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NICE National Institute for Health and Care Excellence

Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab (CDF review of TA472)

Lead team presentation

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Company: Roche

25th February 2020

Key clinical issues

- Is treatment with obinutuzumab plus bendamustine appropriate for people who have already received obinutuzumab and/or bendamustine and are potentially eligible for stem cell transplant?
- Does the updated data from GADOLIN confirm an overall survival benefit, and what does the ‘real-world’ systemic anti-cancer therapy (SACT) data add?

[redacted]

Obinutuzumab (Gazyvaro, Roche)

Marketing authorisation **June 2016**	Obinutuzumab with bendamustine followed by obinutuzumab maintenance is indicated for patients with follicular lymphoma who did not respond to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen
Mechanism of action	Type 2 glycoengineered antibody that binds to the CD20 protein present on B cells, and causes cell death.
Administration and dose	**Induction in combination with bendamustine:** • Cycle 1: 1,000 mg administered intravenously on day 1, 8 and 15 of 1st 28 day cycle • Cycles 2–6: 1,000 mg administered intravenously on day 1 of each 28 day cycle **Maintenance** • 1,000 mg, intravenously every 2 months for 2 years or until disease progression
List price	**Obinutuzumab:** £9,936 cycle 1, £3,312 per cycle thereafter, £3,312 per maintenance dose **Bendamustine** per cycle: £68.46. Total price for induction treatment (cycles1-6): £410.76 A confidential price discount has been agreed

[redacted]

Follicular Lymphoma

- Non-Hodgkin's lymphoma (NHL) is a type of cancer that develops in the lymphatic system. Includes several different conditions, which are classified based on their grade, or type.
- Follicular lymphoma (FL) is one of the most common types of low-grade or indolent (slow growing) NHL
- It is an incurable disease that develops when the body makes abnormal B lymphocytes that collect in lymph nodes or other body organs as follicles (clumps)
- About 1900 people are diagnosed with FL annually in the UK
- Most people have advanced FL at diagnosis

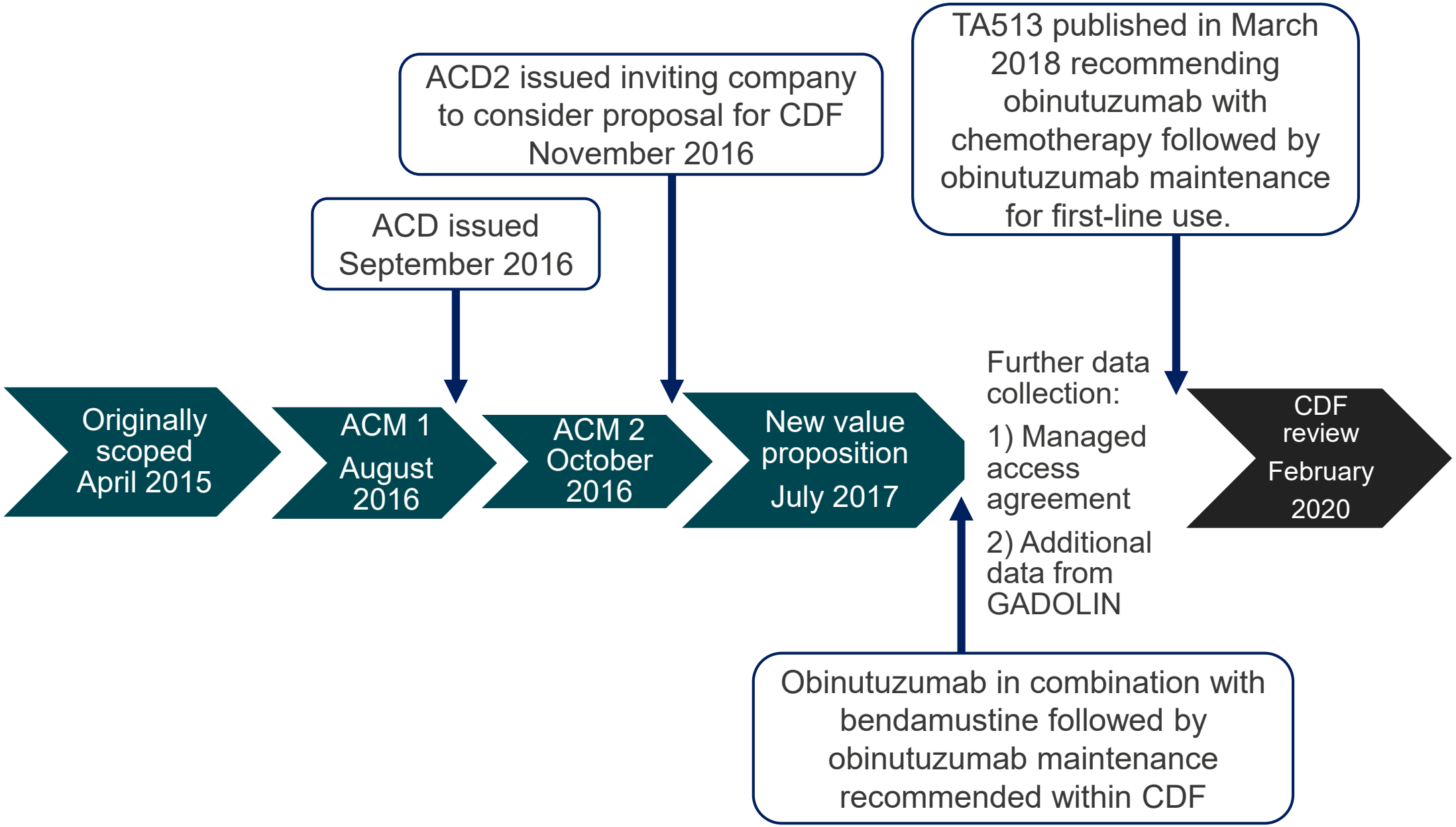
Patient perspective

- Follicular lymphoma can have a significant impact on the quality of life of patients and their carers. The uncertainty of relapse and the need for repeated courses of treatment are physically and psychologically challenging.
- People live with the condition for many years and symptoms include enlarged lymph nodes, weight loss, fevers, night sweats, constant itching or fatigue. Concentration and memory are also affected which impacts working life and social life.
- Main concerns about current treatments are the lack of a durable response and the need for repeated courses of treatment. Patients worry that there will not be effective treatment available if or when they experience relapse.
- There is a unmet need for effective treatments that keep the disease in remission for as long as possible, with fewer side effects and late effects.
- Limited treatment options for people who have experienced relapse, and particularly for those who have not responded to rituximab. Treatments that prolong time in remission are seen as particularly important in an ‘incurable’ condition
- Side effects are manageable. Maintenance treatment does increase the risk of infections and neutropenia but can be minimised by timely treatment.

Current management

- First-line induction treatment is rituximab with chemotherapy (R-chemotherapy) followed by rituximab maintenance therapy.
- NICE guideline 52 on NHL recommends rituximab monotherapy as an option for stage III or IV disease which is still asymptomatic.
- TA 513 recommends obinutuzumab with chemotherapy followed by obinutuzumab maintenance for first-line use when follicular lymphoma international prognostic index (FLIPI) score is 2 or more
- Second-line treatment depends on timing of relapse and is often characterised by multiple lines of treatment as the disease responds and relapses.
- Treatment options for rituximab-refractory FL include single- or multi-agent chemotherapy (including cyclophosphamide, fludarabine, bendamustine or chlorambucil) and best supportive care.

Summary of original appraisal TA472



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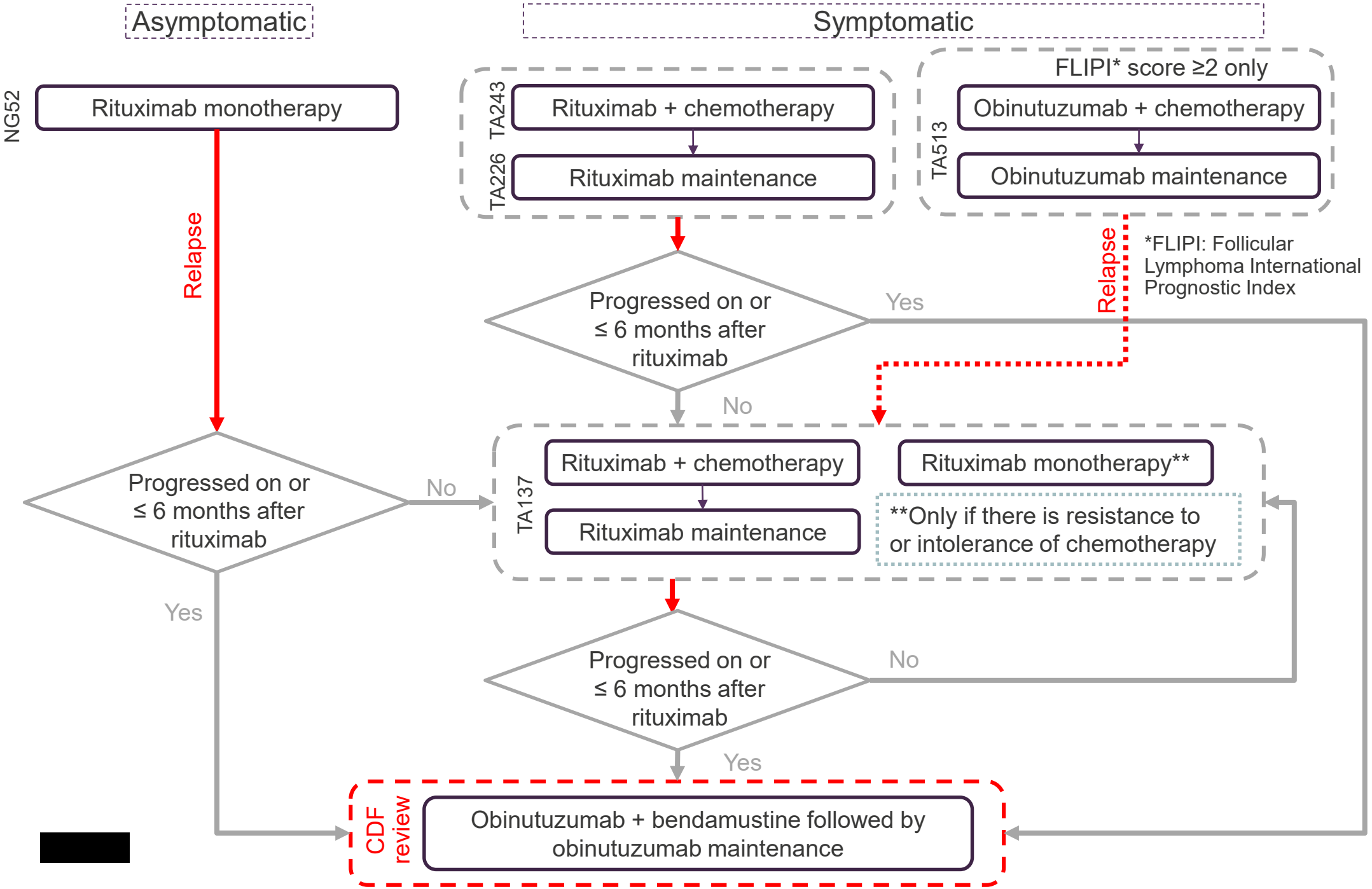
Treatment pathway – Advanced follicular lymphoma (stage III/IV)



Clinical expert comments on population:

- Trial evidence shows a survival benefit with obinutuzumab plus bendamustine for people treated with R-chemotherapy first line
  - Treatment effect is unknown in those previously treated with frontline obinutuzumab and/or bendamustine as this population was not included in GADOLIN
- However, if very good responses were obtained with these agents first line and a much shorter response was obtained after R-chemotherapy second line, it would be inappropriate to deny these patients potentially life prolonging treatment with obinutuzumab plus bendamustine at this stage.
- Treatment effect of obinutuzumab with bendamustine also unclear for patients proceeding to Autologous Stem Cell Transplant (ASCT).
  - Use of obinutuzumab with bendamustine should not be restricted for this patient group as the better minimal residual rates seen may be relevant as ASCT is usually associated with improved outcomes in patients with better remissions prior to transplant.

[redacted]

Primary clinical evidence: GADOLIN

Design	Phase III, open-label, randomised, multicentre
Location	International: 82 sites in 14 countries; 5 sites in UK
Population	Adults with indolent NHL (n=413), 81.1% with FL (n=335) People with FL that relapsed following induction treatment with rituximab monotherapy or R-chemotherapy, or relapsed during or within 6 months of maintenance with rituximab monotherapy
Intervention	Obinutuzumab with bendamustine, followed by obinutuzumab maintenance (n=204)
Comparator	Induction with bendamustine (n=209)
Outcomes	**Primary:** Investigator-assessed PFS **Secondary:** OS, Event free survival, disease free survival, complete response, duration of response, overall response, EQ-5D

Key conclusions from TA472:

TA472 recommendation:
"Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is recommended for use within the CDF as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen, only if the conditions in the managed access agreement for obinutuzumab are followed"

- Main clinical uncertainty: magnitude of OS benefit. Mature OS data from clinical trial likely to resolve uncertainty around treatment effect and produce more robust cost-effectiveness estimates
- Cost effectiveness estimates were largely dependent on duration of treatment effect assumed when extrapolating OS data, which was uncertain due to immaturity of data:
  - plausible that treatment effect was longer than modelled in company's base case. Scenarios exploring a duration of treatment effect on OS between 7-25 years indicated a plausible potential for obinutuzumab with bendamustine to be cost effective.
- Data collection agreement included OS data collection from the clinical trial and observational data from the systemic anti-cancer therapy (SACT) dataset.
- CDF review to consider committee's preferred assumptions from TA472 and use the same model; only OS and PFS data to be updated.

[redacted]

Updated clinical evidence: progression-free survival

Additional 31 months of data collection from GADOLIN compared to last data seen by committee

Results from GADOLIN presented at 2nd committee meeting of TA472 (cut-off April 2016)

	Benda n=171	O-B+O n=164
Patients with event, n	[redacted]	[redacted]
Median PFS, months (95% CI)	14.0 [redacted]	25.3 [redacted]
Stratified hazard ratio (95% CI) p- value	0.52 (0.39, 0.69) <0.0001	

Updated results from GADOLIN (cut-off Nov 2018)

	Benda n=171	O-B+O n=164
Patients with event, n	[redacted]	[redacted]
Median PFS, months (95% CI)	13.7 [redacted]	24.1 [redacted]
Stratified hazard ratio (95% CI) p- value	0.51 (0.39, 0.67) <0.0001	

Source: Table 2, company response to ACD

[redacted]

O-B+O: obinutuzumab with bendamustine followed by obinutuzumab maintenance
Benda: bendamustine

Updated PFS GADOLIN results (Nov 2018)

Updated clinical evidence: overall survival

Additional 31 months of data collection from GADOLIN compared to last data seen by committee

Results from GADOLIN presented at 2nd committee meeting of TA472 (cut-off April 2016)

	Benda n=171	O-B+O n=164
Patients with event, n	[redacted]	[redacted]
Median OS, months (95% CI)	53.9 [redacted]	NE* [redacted]
Stratified hazard ratio (95% CI) p value	0.58 (0.39, 0.86) p=0061	

Updated results from GADOLIN (cut-off Nov 2018)

	Benda n=171	O-B+O n=164
Patients with event, n	[redacted]	[redacted]
Median OS, months (95% CI)	60.3 [redacted]	NE [redacted]
Stratified hazard ratio (95% CI) p value	0.71 (0.51, 0.98) p=0.0343	

Source: Table 3, company response to ACD *NE: not estimable

Hazard ratio is less favourable in the updated results and suggests a 29% reduction in the risk of death with obinutuzumab plus bendamustine

Updated OS GADOLIN results (Nov 2018)

Evidence from systemic anti-cancer therapy (SACT) dataset

- 97 applications for CDF funding for FL; records available for 92 patients. 60% identified as having completed treatment by 28 February 2019 (latest follow up)
- Median treatment duration for all patients was 5.3 months (95% CI: 4.8, 7.8). 46% were still on treatment at 6 months (95% CI: 35, 56) and 28% at 12 months (95% CI: 18, 40)
- OS: minimum follow-up was 4 months from the last CDF application and median follow-up was 12.4 months. Data too immature to provide estimates of median survival. Survival at 6 months was 97% (95% CI: 90, 99) and at 12-months 88% (95% CI: 79, 94).
- SACT data not used in company's model
- KM estimate of OS at 12 months was 88% (95% CI 79% to 94%). KM estimate of OS at 12 months from the final data cut of GADOLIN was [redacted]
- **ERG**: KM estimates of OS at 12 months from SACT and GADOLIN have overlapping confidence intervals but comparison between single arms from separate studies is subject to bias
- 11 patients had an ASCT instead of receiving maintenance therapy with obinutuzumab suggesting that obinutuzumab may be being prescribed as an induction therapy without being followed by a maintenance period in clinical practice.
- **ERG** notes that the duration of time spent on treatment is lower in the SACT cohort than in GADOLIN, although it is difficult to make meaningful comparisons due to immaturity of data.

[redacted]

Key clinical issues

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- Does the updated data from GADOLIN confirm an overall survival benefit, and what does the ‘real-world’ systemic anti-cancer therapy (SACT) data add?

[redacted]

Key cost effectiveness issues

- Rather than using a single hazard function, is it appropriate to use a model that allows for a change in hazard function, in both the PFS and OS Modelling?
  - The ERG considered that using a random change point and two hazard functions better reflected the treatment strategy being modelled and provided a better fit to the observed data.
  - This deviates from TA472, and the company's submission, however the company accepts this updated approach.
- Does the treatment duration data from SACT, albeit immature, have any material impact on the estimate of cost-effectiveness?

[redacted]

Changes to model parameters in CDF review

	Committee preference from TA472	Company base case in CDF review	Company justification for deviation
OS extrapolation	OS modelled using KM data until the time of the last event (4 years) then extrapolated using fully fitted dependent Weibull curves	KM data not used directly to model OS – Weibull curves used to model OS throughout the time horizon. Curve parameters updated from data of final data cut (Nov 2018)	Fitted survival functions applied from month 0 to avoid potentially appending hazards to the tail of a curve past 7 years
PFS extrapolation	Weibull curves fitted independently for both treatment arms for entire time horizon, without direct use of the KM data	Weibull functions fitted to observed PFS data from final data cut of GADOLIN	Weibull function continues to provide conservative long-term PFS estimates
Duration of treatment effect on OS	Various assumptions considered in decision making	Base case updated to assume no cap to duration of treatment effect on OS	Lack of evidence for finite duration of treatment effect on OS from updated trial results
Acquisition costs	Agreed PAS for obinutuzumab. Acquisition cost for bendamustine	PAS updated. eMIT data reduces cost of bendamustine	Most recent prices used

Outstanding issues after technical engagement

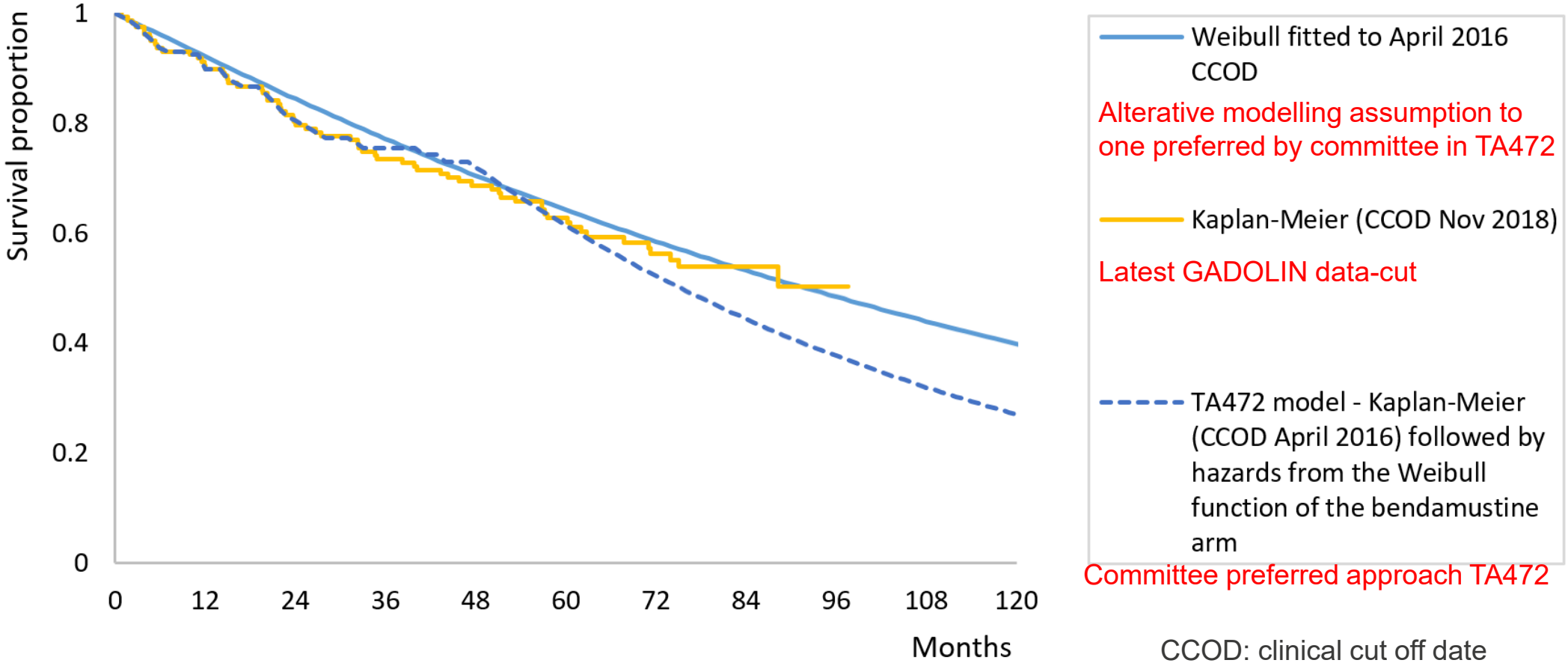
- **Issue 1:** Overall survival modelling approach
- **Issue 2:** Progression free survival modelling approach

[redacted]

Issues 1 and 2: PFS and OS modelling approach

- Company's base case uses Weibull curves assuming proportional hazards, fitted to updated PFS and OS data from the latest data cut of GADOLIN throughout the model time horizon
  - no cap on the maximum duration of treatment effect on OS as no evidence of a declining treatment effect over time

Model comparison: final OS Kaplan Meier for obinutuzumab with bendamustine followed by obinutuzumab maintenance from GADOLIN against two modelling assumptions in TA472



CCOD: clinical cut off date

ERG's critique of PFS and OS modelling approach

- A single hazard function for patients treated with obinutuzumab with bendamustine may not accurately represent the underlying hazards. A model allowing for the change in hazards from induction to maintenance treatment provides a better fit to the updated trial data
- Company re-analysed PFS and OS survival modelling using a Weibull change-point model after clarification using a fixed [i.e. at six months] and random change-point
  - ERG prefers the random change-point model as this allows uncertainty about when maintenance treatment affects the hazard and uses this in its base case analysis.
  - ERG's base case using a random change-point model reduces ICER from company's base case estimate of £17,408 to 15,045 per QALY gained
- **Company**: ERG's approach models survival more accurately during first 24 months of the observed period due to the introduction of additional parameters, and predicts plausible survival estimates

[redacted]

PFS survival curves for Weibull with random change-points

OS survival curves for Weibull with random change-points

Company's cost effectiveness results: base case and scenario analyses incorporating change-point models

Scenario	Incr LY gained	Incr Costs	Incr QALYs	ICER
Company updated base-case	[redacted]	[redacted]	[redacted]	£17,408
Company scenario 6 – Weibull model with change-point at 6 months for PFS	[redacted]	[redacted]	[redacted]	£17,322
Company scenario 7 – Weibull model with random change-point for PFS	[redacted]	[redacted]	[redacted]	£16,383
Company scenario 8 – Weibull model with change-point at 6 months for OS	[redacted]	[redacted]	[redacted]	£15,587
Company scenario 9 – Weibull model with random change-point for OS	[redacted]	[redacted]	[redacted]	£15,902

Incr: incremental

[redacted]

ERG's preferred assumptions and impact on the cost-effectiveness estimate

Scenario	Incr costs	Incr QALYs	ICER	Change from company base case
Company base case	[redacted]	[redacted]	£17,408	--
ERG base case: Weibull survival functions with random change-points for PFS and OS, and using latest eMIT price for bendamustine	[redacted]	[redacted]	£15,045	-£2,003
ERG additional scenario: above with incremental costs adjusted to include 1 additional dose of obinutuzumab in 3rd year of model	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Immature secondary clinical effectiveness evidence from SACT cohort	Data from the SACT cohort are too immature to provide reliable estimates of median OS. The duration of follow-up for OS in the SACT cohort ranged from 4 to 23 months and the median follow-up time for OS was 12.4 months. The limited duration of follow-up in the SACT cohort means that an estimate of median OS cannot be provided.	Unknown
Duration of treatment	Estimates of cost-effectiveness are dependent on the assumption that patients have a similar duration of treatment in clinical practice to in the GADOLIN trial. There is some evidence to suggest that the treatment duration in clinical practice, as measured in the SACT cohort, may be shorter than in the GADOLIN trial, and it is not possible to adjust the estimates of cost-effectiveness to reflect a shorter duration of treatment.	Difficult to predict because the model is based on PFS and OS outcomes from the GADOLIN trial and therefore the model assumes the exact same treatment duration as observed in GADOLIN.

[redacted]

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