NICE National Institute for Health and Care Excellence

Nivolumab for treating relapsed or refractory classical Hodgkin lymphoma [ID972]

Second appraisal committee meeting

Chair's presentation

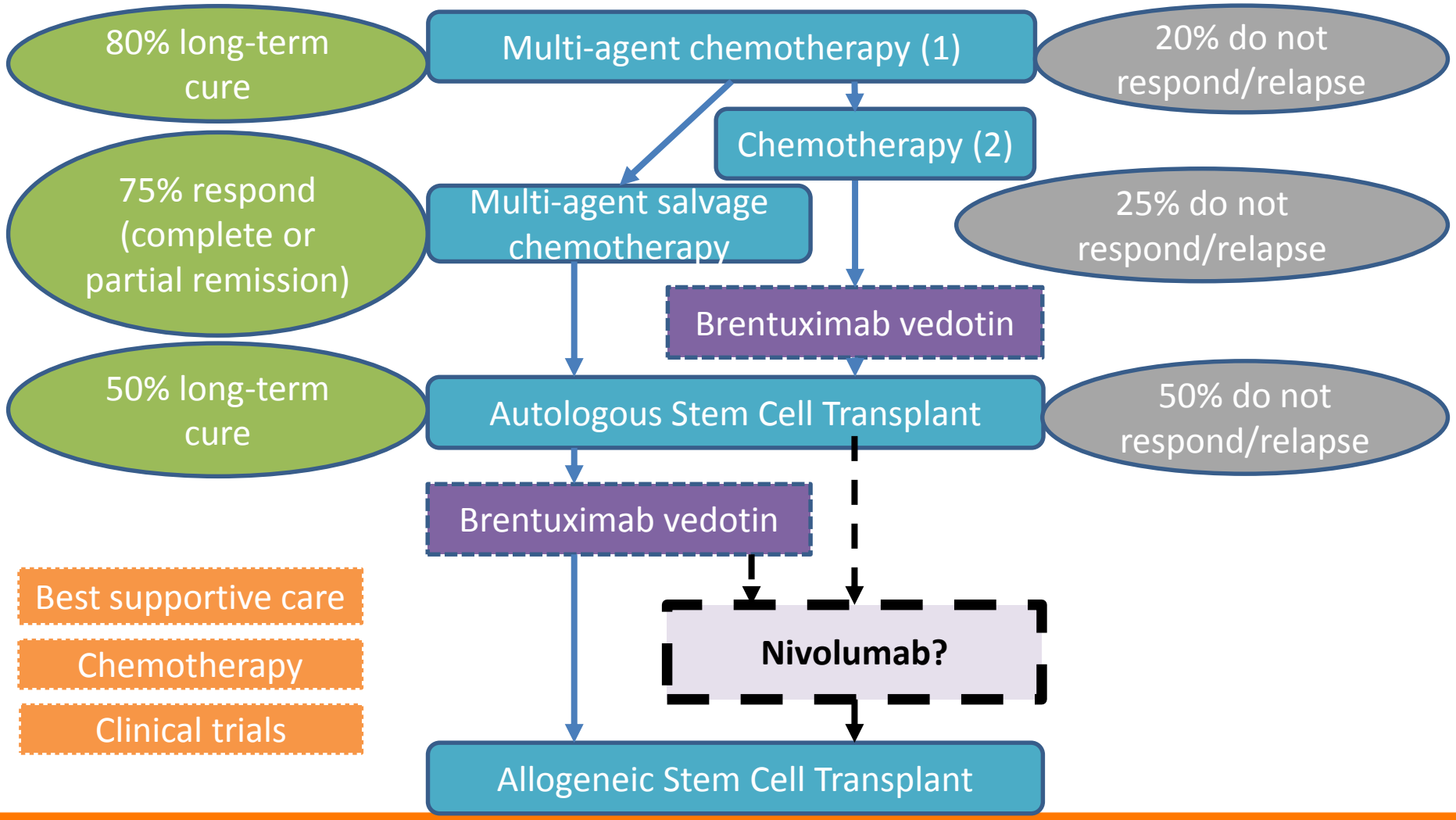
12 April 2017

Nivolumab (Opdivo)
Bristol-Myers Squibb

Mechanism of action	Human monoclonal antibody that blocks PD-1 (programmed cell death protein 1) to promote anti-tumour response
Marketing authorisation	" …for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) after autologous stem cell transplant (autoSCT) and treatment with brentuximab vedotin" Designated Promising Innovative Medicine by MHRA
Administration and dose	3 mg/kg every 2 weeks, administered intravenously
Cost	List price £439 (4 ml vial) or £1,097 (10 ml vial) Average cost of a course of treatment £5,724 per month (not including administration costs) Company has agreed a patient access scheme (PAS) with the Department of Health which provides a simple discount to the list price

Current management

No standard of care, no NICE guidance



Company's clinical evidence
Trial populations

Trial		Previous treatment	No.
CheckMate 205 Phase 2 non-comparative single-arm trial	Cohort A	ASCT → Failure NOT RELEVANT (BTX NAÏVE)	63
	Cohort B	ASCT → BTX → Failure	80
	Cohort C	ASCT → BTX → Failure	57
		BTX → ASCT → Failure	33
		BTX → ASCT → BTX → Failure	8
CA209-039 Phase 1 non-comparative single-arm trial		ASCT → BTX → Failure	15
Total			**193**

Company's clinical evidence

Trial results

	CheckMate 205 Cohort B	CheckMate 205 Cohort C	CA209-039
Number of patients	80	98	15
Median follow-up	15.7 months	8.9 months	23.3 months
Objective response rate (95% CI)	67.5% (54) (57.2, 77.8)	73.0% (73) (64.3, 81.7)	60% (9)
Progression-free survival, median (95% CI)	14.78 months (11.33, NA)	11.17 months (8.51, NA)	12.65 months (5.91, NA)
Overall survival, at 6 months (95% CI)	96.1% (92.0, 100)	94.0% (89.1, 98.8)	NA
Median overall survival was not reached			
Objective response rate and progression-free survival are as assessed by Independent Radiologic Review Committee			

CI, confidence interval; NA, not available

Company's clinical evidence
Indirect comparison with standard of care

- Nivolumab data pooled from 2 trials and extrapolated
- Cheah 2016, a retrospective real-world study conducted in US, chosen as source of comparator data
  - ~70% patients had previous autologous stem cell transplant and brentuximab vedotin
  - Other treatments included alkylators, platinum-based therapies and investigational agents
- Results from subgroup of patients who did not receive investigational agents used to compare with nivolumab

	Objective response rate		Overall survival	Progression-free survival
	Relative risk	%		
Nivolumab pooled cohort		[redacted]	[redacted]	[redacted]
Cheah (excluding patients who received investigational agents)	[redacted]	[redacted]	[redacted]	[redacted]

Company's clinical evidence

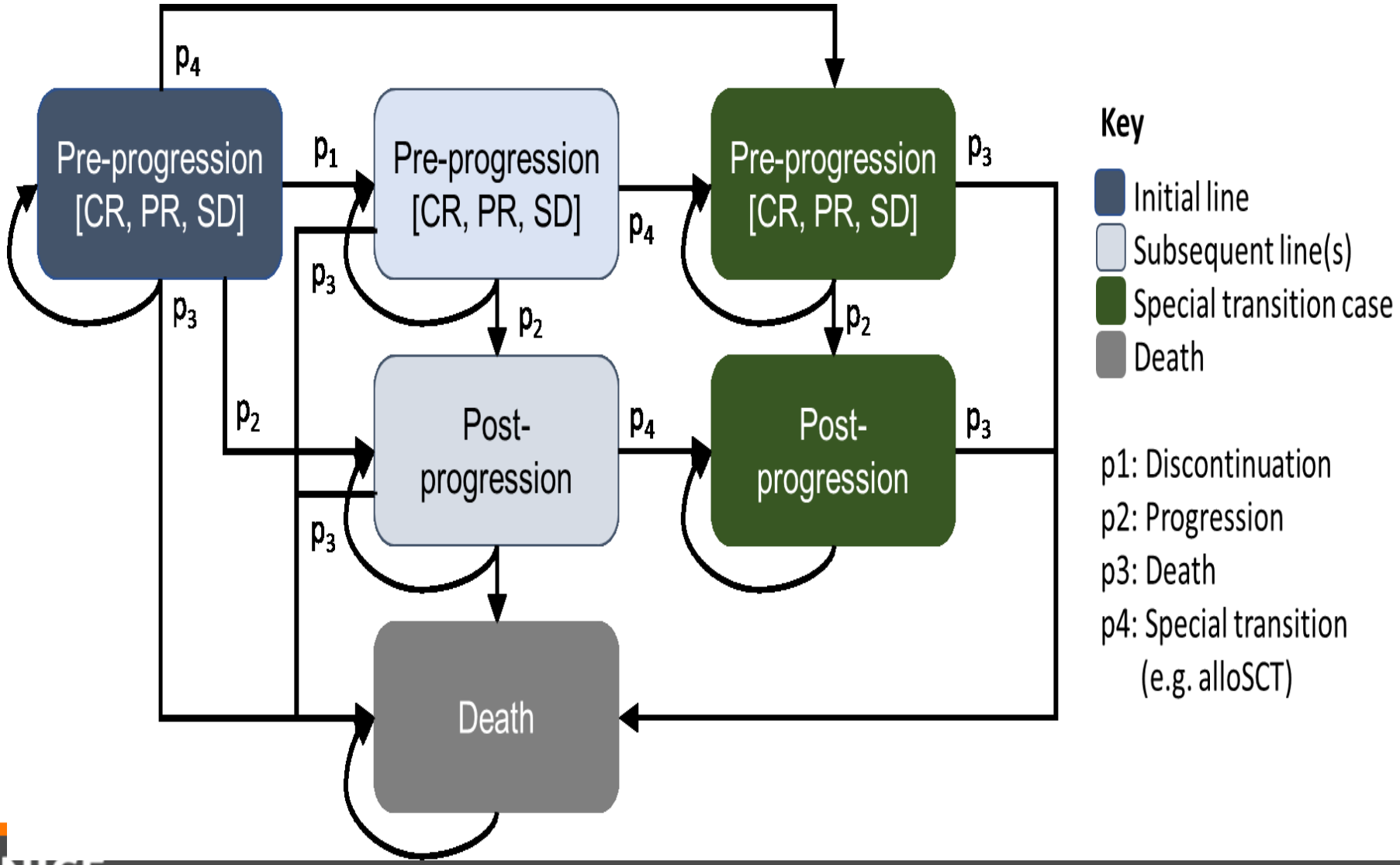
Results: Unadjusted indirect treatment comparison

Cheah (excluding investigational agents) chosen as comparator	Objective response rate		OS (mths)	PFS (mths)
	RR	%		
[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

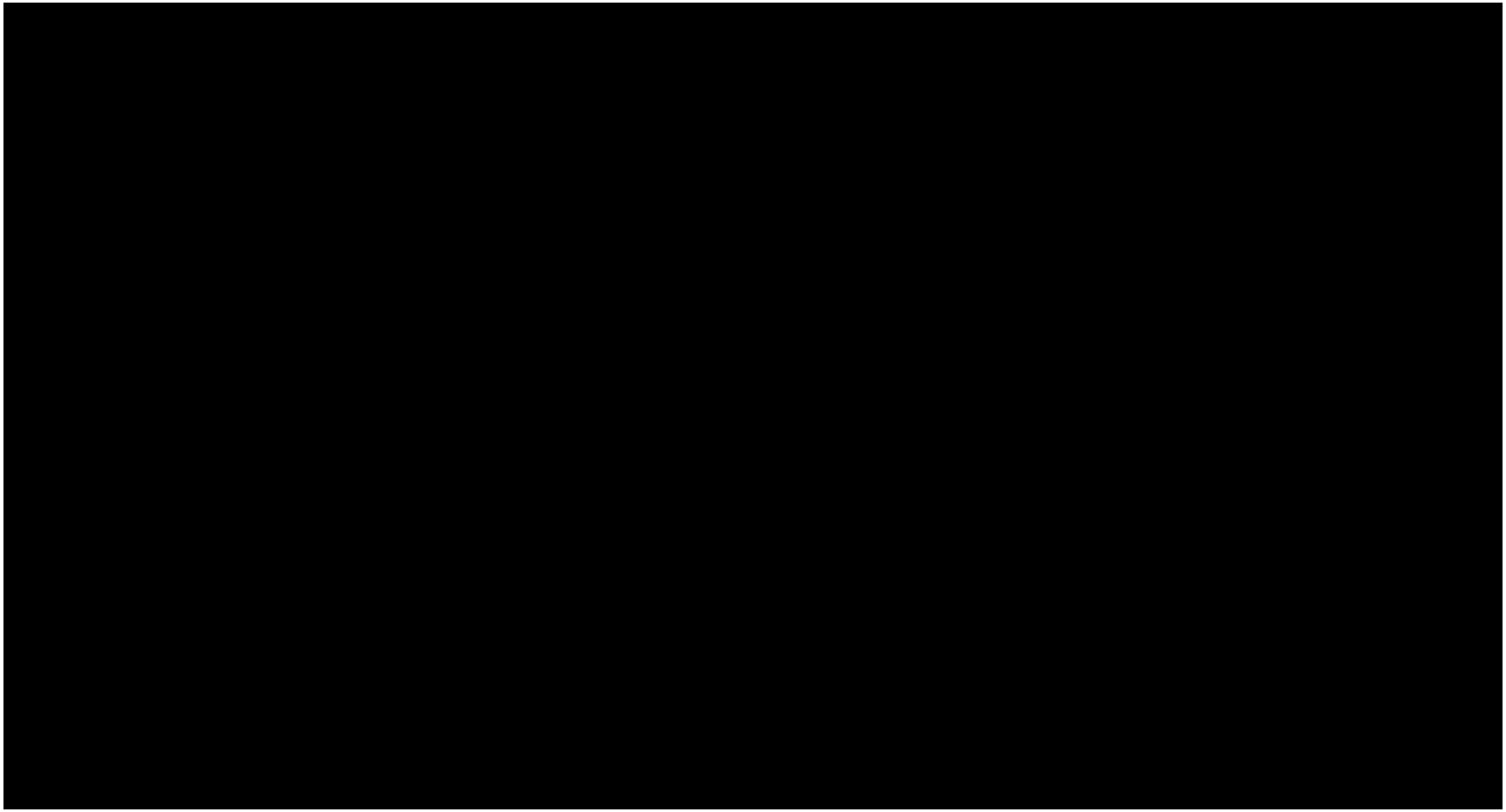
ACD committee's conclusions
Clinical effectiveness

- Trials show nivolumab clinically effective based on response rates
- Trial results biased because of:
  - Single-arm design
  - Small numbers of patients
  - Short follow-up
- Effectiveness of nivolumab compared with standard of care uncertain because:
  - Unadjusted indirect treatment comparison presented; other methods may have been more robust
  - Cheah 2016 may not be reflective of UK practice because of rates of subsequent allogeneic stem cell transplant

Company's model



Company's original overall survival projections for nivolumab (Weibull)



Key assumptions

Assumption	Company	ERG
Nivolumab data	CheckMate205 + CA209-039	CheckMate205 + CA209-039
Nivolumab extrapolation	PFS lognormal, OS Weibull	PFS lognormal, OS Weibull OS Gompertz used to show uncertainty
Standard of care data	Cheah 2016 (excluding patients who received investigational agents)	Cheah 2016 (overall population)
Standard of care extrapolation	PFS exponential, OS exponential	PFS exponential, OS exponential
AlloSCT	Not in base case*	Cost included in base case
Cost of alloSCT	NHS reference/Radford 2016	Radford 2016
Pre-progression utilities	CheckMate205 for nivolumab Swinburn 2015 for SOC	CheckMate205 for nivolumab SOC estimated from CheckMate205 data
Post-progression utilities	Different	Same across all interventions

*Company included alloSCT outcomes + costs in a scenario analysis

Company's base case and ERG's preferred analysis (including PAS discount)

Company's base case					
Treatment	Total		Incremental		ICER per QALY gained
	Costs	QALYs	Costs	QALYs	
Standard of care	£21,090	0.932			
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	**£19,882**

ERG's preferred analysis					
Treatment	Total		Incremental		ICER per QALY gained
	Costs	QALYs	Costs	QALYs	
Standard of care	£23,043	2.102			
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	**£36,525**

Committee considered ERG's preferred analysis potentially plausible, but an alternative extrapolation (Gompertz) for projected long term overall survival with nivolumab increased ICER to £122,825, reflecting level of uncertainty

ACD committee's conclusions

Preferred assumptions

Issue	Committee's preferred assumptions
SOC	Outcomes data from UK to be explored
ITC	Method accounting for differences in trial populations
SOC survival	Results from overall population in Cheah 2016*
Subsequent alloSCT	• AlloSCT long term survival extrapolated independently • Higher rates of subsequent alloSCT* (from UK data where possible)
Costs	Subsequent alloSCT included (ERG preferred cost)*; Mini-BEAM and DexaBEAM excluded*
Utilities	Standard of care pre-progression utilities derived from nivolumab trial* Post-progression utilities the same across all treatments*
ICER	Probabilistic

*In ERG's base case analysis

SOC, standard of care; ITC, indirect treatment comparison; alloSCT, allogeneic stem cell transplant; ICER, incremental cost-effectiveness ratio

ACD committee's conclusions
End of life criteria

Criterion	Data	Met?
1) Short life expectancy, normally less than 24 months	Company: **Median** overall survival ~2 years, decreasing to ~19 months when investigational agents removed ERG: **Mean** life years in model is 2.3 years (excluding investigational agents) Overall population overall survival is 2.9 years	✗
2) Extension to life, normally of at least 3 months, compared with current NHS treatment	Company: Nivolumab likely to increase overall survival to exceeding 42.9 months (CheckMate 205 and CA209-039) ERG: Nivolumab likely to extend life expectancy by at least 3 months	✓

Appraisal Consultation Document (ACD)

- The committee is **minded not** to recommend nivolumab . . .
- The committee recommends NICE requests from the company revised probabilistic cost-effectiveness analyses that:
  - incorporate committee's preferred assumptions for method of indirect comparison, costs and utilities
  - explore the use of UK data for standard of care
  - explore a range of subsequent allogeneic stem cell transplant rates (that are higher than those used in company's original submission and ERG's report)

ACD consultation responses

- Consultee comments from:
  - Royal College of Radiologists
  - Lymphoma Association
  - Royal College of Physicians
- Web comments from:
  - Healthcare professional (within NHS)
  - Healthcare industry (other)
- Company:
  - Bristol-Myers Squibb

Comments from patient and professional groups

- Royal College of Radiologists
  - Higher rates of subsequent alloSCT (in the UK) may impact on cost-effectiveness
  - Better comparison with UK standard of care needed
- Lymphoma Association
  - Nivolumab has potential to act as salvage therapy to enable alloSCT . . . hard to understand why patients will be denied access to this life-saving treatment
  - Flexibility in treatment of evidence needed – phase III trial data difficult to come by in this small patient population
- Royal College of Physicians
  - HL that has relapsed after autoSCT and BTX is rare, with high unmet need – nivolumab is effective in this setting

Company's ACD response
Comments (1)

- Overall population from Cheah 2016 does not represent standard of care:
  - Overall survival not clinically plausible (HMRN data, clinician survey)
  - Use of investigational agents limited, restricted to large centres (clinical opinion)
  - No evidence that population better matches population in nivolumab trial
  - Investigational agents not current NHS practice (clinician comments and survey)
- End of life criteria met because shorter survival without nivolumab expected (HMRN data, clinician survey)
- Poor outcomes post autoSCT + BTX (HMRN data, clinician survey)

Company's ACD response
Comments (2)

- All evidence has not been considered (results of MAIC, comparison with full SLR data, post-autoSCT only population)
- Alternative OS extrapolation (Gompertz) used in ERG's exploratory analysis not plausible because
  - AIC and BIC data do not support
  - Rapidly accelerating hazard not supported by available data or clinical rationale
  - Predicted survival implausibly short
- Nivolumab clinical effectiveness data only immature because so few events to incorporate into analysis (this supports effectiveness of nivolumab)
- Short term impact of subsequent alloSCT included in nivolumab trial data and Cheah data but limited impact on long-term extrapolation because lack of extended follow-up

Company's ACD response

New evidence and revised analyses

Requested in ACD	Provided by company
Revised probabilistic* cost-effectiveness analyses . . . which incorporate the committee's preferred assumptions and:	
Explore the use of UK data for standard of care	Clinician survey** Scenario analyses 1 + 2
Explore a range of subsequent allogeneic stem cell transplant rates (that are higher than those used in company's original submission and ERG's report)	Clinician survey** Scenario analyses 2 + 3
*Revised base case 1 + 2 present probabilistic results; scenario analyses present deterministic results only	
** [redacted] UK physicians who actively treat relapsed or refractory cHL patients who have previously had autoSCT and BTX	
Data also obtained from Haematological Malignancies Research Network but not used in revised analyses	

Company's ACD response
Supportive new evidence (not used in analyses)

- Subsequent alloSCT in patients having nivolumab (Carlo-Stella et al, 2017)
  - 49 patients (may include patients without prior autoSCT + BTX)
  - 27% patients had subsequent therapy after nivolumab (and before alloSCT)
  - Median follow-up 5.6 months
  - 11 patients died (median OS not reached [95% CI, 441-NR], 3 patients' disease progressed
  - 25 patients had Graft Versus Host Disease
- Subsequent alloSCT in patients having PD-1 inhibitors (Merryman 2017)
  - 39 patients, 72% having nivolumab, on average 4 previous systemic therapies includes 8 patients with non-Hodgkin lymphoma)
  - 19 patients had salvage therapy between PD-1 and alloSCT
  - Median follow-up 12 months
  - Subgroup with HL (31) - 1 year OS 90% (71, 97); 1 year PFS 74% (50, 88)
- International physician survey (BMS)
  - [redacted] physicians ([redacted]), data on [redacted] patients
  - Chemotherapy regimens received at 4th line (following BTX at 3rd line)
  - [redacted]
  - [redacted] to Cheah 2016 and UK clinician survey

Company's ACD response
New cost-effectiveness analyses

Analysis	Assumptions
All include committee's preferred assumptions relating to indirect treatment comparison, costs and utilities	
Revised base case 1	With alloSCT (rates from trials).
Revised base case 2	No alloSCT.
Scenario analysis 1	Clinician survey for standard of care data. No alloSCT.
Scenario analysis 2	Clinician survey for standard of care data. With alloSCT.
Scenario analysis 3	Cheah for standard of care data. With alloSCT (rates from clinician survey).

Company's new cost-effectiveness analyses
Revised base case

	Total		Incremental		ICER per QALY gained (deterministic)
Treatment	**Costs**	**QALYs**	**Cost**	**QALYs**	
Standard of care	£23,668	1.212			
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	**£15,181**
Company's original base case					£19,882
Company's original scenario analysis incorporating alloSCT					~£18,500 - £20,500
ERG's original base case					£36,525

Incorporates committee's preferred assumptions relating to:

- Using overall population from Cheah 2016 for standard of care survival analysis
- Including subsequent allogeneic stem cell transplant in survival analysis
- Method of indirect treatment comparison, costs and utilities

Company's new cost-effectiveness analyses

Standard of care OS + PFS	AlloSCT rates	AlloSCT outcomes	ICER
Company's original scenario analysis			
Cheah (excluding patients who had investigational agents) Exponential extrapolation	Perrot (according to trial responder rates)	Cheah (14 patients, lognormal extrapolation)	~£18,500 - £20,500
ERG's original preferred analysis			
Cheah (overall population) Exponential extrapolation	Nivolumab trials + Cheah (actual numbers)	No alloSCT outcome adjustment (except costs)	£36,525
Company's new revised base case analysis 1			
Cheah (overall population) Exponential extrapolation	Nivolumab trials + Cheah (actual numbers)	Lafferty (13 patients, Gompertz extrapolation)	£15,181
Company's new revised base case analysis 2			
Cheah (overall population) Exponential extrapolation	N/A	N/A	£14,365
Company's new scenario analysis 2			
UK Survey (expected OS + PFS) Exponential extrapolation	UK Survey (according to trial responder rates)	Lafferty (13 patients, Gompertz extrapolation)	£16,607
Company's new scenario analysis 3			
Cheah (overall population) Exponential extrapolation	UK Survey (according to trial responder rates)	Lafferty (13 patients, Gompertz extrapolation)	£16,770

Note: all company's new analyses censor overall survival data for nivolumab patients having subsequent alloSCT

Company's new analyses: censoring OS in nivolumab patients having alloSCT

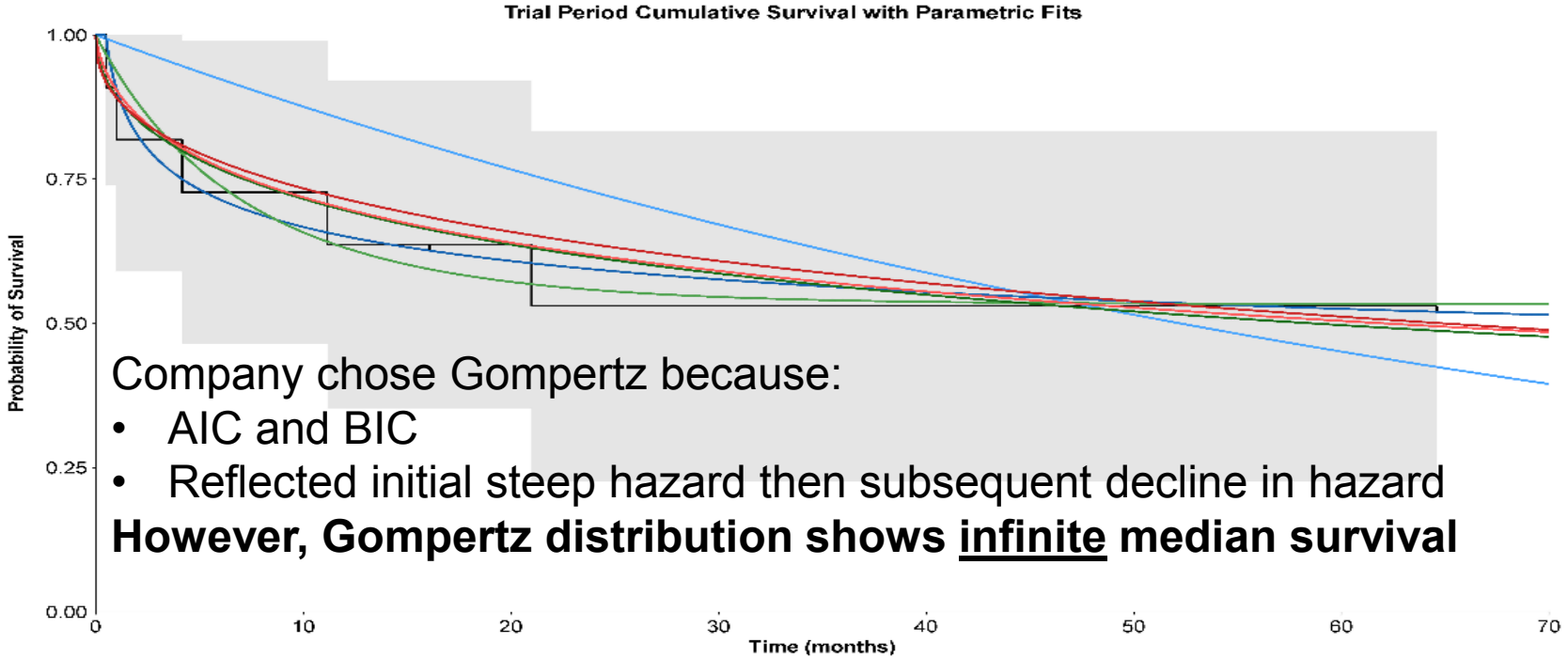
- ACD section 4.14 " . . . It [the committee] acknowledged that there would be some double-counting [in the company's scenario analysis incorporating subsequent allogeneic stem cell transplant] because the overall survival extrapolation used in the base case included some patients who had allogeneic stem cell transplant, but **agreed that it was an acceptable approach**."
- Company's ACD response appendix section 1.1.1 "in order to address the committee's concerns, it has been necessary to censor OS in patients receiving alloSCT".
- Company's revised base case (and all scenario analyses) applies nivolumab OS data where patients receiving alloSCT are censored (*unable to censor in SOC arm because data not available from Cheah 2016*).
- **ERG's critique**: censoring only nivolumab arm is methodologically flawed and likely to bias results in favour of nivolumab; company's original approach, with some double counting, is more appropriate.

Company's new analyses: Using UK outcome data for patients having alloSCT

- Lafferty et al., 2017
- Retrospective case series
- 13 patients with HL having alloSCT after 3 prior therapies (8 of these had prior autoSCT)
- Median follow-up 836 days (~28 months)
- 1 year OS 69%
- 1 year PFS 54%
- Survival data applied to company's revised base case and scenario analyses where subsequent alloSCT is incorporated

Updated after committee meeting

Company's new analyses: Impact of UK alloSCT outcome data on overall survival projections



Company chose Gompertz because:

- AIC and BIC
- Reflected initial steep hazard then subsequent decline in hazard

However, Gompertz distribution shows <u>infinite</u> median survival

Distribution	AIC	BIC	Median Survival	Parameters		
Exponential	55.22	55.62	52.2	λ=0.013		
Generalised gamma	48.63	49.83	86.9	μ=−0.677	σ=0.247	Q=−30.372
Gompertz	49.04	49.84	Inf	θ=−0.110	λ=0.069	
Log−logistic	50.60	51.39	58.6	β=0.522	α=58.610	
Log−normal	50.10	50.90	62.1	μ=4.129	σ=3.159	
Weibull	51.12	51.91	64.9	k=0.431	θ=151.960	

AlloSCT outcomes post nivolumab

- Nivolumab SmPC includes safety concern relating to the “potential risk of complications including acute graft-versus-host-disease and transplant related mortality of allogeneic haematopoietic stem cell transplant following nivolumab therapy”
- Papers included in company’s supportive evidence (not used in analyses) note a potential link between mechanism of action of PD-1 inhibitors (immunomodulatory) and increased chance of Graft Versus Host Disease in patients having transplant
  - Carlo-Stella et al., 2017 [redacted]”
  - Merryman et al., 2017 “AlloSCT after PD-1 blockade appears feasible with a low rate of relapse, but there may be an increased risk of early immune toxicity, which could reflect long-lasting immune alterations triggered by prior PD-1 blockade”

Company's new cost-effectiveness analyses
Standard of care data - treatments

Source	Cheah 2016 (n=[redacted])	Clinician survey (n=[redacted])	HMRN data (n=[redacted])
[redacted]	✓	✓	
[redacted]	✓	✓	✓
[redacted]	✓	✓	✓
[redacted]	✓	✓	
[redacted]	✓	✓	
[redacted]	✓	✓	
[redacted]	✓		
[redacted]	✓		

[redacted] additionally reported by clinicians in survey

[redacted] additionally reported in HMRN data

Company's new cost-effectiveness analyses

Standard of care data - outcomes

Survey question		Mean	Min	Max	Cheah
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

Company's new cost-effectiveness analyses
AlloSCT rates

	Nivolumab trials + Cheah 2016	Perrot 2016	UK clinician survey
Nivolumab arm			
Complete response	[redacted]	[redacted]	[redacted]
Partial response	[redacted]	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]	[redacted]
Standard of care arm			
Complete response	17.72%	[redacted]	[redacted]
Partial response	17.72%	[redacted]	[redacted]
Stable disease	17.72%	[redacted]	[redacted]

ERG's critique of company's new cost-effectiveness analyses

- Scenario analysis 3 most closely matches committee's preferred assumptions (indirect treatment comparison, costs, utilities and UK rates of alloSCT)
- Censoring of nivolumab patients having alloSCT inappropriate
- Error in BSC utilities identified
- Use of Gompertz in post-alloSCT survival extrapolation inappropriate
- Use of MAIC results better, but still limitations
- Sensitivity analysis around post-alloSCT survival shows substantial uncertainty
- Small numbers of patients in all analyses of post-alloSCT survival so caution is warranted

ERG's critique of company's new cost-effectiveness analyses

Modelling post-alloSCT survival

ERG's critique of company's new cost-effectiveness analyses

	ICER per QALY gained
Company's original preferred analysis	£19,882
ERG's original preferred analysis	£36,525
Company's new revised base case	£15,181
- corrected (censoring + BSC utilities)	£26,664
Company's new scenario analysis 3	£16,770
- Corrected (censoring + BSC utilities), Gompertz post-alloSCT survival	£24,623
- Corrected (censoring + BSC utilities), Lognormal post-alloSCT survival	£30,366
- Corrected (censoring + BSC utilities), Weibull post-alloSCT survival	**£31,031**

End of life
Company's new evidence

Criterion	Cheah 2016	UK clinician survey (mean response from [redacted] clinicians)
1) Short life expectancy, normally less than 24 months	Company: **Median** overall survival ~2 years, decreasing to ~19 months when investigational agents removed ERG: **Mean** life years in model is 2.3 years (excluding investigational agents) Overall population overall survival is 2.9 years	Expected **median** overall survival 

Key issues for decision-making

- Which is more appropriate source of data for:
  - Standard of care (Cheah 2016 vs Clinician survey)?
  - UK alloSCT rates (Trials vs Clinician survey)?
  - UK alloSCT outcomes (Cheah 2016 vs Lafferty 2017)?
- What is the most appropriate parametric curve to use for OS and PFS if Lafferty 2017 is used for UK alloSCT outcomes?
- Should OS data be censored selectively for nivolumab patients having alloSCT (nivolumab arm only)?
- Has new evidence been presented to change the committee's conclusions about end of life criteria?