natera™ | Signatera™
Residual disease test (MRD)

Know cancer's next move

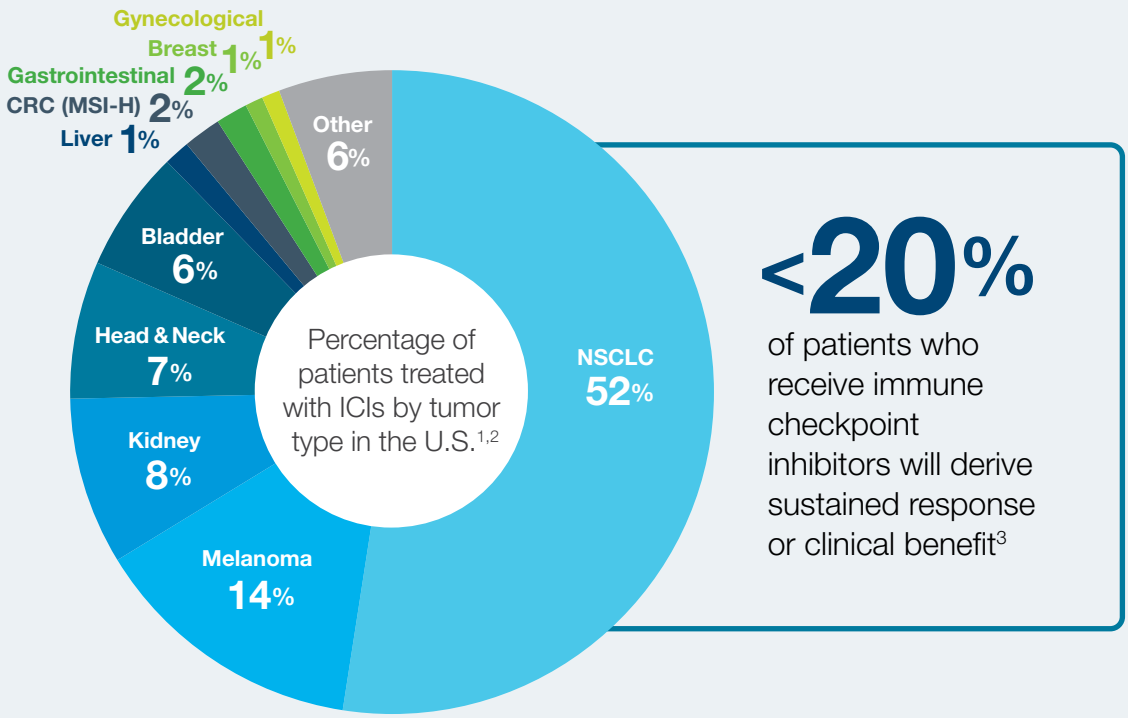
Is the treatment working?

Is the tumor truly progressing?

Is there a need to change or reinitiate treatment?

Signatera™ is a personalized, tumor-informed assay for ultrasensitive detection of molecular residual disease (MRD)

Early intelligence on therapy response can make a world of difference



<20%

of patients who receive immune checkpoint inhibitors will derive sustained response or clinical benefit[3]

Despite dramatic improvements in cancer care using immune checkpoint inhibitors (ICIs), only a minority of patients will benefit from ICI treatment.[3]

Better predictive tools for immunotherapy treatment response are needed

- Standard imaging tools lack the sensitivity to accurately assess pseudoprogression, which occurs in up to 10% of patients treated with immune checkpoint inhibitors[4]
- Tissue-based biomarkers, such as PD-L1 expression, TMB, and MSI-H/dMMR, have variable predictive value to ICI treatment[5-9]

Early biomarkers of treatment response could identify patients who are responding to immunotherapy.

dMMR=deficient mismatch repair; **MSI-H**=microsatellite instability high; **PD-L1**=programmed death-ligand 1; **TMB**=tumor mutational burden

The power of tumor-informed ctDNA detection

ctDNA is a real-time biomarker of tumor burden

- The effect of ICI treatment can be detected by measuring circulating tumor DNA (ctDNA) in the blood much earlier than it can be detected by CT scans or other serum protein biomarkers[10]
- A growing body of published studies across multiple solid tumor types supports using the dynamics of ctDNA during ICI treatment to monitor treatment response and to identify exceptional responders[11-17]

Signatera at a glance

Discover the personalized, tumor-informed approach behind Signatera

In patients with solid tumors receiving immune checkpoint inhibitors, use Signatera ctDNA trends to evaluate response and to optimize treatment duration in exceptional responders.

Tumor-informed approach is key for highly sensitive ctDNA monitoring

0.01% VAF is critical for achieving

baseline ctDNA detection

in patients with metastatic disease across 25 tumor types.[18]

Personalized, tumor informed assay

Tumor-specific, clonal mutations identified by whole-exome sequencing of the patient's tumor tissue to eliminate germline and CHIP mutations

Ultrasensitive ctDNA detection with multiplex PCR technology

Highly sensitive and specific, with a low limit of detection

Optimized for longitudinal monitoring

Only measures clonal mutations, which correlate with tumor burden

Established Medicare coverage

For patients with stage I-IV CRC and patients being treated with Immunotherapy for any solid tumor

CHIP=clonal hematopoiesis of indeterminate potential; **CT**=computed tomography; **ctDNA**=circulating tumor DNA; **ICI**=immune checkpoint inhibitor; **VAF**=variant allele frequency

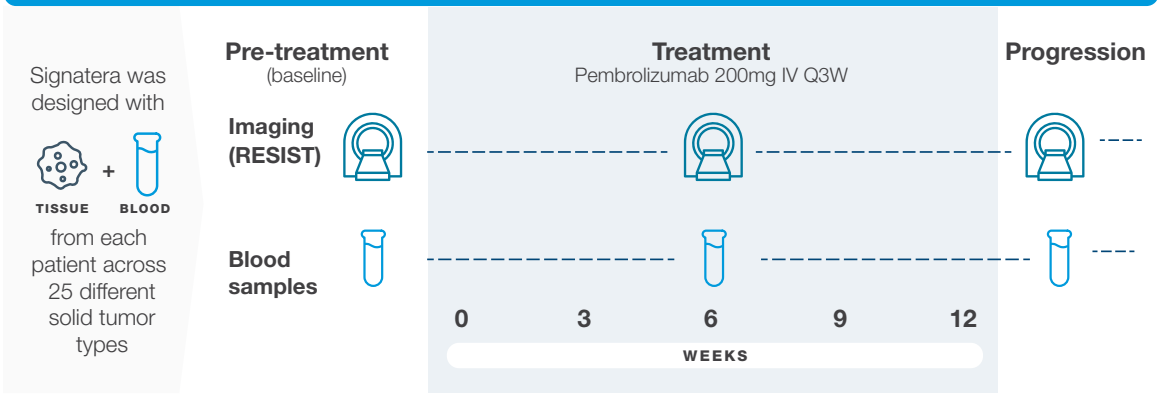
Real-time assessment of immunotherapy response

The Signatera assay was studied in a pan-cancer tumor cohort of patients receiving pembrolizumab treatment

The INSPIRE trial

The prospective phase II INSPIRE trial addressed clinically relevant issues related to the monitoring response to ICIs by assessing baseline ctDNA and ctDNA kinetics[18]

INSPIRE TRIAL DESIGN



Blood samples were drawn at baseline, and pembrolizumab treatment was administered every 3 weeks.

As early as week 6, an increase in ctDNA level predicted a lack of response to pembrolizumab

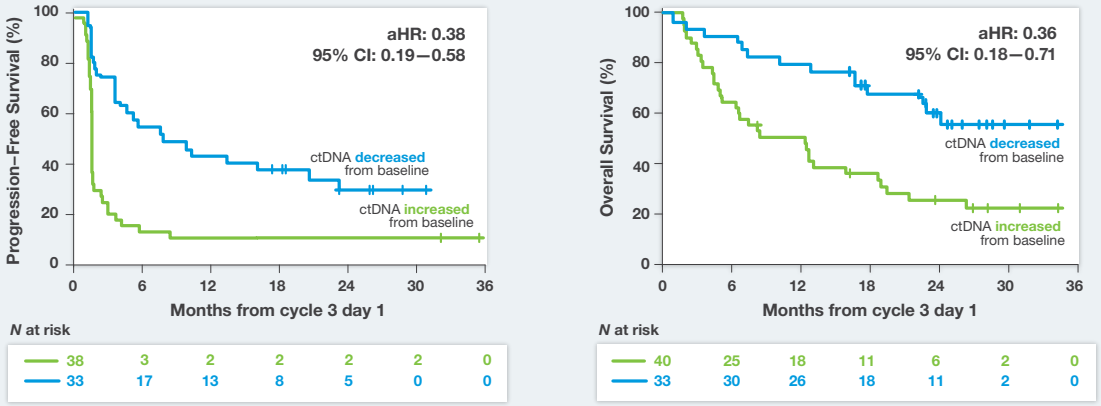
of patients (39/40) with an increase in ctDNA level at the beginning of cycle 3 did not have an objective response.[18]

None of the patients with an increase in both ctDNA and tumor size (n=30) achieved objective response at any time during the study.[18]

Decrease in ctDNA level at week 6 correlates with tumor response and favorable outcomes

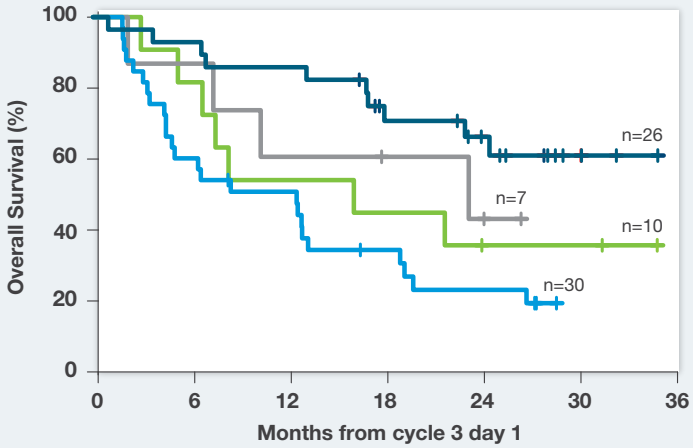
A decrease in ctDNA relative to baseline at the beginning of cycle 3 is a strong predictor of PFS and OS[18]

PFS and OS among patients with both baseline and cycle 3 ctDNA values, stratified according to increase or decrease of ctDNA



The addition of ctDNA monitoring to ICI response assessments can help improve OS predictions made by evaluation of tumor response by CT alone[18]

Risk groupings of patients identified by tumor response assessed on CT scans in conjunction with serial ctDNA values



- Increased ctDNA + PD
- Increased ctDNA + CR/PR/SD
- Decreased ctDNA + PD
- Decreased ctDNA + CR/PR/SD

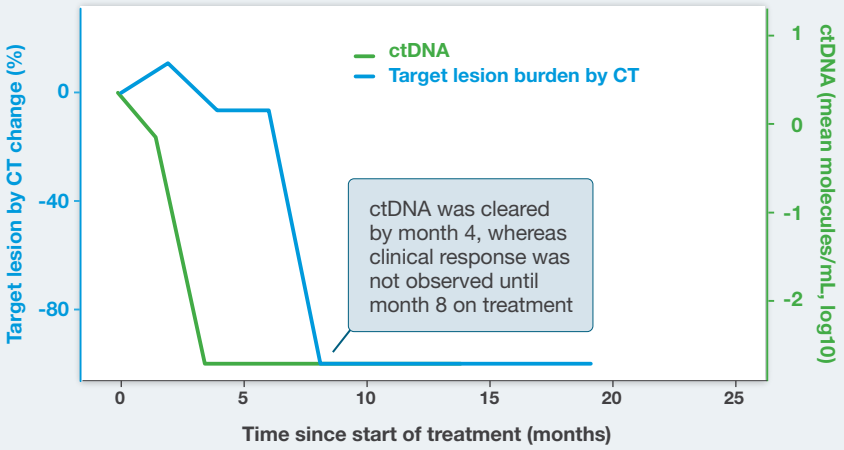
N = 73	Cycle 3 PD	Cycle 3 CR/PR/SD
Cycle 3 increase ctDNA	30	10
Cycle 3 decrease ctDNA	7	26

CR=complete response; **OS**=overall survival; **PD**=progressive disease; **PFS**=progression-free survival; **PR**=partial response; **SD**=stable disease

ctDNA is a sensitive and reliable molecular indicator of true progression

ctDNA dynamics precedes clinical response assessed by CT scans[18]

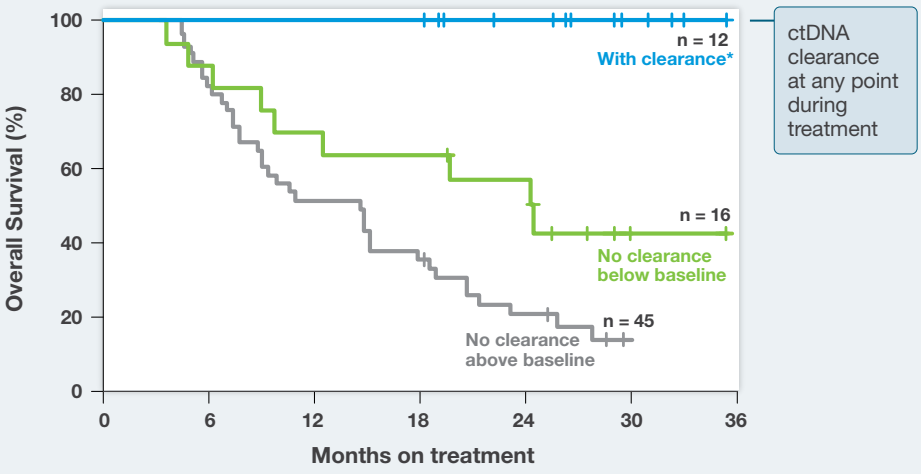
Patient with squamous cell carcinoma of the head and neck who experienced ctDNA clearance followed by durable clinical response



Achieving ctDNA clearance at any time during treatment correlates with durable OS

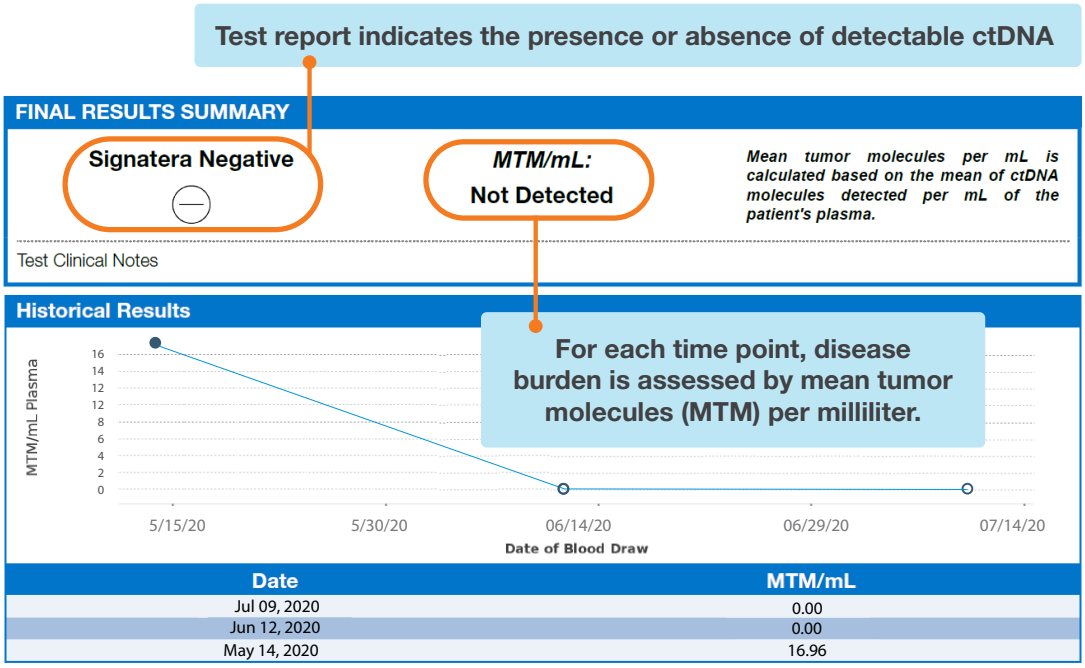
OS was 100% in patients who experienced ctDNA clearance for at least one on-treatment time point[18]

OS among patients with at least two ctDNA time points stratified by clearance of ctDNA



*Median follow-up beyond first clearance of 25.4 months (range 10.8-29.5)

Easy-to-interpret longitudinal report



Meet Natera's team of clinical experts who will support you and your patients

CLINICAL ONCOLOGY SPECIALISTS

- Main point of contact for requisition forms and kits
- Answer provider portal inquiries

CUSTOMER EXPERIENCE

- Acquires tumor tissue from pathology for whole-exome sequencing
- Answers test status inquiries from providers

ONCOLOGY CLINICAL INFORMATION

- Sets blood draw schedule for recurring orders
- Discusses test results with providers and availability of testing programs with providers and patients

PATIENT COORDINATORS

- Place welcome calls to patients
- Schedule mobile phlebotomy for Natera-managed blood draws
- Answer general billing inquiries and questions about compassionate care qualification
- Answer testing-related inquiries from patients

Look deeper – so you can know sooner

Evaluating response at key intervals during immunotherapy treatment is critical in informing decision-making and paving the way for stronger outcomes

- 98% of patients with metastatic disease across 25 tumor types had detectable ctDNA at baseline[18]
- Signatera ctDNA dynamics predicted tumor progression and correlated closely with treatment response to immune checkpoint inhibition[18]
- Clearance of ctDNA at any time is associated with 100% OS at up to 29.5 months of follow-up beyond first clearance[18]

Use Signatera ctDNA monitoring for tumor-informed, response monitoring

- Evaluate non-response at any point during treatment and plan for alternate options
- Help clarify indeterminate radiologic findings, including pseudoprogression
- Identify exceptional responders with ctDNA clearance

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