Anti-GD2 Antibody Therapy Update, May 2018

Summary

- National Institute for Health and Care Excellence (NICE) issued a provisional decision not to approve dinutuximab beta (Qarziba™) for use on the NHS in England and Wales,
- NICE also unable to recommend dinutuximab beta for inclusion in the Cancer Drugs Fund (CDF),
- Clear challenge issued by NICE in Appraisal Consultation Document (ACD) to EUSA Pharma to provide additional evidence and engage in cost negotiations that would allow dinutuximab beta to be entered into the Cancer Drugs Fund,
- NICE consultation period runs until 29 May allowing consultees and members of the public to comment on ACD,
- Final NICE Appraisal meeting scheduled for 12 June after which Final Appraisal Determination (FAD) will be issued,
- For any child who has already started antibody therapy EUSA Pharma will continue to provide dinutuximab beta free-of-charge so that all courses can be completed,
- For any child who has not yet started antibody therapy clinicians must submit an Individual Funding Request (IFR) for approval on the NHS and if this is rejected EUSA Pharma will decide whether or not to provide dinutuximab beta free-of-charge on a case-by-case basis.
- Ongoing uncertainty causing additional distress for UK families who already find themselves in the most difficult and devastating of circumstances,
- Need for NICE, NHS England, and EUSA Pharma to come together as quickly as possible to negotiate conditions under which dinutuximab beta can be included in the CDF,
- Conclusion that dinutuximab beta is not cost-effective is symptomatic of wider problem that the Single Technology Appraisal (STA) method is not fit for purpose in determining the merits of drugs that are developed for rare orphan diseases like childhood cancers,
- Whilst the per patient cost is deemed too high, the STA method gives no dispensation to the patient population involved, nor to the modest overall impact on NHS budget, nor to the lack of new drugs being developed to treat children with cancer. Rather, it actively discourages companies from developing drugs for diseases such as neuroblastoma, by further limiting economic returns that are already restricted by the small numbers of patients affected.

Immunotherapy in high-risk neuroblastoma

There is an obvious unmet need for more effective therapies to treat high-risk neuroblastoma.

The key facts regarding relapse after the end of frontline treatment are:

40-50% of patients who reach the end of treatment with no evidence of disease will go on to experience a relapse.

Of those patients who experience a relapse, 80% will do so within two years of diagnosis. This does not mean that 80% of children who complete treatment will relapse. It means that 8 out of 10 (of all) relapses occur in the first two years after initial diagnosis.

So-called passive immunotherapy using anti-GD2 monoclonal antibodies, given to children in first remission during the maintenance phase of treatment (following myeloablative therapy with peripheral blood stem cell transplant), is used to try and prevent disease recurrence i.e. lower the rate of relapse.

The seminal Children's Oncology Group study ANBL0032, published in New England Journal of Medicine by Yu et. al. in September 2010, showed a 20% improvement in Event-Free Survival (EFS) at 2-years in children treated with antibody therapy plus isotretinoin (13-cis-retinoic acid) versus those treated with standard isotretinoin alone. Longer-term follow-up analysis of the study data, presented at scientific meetings, and contained in submissions by United Therapeutics Corporation to both European Medicines Agency and NICE, demonstrated that this difference narrowed over time. The conclusion from the NICE Appraisal of dinutixmab (Unituxin™) was that it conferred a survival advantage by curing a small number of additional children and extending the survival of others. The basic premise of this was not disputed by Solving Kids' Cancer in its appeal to NICE, the details of which can be found online here. Rather, one of the appeal points (upheld) was that the precise time-point selected by NICE upon which to base its health economic assessment was not appropriate, as too few children had been followed up for that length of time. As a consequence, survival estimates at these later time points were inherently unstable, and too uncertain to be used as a basis for making any decisions.

dinutuximab beta | ch14.18/CHO | APN311 | Qarziba™

Background

The anti-GD2 monoclonal antibody dinutuximab beta (trade name Qarziba™, formerly called Isqette) was originally developed by APEIRON Biologics as APN311 and subsequently sold to EUSA Pharma, a speciality pharmaceutical company based in Hemel Hempstead, UK.

European Marketing Authorisation

In May 2017 dinutuximab beta was granted European Medicines Agency (EMA) approval *under exceptional circumstances*. This means that information about the safety and efficacy of dinutuximab beta was deemed incomplete. Each year the EMA will receive an update from the company and review its decision as necessary. More details on the decision can be found online here.

NICE Appraisal

Dinutuximab beta was first referred to NICE in May 2016 (prior to EMA approval) as a Single Technology Appraisal. Due primarily to ownership changing from APEIRON Biologics to EUSA Pharma, the first Committee meeting was delayed until 23 November 2017. It was apparent, even at this initial meeting, that the attitude of both the Appraisal Committee and NICE team was more accommodating compared to the previous process involving United Therapeutics Corporation's antibody drug, dinutuximab (trade name Unituxin™). That appraisal, culminating in Solving Kids' Cancer undertaking a successful appeal against the decision not recommend dinutuximab for use on the NHS, had evidently informed NICE's approach to dinutuximab beta.

Patient Expert Nicholas Bird – a member of Solving Kids' Cancer's Board of Trustees and father of Adam who died of neuroblastoma in 2013, and Clinical Experts Dr Juliet Gray and Dr Martin Elliot, were able to use their knowledge (of antibody therapy) and prior experience of NICE to clarify points as required by the Committee. Patient and Clinical Experts also advocated strongly for anti-GD2 therapy to be made available on the NHS, given that it was already considered part of standard of care for the treatment of high-risk neuroblastoma, and was readily available elsewhere in Europe and in North America. However, despite this, the Committee concluded that there were too many unanswered questions to reach a decision and a follow-up meeting would be required.

In an STA it is the responsibility of the company to provide any and all evidence that it wishes NICE to take account of. This evidence submission is then scrutinized and critiqued by a so-called Evidence Review Group (ERG) or Decision Support Unit (DSU). The Appraisal Committee then weigh up the information provided by both the company and the ERG/DSU to reach what they believe to be the most plausible conclusions. During appraisal meetings themselves the company are only permitted to respond to questions from the Committee Chair. The role of Patient and Clinical Expert is therefore very important, as these individuals are allowed to speak freely whenever they wish to do so.

It was abundantly clear that had it not been for the UTC antibody appraisal, this first meeting in November would not have taken place. It was also apparent to those ever-present experts mentioned above that it was an indication on NICE's part of a willingness to move the process forward, and a desire to arrive at a solution that worked for all parties.

A second Committee meeting was convened on 11 April 2018. It had originally been hoped that this would take place sooner – in February, but NICE and EUSA were unable to exchange all of the necessary information in time so the meeting was delayed until April.

The second appraisal meeting followed a similar pattern to the first – NICE seemingly keener for a positive resolution than previously with UTC, but also demonstrably frustrated at some of the evidence being presented to them. There was a degree of complication and uncertainty introduced by the randomisation of dinutuximab beta ± IL2 in the SIOPEN clinical trial and the absence of a standard control arm. Much of the debate, therefore, hinged upon the appropriate historic control population against which to assess efficacy (and therefore cost-effectiveness); whether this should be a cohort of patients from the SIOPEN high-risk trial prior to the introduction of antibody therapy (Company preferred) or an adjusted indirect comparison using the isotretinoin-only arm of the Children's Oncology Group ANBL0032 study – the control arm of the UTC antibody appraised previously by NICE (Committee preferred). Further, the clinically preferred administration of dinutuximab beta is now via the so-called *Long-Term Infusion* (LTI) method i.e. over 10-days rather than 5. As yet there are no results using this method, as the trial only closed to recruitment around the turn of this year.

In drawing their conclusions, the NICE Committee determined that the most plausible *Incremental Cost Effectiveness Ratio* (ICER) was above the upper threshold at which they can recommend drugs for use on the NHS. It was also too far above the upper threshold for the drug to be automatically recommended for inclusion in the Cancer Drugs Fund. The CDF contains drugs that cannot yet be recommended outright, but that have the potential to be recommended following a period of additional data collection or once a longer-term follow-up analysis of existing data can be performed. However, for the CDF to come into play the ICER has to be close enough to the upper threshold that there is a realistic possibility of the drug becoming cost-effective with the passage of time. In the case of dinutuximab beta, the Committee felt that was not the case; they therefore issued a provisional decision not to recommend the drug for use on the NHS, nor for inclusion in the CDF.

It is clear from the Appraisal Consultation Document they issued that NICE remain keen for a positive solution that works for all stakeholders. It should be noted that this is not necessarily business as usual where NICE is concerned, as ordinarily the onus would be firmly on the Company to drive the process. This was certainly the case for UTC and dinutuximab.

The provisional guidance from NICE is effectively laced with a challenge to EUSA Pharma. Come back with evidence and a negotiating position that allows dinutuximab beta to be included in the CDF.

There now follows a consultation period during which consultees, commentators and members of the public can submit comments to NICE which will then be considered prior to the issuance of a Final Appraisal Determination (FAD). The consultation period ends on 29 May 2018. A final Committee meeting is scheduled for 12 June 2018, after which a final decision will be published.

For information on how to participate in the Appraisal consultation for dinutuximab beta follow this link to the NICE website.

Impact on high-risk neuroblastoma children in the UK

In the immediate aftermath of the provisional negative guidance from NICE there was fear amongst parents that antibody for children who had already begun treatment would no longer be supplied by EUSA Pharma for any remaining rounds. In response, the company issued a statement reassuring parents that any child who had already received at least the first round of dinutuximab beta would be able to complete the full course of treatment.

For any children who have not yet started antibody therapy, EUSA Pharma stated that the situation would remain as before; that clinicians should follow relevant procedures to request access via an Individual Funding Request (IFR), and in the event of it being declined the company would decide whether or not to supply antibody free-of-charge on a case-by-case basis.

It is understandable that considering the current uncertainty more families may now seek to launch fundraising campaigns for dinutuximab beta as insurance against (1) a negative Final Appraisal Determination by NICE, (2) non-availability via the Cancer Drugs Fund, (3) rejection of an NHS Individual Funding Request, and (4) refusal of EUSA Pharma to supply the drug for free.

The average cost of dinutuximab beta is around EUR 40,000 per cycle, subject to per patient variability relating to body surface area and the precise number of vials that are required. A decision on whether to allow dinutuximab beta to be administered on the NHS free-of-charge if the drug itself were purchased directly would likely be a matter for each individual treatment centre, or hospital trust. Hence, it may be necessary to also pay to have antibody therapy administered as a private non-NHS patient, which would clearly add to the overall cost.

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dinutuximab | ch14.18/SP2/0 | Unituxin™

Due to manufacturing supply issues dinutuximab (Unitixun™), manufactured by United Therapeutics Corporation (UTC) in the United States of America, is not available anywhere outside of North America. All commercialisation of this antibody in Europe has ceased. It is now considered highly unlikely that it will ever be approved or available for use in Europe, including the UK.

Travelling to North America for immunotherapy (dinutuximab + GM-CSF + IL2) would cost between USD 750,000 and USD 1,000,000, depending on the treating institution. This is much more expensive that when families were travelling to America (predominantly to Children's Hospital of Philadelphia) for antibody in 2009/2010, the reason being that dinutuximab itself was supplied free-of-charge back then as part of the ongoing clinical trial. Now it's FDA-approved it would have to be paid for in full.

hu3F8 | Naxitamab™

Humanized 3F8 (hu3F8), the anti-GD2 monoclonal antibody developed by researchers at Memorial Sloan Kettering Cancer Center (MSKCC) in New York is now commercially licensed by YmAbs Therapeutics, Inc (https://www.ymabs.com) under the trade name Naxitamab™.

For patients in first-remission with no evidence of disease Naxitamab™ is currently only available at MSKCC itself. There are ongoing clinical trials elsewhere, but these exclude patients in remission where antibody is given in a minimal residual disease or maintenance setting.

The cost to receive hu3F8 at MSK is approximately USD 250,000 for two cycles.

Commentary

Whilst the negative draft guidance issued by NICE is clearly deeply disappointing for everybody involved and will come as gravely disturbing and distressing news for parents of children who would ordinarily be expected to begin antibody therapy in the coming weeks and months, it is not altogether a surprise.

Compared to dinutuximab (Unituxin™) the data for dinutuximab beta (Qarziba™) is relatively immature – clinical trials only began recruiting patients in 2010. The scientific evidence is also weaker because it was not conducted as a randomised control trial. This is not a criticism, there were very good reasons – the results from the Yu study in America were seen to be so compelling that it was deemed unethical to deny half the children antibody and unacceptable to parents to randomise patients to antibody or no antibody. One can easily see that such a randomisation would have led to many more families fundraising and travelling abroad for antibodies.

The fact is, however, that in attempting to do right by children (and their families) back then, the design of the study has made gaining regulatory approval (EMA approval was granted under exceptional circumstances), and now reimbursement, more difficult. There is more subjectivity and therefore uncertainty over what is the best representative historic control data against which to assess the impact of dinutuximab beta on event-free and overall survival.

None of the complexities of developing effective treatments for rare orphan diseases, for children's cancers, for neuroblastoma, are given any consideration in the NICE methods guidance which governs how a Committee shall conduct Single Technology Appraisals. Limited economic potential hindering the development of new drugs. Children being treated with decades old drugs instead. Clinical research being predominantly the purview of academia, funded largely by charities. Small patient numbers necessitating large cooperative group trials conducted through many recruiting centres in multiple countries across continents, taking many years to enrol sufficient patients to answer clinically relevant questions in any kind of scientifically meaningful way. The impossibility of including all relevant inputs; devastation caused to family units, career prospects, mental health problems, marriage breakdowns, etc. etc. into the complex health economic modelling out of which pops the ICER, the *Incremental Cost Effectiveness Ratio*, the magic number upon which yes or no decisions are based. A number often extremely sensitive to relatively small changes in inputs.

Sadly, the longer NICE continues to use the Single Technology Appraisal method for evaluating drugs for children's cancers the more the institution itself risks becoming yet another barrier to progress that must be overcome. Ultimately, denying children access to the best available treatments because they are too expensive or not deemed cost-effective, when the overall budget impact to the NHS is tiny and there are no readily available alternatives, will deter the development of these new therapies and leave children stuck with nothing other than the old heavy-duty artillery of chemotherapy, radiotherapy and surgery. Toxic treatments that leave so many survivors of childhood cancer with lifelong health deficits and profound daily challenges. It must be that our children deserve more. Dinutuximab beta would cost the NHS around £6 million pounds per year. Against a total budget of around £16 billion pounds that the NHS in England currently spends on medicines every year.

There are therefore two issues running concurrently here, that overlap but that also need to be addressed separately.

1. There is a clear and immediate need for anti-GD2 therapy in the maintenance phase of treatment to be made available on the NHS. We would hope that NICE, NHS England, and EUSA Pharma come together to negotiate terms and conditions under which dinutuximab beta can be included in the Cancer Drugs Fund. This will enable children to access treatment and data to continue to be collected to support full NHS approval later on. It is the most expedient solution to the most immediately pressing problem.

2. The NICE Single Technology Appraisal method is not fit for purpose in determining the suitability of drugs developed for rare diseases in small patient populations for use on the NHS. There is an alternative mechanism called the Highly Specialised Technology (HST) guidance, however, it was not used for either dinutuximab or dinutuximab beta and as things stand today would not be used for future drugs developed to treat children's cancers either. This is because the criteria, as per paragraph 28 of the HST methods guide, are:

28. Topics evaluated through the HST programme will be formally referred to NICE by Ministers. HSTs are selected using the following criteria, **all** of which have to apply:

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS;
- The target patient group is distinct for clinical reasons;
- The condition is chronic and severely disabling;
- The technology is expected to be used exclusively in the context of a highly specialised service;
- The technology is likely to have a very high acquisition cost;
- The technology has the potential for life long use;
- The need for national commissioning of the technology is significant.

Chronic and severely disabling, rather than life-threatening and deadly. Has the potential for life-long use, rather than has the potential to cure after 6-months use. These two criteria exclude dinutuximab, dinutuximab beta, and any other drug that might be developed with the intent to cure children of cancer in the future, from being evaluated through the HST programme.

The upper ICER threshold for approving a drug via a Single Technology Appraisal is around £30,000 per QALY (*Quality-Adjusted Life Year)*. In basic terms using HST guidance, the upper ICER threshold is set higher at around £100,000 per QALY, and the total annual cost to the NHS must not exceed £20 million. Under such conditions dinutuximab beta would indeed be deemed a cost-effective use of NHS resources. As it is some children will die, and others have their lives cut short, if anti-GD2 antibody therapy ceases to be available in the UK on the NHS.

In 2015, Sir Andrew Dillon the Chief Executive of NICE said himself in an article for Channel 4,

"The HST guidance recognises the particular circumstances of these very rare conditions – the vulnerability of very small patient groups with limited treatment options, the nature and extent of the evidence, and the challenge for manufacturers in making a reasonable return on their investment because of the very small populations treated.

In evaluating these drugs, NICE takes into account a greater range of criteria about the benefits and costs of highly specialised technologies than is the case with its appraisals of mainstream drugs and treatments. We do this because applying our standard approach to treatments for very small groups of patients would result in us always recommending against their use. This would be unfair."

It is difficult to envisage, given Sir Andrew's comments, that drugs developed to treat children's cancers are excluded from the HST guidance … and yet they are … and will continue to be.

This too must change.