Disclaimer

The views expressed herein represent those of the presenters and do not necessarily represent the views or practices of their companies or the views of the general Pharmaceutical Industry.
Today’s objectives and Agenda

• To provide updates on current BR in HTA initiative
• To demonstrate potential differences in stakeholders preferences through a case study

• Methodologies and Stakeholders
• Case example:
  – Are preferences really different among stakeholders?
Benefit-Risk Assessment (BRA) and Health Technology Assessment (HTA). Methodologies and Initiatives.

Updates on Recent Development
Regulatory Benefit-Risk (BR) Assessment

should be based on the available tests and clinical trials carried out on the product designed to test the efficacy and safety; and accounting for the potential impact on the evaluation of benefits and risks through the pharmacovigilance activities

[Directive 2001/83/EC*]

authorisation decisions should be based on quality, safety and efficacy, and not including economic and other considerations such as “cost-effectiveness”.

[Community law (Regulation EC 726/2004)*]

* Of the European Parliament and of the Council
European Commission’s view on HTA

“HTA is a way of assessing the ways science & technology are used in healthcare and disease prevention. It covers medical, social, economic, and ethical issues”

“It provides policy-makers with objective information, so they can formulate health policies that are safe, effective, patient-focused and cost-effective”

“HTA should be transparent, unbiased, robust and systematic - firmly rooted in research and the scientific method.”

https://ec.europa.eu/health/technology_assessment/policy_en
http://protectbenefitrisk.eu/
# A Selection of Initiatives on BR in HTA

<table>
<thead>
<tr>
<th>Initiatives</th>
<th>Selected relevant deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory</strong></td>
<td></td>
</tr>
<tr>
<td>FDA (PDUFA V update)</td>
<td>Structured Benefit-Risk Assessment Framework</td>
</tr>
<tr>
<td>EMA</td>
<td>Benefit-Risk methodology project. Effects Table Day 80 Assessment Report</td>
</tr>
<tr>
<td>ICH (in collaboration with EuNetHTA)</td>
<td>ICH E2C(R2) Periodic Benefit-Risk Evaluation; Report PBRER (Jan 2013, Step 5); M4E(R2) CTD (section 2.5.1 and 2.5.6)</td>
</tr>
<tr>
<td>IMI PROTECT Benefit-Risk Integration and Representation</td>
<td>Recommendations on BR methods; Reviews of methods and visualizations; Case studies; PPI. <a href="http://protectbenefitrisk.eu/">http://protectbenefitrisk.eu/</a></td>
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<td><strong>Health Technology Assessment / Reimbursement</strong></td>
<td></td>
</tr>
<tr>
<td>NICE / DSU</td>
<td>DSU (Decision Support Unit) Report (SchHARR February 2011)</td>
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<tr>
<td></td>
<td>Multiple Criteria Decision Analysis for health technology assessment</td>
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<tr>
<td></td>
<td>NICE Guidelines The manual October 2014 (updated Jan 16)</td>
</tr>
<tr>
<td>EVIDEM framework</td>
<td>(Evidence and Value: Impact on Decision Making). Framework including MCDA Value Matrix (VM) (module 5)</td>
</tr>
<tr>
<td>ICER</td>
<td>ICER Evidence Rating Matrix reflecting the magnitude of the difference in net health benefit and certainty</td>
</tr>
<tr>
<td>IQWiG</td>
<td>AHP can be applied both in patients and healthcare professionals</td>
</tr>
<tr>
<td></td>
<td>Working paper AHP; Potential use of DCE to weight patient-relevant outcomes Working paper CA</td>
</tr>
<tr>
<td>ADVANCE-HTA</td>
<td>Theoretical and conceptual considerations; The importance of appropriate service user involvement in HTA evaluations; Orphan medicinal treatments and the value of HTA in industrial policy formation</td>
</tr>
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## A Selection of Initiatives on BR in HTA

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<tr>
<td>ASCO Task Force</td>
<td>Conceptual framework - physician-guided tool to assist the physician and patient in shared decision making</td>
</tr>
<tr>
<td>ESMO-MCBS</td>
<td>ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS)</td>
</tr>
<tr>
<td>American College of Cardiology (ACC) and AHA</td>
<td>Hierarchical grading system to synthesise the benefit and risk of treatments; Three level system to classify the precision and the quality of the underlying evidence and to form an assessment matrix; Point-based system based on 16 questions to evaluate quality of evidence</td>
</tr>
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### Across Decision Makers

<table>
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<tr>
<td>CIRS</td>
<td>UMBRA including CIRS-BRAT Framework (in collaboration with COBRA/iSABRE)</td>
</tr>
<tr>
<td>IMI ADVANCE</td>
<td>(Accelerated development of vaccine benefit-risk collaboration in Europe). Vaccines-focus. (ongoing) <a href="http://www.advance-vaccines.eu">www.advance-vaccines.eu</a></td>
</tr>
<tr>
<td>IMI2 PREFER</td>
<td>Preference-focus (ongoing) <a href="https://www.imi-prefer.eu">https://www.imi-prefer.eu</a></td>
</tr>
<tr>
<td>EUPATI</td>
<td>(European Patients’ Academy on Therapeutic Innovation). Training courses and events; Work with HTAs and EMA. <a href="http://www.eupati.eu">www.eupati.eu</a></td>
</tr>
</tbody>
</table>
The Advance Value Framework

New value framework for evaluation of new medicines
Secondary and primary evidence used to identify decision-makers' value concerns
A generic value tree structured incorporating different evaluation criteria
MCDA methodology proposed for value judgements and preference elicitation

Aris Angelis, Panos Kanavos, Multiple Criteria Decision Analysis (MCDA) for evaluating new medicines in Health Technology Assessment and beyond: The Advance Value Framework, In Social Science & Medicine, Volume 188, 2017, Pages 137-156, ISSN 0277-9536, https://doi.org/10.1016/j.socscimed.2017.06.024
(Some of) The Decision-Makers

- **Patients / Carers**
  - Make decisions for themselves / patients

- **Healthcare providers**
  - Make decisions based on prescribing lists

- **Health Technology Assessors / Payers**
  - Make decisions on cost-effectiveness etc.

- **Regulators**
  - Make decisions on quality, safety, efficacy and benefit-risk balance to individuals and public health

- **Pharmaceutical companies**
  - Make decisions on what to develop for which licenses to apply

Adapted from [http://www.protectbenefitrisk.eu](http://www.protectbenefitrisk.eu)
Systematic Treatments in Advanced Melanoma.
Preferences from Patients, oncologists, and oncology nurses in the United States.

An Example of a Discrete Choice Experiment
Treatment Landscape For Advanced Melanoma in the US for the Past 7 Years

Mar: YERVOY Approval

May: MEKINIST mono & TAFINLAR mono Approvals

Sept: KEYTRUDA mono refractory Accelerated Approval

Sep: OPDIVO + YERVOY combo in BRAFwt accelerated approval

Nov: TAFINLAR + MEKINIST Combo Full Approval

Dec: OPDIVO+ YERVOY combo 1L accelerated approval

Jan: • OPDIVO 1L BRAFwt full approval & BRAFmt accelerated Approval

‘11

Aug: ZELBORAF Approval

‘12

Jan: OPDIVO 1L BRAFwt full approval & BRAFmt accelerated Approval

‘13

May: MEKINIST mono & TAFINLAR mono Approvals

‘14

Sept: KEYTRUDA mono refractory Accelerated Approval

Oct: IMLYGIc Approval

Jan: • OPDIVO 1L BRAFwt full approval & BRAFmt accelerated Approval

Nov: TAFINLAR + MEKINIST Combo Full Approval

Dec: OPDIVO mono refractory Accelerated Approval

‘15

Nov: COTELLIC + ZELBORAF combo Approval

Dec: KEYSRUDA 1L Full Approval

‘16

Oct: YERVOY adjuvant Approval

*as of May 2017
Discrete Choice Experiment

https://doi.org/10.1007/s40258-016-0232-7
DCE Design Challenges (ISPOR Task Force)

- Potential implausible combinations
- Interaction effects
- Cognitive limitations of particular groups of respondents
- Labeled and constant alternatives
- Blocking

https://doi.org/10.1016/j.jval.2012.08.2223
## Attributes and Levels for DCE

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Levels</th>
</tr>
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<tbody>
<tr>
<td><strong>Mode of administration (MoA)</strong></td>
<td>Oral, IV, Subcutaneous</td>
</tr>
<tr>
<td><strong>Dosing Schedule (DS)</strong></td>
<td>(1) Two medicines, where one medicine is taken twice daily, the other medicine is taken once daily&lt;br&gt;(2) Once daily&lt;br&gt;(3) Twice daily&lt;br&gt;(4) 30 minute infusion every 3 weeks&lt;br&gt;(5) 60 minute infusion every 2 weeks&lt;br&gt;(6) 90 minute infusion every 3 weeks&lt;br&gt;(7) medicine by one injection every 3 weeks&lt;br&gt;(8) Two medicines, both are given as a 150 minute infusion every 3 weeks for 3 months (plus/minus: one of the two medicines is continued as 60 minute infusion every 2 weeks for 5 or more months</td>
</tr>
<tr>
<td><strong>Median Duration of Therapy (MDT)</strong></td>
<td>3, 8 and 12 months</td>
</tr>
<tr>
<td><strong>Objective Response Rate (ORR)</strong></td>
<td>15%, 33%, 65% chance of responding</td>
</tr>
<tr>
<td><strong>Progression Free Survival (PFS)</strong></td>
<td>3, 5, 11.5 months</td>
</tr>
<tr>
<td><strong>Overall Survival (OS)</strong></td>
<td>45%, 55% and 75% chance patients survive to 12 months</td>
</tr>
<tr>
<td><strong>Grade 3/4 Toxicities/Adverse Events (AEs)</strong></td>
<td>10%, 32%, 55% likelihood of experiencing a serious side effect</td>
</tr>
</tbody>
</table>
Preferences of All 3 Stakeholders

Difference between largest and smallest coefficient indicates the relative importance of the attribute for each perspective.
Comparison of Relative Importance

Oncologists differed significantly from nurses and patients in the weights assigned to ORR, PFS and AEs (p-values<0.001).

Compared to efficacy and safety, non-clinical attributes had minimum impact on the preferences of all stakeholders.
Limitations

Because of selection criteria imposed on each group of stakeholders, these results may not be generalizable to all potential stakeholders.

The DCE choices were made in response to hypothetical choice profiles and thus do not carry the same clinical, financial, or emotional consequences of actual decisions.

The attributes and levels were arrived at after thorough review of the literature, however, it is possible that some critical attributes were not included in this design.

Similarly, it is possible that individual difference characteristics other than those examined for the subgroup analyses may have been important differentiators in preferences but were omitted from this study.
Publications from the Project

Two manuscripts
• Patient and oncologist preferences for attributes of treatments in advanced melanoma: a discrete choice experiment – *Patient Preference and Adherence, 2017*
• Patient and Oncology Nurse Preferences for the Treatment Options in Advanced Melanoma: A Discrete Choice Experiment – *Cancer Nursing, 2017*

Six conference abstracts
• Patients Only – *Society for Melanoma Research (SMR), 2016 (poster)*
• Oncologists Only – *Society for Melanoma Research (SMR), 2016 (poster)*
• Oncology Nurses Only – *Oncology Nursing Society (ONS), 2017 (poster)*
• Patients and Oncologists – *National Comprehensive Cancer Network (NCCN), 2017 (poster)*
• Patients and Oncology Nurses – *International Conference on Cancer Nursing (ICCN), 2017 (Oral)*
• Patients, Oncologists, and Nurses – *International Society for Pharmacoeconomics and Outcomes Research, 2017 (Oral)*
Concluding Remarks

BREAKING BOUNDARIES
FAINT LINE WHEN TALKING ABOUT BR ASSESSMENT

- Tools for supporting decision-making
- Being quantitative is being more objective
- May increase transparency in complex decision
- Preferences offer more relevant insight
- Opportunities for (bio-)statisticians to drive these efforts
Acknowledgements

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Cathy Anne Pinto
Salome Samant

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Grace DiBonaventura Beyer
Enrique Basurto
Amir Goen

Mayo Clinic
Richard W. Joseph

EFSPI BR-HTA SiG
Susan Talbot (Amgen)
Jixian Wang (Celgene)
An opportunity to practise eliciting preferences

Monday June 4\textsuperscript{th}, 13:15 – 14:45 Veilingzaal
THANK YOU

Kind regards,

Shahrul Mt-Isa

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