NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **MSD**
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submissions** from:
    a. Kidney Cancer Support Network (KCSN)
    b. Kidney Cancer UK (KCUK)
4. **Evidence Review Group report** prepared by the **BMJ Group**
5. **Evidence Review Group report – factual accuracy check**
6. **Technical engagement response from company**
7. **Technical engagement responses and statements from experts:**
    a. Richard Jetten – patient expert, nominated by Kidney Cancer UK
8. **Evidence Review Group critique of company response to technical engagement** prepared the **BMJ Evidence Group**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Pembrolizumab for adjuvant treatment of renal cell carcinoma ID3810

Document B

Company evidence submission

November 2021

File name	Version	Contains confidential information	Date
Pembrolizumab adjuvant RCC ID3810 Document B Final	**1.0**	**Yes**	**04-NOV-2021**

Contents

Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with renal cell carcinoma (RCC) who have had nephrectomy	[redacted]	Wording updated to better reflect the expected population in the marketing authorisation.
Intervention	Pembrolizumab	Pembrolizumab	N/A
Comparator(s)	Established clinical management without pembrolizumab	Established clinical management without pembrolizumab	N/A
Outcomes	• Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	• Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	N/A

B.1.2 Description of the technology being appraised

Table 2 Technology being appraised

UK approved name and brand name	Pembrolizumab (KEYTRUDA®)
Mechanism of action	Pembrolizumab (KEYTRUDA®) 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. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and antitumour inactivity.
Marketing authorisation/CE mark status	The technology does not currently have a UK marketing authorisation/CE marking for the indication in this submission. The expected date of the opinion from the Committee for Human Medicinal Products is in [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Anticipated indication in the UK: [redacted] Current indications in the UK: Melanoma: • Keytruda as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults. • Keytruda as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection. Non-small cell lung carcinoma (NSCLC): • Keytruda as monotherapy is indicated for the first line treatment of metastatic non small cell lung carcinoma in adults whose tumours express PD L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. • Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non squamous non small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

	• Keytruda, in combination with carboplatin and either paclitaxel or nab paclitaxel, is indicated for the first line treatment of metastatic squamous non small cell lung carcinoma in adults. • Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic non small cell lung carcinoma in adults whose tumours express PD L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving Keytruda. Classical Hodgkin lymphoma (cHL): • Keytruda as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. Urothelial carcinoma: • Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum containing chemotherapy. • Keytruda as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD L1 with a combined positive score (CPS) ≥ 10. Head and neck squamous cell carcinoma (HNSCC): • Keytruda, as monotherapy or in combination with platinum and 5 fluorouracil (5 FU) chemotherapy, is indicated for the first line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a CPS ≥ 1. • Keytruda as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD L1 with a ≥ 50% TPS and progressing on or after platinum containing chemotherapy. Renal cell carcinoma (RCC):

	• Keytruda, in combination with axitinib, is indicated for the first line treatment of advanced renal cell carcinoma in adults. Colorectal cancer (CRC): • Keytruda as monotherapy is indicated for the first line treatment of metastatic microsatellite instability high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults. Oesophageal carcinoma • KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 Triple-negative breast cancer • KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease
Method of administration and dosage	Pembrolizumab as monotherapy 200mg every 3 weeks (Q3W) or 400mg every 6 weeks (Q6W).
Additional tests or investigations	N/A
List price and average cost of a course of treatment	£2,630 per 100mg vial.
Patient access scheme (if applicable)	A Patient Access Scheme (PAS) with a simple [redacted] discount has been arranged with NHS England. Therefore, the net cost per vial of pembrolizumab is [redacted]

B.1.3 Health condition and position of the technology in the treatment pathway

Health condition

Renal cell carcinoma

Renal cell carcinoma (RCC) is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer (more than 80% of the cases). There are several types of RCC. The main ones are clear cell (accounting for approximately 75% of cases) (1), papillary and chromophobe. RCC tumours are most commonly staged using tumour, node, and metastasis (TNM) staging (2), and graded via Fuhrman grading (3).

Epidemiology and aetiology

RCC

RCC is the seventh most common cancer in men and the ninth most common cancer in women. Worldwide, there are an estimated 209,000 newly diagnosed cases of RCC and an estimated 102,000 deaths per year (4). In 2017, 10,759 new kidney cancer cases were diagnosed in England. The incidence rate of kidney cancer increases with age and is highest in people over 85 years of age (1). The incidence of RCC is increasing continually in recent decades. Approximately two-thirds of the cases are diagnosed without evidence of metastatic disease (5).

Smoking and obesity are established risk factors for RCC. Several hereditary conditions, such as von Hippel-Lindau disease, predispose patients to having an increased risk of developing clear cell RCC. In the UK, RCC is more common in White males than in Asian or Black males, and is more common in White females than in Black females, but similar to Asian females, but Asian and Black females are similar to each other. Around 1,100 cases of kidney cancer each year in England are linked with deprivation (around 580 in females and around 510 in males) (1).

RCC post-nephrectomy

Where possible, treatment of tumours is surgery with curative intent. Treatment options for localised tumours include laparoscopic or open surgery (nephrectomy), which can be partial (nephron sparing) or total, and ablation techniques including radiofrequency ablation and cryoablation (nephrectomy) (6). NICE cancer service guideline 2, 'Improving outcomes in urological cancer' recommends that surgery can also be considered when there is metastatic disease (7).

Following surgery, patients can then be further classified on their risk of recurrence based on tumour staging and pathology. After nephrectomy, RCC recurs in 20% to 40% of patients with clinically localised disease (8). The greatest risk of recurrence for RCC occurs within the first 5 years after nephrectomy, with the majority of recurrences occurring within 3 years. Tumour stage plays an important role in timing of recurrence; the incidence of RCC recurrence after nephrectomy has been reported to be 7% with a median time of 38 months for T1 tumours, 26% with a median time of 32 months for T2 disease, and 39% with a median time to recurrence at 17 months for T3 tumours (8). Therefore, novel agents with durable clinical benefit and a potential curative effect are still needed.

Treatment pathway

Where the primary tumour has been successfully removed and patients have been declared disease-free, the aim of adjuvant treatment is to prevent recurrence of disease. Micrometastases and individual tumour cells may still be present following surgery or may arise de novo and will develop into larger tumours with the potential to disseminate to distant sites around the body resulting in advanced, unresectable tumours. However, for patients post-nephrectomy, there is currently no globally accepted standard of care in adjuvant RCC, and NICE has not appraised a medical treatment to reduce the risk of recurrence after surgery for renal cell carcinoma before.

The 2021 National Comprehensive Cancer Network (NCCN) guidelines recommend a clinical trial as a potential adjuvant option, as well as post-nephrectomy surveillance (NCCN evidence and consensus category 2A) and adjuvant sunitinib (NCCN evidence and consensus category 3) (9), which shows that novel treatments in the adjuvant

setting are needed to prevent disease recurrence in patients with RCC at increased risk of recurrence.

More recently, the European Society for Medical Oncology (ESMO) has updated their guideline on the use of immunotherapy in early stage and advanced RCC and now recommends that (10):

- For patients at intermediate-high and high risk of recurrence following nephrectomy:
    - Adjuvant pembrolizumab should be considered optional for patients with intermediate- or high-risk operable clear cell RCC (as defined by the KEYNOTE-564 study) after careful patient counselling regarding immature OS and potential long-term adverse events. Treatment should start within 12 weeks of surgery and continue for up to 1 year.
- And for patients following nephrectomy and resection of metastatic lesions:
    - Adjuvant pembrolizumab can be offered to patients with synchronous or early oligometastatic disease after complete resection of their oligometastatic disease.

There is therefore a clear need for an active adjuvant treatment to become available that can effectively prevent disease recurrence and potential progression to advanced (unresectable or metastatic) disease, which are associated with worse survival outcomes, reduced health-related quality of life (HRQoL) and increased healthcare costs. Moreover, offering a clinically effective treatment to patients in the adjuvant setting would offer greater value compared to treatment in the post-adjuvant setting, at which stage the disease is considerably more difficult to treat and associated with significant costs. The availability of a treatment option in this setting will also alleviate some of the uncertainty patients feel with routine surveillance. Pembrolizumab acts by enhancing the ability of the patients' own immune system to recognise and destroy micrometastases or individual tumour cells at an early stage and prevent further tumour growth and dissemination (11).

B.1.4 Equality considerations

No equity or equality considerations are anticipated.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

To identify and select relevant studies, a systematic literature review (SLR) was carried out in accordance with NICE guidance, according to a previously prepared protocol to identify relevant studies that investigated pembrolizumab and any relevant comparator treatments for the indication of interest for this appraisal as described in Table 1. Please refer to Appendix D for full details of the process and methods undertaken.

B.2.2 List of relevant clinical effectiveness evidence

A SLR was performed to identify all relevant published and unpublished randomised controlled trials (RCTs) and non-randomised clinical trials (non-RCTs) relating to pembrolizumab as per the final scope in Table 1.

A single trial was identified from the SLR that provided clinical effectiveness information on pembrolizumab in the patient population of relevance to this submission (adjuvant treatment of RCC post-nephrectomy) (Table 3). At the time of the SLR search, unpublished evidence from KEYNOTE-564 was available, since that time the results of the study (at the first interim analysis [IA1]) have been published in a peer-reviewed journal (12).

Table 3 Clinical effectiveness evidence

Study	A Phase 3, Randomised, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy (KEYNOTE-564)				
Study design	Phase 3, Randomised, Double-Blind, Placebo-Controlled Clinical Trial				
Population	Patients with RCC at intermediate-high or high risk of recurrence following partial or radical nephrectomy or following nephrectomy and resection of metastatic lesions				
Intervention(s)	Pembrolizumab				
Comparator(s)	Standard of care				
Indicate if trial supports application for marketing authorisation	Yes	X	**Indicate if trial used in the economic model**	Yes	X
	No			No	
Rationale for use/non-use in the model	KEYNOTE-564 is the only available trial with data for pembrolizumab in this indication				
Reported outcomes specified in the decision problem	• Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life				
All other reported outcomes	N/A				

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Summary of the methodology of the KEYNOTE-564 study

Trial design

KEYNOTE-564 is a Phase 3, randomised, double-blind, placebo-controlled, multicentre, global study to evaluate the efficacy and safety of pembrolizumab in the adjuvant treatment of RCC post nephrectomy. This study includes participants with RCC with clear cell component with study protocol-defined intermediate-high or high risk of recurrence following nephrectomy, or metastasis stage M1 with no evidence of disease (M1 NED) following nephrectomy and resection of metastatic lesions. Risk categories were based on pathological tumour node metastasis, Fuhrman grade, and presence of sarcomatoid features (3, 13, 14). The intermediate-high risk category included pathologic tumour stage T2 (pT2) with Grade 4 or sarcomatoid; pathologic

tumour stage T3 (pT3), any grade without nodal involvement (N0) or distant metastases (M0). The high-risk category included any pathologic tumour stage T4 (pT4), any grade N0 and M0, any pathologic tumour stage, any grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. (Please note: in general in oncology "tumour" and "lesion" are often used interchangeably. In this submission "tumour" is mostly used as this is the more familiar term and more appropriate term in most cases [e.g. where TNM staging is described], "lesion" is used to reflect the wording of the marketing authorisation and label for this indication, where required.)

Approximately 950 eligible participants were planned to be randomised 1:1 to receive either placebo or pembrolizumab 200 mg, administered by IV infusion every 3 weeks (Q3W).

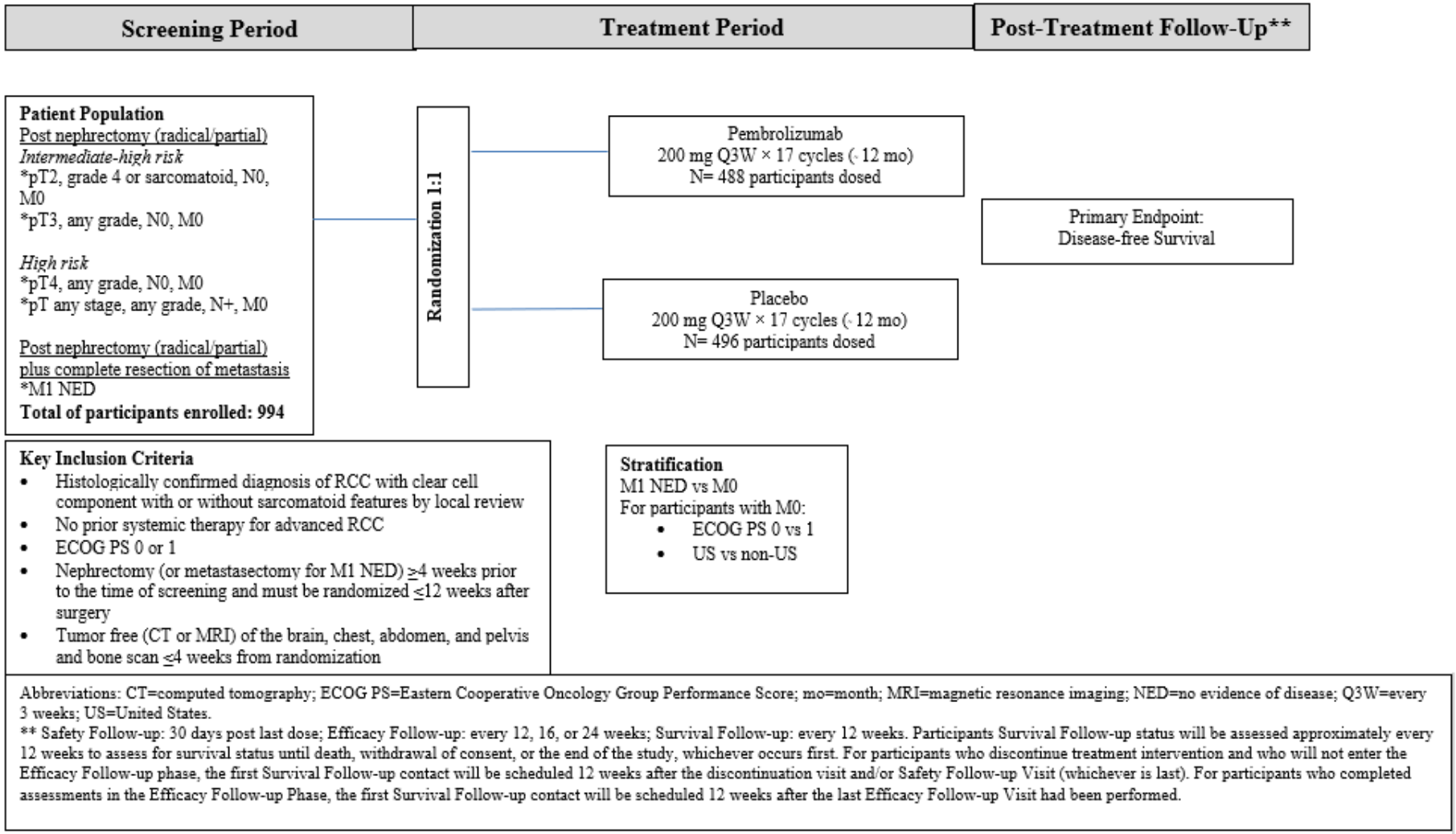
Participants may receive study treatment for up to 17 cycles (approximately 1 year) or until confirmation of disease recurrence or meeting the criteria for discontinuation of study treatment as outlined in the study protocol and described in Appendix L. According to the protocol, scheduled on-treatment imaging assessments will be performed every 12 weeks (Q12W) from randomisation and would not be adjusted for delays in treatment or cycle starts. All participants who complete 17 cycles or discontinue from treatment for a reason other than disease recurrence will undergo radiographic imaging follow-up (Q12W during year 1, every 16 weeks [Q16W] during years 2 to 4, then every 24 weeks [Q24W] in years 5 and beyond) for assessment of DFS.

During the treatment period, participants have routine clinical visits for administration of study intervention and monitoring of safety, well-being, and changes in disease status. Participants complete QoL questionnaires to assess the impact of treatment on HRQoL.

Key safety assessments include the monitoring of adverse events (AEs) and adverse events of special interest (AEOSIs), physical examinations, vital signs, cardiac function via electrocardiograms (ECGs), as clinically indicated, haematology and chemistry laboratories (including thyroid function test), and urinalysis.

The study design is depicted in Figure 1.

Figure 1 KEYNOTE-564 study design



Eligibility criteria

Patient inclusion criteria

Key inclusion criteria for both male and female participants at least 18 years of age were as follows:

- Histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid (i.e. originating from the epithelial-mesenchymal transition) features by local review
- Had intermediate-high risk of recurrence, high-risk or recurrence, or M1 NED RCC as defined by the pathological tumour-node-metastasis and Fuhrman grading status as shown in Table 4
- No prior systemic therapy for advanced RCC
- ECOG PS 0 or 1
- Underwent a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion[s] in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening
- Was tumour free (CT or MRI of the brain, chest, abdomen, and pelvis, and a bone scan ≤28 days from randomisation) as assessed by the investigator

Table 4 Inclusion criteria for intermediate-high risk, high risk, and M1 NED RCC used in the KEYNOTE-564 study

Category	Inclusion criteria (based pathologic TNM staging and Fuhrman grading)	Description
Intermediate-high risk of recurrence RCC	pT2, Grade 4 or sarcomatoid, N0, M0	Tumour was limited to the kidney and >7 cm, the cancer cell nuclei were bizarre, extremely irregular and often multilobed or had histological, cytological, or molecular properties of both epithelial and mesenchymal tumours, no regional lymph node metastasis, no distant metastasis.

Category	Inclusion criteria (based pathologic TNM staging and Fuhrman grading)	Description
	pT3, any grade, N0, M0	Tumour had extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota's fascia, any Fuhrman grade, no regional lymph node metastasis, no distant metastasis.
High-risk of recurrence RCC	pT4, any grade, N0, M0	Tumour involved ipsilateral adrenal gland or invades beyond Gerota's fascia, any Fuhrman grade, no regional lymph node metastasis, no distant metastasis.
	pT any stage, any grade, N+, M0	Tumour was of any stage, any Fuhrman grade, had metastatic involvement of regional lymph node(s), no distant metastasis.
M1 NED RCC	Participants who presented not only with the primary kidney tumour, but also solid, isolated, soft tissue metastases that could be completely resected at one of the following: • the time of nephrectomy (i.e. synchronous) or, • ≤1 year from nephrectomy (i.e. metachronous)	

Patient exclusion criteria

Participants were excluded from the study if they had any of the following:

- Major surgery, other than nephrectomy and/or resection of pre-existing metastases for M1 NED participants, within 12 weeks prior to randomisation.
- Received prior radiotherapy for RCC.
- Has pre-existing brain or bone metastatic lesion.
- Has residual thrombus post nephrectomy in the vena renalis or vena cava.
- Had other medical conditions or history that would interfere with the participant's participation for the full duration of the study, or it was not in the best interest of the participant to participate.

Settings and locations where the data were collected

Clinical investigator study sites were located in the following 21 countries: Argentina, Australia, Brazil, Canada, Chile, Columbia, Czech Republic, Finland, France,

Germany, Ireland, Italy, Japan, Republic of Korea, Netherlands, Poland, Russian Federation, Spain, Taiwan, United Kingdom, and United States. Sixty three of the 994 participants randomised in the KEYNOTE-564 were from trial sites in the UK.

Trial drugs and concomitant medications

Trial treatments

The study interventions of the KEYNOTE-564 study are presented in Table 5.

Table 5 KEYNOTE-564 study interventions

	Pembrolizumab	**Placebo**
Dosage Formulation:	Solution for infusion	Saline solution for infusion
Unit Dose Strength(s):	25 mg/mL (100 mg/4 mL)	0 mg
Dosage Level(s) and Regimen:	200 mg Q3W	0 mg Q3W
Route of Administration:	IV infusion	IV infusion

Concomitant medications

Details on concomitant medications allowed and restricted in the KEYNOTE-564 study are provided in Appendix L.

Assignment, randomisation, and blinding

The KEYNOTE-564 study is a randomised, double-blind, placebo-controlled trial. Details on the method of treatment assignment, stratification, and blinding are provided in Appendix L.

Outcomes assessed

Primary efficacy endpoints

Disease-free survival (DFS) as assessed by the investigator:

Time from randomisation to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first, the criteria for the determination of disease recurrence used are shown in Appendix L.

The primary efficacy endpoint, DFS as assessed by the investigator, is considered an appropriate clinical endpoint for an adjuvant trial that will evaluate the study treatment's impact on disease recurrence and has been explored in a number of ongoing pivotal Phase 3 studies serving as a surrogate for OS assessment (15, 16). DFS has been accepted as a surrogate endpoint to support drug approval for adjuvant settings in which participants are expected to experience cancer symptoms upon recurrence (e.g., adjuvant breast cancer hormonal therapy, adjuvant colon cancer, and adjuvant cytotoxic breast cancer therapy).

In the proposed patient population, participants are entering the trial tumour free. In the adjuvant setting, an investigator determines the absolute recurrence of disease. This assessment is equally appropriate to an independent reviewer determination since it does not involve tumour burden level grading expected with existing advanced metastatic disease. Therefore, DFS as assessed by the investigator is used in the trial as the primary outcome, though DFS as assessed by blinded independent central review (BICR) is also collected.

There are also meaningful patient implications. Remaining in DFS has important psychological benefits; patients knowing their disease has not advanced beyond the early stage is an important outcome.

In treatments for early disease DFS may be the preferred endpoint to demonstrate meaningful clinical benefit. Conventional endpoints, such as PFS and OS, may not be as informative, particularly when the survival benefit is sufficiently distant in time from the initiation of treatment with the novel intervention, which makes collection of a meaningful amount of OS data in typical clinical trial timeframes challenging.

Other endpoints

Other endpoints measured in the KEYNOTE-564 study are summarised in Table 6 and detailed further in Appendix L.

Table 6 Other endpoints measured in the KEYNOTE-564 study

Secondary efficacy endpoints	Overall survival
	Disease recurrence-specific survival 1 (DRSS1) as assessed by the investigator:
	Disease recurrence-specific survival 2 (DRSS2) as assessed by the investigator:
	Event-free survival (EFS) assessed by blinded independent central review (BICR):
	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) global health status/quality of life scores:
	EORTC QLQ-C30 functional subscales: physical functioning:
	Functional Assessment of Cancer Therapy Kidney Symptom Index Disease Related Symptoms (FKSI-DRS):
Exploratory endpoints	Pharmacokinetic parameters and the presence of antidrug antibodies
	Biomarker analyses
	Patient-reported outcomes and utilities
Safety endpoints	Adverse events (AEs)

Summary of the baseline characteristics of trial participants

The baseline demographic and disease characteristics of participants for the two groups were generally well balanced in the intention-to-treat (ITT) population, are representative of this patient population, and are presented in Table 7.

Approximately three-quarters of the participants were enrolled at non-US sites. A majority of the participants were white (75.4%), and a majority were male (71.0%). Most of the participants were under the age of 65 years (66.8%). The median age of participants was 60 years (age range, 25 to 84). A total of 75.3% of participants had a positive tumour tissue PD-L1 expression score at baseline, 85.2% had a baseline ECOG PS score of 0, and 92.5% had undergone radical nephrectomy. The largest proportion of participants had Grade 3 tumours, and most tumours were without sarcomatoid features. Most participants were assessed as N0/M0 (lymph nodes stage and metastatic stage) at baseline, with RCC risk category of M0–intermediate-high.

Table 7 KEYNOTE-564 study ITT population baseline characteristics

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
Sex						
Male	347	(70.0)	359	(72.1)	706	(71.0)
Female	149	(30.0)	139	(27.9)	288	(29.0)
Age (Years)						
<65	338	(68.1)	326	(65.5)	664	(66.8)
>=65	158	(31.9)	172	(34.5)	330	(33.2)
Mean	58.3		58.6		58.4	
SD	10.6		11.0		10.8	
Median	60.0		60.0		60.0	
Range	27 to 81		25 to 84		25 to 84	
Race						
American Indian Or Alaska Native	10	(2.0)	2	(0.4)	12	(1.2)
Asian	63	(12.7)	75	(15.1)	138	(13.9)
Black Or African American	7	(1.4)	5	(1.0)	12	(1.2)
Multiple	8	(1.6)	5	(1.0)	13	(1.3)
American Indian Or Alaska Native Black Or African American	2	(0.4)	0	(0.0)	2	(0.2)
American Indian Or Alaska Native White	3	(0.6)	2	(0.4)	5	(0.5)
Black Or African American White	2	(0.4)	3	(0.6)	5	(0.5)
White Asian	1	(0.2)	0	(0.0)	1	(0.1)
White	372	(75.0)	377	(75.7)	749	(75.4)
Missing	36	(7.3)	34	(6.8)	70	(7.0)
Ethnicity						
Hispanic Or Latino	72	(14.5)	62	(12.4)	134	(13.5)
Not Hispanic Or Latino	381	(76.8)	394	(79.1)	775	(78.0)
Not Reported	21	(4.2)	20	(4.0)	41	(4.1)
Unknown	21	(4.2)	21	(4.2)	42	(4.2)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
Geographic Region of Enrolling Site						
North America	133	(26.8)	125	(25.1)	258	(26.0)
European Union	188	(37.9)	187	(37.6)	375	(37.7)
Rest of World	175	(35.3)	186	(37.3)	361	(36.3)
Region						
US	114	(23.0)	117	(23.5)	231	(23.2)
Non-US	382	(77.0)	381	(76.5)	763	(76.8)
ECOG Performance Scale						
0	421	(84.9)	426	(85.5)	847	(85.2)
1	75	(15.1)	72	(14.5)	147	(14.8)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Type of nephrectomy						
Partial	37	(7.5)	38	(7.6)	75	(7.5)
Radical	459	(92.5)	460	(92.4)	919	(92.5)
PD-L1 Status						
CPS < 1	124	(25.0)	113	(22.7)	237	(23.8)
CPS >= 1	365	(73.6)	383	(76.9)	748	(75.3)
Missing	7	(1.4)	2	(0.4)	9	(0.9)
Primary Tumour						
T1	11	(2.2)	15	(3.0)	26	(2.6)
T2	27	(5.4)	33	(6.6)	60	(6.0)
T3	444	(89.5)	437	(87.8)	881	(88.6)
T4	14	(2.8)	13	(2.6)	27	(2.7)
Tumour Grade						
Grade 1	19	(3.8)	16	(3.2)	35	(3.5)
Grade 2	153	(30.8)	150	(30.1)	303	(30.5)
Grade 3	219	(44.2)	213	(42.8)	432	(43.5)
Grade 4	103	(20.8)	119	(23.9)	222	(22.3)
Missing	2	(0.4)	0	(0.0)	2	(0.2)
Sarcomatoid Feature						
Presence	52	(10.5)	59	(11.8)	111	(11.2)
Absence	417	(84.1)	415	(83.3)	832	(83.7)
Unknown	27	(5.4)	24	(4.8)	51	(5.1)
Lymph Nodes Stage						
N0	465	(93.8)	467	(93.8)	932	(93.8)
N1	31	(6.3)	31	(6.2)	62	(6.2)
Metastatic Staging						
M0	467	(94.2)	469	(94.2)	936	(94.2)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)
RCC Risk Category						
M0-Intermediate-High Risk	422	(85.1)	433	(86.9)	855	(86.0)
M0-High Risk	40	(8.1)	36	(7.2)	76	(7.6)
M0-Others	5	(1.0)	0	(0.0)	5	(0.5)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)

Participants in M0-Intermediate-high risk are pT2 (Grade 4 or sarcomatoid), N0, M0 or pT3 (Any Grade), N0, M0. Participants in M0-high risk are pT4 (Any Grade), N0, M0 or pT Any (Any Grade), N1 or greater, M0. Participants in M1 NED are participants who present not only with the primary kidney tumour but also solid, isolated, soft tissue metastases that were completely resected at the time of nephrectomy (synchronous) or <=1 year from nephrectomy (metachronous). Participants in M0-Others are T2 (grade <= 3) N0 M0 or T1 N0 M0.

Database Cutoff Date: 14DEC2020.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Statistical analysis and definition of study groups in the KEYNOTE-564 study

Objectives and hypotheses

The objectives and hypotheses (and associated endpoints) evaluated in the KEYNOTE-564 study are shown in Table 8. These were evaluated in the adjuvant treatment of participants who have undergone nephrectomy and have intermediate-high risk, high risk, or M1 NED RCC with clear cell component.

Table 8 KEYNOTE-564 study objectives and hypotheses

Objective/Hypothesis	Endpoint(s)
Primary	
• Objective: To compare DFS as assessed by the investigator for participants treated with pembrolizumab vs those receiving placebo • Hypothesis: Pembrolizumab is superior to placebo with respect to DFS	• DFS as assessed by the investigator: time from randomisation to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first
Secondary	
Key Secondary	
• Objective: To compare OS for participants treated with pembrolizumab vs those receiving placebo • Hypothesis: Pembrolizumab is superior to placebo with respect to OS	• OS: time from randomisation to death due to any cause
Other Secondary	
• To compare the safety and tolerability profiles for participants treated with pembrolizumab vs those receiving placebo	• AEs, SAEs, AEs leading to discontinuation, deaths, laboratory values, and vital signs

Objective/Hypothesis	Endpoint(s)
• To compare measures of DRSS as assessed by the investigator, in participants treated with pembrolizumab vs those receiving placebo	• DRSS1 as assessed by the investigator: time from randomisation to the first documented local recurrence of RCC • DRSS2 as assessed by the investigator: time from randomisation to the first documented local recurrence with visceral lesion or occurrence of distant kidney cancer metastasis(es) with visceral lesion, whichever occurs first
• To compare EFS as assessed by the blinded independent radiology review for participants treated with pembrolizumab vs those receiving placebo	• EFS is to be assessed by BICR. EFS is defined as time from randomisation to the first documented local recurrence or occurrence of distant kidney cancer metastasis(es) among participants, which by BICR were considered M0/M1 NED; or disease progression among participants, which by BICR were considered to have M1, or death due to any cause, whichever occurs first.
• To compare DFS and OS according to participants' PD-L1 expression status (positive, negative) for participants treated with pembrolizumab vs those receiving placebo	• DFS as assessed by the investigator: time from randomisation to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first • OS: time from randomisation to death due to any cause
• To evaluate PROs with EORTC-QLQ-C30 and the FKSI-DRS	• Mean change from baseline in EORTC QLQ-C30 global health status/quality of life scores • Mean change from baseline in EORTC QLQ-C30 functional subscales: physical functioning • Mean change from baseline in FKSI-DRS score
Tertiary/Exploratory	
• To evaluate PK parameters and the presence of ADA	• PK parameters (clearance and volume of distribution) • ADA to pembrolizumab
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab	• Biomarker analyses may include germline genetic variation, genetic (DNA) mutations from tumour, tumour and blood RNA variation, proteomics and immunohistochemistry, and other blood-derived biomarkers.

Objective/Hypothesis	Endpoint(s)
• To evaluate PROs with the EORTC QLQ-C30 and FKSI-DRS and to characterise utilities with the EQ-5D-5L	• Scales and subscales for select endpoints of the EORTC QLQ-C30, FKSI-DRS, and EQ-5D-5L

Analysis populations

Efficacy analysis populations

The Intention-to-Treat (ITT) population served as the population for the primary and key secondary efficacy analyses. All randomised participants were included in this population. Participants were analysed in the treatment group to which they are randomised.

Safety analysis populations

The All Participants as Treated (APaT) population were used for the analysis of safety data in this study. The APaT population consisted of all randomised participants who received at least 1 dose of study treatment. Participants were analysed in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. For most participants this was the treatment group to which they are randomised. Participants who had taken incorrect study treatment for the entire treatment period were included in the treatment group corresponding to the study treatment actually received. Any participant who received the incorrect study treatment for one cycle, but received the correct treatment for all other cycles were analysed according to the correct treatment group and a narrative was provided for any events that occur during the cycle for which the participant was incorrectly dosed.

At least 1 laboratory measurement obtained subsequent to at least 1 dose of study treatment was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

Statistical methods

The statistical methods used in the KEYNOTE-564 study are summarised in Table 9 and detailed further in Appendix L.

Table 9 Summary of KEYNOTE-564 statistical methods

Study Design Overview	This is a randomised, double-blind, multicentre Phase 3 study to evaluate the efficacy and safety of pembrolizumab vs placebo as an adjuvant treatment for RCC post nephrectomy.
Treatment Assignment	Approximately 950 participants were to be randomised 1:1 into the following 2 treatment arms: pembrolizumab 200 mg or matching placebo (saline 200 mg infusion) administered IV Q3W. Stratification factors are provided in Appendix L.
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoint	DFS as assessed by the investigator
Key Secondary Endpoint	OS
Statistical Methods for Key Efficacy Analyses	The primary and secondary hypotheses addressing DFS and OS were evaluated by comparing pembrolizumab to placebo using a stratified log-rank test. Estimation of the hazard ratio was done using a stratified Cox regression model. Event rates over time were estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results follow a tiered approach. The tiers differ with respect to the analyses that are performed. There are no Tier 1 events in this study. Tier 2 parameters were assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% CI for the between-treatment differences in percentages were provided using the Miettinen and Nurminen method.

Interim and Final Analyses	Three interim analyses are planned for the study (one interim analysis for DFS and 3 interim analyses for OS). Results were reviewed by an external data monitoring committee. IA1: • Purpose: Interim analysis for DFS and OS. • Timing: When approximately 265 disease recurrence events by investigator assessment have accrued and a minimum follow-up (time from last participant randomised to IA1) of 12 months is achieved. Approximately 94 OS events were expected at this time. IA2: • Purpose: Final analysis for DFS and interim analysis for OS • Timing: Final analysis of DFS when approximately 332 DFS events by investigator assessment have accrued if DFS is not rejected at IA1. Approximately 132 OS events are expected at this time. IA3: • Purpose: Interim analysis for OS • Timing: When approximately 172 OS events have accrued Final analysis: • Purpose: Final analysis for OS • Timing: When approximately 200 OS events have accrued*
Multiplicity	The overall Type I error rate is strongly controlled at 2.5% (1-sided) with a fixed sequence testing procedure to test DFS at alpha level of 2.5% (1-sided) first and pass the alpha to OS if the hypothesis test of DFS is declared successful. A group sequential approach will be used to allocate alpha between the interim and final analyses. The study will be considered a success if DFS is demonstrated to be statistically significant under multiplicity control. Note that if the statistical criterion for success for DFS is met at an IA, a regulatory application may be submitted based on DFS for a full approval consideration and the study could still continue for OS.
Sample Size and Power	The sample size was planned for 950, but the following power calculations are based on 990, which is a number more in line with the actual final number of randomised participants. DFS is the primary endpoint for this study. The expected median DFS time for those not cured in the control group is 45 months; based on 332 events and a Poisson mixture cure rate model with assumed cure rate of 0.3, the study has 95% power to detect a hazard ratio of 0.67 (pembrolizumab vs placebo) at alpha = 2.5% (1-sided).

*This is an approximate value as while Final Analysis will target for 200 events for the purposes of adequate statistical powering, operationally the last-patient-last-visit will necessarily be based on a projection of when the 200th OS event will occur and

consequently the actual number of OS events at the last-patient-last visit could be exactly 200, or +/- a small number of events.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A quality assessment of the KEYNOTE-564 study is provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

The clinical effectiveness results shown in section B.2.6 are from the KEYNOTE-564 study at a 14-JUN-2021 data cutoff, which occurred approximately 6 months after the first interim analysis (IA1, last patient last visit/data cutoff: 14-DEC-2020, database lock date of 26-JAN-2021, data previously published (12)). The final analysis for this study has not yet been reached. IA1 results are shown in Appendix M.

Patient disposition and follow-up duration

As of the 14-JUN-2021 data cutoff, there were no participants in either treatment group who remained on study treatment. At IA1, 190 (38.9%) participants in the pembrolizumab group and 130 (26.2%) participants in the placebo group had discontinued study treatment; [redacted] (Table 10). However, the reason for discontinuation for 1 participant in the pembrolizumab group was updated to be due to physician decision rather than due to an AE as previously reported. As of the 14-JUN-2021 data cutoff, [redacted] of randomised participants ([redacted] participants; [redacted] in the pembrolizumab group and [redacted] in the placebo group) remained ongoing in the study.

The median duration of follow-up increased from 23.9 months at IA1 to [redacted] at the 14-JUN-2021 data cutoff and the duration of follow-up [redacted] between treatment groups (Table 11).

Table 10 Disposition of participants (ITT population) – 14-JUN-2021 cutoff

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
Status for Study Treatment						

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Started	[redacted]		[redacted]		[redacted]	
Completed	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease Relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-Compliance With Protocol	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physician Decision	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated With Covid-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Protocol Violation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated With Covid-19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Status for Trial						
Discontinued	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal By Subject	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Associated With Covid-19, No Further Information	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Association With Covid-19 Unspecified, No Further Information	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Participants Ongoing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.
Database Cutoff Date: 14JUN2021

Table 11 Summary of follow-up duration (ITT population) – 14-JUN-2021 cutoff

Follow-up duration (months)[a]	Pembrolizumab (N=496)	Placebo (N=498)	Total (N=994)
Median (Range)	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]

[a] Follow-up duration is defined as the time from randomisation to the date of death or the database cutoff date if the subject is still alive.
Database Cutoff Date: 14JUN2021

Extent of exposure

Duration of exposure to study treatment was [redacted] between the pembrolizumab group and the placebo group (Table 12 and Table 13). At the 14-JUN-2021 data cutoff [redacted] of the study participants had ongoing study treatment.

Table 12 Summary of drug exposure (APaT population)

	Pembrolizumab (N=488)	Placebo (N=496)
Duration on therapy (months)		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]
Number of Administrations		
Mean	[redacted]	[redacted]
Median	[redacted]	[redacted]
SD	[redacted]	[redacted]
Range	[redacted]	[redacted]

Duration on therapy (months) is calculated as (last dose date - first dose date + 1)/30.4367.Database Cutoff Date: 14JUN2021

Table 13 Exposure by duration (APaT population)

	Pembrolizumab			Placebo		
	(N=488)			(N=496)		
	n	(%)	Person-time	n	(%)	Person-time
Duration of Exposure						
> 0 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=1 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=3 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=6 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=9 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
>=12 m	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Each subject is counted once on each applicable duration category row. Duration of exposure is the time from the first dose date to the last dose date.Person-time is calculated as person time in months.
Database Cutoff Date: 14JUN2021.

Disease-free survival

DFS by investigator assessment

At the 14-JUN-2021 data cutoff, the total number of DFS events was [redacted] ([redacted] in the pembrolizumab group and [redacted] in the placebo group). Pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in DFS compared with placebo at IA1 and [redacted] at the 14-JUN-2021 data cutoff (Table 14). Median DFS was [redacted]. The HR was [redacted] and the log-rank test nominal p-value was [redacted], compared with an HR of 0.68 [95% CI: 0.53, 0.87] and log-rank test p-value of 0.0010 at IA1.

The Kaplan-Meier (KM) curves separated from the outset in favour of pembrolizumab, and at the time of the 14-JUN-2021 data cutoff the curves [redacted] (Figure 2). As of the 14-JUN-2021 data cutoff, the difference in the DFS rates between treatment groups at 12, 18, and 24 months ranged from [redacted] (compared with 9.2% to 9.6% at IA1).

[redacted] treatment effects were observed across the prespecified subgroups, [redacted] (Figure 3).

Table 14 Analysis of DFS (Primary Censoring Rule) based on investigator assessment (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease Recurrence	[redacted]	[redacted]
	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Last Tumour Assessment Showing No Disease Recurrence	[redacted]	[redacted]
No Post-Baseline Disease Status Assessment	[redacted]	[redacted]
	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
	[redacted]	[redacted]

	Pembrolizumab (N=496)	Placebo (N=498)
vs Placebo		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
DFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Database Cutoff Date: 14JUN2021

Figure 2 Kaplan-Meier plot of DFS (Primary Censoring Rule) based on investigator assessment (ITT population)

[redacted]

Figure 3 Forest Plot of DFS HR by subgroup factors based on investigator assessment (primary censoring rule) (ITT population)

DFS by BICR

A sensitivity analysis of DFS by BICR in which participants with evidence of disease at baseline (i.e., non-NED) based on BICR of baseline scans only were censored at baseline showed results consistent with the primary endpoint of DFS by investigator assessment. The HR was [redacted], and the nominal p-value was [redacted]) (Table 15, Figure 4).

Table 15 Analysis of DFS based on BICR (participants with baseline non-NED based on BICR review of baseline scan only are censored at baseline) (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease Recurrence	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Censored At Baseline	[redacted]	[redacted]
Last Tumour Assessment Showing No Disease Recurrence	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
DFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Baseline Non-NED was assessed by BICR review of baseline scan only.

Database Cutoff Date: 14JUN2021

Figure 4 Kaplan-Meier plot of DFS based on BICR (participants with baseline non-NED based on BICR review of baseline scan only are censored at baseline) (ITT population)

Database cutoff date: 14-JUN-2021.

Subgroup analyses

[redacted] treatment effects were observed for DFS by investigator assessment across the prespecified subgroups with [redacted]; estimates in some subgroups had [redacted] CIs when the number of DFS events was small, and results should be interpreted with caution (Figure 5).

Figure 5 Forest Plot of DFS HR by subgroup factors based on investigator assessment (primary censoring rule) (ITT population)

Overall survival

At the 14-JUN-2021 data cutoff there were [redacted] deaths ([redacted] of the total planned 200 OS events at the final analysis). The HR was [redacted], and the median OS [redacted] (Table 16, Figure 6). The p-value [redacted] at the 14-JUN-2021 data cutoff. The upper bound of 95% CI for the OS HR [redacted], and there were [redacted] deaths in the placebo group ([redacted]) compared with the pembrolizumab group ([redacted]).

Table 16 Analysis of OS (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]

	Pembrolizumab (N=496)	Placebo (N=498)
[Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
OS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.

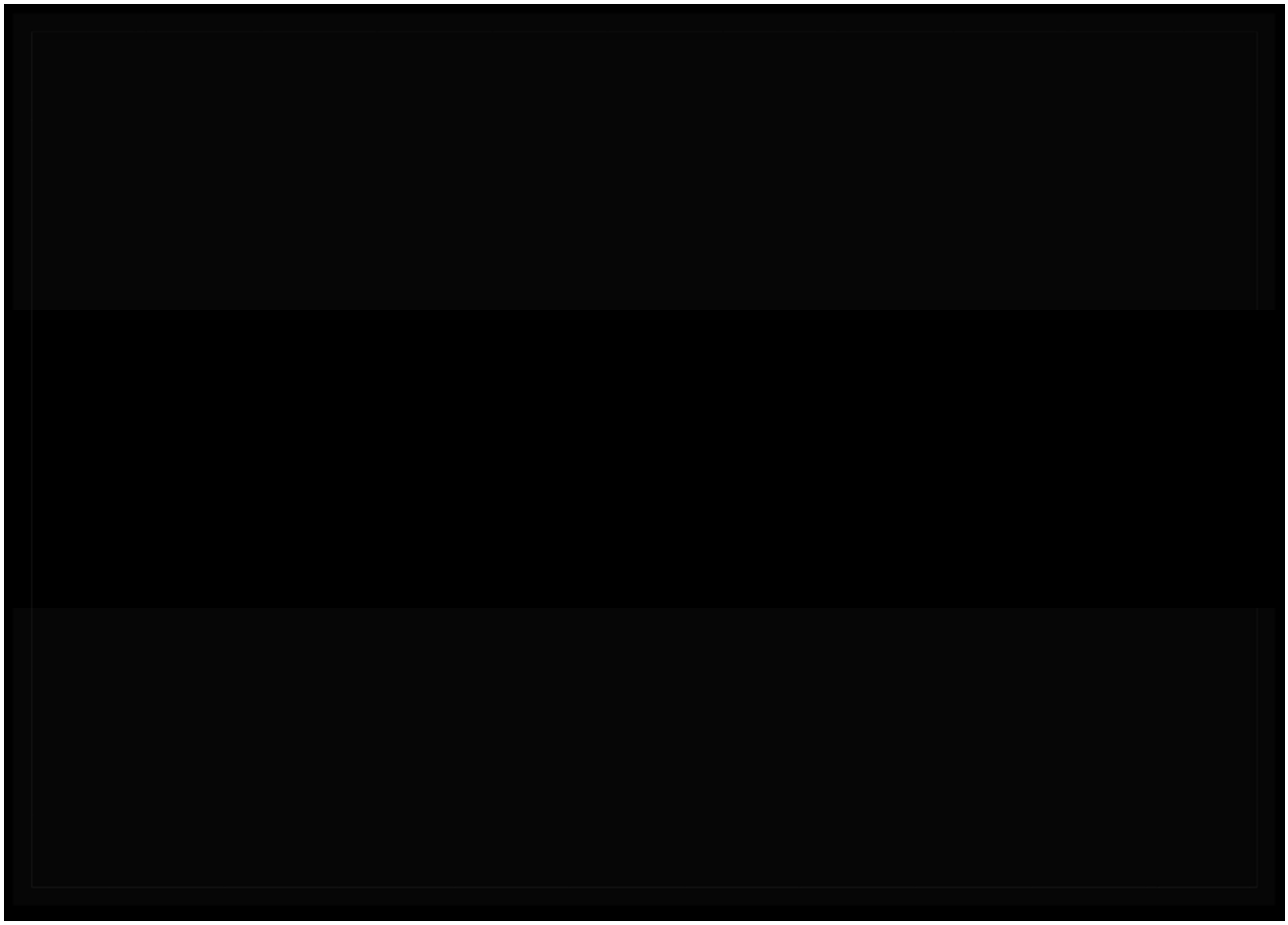
[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Database Cutoff Date: 14JUN2021

Figure 6 Kaplan-Meier plot of OS (ITT population)



Disease recurrence-specific survival (DRSS)

For DRSS1, local disease recurrence was the event of interest; distant disease recurrence or death are competing risk events. For DRSS2, disease recurrence with visceral lesion was the event of interest; local recurrence without visceral lesion, distant metastasis without visceral lesion, or death are competing risk events. Cumulative incidences of the events of interest were estimated by the nonparametric method adjusting for competing risk.

The cumulative incidences of the event of interest in the pembrolizumab group were [redacted] compared with the placebo group over time for both DRSS1 and DRSS2, showing a [redacted] numeric trend in DRSS1 (Table 17, Figure 7) and DRSS2 (Table 18, Figure 8) for pembrolizumab compared with placebo. These data are consistent with both local and distant recurrence contributing to the DFS results.

DRSS1

Table 17 Analysis of DRSS1 based on investigator assessment (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)[a]	[redacted]	[redacted]
Number of Competing Events (%)[b]	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Cumulative Incidence of Event at month 12 (%) (95% CI)	[redacted]	[redacted]
Cumulative Incidence of Event at month 18 (%) (95% CI)	[redacted]	[redacted]
Cumulative Incidence of Event at month 24 (%) (95% CI)	[redacted]	[redacted]

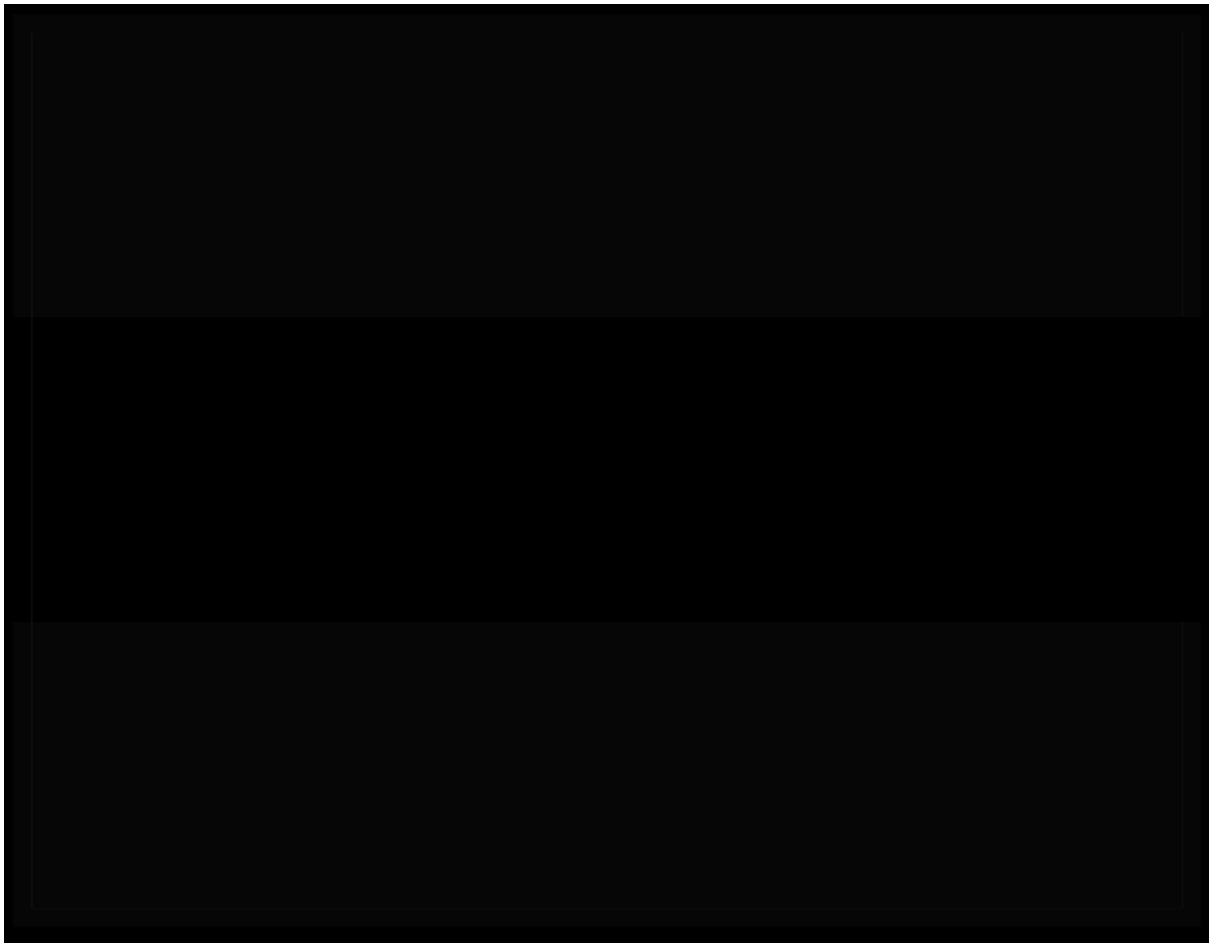
[a] Local recurrence of RCC is counted as event.

[b] Distant kidney cancer metastasis(es) or death are counted as competing event.

Cumulative incidence estimates at specified time points are based on nonparametric estimation of cumulative incidence of the event of interest accounting for competing risk events.

Database Cutoff Date: 14JUN2021

Figure 7 Cumulative incidence plot of DRSS1 based on investigator assessment (ITT population)



DRSS2

Table 18 Analysis of DRSS2 based on investigator assessment (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)[a]	[redacted]	[redacted]
Number of Competing Events (%)[b]	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Cumulative Incidence of Event at month 12 (%) (95% CI)	[redacted]	[redacted]
Cumulative Incidence of Event at month 18 (%) (95% CI)	[redacted]	[redacted]
Cumulative Incidence of Event at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] Local recurrence with visceral lesion or distant kidney cancer metastasis(es) with visceral lesion are counted as event.

[b] Death, local recurrence without visceral lesion, distant metastasis without visceral lesion are counted as competing event.

	Pembrolizumab (N=496)	Placebo (N=498)
Cumulative incidence estimates at specified time points are based on nonparametric estimation of cumulative incidence of the event of interest accounting for competing risk events. Database Cutoff Date: 14JUN2021		

Figure 8 Cumulative incidence plot of DRSS2 based on investigator assessment (ITT population)

Event-free survival

EFS is defined as time from randomisation to the first disease recurrence by BICR among participants who were assessed by BICR with no evidence of disease (i.e., NED) at baseline; or disease progression among participants who were assessed by BICR with evidence of disease (i.e., non-NED) at baseline, or death due to any cause, whichever occurred first. The baseline disease status by BICR determined whether disease recurrence or disease progression was tracked for a participant. A stratified EFS analysis by BICR with baseline disease status based only on baseline scans and

using the strata defined at randomisation and an additional stratum for baseline disease status by BICR of baseline scans only showed [redacted] results with the primary DFS analysis per investigator assessment (Table 19, Figure 9). The HR was [redacted], and the nominal p-value was [redacted].

[redacted] results were obtained based on a sensitivity analysis of EFS by BICR without the additional stratum of baseline disease status by BICR (stratified on randomisation strata only) [redacted] (Table 20).

Table 19 Analysis of EFS based on BICR (baseline disease status based on BICR review of baseline scan only) (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease Progression	[redacted]	[redacted]
Disease Recurrence	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Last Tumour Assessment Showing No Disease Recurrence/Progression	[redacted]	[redacted]
No Post-Baseline Tumour Status Assessment	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
EFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
EFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
EFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by baseline disease status by BICR (NED by BICR versus Non-NED by BICR), then within NED by BICR further stratified by randomisation strata: M0 versus M1 NED by investigator and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator..

[c] One-sided p-value based on log-rank test stratified by baseline disease status by BICR (NED by BICR versus Non-NED by BICR), then within NED by BICR further stratified by randomisation strata: M0 versus M1 NED by investigator and ECOG PS (0 versus 1),US

	Pembrolizumab (N=496)	Placebo (N=498)
participant (Yes versus No) within M0 group by investigator..		
NR = Not reached.		
For participants who were assessed as baseline NED based on BICR review of baseline scan only but had a post-baseline scan that triggered retrospective assessment of the baseline disease, the date of that scan is used as the event date.		
Database Cutoff Date: 14JUN2021		

Figure 9 Kaplan-Meier plot of EFS based on BICR (baseline disease status based on BICR review of baseline scan only) (ITT population)

Database cutoff date: 14-JUN-2021.

Table 20 Analysis of EFS based on BICR (baseline disease status based on BICR review of baseline scan only) (stratified on randomisation strata) (ITT population)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease Progression	[redacted]	[redacted]
Disease Recurrence	[redacted]	[redacted]

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Censored (%)	[redacted]	[redacted]
Last Tumour Assessment Showing No Disease Recurrence/Progression	[redacted]	[redacted]
No Post-Baseline Tumour Status Assessment	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
EFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
EFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
EFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1),US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

For participants who were assessed as baseline NED based on BICR review of baseline scan only but had a post-baseline scan that triggered retrospective assessment of the baseline disease, the date of that scan is used as the event date.

Database Cutoff Date: 14JUN2021

Health-related quality of life/patient reported outcomes

HRQoL/PRO data were not measured at the 14-JUN-2021 data cutoff. Data from IA1 (14-DEC-2020 data cutoff) are shown below for the EQ-5D, IA1 HRQoL/PRO results in terms of the FKSI-DRS and EORTC QLQ-C30 are provided in Appendix M.

EQ-5D

Data from the EQ-5D VAS and EQ-5D utility analyses show no statistically significant differences were observed between pembrolizumab and placebo between the pembrolizumab and placebo arms as summarised in Table 21 and Table 22.

Table 21 Analysis of change from baseline in EQ-5D VAS to Week 52 (PRO FAS population)

Treatment	Baseline		Week 52		Change from Baseline to Week 52	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab	446	84.02 (13.97)	301	80.75 (15.76)	484	-3.36 (-4.90, -1.82)
Placebo	460	83.12 (14.63)	327	82.52 (14.87)	493	-1.78 (-3.27, -0.29)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab vs. Placebo	-1.58 (-3.59, 0.42)	0.1220

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.

For baseline and Week 52, N is the number of subjects in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of subjects in the analysis population in each treatment group.

Database Cutoff Date: 14DEC2020

Table 22 Analysis of change from baseline in mapped EQ-5D-3L utility score to Week 52, based on the UK crosswalk algorithm from EQ-5D-5L to EQ-5D-3L (PRO FAS population)

Treatment	Baseline		Week 52		Change from Baseline to Week 52	
	N	Mean (SD)	N	Mean (SD)	N	LS Mean (95% CI)[a]
Pembrolizumab	446	0.87 (0.15)	301	0.84 (0.17)	484	-0.03 (-0.05, -0.02)
Placebo	460	0.87 (0.16)	327	0.86 (0.16)	493	-0.02 (-0.04, -0.01)

Pairwise Comparison	Difference in LS Means[a] (95% CI)	p-Value[a]
Pembrolizumab vs. Placebo	-0.01 (-0.03, 0.01)	0.3353

[a] Based on a cLDA model with the PRO scores as the response variable with covariates for treatment by study visit interaction, stratification factors metastasis status (M0 versus M1 NED), and within M0 group further stratified by ECOG PS (0 versus 1) and US participant (Yes versus No) as covariates.

For baseline and Week 52, N is the number of participants in each treatment group with non-missing assessments at the specific time point; for change from baseline, N is the number of participants in the analysis population in each treatment group.

Two-sided p-value.

Database Cutoff Date: 14DEC2020.

B.2.7 Subgroup analysis

[redacted] treatment effects were observed for DFS by investigator assessment across the prespecified subgroups with [redacted]; estimates in some subgroups had [redacted] CIs when the number of DFS events was small, and results should be interpreted with caution. The results of the subgroup analyses are presented in Figure 5 in section B.2.6.

B.2.8 Meta-analysis

Pooling of study data via pair-wise meta-analysis was not performed because the KEYNOTE-564 trial is the only trial that compared pembrolizumab to comparators in the population of interest.

B.2.9 Indirect and mixed treatment comparisons

No indirect or mixed treatment comparisons were conducted as the KEYNOTE-564 study directly compared pembrolizumab to the comparator of interest for this appraisal.

Uncertainties in the indirect and mixed treatment comparisons

Not applicable.

B.2.10 Adverse reactions

A summary of the adverse events observed in the KEYNOTE-564 study at the 14-JUN-2021 data cutoff is provided in the subsections below. Detailed adverse events data from IA1 (14-DEC-2020 data cutoff) are also provided in Appendix F.

Summary of adverse events

The overall incidence of AEs was [redacted] in the 2 treatment groups. The percentages of participants who had all-cause and drug-related Grade 3 to 5 AEs, SAEs, and AEs leading to discontinuation of study treatment were [redacted].

No new immune-mediated AEs were observed. No changes in type, nature, outcomes, and management of AEOSI were reported.

Table 23 Adverse events summary (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related[a] adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverseevent	[redacted]	[redacted]	[redacted]	[redacted]

[a] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 14JUN2021.

Most frequently reported adverse events

The most frequently reported AEs (incidence ≥20%) at the 14-JUN-2021 data cutoff were the following in each treatment group (Table 24):

- Pembrolizumab: [redacted].
- Placebo: [redacted].

The AEs with the greatest percentage difference (difference of approximately ≥ 10%) between the pembrolizumab group and the placebo group were [redacted], all of which are known AEs for pembrolizumab (Figure 10).

Table 24 Participants with adverse events (incidence ≥ 10% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 14JUN2021.

Figure 10 Between-treatment comparisons in adverse events - selected adverse events (≥ 10% incidence) and sorted by risk difference (APaT population)

Database Cutoff Date: 14JUN2021

Drug-related adverse events

The most frequently reported AEs considered drug-related by the investigator at the 14-JUN-2021 data cutoff were the following in each treatment group:

- Pembrolizumab (incidence ≥15%): [redacted]; these drug-related AEs are known AEs for pembrolizumab.
- Placebo (incidence ≥10%): [redacted].

Table 25 Participants with drug-related adverse events (incidence ≥ 5% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.
Database Cutoff Date: 14JUN2021.

Grade 3 to 5 adverse events

The percentage of participants with Grade 3 to 5 AEs at the 14-JUN-2021 cutoff was [redacted] in the pembrolizumab group compared with the placebo group ([redacted] versus [redacted], Table 26). The most frequently reported Grade 3 to 5 AEs (incidence ≥2%) were [redacted] in the pembrolizumab group and [redacted] in the placebo group at the 14-JUN-2021 cutoff. The incidence of Grade 3 to 5 AEs of [redacted] was [redacted] in the pembrolizumab group compared with the placebo group (lower bound of the 95% CI of the risk difference was [redacted]), and the incidence of Grade 3 to 5 AEs of [redacted] was [redacted] between groups. The incidences of other Grade 3 to 5 AEs were reported in [redacted] of participants.

The percentage of participants with drug-related Grade 3 to 5 AEs at the 14-JUN-2021 data cutoff was [redacted] in the pembrolizumab group compared with the placebo group ([redacted] versus [redacted], Table 27). Individual drug-related Grade 3 to 5 AEs were reported in [redacted] of participants in the pembrolizumab group and the placebo group.

Table 26 Participants with grade 3-5 adverse events (incidence ≥1% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Hyperglycaemia	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Lipase increased	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.

A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.

MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.

Database Cutoff Date: 14JUN2021.

Figure 11 Between-treatment comparisons in grade 3-5 adverse events - selected adverse events (≥1% incidence) and sorted by risk difference (APaT population)

Database Cutoff Date: 14JUN2021

Table 27 Participants with drug-related grade 3-5 adverse events (incidence ≥1% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Aspartate aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.
Database Cutoff Date: 14JUN2021.

Deaths due to adverse events

There were [redacted] deaths due to AE in the pembrolizumab group or in the placebo group between IA1 and the 14-JUN-2021 data cutoff. [redacted] fatal AEs were reported in the pembrolizumab group ([redacted]) and [redacted] fatal AE was reported in the placebo group ([redacted]) (Table 28). [redacted] deaths were considered drug-related by the investigator. No new safety signals were identified.

Table 28 Participants with adverse events resulting in death up to 90 days of last dose (incidence > 0% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Multiple organ dysfunction syndrome	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Haemorrhage intracranial	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 14DEC2020.				

Other serious adverse events

The percentage of participants who experienced SAEs at the 14-JUN-2021 data cutoff was [redacted] in the pembrolizumab group ([redacted]) versus the placebo group ([redacted]) (Table 29). The most frequently reported SAEs (incidence ≥1%) was [redacted] in the pembrolizumab group. The incidences of [redacted] SAEs were [redacted] in the pembrolizumab group versus the placebo group (lower bound of 95% CI of the risk difference was [redacted]) (Figure 12); these SAEs were each reported in a [redacted] percentage of participants ([redacted]). The incidences of individual SAEs were each reported for [redacted] of participants in the placebo group.

The percentage of participants who had drug-related SAEs at the 14-JUN-2021 data cutoff was also [redacted] in the pembrolizumab group ([redacted]) versus the placebo group ([redacted]) (Table 30). The most frequently reported drug-related SAEs continued to be [redacted] in the pembrolizumab group. The drug-related SAE reported in the placebo group was [redacted] in [redacted].

Table 29 Participants with serious adverse events up to 90 days of last dose (incidence ≥1% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Acute kidney injury	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Every participant is counted a single time for each applicable row and column. A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Serious adverse events up to 90 days of last dose of the initial treatment phase are included. MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded. Database Cutoff Date: 14JUN2021.				

Figure 12 Between-treatment comparisons in serious adverse events - selected adverse events (≥1% incidence) and sorted by risk difference (APaT Population)

Database Cutoff Date: 14JUN2021

Table 30 Participants with serious drug-related adverse events up to 90 days of last dose (incidence ≥1% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]
Diabetic ketoacidosis	[redacted]	[redacted]	[redacted]	[redacted]
Every participant is counted a single time for each applicable row and column. A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding. Serious adverse events up to 90 days of last dose of the initial treatment phase are included. Database Cutoff Date: 14JUN2021.				

Adverse events leading to discontinuation of study treatment

The percentage of participants who had AEs resulting in treatment discontinuation at the 14-JUN-2021 data cutoff was [redacted] in the pembrolizumab group ([redacted]) compared with the placebo group ([redacted]) (Table 31). The most frequent AEs resulting in treatment discontinuation continued to be [redacted] in the pembrolizumab group. The frequencies of the specific individual AEs resulting in treatment discontinuation, from which the total rate is composed, were [redacted]

The percentage of participants with drug-related AEs resulting in treatment discontinuation at the 14-JUN-2021 data cutoff was also [redacted] in the pembrolizumab group ([redacted]) compared with the placebo group ([redacted]). The most frequent drug-related AEs resulting in treatment discontinuation continued to be [redacted] in the pembrolizumab group. The frequencies of these AEs resulting in treatment discontinuation were [redacted]

Table 31 Participants with adverse events resulting in treatment discontinuation (sorted by decreasing incidence) (incidence ≥1% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]	[redacted]	[redacted]
Adrenal insufficiency	[redacted]	[redacted]	[redacted]	[redacted]
Colitis	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable row and column.
A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.
MedDRA preferred terms "Neoplasm progression", "Malignant neoplasm progression" and "Disease progression" not related to the drug are excluded.
Database Cutoff Date: 14JUN2021.

Adverse events resulting in treatment interruption

[redacted] for AEs leading to treatment interruption were noted in the period between IA1 (data shown in Appendix F) and the 14-JUN-2021 data cutoff. The percentage of participants who had AEs resulting in treatment interruption

was [redacted] in the pembrolizumab group ([redacted]) compared with the placebo group ([redacted]) at the 14-JUN-2021 data cutoff. The most frequent AEs resulting in treatment interruption continued to be [redacted] in the pembrolizumab group; and [redacted] in the placebo group. The frequencies of these AEs resulting in treatment discontinuation were [redacted].

The percentage of participants with drug-related AEs resulting in treatment interruption at the 14-JUN-2021 data cutoff was also [redacted] in the pembrolizumab group ([redacted]) compared with the placebo group ([redacted]). The most frequent drug-related AEs resulting in treatment interruption continued to be [redacted] in the pembrolizumab group. The frequencies of these drug-related AEs resulting in treatment interruption were [redacted].

Adverse events of special interest

The incidence of participants who had AEOSI in each AE category was [redacted] for the pembrolizumab group compared with the placebo group at the 14-JUN-2021 data cutoff (Table 32). [redacted] participants died due to an AEOSI. Overall, [redacted] of participants in the pembrolizumab group and [redacted] in the placebo group had at least 1 AEOSI. The majority of AEOSI were [redacted] in severity at the 14-JUN-2021 data cutoff (Table 33).

The most frequently reported AEOSIs (incidence ≥2%) continued to be [redacted]. The events of [redacted] continued to be [redacted] in severity, with exceptions of [redacted] event each for [redacted] (Table 33).

AEOSI resulting in discontinuation of treatment were reported for [redacted] in the pembrolizumab group versus [redacted] in the placebo group at 14-JUN-2021 cutoff (Table 32). Serious AEOSI resulting in treatment discontinuation were experienced by [redacted] of participants in the pembrolizumab group versus [redacted] in the placebo group at the 14-JUN-2021 data cutoff.

Table 32 Adverse event summary AEOSI overall (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related[a] adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious drug-related adverseevent	[redacted]	[redacted]	[redacted]	[redacted]

[a] Determined by the investigator to be related to the drug.

Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.

Database Cutoff Date: 14JUN2021.

Table 33 Participants with adverse events of special interest (AEOSI) by maximum toxicity grade (incidence ≥5% in one or more treatment groups) (APaT population)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Grade 4	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1	[redacted]	[redacted]	[redacted]	[redacted]
Grade 2	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Grade 3	[redacted]	[redacted]	[redacted]	[redacted]

Every participant is counted a single time for each applicable specific adverse event. A participant with multiple adverse events within a bolded term is counted a single time for that bolded term.

A bolded term or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

Only the highest reported grade of a given adverse event is counted for the individual participant.Grades are based on NCI CTCAE version 4.

Non-serious adverse events up to 30 days and serious adverse events up to 90 days following the last dose of initial treatment phase are included.

Database Cutoff Date: 14JUN2021.

B.2.11 Ongoing studies

For the KEYNOTE-564 study, longer-term data from later interim analyses as well as the final analysis are anticipated to become available in the future, with the final analysis for DFS currently anticipated to be available in 2024.

There are no ongoing studies of pembrolizumab in addition to the KEYNOTE-564 study that will provide additional evidence in the next 12 months for the indication being appraised.

[redacted]

B.2.12 Innovation

Pembrolizumab a monoclonal antibody, directly blocks the interaction of PD-1 and its ligands PD-L1 and PD-L2 enabling the immune response of both tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and anti-tumour immunity. Currently, there is no NICE recommended active adjuvant therapy for RCC post-nephrectomy. As evident by clinical and safety data presented, pembrolizumab offers a durable and well tolerated adjuvant treatment option for patients RCC post-

nephrectomy. Therefore, pembrolizumab offers a significant step-change in benefit for these patients in the UK.

Additionally, with pembrolizumab monotherapy there is the option to administer Q6W, which would substantially decrease the logistical and administrative burden on the health system compared to Q3W administration, as well as decreasing the burden on patients who need to travel to cancer treatment centres for each administration.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Participants enrolled in this study are representative of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions. In this study, adjuvant therapy with pembrolizumab demonstrated a [redacted] in DFS, compared with placebo, in this patient population:

- At the prespecified 2.5% overall alpha level (one-sided), pembrolizumab demonstrated a [redacted] in DFS compared with placebo (median DFS was [redacted]; HR [redacted]; and log-rank test nominal p-value was [redacted].
- Consistent benefit in DFS was observed across prespecified subgroups.
- The OS data were immature at the 14-JUN-2021 data cutoff with [redacted] deaths ([redacted] of total planned OS events at the final analysis). For OS, the HR was [redacted] and the median OS was [redacted]. The p-value [redacted] at the 14-JUN-2021 data cutoff. The upper bound of 95% CI of OS HR was [redacted], with [redacted] deaths in the placebo group ([redacted]) compared with the pembrolizumab group ([redacted]).
- Investigator review and BICR of disease recurrence were generally concordant, and there was no evidence of systematic bias in disease recurrence assessments by investigator favouring the pembrolizumab group based on estimation of differential discordance of disease recurrence based on investigator review versus BICR.

- EFS by BICR showed consistent findings with the primary endpoint of DFS per investigator's assessment.

- PRO assessments, including FKSI-DRS scale, EORTC QLQ-C30 global health status/QoL scale, EORTC QLQ-C30 functional scales, and EORTC QLQ-C30 symptom scales, at IA1, generally showed no clinically meaningful mean change from baseline in both the pembrolizumab and placebo groups at Week 52, and the 95% CIs generally overlapped, which suggests no meaningful difference between treatment groups. These findings suggest that HRQoL remained stable in the pembrolizumab group over time, with no evidence that pembrolizumab treatment leads to any significant detrimental impact on HRQoL.

The key safety findings are the following:

- The safety results of this report are generally consistent with the known safety profile for pembrolizumab.

- The incidences of all-cause and drug-related Grade 3 to 5 AEs, SAEs, and AEs leading to discontinuation of study treatment were [redacted] in the pembrolizumab group compared with the placebo group, [redacted].

- Most AEOSI (>90%) were [redacted] in severity and [redacted]. The nature of the AEOSI (severity, outcome, and management) remains consistent with the known safety profile for pembrolizumab.

- The AEOSIs were generally [redacted] with dose interruption, discontinuation, and/or treatment with corticosteroids, as indicated.

These findings therefore show that adjuvant treatment with pembrolizumab has a clear benefit over no active adjuvant treatment (i.e. current routine clinical practice in England and Wales) in this setting, while only incurring a small and manageable additional toxicity burden. Based on the significant DFS efficacy signal, early but promising OS signal, and the acceptable tolerability profile shown in the KEYNOTE-564 IA1 results, ESMO has also published an update to their RCC guidelines to

recommend adjuvant pembrolizumab as an option for patients with intermediate- or high-risk operable clear cell RCC (10), noting also that their recommendation distinguishes adjuvant pembrolizumab from the adjuvant vascular endothelial growth factor receptor (VEGFR)-targeted trials, which gave inconsistent DFS signals and no trend towards OS benefit (10, 17).

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic literature review was conducted on 10-SEP-2020 to identify published literature relating to relevant cost-effectiveness studies including, but not limited to cost-utility, budget impact and cost-minimisation analyses. Full details of the systematic literature review (SLR) search strategy, study selection process and results are presented in Appendix G. No cost-effectiveness study including active treatment meeting the inclusion criteria was identified, indicating that a de novo cost-effectiveness model was required to assess the cost-effectiveness of pembrolizumab compared with routine surveillance in patients with RCC who are at intermediate-high or high risk of recurrence following nephrectomy.

B.3.2 Economic analysis

B.3.2.1 Patient population

The patient population considered for the current appraisal is aligned with that of the expected marketing authorisation: [redacted]. The patient characteristics at baseline reflected in the economic analysis are based on the European cohort from KEYNOTE-564 trial population, as this cohort is expected to be more representative of the patient population in the UK (18). The baseline characteristics are shown in Table 34 below.

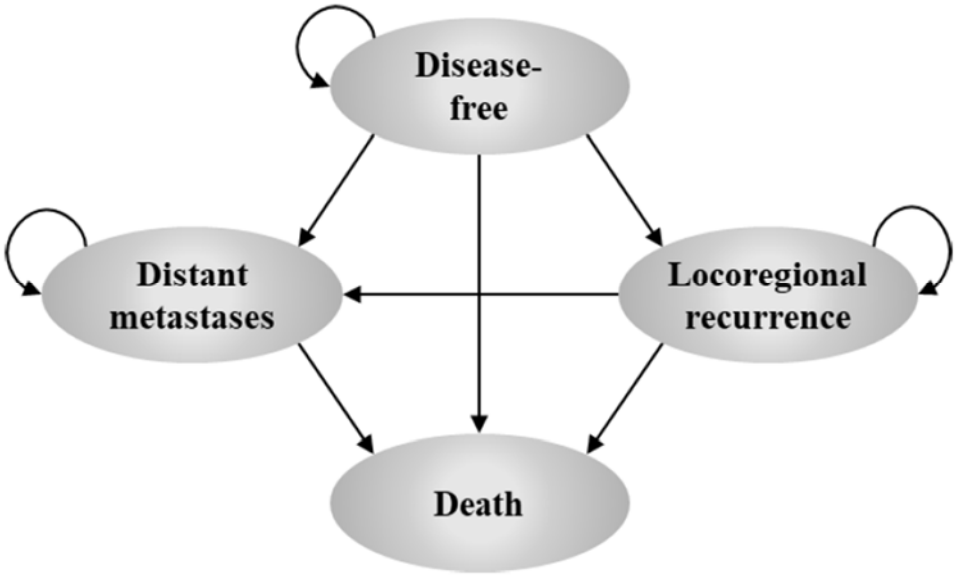
Table 34 Baseline characteristics of the population used in the cost-effectiveness analysis

Patient characteristics	Global Cohort (n=994)	European Cohort (n=375)	Source
Patient age	58.4 years	58.9 years	KEYNOTE-564 Data cut-off 14-DEC-2020
Proportion female	29.0%	26.7%	
Average body weight	83.9kg	84.9kg	

B.3.2.2 Model structure

A de novo Markov cohort model was developed to estimate health outcomes and costs for pembrolizumab compared with routine surveillance (the placebo arm in KEYNOTE-564) in patients with RCC who are at intermediate-high or high risk of recurrence following nephrectomy. The state transition diagram (Figure 13) presents the health states and allowable transitions in the model structure, which are aligned with two of the key objectives of treatment for patients who have undergone nephrectomy, specifically, delaying disease recurrence and prolonging life. The model structure consists of four mutually exclusive health states; disease-free (DF), locoregional recurrence (LR), distant metastases (DM), and death. Recurrent disease was defined and documented in KEYNOTE-564 as either locoregional or metastatic recurrence (or both). Therefore, progression of disease is differentiated in the analysis by type of recurrence given that type of recurrence is a significant prognostic factor in RCC. As such, type of recurrence is expected to result in different health outcomes and associated costs.

Figure 13 Model structure used in the cost-effectiveness analysis



Disease-free health state

All patients enter the model in the disease-free health state, following surgery (partial or radical nephrectomy or metastasectomy). Disease-free survival in KEYNOTE-564 was assessed by the investigator and reported as the time from randomisation to the

first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurred first (18).

The possible transitions from the DF health state were as follows:

- DF → LR
- DF → DM
- DF → death

Locoregional recurrence state

Patients were considered to have locoregional recurrence if disease recurrence occurs and the cancer returns at the primary site or nearby lymph nodes. Patients who experienced LR (defined by the investigator in the KEYNOTE-564 trial) could make the following transitions:

- LR → DM
- LR → death

Distant metastases state

From the DM health state patients could transition only to the death health state.

Patients were considered to have distant metastasis if the cancer has spread from the primary organ (kidney) to a secondary/distant organ or to distant lymph nodes, as defined by the investigator in KEYNOTE-564. Given the low number of OS events in KEYNOTE-564, alternative data sources were required to estimate the transition from the DM health state to death. A network meta-analysis (NMA) of first-line (1L) advanced RCC (aRCC) treatments was incorporated into the economic analysis in order to estimate survival following the transition to the DM state.

Given that 1L treatment for aRCC is expected to differ based on whether a patient received adjuvant treatment or routine surveillance post nephrectomy, survival following transition to the DM state reflected the different 1L aRCC treatments that would be given following either initial adjuvant treatment strategy.

Death state

Death is an absorbing health state in which no costs or benefits were accrued.

B.3.2.3 Intervention technology and comparators

Pembrolizumab was considered in the economic analysis as per the anticipated licensed dosing regimen (i.e. administered intravenously at a fixed dose of 200mg over 30 minutes every 3 weeks [Q3W]). As per the KEYNOTE-564 trial protocol, patients could receive a maximum 17 cycles (approximately 1 year) of pembrolizumab therapy.

The expected marketing authorisation of pembrolizumab is for the [redacted]. The NICE final scope specifies 'established clinical management' as the comparator for this patient population, which consists of regular follow-up with clinical visits and scans to monitor disease recurrence. In the context of the current cost-effectiveness analysis this comparator will be referred to as 'routine surveillance'.

The outcomes observed in the placebo arm of KEYNOTE-564 were considered representative of the outcomes associated with routine surveillance in UK clinical practice for this patient population, given both include regular follow-up but no active treatment. Similar to clinical practice in the UK, CT scans of the chest, abdomen and pelvis were conducted on regular basis in KEYNOTE-564 (19).

B.3.3 Clinical parameters and variables

The clinical parameters for the efficacy of pembrolizumab and routine surveillance were estimated based on patient-level data from KEYNOTE-564 for time spent disease free (including distant metastases free and locoregional recurrence free). Data on adverse event rates and HRQoL were also obtained from KEYNOTE-564 to reflect the impacts on safety and quality of life of the two adjuvant treatment strategies.

Transition probabilities were derived based on primary analyses of patient-level data from KEYNOTE-564, an NMA comparing the efficacy of 1L treatments for advanced or metastatic RCC, a real-world retrospective database analysis, and a targeted

review of published literature to identify relevant clinical inputs not available in the clinical trial data.

For transitions starting from the LR or DM health states, external data were used to estimate transition probabilities. Once patients experienced a recurrence event, no ongoing benefit from adjuvant pembrolizumab was assumed for the transition from post-recurrence health states, as the available follow-up in KEYNOTE-564 was not sufficiently long to estimate treatment-specific transition probabilities after disease recurrence. The use of external data to model outcomes post disease recurrence is consistent with the modelling approach in recent NICE appraisals of adjuvant therapies in lung cancer and melanoma (20, 21).

From the DM health state adjuvant treatment strategies were differentiated by transition probabilities to death based on the mix of 1L aRCC treatments. Treatments for aRCC were expected to differ by adjuvant treatment strategy based on feedback from clinical experts.

B.3.3.1 Modelling transitions from disease-free state

As KEYNOTE-564 is a comparative phase III trial, patient-level data was available to inform the transitions for both arms of the economic analysis. Following the parametric multistate modelling approach described by Williams *et al*. (2017a & 2017b) (22, 23), parametric models were used to estimate the cause-specific hazards of each transition over time for the adjuvant pembrolizumab and placebo arms:

- disease-free → locoregional recurrence,
- disease-free → distant metastases, and
- disease-free → death

Within each weekly cycle of the model, the probability of each of these transitions (as well as the composite probability of any DFS failure event) was calculated as a function of all three cause-specific hazards.

Estimation of cause-specific hazards for each individual transition starting from the disease-free state

Cause-specific hazards of each transition were estimated based on parametric models fitted to patient-level data from the KEYNOTE-564 trial. In order to fit models to each of the three individual health state transitions, standard survival analysis methods were used with one modification to account for competing risks: When analysing time to each specific type of DFS failure, the two competing failure types were treated as censoring events (24, 25). For example, to model the transition from DF → DM, patients who experience a locoregional recurrence or death prior to distant metastases were censored and thus treated as lost to follow-up at the time of the earlier competing event. After these additional censoring criteria are applied to the patient-level time-to-event data for each transition, parametric curve fitting was performed using the survival analysis package *flexsurvreg* in R software (26), similar to the process for fitting parametric functions for a partitioned survival model.

The following three parametric modelling approaches were tested to explore uncertainty in the estimation of transition probabilities starting from the DF state:

1. **Approach 1**: Parametric models separately fitted to each treatment arm: Under this approach, transition probabilities were estimated based on parametric models that were fitted individually to each treatment arm in KEYNOTE-564. Six different parametric models were considered to model transitions from DF → LR and from DF → DM in each treatment arm, including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalized gamma distributions.

2. **Approach 2**: Parametric proportional hazards models with a time-constant treatment effect: Under this approach, transition probabilities in the pembrolizumab and routine surveillance arms were estimated based on jointly-fitted proportional hazards (PH) parametric models that incorporated a time-constant hazard ratio (i.e., exponential, Weibull, or Gompertz) for pembrolizumab versus placebo from KEYNOTE-564.

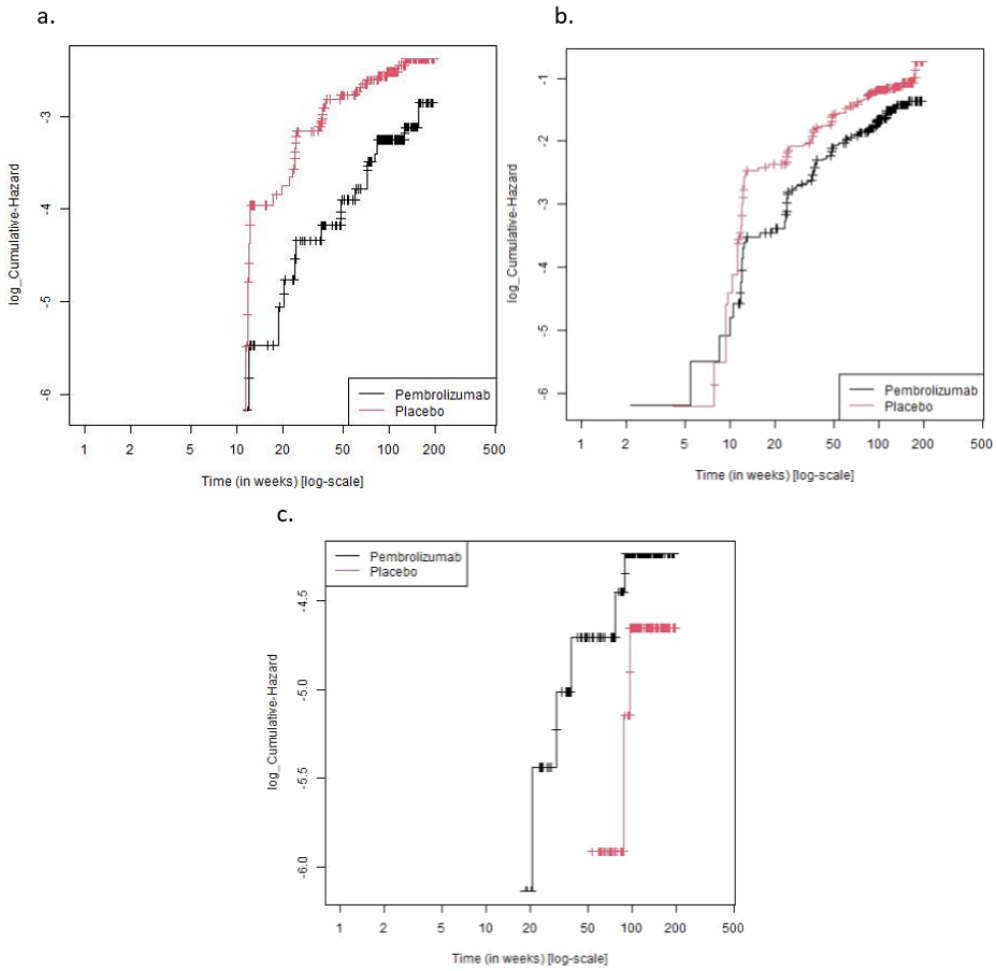
3. **Approach 3**: Parametric proportional hazards models with a time-varying treatment effect: Under this approach, transition probabilities in the

pembrolizumab and routine surveillance arms were estimated based on jointly-fitted proportional hazards models that incorporated a time-varying HR for pembrolizumab versus placebo. Specifically, the models allowed one HR to be estimated for the time period during the first year following initiation of adjuvant therapy (given the protocol-defined maximum treatment duration of 1 year) and a subsequent treatment effect estimated for the time period after 1-year, based on the protocol-defined maximum 1-year treatment duration).

In all approaches, due to the small number of direct transitions from DF → death observed in KEYNOTE-564, exponential distributions were fitted for this transition in each arm.

The validity of using PH models within Approaches 2 and 3 was testing by visual assessment of the DFS KM curves and associated log-cumulative hazards plots (LCH) of the hazard of a DFS event. As shown below in Figure 14 the LCH plots for DFS for pembrolizumab versus placebo cross early on (~12 weeks) before diverging and remaining separate and parallel until the end of follow-up from KEYNOTE-564. That the LCH plots remain parallel for the entirety of the trial follow-up beyond 10-weeks provides strong evidence that the assumption of PH is not violated, and as such, PH models were considered as plausible approaches for modelling transition from the DF state.

Figure 14 Log-cumulative hazards plots of transitions from disease-free state based on investigator assessment, intention-to-treat population (14-JUN-2021 data cut-off)



(a.) LCH plots from DF → LR, (b.) LCH plots from DF → DM, (c.) LCH plots from DF → death.

In all approaches described above, probabilities of each transition from the DF state were calculated based on all three cause-specific hazard functions. Therefore, the predicted DFS curve over time in each treatment arm similarly depended upon all three cause-specific hazard functions. Criteria for the selection of base-case parametric functions are described below.

Calculation of transition probabilities based on cause-specific hazards

For each individual transition starting from the DF state, transition probabilities in each weekly cycle were calculated within the model as a function of the cause-specific hazards for all three types of DFS failure. The following calculation steps were performed:

1. For each cause of DFS failure k (i.e., locoregional recurrence, distant metastases, or death), the average cause-specific hazard within the cycle from week (t-1) to t was calculated as:

$$\overline{h}_k(\mathrm{t}) = H_k(\mathrm{t}) - H_k(\mathrm{t}-1),$$

where $Hk(.)$ is the cause-specific cumulative hazard of cause k (based on the parametric function selected to model cause k).

2. The average hazard of any DFS failure within the cycle from week (t-1) to t, denoted $h\mathrm{D}FS(\mathrm{t})$, was calculated as the sum of the average cause-specific hazard for all three causes within that cycle. This hazard was converted into a probability using the formula:

$$1 - e^{-\overline{h}_{DFS}(\mathrm{t})}$$

3. In each cycle, the relative contribution of each cause k to the overall hazard of DFS failure was derived as:

$$\frac{\overline{h}_k(\mathrm{t})}{\overline{h}_{DFS}(\mathrm{t})}$$

This represents the probability of having had an DFS failure of type *k* given that an DFS failure has occurred within the cycle (27). The relative contribution of cause *k* was then multiplied by the probability of any DFS failure within the cycle to obtain the transition probability corresponding to cause *k*.

The transition probability from disease-free → death was set equal to the maximum of the estimated probability based on parametric modelling of KEYNOTE-564 data and background mortality, given the age and gender distribution of the cohort at the time of a given cycle. All-cause mortality rates by age for men and women in the UK were obtained from the Office for National Statistics (ONS) (28).

Selection of base-case parametric models for transitions from DFS

As noted by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19, assessing model fit is more challenging in the context of multistate models

than for partitioned survival models, as the target outcomes of interest (i.e., the proportions of individuals experiencing the composite endpoint) were determined by a combination of survival models rather than by a single survival model (24).

To select base-case parametric functions, all possible combinations of parametric functions for disease-free → locoregional recurrence, disease-free → distant metastases, and disease-free → death were considered. In accordance with recommendations in the NICE DSU TSD 14 (29), base-case parametric functions were selected such that the same functional form was used to model each health state transition in both the pembrolizumab and routine surveillance arms. The rationale for this approach was to avoid the extrapolated DFS curves following drastically different trajectories, which is not supported by observed DFS in KEYNOTE-564 nor considered clinically plausible.

Base-case parametric functions were selected based on the following criteria:

1. **Fit based on mean squared error (MSE):** Akaike information criterion (AIC), a fit statistic commonly used in partitioned survival models, is not a suitable measure of fit with observed data when modelling competing risks (22). MSE was therefore used as an alternative diagnostic test to assess fit of the predicted DFS curve to the observed KM curve during the within-trial period in each treatment arm.

2. **Visual assessment of fit:** Predictions generated by different combinations of parametric functions were visually assessed against trial data in each treatment arm following the approach described by William et al. (2017) (22). Visual assessment was conducted based on the observed cumulative incidence transitions from DF → LR and DF → DM for the pembrolizumab and routine surveillance arms from KEYNOTE-564 alongside the predicted cumulative incidence estimated by different parametric models presented in Appendix O. The predicted cumulative incidence curves for DF → LR for the pembrolizumab arm all fit the observed data well. The predicted cumulative incidence for routine surveillance indicated that combinations using Gompertz for DF → LR appeared to show the best fit to the observed cumulative incidence, although reasonably close fits were achieved with all the combinations of parametric

models. For observed cumulative incidence for DF → DM in the pembrolizumab arm, all parametric functions assessed produced a close fit to the observed data. For the routine surveillance arm, visual assessment strongly favoured the combination of functions that incorporated Gompertz or generalised gamma (under approach 1) or Gompertz (under approach 2 or 3) for the transitions from DF → DM. Lastly, the PH assumption was assessed through visual inspection of the LCH plots for each transition (see Figure 14).

3. **External validity and clinical plausibility of long-term extrapolations**: Long-term estimates of DFS and OS for routine surveillance were validated against observed KM curves from the placebo arms of previous trials of TKI inhibitors as adjuvant therapy for RCC (Figure 15 and Figure 16). Based on comparability with the KEYNOTE-564 trial population (see Table 35), published KM curves for DFS and OS (where available) from the following trials were compared with DFS and/or OS predictions for routine surveillance: the S-TRAC trial of sunitinib versus placebo (15, 30); the ASSURE trial of sunitinib and sorafenib versus placebo (focusing specifically on the clear-cell, high-risk subgroup results) (16, 31); the PROTECT trial of pazopanib versus placebo (32, 33); and the ATLAS trial of axitinib versus placebo (34). (The SORCE trial of sorafenib versus placebo (35, 36) and the ITT analysis of the ASSURE trial were not used as external validation sources due to the large representation of patients with low-risk and non-clear cell RCC in these trials.)

   Because external data sources were unavailable for pembrolizumab as an adjuvant treatment for RCC, the plausibility of long-term DFS estimates for the pembrolizumab arm was assessed based on discussions with clinical experts. Long-term observed incremental DFS of sunitinib versus placebo of S-TRAC was benchmarked as a lower bound of plausibility against long-term estimates of incremental DFS with pembrolizumab. Incremental DFS benefit observed for sunitinib versus placebo was considered a relevant comparison for external validation given the similarity in baseline characteristics of patients enrolled in S-TRAC and KEYNOTE-564, as shown in Table 35.

Extrapolations which predicted lower incremental DFS with pembrolizumab compared to observed incremental DFS with sunitinib in S-TRAC were excluded given that, due to different mechanisms of action (MoA) between sunitinib (tyrosine kinase inhibitor [TKI]) and pembrolizumab (PD-1 inhibitor), in the absence of long-term follow-up from KEYNOTE-564 it was considered implausible for modelled pembrolizumab incremental DFS to be lower than the observed incremental DFS with adjuvant sunitinib in S-TRAC. In the aRCC setting, TKIs such as sunitinib are given until disease progression and are not considered to have a long-lasting treatment effect following treatment discontinuation. This is contrasted by PD-1 inhibitors such as pembrolizumab which have demonstrated a sustained treatment effect even after treatment is discontinued prior to progression at two years.

Based on feedback from clinical experts, in the absence of long-term follow-up, adjuvant treatment with pembrolizumab is expected to have *at least* a similar magnitude of clinical benefit (i.e. improvement in proportion of patients remaining in DFS) versus routine surveillance as observed with sunitinib in S-TRAC. Regarding external validation of OS estimates resulting from the base-case selection of parametric models to estimate the transition from the DF state, clinical trials of adjuvant TKIs such as S-TRAC have failed to demonstrate statistically significant OS benefits compared to placebo. Furthermore, OS following adjuvant treatment has been affected by the choice of treatment in the aRCC setting (following recurrence), whereas in recent years, the introduction of immunotherapies has led to significant improvements in OS compared to TKIs in the aRCC setting. Therefore, external validation of OS estimates produced in the current economic analysis compared with the OS observed in adjuvant RCC trials would be confounded by availability of life-extending immunotherapies. The plausibility of incremental OS (in life-years) with pembrolizumab versus placebo in the current economic analysis was assessed, however, based on findings from the retrospective analysis of SEER-Medicare data described previously (see section B.3.3.6), which reported that a 1-year increase in time spent in DFS predicted a 0.73-year increase in OS (95% CI: 0.40, 1.05; p<0.001).

Table 35 Comparison of baseline characteristics in KEYNOTE-564 compared with previous trial of adjuvant RCC therapy

	KEYNOTE-564	S-TRAC	PROTECT
Age:			
Median	60	58	59
Range	25-84	21-92	21-88
Sex (%):			
Male	72.1%	74.8%	72%
Female	27.9%	25.2%	28%
Nephrectomy:			
Partial	7.6%	NR	6%
Radical	92.4%		94%
ECOG:			
0	85.5%	71.9%	NR
1	14.5%	27.5%	
M0 Intermediate-high risk	86.9%	91%	92%
M0 High risk	7.2%	9%	8%
M1 NED	5.8%	0%	0%
Risk classification used	**M0 Inter-high:** pT2, G4 or sarcomatoid, N0, M0 or pT3, G_{any}, N0, M0 **M0 High Risk:** pT4, G_{any}, N0, M0 or pT_{any}, G_{any}, N+, M0	**M0 Intermediate-high risk:** pT3, G_{any}, N0, M0 **M0 High-risk:** pT4, G_{any}, N0, M0 or pT_{any}, G_{any}, N+, M0	**M0 Intermediate-high:** pT2, G3-G4, N0, M0 **M0 High risk:** pT4, G_{any}, N0, M0 or pT_{any}, G_{any}, N1, M0

When considering the above criteria, Approach 3 (jointly-fitted models with a time-varying treatment effect) with an exponential function for DF → LR and Gompertz function for DF → DM appeared to provide the best balance between goodness-of-fit with observed data and plausible long-term extrapolations in each arm. The rationale for this selected approach is described more fully below.

Initial exclusions based on requirement of consistent distribution types in both arms: Table 40 and Table 41 list all candidate combinations of parametric functions in each treatment arm. In the pembrolizumab arm, there were a total of 54 candidate combinations, including 36 under Approach 1, 9 under Approach 2, and 9 under Approach 3.

Initial exclusions based on predictive validity and clinical plausibility: As shown in Table 40a and Table 41a, two combinations of parametric distributions under Approach 1 resulted in long-term DFS predictions that were higher for routine surveillance than

pembrolizumab. These combinations of distributions were excluded from further consideration due to clinical implausibility.

Statistical fit: Table 40 and Table 41 present the ranking of all combinations of parametric functions in terms of MSE in each treatment arm. Long-term predictions of DFS, DMFS (i.e. time from randomisation until first date of distant metastases or death), and OS are also reported for each these different scenarios. Overall, MSEs were generally lower in the pembrolizumab arm than the routine surveillance arm. The range of MSE values (i.e., the difference in MSE between the best- and worst-fitting combinations) was also narrower for pembrolizumab than routine surveillance. Because all combinations of distributions yielded comparably low MSEs for pembrolizumab, the choice of base-case parametric models prioritized fit within the routine surveillance arm and clinical plausibility in both arms.

Visual assessment of fit: During the trial period, Figure 22 to Figure 27 in Appendix O present the observed cumulative incidence of transitions from DF → LR in the pembrolizumab and routine surveillance arms, respectively, alongside the predicted cumulative incidence from different combinations of parametric functions. For pembrolizumab, all combinations of parametric functions produced a close visual fit to the observed cumulative incidence of DF → LR. In the routine surveillance arm, combinations that used Gompertz for DF → LR appeared to achieve the best fit with the observed cumulative incidence of DF → LR, although reasonably close fits were achieved with all combinations of functions.

Analogous figures are presented for the cumulative incidence of DF → DM in each treatment arm (Figure 28 to Figure 33 in Appendix O). In the pembrolizumab arm, all combinations of parametric functions produced a close fit with the cumulative incidence of this transition. In the routine surveillance arm, visual assessment strongly favoured combinations of parametric models that used either Gompertz or generalized gamma (under Approach 1) or Gompertz (under Approach 2 or 3) for DF → DM.

Log-cumulative hazard plots, presented in Figure 14 for each transition starting from the DF health state, showed minimal deviations from parallel lines beyond approximately week 12. The lack of separation between the DFS KM curves prior to week 12 may reflect the protocol-defined timing of the first imaging scan for disease

recurrence (week 12 in KEYNOTE-564). The LCH plots favoured Approach #3 (which allowed the treatment effect to differ before 1-year vs. after 1-year) over Approach #2, but generally supported the use of PH models to represent the cause-specific hazards of these transitions. Thus, no further exclusions were applied based on these findings.

External validations of predicted DFS:

For routine surveillance

Across the S-TRAC, ASSURE (high-risk, clear cell RCC subset), and PROTECT trials, 5-year DFS for placebo ranged narrowly from 50.6% to 51.3%. Thus, to better ensure externally valid extrapolations in the routine surveillance arm, further exclusions were applied based on the requirement that predicted 5-year DFS should fall within a range of 51% +/- 2.5 percentage-points (i.e., 48.5% to 53.5%). This criterion resulted in the exclusion of an additional 10 combinations of distributions that overpredicted DFS in the routine surveillance arm to varying degrees: Across the 10 excluded distributions, 5-year DFS ranged from 53.9% (Approach #1/Weibull/Generalized gamma) to 57.7% (Approach #1/Gompertz/Gompertz).

The base case was selected from among the following 6 combinations of distributions that met all preceding criteria, and the remaining 5 of these 6 combinations were considered in scenario analyses of alternative parametric modelling approaches:

- Exponential/Generalized gamma under Approach #1 (separately fitted)
- Exponential/Gompertz under Approach #1 (separately fitted)
- Exponential/Gompertz under Approach #2 (jointly fitted, time-constant treatment effect)
- Weibull/Gompertz under Approach #2 (jointly fitted, time-constant treatment effect)
- Exponential/Gompertz under Approach #3 (jointly fitted, time-varying treatment effect)*
- Weibull/Gompertz under Approach #3 (jointly fitted, time-varying treatment effect)

*Selected as base case after applying all criteria

Of these 6 combinations, five-year DFS was closest to the 51% target when using the Exponential/Gompertz distributions under Approach #3 (50.9%) or Approach #2 (51.2%) and was furthest from this target when using Exponential/Gompertz (52.7%) or Exponential/Generalized gamma (52.1%) under Approach #1. A comparison of observed DFS from external studies with predicted DFS under theses 6 combinations, is presented in Table 36 and supports the base-case selection of Exponential/Gompertz under Approach #2 or #3.

Under the base-case combination of distributions (Exponential/Gompertz, jointly fitted with a time-varying treatment effect before/after 1-year), DFS and OS predictions for routine surveillance demonstrated consistency when compared to long-term DFS data from external studies. Figure 15 plots base-case DFS predictions for routine surveillance based on KEYNOTE-564 against external, digitised DFS data from the placebo arms of prior adjuvant therapy trials in RCC. Figure 16 plots base-case OS predictions for routine surveillance against external, digitised OS data from the same trials (where available). For both DFS and OS, the observed KM curves from external studies closely aligned with and surrounded the modelled OS projections for routine surveillance.

Table 36 External and predictive validation of long-term DFS for routine surveillance versus placebo arms in previous trials of adjuvant therapy

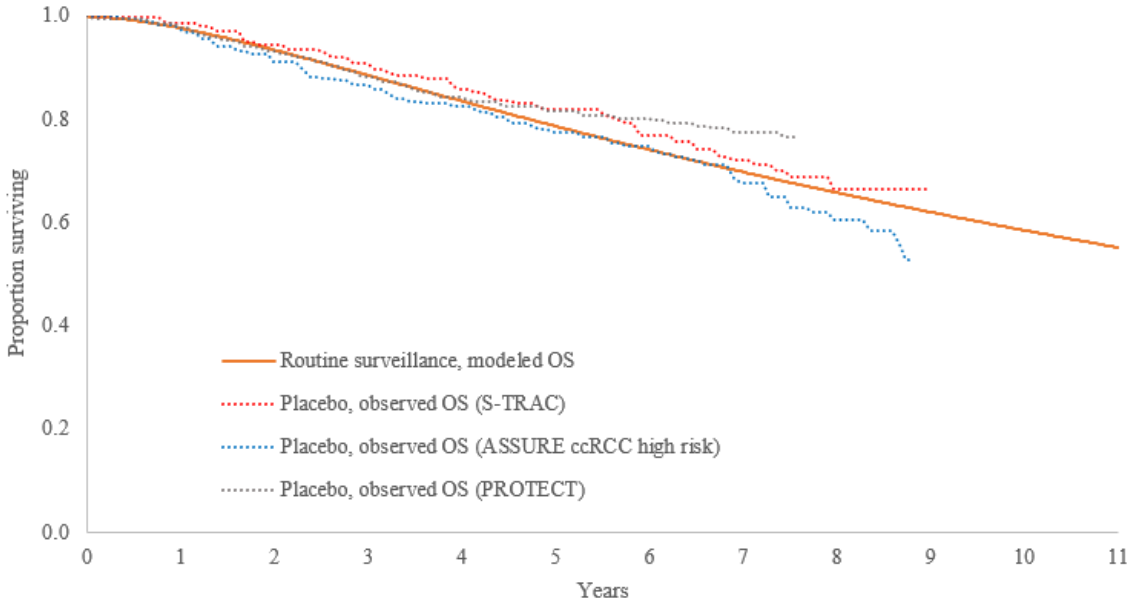
DFS by year	1	2	3	3.5	4	5	7
Placebo, modeled DFS (KEYNOTE-564, data cut-off: 14-JUN-2021)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo, observed DFS (KEYNOTE-564, data cut-off: 14-JUN-2021)	[redacted]	[redacted]	[redacted]	[redacted]	--	--	--
Placebo, observed DFS (S-TRAC) (15)	77.7%	67.3%	59.5%	57.1%	54.7%	51.3%	39.5%
Placebo, observed DFS (ASSURE ccRCC high risk) (31)	78.6%	63.6%	57.6%	54.3%	53.0%	50.6%	38.2%
Placebo, observed DFS (PROTECT) (32)	74.3%	67.0%	61.9%	60.2%	58.7%	50.8%	--
Placebo, observed DFS (ATLAS) (34)	76.7%	65.0%	60.2%	59.2%	54.3%	--	--
Note: Modelled DFS in the routine surveillance arm is based on the base case assumptions outlined in Table 48.							

Figure 15 External and predictive validations of long-term DFS in the routine surveillance arm using base-case assumptions for transitions from DF state

Table 37 External and predictive validation of long-term OS in the routine surveillance arm versus placebo arms in previous trials of adjuvant therapy

OS by year	1	2	3	3.5	4	5	7
Placebo, modelled OS (KEYNOTE-564, data cut-off: 14-JUN-2021)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo, observed OS (S-TRAC) (30)	98.7%	94.5%	90.9%	88.6%	85.8%	81.9%	72.2%
Placebo, observed OS (ASSURE ccRCC high risk) (31)	97.4%	91.3%	86.9%	83.4%	82.6%	77.5%	67.7%
Placebo, observed OS (PROTECT) (33)	97.7%	93.2%	88.2%	86.2%	84.5%	81.6%	77.7%
Note: Modelled OS in the routine surveillance arm is based on the base case assumptions outlined in Table 48.							

Figure 16 Comparison of long-term OS in the routine surveillance arm versus placebo arms in previous trials of adjuvant therapy



For pembrolizumab

Table 38 reports the incremental DFS benefit observed with sunitinib vs. placebo in the S-TRAC trial and that of the 6 combinations of parametric models versus placebo based on KEYNOTE-564 data. Under two of the combinations (Exponential/Generalized gamma and Exponential/Gompertz under Approach #1), the incremental DFS benefit with pembrolizumab at 7 years (11.0-11.2%) was similar to that observed for sunitinib in S-TRAC at this time point. The observed treatment effect size on DFS was larger in magnitude for pembrolizumab vs. placebo in KEYNOTE-564 (HR: [redacted]) than for sunitinib vs. placebo in S-TRAC (HR: 0.76), which supports a larger modelled DFS benefit of pembrolizumab relative to that observed for sunitinib in S-TRAC. These two combinations of distributions under Approach #1 were therefore included as conservative scenario analyses, representing the lower bound of incremental effectiveness with pembrolizumab versus routine surveillance.

Figure 17 plots base-case DFS predictions for pembrolizumab against digitised DFS data from the following sources: the sunitinib arm of the S-TRAC trial (which demonstrated a significant DFS versus placebo); the TKI inhibitor arms of failed adjuvant trials in RCC (in which no significant DFS benefits versus placebo were demonstrated); and the DFS KM curve from KEYNOTE-564. Both predicted and

observed DFS in the pembrolizumab arm distinctly separated from observed DFS reported in the adjuvant TKI inhibitor arms (i.e. higher DFS with pembrolizumab vs TKIs) starting shortly after 1-year following treatment initiation. This divergence of observed pembrolizumab DFS from the observed DFS in previous adjuvant TKI trials including the S-TRAC trial of sunitinib provides supportive evidence for the larger modelled DFS benefit of pembrolizumab relative to the DFS benefit observed for sunitinib in S-TRAC.

Table 38 External validation of modelled incremental DFS benefit with pembrolizumab vs. routine surveillance versus incremental DFS benefit observed in S-TRAC

Incremental % in DFS by year	**1**	**3**	**3.5**	**5**	**7**
Observed, sunitinib vs. placebo (S-TRAC)	10.3%	5.4%	7.9%	8.0%	10.5%
Observed, pembrolizumab vs. placebo (KEYNOTE-564; 14-JUN-2021)	9.5%	9.9%	16.0%	--	--
Modelled, pembrolizumab vs. placebo - Approach 1 -Exponential/Generalized gamma	9.6%	11.0%	11.0%	11.1%	11.2%
Modelled, pembrolizumab vs. placebo - Approach #1/Exponential/Gompertz	8.4%	11.3%	11.3%	11.1%	11.0%
Modelled, pembrolizumab vs. placebo - Approach #2/Exponential/Gompertz	7.0%	12.5%	13.2%	14.6%	15.8%
Modelled, pembrolizumab vs. placebo - Approach #2/Weibull/Gompertz	7.2%	12.3%	12.9%	14.1%	15.0%
Modelled, pembrolizumab vs. placebo - Approach #3/Exponential/Gompertz	6.4%	12.8%	13.6%	15.3%	16.7%
Modelled, pembrolizumab vs. placebo - Approach #3/Weibull/Gompertz	6.8%	12.4%	13.1%	14.3%	15.2%

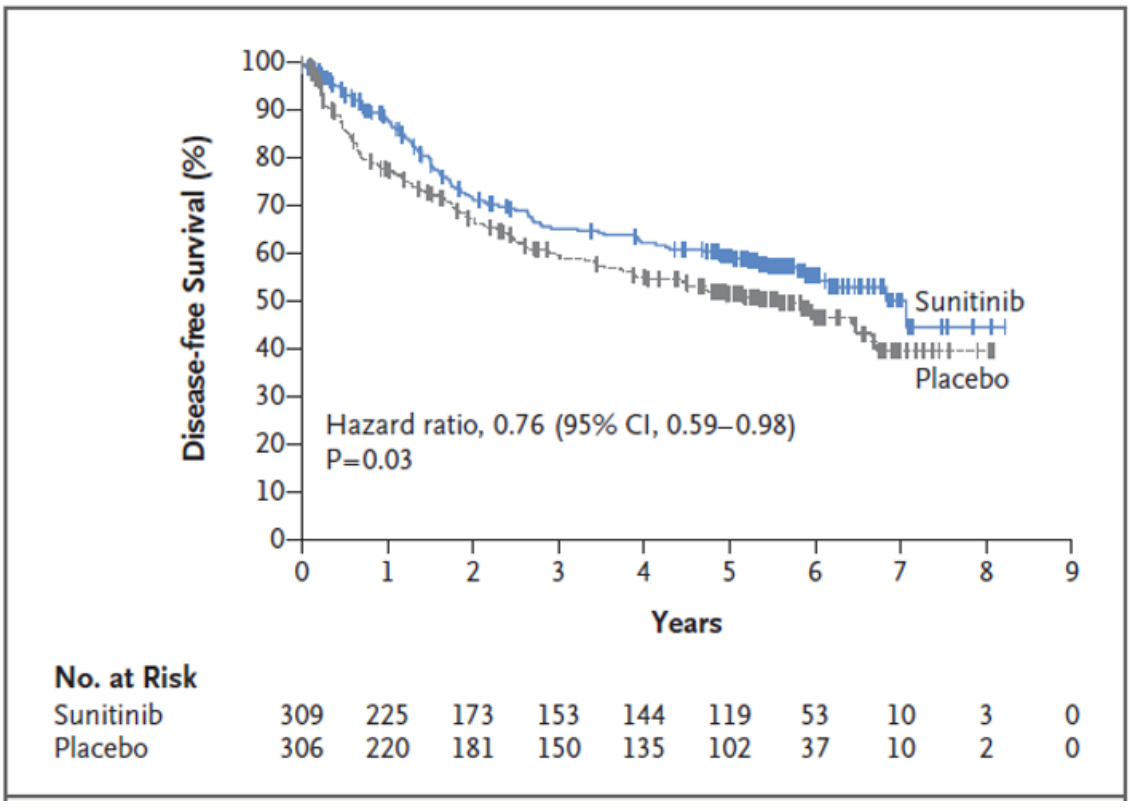
Figure 17 External and predictive validation of long-term DFS in the pembrolizumab arm versus active treatment arms in previous trials of adjuvant therapy (statistically significant DFS benefit observed only in S-TRAC)

Modelled DFS and DMFS using base-case parametric distributions overlaying observed KM data from KEYNOTE-564 are presented in Figure 22 and Figure 23 respectively.

Validation of modelling approach: Separately fitted models offer increased flexibility using fewer assumptions, although they require the estimation of more parameters. NICE DSU TSD 14 recommends separately fit parametric models of the same type as the most appropriate option if the PH assumption appears to be violated (29). Given the gradients of the LCH plots for DFS in each treatment arm for all timepoints after approximately 12-weeks (see Figure 14) are reasonably constant and show no evidence of converging hazards, and considering the visual assessment of the DFS KM curves from KEYNOTE-564, there is no conclusive evidence that the PH assumption is violated. Furthermore, the availability of patient-level data from KEYNOTE-564 enables the implementation of a time-varying HR approach which offers flexibility around the modelling of DFS treatment effect during and after the treatment duration with adjuvant pembrolizumab.

The use of a PH approach requires assumptions about the duration of treatment effect, and whether this is expected to change over time. As observed in KEYNOTE-564, pembrolizumab data available up to a maximum follow-up of 4 years do not show evidence of change to the DFS treatment effect, i.e., the DFS KM curves remain separated, and the LCH plots show no evidence of convergence. External data can also help inform long-term assumptions on the duration of treatment effect. The S-TRAC trial assessing 1-year of adjuvant sunitinib provides mature DFS data with up to 8 years' follow-up and shows an incremental benefit in DFS between adjuvant sunitinib versus placebo ranging from 4.4% to 10.5% at 2- and 7-years respectively. Whilst LCH plots have not been published on the DFS hazards by treatment arm in S-TRAC, visual inspection of the DFS KM curves (see Figure 18 below) shows no evidence of a reduction in treatment effect after 4-years, which is the maximum follow-up available in KEYNOTE-564. At 5- and 6-years, the number of patients at risk in each arm remains sufficient to conclude that no decrease in the DFS treatment effect can be observed for sunitinib.

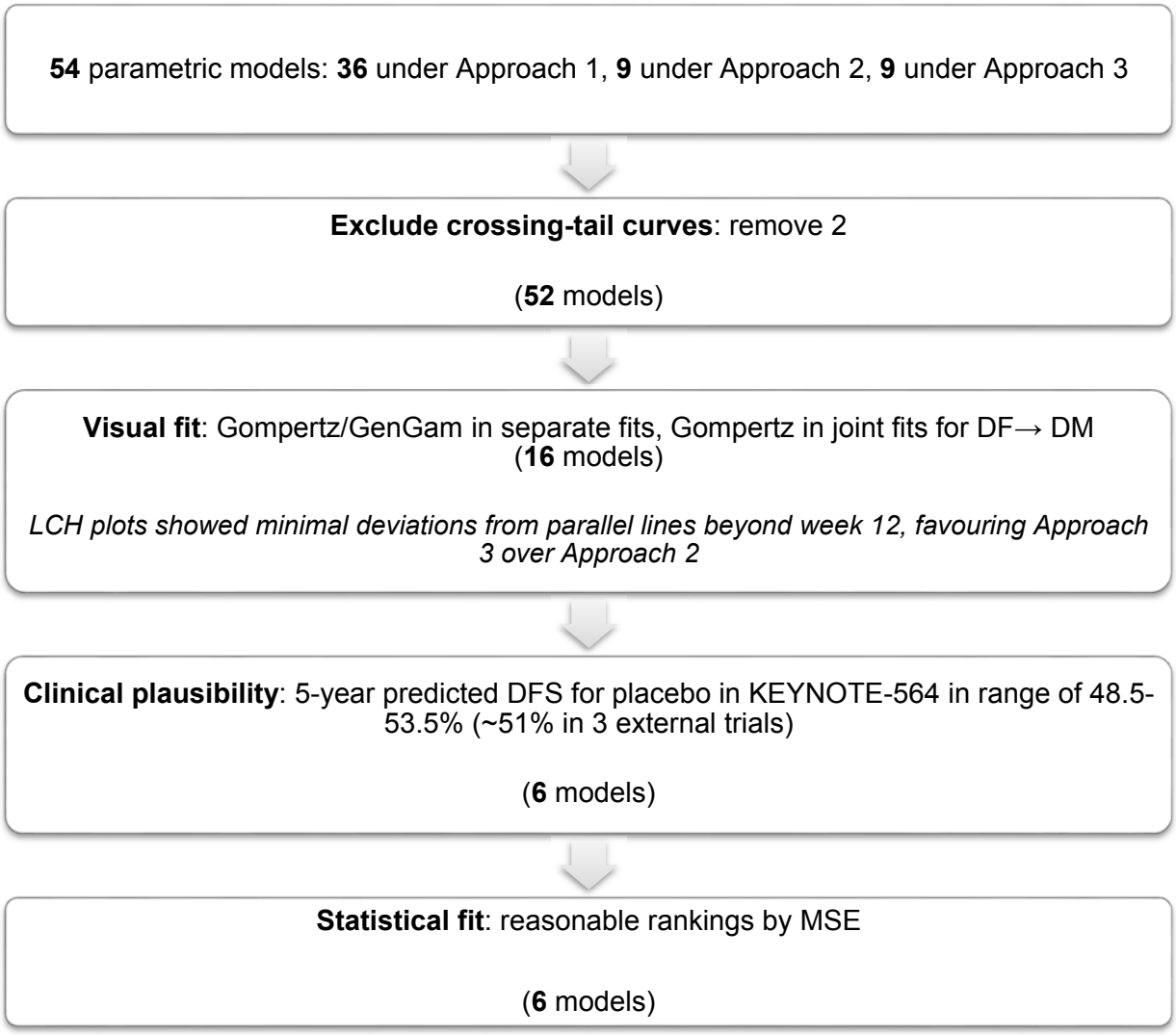
Figure 18 Disease-free survival of adjuvant sunitinib versus placebo in the S-TRAC study (15)



Longer-term data from other KEYNOTE clinical trials has also shown a continued treatment effect post discontinuation of pembrolizumab treatment. In the adjuvant treatment of stage III melanoma, pembrolizumab demonstrated a sustained treatment effect of recurrence-free survival post discontinuation of pembrolizumab at 1-year based on a median follow-up of 3.5-years in KEYNOTE-054 (37). The Phase 3 KEYNOTE-006 trial provides the longest follow-up (median 7 years) of anti-PD-1/L1 therapy for advanced melanoma available to date and shows that outcomes in patients treated with pembrolizumab for up to two years is generally consistent with outcomes seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year maximum treatment duration (38-40). Furthermore, from a biochemical point of view, the mechanism of action of PD-1 inhibitors such as pembrolizumab enable cytotoxic CD8+ T-cells to avoid an exhausted state, thereby allowing them to keep the disease in a state of cancer-immune equilibrium. This can potentially be maintained for up to several decades even in the absence of continued therapy (41, 42). When considering the available evidence, a sustained treatment effect post discontinuation with pembrolizumab reflected in the base-case approach to modelling transitions from the DF health state was considered highly plausible.

The process detailed above of evaluating and selecting parametric models to estimate transitions from the DF health state for the base case is summarised below in Figure 19.

Figure 19 Selection process of parametric models for transitions from disease free health state



Based on the criteria presented above, Approach 3 (jointly fitted with a time-varying treatment effect before/after 1-year) was selected for the base case using exponential for the transition from DF → LR and Gompertz for DF → DM. The rationale for this approach is summarised below in Table 39.

Table 39 Rationale for base-case parametric models to estimate transitions from DF health state

Criteria	Rationale
External validity	Consistency with DFS data for routine surveillance reported in external studies with long-term follow-up
	Other plausible approaches over-predicted DFS with routine surveillance at 7-years compared with external data
	Predicted correlation between DFS and OS was validated with the results from the SEER real-world study
	Independently fit models underestimated pembrolizumab incremental DFS benefit versus routine surveillance at 7-years compared to incremental DFS benefit in S-TRAC with sunitinib which had a less favourable DFS HR.
	External validation of OS with routine surveillance also supported the selected base-case approach
Statistical fit	Ranked 3rd out of 9 by MSE for the placebo arm
Visual fit to DFS KM curves in KEYNOTE-564	Close visual fit (see Figure 20 below)
Duration of treatment effect	Maintenance of treatment effect over time is consistent with: **1**) observed data in KEYNOTE-564 **2**) constant gradient of LCH plots **3**) maintained separation of pembrolizumab and placebo arms DFS KM curves
Flexibility	Time-varying HR approach to reflect potential differences in treatment effect during/after the treatment duration with adjuvant therapy

Figure 20 Modelled DFS and fit to observed DFS in KEYNOTE-564 (data cut-off: 14-JUN-2021) using base-case assumptions for transitions from DF health state

Using the base-case parametric models, adjuvant pembrolizumab was expected to confer incremental gains of 2.88 disease-free life-years and 1.78 overall life-years relative to routine surveillance. These results imply a 0.31-year increase in OS per 1-year increase in DFS with pembrolizumab, a ratio that is plausible and can be considered conservative relative to the ratio of 0.73 years of additional OS per 1 year of additional DFS estimated in the retrospective analysis of SEER-Medicare data (43).

Table 40 Comparison of different parametric models used to estimate DFS in the pembrolizumab arm: Fit with observed data and long-term extrapolations

a. Approach 1: Parametric models fitted separately to each treatment arm: Pembrolizumab

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 1	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	1	G. Gamma	G. Gamma	0.0000394	68	65	60	53	35	14	71	68	62	55	36	14	88	84	76	66	40	16
2	2	Gompertz	G. Gamma	0.0000506	68	64	58	52	34	14	71	67	61	54	34	14	88	84	76	66	39	15
3	3	Log-normal	G. Gamma	0.0000574	67	64	57	50	31	12	71	67	61	53	32	12	88	84	76	66	38	14
4	4	Exponential	G. Gamma	0.0000590	67	63	56	48	27	9	71	67	61	52	30	10	88	84	76	65	36	13
5	5	Log-logistic	G. Gamma	0.0000613	67	63	56	48	28	10	71	67	61	52	30	11	88	84	76	65	36	13
6	6	Weibull	G. Gamma	0.0000618	67	63	56	48	26	9	71	67	61	52	29	10	88	84	76	65	36	13
7	7	G. Gamma	Gompertz	0.0000658	68	65	61	57	43	19	71	68	63	58	43	19	88	84	77	68	45	19
8	11	Gompertz	Gompertz	0.0000891	68	65	60	55	41	18	71	68	63	57	41	18	88	84	77	67	44	19
9	12	Log-normal	Gompertz	0.0000905	68	64	59	53	37	15	71	68	63	57	39	16	88	84	76	67	42	17
10	15	Exponential	Gompertz	0.0000964	67	64	58	52	33	12	71	68	62	56	36	13	88	84	76	67	41	15
11	16	Log-logistic	Gompertz	0.0000976	67	64	58	52	33	13	71	68	62	56	36	14	88	84	76	67	41	16
12	17	Weibull	Gompertz	0.0000983	67	64	58	51	32	11	71	68	62	56	35	13	88	84	76	67	40	15
13	23	G. Gamma	Log-normal	0.0001128	66	62	54	46	26	9	69	64	56	47	26	9	88	83	74	62	32	11
14	27	Gompertz	Log-normal	0.0001435	66	61	53	44	25	9	69	64	56	46	25	9	88	83	74	62	32	11
15	28	G. Gamma	Log-logistic	0.0001601	65	60	51	42	21	7	68	62	53	43	21	7	87	83	73	60	29	9
16	29	Log-normal	Log-normal	0.0001625	65	60	52	43	22	7	69	64	56	46	23	8	88	83	74	62	31	10
17	30	Exponential	Log-normal	0.0001659	65	60	51	41	20	6	69	64	55	45	22	6	88	83	74	62	30	9
18	31	Log-logistic	Log-normal	0.0001716	65	60	51	41	20	6	69	64	55	45	22	7	88	83	74	62	30	10
19	32	Weibull	Log-normal	0.0001727	65	60	51	41	19	6	69	64	55	45	21	6	88	83	74	62	29	9
20	34	G. Gamma	Weibull	0.0001932	65	59	49	37	14	3	67	61	51	38	14	3	87	83	73	58	23	6
21	35	Gompertz	Log-logistic	0.0002014	65	59	50	40	20	7	68	62	53	42	21	7	87	83	73	60	28	9
22	37	Log-normal	Log-logistic	0.0002222	64	59	49	39	18	6	68	62	53	42	19	6	87	83	73	60	27	9
23	38	Exponential	Log-logistic	0.0002279	64	58	48	38	16	5	68	62	53	41	18	5	87	83	73	60	26	8
24	39	Log-logistic	Log-logistic	0.0002342	64	58	48	38	17	5	68	62	53	41	18	5	87	83	73	60	27	8
25	40	Weibull	Log-logistic	0.0002357	64	58	48	37	16	4	68	62	52	41	18	5	87	83	73	60	26	8
26	41	Gompertz	Weibull	0.0002407	64	58	48	36	13	3	67	61	50	38	13	3	87	83	73	58	23	6

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 1	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
27	43	Log-normal	Weibull	0.0002635	64	58	47	35	12	2	67	61	50	37	13	3	88	83	73	58	22	6
28	44	Exponential	Weibull	0.0002707	64	57	46	34	10	2	67	61	50	37	12	2	88	83	73	58	22	5
29	45	Log-logistic	Weibull	0.0002775	64	57	46	33	11	2	67	61	50	37	12	2	88	83	73	58	22	5
30	46	Weibull	Weibull	0.0002793	64	57	46	33	10	2	67	61	50	37	12	2	88	83	73	58	22	5
31	47	G. Gamma	Exponential	0.0002951	64	57	46	33	10	2	66	60	48	35	10	2	87	82	72	56	20	5
32	49	Gompertz	Exponential	0.0003490	63	56	45	32	10	2	66	60	48	34	10	2	87	82	72	56	20	5
33	50	Log-normal	Exponential	0.0003828	63	56	44	31	9	1	66	60	48	34	9	2	87	82	72	56	19	4
34	51	Exponential	Exponential	0.0003888	63	56	44	30	8	1	66	59	48	34	9	1	87	82	72	56	19	4
35	53	Log-logistic	Exponential	0.0003985	63	55	44	30	8	1	66	59	47	33	9	1	87	82	72	56	19	4
36	54	Weibull	Exponential	0.0004007	63	55	43	30	7	1	66	59	47	33	9	1	87	82	72	56	19	4
Note: Shaded boxes indicate higher predicted DFS in routine surveillance arm (excluded from consideration as base case)																						

b. Approach 2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect: Pembrolizumab

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 2	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	13	Exponential	Gompertz	0.0000906	69	66	61	55	35	13	73	70	65	60	38	14	88	84	78	69	43	17
2	21	Weibull	Gompertz	0.0001057	69	67	62	57	39	16	73	70	66	61	42	17	88	84	78	69	45	18
3	25	Gompertz	Gompertz	0.0001287	70	68	66	63	48	21	73	70	67	63	48	21	88	84	78	70	49	21
4	26	Gompertz	Weibull	0.0001382	66	61	52	41	18	5	68	63	53	42	18	5	88	83	74	60	27	8
5	33	Weibull	Weibull	0.0001789	65	59	49	38	15	3	68	63	53	41	16	4	88	83	73	60	25	7
6	36	Exponential	Weibull	0.0002016	65	59	48	36	13	3	68	63	52	40	15	3	88	83	73	59	24	6
7	42	Gompertz	Exponential	0.0002504	64	58	47	34	11	2	66	60	48	35	11	2	87	82	72	57	20	5
8	48	Weibull	Exponential	0.0003355	63	56	45	31	9	1	66	60	48	34	9	1	87	82	72	56	19	4
9	52	Exponential	Exponential	0.0003888	63	56	44	30	8	1	66	59	48	34	9	1	87	82	72	56	19	4

c. Approach 3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect: Pembrolizumab

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 3	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	8	Exponential	Exponential	0.0000731	66	60	50	38	13	3	70	64	54	42	15	3	88	83	74	60	25	6
2	9	Gompertz	Exponential	0.0000738	67	62	54	43	17	4	70	64	55	43	17	4	88	83	74	61	27	8
3	10	Weibull	Exponential	0.0000791	66	61	51	39	14	3	70	64	54	42	15	3	88	83	74	61	25	7
4	14	Exponential	Weibull	0.0000957	66	61	52	40	15	4	70	65	55	44	17	4	88	83	75	61	27	7
5	18	Exponential	Gompertz	0.0001003	69	66	61	56	36	14	73	70	66	60	39	15	88	84	78	69	44	17
6	19	Gompertz	Weibull	0.0001003	68	63	55	45	21	6	70	65	56	46	21	6	88	83	75	62	29	9
7	20	Weibull	Weibull	0.0001043	67	61	52	41	17	4	70	65	56	44	18	4	88	83	75	62	27	8
8	22	Weibull	Gompertz	0.0001115	69	67	62	57	39	16	73	70	66	61	41	16	88	84	78	69	45	18
9	24	Gompertz	Gompertz	0.0001186	70	68	66	62	48	21	73	70	67	63	48	21	88	84	78	70	49	21

Table 41 Comparison of different parametric models used to estimate DFS in the routine surveillance arm: Fit with observed data and long-term extrapolations

a. Approach 1: Parametric models separately fitted to each treatment arm: Routine surveillance

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 1	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	1	Log-normal	G. Gamma	0.0001426	58	54	49	43	27	11	63	60	54	47	29	11	84	79	71	60	34	13
2	2	Weibull	G. Gamma	0.0001427	57	54	48	42	24	9	63	60	54	46	27	9	84	79	71	60	33	12
3	3	Log-logistic	G. Gamma	0.0001436	57	54	48	42	26	10	63	60	54	46	27	10	84	79	71	60	33	12
4	4	G. Gamma	G. Gamma	0.0001551	59	56	52	47	32	13	63	60	55	49	33	13	84	79	71	61	36	15
5	5	Gompertz	G. Gamma	0.0001560	59	57	53	49	34	14	63	60	55	50	35	14	84	79	71	61	38	15
6	6	Exponential	G. Gamma	0.0001818	56	52	45	37	18	5	63	59	53	44	22	6	84	79	70	59	29	9
7	7	G. Gamma	Gompertz	0.0002012	59	57	54	51	38	17	63	61	57	53	39	17	84	79	71	62	41	17
8	8	Gompertz	Gompertz	0.0002464	59	58	56	53	41	18	63	61	58	54	41	18	84	79	72	63	42	18
9	9	Log-normal	Gompertz	0.0003041	58	55	51	47	32	13	63	60	56	51	34	14	84	79	71	61	38	15
10	11	Log-logistic	Gompertz	0.0003204	57	55	50	46	30	12	63	60	56	50	33	13	84	79	71	61	37	14

11	12	Weibull	Gompertz	0.0003242	57	55	50	45	29	11	63	60	56	50	32	12	84	79	71	61	36	14
12	14	Exponential	Gompertz	0.0004072	56	53	47	40	21	6	63	60	55	47	25	8	84	79	71	60	32	11
13	15	Gompertz	Log-normal	0.0004351	55	50	43	36	19	7	59	53	45	37	20	7	83	78	67	54	26	9
14	16	G. Gamma	Log-normal	0.0004575	54	49	42	34	18	6	58	53	45	36	18	6	83	78	67	54	25	8
15	19	Gompertz	Log-logistic	0.0005171	54	49	42	34	17	6	58	52	44	35	17	6	83	78	67	53	24	8
16	20	G. Gamma	Log-logistic	0.0005184	53	48	40	32	16	5	58	52	43	34	16	5	83	78	67	53	23	7
17	23	G. Gamma	Weibull	0.0006273	53	47	38	27	9	2	57	51	40	29	10	2	83	78	66	51	18	4
18	24	Gompertz	Weibull	0.0006300	53	48	39	29	10	2	57	51	41	30	10	2	83	78	66	51	18	5
19	25	Log-normal	Log-normal	0.0006552	53	48	40	32	15	5	58	53	44	35	16	5	83	78	67	53	23	7
20	26	Log-logistic	Log-normal	0.0006719	53	48	39	31	14	4	58	53	44	35	16	5	83	78	67	53	23	7
21	27	Weibull	Log-normal	0.0006808	53	47	39	31	14	4	58	53	44	35	15	4	83	78	67	53	23	7
22	28	Log-normal	Log-logistic	0.0007452	52	47	38	30	14	4	58	52	43	33	15	4	83	78	67	52	22	7
23	29	Log-logistic	Log-logistic	0.0007684	52	46	38	29	13	4	58	52	43	32	14	4	83	78	67	52	21	6
24	30	Weibull	Log-logistic	0.0007787	52	46	38	28	12	3	58	52	43	32	14	4	83	78	67	52	21	6
25	32	Exponential	Log-normal	0.0008943	52	46	37	27	10	2	58	53	44	33	13	3	83	78	67	53	21	6
26	33	Log-normal	Weibull	0.0008947	52	45	36	25	8	2	57	51	40	28	9	2	83	78	66	50	17	4
27	34	Log-logistic	Weibull	0.0009250	52	45	35	25	7	1	57	51	40	28	8	2	83	78	66	50	17	4
28	35	Weibull	Weibull	0.0009392	52	45	35	24	7	1	57	51	40	28	8	1	83	78	66	50	17	4
29	36	Exponential	Log-logistic	0.0009919	51	45	35	25	9	2	58	52	42	31	11	3	83	78	66	51	19	5
30	39	Exponential	Weibull	0.0011788	50	44	33	22	5	1	57	51	39	27	7	1	83	78	66	50	16	3
31	40	Gompertz	Exponential	0.0012895	50	43	32	20	4	0	54	46	34	21	4	0	83	77	64	46	12	2
32	42	G. Gamma	Exponential	0.0013713	49	42	31	19	3	0	54	46	34	21	4	0	83	77	64	46	12	2
33	47	Log-normal	Exponential	0.0017437	49	41	29	18	3	0	54	46	33	20	3	0	83	77	64	46	12	2
34	48	Log-logistic	Exponential	0.0017728	48	41	29	17	3	0	54	46	33	20	3	0	83	77	64	46	12	2
35	49	Weibull	Exponential	0.0017936	48	41	29	17	3	0	54	46	33	20	3	0	83	77	64	46	11	2
36	53	Exponential	Exponential	0.0021905	47	39	27	15	2	0	54	46	33	20	3	0	83	77	63	45	11	2
Note: Shaded boxes indicate higher predicted DFS in routine surveillance arm (excluded from consideration as base case)																						

b. Approach 2: Parametric proportional hazards models jointly fitted with a time-constant treatment effect: Routine surveillance

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 2	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	13	Gompertz	Gompertz	0.0003322	58	55	53	50	38	17	62	59	55	51	38	17	84	79	71	61	40	17
2	17	Weibull	Gompertz	0.0004617	56	52	47	42	26	9	62	59	53	47	28	10	84	79	70	60	34	12
3	21	Exponential	Gompertz	0.0005584	55	51	45	38	20	6	62	58	53	45	24	7	84	79	70	59	31	10
4	31	Gompertz	Weibull	0.0008778	52	46	37	26	8	2	57	50	39	27	8	2	83	77	66	50	17	4
5	38	Weibull	Weibull	0.0011666	51	44	33	22	5	1	57	50	38	26	7	1	83	77	65	49	15	3
6	41	Exponential	Weibull	0.0013596	50	43	31	20	4	1	57	50	38	25	6	1	83	77	65	49	15	3
7	45	Gompertz	Exponential	0.0015122	50	42	31	20	4	0	54	46	34	21	4	0	83	77	64	46	12	2
8	51	Weibull	Exponential	0.0019154	48	40	28	16	2	0	54	46	33	20	3	0	83	77	64	46	11	2
9	54	Exponential	Exponential	0.0021905	47	39	27	15	2	0	54	46	33	20	3	0	83	77	63	45	11	2

c. Approach 3: Parametric proportional hazards models jointly fitted with a time-varying treatment effect: Routine surveillance

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)						Predicted DMFS (%)						Predicted OS (%)					
Under approach 3	*Under all approaches*	DF → LR	DF → DM		4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	10	Gompertz	Gompertz	0.0003193	58	55	53	50	38	17	62	59	55	51	38	17	84	79	71	61	40	17
2	18	Weibull	Gompertz	0.0004877	56	52	47	41	25	9	62	58	53	47	28	10	84	79	70	59	34	12
3	22	Exponential	Gompertz	0.0005975	55	51	45	38	20	6	62	58	52	45	24	7	84	79	70	59	31	10
4	37	Gompertz	Weibull	0.0009971	51	45	35	24	6	1	56	49	37	25	6	1	83	77	65	48	15	3
5	43	Gompertz	Exponential	0.0013854	50	43	31	20	4	0	54	46	34	21	4	0	83	77	64	46	12	2
6	44	Weibull	Weibull	0.0014177	50	42	31	20	4	1	56	48	36	24	5	1	83	77	65	48	14	3
7	46	Exponential	Weibull	0.0016577	49	41	30	18	3	0	56	48	36	23	5	1	83	77	65	47	13	2
8	50	Weibull	Exponential	0.0018980	48	40	28	16	2	0	54	46	33	20	3	0	83	77	64	46	11	2
9	52	Exponential	Exponential	0.0021905	47	39	27	15	2	0	54	46	33	20	3	0	83	77	63	45	11	2

Abbreviations: DF, disease free; DFS, disease-free survival; DM, distant metastases; DMFS, distant metastases-free survival; LR; locoregional recurrence; MSE, mean squared error; OS, overall survival

Figure 21 Predicted versus observed cumulative incidence transitions from the disease-free health state under the base case (data cut-off 14-JUN-2021); Transitions from DF → LR, DF → DM and DF → Death modelled using exponential, Gompertz and exponential distributions, respectively

Figure 22 Base-case modelled DFS over the lifetime time horizon (data cut-off: 14-JUN-2021)

Figure 23 Base-case modelled DMFS over the lifetime time horizon (data cut-off 14-JUN-2021)

Alternative parametric modelling approaches

Based on statistical fit, visual assessment, and the initial exclusions due to non-convergence and crossing DFS curves, further assessments of predictive and external validity identified an additional 5 combinations of distributions for DF → LR / DF → DM considered for inclusion in scenario analysis. Table 42 below reports the alternative parametric distributions which were tested in scenario analyses for the cause-specific hazards of DF → LR and DF → DM for pembrolizumab and routine surveillance.

Table 42 Alternative parametric distributions tested in scenario analyses

Distributions used for DF→LR and DF→DM in scenario analyses	**Rationale for scenario**
Exponential and Generalized gamma under Approach #1 (separately fitted)	Conservative scenario: • The incremental DFS benefit for pembrolizumab vs. routine surveillance under Exponential/Generalized gamma combination under Approach #1 was also similar to that observed for sunitinib vs. placebo in S-TRAC, despite the larger magnitude of the treatment effect size observed with pembrolizumab. • This combination was therefore included as a lower bound of incremental effectiveness for pembrolizumab vs. placebo. However, Exponential/Generalized gamma under Approach #1 yielded close visual and statistical fit with observed DFS in both arms of KEYNOTE-564 (MSE ranking out of 54: #4 for pembrolizumab, #6 for routine surveillance).
Exponential and Gompertz under Approach #1 (separately fitted)	Conservative scenario: • Included based on rationale similar to that described above for Exponential/Generalized gamma under Approach #1.

Exponential and Gompertz under Approach #2 (jointly fitted, time-constant treatment effect)	Plausible scenario: • Exponential/Gompertz under Approach #3 required less strict assumptions regarding the proportionality of hazards over time and was therefore selected for use in the base case. • This scenario modified the base-case distributional assumptions by using the Exponential/Gompertz combination time-constant rather than time-varying treatment effects. However, the external validity of DFS predictions in the routine surveillance arm was comparably robust under this scenario as in the base case. • Additionally, in the exponential model for DF→LR and Gompertz model for DF→DM under Approach #3, the interaction term between treatment group and time (before vs. after 1 year) was not statistically significant at the 5% level, which provides statistical support for the consideration of these distributions under Approach #2.
Weibull and Gompertz under Approach #2 (jointly fitted, time-constant treatment effect)	Plausible scenario: • Although to a lesser extent than the two Approach #1 options above, the Weibull/Gompertz combination also overpredicted 7-year DFS for routine surveillance when considered alongside external data for placebo in S-TRAC, PROTECT, and the high-risk, clear-cell subgroup of ASSURE. However, this combination performed similarly to the base-case distributions in terms of visual assessment, statistical fit, and predictive validity.
Weibull and Gompertz under Approach #3 (jointly fitted, time-varying treatment effect)	Plausible scenario: • Included based on rationale similar to that described above for Weibull/Gompertz under Approach #3

The three transitions starting from the DF state (i.e., DF → LR , DF → DM , and DF → death) are predictably key drivers of the estimation subsequent health outcomes including OS by adjuvant treatment strategy. The use of DFS to estimate long-term OS in the current economic evaluation is supported by a real-world, retrospective analysis that examined the strength of DFS as a predictor for OS in RCC following initial nephrectomy (43). This study collected outcomes data from the Surveillance, Epidemiology and End Results (SEER)-Medicare database (2007-2016) in a cohort of 643 patients with non-metastatic intermediate-high or high-risk RCC who underwent nephrectomy. In the baseline-adjusted multivariable regression analysis, each additional year of DFS was associated with 0.73 years longer OS post-nephrectomy (95% CI: 0.40, 1.05; p<0.001). This retrospective analysis is described in further detail in section B.3.3.6.

B.3.3.2 Modelling transitions from locoregional recurrence

In the absence of sufficient follow-up of patients who experienced LR in KEYNOTE-564, data collected in a retrospective analysis of US SEER-Medicare data was used to inform the transition probability from locoregional recurrence to distant metastases.

In the analysis of SEER data, patients who met the following inclusion/exclusion criteria were identified:

- Diagnosis record of RCC with clear cell component in the SEER registry between 2007 and 2015
- ≥ 66 years old at the first observed diagnosis of RCC
- Intermediate-high risk or high risk, non-metastatic RCC at diagnosis as defined by pathological TNM and Fuhrman grading status
- Received either a radical nephrectomy or a partial nephrectomy after the first observed diagnosis of RCC
- No other (non-renal) cancers before the earliest claim for nephrectomy
- No diagnoses of secondary malignant neoplasm prior to or within 30 days of nephrectomy

In total, 2,437 patients met the above criteria; out of these patients 74 were identified as having a LR, of whom 32 were continuously followed up between initial nephrectomy and date of LR and were included in the transition probability estimation. Locoregional recurrence was identified by an additional nephrectomy after a 90-day treatment-free interval and/or a diagnosis for secondary disease of kidney or renal pelvis or intra-abdominal lymph nodes at least 30 days after the earliest claim for nephrectomy. A case of distant metastases was identified by a diagnosis for metastatic disease at least 30 days after the earliest claim for nephrectomy or initiation of an FDA-approved treatment for metastatic RCC after a 90-day treatment-free interval.

To avoid any immortal time bias, no minimum follow-up requirements were applied after the first date of LR. When modelling the cause-specific hazards of LR → DM, patients were censored at the earliest event of death, loss of follow-up, and end of data. An exponential distribution was fitted to this time-to-event data, given the hazard rate in an exponential model does not depend on time since entry into the health state.

Due to the small number of direct transitions from locoregional recurrence to death in the SEER-Medicare sample, the cause-specific hazards of LR → death was specified using an exponential rate of the DF → death transition in the routine surveillance arm (as estimated from KEYNOTE-564 trial data). As for the transition from DF → death, the transition probability from LR → death was set equal to the maximum of the estimated probability based on parametric modelling of KEYNOTE-564 data and background mortality in the general population. The cause-specific hazards of LR → DM and LR → death are shown in Table 43.

Table 43 Transition probabilities from locoregional recurrence, independent of initial adjuvant treatment strategy

LR → DM		**LR → Death**	
Exponential rate	**SE**	**Exponential rate**	**SE**
0.0042	(0.00102)	0.00006	(0.00004)

Abbreviations: DM, distant metastases; LR, locoregional recurrence; SE, standard error.

Sources: Analysis of SEER-Medicare database; KEYNOTE-564 (data cut-off date: 14-JUN-2021); Office for National Statistics. National life tables, United Kingdom (2017-2019)

B.3.3.3 Modelling transitions from distant metastases

The transition probability from distant metastases to death was estimated based on the distribution of 1L treatments for aRCC accounting for initial adjuvant treatment strategy. First-line treatment options for aRCC recommended by NICE included sunitinib, tivozanib, pazopanib, cabozantinib. Nivolumab in combination with ipilimumab for 1L treatment of aRCC is currently available through the CDF and therefore its associated costs and outcomes are reflected in scenario analysis only. The base-case analysis also considered the cost of second-line therapies for aRCC, however, OS from the DM state was informed by 1L aRCC treatment choice only.

Estimation of the hazard rate of PFS failure and death from distant metastases by adjuvant treatment arm

For each aRCC treatment option, exponential models of OS and progression-free survival (PFS) were estimated using the following approach:

- For sunitinib in the aRCC setting, exponential rates of OS and PFS failure were estimated based on the observed median OS and PFS in the sunitinib arm of KEYNOTE-426, a phase III randomised, open-label, multicentre, global trial to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as 1L treatment for aRCC (44, 45).

- For other aRCC treatment regimens, HRs for OS and PFS versus sunitinib were each obtained from a NMA of trials of 1L aRCC treatments. For each comparator, the model applied time-constant HRs estimated through a fixed-effects NMA of OS and PFS (46). Trials included in the NMA were identified through an SLR of randomised controlled trials of 1L treatments in patients with locally advanced or metastatic RCC with clear-cell histology.

Figure 24 presents the visual fit of modelled PFS and OS for sunitinib in 1L aRCC to the corresponding KM data from KEYNOTE-426. Table 44 reports the exponential rates of OS and PFS failure estimated for sunitinib in aRCC and in Table 45 the HRs of OS and PFS failure for other aRCC treatments versus sunitinib obtained from the NMA are presented alongside the resulting estimates of mean OS and PFS (in weeks) for each regimen.

Figure 24 Exponential models of OS and PFS compared with Kaplan-Meier curves for sunitinib in 1L aRCC

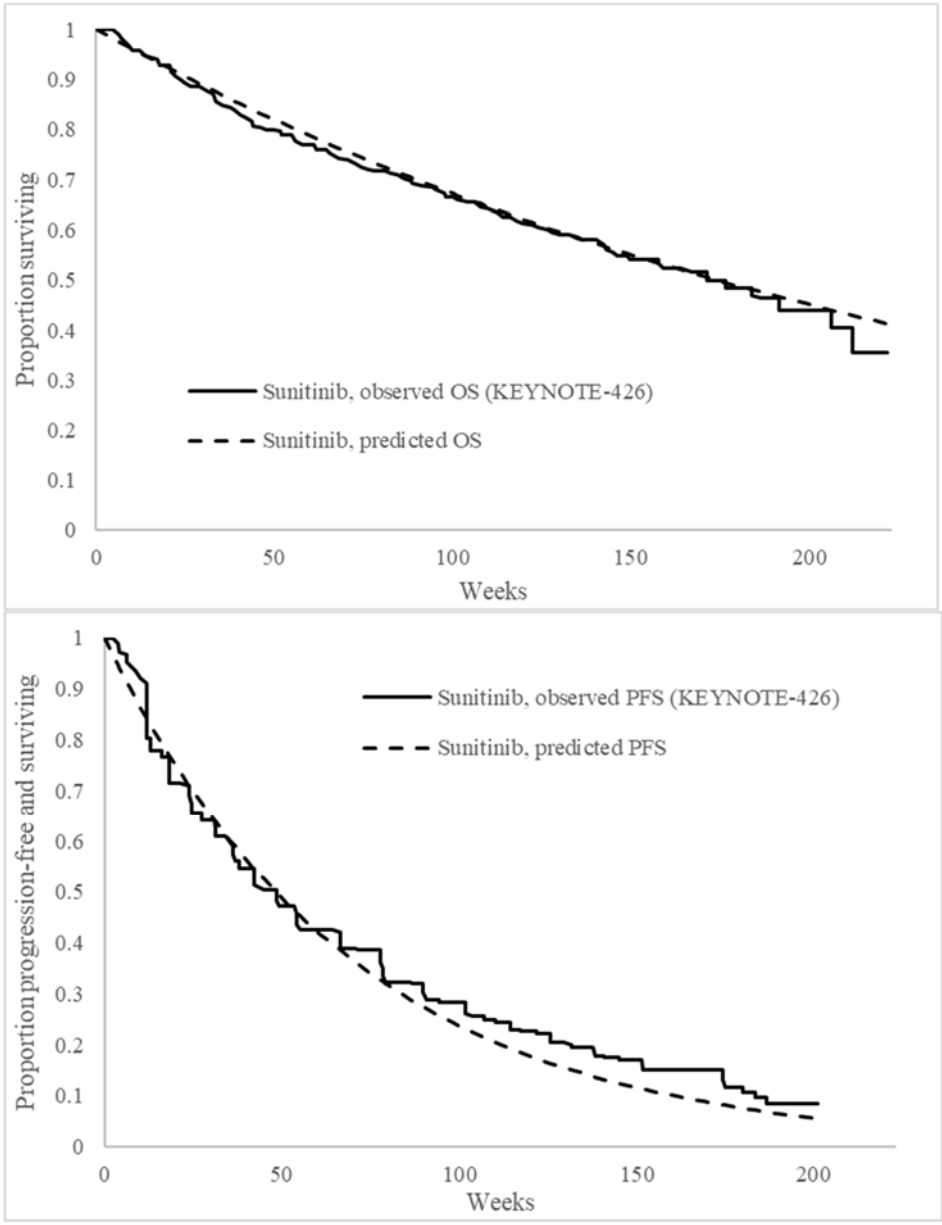


Table 44 Exponential models of OS and PFS with sunitinib in the aRCC setting

Advanced regimen	Exponential model of OS		Exponential model of PFS		Source
	Exponential rate	SE	Exponential rate	SE	
Sunitinib	0.0040	(0.0003)	0.0144	(0.0013)	KEYNOTE-426

Abbreviations: OS, overall survival; PFS, progression-free survival; SE, standard error.

Notes: [1] For sunitinib in the aRCC setting, exponential rates of OS and PFS failure were computed based on the observed median OS and PFS in the sunitinib arm of KEYNOTE-426 (Rini et al. 2021) (45).

Table 45 HRs of OS and PFS failure with other treatment regimens vs. sunitinib in the 1L aRCC setting

Advanced regimen	HR of death vs. sunitinib		HR of progression or death vs. sunitinib		Expected survival in distant metastases state (weeks)	
	HR	SE of ln(HR)	HR	SE of ln(HR)	OS	PFS
Sunitinib	1.00		1.00		252	70
Tivozanib	[redacted]	0.27	[redacted]	0.26	189	59
Pazopanib	[redacted]	0.08	[redacted]	0.08	273	66
Cabozantinib	[redacted]	0.21	[redacted]	0.22	314	145
Nivolumab/ipilimumab*	[redacted]	0.08	[redacted]	0.08	349	78

Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SE, standard error.

* Considered in scenario analysis only

The exponential hazard rate for the transition from DM → death was calculated to reflect the market shares of 1L treatments received for aRCC by adjuvant treatment strategy and was undertaken as follows:

1. Obtain the HRs for PFS and OS for each 1L aRCC treatment versus sunitinib from the NMA (Table 45)

2. Apply these HRs to the exponential hazard rate for PFS and OS for sunitinib (Table 45) to obtain the hazard rate of PFS failure death for each 1L aRCC treatment

3. Calculate mean hazard rate of PFS failure and death weighted by the expected market shares of 1L aRCC treatments by adjuvant treatment strategy (Table 46)

The estimated hazard rate of PFS failure is used to estimate the proportion of time spent in pre- vs post progression to reflect the impact of progression status on HRQoL and cost of disease management following initiation of 1L aRCC treatment. A ratio of time spent in PFS as a proportion of time spent alive was estimated by continuing the calculations as follows:

4. Estimate mean OS and PFS for each 1L aRCC treatment (Table 45) using the exponential hazard rates described in Step 3 above.

5. Use the resulting ratio of mean PFS to mean OS to calculate the proportion of time patients were estimated to remain progression free (Table 47), which was assumed to be constant in each cycle within the DM state

6. Use this proportion to calculate a weighted average disease management cost and utility value for the DM state (see sections B.3.4 and B.3.5.2)

Market shares reflecting the mix of 1L aRCC treatment options available in England and differentiated by adjuvant treatment strategy were based on the following sources and assumptions:

- **Base case**: market shares of 1L aRCC treatments were obtained from data provided by IPSOS for the UK and adapted based on feedback from clinical experts and differences in local availability. The market share of nivolumab plus ipilimumab was set equal to 0% in the base case pending the outcome of the CDF review of TA581. As no other immuno-oncology (IO) treatments in 1L aRCC are currently available in routine commissioning, the base case considered only market shares for an IO-ineligible population.

- **For scenario analysis only:** In the adjuvant pembrolizumab arm, patients were assumed to be eligible to receive an IO aRCC treatment only if they transitioned into the distant metastases state at least 36 months after initiating adjuvant treatment, based on feedback from clinical experts. Patients who developed distant metastases before 36 months received treatment in line with the market shares for an IO-ineligible population (i.e. with market share of nivolumab/ipilimumab set to 0%). For patients who developed distant

metastases on or after the 36-month threshold, market shares of 1L subsequent treatments were assumed equal to those for IO-eligible patients in the routine surveillance arm.

Table 46 Market shares of 1L regimens for aRCC by adjuvant treatment arm and eligibility for IOs

First-line aRCC regimens	First-line aRCC market shares, by adjuvant treatment arm and eligibility for IOs (%)			
	Base case		Scenario analysis only	
	Pembrolizumab	Routine surveillance	Pembrolizumab	Routine surveillance
	IO-ineligible	IO-ineligible	IO-eligible[2]	IO-eligible
Sunitinib	30.0%	30.0%	30.0%	30.0%
Tivozanib	18.0%	18.0%	14.0%	14.0%
Pazopanib	31.0%	31.0%	29.0%	29.0%
Cabozantinib	21.0%	21.0%	13.0%	13.0%
Nivolumab / ipilimumab[1]	0.0%	0.0%	14.0%	14.0%

Source: Adapted from IPSOS market share data with confirmation from UK clinical experts
[1] Nivolumab/ ipilimumab is currently available through the CDF and is not included as a 1L treatment for aRCC in the base case.
[2] Patients are eligible for IO therapy after only 36 months of pembrolizumab treatment initiation

Table 47 Hazards of death from distant metastases by adjuvant treatment arm, based on mix 1L aRCC treatments received

Adjuvant regimen	**Eligibility for rechallenge / IOs in the aRCC setting**	**Expected survival in distant metastases state (weeks): *Weighted average based on 1L aRCC market shares***			**Distant metastases → death: *exponential hazard rate based on expected OS***
		OS	*PFS*	*Ratio of PFS to OS*	
Pembrolizumab	IO-eligible	271	78	0.29	0.0037
Pembrolizumab	IO-ineligible	260	82	0.32	0.0038
Routine surveillance	IO-eligible	271	78	0.29	0.0037
Routine surveillance	IO-ineligible	260	82	0.32	0.0038

B.3.3.4 Overview of health state transitions considered in the economic model

An overview of the approaches used to estimate transitions between health states is provided below alongside a description of how the uncertainty around these approaches was explored in scenario and sensitivity analyses.

Table 48 Overview of health state transitions considered in the base-case analysis

Transition(s)	Base-case estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
DF → LR DF → DM DF → Death [1]	Based on a parametric multistate modelling approach in which different parametric models were fitted to each of the three individual transitions starting from DF and accounting for competing risks Approach 3: proportional hazards model with a time-varying treatment effect before/after 1-year following treatment initiation DF → LR modelled using exponential DF → DM modelled using Gompertz DF → Death modelled using exponential	Patient-level data from KEYNOTE-564 UK life tables for transition DF → Death	Alternative plausible parametric distributions for transitions from DF → LR and DF → DM
LR → DM LR → Death [1]	Distant metastases-free survival (DMFS) depends on all transition probabilities starting from the DF and LR states An exponential model for LR→DM was fitted using a real-world database study (SEER-Medicare), accounting for competing risks. The survival analysis was conducted in a cohort of patients with RCC who underwent nephrectomy and were identified as having a subsequent locoregional recurrence Due to the small number of events in the SEER-Medicare cohort, the exponential rate of LR → death was assumed equal to DF → death in the placebo arm of KEYNOTE-564 No ongoing efficacy of adjuvant treatment was assumed after recurrence. Therefore, the same exponential rates of LR→DM and LR → death are used for each adjuvant treatment strategy	Patient-level analysis of SEER-Medicare database Patient-level data from KEYNOTE-564 UK life tables for transition LR → Death	Exponential rates of each transition varied +/- 20%
DM → Death [1]	OS depends on all transition probabilities in the model Transition probabilities from DM → Death depend upon market shares of 1L aRCC	OS and PFS results from KEYNOTE-426 NMA comparing treatments for	The impact on costs and outcomes of considering nivolumab + ipilimumab as

Transition(s)	Base-case estimation approach	Data source(s)	Scenario or one-way sensitivity analyses performed
	treatments and the efficacy of those 1L treatments with respect to OS Exponential OS distributions were estimated for each 1L treatment based on trials in aRCC. For 1L sunitinib, these distributions were fitted using data from KEYNOTE-426. For other 1L treatments, HRs for OS versus sunitinib were obtained from an NMA of 1L drug trials in aRCC Exponential PFS distributions were similarly estimated for each 1L treatment. Time spent in PFS factors into the calculation of utility and disease management costs in the DM state Expected OS following DM were calculated in each adjuvant treatment arm as a market share-weighted average of expected OS under different 1L treatments. Expected OS was then converted into a weekly hazard of DM → death. Expected PFS following DM was also estimated for each adjuvant treatment	aRCC in terms of OS and PFS Patient-level analysis of SEER-Medicare database UK life tables for transition LR → Death	a 1L aRCC treatment option for patients with IMDC poor- and intermediate-risk was explored in scenario analysis
[1] Transition probabilities to death were constrained to be at least as high as all-cause mortality, as estimated from national life tables given the age and gender distribution of the cohort at each cycle.			

B.3.3.5 Adverse events

The economic analysis included grade 3+ AEs which occurred in at least 5% of the population (at any grade) in either the pembrolizumab or placebo arm (representing 'routine surveillance) of the KEYNOTE-564 trial (18). Risk at any grade was used to determine the set of AEs included in the model, but risks of grade 3 to 5 AEs were incorporated into the model due to their expected impact on resource utilization and quality of life. Grades 3 to 5 AEs occurring with 0% frequency were not included in the model.

Mean durations of the included AEs were also collected from KEYNOTE-564 and were used within the model to estimate the duration of the disutility impact from each AE

regardless of adjuvant treatment arm. Consideration of AE-related disutility and cost is described in sections B.3.4.6 and B.3.5.4, respectively.

Table 49 below presents the incidence and duration of AEs included in the economic analysis.

Table 49 Incidence and duration of adverse events KEYNOTE-564 (14-JUN-2021 data cut-off)

AE type	All-cause grade 3+ AE risk (%), by adjuvant treatment arm		Mean duration (weeks)
	Pembrolizumab	Placebo	
Abdominal pain	0.4%	0.2%	4.9
Alanine aminotransferase increased	2.3%	0.2%	16.4
Arthralgia	0.4%	0.4%	10.1
Aspartate aminotransferase increased	1.6%	0.2%	5.6
Asthenia	0.2%	0.2%	66.1
Back pain	0.2%	0.2%	13.7
Blood creatinine increased	0.2%	0.0%	3.6
Constipation	0.0%	0.2%	4.9
Decreased appetite	0.2%	0.0%	19.3
Diarrhoea	1.8%	0.2%	9.3
Dizziness	0.2%	0.0%	4.0
Dry mouth	0.2%	0.0%	81.0
Dyspnoea	0.2%	0.0%	0.3
Fatigue	1.0%	0.0%	46.9
Hyperglycaemia	1.4%	0.6%	22.7
Hypertension	2.9%	2.6%	35.0
Hyperthyroidism	0.2%	0.0%	5.0
Hypothyroidism	0.2%	0.0%	171.9
Influenza-like illness	0.2%	0.2%	0.7
Myalgia	0.2%	0.0%	168.3
Nausea	0.4%	0.0%	1.8
Pain in extremity	0.4%	0.0%	55.4
Pruritus	0.2%	0.0%	10.9
Pyrexia	0.2%	0.0%	0.4
Rash	0.8%	0.4%	38.0
Upper respiratory tract infection	0.2%	0.0%	3.1
Urinary tract infection	0.4%	0.6%	1.1
Vomiting	0.6%	0.0%	0.4

B.3.3.6 Supporting evidence

DFS as a predictor of OS in an analysis of SEER data

Due to data immaturity, OS in the current economic evaluation is not directly modelled from OS data from KEYNOTE-564. As described in B.3.3, the current modelling approach stratifies mortality risk based on whether a patient has experienced a DFS event (i.e. LR or DM), after which the risk of death increases, reflecting the reduced survival in patients with aRCC. In the absence of mature OS data, the validity of the modelling approach estimating incremental life-years associated with increased time spent disease free was assessed based on a retrospective analysis of SEER-Medicare data collected in US patients aged >65 years. The study objective was to assess the ability of DFS to serve as a predictor for overall survival in patients with intermediate-high risk or high-risk RCC following nephrectomy.

To assess the association between DFS and OS, patients with newly diagnosed non-metastatic intermediate-high or high-risk RCC who underwent nephrectomy were identified from the SEER-Medicare database. Include patients (n=643) were grouped into two cohorts based on experience of recurrence following initial nephrectomy. Recurrence was defined as the first additional nephrectomy, the first diagnosis for metastatic disease or initiation of systemic treatments for aRCC. For patients with recurrence, the index data was defined as the date 30 days before indication of recurrence and for those patients not having experienced recurrence, the index date was randomly assigned based on the distribution of time between first nephrectomy and recurrence among patients in the recurrence cohort.

LR was defined as the first diagnosis for secondary disease of intra-abdominal lymph nodes or kidney and renal pelvis at least 30 days after the earliest claim for nephrectomy or as additional nephrectomy (radical or partial) after the primary treatment-free period. DM was defined as the first diagnosis for metastatic disease at least 30 days after the earliest claim for nephrectomy or initiation of metastatic RCC treatments following the primary treatment-free interval.

Among patients meeting inclusion criteria, 269 were grouped in the recurrence cohort and 374 patients were in the non-recurrence cohort (total N = 674). Follow-up duration

from index date was (mean ± standard deviation [SD]) 25.0 ± 23.0 months and 35.2 ± 26.0 months for the recurrence and non-recurrence cohorts respectively. At index date, mean age was approximately 75 years and the majority of patients were male (see Table 50 below for other reported patient characteristics at baseline).

Table 50 Baseline characteristics of patients with RCC recurrence and without recurrence post-nephrectomy

Baseline characteristics	Patients with recurrence (n = 269)	Patients without recurrence (n = 374)	p-value
Demographic characteristics N (%)			
Age (years) at index date	75.2 ± 6.1	75.7 ± 6.0	0.383
Male, N (%)	174 (64.7%)	216 (57.8%)	0.076
White, N (%)	231 (85.9%)	323 (86.4%)	0.991
Disease characteristics, N (%)			
Risk classification			
Intermediate-to-high risk			
T2, N0, M0	6 (2.2%)	12 (3.2%)	
T3, N0, M0	253 (94.1%)	358 (95.7%)	
High risk			
T4, N0, M0	4 (1.5%)	2 (0.5%)	
T any, N+, M0	6 (2.2%)	2 (0.5%)	
Recurrence type			
Locoregional	29 (10.8%)	-	
Metastatic	240 (89.2%)	-	
CCI,[1] mean ± SD	3.9 ± 1.7	3.7 ± 1.7	0.242

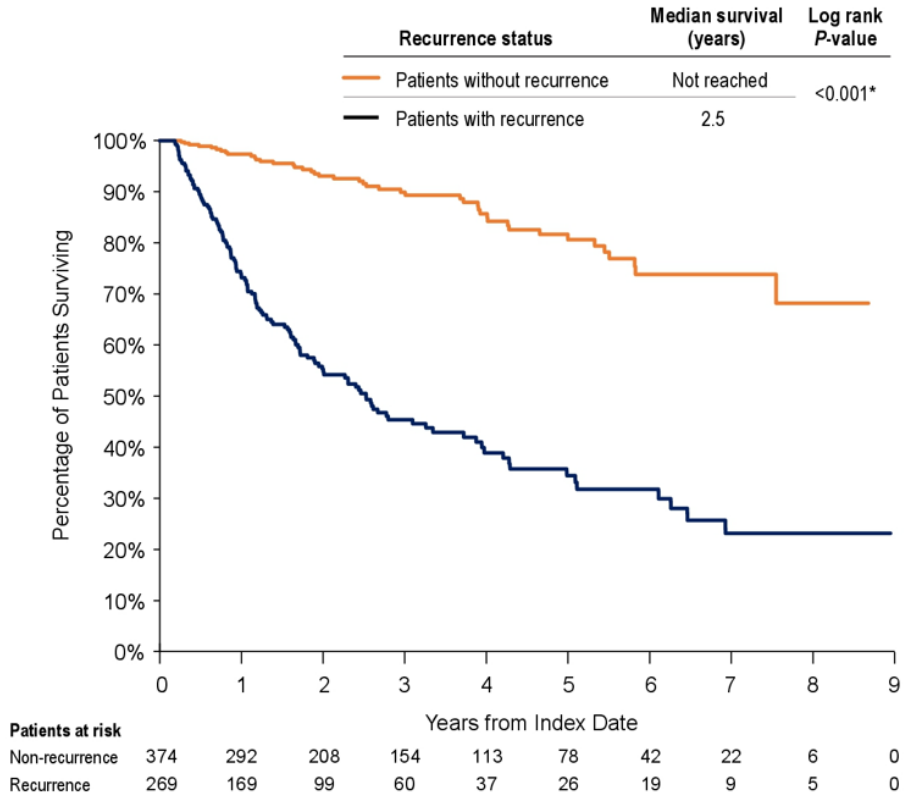
Abbreviations: CCI; Charlson comorbidity index
[1] The conditions included in the CCI are identified using ICD-9 and ICD-10 diagnosis codes reported by Quan, H. et al. (2005) and weighted are based on Quan, H. et al. (2011) (47, 48)

For patients in the recurrence cohort, the median OS from the index date was 2.5 years and in the non-recurrence cohort median OS was not reached. The adjusted HR found a six-fold increased risk of death (95% CI: 4.2-8.5; p<0.001) for patients with versus without recurrence post nephrectomy (see Table 51 below). As shown in Figure 25, the OS KM curves show marked and sustained separation for these two patient groups for the duration of follow-up.

Table 51 Mortality risk by experience of recurrence event from analysis of SEER data

Cox-proportional hazards models	Hazard ratio (95% CI)	p-value
Unadjusted model		
RCC recurrence	5.98 (4.25, 8.41)	<0.001
Adjusted model		
RCC recurrence	6.00 (4.24, 8.48)	<0.001
High risk (vs. intermediate-to-high risk)	1.87 (0.86, 4.09)	0.115
Age (years)	1.07 (1.04, 1.09)	<0.001
Male	1.23 (0.90, 1.67)	0.200
White	1.04 (0.68, 1.61)	0.851
CCI	1.22 (1.11, 1.33)	<0.001
Abbreviations: CCI – Charlson Comorbidity Index; CI – Confidence Interval; RCC – Renal Cell Carcinoma		

Figure 25 Overall survival stratified by recurrence status post-nephrectomy



Landmark analysis (with landmarks points at 1-, 3- and 5-years following initial nephrectomy) was also conducted. For patients with recurrence versus without recurrence at the landmark points of 1-, 3- and 5-years post-nephrectomy, the 5-year survival rates were 37.0% vs. 70.1%, 42.3% vs. 72.8% and 53.2% vs. 78.6%, respectively. The analysis shows that having spent a longer time recurrence free was associated with significantly longer OS. An adjusted regression analysis indicated that

each additional year in DFS was associated with 0.73-0.85 additional OS years (95% CI: 0.52, 1.18 years; p<0.001).

To assess the correlation between DFS and OS, Kendall's Tau was utilised to measure the relationship between time to recurrence or all-cause mortality (DFS) and time to all-cause mortality (OS). Right censoring associated with patients who had not experience DFS and/or OS events during the follow-up period of the study was adjusted for.

Kendall's Tau measures the correlation between two variables and ranges from 0 to 1, where 0 indicates no correlation and 1 indicates perfect correlation; as a rule of thumb for correlation analyses, the strength of association may be described as: negligible (0.0-0.29), low positive (0.30-0.49), moderate positive (0.50-0.69), high positive (0.70-0.89), very high positive (0.90-1.00) (49). The Kendall's tau statistic in the retrospective database study was estimated at 0.70 (95% CI: 0.65-0.74; p<0.001), which indicates that there was a significant positive association between DFS and OS among patients with RCC after the initial nephrectomy evaluated in the SEER study (50).

The findings from this SEER database analysis contrast findings presented by Harshman et al. 2018 (17), who found no strong correlation between DFS and OS in patients with localised RCC. This difference may be explained by the nature of the study question explored in the two studies. Harshman et al. 2018 was a meta-analysis based on aggregated data from published clinical studies which aimed to evaluate whether treatment effects on DFS correspond to treatment effects on OS. The SEER database study used real-world data at the patient level to examine whether DFS was prognostic to OS in patients with intermediate-high and high-risk RCC post nephrectomy. Most clinical studies included in Harshman et al. 2018 reported null results in both DFS and OS and none of the investigated agents significantly improved both DFS and OS compared to trial comparators.

One limitation of this retrospective database study regarding its relevance to the current technology appraisal would be the older age of the SEER population (mean age 75) compared with the population included in KEYNOTE-564 (mean age 60 years). Whilst the clinical trial population may be relatively younger than the trial

population, the patient population likely to receive adjuvant pembrolizumab in UK clinical practice is expected to be older than the trial population, therefore mitigating this limitation.

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

Health-related quality-of-life (HRQoL) was evaluated in the KEYNOTE-564 trial using the EuroQoL EQ-5D-5L (18). The EQ-5D questionnaire contains five health state dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problems) to 5 (extreme problems) (51). For both arms, the questionnaire was administered at cycles 1, 5, 9, 13 and 17, as well as at treatment discontinuation, 30-day follow-up and annually during the follow-up period until disease recurrence or initiation of a new cancer therapy (18). Patient visits with missing EQ-5D-5L responses were excluded.

The estimation of utility values based on data collected in the EQ-5D-5L questionnaire was based on the Full Analysis Set (FAS) population. The FAS population comprised of subjects who were randomised, received a study treatment, and completed at least one EQ-5D-5L questionnaire. Subjects were analysed within the treatment group allocated at randomisation. The compliance of the EQ-5D questionnaires by visit and by treatment is reported below in Table 52 and shows both high rates of compliance and high absolute numbers of patients providing EQ-5D data at all intended visits for both treatment arms.

Table 52 Compliance of EQ-5D by visit and by treatment (FAS Population)

Treatment Visit	Category	Pembrolizumab	Placebo
		N = 484	N = 493
Baseline	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance*	[redacted]	[redacted]
Week 12	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance	[redacted]	[redacted]
Week 24	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance	[redacted]	[redacted]
Week 36	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance	[redacted]	[redacted]
Week 48	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance	[redacted]	[redacted]
Week 52	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance	[redacted]	[redacted]
Week 104	Expected to complete questionnaires	[redacted]	[redacted]
	Completed	[redacted]	[redacted]
	Compliance	[redacted]	[redacted]

**Per protocol, compliance is the proportion of subjects who completed the PRO questionnaire among those who are expected to complete it at each time point (excludes those missing by design).*
(Database Cut-off Date: 14-DEC-2020).

B.3.4.2 Mapping

Although quality of life data was collected in the KEYNOTE-564 trial using the EQ-5D-5L questionnaire, the latest position statement on the use of EQ-5D-5L value set for England by NICE does not recommend using this value set for technology appraisals in England (52), and it recommends utility values to be calculated by mapping the EQ-

5D-5L descriptive system data onto the EQ-5D-3L value set using the mapping function developed by van Hout *et al*. (2012) (53).

B.3.4.3 Health-related quality-of-life studies

Please see Appendix H for a list of studies identified through the SLR of health-related quality of life studies.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

Base-case utility values for the disease-free and locoregional recurrence states were derived through repeated measures regression analyses of patient-level EQ-5D-5L data (mapped to EQ-5D-3L value set) collected in the KEYNOTE-564 trial (18). Utility values were pooled across both arms of KEYNOTE-564 as there was no statistically significant difference observed between the mean utility values estimated for the pembrolizumab and placebo arms (see Table 22). At each visit where the EQ-5D-5L questionnaire was administered, the corresponding EQ-5D-3L score was mapped to the utility using the value set for England.

Disease free and locoregional recurrence

A linear mixed-effects model with patient-level random effects was used to account for the correlation among repeated measures within an individual with the dependent variable of the model being the EQ-5D-5L utility score. The utility for disease-free (without toxicity) was estimated from a regression model that was restricted to patient-visits within the DF state, and that incorporated an independent variable for the presence/absence of grade 3+ AE(s) at each patient-visit.

Distant metastases

The base-case utility for pre- and post-progression within the DM state was estimated through a linear mixed-effects regression model of EQ-5D-3L measurements during the KEYNOTE-426 trial, as this trial provided a larger sample of measurements within the DM state than KEYNOTE-564. The same utility value was used for post-progression within the DM state regardless of the choice of 2L aRCC treatment, as there were insufficient data available to estimate different utility values reflecting potential HRQoL differences associated with different 2L aRCC treatments.

As described in section B.3.5.2, time spent in PFS and OS starting from the DM state was estimated based on HRs (versus sunitinib) estimated in an NMA of 1L aRCC treatments and expected market shares of aRCC treatments in clinical practice in England. The ratio of the estimated PFS to OS was used to estimate HRQoL based on the time spent pre- and post-progression, with corresponding utility values obtained from an analysis of EQ-5D-3L data from KEYNOTE-426 in the aRCC setting.

Health state utility values used in the base case are presented below in Table 53 and reflect decreasing HRQoL as disease severity increases from disease free at adjuvant treatment initiation to post progression within the DM state.

Table 53 Health state utilities in the base-case analysis

Health state	Utilities		Source
	Utility value	SE	
Disease free (without toxicity)	[redacted]	[redacted]	KEYNOTE-564 (14-DEC-2020 data cut-off)
Locoregional recurrence	[redacted]	[redacted]	
Distant metastases (pre progression)	[redacted]	[redacted]	KEYNOTE-426 (24-AUG-2018 data cut-off)
Distant metastases (post progression)	[redacted]	[redacted]	

B.3.4.6 Adverse reactions

The AEs considered in the model include Grade 3+ AEs which occurred in at least 5% of patients (at any grade) in either treatment arm, as described in section B.3.3.

AE-related disutility was applied as a one-time QALY decrement in the first model cycle. Disutility associated with AEs was calculated in each treatment arm as a function of the following: treatment-specific AE risks; the mean durations of these AEs per affected patient in KEYNOTE-564; and the estimated disutility associated with an active grade 3+ AE based on regression analyses of EQ-5D-5L data from the KEYNOTE-564 trial.

The disutility of an active grade 3+ AE was obtained from the same regression model used to estimate the health state utility for disease-free (without toxicity), based on the coefficient associated with the presence of any grade 3+ AE(s). The results of the regression model are presented in Table 54 below.

Table 54 Regression coefficient representing the disutility associated with grade 3+ AEs, based on KEYNOTE-564 data (data cut-off: 14-DEC-2020)

Covariate	Estimate	Standard error	P value
AE status at visit			
During grade 3+ AE	-0.06417	0.009444	p<0.0001
Without grade 3+ AE	(reference)	-	-
Source: Regression analysis of EQ-5D-5L data collected in KEYNOTE-564 (data cut-off: 14 Dec 2020)			

Age-related disutility

The health state utility values presented above did not include an adjustment based on model cycle and thus patient age. A study by Ara and Brazier has suggested that average HRQoL decreases with age (54), however. To account for this, health state utility values described above were adjusted by patient age to reflect the impact of age on HRQoL. The algorithm developed by Ara and Brazier (Table 55) is a linear regression model predicting mean utility values for individuals within the general population, conditional on age (in years), age-squared, and sex and was used to adjust health state utility values as patients age within modelled time horizon.

Table 55 Regression coefficients used for the adjustment of age-related disutility from Ara and Brazier (54)

Parameter	Coefficient
Age (years)	-0.0002587
Age^2	-0.0000332
Male	0.0212126
Intercept	0.9508566

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Details of the SLR conducted to identify relevant cost and health care resource use data to populate the economic model are reported in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

Drug acquisition costs

The drug acquisition costs per treatment are described below, with unit costs for all treatments obtained from the British National Formulary (55). When multiple vial/packages were available, the lowest price per mg was applied.

Intervention – Pembrolizumab

As per KEYNOTE-564 (18), the model uses a 200mg fixed dose of pembrolizumab, administered as a 30-minute IV infusion every three weeks (Q3W). In clinical practice, the option of Q6W dosing is also available (as described in the SmPC and provided in Appendix A), however, this dosing regimen was not explored in the base-case analysis. At the list price of £2,630.00 for a 100mg vial of pembrolizumab, the total drug cost for pembrolizumab per Q3W administration is £5,260 based on two 100 mg vials. A PAS with a simple discount is currently in place for pembrolizumab, reported previously in Table 2.

The relative dose intensity was applied to the drug acquisition cost per infusion of pembrolizumab to account for any delays or interruptions in administration (e.g., due to AEs) as observed in the pembrolizumab arm of KEYNOTE-564.

Table 56 Adjuvant pembrolizumab dosing regimen and relative dose intensity

Adjuvant regimen	Dosing schedule	Relative dose intensity (%)
Pembrolizumab	200 mg IV Q3W, up to 17 cycles (approximately 1 year)	[redacted]
Abbreviations: IV – Intravenous; Q3W – Once every 3 weeks *Source: KEYNOTE-564 (14-DEC-2020 data cut-off)*		

Comparator – Routine Surveillance

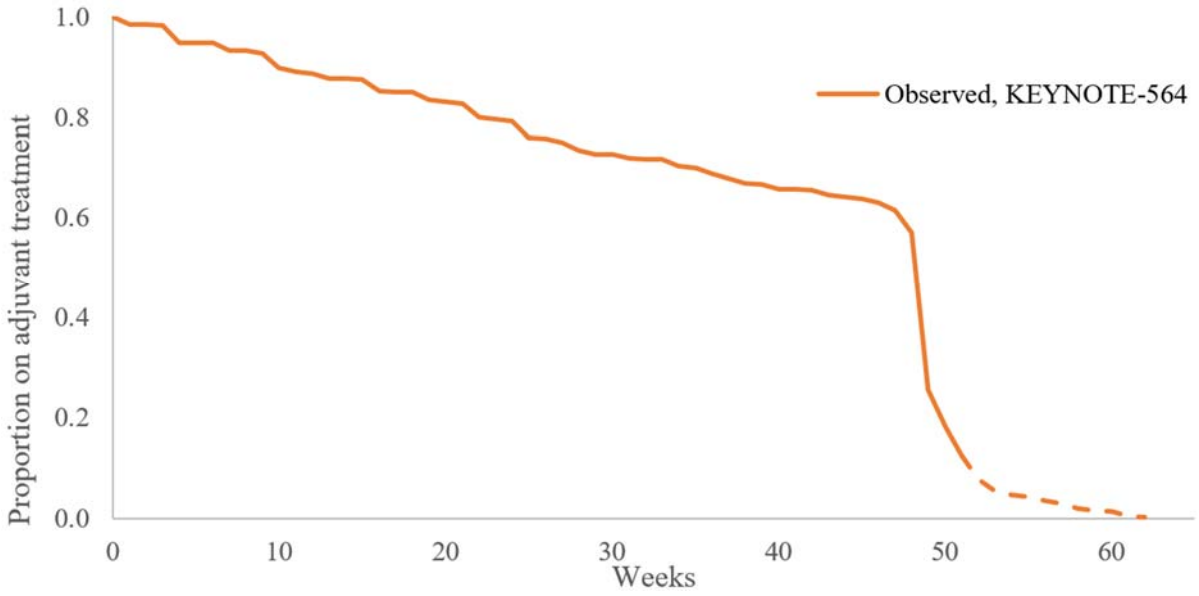
As there are currently no active treatment options available for patients with RCC following nephrectomy, the current standard of care for these patients is routine surveillance, with no associated active therapy costs. The cost of regular clinical follow-up and imaging is described subsequently as part of disease management resource use.

Time on treatment

As per the anticipated licensed indication, patients treated with pembrolizumab are expected to be treated until disease progression or unacceptable toxicity. In line with the KEYNOTE-564 protocol (18), a maximum treatment duration is set whereby patients do not receive pembrolizumab therapy beyond 17 cycles (approximately 1 year). To estimate the of pembrolizumab treatment duration and associated drug costs, time-on-treatment (ToT) KM data from KEYNOTE-564 were used to measure the proportion of patients remaining on treatment following treatment initiation. The use of ToT curves reflects the impact on costs of early discontinuation related to experiencing disease recurrence, AEs and other reasons for discontinuation.

Given the relative completeness of the ToT KM data, the KM data used directly to estimate treatment duration (rather than estimating a parametric model to the KM data). As shown as presented in Figure 26 below, a small percentage of patients in the pembrolizumab arm of KEYNOTE-564 remained on treatment beyond 1 year, as the protocol allowed patients to complete all 17 doses past the 1-year point if there had been earlier delays in treatment. The costs of adjuvant pembrolizumab treatment are calculated based on a fixed 3-weekly interval, and so the costs of the 17th dose are applied at t = 48 weeks from baseline for the percentage of patients still on treatment at this time point. Therefore, the portion of the ToT curve beyond the scheduled 51-week treatment period (represented by the dashed line above) are not included in the estimation of pembrolizumab drug costs.

Figure 26 Adjuvant pembrolizumab time-on-treatment (KEYNOTE-564); 14-DEC-2020 data cut-off



Administration Costs

The time required for the administration of pembrolizumab is 30 minutes. The Health Resource Groups (HRG) code for SB12Z: *Deliver Simple Parenteral Chemotherapy at First Attendance* based on the National Tariff Chemotherapy Regimens List (56). The cost of administration is sourced from the NHS Reference Costs using the SB12Z HRG code, the cost is presented in Table 57 below.

Table 57 Administration costs for adjuvant pembrolizumab

Type of administration required	NHS reference cost code	Setting	Cost
Simple Chemotherapy, at First Attendance	SB12Z	Day case and Reg Day/Night	£299.61

The EMA licence for pembrolizumab as monotherapy also allows treatment to be administered at half the frequency of the Q3W regimen (i.e., 6-weekly [Q6W]) and double the dose (i.e. 400mg), which may be preferred by patients and their treating clinicians due to the increased convenience of this regimen. The Q6W regimen would be expected to reduce the total administration costs accruing during the duration of pembrolizumab adjuvant therapy but is not reflected in the base case.

B.3.5.2 Disease management resource use and unit costs

A systematic literature review was conducted on 10-SEP-2020 to identify costs and resource use in the treatment of and ongoing management of RCC post nephrectomy. Please see Appendix I for details of the search strategy and literature identified.

Health care resource use (HCRU) and unit costs associated with disease management estimated for each of the health state included in the model structure are outlined below.

Disease-free health state

The HCRU associated with the follow-up of RCC patients at intermediate/high- and high-risk of recurrence following nephrectomy reflects the surveillance guidelines published by the Royal Free Hospital (19) and are reported below in Table 58. Patients remaining disease free at 5-years are assumed to no longer receive ongoing follow-up except for a biannual x-ray, based on feedback from clinical experts.

Table 58 Healthcare resource use for disease-free patients

Resource use element	DF – monthly resource use, up to year 2	DF – monthly resource use, years 2-5	DF – monthly resource use, years 5 onwards
	Frequency		
Complete Blood Count	6 Monthly	Annually	-
CT-Scan	Annually	Annually	-
X-ray	-	-	Bi-annually

The unit costs the above healthcare resources were obtained using the relevant NHS reference costs 2019/20 HRG codes for each of the resource use components, shown below in Table 59.

Table 59 Resource use component unit costs

Resource Use Element	Source	Unit Price
Salvage Surgery	NHS England Publication (57)	£6,967.20
Medical Oncologist	Service Code 370 - Medical Oncologist - Total Outpatient Attendances - NHS Reference Costs 2019/20	£192.85
Complete Blood Count	NHS Reference Costs 2019/20 - DAPS05 - Haematology - Directly accessed pathology services	£2.53

Resource Use Element	Source	Unit Price
CT-Scan	NHS Reference Costs 2019/20 - Weighted average of total HRG activity for RD20A, RD21A, and RD22Z	£78.65
Ultrasound Scan	NHS Reference Costs 2019/20 - RD40Z - Ultrasound Scan with duration of less than 20 minutes, without Contrast	£32.82
X-Ray	NHS Reference Costs 2019/20 - RD97Z - Same Day Diagnostic Imaging Admission or Attendance	£45.22

Locoregional recurrence health state

The schedule of follow-up in the LR state was assumed to be similar to the resource use estimates for the DF state for the first 2 years following nephrectomy, based on feedback from clinical experts. Resource use in the LR state also included one-time costs of salvage surgery (nephrectomy) for a proportion of patients who enter this state. The incidence of salvage surgery was obtained from the observed proportion of patients (pooled across treatment arms) who received surgery after experiencing LR as their first DFS failure type in KEYNOTE-564. The cost of surgery was obtained from a publication by NHS England and adjusted for inflation (57). The healthcare resource use for associated with management of patients in the LR health state is presented in Table 60 below.

Table 60 Healthcare resource use in locoregional recurrence health state

Resource use element	LR - One time cost upon entering health state		LR – Monthly Resource Use	
	% Patients	Resource use	% Patients	Resource use
Salvage Surgery	22%	One-off	-	-
Complete Blood Count	100%	One-off	100%	Annually
CT Scan	100%	One-off	100%	Annually
Source:	KEYNOTE-564 (18)		Royal Free Hospital Guidelines (19)	

Distant metastases health state

Healthcare resource utilisation and costs (Table 61) in the DM health state were sourced from the NICE TA650 (pembrolizumab with axitinib for untreated advanced renal cell carcinoma) and accounted for pre- and post-progression status within the DM state (21). For each adjuvant treatment strategy, disease management costs per week in the distant metastases state were calculated as a weighted average of

resource use associated with pre- versus post-progression metastatic disease. These weights were based on the proportion of time spent progression-free within the DM state estimated from the NMA of 1L aRCC treatments (see Table 47 above).

On transition to the DM state, a proportion of patients incurred a one-time cost of salvage surgery, based on the observed proportion of patients undergoing surgery among those who experienced DM as their first DFS failure type in KEYNOTE-564.

Table 61 Frequency of resource use in the DM health state

Health care resource	**One-time cost upon entering DM health state**		**Pre-progression**		**Post-progression**	
	% Patients	Resource use	% Patients	Resource use	% Patients	Resource use
Salvage Surgery	21%	One-off	-	-	-	-
Medical Oncologist	100%	One-off	100%	Monthly	100%	Monthly
Complete Blood Count	100%	One-off	100%	Monthly	100%	Monthly
CT Scan	100%	One-off	100%	3 Monthly	100%	3 Monthly
Source:	KEYNOTE-564 (18), NICE TA650 (21)		NICE TA650 (21)		NICE TA650 (21)	

B.3.5.3 Treatment costs for aRCC in the DM state

The treatment options for patients with confirmed aRCC (i.e. unresectable or metastatic disease) include those recommended by NICE and routinely used in clinical practice (6).

All patients progressing to the DM state were assumed to be eligible for 1L aRCC treatment. The distribution of 1L aRCC treatments was obtained from market share data provided by IPSOS and adapted based on feedback from with clinical experts. Only aRCC treatments available through baseline commissioning were considered in the modelling of costs and outcomes in the aRCC setting, as agreed with NICE at the time of the decision problem meeting for the current appraisal.

The market shares for the included 1L aRCC treatments are presented in Table 46 in Section B.3.3.3. In the base case, only the market shares for the IO-ineligible were considered. Market shares reflecting the treatment of IO-eligible patients were explored in a scenario analysis. This scenario analysis assessed the impact of

including immunotherapies for aRCC treatment currently funded through the CDF (i.e. nivolumab in combination with ipilimumab) but anticipated as a potential treatment option in routine commissioning in 2022. Nivolumab + ipilimumab was included as an available treatment for previously untreated patients with aRCC with intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. In terms of eligibility follow adjuvant treatment with pembrolizumab, patients who had received adjuvant pembrolizumab were assumed eligible for treatment for aRCC with immunotherapy if at least 36 months years had elapsed following the initiation of adjuvant therapy based on feedback provided by UK-based clinical experts. In this scenario analysis, patients receiving routine surveillance only following nephrectomy were considered eligible for nivolumab in combination with ipilimumab regardless of the timing of development of distant metastases following nephrectomy.

The costs of subsequent lines (2L+) of treatment for aRCC were considered in the base-case analysis. Patients treated with adjuvant pembrolizumab who were considered ineligible for immunotherapy (IO-ineligible) in the 1L aRCC setting were assumed to be eligible for nivolumab monotherapy in the 2L+ setting, as it was expected that sufficient time would have elapsed between discontinuing adjuvant therapy and starting 2L aRCC treatment with nivolumab monotherapy for these patients to be considered eligible. Table 62 presents the market shares of 2L aRCC therapies.

Table 62 Distribution of 2L aRCC therapies based on eligibility for immunotherapies

	Adjuvant Pembrolizumab Treatment		Routine Surveillance	
	IO-ineligible	**IO-eligible**	**IO-ineligible**	**IO-eligible**
PD-1/PD-L1 inhibitors				
Nivolumab	0.0%	0.0%	15.0%	0.0%
VEGF/VEGFR inhibitors				
Axitinib	7.0%	7.0%	5.0%	7.0%
Cabozantinib	32.0%	32.0%	25.0%	32.0%
Pazopanib	4.0%	4.0%	0.0%	4.0%
Other treatments				
Everolimus	7.0%	7.0%	5.0%	7.0%
No active treatment	50.0%	50.0%	50.0%	50.0%

The costs of the aRCC treatments were calculated using the licensed doses. For treatments administered intravenously using a dose based on patient body weight, the average body weight from the European cohort in KEYNOTE-564 was used to calculate the required dose per administration. Full vial-sharing was allowed, which excluded costs associated with drug wastage. To account for missed doses and dose reductions, relative dose intensities were reflected in the calculation of drug costs. The cost per treatment cycle for 1L and 2L aRCC treatments are presented in Table 63 and Table 64 below.

Table 63 Costs, dosing and relative dose intensities for 1L aRCC treatments

Drug	Dosing Schedule	Frequency of administration	Total dose required per cycle (mg)	Size of tablet or vial (mg)	Cost per tablet or vial	Cost per cycle (assuming no wastage)	Relative dose intensity	Cost per treatment cycle (list price)	Reference for dosing	Reference for drug costs (55)
Sunitinib	50 mg QD orally for 4 weeks, then 2 weeks off treatment	Q6W	1,400	50	£112.10	£3,138.80	[redacted]	£2,344.68	SmPC	BNF
Pazopanib	800 mg QD orally	Q4W	22,400	400	£37.37	£2,092.53	86.0%	£1,799.58	SmPC	BNF
Tivozanib	1.34 mg QD orally for 3 weeks followed by 1 week without treatment	Q4W	28	1.34	£97.71	£2,052.00	94.0%	£1,928.88	SmPC	BNF
Cabozantinib	60 mg QD orally	Q4W	1,680	60	£171.43	£4,800.13	94.3%	£4,526.53	SmPC	BNF
Nivolumab (initiation phase)	3mg/kg; IV; for up to 4 doses	Q3W	245	240	£2633.00	£2690.30	94.8%	£2,550.41	SmPC	BNF
Ipilimumab (initiation phase)	1mg/kg; IV; for up to 4 doses	Q3W	82	50	£3,750.00	£6,128.00	94.8%	£5,809.58	SmPC	BNF
Nivolumab (maintenance)	480mg; IV; starting 6 weeks after last combo dose	Q4W	480	240	£2,633.00	£5,268.00	94.8%	£4,994.06	SmPC	BNF

QD; Once a day, Q#W; once every # weeks, IV; intravenously
**Source: KEYNOTE-426*

Table 64. Costs, dosing and relative dose intensities for 2L aRCC treatments

Drug	Dosing Schedule	Frequency of administration	Total dose required per cycle (mg)	Size of tablet or vial (mg)	Cost per tablet or vial	Cost per cycle (assuming no wastage)	Relative dose intensity	Cost per treatment cycle (list price)	Reference for dosing	Reference for drug costs (55)
Nivolumab	480 mg IV Q4W	Q4W	480	240	£2,633.00	£5,268.00	92.0%	£4,846.56	SmPC	BNF
Axitinib	5mg orally BD	Q4W	280	5	£62.80	£3,517.00	102.0%	£3,587.34	SmPC	BNF
Cabozantinib	60mg orally QD	Q4W	1680	60	£171.43	£4800.13	100.0%	£4800.13	SmPC	BNF
Pazopanib	800mg orally QD	Q4W	22,400	400	£37.37	£2,092.53	86.0%	£1,574.63	SmPC	BNF
Everolimus	10mg orally QD	Q4W	280	10	89.10	£2,494.80	91.8%	£2,290.23	SmPC	BNF
QD; Once a day, BD; Twice daily, Q#W; once every # weeks, IV; intravenously										

Time-on-treatment and administration costs

Durations of 1L aRCC treatment regimens were modelled using the exponential rates of PFS failure to approximate treatment discontinuation rates (presented in Table 45 in Section B.3.3.3). In scenario analysis, the initiation phase of nivolumab in combination ipilimumab was subject to a maximum treatment duration based on the dosing schedules recommended by NICE (58).

To estimate the costs of 2L+ aRCC therapies, median ToT data was collected from relevant clinical trials, and reported in Table 65 below.

Table 65 Time on treatment for 2L aRCC therapies

Subsequent treatment regimen	ToT (months)		Source
	Median	***Mean***	
PD-1/PD-L1 inhibitors			
Nivolumab	23.9	34.5	Motzer et al. (2015) [CheckMate 025] (59)
VEGF/VEGFR inhibitors			
Axitinib	35.7	51.4	Motzer et al. (2013) [AXIS] (60)
Cabozantinib	36.5	52.7	Motzer et al. (2018) [METEOR] (61)
Pazopanib	32.2	46.4	Sternberg et al. (2013) [VEG105192] (62)
Other treatments			
Everolimus	19.1	27.6	Motzer et al. (2018) [METEOR] (61)

The treatment administration costs reported in Table 66 were obtained from the NHS Reference Costs 2019/20 and were applied for all therapies (63).

Table 66 Unit costs for treatment administration

Regimen	Code	Description	Setting	Cost
Pembrolizumab	SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance	Day case and Reg Day/Night	£299.61
Sunitinib	SB11Z	Deliver Exclusively Oral Chemotherapy	Day case and Reg Day/Night	£226.45
Pazopanib	SB11Z	Deliver Exclusively Oral Chemotherapy	Day case and Reg Day/Night	£226.45
Tivozanib	SB11Z	Deliver Exclusively Oral Chemotherapy	Day case and Reg Day/Night	£226.45

Regimen	Code	Description	Setting	Cost
Cabozantinib	SB11Z	Deliver Exclusively Oral Chemotherapy	Day case and Reg Day/Night	£226.45
Nivolumab in combination with ipilimumab*	SB13Z	Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance	Day case and Reg Day/Night	£331.15
Nivolumab	SB12Z	Deliver Simple Parenteral Chemotherapy at First Attendance	Day case and Reg Day/Night	£299.61
Axitinib	SB11Z	Deliver Exclusively Oral Chemotherapy	Day case and Reg Day/Night	£226.45
Everolimus	SB11Z	Deliver Exclusively Oral Chemotherapy	Day case and Reg Day/Night	£226.45
*Included in scenario analysis only				

B.3.5.4 Adverse event management: unit costs and resource use

A description of the AEs included in the economic analysis and the corresponding incidences are presented in section B.3.3. The impact of adverse events on HRQoL as part of the cost-effectiveness analysis is described in section B.3.4.

The management costs for each of the AEs is derived from the NHS reference costs 2019/20, with the HRG4+ 2017/18 Reference Costs Grouper being used as a guide to allocate an accurate HRG code (64). The costs of treating each AE and the associated HRG codes and descriptions are provided in Table 67.

Table 67. Adverse events costs

AE Type	Unit cost	Description of AE (Source)
Abdominal pain	£203.14	NHS Reference Cost 2019/20, FD05B: Abdominal Pain without Intervention - Regular Day or Night Admissions
Alanine aminotransferase increased	£216.87	NHS Reference Cost 2019/20, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Arthralgia	£273.69	NHS Reference Cost 2019/20, HD24: Non-Inflammatory, Bone or Joint Disorders - Regular Day or Night Admissions (weighted average)
Aspartate aminotransferase increased	£216.87	NHS Reference Cost 2019/20, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Asthenia	£242.80	NHS Reference Cost 2019/20, WH17: Admission Related to Social Factors - Regular Day or Night Admissions (weighted average)

AE Type	Unit cost	Description of AE (Source)
Back pain	£316.15	NHS Reference Cost 2019/20, HC29: Inflammatory Spinal Conditions - Regular Day or Night Admissions (weighted average)
Blood creatinine increased	£310.60	NHS Reference Cost 2019/20, LB37: Miscellaneous Urinary Tract Findings - Regular Day or night Admissions (weighted average)
Constipation	£229.20	NHS Reference Cost 2019/20, FD10: Non-Malignant Gastrointestinal Tract Disorders - Regular Day or Night Admissions (weighted average)
Decreased appetite	£310.66	NHS Reference Cost 2019/20, FD04: Nutritional Disorders - Regular Day or Night Admissions (weighted average)
Diarrhoea	£229.20	NHS Reference Cost 2019/20, FD10: Non-Malignant Gastrointestinal Tract Disorders - Regular Day or Night Admissions (weighted average)
Dizziness	£3.38	eMIT 2020, n/a: Cost of prochlorperazine 3mg Buccal tablets - cost obtained from eMIT
Dry mouth	£3.04	BNF Online [Accessed August 2021], n/a: Cost of AS Saliva Orthana lozenges
Dyspnoea	£262.43	NHS Reference Cost 2019/20, DZ19: Other Respiratory Disorders - Regular Day or Night Admissions (weighted average)
Fatigue	£242.80	NHS Reference Cost 2019/20, WH17: Admission Related to Social Factors - Regular Day or Night Admissions (weighted average)
Hyperglycaemia	£216.87	NHS Reference Cost 2019/20, WH13: Abnormal Findings without Diagnosis - Regular Day or Night Admissions (weighted average)
Hypertension	£149.54	NHS Reference Cost 2019/20, EB04Z: Hypertension - Regular Day or Night Admissions
Hyperthyroidism	£230.01	NHS Reference Cost 2019/20, KA07: Non-Surgical Thyroid Disorders - Regular Day or Night Admissions (weighted average)
Hypothyroidism	£230.01	NHS Reference Cost 2019/20, KA07: Non-Surgical Thyroid Disorders - Regular Day or Night Admissions (weighted average)
Influenza-like illness	£180.96	NHS Reference Cost 2019/20, WJ03: Standard Infectious Diseases without Interventions - Regular Day or Night Admissions (weighted average)
Myalgia	£138.02	NHS Reference Cost 2019/20, HD21: Soft Tissue Disorders - Regular Day and Night Admissions (weighted average)
Nausea	£223.49	NHS Reference Cost 2019/20, FD10M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2
Pain in extremity	£138.02	NHS Reference Cost 2019/20, HD21: Soft Tissue Disorders - Regular Day and Night Admissions (weighted average)
Pruritus	£269.55	NHS Reference Cost 2019/20, JD07: Skin Disorders - Regular Day or Night Admissions (weighted average)

AE Type	Unit cost	Description of AE (Source)
Pyrexia	£0.17	eMIT 2020, n/a: Assumption: Paracetamol 500mg Tablets (32)
Rash	£269.55	NHS Reference Cost 2019/20, JD07: Skin Disorders - Regular Day or Night Admissions (weighted average)
Upper respiratory tract infection	£268.60	NHS Reference Cost 2019/21, CB02: Non-Malignant, Ear, Nose, Mouth, Throat or Neck Disorders
Urinary tract infection	£176.03	NHS Reference Cost 2019/20, LA04: Kidney or Urinary Tract Infections - Regular Day or Night Admissions (weighted average)
Vomiting	£223.49	NHS Reference Cost 2019/20, FD10M: Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2

A one-off cost of AE management associated with each adjuvant strategy was calculated based on the AE incidence observed in KEYNOTE-564 reported previously in Table 49 (see Section B.3.3.5) and weighted by the costs of the AEs reported above in Table 67.

Table 68. One-off adverse event costs by adjuvant treatment strategy

	Pembrolizumab	Routine Surveillance
One-off adverse event cost	£35.97	£12.19

B.3.5.6 Miscellaneous unit costs and resource use

Terminal Care Costs

A terminal care cost was included (£7,125.14; inflated to 2020 costs) and applied upon transition to the death health state. This cost reflects the management associated with terminal care and was obtained from Georghiou and Bardsley (2014) (65).

B.3.6 Summary of base-case analysis inputs and assumptions

Calculations in the economic analysis

For each health state, a specific cost and quality of life weight (i.e. utility value) is assigned within each time period for calculating the cumulative costs and cumulative quality-adjusted life years (QALYs) over the modelled time horizon. A lifetime horizon was used in the base case. Costs and QALYs are discounted with an annual rate of 3.5% in line with the NICE reference case (66).

Summary of base-case analysis inputs

An overview of the key base case inputs is provided in Table 69.

Table 69 Base-case analysis settings

<table>
<tr><th>Setting / Assumption</th><th colspan="3">Base case setting</th></tr>
<tr><td>Model settings</td><td colspan="3"></td></tr>
<tr><td>Time horizon</td><td colspan="3">41.1 years</td></tr>
<tr><td>Cycle length</td><td colspan="3">1 Week</td></tr>
<tr><td>Half cycle correction</td><td colspan="3">Yes</td></tr>
<tr><td rowspan="3">Parametric models used for modelling DF transitions and data sources</td><td>DF → LR</td><td>DF → DM</td><td>DF → Death</td></tr>
<tr><td>Exponential</td><td>Gompertz</td><td>Exponential</td></tr>
<tr><td colspan="3">Parametric models fitted using jointly-fitted time-varying HRs under a PH approach based on patient-level data from KEYNOTE-564</td></tr>
<tr><td rowspan="3">Parametric models used for modelling LR transitions and data sources</td><td colspan="2">LR → DM</td><td>LR → death</td></tr>
<tr><td colspan="2">Exponential</td><td>Exponential</td></tr>
<tr><td colspan="3">An exponential model was fitted to patient-level data from the SEER-Medicare database to estimate transitions from LR → DM. An exponential model was estimated for the transition from of LR → death and was assumed to be equal to that of DF → death observed in the KEYNOTE-564 placebo arm</td></tr>
<tr><td rowspan="3">Parametric models used for modelling DM transitions and data sources</td><td colspan="3">DM → death</td></tr>
<tr><td colspan="3">Exponential</td></tr>
<tr><td colspan="3">For sunitinib, an exponential distribution estimated based on PFS/OS data from KEYNOTE-426. For other 1L aRCC treatments currently available in England, HRs for PFS/OS were obtained from an NMA conducted using data reported in clinical trials of 1L aRCC treatments.</td></tr>
<tr><td colspan="4">HRQoL</td></tr>
<tr><td>Application of utility values</td><td colspan="3">Based on health state</td></tr>
<tr><td>Data source of EQ-5D data to estimate disease-free and locoregional recurrence utility values</td><td colspan="3">KEYNOTE-564</td></tr>
<tr><td>Data source of EQ-5D data to estimate distant metastases utility values</td><td colspan="3">KEYNOTE-426</td></tr>
<tr><td>HRQoL impact of AEs</td><td colspan="3">Applied as a one-off based on incidence and duration of AEs reported in KEYNOTE-564</td></tr>
</table>

Setting / Assumption	Base case setting
Apply age-related disutility?	Yes
Treatment of aRCC	
Use of immunotherapies in the aRCC setting following adjuvant pembrolizumab	Not available as a 1L aRCC treatment in the base case but explored in scenario analysis, with eligibility determined based on time since initiation of adjuvant treatment when a DFS event occurs
Consideration of subsequent lines of therapy in the aRCC setting	Cost of 1L and 2L aRCC treatments included
Drug and administration Costs	
Pembrolizumab treatment duration	Maximum of 17 cycles (approximately 1 year)
Use of vial sharing	Yes
Application of relative dose intensity	Yes
Source of costs	NICE TA's, NHS Reference Costs, eMIT, PSSRU, Guidelines published by the Royal Free Hospital, clinical expert feedback

B.3.7 Base-case results

In the base-case analysis, the estimated mean overall survival was [redacted] years with pembrolizumab and [redacted] years with routine surveillance. Patients treated with pembrolizumab accrued [redacted] QALYs compared with [redacted] in patients treated with routine surveillance.

Base-case incremental cost-effectiveness analysis results

The base-case incremental cost-effectiveness results incorporating the pembrolizumab confidential discount are reported in Table 70 below, with disaggregated results presented in Appendix J. The base-case results show pembrolizumab to be cost-effective compared to routine surveillance. Although these results do not reflect confidential discounts in place on 1L and 2L+ aRCC treatments, given the ICER of £11,068 pembrolizumab would very likely remain cost effective when these discounts are included.

Table 70 Base-case results versus routine surveillance (reflecting PAS discount for pembrolizumab, list prices for subsequent treatments with confidential discounts)

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	Inc. LYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	1.44	1.73	£11,068
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years							

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the parameters included in the cost-effectiveness analysis, a probabilistic sensitivity analysis (PSA) was undertaken using 1,000 samples. The mean values, distributions around the means, and sources used to estimate the parameters are reported in Appendix N.

Table 71 Incremental cost-effectiveness results based on the probabilistic sensitivity analysis results versus routine surveillance (net price)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	
Routine surveillance	[redacted]	[redacted]	[redacted]	1.38	£11,748
ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years					

The incremental cost-effectiveness results obtained from the probabilistic sensitivity analysis are presented in Table 71, and the corresponding scatterplot and cost-effectiveness acceptability curve (CEAC) are presented in Figure 27 and Figure 28. The CEAC shows that there is a 94.2% probability of pembrolizumab being cost-effective versus routine surveillance at the £30,000 per QALY threshold, when the PAS for pembrolizumab is incorporated.

Figure 27 Scatterplot of PSA results (1,000 simulations) versus routine surveillance (net price)

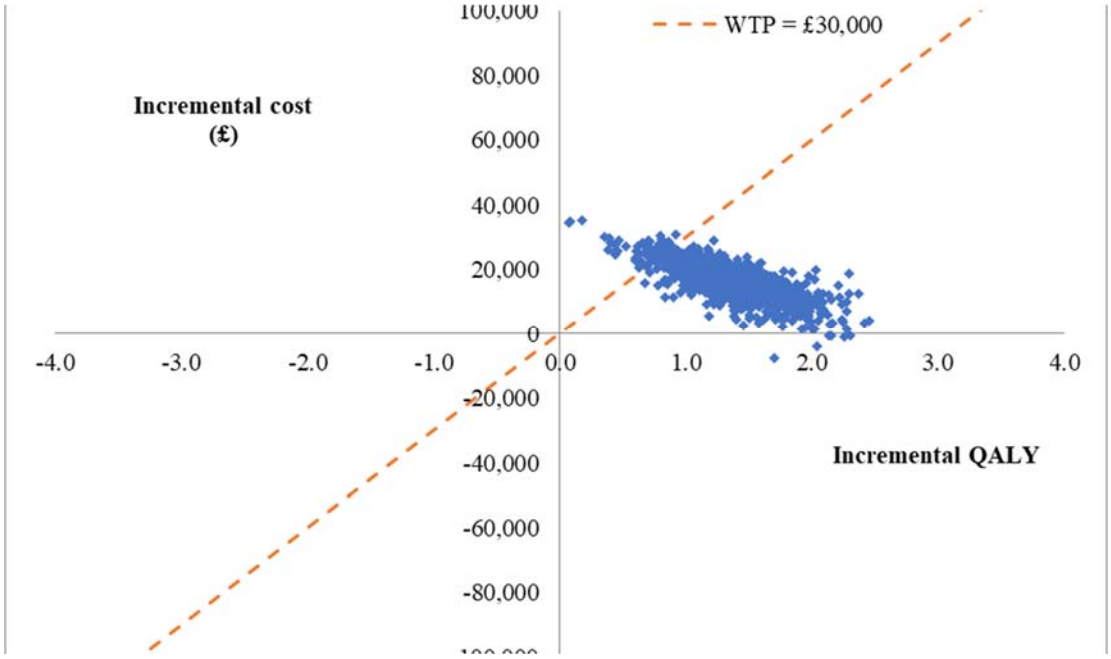
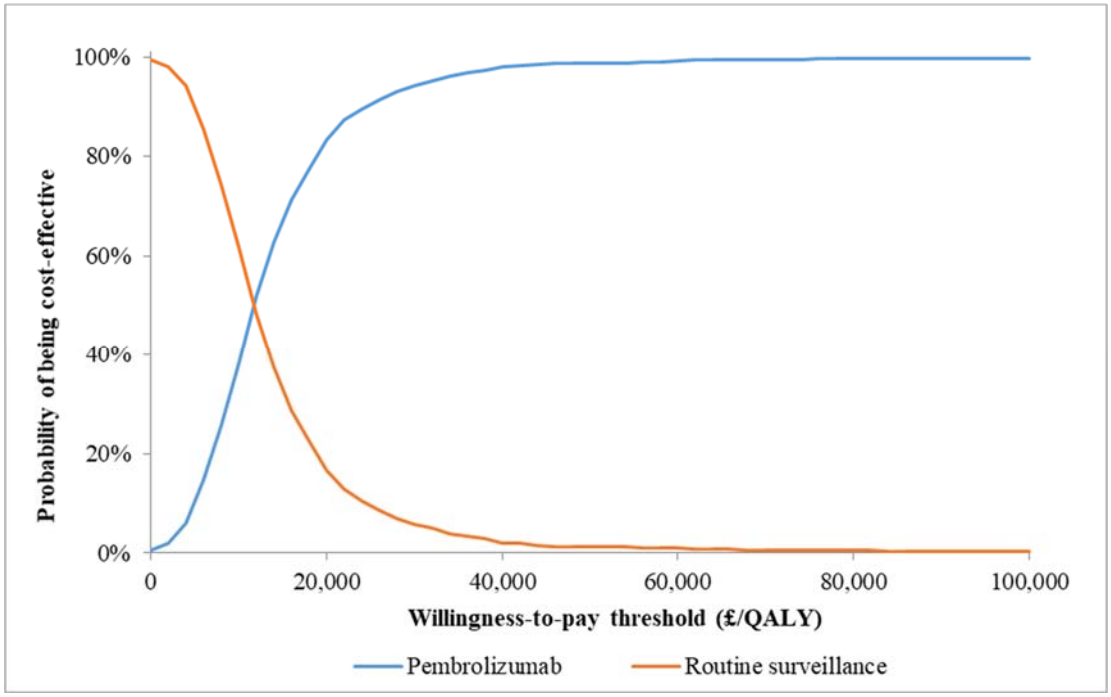


Figure 28 Cost-effectiveness acceptability curve versus routine surveillance (net price)



B.3.8.2 Deterministic sensitivity analysis

Deterministic sensitivity analyses (DSA) were conducted to explore the impact of parameter uncertainty associated with the estimates of cost-effectiveness. The parameters explored are summarised below.

Efficacy estimates

- Varying the exponential rate of LR → DM by +/- 20%
- Varying the exponential rate of LR → death by +/- 20%
- Varying the exponential rates of OS and PFS failure for aRCC treatments by +/- 20%

Utility values

- Vary the utility of the DF health state by upper and lower bound 95% confidence interval
- Vary the utility of the LR health state by upper and lower bound 95% confidence interval
- Vary the utility of the pre-progression DM health state by upper and lower bound 95% confidence interval
- Vary the utility of the post-progression DM health state by upper and lower bound 95% confidence interval
- Vary the disutility of AEs by +/- 20%

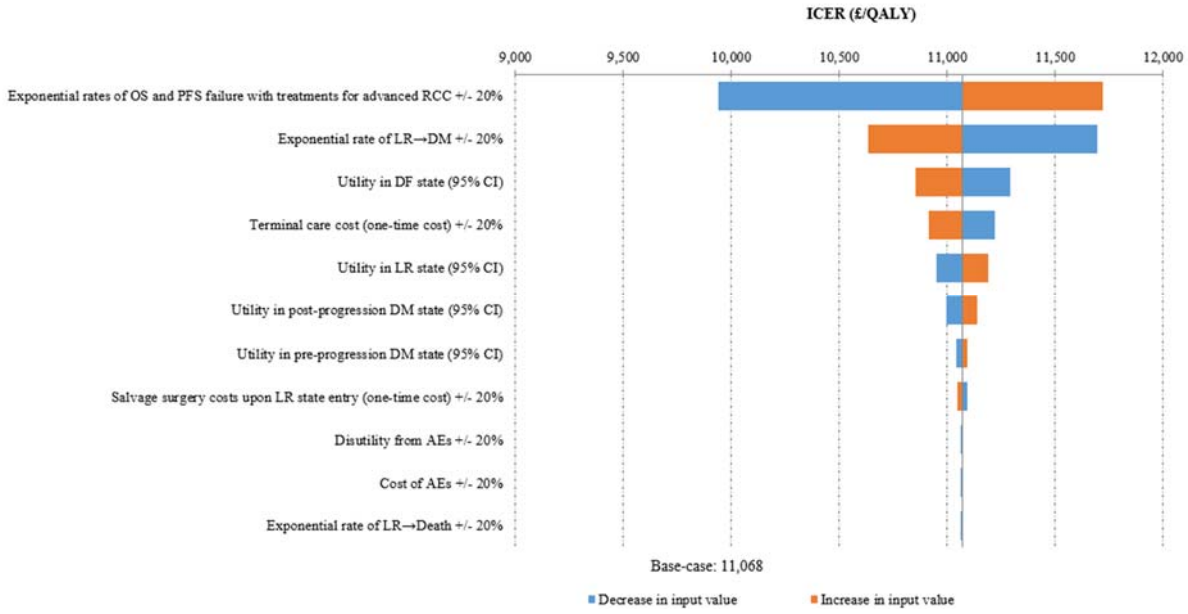
Treatment costs

- Mean patient body weight +/- 20%
- Cost of AEs +/- 20%
- Cost of salvage surgery upon entering LR health state +/- 20%
- Terminal care costs +/- 20%

The results of the DSA for the pairwise comparison of pembrolizumab and routine surveillance are presented graphically within a tornado diagram in Figure 29 sorted by the parameters to which the base-case ICER was from the most to least sensitive.

The inputs to which the ICER showed the most sensitivity were those related to utility values and hazards of PFS/OS failure from the DM state, with cost inputs having a only a minor impact. Overall, the base-case ICER was insensitive to the majority of parameters tested in the DSA.

Figure 29 Tornado diagram presenting the results of the deterministic sensitivity analysis (10 most sensitive parameters)



B.3.8.3 Scenario analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. The scenarios explored are summarised below.

Scenario 1: Model time horizon: 30 years

Alternative combinations of distributions for estimating transition probabilities from DF → LR and DF → DM were explored in the economic analysis. The alternative parametric distributions explored in the scenario analysis are those listed in Table 42. and included following distributions for the transitions from DF → LR and DF → DM:

- Scenario 2: Exponential and Gompertz under Approach 2 (jointly fitted, time-constant treatment effect)

- Scenario 3: Weibull and Gompertz under Approach 3 (jointly fitted, time-varying treatment effect)
- Scenario 4: Weibull and Gompertz under both Approach 2 (jointly fitted, time-constant treatment effect)
- Scenario 5: Exponential and Gompertz under Approach 1 (separately fitted functions)
- Scenario 6: Exponential and Generalised Gamma under Approach 1 (separately fitted functions)

Scenario 7: Including treatment with nivolumab in combination with ipilimumab as an option in the 1L aRCC setting (currently available through the CDF). Patients previously treated with adjuvant pembrolizumab would be eligible for nivolumab + ipilimumab if their transition to the DM state occurs >36 months after initiation of adjuvant treatment.

Scenario 8: Including the cost of 1L aRCC treatments only (i.e. exclusion of 2L+ aRCC treatment costs)

Scenario 9: All health state utility values obtained from KEYNOTE-564 (including DM utility values)

Scenario 10: Remove age-related disutilities

Scenario 11: Remove adverse events disutilities

Scenario 12: Remove half cycle correction

Scenario 13: Removal of relative dose intensities

Scenario 14: 1.5% annual discount rate for costs and benefits (as proposed in the NICE Methods Review, 2021)

Results of the scenario analyses are presented below in Table 72 and show pembrolizumab to remain cost effective in all tested scenarios.

Table 72 Scenario analyses results

Scenario No.	Description	Pembrolizumab			Routine Surveillance			Pembrolizumab vs Routine Surveillance			
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)	Inc. change to base-case ICER (£)
Base Case	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,981	1.44	11,068	-
Scenario 1	30-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	16,034	1.37	11,668	+600
Scenario 2	Approach 2: Exponential/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,171	1.37	12,534	+1,466
Scenario 3	Approach 3: Weibull/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,178	1.32	13,774	+2,706
Scenario 4	Approach 2: Weibull/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,078	1.31	13,798	+2,730
Scenario 5	Approach 1: Exponential/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,885	0.98	22,361	+11,293
Scenario 6	Approach 1: Exponential/ Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,800	0.91	26,092	+15,024
Scenario 7	Inclusion of nivolumab + ipilimumab as an available 1L aRCC therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,173	1.40	10,819	-249
Scenario 8	Exclusion of 2L aRCC treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,796	1.44	14,403	+3,335
Scenario 9	All utilities derived from KEYNOTE-564	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,981	1.43	11,163	+95
Scenario 10	Remove age-related disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,981	1.58	10,127	-941
Scenario 11	Remove adverse event disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,981	1.45	11,043	-25
Scenario 12	Remove half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,981	1.44	11,068	0
Scenario 13	Remove relative dose intensities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,055	1.44	10,427	-641
Scenario 14	1.5% annual discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,429	1.96	6,836	-4,232
Note: [parametric distribution] / [parametric distribution] format refers to DF → LR and DF → DM transitions.											

B.3.8.4 Summary of sensitivity analyses results

The DSA exploring parameter uncertainty showed that the inputs that most affect the ICER were those related to the exponential rates of OS and PFS failure in the 1L aRCC setting and the hazard of transitioning to the DM state from LR. Changes to the utility values, particularly changes to the DF state utility value and to a lesser extent the other health state utility values, were also shown to impact the base-case results.

In the PSA, the probability of pembrolizumab therapy being cost-effective versus routine surveillance at a £30,000 was 94.2%, highlighting the robustness of the base-case results.

The scenario analyses showed that the selection of Approach 1 to model transitions from the DF health state had the largest impact on the base-case results, which resulted in the ICER increasing to £26,092. The jointly-fitted modelling approaches under Approach 2 all yielded relatively similar results to the base case. A reduction in the discount rates of costs and benefits (as proposed in the 2021 NICE Methods Review) also led to a considerable decrease in the ICER. In summary, multiple parameters were tested with the results remaining under the £30,000 willingness-to-pay threshold across all alternate scenarios, with the ICERs ranging from £6,836-26,092 per QALY.

B.3.9 Subgroup analysis

No subgroup analyses were explored in the cost-effectiveness analysis.

B.3.10 Validation

Validation of cost-effectiveness analysis

Comparison with published economic literature

This is the first economic evaluation assessing the cost-effectiveness of pembrolizumab as an adjuvant treatment following nephrectomy for patients with RCC with intermediate-high and high risk of recurrence. No study assessing the cost-effectiveness of pembrolizumab for the target population specified above was identified from the SLR, therefore it was not possible to compare the results of the economic model developed in this appraisal with a previous study.

Clinical benefit

A clinical validation of the cost-effectiveness results was assessed by comparing the efficacy outcomes of pembrolizumab observed in KEYNOTE-564 to the outcomes estimated in the cost-effectiveness model. In particular, the DFS curves predicted for the two model arms were plotted alongside the observed DFS KM curves from KEYNOTE-564 to ensure predicted versus observed DFS were well-aligned during the trial period.

Comparisons against observed data from multiple previous trials in adjuvant RCC were used to validate model predictions of DFS and OS for the routine surveillance strategy up to 7-years and to establish plausibility for the incremental DFS benefit of pembrolizumab versus routine surveillance.

Expert validation

To verify the accuracy and consistency of results of the cost-effectiveness model, internal quality control procedures were undertaken by the model developers to ensure that the mathematical calculations were performed correctly and were consistent with the model's specifications. The model was also independently reviewed by external

health economists, who evaluated the model from an overall health economics perspective in addition to checking for implementation errors.

B.3.11 Interpretation and conclusions of economic evidence

The population included in the economic evaluation was consistent with the intermediate-high and high-risk RCC population eligible for pembrolizumab as per the anticipated licence. Clinical efficacy data from the KEYNOTE-564 trial, which assessed patients in line with the anticipated licenced indication, were used in the economic analysis, the results of which are relevant to all patients who could potentially receive pembrolizumab as adjuvant therapy post nephrectomy.

Generalisability of the analysis to clinical practice in England

The current economic analysis is directly relevant to clinical practice in England. The patient population in KEYNOTE-564 is reflective of UK patients with intermediate-high and high-risk RCC following nephrectomy, and the choice of comparator matches the current UK standard of care following nephrectomy.

The resource utilisation and unit costs are reflective of UK clinical practice and were derived from published guidelines on patient management post nephrectomy, NHS Reference Costs, published clinical guidelines in the UK, and previous NICE technology appraisals in aRCC. Data on HRQoL were obtained from responses to the EQ-5D questionnaire elicited directly from patients enrolled in KEYNOTE-564, many of whom were recruited from the UK and Western Europe.

Strengths and limitations of the economic evaluation

The current economic analysis makes use of the highest quality and most recently available clinical evidence. Head-to-head data from the Phase III KEYNOTE-564 trial comparing pembrolizumab to routine surveillance in nearly 1000 patients with approximately 30 months median follow-up represents a robust data source to evaluate the cost effectiveness of pembrolizumab as adjuvant therapy compared with current UK standard of care.

For the extrapolation of the outcomes collected in KEYNOTE-564 over the long term, external sources relevant to the patient population under assessment were used,

including data and assumptions from previous NICE appraisals of aRCC treatments to reflect UK clinical practice and NICE guidance. The model structure of the current economic evaluation was consistent with those included within previous NICE technology appraisals in the adjuvant setting of other cancers and reflected health outcomes important to patient prognosis and HRQoL.

Consistency and stability of cost-effectiveness results to wide-ranging scenario analyses

The results of the economic analysis were stable to a wide variety of exploratory sensitivity and scenario analyses. In the majority of analyses conducted, pembrolizumab demonstrated cost effectiveness compared with routine surveillance as a more effective adjuvant treatment strategy of patients with RCC at intermediate-high and high risk of recurrence following nephrectomy.

The main limitations identified within this cost-effectiveness analysis are described below.

Lack of mature OS data

At the time of submission, mature data for OS were not available from KEYNOTE-564 and therefore OS could not be modelled based on trial data directly. In the absence of mature OS, data from clinical trials of currently available 1L aRCC treatments incorporated within an NMA were used to estimate overall survival from the DM health state. These estimates reflected the mix of 1L aRCC treatments anticipated to be used in England following adjuvant pembrolizumab versus routine surveillance, which may evolve over time as the mix of available 1L aRCC treatments changes.

Despite the absence of mature OS data, there is strong evidence that the statistically significant improvement in DFS observed in KEYNOTE-564 will translate into a benefit in incremental life-years compared with routine surveillance post nephrectomy. In the retrospective analysis of SEER data in patients with newly diagnosed non-metastatic intermediate-high or high-risk RCC who underwent nephrectomy, experiencing a disease recurrence event was associated with a six-fold increased risk of death. This evidence validates the findings of the current economic analysis which estimated an extension of life-years linked to an increased time spent disease free.

In summary, the results of the current cost-effectiveness analysis demonstrate that pembrolizumab meets NICE's standard for cost effectiveness based on a £30,000 threshold and provides a compelling rationale for the introduction of pembrolizumab as an adjuvant treatment of RCC at intermediate-high or high risk of recurrence following nephrectomy.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

[ID3810] Pembrolizumab for adjuvant treatment of renal cell carcinoma

Clarification questions – MSD responses

December 2021

File name	Version	Contains confidential information	Date
[ID3810] pembrolizumab (RCC) ERG clarification questions – MSD responses v1.0 [ACIC]	**1.0**	**Yes**	**13-DEC-2021**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Survival analysis

A1. Priority question: The ERG notes that table 40 in the CS appendices describes a secondary censoring rule for survival analysis, where events after 2 consecutive missed disease assessments or after new anticancer therapy were censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy. Please confirm if a sensitivity analysis with this secondary censoring rule was conducted and, if so, please provide the results of this sensitivity analysis.

Sensitivity analysis of the outcome disease-free survival (DFS) by investigator assessment using this particular secondary censoring rule was conducted, i.e. that described in the last row of Table 40 in Appendix L of the CS appendices (shown in Table 1).

Table 1. Censoring rules for primary and sensitivity analysis of disease-free survival

Situation	Primary analysis	Sensitivity analysis
No recurrence and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment
No recurrence and no death; new anticancer treatment is initiated	Censored at last disease assessment	Censored at last disease assessment before new anticancer treatment
Recurrence or death documented after ≤1 missed disease assessment and before new anticancer treatment, if any	Event at date of documented recurrence or death	Event at date of documented recurrence or death
Recurrence or death documented immediately after ≥2 consecutive missed disease assessments, or after new anticancer treatment, if any	Event at date of documented recurrence or death	Censored at the last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer treatment, if any

A consistent DFS treatment effect by investigator assessment was observed at the 14-JUN-2021 data cutoff based on the sensitivity analysis in which disease recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after initiation of new anticancer treatment was censored. At the 14-JUN-2021 data cutoff, the HR using this sensitivity analysis was [redacted] and the nominal p-value was [redacted] (shown in Table 2 and Figure 1).

Table 2. Analysis of Disease-Free Survival (Sensitivity Censoring Rule), Based on Investigator Assessment, (ITT Population), KEYNOTE-564

	Pembrolizumab	Placebo
	(N=496)	(N=498)
Number of Events (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Disease Recurrence	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]
Last Assessment Prior To At Least 2 Missed Assessments	[redacted]	[redacted]
Last Tumor Assessment Showing No Disease Recurrence	[redacted]	[redacted]
Last Tumor Status Assessment Prior To New Anti-CancerTherapy Showing No Disease Recurrence	[redacted]	[redacted]
No Post-Baseline Tumor Status Assessment	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a]		

	Pembrolizumab	Placebo
Median (95% CI)	[redacted]	[redacted]
[Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo		
Hazard Ratio (95% CI)[b]	[redacted]	
p-value[c]	[redacted]	
DFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), US participant (Yes versus No) within M0 group by investigator.

NR = Not reached.

Database Cutoff Date: 14JUN2021

Figure 1. Kaplan-Meier plot of disease-free survival (sensitivity censoring rule where events after 2 consecutive missed disease assessments or after new anticancer therapy were censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy), based on investigator assessment, (intention-to-treat population), KEYNOTE-564 (database cutoff date 14-JUN-2021)

These results are therefore consistent with those from the primary analysis of DFS by investigator assessment from the KEYNOTE-564 study at the 14-JUN-2021 data cutoff where the HR was [redacted] with a log-rank test nominal p-value of [redacted] (as described in section B.2.6 of the CS).

A2. The ERG notes the use of trials with adjuvant TKIs were used to validate long-term DFS with adjuvant pembrolizumab. The company reported that in the aRCC setting, TKIs such as sunitinib are given until disease progression and are not considered to have a long-lasting treatment effect following treatment discontinuation, while PD-1 inhibitors such as adjuvant pembrolizumab have

demonstrated a sustained treatment effect even after treatment is discontinued prior to progression at two years. Can the company provide references to substantiate these statements?

While these statements were originally based on feedback from clinical experts (as described in Document B of the submission, under section *B.3.3.1 Modelling transitions from disease-free state, Base-case parametric functions were selected based on the following criteria: 3. External validity and clinical plausibility of long-term extrapolations*), they are nonetheless supported by scientific rationale and published clinical data:

Tyrosine kinase inhibitors such as sunitinib work by inhibiting the cellular signalling mediated by receptors such as platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors, and vascular endothelial growth factor receptors (VEGFRs) that play a role in tumour angiogenesis and tumour growth (1). However, this anti-angiogenic and anti-growth effect is only active while patients are on TKI treatment: it has been found in a Phase 2 study that discontinuation of treatment with sunitinib leads to accelerated endothelial cell proliferation in the primary tumour tissue of RCC patients preoperatively treated with sunitinib, resulting in a compensatory boost of angiogenesis (2). The findings from this study align with clinical evidence that metastases have been observed to regrow considerably during the 2-week treatment break that forms part of sunitinib treatment regimens in RCC (3, 4).

In the context of adjuvant treatment specifically, any tumour micro-metastases that may remain following surgical resection will be small enough not to require support from tumour angiogenesis and so TKI treatment would not be effective at eradicating these cells. It has also been theorised that TKIs are cytostatic rather than cytotoxic and thereby enable micro-metastases adaptation (5, 6). Consequently, it is reasonable to conclude that TKIs such as sunitinib do not have a long-lasting treatment effect following treatment discontinuation.

In contrast, adjuvant treatment with pembrolizumab is expected to promote activation of the immune system and ongoing immune surveillance that will remove any residual microscopic disease after resection to reduce the risk of recurrence. The

mechanism of action of PD-L blockers like pembrolizumab is to help cytotoxic CD8+ T-cells avoid an exhausted state, and promote active immune surveillance, which can potentially be maintained for up to several decades even in the absence of continued therapy:

Cytotoxic CD8+ T-cells (CTLs) are considered to be one of the main effector cell types of the adaptive immune system responsible for combating cancer cells. Functional tumour-reactive T-cells are able to proliferate, produce effector cytokines, and differentiate into memory T-cells that can successfully keep tumours dormant/subclinical for long periods of time, without eradicating the malignant cells completely, in a state termed cancer-immune equilibrium which can potentially be maintained for prolonged periods of time, possibly up to several decades (7, 8). In the period prior to surgical resection of the tumour, when effector CTLs enter the tumour microenvironment they encounter a complicated network of cells and cytokines, including chronic antigen encounter from the tumour, which can induce them to enter an “exhausted state” state in which T-cell effector functions and differentiation into memory T-cells are impaired. PD-L1 is one of the major factors in the tumour microenvironment because of its high expression in many cancer tissues and its capability to down-regulate and induce apoptosis in CTLs, the typical sign of T cell exhaustion is expression of the inhibitory receptor PD-1 and so the PD-1:PD-L1 pathway is a central regulator of T-cell exhaustion (9). Blockade of the PD-1:PD-L1 pathway can “reinvigorate” exhausted CTLs, restoring effector functions, increasing cell numbers, and generation of functional memory T-cells that can provide an ongoing antitumour effect for months to years, even in the absence of continued therapy (10, 11).

The observed long-term post-treatment-cessation effect of anti-PD-1 antibodies in general has been noted (12), and the durable antitumour activity of pembrolizumab has been confirmed in the Phase 3 KEYNOTE-006 trial which provides the longest follow-up (median 7 years) of anti-PD-1/L1 therapy for advanced melanoma available to date and shows that outcomes in patients treated with pembrolizumab for up to two years is generally consistent with outcomes seen in the melanoma cohort of KEYNOTE-001, which did not include a 2-year maximum treatment duration (13, 14).

Subgroups

A3. DFS is reported for subgroups divided by geographical regions of non-US and US. Please provide a subgroup analysis of DFS by geographical regions of the US, Europe, and rest of world.

A forest plot of the hazard ratios for DFS based on investigator assessment by subgroup factors, including the geographic regions of the US, Europe, and rest of world is provided in Figure 2 below.

Figure 2. Forest plot of disease-free survival hazard ratio by subgroup factors, based on Investigator Assessment (primary censoring rule), (intention-to-treat population)

The subgroup analyses are based on unstratified Cox model with treatment as a covariate. Database Cutoff Date: 14-JUN-2021.

Population

A4. Please clarify how many people in the KEYNOTE-564 were recruited from sites in the UK.

In the KEYNOTE-564 study, 86 participants were recruited from sites in the UK. However, 23 of the 86 recruited participants were screening failures, resulting in 63 participants recruited from sites in the UK being randomised into the study (38 into the pembrolizumab arm and 25 into the placebo arm).

Quality of life

A5. For PRO data from the FAS population, please clarify how missing data was accounted for in the outcome reporting. In table 22 on document B, 446 participants contributed data for EQ-5D in the adjuvant pembrolizumab arm at baseline and 301 contributed data at week 52, however 484 participants are shown for the mean change from baseline.

With regard to Table 22 in Document B of the company submission, 484 participants in the pembrolizumab treatment group and 493 participants in the placebo group were included in the Full Analysis Set (FAS), defined as all participants who were randomised, received at least one dose of study treatment, and completed at least one patient reported outcome questionnaire anytime during the study. The N number under “Change from Baseline to Week 52” corresponds to all participants with at least one non-missing EQ-5D datum at any timepoint ranging from baseline to week 52, and so correlates closely with the FAS population number. The constrained Longitudinal Data Analysis (cLDA) model which is used for this analysis implicitly treats missing data as missing at random (MAR). Thus, the cLDA approach models missing data based on observed data of adhering participants from the same treatment group.

As a result, all participants with at least one non missing datum for EQ-5D at any timepoint in the study contribute to the model and the related treatment estimates (i.e. Change from Baseline to Week 52), despite there being fewer participants for whom data were available at the specific timepoints of Baseline and Week 52 (summarised in Table 3).

Table 3 Description of the numbers of participants shown in the results of the analysis of change from baseline in mapped EQ-5D-3L utility score to Week 52, based on the UK crosswalk algorithm from EQ-5D-5L to EQ-5D-3L (PRO FAS population)

Information reported	Pembrolizumab (N)	Placebo (N)	Description of the population
Change from Baseline to Week 52	484	493	Participants with at least one non-missing EQ-5D datum at any timepoint ranging from baseline to week 52
Baseline	446	460	Participants with EQ-5D data available at the baseline timepoint
Week 52	301	327	Participants with EQ-5D data available at the Week 52 timepoint

Section B: Clarification on cost-effectiveness data

For any scenarios requested in Section B, please ensure these are implemented as user selectable options in the economic model "Specifications" tab). If scenarios cannot be implemented as user selectable options, please supply instructions on how to replicate the scenario. Furthermore, if the company chooses to update its base case analysis, please ensure that cost-effectiveness results, sensitivity and scenario analyses incorporating the revised base case assumptions are provided with the response along with a log of changes made to the company base case.

Survival analysis

B1. Priority question: Please provide a rationale for utilising investigator assessed (IA) DFS data for the primary analysis and subsequent modelling

and please clarify why a scenario using blinded independent central reviewer (BICR) DFS was not explored in the economic model?

a) **The ERG considers that Approach 1, using independent parametric models fitted to each treatment arm, is preferable when patient level data from the key trial are available as it limits the number of assumptions that need to be made about the data. Furthermore, based on statistical fit using MSE, Approach 1 had the best fit models out of all approaches. As such, using Approach 1 and selecting the best model fit (based on statistical and visual fit, as well as clinical validity), please provide a scenario using BICR data to inform the DF transitions in the model. The company may want to supply a separate model for the BICR analysis (essentially replacing the IA analysis in the "BICR scenario model"), as the current model is already substantially large and including the BICR scenario in the current model is likely to make it unwieldy.**

The rationale for using investigator-assessed DFS as the primary efficacy endpoint in the KEYNOTE-564 study is provided in the CS, section *B.2.3 Summary of methodology of the relevant clinical effectiveness evidence; Summary of the methodology of the KEYNOTE-564 study; Outcomes assessed; Primary efficacy endpoints; Disease-free survival (DFS) as assessed by the investigator*:

> In the proposed patient population, participants are entering the trial tumour free. In the adjuvant setting, an investigator determines the absolute recurrence of disease. This assessment is equally appropriate to an independent reviewer determination since it does not involve tumour burden level grading expected with existing advanced metastatic disease. Therefore, DFS as assessed by the investigator is used in the trial as the primary outcome, though DFS as assessed by blinded independent central review (BICR) is also collected.

As the assessment of DFS in the adjuvant setting primarily involves determining whether a tumour has re-appeared when at baseline there was none (and whether patients are still alive), this assessment is fairly objective. The criteria for investigator-assessed DFS are unambiguous compared to, for example, the assessment of progression-free survival in the metastatic setting (where treatment never fully

eliminates the tumour and determination of progression requires potentially more subjective judgement around specific tumour characteristics). It is therefore reasonable to conclude that the accuracy of investigator assessment is similar to that of BICR when assessing DFS.

The suitability of investigator-assessed DFS is substantiated by the fact that the concordance and discordance between investigator-assessed and BICR-determined disease recurrence was assessed as part of the KEYNOTE-564 study and a high level of consistency was found between the reported results of these two methods of determining disease recurrence. At the 14-JUN-2021 cutoff the BICR assessment agreed on 89.0% of the investigator assessments in the pembrolizumab arm and 93.0% of the investigator assessments in the placebo arm. There was no evidence of systematic bias in disease recurrence assessments by investigator favouring the pembrolizumab group when differential discordance of disease recurrence based on investigator review versus BICR was estimated. Based on the criteria reported in Mannino et al (15), the estimated difference of early discrepancy rate (0.061) did not cross its threshold value of ≤-0.05 and the estimated difference of late discrepancy rate (-0.103) also did not cross its threshold value of ≥0.075.

It should be noted that the KEYNOTE-564 study itself is designed to statistically test investigator-assessed DFS, and not DFS by BICR, and so the study results in terms of DFS by BICR should be interpreted with caution.

Finally, investigator assessment best reflects real-world practice in the adjuvant setting where physicians would determine the recurrence of disease and recommend the best treatment options for their patients based on the local review of diagnostic imaging, and therefore has the most external validity and generalisability in the context of an appraisal of a treatment to be used on the NHS.

For the reasons outlined above, the investigator assessment of DFS is considered the most appropriate and generalisable and consequently the BICR assessment-based analysis has not been provided.

B2. The company provided extensive analysis to choose an appropriate approach to extrapolate KEYNOTE-564 patient level data for the disease-free (DF) health state transitions. Given that there is a change in the hazards at

week 12 (Figure 14a and b of the CS), please explain why a piecewise modelling approach (observed Kaplan-Meier data with an extrapolated tail) was not considered?

As reported in the CS, based on the planned set of parametric distributions fitted to each transition from the DF state, there were a total of 54 possible combinations of parametric distributions available for consideration, each resulting in a distinct extrapolation of DFS. Given the large number of possible combinations even when considering one-piece distributions alone, it was expected that several combinations would meet internal and external validation requirements, without the need to further expand the set of potential distributions.

Moreover, the planned set of distributions included a variety of multi-parameter (i.e., non-exponential) distributions that allow for changing hazards over time, when applying a one-piece approach. The use of multistate modelling provides further flexibility in the shape of the DFS curve, as the DFS curve is derived as a composite of all three distributions used for DF→LR, DF→DM, and DF → Death. Consequently, a change in hazards around week 12 would not necessarily trigger the need for a piecewise modelling approach.

The 12-week cut point for the change of hazards proposed by the ERG appears to be driven by a review of the log-cumulative hazard plots (which show roughly parallel lines after but not before week 12) whilst ignoring that this trend is an artefact of the trial protocol which specified first patient assessment for disease activity prior at 12 weeks. The DFS KM curves for pembrolizumab and placebo overlap completely for the first 12 weeks of follow-up before markedly separating thereafter. A piecewise approach was not selected for the base case given it would mask differences in disease recurrence which occur independent of the timing of first assessment.

B3. Please clarify what hazard ratios (HRs) were applied in year 1 and year 2 onwards for the company base case using Approach 3 for the disease-free (DF) health state transitions?

a) **How do the HRs used for Approach 3 compare with the HRs from the observed KEYNOTE-564 data for the same periods?**

The Excel® formulas for computing the HRs before and after 1 year from the parameter estimates obtained with Approach 3 (located in the "Raw_Param Estimates" tab of the economic model) are reported below in Table 4. The HRs under the base-case combination of distributions (Approach 3 [Exponential/Gompertz]) are summarised in Table 4 below.

Table 4. Computation of HRs of DFS failure with pembrolizumab vs. routine surveillance using parameter estimates under Approach 3

Distribution	HR before 1 year	HR after 1 year
Exponential or Gompertz	= EXP(trtpn_new)	= EXP(trtpn_new + trtpn_new:g1yr)
Weibull	= EXP(-trtpn_new)^shape	= EXP(-trtpn_new - trtpn_new:g1yr)^shape
Note: Under Approach 3, the trtpn_new covariate was a time-constant binary indicator equal to 1 in the pembrolizumab arm and 0 in the placebo arm, while the trtpn_new:g1yr covariate was a time-varying binary indicator equal to 1 in the pembrolizumab arm during the portion of follow-up after 1 year and 0 otherwise.		

Due to the relatively limited follow-up time of KEYNOTE-564 and the small number of DFS events post year 1 for each transition from the DF state, the estimate of a piecewise HR for the transitions of DF→LR and DF→DM from the trial data would be statistically unstable. Instead, it was considered more robust to estimate the HR for DF→LR and DF→DM across the full duration of trial follow-up, given potential violations of the proportional hazard assumption are minimal. The estimated HRs for DF→LR ([redacted]) and DF→DM ([redacted]) based on observed KEYNOTE-564 data are reported in Table 5 below.

Table 5. HRs of DFS failure with pembrolizumab vs. routine surveillance using parameter estimates under Approach 3

Transition:	DF→LR	DF→DM
KEYNOTE-564		
Overall HR (95% CI), observed	[redacted]	[redacted]

	(■,■)	(■,■)
Approach 3 (company base case)	**Exponential**	**Gompertz**
HR before 1 year, modelled	■	■
HR after 1 year, modelled	■	■
Approach 2 (company plausible scenario)	**Exponential**	**Gompertz**
Constant HR, modelled	■	■
Approach 3 (ERG scenario)	**Exponential**	**Gompertz**
HR before 12 weeks, modelled	■	■
HR after 12 weeks, modelled	■	■

The HRs for DF→LR estimated in the base case (Approach 3) of ■ before 1 year and ■ after 1 year match closely (i.e. are within an absolute difference of ±0.05) to the point-estimate of the HR without a cut point reported in the KEYNOTE-564 study of ■, and fall well within its reported 95% confidence intervals of ■ and ■. This consistency of HRs between Approach 3 and the trial-based HRs provides strong evidence of internal validity of the base-case assumptions. Similarly, the HR estimates for DF→DM estimated in the base case (Approach 3) of ■ before 1 year and ■ after 1 year match closely (i.e. within an absolute difference of ±0.05) to the point-estimated of the HR without a cut point reported in the KEYNOTE-564 study of ■. In contrast, the estimated HRs using the ERGs preferred cutoff are not as closely aligned to the trial reported HRs.

As stated in the CS section B.3.3.1, "A comparison of observed DFS from external studies with predicted DFS…supports the base-case selection of Exponential/Gompertz under Approach #2 or #3". Approach 2 was included in scenario analysis because it achieved the second-closest fit with external, longer-term DFS data from the placebo arms of four prior adjuvant therapy trials in RCC. As seen in Table 5, the modelled HRs under Approach 2 were nearly the same as the trial-observed HRs. Furthermore, Approach 2 (Exponential/Gompertz) with matching HRs from KEYNOTE-564 yielded a similar ICER compared to Approach 3 (£12,497 versus £11,031), respectively, which further supports the robustness of base-case assumptions.

b) Please provide a scenario using Approach 3 applying HRs for 0-12 weeks and week 13 onwards. Please provide the estimates of the HRs used for this scenario.

In the scenario requested by the ERG, there are 9 possible parametric models to inform the transitions from DF → LR and DF → DM. The MSE versus observed DFS, modelled DFS, and OS for pembrolizumab and routine surveillance are reported in Table 6 below.

Table 6. Comparison of different parametric models used to estimate DFS and OS, under Approach 3 with 12-week HR cut point

a. Pembrolizumab

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)								Predicted OS (%)							
Under approach 3	*Under all approaches*	DF → LR	DF → DM		1 yrs	3 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	1 yrs	3 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
9	52	Exponential	Exponential	0.0000731	89.1%	70.4%	62.6%	55.5%	43.5%	30.1%	7.7%	1.1%	98.6%	92.0%	87.4%	82.4%	71.7%	56.0%	19.0%	4.2%
7	40	Gompertz	Exponential	0.0000738	88.5%	70.9%	63.9%	57.7%	46.8%	34.2%	10.5%	1.8%	98.6%	91.9%	87.4%	82.5%	71.9%	56.6%	20.4%	4.8%
8	48	Weibull	Exponential	0.0000791	88.9%	70.6%	62.9%	56.1%	44.5%	31.3%	8.6%	1.4%	98.6%	92.0%	87.4%	82.4%	71.8%	56.2%	19.4%	4.4%
6	33	Exponential	Weibull	0.0000957	88.2%	71.1%	64.4%	58.4%	48.3%	36.5%	13.5%	3.0%	98.5%	91.8%	87.6%	83.0%	73.3%	59.4%	24.6%	6.6%
2	3	Exponential	Gompertz	0.0001003	86.7%	72.7%	68.9%	66.0%	61.3%	55.5%	35.6%	13.1%	98.4%	91.6%	87.9%	84.3%	77.6%	69.0%	43.6%	16.7%
4	19	Gompertz	Weibull	0.0001003	87.7%	71.6%	65.8%	60.7%	51.9%	41.5%	18.4%	4.9%	98.5%	91.8%	87.5%	83.0%	73.5%	60.2%	27.0%	8.0%
5	29	Weibull	Weibull	0.0001043	88.0%	71.3%	64.8%	59.0%	49.3%	38.0%	15.1%	3.7%	98.5%	91.8%	87.6%	83.0%	73.4%	59.6%	25.4%	7.1%
1	2	Weibull	Gompertz	0.0001115	86.5%	72.8%	69.3%	66.7%	62.7%	57.8%	40.0%	16.1%	98.4%	91.6%	87.9%	84.3%	77.7%	69.4%	45.5%	18.4%
3	5	Gompertz	Gompertz	0.0001186	86.1%	73.2%	70.4%	68.5%	66.0%	63.0%	48.6%	21.5%	98.4%	91.6%	87.9%	84.3%	78.0%	70.3%	49.7%	21.7%

b. Routine surveillance

Rank by MSE		Parametric functions		MSE vs. observed DFS	Predicted DFS (%)								Predicted OS (%)							
Under approach 3	*Under all approaches*	DF → LR	DF → DM		1 yrs	3 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs	1 yrs	3 yrs	4 yrs	5 yrs	7 yrs	10 yrs	20 yrs	30 yrs
1	9	Gompertz	Gompertz	0.0002780	77.9%	61.7%	58.5%	56.5%	54.1%	51.5%	39.7%	17.6%	97.6%	88.5%	83.7%	79.1%	71.1%	61.9%	41.3%	17.8%
2	14	Weibull	Gompertz	0.0003746	78.6%	61.1%	56.8%	53.6%	49.0%	43.6%	27.4%	10.1%	97.6%	88.6%	83.7%	79.1%	70.7%	60.5%	35.2%	13.1%
3	19	Exponential	Gompertz	0.0004663	79.1%	60.6%	55.8%	52.1%	46.3%	39.4%	20.8%	6.3%	97.6%	88.6%	83.7%	79.0%	70.5%	59.7%	31.9%	10.7%
4	28	Gompertz	Weibull	0.0007150	79.9%	59.8%	53.0%	47.4%	38.3%	28.3%	9.9%	2.2%	97.8%	88.9%	83.3%	77.6%	66.1%	50.7%	18.2%	4.6%
7	45	Gompertz	Exponential	0.0014598	81.8%	58.2%	49.8%	42.6%	31.3%	19.6%	3.7%	0.4%	98.2%	89.2%	83.2%	76.7%	63.6%	45.9%	12.0%	2.2%
5	37	Weibull	Weibull	0.0009653	80.7%	59.2%	51.5%	45.0%	34.7%	24.0%	6.9%	1.2%	97.8%	88.9%	83.3%	77.6%	65.9%	50.1%	16.6%	3.8%
6	40	Exponential	Weibull	0.0011684	81.2%	58.7%	50.5%	43.7%	32.8%	21.7%	5.2%	0.8%	97.8%	88.9%	83.4%	77.5%	65.8%	49.7%	15.7%	3.4%
8	50	Weibull	Exponential	0.0018550	82.5%	57.6%	48.3%	40.4%	28.3%	16.6%	2.5%	0.2%	98.2%	89.2%	83.2%	76.7%	63.5%	45.6%	11.4%	2.0%
9	52	Exponential	Exponential	0.0021904	83.1%	57.2%	47.4%	39.3%	26.8%	15.0%	1.9%	0.1%	98.2%	89.2%	83.2%	76.7%	63.5%	45.5%	11.1%	1.9%

After applying the same selection process of parametric models for transitions from the DF state as in the base case, described in B.3.3.1 in the CS, only the combination of Exponential/Gompertz for DF → LR / DF → DM was considered plausible out of the 9 combinations under Approach 3 with the 12-week HR cut point. Of note, the most plausible model was the same as that which was selected for the company base case (with the 1-year HR cut point). The HRs before and after 12-weeks for Approach 3 (Exponential/Gompertz) are presented in Table 5 above. Overall, the modelled HRs align closely to the trial observed HRs except the HR of DF → DM (before 12 weeks) which lies outside the 95% CI of the trial observed HR.

Changing the Approach 3 cutoff point from 1-year (company base case) to 12-weeks, the ICER increased marginally from £11,031 (based on the corrected model, see Section C) to £13,366, which provides further validation of the base-case approach.

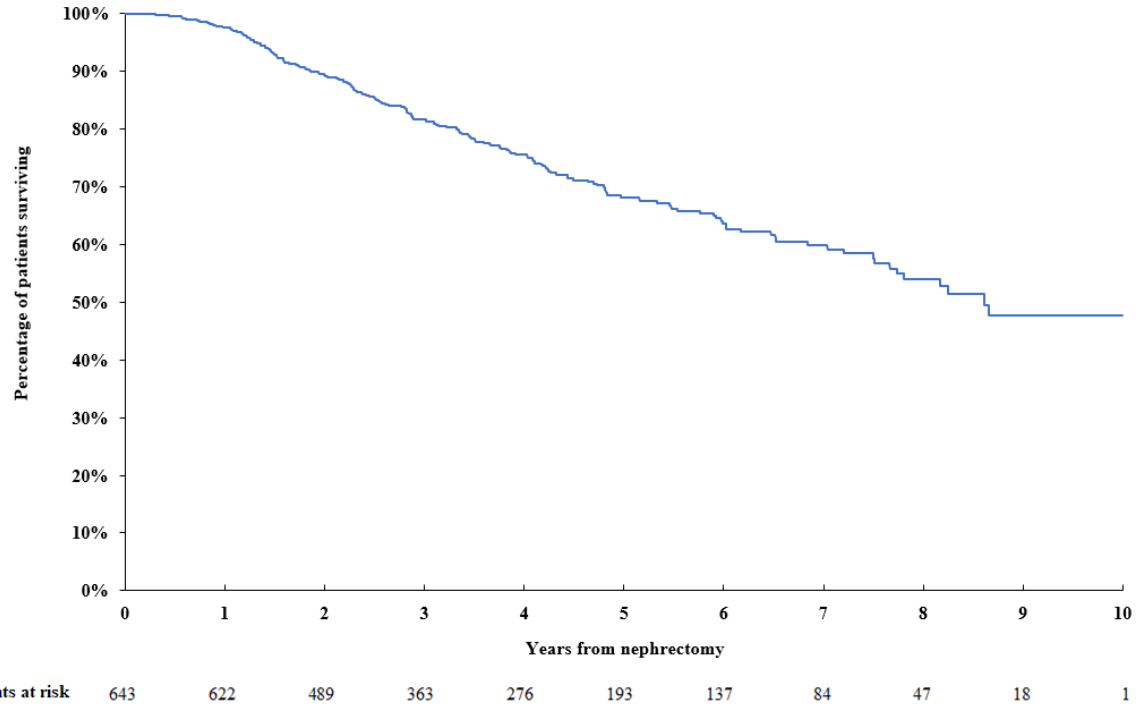
B4. Priority question: The US Surveillance, Epidemiology and End Results (SEER) Medicare database has been used to validate the base case routine surveillance survival estimates in the model.

a) **Using the data used to produce Figure 25 in the CS, please provide a combined overall survival (OS) curve for patients who have had a nephrectomy (i.e. not stratified by recurrence).**

The OS KM curve for the combined population (i.e. not stratified by recurrence) from the SEER Medicare database study is presented in Figure 3 below.

Figure 3. Kaplan-Meier Analysis for overall survival during the study period[1,2] - all patients

Cohort	Total number of patients	Overall survival rate					Censored	Median survival (years)
		1-year	2-year	3-year	4-year	5-year		
All patients (with and without recurrence)	643	98%	89%	82%	76%	68%	462	8.61



Patients at risk	643	622	489	363	276	193	137	84	47	18	1

Notes:

[1] Patients were followed from nephrectomy until the earliest of 1) death, 2) end of Medicare Part A, B, or D eligibility, and 3) end of data availability on December 31, 2016. Follow-up time in months (mean ± SD) was 47.7 ± 27.9.

[2] Survival time was calculated as the time from nephrectomy to the date of death. Patients who did not have a recorded death date after nephrectomy were censored at the last day of follow-up.

The ~10-year observed DFS and OS curves from the SEER-Medicare study cohort have been incorporated in the economic model as additional data for external validation. The "Effectiveness" tab contains updated external validation figures containing KM curves for DFS and OS from the SEER-Medicare study and the original set of external sources (i.e., S-TRAC, PROTECT, ATLAS, and the ccRCC high-risk subset of ASSURE).

Due to the higher starting age of the SEER-Medicare cohort (mean: 75.5 years) relative to patients in KEYNOTE-564 (mean: 58.9 years in the European subset) and in past adjuvant therapy trials, the observed OS curve from SEER-Medicare lies below OS curves of other external studies. To enable a more interpretable comparison of modelled DFS and OS for routine surveillance versus observed SEER-Medicare data,

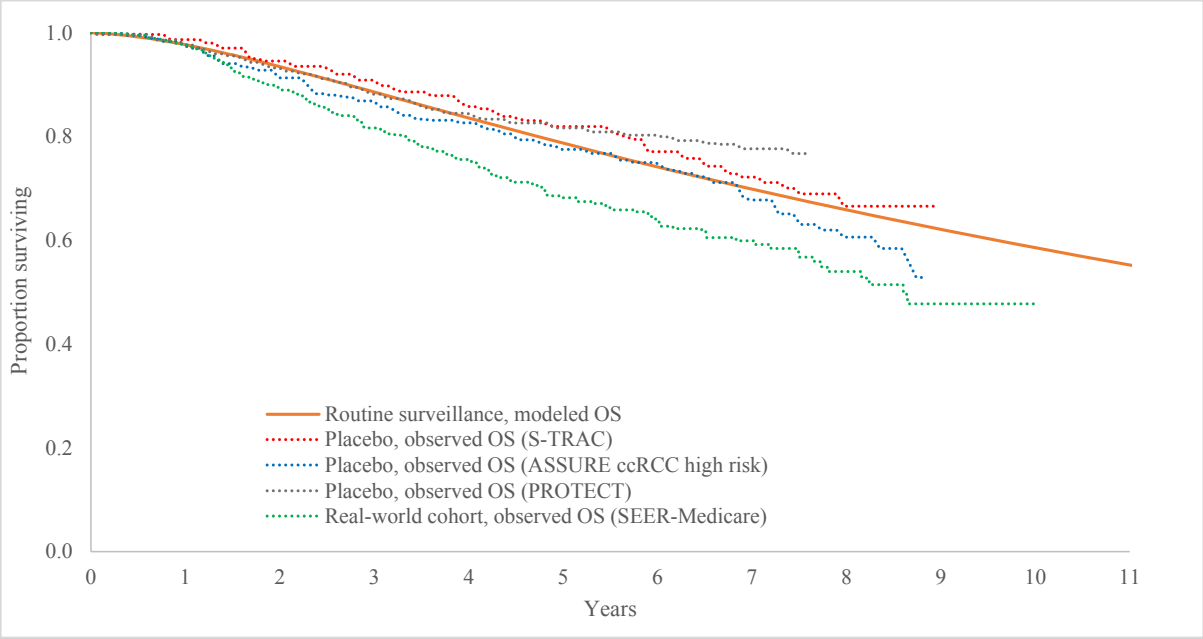
a new dropdown menu has been added to the “Specifications” tab in the economic model:

- “Use mean starting age and percent female from the SEER-Medicare study cohort?” (Yes/No)

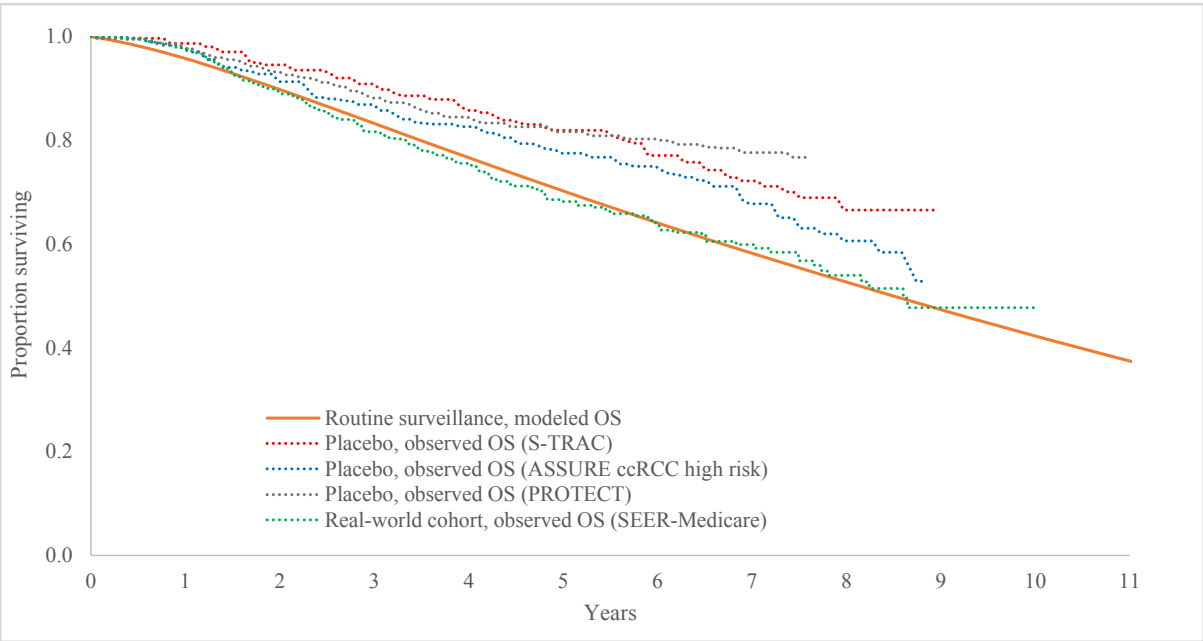
Figure 4 presents the updated OS validation figures before (a) and after (b) changing this dropdown selection from “No” to “Yes”. When using the baseline age and percent female from KEYNOTE-564 (Figure 4 a), modelled OS for routine surveillance based on KEYNOTE-564 is well-aligned with observed OS from prior adjuvant trials. When setting baseline age and percent female in the model’s OS estimates for routine surveillance to those of the SEER-Medicare cohort (Figure 4 b), modelled OS shifts downward, closely aligning with observed OS from SEER-Medicare over a 10-year period. The alignment of modelled OS with real-word data is encouraging and lends further empirical support for the long-term projections of OS under routine surveillance in the economic analysis.

Figure 4. External validations of modelled OS for routine surveillance vs. observed OS in external studies

a. Using starting age and percent female from KEYNOTE-564 (European subset)



b. Using starting age and percent female from the SEER-Medicare study cohort



b) **Please provide an extrapolation of the SEER OS KM data that can be used to validate the OS estimates in the model for routine surveillance. Please provide an explanation of the curve fitting selection process used to determine the final extrapolation model.**

To validate the model's OS extrapolations under routine surveillance, modelled estimates were also compared with extrapolations of the OS curves from SEER-Medicare data. Seven parametric curves (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalized gamma) were fitted using patient-level time-to-event data from the SEER-Medicare cohort (see Figure 5). Given the far older age of the SEER-Medicare cohort, background mortality overtakes the parametric distributions soon after the maximum available follow-up from SEER-Medicare, which limits the extent to which different parametric distributions differ in their tails.

For OS, the log-normal distribution demonstrated the best fit with observed SEER-Medicare data based on lowest AIC/BIC (see Table 7) and was therefore selected as the best option to extrapolate OS for the SEER-Medicare cohort (see Figure 6). Statistical fit was the primary driver of the choice of choice of distribution for SEER-Medicare OS based on the following:

i. The observed OS Kaplan-Meier curves from SEER-Medicare were relatively mature and represented a maximum follow-up of over 10 years.

ii. Because the SEER-Medicare study represented the longest available follow-up of any external study referenced for the present economic model, there was no longer-term data source available to assess the plausibility of extrapolated SEER-Medicare curves.

iii. Given the advanced age of the SEER-Medicare cohort, background mortality overtakes the parametric distributions soon after the available follow-up from SEER-Medicare, which limits the extent to which different parametric distributions differ at the tail.

Figure 5. Visual fit of parametric curves to observed OS from SEER-Medicare data

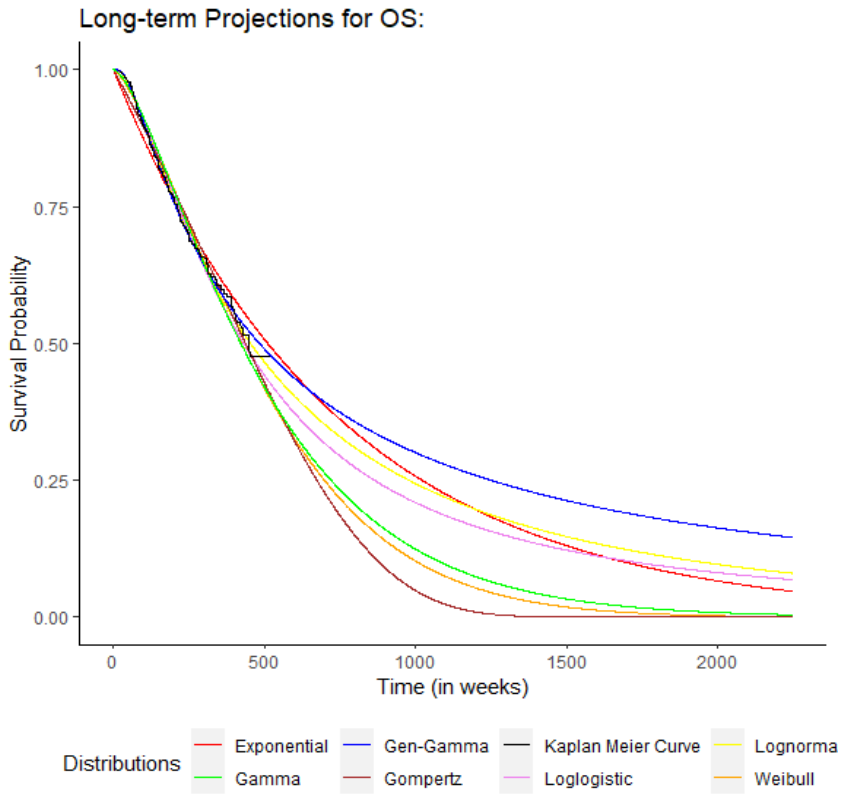
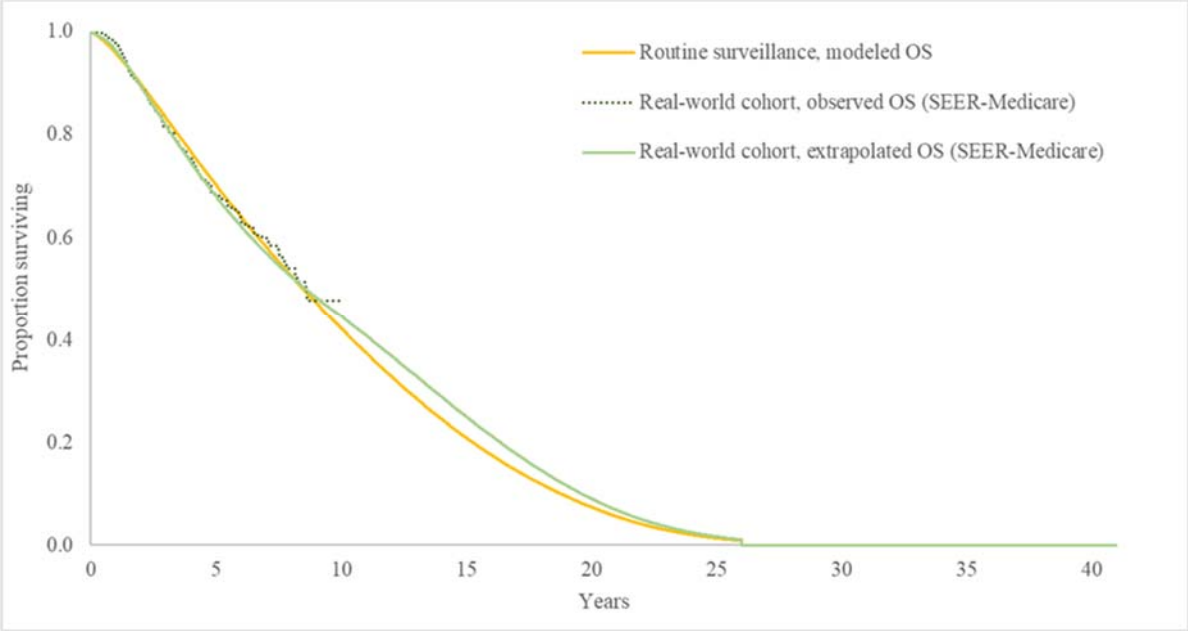


Table 7. Statistical fit of parametric models to observed OS data from SEER database study

Distribution	AIC	BIC
Exponential	2753.9	2758.4
Weibull	2731.9	2740.9
LogNormal	**2716.0**	**2725.0**
Loglogistic	2725.2	2734.1
Gompertz	2747.7	2756.6
Generalized Gamma	2716.3	2729.7
Gamma	2728.0	2736.9

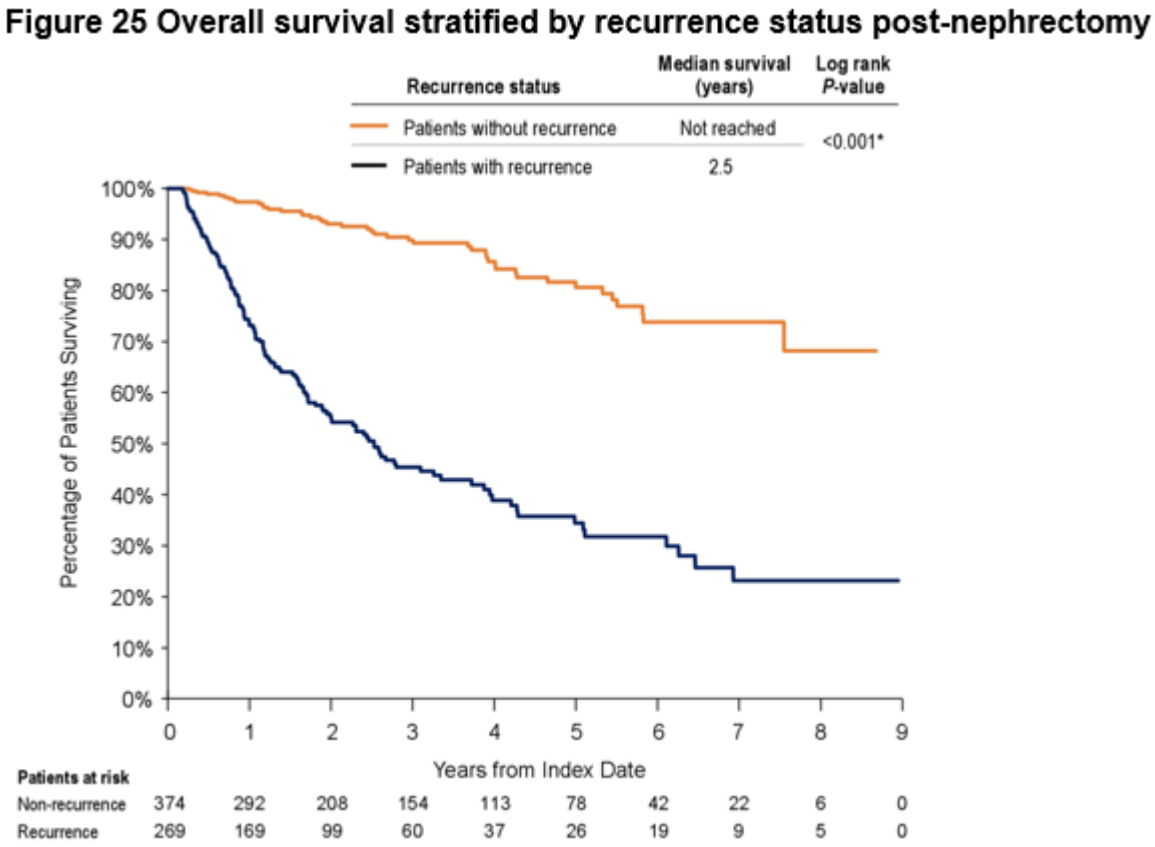
Figure 6. Modelled OS for routine surveillance vs. the best-fitting extrapolation of OS in SEER-Medicare (using starting age and percent female from SEER-Medicare)



c) **In Figure 25, recurrence-free survival for patients with newly diagnosed non-metastatic intermediate-high or high risk RCC who underwent nephrectomy from the SEER database is approximately 90% at 3.5 years. In Table 36, the DFS estimate at 3.5 years for placebo from KEYNOTE-564 is 56.1%. Please explain why DFS is substantially lower for placebo in KEYNOTE-564 compared to real world evidence? The ERG notes that due to the younger and fitter nature of patients in clinical trials, it would be anticipated that better outcomes would be observed in KEYNOTE-564 than from real world evidence**

Question B4.c appears to be the result of confusion regarding Figure 25 from the CS, which reports OS, not DFS, for two cohorts of patients included in the SEER database study, stratified by history of prior disease recurrence during the follow-up of the database study. The comparison described in the question above therefore compares DFS in the placebo arm at 3.5 years to OS of patients included in the SEER study at 3.5 years.

Figure 7. Screenshot of Figure 25 from original CS



As per a follow-up request from the ERG to "produce an RFS curve, as death and progression would be censoring events and compare that to their KEYNOTE data and estimates of RFS in the model", an RFS curve was estimated based on data collected in the SEER database, using the same definition of DFS as in KEYNOTE-564.

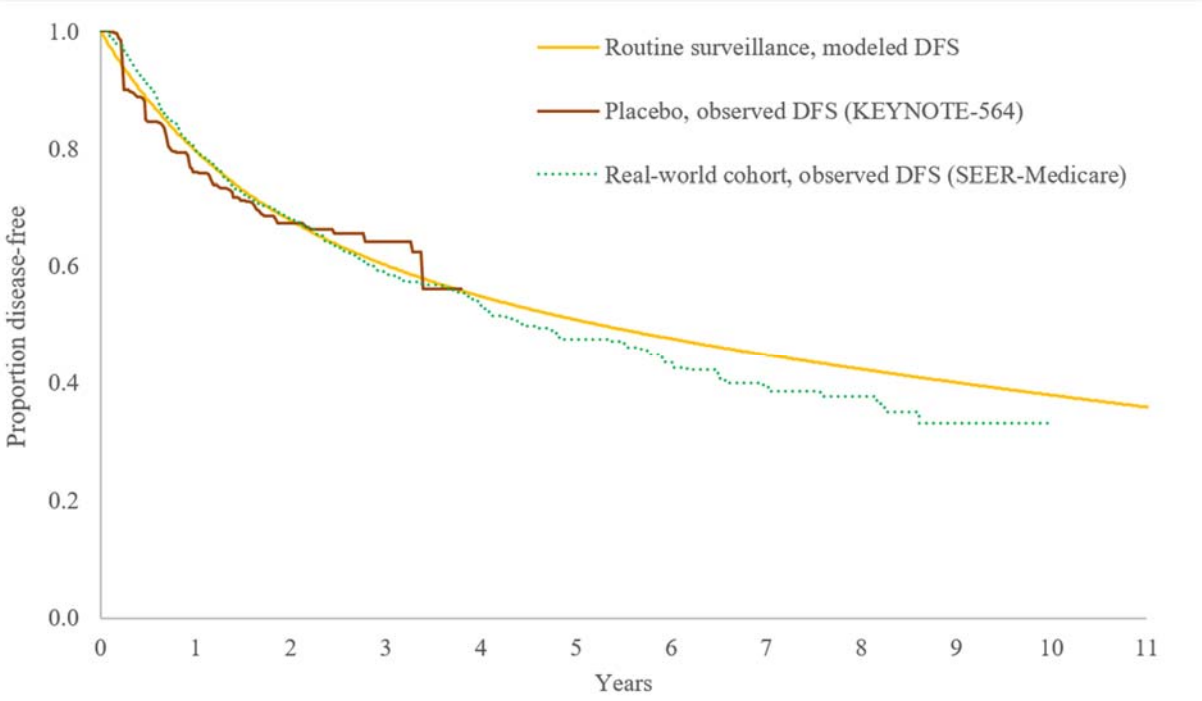
A comparison of the DFS estimates from years 1 to 5 for the modelled routine surveillance arm based on KEYNOTE-564 data with DFS from the observed SEER database study is reported below in Table 8. DFS rates by year show remarkable consistency across the two data sources up to 5 years.

Table 8. Comparison of KEYNOTE-564 modelled DFS and DFS observed in SEER database study

DFS by year	1	2	3	4	5
Modelled, placebo - Approach #3 Exponential/Gompertz	80%	68%	60%	55%	51%
SEER database study reported DFS	80%	68%	59%	53%	48%

Modelled DFS based on the placebo arm in KEYNOTE-564 compared with the observed DFS data from both KEYNOTE-564 and the SEER database study is presented in Figure 8. The modelled DFS for routine surveillance based on trial data strongly correlates with the observed DFS curve from the SEER cohort study, further validating the base-case modelling assumptions around DFS.

Figure 8. Modelled DFS curve for routine surveillance validated against observed DFS from the SEER database study

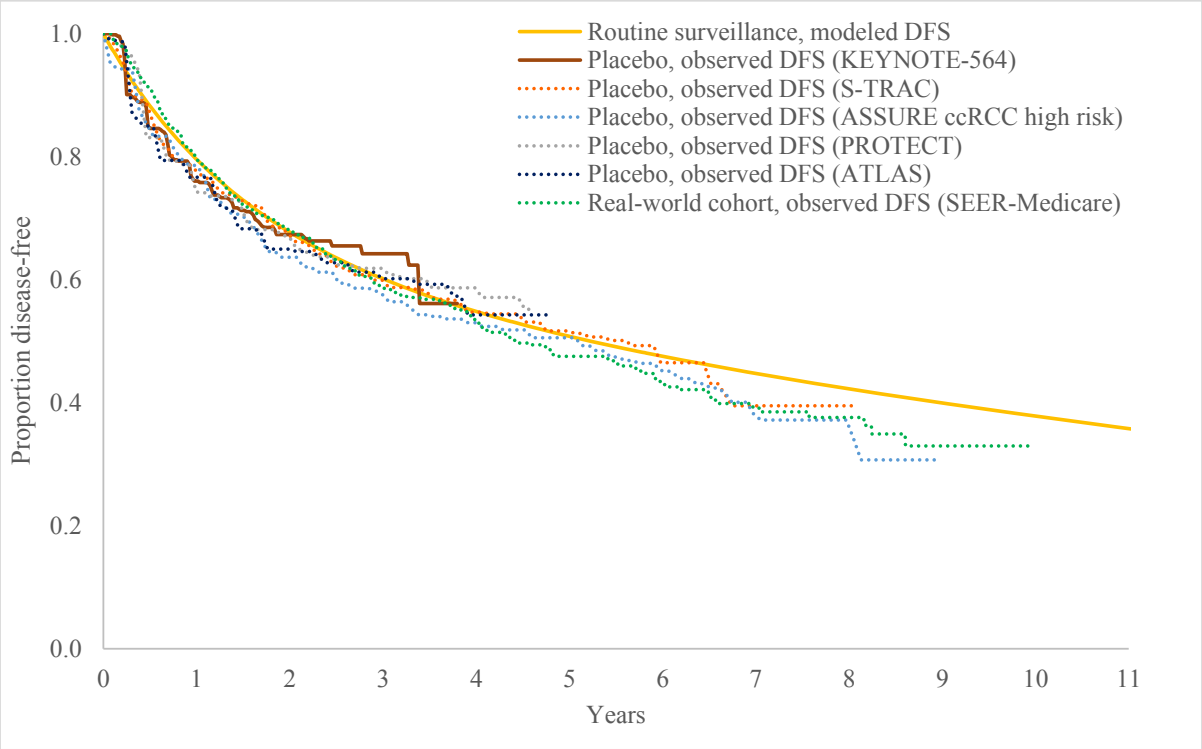


The modelled DFS curve based on data from the placebo arm in KEYNOTE-564 is further compared with other external sources presented in Figure 9, allowing for adjustment of baseline age and percent female to align between the trial and the SEER study populations. Modelled DFS was less sensitive than OS to adjustment of baseline

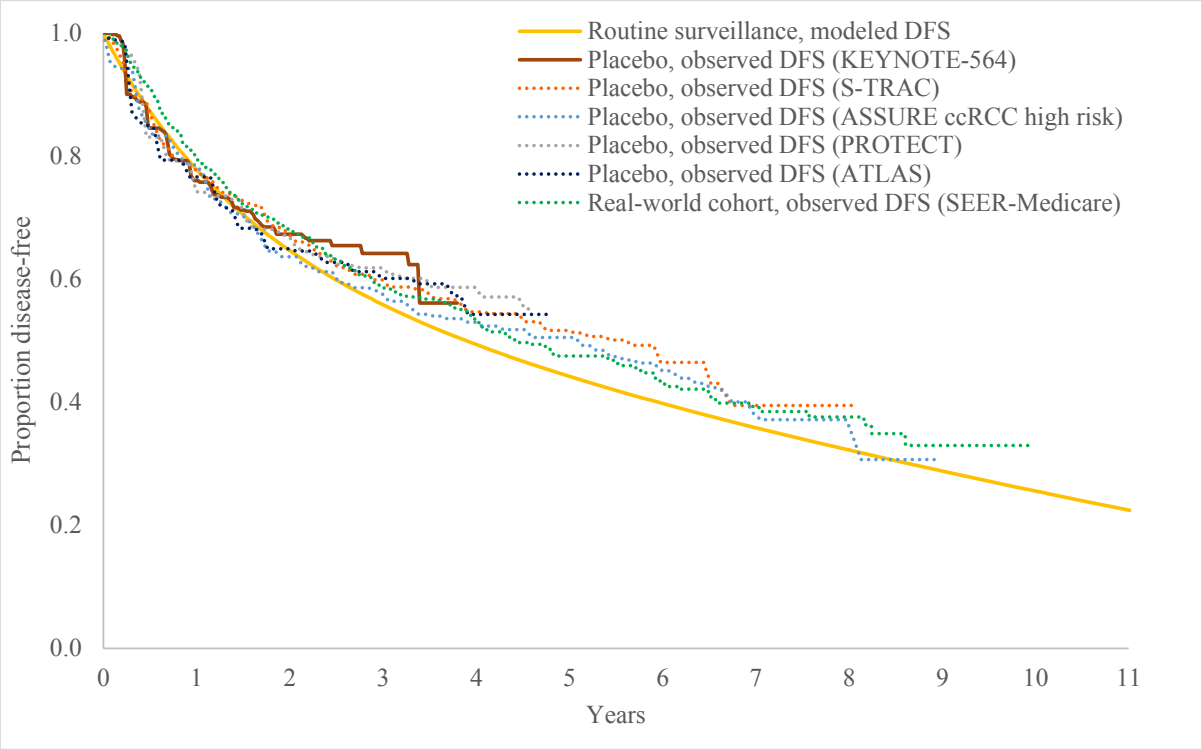
age and percent female (see Company response to question B4.b), which is expected given that the DF → distant metastases transition constitutes the majority of DFS failure events and may not have a strong relationship with age. DFS predictions for routine surveillance aligned well with observed DFS curves from SEER-Medicare and other external studies under both dropdown settings. When using the baseline age and percent female from KEYNOTE-564, modelled DFS for routine surveillance was well-aligned with observed DFS from prior adjuvant trials and the SEER-Medicare study. These results are encouraging and lend further empirical support for the model's long-term projections of DFS under routine surveillance. Of note, when using baseline age and percent female from the SEER-Medicare cohort, modelled DFS for routine surveillance is slightly below the observed DFS from SEER-Medicare over a 10-year period, which suggests some heterogeneity between the real-world retrospective study and the KEYNOTE-564 trial which could impact on DFS.

Figure 9. External validations of modelled DFS for routine surveillance vs. observed DFS in external studies

a. Using starting age and percent female from KEYNOTE-564 (European subset)



b. Using starting age and percent female from the SEER-Medicare study cohort



i) Please extrapolate the recurrence-free survival curve in Figure 25 of CS and compare long-term estimates with long-term DFS estimates used in the economic model.

For the extrapolation of DFS data observed in SEER-Medicare data, the same approach was taken as for the extrapolation of OS.

When extrapolating DFS from the SEER-Medicare data, the risks of DFS failure and death in each cycle (as estimated from the parametric distributions of DFS and OS) was constrained to be at least as high as background mortality in that cycle. The risk of DFS failure in each cycle was further constrained to be at least as high as the risk of death in each cycle.

Consistent with the extrapolation of OS, the log-normal distribution was found to be the most plausible model, due to its lowest BIC and second-lowest AIC (see Table 9) and close visual fit to the observed data (see Figure 10).

Figure 11 presents the modelled DFS for routine surveillance against the log-normal extrapolation of SEER-Medicare data. For this analysis, mean baseline age and percent female of the modelled cohort were based on the characteristics of the SEER-

Medicare study cohort at baseline. As shown in the overlayed DFS curves, modelled DFS for routine surveillance follows a similar trend as the extrapolated DFS curve based on SEER-Medicare data, with a small gap between the two curves most likely due to heterogeneity between the study populations.

(These figures are also available in the "Raw - External KM curves" tab of the Excel® model around column DX.)

Figure 10. Long-term DFS projections based on extrapolation of SEER KM data

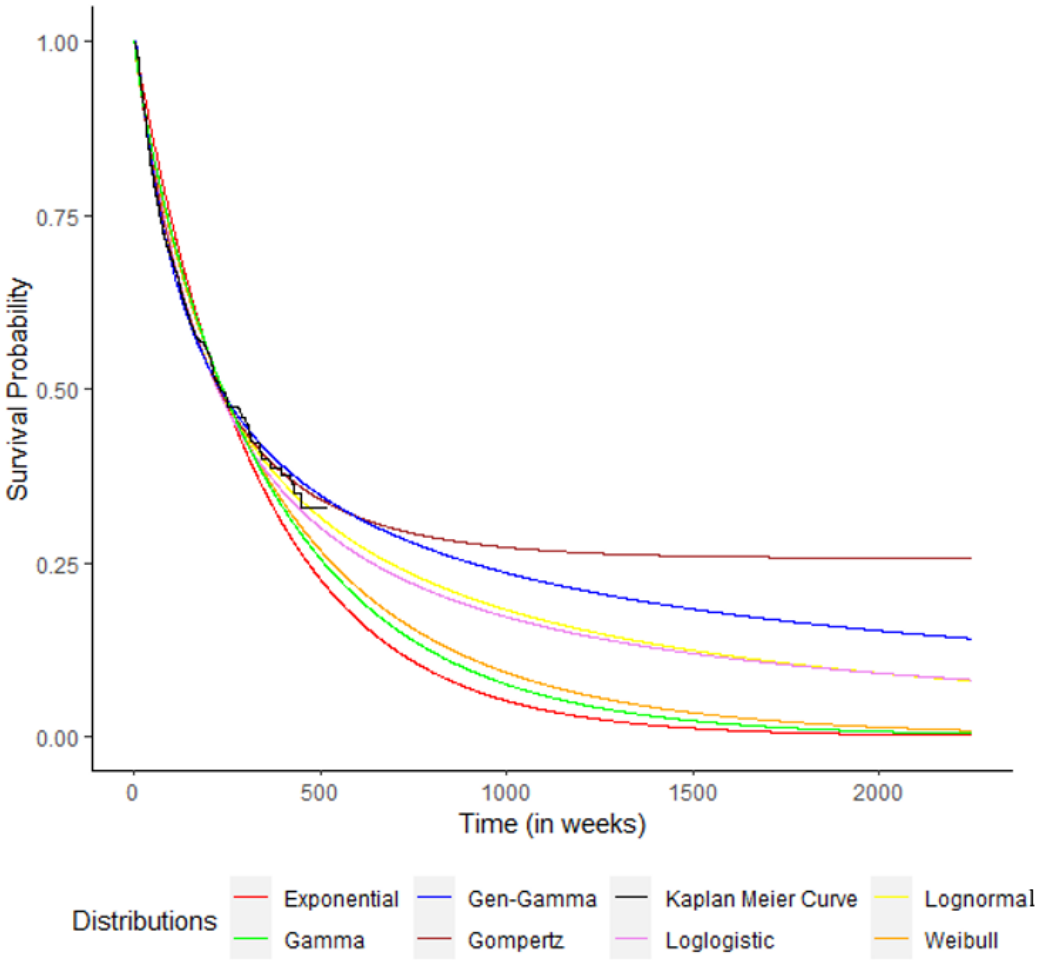
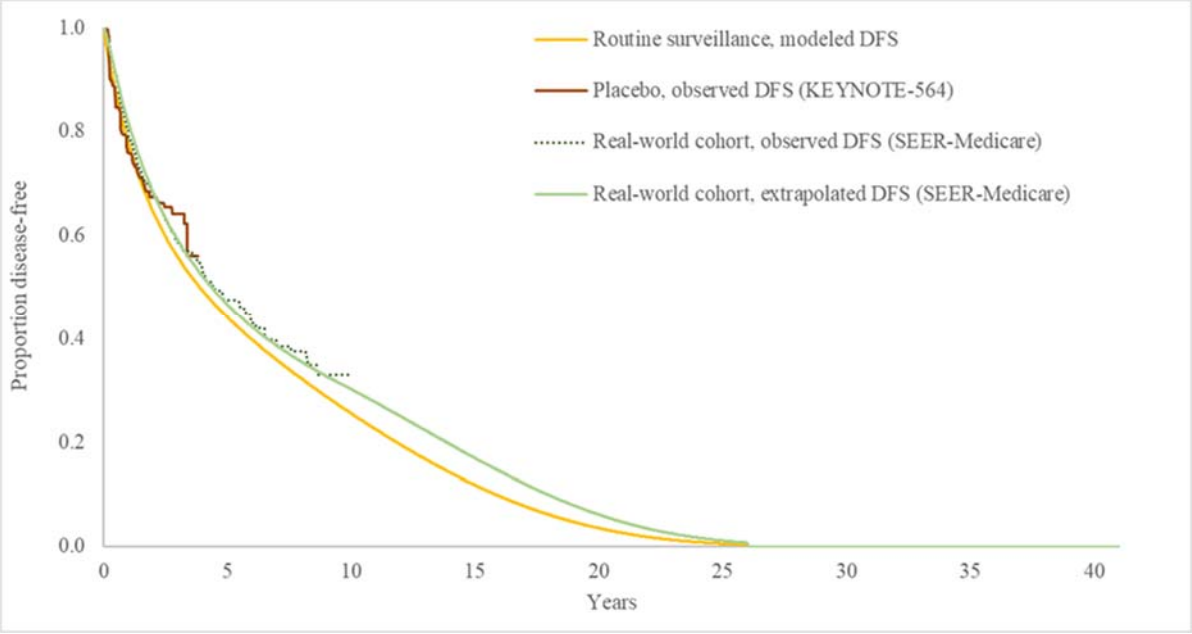


Table 9. Statistical fit of parametric models to observed DFS data from SEER database study

Distribution	AIC	BIC
Exponential	4269.7	4274.1
Weibull	4261.0	4270.0
LogNormal	4228.2	**4237.1**
Loglogistic	4243.3	4252.3
Gompertz	4244.4	4253.3

Distribution	AIC	BIC
Generalized Gamma	**4224.9**	4238.3
Gamma	4264.9	4273.8

Figure 11. Modelled DFS for routine surveillance vs. the best-fitting extrapolations of DFS in SEER-Medicare (using starting age and percent female from SEER-Medicare)



B5. Priority question: The ERG notes that the transition probability per cycle from DF to death and LR to death for both adjuvant pembrolizumab and routine surveillance uses general population mortality estimates from the start of the time horizon of the model, as these estimates are always greater than the single transition probability derived from KEYNOTE-564 (based on the exponential model), suggesting long-term remission.

a) **Please clarify why an exponential model was selected for the parametric modelling of OS for disease-free patients.**

To model OS from the disease-free state, the one-parameter exponential distribution was used as this was the most likely model to converge and produce stable extrapolations when fitted to a transition with very few uncensored events.

Parametric models with multiple parameters may have produced convergent curves, however, even if a distribution converges there is still a high risk of overfitting when

the number of parameters is too large relative to the number of uncensored events in a survival analysis.

b) Please explore a scenario where OS data for disease-free patients from the SEER database (defined in the CS as patients with newly diagnosed non-metastatic intermediate-high or high risk RCC who underwent nephrectomy) are used to inform the DF to death and LR to death transitions for both adjuvant pembrolizumab and routine surveillance (given these are currently the same in the company model). The response to B4 (b) can be used to inform the scenario.

Please see response part (i) below where the alternative scenario has been explored.

The OS curve from the SEER study cohort reflects all transitions to death, regardless of whether death occurred before or after distant metastases. Because most of these deaths would have occurred directly from the DM state, the OS curve derived from SEER would not provide a suitable approximation of transition probabilities directly from DF or LR to death.

i) An alternative to this scenario would be to explore applying a range of increasing standardised mortality ratios to general population mortality estimates (background mortality) to test how sensitive the results are to changes in the DF/ LR to death transitions.

To explore the sensitivity of results to changes in the transition probabilities for DF/LR to death, a user-modifiable standardised mortality ratio (SMR) has been implemented via the “Life Tables” worksheet in the economic model. (The default value has been set to 1, which aligns with the submitted base case.) As expected, the ICER increases in response to increases in this parameter, as higher mortality within the non-metastatic disease states (particularly within the DF state) reduces the future health benefit of preventing/delaying disease recurrences (see Table 10 below). Starting from 1.0, increasing increments of 0.1 in the SMR lead to an increase in the ICER of just under £500. However, an SMR close to or equal 1 is a plausible assumption for the base-case analysis, based on the expectation that most, if not all, disease-related deaths in the target population occur directly from the DM state. The finding that

background mortality exceeds the DF → death transition probabilities estimated from KEYNOTE-564 data provides empirical support for an SMR of 1.

Table 10. Cost-effectiveness results for scenario exploring a standardised mortality ratio (using corrected model):

a. standardised mortality ratio of 1.1

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.39	11,514

b. standardised mortality ratio of 1.2

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.35	11,996

c. standardised mortality ratio of 1.3

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.30	12,477

B6. Priority question: The difference in disease-free survival between routine surveillance and adjuvant pembrolizumab provides an indication of the proportion of patients in which surgery with curative intent was not successful and adjuvant treatment has been beneficial. As such, for these disease-free patients, the treatment effect of adjuvant pembrolizumab may wane over time (i.e. the risk of recurrence in the DF health state for adjuvant pembrolizumab may decline over time to match routine surveillance). Please provide a range of scenarios that test the impact on the ICER if the treatment effect of adjuvant pembrolizumab wanes over time and patients revert to the disease trajectory

of patients on routine surveillance (convergence of DFS curves). As observed data are only available for 3.5 years, please consider time points from year 4 onwards (that is, 3 years after stopping treatment at 1 year). The ERG acknowledges that an unknown and currently unknowable proportion may achieve long-term remission and so the early convergence of DFS curves is very likely to be a conservative estimate

The rationale underlying question B6 relies on the assumption that the benefit in terms of risk of recurrence for adjuvant pembrolizumab may decline over time to match routine surveillance, in patients for whom surgery with curative intent was not successful (i.e. curative) starting 4 years post-nephrectomy.

Clinical advisors in a recent committee meeting for the adjuvant treatment of melanoma with pembrolizumab stated, “The aim of adjuvant treatment is to remove any residual microscopic disease after resection to reduce the risk of relapse and progression to metastatic disease …” In the Final Appraisal Document (FAD), the appraisal committee recognised the value of adjuvant therapy in this setting as described by clinical experts in removing microscopic disease and delaying disease recurrence in the long term (16).

Similarly in the RCC setting, the efficacy of adjuvant pembrolizumab is based on its ability to eradicate residual microscopic disease and the available evidence shows early divergence of the DFS curves at 12 weeks, highlighting the benefit of reduced microscopic disease. This benefit appears sustained up to 40 months in KEYNOTE-564 as illustrated by the continued separation of the DFS curves at the end of follow-up.

The implication of the waning assumption would be that at some unspecified time beyond the maximum follow-up in KEYNOTE-564, patients who have not yet experienced disease recurrence many years after receiving adjuvant treatment with pembrolizumab would no longer benefit from the additional protection from disease recurrence that pembrolizumab provides in patients whose surgery was not curative. However, across tumour types in the adjuvant setting, the duration of treatment effect is often discussed in the context of the proportion of patients who may be considered cured after a specific time point many years following treatment initiation. This discussion of cure potential recognises a more favourable prognosis for patients who

remain disease free after relatively long durations of follow-up, rather than assuming these patients begin to face an increased risk of disease recurrence at some future time point following many years with no recurrence event. In the company base case, the analysis conservatively excludes an assumption of cure where patients would no longer face any risk of disease recurrence beyond a specified time point even though this might be plausible. Therefore, waning of treatment effect would skew the analysis even more conservatively, without a clear clinical rationale for doing so.

Whilst there is limited external data in the adjuvant treatment of RCC, in the S-TRAC trial of adjuvant sunitinib versus routine surveillance described in the CS (section B.3.3.1), no evidence of a decrease in the treatment effect on DFS was observed up to 7-years, as evidenced by the continued separation of the DFS curves. This data lends support to a durable treatment effect in patients remaining disease free many years following partial nephrectomy.

As described in detail in the CS, the extensive evidence of the durability of the treatment effect observed with pembrolizumab both in the metastatic and adjuvant settings with follow-up up to 7-years provides further evidence of a continued treatment effect. Considering the totality of the evidence, it would appear unlikely that patients treated with adjuvant pembrolizumab following partial nephrectomy would begin to follow the disease trajectory of patients having received no active therapy and therefore forego the benefits resulting from the removal of microscopic disease.

Given that the available evidence in the adjuvant treatment of RCC does not provide support for an assumption of long-term treatment effect waning and the absence of a biological rationale, the assumption of treatment effect waning has not been included within the updated economic model nor explored in any scenario analysis.

B7. Please clarify why an age restriction of ≥66 years was applied to the SEER data to estimate LR to DM transitions?

The US Medicare scheme is a federal health insurance program available for adults over the age of 65 years. Therefore, based on the eligibility of the Medicare scheme, the inclusion criteria set for the study was patients 66 years or older.

Health-related quality of life

B8. Priority question: Please provide more detail regarding the specification of the two linear mixed effects regression analyses conducted on KEYNOTE-564 and KEYNOTE-426 EQ-5D-5L data to estimate; the AE-related disutility, the disease-free, locoregional recurrence, and distant metastases health states utility values.

The KEYNOTE-564-based utility/disutility values in the base case were derived from the following two regression models of utility, both of which incorporated patient-level random effects to account for correlation between repeated measurements for the same individual:

1. To estimate the utility for DF (without toxicity) and disutility related to grade 3+ AEs, the first regression specification was fitted specifically to patient-visits with a utility measurement that occurred during each patient's disease-free period (N=972 patients, with 4,795 unique patient-visits). Independent variables included binary indicators for: the absence of any AE during the patient-visit; and the presence of any other-grade (i.e., grade less than 3) AE during the patient-visit. Using the regression output provided below, the DF (without toxicity) utility value was calculated as the sum of the intercept and the coefficient for absence of AEs (i.e., 0.8034 + 0.06417 = 0.86757). The disutility of grade 3+ AEs equalled the intercept minus the DF (without toxicity) utility (i.e., -0.06417).

Table 11. Regression specification #1 (utility records in the DF state only)

Independent variable	Coefficient	SE	p-value
Intercept	[redacted]	[redacted]	[redacted]
Presence of other-grade AE	[redacted]	[redacted]	[redacted]
Absence of any AE	[redacted]	[redacted]	[redacted]

2. To estimate the utility for LR and utility for DM, a second regression specification was fitted using all patient-visits with a utility measurement (N=977 patients, with 5,070 unique patient-visits). Independent variables included binary indicators for: being in the locoregional recurrence state during the patient-visit; and being in the distant metastases state during the patient-visit. In contrast to the first specification,

this specification did not adjust for the presence/absence of AEs; the rationale was to obtain LR and DM utility estimates that incorporated any AE-related disutility associated with subsequent treatments, as the cost-effectiveness model does not separately apply AE-related disutility due to subsequent treatments within the LR and DM states. Using the regression output provided below, the LR utility value was calculated as the sum of the intercept and the coefficient for being in the LR state (i.e., 0.8489 - 0.00994 = 0.83896). The DM utility equalled the sum of the intercept and the coefficient for being in the DM state (i.e., 0.8489 - 0.05091 = 0.79799). (Of note, the base case used DM utility values from the KEYNOTE-426 trial conducted in the first-line advanced RCC setting, while the KEYNOTE-564-based DM utility value of 0.79799 was considered in a scenario analysis.)

Table 12. Regression specification #2 (utility records in any health state)

Independent variable	Coefficient	SE	p-value
Intercept	[redacted]	[redacted]	[redacted]
Locoregional recurrence	[redacted]	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]	[redacted]

The raw outputs from both regression models are provided as screenshots in the “Raw - Utilities” tab of the Excel® model.

B9. Priority question: Adverse event utility decrements applied in the model were estimated based on a regression analysis of KEYNOTE-564 EQ-5D-5L data. These data appear not to have been mapped to EQ-5D-3L before

inclusion in the model per the NICE position statement on the use of the EQ-5D-3L value set for England.

a) **Please clarify whether the AE utility decrement applied in the model is an EQ-5D-5L decrement or an EQ-5D-3L decrement.**
b) **If the former is true, please update the regression analysis utilising EQ-5D-3L data mapped from the trial EQ-5D-5L measurements using the van Hout *et al.* 2012 (1) algorithm with UK value set.**

Based on methodological guidance from NICE, patient responses to the EQ-5D-5L were scored using the crosswalk onto the UK EQ-5D-3L value set through the algorithm developed by van Hout et al. (2012).

The utility value for the DF health state was estimated from a regression model that used the mapped EQ-5D-3L dataset and incorporated an independent variable for the presence/absence of grade 3+ AE(s) at each patient-visit. The same model was run twice, once in the presence of grade 3+ AE(s) and one in the absence of grade 3+ AE(s), the difference in the utility values between the two regression models was used to inform the utility decrement due to AEs, which in turn, reflected the EQ-5D-3L.

Resource use and costs

B10. Priority question: As a proportion of patients on adjuvant pembrolizumab have been treated beyond 12 months and this is likely to happen in the NHS please provide a scenario where either:

- **The time on treatment curve is not truncated; or**
- **RDI is 100%**

A scenario that allows for adjuvant treatment beyond 1 year has not been implemented. A more detailed explanation for the model's apparent truncation of the observed time on treatment (ToT) curve beyond 12 months is provided as follows: In KEYNOTE-564, patients were permitted to complete all 17 doses of adjuvant treatment beyond the 1-year mark if there had been earlier delays in treatment. Consequently, the non-zero portion of the ToT curve beyond 1 year (represented by a dashed line in the "Tx Duration" tab) is due to the receipt of delayed dosages (up to

the maximum of 17 dosages), rather than the receipt of extra dosages beyond the 17th dose. In the model, the cost of each adjuvant pembrolizumab dosage is applied based on a fixed interval of once every 3 weeks, with the last dose occurring at time t = 48 weeks. Based on this setup, increasing the maximum ToT above the default value (51 weeks) will result in the application of more than 17 doses for some patients, which is inconsistent with the observed dosages received by patients in KEYNOTE-564.

In the CS, a scenario analysis exploring the impact of relative dose intensities (RDI) to 100% was originally conducted. The scenario exploring 100% RDI was presented in Table 32 (scenario 13) of the CS and led to a £641 reduction in the ICER.

B11. Please provide a scenario using the alternative dosing regimen of 400 mg Q6W for adjuvant pembrolizumab.

Patients being treated with pembrolizumab will have the benefit of having the option of administration every 6 weeks, as an alternative to administration every 3 weeks that is used in the KEYNOTE-564 study. This can be especially advantageous for patients who live in more remote areas for face difficulties in routinely travelling to the clinic to receive treatment. Consequently, patients who would otherwise choose not to undergo active adjuvant treatment every 3 weeks due to logistical difficulties may be willing to accept to undergo treatment with pembrolizumab every 6 weeks, increasing the number of patients who receive effective therapy.

The cost-savings in total administration costs across the 17 cycles of the Q3W regimen per the KEYNOTE-564 trial protocol and expected use in UK clinical practice versus an equivalent treatment duration using the 400 mg Q6W regimen is estimated at £2,396.88 assuming an equivalent total dose between the two regimens.

[redacted] 13 [redacted] Taking the above into account, the choice of Q6W versus Q3W dosing is not expected to have a significant impact on costs and may well produce cost savings.

Table 13. Costs associated with Q6W vs Q3W dosing

	Q6W regimen			Q3W regimen		
Week	**Dose per cycle**	**Drug Acquisition Cost**	**Drug Administration Cost**	**Dose per cycle**	**Drug Acquisition Cost**	**Drug Administration Cost**
0	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
9		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
15		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
21		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
27		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
33		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
39		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
42	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
48	400mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total		[redacted]			[redacted]	

B12. Priority question: Please provide a scenario which assumes no vial-sharing (drug wastage).

The posology of all treatments of aRCC included in the base-case analysis are flat dosed in nature and not dependent on body weight/surface area. Furthermore, the prescribed doses all correspond to the formulation strengths provided by the drug manufacturers. As such, the exclusion of vial sharing has no impact on the base-case results.

In the scenario analysis exploring the inclusion of nivolumab/ipilimumab in the 1L aRCC setting, the dosing of nivolumab and ipilimumab are weight-based, with doses of 3mg/kg and 1mg/kg, respectively, every three weeks for 4 cycles. Scenario 7 (inclusion of nivolumab/ ipilimumab in as a 1L aRCC treatment) from the CS is reproduced Table 14 below and accounts for vial sharing. A scenario that excludes vial sharing when nivolumab/ipilimumab is included as an available 1L a RCC

treatment is presented in Table 14 below. The results from this scenario analysis show a minor impact on the ICER when vial sharing is not considered.

Table 14. Scenario testing vial sharing for nivolumab in combination with ipilimumab (vial sharing included) – corrected model results

Scenario	Total Costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	£14,699	1.40	£10,481

B13. An oral drug delivery cost (£226.45) has been applied in the model for sunitinib, tivozanib, pazopanib, cabozantinib, axitinib, and everolimus. The ERG's clinical expert advised that oral medications would be dispensed for patients to self-administer at home rather than in a monitored hospital setting. As such, please provide a scenario analysis where oral drug administration costs are zero.

The results of a scenario exploring zero costs for all oral therapies included in the economic analysis is reported below in Table 15 and show a small increase of the new base-case ICER from £11,031 to £11,680.

Table 15. Scenario excluding administration costs for all oral therapies – corrected model results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.44	11,680

B14. Priority question: In the CS, the proportion of patients with locoregional recurrence who had salvage surgery is 22%, based on pooled KEYNOTE-564 data. However, the ERG's clinical expert advised that in the NHS, the majority of patients with locoregional recurrence would receive salvage surgery.

Furthermore, the ERG's clinical expert advised that the estimate of 21% of patients receiving salvage surgery in the distant metastases state was likely an overestimate with the true proportion being closer to 10%.

a) **Please provide the proportion of KEYNOTE-564 European cohort who received salvage therapy in the locoregional recurrence and distant metastases health states.**

Disease-free status (primary censoring rule) based on investigator assessment by subsequent surgery status for the EU participants enrolled in KEYNOTE-564 is reported in Table 16 below.

Table 16. Subsequent surgery status by disease-free status (primary censoring rule) based on investigator assessment

Disease-free Status and Subsequent Surgery Status	Study: KEYNOTE-564	
	Pembrolizumab N[a]=188	Placebo N[a]=187
Disease-free Status for Participants Who Had Subsequent Surgery, n (%)		
Locoregional recurrence	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]
Disease-free Status for Participants Who Had No Subsequent Surgery, n (%)		
Disease-free	[redacted]	[redacted]
Death	[redacted]	[redacted]
Locoregional recurrence	[redacted]	[redacted]
Distant metastases	[redacted]	[redacted]
a: Number of participants: intention-to-treat population Database Cutoff Date: 14JUN2021		

b) **Please clarify what subsequent treatments were given to patients in KEYNOTE-564 for those who progressed from disease free to locoregional recurrence and to distant metastasis, split by study treatment arms.**

The distributions of subsequent therapies for the locoregional health state from the KEYNOTE-564 trial are reported in Table 17 and Table 18 and the distributions of subsequent therapies for the distant metastases from the KEYNOTE-564 trial are reported in Table 19 and Table 20.

Table 17. Summary of subsequent oncologic therapies in patients with locoregional recurrence based on investigator assessment (all-participants-as-treated population)

Category	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]					
Participants who had any subsequent anti-cancer therapy for RCC	[redacted]					
Subsequent drug therapy	[redacted]					
Subsequent radiation	[redacted]					
Subsequent surgery	[redacted]					
Participants could have multiple subsequent oncologic therapies. Database Cutoff Date: 14JUN2021						

Table 18. Summary and duration of subsequent systemic oncologic therapies in patients with locoregional recurrence based on investigator assessment (all-participants-as-treated population)

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
Participants with one or more subsequent systemic oncologic therapy	[redacted]					
avelumab + axitinib	[redacted]					

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bempegaldesleukin + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bempegaldesleukin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
epacadostat + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
epacadostat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pan TIE2/VEGFR2 kinase inhibitor (unspecified)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pan TIE2/VEGFR2 kinase inhibitor (unspecified)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sunitinib malate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sunitinib malate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=17)		Placebo (N=32)		Total (N=49)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)

N = all-participants-as-treated population, participants with locoregional recurrence for disease-free status (primary censoring rule) based on investigator assessment.
† Every participant is counted a single time for each applicable row and column.
†† Percentages are computed using the number of participants with one or more subsequent systemic oncologic therapy as the denominator.
Database Cutoff Date: 14JUN2021

Table 19. Summary of subsequent oncologic therapies in patients with locoregional recurrence based on investigator assessment (all-participants-as-treated population)

Category	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]					
Participants who had any subsequent anti-cancer therapy for RCC	[redacted]					
Subsequent drug therapy	[redacted]					
Subsequent radiation	[redacted]					
Subsequent surgery	[redacted]					
Participants could have multiple subsequent oncologic therapies. Database Cutoff Date: 14JUN2021						

Table 20. Summary and duration of subsequent systemic oncologic therapies in patients with distant metastases based on investigator assessment (all-participants-as-treated population)

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
Participants with one or more subsequent systemic oncologic therapy	[redacted]					
avelumab + axitinib	[redacted]					

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
avelumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
axitinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
axitinib	[redacted]					
pembrolizumab	[redacted]					
belzutifan	[redacted]					
belzutifan	[redacted]					
bempegaldesleukin + nivolumab	[redacted]					
bempegaldesleukin	[redacted]					

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab + interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab + pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
bevacizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib + ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
durvalumab + guadecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
durvalumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
guadecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
everolimus + lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
favezelimab + lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
favezelimab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
interferon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
investigational drug (unspecified) + ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
investigational drug (unspecified)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
ipilimumab	[redacted]					
nivolumab	[redacted]					
investigational drug (unspecified) + nivolumab	[redacted]					
investigational drug (unspecified)	[redacted]					
nivolumab	[redacted]					
ipilimumab	[redacted]					

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab + nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab + nivolumab + zoledronic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ipilimumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
zoledronic acid	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lenvatinib + pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
lenvatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
medroxyprogesterone acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
medroxyprogesterone acetate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pazopanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
sorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
sorafenib	[redacted]					
sunitinib malate	[redacted]					
sunitinib malate	[redacted]					
temsirolimus	[redacted]					
temsirolimus	[redacted]					
tivozanib	[redacted]					

Therapy	Pembrolizumab (N=91)		Placebo (N=134)		Total (N=225)	
	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)	n† (%)††	Mean (SE)
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
tivozanib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

N = all-participants-as-treated population, participants with distant metastases for disease-free status (primary censoring rule) based on investigator assessment.
† Every participant is counted a single time for each applicable row and column.
†† Percentages are computed using the number of participants with one or more subsequent systemic oncologic therapy as the denominator.
Database Cutoff Date: 14JUN2021

i) **In particular, for those patients with a locoregional recurrence who did not have salvage surgery (78%) in KEYNOTE-564, please clarify what treatments they received.**

The distribution of therapies for patients who did not receive salvage surgery upon confirmation of locoregional recurrence is reported below in Table 21.

Table 21. Summary of subsequent oncologic therapies participants with locoregional recurrence for disease-free status (primary censoring rule) based on investigator assessment and had no subsequent surgery

Category	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	[redacted]					
Participants who had any subsequent anti-cancer therapy for RCC	[redacted]					
Subsequent drug therapy	[redacted]					
Subsequent radiation	[redacted]					

Participants could have multiple subsequent oncologic therapies.
Database Cutoff Date: 14JUN2021

B15. Priority question: The ERG's clinical expert advised that the estimated market share of second line advanced RCC therapies did not reflect current clinical practice and that over 50% of patients would be expected to receive cabozantinib and also that fewer than 50% of patients would receive no active therapy. Furthermore, inclusion of second line nivolumab for routine surveillance patients is likely to result in OS gains which are not reflected in the model.

a) **Please provide the unadjusted IPSOS market share data analysis used to estimate the market shares of each of the drugs used in Table 46 and Table 62 of the CS.**

The market shares for 1L aRCC treatments included in the base case were adapted from the IPSOS market share data presented below in Table 22. Firstly, the market shares provided did not sum to 100% due to the exclusion of 1L aRCC setting

therapies unavailable to patients in the UK. The remaining market shares for available therapies were adjusted such that the total market shares equated to 100%. Secondly, the unadjusted market shares included avelumab/axitinib which is currently available through the Cancer Drugs Fund and not considered a routinely available to include as a subsequent therapy. The avelumab/axitinib market share was redistributed to nivolumab/ipilimumab, and since nivolumab/ipilimumab is only available for the IMDC intermediate/poor-risk patients, a portion of the avelumab/axitinib market share was distributed to pazopanib and sunitinib.

Table 22. Distribution of 1L aRCC therapies based on IPSOS market research data (adjusted and unadjusted data)

	1L RCC **IPSOS** market shares (excluding IO therapy)	1L RCC **IPSOS** market shares (including IO therapy)	1L RCC **adjusted** market shares (excluding IO therapy)	1L RCC **adjusted** market shares (including IO therapy)
Pazopanib	31%	25%	31%	29%
Sunitinib	29%	24%	30%	30%
Cabozantinib	21%	17%	21%	13%
Tivozanib	16%	13%	18%	14%
Avelumab/ Axitinib	-	9%	-	-
Ipilimumab/ Nivolumab	-	8%	-	14%

The unadjusted IPSOS market share data for 2L RCC treatments are presented in Table 23 below and have two limitations to note. Firstly, similar to the 1L aRCC data, the market shares did not sum to 100% due to the prior exclusion of unlicensed therapies not reimbursed by the NHS. To account for this, the data were adjusted so that market shares summed to 100%, with the shares being distributed to the therapies with the lowest market shares. Secondly, the market shares did not consider patients receiving no active 2L treatments, therefore, it was assumed that 50% of patients received no active treatment with remaining market shares recalculated to sum 50%, consistent with the assumption in NICE TA650 of pembrolizumab in combination with axitinib in untreated aRCC.

Table 23. Distribution of 2L therapies based on IPSOS market research

	2L RCC **IPSOS** market shares (excluding 1L IO)	2L RCC **IPSOS** market shares (including 1L IO)	2L RCC **modelled** market shares (excluding 1L IO)	2L RCC **modelled** market shares (including 1L IO)
Cabozantinib	45%	63%	25%	32%
Axitinib	10%	14%	5%	7%
Everolimus	8%	11%	5%	7%
Pazopanib	-	6%	-	4%
Nivolumab	26%	-	15%	0%
No active treatment	Not considered in the IPSOS market shares		50%	50%

b) Please provide a scenario where nivolumab is excluded for second-line treatment and instead 50% of patients receive cabozantinib and 50% receive no active treatment in both the routine surveillance and adjuvant pembrolizumab arms.

The results from the scenario analysis exploring the ERG's preferred subsequent therapy distribution of market shares are reported in Table 24 below and show a small reduction in the base ICER from £11,031 to £10,205.

Table 24. Scenario exploring ERG's preferred 2L+ aRCC distribution of market shares

Technologies	**Total costs (£)**	**Total QALYs**	**Incremental costs (£)**	**Incremental QALYs**	**ICER vs. comparator (£/QALY)**
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.44	10,205

B16. Please clarify why 2L+ treatments for aRCC are not discounted in the same way as 1L treatments?

2L+ treatment costs for aRCC were not subject to the same two-stage discounting process used for 1L treatments, given the much shorter expected duration of 2L+ treatments vs 1L aRCC. Across the different 2L+ treatment options in the model, mean ToT ranges from 27.6 to 52.7 weeks, while mean ToT ranges from 59 to 145 weeks for 1L treatments. Because treatment duration was expected to be approximately 1

year or less for all 2L+ treatment options, discounting the stream of 2L+ treatment costs (as was done for 1L treatment costs in the ToT_Advanced tab) would have provided minimal gains in precision, at the expense of greater model complexity. (Of note, 2L+ treatment costs are still discounted from the time of DM entry to cycle 0 within the Markov trace tabs; however, the stream of 2L+ treatment costs was not discounted to the point of 2L treatment initiation when calculating the mean lump-sum cost of each 2L+ treatment regimen.)

B17. Priority question: The frequency estimates in Table 58 to Table 61 of the CS for complete blood count and X-ray resource do not reflect current clinical practice based on feedback from the ERG's clinical expert. Instead, it was suggested that clinicians rely more heavily on CT Scans. As such, please provide the following scenarios:

a) **In the DF health state, please exclude complete blood count costs and remove bi-annual x-rays from year 5 onwards. For CT scans, please assume 6-monthly CT scans up to year 3, annual from years 3 to 5 and then one CT scan at year 7 and a final CT scan at year 10.**

The results using the ERG's preferred healthcare resource utilisation assumptions in the DF health state are presented in Table 25 below and show a £6 reduction in the base-case ICER.

Table 25. Scenario assessing the ERG's preferred healthcare resource frequency for DF

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.44	11,025

b) **In the LR health state, please exclude ongoing annual complete blood counts and assume 100% of patients have ongoing 6-monthly CT scans.**

The results using the ERG's preferred healthcare resource utilisation assumptions in the DF health state are presented in Table 26 below and show a £24 reduction in the base-case ICER.

Table 26. Scenario assessing the ERG's preferred healthcare resource frequency for LR

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.44	11,007

c) In the DM health state, please exclude ongoing pre- and post-progression blood counts.

The results using the ERG's preferred healthcare resource utilisation assumptions in the DF health state are presented in Table 27 below and show a £17 increase in the base-case ICER.

Table 27. Scenario assessing the ERG's preferred healthcare resource frequency for DM

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.44	11,048

B18. The ERG notes that a weighted average of NHS reference cost activity codes; WH08A and WH08B for unspecified Pain with CC score 1+ and 0 (day or night admission), respectively, would be a more appropriate AE cost for "Pain in extremity". Please provide a scenario using the unit cost of £275.72 for the "Pain in extremity" AE.

The cost-effectiveness results using the ERG's proposed assumption for the AE cost associated with 'Pain in extremity' is presented in Table 28 below and showed no nominal impact on the base-case ICER.

Table 28. Scenario exploring the ERG's preferred assumption for the AE cost for 'Pain in extremity'

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER vs. comparator (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.44	11,031

Section C: Textual clarification and additional points

C1. The market share estimates for 2L+ treatments for aRCC provided in Table 62 of the CS (for previously IO-ineligible patients in the adjuvant pembrolizumab arm) do not match the estimates used in the base case model. The 2L+ treatment breakdown used in the adjuvant pembrolizumab arm in the model instead matched that of the IO-eligible routine surveillance arm (tab "Market share", cells G57:H64). Please clarify if the CS or the model is correct and amend as necessary.

An updated version of Table 62 from the CS submission with the correction implemented is presented below with the correction underlined).

Table 29. Correction for Table 62 of the company submission

	Adjuvant Pembrolizumab Treatment		Routine Surveillance	
	IO-ineligible	**IO-eligible**	**IO-ineligible**	**IO-eligible**
PD-1/PD-L1 inhibitors				
Nivolumab	<u>15.0%</u>	0.0%	15.0%	0.0%
VEGF/VEGFR inhibitors				
Axitinib	7.0%	7.0%	5.0%	7.0%
Cabozantinib	32.0%	32.0%	25.0%	32.0%
Pazopanib	4.0%	4.0%	0.0%	4.0%
Other treatments				
Everolimus	7.0%	7.0%	5.0%	7.0%
No active treatment	50.0%	50.0%	50.0%	50.0%

C2. The ERG could not verify the company's estimates of AE costs applied in the model. Instead, the ERG estimated alternative AE costs based on weighted averages of NHS reference costs presented in the below table. Please clarify how the weighted average costs used in the model were calculated. If incorrect, please update the model with corrected AE costs.

Adverse event	Company unit cost estimate (£)	ERG estimate (£)	Source
Hyperthyroidism	230.01	320.01	NHS reference costs – weighted average of: KA07A, KA07B, and KA07C
Hypothyroidism	230.01	320.01	NHS reference costs – weighted average of: KA07A, KA07B, and KA07C
Myalgia	138.96	198.93	NHS reference costs – weighted average of: HD21D, HD21E, HD21F, HD21G, and HG21H
Pain in extremity	138.96	198.93	NHS reference costs – weighted average of: HD21D, HD21E, HD21F, HD21G, and HG21H

An updated cost-effectiveness model has been provided incorporating the cost corrections listed above, the results from all scenarios requested above were produced by the model with the requested ERG corrections. Furthermore, the results from the company have been re-run with the corrected model below.

C3. The ERG could not verify the company's estimates of resource use costs for radiologic examinations. Instead, the ERG estimated alternative radiologic examinations costs based on weighted averages of NHS reference costs in the below table. Please clarify how the weighted average costs used in the model were calculated. If incorrect, please update the model with corrected radiologic examinations costs.

Resource	Company unit cost estimate (£)	ERG estimate (£)	Source
CT scan of abdomen/pelvis	78.65	95.37	NHS reference costs – weighted average of: RD20A, RD21A, and RD22Z
CT scan of chest	78.65	95.37	NHS reference costs – weighted average of: RD20A, RD21A, and RD22Z
MRI of brain	268.10	154.94	NHS reference costs – weighted average of: RD01A, RD02A, and RD03Z

Resource	Company unit cost estimate (£)	ERG estimate (£)	Source
CT scan of brain	78.65	95.37	NHS reference costs – weighted average of: RD20A, RD21A, and RD22Z

As per response to question C2, the changes request have been implemented into the cost-effectiveness model.

Cost-effectiveness results following ERG proposed corrections

Base-case results

The corrected base-case incremental cost-effectiveness results incorporating the pembrolizumab confidential discount are reported in Table 30 below.

Table 30. Base-case results versus routine surveillance (reflecting PAS discount for pembrolizumab, list prices for subsequent treatments with confidential discounts) (with corrected model)

Technologies	Total costs (£)	Total QALYS	Total LYs	Inc costs (£)	Inc. QALYs	Inc. LYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	[redacted]	-	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	[redacted]	1.44	1.73	£11,031
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years							

Probabilistic Sensitivity Analysis

Table 31. Incremental cost-effectiveness results based on the probabilistic sensitivity analysis results versus routine surveillance (net price) (with corrected model)

Technologies	Total costs (£)	Total QALYS	Inc costs (£)	Inc. QALYs	ICER (£/QALY)
Pembrolizumab	[redacted]	[redacted]	-	-	-
Routine surveillance	[redacted]	[redacted]	[redacted]	1.38	£11,709
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; QALYs, quality-adjusted life years					

Figure 12. Incremental cost-effectiveness plane: pembrolizumab versus routine surveillance (with corrected model)

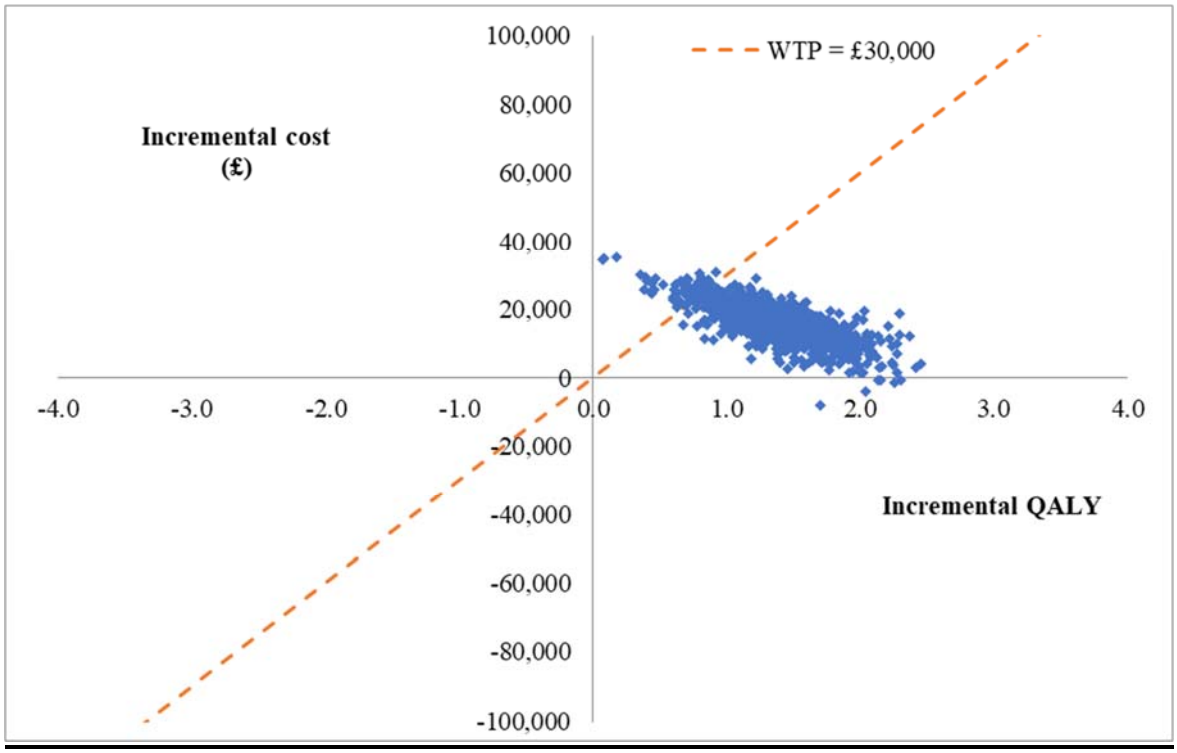
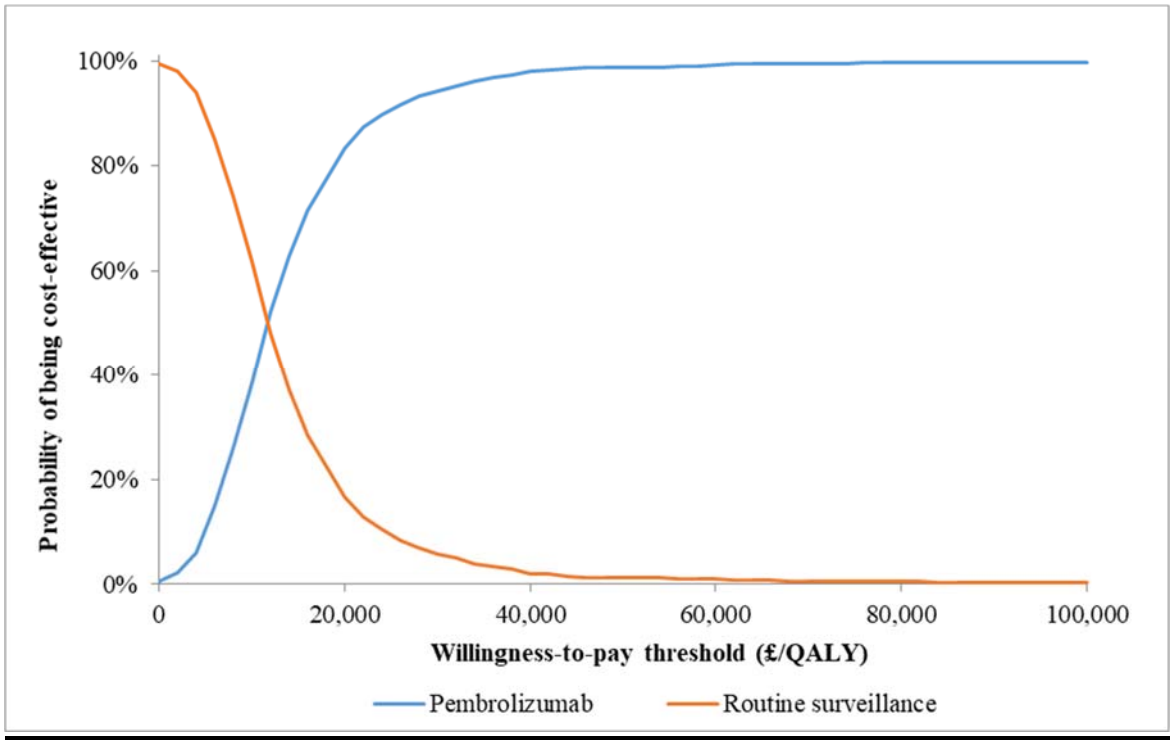


Figure 13. Cost-effectiveness acceptability curve (pembrolizumab versus routine surveillance) (with corrected model)



Deterministic Sensitivity Analysis

Deterministic sensitivity analyses (DSA) were conducted using the corrected model to explore the impact of parameter uncertainty associated with the estimates of cost-effectiveness. The parameters explored are summarised below.

Efficacy estimates

- Varying the exponential rate of LR → DM by +/- 20%
- Varying the exponential rate of LR → death by +/- 20%
- Varying the exponential rates of OS and PFS failure for aRCC treatments by +/- 20%

Utility values

- Vary the utility of the DF health state by upper and lower bound 95% confidence interval
- Vary the utility of the LR health state by upper and lower bound 95% confidence interval
- Vary the utility of the pre-progression DM health state by upper and lower bound 95% confidence interval
- Vary the utility of the post-progression DM health state by upper and lower bound 95% confidence interval
- Vary the disutility of AEs by +/- 20%

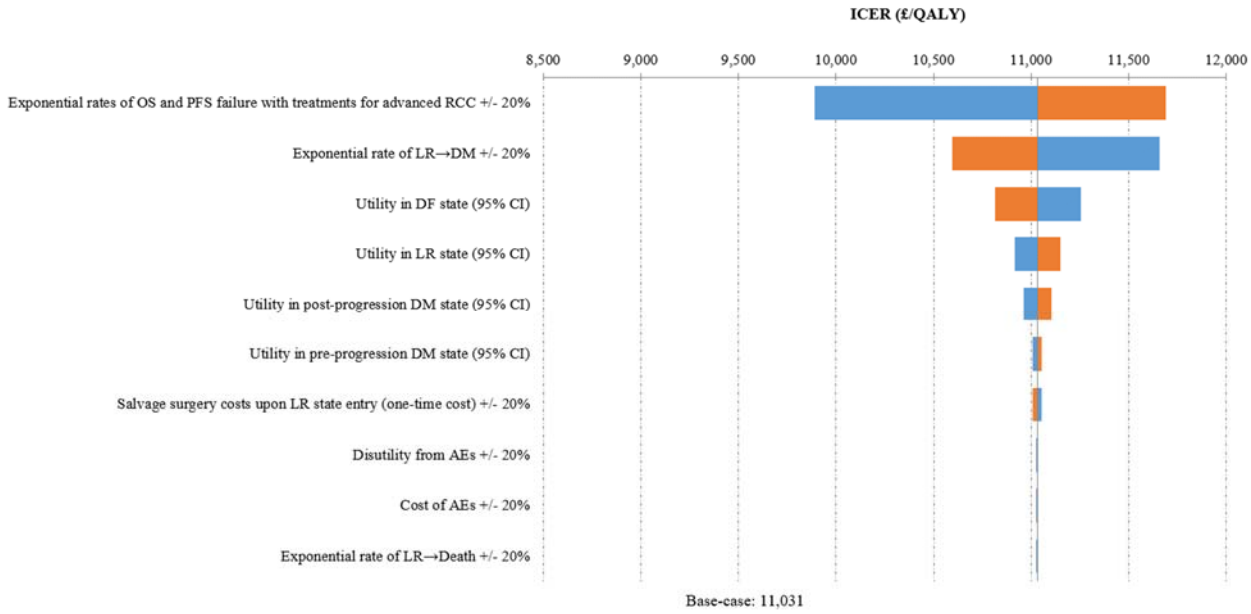
Treatment costs

- Mean patient body weight +/- 20%
- Cost of AEs +/- 20%
- Cost of salvage surgery upon entering LR health state +/- 20%
- Terminal care costs +/- 20%

The results of the DSA for the pairwise comparison of pembrolizumab and routine surveillance are presented graphically within a tornado diagram in Figure 14 sorted by the parameters to which the base-case ICER was from the most to least sensitive.

The inputs to which the ICER showed the most sensitivity were those related to utility values and hazards of PFS/OS failure from the DM state, with cost inputs having a only a minor impact. Overall, the base-case ICER was insensitive to the majority of parameters tested in the DSA.

Figure 14. Tornado diagram presenting the results of the deterministic sensitivity analysis (10 most sensitive parameters) (with corrected model)



Scenario Analysis

Alternative scenarios were tested as part of the sensitivity analysis to assess uncertainty regarding structural and methodological assumptions. The scenarios explored are summarised below.

Scenario 1: Model time horizon: 30 years

Alternative combinations of distributions for estimating transition probabilities from DF → LR and DF → DM were explored in the economic analysis. The alternative

parametric distributions explored in the scenario analysis included following distributions for the transitions from DF → LR and DF → DM:

- Scenario 2: Exponential and Gompertz under Approach 2 (jointly fitted, time-constant treatment effect)
- Scenario 3: Weibull and Gompertz under Approach 3 (jointly fitted, time-varying treatment effect)
- Scenario 4: Weibull and Gompertz under both Approach 2 (jointly fitted, time-constant treatment effect)
- Scenario 5: Exponential and Gompertz under Approach 1 (separately fitted functions)
- Scenario 6: Exponential and Generalised Gamma under Approach 1 (separately fitted functions)

Scenario 7: Including treatment with nivolumab in combination with ipilimumab as an option in the 1L aRCC setting (currently available through the CDF). Patients previously treated with adjuvant pembrolizumab would be eligible for nivolumab + ipilimumab if their transition to the DM state occurs >36 months after initiation of adjuvant treatment.

Scenario 8: Including the cost of 1L aRCC treatments only (i.e. exclusion of 2L+ aRCC treatment costs)

Scenario 9: All health state utility values obtained from KEYNOTE-564 (including DM utility values)

Scenario 10: Remove age-related disutilities

Scenario 11: Remove adverse events disutilities

Scenario 12: Remove half cycle correction

Scenario 13: Removal of relative dose intensities

Scenario 14: 1.5% annual discount rate for costs and benefits (as proposed in the NICE Methods Review, 2021)

Table 32. Scenario analysis results (with corrected model)

Scenario No.	Description	Pembrolizumab			Routine Surveillance			Pembrolizumab vs Routine Surveillance			
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)	Inc. change to base-case ICER (£)
Base Case	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,928	1.44	11,031	-
Scenario 1	30-year time horizon	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,981	1.37	11,629	+598
Scenario 2	Approach 2: Exponential/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	17,121	1.37	12,497	+1,466
Scenario 3	Approach 3: Weibull/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,133	1.32	13,740	+2,709
Scenario 4	Approach 2: Weibull/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18,032	1.31	13,762	+2,731
Scenario 5	Approach 1: Exponential/ Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	21,848	0.98	22,322	+11,291
Scenario 6	Approach 1: Exponential/ Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	23,768	0.91	26,058	+15,027
Scenario 7	Inclusion of nivolumab + ipilimumab as an available 1L aRCC therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,115	1.40	10,778	-253
Scenario 8	Exclusion of 2L aRCC treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	20,742	1.44	14,366	+3,334
Scenario 9	All utilities derived from KEYNOTE-564	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,928	1.43	11,126	+94
Scenario 10	Remove age-related disutility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,928	1.58	10,092	-939
Scenario 11	Remove adverse event disutilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,928	1.45	11,006	-26
Scenario 12	Remove half-cycle correction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,928	1.44	11,031	0
Scenario 13	Remove relative dose intensities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15,001	1.44	10,390	-641
Scenario 14	1.5% annual discount rate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	13,364	1.96	6,803	-4,228

Note: [parametric distribution] / [parametric distribution] format refers to DF → LR and DF → DM transitions.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	Sharon Deveson Kell

2. Name of organisation	Kidney Cancer Support Network
3. Job title or position	Medical Affairs
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney Cancer Support Network (KCSN) was founded in 2006 by cancer patients/survivors Rose Woodward and Julia Black, who started by providing practical and bespoke support to individual patients for access to life-extending cancer drugs to treat metastatic kidney cancer. Empowering patients to take an active role in their own health care, and in decisions affecting the choice, provision, and quality of cancer services throughout the UK, remains the top priority for KCSN. Over the years, KCSN has grown considerably, with a membership of over 1400 kidney cancer patients and carers on its confidential community forum. In addition, our website regularly has over 300 visits per day from people looking for information about kidney cancer, advice, and support. KCSN is unique; originally it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Although KCSN remains patient-led, the group is now a registered charity, which enables it to better meet the growing needs of the kidney cancer community in the UK. Before the COVID-19 pandemic, funding came from trusts, foundations, and the pharmaceutical industry (around 55%), as well as fundraising activities/events organised by the public and kidney cancer community (45%). Since the pandemic, the latter has dropped off by almost 100%.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12	Yes, we have received £15,000 from Merck Sharp and Dohme (MSD) towards our multi-funded community outreach programme consisting of clinician webinars, a community map on our website, and regular patient and carer Click & Chat sessions via Zoom. MSD were not involved in the planning, production, or implementation of the project.

months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	When gathering the information for this submission, we specifically asked for patient and carer experience of using pembrolizumab as an adjuvant treatment for locally advanced kidney cancer through our closed social media channels. We have a dedicated immunotherapy Facebook group specifically set-up to help us collate experiences from patients using these types of medication. Over 1400 patients and carers use these channels to communicate on a regular basis, and we receive in the order of 5-600 interactions and comments a day on our closed Facebook group.
Living with the condition	
6. What is it like to live with the condition? What do carers	KCSN is a patient-led kidney cancer charity with the largest and most active patient and carer membership across the UK. As such, we feel we are in a strong position to feedback how kidney cancer affects the day-to-day lives of people living with this disease.

experience when caring for someone with the condition?	Between 2016-2018, there were around 13,300 new cases of kidney cancer diagnosed annually in the UK (36 cases diagnosed every day) and kidney cancer is the seventh most common cancer affecting British people. Kidney cancer accounts for 4% of all new UK cancer cases (2016-2018). In 2016-2018, nearly 5,000 people died from the disease and about a third of kidney cancer patients will be diagnosed with late-stage disease. In these cases, it is estimated that only 12% of people will survive for five years or more (Cancer Research UK). It is difficult to remain positive in the face of figures like this. Following surgery, patients diagnosed with locally advanced (stage 3) kidney cancer live in constant fear of recurrence of the disease and metastatic spread of the cancer. This leads to stress and anxiety, often affecting the wellbeing of the patients, as well as those close to them. This can have a detrimental effect on family life and the psychosocial wellbeing of all involved. These patients often feel abandoned by the healthcare system since there is little follow-up to check for metastatic spread and currently no adjuvant treatments to reduce the probability of metastatic RCC. Living with kidney cancer takes its toll on patients and their families both physically and psychologically. As a patient-led charity, KCSN encourages patients to ask for help from others to help improve their wellbeing. Stress and anxiety can be reduced by talking about feelings with family, friends, a health professional, or other people who have been through a similar experience. Taking part in activities that the patient enjoys, such as spending time with family and friends, socialising with other patients or carers, or relaxing activities such as walking, meditation or yoga, can also help to reduce stress and anxiety. Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental health. Carers seem to find the psychological impact even harder as they live with a guilt of not being able to do all they can for their loved one. Access to an adjuvant treatment would enable patients and their families to know that they had tried their best to beat the cancer, leading to better family relationships and a subsequent improvement in quality of life and wellbeing for the patient. Without an adjuvant treatment, some patients will go on to develop metastatic RCC, sometimes months or even years after surgery. Metastatic RCC is a devastating disease and is currently incurable. The majority of metastatic RCC patients are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings enormous financial pressures for the patient and their family

	(and additional costs to the state), and can precipitate psychological problems, such as depression, loss of confidence and self-worth. Patients may suffer constant pain from metastatic tumours in the brain, bones, lungs, liver, and other rarer sites. Patients with bone metastases are at risk of bone breaks and spinal cord compression. Metastases in the lungs can lead to breathlessness, and persistent coughing. Spread of the cancer to the brain can lead to severe and debilitating headaches, confusion and, in some cases, paralysis. Kidney function is often compromised, and patients find daily living difficult, often needing periods of rest during the day. Sexual function is affected for both male and female patients, and family life suffers as a result. Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, a process of elimination is used to select the most effective treatment for individual patients. Most patients with metastatic RCC face disease progression, including worsening of symptoms, such as severe pain, fatigue, and shortness-of-breath. Kidney cancer cases are rising year-on-year. There is an unmet need for an effective adjuvant treatment to prevent the spread of this disease and reduce the number of patients who succumb to metastatic kidney cancer with a terminal prognosis. The impact of this on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one is diagnosed with a potentially terminal disease. Finally, there is an unmet need for an effective adjuvant treatment for more aggressive forms of kidney cancer, such as hereditary and rare subtypes, which are inherently difficult to treat. Patients diagnosed with hereditary kidney cancer or rare RCC subtypes currently have very limited treatment options, exacerbating feelings of depression, fear, and low self-worth.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The current treatment pathway for locally advanced kidney cancer is either radical or partial nephrectomy (surgery). Patients are then followed for 5 years after surgery if they have kidney cancer that is of intermediate or high risk of recurrence based on the Leibovich model for clear cell RCC. Patients with low risk of recurrence are followed for 3 years. Follow-up consists of 6 monthly or annual CT scans to check for metastatic spread. European Association of Urology (EAU) guidelines recommend bi-annual CT scans after 5 years (or 3 years for low-risk patients) if the clinician and patient consider this necessary. However, we do not think this proposed follow-up schedule has been taken up consistently by the NHS. During this time, no further treatment is given (adjuvant treatment) to prevent or reduce the risk of spread of the cancer following surgery. Vascular endothelial growth factor (VEGF) inhibitors, such as sunitinib, pazopanib, axitinib and sorafenib have all been investigated in randomised controlled clinical trials as potential adjuvant therapies. None significantly improved patient survival, although patients were subject to the potential toxicities of these drugs for a year without receiving any benefit. However, sunitinib has been approved by the US Food and Drug Administration (FDA) for such use. If the cancer spreads, the treatment pathway is surgery followed by a VEGF inhibitor (either sunitinib, pazopanib, cabozantinib or tivozanib) in the first-line setting. Axitinib, everolimus, cabozantinib, lenvatinib plus everolimus are given in the second/third-line setting, all of which are oral medicines and have similar modes of action (vascular endothelial growth factor receptor (VEGFR) inhibitors or mTOR inhibitors that block angiogenesis). Nivolumab, an immune checkpoint inhibitor, is also recommended for use within NHS England for second- or third-line treatment of metastatic RCC. Immune checkpoint inhibitors are administered as intravenous infusions, requiring outpatient hospital treatment (chemotherapy chair resources), and the associated travel time and expense for the patient and carer. Although these treatments have the potential to improve survival time, they also have significant toxicity. Using currently available drugs, many patients suffer with extreme fatigue, rashes and itching, hand and foot syndrome, chronic diarrhoea, pneumonitis, severe mouth ulcers, nausea and vomiting, hypertension, muscle and joint pain and various immune-related side effects, all of which severely affect quality of life.

These side effects also require additional medicines to help patients manage the side effects and/or tumour pain, and some may even require hospitalisation, the costs of which should be considered.

Other less serious side effects, which still affect the patient's quality of life, are headache, loss of taste, hair loss and change of hair colour, depression, loss of libido, and inability to drive. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment because of severe side effects.

Patients with locally advanced RCC are aware of the potential side effects of these treatments, but they continue to look for adjuvant treatments that can prevent recurrence of the disease with better quality of life. The use of an adjuvant treatment would also reduce the stress and anxiety that these patients and their families regularly face regarding recurrence of the disease. The following quote gives an indication of how much patients are willing to put up with to find an effective adjuvant treatment:

> *"I knew from the information that it was a double-blind trial, and the chances are I would be on a placebo, but I just wanted to help even if it didn't help me, it could help someone else in the future.*
>
> *"The trial I was on was ……. with sorafenib to see if it could prevent reoccurrence in patients at high risk. I personally lasted two and a half years before they took me off the trial because of the severe side effects. If I knew that the drugs would prevent the cancer coming back, I am not sure I would take them if that was how I would have to live my life, it really had a bad effect on me and in my wife's words 'it was like I disappeared' meaning I couldn't do much but sit and just exist. I know it wasn't like that for everyone and if I had to make the decision knowing it would work without such side effects I would do it again."*

In a poll of 141 patients with locally advanced RCC from 8 countries (USA, Canada, UK, Germany, the Netherlands, France, Denmark, and Belgium), 40% said they would take an immunotherapy treatment after surgery for a 50% reduction in the risk of the cancer returning. Only 9% said they would not take adjuvant immunotherapy at all. In the same poll, over a quarter of patients were willing to accept a 25% risk of having side effects to adjuvant immunotherapy that required treatment with steroids (International Kidney Cancer Coalition, IKCC, October 2021).

	The availability of an adjuvant immunotherapy, such as pembrolizumab, offers patients with locally advanced disease hope that they will remain disease free after nephrectomy, and reduces the stress and worry of the cancer returning. This fulfils an unmet need in this patient population, and could potentially dramatically improve their quality of life: *"For me the decision to go on the…….trial for adjuvant therapy was an easy one. After having a radical nephrectomy and IVC tumour removal I am just grateful to be alive. I am currently on the ….. trial and the side effects of immunotherapy have been explained to me in detail. In fact, I am experiencing some of them at the moment, but I am still happy with my decision and do not regret it as the alternative would have been just to be monitored and to keep my fingers crossed the cancer doesn't return. The opportunity to have medication to prevent it coming back rather than wait for it to come back and then have medication was the only choice to make, even with the possible side effects. I would have liked to be offered adjuvant treatment instead of having to go on a trial."* For most patients with locally advanced RCC, the most important treatment outcome would be no recurrence of disease, i.e., a cure for their kidney cancer. Failing to achieve no recurrence of disease, disease stability would be the next best outcome for patients. In addition to treatment outcomes, quality of life is also an important consideration for many patients. Most patients would prefer a treatment that allows them to continue to lead as normal a life as possible, and to contribute both socially and economically to their communities: *"The extra years, which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various ……. enterprises which I manage…….. I'm making a hugely positive contribution to society, and the wider economy, and I wish to be able to carry on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities".* *"…….has enabled me to enjoy every day, do 3 or 4 days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths……".*

	From a psychological point of view, knowing that you have stage 3 cancer and knowing that there is the potential for it to return is very difficult for patients. Nowadays, kidney cancer patients do not exist in silos. They communicate widely within online patient communities; international discussion forums exist where patients talk to one another daily, and patients are more aware of the experiences of others, including their access to innovative treatments, quality of life, and treatment successes and failures. News about lack of access to effective medicines ripples out to other patients and families, destroying their hope and positivity. Information about adjuvant treatments is readily available to patients around the world on websites. Patients and clinicians are right to expect NICE and the pharmaceutical industry to find a way to bring new and innovative treatments to kidney cancer patients in England, so that patients in England have the same choices as patients in other countries and to improve outcomes.
8. Is there an unmet need for patients with this condition?	There is an unmet need for an effective adjuvant treatment to prevent the spread of this disease and reduce the number of patients who succumb to metastatic kidney cancer with a terminal prognosis. The impact of this on the family, as well as the patient, also needs consideration; these families need support during the most difficult time in their lives when a loved one is diagnosed with a potentially terminal disease. There is also a significant unmet need for an effective and safe adjuvant treatment for people with hereditary kidney cancer or rare RCC subtypes, who currently have very limited treatment options.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Nephrectomy is the standard of care for locally advanced RCC; however, the cancer can come back after nephrectomy and adjuvant therapy can be given after surgery to try to prevent recurrence. In the past, VEGF inhibitors and cytokines (such as interleukin 2 and interferon) have been tested as adjuvant therapies for RCC, but the benefit for patients has been inconsistent. The phase 3 KEYNOTE-564 trial looked at the use of pembrolizumab as an adjuvant therapy for patients with clear cell RCC after nephrectomy. During this trial, pembrolizumab was compared to placebo in the

	form of a saline infusion. Patients were treated for one year and monitored for the return of their cancer during and after treatment. Pembrolizumab significantly reduced the relative risk of the cancer returning by about one third (32%). After 2 years, 68.1% of patients on placebo remained disease-free and 77.3% of the patients on pembrolizumab remained disease-free. During the trial, quality of life was assessed. There was only a minor deterioration of quality of life for patients treated with pembrolizumab compared to placebo, which the researchers did not consider statistically significant. Importantly, quality of life remained stable over time. Patients reported that pembrolizumab was tolerable from a patient perspective. Side effects were reported from most patients in the study (96.3% of patients on pembrolizumab and 91.1% on placebo). There were no new side effects reported with pembrolizumab compared with previous trials. The most common immune-related side effects on pembrolizumab affected the thyroid gland (hypo- or hyperthyroidism) and were manageable. Only 7% of patients needed to be treated with high dose corticosteroids to treat immune-related side effects. Pembrolizumab is currently approved by several health authorities around the world for use in combination with axitinib as a first medication for patients with advanced RCC. Together with the survival data from the KEYNOTE-564 trial, these results suggest that quality-of-life does not substantially suffer if pembrolizumab is taken for up to a year after surgery as an adjuvant therapy to prevent recurrence of the cancer. Patients with intermediate/high risk, locally advanced RCC are desperate for an adjuvant treatment that will prevent recurrence of their disease without affecting their quality of life. This will help to address the stress and anxiety felt by patients and their families and improve their psychosocial wellbeing after surgery for RCC. The benefits of pembrolizumab to patients are reduced recurrence of disease with a tolerable side effect profile and little effect on quality of life. This improves the psychosocial wellbeing of both the patient and their family members, allowing them to get on with their lives without the constant worry of the disease returning and a terminal prognosis.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	We understand that immune checkpoint inhibitors are expensive, and we appreciate the budgetary constraints of the NHS. Nonetheless, NICE and the manufacturer need to work collaboratively to negotiate an acceptable patient access scheme to ensure RCC patients can benefit from this clinically effective adjuvant treatment. Pembrolizumab is given intravenously over 30 minutes every 3 weeks until disease progression or drug intolerance. This requires hospital visits every 3 weeks and the provision of chemotherapy chairs for the infusion. Patients will typically be travelling some distance to a regional cancer centre for the pembrolizumab infusions. Some patients may need to take time off work, or have a partner travel with them to treatments, the practical aspects of which can impact the quality of life of both patient and carer. However, balanced against the extra travel and time is the improved side effect profile and enhanced quality of life. Most patients feel much better able to cope with life knowing that they are taking a treatment to prevent the cancer from recurring, and some return to work.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None
Other issues	
13. Are there any other issues that you would like the committee to consider?	Pembrolizumab is the first immune checkpoint inhibitor to be assessed as an adjuvant treatment for locally advanced RCC. Currently, adjuvant treatment to prevent the spread of intermediate/high risk RCC following surgery is an area of unmet need in the UK. An adjuvant treatment is desperately needed for these patients to improve their wellbeing and quality of life following surgery. Carers, family members and friends of kidney cancer patients would also benefit from less worry about recurrence of the disease following surgery. Before the COVID-19 pandemic, the UK cancer survival rates trailed about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including the patient experience as well as overall survival, it is vital that a tolerable and effective adjuvant treatment is made available to patients in order that they have the best possible care. If adjuvant treatment is not accessible, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to other kidney cancer patients in the rest of Europe and North America. Poor UK survival rates might possibly be due to the restrictions in clinical choice brought about by UK regulatory authorities leading to health inequalities between countries. In the absence of biomarkers for the treatment of RCC, clinicians are not able to predict which patients will respond to which drug, and drug selection is accomplished by trial and error. Clinicians should have the

	ability to choose the most effective treatment pathway for individual patients, and without an adjuvant treatment, the clinician's choice is seriously compromised. Some patients will face disease progression following surgery and will ultimately be diagnosed with a terminal condition. They will require treatment for metastatic RCC, along with the psychosocial support and increased cost of treatment that comes with a terminal diagnosis. An adjuvant treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Adjuvant treatment with pembrolizumab is one of the first immune checkpoint inhibitors to show efficacy in intermediate/high risk locally advanced RCC, and has been granted priority review status by the FDA
- Adjuvant pembrolizumab is well tolerated, as well as proven to significantly reduce the relative risk of the cancer returning by about 32% compared to placebo
- Quality of life on adjuvant pembrolizumab was reported as not significantly different to quality of life on placebo, and remained stable over time
- The availability of an adjuvant treatment reduces the stress and anxiety for patients and their families and carers caused by potential recurrence of the disease following surgery, and improves their wellbeing enabling them to continue to contribute socially and economically to society
- Adjuvant pembrolizumab could be used to address an area of significant unmet need in the treatment of hereditary kidney cancer or rare RCC subtypes.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	Sophie-Ann Scott

2. Name of organisation	Kidney cancer UK
3. Job title or position	Health professional-Nurse
4a. Brief description of the organisation (including who funds it). How many members does it have?	Kidney cancer UK is a charity which provides help and support to kidney cancer patients and their families. We offer counselling services and support and advice to our patients on the careline, provide up to date information and education on the disease and treatments on our website, raise awareness, run campaigns, and fund research into kidney cancer. The organisation is funded by donations and each month we communicate with approximately 3900 patients. Our website received 36,000 views per year.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Yes -Bristol Myers Squibb- Covid £10,000 Survey £2,000 Accord £5,000 Total: £17,000 Merck - £7500 -Awaiting payment for a patient survey and the accord project Pfizer - £7500 – Awaiting payment for a patient survey and the accord project

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We have no links with the tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	I listened to patients and their families views in the closed face book support groups and in the Zoom support group meetings. I also gathered information from patients from talking to them on the careline, and from Q and A webinars and our patient survey.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Being diagnosed with kidney cancer can be incredibly stressful for patients and their families, and the challenges they face greatly depend on the stage of their disease. Most people with kidney cancer will receive surgery at some point, which will require a period of recovery. There will be times when the patient and family/carers will be worried about the future and require information and guidance. Waiting for news, scans and procedures can be emotionally draining. Knowledge that there are a variety of treatment options available to them will give them some comfort. Dealing with side effects of drugs can be equally

	exhausting as the symptoms of the cancer, so finding the balance of treatment and quality of life that is right for each patient is important. According to our recent annual survey patients with kidney cancer reported feeling anxious, emotionally low, abandoned after surgery and scared about their cancer returning. Knowledge that there are a variety of treatment options available to them will give patients and their carers some hope and comfort. Patients reported having a range of symptoms from their cancer including fatigue, depression, weight loss, anorexia, anaemia and pain which varies in severity according to the stage of their disease, which can be disabling for many and distressing for both patients and carers. This can affect their life in many ways, they may need to take regular pain medication to control their pain, many people report having less energy to carry out their activities of daily living and have needed to take time off work. Side effects from treatment include fatigue, loss of appetite, nausea, night sweats and rashes, some even report being hospitalised with colitis or pneumonitis too. However, some people report that the drugs work for them and they have fewer side effects and they have no further disease spread which helps to improve their quality of life. Finding the balance of treatment and quality of life that is right for each patient is important.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The treatment and outcome are very much dependant on how early the kidney cancer has been caught. Ideally the tumour is of an early stage and is removed by surgery or cryotherapy and the patient enjoys a life after cancer. This would always be the preferred treatment. However, if the tumour has spread patients will rely on targeted therapies and immunotherapy treatments. Current drug treatments for kidney cancer are very limited in number and have plenty of side effects. Kidney Cancer UK feel that there are significant improvements that could be made in this area. A wider range of options with improved efficacy and fewer side effects. The most commonly used Tyrosine kinase inhibitors (sunitinib and pazopanib) act to extend life and in some cases they work very well and extend life for many years. For others, the extension of life is a matter of months. However, those months can be invaluable for individuals and their families. The introduction of nivolumab (immunotherapy) as a NICE recommended drug was well received by patients and their families. Patients have reported back on how effective this drug has been for them, especially on how it improves their quality of life. I think that having combinations of treatments may give alternate options and even better results as a first line treatment. Giving alternate options for patients can be invaluable especially in an era where personalised medicine may be introduced. It may be found that Pembrolizumab as an adjuvant therapy works for a set of patients where other treatments may fail. A multitude of treatment options is always desirable.
8. Is there an unmet need for patients with this condition?	Yes there is an unmet need for treatment of advanced RCC, it would most certainly improve some outcomes in patients surviving kidney cancer and to be free of cancer for the foreseeable future. We understand that most drug treatments aim to extend the lives of people with kidney cancer and viewing kidney cancer as a chronic disease that can be lived with would be a desirable outcome. Tolerable side effects of a treatment are important if kidney cancer is to be viewed as a chronic disease and patients are to have a good quality of life.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Advantages of the treatment: • Disease control with no metastatic progression • Prolonged survival rate • Reduction in cancer pain and other cancer symptoms • Improvement in their mental health knowing that their treatment is working • Quality of life- living longer and having more time with family and friends • Family and friends feel reassured that their loved ones treatment is working • Patients felt more in control of their lives on treatment
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Disadvantages of a treatment might include: • Poor disease control and metastatic progression • No difference in survival rate • Side effects such as fatigue, low mood, weight loss, poor appetite, urticaria, bone pain, elevated liver enzymes, and in rarer cases colitis and pneumonitis as reported by patients • The patients may have to travel far to the hospital to receive their treatment • Difficulties in taking or using the treatment (for example, receiving IV medication instead of tablets) • Difficult for carers watching loved ones suffer from side effects of the treatment

	• Financial impact of paying for travel to and from the hospital or paying for a carer to accompany them
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients with advanced (stage 3 or 4) disease are likely to require medication to extend their life. People who have failed prior systemic treatment are likely to need another treatment option, which introducing Pembrolizumab will provide.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None known

Other issues	
13. Are there any other issues that you would like the committee to consider?	None known

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- People with advanced kidney cancer have limited treatment options and require a variety of drug choices.
- Pembrolizumab as an adjuvant therapy has an acceptable and improved side effect profile compared to other first line drugs, which will improve people's quality of life and hopefully extend a patient's life.
- In time there will hopefully be more development in immunotherapy treatments and there will be better outcomes in survival rates and a better quality of life for patients living with advanced kidney cancer.
- How the drugs work varies for everyone. A particular group of people may respond really well to Pembrolizumab where other TKI's and targeted therapies may not work for them as a first line treatment.

Thank you for your time.

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Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]

STA Report

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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Ben Mayer	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Charlotta Karner	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Conor Hickey	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

AE	Adverse event
AEOSI	Adverse event of special interest
APaT	All Participants as Treated
aRCC	Advanced renal cell carcinoma
BICR	Blinded independent central review
BNF	British National Formulary
CDF	Cancer Drugs Fund
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CS	Company submission
CT	Computed tomography
DF	Disease-free
DFS	Disease-free survival
DM	Distant metastases
DRSS	Disease recurrence-specific survival
DSU	Decision support unit
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire
EQ-5D	European Quality of Life 5 Dimension
ERG	Evidence review group
FAS	Full analysis set
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index - Disease Related Symptoms
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
IA	Investigator assessed
ICER	Incremental cost-effectiveness ratio
LR	Locoregional recurrence
ITT	Intention to treat
IVRS	Interactive voice response system
IWRS	Integrated web response system
KM	Kaplan Meier
LR	Locoregional recurrence
M(#)	Metastasis
MSE	Mean square error
N(#)	Node

NED	No evidence of disease
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NIHR	National Institute of Health Research
NMA	Network meta-analysis
ONS	Office for National Statistics
OS	Overall survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PD-1	Programmed death 1 (protein)
PD-L1	Programmed death-ligand 1 (protein)
PFS	Progression-free survival
PH	Proportional hazards
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcomes
PPS	Post-progression survival
PSA	Probabilistic sensitivity analysis
Q3W	Once every three weeks
Q6W	Once every six weeks
QALY	Quality-adjusted life-year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RoB	Risk of bias
SEER	Surveillance, Epidemiology and End Results
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STA	Single technology appraisal
T(#)	Tumour
TA	Technology appraisal
TKI	Tyrosine kinase inhibitor
TNM	Tumour, node, metastasis
ToT	Time on treatment
TSD	Technical support document
WTP	Willingness to pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Overview of the ERG's key issues

Table 1 presents a summary of the ERG's key issues on the evidence submitted on the clinical and cost effectiveness of pembrolizumab as adjuvant treatment for [redacted].

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	Immature DFS and OS data from KEYNOTE-564	4.2.5
2	IA versus BICR assessment from KEYNOTE-564	4.2.5
3	Long-term risk of relapse	4.2.5
4	Treatment regimen and resource use for pembrolizumab	4.2.3

Abbreviations: BICR, blinded independent central review; DFS, disease-free survival; IA, investigator assessment; OS, overall survival.

The key difference between the company's preferred assumptions and the ERG's preferred assumptions is around the appropriate way to model transitions from the disease-free health state. However, other secondary differences in the preferred assumptions between the company and ERG's approach include using the complete observed time on treatment data from KEYNOTE-564 as well as assuming 100% of the pembrolizumab dose received, removal of oral administration costs and alternative market shares for subsequent second-line treatment for advanced renal cell carcinoma (aRCC).

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing disease-free survival (DFS).

Overall, the technology is modelled to affect costs by:

- Its higher unit price compared with routine surveillance in the NHS.
- Inclusion of a cap on number of treatment cycles (maximum of 17 treatment cycles).

The modelling assumptions that have the greatest effect on the ICER are:

- Using independent models fitted to each treatment arm instead of the time-varying proportional hazards approach favoured by the company for transitions from the disease-free (DF) health state to the locoregional recurrence (LR) and distant metastases (DM) health states.
- Assuming long-term risk of relapse for patients on pembrolizumab is the same as patients on routine surveillance, at various timepoints after the observed data from KEYNOTE-564.

1.3 The clinical and cost effectiveness evidence: summary of the ERG's key issues

Table 2 to Table 5 presents the ERG's key issues with the company's clinical and cost-effectiveness analysis. All cost-effectiveness analyses presented in this report are inclusive of the company's patient access scheme (PAS) simple discount of [redacted] %. Several secondary issues were identified by the ERG that had minimal impact on the ICER, but were included in the ERG's preferred assumptions, presented in Section 1.4 and discussed in the main body of the ERG report.

Table 2. Issue 1: Immature DFS and OS data from KEYNOTE-564

Report section	4.2.5
Description of issue and why the ERG has identified it as important	The primary clinical data from KEYNOTE-564, DFS, and the secondary outcome of OS were immature ([redacted]. The immaturity of this outcome data adds uncertainty to the evidence and the economic modelling it informs. Transitions from the DF to LR and DF to DM health states are the main drivers of cost-effectiveness in the model and are subject to the greatest amount of uncertainty as DFS data from KEYNOTE-564 are extremely immature [redacted]. Furthermore, OS data from KEYNOTE-564 informing the DF to death and also LR to death transitions are also immature ([redacted]), resulting in background mortality being applied from the beginning of the model time horizon for both arms of the model, which implies long-term remission.
What alternative approach has the ERG suggested?	The ERG considers that without further collection of long-term data in the KEYNOTE-564, the uncertainty around DFS and OS data would remain given the immaturity of the evidence. The company supplied three different approaches to model transitions from the DF to LR and DF to DM health states as well as extensive validation of the estimates of each approach. Nonetheless, without longer-term data from KEYNOTE-564, all approaches are subject to substantial uncertainty. However, the ERG considers that the most robust way to model the DF health state transitions with the limited patient-level data available is to use independent models fitted to each arm of the model (Approach 1) instead of the time-varying proportional hazards model (Approach 3) favoured by the company. Nonetheless, the ERG considers using Approach 1 is only illustrative as it does not overcome the uncertainty around the fundamental issue of immature outcome data from KEYNOTE-564.
What is the expected effect on the cost-effectiveness estimates?	Using Approach 1, the company's ICER post clarification increased from £11,031 to £22,322.
What additional evidence or analyses might help to resolve this key issue?	The company has indicated that they believe pembrolizumab to be a suitable candidate for the CDF as this will allow for additional data collection to reduce uncertainty in DFS and OS and subsequent modelling of the data, and the ERG agrees that only mature data will alleviate these uncertainties. The company has indicated that the next readout from KEYNOTE-564 will be when 332 DFS events have occurred and the final analysis for DFS is anticipated to be available in 2024.

Abbreviations: CDF, Cancer Drugs Fund; DF, disease-free; DFS, disease-free survival; DM, distant metastases; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; OS overall survival.

Table 3. Issue 2: IA versus BICR assessment in KEYNOTE-564

Report section	4.2.5
Description of issue and why the ERG has identified it as important	The primary clinical outcome from KEYNOTE-564 is investigator assessment (IA) DFS and in the model the data informing the transitions from the DF health state are based on IA from KEYNOTE-564. In the trial, DFS as assessed by the investigator was the primary outcome and a sensitivity analysis using BICR assessment was conducted. However, the ERG considers that DFS assessment by BICR is a more robust assessment of clinical efficacy from a trial as it is likely to be unaffected by detection bias. The company explained that the DFS results for investigator assessment and BICR are consistent (IA HR of [redacted] versus BICR HR of [redacted]). The company justified the use of IA DFS data over BICR DFS data as more generalisable to NHS as clinicians would determine the recurrence of disease based on local review of diagnostic imaging. Furthermore, the company explained that there was a high degree of agreement between the IA and BICR assessment (89% and 93% agreement for the pembrolizumab and placebo arms, respectively).
What alternative approach has the ERG suggested?	The ERG ran an illustrative scenario, applying an inflation factor to the DF to LR and DF to DM transition probabilities for the pembrolizumab arm of the model using the ratio of the BICR and IA HRs ([redacted]). Ideally, the ERG would include a robust BICR analysis in its preferred base case assumptions, but as the company did not provide the analysis it could not be included.
What is the expected effect on the cost-effectiveness estimates?	The scenario increased the company's ICER post clarification from £11,031 to £24,822.
What additional evidence or analyses might help to resolve this key issue?	The ERG's scenario is a crude estimate of the impact of using BICR data and stresses that a robust analysis by the company using BICR data from KEYNOTE-564 would be preferred to be presented to the committee to assess the true impact on the ICER.

Abbreviations: BICR, blinded independent central review; CI, confidence interval; DF, disease-free; DFS, disease-free survival; DM, distant metastases ERG, Evidence Review Group; IA, investigator assessment; ICER, incremental cost-effectiveness ratio.

Table 4. Issue 3: Long term risk of relapse

Report section	4.2.5
Description of issue and why the ERG has identified it as important	In recent appraisals of immunotherapy, duration of treatment effect has been considered by committees. Duration of treatment effect is a key issue because immunotherapy is given for a short duration, yet in extrapolations of outcomes, a treatment benefit over the comparator is assumed to continue over a lifetime horizon. Pembrolizumab is given for a maximum of 17 cycles (1 year) but outcome data from KEYNOTE-564 are currently only available for a follow-up of 3.5 years. When considering the KM plot for DFS from KEYNOTE-564, after 1 year of treatment there is a continued separation of the pembrolizumab and placebo curves but there is substantial censoring from 18 months onwards. However, the ERG considers the difference in DFS between routine surveillance and pembrolizumab provides an indication of the proportion of patients in which surgery with curative intent was not successful and adjuvant treatment has been beneficial. As such, for these disease-free patients, the risk of relapse in the DF health state for pembrolizumab treated patients may increase over time to match routine surveillance. The company explained that the aim of adjuvant pembrolizumab is to remove any residual microscopic disease after resection and reduce the risk of relapse and progression to metastatic disease and referred to the continued separation of the KEYNOTE-564 DFS curves for pembrolizumab and placebo. Additionally, the company stated that in the context of adjuvant treatment, the duration of treatment effect is often discussed in terms of cure potential, which has not been included in the base case.
What alternative approach has the ERG suggested?	The ERG conducted three scenarios exploring risk of relapse for the pembrolizumab DF to LR and DF to DM transitions equal to routine surveillance at 4, 7 and 10 years. The ERG acknowledges that an unknown and currently unknowable proportion of pembrolizumab patients may achieve long-term remission and so the early convergence of DFS curves is very likely to be a conservative estimate.
What is the expected effect on the cost-effectiveness estimates?	The increased risk of relapse for pembrolizumab scenarios resulted in a range in the ICER of £16,417 (10 years) to £27,139 (4 years)
What additional evidence or analyses might help to resolve this key issue?	More mature data from KEYNOTE-564 are required to make a robust assessment of the long-term treatment effect with pembrolizumab.

Abbreviations: DF, disease-free; DFS, disease-free survival; DM, distant metastases ERG, Evidence Review Group; IA, investigator assessment; ICER, incremental cost-effectiveness ratio.

Table 5. Issue 4: Treatment regimen and resource use for pembrolizumab

Report section	4.2.3, 4.2.8.1
Description of issue and why the ERG has identified it as important	In KEYNOTE-564, the treatment regimen for pembrolizumab was 200 mg once every three weeks, but the company stated that it can also be administered at a 400 mg dose once every six weeks. The ERG's clinical experts advised that in clinical practice, they would prefer to administer pembrolizumab using the 400 mg dose once every six weeks for patient convenience and to reduce NHS resource use.
What alternative approach has the ERG suggested?	To reflect how pembrolizumab would be used in UK clinical practice, the ERG considers a scenario exploring the pembrolizumab treatment regimen of 400mg once every six weeks is appropriate.
What is the expected effect on the cost-effectiveness estimates?	The company base case ICER post clarification is reduced from £11,031 to £10,866.
What additional evidence or analyses might help to resolve this key issue?	No additional evidence is required as the SmPC for pembrolizumab includes an option to administer pembrolizumab at a 400 mg dose once every six weeks.

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; mg, milligram.

1.4 Summary of ERG's preferred assumptions and resulting ICER

Table 6 presents the ERG preferred assumptions as well as the ERG deterministic and probabilistic base case ICER. Table 7 presents scenarios around the ERG base case.

Table 6. ERG preferred assumptions and base case ICER

Scenario	Incremental costs	Incremental QALYs	ICER (change from company base case
Company base case post clarification	[redacted]	1.44	11,031
Approach 1 combination exponential/ Gompertz - Issue 1	[redacted]	0.98	22,322
Removal of oral administration costs	[redacted]	1.44	11,680
Removal of truncation to the ToT curve for pembrolizumab	[redacted]	1.44	11,409
Removal of pembrolizumab RDI	[redacted]	1.44	11,268
Alternative 2L subsequent treatment market share estimates - 50% cabozantinib and 50% no active treatment	[redacted]	1.44	10,205
ERG's preferred deterministic base case - combination of all scenarios	[redacted]	**0.98**	**23,123**
ERG's preferred probabilistic base case - combination of all scenarios	[redacted]	**0.84**	**28,752**

Abbreviations: Abbreviations: DF, disease-free; DFS, disease-free survival; DM, distant metastases ERG, Evidence Review Group; IA, investigator assessment; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Table 7. Scenarios around the ERG base case

	Results per patient	Intervention	Comparator	Incremental value
0	**ERG base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.98
	ICER (£/QALY)			23,123
1	**400mg Q6W dosing regimen**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.98
	ICER (£/QALY)			22,632
2	**Risk of relapse equal to routine surveillance – 4 years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.79
	ICER (£/QALY)			35,408

Abbreviations: BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; LR, locoregional recurrence; mg, milligram; QALY, quality adjusted life year; RDI, relative dose intensity; SMR, standardised mortality ratio; ToT, time on treatment.

For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2 and 6.3.

2 Introduction and background

2.1 Introduction

Herein is a critique of the evidence submitted to the Single Technology Appraisal (STA) in support of the clinical and cost effectiveness of pembrolizumab (KEYTRUDA®, Merck Sharp & Dohme) in the adjuvant treatment of renal cell carcinoma (RCC) post-nephrectomy.

2.2 Background

Within Section B.1 of the company submission (CS), the company provides an overview of:

- Adjuvant pembrolizumab (hereafter referred to as pembrolizumab), including its mode of action, dose and method of administration (CS, Section B.1.2);
- RCC, including aetiology, prevalence, comorbidities and risk factors for RCC, burden of disease and current disease management (CS, Section B.1.3).

Based on advice from its clinical experts, the Evidence Review Group (ERG) considers the CS to present an accurate overview of the epidemiology and aetiology of RCC, and the management of the disease.

As outlined in the CS, with some supplementary information provided by the ERG:

- RCC is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine and is the most common type of kidney cancer (more than 80% of the cases).[1]
- In 2017, 10,759 new kidney cancer cases were diagnosed in England. The incidence rate of kidney cancer increases with age and is highest in people over 85 years of age.[1]
- When RCC is in its early stages, patients may be symptom-free. As the disease progresses, symptoms may include: a lump in the abdomen; blood in the urine; unexplained weight loss; loss of appetite; fatigue; vision problems; persistent pain in the side.[2]
- The stage of RCC reflects the tumour size, extent of invasion outside of the kidney, the involvement of lymph nodes and whether the tumour has metastasized.[2]
- The staging system most often used for kidney cancer is the TNM (tumour, node, metastasis) system. As shown in Table 8, the TNM system is based on 3 key pieces of information:
    - The size and extent of the main tumour (T);
    - The spread to nearby lymph nodes (N);
    - The spread (metastasis) to distant sites (M).

- Approximately two-thirds of the cases are diagnosed without evidence of metastatic disease.[3]
- Smoking and obesity are established risk factors for RCC. Several hereditary conditions, such as von Hippel-Lindau disease, predispose patients to having an increased risk of developing clear cell RCC.[1]
- In the UK, RCC is more common in White males than in Asian or Black males and is more common in White females than in Black females, but similar to Asian females.[1]
- Around 1,100 cases of kidney cancer each year in England are linked with deprivation (around 580 in females and around 510 in males).[1]
- Where possible, treatment of tumours is surgery with curative intent. Treatment options for localised tumours include laparoscopic or open nephrectomy, and ablation techniques including radiofrequency ablation and cryoablation. [4] NICE Cancer Service Guideline 2, 'Improving outcomes in urological cancer' recommends that surgery can also be considered when there is metastatic disease.[5]
- Following surgery, patients can then be further classified on their risk of recurrence based on tumour staging and pathology. After nephrectomy, RCC recurs in 20% to 40% of patients with clinically localised disease.[6]
- Tumour stage plays an important role in risk and timing of recurrence; the incidence of RCC recurrence after nephrectomy has been reported to be 7% with a median time of 38 months for T1 tumours, 26% with a median time of 32 months for T2 disease, and 39% with a median time to recurrence at 17 months for T3 tumours.[6]
- As an immunotherapy, pembrolizumab acts by stimulating the body's immune system to fight cancer cells. Pembrolizumab targets and blocks PD-1 on the surface of T-cells, which triggers the T-cells to find and kill cancer cells.

Table 8. Renal cancer TCN staging system[7]

Stage	Stage grouping	Stage description*
I	**T1, N0, M0**	The tumour is 7 cm across or smaller and is only in the kidney (T1). There is no spread to lymph nodes (N0) or distant organs (M0).
II	**T2, N0, M0**	The tumour is larger than 7 cm across but is still only in the kidney (T2). There is no spread to lymph nodes (N0) or distant organs (M0).
	T3, N0, M0	The tumour is growing into a major vein (like the renal vein or the vena cava) or into tissue around the kidney, but it is not growing into

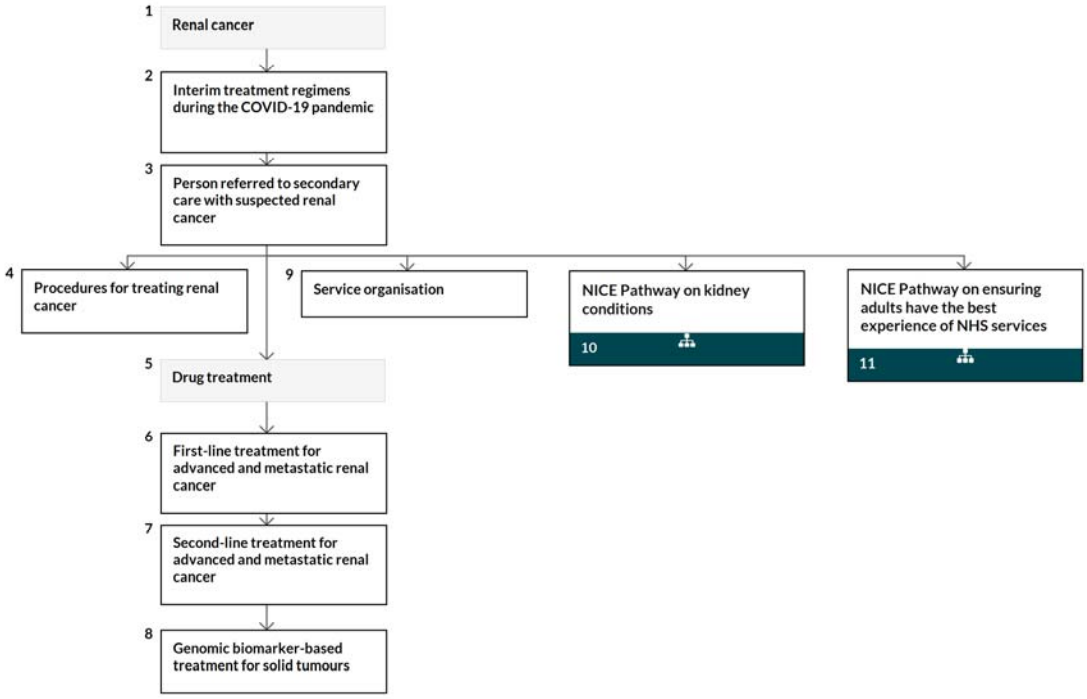
III		the adrenal gland or beyond Gerota's fascia (T3). There is no spread to lymph nodes (N0) or distant organs (M0).
	OR	
	T1 to T3, N1, M0	The main tumour can be any size and may be outside the kidney, but it has not spread beyond Gerota's fascia. The cancer has spread to nearby lymph nodes (N1) but has not spread to distant lymph nodes or other organs (M0).
IV	**T4, Any N, M0**	The main tumour is growing beyond Gerota's fascia and may be growing into the adrenal gland on top of the kidney (T4). It may or may not have spread to nearby lymph nodes (any N). It has not spread to distant lymph nodes or other organs (M0).
	OR	
	Any T, Any N, M1	The main tumour can be any size and may have grown outside the kidney (any T). It may or may not have spread to nearby lymph nodes (any N). It has spread to distant lymph nodes and/or other organs (M1).

2.2.1 Positioning of pembrolizumab in the UK treatment pathway

The CS provides a reasonable overview of current service provision for the management of people with RCC post-nephrectomy, including detail of where pembrolizumab will fit in the treatment pathway.

Currently, people with renal cancer in the UK may be offered drug treatment as first line therapy for previously untreated RCC or interventional procedures to treat the renal cancer (Figure 1). Currently, avelumab with axitinib, and nivolumab with ipilimumab are recommended for use within the Cancer Drugs Fund as options for untreated advanced RCC in adults, while cabozantinib, tivozanib, and pazopanib, and sunitinib are recommended within their marketing authorisation as first-line options for treating RCC.[4] The interventional procedures include laparoscopic cryotherapy, percutaneous cryotherapy, percutaneous radiofrequency ablation, laparoscopic partial nephrectomy, and laparoscopic nephrectomy (including nephroureterectomy).[4]

Figure 1. NICE pathway for renal cell carcinoma[4]



For patients deemed suitable for nephrectomy, treatment is typically followed by routine clinical visits for monitoring of changes in disease status and wellbeing. Following nephrectomy, patients can be classified on their risk of recurrence based on tumour staging and pathology. The company describes the criteria employed within the key trial to identify patients who are at increased risk of recurrence (Table 9). The frequency and duration of follow-up with routine surveillance will typically be dependent on risk of recurrence and fitness of patient. However, the ERG's clinical experts advised with typical routine surveillance following nephrectomy for RCC, a CT scan would be done 6-monthly for the first 3 years and annually for years 3 to 5, with further CT scans possibly being carried out at 7 and 10 years. The ERG's clinical experts also suggested in the current treatment pathway most patients who experience locoregional recurrence will be offered salvage surgery with curative intent, while patients with metastatic disease would likely be offered systemic therapy and managed as per the current NICE pathway. The ERG recognise that further research may be required to determine the treatment pathway beyond adjuvant therapy post-nephrectomy.

Table 9. Risk classification for intermediate-high risk, high risk, and M1 NED RCC used in the KEYNOTE-564 study (reproduced from CS, Table 4)

Category	Criteria based pathologic TNM staging and Fuhrman grading	Description
Intermediate-high risk of recurrence RCC	pT2, Grade 4 or sarcomatoid, N0, M0	Tumour was limited to the kidney and >7 cm, the cancer cell nuclei were bizarre, extremely irregular and often multilobed or had histological, cytological, or molecular properties of both epithelial and mesenchymal tumours, no regional lymph node metastasis, no distant metastasis.

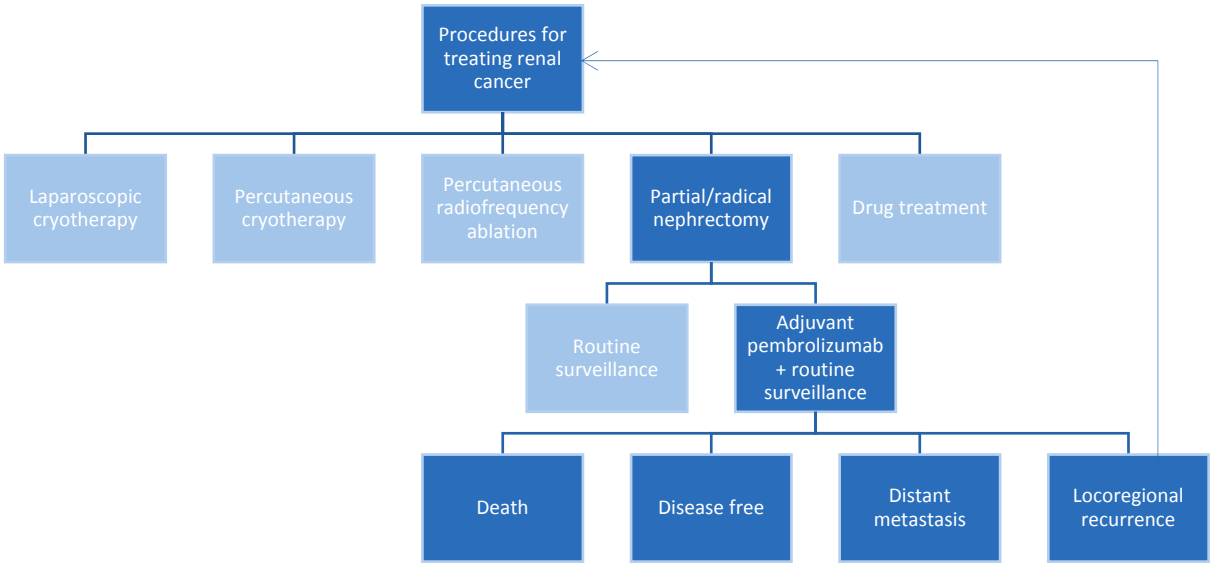
	pT3, any grade, N0, M0	Tumour had extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond Gerota's fascia, any Fuhrman grade, no regional lymph node metastasis, no distant metastasis.
High-risk of recurrence RCC	pT4, any grade, N0, M0	Tumour involved ipsilateral adrenal gland or invades beyond Gerota's fascia, any Fuhrman grade, no regional lymph node metastasis, no distant metastasis.
	pT any stage, any grade, N+, M0	Tumour was of any stage, any Fuhrman grade, had metastatic involvement of regional lymph node(s), no distant metastasis.
M1 NED RCC	Participants who presented not only with the primary kidney tumour, but also solid, isolated, soft tissue metastases that could be completely resected at one of the following: • the time of nephrectomy (i.e. synchronous) or, • ≤1 year from nephrectomy (i.e. metachronous)	

Abbreviations: RCC: renal cell carcinoma; pT: pathologic tumour; N: node; M: metastasis; NED: no evidence of disease

The company explains that where the primary tumour has been successfully removed by nephrectomy and patients have been declared macroscopically disease-free, the aim of adjuvant treatment is to prevent recurrence of disease. Micro-metastases and individual tumour cells may still be present following surgery or may arise *de novo* and will develop into larger tumours with the potential to disseminate to distant sites around the body resulting in advanced, unresectable tumours. At the time of writing there is currently no globally accepted standard of care in adjuvant RCC for patients post-nephrectomy. While alternative options to pembrolizumab in this setting have been investigated previously, none have yet been put forward for NICE technology appraisal as an adjuvant therapy post-nephrectomy to reduce the risk of RCC recurrence and so do not have marketing authorisation for this indication. Data from the S-TRAC study indicated that, in the "highest risk for recurrence" patient population, disease-free survival was increased with the use of adjuvant sunitinib compared with placebo.[8, 9] The ASSURE trial showed no benefit for adjuvant sunitinib or sorafenib in the "intermediate- to high-risk" patient population.[9, 10] The ARISER (adjuvant girentuximab) and PROJECT (adjuvant pazopanib) trials indicated no survival benefit, but subgroup analyses in both trials recommended further investigation.[9]

Current NICE pathway for RCC does not recommend any specific adjuvant treatment following nephrectomy for treating renal cancer (Figure 1). As such, only pembrolizumab compared to established clinical management without pembrolizumab is considered for this appraisal. The company's proposed positioning of pembrolizumab in the NICE pathway is as adjuvant therapy following partial or complete nephrectomy (Figure 2).

Figure 2. Proposed positioning of pembrolizumab in treatment pathway for RCC.



2.3 Critique of the company's definition of the decision problem

2.3.1 Population

The population considered by the company for this STA [redacted]. This patient population group is notably narrower than the NICE final scope, which set to include people with RCC who have had nephrectomy, regardless of risk of recurrence.[11] The ERG agrees that the population considered by the company is appropriate as it is aligned with the proposed marketing authorisation for adjuvant pembrolizumab and reflective of the population included in KEYNOTE-564, the key trial informing the appraisal.

KEYNOTE-564 enrolled participants with RCC with clear cell component with intermediate-high or high risk of recurrence following nephrectomy, or metastasis stage M1 with no evidence of disease (M1 NED) following nephrectomy and resection of metastatic lesions. Full eligibility criteria for KEYNOTE-564 can be found in Sections B.2.3 of the CS. Risk categories were based on pathological tumour node metastasis, Fuhrman grade, and presence of sarcomatoid features. The intermediate-high risk category included pathologic tumour stage T2 (pT2) with Grade 4 or sarcomatoid; pathologic tumour stage T3 (pT3), any grade without nodal involvement (N0) or distant metastases (M0). The high-risk category included any pathologic tumour stage T4 (pT4), any grade N0 and M0, any pathologic tumour stage, any grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and

metastatic lesions. The ERG's clinical experts considered these inclusion criteria to be appropriate and agreed with the classifications used to determined risk categories.

Overall, the ERG is satisfied that the patient population considered in the CS is applicable to that set out in NICE final scope and UK practice.

2.3.2 *Intervention and comparator*

Pembrolizumab (KEYTRUDA®) is a monoclonal antibody of the IgG4/kappa isotype designed to exert a 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. By binding to the PD-1 receptor and blocking the interaction with the receptor ligands, pembrolizumab releases the PD-1 pathway-mediated inhibition of the immune response, and reactivates both tumour-specific cytotoxic T-lymphocytes in the tumour microenvironment and antitumour inactivity.

At the time of writing, pembrolizumab does not have a UK marketing authorisation for adjuvant therapy following nephrectomy in people with RCC. The expected date of the opinion from the Committee for Human Medicinal Products is in [redacted]. The company anticipates the marketing authorisation for the UK to be as [redacted]

The intervention considered within the CS is 200 mg adjuvant pembrolizumab, delivered by intravenous (IV) infusion as a monotherapy every three weeks (Q3W). This is consistent with the intervention provided in KEYNOTE-564, where the treatment regimen for adjuvant pembrolizumab was 200 mg Q3W, restricted to a maximum of 17 cycles of treatment.

Participants of KEYNOTE-564 received either pembrolizumab or placebo for the 17 cycles or until confirmation of disease recurrence or meeting the criteria for discontinuation of study treatment (full details on reasons for discontinuation are given in Appendix L of the CS). Considering the recommended number of cycles of pembrolizumab in the CS, the ERG notes that wording of guidance on how long to continue pembrolizumab for RCC [redacted] the draft Summary of Product Characteristics (SmPC). The draft SmPC advises that, "[redacted]. The ERG notes that the SmPC adds, "[redacted]

[redacted]." The ERG's clinical expert advised that the duration of therapy proposed by the company and employed in the key trial are reasonable and in line with current UK practice.

The ERG notes that the draft SmPC states pembrolizumab as monotherapy can be given either as 200 mg Q3W or 400 mg every six weeks (Q6W). The ERG's clinical experts commented that they would expect the two dosing schedules for pembrolizumab to be of equivalent clinical effectiveness, but added that the Q6W schedule may be preferential with both patients and healthcare professionals given the reduced number of hospital visits required. During clarification, the company also provided a scenario to consider the costs associated with a Q6W regimen and concluded that the choice of Q6W versus Q3W dosing is not expected to have a significant impact on costs and may indeed produce cost savings.

The comparator considered in the CS is standard of care (SoC) which includes routine surveillance and is informed by the placebo arm of KEYNOTE-564, in line with the NICE final scope.[11] The company explained that during the treatment period, participants have routine clinical visits for administration of study intervention and monitoring of safety, well-being, and changes in disease status. Given the absence of current recommendation for adjuvant therapy following nephrectomy, the ERG agrees that currently the only applicable comparator to pembrolizumab within this setting is established clinical management without pembrolizumab.

Table 10. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	ERG comment
Population	People with renal cell carcinoma (RCC) who have had nephrectomy	[redacted]	Wording updated to better reflect the expected population in the marketing authorisation.	Although narrower than the population outlined in the NICE final scope, the ERG is satisfied with the population considered by the company as it is aligned with the proposed marketing authorisation for adjuvant pembrolizumab.
Intervention	Pembrolizumab	Pembrolizumab	N/A	The intervention in considered by the company and that used in the key trial (KEYNOTE-564) matches the intervention specified in the final scope, that is adjuvant pembrolizumab. The ERG notes that the draft SmPC states that pembrolizumab as monotherapy can be given as 200 mg Q3W or 400 mg Q6W, yet the evidence from the key trial KEYNTOE-564 only provides evidence for pembrolizumab 200 mg Q3W. However, during clarification the company provided a scenario to consider the anticipated costs associated with a Q6W regimen.
Comparator(s)	Established clinical management without pembrolizumab	Established clinical management without pembrolizumab	N/A	The ERG agrees that the comparator in KEYNOTE-564 matches that specified in the final scope of established clinical management without pembrolizumab. Participants in

				the comparator arm of the KEYNOTE-564 trial were randomised to receive IV placebo Q3W and standard clinical management.
Outcomes	• Overall survival (OS) • Disease-free survival (DFS) • Adverse effects (AE) of treatment • Health-related quality of life (HRQoL)	• Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life	N/A	The ERG considers that the outcomes of KEYNOTE-564 and the CS match those listed in the NICE final scope. The primary outcome from KEYNOTE-564 and the CS is disease-free survival. The ERG recognises that the OS and DFS data are immature, but that this is unsurprising in a trial of adjuvant therapy and is acknowledged by the company in the submission. The ERG notes that adverse effects were comprehensively reported in the CS. HRQoL data was also captured using the EQ-5D-3L, FKSI-DRS and EORTC QLQ-C30. The ERG considers these appropriate tools for measuring HRQoL.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	Same	Not applicable	The company's model adheres to the decision problem for the comparison of pembrolizumab and SoC. A single de novo Markov model was developed to assess the cost-effectiveness of pembrolizumab compared with routine surveillance as adjuvant treatment. The company

	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.			reports results of a base-case ICER alongside a probabilistic sensitivity analysis.
Subgroups to be considered	NA	• Age • Gender • Race • ECOG Performance scale • PD-L1 status • Metastatic staging • Type of nephrectomy	N/A	The ERG's clinical experts have advised that the subgroups reviewed within the clinical effectiveness sections of the CS are appropriate.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the	No equity or equality considerations anticipated.	N/A	N/A

	marketing authorisation granted by the regulator.			

Abbreviations: NICE: National Institute of Health and Care Excellence; ERG: Evidence review group; RCC: renal cell carcinoma; CS: company submission; OS: overall survival; DFS: disease free survival: HRQoL: health-related quality of life; EQ-5D-3L: European Quality of Life Five Dimension; FKSI-DRS: Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index - Disease Related Symptoms; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer quality of life questionnaire; SoC: standard of care; ICER: incremental cost-effectiveness ratio; ECOG: Eastern Cooperative Oncology Group; PD-L1: programmed death-ligand 1 (protein)

3 Clinical effectiveness

3.1 Critique of the methods review

The company conducted a systematic literature review (SLR) to identify randomised controlled trial (RCT) evidence on the efficacy and safety of pembrolizumab for individuals with RCC who had undergone nephrectomy. Full methods and results of the SLR are reported in Appendix D of the company submission (CS). A summary of the methods, together with the Evidence Review Group's (ERG's) critique of the appropriateness of the methods adopted, is presented in Table 11.

Interventions and comparators specified in the inclusion criteria for the SLR encompassed those listed as relevant to the decision problem as set out in the final scope issued by the National Institute for Health and Care Excellence (NICE).[11] The interventions considered in the SLR also included adjuvant treatment options for RCC post-nephrectomy other than pembrolizumab (such as sunitinib, nivolumab, ipilimumab). However, for reasons outlined in Section 2.2.1, and for the purpose of the CS, only trials comparing pembrolizumab to standard of care were included in the final screening. All trials that did not investigate pembrolizumab were excluded.

The searching of bibliographic databases returned 2,829 citations. Of these citations, 133 full text publications were retrieved from the SLR and were assessed for eligibility. Of the 133 publications, only two citations representing one unique trial met the predetermined inclusion criteria, investigating the efficacy of pembrolizumab for individuals with RCC who had undergone nephrectomy (and investigated pembrolizumab versus placebo, the relevant comparator in the context of the CS).

The included study, KEYNOTE-564 is a phase III RCT comparing pembrolizumab with placebo, both administered in addition to standard of care (SoC) which included routine surveillance. KEYNOTE-564 was used by the company as the primary source of clinical evidence for pembrolizumab and SoC in the economic model.

Overall, the ERG considers the company's SLR to be of satisfactory quality and likely to have retrieved all studies relevant to pembrolizumab, despite limiting inclusion to English-language publications.

Table 11. Summary of ERG's critique of the methods implemented by the company to identify evidence relevant to the decision problem.

Systematic review step	Section of CS in which methods are reported	ERG assessment of robustness of methods
Data sources	B.2.1 & Appendix D, Section D1.1	**The ERG considers the sources and dates searched to be appropriate.** Databases searched: • EMBASE (through the OVID portal) • MEDLINE (through the OVID portal) • Cochrane Registry of Controlled Trials (through the OVID portal) Additional sources: Manual searches were conducted in clinicaltrials.gov to identify RCTs that had not been published but are potentially eligible for inclusion. Conferences searched include: • American Society of Clinical Oncology (ASCO) • American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO-GU) • American Urological Association (AUA) • European Society for Medical Oncology (ESMO) • American Association for Cancer Research (AACR) • European Association of Urology (EAU)
Search strategies	B.2.1 & Appendix D, Section D1.1	**The ERG is satisfied that searches have identified all evidence relevant to the decision problem.** Search strategies for the literature review combined comprehensive terms for the population, interventions and study designs, using free-text and medical subject headings. Searches were conducted in August 2021 and would be expected to capture contemporary research.
Inclusion criteria	B.2.1 & Appendix D, Section D1.1 (table 4)	**The ERG considers it likely that no relevant evidence was excluded based on the eligibility criteria used.** SLR inclusion criteria were in line with the NICE final scope. The original inclusion criteria for the SLR was wider than that of the NICE final scope, and included interventions and comparators not included in the NICE scope. Literature identified from the SLR was then screened against a refined inclusion criteria in line with the NICE final scope for the purpose of the CS. Full reference details are available in the CS Appendix for the included study and for studies excluded at full-text appraisal. The inclusion of relevant studies was limited to English-language publications.
Screening and data extraction	B.2.1 & Appendix D, Section D1.1 (figure 1)	**The ERG considers the reporting of methods for screening and data extraction to be unclear.** Results of the literature screening processes were summarised in PRISMA diagrams. Details on how the data extraction was carried and if the screening was subsequently validated by a second reviewer is

		not reported. The process and methods of data extraction are also not reported.
Tool for quality assessment of included study or studies	B.2.5 & Appendix D, Section D1.3	**The ERG agrees with the company's choice of quality assessment tool.** The company followed an appropriate process of assessing the quality of the key trial by using the Cochrane Collaboration Risk of Bias (RoB) tool. The ERG notes that it is unclear if quality assessment was done by one or two reviewers and, if so, whether the assessments were done independently. The ERG also notes that justification for the risk of bias assigned to each domain is not provided. Detailed reasons in support of the judgement of level of bias for each aspect of trial design would improve the validity of the company's quality assessment. See Appendix 9.1 for ERG validation of the quality assessments.

Abbreviations: CS: company submission; ERG: evidence review group; NICE: National Institute of Health and Care Excellence; SLR: systematic literature review; RoB: risk of bias; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation

In subsequent sections, the ERG focuses on aspects of trial design, conduct and external validity of KEYNOTE-564, the main study that is to the focus of this Single Technology Appraisal (STA). The ERG's assessment of the design, conduct and internal validity of KEYNOTE-564 is summarised in Table 12. The ERG agrees with the company's assessment of KEYNOTE-564 as being at overall low risk of bias for analysis of the outcomes of interest.

Table 12. Summary of ERG's critique of the design and conduct of KEYNOTE-564,[12] the trial evaluating the technology of interest to the decision problem.

Aspect of trial design or conduct	Section of CS providing details on trial characteristic	ERG's critique
Trial conduct		
Randomisation	B.2.3 & Appendix L	**Appropriate** Randomised design with parallel assignment of participants in 1:1 ratio to receive either placebo or pembrolizumab 200 mg, administered by IV infusion every 3 weeks (Q3W). Randomisation was stratified by: • Metastasis status (M0 versus M1 no evidence of disease [NED]) • Within M0 group, there will be 2 stratification factors: a) Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 versus 1) b) USA participant (YES versus NO)

Concealment of treatment allocation	B.2.3 & Appendix L	**Appropriate** Randomisation was carried out using a random number generator, providing each eligible participant with a random and anonymised treatment number. Treatment allocation occurred centrally using the interactive voice response system/integrated web response system (IVRS/IWRS).
Eligibility criteria	B.2.3 & Appendix D, Section D1.1	**Appropriate** Participants with RCC with clear cell component with study protocol-defined intermediate-high or high risk of recurrence following nephrectomy, or metastasis stage M1 with no evidence of disease (M1 NED) following nephrectomy and resection of metastatic lesions. The ERG's clinical experts have advised that the eligibility criteria employed in KEYNOTE-564 were appropriate.
Baseline characteristics	B.2.3 - Table 7	Baseline characteristics were well balanced between the pembrolizumab 200 mg and placebo trial arms. Full baseline characteristics from KEYNOTE-564 are available in appendix 9.3.
Masking appropriate	B.2.3 & Appendix L	**Appropriate** A double-blinding technique was used. Pembrolizumab and placebo were prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The participant and the investigator who is involved in the study treatment administration or clinical evaluation of the participants are unaware of the group assignments. The primary outcome of disease-free survival (DFS) was also assessed by both investigators and blinded independent central review (BICR).
No difference between groups in treatments given, other than intervention versus control	B.2.3 & Appendix L	No evidence to suggest a difference between trial arms in treatments given additional to allocated intervention. Study drug (pembrolizumab or placebo) was given in addition to SoC. Concomitant medications or vaccinations specifically prohibited in the exclusion criteria were not allowed during the ongoing trial. The ERG notes that participants may have received other medications that the investigator deemed to be medically necessary. Any concomitant medication was to be recorded on a case report form, but this data was not reported in the CS.
Dropouts (high drop out and any unexpected imbalance between groups)	B.2.6	The ERG notes that the proportion of patients who discontinued study treatment prior to completing 17 cycles was higher in the pembrolizumab trial arm than the placebo trial arm: 190 (38.9%) participants in the pembrolizumab arm and 130 (26.2%) participants in the placebo arm had discontinued study treatment. The company provide detail on reasons for participant discontinuation, which demonstrates an increased rate of adverse event with pembrolizumab compared to placebo causing the disparity in early treatment discontinuation between trial arms. As of the 14-JUN-2021 data cutoff, [redacted] of randomised participants ([redacted] participants[redacted] in the pembrolizumab arm and [redacted] in the placebo arm) remained ongoing in the study.
Outcomes assessed	B.2.1 & Appendix D, Section D1.1	The outcomes assessed in KEYNOTE-564 and informing the CS were: • Overall survival • Disease-free survival • Adverse effects of treatment • Health-related quality of life

		The ERG considers that the outcomes of KEYNOTE-564 match those listed in the NICE final scope. The ERG notes that the primary outcome from KEYNOTE-564 is disease-free survival. The ERG notes that adverse effects were comprehensively reported in the CS. HRQoL data were also captured using the EQ-5D-3L, FKSI-DRS and EORTC QLQ-C30. The ERG considers these appropriate tools for measuring HRQoL within this setting.
ITT analysis carried out	B.2.4	**Yes** Efficacy outcomes were assessed by analysing the intention to treat population.
Subgroup analyses	B.2.7	Prespecified subgroup analyses were based on: • Age (<65 years vs ≥65 years) • Gender (male vs female) • Race (white vs non-white) • ECOG performance scale (0 vs 1) • PD-L1 status (CPS <1 vs CPS ≥1) • Region (non-US vs US) • Metastatic staging (M0 vs M1 NED) • Type of nephrectomy (Partial vs Radical)
Statistical analysis plan		
Sample size	B.2.4 & Appendix L	**Appropriate** The sample size was planned for 950 and the power calculations provided were based on 990, which is a number more in line with the actual final number of randomised participants.
Power	B.2.4 & Appendix L	For the DFS endpoint, based on a target number of 332 events and one IA at approximately 80% of the target number of events, the study has approximately 95% power to detect a HR of 0.67 at an overall alpha level of 2.5% (1-sided). For the OS endpoint, the power is conditional on the null hypothesis of DFS being rejected, based on a target number of 200 events and 3 interim analyses at approximately 47%, 66%, and 86% of the target number of events, the study has approximately 79% power to detect a HR of 0.67 or approximately 88% power to detect a HR of 0.635 at an overall alpha level of 2.5% (1-sided). The above sample size and power calculations for DFS and OS assume the following: • DFS follow a Poisson mixture cure rate model with assumed cure rate of 0.3. The cure rate of 0.3 is estimated based on historical data. • The median DFS is assumed to be 45 months for those not cured in the control group. • OS follows an exponential distribution with a median of 145 months for the control group. • Enrolment period of 27 months with monthly accrual of 20 participants during the first 5 months and monthly accrual of 30 participants from

		month 6 to month 21, and monthly accrual of 1 participant for the last month. • A yearly drop-out rate of 2% for DFS and 1% for OS.
Analysis for estimate of effect	B.2.4 & Appendix L	The primary and secondary hypotheses addressing DFS and OS were evaluated by comparing pembrolizumab to placebo using a stratified log rank test. Estimation of the hazard ratio was done using a stratified Cox regression model. Event rates over time were estimated within each treatment arm using the Kaplan Meier (KM) method. The analysis of safety results was assessed via point estimates with 95% CIs provided for between-group comparisons.

Abbreviations: M(#): metastasis; NED: no evidence of disease; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IVRS/IWRS: interactive voice response system/integrated web response system; RCC: renal cell carcinoma; DFS: disease-free survival; BICR: blinded independent central review; OS: overall survival; KM: Kaplan Meier

3.2.1 *Internal validity of KEYNOTE-564*

The ERG considers KEYNOTE-564 to be a well-designed and well-conducted RCT. The ERG agrees with the company's assessment of the trial being at low risk of bias, as reported in Appendix 9.1.

3.2.2 *External validity of KEYNOTE-564*

The ERG's clinical experts consider the characteristics of the population comprising KEYNOTE-564 to be generalisable to those undergoing nephrectomy following RCC and likely to be eligible for treatment with pembrolizumab in England if marketing authorisation were approved. However, the ERG's clinical experts did acknowledged that, as is typical in clinical trials, the patients in KEYNOTE-564 were younger and so possible healthier than in those seen in clinical practice. The CS also reports patient demographics of the European subset of participants, representing 37.7% (375/994) of all participants included in the intention to treat (ITT) analysis of KEYNOTE-564. The ERG agrees that the baseline characteristics of the European subgroup demonstrates a general consistency with the total study population characteristics. Sixty three of the 994 participants randomised in the KEYNOTE-564 were from trial sites in the UK.

The study compared intervention with pembrolizumab to placebo, both of which were administered in addition to SoC which included routine surveillance. The study protocol for KEYNOTE-564 proposed that participants would be followed up with radiographic imaging every 12 weeks during year 1, every 16 weeks during years 2 to 4, then every 24 weeks in years 5 and beyond. The company explained that during the treatment period, participants have routine clinical visits for administration of study intervention and monitoring of safety, well-being, and changes in disease

status. The ERG's clinical experts suggested that, while this process of follow-up is appropriate, radiographic imaging may occur less frequently in UK clinical practice with disease free patients undergoing CT imaging every ~6 months for the first 3 years following nephrectomy, and annually for years 3-5 post-nephrectomy.

Following nephrectomy, participants within the KEYNOTE-564 trial attended routine clinical visits to monitor for potential changes in disease status from disease-free to locoregional recurrence, distant metastasis, or death. The ERG notes that in the CS the proportion of patients with locoregional recurrence who had salvage surgery is estimated to be 22%, based on KEYNOTE-564 data. However, the ERG's clinical experts advised that in current practice in the NHS most patients with locoregional recurrence, where the disease extent is limited and removable surgically, would receive salvage surgery. Furthermore, the ERG's clinical experts advised that the estimate of 21% of patients receiving salvage surgery in the distant metastases state was likely an overestimate with the true proportion in clinical practice being closer to 10%.

As described in Section 3.3, both the OS and DFS data at the last data cutoff were immature with median DFS and OS not being reached in either treatment group. The immaturity of this data adds a level of uncertainty to the findings of the KEYNOTE-564 trial. Continuation of the study with further data collection may address the immaturity of the data and improve the validity of results.

Overall, the ERG considers that the findings of KEYNOTE-564 can be broadly applied to UK practice.

3.3 Clinical effectiveness results from KEYNOTE-564

3.3.1 Disease-free survival

DFS was defined by the company as the time from randomisation to the first documented local recurrence, or occurrence of distant kidney cancer metastasis(es), or death due to any cause, whichever occurs first. In the ITT population, based on investigator assessment (IA) at routine follow-up, pembrolizumab demonstrated [redacted] compared with placebo (HR [redacted], p [redacted]). The total number of DFS events [redacted], with [redacted] events in the pembrolizumab arm and [redacted] events in the placebo arm (Table 13). As of the 14-JUN-2021 data cutoff, the difference in the DFS rates between treatment groups at 12, 18, and 24 months ranged [redacted] The company also highlight that the Kaplan-Meier (KM) curves for

DFS separated from the outset in favour of pembrolizumab, and at the time of the latest data cutoff, the curves [redacted] (Figure 3).

Table 13. Summary of events and DFS based on investigator assessment (ITT population) (reproduced from CS, Table 14)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%) Death Disease Recurrence	[redacted]	[redacted]
Number of Censored (%) Last Tumor Assessment Showing No Disease Recurrence No Post-Baseline Disease Status Assessment	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a] Median (95% CI) [Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo Hazard Ratio (95% CI)[b] p-value[c]	[redacted]	[redacted]
DFS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]
DFS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

Abbreviations: CI, confidence interval; Q: quartile; NR, not reached; DFS, disease-free survival.

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), USA participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), USA participant (Yes versus No) within M0 group by investigator.

The ERG notes that a statistically significant result for DFS has been estimated in the ITT population, with a small p-value. However, the DFS data were immature with median DFS not being reached in either treatment group. In the decision problem meeting proforma, the company has indicated that they believe pembrolizumab to be a suitable candidate for the cancer drug fund (CDF) as this will

allow for additional data collection to reduce uncertainty in the follow-up data and associated modelling. The company highlight that the final analysis for this study has not yet been reached. Although the dates for further data being available are yet to be determined, the company has outlined plans to release subsequent data readouts when a target number of events is reached, with interim analysis 2 scheduled for when 332 DFS events have occurred. The company have added that the final analysis for DFS is currently anticipated to be available in 2024. The ERG agrees that attaining mature data will alleviate these uncertainties within the technology appraisal.

Figure 3. Kaplan-Meier plot of DFS, based on Investigator Assessment (ITT population) (reproduced from CS, Figure 2)

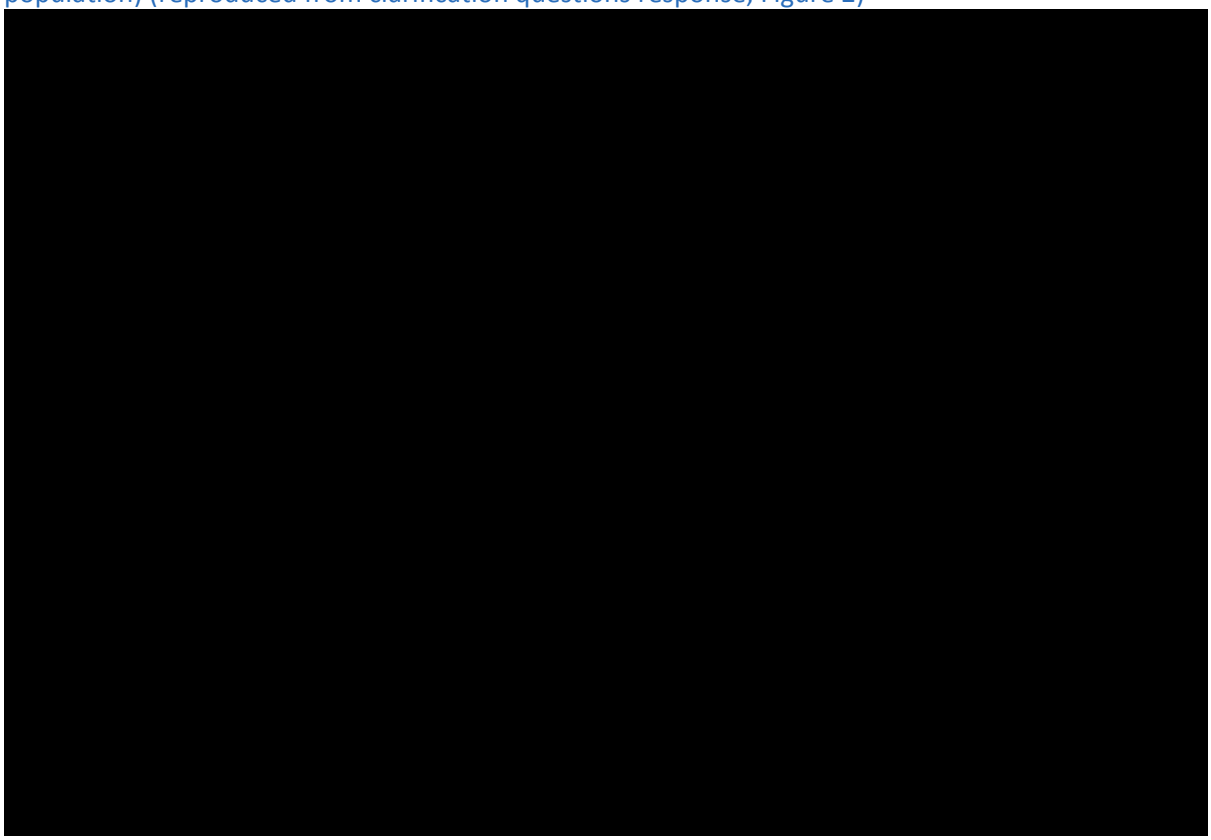
During clarification, the company provided further information around a secondary censoring analysis of IA DFS data. With this sensitivity analysis disease recurrence or death documented immediately after ≥2 consecutive missed disease assessments or after initiation of new anticancer treatment was censored. At the last data cutoff point, the HR using this sensitivity analysis was [redacted] and the nominal p-value was [redacted]. The ERG agrees that these results are

consistent with those from the primary analysis of DFS by investigator assessment from the KEYNOTE-564 study and support the findings of the primary analysis.

Consistent treatment effects were also observed across the prespecified subgroups, with all CIs overlapping the CI for the primary DFS HR (

Figure 4). The ERG acknowledges the consistent direction of effect observed across each of the population subgroups but notes the wide CIs around the point estimates. The ERG considers that the relative imprecision around many of the subgroup analyses is likely due to the small number of DFS events observed within each respective group, and suggest that caution should be taken when interpreting the results. The ERG's clinical expert also advised that, while the subgroup proportions are representative of clinical practice, it should be recognised that the M1 no evidence of disease (NED) subgroup is likely to be a heterogeneous population. The ERG's clinical expert added that a real difference in effect with pembrolizumab based on partial or radical nephrectomy is unlikely, and so further encouraged caution in interpreting the subgroup analysis DFS results. The ERG's clinical experts concurred that they would not interpret the subgroup results with any degree of confidence given the small size of subgroups and relative imprecision of confidence intervals around point estimates.

Figure 4. Forest plot of DFS hazard ratio by subgroup factors, based on Investigator Assessment (ITT population) (reproduced from clarification questions response, Figure 2)



DFS as assessed by the investigator is considered by the company to be an appropriate primary efficacy endpoint for an adjuvant trial, asserting that DFS will evaluate the study treatment's impact on disease recurrence and serve as a surrogate for OS assessment. The ERG agrees that DFS is an appropriate endpoint but holds the view that while DFS and OS are correlated, there is insufficient evidence to suggest the strength of the correlation (i.e. the magnitude of the DFS benefit may not directly translate into the magnitude of the OS benefit).

Furthermore, a sensitivity analysis using blinded independent central review (BICR) assessment was conducted in addition to IA DFS. The company assert that the BICR DFS results are consistent with IA BICR (IA HR of [redacted] versus BICR HR of [redacted] however, the ERG considers this difference in HR for each method of data collection is not immaterial. The company justified the use of IA DFS data as the primary endpoint over BICR DFS data, arguing that IA data is more generalisable and representative of real-world practice, reflecting the process by which clinicians in the NHS would assess patients for disease

recurrence. However, the ERG considers that BICR assessment of DFS is a more methodologically robust approach compared to IA as it is less susceptible to detection bias. As such, during the clarification stage the ERG requested the company to explore a scenario using BICR DFS data to inform the cost-effectiveness model, however the company declined to supply, arguing that IA remained a more appropriate measure of clinical efficacy. Further detail is provided in Section 4.2.5.

As discussed in Section 4.2.5 DFS data from KEYNOTE-564 informs the cost-effectiveness model put forward by the company, specifically the transitions from the disease-free (DF) health state to locoregional recurrence (LR), distant metastasis (DM), or death. Given the uncertainty around transitions from the disease-free health state with the immaturity of the DFS data from KEYNOTE-564, the company has attempted to validate estimates of DFS by comparing KEYNOTE-564 data against that from previous trials of tyrosine kinase inhibitors (TKIs) in the adjuvant setting for RCC (S-TRAC, ASSURE, and PROTECT).[8, 13, 14] The ERG considers this approach to be methodologically appropriate, agreeing that the previous trials of TKIs are suitable for comparison with the KEYNOTE-564 dataset given the similarities in trial design and setting, and the comparability of participant baseline characteristics. The ERG's clinical experts also advised that the populations from previous trials of TKIs were broadly comparable to that in KEYNOTE-564. Further discussion around the use of previous trials TKIs to validate DFS estimates is provided in Section 4.2.5. The company also relies on real-world data from the US Surveillance, Epidemiology and End Results (SEER) Medicare database in an effort to validate disease progression estimates around the KEYNOTE-564 data. The ERG's clinical expert advised that the comparison between KEYNOTE-564 evidence and US SEER database is appropriate, noting that practice in the USA and the UK is broadly similar in terms of surgery and treatment pathway for metastatic disease. The ERG's clinical expert did note that in the USA people may be offered surgery earlier than in the UK and that availability of effective treatments may differ slightly, but highlighted that these differences are unlikely to have a large effect. However, the ERG notes that the company's estimated extrapolations of DFS for routine surveillance from KEYNOTE-564 compared with the SEER observed and extrapolated data, adjusting for age and sex, appear to show that patients in KEYNOTE-564 have poorer outcomes. During clarification, the company proposed that this observed difference between estimated results of the KEYNOTE-564 and SEER datasets may be due to heterogeneity between the study populations. The ERG highlights that the participants involved in clinical trials are typically younger and healthier than patients seen in real-world practice, and so would usually present with more favourable outcomes by comparison. It is unclear if the apparent heterogeneity is a result of the KEYNOTE-564 population have a poorer

prognosis than the SEER population, or that the SEER population are receiving improved standard of care by comparison. The ERG notes that the subgroup analysis of DFS in the KEYNOTE-564 trial suggests a slightly reduced benefit of pembrolizumab against placebo in the USA population compared to the European Union (EU) population, although the difference noted is marginal and not statistically significant. The ERG considers that possible variation in the standard of care between USA and EU practices may be the reason for the difference observed in the subgroup analysis of DFS, and the comparison of KEYNOTE-564 and SEER DFS data. However, the ERG also notes that modelled OS data from KEYNOTE-564 and US SEER data shows less heterogeneity by comparison with the DFS data. The ERG agrees that further collection of DFS and OS data within the KEYNOTE-564 trial would reduce uncertainty around the long-term estimations of patient outcome. Further discussion around the use of US SEER database data by the company is provided in Section 4.2.5.

3.3.2 Overall survival

The company report that mortality was reduced with pembrolizumab compared to placebo. At the latest data cutoff there [redacted] of the total planned 200 OS events at the final analysis), with [redacted] deaths recorded in the pembrolizumab arm and [redacted] deaths in the placebo arm (Table 14). The HR was [redacted] however, the [redacted] arm (Figure 5). Additionally, the [redacted] at the last data cut-off.

Table 14. Summary of overall survival (ITT population) (reproduced from CS, Table 16)

	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]
Kaplan-Meier Estimates (months)[a] Median (95% CI) [Q1, Q3]	[redacted]	[redacted]
person-months	[redacted]	[redacted]
Event Rate / 100 person-months	[redacted]	[redacted]
vs Placebo Hazard Ratio (95% CI)[b] p-value[c]	[redacted]	[redacted]
OS Rate at month 12 (%) (95% CI)	[redacted]	[redacted]
OS Rate at month 18 (%) (95% CI)	[redacted]	[redacted]

OS Rate at month 24 (%) (95% CI)	[redacted]	[redacted]

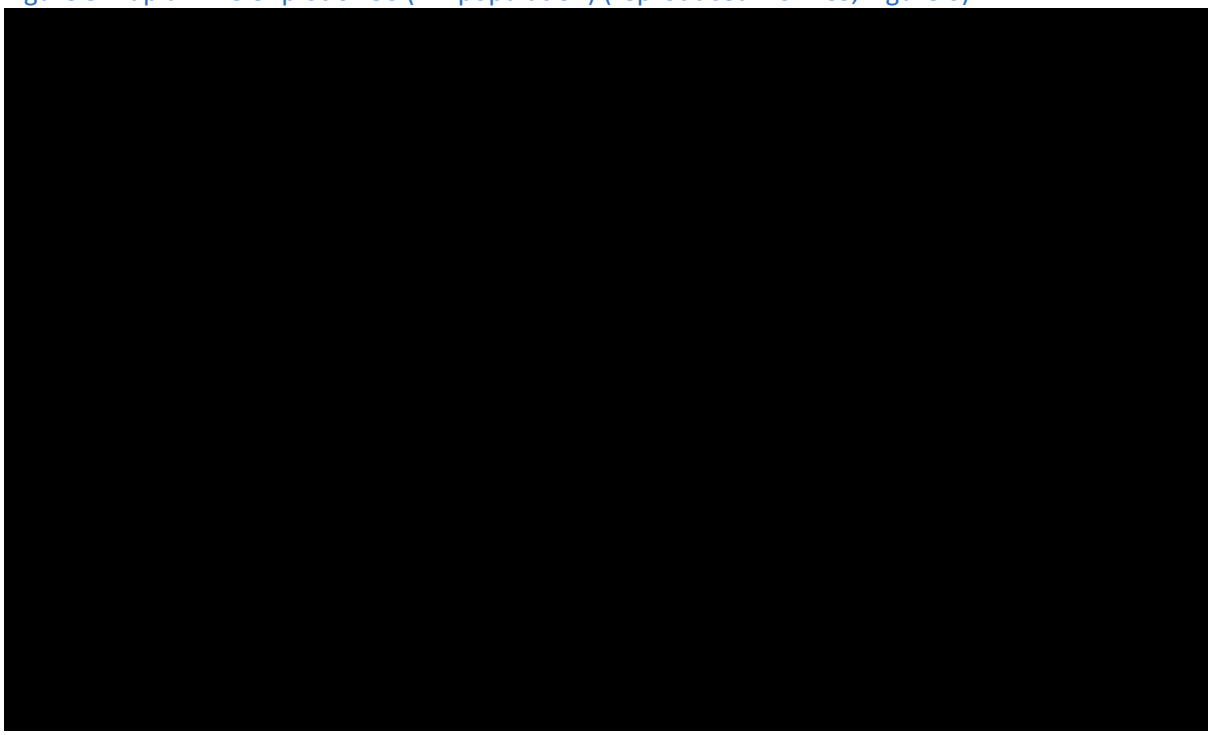
Abbreviations: Abbreviations: CI, confidence interval; Q: quartile; NR, not reached; OS: overall survival

[a] From product-limit (Kaplan-Meier) method for censored data.

[b] Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), USA participant (Yes versus No) within M0 group by investigator.

[c] One-sided p-value based on log-rank test stratified by metastasis status (M0 versus M1 NED by investigator) and ECOG PS (0 versus 1), USA participant (Yes versus No) within M0 group by investigator.

Figure 5. Kaplan-Meier plot of OS (ITT population) (reproduced from CS, Figure 6)



The ERG notes that the OS data from KEYNOTE-564 are extremely immature, adding a significant amount of uncertainty to the outcome data. The company proposes that this uncertainty around the OS benefit associated with pembrolizumab in this indication is expected to be reduced and resolved in future data readouts from the ongoing KEYNOTE-564 study. Although the ERG consider it unlikely that mature OS data would be achieved by the proposed data collection point (estimated for 2024), they expect that uncertainty may be reduced with further data collection.

The ERG also notes that the OS data from KEYNOTE-564 informed the cost-effectiveness modelling for pembrolizumab by the company, informing the health-state transition probabilities for DF to death and LR to death. However, as described in Section 4.2.5, background mortality had to be

applied from the beginning of the model time horizon for both arms of the model given that the OS data used for these transitions are immature. As with DFS, the company attempted to validate long-term predictions of OS for RCC patients by comparing modelled data against observed data from previous trials of TKIs in the adjuvant setting for RCC (S-TRAC, ASSURE, and PROTECT)[8, 13, 14], as well as real world data from the US SEER Medicare database. Again, the ERG considers this to be an appropriate method of validation. The ERG's clinical expert also agreed that the predicted OS at years 1 to 7 for patients receiving routine surveillance appeared reasonable.

3.3.3 *Adverse effects*

Adverse events observed within the KEYNOTE-564 trial at the last cut-off date (14-Jun-2021) were reported for the All Participants as Treated (APaT) population.

The overall incidence of AEs [redacted] between those who were randomised to receive pembrolizumab compared to those randomised to receive placebo (Table 15). The percentages of participants who had all-cause and drug-related Grade 3 to 5 AEs, serious AEs (SAEs), and AEs leading to discontinuation of study treatment were [redacted] in the pembrolizumab arm compared with the placebo arm. Two deaths due to AEs in the pembrolizumab arm (pneumonia and multiple organ dysfunction syndrome) and 1 death due to AEs in the placebo arm (haemorrhage intracranial) were reported, although none of the deaths were considered treatment related by the investigator. No new immune-mediated AEs were observed and no changes in type, nature, outcomes, and management of AE of special interest (AEOSI) were reported.

Table 15. Summary of adverse events (APaT population) (reproduced from CS, Table 23)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse event	[redacted]	[redacted]	[redacted]	[redacted]
with drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with toxicity grade 3-5 drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with serious drug-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]
who died	[redacted]	[redacted]	[redacted]	[redacted]
who died due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to an adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a drug-related adverse event	[redacted]	[redacted]	[redacted]	[redacted]
discontinued drug due to a serious adverse event	[redacted]	[redacted]	[redacted]	[redacted]

discontinued drug due to a serious drug-related adverseevent	[redacted]	[redacted]	[redacted]	[redacted]

The most frequently reported AEs at the latest data cutoff were [redacted] for those receiving pembrolizumab, and [redacted] for those receiving placebo (Table 16).

Table 16. Summary of most frequent adverse events (incidence ≥ 10% in one or more treatment groups, APaT population) (reproduced from CS, Table 24)

	Pembrolizumab		Placebo	
	n	(%)	n	(%)
Participants in population	488		496	
with one or more adverse events	[redacted]	[redacted]	[redacted]	[redacted]
with no adverse events	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]
Blood creatinine increased	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]

The company suggest that this trend of [redacted] is as expected in the comparison of an active treatment (pembrolizumab) versus placebo. The ERGs clinical expert advised that the rate of AEs observed in both the pembrolizumab and placebo treatment arms appeared reasonable and the AEs reported with pembrolizumab were in-line with those expected following one-year of adjuvant PD-L1 therapy.

The costs associated with adverse events were accounted for in the company's model, with Grade 3+ all-cause AEs being included in the analysis. More detail on adverse effects of pembrolizumab reporting in KEYNOTE-564 within the context of cost-effectiveness is reported in Section 4.2.6.

3.3.4 Quality of life

Data on health-related quality of life (HRQoL) outcomes from KEYNOTE-564 are not available from the 14-JUN-2021 data cutoff, however they are available from the first interim analysis (IA1, data cutoff of 14-DEC-2020). The company reports that no statistically significant differences were

observed between pembrolizumab and placebo in HRQoL in terms of change from baseline in EQ-5D.

This EQ-5D data was also used to inform the cost-effectiveness model performed by the company. More information on how the HRQoL data from KEYNOTE-564 informed cost-effectiveness analysis is given in Sections 4.2.6 and 4.2.7.

3.3.5 Other secondary outcomes

3.3.5.1 Disease recurrence-specific survival

The company reported two measures of disease recurrence-specific survival (DRSS). For DRSS1, local disease recurrence was the event of interest; distant disease recurrence or death were competing risk events. For DRSS2, disease recurrence with visceral lesion was the event of interest; local recurrence without visceral lesion, distant metastasis without visceral lesion, or death were competing risk events.

The company reports that the cumulative incidences of the event of interest in the pembrolizumab arm were consistently lower compared with the placebo arm over time for both DRSS1 and DRSS2, showing a favourable numeric trend in DRSS1 and DRSS2 for pembrolizumab compared with placebo (Table 17). The ERG note that these data are consistent with both local and distant recurrence contributing to the DFS results.

Table 17. Summary of DSRR based on investigator assessment (ITT population) (reproduced from CS, Tables 17 and 18)

	DRSS1		DRSS2	
	Pembrolizumab (N=496)	Placebo (N=498)	Pembrolizumab (N=496)	Placebo (N=498)
Number of Events (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Competing Events (%)	[redacted]	[redacted]	[redacted]	[redacted]
Number of Censored (%)	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Incidence of Event at month 12 (%) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative Incidence of Event at month 18 (%) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Cumulative Incidence of Event at month 24 (%) (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]

Cumulative incidence estimates at specified time points are based on nonparametric estimation of cumulative incidence of the event of interest accounting for competing risk events.

3.3.5.2 Event-free survival

Event-free survival (EFS) is defined by the company as time from randomisation to the first disease recurrence by BICR among participants who were assessed by BICR with no evidence of disease (i.e., NED) at baseline; or disease progression or death due to any cause among participants who were assessed by BICR with evidence of disease (i.e., non-NED) at baseline. The baseline disease status by BICR determined whether disease recurrence or disease progression was tracked for a participant.

An EFS analysis by BICR with baseline disease status based on baseline scans showed that participants randomised to receive pembrolizumab were less likely to experience an event (disease recurrence, progression or death) than those receiving placebo (HR [redacted], nominal p-value [redacted]). The company proposes that the EFS data showed [redacted] results with the primary DFS analysis by investigator assessment. The ERG agree that the trend observed with EFS is similar to that seen with IA DFS, but as with BICR DFS, suggest that the difference in magnitude of effect between IA DFS and BICR EFS is not unimportant.

3.4 Conclusions of the clinical effectiveness section

The ERG considers the company's SLR to be of reasonable quality and likely to have retrieved all studies relevant to pembrolizumab, despite limiting inclusion to English-language publications. The ERG also considers KEYNTOE-564, the key study informing the clinical effectiveness of pembrolizumab, to be a well-designed and well-conducted RCT, with an overall low risk of bias and high internal validity. KEYNOTE-564 is the only RCT, at the time of writing, reporting clinical effectiveness of adjuvant pembrolizumab compared to standard care for patients who have undergone nephrectomy for RCC.

The ERG considers the characteristics of the population comprising KEYNOTE-564 to be generalisable to those undergoing nephrectomy following RCC and likely to be eligible for treatment with pembrolizumab in England. The study compared intervention with pembrolizumab to placebo, both of which were administered in addition to SoC which included routine surveillance. The ERG's clinical

experts advised that radiographic imaging as part of routine surveillance may occur less frequently in UK clinical practice than as proposed in the KEYNOTE-564 trial, but did not consider this to significantly impact on the clinical outcomes reported. The ERG also notes that in the CS the proportion of patients with LR who had salvage surgery is estimated to be 22%, based on KEYNOTE-564 data. However, the ERG's clinical experts advised that in current practice in the NHS most patients with LR would receive salvage surgery. Furthermore, the ERG's clinical experts advised that the estimate of 21% of patients receiving salvage surgery in the DM state was likely an overestimate with the true proportion in clinical practice being closer to 10%. However, despite these noted differences, the ERG considers that the findings of KEYNOTE-564 can be broadly applied to UK practice.

For the primary outcome of DFS, the ERG considers that the evidence derived from the ITT population of KEYNOTE-564 supports the company's proposal that pembrolizumab improves DFS compared with SoC. Pembrolizumab was associated with a [redacted] compared with placebo ([redacted]). However, the DFS data were immature with median DFS not being reached in either arm. No significant differences in DFS were found for any of the subgroups explored by the company. The company also provided a sensitivity analysis of DFS by BICR assessment which showed a consistent trend in benefit with pembrolizumab but at a lower magnitude [redacted]). The ERG considers this difference in HR for IA and BICR DFS noteworthy and that BICR assessment is a more methodologically robust approach as it is less susceptible to detection bias.

OS data showed a trend to benefit with pembrolizumab with fewer mortality events in the pembrolizumab trial arm compared to placebo ([redacted] deaths with pembrolizumab versus [redacted] deaths with placebo) and a HR of [redacted]). However, the OS data were [redacted] in the two treatment groups. The percentages of participants who had all-cause and drug-related Grade 3 to 5 AEs, SAEs, and AEs leading to discontinuation of study treatment were [redacted] in the pembrolizumab arm compared with the placebo arm. The most frequently reported AEs were [redacted] for those receiving pembrolizumab, and [redacted] for those receiving placebo. The ERG's clinical expert advised that the noted AEs are typical of pembrolizumab therapy. No statistically significant differences were observed between

pembrolizumab and placebo in health-related quality of life in terms of change from baseline in EQ-5D.

While the evidence from KEYNOTE-564 presented by the company addresses the decision problem defined in the NICE final scope, the ERG has concerns around the external validity and certainty of immature DFS and OS data. Continuation of the study with further data collection may address the immaturity of the data and improve the validity of results.

4 Cost effectiveness

Table 18 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case results.

Table 18. Company's base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Deterministic results					
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	1.44	11,031
Probabilistic results					
Routine surveillance	[redacted]	[redacted]	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	1.38	11,709

Abbreviations: LYG, life year gained; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

4.1 ERG comment on the company's review of cost effectiveness evidence

The company performed two systematic literature reviews (SLRs) to identify published studies that could inform the cost-effectiveness evaluation of pembrolizumab for adjuvant treatment of renal cell carcinoma patients after nephrectomy. The first search (economic SLR) attempted to identify health state utility, resource use, costs and cost-effectiveness/cost-minimisation/budget impact studies. The second search sought to identify studies reporting health-related quality of life (HRQoL) or patient reported outcome (PRO) data. These searches were run on 10 September 2020. The electronic searches had no date limit and conference abstracts from 2016 to 2018 were searched.

A summary of the Evidence Review Group's (ERG's) assessment of the company's economic SLRs is presented in Table 19. Due to time constraints, the ERG was unable to replicate the company's searches and appraisal of identified abstracts.

Table 19: Systematic review summary

Systematic review step	Section of CS in which methods are reported			ERG assessment of robustness of methods
	Cost effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix G	Appendices G & H	Appendix I	Appropriate. The company searched MEDLINE, Embase, Embase-in-progress and Cochrane library. Grey

				literature was also hand searched covering three years of conference abstracts from ISPOR, ASCO, AACR, ESMO, NCCN, ASCO Genitourinary Cancers Symposium, AMCP Annual Meeting, AMCP Nexus, and ISOQOL.
Inclusion/exclusion criteria	Appendix G	Appendices G & H	Appendix I	Appropriate. The searches were restricted to an advanced RCC population who have undergone nephrectomy and have received no prior systemic therapy for locally advanced RCC. No restrictions were placed on intervention, comparators, outcomes, timeframe, or pharmacoeconomic study type. Only English language studies were included.
Screening	Appendix G	Appendices G & H	Appendix I	Appropriate. PRISMA flow diagram provided.
Data extraction	Appendix G	Appendices G & H	Appendix I	Appropriate.
Quality assessment of included studies	Appendix G	Appendices G & H	Appendix I	Appropriate.

Abbreviations: CS, company submission; ERG, evidence review group; HRQoL, health related quality of life.

The economic SLR identified six studies for analysis, of which, three were NIHR Horizon Scanning Centre reports on sunitinib and pazopanib for adjuvant renal cell carcinoma (RCC)[15-17] and three were conference abstracts.[18-20] None of the studies identified an existing economic model addressing the decision problem or provided robust HRQoL or cost data for the adjuvant RCC treatment setting, and hence were not used to inform cost or HRQoL parameters in the model. The HRQoL/PRO SLR also identified six publications (of four unique studies[21-24]) for analysis but none estimated health state utility values and hence were not used to inform the model.

Neither SLR identified a suitable model to use for the cost-effectiveness analyses, thus, the company developed a *de novo* economic model (outlined in Section 4.2.4). Neither SLR identified data used for parameterising this model. Instead, the HRQoL data used in the model came from the KEYNOTE-564 and KEYNOTE-426 trials. While cost and resource use data were sourced from the company's clinical experts, the British National Formulary, NHS Reference Costs 2019-2020,[25] previous NICE

technology appraisals (TAs) and a number of literature sources not identified by the company's SLR. The ERG considers the data sources used by the company to be reasonable.

4.2 Summary and critique of company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 20 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis, with reference to the NICE final scope outlined in Section 2.

Table 20. NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	All relevant health effects for adult patients RCC have been included.
Perspective on costs	NHS and PSS	All relevant costs have been included and are based on the NHS and PSS perspective.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis has been provided by the company. Fully incremental analysis not required as there is only one relevant comparator in the analysis.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime horizon (41.1 years).
Synthesis of evidence on health effects	Based on systematic review	The company performed an appropriate systematic review.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	QALYs based on EQ-5D-5L data from KEYNOTE-564 mapped to EQ-5D-3L and EQ-5D-3L data from KEYNOTE-426 used in the base case analysis.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	EQ-5D-5L data obtained directly from patients in KEYNOTE-564 mapped to EQ-5D-3L, as well as EQ-5D-3L data obtained directly from patients in KEYNOTE-426.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Patients in KEYNOTE-564 and KEYNOTE-426 are representative of the UK population.
Equity considerations	An additional QALY has the same weight regardless of the other	The economic evaluation matches the reference case.

	characteristics of the individuals receiving the health benefit	
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Costs included in the analysis have been sourced using NHS reference costs,[25] BNF[26] and published literature and are reported in pounds sterling for the price year 2020.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate of 3.5% has been used for both costs and health effects.

Abbreviations: ERG, evidence review group; NHS, national health service; PSS, personal social services; RCC, renal cell carcinoma; QALY, quality adjusted life year

4.2.2 Population

The modelled population considered by the company for this Single Technology Appraisal (STA) are [redacted], aligned with the proposed marketing authorisation for pembrolizumab as an adjuvant treatment. The modelled population is narrower than the NICE final scope, which includes people with RCC who have had a nephrectomy but the ERG does not consider this to be unreasonable as the proposed marketing authorisation reflects the clinical data used to estimate cost-effectiveness.[11]

Baseline characteristics of the modelled population are reflective of the European cohort of KEYNOTE-564, which is the key trial for pembrolizumab as adjuvant treatment for RCC post nephrectomy. The company considers the European cohort of KEYNOTE-564 to be representative of the eligible patient population in the UK. The ERG notes that the baseline characteristics of the European and the global cohort are similar. Additionally, the ERG's clinical expert advised that patient population of KEYNOTE-564 is generalisable to the UK patient population. No obvious subgroups were identified that warranted exploration. As such, the ERG considers the modelled population is relevant to the decision problem.

4.2.3 Interventions and comparators

The intervention considered for the economic analysis is pembrolizumab. Pembrolizumab, which is an intravenous (IV) infusion, is delivered as a monotherapy 200 mg every three weeks (Q3W). Additionally, the draft SmPC states that pembrolizumab as monotherapy can be given as 400 mg every six weeks (Q6W). In KEYNOTE-564, the treatment regimen for pembrolizumab was 200 mg Q3W, restricted to a maximum of 17 cycles of treatment and this has been used in the company's

base case analysis, which the ERG considers appropriate. Nonetheless, the ERG explored a scenario using the pembrolizumab 400 mg Q6W dosing regimen and results are reported in Section 6.3.

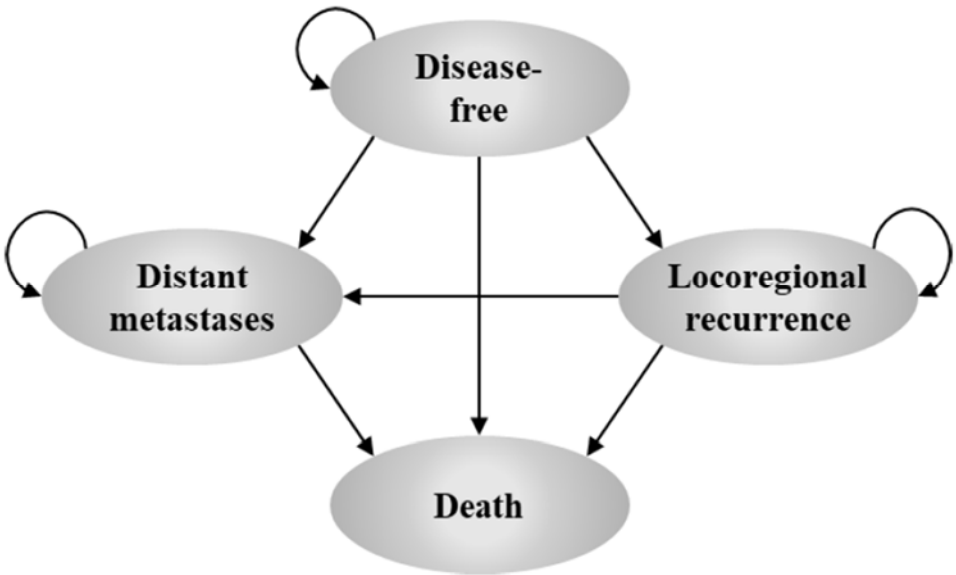
The comparator in the analysis is routine surveillance and is informed by the placebo arm of KEYNOTE-564, in line with the NICE final scope.[11]

4.2.4 *Modelling approach and model structure*

A single *de novo* Markov model was developed in Microsoft© Excel to assess the cost-effectiveness of pembrolizumab compared with routine surveillance as adjuvant treatment [redacted].

The model structure developed by the company aims to estimate the disease pathway after nephrectomy, in that patients remain disease-free, experience a disease recurrence or die. Thus, the health states included in the model are disease free (DF), locoregional recurrence (LR), distant metastases (DM) and death. Figure 6 presents the model schematic.

Figure 6. Model structure (Figure 13 of the company submission)



All patients enter the model in the DF health state following surgery (partial or radical nephrectomy or metastasectomy) and remain here until recurrence of disease or death. Recurrence of disease in the model is defined as either locoregional recurrence (disease at the primary site or nearby lymph nodes) or distant metastases (cancer has spread from the primary site to a secondary/distant

organ/lymph nodes). Transitions from the DF health state to the LR health state, DM health state and death are informed by patient level data from KEYNOTE-564.

In the LR health state, a proportion of patients receive salvage surgery and remain in this health state if their disease does not progress further, or they die (transition to the death state). If the disease progresses, patients transition to the DM health. Transitions from the LR health state to the DM health state are informed by real world data. Transitions from LR to death are assumed to be the same as DF to death, informed by data from KEYNOTE-564.

For patients who transition to the DM health state they can remain here only until death. In the DM health state, patients are assumed to receive first-line treatments for advance RCC (aRCC) and incur the costs and associated utilities of being progression-free, but also for progressed disease (see Section 4.2.7 and 4.2.8 for further details). Additionally, a proportion of patients will receive salvage surgery, based on data from KEYNOTE-564. Costs (but not utilities) of second-line aRCC treatments are also included in the DM health state. The transition from DM to death is based on overall survival (OS) and progression-free survival (PFS) from KEYNOTE-426[27] and a published network meta-analysis (NMA)[28] of first-line aRCC treatments.

For further detail on health state transitions in the model, please refer to Section 4.2.5.

The company assumed a model cycle length of one week with half-cycle correction applied. The model time horizon was set to 41.1 years (lifetime), as the mean age in the European cohort of KEYNOTE-564 at baseline was 58.9 years. The perspective of the analysis was based on the UK NHS, with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.[29]

4.2.4.1 ERG critique

The ERG considers the company's model structure to be appropriate. Type of disease recurrence is a prognostic factor for RCC, with distant metastases associated with higher mortality compared with locoregional recurrence. As such, the company's model structure allows important differences in costs and quality-adjusted life-years (QALYs) to be captured. Furthermore, the model structure has been accepted in a previous appraisal of pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence (TA553).[30]

4.2.5 Treatment effectiveness

The key clinical data for the comparison of pembrolizumab and routine surveillance is from KEYNOTE-564. KEYNOTE-564 is an ongoing Phase 3, randomised, double-blind, placebo controlled, global multicentre trial evaluating the efficacy and safety of pembrolizumab as adjuvant treatment for RCC post nephrectomy. At the latest data cut (14 June 2021), [redacted]. As such, the company could not directly model observed DFS and OS for the base case. Instead, the company estimated cause-specific health-state transition probabilities for the model from which predicted DFS and OS was generated. Table 21 summarises the clinical data used to estimate health-state transition probabilities included in the model, with further detail presented in Sections 4.2.5.1 to 4.2.5.3.

Table 21. Summary of clinical data informing the model health-state transition probabilities

Health state transition	Clinical data informing the transition probability
DF to LR	KM data (time to LR failure) from KEYNOTE-564 (follow-up of nearly 4 years) extrapolated using an exponential model - Approach 3 PH model with time-varying treatment effect (one HR for up to 1 year and HR for year 2 onwards)
DF to DM	KM data (time to DM failure) from KEYNOTE-564 (follow-up of nearly 4 years) extrapolated using an Gompertz model - Approach 3 PH model with time-varying treatment effect (one HR for up to 1 year and HR for year 2 onwards)
DF to death	KM data (time to death) from KEYNOTE-564 (follow-up of nearly 4 years) extrapolated using an exponential model. Maximum of estimated KEYNOTE-564 probability and general population all-cause mortality.
LR to DM	Time to event data from US SEER Medicare database for patients identified with LR who develop DM, extrapolated using an exponential model. No on-going efficacy of adjuvant treatment assumed after recurrence.
LR to death	Assumed to be the same as DF to death transition for routine surveillance. Maximum of estimated KEYNOTE-564 probability and general population all-cause mortality.
DM to death	Transition probability dependent on OS of first-line treatment for aRCC. Treatments included are sunitinib, tivozanib, pazopanib and cabozantinib. For sunitinib, exponential rates of OS were computed based on the observed median OS in the sunitinib arm of KEYNOTE-426. HRs of OS based on a published NMA of first-line treatments then applied to sunitinib estimates. Mean OS calculated and then weighted by market shares for each drug to estimate a weighted mean OS. Weighted mean OS converted back to exponential hazard rate for transition probability. No on-going efficacy of adjuvant treatment assumed after recurrence.

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.

4.2.5.1 *Transitions from the disease-free health state*

The main source of clinical data used to estimate transitions from the DF health state to the LR, DM and death states is from KEYNOTE-564. Patient-level data from KEYNOTE-564 based on investigator assessment (IA) 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, for example locoregional recurrence, the two competing failure types (distant metastases and death) were treated as censoring events.[31, 32]

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.[33, 34]

The company explored the following three approaches to select appropriate standard parametric models (exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised gamma) 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).

As patient-level data were used to inform the three approaches, the company explored parameter uncertainty in the cause-specific hazards of transitions from the DF using the variance-covariance matrix or SE corresponding to the parameter estimates from KEYNOTE-564, as recommended in DSU TSD 14.[35]

The company investigated log-cumulative hazard plots to establish if the assumption of proportional hazards holds and found that for the DF to LR and DF to DM time-to-event data, after approximately 12 weeks (first assessment point in KEYNOTE-564), the PH assumption is not violated. During the

clarification stage, the company explained that the change in hazard at 12 weeks was an artefact of the trial protocol, where the first patient assessment for disease activity occurred at week 12. As such, the company considered that because the change in the hazard was early in the observed data and driven by the first assessment point, Approach 3 was preferred. Nonetheless, the company explored combinations of parametric models for all three approaches for the DF to LR and DF to DM health state transitions, which resulted in a total of 54 combinations of models (36 under Approach 1, 9 under Approach 2 and 9 under Approach 3).

The company selected the best fitting combination of parametric models for each approach based on statistical fit using mean squared error (MSE), visual assessment of cumulative predictions of incidence compared with observed cumulative incidence from KEYNOTE-564 for the DF to LR and DF to DM transitions as well as external validity and clinical plausibility of long-term extrapolations. Figure 7 presents an overview of the company's parametric model selection process.

Figure 7. Company's parametric model selection process (Figure 19 of the CS)

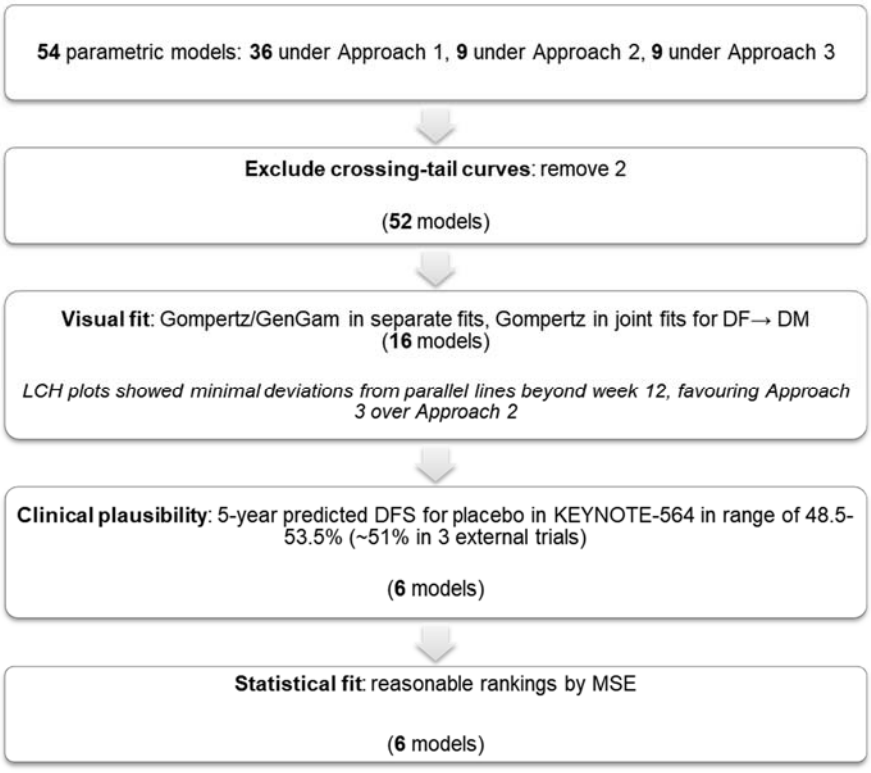


Table 22 presents the final six combinations of parametric models (two for each approach) that were identified as suitable for the model.

Table 22. Final selection of parametric models.

DF to LR	DF to DM	Mean square error ranking out of all approaches – pembrolizumab	Mean square error ranking out of all approaches – routine surveillance
Approach 1			
Exponential	Generalised Gamma	4	6
Exponential	Gompertz	15	14
Approach 2			
Exponential	Gompertz	13	21
Weibull	Gompertz	21	17
Approach 3			
Base case – Exponential	**Base case – Gompertz**	**18**	**22**
Weibull	Gompertz	22	18

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

For the cause-specific hazards of DF to death, the company used an exponential model to extrapolate KEYNOTE-564 data. The company justified the choice of the exponential model based on paucity of data for direct DF to death transitions observed in KEYNOTE-564.

To select the final approach for the remaining DF transitions, the company assessed the external validity of DFS estimates for routine surveillance and DFS benefit of pembrolizumab using observed data from previous trials of tyrosine kinase inhibitors (TKIs) as adjuvant treatment for RCC (ASSURE[10], ATLAS[36], S-TRAC[8, 37] and PROTECT[38]). Furthermore, the company's clinical experts indicated that pembrolizumab is expected to have at least a similar magnitude of clinical benefit as adjuvant sunitinib. Thus, the company assumed estimates of DFS and OS from S-TRAC were a minimum. Of the six combinations of parametric models using the three different approaches, the company selected the Approach 3 combination of exponential distribution for the DF to LR transition and Gompertz distribution for the DF to DM transition for the base case. The remaining five combinations of models were explored in scenario analyses.

The company estimated the overall DFS hazard as the sum of the three competing cause-specific hazards. The company's base case predictions of DFS and OS based on Approach 3 (exponential/Gompertz) are presented in Table 23 for routine surveillance alongside DFS and OS estimates from observed S-TRAC data and Table 24 for pembrolizumab. Furthermore, during the clarification stage, the company provided observed and extrapolated DFS and OS data from the US Surveillance, Epidemiology and End Results (SEER) Medicare database as a further external

validation of the modelled estimates for routine surveillance (presented Table 23). The SEER Medicare data are from US patients over 65 years with newly diagnosed non-metastatic intermediate-high or high-risk RCC who underwent nephrectomy. As part of the clarification response, the company also provided analyses where KEYNOTE-564 data were age and sex matched to US SEER Medicare data.

Table 23. Disease-free and overall survival predictions of base case and scenario parametric models – routine surveillance

Approach/ source	Parametric model combination	Disease-free survival by year					Overall survival by year				
		1 year	3 years	5 years	10 years	30 years	1 year	3 years	5 years	10 years	30 years
Base case: Approach 3	**Exponential (DF → LR) and Gompertz (DF → DM)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S-TRAC (observed)	-	78%	60%	51%	-	-	99%	91%	82%	-	-
SEER data (observed)	-	80%	59%	48%	33%	-	98%	82%	68%	48%	-
SEER data (extrapolated)	Lognormal (DFS and OS)	82%	59%	47%	31%	12%	97%	82%	69%	45%	10%

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

Table 24. Approach 3 (exponential/ Gompertz) disease-free and overall survival predictions – pembrolizumab

Outcome	1 year	3 years	5 years	10 years	30 years
Disease-free survival by year	86%	73%	66%	56%	14%
Overall survival	98%	91%	84%	69%	17%

In response to request from the ERG, the company supplied a comparison of the time-varying HRs from the selected Approach 3 models against the HRs from observed KEYNOTE-564 data and these are presented in Table 25.

Table 25. Pembrolizumab time-varying hazard ratios

Source/ Approach	DF to LR HR	DF to DM HR
KEYNOTE-564 observed data (95% CI)	**0.49* (0.28, 0.86)**	**0.65* (0.50, 0.85)**
Approach 3 (exponential/ Gompertz) – base case		
Year 1	0.53	0.68
Year 2 onwards	0.44	0.61

Abbreviations: CI, confidence interval; DF, disease-free; DM, distant metastases; HR, hazard ratio; LR, locoregional recurrence.

*Overall HR for the observed time to event data, as the company indicated that the HRs become unstable when estimating a post year 1 HR.

As the overall hazard of DFS in a cycle is the sum of the per cycle cause-specific hazards estimated from the parametric models, the company estimated the relative contribution of each cause-specific hazard to the overall DFS hazard to inform the transition probability for each cause.

The company calculated the cause-specific transition probability by first converting the overall DFS hazard per cycle, which was estimated as the sum of the per cycle cause-specific hazards estimated from the parametric models, into a probability. Then, the relative contribution of each specific cause was calculated by dividing the cause-specific hazard by the overall DFS hazard for a model cycle. Lastly, the relative contribution for a specific cause was applied to the overall DFS probability to estimate the transition probability.

In the model, the DF to death transition probability per cycle was set to be the maximum of the estimated KN-564 probability and background mortality, based on Office for National Statistics (ONS) life tables adjusted for age and sex.[39]

4.2.5.2 Transitions from locoregional recurrence health state

From the LR health state, patients can only transition to the DM health state or death. However, data on patients who experienced a locoregional recurrence in KEYNOTE-564 were limited. As such, the company used real-world data from the US SEER Medicare database to estimate LR to DM health state transitions. From the US SEER Medicare database, the company identified patients over 66 years of age with intermediate-high risk or high risk, non-metastatic RCC with a clear cell component

who had received radical nephrectomy or partial nephrectomy at first observed diagnosis of RCC between 2007 and 2015.

Overall, 32 patients with locoregional recurrence (defined as additional nephrectomy after a 90-day treatment-free interval and/or diagnosis for secondary disease of kidney or renal pelvis or intra-abdominal lymph nodes at least 30 days after the earliest claim for nephrectomy) who were continuously followed up between initial nephrectomy and date of locoregional recurrence were identified to be included in the estimation of the LR to DM transition probability. For the 32 locoregional recurrence patients, cases of distant metastases were identified by a diagnosis of metastatic disease at least 30 days after the earliest claim for nephrectomy. The company applied no minimum follow-up requirements after first date of locoregional to avoid immortal time bias.

To estimate the cause-specific hazards of LR to DM, patients were censored at the earliest event of death, loss of follow up or end of data. The company extrapolated the time-to-event data using an exponential model as the hazard rate is not time-dependent (constant hazards). Based on the exponential model fitted to the US SEER Medicare data, the LR to DM per cycle transition was estimated to be 0.0042 (SE 0.00102) and this was assumed to be the same for both pembrolizumab and routine surveillance.

For the LR to death transitions, the company stated that data from the US SEER Medicare database were minimal. Instead, it was assumed that the per cycle LR to death transition was the same as the DF to death transition for routine surveillance. Like with the DF to death transition, in the model, the LR to death transition was the maximum of the estimated probability and background mortality.

4.2.5.3 Transitions from distant metastases health state

The only transition from the DM health state is to the death state and the probability was assumed to be dependent on OS of first-line treatment for aRCC. Furthermore, the DM to death transition probability was the same for pembrolizumab and routine surveillance. The company included NICE recommended treatments for untreated aRCC, which are sunitinib, tivozanib, pazopanib and cabozantinib. As different aRCC treatments are associated with differing OS, the company estimated a weighted OS for first-line aRCC treatment.

To estimate the weighted OS for aRCC treatments, the company first estimated an exponential hazard rate of OS for sunitinib based on the observed median OS in the sunitinib arm of KEYNOTE-426 (40.1 months). KEYNOTE-426 was a trial that compared pembrolizumab in combination with

axitinib against sunitinib for untreated aRCC.[27, 40] The sunitinib OS exponential hazard rate was estimated to be 0.004 (SE 0.0003). To calculate the hazard rates of OS for the remaining treatments, the company obtained HRs of each treatment versus sunitinib from a published NMA[28] of first-line aRCC treatments and applied this to the sunitinib exponential hazard rate of OS. The OS hazard rates of each treatment were then used to estimate mean OS per treatment, and this was then weighted by the estimated market share of each treatment to calculate the weighted average OS for first-line aRCC treatment (Table 26). Data on market share for each of the first-line aRCC drugs was obtained from an IPSOS report and the company adapted the data using clinical expert opinion. Finally, the weighted OS was then converted back to an exponential hazard rate for the DM to death transition probability, estimated to be 0.0038.

Table 26. aRCC data used to estimate DM to death transition probability

Treatment	Market share*	HR vs sunitinib	Mean OS (weeks)
Sunitinib	30%	1.00	252
Tivozanib	18%	1.33	189
Pazopanib	31%	0.92	273
Cabozantinib	21%	0.80	314
Weighted	-	-	260

Abbreviations: aRCC, advanced renal cell carcinoma; DM, distant metastases; HR, hazard ratio; OS, overall survival.

*The company obtained market share data from an IPSOS report and adjusted it using clinical expert opinion.

As with transitions to death from the other health states, the DM to death transition probability per cycle was set to be the maximum of the estimated probability and background mortality, based on ONS life tables adjusted for age and sex.[39]

4.2.5.4 ERG critique

Transitions from the DF to LR and DF to DM health states are the main drivers of cost-effectiveness in the model and are subject to the greatest amount of uncertainty as DFS data from KEYNOTE-564 are extremely immature ([redacted]). Furthermore, OS data from KEYNOTE-564 informing the DF to death and also LR to death transitions are also immature ([redacted]), resulting in background mortality being applied from the beginning of the model time horizon for both arms of the model, which implies long-term remission. The company has indicated that they believe pembrolizumab to be a suitable candidate for the CDF as this will allow for additional data collection to reduce uncertainty in the

modelling of DFS and OS and the ERG agrees that only mature data will alleviate the uncertainties around the modelling of DFS and OS. The company has indicated that the next readout from KEYNOTE-564 will be when 332 DFS events have occurred (Figure 3 of the company submission [CS], Document A) and the final analysis for DFS is anticipated to be available in 2024.

Nonetheless, the company has attempted to extensively validate estimates of DFS and OS produced by the model by comparing these against observed data from previous trials of TKIs in the adjuvant setting for RCC, as well as real world data from the US SEER Medicare database. However, when comparing the company's estimates of DFS for routine surveillance against SEER observed and extrapolated data, adjusting for age and sex, patients in KEYNOTE-564 appear to have poorer outcomes (Figure 8). Without adjusting for age and sex, DFS based on KEYNOTE-564 is almost the same as US SEER Medicare data before diverging then re-converging at 25 years (Figure 9).

Figure 8. Observed and extrapolated DFS for routine surveillance (age and sex adjusted) - KEYNOTE-564 vs SEER Medicare data

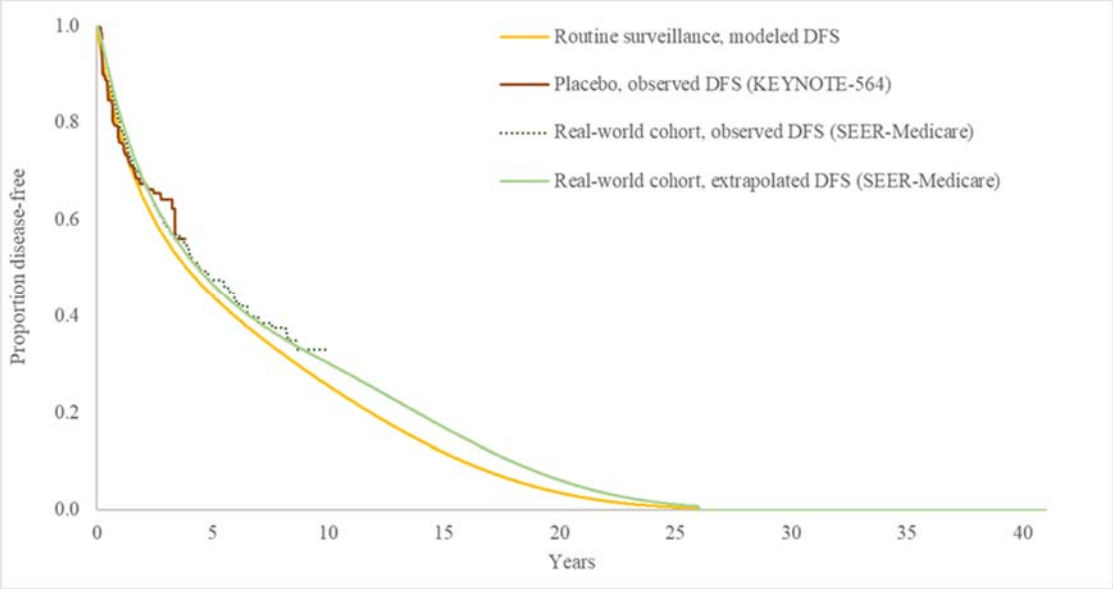
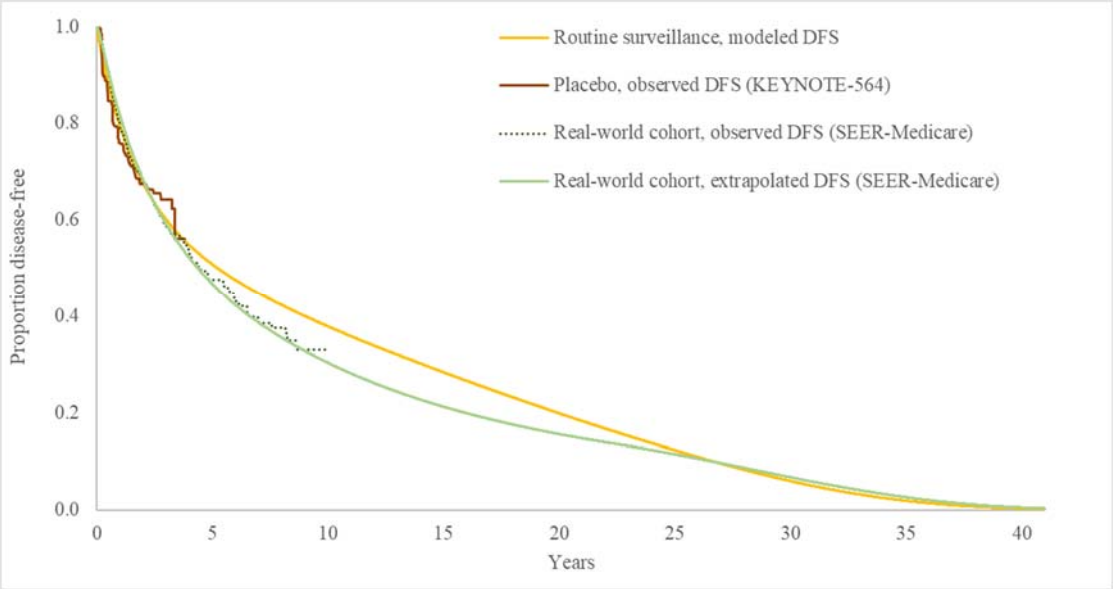


Figure 9. Observed and extrapolated DFS for routine surveillance - KEYNOTE-564 vs SEER Medicare data



In their clarification response, the company acknowledged the unusual finding from the comparison of KEYNOTE-564 placebo data and real world data from the US SEER Medicare database, but consider it is due to heterogeneity between the study populations. However, it is typical that patients in trials are usually fitter than real world and irrespective of the extrapolations and adjustments made for age and sex, observed data from KEYNOTE-564 and the US SEER Medicare database are remarkably similar. Thus, the ERG is cannot be certain whether the US SEER Medicare data or placebo data from KEYNOTE-564 are generalisable to patients who would be seen in clinical practice and this uncertainty can only be resolved with more mature data from the study.

In terms of the modelling of transition probabilities, from a methodological standpoint, the ERG considers that where patient level data are available from a trial, the use of proportional hazards modelling is not necessary and considers that independent models for each treatment arm are preferred, as per the Decision Support Unit Technical Support Document 14 (DSU TSD 14).[41] As such, the ERG considers the company's Approach 1, which fitted independent models to each treatment arm, is a more robust method for extrapolation of the cause-specific time-to-event data used in the model. However, the ERG cautions that even though Approach 1 is more robust, it is still informed by immature data from KEYNOTE-564 and thus is subject to substantial uncertainty.

Nonetheless, the ERG explored the company's two combinations of parametric models under Approach 1 (exponential/Gompertz and exponential/generalised gamma) and found that the

combination of exponential/Gompertz produced results that were slightly more optimistic for routine surveillance, but similar to the company's base case approach for pembrolizumab. Table 27 and Table 28 presents a comparison of the DFS and OS estimates for Approach 1 and Approach 3 (company base case). Though the ERG notes that results between models are very similar. As such, the ERG has included the Approach 1 combination of the exponential model for the DF to LR transitions and the Gompertz model for the DF to DM transitions in its base case. When using the Approach 1 combination exponential/Gompertz, the incremental cost-effectiveness ratio (ICER) almost doubles from £11,031 to £22,322. However, the ERG considers that the inclusion of the Approach 1 combination exponential/Gompertz in the ERG base case is only illustrative as it does not overcome the uncertainty around the fundamental issue of immature outcome data from KEYNOTE-564.

Table 27. Disease-free and overall survival predictions of base case and scenario parametric models – routine surveillance

Approach/ source	Parametric model combination	Disease-free survival by year					Overall survival by year				
		1 year	3 years	5 years	10 years	30 years	1 year	3 years	5 years	10 years	30 years
Company base case – Approach 3	**Exponential (DF → LR) and Gompertz (DF → DM)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Approach 1	**Exponential (DF → LR) and Gompertz (DF → DM)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Approach 1	**Exponential (DF → LR) and generalised gamma (DF → DM)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
S-TRAC (observed)	-	78%	60%	51%	-	-	99%	91%	82%	-	-
SEER data (observed)	-	80%	59%	48%	33%	-	98%	82%	68%	48%	-
SEER data (extrapolated)	Lognormal (DFS and OS)	82%	59%	47%	31%	12%	97%	82%	69%	45%	10%

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

Table 28. Disease-free and overall survival predictions – pembrolizumab

Outcome	1 year	3 years	5 years	10 years	30 years
Company base case - Approach 3 - exponential/Gompertz					
Disease-free survival by year	86%	73%	66%	56%	14%
Overall survival	98%	91%	84%	69%	17%
Approach 1 - exponential/Gompertz					
Disease-free survival by year	87%	72%	64%	52%	12%
Overall survival	98%	92%	84%	67%	15%

Approach 1 - exponential/generalised gamma					
Disease-free survival by year	87%	72%	63%	48%	9%
Overall survival	98%	92%	84%	65%	13%

Aside from the fundamental issue of immature outcome data from KEYNOTE-564, in the model the data informing the transitions from the DF health state are based on investigator assessment. In the trial, DFS as assessed by the investigator was the primary outcome and a sensitivity analysis using blinded independent central review (BICR) assessment was conducted. The company considered that the DFS results for investigator assessment and BICR are consistent (IA HR of [redacted] versus BICR HR of [redacted]). The company justified the use of IA DFS data over BICR DFS data as more generalisable to NHS as clinicians would determine the recurrence of disease based on local review of diagnostic imaging. Furthermore, the company explained that there was a high degree of agreement between the IA and BICR assessment (89% and 93% agreement for the pembrolizumab and placebo arms, respectively).

However, the ERG considers that DFS assessment by BICR is a more robust assessment of clinical efficacy from a trial as it is likely to be unaffected by detection bias. As such, during the clarification stage the ERG requested the company to explore a scenario using BICR DFS data to inform the DF health state transitions in the model, which the company declined to supply for the reasons outlined above. As such, the ERG ran an illustrative scenario, applying an inflation factor to the DF to LR and DF to DM transition probabilities for the pembrolizumab arm of the model using the ratio of the BICR and IA HRs ([redacted]). The scenario increased the ICER from £11,031 to £24,822. The ERG's scenario is a crude estimate of the impact of using BICR data and stresses that a robust analysis by the company would be preferred to be presented to the committee to assess the true impact on the ICER by using BICR DFS data.

In recent appraisals of immunotherapy, duration of treatment effect has been considered by committees.[30, 40] Duration of treatment effect is a key issue because immunotherapy is given for a short duration, yet in extrapolations of outcomes, a treatment benefit over the comparator is assumed to continue over a lifetime horizon. However, this issue is further exacerbated as long-term data tend not to be available to either accept or refute the continued treatment effect for patients who have had a relatively short course of immunotherapy.

For the current appraisal, pembrolizumab is given for a maximum of 17 cycles (1 year) but outcome data from KEYNOTE-564 are currently only available for a follow-up of 3.5 years. When considering the KM plot for DFS from KEYNOTE-564 (Figure 3) after 1 year of treatment, [redacted]. However, the ERG considers the difference in DFS between routine surveillance

and pembrolizumab provides an indication of the proportion of patients in which surgery with curative intent was not successful and adjuvant treatment has been beneficial. As such, for these disease-free patients, the risk of relapse in the DF health state for pembrolizumab treated patients may increase over time to match routine surveillance.

The ERG acknowledges that no evidence currently exists to suggest that over time the risk of relapse for RCC patients who have had adjuvant immunotherapy would be equivalent to patients on routine surveillance. However, a study by Leibovich *et* al.[42] indicates that risk of relapse for patients who have had nephrectomy is the lowest between 5 and 10 years (depending on RCC score) and thus the ERG expects that pembrolizumab is unlikely to result in a lower risk of relapse. Nonetheless, to allow committee to fully consider the impact on the ICER of an increase in the risk of relapse for patients on pembrolizumab, the ERG requested the company to provide a range of scenarios exploring this during the clarification stage. In their clarification response, the company explained that the aim of adjuvant pembrolizumab is to remove any residual microscopic disease after resection and reduce the risk of relapse and progression to metastatic disease and referred to the continued separation of the KEYNOTE-564 DFS curves for pembrolizumab and placebo. Additionally, the company stated that in the context of adjuvant treatment, the duration of treatment effect is often discussed in terms of cure potential, which has not been included in the base case. As such, the company did not supply the increased risk of relapse for pembrolizumab scenarios requested by the ERG.

Instead, the ERG conducted three scenarios exploring risk of relapse for the pembrolizumab DF to LR and DF to DM transitions equal to routine surveillance at 4, 7 and 10 years for committee to consider and results are presented in Section 6.3. The ERG acknowledges that an unknown and currently unknowable proportion of pembrolizumab patients may achieve long-term remission and so the early convergence of DFS curves is very likely to be a conservative estimate. The increased risk of relapse for pembrolizumab scenarios resulted in a range in the ICER of £16,417 (10 years) to £27,139 (4 years). The ERG considers that more mature data from KEYNOTE-564 are required to make a robust assessment of the long-term treatment effect with pembrolizumab.

As mentioned earlier, from the start of the model time horizon, background mortality is applied for both pembrolizumab and routine surveillance as it exceeds the transition probability based on KEYNOTE-564. Furthermore, the LR to death transitions are set equal to the DF to death transition due to a paucity of data. However, the ERG considers that as background mortality is used for the DF to death and LR to death transitions for both arms of the model, it is indicative of long-term

remission, which may be a strong assumption. As such, at the clarification stage, the ERG requested the company to provide a range of scenarios increasing the background mortality using standardised mortality ratios (SMRs). The company explored three scenarios, increasing the SMR from 1.1 to 1.3. The scenarios had a minimal impact on the ICER as it affects both arms of the model equally.

The ERG's clinical experts considered that for patients who are disease-free after nephrectomy, mortality would be close to the general population but there is an increased risk for patients who have recurrent disease. The ERG ran three scenarios increasing the SMR from 1.1 to 1.3 for the LR to death transition for both arms of the model to reflect the ERG's clinical experts' views (Section 6.3), but this had minimal impact on the ICER. The ERG considers, longer term OS data will validate whether the use of background mortality from the start of the model and equally between both arms are valid assumptions.

4.2.6 Adverse events

For the base-case analysis, the company included all cause (treatment emergent) grade 3 or higher adverse events (AEs) that were reported by at least 5% of patients (of any grade) in either treatment arm of KEYNOTE-564 presented in Table 29. The company explained that AE risk at any grade was used to determine the set of AEs to be included in the model, but the proportion experiencing the AE used in the model was based on risks of grade 3 or higher AEs. The mean duration of each AE was obtained from KEYNOTE-564 and used to estimate the disutility impact from each AE irrespective of whether a patient was adjuvant pembrolizumab or placebo. The total disutility and costs of AEs were applied in the first model cycle. Further detail on AE disutility and costs can be found in Section 4.2.7 and 4.2.8.

Table 29. Incidence and duration of adverse events included in the model (Table 41 of the company submission)

AE type	All-cause grade 3+ AE risk (%), by adjuvant treatment arm		Mean duration of AE (weeks)
	Pembrolizumab	Routine surveillance	
Abdominal pain	0.4%	0.2%	4.9
Alanine aminotransferase increased	2.3%	0.2%	16.4
Arthralgia	0.4%	0.4%	10.1
Aspartate aminotransferase increased	1.6%	0.2%	5.6
Asthenia	0.2%	0.2%	66.1
Back pain	0.2%	0.2%	13.7
Blood creatinine increased	0.2%	0.0%	3.6

Constipation	0.0%	0.2%	4.9
Decreased appetite	0.2%	0.0%	19.3
Diarrhoea	1.8%	0.2%	9.3
Dizziness	0.2%	0.0%	4.0
Dry mouth	0.2%	0.0%	81.0
Dyspnoea	0.2%	0.0%	0.3
Fatigue	1.0%	0.0%	46.9
Hyperglycaemia	1.4%	0.6%	22.7
Hypertension	2.9%	2.6%	35.0
Hyperthyroidism	0.2%	0.0%	5.0
Hypothyroidism	0.2%	0.0%	171.9
Influenza-like illness	0.2%	0.2%	0.7
Myalgia	0.2%	0.0%	168.3
Nausea	0.4%	0.0%	1.8
Pain in extremity	0.4%	0.0%	55.4
Pruritus	0.2%	0.0%	10.9
Pyrexia	0.2%	0.0%	0.4
Rash	0.8%	0.4%	38.0
Upper respiratory tract infection	0.2%	0.0%	3.1
Urinary tract infection	0.4%	0.6%	1.1
Vomiting	0.6%	0.0%	0.4
Abbreviations: AE, adverse event.			

4.2.6.1 ERG critique

The ERG considers the company's approach to selecting treatment-emergent AEs to be included in the model is comprehensive and appropriate. In the model, the company supplied an option to use treatment-related adverse events, which reduced the number of included AEs but had minimal impact on the ICER. The ERG considers the short duration of treatment with adjuvant pembrolizumab in KEYNOTE-564 (maximum of 17 cycles) results in limited incidence of AEs and thus minimal impact on HRQoL and costs. As such, AEs in the model are not a primary driver of cost-effectiveness. Furthermore, the ERG's clinical expert considered that adjuvant pembrolizumab is well tolerated and side effects are reversible.

4.2.7 Health-related quality of life

QALYs accrued by the patient cohort in each model cycle are dependent on the utility attributable to each model health state, the partial loss of utility due to adverse events, and an age-related reduction in quality of life. The details of each are given in the following subsections.

4.2.7.1 Health state utility values

Health state utility values (HSUVs) are derived from EQ-5D-5L data from KEYNOTE-564 for the disease free and locoregional recurrence health states, while EQ-5D-3L data from KEYNOTE-426 was used for the distant metastases health state as these data are more reflective of patients with aRCC and due to small number of EQ-5D-5L measurements taken for patients with distant metastases in the KEYNOTE-564 trial.

In KEYNOTE-564, EQ-5D-5L data were collected from the full analysis set (FAS) population at baseline, weeks 12, 24, 36, 48, treatment discontinuation (week 52), 30-day follow up and annually during the follow-up period until disease recurrence or initiation of a new anti-cancer therapy. The FAS population comprised of patients who were randomised, received a study treatment, and completed at least one EQ-5D-5L questionnaire (Section 3.3.4). As reported in Table 52 of the company submission, compliance with EQ-5D-5L questionnaires (defined as the proportion of patients expected to complete the questionnaire in any given visit, excluding those missing by design) exceeded 70% in both treatment arms at all visits.

In KEYNOTE-426, EQ-5D-3L data were collected from the pembrolizumab plus axitinib arm at baseline at the end of each 3-week treatment cycle up to week 24, every 6 weeks from week 24 to week 54 and every 12 weeks from week 54 to week 90. For the sunitinib arm of the trial, EQ-5D-3L measurements were taken at baseline, and at the end of weeks, 4, 6, 10, 12, 16, 18, 22, 24, 30, 36, 42, 48, 54, 66, 78, and 90.[43] Information on KEYNOTE-426 patient compliance with the EQ-5D-3L questionnaire was not provided by the company.

The company conducted two distinct regression analyses of KEYNOTE-564 data (mapped from EQ-5D-5L to EQ-5D-3L using the Van Hout *et al*. algorithm[44]) and another of KEYNOTE-426 EQ-5D-3L data to estimate the HSUVs used in the base case. Linear mixed-effects regression models with patient-level random effects were used for all three analyses to account for correlation of repeated measurements from individuals. As there was no statistically significant difference observed

between mean utility values estimated for the pembrolizumab and placebo arms, pooled utility data for both treatment arms was used for each regression analysis.

1. **Disease-free health state utility and active grade 3+ AE disutility:**
   A first regression analysis was conducted on mapped EQ-5D-3L data from a subset of EQ-5D-5L collected in KEYNOTE-564 with measurements taken during each patient's disease-free period (n=972 patients, with 4,795 unique patient visits). Absence of grade 3+ AEs during a patient-visit and active grade 1-2 AEs were included as predictors. The utility estimate for disease-free patients who were absent of active AEs was used to inform the disease-free health state in the model. The estimated grade 3+ AE disutility (equal to the intercept minus the disease-free utility) was applied independent of health state occupancy in the cost-effectiveness model as described in Section 4.2.7.2.
2. **Locoregional recurrence health state utility:**
   A second regression analysis, using mapped EQ-5D-3L data from the whole EQ-5D-5L dataset from KEYNOTE-564 (n=977 patients, with 5,070 unique patient visits) was conducted and included locoregional recurrence and distant metastases as predictors. Only the locoregional recurrence utility estimate from this analysis was applied in the company base case.
3. **Pre- and post-progression distant metastases health state utility:**
   As KEYNOTE-426 better represented a patient population with aRCC, had longer follow up, and only a small number of EQ-5D-5L measurements were taken for patients with distant metastases in the KEYNOTE-564 trial, the company opted to instead use the KEYNOTE-426 EQ-5D-3L data in a third regression analysis to inform the distant metastases health state. Progressed disease status and presence of grade 3+ adverse events were included as predictors in the regression model. Adverse events were controlled for in the estimation of utility values for both progression free and post progression distant metastases because adverse events were not explicitly modelled for subsequent treatments in the distant metastases health state.

A weighted average of the pre- and post-progression distant metastases utility estimates was applied to the whole distant metastases health state, calculated based on the ratio of weighted average PFS to OS estimates for a range of first-line aRCC treatments. Median PFS and OS for sunitinib were sourced from KEYNOTE-426[27, 45] and constant PFS and OS hazards were calculated assuming an exponential model. PFS and OS hazard ratios for tivozanib, pazopanib, cabozantinib and nivolumab+ipilimumab versus sunitinib were sourced from a published network meta-analysis of

first line treatment of metastatic RCC[46] and applied to the sunitinib exponential rate to estimate mean PFS and OS. Weighted averages of the mean PFS and OS estimates were calculated based on market share estimates for each of the first-line drugs, which were adapted from IPSOS data and validated by the company's clinical experts. An overview of the health state utility values applied to both treatment arms in the base case model is presented in Table 30.

Table 30. Utility values used in the company's base case

Health State	Utility value (SE)	Source
Disease free	[redacted]	KEYNOTE-564
Locoregional recurrence	[redacted]	
Distant metastases (weighted average applied in model)	[redacted]	KEYNOTE-426
Pre-progression estimate	[redacted]	
Post-progression estimate	[redacted]	

Abbreviations: SE, standard error.

4.2.7.2 Adverse event related disutilities

AE-related disutilities were applied as a one-time QALY decrement in the first model cycle, calculated based on the proportion of patients in each treatment arm who experienced each AE, the mean duration of each AE (Section 4.2.6, Table 29), and the company's estimate of the disutility associated with any active grade 3+ AE (0.06417; SE 0.00944). All grade 3+ AEs, which occurred in each treatment arm of KEYNOTE-564, up to 14 December 2020 data cut were considered in the regression (Section 4.2.6, Table 29). The QALY decrements applied to each treatment arm in the company base case are provided in Table 31.

Table 31. AE-related QALY decrements applied in company base case

Treatment arm	AE-related QALY decrement (base case)
Pembrolizumab	[redacted]
Routine Surveillance	[redacted]

Abbreviations: AE, Adverse event.

4.2.7.3 Age related utility decrements

The company also included age-related utility decrements in the base case using the additive model published by Ara and Brazier 2010.[47] A linear regression model (Table 32) predicts mean utility values for individuals within the general population, conditional on age, age-squared, and gender. The modelled time-varying age (starting from 58.9 years) and proportion of males (73.3%) from the European cohort of KEYNOTE-564 were used to calculate an age-related utility decrement (relative to the age- and gender-matched general population utility at baseline) for each model cycle.

Table 32. Linear regression model coefficients used to estimate age-related utility decrements

Parameter	Coefficient
Age (years)	-0.0002587
Age^2	-0.0000332
Male	0.0212126
Intercept	0.9508566

4.2.7.4 ERG critique

The ERG considers the company's approach to estimating utility values is reasonable and consistent with the NICE reference case. Additionally, the use of KEYNOTE-564 and KEYNOTE-426 utility data is preferable to other sources. However, the ERG considers that there are some limitations with the analysis, discussed below, and remain concerned that the company's health state utility estimates are high when compared with the UK general population.

At baseline, the modelled patient cohort had mean age of 59 and was 26.7% female, the corresponding age- and gender-matched general population utility, estimated by Ara and Brazier 2010[47], is 0.836. In addition, Kind *et al.* 1999[48] estimated that the average UK general population utility for people aged 55-64 is 0.80. The company's utility estimates for both the disease-free and locoregional recurrence health state utility values were higher (0.868 and 0.839, respectively). The ERG has concerns that the company's utility estimates are high, given that RCC patients post-nephrectomy are unlikely to have superior quality of life compared to the age- and gender-matched general population. However, the ERG recognises that utility values obtained directly from patients in the key trial are preferred for decision making and such the considers the company's base case approach to be acceptable.

Additionally, the company's utility estimates for pre- and post-progression distant metastases (0.803 and 0.772, respectively) were high in comparison to those used in previous NICE TAs for first-line and further-line treatment of aRCC (see summary presented in Table 33).

Table 33: Overview of utility values (base case) for aRCC from previous NICE TAs

NICE TA	TA intervention	Indication	Treatment arm applied	PFS utility	PPS utility	Source
TA650[49]	Pembrolizumab + axitinib	1L aRCC	All	Utility values based on time-to-death		Estimated from EQ-5D-3L data from KEYNOTE-426.
TA645[50]	Avelumab + axitinib	1L aRCC	All	0.753	0.683	Estimated from EQ-5D-5L data (mapped to EQ-5D-3L) from the JAVELIN Renal 101 trial. Pooled PFS on-treatment and PPS off-treatment estimates used.
TA169[51]	Sunitinib	1L aRCC	Sunitinib	0.770	0.720	Estimated from EQ-5D-3L data from sunitinib trial; UK tariff.
			IFN	0.790	0.690	
TA215[52]	Pazopanib	1L aRCC	All	0.700	0.590	PFS: EQ-5D-3L data (UK tariff) from VEG105192 trial. 15% post progression decrement assumed.
TA512[53]	Tivozanib	1L aRCC	All	0.726	0.649	EQ-5D-3L data from TIVO-1 trial.
TA542[54]	Cabozantinib	1L aRCC	All	0.726	0.649	Published literature (TIVO-1).
TA581[55]	Nivolumab + ipilimumab	1L aRCC	Nivolumab + ipilimumab	0.793	0.751	EQ-5D-3L data from CheckMate 214; UK tariff.
			Sunitinib	0.719	0.699	
TA178[56]	Bevacizumab, sorafenib, temsirolimus	1L aRCC	All	0.780	0.700	Assessment group selected utility values from appraisal of sunitinib as 1L treatment for advanced and/or metastatic RCC (TA169).

Abbreviations: 1L, first-line; PFS, progression free survival; PPS, post progression survival; aRCC, advanced renal-cell carcinoma; TA, technology appraisal; BSC, best supportive care; IFN, interferon

The company's weighted average of pre- and post-progression distant metastases utility values, applied to the distant metastases health state, is uncertain given the underlying market share, PFS and OS assumptions. However, the ERG notes that the company's base case approach is conservative as it positively impacts the routine surveillance arm. Nonetheless, the ERG conducted a scenario analysis (presented in Section 6.3) to evaluate the impact on the ICER of the lower aRCC

pre- and post-progression health state utility values used in previous NICE appraisals. From the range of estimates provided in Table 33, the PFS and post-progression survival (PPS) utility values from TA512 were selected as the first-line aRCC patient population from the TIVO-1 clinical trial aligned with the modelled distant metastases health state, health state utilities were estimated directly from trial measured EQ-5D-3L, the estimates were relatively recent and also used to inform TA542, and the TIVO-1 estimates were approximately at the midpoint of all those used in previous appraisals. As expected, using pre- and post-progression distant metastases utility values from TA512 reduced the ICER from £11,031 to £10,423.

4.2.8 Resource use and costs

The costs included in the economic model consist of drug acquisition costs, administration costs, disease management costs, costs for managing adverse events, subsequent treatment costs and terminal care costs incurred at the end of life. The details of each are given in the following subsections. Unit costs used in the model were inflated to 2020 prices using the ONS Health Consumer Price Index.

4.2.8.1 Drug acquisition costs

Pembrolizumab monotherapy is given as a fixed 200 mg dose administered by IV infusion every three weeks (Q3W). The list price per 100 mg vial is £2,630.00, and the total cost per 200 mg dose is £5,260.00. There is currently a patient access scheme (PAS) discount in place for pembrolizumab of [redacted] As such, the net cost per 100 mg vial of pembrolizumab included PAS discount is [redacted], and the net drug cost per 200 mg dose is [redacted]. Pembrolizumab monotherapy can also be given as a 400 mg infusion every 6 weeks (Q6W). The net drug cost per 400 mg dose [redacted].

No drug acquisition costs were applied to the routine surveillance arm. However, acquisition costs for subsequent lines of treatment are applied to both the pembrolizumab and routine surveillance arm, these costs are detailed further in Section 4.2.8.6. The cost per pack for all drugs are taken from the British National Formulary (BNF)[26] Dosages are taken from each treatments Summary of Product Characteristics (SmPC). The company applied the relative dose intensity (RDI) observed in the pembrolizumab treatment arm of KEYNOTE-564 to account for scheduled doses not received. Pembrolizumab acquisition costs were reduced to 98.9% of the full, post discount cost. Vial sharing was not considered for pembrolizumab as a flat dose is received by all patients.

4.2.8.2 Time on treatment

The company anticipates that the marketing authorisation will specify that patients will be treated with pembrolizumab [redacted]). Fully mature time-on-treatment (ToT) KM data from KEYNOTE-564 were used directly in the model to estimate the proportion of the patient cohort for whom pembrolizumab acquisition and administration costs are applicable. Of note, a small proportion of patients in KEYNOTE-564 remained on pembrolizumab treatment beyond the scheduled 51-week treatment period due to earlier delays in their treatment but no patient received more than 17 treatment cycles. In the model the company truncated the ToT KM curves to zero at after 51 weeks post randomisation, excluding a portion of the treatment course received in KEYNOTE-564 by patients who had delayed treatment. Mean duration of pembrolizumab treatment in KEYNOTE-564 and the mean ToT from the truncated curve applied in model are shown in Table 34.

Table 34: Mean time on treatment (extracted form company base case model)

Source	Mean time on Pembrolizumab treatment (Months)
KEYNOTE-564 (including delayed doses)	[redacted]
Company base case model	[redacted]

4.2.8.3 Administration costs

Administration costs for pembrolizumab were based on the simple parenteral chemotherapy at first attendance cost code (SB12Z) from NHS Reference Costs 2019-2020,[25] which is £299.61. This cost was applied at the beginning of each three-week treatment cycle (every third one-week model cycle) for the proportion of patients remaining on treatment.

4.2.8.4 Disease management costs

Disease management costs were applied in the model for each health state based on the estimated healthcare resource use in each state, and the unit costs associated with each resource. Unit healthcare resource costs and resource use frequencies for each health state were applied equally to the pembrolizumab and routine surveillance arms. The unit costs of healthcare resources considered in the model are provided in Table 35.

Table 35: Unit costs of healthcare resources

Resource	Unit cost (£)	Source
Salvage surgery	6,967.20	NHS. Robot-assisted nephrectomy: Evidence summary report (2014)[57] – estimated cost of keyhole nephrectomy inflated to its 2020 value.
Medical oncologist outpatient visit	192.85	NHS Reference Costs 2019/2020, Service Code 270: Medical Oncologist – Total Outpatient Attendances.[25]
Complete blood count	2.53	NHS Reference Costs 2019/2020, DAPS05: Haematology – Directly accessed pathology services.[25]
CT scan of abdomen/pelvis	95.37	NHS Reference Costs 2019/2020, Weighted average of RD20A, RD21A, and RD22Z: Computerised Tomography Scan of One Area.[25]
X-ray	45.22	NHS Reference Costs 2019/2020, RD97Z: Same day Diagnostic Imaging Admission or Attendance.[25]

Abbreviations: CT, Computerised tomography; NHS, National Health Service

Company estimates for the frequency of resource use and the proportion of patients, for which each resource is applied in each health state, are provided in Tables 58, 60 and 61 of the company submission. These estimates were informed by Royal Free Hospital guidelines,[58] the incidence of salvage surgery observed across treatment arms of the KEYNOTE-564 trial, NICE TA650,[49] and the company's clinical experts. The per-cycle disease management costs applied in the model are provided in Table 36. Note that salvage surgery costs are applied as a single cost on entry to the locoregional recurrence and distant metastases health states.

Table 36. Disease management costs as applied in company base case.

Health state	Application in model	Cost (£)
Disease free	Per 1-week cycle, years 0-2	1.92
	Per 1-week cycle, years 2-5	1.88
	Per 1-week cycle, years 5+	0.43
Locoregional recurrence	Once off on entry of health state	1,661.96
	Per 1 week cycle	1.88
Distant metastases	Once off on entry of health state	1,777.09
	Per 1 week cycle	52.24

4.2.8.5 Adverse event costs

The unit costs of treating AEs are given in Table 67 of the company submission. Unit costs were derived from NHS Reference Costs 2019-2020[25] or were based on the unit drug costs for exclusively pharmaceutical management of an adverse event. AE management costs were applied as a single

cost in the first model cycle, calculated based on the proportion of patients in each treatment arm who experienced each AE (Section 4.2.6, Table 29) and the unit cost of treating each grade 3+ AE. Table 37 presents the total AE management cost for each treatment arm of the model.

Table 37. Adverse event costs applied in company base case

Treatment arm	Total AE management cost (£)
Pembrolizumab	36.71
Routine Surveillance	12.19
Abbreviations: AE, Adverse event	

4.2.8.6 Subsequent treatment costs

The company included subsequent treatment costs associated with the management of aRCC, in first-line and further line (second and later) settings, as a single cost on entry to the distant metastases health state. A weighted average cost of the available NHS treatment options was estimated based on IPSOS market share data (adapted based on the company's clinical experts). The weighted average total, acquisition and administration, cost of treatment in the first-line and further-line aRCC settings (equal in the pembrolizumab and routine surveillance arms of the company base case) was applied to the proportion of the modelled patient cohort that enters the distant metastases state in each cycle. Subsequent treatment dosing was applied in line with the regimen specified in the relevant SmPCs, summarised in Table 38.

Table 38. Drug doses for each subsequent treatment considered in model

Treatment	Dose	Frequency	Type of administration
Sunitinib	50 mg	Daily for 4 weeks, then 2 weeks off treatment (6-week cycle)	Oral
Tivozanib	1.34 mg	Daily for 3 weeks, then 1 week off treatment (4-week cycle)	Oral
Pazopanib	800 mg	Daily (4-week cycle)	Oral
Cabozantinib	60 mg	Daily (4-week cycle)	Oral
Nivolumab (2L+ only)	480 mg	4-weekly	Simple IV
Axitinib (2L+ only)	5 mg	Twice daily (4-week cycle)	Oral
Everolimus (2L+ only)	10 mg	Daily (4-week cycle)	Oral
Abbreviations: 2L+, second-line onwards; IV, intravenous; mg, milligram.			

Unit drug acquisition costs for all subsequent treatments (Table 39) were sourced from the BNF.[26] For sunitinib and pazopanib, non-confidential PAS discounts are available. For pazopanib, a discount of 12.5% is applied in the company base case. For sunitinib, no acquisition costs are applied in the first 6-week treatment cycle, the full list price is applied thereafter. Confidential PAS discounts are available for tivozanib, cabozantinib, axitinib, nivolumab and everolimus. As such, the ERG has produced a confidential appendix to the ERG report, with cost-effectiveness results including all confidential PAS discounts applied.

Table 39. Subsequent treatment costs per pack/vial

Treatment	Pack size/volume	Cost per pack/vial (£)
Sunitinib	50 mg, 28-capsule pack	3,138.80
Tivozanib	1.34 mg, 21-capsule pack	2,052.00
Pazopanib	400 mg, 30-tablet pack	1,121.00
Cabozantinib	60 mg, 30-tablet pack	5,143.00
Nivolumab	40 mg/ 4 ml vial	439.00
Axitinib	5 mg, 56-tablet pack	3,517.00
Everolimus	10 mg, 30-tablet pack	2,673.00

Abbreviations: mg, milligram.

Administration costs (Table 40) were sourced from NHS Reference Costs 2019-2020.[25] Activity codes SB12Z, SB13Z or SB11Z were used dependent on the complexity and means of administration, IV or oral, of each subsequent treatment

Table 40. Unit administration costs used in the model per treatment cycle

Type of Administration (Activity code)	Unit Cost (£)
Oral chemotherapy delivery (SB11Z)	226.45
Simple IV chemotherapy (SB12Z)	299.61
Complex IV chemotherapy (SB13Z)	331.15

Abbreviations: IV, intravenous.

First-line subsequent treatment was assumed to continue until progression based on exponential progression free survival (PFS) curves estimated for each first-line treatment regimen. These PFS curves were estimated based on an exponential curve fit to summary data (median PFS) from the sunitinib arm of KEYNOTE-426 and PFS hazard ratio estimates for each first-line treatment versus sunitinib from Riaz *et al*. 2021,[46] which was a network meta-analysis of first-line treatment of metastatic RCC. These hazard ratios were used to construct exponential PFS and time-on-treatment (ToT) curves for each treatment by adjusting the sunitinib PFS curve for the measured relative PFS

effect. The PFS and ToT curves were identical except for where the drug's SmPC specified a maximum treatment duration and thus the ToT curve was truncated to zero. Acquisition costs were adjusted to account for scheduled doses not received, using the relative dose intensities from previous NICE technology appraisals.[52-54, 59-62] Table 41 provides the acquisition and administration cost breakdown for a full course of each first-line treatment regimen.

Table 41. Subsequent treatment costs: first-line

First-line metastatic RCC treatment	NMA PFS hazard ratio estimates versus sunitinib (Riaz et al.[28])	Constant hazard informing exponential PFS curve	Mean PFS/ToT estimate (months)	Dose intensity (%)	Total undiscounted cost per treatment course (£)	
					Acquisition	Administration
Sunitinib	1.00	0.0144	16.0	74.7	26,055.30	2,742.88
Tivozanib	1.19	0.0171	13.5	94.0	29,192.16	3,427.15
Pazopanib	1.05	0.0151	15.3	86.0	26,901.09	3,868.68
Cabozantinib	0.48	0.0069	33.4	94.3	166,435.51	8,326.32

Abbreviations: RCC, Renal cell carcinoma; NMA, Network meta-analysis; PFS, Progression free survival; ToT, Time on treatment.

Further-line subsequent treatment costs were estimated in a similar fashion to first-line although exponential ToT curves were not explicitly modelled, rather the mean time on treatment was directly estimated (assuming an exponential distribution) from reported median treatment duration from several clinical trials for second-line treatment of aRCC.[63-66] The total acquisition and administration costs for a full course of each further-line treatment regimen was calculated based on the administration frequency outlined in the relevant SmPC, the mean time on treatment and the unit costs per administration; the cost breakdowns are provided in Table 42.

Table 42. Subsequent treatment costs: further-line (second and later)

Further-line metastatic RCC treatment	Median ToT (months)	Source	Mean ToT estimate (assuming exponential curve)	Dose intensity (%)	Total undiscounted cost per treatment course (£)	
					Acquisition	Administration
Nivolumab	5.5	Motzer *et al*. 2015[63]	7.9	92.0	41,804.38	2,584.31
Axitinib	8.2	Motzer *et al*. 2013[65]	11.8	102.0	46,133.02	2,912.14
Cabozantinib	8.4	Motzer *et al*. 2018[22]	12.1	100.0	63,235.08	2,983.16
Pazopanib	7.4	Sternberg *et al*. 2013[66]	10.7	86.0	18,274.10	2,628.03

Everolimus	4.4	Motzer *et al*. 2018[64]	6.3	91.8	15,803.62	1,562.61
Abbreviations: RCC, renal cell carcinoma; ToT, time on treatment.						

In the company's base case, a two-stage discounting approach was adopted for first-line subsequent treatment costs. For the first stage, a total cost for a full course of first-line treatment was discounted as if it were initiated in cycle 0, this cost was then applied in the model on entry to the distant metastases health state and then in the second stage was discounted again to account for the delayed initiation (relative to cycle zero). Further line treatment costs were only discounted via the second stage. The market share estimates applied in the company base case, for both the pembrolizumab and routine surveillance arms, are provided in Table 43. A weighted average of administration and acquisition costs, for a full course of each first-line and further-line treatment (based on the market share estimates for each treatment line), is applied on entry to the distant metastases health state. This total subsequent treatment acquisition cost was £78,494.06, while the total administration cost was £5,553.26.

Table 43. Market share estimates used in Company base case.

Treatment regimen	Market Share estimate (%)
First-line metastatic RCC treatment	
Sunitinib	30
Tivozanib	15
Pazopanib	31
Cabozantinib	21
Nivolumab + ipilimumab	0
Further-line (second and later) metastatic RCC treatment	
Nivolumab	15
Axitinib	5
Cabozantinib	25
Pazopanib	0
Everolimus	5
No active treatment	50
Abbreviations: RCC, renal cell carcinoma.	

The company stated that only aRCC treatments available through routine commissioning were considered in the model, as agreed with NICE. However, the company explored the potential impact of routine commissioning of nivolumab in combination with ipilimumab in a scenario analysis. As nivolumab in combination with ipilimumab for the treatment of aRCC is only funded via the Cancer Drugs Fund, the company's scenario is not discussed further in this report.

The company's base case considered all patients' immunotherapy-ineligible at first line. However, the company included nivolumab monotherapy as a further-line treatment option for both the pembrolizumab and routine surveillance model arms.

4.2.8.7 Terminal care costs

The company included a once off end-of-life cost, applied upon transition to the death health state. This cost reflects the management costs associated with terminal care. A cost of £6,207.60 was sourced from Georghiou and Bardsley 2014[67] and inflated to its 2020 value (£7,125.14).

4.2.8.8 ERG Critique

The ERG considers the company's approach to estimating unit costs and resource use to be generally reasonable except for the company's application of a hospital administration cost of £226.45 to all oral drugs considered in the model. The ERG's clinical expert stated that patients receiving sunitinib, tivozanib, pazopanib, cabozantinib, axitinib, or everolimus would self-administer at home. As such the company's inclusion of a hospital-based administration cost was not considered appropriate by the ERG. In response to clarification questions, the company provided a scenario analysis demonstrating that the removal of oral drug administration costs increased the base case ICER from £11,031 to £11,680 but did not apply this assumption in the updated base case.

In KEYNOTE-564, the treatment regimen for pembrolizumab was 200 mg Q3W, which is reflected in the company base case. However, the company stated that pembrolizumab can also be administered at a 400 mg dose Q6W. [redacted] The ERG's clinical expert advised that in clinical practice, the less frequent regimen would be preferred for patient convenience and to reduce healthcare resource use. At the clarification stage, the ERG requested a scenario exploring the 400 mg Q6W dosing regimen. The company did not provide this scenario but did provide calculations of the total drug acquisition and administration costs associated with each regimen. The company explained that the [redacted]

[redacted]

[redacted]. However, drug administration costs were lower, due to reduced frequency of treatment. The ERG ran a scenario analysis utilising the 400 mg Q6W regimen, which includes the company's base case RDI of 98.9% and the KEYNOTE-564 ToT curve. The scenario exploring pembrolizumab 400 mg reduced the ICER from £11,031 to £10,866.

The company's truncation of KEYNOTE-564 ToT curves at 51 weeks results in an underestimation of the average treatment cost for pembrolizumab. Patients who had treatment delays/interruptions in KEYNOTE-564 could continue treatment past 51 weeks until the maximum of 17 treatment cycles (51 weeks total exposure) had been received. The ERG considers this also likely to happen in clinical practice. A scenario analysis wherein the full ToT curve from KEYNOTE-564 was applied in the model was requested of the company during the clarification stage, such that the model captured the full acquisition costs for the small proportion of patients for whom treatment was delayed in KEYNOTE-564 (presented in Section 6.3). The company declined to provide the requested scenario, explaining that untrucating the ToT KM curve exceeds the maximum number of doses of 17. However, the ERG considers that the ToT KM curve from KEYNOTE-564 is complete and reflects the clinical effectiveness data used in the model, thus it should be used in its entirety. As such, the ERG ran a scenario using the untruncated ToT KM curve and included this in the ERG preferred base case (Section 6.4). Additionally, the ERG ran the scenario removing RDI for pembrolizumab and this has a minimal impact on the ICER, increasing it from £11,031 to £11,268. However, as the pembrolizumab RDI scenario directly affects drug acquisitions costs, this is included in the ERG's base case.

The estimated average cost of subsequent treatment applied in the model is highly uncertain given the reliance on market share assumptions as well as PFS and OS extrapolation. The company assumed an exponential survival model for all subsequent line treatments, without assessing the quality of fit to KM data for any of the subsequent treatments. Additionally, the ERG's clinical expert considered that the second-line market shares did not reflect current clinical practice (taking account of immunotherapies funded via the CDF which are outside the scope of this STA) and estimated that second-line treatment would be 50% cabozantinib and 50% no active treatment.

During the clarification stage, company provided a scenario exploring the sensitivity of the model to a further-line market share breakdown composed of 50% cabozantinib and 50% no active treatment. This scenario reduced the ICER from £11,031 to £10,205 as cabozantinib is relatively more expensive compared to other second-line treatments and so this scenario adversely impacts the routine surveillance arm. However, nivolumab as a second-line immunotherapy is likely to have a beneficial

impact on survival outcomes for patients on routine surveillance which are currently not captured in the model. Additionally, the ERG's clinical experts advised that there is limited evidence available for treating patients who have received immunotherapy with a subsequent immunotherapy. As such, there is uncertainty over whether pembrolizumab patients are likely to receive a subsequent immunotherapy in clinical practice. As such, the ERG has included the company's scenario exploring the ERG's clinical experts' opinion on the distribution of second-line treatment in the ERG base case.

The ERG explored several other issues with the company and independently, including alternative salvage surgery and health state resource use assumptions but these had minimal impact on the ICER. Additionally, the ERG was satisfied with the company's approach for relative dose intensity of treatments other than pembrolizumab, adverse event costs, and terminal care costs. The ERG also noted several minor cost errors in the company's base case at the clarification stage, all of which were addressed in the updated company base case model.

5 Cost effectiveness results

5.1.1 Company's cost effectiveness results

Table 44 below presents the incremental cost-effectiveness results of the company's updated (i.e., post clarification) base case deterministic analysis. In the base case analysis, an incremental quality-adjusted life-year (QALY) gain of 1.44 over routine surveillance along with additional costs of £15,928 for the pembrolizumab arm, generates an incremental cost-effectiveness ratio (ICER) of £11,031 per QALY. A proposed confidential patient access scheme (PAS) discount for pembrolizumab is applied in the company's base case and is therefore reflected in the results presented in this report. Several subsequent treatments included in the model also have confidential PAS discounts in place and as such the Evidence Review Group (ERG) has produced a confidential appendix to the ERG report where PAS discounts for treatments are applied where relevant.

Table 44. Company's base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	1.73	1.44	11,031

Abbreviations: LYG, life year gained; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

5.1.2 Company's sensitivity analyses

5.1.2.1 Probabilistic sensitivity analysis

The company performed probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA, arising from 1,000 simulations, are summarised in Table 45. A PSA scatterplot is presented in Figure 10 and a cost-effectiveness acceptability curve (CEAC) is presented in Figure 11. Based on these analyses, the probability that pembrolizumab is cost effective versus routine surveillance is 83.4% at a willingness to pay (WTP) threshold of £20,000 and 94.2% at a WTP threshold of £30,000. The mean ICER from the company's PSA was £11,709 per QALY.

The ERG considers the parameters and respective distributions chosen for PSA, outlined in Table 65 of the CS Appendix, to be generally sound. The ERG also considers the probabilistic results to be comparable to the deterministic results.

Table 45. Company's base case - PSA results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	1.38	11,709

Abbreviations: ICER, incremental cost effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year;

Figure 10. Cost-effectiveness plane - PSA scatterplot: pembrolizumab vs routine surveillance

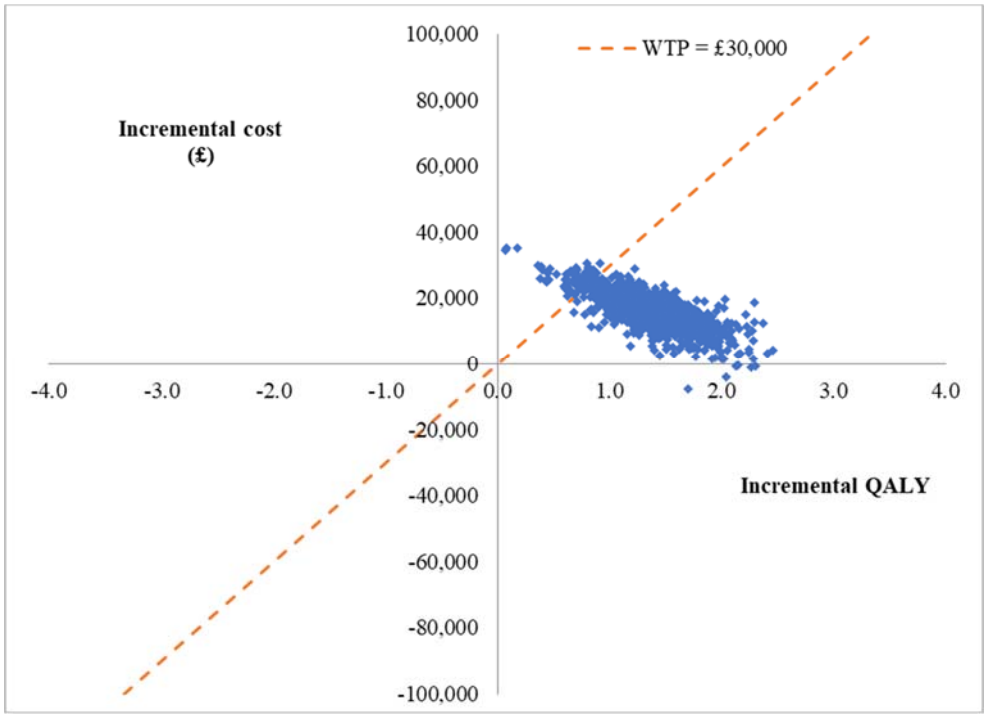
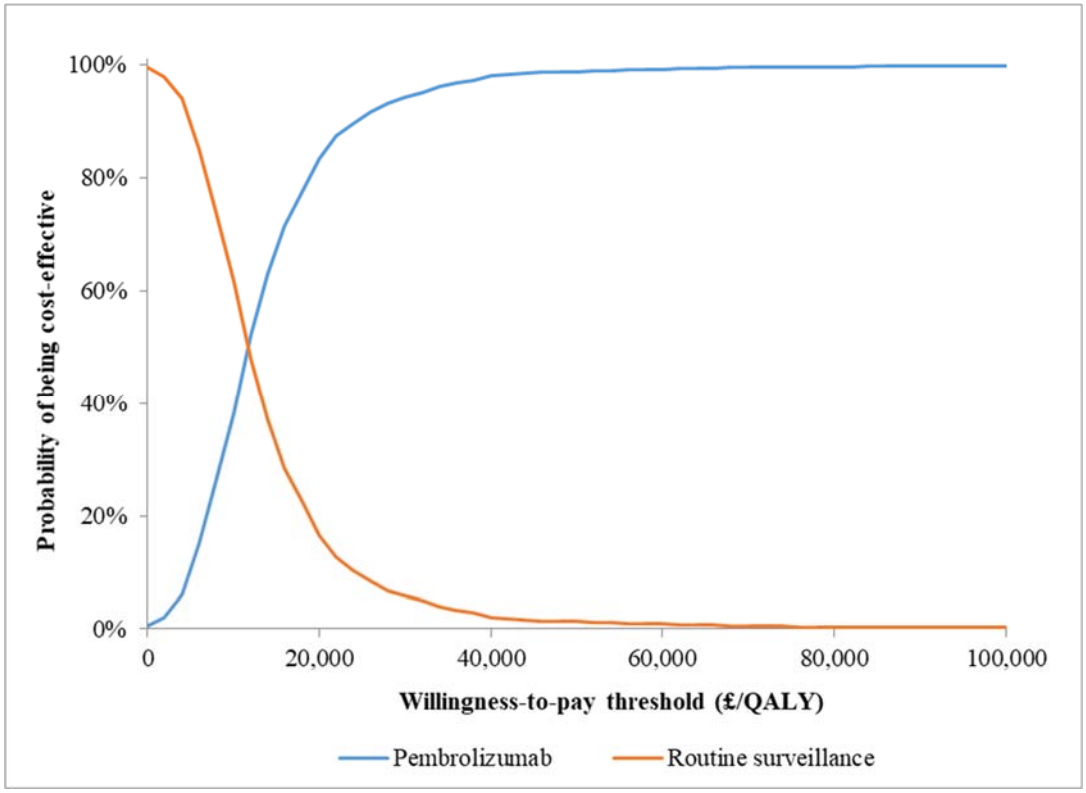


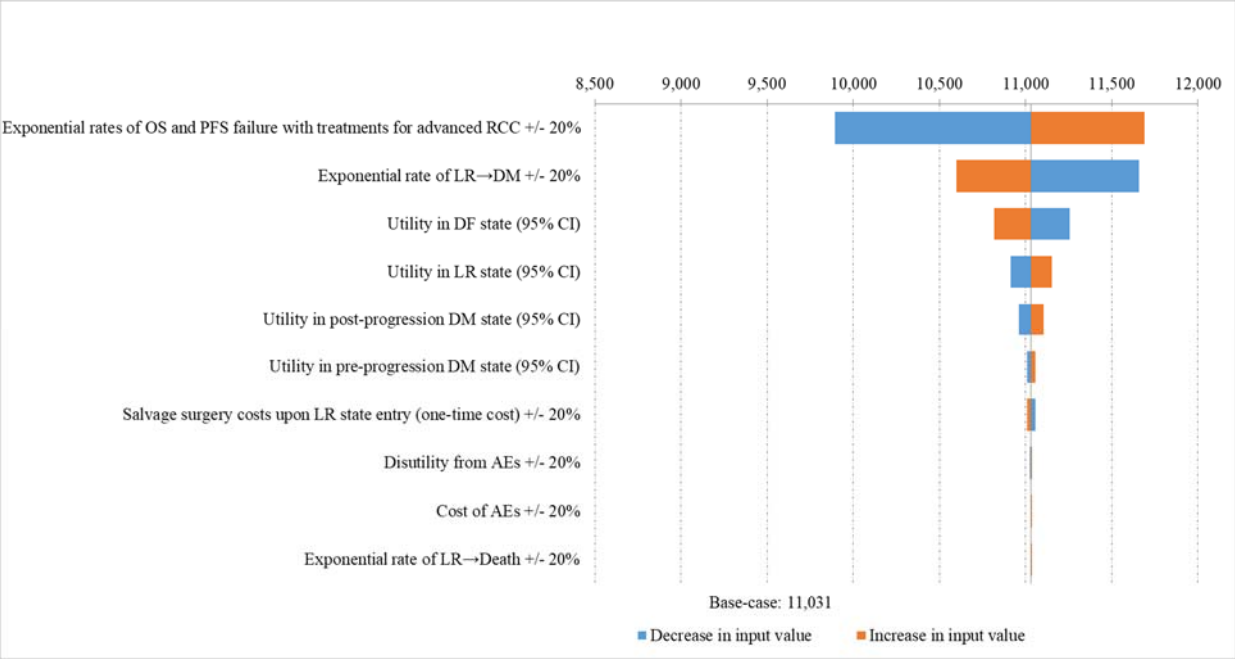
Figure 11. Cost-effectiveness acceptability curve: pembrolizumab vs routine surveillance



5.1.2.2 Deterministic sensitivity analysis

The company conducted one-way sensitivity analyses (OWSAs) to access the impact, on the ICER, of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated using the tornado diagram in Figure 12. The ICER was most sensitive to the progression-free survival (PFS) and overall survival (OS) exponential hazards for first-line and further-line subsequent treatments, followed by the exponential hazard of locoregional recurrence to distant metastases recurrence. In order of importance, utility values for the; disease free, locoregional recurrence and distant metastases health states were also model drivers. Varying the cost parameters of the model had minimal impact on the ICER.

Figure 12. Tornado diagram presenting results of OWSA - 10 most sensitive parameters



5.1.2.3 Scenario analysis

The company undertook a series of scenario analyses to assess the impact of applying alternative assumptions to key model parameters. These scenarios are presented in Table 32 of the company's response to clarification questions. The largest change in ICER occurred when alternative survival distributions were selected to model the transitions from the disease free to locoregional recurrence and distant metastases health states. The ICER increased to £26,058 per QALY where independently fit (Company's approach 1, detailed in Section 4.2.5.1) exponential and generalised gamma distributions were used for the disease free to locoregional recurrence and distant metastases transitions, respectively. Where independently fit exponential and Gompertz distributions were selected the ICER increased to £22,322 per QALY.

The company conducted several additional scenario analyses requested by the ERG; the results are provided in Table 46 below. Several requested scenarios were not provided by the company, as such the ERG have conducted these additional scenario analyses and provided the results in Section 6.3.

Table 46. Additional scenario analyses requested of and conducted by the company

Results per patient	Pembrolizumab (1)	Routine surveillance (2)	Incremental value (1-2)
Company base case			
Total costs (£)	[redacted]	[redacted]	[redacted]

QALYs	[redacted]	[redacted]	1.44
ICER (£/QALY)			11,031
Standardised mortality ratio - 1.1			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	1.39
ICER (£/QALY)			11,514
Standardised mortality ratio - 1.2			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	1.35
ICER (£/QALY)			11,996
Standardised mortality ratio - 1.3			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	1.30
ICER (£/QALY)			12,477
Alternative 2L subsequent treatment market share estimates - 50% cabozantinib and 50% no active treatment			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	1.44
ICER (£/QALY)			10,205
Excluding administration cost (£226.45) for all oral therapies.			
Total costs (£)	[redacted]	[redacted]	[redacted]
QALYs	[redacted]	[redacted]	1.44
ICER (£/QALY)			11,680

Abbreviations: 2L, second-line; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

5.1.3 Model validation and face validity check

For the model validation, the company stated that quality control checks were performed by model developers to ensure calculations were correct and consistent with the model specification. Additionally, the company stated that the model was independently reviewed by external health economists who reviewed the overall health economics approach as well as checking for implementation errors.

The company performed external validation of the model by comparing estimated clinical outcomes from the model against the observed data in KEYNOTE-564 as well as using observed data from previous trials for adjuvant treatment for RCC and real world data to validate model predictions of disease-free survival and overall survival. The ERG considers the company's model validation and face validity check to be robust. However, during the clarification stage, the ERG highlighted some

cost calculation errors to the company, which were subsequently corrected and formed part of the company's updated base case ICER. No further errors in the model were identified by the ERG.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

The Evidence Review Group (ERG) did not identify any additional model errors from those highlighted to the company during the clarification stage, which were subsequently corrected and formed part of the company's updated base case incremental cost-effectiveness ratio (ICER).

6.2 Exploratory and sensitivity analyses undertaken by the ERG

In Section 4 of this report, the ERG has described several scenarios that warrant further exploration in addition to the company's own sensitivity and scenario analyses to ascertain the impact of these changes on the ICER. The deterministic scenarios that the ERG has performed are as follows and results are presented in Section 6.3:

1. Illustrative blinded independent central review (BICR) analysis for disease-free (DF) to locoregional recurrence (LR) and DF to distant metastases (DM) health state transitions – Section 4.2.5.4;
2. Assumption of risk of relapse for pembrolizumab equal to routine surveillance (duration of treatment effect) at 4, 7 and 10 years – Section 4.2.5.4;
3. Standardised mortality ratio (SMR) of 1.1, 1.2 and 1.3 applied to the LR to death transitions for pembrolizumab and routine surveillance - Section 4.2.5.4;
4. DM pre- and post-progression utility values from TA512 – 4.2.7.4;
5. Pembrolizumab 400 mg once every six weeks (Q6W) dosing regimen – Section 4.2.8.8;
6. Removal of truncation to the time on treatment (ToT) curve for pembrolizumab - Section 4.2.8.8;
7. Removal of relative dose intensity (RDI) for pembrolizumab – Section 4.2.8.8;
8. Resource use estimates adapted based on ERG clinical expert opinion – Section 4.2.8.4. Ongoing complete blood count diagnostic tests were excluded from all health states. X-rays of disease-free patients every two years after year 5 were excluded. 6-monthly CT scans were assumed for disease free patients up to year 3, annual from years 3-5, followed by one at year 7 and 10. For Locoregional recurrence patients ongoing 6-monthly CT scans were assumed.

6.3 ERG scenario analysis

Table 47 presents the deterministic results of the ERG exploratory analyses described in Section 6.2. Results reported include the company's proposed patient access scheme (PAS) of [redacted]

Table 47. Results of the ERG's scenario analyses

	Results per patient	Intervention	Comparator	Incremental value
0	**Company base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.44
	ICER (£/QALY)			11,031
1	**Illustrative BICR assessment scenario**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.91
	ICER (£/QALY)			24,822
2a	**Risk of relapse equal to routine surveillance – 4 years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.94
	ICER (£/QALY)			27,139
2b	**Risk of relapse equal to routine surveillance – 7 years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.16
	ICER (£/QALY)			19,593
2c	**Risk of relapse equal to routine surveillance – 10 years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.28
	ICER (£/QALY)			16,417
3a	**SMR of 1.1 applied to the LR to death transition for pembrolizumab and routine surveillance**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.45
	ICER (£/QALY)			11,043
3b	**SMR of 1.2 applied to the LR to death transition for pembrolizumab and routine surveillance**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.45
	ICER (£/QALY)			11,054
3c	**SMR of 1.3 applied to the LR to death transition for pembrolizumab and routine surveillance**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.45
	ICER (£/QALY)			11,065

4	**Pre- and post-progression distant metastases health state utility value estimates from TA512**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.53
	ICER (£/QALY)			10,423
5	**Illustrative pembrolizumab 400mg 6-weekly dosing regimen**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.44
	ICER (£/QALY)			10,866
6	**Removal of truncation to the ToT curve for pembrolizumab**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.44
	ICER (£/QALY)			11,409
7	**Removal of RDI for pembrolizumab**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.44
	ICER (£/QALY)			11,268
8	**ERG's clinical expert's resource use estimates**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	1.44
	ICER (£/QALY)			11,025

Abbreviations: BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; LR, locoregional recurrence; mg, milligram; QALY, quality adjusted life year; RDI, relative dose intensity; SMR, standardised mortality ratio; ToT, time on treatment.

6.4 ERG preferred assumptions

In this section, the ERG presents its base case ICER for pembrolizumab as an [redacted]. The following assumptions were incorporated into the ERG's base case:

- Approach 1 combination exponential/Gompertz for DF to LR and DM transitions;
- Removal of oral administration costs;
- Removal of truncation to the ToT curve for pembrolizumab;
- Removal of pembrolizumab RDI; and

- Alternative subsequent second-line treatment for advanced renal cell carcinoma (aRCC) scenario - 50% cabozantinib and 50% no active treatment.

The ERG has also explored the following scenarios around the ERG base case:

- 400 mg Q6W dosing schedule for pembrolizumab.
- Risk of relapse equal to routine surveillance at 4 years.

The ERG would prefer to include the BICR analysis of DFS and OS in its base case assumptions but as the company did not provide this analysis it could not be included. The ERG's BICR scenario, presented in Section 6.3, is a crude estimate of the impact of using BICR data and stresses that a robust analysis by the company using BICR data from KEYNOTE-564 would be preferred to be presented to the committee to assess the true impact on the ICER.

Table 48 to Table 50 presents the ERG deterministic and probabilistic base case results and Table 51 presents scenarios around the ERG base case. The ERG notes that there is approximately a £5,000 increase in the probabilistic ICER compared with the deterministic ICER and this is driven by the uncertainty around DF transitions when using Approach 1.

The ERG notes that the ERG base case should interpreted with caution as the data from KEYNOTE-564 informing the DF transitions, which are the key model drivers, are immature. As such, the ERG base case is associated with substantial uncertainty and that longer-term data from KEYNOTE-564 are needed to reduce the uncertainty in the cost-effectiveness analysis.

Table 48. ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Deterministic ICER (£/QALY)	Cumulative ICER (£/QALY)
Company base case	4.1	11,031	11,031
Approach 1 combination exponential/ Gompertz	4.2.5.1	22,322	22,322
Removal of oral administration costs	4.2.8.3	11,680	22,976
Removal of truncation to the ToT curve for pembrolizumab	4.2.8.2	11,409	23,534
Removal of pembrolizumab RDI	4.2.8.1	11,268	23,889
Alternative 2L subsequent treatment market share estimates - 50% cabozantinib and 50% no active treatment	4.2.8.6	10,205	23,123

Abbreviations: 2L, second-line; ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; RDI, relative dose intensity; ToT, time on treatment.

Table 49. ERG's deterministic base case results

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	1.17	0.98	23,123

Abbreviations: LYG, life year gained; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

Table 50. ERG's probabilistic base case results

Interventions	Total Costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Routine Surveillance	[redacted]	[redacted]	[redacted]	-	-
Pembrolizumab	[redacted]	[redacted]	[redacted]	0.84	28,752

Abbreviations: LYG, life year gained; QALY, quality adjusted life year; ICER, incremental cost effectiveness ratio.

Table 51. Scenarios around the ERG base case

	Results per patient	Intervention	Comparator	Incremental value
0	**ERG base case**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.98
	ICER (£/QALY)			23,123
1	**400mg Q6W dosing regimen**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.98
	ICER (£/QALY)			22,632
2	**Risk of relapse equal to routine surveillance – 4 years**			
	Total costs (£)	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	0.79
	ICER (£/QALY)			35,408

Abbreviations: BICR, blinded independent central review; ICER, incremental cost-effectiveness ratio; LR, locoregional recurrence; mg, milligram; QALY, quality adjusted life year; RDI, relative dose intensity; SMR, standardised mortality ratio; ToT, time on treatment.

6.5 Conclusions of the cost effectiveness sections

The key trial informing the cost-effectiveness analysis is KEYNOTE-564, which is an ongoing Phase 3, randomised, double-blind, placebo controlled, global multicentre trial evaluating the efficacy and safety of pembrolizumab as adjuvant treatment for RCC post nephrectomy. At the latest data cut (14 June 2021), [redacted]. As such, the lack of mature data from KEYNOTE-564 is a fundamental source of uncertainty in the cost-effectiveness analysis, especially as

transitions from the DF to LR and DF to DM health states are the main drivers of cost-effectiveness in the model. Furthermore, for the DF to death and also LR to death transitions background mortality is applied from the beginning of the model time horizon for both arms of the model, thus long-term occupancy of these health states implies long-term remission.

The company has indicated that they believe pembrolizumab to be a suitable candidate for the Cancer Drugs Fund (CDF) as this will allow for additional data collection to reduce uncertainty in the modelling of DFS and OS. Additionally, the company has indicated that the next readout from KEYNOTE-564 will be when 332 DFS events have occurred (Figure 3 of the CS, Document A) and the final analysis for DFS is anticipated to be available in 2024. Thus, the ERG agrees that further data collection for DFS and OS is needed to resolve the substantial uncertainty in the cost-effectiveness analysis.

Nonetheless, the company has attempted to extensively validate estimates of DFS and OS produced by the model by comparing these against observed data from previous trials of tyrosine kinase inhibitors (TKIs) in the adjuvant setting for RCC, as well as real world data from the US SEER Medicare database. However, the ERG considers that analyses presented in the company submission and ERG report, including the ERG base case, are subject to a substantial amount of uncertainty because of the immature trial data used in the model.

Aside from the fundamental issue of immature outcome data from KEYNOTE-564, in the model the data informing the transitions from the DF health state are based on investigator assessment. In the trial, DFS as assessed by the investigator was the primary outcome and a sensitivity analysis using BICR assessment was conducted. The company considered that the DFS results for investigator assessment and BICR are consistent and the use of investigator assessment (IA) DFS data over BICR DFS data is more generalisable to NHS as clinicians would determine the recurrence of disease based on local review of diagnostic imaging. Furthermore, the company explained that there was a high degree of agreement between the IA and BICR assessment. However, the ERG considers that DFS assessment by BICR is a more robust assessment of clinical efficacy from a trial as it is likely to be unaffected by detection bias and thus should be used to inform the clinical data in the model. Additionally, the ERG stresses that a robust analysis using BICR by the company would be preferred to be presented to the committee to assess the true impact on the ICER by using BICR DFS data.

In recent appraisals of immunotherapy, duration of treatment effect has been considered by committees. Duration of treatment effect is a key issue because immunotherapy is given for a short duration, yet in extrapolations of outcomes, a treatment benefit over the comparator is assumed to continue over a lifetime horizon. For the current appraisal, pembrolizumab is given for a maximum of 17 cycles (1 year) but as DFS and OS data from KEYNOTE-564 are immature, there is substantial uncertainty around the long-term duration of treatment effect. In particular, the ERG considers the difference in DFS between routine surveillance and pembrolizumab provides an indication of the proportion of patients in which surgery with curative intent was not successful and adjuvant treatment has been beneficial. As such, for these disease-free patients, the risk of relapse in the DF health state for pembrolizumab treated patients may increase over time to match routine surveillance.

The ERG acknowledges that no evidence currently exists to suggest that over time the risk of relapse for RCC patients who have had adjuvant immunotherapy would be equivalent to patients on routine surveillance. However, a study by Leibovich *et* al.[42] indicates that risk of relapse for patients who have had nephrectomy is the lowest between 5 and 10 years (depending on RCC score) and thus the ERG expects that pembrolizumab is unlikely to result in a lower risk of relapse. The company explained that the aim of adjuvant pembrolizumab is to remove any residual microscopic disease after resection and reduce the risk of relapse and progression to metastatic disease and referred to the continued separation of the KEYNOTE-564 DFS curves for pembrolizumab and placebo. Additionally, the company stated that in the context of adjuvant treatment, the duration of treatment effect is often discussed in terms of cure potential, which has not been included in the base case.

The ERG acknowledges that an unknown and currently unknowable proportion of pembrolizumab patients may achieve long-term remission and so the early convergence of DFS curves is very likely to be a conservative estimate. However, the ERG considers that more mature data from KEYNOTE-564 are required to make a robust assessment of the long-term treatment effect with pembrolizumab.

7 End of Life

The company has not made a case for pembrolizumab to be considered as an end-of-life treatment, which the ERG considers is appropriate.

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9 Appendices

9.1 Quality assessment

Table 52. Quality assessment of KEYNOTE-564

Question on trial design	Trial Acronym/number	
	KEYNOTE-564 (NCT03142334)	
	Company assessment of risk	ERG agrees or disagrees
Was randomisation carried out appropriately?	LOW	Yes. Randomisation was performed by using a permuted block design with a computer pseudo-random number generator.
Was the concealment of treatment allocation adequate?	LOW	Yes. An Interactive Response Technology System (voice response or web response) was used to determine treatment assignment.
Were the groups similar at the outset of the study in terms of prognostic factors?	Not reported in RoB assessment	Demographic and patient characteristics were well balanced between the two treatment groups at baseline, and randomisation was stratified by: • Metastasis status (M0 versus M1 no evidence of disease [NED]) • Within M0 group, there will be 2 stratification factors: c) Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 versus 1) d) US participant (YES versus NO)
Were the care providers, participants, and outcome assessors blind to treatment allocation?	LOW	Yes. This was a double-blind study. The primary outcome of disease-free survival (DFS) was also assessed by both investigators and blinded independent central review (BICR).
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	LOW	Yes. Although 38.9% participants in the pembrolizumab group and 26.2% participants in the placebo group had discontinued study treatment, the company provide detail on reasons for participant discontinuation, which demonstrates an increased rate of adverse event with pembrolizumab compared to placebo causing the disparity in drop-outs between trial arms. A high proportion of participants remained in the study at the last data collection point.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	LOW	No. All outcomes specified in the study protocol were reported in the clinical study report.
Did the analysis include an ITT analysis?	Not reported in RoB assessment	Yes. Efficacy analysis were performed in the ITT randomised set. The ERG considers this to be appropriate.

If so, was this appropriate? Were appropriate methods used to account for missing data?		
Other sources of bias	LOW	Yes

Abbreviations: CSR, Clinical Study Report; ERG, Evidence Review Group; ITT, intention to treat; N/A, not applicable; RCT, randomised controlled trial; RoB, risk of bias.

9.2 Participant flow

Table 53: Flow of participants (ITT population) through to 14-JUN-2021 cut-off (Reproduced from CS, Table 10)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants in population	496		498		994	
Status for Study Treatment						
Started	[redacted]		[redacted]		[redacted]	
Completed	[redacted]		[redacted]		[redacted]	
Discontinued	[redacted]		[redacted]		[redacted]	
Adverse Event	[redacted]		[redacted]		[redacted]	
Disease Relapse	[redacted]		[redacted]		[redacted]	
Non-Compliance With Protocol	[redacted]		[redacted]		[redacted]	
Physician Decision	[redacted]		[redacted]		[redacted]	
Associated With Covid-19	[redacted]		[redacted]		[redacted]	
Protocol Violation	[redacted]		[redacted]		[redacted]	
Withdrawal By Subject	[redacted]		[redacted]		[redacted]	
Associated With Covid-19	[redacted]		[redacted]		[redacted]	
Status for Trial						
Discontinued	[redacted]		[redacted]		[redacted]	
Death	[redacted]		[redacted]		[redacted]	
Withdrawal By Subject	[redacted]		[redacted]		[redacted]	
Associated With Covid-19, No Further Information	[redacted]		[redacted]		[redacted]	

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Association With Covid-19 Unspecified, No Further Information	[redacted]		[redacted]		[redacted]	
Participants Ongoing	[redacted]		[redacted]		[redacted]	

If the overall count of participants is calculated and displayed within a section in the first row, then it is used as the denominator for the percentage calculation. Otherwise, participants in population is used as the denominator for the percentage calculation.

Database Cutoff Date: 14JUN2021

9.3 Baseline characteristics

Table 54: Demographic and baseline characteristics of randomised participants (ITT population) in KEYNOTE-564 trial (Reproduced from CS, Table 4)

	Pembrolizumab		Placebo		Total	
	n	(%)	n	(%)	n	(%)
Participants	496		498		994	
Sex						
Male	347	(70.0)	359	(72.1)	706	(71.0)
Female	149	(30.0)	139	(27.9)	288	(29.0)
Age (Years)						
<65	338	(68.1)	326	(65.5)	664	(66.8)
>=65	158	(31.9)	172	(34.5)	330	(33.2)
Mean	58.3		58.6		58.4	
SD	10.6		11.0		10.8	
Median	60.0		60.0		60.0	
Range	27 to 81		25 to 84		25 to 84	
Race						
American Indian Or Alaska Native	10	(2.0)	2	(0.4)	12	(1.2)
Asian	63	(12.7)	75	(15.1)	138	(13.9)
Black Or African American	7	(1.4)	5	(1.0)	12	(1.2)
Multiple	8	(1.6)	5	(1.0)	13	(1.3)
American Indian Or Alaska Native Black Or African American	2	(0.4)	0	(0.0)	2	(0.2)

American Indian Or Alaska Native White	3	(0.6)	2	(0.4)	5	(0.5)
Black Or African American White	2	(0.4)	3	(0.6)	5	(0.5)
White Asian	1	(0.2)	0	(0.0)	1	(0.1)
White	372	(75.0)	377	(75.7)	749	(75.4)
Missing	36	(7.3)	34	(6.8)	70	(7.0)
Ethnicity						
Hispanic Or Latino	72	(14.5)	62	(12.4)	134	(13.5)
Not Hispanic Or Latino	381	(76.8)	394	(79.1)	775	(78.0)
Not Reported	21	(4.2)	20	(4.0)	41	(4.1)
Unknown	21	(4.2)	21	(4.2)	42	(4.2)
Missing	1	(0.2)	1	(0.2)	2	(0.2)
Geographic Region of Enrolling Site						
North America	133	(26.8)	125	(25.1)	258	(26.0)
European Union	188	(37.9)	187	(37.6)	375	(37.7)
Rest of World	175	(35.3)	186	(37.3)	361	(36.3)
Region						
US	114	(23.0)	117	(23.5)	231	(23.2)
Non-US	382	(77.0)	381	(76.5)	763	(76.8)
ECOG Performance Scale						
0	421	(84.9)	426	(85.5)	847	(85.2)
1	75	(15.1)	72	(14.5)	147	(14.8)
Type of nephrectomy						
Partial	37	(7.5)	38	(7.6)	75	(7.5)
Radical	459	(92.5)	460	(92.4)	919	(92.5)
PD-L1 Status						
CPS < 1	124	(25.0)	113	(22.7)	237	(23.8)
CPS >= 1	365	(73.6)	383	(76.9)	748	(75.3)
Missing	7	(1.4)	2	(0.4)	9	(0.9)

Primary Tumour						
T1	11	(2.2)	15	(3.0)	26	(2.6)
T2	27	(5.4)	33	(6.6)	60	(6.0)
T3	444	(89.5)	437	(87.8)	881	(88.6)
T4	14	(2.8)	13	(2.6)	27	(2.7)
Tumour Grade						
Grade 1	19	(3.8)	16	(3.2)	35	(3.5)
Grade 2	153	(30.8)	150	(30.1)	303	(30.5)
Grade 3	219	(44.2)	213	(42.8)	432	(43.5)
Grade 4	103	(20.8)	119	(23.9)	222	(22.3)
Missing	2	(0.4)	0	(0.0)	2	(0.2)
Sarcomatoid Feature						
Presence	52	(10.5)	59	(11.8)	111	(11.2)
Absence	417	(84.1)	415	(83.3)	832	(83.7)
Unknown	27	(5.4)	24	(4.8)	51	(5.1)
Lymph Nodes Stage						
N0	465	(93.8)	467	(93.8)	932	(93.8)
N1	31	(6.3)	31	(6.2)	62	(6.2)
Metastatic Staging						
M0	467	(94.2)	469	(94.2)	936	(94.2)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)
RCC Risk Category						
M0-Intermediate-High Risk	422	(85.1)	433	(86.9)	855	(86.0)
M0-High Risk	40	(8.1)	36	(7.2)	76	(7.6)
M0-Others	5	(1.0)	0	(0.0)	5	(0.5)
M1 NED	29	(5.8)	29	(5.8)	58	(5.8)

Participants in M0-Intermediate-high risk are pT2 (Grade 4 or sarcomatoid), N0, M0 or pT3 (Any Grade), N0, M0. Participants in M0-high risk are pT4 (Any Grade), N0, M0 or pT Any (Any Grade), N1 or greater, M0. Participants in M1 NED are participants who present not only with the primary kidney tumour but also solid, isolated, soft tissue metastases that were completely resected at the time of nephrectomy (synchronous) or <=1 year from nephrectomy (metachronous). Participants in M0-Others are T2 (grade <= 3) N0 M0 or T1 N0 M0.

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Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

[ID3810] Pembrolizumab for adjuvant treatment of renal cell carcinoma

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 7 February 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 KEYNOTE study number

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 1.3, Table 4, in the "Description of issue and why the ERG has identified it as important" row, "KEYNOTE-534" is referred to instead of KEYNOTE-564.	Change "KEYNOTE-534" to "KEYNOTE-564".	Correction of a typo.	Thank you for highlighting this error. It has now been corrected in the ERG report.
In section 4.2.5, page 72. , "KEYNOTE-534" is referred to instead of KEYNOTE-564.	Change "KEYNOTE-534" to "KEYNOTE-564".	Correction of a typo.	Thank you for highlighting this error. It has now been corrected in the ERG report.

Issue 2 Location of description of KEYNOTE-564 patient eligibility criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 2.3.1, it is stated in the second paragraph that "Full eligibility criteria for KEYNOTE-564 can be found in Sections B.2.3 and Appendix D of the CS". Appendix D of the CS does not contain the KEYNOTE-564 patient eligibility criteria (it contains the study eligibility criteria of the clinical SLR).	Remove the "and Appendix D" part of the quoted sentence.	Correction of a cross-reference.	Thank you for highlighting this error. It has now been corrected in the ERG report.

Issue 3 Updated wording of marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Following the latest communications with the EMA (after the company submission was made to NICE), the anticipated wording of the marketing authorisation has changed slightly (without changing the underlying population described by the wording) to: "[redacted]"	It may be beneficial to change were the anticipated marketing authorisation reads "[redacted]". This occurs in several places in sections 1 and 2 of the document.	Update to the anticipated marketing authorisation wording.	Thank you for the update on the marketing authorisation wording. The wording has been updated in the ERG report.

Issue 4 Number of citations retrieved from database searches for the systematic literature review of relevant clinical effectiveness data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In section 3.1, third paragraph, it is stated that "The searching of bibliographic databases returned 2,766 citations", this is incorrect, as 2829 citations were identified, as shown in Appendix D Figure 1 of the company submission.	Change 2766 to 2829 in the quoted sentence.	Correction of a typo.	Thank you for highlighting this error. It has now been corrected in the ERG report.

Issue 5 Minor typographical error

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.8. Page 84, Table 38. A closing bracket was missed on the last row of the table	Correction of last row to Everolimus (2L+ only)	Correction of a typo	Thank you for highlighting this error. It has now been corrected in the ERG report.

Issue 6 Immunotherapy eligibility following adjuvant pembrolizumab

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.8. Page 89-90. The ERG have noted that it is unlikely that patients will receive immunotherapy following adjuvant pembrolizumab. However, multiple clinical experts across the UK have all suggested that patients receiving adjuvant pembrolizumab would be eligible for treatment with immunotherapy as long sufficient time has passed between treatment discontinuation and subsequent disease recurrence.	The relevant statement should include discussion of time to disease recurrence following treatment discontinuation as a factor influencing decision to retreat with an immunotherapy.	Clinical expert opinion is consistent that they would retreat with an immunotherapy following a sufficient duration of remaining in DFS following treatment discontinuation. To state that it is unlikely that patients will receive immunotherapy in the advanced RCC setting is inconsistent with all discussions MSD have had on this point with clinical experts.	The ERG has updated its statement about retreatment with an immunotherapy in the ERG report.

Issue 7 Assumed long-term remission in disease-free health state

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 6.5. Page 101-102. The ERG have noted “Furthermore, for the DF to death and also LR to death transitions background mortality is applied from the beginning of the model time horizon for both arms of the model, which implies long-term remission.” However, the patients in the DF and LR states, whose mortality risk is derived from general population, continue to face a risk of transitioning to DM or LF. Therefore, it is inaccurate to link the use of general population mortality to an implication of long-term remission.	Proposal to remove this point, or to link the implication of long-term remission to the use of general population mortality in later years of the model’s time horizon, i.e. the implication of remission in the ‘long term’, if appropriate.	Clinical expert feedback has confirmed that, prior to developing distant metastases, it is reasonable to assume patients face the same risk of death as the age- and sex-matched mortality rates estimated from the general population. Use of general population mortality does not by itself imply long-term remission when patients continue to face of risk of developing distant metastases, which in turn increases mortality risk.	The ERG report has been updated to state that the implication of long-term remission is associated with long-term occupancy of the DF and LR health states.

Issue 8 Confirmation that the BICR/IA DFS adjustment was applied to both treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Section 4.2.5. Page 72. The ERG ran an illustrative scenario whereby an inflation factor was applied to the DF to LR and DF to	Proposal to include additional detail about whether this factor is applied to both treatment arms.	Additional detail is needed to clarify approach.	The inflation factor was applied to the pembrolizumab arm only. This has been stated in the

DM transition probabilities. It is unclear whether this factor was applied to the transition probabilities in both treatment arms.			updated ERG report.

Issue 9 Incorrect marking in ERG Report

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Section 4.2.7. Page 79. The utility data presented from KEYNOTE-426 and KEYNOTE-564 has not yet been published and was incorrectly marked in the company submission	Could the values: [redacted] and [redacted] be marked academic in confidence	Could the values: [redacted] be marked academic in confidence	The marking has been updated in the ERG report.

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Technical engagement response form

Pembrolizumab for adjuvant treatment of renal cell carcinoma [3810]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **11 March 2022.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Younan Zhang
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Merck Sharp & Dohme (UK) Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Immature DFS and OS data from KEYNOTE-564	**NO**	• Please note that in our responses we reference two data cuts from the KEYNOTE-564 study from which DFS and OS results are available: o The first interim analysis (IA1), with a data cutoff date of 14-DEC-2020 and median follow-up duration of 23.9 months. The results from this data cutoff were presented in Appendix M of the submission. o Results from a later 14-JUN-2021 cutoff date, with a median follow-up duration of 29.7 months. The results from this data cutoff were presented in section B.2 of the submission. • The DFS data from KEYNOTE-564 at the 14-JUN-2021 cutoff show a clear and statistically significant improved efficacy for pembrolizumab versus SOC:DFS by investigator assessment HR [95% CIs] was 0.63 [0.50, 0.80] with p-value <0.0001. • The subgroup analysis of DFS by investigator assessment at this cutoff shows statistically significant results in favour of pembrolizumab (i.e. HR upper 95% CI <1) in 10 out of 19 subgroups and HR point-estimates in favour of pembrolizumab in every case, 19 out of 19 subgroups (as originally presented in MSD's clarification question responses and also shown Figure 1 in below).

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		Figure 1. Forest plot of disease-free survival hazard ratio by subgroup factors, based on Investigator Assessment (primary censoring rule), (intention-to-treat population), KEYNOTE-564 14-JUN-2022 data cutoff  • An ESMO Magnitude of Clinical Benefit Scale (MCBS) Scorecard rating of "A was given for pembrolizumab in this indication based on the KEYNOTE-564 IA1 (14-DEC-2020 data cutoff) results, this highlights treatment options to be considered for an accelerated assessment of value and cost-effectiveness. • DFS results from KEYNOTE-564 at the later 14-JUN-2021 cutoff show a continuation of treatment benefit in favour of pembrolizumab from the previous

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		data cut. IA1 reported HR [95% CIs] of 0.68 [0.53, 0.87] and the later 14-JUN-2021 cutoff reported 0.63 [0.50, 0.80]. There is clear and continued separation in the Kaplan-Meier curves with no convergence of the tails of the curves. These results suggest the observed benefit of pembrolizumab will be maintained as the data matures further., • The ERG has noted that the OS results from the KEYNOTE-564 are immature. As this is a study in adjuvant treatment we would not expect mature OS results to be available for a number of years. When mature OS results do become available, such results will be less relevant in the adjuvant setting than, for example, in the metastatic setting where death will occur much sooner following start of novel therapy. While OS results from studies in the adjuvant setting are informative, they are also likely to be confounded due to cross-over and subsequent treatments and will require substantial adjustment. On this basis, MSD considers it possible and appropriate for a decision to be made without mature OS data directly reported from the KEYNOTE-564 study.
Key issue 2: IA versus BICR assessment from KEYNOTE-564	**NO**	• DFS as assessed by the investigator (IA) specifically was the primary endpoint of the KEYNOTE-564 study as pre-defined in the study's protocol and statistical analysis plan (described in section B.2.4 of the submission). • DFS that is investigator assessed (IA) has the best external validity/generalisability to real-world/NHS practice. Tumour recurrence assessment in UK clinical practice is undertaken by the treating clinician, not a blinded committee. Therefore, the IA results best reflect real-world clinical practice and so are the most appropriate outcome to use in NICE's decision making which relates to the treatment of patients in the real world. • NICE have previously made positive recommendations for adjuvant cancer treatment based on investigator assessed outcomes of disease/recurrence/relapse-free survival as the primary endpoint. This demonstrates that DFS by IA is the most appropriate outcome for use in NICE's decision-making:

		o TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (ADAURA study) o TA746 Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer (CheckMate 577 study) o TA684 Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CheckMate 238 study) o TA544 Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (COMBI-AD study) • DFS results by IA and BICR are similar: the 14-JUN-2021 cutoff for DFS by IA was HR (95% CIs) of 0.63 (0.05, 0.80) and for DFS by BICR was 0.78 (0.61, 0.99). There is substantial overlap between the confidence intervals between them. Concordance and discordance between IA and BICR-determined disease recurrence was assessed and a high level of consistency was found. The discrepancy rates found between these two methods did not cross the threshold values based on criteria reported in Mannino et al (1). • Where the results by IA and BICR differ, these may be caused by methodological/administrative procedures associated with BICR (for example, the DFS by BICR results at the 14-JUN-2021 cut-off record one less death in the placebo arm of the KEYNOTE-564 study than the DFS by IA results due the last recorded BICR assessment being carried out on that patient being earlier (when the patient was still alive) than the last recorded IA assessment (by which point the patient had died). • It is MSD's position that IA is more reflective of real-world practice and therefore of more value to the NHS. Where there is apparent discrepancy between IA and BICR results, these are not statistically meaningful and can be explained to some extent by administrative processes and timings.

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Key issue 3: Long-term risk of relapse	**NO**	There are two elements that require consideration when assessing the long-term risk of relapse in patients post-nephrectomy: 1) For surveillance patients, the longer patients remain disease-free, the better the long-term outcomes are for these patients based on Leibovich et al. (2) 2) Whether pembrolizumab treated patients would demonstrate the same pattern in relapse as routine surveillance patients. • MSD believes the mechanism of action for pembrolizumab (discussed in section B1.3 of the company submission) would result in a maintained treatment benefit over time. The observed DFS data from KEYNOTE-564 show no evidence of an increasing hazard over time. Therefore, in the base case analysis MSD assumed a reduced relative risk of relapse associated with adjuvant pembrolizumab that would not wane over time. • The ERG has presented scenarios in which the treatment effect of pembrolizumab wanes at specific time points but acknowledges that there is no available evidence to support this assumption. The way the implement this in the economic model as an abrupt change in the risk of recurrence for all patients remaining in DF after a specified time point is implausible. There is no evidence available to support waning of treatment effect. It is not plausible that if waning did occur it would occur at 4 years or that it would be an immediate loss of benefit. We understand why the assumption is explored but consider it too implausible to be informative in this adjuvant submission. • The ERG also notes a study on the long-term risk of recurrence in patients who received nephrectomy followed by routine surveillance, Leibovich *et al*. (2) This study reported a decreasing risk of recurrence in this population at 5-10 years post nephrectomy indicating that a longer disease-free period results in reduced risk of disease recurrence. The ERG suggests this reference as a rationale for assuming (explored in scenario analysis) that the risk of recurrence in both arms would be equivalent after a certain time point. This would only be possible if the hazard rate for pembrolizumab increases over time, i.e. there is an

		increased risk of relapse compared to routine surveillance patients. The plausibility of changes in treatment effect over time is best informed by log-cumulative hazard plots (LCH), which were presented in the company submission (Figure 14) for transitions from the disease free (DF) health state. The LCH plots for pembrolizumab do not show any change to the trend observed in KEYNOTE-564: the LCH plots are parallel for the routine surveillance and pembrolizumab arms indicating a maintenance of relative efficacy. • Assuming a waning of treatment effect on long-term risk of recurrence to all pembrolizumab-treated patients remaining DF after 4-, 7- or 10-years, as per the ERG scenario analysis, is not supported by the trial data from KEYNOTE-564 evidence nor by feedback from consultant oncologists in the UK, who expect the observed treatment effect to be maintained in the long term. Furthermore, as cited in the company submission, the S-TRAC trial provides long-term data on DFS with adjuvant sunitinib versus routine surveillance alone following nephrectomy with data up to 8 years. Whilst LCH plots are not available for DFS data from this trial, a review of the Kaplan-Meier curves with a focus on the follow-up from 4-8 years, shows the DFS curves to be parallel for the duration of trial follow-up, continuing to the tails of the curves and indicating maintenance of the proportional hazards assumption (see Figure 2 below).

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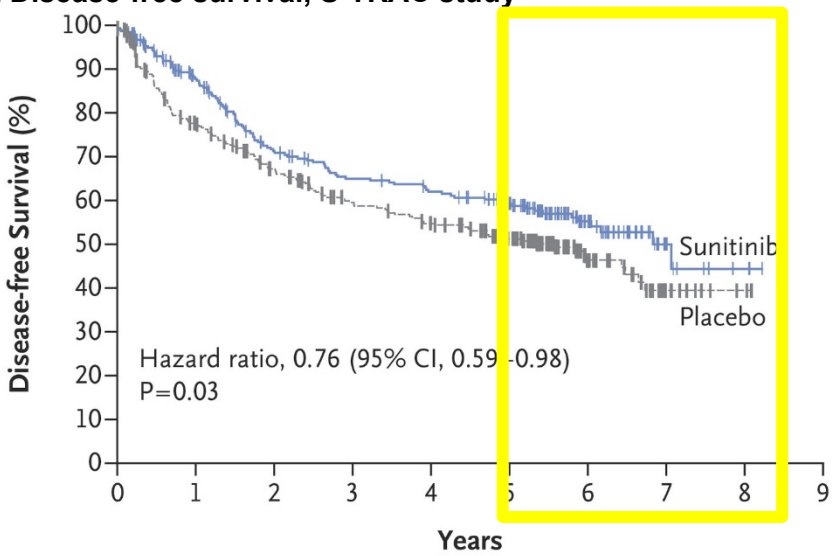
Figure 2 Disease-free survival, S-TRAC study



No. at Risk

Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0

Source: Ravaud et al. (3)

- Further data have recently been published allowing a more quantitative comparison of adjuvant pembrolizumab and adjuvant sunitinib. A network meta-analysis (NMA) was conducted by Laukhtina et al. to compare outcomes and safety profiles of pembrolizumab versus tyrosine kinase inhibitors (TKIs) including sunitinib in patients at high risk after nephrectomy for clinical nonmetastatic RCC (4). Analysis of treatment ranking showed pembrolizumab to be the best treatment with regard to DFS compared to TKIs and placebo. The hazard ratio (HR) of DFS for pembrolizumab [HR: 0.68, 95% CI; 0.53–0.87; p = 0.002] was more favourable compared with other adjuvant TKIs [HR: 0.88, 95% CI 0.49–0.97; p = 0.004] when each was compared with placebo. It can therefore be considered plausible that the lower bound for the treatment effect observed for pembrolizumab would be greater than that observed for adjuvant

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		sunitinib in the S-TRAC trial. Viewing the evidence from KEYNOTE-564, the NMA, clinical expert opinion, and other data from pembrolizumab trials would suggest it is more likely that the long-term treatment effect for pembrolizumab on DFS would be higher than that observed for sunitinib. • There is no evidence of treatment effect waning in the metastatic setting in multiple indications for which there is long-term data for pembrolizumab (KEYNOTE-010 and KEYNOTE-024) (5, 6). For that reason, treatment effect waning is considered implausible in the adjuvant setting where patients have received surgery with curative intent prior to therapy. • MSD acknowledges an absence of confirmatory long-term data for maintenance of treatment effect following pembrolizumab in the adjuvant setting for RCC. However, the external trial data, NMA, and clinical expert opinion suggest the balance is probably in favour of maintenance of treatment effect as modelled in the company base case. It is certainly not supportive of abrupt waning at 4 years and highly unlikely at 7 and 10 years as tested in the scenario analyses.
Key issue 4: Treatment regimen and resource use for pembrolizumab	**NO**	• The recommended dosage for pembrolizumab in adults as specified in the marketing authorisation is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes, therefore consideration of a scenario where pembrolizumab treatment regimen of 400mg once every six weeks is appropriate.

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Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Use of *approach #1 to extrapolate transition probabilities from the DF to LR and DF to DM health states.*	**Section 4.2.5.4**	**NO**	The ERG have included Approach #1 in their base case, which uses separately fitted curves with the exponential and Gompertz distributions to model transitions from DF to LR and DF to DM. The company base case uses Approach #3 as the most plausible method modelling DFS: jointly fitted models, with a time-varying treatment effect with the exponential and Gompertz distributions to model transitions from DF to LR and DF to DM. **Approach #1 is likely to underestimate the benefit of adjuvant pembrolizumab, therefore, Approach #3 is a more plausible method to extrapolate the transitions from the DF health state** • The ERG have cited the availability of patient-level data as the rationale for including Approach #1 (separately fit curves) in its base case. When selecting base case survival models, external data must also be considered. • Table 38 of the company submission reports the observed incremental DFS benefit (versus placebo) in the KEYNOTE-564 and S-TRAC trials which can be seen to increase over time beyond 3. When using Approach #1, incremental DFS benefit remains approximately constant between pembrolizumab and routine surveillance whereas Approach #3 better reflect the trend of increasing DFS benefit observed in these trials.

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Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
			• As described above in the response to Key Issue #3, the incremental DFS benefit between sunitinib and placebo from the S-TRAC trial can be considered a lower bound of the incremental DFS benefit of pembrolizumab versus routine surveillance. When modelling transitions from DF using Approach #1, the resulting incremental DFS benefit for pembrolizumab versus routine surveillance is similar to the DFS benefit observed in S-TRAC, which is considered conservative for the reasons provided above in the response to Key Issue #3. • The use of Approach #3 to model transitions from DF in the company base case was validated by comparing the modelled DFS estimates for routine surveillance to the long-term observed placebo data from S-TRAC (see Table 36 of the company submission). DFS for the routine surveillance arm when using Approach #1 were found to be consistently higher than observed DFS for the routing surveillance arms in the S-TRAC trial beyond 3-years. Specifically, Approach #1 led to an overestimate of the proportion of patient remaining in DFS in the routine surveillance arm of +1.8% and +7.5% at 5- and 7-years respectively. In contrast, using Approach #3 resulted in more accurate estimates of DFS for the routine surveillance arm up to 5-years and 7-years compared to observed DFS for routine surveillance in S-TRAC. • External validation against long-term published data suggests Approach #3 to be the most appropriate of estimating long-term transition probabilities from DF.

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Summary of changes to the company's cost-effectiveness estimate(s)

No changes to the company's preferred cost-effectiveness estimate(s) have been made in response to technical engagement.

References

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3. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant Sunitinib in High-Risk Renal-Cell Carcinoma after Nephrectomy. N Engl J Med. 2016;375(23):2246-54.
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5. Herbst RS, Garon EB, Kim DW, Cho BC, Gervais R, Perez-Gracia JL, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol. 2021;16(10):1718-32.
6. Kaltwasser J. New 5-Year KEYNOTE-024 Data Show Pembrolizumab Continues to Prolong OS in NSCLC: CancerNetwork; 2021 [updated 11-MAY-2021. Available from: https://www.cancernetwork.com/view/new-5-year-keynote-024-data-show-pembrolizumab-continues-to-prolong-os-in-nsclc.

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Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Kidney Cancer UK
4. Did your nominating organisation submit a submission?	☐ **yes, they did** ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ **yes, I agree with it** ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☐ **I have personal experience of the condition** ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was originally diagnosed with RCC in February 2011 (when I was 42) and as a consequence had my right kidney and an infected lympthnode removed surgically. I then spent 7 years telling people I had cheated cancer by just having a kidney removed or as I used to say "I'd played my get out of jail card." Other than the regular scans I pretty much forgot about the cancer. Unfortunately after 7 years I had a regrowth in my right kidney bed, due to its proximity to my vena cava it was again removed surgically. Then 6 months later another regrowth was discovered and I was informed that I would have it treated by a drug called Sunitinib. After 26 days on that drug my treatment was stopped due to high blood pressure and tension headaches. I was then treated with Pazopanib but that again gave me high blood pressure and tension headaches and the treatment was stopped after 7 days. Eventually I was treated with 2 weeks of radiotherapy. Following the radiotherapy I returned to work after 8 months off, only for another regrowth to be discovered after just 3 months.

	I was then treated with Nivolumab. Again I experienced high blood pressure and tension headaches and was forced to take another break from work. It was now February 2020. I had 4 months of Nivolumab treatments, but treatment was then stopped as there was no evidence of the treatment working. By which time I was in significant pain with the cancer, I had been switched to Morphine for pain relief and had built up to 8 doses a day. I had another week of radiotherapy, which removed all my pain, before starting on Cabozantinib in July 2020. I started on a gradually increasing dose, starting on 20 gram tablets every other day until reaching 40 gram tablets every day. I had been on the 40 gram tablets for about a week when I was rushed into hospital. After 24 hours on a ward I was transferred onto ICU with what was later diagnosed as Diabetic Ketoacidosis. It was assumed that this was the result of increasing the Cabozantinib dose, but subsequently when the level of damage to my pancreas was discovered, it was determined that the damage had been caused by the Nivolumab and I was as a result a type 1 diabetic and was insulin dependent. I had been forced to take retirement from work on ill health grounds, after 2 years of battling to try to keep my job and treat the cancer – now I would focus on battling the cancer full time! To date the Cabozantinib has reduced the size of all my tumours and kept them that way. Day to day I endure the various side effects. I am still active but have to take life at a much slower pace. I still mow the lawns, but it's the front one day and the back on another day, maybe several days apart, rather than all in one afternoon!! I don't dwell on my cancer diagnosis, or my very limited life expectancy. I've maxed out my over 50 life insurances and my Coop funeral plan – so financially should the worse happen, I will in a way win financially!! That's the accountant in me! Seriously though, I don't dwell on my situation as I believe in my treatment, it's working and I trust in the next treatment to do the same. The vital issue is that there is another treatment, that there are options. Without the option of future treatments, I would not have hope. As a consultant said to me once, "so long as you've got hope, we can work with you to achieve successful outcomes." Obviously "success" is very subjective in my situation and is different for everyone on this journey.

	Planning is the worse problem – you can't plan to do anything, I never know from day to day how I am going to feel, which side effect I will be suffering from and how ill it will make me. Equally we don't plan anything beyond my next scan results (every 3 months), just in case my condition changes. The day to day experience is much worse for those around me, especially my wife. She sees all the effects of the treatments up close and personal, she listens to me letting off steam on my bad days. Her hopes are built up by each treatment in turn, only to be dashed. She is arguably more broken by this disease than myself, she has to continue to work full time at the same time worrying about me full time. Whereas I am retired at 53 and sit at home watching Netflix and YouTube. Who has the harder life?
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	In a word "**FANTASTIC**," the care is always amazing the treatments are generally appreciated, once you find the one that works for you. The admin and bureaucracy that you have to endure before you get a treatment though is "**FRUSTRATING**." In my own experience this has been exasperated by **NOT** being involved in the decision making process that determines which treatment you are placed on. I know that this is not every patients experience, as differing Trust's appear to work in differing ways. In my case the MDT review my latest CT results and then decide upon an appropriate course of action. Then I have a discussion with my consultant who informs me of my CT results and what the "agreed" course of action is, I have no input and are left with a "take it or leave it option." Which invariably is a case of having no option. I have tried to gain an understanding of how decisions have been reached in the MDT, which disciplines/departments have been consulted, etc. I have asked to attend the MDT but been refused, I have asked for the minutes of the MDT but been refused, on the grounds of patient confidentiality (other patients discussed at the same MDT), I have even asked for redacted minutes of the MDT so I only see the comments relating to myself, but again have been refused. Hence the added "**FRUSTRATION**." This frustration, just adds to the anxiety and stress felt by the patient. Some patients may be fine with this approach, but I need to understand the decisions that have been taken and why, it's my body, it's my cancer so I feel I should be able to understand why one treatment is deemed better for me than another, or why a treatment is not available to me or even to know if ALL possible treatments have been

	considered and why the “decided upon” treatment is right for me. I just want a transparent decision, not one veiled in secrecy.
10. Is there an unmet need for patients with this condition?	I had to take time off work when I was on treatment due to the headache side effects, I was unable to focus on a computer screen without experiencing migraines, which I have never suffered from before. This was common for me on which ever treatment I was on. I still occasionally experience the same on Cabozantinib. A treatment that is suitable for working age adults to enable them to continue their careers despite their diagnosis would be beneficial. I was once asked by a consultant “is work important to you?” At the time I was 49 with nearly 10 years left on the mortgage, of course work was important to me. With hindsight though following that conversation, I have struggled to work due to the side effects of my treatments.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Any immunotherapy treatment is going to be attractive to patients as it gives an opportunity for your own body to be encouraged to fight the cancer, in a basic form that seems more natural. Almost as if you are helping yourself – a DIY solution! If further testing/trials/experience eventually show that Pembrolizumab is less likely to cause Diabetes, as was my experience with Nivolumab, then perhaps Pembrolizumab can be offered to patients where there is hereditary evidence of Diabetes. My own father had late on set Type 2 Diabetes diagnosed when he was 55.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	Side effects – these are numerous and can effect quality of life, but they are not unique to this technology rather they are common to them all, but different people react differently to each treatment and hence can encounter different side effect. The greater the number of treatments the more likely that one of the available treatments will better suit a patient. In my cases I have had 3 aborted treatments, before I've found one that I can tolerate and which works. Covid-19 I started on Nivolumab just as the World descended into Covid lockdowns. At the time I had varying advice from the NHS, ranging from I’d be immune to Covid as I was already on immunotherapy to being at the highest level of risk and the need to self isolate, as I was already on immunotherapy. So there

	will be concern amongst patients to the risks of being on immunotherapy whilst Covid is still rampant. However I am typing this as someone who tested positive to Covid, 3 days ago and so far am fitter than my wife who tested positive to Covid over a week ago. So perhaps the concerns are unwarranted, so long as the vaccinations have been adopted in full (which I have done).
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those patients whose life expectancy is greater than 2 years. This is based upon my understanding of Nivolumab and the fact that it is possible that after 2 years on the treatment the immune system has been "taught" to identify and attack the cancer and active treatment can be stopped. Thus it would seem right to give all patients with a life expectancy of 2 years plus the opportunity to live beyond those 2 years treatment free and hopefully cancer free.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**Age** of the patient possibly. Arguments maybe formed that younger patients with less advanced cancers maybe better candidates for immunotherapy, if the target is drug free existence after 2 years on the treatment. The limiting factor though should be the advancement of the cancer and not the patients age.

Other issues	
15. Are there any other issues that you would like the committee to consider?	**Time**. When you are given a life limiting diagnosis, not wasting time becomes a priority. A successful treatment can buy you time, but starting on a treatment or switching between treatments can take time. Which feels like time wasted to the patient. In my own experience I have heard comments such as “we can start treatment once we have funding approved, which may take a couple of weeks,” then “we will need to get bloods done, then we will book you in for a scan.” Can this not be fast tracked? Funding approved before the patient meeting, bloods and CT organised for the same day as the face to face patient meeting – at least make it feel like some urgency is being applied. When switching from one treatment to another, the patient has to deal with the set back of the current treatment having failed or been unable to tolerate. This is devastating, for both the patient and their loved ones, as you have been pinning all your hopes on that treatment. Then you are told there is another treatment we can switch you onto, the patient’s anxiety is eased, there is another treatment. Then the sucker punch – “before we start the new treatment we will have to wait six weeks for the previous treatment to be out of your system.” The patients anxiety returns immediately, you’ve just been on one treatment for months, which has been ineffective (otherwise why switch treatments), so your cancer is likely to be actively growing or spreading and you have to wait 6 weeks without any treatment. Knowing your cancer has the upper hand and it’s not being treated for at least 6 weeks is sole destroying. Is there any chance of developing a process for “flushing” the previous treatment out of your system? In my own experience the 6 week waiting period was not totally wasted, since I was in pain with my cancer, I successfully argued for radiotherapy treatment to relieve the swelling from the cancer and it’s associated pain. I had to argue for that treatment, otherwise I would have had no treatment at all during that 6 week period. Why is there no incentive to look at alternative available treatments, rather than just following the road map onto the next drug in line?
Topic-specific questions	
1. Is Disease Free Survival (DFS) assessed by Blinded	

independent central review a more robust assessment of clinical efficacy? If so , why? 2. In the NHS how is the recurrence of disease assessed? 3. Do you think CDF data collection is feasible for the intended population for this technology? 4.In your experience does adjuvant treatment have cure potential? 5. In your practice have you seen patients achieve long term remission from adjuvant immunotherapy? If so, what	

proportion would you estimate this to be?	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Continued availability of treatments is vital to maintain patient hope/morale
- The greatest variety of treatments is required as everyone is different and certainly one treatment does not fit all
- The opportunity that a treatment may leave them able to live drug free and hence side effect free is worth pursuing
- Any treatment that enables someone to maintain their career/working life is also worth pursuing
- Availability of treatments also maintains carers and loved ones morale, the journey is not just the patients journey

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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Technical engagement response form

Pembrolizumab for adjuvant treatment of renal cell carcinoma [3810]

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments by **5pm** on **11 March 2022.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.

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- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Younan Zhang
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Merck Sharp & Dohme (UK) Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

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Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response	ERG response
Key issue 1: Immature DFS and OS data from KEYNOTE-564	**NO**	• Please note that in our responses we reference two data cuts from the KEYNOTE-564 study from which DFS and OS results are available: o The first interim analysis (IA1), with a data cutoff date of 14-DEC-2020 and median follow-up duration of 23.9 months. The results from this data cutoff were presented in Appendix M of the submission. o Results from a later 14-JUN-2021 cutoff date, with a median follow-up duration of 29.7 months. The results from this data cutoff were presented in section B.2 of the submission. • The DFS data from KEYNOTE-564 at the 14-JUN-2021 cutoff show a clear and statistically significant improved efficacy for pembrolizumab versus SOC:DFS by investigator assessment HR [95% CIs] was 0.63 [0.50, 0.80] with p-value <0.0001. • The subgroup analysis of DFS by investigator assessment at this cutoff shows statistically significant results in favour of pembrolizumab (i.e. HR upper 95% CI <1) in 10 out of 19 subgroups and HR point-estimates in favour of pembrolizumab in every case, 19	The ERG maintains its opinion presented in the ERG report. As is stated in the ERG report, the ERG recognises that additional data available with future readouts of the KEYNOTE-564 trial may lessen uncertainty around the current data.

		out of 19 subgroups (as originally presented in MSD's clarification question responses and also shown Figure 1 in below). **Figure 1. Forest plot of disease-free survival hazard ratio by subgroup factors, based on Investigator Assessment (primary censoring rule), (intention-to-treat population), KEYNOTE-564 14-JUN-2022 data cutoff**  • An ESMO Magnitude of Clinical Benefit Scale (MCBS) Scorecard rating of "A was given for pembrolizumab in this indication based on the KEYNOTE-564 IA1 (14-DEC-2020 data cutoff) results, this	

		highlights treatment options to be considered for an accelerated assessment of value and cost-effectiveness. • DFS results from KEYNOTE-564 at the later 14-JUN-2021 cutoff show a continuation of treatment benefit in favour of pembrolizumab from the previous data cut. IA1 reported HR [95% CIs] of 0.68 [0.53, 0.87] and the later 14-JUN-2021 cutoff reported 0.63 [0.50, 0.80]. There is clear and continued separation in the Kaplan-Meier curves with no convergence of the tails of the curves. These results suggest the observed benefit of pembrolizumab will be maintained as the data matures further., • The ERG has noted that the OS results from the KEYNOTE-564 are immature. As this is a study in adjuvant treatment we would not expect mature OS results to be available for a number of years. When mature OS results do become available, such results will be less relevant in the adjuvant setting than, for example, in the metastatic setting where death will occur much sooner following start of novel therapy. While OS results from studies in the adjuvant setting are informative, they are also likely to be confounded due to cross-over and subsequent treatments and will require substantial adjustment. On this basis, MSD considers it possible and appropriate for a decision to be made without mature OS data directly reported from the KEYNOTE-564 study.	
Key issue 2: IA versus BICR assessment from KEYNOTE-564	**NO**	• DFS as assessed by the investigator (IA) specifically was the primary endpoint of the KEYNOTE-564 study as pre-defined in the study's protocol and statistical analysis plan (described in section B.2.4 of the submission). • DFS that is investigator assessed (IA) has the best external validity/generalisability to real-world/NHS practice. Tumour recurrence assessment in UK clinical practice is undertaken by the treating clinician, not a blinded committee. Therefore, the IA results best reflect real-world clinical practice and so are the most	The company has not provided any new evidence - the ERG maintains its opinion presented in the ERG report (sections 3.3.1, 3.4 and 4.2.5). The ERG refutes the company's claim that the investigator assessment is the most generalisable to clinical practice as it takes place within the

		appropriate outcome to use in NICE's decision making which relates to the treatment of patients in the real world. • NICE have previously made positive recommendations for adjuvant cancer treatment based on investigator assessed outcomes of disease/recurrence/relapse-free survival as the primary endpoint. This demonstrates that DFS by IA is the most appropriate outcome for use in NICE's decision-making: o TA761 Osimertinib for adjuvant treatment of EGFR mutation-positive non-small-cell lung cancer after complete tumour resection (ADAURA study) o TA746 Nivolumab for adjuvant treatment of resected oesophageal or gastro-oesophageal junction cancer (CheckMate 577 study) o TA684 Nivolumab for adjuvant treatment of completely resected melanoma with lymph node involvement or metastatic disease (CheckMate 238 study) o TA544 Dabrafenib with trametinib for adjuvant treatment of resected BRAF V600 mutation-positive melanoma (COMBI-AD study) • DFS results by IA and BICR are similar: the 14-JUN-2021 cutoff for DFS by IA was HR (95% CIs) of 0.63 (0.05, 0.80) and for DFS by BICR was 0.78 (0.61, 0.99). There is substantial overlap between the confidence intervals between them. Concordance and discordance between IA and BICR-determined disease recurrence was assessed and a high level of consistency was found. The discrepancy rates found between these two methods did not cross the threshold values based on criteria reported in Mannino et al (1). • Where the results by IA and BICR differ, these may be caused by methodological/administrative procedures associated with BICR (for	confines of a clinical trial and is subject to assessment bias. The ERG considers that the BICR was included in the trial to mitigate against this bias. As such, the ERG considers DFS assessed by BICR to be more methodologically robust than IA and should be provided to ensure committee has all the available evidence to make its decision. The ERG considers that the committee should be presented with cost-effectiveness results using BICR in the form of a scenario analysis, in addition to the clinical evidence presented in the CS. Committee members would then be in a position to decide if they consider an analysis based on BICR or IA is the most appropriate for decision making.

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		example, the DFS by BICR results at the 14-JUN-2021 cut-off record one less death in the placebo arm of the KEYNOTE-564 study than the DFS by IA results due the last recorded BICR assessment being carried out on that patient being earlier (when the patient was still alive) than the last recorded IA assessment (by which point the patient had died). • It is MSD's position that IA is more reflective of real-world practice and therefore of more value to the NHS. Where there is apparent discrepancy between IA and BICR results, these are not statistically meaningful and can be explained to some extent by administrative processes and timings.	
Key issue 3: Long-term risk of relapse	**NO**	There are two elements that require consideration when assessing the long-term risk of relapse in patients post-nephrectomy: 1) For surveillance patients, the longer patients remain disease-free, the better the long-term outcomes are for these patients based on Leibovich et al. (2) 2) Whether pembrolizumab treated patients would demonstrate the same pattern in relapse as routine surveillance patients. • MSD believes the mechanism of action for pembrolizumab (discussed in section B1.3 of the company submission) would result in a maintained treatment benefit over time. The observed DFS data from KEYNOTE-564 show no evidence of an increasing hazard over time. Therefore, in the base case analysis MSD assumed a reduced relative risk of relapse associated with adjuvant pembrolizumab that would not wane over time. • The ERG has presented scenarios in which the treatment effect of pembrolizumab wanes at specific time points but acknowledges that there is no available evidence to support this assumption. The way the implement this in the economic model as an abrupt change in the	The company has not provided any new evidence - the ERG maintains its opinion presented in the ERG report (4.2.5).

		risk of recurrence for all patients remaining in DF after a specified time point is implausible. There is no evidence available to support waning of treatment effect. It is not plausible that if waning did occur it would occur at 4 years or that it would be an immediate loss of benefit. We understand why the assumption is explored but consider it too implausible to be informative in this adjuvant submission. • The ERG also notes a study on the long-term risk of recurrence in patients who received nephrectomy followed by routine surveillance, Leibovich *et al*. (2) This study reported a decreasing risk of recurrence in this population at 5-10 years post nephrectomy indicating that a longer disease-free period results in reduced risk of disease recurrence. The ERG suggests this reference as a rationale for assuming (explored in scenario analysis) that the risk of recurrence in both arms would be equivalent after a certain time point. This would only be possible if the hazard rate for pembrolizumab increases over time, i.e. there is an increased risk of relapse compared to routine surveillance patients. The plausibility of changes in treatment effect over time is best informed by log-cumulative hazard plots (LCH), which were presented in the company submission (Figure 14) for transitions from the disease free (DF) health state. The LCH plots for pembrolizumab do not show any change to the trend observed in KEYNOTE-564: the LCH plots are parallel for the routine surveillance and pembrolizumab arms indicating a maintenance of relative efficacy. • Assuming a waning of treatment effect on long-term risk of recurrence to all pembrolizumab-treated patients remaining DF after 4-, 7- or 10-years, as per the ERG scenario analysis, is not supported by the trial data from KEYNOTE-564 evidence nor by feedback from consultant oncologists in the UK, who expect the observed treatment effect to be maintained in the long term. Furthermore, as cited in the company submission, the S-TRAC trial provides long-term data on DFS with adjuvant sunitinib versus routine surveillance alone following	

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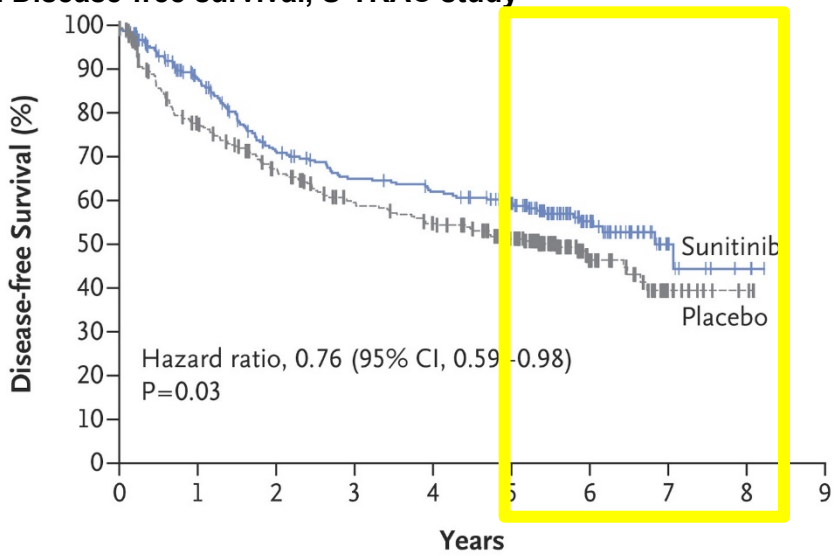
nephrectomy with data up to 8 years. Whilst LCH plots are not available for DFS data from this trial, a review of the Kaplan-Meier curves with a focus on the follow-up from 4-8 years, shows the DFS curves to be parallel for the duration of trial follow-up, continuing to the tails of the curves and indicating maintenance of the proportional hazards assumption (see Figure 2 below).

Figure 2 Disease-free survival, S-TRAC study



No. at Risk

Sunitinib	309	225	173	153	144	119	53	10	3	0
Placebo	306	220	181	150	135	102	37	10	2	0

Source: Ravaud et al. (3)

- Further data have recently been published allowing a more quantitative comparison of adjuvant pembrolizumab and adjuvant sunitinib. A network meta-analysis (NMA) was conducted by Laukhtina et al. to compare outcomes and safety profiles of pembrolizumab versus tyrosine kinase inhibitors (TKIs) including

		sunitinib in patients at high risk after nephrectomy for clinical nonmetastatic RCC (4). Analysis of treatment ranking showed pembrolizumab to be the best treatment with regard to DFS compared to TKIs and placebo. The hazard ratio (HR) of DFS for pembrolizumab [HR: 0.68, 95% CI; 0.53–0.87; p = 0.002] was more favourable compared with other adjuvant TKIs [HR: 0.88, 95% CI 0.49–0.97; p = 0.004] when each was compared with placebo. It can therefore be considered plausible that the lower bound for the treatment effect observed for pembrolizumab would be greater than that observed for adjuvant sunitinib in the S-TRAC trial. Viewing the evidence from KEYNOTE-564, the NMA, clinical expert opinion, and other data from pembrolizumab trials would suggest it is more likely that the long-term treatment effect for pembrolizumab on DFS would be higher than that observed for sunitinib. • There is no evidence of treatment effect waning in the metastatic setting in multiple indications for which there is long-term data for pembrolizumab (KEYNOTE-010 and KEYNOTE-024) (5, 6). For that reason, treatment effect waning is considered implausible in the adjuvant setting where patients have received surgery with curative intent prior to therapy. • MSD acknowledges an absence of confirmatory long-term data for maintenance of treatment effect following pembrolizumab in the adjuvant setting for RCC. However, the external trial data, NMA, and clinical expert opinion suggest the balance is probably in favour of maintenance of treatment effect as modelled in the company base case. It is certainly not supportive of abrupt waning at 4 years and highly unlikely at 7 and 10 years as tested in the scenario analyses.	
Key issue 4: Treatment regimen and resource use	**NO**	• The recommended dosage for pembrolizumab in adults as specified in the marketing authorisation is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30	The ERG has no further comments to add.

for pembrolizumab		minutes, therefore consideration of a scenario where pembrolizumab treatment regimen of 400mg once every six weeks is appropriate.	

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Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG response
Additional issue 1: Use of *approach #1 to extrapolate transition probabilities from the DF to LR and DF to DM health states.*	**Section 4.2.5.4**	**NO**	The ERG have included Approach #1 in their base case, which uses separately fitted curves with the exponential and Gompertz distributions to model transitions from DF to LR and DF to DM. The company base case uses Approach #3 as the most plausible method modelling DFS: jointly fitted models, with a time-varying treatment effect with the exponential and Gompertz distributions to model transitions from DF to LR and DF to DM. **Approach #1 is likely to underestimate the benefit of adjuvant pembrolizumab, therefore, Approach #3 is a more plausible method to extrapolate the transitions from the DF health state** • The ERG have cited the availability of patient-level data as the rationale for including Approach #1 (separately fit	The company has not provided any new evidence - the ERG maintains its opinion presented in the ERG report.

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Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG response
			curves) in its base case. When selecting base case survival models, external data must also be considered. • Table 38 of the company submission reports the observed incremental DFS benefit (versus placebo) in the KEYNOTE-564 and S-TRAC trials which can be seen to increase over time beyond 3. When using Approach #1, incremental DFS benefit remains approximately constant between pembrolizumab and routine surveillance whereas Approach #3 better reflect the trend of increasing DFS benefit observed in these trials. • As described above in the response to Key Issue #3, the incremental DFS benefit between sunitinib and placebo from the S-TRAC trial can be considered a lower bound of the incremental DFS benefit of pembrolizumab versus routine surveillance. When modelling transitions from DF using Approach #1, the resulting incremental DFS benefit for pembrolizumab versus routine surveillance	

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Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG response
			is similar to the DFS benefit observed in S-TRAC, which is considered conservative for the reasons provided above in the response to Key Issue #3. • The use of Approach #3 to model transitions from DF in the company base case was validated by comparing the modelled DFS estimates for routine surveillance to the long-term observed placebo data from S-TRAC (see Table 36 of the company submission). DFS for the routine surveillance arm when using Approach #1 were found to be consistently higher than observed DFS for the routing surveillance arms in the S-TRAC trial beyond 3-years. Specifically, Approach #1 led to an overestimate of the proportion of patient remaining in DFS in the routine surveillance arm of +1.8% and +7.5% at 5- and 7-years respectively. In contrast, using Approach #3 resulted in more accurate estimates of DFS for the routine surveillance arm up to 5-years and 7-years	

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Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	ERG response
			compared to observed DFS for routine surveillance in S-TRAC. • External validation against long-term published data suggests Approach #3 to be the most appropriate of estimating long-term transition probabilities from DF.	

Summary of changes to the company's cost-effectiveness estimate(s)

No changes to the company's preferred cost-effectiveness estimate(s) have been made in response to technical engagement.

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