Cost-effectiveness of nivolumab for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection: an analysis from a Swiss healthcare system perspective

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Background

Melanoma

- Melanoma is a type of skin cancer that occurs when melanocytes, the pigment-producing cells, mutate and become cancerous
- Since this form has high propensity to metastasize, it is considered the most serious skin cancer, accounting for 90% of all skin cancer-related deaths[1]
- It is most severe when it has progressed to stages III and IV, which are associated with a high risk of recurrence[1]
- Better overall survival has been associated with first relapse being local/intransit or nodal, asymptomatic, or resectable[2]

Clinical background of nivolumab

- Nivolumab was the first programmed death-1 (PD-1) immune checkpoint inhibitor to receive European Commission approval (30th July 2018) and Swissmedic (16th August 2018) approval as an adjuvant treatment for patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection, based on promising phase III trial results from the CheckMate 238 (NCT02388906) study
- CheckMate 238 is a phase 3, two-armed, randomized, double-blind study, with the purpose of comparing the efficacy as measured by recurrence-free survival (RFS), provided by nivolumab versus ipilimumab in subjects with completely resected stage IIIB-C or stage IV, with no evidence of disease (NED) melanoma, who are at high-risk for recurrence, for maximum treatment duration of 12 months[3]
- A phase 3 randomised controlled trial comparing ipilimumab to placebo for patients with resected stage III melanoma, CA184-029 (NCT00636168), was used along with CheckMate 238 to form an indirect treatment comparison (ITC) between nivolumab and placebo[4]

Objective

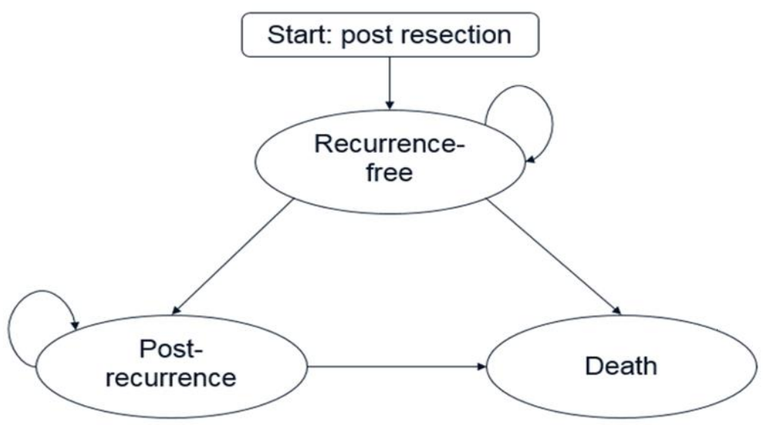
- The aim of this analysis was to assess the cost-effectiveness of nivolumab as an adjuvant treatment for adult patients with melanoma with involvement of lymph nodes or metastatic disease compared to observation, from a healthcare system perspective in Switzerland

Methods

Model structure

- A three-state (recurrence-free, post-recurrence, death) Markov de novo global cost-effectiveness model was adapted to the Swiss setting (**Figure 1**)
- OS and RFS curves from CA184-029 and RFS data from CheckMate 238 data were the key model inputs
- RFS curves informed transitions from recurrence-free to post-recurrence or death; OS curves informed transitions from post-recurrence to death; a HR derived from CA184-029 comparing OS and post-recurrence survival (PRS) informed transitions from post-recurrence to death
- The analysis took a health-care payer perspective, over a 60-year time horizon (life-time horizon)
- An annual discount rate of 3% was applied for both costs and effects
- The model included 28-day cycles
- Since ipilimumab has not received approval in the European Union for this indication, the only comparator included in the analysis was observation, standard of care in Switzerland
- The intervention administration was assumed to be 240mg once every 2 weeks
- Costs for drug acquisition and subsequent therapy were sourced from published prices and clinical expert inputs
- Costs for drug administration, monitoring, and adverse events management were derived from the Swiss outpatient tariff system (Tarmed 1.08 BR); for grade 3&4 adverse events the Swiss inpatient tariff system (Swiss DRG) was considered, and a mean value for the base rate of 8 big hospitals from canton Zürich was used for calculation of the fixed rate per case
- Health states utility values were based on French EuroQol 5-dimention (EQ-5D) tariffs and were obtained from CheckMate 238 collected data
- Input parameters' uncertainty was tested in sensitivity analyses
- Incremental cost-utility ratio (ICUR) was compared to a willingness-to-pay (WTP) threshold of 100,000 CHF (Swiss Francs) per quality adjusted life year (QALY) gained

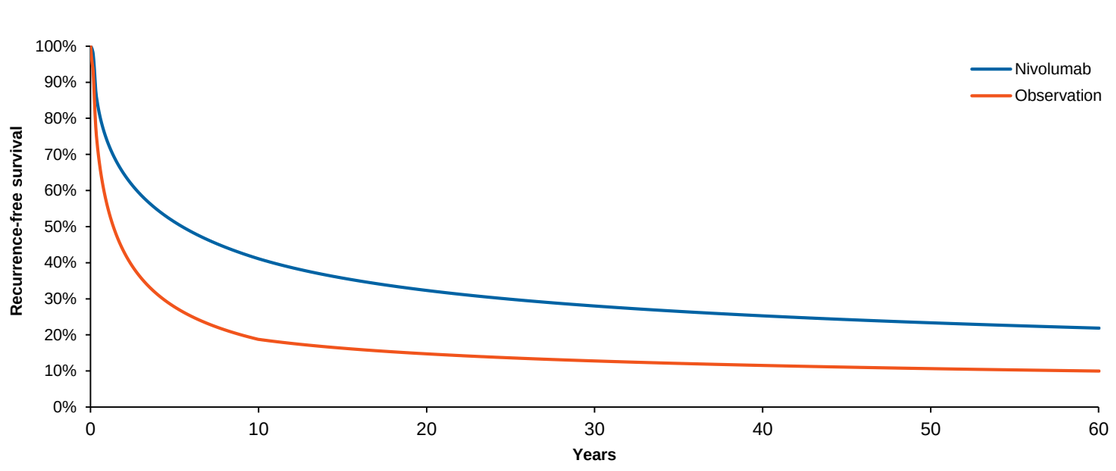
Figure 1. Overview of the cost-effectiveness model structure



Modelling of the key clinical outcomes

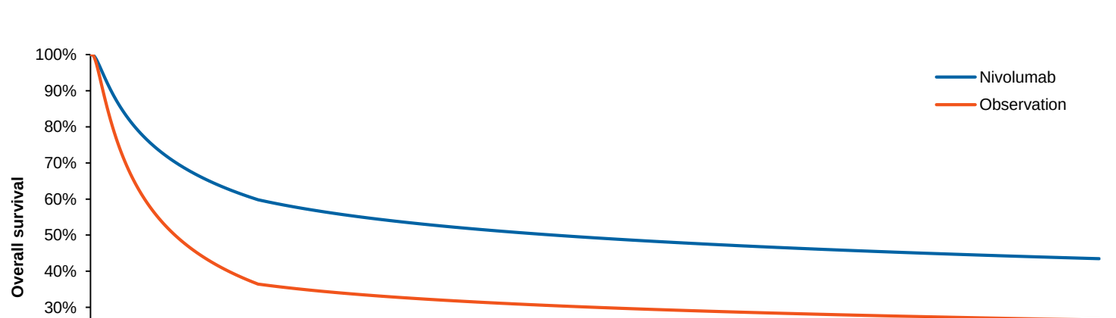
- An indirect treatment comparison (ITC) based on CheckMate 238 24-month cut-off patient-level data and CA 184-029 patient-level data was used to model nivolumab and observation RFS efficacy: the common ipilimumab arm in the two trials allowed to estimate nivolumab against placebo (observation) efficacy
- Parametric models were fitted to the pooled data of these two trials, and were used to generate relevant corrected group prognosis (CGP) based on the characteristics of the population of interest (stage, gender and age)
- An analysis performed on interferon published studies[5] was updated to include more recent randomised controlled trials (RCTs), to inform and model nivolumab OS through a RFS/OS correlation equation
- Observation OS was modelled using parametric curves fitted to CA 184-029 data
- Data from the 8th edition of the American Joint Committee on Cancer (AJCC) was used after 10 years to adjust the long-term survival; this database provided melanoma-specific survival outcomes for patients in different stages from centres in Australia, Europe and North America[6]
- The comparisons for RFS and OS for nivolumab and observation are provided in **Figure 2** and **Figure 3**

Figure 2. RFS curves for each intervention applied in the model, from ITC



ITC, Indirect treatment comparison; RFS, Recurrence-free survival

Figure 3. OS curves for each intervention applied in the model, from correlation equation



OS, Overall survival

Results

Base case – Deterministic analysis

- Nivolumab was associated with an incremental utility of 3.63 QALYs and with incremental life years gained (LYG) of 4.34
- In addition, nivolumab was associated with incremental costs of 64,114 CHF
- These incremental results led to an incremental cost-utility ratio (ICUR) of 17,667 CHF per QALY gained and to an incremental cost-effectiveness ratio (ICER) of 14,764 CHF per LYG when nivolumab was compared to observation (**Table 1**)

Table 1. Incremental costs, QALYs, LYG, ICUR and ICER for nivolumab against observation

Nivolumab vs.	Incremental costs (CHF)	Incremental QALYs	Incremental LYG	Incremental cost per QALY gained (CHF)	Incremental cost per LYG (CHF)
Observation	64,114	3.63	4.34	17,667	14,764

CHF, Swiss Francs; ICER, Incremental cost-effectiveness ratio; ICUR, Incremental cost-utility ratio; LYG, Life years gained; QALY, Quality adjusted life year

Base case – Probabilistic analysis

- Probabilistic ICUR (**Table 2**) was calculated by dividing probabilistic incremental costs by probabilistic incremental QALYs, derived from 1000 simulations
- A probabilistic ICUR of 17,794 CHF per QALY gained was calculated for nivolumab versus observation (**Table 2**)

Table 2. Average Incremental costs, QALYs and ICURs from 1000 probabilistic simulations

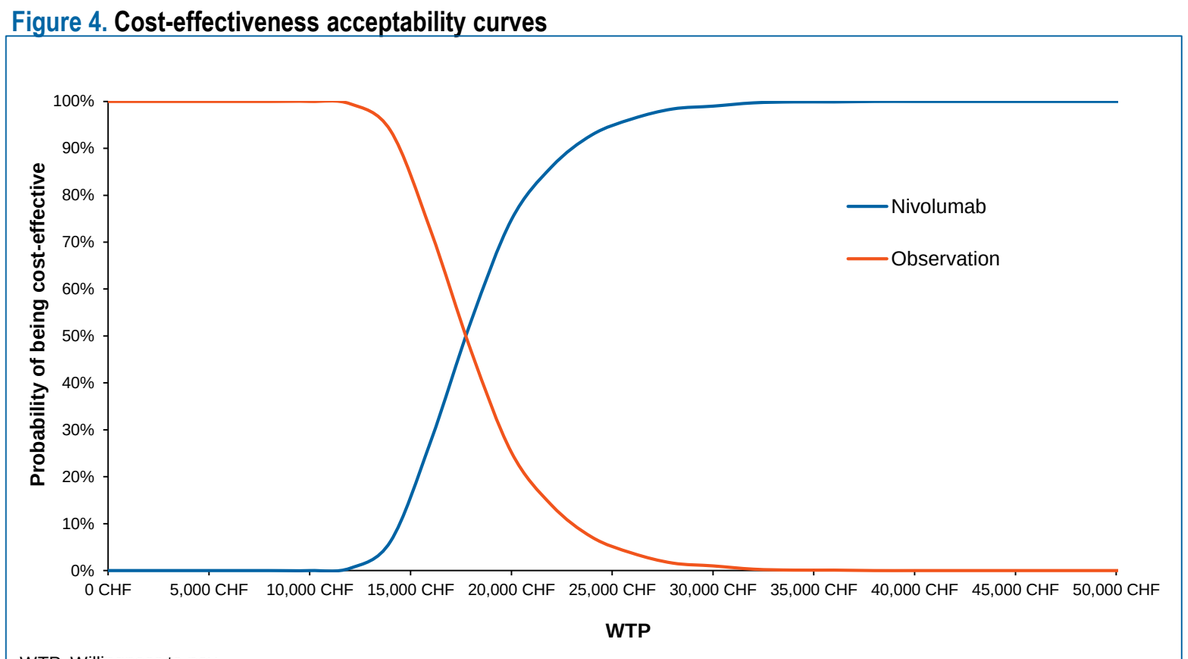
Nivolumab vs.	Incremental costs (CHF)	Incremental QALYs	Incremental cost per QALY gained (CHF)
Observation	63,788	3.58	17,794

ICUR, Incremental cost-utility ratio; QALY, Quality adjusted life year

Base case – Cost-effectiveness acceptability curves (CEACs)

- The CEAC is created using the results of the probabilistic analysis (**Table 2**), and reflects for each treatment the proportion of results that are considered cost-effective in relation to a given threshold
- Nivolumab has approximately 53.2%, 74.8% and 99.0% probability of being cost-effective at a willingness to pay threshold of 18,000 CHF, 20,000 CHF and 30,000 CHF respectively (**Figure 4**)

Figure 4. Cost-effectiveness acceptability curves

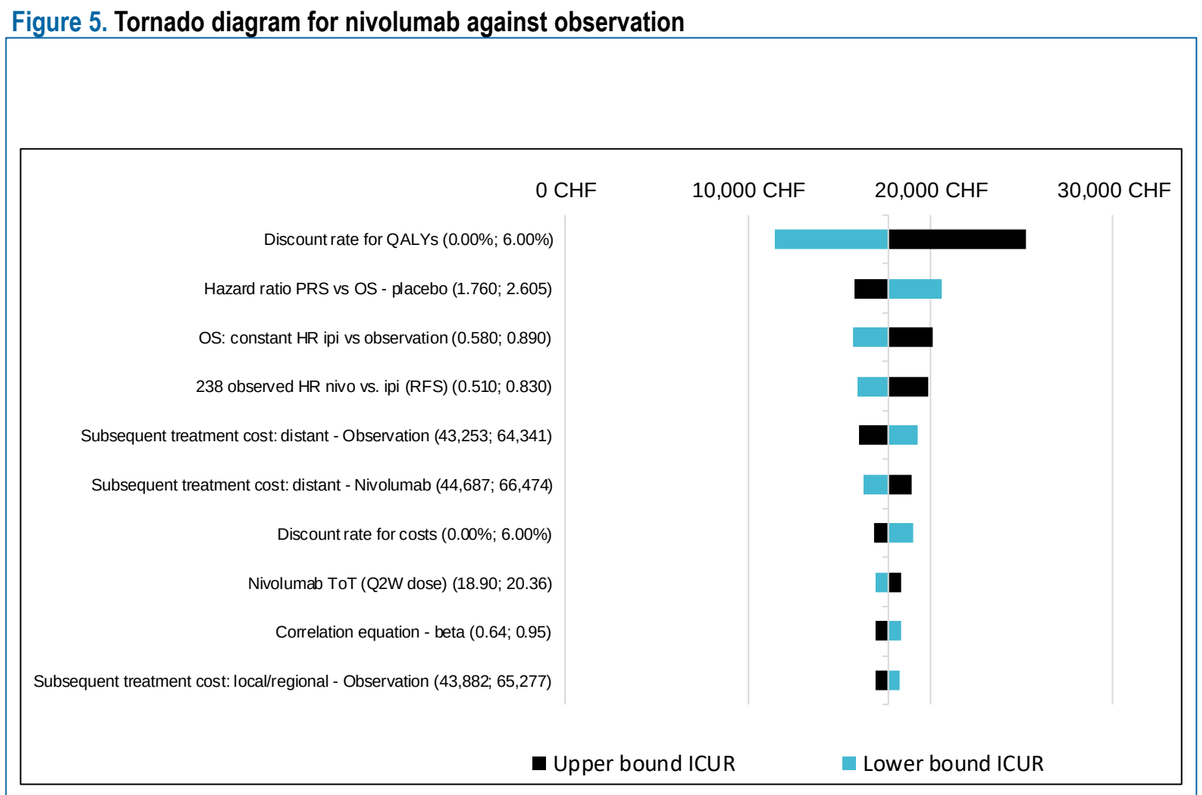


WTP, Willingness to pay

Base case – One way sensitivity analysis (OWSA)

- Upper and lower confidence interval values were used to explore the impact of individual parameters on the results
- The parameters with the highest impact on the results were the discount rate for QALYs and the HR comparing OS vs PRS in the placebo arm
- A tornado diagram of the analysis is presented in **Figure 5**

Figure 5. Tornado diagram for nivolumab against observation



CHF, Swiss Francs; HR, Hazard ratio; ICUR, Incremental cost-utility ratio; OS, Overall survival; PRS, Post-recurrence survival; QALY, Quality adjusted life year; RFS, Recurrence-free survival; ToT, Time on treatment

Conclusions

- Nivolumab is a cost-effective strategy for the adjuvant treatment of melanoma in Switzerland, with an ICUR value significantly lower than a WTP threshold of 100,000 CHF per QALY gained
- Its use could lead to significant health benefit for patients, with higher QALYs compared with observation

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