Challenges in Distinguishing Clinical Signals to Support Development Decisions: Case Studies

David Feltquate MD, PhD
Head of Early Clinical Development, Oncology
Bristol-Myers Squibb, Princeton, NJ
Challenges in Distinguishing Clinical Signals to Support Development Decisions: Case Studies

- What clinical features are associated with a true signal
- What are potential pitfalls
- Case studies
  - Monotherapy
    - Big Signal
    - False Negative
    - Biomarker-enriched
  - Combinations
Case Study 1: Big Signal
PD-1/PD-L1 Pathway

- PD-1/PD-L1 checkpoint pathway important for T-cell inhibition; postulated to be important pathway for tumor immune evasion
- Inhibitors of the pathway lead to T-cell activation
- 20-30% ORR in previously treated MEL (~100 pts), RCC (~30 pts), and NSCLC (~100 pts)
- Durable responses; Pseudoprogression
Big signal led to multiple Phase 3 studies with a variety of PD-1/PD-L1 agents confirming benefit in several tumor types:

- NSCLC (nivolumab, pembrolizumab, atezolizumab)
- Melanoma (pembrolizumab, nivolumab)
- RCC (nivolumab)
- SCCHN (nivolumab)
- Bladder (pembrolizumab)
- Gastric (nivolumab)

...and meaningful benefit* in many tumor types with single arm data:
- SCCHN (pembrolizumab)
- Bladder (atezolizumab, nivolumab, durvalumab)
- Hodgkins (nivolumab, pembrolizumab)
- MSI-H CRC (pembrolizumab)
- Merkel Cell (avelumab)

*FDA approval or Breakthrough Status
Elotuzumab is an immunostimulatory monoclonal antibody that recognizes SLAMF7 (CS-1), a protein highly expressed by myeloma and natural killer cells\(^1\). Elotuzumab causes myeloma cell death potentially via a dual mechanism of action\(^2\).

\(\text{ADCC} = \text{antibody-dependent cell-mediated cytotoxicity; SLAMF7 = signaling lymphocytic activation molecule F7}\)
Case Study 2a: False Negative Signal
Single Agent Elotuzumab in Multiple Myeloma

- Study 1701: Phase 1 dose escalation study of single agent elotuzumab
- No objective responses were observed; Stable disease observed in 9 of 34 patients (26.5%)

- Elotuzumab added to lenalidomide and bortezomib in separate Phase 1 studies
- Led to Confirmatory Phase 3 study (ELOQUENT-2)

### Maximum Percent Reduction in Serum M Protein - Study 1703

1. Richardson PG et al. *Blood* 2014;124:302
ELOQUENT-2 demonstrated clinical benefits of E-Ld compared with lenalidomide and dexamethasone (Ld) alone.

Case Study 2b: False Negative Signal
Single agent PD-1 inhibition in Multiple Myeloma

- Phase 1 study of nivolumab in several hematologic malignancies (CA209-039)
- Single agent nivolumab active in HL, FL, DLBCL, T-cell lymphoma
- No responses in Myeloma

<table>
<thead>
<tr>
<th></th>
<th>Objective Response Rate, n (%)</th>
<th>Complete Responses, n (%)</th>
<th>Partial Responses, n (%)</th>
<th>Stable Disease n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Cell Lymphoma* (n=29)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>8 (28)</td>
<td>2 (7)</td>
<td>6 (21)</td>
<td>14 (48)</td>
</tr>
<tr>
<td>(n=10)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Diffuse Large B-Cell</td>
<td>4 (36)</td>
<td>1 (9)</td>
<td>3 (27)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Lymphoma (n=11)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-Cell Lymphoma† (n=23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycosis Fungoides</td>
<td>4 (17)</td>
<td>0 (0)</td>
<td>4 (17)</td>
<td>10 (43)</td>
</tr>
<tr>
<td>(n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral T-Cell</td>
<td>2 (15)</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Lymphoma (n=5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Myeloma (n=27)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>18 (67)</td>
</tr>
<tr>
<td>Primary Mediastinal B-Cell</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Lymphoma (n=2)</td>
<td></td>
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</tr>
</tbody>
</table>

*Includes other B-cell lymphoma (n=8)
†Includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)
Case Study 2b: False Negative Signal
PD-1 agent in Multiple Myeloma

A Phase II Study of Pembrolizumab, Pomalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma
Ashraf Badros, Mehmet Kocoglu, Ning Ma, Aaron Rapoport, Emily Lederer, Sunita Philip, Patricia Lesho, Cameron Dell, Nancy Hardy, Jean Yared, Olga Goloubeva and Zeba Singh

<table>
<thead>
<tr>
<th></th>
<th>All N=27</th>
<th>Double refractory N=20</th>
<th>High risk cytogenetics N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥ PR), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sCR</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>VGPR</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>8 (30%)</td>
<td>6 (30%)</td>
<td>5 (42%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>3 (10%)</td>
<td>3 (15%)</td>
<td>1 (8%)</td>
</tr>
</tbody>
</table>

Key Lesson in both Case Studies:
Some drugs have little single agent activity but are additive or synergistic when combined with drugs targeting other mechanisms

• Confirmation of signal currently under evaluation with several PD-1/PD-L1 agents
Case Study 3: Biomarker-based Signal Anti-PD-1 treatment in patients with MSI-H

- Phase 1 Single Ascending Dose study
- 3 long-term responders; MEL, RCC, and CRC
- CRC patient identified later as MSI-H
- MSI-H (mismatch repair defect) associated with very high mutational load and TILs

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>No. of Patients</th>
<th>Total No. of Doses</th>
<th>Best Response (duration in months)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>0.3</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>21</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>27</td>
<td>2</td>
</tr>
</tbody>
</table>

*CR and PR by Response Evaluation Criteria in Solid Tumors 1.0 criteria.

Abbreviations: N/A, not applicable; MXR, mixed response defined as regression in some lesions but concomitant progression in others; CR, complete response; PR, partial response.

Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody

Evan J. Lipson¹, William H. Sharman¹, Charles G. Drake¹, Ira Wollner⁶, Janis M. Taube²,³, Robert A. Anders⁴, Haiying Xu⁵, Sheng Yao¹, Alice Pons¹, Lieping Chen¹,³, Drew M. Pardoll¹, Julie R. Brahmer¹, and Suzanne L. Topalian⁶

Published Online First on November 20, 2012, DOI: 10.1158/1078-0432.CCR-12-2625

Clinical Cancer Research
Case Study 3: Biomarker-based Signal Anti-PD-1 treatment in patients with MSI-H

JHU Investigator-sponsored Phase 2a study in MSI-H and MSS CRC
Pembrolizumab

CA209-142: Phase 2 study in previously treated metastatic MSI-H CRC
Nivolumab

A Progression-free Survival in Cohorts with Colorectal Cancer

- No. at Risk
  - Mismatch repair-deficient: 11, 8, 6, 2, 0, 0
  - Mismatch repair-proficient: 21, 2, 1, 0, 0

P<0.001 by log-rank test

- Off treatment
- Nivolumab treatment ongoing
- 1st occurrence of new lesion
- CR or PR
- % change truncated to 100
Case Study 4: Signals with Combination Regimens
Ipilimumab/Nivolumab

- Phase 1 study of ipilimumab/nivolumab in patients with treatment naïve MEL
- Greater ORR (and CRs); greater proportion with “deep responses”; durable; greater toxicity

- Led to confirmatory trials CA209-069 and CA209-067

http://dx.doi.org/10.1016/S1470-2045(15)70076-8

Nishino et al. Journal for ImmunoTherapy of Cancer 2014, 2:17
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http://www.immunotherapyofcancer.org/content/2/1/17
Case Study 4: Signals with Combination Regimens
Ipilimumab/Nivolumab

<table>
<thead>
<tr>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + Ipilimumab 314</td>
</tr>
<tr>
<td>Nivolumab 316</td>
</tr>
<tr>
<td>Ipilimumab 315</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.5 (8.9–16.7)</td>
<td>6.9 (4.3–9.5)</td>
</tr>
<tr>
<td>HR (99.5% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.55 (0.43–0.76)*</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.76 (0.60–0.92)**</td>
<td>--</td>
</tr>
</tbody>
</table>

*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint

Percentage of PFS
PFS per Investigator (months)
0 3 6 9 12 15 18 21 24 27
0 10 20 30 40 50 60 70 80 90 100
NIVO+IPI
NIVO
Ipilimumab
Progression-free Survival (%)

Number of patients at risk:
Nivolumab + Ipilimumab 314
Nivolumab 316
Ipilimumab 315
Case Study 4: Signals with Combination Regimens
CheckMate 012: First-Line Nivolumab ± Ipilimumab in NSCLC

Will this signal with Ipi/Nivo translate into confirmed benefit in a randomized study?
In all-comers? In PD-L1 >1%; PD-L1 >50%?

Based on a September 2016 database lock; \(^3\) determined radiographically per RECIST v1.1 and 3 identified by pathologic evaluation
Case Study 4: Signals with Combination Regimens
Nivolumab + Lirilumab (anti-KIR)

- Lirilumab is a fully human IgG4 mAb that blocks inhibitory KIRs on NK cells and promotes NK-cell activation and tumor cell death
- CA223-001: Phase 1b study evaluating safety and clinical activity of lirilumab combined with nivolumab
- Potential signal was identified in a previously treated SCCHN expansion cohort

Will this signal with Liri/Nivo in patients with PD-L1+ SCCHN tumors translate into confirmed benefit in a randomized study?

<table>
<thead>
<tr>
<th></th>
<th>NCT01714739 (Phase 1/2) Lirilumab + Nivolumab</th>
<th>CheckMate 141 (Phase 3)\textsuperscript{1,2} Nivolumab Monotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>7/29 (24)*</td>
<td>32/240 (13)</td>
</tr>
<tr>
<td>Partial response</td>
<td>3 (10)*</td>
<td>6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>4 (14)*</td>
<td>26 (11)</td>
</tr>
<tr>
<td>DCR, n/N (%)</td>
<td>15/29 (52)</td>
<td>NR</td>
</tr>
<tr>
<td>ORR by PD-L1 expression, n/N (%)\textsuperscript{†}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1%</td>
<td>0/9 (0)</td>
<td>9/73 (12)</td>
</tr>
<tr>
<td>≥1%</td>
<td>7/17 (41)</td>
<td>15/88 (17)</td>
</tr>
<tr>
<td>≥5%</td>
<td>6/11 (54)</td>
<td>12/54 (22)</td>
</tr>
<tr>
<td>≥50%</td>
<td>4/7 (57)</td>
<td>7/19 (37)</td>
</tr>
</tbody>
</table>

*Includes unconfirmed responses.
\textsuperscript{†}Patients at risk, n = 15/41.

Conclusions:

• As we move toward seamless drug development, discerning true positive from true negative signals will become even more important.

• Adequate sample size, clinically meaningful effects, and a focus on key clinical or biologically defined subsets may decrease chances of acting upon false positive and false negative results.

• Similar principles for monotherapy treatments are expected to apply with combination regimens.