MyPathway Study:
A novel precision oncology multiple basket trial

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Disclosures

I have the following financial relationships to disclose:
Stockholder in: Roche
Employee of: Genentech

I will discuss the following off label use and/or investigational use in my presentation:
Trastuzumab and Pertuzumab
Vemurafenib and Cobimetinib
Vismodegib
Erlontinib
Alectinib
Atezolizumab
Questions

• Why study approved drugs in non-approved tumors?
• What are efficient and effective ways to perform these studies?
• What results has MyPathway shown to date?
• What lessons have been learned, and questions have been raised, from MyPathway?
• What are the future directions and impact of MyPathway and similar studies?
Rationale: studying targeted therapies in other tumors

Tumor testing
↓
Identification of “driver” molecular alterations
↓
Need for new treatment options and trial designs

“The molecular alterations that define a tumor may be as relevant, if not more so, than the histopathology that would historically have been used to classify a tumor and direct therapeutic options.”¹

“Basket studies are broadening the population of patients eligible to receive these drugs.”²

2. Hyman D, MSKCC Blog 2015
Benefits of basket trials: efficiency, science, access

**Why DESIGN?**

- Efficiency by studying multiple tumor types simultaneously
- Potential Signals of Activity
- Research on Rare Cancers

**Why ENROLL?**

- Patient participation and contributions
- Access to Targeted Therapies
- Evidence beyond case reports

Ref: Hunter DJ et al., NEJM 2015; Cunnan KM et al., JCO 2017
### Design Considerations

**Sample-size and futility analysis:**
Simon two-stage design

*How and when to stop enrollment in case of lack of efficacy?*

**Assessment:**
How to assess efficacy without a common control group?

**Randomization:**
When should randomization be considered?

### Analytical Considerations

**Are all mutations created equally?:**
Lumping / dividing different molecular alterations

**Alternatives:**
Alternatives to analyzing as single arm trials

**Tumor Site of Origin:**
- Anatomical site and molecular alteration both important
- Consider adaptive designs and subgroup analyses within tumor cohorts
Overall Inclusion Criteria: refractory, metastatic solid tumors; any CLIA lab test; age over 17; ECOG PS 0-2; measurable or evaluable disease

Overall target accrual: 500
Primary endpoint: ORR
Secondary endpoints: PFS, OS, CBR

Phase IIa • NCT02091141 • MyPathway
An Open Label Phase IIa Study Evaluating Trastuzumab/Pertuzumab, Erlotinib, Vemurafenib/Cobimetinib, Vismodegib, Alectinib and Atezolizumab in Patients Who Have Advanced Solid Tumors With Mutations or Gene Expression Abnormalities Predictive of Response to One of These Agents
Enrolling diverse tumor types and alterations

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>HER2</th>
<th>BRAF</th>
<th>Hedgehog Pathway</th>
<th>EGFR</th>
<th>Total</th>
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<tbody>
<tr>
<td>Lung, non–small-cell</td>
<td>30</td>
<td>21</td>
<td>3</td>
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<td>54</td>
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<tr>
<td>Colorectal</td>
<td>40</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>42</td>
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<tr>
<td>Biliary</td>
<td>11*</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>15</td>
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<tr>
<td>Ovary</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>14</td>
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<tr>
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<tr>
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<td>13</td>
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<tr>
<td>Breast</td>
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<td>1</td>
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<td>Small intestine</td>
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<td>6</td>
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<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
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<tr>
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<td>3</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Other (21 tumor types)</td>
<td>20</td>
<td>9</td>
<td>10</td>
<td>5</td>
<td>44</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>151 (66%)</strong></td>
<td><strong>49 (21%)</strong></td>
<td><strong>21 (9%)</strong></td>
<td><strong>9 (4%)</strong></td>
<td><strong>230</strong></td>
</tr>
</tbody>
</table>

NOTE. N = 230.
Promising data from MyPathway

**HER2 amplified / overexpressing CRC**:  
- 38% ORR overall; 50% CBR; DOR = 10 months  
- Superior efficacy in KRAS-WT tumors: 52% ORR; 68% CBR; DOR = 10 months  

**HER2 amplified / overexpressing salivary cancer**:  
- 71% ORR; 86% CBR; DOR = 9 months  

**HER2 amplified / overexpressing bladder cancer**:  
- 33% ORR; 56% CBR; DOR = 6 months  

**HER2 amplified / overexpressing biliary cancer**:  
- 38% ORR; 75% CBR; DOR = 3 months  

**BRAF V600E NSCLC**:  
- Results with vemurafenib monotherapy: 43% ORR; 57% CBR; DOR = 5 months

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1 Hurwitz et al, ASCO-GI 2017; 2 Kurzrock et al, ASCO 2017; 3 Bryce et al, ASCO-GU 2017; 4 Javle et al, ASCO-GI 2017; 5 Hainsworth et al, ASCO 2017
Results: HER2-Amplified / Overexpressing mCRC

Percentage Change from Baseline in Target Tumor Diameter

Best percent change in target lesion size in patients with HER2-amplified/overexpressing\(^a\) mCRC (n=34)

\[
\begin{align*}
38\% \text{* ORR} \\
(13 \text{ out of 34}) \text{ in all HER2-amplified/ overexpressed}\# \text{ cases}
\end{align*}
\]

\[
\begin{align*}
52\% \text{* ORR} \\
(13 \text{ out of 25}) \text{ in KRAS wild type cases}
\end{align*}
\]

* Data for HER2 amplification/ overexpression (excludes patient with mutated HER2)
\(^a\) HER2-positive includes HER2-amplification/overexpression
\# Data irrespective of KRAS mutation

Ref: Hurwitz et al., ASCO GI 2017 and Hainsworth et al., JCO 2018

mCRC=Metastatic colorectal cancer; PD= Progressive disease; PR= Partial response; SD= Stable disease; KRAS = proto-oncogene K-Ras; ORR = Overall Response Rate
HER2-Amplified / Overexpressing mCRC PFS

Median PFS 5.7 months in KRAS wild-type pts

Median PFS 1.4 months in KRAS mutated pts

Hurwitz et al., ASCO GI 2017
Median OS 14.0 months in KRAS wild-type pts

Median OS 5.0 months in KRAS mutated pts

HER2-Amplified / Overexpressing mCRC OS

Hurwitz et al., ASCO GI 2017
Results: salivary cancer

Best percent change from baseline in target lesion size in patients with HER2-positive or Hh-mutated salivary gland cancer^a^

a"Percent change from baseline" represents the maximum reduction/minimum increase in the target lesion size from baseline.

bPatient had a 100% decrease in target lesion size, but had a remaining non-target lesion.

HER2, human epidermal growth factor receptor 2; Hh, Hedgehog; PR, partial response; PTCH-1, patched homolog-1; SD, stable disease.

Kurzrock et al., ASCO 2017
Best percent change in target lesion size in patients with HER2-amplified/overexpressing or HER2-mutated mUC (n=10)\textsuperscript{a}

\textsuperscript{a}Two patients with clinical disease progression were excluded from this plot. One patient did not have a post-baseline tumor assessment, and 1 had an incomplete post-baseline assessment. \textsuperscript{b}“Percent change from baseline” represents the maximum reduction/minimum increase in the target lesion size from baseline.

CR, complete response; HER2, human epidermal growth factor receptor 2; mUC, metastatic urothelial cancer; PD, progressive disease; PR, partial response; SD, stable disease.
Results: HER2+ biliary cancer

Best percent change from baseline in target lesion size in patients with HER2-positive metastatic biliary cancer (n=11)

* indicates patients had mutated HER2.

"Percent change from baseline" represents the maximum reduction/minimum increase in the sum of diameters of target lesion from baseline. Patients with at least a 30% decrease in target lesion size qualify for PR. Patients with least a 20% increase in target lesion size, or the appearance of one or more new lesions, qualify for PD.

HER2, human epidermal growth factor receptor 2; PD, progressive disease; PR, partial response; SD, stable disease.

Javle et al., ASCO GI 2017
Results: BRAF+ NSCLC

MyPathway enrolled V600 (n=14) and non-V600 (n=7) BRAF+ pts

- ORR 29% (6/21) in all BRAF+ pts
- ORR 43% (6/14) in V600 BRAF+ pts

+ = ongoing treatment
V = V600 mutated pt

Hainsworth et al., JCO 2018
MyPathway enrolled V600 (n=14) and non-V600 (n=7) BRAF+ pts

**ORR 29% (6/21)**
- in all BRAF+ pts

**ORR 43% (6/14)**
- In V600 BRAF+ pts

+ = ongoing treatment
V = V600 mutated pt

MyPathway now limits BRAF arm to V600 mutations only
Lessons learned and questions raised

- Targeted therapy can be effective in multiple tumor types
- Molecular alterations and tumor type both matter
- Consider co-mutations (KRAS) and different mutations (BRAF V600) in analysis; follow the science & prioritize
- Separate analyses for HER2 mutations & amplifications
- Pros and cons to local lab (vs. central lab)
- Overarching protocol allows for adding or closing baskets and therapies

- When and how can “tumor agnostic” be determined?
- How will regulators and payors respond to new precision oncology paradigms?
Future directions

• **Larger studies** of specific altered tumor type

• **Meaningful data at scale** may support **combining data** from multiple sources

• **Companion diagnostic** opportunities and challenges

• **Evidence guidelines**

• **Regulatory** guidance and documents
Potential impact

MyPathway and other similar studies could possibly:

- **Improve options** for patients
- **Provide meaningful data** in rare cancers
- **Innovate** study design and biomarker exploration
- **Validate** biomarkers in tumor/blood
- **Drive speed & agility** of drug evaluation and access
- Lead to truly **Personalized Oncology** care
Thank You!