Variation in Health Technology Assessments for Nivolumab Plus Chemotherapy vs Chemotherapy in First-Line Gastro-Oesophageal Adenocarcinoma

HTA5

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Background

- Health technology assessments (HTAs) inform reimbursement decisions. International differences in HTA processes lead to international differences in patient access to new treatments.
- Nivolumab is an anti-PD-1 monoclonal antibody that promotes an immune response to tumours and has been approved for the treatment of multiple cancers.
- The CheckMate-649 trial (NCT02872116) demonstrated clinically meaningful OS and PFS benefits for first-line gastro-oesophageal adenocarcinoma patients treated with nivolumab plus chemotherapy vs chemotherapy alone. [1,2]
- Based on evidence from the CheckMate-649 trial, nivolumab plus chemotherapy was approved for the treatment of first-line gastro-oesophageal adenocarcinoma by the US Food and Drug Administration (FDA) in April 2021, Health Canada, the European Medicines Agency (EMA) and the UK Medicines & Healthcare Products Regulatory Agency (MHRA) in October 2021, and the Australian Therapeutic Goods Administration (TGA) in February 2022.

Objectives

- The objectives of this study are to assess the variation in time to patient access and in the evaluation of comparative benefits between different Health Technology Assessment (HTA) agencies, using HTA submissions for nivolumab plus chemotherapy treatment of first-line gastro-oesophageal adenocarcinoma as an example.

Methods

- The analyses focussed on countries using HTA processes to inform national or regional reimbursement decisions.
- Time to patient access (in months) was evaluated using three measures:
  - Time from regulatory approval to reimbursement
  - Time from regulatory approval to HTA submission
  - Time from HTA submission to reimbursement.
- All times were rounded up to the nearest month. In cases where multiple rounds of HTA submissions occurred, the time to/from the initial HTA submission is used.
- In some countries (e.g., Canada, France, UK), early access schemes were in place which provided nivolumab to gastro-oesophageal adenocarcinoma patients at no cost before national or regional reimbursement decisions. Such early access schemes are not considered in these analyses.
- For Canada, in which reimbursement decisions occur at a provincial level, the reimbursement date for the province with the earliest reimbursement is used.
- HTA evaluation of comparative benefits was assessed using the incremental QALY (ΔQALY) for the base case cost-effectiveness (CE) analysis of the CheckMate-649 trial direct comparison, nivolumab plus fluoropyrimidine and platinum chemotherapy vs fluoropyrimidine and platinum chemotherapy.
- Assessment of HTA evaluation of comparative benefits was limited to HTA agencies for which the ΔQALY of their preferred version of the CE analysis, on which the HTA decision was based, was available.

Results – Time to patient access

Time from regulatory approval to reimbursement

- The time from regulatory approval to reimbursement varied considerably across countries, from 0 months to 18 months for the 15 countries from which information was available (Figure 1).
- The time from regulatory approval to reimbursement also varied considerably across EU countries, with two EU countries, Germany and Slovenia, being at either end of the distribution.
- Several countries that have submitted HTA dossiers are still waiting for reimbursement to commence, therefore once all the data are available, the variation will be even greater.

Time from regulatory approval to HTA submission

- The time from regulatory approval to HTA dossier submission varied from -11 months to +12 months (negative values indicate countries where HTA dossiers may be submitted during the regulatory review process) for the 17 countries from which information was available (Figure 2).
- The time from regulatory approval to HTA dossier submission also varied across EU countries, with Germany and France submitting within one month of EMA approval, and Bulgaria submitting 12 months after.
- Sweden and the Netherlands are not included in Figures 2 and 3 because they did not conduct formal HTA processes for nivolumab in first-line gastric cancer, instead basing their reimbursement decisions on recommendations from clinical organisations (Expert Council in Sweden and Oncology Society (CieBOM) in the Netherlands).

Figure 1. Time from regulatory approval to reimbursement

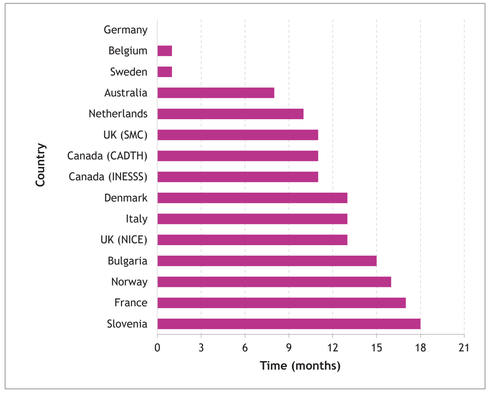


Figure 2. Time from regulatory approval to HTA submission

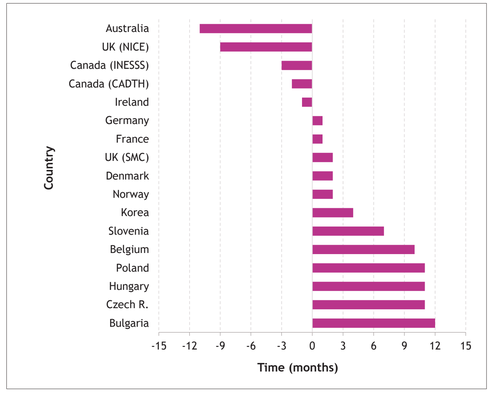
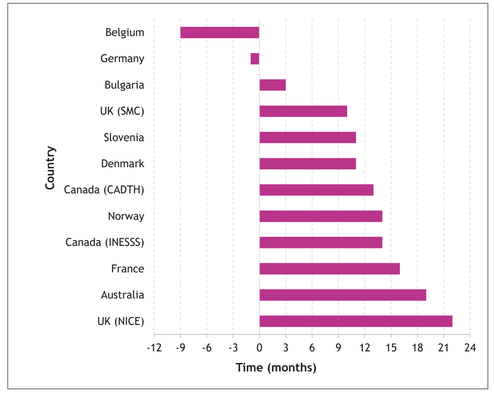


Figure 3. Time from HTA submission to reimbursement



Time from HTA submission to reimbursement

- The time from HTA dossier submission to reimbursement varied from -9 months to + 22 months (negative values indicate countries where HTA dossiers may be submitted after reimbursement commences) for the 12 countries from which information was available (Figure 3).
- The time from HTA dossier submission to reimbursement also varied across EU countries, from Belgium at – 9 months, to France at + 16 months.
- Several countries that have submitted HTA dossiers are still waiting for reimbursement to commence, so the variation will ultimately be even greater.

Results – Evaluation of comparative benefits

- Details of the CE analyses preferred as the basis of HTA decisions were available for six HTA agencies, the Canadian Agency for Drugs and Technologies in Health (CADTH), the French Economic and Health Committee (CEESP), the Danish Medicines Council (DMC), the UK National Institute for Health and Care Excellence (NICE), the Norwegian Medicines Agency (NOMA) and the Australian Pharmaceutical Benefits Advisory Committee (PBAC).

Evaluation of comparative benefits in manufacturer HTA submissions

- For the five HTA agencies included in the analyses, the manufacturer submitted ΔQALY ranged from 0.395 to 1.039 (Table 1, first shaded column). Columns 3 to 8 in Table 1 report some key aspects of the CE analyses which differed between the manufacturer submissions to the five HTA agencies and which contributed to the variation in ΔQALY values.
- Patient populations for the CE analyses varied (Table 1, column 3) due to differences in the licensed indications between countries. The Australian and Canadian regulatory bodies approved nivolumab plus chemotherapy for first-line gastro-oesophageal adenocarcinoma patients with any PD-L1 status ("All Comers"), in line with the intent to treat population of the CheckMate-649 trial. By contrast, European regulators (the EMA and MHRA) restricted the licensed indication to the PD-L1 CPS>=5 subgroup, which was the population in which CheckMate-649's primary endpoints were assessed.
- CheckMate-649 has undergone several database locks, therefore HTA dossiers submitted earlier were based on less mature, more uncertain survival data (Table 1, column 4).
- Different time horizons were used in the HTA submissions because HTA agencies differ in their preferences for the length of time horizons for CE analyses, a (Table 1, column 5). PBAC and CEESP required conservative time horizons of 7.5 and 8 years, respectively, for this indication. By contrast, NICE permitted a 50 year time horizon.
- Different time preference discount rates for benefits were used in the HTA submissions, reflecting the different rates in HTA agency reference cases for CE analyses, and ranging from 1.5% for CADTH to 5% for PBAC (Table 1, column 6).
- Differences in survival models extrapolating overall survival reflect different database locks, different patient populations, HTA agency preference, and in the case of the NICE submission, the use of a different model structure. The CE models submitted to CADTH, CEESP, DMC, NOMA and PBAC all had a 3 health state, partitioned survival structure. By contrast, the CE model for the initial NICE submission was a semi-Markov with four health states, including one for long-term remission.

Evaluation of comparative benefits in manufacturer submitted vs HTA agency preferred analyses

- The ΔQALYs preferred by HTA agencies for CE analyses ranged from -47% to +8% of the ΔQALYs in the manufacturer submissions (Table 1, shaded columns). In 4/6 cases the ΔQALYs preferred by HTA agencies were lower than the manufacturer submitted ΔQALYs, in one case the same (DMC), and in one case higher (CEESP).
- In 4/6 cases, the changes from the manufacturer submitted to the HTA agency preferred CE analyses included different survival models for OS. In one case the survival model for OS in the control arm was changed (PBAC). In one case the survival models for OS in both intervention arms were changed (CADTH). In one case the survival model for OS was changed from a single model (encompassing both treatment arms) to independent models for each arm (CEESP). In one case the CE model structure changed from semi-Markov to partitioned survival, requiring a different approach to survival modelling (NICE).
- The largest difference (-47%) between the manufacturer submitted and HTA agency preferred ΔQALY was for the CADTH submission. The manufacturer used a loglogistic model to extrapolate OS for the intervention treatment arm, whereas CADTH's preferred CE analysis used a Weibull model instead, considerably reducing the estimated overall survival. CADTH's CE analysis used the same survival model as the manufacturer submission to extrapolate OS for the control arm.

Table 1. Evaluation of comparative benefits (ΔQALYs)

Country	HTA Agency	Submitted CE Model settings: Population (PD-L1 status)	Database lock (months follow up)	Time horizon (years)	Discount rate for benefits	OS model for intervention	OS model for control	Submitted ΔQALY	HTA agency preferred ΔQALY	Submitted vs HTA agency preferred ΔQALY	Submitted vs HTA agency preferred key CE model changes
Australia	PBAC	All Comers	12	7.5	5%	Loglogistic	Weibull	0.395	0.390	- 1%	OS model for control arm
Canada	CADTH	All Comers	19	25	1.5%	Loglogistic	1 knot odds	0.418	0.223	- 47%	OS models for both control and intervention arms
Denmark	DMC	PD-L1 CPS>=5	24	15	3.5%	1 knot odds	1 knot odds	0.638	0.638	0%	No changes to benefits side of CE model
France	CEESP	PD-L1 CPS>=5	24	8	2.5%	2 knot hazards (Single model)		0.453	0.490*	+ 8%	OS models changed from single model to independent models
Norway	NOMA	PD-L1 CPS>=5	24	25	4%	1 knot odds	1 knot odds	0.646	0.59	- 9%	Changes to patient age and to utility values
UK	NICE	PD-L1 CPS>=5	12	50	3.5%	Semi-Markov model with long-term remission health state		1.039	0.741	- 28%	Different structure (partitioned survival), updated database lock

* Note that although CEESP's preferred CE analysis for the CM-649 direct comparison had an ΔQALY of 0.490, the CE analyses overall were invalidated due to a major reservation concerning the indirect comparison.

Discussion

Variation in time to patient access

- The variation observed across countries in the time from regulatory approval to reimbursement of nivolumab for the treatment of first-line gastro-oesophageal adenocarcinoma reflects differences in HTA, pricing and reimbursement processes:
  - Some agencies, such as PBAC, NICE, CADTH and INESSS, permit HTA submissions during the regulatory review process.
  - Some countries which typically use HTA based their reimbursement decisions for this indication on recommendations from clinical organisations (Sweden and Netherlands).
  - Some countries permit reimbursement to commence before submission of HTA dossiers (Germany, and in the case of PD-1 inhibitors, Belgium), greatly speeding patient access.
  - For some agencies, multiple rounds of HTA dossier submission can occur (for example, there were three rounds of submission to NICE for this indication).
  - Some countries use reference pricing, which delays patient access until after the reference countries have published their official drug prices.
- Considerable variation in time to patient access was observed between EU countries. The introduction of the Joint Clinical Assessment (JCA) is not expected to change this as the economic aspects of HTA, and pricing and reimbursement processes are beyond its remit.
- Interestingly, the HTA agencies that permit manufacturers to submit during the regulatory process (PBAC, NICE, CADTH, INESSS) were not the earliest to be reimbursed, with their earlier HTA submissions offset by relatively long periods from HTA submission to reimbursement.
- The covid pandemic may have caused staffing problems for some HTA agencies during the period of these analyses, possibly increasing times from HTA dossier submission to reimbursement.

Variation in evaluation of comparative benefits

- Variation in the manufacturer evaluation of ΔQALYs was partly due to differences in trial data submitted by the manufacturer:
  - Depending on the local licensed indication, data for PD-L1 All Comers or CPS>=5 populations.
  - Depending on the timing of the HTA dossier submission, data from different database locks.
- However, differences in the methodological preferences of HTA agencies also contributed to the variation in manufacturer evaluation of ΔQALYs in submitted dossiers:
  - Restricted time horizons of =< 8 years were required by some HTA agencies, despite published reports of a small proportion of gastro-oesophageal patients treated with first-line chemotherapy surviving beyond 8 years.[3]
  - A range of different discount rates for benefits are mandated in HTA agency reference cases.
- Another aspect of the submitted CE analyses which differed between countries and influenced the ΔQALYs, but are not included in Table 1, are the health state utility values, which are calculated using country-specific tariffs.
- The difference between manufacturer submitted and HTA agency preferred comparative benefit varied considerably between countries, mostly due to changes to extrapolation of OS.
- One aspect of OS extrapolations that varied between HTA agency preferred versions of CE analyses was assumptions on treatment effect waning:
  - CADTH used treatment waning as a rationale for using a Weibull model rather than the better fitting loglogistic model to extrapolate OS for the intervention arm.
  - NICE assumed treatment waning would start after 5 years, although they acknowledged that they had no evidence to support this specific assumption.
  - CEESP, DMC, NOMA and PBAC did not include a treatment waning assumption in their preferred versions of the CE analysis.

Conclusions

- Considerable variation was observed between countries using HTAs, in terms of both timing to patient access and the evaluation of benefits.
- Variation in time to patient access was driven by international differences in HTA, pricing and reimbursement processes.
- Countries with the earliest patient access achieved this by reimbursing new treatments ahead of HTA submission, or based on clinical recommendations rather than full HTA.
- Variation in manufacturer evaluation of comparative benefits in HTA submissions was partly due to differences in patient populations and database locks, but also due to differences in HTA agency methodological preferences.
- Variation between the manufacturer submitted vs HTA agency preferred evaluation of comparative benefits were mainly due to changes in overall survival extrapolations.

References

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Dedication

- We dedicate this poster to our colleague, Pernilla Huetson, who passed away before its publication and will be greatly missed.

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