Slides for COMMITTEE only – contains ACIC information

NICE National Institute for Health and Care Excellence

# Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

## 2nd Appraisal Committee Meeting

**Technology appraisal committee B [13/07/2022]**

**Chair:** Dr. Charles Crawley

**Evidence assessment group:** BMJ-TAG

**Technical team:** Henry Edwards, Rufaro Kausi, Susan O'Connell

**Company:** Merck Sharp & Dohme (MSD)

13th July 2022

# Key Points from Appraisal Committee Meeting 1

**The committee agreed:**

- There is an unmet need for effective adjuvant treatments
- Pinitol trial shows that DFS and OS data are promising but immature
- The company model structure is structurally appropriate for decision making but uncertainty in the
  - modelling of long term risk of relapse
  - approaches to modelling transitions from the disease-free health state
  - best estimate of PFS (AI or BICR)
- pembrolizumab is a possible candidate for the Cancer Drugs Fund.

# Key issues from 1st committee meeting

| Issue | Resolved? | Committee comments |
|---|---|---|
| DFS and OS data from the KEYNOTE-564 trial are immature | Resolved | Recognised immaturity of the data adds uncertainty to the cost effectiveness estimates<br>Data collection within the CCDF could help resolve the uncertainty. |
| Long term risk of relapse | No | Requested more scenario analysis with different treatment waning assumptions to explore uncertainty. |
| Transitions from the disease-free health state: (Joint or separate fitting of Exponential & Gompertz extrapolation) | Resolved | Recognise there is unresolvable uncertainty due to data immaturity<br>Agreed to take both approaches into consideration when decision making |
| IA versus BICR assessment from KEYNOTE-564 | No | IA more reflective of UK practice but BICR more methodologically robust.<br>Choice has a large effect on ICER → requested exploration |
| Is the technology eligible for the Cancer Drug Fund (CDF)? | No | Committee has invited a submission to CDF for consideration. |

Abbreviations: BICR, blinded independent central review; DFS, disease free survival; IA, Investigator assessed; OS, overall survival

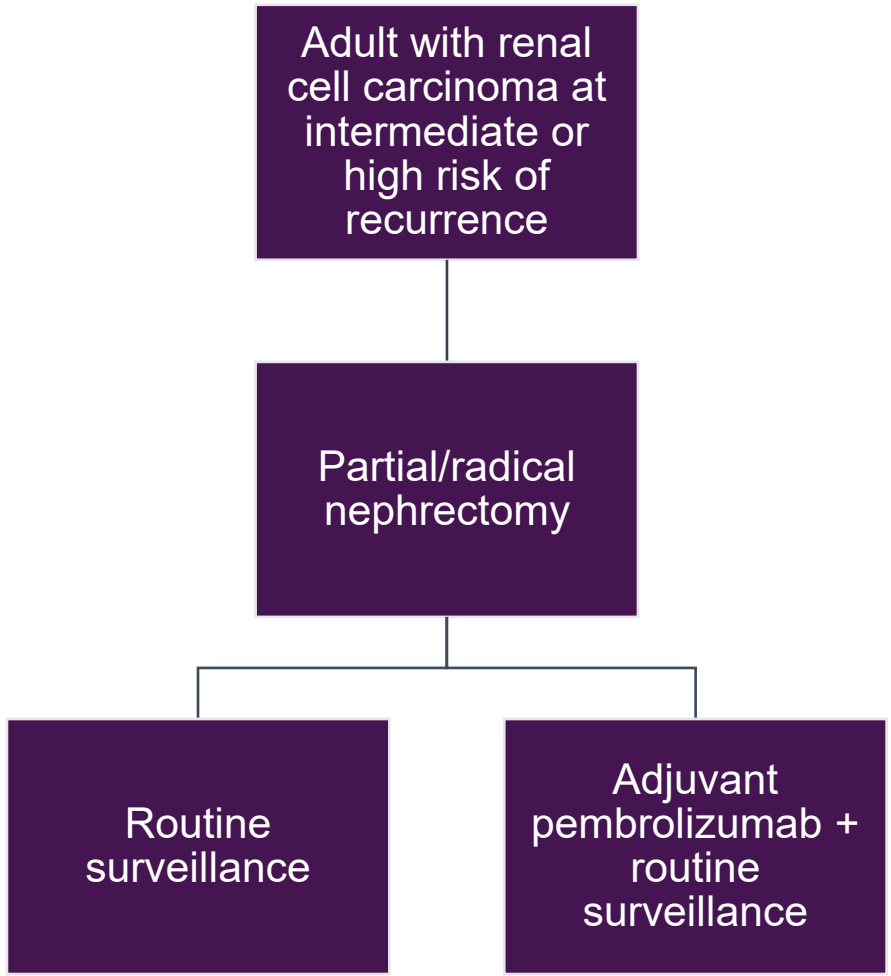
# Recap from 1st meeting

# Summary Disease background

- RCC is the **most  common type of kidney cancer (>80% of cases)** with the highest rate in people over 85 years of age as Incidence rate increases with age.
- ~ 11,000 new cases of kidney cancer in England in 2017.
- Symptoms can include blood in urine, persistent pain in lower back or side, extreme tiredness, loss of appetite, persistent hypertension and night sweats.
- Surgery is performed with curative intent and more than 50% of people diagnosed with Kidney cancer in England between 2013 and 2017 expected to survive their cancer for 10 years or more.

# Treatment pathway

The company's proposed positioning of pembrolizumab in the NICE pathway is as adjuvant therapy following partial or complete nephrectomy.



# Pembrolizumab (KEYTRUDA, MSD)

| | |
|---|---|
| **Marketing authorisation** | • Pembrolizumab as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at intermediate or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. |
| **Mechanism of action** | • Pembrolizumab is a monoclonal antibody (mAB) of the IgG4/kappa isotype designed to exert a dual ligand blockade of the PD-1 pathway by directly blocking the interaction between PD-1 and its associated ligands, PD-L1 and PD-L2 which appear on the antigen-presenting or tumour cells. |
| **Administration** | • Monotherapy 200mg every 3 weeks (Q3W) up to 17 cycles or 400mg every 6 weeks (Q6W). |
| **Price** | • £2,630 per 100mg vial.<br>• £89,420 per patient for 17 cycles (12 months of treatment).<br>• Confidential patient access scheme. |



Abbreviations: MHRA, Medicines and Healthcare products regulatory agency

# Clinical effectiveness

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# KEYNOTE-564

*Phase 3 randomised, double-blind, placebo controlled clinical trial*

*Used in company model*

**Patients**
- ≥18 years
- Advanced or metastatic RCC with clear cell component
- Intermediate or high risk of recurrence
- Treatment-naive
- ECOG performance status 0 or 1
- Nephrectomy>=4 weeks prior to screening
- No brain, chest, abdomen or pelvis tumours

**Pembrolizumab** (n=488
200mg iv Q3 x 17 cycles
(1 year)

*Treat to until disease recurrence or until discontinuation*

**Placebo (n=496)**
(incl. routine surveillance)
200mg iv Q3 x 17 cycles

**Endpoints***

1°
- Disease Free Survival

2°
- Overall Survival
- DRSS 1 & 2 (investigator assessed)
- EFS assessed by BICR
- Adverse Effects
- HRQoL

*Median duration 29.7 months*

**Intermediate-high risk:** pathologic tumour stage T2 (pT2) with Grade 4 or sarcomatoid; pT3, any grade without nodal involvement (N0) or distant metastases (M0)
**High risk:** any pT4, any grade N0 and M0, any pathologic tumour stage, any grade with nodal involvement and M0.

**ERG**
Clinical experts consider the population characteristics to be generalisable to those undergoing nephrectomy for RCC in England.
*NB. Baseline characteristic in backup slides*

Abbreviations: DRSS, disease recurrence-specific survival; BICR, blinded independent central review; IA, investigator assessed EFS, event free survival, RCC, renal cell carcinoma; SoC, Standard of Care

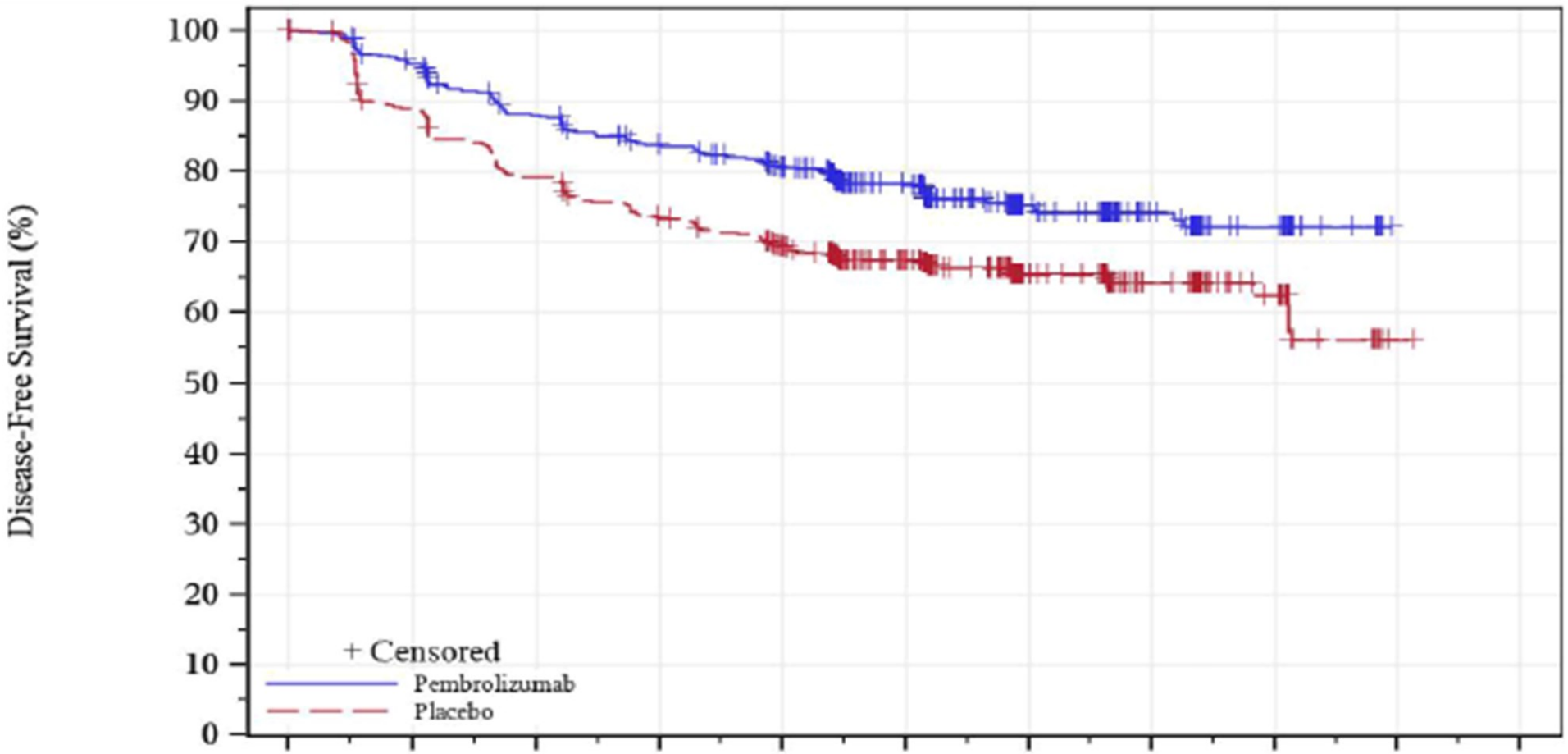
# Results from KEYNOTE-564

| Intent to Treat Population | Pembrolizumab (n=496) | Placebo (n=498) |
|---|---|---|
| Disease Free Survival<br>vs Placebo<br>Hazard Ratio (95% CI)<br>p-value | | 0.63 (0.50 to 0.80)<br><0.0001 |
| Overall Survival<br>vs Placebo<br>Hazard Ratio (95% CI), p value | | [redacted] |
| Adverse events* with toxicity grade 3-5 | [redacted] based on [redacted] patients | [redacted] based on [redacted] patients |

*The most frequently reported AEs at the latest data cut-off were [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] for those receiving pembrolizumab, and [redacted] and [redacted] for those receiving placebo.

Database Cut off date:
**14 JUN 2021**

# Disease Free Survival Kaplan Meier Curve based on investigator assessment

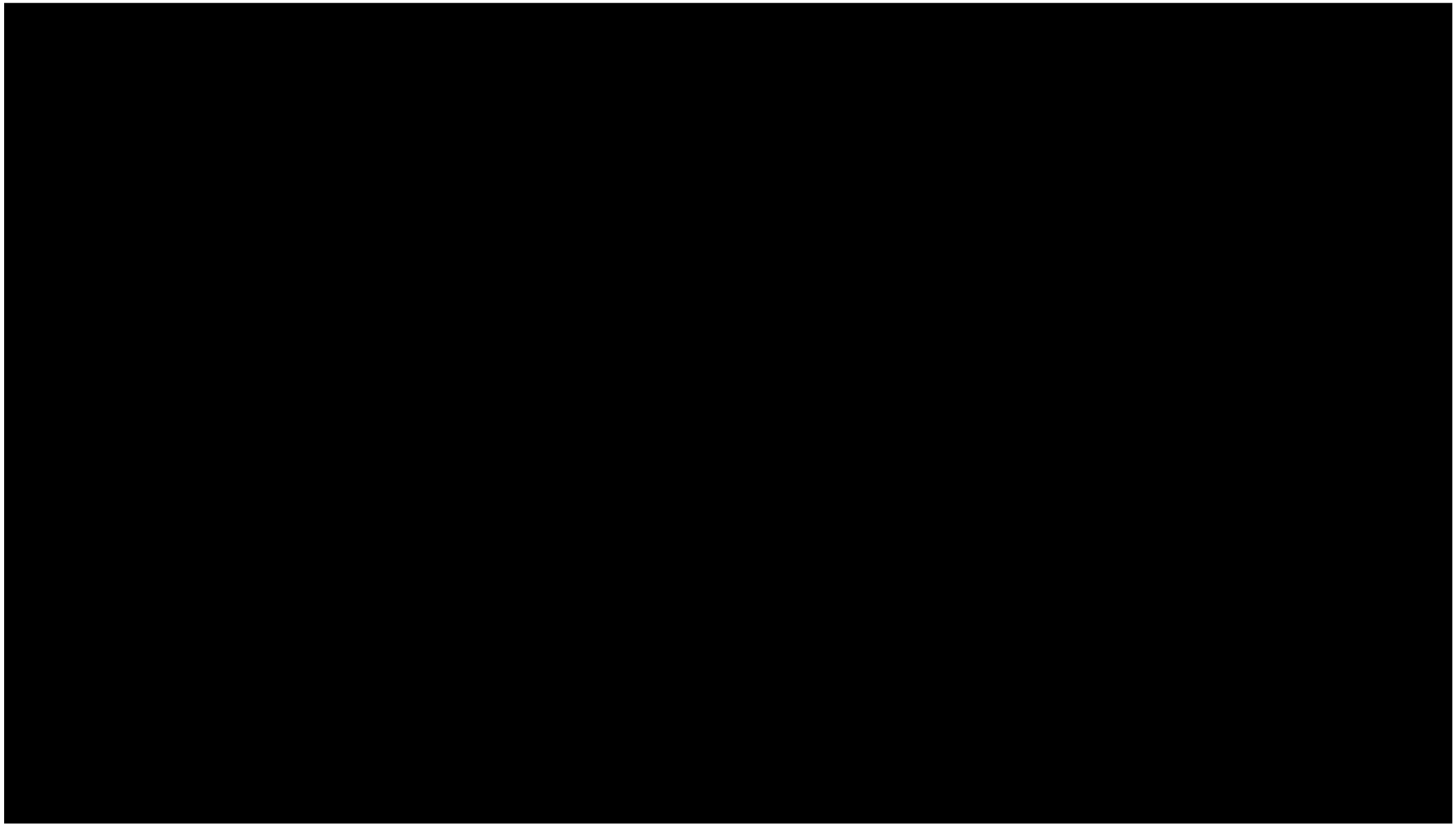



At Risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 496 | 458 | 416 | 389 | 361 | 255 | 135 | 77 | 37 | 0 | 0 |
| Placebo | 498 | 437 | 389 | 356 | 325 | 230 | 125 | 74 | 33 | 1 | 0 |

# Overall Survival Kaplan Meier Curve

Database Cutoff date: 14JUN2021



# Cost effectiveness

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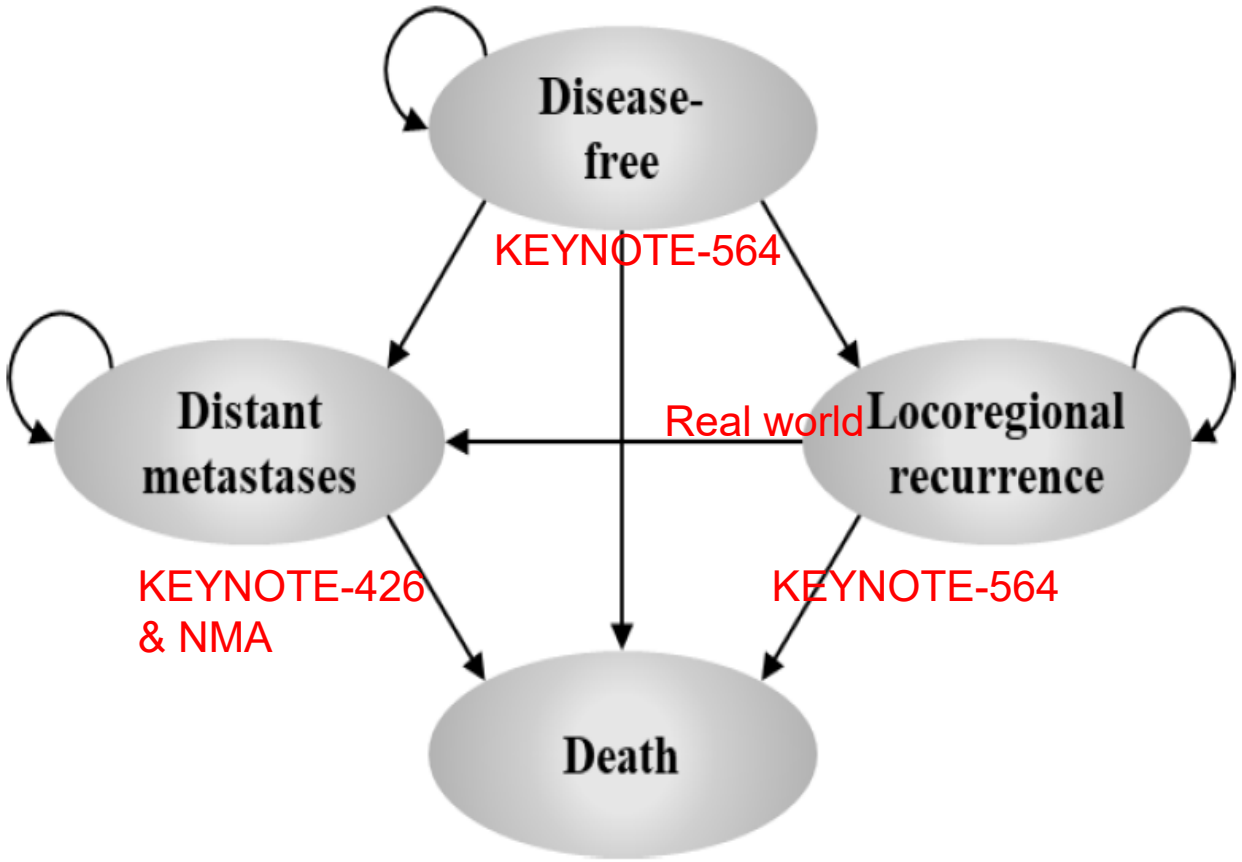
# Company's model structure

*Markov model with 41 year time horizon, 1 week cycle length*

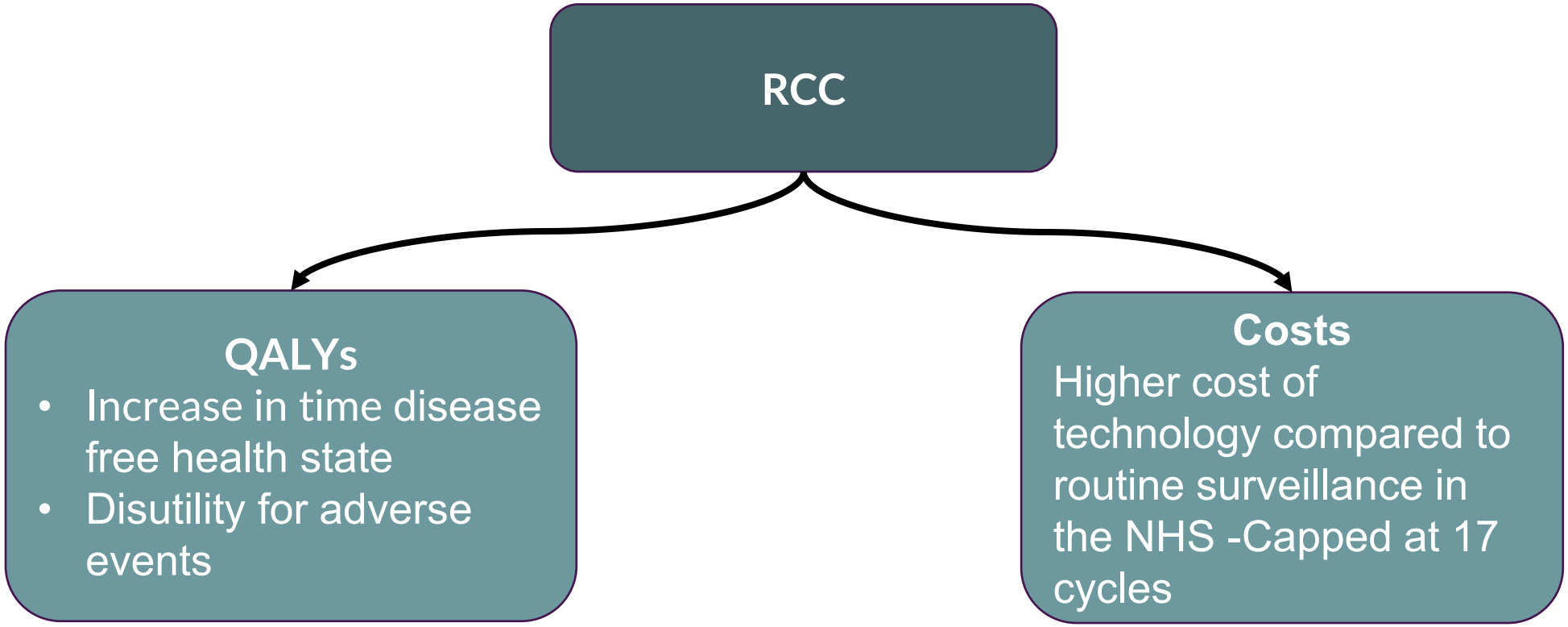



| | |
|---|---|
| **Locoregional recurrence** | • **Disease at the primary site or nearby lymph nodes**<br>• 22% receive salvage surgery |
| **Distant metastases** | • **Cancer spread from primary site to secondary/distant organ/lymph nodes)**<br>• Receive 1st line treatments for (aRCC)<br>• 21% receive salvage surgery<br>• Costs of 2nd line aRCC treatments are included |

**EAG**

- Consider the model structure to be appropriate.
- Previously accepted in TA553 (pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence).
- Company pointed out a correction to the EAG model relating to time on treatment. This correction was accepted by the EAG.

# Where do the QALY and cost differences come from in the model?




**Key model drivers are:**

- Transitions from DF → LR, and DF → DM
- Utility values in DF, L and DM

Abbreviations: DF, disease free; DM, distant metastases; LR, locoregional recurrence; QALY, quality adjusted life year; RCC, renal cell carcinoma

# Recap: Transitions from the disease-free health state *(Joint or separate fitting of Exponential & Gompertz extrapolation)*

**Background**

- Patient-level data from KEYNOTE-564 was used to estimate time to DFS failure (locoregional recurrence, distant metastases or death).
- The company explored different approaches to select appropriate standard parametric models to estimate cause-specific hazards for DF to LR and DF to DM transitions:

  **Approach 1:** standard parametric models fitted independently to pembrolizumab and placebo data from KEYNOTE-564. → EAG preferred

  **Approach 3**: standard PH parametric models (exponential, Weibull and Gompertz) jointly fitted to pembrolizumab and placebo data from KEYNOTE-564 with a HR for pembrolizumab versus placebo applied to year one and another HR applied for year two onwards (time-varying PH model). → Company preferred

**ACD conclusion**

The committee concluded that either extrapolation approach could be justified, but noted that the extrapolations were informed by immature data and subject to uncertainty

# Summary of responses to appraisal consultation document

# ACD consultation responses

**Received consultation responses from:**

- Company: Merck Sharp & Dohme (MSD) – to be presented in discussion
- Action Kidney Cancer

**No responses received from other consultees**

# Consultation Comments - Action Kidney Cancer

## Agreed there is an unmet need

- ***Unmet need -*** Adjuvant treatment to prevent the spread of intermediate/high risk RCC following surgery is an area of serious unmet need in England.
- ***Benefits outweigh the adverse effects -*** Benefits of adjuvant pembrolizumab to patients are reduced recurrence of disease with a tolerable side effect profile and little effect on quality of life.

## Noted potential access issues

- ***Clinical options -*** Without an adjuvant treatment, the clinician's ability to choose most effective treatment is seriously compromised.
- ***Inequity*** - the treatment is available to patients who have private health insurance or who can afford a private prescription, thus creating two-tier access for patients.

## Disagreed with the draft recommendations

- ***Disappointed -*** this innovative and clinically effective treatment for intermediate/high risk, locally advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups.

# Key Issues for Discussion:

**Issue 1: Long term risk of relapse**
**Issue 2: IA versus BICR assessment**
**Issue 3: CDF**

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Abbreviations: BICR, blinded independent central review; IA, investigator assessed; DFS, Disease Free Survival; CDF, Cancer Drugs Fund

# Recap - Long term risk of relapse

**EAG**

- Scenario - assumed that the risk of relapse was equal to that seen in routine surveillance data:
  - explored at 4, 7 and 10 years – has a large impact on ICER

**Clinical expert noted**

- Early indications are findings from KEYNOTE-564 are likely to be maintained.
- ~30% of patients go on to have long-term durable remission.
- Longer someone remains disease free the lower the risk of recurrence.

**Company**

- EAG waning assumption as an abrupt change in the risk of recurrence is implausible:
  - patients have received surgery with curative intent prior to therapy.
- No evidence of waning in the metastatic setting in multiple indications with long-term data for Pem
- Plausibility of changes best informed by log-cumulative hazard plots for transitions from DF state
- Trial data shows that there is a difference in risk of relapse between the two treatment arms.

**Committee**

- Absence of evidence - precedent of applying a waning effect in other NICE TA for immunotherapies
- Long-term effect uncertain – further exploration needed with different waning assumptions

NICE Abbreviations: EAG, Evidence Assessment Group

# Key issue 1: Long term risk of relapse

**Consultation Comments - Company**

- Unable to identify any NICE HTAs in the ***adjuvant setting*** that included waning
  - a number applied a treatment stopping rule and no assumptions regarding waning
- Curative intent of adjuvant pembrolizumab → implausible that treatment effect waning would necessarily apply to all patients who remain disease free.
- Explored assumptions around treatment effect waning
  - At 7 or 10 years - either 15% or 20% of Pem arm will experience risk of relapse equal to routine surveillance arm i.e. 80% or 85% of Pem arm achieve long term remission
  - Limited impact on cost-effectiveness results using both IA and BICR assessment of DFS.
  - Included a 'wash out' period - risk of relapse gradually increases over two years until equal to routine surveillance arm

**EAG response to new evidence:**

- Company exploration less conservative than EAG's → little impact on the ICER
- Unclear how the company selected the 15% or 20%
- Disagree with 'cliff edge' comment - EAG approach presents a gradual waning
- Presented further scenarios - risk of relapse from 20% to 100%, excluding 'wash-out' period.

- Is an assumption of 15%-20% reasonable?
- Is it reasonable to compare risk of relapse in the metastatic setting and in the adjuvant setting?

# Key issue 1: Long term risk of relapse

**Company relapse scenario - Approach 3 Investigator assessed DFS, waning timepoint of 7 years, 2-year wash out period, 15% of patients affected.**

# Key issue 1: Long term risk of relapse

## Example of the EAG risk of relapse scenario - Approach 1 Investigator assessed DFS, waning timepoint of 7 years, 100% of patients affected.

# Recap: IA versus BICR assessment from KEYNOTE-564

**Background**

- KEYNOTE-564 - primary outcome was investigator assessed (IA) DFS
- Blinded independent central review (BICR) PFS a secondary outcome
- IA HR of 0.63 [95% CI: 0.50 to 0.80] versus BICR HR of [redacted]

**EAG**

- IA and BICR analyses of DFS are expected to be similar but are not – unclear why
- Two sets of analyses are equally plausible but - BICR is less likely to be affected by detection bias and therefore more robust

**Company**

- Substantial overlap in the confidence intervals
- IA is more generalisable to NHS as clinicians would determine the recurrence of disease based on local review of diagnostic imaging

**Clinical expert considers**

- BICR assessment is more methodologically robust: IA reflective of UK clinical trial practice.
- KEYNOTE-564 is a blinded trial which so there shouldn't be any bias in the assessment.

***Large impact on ICER***

Abbreviations: BICR, blinded independent central review; EAG, Evidence Assessment Group; IA, investigator assessed; HR, hazard ratio

# Key issue 2: IA versus BICR assessment from KEYNOTE-564

**Committee conclusions**

- Uncertain why the results differed
- IA is reflective of UK clinical practice but BICR data is plausible and may be more robust..
- ***Concluded there is considerable uncertainty around IA and BICR assessments and requested the company provide further analysis to help resolve the uncertainty.***

**Consultation comments from the company**

- Have provided BICR data but
  - IA reflects UK clinical practice; BICR was retrospective → significant limitations.
    - effectively different datasets, contributes to differences in results observed
  - The DFS BICR analysis was only conducted on patients who were determined to have *no evidence of disease* at baseline
  - KEYNOTE-564 was not powered for an endpoint of DFS by BICR.
  - Curve fitting using BICR → small impact on cost effectiveness results

**EAG response to new evidence:**

- Still unclear which is more appropriate - both are impacted by data immaturity
- Issues has the biggest impact on the ICERs (company model only deterministic)
- Both approaches may offers a plausible range

# Key issue 2: IA versus BICR assessment from KEYNOTE-564

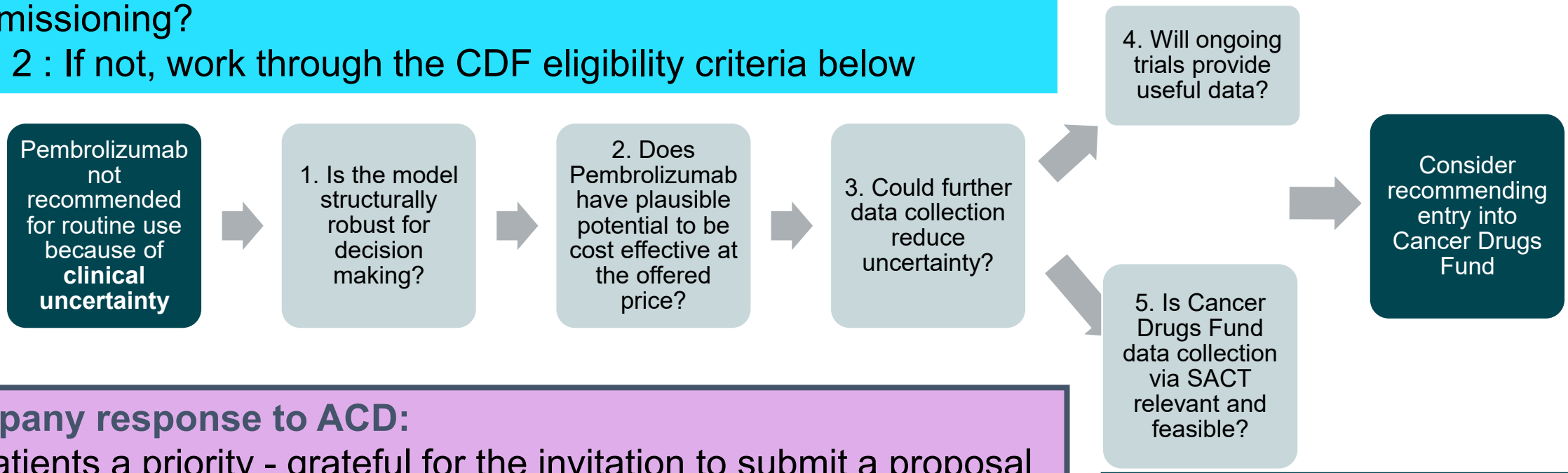
**Table 2. Disease-free survival predictions – pembrolizumab**

| Outcome | 1 year | 3 years | 5 years | 10 years | 30 years |
|---|---|---|---|---|---|
| **Company scenario - Approach 3 - exponential/Gompertz** | | | | | |
| BICR Disease-free survival by year | ■ | ■ | ■ | ■ | ■ |
| **Approach 1 - exponential/ generalised gamma** | | | | | |
| BICR Disease-free survival by year | ■ | ■ | ■ | ■ | ■ |
| | | | | | |
| **Company base case - Approach 3 - exponential/Gompertz** | | | | | |
| IA Disease-free survival by year | ■ | ■ | ■ | ■ | ■ |
| **Approach 1 - exponential/Gompertz** | | | | | |
| IA Disease-free survival by year | ■ | ■ | ■ | ■ | ■ |

- Which predictions look most clinically plausible ?

# Issue 3: CDF - Will data collection resolve the uncertainties?

Step 1: Can Pembrolizumab be recommended for routine commissioning?
Step 2 : If not, work through the CDF eligibility criteria below




## Company response to ACD:

- Patients a priority - grateful for the invitation to submit a proposal for CDF
- Trial data are robust - majority of plausible ICERs are well below usual decision-making thresholds, → strong candidate for baseline commissioning.
- CDF exit process a concern for sustainable access
- Next interim analysis (would give ~50 additional events compared to the data cut we submitted within the economic analysis.

## Action Kidney Cancer

- Concern that collected data during the CDF will resolve the uncertainties.
- Preferable for Pem to be available in baseline commissioning.

# Other considerations

**Equality considerations**

- ACD: Use of Pembrolizumab is not expected to raise any equalities issues.
- No issues raised during consultation

**Innovations**

- ACD: no additional benefits that had not been captured in the QALY.

**Company response**

- No NICE recommended active adjuvant therapy for RCC post-nephrectomy.
- Pembrolizumab offers the first and a durable and well tolerated adjuvant treatment
- Option to administer Q6W, would decrease the logistical and administrative burden on the health system, as well as decreasing the burden on patients who need to travel to cancer centres
- Pembrolizumab offers a step-change in benefit for these patients in the UK
    - alleviates some of the uncertainty, feelings of being abandoned, low emotional status, and anxiety about the cancer

# Company and ERG base case assumptions

| Assumption | Company base case | ERG base case | Impact |
|---|---|---|---|
| Survival extrapolations | Joint fitting for the placebo, with a hazard ratio applied forPembrolizumab (approach 3) | Independently fitted to both placebo andPembrolizumab data (approach 1) | Large |
| Long term risk of relapse | Extrapolation curves remain separated, as modelled | No change but explored in base case | Large |
| IA versus BICRassessment | IA used in base case | IA used in base case, BICR approximation explored as a scenario | Large |

# Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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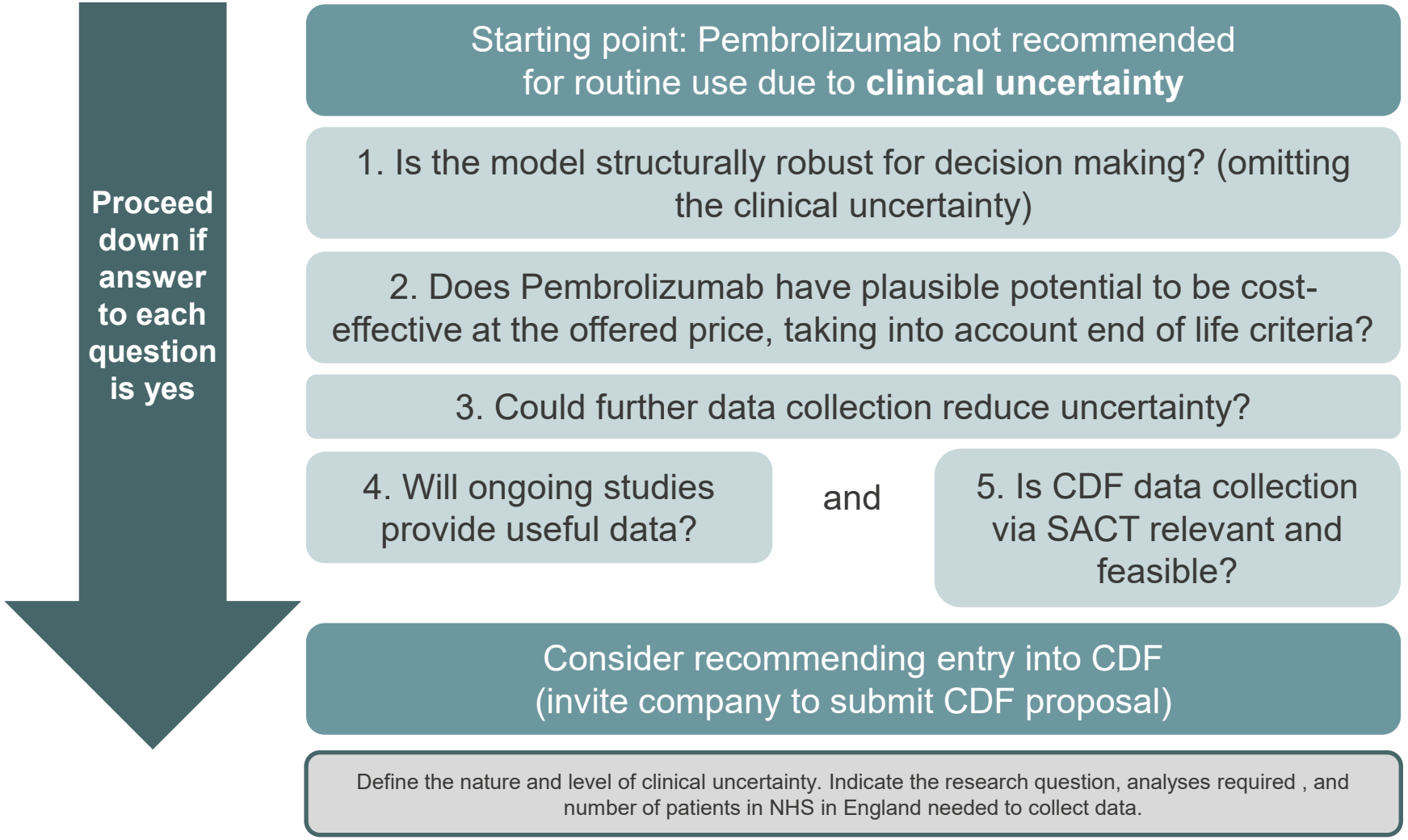
# Thank you.

# Back up slides

# Issue 3 : Committee considers pembrolizumab to be suitable for the Cancer Drugs Fund

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Abbreviations: CDF, Cancer Drug Fund

# Issues Resolved during Committee Meeting 1

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# Key issue resolved: Immaturity of the data

Will further data collection add certainty to the clinical evidence and economic modelling? Is further data collection feasible?

The committee has invited the company to make a submission for the Cancer Drugs Fund.

# Key issue resolved: Transitions from the disease-free health state (Joint or separate fitting of Exponential & Gompertz extrapolation)

Is fitting separate curves to Pembrolizumab and placebo (Approach 1) more robust than a jointly fitted curve and use of a hazard ratio (Approach 3) ?

The committee has no preference for either approach - would take both approaches into consideration when decision making.
Considered that either extrapolation approach could be justified, but were informed by immature data and subject to uncertainty.


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Abbreviations: DF, disease free; DFS, disease free survival; LR, local recurrence; OS overall survival

# Key issue resolved: Transitions from the disease-free health state

## Log-cumulative hazards plots (LCH) of the hazard of a DFS event

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Abbreviations:
DF, disease free
DM, distant metastases
LR, locoregional recurrence

# Key issue 2: IA versus BICR assessment from KEYNOTE-564

## Disease-free survival predictions parametric models – routine surveillance

| Approach/ source | Parametric model combination | Disease-free survival by year | | | | | Source |
|---|---|---|---|---|---|---|---|
| | | 1 year | 3 years | 5 years | 10 years | 30 years | |
| **BICR DFS** | | | | | | | |
| BICR DFS Company scenario – Approach 3 | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Table 2 EAG response to ACD |
| BICR DFS - Approach 1 | Exponential (DF → LR) and G.Gamma (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Table 2 EAG response to ACD |
| **IA DFS** | | | | | | | |
| Company base case – IA DFS - Approach 3 | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Table 27 ERG report |
| IA DFS - Approach 1 | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Table 27 ERG report |

# Key issue 2: IA versus BICR assessment from KEYNOTE-564

**The company's modelled BICR DFS based on Approach 3**

Source: Figure 3 Company's Response to ACD

**The company's modelled BICR DFS based on Approach 1(EAG's preferred method)**

Source: Figure 2. EAG response to ACD

**Questions for committee:**

- Which assessment is valid (IA/BICR)?

# Transitions from the disease-free health state
## *(Joint or separate fitting of Exponential & Gompertz extrapolation)*

Is fitting separate curves to Pembrolizumab and placebo (Approach 1) more robust than a jointly fitted curve and use of a hazard ratio (Approach 3) ?

- Patient-level data from KEYNOTE-564 was used to estimate time to DFS failure (locoregional recurrence, distant metastases or death).
    - The company considered each failure as a competing risk, such that for a specific DFS failure, the two competing failure types (distant metastases and death) were treated as censoring events
- Once KEYNOTE-564 time-to-event data using competing risk censoring was obtained, the company followed a parametric multistate modelling approach to estimate cause-specific hazards of each transition from the DF health state over time

## Transitions from the disease-free health state
## *(Joint or separate fitting of Exponential & Gompertz extrapolation)*

The company explored the following three approaches to select appropriate standard parametric models to estimate cause-specific hazards for DF to LR and DF to DM transitions:

**Approach 1:** standard parametric models fitted independently to pembrolizumab and placebo data from KEYNOTE-564.

**Approach 2**: standard proportional hazards (PH) parametric models (exponential, Weibull and Gompertz) jointly fitted to pembrolizumab and placebo data from KEYNOTE-564 with a time-constant hazard ratio (HR) for pembrolizumab versus placebo applied (PH model).

**Approach 3**: standard PH parametric models (exponential, Weibull and Gompertz) jointly fitted to pembrolizumab and placebo data from KEYNOTE-564 with a HR for pembrolizumab versus placebo applied to year one and another HR applied for year two onwards (time-varying PH model).

Abbreviations: aRCC, advanced renal cell carcinoma; DF, disease free; DM, distant metastases; HR, hazard ratio; LR, locoregional recurrence; NMA, network meta-analysis; OS, overall survival; PH, proportional hazards; SEER, Surveillance, Epidemiology and End Results.

# Transitions from the disease-free health state

## Log-cumulative hazards plots (LCH) of the hazard of a DFS event

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Abbreviations:
DF, disease free
DM, distant metastases
LR, locoregional recurrence

# Key issue 3: (Joint or separate fitting of Exponential & Gompertz extrapolation)

**Company:** External validation against long-term published data suggests Approach #3 (jointly fitted curve) to be the most appropriate of estimating long-term transition probabilities from DF.

Approach #1 is likely to underestimate the benefit of adjuvant pembrolizumab

**ERG comments:** As patient level data is available for both Pembrolizumab and placebo arms, the ERG considers fitting independent models to each treatment arm (Company Approach #1) a more robust method for extrapolation of the cause-specific time-to-event data used in the model.

**Other considerations: The** ERG cautions that even though Approach #1 is more robust, it is still informed by immature data and subject to substantial uncertainty.

# Approach 3 (Company base case), placebo arm only

External and predictive validations of long-term DFS in the routine surveillance arm using base-case assumptions for transitions from DF state

# Approach 3 (Company base case), pembrolizumab

External and predictive validations of long-term DFS in the pembrolizumab arm versus active treatment arms in previous trials of adjuvant therapy (statistically significant DFS benefit observed only in S-TRAC)

# Approach 3 (Company base case)

Base-case modelled DFS over the lifetime time horizon (data cut-off: 14-JUN-2021)

# Comparison of Approach 1 and 3

**Disease-free predictions of base case and scenario parametric models**

| Approach/ source | Parametric model combination | Disease-free survival by year | | | | |
|---|---|---|---|---|---|---|
| | | 1 year | 3 years | 5 years | 10 years | 30 years |
| **Placebo** | | | | | | |
| **Company base case – Approach 3** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ERG preferred – Approach 1** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ***S-TRAC (observed)*** | - | 78% | 60% | 51% | - | - |
| ***SEER data (observed)*** | - | 80% | 59% | 48% | 33% | - |
| ***SEER data (extrapolated)*** | Lognormal (DFS and OS) | 82% | 59% | 47% | 31% | 12% |
| **Pembrolizumab** | | | | | | |
| **Company base case – Approach 3** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ERG preferred – Approach 1** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations: DF, disease-free; DM, distant metastases; LR, locoregional recurrence.**

# Comparison of Approach 1 and 3

**Overall survival predictions of base case and scenario parametric models**

| Approach/ source | Parametric model combination | Overall survival by year | | | | |
|---|---|---|---|---|---|---|
| | | 1 year | 3 years | 5 years | 10 years | 30 years |
| **Placebo** | | | | | | |
| **Company base case – Approach 3** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ERG preferred – Approach 1** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| ***S-TRAC (observed)*** | - | 99% | 91% | 82% | - | - |
| ***SEER data (observed)*** | - | 98% | 82% | 68% | 48% | - |
| ***SEER data (extrapolated)*** | Lognormal (DFS and OS) | 97% | 82% | 69% | 45% | 10% |
| **Pembrolizumab** | | | | | | |
| **Company base case – Approach 3** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **ERG preferred – Approach 1** | Exponential (DF → LR) and Gompertz (DF → DM) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

**Abbreviations: DF, disease-free; DM, distant metastases; LR, locoregional recurrence.**