IP14.

MANAGED ENTRY SCHEMES: HYPE vs REALITY

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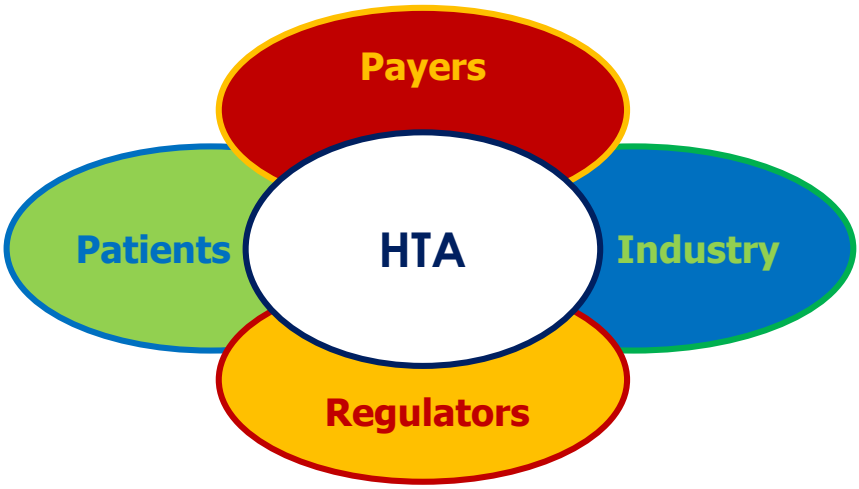
AGENDA

- The Growing Pressure on HTA
- MES – a Potential Solution?
- MES in Australia – History
- MES in Australia – Ipilimumab, a Case Study
- MES – Hype vs Reality & the Future

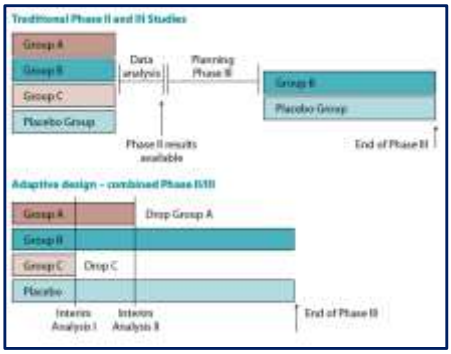
THE GROWING PRESSURE ON HTA

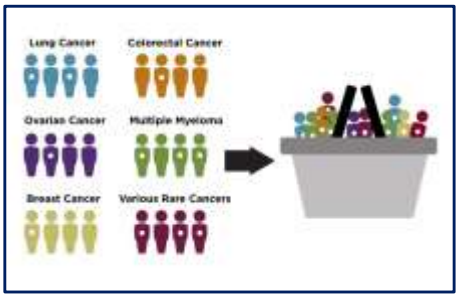


THE GROWING PRESSURE ON HTA

Industry

- Non-traditional / adaptive CT programs





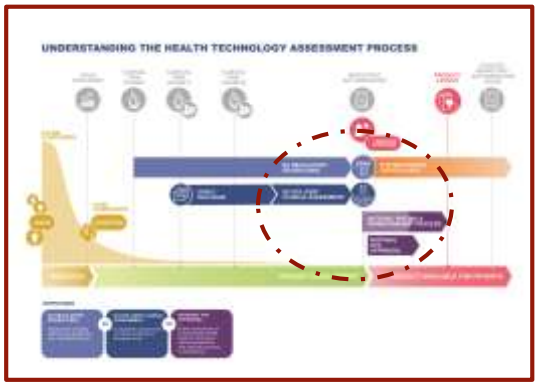
THE GROWING PRESSURE ON HTA

Regulators
- Priority reviews / combined Reg/HTA evaluations

FDA
PRIORITY REVIEW

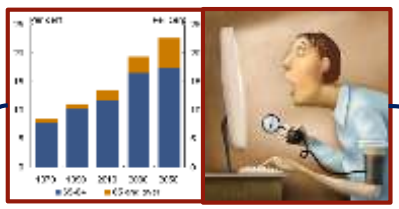
PRIME – PRIORITY MEDICINES

TGA Priority Review

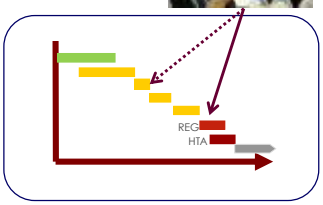


THE GROWING PRESSURE ON HTA

Patients
- Demand for early access



Patient Demand for Access via Industry programs is Beginning Earlier

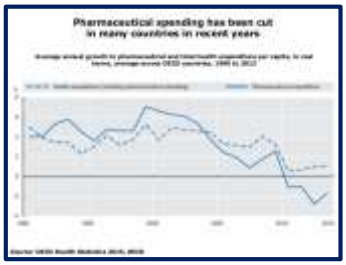


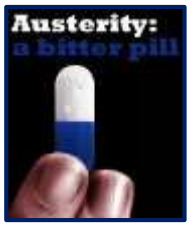
Patient Demand for HTA Access via Media/ Social Media is Increasing

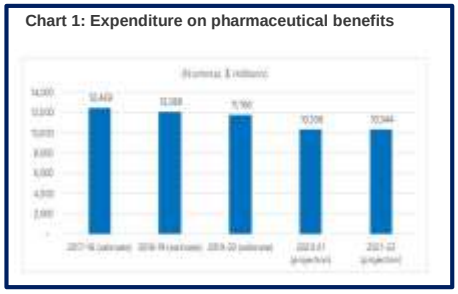
The Sun-Herald
THE SUNDAY AGE

THE GROWING PRESSURE ON HTA

Payer
- Budget & Austerity Measures







THE GROWING PRESSURE ON HTA

Clinical Uncertainty:
- Phase I/II data, single arm, surrogate endpoints, trial cross-over
- treatment algorithm, comparative effectiveness
- long-term safety

Economic Uncertainty:
- utilities, time horizon
- extrapolation method

Financial Uncertainty:
- utilization, budget

Political Uncertainty:
- health care prioritization
- fiscal situation

HTA

MES – THE PANACEA?

Managed Entry Scheme

Performance Based Risk Sharing Arrangements

Coverage with Evidence Development

Managed Access Program

- "… represent one mechanism for reducing uncertainty through greater investment in evidence collection while a technology is used within a health care system." *Garrison, Towse, Briggs et al. Value in Health 2013;16: 703-719*

- "… generation of additional evidence to support the "real-world" value of promising health technologies as a condition for provisional coverage. As such, it represents a middle ground between the conventional "yes" or "no" reimbursement decisions, giving the opportunity to satisfy all parties (decision-makers, pharmaceutical companies, as well as end users)." *Comparative Effectiveness Research in Health Services. Levy & Sobolev, Eds 2016*

MES IN AUSTRALIA - HISTORY

- While the first example of CED in Australia was specific to bosentan for the treatment of PAH (2004), a formal mechanism for PBS reimbursement with the promise of future data was not introduced until 2011.
- Initially termed Managed Entry Scheme (MES) it is now also known as Managed Access Program (MAP).

Table 1: Medicines identified as potential MES candidates by PBAC since introduction of formal MES policy (2011-2016)

Medicine	MES
Ipilimumab for metastatic melanoma (2012)	• Pay for performance with rebates payable should 2 year OS rates in real world clinical practice in Australia not align with 2 year OS clinical trial data
Ivacaftor for cystic fibrosis (2014)	• Pay for performance with rebates applicable for patients subsequently assessed as non-responders
Eculizumab for atypical haemolytic uraemic syndrome (2014)	• Pay for performance with rebates applicable for patients who do not achieve an agreed clinical outcome over an agreed time period
Trametinib for metastatic melanoma (2014)	• Pay for performance with rebates applicable should trametinib fail to deliver claimed benefits
Crizotinib for non-small cell lung cancer (2014)	• Pay for performance with rebates applicable should crizotinib fail to deliver claimed benefits
Pembrolizumab for metastatic melanoma (2015)	• PBS list with provision for future clinical trial evidence to support a potential price increase
Nivolumab for non-small cell lung cancer (2016)	• PBS list with provision of future evidence to confirm effectiveness of nivolumab in NSCLC patients ≥ 75 years of age

http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd

MES IN AUSTRALIA - IPILIMUMAB

Key Study (CT-020)

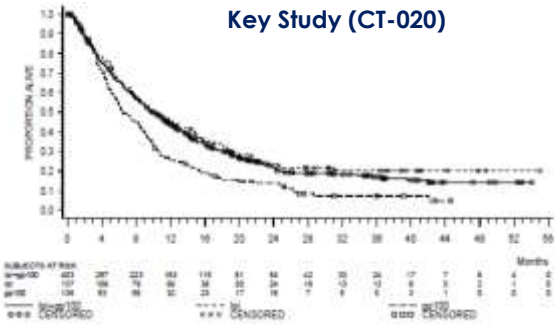


Table B.1: Results of Survival for CT-20 (ITT)

Outcome	IPI (%)	gp100 (%)	IPI vs. gp100 RR(95% CI)	IPI vs gp100 RD (95% CI), p
1 yr survival	45.6	25.3	1.84 (1.31, 2.59)	0. 21 (0.10, 0.32) p=0.0002
2 yr survival	23.5	13.7	1.67 (1.00, 2.80)	0.09 (0.00, 0.18) p=0.04

CI = confidence interval; n = number of participants with event; N = total participants in group

Ipilimumab for Metastatic Melanoma

- TGA registration – June 2011
- IPI HTA submission – July 2011 PBAC mtg
- IPI HTA re-submission – Mar 2012 PBAC mtg
- IPI HTA re-submission – Nov 2012 PBAC mtg
- PBS reimbursement – August 2013

"The PBAC, although concerned about the cost-effectiveness of ipilimumab if the claimed survival gain were not observed in practice, recommended the listing of ipilimumab for metastatic melanoma, subject to risk-share arrangements."

PBAC PSD Nov 2012

MES IN AUSTRALIA - IPILIMUMAB

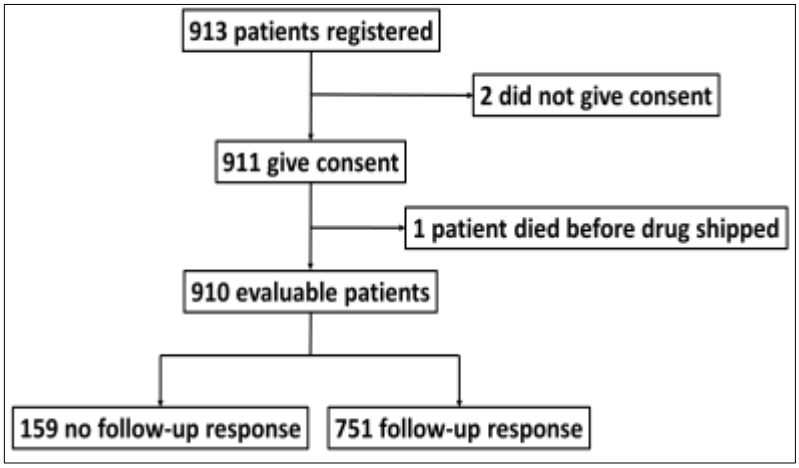
METHODS:

IPI MES RISK SHARE ARRANGEMENT

- **OS at 2-years** was to be assessed in the **'real-world' setting** for all patients initiated on ipilimumab during the **first full year of PBS listing**.
- Results would then be compared to the **2 year OS data** from the key **ipilimumab clinical trial (23.5%)**
- The sponsor to **rebate the cost of difference in performance between observed versus predicted OS benefits** of ipilimumab should observed OS be less than that seen in the key clinical trial.

MES IN AUSTRALIA - IPILIMUMAB

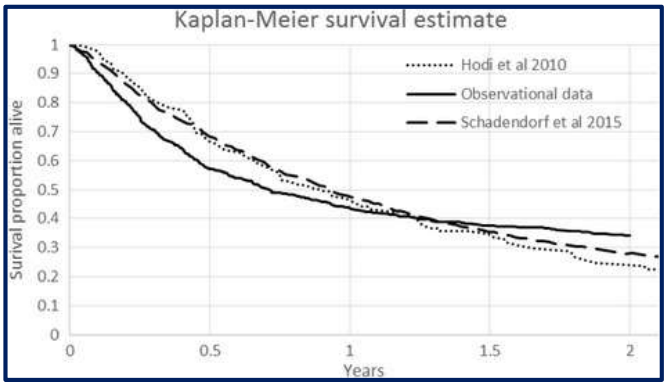
RESULTS:



MES IN AUSTRALIA - IPILIMUMAB

RESULTS:

Population	Proportion alive
Clinical Trial (Hodi - 020)	23.5%
MES - Pts registered	23.89%
MES - Evaluable pts	23.96%
MES - Follow-up response	29.03%
MES - Censored patients	34.20%



MES IN AUSTRALIA - IPILIMUMAB

CONCLUSION:

While results for this project support the use of MES to allow earlier access to innovative medicines in areas of high clinical need, it does not necessarily translate that this is the solution every time.

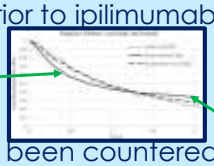
Indeed, as cited by Garrison et al, "*It is critical for policy makers to recognise the* ***benefits, limitations and methodological challenges in using RW data****, and the need to consider carefully the costs and benefits of different forms of data collection in different situations.*"

Garrison et al. Value Health. 2007 Sept-Oct; 10(5): 326-335

MES IN AUSTRALIA - IPILIMUMAB

INSIGHTS & LEARNINGS - 1:

- The inherent inability of RW data to directly mirror the strong internal validity of a clinical trial is a significant risk.
- Ipilimumab MES - there was likely an initial cohort of patients that were extremely unwell due to the lack of an effective PBS listed therapy prior to ipilimumab PBS listing
  - **9.4% ECOG status** of 2 or 3 vs **1.2% in CT**
  - **28.9% brain metastases** vs **11.4% in CT**



- This negative impact on the OS numbers may have been countered by the availability of medicines not listed on the PBS and used post ipilimumab *(e.g. dabrafenib, tremetinib, pembrolizumab & nivolumab)* via compassionate access programs.
- Future MESs need to explicitly define the research question and factor in potential unintended consequences associated with treating patients in the RW setting.

MES IN AUSTRALIA - IPILIMUMAB

INSIGHTS & LEARNINGS - 2:

- Setting up of the MES was both **resource intensive and costly.** To do so on a regular basis and across multiple jurisdictions is not seen by sponsor companies as sustainable.
- While the conditions of the program in relation to obtaining 2 year survival data were clearly stated at the time of clinician / patient enrolment, **unconfirmed outcomes status was approximately 40% at the 2 year anniversary of the program.** Significant effort and resources were required to gather the full set of data.
- Future MESs should **establish robust and comprehensive reporting systems** as a key component of the undertaking.

MES IN AUSTRALIA - IPILIMUMAB

INSIGHTS & LEARNINGS - 3:

- While the ipilimumab MES was established as a pragmatic solution to delivering access to Australian patients in the face of data uncertainty, it was raised and implemented as a **last resort** option (*i.e. 3rd PBAC submission ~ 2 years*).
- With the recent introduction of Regulatory priority review & provisional registration in Australia discussions specific to provisional reimbursement/ MES may be better occurring prior to PBAC submissions and /or after a first-time PBAC rejection.

MES - HYPE VS REALITY & THE FUTURE

- Growing pressure on HTA with demand for early access to innovative medicines in the face of clinical / economic uncertainty & budgetary constraints.
- MES is one potential solution – but needs to be carefully considered on a case by case basis.
- Additional transparency from other MESs, together with learnings from the patient, clinician and payer's perspective are needed to ensure the environmental push for earlier access to breakthrough medicines can be realised – either via MES or other means.