Simsen Personal® – A personalized, tumor-guided sequencing platform for ultrasensitive ctDNA detection in clinical trials

Niki Rostamzadeh[1], My Vu[1], Jonna Eriksson[1], Johanna Svensson[2], Anna Rohlin[2], Stefan Filges[1]

1. Simsen Diagnostics AB, Gothenburg, Sweden
2. Sahlgrenska University Hospital

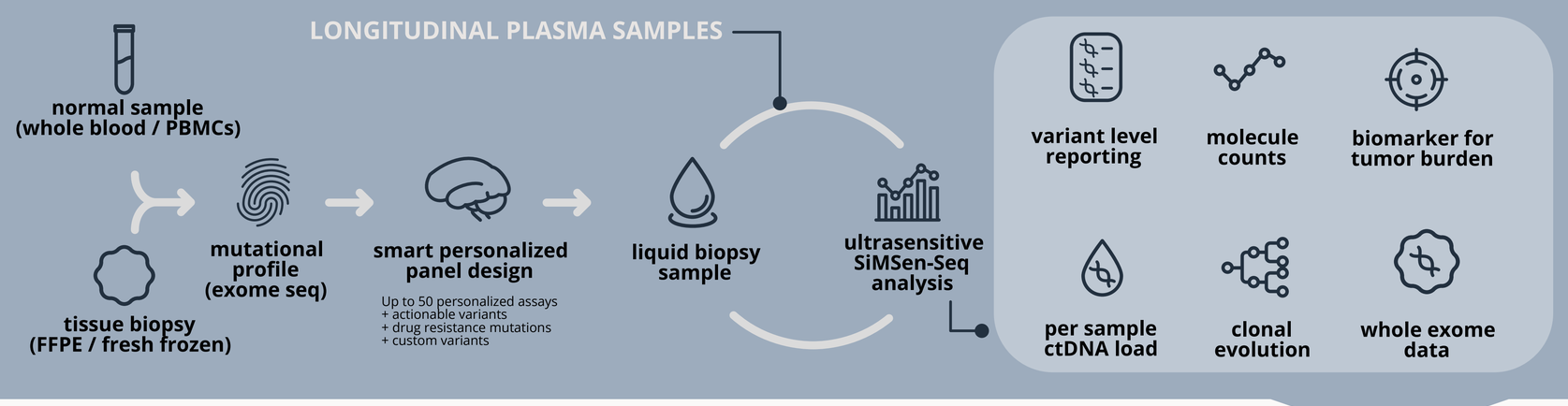
BACKGROUND

Cancer management urgently requires novel biomarkers for detecting therapy response, minimal residual disease (MRD) and relapse. Recent FDA guidance also recommends using ctDNA as a biomarker in oncology trials to evaluate treatment efficacy and improve clinical trials design[1] .

Personalized cancer monitoring based on each tumors unique mutational profile offers the most sensitive and specific approach to detect circulating tumor DNA and is unlikely to be affected by biological noise, such as CHIP. Here we present Simsen Personal, our personalized, tumor-informed platform for ultrasensitive mutation detection based on SiMSen-Seq[2,3].

METHOD

Simsen Personal® uses whole-exome sequencing of both tumor and normal samples to generate a personalized liquid biopsy panel based on our SiMSen-Seq technology for library preparation and UMI error correction. Customer provided mutational profiles can also be used. Each patient-specific panel contains up to 50 selected somatic variants, enabling ultra-sensitive detection down to 0.001% or 10 parts per million (PPM). Each bespoke panel can also include clinically relevant or custom variants[2,3].



RESULTS

ctDNA detection in lung cancer patients

The following describes preliminary results from an ongoing clinical study of immunotherapy in lung cancer patients. We used customer-provided tumor mutational profiles of their choice containing 5 - 16 mutations per patient, which were used to design Simsen Personal panels. Baseline cfDNA was significantly increased in non-responders (Fig. 1A). ctDNA status both at baseline and during treatment was significantly prognostic of overall survival (Fig. 1 C-D).

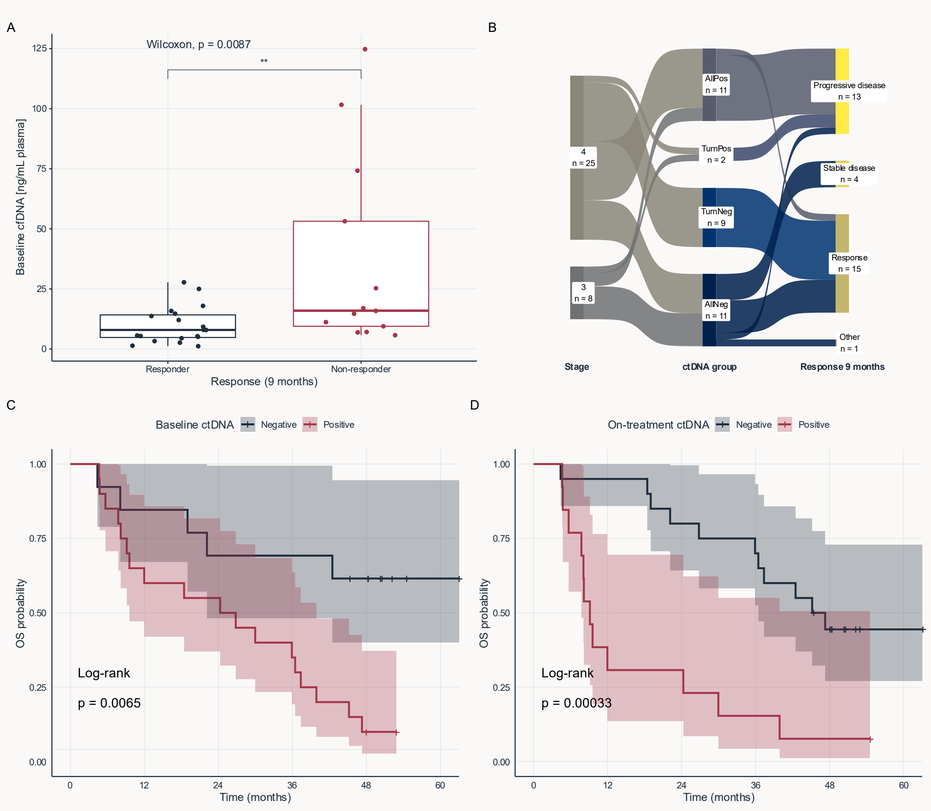


Figure 1. (A) Baseline cell-free DNA (B) Sankey diagram of ctDNA over time (C) Overall survival versus ctDNA status at baseline (D) Overall survival status versus on-treatment ctDNA (at any time during treatment).

Time courses for analyzed patients are shown in Figure 2 with detailed ctDNA dynamics for a subset of patients shown in Figure 3.

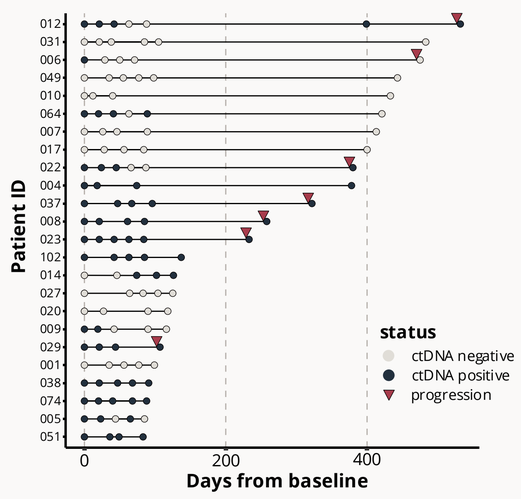


Figure 2. Time courses for a subset of patients (preliminary data).

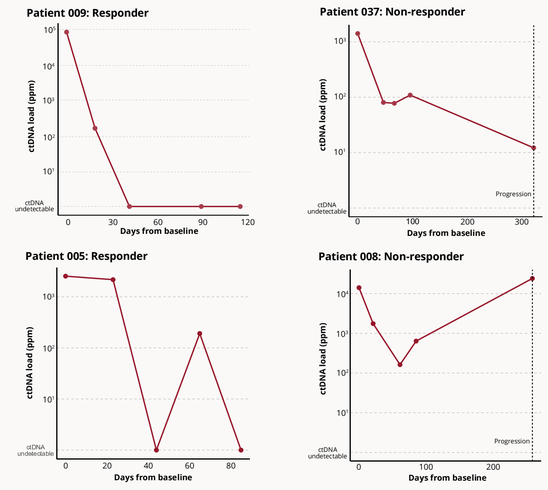


Figure 3. Selection of individual patient profiles.

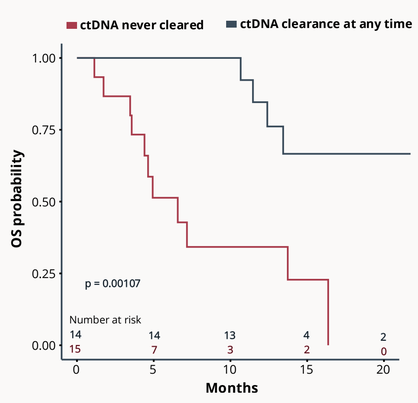


Figure 4. ctDNA clearance predicts survival.

ctDNA detection clearance predicts survival in uveal melanoma

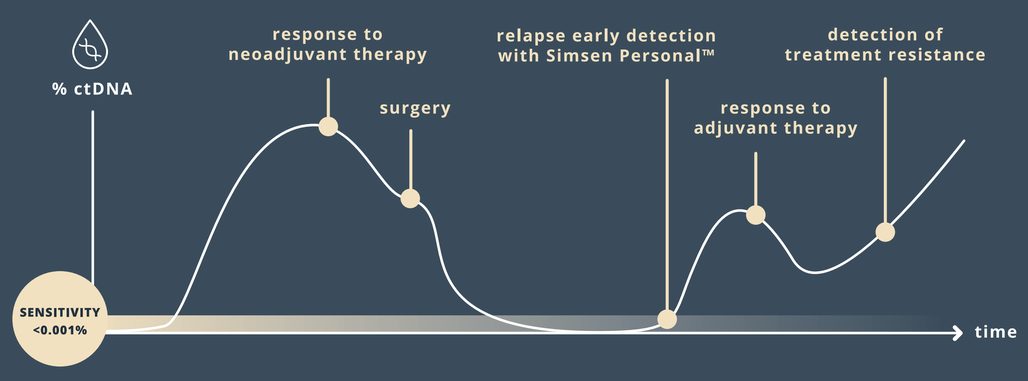
SiMSen-Seq was used to evaluate the treatment response of metastatic uveal melanoma patients undergoing an immunotherapy regimen using an HDAC inhibitor combined with PD-1 inhibition in the phase 2 PEMDAC trial[4].

Three of four patients with partial response had a decrease of ctDNA to undetectable levels during treatment, the fourth responder had no detectable levels at any timepoint (data not shown). ctDNA clearance during treatment was highly predictive of overall survival, compared to patients whose ctDNA never fell below the detection limit (Figure 4). ctDNA also proved to be a superior predictor of patient outcomes than protein-based markers used in the clinic today[4].

DISCUSSION

Simsen Personal detects circulating tumor DNA down to 0.001 due to the SiMSen-Seq error correction using UMI. Here we have demonstrated clinical results of flexible, ultrasensitive ctDNA analysis suing SiMSen-Seq in both lung cancer and uveal melanoma.

Personalized cancer monitoring allows the monitoring of complex ctDNA dynamics with drastic lead-time for recurrence detection compared to standard-of-care approaches. Personalized ctDNA monitoring is also an ideal tool to evaluate drug efficiency in clinical trials and long-term monitoring of cancer patients.



CONCLUSIONS

Personalized ctDNA monitoring provides the most flexible and sensitive method for ctDNA detection for use in MRD and recurrence detection. Due to reduced sequencing need for personalized panels compared to off-the shelf multi-gene panels, personalized sequencing is both more sensitive and more affordable for longitudinal monitoring.

- ultrasensitive detection of MRD & recurrence
- tumor informed & cancer-type agnostic
- determine treatment efficacy in clinical trials
- more cost-effective longitudinal monitoring

REFERENCES

1. FDA, Use of Circulating Tumor DNA for Early Stage Solid Tumor Drug Development Guidance for Industry, 2022
2. Ståhlberg, Krzyzanowski, Jackson, *et al*., Simple, multiplexed, PCR-based barcoding of DNA enables sensitive mutation detection in liquid biopsies using sequencing, Nucleic Acids Research, 2016
3. Ståhlberg, Krzyzanowski, Egyud, *et al*., Simple multiplexed PCR-based barcoding of DNA for ultrasensitive mutation detection by next-generation sequencing. Nature Protocol, 2017
4. Ny, Jespersen, Karlsson, *et al*., The PEMDAC phase 2 study of pembrolizumab and entinostat in patients with metastatic uveal melanoma, Nature Communications, 2021