For Public

Lenalidomide for treating multiple myeloma after 1 prior treatment with bortezomib (part-review of TA171) STA

5th Appraisal committee meeting, 23 March 2017

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Company: Celgene

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Evidence Review Group: PenTAG with Matrix

Chair: Amanda Adler

Key issues for consideration

- Do the Committee's conclusions remain the same for:
  - Comparators (melphalan, bortezomib)?
  - Modelling approach (crude or proxy)?

- Is there an unmet need?

Lenalidomide (Revlimid)

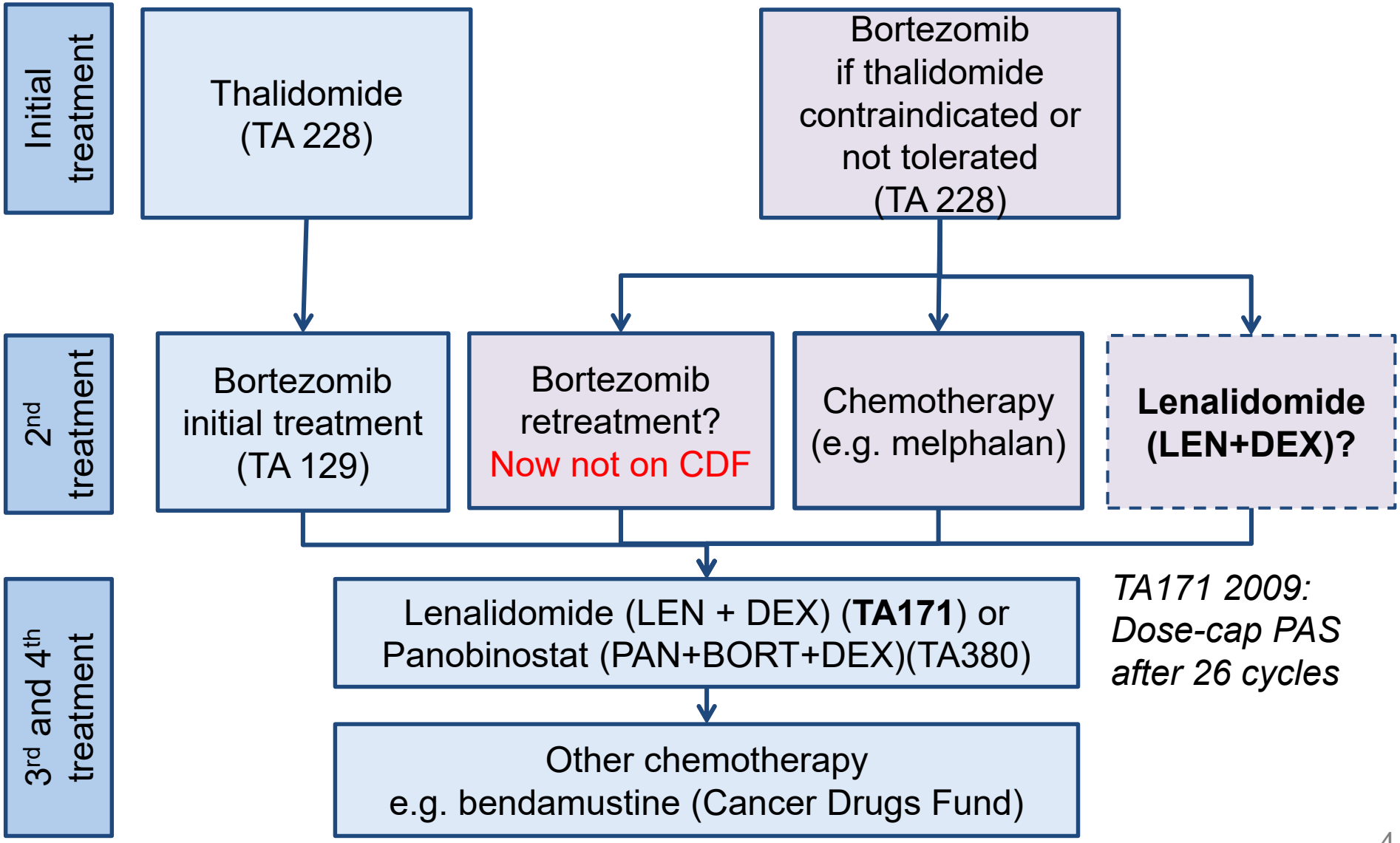
- Marketing authorisation: combined with dexamethasone for adults who had at least 1 prior therapy*

History of TA171	
2009	• Lenalidomide recommended after ≥ 2 therapies • PAS: company pays for treatment after 26 cycles of treatment
2012	• NICE decides to review lenalidomide after 1 prior therapy with bortezomib • Rationale: treatment pathway changed & new evidence

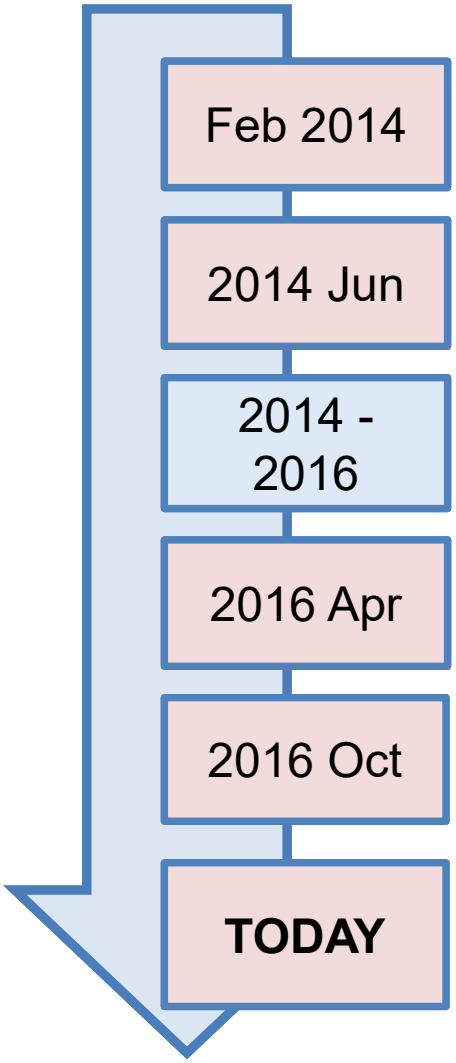
* In 2015: the marketing authorisation was extended to include lenalidomide monotherapy for adult patients with previously untreated multiple myeloma who are not eligible for transplant. This will be considered in a NICE technology appraisal (ID474), which is currently suspended

Multiple myeloma treatment pathway

for people unsuitable for stem cell transplantation with high dose chemotx



History of this appraisal



ACD1: not recommended: complex PAS did not apply

ACD2: not recommended: complex PAS did not apply

Appraisal suspended; new evidence submitted
TA171 PAS (26 cycle dose cap) extended to this indication

No ACD/FAD: NICE requested additional evidence

ACD3: not recommended

New consultation comments
No new data, no change in PAS & no changes to modelling

Decision problem

	NICE scope	Company decision problem
Pop.	Adults with myeloma contraindicated to thalidomide whose disease progressed after bortezomib (+ not for stem cell transplant)	
Comp.	1. Chemotherapy: melphalan, vincristine, cyclophosphamide, doxorubicin 2. Bortezomib • Monotherapy • + dexamethasone 3. Bendamustine	1. Melphalan 2. Previous modelling included bendamustine & bortezomib, current analyses focus on melphalan
Outcomes	• Progression-free survival • Response rates • Time to next treatment • Mortality • Adverse effects of treatment • Health-related quality of life	Did not provide time to next treatment (not reported in main trial)
Subgroups	None	

Committee concluded taken later in treatment pathway→ **not** a comparator

Bortezomib retreatment **no longer** on CDF. Discussed at 3rd + 4th meeting. Consultation comments regarding this today

Sources of clinical evidence: survival

No trials comparing lenalidomide with chemotherapy

	Lenalidomide		Chemotherapy
Analysis	Pooled 2 RCTs MM009/10		Petrucci et al 1989
Population	About 35% of patients had 1 prior therapy and about 65% had had at least 2 prior therapies		Patients with disease relapsed or refractory to chemotherapy. # of prior therapies was not reported
Treatment	Lenalidomide + dexamethasone n=353	Placebo + dexamethasone n=351	Melphalan + prednisolone n=34
1°endpoint	PFS		N/A
PFS*	11.1 months	4.6 months	Not reported
OS*	38.0 months	31.6 months	8 months

* median

Approaches to overcome lack of trial head-to-head data

1. **Crude indirect comparison:**
   - Compares
     - lenalidomide arms from pooled MM009/10 trials with
     - melphalan data from observational study (Petrucci 1989)
   - Committee identified limitations and implausible results, including:
     - modelled survival benefit LEN+DEX vs. melphalan = 32.4 months whereas
     - trial survival benefit LEN+DEX vs. placebo + DEX = 6.4 months
2. **Proxy comparison**
   - Instead:
     - assume dexamethasone and chemotherapy equally effective and
     - use data from RCTs (as presented in 4th committee meeting)

Committee considerations crude vs. proxy approach

	Crude	Proxy
Risk of bias	High: different populations, confounding	Low: large randomised comparison
Treatments after chemo	Need to adjust for subsequent treatments (company assumed all people had 3rd line lenalidomide if not had before) → illogical results (compared with bortezomib)	48% people in dexamethasone arms had 3rd line lenalidamide→ adjustment unnecessary
Estimating effect size between lenalidomide and chemo	Needed to estimate HRs from median values (statistical approach technically incorrect)	Patient level data available

Assuming clinical effectiveness dexamethasone = chemotherapy

- Facon et al 2006 randomised trial melphalan (n=122) vs. dexamethasone (n=127):
- ERG: Facon showed
  - longer progression free survival with melphalan (22.4 months) than with dexamethasone(12.6 months) and patients not representative of population for appraisal.
  - Longer, non-significant overall survival for melphalan (but underpowered?)
  - Overall ERG preferred proxy method over crude method
- Committee: chemotherapy expected to be more effective than dexamethasone → proxy method favours lenalidomide→ may underestimate ICER vs. melphalan
- Committee concluded to use proxy approach

Lenalidomide vs melphalan proxy approach: results company and ERG

Analysis	ICER
Company base case*	[redacted]
ERG base case • shorter PFS for dexamethasone (melphalan) • company model had implausibly long extrapolated PFS tail for dexamethasone ↓ PFS→ ↓ time on melphalan → ↓ melphalan benefit	[redacted]

* ERG identified an error in how company incorporated melphalan costs using proxy approach. Company agreed with ERG's correction. Results include correction.

Key committee conclusions in ACD3

Conclusion	ACD
Bortezomib **not** comparator – heard from NHS England retreatment not commissioned	4.3
Cytotoxic chemotherapy **is** comparator – heard from clinical experts that is a treatment option after 1st relapse	4.3
Modelling based on crude indirect comparison • High risk of bias, relied on technically incorrect statistical techniques • Adjusting for subsequent treatments gave illogical results • Lacked external validity • Not suitable for decision making	4.10 -4.13
Modelling assuming melphalan = dexamethasone (proxy method) preferable, but may **underestimate** ICER lenalidomide vs. melphalan	4.14- 4.15
Most plausible ICER, above £[redacted]- £[redacted]K per QALY gained	4.20
Did not meet criteria for Cancer Drugs Fund. Clinical evidence from MM-009/010 for lenalidomide relatively mature (e.g. median overall survival LEN-DEX observed at 50 months MM-009)	4.23
End of life criteria **not** met – life expectancy >24 months	4.25

Consultation comments

Comments were received from:

- Company – no new data or modelling
- UK Myeloma Forum*
- Myeloma UK

Themes

1. Relevant 2nd-line comparators after bortezomib
2. Crude vs proxy approaches in absence of head-to-head data
3. Unmet need

* Comments endorsed by: National Cancer Research Institute; Association of Cancer Physicians; Royal College of Physicians & Royal College of Radiologists

2nd-line comparators after bortezomib

Comparators: chemotherapy

- "…there is absolutely no evidence in the modern era to suggest that conventional chemotherapy is a suitable 2nd line treatment". (UK Myeloma Forum)

Recap of committee conclusions bortezomib as comparator

Jan 2016 retreatment with bortezomib removed from CDF

NHS England (NHSE) →NICE: We do not commission bortezomib retreatment for patients relevant to this appraisal

Company: not funded→ not comparator (provided supporting email from NHSE pharmacist to NHS clinician)

Heard not funded, but clinicians considered it a comparator. **Concluded:**

- If disease suitable for bortezomib retreatment: comparators bortezomib and chemotherapy
- If retreatment not suitable or not available: comparator is chemotherapy

Concluded: no longer commissioned → no longer a comparator

ACM = Appraisal Committee meeting

Comments
Comparators: bortezomib 2nd line

- "..change in commissioning for bortezomib retreatment communicated from NHS England appears to be in direct contradiction of NICE TA129" (UK Myeloma Forum)
  - N.B. TA 129 bortezomib 2nd line "having received one prior therapy" preceded TA228 which recommends bortezomib 1st line. Hence bortezomib 'retreatment' as a 2nd treatment not considered in TA129
- "regardless of access to bortezomib a large number of patients would not be suitable to receive 2nd line bortezomib due to poor depth or duration of response to 1st line bortezomib or because of prior bortezomib associated toxicity" (UK Myeloma Forum)

⊙ ***Does the Committee's conclusion that cytotoxic chemotherapy is a comparator but bortezomib is not a comparator remain the same?***

Crude indirect comparison using observational data or using randomised control trial with high-dose dexamethasone as a proxy

Company comments: clinical effectiveness data lenalidomide vs. melphalan

- “Celgene agree that the Petrucci 1989 data is uncertain due to the issues highlighted by the committee and ERG in the ACD”
- “Petrucci 1989 data whilst subject to limitations should not be discounted fully as only source of melphalan data available”
- Company sourced data from Haematological Malignancy Research Network (HMRN) registry of northern England, but patients much older than trial patients, little data on patient characteristics making adjusting for covariates impossible

Company comments: crude vs. proxy approach strengths and limitations

Assumption clinical effectiveness dexamethasone = melphalan "uncertain"

- "[Facon 2006] was underpowered and we cannot be certain that melphalan and dexamethasone would have equal outcomes"
- N.B. If not equal, would likely favour lenalidomide

Calculating hazard ratios from median values in naïve approach

- Reiterated: "analysis based on Petrucci 1989 dataset which uses digitised KM curves and the Guyot 2012 algorithm to generate simulated individual patient level data ….produced a very similar ICER (£[redacted]) to that using the 'crude HR' from the medians"
  - N.B. discussed by Committee at 3rd meeting
- Company suggest this method overcomes limitations of 'crude HR'
  - N.B. does not overcome confounding

Company comments: Treatment after lenalidomide in trials (proxy approach) may not reflect UK clinical practice

- 48% patients on dexamethasone in MM trials went on to have lenalidomide 3rd line
- Company's experts say all patients would receive lenalidomide 3rd line (if they did not have it before).
  It is standard of care at 3rd line
  - N.B. might improve survival for melphalan→ ↑ ICER?
- Adjusting for 3rd treatments resulted in plausible results lenalidomide vs. melphalan comparison
  - post-progression life years without 3rd line lenalidomide 0.72;
  - with 3rd line lenalidomide 2.73.
  - Reiterated that Committee concerned with lenalidomide vs. bortezomib

⊙ ***Has the committee seen anything to change its conclusions on the modelling approach?***

Unmet need

Unmet need

- "(there is an) unnecessary and illogical gap in the myeloma treatment pathway". (Myeloma UK)
- "For myeloma patients at first relapse, who cannot have thalidomide or [bortezomib], there is no available novel agent combination for them to receive […]
- "As a consequence [patients are] receiving a sub-optimal treatment combination at an extremely critical time in their disease pathway [and] they may not fully benefit from approved NICE guidance further down the treatment pathway". (Myeloma UK)
- "Lenalidomide should be available for 2nd line patients who have previously been treated with bortezomib and for whom further bortezomib is not suitable…[the draft recommendation] is likely to have an adverse impact on patient outcomes" (UK Myeloma Forum)

⊙ ***What is the Committee's view on the unmet need for 2nd line treatment?***

Issues for discussion

- Has the committee seen any new evidence to change its decision:
  - Comparators?
  - Approach to modelling (crude, proxy)?
- Is there an unmet need?