**Mogamulizumab NICE Appeal**

On behalf of the professional bodies representing UK clinical experts in the field of Cutaneous T Cell Lymphoma and Sezary Syndrome, we wish to appeal the recent NICE decision concerning mogamulizumab.

The clinical community is unanimous in our feeling that the final appraisal document (FAD) issued by NICE demonstrates fundamental misunderstanding of the current picture regarding the efficacy of mogamulizumab in relation to Mycosis Fungoides and Sezary Syndrome and our appeal will address these issues

1. The FAD quotes “limitation in trial design” with particular reference to the fact that Vorinostat is not standard treatment in the UK. We recognise that Vorinostat does not have a licence in the UK. We do however strongly feel that Vorinostat is an entirely meaningful comparator in the MAVORIC trial. Standard of care quoted in the FAD refers to Bexarotene, interferon and methotrexate. However, the data assessing the efficacy of these agents is relatively small. The strongest available data relates to the phase II studies published for Bexarotene which demonstrates an ORR of 31 % (Duvic et al 2001). This compares with similar more recent studies published on Vorinostat with similar patient populations demonstrating an ORR of 24%. (Duvic et al 2007) It is also quite clear that although Vorinostat does not have a licence in the UK, the trial data demonstrating its efficacy is more recent and robust in terms of endpoints than historical data for other examples of standard of care such as interferon or methotrexate in this group of patients.
2. We also consider that the decision is inconsistent with previous NICE decisions. Specifically there are examples where drugs have been approved by NICE on the basis of clinical trials where the control arm was not “standard of care” ([https://www.nice.org.uk/guidance/ta171/documents/multiple-myeloma-lenalidomide-final-appraisal-determination3](https://jpn01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.nice.org.uk%2Fguidance%2Fta171%2Fdocuments%2Fmultiple-myeloma-lenalidomide-final-appraisal-determination3&data=04%7C01%7CLinda.McNamara%40kyowakirin.com%7C35d98b7d9dc24c34573808d8e8a8a8f1%7C34db9a5d91ba486ebb82d37d2ee1d84c%7C0%7C1%7C637515159258088834%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=O31AMDy0Y2R0fv1WdiWeSDJU5ObYixVlAeXXZkV5GfY%3D&reserved=0)). It is therefore incorrect for the results of the MAVORIC trial to be disregarded on the basis of an unlicensed control arm when this approach has not been consistently applied for other NICE oncology assessments.
3. In the FAD, the panel state that mogamulizumab does not meet the NICE criteria for being considered a life extending treatment at the end of life. We presume that the panel have made this statement because the MAVORIC trial was not designed to demonstrate an overall survival difference between the two treatments. The trial also included a cross-over which further impairs the ability of the trial to show a difference in survival. Firstly, we have grave concerns that NICE appear to be discriminating against cross-over designs. All clinical trials should be designed in the best interest of the participating patient. In the MAVORIC trial, patients were given the opportunity to receive the potential benefit of the trial drug irrespective of the arm they were randomised to. This is clearly in the best interest of the patient and it has a positive impact on the ability to accrue patients to the trial in the intended time interval. These are positive attributes for any clinical trial and should be encouraged and certainly not disincentivised.

In terms of consistency of NICE decisions, approvals have been made by NICE from trials in which the arms cross over (see below) and so again, approval should not be withheld on the basis of a cross over trial.

1. Prolongation of life is clearly an important aspect in the NICE approval process and the FAD indicates that there was no evidence to suggest that mogamulizumab could prolong life in this group of patients. We strongly disagree with this interpretation. We fully recognise that estimations on impact on survival in this setting are complex. However, we should not let the complexity distract us from identifying a prolongation of life, if in fact it exists. We have studied the data from MAVORIC in detail and have also studied the “Real World” data made available to the panel from the HES database. The HES data demonstrates that in this patient population the median survival is 17.83 months after at least one line of systemic therapy. If we compare this with the outcome for the cohort of patients in MAVORIC who were randomised to receive mogamulizumab, there is a stark difference. When the paper was published (Kim 2018) the analysis was performed after a data lock in December 2016. This constituted a median follow up of 17 months. The data has now been re-analysed with a second data lock in March 2019. This second analysis has occurred 27 months after the initial analysis. On this occasion, the median survival for the patients randomised to receive mogamulizumab is 57.2 months. Clearly this is not a randomised comparison but a difference of this magnitude gives a clear indication of what as clinicians, we are observing directly in our patients who we have treated with mogamulizumab. Specifically, mogamulizumab dramatically changes the course of disease in patients for whom, hitherto, we have had no effective treatment.
2. The most striking aspect for the efficacy of mogamulizumab relates to its mode of action. Throughout the field of oncology, we have recognised that the most aggressive tumours with the worst prognosis respond the least well to any given therapy. Until the appearance of mogamulizumab, this was the case for Sezary syndrome. This is a disease with a documented median survival of 32 months from diagnosis and for which, over the last 30 years, we have had no effective therapy in terms of survival or even disease control. Mogamulizumab targets the circulating malignant lymphocytes resulting in a rapid fall in the number of circulating cells as demonstrated in the MAVORIC study. A recent further analysis of the data from this study has revealed that the highest response rate was seen in patients with the highest number of circulating malignant T-cells (B2 disease). This data is about to be submitted for publication. Until the arrival of mogamulizumab, patients with B2 disease had the shortest survival and the poorest response to current therapies. Every clinician managing patients with Sezary Syndrome recognises that mogamulizumab is dramatic in its efficacy and is transforming the course of the disease in those patients fortunate enough to receive it.

MAVORIC is the largest randomised clinical trial ever performed in CTCL. It was designed with the interest of the participating patients at its centre. It was carefully conducted by centres all over the world and its medical importance was illustrated by its publication in the Lancet. Mogamulizumab has compelling clinical trial evidence to support its efficacy. The clear mode of action demonstrates why it is effective in Sezary Syndrome and the Real World clinical experience confirms these findings.

We have been looking after CTCL patients for over 30 years and during that time we have not encountered a drug with this impact on Sezary Syndrome.

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On behalf of the UK Cutaneous Lymphoma Group

Duvic M, Martin AG, Kim Y, et al. Worldwide Bexarotene Study Group Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001;137(5):581–593

Madeleine Duvic, Rakshandra Talpur, Xiao Ni, Chunlei Zhang, Parul Hazarika, Cecilia Kelly, Judy H. Chiao, John F. Reilly, Justin L. Ricker, Victoria M. Richon, Stanley R. Frankel; Phase 2 trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109 (1): 31–39. doi: <https://doi.org/10.1182/blood-2006-06-025999>

Examples of cross over trials which have led to approval by NICE:

1. <https://www.nice.org.uk/guidance/ta488/documents/final-appraisal-determination-document>

2. <https://www.nice.org.uk/guidance/ta432/documents/final-appraisal-determination-document>

3. <https://www.nice.org.uk/guidance/ta653/documents/final-appraisal-determination-document>

4. <https://www.nice.org.uk/guidance/ta357/documents/melanoma-unresectable-metastatic-pembrolizumab-after-ipilimumab-id760-final-appraisal-determination-document2>