Selinexor with bortezomib and low-dose dexamethasone for treating relapsed or refractory multiple myeloma [ID3797]

PART 1 for PROJECTOR: contains **noCON** information

HST appraisal committee

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Company: Menarini-Stemline UK

10th January 2024

Selinexor with bortezomib and low-dose dexamethasone for treating relapsed or refractory multiple myeloma

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Relapsed or refractory multiple myeloma

Incurable, relapsing, remitting cancer of plasma cells of unknown cause

- **Epidemiology**: ~5,800 new cases in UK
    - more common in elderly, men and people of African family background
- **Classification**
    - Relapsed: previously treated myeloma that progresses and needs new therapy
    - Refractory: no response to therapy or progression within 60 days of last therapy
- **Symptoms**: infections, bone pain, fractures, fatigue, hypercalcaemia, kidney issues
- **Prognosis**: 5-year survival for adults in England and Wales is ~50%
- **Therapy**: increase time to progression, depth of response, duration of survival; maintain or improve health-related quality of life
    - Treatment is personalised: age, frailty, cytogenetics, comorbidities, side effects of treatments, previous class/drug exposure and refractoriness

Patient and clinical perspectives

Submissions from Myeloma UK, UK Myeloma Society

Living with RRMM

- Highly individual and complex cancer
- More significant disease burden
- Moderate or high effect on quality of life, constant possibility of relapse has huge psychological impact
- Affects all aspects of life for people and carers: social, relationships, financial, physical, emotional

Current therapies

- Later lines have worse outcomes (decreased remission times, more side effects; therapies less effective, harder to tolerate)

Unmet need

- More options needed: MM is varied; individual response to therapies affects future options
- SEL: novel mechanism of action, oral, manageable side effects

Myeloma has had a major impact on my quality of life … and mental health

… My husband is very supportive and he was driving me to and from hospital appointments … he puts his life on hold as well

People with RRMM often experience more significant disease burden because of its progressive nature and the cumulative effects of treatment, which can result in reduced quality of life

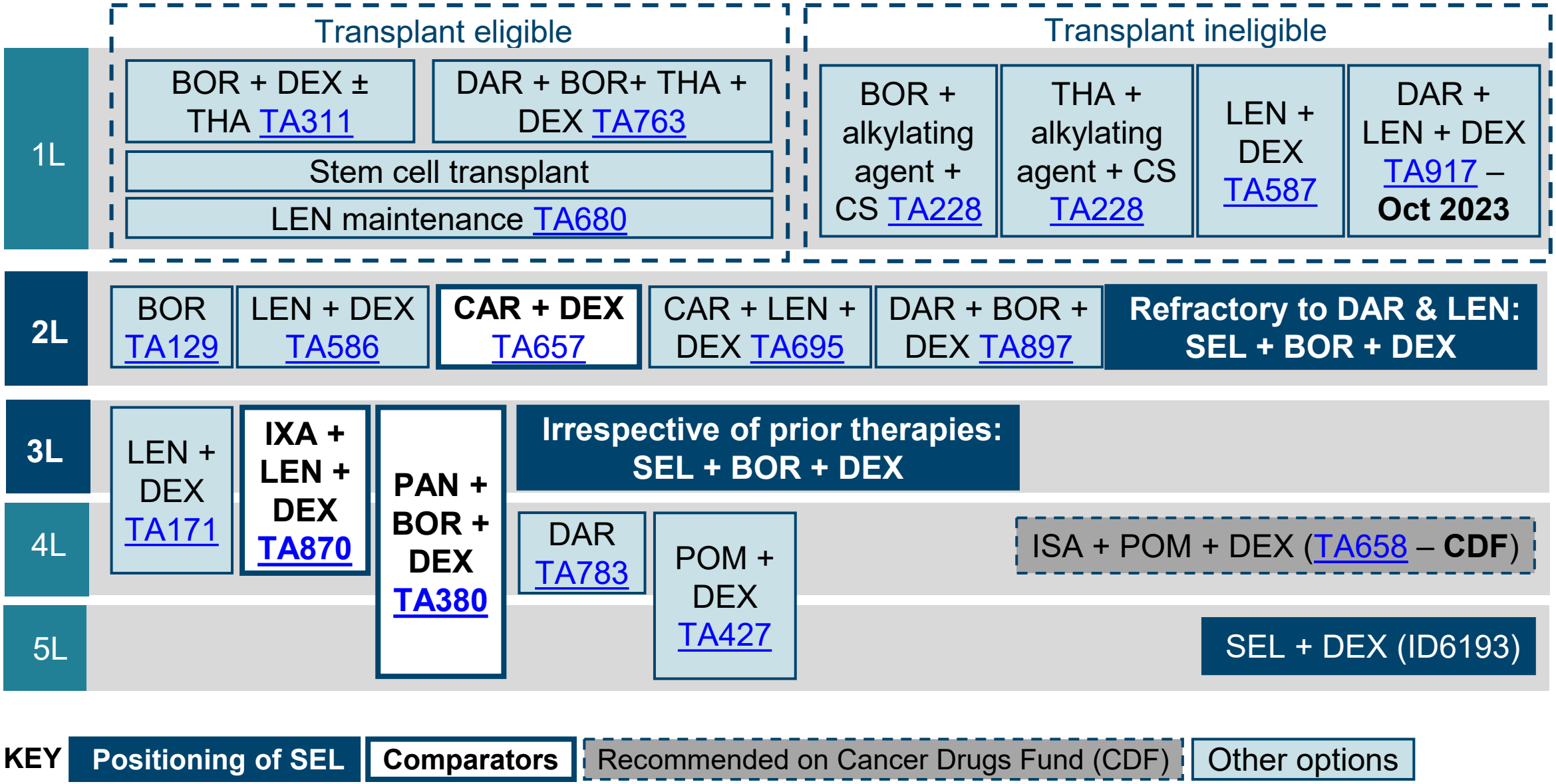
Abbreviations: MM, multiple myeloma; RR, relapsed or refractory; SEL, selinexor

Selinexor (Nexpovio, Menarini-Stemline UK)

Selinexor is a first-in-class selective inhibitor of exportin 1

Marketing authorisation in February 2023	• Selinexor in combination with bortezomib and dexamethasone for the treatment of adults with multiple myeloma who have received at least 1 prior therapy
Mechanism of action	• Reversible selective inhibitor that blocks exportin 1 preventing cancer cells from exporting cargo proteins from the nucleus e.g. tumour suppressor proteins
Administration	• 35-day cycle: ○ Selinexor 100mg orally 1x/week on Day 1 ○ Bortezomib 1.3mg/m^2 subcutaneously 1x/week on Day 1 for 4 weeks, then 1 week off ○ Dexamethasone 20mg orally 2x/week on Days 1 and 2
List price of selinexor	• £3,680 per 8x20mg (£23 per mg) • Per cycle: £9,200 • Patient access scheme in place

Treatment pathway and positioning of SEL+BOR+DEX



KEY **Positioning of SEL** | **Comparators** | Recommended on Cancer Drugs Fund (CDF) | Other options

Abbreviations: BOR, bortezomib; CAR, carfilzomib; CS, corticosteroid; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor; THA, thalidomide

Treatment pathway: EAG comments

Combination therapies with more agents preferred
Company's positioning of SEL+BOR+DEX is narrower than its marketing authorisation

EAG clinical advisors' comments

- 1L for SCT ineligible: DAR+LEN+DEX (TA917 published in October 2023) likely to become most used in NHS
- 2L: BOR+DEX more likely used than BOR monotherapy
- 3L: many people LEN and DAR exposed (limited options → unmet need)
  - PAN+BOR+DEX used for minority (toxicity)
  - Similar concerns about toxicity with SEL+BOR+DEX

What are the relevant comparators for SEL+BOR+DEX at 2nd and 3rd line?

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Abbreviations: 1/2/3L, 1st/2nd/3rd line; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; LEN, lenalidomide; PAN, panobinostat; SCT, stem cell transplant; SEL, selinexor

Key issues

No.	Issues	ICER impact	
		2nd line	3rd line
1	Relevant comparators	-	Large
2a	Indirect treatment comparisons at 3rd line	-	Large
2b	Extrapolations of PFS, OS and ToT	Variable	Large
	Comparator extrapolations: baseline using SEL+BOR+DEX or BOR+DEX	Large	Large
3	OS benefit	Large	Large
4	Cost of subsequent therapies	Small	Small
5	Modelling adverse events	Small	Large
6	Modelling of health state utilities	Small	Large

Abbreviations: BOR, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; SEL, selinexor; ToT, time on treatment

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Key clinical trial results – BOSTON* (15th Feb 2021 data cut)

Compared to BOR+DEX, SEL+BOR+DEX statistically significantly improves 2nd line PFS, but not 3rd line PFS or OS at 2nd or 3rd line
BOR+DEX not relevant 2nd or 3rd line comparators (as per appraisal scope)

	Median values (95% CI)			
	2nd line		3rd line	
	SEL+BOR+DEX	BOR+DEX	SEL+BOR+DEX	BOR+DEX
N	99	99	65	64
PFS, months	21 (13 – NE)	11 (7 – 16)	13 (9 – 26)	9 (8 – 13)
Hazard ratio	0.6 (0.4 – 0.95), p=0.01		0.75 (0.5 – 1.2), p=0.12	
OS, months	NE (27 – NE)	33 (25 – NE)	37 (32 – NE)	29 (22 – NE)
Hazard ratio**	0.9 (0.6 – 1.5), p=0.34		0.6 (0.3 – 1.2), p=0.07	

Follow up duration not provided for subgroups; entire cohort median follow-up time was 13.5 months for SEL+BOR+DEX (n=195) and 24.5 months for BOR+DEX (n=207); missing patients are those at 4th line

**Adjusted for cross-over in BOR+DEX

*Back-up slide 33

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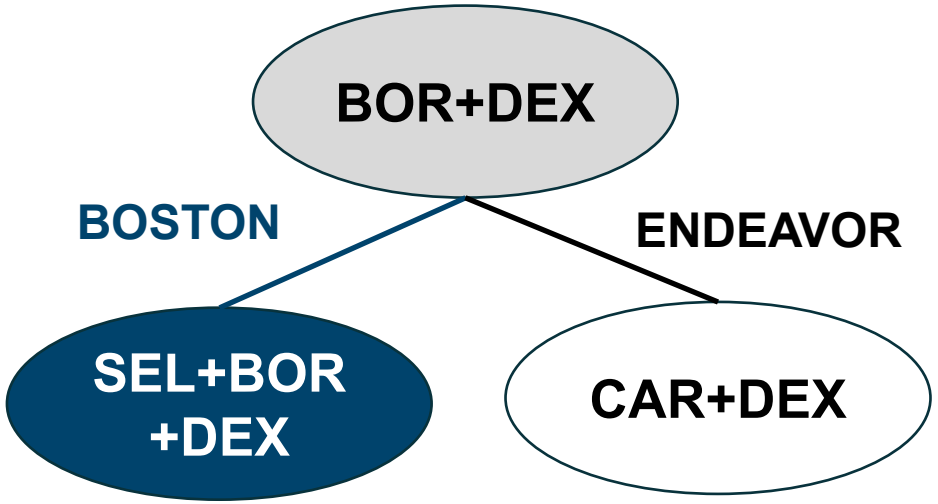
Abbreviations: BOR, bortezomib; CI, confidence interval; DEX, dexamethasone; LEN, lenalidomide; n, number; NE, not evaluable; OS, overall survival; PFS, progression free survival; SEL, selinexor

NMA: 2nd line*

EAG: Company's NMA which approximates a Bucher ITC is appropriate. Greater uncertainty in OS than PFS because of wider credible intervals

Compared to SEL+BOR+DEX, CAR+DEX results in a numerical, but not statistically significant, improvement in PFS and OS



Outcome	Hazard ratios (95% CrI) for CAR+DEX vs	
	SEL+BOR+DEX	BOR+DEX
PFS	0.73 (0.31 – 1.67)	0.45 (0.26 – 0.80)
OS	0.89 (0.32 – 2.45)	0.77 (0.39 – 1.53)

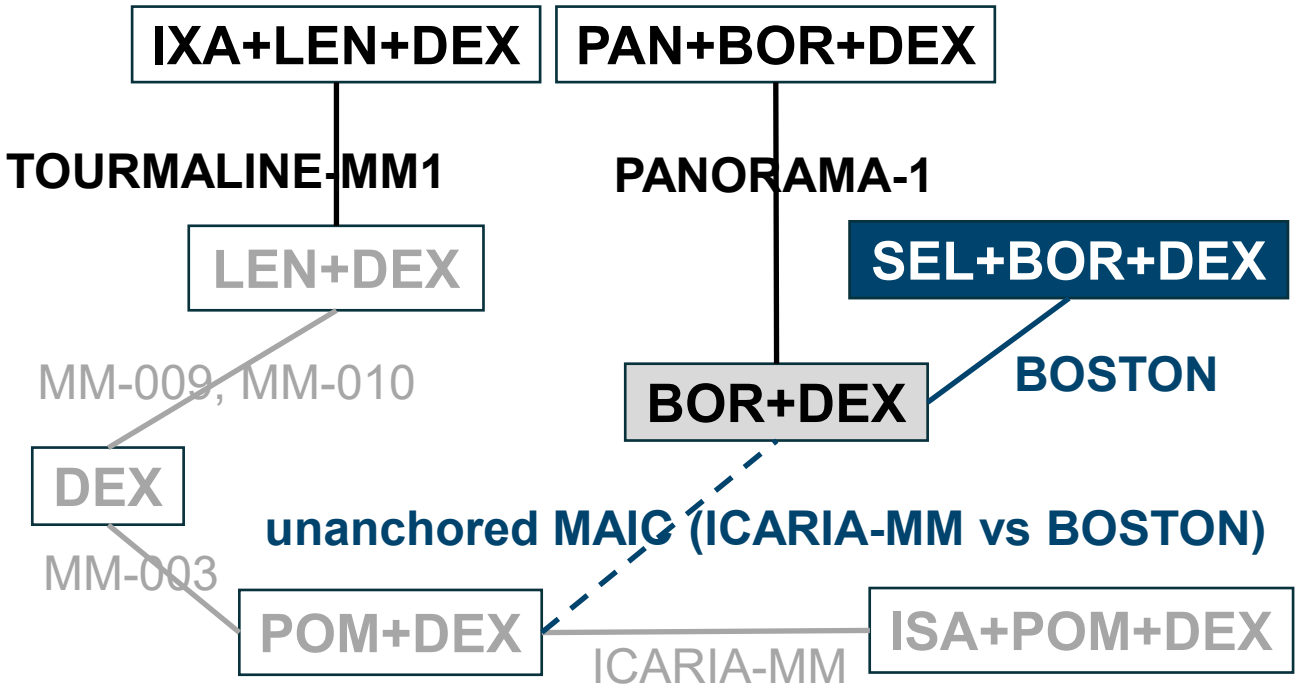
*Back-up slide 34

Abbreviations: BOR, bortezomib; CAR, carfilzomib; CrI, Credible Interval; DEX, dexamethasone; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; SEL, selinexor

Key Issue 2a: ITC for 3rd line*

EAG: PAN+BOR+DEX NMA is Bucher-like comparison of BOSTON and PANORAMA-1; appropriate

IXA+LEN+DEX: Company prefers NMA while EAG prefers unanchored MAIC that overcomes NMA limitations



EAG comments on NMA limitations

- potential violation of proportional hazards throughout networks
- uses MAIC to connect network
- uses BOSTON BOR+DEX data twice
- uses 'by-arm' median PFS data from MM-009 and MM-010
- includes trials likely not representative (5+ prior lines; from 2003) or OS unadjusted for crossover

*Back-up slide 35

Abbreviations: BOR, bortezomib; DEX, dexamethasone; ITC, indirect treatment comparison; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PAN, panobinostat; PFS, progression free survival; POM, pomalidomide; SEL, selinexor

ITC results: 3rd line

Compared to IXA+LEN+DEX and PAN+BOR+DEX, SEL+BOR+DEX results in a numerical, but not statistically significant, improvement in OS, but not PFS

Comparators	Baseline	Hazard ratios			
		NMA (95% CrI)		Unanchored MAIC (95% CI)	
		PFS	OS	PFS	OS
IXA+LEN+DEX	SEL+BOR +DEX	0.7 (0.1 – 3.3)	1.1 (0.2 – 5.2)	0.66 (0.3 – 1.3)	1.3 (0.6 – 2.6)
PAN+BOR+DEX		0.8 (0.3 – 2.3)	1.2 (0.5 – 3.5)	NR	NR
SEL+BOR+DEX	BOR+DEX	0.8	0.77	NR	NR
IXA+LEN+DEX		0.56	0.85	0.37 (0.23 – 0.6)	0.48 (0.3 – 0.8)
PAN+BOR+DEX		0.64	0.96	NR	NR

Which model should be used to estimate treatment effectiveness at 3rd line: NMA or unanchored MAIC?

Abbreviations: BOR, bortezomib; CI, Confidence Interval; CrI, Credible Interval; DEX, dexamethasone; ITC, indirect treatment comparison; IXA, ixazomib; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; NR, not relevant; OS, overall survival; PAN, panobinostat; PFS, progression free survival; SEL, selinexor

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Key issue 2b: Extrapolations of PFS, OS and ToT

Company and EAG disagree on violation of PH assumption, extrapolations and baseline for comparators

BOSTON KM PFS, OS, ToT data for SEL+BOR+DEX and BOR+DEX at 2L and 3L

PH assumption checked using standard tests

Extrapolations: IF or JF Survival curves (best statistical fit visual inspection, clinical plausibility)

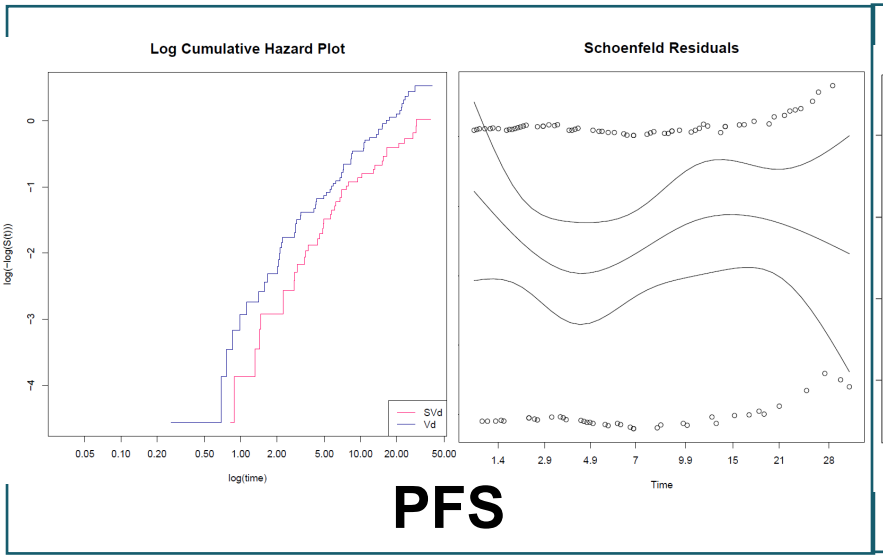
Comparators:
- PFS and OS: ITC results applied to baseline SEL+BOR+DEX
- ToT: PFS ITC HRs applied to baseline ToT for SEL+BOR+DEX

PH assumption valid?		
Outcome	Company	EAG
2nd line		
PFS	No	No
OS	Yes	No
ToT	Yes	No
3rd line		
PFS	Yes	No
OS	Yes	No
ToT	Yes	No

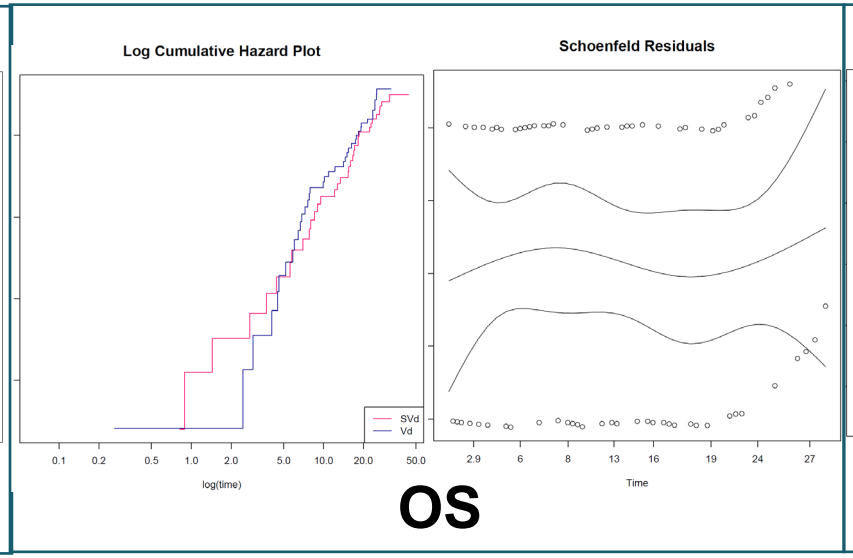
EAG comments
- Patient-level data from BOSTON → IF models more robust
- Baseline for comparators: BOR+DEX more appropriate (common network comparator)

Abbreviations: 2/3L, 2nd/3rd line; BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; IF, independently fitted; ITC, indirect treatment comparison; JF, jointly fitted; KM, Kaplan-Meier; OS, overall survival; PFS, progression free survival; PH, proportional hazards; SEL, selinexor; ToT, time on treatment

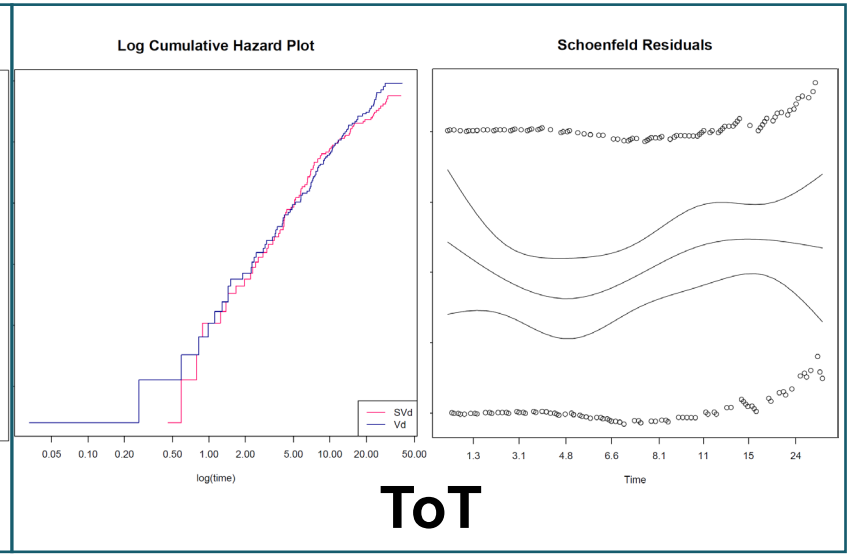
2nd line log-log and Schoenfeld residual plots



PFS



OS



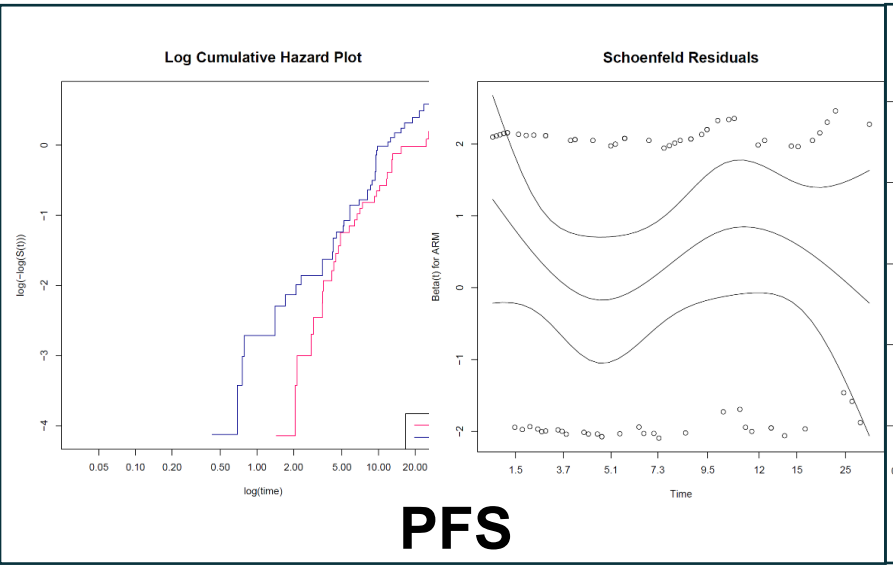
ToT

	Company's base case				EAG's base case			
	Distribution	Mean life years			Distribution	Mean life years		
		SEL+BOR+DEX	BOR+DEX	CAR+ DEX		SEL+BOR+DEX	BOR+DEX	CAR+ DEX
PFS	IF gamma	2.3	1.4	3.2	IF Weibull	2.5	2.2	2.9
OS	JF gamma	3.9	3.2	4.3	IF Weibull	3.1	3.1	3.1
ToT	JF gamma	1.1	1	1.5	IF Gompertz	1.4	1.5	2.2

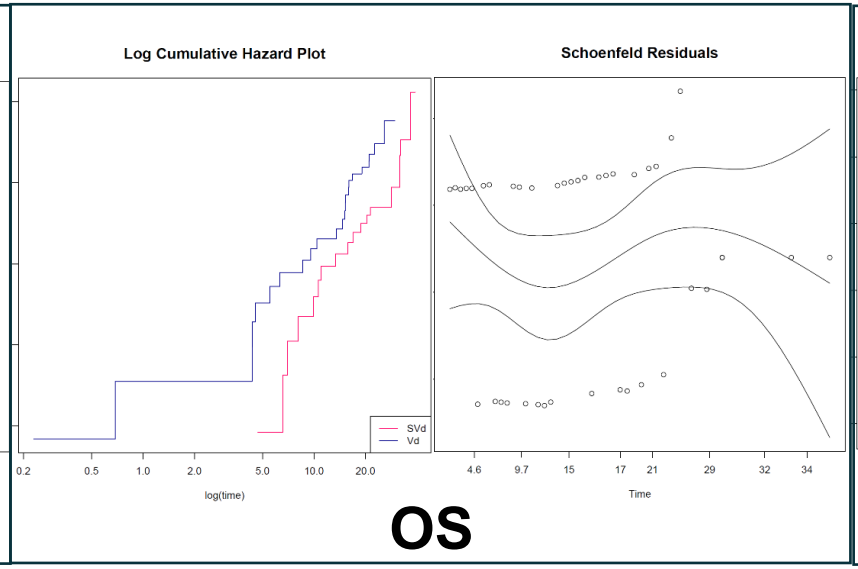
Is the PH assumption violated? Which extrapolations are preferred? Which baseline should be applied for comparators' extrapolations: SEL+BOR+DEX or BOR+DEX?

Abbreviations: 2L, 2nd line; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; IF, independently fitted; JF, jointly fitted; OS, overall survival; PFS, progression free survival; PH, proportional hazards; SEL, selinexor; ToT, time on treatment

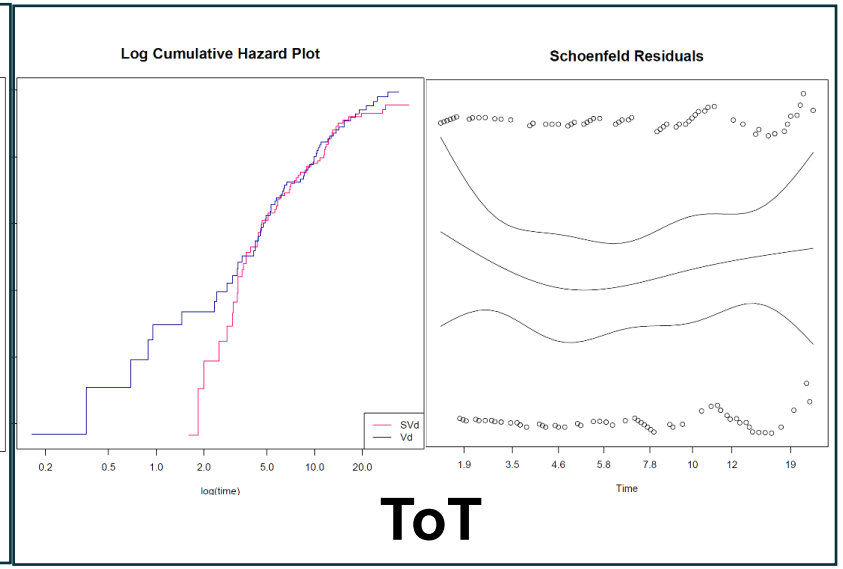
3rd line log-log and Schoenfeld residual plots



PFS



OS



ToT

	Company's base case					EAG's base case				
	Distribution	Mean life years				Distribution	Mean life years			
		SEL+BOR+DEX	BOR+DEX	IXA+LEN+DEX	PAN+BOR+DEX		SEL+BOR+DEX	BOR+DEX	IXA+LEN+DEX	PAN+BOR+DEX
PFS	JF lognormal	1.9	1.3	2.7	2.3	IF lognormal*	1.79	1.40	2.75	2.18
OS	JF Weibull	3.9	2.5	3.7	3.4	IF Weibull	2.86	2.86	2.86	2.86
ToT	JF log-logistic	1	0.95	1.6	1.4	IF generalised gamma**	1.23	0.89	2.35	1.38

Is the PH assumption violated? Which extrapolations are preferred? Which baseline should be applied for comparators' extrapolations: SEL+BOR+DEX or BOR+DEX?

Abbreviations: 3L, 3rd line; BOR, bortezomib; DEX, dexamethasone; IF, independently fitted; IXA, ixazomib; JF, jointly fitted; LEN, lenalidomide; OS, overall survival; PAN, panobinostat; PFS, progression free survival; PH, proportional hazards; SEL, selinexor; ToT, time on treatment; *OS capped at 10 years; **capped to PFS

Key issue 3: OS benefit

Company assumes OS benefit for all therapies whereas EAG assumes none

Background

- Company base case: OS benefit as per BOSTON KM and ITCs
- EAG considered:
  - OS data in BOSTON is immature and uncertain
  - No statistically significant OS differences for all comparators
  - OS benefit includes varying impact of subsequent therapies after progression
  - After 1L, OS likely similar despite therapies at different lines (EAG clinical advisors)
- EAG base case: no OS benefit for all therapies; use BOR+DEX as baseline for OS
  - Scenario: OS with Weibull for SEL+BOR+DEX and estimate comparator OS using EAG preferred ITC HRs applied to BOR+DEX Weibull OS at 2L and 3L

Should an OS benefit for all treatments be modelled?

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Abbreviations: 1/2/3L, 1st/2nd/3rd line; BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; OS, overall survival; SEL, selinexor

Key issue 4: Costs of subsequent therapies*

Background

- Company: included cost of subsequent therapies using weighted average of treatments available in the NHS after 2L or 3L (BOSTON data)
- EAG: subsequent therapies do not reflect UK clinical practice
  - People who had IXA+LEN+DEX would not have LEN+DEX (company assumes 56%)
  - At 3L and 4L, chemotherapy not used often; minority have DAR monotherapy
  - Bendamustine not available; use cyclophosphamide-based chemotherapy or ISA+POM+DEX in CDF

Company

- Provided market share data for 3L and 4L therapies; research conducted by company

EAG base case

- Used market share data and assumptions on current NHS treatment pathway, adjusted for proportion of people from BOSTON having subsequent therapies (79.5%)

How should cost of subsequent therapies be modelled?

*Back-up slide 44

Abbreviations: 2/3/4L, 2nd/3rd/4th line; CDF, Cancer Drugs Fund; DAR, daratumumab; DEX, dexamethasone; ISA, isatuximab; IXA, ixazomib; LEN, lenalidomide; POM, pomalidomide

Key Issue 5: Modelling of adverse events*

Company: AEs weekly events for duration of therapy and weekly disutility
EAG: AEs one-off event and one-off disutility in Cycle 1, as in other NICE TAs

Company

- **Base case:** Grade 3+ TEAEs in ≥5% from BOSTON included as weekly rates for duration on therapy
- **Scenario:** one-off impact in Cycle 1

EAG comments

- Company's approach is inappropriate
  - Favours therapies with shorter PFS (SEL+BOR+DEX only)
- Company assumed all AEs are managed in primary and secondary care
- EAG clinical experts: AEs largely managed in secondary care
- EAG base case: AEs one-off event; AE in secondary care

How should AEs be modelled?

*Back-up slide 45

Abbreviations: AE, adverse event; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; SEL, selinexor; TA, technical appraisal; TE, treatment-emergent

Key issue 6: Health state utility values

Company: utilities independent of lines of therapy
EAG: utilities specific to line of therapy

Company

- Used BOSTON EQ-5D-5L data for health state utilities
- **Base case:** pooled utilities from BOSTON arms and assumed HRQoL not dependent on therapy, lines of therapy or differences in TEAE profiles
- **Scenario:** Hatswell (2019) used in previous NICE TAs

EAG comments

- Hatswell showed utility differences in lines of therapy
  - BOSTON utilities should be based on lines of therapy and progression status
  - EAG base case: BOSTON EQ-5D-5L data, line of therapy as covariate
  - Scenarios: 2L progressed utilities = 3L progression-free utilities; Hatswell utilities

Health state	Company					EAG base case	
	BOSTON EQ-5D-5L			Scenario: Hatswell		BOSTON by line of therapy	
	SEL+BOR+DEX	BOR+DEX	Base case	2L	3L	2L	3L
Progression free	0.700	0.694	0.697	0.620	0.590	0.706	0.694
Progressed	0.663	0.657	0.660	0.550	0.520	0.668	0.659

Abbreviations: 2/3L, 2nd/3rd line; AE, adverse event; BOR, bortezomib; DEX, dexamethasone; EQ-5D, EuroQol-5D; HRQoL, health-related quality of life; SEL, selinexor; TA, technical appraisal; TE, treatment-emergent

How should utilities be modelled?

Company and EAG base case assumptions*

Assumption	Company base case	EAG base case
OS benefit	As per BOSTON KM and ITCs	All therapies, OS = BOR+DEX
Cost of subsequent therapies	Weighted average of therapies after 2L and 3L (BOSTON data); exclude therapies not available in NHS	Used market share data and assumptions on current NHS pathway, adjusted for % from BOSTON having subsequent therapies (79.5%)
Administration cost for oral chemotherapy	Excluded	Included
AE modelling	Weekly event	One-off event in Cycle 1
Resource use	• Based on assumptions in TA897 • Urinary light chain excretion included	• Serum light chain reaction used in routine practice • Many resources used more frequently
End of life care cost	£4,823 based on Round (2015)	£13,712 based on Personal Social Services Research Unit (TA987 and TA870)

*Back-up slide 46

NICE Abbreviations: 2/3L, 2nd/3rd line; AE, adverse event; BOR, bortezomib; DEX, dexamethasone; ITC, indirect treatment comparison; KM, Kaplan-Meier; OS, overall survival; SEL, selinexor; TA, technical appraisal

Assumption	Company base case	EAG base case
2nd line (CAR+DEX)		
Treatment effectiveness	vs SEL+BOR+DEX: **PFS** 0.7; **OS** 0.9	vs BOR+DEX: **PFS** 0.5; **OS** 0.8
Extrapolations of PFS, OS and ToT	**PFS:** IF gamma **OS and ToT:** JF gamma	**PFS and OS:** IF Weibull **ToT:** IF Gompertz
Utility values	**Progression free:** 0.697 **Progressed:** 0.660	**Progression free:** 0.706 **Progressed:** 0.668
3rd line		
Treatment effectiveness	SEL+BOR+DEX vs IXA+LEN+DEX: **PFS** 0.7; **OS** 1.1 vs PAN+BOR+DEX: **PFS** 0.8; **OS** 1.2	BOR+DEX vs IXA+LEN+DEX: **PFS** 0.4; **OS** 0.5 vs PAN+BOR+DEX: **PFS** 0.64; **OS** 0.96
Extrapolations of PFS, OS and ToT	**PFS:** JF lognormal **OS:** JF Weibull **ToT:** JF log-logistic	**PFS:** IF lognormal **OS:** IF Weibull **ToT:** IF generalised gamma
Utility values	**Progression free:** 0.697 **Progressed:** 0.660	**Progression free:** 0.694 **Progressed:** 0.659

Abbreviations: BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; IF, independently fitted; IXA, ixazomib; JF, jointly fitted; LEN, lenalidomide; OS, overall survival; PAN, panobinostat; PFS, progression free survival; SEL, selinexor; ToT, time on treatment

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

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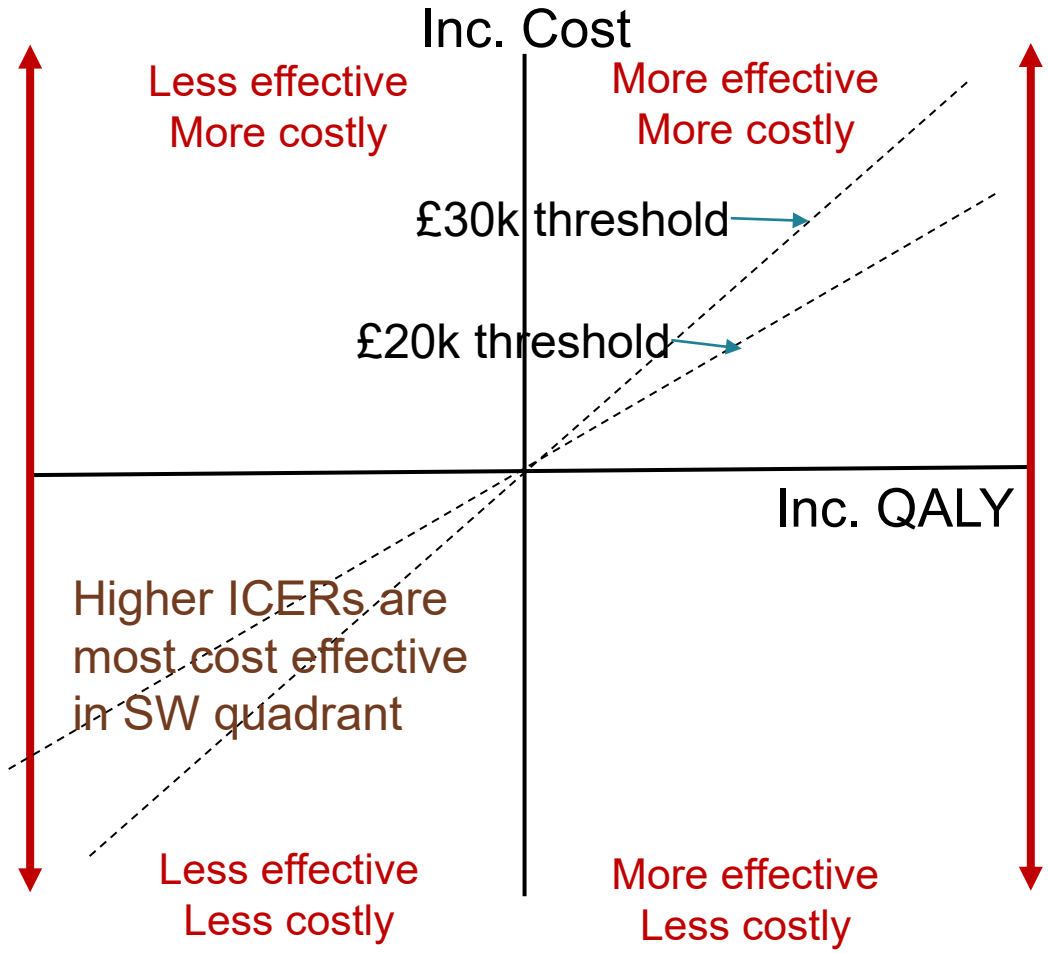
Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme

Drivers of cost-effectiveness results at 2nd line

All ICERs for company and EAG's base cases and scenarios are in SW quadrant

2nd line: SEL+BOR+DEX vs CAR+DEX	ICER/QALY
Company revised base case	**SW quadrant**
Scenarios altering: time horizon, comparative efficacy, PFS/OS/ToT curves, comparator ToT, AE as one-off event, no discounting, SEL full weekly dosage, subsequent therapies costed after stopping, drug wastage excluded, utility source, utility decrements	SW quadrant
EAG base case	**SW quadrant**



Abbreviations: AE, adverse event; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; inc, incremental; k, thousand; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; SEL, selinexor; SW, south west; ToT, time on treatment

Drivers of cost-effectiveness results at 3rd line

For both 3L therapies, SEL+BOR+DEX was dominated in the EAG's base cases (less effective and more costly than comparators)

3rd line: SEL+BOR+DEX vs IXA+LEN+DEX	ICER/QALY
Company revised base case	>£30,000
All company scenarios	>£30,000
EAG base case	**SEL+BOR+DEX dominated**
3rd line: SEL+BOR+DEX vs PAN+BOR+DEX	**ICER/QALY**
Company revised base case	<£30,000
Drivers: comparative efficacy, PFS/OS/ToT curves, comparator ToT, AE as one-off event, SEL full weekly dosage, utility source	Varied in both directions
EAG base case	**SEL+BOR+DEX dominated**

Abbreviations: AE, adverse event; BOR, bortezomib; DEX, dexamethasone; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; k, thousand; OS, overall survival; PAN, panobinostat; PFS, progression free survival; QALY, quality-adjusted life year; SEL, selinexor; ToT, time on treatment

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Other considerations

Company suggests benefits not captured in QALY calculations

- Treatment-specific HRQoL effects are captured via AEs (subtractive effect on QALYs): potentially overlooks treatment benefits when selecting therapy
- Oral administration of SEL (convenient and minimally invasive) vs comparators delivered intravenously in hospital setting
- Carer HRQoL not included

Equality considerations

- No potential issues raised by stakeholders
- But, MM is more common in men, older people (≥75 years) and people of African and Caribbean family background

Are there any uncaptured benefits?
Are there any equality issues to consider?

Abbreviations: AE, adverse event; HRQoL, health-related quality of life; MM, multiple myeloma; QALY, quality-adjusted life year; SEL, selinexor

Selinexor with bortezomib and low-dose dexamethasone for treating relapsed or refractory multiple myeloma

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

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Assumptions	Considerations
Relevant comparators at 3L	IXA+LEN+DEX and/or PAN+BOR+DEX?
ITC at 3L	NMA vs unanchored MAIC?
Extrapolations of PFS, OS and ToT Comparator extrapolations	• PH assumptions violated? • Distributions independently fitted or jointly fitted with BOR+DEX? • Which distributions should be used? • Which baseline should be applied for comparators HRs from ITC? SEL+BOR+DEX or BOR+DEX?
OS benefit	Should an OS benefit for all treatments be included?
Subsequent therapies cost	Company's or EAG's approach?
Modelling of AEs	Weekly event vs one-off event?
Modelling of utilities	Company's independent of line of therapy vs EAG's by line of therapy?
Other considerations	Uncaptured benefits? Equality issues?
ICER threshold	Preferred ICER threshold?
Preferred ICER	Preferred ICER?

Abbreviations: 3L, 3rd line; AE, adverse event; BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; IXA, ixazomib; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PAN, panobinostat; PFS, progression free survival; PH, proportional hazard; SEL, selinexor; ToT, time on treatment

END OF PART 1

THANK YOU

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Selinexor with bortezomib and low-dose dexamethasone for treating relapsed or refractory multiple myeloma

Back-up slides

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BOSTON trial design	Phase 3, randomised, open-label. Stratified by: prior proteosome inhibitor therapies, # prior anti-MM therapies, Revised International Staging System stage at entry (165 sites in 21 countries)
Population	402 adults (≥18 years) with RRMM with 1–3 prior lines of treatment (inc. BOR, CAR, IXA, DAR, LEN, POM): 49% 2L, 32% 3L, 19% 4L
Interventions	SEL+BOR+DEX n=195 vs BOR+DEX n=207
Treatment crossover	77 (37%) cross over from BOR+DEX to SEL+BOR+DEX or SEL+DEX after progression
Primary outcome	PFS (independent review committee masked to treatment group) Primary analysis, pre-specified: 18 February 2020 Updated analysis, conducted at request of CHMP: 15 February 2021 (used in model)
Key secondary outcomes	OS, RR, HRQoL, AEs
EAG comments	**Baseline characteristics:** few ECOG PS ≥2 (typical in trials). Prior SCT differed despite stratified randomisation (ITT population; SEL+BOR+DEX: 39%; BOR+DEX: 30%) and 2L (SEL+BOR+DEX: 39%; BOR+DEX 23%) **Dropouts:** Higher in SEL+BOR+DEX; company's sensitivity analyses: magnitude of bias low **Sample size and power:** 80% power to detect difference of 4.1 months in median PFS. High risk of missing clinically important differences. Lower power in prespecified 2L and 3L subgroups

Abbreviations: 2/3/4L, 2nd/3rd/4th line; AE, adverse event; BOR, bortezomib; CAR, carfilzomib; CHMP, Committee for Medicinal Products for Human Use; DAR, daratumumab; DEX, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance status; HRQoL, health-related quality of life; ITT, intention-to-treat; IXA, ixazomib; LEN, lenalidomide; n, number; OS, overall survival; PFS, progression free survival; POM, pomalidomide; RR, response rate; RRMM, relapsed or refractory multiple myeloma; SCT, stem cell transplant; SEL, selinexor

Link to slide 10

Company NMA methodology

Company

- Bayesian NMA using Markov chain Monte Carlo simulation in WinBUGS
- Burn-in of 50,000 iterations and 20,000 further samples for analysis
- Random effects models (significant heterogeneity in studies)
- Vague priors used for all parameters than for between-study standard deviation, for which an informative half-normal distribution, HN(0,0.322), was used
- Sensitivity analyses using first-order random intercept model fractional polynomial models (PH do not hold in many trials): uncertainty around HRs large due to limited number of studies per comparisons

EAG comments

- Concerns about suitability of network for constant-HR NMAs apply to fractional-polynomial models
- Presents ITCs results for each comparator vs BOR+DEX and SEL+BOR+DEX
- EAG's preferred modelling: use BOR+DEX PFS and OS curves as baseline throughout analyses using IF curves, as PH assumption potentially violated throughout BOSTON analyses

Link to slide 11

Abbreviations: BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; IF, independently fitted; ITC, indirect treatment comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazard; SEL, selinexor

Company's NMA at 3rd line

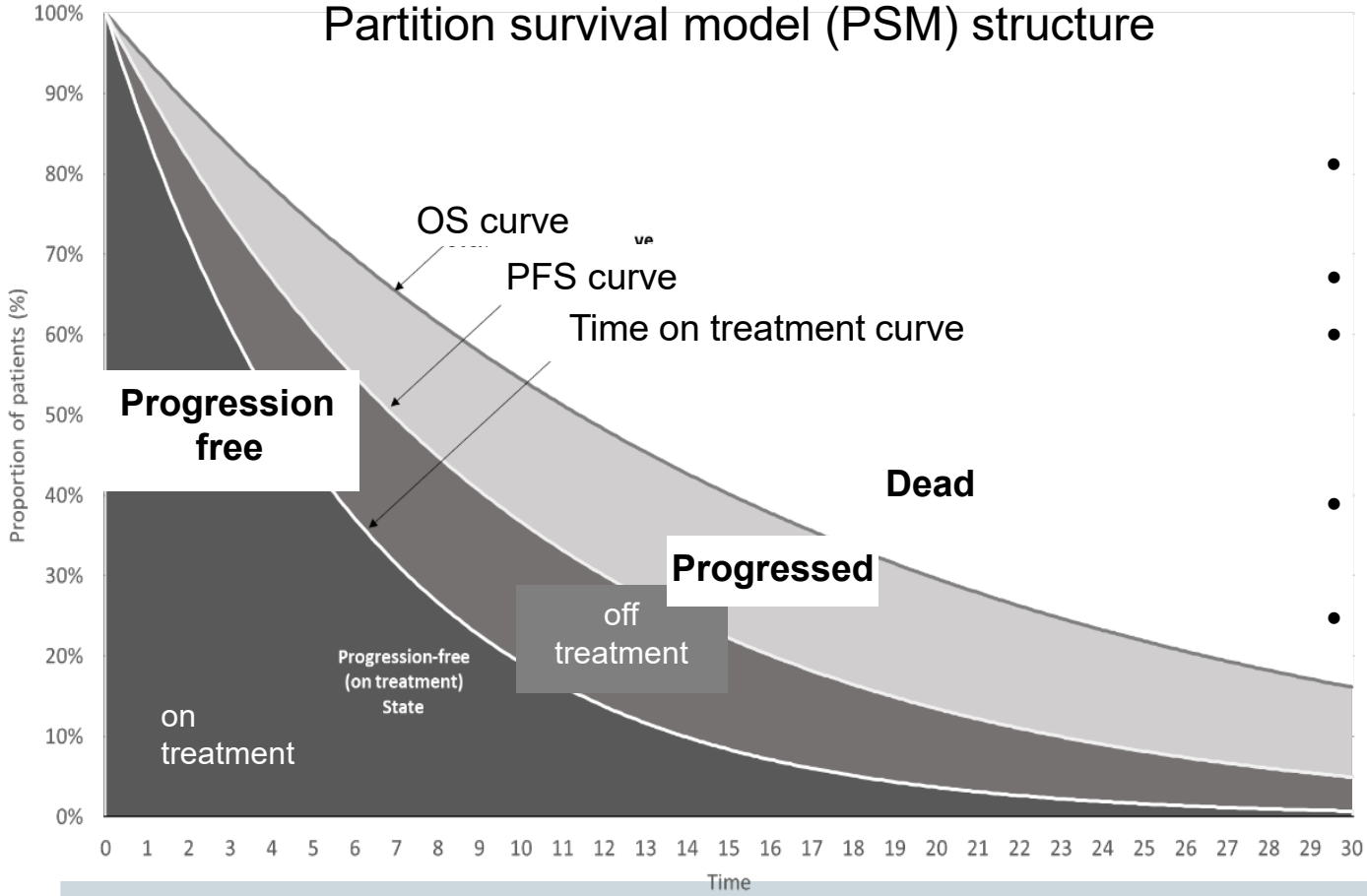
EAG comments

- For PAN+BOR+DEX, NMA is appropriate, reflects Bucher-like comparison between SEL+BOR+DEX (BOSTON) and PAN+BOR+DEX (PANORAMA-1)
- For IXA+LEN+DEX, updated network still at high risk of bias because of:
  - unanchored MAIC between POM+DEX (ICARIA-MM) and BOR+DEX (BOSTON)
  - double use of BOR+DEX BOSTON data to estimate POM+DEX vs BOR+DEX HR and BOR+DEX vs SEL+BOR+DEX HR
  - use of by-arm median PFS data from MM-009 and MM-010
  - potential violation of PH assumption for many contrasts in network for PFS and OS
  - included MM-003 (median 5 previous lines of anti-MM)
  - substantial heterogeneity in trials (MM-009 and MM-010 in 2003 with mixed 2L / 3L)
  - unadjusted crossover in MM-009, MM-010 and MM-003
    - MM-009/MM-010, 48% DEX crossed over on progression or unblinding to LEN+DEX or other LEN-based regimen. Adjusting for crossover, OS reduced. HRs likely favour LEN+DEX over DEX → change in OS estimate in favour of IXA+LEN+DEX vs BOR+DEX or SEL+BOR+DEX in company's NMA if adjusted HRs used. Lack of OS adjustment in MM-003 bias results in opposite direction (favour SEL+BOR+DEX). Cumulative impact of adjusting for crossover in OS analyses is unknown; reflects major uncertainty and limitation in OS NMAs
- Treatment effect modifiers may be imbalanced across network, especially OS for subsequent therapies

Link to slide 12

Abbreviations: 2/3L, 2nd/3rd line; BOR, bortezomib; DEX, dexamethasone; HR, hazard ratio; IXA, ixazomib; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; MM, multiple myeloma; NMA, network meta-analysis; OS, overall survival; PAN, panobinostat; PFS, progression free survival; PH, proportional hazard; POM, pomalidomide; SEL, selinexor

Company's model overview



- PSM with 3 health states (PFS divided into on or off treatment, toxicity dependent)
- Start in PFS and start 2L or 3L (on treatment)
- Extrapolations of PFS, OS and ToT, using standard parametric curves estimate % in HS (Progressed HS = OS – PFS)
- 1 week cycle; half-cycle correction; 35-year time horizon; NHS/PSS perspective; 3.5% discount rate
- Baseline characteristics: 2L (3L): age 67 years (65), male 55% (67%), ECOG 0.68 (0.77), weight 76kg (77), BSA 1.83m^2 (1.85)

Compared to current therapies, technology affects **costs** by:
- lower cost per cycle
- lower (2L) or higher (3L) administrative costs

Technology affects **QALYs** by:
- 2L: reducing PFS and OS
- 3L: reducing PFS and increasing OS

Assumptions with greatest ICER effect:
- Estimation of PFS, OS and ToT
- Including OS benefit
- Costs of subsequent therapies
- Impact of adverse events are for duration people on treatment

Abbreviations: 2/3L, 2nd/3rd line; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; HS, health state; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life year; ToT, time on treatment

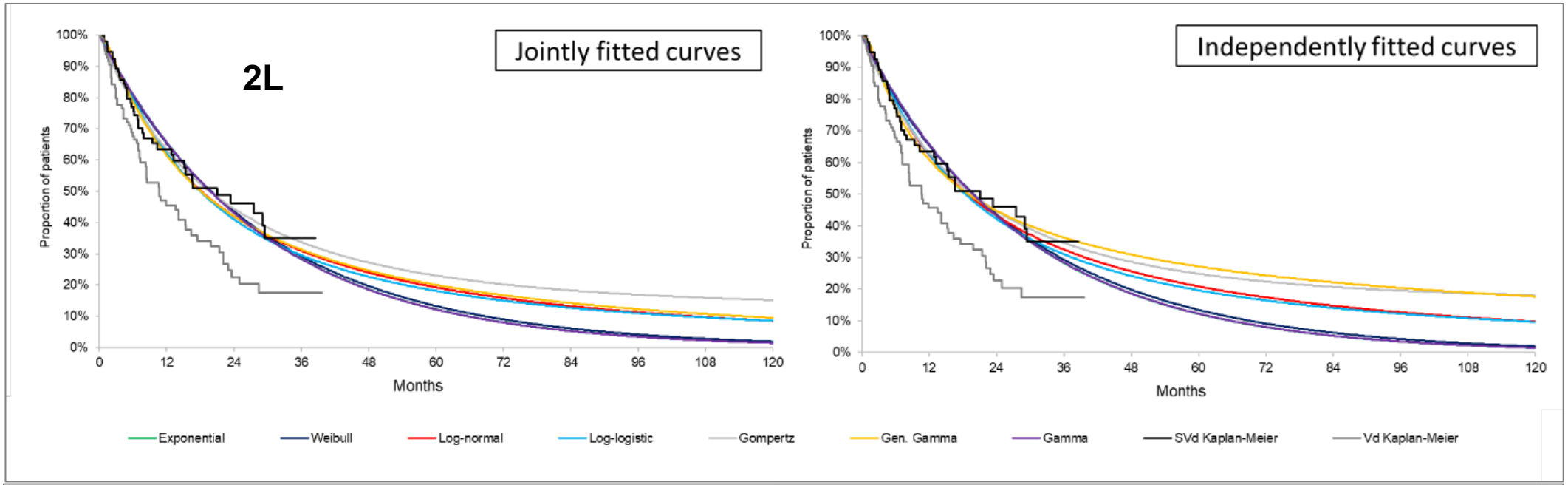
How company incorporated evidence into model

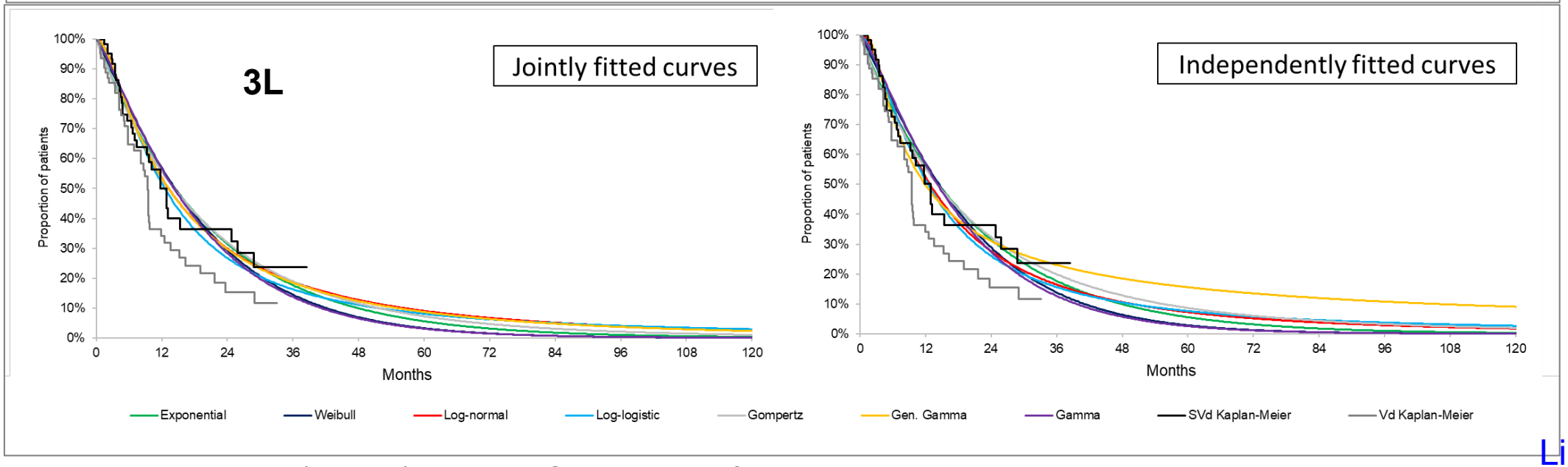
Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	From BOSTON
Intervention efficacy	PFS, OS (adjusted for cross-over treatment in BOR+DEX), ToT: BOSTON updated analysis at 15 Feb 2021
Comparators efficacy	ITCs at 2L and 3L used SEL+BOR+DEX as baseline
Utilities	Health state utilities: BOSTON EQ-5D-5L utilities treatment independent Adverse event-related disutility: weekly
Adverse events (AEs)	BOSTON (SEL+BOR+DEX and BOR+DEX) Comparator AEs
Costs	Drug acquisition, administration costs, subsequent therapies, health-state specific resource use, adverse events, and one-off cost of terminal care
Resource use	NICE TA897, TA870
Discontinuation	ToT from BOSTON: SEL+BOR+DEX ToT from comparators: ITC

Abbreviations: 2/3L, 2nd/3rd line; BOR, bortezomib; DEX, dexamethasone; EQ-5D, EuroQol-5D; ITC, indirect treatment comparison; OS, overall survival; PFS, progression free survival; SEL, selinexor; TA, technology appraisal; ToT, time on treatment

Company parametric extrapolations of PFS at 2L and 3L (BOSTON)





Link to slide 15

Abbreviations: 2/3L, 2nd/3rd line; PFS, progression free survival

Company predicted PFS at 2L and 3L (BOSTON)

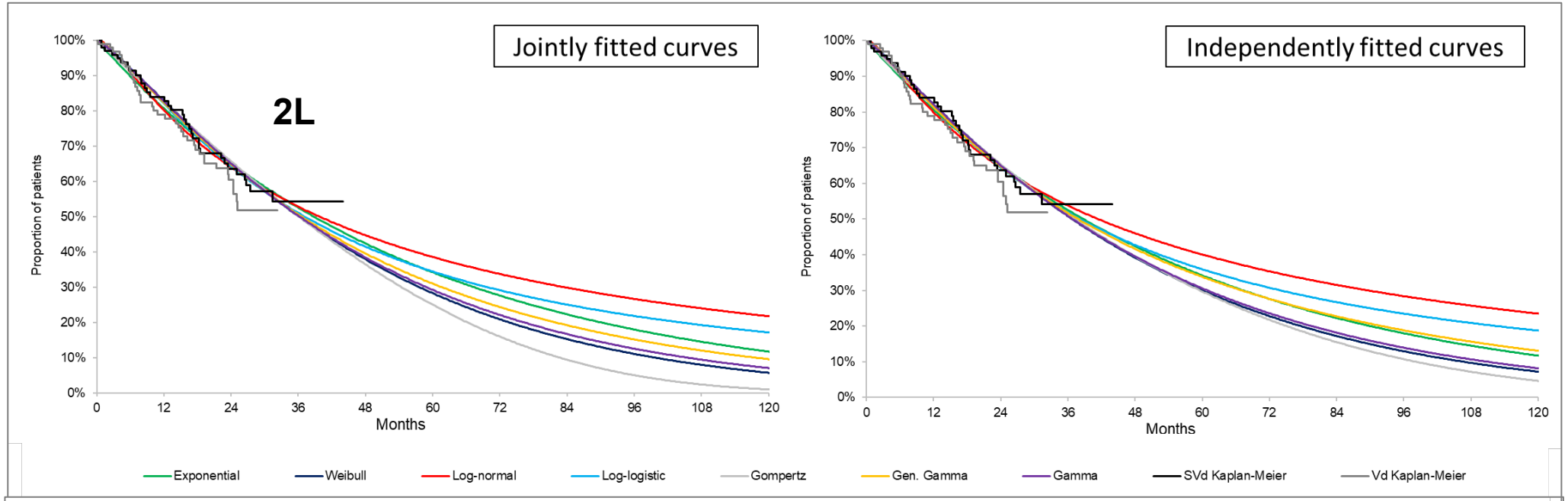
Distributions	Summary survival: 2L (%)					Summary survival: 3L (%)				
	Median months	1Y	2Y	5Y	10Y	Median months	1Y	2Y	5Y	10Y
Kaplan-Meier	21	64	46	-	-	12.9	50	36	-	-
Jointly fitted curves										
Exponential	19.8	66	43	12	1	14.3	56	32	6	0
Weibull	19.8	65	44	13	2	14.3	57	29	3	0
Lognormal	18.2	62	42	19	8	13.1	54	30	9	3
Loglogistic	17.9	62	41	18	9	12.4	52	27	8	3
Gompertz	19.5	63	45	23	15	14.3	56	32	7	1
Generalised gamma	17.9	62	42	20	9	13.1	54	30	9	2
Gamma	19.5	66	43	12	1	14	57	28	3	0
Independently fitted curves										
Exponential	19.8	66	43	12	1	14.3	56	32	6	0
Weibull	19.8	65	44	13	2	14.3	57	29	3	0
Lognormal	18.6	62	43	21	10	12.6	53	28	7	2
Loglogistic	18.4	63	42	20	10	12.4	52	26	8	3
Gompertz	19.5	63	45	25	18	14	55	32	9	2
Generalised gamma	18.9	61	45	27	18	11.7	50	31	16	9
Gamma	19.8	66	43	12	1	14.3	56	32	6	0

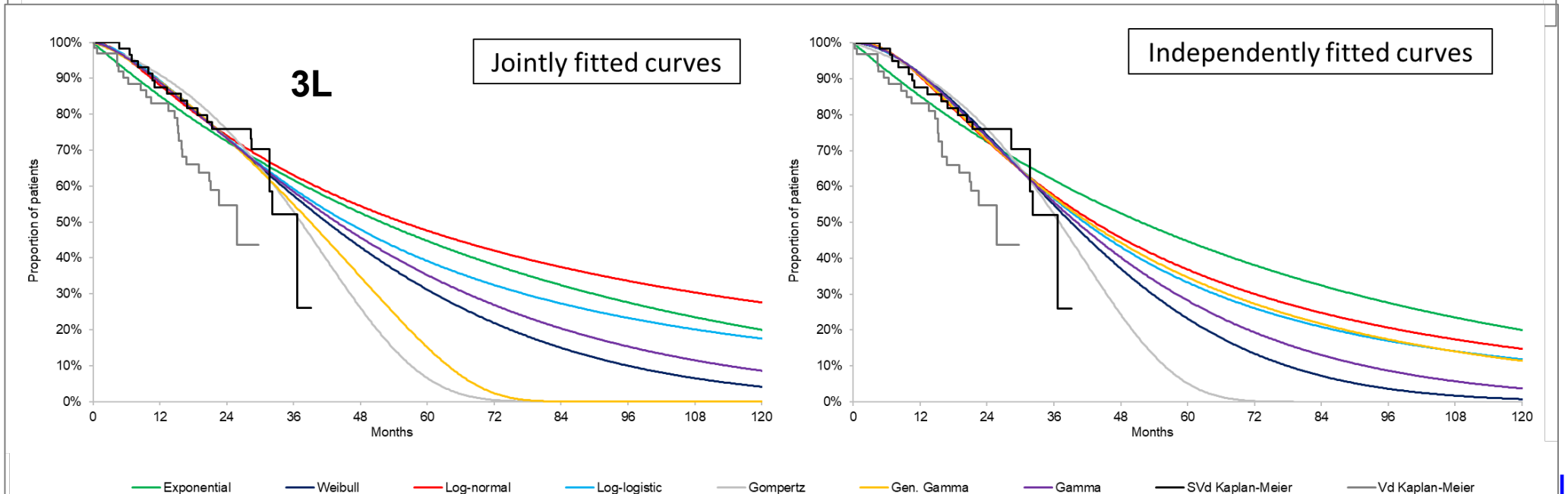
NICE

Abbreviations: 2/3L, 2nd/3rd line; PFS, progression free survival; Y, year

Link to slide 15

Company parametric extrapolations of OS at 2L and 3L (BOSTON)





Abbreviations: 2/3L, 2nd/3rd line; OS, overall survival

Link to slide 15

Company predicted OS at 2L and 3L (BOSTON)

Distributions	Summary survival: 2L (%)					Summary survival: 3L (%)				
	Median months	1Y	2Y	5Y	10Y	Median months	1Y	2Y	5Y	10Y
Kaplan-Meier	NR	84	64	-	-	36.7	88	76	-	-
Jointly fitted curves										
Exponential	38.6	81	65	34	12	51.7	85	72	45	20
Weibull	36.1	83	65	28	6	42.1	89	73	31	4
Lognormal	39.6	80	64	39	22	55.7	88	74	48	28
Loglogistic	37	82	64	34	17	45.5	89	73	39	18
Gompertz	36.1	83	66	25	1	37.5	91	76	7	0
Generalised Gamma	36.6	82	65	31	10	39.1	89	73	15	0
Gamma	36.1	83	65	29	7	43.9	89	73	35	9
Independently fitted curves										
Exponential	38.6	81	65	34	12	51.5	85	73	45	20
Weibull	36.6	82	65	30	7	38.9	92	74	23	1
Lognormal	41.4	80	65	40	23	43.2	91	73	37	15
Loglogistic	38.2	82	65	36	19	41.4	91	74	33	12
Gompertz	37.3	82	65	30	5	36.8	91	76	5	0
Generalised Gamma	37.7	82	65	34	13	42.1	91	73	35	11
Gamma	36.8	82	65	31	8	40.0	91	74	28	4

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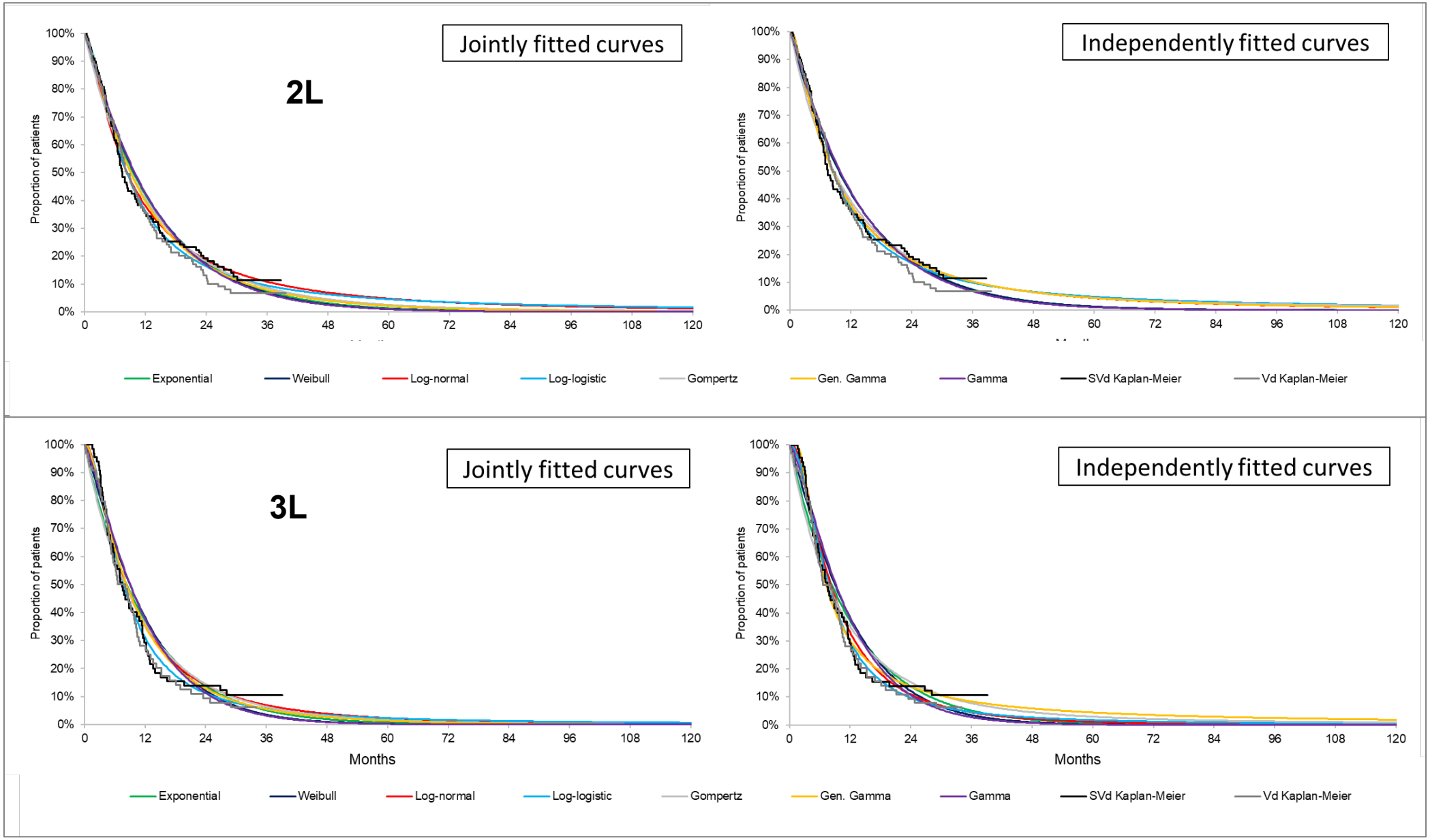
Abbreviations: 2/3L, 2nd/3rd line; OS, overall survival; Y, year

Link to slide 15

Company parametric extrapolation of ToT for SEL+BOR+DEX at 2L and 3L (BOSTON)



Abbreviations: 2/3L, 2nd/3rd line; ToT, time on treatment

Link to slide 15

Company predicted ToT for SEL+BOR+DEX at 2L and 3L (BOSTON)

Distributions	Summary survival: 2L (%)					Summary survival: 3L (%)				
	Median months	1Y	2Y	5Y	10Y	Median months	1Y	2Y	5Y	10Y
Kaplan-Meier	7.4	35	19	-	-	-	-	-	-	-
Jointly fitted curves										
Exponential	9.4	42	18	1	0	8.3	37	14	1	0
Weibull	9.7	43	17	1	0	9	38	12	0	0
Lognormal	8.3	38	19	5	1	8	35	14	2	0
Loglogistic	8.3	36	16	5	2	7.6	31	11	2	1
Gompertz	9	41	18	3	0	7.8	36	15	2	0
Generalised Gamma	9	40	17	2	0	8.3	35	13	1	0
Gamma	9.9	43	17	1	0	9	38	11	0	0
Independently fitted curves										
Exponential	9.4	42	18	1	0	8.3	37	14	1	0
Weibull	9.4	42	18	1	0	9	38	12	0	0
Lognormal	8.3	38	18	4	1	8	33	11	1	0
Loglogistic	8.3	37	17	5	2	7.6	30	10	2	0
Gompertz	8.5	39	19	4	2	7.6	35	15	3	1
Generalised Gamma	8.3	38	18	4	1	7.1	30	14	4	2
Gamma	9.7	43	17	1	0	9.2	38	11	0	0

NICE

Abbreviations: 2/3L, 2nd/3rd line; BOR, bortezomib; DEX, dexamethasone; SEL, selinexor; ToT, time on treatment; Y, year

Link to slide 15

EAG's preferred assumptions for subsequent therapy proportions

Treatment and line	2L (%)				3L (%)					
	SEL+BOR+DEX		CAR+DEX		SEL+BOR+DEX		IXA+LEN+DEX		PAN+BOR+DEX	
	Market share	% based on attrition	Market share	% based on attrition	Market share	% based on attrition	Market share	% based on attrition	Market share	% based on attrition
3L										
IXA+LEN+DEX	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A
PAN+BOR+DEX	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A
Chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A
4L										
IXA+LEN+DEX*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PAN+BOR+DEX*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POM+DEX†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy†	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5L										
PAN+BOR+DEX‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
POM+DEX‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Chemotherapy‡	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

% based on attrition (79.5%)

*For 2L at 4L, market share for IXA+LEN+DEX and PAN+BOR+DEX are switched to capture people who did not get those treatments in previous line

†Market share for each treatment multiplied by remaining proportion not on IXA+LEN+DEX or PAN+BOR+DEX

‡ For 2L, proportion based on % that did not receive treatment in previous line

Abbreviations: 2/3/4/5L, 2nd/3rd/4th/5th line; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; POM, pomalidomide; SEL, selinexor

Link to slide 19

Key Issue 5: Modelling of adverse events*

Company: AEs weekly events for duration of therapy and weekly disutility
EAG: AEs one-off event and one-off disutility in Cycle 1, as in other NICE TAs

Therapy	Disutilities	
	Company base case (weekly)	EAG base case: one-off disutility applied in cycle 1
SEL+BOR+DEX	-0.0078	-0.018 (2L); -0.019 (3L)
BOR+DEX	-0.0036	-
CAR+DEX	-0.0012	-0.004
IXA+LEN+DEX	-0.0015	-0.011
PAN+BOR+DEX	-0.0152	-0.008

Link to slide 20

NICE

Abbreviations: AE, adverse event; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; SEL, selinexor; TA, technical appraisal; TE, treatment-emergent

Other issues

Secondary issues identified by EAG:

- Company's positioning of SEL+BOR+DEX at 2L is for subgroup whose condition is refractory to lenalidomide and daratumumab (narrower than NICE final scope)
- Administration cost for oral chemotherapy should be included
- Resource use assumptions should be more reflective of NHS
- End of life care cost from PSSRU should be used

QALY weightings for severity parameters	2L	3L
Starting age (years)	67.18	65.33
Proportion male (%)	55%	67%
Expected total QALYs for general population	10.1	10.8
Most effective comparator	CAR+DEX	IXA+LEN+DEX
Total QALYs that people living with a condition would be expected to have with current treatment	2.9	2.5
QALY shortfall (absolute)	7.2	8.2
QALY shortfall (relative)	71%	76%
QALY modifier	1.0	1.0

Abbreviations: 2/3L, 2nd/3rd line; BOR, bortezomib; CAR, carfilzomib; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; SEL, selinexor

Link to slide 22