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

PART 1 for PROJECTOR: contains **no CON** information

Second HST appraisal committee meeting

Chair: Paul Arundel

Lead team: Carrie Gardner, Jonathan Ives, Stuart Mealing

External assessment group: BMJ Technology Assessment Group

Technical team: Sharlene Ting, Victoria Kelly, Alan Moore, Emily Crowe

Company: Menarini-Stemline UK

7th March 2024

Draft guidance consultation

Committee preferred EAG base case for second and third-line comparisons

DG optimised recommendation at second line

Selinexor with bortezomib and dexamethasone is recommended as an option for treating multiple myeloma in adults, only if:

- they have only had 1 previous line of treatment, and
- their condition is refractory to both daratumumab and lenalidomide, and
- the company provides selinexor according to the commercial arrangement

Not recommended at third line after 2 previous lines of any treatment

DG consultation responses

- Company: feedback on EAG's assumption of equivalent overall survival benefit for all treatments; revised PAS
- Myeloma UK
- Clinical experts
- 1 web comment

Abbreviations: DG, draft guidance; EAG, Evidence Assessment Group; PAS, patient access scheme

Committee ACM1 considerations: 3rd line positioning

RECAP

Issue	Committee considerations
Comparators	IXA+LEN+DEX (LEN-sensitive), PAN+BOR+DEX (LEN-refractory)
BOSTON population	May not be representative of NHS patients: 68% did not have prior LEN
BOSTON LEN-refractory subgroup (n=106)	SEL+BOR+DEX statistically significantly improved PFS and OS vs BOR+DEX (analysis not by line of treatment)
Indirect treatment comparisons	SEL+BOR+DEX no statistically significant differences in PFS and OS (vs IXA+LEN+DEX unadjusted MAIC; vs PAN+BOR+DEX NMA)
Long-term extrapolations of PFS, OS and ToT	PH assumption violated, independently fitted models and EAG's extrapolations (BOR+DEX as baseline for comparators) preferred
OS benefit	Differences should be modelled, but lack of evidence of OS benefit. Preferred EAG's base case (no differences in OS between treatments, OS relative to BOR+DEX used for all treatments)
Subsequent treatments	Preferred EAG's base case but acknowledged EAG's distributions of subsequent treatments did not reflect clinical experts' opinion at ACM1. Should be modelled accurately
Adverse events	EAG's base case (one-off event in cycle 1)
Health state utilities	EAG's base case (approach by line of treatment)

Abbreviations: ACM, appraisal committee meeting; BOR, bortezomib; DEX, dexamethasone; EAG, Evidence Assessment Group; IXA, ixazomib; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; n, number; NMA, network meta-analysis; OS, overall survival; PAN, panobinostat; PFS, progression free survival; PH, proportional hazards; SEL, selinexor; ToT; time on treatment

Draft guidance consultation: feedback from stakeholders

Feedback from Myeloma UK and web comment

- **Not recommended at 3L, especially if refractory to IXA+LEN+DEX or intolerant of PAN+BOR+DEX:** unreasonable; reconsider for routine commissioning
- **3L comparators:** not appropriate for all (some people may be LEN-refractory or cannot take PAN+BOR+DEX)
- **Significant unmet need:**
  - Primary refractory myeloma is rare with DAR+LEN treatment
  - Some people may choose not to have DAR at 1L
  - Current evolving treatment pathway → lack of 3L options for MM refractory to existing treatments
- **SEL+BOR+DEX:** innovative, clinically effective and safe for people who cannot have IXA+LEN+DEX or PAN+BOR+DEX, may facilitate future treatment with innovative medicines, significant impact on health and psychological well-being
- **MM pathway:** patient and clinical expert knowledge critical to ensuring real-world requirements and outcomes are considered
- **Equality:** may be discriminatory based on average age at 3L

Abbreviations: 1/3L, 1st/3rd line; BOR, bortezomib; DAR, daratumumab; DEX, dexamethasone; IXA, ixazomib; LEN, lenalidomide; MM, multiple myeloma; PAN, panobinostat; SEL, selinexor

Key issue: OS benefit

Company prefers to model OS based on BOSTON/ITC data

EAG prefers to assume no difference in OS benefit between treatments

Background

- Company base case: used OS data from BOSTON and ITCs
- EAG base case: no OS difference between treatments, used BOR+DEX OS curve
  - BOSTON OS immature and uncertain
  - No statistically significant OS differences for any comparisons
  - OS benefit likely includes varying impacts of subsequent treatments after disease progression
  - EAG clinical advisers: after 1L, OS is likely to be similar irrespective of treatments received at different lines, as people are unlikely to be off treatment until their 6L of treatment
- Committee: OS differences should be modelled. Because of lack of evidence, preferred EAG's base case

Abbreviations: 1/6L, 1st/6th line; BOR, bortezomib; DEX, dexamethasone; EAG, Evidence Assessment Group; ITC, indirect treatment comparison; OS, overall survival

OS benefit: company feedback and EAG critique (1)

Company DG consultation feedback	EAG critique
Incorrect that OS is same after 1L • Disease control and OS rates decrease rapidly from 1L and continue to decrease over subsequent lines (61% have 2L, 38% have 3L, 1% have 5L [Yong et al 2016]) → implausible that OS is similar for all across treatment lines	• Agrees OS is different for people at different lines of treatment • EAG's initial comments "*patients' OS is likely to be similar irrespective of the treatments they receive at different lines*" relates to an expected similarity in OS between patients receiving different treatments at a certain line, e.g. at 3L, and not an expected similarity in OS between different lines
SEL+BOR+DEX OS benefit is clinically plausible • New mode of action • Adding treatments with new mechanisms of action into treatment pathway will likely improve OS outcomes	• Agrees possible for different treatments to provide different OS outcomes for people with RRMM but theory needs proof with appropriate evidence • Does not consider company evidence is adequately robust to justify OS benefit for SEL+BOR+DEX vs 3L comparators • Company has not provided further evidence from BOSTON or real-world data to support SEL+BOR+DEX improves OS vs current NHS treatments

Abbreviations: 1/2/3/5L, 1st/2nd/3rd/5th line; BOR, bortezomib; DEX, dexamethasone; DG, draft guidance; EAG, Evidence Assessment Group; OS, overall survival; RRMM, relapsed or refractory multiple myeloma; SEL, selinexor

OS benefit: company feedback and EAG critique (2)

Company DG consultation feedback	EAG critique

SEL+BOR+DEX statistically significantly improves OS vs BOR+DEX in BOSTON's LEN-refractory subgroup (27 vs 19 months; HR=0.53; 95% CI: 0.30, 0.95; p=0.03)
• No data on LEN-refractory subgroup for comparators
• ITC on full population: no statistically significant differences in PFS and OS for SEL+BOR+DEX vs 3L comparators
	• Agrees LEN-refractory subgroup showed larger OS difference than in BOSTON ITT population
	• Notes that subgroup analysis:
	  • is not pre-specified or reported in CSR
	  • includes all BOSTON patients (2L, 3L, 4L; n=106), not for 3L alone (n=41) for 3L comparisons
	• No ITC because no comparative data at 3L in LEN-refractory subgroup

No statistically significant differences for *both* OS and PFS vs comparators at 2L/3L
• EAG has taken pessimistic approach when considering ITC results
	• Disagrees there is similar uncertainty or risk of bias for PFS and OS because:
	  • PFS is primary outcome of key trials
	  • BOSTON's PFS is more mature than its OS
	  • OS confounded by different subsequent treatment use in key trials
	  • BOSTON OS is sensitive to adjustment
	• Longer term OS and impact of subsequent treatment use are needed to justify including OS benefit for any treatment

Abbreviations: 2/3/4L, 2nd/3rd/4th line; BOR, bortezomib; CI, confidence interval; CSR, clinical study report; DEX, dexamethasone; DG, draft guidance; EAG, Evidence Assessment Group; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention to treat; LEN, lenalidomide; n, number; OS, overall survival; p, probability; PFS, progression free survival; SEL, selinexor

OS benefit: feedback from clinical experts

Clinical experts consider OS differs between treatments after 1L and clinical data supports OS benefit of SEL+BOR+DEX in LEN-refractory subgroup

Clinical experts DG response

- Disagree that OS likely similar despite different lines of treatment
  - Studies show difference in OS between interventions after 1L: (Dimopoulos et al 2023, Sonneveld et al 2022)
  - OS favoured SEL+BOR+DEX vs comparators in NMA (but not statistically significant)
- Good clinical data that support potential OS benefit of SEL+BOR+DEX in LEN-relapsed/refractory subgroup (Mateos et al 2023 abstract)
- Clinically, IXA+LEN+DEX preferred for LEN-sensitive subgroup

How should OS benefit be modelled? Company ITC or EAG no differences in OS between treatments?

Abbreviations: 1L, 1st line; BOR, bortezomib; DEX, dexamethasone; DG, draft guidance; IXA, ixazomib; LEN, lenalidomide; NMA, network meta-analysis; OS, overall survival; SEL, selinexor

Key issue: Costs of subsequent therapies

Background

- Company base case at ACM1: used BOSTON data and weighted average of treatments available in the NHS after 2L or 3L
- EAG base case at ACM1: used company market share data and assumptions on current NHS treatment pathway, adjusted for proportion from BOSTON having subsequent therapies (~80%)
- Feedback from clinical experts at ACM1:
  - 80% having subsequent therapies likely too high, studies suggest 20% remain on treatment at 4L and 5L
  - After 3L, no significant differences in subsequent treatments based on whether people had SEL+BOR+DEX or PAN+BOR+DEX
  - After 3L, MM is likely LEN-refractory, more likely to have POM+DEX at 4L
- Committee: preferred to have seen subsequent treatments modelled more accurately based on the treatment pathway seen in NHS clinical practice

Abbreviations: 2/3/4/5L, 2nd/3rd/4th/5th line; ACM, appraisal committee meeting; BOR, bortezomib; DEX, dexamethasone; EAG, Evidence Assessment Group; LEN, lenalidomide; MM, multiple myeloma; PAN, panobinostat; POM, pomalidomide; SEL, selinexor

Costs of subsequent therapies: EAG scenarios

At NICE request, EAG explored alternative assumptions for subsequent treatment costs

- **Scenario 1 (clinical experts feedback at ACM1):**
  - 20% of people at 3L go on to subsequent treatment; no differences in subsequent treatments regardless of 3L treatment;
  - at 4L, 80% have POM+DEX and 20% have chemotherapy;
  - at 5L, 20% have POM+DEX and 80% chemotherapy.
- **Scenario 2 (no difference in cost of subsequent treatments for SEL+BOR+DEX and comparators):**
  - Subsequent treatment costs linked to duration spent in progressed state → EAG estimated one-off cost of £15,366 using weighted weekly subsequent treatment cost x duration (company assumed to be 9 months)
  - Since 1 subsequent treatment cost is assumed for all treatments, incremental cost = £0
  - Scenario 2 favours SEL+BOR+DEX because estimated PFS is shorter vs longer PFS for PAN+BOR+DEX and IXA+LEN+DEX

How should cost of subsequent therapies be modelled?
Is scenario 2 clinically plausible?

Abbreviations: 3/4/5L, 3rd/4th/5th line; ACM, appraisal committee meeting; BOR, bortezomib; DEX, dexamethasone; EAG, Evidence Assessment Group; IXA, ixazomib; LEN, lenalidomide; PAN, panobinostat; PFS, progression free survival; POM, pomalidomide; SEL, selinexor

Company and EAG base case assumptions

Assumption	Company original base case	Company revised 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	• 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)	

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

Assumption	Company original base case	Company revised base case	EAG base case
Treatment effectiveness at 3L	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 at 3L	**PFS:** JF lognormal **OS:** JF Weibull **ToT:** JF log-logistic	**PFS:** IF lognormal **OS:** IF Weibull **ToT:** IF generalised gamma	
Utility values at 3L	**Progression free:** 0.697 **Progressed:** 0.660	**Progression free:** 0.694 **Progressed:** 0.659	

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; SEL, selinexor; ToT, time on treatment

Cost-effectiveness results

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

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

Drivers of cost-effectiveness results at 3rd line

EAG attributes differences in deterministic and probabilistic results for IXA+LEN+DEX to uncertainty in unanchored MAIC estimates

SEL+BOR+DEX vs IXA+LEN+DEX	ICER	
	Deterministic	Probabilistic
Company revised base case (EAG base case but including OS benefit)	**SW quadrant**	**SEL+BOR+DEX dominated**
Scenarios 1 and 2 on cost of subsequent treatments	SEL+BOR+DEX dominated	SW quadrant
EAG base case (no OS benefit)	**SEL+BOR+DEX dominated**	
Scenarios 1 and 2 on cost of subsequent treatments		
SEL+BOR+DEX vs PAN+BOR+DEX	**Deterministic**	**Probabilistic**
Company revised base case (EAG base case but including OS benefit)	**>£30,000**	
Scenarios 1 and 2 on cost of subsequent treatments	<£30,000	>£30,000
EAG base case (no OS benefit)	**SEL+BOR+DEX dominated**	
Scenarios 1 and 2 on cost of subsequent treatments		

Abbreviations: BOR, bortezomib; DEX, dexamethasone; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; IXA, ixazomib; LEN, lenalidomide; MAIC, matching-adjusted indirect comparison; OS, overall survival; PAN, panobinostat; QALY, quality-adjusted life year; SEL, selinexor; SW, south west

Other considerations

Equality considerations

- Negative recommendation at 3rd line may potentially be discriminatory based on average age of people at that point in the treatment pathway

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

Assumptions	Considerations
OS benefit	Should an OS benefit for all treatments be included?
Subsequent therapies cost	EAG's original approach or approach based on feedback from clinical experts at ACM1 (scenario 1) or no differences between treatments (scenario 2)?
Other considerations	Uncaptured benefits? Equality issues?
ICER threshold	Preferred ICER threshold?
Preferred ICER	Preferred ICER?

Abbreviations: ACM, appraisal committee meeting; EAG, Evidence Assessment Group; ICER, incremental cost-effectiveness ratio; OS, overall survival

END OF PART 1

THANK YOU

NICE National Institute for Health and Care Excellence

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

Back-up slides: slides from ACM1

NICE National Institute for Health and Care Excellence

Relapsed or refractory multiple myeloma

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

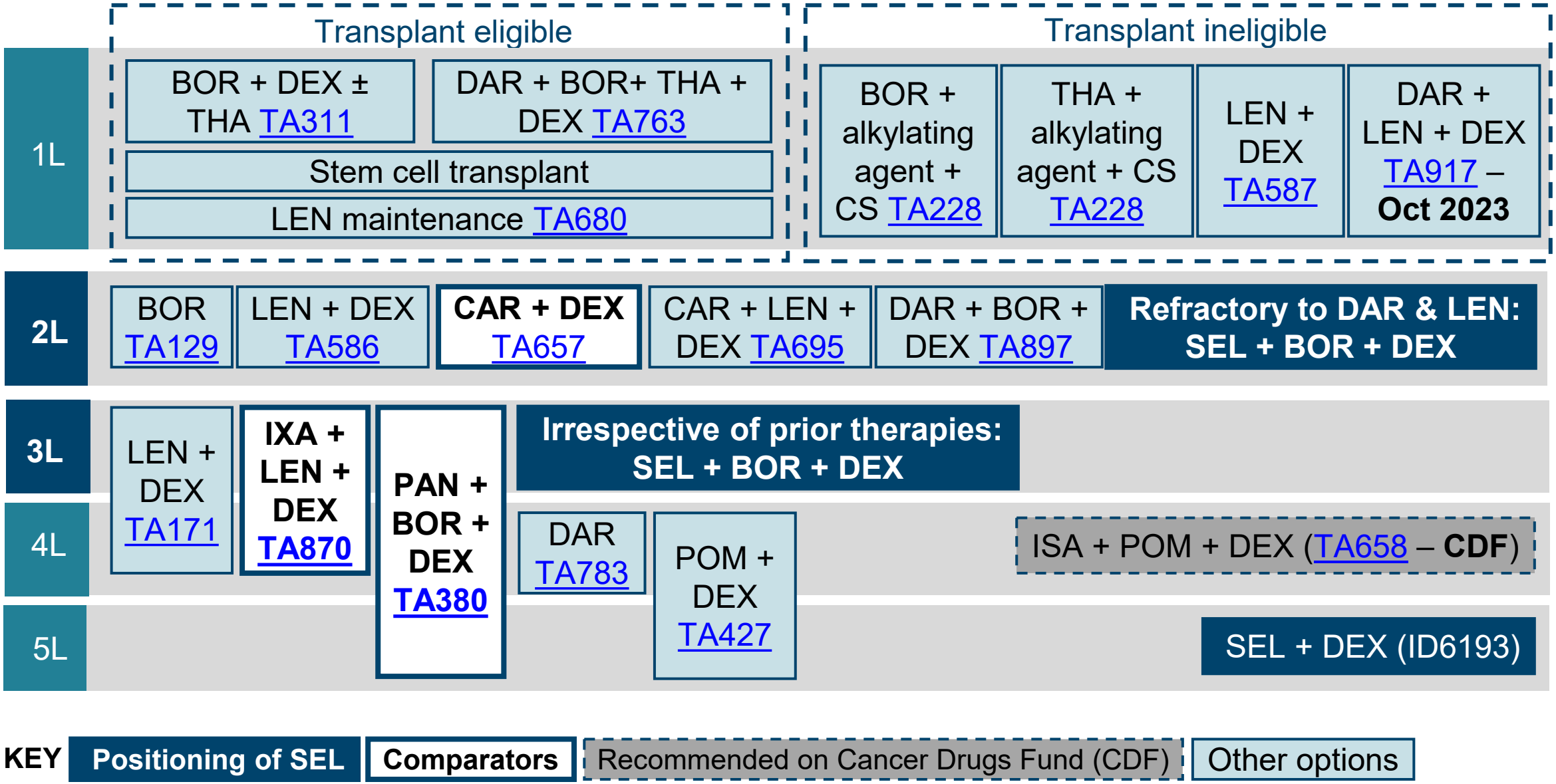
- **Epidemiology**: ~5,800 new cases in UK
    - more common in elderly, men and people of African family background
- **Classification**
    - Relapsed: previously treated myeloma that progresses and needs new therapy
    - Refractory: no response to therapy or progression within 60 days of last therapy
- **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

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



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

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

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

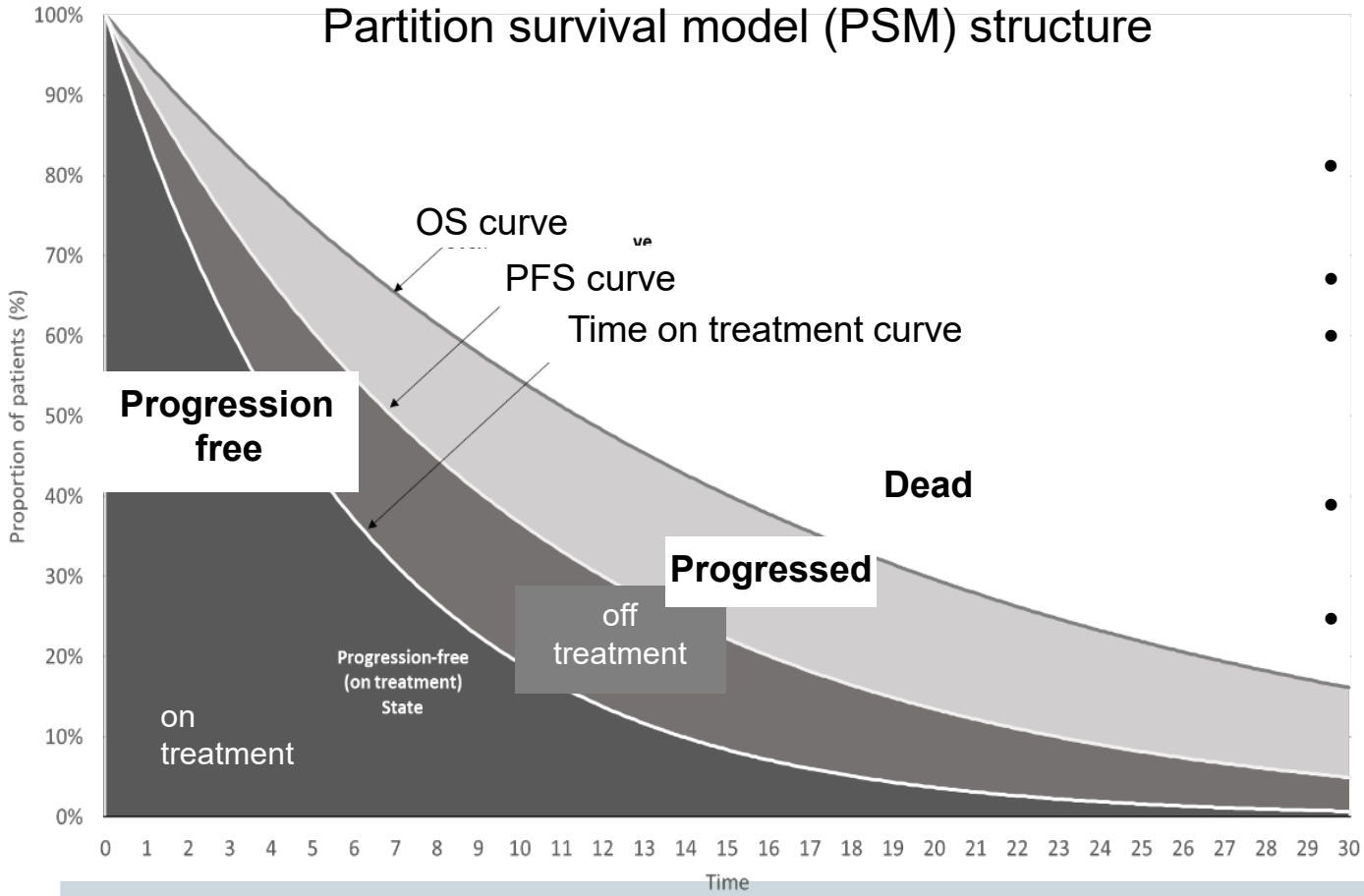
ITC results: 3rd line

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

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

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