

A systematic review of cost-effective analyses of pembrolizumab for several indications

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Abstract

Introduction: Pembrolizumab is a promising immune checkpoint inhibitor engaging on the Programmed-Death-1(PD-1)-receptor. [1,2,3,4] A problem with pembrolizumab is the potential high budget impact. [5] In this review different cost-effective analyses are reviewed.

Materials and Methods: During this review a systematic search on PubMed is done and 'pembrolizumab' and 'cost effectiveness' are used as search terms. In a qualitative analysis the relevant articles will be studied on several key points.

Results: The PubMed search delivered 33 hits. Also, two articles were found by snowballing. 17 records were excluded, and 7 full-text articles were excluded. Resulting in 11 articles remaining for the qualitative analysis. Pembrolizumab was only found cost-effective for non-small-lung-cell-cancer in US perspectives. Pembrolizumab was found cost-effective for melanoma in all articles and not found cost-effective for bladder cancer in any of the articles. One article studying Hodgkin's lymphoma was reviewed, which established pembrolizumab as cost-effective.

Conclusion: The cost-effectiveness of pembrolizumab is very different for different countries and indications. The overall conclusions in countries are similar but there is a lot of difference in exact outcomes for the same countries and indications due to difference in setups of the cost-effectiveness analyses.

Introduction

Pembrolizumab (brand name: Keytruda) is a promising and innovative cancer therapy for a lot of indications. Pembrolizumab falls into the category 'immune checkpoint inhibitors' and engages on the 'programmed death-1' (PD-1)-receptor.[1] This a receptor existing on T-cells. A PD-1-receptor bound by a PD-L1 ligand inhibits the working of T-cells. Tumor cells often possess a PD-L1 ligand as a result of a mutation. Pembrolizumab inhibits the binding of the negative PD-1 or PD-2 regulators to this receptor. By inhibiting these negative regulators, pembrolizumab induces programmed cell death by a T-cell response. [2,3,9] This process is also shown in figure 1. Pembrolizumab has proven its efficacy by prolonging the overall survival (OS) and progression-free survival (PFS) for several types of cancers, such as non-small-lung-cancer (NSCLC), melanoma, bladder cancer, head/neck cancers and Hodgkin's lymphoma.[9] Pembrolizumab has a lot of adverse effects. Very common adverse effects (frequency>10%) are diarrhea, itch, skin rash and fatigue. [1]

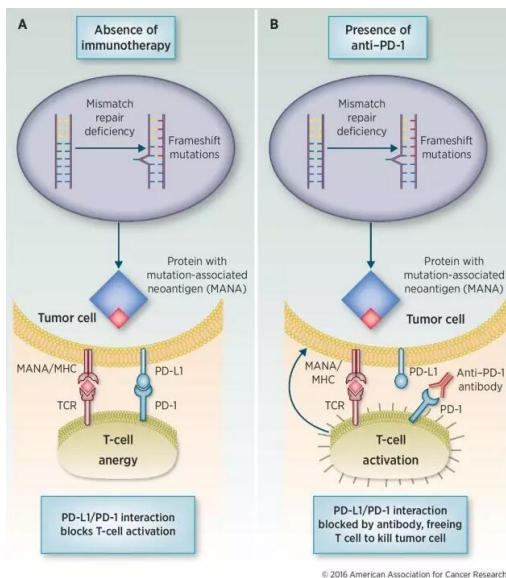


Figure 1, in this figure a schematic overview of the workings mechanism of pembrolizumab is shown. On the left side of the image a tumor with a frameshift mutation is visible. This mutation leads to expression of a PD-L1 regulator and therefore the blockade of a T-cell response. On the right side an anti-PD-1 antibody (for example pembrolizumab) is added, engaging on the PD-L1-receptor. This prevents the T-cell blockade and therefore leads to cell death. This picture is adopted from an internet source.[3]

The Dutch ministerial of Health did not directly reimburse the therapy in 2016 but asked for the advice of 'Zorginstituut Nederland' (ZIN), due to the potential high budget impact. [5] Pembrolizumab was put on hold in the meantime. In 2017 the ZIN gave a negative advice about reimbursement of pembrolizumab by the government for non-small-cell-lung-cancer (NSCLC) with PD-L1 expression. In the study of the ZIN pembrolizumab was evaluated according to its effectiveness, cost-effectiveness, necessity and practicability. Pembrolizumab was compared to the standard therapy of NSCLC before the introduction of nivolumab: docetaxel. ZIN found that the overall survival gain only was clinically relevant in patients with an PD-L1 expression of $\geq 50\%$. However, the smaller amount of adverse effects of pembrolizumab in comparison to docetaxel still gave pembrolizumab a therapeutically advantage in the treatment of patients with NSCLC (both squamous and non-squamous) with only $>1\%$ PD-L1 expression. ZIN found an Incremental Cost-Effectiveness Ratio (ICER) of €113,000 per quality-adjusted life year (QALY). The WTP used in the analyses was €80,000/QALY. This, in combination with the great target audience leads to a total increase in drug price of €46-86 million and therefore a negative advice. ZIN said that the drug acquisition prices should decrease with at least 30% in order to reimburse pembrolizumab for NSCLC with PD-L1 expression ($>1\%$). [6]

After this advice pembrolizumab was held on hold for the indication of NSCLC, until a new price agreement with the pharmaceutical industry could be made. However, in the meantime pembrolizumab did get reimbursed for treatment of melanoma. In April 2017 was pembrolizumab also put on hold for treatment of Hodgkin's lymphoma and head and neck cancer. [7] After negotiations the drug price was confidentially reduced and pembrolizumab was reimbursed for all the noted indications in June 2017 until at least 2020. One of the agreements with the pharmaceutical was that no public pronouncements would be done about the exact price. It is known that the drug price fell with 6,6% in the time between 2016 and 2017 independently of the negotiations. [8] Pembrolizumab was together with Nivolumab one of the first drugs in the Netherlands which was not directly reimbursed but put on hold first. [5] This makes the cost-effectiveness of pembrolizumab a very interesting subject. It raises questions about the cost-effectiveness of pembrolizumab and if pembrolizumab will still be reimbursed after 2020.

The advice of the ZIN was given after they made a Health technology assessment (HTA). In an HTA, research is done about the cost-effectiveness, safety, efficacy of an innovation in the health care. Furthermore, research is done about how the innovation fulfills the needs of a patient. An HTA takes place when there is indication that the innovation is promising. An innovation can be a new technology, but also a new medicine or a known medicine for another indication. The goal of an HTA is determining if the innovation is the best choice to invest in. [6,10] With HTAs the authorities try to provide the best healthcare as possible. In the Netherlands HTAs are done by the ZIN. [6] In the UK the Technology Assessment Teams (TARs) provide HTAs for the National Institute for Health and Care Excellence (NICE). The NICE uses this research for independent advice given by different committees. A Dutch HTA has only been made for pembrolizumab as treatment for NSCLC. [10] However, the NICE published several HTAs about way more indications. Indications on which NICE published an HTA about are:

- Advanced melanoma which is not previously treated with ipilimumab; [10]
- Advanced melanoma after disease progression treated with ipilimumab; [11]
- Relapsed or refractory classical Hodgkin's lymphoma; [13]
- Locally advanced or metastatic urothelial carcinoma in second line, after platinum-containing chemotherapy; [14]
- Untreated PD-L1 positive urothelial cancer when cisplatin is unsuitable; [15]
- Untreated PD-L1 positive metastatic NSCLC; [16]
- In combination with pemetrexed and platinum chemotherapy for untreated PD-L1 positive metastatic NSCLC; [17]
- PD-L1 positive NSCLC in second line, after chemotherapy; [18]

Most of the by NICE made recommendations are positive. Striking is that pembrolizumab is found to be non-cost-effective for melanoma (if not previously treated with ipilimumab) but still is recommended because no other immunotherapies are currently recommended by NICE. Furthermore, pembrolizumab was only found to be cost-effective for treatment of Hodgkin's lymphoma if patients were unable to undergo autologous stem cell transplant. In all cases, pembrolizumab was only cost-effective if the treatment was stopped after maximal 2 years of interrupted treatment and if the company provided pembrolizumab according to the agreement. NICE was unable to give advice about pembrolizumab for head and neck cancer after platin-based chemotherapy, because the pharmaceutical company Merck Sharp & Dohme UK was not willing to give the needed data. [12]

In a cost-effective analysis a specific therapy is studied on its cost-effectiveness. Cost-effectiveness can be expressed in an ICER, like mentioned earlier. An ICER can be expressed in costs per life year gained (Costs/LY) or in costs per quality adjusted life year (Costs/QALY) compared to another treatment strategy. When the ICER is expressed in QALYs, the amount of life years gained are adjusted to the quality of these life years with a utility score. [9] This score runs from 0 until 1. 1 means perfect health and 0 means death. For example, the quality of gained life years decreases when a drug has a lot of severe adverse effects. An ICER using QALYs is more interesting when looking at cancer treatments,

because most cancer medicine have severe adverse effects. Therefore, this is the only studied cost-effective parameter in this review. For the costs in an ICER different perspectives can be used. In the Netherlands a societal perspective is used and in countries such as the United Kingdom (UK) and the United States of America (USA) the healthcare perspective is often used. [5,10] In a healthcare perspective, only direct medical costs are included. In a societal perspective also indirect costs for the society and patient, such as the sick leave of patients, are included. The formula to calculate an ICER (using QALYs) is given below:

$$ICER = \frac{\Delta Costs}{\Delta QALYs}$$

Equation 1: the formula for calculating the ICER using QALYs. The difference in costs between the two therapies are divided by the difference in QALYs gained with the two therapies.

A therapy is found to be cost-effective when the ICER does not outreaches the Willingness-to-pay (WTP) of a country. The WTP differs per country and therefore, so does cost-effectiveness. [9]

Due to the current dilemma about the reimbursement of pembrolizumab and the social relevance of the drug, in this review a systematic analysis is given of pembrolizumab for different indications. Different cost-effective analyses are compared by looking at the setup of the study and other parameters.

Material and methods

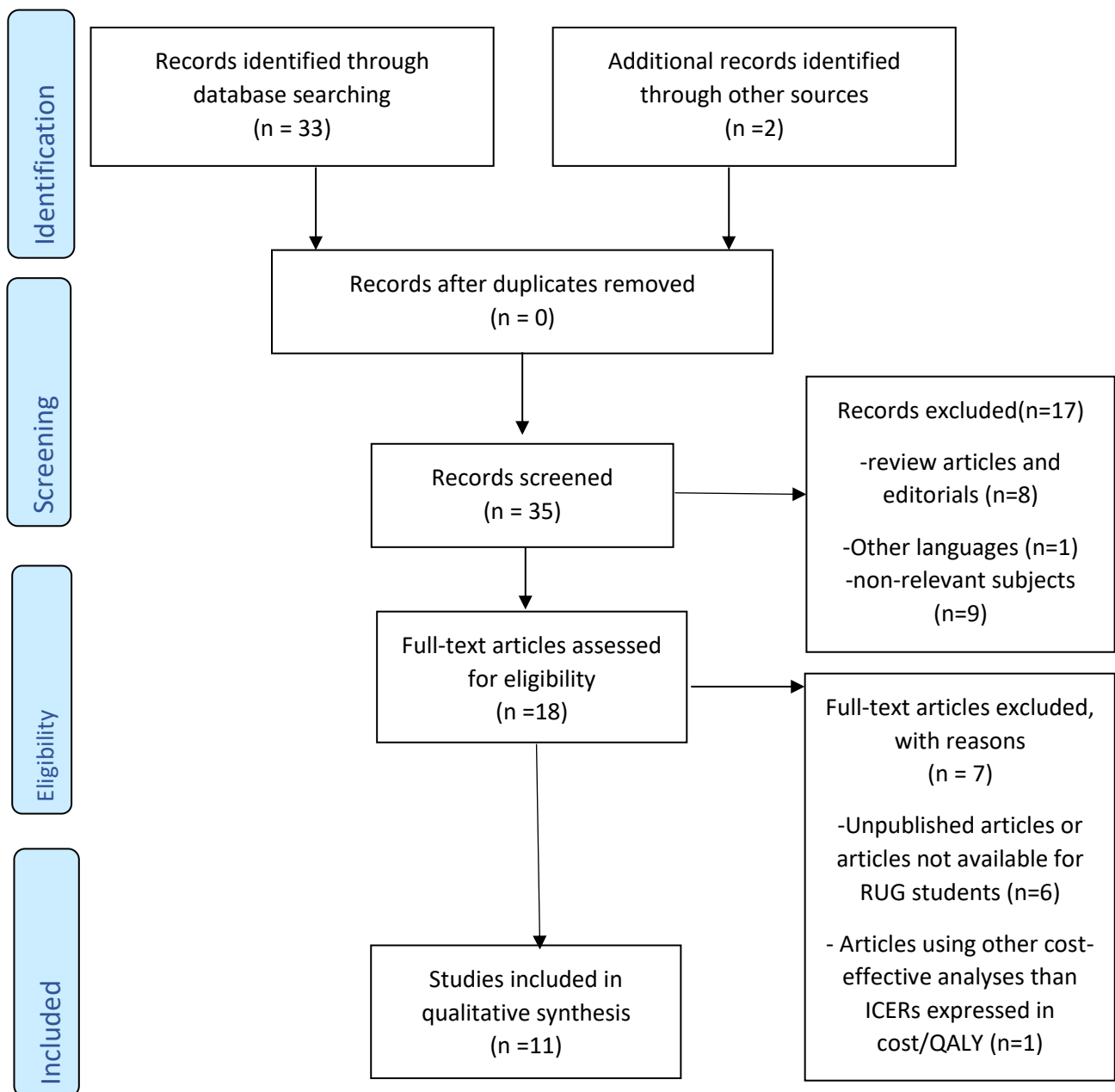
During this study a systematic search on PubMed in April 2019 is performed and 'pembrolizumab' AND 'cost effectiveness' are used as search terms. The supplementary concept will be pembrolizumab. The mesh terms are costs and cost analyses. Additional terms are costs, costs and costs analysis, Keytruda, economics, analysis, costing, effective, cost, pembrolizumab and economic. Review articles, editorials, articles in languages different than Dutch or English and studies with non-relevant subjects found by PubMed are excluded based on their records. Unpublished articles or non-available articles and articles using another cost-effectiveness analyses than Costs/QALYs are also excluded based on their (availability of) full texts. During the search, some other articles might come up by the analyses the of the articles in the database. A process named 'snowballing'. In the qualitative analysis the articles will be studied on several key points. The studies will be compared in terms of their studied indication, their used perspective in which country and if the studies are funded. Furthermore, the studies will be analyzed on their used model, inputs in this model and their used sensitivity analyses. The outcomes of the different studies will also be compared. The outcomes will be compared in terms of their incremental costs per patient, incremental QALYs per patient, ICER, WTP and their conclusion based on the ICER, WTP and sensitivity analyses.

Results

Included studies

The PubMed search delivered 33 hits. Also, two articles were found by snowballing. In total, 17 records were excluded. 8 review articles and editorials were excluded and one article in a different language was excluded. There were found 9 studies with non-relevant subjects. This were articles studying for example pembrolizumab in combination therapy, fixed dosing of pembrolizumab or the budget impact of pembrolizumab. In total, 18 full-texts were screened and of these full-texts 7 articles were excluded. Furthermore, 6 articles were not available for RUG students and one article used a cost-effectiveness analyses different from an ICER with costs/QALYs. Resulting in 11 articles remaining for the qualitative analysis. The systematic search is also illustrated in figure 2.

Figure 2, in this Prisma the systematic search during this review is illustrated



Outcomes of the studies

Different aspects of the studies are represented in three tables. In table 1 the different indications, the PD-L1 levels of the patients, the line of treatment, the comparator, the perspective and the possible funding are shown. In table 2 the used models, the stages, the costs, the utilities, the target population, the sensitivity analysis and the time horizon are shown. In table 3 the costs, QALYs, ICERs, discount rate, WTPs and the overall conclusions are visible. In all the tables the analyzed studies are numbered from 1 until 11. When describing the results, the articles will be named by this numbering. In the table the corresponding references of each number can be found.

Non-small-cell-lung cancer

Looking at table 1, it is visible that most of the studies (n=5) study NSCLC as indication and that almost all of them include patients with a tumor proportion score of PD-L1 of >50%. One of the five studies use Nivolumab as comparator (study 1), the other four use platinum-based chemotherapy as comparator (study 2-5). One study analyses the cost-effectiveness of pembrolizumab in both the USA and UK (study 3). Two other studies were American (1,2), one other was British (4) and one other was French (5). All studies use a comparable perspective, including only direct medical costs. Study number 2 and 5 are both funded and use both a similar partitioned-survival model (shown in table 1 and 2). The British study, the 1st American and study 3 use a Markov model. All five studies used the same stages: progression-free, progressive disease and death and all studies used comparable sensitivity analyses. The time horizon of the studies differs from 5 years, 10 years, 20 years and full-life time horizons (table 2). In the two American studies and the French study (number 1,2 and 5) pembrolizumab was found to be cost-effective. In study number 3 pembrolizumab was only found cost-effective in the USA. The studies finding pembrolizumab cost-effective all use a WTP of approximately USD 100,000/QALY. The British studies pembrolizumab was not found cost-effective due to the lower WTP. (table 3). Study 2 and 4 included adverse effects (AEs) of grade ≥ 3 and with a frequency of $\geq 5\%$ in their utility score. Study 5 included all the AEs when an utility decrement between the progressive-free state with or without AEs.

With Nivolumab as comparator in the 1st study, pembrolizumab was still found cost-effective. In this study it was also found that pembrolizumab was more cost-effective when it was used in patients with a higher PD-L1 score. Striking are the relatively high discount rates used in this study of 10% and 20%. In all the other studies discount rates around 3% were used. In study number 5 the cost-effectiveness of pembrolizumab for non-squamous NSCLC was compared to pembrolizumab for squamous NSCLC. In both cases pembrolizumab was found to be cost-effective, however pembrolizumab was found to have a 10% bigger change to be cost-effective in non-squamous NSCLC than in squamous NSCLC. (table 3)

Looking back at table 1, it is visible that study number 1 investigated only the second-line use of pembrolizumab. This was thus found cost-effective. The other studies investigated first-line use or first and second line use. In table 3 it is also visible that study 3 compared the ICERs with end-of-life-adjustments to ICERs without end-of-life adjustments. End-of-life-adjustment lead to a lower ICER.

Melanoma

Looking at table 1, it is visible that three studies with melanoma as indication are analyzed. Two of these studies use a similar American perspective: the US healthcare perspective (study 6) and the US-payer perspective (study 8). One of these studies uses the Portuguese national health service perspective (study 7). None of the patients in the studies were tested on their PD-L1 expression. In study 6 and in the Portuguese study (study 7), pembrolizumab was both a first- and second-line treatment and compared to ipilimumab. In the other American study Pembrolizumab is tested as first line treatment administrated every two and every three weeks with ipilimumab as second line treatment. In this study pembrolizumab is compared to dacarbazine, nivolumab, ipilimumab and a combination of nivolumab and ipilimumab. All three studies are funded.

In table 2 it is visible that studies number 6 and 7 use a similar partitioned-state survival model with progression-free, progressive disease and death as stages. It is also visible that the study 8 uses a Markov model with the stages: progression-free survival, 1st progression, 2nd progression, 3rd progression and death. In study 6 AEs of stage 3-4 were included in the utility score, in study 7 AEs of stage 3-5 were included in the utility score and in the study 8 AEs of stage 1-4 were included. In the studies 7 and 8 a life-time time horizon was used. In the study 6 a 20-year life-time horizon was used. Similar sensitivity analyses were done in all studies.

Looking at table 3, it is visible that all three studies found pembrolizumab to be cost-effective. Striking is that the WTP of Portugal is only approximately USD 55,758.80/QALY and the WTP of the US is USD 100,000/QALY but the ICER found to be way cheaper in Portugal. In the study 8 it was found that pembrolizumab was only cost-effective for three weeks administration and most cost-effective when compared to dacarbazine and nivolumab. Not all ICERs could be found in the study. The Portuguese study uses a higher discount rate (5%) than the two American studies (3%). In study 6 pembrolizumab has the highest change to be cost-effective. In study 8 is only looked to the BRAF wild type of melanoma. In the two other studies no distinction was made.

Bladder cancer

In table 1 it is visible that two studies about pembrolizumab for bladder cancer were analyzed. Both studied pembrolizumab as second-line treatment and used as comparator standard chemotherapy. None of the studies were funded. Study 9 used the US, UK, Canadian and Australian payers' perspective. Study 10 used societal perspective of the US healthcare system. However, the included costs of both studies were very similar (table 2). In study 10, the difference influence of testing of the PD-L1 levels was also included (table 1). Looking at table 2, it is visible that in study 9 a Markov model was used. In study 10 a microsimulation model was used. Both models included the same stages: progression-free, progressive disease and death. Both studies used a time horizon of 5 years. In table 3, it is visible that pembrolizumab was only found to be cost-effective with a WTP of USD 150,000/QALY in both studies. Therefore, Pembrolizumab was not found to be cost-effective in Canada, Australia and the UK, but was cost-effective in the US according to the first study. In this study they used a WTP of USD 150,000/QALY. In the other (also American) study pembrolizumab was not established as cost-effective because they used a WTP of USD 100,000/QALY. However, according to study 10 pembrolizumab was more cost-effective when patients were treated according to their PD-L1 levels. In the study 10 a discount rate of 3% was used for Australia, the US and the UK. A discount rate of 1.5% was used for Canada. In study 11 et al a discount rate of 3% was used as well.

Classical Hodgkin's lymphoma

Looking at table 1, it is shown that one study looking at pembrolizumab for the indication of Classical Hodgkin's lymphoma. The study looked at Pembrolizumab in both first- and second-line treatment. The comparator was Brentuximab and the perspective was a US payers' perspective. The study was funded. In the study a Markov model was used with the stages: progression-free, progressive disease and death (table 2). The utility score included AEs effects of level three and more. With a WTP of USD 20,000/QALY pembrolizumab was found to be cost-effective. Striking is that this WTP lays lower than the other used WTPs of the USA.

Table 1, in this table the various studied indications, PD-levels in patients, line of treatment, comparator, perspective and funding found in the different studies are shown.

| Reference, country, year | Indication | PD-L1 level (in tumor proportion score) | Line of treatment | Comparator | Perspective | Funding |
|---|---------------------------------|--|--|--|--|---|
| 1) <i>PN Aguir et al, USA, 2017</i> [19] | NSCLC | TPS ¹ I >1 % TPS II > 50% | Second line | Docetaxel was given to PD-L1 negative patients | US ² Medicare system | None |
| 2) <i>Min Huang et al, USA, 2017</i> [20] | NSCLC | TPS > 50% | First line | Standard-of-care platinum-based chemotherapy in first line | US third party public health care payer perspective | Merck & Co. Received grants and honoraria from Merck, BMS, Gentech, Heat biologics, Altor biosciences, foundation medicine and Clovis |
| 3) <i>M Georgivina et al, USA, 2019</i> [21] | NSCLC | TPS > 50% | First and second line | Standard platinum-based chemotherapy | British National Health System perspective and US cost perspective | None |
| 4) <i>X Hu et al, USA, 2018</i> [22] | NSCLC | TPS > 50% | First line | Standard platinum-based chemotherapy | UK ³ healthcare | None |
| 5) <i>C Chouaid et al, France, 2018</i> [23] | Squamous and non-squamous NSCLC | TPS > 50% | First line | Standard of care platinum-based chemotherapy | France healthcare system perspective | Merck & Co |
| 6) <i>J Wang et al, USA, 2017</i> [24] | Advanced melanoma | No test was performed | First line and second line (every 3 weeks) | Ipilimumab | US healthcare perspective | Merck & Co. |
| 7) <i>L S Miguel et al, Portugal, 2017</i> [25] | Advanced melanoma | No test was performed | First line and second line (every 3 weeks) | Ipilimumab | Portuguese national Health Service perspective | Merck, Sharpe & Dohme |

¹ Tumor proportion score (TPS)

² United states (US)

³ United Kingdom (UK)

| | | | | | | |
|--|---|---|--|--|--|---|
| 8) <i>C G Kohn, S B Zeichner et al, USA, 2017 [26]</i> | BRAF ⁴ Wild-type advanced melanoma | No test was performed | First line followed by ipilimumab second line, studied for every two weeks and every 3-week administration of pembrolizumab. | Comparators are DAC ⁵ , NIVO ⁶ +IPI ⁷ , IPI, NIVO | US-payer perspective | Acerta Pharma (Inst), infinity Pharmaceuticals (Inst), Onyx Pharmaceuticals (Inst), Janssen Oncology (Inst), Gilead sciences (Inst), Celgene (Inst), TG Therapeutics (Inst), Genentech (Inst), Pharmacyclics ((Inst), AbbVie (Inst) |
| 9) <i>M Sarfaty et al, Canada, 2018 [27]</i> | Advanced bladder cancer | No test was performed | Second line | Chemotherapy (docetaxel and paclitaxel) | US, British, Australian and Canadian payers' perspective | None |
| 10) <i>S D Criss et al, USA, 2019 [28]</i> | Advanced urothelial carcinoma of the ladder | Strategy 1: all patients with pembrolizumab Strategy 2: all patients with second-line chemotherapy Strategy 3: patients with TPS ≥ 1% with pembrolizumab, Patients with no TPS expression with second-line chemotherapy | Second line | Second-line chemotherapy (docetaxel or paclitaxel) | Societal perspective of the US healthcare system | None |
| 11) <i>S Large et al, USA, 2018 [29]</i> | Classical Hodgkin's lymphoma | No test was performed | Second line (patients relapsing after ASCT ⁸), first line (patients ineligible for ASCT) | Brentuximab vedotin | US payer perspective | By Merck & Co, Takeda, BMS |

⁵ Dacarbine (DAC)

⁶ Nivolumab (NIVO)

⁷ Ipilimumab (IPI)

⁸ autologous stem cell transplantations (ASCT)

Table 2: in this table the used models, stages, costs, utilities, target population, sensitivity analyses and time horizon are visible.

| Reference, country, year | Model | Stages | Costs | Utility (AEs ⁹ included yes/no) | Target population | Sensitivity analysis | Time horizon |
|--|--|--|---|--|-------------------|--|------------------------|
| 1) <i>PN Aguir et al, UerSA, 2017. [19]</i> | Decision-analytic model (Markov model) | Progression-free disease, post-progression-free disease and death | Direct medical costs: Costs of PD-L1 testing, drug acquisition, adverse events, administration costs, monitoring costs, end-of-life costs. | Based on a UK study on health utilities for advanced NSCLC treated with chemotherapy or immunotherapy. | Keynote-010 [30] | DSA ¹⁰ was performed, CI ¹¹ of 95% were performed on parameters. Also, the probability of reaching the WTP was determined. | 5 years |
| 2) <i>Min Huang et al, USA, 2017 [20]</i> | Partitionate-survival model | Progression-free, progressive disease and death | Direct medical costs: Drug acquisition, administration, pre-medication, disease management, subsequent therapy, terminal care, AE management. 80% costs were payed third-party public healthcare payers. | Gathered with a Euro-Qol-5 dimension. Included AEs of level 3 or more ($\geq 5\%$ patients) | Keynote-24 [31] | DSAs was used to test the sensitivity of the model for changes. A probabilistic sensitivity analysis was used to test the robustness of the model. | 20 years |
| 3) <i>M Georgivina et al, USA, 2019 [21]</i> | Bayesian Markov model | From stable disease (in first line treatment) to: progressive disease, death, discontinuation due to treatment-related adverse effects, discontinuation due to disease progression, all possible after first or second line treatment. | Based on UK or US costs for treatment care and testing, direct medical costs: PD-L1 testing, enrolling pembrolizumab treatment, treatment initiation, next line treatment or no further anti-cancer treatment, terminal care and immune-related side effects. In one ICER end-of-life adjustments. In the other ICER no end-of-life adjustments. | Based on a UK study on health utilities for advanced NSCLC treated with chemotherapy or immunotherapy. | Keynote-24 [31] | A traditional Weibull model was used. | Full-time life horizon |

⁹ Adverse effects (AEs)

¹⁰ One-way deterministic sensitivity analyses (DSA)

¹¹ Confidence Interval (CIs)

| | | | | | | | |
|--|---|--|---|---|---|--|---|
| 4) <i>X Hu et al, USA, 2018 [22]</i> | Markov model | Progression-free, Progressive disease, death | Direct medical costs: drug acquisition costs drug administration costs disease management costs, costs for AEs, PD-L1 costs | Utility values were gathered from published and disutilities were gathered from the K024 study. AEs of \geq grade 3 and with a frequency of $\geq 5\%$ in patients were included. | Keynote-24[31] | One-way sensitivity analysis, the parameters varied +/- 20% and the discount rate was measured from 0 till 6%. Probabilistic sensitivity analyses were used to determine uncertainty in parameters and the robustness of the model. The impact of Informal care costs was also determined. Three different scenarios were also performed: without restriction of pembrolizumab, with BNF ¹² prices instead of eMIT ¹³ prices, with different discount rates. | Full-time life horizon (run till 99% of the patients die) |
| 5) <i>C Chouaid et al, France, 2018 [23]</i> | A partitioned-survival model (published by Huang et al, but adapted to French HTA guidelines) | Progression-free (initial state of patient until progression), progressive disease (health state after progression), death (absorbing state) | Direct medical costs: Acquisition costs for drugs reimbursed, transportation costs, premedication costs (to prevent anemia and nausea in chemotherapy), PD-L1 test costs, second line costs, terminal costs | Utility inputs estimated based on the preference of health states of the French population. Gathered from EuroQol-5 dimensions. All AEs were included, when a utility decrement was visible between progression-free state with or without AEs. | Keynote-024 and explorations in the population to include more patients with squamous NSCLC. [31] | The robustness was determined by sensitivity and scenario analyses. DSA was performed on initial weight and body surface area, PD-L1 test cost, administration cost, management costs, terminal care cost, parameters of parameter survival modeling and PSA ¹⁴ was also performed. | 10-year time horizon |

¹² British National Formulary (BNF)

¹³ Electronic Marketing Information tool (eMIT)

¹⁴ probabilistic sensitivity analysis (PSA)

| | | | | | | | |
|---|---|---|--|--|---|--|-----------------------------|
| 6) <i>J Wang et al, USA, 2017 [24]</i> | A partitionat-survival model | Progression-free, post-progression, death | Direct medical costs: Unit cost drugs, administrative cost drug, cost of adverse event management (grade 3 and 4), management costs, death-related costs | Collected from KN006 ¹⁵ with EuroQol-5D. The difference between grade 3-4 AEs and no AEs was compared and used as disutility. | Keynote-006 (patients with advanced melanoma who were ipilimumab-naïve) [32] | The impact of change in different variabilities was determined by scenario analyses. Sensitivity analysis were done by varying variabilities across 95% CI. Also, a probabilistic sensitivity analysis was done by specified probability distributions of the variabilities. | 20-year time horizon |
| 7) <i>L S Miguel et al, Portugal, 2017 [25]</i> | A partitioned state-transition model (developed by Merck & Co. and adapted to Portugal) | Progression-free survival, post-progression and death | Direct costs: Drug acquisition, disease management, drug administration | HR-Euro-Qol was collected from the KN006 trial and capture grade 3-5 AEs. | KN006-trial [32] | One-way deterministic sensitivity analyses were done under: health state costs, AE costs, vial sharing, dug intensity, subgroup analysis, time horizon, discount rate. PSA was performed with a second-order Monte Carlo simulation. | Lifetime horizon (40 years) |
| 8) <i>C G Kohn, S B Zeichner et al, USA, 2017[26]</i> | A comprehensive Markov model | Progression-free survival (either with or without AEs), 1 st progression (and switch to second line), 2 nd progression (and switch to third line), 3 rd progression, death | Direct medical costs: (drug acquisition, drug administration, disease management, AE management) | Utility scores derived from published studies. Grad 1-4 AEs were included. | Checkmate-066[35], checkmate-067[36], checkmate-037[37], KN006[32] and NCT00094653[38]. | AEs and utilities were changed over a 95% CI. Drug costs were varied 20%. Also, Monte Carlo simulation were performed. | Lifetime horizon |
| 9) <i>M Sarfaty et al, Canada, 2018 [27]</i> | A Markov model | Progression-free, progressive disease, death | Direct medical costs (drug, administration and AE costs) | Keynote-045 and the EORTC QLQ-C30 was used. | Keynote-045 [33] | All utilities were varied within a 10% range and the drugs costs were varied within a 20% range. The model was also tested with PSA and ran 10 000 times. | 5 years |
| 10) <i>S D Criss et al, USA, 2019 [28]</i> | A microsimulation model | Progression-free, progressive disease, death | Medical costs (drug therapy and administration, PD-L1 testing, treatment of AE, | Gathered from Keynote-045 together with extra data for estimates for | Keynote-045 [33] | A 1-way sensitivity analysis was performed on key parameters. 95% CI were | 5 years |

¹⁵ Keynote-006(KN006)

11) *S Large et al, USA, 2018 [29]*

| | | | | | | |
|--------------------------|--|---|--|------------------|--|----------|
| | | surveillance and supportive care) | progression-free and progressive diseases utilities. | | performed, and each parameter was tested at the upper and lower limit. | |
| Three state Markov model | Progression-free, progressive disease, death | Drug acquisition, Drug administration, disease management, adverse events costs | EQ-5D-3L domain scores from Keynote-0-87. Included AEs of level 3 or above ($\geq 5\%$ patients) were included. | Keynote-087 [34] | A DSA was performed to determine the impact of changing key parameters. A PSA was performed (100,000 simulations). Also, scenario analyses were performed. | 20 years |

Table 3, in this table the incremental costs per patient, the incremental QALYs per patient, the ICER, the discount rate, the willingness to pay and the conclusion of each study is visible.

| Reference, country, year | Incremental costs per patient | Incremental QALY per patient | ICER | Discount rate (both costs and outcomes) | Willingness to pay | Conclusion |
|---------------------------------------|--|--|--|---|--|---|
| 1) PN Aguir et al, USA, 2017. [19] | USD 82,201 | TPS I:0,346 TPS II: 0,409 | USD ¹⁶ 98,421/QALY for TPS I USD 80,735/QALY for TPS II | 10% and 20% | USD 100,000/QALY | Yes, pembrolizumab is cost-effective. The parameters with most influence were bodyweight and drug acquisition costs. The cost-effectiveness increased with a higher discount rate. Pembrolizumab was more cost-effective in patients with a higher TPS. |
| 2) Min Huang et al, USA, 2017 [20] | USD 102,439 | 1,05 | USD 97,621/QALY | 3% a year | USD 140,392–382,536/QALY or USD 100,000-150,000/QALY USD 50,000-100,000/QALY | Yes, however AEs with an incidence rate <5% were not included. Pembrolizumab was cost-effective under USD 100,000/QALY if costs increased 3% and under USD 150,000/QALY if costs increased 59%. |
| 3) M Georgivina et al, USA, 2019 [21] | British perspective: USD 99,000- 34,000 = 65,000 US perspective: USD 132,000-74,000= 59,000 | In both England and the US: 1,93-1,11 = 0,82 | (without dependency) Without end-of-life adjustment: British perspective: USD 81,000/QALY US perspective: USD 74,000/QALY | 3% a year | British threshold: USD 42,048/QALY US threshold: USD 100,000/QALY | UK: No, only cost-effective under the assumption of no dependency USA: Yes, pembrolizumab was cost effective in almost all sub analyses of the USA. |

¹⁶ United States Dollar (USD)

| | | | | | | |
|---------------------------------------|---|---|---|-------------|--------------------------------------|--|
| | | | With end-of-life adjustment: British perspective: USD 34,000/QALY US perspective: USD 31,000/QALY | | | |
| 4) X Hu et al, USA, 2018 [22] | GBP 72,465 | 0,83 | GBP 86,913/QALY | 3.5% a year | GBP ¹⁷ 30,000-50,000/QALY | No, the probability of pembrolizumab as cost-effective is 29,4%. The ICER is most sensitive to duration of median OS. A discount of >50% is needed to be cost-effective. |
| 5) C Chouaid et al, France, 2018 [23] | Squamous sub-group (only SoC): €62,032 Non-squamous subgroup: €-14,947-€47,064 | Squamous subgroup: 0,74 Non-squamous subgroup: 0,85-1,32 | Squamous sub-group: €84,097/QALY Non-squamous subgroup: €78,729/QALY | 4% a year | €100,011/QALY | Yes, Pembrolizumab has a 60% change to be cost-effective for the squamous subgroup and 70% change to be cost-effective for the non-squamous subgroup. Change of three variabilities led to signification changes in the ICER: treatment duration, second-line costs, efficacy duration of pembrolizumab. |

¹⁷ British Pound (GBP)

| | | | | | | |
|---|--|---|---|---|--|---|
| 6) <i>J Wang et al, USA, 2017 [24]</i> | USD 63,680 | 0,79 (much of the survival in progression-free survival). | USD 81,091/QALY | 3% a year | USD 100,000-150,000/QALY | Yes, pembrolizumab has an 83% change to have an ICER below USD 100,000 and is therefore likely to be cost-effective and the model is robust to the sensitivity analyses. |
| 7) <i>L S Miguel et al, Portugal, 2017 [25]</i> | €46,233 | 0,98 | €47,221/QALY (with treatment for two years) | 5% a year | €50,000/QALY | Yes, the change of the ICER to be below €50,000 is 75% |
| 8) <i>C G Kohn, S B Zeichner et al, USA, 2017[26]</i> | - | - | <p><i>Pembrolizumab administrated every three weeks with Ipilimumab as second-line treatment:</i> DAC: Dominant, IPI: Dominant PEM (compared with every two weeks): USD 931,125 NIVO: USD 66,800 NIVO + IPI: 463,582 (all per QALY)</p> <p><i>Pembrolizumab administrated every two weeks:</i> DAC: USD 106,447 IPI: USD 138,533 PEM (compared with every three weeks): USD 931,125 NIVO: USD 66,800 NIVO+IPI: USD 1,710,800 (all per QALY)</p> | 3% a year | USD 100,000/QALY | Yes, pembrolizumab administrated every three weeks has a 69% change to be cost-effective in all cases expect for comparing with nivolumab in combination with ipilimumab. Pembrolizumab administrated every two weeks is not cost-effective in all the cases. |
| 9) <i>M Sarfaty et al, Canada, 2018 [27]</i> | US: USD 44,325 UK: USD 33,271 Canada: USD 33,869 | US, UK and Australia: 0,36. Canada: 0,37 | US: 122 557/QALY, UK: 91 995/QALY, Canada: 90 099/QALY, Australia: | 3% a year for US, UK and Australia, 1.5% a year for Canada | US: 50,000-150,000/QALY, UK: 25,000-38,000/QALY. | Pembrolizumab would be considered cost-effective in the US, but not in the |

| | | | | | | |
|--|--|--|---|-----------|--|---|
| | Australia: USD 36,154 | | 99 966/QALY. All in USD. | | Canada and Australia: no explicit WTP. Used for Canada: 16,000-80,000/QALY. Used for Australia: 32,000-60,000/QALY. (All in USD) | other examined countries due to the higher WTP. However, the costs are the highest in the USA. The exploration of the OS had the biggest effect on the ICER. There is a 100% probability of Pembrolizumab to cost-effective with a WTP of USD 150,000/QALY. |
| 10) <i>S D Criss et al, USA, 2019 [28]</i> | Costs of strategy 1 compared to strategy 2: USD 12,994 Costs of strategy 3 compared to strategy 2: USD 10,347 | QALY of strategy 1 compared to strategy 2: 0,07 QALY of strategy 3 compared to strategy 2: 0,08 | ICER of strategy 1 compared to strategy 2: USD 197,383/QALY. ICER of strategy 3 compared to strategy 2: USD 122,933/QALY | 3% a year | USD 100,000/QALY | No, treatment with pembrolizumab is not cost-effective. Testing on the PD-1 status improves the cost-effectiveness. The ICERs were most sensitive to price per mg pembrolizumab, survival and utility inputs. |
| 11) <i>S Large et al, USA, 2018 [29]</i> | USD -63,378 | 0,500 | Dominant | 3% a year | USD 20,000/QALY | Yes, pembrolizumab has a 99,6% change of being cost-effective. Change in drug acquisition has the largest effect on the ICER. |

Discussion

Unfortunately, this review only analyzed 11 studies. The search terms only delivered 33 hits on PubMed and during the systematic search more than half the articles found in the PubMed database were excluded. Most articles were excluded on base of their content. Also, a lot of the articles were review articles or editorials or not available for RUG students. Most of the found articles studied pembrolizumab as treatment for NSCLC. Other studied indications were melanoma, bladder cancer and Hodgkin's lymphoma.

Looking at the result per indication, when compared to platin-based chemotherapy pembrolizumab seems only to be cost-effective for NSCLC in the USA and France, where a WTP of 100,000 is used. In the UK, using a WTP of maximal GBD 50,000/QALY pembrolizumab is not found to be cost-effective for NSCLC when compared to platin-based chemotherapy. The two types of models (Markov model or a partitioned survival model) seem to lead to similar conclusions. Furthermore, the incremental costs and QALYs in most of the articles are similar. The difference in incremental costs between countries is also not very big. Namely, in the article determining the cost-effectiveness of pembrolizumab in both the UK and US, the costs are comparable. The incremental costs in the USA were USD 59,000 and in the UK USD 65,000. The QALYs in both countries were the same. [20,21,22,23]

However the overall conclusions in the studies are similar, the exact incremental costs and QALYs of the study of Huang et al. are very different from the other articles. The incremental costs and QALYs are both higher than in the other studies. [20] Most studies compared their results with the study of Huang et al. and explained the differences by for example the more mature used Keynote-024 study with longer follow-up time. Other given reasons were the differences between the used time horizon, the inclusion of comparable therapies, the Markov model the studies used instead of the partitioned-survival model or the difference in obtaining utility data. [21,22,23] The study of Huang et al did obtain their utility data from the EQ-5D-3OL data and another study obtained for example their utility data by real-world surveys on patients.[22] It is plausible that the differences in QALYs and costs between the other studies are also caused by similar reasons.

In the study of C Chouaid et al other subgroups were used: squamous and non-squamous patients. It was visible that pembrolizumab was slightly more cost-effective for non-squamous patients. [22] In the other studies there was no distinction made between these two groups. [20,21,23] Therefore, it is hard to say what the exact influences are of the grouping of squamous and non-squamous cancer.

In the study of P N Aguir et al, using a different comparator (docetaxel) than the four other studies, an ICER just below the WTP of USD 100,000/QALY was found. The incremental QALYs per patient were much lower than the incremental QALYs per patient found in the other studies. This could be caused by the difference in comparator. The absolute QALYs gained by docetaxel could lay higher than the QALYs gained by platin-based chemotherapy. Striking about this study are the relatively high discount rates which were used (10% and 20%). These high discount rates will probably have led to a lower ICER. In the study is also stated that higher discount rates lead to a higher cost-effectiveness. However, the impact of discount rates is questionable because the average life expectancy of someone with NSCLC is not very high. [19]

As noted in the introduction, several indications for pembrolizumab are reviewed by NICE. In one NICE report pembrolizumab as first line treatment for NSCLC was compared to treatment with platin-based chemotherapies in patient with a TPS $\geq 50\%$, like in the studies of Min Huang et al., M Georgivina et al., X Hu et al. and C Chouaid et al. In the NICE report, which also used a healthcare perspective, it was concluded that pembrolizumab was cost-effective for the first-line treatment of NSCLC. Remarkable, because the British cost-effective analyses did not establish pembrolizumab as cost-effective. The

difference could be the commercial deals of NHS with the pharmaceutical companies. Also, the NICE report stated pembrolizumab as most likely to be cost-effective for an end-of-life (EoL) treatment and the NICE used therefore EoL adjustment. The EoL thresholds constituted when the treatment is needed for a small group of patients, the maximal treatment duration is 24 months and the life-extension is >3 months. In the study of M Georgivina et al. end-of-life adjustment was also investigated and it was visible that the adjustment led indeed to a lower ICER. [16]

In the results it is visible that pembrolizumab is found to be cost-effective for melanoma when compared to ipilimumab. All three of the analyzed articles concluded that pembrolizumab was cost-effective for melanoma. [24,25,26] Remarkably, melanoma was two times found to be cost-effective for a WTP of USD 100,000/QALY in the USA and was found to be cost-effective for a WTP USD 55,953.89/QALY in Portugal with a quite lower ICER. The incremental QALYs are higher and the incremental costs are lower in this Portuguese study than in the study of J Wang et al. So, this difference could have been caused by the difference in (estimation of) medical costs between the countries or the included utilities. [24,25]

In the study of C G Kohn et al. it was found that pembrolizumab was most cost-effective when administrated every three weeks. In the two other studies pembrolizumab was only registered in this most cost-effective option of every 3 weeks. [24,25,26]

In the study of C G Kohn et al. pembrolizumab is not only compared to ipilimumab but also to dicarbazine, nivolumab and combination therapy of ipilimumab with nivolumab. Pembrolizumab was only not found cost-effective when compared to the combination therapy. Another difference between the two other studies and the study of C G Kohn et al. was the fact that the study of C G Kohn et al. only included BRAF-type melanoma and the other two studies did not distinguish between BRAF and non-BRAF melanoma. The incremental costs and QALYs are not published in the study of L S Miguel et al and it is therefore hard to establish the influence of including only patients with BRAF-type melanoma in the study.[26]

NICE reviewed the use of pembrolizumab also as treatment for melanoma as second line treatment after using ipilimumab, compared standard chemotherapy. The NICE concluded pembrolizumab as cost-effective as end-of-life treatment, under the same circumstances as noted before. [11] NICE did also review the use of pembrolizumab as first line treatment for melanoma and gave a positive advice. [10] In the study of J Wang et al. and L S Miguel et al. no extinction was made between first- and second-line treatment, while the line of treatment can lead to a different ICER. Pembrolizumab might be more effective in first line treatment and the treatment duration in second line treatment might be shorter. Because no distinction was made it is hard to compare the results to NICE. The NICE uses a threshold of WTP GBD 50,000/QALY and therefore the ICER found by NICE was probably lower than in the studies of C G Kohn et al. and J Wang et al. [24,25]

Pembrolizumab for second line treatment of bladder cancer was only found to be cost-effective in one of the studies with a WTP of USD 150,000/QALY compared to chemotherapy (paclitaxel and docetaxel). [27] In the other study using the same comparator pembrolizumab was not found to be cost-effective. [28] Striking is the difference in incremental QALYs and costs between the studies, while they both are using the same comparator and include similar costs. The study establishing pembrolizumab as not cost-effective used a microsimulation model and the other a Markov model. This could have led to difference in outcomes. The studies could also differ in their included utility inputs.

The NICE also reviewed pembrolizumab as second line treatment for bladder cancer when cisplatin treatment was unsuitable compared to docetaxel or paclitaxel. NICE established in some estimations pembrolizumab as cost-effective, while in other estimations the ICER outreached the WTP of GBP 50,000/QALY. NICE still gave a positive advice about reimbursing pembrolizumab because pembrolizumab significantly improves survival compared to docetaxel and paclitaxel. [15] Striking is

that NICE gave a positive advice for pembrolizumab, while it was in both studies not even found cost-effective with a WTP of USD 100,000/QALY. NICE used EoL adjustments and had the financial agreement with the companies, which both could play a part.

Only one article was found studying pembrolizumab as treatment for Hodgkin's lymphoma in first and second line and used brentuximab vedotin as comparator. In this study pembrolizumab was considered as cost-effective with a remarkably low WTP of USD 20,000/QALY. In other American studies the used WTP was around USD 100,000/QALY and sometimes even USD 150,000/QALY. [29] NICE also reviewed pembrolizumab as second line treatment for Hodgkin's lymphoma and used standard care as comparator. NICE gave only positive advice about pembrolizumab for Hodgkin's lymphoma as first line EoL-treatment and with the financial deal the NICE made with the pharmaceutical company when patients did not have an autologous stem cell transplant. Pembrolizumab was not recommended when the patient had already an autologous stem cell transplant and brentuximab. [13] The study did not make a distinction between these two. Therefore, the study and the NICE report are hard to compare.

Overall, there is a lot of difference between the different indications. The difference between the indications can for example be caused by the alternative comparator. Also, the difference between the indications can be caused by the seriousness of the outcomes of the indication and the engagement of pembrolizumab on the different types of cancers. This can be seen in the difference in incremental QALYs per patient. It is visible that pembrolizumab for bladder cancer gains relatively low incremental QALYs [27,28] and pembrolizumab for melanoma and NSCLC relatively high QALYs. [19,20,21,22,23]

The amount of engagement of Pembrolizumab on the tumor cells is correlated with the PD-L1 expression of the tumor cells. Especially in the NSCLC treatment it is visible that a higher PD-L1 expression leads to a better cost-effectiveness. It is notable that for some indications, such as NSCLC, pembrolizumab treatment is dependently of the PD-L1 expression, but for other indications the PD-L1 expression is not tested. In all the articles studying the influence testing PD-L1 expression the conclusion is that testing on a high(er) PD-L1 expression leads to higher cost-effectiveness of pembrolizumab. [19,28] Therefore, it is interesting to establish the effect of PD-L1 testing at the other indications.

In all studies similar perspectives were used. All studies only included direct medical costs. It is interesting to establish the effect of different perspective, such as the societal perspective. This perspective also includes indirect costs. The study of S D Criss et al claimed to be using the societal perspective but this study used similar direct costs as other studies. [28] The ZIN used the societal perspective for its HTA review about pembrolizumab for NSCLC, compared to docetaxel. In this review an ICER of €113.129/QALY was found. [5] The ICER is higher than the ICER found in the study of PN Aguir et al, of €71,910/QALY, which is a comparable study.[19] However, the expectation is that a societal perspective leads to a lower ICER because indirect costs coming together with patients, such as absence in work through sickness. This difference can be caused by the high discount rates used by PN Aguir et al, the differences in costs between the Netherlands and the UK, or differences in utility inputs.

In all the reviewed articles the discount rates used for costs and effects were even. It is also interesting to determine the effect of using different discount rates for costs and effects. Something which is very common in for example the Netherlands.

Striking is that 5 of the 11 studies were funded and all five studies conclude that Pembrolizumab is cost-effective for the different indications. [20,23,24,25,29] The six other studies did half of the time establish pembrolizumab as cost-effective and half of the time as not cost-effective. [19,21,22,26,27,28] It is possible that funding has an influence on the results of a research, but this cannot be concluded on the base of these findings.

Strengths of this review is the extensive amounts of parameters analyzed in each study, also cost-effectiveness analyses for a lot of countries are reviewed. The weakness of this review lays in the small number of reviewed articles and the difference between the articles reviewed per indication. This review only included two articles which looked at bladder cancer and only one review which looks at Hodgkin's disease. This makes it very hard to make conclusions about these indications and compare these indications with other indications. In a follow-up study it would be desirable to include more articles in the review with different setups by using more and different databases. This also leads to more accurate conclusions about for example the influence of the noted PD-L1 levels, the influence of discount rates, influence of different perspectives and the influence of administration influence.

Conclusion

The overall conclusions in countries are similar but there is a lot of difference in exact outcomes for the same countries and indications due to difference in setups of the cost-effectiveness analyses. Pembrolizumab was only found cost-effective for NSCLC in the US, due to the relative high indication of the WTP in this country. Pembrolizumab was found to be cost-effective in every reviewed study for melanoma. Pembrolizumab was not found to be cost-effective for bladder cancer in any of the studies. Pembrolizumab was found cost-effective for Hodgkin's lymphoma in the reviewed study.

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