AHFS Final Determination of Medical Acceptance: Off-label Use of Cetuximab in Combination with Chemotherapy for the First-line Treatment of Advanced Non-small Cell Lung Cancer

Drug/Drug Combination: Cetuximab

Off-label Use: First-line treatment of advanced non-small cell lung cancer

Criteria Used in Selection of Off-label Use for Review:

- Periodic review of prior Final Determination for the purpose of updating medical acceptance. The current Final Determination supersedes the past review originally published in October 2008. In 2008, each cetuximab-containing regimen was addressed separately; however, based on new and updated data, the proposed determination for the current review was "cetuximab in combination with chemotherapy." At the time of the original review, a determination of "not fully established" was made for each of the following regimens for the first-line treatment of advanced non-small cell lung cancer: cetuximab combined with gemcitabine and a platinum-containing agent, cetuximab combined with a taxane and a platinum-containing agent, and cetuximab combined with vinorelbine and cisplatin.

Strength of Evidence: Level 2 (Moderate strength/quality)

Strength of Study End Point(s): Overall survival

Grade of Recommendation: Not fully established (Equivocal)

Narrative Summary:

Non-small Cell Lung Cancer:

Efficacy and safety of cetuximab in combination with various chemotherapy regimens as first-line therapy for advanced (stage IIIB [with malignant pleural effusion] or IV [metastatic]) non-small cell lung cancer (NSCLC)† has been studied in several randomized studies. [10001, 10002, 10004, 10006, 10019]

Use of cetuximab either concurrently with or following carboplatin and paclitaxel therapy was investigated in a randomized phase 2 study (S0342) in 242 patients with previously untreated stage IIIB or IV NSCLC.[10004] Patients in both treatment groups received carboplatin (at the dose required to obtain an area under the plasma concentration-time curve [AUC] of 6 mg/mL per minute) and paclitaxel (225 mg/m^2 by IV infusion) in 21-day cycles for 4 cycles; cetuximab (initial dose of 400 mg/m^2 by IV infusion followed by 250 mg/m^2 by IV infusion once weekly) was initiated either concurrently with or following completion of carboplatin and paclitaxel therapy and was continued until disease progression, unacceptable toxicity, or withdrawal of patient consent.[10004] At a median follow-up of 32 months, overall survival (10.9 versus 10.7 months), progression-free survival (4.3 versus 4.4 months), and response rates (32 versus 30%) were similar in both treatment groups; however, the incidence of grade 3/4 sensory neuropathy was higher in patients receiving concurrent therapy compared with those receiving sequential therapy (15 versus 5%, respectively).[10004] About one-third of patients underwent epidermal growth factor receptor (EGFR) testing (using fluorescent in situ hybridization [FISH]

methodology); those with EGFR-positive tumors had longer median progression-free survival (6 versus 3 months) and overall survival (15 versus 7 months) compared with those with EGFR-negative tumors.[10005] Overall survival favored EGFR-positive patients receiving cetuximab concurrently with chemotherapy.[10005]

Efficacy and safety of cetuximab administered concurrently with up to 6 cycles of chemotherapy and then continued alone as maintenance therapy have been evaluated in two phase 3, open-label, randomized studies (First-line Erbitux in Lung Cancer [FLEX] and BMS-099) in patients with previously untreated stage IIIB or IV NSCLC.[10001, 10002] Patients in these studies received either cetuximab and chemotherapy (either cisplatin and vinorelbine or carboplatin and a taxane) or chemotherapy alone.[10001, 10002] The studies included patients with any histologic cell type but excluded those with metastatic CNS disease and those who had received prior anti-EGFR therapy.[10001, 10002] Patient enrollment in the BMS-099 study was independent of EGFR expression status, while enrollment in the FLEX study required immunohistochemical (IHC) evidence of EGFR expression (using the Dako EGFR pharmDx® test kit).[10001, 10002] In the BMS-099 study, patients were stratified according to their baseline ECOG performance status (0 or 1), intended taxane (paclitaxel or docetaxel), and study site.[10002]

In the FLEX study, 1125 patients were randomized to receive vinorelbine (25 mg/m^2 by IV infusion on days 1 and 8) and cisplatin (80 mg/m^2 by IV infusion on day 1) in 21-day cycles either alone or in combination with cetuximab (initial dose of 400 mg/m^2 as a 2-hour IV infusion on day 1 followed by 250 mg/m^2 by IV infusion over 1 hour once weekly); cetuximab was continued until disease progression or unacceptable toxicity occurred, while vinorelbine and cisplatin were administered for up to 6 cycles.[10001] In the BMS-099 study, 676 patients were randomized to receive carboplatin (administered on day 1 at the dose required to obtain an AUC of 6 mg/mL per minute) and a taxane (paclitaxel 225 mg/m^2 as a 3-hour IV infusion or docetaxel 75 mg/m^2 as a 1-hour IV infusion on day 1) in 21-day cycles either alone or in combination with cetuximab (initial dose of 400 mg/m^2 as a 2-hour IV infusion followed by 250 mg/m^2 by IV infusion over 1 hour once weekly); cetuximab was continued until disease progression or unacceptable toxicity occurred, while carboplatin and a taxane were administered for up to 6 cycles.[10002]

In the FLEX study, the primary measure of efficacy was overall survival.[10001] At a median follow-up of 23.8 months, median overall survival was 1.2 months longer (11.3 versus 10.1 months; hazard ratio of 0.87) and the rate of survival at 1 year was higher (47 versus 42%) for patients receiving cetuximab in combination with cisplatin and vinorelbine compared with those receiving cisplatin and vinorelbine alone.[10001] Median progression-free survival was 4.8 months in both treatment groups.[10001] The overall response rate was 36% for patients receiving cetuximab in combination with chemotherapy and 29% for those receiving chemotherapy alone.[10001] Subset analysis suggested that ECOG performance status, smoking status, histologic type, gender, and age did not influence the treatment effect on overall survival.[10001]

Subset analysis of the FLEX study results based on ethnicity indicated that characteristics associated with a more favorable prognosis (i.e., adenocarcinoma histology, female gender, never smoked) were more common in Asian patients than in Caucasian patients and that the median survival of Asian patients was 10 months longer than that of Caucasian patients.[10001] However, a higher proportion of Asian patients received oral tyrosine kinase inhibitors following their assigned study treatment, and the possibility that additional EGFR-targeted therapy might have contributed to an improved survival rate for these patients cannot be ruled out.[10001] The addition of cetuximab to chemotherapy did not significantly improve survival of Asian patients or other non-Caucasian patients.[10001] In contrast, median overall survival of Caucasian patients (84% of patients in the study) was longer for those receiving cetuximab in combination with chemotherapy compared with those receiving chemotherapy alone (10.5 versus 9.1 months).[10001] Subset analysis based on tumor histology indicated that median survival times for patients receiving cetuximab in combination with chemotherapy compared with those receiving chemotherapy alone were 12 versus 10.3 months, respectively, for patients with adenocarcinoma and 10.2 versus 8.9 months, respectively, for those with squamous cell carcinoma.[10001]

In the FLEX study, grade 3 or 4 febrile neutropenia (22 versus 15%), acneiform rash (10 versus less than 1%), infusion-related reactions (4 versus 1%), and diarrhea (5 versus 2%) occurred more frequently in patients

receiving cetuximab in combination with cisplatin and vinorelbine than in those receiving cisplatin and vinorelbine alone.[10001]

In the BMS-099 study, the primary measure of efficacy was progression-free survival assessed by an independent radiologic review committee.[10002] The addition of cetuximab to carboplatin and taxane therapy improved the overall response rate (25.7 versus 17.2%) but did not substantially improve median progression-free survival (4.4 versus 4.2 months) or median overall survival (9.7 versus 8.4 months). [10002] Subgroup analyses suggested that the addition of cetuximab to chemotherapy had a greater effect on progression-free survival in certain subgroups of patients (those with an ECOG performance status of 0, those receiving docetaxel, and those with squamous cell histology) than in the overall study population; however, similar trends were not observed for overall survival. [10002] Grade 3 or 4 acneiform rash (10.5 versus 0%), infusion-related reactions (4.6 versus 0.9%), hypomagnesemia (8.8 versus 0.7%), diarrhea (5.2 versus 2.5%), dehydration (8.6 versus 4.7%), and neutropenia (62.5 versus 56%) occurred more frequently in patients receiving cetuximab in combination with carboplatin and a taxane than in those receiving carboplatin and a taxane alone.[10002]

Post-hoc analyses of the FLEX and BMS-099 studies were performed in an attempt to identify tumor markers that would predict which patients might benefit from the addition of cetuximab to chemotherapy as first-line treatment for advanced NSCLC.[10016, 10017, 10018] Comparisons of outcomes between treatment groups according to tumor marker status revealed no significant associations between efficacy (i.e., overall survival, progression-free survival, tumor response) and *KRAS* mutation status, EGFR mutation status, EGFR gene copy number (assessed by FISH methodology), or phosphatase and tensin homolog (PTEN) gene expression (assessed by IHC methodology) that would identify patients who might benefit from receiving cetuximab in addition to chemotherapy.[10016, 10017] In the BMS-099 study, EGFR expression (assessed by IHC methodology and described as either positive or negative) was not associated with improved efficacy for cetuximab and chemotherapy compared with chemotherapy alone.[10017] However, in the FLEX study, addition of cetuximab to chemotherapy was associated with a survival benefit in patients with high EGFR expression (IHC score of 200 or greater on a scale of 0–300); among patients with high EGFR expression, overall survival was 12 months for those receiving cetuximab and chemotherapy compared with 9.6 months for those receiving chemotherapy alone.[10018]

Although combined therapy with cetuximab and chemotherapy prolonged overall survival in the FLEX study, the magnitude of the benefit was modest and the same benefit was not observed in the BMS-099 study; in addition, combined therapy did not prolong progression-free survival in either study.[10001, 10002, 10021, 10022, 10023] Therefore, the role of the drug in combination with chemotherapy for the treatment of previously untreated advanced NSCLC is unclear. [10021, 10022, 10023] In addition, although exploratory analyses in the FLEX and BMS-099 studies suggested that overall survival results were generally consistent across most patient subgroups, exploratory analyses of progression-free survival in the BMS-099 study suggested some differences in treatment effect in certain patient subgroups (as compared with the overall population).[10001, 10002] Additional studies are needed to validate predictive tumor biomarkers and identify subgroups of patients with previously untreated advanced NSCLC who might derive clinical benefit (e.g., prolonged progression-free survival, prolonged overall survival, improved quality of life) from the addition of cetuximab to chemotherapy.[10017, 10021, 10022, 10023] The AHFS Oncology Expert Committee concluded that use of cetuximab in combination with various chemotherapy regimens as first-line therapy for advanced (stage IIIB [with malignant pleural effusion] or IV [metastatic]) NSCLC currently is not fully established because of equivocal evidence.

References:

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10022. Socinski MA, Evans T, Gettinger S et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013; 143(5 Suppl):e341S-68S.

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Oncology Expert Committee Voting Results:

Proposed Level of Evidence: Level 2 (Moderate strength/quality); overall survival

Concur with rating: 5 votes

Do not concur with rating: 0 votes

Grade of Recommendation:

Recommended use (Accepted): 1 vote

Reasonable choice (Accepted, treatment option): 1 vote

Not fully established (Unclear risk/benefit or equivocal): 3 votes

Not recommended (Unaccepted): 0 votes

Proposed Consensus Recommendation:

Although combined therapy with cetuximab and chemotherapy prolonged overall survival in the FLEX study, the magnitude of the benefit was modest and the same benefit was not observed in the BMS-099 study; in addition, combined therapy did not prolong progression-free survival in either study.[10001, 10002, 10021, 10022, 10023] Therefore, the role of the drug in combination with chemotherapy for the treatment of previously untreated advanced NSCLC is unclear.[10021, 10022, 10023] In addition, although exploratory analyses in the FLEX and BMS-099 studies suggested that overall survival results were generally consistent across most patient subgroups, exploratory analyses of progression-free survival in the BMS-099 study suggested some differences in treatment effect in certain patient subgroups (as compared with the overall population).[10001, 10002] Additional studies are needed to validate predictive tumor biomarkers and identify subgroups of patients with previously untreated advanced NSCLC who might derive clinical benefit (e.g., prolonged progression-free survival, prolonged overall survival, improved quality of life) from the addition of cetuximab to chemotherapy.[10017, 10021, 10022, 10023] The AHFS Oncology Expert Committee concluded that use of cetuximab in combination with various chemotherapy regimens as first-line therapy for advanced (stage IIIB [with malignant pleural effusion] or IV [metastatic]) NSCLC currently is not fully established because of equivocal evidence.

Concur with recommendation: 5 votes

Do not concur with recommendation: 0 votes

Oncology Expert Committee Members' Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:

Reviewer #2: Studies are inconclusive and show no evidence to support routine use. Need more definitive research to show benefit and possibly define subgroups that would benefit.

Reviewer #3: [Specific patient population] Adenocarcinoma/squamous cell subtype – performance score of 0-1.

Reviewer #5: One positive (barely) and one negative study. Because of the marginal p-value for the positive study, I indicated not fully established. [Use is] reasonable for typical adenocarcinoma histology in female nonsmokers. Unfortunately, EGFR expression test by IHC is not an approved test (I believe).

Comments on Draft Narrative Summary:

Reviewer #1: Agree with narrative summary as the narrative clearly states the need for additional research.

Reviewer #3: Agree with summary as written.

Comments on Proposed Consensus Recommendation:

None.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Raymond Hohl, M.D., Ph.D.; Beth Faiman, Ph.Dc., RN, ANP-BC, AOCN; Mandy Gatesman, Pharm.D., BCOP; Christine Gegeckas, RPh, BCOP; LeAnn Norris, Pharm.D., BCPS, BCOP

External Consultants: None

Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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