THE LONDON SCHOOL OF ECONOMICS AND POLITICAL SCIENCE

DEPARTMENT OF HEALTH POLICY

SUMMATIVE ASSESSMENT COVER SHEET

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COURSE CODE:	**HP4B9E**
ASSESSMENT TITLE: (E.g. Title of essay(s) attempted)	Cost-effectiveness analysis of neo-antigen cancer vaccines combined with immune checkpoint inhibitors as novel treatment for melanoma
QUESTION(S) ATTEMPTED: (If applicable, e.g. 1 and 3)	**Objective**. To assess the cost-effectiveness of neo-antigen cancer vaccines as add-on to immune-checkpoint inhibitor-based (ICI) therapy (1,2) with the following specific aims: 1. To assess the ICER for neo-antigen cancer vaccines in combination with nivolumab (BMS) or pembrolizumab (Merck) as novel treatment of melanoma from UK and US perspectives. 2. To evaluate how ICER is affected by vaccine efficacy in a sensitivity analysis. 3. To evaluate how ICER is affected by tumor response to ICI in a sensitivity analysis. 4. To assess the added value of DICE modelling. *Focus on Q1/2, from UK perspective. Q3/4 addressed*.
WORD COUNT: Excludes references and appendices.	**4,999** (including body of text, excluding Abstract, References, Tables, Figures and legends.)

Please tick this box if you would be happy for your assessment to be shared with future cohorts: ☒

[Insert question number (if applicable) and title]

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Cost-effectiveness analysis of neo-antigen cancer vaccines combined with immune checkpoint inhibitors as novel treatment for melanoma

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ABSTRACT

Cancer immuno-therapy based on checkpoint-inhibitors has triggered a paradigm shift in cancer treatment. The mode of action of checkpoint inhibitors makes combination therapies scientifically attractive. However, questions remain on the economic viability of add-on therapies given current pricing of nivolumab and pembrolizumab. Here, the question of incremental cost-effectiveness of add-on approaches, exemplified by neo-antigen vaccines, was addressed using a 3-state Markov model. Markov transition probabilities were estimated by Weibull regression of overall survival and progression-free survival data from two Phase III studies in which efficacies of nivolumab and pembrolizumab were evaluated in melanoma patients. To estimate the treatment effect of a hypothetical neo-antigen vaccine, ipilimumab was used as a proxy, because it was used as an add-on to nivolumab in one of the two Phase III studies. Relative risk of the ipilimumab-nivolumab combination versus nivolumab-only was used for the base case analysis. Utilities were derived from a UK-based analysis using a gamble method. Prices were found in NICE appraisal reports. The base-case analysis showed that adding immuno-therapy to checkpoint inhibitors was not cost-effective when efficacy was based on the ipilimumab treatment effect and with a willingness-to-pay limit of £100,000. However, sensitivity analysis revealed that when the treatment effect of adding vaccines to checkpoint inhibitors was increased from 1.3 to 2, combination becomes cost-effective. Extending a treatment effect >1 beyond a two-year treatment period, which can be immunologically justified, also led to cost-effectiveness. The results are aligned with published cost-effectiveness studies and suggest that there is a health-economic justification for further neo-antigen vaccine development, under the assumption that a certain minimal efficacy can be achieved. This approach can inform

R&D development decisions on indication and clinical endpoints in vaccine/checkpoint-inhibitor studies. The case for combination treatment will also benefit from further research into innovative pricing mechanisms such as indication-based pricing. (298 words).

INTRODUCTION

Cancer treatment has been revolutionized by the advent of immuno-therapies aiming to liberate anti-tumor T cells from tumor-induced immune-suppression (16,45). The key finding was that tumors develop mechanisms to suppress anti-tumor immune responses. Groundbreaking work, that led to a paradigm shift in tumor immunology and a 2018 Nobel Prize to Allison and Honjo (https://www.nobelprize.org/prizes/medicine/2018/allison/lecture/), has identified the molecules responsible for functional shut-down of anti-tumor T cells (16). Prominent amongst these are CTLA-4 ('cytotoxic T lymphocyte-associated protein-4'), PD-1 ('Programmed Death-1') and its ligand PD-L1 (13,16,45). A monoclonal antibody against CTLA-4, called *Ipilimumab* (1), made it to the clinic first, indicated for melanoma and renal cell carcinoma. More recently, two monoclonal antibodies targeting PD-1 have been licensed, *Pembrolizumab* (2) and *Nivolumab* (3), indicated for melanoma and other cancers. Whereas these novel treatments, collectively referred to as 'checkpoint inhibitors', are remarkably successful, their efficacy is not 100% (16). One innovative option to increase efficacy is to combine the checkpoint inhibitors with therapeutic vaccines that target novel antigens produced by the tumors (12). Novel antigens, also referred to as *neo-antigens*, result from the numerous mutations that tumors acquire. The concept to use these mutated neo-antigens for personalized vaccines has gained traction with the publication of promising results from several small studies (26,35,40). The approach requires acquiring individual DNA sequence data from tumor samples and using cutting-edge algorithms to predict which mutations are immunologically relevant. Critical for success is the *combination of checkpoint inhibitors with neo-antigen vaccines*. Immunologically, this makes sense: checkpoint

inhibitors release the breaks and vaccines can further push a highly targeted population of anti-tumor T cells (12).

The current checkpoint inhibitor therapies are cost-effective (5,37,46) although not in every indication (18). The urgent question is whether efficacy improvement by combination with a personalized vaccine can be justified from a payers' perspective (11,14,24). Current therapies with checkpoint inhibitors are costly and sustainability from a health economic perspective has been questioned (14). However, because of the immunological synergy between checkpoint inhibitors and neo-antigen vaccines, the combination has the potential to be highly efficacious. Therefore, the question of interest is how incremental cost-effectiveness of the combination is influenced by vaccine efficacy. The proof-of-concept studies (35,40) suggest that the combination approach can work from a clinical perspective. However, these studies are small and not properly controlled and vaccine efficacy cannot be estimated from them. No other clinical studies evaluating neo-antigen vaccines combined with checkpoint inhibitors are available. Nevertheless, it would be helpful for the further development of such therapies to evaluate how good they *should be* in order to justify the R&D investments and eventual pricing and to inform clinical trial design. This is the topic of this dissertation, addressed by creating a 3-state Markov model using data from two Phase III studies with pembrolizumab, Keynote-006 (38,41) and nivolumab, CheckMate-067 (20,28 ,50) (Table 1). I obtained the data by digitizing published overall and progression-free survival curves (7,8,22,34). Markov state transition probabilities were obtained by conducting a Weibull regression on the resulting digitized data (9).

The treatment effect of ipilimumab as an add-on to nivolumab versus nivolumab alone was used as a proxy for the expected/desired efficacy of a hypothetical vaccine because data for this combination could be obtained from the CheckMate-067 study (Table 1) (20,28,50). I used the Keynote-006 study (Table 1) (38,41) as well, for the following reasons. First, both nivolumab and pembrolizumab are currently being used to treat melanoma and neo-antigen vaccines as an add-on would be expected to complement either therapy. Second, using an independent dataset with a different treatment modality, provides a useful control. Third, both studies were conducted in melanoma patients (28,38), as were the two neo-antigen vaccine studies (35,40). Therefore, standard-of-care treatment with checkpoint inhibitors will be compared to standard-of-care treatment combined with neo-antigen vaccines, taking data with ipilimumab (CheckMate-67) as a proxy for combination treatment

The resulting Markov model revealed that under base-case conditions (i.e., vaccine efficacy mimicking the treatment effect of ipilimumab) cost-effectiveness was not reached. However, the outcome was sensitive to vaccine efficacy. The sensitivity analysis provided guidelines for future neo-antigen vaccine development which can inform indication, clinical trial design and clinical endpoint definition.

Name	**CheckMate-067**	**Keynote-006**
Sponsor	Bristol-Myers Squibb	Merck, Sharpe & Dome
ClinicalTrials.gov ID	NCT01844505	NCT01866319
# of subjects rnd	945	834
Age range (mean)	25-90 (59)*	22-89 (63)**
Gender (♂/♀)	202/114*	174/103**
Study	Randomized, dble-blind Ph III	Randomized, dble-blind Ph III
Population	Untreated adv melanoma	Untreated adv melanoma
Outcomes	OS & PFS	OS & PFS
Comparison	Nivo vs Nivo/Ipi vs Ipi	Pembro vs Ipi
Comparison !	Nivo/Ipi vs Ipi	Pembro 3 vs Ipi
OR (95% CI)	5.94 (4.14 – 8.51)	3.81 (2.50 – 5.82)
RR (95% CI)	3.06 (2.39 – 3.91)	2.77 (1.98 – 3.89)
Comparison!	Nivo vs Ipi	
OR (95% CI)	3.42 (2.39 – 4.90)	
RR (95% CI)	2.34 (1.81 – 3.03)	
Comparison!***	Nivo/Ipi vs Nivo	
OR (95% CI)	1.73 (1.26 – 2.83)	
RR (95% CI)	1.31 (1.12 – 1.52)	
References	20,28,50	38,41
* Based on the Nivolumab group; ** Based on the Pembrolizumab, every 3 wks group; *** Calculated with medcalc.org, ***!*** based on numbers of patients experiencing complete or partial responses (41,50)		
Abbreviations: Nivo = Nivolumab; Ipi = Ipilimumab; Pembro = Pembrolizumab; OS = Overall Survival; PFS = Progression-Free Survival		

Table 1*. Overview of the CheckMate-67 and Keynote-006 Phase III clinical studies including published and calculated OR and RR results and references.*

METHODS

Data. Overall survival (OS) and progression-free survival (PFS) data were obtained as described (7,8,22) from two Phase III studies using pembrolizumab and nivolumab in different combinations in melanoma patients (Table 1) (20,41). Data were captured by digitizing published Kaplan-Meier survival curves (19,22,27,34) into .cvs files using WebPlotDigitizer 4.2 software. To ensure that timepoints of the digitized data files were matching and could be used for further statistical analysis, linear interpolation was used with the equation: $y = y_1 + (x-x_1) * (y_2-y_1)/(x_2-x_1)$ (7,22) using Excel. The interpolation was done with a 2-week period. The resulting dataset was transferred into a STATA-15 worksheet to allow Weibull regression (7). Proportional Hazard (PH) Weibull regression was performed for each of the study arms of the two studies, using the PFS and OS data. Tables 2-5 show the results of the Weibull PH regression analyses for the OS and PFS data from the nivolimumab-only and pembrolizumab-only arms of the CheckMate-067 and Keynote-006 studies.

The resulting λ and γ parameters `(_cons = ln` λ and `p =` γ in STATA-15, with Weibull PH regression ran under `streg, nohr` command; Tables 2-5) were used to determine the Markov transition probabilities according to the following formula (8,9,15):

$$tp\ (t_u) = 1 - \exp\{\lambda(t-u)^{\gamma} - \lambda t^{\gamma}\} \quad \text{(i)}$$

in which $tp\ (t_u)$ is the estimate of the transition probability between time-points t and u. RR was used to estimate the treatment effect τ (9). The τ value was then used to calculate transition probabilities for the treatment with treatment effect τ as follows (9):

$$tp\ (t_u) = 1 - \exp\{\tau[\lambda(t-u)^{\gamma} - \lambda t^{\gamma}]\} \quad \text{(ii)}$$

In this case, the treatment effect τ was estimated using the treatment effect of adding ipilimumab to nivolumab in the CheckMate-067 study: i.e., the RR comparing the nivolumab/ipilimumab arm with the nivolumab-only arm, based on the methodology in (9). Given that ipilimumab is taken as the proxy for neo-antigen vaccination, τ value derived from the CheckMate-067 study is taken as the base-case efficacy of a hypothetical vaccine. Note that γ<1 in 3/4 regressions (and significantly so) indicating that (i) exponential modelling would only have worked for Keynote-006 OS data (Table 4) and (ii) hazard rates decrease over time (9).

_t	Coef.	Std. Err	Z	P>|z|	[95% Conf.	Interval]
_cons	-4.598754	.2940729	-15.63	0.000	-5.173912	-4.021168
/ln_p	-.2089007	.0677889	-3.08	0.002	-.3417644	-.076037
P	.8114758	.055009			.7105156	.926782
1/p	1.232323	.0835377			1.079002	1.407429

***Table 2**. STATA-15 output for Weibull PH regression on CheckMate-067 OS data. Log likelihood = -455.00896, LR chi2(0) = 0.00*

_t	Coef.	Std. Err	Z	P>|z|	[95% Conf.	Interval]
_cons	-3.045019	.1790864	-17.00	0.000	-3.396022	-2.694016
/ln_p	-.4387673	.056273	-7.80	0.000	-.5490602	.3284743
P	.6448308	.0362865			.5774923	.7200214
1/p	1.550794	.0872678			1.388848	1.731625

***Table 3**. STATA-15 output for Weibull PH regression on CheckMate-067 PFS data. Log likelihood = -546.341822, LR chi2(0) = 0.00*

_t	Coef.	Std. Err	Z	P>|z|	[95% Conf.	Interval]
_cons	-5.390781	.3985977	-13.52	0.000	-6.172018	-4.609544
/ln_p	.0517782	.081807	0.63	0.527	-.1085607	.212117
P	1.053142	.0861544			.8971245	1.236293
1/p	.9495395	.077679			.80887	1.114673

Table 4. *STATA-15 output for Weibull PH regression on Keynote-006 OS data. Log likelihood = -323.85536, LR chi2(0) = 0.00*

_t	Coef.	Std. Err	Z	P>|z|	[95% Conf.	Interval]
_cons	-3.367661	.207415	-16.24	0.000	-3.774187	-2.961135
/ln_p	-.2122797	.0585662	-3.62	0.000	-.3270674	-.097492
P	.8087384	.0473648			.7210351	.9071096
1/p	1.236494	.0724168			1.102403	1.386895

Table 5. *STATA-15 output for Weibull PH regression on Keynote-006 PFS data. Log likelihood = -448.07921, LR chi2(0) = 0.00*

Markov model. The Markov model was created in Excel based on published examples (8,9). A 3-state Markov model was created: (I) healthy, (II) progression and (III) death (Fig.1). The assumption is that there is no possibility to go back from progression to health. This could be a limitation (see Discussion). Using formula (i), the λ and γ parameters for OS were used to estimate the probability to move from State I (healthy) or State II (sick) to State III (death), defined as *pDeath* (8). The λ and γ parameters for PFS were used to estimate the probability to move from State I (healthy) to State II (progression), defined as *pSick* (8). Probabilities to stay in the same state were defined as *1 – (pDeath+pSick)* and *1 - pDeath* for State I and II, respectively (8). The resulting transition matrix, showing the 2-week transition probabilities from I or II to III (*pDeath*) and from I to II (*pSick*) is shown in Table 6. This is the transition matrix for the control situation, in which only checkpoint inhibitors are used for treatment of melanoma. In

the comparison, i.e., checkpoint inhibitors combined with a neo-antigen vaccine, a new transition matrix was calculated using formula (ii) and using the values from Table 6, thereby incorporating τ.

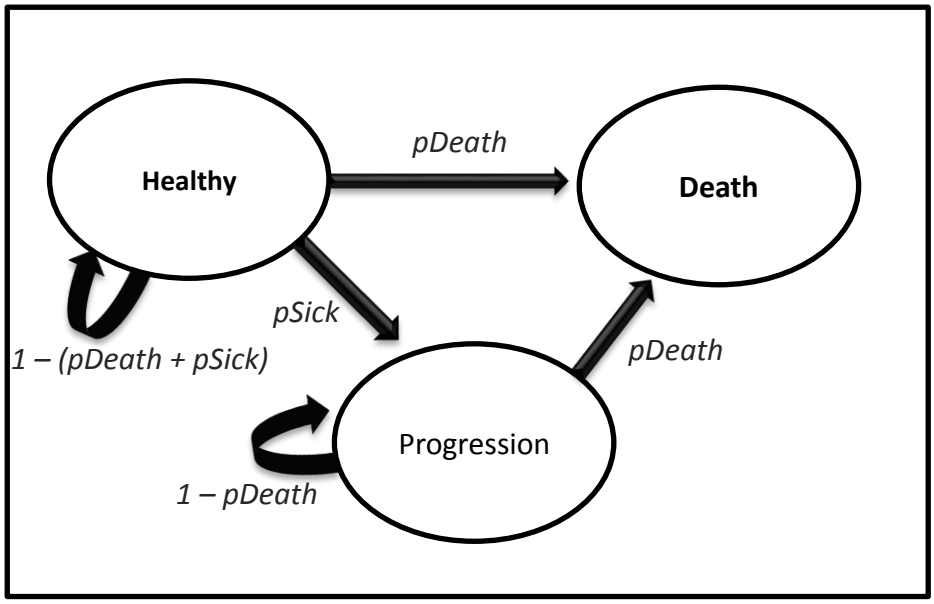

Fig.1. *Diagram of the 3-state Markov model, including (I) Healthy, (II) Progression and (III) Death.*

Transition matrix	**pDeath**	**pSick**
CheckMate-067	0.00757902	0.02646614
Keynote-006	0.00488851	0.0255777

Table 6*. Transition probabilities for the Markov model derived from Weibull regression.*

The Markov model was constructed with a 2-week cycle and a 20-year horizon. To adjust for age-dependent mortality, I used life table data derived from (9). The probabilities are adjusted for age and gender in the two studies (Table 7). Thus, I used the mean age at study start and the gender balance for each study (Table 1) to calculate adjusted mortality transition probabilities per cycle for each study (Table 7). The cost and doses were calculated based on NICE appraisals (31-33) and shown in Table 8. A discount rate of 3.5%/year was applied for costs.

Age	**Males**	**Females**	KN-006/yr	CM-67/yr	KN006/cycle	CM67/cycle
35-44	1.51	0.99	0.00131656	0.00132228	5.4857E-05	5.5095E-05
45-54	3.93	2.6	0.00343524	0.00344987	0.00014314	0.00014374
55-64	10.9	6.7	0.0093376	0.0093838	0.00038907	0.00039099
65-74	31.6	19.3	0.0270244	0.0271597	0.00112602	0.00113165
75-84	80.1	53.5	0.0702048	0.0704974	0.0029252	0.00293739
85+	187.9	154.8	0.1755868	0.1759509	0.00731612	0.00733129

Table 7*. Transition probabilities for death per age strata, given as numbers of deaths per 1000 for males and females per year, translated as probabilities per year and per 2-week cycle for each study, adjusted for the gender ratio in each study. KN-006 = Keynote-006; CM-67 = CheckMate-67.*

	Nivolumab	**Pembrolizumab**	**Ipilimumab**
Costs	£439 / 40 mg	£1315 / 50 mg	£3750 / 50 mg
	£1039 / 100 mg		£15000 / 200 mg
Dose	3 mg/kg /2 wks**	2 mg/kg /3 wks**	3 mg/kg (4x)
Ave. weight* (♂)	83.9 kg	83.9 kg	83.9 kg
Ave. weight* (♀)	70.6 kg	70.6 kg	70.6 kg
Ave.weight*(study)	79.1 kg	78.95 kg	79,1 kg
Dose (per subject)	237.3 mg	157.9 mg	237.3 mg
Price per dose	£2488.64	£4152.90	£17797.21
Price per year	£64704.71	£70599.30	£71188.83

Table 8*. Costs per treatment. Data from the NICE appraisals for the three different antibodies (31-33). * Average UK weights adjusted for study gender ratios. ** dose per every 2 or 3 weeks*

To calculate QALYs, I used utility values for melanoma patients in the UK (6). Population utilities for various disease states in advanced melanoma were measured in 140 subjects in the UK and Australia, using a gamble method, which is based on

decision making under uncertainty. Scores vary between 1 (full health) and 0 (dead). The mean utility values for the UK population per disease state were (6):

- Partial response: 0.85
- Stable disease: 0.77
- Progressive disease: 0.59

Here, I defined 'healthy' (State I, Fig.1) as stable disease (U= 0.77). I used the partial response utility value of 0.85 in the sensitivity analysis to model the possibility that vaccines could be curative. State II has a utility of 0.59, State III has a utility of 0. The calculate QALYs in my model, I used the stated utility values (6) and a discount rate of 3.5%/year.

For both nivolumab and for pembrolizumab, a two-year treatment period was used in the model. Ipilimumab is given in four doses. Ipilimumab is used as a proxy for the neo-antigen vaccine and injection of four doses is a reasonable assumption for this type of vaccine; therefore, this was kept as-is in the model. The treatment effect τ was applied for the two-year treatment period and was assumed to revert to 1 after that (but varied in sensitivity analysis). Because of the short cycle and long horizon (therefore, many cycles), no half-time correction was done.

ICER. The ICER (incremental cost-effectiveness ratio) was calculated as $\Delta Cost/\Delta QALY$, with $\Delta Cost = C_\tau - C_0$ and $\Delta QALY = QALY_\tau - QALY_o$, in which τ and 0 represent the experimental treatment group and the standard treatment group, respectively.

Sensitivity analysis. Deterministic sensitivity analysis was conducted by varying the treatment effect τ from 1.3 (the base-case value) to 2.5. In addition, the utility value of

healthy was increased from 0.77 to 0.85 to account for the possibility that the vaccine could induce a partial response, improving the utility of the 'healthy' state. The Markov model was made probabilistic using the methods and templates described in (9). Specifically, because the objective of the current analysis was to determine how hypothetical vaccine efficacy (defined as τ) would relate to cost-effectiveness, a probabilistic sensitivity analysis was done by using random sampling from a lognormal distribution for τ (9). Treatment effect during the first two years and a residual treatment effect for the remaining period were independently varied, both with lognormal distribution. Costs of the add-on treatment, the ipilimumab proxy, were made probabilistic by using random sampling from a gamma distribution for costs of ipilimumab (9). Costs of nivolumab and pembrolizumab were kept constant because it was assumed that decision makers contemplating R&D investments into neo-antigen vaccines would not have power to influence those prices. Utility was varied with a beta distribution (9) Probabilities of cost-effectiveness were calculated as a function of willingness-to-pay threshold, starting with the UK limit of £100,000 per QALY gained for cancer patients. All sensitivity analyses were conducted in the Excel model.

RESULTS

Data acquisition. Literature review identified the CheckMate-067 (20,28,50) and Keynote-006 (38,41) Phase III studies (Table 1) as best suited for the current purpose because:

- They were conducted in melanoma patients,
- CheckMate-67 had the unique comparison of add-on immunotherapy (ipilimumab) versus checkpoint inhibitor therapy alone (nivolumab),
- Keynote-006 provided a useful independent control because pembrolizumab targets PD-1 as well.

Details of the studies are shown in Table 1. In the CheckMate-067 study, subjects were randomized for PD-L1 and BRAF mutation status, as well as for American Joint Committee metastasis stage (28). Discontinuation in the study was mostly caused by disease progression but also by toxicity of the combination treatment (28). In the Keynote-006 study, subjects were randomized according to PD-L1 status, disease stage and line of therapy (38). Some discontinuation resulting from treatment adverse events was noted but lower than the CheckMate-067 study (38). Thus, whilst not identical, the two studies were deemed to be sufficiently similar to justify using them in this dissertation.

Long-term survival data have been published for both studies (20,41). The published Kaplan-Meier survival curves were deemed to be of sufficient quality to be scanned. Digitizing, data processing and data analysis in STATA-15 yielded Kaplan-Meier survival graphs for OS and PFS data for both studies (Figs.2/3). Right censoring was only applied for subjects surviving until end of study, implying that no censoring was

used for subjects lost-to-follow up or discontinuing. The data were then used for proportional hazard Weibull regression analysis to allow estimation of Markov transition probabilities (9) as shown in Table 6.

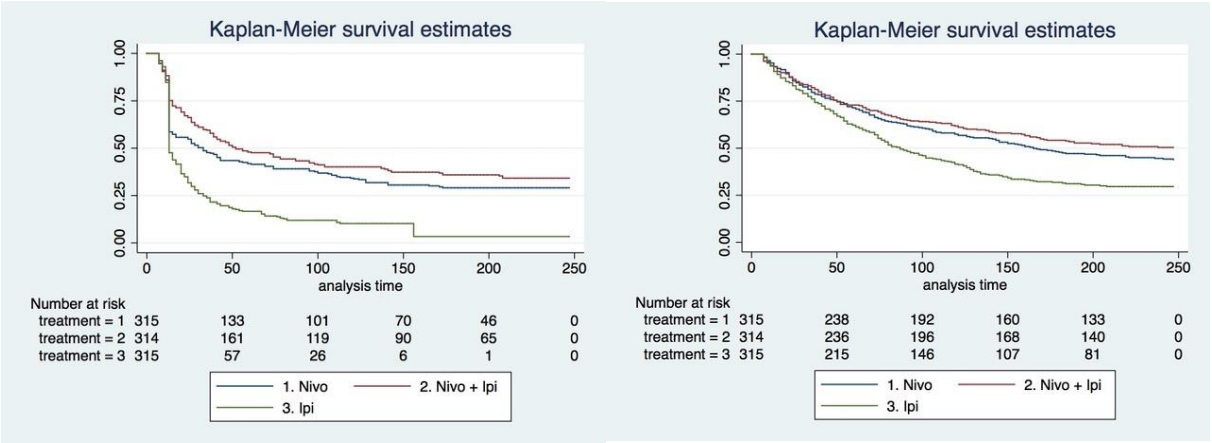

Figure 2*. STATA-15 output of scanned Kaplan-Meier survival plots for OS (left) and PFS (right) from the CheckMate-067 study. Analysis time is expressed in 2-week intervals. Derived by digitizing Fig.2 from (20).*

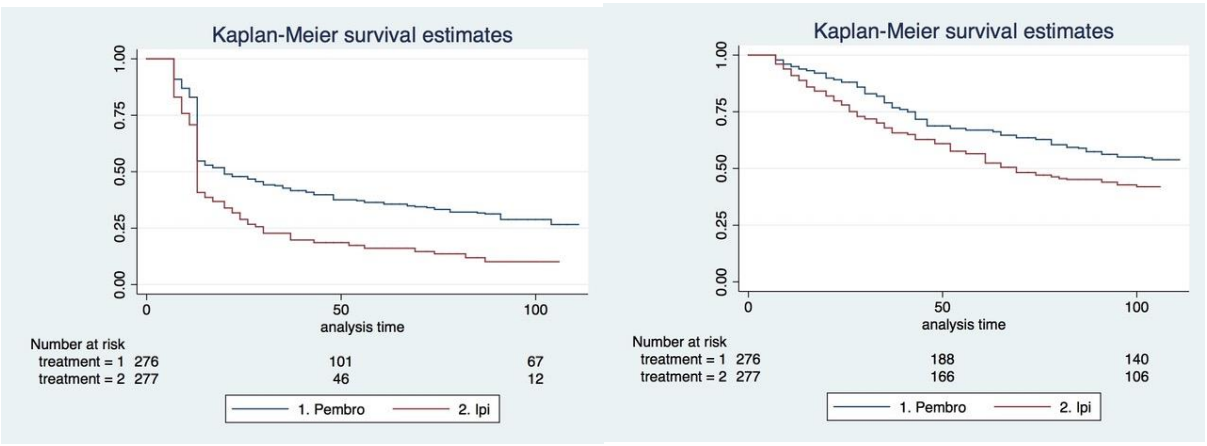

Figure 3*. STATA-15 output of scanned Kaplan-Meier survival plots for OS (left) and PFS (right) from the Keynote-006 study. Analysis time is expressed in 2-week intervals. Derived by digitizing Fig.2 from (41).*

Markov model. A Markov model (Fig.1) was created in Excel for each of the two following cases:

(1) Modelling the nivolumab-only arm from the CheckMate-067 study and applying a τ value of 1.3. τ was derived by comparing the nivolumab and nivolumab+ipilimumab arms in the CheckMate-067 study (Table 1) and this was

selected to model the treatment effect of immune-therapy on top of a checkpoint inhibitor. The treatment effect was calculated on the basis of numbers of patients experiencing complete or partial responses (41,50).

(2) Modelling the pembrolizumab arm of the Keynote-006 study and applying the same τ value as treatment effect.

The model was run with 2-week cycle time, a 20-year horizon, from the perspective of R&D decision makers. I used UK pricing data. Life tables (9) were used to include mortality probabilities, with age at start derived from the mean age at study start of the two Phase III studies. The base case Markov-modelling output for CheckMate-067 modelling is shown in Fig.4, upper panel. Applying treatment effect $\tau = 1.3$ to the base case, i.e., immuno-therapy op top of nivolumab, is shown in the lower panel (Fig.4). Similar graphs were obtained with the pembrolizumab and pembrolizumab + treatment effect simulation.

Under base case conditions ($\tau = 1.3$, utility scores applied, costs and QALYs discounted at 3.5%/year), ICERs were calculated for both conditions.

For CheckMate-067 (Nivo * τ vs Nivo) the model yielded the following:

- Incremental costs: £76,364/year
- Incremental benefit: 0.34 QALY
- ICER = £227,443/QALY for the addition of ipilimumab on top of nivolumab.

For Keynote-006 (pembro * τ vs pembro) the model yielded the following:

- Incremental costs: £71,341/year
- Incremental benefit: 0,23 QALY

- ICER = £311,208/QALY for the addition of ipilimumab on top of pembrolizumab.

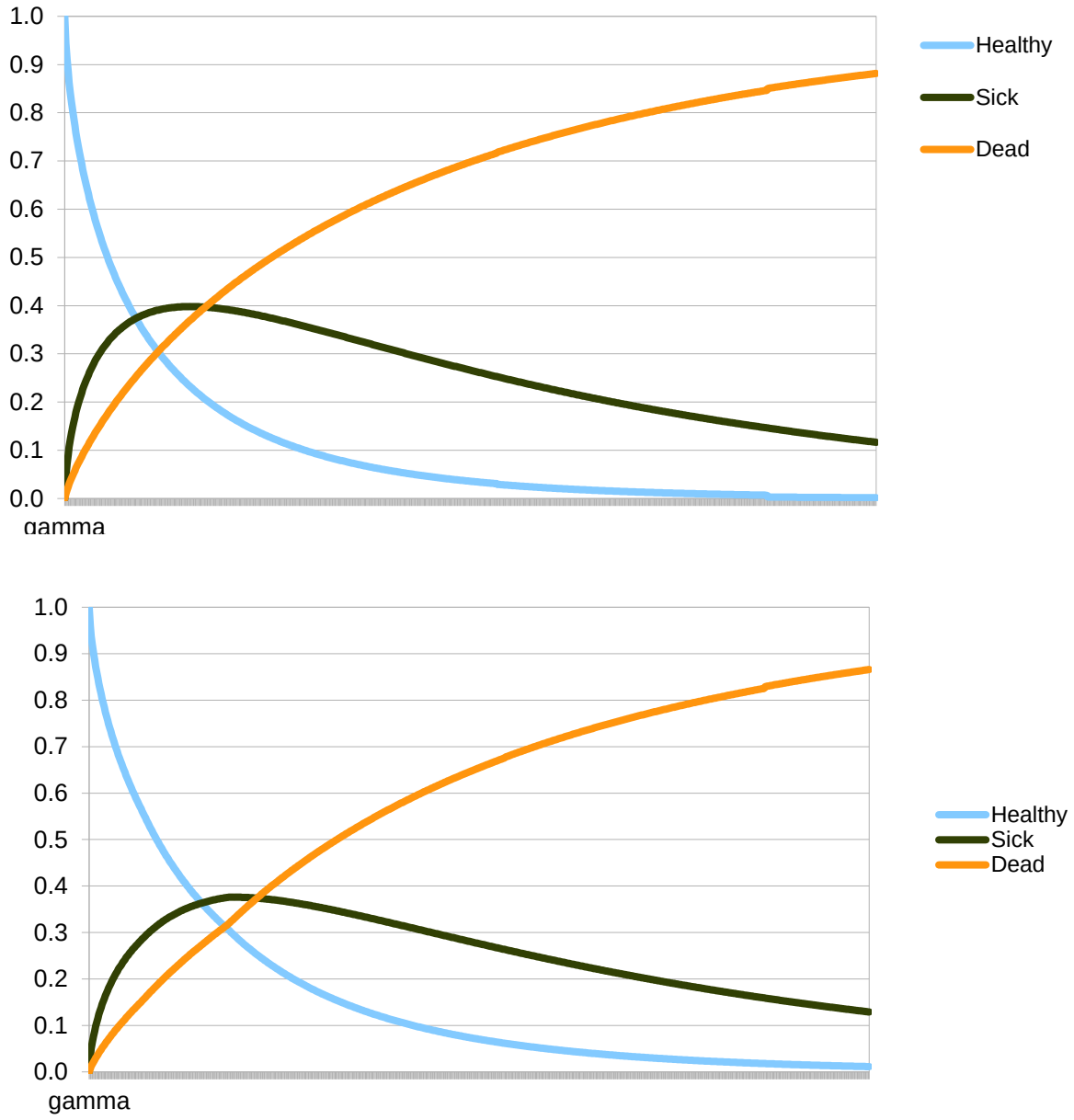

***Figure 4**. Visual representation of Markov modelling of CheckMate-067 data in Excel. The three states (Healthy, Sick, Death) are indicated in different colors. The base case of nivolumab-only is shown in the upper panel. Applying the estimated treatment effect of $\tau = 1.3$, mimicking the effect of ipilimumab on top of nivolumab, results in the modelling shown in the lower panel. Proportions in each state are indicated on the y-axis. Analysis time in 2-week periods over the 20-year horizon is indicated on the x-axis. Similar output was obtained for the Keynote-006 study (not shown).*

Evidently, adding ipilimumab (as proxy immuno-therapy) on top of the anti-PD1 checkpoint inhibitors exceeds the UK payer threshold of £100,000/QALY by a large

margin and is therefore not cost-effective. The main issue appears to be the denominator – thus, limited therapeutic benefit. It is therefore of interest to consider which factors could affect the calculated ICER values and how it is sensitive to treatment effect.

Sensitivity analysis. A 2-way sensitivity analysis was done by improving treatment effect τ stepwise from 1.3 to 2.5 and changing the healthy-state utility from 0.77 to 0.85 (6). The results are shown in Table 9, with results for CheckMate-067 and Keynote-006 shown in pink and blue, respectively. Improving treatment effect τ had a clear positive impact, as expected. A treatment effect of 2.5 resulted in cost-effectiveness in one case. If the addition of a neo-antigen vaccine to current checkpoint inhibitors results in partial responses, as suggested by the clinical studies (35,40), then a healthy state utility of 0.85 can be justified. In that case, a treatment effect of 2.5 appears to approach cost-effectiveness in both cases, based on current prices for ipilimumab and 4 injections. Overall, cost-effectiveness is reached at lower τ with nivolumab as compared to pembrolizumab, which seems to be related to higher incremental effectiveness.

$\tau: \rightarrow$ $U_h \downarrow$	1.3	1.7	2	2.5		1.3	1.7	2	2.5
0.77	227,443	130,236	107,836	90,253		311,208	171,259	139,713	115,137
0.85	203,889	116,245	96.056	80,206		279,484	153,081	124,583	102,380

***Table 9**. ICER values in £ per QALY gained for different values of τ (upper row) and different utilities for the healthy state (left column). CheckMate-67 and Keynote-006 results are shown in pink and blue, respectively.*

A condition in the Markov model so far is that the treatment effect is limited to two years, i.e., the duration of treatment with checkpoint inhibitors. However, because (i) immune cell memory can persist for life and (ii) tumor-induced immune-suppression might be minimal under conditions of minimal residual disease, I introduced the change of a persistent treatment effect. There is some published justification for this (44). I ran the Markov model with a τ=1.3 for the first two years (the original ipilimumab effect) and then keeping it at that level for the remaining time to reflect T cell memory. I also took a health utility value of 0.85 for this simulation. In this case, the ICER for CheckMate-067 is £72,235/QALY and for Keynote-006 it is £89,699/QALY. This suggests that *persistence* of a functional vaccine-induced T cell response has a major impact on cost-effectiveness, even if the treatment effect is relatively small and not cost-effective when limited to two years. Overall, this suggests that a neo-antigen vaccine with a treatment effect of τ=2.5 or more for progression and mortality parameters, at a price of £71,189 (current price for ipilimumab) and given at 4 doses could be cost-effective, assuming it results in partial regression (justifying better QoL utility). If the vaccine effect persists beyond 2 years, the cost-effectiveness improves and a lower treatment effect becomes cost effective.

To further model this, I conducted a probabilistic sensitivity analysis by varying simultaneously treatment effect, longevity of treatment effect, utility (6) and costs of add-on therapy for the CM-067 study. The desired (arbitrary) values, confidence intervals and distributions (9) are shown in Table 10. Monte Carlo simulation was done with 1,100 repeats. Note that the desired long-lived τ is lower than the immediate (2 year) τ to allow for immune memory waning over time.

Variable	Mean	95% CI	SE	Distribution
τ (2 year)	1.75	1-2.5	0.38	Lognormal
τ (2-20 year)	1.1	1-1.2	0.05	Lognormal
Utility	0.81	0.77-0.85	0.02	Beta
Cost/dose	£20,000	£15k-25k	£2551	Gamma

***Table 10**. Parameters in probabilistic sensitivity analysis*

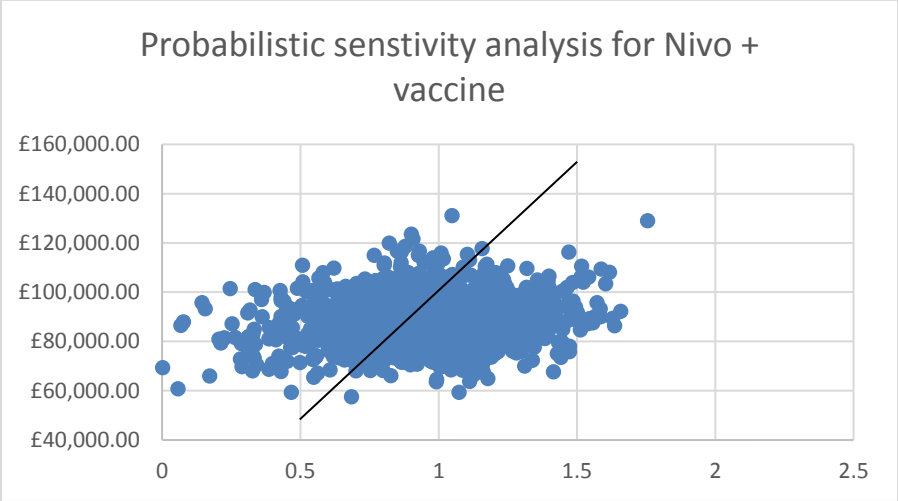

***Figure 5.** Monte Carlo simulation (1,100x) under conditions as in Table 10. QALYs (X-axis) versus costs (Y-axis). ICER of £100,000/QALY is indicated by the straight line.*

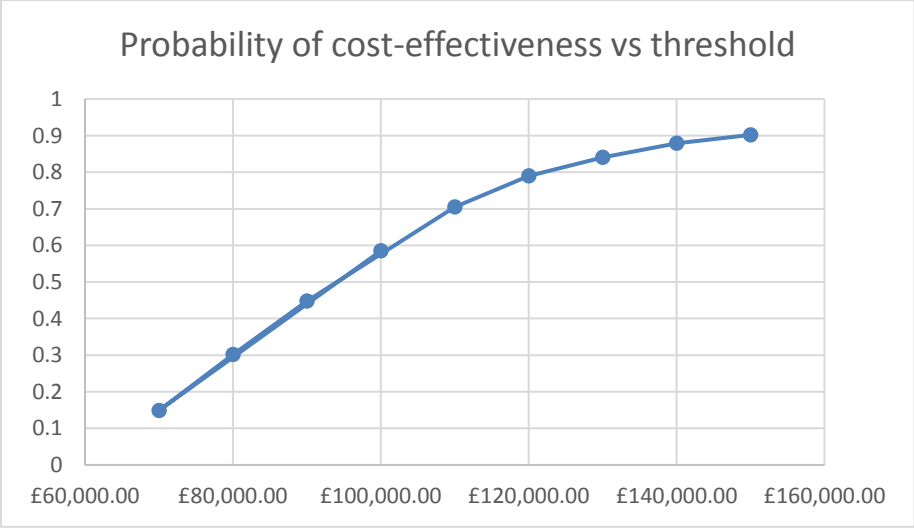

***Figure 6**. Probability of cost-effectiveness (Y-axis) versus willingness-to-pay threshold (X-axis)*

The outcome of the probabilistic analysis is shown in Fig.5, based on the parameter variability in Table 10 result in a probability of being cost-effective of 0.6. When further analyzed versus willingness-to-pay thresholds, probability of cost-effectiveness goes up to 0.8 at a threshold on £120,000/QALY (Fig.6). Thus, it appears that some uncertainty in vaccine efficacy, as modelled here, and between 1 and 2.5 (Table 10) is acceptable. Note that a value of 1 is included (i.e., no efficacy).

DISCUSSION

Checkpoint inhibitors are efficacious (20,28,38,39,41,50) and cost-effective (5,36,46). However, given their pricing, a key question is how *combination* therapies can be justified from a health-economic perspective (14,24). The current dissertation addresses this by creating a 3-state Markov model based on OS and PFS data from two Phase III studies that evaluate the efficacy of pembrolizumab and nivolumab in melanoma patients. Base-case modelling, using a treatment effect estimated from the CheckMate-067 study, revealed that *if a therapeutic neo-antigen vaccine would be as good as ipilimumab when used in combination with either nivolumab or pembrolizumab, it would not be cost-effective*. However, the sensitivity analysis showed that vaccine efficacy, captured by treatment effect τ, is critical. Thus, if personalized neo-antigen vaccines fulfil their promise of efficacy (35,40), then a 4-dose vaccine at a total price of ~£80,000 has a good probability of being cost-effective, given current prices for pembrolizumab and nivolumab. In the sensitivity analysis τ=2 was (close to) cost-effective with ICER values close to £100,000. In the probabilistic analysis, τ=1.75 with a 95% CI of 1-2.5 resulted in a 60% probability of reaching cost-effectiveness. The experience with checkpoint inhibitors suggests that achieving such treatment effects is a reasonable expectation. For example, comparing nivolumab or pembrolizumab with ipilimumab yielded RR values of 2.34 and 2.77, respectively (Table 1). Comparing nivolumab with chemotherapy (dacarbazine) (39) yielded a RR of 2.99. This suggests that such treatment effects are realistic for immuno-therapy. Thus, I conclude that Markov modelling, whilst acknowledging several simplifications and assumptions (see below), does show a path forward for the development of neo-antigen cancer vaccines.

The issue of lack of clinical data for neo-antigen cancer vaccines (35,40) was addressed by using data from the CheckMate-067 (20,28,38,50) study, i.e., ipilimumab combined with nivolumab versus nivolumab-alone, as a proxy for the addition of a neo-antigen vaccine to the current standard-of-care checkpoint inhibitors. This makes sense for three reasons. First, from an immunological perspective, neo-antigen vaccines can only possibly work when combined with checkpoint inhibitors (12). Second, ipilimumab targets anti-tumor immune responses, sharing some of its mode of action with neo-antigen vaccines. Third, the price comparisons are realistic because the financial room upwards from current pricing of nivolumab and pembrolizumab is limited and it is anticipated that a personalized neo-antigen cancer vaccine will be costly (because it requires the patients' own DNA sequence data and needs to be custom-made). Current ipilimumab pricing and dosing is a realistic starting point. I have used UK data for pricing (31-33). The key data set was obtained by using published Kaplan-Meier graphs for overall survival and progression-free survival for the CheckMate-67 study, focusing on the nivolumab-only and the nivolumab+ipilimumab arms. To limit bias due to the selection of a single-study and single checkpoint inhibitor, I also used data from the Pembrolizumab-only arm in the Keynote-006 study. Utility values were derived from a UK- and Australia-based study using standard gamble techniques (6). These values are close to published EQ-5D values for melanoma (30) and were also used in other health economic evaluations (27). Weibull regression was used to estimate transition probabilities, based on (9) and justified by its use in several published studies (17,27,30,36,46). However, its appropriateness in immuno-oncology has been questioned (4). Benedict argue, in their critique on (27), that "PFS curves often exhibit sharp drops followed by long plateaus" (4) (as is the case here – Figures

2/3) and that this complicates fitting (4,23). This response pattern is considered to be a characteristic of immuno-oncology therapies and differs from conventional anti-cancer agents (17). Therefore, using Weibull regression is justified by precedent but one particular limitation, namely an underestimation of survival (4,23), should be acknowledged.

In the next sections, I will review model choice, its assumptions and perspective and then discuss whether Markov-model limitations could be improved by more individualized models. The outcomes of the modelling approach are compared with current literature.

Sonnenberg & Beck argue that “Markov models are particularly useful when a decision problem involves a risk that is ongoing over time” (42). A Markov model assumes that patients can be categorized in any number of defined health states, referred to as the Markov states (9,42). Risk is then defined as the probability of moving from one state to another. Markov models are therefore appropriate for modelling cancer therapies: disease states are usually well-defined and clinical trial data are presented as overall survival and progression-free survival, thereby defining the three basic Markov states that I used in my modelling. Evaluating the impact of a neo-antigen vaccine in a Markov model is appropriate because the vaccine acts as an anti-tumor therapy. Whereas in infectious disease modelling, dynamic models would be required for vaccination studies (9), due to herd immunity and pathogen transmission rates, this is not the case for therapeutic cancer vaccines. The current modelling is done from the perspective of UK R&D decision makers that are faced with investment decisions for neo-antigen vaccine development and where upfront definition of a target product profile would

require making estimates of vaccine efficacy. This could then inform decisions on the tumor type(s) to target, the vaccine technology to be used and the endpoints of clinical studies. The novelty of the current approach is that it represents upfront modelling, without clinical data, whereas usually economic modelling is done based on existing data to inform healthcare decision makers. However, the current 3-state Markov model is relatively basic and therefore has its limitations. Several potential improvements are identified.

First, the model could be improved by estimating the probability of curative responses, which would translate in a transition probability from State II (progression) back to State I (healthy) that is >0. Based on the immunology of anti-tumor T cells, this is a reasonable assumption.

Second, the model could be refined by including right censoring due to discontinuation and by including costs for adverse event and other treatments. Not including this in the current model assumes that these variables are not affected by addition of the neo-antigen vaccines. This is a limitation and should be addressed in more refined modelling.

Third, further improvement in the model would be to introduce patient stratification, on BRAF status (which is relevant for melanoma), PD-L1 status (which can affect the efficacy of checkpoint inhibitors) and on disease progression states. Indeed, Gibson argue that a 3-state Markov model is too simplistic to capture immune-response based therapy effects and they evaluate a 6-state model (17). For this, patient-level data are required (17) because general OS and PFS data are too limited. Alternatively, patient-level simulation models can be envisioned, for example using discrete event simulation (DES) (9). If patient-level data are available (which was not the case in the present

dissertation), then DES is attractive because it allows for patient heterogeneity and does not assume the no-memory feature of Markov (9). Gibson found that DES resulted in different outcomes with regards to QALYs gained as compared to Markov, irrespective of the number of Markov states used in the model (17). This contrasts with findings from Karnon (25) who compared multi-state Markov with DES in an evaluation comparing chemotherapy/tamoxifen treatment with tamoxifen-only in breast cancer patients. In their case, outcomes were remarkably similar (ICERs £3365 and £3483 for Markov and DES, respectively). Goeree found that partitioned survival and Markov models yielded very similar outcomes for nivolumab in NSCLC (18), whereas Williams (48) show that model choice, notably multi-state modeling with patient-level data, does affect outcome. An alternative method that was considered after attending a workshop at the HTAi meeting in Cologne (2019) was DICE (10), because it integrates Markov modelling and discrete event simulation. However, I decided that, given the limited data set (digitized OS and PFS data), Markov modelling would be most appropriate for the current purpose. Nevertheless, with the advance of personalized medicine, modelling patient heterogeneity will be important for health economic modelling. Hoogendoorn developed a patient-level simulation model for COPD to capture diversity in the patient population and outcomes (21). Although beyond the scope of this dissertation, I recommend that this type of patient-level modelling (21,29) should be the way forward for more detailed prospective health economic evaluation of personalized neo-antigen cancer vaccines.

Fourth, duration of treatment effect is unknown. There are no data to estimate whether the treatment effects of neo-antigen cancer vaccines would be limited to two years (base-case and as was assumed for nivolumab and pembrolizumab) or whether more long-lived effects might manifest themselves. There is some evidence for sustained

effects for immuno-therapy (44), as was modelled here by continuing the treatment effect. Tarhini (44) used treatment-free periods as a metric to evaluate this, and concluded that nivolumab+ipilimumab can be cost-effective when considered from this perspective. Further research into immune-mediated mechanisms behind sustained responses may help inform this modelling approach. This uncertainty was dealt with in the sensitivity analysis.

Several other health economic evaluations have been performed (27,30,34,36,37). Both pembrolizumab and nivolumab were cost-effective for the treatment of melanoma (5,30,34,37,46,47). Nivolumab/ipilimumab combination therapy compared to nivolumab alone was not cost-effective for melanoma with an ICER of $454,092/QALY in the US setting (34). This was confirmed in a systematic review (46). Kohn (27) found, using a 4-state Markov model that immune-therapies (nivolumab and pembrolizumab) are cost-effective compared to chemotherapy in melanoma, but that nivolumab/ipilimumab versus nivolumab was not, with an ICER of $198,867/QALY. Therefore, the outcome of my model (lack of cost-effectiveness) is aligned with these outcomes. As discussed above, a simplification in my model was to only include costs of treatment and the impact of age-related mortality. Costs of adverse events management and additional costs related to treatment or end-of-life treatment were excluded in my model. Although a limitation, comparison with more sophisticated models (27,30,34,47) suggests that this may not have affected the eventual outcome. Verma report that for non-small cell lung cancer, overall cost-effectiveness outcomes are sensitive to patients' PD-L1 status (46), stressing the need to account for patient heterogeneity.

The published (27,30,46) and present (Table 9, Fig.5) cost-effectiveness outcomes illustrate the challenge of adding a therapeutic modality on top of checkpoint inhibitors. Any vaccine would have to display a high level of efficacy. The problem is illustrated by the example of Sipuleucal-T, a personalized vaccine that was FDA-approved in 2010 for treatment of metastatic prostate cancer (24). Phase III studies showed a 4.1 month median survival benefit at a price of $93,000, resulting in a non-cost-effective ICER of $280,000/QALY. A plausible reason for the limited efficacy is that the vaccine was evaluated without checkpoint inhibitors. The current excitement about neo-antigen cancer vaccines centers around their combination with checkpoint inhibitors (12). However, the pricing challenge of checkpoint inhibitors and combination therapies has raised concerns on sustainability (14,43). Price differentiation may provide a way forward. Cole (11) proposed indication-based pricing (IBP) as a solution to encourage competition, taking checkpoint inhibitors as an example. There has been a debate whether this would lead to higher or lower prices (11) but Cole argue that this current debate is too limited because it underestimates dynamic effects, i.e. increasing competition. In their words: “economic theory indicates that – in the short term – indication-based pricing can improve overall welfare if it means greater patient access, but payers may (or may not) be worse off. However, the potential longer-term (dynamic) effects of IBP are sometimes neglected - optimised incentives for R&D and potential for increased price competition at the indication-level, driving down prices and delivering better value to the health system” (11). IBP may also be applicable for combination therapies that suffer from the ‘not cost-effective at price zero’ problem (11), which is not efficient. I argue that IBP provides an important framework and that further research and innovation in this area should accompany the development of neo-antigen cancer vaccines.

CONCLUSION

Additional immuno-therapy on top of checkpoint inhibitors is not cost-effective when the treatment effect is comparable to ipilimumab. The outcome is sensitive to treatment effect and longevity of the response. Models using patient-level data are recommended because these take into account patient heterogeneity (21,29,48). Sustainability of immune-oncological approaches whilst maintaining innovation requires innovative pricing models such as indication-based pricing (11).

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