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BBS PSI Scientific Meeting:

Empower the immune system to fight cancer

Cancer Immunotherapy from the Health Technology Assessment (HTA) and Payer Perspectives

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Disclaimer and Acknowledgements

The views expressed in this presentation are those of the presenter, not necessarily those of Xcenda or AmerisourceBergen.

At the same time, fully acknowledging contributions made by my colleagues at Xcenda and the speakers and participants of past BBS HTA Seminars.

Table of Contents

Introduction and Extra Acknowledgement

Navigating Coverage and Reimbursement for Immunotherapy in Oncology: Perspectives on Challenges and Opportunities in the HTA Evaluation Process

Introduction and Overview of IO

Immunotherapy in oncology (also referred to as immuno-oncology or IO) represents a promising new treatment category. Modern IO therapies use T-cells (white blood cells) that are stimulated to recognize and attack cancer cells, thereby equipping the body's own natural defenses to fight cancer.

IO is a fairly broad category of treatment, encompassing different mechanisms of action for therapies. Perhaps the most well-known IO treatments are checkpoint inhibitors, which include PD-1 inhibitors (pembrolizumab [marketing approval for MM, NSCLC, HNSCC (US only)], nivolumab [MM, NSCLC, RCC, HL, HNSCC (US only)]), PD-L1 inhibitors (atezolizumab [NSCLC]), and CTLA-4 inhibitors (ipilimumab [MM]). Chimeric antigen receptor (CAR) T-cell therapies (eg, adoptive cell therapies) that are in development for B-cell malignancies (leukemias and lymphomas) also fall into the category of IO, as do oncolytic viruses (approved for MM) and cancer vaccines (in development for several solid tumor types).

All of these specific treatment types within IO have shown promising results in comparison to traditional chemotherapeutic agents and other targeted therapies for both solid tumors and hematologic malignancies. The IO category seems poised for success, with FiercePharma listing an upcoming IO drug release in its predicted top 10 launches of 2017. Despite being hailed as the future of oncology, given the high cost of therapy and payer skepticism toward new oncologic agents, obtaining coverage and reimbursement for IO therapies can be difficult. In this article, we will discuss the challenges of obtaining approval from global HTA authorities and local market payers, and we will present some potential solutions to address evaluator concerns that may negatively impact IO therapy coverage and reimbursement within a given market.

http://www.xcenda.com/htaqspring2017-io

http://bbs.ceb-institute.org/

What is HTA?

Health Technology Assessment

A form of **policy research** that examines short- and long-term consequences of the application of a **health-care technology**[1]

Properties assessed include: evidence of safety, efficacy, patient-reported outcomes, real world effectiveness, cost and cost-effectiveness[2]

Multidisciplinary process that summarizes information about the **medical, social, economic and ethical** issues related to the use of a health technology in a **systematic, transparent, unbiased, robust manner**[1]

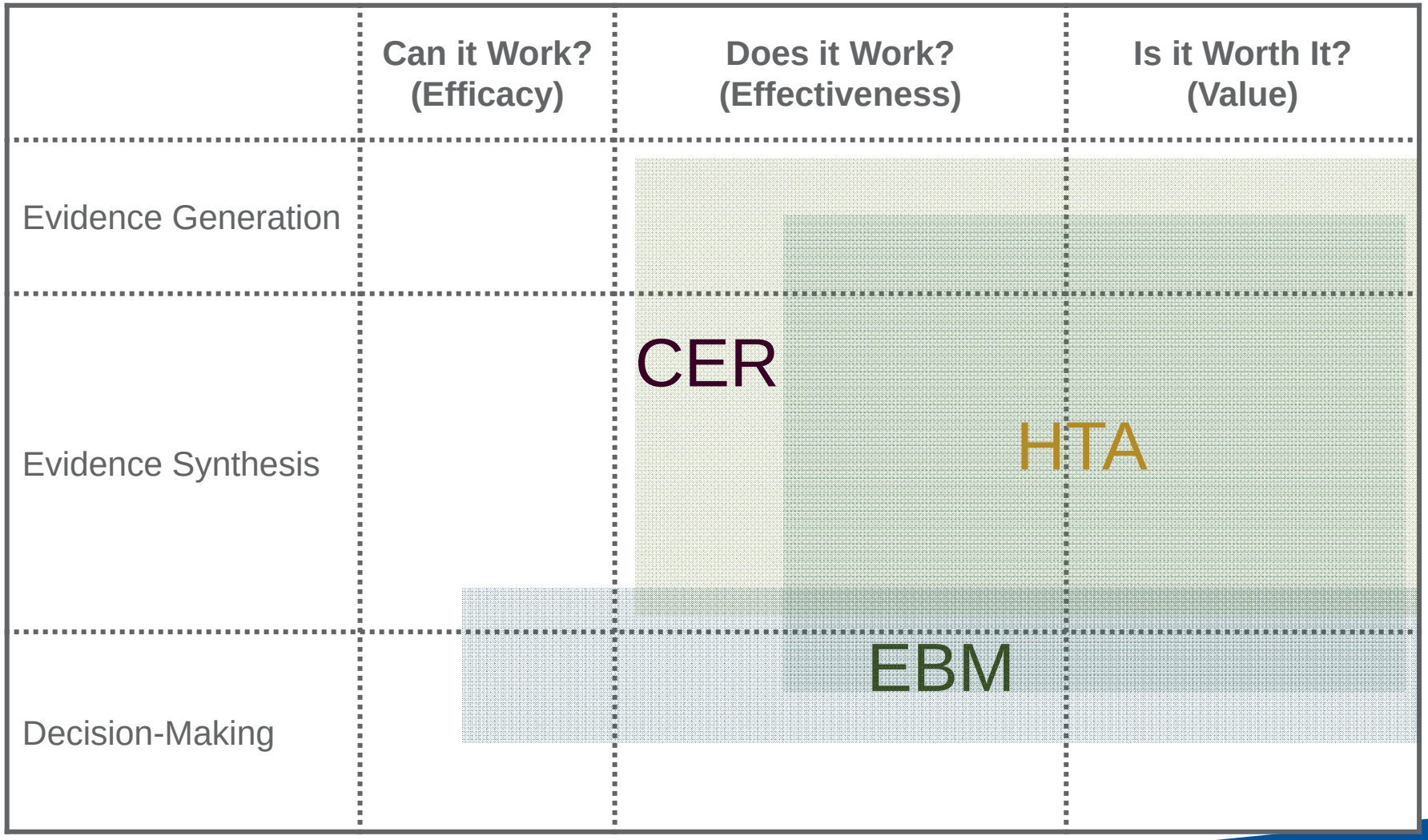
1. http://www.euro.who.int/__data/assets/pdf_file/0018/90432/E87866.
2. http://www.inahta.org/upload/HTA_resources/HTA Decision Makers.

What is the role of HTA?

Evidence-based Medicine (EBM)	> EBM is an **evidence synthesis and decision process** used to assist patients' and/or physicians' decisions. > It considers evidence regarding the effectiveness of interventions and patients' values and is mainly concerned with individual patients' decisions, but is also useful for developing clinical guidelines as they pertain to individual patients.
Comparative Effectiveness Research (CER)	> CER includes **both evidence generation and evidence synthesis.** > It is concerned with the **comparative assessment** of interventions in routine practice settings. > The outputs of CER activities are useful for clinical guideline development, evidence-based medicine, and the **broader social and economic assessment of health technologies** (i.e., HTA).
Health Technology Assessment (HTA)	> HTA is method of **evidence synthesis** that considers evidence regarding clinical effectiveness, safety, cost-effectiveness, and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. > A major use of HTAs is in **informing reimbursement and coverage decisions**, in which case HTAs should include benefit-harm assessment and economic evaluation.

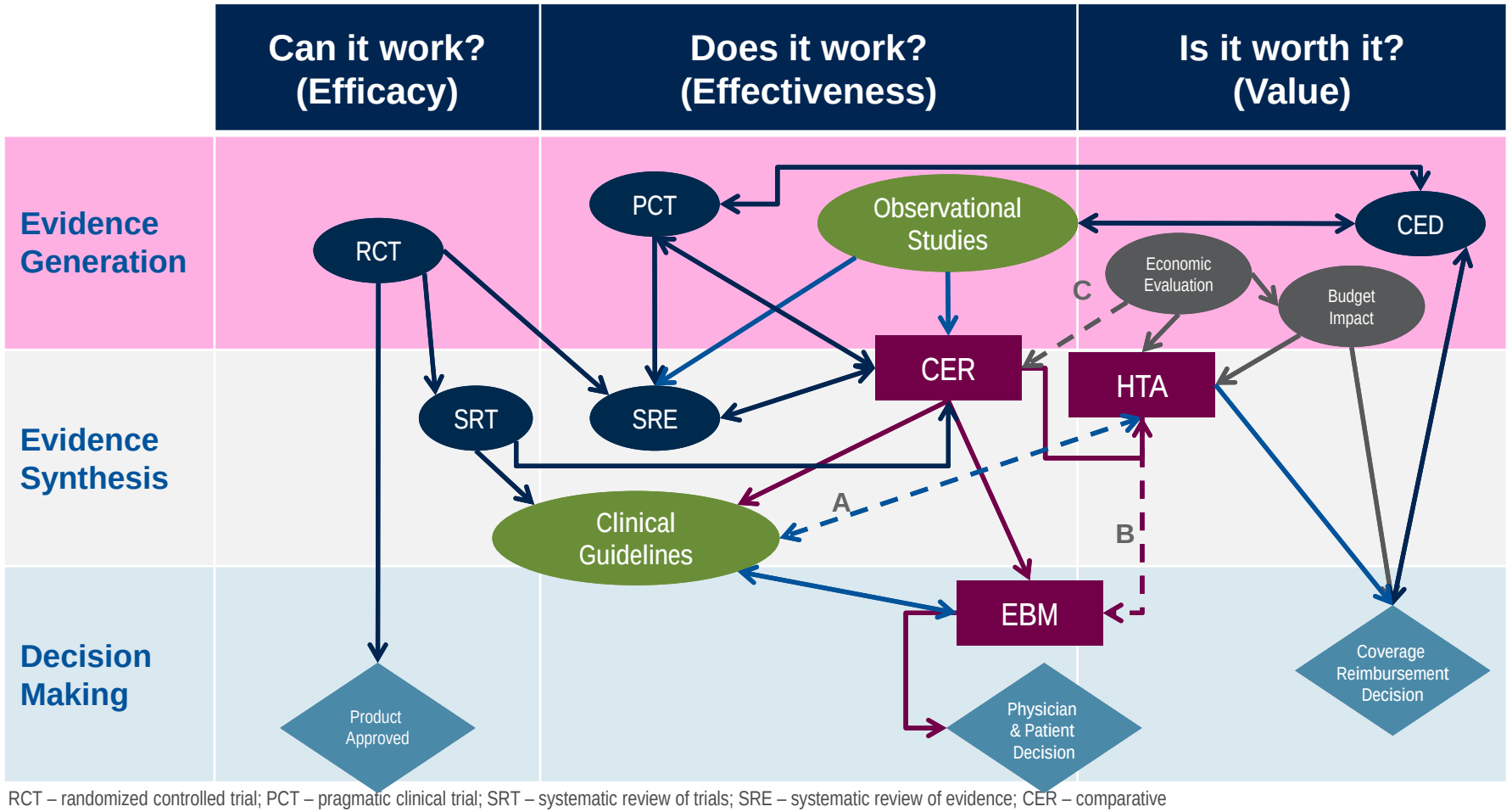
Source: Luce BR, Drummond M, Jönsson B, et al. *Milbank Quarterly*. 2010;88(2):256-276.

Confusion Exists Concerning Appropriate Definitions of CER, HTA, and EBM



Source: Luce BR, Drummond M, Jönsson B, et al. *Milbank Quarterly*. 2010;88(2):256-276.

Redefined Relationships of Evidence Processes



RCT – randomized controlled trial; PCT – pragmatic clinical trial; SRT – systematic review of trials; SRE – systematic review of evidence; CER – comparative effectiveness research; HTA – health technology assessment;
EBM – evidence-based medicine; CED – coverage with evidence development.

Solid lines indicate clear relationships, and dotted lines indicated disputed relationships. Diamonds represent decision processes, and circles and ovals represent all other evidence activities, except for the rectangles, which are reserved for EMB, HTA, and CER.

Why HTA?

Informed decision making in healthcare, main purpose[1]

Includes decisions made at the patient level, healthcare provider level, up to the national level[2]

Address the impact of the intervention including direct and indirect consequences[2]

Inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value[1]

Directly-related to evidence-based medicine[2]

1. http://www.nlm.nih.gov/nichsr/hta101/ta10104.html#Heading7.

2. http://www.inahta.org/upload/HTA_resources/HTA Decision Makers.

Who Uses HTA?

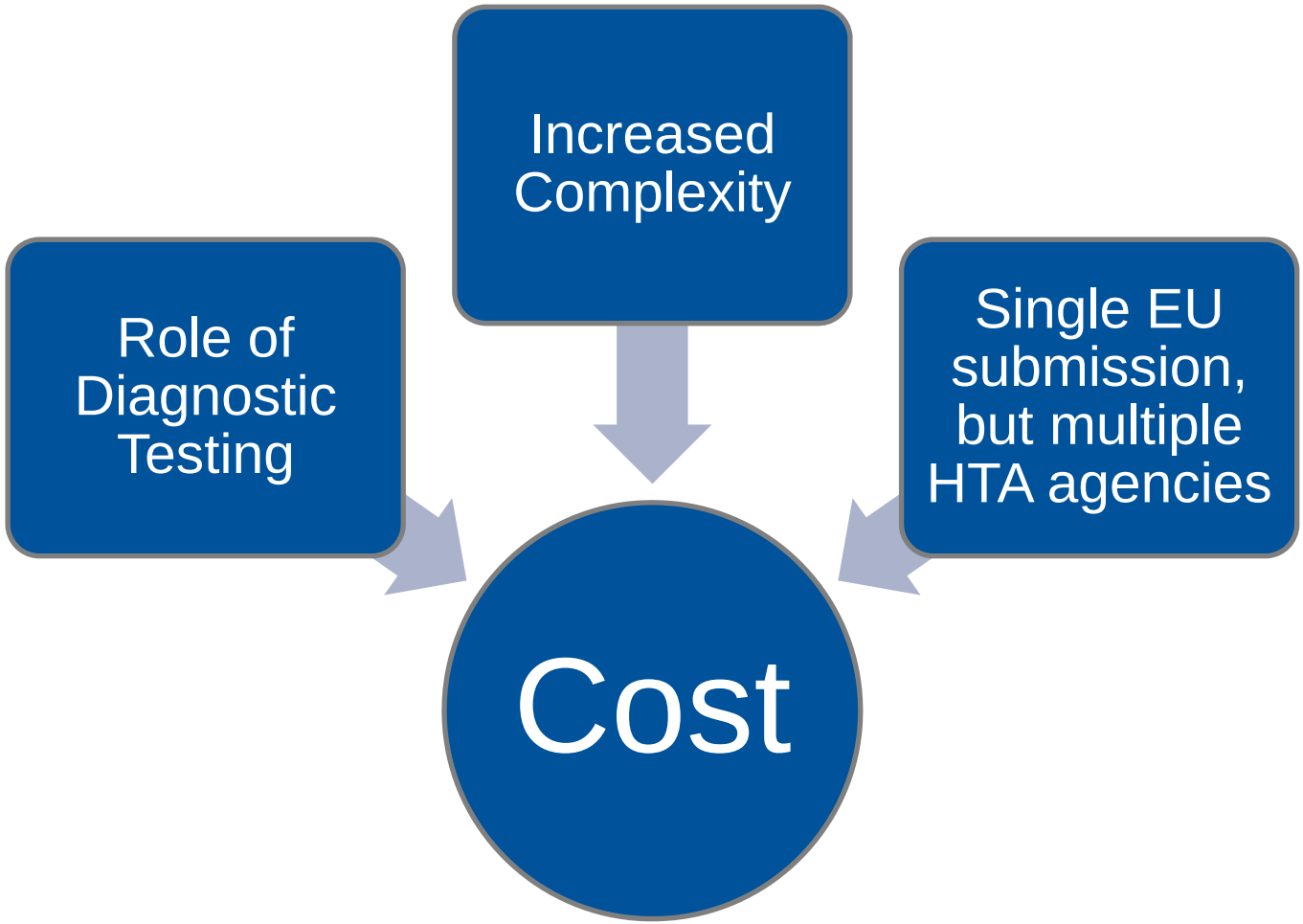
Different healthcare decision makers	Regulatory agencies
	Healthcare payers
	Clinicians and patients
	Hospitals and clinics
	Healthcare product companies
	Managed care organizations
	Government and private sector payers

Source: http://www.inahta.org/upload/HTA_resources/HTA Decision Makers.

Key HTA and Payer and Industry Challenges for Immunotherapy in Oncology

- **COSTS**
- **ROLE OF DIAGNOSTIC TESTING**
- **INCREASED COMPLEXITY**
- **SINGLE EU SUBMISSION, BUT MULTIPLE HTA AGENCIES**

Challenges for Immunotherapy in Oncology Mainly Center around Cost



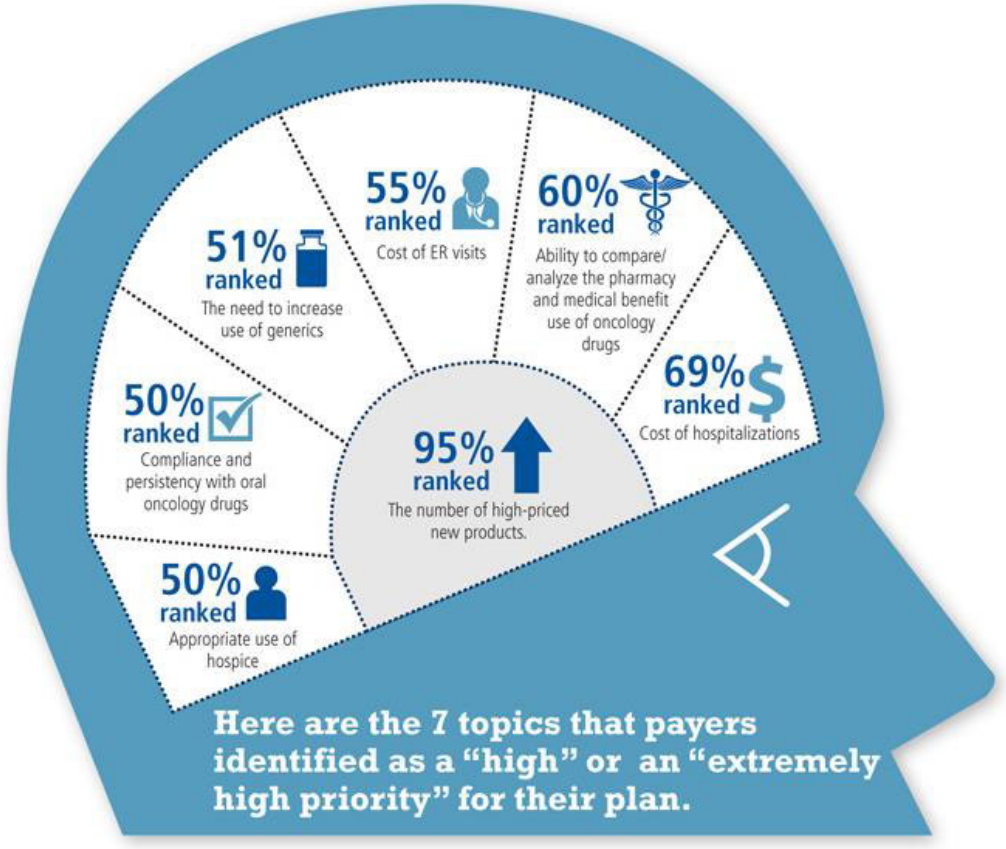
Payer and Industry Challenges with Costs

- **Funding IO drugs in addition to already expensive oncology treatments with fixed budgets**
- **Difficulties measuring value of the drugs vs. costs to the healthcare system (QALY, ICER)**
- **Manufacturers may need to work out discounts with payers to gain access**
- **Potential for misuse of information by different stakeholders**
- **“Burnt” feeling in the past from having to deal with treatment failures / sub-optimal therapies**

Even US payers are reaching a tipping point where budgetary considerations are inevitable

High drug prices coming under increased scrutiny

- 95% of surveyed payers ranked high-priced new products as a “high” or an “extremely high” priority
- In 2012, the makers of Zaltrap® were forced to lower the price due to negative publicity



Source: 7 Oncology Trends on Payers’ Minds. http://www.xcenda.com/Insights-Library/Payer-Perspectives/7-Oncology-Trends-on-Payers-Minds/.

Payer and Industry Challenges with Diagnostic Testing

- **Inability to easily identify which tests actually reduce costs**
- **Difficulty in tracking the use of molecular tests resulting in high overall costs from indiscriminate use**
- **Difficulty of enforcing protocols to ensure physicians provide appropriate care based on test results**
- **May be difficult to develop even if the target is known**
- **Lack of longitudinal accounting to allow for long-term savings from near-term testing due to patient turnover**

"Generating high-quality health economic evidence will provide reimbursement confidence that will allow payers to more rapidly adopt tests and align physician incentives with patient care and outcomes, rather than procedures" – Davis et al

Source: Davis, JC, et.al. Nature Reviews/Drug Discovery; Vol. 8, April 2009, p. 279-286

Payer and Industry Challenges with IO Complexity

- **Populations meet very specific requirements and often too small to be split across many subgroups**
- **Increased complexity often translates into higher development costs**
- **Difficulties may exist in determining where these therapies fit in the line of therapy (2nd , 3rd line?)**
- **IO drugs may result in a vastly improved safety profile, which may be less quantifiable as part of the benefit-risk equation**
- **Therapy might be used in non oncology indications with a different dose regimen leading to challenges in price negotiations**

HTA Challenges - Case study of Opdivo (nivolumab)

Australia	Canada	Germany	United Kingdom
			
No ICER threshold set by PBAC; Favorable recommendation more likely with an ICER around $30,000 than with an ICER above $70,000	No explicit ICER threshold; Generally <80,000 CAD per QALY is favorable	Cost is not considered in initial appraisal	£20,000–£30,000 per QALY gained is generally considered cost-effective
Immunotherapy – Spotlight on Opdivo (nivolumab)			
Not Recommended	**Conditional Funding**	**Major Added Benefit**	**Not Recommended**
PBAC recommended not to list in the PBS for SQ or NSQ as the submitted ICER of $45,000-$75,000 was viewed as significantly underestimated. Additionally, for NSQ, an economic comparison to pemetrexed was not presented and was considered by PBAC to be a relevant main comparator.	pCODR recommended conditional funding based on improvement of the drug's cost-effectiveness to an acceptable level compared to docetaxel. SQ: Submitted ICER $151,560/QALY; EGP reanalysis $193,918-$219,660/QALY NSQ: Submitted ICER $133,520/QALY; EGP reanalysis $183,386-$236,851/QALY	IQWiG determined that nivolumab has a major added benefit over appropriate comparator of docetaxel for people with NSCLC under 75-years old with relatively good performance status.	SQ: Submitted ICER of £85,950/QALY compared to docetaxel. ERG revised analysis resulted in ICER of £132,989/QALY. NSQ: Submitted ICERs of £103,589/QALY and £126,861/QALY compared to docetaxel alone or with nintedanib, respectively. The committee reported the most likely ICER is £91,100 and £93,400/QALY compared to docetaxel alone or with nintedanib, respectively.

David Campbell and Dylan Mezzio, Xcenda HTA Quarterly, http://www.xcenda.com/Insights-Library/HTA-Quarterly-Archive-Insights-to-Bridge-Science-and-Policy/HTA-Quarterly-Late-Spring-2016/Therapeutic-Spotlight-New-NSCLC-Treatments-Hope-Patients-Complexity-Treatment-Sequence-Market-Access/

Statisticians to the Rescue

"Data don't make any sense,
we will have to resort to statistics."

Statistical Expertise to Overcome the IO Challenges

Survival Modelling with Application to HTA

- Correlations with surrogate endpoints

Validation of surrogate endpoints in Oncology trials

- May also include the use of composite endpoints

Network Meta-Analysis (NMA)

- What is the most appropriate type(s) of NMA (indirect treatment comparison) to use for HTA purposes in Oncology?
- How viable is this for IO treatments?

Patient Reported Outcomes

- Statistical analysis for HTA purposes, especially if used in real-world evidence studies

Statistical Expertise to Overcome the IO Challenges (2)

Appropriate inclusion and analyses of Real-world Evidence (RWE), "Big Data"

- Increasing the validity / generalizability of RWE data
- IMI GetReal (best practices), eg. Mathematical modelling to predict relative effectiveness from RCT efficacy data

Statistical input into pricing schemes separate from reimbursement as part of market access

- Includes more involvement in the value frameworks

Possibility, if any, of combining approaches to analysis/appraisal between HTA bodies

- Also increasing interest (demand) for more convergence between regulatory and reimbursement

Statistical Expertise to Overcome the IO Challenges (3)

Switching (Cross-over correction) in Oncology Trials

- Exclude switchers
- Censoring at switch
- Time varying covariate
- Inverse Probability of Censoring Weighting (IPCW; observational)
- Rank Preserving Structural Failure Time (RPSFT; randomisation based)
- Two-stage Accelerated Failure Time

Statistical expertise needed which is able to deal with rare, orphan indications and the trend with IO towards personalized medicine

- Possible need for more pragmatic studies

Source: Watkins C. et.al, Adjusting overall survival for treatment switches: Commonly used methods and practical application. Pharm Stats 2013 Nov-Dec;12(6):348-57

Statistical Expertise to Overcome the Challenges (4)

Use of Multi Criteria Decision Analysis (MCDA) as an alternative to cost per QALY?

- To better capture other dimensions of cost and benefit
- Favorable safety profile
- Reduction in use of cytotoxic regimens / surgeries / hospital days
- improved quality of life
- Improved various social values / enhanced well-being / convenience

Increased need for combining epidemiological with clinical data across the product life cycle

- Avelumab in Merkel Cell Carcinoma
- Projecting advanced melanoma incidence and prevalence combining with clinical and registry-based data

Example: Projecting cancer incidence and prevalence combining with clinical and registry-based data

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ISPOR 17th Annual European Congress
November 8 – 12, 2014
Amsterdam, The Netherlands

Patient Count Projections for Advanced Melanoma by Line of Therapy and Other Clinical Characteristics in EU Countries: Results from the UK, Germany, France, Italy and Spain (EU-5)

Beatrice Gueron, PhD[2]; Jonathan Kish, PHD, MPH[1]; Ken O'Day, PhD, MPA[1]; Marie-Josée Martel, PhD[1]; Melinda Manley Daumont, MA, PhD[2]
[1]Xcenda, Palm Harbor, FL; [2]Global Health Economics and Outcomes Research -Europe, Bristol-Myers Squibb, Rueil-Malmaison, France

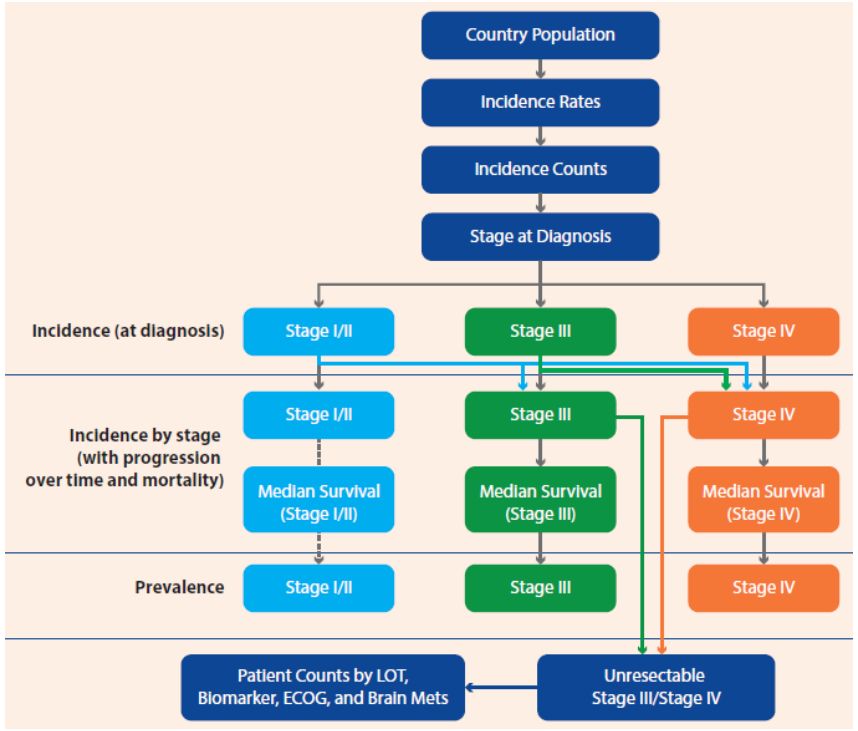
OBJECTIVES: To forecast the number of advanced melanoma (AM) patients newly initiating treatment over 5 years (2014-2018) by line of therapy and clinical/tumor characteristics (BRAF/PD-L1 mutations status and brain metastases).

RESULTS:

- Projected number of incident melanoma cases for 2014 *:
  Germany= 23,100; UK=18,900; France=12,400; Italy=12,000; Spain=5,800
  Of incident cases, 11.3%-13.0% were treatment eligible AM.
- Number of AM patients eligible for 1st & 2nd line treatment in 2018 :
  Germany=3,700 and 1,700; UK=3,100 and 1,400 ; France=1,900 and 500; Italy=1,800 and 1,000; Spain=1,100 and 400, representing approximately 10.8-12.0% of incident cases.

CONCLUSIONS:

- While melanoma incidence is projected to increase over the next 5 years the majority of incident cases will be diagnosed in earlier disease stages.
- From the incident melanoma population, AM patients initiating treatment is expected to be 12% in 2018, a slight decline from 13% in 2014.



* Rounded to nearest 100
Presented at ISPOR 17th Annual European Congress, November 8-12, 2014

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In Conclusion

- Ultimate success in the market place for Oncology immunotherapies will be driven, as it is the case for all products, by the relevance & strength of clinical & economic evidence provided to payers & HTA bodies

- Since differing HTA bodies can still be expected to view the same data and impact on heath care to its population differently and with the increased complexity of IO therapies, more modeling and all-inclusive quantitative statistical approaches are needed

- Closer involvement of statisticians in applying the most appropriate quantitative methods and models to IO therapies, including the use of data sources outside of the traditional RCT setting, and communicating these results to payers will be essential to meeting these challenges

Thank you

Comments, Critiques & Questions

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Where knowledge,
reach and partnership
shape healthcare delivery.