Questions for clinical experts – June 2019

1. Sections 3.2 of the Appraisal Consultation Document states that the committee heard that some chemotherapeutic agents offered third line for double refractory follicular lymphoma are more effective than others.

a. Can the you please expand on this?

- Selection of chemotherapy regimens in 1st and 2nd lines in the UK consists largely of R-CVP, R-bendamustine, R-CHOP or single-agent rituximab; with clinician- and patient-choice based ultimately on the goal of treatment (either maximise activity/disease control [e.g. R-CHOP or R-bendamustine] OR maximise tolerability/QoL [e.g. R-CVP or R])

- For example, trial data suggests a lower risk of progressive disease following R-CHOP versus R-CVP in long-term follow-up of front-line symptomatic FL patients (https://ascopubs.org/doi/10.1200/JCO.2017.74.1652), although consideration of the potential cardiotoxic effects of R-CHOP may favour R-CVP in patients with previous history of cardiac disease, thus necessitating use of R-CHOP for second or later lines in some patients

- This is consistent with HMRN real-world dataset, whereby ~42% of patients received R-CVP front-line versus ~18% R-CHOP

- As noted in the NICE ACD (Sept 2018) (Section 3.2), the current lack of an evidence-based standard of care in third-line treatment of follicular lymphoma (FL) limits the choice of a suitable chemotherapy regimen to that which the patient has not already received, and progressed or failed to respond to, in previous lines

- [redacted] – refractoriness in particular to the intensive R-CHOP or R-bendamustine regimens is commonly accepted by clinicians as reflective of a high-risk, poor-prognostic group of patients

- Having potentially exhausted the availability of the most effective chemotherapeutic options in earlier lines, this very high-risk subgroup of double-refractory FL patients is currently limited to conventional single-agent or combination chemotherapy in 3rd line (or, in some cases, best-supportive care for those patients who can no longer tolerate chemotherapy) with increasingly shorter remissions for each subsequent line of treatment owing to the relapsing/remitting nature of the disease

2. Section 3.23 of the Appraisal Consultation Document, NICE's provisional guidance, discusses whether the treatment meets 'end of life criteria' (according to our methods guide section 6.10, the population has to have a short life expectancy of normally <24 months, and there should be sufficient evidence that the treatment could offer an extension of life of normally > 3 months vs standard NHS treatment). The Appraisal

Consultation Document states that there is some uncertainty about whether these criteria had been demonstrated.

a. What are your thoughts on:

i. the life expectancy for the population considered in this appraisal (that is, patients with follicular lymphoma with disease refractory to rituximab and an alkylating agent who would be fit enough to receive chemotherapy third line),

ii. how much would you expect idelalisib to extend life vs existing chemotherapeutic treatments, on average? We recognise that your clinical experience with idelalisib long term is likely to be limited.

- It will be important to understand the opinion of the clinical experts on this based on their experiences with idelalisib alongside other chemo-therapeutic options in the treatment of double-refractory FL. This is what prompted the clinical community to compile their independent clinical consensus letter (*uploaded to NICE docs*) in support of this appraisal given the absence of a current, evidence-based standard of care for these patients

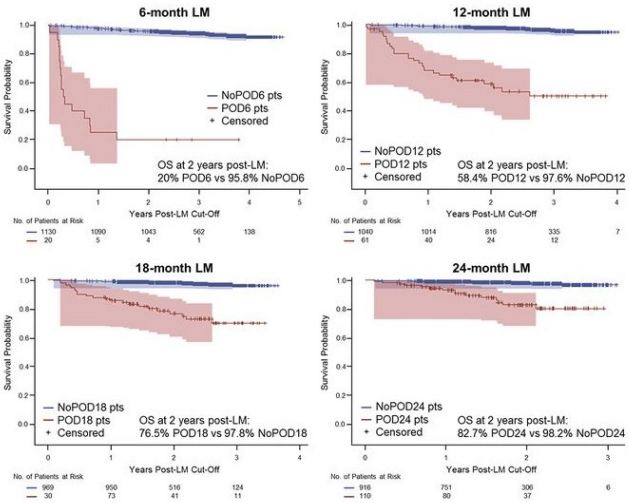
- The letter also points out the analysis around progression of disease within 24 months of treatment initiation (or 'POD24') as a critical determinant of survival for FL patients at first relapse. Casulo *et al* (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4879714/) was one of the first publications to look at the significance of POD24

- The GALLIUM study (http://www.bloodjournal.org/content/130/Suppl_1/1490) went one step further and performed landmark (LM) analyses on POD24 looking at the post-progression mortality rates for all POD24 patients on study, and looked specifically at those progressing within 6 months compared to <12 months, <18 months, and <24 months

- Estimated 2-year OS KM analyses for these patients is captured below, and shows a particularly dire prognosis for those relapsing within 6 months (i.e. rituximab-refractory). This 6-month cut-off for refractoriness is now used in many study protocols

- The letter written by the clinical community acknowledges further that the patients in this POD24 analysis were a group of patients at first relapse, whereas patients in the DELTA study were refractory to both rituximab and an alkylating agent, thus it would very reasonable to assume the DELTA study patients are even higher risk relapsed group than in the POD24 analysis

Figure 1. LM Analysis per POD Time



LM, landmark

Table 1. Post-Progression Mortality Rates Stratified by Time of Progression

Time of Progression, Months	N	OS Events	Pt Years at Risk	Deaths/100 Pt-Yrs (95% CI)
0–6	22	18	22.2	81.0 (51.2–100)
6–12	58	27	111.6	24.2 (16.6–35.3)
12–18	46	9	102.2	8.8 (4.6–16.9)
18–24	29	2	52.5	3.8 (1–15.2)

Table 2. PFS and POD Events at 24 Months by Treatment Arm

	R-Chemo (n=601)	G-Chemo (n=601)
Absolute risk of a PFS event before 24 months, %	18.94 (95% CI: 15.94–22.42)	12.53 (95% CI: 10.06–15.55)
Relative risk reduction, G-chemo vs R-chemo (95% CI)	33.85 (12.76–49.84)	
PFS events at 24 months		
All	107	71
POD24 events (PD or death due to PD)	98	57
noPOD24 events (death not due to PD)	9	14

3. The company presented data that suggests that, compared with chemotherapy, idelalisib is superior for overall survival, but inferior for progression free survival. The company recognise that this is counterintuitive, but argue that "Across both samples, PFS was defined as time from initiation of treatment to date of first disease progression or death from any cause. However, according to the study protocol, trial subjects were subject to regular imaging-based tumour assessments, performed at ~8- to 12-week intervals at Visits 1, 6, 9, 11, 13, and 15 (corresponding to baseline, Weeks 8, 16, 24, 36, and 48) and every 12 weeks thereafter and at an end-of-treatment. By contrast, HMRN patients, as is the NHS standard of care, may have an interim treatment scan, but be routinely scanned only at the end of treatment or if they become symptomatic and disease progression is suspected. As such, the HMRN dataset will systematically overpredict PFS in comparison to DELTA. Along with other issues of comparability across the two datasets, PFS comparison is rendered almost meaningless".

a. Is this rationale plausible?
b. In your experience, could this data reflect a true difference, i.e. might idelalisib make people live longer while making the disease progress sooner vs standard NHS treatment?
c. Because the of the counterintuitive relationship described above, the company present cost-effectiveness analyses that assume progression free survival is the same in both intervention and comparator arms (rather than being superior in the comparator arm, as suggested by clinical data). Is this assumption realistic?

- The interpretation implied by NICE in this question is surprising – the rationale explained in our ACD response is clear in that, owing to significant differences in the way in which progressive disease is monitored in a clinical trial versus clinical practice, there is a likely systematic over-prediction of the timing of true disease progression events observed in clinical practice (i.e. HMRN cohort) compared to the rigorous, routine clinical assessment performed in the DELTA study

- Put simply, the disease progression events seen in the DELTA study will have been identified sooner due to more rigorous patient follow-up versus the HMRN cohort, making comparisons between the two cohorts very challenging, if not impossible with regards to PFS – hence our recommendation not to draw such comparison

- To infer from these data that idelalisib is somehow making the actual disease progress sooner than current chemotherapy options in the third-line FL setting is certainly not our interpretation, and is contrary to the licensing terms of the FDA and EMA who deemed the OS and PFS outcomes of the DELTA study a sufficient gain compared with current treatment options in the 3rd line setting to warrant a license based on Phase 2 data – this was even at the earlier data-cut, to which we now present further consistent and compelling evidence from longer follow-up (Aug 2018 data-cut

- Given these considerations, we believe that our assumption of equal PFS in comparisons B2 and B3 is, in fact, highly conservative against idelalisib.