NICE National Institute for Health and Care Excellence

Slides for the public

Idelalisib for treating refractory follicular lymphoma [ID1379]

1st appraisal committee meeting

Lead team presentation

Lead team: Nigel Westwood, Diar Fattah, Stephen Palmer

Chair: Amanda Adler

ERG: Kleijnen Systematic Reviews

NICE technical team: Adam Brooke and Ahmed Elsada

6th September 2018

Follicular lymphoma disease background

- Most common indolent non-Hodgkin lymphoma in the UK
- Median age at diagnosis in UK 60-65 years
- Male: Female ratio: 0.9
- Median life expectancy from diagnosis: 18 years in rituximab era

*FL = follicular lymphoma

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Lead team presentation - clinical

Patient Perspective

- The most common symptom is a painless swelling in the lymph nodes but can extend to B-symptoms including weight loss, fever, night sweats, fatigue and the complications of bone marrow diseases.
- Depression and stress from reduced life expectancy are commonly reported.
- The aim of treatment is to control symptoms and extend remission in order to improve quality of life.

- ‘Double refractory’ patients are those that are refractory to both rituximab and an alkylating agent and are considered to have the worst prognosis.

- At 3rd line, there is a lack of standard of care, current treatment consists of a variety of chemotherapies and other treatment options including radiotherapy, palliative options and salvage treatment with the aim to perform allogenic stem cell transplant.
- Re-treatment with rituximab or rituximab-containing regimens is an option, depending on response to rituximab, time since relapse and patient characteristics.

Follicular Lymphoma International Prognostic Index (FLIPI)

- Current NICE guidelines use FLIPI classification system for stratification of risk of death in assessment of treatment options.
- An updated index FLIPI2 measures prognostic factors for disease progression but is not used in this appraisal.
- FLIPI score combines patient characteristics with the Ann Arbor staging system to predict survival as low, intermediate or high.

<table>
<tr><th>FLIPI score (1 point for each factor)</th><th>Ann Arbor classification system</th></tr>
<tr><td>• Age >60 years
• Haemoglobin level <12g/dl
• Lactate dehydrogenase level > upper limit of normal
• ≥ 4 nodal sites of disease
• Ann Arbor Stage III-IV</td><td rowspan="3">Stage I: Single lymph node
Stage II: Multiple lymph node groups on same side of diaphragm.
Stage III: Multiple lymph nodes on both sides of diaphragm.
Stage IV: Multiple extranodal sites or lymph nodes and extranodal disease.
For all stages:
A/B: Absence or presence of B symptoms including weight loss >10%, fever, drenching night sweats.</td></tr>
<tr><th>Risk category</th></tr>
<tr><td>• Low (0 or 1)
• Intermediate (2)
• High (≥3)</td></tr>
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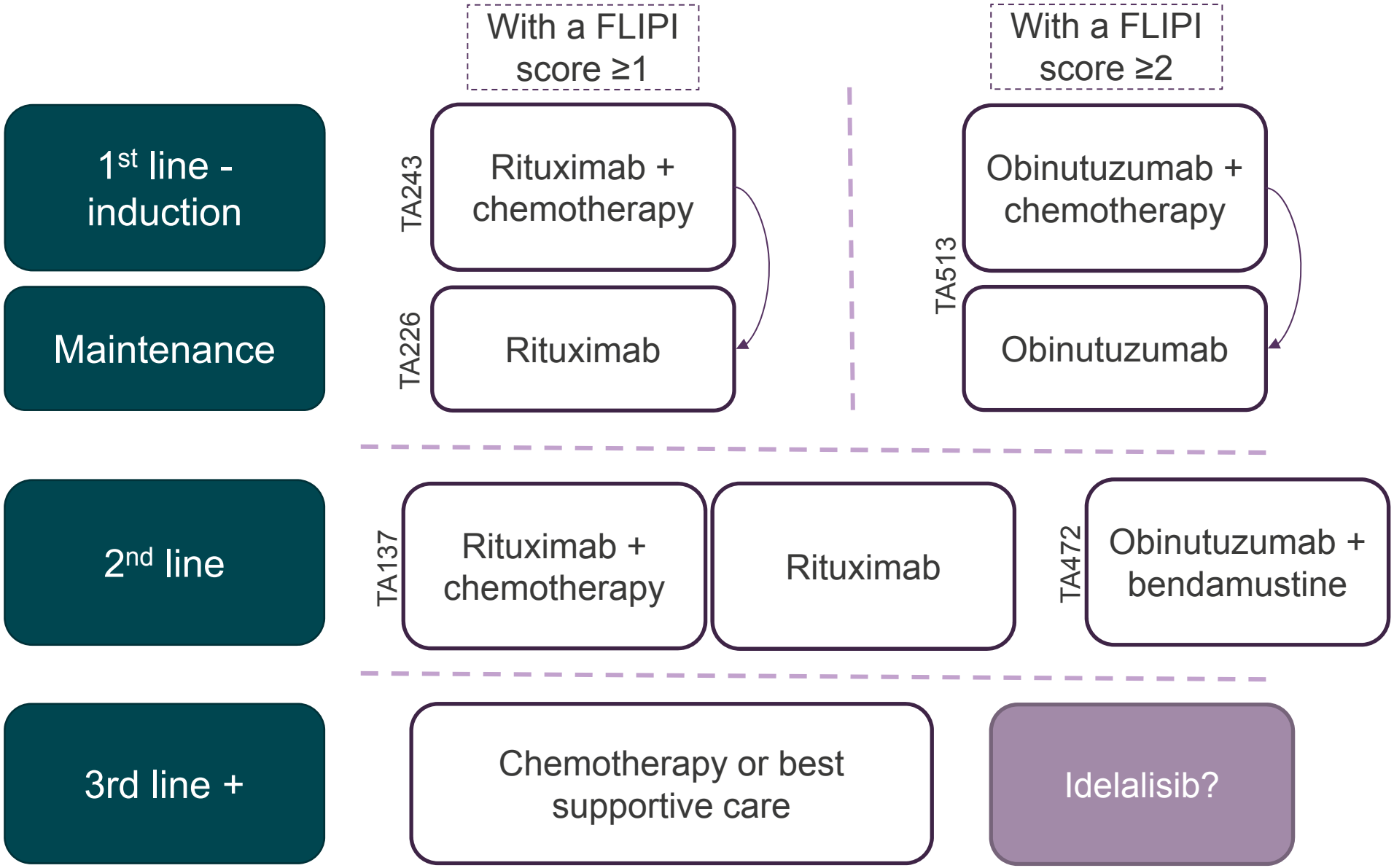
Treatment– advanced symptomatic disease



- ***Where would idelalisib fit in the treatment pathway? What are the relevant comparators?***
- ***What is the role of stem-cell transplantation in this population?***

Idelalisib (Zydelig®, Gilead)

Mechanism	• Phosphatidylinositol 3-kinase p110δ (PI3Kδ) inhibitor. • Blocks signalling pathways that drive the growth and metabolism of malignant cells in lymphoid tissue and bone marrow
Marketing authorisation	• Marketing authorisation (September 2014): "Monotherapy for the treatment of adult patients with follicular lymphoma that is refractory to two prior lines of treatment"
Administration and dose	• 150mg tablet, administered orally twice daily
List price	• £3,114.75 per pack of 60 150mg tablets. • Confidential price discount has been agreed.
Appraisal history	• Company suspended appraisal in 2014 due to safety concerns about the toxicity of idelalisib

Decision problem

Decision problem in line with scope

	Final scope issued by NICE
Population	Follicular lymphoma refractory to 2 prior lines of therapy
Intervention	Idelalisib

Comparators	• Chemotherapy regimens
	  • cyclophosphamide- or fludarabine-containing regimens
	  • bendamustine
	  • chlorambucil
	When chemotherapy is unsuitable:
	• Best supportive care

Outcomes	• overall survival • progression-free survival • response rates • duration of response/remission • adverse effects of treatment • health-related quality of life

❖ ***For whom chemotherapy is unsuitable – given the toxicities of idelalisib, would these patients be offered idelalisib?***

Clinical evidence: overview

Study	DELTA (Study 101-09) (n=72/125)	Compassionate use programme (CUP) (n=79)
Study design	Phase II, open label, **single arm** study	Retrospective observational convenience data - Britain and Ireland
Population	Relapsed indolent non-Hodgkin's lymphoma refractory to rituximab and chemotherapy containing an alkylating agent	Refractory or relapsed follicular lymphoma
Intervention	Idelalisib	Idelalisib
Comparison	None	None
Outcomes	• 1◦ outcome – overall response rate • Overall survival • Progression-free survival • Response rates • Duration of response/remission • Adverse effects of treatment • Health-related quality of life	• Overall response rate • Progression-free survival • Overall survival • Adverse effects of treatment

DELTA Study design – no control group

- Phase II, open label study
- 72 people aged ≥ 18 years with follicular lymphoma with 53 other indolent non-Hodgkin lymphoma subtypes
- Prior treatment with ≥ 2 prior regimens and refractory to both rituximab and an alkylating agent.

↓

Idelalisib

↓

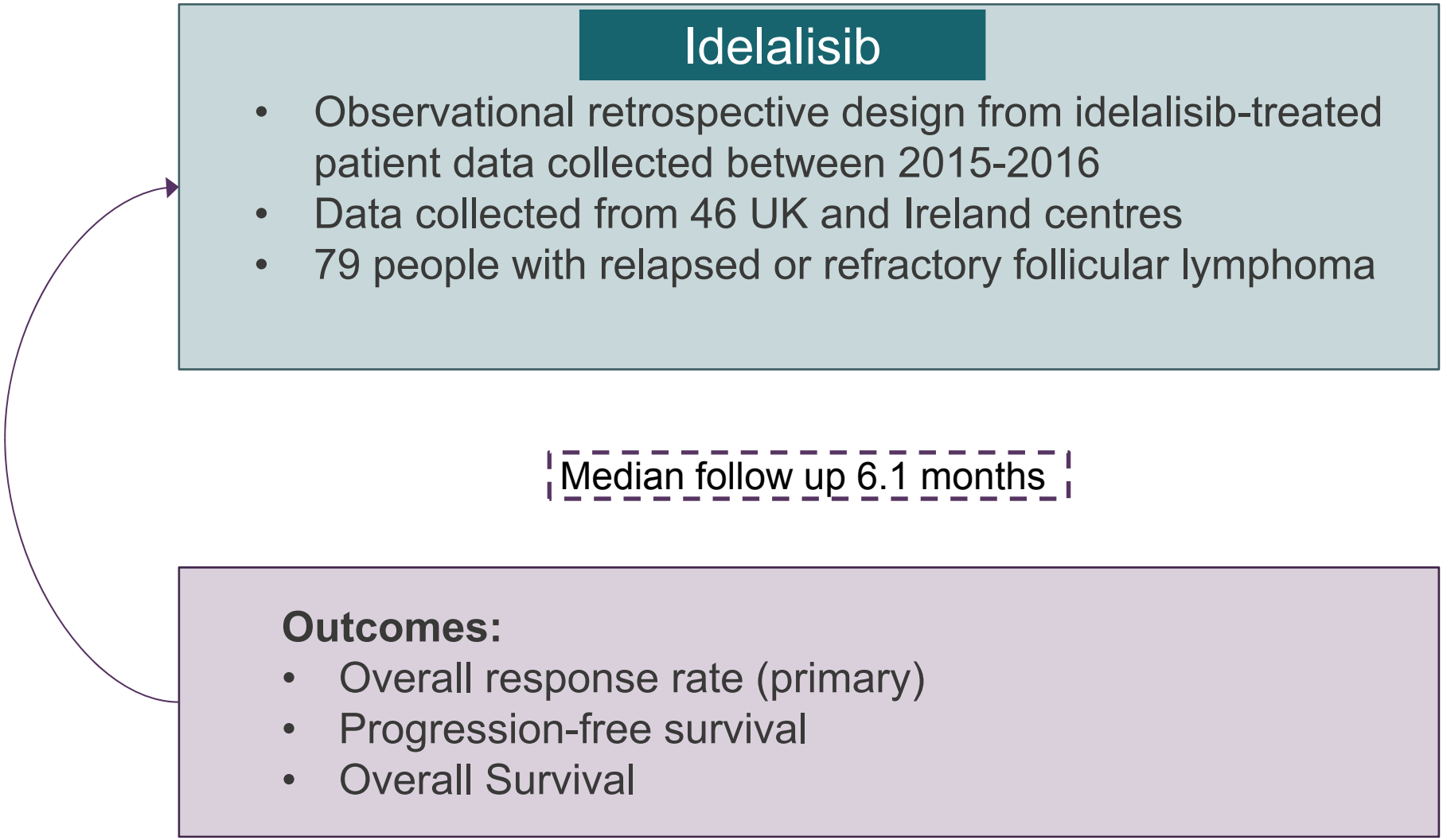
Follow up until 80% of patients have progressed

↓

Outcomes response endpoints were assessed by both the investigator and an independent review committee **:**

- Overall response rate (primary)
- Progression-free survival
- Overall survival
- Health related quality of life (FACT-Lym questionnaire)
- Adverse event and safety data

CUP cohort study design – no control group



Baseline characteristics

Baseline characteristic	DELTA (n=72)	CUP Cohort (n=79) 46 of 51 centres approached
Median age, years (range)	62 (33–84)	64 (29-86)
Sex, male, n (%)	39 (54.2)	40 (51)
Median time since diagnosis, years (range)	4.7 (0.8–18.4)	4.5 (0.4-24.6)
Performance status, n (%)	ECOG 0-1: 66 (91.7) ECOG 2-4: 6 (8.3)	ECOG 0-1: 59 (75) ECOG 2-4: 20 (25)
High (≥3) FLIPI risk score at baseline, n (%)	39 (54.2)	59 (75)
Prior therapy		
Median prior regimens (range)	4 (2–12)	3 (1-13)
Median time since completion of last treatment, months (range)	4.3 (0.7–39.1)	8.6 (0.9-99.2)
Rituximab, n (%)	72 (100)	78 (99)
Alkylating agent, n (%)	72 (100)	78 (99)
Refractory to ≥2 regimens , n (%)	57 (79.2)	NR
Refractory to most recent regimen, n (%)	62 (86.1)	NR

- ***Which population is most representative of the UK population?***
- ***Which are associated with length and/or quality of life? What risk factors are absent?***
- ***20% of the DELTA population are refractory to only 1 regimen, how may this affect the generalisability of the trial to the marketing authorisation population?***

Results summary

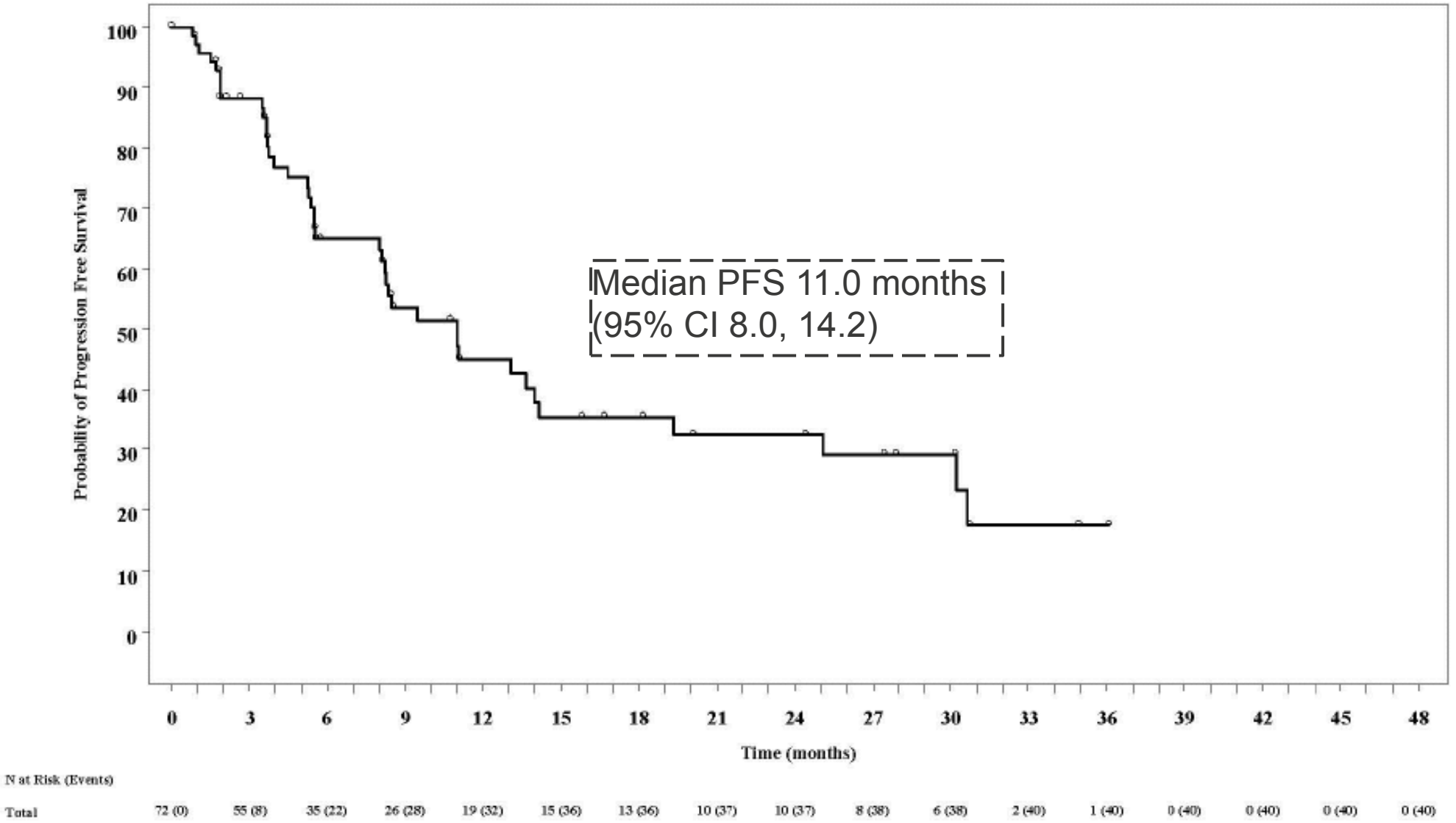
	DELTA* (n=72)	CUP cohort (n=65/79)	Used in modelling?
Overall response n (%)	40 (55.6)	37 (57)	x
Complete response	10 (13.9)	10 (15)	x
Partial response	30 (41.7)	27 (42)	x
Stable disease	23 (31.9)	not reported	x
Progressive disease	8 (11.1)	not reported	x
Survival (95% CIs)			
Progression, number (%)	40 (55.6)	not reported	To estimate time to progression
Median progression free survival months	11.0 (8.0, 14.2)	7.1 (5.0, 9.1)	
Died, number, %	24 (33.3)	not reported	Value from DELTA but only in 'Comparison B'
Median overall survival months	not reached but estimated at 38.1	not reached	

ERG comment

- Only 65 participants were included in the response data for CUP cohort.
- Unconfirmed complete responses presented for the CUP cohort.

* independent review committee assessed

DELTA: Progression-free survival



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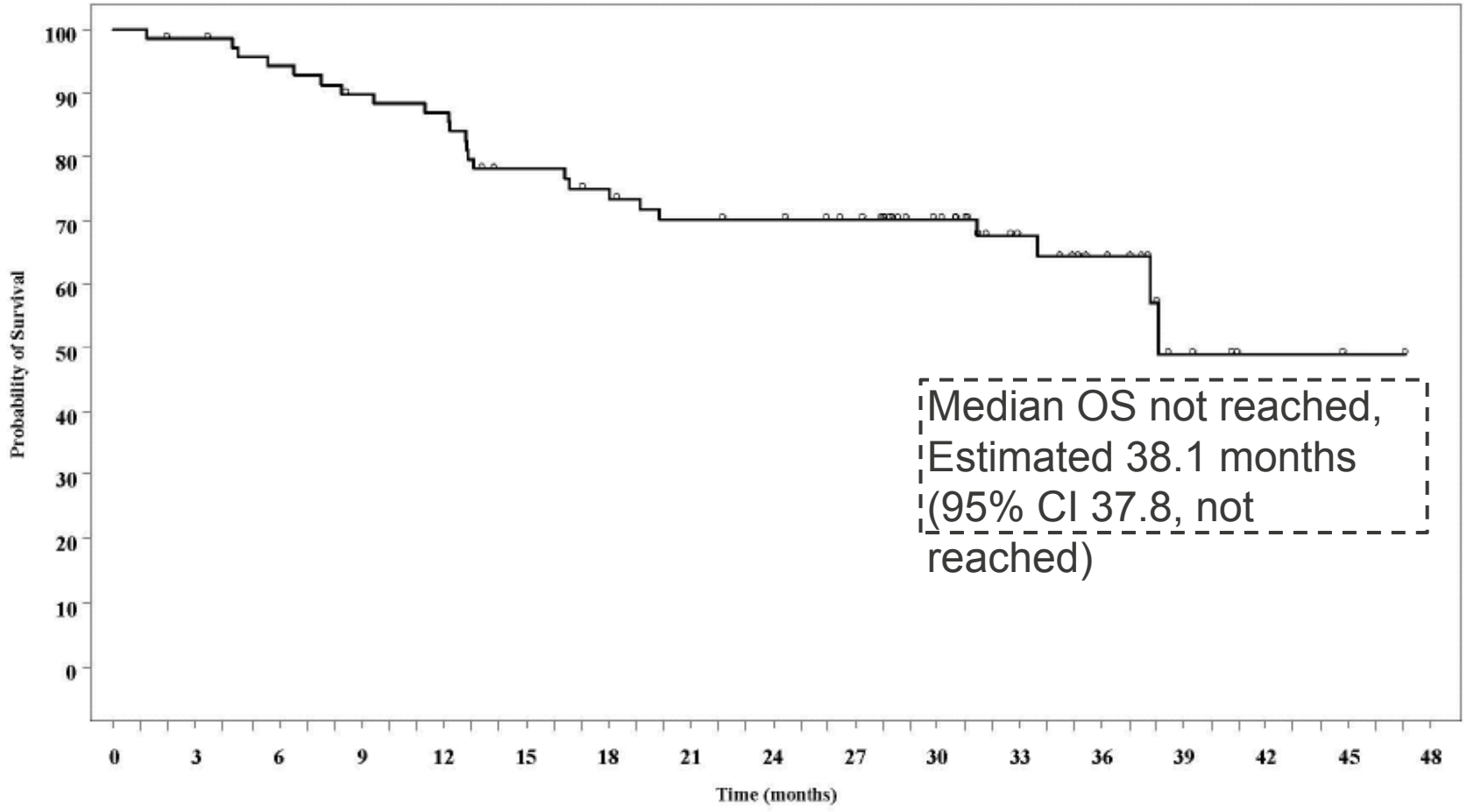
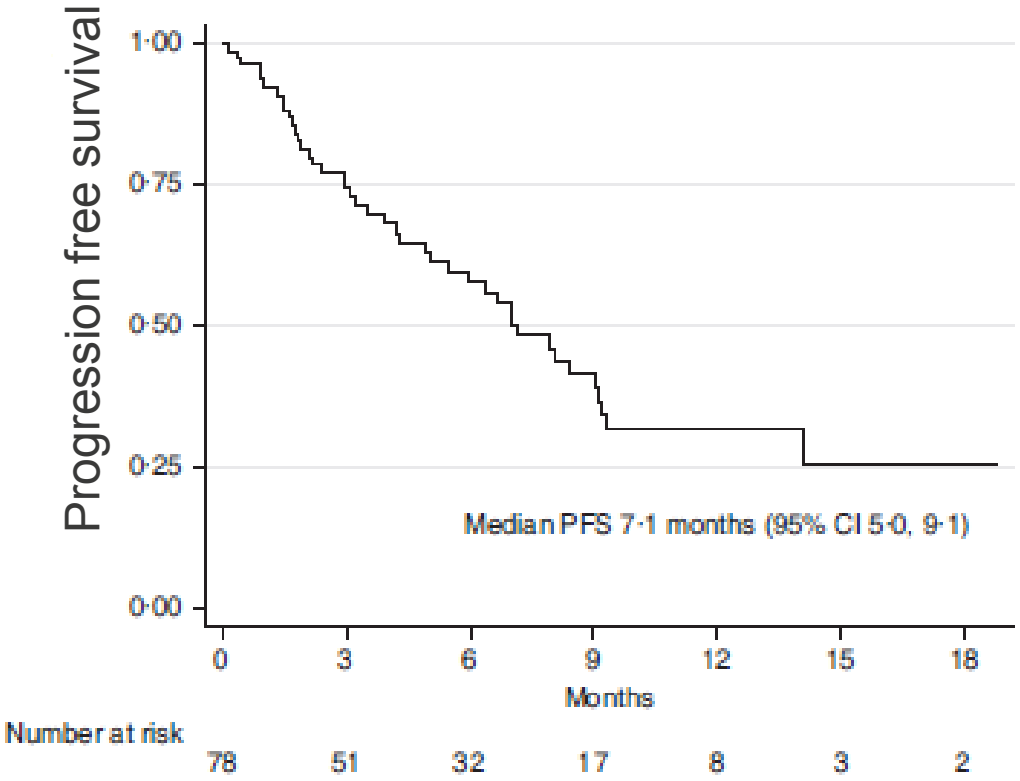
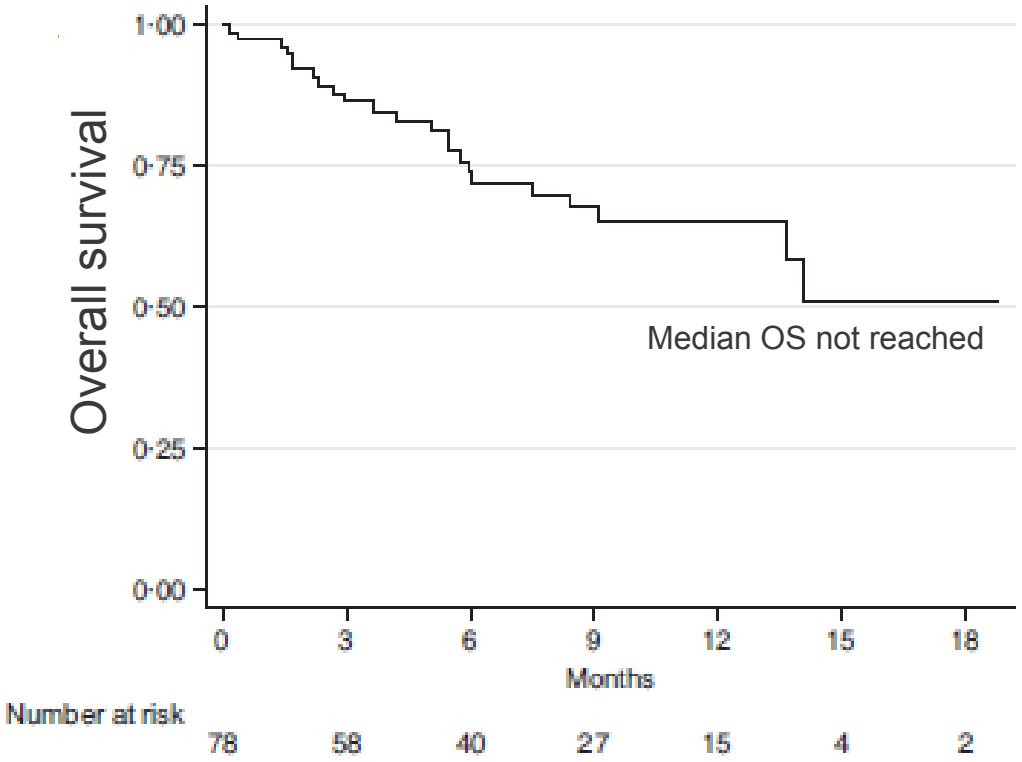
DELTA: Overall survival



N at Risk (Events)																
Total	72(0)	69(1)	65(4)	61(7)	59(9)	51(15)	48(17)	44(20)	43(20)	40(20)	31(20)	21(21)	14(22)	5(24)	2(24)	1(24)	0(24)

Compassionate Use Programme (CUP) cohort progression-free and overall survival





- 24 people received treatment post-idelalisib including 8 people who went on to receive allogenic or autologous stem cell transplant.

Comparing idelalisib to chemotherapy - methods

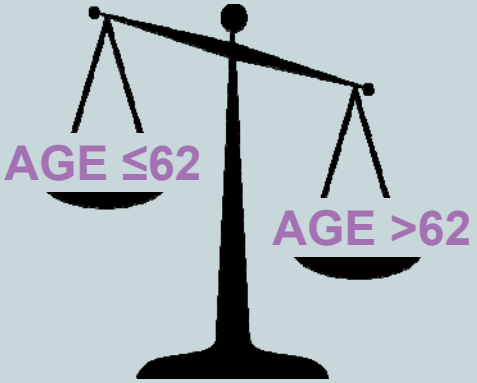
- DELTA and CUP had data only for idelalisib. To address the decision problem, the company used 2 comparison methods.

Intra-patient comparison – last previous line of therapy

- For each patient, company collected progression free survival from the last previous line of therapy directly before idelalisib treatment.
- These data were pooled to create a 'cohort' reflecting the distribution of potential chemotherapy treatments immediately preceding idelalisib for each study.
- Company compared data for idelalisib to pooled data from the 'cohort' for each study.

Matching adjusted indirect comparison

- Company used Haematological Malignancy Research Network (HMRN) to identify a cohort of patients. Company matched baseline patient characteristics to adjust for difference in prognostic factor and treatment effect modifier between studies.



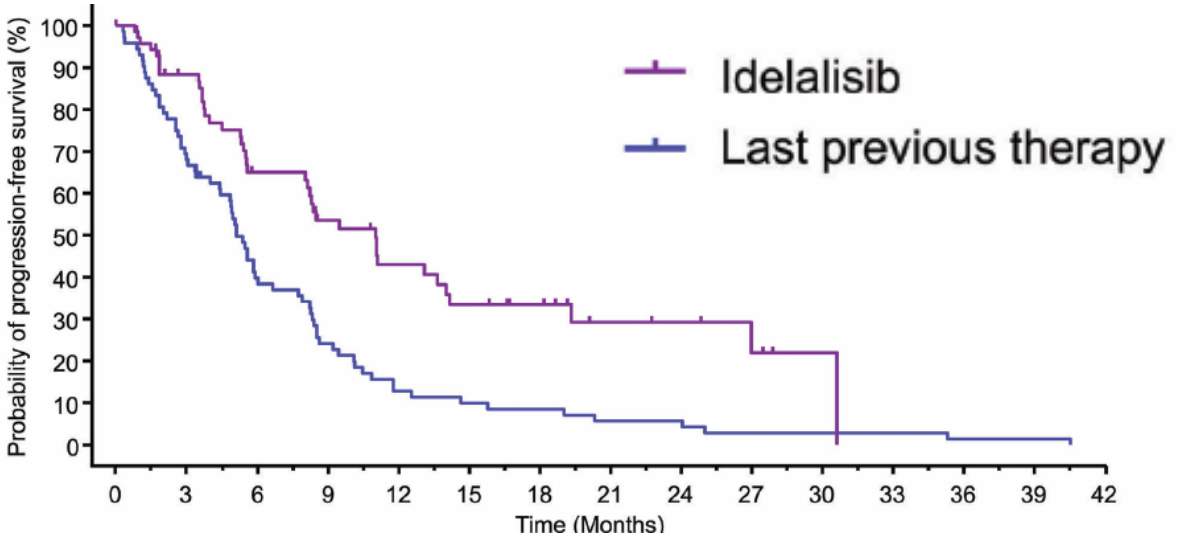
Individual patient data

Need to increase weighting of younger participants to match distribution of summary patient data

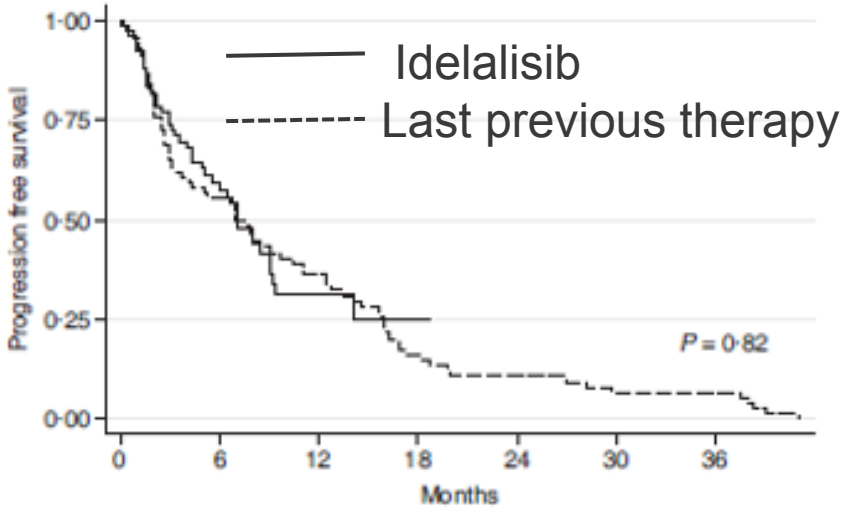
Summary patient characteristics

Intra-patient (previous line of therapy) progression free survival comparison

DELTA



CUP cohort

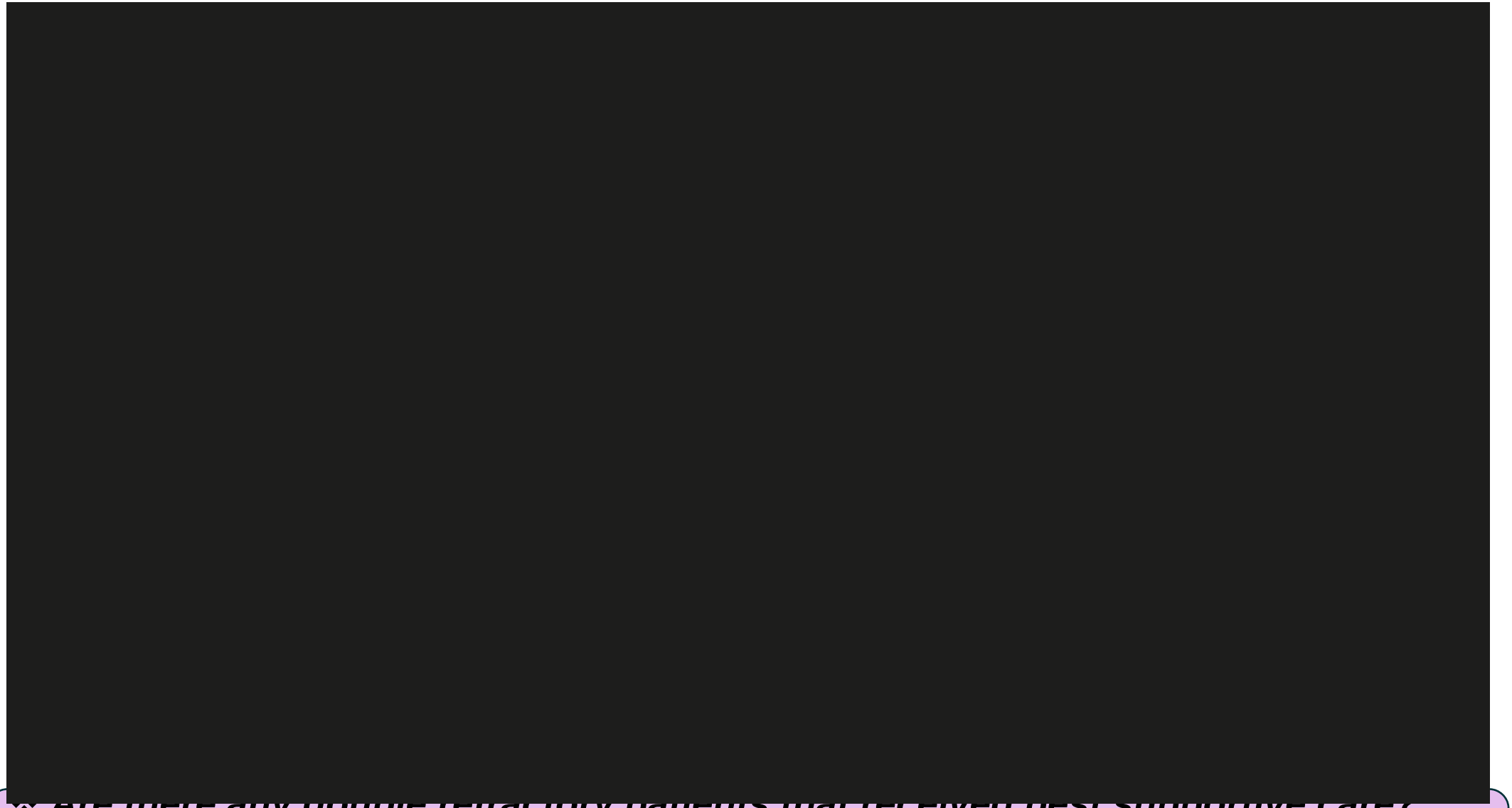


ERG comment

- Difference may result from differences between populations or methods of assessing progression
- Progression in DELTA for previous therapies is based on clinician recall and may be biased. CUP cohort does not use objective measures of progression because of the clinical practice setting either for idelalisib or previous therapies.
- These comparisons are highly unreliable and should be interpreted with extreme caution

❖ ***Are intra-patient comparisons valid? Do they create blended comparators?***

Matching adjusted indirect comparison - Haematological Malignancy Research Network (HMRN) cohort



- ***Are there any double refractory patients that received best supportive care?***
- ***Does this population reflect UK clinical practice for patients that would receive idelalisib?***

Matching adjusted indirect comparison - direction of adjustment

- ***Should the effect be estimated in DELTA or HMRN?***

Matching adjusted indirect comparison

Characteristic	DELTA (n=72)
Male, n (%)	39 (54.2)
Median age, years (range)	62 (33–84)
Stage III or IV, n (%)	60 (83.3)
Bulky disease, n (%)	16 (22.2)
Median time since diagnosis, years (range)	4.7 (0.8–18.4)
Median lines of prior therapy (range)	4 (2–12)
Prior autologous stem cell transplant, n (%)	12 (16.7)
Outcome	Idelalisib
2-year overall survival (%)	69.8
1-year progression free survival (%)	43.0

[redacted]

- ***Why is the variable 'median time since diagnosis' sensitive to adjustment?***
- ***What risk factors for progression and death should be included?***

ERG comments on HMRN matching adjusted indirect comparison

[redacted]

- ***Is the matching adjusted indirect comparison performed on the HMRN cohort a reliable estimate of relative effectiveness?***

Matching adjusted indirect comparison – overall survival for chemotherapy

[redacted]

Safety profile overview – DELTA

Adverse event	DELTA population (N=72)
Any adverse event, n (%)	71 (98.6)
Grade ≥3 adverse event, n (%)	48 (66.7)
Treatment-related adverse event	61 (84.7)
Treatment-related Grade ≥3 adverse event, n (%)	41 (56.9)
Any serious adverse event, n (%)	36 (50.0)
Treatment-related serious adverse event, n (%)	24 (33.3)
Adverse event leading to dose reduction, n (%)	22 (30.6)
Adverse event leading to study drug discontinuation, n (%)	18 (25.0)
Adverse event leading to death, n (%)	6 (8.3)
Death on study drug or within 30 days of last study drug dose, n (%)	7 (9.7)

ERG comment

- ERG anticipated severe immune related adverse events in light of common risks associated with idelalisib and an extensively pre-treated population.
- Company did not report adverse events for chemotherapy so ERG could not comment on the relative safety profile.
- In economic modelling, chemotherapy was considered equivalent to idelalisib adverse events.

Key issues – clinical effectiveness

- Which patients would receive idelalisib in clinical practice?
  - Would patients who get best supportive care be otherwise fit enough for idelalisib?
- Which population – single arm trial or cancer registry best reflects UK population likely to take idelalisib?
- What is the role of stem-cell transplantation in this population?
- Which method provides the best estimates of relative treatment effect?
  - Intra-patient comparison
    - If so, what biases arise when using same-patient prior therapy from the same study as a comparator?
  - MAIC
    - If so, should DELTA or HMRN be the population to which to match?
      - If DELTA, which variables should included as potential confounders of progression and death or effect modifiers?
    - What bias remains in the estimates? Which direction is the bias?
- Is the evidence currently sufficient to determine the clinical effectiveness of idelalisib compared to established practice?

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Slides for the public

Lead team presentation - cost

Modelling approach

- Company presents 4 sets of results that varied model transition probabilities and source of comparison data (Comparisons A-D)
  - Comparisons A and C used prior line of therapy intra-patient data as a proxy comparator for current chemotherapy.
    - ◊ Company uses a hazard ratio of 0.75 to prior therapy data to account for decreased effectiveness with additional lines of therapy (i.e. the estimated effect is 25% worse than the observed data)
  - Comparison B used matching adjusted indirect comparison with HMRN cohort data
  - Comparison D estimated outcomes for best supportive care for chemotherapy ineligible patients

ERG comment

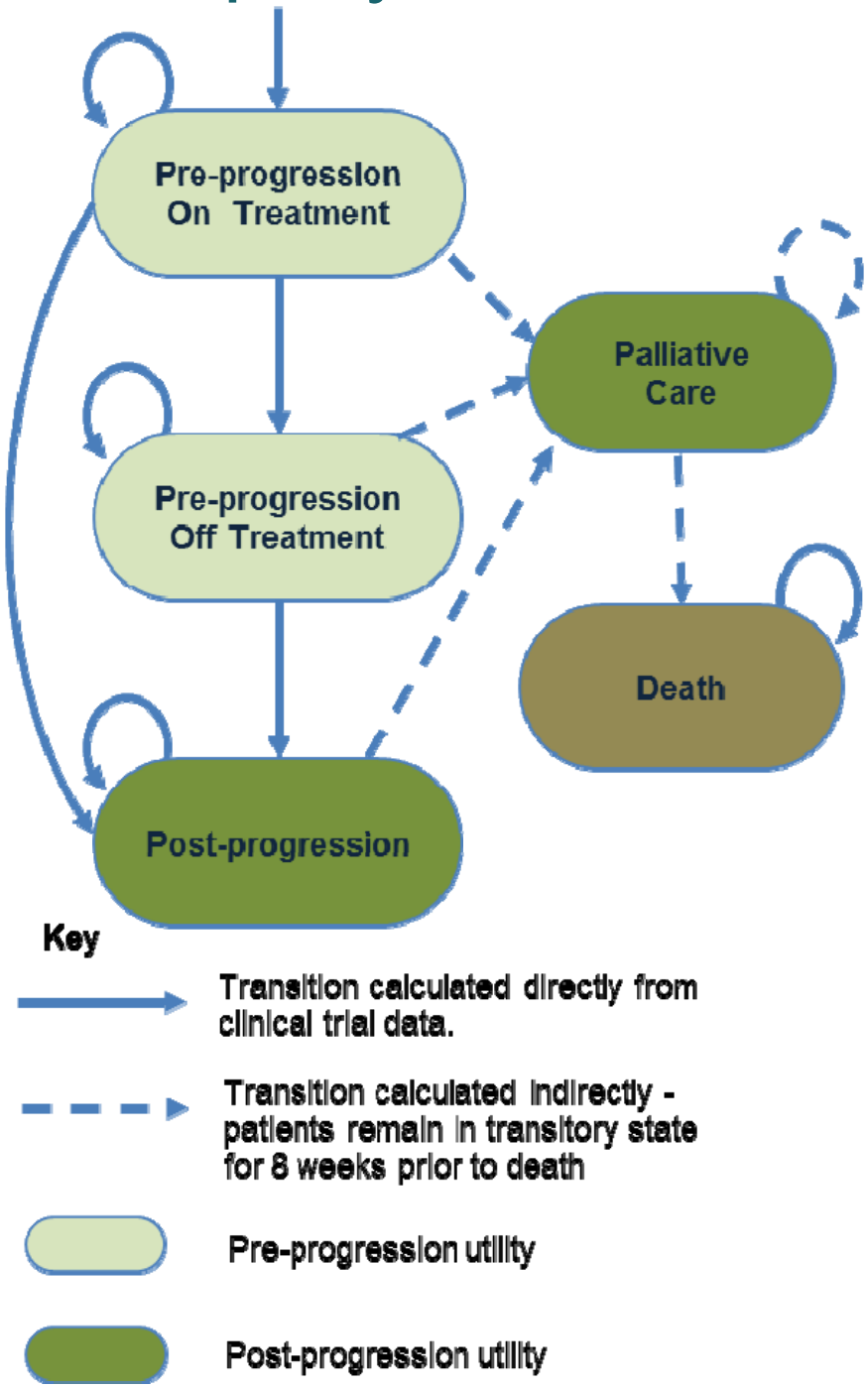
- The clinical inputs were generated from non-randomised evidence from different single arm studies or different time points within the same study.
- A covariate adjusted survival analysis would have reduced bias from the confounding variable 'number of prior lines of therapy' but this approach was not used.
- The ERG could not verify the source of the hazard ratio estimate and note that the estimate was 0.9 in other health technology assessment submissions.

Choice of comparison in economic model

Comparison	Idelalisib data source	Comparator data source	Model type
A (company base case)	DELTA	Chemotherapy: DELTA data from 'intra-patient' previous line of treatment as a proxy for current chemotherapy. Hazard ratio applied	Markov cohort – state transition
B	DELTA	Chemotherapy: Matching adjusted survival data from chemotherapy regimens of HMRN cohort	Partitioned survival model
C	Data from CUP cohort and DELTA idelalisib	Chemotherapy Time to progression data from 'intra-patient' previous line of treatment as a proxy for current chemotherapy. Hazard ratio applied	Markov cohort – state transition
D	DELTA	Best supportive care: No treatment costs because company assumes instant disease progression	Markov cohort – state transition

❖ ***Which, if any, of these analyses are appropriate?***

Company's Markov model structure (A, C and D)



- Pre-progression state divided into on- and off-treatment because patients can withdraw from active treatment before disease progression

- It is possible to transition to death from any of the health states via the transitory palliative care health state. This captures the heightened cost of palliative care in the 8 weeks preceding death.

- 1-week cycle length
- Time horizon =38 years, assumed to be lifetime

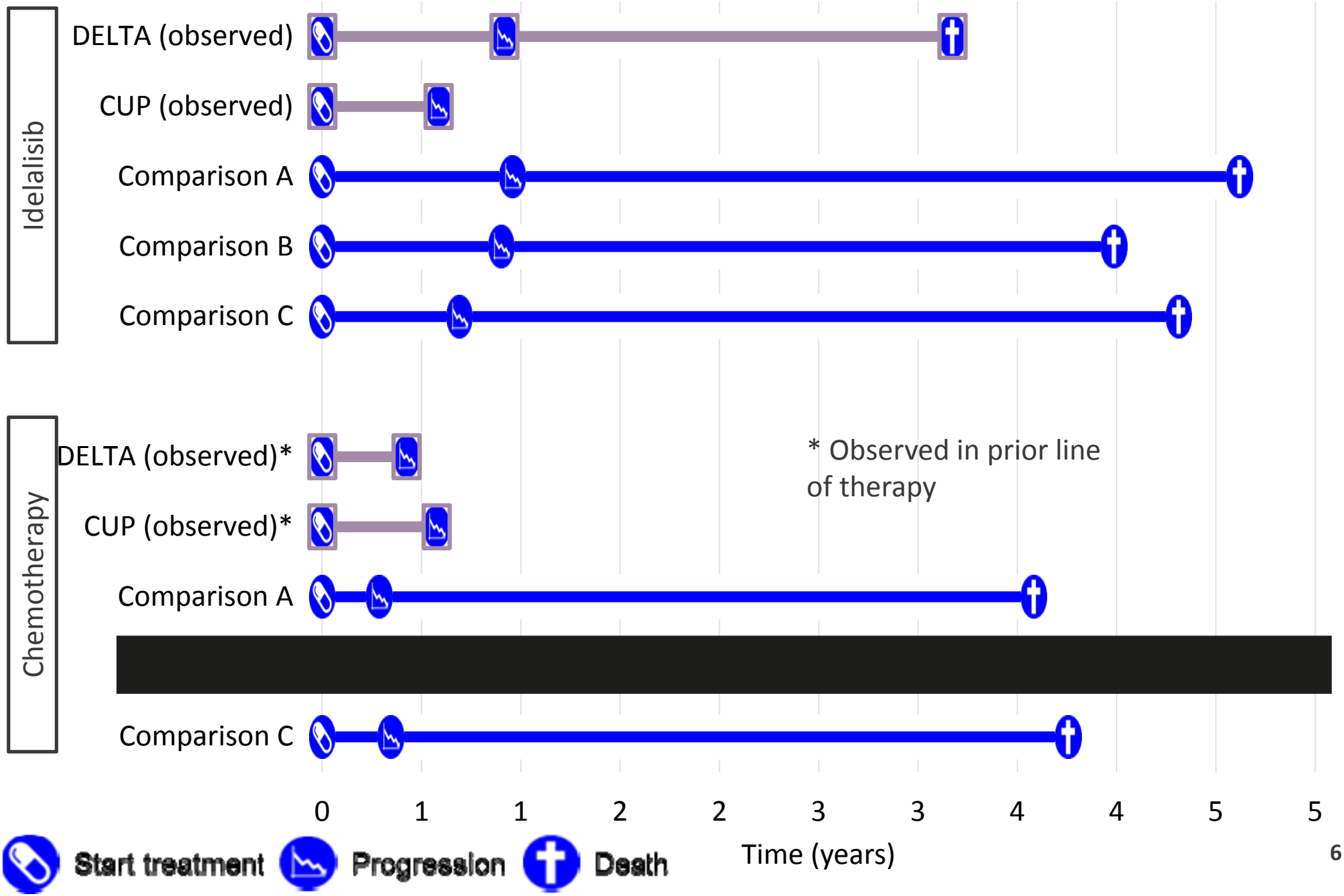
ERG comment

- Model structure is consistent with other Markov models used in oncology.
- Choice of time horizon and discounting are appropriate. Half cycle correction is necessary.

Company and ERG-corrected deterministic cost-effectiveness results

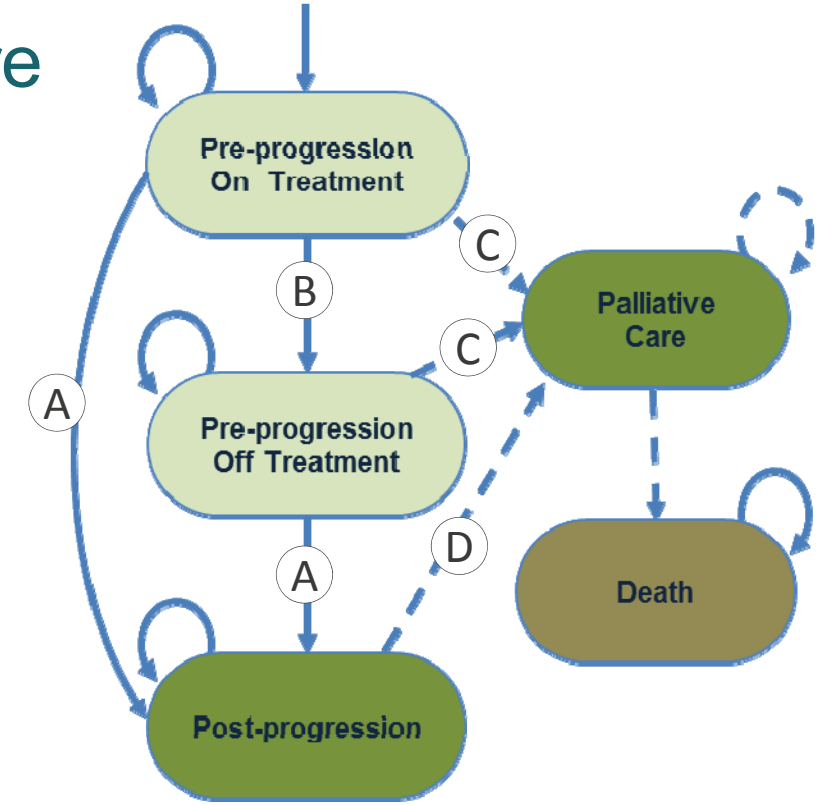
	Technologies	Total		Incremental		ICER (£/QALY)	ERG-corrected (£/QALY)
		Costs	QALYs	Costs	QALYs		
Comparison A (company base case)	Chemotherapy Regimens	£XXXX	2.80	-	-	£26,076	£32,882
	Idelalisib	£XXXX	3.71	£23,762	0.91		
Comparison B	Chemotherapy Regimens	£XXXX	1.44	-	-	£19,872	£21,559
	Idelalisib	£XXXX	3.19	£34,924	1.76		
Comparison C	Chemotherapy Regimens	£XXXX	2.92	-	-	£47,011	£58,754
	Idelalisib	£XXXX	3.41	£22,712	0.48		
Comparison D	Best supportive care	£XXXX	2.50	-	-	£25,272	£29,639
	Idelalisib	£XXXX	3.71	£30,473	1.21		

Summary of median survival estimates



Comparison A (base case) structure

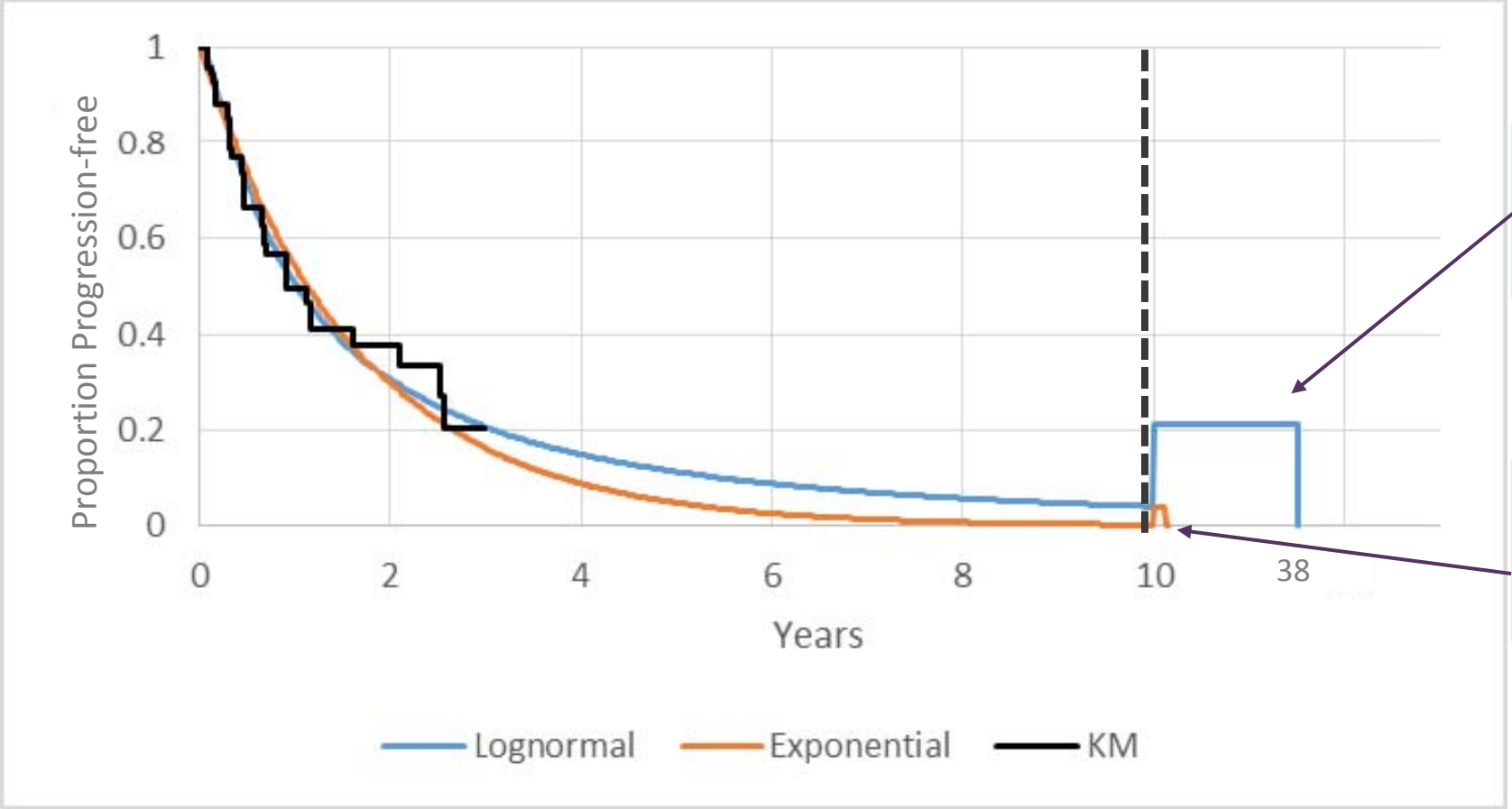
- Cohort level state transition model
- Uses intra-patient data from previous line of treatment from DELTA as comparator
- Hazard ratio is applied to prior treatment (chemotherapy) outcomes
- Because company considers pre- and post-progression survival equivalent for both arms, the key driver of the model is the difference in time to progression



Idelalisib	Chemotherapy regimens
Dataset used: DELTA	Dataset used: DELTA (prior line of treatment)
A. Idelalisib time to progression	A. Prior treatment time to progression (hazard ratio adjusted)
B. Idelalisib time on treatment	B. Prior treatment time on treatment (hazard ratio adjusted)
C. Idelalisib pre-progression survival*	C. Idelalisib pre-progression survival*
D. Idelalisib post-progression survival	D. Idelalisib post-progression survival

*Estimated hazard ratio of 5.71 vs age/sex-matched general population

Comparison A key driver - time to progression for idelalisib (DELTA)



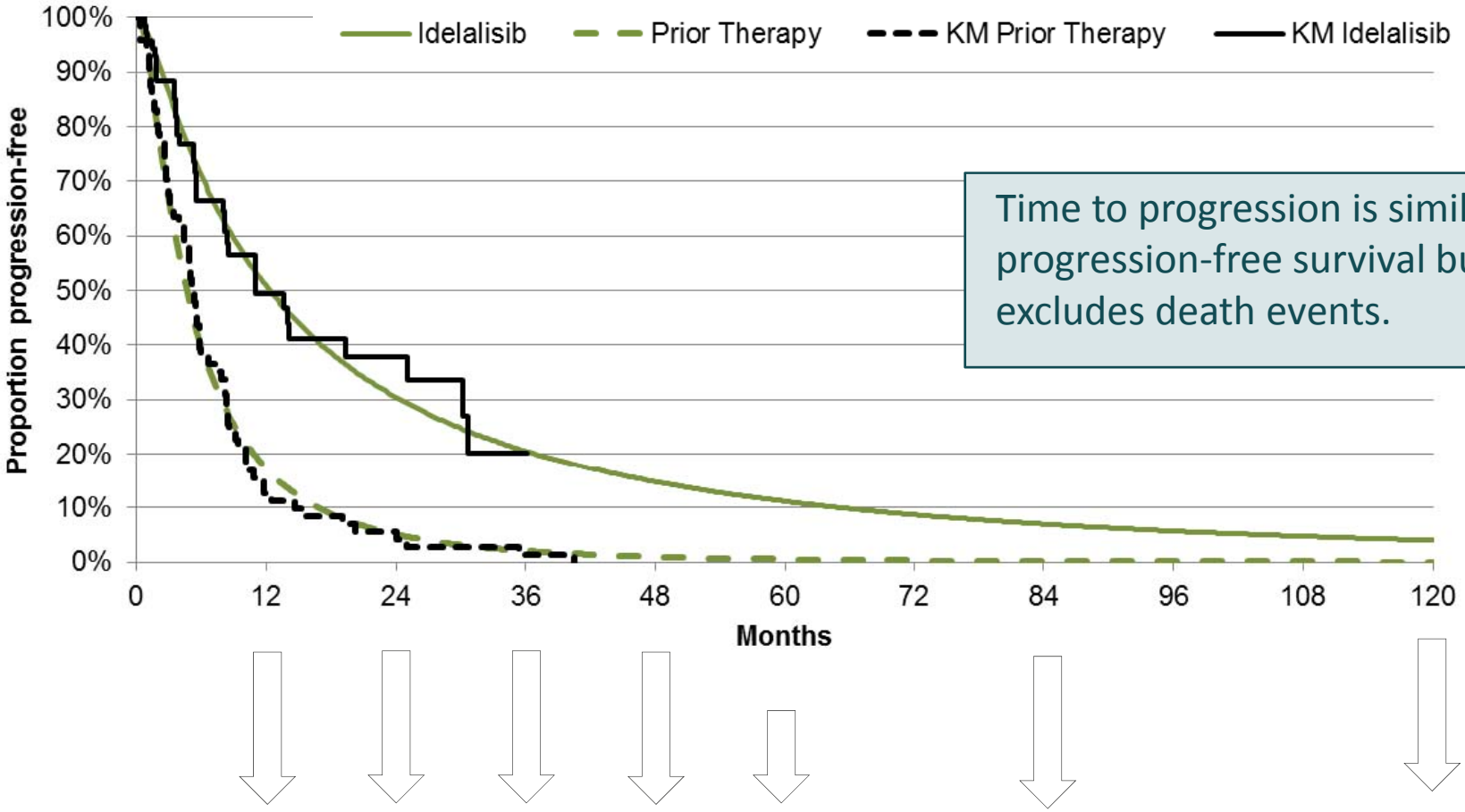
Lognormal: 13.6% of contribution comes from >10 years

Exponential: 0.2% of contribution comes from >10 years

Extrapolation	ICER (£/QALY)
Log-normal (base case)	£32,882
Exponential (ERG scenario)	£39,542

Company chose same curve to extrapolate both idelalisib arm and prior therapy arm based on best fit

Comparison A key driver – difference in time to progression



Time to progression is similar to progression-free survival but excludes death events.

Proportion of patients progressed (%)								
Idelalisib (lognormal)	49	70	79	85	89	93		96
Idelalisib (exponential)*	45	70	84	91	95	99		100
Prior Therapy (lognormal)	83	95	98	99	99	100		100
Prior therapy (exponential)*	81	94	99	100	100	100		100

*not shown on graph

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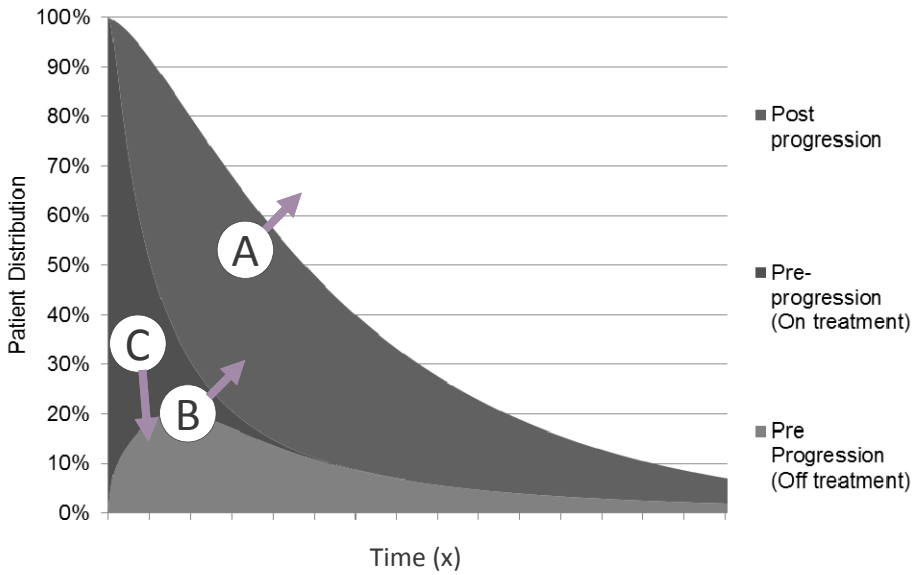
❖ ***Which extrapolation is more appropriate? Are these data clinically plausible?***

Comparison B structure – Partitioned survival

- Uses area-under-the-curve from overall survival, progression-free survival and time on treatment data to estimate state transitions.
- Uses matching-adjusted indirect comparison (company preferred) with HMRN survival data
- Overall survival more influential to QALY-gain than progression-free survival in this model so difference in overall survival between the 2 treatment arms is a **key driver**



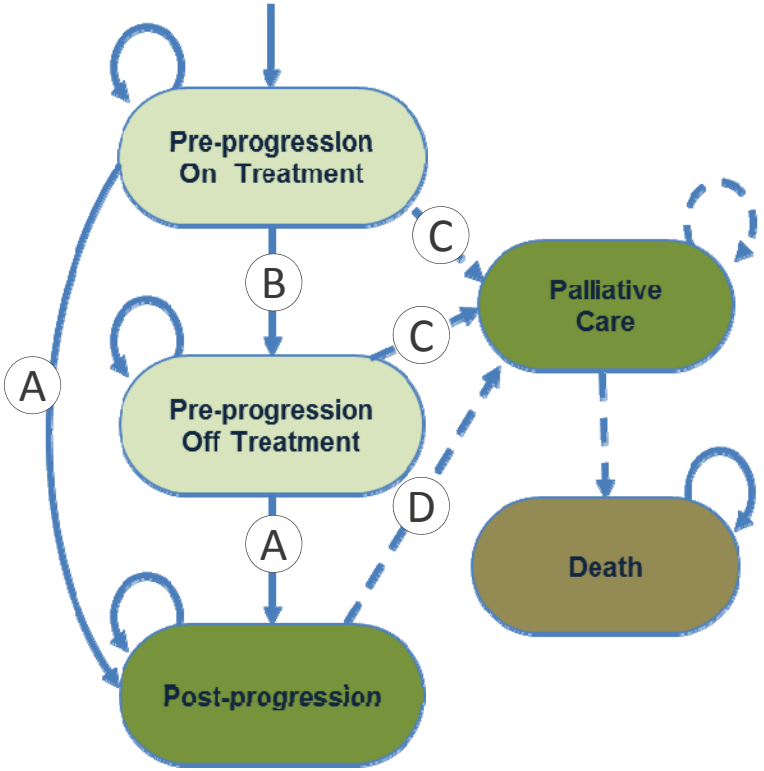
Idelalisib	Chemotherapy regimens
Dataset used: DELTA	Dataset used: HMRN
A. Idelalisib overall survival	A. MAIC adjusted "chemotherapy" overall survival
B. Idelalisib progression free survival	B. MAIC adjusted "chemotherapy" progression free survival
C. Idelalisib time on treatment	Dataset used: DELTA
	C. Prior treatment time on treatment

Comparison B key driver – difference in overall survival

❖ ***Are these data clinically plausible?***

Comparison C structure

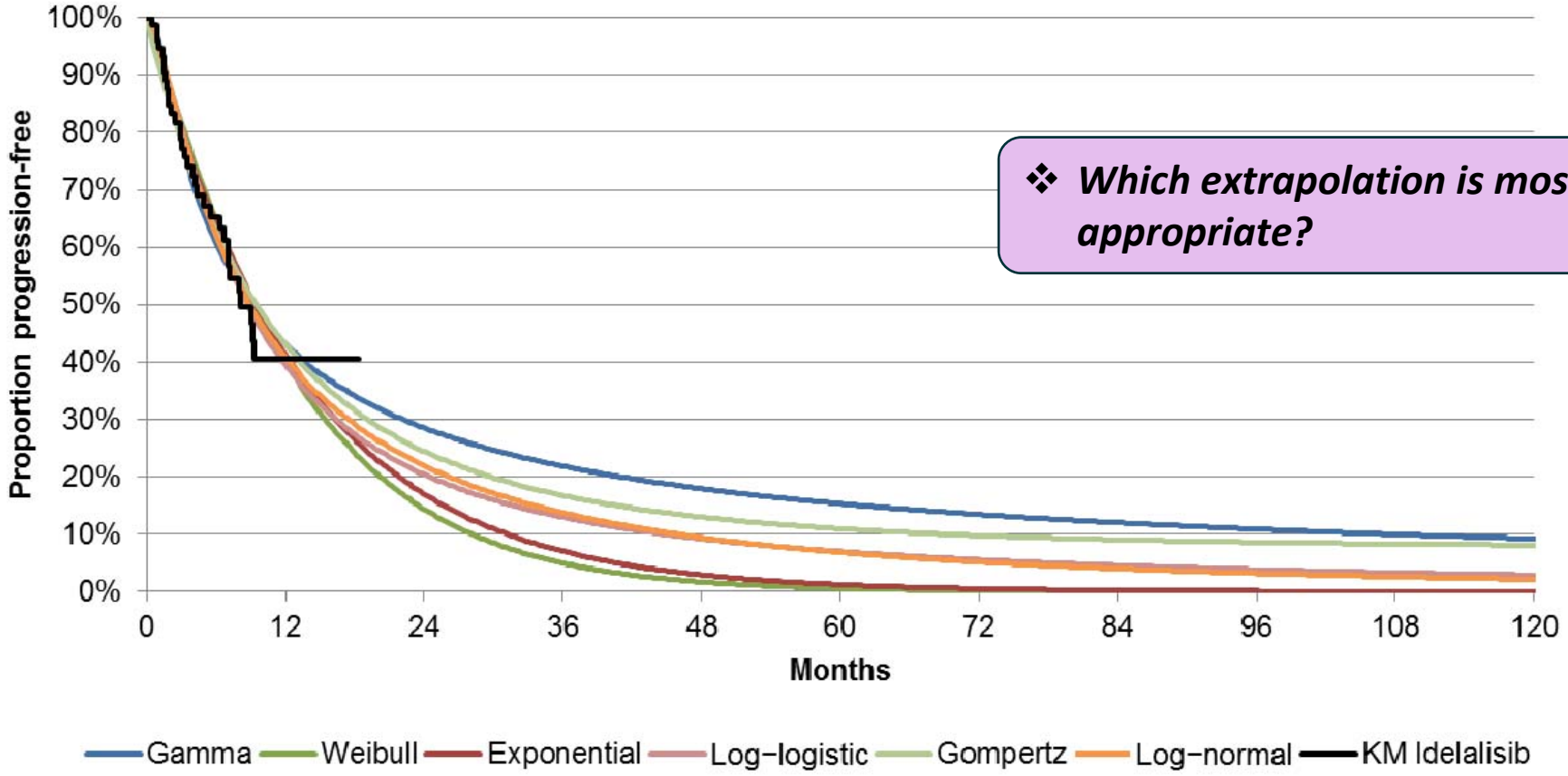
- Cohort level state transition model
- Same structure as Comparison A but uses time to progression from CUP cohort data for idelalisib and chemotherapy regimens instead of from DELTA
- Similar limitations to Comparison A and the key driver of the model is the difference in time to progression
- Model is sensitive to the hazard ratio adjustment for prior therapy.



Idelalisib	Chemotherapy regimens
Dataset used: CUP cohort	Dataset used: CUP cohort
A. Idelalisib time to progression	A. Prior treatment time to progression (hazard ratio adjusted)
Dataset used: DELTA	Dataset used: DELTA
B. Idelalisib time on treatment	B. Prior treatment time on treatment (hazard ratio adjusted)
C. Idelalisib pre-progression survival*	C. Idelalisib pre-progression survival*
D. Idelalisib post-progression survival	D. Idelalisib post-progression survival

*Estimated hazard ratio of 5.71 vs age/sex-matched general population

Comparison C key driver – time to progression for idelalisib (CUP)

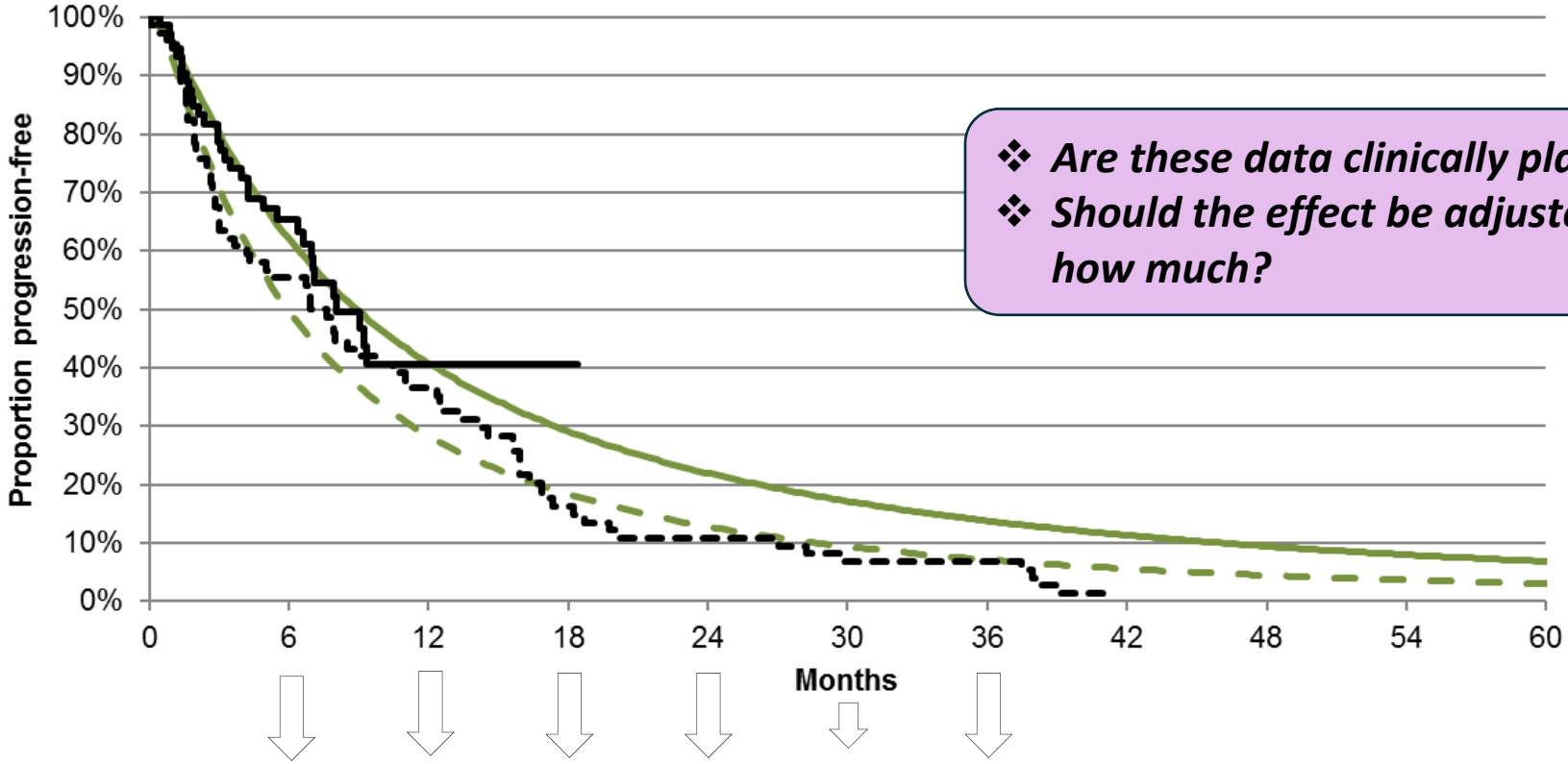


❖ ***Which extrapolation is most appropriate?***

Extrapolation	ICER (£/QALY)
Log-normal (base case)	£58,754
Exponential (ERG scenario)	£95,120

Company chose same curve to extrapolate both idelalisib arm and prior therapy arm based on best fit.

Comparison C key driver – difference in time to progression and hazard ratio



- ***Are these data clinically plausible?***
- ***Should the effect be adjusted? If so, by how much?***

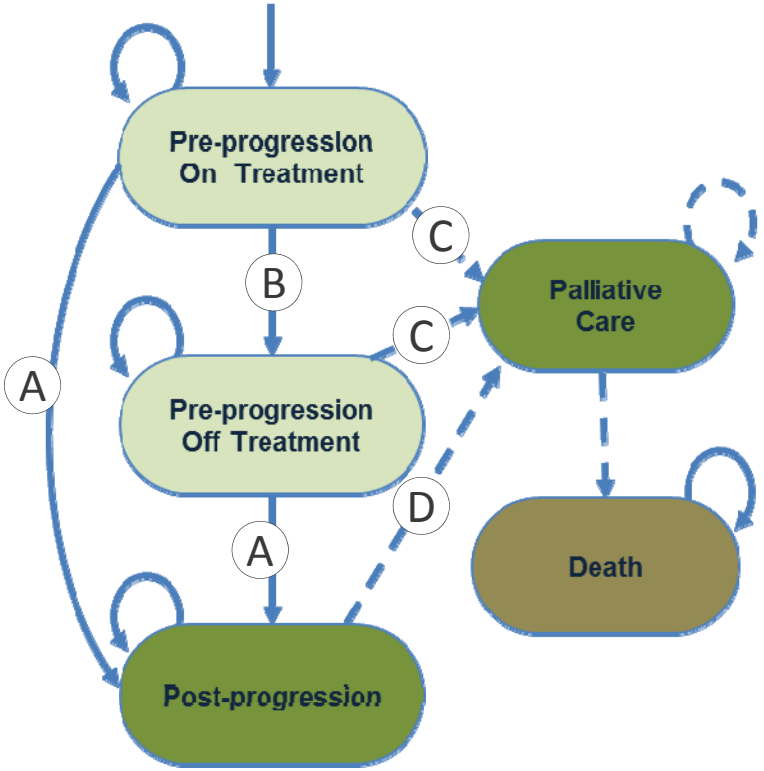
Proportion of patients progressed (%)						
Idelalisib	38	59	71	78	83	86
Prior Therapy	50	72	82	87	91	93
Prior Therapy (HR adjusted)*	61	81	90	94	96	97

Hazard ratio	ICER (£/QALY)
0.75 (base case)	£58,754
1 (no adjustment for prior therapy bias)	£92,801

*not shown on graph

Comparison D structure

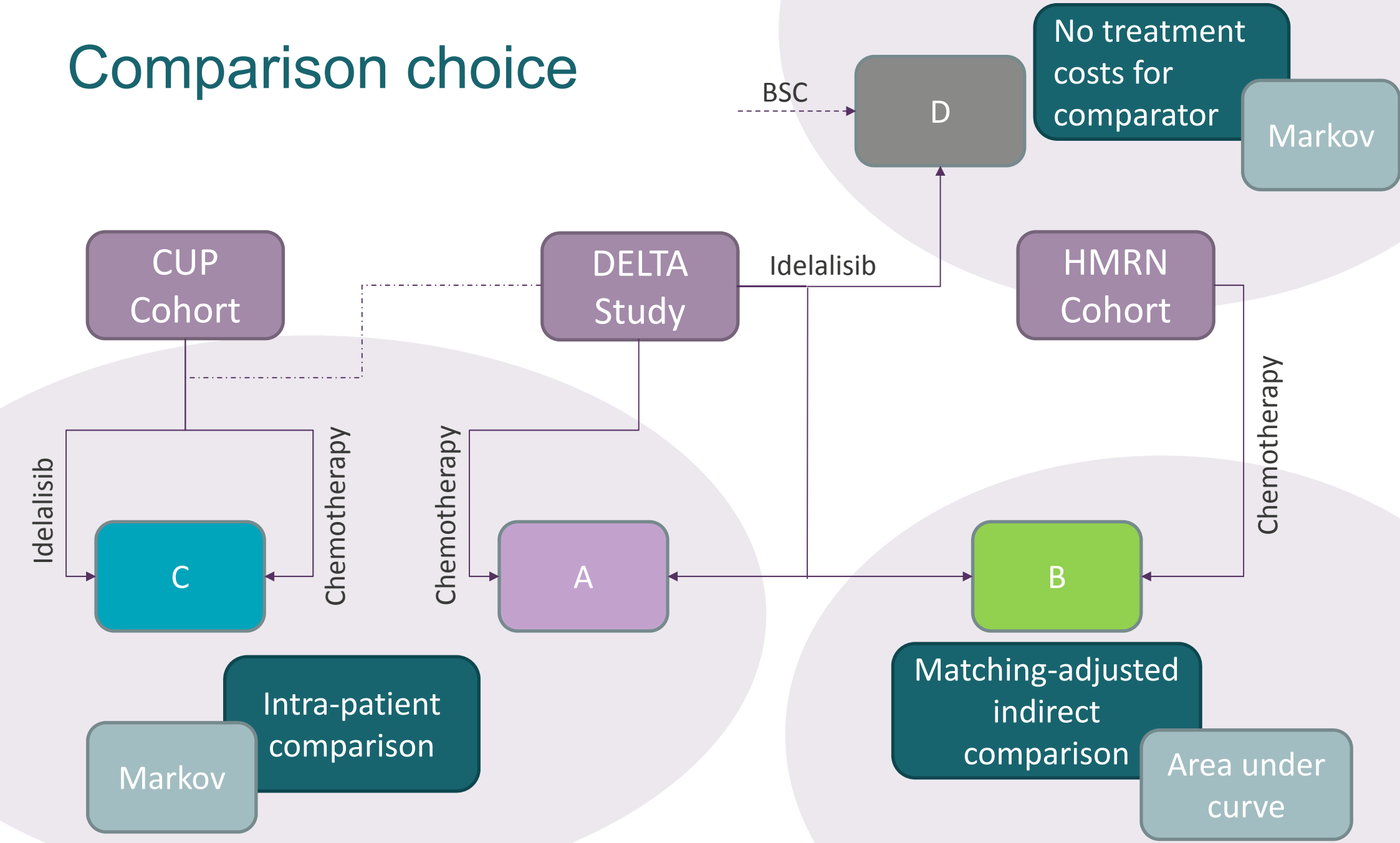
- Cohort level state transition model
- Best supportive care is comparator for those that are not eligible for chemotherapy
- Same structure as Comparison A but, in absence of data, company assumes that the disease instantly progresses on best supportive care.
- Key driver in difference is the idelalisib time to progression



Idelalisib	Best Supportive Care
Dataset used: DELTA A. Idelalisib time to progression B. Idelalisib time on treatment C. Idelalisib pre-progression survival* D. Idelalisib post-progression survival	• No treatment costs since instant disease progression is assumed. Dataset used: DELTA D. Idelalisib post-progression survival

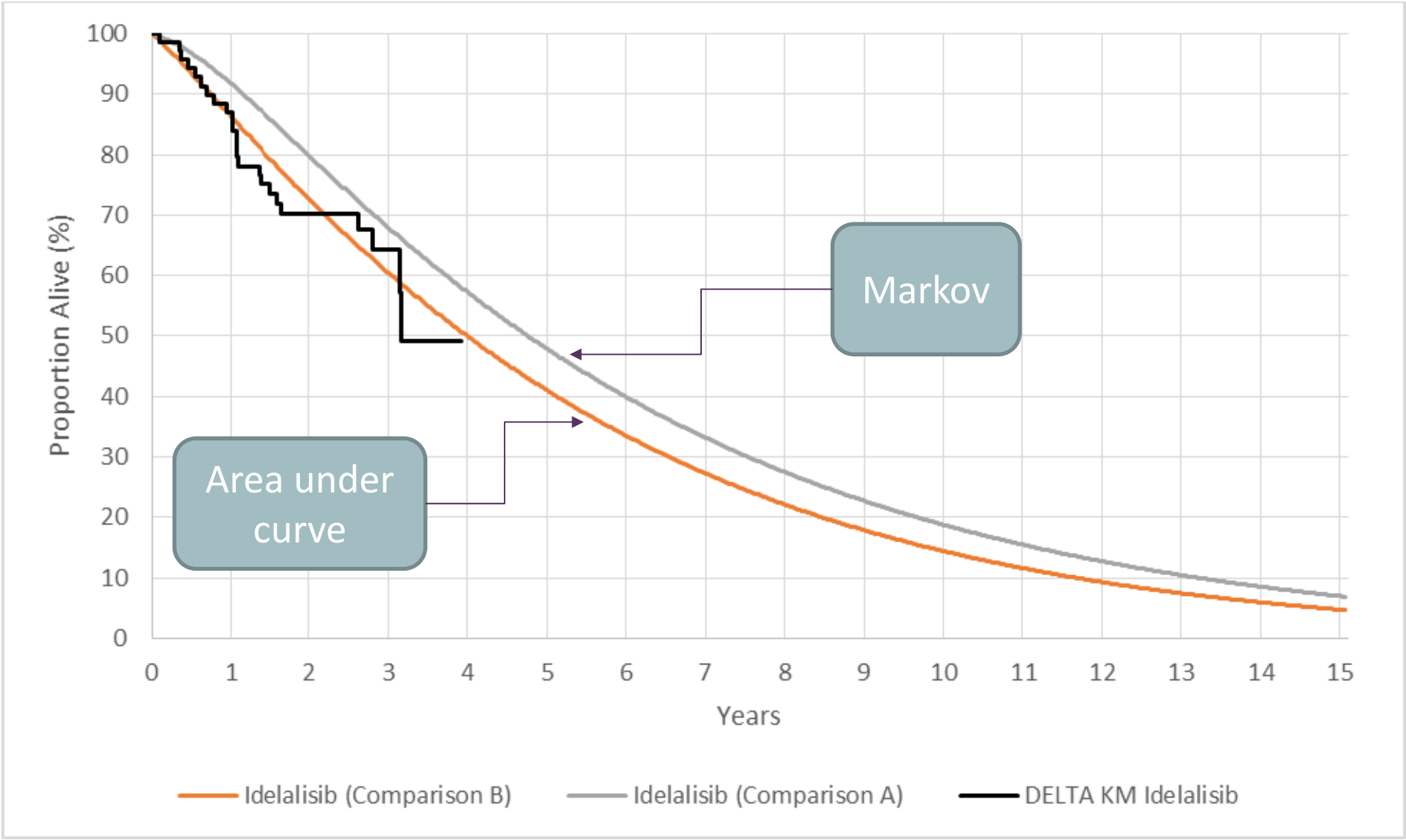
*Estimated hazard ratio of 5.71 vs age/sex-matched general population

Comparison choice



❖ ***For chemotherapy, which set of analyses (A-C) is best for decision making? If best supportive care is a comparator, is D reasonable?***

Model outputs – idelalisib overall survival



Utility values

- Company used published literature (Wild et al, 2006) to source utility estimates for progression-free survival and post-progression survival states. Wild et al assessed HRQL using EQ-5D questionnaires in 222 UK patients with follicular lymphoma.
- Patients were categorised into two broad groups to represent "progression-free" and progressed.

ERG comment

- We would have preferred the company to use FACT-G data collected in DELTA mapped to EQ-5D or to validate these utility values
- We were unable to verify the source of these utility estimates
- The derivation and choice of utility estimates are not replicable or transparent

Alternative utility inputs

- ERG identified 2 other sources of utility data presented as scenario analyses:

Health state	Wild et al 2006 (Base case)	Bec et al. 2014	GADOLIN trial
Progression free (on treatment)	0.81	0.71	0.82
Progression free (off treatment)			0.81
Progressed disease	0.62	0.51	0.76

Bec et al measured HRQL through the EQ-5D questionnaire in previously treated indolent non-Hodgkin's lymphoma in western Europe populations using French tariffs.

GADOLIN trial (TA472) measured HRQL through EQ-5D and FACT-Lym questionnaires in rituximab-refractory follicular lymphoma. EQ-5D results were limited for late disease progression because follow up was for 2 years.

	Wild et al. 2006 (Base case)	Bec et al. 2017	GADOLIN trial
Comparison A	£32,882	£36,526	£35,893
Comparison B	£21,559	£26,081	£17,766
Comparison C	£58,754	£65,305	£64,103
Comparison D	£29,639	£32,979	£32,081

❖ ***What is the most appropriate source of utility data?***

Utility values – adverse events

Adverse Event	Utility Decrement
Acute kidney injury	-0.06
Anaemia	-0.12
Asthenia	-0.12
Colitis	-0.05
Dehydration	-0.10
Diarrhoea	-0.05
Dyspnoea	-0.05
Febrile neutropenia	-0.15
Hypokalaemia	-0.12
Hypotension	-0.06
Neutropenia	-0.09
Pneumonia	-0.20
Pyrexia	-0.11
Thrombocytopenia	-0.11

ERG comment

- Company uses the same incidence of adverse events for idelalisib and chemotherapy, implicitly assuming no difference in utilities. Comparative safety evidence does not exist to support this conclusion so it is unclear if this is a valid assumption.

- There is a risk of serious infection, such as pneumonia, when using idelalisib.
- Regular monitoring for cytomegalovirus (CMV) and other tests are required by the PRAC risk assessment plan and accounted for in the economic model

❖ ***Is it appropriate to assume adverse event incidence is equivalent?***

ERG corrections and scenarios

Errors

- Comparison A, C and D
  - Correcting time-to-event transition probabilities
  - Correcting implementation of post-progression survival
- Comparison B
  - Applying hazard ratio to time on treatment

Judgement – all comparisons

- Implementing idelalisib wastage costs
- Implementing age-adjusted utility decline
- Using mean dose intensity estimate from DELTA for chemotherapy

Scenarios

1. 50% reduction in rituximab price from use of rituximab biosimilar
2. A hazard ratio of 1 used to adjust for prior therapy as proxy for current comparator
3. Alternative utility data identified in literature search
4. Cytomegalovirus (CMV) monitoring costs doubled from clinical expert estimates
5. Drug costs for chemotherapy based on cheaper CHOP regimen only
6. Other plausible distributions are chosen for relevant time-to-event curves

ERG exploratory analyses – all comparisons

	Comparison A	Comparison B	Comparison C	Comparison D
Scenarios	**ICER (£)**	**ICER (£)**	**ICER (£)**	**ICER (£)**
Company base-case	£26,076	£19,872	£47,011	£25,272
ERG corrected	£32,882	£21,559	£58,754	£29,639
Scenario 1 – Rituximab price reduction	£35,202	£22,091	£62,922	£29,789
Scenario 2 – Hazard Ratio=1 for adjusting prior line treatment outcomes	£35,980	£21,004	£92,801	£29,639
Scenario 3a –Utility inputs from Bec et al. 2014	£36,526	£26,081	£65,305	£32,979
Scenario 3b –Utility inputs from GADOLIN trial	£35,893	£17,766	£64,103	£32,081
Scenario 4 – Increased CMV monitoring	£33,416	£21,787	£59,746	£30,025
Scenario 5 – Cheaper chemotherapy costs	£37,953	£22,740	£67,870	£29,961
Scenario 6a – Using different time to progression extrapolation (exponential)	£39,542	-	£95,120	£33,771
Scenario 6b – Using different time on treatment extrapolation (lognormal)	£34,542	£22,560	£61,772	£30,596
Scenario 6c – Using different post progression survival extrapolation (lognormal)	£29,455	-	£41,131	£27,990
Scenario 6d – Using different progression free survival extrapolation (loglogistic)	-	£21,791	-	-
Scenario 6e – Using different overall survival extrapolation (lognormal)	-	£16,855	-	-

Innovation and Equality

Innovation

- Company comments
  - Idelalisib is the first PI3Kδ inhibitor to be licensed for follicular lymphoma
  - Offers a different mode of action to patients that have poor response to immunotherapy and chemotherapy
  - Convenience of an oral treatment compared to intravenous chemotherapy
  - Adverse event profile contrasts to chemotherapy
- Professional comments
  - Idelalisib could be used in a key area of unmet need in the follicular lymphoma treatment pathway

Equality

- No equality concerns have been identified

End of life – company makes a case

Criterion	Data source	Overall survival	
		Median (months)	Mean
Short life expectancy, normally < 24 months	HMRN cohort data chemotherapy	[redacted]	-
	HMRN MAIC-adjusted data chemotherapy		-
	Base case (A) economic analysis chemotherapy	-	60.1
Extension to life, normally of a mean value of ≥ 3 months		**Increase with idelalisib**	
		Median (months)	Mean
	DELTA difference to HMRN MAIC adjusted overall survival	[redacted]	-
	Base case (A) economic analysis idelalisib difference to chemotherapy	-	16.0

ERG comment

- [redacted]

❖ ***Are the end of life criteria met?***

Key issues – cost effectiveness

- Which comparison (A-D) gives the most appropriate data for the comparator?
- What is the most appropriate distribution for extrapolation of time to progression in the DELTA idelalisib arm?
- What is the most appropriate utility data for people with progression free and progressed follicular lymphoma?
- Is it appropriate to assume adverse events are equivalent for idelalisib and chemotherapy?
- What is the most plausible ICER?
- Are the end of life criteria met?