EE344

Updated Cost-Effectiveness Analysis of Pembrolizumab as an Adjuvant Therapy for Renal Cell Carcinoma After Nephrectomy in the United States

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Background

- Globally, there are an estimated 434,419 newly diagnosed cases of kidney cancer and 155,702 attributable deaths per year[1]
  - Renal cell carcinoma (RCC) is the most common type of kidney cancer (90%)[2]
  - Most patients initially present with localized (65%) or regional (17%) disease[3]
  - These patients are usually managed with surgery in the form of a radical or partial nephrectomy, but a proportion of patients eventually develop recurrence, with metastatic five-year survival of 12%[4]
- For patients at increased risk of recurrence post-nephrectomy, there is a need for effective adjuvant therapies to prevent recurrence of RCC and improve survival
- Pembrolizumab monotherapy was approved in 2021 by the Food and Drug Administration as adjuvant treatment of RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, based on prolonged disease-free survival (DFS) versus placebo in the Phase 3 KEYNOTE-564 trial (hazard ratio [HR]: 0.63; 95% confidence interval [CI]: 0.50-0.80; *P*<0.001) (data cutoff date: 14 Jun 2021)[5]
- In the recent third interim analysis (IA3) of KEYNOTE-564 (data cutoff date: 15 Sep 2023), adjuvant therapy with pembrolizumab demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) relative to placebo (HR: 0.62; 95% CI: 0.44-0.87; *P*=0.005)[6]
- The introduction of pembrolizumab in this population warrants an understanding of its long-term benefit and costs from the perspective of US healthcare payers
  - In a prior economic evaluation based on an earlier readout from KEYNOTE-564, pembrolizumab was found to be cost-effective versus the strategy of routine surveillance alone (ie, no adjuvant therapy) from a US health sector perspective[7]; however, the results were subject to uncertainty due to immature OS data at the time of the analysis

Objectives

- To conduct an updated cost-effectiveness analysis of adjuvant pembrolizumab versus routine surveillance alone for RCC post-nephrectomy, incorporating longer-term data from IA3 of KEYNOTE-564 that showed significantly improved OS with pembrolizumab

Methods

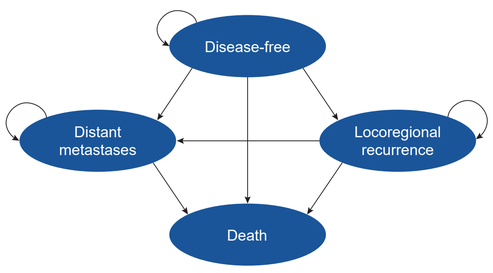
Model attributes

Attribute	Model specifications
Target population	Adult patients (ages 18 years or older) who have undergone nephrectomy for intermediate-high risk, high risk, or M1 no evidence of disease RCC
Treatment	Pembrolizumab 200 mg administered intravenously (IV) every 3 weeks for up to 17 cycles (~1 year)
Comparator	Routine surveillance
Time horizon	Lifetime
Cycle length	Weekly with half cycle correction
Discount rate	3% annually for both costs and effectiveness
Outcomes	• Costs, in total and by cost category • Life-years (LYs) and quality-adjusted LYs (QALYs) • Incremental cost-effectiveness ratio (ICER): incremental cost per QALY gained and per LY gained

Model structure

- A previously developed Markov cohort model with four states – disease-free (DF), locoregional recurrence (LR), distant metastases (DM), death – was updated to estimate lifetime costs from a US health sector perspective, QALYs, and LYs (**Figure 1**)
- The model was constructed in Microsoft® Excel® using a Markov cohort structure, an approach that is commonly used in National Institute for Health and Care Excellence (NICE) submissions to model adjuvant oncology indications
- The model structure allowed for extrapolation of the following survival endpoints in each treatment arm:
  - Disease-free survival (DFS), defined as time to LR, DM, or death, whichever occurs first: depends on all transition probabilities starting from the DF state
  - Overall survival (OS), defined as time to death: depends on all transition probabilities in the model

Figure 1. Model schematic



Model inputs: Transition probabilities

- In contrast to the original model, which relied on supplemental data sources to inform post-recurrence transition probabilities, all transition probabilities in the updated model were directly fitted to patient-level KEYNOTE-564 data
  - Transition probabilities were estimated via a parametric multistate modeling approach[8-11] in which different parametric functions were fitted to each individual health state transition, accounting for competing risks
  - In each weekly cycle, all transition probabilities to death were constrained to be at least as high as background mortality[12]

Transitions starting from DF

- For DF→death, exponential distributions were used due to few events
- For DF→LR and DF→DM, candidate distributions included: (1) seven distributions separately fitted to each arm (exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, generalized gamma); (2) three proportional hazards distributions (exponential, Weibull, Gompertz) jointly fitted to both arms with a time-constant hazard ratio for pembrolizumab versus placebo; and (3) three proportional hazards distributions (exponential, Weibull, Gompertz) jointly fitted to both arms with a time-varying HR that allowed the treatment effect to differ before versus after 1 year from randomization
- All transition probabilities from DF depended upon all three cause-specific hazard functions
  - Base-case distributions were therefore selected from all 67 possible combinations of distributions for DF→LR and DF→DM, including 49 (7×7) under approach #1, 9 (3×3) under approach #2, and 9 (3×3) under approach #3
  - The selection process is summarized in **Figure 2**

Transitions starting from LR

- For LR→DM and LR→death, exponential distributions were fitted within the subset of patients in KEYNOTE-564 who experienced LR as their first DFS failure event; separate exponential distributions were fitted for each trial arm

Transitions starting from DM

- For DM→death, an exponential model was fitted within the subset of patients in KEYNOTE-564 who experienced DM either as their first DFS failure event or following an earlier LR; a separate exponential distribution was fitted for each trial arm

Figure 2. Summary of selection process for base-case parametric distributions of DF→LR and DF→DM

Step 0: All candidate combinations of parametric distributions
67 combinations of distributions

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Step 1: Initial exclusions based on clinical plausibility (implausible crossing of the predicted DFS curves for pembrolizumab and routine surveillance) and nonconvergence
49 combinations of distributions

↓

Step 2: Visual assessment of fit between predicted vs observed cumulative incidence curves for DF→LR and DF→DM
14 combinations of distributions

↓

Step 3: Statistical fit between predicted vs observed DFS based on mean squared error and proportional hazards testing
9 combinations of distributions

↓

Step 4: External validations of long-term DFS and OS under routine surveillance (based on placebo data from past adjuvant therapy trials)
9 finalist combinations of distributions, including 1 base-case combination (log-normal for DF→LR and log-normal for DF→DM under approach #1)

DF, disease-free; DFS, disease-free survival; DM, distant metastases; LR, locoregional recurrence; OS, overall survival.

Safety

- Adverse event (AE) risks were considered for grade 3+ AE types with a frequency of ≥5% (all-cause, all grades) in either arm of KEYNOTE-564
- The mean duration (in weeks) per episode and the mean number of episodes per patient who had a particular AE type were obtained from KEYNOTE-564, pooling across both treatment arms

Utility inputs

- Utility was linked to patients' health state in each cycle (**Table 1**)
  - Health state utilities were derived through primary analyses of EuroQol-five dimension-five level questionnaire (EQ-5D-5L) data from KEYNOTE-564
  - Linear mixed-effects regression analyses with patient-level random effects were performed using repeated measures data from patient visits in which both health state and EQ-5D-5L were assessed
- AE-related disutility was applied as a one-time QALY decrement in the first model cycle
  - AE-related QALY decrement was calculated in each treatment arm as a function of treatment-specific AE risks; the mean number of episodes among patients with a given AE; the mean duration of these AEs per episode; and the estimated disutility associated with an active grade 3+ AE based on regression analyses of EQ-5D-5L data from KEYNOTE-564 (**Table 1**)

Cost inputs

- Drug costs for adjuvant pembrolizumab were calculated based on wholesale acquisition cost (WAC) ($5,668.68 per 100 mg of pembrolizumab), trial-based dosing, relative dose intensity of pembrolizumab in KEYNOTE-564 (98.9%), and the observed Kaplan-Meier curve for time on treatment (ToT) in KEYNOTE-564
- Other direct health care cost inputs (including costs of salvage surgery in the LR state, subsequent treatment costs in the DM state, AEs, disease management, and terminal care) are summarized in **Table 1**
- Cost inputs have been inflation-adjusted to 2024 USD where applicable

Table 1. Utility and cost inputs

Parameter	Value	Notes and sources
Utility by health state, mean (SE)		KEYNOTE-564
DF (without toxicity)	0.902 (0.005)	
LR	0.869 (0.021)	
DM	0.831 (0.010)	
Disutility during a grade 3+ AE (2024 USD)	-0.079 (0.009)	
Unit costs of drug administration (2024 USD)		
IV infusion, single or initial drug (up to 1 hour)	129.16	CMS Physician Fee Schedule 2024B (CPT: 96413)
IV infusion, each sequential treatment	63.58	CMS Physician Fee Schedule 2024B (CPT: 96417)
Oral drug dispensing	0	Assumption
Costs of AEs (one-time cost at model entry) (2024 USD)		Costs per AE episode were obtained from the 2020 HCUP National Inpatient Sample.[13] AE risks were obtained from KEYNOTE-564.
Pembrolizumab	1,951.48	
Routine surveillance	796.12	
Lump-sum costs of subsequent treatments upon entering DM, by model arm (2024 USD)		Estimated based on the market shares of subsequent treatments in each model arm (unpublished market research data; clinician input), WAC prices (Red Book, accessed June 2024), recommended dosing, administration cost,[14] and mean ToT. Mean ToT for 1L and 2L regimens in the DM state were estimated based on clinical trials in first- and second-line advanced RCC settings.[15-17]
Subsequent 1L treatment costs in DM state		
Pembrolizumab arm (if DFS ≥12 months)	575,141	
Pembrolizumab arm (if DFS <12 months)	464,017	
Routine surveillance arm	575,141	
Subsequent 2L treatment costs in DM state		
Both arms	93,385	
Disease management costs by health state (2024 USD)		Based on an analysis of SEER-Medicare data.[18] The cost of salvage surgery upon LR state entry was based on the unit cost per nephrectomy procedure from Lai 2022[18] and the observed frequency of surgery in patients who had LR in KEYNOTE-564.
Weekly cost in DF state, up to year 3	115.78	
Weekly cost in DF state, years 3-5	78.55	
Weekly cost in DF state, years 5+	72.69	
One-time salvage surgery cost at LR entry	5,123.33	
Weekly cost in LR state	183.06	
One-time cost at DM state entry	14,376.85	
Weekly cost in DM (pre-progression) state	299.79	
Weekly cost in DM (post-progression) state	389.64	
Terminal care cost (one-time cost upon death)	18,381.07	

AE, adverse event; CMS, Centers for Medicare & Medicaid Services; DF, disease-free; DFS, disease-free survival; DM, distant metastases; HCPCS, Healthcare Common Procedure Coding System; HCUP, Healthcare Cost and Utilization Project; IV, intravenous; LR, locoregional recurrence; PFS, progression-free survival; SE, standard error; SEER, Surveillance, Epidemiology, and End Results Program; ToT, time on treatment; USD, United States dollars; WAC, wholesale acquisition cost.

Sensitivity analyses

- One-way deterministic sensitivity analyses (DSAs) and scenario analyses were conducted to examine the influence of specific inputs and assumptions
- Probabilistic sensitivity analysis (PSA) with 1,000 iterations was also conducted to estimate the probability of each treatment being cost-effective under different willingness-to-pay thresholds
  - In each iteration, inputs were randomly drawn from specified distributions, using standard errors or variance-covariance matrices from original data sources where available

Model validation

- Internally validations were performed by plotting modeled DFS and OS in each arm against observed Kaplan-Meier curves from KEYNOTE-564
  - Modeled versus observed cumulative incidence curves for DF→LR, DF→DM, and DF→death were similarly compared
- External validations were performed by comparing modeled survival endpoints in the routine surveillance arm against Kaplan-Meier curves from the placebo arm of previous adjuvant therapy trials[19-22]

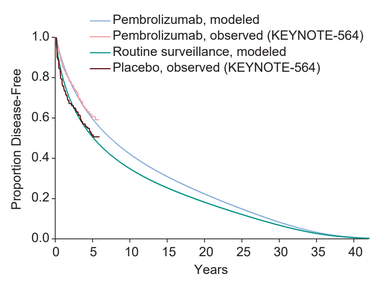
Results

Base-case survival projections

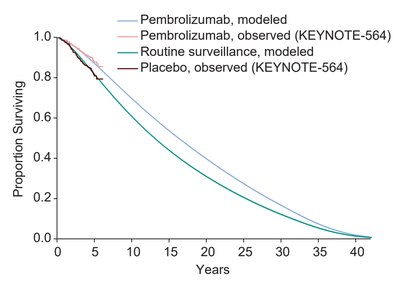
- Under base-case distributional assumptions, modeled DFS and OS for the pembrolizumab and routine surveillance arms closely aligned with DFS and OS Kaplan-Meier curves during the available follow-up period of KEYNOTE-564 (**Figures 3a-b**)
- Longer-term projections of DFS and OS in the routine surveillance arm were also in line with external data from the placebo arms of several prior trials of adjuvant treatments for RCC post-nephrectomy (**Figures 4a-b**)

Figure 3. Modeled vs observed DFS and OS for pembrolizumab and routine surveillance

a. DFS



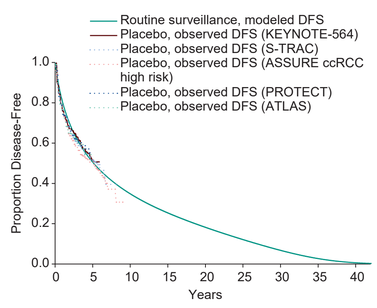
b. OS



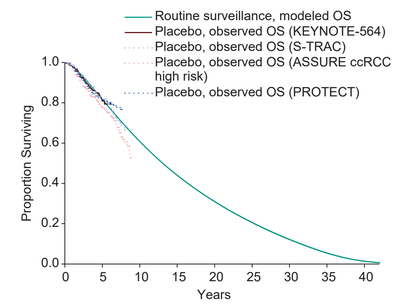
DFS, disease-free survival; OS, overall survival.

Figure 4. Validations of modeled DFS and OS in the routine surveillance arm vs external studies

a. DFS



b. OS



DFS, disease-free survival; OS, overall survival.

Base-case cost-effectiveness results

- Compared to routine surveillance, pembrolizumab increased total costs by $126,631 and provided gains of 1.29 QALYs and 1.45 LYs, with incremental cost-effectiveness ratios of $98,187/QALY and $87,415/LY (**Table 2**)
- The life expectancy gains with pembrolizumab were attributable to longer DFS (1.25 additional LYs in the disease-free state) as well as longer post-recurrence survival (0.20 additional LYs post-recurrence)
- The higher up-front costs of adjuvant pembrolizumab were partly offset by reductions in costs of subsequent treatments in the DM state
- Despite lower risks of LR and DM with pembrolizumab vs routine surveillance, disease management costs were higher in the pembrolizumab arm due to prolonged survival

Table 2. Base-case results

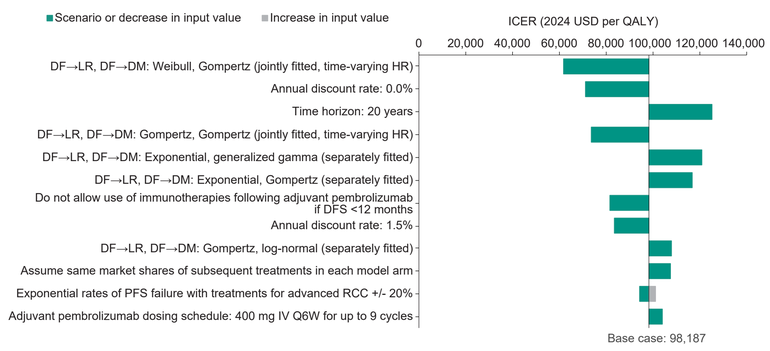
Outcomes	Pembrolizumab	Routine surveillance	Δ
Costs (2024 USD)			
Total costs	**626,818**	**500,187**	**126,631**
Adjuvant treatment costs (DF state)	153,184	0	153,184
Subsequent treatment costs (DM state)	340,651	375,804	-35,153
AE costs	1,951	796	1,155
Disease management costs	123,360	115,207	8,153
Terminal care costs	7,672	8,381	-709
Effectiveness			
Total QALYs	**11.38**	**10.09**	**1.29**
DF state	7.78	6.65	1.13
LR state	0.56	0.48	0.08
DM state	3.05	2.96	0.09
AE-related disutility	-0.0098	-0.0038	-0.0060
Total LYs	**12.94**	**11.49**	**1.45**
DF state	8.62	7.37	1.25
LR state	0.64	0.55	0.09
DM state	3.67	3.57	0.10
ICERs (2024 USD) of pembrolizumab vs routine surveillance			
Incremental cost per QALY gained	**-**	**-**	**98,187**
Incremental cost per LY gained	**-**	**-**	**87,415**

AE, adverse event; DF, disease-free; DM, distant metastases; ICER, incremental cost-effectiveness ratio; LR, locoregional recurrence; LY, life-year; QALY, quality-adjusted life-year; USD, United States dollars.

DSA and scenario analysis results

- Across all DSAs and scenario analyses, the ICER of pembrolizumab vs routine surveillance ranged from $61,724/QALY to $125,139
  - The tornado diagram presents DSAs and scenario analyses with the largest influence on the ICER (**Figure 5**)
- The ICER was most sensitive to the distributional assumptions determining transition probabilities from the DF state, as well as the annual discount rate, time horizon, and market shares of subsequent treatments in the DM state
  - Other moderately influential parameters and assumptions included the efficacy of subsequent treatments in the DM state and the dosing schedule of adjuvant pembrolizumab
- The results were not sensitive to high/low variation in exponential rates of transitions starting from the LR or DM states; drug administration costs; state-specific disease management costs; terminal care costs; health state utilities; or AE-related costs and disutilities

Figure 5. Tornado diagrams based on DSAs/scenario analyses for pembrolizumab vs routine surveillance



DF, disease-free; DFS, disease-free survival; DM, distant metastases; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IV, intravenously; LR, locoregional recurrence; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; QALY, quality-adjusted life year; RCC, renal cell carcinoma; USD, United States dollars.

PSA results

- In probabilistic simulations that considered parameter uncertainty, pembrolizumab had a 78.1% probability of cost-effectiveness at the commonly cited willingness-to-pay threshold of $150,000/QALY (**Figure 6**)
- The probabilistic ICERs of pembrolizumab vs routine surveillance (calculated based on Δcosts, ΔQALYs, and ΔLYs averaged over 1,000 PSA simulations) were $95,279/QALY and $84,780/LY (**Figure 7**), similar to the base-case ICERs

Figure 6. Cost-effectiveness acceptability curves based on 1,000 probabilistic simulations

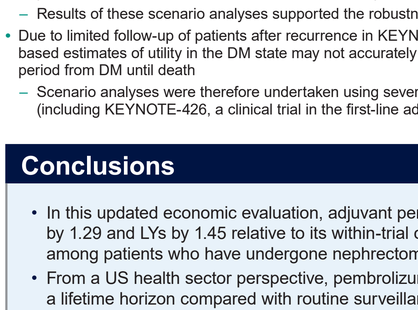
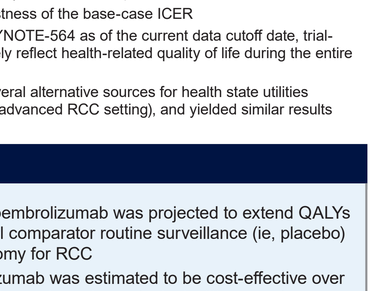


Figure 7. Scatterplot of incremental costs and effectiveness over 1,000 probabilistic simulations



ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life year; RCC, renal cell carcinoma; USD, United States dollars.

Discussion

Strengths of the economic evaluation:

- The Markov cohort structure is a well-established modeling approach and has been commonly used in prior health technology appraisals of neoadjuvant/adjuvant treatments in other oncology indications
- In the updated model, all transition probabilities were directly estimated using direct, head-to-head comparative data from the IA3 analysis KEYNOTE-564, representing a 57.2-month median follow-up period (as measured from randomization until the data cutoff date)
  - The inclusion of longer-term DFS data from KEYNOTE-564, as well as the ability to estimate post-recurrence transition probabilities using KEYNOTE-564 data, helps to address uncertainty regarding long-term survival extrapolations in the original model and the lack of data to inform transitions from the LR and DM states in the original model
- Consistent with methodological guidance,[10,23] the selection of parametric distributions to model transitions starting from the DF state were based on goodness-of-fit with observed trial data and validations of long-term survival predictions against external data
  - Long-term DFS and OS predictions in the routine surveillance arm closely aligned with placebo arm results from multiple prior trials of adjuvant therapies for RCC
- Given the 1-year maximum duration of adjuvant pembrolizumab, time on treatment in the adjuvant pembrolizumab arm was precisely estimated based on observed, mature Kaplan-Meier data from KEYNOTE-564, without the need for extrapolation
- AE-related disutility and most health state utility inputs were directly obtained from the KEYNOTE-564 trial and were measured using the EQ-5D, the utility measure preferred by NICE

Limitations of the economic evaluation:

- Although the updated model benefited from longer-term KEYNOTE-564 data based on the IA3 analysis, it was nevertheless necessary to extrapolate DFS and OS beyond the available follow-up period from KEYNOTE-564, given the lifetime horizon of this economic evaluation
  - There is inherent uncertainty in extrapolating long-term survival based on data from the available follow-up period of a clinical trial; therefore, multiple scenario analyses were undertaken using alternative distributional assumptions, including conservative scenarios that assumed a smaller incremental DFS benefit of pembrolizumab vs routine surveillance than that implied by the base-case parametric functions
  - Results of these scenario analyses supported the robustness of the base-case ICER
- Due to limited follow-up of patients after recurrence in KEYNOTE-564 as of the current data cutoff date, trial-based estimates of utility in the DM state may not accurately reflect health-related quality of life during the entire period from DM until death
  - Scenario analyses were therefore undertaken using several alternative sources for health state utilities (including KEYNOTE-426, a clinical trial in the first-line advanced RCC setting), and yielded similar results

Conclusions

- In this updated economic evaluation, adjuvant pembrolizumab was projected to extend QALYs by 1.29 and LYs by 1.45 relative to its within-trial comparator routine surveillance (ie, placebo) among patients who have undergone nephrectomy for RCC
- From a US health sector perspective, pembrolizumab was estimated to be cost-effective over a lifetime horizon compared with routine surveillance, based on a typical willingness-to-pay threshold
  - One-way and probabilistic sensitivity analyses supported the robustness of the cost-effectiveness conclusions

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