Optimizing targeted therapy and immune checkpoint blockade therapy in Kras mutant lung cancer

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KRAS is the most commonly identified driver oncogene in lung cancer. However, to date there is no effective therapy available for KRAS mutant lung cancers. To identify the most effective treatment, we focused on the impact of Kras signaling targeted therapy (MEK inhibition) on the immune microenvironment, in order to formulate a combinatorial treatment strategy using targeted therapy and immunotherapy. To enhance tumor apoptosis and promote T cell activation simultaneously while under MEK inhibition, we hypothesized that intermittent administration of MEK inhibitor will confer T cells temporal release from MEK signaling inhibition but maintain tumor growth suppression. This schedule enables T cell activation and therefore immunotherapy can be combined based on the change in T cell activation/inhibition markers during the treatment.

Ex vivo T cell study showed that pulsatile treatment of MEK inhibitor showed highly increased CTLA-4 expression and mild increase of PD-1 expression in CD8+ T cells and CD4+Foxp3- T cells, compared to the standard regimen of continuous treatment. This result was confirmed in vivo, in intermittently treated Kras mutant mouse model as well. Moreover, CD8+ T cells from the pulsatile group showed an increase of Ki-67 and 4-1BB expression, suggesting that CD8+ T cells are more activated in pulsatile group. Pulsatile treatment of MEK inhibitors also showed increase of CD44+CD62L- population in antigen-specific Pmel-1 CD8+ T cells compared to continuous treatment. In vivo tumor study showed intermittent treatment suppressed tumor growth better than continuous treatment. Based on these observations, we are testing combination of intermittent MEK inhibitor treatment with anti-CTLA-4 antibody to maximize anti-tumor T cell activity.

In summary, we found that pulsatile/intermittent treatment with MEK inhibitor showed better response and more activated phenotype of T cells including increased CTLA-4 expression compared to continuous treatment. This study suggests that optimized intermittent schedule of MEK inhibitor treatment is essential to maximize T cell mediated anti-tumor activity in combination with anti-CTLA-4 therapy and this will benefit Kras mutant lung cancer patients. This work has the potential to inform the design of future clinical trials using targeted therapy in combination with immune checkpoint blockade.