Next-Generation Immuno-Oncology Biomarkers: Insights for Developing Companion Diagnostics for the Future of Immuno-Oncology (I/O)

Companion Diagnostics Forum
Princeton, NJ
December 7, 2017

Disclaimer –
Some of the companies listed in this document may be DeciBio Consulting clients or customers
Based on an analysis of ~1,000 immuno-oncology (I/O) clinical trials and discussion with clinical and industry experts, we have identified 3 trends that are likely to shape the I/O biomarker and CDx landscape in the mid-long term.

Key I/O Biomarker / CDx Trends / Hypotheses

1. The I/O biomarker space is rapidly expanding beyond PD-L1, MSI

2. I/O will drive significant changes to the cancer diagnostic technology and testing landscape

3. Immune response monitoring represents a material market opportunity for Dx companies

Note: * Includes information only from I/O trials that contain sufficient biomarker information; database includes trials that were open, active, and enrolling as of 11/2016 – the BioMAP does not currently include data from trials that were completed, withdrawn, or terminated before 11/2016
To monitor the rapidly-changing immuno-oncology biomarker landscape, we have developed a “living” database of biomarkers being explored in I/O clinical trials; to-date, we have captured data from >1,000 I/O clinical trials.

1. Identify I/O Clinical Trials with Biomarker Information
   - We use clinicaltrials.gov to identify active I/O clinical trials
     - Trials without reference to biomarker data are excluded from the analysis
     - Trials are cross-referenced with ASCO, AACR, and ESMO conference abstracts for biomarker additional information
   - To-date, we have identified ~1,400 relevant trials and have captured data from ~1,000 trials
     - Early analysis has focused on industry-sponsored trials, and later stage trials

2. Extract Biomarker Data
   - From each trial and/or conference abstract we capture trial and biomarker-related data, including:
     - Trial start date and phase
     - Target enrollment volume
     - Primary and collaborating sponsors
     - Types of biomarkers and purpose of analysis
     - Analytical technologies used
     - Sample types analyzed
     - Indication(s)
     - Drugs / other interventions

3. Aggregate and Visualize
   - The data is imported into Tableau to allow visualization and segmentation of the data by multiple parameters, including:
     - Trial Phase
     - Trial start date
     - Sponsors
     - Biomarker and type
     - Biomarker purpose
     - Technology utilization
     - Biomarker sample type
     - Indication

Note: * Includes information only from I/O trials that contain sufficient biomarker information; database includes trials that were open, active, and enrolling as of 11/2016 – the BioMAP does not currently include data from trials that were completed, withdrawn, or terminated before 11/2016
To further characterize these trends and test our hypotheses, we conducted interviews with clinical and commercial immuno-oncology experts that have direct experience with “next-gen” biomarkers.

Example Institutions / Affiliations Include:

- Cambridge University Hospitals
- Gustave Roussy Cancer Campus Grand Paris
- Quest Diagnostics
- UCLA
- Montefiore Health System, Inc.
- Guy’s and St Thomas’ NHS Foundation Trust
- The University of Texas MD Anderson Cancer Center
- UW Medicine School of Medicine

Note: * Select examples of interviewee institutions, most industry interviewees requested to remain anonymous; ** European interviews were conducted in Spain, France, UK, and Germany.
Clinical trial analysis reveals that there is more to immuno-oncology biomarkers than PD-L1, immuno-oncology (I/O) is entering the phase of “next-generation” biomarkers.

Map of all I/O Biomarker Trials by Biomarker Type*

- From ~1,000 I/O clinical trials analyzed to-date, we captured >4,600 mentions of >1,200 different biomarkers
  - Biomarker Mention = Reference to a distinct combination of a biomarker + test purpose + technology + sample type
  - Of all biomarkers mentioned, ~90% would be considered I/O – specific markers (non-I/O-specific markers include ALK, EGFR, HER2, etc.)
- The breakdown of biomarkers by biomarker type is:
  - Protein – 39%
  - Nucleic Acid – 25%
  - Cell – 12%
  - Cell / Protein – 12%
  - Other – 1%
  - Not Specified – 11%
- The exploration of biomarkers in I/O clinical trials has been accelerating; since 2014, the average number of biomarker mentions / trial has grown from ~4.5 to ~7.8

Note: * DeciBio BioMAP
PD-L1 remains the most commonly explored biomarker; combined, the top 15 I/O biomarkers comprise ~65% of all biomarker mentions

Aside from PD-L1, the most commonly-explored I/O biomarkers / biomarker for predictive purposes are:
- Tumor-infiltrating immune cells
- Peripheral immune cell populations
- Gene expression profiles
- PD-1
- Tumor mutation burden

The most commonly-explored I/O biomarkers / biomarker for monitoring purposes are:
- Peripheral immune cell populations and phenotypes (including therapeutic cells)
- Cytokine profiles and other, unspecified immune response markers
- Gene expression profiles

The fastest-growing biomarkers include PD-1 / L1, TILs, CTCs, tumor mutation burden (TMB) / genomic profiling, gene expression profiling
- These markers are all growing at >80% over the past three years (vs. ~70% for the overall landscape)

Notes:
* Excludes non-I/O specific biomarkers (e.g., HER2, ALK, EGFR, BRAF for exclusion of targeted-therapy-eligible patients); includes biomarkers for all purposes
Multiple trials exploring "next-gen" biomarkers are expected to yield results in 2018; we expect to see gene expression signatures and tumor mutation burden play a key role in upcoming trials.

Timeline of Select Trials with 2018 Primary Completion Dates*

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Phase</th>
<th>Sponsor</th>
<th>Enrollment</th>
<th>End-Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02367794</td>
<td>Phase 3</td>
<td>Hoffmann-La Roche</td>
<td>1021</td>
<td></td>
</tr>
<tr>
<td>NCT02435433</td>
<td>Phase 3</td>
<td>Eli Lilly and Company</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>NCT02439450</td>
<td>Phase 1/2</td>
<td>Heat Biologics</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>NCT02580058</td>
<td>Phase 3</td>
<td>Pfizer</td>
<td>546</td>
<td></td>
</tr>
<tr>
<td>NCT02101853</td>
<td>Phase 3</td>
<td>National Cancer Institute (NCI)</td>
<td>598</td>
<td></td>
</tr>
<tr>
<td>NCT02324257</td>
<td>Phase 1</td>
<td>Hoffmann-La Roche</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>NCT01772004</td>
<td>Phase 1</td>
<td>EMD Serono</td>
<td>1756</td>
<td></td>
</tr>
<tr>
<td>NCT02564263</td>
<td>Phase 3</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
<td>720</td>
<td></td>
</tr>
<tr>
<td>NCT01375842</td>
<td>Phase 1</td>
<td>Genentech, Inc.</td>
<td>661</td>
<td></td>
</tr>
<tr>
<td>NCT02517398</td>
<td>Phase 1</td>
<td>EMD Serono R&amp;D</td>
<td>702</td>
<td></td>
</tr>
<tr>
<td>NCT02595944</td>
<td>Phase 3</td>
<td>National Cancer Institute (NCI)</td>
<td>714</td>
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<tr>
<td>NCT02655822</td>
<td>Phase 1</td>
<td>Corvus Pharmaceuticals, Inc.</td>
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<tr>
<td>NCT02992210</td>
<td>Phase 1/2</td>
<td>Shenzhen Geno-Immune Med. Inst.</td>
<td>100</td>
<td></td>
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<tr>
<td>NCT01896999</td>
<td>Phase 1/2</td>
<td>National Cancer Institute (NCI)</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>NCT02835729</td>
<td>Phase 1/2</td>
<td>NewLink Genetics Corporation</td>
<td>138</td>
<td></td>
</tr>
<tr>
<td>NCT01351103</td>
<td>Phase 1</td>
<td>Novartis Pharmaceuticals</td>
<td>170</td>
<td></td>
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<tr>
<td>NCT02904226</td>
<td>Phase 1/2</td>
<td>Jounce Therapeutics, Inc.</td>
<td>282</td>
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<tr>
<td>NCT02608268</td>
<td>Phase 1/2</td>
<td>Novartis Pharmaceuticals</td>
<td>250</td>
<td></td>
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<tr>
<td>NCT02178722</td>
<td>Phase 1/2</td>
<td>Incyte Corporation</td>
<td>463</td>
<td></td>
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<tr>
<td>NCT02242942</td>
<td>Phase 3</td>
<td>Hoffmann-La Roche</td>
<td>445</td>
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<tr>
<td>NCT02208362</td>
<td>Phase 1</td>
<td>City of Hope Medical Center</td>
<td>100</td>
<td></td>
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<tr>
<td>NCT02684006</td>
<td>Phase 3</td>
<td>Pfizer</td>
<td>830</td>
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<tr>
<td>NCT01633970</td>
<td>Phase 1</td>
<td>Genentech, Inc.</td>
<td>240</td>
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<tr>
<td>NCT01822509</td>
<td>Phase 1</td>
<td>National Cancer Institute (NCI)</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

* Includes trials exploring "next-gen" I/O biomarkers (e.g., excluding PD-L1 and markers for non-immunotherapies) for predictive purposes, with a primary completion date in 2018 and enrollment of >100 patients
Stakeholders identify TMB and tumor-infiltrating immune cells as the I/O markers likely to have the highest near-term clinical impact; many expect that multiple different biomarkers and modalities will ultimately be integrated.

Stakeholder Feedback on Emerging I/O Biomarkers

- **TMB**: Multiple trials are underway and the test is highly accessible (oncologists are already getting TMB results on every report they get from Foundation Medicine); readout is objective.

- **Tumor Infiltrating Immune Cells**: Considered the most direct and simplest way (i.e., H&E or IHC) to measure tumor inflammation; however, which immune cells, markers, and cutoffs are most relevant is to-be-determined.

- **Gene Expression Profiling (GEP)**: Feedback has been mixed – waiting for conclusive data and standardization of signatures; however, multiple technologies are available (e.g., RNA-seq, NanoString, Fluidigm, PCR).

- **Other Checkpoint Targets (e.g., LAG3, IDO, OX40)**: All being explored, but mostly early stage, and often as part of multiplex IHC panels; clinicians expect that the checkpoint targets will be part of the Dx strategy for any of the corresponding drugs.

- **TCR Clonality**: Clinicians are intrigued about the possibility of using TCR analysis for both predictive and immune response monitoring assays (e.g., TCR diversity and TCR clonal expansion).

- **Cytokines**: Cytokines profiles offer a relatively simple way (i.e., ELISA) to assess potential responses to immunotherapy, however, evidence to-date is limited and trials are mostly exploratory.

No single marker is expected to be used exclusively, multiple markers are likely to be integrated.

Note: * TME = Tumor Microenvironment
Source: DeciBio BioMAP; DeciBio interviews and analysis
Tissue analysis by IHC accounts for the largest share of biomarker mentions (~42%); flow cytometry (19%) is commonly used for monitoring assays; while sequencing is relatively small (12%), its use is growing rapidly.

Cumulative Distribution of Biomarker Technology Utilization*

- **IHC** remains most widely-used for biomarker analysis, driven by testing for PD-L1 and tumor-infiltrating immune cells.
- **Sequencing** is the fastest-growing technology, with its share in clinical trials growing by 15% annually (CAGR) over the past three years.
- **Flow cytometry** is used most broadly for monitoring-based assays.
- Few technology platforms are mentioned by name, however, those identified most commonly are:
  - NanoString for gene expression profiling
  - Luminex for cytokine analysis
  - Foundation Medicine for comprehensive genomic profiling and TMB
  - Fluidigm for gene expression profiling and CYTOF
  - CellSearch for CTCs

Note: * Excludes biomarkers for which no technology was mentioned and/or for which the technology could not be discerned, as well as non I/O-specific biomarkers (e.g., HER2, ALK, EGFR, etc.)
Stakeholders anticipate that tumor-mutation burden and gene-expression signatures will be common companion diagnostics for cancer immunotherapies, but that only a small share of labs will be equipped to conduct these assays.

Current In-House Access to Diagnostic Platforms (N = 15)

<table>
<thead>
<tr>
<th>Assay / Biomarker Type</th>
<th>Current In-house Capability</th>
<th>Appetite to In-Source</th>
<th>Estimated Community Onc. Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 IHC</td>
<td>High</td>
<td>N/A</td>
<td>High</td>
</tr>
<tr>
<td>Immune cell populations / phenotypes (flow cytometry)</td>
<td>High</td>
<td>N/A</td>
<td>Mod. / Low</td>
</tr>
<tr>
<td>Cytokine profiles</td>
<td>High</td>
<td>N/A</td>
<td>Mod. / Low</td>
</tr>
<tr>
<td>Tumor mutation burden (NGS)</td>
<td>Mod. / High</td>
<td>Mod. / High</td>
<td>Low</td>
</tr>
<tr>
<td>ELISPOT / Interferon-Gamma Release Assay (IGRA)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Mod. / Low</td>
</tr>
<tr>
<td>Gene expression signature (RNA-Seq)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Gene expression signature (NanoString)</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>Multiplex quantitative IHC (≥5 antibodies)</td>
<td>Low</td>
<td>Mod. / High</td>
<td>Low</td>
</tr>
<tr>
<td>Liquid biopsy for cfDNA / ctDNA</td>
<td>Low</td>
<td>Mod. / Low</td>
<td>Low</td>
</tr>
<tr>
<td>T-cell receptor repertoire analysis (NGS or PCR)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Liquid biopsy for CTCs</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

Share of Respondents: <20% >80%

- IHC is the only technology widely available in-house at both AMCs* and community hospitals / oncology practices:
  - Community practices generally only have access to IHC, and, to a lesser extent, ELISA, and, PCR platforms
- AMCs showed the greatest appetite for in-sourcing multiplex IHC, and gene expression analysis (either by RNAseq or NanoString)
- Stakeholders indicated that, despite in-house NGS access, TMB testing and liquid biopsies are likely to be sent to reference labs:
  - Community practices appear content to outsource all next-generation biomarker testing

~85% of cancer patients are diagnosed and treated in the community setting.

Note: * AMC = academic medical center
Sources: DeciBio interviews and analysis
Generally, stakeholders are not averse to outsourcing next-gen companion diagnostic testing, citing multiple reasons for favoring centralization.

Feedback on Testing Centralization / Decentralization

**Commentary Supporting Increasing Centralization (N = 10)**

- Drivers for Centralization:
  - Lack of in-house expertise (e.g., bioinformatics, interpretation, scoring)
  - Lack of test request volume
  - Saves time and money in near term

**Commentary Supporting Increasing De-centralization (N = 5)**

- Drivers for De-centralization:
  - Reduce turnaround time (TAT)
  - Preference for internal processes
  - Keeping control of sample
  - Less costly in the long run

**Interviewee Share**

- 66%
- 34%

- **Only AMCs are positioned to bring biomarker testing in-house**

- **TAT will need to be improved (from ~3 weeks to ~1 week) to drive rapid adoption**

**Future I/O CDx testing is increasingly likely to be conducted in a centralized setting**

Source: DeciBio Interviews and Analysis
The majority of biomarkers identified are for predictive and exploratory purposes; immune and response monitoring also comprise a material share of mentions.

Cumulative Distribution of Biomarker Testing by Purpose

<table>
<thead>
<tr>
<th></th>
<th>Predicting Rx Response</th>
<th>Immune Monitoring</th>
<th>Exploratory / Not Specified</th>
<th>Inclusion Criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>567</td>
<td>404</td>
<td>534</td>
<td>469</td>
<td></td>
</tr>
<tr>
<td>Percentage</td>
<td>22%</td>
<td>16%</td>
<td>21%</td>
<td>19%</td>
<td></td>
</tr>
</tbody>
</table>

- >40% of biomarker mentions are in the context of predicting response to therapy*
  - Phase 3 trials have disproportionately more biomarkers for inclusion criteria and predicting therapy response (54%), and few trials for immune / response monitoring (6%)

- Biomarkers for monitoring immune responses or the patient response to therapy comprise ~26% of biomarker mentions

- Multiple markers and technologies are being explored for immune monitoring assays
  - Immune cell populations and phenotypes (flow cytometry, sequencing)
  - Antigen-specific immune responses (Interferon-gamma release assays / ELISPOT assays)
  - Peripheral cytokine profiles (ELISA)
  - T-cell receptor repertoire analysis (sequencing, PCR)

Note: * Predictive markers include inclusion criteria markers and exploratory correlations of baseline markers to therapy response
Source: DeciBio BioMAP
Though immune monitoring is not currently used in routine clinical care, most stakeholders expect immune monitoring assays to become commonplace in clinical care in the next 5 – 7 years.

Likelihood of Routine Immune Monitoring in 5 Years (N = 15)

- **Highly Likely (N = 9)**
  - “…any assay would need to be validated against radiology, however, I would love to use a blood test that would allow me to reduce the number of scans…”
  - “…the difference between getting a results in 2 weeks vs. 3 months, which is when we do our first scan is huge, there’s a lot that we can happen in the first few weeks that I’d like to monitor…”
  - “…early and frequent monitoring would help me adjust my therapy strategy; I’d like to give monotherapies for 1L treatment, and add a combo therapy only if the initial immune response looks low …”

- **Somewhat Likely (N = 3)**
  - “…As the cost of these drugs goes up, especially for IO / IO combos, I can see payors pushing monitoring tests to identify non-responders earlier …”

- **Highly Unlikely (N = 3)**
  - “…Ultimately, the only thing that matters is tumor progression, which you will always need to measure by imaging, the molecular assay data isn’t there yet…”

- The majority of stakeholders expect to be conducting immune monitoring in the routine management of patients on immunotherapies in 5-7 years

- The primary drivers for immune monitoring testing are:
  - Informing the timing and frequency of radiographic imaging
  - Distinguishing between pseudo-progression and true progression; identifying hyperprogression
  - Managing adverse events
  - Adjusting treatment strategies

- Clinicians estimate immune monitoring would be performed every 2 - 4 weeks for the first 3-months post treatment, and every 8 - 12 weeks throughout the first year

- KOLs anticipate that payors would be open to reimbursing monitoring assays to limit the use of expensive immunotherapies / combinations in non-responsive patients (e.g., Kymriah model)
A high-level market analysis suggests that immune monitoring testing could represent an annual Dx market opportunity of ~$65 M in 2022, with an upside of up to ~$110 M based on adoption rates and technology utilization.

### High-Level Immune Monitoring Market Analysis

<table>
<thead>
<tr>
<th>Input</th>
<th>Assumptions (2022)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Case</td>
<td>Base Case</td>
</tr>
<tr>
<td>Incidence of metastatic cancer*</td>
<td>~1.7M</td>
<td></td>
</tr>
<tr>
<td>% treated with immunotherapies</td>
<td>~35%</td>
<td>~45%</td>
</tr>
<tr>
<td>% adoption of immune-monitoring</td>
<td>~20%</td>
<td>~35%</td>
</tr>
<tr>
<td># tests / patient</td>
<td>~4</td>
<td>~6</td>
</tr>
</tbody>
</table>

#### % testing volume by technology

<table>
<thead>
<tr>
<th>Technology</th>
<th>Low Case</th>
<th>Base Case</th>
<th>High Case</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow cytometry</td>
<td>~35%</td>
<td>~30%</td>
<td>~25%</td>
<td>Flow cytometry for peripheral blood cell population analysis, and ELiSA for cytokine analysis are anticipated to be most widely used for monitoring</td>
</tr>
<tr>
<td>ELISA</td>
<td>~35%</td>
<td>~30%</td>
<td>~25%</td>
<td></td>
</tr>
<tr>
<td>PCR</td>
<td>~5%</td>
<td>~7%</td>
<td>~10%</td>
<td>Sequencing, for T-cell receptor clonality analysis was also identified as promising, and represents a significant upside</td>
</tr>
<tr>
<td>Sequencing</td>
<td>~5%</td>
<td>~7%</td>
<td>~10%</td>
<td></td>
</tr>
<tr>
<td>Other*</td>
<td>~20%</td>
<td>~26%</td>
<td>~30%</td>
<td></td>
</tr>
</tbody>
</table>

#### $ / test by technology

<table>
<thead>
<tr>
<th>Technology</th>
<th>$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow cytometry</td>
<td>$10 – 15</td>
<td>Pricing assumptions reflect estimated manufacturer per-sample kit / reagent prices</td>
</tr>
<tr>
<td>ELISA</td>
<td>$10 – 15</td>
<td>Assumes a blend of IVD and LDT adoption (e.g., kits vs. ASR/RUO reagents), weighted towards LDTs</td>
</tr>
<tr>
<td>PCR</td>
<td>$20 – 30</td>
<td></td>
</tr>
<tr>
<td>Sequencing</td>
<td>$150 - 250</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>$50 – 100</td>
<td></td>
</tr>
<tr>
<td><strong>Total Market (2022)</strong></td>
<td>~$25 M</td>
<td>~$65 M</td>
</tr>
</tbody>
</table>

I/O immune monitoring is a meaningful market opportunity for Dx companies to consider.

Note: * Other includes ELISPOT, Luminex and other bead-based arrays, NanoString analysis, tetramer analyses, and various other assay types
Sources: WHO, CDC.gov, cancerresearchuk.org, DeciBio interviews and analysis
Based on our secondary and primary research, we have identified five key questions that diagnostic companies should consider when planning for the future of immuno-oncology diagnostics

Key Questions for Dx Companies

1. How do established cancer diagnostic technology companies (e.g., IHC, PCR-oriented) adapt to the increasing complexity and technological shifts for future I/O companion diagnostics?

2. How do Dx kit / instrument makers that rely on a distributed cancer Dx model fit into a landscape that may become increasingly service-oriented?

3. How can Dx companies position themselves to capitalize on the immune monitoring market opportunity?

4. How do “next-gen” biomarker technology companies differentiate and establish themselves as optimal CDx partners?

5. How do Dx companies prepare for the increasing integration of different classes of biomarkers (e.g., genomics, proteomics, cellomics) as well as other clinical and diagnostic information (e.g., radiology, clinical history, etc.)
Thank you for your time and attention – I am happy to answer any questions

Special Thanks To:

- Tom Fare and the PlanetConnect team
- Colleagues at DeciBio who contributed to this analysis
  - Colin Enderlein – Analyst
  - Pranay Madan – Data Product Manager
  - Stephane Budel – Partner
  - David Cavanaugh – Partner
- All stakeholders who participated in primary research

For more information about DeciBio and our Immuno-Oncology BioMAP, visit us at www.DeciBio.com
There are over 440 primary and secondary sponsors associated with the trials analyzed to-date; while the NCI is the top overall sponsor, industry players comprise the primary sponsors of I/O biomarker-driven trials

Summary of Trial-Sponsorship by Sponsorship Status for I/O-specific Biomarkers*

- Industry players account for ~39% of all primary sponsors of I/O clinical trials included in our analysis
- Overall, the top 25 sponsors are involved as a primary or secondary sponsor in ~50% of all I/O trials
- Excluding PD-L1 and non-I/O-specific markers, the leading sponsors of “next-gen” biomarkers include:
  - Roche / Genentech (focus on PD-L1+ TILs, TMB, GEP)
  - Novartis (focus on MSI, GEP, LAG3, and CD8+ TILs)
  - Merck (focus on GEP, MSI/dMMR, TILs)
  - AstraZeneca / MedImmune (focus on GEP, TILs, IFNγ)
- Trial analysis reveals differences in biomarker strategy: e.g., Merck participates in a broad number of trials as a secondary sponsor, while companies like Roche, and Novartis conduct most biomarker trials as primary sponsors

Note: * Excludes trials exploring solely PD-L1, as well as non I/O-specific biomarkers (e.g., HER2, ALK, EGFR, etc.)