Drivers of health technology assessment decisions for relapsed-refractory multiple myeloma treatments; a country comparison.

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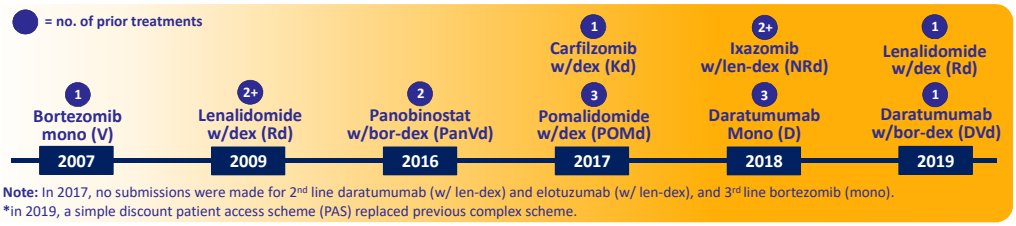
Introduction

- Multiple myeloma (MM) is a B-cell malignancy, which leads to malignant plasma cell accumulation, mainly in bone marrow. Symptoms include: bone pain, fractures, spinal cord compression, anaemia, repeated infections, hypercalcaemia, unusual bleeding, thickened blood, and kidney disorders[1,2].
- Survival of patients with MM has improved in recent years due to the introduction of a number of new therapies, however, MM remains an incurable malignancy. Most patients experience relapse or are refractory to treatment (relapsed and/ or refractory MM; RRMM)[3].
- Furthermore, therapies for RRMM can elicit several severe adverse events, thus, tolerability is a key concern[5].

Figure 1: Timeline of NICE RRMM health technology appraisals



Note: In 2017, no submissions were made for 2nd line daratumumab (w/ len-dex) and elotuzumab (w/ len-dex), and 3rd line bortezomib (mono).
*in 2019, a simple discount patient access scheme (PAS) replaced previous complex scheme.

Objectives

- To analyse the variations between NICE (England and Wales), SMC (Scotland), HAS (France), G-BA (Germany), PBAC (Australia), and CADTH (Canada) HTA recommendations for RRMM treatments.
- To identify the key drivers of decisions.

Methods

- The SIRIUS Oncology HTA database was used to identify all RRMM assessments (2nd, 3rd, and 4th-line treatments for MM) made by NICE from 2010 to August 2019. The database contains data for appraisals equivalent to NICE for the SMC, HAS, G-BA, PBAC, and CADTH.

Results

Table 1 summarises the decisions made by the HTA bodies, classified in a traffic light system based on decision (not reimbursement).

Table 1: Decisions made by HTA bodies

RRMM therapy	NICE	SMC	HAS	G-BA	PBAC	CADTH
Lenalidomide (w/ dex)[a]	✓[d]	✓[e]	-	-	-	-
Daratumumab (w/ bor-dex)[b]	✓	✓[e]	ASMR IV[f]	Considerable added benefit	✗	✓
Daratumumab (mono)	✓[d]	✓[e]	ASMR V[f]	Not proven[h]	-	✗
Ixazomib (w/ len-dex)	✓[d]	-	ASMR V[f]	Non-quantifiable added benefit	-	✗
Carfilzomib (w/ dex)	✓[d]	✓	ASMR III[f]	Considerable added benefit	✓	✓
Daratumumab (w/ len-dex)[b]	-*	-*	ASMR IV[f]	Considerable added benefit	✗	✓
Bortezomib (monotherapy)	-*	Pre-2010	Pre-2010	Pre-2010	Pre-2010	Pre-2010
Elotuzumab (w/ len-dex)[c]	-*	-	-	Hint of minor benefit	-	-
Pomalidomide (w/ dex)	✓[d]	✓	ASMR III[f]	Considerable added benefit	✓	✓
Panobinostat (w/ bor-dex)	✓	✓	ASMR V[g]	Non-quantifiable added benefit	-	-

[a]Corresponds to NICE TA586, 2019 (lenalidomide with dex after treatment with bor); [b]HAS, G-BA, PBAC, and CADTH considered daratumumab combination therapies in one submission; [c]Manufacturer did not intend to seek UK reimbursement due to cost-effectiveness thresholds[5]; [d]Optimised NICE recommendations; [e]Restricted use within NHS Scotland; [f]SMR important; [g]SMR moderate; [h]Added benefit not proven, but approved under "special conditions".

Key:
- No submission
-* Terminated appraisal
✓ Positive decision (All HAS decisions either "recommend inclusion on list of reimbursable products" or "approval for hospital treatment").
✗ Negative decision
✓ Positive decision, under special conditions [inc. NICE Cancer Drugs Fund (CDF), PBAC Highly Specialised Drugs Program (HSDP), and G-BA "special conditions].

NICE

Four positive decisions (PAS) and three positive through special conditions of the CDF.

- Four positive decisions (Rd, Kd, POMd, PanVd) providing the companies provide discount agreed in the PAS.
- Three positive through **CDF** (DVd, D, NRd), while mature OS data collected (MAA).
- The committee recognised the **need for effective and tolerable treatments for RRMM** for 3rd line, onwards; Pomalidomide was less effective than panobinostat but is an **oral treatment with lower toxicity**. Panobinostat had **improved OS and PFS**, but limitations in MAIC.
- For lenalidomide, the committee appreciated **the unmet need for a 2nd line treatment**.
- For carfilzomib, **key drivers were PFS benefit, cost-effectiveness, and end-of-life benefit**.

NICE key drivers: Cost-effectiveness (PAS required in 4/7 appraisals), unmet need.

SMC

All six appraisals had a positive decision (PAS in five).

- **SMC were willing to accept higher costs and greater uncertainty in cost-effectiveness estimates because therapies have orphan status** (all but POMd).
- **Key drivers were: increased time to progression** for lenalidomide appraisal and **improved PFS** in the other five appraisals which were all accepted providing continued availability of the PAS.
- Three appraisals were "**accepted for restricted use**" (DVd, D, Rd).
- Three appraisals were resubmissions: lenalidomide was re-positioned for 1 prior therapy (i.e. 2nd line); daratumumab monotherapy resubmission addressed concerns over comparative clinical data; reason for pomalidomide resubmission not stated.

SMC key drivers: Orphan designation, improved PFS, cost-effectiveness (PAS required in 5/6 appraisals).

HAS

All seven appraisals had a positive decision, with varied SMR and ASMR ratings.

- **Fatal nature of RRMM with 3-5 year survival rates was a key driver** in five decisions: one ASMR III (Kd); two with ASMR IV (DVd, DRd); two with ASMR V (D, NRd) (all had an SMR of important).
- Key driver in panobinostat appraisal was that **treatment was needed as a last resort for patients in "therapeutic impasse"** (SMR of moderate, AMSR V).
- **Modest gain in PFS** in pomalidomide appraisal and **no valid alternative drug therapy at this treatment stage** was a key driver (SMR of important and ASMR III).
- All drugs noted to have **"curative intent"**.

HAS key drivers: Fatal nature of disease, no alternative treatments.

G-BA

Eight positive decisions; one of which under special conditions. Variation in added benefit shown.

- In the daratumumab monotherapy appraisal, added benefit was not proven (indicates negative decision). However, it was **approved for use only under "special conditions"**. Use of a **single-arm trial design was criticised**, alongside use of non-adjusted indirect comparison (IC).
- **Increased OS was a key driver** in four appraisals (DVd, DRd, Kd, POMd) with an indication of considerable added benefit.
- **Improved PFS and OS from interim analysis** for elotuzumab (hint of minor added benefit).
- OS not significant for panobinostat or ixazomib (non-quantifiable added benefit). **PFS improved** for panobinostat.

G-BA key drivers: Improved OS and PFS, trial and IC design.

PBAC

Two positive decisions under special conditions (HSDP) and two negative.

- Two negative decisions (DVd, DRd) were driven by **very high and uncertain ICERs** and clinician preference to have both daratumumab combination therapies available alongside monotherapy (no submission).
- Carfilzomib and pomalidomide were positive decisions, approved through Section 100 Highly Specialised Drugs Program (HSDP). Both were resubmissions; **economic concerns from original submission had been addressed**.
- **Key drivers in positive decisions were superior comparative efficacy (OS, PFS) and cost-effectiveness**, despite different/ slightly inferior safety profiles to comparators.

PBAC key drivers: Improved OS and PFS, cost-effectiveness (ICERs).

CADTH

Four positive decisions under special conditions and two negative.

- Negative decisions (D, NRd) driven by **considerable uncertainty over survival outcomes** (both) **and QoL** (D only). Net clinical benefit not found and uncertainty in the clinical data led to uncertain cost-effectiveness estimates.
- **The four positive decisions** (DVd, DRd, Kd, POMd) **required improvement to be made in cost-effectiveness**. Adverse effects manageable and improvement/ maintenance of QoL noted. In three appraisals, there was **improved PFS and trend towards OS benefit**. For pomalidomide, **significant improvements found in OS and PFS**.

CADTH key drivers: Improved OS and PFS, cost-effectiveness.

Conclusions

- In each of the scope countries, RRMM patients have access to at least three reimbursed treatments; however, despite regulatory approval being granted for efficacious treatments, there is inconsistent access across countries, reducing the number of treatment options for patients with RRMM.
- Cost-effectiveness is a key driver in the UK, Australia, and Canada; PASs were required in four NICE appraisals and five SMC appraisals, whilst improvements in cost-effectiveness were required by CADTH.
- Improvements in OS and PFS were key to SMC, G-BA, PBAC, and CADTH decisions. MAAs in the UK allowed patient access whilst mature clinical data are collected.
- The need for effective and tolerable treatments was important for NICE and HAS, whilst in Scotland, the SMC were willing to accept higher costs because therapies had orphan designation (all but pomalidomide w/ dex).
- Negative decisions and positive decisions under special conditions stemmed from uncertainty around clinical outcomes, leading to cost uncertainties. For G-BA, a negative outcome was driven by a single-arm trial design. For PBAC and CADTH, immature clinical data leading to cost-effectiveness uncertainties led to two negative decisions by each body.

References:
1. Avet-Loiseau H., 2019. Blood, 133(7), 621.
2. NHS multiple myeloma symptoms, 2018. www.nhs.uk/conditions/multiple-myeloma/symptoms/
3. Nijhof I.S., 2018. *Drugs*, 78(1):19-37.
4. Nassim M., 2019. HemaSphere, 3(S1), 318.
5. The Pharma Letter, 2016. www.thepharmaletter.com/article/b-ms-decide-not-to-submit-emplicitt-for-reimbursement-in-uk

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Abbreviations: ASMR, improvement in actual benefit; AUS, Australian dollar; bor, bortezomib; CADTH, Canadian Agency for Drugs and Technologies in Health; carf, carfilzomib; CDF, Cancer Drugs Fund; dara, daratumumab; dex, dexamethasone; elo, elotuzumab; EMA, European Medicines Agency; G-BA, Gemeinsamer Bundesausschuss [German HTA body]; HAS, Haute Autorité de Santé [French HTA body]; HSDP, Highly Specialised Drugs Program; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; IC, indirect comparison; inc., including; ixaz, ixazomib; len, lenalidomide; MAA, managed access agreement; MAIC, matching adjusted indirect comparison; MM, multiple myeloma; mono, monotherapy; NICE, National Institute for Health and Care Excellence; OS, overall survival; pano, panobinostat; poma, pomalidomide; PAS, patient access scheme; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression free survival; QALY, quality-adjusted life year; QoL, quality of life; RRMM, relapsed-refractory multiple myeloma; SMC, Scottish Medicine Consortium; SMR, actual benefit; w/, with; UK, United Kingdom.

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