Title: Early circulating tumor DNA (ctDNA) changes during treatment with immune checkpoint inhibitors (ICI) may predict clinical outcomes in advanced stage melanoma/skin cancer patients (pts)

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Scientific Abstract:

Background: ctDNA monitoring has shown promising results in predicting relapse in resected solid tumors. Its role in treatment response assessment and predicting survival outcomes in the unresectable or metastatic disease setting merits further investigation. In our study, we attempt to assess the role of early ctDNA changes in predicting disease response, progression, and overall survival outcomes in pts with advanced stage melanoma/skin cancer treated with ICI therapy.

Methods: A retrospective analysis using a personalized, tumor-informed ctDNA assay (Natera) on prospectively collected plasma samples from pts with unresectable stage III/IV melanoma/skin cancer treated with anti-PD-1 based therapy at the University of Wisconsin (Madison) was performed. Baseline ctDNA levels were assessed prior to the start of treatment and at 3-4 weeks (i.e. prior to the second treatment dose). A logistic regression model was used to evaluate the odds of overall disease control [complete response + partial response + stable disease, per RECIST version 1.1] based on the change in ctDNA levels (decrease vs increase) between both time points. Cox proportional hazard models were used to investigate the effects of ctDNA level change on progression free survival (PFS) and overall survival (OS).

Results: 46 pts were evaluated. 82% melanoma, 14% Merkel cell carcinoma, 2% skin adenocarcinoma and 2% squamous cell carcinoma. 77% were treated with dual ICI (anti-PD-1 based) therapy and 23% with anti-PD-1 monotherapy. Median follow up was 12.1 months. Median change in ctDNA levels from baseline were -4.83 MTM/mL among pts with ctDNA decrease and +37.39 MTM/mL among pts with ctDNA increase. A qualitative decrease in ctDNA level was associated with overall disease control (OR 65.00, 95% CI 11.88-587.89, $p<0.0001$), longer PFS (HR 0.08, 95% CI 0.03-0.22, $p<0.0001$), and longer OS (HR 0.17, 95% CI 0.05-0.54, $p=0.0008$) compared to an increase in ctDNA level from baseline to 3-4 weeks after starting ICI therapy. Median PFS was not reached (NR) and 1.63 months; and median OS was NR and 5.57 months among pts with ctDNA decrease and ctDNA increase, respectively.

Conclusions: We found that early ctDNA dynamics after 3-4 weeks of ICI initiation in pts with advanced melanoma/skin cancer appears to be a candidate strategy to predict treatment response, risk of progression, and potentially long-term survival. Larger prospective studies are warranted to validate the utility of ctDNA in treatment monitoring.

Figure 1. Progression-free survival difference between ctDNA decrease vs ctDNA increase 3-4 weeks after initiation of therapy.

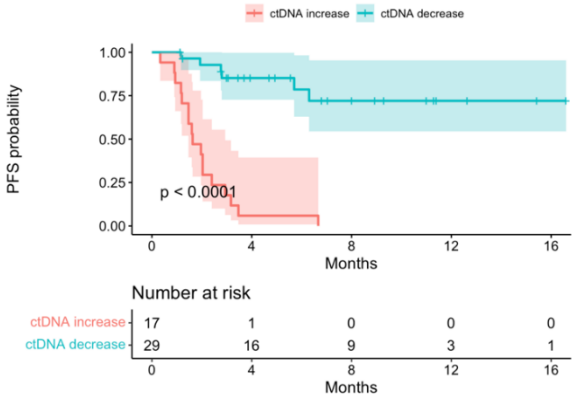
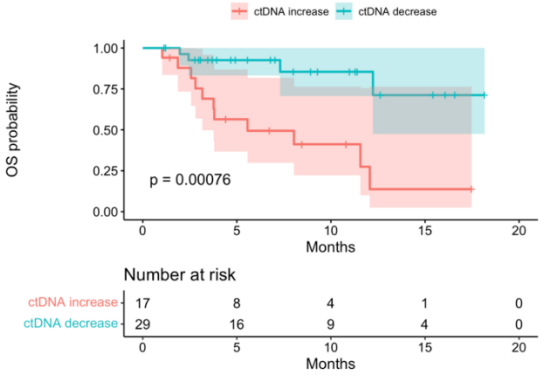


Figure 2. Overall survival difference between ctDNA decrease vs ctDNA increase 3-4 weeks after initiation of therapy.



Written Lay Abstract:

How blood tests can help us treat skin cancer.

When someone has cancer, a special type of DNA called circulating tumor DNA (ctDNA) can be found in the blood. Doctors can take blood samples to test levels of ctDNA. For this study, the researchers wanted to know if testing for ctDNA in the blood can tell us whether a cancer treatment is working. They looked at ctDNA levels of patients with melanoma and other advanced stages of skin cancer before and after treatment to see if changes were linked to cancer outcomes.

The researchers tested blood from 46 patients before one dose of immunotherapy treatment, and 3-4 weeks after treatment. Researchers followed these patients up to 20 months after treatment to see whether their cancer progressed (spread or grew).

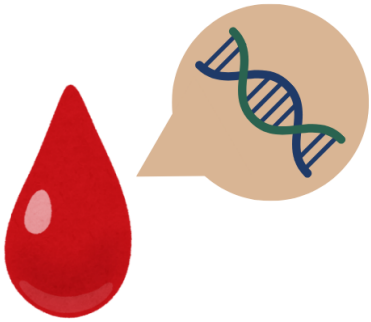
They found that patients with lower ctDNA levels 3-4 weeks after starting immunotherapy treatment tended to have better outcomes and were more likely to survive compared to patients with higher ctDNA levels. Patients with higher ctDNA levels at 3-4 weeks tended to have cancer that progressed (grew or spread) even with treatment.

This research tells us that testing a patient's blood for ctDNA levels before and during cancer treatment could tell us if the treatment is working, if the cancer is progressing, and if the patient has a good chance of surviving. Future studies with many more cancer patients are needed to tell if ctDNA blood tests can correctly tell us possible patient outcomes.

Visual Lay Abstract:

How blood tests can help us treat skin cancer

the goal



When someone has skin cancer, circulating tumor DNA (ctDNA) can be found in the blood

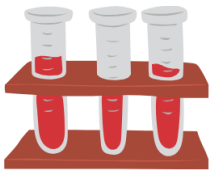
Testing blood for ctDNA may tell us whether cancer treatments are working

the findings

Patients with better cancer outcomes had lower ctDNA levels as early as 3-4 weeks after immunotherapy (cancer treatment)

Next, we need studies with more patients to see if this ctDNA blood test can help us find the best treatment strategy for cancer patients

the study



We tested ctDNA levels in blood from 46 advanced skin cancer patients before and after cancer treatment

Carbone Cancer Center
UNIVERSITY OF WISCONSIN
SCHOOL OF MEDICINE AND PUBLIC HEALTH

Vincent Ma, Yeonhee Park, Janmesh Patel, Madison Harris, Matthew Mannino, Jennifer Schehr, Alexander Birbrair, Shuang Zhao, Joshua Lang. ASCO 2024.