A Phase Ib Study to Evaluate Induction of pCDC2 in Skin Biopsies from Patients with Solid Tumors Treated with DNA-damaging Chemotherapies

Amy Sun1, Raymond L. Lam1, Anna C. Pavlick2, Amy Hamran1, Robert Iannone1, Gary Herman1, Lisa M. Dauffenbach3, Christopher A. Kerfoot4, Pearl Huang5 and Donald A. Bergstrom1

1Merck & Co., Inc. 351 N. Summittown Pike North Wales, PA 19454-1099; 2NYU Cancer Institute, 160 East 34th Street, NY, NY 10016; 3Mosaic Laboratories, LLC, 12 Spectrum Pointe Drive, Lake Forest, CA 92630

Abstract

Objective: We report a Phase Ib study to evaluate induction of phospho-CDC2 (pCDC2) in skin biopsies from patients treated with DNA-damaging therapies. Because pCDC2 is a known substrate of DNA damage kinases, we sought to determine if DNA-damaging chemotherapy could induce and detect pCDC2 levels in skin biopsies. We examined the expression of pCDC2 in skin biopsies from patients treated with DNA-damaging chemotherapy, including cisplatin, carboplatin, and gemcitabine-containing regimens, and its correlation with clinical outcomes in patients with advanced solid tumors.

Methods

1. Participants: Patients with solid tumors and performance status ≤2 on the Eastern Medical Oncology Group (ECOG) were eligible if they had received chemotherapy up to 24 hours post-infusion of standard regimens containing gemcitabine, cisplatin or carboplatin.

2. Design: A single dose escalation design was used with 3 overlapping cohorts. Safety assessments included procedure-related adverse event collection, and patients were monitored for 24 hours post-chemotherapy.

3. Outcomes: The objectives of this study were to develop a quantitative IHC assay for pCDC2, to clearly define induction changes in pCDC2 over the time course, and to determine if pCDC2 levels correlated with clinical outcomes.

Results

1. pCDC2 levels were significantly increased from baseline to 24 hours post-chemotherapy and were significantly higher than the prior timepoints. pCDC2 levels were significantly higher in patients treated with cisplatin-containing regimens compared with patients treated with carboplatin-containing regimens and pCDC2 levels were higher in patients treated with gemcitabine-containing regimens compared with patients treated with cisplatin-containing regimens. Significant induction of pCDC2 in response to chemotherapy occurred over the time course, only in patients treated with pCDC2 levels.

Conclusion

1. ECM: pCDC2 is a potential target engagement biomarker for development of Wee1 kinase inhibitors. pCDC2 induction by DNA damage is a direct measure of target engagement.

Key Eligibility Criteria

- Patients with solid tumors (N=15) and performance status ≤2 on the Eastern Medical Oncology Group (ECOG) were eligible if they had received chemotherapy up to 24 hours post-infusion of standard regimens containing gemcitabine, cisplatin or carboplatin.

Study Design

Figure 1. Methods

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