For public

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

6th Appraisal committee meeting, 1st February 2018

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Company: Celgene

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Evidence Review Group: PenTAG with Matrix

Chair: Amanda Adler

Key issues for consideration

- How should the committee approach the company's case for "wider cost savings"?
  - What uncertainties surround calculating wider cost savings?
  - Are the estimates of the number of people who will take lenalidomide second line plausible?
- How should the committee take into account unmet need in its decision making?

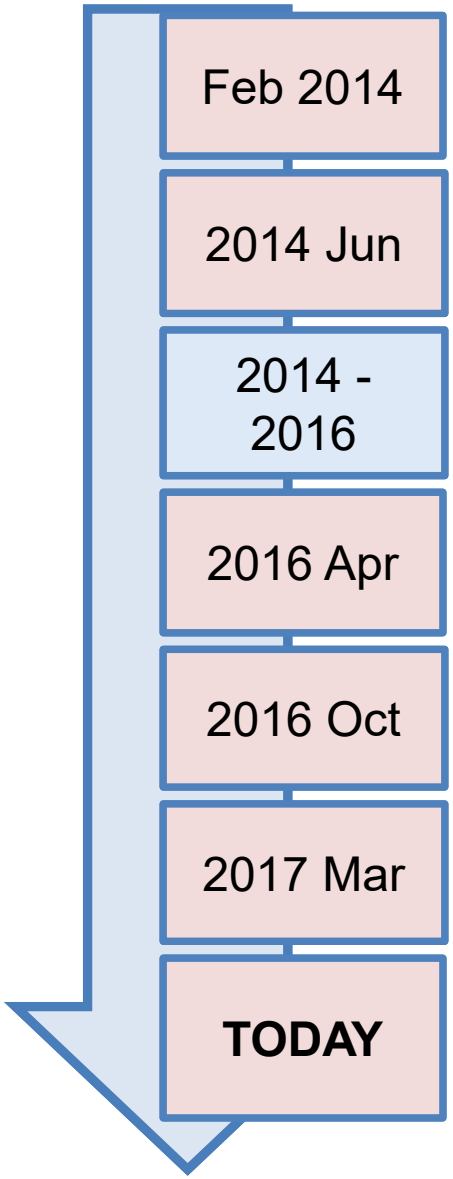
Lenalidomide (Revlimid)

Marketing authorisation and background

2007	• Marketing authorisation for multiple myeloma: combined with dexamethasone for adults who had at least 1 prior therapy
2009	• Lenalidomide recommended by NICE **only** after 2 or more therapies (met end of life criteria at this point in treatment pathway) (TA171) • PAS: company pays for treatment after 26 cycles of treatment
2012	• NICE decides to review lenalidomide after 1 prior therapy with bortezomib (i.e. 2nd line) – THIS appraisal (ID667) • Rationale: treatment pathway changed + new evidence
2014	• Appraisal starts (see next slide) - today's appraisal (ID667)
2015	• Marketing authorisation extended to include lenalidomide + dexamethasone for adult patients with previously untreated multiple myeloma (i.e. 1st line) not eligible for transplant. Committee B considering this today (ID474) for first time
2017	• Marketing authorisation extended to include lenalidomide monotherapy for newly diagnosed multiple myeloma having undergone autologous stem cell transplant (ID475- suspended)

History of this appraisal

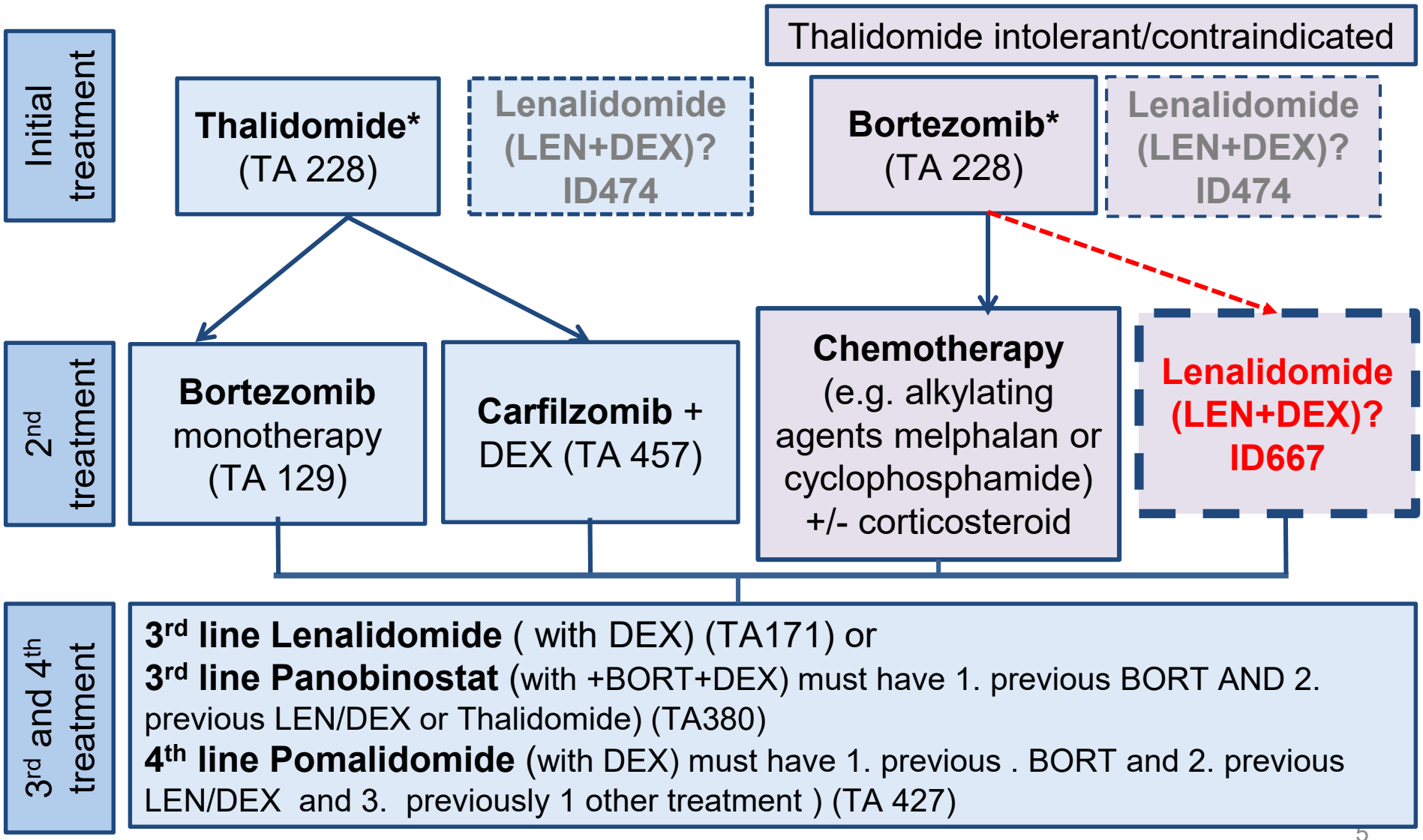
ACD = appraisal consultation document, FAD = final appraisal determination, PAS = patient access scheme



Feb 2014	ACD1: not recommended: so complex PAS did not apply
2014 Jun	ACD2: not recommended: so complex PAS did not apply
2014 - 2016	Appraisal suspended; company submitted new evidence TA171 PAS (26 cycle dose cap) extended to this indication
2016 Apr	No ACD/FAD: NICE requested additional evidence
2016 Oct	ACD3: not recommended
2017 Mar	FAD not issued: company proposed new PAS
TODAY	**No changes to committee's preferred modelling approach, but new PAS and company has modelled "wider benefits"**

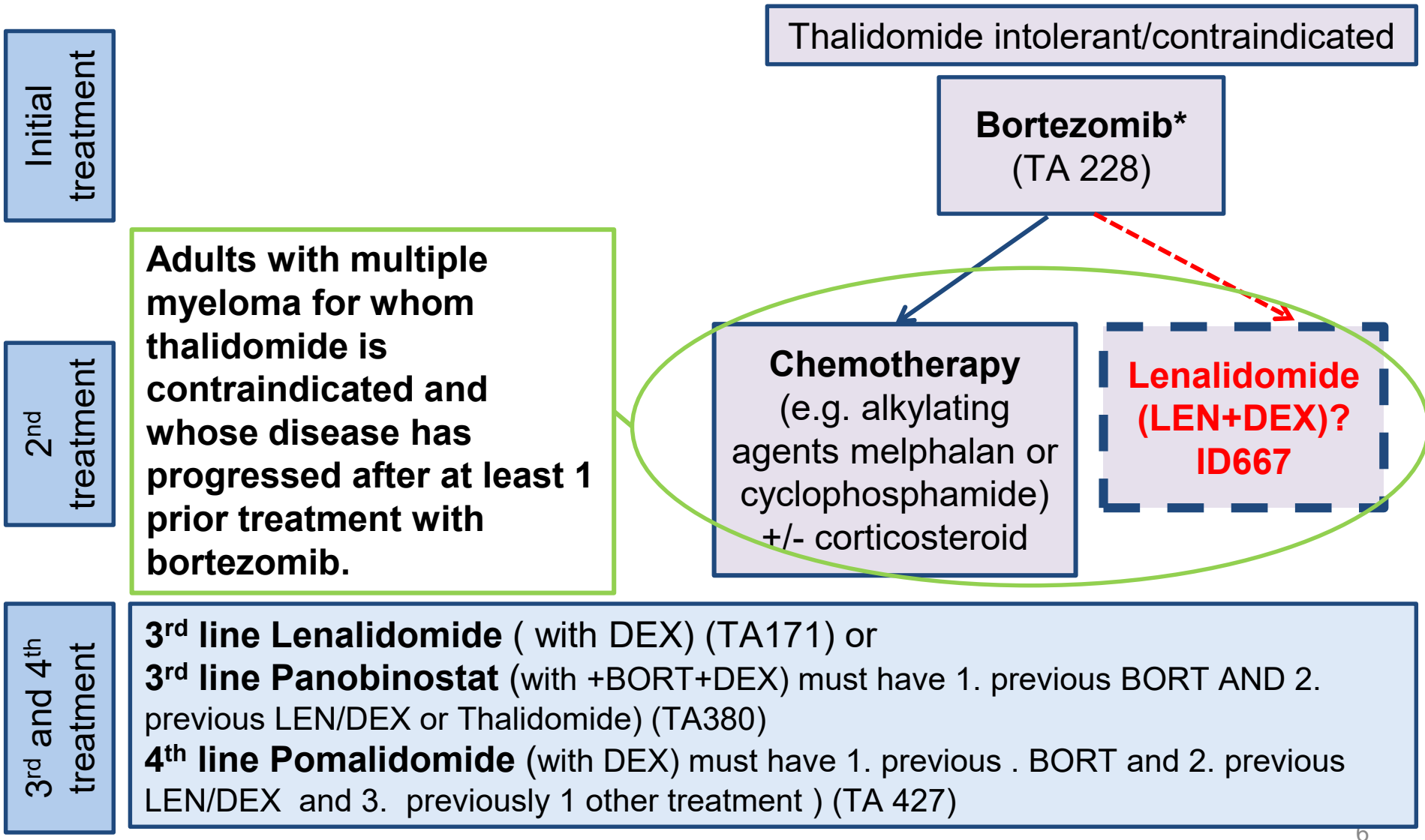
Clinical pathway of care

for those who are not eligible for transplantation



* Taken in combination with alkylating agent + corticosteroid, DEX = dexamethasone, BORT bortezomib

Scoped population



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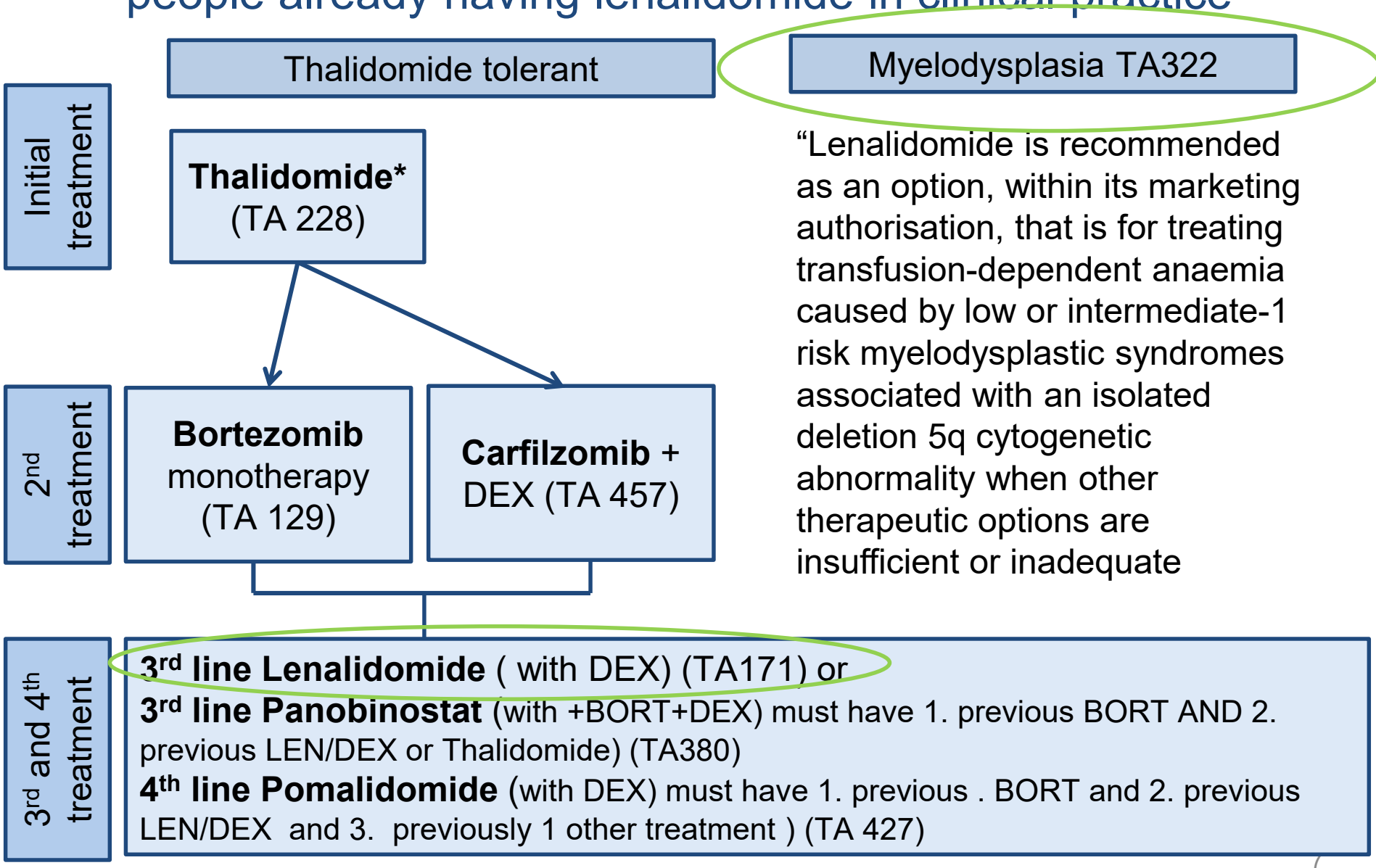
‘Wider benefit’ population

people already having lenalidomide in clinical practice



“Lenalidomide is recommended as an option, within its marketing authorisation, that is for treating transfusion-dependent anaemia caused by low or intermediate-1 risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate

* Taken in combination with alkylating agent + corticosteroid, DEX = dexamethasone, BORT bortezomib

Recap: decision problem

	NICE scope	Company decision problem at 5th meeting
Population	Adults with myeloma contraindicated to thalidomide whose disease progressed after bortezomib (+ not suitable for stem cell transplant)	
Comparator	1. Chemotherapy: melphalan, vincristine, cyclophosphamide, doxorubicin 2. Bortezomib • Monotherapy • + dexamethasone 3. Bendamustine	1. Melphalan

Bortezomib retreatment **no longer** on CDF. Discussed at 3rd + 4th meeting. Heard from NHS England bortezomib re-treatment not commissioned → **not** a comparator

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

Recap: sources of clinical evidence: survival

No trial compares 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; number prior therapies not reported
Treatment and control	Lenalidomide + dexamethasone ('LEN-DEX') n=353	Placebo + dexamethasone n=351 *Not used in NHS*	Melphalan + prednisolone n=34 *No control group*
1°endpoint	PFS		N/A
PFS*	11.1 months	4.6 months	Not reported
OS*	38.0 months	31.6 months	8 months

* median; PFS = progression free survival; OS = overall survival

Recap: 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**
     - assumes dexamethasone and chemotherapy equally effective and
     - uses data from randomised controlled trial (as presented in 4th committee meeting)

Committee preferred 'proxy' comparison because it provides a randomised comparison (no confounding), provides more patients, avoids need to adjust for 3rd line treatment, and uses patient level data

Recap: lenalidomide vs melphalan 'proxy' approach: results company & ERG

Based on current operational complex PAS (26 cycle dose cap):

Analysis	ICER
Company base case*	£[redacted]
ERG base case • shorter PFS for dexamethasone (melphalan) • company model had implausibly long tail when extrapolating PFS for dexamethasone	>£[redacted]
Both of these ICERs may underestimate the true ICER: • Melphalan expected to be more effective than dexamethasone. Using dexamethasone as a proxy may result in overestimate of the relative effectiveness of lenalidomide compared with melphalan	

* ERG (Evidence Review Group) identified an error in how company incorporated costs of melphalan using proxy approach. Company agreed with ERG's correction. Results include correction.

Recap: consultation comments (3rd ACD issued after 4th meeting): 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)
- "…[the draft recommendation] is likely to have an adverse impact on patient outcomes" (UK Myeloma Forum)

Committee agreed that there is an unmet need. Acknowledged that patients required to take a treatment that is less effective than later treatments recommended by NICE

Committee conclusions at 5th (last) meeting

Bortezomib (retreatment) **not** comparator – heard from NHS England it does not commission retreatment
Cytotoxic chemotherapy **is** comparator – heard from clinical experts that is an option after 1st treatment then relapse
There is an unmet need for this population at 2nd line because cytotoxic chemotherapy not considered very effective
Modelling based on crude indirect comparison not suitable for decision making
Modelling assuming melphalan = dexamethasone ('proxy' method) preferable, but may **underestimate** ICER lenalidomide vs. melphalan
Most plausible ICER, >£[redacted]- £[redacted]K per QALY gained
Cancer Drug Fund criteria **not** met. Data for overall survival from MM-009/010 for lenalidomide relatively mature providing a median overall survival for LEN-DEX of 50 months (MM-009)
End of life criteria **not** met – life expectancy >24 months. n.b. committee aware that criteria met historically in appraisal of lenolidamide 3rd line
Lenalidomide not recommended

New patient access scheme – dose capping

- New approved complex PAS where cost of lenalidomide is capped at a lower number of cycles than in the current PAS (26 cycles)
- Will apply to **all indications**
  - Multiple myeloma
    - This appraisal: 2nd line after bortezomib for people ineligible for thalidomide and for whom stem cell transplant not suitable
    - Existing NICE guidance: 3rd line after 2 or more prior therapies (TA171)
    - Today's new appraisal: 1st line (ID474)
  - Non-myeloma: Myelodysplastic syndromes with isolated deletion 5q cytogenetic abnormality (TA322)
- Company makes case for 'wider benefits': NHS will save money if NICE recommends lenalidomide for 2nd line treatment of multiple myeloma because NHS would pay for fewer cycles of treatment with lenalidomide for 3rd line multiple myeloma (TA171) and for myelodysplastic syndrome (TA322)

Incorporating wider benefits in technology appraisals

NICE methods guide

- [6.2.21]…The concept that underlies the Committee decision-making is that of the opportunity cost of programmes that could be displaced by the introduction of new technologies.
- [5.12.7] If implementation of the technology could have substantial resource implications for other services, the effects on the submitted cost-effectiveness evidence for the technology should be explored

Incorporating wider benefits of new PAS

previously recommended technologies

TA428 pembrolizumab for treating PD-L1 positive non-small-cell lung cancer after chemotherapy	TA484 nivolumab for previously treated non-squamous (squamous, TA483) non-small cell-lung cancer
Took into account, but did not calculate savings	**Did not consider incorporating benefits in modelling to be within NICE methods**
• Most plausible ICER range = £45K-£62K • "*It [the committee] was also aware that there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications*" • End of life criteria met • A scenario analysis including modelled savings wasn't presented	• Most plausible ICER £49K (TA484); £50K (TA483) • *"there would be a wider benefit to the NHS because the simple discount agreed in the patient access scheme would apply across all indications…. taking this into account was outside its approved methods [it] was also concerned that there were no details on how the discounts were calculated and applied. It concluded that it was not appropriate to incorporate these benefits into the economic model, taking into account the most plausible ICER and the uncertainty identified*"

Wider benefits calculated by company

- If NICE recommends lenolidomide 2nd line with new PAS, NHS will save money at 3rd or subsequent lines (excluded myelodysplastic syndromes population from wider benefits calculation)
- 3rd line population larger than potential 2nd line population because it's not restricted to people who are ineligible for thalidomide or stem cell transplant:

THIS APPRAISAL (2ND LINE)

Only people not eligible for thalidomide

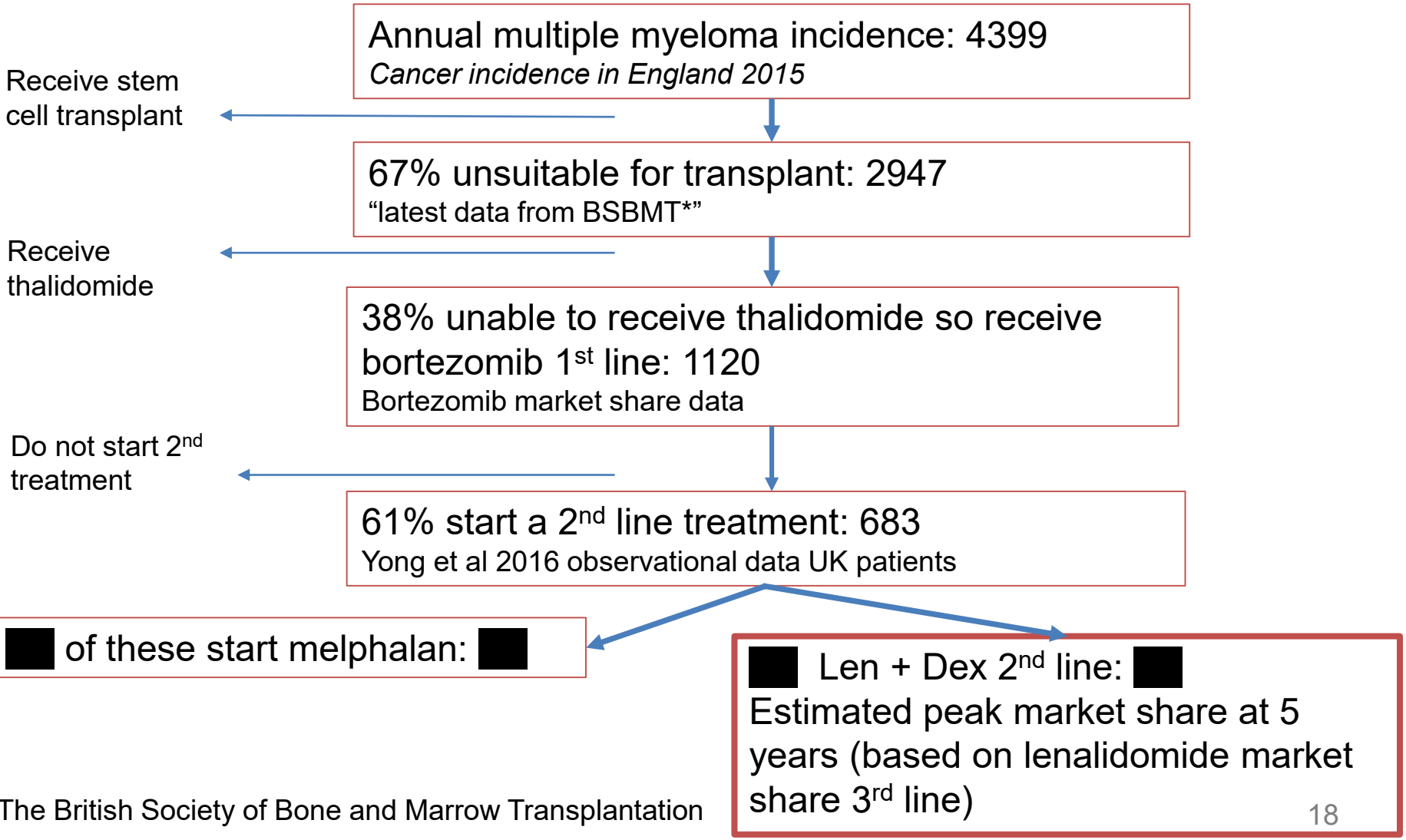
TA171 (3RD LINE)

Includes people who are & are not eligible for thalidomide

Company estimated, if NICE recommends lenolidomide 2nd line:

- Number of NHS patients who would receive lenolidomide 2nd line
- Number of NHS patients who would receive lenolidomide 3rd line
- For every 2nd line patient there would be [redacted] patients treated 3rd line
- Money saved per 3rd line patient under new PAS ([redacted])
- Money saved for each 2nd line patient ([redacted] x [redacted])
- Methods for estimations described on next slides….

Estimating 2nd line population who would receive lenalidomide, if recommended



*The British Society of Bone and Marrow Transplantation

Estimating 3rd line patients who would receive lenalidomide, if recommended 2nd line

- Company estimated number of 3rd line patients currently receiving lenalidomide for multiple myeloma = **3,409** (based on sales and prescription data company had 'on file')
- Adjusted this for people who are anticipated to have lenalidomide 2nd line if recommended and would go on to have a 3rd line treatment
  - [redacted] have lenalidomide 2nd line treatment, and of these, 78% go on to have a 3rd line treatment (the estimate for those people progressing to 3rd line was from model for this appraisal)
  - = **386** people
- 3rd line population **3,409** minus **386** = **3023**

How the company calculated 'wider savings' from PAS change

- Difference in 3rd line lenalidomide cost with new PAS
  - Company used its model to calculate savings using assumptions for 3rd line lenalidomide costs after melphalan, in melphalan cohort

    = [redacted]
- Calculated 'number of people in the *TA171 3rd line benefitting population for each person receiving lenalidomide 2nd line'* from estimates of:
  - 2nd line population receiving lenalidomide, if recommended n=[redacted]
  - *TA171 3rd line benefitting population* n = 3023

    = 3,023/ [redacted] = [redacted]
- To derive the **total** wider savings per person receiving lenalidomide second line

  = [redacted] * [redacted] = -[redacted]
- Applied these savings to the total modelled costs for lenalidomide taken 2nd line

Company's revised base case with new PAS and including 'wider savings'

	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER
Melphalan	[redacted]	[redacted]	-	-	-
Len + dex (including wider savings)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG critique of company's new approach

- Modelling structure and assumptions (other than PAS) remain same as previous meeting, incorporating corrections and committee's preferred assumptions
  - Note: Modelling did not include one of ERG's preferred assumptions - shorter tail to the curve when extrapolating PFS for dexamethasone, the melphalan proxy (N.B. the committee had included the results of this ERG scenario, and the company's approach in its preferred ICER range)
- Company implemented PAS correctly in model
  - cycle cap modelled correctly
  - old PAS modelled in comparator arm
  - new PAS in intervention arm
- Cost savings with new PAS for each 3rd line patient not calculated correctly

ERG critique: assumptions on patient numbers 2nd and 3rd line

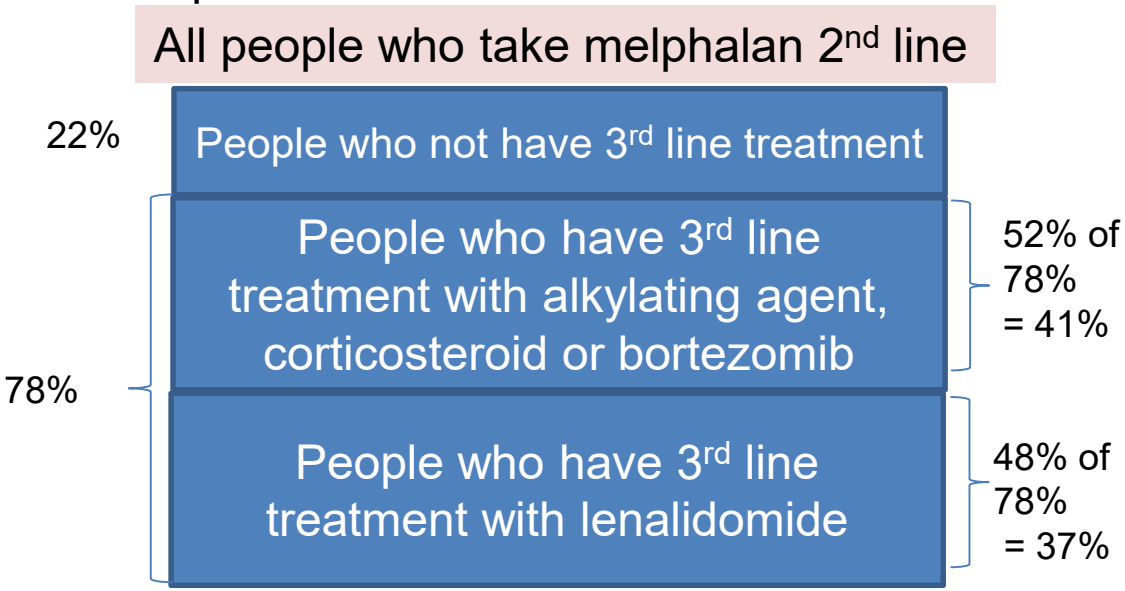
Assumption	Source	ERG comment
Annual MM incidence: 4,399	ONS data	Appropriate
Unsuited for transplant 67%	BSBMT 2016 activity	Link in company references does not work → unclear source
Not able to tolerate thalidomide: 38%	Bortezomib market share	
Starting 2nd line therapy: 61%	Yong et al (2016)	Patients from several European countries, not restricted to thalidomide ineligible receiving bortezomib 1st line → Uncertain
Uptake lenalidomide at 5 years (2nd line): [redacted]%	Company estimates	Plausible, but no way to check
Starting 3rd line: 78%	From model	Agree
Current 3rd line lenalidomide: 3,409	Sales and prescription data	Not in public domain → Unable to verify %

◉ *Are the company's estimates of numbers who would take lenalidomide 2nd line plausible?*

ONS = Office of National Statistics; BSBMT = British Society of Bone and Marrow transplantation

ERG: company's cost savings estimate incorrect

- To use model to work out cost saving of new PAS vs. old PAS for people receiving lenalidomide 3rd line who cannot take thalidomide need to use data from sub-population of people in the melphalan cohort who received treatment with lenalidomide 3rd line.
- Company have not done this. It has isolated the lenalidomide drug costs from the whole population in melphalan arm
- This means that the proportion of people who do **not** have a 3rd line treatment 22% and the proportion of people who received a 3rd line treatment other than lenalidomide (52% of people who have a 3rd line treatment) from the whole melphalan cohort have been included in the company's calculation



ERG corrects company's saving estimate: [redacted]_/ (48% x 78%) = [redacted] This adjusts to estimate savings for people starting lenalidomide 3rd line rather than whole population starting melphalan 2nd line

ERG exploratory analyses
of 3rd line use of LenDex

1) Tested a scenario in which all people receive lenalidomide 2nd line (if it is recommended)

2) Used alternative way to estimate 3rd line lenalidomide use (rather than prescription data-on-file from company)

- Myeloma incidence x % reaching 2nd line x % reaching 3rd line = 2,105 (using company's estimates)
- Estimate of relative population sizes at 3rd line to 2nd line becomes 3.5 rather than [redacted]
  - However, clinical advice to ERG: Sizes likely to be closer to [redacted] than 3.5

3) Estimated impact of lenalidomide being available 1st line on 3rd line use

- Assuming that if lenalidomide recommended 1st line (today's next appraisal ID474) → 3rd line use of lenalidomide would drop
- Clinical advice to ERG: if lenalidomide recommended 1st line then people may increasingly use pomalidomide instead of lenalidomide 3rd line
- Difficult to quantify, but if one assumes a 50% reduction in 3rd line use then estimate of relative population sizes at 3rd line to 2nd line becomes 3.07 rather than [redacted]

ERG results of exploratory analyses

	ICER (£/QALY) LEN + DEX vs. MP	ICER including ERG correction
Company base case	[redacted]	Len dominates
ERG's results 1 change at a time		
1. **No** 'Wider Benefits' - no cost saving from 3rd line LEN in people who can take thalidomide (out of scope)	[redacted]	No change
2. ERG's preferred modelling of DEX PFS (from previous meetings)	[redacted]	>Len dominates
3. If lenalidomide recommended 2nd line, 100% of people receive it	[redacted]	>Len dominates
4. Halve number of 3rd line LEN patients (e.g. more people get pomalidomide if lenalidomide were available 2nd line)	[redacted]	Scenario results not presented
5. Lower estimate of 3rd line LEN patients (from 3,409 to 2,105)	[redacted]	[redacted]

ICERs are expected to be higher than these values because current model assume high dose dexamethasone alone no better or worse than melphalan

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