Are Accelerated Approval Mechanisms a Predictor to Early Access and Coverage? A Global Study of Cancer Drugs

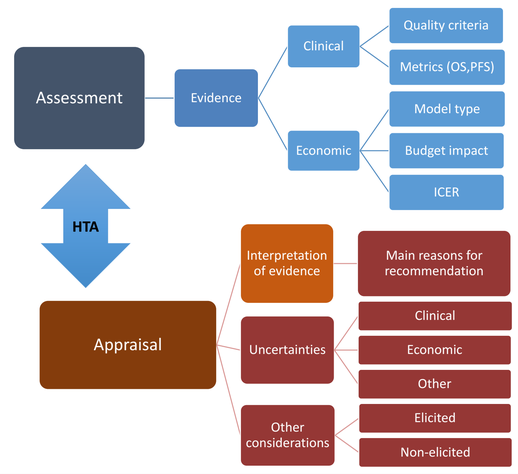
Tzouma V[1], Efthymiadou O[1], Mills M[1] and Kanavos PG[1]

Background

- **Accelerated regulatory pathways** created by the **FDA** in the US, the **EMA** in the EU and other regulators have the capacity to dramatically change the patient treatment paradigm. Drugs that are of major interest for public health or that are therapeutic innovations may be subject to these accelerated approval procedures; **cancer treatments** are key among them.
- **Aim**: To explore the **interrelationship** between **accelerated approval schemes** for cancer drugs and **national HTA processes** across four jurisdictions globally (**England, Scotland, Australia** and **Canada**), by investigating the impact HTA and value assessment has on drugs approved through accelerated pathways.

Methods

- **16 drug-indication pairs** with cancer indications (**melanoma, lung** and **haematology**) were selected based on whether they received accelerated approval in the US or Europe via one of the FDA Accelerated Approval pathways or the EMA Conditional Marketing Authorisation (CMA), or both, until December 2015.
- In-depth analysis of HTA impact on coverage and funding pathways in the four selected countries relied on an analytical methodological framework investigating: **(a) Similarities and differences in clinical and economic evidence submitted; (b) Evidence interpretation; (c) Uncertainties; (d) Other considerations, drug or therapeutic-area related; and (e) Time difference between MA and HTA recommendation.**



Results

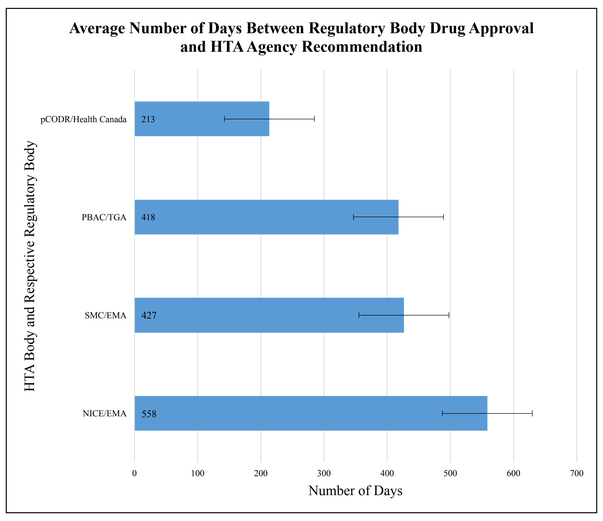
Marketing Authorisation dates and decisions and HTA dates and recommendations for 16 oncology drug-indication pairs across 4 countries

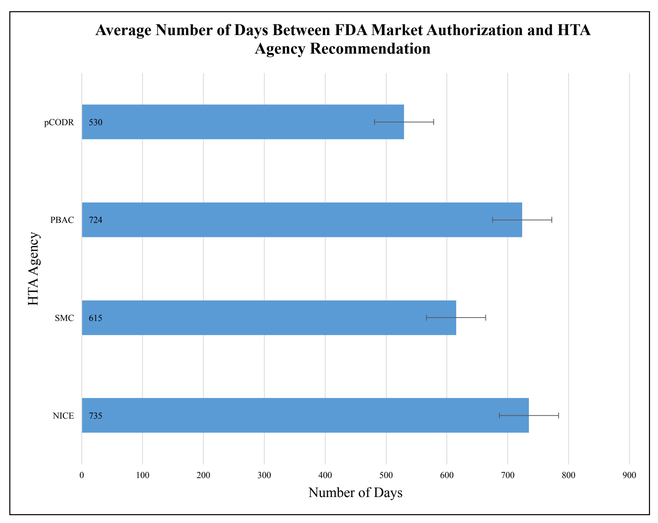
Drug INN Name	Drug Indication	FDA Market Authorization Date	EMA Market Authorization Date and Approval Type	NICE Reimbursement Decision Date and Days since EMA approval	SMC Reimbursement Decision Date and Days since EMA approval	TGA Market Authorization Date and Approval Type	PBAC Reimbursement Decision Date and Days since TGA approval	Health Canada Market Authorization Date and Approval Type	pCODR Reimbursement Decision Date and Days since Health Canada approval
Ceritinib	ALK+ NSCLC previously treated with Crizotinib	29/04/2014 BTD / AA / PR	05/06/2015 CMA	20/05/2016 350 Days	06/11/2015 154 Days	31/03/2016 MA	01/11/2016 215 Days	27/03/2015 CMA	21/03/2017 725 Days
Crizotinib	ALK+ NSCLC previously treated	26/08/2011 FTD / BTD / AA / PR	23/10/2012 MA	21/12/2016 1520 Days	06/09/2013 318 Days	27/09/2013 MA	01/11/2014 400 Days	25/04/2012 CMA	02/05/2013 372 Days
Osimertinib mesylate	EGFR T790M + NSCLC	13/11/2015 FTD / BTD / AA / PR	02/02/2016 MA* / AA	04/10/2016 245 Days ***	13/02/2017 377 Days	03/08/2016 MA	N/A	05/07/2016 CMA	01/04/2016 -95 Days **
Afatinib	EGFR TKI-naive with NSCLC with EGFR mutations	12/07/2013 FTD / PR	25/09/2013 MA	17/03/2014 173 Days	08/11/2013 44 Days	07/11/2013 MA	01/07/2015 601 Days	01/11/2013 MA	02/05/2014 182 Days **
Pembrolizumab	NSCLC with PD-L1 expression ≥1% TPS, previously treated with at least one prior chemotherapy regimen.	24/10/2016 BTD / AA / PR	29/07/2016 MA	02/12/2016 126 Days ***	09/12/2016 133 Days	16/04/2015 MA	01/03/2017 685 Days	16/04/2015 CMA	03/11/2016 567 Days
Nivolumab	Squamous NSCLC previously treated	04/03/2015 PR	28/10/2015 MA	N/A	10/06/2016 226 Days	12/01/2016 MA	01/11/2016 294 Days	26/02/2016 MA	03/06/2016 98 Days **
Pembrolizumab	Unresectable or metastatic melanoma	18/12/2015 BTD / AA / PR	17/07/2015 MA	09/10/2015 84 Days	09/10/2015 84 Days	16/04/2015 MA	01/03/2015 -46 Days	19/05/2015 CMA	16/11/2015 181 Days **
Nivolumab	Unresectable or metastatic melanoma	22/12/2014 FTD / BTD / AA / PR	19/05/2015 MA / AA	18/02/2016 275 Days ***	08/07/2016 385 Days	11/01/2016 MA	01/11/2015 -71 Days	25/09/2015 CMA	01/04/2016 189 Days **
Vemurafenib	BRAF-V600+ melanoma.	17/08/2011 FTD / PR	17/02/2012 MA / AA	02/11/2012 259 Days	08/11/2013 630 Days	10/05/2012 MA	01/03/2013 295 Days	15/02/2012 MA	01/06/2012 107 Days **
Ipilimumab	Melanoma previously untreated	25/03/2011 FTD / PR	13/07/2011 MA	12/06/2014 1065 Days	10/11/2014 1216 Days	04/07/2011 MA	01/11/2012 486 Days	10/09/2014 MA	22/12/2014 103 Days **
Pembrolizumab	Refractory classical Hodgkin lymphoma (cHL), or after relapse from 3 or more prior therapies.	14/03/2017 BTD / AA / PR	02/05/2017 MA	N/A	N/A	13/9/2017 MA	N/A	08/09/2017 CMA	N/A
Nivolumab	Refractory classical Hodgkin lymphoma after ASCT and brentuximab vedotin treatment	17/05/2016 BTD / AA / PR	21/04/2017 MA	02/06/2017 42 Days ***	09/06/2017 49 Days	30/5/2017 MA	N/A	N/A	N/A
Brentuximab Vedotin	Refractory CD30+ Hodgkin lymphoma after ASCT or 2 prior therapies	19/08/2011 FTD / BTD / AA / PR	25/10/2012 CMA	28/06/2017 1707 Days	05/09/2014 680 Days	19/12/2013 MA	01/11/2016 1048 Days	01/02/2013 CMA	29/08/2013 209 Days
Ibrutinib	Refractory mantle cell lymphoma	13/11/2013 FTD / BTD / AA / PR	24/07/2014 MA	N/A	08/07/2016 715 Days	20/04/2015 MA	01/11/2016 547 Days	24/06/2016 CMA	19/07/2016 25 Days
Ibrutinib	Chronic lymphocytic leukaemia previously treated	12/02/2014 FTD / AA / PR	24/07/2014 MA	25/11/2016 855 Days	10/03/2017 960 Days	20/04/2015 MA	01/11/2016 547 Days	17/11/2014 MA	05/03/2015 108 Days **
Ibrutinib	Waldenström's macroglobulinaemia previously treated or first-line when applicable	29/01/2015 BTD / PR	03/07/2015 MA	N/A	N/A	20/4/2015 MA	N/A	31/03/2016 MA	03/11/2016 217 Days

Legend: Green box: List; Yellow box: List with criteria; Red box: Do not list; Orange box: Not submitted; Grey box: Deferred/Under review; FTD: Fast Track Designation; BTD: Breakthrough Therapy Designation; AA: Accelerated Approval (FDA) or Accelerated Assessment (EMA); PR: Priority Review; MA: Marketing Authorisation; CMA: Conditional Marketing Authorisation; * = CMA to MA after conditions have been met; ** = Pre-NOC Submission (Parallel Processing); *** = Early Access to Medicines Scheme

Dates of regulatory decisions of the 16 drug-indication pairs and HTA recommendation dates for the HTA agencies in England (NICE), Scotland (SMC), Australia (PBAC) and Canada (pCODR): Regardless of early access scheme granted, timing of HTA recommendation varies widely.

Time difference between regulatory approval and HTA recommendation





Average length of time for HTA agencies in England, Scotland, Australia and Canada to publish an HTA recommendation following either MA in Europe, Australia or Canada (left-hand figure), or FDA approval (right-hand figure): FDA approval happened earlier than MA in other countries, with the exception of pembrolizumab in lung cancer and melanoma. The potential time frame from when the drug is in the market (FDA approval), and thus potentially could be accessed by patients, is longer than the amount of time between regulatory approval and HTA recommendation dates in other countries. Additionally, the speed at which pCODR reaches a recommendation becomes less significantly different to the time the other HTA bodies reach a decision when held to the baseline of FDA approval.

Clinical and economic evidence submitted

		Lung Cancer						Melanoma				Haematological Cancer					
		Ceritinib	Crizotinib	Osimertinib Mesylate	Afatinib	Pembrolizumab	Nivolumab	Pembrolizumab	Nivolumab	Vemurafenib	Ipilimumab	Pembrolizumab	Nivolumab	Brentuximab Vedotin	Ibrutinib (MCL)	Ibrutinib (CLL)	Ibrutinib (WM)
NICE	Pivotal Trial	ASCEND-2 & ASCEND-1	PROFILE 1007	AURA & AURA2	LUX-Lung 3 & LUX-Lung 6	KEYNOTE-010 & KEYNOTE-01	x	KEYNOTE 006 & KEYNOTE 001	CheckMate-066 & CheckMate-067 & CheckMate-037	BRIM3	CA184-024 & MDX010-08 & BREAK-3 & BRIM-3	x	CheckMate 205	SG035-0003	x	RESONATE	x
	Clinical Trial Design	NRCT	RCT	NRCT	RCT	RCT	x	RCT	RCT	RCT	RCT	x	NRCT	NRCT	x	RCT	x
	Trial Phase	Phase 1 & 2	Phase 3	Phase 1 & 2	Phase 3	Phase 1, 2 & 3	x	Phase 1 & 3	Phase 3	Phase 3	Phase 3	x	Phase 2	Phase 2	x	Phase 3	x
	Economic Analysis	CUA	CUA	CUA	CUA	CUA	x	CUA	CUA	CUA	CUA	x	CUA	CUA	x	CUA	x
	Risk Sharing Agreement	PAS	PAS	MAA	PAS	PAS	x	PAS	None	PAS	PAS	x	PAS	PAS	x	PAS	x
SMC	Pivotal Trial	ASCEND-2 & ASCEND-1	PROFILE 1007	AURA & AURA2	LUX-Lung 3 & LUX-Lung 6	KEYNOTE-010	CheckMate 017	KEYNOTE 006	CheckMate-066 & CheckMate-067 & CheckMate-037	BRIM3	CA184-024	x	CheckMate 205	SG035-0003	MCL-3001	RESONATE	x
	Clinical Trial Design	NRCT	RCT	NRCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	x	NRCT	NRCT	RCT	RCT	x
	Trial Phase	Phase 1 & 2	Phase 3	Phase 1 & 2	Phase 3	Phase 2 & 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	x	Phase 2	Phase 2	Phase 3	Phase 3	x
	Economic Analysis	CUA	CUA	CUA	CMA	CUA	CUA	CUA	CUA	CUA	CUA	x	CUA & CEA	CUA	CUA	CUA	x
	Risk Sharing Agreement	PAS	PAS	PAS	PAS	PAS	PAS	PAS	PAS	PAS	PAS	x	PAS	None	PAS	PAS	x
PBAC	Pivotal Trial	ASCEND-5	PROFILE 1007	x	LUX-Lung 3 & LUX-Lung 6	KEYNOTE-024	CheckMate 017	KEYNOTE 006	CheckMate-066	BRIM3	MDX010-020	x	x	SG035-0003	MCL-3001	RESONATE	x
	Clinical Trial Design	RCT	RCT	x	RCT	RCT	RCT	RCT	RCT	RCT	RCT	x	x	NRCT	RCT	RCT	x
	Trial Phase	Phase 3	Phase 3	x	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	x	x	Phase 2	Phase 3	Phase 3	x
	Economic Analysis	CMA	CUA	x	CUA	CEA	CEA	CUA	CMA	CUA	CUA & CEA	x	x	CUA	CUA	CEA	x
	Risk Sharing Agreement	RSA	MES	x	None	None	None	MES	MES	None	P4P	x	x	RSA	None	None	x
CADTH	Pivotal Trial	ASCEND-5	PROFILE 1007	AURA3	LUX-Lung 3 & LUX-Lung 6	KEYNOTE-010	CheckMate 017	KEYNOTE 006 & KEYNOTE 002	CheckMate-066 & CheckMate-067 & CheckMate-037	BRIM-3	CA184-024	x	x	SG035-0003	MCL-3001	RESONATE	PCYC-1118E & PCYC-1127
	Clinical Trial Design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	x	x	NRCT	RCT	RCT	NRCT
	Trial Phase	Phase 3	Phase 3	Phase 3	Phase 3	Phase 2 & 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	x	x	Phase 2	Phase 3	Phase 3	Phase 2 & 3
	Economic Analysis	CUA & CEA	CUA & CEA	CUA	CUA & CEA	CUA & CEA	CUA & CEA	CUA & CEA	CUA & CEA	CUA & CEA	CUA	x	x	CUA & CEA	CUA	CUA & CEA	CUA & CEA
	Risk Sharing Agreement	PA	PA	PA	PA	PA	PA	PA	PA	PA	PA	x	x	PA	PA	PA	None

Type of evidence submitted to the HTA body for approval, type of economic model used, and pricing arrangements negotiated: Although most HTA bodies received submissions with similar clinical and economic evidence, recommendation outcomes vary greatly.

Uncertainties most commonly discussed across countries

Clinical Uncertainties

- Lack of adequate clinical trials to show the comparative effectiveness to what is currently the standard of care (SoC)
- Inability of clinical trials to establish a clear net clinical benefit
- Uncertainty about whether adverse events are more or less tolerable than current best practice

Economic Uncertainties

- Uncertainty around the setup of the economic analysis model and the ICER range
- Uncertainty around the comparators selected

Top five social-value judgements considered by HTA agencies

England - NICE

1. Unmet clinical need
2. Special criteria (end-of-life, orphan)
3. Extension of life
4. Innovative compound
5. Higher comparative safety

Scotland - SMC

1. Unmet clinical need
2. Special criteria (end-of-life, orphan)
3. Impact on patient's work/activities
4. Impact on the society/health budget
5. Innovative compound

Australia - PBAC

1. Unmet clinical need
2. Impact on the society/health budget
3. Extension of life
4. Quality of life
5. Higher comparative safety

Canada - pCODR

1. Unmet clinical need
2. Emotional burden on carers
3. Impact on the society/health budget
4. Quality of life
5. Higher comparative safety

Social value judgements can be seen as the reasoning behind recommendation variations. PBAC discussed social values the most infrequently, and rejected the highest amount of drugs among the study agencies. PBAC rejections were all due to issues of cost-effectiveness, often in the face of uncertain clinical benefit.

Cohen's kappa scores measuring inter-rater agreement

	NICE	SMC	PBAC	pCODR
NICE	x	0.7333	-0.2195	-0.0526
SMC	x	x	-0.2195	-0.0526
PBAC	x	x	x	-0.1940
pCODR	x	x	x	x

Cohen's kappa scores seen were calculated to provide a statistical measure of agreement between the HTA agencies in interpreting the same evidence. Substantial agreement was found between NICE and SMC. None of the other Cohen kappa scores had any agreement between HTA agencies and their respective recommendations across drug-indication pairs. Although kappa values are not as robust as would be preferred, their values highlight the low level of agreement between the various HTA body recommendations.

Conclusions

- Despite the early regulatory approval schemes, HTA agencies do require robust clinical and economic evidence that would allow a positive coverage recommendation.
- However, social value judgements can act as decision modifiers enabling HTA agencies to arrive at positive – mostly restricted - recommendations.

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Author affiliations: [1] London School of Economics and Political Science, UK