NICE National Institute for Health and Care Excellence

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# Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [ID1498]

# Lead team presentation

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Company: Merck Sharp & Dohme

8th April 2021

# Key issues

*Affects cost effectiveness results*

## Comparators

- What are the relevant comparators?

## KEYNOTE-177 trial

- How to deal with a blended comparator including treatments not offered in NHS?

## Indirect treatment comparison

- Can one assume equivalence for:
  - FOLFOX/FOLFIRI and CAPOX
  - Cetuximab and panitumumab-containing regimens
- Are the effectiveness estimates affected by RAS status?

## Extrapolations

- Is the use of equal post-progression survival (PPS) for all comparators justified?
- Is there evidence to support an ongoing treatment effect for pembrolizumab?

## Utilities

- Are treatment-specific or pooled utility values more appropriate?
- Should model include a disutility for adverse events?

## Costs and resource use

- Should costs for bevacizumab be assumed to be equal to cetuximab or FOLFOX/FOLFIRI?
- Should 6 or 4-weekly administration costs and resource use be modelled for pembrolizumab?
- Should guidance include a stopping rule for pembrolizumab?

# Metastatic colorectal cancer (mCRC)

- **Definition:** malignant tumour in large intestine which spreads to and beyond nearby lymph nodes
- **General symptoms:** change in bowel habit, abdominal discomfort, nausea, fatigue, feeling of incomplete bowel emptying
- **Survival:** determined by disease stage
  - Metastatic CRC survival rates: 1-year = 44%, 5-year = 10%
- **Treatment aims:** prolong survival, improve quality of life

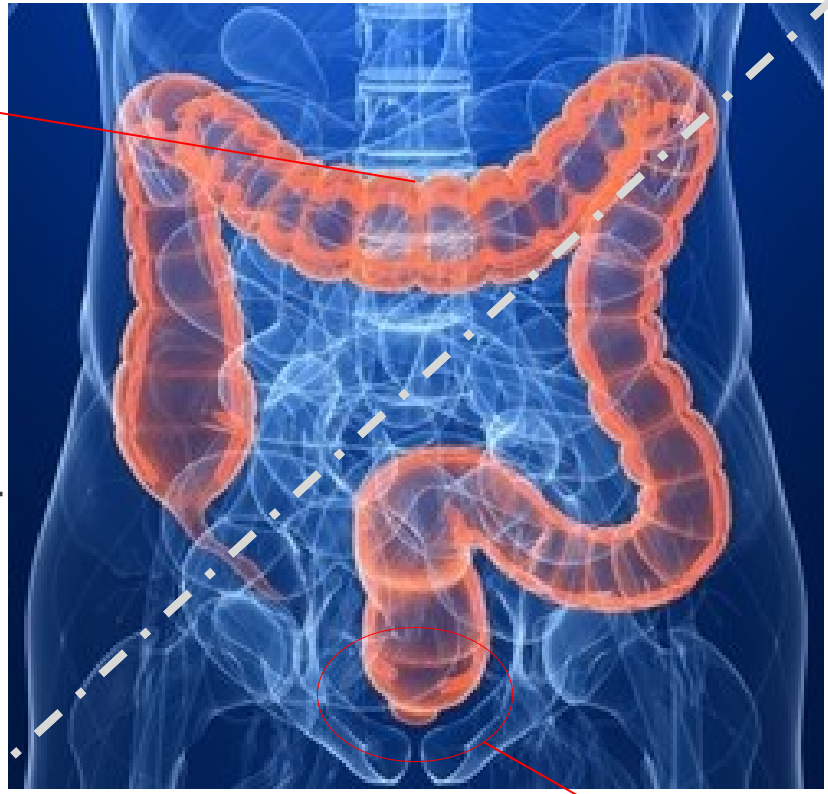
Colon: 2/3 of mCRC

**R- sided tumours:**

**Overall survival:** Worse - more likely advanced at diagnosis

**Common histology:** high microsatellite instability (MSI-H)/ DNA mismatch repair (dMMR)

**Responds best to:** immunotherapy



Rectum: 1/3 of mCRC

**L- sided tumours:**

**Overall survival:** Better

**Common histology:** KRAS and p53 mutant

**Responds best to:** adjuvant chemotherapy and targeted therapy

Source: colorectal.jpg (480×289) (qtxasset.com)

# Definitions of DNA mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H)

## Underlying pathology (genotype)

**MMR deficiency**

- MMR proteins correct single base nucleotide ‘mismatches’ - insertions or deletions - during DNA replication and recombination
- Mismatch repair (MMR) **deficient** cells can have many mutations
- MMR deficiency most common in colorectal, other gastrointestinal, and endometrial cancer
- MMR deficiency may be found in inherited disorders Lynch syndrome.
- Knowing if a tumor is MMR deficient may help plan treatment

## Resultant characteristics (phenotype)

**MSI-H**

- Describes cancer cells that have a greater than normal number of genetic markers called microsatellites - short, repeated, sequences of DNA
- Results from MMR deficiency
- Microsatellite instability most common in colorectal, other gastrointestinal, and endometrial cancer
- Presence of microsatellite instability high may help plan treatment

# Characteristics of MSI-H/dMMR colorectal cancers

- **Identification:** Positive for ≥1 of:
  - **dMMR:** Immunohistochemical staining (IHC) for any MMR protein loss
  - **MSI-H:** Polymerase chain reaction (PCR) for microsatellite instability
- **Prevalence**: MSI-H/dMMR occurs in 4% of metastatic CRC
- **Outcomes vs. metastatic non-MSI-H/dMMR:** Worse mortality rates and response to standard chemotherapy
- **Treatments**: Currently no MSI-H/dMMR mCRC specific treatments

# Pembrolizumab, Keytruda®

*Marketing authorisation includes no stopping rule; choice of dosing intervals*

| | |
|---|---|
| **Marketing authorisation** | 1st line treatment of 'unresectable or metastatic microsatellite instability-high or mismatch repair deficient colorectal cancer in adults' |
| **Mechanism of action** | Humanised monoclonal anti-programmed cell death-1 (PD-1) antibody<br>• A 'checkpoint inhibitor'<br>• *'Cancer cells may use the PD-1 pathway to hide from T cells. This stops T cells from attacking cancer cells'*<br>• *Pembrolizumab 'works by blocking the PD-1 pathway and to help prevent cancer cells from hiding' and 'helps the immune system do what it was meant to do: detect and fight cancer cells.'* |
| **Administration** | 200mg every 3 weeks or 400mg every 6 weeks, intravenously |
| **Additional testing in NHS** | NICE diagnostics guidance 27 'Molecular testing strategies for Lynch syndrome in people with colorectal cancer' recommends:<br>• *"Offer testing to all people with colorectal cancer, when first diagnosed, using immunohistochemistry for mismatch repair proteins or microsatellite instability testing"* |
| **List price** | • £2,630 per 100 mg vial so each 200mg administration = £5,260<br>• Commercial arrangement, available to NHS at discount |

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*https://www.keytruda.com/how-does-keytruda-work/*

# Patient perspective

## *Unmet need for treatments for this type of colorectal cancer*

**Quality of life impact**

- Diagnosis and current treatment significantly impact quality of life
  - *"Tolerating the fortnightly chemotherapy regime is very debilitating both physically and mentally."*
  - *"The risk of permanent peripheral neuropathic damage is high"*

**Limited options for people with MSI-H/dMMR disease**

- Current options for this bowel cancer population inadequate
  - No other potentially curative treatments
- Bowel cancer patients vary in nature (lynch syndrome, MSI high etc), but all given the same treatment lines.

**Pembrolizumab superior to current standard care**

- Faster and less frequent treatment without need for time in hospital
- Less toxicity (no sickness, diarrhoea, fatigue)
- Significant response rates to treatment
- Patients welcome targeted personalised approach: should be standard of care

# Patient organisation perspective

## Bowel Cancer UK

*High unmet need, patients would value new treatments*

**Unmet need**

- Survival rates for mCRC poor, <10% survive more than 5 years
- Limited NHS treatment options for advanced bowel cancer, especially MSI-H/dMMR disease
- Current standard care may not work for genetic profile
- Side effects from current treatments impact quality of life both physically and emotionally

**New treatment**

- Fewer hospital visits, reduced travel time and cost than chemotherapy:
  - three weekly 30 minute infusion opposed to two weekly 48 hour pumps
- Patients would value additional treatment options that extend life and have fewer side effects
- Personalised treatment necessary if outcomes are to improve in mCRC
- Newly diagnosed and younger people expected to benefit most

# NHS metastatic colorectal cancer pathway

*Currently no MSI-H/dMMR specific treatments; company positions pembrolizumab 1st line*

**KEY**
- Current standard care for MSI-H /dMMR mCRC
- Company's positioning for pembrolizumab

**Diagnosis of metastatic colorectal cancer**

Genetic testing
*RAS, BRAF V600E, MSI*

**All CRC types**

- FOLFOX / mFOLFOX6
- CAPOX
- FOLFIRI
- Tegafur with uracil (with folinic acid) **TA61**
- Capecitabine **TA61**
- Raltitrexed (if folinic acid & fluorouracil not tolerated / unsuitable)

**RAS wild-type specific**

- Panitumumab with FOLFOX, mFOLFOX6 or FOLFIRI **TA439**
- Cetuximab with FOLFOX, mFOLFOX6 or FOLFIRI **TA439**

**MSI-H/dMMR specific**

- Pembrolizumab monotherapy
- *During COVID19: pembrolizumab available for MSI-H/dMMR*
- *During COVID19: nivolumab available for MSI-H/dMMR*

**Not recommended at 1st line:**

- Bevacizumab with 5-FU/FA, with or without irinotecan **TA118**
- Bevacizumab with oxaliplatin and either fluorouracil + folinic acid or capecitabine **TA212**

Abbreviations: FOLFIRI, folinic acid plus fluorouracil plus irinotecan; FOLFOX, folinic acid plus fluorouracil plus oxaliplatin; mFOLFOX6, modified FOLOFOX6.

# Testing for high microsatellite instability or DNA mismatch repair deficiency

*NICE methods guide for technology appraisals includes genetic testing costs*

NICE methods guide:

- "*The use of a technology may be conditional on the presence or absence of a particular biomarker. If a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated* ***costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness****.*"

NICE diagnostics guidance 27: Molecular testing strategies for Lynch syndrome in people with colorectal cancer ***recommends routine testing***:

- "*Offer testing* ***to all people with colorectal cancer****, when first diagnosed, using immunohistochemistry for mismatch repair proteins or microsatellite instability testing to identify tumours with deficient DNA mismatch repair, and to guide further sequential testing for Lynch syndrome"*
- ***"Do not wait for the results*** *before starting treatment*."

ERG: correct to exclude MSI-H/dMMR testing costs as routinely performed in NHS



◉ *Should the model for testing be included in the appraisal?*

# Decision problem

*Company excludes 3 comparators in NICE scope*

| | Final scope NICE | Company |
|---|---|---|
| **Population** | Adults with metastatic colorectal cancer + high microsatellite instability or mismatched repair deficiency | Scope |
| **Intervention** | Pembrolizumab | Scope |
| **Comparators** | **All patients (6)**<br>1. Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)<br>2. Folinic acid plus fluorouracil plus irinotecan (FOLFIRI)<br>3. Capecitabine plus oxaliplatin (CAPOX)<br>4. Capecitabine<br>5. Tegafur with uracil (with folinic acid)<br>6. Raltitrexed (when folinic acid + fluorouracil not tolerated or unsuitable)<br>**RAS wild-type**<br>1. Panitumumab with FOLFOX or FOLFIRI<br>**RAS wild-type, EGFR expressing**<br>1. Cetuximab with FOLFOX or FOLFIRI | Company exclude:<br>1. Capecitabine<br>2. Tegafur with uracil (with folinic acid)<br>3. Raltitrexed |

EGFR: Epidermal growth factor receptor

# Pembrolizumab at 1st line - comparators

*Company excludes 3 scoped comparators : capecitabine, tegafur, raltitrexed*

## CAPECITABINE MONOTHERAPY

**Company:** only elderly / frail with poor performance status i.e. Eastern Cooperative Oncology Group [ECOG] score ≥2

- *N.B. technical team notes "pembrolizumab may be used with appropriate medical management in these patients" in marketing authorisation*

**Clinical experts:** Relevant

- Small number who have capecitabine, though frail, can instead have pembrolizumab
- Literature supports equivalence of capecitabine and 5FU

## TEGAFUR WITH URACIL (WITH FOLINIC ACID)

**Company:** regimen discontinued in UK

**Clinical experts:** not a comparator. Rarely used

## RALITREXED

**Company***:* rarely used

**Clinical experts:** not a comparator.

Only specific indications e.g. angina on 5-FU based chemotherapy

**ERG:** company's choice of comparators reasonable

- *Who would get capecitabine, tegafur, raltitrexed?*
- *What effect would including capecitabine have on cost-effectiveness results?*

# Confirmed MSI-H/dMMR mCRC: comparators

◉ *What would patients in the NHS receive if not pembrolizumab?*

Confirmed MSI-H/dMMR mCRC

**All CRC types**

- FOLFOX / mFOLFOX6
- CAPOX
- FOLFIRI

**Company excludes:**

- Tegafur with uracil (with folinic acid) **TA61**
- Capecitabine **TA61**
- Raltitrexed (if folinic acid & fluorouracil not tolerated / unsuitable)

**RAS wild-type specific**

- Panitumumab with FOLFOX, mFOLFOX6 or FOLFIRI **TA439**
- Cetuximab with FOLFOX, mFOLFOX6 or FOLFIRI **TA439**

**MSI-H/dMMR specific**

- Pembrolizumab monotherapy
- *During COVID19: pembrolizumab available for MSI-H/dMMR*
- *During COVID19: nivolumab available for MSI-H/dMMR*

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# Clinical effectiveness

1. *KEYNOTE-177 trial: pembrolizumab improves progression free survival and overall survival vs. standard care. Control arm not representative of NHS practice.*
2. *Pembrolizumab vs. comparators not in KEYNOTE-177: company uses fractional polynomials network meta-analysis in full mCRC population, even though some comparators limited to RAS wild-type disease*
3. *KEYNOTE-177 subgroup analyses show difference in estimates for RAS wild type vs mutant disease*

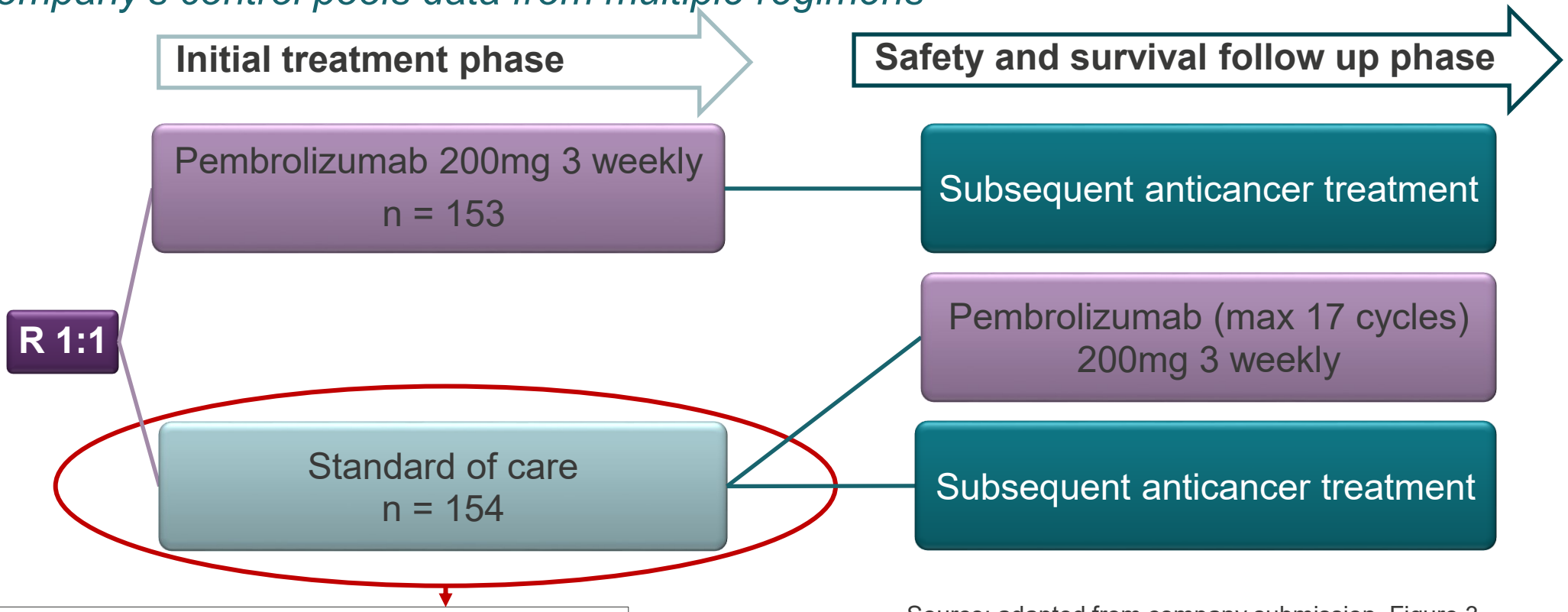
# Key trial: KEYNOTE-177 (only MSI-H/dMMR mCRC)

*Company' s trial compares pembrolizumab with clinician-choice standard of care (SOC). SOC includes bevacizumab not used in NHS; trial had stopping rule*

| | |
|---|---|
| | N=307; 120 centres, 6 centres in UK, n=20 from UK |
| Control arm | Standard of care, clinician choice of:<br>• chemotherapy (FOLFOX/FOLFIRI) +/- bevacizumab or cetuximab |
| Treatment length | Maximum 35 cycles (2 years) – 'stopping rule'<br>Retreatment if stopped early due to stable disease: maximum 17 cycles (1 year) |
| Median follow-up | Pembrolizumab: 28 months (0 to 48), SOC: 27 months (1 to 47) |
| Inclusion criteria | Adults with:<br>• Recurrent or newly diagnosed locally confirmed MSI-H/dMMR stage 4 mCRC<br>• No prior systemic therapy<br>• ECOG 0-1, life expectancy ≥3 months |
| 1º endpoints | • Progression-free survival (PFS), assessed by RECIST 1.1<br>• Overall survival |
| 2º endpoints | • Overall response rate |
| Exploratory endpoints | • Progression-free survival on next line of therapy (PFS2) |
| Data analysis | Interim analysis 2: 19 FEB 2020. No further data cuts confirmed.<br>Estimated completion date: FEB 2023. |
| Quality of life | EQ-5D-3L |

# KEYNOTE-177 trial schema: standard of care

*Company's control pools data from multiple regimens*




Source: adapted from company submission, Figure 3

**Pooled comparator: Standard of care**

| Treatment option | Number on treatment (%) |
|---|---|
| FOLFIRI | 16 (11) |
| FOLFOX | 11 (8) |
| FOLFIRI + bevacizumab | 36 (25) |
| FOLFOX + bevacizumab | 64 (45) |
| FOLFIRI + cetuximab | 11 (8) |
| FOLFOX + cetuximab | 5 (4) |

Source: Company submission, Table 16

Outcomes of SOC group likely biased: most patients received treatment not available in NHS

# KEYNOTE-177: control arm standard of care

*Company's pooled control includes bevacizumab unavailable in NHS + excludes CAPOX*

## Bevacizumab

Not recommended in NHS

**KEYNOTE-177**: ~70% control arm had bevacizumab

**Company:** exploratory analyses excluding people on bevacizumab (SOC n=[redacted], pembrolizumab n=[redacted])

**ERG**:

- Bevacizumab combinations more effective than FOLFOX, FOLFIRI or CAPOX (median PFS ~1.3 months longer)
- Scenarios excluding bevacizumab uncertain: small sample size and randomisation broken

**Choice of treatment controls (n=143)**

| Treatment option | Number on treatment (%) |
|---|---|
| FOLFIRI | 16 (11) |
| FOLFOX | 11 (8) |
| FOLFIRI + bevacizumab | 36 (25) |
| FOLFOX + bevacizumab | 64 (45) |
| FOLFIRI + cetuximab | 11 (8) |
| FOLFOX + cetuximab | 5 (4) |

## Pooling of standard care

**KEYNOTE-177:** 'Clinician's choice' then 'blended comparator'

**ERG**: Comparing pembrolizumab to individual SOC comparators breaks randomisation

However, KEYNOTE-177 best data source for pembrolizumab vs. CAPOX, FOLFOX, FOLFIRI

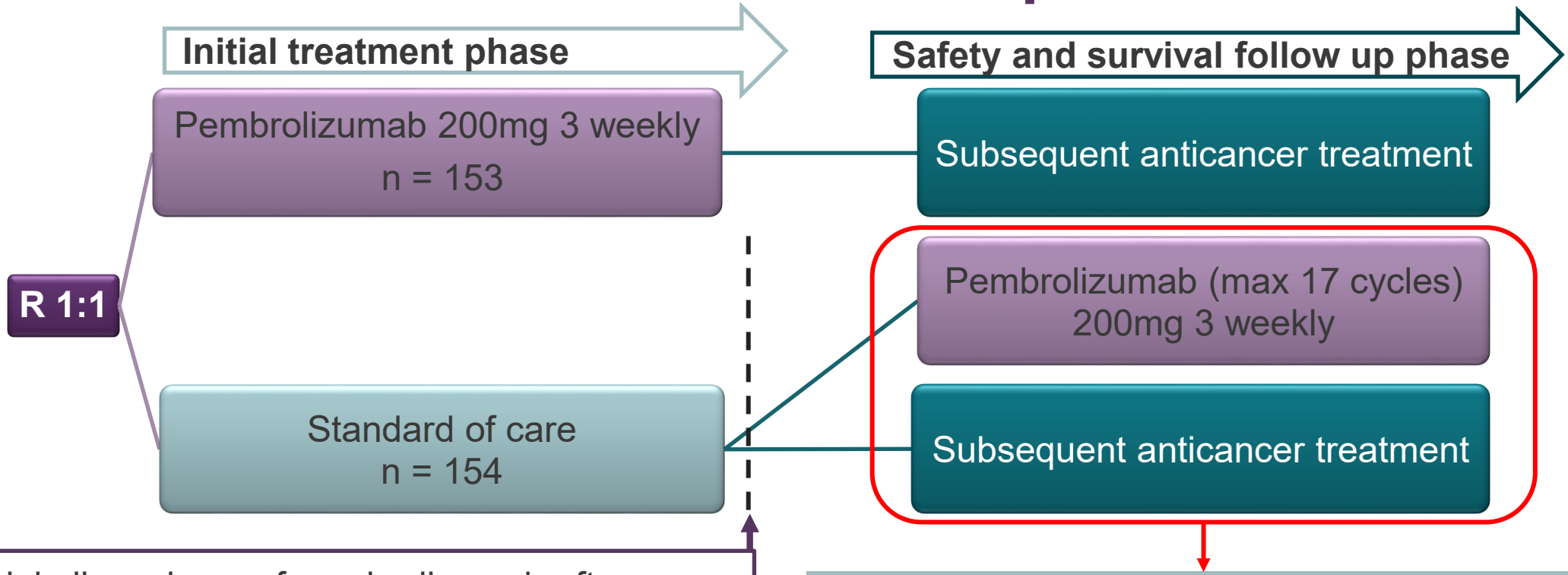
**Clinical experts:** KEYNOTE-177 SOC reflects NHS clinical practice except:

- Use of bevacizumab
- No use of CAPOX

- ◉ *Is bevacizumab likely to offer a survival benefit?*
- ◉ *What is committee's view on 'pooling' and modelling with a blended comparator?*
- ◉ *Should people taking bevacizumab be excluded from the analyses?*

*Source: Company submission, Table 16*

# KEYNOTE-177 trial schema: subsequent treatments




Trial allowed use of pembrolizumab after progression on SOC:

- at investigators discretion
- according to crossover criteria

**Subsequent checkpoint inhibitor use in:**

- **~50% SOC arm:** underestimates clinical effectiveness pembrolizumab vs. SOC
- [redacted]% pembrolizumab arm

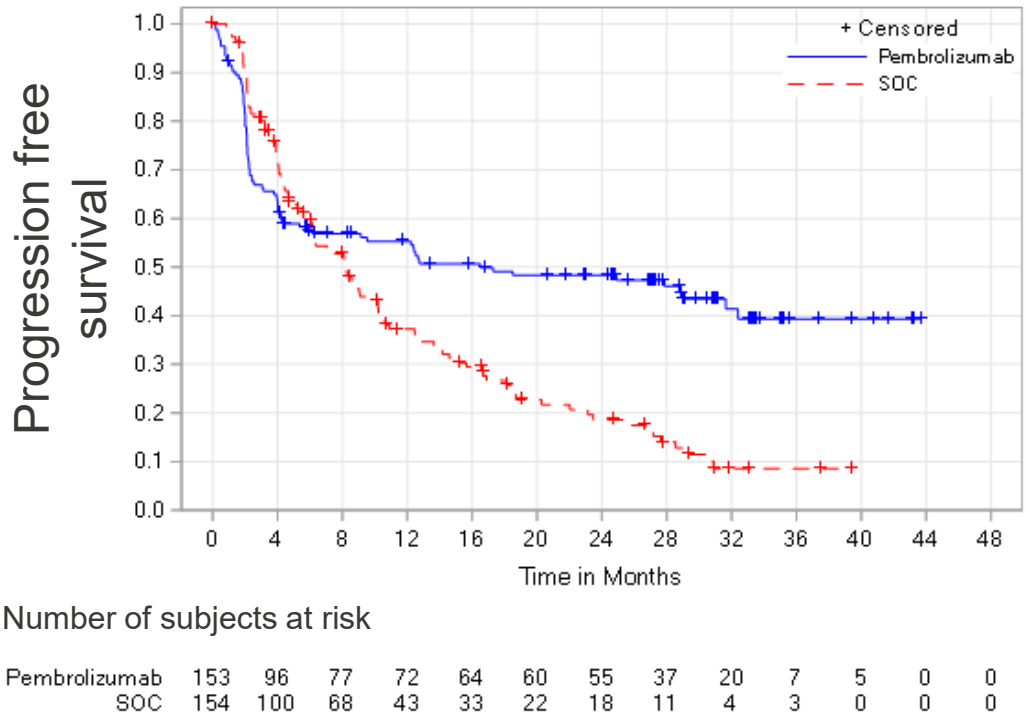
| **Subsequent anti-cancer therapies in ≥5% patients on SOC arm** | **n (%)** |
|---|---|
| Pembrolizumab | 56 (36) |
| Other anti cancer therapy | [redacted] |
| Anti-PD1/PDL1 therapies | 35 (23) |
| Chemotherapy | [redacted] |
| Folic acid derivative | [redacted] |
| VEGF inhibitor | [redacted] |

Source: Figure adapted from company submission, Figure 3
Table adapted from clinical study report, Table 14.1-10

# KEYNOTE-177 Results

*Results for progression-free survival (PFS) and less mature overall survival (OS)*
*Intention to treat analyses (ITT), data cut-off 19 Feb 2020*

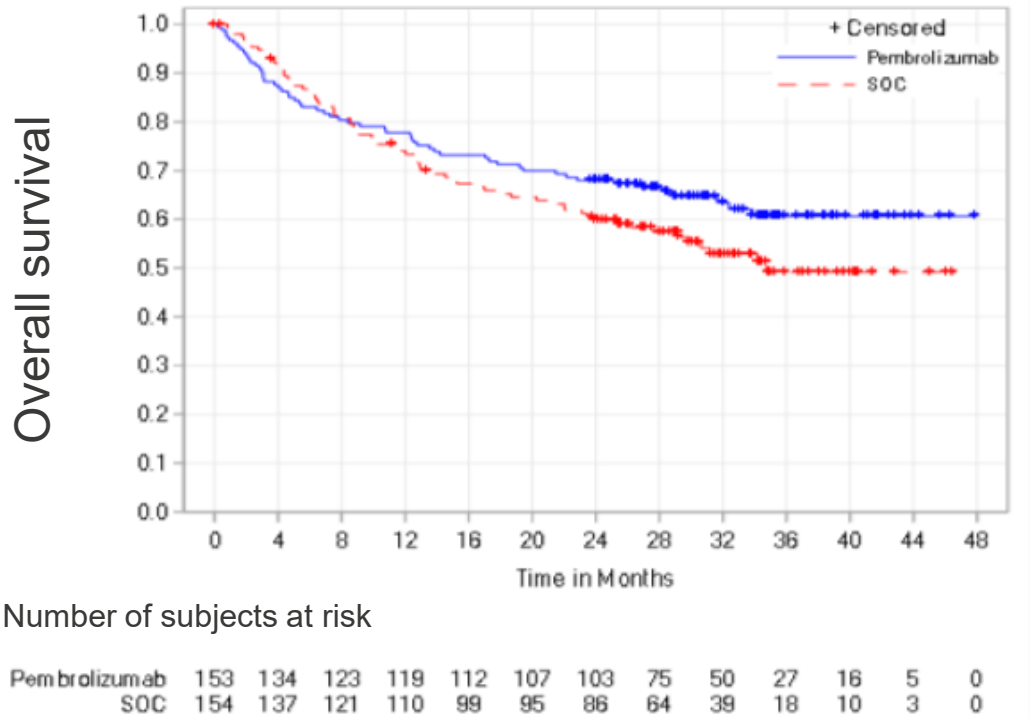
## Kaplan–Meier PFS cut-off 19 Feb 20




Number of subjects at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 153 | 96 | 77 | 72 | 64 | 60 | 55 | 37 | 20 | 7 | 5 | 0 | 0 |
| SOC | 154 | 100 | 68 | 43 | 33 | 22 | 18 | 11 | 4 | 3 | 0 | 0 | 0 |

## Kaplan–Meier OS cut-off 19 Feb 20




Number of subjects at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 153 | 134 | 123 | 119 | 112 | 107 | 103 | 75 | 50 | 27 | 16 | 5 | 0 |
| SOC | 154 | 137 | 121 | 110 | 99 | 95 | 86 | 64 | 39 | 18 | 10 | 3 | 0 |

| 1º outcome | Pembrolizumab, Nº of events (%) (N = 153) | SoC, Nº of events (%) (N = 154) | Hazard Ratio (95%CI) |
|---|---|---|---|
| Progression free survival | 82 (54) | 113 (73) | **0.60 (0.45 to 0.80)** |
| Overall survival | 56 (37) | 69 (45) | **0.77 (0.54 to 1.09)** |

Source: adapted from company submission, Tables 20 and 28 Figure 4, page 47 Figure 8, page 61

# Impact of subsequent checkpoint inhibitor use in control arm

*Company states pembrolizumab's benefit maintained after progression*

## Progression free survival (PFS) 2

**Definition:** time from randomisation to 1st of:

- **PFS:** disease progression or death
- **PFS2:** disease progression on next line of therapy or death

**KEYNOTE-177 median progression free survival on 1st and 2nd lines of therapy.**

| PFS | Median PFS (months) | | Hazard ratio (95% confidence interval) Pembrolizumab v SOC | In final model |
|---|---|---|---|---|
| | Pembrolizumab (N = 153) | SOC (N = 154) | | |
| 1st line (PFS) | 17 (5 to 32) | 8 (6 to 10) | **0.60 (0.45, 0.80)** | **Yes** |
| 2nd line (PFS2) | Not reached | 24 (17 to 33) | **0.63 (0.45, 0.88)** | **No** |

**Company conclusion:** Longer PFS2 with pembrolizumab vs. SOC
Benefit of pembrolizumab maintained after progression despite SOC checkpoint inhibitor use

## Mitigating the bias

- **Company:** scenarios adjusting overall survival results using simplified 2-stage model.
- **ERG and company:** overall survival not used in base case. Instead use pembrolizumab post progression survival for standard care

◉ *How should the potential bias in overall survival be factored into decision making*?

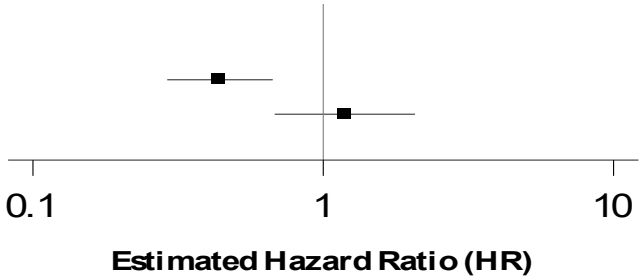
Source: adapted from company submission appendices, Table 108

# KEYNOTE-177 PFS in KRAS subgroups

*No effect in KRAS mutant subgroup compared with KRAS wild-type*

**Data cut off 19 Feb 2020**

| | # event/N | HR | 95% CI |
|---|---|---|---|
| **KRAS/NRAS-2** | | | |
| KRAS/NRAS all Wild type | 95/151 | 0.44 | (0.29, 0.67) |
| KRAS or NRAS Mutant | 51/74 | 1.19 | (0.68, 2.07) |




◉ *Should KRAS mutant and wild-type disease be modelled separately?*

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*Source: adapted from company submission, Figure 10, page 63 and ERG report, Table 19, page 58*

# KEYNOTE-177 Adverse Effects

*More frequent in SOC arm than pembrolizumab arm.*
*Company includes adverse events in model*

| Adverse events | Any grade, >10% patients | | CTCAE grade 3+, >5% of patients (used in model) | |
|---|---|---|---|---|
| | Pembro (%) | SOC (%) | Pembro (%) | SOC (%) |
| **Discontinued drug-related SAE, n (%)** | 7 (5) | 5 (4) | | N/A |
| **Adverse events** | | | | |
| Anaemia | [redacted] | [redacted] | 5 | 11 |
| Neutropenia | [redacted] | [redacted] | 0 | 15 |
| Diarrhoea | [redacted] | [redacted] | 6 | 11 |
| Abdominal pain | [redacted] | [redacted] | 5 | 6 |
| Fatigue | [redacted] | [redacted] | 4 | 9 |
| Neutrophil count decreased | [redacted] | [redacted] | 0 | 17 |
| Hyponatraemia | [redacted] | [redacted] | 5 | 3 |
| Hypokalaemia | [redacted] | [redacted] | 1 | 6 |
| Hypertension | [redacted] | [redacted] | 7 | 5 |
| **Total with ≥1 AE** | 97 | 99 | 56 | 78 |

Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; Pembro, pembrolizumab; SOC, standard of care.

◉ *How well tolerated is pembrolizumab compared to comparators?*

Source: adapted from company submission, tables 44 and 54, KEYNOTE-177 clinical study report, Table 12-2

# Only some comparators have 'direct' evidence

## Source of evidence for comparators:

**Pembrolizumab vs standard of care: MSI-H/dMMR only**

- FOLFOX / mFOLFOX6
- FOLFIRI
- Cetuximab with FOLFOX, mFOLFOX6 or FOLFIRI

**KEYNOTE-177 clinical trial pooled**

- CAPOX*
- Panitumumab with FOLFOX, mFOLFOX6 or FOLFIRI*

**Indirect treatment comparison using: KEYNOTE-177, NO16966, Porschen 2007, TREE-1, PRIME**

- Capecitabine
- Tegafur with uracil (in combination with folinic acid)
- Raltitrexed

**Company provides no evidence**

*No MSI-H/dMMR specific clinical trials. Company uses full mCRC population for comparators in indirect comparison

# Company's and ERG's equivalence assumptions

**All CRC types**

| | |
|---|---|
| FOLFOX | (m)FOLFOX6 |
| FOLFIRI | CAPOX |

**Company and ERG assume = efficacy**
1st line mCRC RCTs: similar median PFS and OS

**RAS wild-type**

| | |
|---|---|
| Cetuximab + FOLFOX | Cetuximab + FOLFIRI |
| Panitumumab + FOLFIRI | Panitumumab + FOLFOX |

**ERG assume = efficacy**
No significant difference in TA439 network meta-analysis

**Equivalence assumptions accepted in recent mCRC appraisals TA668 and TA439**
excluding CAPOX: not a comparator in either appraisal

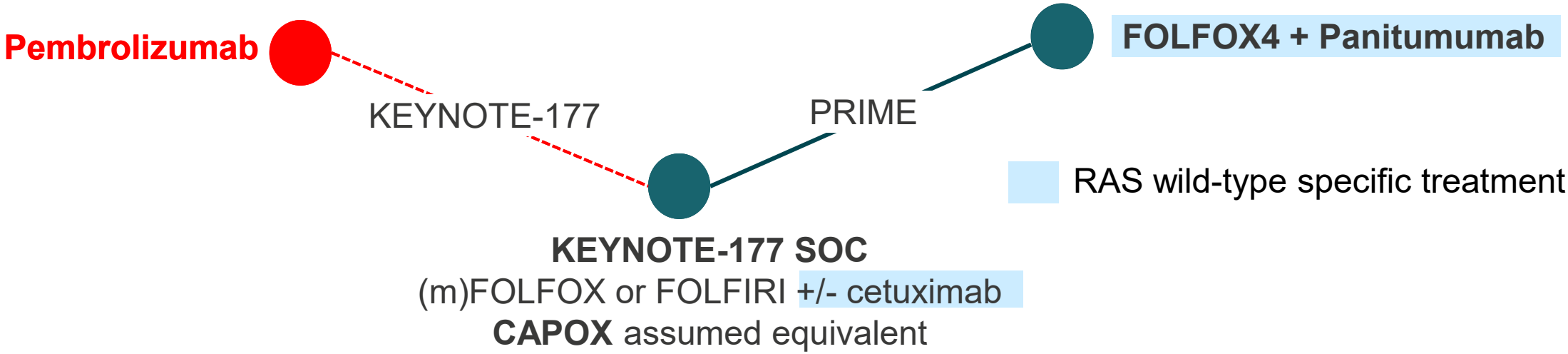
**TA668**: Encorafenib + cetuximab for previously treated BRAF V600E mutation-positive mCRC
**TA439**: Cetuximab and panitumumab for previously untreated metastatic colorectal cancer

**Source for comparator data** **KEYNOTE-177** **Indirect treatment comparison**

◉ *What is the committee's view on assuming these treatments equally effective?*

# Company's indirect comparisons – OS and PFS

*Direct head to head data not available for every comparator in NICE scope. Company network uses ITT population, defines SOC per KEYNOTE-177, assumes CAPOX = SOC*




**Company uses fractional polynomials** because proportional hazards assumption violated for PFS and OS in some studies.
Company accounts for varying hazards over time.
**ERG**: agree with company's approach

**Limitations**
Pooled KEYNOTE-177 SOC regimens using ITT:

- No specific MSI-H/dMMR comparator data
- No individual comparison with cetuximab combinations
- Not RAS mutation specific

◉ *Reasonable to assume CAPOX equally effective as standard of care?*

# Company's network meta-analysis results

[redacted]

| Month | Time-varying hazard ratio for Panitumumab + FOLFOX vs pembrolizumab (from PRIME and KEYNOTE-177) | |
|---|---|---|
| | Company | ERG |
| **Progression free survival** | | |
| **12** | [redacted] | [redacted] |
| **24** | [redacted] | [redacted] |
| **40** | [redacted] | [redacted] |
| **Overall survival** | | |
| **12** | [redacted] | Not conducted* |
| **24** | [redacted] | |
| **40** | [redacted] | |

Hazard ratio <1 favours pembrolizumab
*Overall survival data immature and not in company's model

Source: Inverse hazard ratios of ERG report, table 25 and table 27, pages 78 and 80 (provided separately by ERG)

◉ *Are the company's estimates of progression free survival acceptable?*

# Duration of treatment and stopping rules

*Duration of treatment drives costs*

**Company:** KEYNOTE177: n =150 (98%) in pembrolizumab arm received ≤35 cycles

**ERG:** maximum treatment duration unclear

- KEYNOTE-177 and model: maximum 35 cycles
- Draft summary of product characteristics: “until disease progression or unacceptable toxicity”
  - Impact on PFS unclear
  - Model sensitive to stopping rule removal

**Clinical experts:**

- Duration likely aligned with trial evidence in clinical practice: max 35 cycles
- KEYNOTE-177: allowed pembrolizumab retreatment (max 17 cycles) if stopped early due to good response.
  - But, not specified in marketing authorisation
  - Clinicians prefer to retreat if appropriate

◉ *Reasonable to stop treatment at 35 cycles regardless of whether disease progressed?*

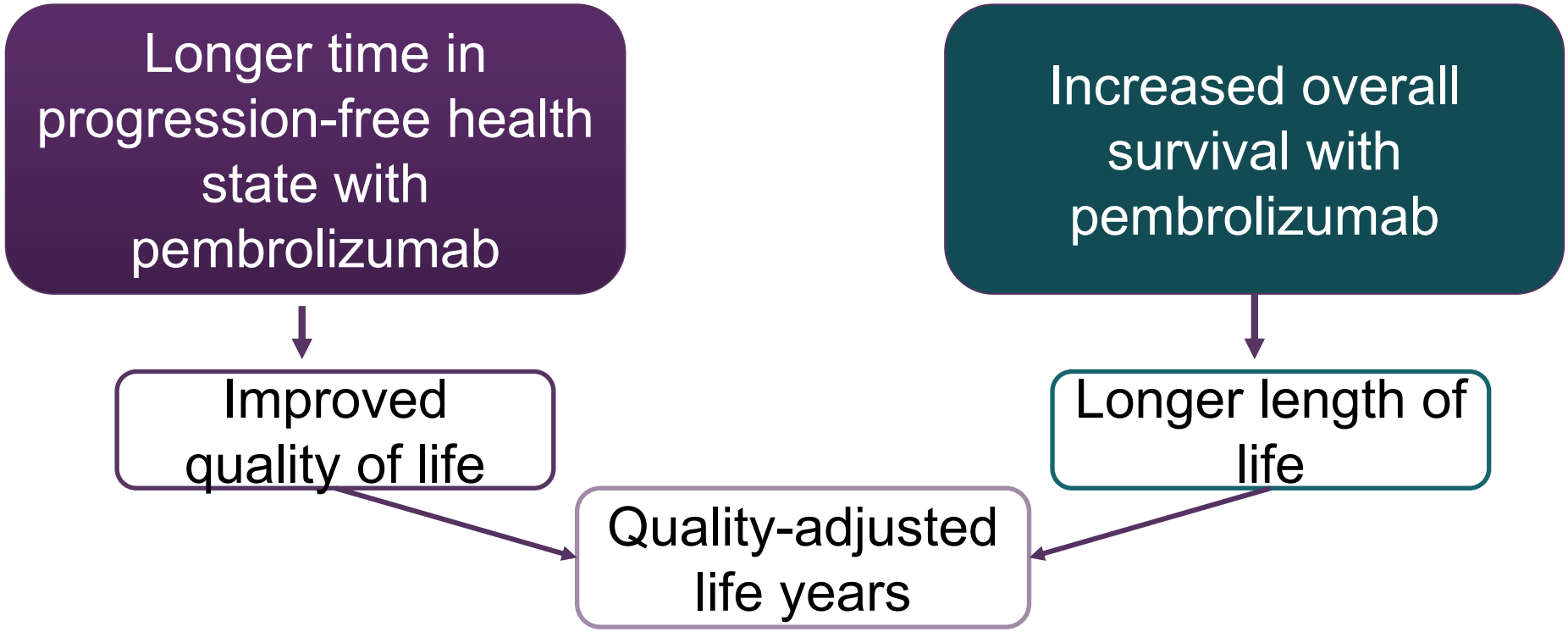
# Cost effectiveness

1. *Company uses a 3-health state semi-Markov transition model*

2. *Company models clinical inputs from KEYNOTE-177 trial for utilities, transition probabilities, baseline characteristics*

3. *Cost effectiveness results robust to changes in extrapolations.*

# Overview: how quality-adjusted life years accrue

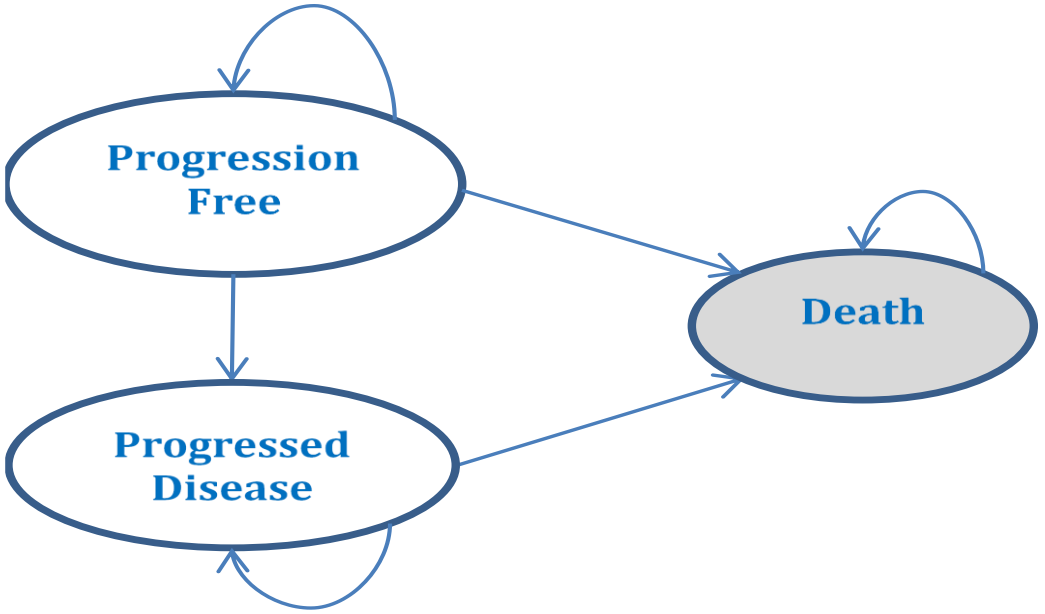


# Company's cost effectiveness model

*Company submit partitioned survival and amended state-transition models. 3-health state semi-Markov transition model used in base case.*

**Company's key assumptions for its model:**

- 1 week cycle length, ½ -cycle correction
- Time horizon 40 years
- Mean age 61 as in KEYNOTE-177
- General population mortality applied to progression free and progressed disease utilities: utility decreases with age
- Pembrolizumab = max 35 cycles
  i.e. stopping rule at 35 cycles
- No reuse of pembrolizumab despite use in KEYNOTE-177
- No administration cost for oral treatments
- Equal monitoring regardless of treatment
- Vial sharing for SOC treatments
- No extra cost for MSI-H/dMMR tests: routine in NHS




◉ *What is the committee view on the company's assumptions?*

# How company incorporated evidence into its model

*Company uses clinical data from KEYNOTE-177 for key model inputs*

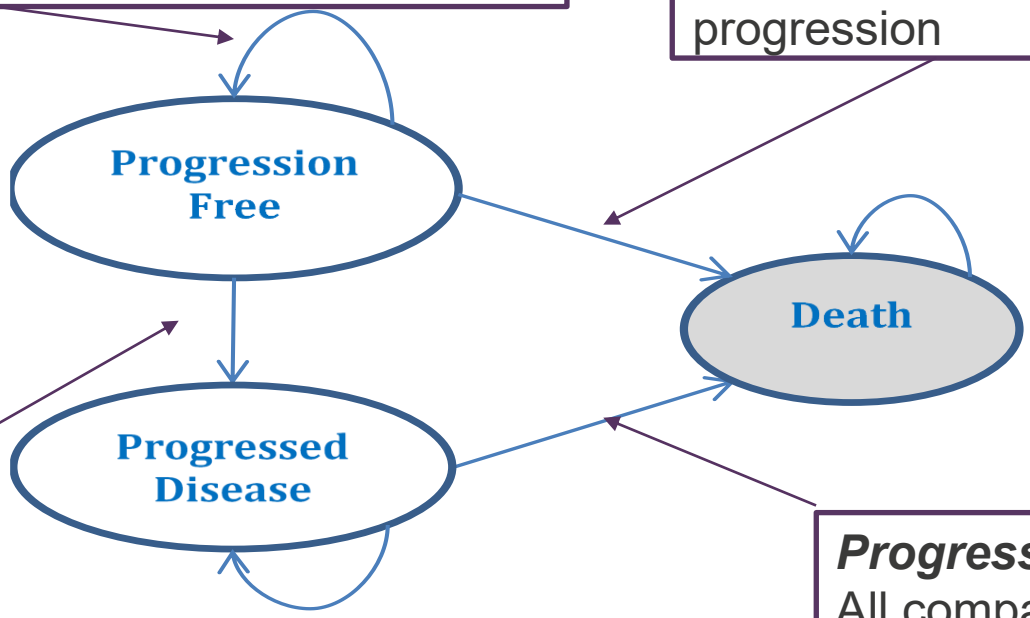
| Input | Evidence Source |
|---|---|
| Baseline characteristics | Whole population from KEYNOTE-177 |
| Treatment effect:<br>- Pembrolizumab, KEYNOTE-177 SOC, CAPOX<br>- Panitumumab + FOLFOX/ FOLFIRI | - KEYNOTE-177 individual patient level data from whole population<br>- Hazard ratios from network meta-analysis |
| Adverse events | Weekly rates Grade 3 or higher KEYNOTE-177 |
| HRQoL data | EQ-5D-3L from KEYNOTE-177 |
| Utilities | Based on KEYNOTE-177 health state for pembrolizumab and SOC<br>Non-trial comparators: KEYNOTE-177 SOC utilities<br>Decrement by age: Ara and Brazier, 2010 |
| Duration of treatment | Time on treatment data from KEYNOTE-177:<br>• Pembrolizumab: stopping rule at 35 cycles<br>• SOC: continued until disease progression or death<br>• Non-trial comparators: KEYNOTE-177 SOC time on treatment |

# Clinical data used in health state transitions

*Company uses KEYNOTE-177 data with treatment effect from indirect comparison*

***Progression free to progression free***
KEYNOTE-177 treatments: KEYNOTE-177 PFS
Non-trial comparators: network treatment effect applied to KEYNOTE-177 SOC PFS

***Progression free to death***
All comparators: PFS minus time to progression




***Progression free to progressed disease***
KEYNOTE-177 treatments: KEYNOTE-177 time to progression
Non-trial comparators**:** network treatment effect applied to KEYNOTE-177 SOC time to progression

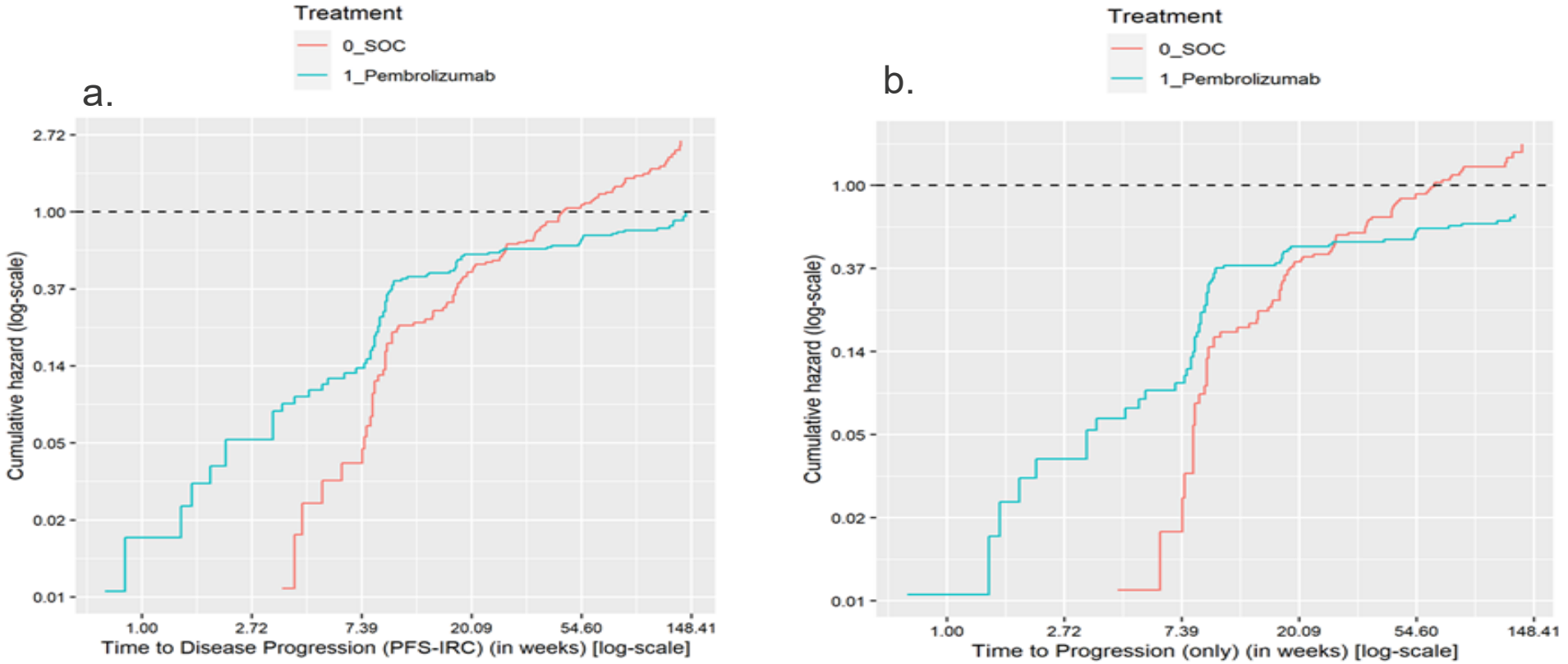
***Progressed disease to death***
All comparators: Pembrolizumab post progression survival

**Definitions: Time from:**
Progression Free Survival (PFS): treatment initiation to tumour progression or death
Time To Progression (TTP): treatment initiation to tumour progression only
Post Progression Survival (PPS): tumour progression to death

# Plots to test proportional hazards: PFS and time to progression

*Proportional hazards do not hold. Company fitted independent treatment curves.*

**Log-cumulative hazards plot for a) PFS and b) time to progression, excluding surgery patients**




Source: adapted from company submission, figures 22 and 27

**Company:** Proportional hazards do not hold: independent curves fitted

- Explored 1- and 2-piece (with 10- and 20- week cut-off) parametric curves

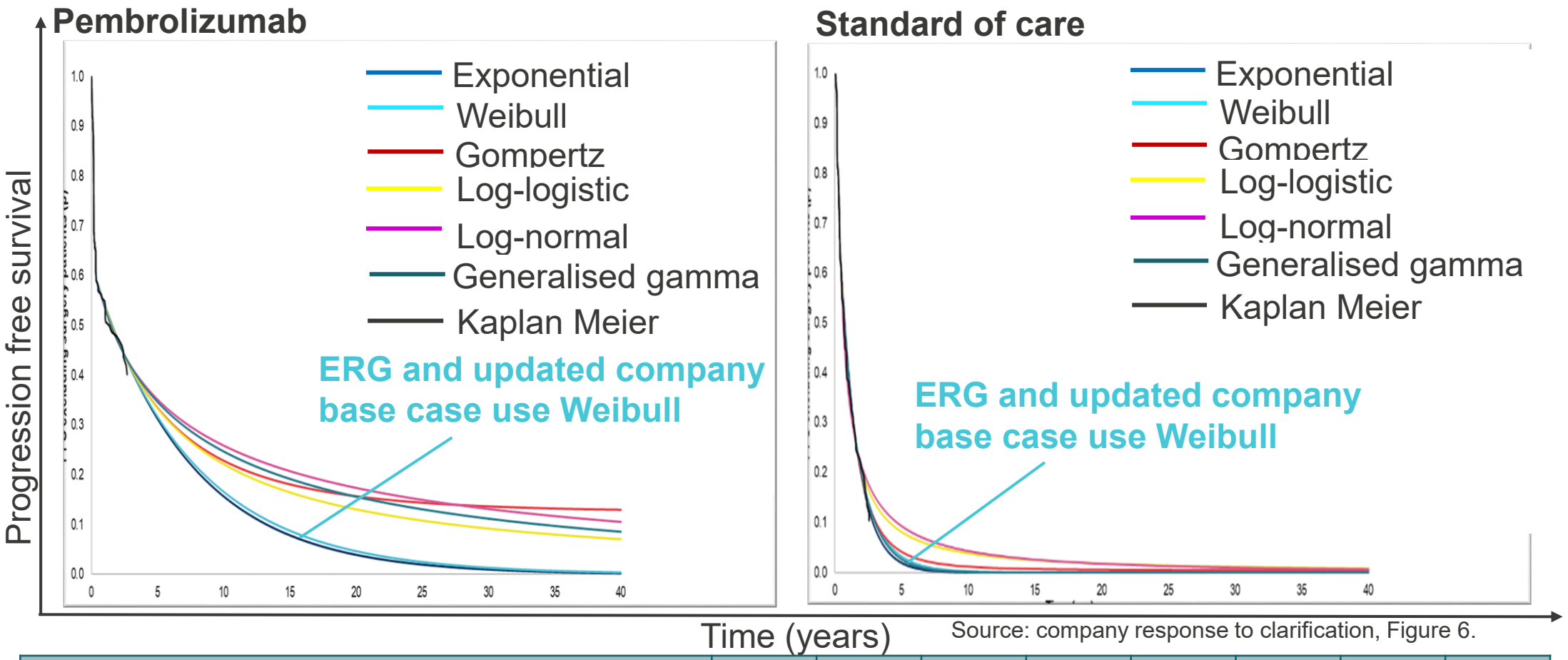
**ERG:** Proportional hazards tests only for population excluding surgery patients (not used in final model)

- Increasing hazard rate in SOC arm.

◉ *Do the hazard plots have face validity?*
◉ *Do proportional hazards hold? Is the company's approach acceptable?*

# Company extrapolates progression-free survival beyond trial

*Company and ERG prefer 2-piece curves, Kaplan–Meier to 20 weeks then Weibull distribution*



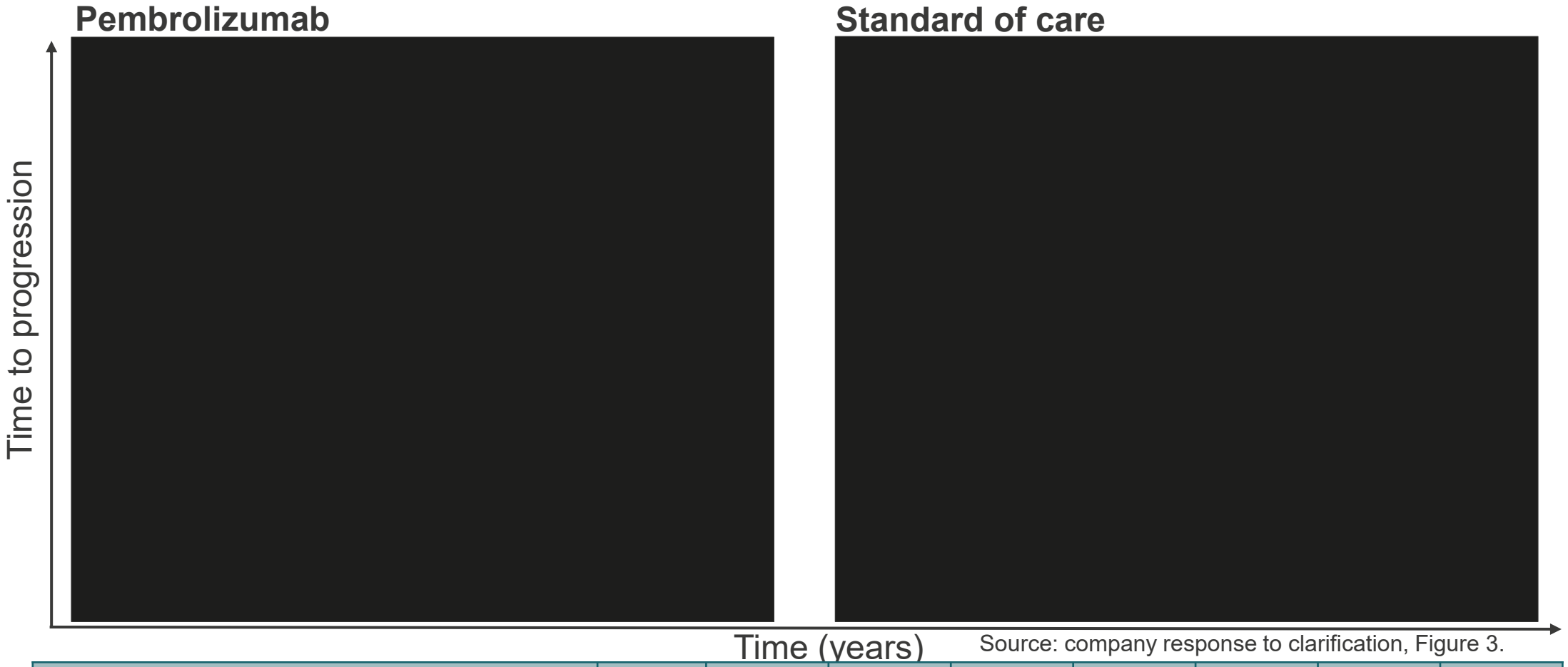

Source: company response to clarification, Figure 6.

| Predicted progression-free (alive) at year: | | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 |
|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | Exponential | 31% | 16% | 8% | 4% | 2% | 1% | 1% | 0% |
| | Weibull | 32% | 17% | 9% | 5% | 3% | 1% | 1% | 0% |
| FOLFOX/FOLFIRI/ CAPOX | Exponential | 2% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| | Weibull | 3% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |

- *Is the 20-week cut-off appropriate? Is the model sensitive to time of cut-off?*
- *Is Weibull appropriate to extrapolate PFS?*

# Extrapolating time to progression (TTP)

*Company and ERG prefer 2-piece curves, Kaplan–Meier to 20 weeks then Weibull distribution*




Source: company response to clarification, Figure 3.

| Predicted progression-free at year: | | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 |
|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | Exponential | *** | *** | *** | *** | *** | *** | *** | *** |
| | Weibull | *** | *** | *** | *** | *** | *** | *** | *** |
| FOLFOX/FOLFIRI/ CAPOX | Exponential | *** | *** | *** | *** | *** | *** | *** | *** |
| | Weibull | *** | *** | *** | *** | *** | *** | *** | *** |

- *Is the 20-week cut-off appropriate? Is the model sensitive to time of cut-off?*
- *Is Weibull appropriate to extrapolate time to progression?*

# Extrapolating post progression survival (PPS)

*Company and ERG use 1-piece Weibull curves. PPS for comparators = to pembrolizumab*

**Company**: Pembrolizumab PPS for comparators: gain in PFS = gain in OS.

| Predicted alive at year: | | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 |
|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab + all comparators | Weibull | *** | *** | *** | *** | *** | *** | *** | *** |

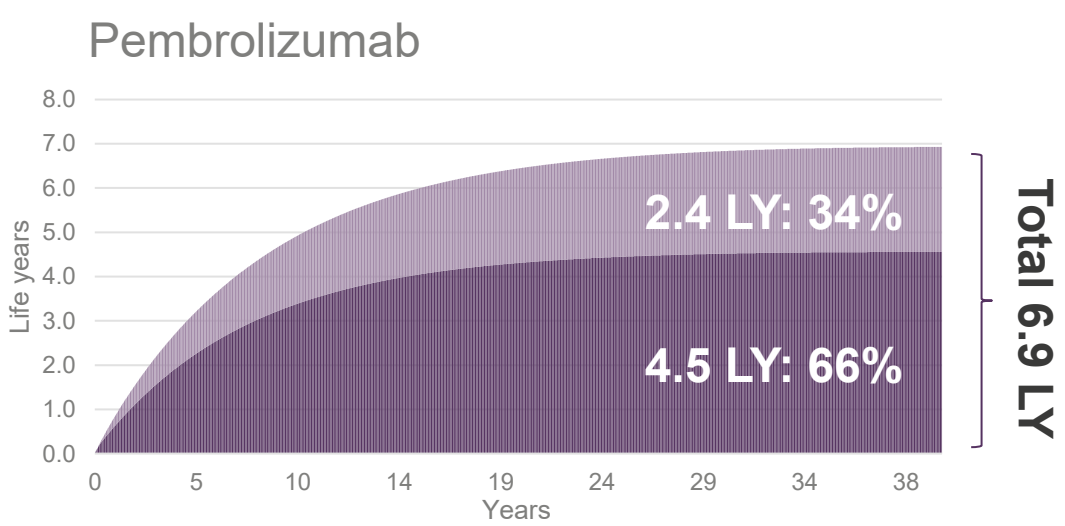
◉ *Weibull distribution acceptable to extrapolate post progression survival*?

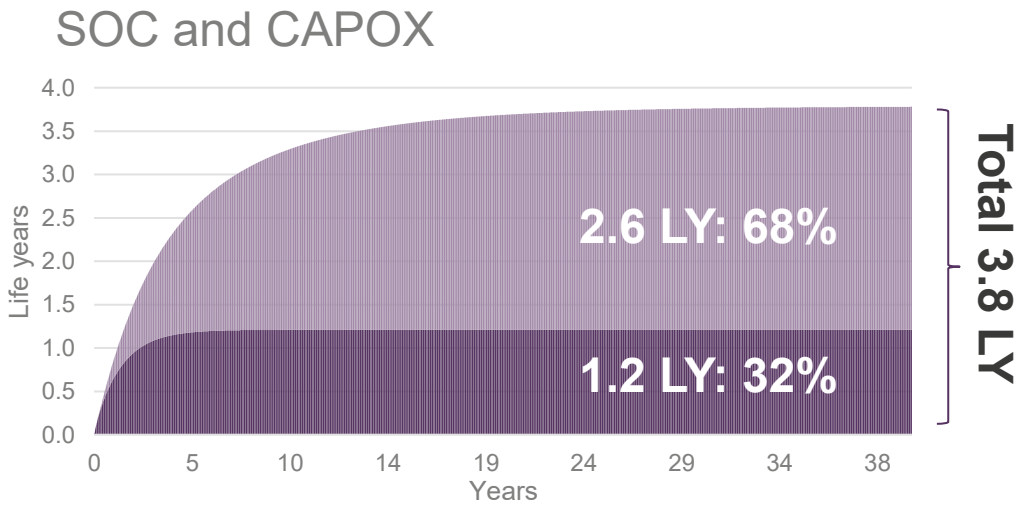


*Source: ERG report, Table 38.*

# Life year accrual over time in company's model

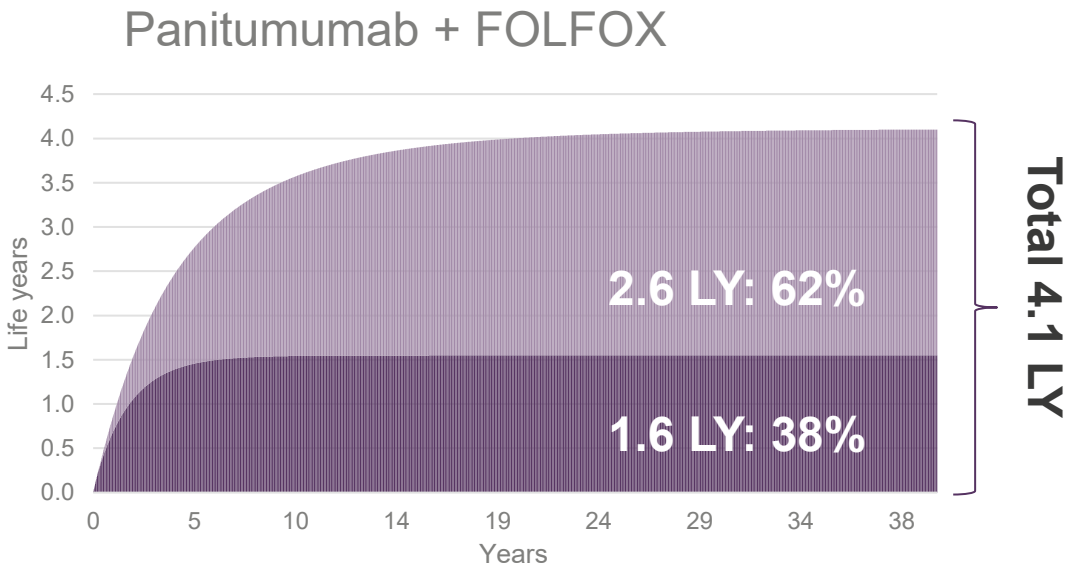
*Longer life with more time in progression free state with pembrolizumab*




KEY:

- Progression free
- Progressed disease




NICE



*Source: ERG report, Table 38.*

# Company's modelling of post progression survival (PPS)

*Company uses equal value for all comparators and assumes no ongoing treatment effect*

## Effect of all drugs stops on progression

**ERG:**

- Long-term OS data immature – further follow-up needed
- KEYNOTE-177: continued separation of PFS curves after discontinuation

**Clinical experts:** expect lifelong benefit in ~30-50% people having pembrolizumab

*"A dramatic benefit compared to SOC which only very rarely achieves this sort of advantage."*

## Company assumes equal PPS for comparators

**ERG**: Assumption avoids SOC crossover issue, but adjusting better

Mortality rate post progression with pembrolizumab vs. comparators uncertain:

- Especially RAS wild-type after panitumumab or cetuximab combination.
- Company's assumption supported by KEYNOTE-177 PFS and PFS2 which have similar hazard ratios

**Clinical expert:**

- Post-progression treatment may differ by 1st line treatment
- No evidence of worse outcomes based on RAS status in KEYNOTE-177
    - although different treatment options than used in NHS

◉ *Is use of equal post-progression time for all comparators justified?*
◉ *Does the evidence support an ongoing treatment effect for pembrolizumab?*

# Summary: extrapolating clinical outcomes vs. SOC

| Input | Company's initial base case | ERG base case and revised company base case | Additional scenarios | Impact on ICER |
|---|---|---|---|---|
| Progression free survival (PFS) | 2-piece **exponential** after 20 week cut-off | 2-piece **Weibull** with 20 week cut-off | 2-piece **Weibull** with 10-week cut-off | Minimal |
| Time to progression (TTP) | 2-piece **exponential** after 20 week cut-off | 2-piece **Weibull** with 20 week cut-off | 2-piece **Weibull** with 10-week cut-off | Minimal |
| Post progression survival | Equal for all comparators **Weibull** for pembrolizumab arm only | | **Lognormal** | Minimal |

# Health-related quality of life

# Company's quality of life inputs

*Utilities by health state + disutility for adverse events*

**KEYNOTE-177:** QoL at cycles 1 – 5 to 1 year/End of Treatment & 30 days post-treatment

**Company:** Utilities use mean EQ-5D-scores by disease status
**Treatment-specific** utilities in progression-free health state

**ERG**:

- Treatment specific utilities plausible: shorter and fewer hospital visits with pembrolizumab
- AE disutility inappropriate: causes double counting
- Similar utility values in KEYNOTE-177 SOC and for RAS wild-type patients in literature (0.778, Bennett et al. 2011). No evidence for utility difference by RAS status

| Health state | Pembrolizumab utility value | Comparator utility values | | | Scenario Pooled utility values |
|---|---|---|---|---|---|
| | | FOLFOX/ FOLFIRI | CAPOX | mFOLFOX6 + panitumumab | |
| **Progression-free** | 0.843 | 0.787 | | | 0.819 |
| **Post-progression** | 0.730 | 0.730 | | | 0.730 |
| **Adverse event disutility** | 0.031 | 0.031 | 0.025 | 0.065 | N/A |
| **Progression-free – no AE** | NA | NA | | | 0.833 |

*Source: adapted from company submission, Table 60 and company response to clarification, Table 4*

- *Are utility values that are treatment-specific or pooled across treatments best?*
- *How should disutility from adverse events be modelled?*

# Costs

# Company's costs inputs

*Most from NHS reference costs. Excludes cost of testing for high microsatellite instability/mismatch repair deficiency*

| Type | Cost | Frequency | Source |
|---|---|---|---|
| **Disease management costs** | | | |
| Visit to consultant | £187 | 2 weekly until progression | NHS reference costs 2018/19 |
| CT scan | £116 | 3 monthly until progression | |
| MRI scan | £206 | 2 in total | |
| Tumour marker test | £14 | 4 monthly until progression | TA439 inflated to 2018/19 |
| Liver function test | £29 | 4 monthly until progression | |
| Best supportive care | £1,600 | Monthly post progression | |
| Surgery | £10,919 | KEYNOTE-177 rates; non-trial comparators = SoC rate | TA439, inflated to 2018/19 x1.6 for multiple surgeries |
| Terminal care cost | £5,157 | Once | Round et al. 2015 inflated to 2018/19 |
| **Adverse event costs** | | | |
| Common AEs in KEYNOTE-177 | £93-£13,258 | Rate as per KEYNOTE-177 | NHS reference costs, most as per TA439 |
| Anaemia | £799 | | Crathorne et al. (2013) as TA439 |

NICE

◉ *Do these values have face-validity?*

# Company's costs for treatments

| Treatment | List price cost | Frequency | Source |
|---|---|---|---|
| mFOLFOX6 | £36 | 2 weekly | Drugs and pharmaceutical electronic market information tool (eMIT 2018) |
| FOLFIRI | £40 | | |
| CAPOX | £16 | Weekly | |
| Panitumumab + FOLFOX6* | £1643 | Weekly | |
| Cetuximab* | £1289 | Once | Monthly Index of Medical Specialities (MIMS 2020) |
| | £806 | Weekly | |
| **Drug administration costs (aligned with TA428, TA519 and TA661)** | | | |
| Pembrolizumab | £254 | 3 or 6 weekly | Outpatient visit, NHS Reference Costs 2018/19 |
| mFOLFOX6, FOLFIRI, CAPOX, Panitumumab | £385 | 2 weekly | Daycase and reg day/night. NHS Reference Costs 2018/19 |
| Cetuximab | £385 | Weekly | |
| **Subsequent treatment costs**** | | | |
| Pembrolizumab | £8,305 | Once | Clinical expert estimate |
| SOC | £8,086 | | |

* Confidential discount available to the NHS

** Pembrolizumab and cetuximab not included as subsequent treatments despite use in KEYNOTE-177

NICE

◉ *Do these values have face-validity?*

# Company's modelling of relative dose intensity and time on treatment

*More people received planned doses and for longer with pembrolizumab than SOC*

## Relative dose intensity

**Definition:** % planned chemotherapy actually received by patient

- Accounts for missed/reduced doses

**KEYNOTE-177:** pembrolizumab 97% vs. standard of care 89%

- Reflects higher toxicity of SOC
- Included in company's base case

## Time on treatment

Modelled using KEYNOTE-177 data:

- Mean: Pembrolizumab ** weeks, SOC and non-trial comparators ** weeks
- <10% of pembrolizumab arm had ≥2 years treatment

◉ *Are the KEYNOTE-177 relative dose intensity and time on treatment generalisable to the NHS?*

# Costs of bevacizumab in KEYNOTE-177

*Company replaces costs of bevacizumab with cetuximab for NHS*

**KEYNOTE-177 standard of care arm**
**70%** had **bevacizumab** combination treatment not NHS care

**Company**:
Bevacizumab costs what cetuximab costs in NHS

**ERG**:
SOC = FOLFOX (50%) and FOLFIRI (50%) costs in NHS

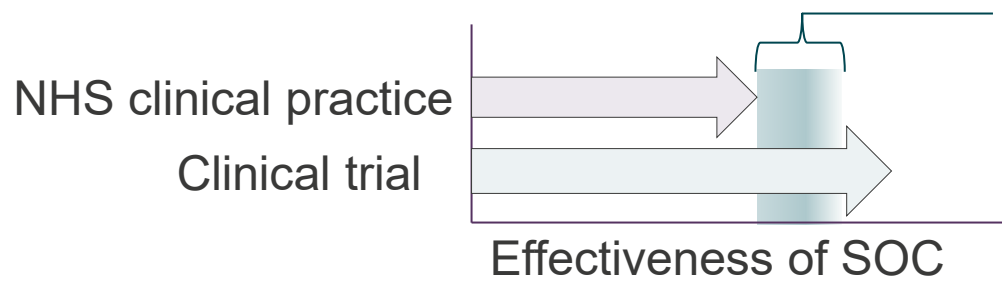
**Effect of assumptions compared with standard care in the NHS:**

| | Company | ERG |
|---|---|---|
| **Costs of SOC** | **Overestimated**<br>Cetuximab = RAS wild-type only<br>(<50% mCRC RAS wild-type in NHS) | **Underestimated**<br>Costs do not include cetuximab<br>(12% SOC arm) |
| **Treatment effect** | **Overestimated**<br>Bevacizumab more effective than NHS standard care | **Overestimated**<br>Bevacizumab more effective than FOLFOX/FOLFIRI |
| **Impact on ICER** | Pembrolizumab appears **more cost effective** | Pembrolizumab appears **less cost effective** |

◉ *Which approach to modelling costs for KEYNOTE-177 standard care is most appropriate?*

# RECAP: Potential bias in the evidence

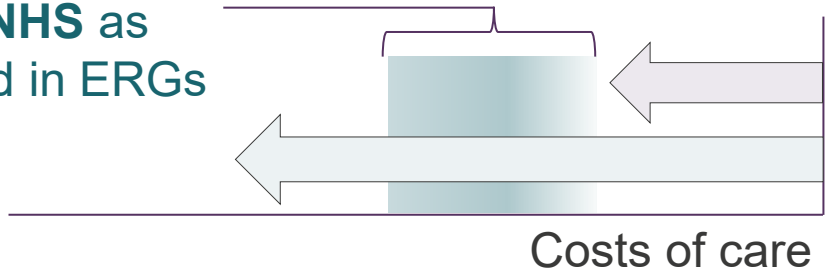
**Clinical evidence**




**Additional effectiveness from bevacizumab**. Clinical trial overestimates SOC as bevacizumab included (not recommended in NHS but considered effective)

**Costs**

**True cost of SOC in NHS** as cetuximab not included in ERGs costs



# Pembrolizumab dosing regimens

*3 weekly dosing in KEYNOTE-177 trial but 6 weekly dosing likely in NHS*

**Marketing authorisation:** IV infusion over 30 mins, both:

- 200 mg, every 3 weeks as KEYNOTE-177 protocol
- 400 mg, every 6 weeks

**Company:** Revised base case includes 6 weekly administration and visits

**ERG:**

- Expect doses to be equally effective
- 6 weekly dosing preferred by clinicians: patient convenience, resource use
  - Oncologist visit schedule align to cycle length
  - Model sensitive to changes in oncologist visits frequency

**Clinical experts:**

- May change to 6-weekly dosing after 3-6 months, once clinical/radiological response confirmed
- Increased telephone consultations in COVID-19:
  - mid-cycle telephone appointments, 6 weekly dosing
- Liver function monitoring every 6 weeks only
- No central venous line: fewer infections

# Innovation

*Company and clinical experts state innovative in MSI-H/dMMR population*

**Company:**

- 1st checkpoint inhibitor at 1st line
- Only treatment specific to MSI-H/dMMR
- Significantly better PFS and OS than comparators
- Well tolerated: less toxic than comparators

**Clinical experts:**

- Step-change with large and increasing divergence of survival curves over ≥ 2 years.
- Toxicity considerably lower than comparators
- Possibility of chemo-free treatment
- Some patients may never relapse

◉ *Is pembrolizumab innovative?*

# Issues addressed during technical engagement

| Issue | Stakeholder responses | Technical team |
|---|---|---|
| Non-trial comparators' time on treatment overestimated when PFS used | **Clinical expert**: 8-9 months as per ERG<br>**Company:** Time on treatment from KEYNOTE-177 SOC used for non-trial comparators | Aligns with TA439 mean treatment duration for panitumumab |
| Subsequent treatment costs included cetuximab (16%): not recommended at 2nd line in NHS | **Company** removed cetuximab and added to FOLFIRI (38%+16%) | Consistent with NHS treatment options |

# Assumptions summary: company and ERG base case

*Company accepted most ERG assumptions after technical engagement*

| Assumption | ERG base case | Company base case (from TE) |
|---|---|---|
| **Progression free health state** | | |
| **Modelled using** | Progression free survival and time to progression K-M data to week 20, then Weibull distribution | |
| **Administration / consultant appointments for pembrolizumab** | 400mg once every 6 weeks | |
| **Utilities** | Treatment specific KEYNOTE-177 SOC for all comparators | |
| **AE disutility** | Included* | |
| **Bevacizumab treatment costs SOC arm** | **FOLFOX (50%) and FOLFIRI (50%)** | **Cetuximab** |
| **Progressed disease health state** | | |
| **Modelled using** | Post progression survival for pembrolizumab Weibull distribution | |
| **Distribution of subsequent treatments** | Clinical expert estimate (with no cetuximab) | |
| **Treatment effect** | Stops at progression for all drugs | |
| **Utilities** | Equal for all drugs | |

*Sceneries show limited impact on ICER of removing AE disutility so included in ERG base case.

# Equalities

*Variation in local MSI-H/dMMR testing procedures could restrict access*

**Clinical expert:**

- Access to MSI-H/dMMR testing varies:
  - NICE diagnostics guidance 27 recommends routine testing
  - Local testing not always standard/timely
  - No access to pembrolizumab at later lines for MSI-H/dMMR patients given emergency chemotherapy because of testing delays

◉ *Is this an equalities issue?*

# Cost-effectiveness results

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

# Key issues

*Affects cost effectiveness results*

## Comparators

- What are the relevant comparators?

## KEYNOTE-177 trial

- How to deal with a blended comparator including treatments not offered in NHS?

## Indirect treatment comparison

- Can one assume equivalence for:
  - FOLFOX/FOLFIRI and CAPOX
  - Cetuximab and panitumumab-containing regimens
- Are the effectiveness estimates affected by RAS status?

## Extrapolations

- Is the use of equal post-progression survival (PPS) for all comparators justified?
- Is there evidence to support an ongoing treatment effect for pembrolizumab?

## Utilities

- Are treatment-specific or pooled utility values more appropriate?
- Should model include a disutility for adverse events?

## Costs and resource use

- Should costs for bevacizumab be assumed to be equal to cetuximab or FOLFOX/FOLFIRI?
- Should 6 or 4-weekly administration costs and resource use be modelled for pembrolizumab?
- Should guidance include a stopping rule for pembrolizumab?

# Back up slides

# NMA by RAS status

*Different effect for pembrolizumab versus SOC dependant on RAS mutation status*

**ERG:**

- Clinical benefit not maintained in RAS mutant
  - No overlap in 95% Cis: unlikely be chance finding
  - **Differs** from other subgroup analyses: warrants further research in powered study
- Standard care in ITT **not representative of NHS practice:** treatment decisions made on RAS status

**Company:**

- **Inappropriate to perform NMA analyses** by RAS status:
  - Small population, results uncertain
  - Differences in baseline characteristics between treatment arms in RAS subgroups
  - 27% KEYNOTE-177 do not have RAS status determined
  - Pembrolizumab targets PDL-1 signalling pathway: independent of RAS pathway
  - Cox regression analyses performed by EMA suggests interaction
    - Limitations of subgroup analyses noted
    - EMA recommendation not restricted by RAS status

**Clinical experts:**

- No biological explanation for poor response in RAS mutant:
  - MSI-H/dMMR only predictive biomarker for response in previous RCTs
- Advise recommendation in whole MSI-H/dMMR population, clinician discretion to use where benefit.

# KEYNOTE-177 patient characteristics by RAS status

*Baseline characteristics differ between RAS wild-type and RAS mutant groups*

**Key KEYNOTE-177 study patient baseline characteristics by RAS status**

| | Pembrolizumab | | SOC | |
|---|---|---|---|---|
| | RAS wild-type | Non-RAS wild-type | RAS wild-type | Non-RAS wild-type |
| N | 75 | [redacted] | 76 | [redacted] |
| Gender | | | | |
| Male | [redacted] | [redacted] | [redacted] | [redacted] |
| Female | [redacted] | [redacted] | [redacted] | [redacted] |
| Age (Years) | | | | |
| <65 | [redacted] | [redacted] | [redacted] | [redacted] |
| >=65 | [redacted] | [redacted] | [redacted] | [redacted] |
| Mean | [redacted] | [redacted] | [redacted] | [redacted] |
| ECOG | | | | |
| 0 | [redacted] | [redacted] | [redacted] | [redacted] |
| 1 | [redacted] | [redacted] | [redacted] | [redacted] |
| Site of Primary Tumour | | | | |
| Right | [redacted] | [redacted] | [redacted] | [redacted] |
| Left | [redacted] | [redacted] | [redacted] | [redacted] |

# ERG prefers NMA by RAS status

*ERG states separate analyses reduce clinical heterogeneity and reflects NHS pathway*

**RAS mutant mCRC**

**Comparators**: CAPOX, FOLFOX or FOLFIRI - assume equal clinical effectiveness

**NMA vs direct evidence:** No NMA. KEYNOTE-177 SOC arm for comparators (FOLFOX/FOLFIRI +/- bevacizumab or cetuximab)

**Potential bias:** favours standard of care. ~70% of SOC arm had bevacizumab - more effective than FOLFOX/FOLFIRI alone

**RAS wild-type mCRC**

**Comparators**: FOLFOX or FOLFIRI +/- cetuximab or panitumumab, CAPOX

**Preferred NMA**: RAS wild-type specific network

**ERG preferred source of comparator data:**

- CAPOX, FOLFOX, FOLFIRI = KEYNOTE-177 RAS wild-type subgroup analysis
- Cetuximab + FOLFOX/FOLFIRI = CRYSTAL, OPAL and TAILOR phase 3 RCTs
- Panitumumab + FOLFOX = PRIME phase 3 RCT

**Potential bias:** favours standard care. KEYNOTE-177 SOC included bevacizumab

Selection bias: *post-hoc analyses* in PRIME, CRYSTAL and OPAL: randomisation broken and non-MSI-H/dMMR specific

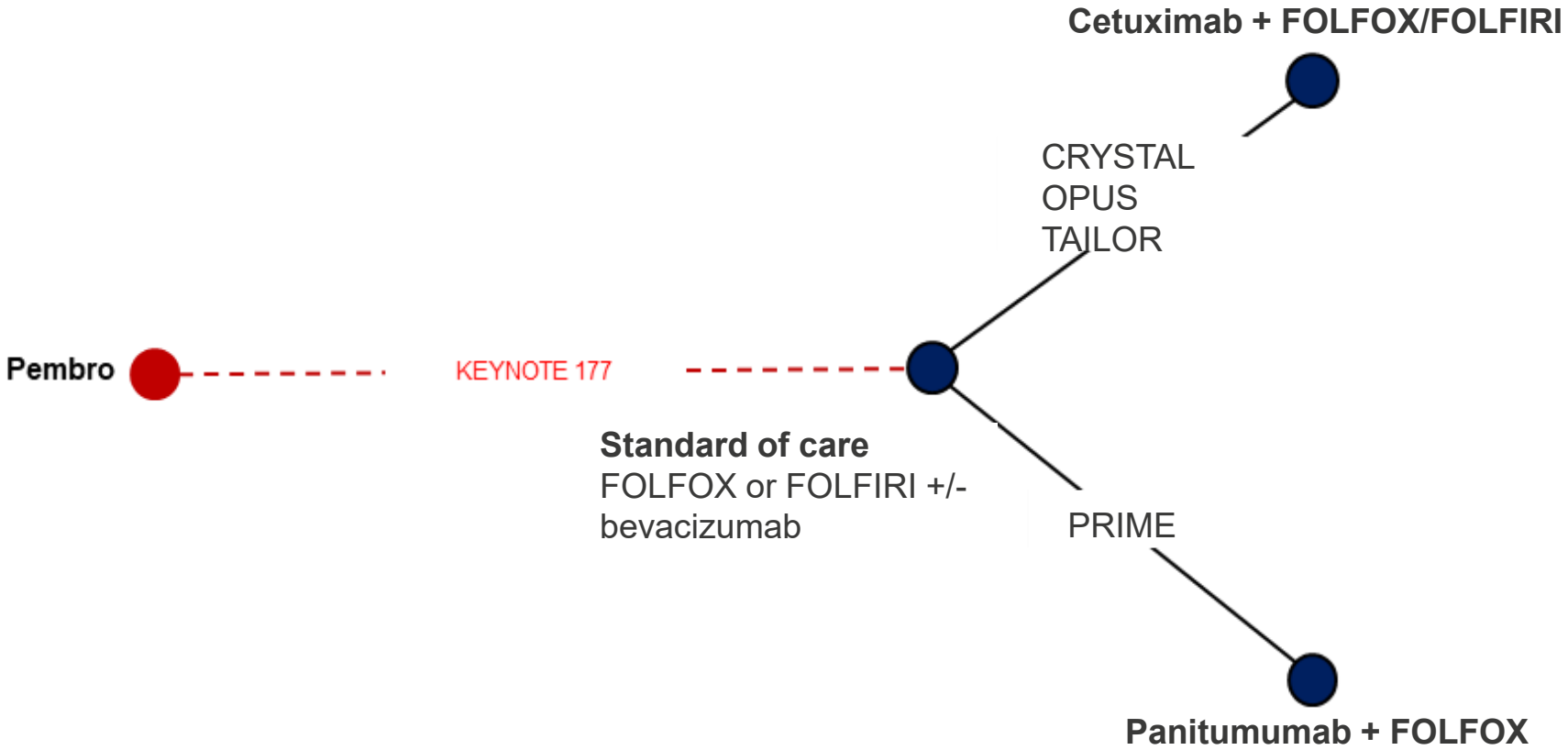
**Alternative approach:** assume equivalent clinical effectiveness between cetuximab + FOLFOX and panitumumab + FOLFOX (no statistically significant difference in the NMA from TA439).

*N.B Equivalence between cetuximab and panitumumab combinations accepted in TA668 (Encorafenib + cetuximab for previously treated BRAF V600E mutation-positive mCRC)*

# ERG's PFS NMA for RAS wild-type mCRC

*ERG prefers NMA for RAS wild-type patients only*

**Company's network of evidence for PFS.**




**Notes**

- No RCT for panitumumab + FOLFIRI
- FOLFOX and FOLFIRI assumed to be equivalent with CAPOX

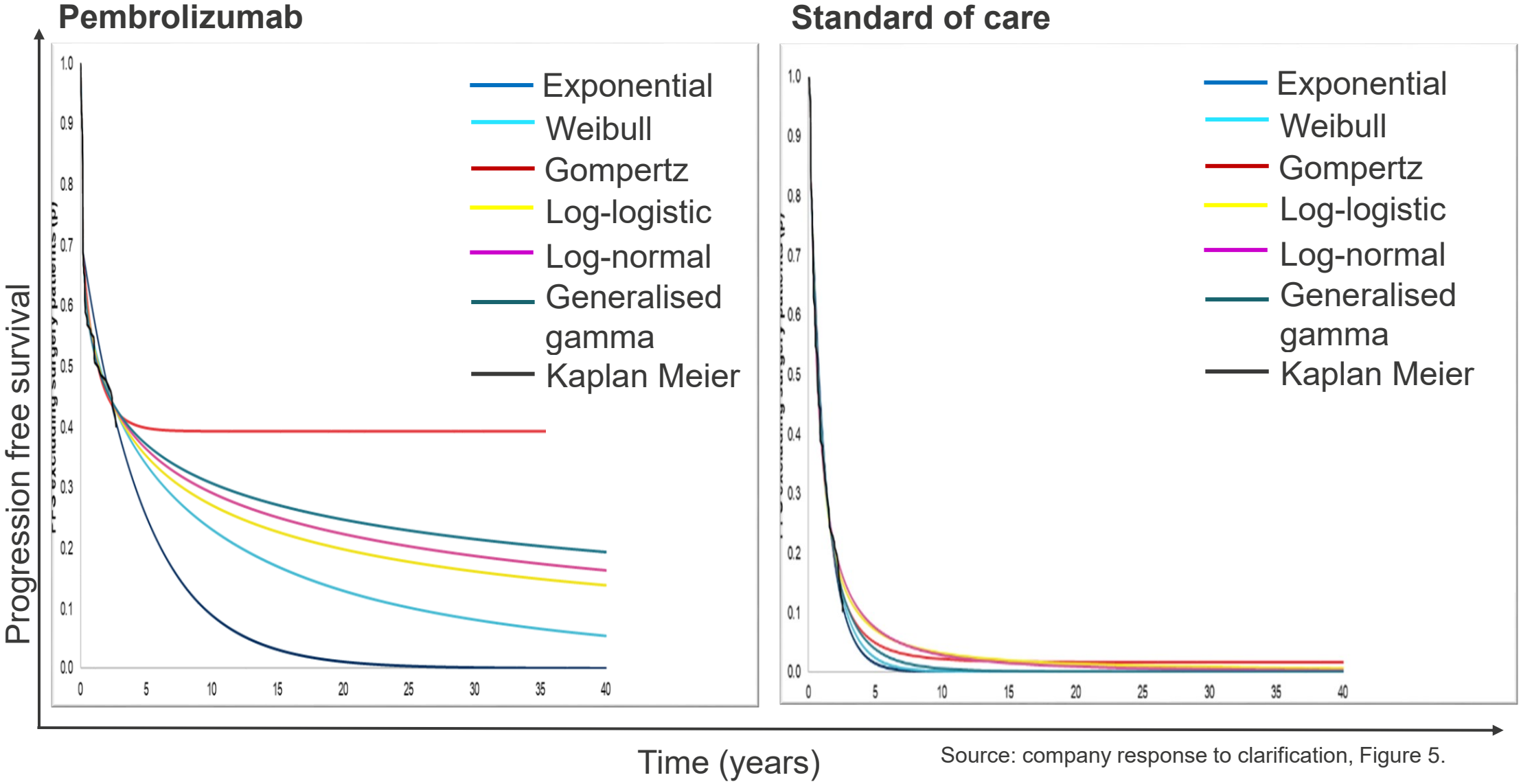
◉ *Is a separate network for RAS wild-type appropriate for decision making?*
◉ *Are treatment effects from the whole mCRC population generalizable to MSI-H/dMMR?*



Source: adapted from ERG report, Figure 4

# Company extrapolates progression-free survival beyond trial

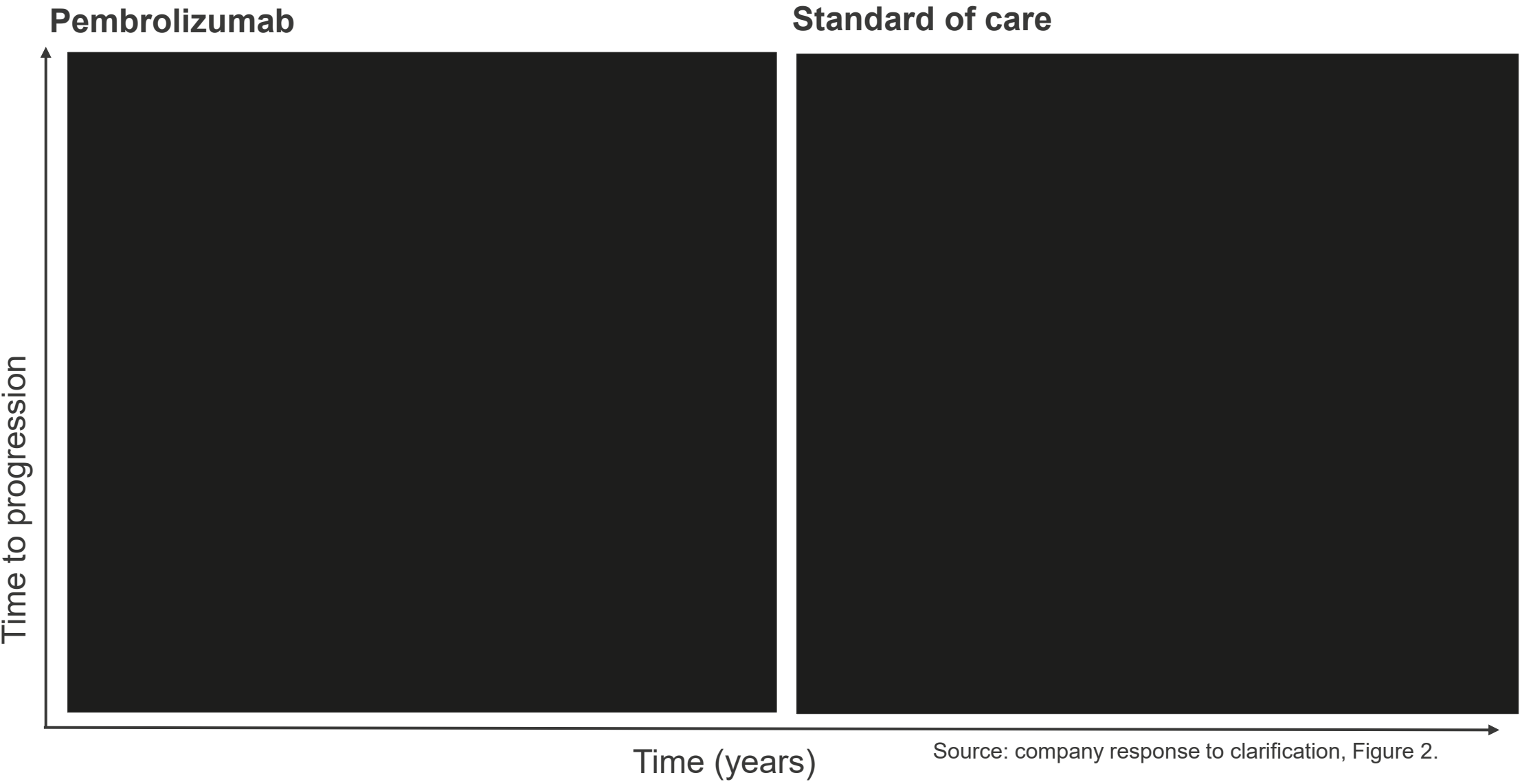
*Company considers 2-piece curves, Kaplan–Meier to 10 weeks then parametric distributions*




Source: company response to clarification, Figure 5.

# Extrapolating time to progression (TTP)

*Company considers 2-piece curves, Kaplan–Meier to 10 weeks then parametric distribution*




Source: company response to clarification, Figure 2.