

Off-label uses included in the table represent only those uses that have been submitted via a formal application process. Additional off-label uses for this drug can be found in either the on-line or printed version of the American Hospital Formulary Service Drug Information (AHFS DI).

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
First-line therapy for stage IIIB (with malignant pleural effusion) and stage IV non-small cell lung cancer	Cetuximab 400 mg/m ² (week 1) IV followed by 250 mg/m ² weekly, plus Cisplatin 80 mg/m ² IV infusion day 1 and Vinorelbine 25 mg/m ² as an IV injection on days 1 and 8. Cycle with cisplatin and vinorelbine repeats every 3 weeks for a total of 6 cycles, then cetuximab continued as maintenance therapy. ¹	Moderate quality; Overall survival	Reasonable choice for patients with confirmed EGFR expressing NSCLC who are not candidates to receive a bevacizumab containing regimen (Accepted)	No conflicts of interest were disclosed during this review.	October 2008
First-line therapy for stage IIIB (with malignant pleural effusion) and stage IV non-small cell lung cancer	Carboplatin (dose calculated to yield a target AUC of 6) by IV infusion on day 1 Paclitaxel 225 mg/m ² IV infusion on day 1 Cycle of carboplatin and paclitaxel repeats every 3 weeks for a total of 4 cycles (SWOG 0342 study) ^{4,5} or for a maximum of 6 cycles (BMS 099) ^{2,3} BMS 099: Cetuximab 400 mg/m ² (week 1), followed by 250 mg/m ² weekly until disease progression ² SWOG 0342: Cetuximab administered at same dosage either concurrently with or sequentially after carboplatin/paclitaxel therapy.	Moderate quality; Overall survival (BMS 099) Moderate quality; Overall survival (SWOG 0342)	Not fully established	No conflicts of interest were disclosed during this review.	October 2008
First-line therapy for stage IIIB (with malignant pleural effusion) and stage IV non-small cell lung cancer	Cetuximab 400 mg/m ² (day 1 of week 1) IV, followed by 250 mg/m ² weekly. ² Carboplatin (dose calculated to yield a target AUC of 6) by IV infusion on day 1 Docetaxel 75 mg/m ² IV infusion on day 1 Cycle with carboplatin and docetaxel repeats every 3 weeks for a total of 6 cycles, then cetuximab continued as maintenance therapy.	Moderate quality; Overall survival	Not fully established	No conflicts of interest were disclosed during this review.	October 2008

AUC: Area under the curve

Off-label Use (condition and patient population)	Regimen	Strength of Evidence; Strength of Study End Point(s)	Grade of Recommendation	Disclosure Information	AHFS Publication Date
First-line therapy for stage IIIB (with malignant pleural effusion) and stage IV non-small cell lung cancer	<p>Cetuximab 400 mg/m² (week 1) IV administered as a 2-hour infusion, followed by 250 mg/m² weekly administered as a 1-hour infusion⁶</p> <p>Cisplatin 75 mg/m² IV infusion on day 1 Gemcitabine 1250 mg/m² IV infusion on days 1 and day 8</p> <p>Cycle with cisplatin and gemcitabine repeats every 3 weeks for a maximum of 6 cycles, then cetuximab continued as maintenance therapy.</p>	Low quality; Overall survival	Not fully established	No conflicts of interest were disclosed during this review.	October 2008
First-line therapy for stage IIIB (with malignant pleural effusion) and stage IV non-small cell lung cancer	<p>Cetuximab 400 mg/m² (week 1) IV administered as a 2-hour infusion, followed by 250 mg/m² weekly administered as a 1-hour infusion⁶</p> <p>Carboplatin (dose calculated to yield a target AUC of 5) by IV infusion on day 1 Gemcitabine 1000 mg/m² IV infusion on days 1 and day 8</p> <p>Cycle with carboplatin and gemcitabine repeats every 3 weeks for a maximum of 6 cycles, then cetuximab continued as maintenance therapy until disease progression</p>	Low quality; Overall survival	Not fully established	No conflicts of interest were disclosed during this review	October 2008

AUC: Area under the curve

Cetuximab with vinorelbine and cisplatin

- The FLEX study is a phase 3, multicenter, randomized study (n=1125) comparing the regimen of cetuximab, vinorelbine, and cisplatin with vinorelbine and cisplatin without concurrent cetuximab as primary treatment for stage IIIB (with a malignant pleural effusion) and stage IV non-small cell lung cancer (NSCLC) patients.¹ All patients' cancers were confirmed by immunohistochemistry (IHC) to be expressing the epidermal growth factor receptor protein (EGFR-positive); patients with an ECOG performance status (PS) of 0–2 were included.¹ All NSCLC histologies were included.¹
- The primary end point was overall survival, with secondary objectives of response rate, progression-free survival, disease control, quality of life, and safety. The study was powered to detect a difference in overall survival (OS) based on a hazard ratio (HR) of 0.8.¹
- The OS was 10.1 and 11.3 months (HR: 0.87, 95% CI= 0.762-0.996 [p=0.044]) and the 1-year survival rate was 42 and 47% for the chemotherapy alone and chemotherapy plus cetuximab arms, respectively.¹
- The response rates were 29 and 36% for chemotherapy alone versus the cetuximab-containing regimen, respectively; the progression-free survival was identical for both groups (4.8 months) while time-to-treatment failure was 4.2 and 3.7 months for the cetuximab-containing regimen and the chemotherapy-alone regimen, respectively. (p=0.0015)¹
- A subgroup analysis revealed a higher OS in patients in the Asian subgroup compared with the Caucasian cohort (19.5 versus 9.6 months, respectively). A higher percentage (61 versus 17%) of the Asian subgroup received a tyrosine-kinase inhibitor (TKI) at the time of relapse following their initial study regimen.¹ For the Caucasian patients (84%), the OS was 10.5 and 9.1 months, with 1-year survival rates of 45 and 37% (HR: 0.8; 95% CI = 0.694-0.928 [p=0.003]) for the cetuximab-containing and chemotherapy alone arms, respectively.¹
- The incidence of febrile neutropenia was high in both treatment arms, with a slightly higher incidence (22 versus 15%) in the cetuximab-containing arm relative to the chemotherapy-alone arm.¹ Grade 3 acneiform rash was reported at an incidence of 10% in the cetuximab arm compared with less than 1% in the chemotherapy-alone arm.¹
- Additional post-study treatment was given to 54 and 61% of the patients at the time of progression for the cetuximab-containing and chemotherapy-alone arms, respectively.¹ The use of radiation therapy and chemotherapy was similar in both groups; however, TKI therapy was used more frequently (27 vs 17%) in the chemotherapy alone containing arm.¹
- The efficacy results were reported based on an intent-to-treat analysis; however, the OS failed to meet the study objective with a reported HR of 0.87 compared with the presumptive HR of 0.8.¹
- EGFR and KRAS mutation status is not known for this patient population; there are no plans to collect this data for this study.

Cetuximab with carboplatin and paclitaxel (or docetaxel)

- BMS 099 is a phase 3 randomized study (n=676) comparing the regimen of cetuximab, carboplatin, and a taxane (docetaxel or paclitaxel, selected by the investigator for the individual patient) with carboplatin and a taxane without cetuximab as primary treatment for stage IIIB (with a malignant pleural effusion) and stage IV NSCLC.^{2,3} No EGFR testing was required for enrollment in the study.² All patients had an ECOG performance status of 0–1.² All NSCLC histologies were included.²
- The primary end point was progression-free survival (PFS), assessed by the Independent Radiologic Review Committee (IRRC); the secondary end points were response rate (assessed by IRRC and the investigators), overall survival, quality of life, safety, and PFS (assessed by the investigators).² The study was powered to determine an improvement in PFS based on a HR of 0.75.²

- PFS was slightly prolonged with the cetuximab arm compared with the carboplatin-taxane arm (4.4 versus 4.24 months, respectively) (HR: 0.9, 95% CI= 0.761-1.069 [p=0.23]); the objective response rate also was slightly higher for the cetuximab arm compared with carboplatin plus a taxane (25.7 versus 17.2%, respectively).² Both assessments reflect the analysis performed by the blinded, Independent Radiologic Review Committee (IRRC).²
 - The overall survival was improved (but not a statistically significant improvement) for the cetuximab-containing arm compared with the carboplatin-taxane arm (9.7 versus 8.4 months, respectively) (HR: 0.89, 95% CI=0.75-1.05 [p=0.17]).³
 - The incidence of febrile neutropenia was similar between both groups (i.e., less than 5%).²
 - The study failed to meet its study objective of an improvement in PFS with a HR of 0.89 compared with the presumptive HR of 0.8.²
 - The investigators plan to perform EGFR testing using gene copy detection by FISH; analysis of both the presence and impact of either an EGFR and/or a KRAS mutation on response will be evaluated.²
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- A second study, SWOG 0342, is a phase 2 randomized trial (n= 242) comparing carboplatin and paclitaxel plus concurrent cetuximab therapy with a sequential regimen of carboplatin and paclitaxel followed by cetuximab therapy as first-line therapy for stage IIIB (with a malignant pleural effusions) and stage IV NSCLC.^{4,5} EGFR testing was not required for enrollment in the study; however, one-third of the patients consented to having EGFR testing performed using gene copy number by FISH.⁵ All patients had an ECOG performance status of 0–1. All NSCLC histologies were included.⁴
 - The primary end point was overall survival.^{4,5} The study was powered to show a difference of 30% between groups based on an HR of 1.3.⁴
 - The median overall survival was slightly higher with the concurrent versus the sequential regimen (11 versus 10 months, respectively).⁴ The PFS was identical at 4 months for both groups, and the objective response rate was similar for the concurrent and sequential groups (34 versus 31%, respectively).⁴
 - The incidence of grade 3 and 4 febrile neutropenia was low for both regimens; however, a statistically significant increase was reported with the concurrent arm relative to the sequential arm (5 versus 1%, respectively; p=0.04).⁴ Reports of grade 3 and 4 peripheral neuropathy were higher with the concurrent versus the sequential schedule (14 versus 6%, respectively [p=0.04]).⁴
 - In the subset analysis based on one-third of the enrolled patients who consented to EGFR testing, both the mean PFS and OS were significantly higher for the EGFR-positive than the EGFR-negative patients (PFS: 6 versus 3 months, respectively [p =0.001];⁵ OS: 15 versus 7 months, respectively [p=0.046], with a corresponding HR of 0.45 and 0.58 for PFS and OS, respectively). The 1-year PFS was higher in EGFR-positive patients (20 months) compared with 3 months in EGFR-negative patients.⁵
 - The 1-year survival and response rates were higher for the EGFR-positive than the EGFR-negative patients (1-year survival: 58 versus 32%, respectively; response rate: 45 versus 26%, respectively).⁵ The disease control (all responses plus stable disease) rate was higher for the EGFR-positive patients than for the EGFR-negative patients (81% versus 55%).⁵
 - Although the survival rates were numerically higher for EGFR-positive patients in both the concurrent and sequential groups, significance was only demonstrated for the concurrent group (HR 0.43 and 0.83 for the concurrent and sequential groups, respectively).⁵
 - The investigators plan to perform EGFR testing using protein expression analysis by IHC; analysis of the presence and the impact of an EGFR mutation on response will be evaluated.⁵

Cetuximab with gemcitabine-carboplatin (or cisplatin)

- BMS CA225100 is a phase 2, randomized, open-label, non-comparative study (n=131) evaluating the benefit of concurrent cetuximab in combination with a gemcitabine-platinum (carboplatin or cisplatin, selected by the investigator before randomization) containing regimen as

primary treatment for stage IIIB (with a malignant pleural effusion) and stage IV NSCLC.⁶ Patients were enrolled irrespective of the EGFR status.⁶ All patients had an ECOG performance status of less than 2; all NSCLC histologies were included.⁶

- The primary end point was response rate; secondary end points are PFS, OS, disease control rate, duration of response, and time to response.⁶
- The objective response rate was higher with the cetuximab arm compared with chemotherapy alone (27.7 versus 18.2%, respectively).⁶ The disease control (all responses plus stable disease) rate was similar for both groups (75.4 versus 74.2% for chemotherapy plus cetuximab and for chemotherapy alone, respectively).⁶
- Both the PFS and OS were improved with the cetuximab-containing regimen compared with chemotherapy alone (median PFS: 5.09 versus 4.21 months, respectively; OS: 11.99 versus 9.26 months, respectively).⁶ The response duration is essentially similar at 5.09 and 4.9 months for the cetuximab and chemotherapy-alone arms, respectively.⁶ The 1-year survival rates are higher with the cetuximab regimen (49.9%) compared with chemotherapy alone (37.5%).⁶ Numerically, higher responses were reported in the cetuximab arm; however, no statistical analysis has been reported with these data.⁶
- The incidence of grade 3 or 4 febrile neutropenia was higher with the cetuximab arm than with the chemotherapy-only arm (4.7 versus 1.5%, respectively); grade 3 or 4 thrombocytopenia was also higher in the cetuximab than in the chemotherapy-only group (57.8 versus 44.6%, respectively).⁶ Acneiform rashes were reported in 14% of patients receiving cetuximab.⁶
- The investigators have no plans to perform EGFR testing; additionally, no assessment for the presence of either an EGFR or KRAS mutation will be performed.⁶

Discussion:

Background:

Epidermal growth factor receptor (EGFR) is overexpressed in 40–80% of patients with non-small cell lung cancer (NSCLC).⁷ EGFR-targeted therapy using a small-molecule tyrosine kinase inhibitor (TKI) initially was evaluated in combination with chemotherapy as first-line therapy for advanced-stage NSCLC, but showed no survival benefit compared with chemotherapy alone.⁸ Subsequently, cetuximab, an EGFR-monoclonal antibody, has shown activity as a single agent in relapsed and refractory patients;⁹ more recently, the drug has been evaluated in combination with various chemotherapy regimens as first-line therapy for advanced-stage (i.e., stage IIIB and IV) NSCLC.^{1,2,4,6}

Results from the FLEX study, in which all patients were EGFR positive (i.e., using protein expression by IHC), demonstrated a survival advantage of 1.2 months with an 11% improvement in overall survival and a 5% improvement in 1 year survival for all patients receiving cetuximab with vinorelbine/cisplatin compared with patients receiving chemotherapy alone.¹ The progression-free survival was similar for both groups.¹ The survival benefit was observed across all performance-status groups, in both smokers and nonsmokers, for all histology types, in both genders, and for patients older than 65 years.¹ The subgroup of patients with Asian ethnicity, in which a higher percentage of patients had prognostic characteristics commonly associated with an EGFR mutation, such as adenocarcinoma histology, female gender, and a never-smoking history,¹⁰ was shown to have a 7-month improvement in survival compared with the remaining Caucasian patients.¹ However, a higher percentage of Asian patients received oral TKI therapy following their initial study treatment; therefore, the contribution of additional EGFR-targeted therapy to an improved survival rate in this subgroup cannot be ruled out as a possible factor.¹¹ Although numerically higher survival rates were reported in this group, there was no statistically significant improvement in survival with the addition of cetuximab for the Asian subset.¹

In the FLEX study, the overall survival (OS) for Caucasian patients (84% of the study population) was 9.6 months; the OS was 12 and 10.2 months for patients in this subgroup with adenocarcinoma (44%) and squamous (36.6%) histologies, respectively.¹ The incidence of febrile neutropenia with the cetuximab and vinorelbine/cisplatin regimen was higher (22%) compared with other commonly used first-line regimens, such as carboplatin and paclitaxel administered with or without cetuximab (4-5%).^{2,4,12} The activity of this regimen of cetuximab with vinorelbine and cisplatin in the presence of either an EGFR or KRAS mutation is not known at this time.¹¹ One concern is the high incidence of febrile neutropenia with this regimen, which is a clinically important consideration when selecting patients in whom treatment is noncurative and, therefore, may have a negative impact on quality of life.¹³

Conflicting data have been reported for the regimens using a combination of a platinum agent (i.e., carboplatin or cisplatin) and a taxane (i.e., paclitaxel or docetaxel) with cetuximab.^{2,3,4,5} In the BMS 099 study, in which EGFR testing was not performed, the reported PFS was similar for groups receiving cetuximab and those not receiving the drug, and, therefore, failed to meet the study objective of a 25% improvement in this end point.² The median OS was slightly improved by 1.3 months with the addition of cetuximab,³ although the improvement was not statistically significant; the median reported OS of 9.7 months was lower than that reported with other cetuximab-based regimens and is comparable to survival with chemotherapy alone.^{12,14} In the SWOG study, there was no difference in 1-year PFS and survival between the concurrent and sequential cetuximab arms; however, grade 3/4 febrile neutropenia and peripheral neuropathy rates were higher with the concurrent arm.⁴ The subset analysis based on patients who had EGFR gene copy detection performed revealed an association between EGFR status and response, characterized by a statistically significant improvement in both PFS and OS in EGFR-positive patients, with a high survival of 15 months in EGFR-positive patients.⁵ A subset analysis of responses for patients based on their prognostic features (e.g., ethnic background, histology, gender) has not been reported for either of the taxane-platinum based studies.^{2,3,4,5} There are plans to correlate EGFR detection in both the BMS and SWOG studies using the 2 currently available methods (IHC and FISH).^{2,4} Additionally, data will be collected to determine if an association exists between the presence of an EGFR or a KRAS mutation and the impact on activity of the cetuximab-based regimen.^{2,4}

Gemcitabine and cisplatin (or carboplatin) with cetuximab has produced an improvement in both the median PFS, 1-year survival, and OS rates compared with chemotherapy alone in a small number of patients.⁶ These responses are higher than reported with other cetuximab-containing regimens; however, in the absence of a statistical analysis, the clinical benefit cannot be fully determined.¹¹ There are no plans to establish a correlation between response and EGFR status; additionally, assessment of response in the presence of mutations will not be established with this combination.⁶ Therefore, the use of this regimen is not fully established.¹¹

Summary:

The predictive and prognostic value of using EGFR testing in advanced-stage NSCLC patients for the selection of cetuximab-based therapy is not fully established at this time.¹¹ Additional data are needed from ongoing studies to determine not only the clinical importance of this biomarker, but also to confirm the appropriate testing or detection method that should be used for EGFR screening.¹¹ Both EGFR (by FISH) and KRAS mutations have been shown to have predictive value as described with responses to TKI therapy in the presence of an EGFR mutation⁸ and the lack of a response to cetuximab in patients with colorectal cancer who harbor a KRAS mutation.¹⁵ Information about the activity of cetuximab in the presence of either an EGFR or KRAS mutation will be useful in identifying a subset of patients for whom this therapy would be most beneficial, and thereby, help in the selection of appropriate therapy using a pharmacogenomic-guided approach.¹¹

Recent data from the ECOG 4599 study have demonstrated higher survival rates with the addition of bevacizumab to the standard carboplatin-paclitaxel regimen; however, some patients are not candidates for such therapy, either based on histology (i.e., squamous-cell) or the presence of a clinically relevant medical condition, and therefore would be treated with an alternative regimen.^{11,14} Although data from the FLEX study have shown improved survival in EGFR-positive patients with the addition of cetuximab, the subset analysis revealed a survival of only 9.6 months for the Caucasian population.² The reported survival in the BMS 099 is reported as 9.7 months.³ Thus, these results are essentially no different than the overall survival of 8–10 months reported for stage IIIB/IV NSCLC patients receiving chemotherapy alone.^{12,13} The one exception, however, is the 5-month improvement in survival reported for EGFR-positive patients in the SWOG study.⁴ PFS rates have not been significantly improved with the addition of cetuximab to current regimens, with the exception of a 2-month improvement with the gemcitabine-platinum regimen, but based only on a small number of patients.⁶

Although not a full consensus recommendation by the Oncology Expert committee, vinorelbine-cisplatin with cetuximab may be considered a reasonable choice for patients who are not candidates to receive a bevacizumab-containing regimen.¹¹ The safety and efficacy of this regimen has only been established in EGFR-positive patients using EGFR protein expression testing by IHC; the selection of patients using EGFR gene copy number by FISH for this regimen is not fully validated.^{1,2,4} Based on the results of the FLEX study, only patients who are confirmed as EGFR-positive should receive this combination at this time.¹¹ However, given the modest improvement in survival rates reported to date the following important considerations must be weighed carefully in any decision to use cetuximab regimens: 1) comparative cost, 2) the resource-intensive (i.e., weekly infusions) nature of the regimen, 3) clinically important toxicity (e.g., myelosuppression and rash), and 4) compromised quality of life.^{11,13} Additionally, the use of this

regimen should be viewed in the context of the FLEX study results which failed to meet its study objective and therefore did not show an improvement of 20% in PFS with this regimen compared with chemotherapy alone.¹

Additional data are being collected from the ongoing BMS 099 and SWOG 0342 studies.^{2,4} Until additional information from a subset analysis and data from the planned biomarker evaluation are collected, a population of patients for whom such therapy would provide a clinical benefit cannot be identified; therefore, the use of cetuximab with a platinum-taxane regimen as first-line therapy is not fully established at this time.¹¹ Because EGFR testing will not be performed for patients receiving the gemcitabine-platinum-cetuximab combinations in the BMS CA2251000 study, no correlations between response and biomarker expression can be made to fully establish the role of these regimens.¹¹

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