NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]

Appraisal Committee Meeting – 25 June 2019

The NICE technical team asked the clinical experts for answers to a number of questions. The responses from one of the clinical experts and from the company are given below.

Response from Professor Andrew Pettitt
Honorary Consultant Haematologist, University of Liverpool & Clatterbridge Cancer Centre NHS Foundation Trust – clinical expert, nominated by the NCRI-ACP-RCP-RCR

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?

To be defined as double refractory, patients need to have failed (i.e. no response or relapse within 6 months of responding) rituximab (R) and at least one chemotherapy regimen. Since R is nowadays always given in combination with chemotherapy, the definition effectively means failing at least one R-chemo regimen. In the frontline setting, 3 different R-chemo regimens are used depending on circumstance: BR (bendamustine + R), R-CHOP and R-CVP. To complicate things, ofatumumab (O) can now be used an alternative to R, meaning that there are 6 different chemoimmunotherapy regimens from which to choose. BR/O+B is more effective than O/R-CHOP which, in turn, is more effective than O/R-CVP. On the other hand, O/R-CVP is better tolerated than O/R-CHOP and BR/O+B. The choice of chemotherapy regimen depends on several factors including patient age, fitness and co-morbidity and the clinical behaviour of the lymphoma. O/R-CHOP is used if there is any suspicion of high-grade transformation but is contraindicated in patients with cardiac comorbidity, while BR/O+B depletes T cells an can cause life-threatening infection especially in older patients. Patients who don't respond to or progress after CIT currently receive a different CIT regimen as second-line treatment. Younger, fitter patients may a receive "salvage" regimen followed by autologous stem-cell transplantation (ASCT) if they respond. There are number of different salvage regimens but they are all more intensive than the 3 main frontline options and not suitable for older or less fit patients. In general, patients will progressive through progressively stronger treatment regimens. Older and less fit patients are likely to start with R-CVP and stop at R/O-CHOP or BR/O+B due to intolerance, whereas younger fitter patients are likely to start with R/O-CHOP or BR/O+B and move through to salvage CIT/ASCT. Consequently, most patients run out of credible treatment options after 1-3 lines of CIT. There are currently no credible treatment options for patients who are refractory to BR or R-CHOP as salvage CIT is unlikely to be effective in this setting.

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 6.2.10, 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),

As explained above, being refractory to an alkylating agent (CVP, CHOP or bendamustine) and rituximab effectively means being refractory to CVP, CHOP or bendamustine in combination with rituximab. This situation might arise after the first, second or third line of CIT depending on the sequencing of treatment. Patients who are resistant to R-CVP might respond to R-CHOP or BR if they are able to tolerate these regimens, but patients who are resistant to R-CHOP or BR (irrespective of whether the regimens are given as first, second or third line treatment) are unlikely to respond to salvage CIT/ASCT and have no other credible treatment options. In the absence of effective treatment, survival is likely to be substantially less than 24 months (I would estimate somewhere in the order of 6 months on average if pushed). The situation is likely to be very similar for patients who are refractory to O+B or O-CHOP, as well as for those patients who are refractory to R-CVP and unable to tolerate BR/O+B or R/O-CHOP.

    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.

Compared to further (ineffective) CIT, idelalisib is likely to prolong life for substantially longer than 3 months. If pushed, I would estimate somewhere in the order of 12 months on average, although it could be much longer than this for some patients.

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?

Yes. Regular imaging-based assessments are likely to identify progression at an earlier stage than clinically based assessments. This is a particular issue for those patients with predominantly abdominal disease that cannot be detected by physical examination.

    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?

No, I think this is highly unlikely. I’ve never heard of such a thing.

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?

If overall survival is superior in idelalisib-treated patients compared to CIT-treated patients in the HMRN dataset, I would expect PFS to show a similar pattern. Consequently, I think the company's assumptions are actually quite conservative.

If you have any questions, please let me know. We are currently preparing slides for the June meeting so the earlier you can reply the better. Thank you for your time.

I would like to take this opportunity to emphasise that idelalisib fulfils a genuine unmet need in patients with relapsed or refractory FL who have exhausted CIT options.