Public slides – part 1 (Redacted)

Lead team presentation – Clinical

Lenalidomide in combination with dexamethasone for previously untreated multiple myeloma

1st Appraisal Committee meeting

Committee B, 1 February 2018

Lead team: Susan Faulds, Chris O'Regan, Nigel Westwood

Companies: Celgene

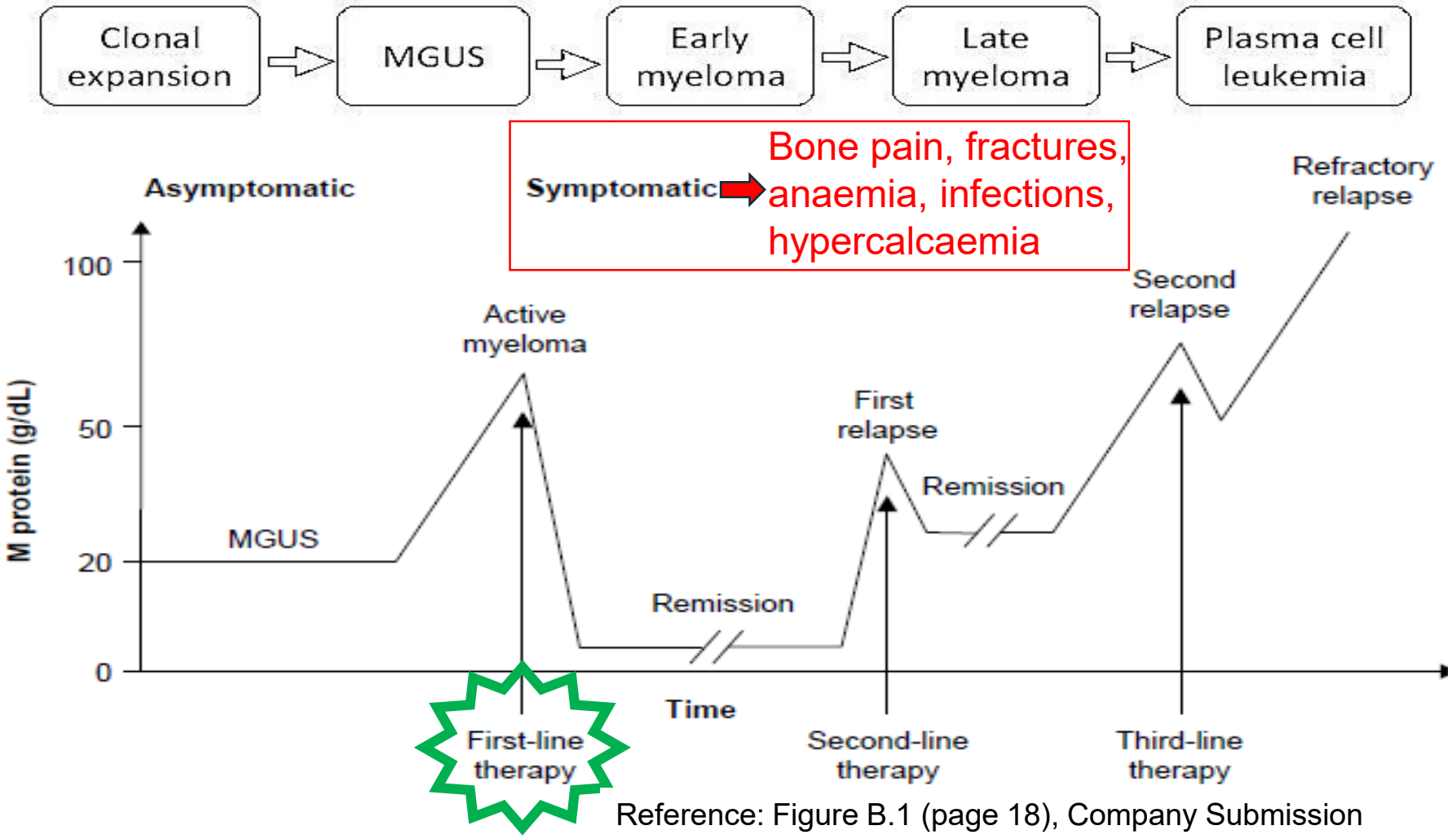
Chair: Amanda Adler

Evidence review group: Southampton Health Technology Assessments Centre (SHTAC)

NICE team: Thomas Strong, Ahmed Elsada, Elisabeth George

Multiple myeloma
Disease background

5-year survival rate is approximately 47%



Reference: Figure B.1 (page 18), Company Submission
MGUS: Monoclonal gammopathy of undetermined significance

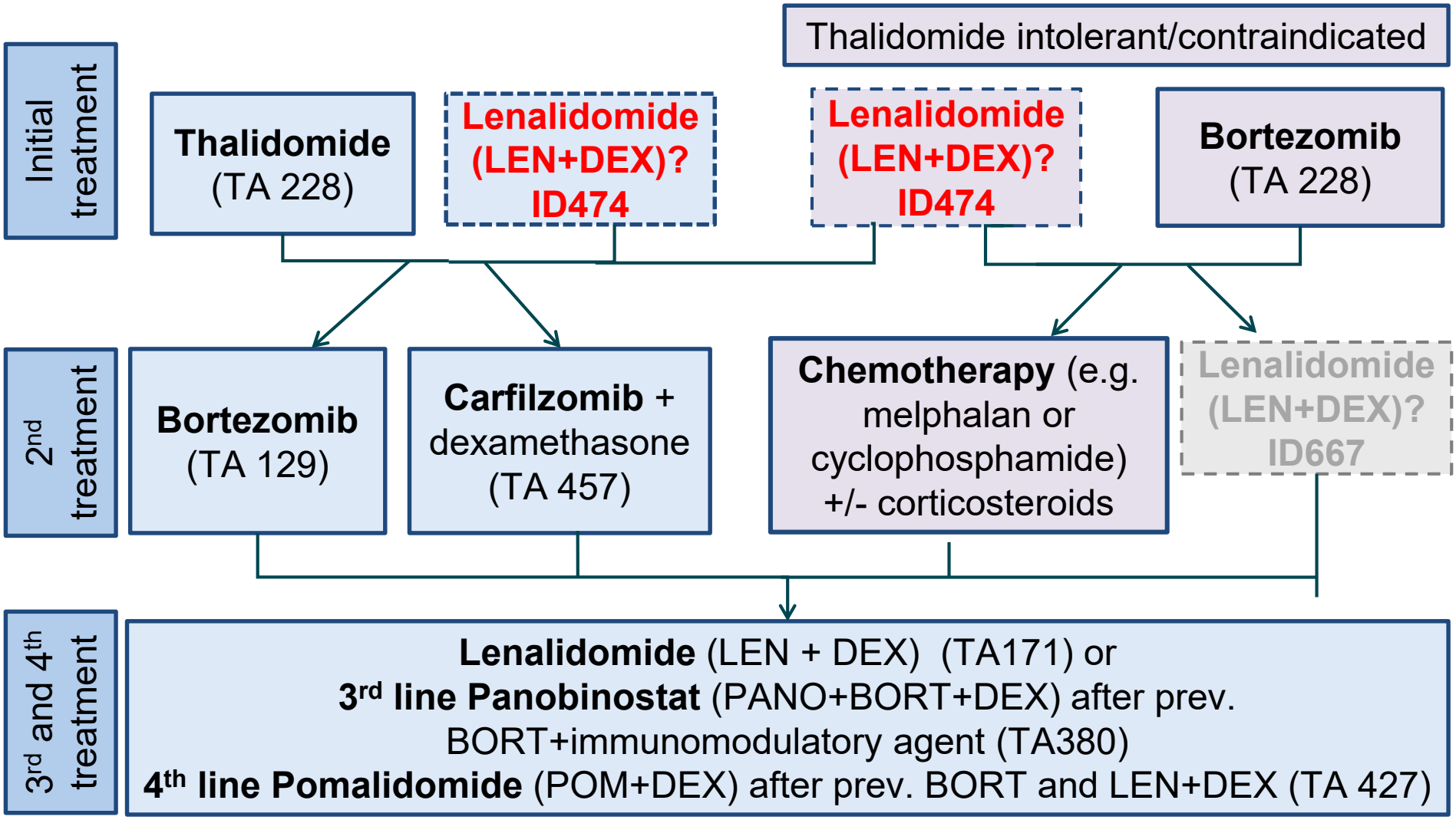
Lenalidomide (Revlimid)
Celgene

Marketing authorisation	Indicated as combination therapy for people with Newly Diagnosed Multiple Myeloma (NDMM) who are not eligible for transplantation
Administration & dose	• Oral, 25 mg/day on days 1–21 of a 28 day cycle. Taken until disease progression or unacceptable toxicity • Contraindications for lenalidomide are the same as thalidomide: pregnancy and hypersensitivity
Mechanism of action	A structural analogue of thalidomide. Has anti-neoplastic, anti-angiogenic, pro-erythropoeitic and immunomodulatory properties.
Cost	New approved complex PAS where cost of lenalidomide is capped at a lower number of cycles than in the current PAS (previously 26 cycles) Average cost per course without PAS: £[redacted] Average cost per course with PAS: £[redacted]

Source: Table B.2 (page 15-16), company submission

Clinical pathway of care

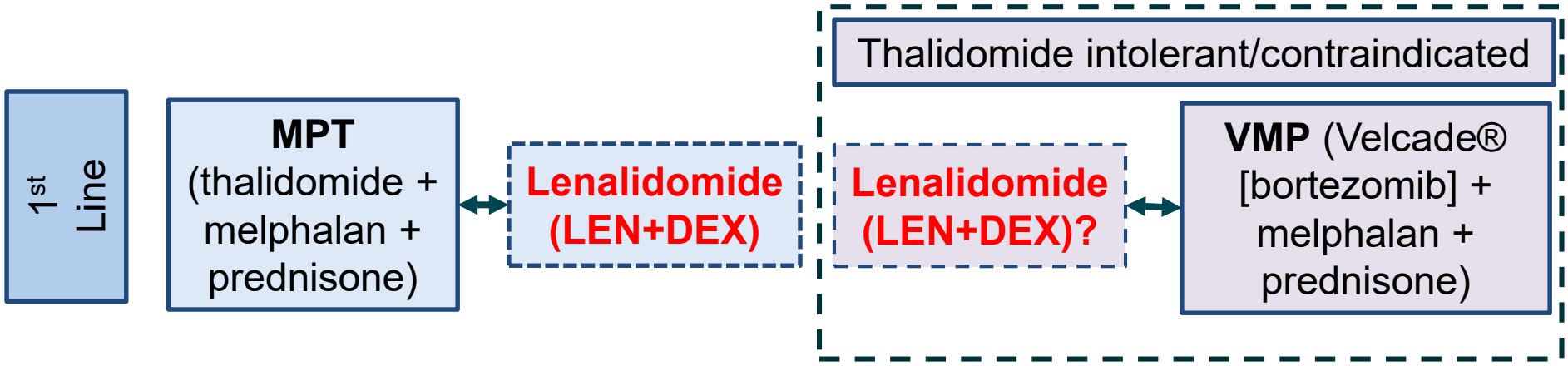
for those who are not eligible for transplantation



⊙ ***Where will the technology be used in the treatment pathway?***

Company's decision problem

for those who are not eligible for transplantation



MPT is comparator is key trial. Company does not include CTD (cyclophosphamide + thalidomide + dexamethasone) as it is unlicensed, and clinically equivalent to MPT, with similar costs

Company focuses only on population who cannot take thalidomide

<u>Subsequent therapies</u>

Company model that people have subsequent treatment or retreatment with thalidomide, bortezomib or lenalidomide based regimes

Company's decision problem

Comments from Evidence Review Group (ERG) and stakeholders

Choice of comparators	Unable to take thalidomide
• Clinical expert: In NHS, CTD used in preference to MPT; clinicians consider them similar • ERG identified a meta-analysis: no difference between MPT and CTD • "CVD" is an alternative bortezomib-based 1st line treatment in UK, but ERG could find no evidence to compare it to lenalidomide	• Expert advice to ERG estimates group is ~50% of the full 1st line population • Company: bortezomib has a 1st line market share of 38% • Lenalidomide contraindications same as thalidomide: pregnancy and hypersensitivity • People may be unable to take thalidomide due to existing/drug-related peripheral neuropathy, previous thrombosis or impaired renal function • Elderly may not tolerate 3 drug combinations • Committee previously noted some people who cannot have thalidomide can use lenalidomide

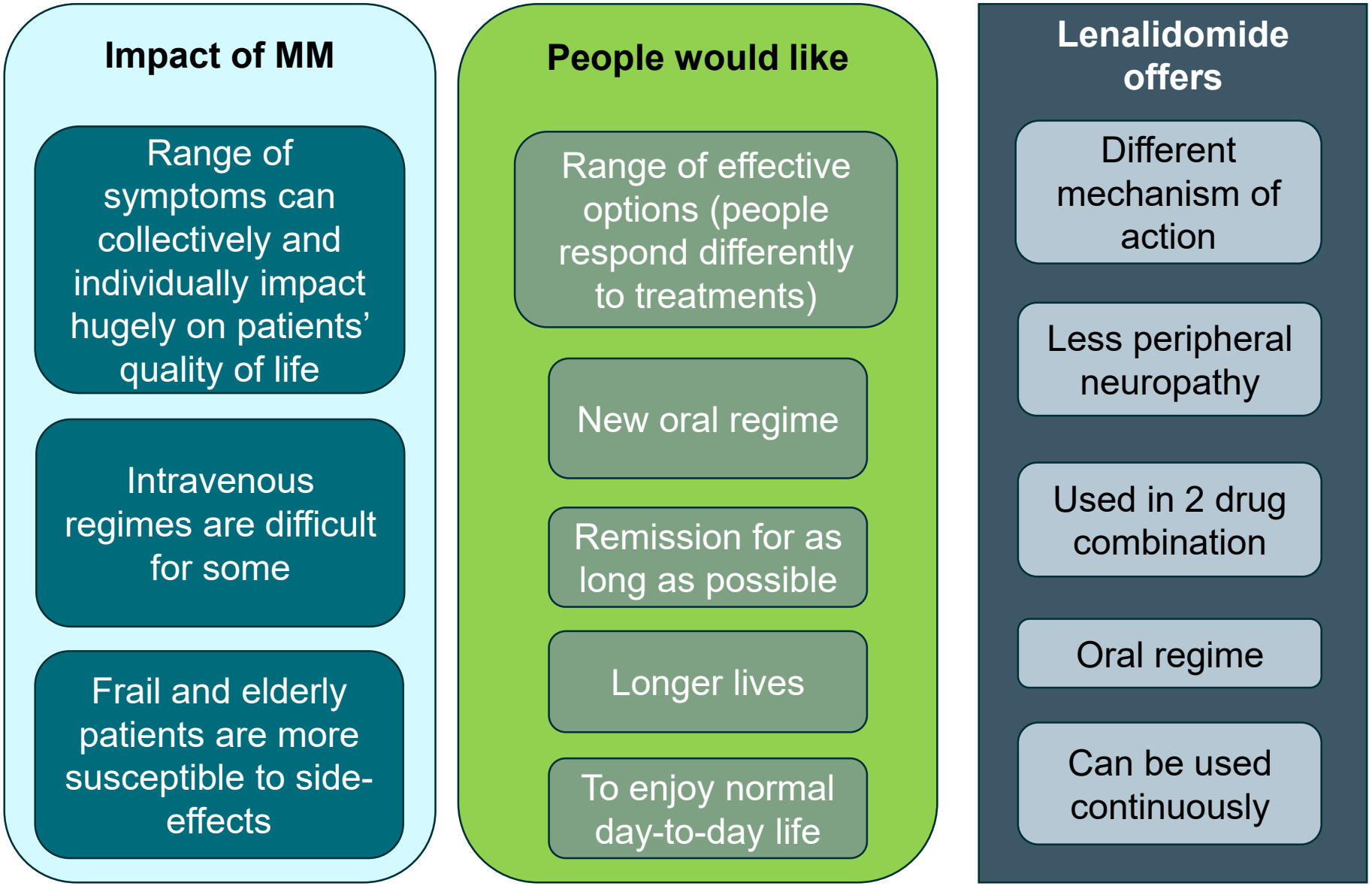
⊙ ***Does company's choice of comparators reflect current practice?***

CDF clinical lead perspective

- Intolerant/contraindicated to thalidomide was never defined in TA228: 'Bortezomib and thalidomide for the 1st line treatment of multiple myeloma'
- Clinical practice in England has changed, and now at least 50% of 1st line transplant ineligible population receive bortezomib-based therapy, as clinicians want to use most clinically effective option even if not cost-effective
- Sole criterion for contraindication to thalidomide based on the lenalidomide trial data is potentially pre-existing and significant neuropathy – other risk factors for thalidomide or lenalidomide (e.g. risk of thromboembolism, infection) cannot be used as compared with MPT, lenalidomide had:
  - Higher levels of thrombosis (8% vs. 5%)
  - Higher grade 3 and 4 infection rates (29% vs 17%),
  - Possible lower overall survival in subgroup of people with severe renal function (hazard ratio 1.20; 95% confidence interval 0.76–1.92)
- NHS England wish NICE in this appraisal to define what is meant by intolerance of and contraindication to thalidomide-based treatment

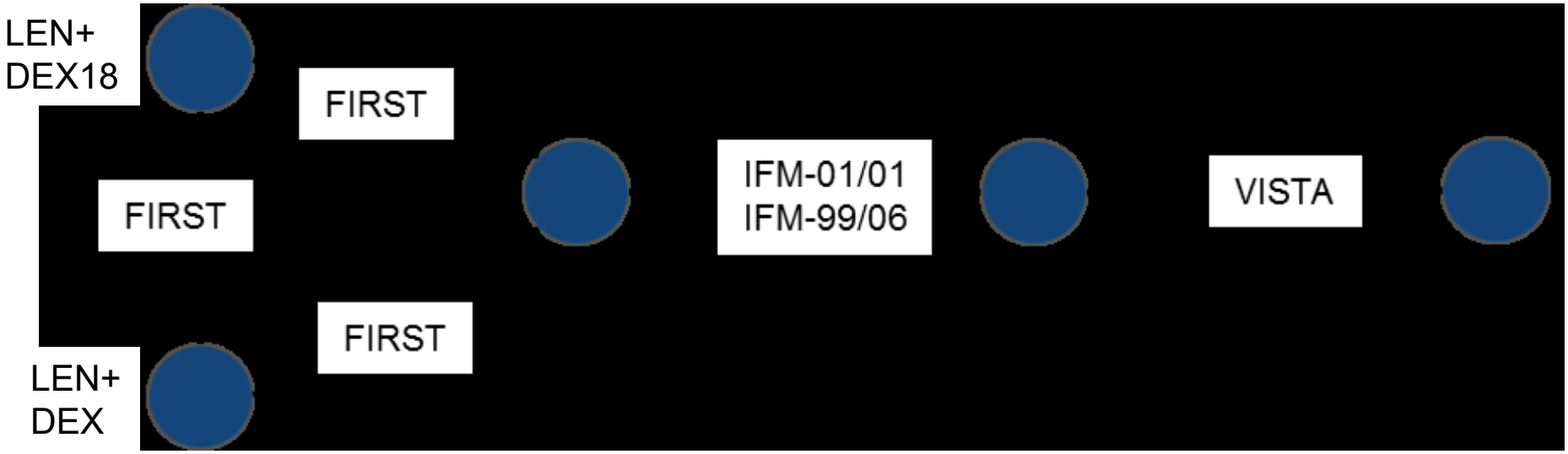
⊙ ***Is it acceptable to focus on those unable to have thalidomide?***
⊙ ***How is intolerance to thalidomide defined in clinical practice?***

Clinical and patient perspective



Clinical evidence

- FIRST randomised controlled trial (RCT) compares continuous LEN+DEX with LEN+DEX limited to 18 cycles (LEN+DEX18) and with MPT
  - Company state that LEN+DEX limited to 18 cycles is not of relevance to the decision problem for this appraisal
- Further RCTs included so overall survival and progression-free survival of LEN+DEX could be indirectly compared to VMP
- Melphalan and prednisone (MP) included to connect the network



Source: Figure B.14 (page 67), company submission

Clinical evidence
ERG comments

- Evidence for lenalidomide is based on large international multi-centre RCT (n=1623 patients randomised), with relevant outcomes measures, and had a long follow-up (median follow-up 67 months)
- No substantial differences between age, gender, race or biochemical parameters between treatment arms in the FIRST trial
- All the RCTs in the network are of good methodological quality and have been included in previous NICE appraisals
- None of the included trials recruited people who were intolerant of, or who had contraindications to, thalidomide
    - Clinical expert advice to ERG suggests that results unlikely to differ between patients that can and cannot take thalidomide

FIRST

Key results at January 2016 data cut-off

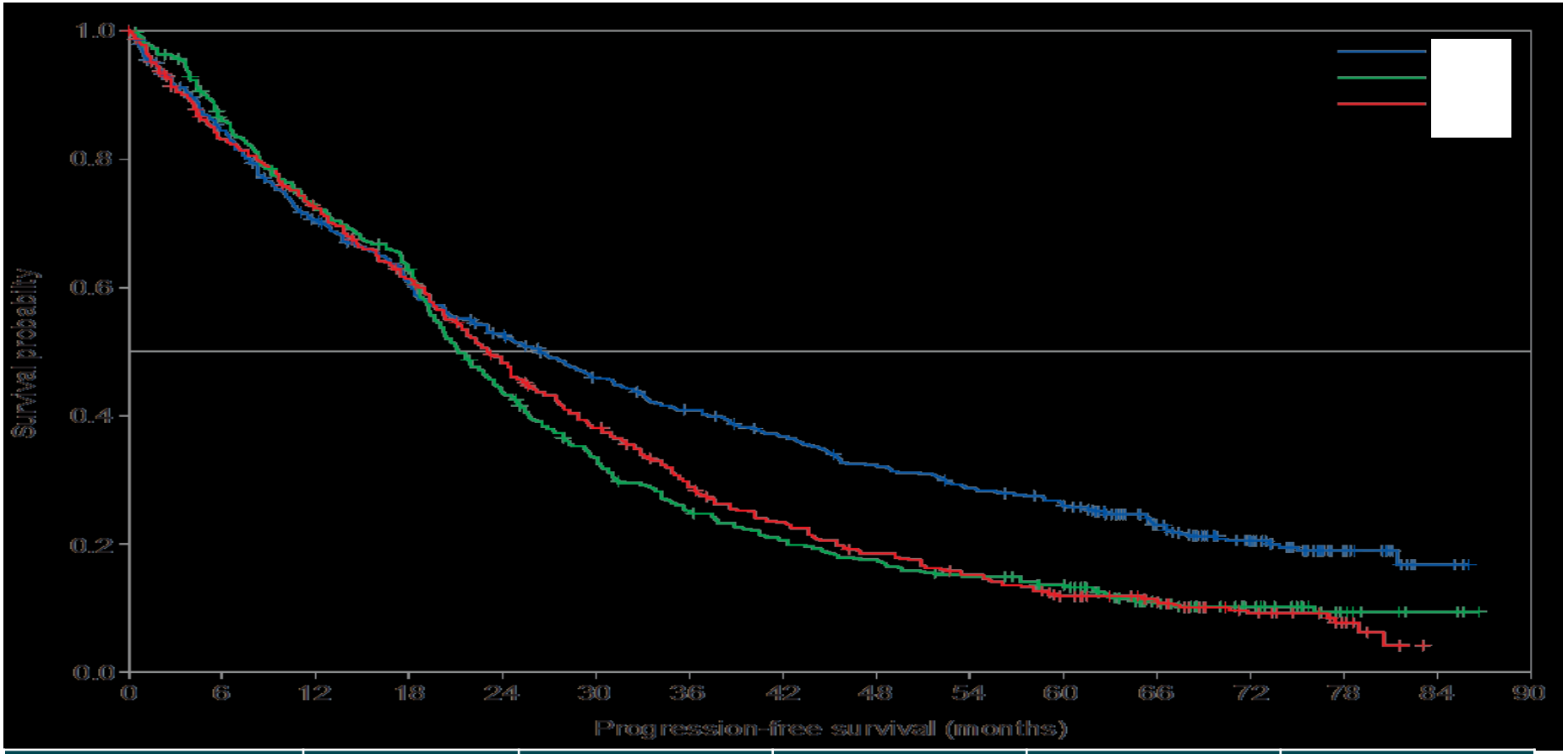
	LEN+DEX (n=535)	MPT (n=547)	Hazard ratio (95% CI)
Primary outcome			
Median PFS, months	26.5	23.0	0.74 (0.65–0.85)
Secondary outcomes			
OS, median, months	59.1	49.1	0.78 (0.62–0.92)
ORR, %	80.7	67.5	OR: 2.02 (1.53–2.68)
Median TTP, months	31.3	24.4	0.64 (0.54–0.75)
Median months to 2nd line treatment, months	36.7	26.7	0.63 (0.54–0.73)

PFS, Progression-free survival; OS, overall survival; OR, odds ratio; TTP, time-to-progression
Source: adapted from table B.14 (page 45), company submission

⊙ ***Is lenalidomide-based therapy more effective than thalidomide-based therapy?***

FIRST

PFS, January 2016

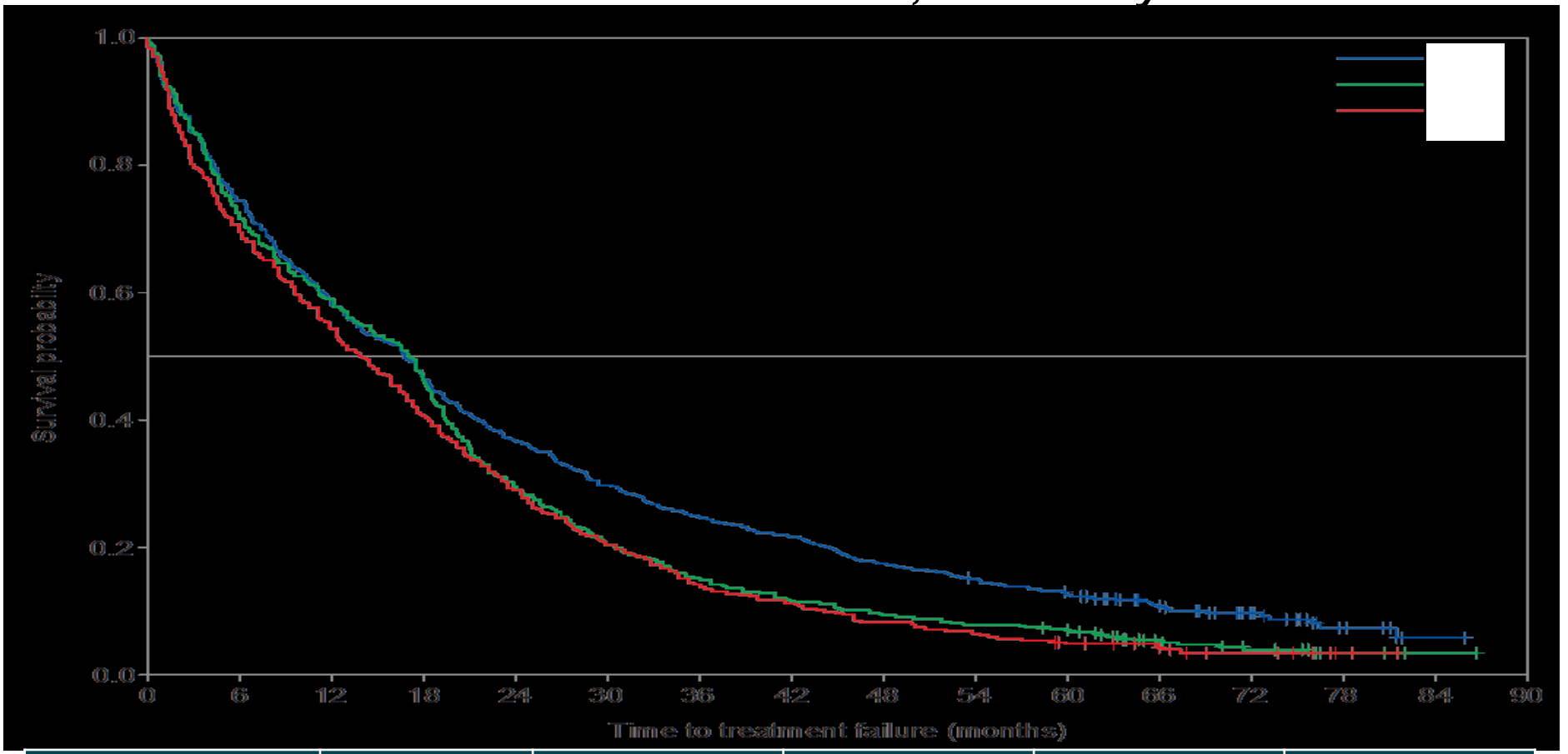


Month Number at risk	0	24	48	72	90
LEN+DEX	535	268	155	51	0
MPT	547	319	90	20	0

Source: Adapted from figure B.6 (page 52), company submission

FIRST

Time to treatment failure, January 2016

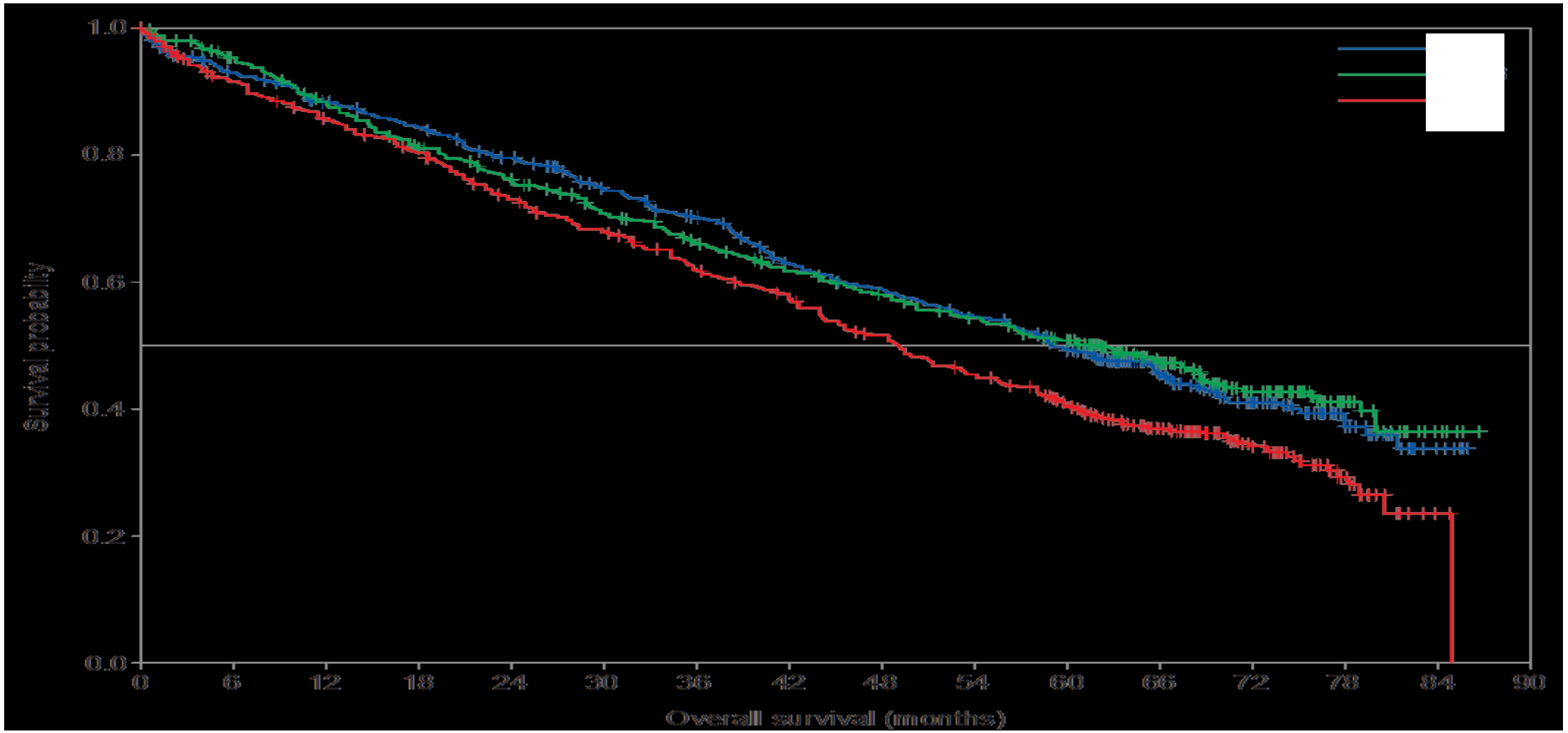


Month Number at risk	0	24	48	72	90
LEN+DEX	535	197	94	24	0
MPT	547	159	46	9	-*

*0 at 84 months; Source: Adapted from figure B.8 (page 56), company submission

FIRST

OS, January 2016



Month Number at risk	0	24	48	72	90
LEN+DEX	535	403	277	97	0
MPT	547	375	254	78	0

Source: Adapted from figure B.7 (page 53), company submission

FIRST

Myeloma therapies 2nd line and beyond (post hoc analysis)

	LEN+DEX (n=535) n (%)	MPT (n=547) n (%)
Patients who had any subsequent therapy[a]	299 (55.9)	381 (69.7)
type of drugs in all subsequent therapy regimens:		
Lenalidomide	75 (25.1)	264 (69.3)
Bortezomib / carfilzomib	236 (78.9)	277 (72.7)
Thalidomide	67 (22.4)	38 (10.0)
Glucocorticoid	277 (92.6)	357 (93.7)
Alkylating agents	213 (71.2)	188 (49.3)
Other therapies	93 (31.1)	99 (26.0)

[a]Based on the ITT population.
Source: Table B.16 (page 63), company submission

⊙ ***Do the therapies used 2nd line and beyond in the trial reflect current clinical practice in the NHS?***

Indirect comparison

- Company modelled using fixed effects and constant hazard ratios. It explored using random effects and fractional polynomials.
- ERG consider:
  - There is uncertainty because the network has few trials
  - Baseline characteristics were well distributed across the four trials
  - Using fixed effects and constant hazard ratios in primary analysis appropriate

Comparison	**Progression-free survival HR (95% Credible Interval)**	**Overall survival HR (95% Credible Interval)**
LEN+DEX vs. MPT	**0.74 (0.65, 0.85)**	**0.78 (0.67, 0.91)**
LEN+DEX vs. VMP	0.74 (0.52, 1.05)	**0.70 (0.50, 0.98)**
VMP vs MPT*	1.00 (0.72, 1.38)	1.11 (0.82, 1.50)

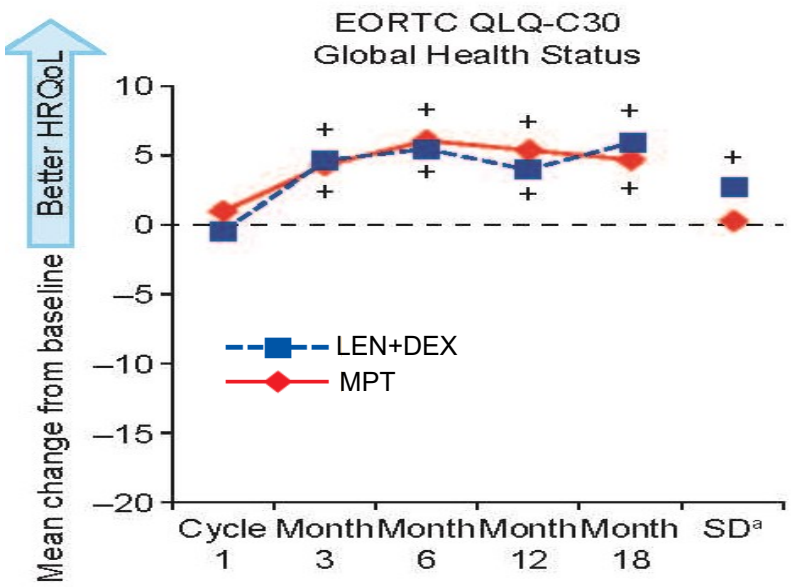
*VMP vs. MPT comparison is used to inform the economic model
Source: Adapted from table A.6 (page 13), company submission; Bold values where p≤0.05

⊙ ***Is the company's approach to the indirect comparison appropriate?***
⊙ ***Is LEN+DEX clinically effective compared to VMP?***

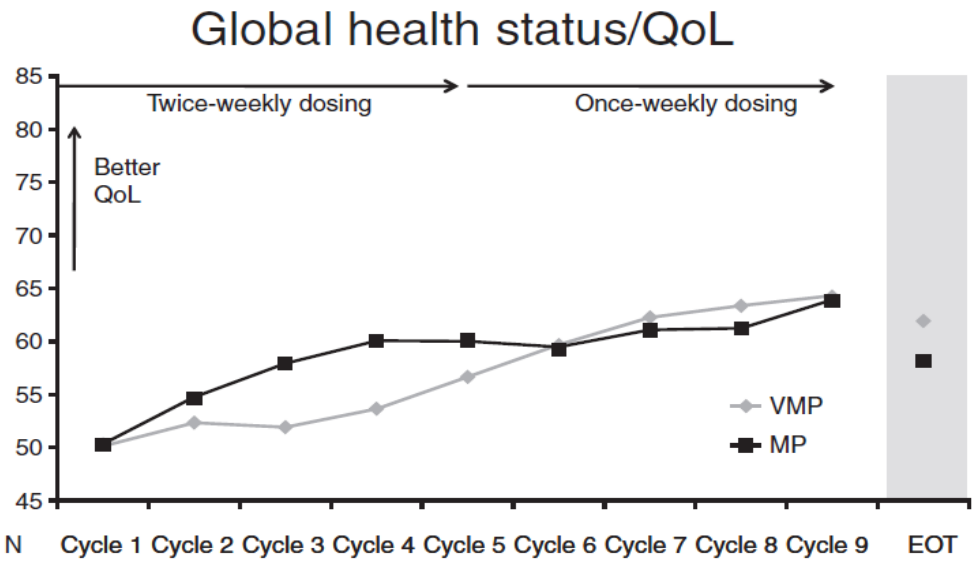
Health-related quality of life (HRQoL)

- LEN+DEX: no significant differences between arms in European Organisation for Research and Treatment of Cancer (EORTC) or 5-dimension European Quality of Life (EQ-5D) questionnaires, but significantly greater reduction in disease symptoms and side effects of treatment in EORTC
- VMP: EORTC only; transitory HRQoL decrements and relatively lower HRQoL during early treatment cycles

FIRST trial



VISTA trial



Source: Figure B.9 (page 59), company submission and Figure 1, Delforge 2012

Adverse events

- Grade 3+ adverse events with incidence over 5% used to inform economic model

		LEN+DEX (FIRST)	MPT (FIRST)	VMP (VISTA*)
Key Grade 3+ adverse event, %	Neutropenia	30	45	40
	Thrombocytopenia	9	11	38
	Anaemia	19	19	19
	Leukopenia	5	10	24
	Peripheral neuropathy	1	9	13
Serious adverse events, %		71	50	46
Discontinuations due to treatment related AEs, %		12	14	15

*Naïve comparison
Sources: Adapted from table D.63 (page 34), Company appendices

In FIRST, peripheral sensory neuropathy was the only adverse event that lead to discontinuation in more than 2% of patients, at 6.7% in the MPT group

Key issues for consideration
Clinical evidence

- Is it acceptable to focus the value proposition on those unable to have thalidomide?
- How is contraindication to thalidomide defined in clinical practice?
- Do the comparator treatments chosen by the company reflect NHS practice in England?
- Do the therapies 2nd line and beyond used in the trial represent NHS practice in England? If not, are the excluded subsequent therapies used in NHS practice associated with a survival benefit?
- Is the clinical evidence based on a network of patients who **can** take thalidomide generalisable to UK clinical practice for people who **cannot** take thalidomide?
- Is the company's approach to the indirect comparison appropriate to make a comparison of LEN+DEX vs. VMP?

Public slides – part 1 (Redacted)

Lead team presentation – Economic

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NICE team: Thomas Strong, Ahmed Elsada, Elisabeth George

Cost-effectiveness
People who can take thalidomide

- Company considered that LEN+DEX is not cost-effective compared with MPT (thalidomide + melphalan + prednisone) for population able to have thalidomide
- Company's deterministic incremental cost effectiveness ratio (ICER) for this population = £[redacted]/QALY
- The company's cost-effectiveness case focuses on the comparison of LEN+DEX with VMP (bortezomib + melphalan + prednisone)

Base-case Results (deterministic)
LEN+DEX *vs*. VMP

	Treatment	Total		Incremental		ICER (£/QALY)
		Costs	QALYs	Costs	QALYs	
Company base case	VMP	[redacted]	[redacted]	-	-	-
	LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ERG base case	VMP	[redacted]	[redacted]	-	-	-
	LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

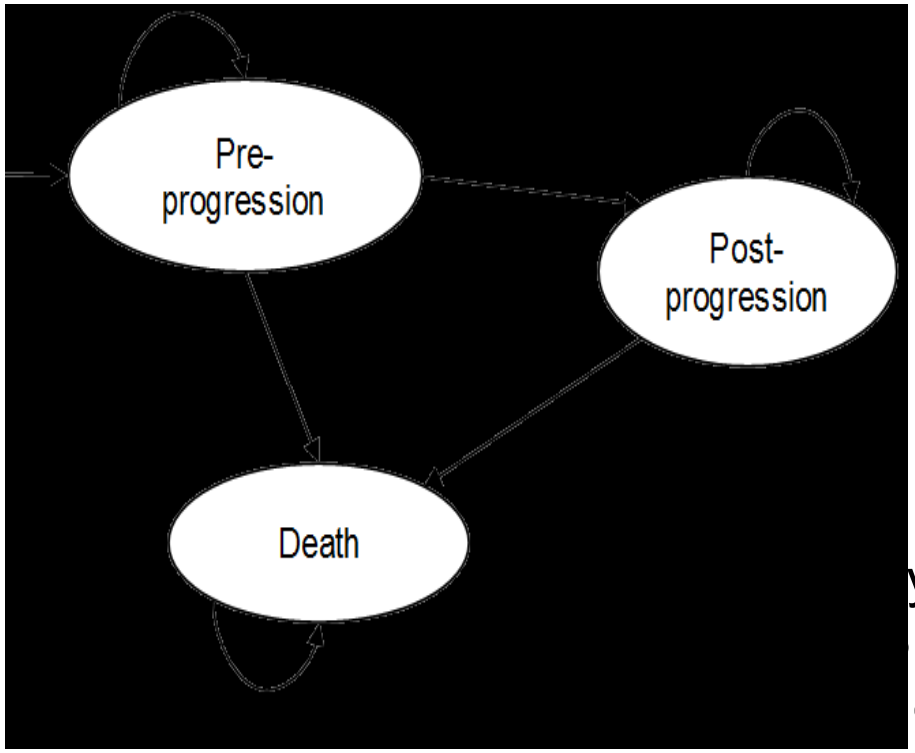
Model Structure

Quality of life in the model is driven by:

1) **The treatment received before progression** i.e. LEN+DEX or VMP

2) **The length of time spent progression-free** – the same lower utility is assumed upon disease progression

Hybrid model structure: partitioned survival analysis (time period <92 weeks), thereafter multi-state Markov model



years
years
days

Key Model Inputs and Assumptions

Parameter	Source	Input
Effectiveness: LEN+DEX PFS	FIRST trial	Kaplan-Meier data for t=0-92, then constant transition probability
Effectiveness: LEN+DEX OS		
Effectiveness: VMP PFS	Indirect comparison HR applied to FIRST trial MPT Kaplan-Meier data	
Effectiveness: VMP OS		
Cost of treatment: Time on treatment LEN+DEX	FIRST trial	Curve fitted to Kaplan-Meier data
Cost of treatment: Time on treatment VMT	Company assumption / ERG assumption	Equal to PFS / Same as MPT
Cost of 1st line treatment: acquisition cost LEN+DEX	Complex PAS	[redacted]
Cost of 1st line treatment: acquisition cost VMT	Monthly Index of Medical Specialities (MIMs)	£4,238 per cycle
Utility for LEN+DEX	FIRST trial	EQ-5D data
Utility for VMT	VISTA trial	EORTC data mapped to EQ-5D

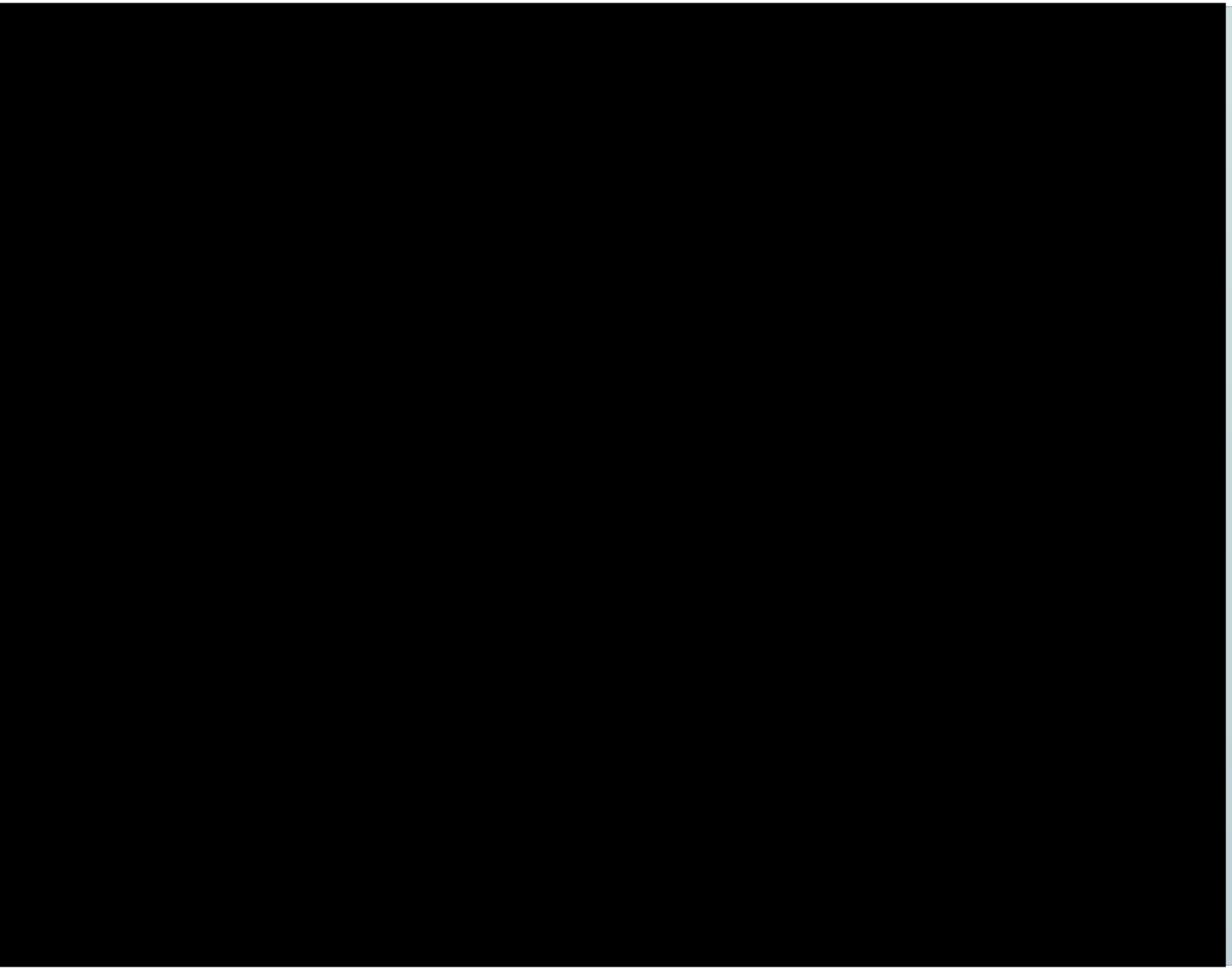
Summary of Survival Estimates

Median estimates (years)

*Time on treatment not reported

Mean estimates (years)

Hazard Rate and Relative Treatment Effect (company and ERG)



- Kaplan–Meier data up to 92 weeks (1.8 years), then parametric curve
- Increase in ‘tail’ of model as company assume mortality must be greater or equal to general population mortality
- **Are the rates over time clinically plausible?**

Overall Survival Curves (company and ERG)

⊙ **Are the model predictions of overall survival clinically plausible?**

Life Years & Proportion of Life Years by Health State (company and ERG)

- **For both LEN+DEX and VMP, ~[redacted]% of LYs occur pre-progression, and ~[redacted]% occur post progression – is this clinically plausible?**

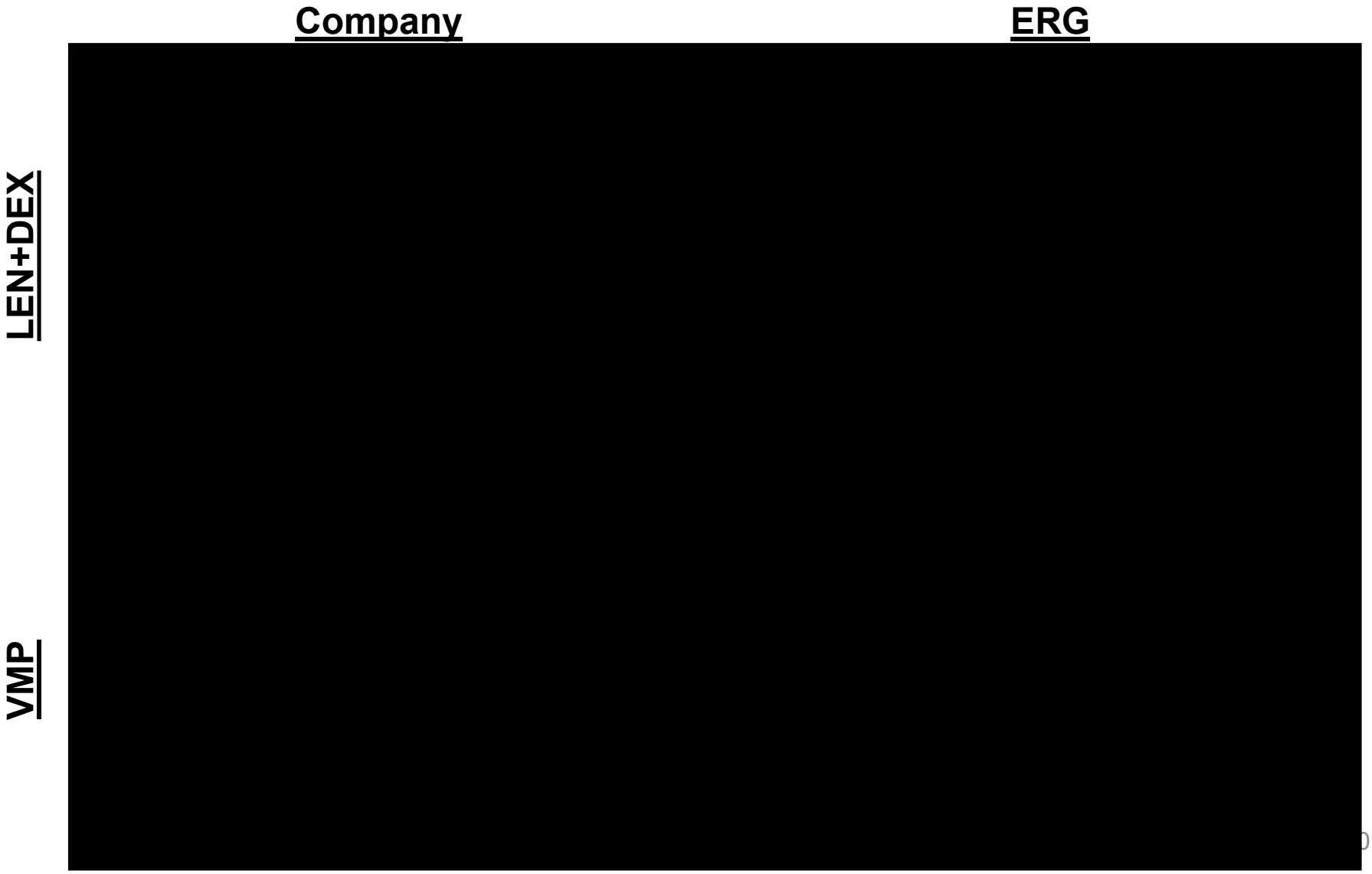
Incremental Life Years over Time (company and ERG)

- LEN+DEX increases survival by ~[redacted] years compared with VMP
- ~[redacted]% of that benefit occurs beyond the end of the trial (~5.6 years)

- **Is the survival benefit plausible?**

QALYs by Health State

Difference between company and ERG in **red**



Average Utility (company, ERG very similar)

- When treatment starts, quality of life is slightly above the midpoint between “perfect health” and “dead”
- **Does the model reflect the average quality of life of patients over time?**

Summary of Costs by Category

ERG Critique

Company's base case	ERG critique
Company generated overall survival curve for VMP using hazard ratio (HR) for VMP *vs.* MPT from network meta-analysis (HR 1.11)	HR uncertain with a wide credible interval (95% CrI 0.82–1.50) Treatments assumed similar in previous TA
To estimate time to treatment failure (TTF): • Weibull curve fitted to LEN+DEX arm and exponential curve to MPT arm • For VMP, assumed equal to PFS up to maximum treatment duration	• Company should use same curves for both arms; ERG prefers Weibull • PFS similar for MPT and VMP, and so TTF should be too
Benefit on quality of life of LEN+DEX compared with VMP continues after VMP stops	Utility value should be the same between treatments after stopping VMP, as no evidence of continued benefit
Treatments 2nd line and beyond include thalidomide and LEN+DEX, as per trial	Should not include thalidomide or LEN+DEX: company models patients who can't have thalidomide; re-treating with LEN+DEX not standard practice

ERG's Exploratory Analyses

	ICER
Company's base case	[redacted]
VMP=MPT wrt overall survival	[redacted]
Time to treatment failure changes (Weibull curve for both arms, and TTF similar for MPT and VMP)	[redacted]
Equal utility after stopping VMP	[redacted]
No 2nd/3rd line thalidomide*	[redacted]
No 2nd/3rd line thalidomide and no LEN+DEX re-treatment ("**ERG alternative analysis**")*	[redacted]
*ERG excluded costs but not effects of these treatments – ERG considers analyses "exploratory"	

These changes + other minor changes and corrections = "**ERG preferred analysis**" (**ICER = £**[redacted])

End of life

- Company has not made a case
- Neither the company's nor the ERG's survival estimates support LEN+DEX as an end-of-life treatment

Equality

Issue identified at scoping stage:

- People with multiple myeloma attend specialist treatment units for injectable treatment. These patients are often less mobile or live a long distance from their treatment centre meaning they are less likely to receive these treatments

Preliminary view as to what extent these potential equality issues need addressing by the Committee

- The benefits of different mode of administration will be taken into account in the appraisal.

⊙ ***Any further equality considerations to be taken into account?***

Innovation

- Company consider that lenalidomide represents a step-change in the management of transplant-ineligible NDMM, as:
  - Compared with thalidomide and bortezomib, it has a different mechanism of action and toxicity profile, which allows for continuous use to suppress residual disease and extend the period of first remission.
  - As an oral therapy, lenalidomide provides an alternative to IV and injectable therapies such as bortezomib, which have to be given in the hospital setting.
  - It may be given in a two-drug combination that does not include melphalan, which may be more tolerable to older frail patients.

⊙ ***Any innovation considerations to be taken into account?***

Issues for Consideration

- Is the model structure appropriate for decision-making?
- What is the committee's opinion on the ERG's change to:
  - TTF, so that VMP is equal to MPT, and a Weibull distribution is used
  - Using the same HRQoL after MPT/VMP treatment has finished
- What is the most plausible effectiveness of VMP relative to MPT ? Equivalence or superiority of MPT (reducing the risk of death by 10%)?
- Should the following subsequent treatments be included in the model:
  - Thalidomide?
  - Retreatment with lenalidomide and dexamethasone?
  - Newer treatments (POM+DEX and PANO+PORT+DEX)?
- Are there any innovation and equality considerations?
- What is the most plausible ICER?