Combination Therapy of TILs and BRAF Inhibitors to Treat BRAF Inhibitor-Resistant Metastatic Melanoma

BRAF and MEK inhibitors are actively used, often together, for the treatment of metastatic melanoma in patients with $BRAF^{V600}$ mutations. However, about 50% of patients will develop resistance . A combination treatment regimen using BRAFi in combination with TILs in mouse models of BRAFi-resistant melanoma showed an almost 50% reduction in tumor growth compared to either treatment alone. This may be due to the upregulation of the mannose 6-phosphate receptor (M6PR) on the tumor surface, which is a receptor for granzyme B that cytotoxic T cells use to kill tumors. Upregulation of M6PR was shown in patient derived xenografts from drug naïve and BRAFi-resistant patients, and upregulation of M6PR was shown to sensitize melanoma cells to the cytotoxic effects of TILs. Interestingly, a clinical trial in humans has shown that BRAFis can be used in combination with TILs in treatment naïve patients, and this trial demonstrated a better response rate than historical controls of BRAFi therapy alone, and had a lower attrition rate of 6% compared with historical TIL attrition rates of 32% due mainly to disease progression prior to ACT. These inhibitors are also approved for $BRAF^{V600}$ mutant lung cancer and thyroid cancer.

COMMERCIAL OPPORTUNITY

- Melanoma is a skin cancer with high metastatic potential responsible for 80% of skin cancer–related deaths. Approximately 50% of patients with melanoma have the $BRAF^{V600E}$ mutation in their tumors. The American Cancer Society estimates that in 2019 about 96,480 new melanomas will be diagnosed, and there will be about 7,230 estimated deaths. Of those patients treated with BRAF and MEK inhibitors, resistance to therapy frequently develops.
- The FDA approved BRAF and MEK inhibitors currently on the market include the 2012 FDA-approved Vemurafenib (Genentech), a BRAF inhibitor for patients with $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma, the BRAF inhibitor Dabrafenib (Glaxo Smith Kline) approved by the FDA in 2013 to treat patients with $BRAF^{V600}$ mutation-positive advanced melanoma, and the MEK inhibitor Trametinib (Glaxo Smith Kline) approved by the FDA in 2013 for the treatment of $BRAF^{V600}$ unresectable or metastatic melanoma. Both Dabrafenib and Trametib have also been approved for metastatic non-small cell lung cancer and locally advanced or metastatic anaplastic thyroid cancer with $BRAF^{V600E}$ mutations.
- A TIL therapy (Lifileucel) for patients with unresectable melanoma who have also received BRAF/MEK inhibitor therapy is being developed by Iovance Biotherapeutics Inc., and is reported to be in Phase IIIC/IV. It has been given Fast Track Designation and Orphan Drug Designation in advanced melanoma by the FDA.

TECHNOLOGY

HLA-A2+ TILs that recognized HLA-A2+ matched WM35 tumor cells were obtained from metastatic melanoma patients. Compared to cells treated with DMSO, PLX4720-treated WM35 cells showed a greater percent cytotoxicity after 4 and 8 hours of treatment with the BRAF inhibitor PLX4720. These cells also showed a significantly greater expression of M6PR ($p< 0.0001$). Efficiency of TILs to kill M6PR knock-out WM983B melanoma cells in the presence of PLX4720 was no different from controls. Additionally, incubation of melanoma cell lines that over-express M6PR with TILs resulted in a significantly greater percent cytotoxicity than for control cells. Human melanoma cells lines (BRAF inhibitor-sensitive ones, WM983B, and BRAF inhibitor-resistant ones, WM983B BR) were used to generate xenograft models. BRAF-inhibitor PLX4720 was administered daily at a dose 50 mg/kg for 10 days via oral gavage. Starting from Day 24 of treatment with TILs (and/or combination of TILs and BRAFi), the tumor area in these mice decreased significantly in animals that were exposed to a combination of TILs and BRAFi as opposed to those exposed to vehicle, or TILs alone, or BRAFi alone ($p< 0.0001$) with an approximately 50% decrease in tumor size.

PUBLICATION/PATENT

- Clin Cancer Res; 25(9) May 1, 2019 by Atay et al.
- Provisional Patent Application filed on February 13, 2019 for Drs. Sarnaik and Gabrilovich

CONTACT

Haskell Adler PhD MBA CLP
Senior Licensing Manager
Registered Patent Agent
Haskell.Adler@Moffitt.org
(813) 745-6596

LICENSING OPPORTUNITY

MOFFITT CANCER CENTER

19MA007.2020.01