UpRi (NaPi2b) Diagnostic Development Path

April 16, 2021
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Today’s Agenda

1. Background – Characteristics of an Optimal Immunohistochemistry (IHC) Diagnostic Assay

2. RoadMap to Commercial Dx Assay – Start with a Clinical Research Assay Evaluating Multiple Scoring Methods and Determine Predictive Ability of Biomarker

3. Selection of Scoring Method Optimal for Commercialization

4. Transition to a Commercial Assay in UPLIFT to Support Launch
The Optimal Diagnostic Assay is Robust, Predictive and Reproducible

**Robust**
- Dynamic range allows for distinctions to be made between lower and higher expressors

**Predictive**
- Biomarker positive patients enriched for response

- Stain Negative
- Stain Positive

  - 33% Respond with Biomarker
  - 20% Respond without Biomarker

**Reproducible**
- Clear guidelines on how to read assay
- Can be performed outside of a central lab
- Reads the same regardless of lab

Reads the Same in
- Athens, Greece
- Athens, NY
- Athens, GA
Strategy Designed to Deliver a Robust, Predictive and Reproducible Commercial Diagnostic Assay

Today’s Objective:
Describe Next Steps in Assay Development
Strategy Designed to Deliver a Robust, Predictive and Reproducible Commercial Diagnostic Assay

<table>
<thead>
<tr>
<th>Platform/Assay Validation</th>
<th>Preclinical</th>
<th>Phase I Clinical (Dose Escalation and Expansion)</th>
<th>UPLIFT Registration Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Methods Evaluated (Tumor Proportion Score (TPS), Intensity, H-score (TPS x Intensity), PS2+)</td>
<td></td>
<td>Single Robust, Reproducible Method</td>
<td></td>
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<tr>
<td>Preclinical Mouse Cutoff</td>
<td>Prelim Clinical Cutoff</td>
<td>Proposed Cutoff</td>
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<td></td>
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<td>Validate Cutoff</td>
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</table>
An IHC Assay is Comprised of a Sample, a Platform, a Stain, and a Scoring Method

Sample

Platform
QualTek TechMate

Stain

Brown Stain (DAB) Visualizes Target Protein

Blue Counterstain Delineates (Acidic) Cell Structures

Scoring Method

• IHC readout:
  – % cells expressing at a given intensity of 1+ or 2+ or 3+
Different Scoring Methods (H-score, TPS, PS2+) Combine Tumor Proportion and Intensity in Different Ways

\[ H = (1 \times \text{percent } “1+”) + (2 \times \text{percent } “2+”) + (3 \times \text{percent } “3+”) \] Accounts for intensity and proportion

TPS = Percent “1+” + Percent “2+” + Percent “3+” Accounts for proportion with any intensity above 0

PS2+ = Percent “2+” + Percent “3+” Accounts for proportion of only higher Intensity

We Have been exploring scoring methods to understand what matters most: proportion, intensity or the combination?

### Example Scores

<table>
<thead>
<tr>
<th>Intensity</th>
<th>H-score</th>
<th>TPS</th>
<th>PS2+</th>
</tr>
</thead>
<tbody>
<tr>
<td>33% 3+</td>
<td>~100</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>25% 2+, 50% 1+</td>
<td>100</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>100% 1+</td>
<td>100</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>
### Scoring Method Affects Reproducibility Across Readers and Labs

Numerical values are assigned according to brown intensity, but the reader is required to cut the data along a continuum.

<table>
<thead>
<tr>
<th>Scoring Method</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H-Score</strong></td>
<td>$H = (1 \times \text{percent } &quot;1+&quot;) + (2 \times \text{percent } &quot;2+&quot;) + (3 \times \text{percent } &quot;3+&quot;)$</td>
</tr>
<tr>
<td><strong>Tumor Proportion Score</strong></td>
<td>$\text{TPS} = \text{Percent } &quot;1+&quot; + \text{Percent } &quot;2+&quot; + \text{Percent } &quot;3+&quot;$</td>
</tr>
<tr>
<td><strong>Tumor Proportion Score 2+ (PS2+)</strong></td>
<td>$\text{PS2+} = \text{Percent } &quot;2+&quot; + \text{Percent } &quot;3+&quot;$</td>
</tr>
</tbody>
</table>
IHC Companion Diagnostic Assays are Common and Use Different Scoring Methods

Examples of Approved Diagnostics

- **Scored by Tumor Proportion Score**
  - **PD-L1**
    - TPS >1%
    - TPS >50%

- **Scored Based on Intensity**
  - **HER-2/neu**
    - 1+, 2+, 3+
The Optimal Diagnostic Assay is Robust, Predictive and Reproducible

Robust
- Dynamic range allows for distinctions to be made between lower and higher expressors

Predictive
- Biomarker positive patients enriched for response

Reproducible
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Reads the Same in
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Sensitivity
- 33% Respond with Biomarker
- 20% Respond without Biomarker

Stain Negative
Stain Positive
Responder
Mouse PDX Models Used to Calibrate NaPi2b Research Assay with Broad Dynamic Range

Robust

Change in Tumor Volume

- H-score 290
- Increasing H-score
- H-score 0
Our NaPi2b Assay Has a Broad Dynamic Range Across Clinical Samples Using H-score or TPS

- Patients enrolled in the UpRi Phase I study have a broad range of NaPi2b expression levels.
- Only a few have zero NaPi2b expression, consistent with lineage marker.
- Tissue bank samples demonstrate similar broad dynamic range.
- Broad dynamic range allows the assay to distinguish high expression from low expression using either H-score or TPS.

Robust
TPS is a Component of H-Score, is Correlated with H-Score and Offers Similar Prevalence

Robust

TPS ≥ 75% is 62% of samples tested

H-score ≥ 110 is 68% of samples tested
The Optimal Diagnostic Assay is Robust, Predictive and Reproducible

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Biomarker positive patients enriched for response
- Stain Negative
- Stain Positive
- Responder

33% Respond with Biomarker
20% Respond without Biomarker
In the Clinic, Higher NaPi2b Expression by H-Score Selected for Enhanced Response

<table>
<thead>
<tr>
<th></th>
<th>All (n = 47)</th>
<th>Higher NaPi2b (n = 31)</th>
<th>Lower NaPi2b (n = 13)</th>
<th>NaPi2b Not Yet Determined (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR; n(%)</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR; n(%)</td>
<td>11 (23)</td>
<td>8 (26)</td>
<td>2 (15)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>SD; n(%)</td>
<td>19 (40)</td>
<td>13 (42)</td>
<td>5 (38)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>ORR; n (%)</td>
<td>13 (28)</td>
<td>10 (32)</td>
<td>2 (15)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>DCR; n (%)</td>
<td>32 (68)</td>
<td>23 (74)</td>
<td>7 (54)</td>
<td>2 (67)</td>
</tr>
</tbody>
</table>

- Higher NaPi2b Expression defined as at or above the lowest H-score at which response was observed in dose escalation (H-110)

Data as of December 3, 2020
TPS\(\geq75\) Selects for Enhanced Response as Well as H-score 110

| CR; n(%)   | 2 (4) | 2 (8) | 0 | 0 |
| PR; n(%)  | 11 (23) | 8 (31) | 2 (11) | 1 (33) |
| SD; n(%)  | 19 (40) | 11 (42) | 7 (39) | 1 (33) |
| ORR; n (%) | 13 (28) | 10 (39) | 2 (11) | 1 (33) |
| DCR; n (%) | 32 (68) | 21 (81) | 9 (50) | 2 (67) |

Data Cutoff: December 3, 2020
Unique Advantages of Dolaflexin Platform have Implications for Scoring Methodology

- High DAR means each internalization delivers more payload. Therefore, intensity of expression may be less important than proportion of expression
- Controlled Bystander effect means not all cells need to express

Based on Our ADC Technology, Tumor Proportion Score (TPS) is Similarly Predictive of Enriched Response
The Optimal Diagnostic Assay is Robust, Predictive and Reproducible

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**Athens, NY**

**Athens, GA**
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H-Score

\[ H = (1 \times \text{percent } "1+") + (2 \times \text{percent } "2+") + (3 \times \text{percent } "3+") \]

Tumor Proportion Score

\[ \text{TPS} = \text{Percent } "1+" + \text{Percent } "2+" + \text{Percent } "3+" \]

Tumor Proportion Score 2+ (PS2+)

\[ \text{PS2+} = \text{Percent } "2+" + \text{Percent } "3+" \]

Numerical values are assigned according to brown intensity, but the reader is required to cut the data along a continuum.

Reproducible

Reader Must Distinguish Blue from Beige from Tan from Brown

Reader Must Distinguish Blue from any Brown

Reader Must Distinguish Tan from Beige
Leica Biosystems is our Commercial Diagnostic Partner

- ~5000 clinical BOND instruments placed globally
- 2nd largest automated stainer installed base worldwide
- Presence in major IHC reference labs and top 50 cancer centers
- Clinical Portfolio
  - >400 IVD products
  - >190 CE mark in Europe
  - ~150 FDA registered/cleared/approved
  - PMA-approved HER2 Oracle CDx
  - ~50 IVD in China

Reproducible
UPLIFT: Single-Arm Registration Strategy in Platinum-Resistant Ovarian Cancer

Patient Population:
Enrolling Regardless of NaPi2b Expression

Inclusion Criteria:
Platinum-Resistant Ovarian Cancer
1 – 4 Prior Lines
Patients with Baseline Peripheral Neuropathy

Exclusion Criteria:
1 – 2 Prior Lines Bev-naïve
Primary Platinum-Refractory Disease

Global: US, Europe, Australia, Canada
Dose: 43 mg/m² q4w
Amendment to Current Protocol

Primary Endpoint:
Confirmed ORR in high NaPi2b (N = ~100)

Key Secondary Endpoint:
Confirmed ORR in overall population (N = up to 180 including 100 high NaPi2b)

Other Secondary Endpoints:
• Duration of Response
• Safety

Prospectively-defined retrospective analysis seeks to validate NaPi2b biomarker cutoff with proposed commercial assay
Summary

- Followed a roadmap to establish a robust, predictive and reproducible commercial diagnostic assay

- Established a clinical research assay with a broad dynamic range that demonstrated that selection by NaPi2b expression enhanced response
  - H-Score is a combination of Tumor Proportion Score (TPS) and Intensity Score
  - NaPi2b Expression by H-Score $> 110$ and by TPS $> 75$ similarly enrich for response

- To support launch, a commercial assay has been developed using the TPS methodology
  - Robust, reproducible platform widely available in hospital and reference labs
  - UPLIFT is designed to validate predictiveness of proposed commercial diagnostic assay
# Goals and Anticipated Milestones for 2021

<table>
<thead>
<tr>
<th>Upifitamab Rilsodotin UpRi (XMT-1536)</th>
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<tbody>
<tr>
<td><strong>Q1 2021:</strong> Initiate UPLIFT single-arm registration strategy as amendment</td>
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<tr>
<td><strong>Q3 2021:</strong> Initiate UPGRADE combination dose escalation umbrella study</td>
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<td><strong>2H 2021:</strong> Report updated interim data from NSCLC expansion cohort</td>
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<tr>
<td><strong>2H 2021:</strong> Report dose escalation data</td>
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<td><strong>Q4 2021:</strong> Outline further development path</td>
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<th>XMT-1660</th>
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<tbody>
<tr>
<td><strong>Q4 2021:</strong> Complete IND-enabling studies to initiate Phase I dose escalation in 2022</td>
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<tr>
<td><strong>Q4 2021:</strong> Complete IND-enabling studies to initiate Phase I dose escalation in 2022</td>
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<td><strong>Q4 2021:</strong> Disclose target</td>
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<th>Corporate</th>
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<tr>
<td><strong>Continue to leverage proprietary platforms to expand pipeline</strong></td>
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<tr>
<td><strong>Proactively evaluate potential for collaborations that maximize value</strong></td>
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Accelerating ADC Innovation

...because patients are waiting