Title

MODULATION OF THE CYCLOOXYGENASE PATHWAY IS ASSOCIATED WITH EFFICACY IN A RANDOMIZED PHASE II TRIAL OF ERLOTINIB AND CELECOXIB OR PLACEBO IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

Authors

Fishbein, Michael C
Gardner, Brian
Milne, Ginder L
et al.

Publication Date

2013

Peer reviewed

POSTER SESSION 3 - PROGNOSTIC AND PREDICTIVE BIOMARKERS
WEDNESDAY, OCTOBER 30, 2013 - 09:30-16:30

P3.06-043 MODULATION OF THE CYCLOOXYGENASE PATHWAY IS ASSOCIATED WITH EFFICACY IN A RANDOMIZED PHASE II TRIAL OF ERLOTINIB AND CELECOXIB OR PLACEBO IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

Michael C. Fishbein[1], Brian Gardner[1], Ginder L. Milne[2], Marianna Koczywas[3], Mihaela Cristea[3], Jonathan E. Dowell[4], Hejing Wang[1], Robert A. Figlin[5], Robert M. Elashoff[1], Steven M. Dubinett[1], Karen L. Reckamp[3]

[1]*David Geffen School Of Medicine At Ucla/United States Of America,* [2]*Vanderbilt University/United States Of America,* [3]*City Of Hope/United States Of America,* [4]*University Of Texas Southwestern/United States Of America,* [5]*Cedars Sinai/United States Of America*

Background: Combined epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy and cyclooxygenase-2 (COX-2) inhibition has been shown to potentiate responses in NSCLC, and may overcome resistance in wild type *EGFR* tumors. Several biomarkers have been used to evaluate effective targeting of the COX-2 pathway. COX-2 expression by immunohistochemistry (IHC) and urinary 11α-hydroxy-9,15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid (uPGEM) have identified patients who may derive benefit from COX-2 inhibition. We evaluated these markers in association with PFS and tumor response in our randomized, placebo controlled trial of erlotinib and high dose celecoxib in advanced NSCLC patients.

Methods: Pts with stage IIIB/IV NSCLC who progressed following at least one line of therapy or refused standard chemotherapy were randomized to erlotinib (150mg/day)/high dose celecoxib (600mg/2x day) v E/P. Urinary prostaglandin E2-metabolite (uPGEM) was assessed at baseline, week 4 and week 8 of therapy. Immunohistochemical evaluation of COX-2 was performed on archival tissue.

Results: 87 pts had urine assessed and 38 pts had additional evaluable tissue following *EGFR* mutation analysis. PFS was significantly improved in patients with wild type *EGFR* tumors (3.2 v 1.8 months, HR = 0.54, p = 0.03). Previously established normal uPGEM levels for men and women were used to determine high and low baseline values. 59 pts (67%) had high and 29 pts (33%) had low uPGEM at baseline. Elevated baseline uPGEM was associated with improved PFS for patients who received high dose celecoxib (5.6 v 2.2 months, p = 0.09). Pts with low baseline uPGEM did not benefit from celecoxib. Further assessment of COX-2 and E-cadherin was performed by IHC and correlations will be presented.

Conclusion: UPGEM is an easily assessed biomarker that is associated with improved outcomes in patients treated with high dose celecoxib and erlotinib with advanced NSCLC. Tumor levels of COX-2 and E-cadherin may refine our ability to best define a population who will benefit from COX-2 and EGFR targeted therapy in future studies. Supported by NIH 1P50 CA90388, K12 CA01727, Phase One Foundation and medical research funds from the Dept of Veterans' Affairs.

Keywords: Targeted therapy, Cyclooxygenase, Epidermal growth factor receptor, Biomarkers

POSTER SESSION 3 - PROGNOSTIC AND PREDICTIVE BIOMARKERS
WEDNESDAY, OCTOBER 30, 2013 - 09:30-16:30

P3.06-044 KRAS, EGFR MUTATIONS AND EGFR GENE COPY STATUS AS PREDICTIVE MARKERS OF RESPONSE AND TIME TO PROGRESSION IN EGFR WILD-TYPE STAGE IV NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH EGFR TYROSINE-KINASE INHIBITORS.

Manuel Domine, Federico Rojo, Tatiana Hernández, Sandra Zazo, Gloria Serrano, Cristina Chamizo, Cristina Caramés, Juan Madoz, Irene Moreno, Nuria Pérez González, Carolina Ortega, Nerea Carvajal, Francisco Lobo, Carmen Laura Auz, Victoria Casado, Gustavo Rubio, Ana León, Jose Ignacio Martín Valades, Yann Izarzugaza, Juan Luis Arranz, Maria Jesús Fernández-Aceñero, Alberto Lendinez, Mauro Oruezabal, Brezo Martinez-Amores, Natalia Ramirez, Jesús García Foncillas

Translational Oncology Division, ISS-Hospital Universitario Fundación Jiménez Díaz/Spain

Background: KRAS mutations on codons 12, 13 and 61 result in the constitutive activation of protein, which may render tumor cells independent of Epidermal Growth Factor Receptor (EGFR) signalling and thereby resistant to tyrosine-kinase inhibitor (TKI) therapy in NSCLC patients. This study was aimed to evaluate the associations of KRAS and EGFR copy number alteration and mutations with response and time to progression (TTP) in EGFR TKI treated patients.

Methods: KRAS mutations on codons 12, 13 and 61 result in the constitutive activation of protein, which may render tumor cells independent of Epidermal Growth Factor Receptor (EGFR) signalling and thereby resistant to tyrosine-kinase inhibitor (TKI) therapy in NSCLC patients. This study was aimed to evaluate the associations of KRAS and EGFR copy number alteration and mutations with response and time to progression (TTP) in EGFR TKI treated patients.

Results: KRAS mutation was detected in 15 (17.8%) cases, EGFR mutation in 27 (32.1%) and EGFR amplification in 8 (9.5%). Significant differences were detected in response rates for wild-type compared with mutant KRAS (20 vs 0%, p=0.023), mutant compared with wild-type EGFR (59 vs 8%, p=0.007), and EGFR-amplified compared with non-amplified (71 vs 18%, p=0.005). Additionally, significant benefit from TKI therapy was observed for KRAS wild-type compared with KRAS mutated patients (median TTP 7 vs. 3 months, p=0.001), for EGFR-mutated compared with wild-type patients (14 vs. 4 months, p=0.004) and for EGFR-amplification in contrast to non-amplified cases (11 vs. 5 months, p=0.001). KRAS and EGFR mutations or EGFR amplification did not correlated with overall survival (18 vs. 19 months, p=0.406; 16 vs. 21 p=0.094; 25 vs. 17 months, p=0.103, respectively). Combined analysis of favourable status of three biomarkers strongly predicted benefit to TKI therapy (median TTP 15 vs. 3 months, p<0.001).

Conclusion: Combined analysis of KRAS mutation, EGFR mutation and EGFR amplification in EGFR TKI treated NSCLC might provide superior predictive information than single biomarker study in these patients

Keywords: Biomarkers, Tirosine-kinase inhibitors, NSCLC, metastatic