Ventana and Dako: Response:

Regarding Dr. David Rimm, Dr. Fred Hirsch, and others: Comment to the FDA in follow up to Public Workshop - Complexities in Personalized Medicine: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies, March 24, 2015

In regard to the separate responses written by Dr. David Rimm and Dr. Fred Hirsch, as well as Fight Colorectal Cancer, Ventana and Dako and the members of the Blueprint Committee appreciate all of the thoughtful insights. Since many of the comments are similar, we have combined our responses and respectfully submit them below:

As we read and summarize the main points by Dr. Rimm, his observations that the Blueprint proposal does not include outcome information or "address clinical utility" and does not include "common open platforms besides Ventana and Dako" are correct. The working team has considered these points and has agreed that those important considerations are beyond the scope of this initial study. The rationale behind this initial Blueprint project is stated below (it is contemplated that his points will be addressed with further studies that will be performed after regulatory approvals to compare the diagnostics and therapeutics from a clinical concordance and outcome basis):

- Without negatively impacting any of the current trials nor delaying access to patients, our goal is to provide key stake holders with a data set as soon as possible to understand if there are any potential significant analytical differences between the four IUO assays. This initial data set will provide information on comparability of the assays themselves. While the Diagnostic and Pharmaceutical companies understand some of the practical limitations to potentially having four diagnostic tests approved with four different drugs, we are committed to providing data in regard to analytical assay comparability. The pre-marketing assessment will only compare the 4 IUO assays, which are co-developed with the pharmaceutical companies' data for each individual PDL1 therapeutic. LDTs, other platforms, and systems that are not co-developed with the drugs are out of scope. Furthermore, we firmly believe that the focus on the pre-marketing data for analytical comparison of the assays is the fastest study approach and can provide immediate insight to see if the assays themselves have analytical differences that can inform if the future comparison of the assays on clinical cohorts will be potentially more or less challenging. We also want to emphasize that IUO assays are designed to include validation of the specificity of the assays for the biomarker, the clinical utility, and the "measurement" of PDL1. It is the burden of the manufacturer to produce these data to FDA.

Ventana and Dako fundamentally disagree with Dr. Rimm's statement that "While it is true that existing companion diagnostic tests are based on traditional immunohistochemistry (IHC), the recent failure of IHC in the EGFR setting and most recently in the MetMab trial should be a warning beacon that this technology is obsolete". In fact, there are no existing data that the diagnostic assays for these therapeutics are responsible for their failures. When a CDx is developed in collaboration with a pharma partner, the diagnostic and pharma partners both share the risk of the programs. This has nothing to do with the basis of IHC. In fact, IHC remains proven technology for anatomic pathology laboratories and will continue to be used as the main technology due to its ease of use, accuracy, and global access.

-Finally, we agree with Dr. Rimm that the biostatistical considerations for the Blueprint are "vague" at this point. As developers of CDx assays, we understand that the full study design awaits completion of some basic comparisons of the dynamic ranges of the assays.

The Blueprint Working group would also like to invite Dr. Hirsch or another representative from IASLC to participate in the third party review of the samples that will be assessed in our study. We will be inviting a number of organizations to nominate a representative for the study and will look forward to working with those pathologists to help with the performance comparison.

Thank you,

Doug Ward, Dave Stanforth, Abigail McElhinny

Blueprint Working Committee