Technology Guidance

Daratumumab

for treating newly diagnosed light chain (AL) amyloidosis

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) for inclusion on the MOH List of Subsidised Drugs for treating patients with newly diagnosed light chain (AL) amyloidosis in view of the uncertain extent of clinical benefit and uncertain cost-effectiveness compared with the current treatment option.

Clinical indication, subsidy class and MediShield Life claim limit for daratumumab for AL amyloidosis are provided in the Annex.

Published: 8 February 2023

Factors considered to inform the recommendations for funding

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone (DBCd) for treating newly diagnosed systemic light chain (AL) amyloidosis. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical and patient experts from the public healthcare institutions and local patient and voluntary organisations. Published clinical and economic evidence for daratumumab was considered in line with its registered indication. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of daratumumab and provided clinical advice on its appropriate and effective use based on the available evidence.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. Systemic AL amyloidosis refers to a group of disorders in which the plasma cells produce misfolded immunoglobulin light chains which form amyloid fibrils that deposit in organs and cause organ dysfunction. The condition usually affects the heart and kidneys, as well as the nervous system.

2.2. The Committee noted that approximately 44 patients are diagnosed with AL amyloidosis each year in Singapore. The Committee noted that DBCd is a HSA-approved treatment for AL amyloidosis; prior to its approval, bortezomib in combination with cyclophosphamide and dexamethasone (BCd) was commonly used to treat this condition in local practice.

2.3. The Committee heard that local clinical experts supported the use of haematological response rates as surrogate endpoints for survival for patients with AL amyloidosis.

2.4. The Committee considered testimonials from local patient experts about their experience with AL amyloidosis and the treatments they have received. The Committee heard that these patients experienced a wide range of symptoms that had a significant negative impact on their daily lives, such as bowel problems, lethargy, weakness, nausea, loss of weight and appetite, and swollen legs. The Committee noted that the cost of transport to receive treatment, and treatment affordability including the cost of medications, imaging tests and hospitalisation were common concerns expressed by the patients.

Clinical effectiveness and safety

3.1. The Committee reviewed the available clinical evidence from the pivotal randomised, open-label trial (ANDROMEDA) which compared DBCd with BCd in 388 patients with newly diagnosed AL amyloidosis. Between-group comparisons showed a statistically significant difference in the primary outcome (haematological complete response rate) favouring DBCd over BCd. However, the results for both overall survival (OS) and major organ deterioration-progression free survival (MOD-PFS) were immature. Compared with BCd, the cross-over adjusted MOD-PFS was longer with DBCd and the Kaplan-Meier curves separated at approximately 7 months, suggesting a treatment benefit of DBCd, but the result did not cross the prespecified stopping boundary.

3.2. In terms of safety, the Committee noted that serious treatment emergent adverse events (TEAE) were numerically higher in the DBCd arm compared with BCd. The most commonly reported grade 3 and above adverse events were lymphopenia, pneumonia, cardiac failure, diarrhoea, syncope and neutropenia.

3.3. Overall, the Committee agreed that DBCd was superior to BCd based on haematological response rate and MOD-PFS, however the magnitude of survival benefit associated with DBCd remained uncertain given the immature trial data. In terms of safety, the Committee agreed that DBCd was inferior to BCd.

Cost effectiveness

4.1. The company of daratumumab was invited to submit a value-based pricing (VBP) proposal for funding consideration.

4.2. The Committee reviewed a cost effectiveness analysis conducted by ACE comparing DBCd with BCd for treating patients with newly diagnosed AL amyloidosis. At the price proposed by the company, results showed that DBCd was associated with a base-case incremental cost-effectiveness ratio of more than SG$105,000 per quality-adjusted life year gained compared with BCd.

4.3. The Committee noted that the magnitude of clinical benefit remained a key uncertainty of the model, given the immature survival data and the surrogacy relationship assumed between haematological response and overall survival. Overall, the Committee concluded that DBCd was unlikely to represent a cost-effective option for newly diagnosed AL amyloidosis in the local setting based on the company's proposal.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million to less than SG$3 million in the first year of listing daratumumab on the MOH List of Subsidised Drugs for newly diagnosed AL amyloidosis.

Additional considerations

6.1. The Committee acknowledged that, contingent on funding, the company of daratumumab had agreed to implement a patient assistance programme (PAP) for eligible patients which would provide further savings to patients.

Recommendations

7.1. Based on available evidence, the Committee recommended not listing daratumumab (in combination with bortezomib, cyclophosphamide and dexamethasone) on the MOH List of Subsidised Drugs for treating patients with newly diagnosed AL amyloidosis in view of the uncertain extent of clinical benefit and uncertain cost effectiveness compared with the current treatment option based on the company's proposal.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class	MediShield Life claim limit per month (implementation date)
Daratumumab 1800 mg/15 mL solution for subcutaneous injection	Daratumumab in combination with bortezomib, cyclophosphamide and dexamethasone for patients with previously untreated light chain (AL) amyloidosis. Treatment with daratumumab should be continued until disease progression or for a maximum of 24 cycles.	Not recommended for subsidy	$2000 (1 Apr 2023)