ctMoniTR Step 2
Module 1 Findings

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Friends of Cancer Research
on behalf of the ctMoniTR Step 2 Working Group
**ctMoniTR Overview**

*Do changes in ctDNA reflect response to treatment?*

**ctMoniTR Step 1**
- 5 clinical trials
- 200 patients
- Advanced NSCLC Treated with anti-PD(L)1

**ctMoniTR Step 2**
- 22 clinical trials
- 3,000 patients
- 8 advanced tumor types
- 16 different therapies

**Module 1**
- aNSCLC
- TKI

**Module 2**
- aNSCLC
- Anti-PD(L)1 or chemo

**Module 3**
- Adv. Solid Tumors
- Anti-PD(L)1 or TKI

**Focus for today**
Module 1 Overview

- 8 Clinical Trials
- 8 Different TKIs
- 1015 Patients
- 5 Assays

Baseline ctDNA (T0) - Up to 14 days before Index
On Treatment ctDNA (T1) - Up to 10 weeks from Index

ctDNA Timing
1st RECIST Timing
Module 1 Overview

Inclusion Criteria

• aNSCLC (93% stage IV)
• Treated with TKI (anti-EGFR, ALK, MET, RET)
• Long-term outcomes – PFS, OS
  • Analyses presented for OS, but results are similar for PFS

Assay Details

• 5 different assays
• ddPCR (n=539 patients) and NGS (n=476 patients)
• Limit of detection for NGS: %VAF 0.1–0.5
Module 1 Approach

**RO1**
Early ΔctDNA associations with long-term clinical outcomes

**RO2**
ΔctDNA complementing 1st RECIST/ BOR

**RO3**
Combining ΔctDNA with 1st RECIST to improve associations with outcomes

- Align on statistical analysis plan
  - Project Members

- Upload patient-level data to secure portal
  - Trial sponsors

- Review data and share private dataset report
  - CRAB/ Trial Sponsors

- Perform analyses
  - CRAB

- Discuss findings and next steps
  - Project Members

- Align on key findings and disseminate results
  - Project Members
Molecular Response as a Percent Change

ΔctDNA Metrics
- Max VAF
- Calculate as percent change from T0 to T1
  - For those with multiple ctDNA values within the first 10 weeks, use "best" (i.e., lowest) ctDNA for T1

Molecular Response
- "Decrease" = >50% decrease
- "Increase" = >20% increase
- "Intermediate" = 50% decrease to 20% increase
- "ND/ND" = not detected

Statistical Analysis
- Kaplan Meier plots
- Multivariable Cox proportional hazards models stratified by cohort, included demographic and clinical confounders

Categorizing the samples by percent change did not demonstrate separation of Kaplan-Meier Curves
Molecular Response Based on Detection

<table>
<thead>
<tr>
<th>T0/T1</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND/ND</td>
<td>Not detected at T0 or T1</td>
</tr>
<tr>
<td>D/ND</td>
<td>Detected at T0, not detected at T1</td>
</tr>
<tr>
<td>D/D</td>
<td>Detected at T0 and T1</td>
</tr>
</tbody>
</table>

OS multivariable associations, HR (p-value)

<table>
<thead>
<tr>
<th>Comparator</th>
<th>ND/ND</th>
<th>D/ND</th>
<th>D/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND/ND</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/ND</td>
<td>2.95 (0.001)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>D/D</td>
<td>6.25 (0.001)</td>
<td>2.12 (0.001)</td>
<td>-</td>
</tr>
</tbody>
</table>

Patients with non-detected ctDNA on treatment (D/ND) have stronger association with improved survival compared with patients with detected levels of ctDNA on treatment (D/D).

*The ND/D category had very few patients (n=6) so further analyses did not include this category.
Molecular Response Based on Detection

<table>
<thead>
<tr>
<th>T0/T1</th>
<th>Deaths / N</th>
<th>Median (Yrs)</th>
<th>1-Yr Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND/ND</td>
<td>16/187</td>
<td>NR</td>
<td>96% (93, 99)</td>
</tr>
<tr>
<td>D/ND</td>
<td>114/394</td>
<td>3.2 (2.6, NR)</td>
<td>87% (84, 91)</td>
</tr>
<tr>
<td>D/D</td>
<td>72/135</td>
<td>1.5 (1, 2.2)</td>
<td>57% (48, 66)</td>
</tr>
</tbody>
</table>

Patients with non-detected ctDNA on treatment (D/ND) have stronger association with improved survival compared with patients with detected levels of ctDNA on treatment (D/D).

*The ND/D category had very few patients (n=6) so further analyses did not include this category.*

**OS multivariable associations, HR (p-value)**

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Reference</th>
<th>ND/ND</th>
<th>D/ND</th>
<th>D/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND/ND</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/ND</td>
<td>2.95 (&lt;0.001)</td>
<td>-</td>
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</tr>
</tbody>
</table>

**Overall Survival**

*The graph shows the overall survival rates for different molecular response categories over time (from 70 days after enrollment).*

**Reference**

- ND/ND
- D/ND
- D/D
Comparing Molecular and Radiographic Response

Do patients with ND ctDNA on treatment correlate with responders as defined by 1st RECIST (within the first 10 weeks after index)? Or BOR?

<table>
<thead>
<tr>
<th>BOR</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4</td>
<td>28</td>
<td>3</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>483</td>
<td>128</td>
<td>0</td>
<td>611</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>25</td>
<td>132</td>
<td>0</td>
<td>157</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>536</td>
<td>264</td>
<td>24</td>
<td>828</td>
</tr>
</tbody>
</table>

Combine CR and PR into “Responders”

Combine SD and PD into “Non-responders”

BOR: Best Overall Response; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease
Comparing Molecular and Radiographic Response

Distribution of Responders vs. Non-Responders across molecular response categories for 1st RECIST and BOR is similar.
Combining Molecular Response and Radiographic Response at 1st RECIST

**Analysis 1**
Radiographic response + outcomes (no ∆ctDNA)
Kaplan Meier, Cox model
Categories
- Responder
- Non-Responder

**Analysis 2**
Radiographic response + ∆ctDNA + outcomes
Kaplan Meier, Cox model
Categories
- ND/ND + Responder
- ND/ND + Non-Responder
- D/ND + Responder
- D/ND + Non-Responder
- D/D + Responder
- D/D + Non-Responder

**Analysis 3**
Compare models
Does combining molecular and radiographic response improve associations with outcomes?
**Likelihood Ratio Test**
Compare full model to reduced model
- Full model: ctDNA x 1st RECIST
- Reduced model: ctDNA

**Analysis 4**
PR/ SD + ∆ctDNA + outcomes
Kaplan Meier, Cox model
Categories (within PR or SD)
- ND/ND
- D/ND
- D/D

**aNSCLC + TKI**
Analysis 1

Radiographic response + outcomes (no ΔctDNA)

Overall Survival

Radiographic Response Measured at 1st RECIST

<table>
<thead>
<tr>
<th></th>
<th>Deaths / N</th>
<th>Median (Yrs)</th>
<th>1-Yr Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>103/408</td>
<td>NR</td>
<td>87% (84,91)</td>
</tr>
<tr>
<td>Non-Responder</td>
<td>75/254</td>
<td>2.6 (2.1, NR)</td>
<td>82% (77,87)</td>
</tr>
</tbody>
</table>

OS Multivariable analysis

HR = 1.21 (0.87, 1.67) P = 0.254

There is no apparent separation between responders and non-responders at 1st RECIST and their association with OS.
**Analysis 2**

**Radiographic response + ΔctDNA + Outcomes**

Incorporating radiographic response at 1st RECIST into molecular response categories does not improve the degree of association with survival for those with ND ctDNA on treatment.

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths / N</th>
<th>Median (Yrs)</th>
<th>1-Yr Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND/ND Responder</td>
<td>8/102</td>
<td>NR</td>
<td>97% (94,100)</td>
</tr>
<tr>
<td>ND/ND Non-responder</td>
<td>7/73</td>
<td>NR</td>
<td>94% (89,100)</td>
</tr>
<tr>
<td>D/ND Responder</td>
<td>76/238</td>
<td>3.5 (2.7, NR)</td>
<td>87% (82, 91)</td>
</tr>
<tr>
<td>D/ND Non-responder</td>
<td>35/128</td>
<td>2.1 (2.0, NR)</td>
<td>88% (82, 94)</td>
</tr>
<tr>
<td>D/D Responder</td>
<td>19/48</td>
<td>NR</td>
<td>70% (57, 83)</td>
</tr>
<tr>
<td>D/D Non-Responder</td>
<td>33/53</td>
<td>1.0 (0.6, 2.1)</td>
<td>48% (34, 63)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ΔctDNA Category</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND/ND</td>
<td>0.95 (0.34, 2.64); p=0.917</td>
</tr>
<tr>
<td>D/ND</td>
<td>0.91 (0.60, 1.39); p=0.675</td>
</tr>
<tr>
<td>D/D</td>
<td>1.93 (1.04, 3.58); p=0.037</td>
</tr>
</tbody>
</table>
Analysis 3

Does combining molecular and radiographic response improve associations with outcomes?

Compare full model to reduced model

- **Full model:** $\Delta$ctDNA x 1st RECIST (+/- covariates)
- **Reduced model:** $\Delta$ctDNA only (+/- covariates)

- Likelihood ratio test for association between OS and 1st RECIST above and beyond $\Delta$ctDNA:
  - ChiSq = 4.7, DF = 3, P = 0.195

Radiographic response at 1st RECIST does not provide additional value in characterizing the association with OS beyond the contribution of molecular response.
Analysis 4

PR/ SD + ∆ctDNA + Outcomes

For patients classified as SD at 1st RECIST, molecular response differentiates associations with overall survival

<table>
<thead>
<tr>
<th>Comparison</th>
<th>PR</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>D/ND vs. ND/ND</td>
<td>2.05 (0.82, 5.13); p=0.124</td>
<td>4.80 (1.78, 12.92); p=0.002</td>
</tr>
<tr>
<td>D/D vs. ND/ND</td>
<td>3.32 (1.18, 9.33); p=0.023</td>
<td>19.93 (5.89, 67.44); p&lt;0.001</td>
</tr>
<tr>
<td>D/D vs. D/ND</td>
<td>1.62 (0.95, 2.75); p=0.077</td>
<td>4.15 (2.07, 8.33); p&lt;0.001</td>
</tr>
</tbody>
</table>

Overall Survival

**PR at 1st RECIST**

![Graph showing Overall Survival for PR at 1st RECIST]

**SD at 1st RECIST**

![Graph showing Overall Survival for SD at 1st RECIST]

Years from 70 Days after Enrollment
Module 1 Key Takeaways

- Harmonizing data across 8 clinical trials was feasible
- In aNSCLC treated with TKI:
  - Among patients who had detected ctDNA at baseline, patients with non-detected ctDNA on treatment (D/ND) were associated with improved OS (and PFS) compared to patients with detected levels of ctDNA on treatment (D/D)
  - Molecular response associated with OS (and PFS) while radiographic response at 1st RECIST did not
  - Among patients who were categorized as having SD at 1st RECIST, molecular response identified patients with improved associations with OS (and PFS)
## Strengths and Limitations of the Analysis

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td><strong>Large Dataset</strong></td>
<td></td>
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<tr>
<td>• 8 clinical trials</td>
<td>• Did not have an external validation dataset</td>
</tr>
<tr>
<td>• 1015 patients</td>
<td></td>
</tr>
<tr>
<td>• 8 distinct TKI regimens</td>
<td>• Potential differential in features due to variability despite sensitivity analyses</td>
</tr>
<tr>
<td><strong>Variability</strong></td>
<td></td>
</tr>
<tr>
<td>• Assay types</td>
<td>• Unable to answer some questions because of anonymization</td>
</tr>
<tr>
<td>• Sampling timing for ctDNA/RECIST</td>
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<tr>
<td><strong>Patient-level data</strong></td>
<td></td>
</tr>
<tr>
<td>• Multivariable models account for patient-level confounders</td>
<td>• Prospective analyses would be prespecified</td>
</tr>
<tr>
<td>• Interrogated ctDNA metrics</td>
<td></td>
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<tr>
<td><strong>Retrospective analysis</strong></td>
<td></td>
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<tr>
<td>• Opportunity to analyze multiple datasets with different approaches to data collection</td>
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</tbody>
</table>
Contextualizing Findings

• Module 1 is not a validation of Step 1 (aNSCLC + anti-PD(L)1)
  • Different treatments (TKI vs. PD(L)1)
  • Different methods of defining change (detection vs. % change)

• However, in both cases, molecular response associates with improved outcomes

• Module 2 focuses on aNSCLC + anti-PD(L)1 or chemo
  • Allows us to validate Step 1
  • Consider a different treatment
  • Potential to analyze whether ctDNA can identify a more effective treatment in a randomized controlled trial
THANK YOU TO OUR PROJECT PARTNERS