Predicting The Unknown – How Health Technology Assessment Bodies Deal with Uncertainty, The Impact on Patient Access to Immuno-oncology Therapies

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Background

- Patient access to immuno-oncology (IO) therapies (focused on PD-1/PD-L1 inhibitors) differs across countries despite appraisal of similar pivotal clinical trial evidence
- Differences in the management of uncertainty across Health Technology Assessment (HTA) bodies is a key driver of this variation
- This study explored how different HTA bodies manage uncertainty and how this impacts patient access to IO therapies

Methods

- A two phased approach assessed variation at the individual technology decision level in the appraisal of selected PD-1/PD-L1 inhibitors across HTA bodies in Canada, England, Australia and France as of September 2019

1. Desk Research	2. Primary research
Evidence submitted, patient and expert input, and HTA recommendations were extracted from HTA appraisals using Hutton et al. 2006 analytical framework[1]	Two payer interviews per market were conducted to further explore findings and hypotheses with external experts and identify other drivers and challenges of HTA decision-making

Results

- HTA outcomes and time to access varies across countries

Figure 1. Time from registration to listing (days)

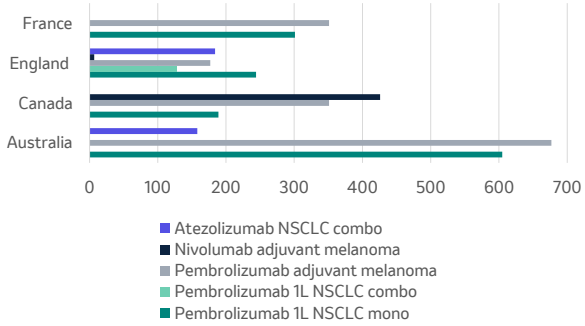

Figure 2. Time from registration to HTA outcome (days)

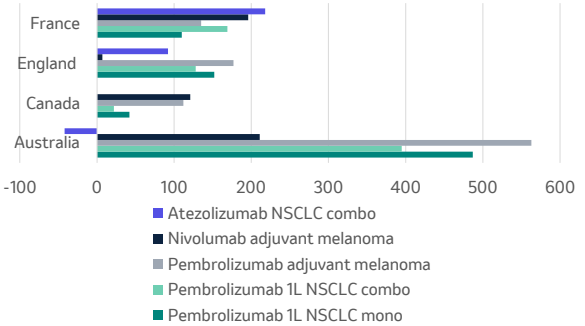

Figure 1 and 2: The analysis has been completed by Michael Wonder with the information sourced from the MAESTrO database.

Abbreviations: CDF, Cancer Drug Fund; SMR, service medical rendu; ASMR, l'amélioration du service médical rendu ; NSCLC, non-small cell lung cancer; OS , overall survival

1. Hutton J et al.. Framework for describing and classifying decision-making systems using technology assessment to determine the reimbursement of health technologies(fourth hurdle systems). International Journal of Technology Assessment in Health Care 2006;22(1):10–8

Results Contd.

Table 1. HTA outcomes of PD-1/PD-L1 inhibitors as reviewed September 2019

Medicine	Indication				
Pembrolizumab	1L NSCLC monotherapy	Initial Re-appraisal		Initial: CDF Re-appraisal	SMR Important, ASMR 3
Pembrolizumab	1L NSCLC combo**	Initial Re-appraisal		CDF	SMR Important, ASMR 3
Pembrolizumab	Adjuvant melanoma			CDF	SMR Important, ASMR 3
Nivolumab	Adjuvant melanoma	Initial Re-appraisal Re-appraisal		CDF	SMR Important, ASMR 3
Atezolizumab	NSCLC combo*				

*Combination therapy included atezolizumab + bevacizumab + carboplatin + paclitaxel. **Combination therapy included pembrolizumab + platinum + pemetrexed

Recommended | Not recommended | Recommended with conditions

- Key sources of uncertainty across HTA appraisals included: the role of biomarkers to define subpopulations, approaches to extrapolation and modelling time horizons and use of surrogate endpoints
- Across countries, variations exist in approaches to managing these uncertainties

Figure 3. Sources of uncertainty and variation in acceptance/consideration

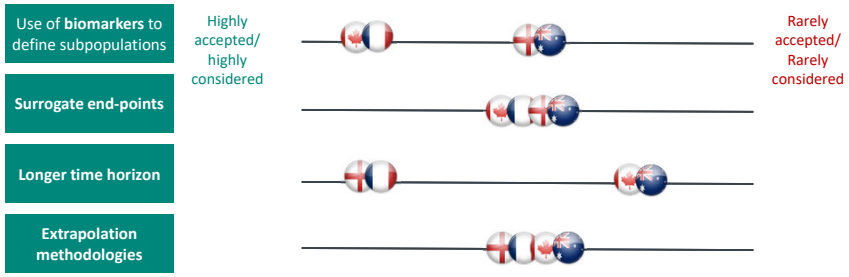

Table 2. Approach to management of biomarkers and surrogate endpoints

	Use of biomarkers to define sub-groups	Surrogate end-points
	Accept the use of biomarkers to manage uncertainty as facilitates the identification of patient groups with higher response rate	Accepted if there is a high unmet need and endpoint is validated
		Accepted when long term survival data collection are not feasible and there is a high unmet need
	Sub-group analyses are considered when cost-effectiveness in the entire population is uncertain	Only considered if there is evidence of correlation with OS gain. Funding via CDF is possible until mature OS data are generated
	Biomarkers are evaluated but HTA recommendations in the entire indicated population are more common	Only accepted if there is a high unmet need and evidence of a strong correlation with OS

Table 3. Approach to management of time horizon and extrapolation methodologies

	Length of time horizon	Extrapolation methodologies
	Shorter time horizons of 5-10 year are preferred in oncology to manage uncertainty	Acceptance of extrapolation methods can vary in each economic review – partition survival models are more common
	Life-time horizon is preferred however impact of cost/QALY on pricing negotiations is minimal. Budget impact is a key decision driver	Inconsistent approach as models are reviewed on a case by case basis. However budget impact is the key decision driver
	Longer time horizons are accepted which may be because the CDF allows more conclusive OS data to be collected to manage uncertainties	A partition survival model is most commonly used. 2 year stopping rules are often implemented which can help manage uncertainty
	Shorter time horizons are preferred to manage uncertainty on extrapolation	Conservative approaches are preferred in economic modelling to manage uncertainty

Conclusions

- Variation in HTA bodies evaluation of key sources of uncertainty can impact HTA decision making of PD-1/PD-L1 inhibitors
- Patient access and time to access differs across countries potentially as a result of HTA evaluation variation
- Understanding the reasons for variation and aligning across stakeholders on approaches to address uncertainty could help improve efficiency of decision-making for future assessments and improve access for patients