Multi-stakeholder perspective on assessing the long-term clinical benefit of cancer immunotherapy

ISPOR Educational Symposium

4 November 2019

Disclaimer

- **The views and opinions expressed by the presenters do not necessarily reflect those held by BMS.**

Presenters

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20 years' experience in P&R, market access, and health outcomes

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Lou Garrison

Professor Emeritus of
The CHOICE Institute

Previous ISPOR president

Co-chair of ISPOR
Good Practice and Special Task Forces

Phil McEwan

Professor and Technical Director at Centre for Health Economics, Swansea University

Managing Director,
HEOR Ltd

Agenda

1. **Introduction** — David Sykes, MSc
2. **Overview of cancer immunotherapies** — Associate Professor Gustav Ullenhag
3. **Multi-stakeholder primary research** — Professor Phil McEwan
   - Methodology
   - Results: key issues to address
   - Development of conceptual checklist
4. **Case study: ipilimumab for the treatment of advanced melanoma** — Professor Lou Garrison
5. **Conclusion** — David Sykes

Objectives

1
Review the biological mechanism by which patients derive benefit from cancer immunotherapy and how this differs from conventional oncology treatments

2
Summarize the key challenges for demonstrating the long-term survival benefit of cancer immunotherapy

3
Present a conceptual checklist for evaluating and communicating the long-term clinical benefit of cancer immunotherapy

4
Demonstrate how the proposed checklist could help manufacturers with HTA submissions, using ipilimumab as an example

Patron Saint of Cancer Patients (1265-1345)

St. Peregrine Laziosi, OSM

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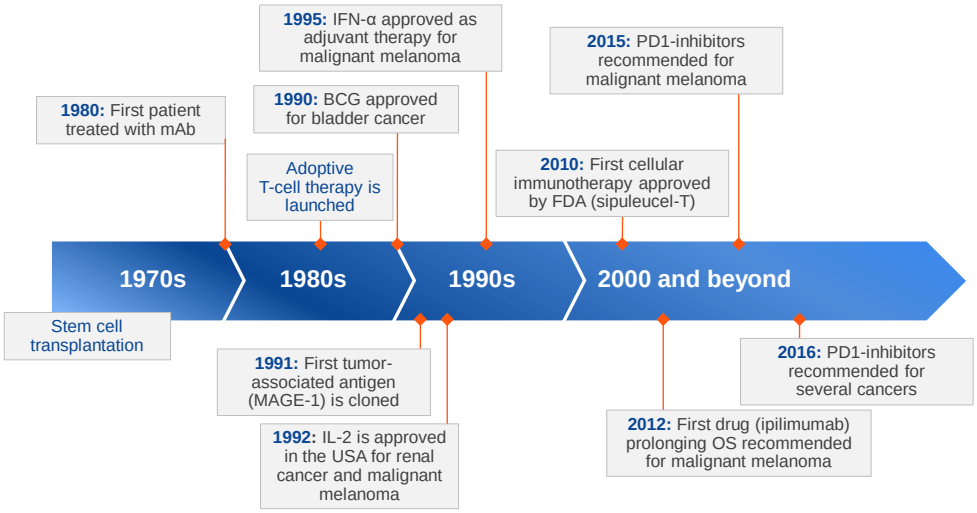
Milestones in development of cancer immunotherapy



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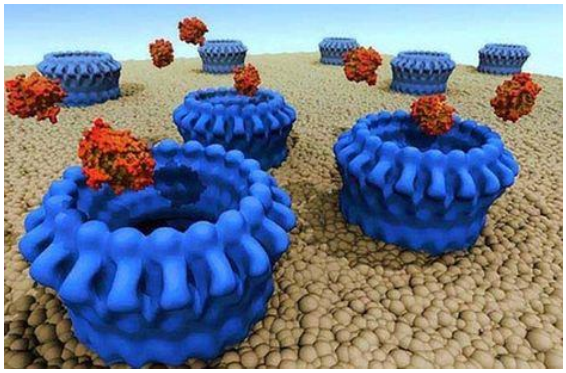
Mechanism of action of cancer immunotherapies

Unspecific versus specific

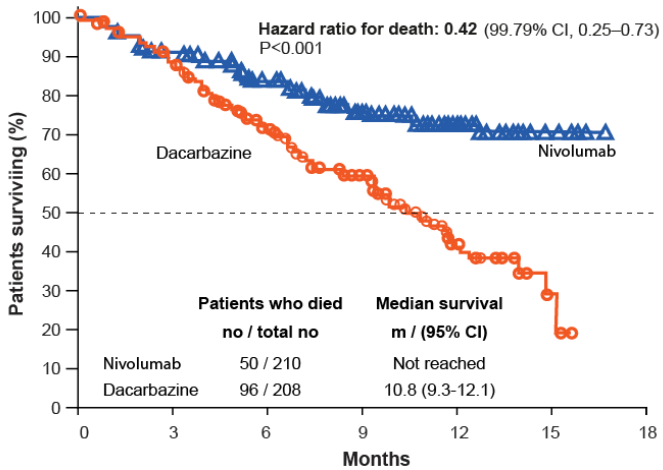
Passive versus active

- Checkpoint antibodies target a patient's immune system rather than directly attacking the tumor
- The resulting immunological response can persist even after treatment has stopped, leading to prolonged durable responses and improved survival in some patients
  - Tolerability has also improved compared with traditional therapies



The plateau effect of cancer immunotherapy

Long-lasting responses to immunotherapy lead to a 'plateau' in OS compared with chemotherapy



Robert C et al. N Engl J Med 2015; 372: 320-30

Assessing the clinical benefit of cancer immunotherapies

Standard efficacy endpoints in Phase II/III trials in oncology include:

- Overall survival ('gold standard' outcome)
- Progression-free survival (PFS)
- Overall response rate (ORR)
- Disease-free survival (DFS)

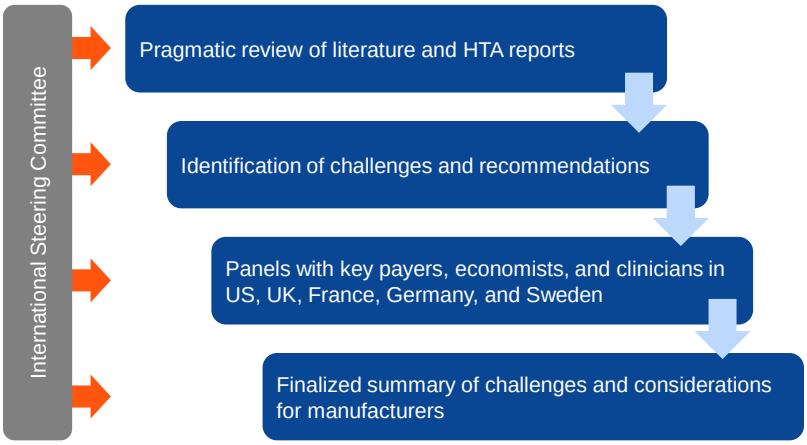
BUT

- Pseudo-progression can lead to an inaccurate estimate of PFS
- Response to IO therapy is variable and can be delayed

How can manufacturers best address these uncertainties?

Multi-stakeholder research

Overview of primary research methods



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Multi-stakeholder research

International steering committee

Lou Garrison

- Professor Emeritus of CHOICE Institute
- Previous ISPOR president
- Co-chair of ISPOR Good Practice and Special Task Forces

Phil McEwan

- Professor and Technical Director at Centre for Health Economics, Swansea University
- Managing Director of HEOR Ltd

Bengt Jonsson

- Professor Emeritus of Health Economics at Stockholm School of Economics

Michael Atkins

- Professor of Oncology and Medicine
- Past president of the International Society for Biological Therapy of Cancer

Peter Neumann

- Director at the Institute for Clinical Research and Health Policy Studies at Tufts Medical Center

Paolo Ascierto

- Director of the Unit of Melanoma, Cancer Immunotherapy and Innovative therapy at University of Naples

Andrew Briggs

- Co-chair of Joint Society for Medical Decision Making and ISPOR Task Force on Modeling Methods

Gérard de Pouvourville

- Chair Professor for Health Economics at ESSEC business school

Kevin Harrington

- Professor of Biological Cancer Therapies at The Institute of Cancer Research
- Consultant oncologist at The Royal Marsden

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Multi-stakeholder research

Double-blinded, country-level, multi-stakeholder panels

Double-blind panels were convened in the US, UK, France, Germany, and Sweden

- 4–6 stakeholders from each country
- Multidisciplinary: clinicians, health economists, and payers

Feedback informed development of the final conceptual checklist

- Panels discussed the key challenges identified by the steering committee and how to address them

Multi-stakeholder research

Summary of the key issues to address

Our steering committee and panels identified several key issues that stakeholders need to address

Lack of understanding of MOA in cancer immunotherapies

- Importance of understanding the underlying biological model and non-conventional response patterns

Limited clinical evidence at HTA submission

- Supporting immature survival data with real-world evidence and/or surrogate endpoints

Limitation of standard HTA methods to measure long-term survival

- Heterogeneity in treatment effect and outcomes
- Standard parametric survival models
- Alternative survival modeling methods
- Estimation of the lifetime survival benefit

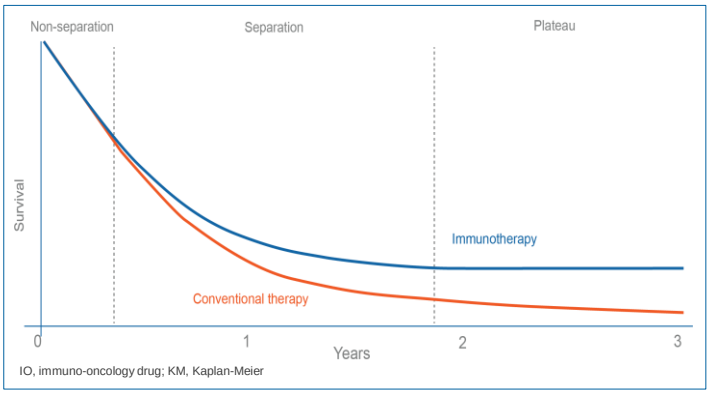
Key learnings from the double-blinded country-level multi-stakeholder panels

Feedback from country panels about payers' decision-making positions fell into issues of mechanism of action and analysis of survival benefit

					
Critical to educate stakeholders to help them understand the mechanism of action of immunotherapies and its implications	✓	✓	✓	✓	✓
Different agencies consider long-term clinical benefit of cancer immunotherapy differently	✓	✓	✓	✓	✓
Be consistent in HTA submissions to make immunotherapy treatment effect better understood			✓		✓
The existing HTA methods are unlikely to change			✓	✓	
The extrapolated tail of the survival curve is not considered		✓	✓		
Considering longer-term benefits in the initial decision-making is not possible		✓	✓		
Acceptance that survival modeling for immunotherapies must differ from standard approaches					✓
Capture all key benefits of the plateau effect, including cost- savings and utility benefits from treatment-free intervals	✓				

Mechanism of action of IOs

Underlying mechanism of action for IOs underpins the challenges in demonstrating the long-term benefit of these drugs



IO, immuno-oncology drug; KM, Kaplan-Meier

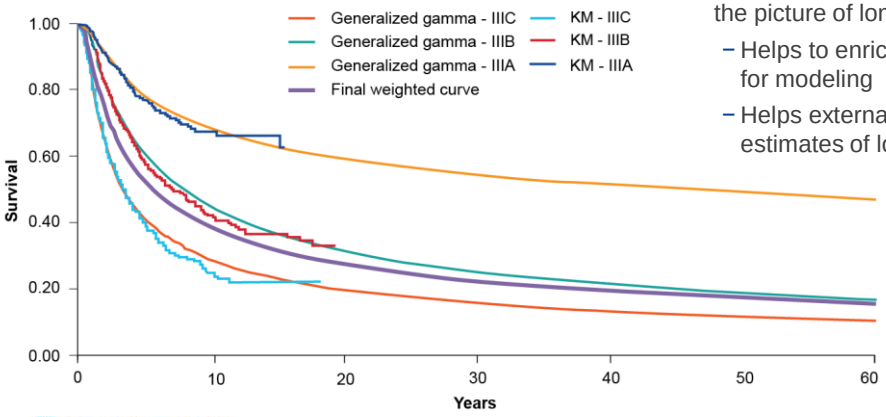
Statistical modeling should be supported by a biological model that can:

- support the presence of the plateau in survival
- help identify and locate the plateau on a Kaplan-Meier (KM) curve
- support innovative, emerging statistical methods that move beyond proportional curve-fitting

Limited clinical evidence at HTA submission

Supporting immature OS data with real world evidence

AJCC 7th edition registry data



RWE is not yet commonly used in HTA

- Recommendations are to develop and make greater use of registry data to build the picture of long-term survival with IOs
  - Helps to enrich the available data for modeling
  - Helps external validation of model-based estimates of long-term survival

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NICE TA558 (2018) Nivolumab for adjuvant treatment of resected stage III and IV melanoma

Limited clinical evidence at HTA submission

Immature OS creates a need to find surrogate endpoints

Surrogate endpoint for OS with IOs have been challenging to validate

- Neither PFS or ORR have been validated as surrogates for IOs

Durable response rate (DRR) and intermediate response endpoint (IME) have been described as 'promising' surrogates

- Highly associated with OS
- DRR is a composite of standard response criteria and a prospective duration of 6 months
- IME requires a complex analysis of patient lesion information within 1 year post randomization

Treatment-free interval (TFI) and treatment-free survival (TFS) are potential surrogates for hematologic malignancies

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Branchoux et al. Crit Rev Oncol Hematol 2019;137:35-42

Addressing heterogeneity in treatment effect and outcomes

Some patients experience prolonged survival after treatment with immunotherapies, but we cannot predict who these will be

- Frequently noted by HTA agencies
- No reliable biomarkers to predict outcomes, many examined
- Being unable to identify the heterogeneity in a predictable way limits the ways in which statistical modeling might better predict survival

> "…to date no patient characteristics or biomarkers have been identified which can prospectively target treatments to the small minority of patients most likely to benefit from the very substantial life extension which may be possible as a result of treatment with ipilimumab.
>
> The practical problem of reliably estimating the magnitude of such benefits from the results of clinical trials with limited follow-up also remains unresolved.[1]"

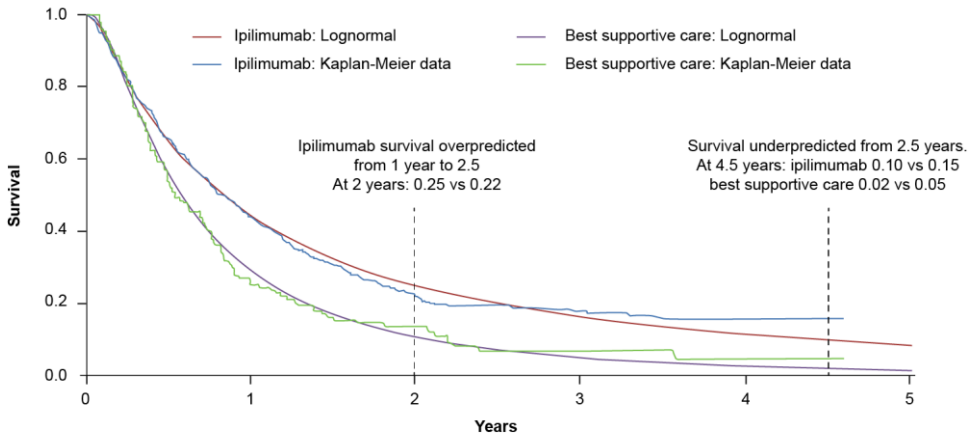
1. Dickson R *et al.* Ipilimumab for previously treated unresectable malignant melanoma: A Single Technology Appraisal. LRiG, The University of Liverpool, 2011.

Limitations of using parametric models for analyzing IOs

Standard parametric modeling may be inappropriate for immunotherapies

- Standard recommended approaches to survival analysis use Cox or simple regression models to test for proportional hazards (PH):
  - Yes: Cox PH models, exponential, Weibull, Gompertz
  - No: accelerated failure time models – Weibull, lognormal, loglogistic
- Traditional focus is on statistical and visual to observed data
- Ignores underlying biology of disease
- Can create poor extrapolations with non-proportional hazard, delayed effect, and long-term survival – such as seen with immunotherapies

Survival modeling should reflect key issues with immunotherapy



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Larkin J *et al.* PLOS ONE 2015. https://doi.org/10.1371/journal.pone.0145524

Several alternative, more flexible survival modeling approaches have emerged

- Piecewise parametric models
- Cubic spline models
- Mixture distribution models
- Response-based survival models

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Conceptual checklist for healthcare decision makers and manufacturers

The checklist presents a set of issues to be addressed, linked to the key challenges

It is recommended that manufacturers:

- approach the questions systematically as they consider evidence generation and modeling, and
- determine whether each topic or item is applicable, as well as whether additional evidence is needed

Checklist

Checklist for healthcare decision makers and manufacturers

Mechanism of action

- Representation of the underlying biological model
- Possibility of cure underlying the long-term survival
- Addressing pseudo-progression

Limited clinical trial evidence at HTA filing

- Duration of follow-up and maturity of OS and PFS
- Availability and use of intermediate and/or surrogate endpoints

Model structure and survival extrapolation methodology

- Use of non-standard model structure to capture immunotherapy effect
- Capturing heterogeneity in treatment effect and outcomes
- Availability and use of biomarkers to predict long-term survival
- Shape of the survival curve/plateau and smoothing estimators of the hazard function
- Clinical plausibility and validation of the extrapolation using real-world evidence or other data

HTA submission

- Linking central points with payer, clinician, and patient perspectives on immunotherapy

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Checklist

Checklist for healthcare decision makers and manufacturers

Mechanism of action	Addressed	N/A	Evidence generation required
Representation of the underlying biological model			
Possibility of cure underlying the long-term survival			
Addressing pseudo-progression			

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Checklist

Checklist for healthcare decision makers and manufacturers

Limited clinical trial evidence at HTA filing			
	Addressed	N/A	Evidence generation required
Duration of follow-up and maturity of OS and PFS			
Availability and use of intermediate and/or surrogate endpoints			
Use of non-standard model structure to capture immunotherapy effect			

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Checklist

Checklist for healthcare decision makers and manufacturers

Model structure and survival extrapolation methodology			
	Addressed	N/A	Evidence generation required
Use of non-standard model structure to capture immunotherapy effect			
Capturing heterogeneity in treatment effect and outcomes			
Availability and use of biomarkers to predict long-term survival			
Shape of the survival curve/plateau and smoothing estimators of the hazard function			
Clinical plausibility and validation of the extrapolation using real-world evidence or other data			

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Checklist for healthcare decision makers and manufacturers

HTA submission			
	Addressed	N/A	Evidence generation required
Linking central points with payer, clinician, and patient perspectives on immunotherapy			

Case study

Case study: ipilimumab in melanoma

NICE Technology Appraisal 268: Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma

- Published 12 December 2012
- One Appraisal Consultation Document
- Supplementary analyses submitted by BMS
- Two clarification letter and response between NICE ERG and BMS
- Final Appraisal Determination

Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme.

NICE, TA 268

Case study

Case study: ipilimumab in melanoma

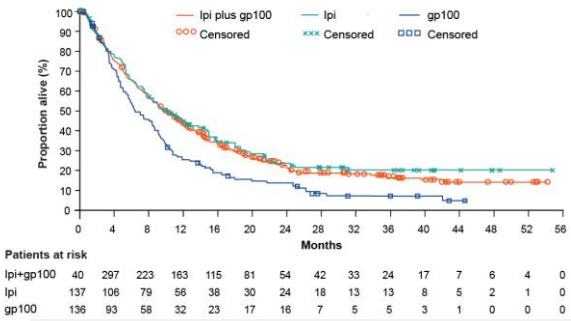
One Phase 2 and one Phase 3 RCT were used for efficacy

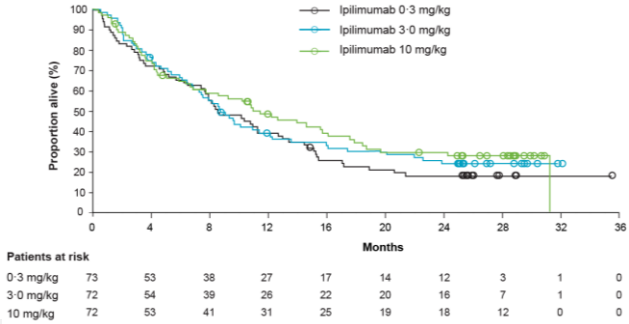
	Hodi et al. 2010[1] NCT00094653	Wolchok et al. 2010[2] NCT00289640
Study type	Randomized, double-blind, multicenter, Phase 3	Randomized, double-blind, multicenter, dose-ranging, Phase 2
Primary endpoint	Best ORR, later amended to OS	Best ORR
Secondary endpoints	OS Best ORR DOR PFS at week 24	DCR Median OS and survival at 1 year PFS at week 24.
Duration of follow-up	55 months Median for OS: 17.2–27.8 months	Median for OS: 8.3–10.7 months

Hodi FS et al. N Engl J Med 2010;363:711-23. Wolchok JD et al. Lancet Oncol 2010;11:155-64.

Case study

Case study: ipilimumab in melanoma





Both OS curves showed a plateau

- Both studies were effectively underpowered at the points when the plateau occurred
- Both OS curves required extrapolation for long-term OS
- Both show non-PH

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Hodi FS et al. N Engl J Med 2010;363:711-23. Wolchok JD et al. Lancet Oncol 2010;11:155-64.

Case study

Case study: ipilimumab in melanoma

BMS undertook several approaches to extrapolation of long-term survival

All approaches were framed as designed:
"in order to achieve a good fit … the method delivers the best fit (in terms of the Akaike Information Criterion [AIC]) was used for the base case of the model."

- Single-curve fit: Weibull, exponential, lognormal, log-logistic and Gompertz functions with the best fitting curve chosen using the minimum AIC.
- Two-part curve fit: Kaplan Meier data to 18 months, and a curve fitted to the data from 18 months onwards – **this method followed recognizing that the PH approach was not appropriate to the data**

Validation of model projections was undertaken with reference to another study in melanoma, of IL-2, with 11 years of follow-up

In response to the appraisal consultation document, BMS used long-term survival data from the AJCC – real-world evidence of long-term survival that can validate results and help calibrate model

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AJCC, American Joint Committee on Cancer

Case study

Case study: ipilimumab in melanoma

The NICE Evidence Review Group attempted a different method

Their approach was also directed towards good statistical fit

- Justified by yielding *"…reasonable estimates, minimizing uncertainty due to projection assumptions."*
- Made repeat mentions that there were
  "To date no patient characteristics or biomarkers have been identified which can prospectively target treatments to the minority of patients most likely to benefit from treatment with ipilimumab."
- Used different approaches to response-based modeling, based on best ORR at 24 weeks
- Found poor statistical fit and projections, due in part to:
  - immature data for OS
  - best ORR at single time-point not informative

Committee concluded that ERG attempts were no better at reducing long-term uncertainty than BMS methods

Checklist

Checklist for healthcare decision makers and manufacturers

Many points about the mechanism of action were made by BMS, but none linked to the immune-related treatment effect or long-term survival

	Addressed
Mechanism of action	Supportive data from earlier-phase studies used in the submission but not linked to long-term survival modeling
Representation of the underlying biological model	Immune response a part of the presented analysis but not linked to long-term survival modeling
Possibility of cure underlying the long-term survival	Durable biological effect mentioned only in passing
Addressing pseudo-progression – a factor or not?	Addressed by discussing delayed immune-related response

Checklist

Checklist for healthcare decision makers and manufacturers

Little use was made of available trial data to support long-term survival benefit modeling specifically for immunotherapy

	Addressed
Use of available clinical evidence	
Duration of follow-up and maturity of OS and PFS	×
Availability and use of intermediate and/or surrogate endpoints	×

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Checklist

Checklist for healthcare decision makers and manufacturers

The model structure broke away from single-curve fits in recognition of the plateau and non-PH

The target was still good statistical fit

	Addressed
Model structure and survival extrapolation methodology	
Capturing heterogeneity in treatment effect and outcomes	×
Availability and use of biomarkers to predict long-term survival	×
Shape of the survival curve/plateau and smoothing estimators of the hazard function	The use of the two-part curve and 18-month cut-point targeted the plateau
Clinical plausibility and validation of the extrapolation using real-world evidence or other data	Validation using IL-2 long-term analysis and AJCC registry data

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Checklist

Checklist for healthcare decision makers and manufacturers

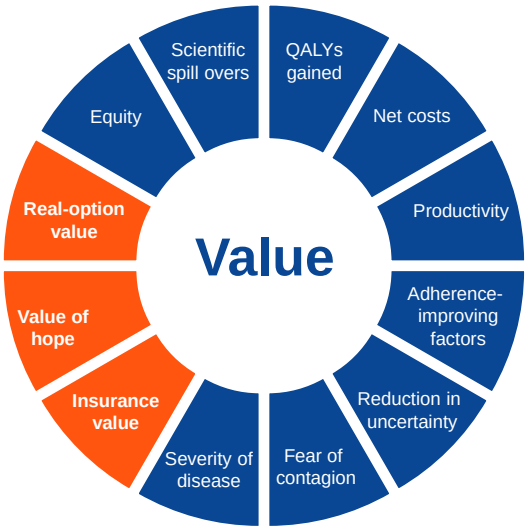
Limited use was made of the perspectives of other stakeholders

BMS revised their modeling to respond to NICE using clinical opinion – led to use of AJCC data

	Addressed
HTA submission	
Linking central points with payer, clinician, and patient perspectives on immunotherapy	Clinical experts used to update assumptions and use AJCC data at 15 years to calibrate OS

Checklist

What is the future of value assessment?



Conclusions

- IOs have provided a paradigm shift in cancer outcomes, with the possibility of durable long-term responses and significantly improved OS
- This has presented HTA agencies with a new challenge as to how they appropriately measure long-term clinical benefit
- Several methodological issues highlighted in this session demonstrate the gap between the evolution of HTA thinking and current clinical science
- Clinical applications of IOs in earlier lines of treatment, where OS may not be the most appropriate endpoint, could widen this gap
- We have presented a checklist that aims to help manufacturers and decision-makers better understand and more clearly articulate the long-term clinical benefit of IOs
- All stakeholders need to collaborate to change the paradigms of drug assessment and clinical study design, to better support access to reimbursed IOs