Obinutuzumab in combination with bendamustine for treating rituximab-refractory follicular lymphoma

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee A

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ERG ScHARR

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Key issues for consideration

- How generalisable are the results from the GADOLIN trial to clinical practice in England?
- What are the most relevant comparators for O-benda+O in clinical practice in England?
- What is the most reliable data on which to project the long term benefit of the combination treatment?

Disease background

- Lymphomas are cancers of the lymphatic system
- Divided into Hodgkin’s and non-Hodgkin’s lymphomas.
- Non-Hodgkin's lymphoma includes a number of different conditions, which may be classified based on their grade, or type
- Low-grade, or ‘indolent’, non-Hodgkin’s lymphomas are slow growing, and often have long survival times but low cure rates
- Follicular lymphoma is one of the most common types of indolent non-Hodgkin’s lymphoma.
- In 2012, approximately 11,400 people were diagnosed with non-Hodgkin’s lymphoma in England, of whom approximately 2,050 had follicular lymphoma.
- Approximately 87% of people with follicular lymphoma survive for 5 years or more

Current management

- Advanced follicular lymphoma initial treatment with chemotherapy in combination with rituximab, often followed by maintenance therapy with rituximab.
- Most relapse after the initial response, and treatment is often characterised by multiple lines of treatment as the disease responds and relapses.
- Cancers that do not respond to rituximab or relapse soon after finishing treatment are termed ‘rituximab refractory’.
- Treatment options for rituximab-refractory follicular lymphoma include single- or multi-agent chemotherapy (for example, including cyclophosphamide, fludarabine, bendamustine or chlorambucil) and best supportive care.

Related NICE Technology Appraisals

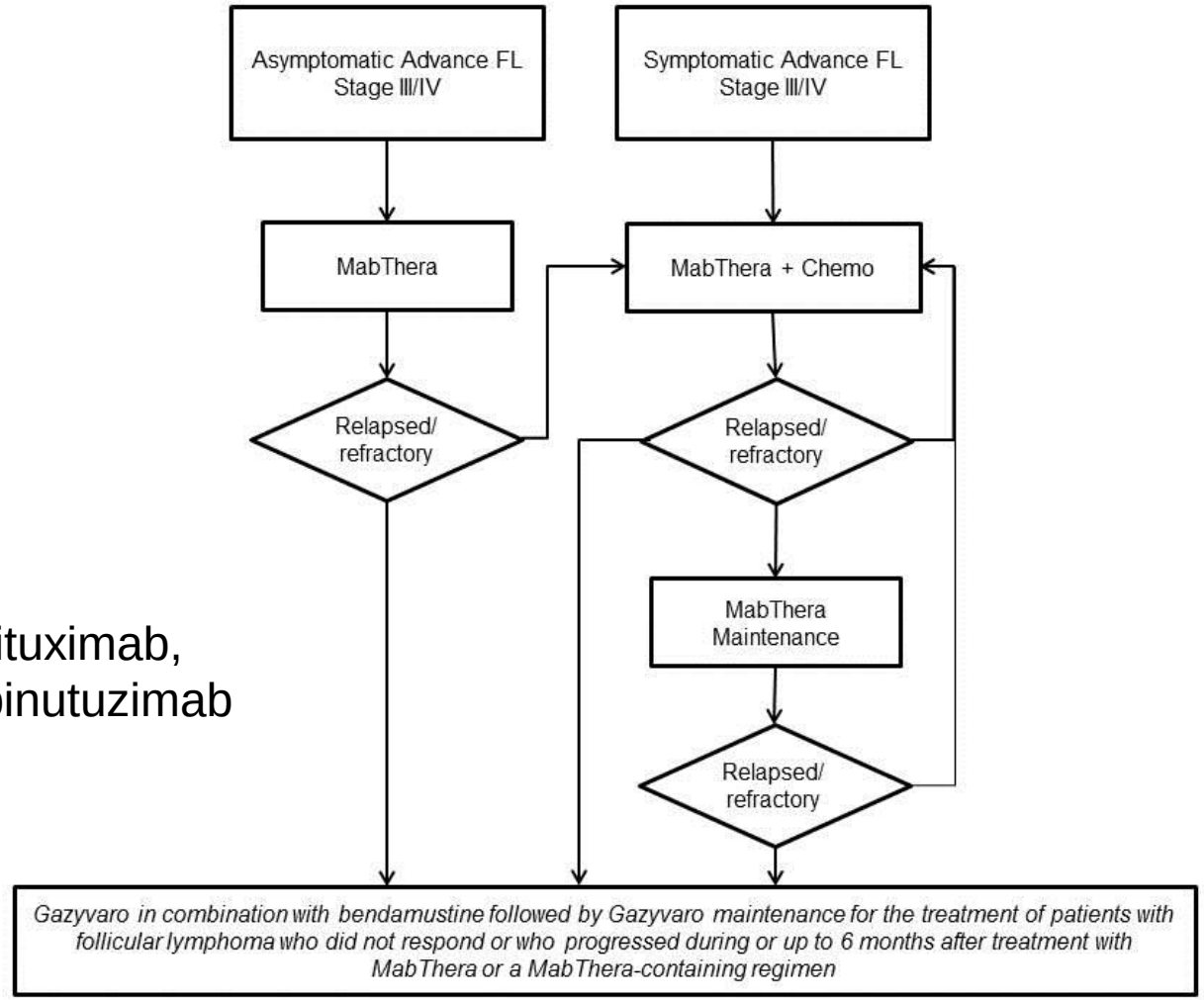
- Idelalisib for treating follicular lymphoma that is refractory to 2 prior treatments' (terminated appraisal; 2014). NICE Technology Appraisal 328.
- Bendamustine for the treatment of indolent (low grade) non-Hodgkin's lymphoma that is refractory to rituximab' (terminated appraisal; 2010). NICE Technology Appraisal 206.
- Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma: Review of technology appraisal guidance 37' (2008). NICE Technology Appraisal 137.

Related Guidelines

- Improving outcomes in haematological cancers' (2003) NICE guidance on cancer services. Review in progress, publication date TBC.
- Guidelines in development: - Non-Hodgkin's lymphoma: diagnosis and management of non-Hodgkin's lymphoma'. Publication expected July 2016.
- Related NICE Pathways:- Blood and bone marrow cancers (2015) NICE pathway

Treatment pathway (Figure 5, Company submission

- MabThera = rituximab,
- Gazyvaro =obinutuzimab



Impact on patients and carers

David Thompson

Patient Perspective

- Early stages may be painless and slow progressing with long survival rates but low cure rates
- Disease tends to respond and relapse thus requiring multiple lines of treatment

Later stages may include

- “Rubbery” lumps in neck, armpit, groin, stomach
- Frequent and persistent infections, fever, drenching night sweats, severe fatigue, itching, weight loss and pain in chest, abdomen, bones
- Huge impact on quality of life
- Quality of life of carers, family and friends also reduced
- Frequent quick relapse after treatment

Patient perspective on treatment

- Symptoms and treatment toxicity impose a burden on patients impacting on health related quality of life
- The most serious common treatment adverse events include neutropenia, infections, platelet deficiency. Less common include infusion related reactions (if given premedications), cardiac disorders and second malignancy
- iv obinutuzumab on days 1, 8 and 15 of cycle 1, and day 1 of 28 days for cycles 2-6 i.e. 8 visits in 20 weeks. Maintenance dose is every 2 months for 2 years unless disease progression i.e.12 times in 2 years
- iv bendamustine on days 1 and 2 every 3 weeks for 6 cycles i.e. 12 times in 15 weeks
- Visits to hospitals impose an additional burden on patients. Local iv centres or iv at home may be available in some locations

What patients want

An additional effective treatment option to:

- Extend progression-free survival
- Increase response rates
- Increase duration of response
- Extend treatment free interval
- Reduce adverse side effects
- Improve health related quality of life
- Extend life

Treatment being appraised

- Obinutuzumab (Gazyvaro, Roche Products) is a type 2 glycoengineered antibody that binds to the CD20 protein present on B cells, except stem or plasma cells, and causes cell death. It is administered by intravenous infusion.

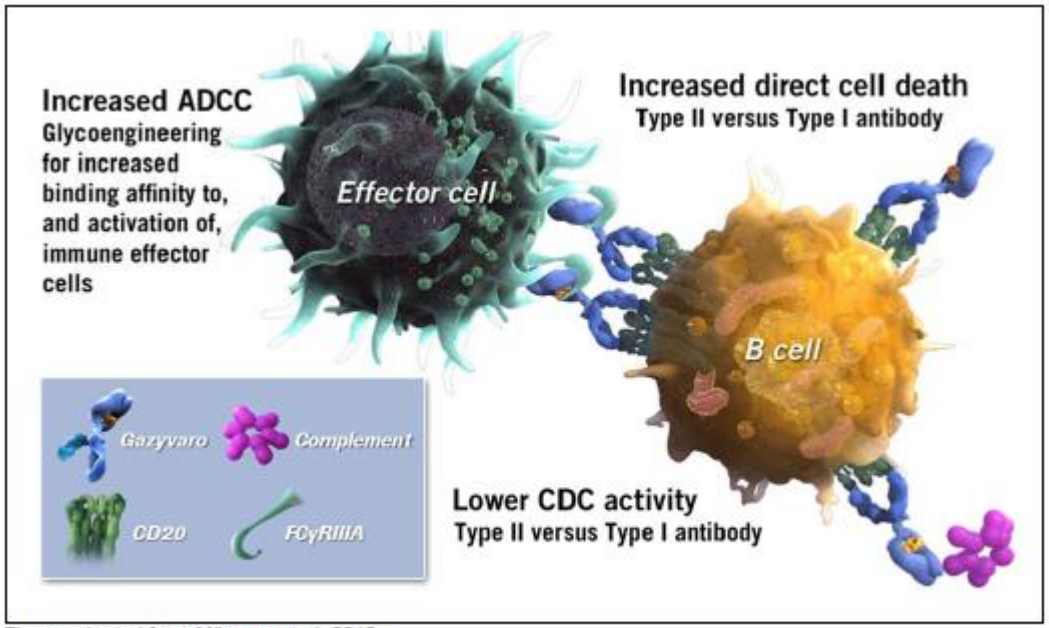


Figure adapted from Mössner et al. 2010
ADCC, Antibody-dependent Cellular Cytotoxicity; CDC, Complement Dependent Cytotoxicity; CD20, B-lymphocyte antigen CD20; FcγRIIIA, Receptor III for the Fc Region of Immunoglobulin G

Treatment being appraised

- Marketing authorisation: Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance for patients with follicular lymphoma whose disease did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Company decision problem (1)

	NICE scope	Company's decision problem	
		Same as NICE scope?	Company comment
Population	Patients with follicular lymphoma refractory to rituximab or rituximab containing regimens	✓	Refractory defined as a relapse during, or within 6 months of completing treatment with rituximab
Intervention	Obinutuzumab in combination with bendamustine, followed by bendamustine maintenance therapy	✓	Intervention consistent with NICE scope

Company decision problem (2)

	NICE scope	Company's Decision problem	
		Same as NICE scope?	Company comment
Comparator(s)	• Chemotherapy regimens without rituximab (cyclophosphamide- or fludarabine-containing regimens, bendamustine or chlorambucil) • Best supportive care	×	Bendamustine monotherapy only licenced treatment for rituximab-refractory follicular lymphoma at time of GADOLIN trial. Indirect comparison with other chemotherapy regimens or BSC not feasible

Company decision problem (3)

	NICE scope	Company's decision problem	
		Same as NICE scope?	Company comment
Outcomes	• Overall survival • Progression free survival • Treatment response rates • Duration of response /remission • Adverse effects of treatment • Health related quality of life	✓	Outcomes consistent with the NICE final scope

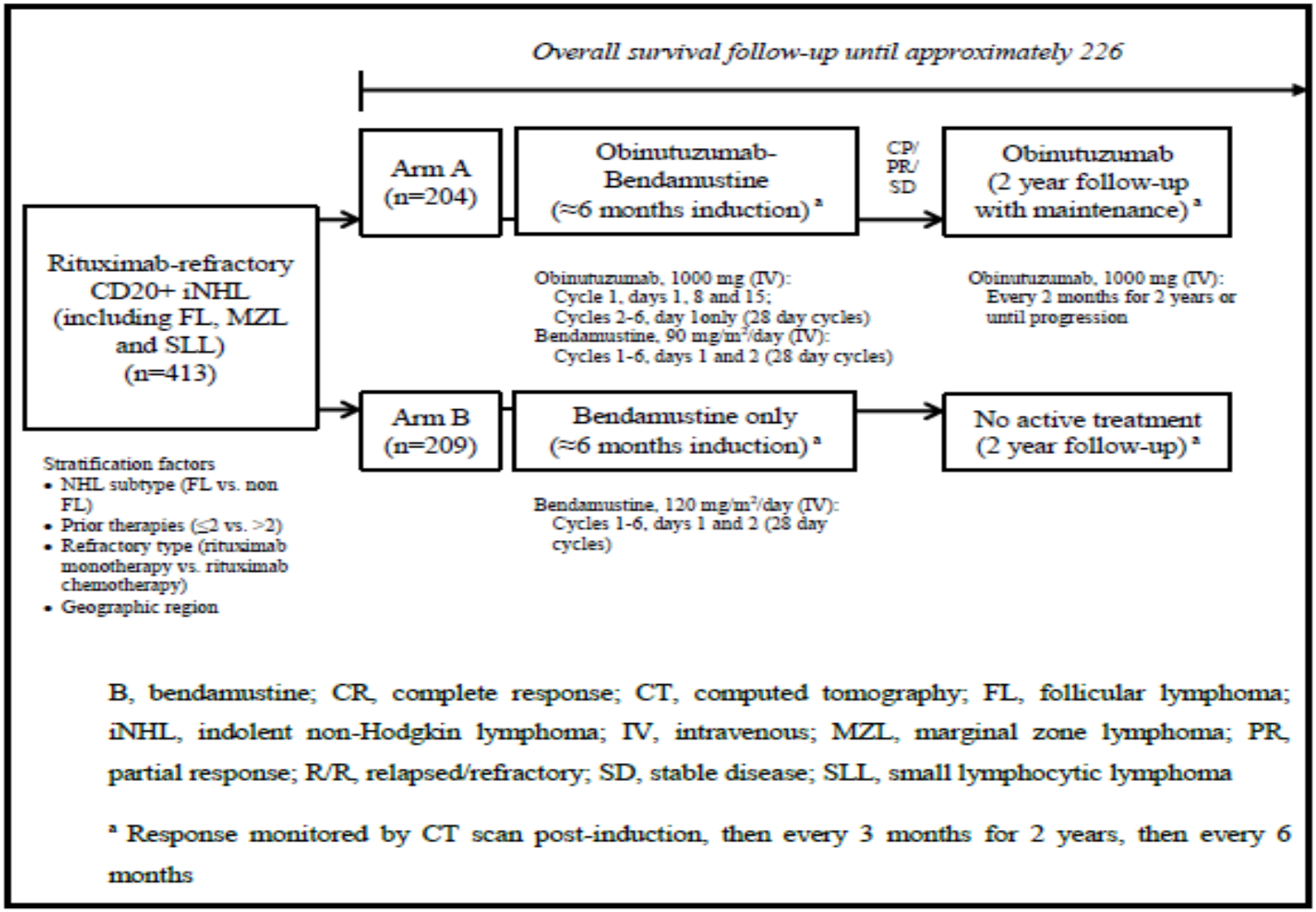
Clinical evidence

- The company's systematic review of RCTs of obinutuzumab for treating rituximab-refractory FL identified and included only one relevant study:- The GADOLIN study
- GADOLIN compared obinutuzumab in combination with bendamustine as induction (O-benda), followed by obinutuzumab monotherapy as maintenance (+O), with bendamustine alone (induction only) in patients with rituximab-refractory disease

Clinical trial design (1): GADOLIN

Population	Indolent non-Hodgkin's Lymphoma Patients with rituximab-refractory follicular lymphoma • relapsed following following induction treatment with rituximab monotherapy • or relapsed following induction treatment with R-chemotherapy • or relapsed during or within 6 months of completing maintenance treatment with rituximab monotherapy
Design	Multicentre, randomised, open-label, Phase III 413 Indolent non-Hodgkin's Lymphoma (81.1% with follicular lymphoma)

Clinical trial design (2) GADOLIN



B, bendamustine; CR, complete response; CT, computed tomography; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; IV, intravenous; MZL, marginal zone lymphoma; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma

[a] Response monitored by CT scan post-induction, then every 3 months for 2 years, then every 6 months

Outcome measures

Primary End Point

Progression free survival (median, months)
-calculated from time of randomisation to first occurrence of progression, or relapse, or death

Secondary End Points

- Event Free Survival
  -defined as the time between the date of randomisation and the date of disease progression/relapse based on IRC assessments, death from any cause on study, or start of a new anti-lymphoma therapy
- Overall survival (median, months)
- Disease free survival
  as the time from the first occurrence of a documented CR, as assessed by the IRC, until relapse defined on the basis of the IRC assessments or death from any cause on study
- Cont.…

Outcome Measures

- Complete response (%)
- Best overall response (%)
  Assessed by the IRC and by the investigator during treatment and up to 12 months after the start of treatment
- End of treatment overall response (%)
  defined as the response occurring at the end of (initial/induction) treatment, i.e. the first response assessment that occurred after the last dose of (initial/induction) treatment and before start of maintenance or follow-up phases
- Duration of response (median, months)
  Defined as the time from a best overall response of CR or PR to the first occurrence of progression/relapse (based on the IRC assessment) or death from any cause on study

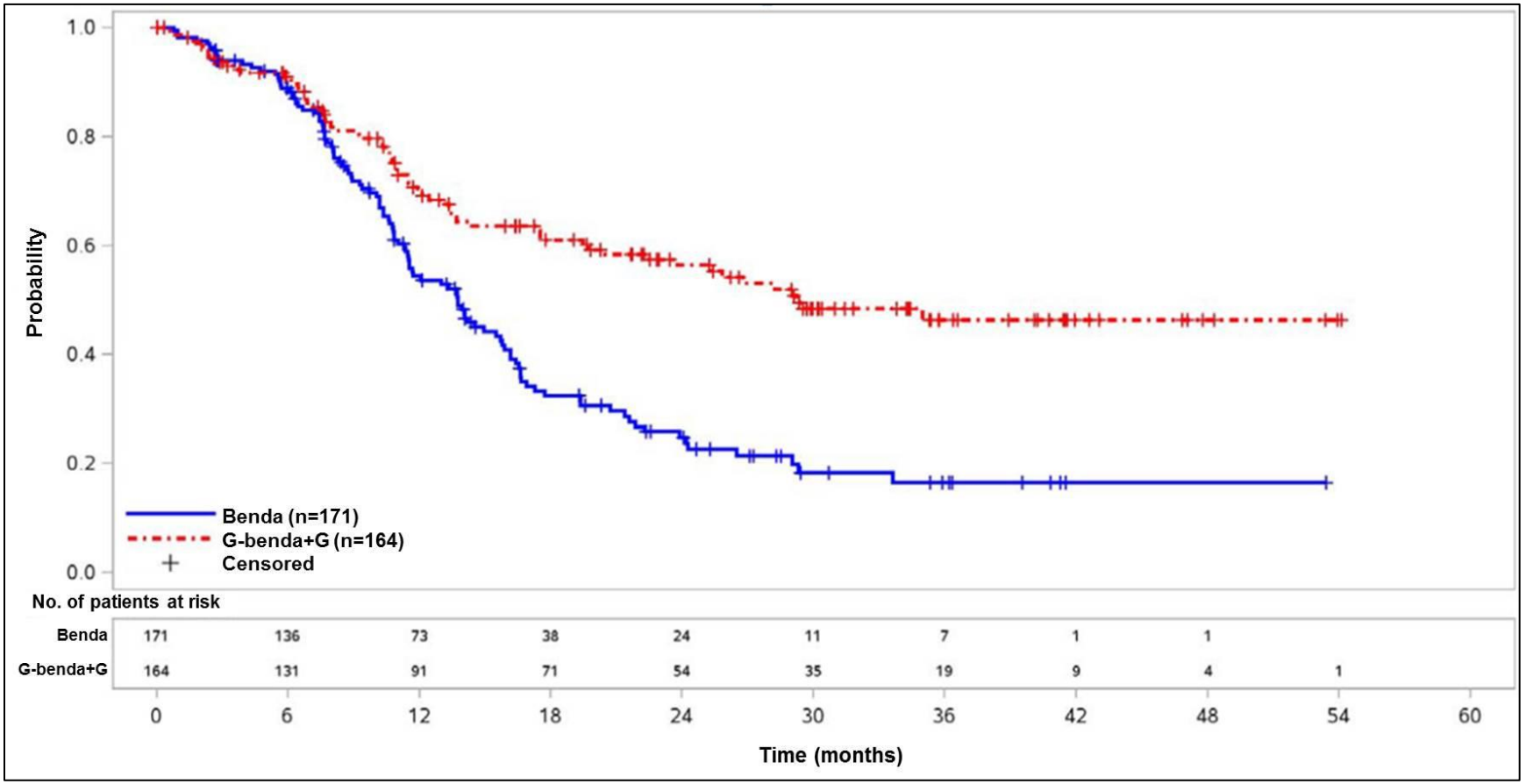
Health-related patient reported outcomes

- Changes from baseline, by visit, were assessed by the Functional Assessment of Cancer Therapy for Patients with Lymphoma (FACT-Lym) instrument
- EuroQol-5 Dimension (EQ-5D) Health Index Scale summary scores at baseline, during treatment, and following treatment discontinuation or completion (both progression-free and after disease progression) were also assessed.

Trial Results (1): GADOLIN FL population Tables 32-38,company submission

Outcome	O-benda+O	Bendamustine	HR (95% C.I) {p value}
Progression free survival (median, months)	29.2	13.8	0.47 (0.34 to 0.64) {<0.0001}
Overall survival (median, months)	NR	NR	0.62 (0.39 to 0.98) {0.0379}
Complete response (%)	15.2	19.3	0.82 (0.46 to 1.46) {0.5041}
Best overall response (%)	76.2	78.9	2.73* (0.50 to 1.41) {0.5098}
End of treatment overall response (%)	67.7	65.3	1.09* (0.69 to 1.73) {0.6972}
Duration of response (median, months)	NR	11.6	0.39 (0.27 to 0.55) {NR}
O-benda +O – obinutuzumab + bendamustine + obinutuzumab maintenance; HR-Hazard: ratio; C.I – confidence interval. NR- Not reported.*Odds ratio			

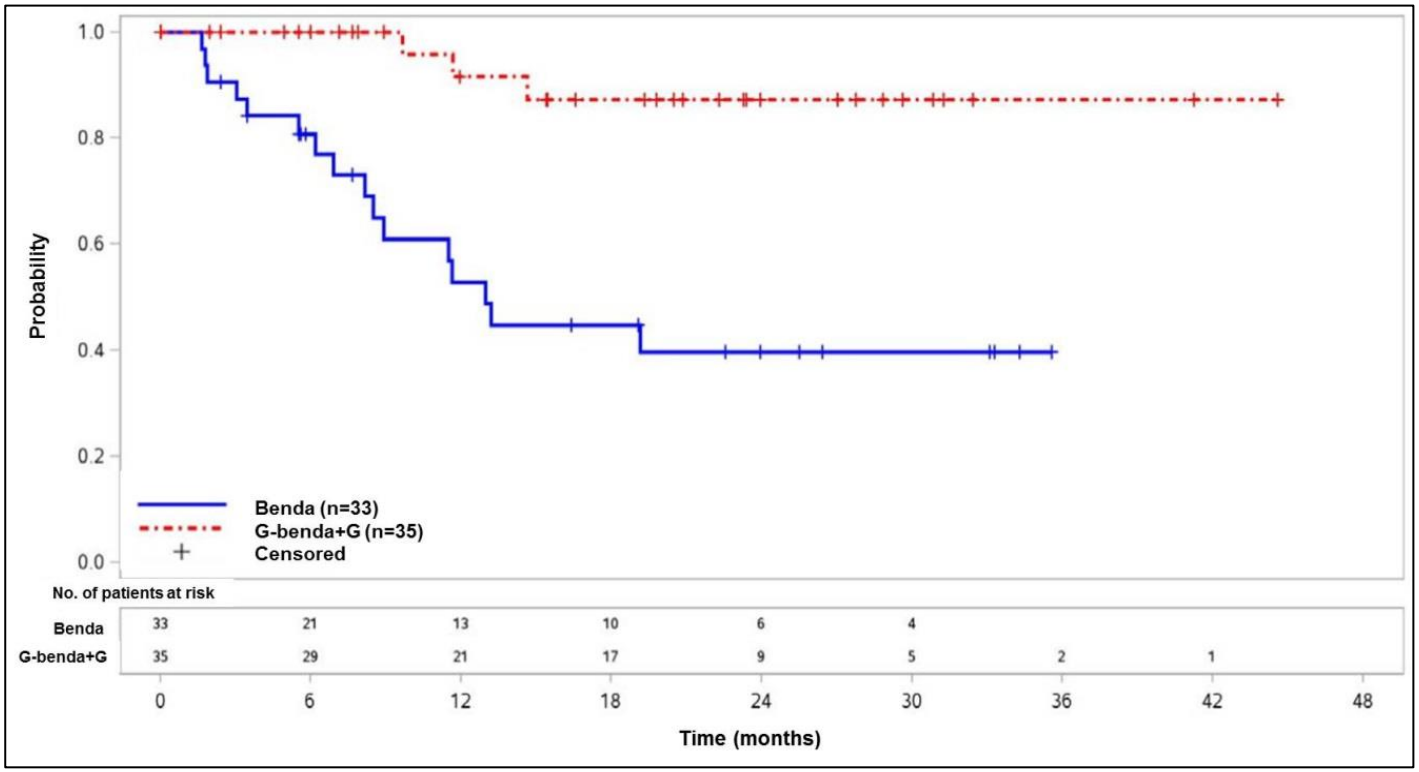
Trial Results (2) KM plot of progression free survival in FL ITT population (Figure 9, company submission)



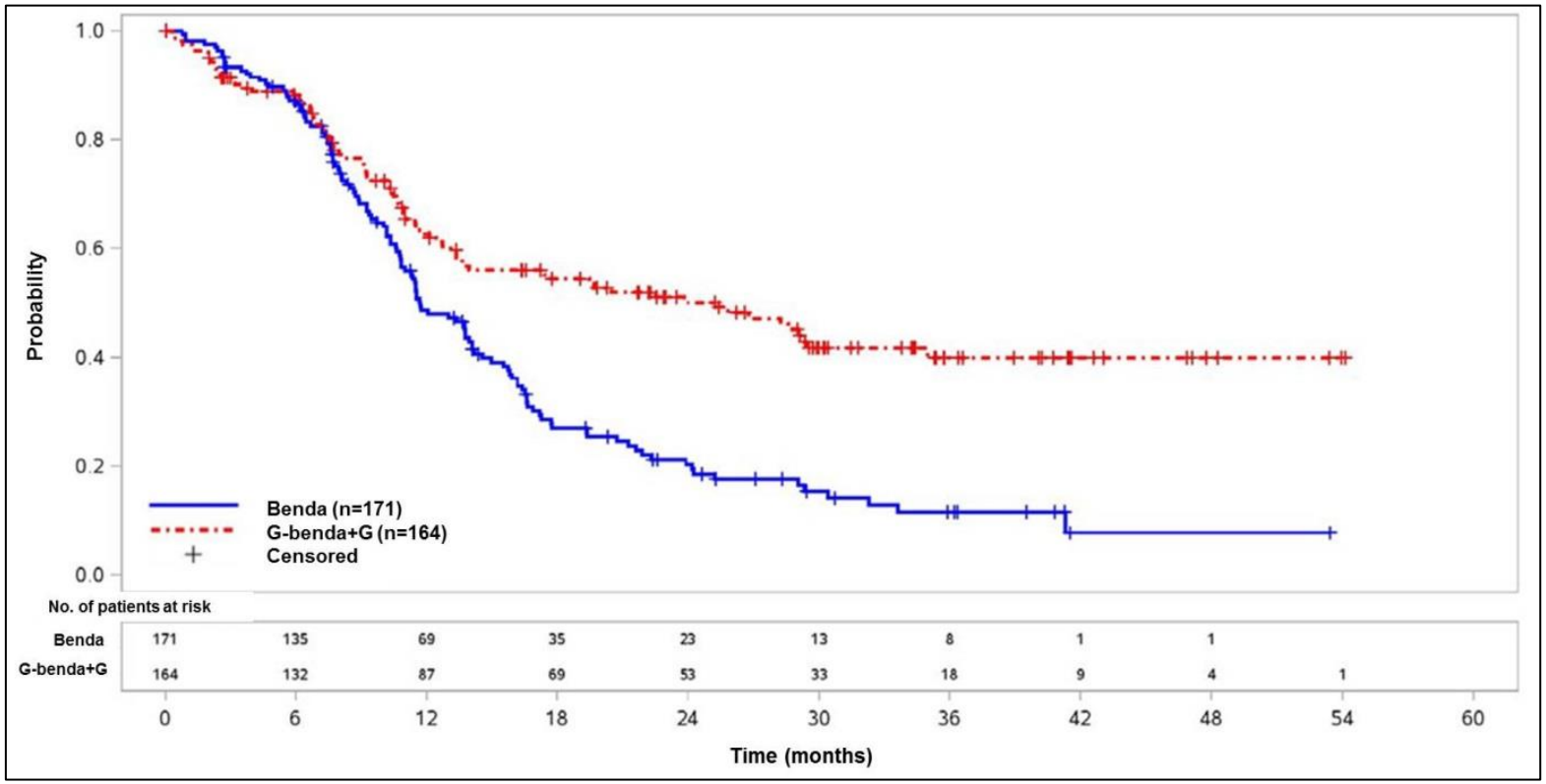
Trial Results (3): GADOLIN FL population (Tables 32-39, CS)

Outcome	O-benda+O	Bendamustine	HR (95% C.I) {p value}
Disease free survival (median, months)	NR	13.0	0.14 (0.04 to 0.48) {NR}
Event free survival (median, months)	25.3	11.7	0.52 (0.39 to 0.69) {<0.0001}
Time to start of new anti-lymphoma treatments (median, months)	NR	18.2	0.61 (0.45 to 0.83) {NR}
O-benda +O – obinutuzumab + bendamustine + obinutuzumab maintenance; HR-Hazard: ratio; C.I – confidence interval. NR- Not reported.*Odds ratio			

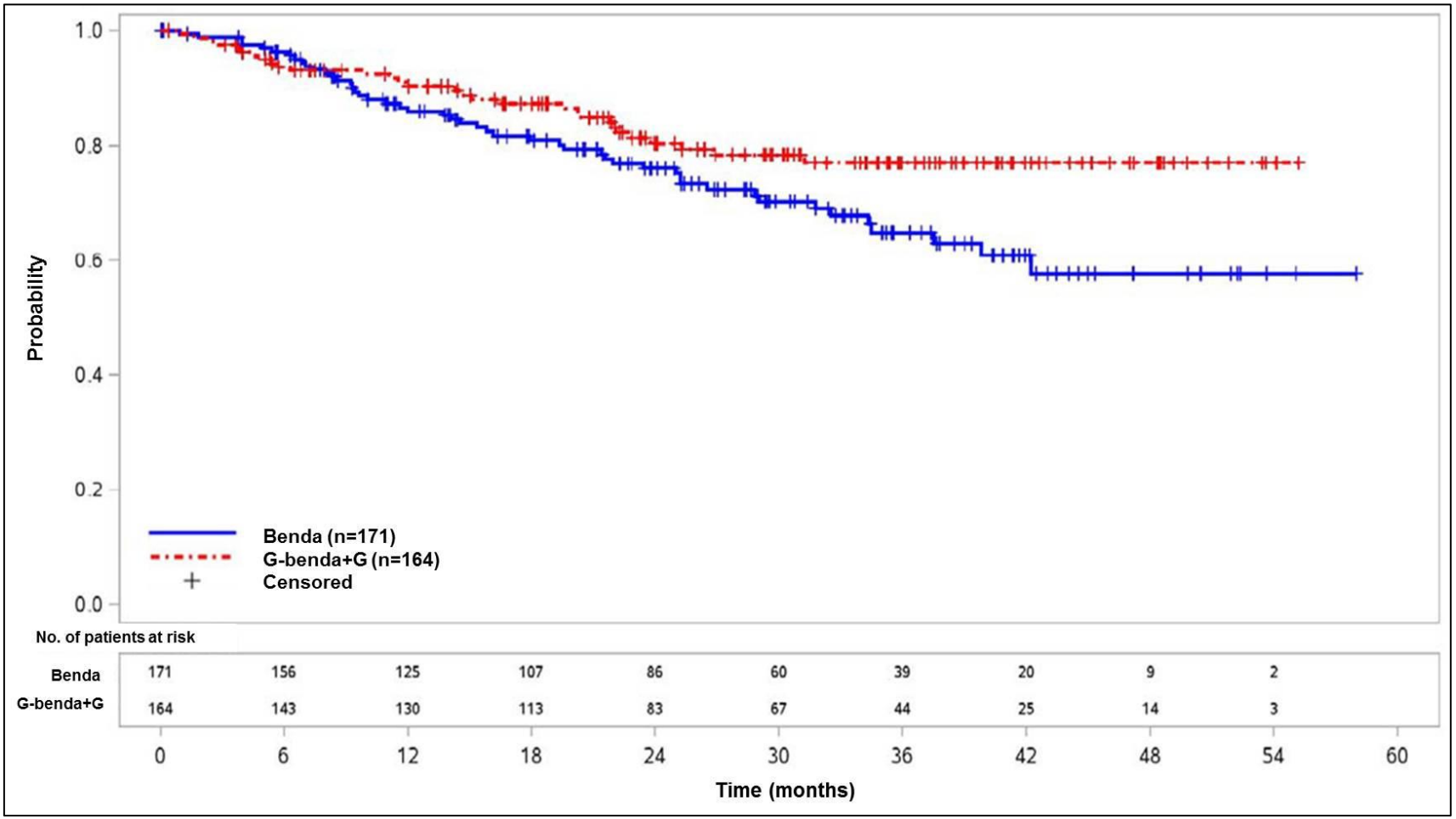
Trial Results (4) KM plot of disease free survival in FL ITT population with CR (Figure 10, company submission)



Trial Results (2) KM plot of event free survival in FL ITT population (Figure 11, company submission)



Trial Results (2) KM plot of overall survival in FL ITT population (Figure 12, company submission)



Median PFS Results (3):subgroup analysis FL population by rituximab refractory status(Table 8, ERG report)

Population	O-benda+O	Bendamustine	HR (95% C.I) {p value}
FL refractory to rituximab induction (n=67)	xxx	xxx	xxxxxxxx
FL refractory to rituximab + chemotherapy induction (n=122)	xxx	xxx	xxxxxxx
FL refractory to rituximab maintenance (n=142)	xxx	xxx	xxxxxx
FL-folicular lymphoma, PFS- progression free survival; O-benda+O obinutuzumab + bendamustine + obinutuzumab maintenance; HR-Hazard: ratio; C.I – confidence interval. NR- Not reported.*Odds ratio			

Median OS Results(4):subgroup analysis FL population by rituximab refractory status

Population	O-benda+O	Bendamustine	HR (95% C.I) {p value}
FL refractory to rituximab induction (n=67)	NR	NR	xxxxxxx
FL refractory to rituximab + induction chemotherapy (n=122)	NR	NR	xxxxxxx
FL refractory to rituximab + maintenance chemotherapy (n=142)	NR	NR	xxxxxxx
FL-folicular lymphoma, OS-overall survival; O-benda+O– obinutuzumab + bendamustine + obinutuzumab maintenance; HR-Hazard: ratio; C.I – confidence interval. NR- Not reported			

Adverse events overview FL population

- 98.8% of patients in both trial arms had at least 1 adverse event
- serious adverse event: 39.0% O-benda+ O vs. 34.5% benamustine
- most common grade 3-5 adverse event neutropenia
  - 32.3% for O-benda+ O and 24.4% bendamustine

Results – HRQoL FL population

- No statistically significant differences in the EQ-5D score for O-benda+O vs.bendamustine
- Greater proportion of patients reported improvement in lymphoma subscale (FACT-Lym) for O-benda+O vs. bendamustine
  - At time point 6, worsening from baseline of FACT-Lym Trial Outcome Index was 8.0 months (95% C.I 5.8 to 15.1) for O-benda+O vs.4.6 months (95% C.I 3.8 to 6.4) for bendamustine.

Mixed treatment comparison

- Company stated systematic review did not identify any relevant additional studies of bendamustine so indirect comparison was not feasible.
- Also stated that studies in follicular lymphoma rituximab refractory population heterogeneous so meta-analysis was also not feasible.

Evidence Review Group's critique (1) Generalisability

- Approximately 81% of the whole trial population included people with FL
- Patients with stage I/II follicular lymphoma were included in the GADOLIN trial.
  - Draft NICE clinical guidelines for the management of follicular lymphoma suggest that chemo immunotherapy would not be offered at stage I and would only be offered to patients with symptomatic stage II disease when radiotherapy not suitable
  - FL subgroup of GADOLIN trial is therefore not absolute reflection of the population with FL in England who would be considered for chemo immunotherapy.
- Rituximab monotherapy as induction treatment not widely used in clinical practice in England
- Rtuximab in combination with bendamustine increasingly being used as first-line treatment regimen, therefore relevance to clinical practice unclear.

Evidence Review Group's critique (2) Comparators

- Bendamustine not an appropriate comparator in subgroup of people whose disease had relapsed within or during 6 months of completing maintenance treatment with rituximab maintenance therapy.
  - R-chemotherapy (excluding R-bendamustine) the relevant comparator in this patient population
- Although bendamustine monotherapy has a marketing authorisation for Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen, there is no NICE guidance (terminated appraisal) and it is no longer funded by the CDF
  - In clinical practice these patients would be re-treated with rituximab in combination with alternative chemotherapy regimens (and would not be considered truly refractory).

Evidence Review Group's critique (3) Outcomes

- GADOLIN follow-up to 2 years or until disease progression (whichever occurs first), long-term efficacy of obinutuzumab to be unknown and the optimum duration of treatment uncertain
- Clear separation in KM curves for progression free survival at 6 months, unclear how much of the PFS improvement was due to obinutuzumab maintenance therapy as opposed to obinutuzumab in combination with bendamustine induction therapy.
- Overall survival data immature
- Lack of head to head trials comparing obinutuzumab in combination with bendamustine with other relevant interventions

Key issues for consideration (1)

- Generalisability of results from the GADOLIN trial to clinical practice IN England?
  - 81% of the whole trial population included people with FL
  - Patients refractory to Rituximab induction monotherapy alone – relevant to UK practice?
  - Patients who relapse during or shortly after rituximab maintenance therapy are better regarded as relapsed rather than refractory?
  - Patients whose disease had relapsed following induction treatments with R-chemotherapy 'truly' refractory?
- Most relevant comparators for O-benda+O in clinical practice in England?
  - bendamustine monotherapy?
  - standard immunochemotherapy?
  - autologous or allogenic transplant?
  - other?

Key issues for consideration (2)

- What is the most reliable data on which to project the long term benefit of the combination treatment
- Progression free survival data?
  - 15.4 month PFS gain for shown O-benda+O shown by K-M curves diverging from 6 months onwards when the O-benda-O arm started maintenance obinutuzumab.
  - At the final analysis before unblinding, 63.3% of patients on benda and 40.9% on the benda and O-benda+O arm progressed
- Overall survival data?
  - latest data cut, 28.1% of patients on benda and 18.3% on O-benda-O arm had died
- Do results from subgroups within the trial better reflect the likely efficacy in clinical practice or is the FL ITT population more appropriate?