



Team Progress Updates

SU2C–American Cancer Society Lung Cancer Dream Team: “Targeting KRAS Mutant Lung Cancers”



Mutations in the KRAS gene are found in 20 to 25 percent of lung cancers. These cancers do not respond well to standard lung cancer treatments and are notoriously difficult to treat. Scientists are working to develop new drugs that specifically target biological pathways disrupted by the mutant KRAS gene.

The goal of the Dream Team has been to develop and bring together these two highly promising therapeutic approaches of targeted therapy and immunotherapy: Combining types of therapies and also working to predict which patients will benefit from the therapy.

The team is currently conducting a myriad of clinical trials, including trials combining targeted therapies called MEK inhibitors with checkpoint inhibitors that are specific for the PD-1 receptor. MEK inhibitors modulate overactive cellular signaling pathways; the PD-1 receptor is a protein found on the surface of immune cells called T cells. To maximize the benefit of immunotherapy, the team is also analyzing samples from patients who have been treated with immune checkpoint inhibitors. The team seeks to identify ways to predict which patients are more likely respond to immunotherapy.

The team has reported the following progress:

December 2018

- The team is accruing patients in six clinical trials. Four of these involve the use of the MEK inhibitor trametinib, one involves the MEK inhibitor cobimetinib, and one involves a novel dual MEK/RAF inhibitor. In addition to conducting safety and dosage analysis, the team is performing extensive immune and genetic assays to address mechanisms of sensitivity and resistance to the combination therapies.
- The team has built one of the largest collections ever amassed of tumor/normal paired samples from commercial anti-PD-1 inhibitor (checkpoint inhibitor) treatment. Approximately 500 samples have been sequenced, which will allow novel insights into determinants of response and resistance to anti-PD-1 therapy and predictions of immunotherapy response.
- Team members are investigating responsiveness to PD-1 blockade in the neoadjuvant setting of non-small cell lung cancer.
- Digitalized immunofluorescence analysis of tumors using specific panels to analyze PD-L1 status continues. Analysis includes more than 800 slides from 209 cases across five institutions to





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define the distance and interactions of single cells in lung cancer biopsies for possible use as an indicator in future clinical trials.

- The team is planning to initiate new clinical trials integrating targeted therapies and immunotherapies for treatment of KRAS-mutant lung cancer.

June 2018

- The team has found an advantage in combining inhibitors at the onset of treatment rather than waiting for resistance to the mutant KRAS targeted inhibitor to appear.
- The team has further observed that combining a PI3 kinase inhibitor with a KRAS inhibitor is a particularly effective treatment strategy.
- The team has tested a high dose of MEK inhibitor administered intermittently in combination with a checkpoint inhibitor. Preliminary results suggest the combination is more effective than each agent alone.
- The team has four clinical trials that are actively accruing. Three of these involve the use of the MEK inhibitor trametinib. One of the new clinical trials will test the combination of checkpoint inhibitor (anti-PD-1 antibody) with a vaccine that can activate the immune system against cells with mutant KRAS and a tumor-associated protein called mesothelin.

December 2017

- The Team has seen the potential of combining two approved drugs, palbociclib and ribociclib, with a selective mutant KRAS inhibitor.
- The Team has identified numerous proteins that can be used to predict response and resistance to immunotherapy among non-small cell lung cancer patients.
- Based on promising results from their laboratory experiments, the Team is planning new clinical trials. One involves combining an epigenetic inhibitor with immunotherapy. Another trial involves testing a MEK inhibitor in patients that have a KRAS mutation.

June 2017

- Three clinical trials on the combination of MEK inhibitors and PD-1 blockade are actively accepting patients.
- The Team has identified new inhibitors and promising inhibitor combinations from its preclinical experiments. As a result of positive results in these experiments, 5 new clinical trials are planned.



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- Intermittent administration of MEK inhibitors has been found to be better than continuous treatment. This intermittent administration is also more efficient in activating the immune system in mouse models.

December 2016

- The Team is continuing to accrue patients in their three active clinical trials. Several more clinical trials are being planned.
- Preclinical mouse models of human lung cancer have been developed and being used to test several combination therapies.
- Patient biopsy analysis continues to help define the determinants of response to PD-1 pathway blockade and biomarkers of anti-PD1 therapy resistance.

June 2016

- The team has revealed a mechanism of action for KRAS inhibitors, which allows for the development of more rational drug combinations using this class of drugs.
- Team members have identified new inhibitors that work in combination with KRAS inhibitors and are testing these combinations in pre-clinical models, including one specific drug combination, which includes trametinib (FDA-approved for melanoma).

December 2015

- Work has been initiated in the study of new drugs that block the mutant KRAS protein.
- The team has begun to assemble an unprecedented collection of tumor and blood specimens from patients treated with PD-1 inhibitors, a type of checkpoint blocker immunotherapy, learning more about why some patient's tumors respond to these drugs, while others do not.
- Critical studies in state-of-the-art laboratory animal model systems to explore the best way to combine KRAS blocking medicines with immunotherapies were initiated.