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How Effective are Managed Access Agreements as a Vehicle for Earlier Reimbursement in the Presence of Uncertainty? Lessons from the New Cancer Drugs Fund

Ron Akehurst, BresMed Health Solutions
Steve Williamson, NHS England
Jennifer Lee, Janssen-Cilag Limited
Stephen Palmer, Centre for Health Economics, University of York

BresMed™

About the presenters

Professor Ron Akehurst	Moderator	Chairman, BresMed Health Solutions and Emeritus Professor of Health Economics, University of Sheffield
Steve Williamson	CDF/NHSE perspective	Cancer Drugs Fund, Pharmacy Lead
Jennifer Lee	Manufacturer perspective	Director of Health Economics, Market Access, Reimbursement & Advocacy, Janssen-Cilag Limited
Professor Stephen Palmer	Academic perspective	Centre for Health Economics, University of York. Member of NICE Appraisal Committee and Decision Support Unit

Breakout Session 9, Wednesday, 6 November	Agenda	Discussion Leader
08.30–08.40	Opening, introductions and objectives	Ron Akehurst
08.40–08.50	Presentation: Cancer Drugs Fund/NHS England perspective	Steve Williamson
08.50–09.00	Presentation: Manufacturer perspective	Jennifer Lee
09.00–09.10	Presentation: Academic perspective	Stephen Palmer
09.10–09.30	Q&A/discussion	Ron Akehurst

Introduction

- Cancer Drugs Fund (CDF) re-established mid-2016
  - New approach – 'Recommended for use within the CDF'
  - Interim reimbursement – drug with the plausible potential to be cost-effective but remaining clinical uncertainty
  - Managed access agreements between companies and NHS England
  - Evidence collection
    - Systemic Anti-Cancer Therapy (SACT) dataset
    - Clinical studies
- Ring-fenced budget
  - Budget is £340m
  - Rebates
- So far two treatments have been reappraised under the new CDF framework. Both were accepted for routine commissioning

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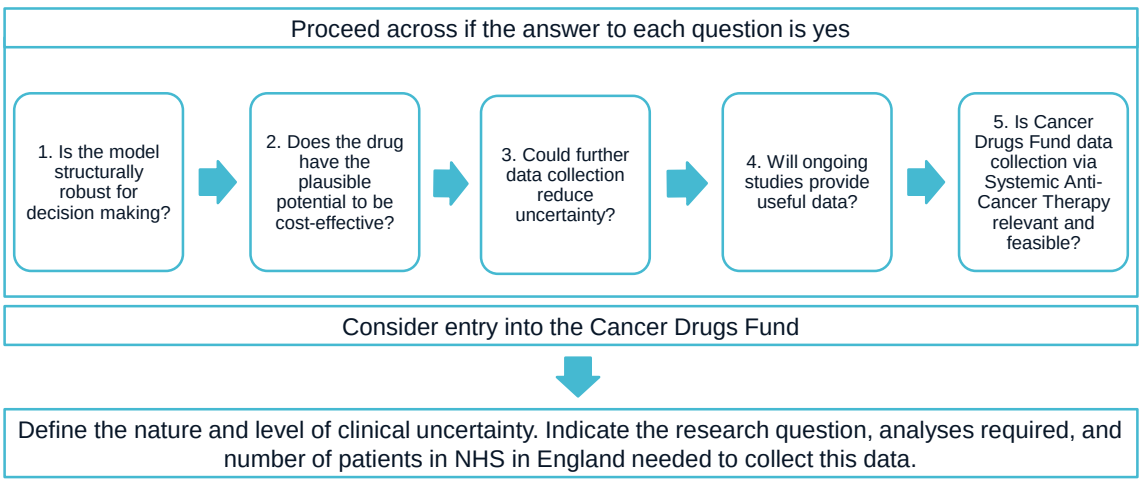
Five questions to determine relevance for the Cancer Drugs Fund



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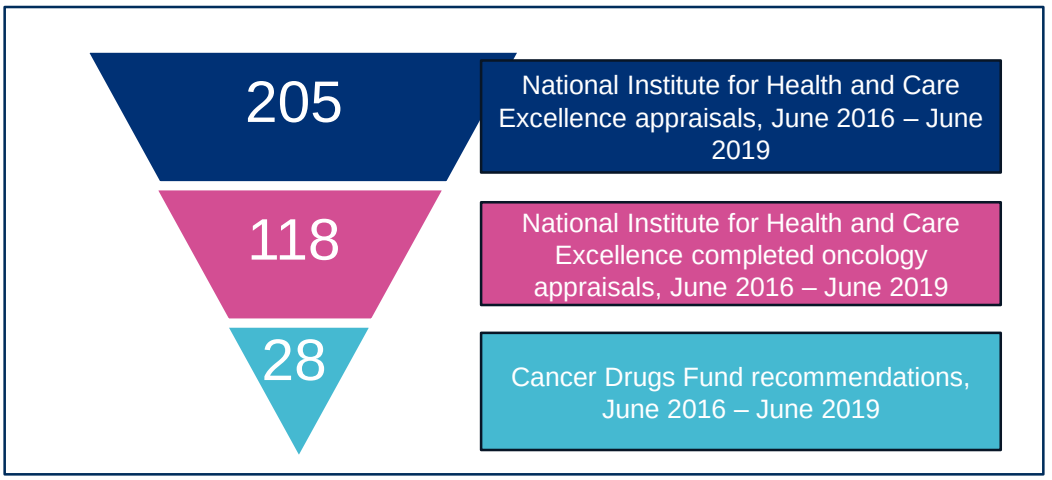
Findings … Appraisals/recommendations for the Cancer Drugs Fund



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Initial findings – Cancer Drugs Fund

Primary sources of uncertainty	Acknowledged as area of uncertainty	Addressed in DCA
Overall survival	**28**	**27**
Health-related quality of life	**14**	**4**
Single-arm study	**13**	**3**
Persistence of treatment effect	12	10
Progression-free survival	12	9
Comparator Efficacy	10	3
Time-on-treatment	8	12
Subsequent treatment	7	5
Surrogacy	5	5
SCT rate	5	3
Subgroup efficacy	3	5
Use of IVIg	3	3
Cure rate	3	2
Generalisability	3	2
Retreatment	3	2
Pre-progression mortality	1	1

Primary sources of uncertainty identified by the committees

- Overall Survival data collected is to be addressed in 27/28 Cancer Drugs Fund ‘cases’
- Health related quality of life data was identified as a source of uncertainty in 14 appraisals, with further data anticipated to be collected in only four DCAs
- Single-arm studies were cited as a source of uncertainty in 13 appraisals but with only three DCAs targeted at collecting evidence which will resolve this uncertainty

Source of data collection

- 22/28 appraisals will collect data from an ongoing clinical study as the primary source of evidence
- 6/28 appraisals will collect ‘external’ data as the primary source of new evidence

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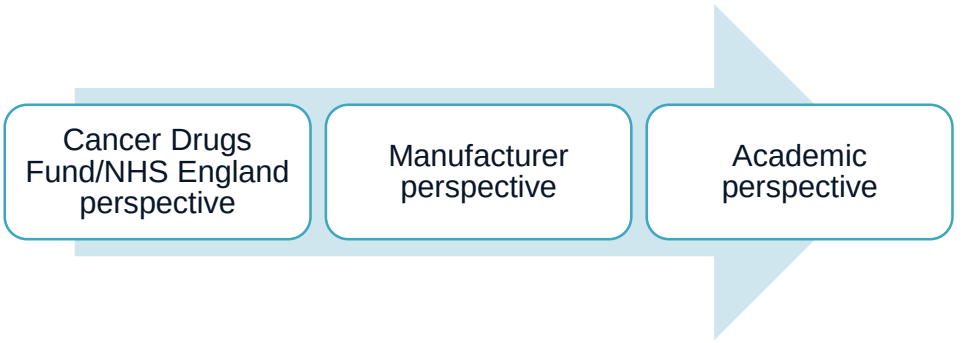
Subject for debate

Does the Cancer Drugs Fund currently provide the optimal framework for managed access in England and what learnings can be taken from alternative countries or approaches?



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The Cancer Drugs Fund: NHS England Perspective

Steve Williamson
Lead Cancer Pharmacist
NHS England and NHS Improvement
On Behalf of the CDF Team

Declarations

None

I am speaking as public sector employee so no payment or payment in kind has been received for participating in this sponsored session

Agenda

1. A quick refresher on the NICE and CDF process
2. Entry into the CDF: Dealing with uncertainty
3. Engagement with manufacturers in the CDF process

NICE CDF Recommendations

- NICE makes one of three decisions on whether a cancer drug should be made available for patients through the National Health Service. The decisions are:

1. Yes – the drug should be routinely commissioned
2. No – the drug should not be routinely available
3. Recommended to the Cancer Drugs Fund – for a drug which
   - Has key uncertainties as to the clinical and cost effectiveness which can be resolved with data maturity/collection

   and

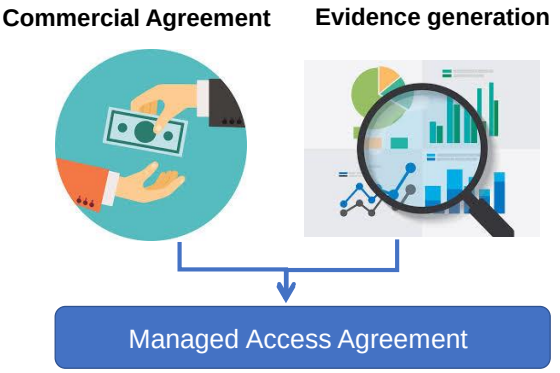
   - At the time of appraisal the drug has a range of plausible cost effectiveness estimates which at least crosses the NICE threshold of cost effectiveness

NICE and CDF delivering unprecedented access

- Decisions by NICE for new cancer drug indications over the last 4 years include:
  - Ninety-seven positive routine commissioning recommendations, including 'optimised' recommendations which, arguably clinicians would have implemented anyway
  - Only three of the optimised NICE recommendations had significant clinical restrictions on grounds of insufficient clinical and cost effectiveness evidence
  - Twenty-eight referred to the CDF, two exits from CDF*. No refusals to enter CDF
    - ❖*Since recommended for routine commissioning
- Nineteen negative recommendations: four valued by clinicians for treatment pathways but two of these have drugs in the same class in routine commissioning

See: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/TA-cancer-recommendations.xlsx

Clear entry and exit for all CDF topics



CDF Recommendations: Commercial Agreement

- CDF drug approvals require a Commercial Agreement which ensures that they are within the range for cost-effectiveness that NICE normally considers an efficient use of NHS resources
- Commercial Agreements for the CDF offer more flexibility in terms of structure than those for routine commissioning and are highly confidential between the company and the CDF. These are indication-specific and time-limited to the Managed Access Agreement period
- The drug is subsequently re-appraised once data maturity/collection has been achieved. It is then subject to a final decision as to whether it will be approved for baseline commissioning.

CDF Recommendations: Evidence Generation

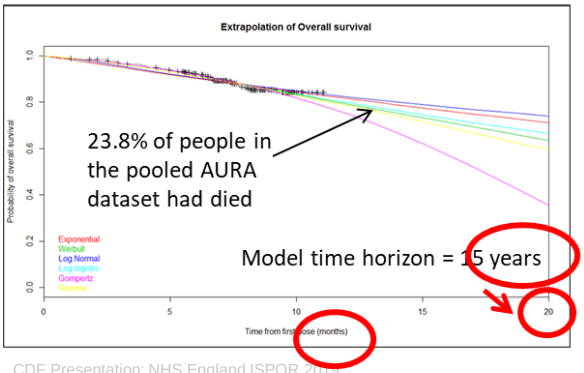
Systemic Anti-Cancer Therapy (SACT) dataset collection	• May be linked to other Public Health England sources
Clinical studies	• Ongoing studies • New study/ data collection

Other established tumour registries could be used if we are able to set up the necessary arrangements for sharing data

Case Study: Uncertainty in overall survival

TA416 Osimertinib - locally advanced/metastatic EGFR T790M mutation-positive NSCLC

Immature survival data = uncertain long-term benefit = uncertainty in cost-effectiveness estimates



Osimertinib vs platinum-doublet therapy

Assumptions	ICER (£/QALY)
Company's	£41,705
Committee's preference (alternative extrapolation)	Between £60,663 and £70,776[a]

NICE and CDF Process to Identify Uncertainty Early

DP Triage Process: NICE prepare a **RAG** assessment of likelihood of entry to CDF

- Will the technology have a conditional marketing authorisation for this indication?
- Is the technology part of the Medicines and Healthcare products Regulatory Agency's Early Access to Medicines Scheme?
- How robust will the clinical evidence be at the time of submission (for example is the Marketing Authorisation Application based on a single-arm trial?)
- Is it likely that further clinical data would impact committee decision-making? (for example, longer-term survival data for immune-oncology products)
- Has the company expressed an interest in the CDF as an option?

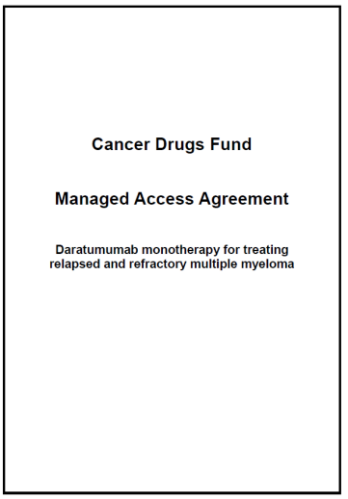
If the drug identified as being a potential candidates for the CDF then we will engage with the company as needed

Understanding Uncertainty: Early Engagement with Manufacturers

Early understanding of whether entry to the CDF is a possibility is key for NICE, NHS England and manufacturers. Manufacturers have multiple opportunities for engagement.

- **Office for Market Access:** Companies able to engage with NICE early in product development See https://www.nice.org.uk/about/what-we-do/life-sciences/office-for-market-access
- **Scoping Process:** To define the decision problem and start to identify potential uncertainty
- **Budget Impact Process:** Understanding the likely use and uptake of new technology
- **NHS England Pharm Surgeries:** Companies have chance to seek advice on decision problem
- **Technical Engagement pre-committee:** Narrowing down decision problem, highlighting uncertainties

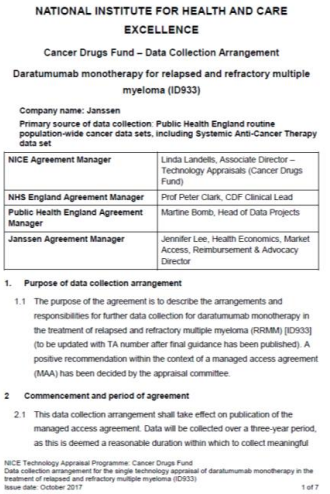
Transparent publication of MAAs = Clarity on uncertainty



Cancer Drugs Fund

Managed Access Agreement

Daratumumab monotherapy for treating relapsed and refractory multiple myeloma



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Cancer Drugs Fund – Data Collection Arrangement

Daratumumab monotherapy for relapsed and refractory multiple myeloma (ID933)

Company name: Janssen

Primary source of data collection: Public Health England routine population-wide cancer data sets, including Systemic Anti-Cancer Therapy data set

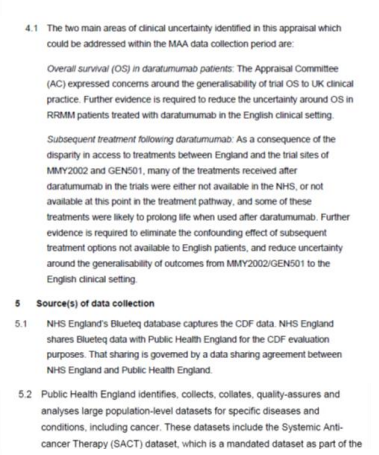
NICE Agreement Manager	Linda Landells, Associate Director – Technology Appraisals (Cancer Drugs Fund)
NHS England Agreement Manager	Prof Peter Clark, CDF Clinical Lead
Public Health England Agreement Manager	Martine Bomb, Head of Data Projects
Janssen Agreement Manager	Jennifer Lee, Health Economics, Market Access, Reimbursement & Advocacy Director

1. Purpose of data collection arrangement

1.1 The purpose of the agreement is to describe the arrangements and responsibilities for further data collection for daratumumab monotherapy in the treatment of relapsed and refractory multiple myeloma (RRMM) [ID933] (to be updated with TA number after final guidance has been published). A positive recommendation within the context of a managed access agreement (MAA) has been decided by the appraisal committee.

2 Commencement and period of agreement

2.1 This data collection arrangement shall take effect on publication of the managed access agreement. Data will be collected over a three-year period, as this is deemed a reasonable duration within which to collect meaningful



4.1 The two main areas of clinical uncertainty identified in this appraisal which could be addressed within the MAA data collection period are:

Overall survival (OS) in daratumumab patients: The Appraisal Committee (AC) expressed concerns around the generalisability of trial OS to UK clinical practice. Further evidence is required to reduce the uncertainty around OS in RRMM patients treated with daratumumab in the English clinical setting.

Subsequent treatment following daratumumab: As a consequence of the disparity in access to treatments between England and the trial sites of MMY2002 and GEN501, many of the treatments received after daratumumab in the trials were either not available in the NHS, or not available at this point in the treatment pathway, and some of these treatments were likely to prolong life when used after daratumumab. Further evidence is required to eliminate the confounding effect of subsequent treatment options not available to English patients, and reduce uncertainty around the generalisability of outcomes from MMY2002/GEN501 to the English clinical setting.

5 Source(s) of data collection

5.1 NHS England's Blueteq database captures the CDF data. NHS England shares Blueteq data with Public Health England for the CDF evaluation purposes. That sharing is governed by a data sharing agreement between NHS England and Public Health England.

5.2 Public Health England identifies, collects, collates, quality-assures and analyses large population-level datasets for specific diseases and conditions, including cancer. These datasets include the Systemic Anti-cancer Therapy (SACT) dataset, which is a mandated dataset as part of the

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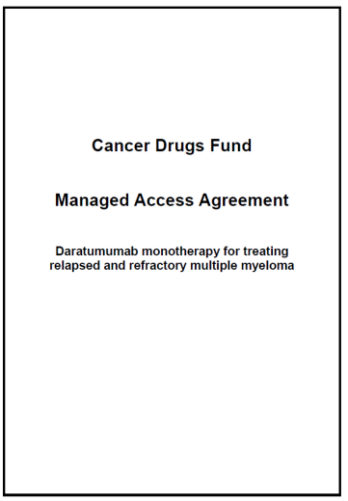

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Managed Access Agreement

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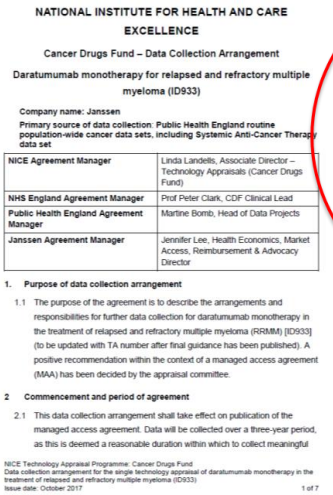

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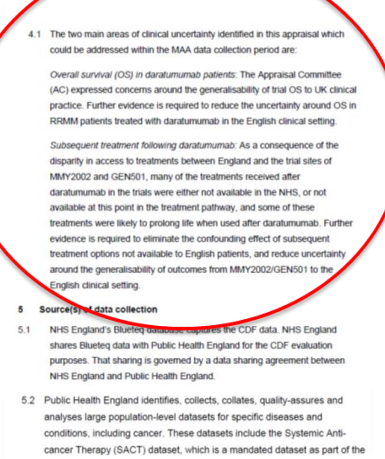
Issue date: October 2017 1 of 7



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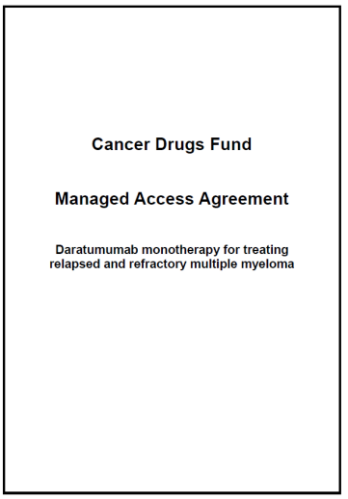

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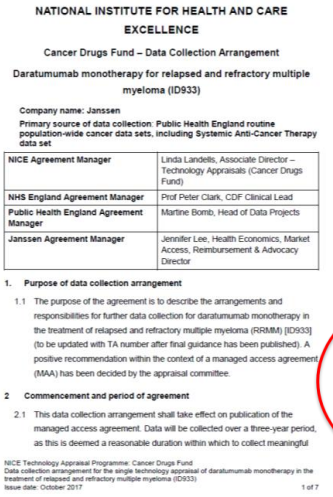

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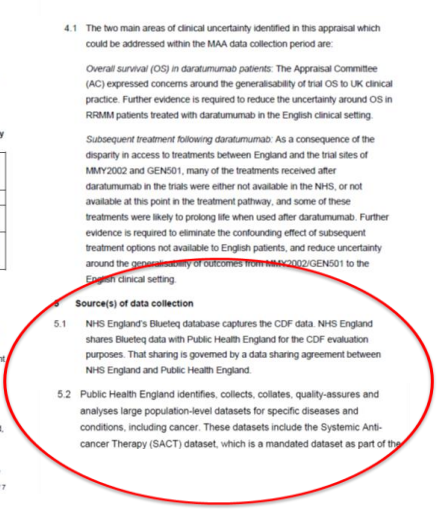

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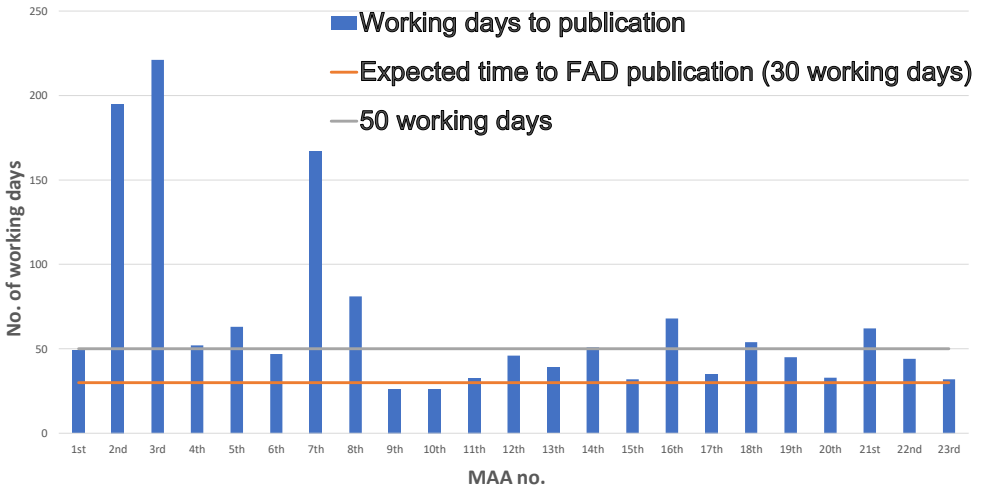
How long does it take to produce a Managed Access Agreement?



Thank you

stevewilliamson@nhs.net

www.england.nhs.uk/cancer/cdf

NHS England and NHS Improvement

Jane Kielt, *Mystic Seaport*
A retired art teacher and world traveler, Jane finds painting watercolors healing as she lives through multiple myeloma.

Jennifer Lee
Director of HEMAR & Advocacy
Janssen UK

Benefits of the Cancer Drugs Fund

- Allows conditional approval => access to much needed innovative medicines in the face of uncertainty
- Reduced the proportion of appraisals not recommended from 41%[1] to 24%[2]
- Clearly the right avenue for some appraisals:
  - TA492: Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable
  - TA522: Pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable

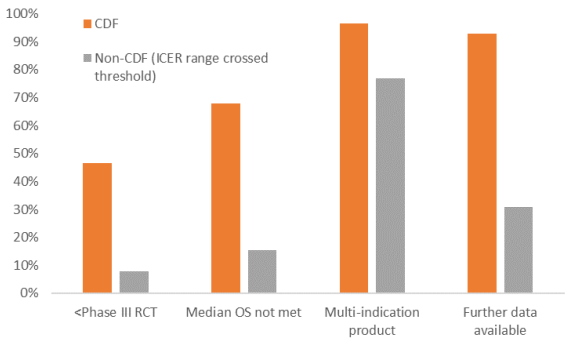
Both appraisals based on Phase II single arm trial data with Phase III trial data anticipated within 2 years

[1]NICE appraisals from 2000 to June 2016 (https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data/cancer-appraisal-recommendations), [2]Janssen systematic search of NICE website

Comprehensive assessment of the evidence base reveals trends for CDF recommendations

A systematic search of the NICE website was conducted on cancer appraisals published between June 2016 and June 2019

- 118 cancer STAs
- 28 CDF recommendations
- 11 Not recommended
- 13 Recommended for baseline commissioning despite plausible ICER range crossing CE threshold



Clear trend towards the CDF being favoured in instances of Phase I/II trial data and immature OS

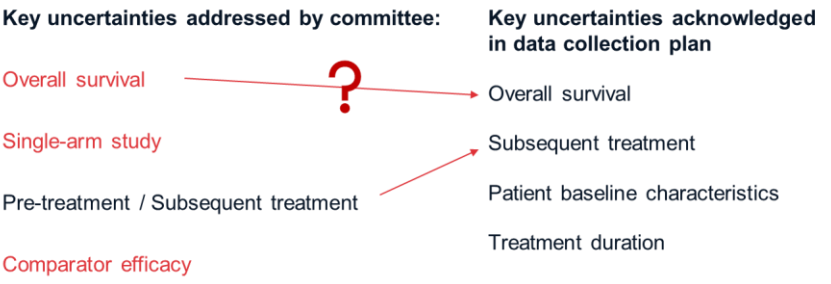
Emerging pipeline could impact the sustainability of the CDF

Accelerated licensing based on Phase I/II trial evidence	Treatments assessed early in patient pathway = highly immature OS	Therapies with curative intent; e.g. Cell and gene therapy	Targeted therapy; e.g. tumour agnostic treatments

CDF data collection is resource intensive with PHE analysts actively chasing missing data

CDF not suitable for all medicines as uncertainty pertaining to comparative effectiveness cannot be resolved

Case study: Daratumumab monotherapy for relapsed and refractory multiple myeloma (TA510)



Key uncertainty of comparative effectiveness **will not be** addressed
Key uncertainty of OS may not be adequately addressed

Daratumumab was moving earlier in the pathway meaning monotherapy re-appraisal impact will be limited

Case study: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573)

Key uncertainties addressed by committee:

- Long term survival for patients on DARA/BOR/DEX
- Relative efficacy versus CAR/DEX
- Subsequent treatment (methods for adjusting OS for non-UK subsequent treatments)
- HRQoL (the most appropriate utility values to be used)

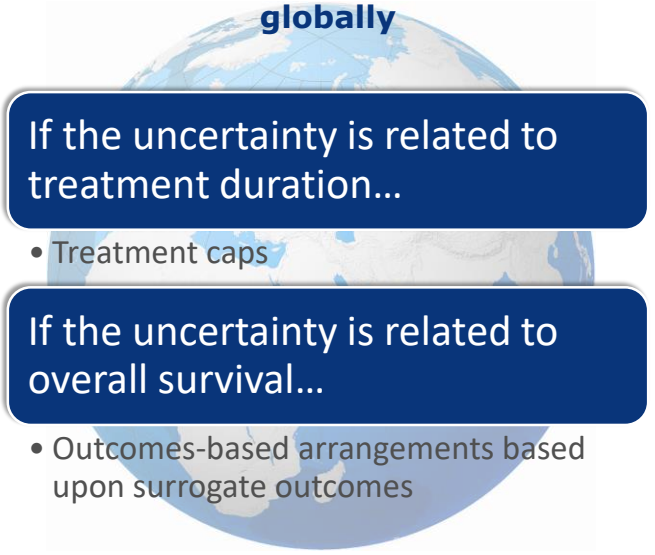
Key uncertainties acknowledged in data collection plan

Key areas of uncertainty is OS in daratumumab patients

- Despite 4 years of follow-up median OS for DARA/BOR/DEX has not yet been reached in CASTOR
- Based on event rates already observed, median OS is expected to be reached by January 2021 (after 6 years)

Key uncertainty of OS **will be reduced but not fully addressed** as event rates have considerably reduced and median will not be met at final analysis

There are alternative mechanisms to reducing uncertainty…more flexible pricing options used globally



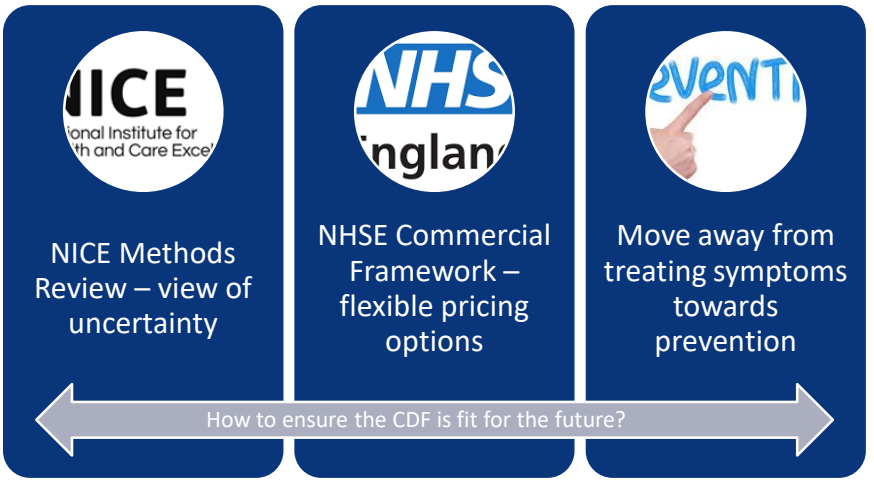
If the uncertainty is related to treatment duration…

- Treatment caps

If the uncertainty is related to overall survival…

- Outcomes-based arrangements based upon surrogate outcomes

Future considerations



Thank you

CDF Issue Panel:
Academic Perspective

Stephen Palmer
Professor of Health Economics
Centre for Health Economics
University of York, UK

ISPOR Europe 2019, Copenhagen, Denmark

CDF objectives and main considerations

- Objectives
  - Faster access to most promising new cancer treatments
  - Stronger value for money for taxpayers
- Different mechanisms
  - Managed entry (MEA) and further data collection
  - Commercial pricing agreement (CAA) - *temporary indication specific pricing?*
  - Expenditure control mechanism (ECM)
- Main considerations
  - Incremental cost-effectiveness ratios (ICERs) have plausible potential for satisfying routine use
  - Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
  - Data collected (including from research underway) will be able to inform a subsequent update of the guidance

Challenges of establishing plausible ICER potential

- Evidential challenges
  - Quantification of bias and adjustment for confounding
  - Immaturity of evidence and relevance of surrogate endpoints
  - Value attributes
- Pricing challenges
  - Affordability vs value
  - Differential value across indications
  - Separation between appraisal (NICE) and price negotiation (NHS England)
- Issues
  - Lack of consensus on approaches to evidential challenges
  - Indication specific pricing not permitted
  - Current NICE assessments not sufficient to appropriately inform MEA and price negotiation

What assessments are needed?

- 1. Value of a technology
  - Is value > threshold (opportunity cost)?
- 2. Value of evidence
  - Is additional evidence valuable?
  - What type of evidence is most valuable? Will approval affect the prospects of acquiring it?
  - ***Ensure benefits of early access for current patients exceed benefits foregone for future patients***
- 3. Cost of decision reversal
  - Costs committed by approval that cannot be recovered (e.g. capital, training)
  - Initially negative NHE (when treatment decisions can be changed)
  - ***Ensure the benefits of early approval greater than opportunity costs of delay***

Ref: K. Claxton, S. Palmer, L. Longworth, et al. A comprehensive algorithm for approval of health technologies with, without, or only in research: the key principles for informing coverage decisions. Value Health, 19 (2016), pp. 885-891

Can main uncertainties in ICER be resolved through routine data collection?

Increasing concern with uncertainty

Theme	No. of FADs where theme is mentioned (n=29)	No. of FADs where theme is noted in the uncertainty sections (n=29)	No. among FADs where uncertainty is noted in the headline summary (n=19)
Immature survival data	27	23	16
Lack of relevant comparator(s)	16	12	10
Trial design	15	9	8
Relevant patient population	18	9	4
Quality of Life data	19	6	4
Cost estimates	8	6	4
Downstream pathway	5	3	2
Use of observational data	2	2	2
Optimum duration of use	2	2	2
Cost-effectiveness model design	4	1	1
Incidence of AEs	1	1	0

Morrell, et al. Will the reformed Cancer drugs fund address the most common types of uncertainty? An analysis of NICE cancer drug appraisals. BMC Health Serv Res. 2018;18(393). https://doi.org/10.1186/s12913-018-3162-2.

Will data collected (including from research underway) be able to inform guidance update?

- Challenges of re-assessment
  - Have the main uncertainties been resolved?
  - Is the decision problem the same?
  - Should other sources of uncertainties (e.g. size of eligible population in future, emergence of new treatments) have been considered?
  - Possible loss aversion from conditional reimbursement
- Differential value between indications will remain
  - Challenge of single price for a product
  - Distorts incentives for multi-indication products

Ref: van de Wetering EJ, van Exel J, Brouwer WB. The challenge of conditional reimbursement: stopping reimbursement can be more difficult than not starting in the first place! Value Health. 2017;20(1):118–125.

A way forward for the NHS and CDF?

- Appraisal and price negotiation
  - Develop NICE uncertainty assessments to more directly inform CDF considerations
  - More explicit linkage between NICE assessment and NHSE/CDF pricing agreements
  - Development of pricing schemes which can 'buy out' or address uncertainties
- CDF
  - More explicit about uncertainties that can and can't be resolved via routine data collection
  - Clarity in how the data collection will be used to inform re-appraisal
- System level
  - Development of routine data systems (e.g. SACT) to address broader range of uncertainties
  - Separation of CDF role from indication specific pricing and cost control

Thank you

Questions & Answers

Does the current Cancer Drugs Fund system provide an effective approach to managing uncertainties?

What lessons can be drawn from how other countries implement Managed Access Agreements?

Are there alternative processes or mechanisms that could be developed to help improve managed access in England and more widely?