Detection of Co-occurring and Potential Resistance Mutations in Cell-Free, Circulating Tumor DNA from Patients with BRAF\textsuperscript{mutant} Metastatic Melanoma Undergoing Treatment with BRAF-Targeted Therapies

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Abstract #4099

Introduction

Melanoma patients with BRAF\textsuperscript{mutant} tumors often develop resistance to BRAF-inhibitor therapies. Co-occurring mutations, present at the time of treatment initiation, have been identified in patients with primary treatment resistance, and NRAS mutations have been associated with secondary resistance. We tested the ability of multiplex mutation detection assays to identify possible co-occurring and resistance mutations in cell-free circulating tumor DNA (ctDNA) from patients undergoing treatment with BRAF-targeted therapies.

Methods

Purified ctDNA samples remaining from a previous longitudinal study of metastatic melanoma patients, which measured BRAF\textsuperscript{mutant} and NRAS\textsuperscript{mutant} ctDNA using droplet digital PCR (ddPCR) duplex assays, were used for this study. Twelve samples from 6 patients with BRAF V600E mutant (V600E) tumors, who were treated with BRAF-inhibitor therapy, were separately analyzed in different laboratories using the two different multiplex assays (Oncomine and OnTarget). Oncomine (cotton DNA assay) used approximately 20ng DNA, OnTarget used approximately 30ng DNA. Patient samples were chosen based on clinical response or disease progression at the time of blood draw.

Results Summary

• Among 10 samples with BRAF V600E detected by ddPCR
  • On-Target detected V600E in 9/10
  • Oncomine detected V600E in 8/9
  • 1 sample missed by On-Target and Oncomine had 0.01% fractional abundance in ddPCR
• Neither assay detected V600E DNA when it was not detected by ddPCR

Co-occurring and potential resistance mutations in cell-free circulating tumor DNA from patients undergoing treatment with BRAF-targeted therapies. Results are shown for two patients.

Conclusions

Co-occurring and potential resistance mutations (e.g. NRAS) are detectable in the plasma of metastatic melanoma patients using OnTarget, Oncomine or ddPCR assays. While ddPCR had the highest sensitivity to detect BRAFV600E, both OnTarget and Oncomine have high sensitivity, detecting BRAFV600E nearly all cases, down to 0.04-0.06% fractional abundance. These findings suggest that these assays may help inform treatment choices, such as switching therapies when resistance mutations emerge.

References


Serial Monitoring and Comparison of ddPCR Copies, RECIST Scores and LDH Levels in Melanoma Patients Undergoing Sunitinib Treatment

Monday, November 27, 2017, 2:30 PM - 4:00 PM

Presentation Room 101

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Workway of Assays to Analyze Plasma Samples of Interest

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References


1. Make Droplets
2. Cycle Droplets
3. Read Droplets

Droplet Generator
Bulk PCR Thermocycler
Optical Reader

Patient 09-012 Plasma (BRAF V600E)