Trial	Inclusion criteria	Exclusion criteria
Kelly 2001[48]	Histologically or cytologically confirmed NSCLC (primarily squamous cell, large cell, or adenocarcinoma). Patients with stage IV or selected stage IIIB disease by the International Staging System (lung cancer). Stage IIIB patients had to have a positive pleural effusion or multiple ipsilateral lung nodules. Bidimensionally measurable or assessable disease, PS of 0 or 1, neutrophil count ≥1500/μl, platelet count greater than or equal to institutional lower limits of normal, haemoglobin ≥9 mg/dl, serum creatinine ≤1.5 mg/dl or a calculated creatinine clearance ≥60 ml/minute, bilirubin level ≤2.0 mg/dl, AST less than or equal to twice the institutional upper limits of normal, or less than or equal to four times the institutional upper limits of normal if the patient had liver metastases. Previous surgery and radiotherapy were allowed	Prior chemotherapy or biologic therapy, brain metastases, grade 2 or higher peripheral neuropathy
Scagliotti 2002[43]	Locally advanced (stage IIIB with either pleural effusion or N3 supraclavicular nodal disease), recurrent, and/or metastatic (stage IV) NSCLC. The neoplastic disease must have been clinically assessable, as defined by objective imaging studies consistent with and supported by a pathological (histological or cytological) diagnosis of NSCLC. The presence of at least one unidimensional measurable disease was mandatory and bidimensionally measurable disease was preferable. Although patients were required to be chemotherapy or immunotherapy naive, radiotherapy was permitted if concluded at least 4 weeks before entering the study (provided the irradiated site was not the only site of measurable disease), and prior surgery was allowed if the patient met all the other criteria specified. Patients were to have an ECOG PS of 0–2 and a life expectancy of at least 12 weeks. Adequate bone marrow reserve (WBC count 3.5×10^9/l, platelets 100×10^9/l, haemoglobin 10 g/l, and haematocrit 30%) and liver and renal function (creatinine 1.5 times the upper limit of normal)	Active infection, symptomatic CNS metastases requiring emergency radiotherapy and/or corticosteroids, serious concomitant systemic disorders, second primary malignancy (except in situ carcinoma of the cervix or non-melanomatous skin cancers), and severe cardiovascular diseases. Patients who were pregnant or breast feeding
Schiller 2002[47]	Confirmed disease, measurable or non-measurable; aged at least 18 years; adequate haematological function (as indicated by a white cell count of at least 4000/mm^3 and a platelet count of at least 100,000/mm^3), hepatic function [as indicated by a bilirubin level that did not exceed 1.5 mg per decilitre (25.6μmol/l)] and renal function [as indicated by a creatinine level that did not exceed 1.5 mg per deciliter (132.6μmol/l)]. Prior radiotherapy at symptomatic sites was permitted provided that the indicator sites (the sites that were followed to determine whether or not there was a response) had not been irradiated and that the radiotherapy had been completed before chemotherapy was initiated. Patients with stable brain metastases were eligible	Prior chemotherapy

Trial	Inclusion criteria	Exclusion criteria
Fossella 2003[44]	Adults (aged ≥18 years) with histologically or cytologically confirmed locally advanced or recurrent (stage IIIB) or metastatic (stage IV) NSCLC, KPS ≥70%, and at least one measurable or assessable lesion were recruited. Adequate organ function was required, as evidenced by absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, haemoglobin ≥9.0 g/dl, hepatic enzyme levels ≤2 × ULN range, alkaline phosphatase levels ≤5 × ULN, total bilirubin levels no more than the ULN, and serum creatinine levels ≤1.5 mg/dl (or creatinine clearance ≥60 ml/minute)	Prior chemotherapy treatment with a biologic response modifier, previous or concurrent malignant disease (except cone-biopsied carcinoma in situ of the cervix or adequately treated basal or squamous cell carcinoma of the skin), history of brain or leptomeningeal metastases (except if adequately treated and radiologically stable for at least 4 weeks), peripheral neuropathy of National Cancer Institute common toxicity criteria grade 2 or above, major surgery within 2 weeks of study entry, radiotherapy within 4 weeks of study entry, or other serious concomitant illness
Gebbia 2003[49]	Histologically confirmed diagnosis of locally advanced, inoperable stage IIIB (cytologically positive pleural effusion and/or supraclavicular nodes) or metastatic stage IV NSCLC; aged 18–75 years; PS <2 according to the ECOG criteria; life expectancy of at least 3 months; adequate bone marrow function (WBC/4000/MMC, PTL/120,000/MMC, Hb/10 g%); serum bilirubin <2 mg%, serum transaminases less than two times the normal value; serum creatinine <1.5 mg%, BUN <50 mg%; normal cardiac function as evaluated by ECG; no signs of CNS metastases. Absence of severe, uncontrolled metabolic, respiratory, cardiovascular, neurological and infectious diseases was mandatory. Absence of second malignancies with the exception of adequately managed in situ uterine or cutaneous basal cell carcinomas, and geographical accessibility to the oncological centres in order to guarantee a correct follow-up were also necessary prerequisites for inclusion into the trial. Previous radiotherapy was allowed if patients had measurable disease outside of radiotherapy fields. Because evaluation of ORR was one of the study aims all enrolled patients had to present bidimensionally measurable disease according to the WHO criteria	Prior chemotherapy
Gridelli 2003[45]	Histological or cytological proof of NSCLC and aged <70 years. Stage IV disease or stage IIIB disease with malignant pleural effusion or supraclavicular nodes. ECOG PS of 0, 1 or 2; adequate haematology (absolute neutrophil count 2000/l, platelets 100,000/l, and haemoglobin 10 g/dl) and biochemistry (serum creatinine 1.25 × ULN, AST and ALT and bilirubin 1.25 × ULN, unless as a result of liver metastases); willing and able to complete QoL questionnaires. Could have received prior radiotherapy	Prior chemotherapy, brain metastases or a history of prior invasive malignancy
Smit 2003[46]	Histologically or cytologically confirmed NSCLC stage IIIB (caused by malignant pleural effusion or supraclavicular lymph nodes only) and stage IV disease according to the revised staging system of the American Joint Committee on Cancer. Aged between 18 and 76 years, WHO PS 2, measurable disease, no previous chemotherapy with the exception of prior neoadjuvant or adjuvant chemotherapy that ended >1 year before entry, and adequate haematological, renal and hepatic function. Previous radiotherapy was allowed provided that an interval of at least 4 weeks had elapsed and the radiotherapy field did not include all measurable lesions used as target lesion. Patients with pre-existing brain metastases or leptomeningeal disease who were treated with radiotherapy, stable without medications (e.g. corticosteroids), and asymptomatic were eligible	

Trial	Inclusion criteria	Exclusion criteria
Chen 2004[51]	Cytological or histological diagnosis of NSCLC; stage IIIB, IV or recurrence after surgical treatment; aged 18–80 years; no prior chemotherapy, immunotherapy or radiotherapy; a PS of 0–2 on the WHO scale; bidimensionally measurable disease; and adequate bone marrow reserve with a WBC count ≥4000 mm^3, platelets ≥100,000 mm^3, and haemoglobin × 10 g/dl	Signs or symptoms of brain metastases; inadequate liver function (bilirubin 41.5 × ULN and ALT/AST 43 × ULN); or inadequate renal function with creatinine 42.0 mg/dl were excluded from the study
Douillard 2005[53]	Histologically or cytologically confirmed stage IV NSCLC (squamous cell, large cell, adenocarcinoma or undifferentiated NSCLC). At least one measurable or assessable lesion outside irradiated fields, i.e. cutaneous or lymph node ≥1010 mm assessed by clinical measurement; limited pulmonary nodule ≥1010 mm detected by standard chest X-ray or ≥2010 mm using CT scan; others lesions ≥2010 mm at CT scan. Age 18–75 years; WHO PS ≤2; and adequate bone marrow (neutrophil count ≥1.5 × 10^9/l, platelet count ≥100 × 10^9/l), renal and hepatic functions (creatinine ≤140 mmol/l, total bilirubin ≤1.5 × ULN, transaminases ≤2.5 × ULN, alkaline phosphatases ≤5 × ULN except for isolated bone metastases). Previous radiotherapy was allowed if it involved <25% of bone marrow and was completed 4 weeks before study entry. Previously irradiated or clinically asymptomatic brain metastases and any weight loss during the last 6 months were admitted	Stages IIIB (including wet T4); National Cancer Institute Common Terminology Criteria (NCI CTC) peripheral neuropathy grade >1; prior chemotherapy or biological therapy for metastases; lymphangitis carcinomatosa, ascites or pleural effusion as the only target
Martoni 2005[54]	Histological or cytological diagnosis of NSCLC; stages IIIB or IV, or recurrent disease after an operation for primary NSCLC; KPS) ≥70; no prior chemotherapy or radiotherapy; adequate marrow (granulocyte count >1500/ll; platelet count of at least 100,000/ll), cardiac, hepatic and renal (serum creatinine <1.5 mg/dl) functions	Symptomatic brain metastases, previous or concomitant malignancies, with the exception of in situ carcinoma of the cervix and adequately controlled, non-melanoma skin cancer
Thomas 2006[58]	Aged between 18 and 70 years, with a histological or cytological diagnosis of NSCLC, with an ECOG score ≤2 and a life expectancy ≥12 weeks. Patients had to present a stage IV disease, but without brain metastasis or stage IIIB disease with malignant pleural effusion proven by cytology. Previous radiotherapy was allowed. Normal hepatic and renal functions, and an adequate bone marrow reserve were required: total bilirubin ≤1.25 × ULN, AST and ALT <3 × ULN, ALP <2.5 × ULN, and creatinine concentration ≤110 mol/l, white blood cells ≥4 × 10^9/l with neutrophils >1.5 × 10^9/l platelets ≥100 × 10^9/l, haemoglobin ≥10 g/dl. In addition, patients were required to have at least one bidimensionally measurable target lesion outside the irradiation field, ≥2 cm on a CT scan. Bone metastases and pleural or peritoneal effusions were not considered as measurable lesions	Prior chemotherapy
Chen 2007[52]	Cytological or histological diagnosis of NSCLC; stages IIIB or IV; aged 18–80 years; with no prior chemotherapy, immunotherapy, or radiotherapy; with a PS of 0–2 on the WHO scale; bidimensionally measurable disease; and adequate bone marrow reserve with a WBC count ≥4000 mm^3, platelets ≥100,000 mm^3 and haemoglobin ≥10 g/dl	Symptomatic brain metastases; inadequate liver function (total bilirubin >1.5 × ULN and ALT/AST >3 × ULN); or inadequate renal function with creatinine >2.0 mg/dl

Trial	Inclusion criteria	Exclusion criteria
Helbekkmo 2007[55]	Chemo-naive patients with histologically or cytologically confirmed NSCLC stage IIIB or IV, not candidates for curative treatment. WHO PS 0–2 and ability to understand oral and written study information. No upper age limit was defined. WBC count $>3.0 \times 10^9$ cells 1^{-1}, platelet count $>100 \times 10^9$ cells 1^{-1}, serum creatinine $<1.5 \times$ ULN and bilirubin and serum transaminase levels $<2 \times$ ULN	Other active malignancies, pregnancy, or breast feeding
Langer 2007[56]	Advanced, incurable, chemotherapy-naive NSCLC; ECOG PS 2; age at least 18 years; adequate physiological indices, including absolute neutrophil count of at least 2000; platelets at least 100,000; creatinine ≤ 1.5 mg/dl; bilirubin ≤ 1.5 mg/dl	Prior radiotherapy to assessable disease (unless disease progression was confirmed at that site by physical examination, radiography, or pathology) or had pre-existing grade 2 or higher sensory neuropathy, CNS metastases untreated or actively growing despite prior radiation or surgery, or other active concurrent malignancies. Pregnancy, allergies to polyoxyethylate castor oil and significant comorbidities precluding chemotherapy, including active congestive heart failure and recent myocardial infarction
Ohe 2007[57]	Histologically and/or cytologically documented NSCLC, clinical stage IV or IIIB (including only patients with no indications for curative radiotherapy, such as malignant pleural effusion, pleural dissemination, malignant pericardiac effusion, or metastatic lesion in the same lobe), at least one target lesion > 2 cm, aged 20–74 years, ECOG PS of 0 or 1, adequate haematological, hepatic and renal functions, partial pressure of arterial oxygen (PaO_2) ‡ 60 torr, expected survival > 3 months, able to undergo first course treatment in an inpatient setting	Prior chemotherapy, prior surgery and/or radiotherapy for the primary site
Chang 2008[50]	Histologically confirmed stage IIIB or IV NSCLC, measurable disease, aged > 18 years, ECOG PS 2 or better, allowed to have received prior radiotherapy if performed more than 4 weeks prior to enrolment, on < 30% of the marrow-bearing bones, patients with asymptomatic brain metastasis were allowed provided it was not the only disease site, adequate baseline bone marrow, hepatic and renal function	History of prior or concomitant malignancy, pregnant or lactating women
Scagliotti 2008[61]	Chemotherapy-naive patients with histologically or cytologically confirmed NSCLC, classified as stage IIIB not amenable to curative treatment or stage IV, with at least one unidimensionally measurable lesion according to the Response Evaluation Criteria in Solid Tumors, with an ECOG PS of 0 or 1, and at least 18 years of age. Patients had adequate bone marrow reserve and organ function including calculated creatinine clearance ≥ 45 ml/minute based on the standard Cockcroft–Gault formula. Prior radiotherapy was permitted if it was completed at least 4 weeks before study treatment and patients had fully recovered from its acute effects	Peripheral neuropathy National Cancer Institute Common Toxicity Criteria grade 1, progressive brain metastases, or uncontrolled third-space fluid retention before study entry. Unable to interrupt aspirin and other non-steroidal anti-inflammatory drugs or if they were unable or unwilling to take folic acid, vitamin B_{12} or corticosteroids

Trial	Inclusion criteria	Exclusion criteria
Gronberg 2009[62]	Chemotherapy-naive and aged > 18 years old, stage IIIB (ineligible for curative radiotherapy) or stage IV NSCLC, WHO PS of 0 to 2, adequate bone marrow and liver function and creatinine clearance 45 ml/minute (Cockroft–Gault formula)	
Mok 2009[15] and Fukuoka 2011[64]	Aged ≥18 years, histologically or cytologically confirmed stage IIIB or IV NSCLC with histological features of adenocarcinoma (including bronchoalveolar carcinoma), non-smokers (patients who had smoked < 100 cigarettes in their lifetime) or former light smokers (stopped smoking at least 15 years previously and had a total of ≤10 pack-years of smoking)	Prior chemotherapy or biological or immunological therapy
Tan 2009[59]	Between 18 and 75 years, histologically or cytologically (fine-needle aspiration) proven NSCLC, stage IIIB (with supraclavicular nodal metastases or pleural effusion), stage IV or relapsing (locally or distant) after a local treatment; KPS of ≥80%; life expectancy > 12 weeks; previously untreated with chemotherapy or immunotherapy; adequate bone marrow, hepatic and renal function; neutrophils $\geq 2.0 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; haemoglobin > 11 g/dl or 6.8 mmol//l; total bilirubin ≤1 × ULN; transaminases < 2.5 × ULN; alkaline phosphatases < 5 × ULN; creatinine ≤ULN or creatinine clearance ≥60 ml/minute; with the presence of at least one measurable indicator lesion (RECIST criteria) not previously irradiated and assessed by conventional CT scan (longest diameter ≥20 mm, spiral on CT scan or ≥10 mm on magnetic resonance imaging)	
Maemondo 2010[63]	Presence of advanced NSCLC harbouring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 is substituted by methionine), aged ≤75 years	History of chemotherapy
Mitsudomi 2010[65]	Initially, only patients with postoperative recurrence were eligible, because these surgical specimens were expected to ensure good sample quality. However, because of the initial slow accrual, the protocol was amended on 10 July 2006 to include patients with stage IIIB/IV disease. Histologically or cytologically confirmed NSCLC, harbouring activating EGFR mutations (either exon 19 deletion or L858R in exon 21), aged ≤75 years, WHO PS 0–1, measurable or non-measurable disease according RECIST, adequate organ function. Patients with postoperative recurrence, treated with adjuvant therapy other than CIS + DOC, were included when the interval between the end of adjuvant chemotherapy and registration exceeded 6 months for PLAT doublet therapy and >1 month for oral tegafur plus uracil therapy	Previous drug therapy that had targeted EGFR, history of interstitial lung disease, severe drug allergy, active infection or other serious disease condition, symptomatic brain metastases, poorly controlled pleural effusion, pericardial effusion or ascites necessitating drainage, active double cancer, or severe hypersensitivity to drugs containing polysolvate 80. Pregnancy or lactation, or patients whose participation in the trial was judged to be inappropriate by the attending doctor

Trial	Inclusion criteria	Exclusion criteria
Treat 2010[60]	Histologically confirmed diagnosis of stage IIIB (with pleural or pericardial effusion), stage IV or recurrent NSCLC. Mixed tumours were categorised by the predominant cell type unless small-cell anaplastic elements were present, in which case the patient was ineligible. All patients were required to be ≥18 years of age and have measurable or evaluable disease (according to ECOG solid tumour criteria); an ECOG PS of 0 or 1; and adequate bone marrow reserve (neutrophils > 1500/mm^3, platelets > 100,000/mm^3), adequate hepatic function (aspartate transaminase ≤5 × institutional ULN and serum bilirubin ≤1.5 mg/dl × institutional ULN), and adequate renal function (creatinine clearance ≥40 ml/minute or serum creatinine ≤1.5 mg/dl). Stage IV patients with brain metastases were eligible provided the brain metastases were, in the opinion of the site investigator, clinically stable after treatment with surgery or radiotherapy	Prior chemotherapy for this diagnosis. No previous irradiation to the only area of measurable or evaluable disease, unless that site had subsequent progression of disease documented by physical examination, radiograph or pathology. Pregnant or breastfeeding women. Patients with a known or suspected hypersensitivity to agents that utilise polyoxyethylated castor oil

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CNS, central nervous system; Hb, haemoglobin; ULN, upper limit of normal value; WBC, white blood cell;