The role of ctDNA in drug development across solid tumors

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Agenda

MRD testing technologies

Clinical data

Applications in clinical development

Closing thoughts
ctDNA MRD Testing is focused on residual disease detection and applications in cancer monitoring

Uses of ctDNA testing

- Molecular residual disease (MRD) status
- Surveillance for early recurrence monitoring
- Treatment response monitoring
- Asymptomatic cancer screening
- Cancer therapy selection
Signatera FDA designation and Medicare coverage

3 breakthrough device designations by the FDA
May 2019, March 2021

- As a lab-developed test (LDT), Signatera does not need FDA approval for clinical use
- Breakthrough helps clear regulatory pathway to support biopharma studies

Final coverage for colorectal cancer (CRC)
September 2020

- Finalized a local coverage determination (LCD) to provide Medicare benefits for serial use of Signatera in patients with stage II or III CRC

Draft immunotherapy coverage
September 2020

- Draft LCD proposes coverage of Signatera for immunotherapy response monitoring in all clinically validated solid tumors
Why personalized and tumor-informed?

<table>
<thead>
<tr>
<th>Technique</th>
<th>Approach</th>
<th>Limit of detection</th>
<th>Advantages/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidate gene analysis</td>
<td>qPCR, dPCR, ddPCR</td>
<td>0.01% to 1%</td>
<td>• Can only query small number of specific variants or mutations concurrently</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Only able to monitor known mutations</td>
</tr>
<tr>
<td>Tumor-informed NGS</td>
<td>CAPP-seq, PCM assay,</td>
<td>&lt;0.01% to 1.0%</td>
<td>• Highly sensitive and specific to detect small traces of ctDNA</td>
</tr>
<tr>
<td></td>
<td>Signatera™️, RaDaR®</td>
<td></td>
<td>• Quantitative measurement, ideal for monitoring MRD over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Requires WES of tumor tissue to design personalized assay</td>
</tr>
<tr>
<td>Tumor-naïve NGS</td>
<td>SAFE-SeqS, TEC-seq,</td>
<td>0.01% to &gt;0.1%</td>
<td>• Does not require a priori knowledge of the molecular alteration</td>
</tr>
<tr>
<td></td>
<td>Guardant360®, FoundationOne® Liquid</td>
<td></td>
<td>• Not designed for monitoring MRD in solid tumors</td>
</tr>
</tbody>
</table>

Signatera™ residual disease test (MRD)

The personalized and tumor-informed approach

Sequence tumor tissue to identify unique signature of tumor mutations

Custom design and manufacture personalized mPCR assay for each patient, targeting top clonal mutations found in tumor

Use personalized assay to test patient’s blood for presence of circulating tumor DNA (ctDNA)
What is needed in an AV study | High sensitivity, high specificity

- Sensitivity of at least 0.01% VAF
- LOD confirmation with clinical samples
- Specificity needs to be > 99%
- Well designed AV studies
- Consistent performance across multiple patient samples

### Proportion of positive results (PPR) for estimating analytical sensitivity

<table>
<thead>
<tr>
<th>Intended MTM per mL plasma</th>
<th>Intended VAF</th>
<th>Empirical PPR pos/[pos+neg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.15</td>
<td>0.0075%</td>
<td>72/76 (94.7%)</td>
</tr>
<tr>
<td>0.2</td>
<td>0.0100%</td>
<td>75/76 (98.7%)</td>
</tr>
<tr>
<td>0.3</td>
<td>0.0150%</td>
<td>76/76 (100%)</td>
</tr>
<tr>
<td>0.4</td>
<td>0.0200%</td>
<td>76/76 (100%)</td>
</tr>
</tbody>
</table>

Source: Natera internal data from Signatera analytical validation
Optimizing sensitivity and specificity: a delicate balance

- Adding more targets above 16:
  - Negative impact to specificity
  - Unclear impact to sensitivity
  - Higher failure rate in certain histologies
- 16 ensures stable algorithm and workflow across histologies
  - Variable targets per patient complicates development, validation and commercialization

Expected sample sensitivity and specificity by variants tracked

High performance and consistent results across multiple tumor types

**Positive Signatera result, without further treatment, has predicted relapse with overall PPV > 98%.**

Decrease from baseline or clearance of ctDNA is predictive of outcomes

94 patients with various solid tumors in the Phase II INSPIRE trial treated with single agent pembrolizumab (200 mg IV q3W).

98% of patients had detectable baseline ctDNA

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IMvigor010 data demonstrated the predictive power of Signatera ctDNA for treatment benefit

809 patients in IMvigor010 ITT population
- Atezolizumab (n=406)
- Observation (n=403)

- 190 with insufficient tumour, matched normal or plasma sample
- 4 failed tumour library prep
- 31 did not have C1D1 data
- 3 failed quality control checks

581 ctDNA-evaluable patients (72% of ITT population)
- Observation (n=281)
  - ctDNA(+): 98 (35%)
  - ctDNA(−): 183 (65%)
- Atezolizumab (n=300)
  - ctDNA(+): 116 (39%)
  - ctDNA(−): 184 (61%)

Key results
41% increase in OS benefit for Signatera ctDNA-positive patients treated with atezolizumab, while no treatment benefit was observed in the ctDNA-negative population

41% increase in OS benefit for Signatera ctDNA-positive patients treated with atezolizumab, while no treatment benefit was observed in the ctDNA-negative population

MIBC = muscle invasive bladder cancer

ctDNA clearance was associated with improved outcomes in the atezolizumab arm

**ctDNA clearance at C3D1 occurs at higher rate in treatment arm vs. obs**

<table>
<thead>
<tr>
<th>Group</th>
<th>ctDNA (+) → (‒) (n=18)</th>
<th>ctDNA (+) → (+) (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>HR, 0.41 (95% CI: 0.10, 1.70)</td>
<td>HR, 0.26 (95% CI: 0.12, 0.56)</td>
</tr>
</tbody>
</table>

*Assessed using Fisher exact test.*

IMvigor011 | Adjuvant atezolizumab vs placebo in MIBC patients who are ctDNA positive following cystectomy

Post cystectomy for high-risk urothelial cancer

Serial ctDNA testing

Positive

Negative

20 weeks

PFS
Primary endpoint

OS
2nd endpoint

atezolizumab

placebo

R


The VEGA trial: the non-inferiority of observation vs. adjuvant CAPOX in GALAXY participants with absence of ctDNA at 1-month post-surgery.

The ALTAIR trial: the superiority of FTD/TPI over placebo in GALAXY participants with ctDNA positive after the standard therapy.
Signatera ctDNA detection rates pre- and post-surgery

Across multiple studies in CRC, Signatera has shown to have pre-surgical detection 89-94%\(^1\)\(^-\)\(^2\)

2. CIRCULATE data on file.

*History of chemotherapy prior to surgery within 6 months
Prospective trials to assess association of MRD-positivity with treatment response

<table>
<thead>
<tr>
<th>Trial/ NCT#</th>
<th>Stage / Tumor type</th>
<th>Description</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERMAID-1 NCT04385368</td>
<td>Stage II/III NSCLC</td>
<td>Durvalumab + chemo vs chemo for MRD+ after resection</td>
<td>3</td>
</tr>
<tr>
<td>MERMAID-2 NCT04642469</td>
<td>Stage II/III NSCLC</td>
<td>Durvalumab vs placebo for MRD+ after resection and possible neoadj/adjuv treatment</td>
<td>3</td>
</tr>
<tr>
<td>CATHAYA NCT04611776</td>
<td>Stage IB-IIIB NSCLC</td>
<td>Atezolizumab + chemo vs placebo + chemo for MRD+ after resection</td>
<td>2</td>
</tr>
<tr>
<td>IMvigor011 NCT04660344</td>
<td>Muscle-invasive bladder cancer</td>
<td>Atezolizumab vs placebo for MRD+ after resection</td>
<td>3</td>
</tr>
<tr>
<td>ISPY-2 NCT01042379</td>
<td>Neoadjuvant breast cancer</td>
<td>ctDNA dynamics pre- and post-neoadjuvant chemotherapy prior to resection</td>
<td>2</td>
</tr>
<tr>
<td>c-TRAK-TN NCT03145961</td>
<td>High risk, early stage TNBC</td>
<td>Pembrolizumab vs placebo for MRD+ after resection and possible neoadj/adjuv tx</td>
<td>2</td>
</tr>
<tr>
<td>LEADER NCT03285412</td>
<td>Stage I-III breast cancer (ER+, HER2-)</td>
<td>Ribocilcib + endocrine therapy vs endocrine therapy for MRD+ patients after possible neoadj/adjuv tx</td>
<td>2</td>
</tr>
<tr>
<td>DARE NCT04567420</td>
<td>Stage II-III breast cancer (ER+, HER2-)</td>
<td>Palbocilcib + fulvestrant vs SoC endocrine tx for MRD+ patients treated with adjuvant aromatase inhibitor/tamoxifen</td>
<td>2</td>
</tr>
<tr>
<td>CIRCULATE-Japan UMIN000039205</td>
<td>Stage II-III CRC</td>
<td>Treatment escalation with experimental therapies in MRD+ patients after surgery, and treatment de-escalation (no chemo) in MRD- patients after surgery</td>
<td>3</td>
</tr>
<tr>
<td>MGH 18-397 NCT03803553</td>
<td>Stage III CRC</td>
<td>Nivolumab, Encorafenib/Binimetinib/Cetuximab, FOLFIRI, or active surveillance as appropriate for MRD+</td>
<td>3</td>
</tr>
<tr>
<td>COBRA NCT04068103</td>
<td>Stage IIA colon cancer</td>
<td>FOLFOX6 or CAPOX vs surveillance for resected MRD+</td>
<td>2/3</td>
</tr>
<tr>
<td>TAPISTRY NCT04589845</td>
<td>TMB-high, advanced solid tumors</td>
<td>TKIs vs atezolizumab vs ipatasertib vs trastuzumab vs idasanutlin vs GDC-0077</td>
<td>2</td>
</tr>
<tr>
<td>NCT04510285</td>
<td>HER2+ esophagogastric tumors</td>
<td>Trastuzumab + placebo vs trastuzumab + pembrolizumab in MRD+</td>
<td>2</td>
</tr>
</tbody>
</table>

Using ctDNA to bring life-saving therapeutics to patients

- Clinical studies and data shows strong correlation for quantification of ctDNA levels and clinical outcomes

- ctDNA can serve as a biomarker in various manners including prognostic, predictive, monitoring, and treatment response

- ctDNA status has the potential to be used as:
  - A surrogate endpoint of treatment efficacy to accelerate clinical trial results
  - A stratification method to identify the subset of patients who may still benefit from therapies studied in trials that failed to meet their primary endpoint
Open questions | Guidance needed from FDA / PMDA

- Pathway for treatment-related ctDNA dynamics to become a surrogate endpoint for drug approvals

- Pathway for updating label based on MRD data using retrospective banked samples
  - Complementing other surrogate endpoints with ctDNA, or work through regulatory paradigms like accelerated approvals?
Thank you!

Questions

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