Innovation, Uncertainty and Reimbursement Processes in Precision Medicine: The Case of PD-L1

Monday, October 17, 2016
MaRS Discovery District, Toronto

This session was generously sponsored by Merck Canada Inc.
Meet the Panel

Moderator:
- Barry Stein (Colorectal Cancer Association of Canada)

Speakers:
- Lillian Siu (Princess Margaret Cancer Centre)
- Reiner Banken (Reiner Banken Consulting)
- Scott Gavura (Cancer Care Ontario)
Session Overview

● Developments in precision medicine provide hope of highly targeted treatments, improving both clinical benefits for patients and effective use of scarce resources in health care. Promising diagnostic tests for selecting groups of patients for treatment are being introduced in health care at an increasingly rapid pace. Early access for high medical need must take into account and manage the uncertainties around value for the patient and for the health system.

● PD-L1 testing in cancer care is the first example where multiple drugs are targeting the same molecular pathway, each drug with its own companion diagnostic test. In spite of the unprecedented collaboration between the different companies involved (Blueprint Project), the drugs are starting to enter the Canadian Health Care System with great uncertainties on the need and benefits for PD-L1 testing and the appropriate choice of a companion diagnostic test for a specific drug.

● The session aims for a dialogue on patient, clinician, health technology assessment and payer perspectives on introducing PD-L1 drugs and companion diagnostics under great uncertainty and a rapidly evolving evidence base.
**Session Timing**

<table>
<thead>
<tr>
<th>Time</th>
<th>Person</th>
<th>Activity</th>
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<tbody>
<tr>
<td>15:00</td>
<td>Reiner Banken</td>
<td>Open the session and introduce Barry Stein</td>
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<tr>
<td>15:05</td>
<td>Barry Stein</td>
<td>Introduce session and introduces Lillian</td>
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<tr>
<td>15:10</td>
<td>Lillian Siu</td>
<td>Presentation</td>
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<td>15:20</td>
<td>Barry Stein</td>
<td>Introduce Reiner</td>
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<td>15:22</td>
<td>Reiner Banken</td>
<td>Presentation</td>
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<td>15:32</td>
<td>Barry Stein</td>
<td>Introduce Scott</td>
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<td>15:34</td>
<td>Scott Gavura</td>
<td>Presentation</td>
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<td>15:44</td>
<td>Barry Stein</td>
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<td>15:50</td>
<td>All</td>
<td>Comments from presenters : 2 minutes each</td>
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<td>16:00</td>
<td>All</td>
<td>Questions from audience</td>
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<tr>
<td>16:13</td>
<td>Barry Stein</td>
<td>Closing of session</td>
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Promises and Challenges of PD-L1 in Clinical Practice

Lillian L. Siu, MD
Princess Margaret Cancer Centre, Toronto, Canada

CAPT 2016, October 17, 2016, MaRS Discovery District
Interactions Between Antigen Presenting Cells, T Cells and Tumor Cells

Adapted from Zang et al. Clinical Cancer Research 2007
Analytical and Clinical Characteristics of Biomarkers

Discovery

Clinical validity:
The test result shows an association with a clinical outcome of interest

Analytical validity:
The test’s performance is established to be accurate, reliable, and reproducible

Clinical utility:
Use of the test results in a favorable benefit to risk ratio for the patient
## Comparison of PD-L1 Assays

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>mAb</th>
<th>Target</th>
<th>FDA approved</th>
<th>Companion Diagnostic Assay PD-L1+</th>
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<tbody>
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<td>IHC assay developer</td>
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<tr>
<td>pembrolizumab (Keytruda, MK-3475)</td>
<td>Merck Sharp &amp; Dohme</td>
<td>humanized IgG4</td>
<td>PD-1</td>
<td>Melanoma, NSCLC, SCCHN</td>
<td>Dako</td>
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<tr>
<td>nivolumab (Opdivo, BMS-936558)</td>
<td>Bristol-Myers-Squibb</td>
<td>human IgG4</td>
<td>PD-1</td>
<td>Melanoma, NSCLC, renal, HD</td>
<td>Dako</td>
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<tr>
<td>durvalumab (MEDI-4736)</td>
<td>MedImmune/ AstraZeneca</td>
<td>human Fc-modified IgG1</td>
<td>PD-L1</td>
<td>Bladder*</td>
<td>Ventana</td>
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<tr>
<td>atezolizumab (MPDL3280A, RG7446)</td>
<td>Genentech/ Roche</td>
<td>human Fc-modified IgG1</td>
<td>PD-L1</td>
<td>Bladder, NSCLC*</td>
<td>Ventana</td>
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* FDA Breakthrough Designation Therapy status

TCs = tumor cells; TIC= tumor-infiltrating immune cells; n/a, not applicable

Hansen, Siu JAMA Oncology, 2016
“Companion” vs “Complementary” Diagnostic

• Companion Diagnostic:
  – “Provides information that is essential for the safe and effective use of a corresponding drug or biological product”
  – e.g. PD-L1 IHC 22C3 for pembrolizumab in NSCLC

• Complementary Diagnostic:
  – ”Not required but aids risk/benefit assessment for drug use in individual patients”
  – e.g. PD-L1 IHC 28-8 for nivolumab in NSCLC and melanoma, PD-L1 IHC SP142 for atezolizumab in bladder cancer
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Device Trade Name</th>
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<tbody>
<tr>
<td>Trastuzumab</td>
<td>HER2 FISH PharmDx Kit</td>
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<tr>
<td>Pertuzumab</td>
<td>HERCEPTEST</td>
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<tr>
<td>Trastuzumab</td>
<td>INSITE HER-2/NEU KIT</td>
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<td></td>
<td>Bond Oracle Her2 IHC System</td>
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<td></td>
<td>SPOT-LIGHT HER2 CISH Kit</td>
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<td>HER2 CISH PharmDx Kit</td>
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<td></td>
<td>INFORM HER2 DUAL ISH DNA Probe Cocktail</td>
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<td></td>
<td>PATHVYSION HER2 DNA Probe Kit</td>
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<td></td>
<td>PATHWAY ANTI-HER2/NEU (4B5) Rabbit Monoclonal Primary Antibody</td>
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<tr>
<td>Olaparib</td>
<td>BRACAAnalysis CDx™</td>
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<tr>
<td>Imatinib</td>
<td>DAKO C-KIT PharmDx</td>
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<tr>
<td>Gefitinib</td>
<td>THERASCREEN® EGFR RGQ PCR Kit</td>
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<tr>
<td>Afatinib</td>
<td>CUBAS® EGFR Mutation Test</td>
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<tr>
<td>Erlotinib</td>
<td>VENTANA ALK (D5F3) CDx Assay</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>VYSIS ALK Break Apart FISH Probe Kit</td>
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<tr>
<td>Crizotinib and Panitumumab</td>
<td>cobas® KRAS Mutation Test</td>
</tr>
<tr>
<td>Cetuximab and Panitumumab</td>
<td>COBAS 4800 BRAF V600 Mutation Test</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>THxID™ BRAF Kit</td>
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http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm
PD-L1 Assays

Challenges:

– Different antibodies being used
– Variable definitions for biomarker positivity (which cells/tissue components, different staining thresholds used as cut-offs)
– Lack of standardization and harmonization
– Challenging to make comparisons across trials that used different assays with different definitions
Blueprint and Other PD-L1 Comparative Projects

**PD-L1 Membrane Staining**
- All three PD-L1 assays showed similar patterns of staining (Figure 1)

**Figure 1. IHC Images from the Three Diagnostic Assays**

The Blueprint Project: Harmonizing Companion Diagnostics Across a Class of Targeted Therapies, AACR 2016; Ratcliffe et al AACR 2016
An HTA perspective on Innovation, Uncertainty and Reimbursement: The case of PD-L1

Canadian Association for Population Therapeutics Annual Conference
Toronto, October, 17th, 2016

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Conflicts of interest

• Work in a governmental HTA agency for many years.
• Work as a consultant with different companies over the last 12 months.
• Recent work with Roche Diagnostics on PD-L1 in Canada.
The origin of Health Technology Assessment

Request of the US Congress Senate Committee on Human Resources to OTA in 1974: « whether a reasonable amount of justification should be provided before costly new medical technologies and procedures are put into general use»

Decisions based on needs expressed by physicians

Decisions based on (informed by) a formal and transparent assessment of the evidence
Reasoning in HTA

- HTA depends on available primary studies.
- HTA must deal with uncertainties in knowledge.
- HTA can be a hurdle or an enabler for innovations.

The case of PD-L1

- PD-L1 assays inform decision-making for PD-L1 immunotherapies for an increasing array of cancers.
- Rapidly evolving knowledge on the role of PD-L1 immunotherapies in treatment algorithms and the place of PD-L1 assays (ex resistance).
- Different commercial PD-L1 assays for different PD-L1 drugs and laboratory developed PD-L1 tests (30 to 50% in the US)
- Patient benefits with PD-L1 immunotherapies, increased for PD-L1 positive cancers
- Immunotherapies costing around 10 000$ per month, PD-L1 assays around 100$ for each test
Decision-making for introducing PD-L1 tests

1. Mandatory HTA process only in Québec. HTA informing central decision-making processes. No decision-making at the hospital level.

2. Fragmented decision-making at the provincial and the hospital level in Ontario, centralised assessment process if dedicated funding. HTA if involvement of HQO.

3. Ad hoc assessment of companion and complementary diagnostics. No integrated assessment frameworks for assays and drugs.

4. No evidence development pathways in health systems in Canada (such as real world evidence development, coverage with evidence development, adaptive pathways, living labs).
Challenges

• How to provide patient access to PD-L1 assays for patient and for health systems benefit?
  
  • How to introduce PD-L1 tests under evolving uncertainties of analytic and clinical validity and clinical utility?
  
  • How to develop dynamic HTA systems linked to collaborative, patient-centered evidence-development pathways?
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A Payer’s Perspective: Innovation, Uncertainty and Reimbursement Processes in Precision Medicine in Oncology

CAPT 2016

Scott Gavura, Director, Provincial Drug Reimbursement Programs
The speaker has no financial or other conflicts of interest to report.
Balancing funding obligations and demands

**Financial obligations**
- Manage spending within budget
- Grow spending at sustainable rate
- Measure and ensure appropriateness of spending

**Treatment expectations**
- Address clinician expectations to fund “standard of care"
- Consider specific patient circumstances
- Deliver best possible population-level outcomes
- Maximize equity
Drug costs for claims approved under the New Drug Funding Program.
Implementation challenges

• Drug-specific funding decisions in face of uncertainty
• Multiple new entrants, simultaneously
  • Further increasing uncertainty
• Need to ensure testing in place, simultaneously with drug funding
  • Unique drug/test pairing increases challenge.

The result: Complexity of incorporating adaptive pathways into population-level funding programs.
Can we collect and use real-world evidence?

• The vision: a “learning” health system/reimbursement system
  • Ideally, link payment to outcomes realized vs. expected/anticipated

• Validate assumptions we made during our assessment
  – Possible to confirm clinical- and cost-effectiveness?

• Increase overall confidence in our reimbursement decisions
  – Resolve uncertainty remaining from decision-making process
Can RWE do all this?

- Insufficient information often available to demonstrate a new treatment provides a meaningful clinical benefit.
- Rapid introduction of new therapies means study population may not be representative of target population (e.g., exposure to other therapies)
- Evolving understanding of PD-L1 expression and relationship with tumor response
What data could RWE encompass?

- Treatment data / Rx claims data
- Outcomes data
- Genomic data
- Socioeconomic data
- Patient-generated data (e.g., PRO’s)
What barriers exist?

• There’s a lack of consensus on the implementation approach.
• There’s an incremental cost to collecting, cleaning maintaining and analyzing datasets developed expressly for RWE use.
  – Build this into implementation plans?
• We lack a common framework (across multiple stakeholders, gov’t and non gov’t) that defines how RWE data will be integrated and used.
A Payer’s Perspective: Innovation, Uncertainty and Reimbursement Processes in Precision Medicine in Oncology

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scott.gavura@cancercare.on.ca
Immuno-Oncology Policy

TO REIMBURSE PD-L1 PREDICTIVE BIOMARKERS … OR NOT?

THAT IS THE QUESTION.

CAPT
Toronto
October 17, 2016

Barry D. Stein
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• Immunotherapy targets the body’s immune system, rather than the tumour itself. Selectively recognises & targets cancer cells, not healthy cells.

• Gives long-lasting memory to the immune system, enabling it to continually adapt to the cancer over time & provide durable, long-term response to cancer with fewer side effects.

• Several drugs have already been developed and many more are in pre-clinical and clinical development stage targeting advanced melanoma, lung, bladder, prostate, colorectal and pancreatic cancer, providing hope for patients in some cases where no effective treatments were previously available.

• How can we ensure patient access to this new and possibly game changing technology?
Policymakers, Regulatory Authorities, Health Professionals & Patients Require A Better Understanding of IO In Cancer Treatment

- The complexity of immuno-therapy drugs, the high number of patients and the high costs of these drugs necessitate a better understanding of IO drugs and their predictive biomarkers being used in clinical practice to identify the appropriate patient for the right drug.

- IO therapies and their predictive biomarkers are somewhat imprecise and variable, but are being integrated into cancer plans and policies.

- Need to ensure alignment between regulatory and reimbursement authorities taking into account the benefits of IO.

- The PD-L1 (Programmed-death ligand1) protein is at the center of clinical decisions for selecting patients who are most likely to benefit from immuno-therapy in connection with checkpoint blockade drugs.
PD-L1, New Combinations & Future Biomarkers

• The next 5-10 years will see an increasing role for immunotherapy and select predictive biomarkers will be vital in determining the appropriate responders.

• For those that do not respond, we may be able to turn non immunogenic tumours into ones that become amenable to immunotherapy by doing such things such as combining anti PD-L1 therapies with MEK* inhibitors in Microsatellite-Stable mCRC patients...providing more hope for patients.

• PD-L1 predictive biomarkers are under fire and attention is beginning to turn the possibility of other biomarkers such as TMB (Tumour Mutational Burden).

• At present however, selecting patients based on PD-L1 expression, however imperfect, seems to be the most significant marker for some types of cancer such as NSCLC as highlighted at the recent ESMO 2016 annual meeting.

*A MEK inhibitor is a drug that inhibits mitogen activated protein kinase enzymes MEK1 and or MEK2. They have the potential for treatment in KRAS/BRAF mutated CRC.
ANTI PD-L1 THERAPY AT ITS BEST

Figure 1: Inactivation of T cells limits damage to normal tissue.

Figure 2: Inactivation of T cells reduces tumor cell death and elimination.

Figure 3: Blocking the PD-1/PD-L1 interaction enables active T cells and tumor cell death and elimination.