Immuno-Oncology Biomarkers in Clinical Development and Patient Selection

NIHR DEC UK Diagnostics Forum: “Diagnostics in Times of Change”

Tuesday 16th May 2017, Lady Margaret Hall, Oxford

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Integrated Medicines
Targeted Therapies: Expedited Development and Approval Timelines\textsuperscript{1,2,3}

- Roche co-developed PLX4032/vemurafenib with Plexxikon from October 2006\textsuperscript{1} subsequent to IND filing; consequent Phase 1 study shows a 81% response rate in 38 metastatic melanoma patients with \textbf{BRAF}\textsuperscript{V600E} mutation.

- Clinical development proceeded directly to Phase 3; widely anticipated efficacy and limited trial crossover opportunity slowed enrollment; trial modified to reach 675 total patients\textsuperscript{1}.

- FDA review of drug (Rx) and companion diagnostic (CDx) completed in 3.6 months with approval on 17\textsuperscript{th} August 2011\textsuperscript{3}.

- Approval credits coordination of Rx-CDx regulatory submissions and clear efficacy of drug in target population\textsuperscript{3}.

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1. \url{http://www.roche.com/investors/updates/inv-update-2006-10-05.htm}, accessed 11\textsuperscript{th} October 2016

2. Chapman et. al NEJM 364;26 30 June 2011


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*Data for 209 patients in the vemurafenib group (Panel A) and 158 patients in the dacarbazine group (Panel B). Each bar represents data for an individual patient. Colours indicate the tumour sub-stage for each patient. The percent change from baseline in the sum of the diameters of the target lesions is shown on the y axis. 

\textit{Negative values indicate tumour shrinkage.}
Targeted Therapies Only Provide Benefit When Target is Present$^{1,2}$

Kaplan–Meier curves for progression-free survival$^2$

1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium "From testing to therapy – the PD-L1 continuum". European Society of Pathology 28th Congress (2016),
Targeted therapies work rapidly but may show little long-term benefit\(^1,\!2,\!3\)

1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium “From testing to therapy – the PD-L1 continuum”. European Society of Pathology 28\(^{th}\) Congress (2016),
3. Friboulet L et al. Cancer Discovery 2014;4:662-673 (Figure C)
## Key Differences Between Targeted Therapy and Immunotherapy

<table>
<thead>
<tr>
<th>Targeted Therapy</th>
<th>Immuno Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tends to be organ specific?</td>
<td>Pan tumor potential</td>
</tr>
<tr>
<td>Patients negative for biomarker get no benefit</td>
<td>Patients negative for biomarker still get benefit</td>
</tr>
<tr>
<td>Benefits seen early</td>
<td>Benefit not always seen early</td>
</tr>
<tr>
<td><em>Duration of benefit limited</em></td>
<td><em>Extended duration of benefit</em></td>
</tr>
<tr>
<td>Impact on survival limited</td>
<td>Impact on overall survival</td>
</tr>
<tr>
<td>Biomarker in tumour cells</td>
<td>Biomarker on tumour cells and other cells in tumour microenvironment</td>
</tr>
</tbody>
</table>

1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium “From testing to therapy – the PD-L1 continuum”. European Society of Pathology 28th Congress (2016)
Regulating the T-cell Response: Immune Checkpoints and Checkpoint Inhibitors

CD28 = cluster of differentiation 28; CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed death receptor-1; PD-L1 = Programmed Death Ligand 1
CD80 & CD86 = Ligands for CD28 (+ve) and CTLA4 (-ve)

Resisting Cell Death is one Hallmark of Cancer$^{1,2,3}$

The tumour cell releases antigens, presumably altered proteins due to expressed mutations (frameshifts and truncations), that are presented to dendritic cells that prime and activate T cells which then traffick to the tumour

This is more likely with higher mutational burden (pleomorphic/higher grade tumours)

_Tumour may look inflamed but is not ablated_

1. Professor Ken Bloom LSO3 Roche Diagnostics Symposium “From testing to therapy – the PD-L1 continuum”. European Society of Pathology 28th Congress (2016).
3. Text adapted by E Blair
Patterns of immune cell infiltration

1. Professor John Gosney, 11th October 2016, personal communication and used with permission.
Immune Checkpoint Inhibitors Provide Durable Long-term Survival for Patients with Advanced Melanoma

Overall Survival (%) vs Years

- IPI (Pooled analysis)$^1$
- NIVO Monotherapy (Phase 1 CA209-003)$^2$
- NIVO Monotherapy (Phase 3 Checkmate 066)$^3$

N=210
N=107
N=1,861

Combination Therapies: A Promising Treatment Strategy*1

*Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

Towards Precision Immuno-Therapy

1. Kim JM & Chen DS (2016) Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure)
   Annals Oncology 27: 1492 – 1504.

** EB superficial interpretation

BMS**
Merck

Roche

AZ
BMS

Roche
Biomarker ‘Positivity’ in Targeted Therapy and Immunotherapy: Present, Absent or Graduated?¹

Oncogenic Biomarkers:

* **EGFR mutation**
* **ALK fusion**

Biologically Active protein: **PD-L1**

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**Your tumour is ‘negative’**

- **Oncogenic mutation or fusion gene is ABSENT**
- **You will not benefit from therapy**

**Your tumour is ‘positive’**

- **Oncogenic mutation or fusion gene is PRESENT**
- **You will benefit from therapy**

**Biological continuum of biomarker expression**

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Biomarker Status</th>
<th>Chance of Benefit from Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>Biomarker is ABSENT or at low level</td>
<td>You are unlikely to benefit from therapy</td>
</tr>
<tr>
<td>25%</td>
<td>Biomarker is PRESENT at intermediate level</td>
<td>You may benefit from therapy</td>
</tr>
<tr>
<td>50%</td>
<td>Biomarker is PRESENT at a high level</td>
<td>You are likely to benefit from therapy</td>
</tr>
<tr>
<td>80%</td>
<td>Biomarker is PRESENT</td>
<td>Higher chance of response</td>
</tr>
</tbody>
</table>

**How do we define ‘positive’?**

- Where do we set the cut-off value?
- How does the cut-off value relate to response?

1% 80% 50% 25%

**How much less responsive will this patient be………compared with this one?**

- Lower chance of response
- Higher chance of response

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¹ PD-L1 = Programme Death Receptor Ligand 1

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1. Professor Keith Kerr, ESMO 2016 Controversy of the Day Session 8th October 2016: The current way to measure PD-L1 biomarkers will not stand the test of time, “No”
First-Line Monotherapy in PD-L1 Expressing NSCLC

BMS CheckMate 026 Press Release\(^1,3\)

- “CheckMate 026, a trial investigating the use of OPDIVO® (nivolumab) as monotherapy, did not meet its primary endpoint of progression-free survival in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed PD-L1 at \(\geq 5\%\).”

Merck KEYNOTE-024 Press Release\(^2,4\)

- “KEYNOTE-024 trial investigating the use of KEYTRUDA® (pembrolizumab), in patients with previously untreated advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more), met its primary endpoint (PFS).”

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3. Socinski et al ESMO 2016,
Problems with PD-L1 and IHC*,1,2

Not a ‘perfect’ biomarker:

- Responses seen in patients below selected thresholds – ‘negative’, aka ‘low expressors’
- Affected by prior radiation and chemotherapy²
- Expression is dynamic over time (archival 2L vs fresh 1L)²
- Expression is heterogeneous – biopsy sampling “error”²

Consequently, there is ‘noise’, ‘variability’, ‘error’ around the specific value, including the selected threshold (cut off)

<table>
<thead>
<tr>
<th>Dako</th>
<th>Dako</th>
<th>Ventana</th>
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</thead>
<tbody>
<tr>
<td>28-8</td>
<td>22C3</td>
<td>SP142</td>
</tr>
</tbody>
</table>

*IHC = Immunohistochemistry; staining of tissue sections with specific antibodies & detection by 2⁰ reagents, may be based on counting of tumour and/ or immune cells

1. Professor Keith Kerr, ESMO 2016 Controversy of the Day Session 8th October 2016: The current way to measure PD-L1 biomarkers will not stand the test of time, “No”.

Beyond PDL1 – Tumour Mutation Burden (TMB\(^1\)) Analysis in Failed Checkmate 026\(^2\)

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**Table:**

<table>
<thead>
<tr>
<th>TMB</th>
<th>Nivolumab mPFS (mo)</th>
<th>Chemo mPFS (mo)</th>
<th>Nivolumab ORR (%)</th>
<th>Chemo ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ((&lt;99 mutations detected))</td>
<td>4.2 (HR 1.82)</td>
<td>6.9</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>Medium (100 – 242)</td>
<td>3.6 (HR 1.82)</td>
<td>6.5</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>High ((\geq243 mutations))</td>
<td>9.7 (HR 0.62 [95% CI; 0.38 – 1])</td>
<td>5.8</td>
<td>46.8</td>
<td>28.3</td>
</tr>
</tbody>
</table>

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2. Peters S (2017) Impact of tumor mutation burden on the efficacy of first-line nivolumab in stage IV or recurrent non-small cell lung cancer: an exploratory analysis of CheckMate -026 AACR Abstract # CT082
Biomarkers Associated with Tumour Genetic Instability 1 – Results


• High mutational burden creates neo-antigens (clonal > sub-clonal) that attract immune cells that give strong response to checkpoint inhibitors

• This activation, expansion and differentiation of T-cells and other cytotoxic immune cells is reflected by immuno-profiling of cell-associated and soluble factors [in liquid biopsies]

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Biomarkers Associated with Tumour Genetic Instability 2 – Causal Events

- **Hereditary:** High Microsatellite Instability (MSI) due to poor MMR from absent MLH1, MSH2, MSH6 or PMS2\(^a\) (CRC)

- **Epigenetic:** Methylation of MGMT\(^a\) promoter leads to poor MMR (GBM) as expression blocked

- **Environmental:** Smoking, diet and other factors induce certain types of mutation (lung, bladder)

\(^1\) Leads to high tumour mutational burden (TMB)

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\(^1\) GM Frampton et al (2016) "Assessment and comparison of tumour mutational burden and microsatellite instability status in >40,000 cancer genomes" Annals of Oncology 27 (Supplement 6): vi15–vi42


\(^a\) O6-methylguanine-DNA methyltransferase (MGMT); MutL homolog 1 (MLH1); MutS homolog 2 (MSH2); MutS homolog 6 (MSH6); PMS1 endonuclease homolog 2 (PMS2)
Acquired resistance to IO Products 1: Direct Effects

- Anti-PDL1 targets ligand on tumour cells; opportunity for changes to PDL1 that affect Mab binding
- Anti-PD1 targets receptor on immune cells; changes to PD1 not universal but impact of receptor density known

1E Blair hypothesising without licence
Acquired resistance to IO Products 2: Indirect Effects$^1,2,3$

- Gene cluster approach – immune cells (CD8, DØ, MØ) vs DNA regulation & repair
- Regulatory pathways - Jak1,2; B2M; IFNγ; GBP1

$^1$DS Shin et al (2016) "Primary Resistance to PD-1 Blockade Mediated by JAK1/2 Mutations" Cancer Discov; 7(2); 1–14
$^2$L Verlingue et al (2017) "RNAseq Analysis of MATCH-R Trial Tumour Biopsies" (sic) AACR Abstract #1011
$^3$JM Zaretsky et al (2016) "Mutations Associated with Acquired Resistance to PD1 Blockade in Melanoma" NEJM 3759: 819 - 829
Other key questions in IO*

1. Why do some patients survive and some die after stopping treatment?

2. How long do patients need to be treated for sustained response?

3. Can predictive biomarkers be found to aid patient selection?

*Data from Long GV et al (2016) SMR
Precision Medicine Requires Precision Diagnosis\textsuperscript{1}

One size fits all: same diagnosis same prescription

Right Drug
Right Patient
Right Time
Right Dose

Drug is toxic but is beneficial

Drug is NOT toxic but is also NOT beneficial

Drug is toxic and is NOT beneficial

Drug is NOT toxic and is beneficial

1. Professor Ken Bloom, LSO3 Roche Diagnostics Symposium “From testing to therapy – the PD-L1 continuum”. European Society of Pathology 28\textsuperscript{th} Congress (2016), adapted by E Blair
Thank you and….

….Any questions?

Eddie Blair

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