Drug-device co-development in the era of precision medicine:

Approval of Tafinlar and Mekinist combination therapy and next generation sequencing companion diagnostic in non-small cell lung cancer

Allison Florance, Shunguang Wang, Anthony D’Amelio Jr., and Tomas Haas

EFSPI: 6 October 2017
What is Precision Medicine?

- Deliver **right drug** to **right patient** at **right dose** at **right time**

**FROM**

"One Size Fits All"

**TO**

"Personalized Medicine"

Precision Medicine Leverages

- Tumor Biology
- Biomarkers (PD, Predictive, Imaging)
- Translational Medicine

**To Deliver**

- Better Patient Selection
- Better Patient Outcomes (Efficacy/Safety)

**Resulting In**

- More Efficient Clinical Dev
- Improved Benefit / Risk
- Stronger Value Proposition (for PM Stakeholders)
Phase II Study BRF113928: BRAF V600E NSCLC
Dabrafenib Monotherapy / Dabrafenib + Trametinib Combination Trial

**Cohort A (monotherapy), planned n = 60**
- Stage IV NSCLC
  - BRAF V600E
  - ECOG PS 0-2
  - ≥ 1 Platinum-based chemotherapy
- Dabrafenib 150 mg BID
- Stage 1 n = 20
- Expansion n = 20

**Cohort B (combination D + T), planned n = 40**
- Stage IV NSCLC
  - BRAF V600E
  - ECOG PS 0-2
  - 1-3 Prior treatments (≥ 1 platinum-based chemotherapy)
- Dabrafenib 150 mg BID, Trametinib 2 mg QD
- Stage 1 n = 20
- Expansion n = 20

**Cohort C (combination D + T first line), planned n = 25**
- Stage IV NSCLC
  - BRAF V600E
  - ECOG PS 0-2
  - No prior treatment
- Dabrafenib 150 mg BID, Trametinib 2 mg QD
- n = 25

**Statistical assumptions:**
- **2L Cohort A:** Primary, Original (n=40) 92.6% power to detect 30% ORR. Per FDA guidance expanded to 60 pts, ORR of 30% @95% CI (18.9%, 43.2%).
  - Secondary: DoR, PFS, OS, safety and tolerability, pop PK
- **2L Cohort B:** Primary, 92.2% power to detect 55% ORR (n = 40)
  - Secondary: DoR, PFS, OS, safety and tolerability, pop PK
- **1L Cohort C:** Primary, 92.2% power to detect 60% ORR (n = 25)
  - Secondary: DoR, PFS, OS, safety and tolerability, pop PK

**Primary endpoint for each cohort:**
- investigator-assessed ORR

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Oncology

EFSPI presentation| October 8, 2017| Allison Florance| Confidential
~2% BRAF mutations in NSCLC

Europe
All histology (Biomarkers France) (n = 17,664)

- Full WT 15%
- EGFR 11%
- KRAS 29%
- Unknown 35%
- BRAF 2%
- HER2 1%
- PIK3CA 2%
- ALK 5%

US
Adenocarcinoma (Lung Cancer Mutation Consortium) (n = 733)

- No oncogenic driver detected 36%
- EGFR (sensitizing) 17%
- EGFR (other) 4%
- HER2 3%
- KRAS 25%
- Mut >1 gene 3%
- MET 1%
- NRAS 1%
- MEK1 <1%
- ALK 8%
- PIK3CA 1%
- BRAF 2% (V600E 1.6%)


Oncology
What is a companion diagnostic?

“An in vitro diagnostic device (IVD) provides information that is essential for the safe and effective use of a corresponding therapeutic product”.

- Identifying patients most likely to benefit from therapy
- Identifying patients likely to be at increased risk of serious adverse reactions as a result of therapy
- Monitoring therapeutic response for the purpose of adjusting treatment (schedule, dose, discontinuation) to achieve improved safety or effectiveness

FDA assesses, through premarket approval (PMA), the safety and effectiveness of the IVD companion diagnostic device

- Analytical validation: precision, accuracy, detection capability....
- Clinical validation: pivotal drug-device clinical trial
- Submission to Center for Devices and Radiological Health (CDRH)
What is PMA IVD

- Total System (Not Just Assay or Biomarker)
  - Sample collection devices, transport, stability
  - Sample processing and assay reagents/disposables
  - Hardware and software

- IVDs have to be compliant with:
  - Specific Labeling Requirements
  - 510(k)/PMA
  - Registration & Listing
  - Import/Export regulations
  - IDE principles
Oncomine Dx Target Test

• Collaboration with Thermo Fisher and Pfizer.

• First NGS for multiple indications in NSCLC

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>Targeted therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>BRAF V600E</td>
<td>TAFINALAR (dabrafenib) in combination with MEKINIST (trametinib)</td>
</tr>
<tr>
<td>ROS1</td>
<td>ROS1 fusions</td>
<td>XALKORI (crizotinib)</td>
</tr>
<tr>
<td>EGFR</td>
<td>L858R, Exon 19 deletions</td>
<td>IRESSA (gefitinib)</td>
</tr>
</tbody>
</table>

• Detects actionable mutations in one test which reduces turnaround time, delay of target treatment, and avoids hierarchical testing

• PMA includes analytical validation studies and clinical bridging study
Efficacy in BRAF V600E populations (ITT and BRAFV600E)

- ORR in BRAF V600E centrally confirmed population is consistent with ORR in ITT

<table>
<thead>
<tr>
<th>Population</th>
<th>Investigator assessment</th>
<th>IRC assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responder n (%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Combination 2L+ ITT (N=57)</td>
<td>38 (66.7)</td>
<td>(52.9, 78.6)</td>
</tr>
<tr>
<td>BRAF V600E centrally confirmed (N=22)</td>
<td>16 (72.7)</td>
<td>(49.8, 89.3)</td>
</tr>
<tr>
<td>Combination 1L ITT (N=36)</td>
<td>22 (61.1)</td>
<td>(43.5, 76.9)</td>
</tr>
<tr>
<td>BRAF V600E centrally confirmed (N=23)</td>
<td>14 (60.9)</td>
<td>(38.5, 80.3)</td>
</tr>
</tbody>
</table>
Max. Target Lesion Reduction

From Baseline Sum of diameters by Best Confirmed Response by Investigator

Combination 2\textsuperscript{nd} line plus

Combination 1\textsuperscript{st} line

* Maximum change from baseline was 0%
Some patients were evaluated as PD due to new lesion, despite the target lesions were SD
# Large scale analytical validation studies

- 32 validation studies for hundreds of variants

<table>
<thead>
<tr>
<th>ID</th>
<th>Study</th>
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<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Analytical accuracy</td>
<td>17</td>
<td>External panel reproducibility</td>
</tr>
<tr>
<td>2</td>
<td>Limit of Blank</td>
<td>18</td>
<td>External sample processing reproducibility</td>
</tr>
<tr>
<td>3</td>
<td>Limit of Detection</td>
<td>19</td>
<td>Tissue heterogeneity</td>
</tr>
<tr>
<td>4</td>
<td>DNA/RNA input</td>
<td>20</td>
<td>Extraction method equivalency (DNA, RNA)</td>
</tr>
<tr>
<td>5</td>
<td>Tissue input</td>
<td>21</td>
<td>Specimen equivalency</td>
</tr>
<tr>
<td>6</td>
<td>Tumor content</td>
<td>22</td>
<td>Workflow tolerances</td>
</tr>
<tr>
<td>7</td>
<td>Inclusivity/Cross-reactivity</td>
<td>23</td>
<td>Tissue Fixation</td>
</tr>
<tr>
<td>8</td>
<td>Endogenous Interference</td>
<td>24</td>
<td>Contamination</td>
</tr>
<tr>
<td>9</td>
<td>Exogenous interference</td>
<td>25</td>
<td>Stability</td>
</tr>
<tr>
<td>10</td>
<td>Anti-microbial testing</td>
<td>26</td>
<td>Shelf-life stability</td>
</tr>
<tr>
<td>11</td>
<td>External panel reproducibility</td>
<td>27</td>
<td>Designated hold times in-use stability</td>
</tr>
<tr>
<td>12</td>
<td>External sample processing reproducibility</td>
<td>28</td>
<td>Kit lot interchangeability</td>
</tr>
<tr>
<td>13</td>
<td>Precision</td>
<td>29</td>
<td>Sample stability (extracted DNA and RNA)</td>
</tr>
<tr>
<td>14</td>
<td>Tissue heterogeneity</td>
<td>30</td>
<td>Stored slide stability</td>
</tr>
<tr>
<td>15</td>
<td>Extraction method equivalency (DNA, RNA)</td>
<td>31</td>
<td>Stored block stability</td>
</tr>
<tr>
<td>16</td>
<td>Specimen equivalency</td>
<td>32</td>
<td>Transport stability</td>
</tr>
</tbody>
</table>
Bridging Study for MEK-TAF

• Primary objectives
  – Concordance between CTA and CDx
  – Efficacy in CDx(+) patients in Cohort B and Cohort C
## Challenges and Mitigation Strategies

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CDx development delayed</strong></td>
<td>- Alerted the regulatory authorities, and kept them informed of the progress</td>
</tr>
<tr>
<td>- due to GSK-Novartis Oncology acquisition</td>
<td>- Staggered submissions worldwide depending on need for CDx</td>
</tr>
<tr>
<td><strong>Different data structures</strong></td>
<td>- Maintained constant contact between CDx and clinical teams</td>
</tr>
<tr>
<td>- CDx data in Novartis standards</td>
<td>- Ensure delivery of CDx related data was in appropriate formats dependent on specific analysis</td>
</tr>
<tr>
<td>- Clinical data in GSK standards</td>
<td></td>
</tr>
<tr>
<td><strong>Sequential study design</strong></td>
<td>- Engaged HAs before 1st patient was enrolled in combination cohorts</td>
</tr>
<tr>
<td>- Cohorts were not randomized and were not run in parallel</td>
<td>- Emphasized the rarity of BRAF V600E NSCLC</td>
</tr>
</tbody>
</table>
### Challenges and Mitigation Strategies

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<tr>
<td><strong>Missing CDx results</strong></td>
<td>- Propensity score, t-test, Fisher exact test to check covariate imbalance</td>
</tr>
<tr>
<td>- Some patients had no leftover specimen for re-testing</td>
<td>- Logistic regression to identify covariates correlated with CDx results and clinical outcome</td>
</tr>
<tr>
<td>- Some specimen did not yield valid CDx results</td>
<td>- Multiple imputation to impute missing CDx results</td>
</tr>
<tr>
<td><strong>Missing CTA(-) results</strong></td>
<td>- Sensitivity analysis assuming different negative percent agreement (NPA)</td>
</tr>
<tr>
<td>- No CTA (-) patients enrolled in original trial</td>
<td></td>
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</tbody>
</table>
Conclusions

• In BRAF V600E mutation-positive metastatic NSCLC, dabrafenib in combination with trametinib demonstrated:
  – Clinically meaningful efficacy
    – High and durable response rate
    – Overall efficacy consistent among ITT and BRAF V600E populations and also consistent between IRC and Investigator assessment
    – Results demonstrate clinical efficacy in CDx(+) patients
  – Manageable safety profile

• The clinical and CDx data from BRF113928 support the indication of dabrafenib plus trametinib as a treatment for advanced or metastatic NSCLC patients with BRAF V600E mutation plus the approval of the Oncomine NGS test
Thank you