Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable

PART 1

Confidential information redacted

Technology appraisal committee C [9 June 2026]

Chair: Richard Nicholas

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Company: Johnson & Johnson Innovative Medicine

Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable

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

NICE National Institute for Health and Care Excellence

Background on mantle cell lymphoma (MCL)

Causes and epidemiology

- MCL characterised by excess malignant B-cells from the mantle zone of the lymph node
- MCL is a rare type of non-Hodgkin's lymphoma (NHL), about 5% of NHL in the UK is MCL
- Approximately 600 new cases of MCL in the UK per year, of which ~140 eligible for autologous stem cell transplant (ASCT)

Diagnosis and classification

- Typically a high grade (fast growing) lymphoma, but also has low grade features (relapsing)
- Most patients diagnosed when cancer is advanced, ~70% have stage IV cancer
- Median age at diagnosis of 72 – so most are ASCT-ineligible (typically available for those ≤65)

Symptoms and prognosis

- Commonly manifests as painless swollen lymph nodes, but presentation can be heterogenous
- Incurable, relapsing disease course, with worse outcomes with each further treatment line
- For people ≤65 with untreated MCL, median PFS is ~8.5 years and OS is ~12.7 years

ASCT, autologous stem cell transplant; MCL, mantle cell lymphoma; NHL, non-Hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival

Patient perspectives

Urgent need for better tolerated treatments

Submissions from Lymphoma Action + patient expert

- Fast growing nature of MCL means symptoms can develop quickly, including swollen lymph nodes, enlarged spleen, bruising or bleeding, being more prone to infections, symptoms of anaemia, weight loss, night sweats, fever, fatigue
- Relapsing disease causes significant anxiety for patients and carers
- Intensity of chemotherapy is difficult to endure with numerous short- and long-term side effects
- Not everyone will qualify for or choose autologous stem cell transplant – eligibility dependent on age + health, and whether a person can tolerate harsh chemotherapy prior to transplant
- Need for better tolerated treatments with fewer side effects

"It is very hard to live with this type of lymphoma, as although I am in remission I know it will come back at some point"

"The side-effects (of chemotherapy) were insomnia and extreme tiredness plus hair loss"

Clinical perspectives

Ibrutinib allows avoidance of ASCT with no loss of efficacy

Submissions from clinical experts

- Main aim of treatment is to induce remission of the lymphoma for as long as possible, prolong survival, minimise toxicity
- Treatment pathway is well-defined and, in the UK, follows British Society for Haematology guidelines
- Induction chemotherapy for ASCT-eligible patients usually involves the 'NORDIC' regimen – 70–80% of NHS trusts use this or variations
- ASCT eligibility generally includes <65 years old and no comorbidities that prevent intensive treatment
- ASCT requires ~4-week inpatient stay + ~6 months of physical recovery – something that could be avoided with ibrutinib
- Expect that ibrutinib will improve both quality and length of life versus current care, and will increase system capacity

"There is a significant and clinically meaningful survival benefit; ability to omit ASCT represents a step change."

"This technology will be transformative in how we manage our younger patients. Easier to deliver than current standard of care. Potentially avoid need for any hospital admissions during delivery of care."

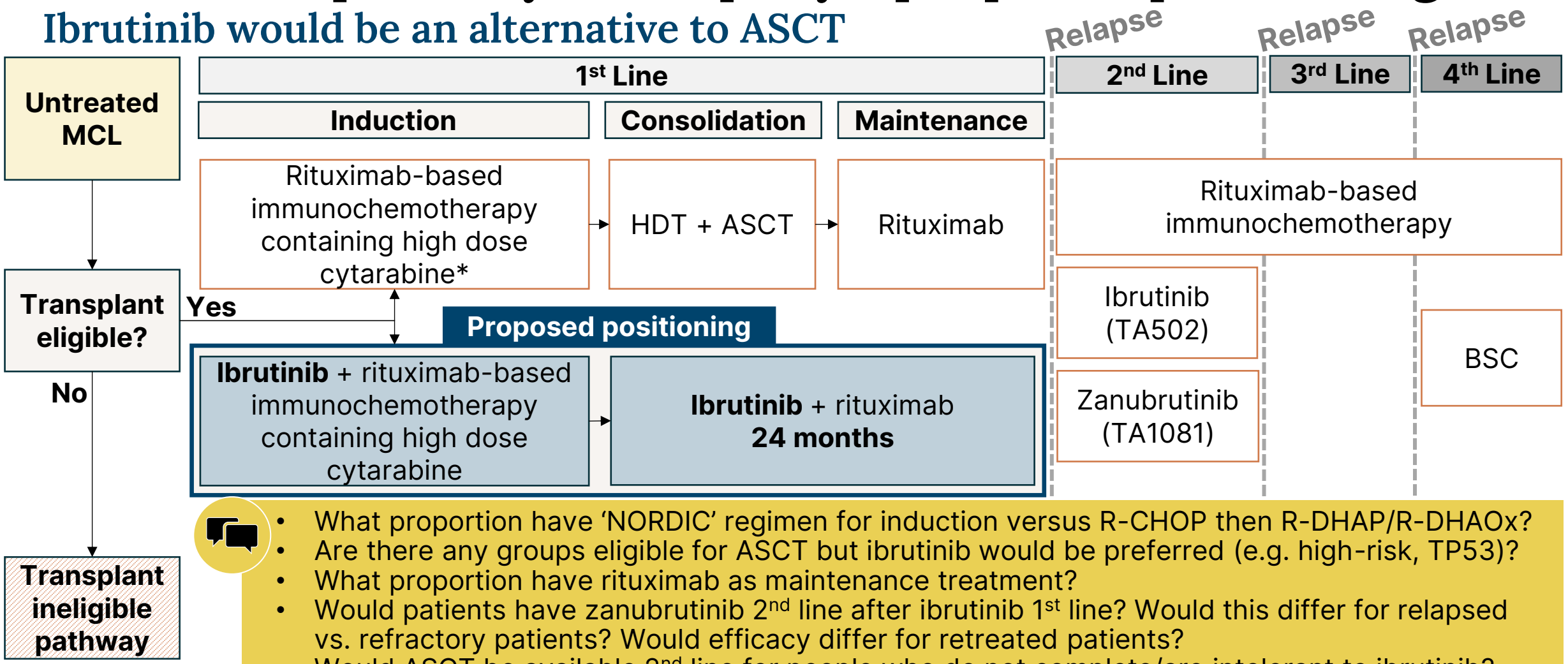
NICE ASCT, autologous stem cell transplant.

Equality and health inequality considerations

- No potential equality or health inequality issues were raised at the scoping consultation, in the submissions, or in the EAG report.
- Committee lead team – note that ibrutinib is only available for people who can have ASCT – in the NHS, this typically means 65 years old or younger
- NICE note that a previous appraisal – ibrutinib for treating relapsed or refractory mantle cell lymphoma (TA502) – highlighted that ibrutinib would offer an alternative treatment for people who are older or frailer
    - ↳ May be less relevant here as the ASCT-eligible population are generally younger and fitter

Treatment pathway – company's proposed positioning

Ibrutinib would be an alternative to ASCT



- What proportion have 'NORDIC' regimen for induction versus R-CHOP then R-DHAP/R-DHAOx?
- Are there any groups eligible for ASCT but ibrutinib would be preferred (e.g. high-risk, TP53)?
- What proportion have rituximab as maintenance treatment?
- Would patients have zanubrutinib 2nd line after ibrutinib 1st line? Would this differ for relapsed vs. refractory patients? Would efficacy differ for retreated patients?
- Would ASCT be available 2nd line for people who do not complete/are intolerant to ibrutinib?

*__NORDIC (80% in model):__ R-maxi-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine) alternating with rituximab + cytarabine

*__R-CHOP then R-DHAP/R-DHAOx (20% in model):__

- R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
- R-DHAP: rituximab, dexamethasone, high-dose cytarabine and cisplatin
- R-DHAOx: rituximab, dexamethasone, high-dose cytarabine and oxaliplatin

Ibrutinib (IMBRUVICA®, Johnson & Johnson Innovative Medicine)

Marketing authorisation	• Ibrutinib in combination with R-CHOP alternating with R-DHAP (or R-DHAOx) without ibrutinib, followed by ibrutinib monotherapy, is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who would be eligible for autologous stem cell transplantation (ASCT) • Granted by MHRA via International Recognition, August 2025
Mechanism of action	• Small-molecule Bruton's tyrosine kinase (BTK) inhibitor • BTK inhibition blocks B-cell receptor signalling, induces apoptosis, and blocks B-cell migration and adhesion
Administration	Oral, 560 mg tablet once daily • Induction: ▪ Ibrutinib with R-CHOP on Days 1–19 of Cycles 1, 3 and 5 (21-day cycle) ▪ R-DHAP or R-DHAOx without ibrutinib on Cycles 2, 4, 6 (21-day cycle) • Maintenance: ▪ Ibrutinib daily for 24 months. Rituximab (375 mg/m^2) may be added
Price	• List price of ibrutinib is £5,723.20 per 28 pack of 560 mg tablets • A patient access scheme discount is available

- What are the criteria used in the NHS to assess ASCT eligibility?
- Would these criteria remain consistent over time if ibrutinib were to become available?

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
R-DHAP, rituximab, dexamethasone, high-dose cytarabine and cisplatin
R-DHAOx, rituximab, dexamethasone, high-dose cytarabine and oxaliplatin

Key issues

Issues	ICER impact
Decision problem issues	
Uncertainty in the percentage of patients who have rituximab maintenance	Small
Uncertainty as to the comparator induction regimen	Small
Clinical effectiveness issues	
Uncertainty in the effect of ibrutinib on HRQoL – in appendix	Unknown
Uncertainty as to the method of adjustment for rituximab maintenance	Small
Cost-effectiveness issues	
Model structure: the modelling of ASCT	Unknown
Treatment effectiveness and extrapolation: pre-failure mortality	Large
Treatment effectiveness and extrapolation: 2nd line treatment effectiveness	Medium
Resource use and costs: the cost of ASCT	Large
Resource use and costs: subsequent treatment for ibrutinib patients	Large

NICE ASCT, autologous stem cell transplant; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio

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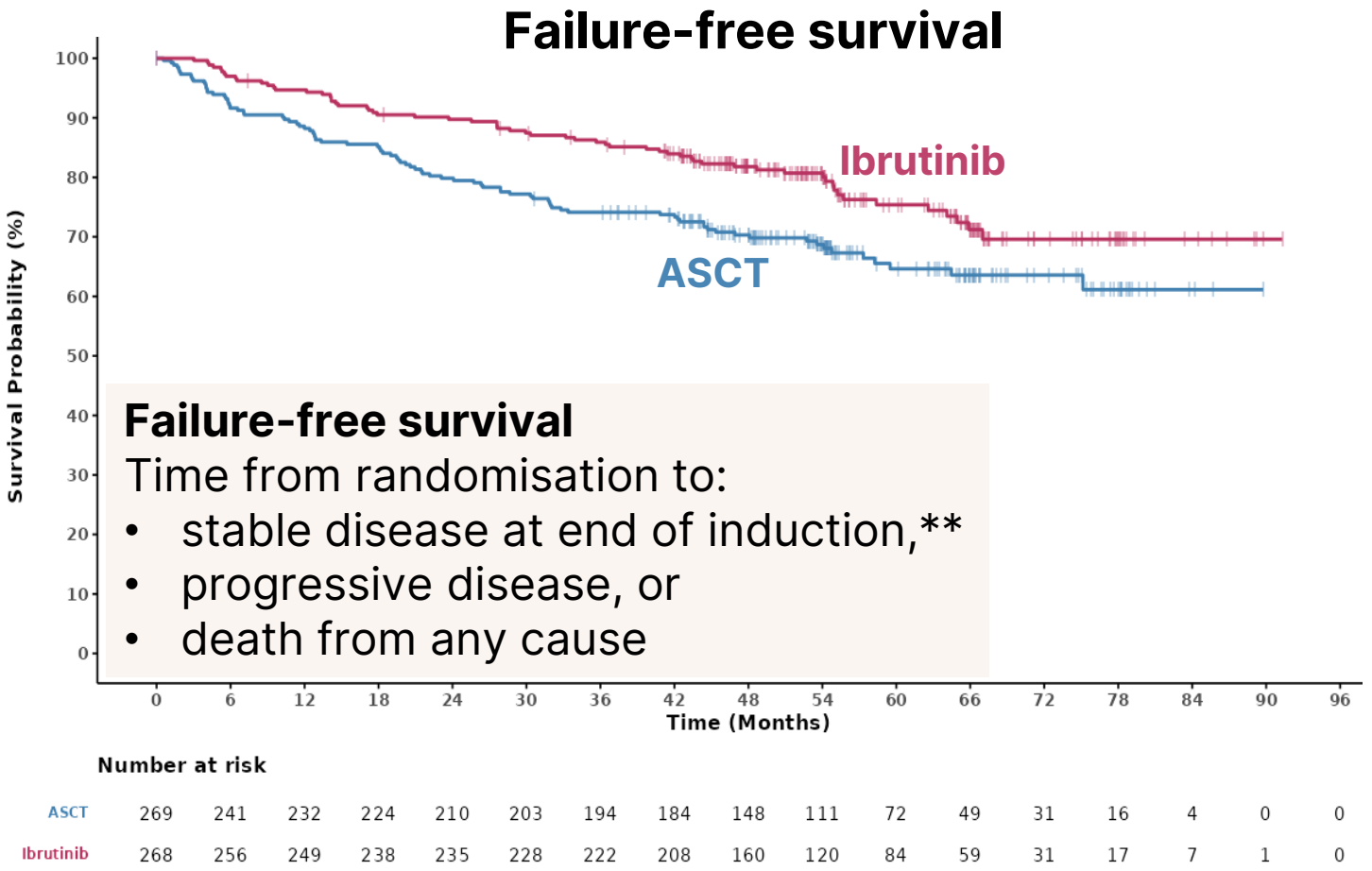
Clinical evidence – TRIANGLE

	TRIANGLE
Design	Phase 3, open-label RCT, investigator-initiated
Population	Untreated stage II–IV MCL eligible for ASCT
Intervention	• **Arm I:** Ibrutinib with R-CHOP alternating with R-DHAP/R-DHAOx without ibrutinib, then ibrutinib maintenance with optional rituximab (n=268)
Comparator	• **Arm A**: Rituximab-based induction, HDT + ASCT consolidation, optional rituximab maintenance (n=269) • Arm A+I: license not granted – no extra benefit observed with addition of ibrutinib to ASCT – see appendix
Outcomes	Primary: Failure-free survival (FFS) Secondary: various including OS, PFS, safety ↳ HRQoL **not** captured
Locations	Europe (165 sites in 13 countries, 0 in the UK)
Use in company's model	• Baseline patient characteristics • Transition probabilities from 1st line treatment • Adverse event frequencies

ASCT, autologous stem cell transplant; FFS, failure-free survival; HDT, high-dose therapy; HRQoL, health-related quality of life; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

TRIANGLE – outcomes*

Ibrutinib prolonged failure-free survival vs. ASCT; better PFS + OS



Failure-free survival

Time from randomisation to:

- stable disease at end of induction,**
- progressive disease, or
- death from any cause

	Ibrutinib (N=268)	ASCT (N=269)
Failure-free survival		
Events, n (%)	61 (22.8%)	87 (32.3%)
Median	NE	NE
Hazard ratio (95% CI)	0.639 (0.428, 0.953), p=0.0068	
Progression-free survival		
Events, n (%)	60 (22.4%)	87 (32.3%)
Median	NE	NE
Hazard ratio (95% CI)	0.633 (0.424, 0.946), p=0.0060	
Overall survival		
Events, n (%)	33 (12.3%)	60 (22.3%)
Median	NE	NE
Hazard ratio (95% CI)	0.522 (0.341, 0.799), p=0.0023	
Adverse events	Similar between arms	

See appendix for subgroup analysis

*Supplementary analyses were requested by the EMA to assess superiority of ibrutinib over ASCT. Given that these analyses were not prespecified, all statistically significant efficacy outcomes were deemed 'nominally' significant.
**1 patient (0.4%) in the ibrutinib arm and 5 patients (1.9%) in ASCT arm had stable disease at end of induction.
ASCT, autologous stem cell transplant; CI, confidence interval; OS, overall survival; PFS, progression-free survival.

Small ICER impact

Key issue: Rituximab maintenance use

Company adjust TRIANGLE outcomes data to assess 85% rituximab use

Background:
- At the time of TRIANGLE design, rituximab maintenance was not routine clinical practice
- Approximately 60% of the Full Analysis Set in each arm of TRIANGLE had rituximab maintenance

Company:
- Now treatment guidelines recommend rituximab maintenance
- Clinical advice → ~85% have rituximab in NHS; not 100% due to infections, inability to travel
- Conducted Inverse Probability of Censoring Weights (IPCW) analysis to adjust TRIANGLE population to reflect 85% rituximab maintenance
- Unadjusted and adjusted HRs were similar, model uses unadjusted data

EAG:
- Unclear on proportion who would have rituximab in NHS – asked company for 100% scenario
- Unclear if IPCW is best method – asked company for Two-Stage Estimation (TSE) scenario
  ↳ EAG think both IPCW and TSE are appropriate
- Similar HRs for both methods and regardless of proportion; use unadjusted (same as company)

Clinical expert: Majority of patients (~90%) would have rituximab maintenance

Are the committee satisfied that increased rituximab maintenance use would not significantly alter the relative treatment effect?

ICER, incremental cost-effectiveness ratio; IPCW, Inverse Probability of Censoring Weights; HR: hazard ratio; TSE, Two-Stage Estimation.

See appendix for description of IPCW and TSE

Other clinical evidence used in the model (1/2)

	RAY-3001	MANTLE-FIRST
Design	Phase 3, open-label RCT	Retrospective cohort study
Population	Relapsed/refractory MCL – minority ([redacted]) had ASCT as a 1st line treatment • Subgroup 1: **after exactly 1 prior line**	Relapsed/refractory MCL
Intervention	Ibrutinib, n=139 • Subgroup 1, n=57 ← Used in the model	• Ibrutinib, n=50 • Bendamustine + rituximab, n=54 • Bendamustine + rituximab + cytarabine, n=76 • Other regimens, n=81
Comparator	Temsirolimus*, n=141 ← Not used in the model *Not NICE-approved (TA207)	
Outcomes	Primary: PFS Secondary: various including OS, safety, EQ-5D-5L	Primary: OS Secondary: PFS, response rates
Locations	Global, including 27 patients from the UK	Italy (most patients), Spain and UK
Use in company model	• Transition probabilities (progression, mortality) for 2nd line treatment • Utility values for 2nd line and progressed health states (pooled with SPARK) • Company had access to IPD	• Relative efficacy adjustment of subsequent treatments

ASCT, autologous stem cell transplant; EQ-5D, Euroqol 5-dimensions; IPD, individual patient data; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

Other clinical evidence used in the model (2/2)

	SHINE	SPARK
Design	Phase 3, double-blind RCT	Phase 2, single-arm, open-label trial
Population	Untreated MCL, **ineligible for ASCT**	Relapsed/refractory MCL
Intervention	Ibrutinib with bendamustine and rituximab, n=262	Ibrutinib, n=111
Comparator	Placebo with bendamustine and rituximab, n=261	-
Outcomes	Primary: PFS Secondary: various including OS, safety, EQ-5D-5L	Primary: PFS Secondary: various including OS, safety, EQ-5D-5L
Locations	Global, including 30 patients from the UK	US, Germany, Poland, UK (20 patients)
Use in company model	• Utility values for 1st line failure-free health state	• Utility values for the 2nd line and progressed disease health states (pooled with RAY-3001)

ASCT, autologous stem cell transplant; EQ-5D, Euroqol 5-dimensions; MCL, mantle cell lymphoma; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial.

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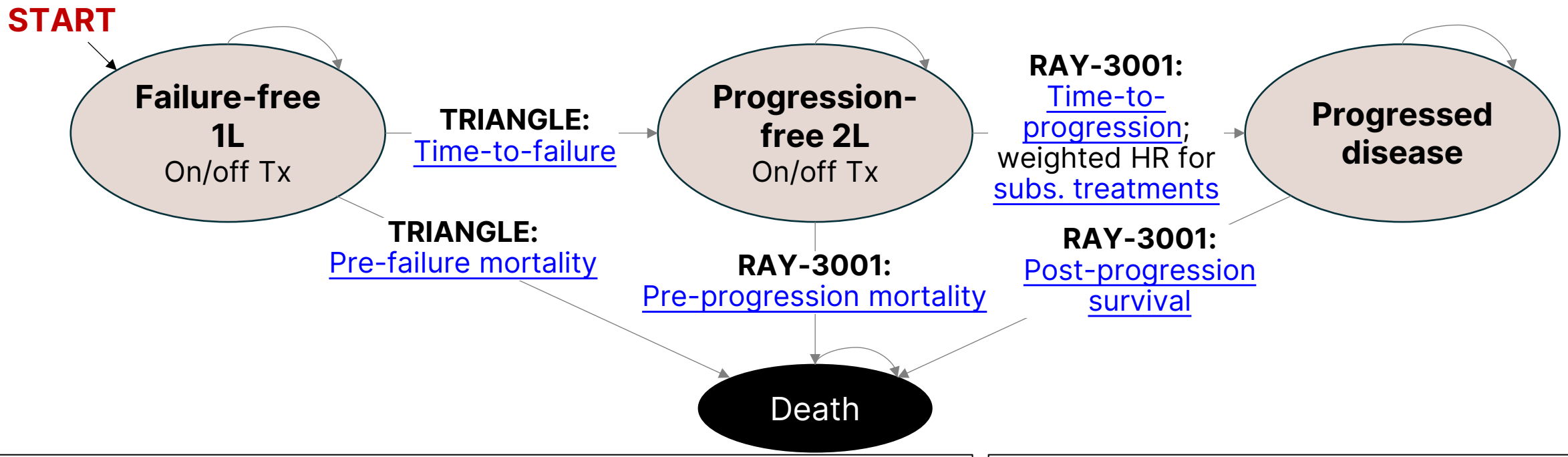
Company's model structure and source of transition probabilities



Semi-Markov, 4 health states (lifetime 43-year time horizon)*:

- Start in **failure-free 1L** until treatment failure (stable disease at the end of induction or disease progression) or death
- Patients in **progression-free 2L** start active 2nd line treatment and remain in this state until disease progression or death
- Patients in **progressed disease** have 3rd line treatment and remain in this state until death

Ibrutinib affects **QALYs** by:

- First-line treatment effectiveness
- Types and efficacy of 2nd line treatment

Ibrutinib affects **costs** by:

- Avoiding costs of ASCT
- Incurring ibrutinib acquisition costs
- Second-line treatment costs

*Note that treatment waning is not included in the model.
1L, 1st line; 2L, 2nd line; ASCT, autologous stem cell transplant; HR, hazard ratio; QALY, quality-adjusted life year; Tx, treatment.

Transition probabilities – overview

Model uses TRIANGLE for 1st line transitions, but not for 2nd line or PD

Transition probability	Ibrutinib regimen	ASCT regimen
FF 1L to death	Per cycle probability of death (constant): [redacted]	Per cycle probability of death (constant): [redacted]
FF 1L to PF 2L	Exponential curve fit to time-to-failure	Gamma curve fit to time-to-failure
PF 2L to death	Per cycle probability of death (constant): [redacted]	
PF 2L to PD	Log-logistic curve fit to ibrutinib TTP + HR of 1.103	Log-logistic curve fit to ibrutinib TTP + HR of 1.012
PD to death	Exponential curve fit to post-progression survival	

EAG key issues (see next slides):

- ASCT short-term mortality risk overweighted – very limited evidence of different pre-failure mortality rates from TRIANGLE, risk is constant – implausible
- ASCT long-term benefits uncaptured – using RAY-3001 for 2L+ transitions does not capture long-term benefits as RAY population mostly did not have ASCT at 1L
- Second-line effectiveness overestimated for ibrutinib + underestimated for ASCT

Key:

Benefit for ibrutinib
No difference
Benefit for ASCT

Key questions for the following slides:

- Does the model sufficiently capture the short-term risks and long-term benefits of ASCT?
- Are the model structure and inputs appropriate for decision-making?
- Is RAY-3001 a suitable source to inform 2nd and 3rd line transition probabilities?

1L, 1st line; 2L, 2nd line; ASCT, autologous stem cell transplant; FF, failure-free; HR, hazard ratio; PD, progressed disease; PF, progression-free; TTP, time-to-progression

Large ICER impact

Key issue: Pre-failure mortality

EAG: Pre-failure mortality risk of ASCT is overestimated

Transition probability	Ibrutinib regimen	ASCT regimen	Source
FF 1L to death	Per cycle probability of death: [redacted]	Per cycle probability of death: [redacted]	TRIANGLE: Pre-failure mortality

Company:

- Limited number of pre-failure mortality events in TRIANGLE (11/268 for ibrutinib; 22/269 for ASCT)
  ↳ So, parametric extrapolation not possible, constant per cycle probability of death preferred
- Higher mortality for ASCT is consistent with toxicity + mortality risk → supported by clinical advice

EAG:

- Very limited data from TRIANGLE to support different pre-failure mortality rates between arms
- Higher mortality risk at 1st line for ASCT is constant over time horizon of the model – whereas it would be expected that the mortality risk is higher in the short-term, then reduces long-term
- Would prefer parametric modelling, despite uncertainty, or separate tunnel states to capture ASCT-specific mortality risk – but company did not provide either
- EAG base case assumes constant equal pre-failure mortality; ASCT set equal to ibrutinib ([redacted])

NICE: 2 scenarios – ASCT pre-failure mortality risk higher for 6 or 12 months, then equal to ibrutinib

- Does the evidence support an increased risk of pre-failure mortality for ASCT?
- How should the model capture pre-failure mortality?

NICE

ASCT, autologous stem cell transplant; FF, failure-free; ICER, incremental cost-effectiveness ratio.

Large ICER impact

Time-to-failure extrapolation

Cost-effectiveness of ibrutinib very sensitive to TTF extrapolation

Transition probability	Ibrutinib regimen	ASCT regimen	Source
FF 1L to death	Per cycle probability of death: [redacted]	Per cycle probability of death: [redacted]	TRIANGLE: Pre-failure mortality
FF 1L to PF 2L	Exponential curve fit to TTF	Gamma curve fit to TTF	TRIANGLE: Time-to-failure (TTF)

Company:

- TTF similar to FFS but people who experience pre-failure mortality are censored in TTF
- FFS landmarks were reconstructed from curves fit to TTF + pre-failure mortality risk (as above)
- Clinical plausibility of reconstructed FFS landmarks was main consideration in TTF curve selection
- Base case uses exponential curve for ibrutinib and gamma for ASCT

EAG:

- Consider reconstructed FFS curves unsuitable for clinical validation, as they incorporate different pre-failure mortality risks – which EAG does not think is supported by evidence (see previous slide)
- Note clinical estimations were not gathered by structured expert elicitation
- Present scenario analysis using log-normal for ASCT – best statistical fit, more optimistic in the long-term, increases the ICER – though note implausible under EAG base case assumptions

- Is the company's use of reconstructed FFS appropriate to validate TTF extrapolation?
- What is the committee's preferred TTF extrapolation?

ASCT, autologous stem cell transplant; FF, failure-free; FFS, failure-free survival; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; PF, progression-free; TTF, time-to-failure

Medium ICER impact

Key issue: 2nd line transitions – suitability of RAY-3001

RAY-3001 did not include people who had ibrutinib 1L; only few who had ASCT

Transition probability	Ibrutinib regimen	ASCT regimen	Source
PF 2L to death	Per cycle probability of death: [redacted]		RAY-3001: Pre-progression mortality
PF 2L to PD	Log-logistic curve fit to ibrutinib TTP + HR of 1.103	Log-logistic curve fit to ibrutinib TTP + HR of 1.012	RAY-3001: Time-to-progression (TTP); weighted HR from MANTLE-FIRST + subsequent treatments

Company:

- Most patients in TRIANGLE remained alive and failure-free, so had to use other sources in model
- At 2nd line, usual treatment in the NHS is mainly either zanubrutinib (most patients) or ibrutinib
- RAY-3001 trial is most suitable as it reports efficacy of ibrutinib at 2nd line (company assumes equal efficacy of ibrutinib with zanubrutinib, so RAY-3001 outcomes can be generalised to NHS)

EAG:

- Use of RAY-3001 data in both arms of the model assumes efficacy of 2nd line ibrutinib/zanubrutinib is not affected by 1st line ibrutinib → clinical advice suggests lower efficacy in retreated patients – so 2nd line efficacy for ibrutinib is overestimated
- Use of RAY-3001 for ASCT does not capture long-term expected benefit of ASCT – as only minority ([redacted]) in RAY-3001 had ASCT as a 1st line treatment – so any long-term benefits underestimated

NICE

- Is RAY-3001 a suitable source to inform 2nd line transition probabilities?
- Would 2nd line ibrutinib/zanubrutinib efficacy be different due to first-line exposure?
- Do the 2nd line transitions adequately capture the effects of 1st line treatment?

Large ICER impact

Key issue: Subsequent treatments (1/2)

EAG questions whether patients would have zanubrutinib after ibrutinib

Company:
- Second-line treatment distribution was informed by clinical advice gathered from 5 clinicians
- Distributions submitted independently and averaged – experts agreed this average was plausible
- Experts noted that early-progressors were less likely to have zanubrutinib after ibrutinib

EAG: Clinical advice questions whether zanubrutinib would be used after ibrutinib
- Provide a scenario analysis that uses an alternative subsequent treatment distribution for ibrutinib
- Largely agree with ASCT 2nd line distribution

	Subsequent treatment	First-line treatment			
		Company		EAG scenario	
		Ibrutinib	ASCT	Ibrutinib	ASCT
Second-line treatment	Ibrutinib	-	10%	-	10%
	Zanubrutinib	58%	85%	-	85%
	R-BAC	31%	2%	59.5%	2%
	BR	10%	2%	39.5%	2%
	BSC	1%	1%	1.1%	1%
Third-line treatment	R-BAC	42%	67%	-	50%
	BR	33%	16%	-	25%
	BSC	25%	16%	100%	25%

Subsequent treatment distributions also affect the weighted HRs applied to 2nd line PFS in the model (see next slide)

ASCT, autologous stem cell transplant; BR, bendamustine and rituximab; BSC, best supportive care; HR: hazard ratio; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; R-BAC, rituximab, bendamustine and cytarabine.

Would zanubrutinib 2nd line be used after ibrutinib? What determines this? (e.g. incomplete 1st line; relapsed vs. refractory; early/late progression)?

Key issue: Subsequent treatments (2/2) – efficacy adjustment

Medium ICER impact

Model adjusts 2nd line PFS by subsequent treatment distribution

Company:

- Progression-free to progressed transition (2nd line) is affected by 2nd line treatments received
- Company model adjusts progression risk using HR of 1.26 (for BR, R-BAC, BSC vs BTKi) derived from MANTLE-FIRST (cohort study of ibrutinib and R-chemos), weighted by subsequent treatment

1st line treatment	2nd line treatment					
	Ibrutinib	Zanubrutinib	R-BAC	BR	BSC	Weighted average HR
Ibrutinib	-	57.6%	31.3%	10.0%	1.1%	1.103
ASCT	10.0%	84.8%	2.4%	2.0%	0.8%	1.012
HR vs. 2nd line ibrutinib	-	1.00	1.26	1.26	1.26	-

Patients in ibrutinib arm progress faster on 2nd line treatment as higher proportion on chemotherapy

EAG:

- Company applies a single HR for BR, R-BAC **and** BSC – unlikely to be valid
- MANTLE-FIRST shows benefit of ibrutinib is more pronounced amongst early progressors on 1st line treatment (<24 months) vs. late progressors – but this is not captured by the company's model
- Include scenario analyses with HR as per the MANTLE-FIRST publication – HR of 1.00 for ibrutinib vs. R-BAC and with HR of 0.56 for ibrutinib vs. BR/BSC

- Which HRs are appropriate to adjust 2nd line PFS in the model?
- MANTLE-FIRST also showed a benefit for ibrutinib vs. R-BAC in OS – should this be modelled in the 2L to death transition probability?

NICE

ASCT, autologous stem cell transplant; BR, bendamustine and rituximab; BSC, best supportive care; BTKi, Bruton's Tyrosine Kinase inhibitor; HR: hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; R-BAC, rituximab, bendamustine and cytarabine.

ASCT costs

Company and EAG disagree on ASCT cost

Large ICER impact

Company:

- ASCT cost split into 3 →

Apheresis	HDT	Transplant
£6,387*	£2,150	£42,041

- ASCT cost taken from NG52 (based on tariff) + inflated
- Note NG52 comments about NHS reference costs →
- Both TA895 + TA1048 used the same approach

EAG:

- Note limited information on which components are included in NG52 cost – potential for double-counting
- Also note that it is 10 years old
- Prefer using NHS reference cost for transplant, accept company's separate costs for apheresis + HDT

NICE:

- Further source: NHS payment scheme 25/26 (tariff):
  - ↳ SA26A, Peripheral Blood ASCT, 19 years+: **£35,119**
  - ↳ SA34Z, Peripheral Blood Stem Cell Harvest: **£2,304**

NICE guideline NG52 on NHL, 2016

"The cost of autologous transplantation was estimated to be **£34,000**… an alternative NHS Reference cost of **£16,359** was available but thought to be a considerable underestimate"

NHS cost collection 24/25 (ref. cost)

£21,247 – Peripheral Blood ASCT, 19 years and over (SA26A; average of elective and non-elective inpatient and night/day admissions)

Committee conclusions in TA895

"There was some uncertainty about the true cost of ASCT in the NHS, but the company's estimate [based on NG52] was more appropriate."

- Which ASCT costs are appropriate to use in the model?
- Is stem cell apheresis usually done as a day case or as inpatient?

*Weighted average inpatient: SA34Z NHS cost collection

ASCT, autologous stem cell transplant; HDT, high-dose therapy; ICER, incremental cost-effectiveness ratio.

Other cost issues: Relative dose intensity and wastage

RDI: Medium
Wastage: Small impact

EAG set RDI to 100% for all treatments and include ibrutinib wastage

Company:

RDI

- Ibrutinib RDI in TRIANGLE was 95.2% – applied in the model for 1st line ibrutinib use
- RDI was not collected for other treatments in TRIANGLE – so assume 100% RDI for drug components of ASCT and subsequent treatments

Wastage

- Model includes vial wastage for IV treatments; after clarification, company present scenario that captures pack wastage for ibrutinib

EAG:

RDI

- EAG base case applies 100% RDI to all drug treatments (including ibrutinib)

Wastage

- EAG base case includes ibrutinib pack wastage

Committee lead team: agree with EAG's approach to RDI and wastage

NICE ASCT, autologous stem cell transplant; IV, intravenous; RDI, relative dose intensity.

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Uncertainty as to the method of adjustment for rituximab maintenance	Small
Cost-effectiveness issues	
Model structure: the modelling of ASCT	Unknown
Treatment effectiveness and extrapolation: pre-failure mortality	Large
Treatment effectiveness and extrapolation: 2nd line treatment effectiveness	Medium
Resource use and costs: the cost of ASCT	Large
Resource use and costs: subsequent treatment for ibrutinib patients	Large

ASCT, autologous stem cell transplant; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio

Summary of company and EAG base case differences

Assumption	Company base case	EAG base case
ASCT cost	**£42,041** • NICE guideline NG52 cost inflated to 2024 prices	**£21,247** • NHS cost collection 24/25; SA26A, average of elective and non-elective inpatient and night/day admissions
Pre-failure mortality	• Ibrutinib: [redacted] per cycle • ASCT: [redacted] per cycle	Both arms assumed equal risk to ibrutinib for entire time horizon
Relative dose intensity	• Ibrutinib: 95.2% (TRIANGLE) • All other treatments: 100%	All treatments: 100%
Wastage	Vial wastage included, pack wastage for ibrutinib not included	Vial wastage included, pack wastage for ibrutinib included

NICE ASCT, autologous stem cell transplant.

Results – cost-effectiveness ranges

Confidential discounts in place for other treatments in the pathway – ICERs in Part 2
ICER ranges presented below

Ibrutinib versus ASCT

Company base case probabilistic ICER:

- <£25,000 per QALY gained

EAG base case probabilistic ICER:

- >£35,000 per QALY gained

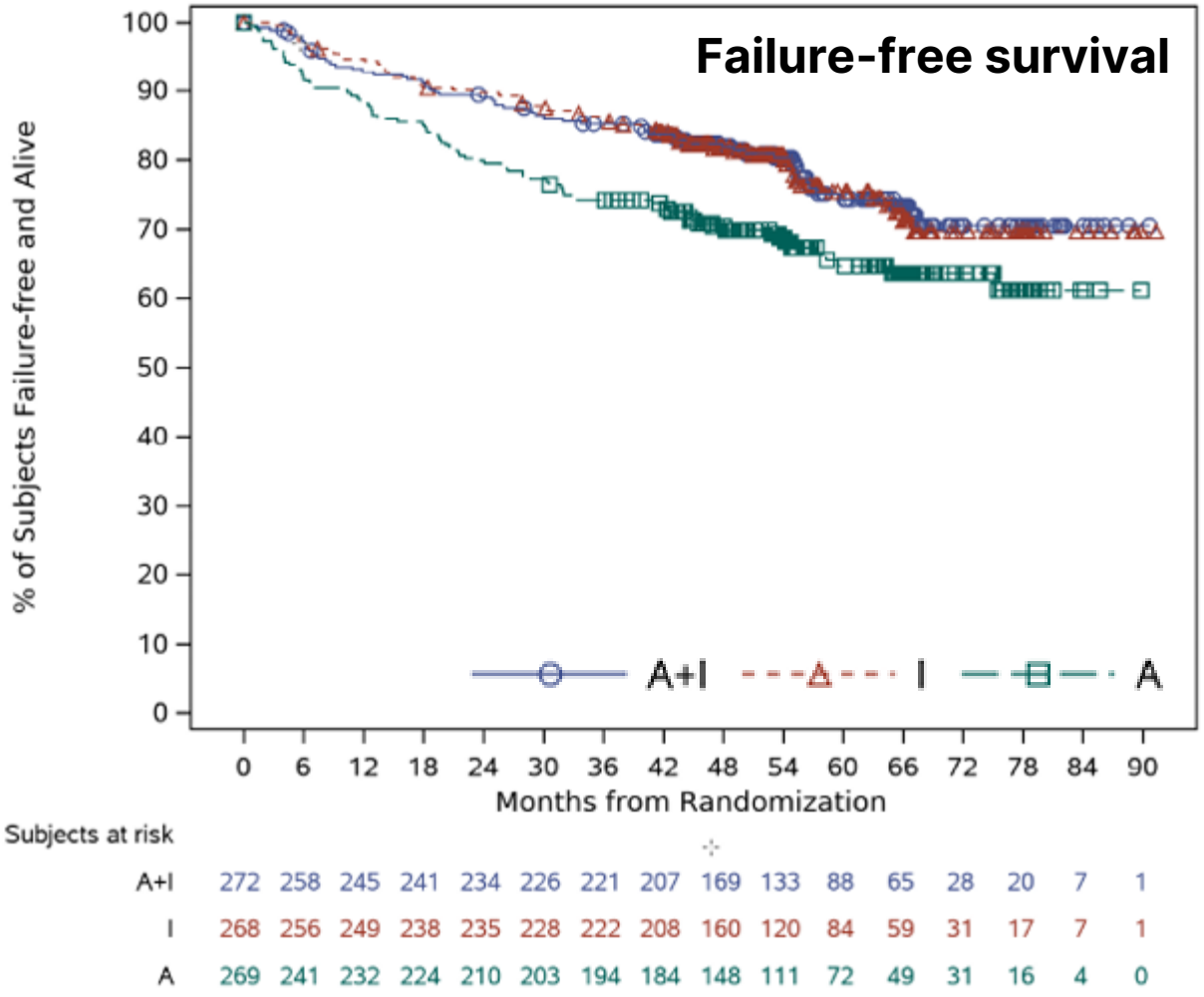
ASCT, autologous stem cell transplant; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

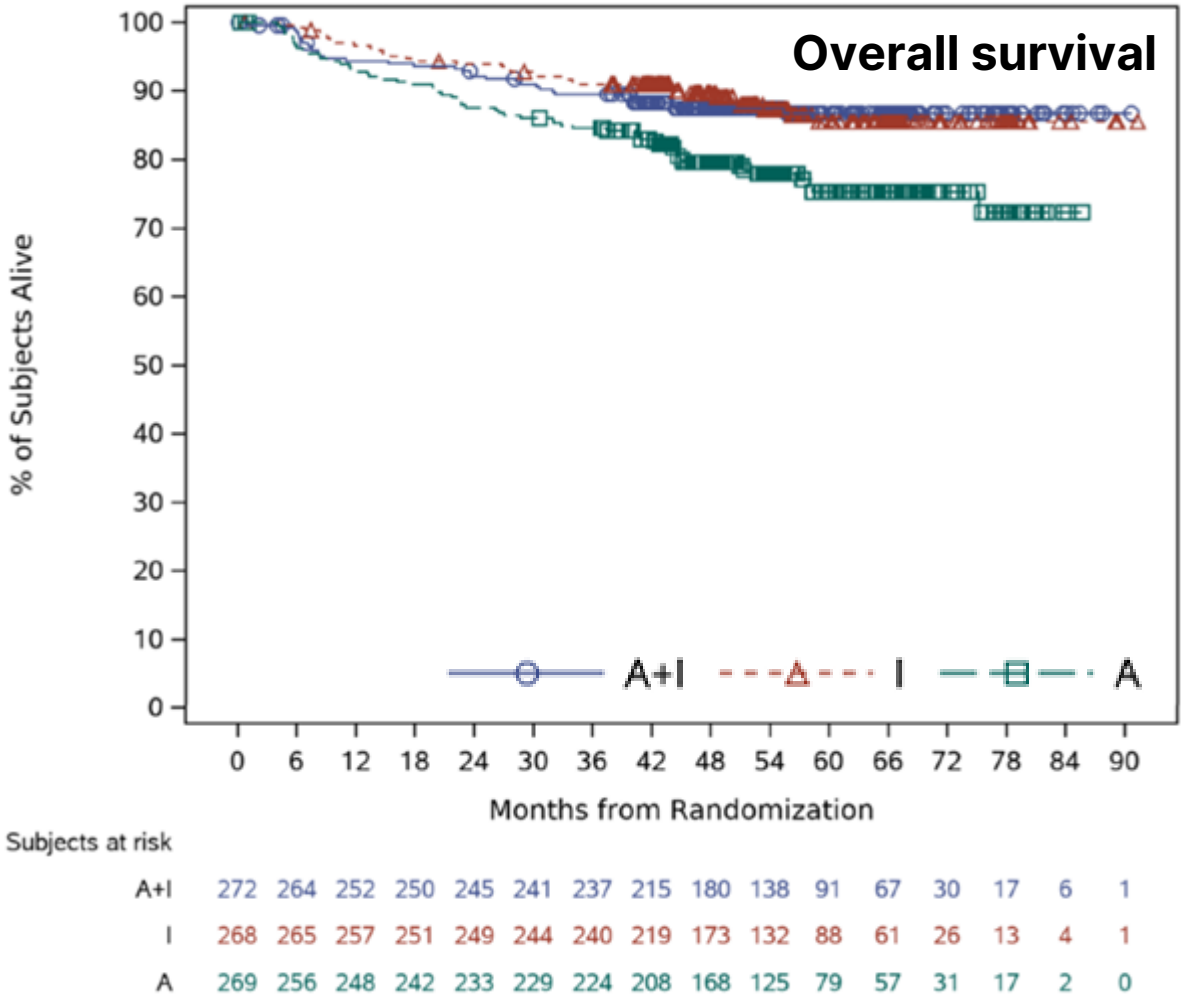
Ibrutinib with R-CHOP for untreated mantle cell lymphoma when an autologous stem cell transplant is suitable

Supplementary appendix

NICE National Institute for Health and Care Excellence

TRIANGLE – outcomes in A+I arm





EMA conclusions: The results from TRIANGLE did not demonstrate any additional benefits of combining ibrutinib with ASCT and provided no clear indications of such benefits in any specific subgroup.

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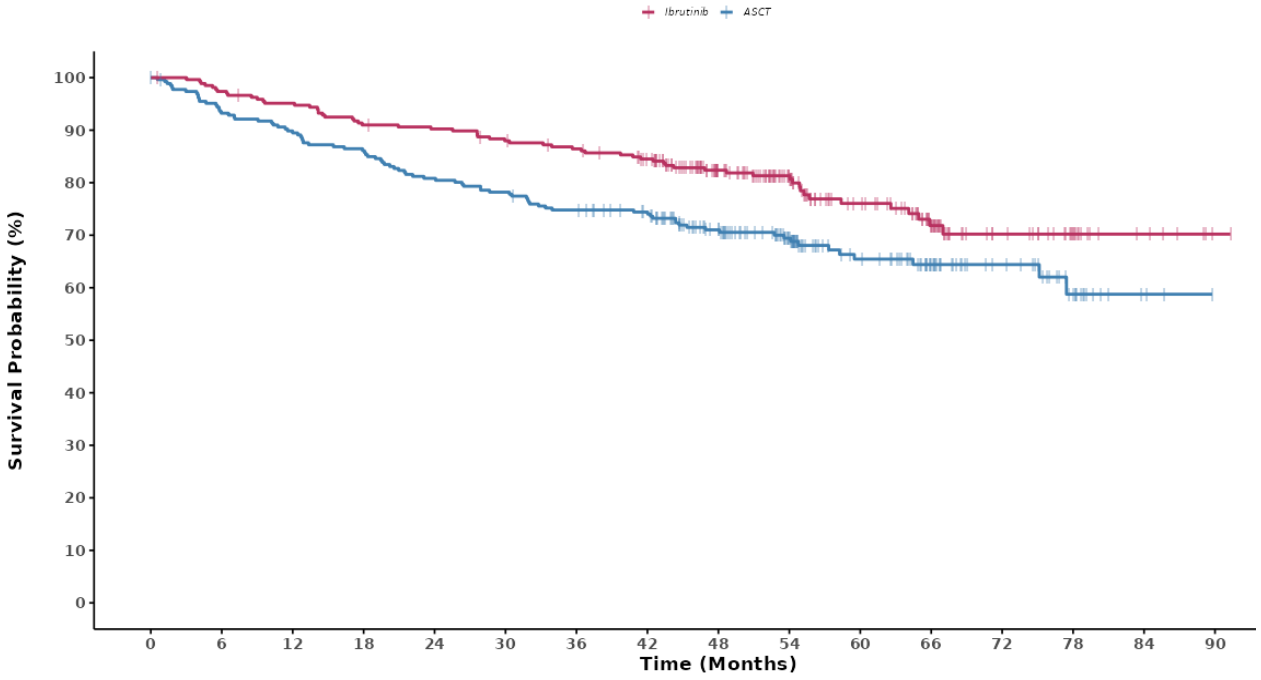
ASCT, autologous stem cell transplant;
EMA: European Medicines Agency.

TRIANGLE – progression-free and overall survival

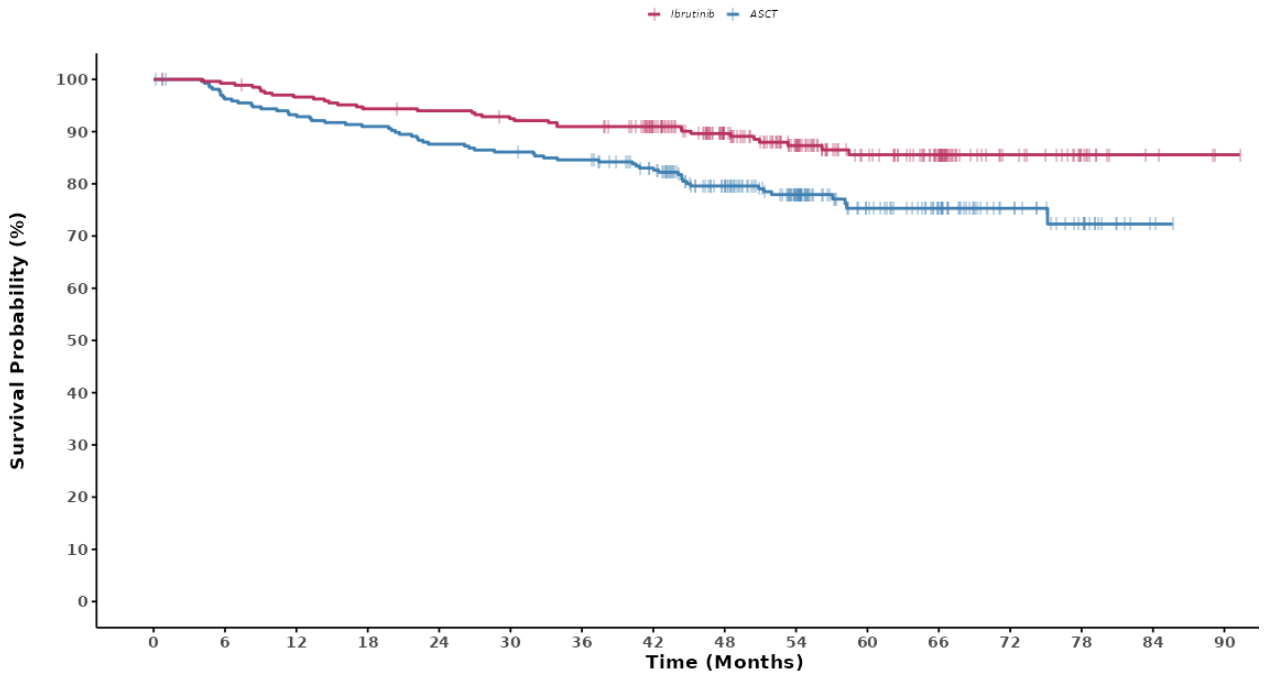
Progression-free survival



Number at risk

ASCT	269	248	238	229	215	208	198	188	151	114	74	51	32	16	4	0
Ibrutinib	268	260	253	242	239	232	226	212	163	122	86	59	31	17	7	1

Overall survival



Number at risk

ASCT	269	256	248	242	233	229	224	208	168	125	79	57	31	17	2	0
Ibrutinib	268	265	257	251	249	244	240	219	173	132	88	61	26	13	4	1

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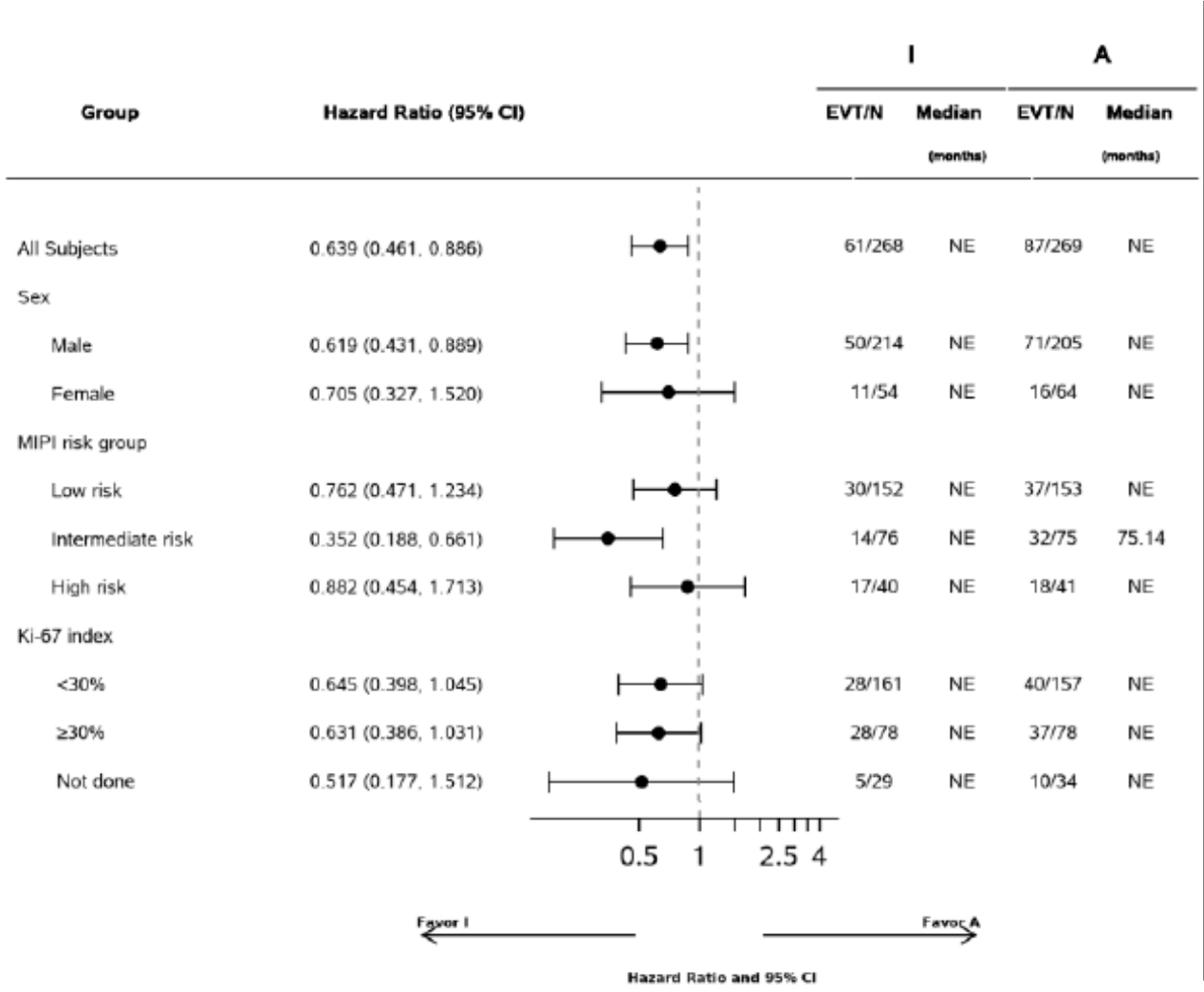
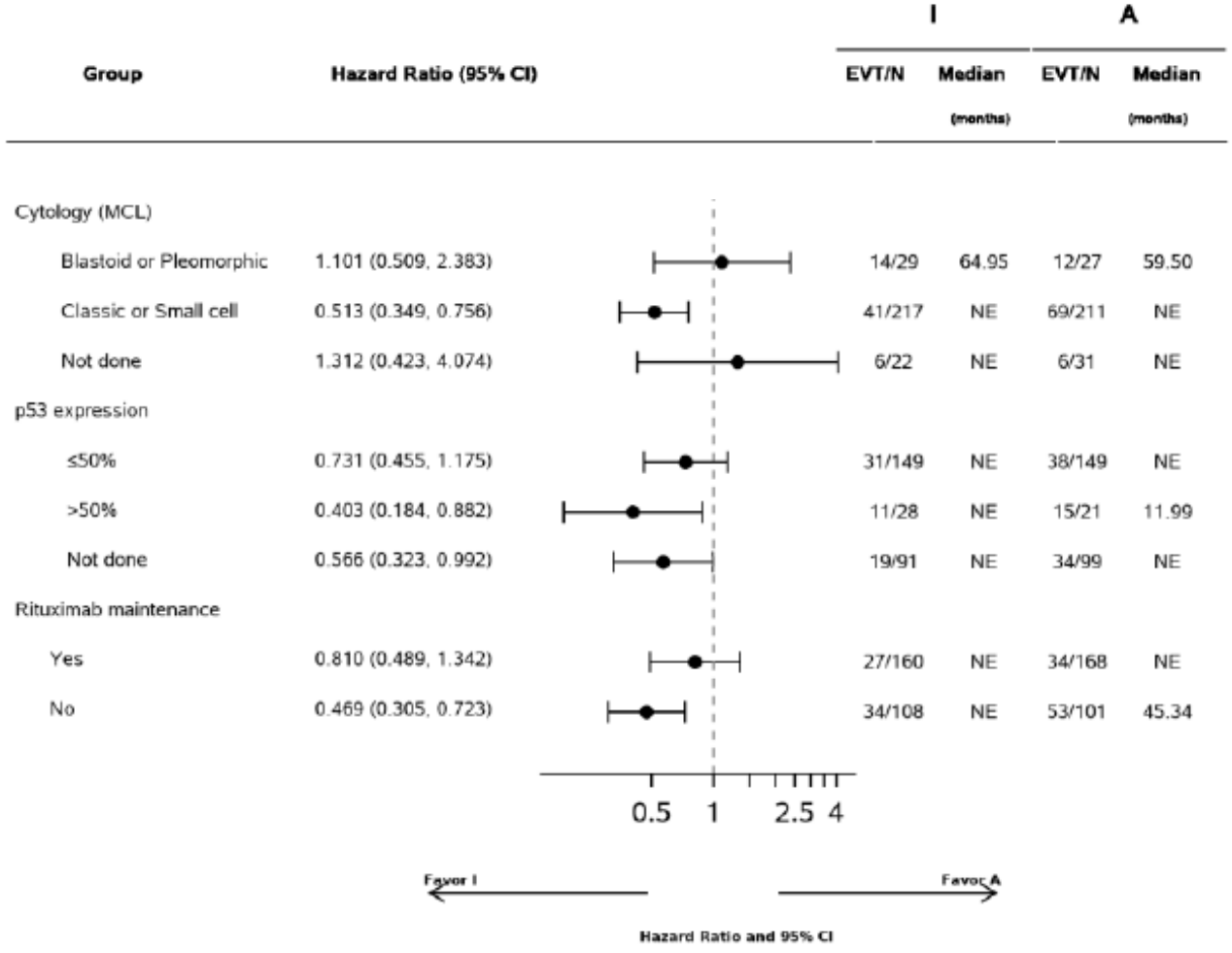
NICE ASCT, autologous stem cell transplant.

TRIANGLE – failure-free survival subgroup analysis





Company: rituximab maintenance subgroup results should be interpreted with caution given the "yes" subgroup represents an enriched population of patients that successfully completed induction with ibrutinib or consolidation with ASCT

Back to main deck

NICE

ASCT, autologous stem cell transplant; CI, confidence interval; EVT, events; MCL, mantle cell lymphoma; NE, not estimable.

IPCW and TSE adjustment methods – TSD16

Inverse Probability of Censoring Weighting (IPCW)

- Patients are artificially censored at the time of switch, and remaining observations are weighted based upon covariate values and a model of the probability of being censored.
- This allows patients who have **not** been artificially censored to be weighted to reflect similarities to patients who **have** been censored to remove the selection bias caused by censoring – patients who do not switch and have similar characteristics to patients who did receive **higher weights**.
- The following **covariates** were included in the IPCW: cytology, Ki-67, P-53, bone marrow involvement, B-symptoms, lactate dehydrogenase, white blood count, Eastern Cooperative Oncology Group Performance Status, Serum Beta-2-microglobin, complete responder (yes/no), treatment failure (yes/no)

Two-Stage Estimation (TSE) Method

- Two-stage methods first estimate a treatment effect specific to switching patients and the survival times of these patients are adjusted, subsequently allowing the treatment effect specific to experimental group patients to be estimated.
- The same set of covariates used in the IPCW analysis were used

See EAG report section 3.2.5 for more information

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IPCW, Inverse Probability of Censoring Weighting; TSE, Two-Stage Estimation.

TRIANGLE – rituximab maintenance adjustment results

Endpoint	Method	R-maintenance	HR (95% CI), p-value
FFS	Unadjusted	Arm I: 59.7% Arm A: 62.5%	[redacted]
	IPCW	100%	[redacted]
	IPCW	85%	[redacted]
	TSE Exponential		[redacted]
	TSE Weibull		[redacted]
	TSE Gamma		[redacted]
	TSE Log-logistic		[redacted]
	TSE Log-normal		[redacted]
OS	Unadjusted	Arm I: 59.7% Arm A: 62.5%	[redacted]
	IPCW	100%	[redacted]
	IPCW	85%	[redacted]
	TSE Exponential		[redacted]
	TSE Weibull		[redacted]
	TSE Gamma		[redacted]
	TSE Log-logistic		[redacted]
	TSE Log-normal		[redacted]

*98.33% CI

CI, confidence interval; FFS, failure-free survival; HR, hazard ratio; IPCW, Inverse Probability of Censoring Weighting; OS, overall survival; TSE, Two-Stage Estimation.

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TRIANGLE – pre-failure mortality

Treatment	Ibrutinib	ASCT
Pre-failure mortality events	11/268	22/269
Total number of FFS person-years	[redacted]	[redacted]
Pre-failure annual mortality rate	[redacted]	[redacted]
Per cycle (21-day) probability	[redacted]	[redacted]

Back to model structure
Back to pre-failure mortality

ASCT, autologous stem cell transplant; FFS, failure-free survival.

TRIANGLE – time-to-failure (1/2)

[redacted]

[redacted]

	Ibrutinib regimen				ASCT regimen			
Distribution	AIC	AIC rank	BIC	BIC rank	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	1	[redacted]	1	[redacted]	7	[redacted]	6
Weibull	[redacted]	3	[redacted]	3	[redacted]	5	[redacted]	4
Gompertz	[redacted]	2	[redacted]	2	[redacted]	2	[redacted]	2
Log-logistic	[redacted]	6	[redacted]	6	[redacted]	4	[redacted]	3
Log-normal	[redacted]	5	[redacted]	5	[redacted]	1	[redacted]	1
Gamma	[redacted]	4	[redacted]	4	[redacted]	6	[redacted]	5
Generalised Gamma	[redacted]	7	[redacted]	7	[redacted]	3	[redacted]	7

Back to model structure
Back to TTF extrapolation

AIC, Akaike Information Criteria; ASCT, autologous stem cell transplant; BIC, Bayesian Information Criterion

TRIANGLE – time-to-failure (2/2)

Reconstructed FFS landmarks

(includes pre-failure mortality risk – company base case assumptions)

	Ibrutinib regimen			ASCT regimen		
Distribution	**10 year (%)**	**15 year (%)**	**20 year (%)**	**10 year (%)**	**15 year (%)**	**20 year (%)**
Clinical expert estimates (mean)						
Upper plausible limit	64.0	50.6	37.0	52.8	41.8	31.4
Most likely	**57.0**	**42.0**	**28.0**	**44.6**	**33.6**	**22.0**
Lower plausible limit	47.6	32.0	15.0	36.0	27.2	12.6
Extrapolations						
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company base case

Back to main deck

NICE ASCT, autologous stem cell transplant; FFS, failure-free survival.

Survival landmarks under different assumptions

ASCT

	FFS			OS		
	10-year	15-year	20-year	10-year	15-year	20-year
Clinical experts - most likely (mean)	44.6	33.6	22.0	56.0	44.4	30.4
Clinical experts - upper bound of plausibility (mean)	52.8	41.8	31.4	67.5	56.5	41.8
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case with TTF log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case + 6m increased mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case + 12m increased mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case with TTF log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case with TTF log-normal + 6m increased mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case with TTF log-normal + 12m increased mortality	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Ibrutinib

	FFS			OS		
	10-year	15-year	20-year	10-year	15-year	20-year
Clinical experts - most likely (mean)	57.0	42.0	28.0	67.0	53.0	37.0
Clinical experts - upper bound of plausibility (mean)	64.0	50.6	37.0	73.8	61.6	44.6
Company + EAG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Bold values = greater than upper bound of plausibility

Back to main deck

NICE

ASCT, autologous stem cell transplant; FFS, failure-free survival; OS, overall survival; TTF, time-to-failure.

RAY-3001 – pre-progression mortality

Treatment	Ibrutinib arm of RAY-3001 (1 prior line subgroup)
Total number of PFS person-years	[redacted]
Number of deaths in PFS	[redacted]
Annual mortality rate	[redacted]
Per-cycle (21-day) probability	[redacted]

Back to model structure
Back to 2nd line transitions

NICE ASCT, autologous stem cell transplant; PFS, progression-free survival.

RAY-3001 – time-to-progression

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	1	[redacted]	1
Weibull	[redacted]	3	[redacted]	3
Gompertz	[redacted]	4	[redacted]	4
Log-logistic	[redacted]	7	[redacted]	6
Log-normal	[redacted]	5	[redacted]	5
Gamma	[redacted]	2	[redacted]	2
Generalised Gamma	[redacted]	6	[redacted]	7

Reconstructed OS landmarks

(company base case assumptions)

	Ibrutinib regimen			ASCT regimen		
Distribution	10 year (%)	15 year (%)	20 year (%)	10 year (%)	15 year (%)	20 year (%)
Clinical expert estimates						
Clinical expert estimates (OS)	67.0	53.0	37.0	56.0	44.4	30.4
Extrapolations						
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company base case

Back to model structure
Back to 2nd line transitions

AIC, Akaike Information Criteria; ASCT, autologous stem cell transplant; BIC, Bayesian Information Criterion; OS, overall survival.

RAY-3001 – post-progression survival

Distribution	5-year (%)	10-year (%)	15-year (%)	20-year (%)
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	[redacted]	[redacted]	[redacted]	[redacted]

Company base case

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	2	[redacted]	1
Weibull	[redacted]	3	[redacted]	3
Gompertz	[redacted]	1	[redacted]	2
Log-logistic	[redacted]	5	[redacted]	5
Log-normal	[redacted]	6	[redacted]	6
Gamma	[redacted]	4	[redacted]	4
Generalised Gamma	[redacted]	7	[redacted]	7

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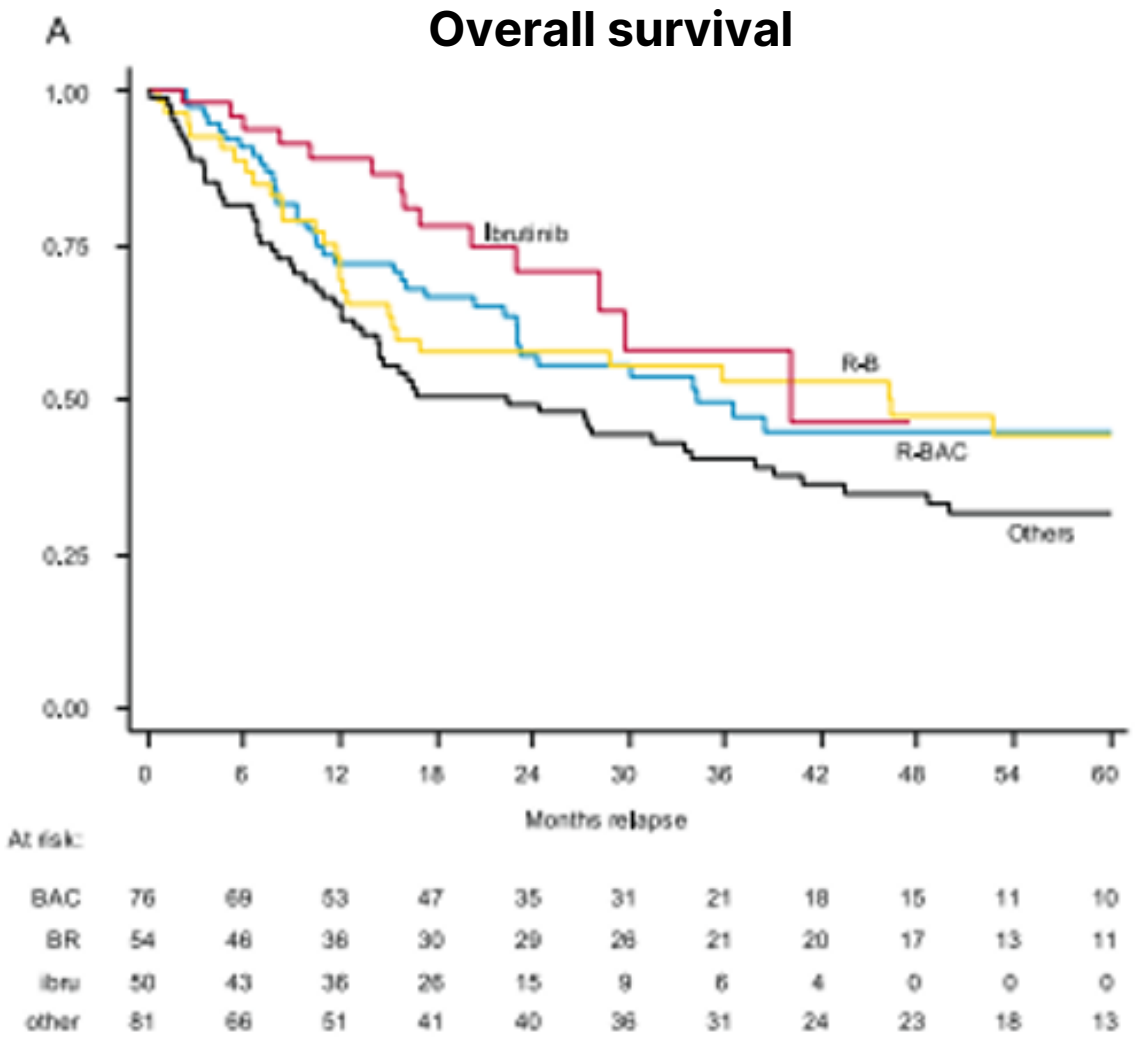
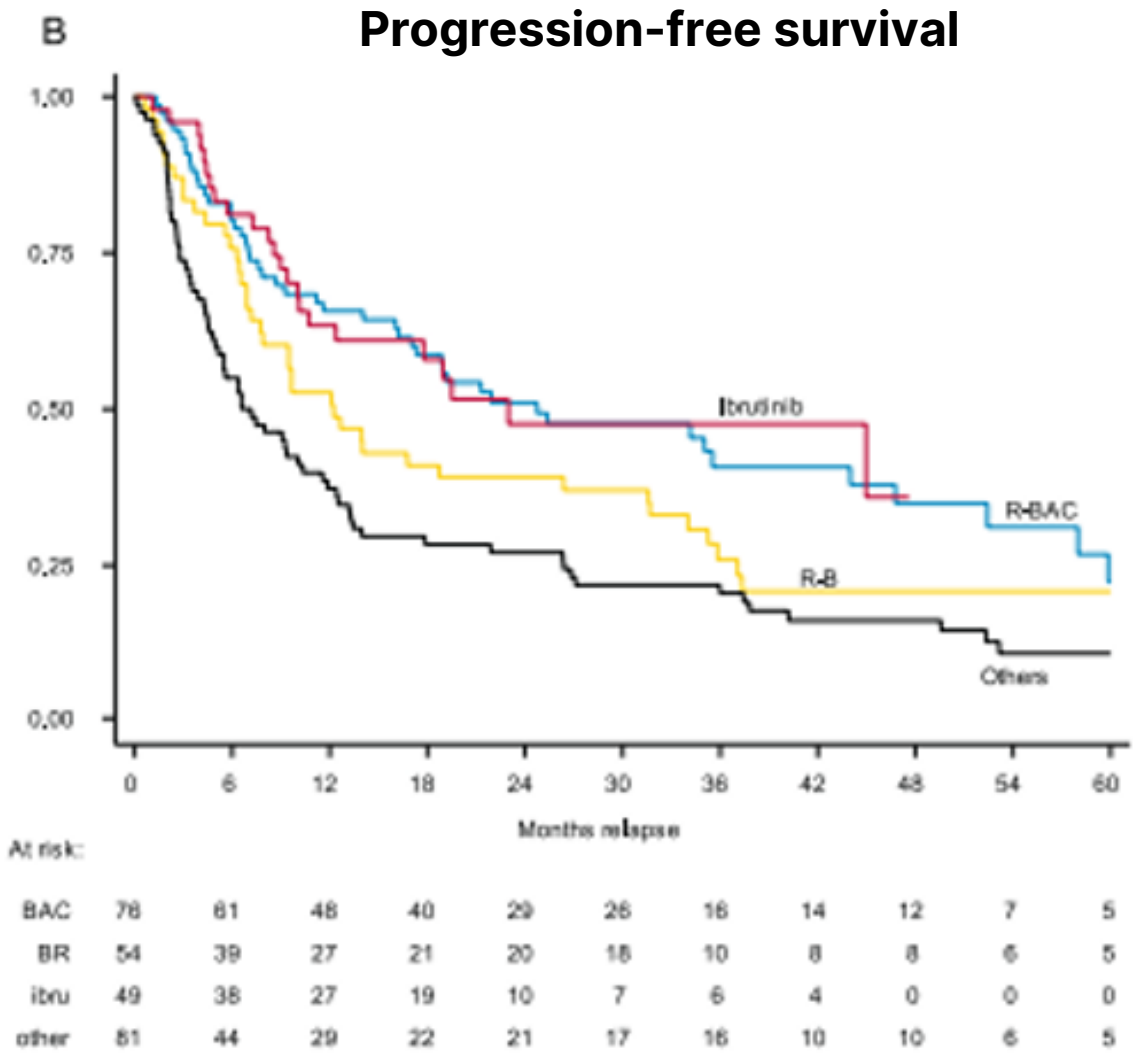
AIC, Akaike Information Criteria; BIC, Bayesian Information Criterion.

MANTLE-FIRST – overall population results

Figures from: Visco C, Di Rocco A, Evangelista A, et al. (2021) Leukemia 35(3):787-795. doi: 10.1038/s41375-020-01013-3.





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NICE R-B; bendamustine and rituximab; R-BAC, rituximab, bendamustine and cytarabine.

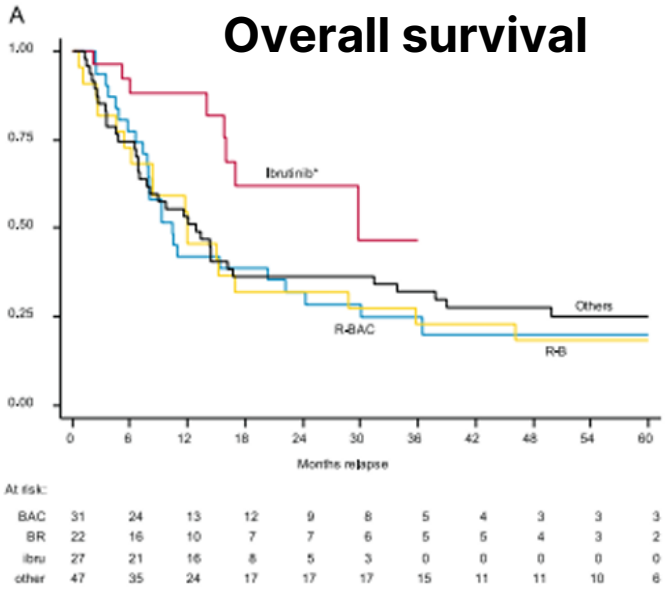
MANTLE-FIRST – early vs. late progressors

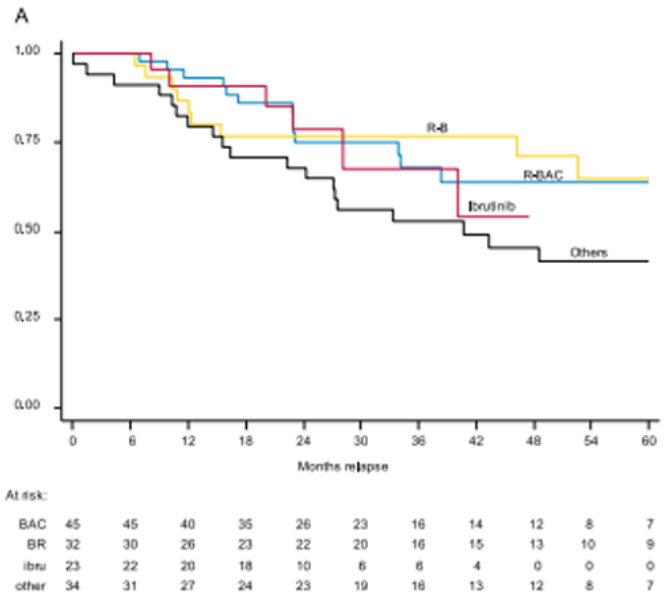
Figures from: Visco C, Di Rocco A, Evangelista A, et al. (2021) Leukemia 35(3):787-795. doi: 10.1038/s41375-020-01013-3.

Early progressors

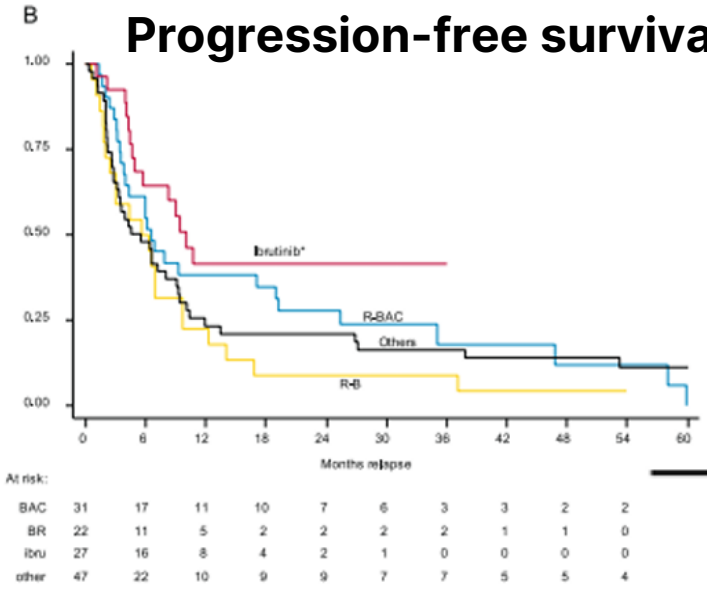
Late progressors

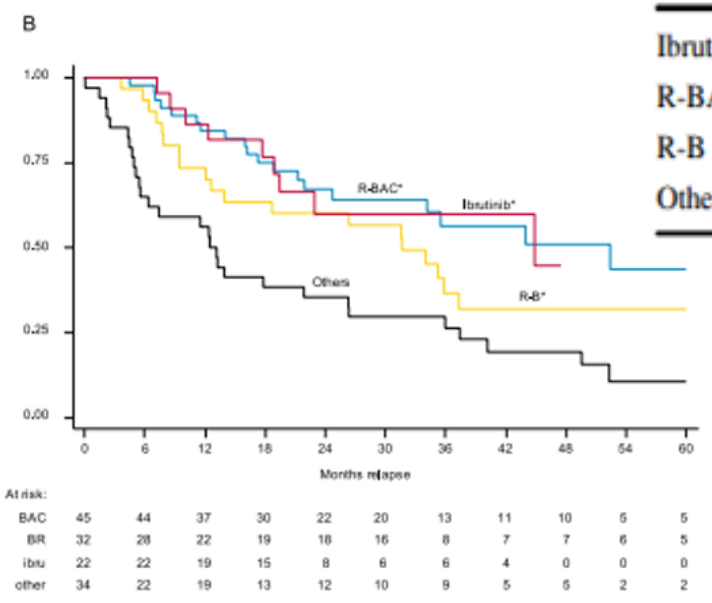
Overall survival





Progression-free survival





Overall survival analysis by early vs. late

	Late-POD		Early-POD	
	HR	95% CI	HR	95% CI
Ibrutinib (reference)	1.00	–	1.00	–
R-BAC	1.01	0.38–2.65	2.78	1.25–6.19
R-B	0.85	0.31–2.37	2.41	1.04–5.56
Others	2.01	0.81–4.99	2.17	1.00–4.70

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CI, confidence interval; HR, hazard ratio; POD, progression of disease; R-B; bendamustine and rituximab; R-BAC, rituximab, bendamustine and cytarabine.

NICE

Unknown ICER impact

Key issue: Utility values

HRQoL data were not collected in TRIANGLE; alternative sources used

Company:

- TRIANGLE didn't collect HRQoL + didn't find studies reporting HRQoL for transplant-eligible patients
- Instead use SHINE for FF 1L – transplant-ineligible patients and have access to IPD
- PF 2L and PD use values accepted in previous TAs
- One-off QALY loss applied to account for AEs – calculated using AE frequencies from TRIANGLE

EAG:

- Clinical advice → note that toxic effects of ASCT can be serious and fatal, but short-term; whereas extended treatment duration with ibrutinib means that there will be long-term negative HRQoL impact
- Think company approach is reasonable and do not use different approach in EAG base case

Clinical experts: expect that ibrutinib will improve quality of life due to avoiding ASCT toxicity

State	Utility value: mean (SE)	Source
FF 1L	[redacted]	• MMRM fit to SHINE EQ-5D (5L cross-walked to 3L) data to account for population differences with TRIANGLE • Treatment independent
PF 2L	0.780 (0.010)	• Aligned with TA502 + TA1081 • Originally from pooled EQ-5D-5L from patients in the ibrutinib arms of RAY-3001 and SPARK • Treatment independent
PD	0.680 (0.024)	

	Ibrutinib	ASCT
One-off QALY loss due to AEs*	−0.0138	−0.0181

*Did not include AEs associated with subsequent treatments.

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AE, adverse event; ASCT, autologous stem cell transplant; EQ-5D, Euroqol 5-dimensions; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; PF, progression-free; PD, progressed disease; QALY, quality-adjusted life year.