Team Progress Updates

SU2C–Melanoma Research Alliance Melanoma Dream Team:
"Personalized Medicine for Patients with BRAF WildType (BRAFwt) Cancer"

Patients with metastatic melanoma have a bleak prognosis, with a median survival of six to nine months and a five-year survival rate of about 16%. About half of patients with metastatic melanoma have a mutation in a gene called BRAF in their tumors, and there are approved drugs to help prolong their survival. However, the other half of patients have no mutation in the BRAF gene and are said to be BRAF wild type (BRAFwt); very little progress has been made in identifying new drugs to treat them.

This Dream Team is analyzing the genomes of metastatic melanoma patients who are BRAFwt in order to match potentially effective drugs—approved or experimental—to the individual patient. Team members are also exploring the biological makeup of BRAFwt and BRAF-mutant cancer cells and testing these cells in the laboratory for sensitivity to 100 potential new treatments. Researchers are using these data to predict the sensitivity of BRAFwt melanomas to specific drugs and testing these predictions in laboratory studies.

A clinical trial is underway to determine whether this personalized approach significantly improves clinical outcome. The goal is a 30 percent improvement in tumor response relative to the standard of care.

The team reported the following progress:

June 2016:

- Continued enrollment of patients in the clinical trial across eight different centers, with 9 additional patients enrolled on the trial since the last report period.
- Modification of the clinical trial to focus on one particular drug called MEK162 because this was the drug to which 20 of the initial 23 patients profiled were matched.
- Continued progress in their laboratory studies to predict which drugs and drug combinations are likely to be the most effective against cancer cells based on the cells' genetic and molecular make-up.
- 19 patient tumors have been grown in laboratory mice. This methodology allows the researchers to test drugs and drug combinations against the tumors.

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December 2015:

- Continued enrollment of patients in the clinical trial across eight different centers, with 18 additional patients on the trial since the last report period.
- An average time of 22 days from tumor biopsy to Tumor Board Assessment for treatment recommendations.
- Continued success in growing patients' tumors in laboratory mice for analysis and drug testing. Ten patient-derived tumors have been successfully grown in laboratory mice, with several other tumors in different stages of the process.

June 2015:

- Reopening of the clinical trial after the lead clinical and coordination site moved to Yale University, with new patient enrollment.
- Progress in identifying subtypes of metastatic melanoma. By understanding the biology of these subtypes the Dream Team is developing new drugs that will be most effective in different subtype.
- Success in growing patients' tumors in laboratory mice for analysis and drug testing.

December 2014:

- Rapid (average time of 4 weeks) molecular profiling and Tumor Board assessment of their first two clinical trial patients.
- Progress in development of algorithms for tumor genomic-profile drug (TGPD) matching using tumor cells grown in the laboratory.
- Sharing of data and biocomputing methods with other Dream Teams and with the scientific community at large through scientific publications.

June 2014:

- Opening of the clinical trial and recruitment of the first patients.
- The availability of a pool of 30 drugs to use in the trial, 10 of which are new investigational drugs, with negotiations continuing to obtain an additional six agents.
- Continuing studies of cellular programs in melanoma cells that can be targeted to kill the tumor, and development of promising new drugs that they hope to move to clinical trials.

Team Progress Updates

December 2013

- Completed enrollment and molecular profiling of all five patients enrolled on the pilot feasibility trial.
- Assessed different strategies to analyze and compile data from the public domain that can be used to define, evaluate, and contrast algorithms to predict tumor sensitivity to drugs.
- Continued evaluation of various BRAFwt cell lines to help define mechanisms of drug response/resistance.
- Continued studies of cellular programs in melanoma cells that can be targeted to kill the tumor.
- Obtained agreement from pharmaceutical companies to provide 9 novel targeted agents and continued discussions to obtain 8 additional agents.
- Wrote a final draft of the clinical protocol for the randomized trial.
- Submitted an Investigational New Drug (IND) application, which is required in order to begin the randomized clinical trial.

June 2013:

- First, they have enrolled, biopsied, completed molecular characterization, and held Tumor Boards for three of the five patients needed for the pilot clinical trial. The final two patients for the clinical trial have consented and will go through the process soon. This has led to insights into the process and to subsequent refinement of procedures.
- Second, they have accumulated a pool of 27 agents to test and are negotiating with companies to obtain eight additional investigational agents.
- Third, they have drafted a clinical protocol for the randomized clinical trial and have scheduled an additional meeting with the FDA regarding submission of the Investigational New Drug (IND) application for the clinical trial.
- Finally, they have continued to assess different strategies to analyze data from the public domain that can be used to evaluate multiple algorithms to predict tumor drug sensitivity, to evaluate BRAFwt melanoma cell lines to determine drug response and resistance, and to study melanoma cell pathways that can be targeted to kill tumors.

October 2012:

- First, they have designed, drafted, and obtained preliminary regulatory approval for the pilot clinical trial, with the first patient enrolled on November 27, 2012.
- Second, they have assessed different algorithms (sets of mathematical formulas) designed to identify the best treatment for a patient's cancer based on genomic analysis of that patient's

tumor, algorithm development strategies, and compilation of public domain data that can be used to define, evaluate, and contrast algorithms.

- Third, they have continued analysis of various BRAFwt melanoma cell lines to help identify ways that cancer cells respond or become resistant to drugs that inhibit two protein targets (MEK and ERK).
- Finally, they have obtained agreement from pharmaceutical companies to supply 22 novel targeted drugs, and initiated a formal dialog with the FDA regarding submission of Investigational New Drug (IND) and Investigational Device Exemption (IDE) regulatory applications necessary to begin the randomized clinical trial.