehensive geriatric assessment and quality of life, subgroup analyses of randomised controlled trials

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Results summary**
Weissman 2011[60]	NR	NR	TOI FACT-L	After six cycles of treatment, the mean change in QoL from baseline, as measured by TOI of the FACT-L scale, was –4.7 in the gemcitabine plus oxaliplatin arm and –6.4 in the paclitaxel plus carboplatin arm
Wheatley-Price 2008[61]	NR	NR	EORTC QLQ-C30 and QLQ-C13	QoL benefits were similar in elderly and young patients
Hensing 2003[51]	NR	NR	TOI-L TOI-NTTX FACT-L FACT-NTTX	QoL did not differ between patients aged ≥70 years and those aged <70 years, nor did the two groups demonstrate a differential rate of change over time

TOI=Trial Outcome Index; TOI-L=Trial Outcome Index; NTTX=Neurotoxicity and Taxane Toxicity; FACT-L=Functional Assessment of Cancer Therapy-Lung; EORTC C30=European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire; QLQ-C13=EORTC Quality of Life Cancer Questionnaire – Lung Cancer; QoL=quality of life; NR=not reported

7.5 Summary and discussion

The 13 included studies[49-63] that reported subgroup analyses of RCTs all focussed on NSCLC. The proportion of older patients in each study was relatively small, and older patients in these studies generally had a good PS. Not all subgroup analyses had been planned as part of the original RCT design, and not all trials had stratified patients by age at randomisation. Any results should therefore be interpreted with caution.

In terms of efficacy, results for older patients seem to be comparable to those of younger patients across all outcomes, with a definite trend for older patients achieving a longer PFS/TTP than younger patients in some trials. Taking into account that the smaller numbers of patients may affect the robustness of the results, the data suggest that chemotherapy given to older patients confers survival benefit similar to that of younger patients.

The tolerability results were again difficult to compare given the variation in how outcomes were reported, but the data generally suggest that older patients can be administered cycles and doses of chemotherapy that are similar to those used to treat younger patients. Older patients generally had higher rates of treatment discontinuation due to progressive disease or AEs than younger patients. This finding mirrors the tolerability data from the included RCTs of older patients only. Adverse event data suggest that, generally, older patients have a slightly higher incidence of haematological AEs but results are generally comparable with younger patients.

None of the studies reported use of CGA tools, and only a few studies reported QoL outcomes. Results for reported QoL suggest that there are no differences between older and younger patients in terms of QoL scores.

Based on authors' conclusions, none of the studies found that chemotherapy was infeasible or intolerable in older patients; rather, that chemotherapy was effective and sustainable despite older patients having slightly higher rates of AEs.

8 POOLED ANALYSES OF RANDOMISED CONTROLLED TRIALS

8.1 Study characteristics

Four studies[64-67] that pooled data from RCTs were included in the review. Study characteristics are presented in Table 12. All studies focussed on NSCLC.

A further six studies[68-73] were identified; however, they were not included in the review because the pooled data were derived from studies already included in the review, either as an RCT or as a subgroup analysis. However, as the findings of the excluded studies[68-73] may be of interest, summary information regarding these studies is presented in Table 13.

The definition of 'older' was >70 in all studies except for the Fruh et al study,[67] which used >65 years as the cut-off age to describe the older population. All studies compared older patients with younger patients.

The study with the largest proportion of older patients was Comella et al[66] with 56% of patients aged ≥70. The remaining studies had <30% of older patients. Two studies[65,67] pooled data from five trials, whereas Comella et al[66] pooled data from three trials and Blanchard et al[64] pooled data from two trials. Two studies[65,66] pooled data from trials that were conducted between 1996 and 2004/2006. Details of study years were not presented by Blanchard et al[64] or Fruh et al.[67] Two studies[64,67] appear to have used individual patient data (IPD).

A total of 11 different regimens were delivered across the studies to patients with NSCLC. Two studies[65,67] did not state the stage of disease targeted by treatment. Blanchard et al[64] and Comella et al[66] focussed on patients with locally advanced or metastatic disease.

Table 12 Study characteristics, pooled analyses of randomised controlled trials

Study	Study details	Population	Intervention, n	Purpose	Authors conclusions
Blanchard 2011[64]	Retrospective analysis of two phase III RCTs (Southwest Oncology Group trials 9308 and 9509) Multicentre USA Appear to have used IPD	Stage III/IV No prior chemotherapy <70 years=80% ≥70 years=20% Male: <70=69% ≥70=66% PS: <70: 0=37%, 1=63% ≥70: 0=33%, 1=67%	S9308 – cisplatin vs cisplatin plus vinorelbine (only combination treatment included in this analysis) S9509 – carboplatin plus paclitaxel vs cisplatin plus vinorelbine (n=616)	Investigate the safety, feasibility, and outcomes of platinum doublet therapy in patients aged ≥70 years with advanced NSCLC compared with patients <70 years	Although patients aged ≥70 years derived initial benefit from platinum-based therapy, survival was better in younger patients. Additional studies in this growing patient population are needed to develop treatment strategies that minimise toxicity and increase efficacy
Pallis 2011[65]	Meta-analysis of five phase III RCTs of the Hellenic Oncology Research Group Multicentre Greece 1996–2004	<70 years=77% ≥70 years=23% Male: <70=87.4% ≥70=91.5% PS: <70: 0-1=78.1%, 2=21.9% ≥70: 0-1=80.4%, 2=19.6%	Docetaxel/cisplatin vs docetaxel/gemcitabine (n=406) Docetaxel vs docetaxel/cisplatin (n=319) Vinorelbine/cisplatin vs docetaxel/gemcitabine (n=389) Docetaxel vs docetaxel/gemcitabine (n=312) Oral vinorelbine vs docetaxel/gemcitabine (n=419)	The objective was to determine (i) the number of elderly (>70 years) patients with advanced/metastatic NSCLC enrolled in phase III trials of the Hellenic Oncology Research Group, (ii) the treatment-related toxicity observed in these patients compared with their younger counterparts, and (iii) the differences in terms of response rate, TTP and OS between younger and older patients	This report supports the feasibility of chemotherapy treatment for older NSCLC patients. Optimisation of treatment of older NSCLC patients requires the design of prospective older-specific phase III trials for these patients
Comella 2008[66]	Retrospective analysis of three Southern Italy Cooperative Oncology Group trials 1999-2006	Locally advanced or metastatic NSCLC <70 years=44% ≥70 years=56% Male: <70=92 1% ≥70=89%	Paclitaxel plus gemcitabine (n=259)	To retrospectively compare the tolerability, activity and efficacy of the combination of paclitaxel plus gemcitabine according to the age of patients entered in the group's prospective, randomised trials	Paclitaxel plus gemcitabine were similarly tolerated and active in younger and elderly patients. This regimen should be considered an option for the management of fit elderly patients

Study	Study details	Population	Intervention, n	Purpose	Authors conclusions
		PS: <70: 0–1=100% ≥70: 0-1=98%, 2=2%			
Fruh 2008[67]	Pooled analysis of five cisplatin-based trials Appear to have used IPD	<65 years=3,269 (71%) >65 years=29% 65-69 years=901 ≥70=414	Cisplatin plus vinorelbine n=1888 (41%) Cisplatin plus one drug n=1373 (30%) Cisplatin plus two drugs n=1323 (29%)	This pooled analysis was undertaken to assess the efficacy and toxicity of adjuvant cisplatin-based chemotherapy in elderly patients with NSCLC	Adjuvant cisplatin-based chemotherapy should not be withheld from elderly patients with NSCLC purely on the basis of age

RCT=randomised controlled trial; PS=performance status; NSCLC=non-small cell lung cancer; TTP=time to tumor progression; OS=overall survival; IPD=individual patient data

Table 13 Excluded pooled analyses

Study	Purpose	Author conclusions
Des Guetz 2012[68]	To establish the benefit-to-risk ratio of doublet chemotherapy vs single-agent in patients with advanced NSCLC aged >70 years	NR
Qi 2012[70]	The current literature-based meta-analysis was performed to evaluate the efficacy (OS, TTP, 1-year survival rate, and ORR] and the toxicity profile of doublet cytotoxic agents compared with single third-generation cytotoxic agent as first-line treatment for elderly patients with advanced NSCLC	Results indicated that doublet therapy was superior to a single third-generation cytotoxic agent for elderly patients with advanced NSCLC. The optimal dosage and schedule of platinum-based doublet should be investigated in future prospective clinical trials. Gemcitabine-based doublet could be considered for elderly patients who were not suitable for platinum-based chemotherapy
Xu 2012[73]	To evaluate the efficacy and safety of doublets and single-agent chemotherapy for elderly patients with NSCLC	Compared with single-agent chemotherapy, doublet chemotherapy could increase the overall response rate and 1-year survival rate significantly. Therefore, doublet chemotherapy would be more appropriate for elderly patients with advanced NSCLC as the first-line chemotherapy regimen. However, further prospective RCTs in elderly NSCLC patients are needed to verify the findings in this study
Qiu 2011[71]	To compare the efficacies and toxicities of non-platinum doublets (doublets group) with a non-platinum single agent (single-agent group) in previously untreated advanced NSCLC patients with elderly age and/or poor PS	Except for neutropenia and thrombocytopenia, the non-platinum doublets could increase ORR, and might improve OS for NSCLC patients with elderly age and/or poor PS without addition of more side-effects; however, the doublets showed an increased rate of neutropenia and thrombocytopenia. The addition of doublets may not improve PFS and 1-year survival
Russo 2009[72]	To assess the efficacy and tolerability of gemcitabine-based doublets compared with single-agent chemotherapy for elderly patients with NSCLC	Gemcitabine-based doublets appeared to be effective and feasible compared with single agents in the treatment of elderly patients with advanced NSCLC who were not suitable for full-dose, platinum-based chemotherapy. Further prospective, elderly specific, phase III trials will be necessary
Pallis 2008[69]	To retrospectively evaluate the impact of age on efficacy and toxicity of chemotherapy regimens in patients with advanced NSCLC treated with the docetaxel-gemcitabine combination	The docetaxel/gemcitabine regimen has a comparable efficacy and tolerance in young (<70 years) and elderly (≥70 years) patients

NSCLC=non-small cell lung cancer; OS=overall survival; TTP=time to disease progression; ORR=objective response rate; RCT=randomised controlled trial; PS=performance status

8.2 Efficacy evidence

Outcomes relating to PFS, OS and ORR reported in the four pooled RCT analyses[64-67] are presented in Table 14.

Three studies[64-66] reported PFS and compared results between those aged <70 and those aged >70. There were no statistically significant differences reported, and PFS was similar across all arms even when compared between age groups. In the older patients, the median PFS reached 4.2 months,[66] and in the younger patients the highest median PFS was 5.5 months.[66]

Three studies[64-66] reported OS. Two[64,65] of the three studies reported statistically significant OS results for comparisons between older and younger patients. In Blanchard et al[64] OS was significantly higher in the younger patient cohort (median 9 months vs 7 months; p=0.04); in Pallis et al,[65] median OS was 10 months in younger patients and 8.83 months in older patients (HR 0.85; 95% CI 0.75 to 0.96; p=0.008). For older patients, the median OS ranged from 7[64] to 11.1[66] months, which is similar to results for younger patients, which ranged from 9[64] to 10 months.[65] Fruh et al[67] reported HRs for OS, and concluded that there were no statistically significant differences between age and treatment effect.

Three studies[64-66] compared ORR between older and younger patients, and reported broadly similar results: older patients achieved an ORR of approximately 30%,[64-66] whereas the younger patients achieved between 27%[64] and 36%.[66] There were no statistically significant results reported.

Table 14 Survival outcomes, pooled analyses of randomised controlled trials

Study	Comparisons	Median PFS (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Blanchard 2011[64]	<70 years	4 (3 to 5)	p=0.71	9 (8 to 10)	p=0.04	27% (23 to 31)	p=0.51
	>70 years	4 (4 to 5)		7 (6 to 8)		30% (22 to 38)	
Pallis 2011[65]	<70 years overall	3.8	1.00 (0.89 to1.12) p=0.97	10	0.85 (0.75 to 0.96) p=0.008	28.3%	1.15 (0.90 to 1.46)
	≥70 years overall	4.0		8.83		29.7%	
Comella 2008[66]	<70 years	5.5	p=0.021	9.1	p=0.216	36%	NR
	>70 years	4.2		11.1		30%	NR
Fruh 2008[67]	Overall <65 years 65-69 years ≥70 years	NR	NR	NR	Overall=0.89 (0.82 to 0.96) p=<0.005 <65=0.86 (0.78 to 0.94) 65-69=1.01 (0.85 to 1.21) ≥70=0.9 (0.70 to 1.16) No statistically significant interaction (p=0.26) or test for trend (p=0.29) between age and treatment effect	NR	NR

PFS=progression-free survival; TTP=time to progression; OS=overall survival; ORR=objective response rate; CI=confidence interval; NR=not reported
a Values are PFS, unless otherwise stated.

8.3 Tolerability evidence

Data relating to tolerability are presented in Table 15. All studies[64-67] reported at least one outcome relating to cycles administered, discontinuations and/or AEs. None of the studies reported dose modifications.

Fruh et al[67] reported that the proportion of patients aged <65 who received four cycles was 31%, compared with 19% of those aged ≥70. Comella et al[66] and Blanchard et al[64] compared median cycles between those aged <70 and ≥70, with the older patients receiving a median of three cycles and the younger patients receiving a median of four cycles in both studies.

Withdrawals of treatment due to progressive disease and toxicity were high. Blanchard et al[64] reported that disease progression was the most common reason for withdrawal in the <70 group (41%) and toxicity was the most common in the ≥70 group (36%). In Comella et al,[66] reported rates of withdrawal due to disease progression were 63% in the <70 group and 58% in the ≥70 group.

Rates of haematological AEs were 76% and 83% for younger and older patients, respectively, in the Blanchard et al study,[64] and 17% and 21%, respectively, in the Pallis et al study.[65] Non-haematological toxicity for older versus younger patients was 53% versus 57% in Blanchard et al,[64] and 9% versus 15% in Pallis et al.[65] Fruh et al[67] compared overall grade 3-5 toxicity between younger and older patients, resulting in rates of 72% for those aged <65 and 76% for those aged >70.

Table 15 Tolerability outcomes, pooled analyses of randomised controlled trials

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Blanchard 2011[64]	Aged <70 years: Median cycles: Overall=4 (range, 2–6) Cisplatin plus vinorelbine=3 Paclitaxel plus carboplatin=5	Aged <70 years: withdrawals due to disease progression=41%	NR	Haematological=76% Anaemia=20% Neutropenia=70% Infection=13% Non-haematological=53% Nausea=14% Toxic deaths=16 (3%)
	Aged ≥70 years Median cycles: Overall=3 (2–5) (p=0.06). Cisplatin plus vinorelbine=2 (p=0.01) Paclitaxel plus carboplatin=4 (p=0.07)	Aged ≥70 years withdrawals due to toxicity=36%	NR	Haematological=83% Anaemia=13% Neutropenia=79% Infection=12% Non-haematological=57% Fatigue=15% Toxic deaths=5 (4%)
Pallis 2011[65]	NR	NR	NR	<70 years All grade III/IV=19% Haematological=17% Non-haematological=9%
	NR	NR	NR	≥70 years All grade III/IV=13% Haematological=21% Non-haematological=15%
Comella 2008[66]	<70 Median cycles=4 (range 1-6)	Disease progression=63% Deterioration of clinical status=19% Patients refusal=10% Toxicity=5% Other reasons=3%	NR	Neutropenia=7%
	≥70 Median cycles=3 (range 1-6)	Disease progression=58% Deterioration of clinical status=21% Patients refusal=14% Toxicity=6% Other reasons=3%	NR	Neutropenia=12%
Fruh 2008[67a]	<65 No. of cycles: ≤2=23%, 3=46%, 4=31% Dose mg/m^2: Missing=1%	NR	NR	Overall toxicities: Grade 3-5=72% Grade 4-5=34% Neutropenia grade 3-5=58%, grade 4-5=29%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
	<175=19% 175-274=16% 275-374=43% ≥375=21%			Nausea and vomiting grade 3-5=18% Toxic deaths=0.8%-0.7%
	65-69 No. of cycles: ≤2=27%, 3=45%, 4=28% Dose mg/m^2: Missing=1% <175=23% 175-274=17% 275-374=42% ≥375=17%	NR	NR	Overall toxicities: Grade 3-5=69% Grade 4-5=36% Neutropenia grade 3-5=53%, grade 4-5=31% Nausea and vomiting grade 3-5=17% Toxic deaths=1.5%-1.4%
	Aged ≥70: No. of cycles: ≤2=42%, 3=39%, 4=19% Dose mg/m^2 Missing=0% <175=42% 175-274=16% 275-374=32% ≥375=10%	NR	NR	Overall toxicities: Grade 3-5=76% Grade 4-5=41% Neutropenia grade 3-5=61%, grade 4-5=35% Nausea and vomiting grade 3-5=22% Toxic deaths=2.4%-1.9%

NR=not reported

[a] When comparing the received number of chemotherapy cycles, as well as the total dose of cisplatin received, according to the three age groups using the Kruskal-Wallis test, elderly patients received significantly fewer cycles ($p<0.0001$) and a significantly lower total cisplatin dose ($p<0.0001$)

8.4 Comprehensive geriatric assessment and quality of life

There were no CGA or QoL measures presented by the pooled analysis studies.

8.5 Summary and discussion

The four included studies[64-67] that pooled data from RCTs all focussed on NSCLC. The studies included large numbers of patients from RCTs; however, the proportion of older patients was less than 30% in three studies.[64,65,67] Two of the included studies appeared to use IPD.[64,67] The definition of older was >65[67] or >70,[64-66] and the majority of patients had a good PS.

Efficacy results were broadly similar in older and younger patients across all outcomes, suggesting that chemotherapy is equally effective for older people and younger people with NSCLC who have a good PS. Tolerability results followed the same trend, with younger and older patients having comparable outcomes, and chemotherapy regimens being tolerable across age groups.

There were no CGA or QoL results reported. The authors' conclusions supported the use of chemotherapy for the treatment of fit older patients with NSCLC.

9 COMPARATIVE COHORTS

9.1 Study characteristics

Four studies[74-77] that compared two or more non-randomised treatment arms were included in the review. Three studies[74,76,77] focussed on NSCLC and one study[75] investigated SCLC. Study characteristics are presented in Table 16.

9.1.1 Non-small cell lung cancer

All studies were phase II.[74,76,77] One study was conducted in Japan[74] and two were performed in the USA[75] and USA/Canada.[76] Two studies were funded by research grants,[74,77] and Marsland et al[76] did not report the funding source.

All studies treated patients with stage IIIB/IV disease who were chemotherapy naïve. Approximately half of the patients enrolled in Fujita et al[74] were EGFR+. The largest study was Marsland et al[76] with 121 enrolled patients, and the smallest study was Fujita et al[74] which enrolled 54 patients. The definition of 'older' ranged between >65[77] and >70,[74,76] and the median age varied from 72.4 years[76] to 81 years.[74] Performance status of patients across the studies was primarily 0-1; however, Marsland et al[76] reported 41% and 28.3% of patients with PS 2 in the respective treatment arms.

9.1.2 Small cell lung cancer

The Gridelli et al study[75] was a phase I/II study conducted in Italy between 2000 and 2005. Included patients had extensive SCLC. The study compared four gemcitabine-based regimens and enrolled 78 patients aged ≥70.

Table 16 Study characteristics, comparative cohorts

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
NSCLC						
Fujita 2012[74]	Phase II Open-label Multicentre Japan 2006-2009 Supported by Health Promoting Association for Respiratory Medicine of Nishi-Nippon	Chemotherapy-naïve Stage IIIB/IV Activating EGFR mutations ≥70 years	Patients with EGFR mutations received gefitinib (n=22)	Median age: 81 years (71-85) Male:23% ECOG PS: 0=36%, 1=64%	Primary: ORR Secondary: disease control rate, 1-year survival rate, OS, TTF, toxicity	Treatment customisation based on EGFR mutation status deserves consideration, particularly for elderly patients who often cannot receive second-line chemotherapy due to poor organ function or comorbidities
			Patients without EGFR mutations received vinorelbine or gemcitabine (n=32)	Median age: 79 years (72–89) Male: 47% ECOG PS: 0=12.5%, 87.5%		
Mc Kean 2011[77]	Phase II Multicentre USA and Canada 2004-2006 Supported in part by Public Health Service grants	Stage IIIB/IV Chemotherapy naïve >65 years	Carboplatin plus paclitaxel followed by gefitinib (n=34)	Median age: 75 years (65-89) Male: 59% PS: 0=26%, 1=68%, 2=2%	Primary: progression at 6 months Secondary: tumour response rates, OS, PFS and AEs	NR
			Gefitinib (n=28)	Median age: 80 years (65-91) Male: 57% PS: 0=29%, 1=54%, 2=18%		
Marsland 2005[76]	Phase II USA 1999-2000	Stage: IIIB/IV Chemotherapy naïve >70 years with a PS of 0-2 or >18 years with a PS of 2	Sequential paclitaxel and carboplatin (n=61)	Median age: 73.5 years (35.6-85.3) Male: 57.4% ECOG PS: 0=16.4%, 1=42.6%, 2=41%	Primary: 1-year survival Secondary: toxicity and QoL	These drugs and treatment schema were well tolerated when administered in the community setting and resulted in survival rates that were similar to what is reported in the literature with combination therapy administered to 'high risk'

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
			Paclitaxel plus carboplatin (n=60)	Median age: 72.4 years (45.9-86.5) Male: 60% ECOG PS: 0=15%, 1=56.7%, 2=28.3%		patients. Finding the optimal chemotherapy regimen that can be tolerated remains a challenge in elderly patients
SCLC						
Gridelli 2012[75]	Phase I/II Multicentre Open-label Italy 2000-2005	Extensive disease ≥70 years	Gemcitabine plus vinorelbine (n=30)	Median age: 74 years (70-82) Male: 90% PS: 0-1=93.3%, 2=6.7%	Primary: ORR, toxicity Secondary: OS, PFS, QoL	In elderly patients with extensive SCLC, gemcitabine plus vinorelbine, gemcitabine plus etoposide, and gemcitabine plus cisplatin are not active enough and do not merit further studies. Gemcitabine plus carboplatin might deserve further attention
			Gemcitabine plus etoposide (n=10)	Median age: 73 years (70-78) Male: 90% PS: 0-1=90%, 2=10%		
			Gemcitabine plus cisplatin (n=12)	Median age: 76 years (71-83) Male: 66.7% PS: 0-1=83.3%, 2=16.7%		
			Gemcitabine plus carboplatin (n=26)	Median age: 73 years (70-82) Male: 96.2% PS: 0-1=88.5%, 2=11.5%		

EGFR=epidermal growth factor receptor; ECOG=Eastern Cooperative Oncology Group; PS=performance status; PFS=progression-free survival; OS=overall survival; QoL=quality of life; AEs=adverse events; ORR=objective response rate; TTP=time to progression; TTF=time to treatment failure; NR=not reported

9.2 Efficacy evidence

Outcomes reported on PFS/TTP/TTF, OS and ORR are presented in Table 17.

9.2.1 Non-small cell lung cancer

One study[77] reported median TTP, and patients achieved 3.9 months (95% CI 2.9 to 6.3) for carboplatin plus paclitaxel followed by gefitinib compared with 4.9 months (95% CI 3.9 to 6.4) for gefitinib alone. Gefitinib was compared with vinorelbine or gemcitabine in Fujita et al[74] and the results for time to treatment failure (TTF) were significantly higher for the gefitinib arm (9.7 vs 2.9 months; p=0.0008).

Overall survival was reported by all three studies,[74,76,77] with one statistically significant result: Fujita et al[74] reported that patients in the gefitinib arm had a significantly longer OS of 27.9 months (95% CI 22.4 to undetermined) compared with those in the vinorelbine or gemcitabine arm, who had a median OS of 14.9 (95% CI 11 to 22.4; p=0.016). The lowest OS was reported by Mc Kean et al[77] in the carboplatin plus paclitaxel arm, with patients achieving a median OS of 7.9 months (95% CI 5.7 to 11.2).

Two studies[74,76] reported ORR. Patients with EGFR mutations in the gefitinib arm had an ORR of 45.5% (95% CI 24.4% to 67.8%) compared with patients without EGFR mutations in the vinorelbine or gemcitabine arm, who had an ORR of 18.8% (95% CI 7.2% to 36.4%); the result was not statistically significant (p=0.067).

9.2.2 Small cell lung cancer

Gridelli et al[75] investigated gemcitabine with either vinorelbine, etoposide, cisplatin or carboplatin. and reported outcomes for PFS, OS and ORR. None of the results were statistically significant. Results for PFS favoured gemcitabine plus carboplatin (5.8 months), OS favoured gemcitabine plus etoposide (9.2 months), and ORR showed a clear advantage of gemcitabine plus carboplatin, achieving 61.5% (all other gemcitabine regimens had an ORR of <37%).

Table 17 Survival outcomes, comparative cohorts

Study	Intervention	Median PFS/TTP/TTF (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
NSCLC							
Fujita 2012[74]	Gefitinib	TTF: 9.7	p=0.0008	27.9 (24.4 to undetermined)	p=0.016	45.5 (24.4 to 67.8)	p=0.067
	Vinorelbine or gemcitabine	TTF: 2.9		14.9 (11 to 22.4)	NR	18.8 (7.2 to 36.4)	NR
Mc Kean 2011[77]	Carboplatin plus paclitaxel followed by gefitinib	TTP: 3.9 (2.9 to 6.3)	NR	7.9 (5.7 to 11.2)	NR	NR	NR
	Gefitinib	TTP: 4.9 (3.9 to 6.4)	NR	10.9 (7.4 to 15.7)	NR	NR	NR
Marsland 2005[76]	Sequential paclitaxel and carboplatin	NR	NR	8.2 (<1.0 to 18.8)	NR	22.4	NR
	Paclitaxel plus carboplatin	NR	NR	9.2 (<1.0 to 22)	NR	60.9	NR
SCLC							
Gridelli 2012[75]	Gemcitabine plus vinorelbine	3.5 (2.5 to 4.8)	NR	5.3 (4.4 to 9.2)	NR	36.7 (19.9 to 56.1)	NR
	Gemcitabine plus etoposide	3.5 (1.4 to 7.1)	NR	9.2 (2.8 to 11.3)	NR	10 (0.2 to 44.5)	NR
	Gemcitabine plus cisplatin	3.9 (2.1 to 4.8)	NR	5.1 (3.5 to 9.4)	NR	16.7 (2.1 to 48.4	NR
	Gemcitabine plus carboplatin	5.8 (5.1 to 6.4)	NR	8.5 (7.8 to 12.9)	NR	61.5 (40.6 to 79.8)	NR

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; PFS=progression-free survival; TTF=time to treatment failure; TTP=time to progression; OS=overall survival; ORR=objective response rate; CI=confidence interval; NR=not reported

[a] Values are PFS, unless otherwise stated

9.3 Tolerability evidence

Tolerability outcomes for comparative cohorts are presented in Table 18.

9.3.1 Non-small cell lung cancer

The number of median cycles delivered was reported by two studies.[76,77] In Mc Kean et al,[77] patients received a median of five cycles (range 1–19) in the gefitinib arm and six cycles (range 1–54) in the carboplatin and paclitaxel followed by gefitinib arm. Marsland et al[76] compared sequential paclitaxel then carboplatin with concurrent paclitaxel plus carboplatin and found the sequential arm delivered fewer cycles of paclitaxel (median 3.5) and carboplatin (median 3) than the concurrent arm (median 4).

Discontinuations were reported by two studies:[74,77] 52% of patients in the gefitinib arm discontinued treatment due to AEs in Fujita et al,[74] and 65% and 79% discontinued treatment due to progression of disease in the respective treatment arms of McKean et al.[77]

Adverse events were presented by all three studies.[74,76,77] Neutropenia was commonly reported and varied from 0% in McKean et al[77] to 46.9% in the Fujita et al study,[74] which also reported a high rate of leukocytopenia (46.9%). Grade 3-4 AEs occurred in 76% and 36% of patients, respectively, in Mc Kean et al.[77]

9.3.2 Small cell lung cancer

Gridelli et al[75] reported grade 3 neutropenia in two arms (16.7% and 10%), and anaemia and thrombocytopenia in one arm (20% and 10%, respectively).

Table 18 Tolerability outcomes, comparative cohorts

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
NSCLC				
Fujita 2012[74]	NR	Gefitinib: Discontinuation due to AEs=52%	NR	Grade 3-4: ALT=5 (22.7%) AST=3 (13.6%)
	NR	Vinorelbine or gemcitabine: Discontinuations NR	NR	Grade 3-4: Anaemia=4 (12.5%) Leukocytopenia=15 (46.9%) Neutropenia=15 (46.9%) Febrile neutropenia=4 (12.5%)
Mc Kean 2011[77]	Carboplatin and paclitaxel followed by gefitinib: Median cycles=6 (range 1-54)	Most common reason for stopping treatment: Cancer progression n=23/34 (65%)	NR	Grade 3-4=76% Grade 3: Fatigue=24% Dyspnoea=15% Neutropenia=12%
	Gefitinib: Median cycles=5 (range 1-19)	Most common reason for stopping treatment: Cancer progression n=22/28 (79%)	NR	Grade 3-4=36% Grade 3: Fatigue=11% Dyspnoea=4% Neutropenia=0%
Marsland 2005[76]	Paclitaxel: Median cycles=3.5 (range 1-13) Carboplatin: Median cycles=3 (range 1-16)	NR	Dose was reduced in the event of grade 3 toxicities: 12.5% for paclitaxel and 20% for carboplatin	Grade 3: Neuropathy=14.3% Fatigue=19% Grade 3-4: Neutropenia=15% Leukopenia=15%
	Paclitaxel plus carboplatin: Median cycles=4 (range 1-10)	NR	NR	NR
SCLC				
Gridelli 2012[75]	NR	NR	NR	Gemcitabine plus vinorelbine: (grade 3) neutropenia=16.7%
	NR	NR	NR	Gemcitabine plus etoposide: (grade 3) Anaemia=20% Neutropenia=10% Thrombocytopenia=10%
	NR	NR	NR	Gemcitabine plus cisplatin: NR
	NR	NR	NR	Gemcitabine plus carboplatin: NR

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; AE=adverse event; ALT=alanine transaminase; AST=aspartate aminotransferase; NR=not reported

9.4 Comprehensive geriatric assessment and quality of life

Outcomes relating to CGA and QoL for comparative cohorts are presented in Table 19.

9.4.1 Non-small cell lung cancer

Marsland et al[76] used FACT-L and FACT-G to report QoL measures. Results showed that although the first cycle of chemotherapy resulted in a perceived QoL reduction, towards the end of the study there were no differences from baseline measurements.

9.4.2 Small cell lung cancer

Gridelli et al[75] measured CGA at baseline and reported outcomes at intervals throughout the study, using CCI, ADL and IADL.

Table 19 Comprehensive geriatric assessment and quality of life, comparative cohorts

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Results summary**
Marsland 2005[76] (NSCLC)	NR	NR	FACT-L FACT-G	At cycle 1, results indicate that, in general, patients felt that their QoL (physical and functional) had decreased. From cycles 3 through 6, there were no significant changes from baseline, indicating no changes (positive or negative) in QoL later in the study
Gridelli 2012[75] (SCLC)	CCI ADL IADL	Baseline measure	NR	NR

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; FACT-L=Functional Assessment of Cancer Therapy-Lung; FACT-G=Functional Assessment of Cancer Therapy-General; QoL=quality fo life; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; CCI=Charlson Comorbidity Index; NR=not reported

9.5 Summary and discussion

Four studies[74-77] compared non-randomised treatment arms and enrolled only older patients. The studies were relatively small phase I/II studies, with the largest enrolling only 121 patients. Results should therefore be interpreted with caution. Patients generally had a good PS.

Efficacy outcomes were not well reported. Only one study[77] reported median TTP, which favoured gefitinib alone over carboplatin plus paclitaxel followed by gefitinib in older patients with NSCLC. Another study[74] reported TTF, and found that gefitinib was statistically significantly better than gemcitabine or vinorelbine. One study,[75] which focussed on SCLC, reported PFS and found a slight advantage for gemcitabine plus paclitaxel compared with other gemcitabine-containing regimens for patients with SCLC. Overall survival was reported by all studies,[74-77] but only one reported statistically significant results: Fujita et al[74] found that gefitinib achieved a significantly longer OS than either vinorelbine or gemcitabine for older patients with NSCLC (note that patients treated with gefitinib were EGFR+, whereas patients treated with vinorelbine or gemcitabine were not).

In terms of tolerability, outcomes were poorly reported making it difficult to compare and draw firm conclusions. One study[75] reported using CGA tools as an outcome measure, and one study[76] reported QoL outcomes.

The authors' conclusions for two NSCLC studies suggest that chemotherapy is a feasible option for older patients; however, Gridelli et al[75] suggest that although gemcitabine plus carboplatin was effective enough to warrant further investigation, gemcitabine with vinorelbine, etoposide or cisplatin were not sufficiently effective to merit further study.

10 SINGLE COHORTS

10.1 Study characteristics

A total of 95 single cohort studies[78-176] (reported in 99 publications) were included in the review. Eighty-four studies[73,78-91,93-101,104-108,110-113,115,117,119-126,128-144,146-149,151-164,166-173,175,176] focussed on patients with NSCLC, and 11[92,102,103,109,114,116,118,127,145,150,165] focussed on SCLC.

Due to the large volume of data, study characteristics for single cohorts are presented in Appendix 4.

10.1.1 Non-small cell lung cancer

Of the NSCLC studies, 16 studies[97,98,110,113,119,120,128,132,134,136,144,151,156,161,164,176] enrolled both older and younger patients, and the remainder enrolled only older patients. The majority of studies were phase II studies and there were no UK-based studies. Studies were conducted between 1997[94] and 2011.[86,138] Studies included small numbers of patients: those that recruited only older patients ranged from 9 patients in Sequist et al[162] to 122 patients in Tibaldi et al,[172] and studies studies that recruited both older and younger patients ranged from 13 patients aged >70[120] to 623 patients aged >65.[132]

The definition of older varied from >65[85,86,94,95,122,123,126,128,132,134-137,154,158,176] to >80,[93] but the majority of studies used >70 as the age cut-off for inclusion. In most of the studies the proportion of males was above 60%, but this ranged from 20% in Oshita et al[152] to 97% in Maestu et al.[140] The majority of studies treated patients with stage IIIB/IV disease.

10.1.2 Small cell lung cancer

Eleven studies[92,102,103,109,114,116,118,127,145,150,165] focussed on patients with SCLC. Five[92,109,116,127,145] were phase II studies, five[102,103,118,150,165] were phase I, and one study[114] did not report the phase. Studies were conducted between 1998[150,165] and 2009.[114,145] The smallest study[118] enrolled 12 patients, and the largest study[127] enrolled 46 patients. The definition of 'older' varied from >65[109,127] to >76.[102]

10.2 Efficacy evidence

Survival outcomes for single cohorts are presented in Table 20, which details outcomes for studies that present data solely for older patients, or compares results between older and younger patients. A total of 88 studies[78,79,81-83,85-98,100-145,148-155,157-162,164,166-176] reported at least one outcome of interest.

10.2.1 Non-small cell lung cancer

Of the included NSCLC studies that reported efficacy outcomes, 63[78,79,81-83,86-90,93-98,100,101,104-108,110-112,115,120-123,126,128,129,132-144,148,151,154,155,157-160,162,164,167-175] reported outcomes for PFS/TTP. Of the studies that reported PFS/TTP, only six studies[111,129,135,137,158,162] reported PFS/TTP gains of ≤3 months. The highest reported PFS for older patients was in Asami et al[78,79] with 12.9 months (95% CI 2.2 to 23.6), and the highest reported TTP for older patients was 8.6 months.[132]

Ten studies[78,79,85,91,117,124,125,142,158,169,176] did not report any data for OS. The lowest reported median OS was Bauman et al[83] with a median OS of 3.2 months for patients treated with imatinib plus paclitaxel who had a PS of 2, however 31 studies[83,86,88,93,96,98,110,113,115,119,120,123,128-132,136,139,143,148,149,151,153,155,157,160,161,167,168,174] achieved a median OS of ≥10 months. The highest reported median OS was 33.8 months for gefitinib.[139]

Sixty-two studies[78,79,81-83,85,87-91,93-95,97,100,101,104-108,110,111,115,117,119,120,122-126,128-132,134-139,141,144,148,149,151-155,164,166-176] reported ORR, with the lowest reported by Kanard et al[126] for vinorelbine (3.4%) and the highest was reported by Maemondo et al[139] for gefitinib (74.2%).

10.2.2 Small cell lung cancer

Of the ten single cohort studies[92,102,103,109,114,116,118,127,145,150] that focussed on SCLC and reported efficacy outcomes, six[92,109,114,116,127,145] reported PFS/TTP. Five of the studies[92,114,116,127,145] reported a median PFS/TTP gain of >3 months; Hainsworth et al[109] reported a median PFS of only 2 months. The highest PFS was reported by Murata et al,[145] with 10 months (95% CI 5 to 27) for patients with limited disease.

Overall survival was reported by all studies[92,102,103,109,114,116,118,127,145,150] with the exception of Fujiwara et al.[102] The lowest OS was reported by Hainsworth et al,[109] with patients achieving a median OS of 4 months; all other studies achieved an OS of >9 months.

All studies with the exception of Hainsworth et al[109] reported ORR. Studies achieved an ORR of >60%, except for Chee et al[92] (31%). The highest reported ORR was 89% (95% CI 79 to 99) and was reported by Inoue et al.[116]

Table 20 Survival outcomes, single cohorts

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
NSCLC							
Older patients only							
Baek 2012[81,82]	Gemcitabine plus UFT	4.6 (3.7 to 5.5)	NR	6.1 (5.1 to 7.0) 1-year survival rate: 29.1%	NR	25 (12.3 to3 7.7)	NR
Bauman 2012[83]	Imatinib plus paclitaxel All patients	3.6	NR	7.3	NR	32 (17.4 to 50.5)	NR
	Frail	3.2	p=0.02	4.8	p=0.02	NR	
	Non frail	4.5		12			
	PS 0-1	NR	NR	8.3	p=0.04		
	PS 2			3.2			
Firvida 2012[100,101] (abstract only)	Erlotinib	3.9 (1.4 to 6.4)	NR	9.9	NR	25	NR
Kurata 2012[131]	Carboplatin plus gemcitabine	NR	NR	14.2	NR	22.2(11.1 to 33.3)	NR
Lim 2012[138]	Gemcitabine plus carboplatin	5.9 (4.5 to 7.3)	NR	9.6 (8.2 to 11.0)	NR	55.0 (39.8 to 69.3)	NR
Maemondo 2012[139]	Gefitinib	12.1	NR	33.8	NR	74.2 (57.9 to 90.5)	NR
Merismsky 2012[144]	Oral erlotinib	4.57 (0.68 to 5.22)	NR	7.29 (6.27 to 8.67)	NR	14	NR
Schuette 2012[161]	Pemetrexed	NR	NR	11.1 (9.5 to 12.2)	NR	NR	NR
Takatani 2012[167]	Vinorelbine plus carboplatin	NR	NR	NR	NR	15.4	NR
	Vinorelbine plus carboplatin	TTP:3.2 (2 to 4.4)	NR	12 (10.6 to 13.5) 1-year survival: 52.9% (36.2% to 69.6%)	NR	14.6 (38 to 25.4)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
				2-year survival: 16.3% (3.0% to 29.6%)			
Tibaldi 2012[171]	Sequential cisplatin or gemcitabine followed by docetaxel	5.1	NR	8.6	NR	16.7	NR
Asami 2011[78,79]	Gefitinib	12.9 (2.2 to 23.6)	NR	NR	NR	59 (33 to 81)	NR
Borghaei 2011[86]	Bevacizumab plus erlotinib	6.6 (3.6 to 14.9)	NR	14.1 (6.2 to undefined)	NR	NR	NR
Kobayashi 2011[129]	Gefitinib	2.7 (0 to 5.7)	NR	11.9 (7.8 to 16.0)	NR	20 (8 to 39)	NR
Kunimasa 2011[130]	EGFR=gefitinib Non-EGFR=vinorelbine or gemcitabine	NR	NR	EGFR: 27.9 (24.4 to undeterminable) Non-EGFR: 14.9 (11.0 to 22.4)	NR	EGFR: 45.5 (24.4 to 67.8) Non-EGFR: 18.8 (7.2 to 36.4)	NR
Mansueto 2011[142]	Oral vinorelbine	TTP: 7.8	NR	NR	NR	NR	NR
Nishiyama 2011[148]	S-1	4.0 (4.0 to 9.8)	NR	12.1 (13.8 to 25.5)	NR	27.6 (11.3 to 43.9)	NR
Terai 2011[169]	Carboplatin plus paclitaxel	4.17 (2.18 to 6.16)	NR	NR	NR	21.3 (9.6 to 33.0)	NR
Xu 2011[174]	Erlotinib	TTP: 6.4	NR	12.7	NR	48.6	
Cai 2010[89]	Docetaxel	TTP:4.2	NR	6.1	NR	35	NR
Kim 2010[128]	Docetaxel plus carboplatin	6.9 (6.25 to 7.55)	NR	13.1 (10.20 to 16.07)	NR	46.5 (31.6 to 61.4)	NR
Rossi 2010[158]	Erlotinib	TTP: 3 (1 to 24)	NR	NR	NR	16	NR
Rozzi 2010[159]	Paclitaxel plus carboplatin	TTP: 5.7 (3.1 to 8.6)	NR	9 (4.4 to 13.9)	NR	NR	NR
Blakely 2009[85]	Pemetrexed plus gemcitabine	NR	NR	NR	NR	17.8 (9.3 to 31.4)	NR
Boukovinas 2009[87]	Gemcitabine plus docetaxel	TTP: 4.1 (range 0.5-32.1)	NR	9.4 (1.1 to 45.6)	NR	31.2 (20.82 to 41.5)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Du 2009[95]	Docetaxel	5.3	NR	8.5	NR	35.7	NR
Feliu 2009[97]	Docetaxel plus cisplatin	TTP: 5.2	NR	8.9	NR	31 (17.8 to 47.2)	NR
Han 2009[110]	Weekly docetaxel and cisplatin	5.0 (4.1 to 5.7)	NR	10.9 (9.6 to 12.2)	NR	39.6 (25.7 to 53.5)	NR
Igishi 2009[115]	UFT plus vinorelbine Phase II	5.0 (0.5 to 32.5)	NR	11.8 (2.7 to 34.8)	NR	27 (13 to 40)	NR
Lee 2009[136]	Gemcitabine plus cisplatin	TTP: 5.75 (4.40 to 7.11)	NR	10.3 (7.85 to 12.74)	NR	41.7 (27.8 to 55.6)	NR
Sequist 2009[162]	Pemetrexed plus gemcitabine	1.7 (1.5 to 2.5)	NR	3.9 (1.6 to 14.3)	NR	NR	NR
Yoshimura 2009[175]	Docetaxel plus carboplatin	4.4 (3.4 to 5.4)	NR	9.9 (7.6 to 12.2)	NR	46.7 (28.8 to 64.6)	NR
Ebi 2008[96]	Gefitinib	4 (3 to 8)	NR	10 (7 to 20)	NR	NR	NR
Gadgeel 2008[104]	Docetaxel plus calecoxib	3.4 (2.0 to 3.8)	NR	5.7 (2.6 TO 9.1)	NR	19	NR
Gridelli 2008[106]	Gemcitabine	3.7 (2.5 to 4.7)	NR	9.4 (6.3 to 11.6)	NR	17.6 (8.4 to 30.9)	NR
Kaira 2008[124]	S-1 and gemcitabine	NR	NR	NR	NR	42.9	NR
Lee 2008[137]	Docetaxel	2.2 (1.6 to 2.9)	NR	8.7 (4.6 to 12.7)	NR	23 (12 to 38)	NR
Oshita 2008[152]	Nedaplatin and irinotecan followed by sequential gefitinib	NR	NR	8.7	NR	All 3 treatments: 42.9 Nedaplatin and irinotecan: 39.3	NR
Pino 2008[154]	Paclitaxel and gemcitabine followed by maintenance paclitaxel	5 (3 to 6)	NR	7 (5 to 9)	NR	All 3 treatments: 32 (19 to 45) Paclitaxel and gemcitabine: 30 (18 to 42)	NR
Rossi 2008[157]	Paclitaxel	TTP: 5 (1 to 23)	NR	12 (1 to 36)	NR	NR	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
		ECOG PS 0 TTP: 6 ECOC PS 1 TTP: 6 ECOG PS 2 TTP: 2		ECOG PS 0: 15 ECOC PS 1: 13 ECOG PS 2: 3			
Simon 2008[164]	Docetaxel plus gefitinib	6.9 (3.95 to 7.8)	NR	9.6 (4.6 to 16.3) Males vs females: 4.8 vs 22.8	p=0.0002	40 (26 to 57)	NR
Tibaldi 2008[173]	Sequential gemcitabine followed by docetaxel	TTP: 4.8 (3.6 to 6.0) ECOG PS 0-1 vs 2 TTP: 4.8 (2.6 to 7.0) vs 4.0 (0.6 to 7.3)	NR	8.0 (5.6 to 10.5) ECOG PS 0-1 vs 2 8.7 (7.4 to 9.9) vs 5.4 (1.3 to 9.4)	NR	16 (7.6 to 28.3)	NR
Jackman 2007[121]	Erlotinib	TTP: 3.5 (2.0 to 5.5)	NR	5.3 (7.8 to 14.6)	NR	NR	NR
Juan 2007[123]	Paclitaxel	TTP: 4.7 (3.0 to 6.3)	NR	7.8 (6.5 to 9.1) PS 0-1 vs 2 10.1 (9.2 to 11.6) vs 4.9 (2.3 to 7.8)	NR	44 (34.3 to 53.7)	NR
Kaira 2007[125]	Docetaxel plus carboplatin	NR	NR	NR	NR	36	NR
LeCaer 2007[134]	Docetaxel plus gemcitabine	TTP: 4.93 (4.23 to 6.90)	NR	7.07 (5.63 to 8.83)	NR	34 (21.6 to 48.7)	NR
LeCaer 2007a[135]	Docetaxel	TTP: 2.16 (1.63 to 3.56)	NR	4.33 (1.73 to 11.10)	NR	10 (3.7 to 22.6)	NR
Maestu 2007[141]	Gemcitabine plus vinorelbine	TTP: 5.7 (4.9 to 6.5)	NR	6.7 (4.6 to 8.8)	NR	22 (12 to 32)	NR
Buffoni 2006[88]	Cisplatin plus vinorelbine	TTP: 5.14 <3 cycles, TTP: 2.3 >3 cycles, TTP: 7.8	NR	7.4 <3 cycles: 5.4 >3 cycles: 12.2	NR	33	NR
Giorgio 2006[105]	Carboplatin plus paclitaxel	TTP: 4.1 (2.8 to 8.5)	NR	8.7 (5.1 to 11.8)	NR	25 (15.3 to 38.6)	NR
Hesketh 2006[111]	Strata 1:	4.7 (2.7 to 4.2)	NR	9.1 (7.1 to 12.7)	NR	19 (11 to 30)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
	Sequential vinorelbine and docetaxel			12-month survival rate: 41% 24-month survival rate: 13%			
	Strata 2: Sequential vinorelbine and docetaxel	2.6 (1.9 to 4.2)	NR	5.5 (3.1 to 6.5)	NR	11 (3 to 25)	NR
Ishimoto 2006[120]	Carboplatin plus docetaxel	4.8 (4.0 to 5.3)	NR	11.8 (11.3 to 18.4)	NR	30 (17.3 to 42.7)	NR
Martoni 2006[143]	Sequential gemcitabine and vinorelbine	TTP: 6 (4 to 8)	NR	10 (6 to 14)	NR	NR	NR
Pujol 2006[155]	Paclitaxel plus carboplatin	7.5 (6.2 to 9.4)	NR	13.6 (7.5 to 17)	NR	43 (30 to 57)	NR
Santo 2006[160]	Gemcitabine plus vindesine	TTP: 7.1 (5.1 to 9.0)	NR	12.2 (7.4 to 17.3)	NR	NR	NR
Stinchcombe 2006[166]	Phase II Docetaxel and gefitinib	NR	NR	6.5 (3.6 to 9.0) ECOG PS: 0-1 vs 2 7.2 (3.6 to 00) vs 4.6 (0.9 to 00)	NR	31	NR
Tibaldi 2006[170]	Docetaxel	TTP: 4.0 (2.5 to 5.7)	NR	6 (4 to 9.7)	NR	21.20 (8.98 to 38.91)	NR
Hirsch 2005[112]	Sequential vinorelbine followed by gemcitabine	TTP: 3.5	NR	8.0	NR	NR	NR
Ichinose 2005[113]	NR	NR	NR	13.2	NR	NR	NR
LeCaer 2005[133]	Carboplatin plus vinorelbine	TTP: 4.3 (0.2 to 13.8)	NR	7.8 (4.0 to 11.6)	NR	NR	NR
Okamoto 2005[151]	Carboplatin plus paclitaxel	TTP: 4.0 (2.5 to 5.6)	NR	12.3 (7.8 to 17.8)	NR	28 (12.0 to 40.4)	NR
Cappuzzo 2004[91]	Gefitinib	NR	NR	NR	NR	5	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Gridelli 2004[107]	Oral vinorelbine	3.7 (2.5 to 4.5)	NR	8.2 (6.2 to 11.3)	NR	13	NR
Kanard 2004[126]	Oral vinorelbine	3.5 (2.2 to 5.4)	NR	7.5 (5.0 to 12)	NR	3.4 (0.4 to 11.9)	NR
Ohe 2004[149]	Cisplatin plus docetaxel	NR	NR	15.8	NR	52 (31 to 67)	NR
Oshita 2004[153]	Nedaplatin plus irinotecan	NR	NR	13.7	NR	65.8	NR
Takigawa 2004[168]	Docetaxel	6.1 (5.6 to 6.6)	NR	15.6 (11.4 to 19.8)	NR	40 (15 to 65)	NR
Chen 2003[93]	Vinorelbine plus gemcitabine	TTP:5.5	NR	10	NR	65 (44.1 to 85.9)	NR
Choi 2003[94]	Paclitaxel plus carboplatin	TTP: 5.1 (0.5 to 21.6)	NR	8.5 (2.1 to 33.6)	NR	40	NR
Feliu 2003[98]	Cisplatin plus gemcitabine	TTP: 4.6	NR	10.1	NR	NR	NR
Hainsworth 2003[108]	Docetaxel plus gemcitabine	6 (3.5 to 18.5)	NR	7	NR	28	NR
Jatoi 2003[122]	Carboplatin plus paclitaxel	3.8	NR	7	NR	14 (4.7 to 32.5)	NR
Maestu 2003[140]	Carboplatin plus gemcitabine	TTP: 8 (6.4 to 9.6)	NR	9 (7.5 to 10.5)	NR	NR	NR
Inoue 2002[117]	Docetaxel	NR	NR	NR	NR	18	NR
Beretta 2000[176]	Gemcitabine followed by vinorelbine	NR	NR	NR	NR	34.9 (27.6 to 42.2)	NR
Older versus younger patients							
Laskin 2012[132]	Bevacizumab <65	TTP: 7.6 (7.3 to 8.0)	NR	14.6 (13.7 to 15.7)	NR	52.4	NR
	Bevacizumab >65	TTP: 8.2 (7.5 to 8.7)		14.6 (13.0 to 15.4)		49.3	
	Bevacizumab <70	TTP: 7.7 (7.4 to 8.1)		14.6 (13.8 to 15.4)		52.0	
	Bevacizumab	TTP: 8.6 (7.3 to 9.2)		14.6 (11.0 to 17.1)		49.0	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
	>70						
Camerini 2010[90]	Vinorelbine Overall	TTP: 4.0 (2 to 22)	NR	8.0 (3 to 35)	NR	18.6	NR
	<77	TTP: 3.5 (2 to 5)	p=0.001	6.5 (4 to 13)	p=0.048		
	>77	TTP: 4.5 (3 to 6)		9.5 (6 to 12)			
	PS2	NR	NR	9.0 (6 to 12)	p=0.038		
	P23			5.0 (4 to 11)			
Tibaldi 2005[172]	Gemcitabine Overall	TTP: 3.2 (2.2 to 4.2)	NR	5.4 (3.4 to 7.4)	NR	15.3 (8.6 to 21.9)	NR
	<75	NR		5.62		14.5	
	>75			5.29		13.3	
Inoue 2006a[119]	Paclitaxel plus carboplatin Overall	NR	NR	14	NR	45 (30 to 60)	NR
	<75			NR		47	
	>75					44	
SCLC							
Murata 2011[145]	Carboplatin plus irinotecan All	6 (1 to 27)		14 (4 to 46)	NR	83.3 (65.3 to 94.4)	NR
	Limited disease	10 (5 to 27)	p=0.016	26 (11 to 46)	p=0.025	87.5 (47.4 to 99.7)	p=0.71
	Extensive disease	4 (1 to 13)		11 (4 to 28)		81.8 (59.7 to 94.8)	
Chee 2010[92]	Pemetrexed plus carboplatin <70	TTP: 4.2 (2.5 to 4.5)	NR	9.2 (5.4 to 11.6)	NR	31 (15 to 51)	NR
	>70	TTP:4.2 (1.4 to 6.1)		10.8 (2.2 to 14.3)		41 (18 to 67)	
Igawa 2010[114]	Amrubicin	Overall: 6.6 Dose of 40 mg: 7.6	NR	9.3 Older patients vs poor PS:	p=0.48	70 35 mg vs 40 mg: 66 vs 73	p=0.51

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
				9.0 vs 9.3			
Inoue 2010[116]	Amrubicin plus carboplatin	5.8 (5.1 to 6.2)	NR	18.6 (16.1 to 19.4)	NR	89 (79 to 99)	NR
Kim 2008[127]	Irinotecan plus cisplatin	8.32 (6.8 to 9.8)	NR	10.4 (7.6 to 13.2)	NR	76.1 (63.8 to 88.4)	NR
Fujiwara 2006[102]	Topotecan plus cisplatin	NR	NR	NR	NR	60	NR
Fukuda 2006[103]	Carboplatin plus etoposide	NR	NR	16.4	NR	77	NR
Inoue 2006[118]	Amrubicin plus carboplatin	NR	NR	12.7	NR	83	NR
Okamoto 2006[150]	Carboplatin plus irinotecan	NR	NR	13.3	NR	89	NR
Hainsworth 2004[109]	Docetaxel plus gemcitabine	2	NR	4	NR	NR	NR

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; PFS=progression-free survival; TTP=time to progression; OS=overall survival; ORR=objective response rate; CI=confidence interval; UFT=tegafur-uracil; S-1=tegafur, gimeracil and oteracil; NR=not reported

[a] Values are PFS, unless otherwise stated.

10.3 Tolerability evidence

Tolerability outcomes for the included single cohorts are presented in Appendix 5.

10.3.1 Non-small cell lung cancer

Twenty-four studies[85,87,88,90,94,98,105,107,115,128,133-137,143,149,155,160,170,172,173,175,176] reported dose intensity estimates, either as RDI, median dose intensity (MDI), delivered dose intensity (DDI), or simply 'dose intensity'. The majority of studies reported that a dose intensity of >70% was achieved. Three studies reported that 94%,[154] 90%[149] and 48%[111] of patients received all planned cycles, and four studies[87,90,149,176] reported the proportion of the planned dose administered, all of which were >80%.

Forty-two single cohort studies[78,79,83,85,87-89,93,96,100,101,105,107,108,110-112,117,119-121,123,126,128,129,133-137,143,144,148,151-153,155,157,162,168,170,172,175,176] reported information relating to discontinuations or withdrawals. The most common reason for discontinuation of treatment was disease progression. Forty-four studies[78,79,83,85,87,88,90,93,98,100,101,105,107,108,110,111,113,115,117,119,121-124,126,128,129,131,136,139-141,144,153-155,160,162,168,170,172,174,175] reported dose modifications. The most common reason for dose modifications was haematological toxicity.

Forty-seven single cohort studies[78,79,83,85-89,93,94,96-98,100,101,105,107,108,110,111,113,115,119-122,126,128,129,131,133-136,139-141,143,152,153,155,162,166-169,171,175,176] reported grade 3 or higher AEs. Rates for haematological AEs such as thrombocytopenia, neutropenia and leukopenia were approximately 40%, with a few exceptions. Kurata et al[131] reported thrombocytopenia (52%) and neutropenia (60%), Yoshimura et al[175] reported leukopenia (80%) and neutropenia (86.7%), Takigawa et al[168] reported leukopenia (60%) and neutropenia (87%), and neutropenia rates of 50%,[153] 64.8%,[152] 67%,[167] 68%[133] and 70%[119] were also reported.

10.3.2 Small cell lung cancer

Outcomes relating to tolerability were reported by eight studies.[102,103,109,114,116,118,127,145] Dose intensity was reported by two studies:[127,145] Murata et al[145] reported that 90% and 82.1% of the planned doses of carboplatin and irinotecan were delivered. Kim et al[127] reported that the RDI of both irinotecan and cisplatin was >70%. Treatment discontinuations/withdrawals were poorly reported, with only two studies[102,109] reporting this information. Dose reductions and/or modifications were reported by four studies;[102,114,116,145] however, the data were presented in different ways and are therefore difficult to compare. Seven studies[102,103,109,114,116,145] reported grade 3-4 AEs, with the majority of studies showing high rates of haematological toxicity.

10.4 Comprehensive geriatric assessment and quality of life

Table 21 details the use of CGA tools and QoL measures reported in the single cohort studies. All studies that reported CGA and QoL outcomes focussed on NSCLC.

The authors of four studies[90,134,135,141] reported using CGA tools. Four tools were used in the studies: CCI, ADL, IADL and Basic Activities of Daily Living (BADL). Three studies[90,134,135] used CGA tools as an inclusion criterion to select patients for trial entry. One study[141] used CGA tools to measure comorbidities at baseline.

The results of four QoL measures (EQ-5D, LCSS, KPS, and the EORTC QLQ-C30) were reported by five studies.[95,133,134,155,161] The studies generally found that QoL scores improved from baseline during chemotherapy treatment. Full details of outcomes are presented in Appendix 7.

Table 21 Comprehensive geriatric assessment and quality of life, single cohorts

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Results summary**
Schuette 2012[161]	NR	NR	EQ-5D	A small, statistically significant improvement of this score was noted after the second treatment cycle
Du 2009[95]	NR	NR	LCSS KPS	The QoL of patients was improved after chemotherapy. Mean KPS was increased from 75.5 at baseline to 87.7 ($p<0.01$); LCSS scores of cough, haemoptysis, chest pain and dyspnoea were increased from 64, 65, 62 and 65 to 90, 92, 87 and 88, respectively
Camerini 2010[90]	BADL IADL	As measure of eligibility criteria for inclusion	NR	NR
LeCaer 2007[134]	CCI	As measure of eligibility criteria for inclusion	LCSS	The score increased among patients who progressed, although the difference was not significant because of the small number of patients concerned. These scores did not change significantly over time
LeCaer 2007[135]	CCI	As measure of eligibility criteria for inclusion	NR	NR
Maestu 2007[141]	CCI IADL ADL	Baseline measures of comorbidity	NR	NR
Pujol 2006[155]	NR	NR	LCSS	There was no significant change over time in the total score
LeCaer 2005[133]	NR	NR	EORTC QLQ-C30	A significant improvement in QoL between baseline and cycles 1, 3, and 5 was noted in all 40 patients with regard to emotional function ($p=0.006$) and insomnia ($p=0.008$) on the QLQ-C30 questionnaire, and a trend toward an improvement was noted in general health ($p=0.09$), dyspnoea ($p=0.05$), cough ($p=0.07$), and pain ($p=0.09$)

EQ-5D=EuroQoL – 5D questionnaire; BADL=Basic Activities of Daily Living; ADL= Activities of Daily Living; IADL= Instrumental Activities of Daily Living; CCI=Charlson Comorbidity Index; LCSS=Lung Cancer Symptoms Scale; KPS=Karnofsky performance status; QoL=quality of life; EORTC QLQ-C30=European Organisation for research and Treatment of Cancer Quality of Life Cancer Questionnaire; NR=not reported

10.5 Summary and discussion

There were 95 single cohort studies[78-176] included in the review, the majority of which focussed on patients with NSCLC. The studies provided an abundance of evidence; however, they were predominantly small and heterogeneous, and therefore did not allow appropriate comparison across the studies. Clinical consensus suggests that the data from single cohort studies are difficult to interpret in any meaningful way; however, the data have been included in this report for completeness and to show the extent of the evidence base.

In general terms, NSCLC and SCLC single cohort data support the evidence from RCTs, subgroups of RCTs, pooled analyses and comparative cohorts in that chemotherapy can be effective and tolerated by older patients with lung cancer.

11 RETROSPECTIVE DATA

11.1 Study characteristics

A total of 47 studies[177-224] (reported in 48 references) that reported retrospective data were included in the review. Study characteristics are presented in Table 22.

Thirty-nine studies[177-215,224] included patients with NSCLC, six studies[216-219,222,223] focussed on patients with SCLC and two studies[220,221] recruited mixed populations.

11.1.1 Non-small cell lung cancer

Nineteen studies[177-195,224] that focussed on patients with NSCLC presented information on older patients only and 20 studies[196-215] compared older patients with younger patients. The majority of the studies were conducted in Asia; however, seven studies[177,180,186,195,205,206,209] were conducted in Europe and seven studies[178,191,198,200,207,208,215] in North America, two studies in Brazil[184,204]and one study in South Africa.[214] The studies were conducted over a long period of time, between 1990[196] to 2012.[196] The definition of older was most commonly >70 years or more.

Most studies included patients with stage IIIB/IV NSCLC with an ECOG PS of predominantly 0-1. The majority of studies also included higher proportions of males than females. Only 12 studies[177,182,184-187,189,192,194,197,202,204]recruited less than 100 patients. Two studies were particularly large and included 21,019[179,224] and 21,285[191]patients.

11.1.2 Small cell lung cancer

Four studies[217,218,222,223] that focussed on patients with SCLC compared older with younger patients and two studies[216,219] included only older patients. The definition of older was as low as ≥60 years,[216] but was most commonly >70 years. The studies were relatively small, with the number of patients ranging from 28[216] to 480.[223] Where reported, studies were conducted in Brazil,[216] Japan,[218] Spain,[222] and Canada.[219]

11.1.3 Mixed populations

Two studies[220,221] reported on mixed[221] (NSCLC and SCLC) or undefined[220] (lung cancer) populations of patients with lung cancer. Both were conducted in Japan between 2000[220] and 2009,[221] and both recruited less than 100 patients. Nakao et al[221] defined 'older' as ≥70 and Koyama et al[220] used ≥65 years.

Table 22 Study characteristics, retrospective data

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
NSCLC					
Older patients only					
Das 2012[177]	Retrospective analysis of audit data Multicentre UK 2004-2010	Aged ≥75 Male: 71% ECOG PS: 0/1=86%	Platinum-based doublet=80% Single agent=8.5% Tyrosine kinase inhibitor=11.5% (n=70)	To assess whether the outcomes reported can be reproduced in routine practice. Audit of consecutive NSCLC patients over the age of 75 treated in the North Trent Cancer Network between 2004 and 2010	This analysis suggests that systemic treatment should be considered for patients over the age of 75 and the outcomes for platinum doublet chemotherapy are in keeping with those reported by Quoix et al
El-Gehani 2012[178]	Population-based, retrospective, chart review Single centre Canada 2007-2009	Stage IV EGFR wild-type or unknown Aged ≥70 years	BSC alone=290 Chemotherapy=59 (n=349)	NR	This study demonstrates that in the elderly Albertan population, a significant majority of patients do not receive chemotherapy primarily due to poor PS. This possibly explains the underrepresentation of these patients in lung cancer clinical trials. For those elderly patients who are fit to receive chemotherapy, survival is comparable to the broader population of advanced NSCLC but is hindered by toxicities and subsequent delays in chemotherapy administration. Further interrogation into the risk to benefit ratio determinants are needed
Feliciano 2012[179,224]	Retrospective analysis of SEER-Medicare registry data 2001-2005	Advanced NSCLC Survived ≥30 days after diagnosis Aged ≥66 years Male: NR Stratified into good/poor disability status Poor=1916 Good=19,103	Chemotherapy Poor=13.7% Good=40.8% (n=21,019)	Analysis of factors associated with survival in patients stratified by disability status model	Both groups of patients derived significant survival benefit from chemotherapy but rates of chemotherapy use are much lower in the poor disability status group. The small sample size of patients with poor disability status may help to explain the non-significant benefit of doublet chemotherapy in those patients. There is a need to identify those patients with poor disability status who are likely to benefit most. Future work will attempt to distinguish

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
					patients with declining status over time, compared with those with stable poor disability status
Inal 2012[180]	Retrospective analysis of hospital records Single centre Turkey 2005-2011	Locally advanced or metastatic NSCLC No previous chemotherapy or radiotherapy Aged ≥65 years Male: 88% PS 0-1: Gemcitabine plus cisplatin =57.1% Docetaxel plus cisplatin=56.0% Paclitaxel plus cisplatin=68.0% PS 2-3: Gemcitabine plus cisplatin =42.9% Docetaxel plus cisplatin=44.0% Paclitaxel plus cisplatin=32.0%	Gemcitabine plus cisplatin Docetaxel plus cisplatin Paclitaxel plus cisplatin (n=107)	To evaluate the efficacy and side-effects of cisplatin-based therapy specifically for the elderly	The response rate, median PFS and OS were similar among the three treatment arms. Grade III-IV thrombocytopenia was higher in the gemcitabine plus cisplatin arm, while the gemcitabine plus cisplatin regimen was more favourable than the other cisplatin-based treatments with regard to sensory neuropathy
Irisa 2012[181]	Retrospective analysis of medical records Single centre Japan 2003-2009	Advanced NSCLC Aged >70 years Male: 66% PS: 0–1=79.6%, ≥2=20.4%	Combination=87 (53.7%) Single agent=35 (21.6%) EGFR-TKIs=40 (24.7%) First-line=162 (100%) Second-line therapy=95 (58.6%) Third-line therapy=36 (22.2%) (n=162)	To analyse prognostic factors and validate classic CCI and comorbidity scores in elderly patients with advanced NSCLC treated with chemotherapy or EGFR-TKIs	CCI and the number of comorbidities are independent predictors of survival in elderly patients undergoing systemic chemotherapy including EGFR-TKIs for advanced NSCLC. These factors should be taken into consideration in the pre-treatment assessment as important factors predicting survival outcome
Kim 2012[182]	Retrospective review of medical records Single centre Korea	Advanced NSCLC Aged ≥75 years Male: 77% ECOG PS: 0=8.3%, 1=68.8%, 2-4=22.9%,	Systemic chemotherapy as a first-line therapy Platinum-based doublet=90% Vinorelbine=2%	As the number of elderly patients diagnosed with NSCLC increases, the number of these patients receiving chemotherapy also increases. However, limited	Patients aged ≥75 years with advanced NSCLC may obtain clinical benefit from the administration of platinum-based doublet or single-agent chemotherapy. However,

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
	2002-2008	NR=10	Gemcitabine=4% Docetaxel=4% (n=48)	data exist regarding the use of chemotherapy in advanced NSCLC patients who are aged ≥75 years	oncologists must consider the aspect of safety in relation to the clinical benefits when managing this patient group
Lang 2012[183]	SEER-Medicare 2002-2007	Stage IIIB/IV NSCLC Aged ≥65 years Male: 55%	First-line IV chemotherapy (n=8368)	To describe first-line chemotherapy treatment patterns and costs among elderly advanced NSCLC patients	Platinum-based therapies were found to be administered most frequently in this elderly advanced NSCLC population. Treatment discontinuation and AEs were found to be common. Selected AEs and triplet therapy were associated with higher costs
Linsalmeida 2012[184]	Retrospective analysis of hospital database Single centre Brazil 2008-2012	Metastatic NSCLC Aged ≥60 years Male: NR ECOG PS 0-1=95%	Platinum-based chemotherapy (n=46)	To evaluate the feasibility of platinum rescue scheme in elderly patients with metastatic NSCLC	Lower doses of platinum chemotherapy could reduce toxicity and allow combining the platinum agent in the second line. It was feasible to improve median TTP and OS with platinum in both first and second lines. In this analysis, elderly patients with adenocarcinoma metastatic NSCLC showed a trend toward a higher OS rate in patients undergoing therapy based on carboplatin + paclitaxel followed by carboplatin + gemcitabine, with acceptable toxicities
Passaro 2012[185]	Retrospective analysis	Non-squamous advanced/metastatic NSCLC Aged ≥65 Male: 72% ECOG PS: 0=58%, 1-2=42%	Second-line pemetrexed (n=65)	To evaluate age-related efficacy and safety of second-line pemetrexed	Long-term survival and good tolerability resulted in elderly patients treated with pemetrexed in second-line treatment; in this setting, single agent may be recommended too, in patients with a good ECOG PS, independently from age
Genestreti 2011[186]	Retrospective analysis of hospital records Multicentre (3) Italy 2007-2009	Stage IV NSCLC Aged≥ 70 years Male: 78% PS: 0-1=100%	Carboplatin plus gemcitabine (n=36)	To determine the toxicity and response rates for the combination; secondary end-points were PFS and OS	Carboplatin plus gemcitabine is a safe and active regimen in elderly advanced NSCLC patients with good PS

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
Platania 2011[187]	2006-2009	Previously treated metastatic NSCLC Aged ≥70 years Male: 49% PS: 0-1=95%, 2-3=5%	Erlotinib (n=43)	To evaluate the clinical efficacy and the safety profile of molecularly targeted therapies as a palliative approach in elderly populations affected by advanced thoracic neoplasms	The use of erlotinib after chemotherapy failure in an unselected elderly population affected by NSCLC showed moderate efficacy and a moderate safety profile. However, erlotinib represents a valid option in this setting, but other factors such as biological information, comorbidities and concomitant medications need to be carefully take into consideration in this particular subset of cancer patients
Yi 2011[188]	2005-2009	Advanced NSCLC Aged >70 Male: NR	Cisplatin based=79 (41.4%) Carboplatin based=112 (58.6%) (n=191)	To identify prognostic factors in elderly patients with advanced NSCLC treated with platinum-based doublet chemotherapy	Platinum-based doublet chemotherapy might be effective and tolerable in fit, elderly patients with advanced NSCLC. However, platinum doublet chemotherapy should be considered for selected patients
Zauderer 2011[189]	Retrospective analysis of hospital records Single centre 2008-2009	Metastatic NSCLC Aged ≥70years Male: NR Median KPS=80% (range 60-90%)	Doublet therapy=80% (Platinum doublet 64%) (n=70)	Retrospective evaluation of toxicities and outcomes of elderly patients with metastatic NSCLC to help refine the CGA for further prospective study in lung cancer	Many in this cohort experienced significant toxicity and 44% required hospitalisation. Yet, others tolerated therapy well and possibly derived benefit from platinum treatment. Physician assessment of KPS was not predictive of treatment tolerance. Therefore, we plan to prospectively assess a version of the CGA including factors such as albumin, ADL/IADL dependence, and 'get up and go' functional status to identify who will best tolerate doublet chemotherapy
Chen 2010a[190]	Retrospective analysis of registry data Single centre Taiwan 2000-2006	Advanced NSCLC Aged ≥80 at diagnosis Male: 56.2% ECOG PS: 0-1=41.9%, 1-3=15.2%, 3-4=42.9%	Supportive care only=93 (45.8%) Chemotherapy=17 (8.4%) Palliative radiotherapy=28 (13.8%) EGFR-TKI therapy=65 (32.0%)	To characterise the treatment modalities and outcomes for octogenarians with advanced NSCLC and to investigate the impact of EGFR-TKI on survival	For octogenarians with advanced NSCLC, EGFR-TKI may play an important role in the initial treatment modalities. Further large-scale elderly specific clinical trials for EGFR-TKI as first-line therapy are warranted

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
			(n=203)		
Davidoff 2010[191]	Registry study Multicentre US 1997-2002	Advanced NSCLC (stage IV and IIIB with pleural effusion) Aged ≥66 years Male=55.2% Poor baseline PS indicators, count 0=64.4% 1=19.8% 2=15.9%	No chemotherapy=75% First-line chemotherapy (within 90 days)=26% (n=21,285)	Platinum-doublet chemotherapy regimens have been shown to extend survival in fit patients with advanced NSCLC. This study extends recent population-based analyses focusing on treatment and survival benefit from use of platinum-doublet therapy, and addressing the role of PS	Most elderly patients with advanced NSCLC do not receive chemotherapy, yet there are clear survival benefits, even with controls for age, comorbidity and PS. The benefit of platinum-based doublet regimens is greater than single-agent chemotherapy. Claims-based proxy indicators of poor PS were independent predictors of treatment and merit further exploration
Kim 2010[192]	Retrospective review of hospital records Single centre Japan 1992-1999 2000-2003	NSCLC Initial treatment Aged ≥70 years 1992-1999 Male: 84% ECOG PS: 0-1=93%, 2=7% 2000-2003 Male: 78% ECOG PS: 0-1=91%, 2=9%	1992-1999 Platinum plus second generation=41 (56%) Platinum plus third generation=20 (27%) Non-platinum-based etoposide=3 (4%) Non-platinum-based third generation (mono)=7 (10%) Non-platinum-based third generation (doublet)=2 (3%) 2000-2003 Platinum plus third generation=83 (55%) Non-platinum-based third generation (mono)=29 (20%) Non-platinum-based third generation (doublet)=31 (21%) Gefitinib=6 (4%) Initial treatment n=74 Second-line n=149	Review of data on chemotherapy regimens used in the treatment of elderly NSCLC patients at our institute, and compared regimens and patient outcomes before and after year 2000	In and after the year 2000, chemotherapy regimens changed greatly and survival of elderly patients significantly improved in our institute, and this improvement appears to be attributable mostly to the effect of salvage chemotherapy. These results suggest that even elderly patients should be offered salvage chemotherapy regardless of age, if possible

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
Li 2010[193]	Retrospective review of medical records Single centre China 2000-2007	Stage IIIB and stage IV NSCLC Aged ≥70 years Male=75% ECOG PS cisplatin plus vinorelbine: 0=28%, 1=38%, 2=34% ECOG PS cisplatin plus gemcitabine: 0=24%, 1=40%, 2=36% ECOG PS vinorelbine: 0=23%, 1=46%, 2=31% ECOG PS gemcitabine: 0=23%, 1=41%, 2=36%	Cisplatin plus vinorelbine/gemcitabine Vinorelbine/gemcitabine (n=102)	Compare the efficacy and toxicity of cisplatin-based combination regimens (cisplatin plus vinorelbine or cisplatin plus gemcitabine) with single-agent regimens (vinorelbine or gemcitabine) in these patient populations	Elderly patients ≥70 years with advanced NSCLC can tolerate and benefit from cisplatin-based combination chemotherapy. Cisplatin-based chemotherapy may be considered as an option in the treatment of elderly patients with advanced NSCLC
Uruga 2010[194]	Retrospective analysis of hospital records Single centre Japan 2006-2007	Advanced NSCLC Positive for EGFR mutations Chemo naïve=66% Aged ≥70 years Male: 11% ECOG PS: 0=44.4%, 1=33.3%, 2=11.1%, 3=11.1%	Gefitinib (n=9)	To retrospectively evaluate the efficacy and safety of gefitinib in elderly patients with advanced NSCLC harbouring EGFR mutations	Gefitinib is very efficacious and safe for elderly patients with adenocarcinoma of the lung harbouring an EGFR-TKI mutation. The present data support the use of gefitinib in this particular subgroup
Luciani 2009[195]	Retrospective analysis of hospital records Single centre Italy 1998-2007	Stage III/IV NSCLC No previous chemotherapy Aged ≥70 years Male: 73% PS: 0–1=92.5%, 2=7.5%	Vinorelbine=46.7% Gemcitabine=16.8% Cisplatin plus vinorelbine=11.2% (n=107)	In elderly patients treated with chemotherapy for advanced NSCLC, adequate dose intensity is frequently difficult to achieve. This study assessed the DDI and its impact on clinical outcome	These data suggest that in elderly patients treated with chemotherapy for advanced NSCLC an adequate dose intensity has a significant positive impact on both response rate and OS
Older versus younger patients					
Kawaguchi 2012[196]	Retrospective analysis of Japanese large lung cancer database 1990-2005	Stage IIIB and IV NSCLC Male=74% Receiving chemotherapy Aged 70-74=991 (61%)	Chemotherapy No chemotherapy (n=3976)	Determine whether it is valid and appropriate to use chemotherapy for patients aged ≥80, as well as those aged 70-79	After adjustment for PS, a trend of survival benefit of chemotherapy remained in patients aged ≥80 yearsr

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
		Aged 75-79=648 (48%) Aged ≥80=286 (28%) Not receiving chemotherapy Aged 70-74=626 (39%) Aged 75-79=701 (52%) Aged ≥80=724 (72%) WHO PS (chemotherapy/no chemotherapy) 70-74: 0=14/21%, 1=34/50%, 2=21/20%, 3=18/7%, 4=12/2%, unknown=1/1% 75-79: 0=15/20%, 1=33/45%, 2=19/20%, 3=19/11%, 4=12/3%, unknown=13 2/1% ≥80: 0=14/13%, 1=31/40%, 2=23/22%, 3=20/17%, 4=11/7%, unknown=2/1%			
Tomita 2012[197]	Retrospective evaluation of hospital records Single centre Japan 2004-2010	Previously treated advanced or recurrent NSCLC Aged <70 years: n=27 Aged ≥70 years: n=27 Male: 70% <70 ECOG PS: 0=29.6%, 1=63.0%, 2=7.4% >70 ECOG PS: 0=29.6%, 1=59.3%, 2=11.1%	S-1 (n=54)	The efficacy and safety of S-1 monotherapy for previously treated NSCLC was evaluated with respect to age (<70 years as the younger group and ≥70 years as the older group), and the efficacy of S-1 monotherapy was compared between histopathological types (adenocarcinoma vs. non-adenocarcinoma)	S-1 monotherapy may be equally effective and tolerated in patients <70 years and those ≥70 years. Additionally, adenocarcinoma may have a higher disease control rate than non-adenocarcinoma
Tsao 2012[198]	Retrospective subgroup analysis of Biomarker-Integrated Approaches of	Chemo-refractory NSCLC Aged <65: n=159 Aged 65-70: n=41	Erlotinib Erlotinib-bexarotene Vandetanib Sorafenib	To retrospectively evaluate the efficacy and safety/toxicity results among the four treatment arms of the BATTLE study for	Fit elderly NSCLC patients should be considered for salvage targeted therapy. In this subset of patients, older men seem to have significant

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
	Targeted Therapy for Lung Cancer Elimination (BATTLE) RCT Single centre US	Aged 70-75: n=32 Aged≥75: n=23 Male: 54% <65 ECOG PS: 0=10%, 1=75%, 2=15% <70 ECOG PS: 0=6%, 1=81%, 2=13% <75 ECOG PS (n=232): 0=9%, 1=77%, 2=15% >65 ECOG PS (n=96): 0=7%, 1=80%, 2=13% >70 ECOG PS (n=55): 0=9%, 1=77%, 2=14% >75 ECOG PS: 0=0, 1=83%, 2=17%		elderly population subgroups (defined here as age ≥65, ≥70, and ≥75 years) compared with younger patients (<65, <70, <75 years), and explore differences in biomarker profiles	clinical benefit from certain agents. Tumor biomarker analysis demonstrates sex and age variations, and is hypothesis generating
Tsubata 2012[199]	Retrospective analysis of hospital records Matched cohort Single centre Japan 2004-2009	NSCLC Aged <70: n=56 Aged ≥70: n=56 Male: 71.4% <70 ECOG PS: 0=73.2%, 1=19.6%, 2=7.1% ≥70 ECOG PS: 0=73.2%, 1=23.2%, 2=3.6%	<70 / ≥70 Platinum doublet=36 (64.3%)/22 (39.3%) Non-platinum doublet=10 (17.9%)/8 (14.3%) Single agent=6 (10.7%) / 15 (26.8%) EGFR-TKI=4 (7.1%) / 11 (19.6%) (n=112)	The number of elderly patients with NSCLC is increasing in Japan. The study compared the safety and efficacy of chemotherapy in elderly and non-elderly NSCLC patients who received chemotherapy at Shimane University Hospital	This retrospective study suggests that elderly patients can safely receive effective chemotherapy similar to non-elderly patients under careful observation and management
Kim 2011[201]	Retrospective review of medical records 2002-2010	Stage IIIB or IV NSCLC Aged ≥70: n=221 Aged <70: n=58 Male: NR	Gefitinib (n=279)	To evaluate the efficacy and safety of gefitinib treatment in elderly patients with advanced NSCLC	The efficacy and tolerability of gefitinib in elderly patients with NSCLC were comparable to non-elderly patients, suggesting that gefitinib should be considered as a reasonable treatment option in elderly patients with advanced NSCLC
Ansari 2011[200]	Retrospective analysis Phase III RCTl Multi-centred USA	Stage IIIB or IV NSCLC Chemo-naïve Aged <70: n=797 Aged 70–74: n=188 Aged 75–79: n=109 Aged ≥80: n=41	Gemcitabine plus carboplatin: <70=260 (32.6%) 70–74=65 (34.6%) 75–79=38 (34.9%) ≥80=16 (39.0%)	Sufficient data are currently unavailable to assist in defining suitable regimens for patients ≥70 years with advanced NSCLC	Based on the similarity of patient outcomes across age groups, doublet chemotherapy is feasible among carefully selected elderly patients with good PS

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
	2000-2005	<70 male=59.8% 70–74 male=62.2% 75–79 male=63.3% ≥80 male=61.0% <70 ECOG PS: 0=38 4%), 1=60.9%, 2=0.5% 70–74 ECOG PS: 0=33.5%, 1=66.5%, 2=0.0 75–79 ECOG PS (n=39): 0=35.8%, 1=61.5, 2=0.0 ≥80: 0=46.3%, 1=53.7%, 2=0.0	Gemcitabine plus paclitaxel: <70=270 (33.9%) 70–74=57 (30.3%) 75–79=35 (32.1%) ≥80=15 (36.6%) Paclitaxel plus carboplatin: <70=267 (33.5%) 70–74=66 (35.1%) 75–79=36 (33.0%) ≥80=10 (24.4%) (n=1135)		
Masago 2011[202]	Retrospective analysis of hospital records Single centre Japan 2003-2010	Advanced NSCLC Aged <75: n=60 Aged ≥ 75: n=20 Male: 40% PS: 0-1=87.5%, ≥2=12.5%	Gefitinib (n=80)	To analyse the factors independent of EGFR gene mutations that affect the PFS of patients with advanced NSCLC after gefitinib therapy	The study showed that EGFR mutations and age ≥75 years were good predictive factors for PFS after gefitinib therapy, suggesting that first-line gefitinib treatment for older patients is efficacious regardless of EGFR mutational status
Wu 2010[203]	Retrospective review of previously published data Japan 1998-2005	NSCLC Failed previous chemotherapy Aged <70: n=293 (64%) Aged ≥70: n=168 (36%) Male: 64% <70 PS: 0=0.7%, 1=39.6%, 2=56.7%, 3=2.7%, 4=0.3% ≥70 PS: 0=0.0, 1=41.1%, 2=57.7%, 3=1.2%, 4=0.0	Docetaxel alone: n=185 Docetaxel plus ifosfamide: n=50 Docetaxel plus gemcitabine: n=36 Docetaxel plus tegafur+uracil: n=24 Gemcitabine alone: n=20 Gemcitabine plus tegafur+uracil: n=45 Gemcitabine plus vinorelbine: n=17 Gefitinib alone: n=63 Gefitinib plus vinorelbine: n=21 (n=461)	To find out whether there are differences in tolerance and efficacy between young and old patients receiving salvage chemotherapy or salvage targeted therapy with EGFR-TKI	There were no differences in the efficacy of salvage chemotherapies and EGFR-TKI therapy, in terms of response rate, control rate, and OS, in elderly and non-elderly patients, and the therapies had acceptable toxicities. Age itself should not preclude patients with NSCLC from second-line salvage therapy

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
Murialdo 2009[204]	Retrospective review of clinical records Single centre Brazil 2001-2005	Stage III/IV NSCLC Chemotherapy naïve Aged<70: n=56 Aged ≥70: n=27 All male: 82% <70 male: 81.5% ≥70 male: 83.9% <70 PS: 0=41.1%, 1=46.4%, >2=5.3%, NA=7.1% ≥70 PS: 0=37.0%, 1=48.1%, >2=0, NA=14.8%	Carboplatin plus gemcitabine (n=83)	Retrospective evaluation of 83 chemotherapy-naïve patients treated with carboplatin and gemcitabine to evaluate the efficacy and tolerability of the regimen. In addition, whether there was any difference in efficacy and tolerability in the elderly group	Data confirm that carboplatin-gemcitabine is an active and well-tolerated regimen in advanced NSCLC and could be investigated in elderly patients
Provencio 2009[205]	Achilles Study Retrospective analysis of the database of six clinical trials Multicentre Spain 1998-2005	Stage IIIB (with pleural effusion) or IV NSCLC Aged <70=1,373 (83%) Aged ≥70=280 (17%) Male: 85.4%	Different doublet combinations (n=1653)	To discern whether clinical characteristics, toxicity, response rate, treatment and survival differ between patients aged ≥70 and younger patients	The oldest age group represented a small percentage of all patients included in clinical and pharmacogenetic trials. Although this might indicate bias when interpreting the results, age is not a contraindication to the treatment of the 'fit' elderly. Patients with good PS can be treated with standard doublets. We believe that special attention should be paid to cases with high risk of neutropenia. Research in this population should now be aimed at finding more selective treatments, based on the genetic differences that older patients have
Yildirim 2009[206]	Retrospective review of medical records Single centre Turkey 2004-2008	NSCLC Aged <75: n=28 (70%) Aged ≥75: n=12 (30%) Male: 87.5%	Chemotherapy first-line cisplatin plus vinorelbine/gemcitabine= 22 (61.0%) Carboplatin plus vinorelbine=8 (22.5%) Single agent=6 (16.5%) Second-line Docetaxel=17 (42.5%) Radiotherapy=15	NSCLC is a disease that affects the elderly. However, most patients aged >70 years are less likely to receive standard therapy than their younger counterparts and the aim of the present study was to determine age-dependent variation in efficacy	Patients aged >75 years appear to deserve the same standard therapy for NSCLC as that given to younger cases

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
			(37.5%) (n=187)		
Altundang 2007[207]	Retrospective analysis of hospital records Matched cohort Single centre USA 1997-2004	NSCLC Chemotherapy-naïve Aged <80=92 Aged ≥80=46 <80 male: 50% ≥80 male: 50% <80 ECOG PS: 0-1=77.2%, 2-3=17.4%, NA=5.4% ≥80 ECOG PS: 0-1=58.7%, 2-3=34.8%, NA=3 (6.5%)	Chemotherapy Platinum doublets in <80=73/92 (79%) ≥80=20/46 (43%) (n=138)	Because the life expectancies of 80-year-old men and women are 87.3 years and 89.0 years, respectively, advanced NSCLC not only causes morbidity but may also rob them of many years of meaningful life. Therefore, it is important to learn whether there is a role for chemotherapy in these patients	The data indicate that selected patients aged ≥80 years may tolerate and benefit from chemotherapy, and prospective evaluation of these patients is indicated
Pepe 2007[208]	Retrospective analysis of JBR.10 Multicentre US and Canada 1994-2001	Stage IB or stage II NSCLC Aged ≤65: n=327 Aged >65: n=155 ≤65 male: 68.0% >65 male: 59.7% ≤65 PS: 0=56.7%, 1=43.3% >65 PS: 0=35.8%, 1=64.2%	Vinorelbine and cisplatin: ≤65=165, >65=77 Observation: ≤65=162, >65=78 (n=482)	To evaluate the influence of age on survival, adjuvant chemotherapy delivery, and toxicity in National Cancer Institute of Canada Clinical Trials Group study JBR.10	Despite elderly patients' receiving less chemotherapy, adjuvant vinorelbine and cisplatin improves survival in patients aged >65 years with acceptable toxicity. Adjuvant chemotherapy should not be withheld from elderly patients
Pentheroudakis 2006[209]	Retrospective analysis of hospital records centres Greece 1992-1999	Squamous lung cancer Aged ≤70: n=172 Aged >70: n=64 Male: 8.5% PS 2 or 3=20% and 30% (sig. different)	Chemotherapy: ≤70=82%, >70=63% Radiotherapy (incl. adjuvant): ≤70=48%, >70=29% (n=236)	To determine the epidemiological, management and outcome characteristics of such patients aged >70 years and compare them with a younger patient cohort from the same population	Older patients are less fit, develop bony but not brain metastases, receive antineoplastic treatment less often, and survive as long as younger patients. Squamous lung carcinoma may follow a more indolent clinical course in the elderly, a hypothesis worth validating by case cohort studies and molecular profiling, with the hope of rationally individualising patient treatment
Chen 2005[210]	Retrospective analysis of three	Stage IIIb or IV NSCLC Chemotherapy-naïve	Vinorelbine plus gemcitabine	To determine the appropriate chemotherapy regimen for	Advanced age alone should not preclude chemotherapy. New single-

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
	clinical trials[225,226] Taiwan 1998-2002	n=40 Aged <70: n=23 Aged ≥70: n=17 Male: 80% <70 ECOG PS: 1=56.5%, 2=43.5%, ≥70 ECOG PS: 1=35.3%, 2=64.7%	(n=40)	inoperable, chemotherapy-naïve NSCLC in elderly patients	agent drugs, and non-platinum-based or platinum-based doublets, can all be considered as appropriate treatment for selected fit elderly patients with advanced NSCLC
		Aged <70: n=46 Aged ≥70: n=44 Male: 76% <70 ECOG PS: 1=56.5%, 2=43.5% ≥70 ECOG PS: 1=61.4%, 2=38.6%	Paclitaxel plus carboplatin vs paclitaxel plus gemcitabine (n=90)		
		Aged <70: n=70 Aged ≥70: n=70 Male: 73% <70 ECOG PS: 0=21.4%, 1=37.2%, 2=29 (41.4%) ≥70 ECOG PS: 0=8.6%, 1=41.4%, 2=50%	Vinorelbine plus cisplatin vs paclitaxel plus cisplatin therapy (n=140)		
Hotta 2005[211]	Retrospective analysis of hospital records Multicentre Japan 2000-2003	NSCLC Aged <75: n=258 Aged ≥75: n=92 Male: 67% <75 PS: 0-1=66%, 1-2=34% ≥75 PS: 0-1=58%, 1-2=42%	Gefitinib (n=350)	To evaluate the influence of aging on safety and efficacy of gefitinib treatment in patients with NSCLC	Treatment with gefitinib appeared to be as safe and effective in elderly patients (aged ≥75 years) with NSCLC as in non-elderly patients
Kaneda 2004[212]	Retrospective review of hospital records Single centre Japan	Stage IIIB or IV NSCLC Aged <69: 74% Aged ≥70: 27% Male: 37%	Gefitinib (n=101)	To identify the potential predictive features associated with the response and survival benefit of gefitinib administration	Gefitinib provided clinical benefit for the following factors 'female', 'good PS' and 'non-smoker'. A low smoking index is reported as a novel predictive

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
	1998-2003	PS: 0=15%, 1=62%, 2=17%, 3=7%			prognostic factor following a single regimen of gefitinib
Langer 2003[214]	Retrospective analysis of ECOG 5592[227] Multi-centred North America and South Africa 1993-1994	Stage IIIB or IV NSCLC Chemotherapy-naïve Aged <70: n=488 Aged ≥70: n=86 Male: 64% ≥70 ECOG PS:0=33%, 1=67% <70 ECOG PS: 0=26%, 1=74%	Cisplatin plus etoposide/paclitaxel (n=574)	To systematically examine whether advanced age compromises outcome or exacerbates toxicity	Response rate, toxicity, and survival in fit, elderly NSCLC patients receiving platinum-based treatment appear to be similar to those in younger patients, although patients aged ≥70 years have more comorbidities and can expect more leukopenia and neuropsychiatric toxicity. Advanced age alone should not preclude appropriate NSCLC treatment
Rocha Lima 2002[215]	Retrospective analysis of two RCTs (CALGB 8931 and CALGB 9130) Multicentre US	CALGB 8931 Extensive stage IIIB or stage IV NSCLC No prior chemotherapy Aged <50=22 (8%) Aged 50–59=77 (29%) Aged 60–69=123 (46%) Aged 70–79=31 (16%) Male=NR ECOG PS: 0-1=100% CALGB 9130 Stage IIIA/IIIB NSCLC No prior chemotherapy Aged <50=29 (11%) Aged 50–59=69 (28%) Aged 60–69=98 (39%) Aged 70–79=54 (22%) Male=NR ECOG PS: 0-1=100%	CALGB 8931 Vinblastine-cisplatin plus hydrazine sulphate Vinblastine-cisplatin plus placebo n=253 CALGB 9130 Vinblastine-cisplatin followed by thoracic radiation plus carboplatin Vinblastine-cisplatin followed by thoracic radiation (n=250)	The results from two National Cancer Institute-approved cooperative group trials (Cancer and Leukemia Group B trial 8931 [CALGB 8931] and CALGB 9130) were analysed retrospectively to determine the participation, tolerance of treatment, and outcome of patients aged 70 years	No patients aged 80 were entered on either trial despite their potential eligibility. Patients in the oldest cohort showed no negative impact of age on treatment tolerance, response to treatment, or survival. The aggregate clinical judgment of patients and physicians can identify septuagenarians who should not be denied active consideration for aggressive management of their advanced NSCLC
Vansteenkiste 2003[213]	Retrospective analysis of an RCT	Stage IIIB/IV NSCLC Aged <65: n=88 Aged ≥65: n=81 Male=NR KPS E/60%	Cisplatin plus vindesine Gemcitabine (n=169)	We previously reported that treatment of patients with symptomatic advanced NSCLC with single agent gemcitabine resulted in a superior clinical benefit response rate compared	Both gemcitabine and the cisplatin plus vindesine regimens yield a symptom control rate much higher than expected by the objective tumour response rate. Gemcitabine is equally effective in controlling 'disease-

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
				with cisplatin-based combination chemotherapy. We now report the detailed individual symptom control analysis, and the influence of cisplatin-use, age, PS and duration of treatment	specific' symptoms, but superior in controlling 'constitutional' symptoms. Most of the symptom control was achieved during the first 3 cycles of treatment, with some further improvement thereafter in the gemcitabine arm
SCLC					
Older patients only					
Almeida 2012[216]	Retrospective analysis of registry data Brazil 2005-2010	Extensive neuroendocrine SCLC Extensive staging Aged ≥60 Male: 75% ECOG PS: 0-1=89%	Etoposide plus cisplatin (n=28)	To examine the efficacy and toxicity of etoposide/cisplatin therapy for elderly patients, retrospectively	Etoposide/cisplatin scheme to treat extensive NSCLC showed to be safe and effective with low toxicity for Brazilian elderly patientss. These results are in accordance with the literature
Fisher 2012[219]	Retrospective population-based study Canada 2004-2008	SCLC Aged 75-79 years Aged 80+ years Male: 57% 75-79 ECOG PS: 0-2=46%, 3-4=39%, missing=15 ≥80 ECOG PS: 0-2=32%, 3-4=47, missing=22%	Carboplatin plus etoposide=55 (47%) Cisplatin plus etoposide=36 (31%) Oral etoposide=25 (21%) Cyclophosphamide plus Adriamycin and vincristine=1 (1%) (n=171)	To assess the uptake and tolerance of chemotherapy among patients aged ≥75 years diagnosed with SCLC in years 2004–2008 in Alberta, Canada, and to assess their survival	Results suggest that a significant proportion of elderly patients are able to tolerate chemotherapy and receive a survival benefit from it while those who experience toxicity may receive a survival benefit from a reduction in chemotherapy dose as opposed to stopping treatment
Older versus younger patients					
Andrea 2012[217]	Retrospective review of hospital records Single centre 2003-2010	SCLC Aged <65: 54 (56.25%) Aged ≥65: 42 (43.75%) Male: NR	Carboplatin plus etoposide (n=96)	To evaluate whether there are differences in OS according to the age (comparing >65 vs <65 years), in patients treated with the same scheme of chemotherapy	The hybrid scheme carboplatin 300 mg/m^2 IV on day 1, with etoposide 100 mg/m^2 per day (IV on day 1 and oral days 2 to 5), provides an acceptable OS, without significant differences comparing older and younger than 65 years old, both in limited and extended stage

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
Asai 2012[218]	Retrospective study Single centre Japan 2006-2009	Refractory relapsed SCLC (one or two previous treatments) Aged <70: n=18 Aged ≥ 70: n=18 <70 male: 75% ≥70 male: 100% <70 ECOG PS: 0=43.8%, 1=56.2% ≥ 70 ECOG PS: 0=10%, 1=90%	Amrubicin (n=36)	To examine the efficacy and safety of amrubicin for elderly patients with refractory relapsed SCLC as second or third-line chemotherapy	Amrubicin could be one of the effective tools in the treatment of elderly patients with refractory relapsed SCLC as third-line chemotherapy, and the recommended dose is 30 mg/m^2 for three consecutive days
Safont 2009[222]	Retrospective analysis of the Spanish Lung Cancer Group RCT 15 centres Spain 1994-1998	SCLC: limited disease /extensive disease <70=54/46% ≥70=39/61% Aged <70: n=338 Aged ≥70: n=64 Male: NR <70 KPS: 60-80=50%, 80-100=50% ≥70 KPS: 60-80=64%, 80-100=36%	Etoposide plus cisplatin High-dose epirubicin plus cisplatin (n=402)	To evaluate differences concerning efficacy, toxicity, TTP and OS according to age (younger vs older than 70 years)	Age was likely to be a negative prognostic factor for OS of elderly patients with limited disease. It also seemed to be related to a greater dose reduction, which may explain that toxic episodes and delays occurred more frequently in the younger patients receiving the full scheduled dose. However, the definitive reason to explain this could not be established due to the characteristics of our analysis
Garst 2005[223]	Retrospective analysis of five trials Multicentre	Relapsed SCLC Aged <65: n=319 Aged ≥65: n=161 Male: NR <65 PS: 0=25%, 1=53%, 2=22%, unknown=<1% <65 PS: 0=22%, 1=60%, 2=18%, unknown=0	Topotecan (n=480)	To investigate the safety and efficacy of topotecan (an approved treatment for relapsed SCLC) in older patients	This is the first demonstration of the safety and efficacy of topotecan in older patients with recurrent SCLC. Future studies are needed to fully characterise the role of topotecan in the treatment of older patients
Mixed or undefined populations					
Koyama 2010[220] (abstract only)	Retrospective analysis Single Centre	Lung cancer Aged ≥65: n=49 Aged <65: n=36	Chemotherapy (n=85)	To clarify the difference of QoL profile during chemotherapy between elderly patients and	Continuation of chemotherapy for elderly patients with lung cancer markedly deteriorated physical QoL.

Study	Study summary	Population summary	Intervention, n	Purpose	Author conclusions
	Japan 2000-2008			young patients	KPS could be useful to estimate functional QoL in case that QoL data are missing
Nakao 2010[221]	Retrospective analysis of hospital records Single centre Japan 2003-2009	Stage III/IV NSCLC: n=21 SCLC: n=30 Aged <70 years: n=29 Aged ≥70 years: n=22 <70 male: 72% ≥70 male: 86% <70 ECOG PS: 0=17%, 1=66%, 2=17%, 3=0 ≥70 ECOG PS: 0=9%, 1=64%, 2=23%, 3=5%	Amrubicin (n=51)	Evaluates the toxicity and effect of amrubicin especially in elderly patients with previously treated lung cancer	Amrubicin monotherapy might be equally tolerated by elderly and younger patients. Further studies are needed to investigate the benefit of amrubicin monotherapy among elderly patients with previously treated lung cancer

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; BSC=best supportive care; PS=performance status; SEER=Surveillance, Epidemiology and End Results; PFS=progression-free survival; OS=overall survival; TKI=tyrosine kinase inhibitor; CCI=Charlson Comorbidity Index; QoL=quality of life; CGA=comprehensive geriatric assessment; AE=adverse event; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; DDI=delivered dose intensity; RCT=randomised controlled trial; WHO=World Health Organisation; S-1=tegafur gimeracil, and oteracil; IV=intravenous; NR=not reported; TTP=time to progression; KPS=Karnofsky performance status;

11.2 Efficacy evidence

Outcomes relating to PFS/TTP, OS and ORR reported in retrospective data studies are presented in Table 23 which details outcomes for studies that reported data solely for older patients, or compared results between older and younger patients.

11.2.1 Non-small cell lung cancer

Twenty studies[177,180,182,184-187,193,194,197,198,200-205,207,211,214] reported PFS/TTP. The lowest median PFS for older patients was 2.1 months,[184] the highest PFS for older patients was 18.8 months.[202] Only five studies[184,187,197,198,201] reported a PFS gain of ≤3 months.

Overall survival was reported by 29 studies.[177,178,180,182,186-188,190-201,203-207,209-211,214,215] The lowest median OS was 1.9 months,[190] and the highest was 24.4 months.[199] Fifteen studies[178,186,188,193-195,197,199,201,204,206,207,209,210,215]reported an OS gain of ≥10 months.

Objective response rates were reported by 23 studies.[177,180-182,185-188,193-195,197,200,203-205,207,209-212,214,215] The lowest ORR was reported by Tomita et al[197] (4.8%) and the highest was reported by Chen et al[210] (88%).

11.2.2 Small cell lung cancer

Two studies[223,222] reported median PFS rates. Garst et al[223] reported 2.5 months for patients aged <65 and 2.9 months for patients aged >65. Safont et al[222] reported 8.3 months for patients aged <70 and 7.4 months for patients aged ≥70 years.

Five studies[216,217,219,222,223] reported results for OS. The lowest median OS was 3 months for patients aged 75–79,[219] and the highest reported OS was 10.8 months[222] for younger patients aged <70 years. Two studies[216,217] reported a 10-month OS for older patients.

Objective response rates were reported in four studies,[216,218,222,223] which ranged from 12.5%[218] for patients aged ≥70 receiving second-line amrubicin to 84%[222] for patients aged ≥70 years receiving epirubicin plus cisplatin.

11.2.3 Mixed populations

One study[221] presented outcomes for mixed populations of patients with lung cancer. Nakao et al[221] presented oucomes for PFS, OS and ORR. The lowest PFS was 1.6 months for both older and younger patients with NSCLC, and the highest was 5.4 months for younger patients with SCLC. Overall survival ranged from 5.9 to 13.2 months for those with NSCLC and ORR ranged from 0% for patients aged ≥70 with NSCLC to 61.5% for patients aged <70 years with SCLC.

Table 23 Survival outcomes, retrospective data

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
NSCLC							
Older patients only							
Das 2012[177]	NR	7	NA	8 (range 2 to 35)	NA	34	NA
El-Gehani 2012[178]	BSC only	NR	NR	2.3	NR	NR	NR
	Chemotherapy	NR		11.6		NR	
Feliciano 2012[179,224]	Poor disability status No chemotherapy vs chemotherapy	NR	NR	NR	0.53 (0.46 to 0.61) p<0.001	NR	NR
	Good disability status No chemotherapy vs chemotherapy	NR	NR	NR	0.43 (0.42 to 0.44) p<0.001	NR	NR
Inal 2012[180]	Gemcitabine	5.0 (1 to 15)	P>0.05	7.1 (1 to 29)	P>0.05	36.7	P>0.05
	Docetaxel plus cisplatin	5.0 (1 to 23)		7.4 (1 to 58)		41.7	
	Paclitaxel plus cisplatin	5.0 (1 to 27)		7.1 (2 to 32)		33.3	
Irisa 2012[181]	First-line combination	NR	NR	NR	NR	24.1	NR
	First-line single agent	NR	NR	NR	NR	14.2	NR
	First-line EGFR-TKIs	NR	NR	NR	NR	40.0	NR
	Second-line combination	NR	NR	NR	NR	9.5	NR
	Second-line single agent	NR	NR	NR	NR	9.3	NR
	Second-line EGFR-TKIs	NR	NR	NR	NR	25.8	NR
	Third-line combination	NR	NR	NR	NR	11.1	NR
	Third-line single agent	NR	NR	NR	NR	15.8	NR
	Third-line EGFR-TKIs	NR	NR	NR	NR	37.5	NR
Kim 2012[182]	≥75	5.7 (4.93 to 6.47)	NA	8.2 (4.44 to 11.96)	NA	33.3	NA
Linsalmeida 2012[184]	Carboplatin plus gemcitabine (4) Adenocarcinoma	2.1 2.7	NR	NR	NR	NR	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
	Squamous cell carcinoma						
	Carboplatin plus paclitaxel (39) Adenocarcinoma (18) Squamous cell carcinoma (21)	 2.9 2.9	NR	NR	NR	NR	NR
Passaro 2012[185]	All	4.1 (2.9 to 5.4).	NA	NR	NA	43.1	NA
	65-74	4.4	p=0.7	NR	NR	NR	NR
	≥75	3.5		NR		NR	
Genestreti 2011[186]	Carboplatin plus gemcitabine	5 (4 to 7)	NA	11 (8 to inf.)	NA	22	NA
Platania 2011[187]	≥70 years	3 (0.4 to 28.4)	NA	8.4 (0.7 to 43.6)	NA	14	NA
Yi 2011[188]	Chemotherapy	NR	NA	10 (8.3 to 11.7)	NA	40.3	NA
Zauderer 2011[189]	Chemotherapy	NR	NA	NR	NA	NR	NA
Chen 2010[190]	Supportive care	NR	NR	1.9	Between supportive care and the three other groups combined p<0.001 No difference between the three treatment groups (p=0.76)	NR	NR
	Chemotherapy	NR		5.1		NR	
	Palliative radiotherapy	NR		3.8		NR	
	EGFR-TKI therapy	NR		7.3		NR	
Davidoff 2010[191]	No chemotherapy	NR	NR	2.5	p<0.001	NR	NR
	Chemotherapy	NR		7.1		NR	
Kim 2010[192]	1992-1999	NR	NR	6.7	NA	NR	NR
	2000-2003	NR	NR	8.1	NA	NR	NR
Li 2010[193]	Combination therapy	7.9 (5.62 to 10.18)	p=0.03	11.1 (9.24 to 12.96)	p=0.06	46	p=0.03
	Single therapy	5.8 (4.78 to 6.82)		8.9 (7.68 to 10.14)		25	
Uruga 2010[194]	Gefitinib	13.0	NA	17.2	NA	66.7	NA

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
Luciani 2009[195]	Total	NR	NA	9 (6.77 to 11.22)	NA	42	NA
	<80% dose intensity	NR	NR	7 (3.5 to 10.4)	p<0.0001	33	p<0.01
	>80% dose intensity	NR		10 (6.7 to 13.2)		55	
Older versus younger patients							
Kawaguchi 2012[196]	70-74 chemotherapy	NR	NR	6.61	p<0.001	NR	NR
	70-74 no chemotherapy	NR	NR	2.57		NR	NR
	75-79 chemotherapy	NR	NR	5.40	p<0.001	NR	NR
	75-79 no chemotherapy	NR	NR	2.76		NR	NR
	≥ 80 chemotherapy	NR	NR	4.18	p=0.006	NR	NR
	≥80 no chemotherapy	NR	NR	2.60		NR	NR
Tomita 2012[197]	<70 (n=23)	3.5	p=0.115	15.1	p=0.187	13.0	p=0.609
	≥70 (n=21)	2.5		6.0		4.8	
Tsao 2012[198]	Age <65 Age >65	NR	p>0.05	NR	p>0.05	NR	p>0.05
	Age <70 Age >70	NR	p>0.05	NR	p>0.05	NR	p>0.05
	Age <75 Age >75	NR	p>0.05	NR	p>0.05	NR	p>0.05
	Men Age <65 Age >65	1.8 vs 2.8	p=0.0068	NR	0.62 (0.43 to 0.88) p=0.008	NR	NR
	Men Age <70 Age >70	1.84 vs 2.80	p=0.09	7.6 vs 11.3	p=0.31	NR	NR
	Women Age <70 Age >70	NR	NR	6.50 vs 9.03	p=0.57	NR	NR
	Women Age <75 Age >75	NR	NR	6.28 vs 9.00	p=0.43	NR	NR
Tsubata 2012[199]	<70	NR	NR	18.6	p=0.33	NR	NR
	≥70	NR	NR	24.4		NR	NR
Kim 2011[201]	<70	2.9	NR	9.7	NR	NR	Response rate was slightly better in elderly patients
	≥70	3.9		10.5		NR	
Ansari 2011[200]	Aged <70	4.5 (4.2 to 5.1)	NR	8.6 (7.9 to 9.5)	NR	30.1 (26.9 to 33.4)	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
	Aged 70–74	4.3 (3.5 to 5.6)		8.8* (7.5 to 10.3)		28.2 (21.9 to 35.2)	
	Aged 75–79	4.5 (4.1 to 5.1)		6.5* (5.6 to 9.3)		24.8 (17.0 to 34.0)	
	Aged 80+	5.6 (3.7 to 6.9)		7.9 (6.3 to 10.3)		24.4 (12.4 to 40.3)	
Masago 2011[202]	<75	4.7 (2.6 to 10.2)	p=0.0399	NR	NR	NR	NR
	≥75	18.8 (2.7 to 32.0)		NR		NR	
Wu 2010[203]	<70 all therapies	4.1 (3.6 to 4.6)	p=0.08	9.3 (8.0 to 10.7)	p=0.5	24	p=0.2
	≥70 all therapies	4.4 (3.6 to 5.2)		8.3 (6.7 to 9.9)		19	
Murialdo 2009[204]	<70	7	p=0.28	11	p=0.25	44.6	p=0.46
	≥70	5		6.5		39.3	
Provencio 2009[205]	<70	4.4	p=0.61	7.6	p=0.49	33.3	p>0.05
	≥70	4.5		7.5		32.8	
Yildirim 2009[206]	<75	NR	NR	13	p=0.06	NR	NR
	≥75	NR		10		NR	
Altundang 2007[207]	<80	3.91 (3.35 to 5.45)	0.63 (0.39 to 1.02) p=0.06	9.8 (7.72 to 13.4)	p=0.43	47	NR
	≥80	5.55 (3.88 to 8.02)		10.7 (6.87 to 18.2)		41	
Pepe 2007[208]	≤65 all	NR	NR	NR	0.77 (0.57 to 1.03)	NR	NR
	>65 all	NR		NR	p=0.08	NR	
	≤65 observation	NR	NR	NR	0.77 (0.54 to 1.09)	NR	NR
	≤65 chemotherapy	NR		NR	p=0.14	NR	
	>65 observation	NR	NR	NR	0.61 (0.38–0.98)	NR	NR
	>65 chemotherapy	NR		NR	p=0.04	NR	
Pentheroudakis 2006[209]	≤70	NR	NR	18	p=0.02	33	p=0.8
	>70	NR		17		32	
Chen 2005[210]	Vinorelbine plus-Gemcitabine <70	NR	NR	12.5	p=0.213	60.9	p=0.086
	Vinorelbine plus-Gemcitabine ≥ 70	NR		10		88	
	Paclitaxel plus-carboplatin vs paclitaxel plus-gemcitabine <70	NR	NR	11.6	p=0.284	30.4	p=0.173
	Paclitaxel plus-carboplatin vs paclitaxel-plus-gemcitabine ≥70	NR		9.5		50	
	Vinorelbine plus cisplatin vs paclitaxel	NR	NR	15	p=0.598	38.6	p=0.18

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
	plus cisplatin therapy <70						
	Vinorelbine plus cisplatin vs paclitaxel plus cisplatin therapy ≥70	NR		11.7		38.6	
Hotta 2005[211]	Gemcitabine <75	3.8 (0.1 to 23.9)	NR	9.3 (0.1 to 35.2)	NR	21.3	NR
	Gemcitabine ≥75	3.2 (0.11 to 21.2)		7.6 (0.1 to 21.2)		17.4	NR
Kaneda 2004[212]	<70	NR	NR	NR	p=0.917	17.6	p>0.05
	≥70	NR		NR		25.9	
Langer 2002[214]	<70	4.37	p=0.29	9.05	p=0.29	22 (18 to 25)	p=0.67
	≥70	4.30		8.53		23 (15 to 34).	
Rocha Lima 2002 (CALGB 8931)[215]	<50	NR	NR	7.6	p=0.63	31.8	p=0.271
	50–59	NR		9.3		32.5	
	60–69	NR		7.7		29.3	
	70–79	NR		5.7		16.3	
Rocha Lima 2002 (CALGB 9130)[215]	<50	NR	NR	10.9	p=0.84	58.6	p=0.329
	50–59	NR		12.7		71.0	
	60–69	NR		15.4		62.2	
	70–79	NR		13.4		55.6	
SCLC							
Older patients only							
Almeida 2012[216]	Etoposide plus cisplatin	NR	NR	10	NR	16.6	NR
Fisher 2012[219]	Chemotherapy: completed (75–79)	NR	NR	3	p=0.21	NR	NR
	Chemotherapy: completed (≥80)	NR		7		NR	
Older versus younger							
Andrea 2012[217]	Carboplatin plus etoposide aged <65	NR	NR	8.23 (<1 to 24)	NR	NR	NR
	Carboplatin plus etoposide aged ≥65	NR		10 (1 to 22)		NR	
Asai 2012[218]	Amrubicin second line <70	NR	NR	NR	NR	40.0	p=0.314
	Amrubicin second line ≥70	NR		NR		12.5	
	Amrubicin third line	NR	NR	NR	NR	37.5	p=0.664

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) P value	Median OS (95% CI) Months	Hazard ratio (95% CI) P value	ORR % (95% CI)	Hazard ratio (95% CI) P value
	<70						
	Amrubicin third line ≥70	NR		NR		50.0	
Garst 2005[223]	<65 years	2.5 (2.1 to 2.7)	NR	4.9 (4.9 to 5.9)	NR	15	NR
	≥65 years	2.9 (2.6 to 3.4)		6.7 (5.4 to 7.4)		14	
Safont 2009[222]	<70 years etoposide plus cisplatin	NR	NR	NR	NR	76	p>0.05
	<70 years epirubicin plus cisplatin	NR		NR		83	
	≥70 years etoposide plus cisplatin	NR		NR		79	
	≥70 years epirubicin plus cisplatin	NR		NR		84	
	<70	8.3	p=0.02	10.8	p=0.03	NR	NR
	≥70	7.4		9.7		NR	NR
Mixed population							
Nakao 2010[221]	<70 NSCLC	1.6	p=0.563	5.9	p=0.4999	6.3	p=1
	≥70 NSCLC	1.6		13.2		0	
	<70 SCLC	5.4	p=0.039	11.2	p=0.015	61.5	p=0.484
	≥70 SCLC	2		9.2		47.1	

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; PFS=progression-free survival; TTP=time to progression; OS=overall survival; ORR=objective response rate; CI=confidence interval; BSC=best supportive care; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; NR=not reported

11.3 Tolerability evidence

Data relating to tolerability outcomes reported in retrospective data studies are presented in Table 24.

11.3.1 Non-small cell lung cancer

Five studies[177,182,186,195,199,208] presented data regarding dose intensity, RDI or the proportions of planned treatment received. Where RDI was reported, all studies reached an RDI of >70% for treatments administered. Discontinuations and withdrawals were reported by eight studies,[183,195,197,198,202,208,211,215] with the most common reason for discontinuation being disease progression or toxicity. Dose modifications and/or reductions were reported by ten studies,[177,178,183,186,187,189,197-199,211] and, again, the most common reason for dose modification was toxicity.

Adverse event data were reported in 21 studies,[177,180-183,186-189,193,195,197-199,203-205,208,210,214,215] but comparisons across studies were difficult to conduct. Where studies compared older with younger patients, the trend generally suggests that rates of haematological and non-haematological AEs were similar.

11.3.2 Small cell lung cancer

Safont et al[222] reported a dose intensity of >85% for all treatments administered. Three studies[219,222,223] presented data for dose modifications, and as for data from NSCLC, the most common reason for dose modification was toxicity. Two studies[218,223] reported data for AEs; however, the data were not amenable to comparison.

11.3.3 Mixed populations

Two studies[220,221] reported data for AEs, and where comparisons between older and younger patients were made, the results were similar.

Table 24 Tolerability outcomes, retrospective data

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
NSCLC				
Older patients only				
Das 2012[177]	53% received the 4+ planned cycles of treatment (range 1-17)	NR	Dose reduction due to toxicity=30% Delayed due to toxicity=38%	Any grade 3-4=39% Neutropenic sepsis=13%
El-Gehani 2012[178]	Median cycles=4	NR	Dose reduction=14% Delays due to toxicity=44%	NR
Genestreti 2011[186]	Median cycles=3 (range 3-6) RDI: Carboplatin=93% Gemcitabine=90%	NR	Dose reduction=13 (36%) Delays chemotherapy=16 (44%) Overall delay=28 weeks	Toxic deaths=0 Grade 3: Anaemia=4 (11.1%) Neutropenia=4 (11.1%) Thrombocytopenia=8 (22.2%) Grade 4: Anaemia=2 (5.6%) Neutropenia=2 (5.6%) Thrombocytopenia=2 (5.6%)
Inal 2012[180]	Gemcitabine Median cycles=3.5	NR	NR	Neutropenia=39.4% Thrombocytopenia=21.2% Anaemia=12.1% Nausea/vomiting=21.2% Sensory neuropathy=3.0%
	Docetaxel plus cisplatin Median cycles=5.0	NR	NR	Neutropenia=33.3% Thrombocytopenia=2.8% Anaemia=19.4% Nausea/vomiting=30.6% Sensory neuropathy=22.2%
	Paclitaxel plus cisplatin Median cycles=4.0	NR	NR	Neutropenia=30.8% Thrombocytopenia=3.8% Anaemia=15.4% Nausea/vomiting=29.2% Sensory neuropathy=23.1%
Irisa 2012[181]	First line	NR	NR	42%
	Second line	NR	NR	25.3%
	Third line	NR	NR	27.8%
Kim 2012[182]	RDI=83.2% Median cycles=4 (range 1-6)	NR	NR	Grade 3: Leukopenia=19 (40.43%) Thrombocytopenia=8 (17.02%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Anaemia=5 (10.64%) Febrile neutropenia=4 (8.51%) Diarrhoea=7 (14.89%) Mucositis=11 (23.40%) Peripheral neuropathy=2 (4.26%) Anaphylaxis=1 (2.13%) Grade 4: Leukopenia=7 (14.89%)
Lang 2012[183]	Average duration of first-line therapy=4.2±2.8 months	Discontinuation=64% Died during therapy/within median of 2.8 months=92% (of discontinued patients)	Gap in therapy=19% Modifications=11%	Dehydration=40% Infusion reaction=39% Anaemia=39% Bacterial/fungal infections=18% Haemorrhage=13% Thromboembolic events=17%
Passaro 2012[185]	Median cycles=5.8	NR	NR	NR
Platania 2011[187]	NR	NR	Dose reduction=16 (37%) Due to: Grade 3-4 non-haematological toxicities=15 (94%) Serious liver deterioration=1 (6%)	Total patients=16 (37%)
Yi 2011[188]	Median number of cycles=4 (range 1–6)	NR	NR	Neutropenia=33.1% Thrombocytopenia=17.1% Treatment-related death=6.3%
Zauderer 2011[189]	NR	NR	40% completed 4 cycles without dose reduction	Grade 4 haematological=6% Grade 3-4 non-haematological=39%
Li 2010[193]	Combination therapy Median cycles=3 (range 1-6)	NR	NR	Anaemia=13 (24%) Neutropenia=19 (35%) Thrombocytopenia=7 (13%) Nausea/emesis=9 (17%) Fatigue=8 (15%)
	Single agent Median cycles=3 (range 1-6)			Anaemia=3 (6%), p=0.04 Neutropenia=7 (15%), p=0.02 Thrombocytopenia=5 (10%), p=0.69 Nausea/emesis=6 (13%), p=0.55 Fatigue=5 (10%), p=0.51
Luciani 2009[195]	Median number of cycles=3.0 (range 0.5–7.0)	Disease progression=27 (58%) Toxicity=19 (40%) Patient choice=1 (2%)	NR	Grades 3–4: Haematological=15.0% Non-haematological=2.8%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	RDI: ≤80%=64% >80%=36%			Granulocytopenia=28.0% Fatigue=24.3% Febrile neutropenia=1.9%
Older versus younger patients				
Tomita 2012[197]	<70 Received standard regimen=96.3% Mean cycles=2.67	Therapy discontinuation, schedule modification or dose reduction due to intolerable toxicities or patient refusal=11 (40.7%)	Modified regimen=3.7%	Grade 3 anaemia=1 (3.7%)
	≥70 Received standard regimen=85.2% Mean cycles=2.48	Therapy discontinuation, schedule modification or dose reduction due to intolerable toxicities or patient refusal=15 (55.6%)	Modified regimen=14.8%	Grade 3 anaemia=5 (18.5%)
Tsao 2012[198]	Overall compliance with treatment by age groups or by sex–age groups in almost all patients was not statistically significantly different, with an average of 95% compliance in each treatment arm. The only exception was in women aged ≥70 years treated on the erlotinib+bexarotene arm, who had worse compliance (81.6% vs 99.3%, p=0.04)	Treatment discontinuation rates caused by toxicity were similar among the age groups: 14.5% for patients aged <65 years, 12.5% for those aged ≥65 years, 14.6% for those aged ≥70 years, and 13% for those aged ≥75 years, with higher treatment-discontinuation rates in the sorafenib and vandetanib treatment arms for all ages	Women aged ≥65 years (25.6% vs 10.3%, p=0.03) and those aged ≥70 years (35% vs 11.3%, p=0.0076) were also more likely to require dose reductions, irrespective of treatment arm. No other subgroups had significant dose-reduction differences.	No differences were seen among the overall age groups in rate of grade 3-4 haematological toxicities Older women aged ≥65 years had more grade 3-4 non-haematological toxicities (69.2% vs 50%, p=0.05), especially in the sorafenib treatment arm (p=0.04). In contrast, younger men (age <65 years and <70 years) had more grade 3-4 non-haematological toxicities (51.3% vs 33.3%, p=0.041; 50.5% vs 24.2%, p=0.0085)
	70–74 Mean (SD) cycles=3.7 (1.9)	NR	NR	Grade 3: Neutropenia=28 (15.6%) Thromobocytopenia=46 (25.6%) Anaemia=21 (11.7%) Grade 4: Neutropenia=31 (17.2%) Thromobocytopenia=11 (6.1%) Anaemia=0 (0%)
	75–79 Mean (SD) cycles=3.5 (1.8)	NR	NR	Grade 3 Neutropenia=20 (19.6%) Thromobocytopenia=21 (20.6%) Anaemia=7 (6.9%) Grade 4: Neutropenia=15 (14.7%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Thromobocytopenia=7 (6.9%) Anaemia=1 (1.0%)
	≥80 Mean (SD) cycles=3.3 (2.0)	NR	NR	Grade 3: Neutropenia=2 (4.9%) Thromobocytopenia=6 (14.6%) Anaemia=2 (4.9%) Grade 4: Neutropenia=9 (22.0%) Thromobocytopenia=3 (7.3%) Anaemia=1 (2.4%)
Tsubata 2012[199]	<70 RDI: Platinum-doublet=80.2% Non-platinum doublet=77.5% Single agent=82.6% EGFR-TKI=90.7%	NR	Dose modifications due to AEs: Platinum-doublet=22.3% Non-platinum doublet=20.0% Single agents=0% EGFR-TKI=25.0%	Neutrophils=13%
	≥70 RDI: Platinum-doublet=75.6% Non-platinum doublet=81.9% Single agent=85.7% EGFRTKI=84.2%	NR	Dose modifications due to AEs: Platinum-doublet=31.8% Non-platinum doublet=12.5% Single agents=26.7% EGFR-TKI=45.5%	Neutrophils=17%
Masago 2011[202]	<75	Withdrawals due to toxicity=6/60 (10%)	NR	NR
	≥75	Withdrawals due to toxicity=5/20 (25%)	NR	NR
Wu 2010[203]	<70	NR	NR	Anaemia=4% Leukopenia=19% Neutropenia=25% Fatigue=4%
	≥70			Anaemia=8%, p=0.1 Leukopenia=25%, p=0.1 Neutropenia=33%, p=0.09 Fatigue=10%, p=0.01
Murialdo 2009[204]	<70	NR	NR	Grade 3-4 neutropenia=21.4%
	≥70			Grade 3-4 neutropenia=25.5%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Pepe 2007[208]	≤65 Doses delivered Vinorelbine: <10=50.7%, 10-15=46.7%, 16=2.7% Cisplatin: <5=27.3%, 5-7=21.3%, 8=51.3% Mean dose intensity (mg/m^2/week): Cisplatin=18.0 (72.0%), Vinorelbine=13.2 (52.8%)	Discontinuations due to refusal=23%	NR NR	Neutropenia=66.7% Nausea=9.3% Anorexia=8.0% Lethargy=12.7%
	>65 Doses delivered Vinorelbine: <10=71.4%, 10-15=28.6%, 16=0% Cisplatin: <5=49.2%, 5-7=19.1%, 8=31.8% Mean dose intensity (mg/m^2/week): Cisplatin=14.1 (56.4%), Vinorelbine=9.9 (39.6%)	Discontinuations due to refusal=40%, p=0.01		Neutropenia=65.1% Nausea=12.7% Anorexia=12.7% Lethargy=14.3%
Provencio 2009[205]	No statistically significant difference in the treatment received was observed between the two groups. They had similar numbers of cycles or dose intensity	NR	NR	<70 Neutropenia=20.0% Nausea/vomiting=16.5% ≥70 Neutropenia=26.0%, p=0.05 Nausea/vomiting=13.5%
Chen 2005[210]	Vinorelbine plus gemcitabine <70 Median cycles=6	NR	NR	Leukopenia=10 (43.5%) Anaemia=2 (8.7%) Thrombocytopenia=2 (8.7%) Fatigue=3 (13%)
	Vinorelbine plus gemcitabine ≥70 Median cycles=5	NR	NR	Leukopenia=9 (53%), p=0.283 Anaemia=6 (35.3%), p=0.01 Thrombocytopenia=3 (17.6%), p=0.914 Fatigue=4 (23.5%), p=0.854
	Paclitaxel plus carboplatin vs paclitaxel plus gemcitabine <70 Median cycles=4	NR	NR	Leukopenia=7 (15.2%) Anaemia=4 (8.7%) Thrombocytopenia=2 (4.3%) Grade 2–4 peripheral neuropathy=15 (32.6%)
	Paclitaxel plus carboplatin vs	NR	NR	Leukopenia=3 (6.8%), p=0.209

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	paclitaxel plus gemcitabine ≥70 Median cycles=4			Anaemia=9 (20.5%), p=0.001 Thrombocytopenia=3 (6.8%), p=0.76 Grade 2–4 peripheral neuropathy=19 (43.1%), p=0.125
	Vinorelbine plus cisplatin vs paclitaxel plus cisplatin therapy <70 Median cycles=4	NR	NR	Leukopenia=9 (12.9%) Anaemia=5 (7.1%) Fatigue=3 (4.3%) Grade 2–4 peripheral neuropathy=21 (30%)
	Vinorelbine plus cisplatin vs paclitaxel plus cisplatin therapy ≥70 Median cycles=4	NR	NR	Leukopenia=14 (20%), p=0.038 Anaemia=12 (17.1%), p=0.001 Fatigue=16 (22.8%), p=0.006 Grade 2–4 peripheral neuropathy=38 (54.3%), p=0.026
Hotta 2005[211]	<75 Median treatment duration=64 days	Discontinuations=206 (80%) Due to: Disease progression=141 (68%) AEs=36 (17%)	Treatment interruptions=46 (18%) Due to AEs=37 (80%)	NR
	≥75 Median treatment duration=45 days	Discontinuations=70 (76%) Due to: Disease progression=40 (57%) AEs=13 (19%)	Treatment interruptions=16 (17%) Due to AEs=15 (94%)	NR
Langer 2002[214]	<70 males	NR	NR	Grade 3: Leukopenia=39% Granulocytopenia=11% Thrombocytopenia=8% Anaemia=17% Nausea=22% Vomiting=7% Neurosensory=15% Neuromotor=8% Neuroclinical=10% Grade 4 Leukopenia=17% Granulocytopenia=64% Thrombocytopenia=2% Vomiting=6%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	<70 females			Grade 3: Leukopenia=36% Granulocytopenia=19% Thrombocytopenia=7% Anaemia=26% Nausea=28% Vomiting=10% Diarrhoea=3% Neurosensory=17% Grade 4: Leukopenia=13% Granulocytopenia=60% Thrombocytopenia=4% Vomiting=11% Diarrhoea=3%
	≥70 Males	NR	NR	Grade 3: Leukopenia=38% Granulocytopenia=5% Thrombocytopenia=13% Anaemia=24% Nausea=25% Vomiting=7% Neurosensory=17% Neuromotor=10% Neuroclinical=12% Grade 4: Leukopenia=42% Granulocytopenia=80% Thrombocytopenia=3% Vomiting=12%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	≥70 females			Grade 3: Leukopenia=32% Granulocytopenia=11% Thrombocytopenia=7% Anaemia=25% Nausea=43% Vomiting=14% Diarrhoea=4% Neurosensory=18% Grade4: Leukopenia=32% Granulocytopenia=71% Thrombocytopenia=11% Vomiting=11% Diarrhoea=11%
Rocha Lima 2002 [215]	NR	Withdrew due to toxicity: <50=13.6% 50–59=15.6% 60–69=18.7% 70–79=14%	NR	Grade ≥3 haematological toxicity: 50–59=65% 60–69=76% 70–79=81%, p=0.026
	NR	% of patients who completed all protocol therapy was assessed <50=72.4% 50–59=75.4% 60–69=78.6% 70–79=79.6%	NR	Severe or greater haematological Toxicity: 40–49=65% 50–59=71% 60–69=84% 70–79=83%, p=0.028
SCLC				
Older patients only				
Fisher 2012[219]	Completed cyles: 1=30 (26%) 2=12 (10%) 3=14 (12%) 4+=61 (52%)	NR	Dose reduction=33%	NR
Older versus younger				
Asai 2012[218]	<70	NR	NR	Neutropenia=2 (25%) Leukopenia=2 (25%) Anaemia=0 (0%) Thrombocytopenia=1 (12.5%) Febrile neutropenia=1 (12.5%)
	≥70	NR	NR	Neutropenia=3 (30%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Leukopenia=2 (20%) Anaemia=1 (10%) Thrombocytopenia=1 (10%) Febrile neutropenia=0 (0%)
Safont 2009[222]	<70 Median cycles=4.9 Dose intensity: Cisplatin=487 mg/m^2 (88%) Epirubicin'=487 mg/m^2 (88%) Etoposide'=1490 mg/m^2 (88%)	NR	Delay=13 days	NR
	≥70 Median cycles=4.8 Dose intensity: Cisplatin=437 mg/m^2 (86%) Epirubicin'=437 mg/m^2 (87%) Etoposide'=1371 mg/m^2 (87%)		Delay=13 days	
Garst 2005[223]	Aged <65 years Median cycles=3 (range, 1-22)	Discontinuations due to AEs=30 (9%)	Dose reductions=11% Treatment delays=36%	Grade 3: Anaemia=92/313 (29%) Leukopenia=156/313 (50%) Neutropenia=61/312 (20%) Thrombocytopenia=92/313 (29%) Dyspnoea=25 (8%) Grade 4: Anaemia=8/313 (3%) Leukopenia=100/313 (32%) Neutropenia=225/312 (72%) Thrombocytopenia=75/313 (24%) Dyspnoea=12 (4%)
	Age ≥65 years Median cycles=4 (1-15)	Discontinuations due to AEs=19 (12%)	Dose reductions=18% Treatment delays=50%	Grade 3: Anaemia=51/157 (33%) Leukopenia=88/157 (56%) Neutropenia=27/157 (17%) Thrombocytopenia=44/157 (28%) Dyspnoea=16 (10%) Grade 4: Anaemia=6/157 (4%) Leukopenia=48/157 (31%) Neutropenia=121/157 (77%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Thrombocytopenia=55/157 (35%) Dyspnoea=4 (3%)
Mixed population				
Koyama 2010[220]	NR	NR	NR	Grade 3 and 4 neutropenia was more frequently observed in ≥65 age group. However, there was no difference in other toxicities among age groups
Nakao 2010[221]	<70 Mean cycles 2.83 (range 1-10) Mean dose=37.35 (range 30-45)	NR	NR	Leukopenia=48.3% Neutropenia=65.5% Anaemia=20.7% Thrombocytopenia=13.8% Febrile neutropenia=20.7%
	≥70 Mean cycles=2.36 (range 1–9) Mean dose=35.87 (range 30-40)			Leukopenia=59.1% Neutropenia=77.3% Anaemia=22.7% Thrombocytopenia=31.8% Febrile neutropenia=22.7%

RDI=relative dose intensity; SD=standard deviation; EGFR=epidermal growth factor receptor; TKI=tyrosine kinase inhibitor; AE=adverse event; NR=not reported

11.4 Comprehensive geriatric assessment and quality of life

Table 25 presents information on CGA and QoL reported in the retrospective data studies.

None of the studies utilised a CGA tool. Four studies[210,213,214,220] reported data on QoL outcomes using eight different measures. Two studies[210,220] reported worse QoL symptoms during chemotherapy compared with baseline scores and two studies[213,214] reported that there was little difference in QoL for older versus younger patients.

Table 25 Geriatric assessment and quality of life, retrospective data

Study	Geriatric assessment		Quality of life	
	Tool(s) used	How tool was used	Tool(s) used	Results summary
NSCLC				
Chen 2005[210]	NR	NR	LCSS	The LCSS scores showed significantly worse appetite, fatigue, dyspnoea, disease severity, daily activity, and QoL after treatment. However, the difference in the deterioration of the scale scores was very small between the two age groups
Langer 2002[214]	NR	NR	FACT-L QoL scale	QoL was assessed at baseline, at 6 weeks, at 3 months, and at 6 months. No statistically significant differences were found in either baseline QoL (p=0.20) or changes in QoL over time (p=0.12) between younger and older males. Among female patients, older patients had higher scores at baseline on the FACT-L instrument than younger women (114.5 vs 104.1; p=0.003). Older women also had less change in QoL over time (p=0.003). A model that assumed no association between differential missing data and survival produced similar but not identical results and resulted in the same conclusions. It should be noted that substantially fewer patients were assessed at 3 and 6 months than at baseline. Those who did not undergo 6-month evaluation were presumably sicker, had progressive disease, or had died
Vansteenkiste 2003[213]	NR	NR	Overall symptom control Normal daily activities Overall QoL	Gemcitabine was equivalent to cisplatin plus vindesine in 'disease-specific' symptom control but superior in 'constitutional' symptom control. Symptom improvement was not affected by age and only marginally by baseline KPS. Most of the symptom improvement occurred in the first 3 cycles, with some further symptom improvement in the following cycles in the gemcitabine arm only
Mixed or undefined populations				
Koyama 2010[220] (abstract only)	NR	NR	Physical domain Functional QoL	Continuation of chemotherapy for elderly patients with lung cancer markedly deteriorated physical QoL. KPS could be useful to estimate functional QoL in cases where QoL data are missing

LCSS=Lung Cancer Symptoms Scale; FACT-L=Functional Assessment of Cancer Therapy-Lung; QoL=quality of life; KPS=Karnofsky performance status; NR=not reported

11.5 Summary and discussion

Heterogeneity and lack of methodological quality of the included retrospective studies mean that useful comparison across studies and outcomes was not possible. Clinical consensus suggests that the data from retrospective studies is difficult to interpret in any meaningful way; however, the data have been included for completeness to show the size of the evidence base. It should be noted that although retrospective evidence is not ranked as highly as evidence derived from RCTs, many of the retrospective studies included patients who more closely reflect patients seen in routine clinical practice.

In general terms, the retrospective data support the evidence from RCTs, subgroups of RCTs, pooled analyses and cohort studies that chemotherapy is effective and tolerable in older patients with lung cancer.

12 DISCUSSION

The World Health Organisation[5] states that most countries of the developed world use the chronological age of 65 years to define 'elderly' or 'older' populations, whereas the British Geriatrics Society[6] describes geriatric medicine as being mainly concerned with people aged over 75 years. As expected, one of the key findings of this review is that there is no commonly used definition to describe the age (or age range) of 'older' patients who participate in lung cancer studies. The age of patients described as 'older' ranged from over 60 years to over 80 years across the included studies.

The availability of relevant data from 36 RCTs focussing solely on older patients with lung cancer is significant and reflects the fact that lung cancer is a highly prevalent disease, especially in the older population. The proportion of RCTs that focussed only on patients with NSCLC was high and reflects the fact that, as the most common form of lung cancer, NSCLC is the subject of much clinical reseach. There were fewer RCTs that focussed on patients with SCLC; given that SCLC is becoming rarer, this comes as no surprise.

Data from the included RCTs are not generalisable to the older population. Strict patient selection processes ensure that patients who are recruited to RCTs are generally fitter and healthier than patients seen in routine clinical practice. Lung cancer research in less-fit patients is very hard to conduct because the survival of patients with lung cancer is poor. However, data may be generalisable to the subgroup of older lung cancer patients seen in routine clinical practice who are generally fit and healthy. The results of trials must be considered in light of their location as there may be differences in how patients respond to treatment in different geographical areas. This is especially relevant for EGFR mutation status (many of the included studies pre-dated testing for this mutation).

Evidence from the included non-RCT studies was generally derived from single-centre studies that selectively recruited populations; indeed the characteristics of the patient populations in the cohort studies indicate that patients were slightly more frail than patients included in the RCTs, as the percentage of patients in cohort studies with an ECOG PS ≥ 2 was higher. Evidence from the retrospective studies may be more generalisable to the older population in general, as patients included in these studies were not selected for fitness or comorbidity.

Taking all of this into consideration, this review presents evidence which shows that chemotherapy can be effective for older people with lung cancer. Comparisons across studies, regimens, measures and populations are difficult. However, there are data to suggest that chemotherapy does confer survival benefit to older patients, and studies generally concluded that chemotherapy is a feasible treatment option for older people with lung cancer.

Although the majority of studies reported comprehensive data relating to tolerability, the data were difficult to interpret because of variations in measures used and outcomes reported. The measurement of tolerability is often subjective in clinical practice, and therefore results are variable and not necessarily objective. In general terms, it seems that older people can tolerate chemotherapy, but for some patients, treatment comes with a higher risk of serious AEs compared with younger patients. Relative dose intensity measures generally showed that older patients can tolerate the standard chemotherapy doses administered in the studies. In the studies that comparedtolerability rates between older and younger populations, the discontinuation rates were generally higher in the older population.

The use of QoL measures was infrequently and inconsistently reported across all study types, making it difficult to draw conclusions for the older population. This review highlights how poorly all study types collected QoL data, which is a key factor when considering palliative treatments for patients with lung cancer. Many of the tools used for QoL were also utilised as CGA measures and vice versa – there appears to be little distinction between the two measures as described by authors.

There are severely limited data relating to the use of CGA in studies to guide decisions regarding the choice of treatment. Clinical advisors to the review suggest that CGA is not widely utilised in the UK as there may have been a lack of focus in oncology on the specific implications of age and treatment/outcomes.

12.1 Strengths and limitations of the review

One of the main strengths of this review is that a large volume of evidence from a wide range of studies has been collated. A comprehensive evidence base is now available that describes how older patients with lung cancer are treated in clinical trials and clinical studies. However, the inclusion criteria employed in this review were deliberately broad and led to the inclusion of diverse studies: study populations were often very different in terms of disease stage and histology, treatment type and line of treatment across the studies. As there is considerable heterogeneity, it was not possible to make firm conclusions for specific subgroups of older patients with lung cancer.

The overall quality of the included studies was poor and, therefore, the results must be viewed with caution. Many of the studies selected fitter, healthier patients and the results are not necessarily generalisable to the population of older people seen in routine clinical practice.

The focuss of the review is the extent to which older patients with lung cancer can tolerate chemotherapy, and it is anticipated that the data collected will help clinicians to make informed decisions about how to treat older patients with lung cancer. Using the data available, it has been possible to make some comparisons between older and younger patients, which will help to indicate how useful chemotherapy is in clinical practice for this specific patient population.

There was great variability across studies in terms of which outcome measures were utilised and how these outcomes were reported; meaningful interpretation and comparison of tolerability, QoL and CGA outcomes were therefore difficult.

Although the results of this review highlight that chemotherapy may be a viable treatment option for older people with lung cancer, it should be noted that any conclusions drawn are not treatment recommendations; the evidence should instead be used to enable clinicians and patients to have meaningful discussions about treatment options.

13 CONCLUSIONS

There is much research into the treatment of older people with lung cancer, but it is of poor quality. There is a lack of uniformity in lung cancer trials, such as the definition of 'older' or 'elderly', and the use and reporting of standard assessment measures for outcomes such as tolerability, QoL and CGA.

Chemotherapy can benefit some older patients but individual decisions/discussions are important. Patients, regardless of age, should have an opportunity to discuss treatment options with healthcare professionals. Age alone should not be a barrier to palliative chemotherapy for patients with NSCLC and SCLC, as other factors including fitness, comorbidities and personal choice should be taken into account.

13.1 Suggested research priorities

Research has moved forward in recent years, with an increasing understanding of cancer subtypes at a molecular level. As such, future research into the treatment of older patients with lung cancer should focus on histology and mutation status to enable clinicians to offer more targeted treatments to older patients.

It is essential that future research adopts more uniform definitions and standardised assessment tools that measure outcomes objectively. Outcomes should also be reported consistently to enable meaningful synthesis of data, so that each study adds valuable information to the evidence base.

Future trials could make more use of structured, standardised CGA assessments as part of their inclusion criteria; it is possible that the lack of use of CGA tools in clinical practice in the UK is due to the limited research available to support their use.

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15 APPENDICES

Appendix 1: Literature search strategies

Elderly Cancer Search History (35 searches)
Ovid MEDLINE® and Ovid OLDMEDLINE® 1946 to Present with Daily Update

# ▲	Searches	Results
1	exp Breast Neoplasms/	206832
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	57204
3	exp Colorectal Neoplasms/	139935
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	63395
5	exp Lung Neoplasms/	165165
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	116112
7	exp Carcinoma, Renal Cell/	20951
8	((renal cell or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	21641
9	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ or exp Leukemia, Myeloid, Chronic-Phase/ or exp Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative/	15723
10	(chronic myel$ adj2 leuk?emia).ti,ab.	19580
11	exp Lymphoma, Non-Hodgkin/	80985
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	28219
13	or/1-12	663599
14	*"Aged, 80 and over"/ or *Aged/	21737
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	392827
16	14 or 15	401572
17	13 and 16	15012
18	182hemotherapy$.tw. or drug therapy.fs.	1734499
19	(adjuvant adj5 chemotherap$).tw.	17651
20	exp Antineoplastic Agents/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Chemotherapy, Adjuvant/	821443
21	or/18-20	2172920
22	exp Medication Adherence/ or adherence.tw.	58141
23	(survival adj benefit$).tw.	7695
24	(recurrence risk$ or relapse-free survival).tw.	6612
25	exp Drug Toxicity/ or exp Drug Tolerance/ or exp Safety/ or exp Treatment Outcome/ or exp Disease-Free Survival/	719437
26	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw.	208607
27	(side effect$ or undesirable effect$ or treatment-emergent or treatment-related or tolerability or safety or toxic effect$ or dose intensity or toxicity).tw.	617560
28	(clinical adj5 (effectiveness or efficacy or effect$ or benefit$)).tw.	113247
29	exp "Quality of Life"/ or (quality of life or qol).tw.	164254
30	or/22-29	1568681
31	21 and 30	520864
32	17 and 31	2926
33	(animals not (humans and animals)).sh.	3760147
34	32 not 33	2924
35	**limit 34 to (182hemoth language and yr="2000 -2013")**	2146

EMBASE Search History (33 searches)
Embase 1974 to 2013 May 24

# ▲	Searches	Results
1	exp breast cancer/	258454
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	75564
3	exp colon carcinoma/ or exp colon cancer/ or exp colorectal cancer/ or exp rectum cancer/ or exp rectum carcinoma/	158617
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	89748
5	exp lung tumor/ or exp lung cancer/	241425
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	160685
7	exp kidney cancer/	65356
8	((renal or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	62964
9	exp chronic myeloid leukemia/	28802
10	(chronic myel$ adj2 leuk?emia).ti,ab.	24827
11	exp nonhodgkin lymphoma/	116117
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	37418
13	or/1-12	878499
14	exp geriatric patient/ or *aged/	50605
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	531929
16	14 or 15	546878
17	13 and 16	22973
18	183hemotherapy$.tw.	353300
19	(adjuvant adj5 chemotherap$).tw.	26741
20	exp antineoplastic agent/ or exp consolidation chemotherapy/ or exp multimodal chemotherapy/ or chemotherapy/ or exp induction chemotherapy/ or exp cancer combination chemotherapy/ or exp maintenance chemotherapy/ or exp cancer chemotherapy/ or exp adjuvant chemotherapy/ or exp combination chemotherapy/	1462883
21	or/18-20	1546201
22	(clinical adj5 (effectiveness or efficacy or effect$ or benefit$)).tw.	165108
23	*patient compliance/ or adherence.tw.	149576
24	(survival adj benefit$).tw.	12002
25	(recurrence risk$ or relapse-free survival).tw.	9402
26	exp drug toxicity/ or exp drug tolerance/ or exp drug safety/ or exp treatment outcome/ or exp disease free survival/	1218587
27	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw.	311356
28	(side effect$ or undesirable effect$ or treatment-emergent or treatment-related or tolerability or safety or toxic effect$ or dose intensity or toxicity).tw.	886887
29	exp “quality of life”/ or (quality of life or qol).tw.	277356
30	or/22-29	2407159
31	21 and 30	418422
32	17 and 31	5575
33	**limit 32 to (human and 183hemoth language and yr=”2000 – 2013”)**	**4047**

Search History

[Breast Neoplasms] explode all trees 7763
breast cancer* or breast neoplasm* or breast tumour* or breast carcinoma*:ti,ab,kw (Word variations have been searched) 14703
[Colorectal Neoplasms] explode all trees 4628
"colorectal cancer":ti,ab,kw (Word variations have been searched) 4311
[Lung Neoplasms] explode all trees 4272
"lung cancer":ti,ab,kw (Word variations have been searched) 6836
[Carcinoma, Renal Cell] explode all trees 419
kidney cancer or renal cell cancer:ti,ab,kw (Word variations have been searched) 789
[Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees 304
"chronic myeloid leukaemia":ti,ab,kw (Word variations have been searched) 101
[Lymphoma, Non-Hodgkin] explode all trees 1136
non-hodgkin's lymphoma:ti,ab,kw (Word variations have been searched) 1203
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 30561
(senil* or geriatr* or older or elder* or late-life or later-life or late*):ti,ab,kw (Word variations have been searched) 67255
Aged] explode all trees 554
#14 or #15 67394
#13 and #16 2332
(184hemotherapy* or drug therap*):ti,ab,kw (Word variations have been searched) 111982
MeSH descriptor: [Drug Therapy] explode all trees 108765
#18 or #19 173119
#17 and #20 1068

Web of Knowledge

Results:
Topic=(breast cancer* or colorectal cancer* or renal cell carcinoma* or chronic myeloid leukemia* or non-hodgkin lymphoma*) AND Topic=(184hemotherapy* or Bevacizumab or Avastin or Cetuximab or Erbitux or Everolimus or Afinitor or Fulvestrant or Faslodex or Lapatinib or Tyverb or Bendamustine or Levact or Bortezomib or Velcade or Rituximab or Mabthera or Rituxan) AND Topic=(aged or senil* or geriatr* or older or elder*)

Refined by: Languages=(ENGLISH) AND Web of Science Categories=(ONCOLOGY OR HEMATOLOGY) AND Document Types=(PROCEEDINGS PAPER OR MEETING ABSTRACT) AND Research Areas=(ONCOLOGY OR HEMATOLOGY)

Timespan=2000-01-01 – 2013-02-03. Databases=Conference Proceedings Citation Index-Science (CPCI-S).

Appendix 2: Quality assessment

The quality of RCTs was assessed using criteria based on CRD guidance.

- Was the method used to assign participants to the treatment groups really random?*
- Was the allocation of treatment concealed?**
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for withdrawals stated?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Was an intention-to-treat analysis included?
- Was the study sufficiently powered for the primary outcome (s)?

**(Computer-generated random numbers and random number tables were accepted as adequate, while inadequate approaches included the use of alternation, case record numbers, birth dates and days of the week)*

*** (Concealment was deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches included: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).*

Items were graded in terms of ✓ yes (item properly addressed), ✕ no (item not properly addressed), ✓/✕ partially (item partially addressed), **?** Unclear/not enough information, or **NA** not applicable

Appendix 3: Excluded studies

Study	Reason for exclusion
Abou-Mourad 2008[228]	Foreign language
Altavilla 2000[229]	Outcomes
Bearz 2007[230]	Letter
Belfihadj 2011[231]	Population
Bianco 2001[232]	<2000
Bianco 2002[233]	<2000
Breen 2007[234]	Outcomes
Buccheri 2000[235]	<2000
Chang 2011[236]	Treatment/comparator
Chen 2008[237]	Population
Chen 2007[238]	Outcomes
Chen 2003[239]	Foreign language
Cobo Dols 2007[240]	Foreign language
Corre 2011[241]	Outcomes
Costa 2006[242]	Outcomes
Cuffe 2011[243]	Outcomes
Cuffe 2012[244]	Outcomes
Des Guetz 2012[68]	Analysed studies already included
Di Maio 2003[245]	Outcomes
Ding 2013[246]	Foreign language
Fabre 2011[247]	Outcomes
Ganti 2010[248]	Outcomes
Green 2011[249]	Outcomes
Gridelli 2008[250]	Outcomes
Gridelli 2012[251]	Outcomes
Gridelli 2002[252]	<2000
Gronberg 2010[253]	Outcomes
Gu 2011[254]	Population
Gu 2011[255]	Population
Hainsworth 2000[256]	<2000
Hainsworth 2001[257]	<2000
Hardy 2010[258]	Not relevant
Hesketh 2007[259]	Outcomes
Higton 2010[260]	Outcomes/population
Janssen-Heijnen 2007[261]	Outcomes
Jatoi 2003[262]	Outcomes
Jeremic 2004[263]	Outcomes
Kanat 2003[264]	Letter
Karampeazis 2011[265]	Outcomes
Keating 2010[266]	Outcomes
Kelly 2001[267]	Outcomes
Kulkarni 2008[268]	Population
Lee 2003[269]	Study design
Liang 2010[270]	Treatment/comparator
Liu 2011[271]	Outcomes
Lou 2010[272]	Foreign language
Maione 2005[273]	Outcomes
Martoni 2001[274]	<2000
Massacesi 2004[275]	Outcomes
Matsui 2001[276]	<2000
Min 2004[277]	Population
Moscetti 2005[278]	Population
Nakamura 2000[279]	<2000
Ngeow 2010[280]	Outcomes
Oshita 2001[281]	Outcomes

Study	Reason for exclusion
Ozkaya 2011[282]	Foreign language
Pallis 2008[69]	Analysed studies already included
Peake 2003[283]	Outcomes
Pereira 2004[284]	<2000
Perrone 2004[285]	Letter
Pezzuolo 2010[286]	Foreign language
Qi 2012[70]	Analysed studies already included
Qiu 2011[71]	Analysed studies already included
Quoix 2001[287]	<2000
Rasco 2010[288]	Outcomes
Reckamp 2011[289]	Outcomes
Reddy 2005[290]	Outcomes
Ricci 2000[291]	<2000
Russo 2009[72]	Analysed studies already included
Saito 2011[292]	Outcomes
Sasaki 2006[293]	Outcomes
Satoh 2009[294]	Outcomes
Satoh 2003[295]	Outcomes
Saxena 2012[296]	Outcomes
Shiroyama 2012[297]	Outcomes
Socinski 2007[298]	Outcomes
Song 2002[299]	Foreign language
Sorio 2006[300]	Outcomes
Sorraritchingchai 2004[301]	Foreign language
Stinchcombe 2012[302]	Outcomes
Stinchcombe 2013[303]	Outcomes
Sugiyama 2011[304]	Foreign language
Sun 2005[305]	Foreign language

Study	Reason for exclusion
Sun 2011[306]	Foreign language
Syrigos 2007[307]	Foreign language
Tamura 2009[308]	Foreign language
Tibaldi 2001[309]	<2000
Toffalorio 2012[310]	Treatment/comparator
Ueda 2002[311]	<2000
Waechter 2005[312]	Population
Wagner 2008[313]	Outcomes
Wang 2003[314]	Outcomes
Wang 2012[315]	Foreign language
Wang 2011[316]	Foreign language
Wang 2007[317]	Foreign language
Wozniak 2011[318]	Outcomes
Xu 2012[73]	Analysed studies already included
Xu 2006[319]	Foreign language
Yamamoto 2009[320]	Outcomes
Yano 2010[321]	Outcomes
Yin 2008[322]	Foreign language
Yin 2003[323]	Foreign language
Yu 2011[324]	Outcomes
Yu 2011[325]	Outcomes
Yu 2012[326]	Treatment/comparator
Zhang 2006[327]	Foreign language
Zhang 2009[328]	Foreign language
Zheng 2012[329]	Study design

Appendix 4: Study characteristics, single cohorts

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
NSCLC						
Older patients only						
Baek 2012[81,82]	Phase II Multicentre Korea 2008-2010	Stage IIIB/IV Aged ≥70	Gemcitabine plus UFT (n=48)	Median age: 74.5 years (70-84) Male: 60.4% ECOG PS: 1=85.4%, 2=14.6%	Primary: ORR Secondary: PFS, OS, toxicity	The combination of gemcitabine and UFT was effective in disease control and a well-tolerated first-line regimen in elderly patients with advanced NSCLC
Bauman 2012[83]	Phase II Multicentre Single stage Open-label USA Supported by Novartis, Inc. 2006-2010	First-line Stage IIB/IV Aged >70	Imatinib and paclitaxel (n=34)	Median age: 74.5 years (70-86) Male: 68% ECOG PS: 0=29%, 1=53%, 2=11%	Primary: ORR Secondary: median PFS, OS, toxicity	The combination of imatinib and paclitaxel had encouraging activity as measured by the primary endpoint of ORR. However, PFS and OS were typical for elderly patients treated with single-agent chemotherapy and the regimen is not recommended for further study
Firvida 2012[100,101] (abstract only)	Spain	Stage IIIB/IV First-line Aged >70	Erlotinib (n=31)	Median age: 78 years (70-85) Male: 48% ECOG PS: 2=48%	Primary: PFS Secondary: OS	The results suggest that erlotinib monotherapy is an effective and well-tolerated treatment option for elderly patients with advanced NSCLC and non-squamous histology
Kurata 2012[131]	Phase I/II Multicentre Japan West Japan Thoracic Oncology Group funded itself	Stages II, IIIA, IIIB/IV Chemotherapy I Aged >70	Carboplatin plus gemcitabine (n=75) Phase I: n=25 Phase II: n=55	Phase I: Median age: 76 years (72-83) Male: 60% PS: 0=32%, 1=64%, 2=4%	Phase I outcomes: toxicities, dose-limiting toxicities response to treatment and recommended dose for the phase II study	Although the recommended dosage is restricted to a lower level compared with younger patients, combination therapy using carboplatin with gemcitabine is tolerable and promising for elderly patients with advanced NSCLC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	2005-2007			Phase II: Median age: 76 years (71-86) Male: 67% PS: 0=36%, 1=64%, 2=0	Phase II outcomes: Primary: Objective response Secondary: PFS and OS	
Lim 2012[138]	2007-2011	Stage: IIIB/IV First-line Aged 70-89	Gemcitabine plus carboplatin (n=40)	Median age: 73.9 years (70.0-84.6) Male: 67.5% ECOG PS: 0-1=92.5%, 2=7.5%	Outcomes: efficacy, safety	Gemcitabine and carboplatin combination chemotherapy can be considered as an effective and manageable treatment option in elderly advanced NSC LC patients with good PS
Maemondo 2012[139]	Phase II Multicentre Japan Supported by a grant from the Tokyo Cooperative Oncology Group 2008-2009	Stage: IIIB/IV or postoperative recurrent First-line Harbouring EGFR mutations (T790M mutations were excluded Aged >75	Gefitinib (n=31)	Median age: 80 years (75-87) Male: 81% PS: 0=55%, 1=39%, 2=6%	Primary: ORR Secondary: PFS, OS, toxicities	This is the first study that verified safety and efficacy of first-line treatment with gefitinib in elderly patients having advanced NSCLC with EGFR mutation. Considering its strong anti-tumour activity and mild toxicity, first-line gefitinib may be preferable to standard chemotherapy for this population
Takatani 2012[167]	Phase I/II Japan Independent collaborative (non-sponsored) group study 1999-2005	Stage: IIIB/IV Previously untreated Aged >75	Phase I: Vinorelbine and carboplatin (n=13)	Median age: 80 years (76-83) Male: 76% PS: 0=38%, 1=62%	Outcomes: maximum tolerated dose, recommended dose	Use of 20 mg/m^2 vinorelbine on days 1 and 8, followed by carboplatin AUC of 4 mg/mL/min on day 1 every 4 weeks warrants a phase III study for elderly patients with advanced NSCLC
Tibaldi 2012[171]	Phase II Multicentre Italy 2008-2001	Stage: IIIB/IV First-line Chemotherapy naïve Aged >70	Sequential cisplatin or gemcitabine followed by docetaxel (n=30)	Median age: 75 years (70-82) Male: 80% ECOG PS: 0=27%,	Primary: PFS rate at the end of sequential treatment Secondary:	The incorporation of cisplatin in a sequential schedule of gemcitabine followed by docetaxel is feasible but did not yield a substantial advantage to deserve further

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
				1=73%	Response rate, toxicity, survival	investigations
Asami 2011[78,79]	Phase II Japan 2008-2009	First-line Stage: IIIB-IV Chemotherapy naïve with EGFR mutations Aged >75	Gefitinib (n=17)	Median age: 81 years (75-88) Male: 24% ECOG PS: 0-1=83%, 2=17%	Primary: response rates Secondary: Disease control rate, PFS, OS and toxicity profile	First-line treatment with gefitinib was effective and well tolerated in elderly patients with EGFR mutations. In elderly patients harbouring activated EGFR mutation, gefitinib is well tolerated and shows a promising activity
Borghaei 2011[86]	Phase II USA 2007-2011	Stage: IIIB/IV Chemotherapy naïve Aged >65	Bevacizumab plus erlotinib (n=26)	Median age: 74 years (70-84) ECOG PS: 1=62%	Primary: PFS Secondary: Toxicity, response rate, OS	Our data suggest that a non-cytotoxic combination of erlotinib and bevacizumab is effective and well tolerated for the first-line management of elderly patients with advanced NSCLC. Correlation of outcome with EGFR and smoking status is pending
Kobayashi 2011[129]	Phase II Multicentre Japan 2004-2005	Stage: IIIB/IV First-line Aged >70	Gefitinib (n=30)	Median age: 78.5 years (70-87) Male: 47% ECOG PS: 0=20%, 1=70%, 2=10%	Primary: response rate Secondary: disease control rate, PFS, OS, toxicity	Gefitinib as a first-line therapy is active and well tolerated in elderly patients with pulmonary adenocarcinoma, especially in those who have never smoked
Kunimasa 2011[130]	Multicentre Japan	Stage: III/IV Chemotherapy naïve EGFR exon 19 codon 746–750 deletion and exon 21 L858R mutation Aged >70	Gefitinib EGFR+ (n=22) Vinorelbine or gemcitabine Non-EFGR+ (n=32)	NR	Outcomes: response rate, OS	Treatment customisation based on EGFR mutation status deserves consideration, especially for elderly patients who often cannot receive second-line chemotherapy due to poor organ function or comorbidities
Mansueto 2011[142]	Italy	Stage: IIIB/IV First-line	Oral vinorelbine	Median age: 78.1 years (71-84)	Primary: TPP	In our experience, oral vinorelbine seems to be an

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
		Aged >70 or unfit	(n=38)	ECOG PS: 0=2.6%, 1=63.2%, 2=34.2%	Secondary: response rate, toxicity	option for elderly, unfit patients with metastatic NSCLC not suitable for first-line combination chemotherapy. Oral formulation allows a good compliance to chemotherapy, reduces costs for treatment and AE management, and finally helps patients' QoL. Treatment was very well tolerated, without any need for dose adjustment. Updated results on survival will be presented at the meeting
Nacci 2011[146,147] (abstract only)	Italy 2009-2010	Stage: IIIB/IV First-line	Gemcitabine (n=50)	Median age: 76 years (64-85) Male: 86% WHO PS: 0=16%, 1=38%, 2=46%	Outcomes: efficacy, tolerability	A modified schedule of gemcitabine with a lower dose intensity than standard may be beneficial in terms of both disease control and tolerability when employed in elderly or PS 2 patients with advanced NSCLC
Nishiyama 2011[148]	Phase II Multicentre Japan 2005-2009	Stage: IIIA/IIIB/IV First-line Chemotherapy naïve Aged >70	S-1 (tegafur, gimeracil, and oteracil) (n=29)	Median age: 78 years (70-85) Male: 76% ECOG PS: 0=27.6%, 1=72.4%	Primary: response rate Secondary: toxicity, disease control rate, PFS, OS	S-1 monotherapy was effective and well tolerated as a first-line treatment for elderly patients with advanced NSCLC. The results of this study warrant further investigations of this regimen, including an RCT
Terai 2011[169]	Phase II 2007-2010	First-line Aged >70	Carboplatin and paclitaxel (n=47)	Median age: 77 years (70-85) Male: 76.6% PS: 0-1=95.7%	Primary: PFS Secondary: ORR, OS, toxicity	The combination of bi-weekly carboplatin and paclitaxel is an active first-line treatment with a tolerable toxicity profile for advanced NSCLC in elderly patients
Xu 2011[174]	Phase II China Supported by the Foundation of Health	Stage: IIIB /IV First-line Aged >70	Erlotinib (n=35)	Mean age: 75.6 years (70-81) Male: 68.6%	Primary: disease control rate Secondary: ORR, TTP, clinical benefit	The results suggest that erlotinib monotherapy is an effective and well-tolerated treatment option for Asian elderly patients with advanced

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Department of Hubei Province, China				response, survival, safety	NSCLC
Cai 2010[89]	China 2004-2007	Stage: IIB/IV Chemotherapy naïve Aged >70	Docetaxel (n=42)	Median age: 73.2 years (65-79) Male: 69%	Outcomes: efficacy, toxicity, OS	Single-agent docetaxel for elderly patients with advanced NSCLC is an efficient and well-tolerated chemotherapeutic approach with a low toxicity level
Camerini 2010[90]	Phase II Italy 2006-2009	Stage: IIB/IV First-line/second-line Aged >70	Vinorelbine (n=43)	Median age: 77 years (70-89) Male: 84% ECOG PS: 2=84%, 3=16%	Primary: response rate, safety Secondary: TTP, OS, complete response, partial response	Single-agent oral vinorelbine is extremely safe in elderly patients with advanced NSCLC and ECOG PS of 2 or more and may represent a valid option in this very special population
Rossi 2010[158]	Phase II Italy	Pretreated Stage: IIIB/IV Aged ≥65	Erlotinib (n=31)	Median age: 75 age (65-85) Male: 90% PS: 0=13%, 1=48%, 2=32%, 3=7%	Outcomes: activity, toxicity	Results confirmed the activity and safety of erlotinib as second- and third-line treatment in elderly patients with advanced NSCLC, especially in terms of median survival. Although the trial does not permit definitive conclusions to be drawn about the role of a particular clinical characteristic predictive of response, the 'clinical benefit' was documented, especially in females, in patients with adenocarcinoma histology and skin rash, confirming previous retrospective data
Rozzi 2010[159]	Phase II Italy 2005-2008	First-line Stage: IIIB/IV Aged >70	Paclitaxel plus carboplatin (n=36)	Median age: 74 years (70-83) Median ECOG PS=1	Outcomes: efficacy, toxicity	Study confirms the substantial activity of weekly regimen of paclitaxel and carboplatin. Due to its favourable profile of toxicity, this schedule could represent an interesting

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
						therapeutic option in selected chemotherapy-naïve elderly patients with advanced NSCLC
Seto 2010[163]	Phase I/II Japan Partial financial support from by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan) and Eli Lilly Co., Ltd. (Kobe, Japan) 2005-2006	Stage: IIIB/IV Chemotherapy I Aged >70 years	Phase I: Gemcitabine plus TS-1 (n=22)	Median age: 76 years (70-85) Male: 82% ECOG PS: 0=32%, 1=68%	Primary: maximum tolerable dose, dose limiting toxicity	TS-1 with gemcitabine is a promising doublet regimen in elderly patients with advanced NSCLC with acceptable toxicities
			Phase II: Gemcitabine plus TS-1 (n=37) (Patients included from phase I=10)	Median age:77 years (70-85) Male:73% ECOG PS: 0=38%, 1=62%	Primary: ORR Secondary: PFS, OS, toxicity	
Blakely 2009[85]	Phase II Multicentre USA 2005-2006	Stage IIIB-IV Aged >65	Pemetrexed plus gemcitabine (n=45)	Median age: 72.4 years (46.1-88) Male: 56% PS: 0=11% 1=60% 2=29%	Primary: OS Secondary: PFS, toxicity	NR
Boukovinas 2009[87]	Phase II Multicentre Greece 2002-2006	Stage IIB Chemotherapy naïve Aged >70	Gemcitabine and docetaxel (n=77)	Median age: 72 years (70-78) Male: 67 (87%) ECOG PS: 0=44.2%, 1=39.0% 2=16.9%	Primary: ORR Secondary: survival, toxicity	The gemcitabine plus docetaxel regimen is an active and well-tolerated front-line chemotherapy for elderly patients with lung adenocarcinomas and merits further evaluation in prospective randomised trials
Du 2009[95]	China 2006-2007	Aged >65	Docetaxel (n=28)	Median age: 71 years (65-79)	Outcomes: response rates, QoL, TTP, OS, toxicity	Weekly dose docetaxel monotherapy schedule is a feasible, well-tolerated, and active scheme in the treatment of the elderly patients with advanced NSCLC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Igishi 2009[115]	Phase I/II Japan Phase I: 2002-2003 Phase II:2003-2006 The cut-off date for updating survival was July 24, 2007	Stage IIIB/IV Aged >70	UFT plus vinorelbine (Phase I: n=12) (Phase II: n=30)	Phase I Median age: 69 years (53-81) Male: 83% ECOG PS: 0=17%, 1=83%	Phase I Outcomes: Maximum tolerated dose and recommended dose	This combination of UFT and vinorelbine is both feasible and active in the treatment of elderly patients with advanced NSCLC
				Phase II Median age: 78 years (71-86) Male: 67% ECOG PS: 0=47%, 1=55%	Phase II Primary: ORR Secondary: Survival, toxicity, time to progression	
Sequist 2009[162]	Phase II Single Institution Open label USA Supported by Eli Lilly and Company and Elsa U. Pardee Foundation 2005-2006	First-line Aged >70	Pemetrexed and gemcitabine (Planned n=55) (Actual: n=9)	Age: 70-82 years Male: 78% PS: 0=22.2%, 1=66.7%, 2=11.1%	Outcomes: Objective response rate, safety	Bi-weekly pemetrexed and gemcitabine was too toxic in this cohort of elderly patients with newly diagnosed advanced NSCLC
Yoshimura 2009[175]	Phase II Japan 2003-2006	Stage: IIIB/IV Chemotherapy naïve Aged >70	Docetaxel and carboplatin (n=30)	Median age: 75 (70-84) Male: 66.7% ECOG PS: 0=6.7%, 1=76.7%, 2=16.7%	Primary: response rate Secondary: PFS, OS, safety	Docetaxel combined with carboplatin was an active treatment with manageable toxicity for the treatment of elderly patients with chemotherapy naïve NSCLC
Attia 2008[80]	Phase I/II USA 2001-2004	Stage: IIIB/IV Aged >70	Vinorelbine plus exisulind (Phase I: n=14) (Phase II: n=30)	Median age: 78 years (71-91) Male: 56.8% ECOG PS: 0=38.6%, 1=56.8%, 2=4.5%	Outcomes: Tolerated dose, TTP	This combination is safe, seems to have activity in the elderly with advanced NSCLC and a PS <2, and warrants further investigation
Ebi 2008[96]	Phase II	Chemotherapy naïve	Gefitinib	Median age: 80 years	Outcomes: OS,	Gefitinib monotherapy is

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Multicentre Japan 2004-2006	Aged >75	(n=49)	(75-90) Male: 35% PS: 0=27% 1=49% 2=24%	PFS	effective and relatively well tolerated in chemotherapy-I elderly patients with advanced NSCLC. Gefitinib has potential as a first-line therapeutic option in elderly patients with advanced NSCLC
Gadgeel 2008[104]	Phase II USA 2001-2004	Stage: IIIB-IV Aged >70	Docetaxel plus calecoxib (n=34)	Median age: 73 years (51-82) Male: 71% PS 2: 56%	Outcomes: survival, response, toxicity	In these 'special populations' of patients with advanced NSCLC, the addition of celecoxib to docetaxel did not seem to improve the outcome compared with single-agent docetaxel
Gridelli 2008[106]	Phase II Italy Associazione Italiana per la Ricerca sul Cancro (AIRC) 2002-2003	Stage: IIIB/IV Aged >70	Gemcitabine (n=51)	Median age: 76 years (70-83) Male: 80% PS: 0=33%, 1=70%	Outcomes: OS, TTP	Gemcitabine at prolonged constant infusion produced a response rate lower than that required by study design and should no longer be of interest for the treatment of elderly patients with advanced NSCLC
Kaira 2008[124]	Phase I Open label Single centre Japan 2005-2007	Stage: IIIB/IV Chemotherapy and radiotherapy naïve Aged >70	S-1 and gemcitabine (n=16)	Median age: 76 years (70-86) Male: 62.5% ECOG PS: 0=31.3%, 1=68.7%	Maximum tolerated dose	The combination of S-1 plus gemcitabine is a feasible and well-tolerated regimen for the treatment of elderly patients
Lee 2008[137]	Phase II Korea Partly supported by a grant from Seoul National University Bundang Hospital Clinical Research Fund 2004-2007	Stage: IIB/IV Aged >65 years with ECOG PS <2 Aged <65 years with ECOG PS 2	Docetaxel (n=40)	Median age: 66 years (33-80) Male: 60% ECOG PS: 0-1=25%, 2=75%	Primary: response rate to treatment Secondary: PFS, OS	Weekly low-dose docetaxel therapy provides a reasonable alternative for NSCLC salvage treatment in pretreated elderly patients or in patients with a reduced PS

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Oshita 2008[152]	Phase II Japan Supported in part by Kanagawa Health Foundation and Kanagawa Prefectural Hospitals Cancer Research Fund 2002-2005	Stage: IIIB/IV Chemotherapy naïve Aged >70	Nedaplatin and irinotecan followed by sequential gefitinib (n=28)	Median age: 74 years (70-81) Male: 20% ECOG PS: 0=21%, 1=79%	Outcomes: response rates, toxicity, OS	Nedaplatin and irinotecan followed by gefitinib is feasible for elderly patients with unresectable NSCLC
Pino 2008[154]	Phase II Multicentre Italy	Stage: IIIB/IV First-line Aged >65	Paclitaxel and gemcitabine followed by maintenance paclitaxel (n=53)	Median age: 73 years (67-82) Male: 96% ECOG PS: 0=40%, 1=51%, 2=9%	Primary: bjective response rate Secondary: safety profile, survival, TTP, 1- and 2- year survival	Bi-weekly paclitaxel and gemcitabine followed by weekly paclitaxel is well tolerated and active as first-line therapy for elderly NSCLC patients
Rossi 2008[157]	Phase II Italy 2003-2005	Stage: IIIB/IV Chemotherapy naïve Aged >70	Paclitaxel (n=27)	Median age: 73 years (70-83) >80 years: 26% Male:89% ECOG PS: 0=40.7%, 1=37.0% , 2=22.2%	Outcomes: activity, toxicity	The study confirmed that paclitaxel 80 mg/m^2 weekly is active in patients with locally advanced and metastatic NSCLC with a good safety profile; this schedule might be considered an alternative choice to gemcitabine or vinorelbine as first-line treatment in elderly patients, particularly patients with comorbidities
Tibaldi 2008[173]	Phase II Multicentre Italy 2005-2006	Stage: IIIB- First-line Aged >70	Sequential gemcitabine followed by docetaxel (n=56)	Median age: 76 years (70-84) Male: 82% ECOG PS: 0=12.5%, 1=67.8%, 2=19.6%	Primary: response rate Secondary: toxicity, TTP, survival	Sequential gemcitabine and docetaxel is a well-tolerated and effective regimen in elderly advanced NSCLC patients
Jackman 2007[121]	Phase II Multicentre USA	Stage: IIIB/IV Chemotherapy naïve (n=80)	Erlotinib	Median age: 75 years (70-91)	Primary: median survival, 1- and 2-year survival	Erlotinib monotherapy is active and relatively well tolerated in chemotherapy-naıve elderly

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Supported by grants: National Institute of Health, National Cancer Institute Specialised Program of Research Excellence in Lung Cancer, Genentech Inc., Doris and William Krupp Research fund in Thoracic Oncology 2003-2005	Aged >70		Male: 50% ECOG PS: 0=16%, 1=74%, 2=10%	Secondary: radiographic response rate, TTP, QoL, toxicity, symptom improvement	patients with advanced NSCLC. Erlotinib merits consideration for further investigation as a first-line therapeutic option in elderly patients
Juan 2007[123]	Phase II Spain	Stage: IIIA/IIIB/IV Chemotherapy naïve Aged >65	Paclitaxel (n=57)	Median age: 74 years (65-84) >70 years: 70% >80 years: 16% Male: 89.5% PS: 1=38.5%, 2=61.5%	Primary: toxicity, OS	The low toxicity profile and efficacy of low-dose weekly paclitaxel justified its usage in this group of poor prognosis elderly patients with advanced NSCLC and comorbidities. A comorbidity index should be introduced in prospective oncological studies in the elderly to ensure compatibility
Kaira 2007[125]	Phase I Japan 2000-2002	Stage: IIB/IV Chemotherapy and radiotherapy naïve Aged >70	Docetaxel and carboplatin (n=25)	Median age: 76 years (70-86) Male: 68% ECOG PS:, 0=24%, 1=68%, 2=8%	Outcomes: toxicity, response rate	The combination of docetaxel and carboplatin is a feasible and well-tolerated regimen for the treatment of elderly patients with advanced NSCLC. This regimen merits further investigation in phase II trials

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
LeCaer 2007a[135]	Phase II Multicentre France Supported by Sanofi Aventis Oncology, Jansen Cilag DHRC Assistance Publique Hopitaux de Marseille 2003-2004	Stage: IIIB/IV Aged >65	Docetaxel (n=50)	Mean age: 76.6 years (70-84) Male: 88% ECOG PS: 0=22% 1=46% 2=32%	Primary: objective response rate, safety, tolerability Secondary: disease control rate, PFS, OS, QoL	In frail elderly patients selected on the basis of their age, general condition and comorbidity, weekly docetaxel monotherapy has acceptable toxicity and does not negatively affect QoL. In contrast, it has only moderate activity
Maestu 2007[141]	Multicentre Spain 2001-2003	Stage: IIIA/IIIB/IV Chemotherapy I Aged >70	Gemcitabine plus vinorelbine (n=59)	Median age: 74 years (70-83) 70-74: 57.6% >74 years: 42.4% Male: 90% ECOG PS: 0=3.4%, 1=55.9%, 2=40.7%	Primary response rate Secondary: OS, TTP, tolerability	This bi-weekly combination is feasible in elderly lung cancer patients with a high burden of comorbidity and dependence. Toxicity is acceptable, whereas response rate and survival fall in the range of active regimens. ADL and IADL indices allow the identification of elderly patients with a worse prognosis
Buffoni 2006[88]	Phase II Italy 2001-2003	Stage: IIIA/IIIB/IV Aged ≥70	Cisplatin and vinorelbine (n=30)	Median age: 73 years (70-77) Male: 90% ECOG PS: 0=10%, 1=77%, 2=13%	Primary: assessment of response rate Secondary: efficacy, toxicity, OS	At this dose and schedule, the combination of vinorelbine and cisplatin obtained a response rate and survival comparable to the most active regimens. Non-haematological toxicity was mild, whereas neutropenia was the most relevant toxicity
Giorgio 2006[105]	Phase II Italy Multicentre 1999-2004 Median follow-up: 14.3 months (3-36)	Stage: IIIB/IV First-line Aged >70	Carboplatin and paclitaxel (n=40)	Median age: 74 years (70-78) Male: 77.5% ECOG PS: 0=35%, 1=45%, 2=20%	Outcomes: treatment dose intensity, treatment toxicity, ORR, TTF	The combination of paclitaxel and carboplatin has demonstrated to be active and safe in an age-selected population

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Hesketh 2006[111]	Phase II USA Supported in part by the following PHS Cooperative Agreement grant number awarded by the National Cancer Institute, and in part by GlaxoSmithKline and Aventis 2001-2003	Stage IIB	Strata 1: Sequential vinorelbine and docetaxel (n=75)	≥70 years Median age:76 years (70-88) Overall >80 years:20% Male: 53% Zubrod PS: 0-1	Outcomes: survival, efficacy, toxicity, patient impact of treatment report	Sequential vinorelbine and docetaxel is a well-tolerated and effective regimen in comparison with reports of other treatments tested in patients with advanced NSCLC aged ≥70 and/or with a PS of 2
			Strata 2: Sequential vinorelbine and docetaxel (n=42)	Median age: 77 years (44-85) Overall >80 years: 20% Male:55% Zubrod PS: 2		
Martoni 2006[143]	Italy 2000-2003	Stage: IIB/ First-line Chemotherapy and radiotherapy naïve Aged >70	Sequential gemcitabine and vinorelbine (n=52)	Median age: 76 (70-85) Male: 85% Median KPS: 80 (70-100)	Primary: time to progression Secondary: objective remission, OS	The planned sequential administration of GEM and VNR suggests that the TTP can be increased with the use of the 2 single agents in elderly patients with locally advanced or metastatic NSCLC
Pujol 2006[155]	Phase II Multicentre France Supported by Bristol-Myers Squibb, Rueil-Malmaison, France 2002-2003	Stage: IIIB/IV First-line Aged >70	Paclitaxel and carboplatin (n=51)	Median age: 74 years (69-88) Mean age: 75.2 years (4.7) Male: 75% ECOG PS: 0=29%, 1=61%, 2=10%	Primary: ORR Secondary: QoL, safety, OS, PFS	The combination of weekly paclitaxel plus monthly carboplatin was feasible and active as a first-line treatment for elderly patients with NSCLC with a good safety profile. These results deserve further analysis to compare the standard care for these patients (monotherapies) with this doublet
Santo 2006[160]	Phase II Italy Supported by GIVOP (Gruppo Interdisciplinare	Stage: IIIB/IV Aged >70 or <70 with KPS <60	Gemcitabine and vindesine (n=44)	Median age: 70 years (43-79) Male: 81.8% Median KPS: 60;	Primary: treatment response Secondary: TTP, OS	Gemcitabine plus vindesine is an active and well-tolerated schedule

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Veronese di Oncologia Polmonare) 1998-2001			>60=43.2%, <60=25		
Stinchcombe 2006[166]	Phase I/II Multicentre USA 2003-2005	Stage: IIIB/IV Aged >70	Docetaxel and gefitinib (n=26)	Median age: 75.70 years (72.25-78.75) Male: 65% ECOG PS: 0=81%, 2=19%	Phase I Maximum tolerated dose, recommended dose Phase II Primary: response rate Secondary: TTP, overall toxicity profile	The combination of weekly docetaxel and gefitinib had activity; however, unexpected toxicity was observed in the elderly patient population
Tibaldi 2006[170]	Phase II Italy 2002-2005	Stage: IIB/IV Second-line Aged >70	Docetaxel (n=33)	Median age: 74 years (70-83) Male: 88% ECOG PS: 0=9%, 1=67%, 2=24%	Outcomes: ORR, OS, TTP, toxicity	Our modified schedule of docetaxel is an active and well-tolerated second-line treatment in elderly patients with advanced-stage NSCLC and has a favourable toxicity profile
Hirsh 2005[112]	Phase II Multicentre Canada Sponsored in part by GlaxoSmithkline 2001-2003	Stage: IIIB-Pleural effusion /IV-Metastatic Aged >70	Sequential vinorelbine followed by gemcitabine (n=42)	Median age: 75 years (58-89) Male: 76.1% ECOG PS: 0=9.5%, 1=40.5%, 2=50.0%	Primary: efficacy determined by survival Secondary: response rate, TTP, treatment-related toxicity	This sequential treatment offers excellent palliative treatment with minimal toxicity for high-risk patients with metastatic NSCLC
LeCaer 2005[133]	Phase II Open Multicentre France Supported by a grant from Pierre Fabre Oncology Pharmaceuticals (France)	Stage: IIIB/IV First-line Chemotherapy naïve Aged >70	Carboplatin combined with vinorelbine (n=40)	Median age: 72 years (70-82 Male: 77.5% ECOG PS: 0=37.5%, 1=22.5%	Primary: ORR Secondary: OS, event-free survival, tolerability, QoL	Carboplatin/vinorelbine is well tolerated by elderly patients with extensive-stage NSCLC. Efficacy is low but similar to that of other treatments used in this setting

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	2000-2002					
Tibaldi 2005[172]	Phase II Multicentre Italy 1998-2002	Stage: IIIB/ IV Chemotherapy naïve	Gemcitabine (n=122)	Median age: 75 years (70-84) 70-75 years: 50.8% >75 years: 49.2% Male: 86.9% ECOG PS:0=34.4%, 1=45.1%, 2=20.5%	Primary: response rates Secondary: tolerability, PFS, OS	Although increased dose intensity of gemcitabine in elderly NSCLC patients is feasible without severe toxicities, this does not seem to be associated with an increased activity and efficacy compared with standard gemcitabine regimens with lower dose intensities
Capuzzo 2004[91]	Multicentre Italy 2001-2003	Stage: III/IV Aged >70	Gefitinib (n=40)	Median age: 74 years (70-88) Male: 82.5%	Primary: response rate, safety	Gefitinib is safe and well tolerated in elderly pretreated NSCLC patients. The disease-control rate achieved suggests that this drug could represent a valid option in the management of this unfavourable subgroup of patients
Gridelli 2004[107]	Phase II Multicentre International: Italy, Germany, Finland, France, Switzerland and Spain Pierre Fabre supported the study entirely in terms of grants, equipment and drugs) 2001-2002	Stage: IIIB/IV or delayed relapse of any stage becoming unresectable Chemotherapy naïve Aged >70	Oral vinorelbine (n=56)	Median age: 74: years (70-82) Male: 75% KPS: 100=18%, 90=34%, 80=48%	Primary: response rate Secondary: duration of response, PFS, OS, toxicity, clinical benefit, drug pharmacokinetic, inter-individual variability	Oral vinorelbine appears to be a reasonable alternative to intravenous vinorelbine, both in terms of activity and tolerability, in advanced, elderly NSCLC patients

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Kanard 2004[126]	Phase II Multicentre USA Supported in part by Public Health Service grants 2001-2002	Stage: IIB/IV First-line Radiation naïve Aged >65	Oral vinorelbine (n=58)	Median age: 73 years (65-87) Male: 69% ECOG PS: 0=29%, 1=59%, 2=12%	Primary: tumour response rate Secondary: TTP, OS	Oral vinorelbine, as prescribed in this trial, provides minimal activity in the treatment of advanced NSCLC in patients aged ≥65 years
Ohe 2004[149]	Phase II Japan Supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, a grant from the Ministry of Health, Labour and Welfare for 2nd Term Comprehensive Strategy for Cancer Control, Japan and a Bristol Myers Squibb Unrestricted Grant 2000-2002	Stage: IIIA/IIIB/IV Chemotherapy naïve Aged >75	Cisplatin and docetaxel (n=33)	Median age: 77 years (75-86) Male: 78.8% ECOG PS: 0=21%, 1=79%	Outcomes: objective tumour response, OS, toxicity	Cisplatin and docetaxel administered in three consecutive weekly infusions was safe and effective for the treatment of elderly patients with chemotherapy-naïve NSCLC
Oshita 2004[153]	Phase II Japan Supported in part by Kanagawa health Foundation 2000-2002	Stage: IIB, IIIA, IIIIB/IV Chemotherapy naïve Aged >70	Nedaplatin and irinotecan (n=38)	Median age: 74 years (71-84) Male: 71% ECOG PS: 0=10.5%, 1=89.5%	Outcomes: ORR, toxicity, survival	Nedaplatin combined with irinotecan is an active for elderly patients with NSCLC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Takigawa 2004[168]	Phase II Multicentre Japan Supported in part by a grant from the Ministry of Health, Labour and Welfare of Japan 1999-2001	Stage: IIIA, IIIB/IV Chemotherapy naïve Aged >76	Docetaxel (n=15)	Median age: 78 years (76-87) Male: 80% ECOG PS: 0=20%, 1=66.7%, 2=13.3%	Primary: efficacy, safety, tolerability, pharmacokinetic profile Secondary: QoL, PFS, OS, ORR	Although the validity of the results of this study is limited due to the small sample size, docetaxel appears effective in selected elderly patients with advanced NSCLC
Berardi 2003[84]	Phase II Italy 1998-2002	Stage: IIIB/IV Aged >70	Gemcitabine plus cisplatin (n=48)	Median age: 74 years (70-78) Male: 80%	Primary: response rates Secondary: OS, toxicity	At this dose and schedule the combination of gemcitabine and cisplatin appears to be an active and well-tolerated regimen for elderly patients with advanced NSCLC
Chen 2003[93]	Phase II Taiwan 1998-2001	Stage: IIIB/IV Aged >80	Vinorelbine plus gemcitabine (n=20)	Median age: 83 years (80-88) Male: 80% WHO PS: 1=20%, 2=80%	Primary: TTP, ORR, toxicity	The combination of vinorelbine and gemcitabine in very old patients with advanced NSCLC is a highly active regimen with an acceptable toxicity profile
Choi 2003[94]	South Korea Supported by KOSEF through SRCMTRC 1997-2001	Stage: IIIB/IV, or recurrent disease after prior surgery or radiation Chemotherapy I Aged >65 or <65 with ECOG PS 2	Paclitaxel plus carboplatin (n=35)	Median age: 67 years (48-78) Male: 77% PS: 2=74%	Primary: ORR, TTP, toxicity	The modified regimen with attenuated doses of paclitaxel plus carboplatin combination chemotherapy was effective and well tolerated in patients with advanced NSCLC aged ≥65 years and/or in those with ECOG PS 2
Hainsworth 2003[108]	Phase II Multicentre USA 1999–2000 Supported in part by grants from Aventis, Inc., Eli Lilly, Inc.,	Stage: IIIB/IV Aged ≥70 or <70 with coexistent medical illness and/or poor PS	Docetaxel plus gemcitabine (n=64)	Median age: 71 years (51-85) Male: 75% ECOG PS: 0=13%, 1=59%, 2=25%	Primary: feasibility, toxicity, efficacy, PFS	The combination of weekly docetaxel/gemcitabine is active and relatively well tolerated in most patients with advanced age or poor PS with advanced NSCLC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	and The Minnie Pearl Cancer Foundation					
Jatoi 2003[122]	Phase II Multicentre USA Supported in part by Public Health Service grants 2000-2001	Single stage Stage: IV or recurrent unresectable Aged >65	Carboplatin and paclitaxel (n=49)	Median age: 73 years (65-85) Male: 59.2% ECOG PS: 0=30.6%, 1=46.9%, 2=22.5%	Primary: tumour response Secondary: survival	Low-dose weekly carboplatin and paclitaxel, as prescribed in this trial, provides modest activity in the treatment of advanced non-SCLC patients aged ≥65 years. However, the relatively mild toxicity profile observed suggests that this regimen might remain an option for patients at increased risk for myelosuppression or with a poor PS
Maestu 2003[140]	Phase II Spain 1998-2000	Stage: IIIA/IIIB/IV Aged >70 or 65-70 years and frail	Carboplatin plus gemcitabine (n=88)	Median age: 74 years (65-83) 65-70 years:6.8% 70-74 years:38.6% >74 years:54.5% Male: 97% ECOG PS: 0=7% 1=59%, 2=34%	Outcomes: ORR, OS, tolerability	The combination carboplatin-gemcitabine at these doses is feasible in elderly patients with advanced NSCLC. Tolerability and toxicity are acceptable. Response rate and survival stand in the range of the most active regimens. Comorbidity and PS showed prognostic independence
Inoue 2002[117]	Phase I Japan Supported by Grants-In-Aid for Cancer Research from the Ministry of Health and Welfare, Japan, the Second Term Comprehensive 10-year strategy for	Stage: IIIA/IIIB/IV Received <1 chemotherapy regimen Aged >70 years	Docetaxel (n=11)	Median age: 73 years (70-78) Male: 82% ECOG PS: 0=18%, 1=82%	Outcomes: dose limiting toxicity, the maximal tolerable dose, response rates	In this phase I trial, the maximum tolerated dose of weekly administration of docetaxel to elderly NSCLC patients was 30 mg/m^2/week, with neutropenia and diarrhoea as dose-limiting toxicities. The recommended dose for future trials is 25 mg/m^2/week. Although this treatment was generally well tolerated, 27% of patients

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Cancer Control, Japan 2000-2001					experienced grade 3 or 4 neutropenia
Fidias 2001[99]	Phase II USA 1998-2000	Stage: IIIB/IV Aged >70	Paclitaxel (n=35)	Median age: 76 years (70-85) Male: 68% PS: 0-1=80%, 2=17%, 3=3%	Primary: toxicity, response	Paclitaxel administered as a weekly 1-hour infusion at a dose of 90 mg/m^2 is a safe and effective therapy for elderly patients with advanced NSCLC. Its pharmacokinetics in elderly patients do not appear to differ from historical data for younger patients, and there was no suggestion of a change in drug clearance after repeated weekly dosing
Older and younger patients						
Laskin 2012[132]	Phase IV Multicentre International Canada, Italy, Spain, Russia, China, The Netherlands and Germany F.Hoffmann-La Roche 2006-2008	First-line Stage: IIIB/IV Aged >65	Bevacizumab plus standard of care chemotherapy (n=2212) (<65: n=1589) (>65: n=623)	Mean age: 70.6 years (66-86) Male: 62.8% ECOG PS: 0=31.6%, 1=61.3%, 2=7.1%	Primary: safety Secondary: efficacy, TTP, OS, safety, ORR, disease control rate	Patients older than 65 years with non-squamous NSCLC derive a similar clinical benefit from first-line bevacizumab-based therapy as their younger counterparts and do not experience increased toxicity
Merimsky 2012[144]	Phase IV Open-label Multicentre International 2007-2009	Stage: IIIB/IV Aged ≥70	Oral erlotinib (n=6580) (≥70: n=485 [7.3%])	Median age: 77 years (70-91) Male: 54% ECOG PS: 0=15%, 1=48%, 2=29%, 3=9%	Primary: PFS, OS	Erlotinib was effective and well tolerated, and may be considered for elderly patients with advanced NSCLC who are unsuitable for standard first-line chemotherapy or radiotherapy

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Rodriguez 2012[156]	Single centre USA Funded by a Medical Student Training in Aging Research (MSTAR) Grant 2006-2010	Stage: IB/IIB and higher Neoadjuvant therapy naïve Aged >70	Adjuvant chemotherapy (n=99) (>70: 30%) (<70: 70%)	>70 male: 46.7% <70 male: 46.4%	Outcomes: determine age-related biases	Patients undergoing lobectomy who were aged ≥70 years received adjuvant chemotherapy less often than did younger patients
Schuette 2012[161]	Phase IV Prospective Non-Interventional Multicentre Germany and Austria Funded by Lilly Deutschland GmbH, Bad Homburg, Germany 2007-2009	Stage: IIIA/IIIB/IV Second-line Aged ≥70	Pemetrexed (n=521) (≥70 years: 188 [36%]) <70 years: 333 (64%)	Median age: 66.3 years (39-86) Male: 69.7% Karnofsky Index: Median=80% >80%=61.7%, 70%=23.9%, 60%=9.6%, 50%=4.3%	Primary: Karnofsky Index benefit response (after cycle 2) Secondary: HR-QoL, reasons for treatment discontinuations	In this large prospective, non-interventional study of second-line pemetrexed treatment in patients with advanced NSCLC, including 36% elderly patients (≥70 years), physician-rated PS and self-rated HR-QoL were maintained or improved in the majority of patients
Kim 2010[128]	Phase II Single centre Republic of Korea 2005-2008	Stage: IIIB/IV Aged >65	Docetaxel and carboplatin (n=43) (65-74=48.8%) (>75=51.2%)	Median age: 74 years (65-84) Male: 90.6% ECOG PS: 0-1=90.6%, 2=9.4%	Primary: response rate Secondary: OS, PFS, toxicity	The combination chemotherapy with docetaxel and carboplatin was effective with tolerable toxicities in elderly patients with advanced NSCLC
Feliu 2009[97]	Phase II Spain 2004-2005	Stage: IIIB/IV Aged ≥70 years	Docetaxel plus cisplatin (n=42) [≥75=20 (48%)] [70-74=22 (52%)]	Median age: 75 years (70-80) ECOG PS: 0=14%, 1=69%, 2=17%	Feasibility, toxicity, efficacy, TTP, OS.	The combination of low-dose cisplatin and docetaxel for elderly patients with advanced NSCLC is an efficient and well-tolerated chemotherapeutic approach

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Han 2009[110]	Phase II Multicentre China 2004-2006 Median follow-up=12.4 months	Stage: IIIB-/IV First-line ECOG PS of 0-1 Aged >70	Weekly docetaxel and cisplatin (n=48) (<75: 47.95) (>75: 52.1%)	Median age: 76 years (70-86) Male: 62.5% ECOG PS: 0=22.9%, 1=77.1%	Outcomes: safety, efficacy, tolerability	The combination of weekly docetaxel and cisplatin is a well-tolerated treatment modality with encouraging activity and survival outcome in previously untreated elderly patients with advanced NSCLC
Lee 2009[136]	Phase II Korea Supported by grants from the special clinical fund of Gyeongsang National University Hospital 2005-2007	Stage: IIIB/IV Previously un-treated Aged >65 with ECOG PS 0-2 or <65 with ECOG PS 2	Gemcitabine and cisplatin (n=48) (>65: 68.8%)	Median age: 67 years (38-76) Male: 77.1% ECOG PS: 0-1=20.8%, 2=79.2%	Outcomes: ORR, OS, TTP, toxicity	Results indicate that this regimen is a feasible treatment for elderly or poor PS patients with unresectable NSCLC. Nevertheless, the morbidity due to myelosuppression and infection following this treatment should be carefully considered
Simon 2008[164]	Phase II USA Sanofi-Aventis Pharmaceuticals and Astra-Zeneca Pharmaceuticals provided research funds and the drugs used in the study 2003-2005	Stage: IIIB/IV First-line Chemotherapy naïve >70 years	Docetaxel and gefitinib (n=44) <75: 55% >75: 45%	Age at diagnosis: 75 years (70-85) Male: 59% ECOG PS: 0=55%, 1=45%	Primary: response rate Secondary: OS, PFS, toxicity	Docetaxel combined with gefitinib is active and well tolerated in patients with advanced NSCLC who are aged ≥70 years. This paradigm of treatment merits further investigation as a first-line treatment strategy
LeCaer 2007[134]	Phase II Multicentre France This study was supported by Sanofi Aventis Oncology, Lilly Oncology, Jansen Cilag DHRC Assistance Publique	Stage: IIIB/IV-pleural Chemotherapy naïve Aged >65	Docetaxel plus gemcitabine (n=50) (70-79: 84%)	Median age: 73.7 years (65-82) Male: 78% ECOG PS: 0=42%, 1=54%, 2=4%	Primary: ORR Secondary: disease control rates, PFS, OS, QoL, safety, tolerability	Platinum-free dual-agent chemotherapy gives similar results in patients >65, selected on the basis of their precise age and comorbidity, to that reported in younger patients

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Hospitaux de Marseille 2003-2004					
Inoue 2006a[119]	Phase II Multicentre Japan 2002-2004	Stage: IIIB/IV, or postoperative recurrent Chemotherapy and radiotherapy I Aged >70	Paclitaxel and carboplatin (n=40) (>75: 63%)	Median age: 75 years (70-81) ECOG PS: 0=28%, 1=72%	Outcomes: response, survival, toxicity	Weekly paclitaxel and carboplatin combination chemotherapy was an effective and safe regimen in elderly patients with advanced NSCLC. A randomised trial comparing this treatment with the conventional tri-weekly regimen of paclitaxel and carboplatin is warranted
Ishimoto 2006[120]	Phase II Multicentre Japan 2003-2005	Stage: IIB/IV Aged >20 years	Carboplatin combined with docetaxel (n=50) (>70: 26%)	Median age: 65 years (34-79) Male: 84% ECOG PS: 0=42%, 1=56%, 2=2%	Primary: RR Secondary: OS, toxicity	Bi-weekly docetaxel plus carboplatin has a similar efficacy and lower toxicity compared with a standard tri-weekly regimen of docetaxel plus carboplatin, which is a suitable regimen for outpatients, including elderly patients
Ichinose 2005[113]	Phase II Multicentre Japan 2000-2002	Stage: IIIB Aged <75 vs ≥75	Gemcitabine plus tegafur and uracil (UFT) (<75: n=23) (≥75 n=21)	Median age: 78 years (75-89) Male: 52.4% ECOG PS: 0=38%, 1=62%	Primary: efficacy, toxicity	This combination chemotherapy demonstrated a promising effectiveness and acceptable toxicity in patients with advanced NSCLC, even in patients >75 years
Okamoto 2005[151]	Phase II Japan 2001-2003 Median follow-up=12.3 months	Stage: IIIB/IV Chemotherapy I Aged >70	Carboplatin and paclitaxel (n=25) (<75=40%) (>75=60%)	Median age: 76 years (70-83) ECOG PS: 0=44%, 1=56%	Primary: ORR Secondary: toxicity	The combination carboplatin–paclitaxel at these doses is a feasible treatment option with a favourable toxicity profile for fit elderly patients with advanced NSCLC
Feliu 2003[98]	Phase II Spain 1999-2001	Stage: IIIB/IV Aged ≥70	Cisplatin (CDDP) plus gemcitabine (GEM) (n=46)	Median age: 74 years (70-81) Male: 91%	Feasibility, toxicity, efficacy, TTP, partial response rate	The combination of low-dose cisplatin and gemcitabine for elderly patients with advanced NSCLC is an effective and

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
			(≥75=39%) (70-74=61%)	ECOG PS: 1=65%, 2=57%		well-tolerated chemotherapeutic approach
Beretta 2000[176]	Phase II Italy The Associazione Oncologica Bergamasca supported this study	Stage: IIIA/IIB/IV Chemotherapy naïve, elderly/unfit Aged >65	Gemcitabine followed by vinorelbine (n=43) (>65=60%) (<65=40%)	Median age: 66 years (48-75) Male:83.7% >65 ECOG PS: 0=42%, 1=58%	Primary: efficacy, toxicity Secondary: OS, stage, response	Results show that the combination of gemcitabine and vinorelbine is active and well tolerated in NSCLC, and thus encourage its use in elderly or unfit patients
SCLC						
Murata 2011[145]	Phase II Japan 2005-2009	Limited /extensive disease Chemotherapy naïve Aged >70	Carboplatin and irinotecan (n=30) (>75=50%) (>80=26.7%)	Median age: 76 (70-86) Male: 87% ECOG PS: 0=6.7%, 1=83.3%, 2=10%	Primary: response rate Secondary: toxicity, survival	This chemotherapy is safe and effective for elderly patients with SCLC
Chee 2010[92]	Phase II Open-label USA 2006-2007	Extensive stage Aged <70 vs >70	Pemetrexed disodium plus carboplatin (<70: n=29) (>70: n=17)	<70 Median age: 62 years (48-69) PS: 0=41.4%, 1=55.2%, 2=3.4% >70 Median age: 75 years (70-80) PS: 0=41.2%, 1=35.3%, 2=23.5%	Primary: response rates Secondary: toxicity, OS, TTP	Although well tolerated, the combination of pemetrexed and carboplatin is not as effective as standard therapy in patients with untreated extensive-stage SCLC
Igawa 2010[114]	Japan 2003-2009	Extensive disease First-line Aged >75	Amrubicin (n=27)	Median age:73 (55-82) Male: 82% ECOG PS: 0-1=48%, 2=44%, 3=8%	Outcomes: efficacy	Amrubicin exhibits activity and acceptable toxicities for elderly and poor-risk patients with extensive disease SCLC in the first-line treatment setting
Inoue 2010[116]	Phase II Japan 2005-2007	Extensive/limited disease Chemotherapy and radiotherapy naïve	Amrubicin and carboplatin (n=36)	Median age: 76 years (70-83) Male: 58.7%	Primary: ORR Secondary: PFS, OS, toxicity profile	Amrubicin combined with carboplatin is quite effective for SCLC with acceptable toxic effects even for the elderly population. Further evaluation

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
		Aged >70 years		ECOG PS: 0=47%, 1=53%		of this regimen is warranted
Kim 2008[127]	Phase II Korea 2003-2007	Extensive disease Aged >65	Irinotecan and cisplatin (n=46)	Median age: 70 years (65-81) Male: 80.4% ECOG PS: 0=8.7%, 1=28.3%, 2=43.5%, 3=13.0%	Outcomes: efficacy, toxicity, OS, PFS response rates	Results indicate that combination chemotherapy with irinotecan and cisplatin is an effective treatment for elderly patients with extensive-disease SCLC who have good ECOG PS and physicians should be aware of the mortality and morbidity due to myelosuppression following this treatment in elderly extensive-disease SCLC patients with poor ECOG PS
Fujiwara 2006[102]	Phase I Japan 2001-2004	No prior anticancer therapy Aged ≥76	Topotecan plus cisplatin (n=21)	Median age: (76–82) Male: 90.5% ECOG PS: 0=23.8%, 1=61.9%, 2=14.3%	Primary: maximum tolerated dose Secondary: anti-tumor activity	The combination chemotherapy of 3-day topotecan and cisplatin appears to be tolerable and effective in elderly patients with SCLC
Fukuda 2006[103]	Phase I Japan	Chemotherapy naïve Any stage of SCLC Aged ≥75	Carboplatin plus etoposide (n=26)	Median age: 78 years (75-82) Male: 81% ECOG PS: 0=35%, 1=42%, 2=23%	Primary: optimal doses of carboplatin plus etoposide	A dose of carboplatin of AUC=4 and etoposide of 100 mg/m² was recommended in this regimen
Inoue 2006b[118]	Phase I Japan 2003-2005	Stage IIIA/IIIB/IV Chemotherapy and radiotherapy naïve Aged >70	Amrubicin combined with carboplatin (n=12)	Median age: 74 years (71-77) Male: 75% ECOG PS: 0=33.3%, 1=66.7%	Primary: dose limiting toxicity, maximal tolerable dose Secondary: response rate, survival	The maximum tolerated dose of this combination was amrubicin 40 mg/m^2 and carboplatin AUC 4.0, and the recommended dose for a phase II trial is a combination of amrubicin 35 mg/m^2 and carboplatin AUC 4.0. We are now conducting a multicentre phase II trial of this regimen to determine the activity of this combination for elderly patients with SCLC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Okamoto 2006[150]	Prospective non-phase I Japan Supported in part by Grants-in-Aid for Cancer Research and for the Second-Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labour and Welfare (Tokyo) 1998-2003	Limited /extensive disease Previously treated or untreated Aged >70	Carboplatin and irinotecan with granulocyte colony-stimulating factor (n=18)	Median age: 75 years (70-85) Male: 77.8% ECOG PS: 0=22.2%, 1=50%, 2=27.8	Primary: feasibility, efficacy Secondary: ORR, OS	The combination of carboplatin and irinotecan with granulocyte colony-stimulating factor support was an effective and non-toxic regimen in elderly SCLC patients and should be further evaluated in phase III trials
Soda 2006[165]	Phase I Japan 1998-2003	Any disease stage Aged >75	Carboplatin plus etoposide (n=26)	Median age: 78 years (75-82) Male: 80% PS: 0=34.6%, 1=42.3%, 2=23.1%	Primary: maximum tolerated dose	A dose of carboplatin of AUC=4 and etoposide of 100 mg/m^2 was recommended in this regimen
Hainsworth 2004[109]	Phase II Multicentre USA Supported in part by grants from Aventis, Inc., Eli Lilly, Inc., and The Minnie Pearl Cancer Foundation 2000-2002	SCLC Chemotherapy and radiotherapy naïve Advanced SCLC Aged >65	Docetaxel plus gemcitabine (n=40)	Median age: 72 years (56-88) Male: 60% ECOG PS: 0=20%, 1=35%, 2=45%	Feasibility, toxicity, efficacy	Although relatively well tolerated, the weekly regimen of gemcitabine and docetaxel possessed only modest activity in this group of patients with unfavourable prognosis. The regimen offered no potential advantages over standard treatment approaches and is not recommended for further development

NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; UFT=uracil-tegafur; EGFR=epidermal growth factor receptor; PS=performance status; AUC=area under the curve; PFS=progression-free survival; OS=overall survival; QoL=quality of life; HR-QoL=health-related QoL; CGA=comprehensive geriatric assessment; AE=adverse event; ORR=objective response rate; TTP=time to progression; TTF=time to treatment failure; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; KPS=Karnofsky performance status; ECOG=Eastern Cooperative Oncology Group; WHO=World Health Organisation; S-1=tegafur, gimeracil, and oteracil; RCT=randomised controlled trial; NR=not reported

Appendix 5: Tolerability outcomes, single cohorts

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Bauman 2012[83]	Imatinib plus paclitaxel: Median paclitaxel cycles=2 (0-6)	Patients unevaluable prior to first assessment due to withdrawal/death, n=6 Death due to pre-existing coronary artery disease, n=2	Imatinib reduction due to neutropenia, neuropathy and fatigue, n=9 (26%) Paclitaxel reduction due to neuropathy, elevated bilirubin or fatigue, n=4 (15%)	Death: (n=2), due to: infection n=1, pneumonitis n=1 Grade 3: Neutropenia=12% Fatigue=29%
Firvida 2012[100,101] (abstract only)	NR	Erlotinib: Withdrew due to grade 3 diarrhoea and eye perforation=2	Dose reduction, n=4 (14%)	Grade 3-4: Skin rash=12%
Kurata 2012[131]	Phase I Carboplatin plus gemcitabine: Median cycles=3.0 (range 1-9) Phase II Carboplatin plus gemcitabine: Median cycles=3.0 (range 1-6)	NR	After the first course Dose reduction, n=4 Treatment related: Level 2b, n=2 Level 3, n=2 Median length of delay before starting the subsequent course= 25 days (21 to 41) Among 83 courses – proceeded to the next course without delay=58%, as stipulated in the protocol Phase II: Dose reductions n=12 Median length of delay before starting subsequent course=27 days (21 to 46)	Grade 3-4: Thrombocytopenia=52% Platelet transfusions=16% Leukopenia=52% Neutropenia=60% Anaemia=40%
Maemondo 2012[139]	Gefitinib	NR	Dose reduction=14 (45%)	Treatment-related death n=1 Grade 3 AEs=29% Grade 3-4: AST/ALT=19%
Merimsky 2012[144]	NR	Discontinuations due to AEs=10%	Does reductions=27%	NR

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Takatani 2012[167]	Phase I Vinorelbine plus carboplatin: Maximum tolerated dose=level 4 Recommended dose=level 3 Level 1: 10 mg+AUC 4, n=3 Level 2: 15 mg+AUC 4, n=3 Level 3: 20 mg+AUC 4, n=3 Level 4: 25 mg+AUC 4, n=3	NR	NR	Dose-limiting toxicities=0/3 Grade 3-4=0/3 Level 2: Dose-limiting toxicities=0/3 Grade 3-4=0/3 Dose-limiting toxicities=0/3 Grade 3: Anaemia=2/3 Leukopenia=2/3 Neutropenia=1/3 Grade 4: Neutropenia=1/3 Dose-limiting toxicities=2-Grade 4 Neutropenia that lasted >4 days Grade 3: Anaemia=1/3 Leukopenia=2/3 Neutropenia=2/3 Thrombocytopenia=1/3
Tibaldi 2012[171]	Sequential cisplatin or gemcitabine followed by docetaxel: Total cycles=126 Cisplatin, gemcitabine and docetaxel median cycles=4 (1-6)	NR	NR	Grade 3: Neutropenia=10% Asthenia=10%
Xu 2012[174]	Erlotinib	NR	Dose reduction to 100 mg due to severe skin rash and diarrhoea (patient had progressive disease)=1	NR
Asami 2011[78,79]	Gefitinib: Continued protocol treatment >3 months, n=15	All patients were able to continue without discontinuation due to gefitinib toxicity Discontinued protocol <3 months – cancer/progressive disease, n=2	Temporary withdrawal n=4 – due to Grade 3-increased levels AST/ALT and/or skin rash.	>Grade 3: Skin rash=12% AST/ALT=18%
Borghaei 2011[86]	Bevacizumab plus erlotinib: Off protocol n=20 Median cycles=4 (1-40) On protocol n=6 Range 4-33 cycles	NR	NR	Grade 3-4: Hypertension, n=5 Fatigue, n=1 Rash, n=3 Diarrhoea, n=3 Anorexia, n=1

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
				Infection with neutropenia, n=1
Kobayashi 2011[129]	Gefitinib	n=29 Discontinuations: Disease progression, n=19 No benefit over toxicity decided by the treating physicians, n=5 Patient request, n=5	Dose reductions, n=6 Chemotherapy after gefitinib: (n=14) Re-administration of gefitinib, n=5 Docetaxel, n=4 Carboplatin plus paclitaxel, n=3 Paclitaxel, n=1 S-1, n=1 No clear explanation about the influence of this therapy	Grade 3-4: Haemoglobin=13%
Mansueto 2011[142]	Oral vinorelbine: (60mg) Total cycles=354 Mean cycles per patient=9.3	NR	NR	NR
Nishiyama 2011[148]	S-1: Median cycles=3 (range 1-19) ≥1 cycle=7/29 (24%)	n=7 Discontinued treatment after 1 cycle due to: Progressive disease, n=3 Toxicity (grade 3), n=2 Toxixty (grade 1-2), n=2 n=29 Subsequent cycles: Progressive disease=58.6% Toxicities=34.6% Patient request=3.9% Doctor's decision=7.7%	NR	NR
Terai 2011[169]	Median cycles=3 (1-6)	NR	NR	Neutropenia=28% Leucopenia=19% Anaemia=11%
Cai 2010[89]	Docetaxel: 136 cycles, n=44 Each patient received=2-4cycles Median cycles=3.5	Death due to complications before completing cycle1, n=2	NR	Neutropenia=27.5% Thrombocytopenia=25% Nausea and vomiting=12.5% Diarrhoea=10%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Camerini 2010[90]	Vinorelbine: All patients received at least 2 cycles >4 cycles=58.1% (25 of 43) Total cycles=187 Median cycles=4 (range, 2-9) Dose intensity (excluding escalation dose patients)=59.7 mg week, corresponding to 99.6% of the planned dose	NR	One step dose reduction of 25%, n=1 due to grade 3 neutropenia Dose escalations to 80 mg after first 2 cycles n=2 Dose delay – few days for a total of 5 cycles n=3 due to personal references	NR
Kim 2010[128]	Docetaxel and carboplatin: Total cycles=188 Median cycles=5 (1-8) RDI: Docetaxel=90.4% Carboplatin=92.7%	Discontinuations: AEs after 1 cycle n=2 Reasons for early stoppage of treatment were disease progression or withdrawal from treatment	Delayed treatments=13 (30%) Dose reductions=10 (23.3%)	Neutropenia=37.2% - with a fever=21% but all were treatable Anaemia=18.6%
Rozzi 2010[159]	Median cycles=4	NR	NR	NR
Blakely 2009[85]	Pemetrexed plus gemcitabine Mean cycles=5.1 Median DDI gemcitabine=0.994 Median DDI pemetrexed=0.030	Discontinuations=31%	Cycles delayed gemcitabine=10 Cycles delayed pemetrexed=21 Cycles reduced gemcitabine=9 Cycles reduced pemetrexed=8	Grade 3-4 AEs=49%
Boukovinas 2009[87]	Gemcitabine plus docetaxel: Total cycles=314 Median cycles=3 (1-9) >3 cycles=46.8% Mean dose intensity: Gemcitabine=733 mg week Docetaxel=31.0 mg week Planned doses: Gemcitabine=85.5% Docetaxel=94% Time of analysis – completed treatment as per protocol 41.6%	Disease progression, n=33 (42.9%) Treatment related, n=5 (6.5%) Sudden death not directly related to disease, n=1 (1.3%) Consent withdrawal, n=5 (6.5%)	Treatment delay=66 (21%) cycles Delay >7 days=29 (9.2%) cycles, due to: Haematological=8 cycles (2.5%) Non-haematological=7 cycles (2.2%) Unrelated to treatment=51 cycles (16.2%) Dose reductions=30 cycles (9.6%) due to: Haematological=9 cycles (29%) Non-haematological=6 cycles (1.9%) Haematological and non-haematological=15 cycles (4.8%)	Neutropenia=13%
Feliu 2009[97]	Total courses=166 Median cycles=4	NR	NR	Neutropenia=7 (17%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Han 2009[110]	Weekly docetaxel and cisplatin: Total cycles=148 Mean cycles=3 (1-6)	n=2 Lost to follow-up n=2 Death n=1	Overall delays=24 (16.2%) cycles Overall dose reductions=15 (10.1%) cycles	Grade 3: Anaemia=13.0% Neuropathy=10.9% Diarrhoea=10.9% Stomatitis=10.9%
Igishi 2009[115]	UFT plus vinorelbine: Phase I Total cycles per patient=52 Median cycles per patient= 4.3 (range, 2-20)	NR	NR	NR
	UFT plus vinorelbine: Phase II Total cycles=232 Median cycles per patient=4 (1-46) Mean dose intensity of the planned dose: UFT=78% Vinorelbine=90%	NR	Phase II Most common cause for delay was leukopenia or neutropenia=48/52 cycles Dose reductions: UFT from 600 to 400 mg n=9 due to: Grade 1-2 Anorexia n=8 Diarrhoea n=1 Dose reduction of UFT from 600 to 400 mg= Was reduced in most common AEs (< grade 3) gastrointestinal toxicity such as anorexia and constipation	Phase II Grade 3: Leukopenia=20% Neutropenia=30% Pneumonitis=10% Grade 4: Leukopenia=0% Neutropenia=10% Pneumonitis=0%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Lee 2009[136]	Gemcitabine plus cisplatin: Total cycles=166 Median cycles per patient=3 (range 1-6) Actual dose: Gemcitabine=638.8 mg week Cisplatin=16.2 mg week Relative dose: Gemcitabine=85.2% Cisplatin=86.4%	Received only 1 cycle, n=3 Due to: treatment-related death; Neutropenic sepsis, n=1 Necrotising pneumonia, n=2	Delayed for a median of 2 weeks=22 cycles (13.3%) Dose reductions: 23 cycles and 11 cycles, administration of gemcitabine and cisplatin was omitted on day 8 or 15	Grade3: Leukopenia=12.5% Neutropenia=16.7% Anaemia=14.6% Thrombocytopenia=16.7% Asthenia=10.4% Infection=14.6% Grade 4: Leukopenia=10.4% Neutropenia=12.5% Anaemia=0% Thrombocytopenia=4.2% Asthenia=0% Infection=12.5%
Sequist 2009[162]	Bi-weekly pemetrexed and gemcitabine: Range of cycles administered=1-5 1 cycle=4 3 cycles=2 4 cycles=1 5 cycles=2	Disease progression, n=2 Intolerance and declining PS, n=7 Died within 30 days of cycle 1, n=2 due to: Haemoptysis, n=1 Respiratory failure related to pneumonia and underlying disease, n=1 Lost to follow-up, n=1 (8/9 patients were hospitalised during therapy)	Study was closed early for intolerance	(Deaths=2) Treatment-related toxicity, at least 1 grade 3 or higher=6/9 Grade 3: Fatigue=11% Infection/fever without neutropenia=33% Neutropenia=11% Dyspnoea/respiratory failure=11% Bleeding/haemoptysis=22% Grade 4: Fatigue=11% Infection/fever without neutropenia=11% Pneumonitis=11% Hypoxia=22% Pulmonary embolism=11% Grade 5: Dyspnoea/respiratory failure=22% Bleeding/haemoptysis=11%
Yoshimura	Docetaxel plus carboplatin:	n=5	Frequency of dose reduction=10/30	Leukopenia=80.0%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
2009[175]	(60 mg + AUC 5) Total cycles=99 Median cycles=3.5 (1-6) Planned dose intensity: Docetaxel=20.0 mg/week Carboplatin=AUC 1.7 mg/week Actual median weekly dose intensities: Docetaxel=15.7 mg (78.5%) Carboplatin=AUC 1.3 mg (76.5%)	Received 1 cycle due to: Grade 3 febrile neutropenia n=1 Pneumonitis n=1 Diarrhoea n=1 Disease progression n=2	33% Delayed >6 days due to toxicity=4 (4.0%) Second-line: n=11 Gefitinib n=5 Gemcitabine n=2 Paclitaxel n=1 Pemetrexed n=1 Amrubicin n=1 Vinorelbine n=1	Neutropenia=86.7% Febrile neutropenia=16.7% Anaemia=16.7% Infection=10% Nausea=10% Anorexia=30% Diarrhoea=13.3%
Ebi 2008[96]	NR	Discontinuation due to progressive disease=31/49	NR	Grades3-5: Dermal=20% Anorexia=12% Fatigue=10% Hepatic=22%
Kaira 2008[124]	S-1 and gemcitabine: Overall median cycles=4 (1-6)	NR	Dose reductions in gemcitabine at level 3: 3 patients=13.6%	NR
Lee 2008[137]	Docetaxel (25 mg): Total cycles=112 Median cycles per patient=2 (1-6) Received the planned 6 cycles= 5 (13%) RDI=95% Mean dose intensity=17.8 mg/m^2/week	n=3 Early discontinuations before response evaluation=8%, due to: Severe fatigue rejected further treatment n=2 Death n=1 n=35 Further discontinuations/withdrawal: Disease progression n=25 Toxicity n=6 Concurrent disease n=1 Patients decision to end treatment n=3 Could not complete the planned treatment due to toxicity: >65 years=23%, >70 years=23%	NR	NR

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Oshita 2008[152]	Nedaplatin and irinotecan followed by sequential gefitinib: First stage: Nedaplatin and irinotecan: Received treatment n=28 Total cycles=71 2-3 cycles=n=25	After the first cycle: Disease progression n=1 Toxicity n=2	NR	Grade 3-4: Haemoglobin=22.5% Leukocytes=39.4% Neutrophils=64.8% Platelets=22.5%
Pino 2008[154]	Paclitaxel and gemcitabine followed by maintenance paclitaxel Total planned cycles=94% Total cycles and patients evaluable for toxicity=123 cycles, n=48	NR	Dose reductions due to myelosuppression n=8 (17%)	NR
Rossi 2008[157]	Paclitaxel (80 mg): Median cycles=1 (range 1-5)	n=16 Toxicity in first cycle, grade 3 asthenia n=1 Non-responding, did not carry on treatment as planned by the protocol n=15 n=3 Considered non-responders-stopped treatment after first cycle Deaths n=2 (not related to therapy) Patient refusal n=1	NR	NR
Jackman 2007[121]	Erlotinib	Removed from the protocol due to treatment-related toxicity n=12 Withdrew consent before restaging scans n=1 Lost to follow-up n=1	Received dose reduction to 100 mg n=13	Treatment-related death n=1

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Juan 2007[123]	Paclitaxel: Total cycles=530 Median cycles per patient=10 weeks (1-23)	n=7 Received <4 weeks of treatment due to: Hypersensitivity reaction n=1 Heart attack n=1 Rapid deterioration of PS due to progressive disease n=4 Withdrawn from study n=1 Due to severe chronic hepatopaty and developed grade 4 neutropenia and grade 3 thrombocytopenia with slow recuperation	Number of omitted cycles=24	NR
LeCaer 2007[134]	Docetaxel plus gemcitabine: Median cycles=2+0.6 (16 weeks of treatment) Dose intensity: Docetaxel: Cycle1=81.7% Cycle 2=83.3% Cycle 3=69.2% Total=81.7% (67.1-88.9) Gemcitabine: Cycle 1=96.1% Cycle 2=98.5% Cycle 3=91.0% Total=92.9% (74.7-99.4)	Progression n=15 Toxicity n=11 Fatigue n=6 Infection n=2 Ungueal n=1 Interstitial pneumonia n=2 Intercurrent conditions n=2 Ischemic colitis n=1 Pulmonary embolism n=1 Patient's decision n=3	NR	Death attributed to treatment n=1 Grade 3-4: Anaemia=12% Neutropenia=12% Fatigue=30% Alopecia=10% Red cell transfusions=18% Platelets=1.3%
LeCaer 2007a[135]	Docetaxel: Mean cycles=1.5+0.8 RDI: Overall=91.7% Cycle 1=96.8% Cycle 2=92.6% Cycle 3=83.3%	n=46 Progression n=27 Toxicity n=12 Intercurrent disease n=6 Patient decision n=1	NR	Fatigue=30%
Maestu 2007[141]	Gemcitabine plus vinorelbine: (1750 mg+30 mg)	NR	Delayed number of cycles=53 (13.9%)	Grade 3–4 neutropenia appeared in 6.8% of the courses. No

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Total cycles=381 Median cycles per patient=6 (range 1-5)		Treatment reduced by 75%=19 cycles (4.9%)	thrombocytopenia grade 3–4 was registered
Buffoni 2006[88]	Cisplatin plus vinorelbine: Total cycles=120 Median cycles=4 MDI: Cisplatin=90% Vinorelbine=90%	n=4 Treatment discontinuations before completing third cycle due to: Early progression n=1 (Toxic death n=3) Chemotherapy omitted on day 8=5 (17%)	Dose reductions of 30%= 7 (23%) Treatment delay on day 1=8 (27%)	Grade 3 neutropenia=20% Grade 4 neutropenia=43% Treatment-related deaths (n=3) due to: Neutropenia fever n=2 Acute pulmonary oedema n=1
Giorgio 2006[105]	Carboplatin plus paclitaxel: Total cycles=160 Median cycles per patient=4 (2-6) Paclitaxel: MDI= 90% (83-102) Carboplatin: MDI= 89% (80-105)	Early stop of treatment: Progressive disease=15%	(Febrile neutropenia n=2) Febrile neutropenia=chemotherapy was administered at 75% of planned dose	Grade 3-4: Neutropenia=37.5% Malaise/fatigue=10%
Hesketh 2006[111]	Strata 1: Sequential vinorelbine and docetaxel: 6 planned cycles n=36 (48%) Median cycles=5	Discontinuations: AEs=14 (19%) (Death due to pneumonia n=1)	Dose reductions n=31 (41%)	Treatment-related deaths: Pneumonia n=1 Grade 3: Fatigue/malaise=19% Neutropenia=20% Grade 4: Neutropenia=12%
	Strata 2: Sequential vinorelbine and docetaxel 6 planned cycles=16 (38%) Median cycles=5	Discontinuations: AEs=3 (7%) (Death n=2)	Dose reductions n=12 (29%)	Treatment-related deaths n=2: Respiratory failure n=1 Renal failure, dyspnoea and a cardiac conduction abnormality n=1 Grade 3: Fatigue/malaise=14% Neutropenia=14% Grade 4: Neutropenia=17%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Inoue 2006a[119]	Paclitaxel plus carboplatin: (70 mg + AUC 6) >3 cycles=60% Median cycles=3 (1-5)	3/4 of patients that withdrew=>75 years	Dose reductions in patients who received >3 cycles=13% Cancelling the administration of paclitaxel on day 8 and/or day 15=28% of all treatment cycles	Treatment-related death by severe respiratory infection due to neutropenia n=1 Neutropenia=70% Leukocytopenia=30% Anaemia=13% Thrombocytopenia=15% Infection=10%
Ishimoto 2006[120]	Carboplatin combined with docetaxel (bi-weekly) 1-2 cycles n=24 Received 132 cycles n=50 Median cycles=3 (1-6)	n=18 Terminated treatment due to disease progression n=15 Discontinued due to toxicity n=3	NR	Neutropenia=38% Anaemia=20% Thrombocytopenia=10%
Martoni 2006[143]	Sequential gemcitabine and vinorelbine: Gemcitabine: Median cycles=3 (1-3) RDI=94% (33-100) Vinorelbine: Started treatment n=32 Median cycles=4 (1-10) RDI=75% (33-100)	n=11 Gemcitabine: Non-evaluable for response: (41/52) Received only 1 cycle (gemcitabine) n=8 Loss to follow-up n=2 Patient refusal n=1 n=20 Did not start vinorelbine: Non-evaluable due to interrupted gemcitabine n=11 Progressive disease n=9 Deaths in first 5 months of therapy n=2 (unrelated to toxicity)	NR	Gemcitabine=NR Vinorelbine: Neutropenia=22%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Pujol 2006[155]	Paclitaxel plus carboplatin: Total cycles=209 Median cycles per patient=4 (1-6) Completed cycles=174 (83%) Paclitaxel: Mean (+SD) relative dose intensity=0.85+0.15 Carboplatin: Mean (+SD) relative dose intensity=0.95+0.07	n=33 Treatment-related toxicity n=11 Relapse/disease progression n=9 AEs not related to treatment n=9 Patient's request n=2 Deaths n=2 (not treatment related) Number of paclitaxel cycles not administered on: Day 8=8 (4%) Day 15=27 (13%)	Delays out of 584 infusions=26 (4%)	Neutropenia=39% Anaemia=18%
Santo 2006[160]	Gemcitabine plus vindesine: Total cycles=205 Median cycles per patient=5 (2-8) Gemcitabine: Dose intensity=94% Vindesine: Dose intensity=87%	NR	Administered at full doses=121 (59%) cycles Gemcitabine: Dose reductions due to: Neutropenia (11.4%) Thrombocytopenia (13.7%) Vindesine: Dose reductions due to: Grade 2-3 neurotoxicity Constipation=6.8%	NR
Stinchcombe 2006[166]	Phase II Docetaxel plus gefitinib: Median cycles=2 Received 4 cycles=35%	NR	NR	First cycle: Grade 3-5=46% Grade 3: Gastrointestinal=41% Nausea=14% Anorexia=9% Vomiting=14% Dehydration=23% Infection=14% Diarrhoea=23% Grade 5: Pneumonitis=5%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Tibaldi 2006[170]	Docetaxel: (37.5 mg in 250 mL of normal saline) Total cycles=132 Median cycles=4 (1-6) Planned dose intensity= 25 mg weekly DDI= 20.6 mg weekly RDI=82.4%	n=6 Grade 2 diarrhoea n=2 Herpes zoster syndrome n=1 Allergic reaction to therapy after second administration n=1 Patient refusal after first cycle n=1 Death n=1	Treatment delays=20 (15% of the courses) due to: Grade 2 mucositis Grade 2-3 diarrhoea Grade 2 skin toxicity 7 other reasons not related to toxicity Dose reduced by 25%=20 administrations Dose reduced by 50%=2 administrations	NR
Hirsch 2005[112]	Sequential vinorelbine followed by gemcitabine: Vinorelbine: Total cycles=126 Median cycles=3 per patient Gemcitabine: Received treatment n=25 (59.5%) Total cycles=74 Median cycles per patient=1 Continued vinorelbine n=10 Continued gemcitabine n=1	Not treated with gemcitabine n=17 due to: Progressive disease, deterioration in PS and/ or patient refusal	NR	NR
Ichinose 2005[113]	Median cycles=3 39 (89%) patients received at least two cycles of treatment	NR	The administration of gemcitabine on day 15 was skipped in 10 (5%) of a total of 196 cycles.	Grade 3: Leukopenia=13% Neutropenia=16%
LeCaer 2005[133]	Carboplatin plus vinorelbine: Total cycles=136 3 cycles n=29 5 cycles n=16 6 cycles n=2 Mean cycles per patient=3.4 RDI: Carboplatin=100% Vinorelbine=91.1%	Toxicity n=2 Intercurrent events n=3 Progressive disease n=2 Patient decision n=1 Assessable for response n=32 Number of patients who then discontinued due to progressive disease n=14	NR	Grade 3-4 toxicity=69 cases (50.7% of cycles) Death n=1 (febrile neutropenia during treatment,died of septic shock) Grade 3-4: Anaemia=13% Neutropenia=68% Fatigue=18%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Tibaldi 2005[172]	Gemcitabine: (150 mg diluted in 250 ml of normal saline) Total cycles=371 Median cycles=4 (2-4) DDI=976.7 mg weekly (SD+61.1) RDI=0.98 There were no differences in the number of cycles administered to <75 or >75 years	n=11 Toxicity n=1 Deaths n=7 Patient refusal n=2 Continued therapy elsewhere n=1	Treatment delays=10 (2.6% of the courses) due to: Neutropenia=3 episodes Thrombocytopenia=2 episodes Fever=3 episodes Other reasons=2 episodes Dose reduced by 25% n=11 Dose reduced by 50% n=7	NR
Kanard 2004[126]	Oral vinorelbine: Median cycles=3 (1-13) Total cumulative cycles=203	n=3 Deaths: Suicide n=1 Fatal vascular accident n=1 Chronic obstructive pulmonary disease n=1	Dose reductions n=6 due to toxicity Cycles with dose reduction=18 Treatment after disease progression: Patients treated with vinorelbine, gemcitabine or docetaxel n=3 Erlotinib n=1 Did not receive second-line therapy n=6	(Death may be related to treatment n=1) Most severe events: Grade 3 n=21 Grade 4 events n=7 Grade 5 events n=5 Grade 3-5 Thrombosis n=5 Fatigue n=6 Leukopenia n=2 Dyspnea n=10 Infection n=3
Gridelli 2004[107]	Oral vinorelbine: (Cycle 1=80 mg followed by 80 mg) Total cycles=201 Median cycles per patient=3 (1-16) 1 cycle n=11 >6 cycles n=13 Median weeks under treatment=9.3 (2.9-31.3) Total doses=471 Median doses per patient=7 (1-25) MDI-week=46.5 (21-77.3)	n=9 Deaths n=2 Withdrawal of consent n=2 Received radiotherapy after 1 cycle n=1 AEs n=4 Dose omitted=126 administrations due to haematological (73%) Neutropenia, reason: 92 doses omitted n=34 Discontinuation n=1	At least 1 delay n=9 but never exceeded 9 days Dose escalation to 80 mg cycle 2=30/40 patients (67%) Remained on 60 mg n=15 (33%) due to: Toxicity n=8 Not specified by investigator n=7 Dose reduction from 80 mg to 60 mg n=12	Grade 3: Leukopenia=30% Neutropenia=20% Fatigue=11% Grade 4: Neutropenia=30% (Febrile neutropenia 2 cases in same patient)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Median RDI=65% (34.9-103.1) Cumulative dose per patient=439mg			
Ohe 2004[149]	Cisplatin plus docetaxel: Total cycles=101 Median cycles=3 (1-15) 1 cycle n=2 2 cycles n=12 3 cycles n=13 >4 cycles n=6 15 cycles n=1 Planned administrations that were carried out=272/303 (90%) Median actual dose intensities: Cisplatin=16.7 mg per week (11.1-20-4) Docetaxel=13.4 mg per week (8.9-16.4) Projected dose intensities: Cisplatin=18.8 mg per week Docetaxel=15 mg per week	NR	NR	NR
Oshita 2004[153]	NR	n=8 Received 1 cycle due to: Progressive disease n=2 (Treatment-related death n=1) Grade 3 diarrhoea n=1 Persistent grade 2 nausea n=1 Pneumonitis n=1 Pneumonia n=1 Patient refusal n=1	Irinotecan delay on day 8 n=8	Death n=1 Grade 3-4 Leukocyte=37% Grade 3: Neutropenia=29% Grade 4 neutropenia=50% Grade 3-5 neutropenic fever=29% (Dose-limiting toxicities n=11)
Takigawa 2004[168]	Docetaxel: Total cycles=49 Median cycles=2 (1-12) All patients received least 2 cycles	Received 1 cycle: Progression n=1 Treatment-related interstitial lung toxicity n=1	Reduced dose of 50 mg n=4 due to: Grade 4 neutropenia lasting 3 days n=3 Grade 3 neutropenic fever n=1 Grade 3 nausea n=1	Grade 3-4: Leukocytes=60% Neutrophils=87% Nausea=13% Dyspnoea=13%

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	Median interval between each cycle=22days (19-30)		Grade 4 neutropenia and grade 3 nausea n=1	Neutropenic fever=33% Fatigue=20%
Chen 2003[93]	Vinorelbine plus gemcitabine: Total cycles=84 Median cycles per patient=4 (1-6) >2 cycles n=19 Scheduled Injections: Day 1=84 Day 8=81 Day 15=81 Scheduled dose administered: Day 1=92.6% Day 8=79.6% Day 15=52.2%	Death n=1 due to disease progression Cerebral infraction after 3 cycles n=1 Injections omitted: Day 8=9 Day 15=27 Radiotherapy: Not eligible n=2 (Death due to disease progression n=1) Patient refusal n=2	Dose reduction n=18 (90%) due to: Myelosuppression n=12 Fatigue n=2 Myelosuppression and fatigue n=4 Half dose injections: Day 1=4 Day 8=8 Day 15=18 75% dose injection: Day 1=17 Day 8=14 Day 15=11 Stage IIIB without malignant effusion: radiotherapy after 3-6 cycles n=3	Toxic death n=1 Grade 3: Leukopenia=15% Neutropenia=20% Thrombocytopenia=15% Anaemia=30% Fatigue=10% Grade 4: Leukopenia=10% Neutropenia=20% Blood component transfusion n=14 including: 66 units of packed RBS n=14 32 units of fresh frozen plasma n=5 18 units of platelets n=1
Choi 2003[94]	Paclitaxel plus carboplatin: Cycles 1-6 Total cycles=163 6 cycles n=11 (31%) Received further courses due to continued tumour shrinkage or remission 7 cycles n=1 8 cycles n=3 9 cycles n=1 Ratio of administered dose to planned dose=0.89	NR	NR	Grade 3: Leukopenia=1 cycle Neutropenic fever=1 case
Feliu 2003[98]	Total courses=190 courses median courses per patient=4.1 (1–6) MDIs were 15.3 and 634 mg/m² per week for cisplatin and gemcitabine,	NR	Treatment delay due to neutropenia=5	Leukocytes=6 (13%)

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
	respectively >90% doses=40 (87%)			
Hainsworth 2003[108]	Completed 2 course=53 (83%) Median number courses=3 (1-6).	Discontinued treatment due to: Congestive heart failure=2 Thrombophlebitis/pulmonary emboli=1 Pneumonia=1 Gastrointestinal bleeding from esophageal varices=1	Docetaxel doses administered on days 1, 8, and 15 were 100%, 96%, and 84%, respectively. The corresponding gemcitabine doses were 99%, 94%, and 80%	Alopecia=21 (33%) Fatigue/asthenia=15 (23%)
Jatoi 2003[122]	Carboplatin plus paclitaxel: Cumulative cycles=158 Distribution of administered cycles: Cycle 1=49 Cycle 2=40 Cycle 3=30 Cycle 4=25 Cycle 5=15 Cycle 6=9	NR	Dose reduction due to toxicity in prior cycle=15 Total number of dose reductions=17 (due to neurological toxicity=2; liver function test abnormalities)	Death n=1: Grade 3: Dyspnoea=12.5%
Maestu 2003[140]	Carboplatin plus gemcitabine: Total cycles=400 Median cycles per patient=4 (1-6)	NR	Delay in courses on day 1 of therapy=20 (5%) Treatment reduced (gemcitabine) by 75%=33 cycles (8.2%) Treatment reduced (gemcitabine) by 25%=33 cycles (8.2%) Gemcitabine cycles omitted on day 8=59 (14.7%)	Toxic death n=1 Number of cycles with AEs: Grade 3: Neutropenia=42 (10.5%) Grade 3-4=13% Leukopenia=26 (6.5%) Thrombocytopenia=13 (3.2%) Grade 4: Neutropenia=10 (2.5%) Leukopenia=0 Thrombocytopenia=5 (1.3) Number of patients and adverse affects: Grade 3: Anaemia=12 (13.6%)
Inoue 2002[117]	Docetaxel Median cycles=2 (1-2)	n=3 Received only 1 treatment cycle: Disease progression n=2 Physicians decision n=1	Number of patients with dose limiting toxicities at dose level 2=3/5	NR

Study	Treatment administered and/or compliance to regimen	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Patients with grade 3-4 adverse events, toxic death
Beretta 2000[176]	Gemcitabine followed by vinorelbine: All evaluable patients: Completed at least 2 cycles Median cycles per patient= 4 (0.5-6) Total cycles=146 Planned dose=93% Mean dose intensity=92%	n=3 Failed to complete first treatment cycle: Death n=1 Developed pulmonary cavitation with infection n=1 Refused to continue treatment n=1	NR	Grade 3-4: Granulocytopenia=35%
Older versus younger patients				
Rodriguez 2012[156]	Adjuvant chemotherapy: Overall: Received treatment=53 (55%) <70 vs >70 years: Received treatment=46 (66.7%) vs 7 (25%) p<0.01 Median cycles=4 (2-4) vs 2 (1-2) p=0.04 Stage IB: Chemotherapy received=21/41 (51.2%) vs 2/18 (11.1%) p<0.01 Stage II or higher Chemotherapy received=25/28 (89.3%) vs 5/10 (50%) p=0.02 Stage IB >4 cm and stage II or higher: Chemotherapy received=38/45 (84.4%) vs7/21 (33.3%) p<0.01	NR	NR	NR
Schuette 2012[161]	Pemetrexed: At least 1 dose=516 (99.0%) Completed at least 2 cycles=471 (90.4%) Completed at least 6 cycles=254	(Died before the first dose n=2 Lost to follow-up/missing data n=2) Early discontinuations: Disease progression=27.7% Death=14.3%	Dose delay: At least 1=232 (49.3%) Due to toxicity=33 (7.0%) Scheduling conflicts=35% At least one dose reduction during	Deaths due to grade 3-4 toxicity (n=2) Solicited Grade 3-4 Patients with toxicities during cycles: Cycle1=11% Cycle 2=8.5%

	(48.8%) Completed at least 9 cycles=110 (21.1%) Completed the treatment schedule as planned by the physician=28.9% Continued treatment after the observational period=25 (4.8%) Median cycles=5 (1-9)	Patient decision=14.1% (Toxicity=4.5%) Other reasons=3.9% Loss to follow-up=1.2%	the study was documented for 25 (4.8%) patients. Of these patients, 10 (40.0%) received a dose ≤75% of the previous dose and 1 patient (4%) received a dose of ≤ 50% of the previous dose	Cycle 3=9.0% Cycle 4=9.3% After 4 cycles=<5% <70 vs >70 years: Fatigue/asthenia= 16.4% vs 15.0% Karnofsky index >80% vs <80%: Fatigue/asthenia= 9.9% vs 25.9% Neutropenia= 6.5% vs 12.4% Overall, any toxicity at grade 3-4=23.8% Red blood cell transfusions=24.2%
Tibaldi 2008[173]	Gemcitabine: Total cycles=371 Median cycles=4 (2-4) DDI=976.7 mg weekly (SD+61.1) RDI=0.98 There were no differences in the number of cycles administered to <75 or >75 years	n=11 Toxicity n=1 Deaths n=7 Patient refusal n=2 Continued therapy elsewhere n=1	Treatment delays=10 (2.6% of the courses) due to: Neutropenia=3 episodes Thrombocytopenia=2 episodes Fever=3 episodes Other reasons=2 episodes Dose reduced by 25% n=11 Dose reduced by 50% n=7	NR
Okamoto 2005[151]	Carboplatin plus paclitaxel: Total cycles=65 Median cycles per patient=3 (1-4) >3 cycles=60% Mean cycles: >75 years=2.7 >75 years=2.5	n=3 Received 1 treatment cycle due to: Paclitaxel-induced hypersensitivity reaction n=3 Patient refusal n=2	Treatment delays out of 40 courses=40% (After the first course and 12/16 were within 7 days) Delayed >1 week (10-21 days)=4 course due to: Prolonged leukopenia =2 courses Neuropathy=2 courses	Grade 3: Leukopenia=32% Neutropenia=28% Neuropathy=12% Arthralgia=16% Myalgia=16% Grade 4: Leukopenia=8% Neutropenia=40% Neuropathy=0% Arthralgia=0% Myalgia=0% Grade 3-4:

				<75 years vs >75 years Haematological toxicities= 60% vs 73% Non-haematological toxicities= 40% vs 33%
SCLC				
Murata 2011[145]	Carboplatin plus irinotecan: Chemotherapy: Total cycles=109 Median cycles=4 (1-4) Carboplatin: Mean individual dose=4.5mg 90% of planned dose Irinotecan: Mean individual dose=40.6mg 81.2% of planned dose	NR	Received carboplatin- dose reduction n=1 (3%) Received irinotecan dose reduction n=9 (30%) Irinotecan dose cancelled on day 8 n=12 (11%) Number of chemotherapy courses delayed=38 (35%)- Delayed in less than a week=33/38 (86.8%)	Grade 3-4: Leukopenia=43% Neutropenia=83% Thrombocytopenia=46% Anaemia=60% Diarrhoea=20% Infection=23.3%
Igawa 2010[114]	Amrubicin: Median cycles=4 (1-6)	NR	40 mg dose reductions after the second cycle n=3 (20%)	Grade 3-4: Leukopenia=56% Neutropenia=63% Thrombocytopenia=15% Anaemia=19% Febrile neutropenia=15% Dose of 35mg: Leukopenia=67% Neutropenia=75% Thrombocytopenia=17% Anaemia=8% Febrile neutropenia=13% Dose of 40mg: Leukopenia=27% Neutropenia=33% Thrombocytopenia=13% Anaemia=20% Febrile neutropenia=13%

Inoue 2010[116]	Amrubicin plus carboplatin: Median cycles=4 (2-7) >3 cycles n=32 (89%)	NR	Dose reductions=31%	>Grade 3: Neutropenia=97% Anaemia=28% Thrombocytopenia=28% Febrile neutropenia=17% Infection=14% Nausea/vomiting=11%
Kim 2008[127]	Irinotecan plus cisplatin: Total cycles=194 Median cycles=5 (1-6) Cycles and number of patients who received chemotherapy: Cycles 1 n=3 (6.5%) Cycles 2 n=9 (19.6%) Cycles 3 n=6 (13.0%) Cycles 4 n=4 (8.7%) Cycles 5 n=5 (10.9%) Cycles 6 n=19 (41.3%) Actual dose intensity (mg/m^2/ week) Irinotecan=32.5% Cisplatin=11.6% RDI: Irinotecan=72.2 % Cisplatin=77.9%	NR	NR	NR
Fujiwara 2006[102]	Total cycles=59 Median cycles=3 (1-4)	Consent withdrawal=1	Dose reductions in 1 out of 6 patients due to treatment toxicity	Grade 3/grade 4: Leukopenia=7 (37%)/10(53%) Neutropenia=6 (32%)/10 (53%) Anaemia=3 (16%)/2(11%) Thrombocytopenia=2 (40%)
Fukuda 2006[103]	Carboplatin plus etoposide: Total cycles administered through 6 dose levels=88	NR	NR	All dose levels Grade 4 haematological toxicities=62% Dose-limiting toxicities=23% All treatment cycles: Blood transfusion=27%

Inoue 2006b[118]	Amrubicin combined with carboplatin: Total cycles=41 Median cycles per patient=4 (1-4)	NR	NR	NR
Hainsworth 2004[109]	A median of 2.5 courses was received by each patient (range 0-7)	Discontinued treatment because of rapid tumour progression=4 Discontinued 2 courses of treatment because of other reasons=7	NR	Leukopenia=15% Thrombocytopenia=17% Fatigue=25% Dyspnoea=20% Nausea/emesis=10%

AUC=area under the curve; AE=adverse event; AST=aspartate aminotransferase; ALT=alanine aminotransferase; UFT=tegafur-uracil; RDI=relative dose intensity; MDI-median dose intensity; DDI=delivered dose intensity; SD=standard deviation; S-1=tegafur, gimeracil, and oteracil; PS=performance status; NR=not reported;

Appendix 6: Comprehensive geriatric assessment, all study types

Study	Results
RCTs	
LeCaer 2012[41]	CCI, ADL, IADL The CGA allowed us to select a population of vulnerable elderly patients: respectively 43% and 38% of patients in arm A and B were dependent in the IADL, and 59.1% and 66% had a CVI score above 1
Biesma 2011[9]	CCI, CIRS-G, ADL, IADL, TUG, Mini-Mental State Examination (MMSE), GDS-15, PANAS, GFI The completion rate of the CGA questionnaires at baseline was 98%. Both groups were well balanced for all domains and assessments. Percentage of patients with two or more comorbidities was 38% in the carboplatin plus gemcitabine arm and 25% in the carboplatin plus paclitaxel arm not significant. Almost half of patients had limitations in IADL, and more than a quarter had abnormal depression scores. Baseline deficits in emotional functioning (QLQ-C30), role functioning (QLQ-C30) or GDS scores were more likely to experience >grade 2 neuropsychiatric toxic effects. There were no significant interactions between CGA scores and treatment
LeCaer 2011[29]	CCI, ADL, IADL The CGA allowed us to select a population of fit elderly patients, with a mean MMSE of 29.7, only moderate malnutrition, independence in the ADL and IADL scores, and a high global score (EGS *K*=18/20 on average) in both arms
Gridelli 2003[20]	The addition of baseline values of the geriatric scales to the multivariate analysis did not affect the primary study results, which indicated that the degree of ADL and IADL dependency does not affect treatments under investigation in the MILES study
Comparative cohorts	
Gridelli 2012[75]	The CCI score was >2 in 26.9%. Number of comorbidities and the CCI score tended to be higher in the gemcitabine plus etoposide arm. Baseline assessment of ADL and IADL were missing for 8% and 6% of patients, respectively. Seventeen percent of patients had some ADL dependency, and 40% was dependent in more than 50% of IADL
Single cohorts	
Camerini 2010[90]	BADL, IADL Used to screen patients, no results presented
LeCaer 2007[134]	CCI Used to screen patients, no results reported
LeCaer 2007[135]	CCI Used to screen patients, no results reported
Maestu 2007[141]	CCI, ADL Published article presents correlations between CGA and numerous variables

CCI=Charlson Comorbidity Index; GDS=Geriatric Depression Scale; ADL= Activities of Daily Living; BADL=Basic Activities of Daily Living; IADL=Instrumental Activities of Daily Living; TUG=Timed Up and Go test; PANAS=Positive and Negative Affect Schedule; GFI=Groningen Frailty Indicator; CIRS-G=Cumulative Illness Rating Scale for Geriatrics

Appendix 7: Quality of life, all study types

Study	Tool used	Results	Compliance
RCT			
Chen 2012[12]	FACT-L questionnaire (subscales: physical well-being, social/family well-being, emotional well-being, functional well-being lung cancer symptom-specific, lung cancer)	Most FACT-L subscales showed no significant change at the end of treatment for both treatment arms, except that patients in the erlotinib arm had significantly better physical well-being than patients in the vinorelbine arm. Most patients in both arms had stable pulmonary symptoms (lung cancer subscale) at the end of treatment	NR
LeCaer 2012[41]	Spitzer Index LCSS	The median global LCSS score, the median symptom score and the global Spitzer score were similar	Patients completing the QoL assessments in gemcitabine followed by erlotinib vs erlotinib followed by gemcitabine arms: Baseline=75% vs 73% At 8 weeks=26% vs 78% At 16 weeks=43% vs 38%
Biesma 2011[9]	EORTC QLQ-C30, QLQ-C13	There was no difference in the change in global QoL scores (from baseline to week 18) between both arms, nor at week 12. The number of QoL responders did not differ significantly between the carboplatin plus gemcitabine arm and the carboplatin plus paclitaxel arm at the end of treatment (n=7 [8%] and n=9 [10%] responders, respectively) nor at week 18 (n=11 [12%] and n=4 [5%] responders, respectively). The baseline global QoL was lower in patients not completing week 18 questionnaires than those completing week 18 questionnaires (p=0.001). The mixed-effects model indicated that global QoL scores were lower for patients with worse baseline PS scores (p=0.001) and for patients with lower baseline global QoL scores (p<0.001). There were no associations between the global QoL and treatment, age, sex, pretreatment weight loss or extent of disease. There were also no significant interactions between QoL scores and treatment	Baseline QoL assessments were available from 89 (99%) in the carboplatin plus gemcitabine arm and 88 (97%) in the carboplatin plus paclitaxel arm. QoL data at week 18 were available from 50 patients receiving carboplatin plus gemcitabine and 44 patients receiving carboplatin plus paclitaxel
LeCaer 2011[29]	Spitzer Index LCSS	The median global LCSS score, the median symptom score and the global Spitzer score were similar in the two arms and showed little deterioration of QoL after treatment	Approximately 75% of the patients completed the QoL assessment before treatment

Study	Tool used	Results	Compliance
			(docetaxel plus gemcitabine followed by erlotinib vs erlotinib followed by docetaxel plus gemcitabine): Before treatment=39 vs 37 At 8 weeks=29 vs 27 At 16 weeks=11 vs 8
Quoix 2011[36]	EORTC QLQ-C30 and QLQ-LC13 at baseline, week 6, and week 18	At week 6, the global QoL scores were similar (mean 54.7 in the monotherapy group vs 56.9 in the doublet chemotherapy group), but more patients in the monotherapy group had pain (30.2 vs 18.7, p=0.003) and dyspnoea (47.4 vs 36·8, p=0·014), and more in the doublet chemotherapy group had diarrhoea (18.4 vs 8.8, p=0·003). At week 18, the global QoL score was similar (58.2 vs 61.8), but role functioning and fatigue were worse in the doublet chemotherapy group than in the monotherapy group (–1.9 vs –15.3, p=0.026 and –0.6 vs 12.4, p=0.039)	The completion rate for QoL questionnaires was 94% at baseline, 62% at week 6, and 49% at week 18
Stinchcombe 2011[40]	TOI-L	Gemcitabine: Improved=11.4% No change=27.3% Worsened=25.0% Other=36.4% Erlotinib: Improved=11.8% No change=17.6% Worsened=23.5% Other=47.1% Gemcitabine+erlotinib: Improved=13.7% No change=17.6% Worsened=17.6% Other=51.0%	NR
	LCSS	Gemcitabine: Improved=15.9% No change=15.9% Worsened=20.4% Other=47.7% Erlotinib: Improved=25.5% No change=15.7% Worsened=15.7% Other=43.1% Gemcitabine+erlotinib: Improved=27.4%	

Study	Tool used	Results	Compliance
		No change=7.8% Worsened=11.8% Other=52.9%	
	FACT-L	Gemcitabine: Improved=18.2% No change=20.4% Worsened=18.2% Other=43.2% Erlotinib: Improved=17.6% No change=11.8% Worsened=13.7% Other=56.9% Gemcitabine+erlotinib: Improved=15.7% No change=13.7% Worsened=15.7% Other=54.9%	
Hu 2010[23]	KPS	Before treatment, KPS scores in the experimental group and control group were 70±5 and 71±7, respectively, after treatment the scores were 81±11 and 78±10, respectively, there were significant difference when compared between before treatment and after treatment in both two groups ($p<0.01$); However, the enhancement of KPS in the experimental group was markedly higher than in the control ($p<0.05$); when compared with the improvement rate of KPS scores before treatment and after treatment, the data were 76.2% in the experimental group and 45.0% in the control group, the difference between two groups was also significant ($p<0.05$)	NR
Jatoi 2010[24]	FACT-G	No clinically or statistically significant differences between groups over time for emotional and social well-being. However, infliximab-/docetaxel-treated patients had lower levels of functional and physical well-being	NR
Crino 2008[15]	FACT-L TOI PSI	Overall QoL improvement rates were higher with gefitinib than with vinorelbine (24.3% vs 10.9%; OR 2.97; 95% CI 1.06 to 8.34 for FACT-L analyses and 22.9% vs 6.3%; OR 5.47; 95% CI 1.61 to 18.56 for TOI analyses). The overall disease-related improvement rates of the Lung Cancer Subscale scores of the FACT-L and PSI rates were similar for gefitinib and vinorelbine (42.9% vs 39.1%; OR 1.19; 95% CI 0.57 to 2.48 for LCS analyses and 36.6% vs 31.0%; OR 1.20; 95% CI 0.43 to 3.33 for PSI analyses)	NR
Leong 2007[30]	EORTC QLQ-C30 and QLQ-LC13	The QoL of patients in all three arms improved over the treatment period. In particular, specific symptom scores suggested that there were improvements in the severity of cough and haemoptysis over the treatment period. On comparing patients with different PS, the results suggested that the change in QoL with respect to breathlessness was most marked in patients with a PS of ECOG 3 in contrast to	94%

Study	Tool used	Results	Compliance
		patients with a PS of ECOG 0-1 and ECOG 2	
Lilenbaum 2007[32]	FACT-L TOI	Average change: Weekly schedule=2.4 (10.9) Every 3 week schedule=-2.3 (13.6)	104 patients (94%) completed a FACT-L questionnaire at baseline. Compliance was variable throughout the study, with only a 65% rate of completion in the second cycle
Kudoh 2006[27]	Visual face scale for global QoL (primary QoL analysis); eight disease-related symptom items (secondary QoL Analysis) derived from the Lung Cancer Working Party, Medical Research Council and the Functional Living Index, Cancer	In terms of global QoL, no significant difference was observed between the two arms (OR 1.30; 95% CI 0.80 to 2.11). Docetaxel was associated with significantly better improvement in the overall symptom score than vinorelbine (OR 1.86; 95% CI 1.09 to 3.20). When the eight-symptom scores were analysed separately, the docetaxel arm showed significantly better improvement in anorexia and fatigue than the vinorelbine arm. These results did not change when the QoL data were re-analysed with the missing information from the 28 surveys assigned as unimproved	179 (92.2% at 3 weeks, 83.2% at 9 weeks, and 69.8% at 12 weeks). Compliance rates were not significantly different between the arms (p=0.311).
Gridelli 2003[20]	EORTC QLQ-C30 and QLQ-LC13	No statistically significant differences in functional and symptom scales between patients assigned to the combination and single-drug treatments. Hair loss, as estimated by patients, was statistically significantly worse for those who received gemcitabine (p=0.03), only	346 (59%)
Frasci 2001[17,45]	Modified LCSS	Overall, 106 of 120 patients each had at least one symptom at diagnosis. Fourteen patients in the gemcitabine plus vinorelbine arm (26%) showed temporary symptom relief during the treatment, compared with eight (15%) in the vinorelbine arm. In particular, cough (31% vs 17%) and shortness of breath (28% vs 11%) were more frequently improved by combination therapy. The probability of being alive without symptom deterioration at 6 months was 43% and 22% in the gemcitabine plus vinorelbine and vinorelbine arms, respectively	NR
Gridelli 2001[44]	EORTC QLQ-C30	No significant difference was detected between treatments on the scales measuring emotional function, sleep disturbance, appetite loss, diarrhoea, and the financial impact of illness	NR
Subgroup			
Weissman 2011[60]	TOI FACT-L	–4.7 in the gemcitabine plus oxaliplatin arm and –6.4 in the paclitaxel plus carboplatin arm	NR
Wheatley-Price 2008[61]	EORTC QLQ-C30	QoL benefits were similar in elderly and young patients, with age–treatment interaction p=0.26, 0.44, and 0.44 for cough, dyspnoea and pain, respectively. Elderly erlotinib patients, compared with younger patients, had a significantly longer time to deterioration for cough (7.4 vs 3.2 months; p=0.04) and dyspnoea (8.0 vs 2.8 months, p=0.07) but not for pain (2.9 vs 2.8 months, p=0.47). Younger erlotinib patients, compared with elderly patients, had significantly improved time to deterioration in	

Study	Tool used	Results	Compliance
		dyspnoea (4.6 vs 3.1 months, p=0.04) and pain (2.8 vs 1.9 months; p<0.01) but not cough (4.9 vs 3.9 months; p=0.20)	
Hensing 2003[51]	TOI-L TOI-NTTX	Baseline: QoL did not differ between the two age groups (TOI-L, p=0.70; TOI-NTTX, p=0.89) Over time: To determine whether the change in QoL over time differed by age group, a mixed model was run with two factors – age category and assessment point – and an interaction term (age category x assessment point) There was a significant effect of assessment point (p<0.0001 for both TOI-L and TOI-NTTX), indicating that QoL changed over time. However, neither the main effect of age (TOI-L p=0.73; TOI-NTTX p=0.42) nor the interaction term (TOI-L p=0.49; TOI-NTTX p=0.42) was significant. Thus, QoL did not differ between patients aged ≥70 years and patients younger than 70 years, nor did the two groups demonstrate a differential rate of change over time	Baseline: QoL date=218 (n=164 [95.6%] <age 70 years; >70 years (n=66 [99%]). Data completion rates and reasons for missing data did not differ between the two age groups.
Comparative cohorts			
Marsland 2005[76]	FACT-L FACT-G	At cycle 1, the FACT-G median score changes from baseline were significantly lower (p=0.006). At cycle 2, only 2 of the FACT-G components, physical well-being and functional well-being, were significantly lower than baseline (p=0.021 and 0.035, respectively). These results indicate that, in general, patients felt that their QoL (physical and functional) had decreased. One of the components, emotional well-being, was marginally higher than baseline (p=0.052), possibly suggesting that the patients were receiving emotional support from family members and the health professionals within their healthcare network. From cycles 3 through 6, there were no significant changes from baseline, indicating no changes (positive or negative) in QoL later in the study	NR
Single cohorts			
Schuette 2012[161]	EQ-5D	Results not presented by age group	Compliance not presented by age group
Du 2009[95]	LCSS KPS	The QoL of patients was improved after chemotherapy. Mean KPS was increased from 75.5 at baseline to 87.7 (p<0.01); LCSS scores of cough, haemoptysis, chest pain and dyspnoea were increased from 64, 65, 62 and 65 to 90, 92, 87 and 88, respectively	NR
LeCaer 2007[134]	LCSS	Before treatment, QoL was analysed in 44 patients who completed the initial assessment; the global median LCSS score was 3.16 (95% CI 0.07 to 8.00) the mean symptom score was 2.16 (95% CI 0.08 to 5.28) and the mean Spitzer score was 7.5 (95% CI 3 to 10)	NR
Pujol 2006[155]	LCSS	Median scores: Baseline=28.5 Cycle 1=22.1 Cycle 2=18.6 Cycle 3=22.0	Baseline=51/51 Cycle1=51/51 Cycle 2=46/51 Cycle 3=37/51 Cycle 4=31/51

Study	Tool used	Results	Compliance
		Cycle 4=24.0 Cycle 5=22.9	Cycle 5=24/51
LeCaer 2005[133]	EORTC QLC-C30 Spitzer Index	A significant improvement in QoL between baseline and cycles 1, 3, and 5 was noted in all 40 patients with regard to emotional function (p=0.006) and insomnia (p=0.008) on the QLQ-C30 questionnaire, and a trend toward an improvement was noted in general health (p=0.09), dyspnoea (p=0.05), cough (p=0.07), and pain (p=0.09). After normalising the QoL scores at cycles 1, 3, and 5 according to baseline values, the comparison of changes in QoL between patients with disease control (OR + SD) and those with disease progression showed a significant improvement in the general health of the patients with disease control (QLQ-C30, p=0.009) and a trend toward an improvement in pain (p=0.09) and emotional function (p=0.08). This significant improvement was also found with the Spitzer health index (p=0.03) and, to a lesser extent, with the total Spitzer QOL score (p=0.052)	The QoL questionnaires were completed by 39 patients (97.5%) at enrolment, 31 patients (77.5%) after the first cycle, 22 patients (55%) after the third cycle, and 11 patients (27.5%) after the fifth cycle. The questionnaires were completed by 11 patients (27.5%) at all 4 time points, by 11 patients (27.5%) at 3 time points, 9 patients (22.5%) at 2 time points, 8 patients (20%) at 1 time point, and never by only 1 patient
Retrospective			
Chen 2005[210]	LCSS	The LCSS scores showed significantly worse appetite, fatigue, dyspnoea, disease severity, daily activity, and QoL after treatment. However, the difference in the deterioration of the scale scores was very small between the two age groups	<70=69/70 ≥70=45/70
Langer 2002[214]	FACT-L QoL scale	QoL was assessed at baseline, at 6 weeks, at 3 months, and at 6 months. No statistically significant differences were found in either baseline QoL (p=0.20) or changes in QoL over time (p=0.12) between younger and older males. Among female patients, older patients had higher scores at baseline on the FACT-L instrument than younger women (114.5 vs 104.1; p=0.003). Older women also had less change in QoL over time (p=0.003). A model that assumed no association between differential missing data and survival produced similar but not identical results and resulted in the same conclusions. It should be noted that substantially fewer patients were assessed at 3 and 6 months than at baseline. Those who did not undergo 6-month evaluation were presumably sicker, had progressive disease, or had died	Aged <70 Baseline=91.4 % 6 weeks=64.8% 3 months=50.2% 6 months=34.8% Aged ≥70 Baseline=89.8 % 6 weeks=59.1% 3 months=42.0% 6 months=21.6%
Vansteenkiste 2003[213]	Overall symptom control Normal daily activities	Symptom control in both arms was similar for 'disease-specific' symptoms such as cough, dyspnoea, pain or haemoptysis. A significantly larger number of gemcitabine patients had better scores for 'constitutional' items such as anorexia (p=0.007),	Overall symptom control <65

Study	Tool used	Results	Compliance
	Overall QoL	ability to carry on with daily activities (p=0.04) and overall impression of QoL (p=0.008). Fatigue was the most difficult item to control in both arms Although there was a tendency towards better symptom control in patients with a baseline KPS >80%, the differences were not significant in this patient group, there was only a trend towards a better score for the question on overall symptoms	years=70/88 ≥65 years=64/81 Normal daily activities <65 years=64/88 ≥65 years=53/81 Overall QoL <65 years=62/88 ≥65 years=52/81
Koyama 2010[220]	Physical domain Functional QoL	The total score of physical domain was significantly deteriorated during chemotherapy in patients aged ≥65 (p=0.044 by repeated ANOVA), while that in those aged <65 was not altered. Interestingly, significant correlation between KPS and total score of functional QoL domain was observed (r=0.454)	NR

FACT-L=Functional Assessment of Cancer Therapy-Lung; FACT-G=Functional Assessment of Cancer Therapy-General; LCSS=Lung Cancer Symptom Scale; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire; EORTC QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire Lung Cancer-Specific Module; TOI=Trial Outcome Index; TOI-L=Trial Outcome Index (Lung); NTTX=Neurotoxicity and Taxane Toxicity; ANOVA=analysis of variance; PSI=Pulmonary Symptom Improvement; EQ-5D= EuroQoL-5D questionnaire KPS=Karnofsky performance status; QoL=quality of life; OR=odds ratio; CI=confidence interval; NR=not reported