Post-Diagnostic Aspirin Use and Survival from PIK3CA Mutant Colorectal Cancer: Potential Mechanisms

1 Activation of the PI3K signaling pathway is one of the most frequent occurrences in human cancer, and considerable research has been devoted to the development of PI3K pathway inhibitors as potential cancer therapies.

2 Previous studies suggest a differential survival benefit from post-diagnostic aspirin use in patients whose tumor harbors a mutation in the PIK3CA gene, encoding the catalytic subunit of PI3K (phosphatidyl inositol 3 kinase).

3 We hypothesize that this survival advantage is restricted to PIK3CA mutations that result in novel acetylation sites, which aspirin then acts on.

4 Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, protect against the development of colorectal cancer and are usually associated with decreased reoccurrence and improved outcome after primary treatment in the 15-20% of patients who possess the PIK3CA mutation.

5 Although there have been studies demonstrating a survival benefit as it pertains to regular aspirin use in PIK3CA mutated colorectal cancer, the mechanisms underlying this correlation are largely unclear.

6 Our plan is to utilize labeled aspirin to investigate this hypothesis with recombinant proteins and colorectal cancer cells with and without specific PIK3CA mutations.

7 **Applying mass spectrometry, we catalogued the acetylation of the aspirin on the intended sites and described the effects on the recombinant proteins and cell lines**.

[RESULTS NOT SHOWN]

8 To complement these mechanisms, a survival analysis will be conducted to determine whether post-diagnostic aspirin use is associated with a survival benefit in patients who have PIK3CA positive tumors in comparison to patients who do not harbor the mutation.