

Horizon Scanning in Oncology

Cetuximab (Erbitux[®]) in
EGFR-expressing Non-
Small Cell Lung Cancer



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1 Drug description

Generic/Brand name:

Cetuximab/Erbitux®

Developer/Company:

Cetuximab was developed by ImClone Systems Incorporated (Head office: New York, USA) and is manufactured by Bristol-Myer Squibb (Head office: Princeton, USA). Outside the USA and Canada, ImClone Systems Incorporated granted exclusive rights for development and commercialization of Cetuximab to Merck KGaA, Darmstadt, Germany [1].

developer: Imclone System

manufacturer: Bristol-Myer Squibb

Description:

Cetuximab belongs to the pharmacotherapeutic group of antineoplastic agents and monoclonal antibodies (ATC code: L01XC06).

monoclonal antibody

It is a chimeric murine or human monoclonal IgG₁ antibody designed to specifically direct against the epidermal growth factor receptor (EGFR) on the surface of tumour cells. By binding to the EGFR, tumour cells no longer receive messages needed for growth, progression and spread. Therefore, cetuximab inhibits the proliferation and induces apoptosis of human tumour cells expressing EGFR [2].

directs against EGFR

The recommended treatment regimen consists of an initial starting dose of 400 mg/m² body surface area intravenous (IV) infusion over two hours on day 1, followed by a weekly 250 mg/m² IV infusion over one hour in combination with a platinum-based double-agent chemotherapy regimen until disease progression or unacceptable toxicity [3]. Both Phase III [1, 4] trials included in this report examined the clinical effectiveness and safety of cetuximab using this treatment regimen.

treatment regimen

2 Indication

Cetuximab in combination with double-agent platinum-based chemotherapy (cisplatin and vinorelbine) is indicated for first-line treatment of advanced and recurrent non-small cell lung cancer (NSCLC) [5]. Patients eligible for the cetuximab chemotherapy regimen are ≥ 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 to 2 and suffer from EGFR-expressing non-small cell lung cancer.

first-line treatment of advanced and recurrent NSCLC

3 Burden of Disease

lung cancer one of the leading types of cancer causing death

Lung cancer is one of the leading types of cancer and causes of cancer deaths worldwide [6]. Generally, one can differentiate between small-cell lung cancer (SCLC 15%) and non-small cell lung cancer (NSCLC 85%) [5, 7]. Its primary risk factors are first-hand and second-hand smoke [5].

poor prognosis due to late diagnosis

Often, lung cancer is diagnosed in advanced stages of the disease, therefore prognosis is poor [6, 7]. In patients with advanced disease, performance status¹ is used to estimate patient's prognosis and to establish a treatment plan. Patients with advanced disease and good prognosis (ECOG PS 0 to 1) are treated with double-agent chemotherapy, whereas patients with poor prognosis (ECOG PS 2 to 4) receive single-agent chemotherapy or best-supportive care [5, 7, 8].

Although early stage lung cancer can be managed curatively, a population wide screening to detect lung cancer at an early stage is not recommended. Currently, several trials are ongoing to find out whether screening benefits lung cancer patients or not [5].

prognostic factors for prediction of survival

Early-stage disease, good performance status (ECOG PS 0, 1 or 2), absence of significant weight loss (not more than 5%) and female gender are the most important prognostic factors regarding the prediction of survival of NSCLC patients. Age and histological subtypes do not play a major role in prognosis of tumour development [5] but in choice of treatment modalities and chemotherapeutic agents. Other prognostic and predictive factors for lung cancer response to cetuximab are biomarkers like epidermal growth factor receptor (EGFR) expression and mutational state, the occurrence of downstream signal transduction pathway modifications (K-Ras mutation) and others [5]. Unfortunately, the literature in the field of predictive factors is highly contradictory and controversial. For metastatic colorectal cancer, it was shown that the efficacy of cetuximab is clearly related to the absence of K-RAS mutations, but similar data for NSCLC are lacking or challenging to interpret (follow up of the FLEX trial, ASCO 2008, Pirker et al.)

staging system of NSCLC – stages I-IV

The most commonly used staging system of cancers in the trials included in this assessment is stage I-IV according to Union internationale contre le cancer (UICC) where stage I refers to a locally restricted, small primary tumour and stage IV represents metastatic, systemic disease. In its guidelines the National Comprehensive Cancer Network cites the international staging system for lung cancer with reference to the American Joint Committee on Cancer (www.cancerstaging.net), where stages 0-IV are defined in detail regarding existence and size of primary tumour, existence and dimension of regional lymph nodes and distant metastasis [5].

3900 new cases of lung cancer were diagnosed in Austria 2006

Overall, 3,900 new cases of lung cancer were diagnosed in Austria in 2006, of which 31% were advanced, 13.3% were given death certificate only, and in 19.5% of lung cancer patients cancer stage was not specified [9].

¹ Generally assessed by applying the Eastern Cooperative Oncology Group (ECOG) or Karnofsky scale 7. Stinchcombe, T.E. and M.A. Socinski, *Current treatments for advanced stage non-small cell lung cancer*. Proc Am Thorac Soc, 2009. 6(2): p. 233-41..

As no detailed data on incidence, survival rates and tumour development within the different NSCLC stages could be found for Austria, data from the United States of America (USA) will be shown in the following paragraphs.

Overall, the incidence of NSCLC in the USA was 52 per 100,000 per year in 2006. Among males, the incidence was 63 per 100,000 per year, whereas within females it was 45 per 100,000 per year in 2006 [10].

males more often affected than females

At the time of diagnosis of NSCLC, 17.5 (males 19.9 and females 15.3) of 100,000 US-citizens are under 65 years of age and 315.2 (males 406.0 and females 252.3) of 100,000 US-citizens are aged \geq 65 years [10]. On average, patients are 71 years old at the time of diagnosis of lung and bronchus cancer.

majority of NSCLC patients \geq 65 years

In 2005 the 1-year survival rate for patients with cancer of the lung and bronchus of all stages was 44.4% [10]. The 5-year survival rate in NSCLC depends on both tumour stage and patient's age at diagnosis and is 17.2% for all stages of NSCLC. Furthermore, the five-year survival rate is 54.2%, 25.2%, 3.7% and 8.5% for localized, regional, distant and unstaged NSCLC, respectively. In addition, it is 25.7% in individuals aged under 45 years and decreases to 15.1% in patients $>$ 65 years of age [10].

survival rate depends on tumour stage and patient's age at diagnosis

4 Current treatment

Treatment of NSCLC is based on cancer stage (I-IV) at diagnosis and ECOG performance status and can encompass surgery, radiotherapy, chemotherapy, targeted therapy and best supportive care [5, 6] as well as multi-modal approaches. Patients with early stage disease are treated with surgery, whereas individuals with locally advanced disease are either treated with radiotherapy alone or in combination with chemotherapy, and neo-adjuvant approaches. Patients with advanced disease are treated either with chemotherapy alone [8] or targeted therapy alone, or with a combination of both. The targeted therapeutic agents gefitinib, erlotinib and bevacizumab have been licensed for NSCLC in several countries.

choice of treatment depends on cancer stage, ECOG performance status

According to Stinchcombe and Socinski 2009, the current standard of treatment as first-line therapy in patients with advanced NSCLC is a double-agent chemotherapy regimen, consisting of one platinum-based agent (cisplatin, carboplatin) in combination with a second agent (paclitaxel, gemcitabine, vinorelbine or docetaxel and pemetrexed in patients with non-squamous histology) [5, 7].

current standard first-line therapy is a double-agent chemotherapy

Besides the targeted agents already licensed for NSCLC treatment (see above), multiple additional agents are in phase I, II or III developmental stages [11].

5 Current regulatory status

cetuximab approved for squamous cell carcinoma of the head and neck and colorectal cancer

Cetuximab was approved for squamous cell carcinoma of the head and neck by the European Medicines Agency (EMA) in March 2006 and by the United States Food and Drug Administration (FDA) in May 2006. Furthermore, it was approved for EGFR-expressing colorectal cancer by EMA in March 2004 and by FDA in February 2004 [12, 13].

indicated for the use in EGFR-expressing colorectal cancer

Cancer of the colon or rectum:

The use of cetuximab is indicated in EGFR-expressing colorectal cancer in combination with other anti-cancer medicines or as a single-agent when previous cancer therapy containing both irinotecan and oxaliplatin has failed. Its use is not recommended in patients whose tumour has K-RAS mutations [12, 13].

indicated for the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck

Head and neck cancer:

For the treatment of locally or regionally advanced squamous cell carcinoma of the head and neck, cetuximab is approved in combination with radiation therapy. In recurrent or metastatic squamous cell carcinoma of the head and neck, cetuximab can be used in combination with platinum-based anticancer therapy like cisplatin and carboplatin [12, 13].

6 Evidence

two phase III trials evaluating the effectiveness of cetuximab in NSCLC

Based on a literature search in the databases PubMed, Embase and CRD and on a hand search, two Phase III trials and six Phase II trials evaluating the effect of cetuximab in patients with advanced lung cancer were found [14-19]. Four of these trials were single-arm trials [14, 15, 17, 18] with the purpose of finding the most promising modality of combining cetuximab with different standard of care chemotherapy regimens. None of these four studies assessed cetuximab in combination with cisplatin or vinorelbine and two of them evaluated cetuximab in combination with a taxane (paclitaxel or docetaxel) plus carboplatin, the same regimen as used in the BMS 099 trial. The remaining two phase II trials [16, 19] were two-arm trials assessing the activity and safety of cetuximab in combination with platinum-based double-agent chemotherapy in comparison to platinum-based double-agent chemotherapy alone in patients with advanced NSCLC.

6.1 Efficacy and safety – Phase III studies

Reference	NCT00112294 (BMS 099), Abstract [20], not published [4]	NCT00148798 (FLEX), published [1]
Sponsor	Merck KGaA, ImClone LLC	Merck KGaA
Country	Multicenter – United States	Multicenter – Europe, Asia, America
Design	Randomized, open-label, active control	Randomized, open-label, active control
Participants	676 patients (pts) (I 338 vs C 338); median age 65 years (34-87 years)	1125 pts (I 557 vs C 568); median age I 59 years (18-78 years), C 60 years (20-83 years)
Treatment	<u>I</u> (ntervention): taxane, carboplatin and cetuximab <u>C</u> (ontrol): taxane, carboplatin alone (max 6 cycles, 1 cycle=3 weeks) Chemotherapy: taxane (either paclitaxel 225 mg/m ² dL infusion over 3h on d1, then every 3 weeks, or docetaxel 75 mg/m ² dL infusion over 1h on d1, then every 3 weeks, and carboplatin (infusion over 0.5h on d1, then every 3 weeks); Cetuximab: IV infusion on d1; initial dose of 400 mg/m ² , from d8 onwards 250 mg/m ² weekly	<u>I</u> (ntervention): cisplatin, vinorelbine and cetuximab <u>C</u> (ontrol): cisplating, vinorelbine alone (max 6 cycles, 1 cycle=3 weeks) Chemotherapy (one cycle): cisplatin (80 mg/m ² intravenous (IV) infusion on day (d) 1) and vinorelbine 25 mg/m ² IV infusion on d1, 8 of every 3-week cycle for up to 6 cycles); Cetuximab: IV infusion on d1; initial dose of 400 mg/m ² over 2h, from d8 onwards 250 mg/m ² weekly
In-/exclusion criteria	Stage IIIb with malignant pleural effusion or stage IV NSCLC, recurrent disease after surgery or radiation therapy, age ≥18 years, ECOG PS* 0-1 at study entry	Inclusion criteria: chemotherapy-naive stage IIIb or IV NSCLC, EGFR expression, age ≥18 years, ECOG PS 0-2, adequate organ function, presence of at least one bi-dimensionally measurable tumour lesion; Exclusion criteria: brain metastases, previous treatment with EGFR-targeted drugs or monoclonal antibodies, major surgery within 4 weeks or chest irradiation within 12 weeks before study entry, active infection, pregnancy, symptomatic peripheral neuropathy
Follow-up	cetuximab continued as single-agent until disease progression or unacceptable toxicity; Pts of both arms were assessed every 6 weeks post dosing until disease progression or start of secondary chemotherapy	cetuximab continued after end of chemotherapy until disease progression or unacceptable toxicity; median follow-up time 23.8 months (95% CI: I 22.1, 24.9 vs C 22.4, 24.8)
Outcomes	<u>Primary</u> : progression-free survival (PFS) <u>Secondary</u> : tumour response, overall survival, symptom response and symptomatic progression, safety	<u>Primary</u> : overall survival (OS) <u>Secondary</u> : progression-free survival, best overall response (OR), quality of life, safety

Results	<p><u>Median PFS</u>: I 4.4 months (95% CI: 4.11, 5.06) vs C 4.24 months (95% CI: 3.94, 4.63); HR=0.902 (95% CI: 0.761, 1.069; p=0.2358)</p> <p><u>Response rate</u>: Odds Ratio: 1.675 (95% CI: 1.152, 2.436)</p> <p><u>OS</u>: not significantly different between I and C: HR= 0.931 (99.99% CI: 0.638, 1.359; p=0.4639)</p> <p><u>Median survival</u>: I 9.53 months vs C 8.38 months</p>	<p><u>Median OS</u>: I 11.3 months (95% CI 9.3-12.4) vs C 10.1 months (95% CI 9.1-10.9), HR= 0.871 (95% CI 0.762-0.996; p= 0.044); 1-year survival 47% and 42%, respectively</p> <p><u>Median PFS</u>: 4.8 months in both groups (I 95% CI 4.2-5.3, C 95% CI 4.4-5.4); HR=0.943 (95% CI 0.825 – 1.077); p= 0.39)</p>
Adverse events (AEs)	<p>Grade 3/4 AEs (I vs C):</p> <p>Acneiform rash (10.8% vs 0%); infusion reaction (5.5% vs 0.9%)</p> <p>AEs (any grade) that led to discontinuation of study drugs (I vs C):</p> <p>cetuximab 30.5% vs 0%; (99 of 325 vs. 0 of 320), taxane 24.6% vs 17.2% (80 of 325 vs. 55 of 320), carboplatin 24.0% vs 16.6% (78 of 325 vs 53 of 320)</p> <p>Selected cardiac events: I 3.7% vs C 1.6%</p>	<p>Grade 3/4 AEs (I vs C):</p> <p>Acne like skin rash grade 3: 10% vs 1% (p=0.0001); haematological adverse effects: febrile neutropenia grade 3/4: I 16%/6% vs C 11%/4% (p=0.0086); leucopenia grade 3/4: I 15%/10% vs C 14%/5% (p=0.02); sepsis grade 3/4: I 0%/2% vs C 1%/1% (p=0.053); treatment-related deaths: 3% (15 of 548) vs 2% (10 of 562); cardiac events** grade 3/4: I 2%/4% (31 pts of 548) vs. C 3%/2% (28pts of 562pts), (p=0.69)</p>
Commentary	<p>Addition of cetuximab to taxane and carboplatin resulted in increased toxicity, although safety profile was consistent with previous clinical studies and treatment was tolerable and feasible. Certain patients benefit more from therapy with cetuximab.</p>	<p>No significant differences were found in assessing quality of life – results might be affected by the low return rate of the questionnaires (70% at baseline, <15% at end of study).</p>

* *ECOG PS: Eastern Cooperative Oncology Group performance status (details at: http://ecog.dfc.harvard.edu/general/perf_stat.html)*

** *Cardiac events consisted of five medical concepts: arrest, arrhythmia (I: 12 vs. C: 17), congestive heart failure (9 vs. 9), ischemia or infarction (8 vs. 4) and sudden death (2 vs. 0)*

Abbreviations: pts – patients, I – intervention group, C – control group, vs – versus, IV - intravenous, NSCLC – Non-small Cell Lung Cancer, EGFR – epidermal growth factor receptor, OS – overall survival, OR – overall response, PFS – progression free survival, AE – adverse events, CI – confidence interval, HR – Hazard Ratio, p – p-value.

6.2 Efficacy and safety - further studies

Rosell et al. 2008 [19] conducted a phase II trial comparing cisplatin and vinorelbine alone and in combination with cetuximab in patients with EGFR-expressing, advanced NSCLC. The main purpose of this trial was to assess the add-on activity of cetuximab to standard of care chemotherapy in advanced NSCLC. The dosing regimen and mode of administration of drugs as well as eligibility criteria for patients match with those from the FLEX-trial [1]. Main outcomes of this study were median progression-free survival (I: 5.0 months (95% CI: 4.5, 5.8) months vs. C: 4.6 months (95% CI: 2.5, 6.0); HR 0.71 (95% CI: 0.4, 1.2)), progression-free survival rates at 12 months (I: 15% (95% CI: 1%, 29%) vs. C: 0%), and best overall response rate (all partial responses) (I: 15 pts (35%; 95% CI: 21%, 51%) vs. C: 12 pts (28%; 95% CI: 15%, 44%). Regarding the safety of treatment, non-haematological grade 3/4 adverse events were similar in the two groups but differences between treatment arms were observed concerning the following grade 3/4 adverse events: asthenia (I: 19% vs. C: 2%), respiratory symptoms (I: 12% vs. C: 2%) and skin toxicities (I: 10% vs. C: none).

Butts et al. 2007 [16] assessed the efficacy of cetuximab with gemcitabine/platinum chemotherapy (I: 65 patients), or gemcitabine/platinum chemotherapy alone (C: 66 patients) in first-line therapy for advanced/metastatic NSCLC in an open-label, non-comparative randomized phase II trial. None of the patients reached complete response – 18 out of 65 patients in the cetuximab-arm (27.7%; 95% CI: 17.3%, 40.2%) and 12 out of 66 patients (18.2%; 95% CI: 9.8%, 29.6%) in the control-arm achieved partial response. The median progression free survival was 5.09 months (95% CI: 4.17, 5.98) and 4.21 months (95% CI: 3.81, 5.49), respectively. Median overall survival for the intervention group was 11.99 months (95% CI: 8.8, 15.2) and 9.26 months for the control group (95% CI: 7.43, 11.79).

Discontinuation of treatment was due to study drug toxicity (I: 12 pts (18.5%) vs. C: 7 pts (10.6%)) and disease progression/relapse (I: 32 pts (49.2%) vs. C: 17 (25.8%)). The most common grade 3/4 adverse events in the cetuximab-arm were acneiform rash (I: 9 pts (14.1%) vs. C: 0 pts), thrombocytopenia (I: 37 pts (57.8%) vs. C: 29 pts (44.6%)) and anaemia (I: 17 pts (26.6%) vs. C: 13 pts (20.0%)).

evaluation of the add on activity of cetuximab to standard of care
main outcomes were median progression free survival, progression free survival at 12 months and best overall response rate

gemcitabine and platinum chemotherapy with or without cetuximab

discontinuation of treatment due to study drug toxicity and disease progression/relapse

7 Estimated costs

One 100 ml vial Erbitux® (5mg/ml) solution is approximately € 980. For one patient an 18-week course is therefore expected to be around € 17,640 (assuming a body surface area of 1.7m² and therefore using 1 vial per week). The initial starting dose of cetuximab of 400 mg/m² is not included in this calculation and would be an additional € 1,960 (2 vials à € 980). These costs arise in addition to current chemotherapy regimens.

As no long term data for the use of cetuximab in NSCLC patients are available, we based the calculation of treatment costs on the median duration of treatment presented in the FLEX-trial [1].

treatment costs with cetuximab are additional to standard chemotherapy

8 Ongoing research

further 6 trials are evaluating cetuximab in NSCLC

Overall, six phase III trials evaluating cetuximab in NSCLC are registered at the freely accessible webpage www.clinicaltrials.gov, where international clinical trials are registered.

Two of these six trials are already completed [1, 4], three are currently recruiting patients and one is not yet open for participant recruitment.

NCT00095199: will assess whether the addition of cetuximab to either docetaxel or pemetrexed is effective in treating patients with recurrent or progressive NSCLC after failure of an initial platinum-based cancer therapy. Estimated study completion date is October 2009.

NCT00946712: will compare how well carboplatin and paclitaxel work with or without bevacizumab and/or cetuximab in treating patients with stage IV or recurrent NSCLC. Estimated study completion date is June 2012.

NCT00820755: is evaluating the activity and safety of cetuximab after platinum-based chemotherapy in combination with cetuximab as first-line treatment for individuals with advanced NSCLC.

NCT00533949: will find out how well high-dose radiation therapy given in combination with cetuximab works compared to standard-dose radiation therapy and chemotherapy in treating patients with newly diagnosed stage III NSCLC that cannot be removed by surgery.

9 Commentary - English

higher toxicity rates and more serious adverse events in the cetuximab arm

Both phase III trials evaluating safety and efficacy of adding cetuximab to platinum-based double-agent chemotherapy showed higher toxicity rates and more serious adverse events in the cetuximab arm than in the control arm. The most common adverse events were acne like skin rash, cardiac events, febrile neutropenia, leucopenia, asthenia, respiratory symptoms, anaemia and treatment related deaths [1, 4, 16, 19, 20]. In mCRC the occurrence of skin toxicity is known to correlate with treatment responses. In this regard, studies investigating “*dose escalation until toxicity occurs*” are under way.

one trial addressed quality of life

Only one trial addressed quality of life of NSCLC patients treated with cetuximab and chemotherapy and could not show significant differences between the study arms [1], probably due to the fact that only few questionnaires assessing quality of life were returned.

minor increases of PFS or OS in the cetuximab arm

Minor increases in either PFS or median OS were found, if cetuximab was added to chemotherapy. On average, PFS is longer in patients receiving chemotherapy and cetuximab (4.4 to 5.09 months) than in patients treated with chemotherapy alone (4.24 to 4.8 months). In terms of OS, trial results show a difference of 0 to 2.73 months between study groups (I: 8.3 to 11.99 months vs. C: 7.3 to 10.1 months). Accordingly, shortly before this assessments was published, a meta-analysis of four phase II/III trials [1, 16, 19, 20] was pre-

meta-analysis of 2 phase II and 2 phase III studies

sented at the ECCO 15 – 34th ESMO Multidisciplinary Congress² that concluded that cetuximab improves the efficacy of NSCLC therapy when added to a standard first-line chemotherapy (OS (HR 0.878; 95% CI: 0.795 to 0.969; p=0.01), PFS (HR 0.899; 95% CI: 0.814 to 0.993; P=0.036), and overall response rate (odds ratio 1.463; 95% CI: 1.201 to 1.783; p<0.001)) [21].

While overall and 1-year survival results of the FLEX trial favour the double-agent chemotherapy in combination with cetuximab, BMS 099 could not show superiority of chemotherapy plus cetuximab compared to chemotherapy alone. It is assumed that this is because patients were selected by their EGFR status in the FLEX-trial but not in BMS 099 [22], although EGFR positivity was defined quite liberal in the FLEX study as “*demonstration of the existence of at least a single EGFR expressing tumor cell.*” Thus, giving reason for hope that more stringent definitions will allow the characterisation of patient populations with a high probability of treatment responses.

Patient selection plays an essential role in the treatment of advanced NSCLC with targeted therapies, such as tyrosine kinase inhibitors and monoclonal antibodies [18]. The selection of patients on the basis of biomarkers is not standardized yet and it is unclear which patients will benefit the most from any given therapy. Therefore, before the widespread clinical use of biomarkers for patient selection and choice of treatment, the detection and use of biomarkers in prediction of patient survival needs to be urgently clarified in prospective clinical trials [1, 23, 24]. Nevertheless, despite the uncertainty surrounding the predictive potential of biomarkers with regards to NSCLC, the EMEA has narrowed down the indication of cetuximab for the treatment of mCRC: since 2008, it is only authorized for K-RAS wild-type mCRC.

Merck KGaA already applied for marketing authorisation of cetuximab in NSCLC at the EMEA which was refused by the EMEA in July 2009 due to major concerns whether the additional benefits could outweigh the side effects caused by cetuximab therapy [25].

Finally, the risks and benefits of adding cetuximab to standard of care chemotherapy in patients with advanced or metastatic NSCLC have to be balanced carefully. The application of cetuximab is, not only from the patient’s perspective – minor benefit and high risk of minor side effects – questionable, but also from the societal perspective regarding the economic impact of the therapy. Treatment costs for cetuximab therapy are high in comparison to the benefit gained and arise in addition to chemotherapy.

FLEX trial favoured the addition of cetuximab to chemotherapy, BMS 099 not

patient selection plays an essential role

use of biomarkers for patient selection needs to be clarified in prospective trials

application for marketing authorisation refused by EMEA

risks and benefits have to be balanced carefully

10 Commentary - German

Die beiden eingeschlossenen Studien zu Cetuximab in Kombination mit einer Standardchemotherapie bei Patienten mit nicht-kleinzelligem Lungenkarzinom (NSCLC) zeigen höhere Toxizitätsraten und einige schwerwiegendere Nebenwirkungen im Cetuximab-Arm verglichen mit dem Kontroll-Arm. Die bedeutendsten Nebenwirkungen waren akneiformer Hautaus-

höhere Toxizitätsraten und schwerwiegendere Nebenwirkungen im Cetuximab arm

² ECCO – European Cancer Organisation; ESMO – European Society for Medical Oncology

	schlag, kardiologische Ereignisse, febrile Neutropenie, Leukopenie, Asthenie, Atemwegsbeschwerden, Anämie und behandlungsbedingte Todesfälle [1, 4, 16, 19].
1 Studie untersuchte Lebensqualität	Nur eine Studie erhob die Lebensqualität von NSCLC-PatientInnen und konnte im Vergleich der Studienarme – Chemotherapie ± Cetuximab – keine signifikanten oder klinisch relevanten Unterschiede aufzeigen [1].
minimale Verbesserung bei PFS und OS	Im Hinblick auf progressionsfreies Überleben (PFS) und Gesamtüberleben (OS) konnten nur minimale Verbesserungen bei der zusätzlichen Verabreichung von Cetuximab zur Chemotherapie beobachtet werden. Durchschnittlich beträgt das progressionsfreie Überleben des nicht-kleinzelligen Lungenkarzinoms mit der Kombination Standardchemotherapie plus Cetuximab 4.4 bis 5.09 Monate) und mit Chemotherapie alleine 4.24 bis 4.8 Monate. Das OS verlängert sich im Durchschnitt um 0 bis 2.73 Monate bei zusätzlicher Verabreichung von Cetuximab zu Chemotherapie (I: 8.3 bis 11.99 Monate; C: 7.3 bis 10.1 Monate). Eine Metaanalyse [21], die kurz vor Erscheinen dieses Berichts am 15. Kongress der European Cancer Organisation (ECCO 15) präsentiert wurde, schlussfolgerte, dass Cetuximab in Kombination mit Standard first-line Chemotherapie die Wirksamkeit der NSCLC-Therapie verbessert ((OS (HR 0.878; 95% CI: 0.795, 0.969, p=0.01), PFS (HR 0.899; 95% CI: 0.814, 0.993; P=0.036), and ORR (odds ratio 1.463; 95% CI: 1.201, 1.783; p<0.001)).
Meta-analyse zu cetuximab	
FLEX Studie favorisiert Cetuximab mit Chemotherapie, BMS 099 nicht	Während in der FLEX-Studie die Kombination Chemotherapie plus Cetuximab zu einer höheren Gesamt- und 1-Jahres-Überlebensrate als Chemotherapie alleine führte, konnte dieses Ergebnis von der BMS 099-Studie nicht bestätigt werden. Man nimmt an, dass dieser Unterschied in der PatientInnenselektion zu finden sei, weil bei der FLEX-Studie die PatientInnen mittels EGFR-Status ausgewählt wurden und innerhalb BMS 099 nicht [22]. Das positivere Ergebnis der FLEX Studie konnte erreicht werden, obwohl die Definition eines positiven EGFR Status sehr weitgefasst war (<i>Nachweis einer einzigen EGFR positiven Tumorzelle</i>). Dies lässt hoffen, dass mittels Einsatz stringenterer Kriterien (EGFR Expression, Mutation, und K-RAS Status) die Identifikation von PatientInnen-Subgruppen mit hoher Wahrscheinlichkeit eines Therapieansprechens möglich wird.
Patientenselektion spielt eine wichtige Rolle bei der Therapiewahl	PatientInnenselektion spielt eine wesentliche Rolle in der Behandlung von PatientInnen mit NSCLC mit gezielten Therapien wie Tyrosinkinase-Inhibitoren und monoklonalen Antikörpern [18]. Da die PatientInnenselektion mittels Biomarkern noch nicht standardisiert und im Einzelfall unklar ist, welcher Nutzen für PatientInnen daraus entsteht, sollten Biomarker vor der breiten klinischen Anwendung für PatientInnenselektion, Therapiewahl und Vorhersage des Krankheitsverlaufs in prospektiven klinischen Studien dringend sorgfältig untersucht werden [1, 23, 24]. Im Falle von mCRC hat der K-RAS Mutationsstatus, allerdings basierend auf Ergebnissen retrospektiver Studien, Eingang in die EMEA Zulassung von Cetuximab gefunden.
Verwendung von Biomarkern zur PatientInnenselektion muss in prospektiven Studien abgeklärt werden	
Antrag auf Zulassung von Cetuximab für NSCLC wurde von der EMEA abgelehnt	Merck KGaA hat einen Antrag auf Zulassung von Cetuximab bei PatientInnen mit NSCLC bei der EMEA eingereicht, welcher im Juli 2009 aufgrund erheblicher Bedenken zu Nutzen und Risiken der Therapie abgelehnt wurde [25].
sorgfältige Abwägung zwischen Risiken und Nutzen	Schlussendlich müssen Risiken und Nutzen von Cetuximab in Kombination mit Standardtherapie sorgfältig abgewogen werden. Der Einsatz von Cetuximab ist nicht nur aus PatientInnenperspektive – geringer Nutzen und mögliche Nebenwirkungen – fraglich, sondern auch aus gesellschaftlicher

Perspektive im Hinblick auf die ökonomischen Auswirkungen der Therapie.
Die Behandlungskosten von Cetuximab sind im Vergleich zum Nutzen hoch
und entstehen zusätzlich zur Standard(chemo)therapie.

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