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Mr Andy McKeon
Vice Chair
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19 August 2016

Dear Mr McKeon

Re: Final Appraisal Determination for Dinutuximab for Treating High-Risk Neuroblastoma

We refer to your letter of 5 August 2016 setting out your initial views as to our grounds of appeal ("Scrutiny Letter"). Solving Kids' Cancer is pleased that you have accepted our ground 1(b) submission that NICE has exceeded its power as a valid appeal point. We will provide a detailed written submission on this point by Friday, 26 August 2016 as requested. However, we also would be grateful if you could review your initial position with respect to a number of our arguments that you indicated you are not minded to consider as valid appeal points. Specifically, we wish to elaborate on our ground 1.1(a) and ground 2.1 submissions concerning use of the Single Technology Appraisal ("STA") process and provide further evidence to support our ground 1.3(a) and 2.2 submissions relating to the use of a 10-year cure point. Our comments on these are set out in more detail below.

Ground 1(a) – NICE has failed to act fairly

1.1 Dinutuximab should have been appraised through the Highly Specialized Technologies Programme

We wish to clarify this ground 1.1 procedural unfairness point. The Scrutiny Letter states *"the critical point here to be that NICE is bound to consider a technology in accordance with the referral made by Ministers"* and suggests that NICE is somewhat detached from selecting the appraisal route to be used for a technology. We respectfully disagree with this view. NICE is responsible for drafting the Block Scoping Report ("BS Report"), which forms the basis for the Secretary of State for Health's formal referral of a technology to NICE. Significantly, the BS Report clearly sets out the appraisal process to be used for the technology.

The importance of the BS Report cannot be overstated, as it is NICE's summary of the Institute's consultation on the scope of an appraisal and scoping workshop discussions. The NICE Guide to the Processes of Technology Appraisal ("Processes Guide") reinforces the importance of the BS Report, indicating that it is the "information" that Ministers use to choose the appraisal route for a technology that they decide to refer:

> *"NICE submits a report to the Department of Health summarising the results of the consultation and scoping workshop discussions (known as the block scoping report). This information helps ministers to decide whether or not the technology should be formally referred to NICE for appraisal and whether it should be referred as an MTA or an STA."* (Paragraph 2.5.19)

The NICE Interim Process and Methods of the Highly Specialised Technologies Programme ("HST Methods Guide") confirms that the referral process for the HST Programme *"is similar to that of the current process for the selection of technology appraisals."* NICE therefore plays a key part in the referral process and is ultimately responsible for recommending the appropriate appraisal route for a technology.

The BS Report for dinutuximab clearly indicates that the product should be assessed *via* the STA procedure and not the Multiple Technology Appraisal ("MTA") or HST programme (*see* process section of BS Report). NICE appears to have reached this decision after considering whether dinutuximab should be appraised in a STA or MTA, following receipt of a consultation comment on the scope of the appraisal. The BS Report template, however, envisages that NICE also may recommend that a technology is assessed *via* the HST programme. However, at no point does NICE appear to have contemplated whether an appraisal through the HST programme was more appropriate than a STA.

NICE based its decision to evaluate dinutuximab in a STA in order to issue timely guidance. The BSR states:

> *"[g]iven the potential difference in timings of both products an MTA would mean guidance on dinutuximab would not be timely."* (main points from consultation)

Further, NICE's response to comments on the draft scope and provisional matrix states:

> *"NICE aims to issue guidance within 6 months after the technology receives its marketing authorisation. Therefore, in order to issue timely guidance, this topic has been referred as an STA."* (page 3)

Thus, the decisive factor for NICE selecting the STA process was time. However, the HST programme is designed to provide prompt guidance on emerging technologies. The HST Process Guide states that:

> *"draft recommendations .... are anticipated to be issued within approximately 3-4 months of confirmation from the European Commission that a marketing authorization has been granted."* (paragraph 21)

We submit that the appraisal process was unfair, as NICE based its decision to appraise dinutuximab in a STA on an immaterial fact - time - and as a result dinutuximab was appraised on standard STA methodologies, which were always likely to produce negative outcome. For the reasons set out in our appeal letter, we consider that dinutuximab should have been appraised through the HST programme.

In the alternative, we submit that NICE failed to take into account a material fact, that is, the availability and suitability of the HST programme for the appraisal of dinutuximab. The BS Report and the consultation on the draft scope only evidence that NICE considered the suitability of appraising dinutuximab in a STA and MTA. The Institute did not provide any

reasons why a STA was more appropriate for assessing dinutuximab than the HST programme.

In order for a consultation to be fair, it is incumbent on NICE to provide adequate reasons for its decisions. This is best characterised by the Sedley requirements from one of the leading cases in this area, which require among other things that a consultation *"must include sufficient reasons for particular proposals to allow those consulted to give intelligent consideration and an intelligent response."*[1] Consultees cannot properly respond if they do not know on what basis a proposal is being made. The Supreme Court recently endorsed the Sedley requirements and clarified that the degree of specificity with which a consultant body consults may be influenced by the characteristics of those consulted.[2] A greater level of specificity is required where the consultees are less familiar with the issues being consulted on. Further, consultant bodies have an obligation to briefly mention alternative options where it is necessary to allow consultees to provide an intelligent response.

We note that the consultation on the draft scope included the question:

> *"NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)"* (page 4)

NICE provided a link to the Institute's Processes Guide that only discusses the STA and MTA processes. Given the consultation group included patient and carer groups who are not familiar with the Institute's appraisal processes, we believe it was unfair for NICE not to mention the possibility of appraising dinutuximab through the HST programme. Further, NICE should have provided reasons for not selecting the HST programme given the importance of the appraisal route for orphan medicines.

NICE's failure to notify Solving Kids' Cancer and other consultees of the availability of the HST programme discriminates against dinutuximab and other technologies for rare conditions. We submit that had NICE explored, or at the minimum raised, the possibility with consultees, of using the HST programme, dinutuximab may not have been appraised on standard STA methodologies. The latter were always likely to produce negative outcome. NICE's failure to take into account the HST programme, and its choice of the STA process based on an irrelevant factor, make the appraisal process unfair and unreasonable.

1.3 The analysis of ANBL0032, and specifically the resultant use of a 10-year cure point, was inadequately explored

We maintain our position that the NICE Committee chose an interpretation of the data that is not supported by the international neuroblastoma research community, does not accord with standard practise in the case of rare paediatric cancers, was not used or referred to by either

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[1] *R v Brent London Borough Council, ex parte Gunning* (1985) 84 LGR 168 at 169.

[2] R (on the application of Moseley) v Haringey LBC [2014] UKSC 56; [2014] 1 WLR 3947 at 39 and 41.

the FDA or EMA, and about which there was no expert opinion or insight available to enter into meaningful dialogue with the ERG, or indeed the Committee itself.

The Scrutiny letter states *"[f]or this to be a valid appeal point there would need to be evidence from the research community that the Committee's analysis of the data and the adoption of the 10-year cure point was unreasonable, for example in the form of their own published paper."* It is impossible to address this issue in the form of a published paper, as there are no papers that specifically on this point. Rather the evidence lies in the body of the neuroblastoma literature; none of these independent publications use a 10-year time point, either to report survival rates or to design the study.

In response to your request for independent evidence from the scientific community, Dr Wendy B. London, lead statistician for the neuroblastoma committee of the Children's Oncology Group, study statistician for the ANBL0032 trial and Associate Professor of Paediatrics at Harvard Medical School provided the following authoritative statement on the use of the 10-year cure point:

> *"In the past 25 years of clinical trials conducted by the COG for high-risk neuroblastoma patients, there have been no trials that used the 10-year time point for study design or reporting of results (Table 1).*
>
> *The overall survival curve at the 10-year time point is statistically unstable. Due to the many deaths and censored observations prior to the 10-year time point, the sample size at 10-years is small. As a result, the point estimate at 10-years has a very wide confidence interval around it. It is inappropriate to use an estimate with such a wide confidence interval for decision making. Furthermore, if additional follow-up data for patients censored prior to the 10-year time point become available, then the curve at 10-years could improve dramatically.*
>
> *In summary, due to the very wide confidence intervals on the 10-year OS, which exist as a result of the very small number of patients at risk for an event at 10 years, there is too much uncertainty and variability in the 10-year time point for it to be used for decision making. In COG, we would never cite such an unstable time point in a manuscript or presentation."*[3]

Ground 2 – The recommendation is unreasonable in the light of the evidence submitted to NICE

2.1 Dinutuximab should have been appraised through the Highly Specialized Technologies Programme

For the reasons set out above in relation to Ground 1.1(a), NICE acted unreasonably in assessing dinutuximab in a STA. It was perverse and unreasonable for NICE to select and then proceed with the appraisal of dinutuximab in a STA without considering the HST programme. This is because the ICERs generated for orphan drugs are almost always outside the cost-effectiveness thresholds acceptable to NICE when running its standard technology appraisal processes. Thus, dinutuximab was likely to be "cost ineffective" as a matter of

[3] Table 1 referred to in Dr Wendy B. London's statement is attached to this letter.

default in a STA. It is unreasonable to follow a process which would inevitably result in a negative recommendation.

Finally, it was unreasonable for NICE to apply the STA process on the basis of its timeliness, when its own guidance indicates that the STA process aims to produce guidance within 6 months of marketing authorisation. The HST process is even faster, aiming to produce guidance within 3 or 4 months of approval.

2.2 It was unreasonable for the Institute to use of a 10-year cure point, given the evidence before it.

For the reasons set out above in relation to Ground 1.3(a), NICE acted unreasonably in selecting a 10-year cure point from the March 2014 data cut as the basis for effectiveness. NICE chose an interpretation of the data that is not supported by the research community, as evidenced by the statement provided by Dr Wendy B. London, the study statistician for the ANBL0032 trial and Associate Professor of Paediatrics at Harvard Medical School.

Next Steps

For the reasons stated above, Solving Kids' Cancer respectfully asks you to reconsider your initial views for the ground 1(a) and 2 points above.

We look forward to hearing from you in due course.

Yours sincerely

and

Chief Executive and Chair of Trustees, Solving Kids' Cancer

Table 1. COG high-risk neuroblastoma trials, 1991-2016

Study number	Clinical Trial Title	Design/reporting time point	Reference
CCG 3891	Conventional Dose Chemoradiotherapy vs Ablative Chemoradiotherapy With Autologous BMT for High-Risk Neuroblastoma	3-year	1
POG 9341/9342	Treatment of Patients >365 Days at Diagnosis with Stage IV and Stage IIB/III (N-myc) NBL - A Phase III Study	2-year	2
POG 9640	Treatment of Patients with High Risk Neuroblastoma (A Feasibility Pilot) Using Two Cycles of Marrow Ablative Chemotherapy Followed By Rescue With Peripheral Blood Stem Cells (PBSC), Radiation Therapy	2-year	3
A3973	A Randomized Study of Purged vs. Unpurged PBSC Transplant Following Dose Intensive Induction Therapy for High Risk NBL	2-year	4
ANBL0032	Phase III Randomized Study of Chimeric Antibody 14.18 (Ch14.18) in High Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue	3-year	5
ANBL00P1	A Pilot Study of Tandem High Dose Chemotherapy with Stem Cell Rescue Following Induction Therapy in Children with High Risk Neuroblastoma	1-year	6
ANBL0532	Phase III Randomized Trial of Single vs. Tandem Myeloablative Consolidation Therapy for High-Risk Neuroblastoma	3-year	7
ANBL0931	A Comprehensive Safety Trial of Chimeric Antibody 14.18 (ch14.18) with GM-CSF, IL-2 and Isotretinoin in High-Risk Neuroblastoma Patients Following Myeloablative Therapy	3-year	(too soon)
ANBL09P1	A COG Pilot Study of Intensive Induction Chemotherapy and 131I-MIBG Followed by Myeloablative Busulfan/Melphalan (Bu/Mel) for Newly Diagnosed High-Risk Neuroblastoma	1-year	(too soon)
ANBL12P1	Pilot Study Using Myeloablative Busulfan/Melphalan (BuMel) Consolidation Following Induction Chemotherapy for Patients with Newly Diagnosed High-Risk Neuroblastoma	3-year	(too soon)

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