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UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

K-RAS TESTING IN METASTATIC COLORECTAL CANCER

1. Purpose This Under Secretary for Health Information Letter provides information regarding testing for K-RAS mutations in patients with metastatic colorectal cancer who are candidates for therapy with an epidermal growth factor receptor (EGFR) monoclonal antibody (mAb).

2. Background

a. K-RAS is a protein which in humans is encoded by the K-RAS gene. Like other members of the Ras family, the K-RAS protein is a component of the Ras/Raf/Mek/Erk signaling pathway. While the protein product of the normal (unmutated) K-RAS gene performs an essential function in normal tissue signaling, mutated K-RAS genes are potent oncogenes that play a role in promoting cancers through the enhanced and unregulated production of growth factors. When present, suppression of growth factors can be used to treat these cancers.

b. Cetuximab (Erbix®) and panitumumab (Vectibix®) are monoclonal antibodies directed against EGFR and have been used successfully in combination therapy to treat metastatic colorectal cancer, improving progression free survival and overall survival. However, a substantial number of patients do not respond to EGFR mAb therapy. Measurement of EGFR through immunohistochemistry has not shown a correlation between EGFR expression and response to EGFR mABs, prompting investigation into other predictive markers of response (See Subparas 4.a-e.). A predictive marker that helps identify patients not likely to benefit from EGFR mAb therapy is valuable to the health care system due to the expense and potential toxicity of such therapy.

c. EGFR promotes cell growth through a series of signaling proteins that include K-RAS. Mutated K-RAS can activate cells independently of EGFR, rendering the tumor cells insensitive to inhibition by mAb to EGFR. Correlative analyses of cetuximab and panitumumab trials in metastatic colorectal cancer by K-RAS mutational status found that patients with a mutation in codon 12 or 13 did not derive benefit from cetuximab or panitumumab (See Subpars. 4.f.- k.).

d. The American Society of Clinical Oncology (ASCO) issued a provisional clinical opinion (PCO) to offer timely clinical direction. The PCO recommends all patients who are candidates for EGFR mAb therapy for metastatic colorectal cancer undergo K-RAS mutation testing of their tumors in a Clinical Laboratory Improvement Amendments (CLIA) accredited laboratory. Treatment with these agents is restricted to those patients with wild-type K-RAS (no mutation detected) (See Subpar. 4.1.).

e. Evidence for the PCO is from a retrospective systematic review that identified post hoc analyses on subsets of patients from five randomized, controlled trials of cetuximab or panitumumab that evaluated outcomes in patients with metastatic colorectal cancer in whom the K-RAS mutational status was measured. Also included were five single-arm trials with retrospective evaluation of response in relation to K-RAS mutational status. Overall, this review found evidence of a correlation between the presence of a K-RAS mutation in codon 12 or 13 and lack of response to anti-EGFR mABs in metastatic colorectal cancer and found evidence of improvement in tumor response, progression free survival and/or overall survival in response to anti-EGFR mAB therapy only in patients with wild-type K-RAS (no mutation in codon 12 or 13).

3. Other Recommendations

a. Specimens typically available for analysis are formalin-fixed paraffin-embedded tissue blocks (FFPE). The tissue block should be adequately fixed and properly processed, and contain an adequate amount of viable tumor tissue. The testing methods have variable sensitivities and specificities. Testing should be completed by a Department of Veterans Affairs reference laboratory, an outside reference laboratory, or a local CLIA-accredited laboratory that has validated the testing method. Recent studies show a high concordance between primary tumors and related metastases with regard to K-RAS mutation status (See Subpars. 4.m-n).

b. For patients who do not have tissue samples available for analysis or available tissue is inadequate for analysis, and do not have a metastases that is readily accessible for biopsy, treatment that includes an EGFR mAb is at the discretion of the provider and patient.

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