All Wales Medical Genomics Laboratory
Institute of Medical Genetics
Heath Park
Cardiff CF14 4XW

Managing Director: Clive Morgan
Head of Genetic Laboratory: Sian Morgan, FRCPath

3rd July 2020

Dear Medical Director

Re: Phased introduction of NTRK gene fusion testing for patients with solid tumours in Wales

I am writing to advise you regarding genetic testing for the recently published NICE Technology Appraisal Final Appraisal Determination (FAD) for larotrectinib and entrectinib for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours. The FADs can be found at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10229 and https://www.nice.org.uk/guidance/gid-ta10414/documents/final-appraisal-determination-document

Larotrectinib and entrectinib are recommended for use in NTRK fusion-positive solid tumours if:

- the disease is locally advanced or metastatic or surgery could cause severe health problems and
- the patient has no satisfactory treatment and has already been treated with all available NHS-funded systemic therapy options for which clinical benefit has been established.

The introduction of TRK inhibitors into routine clinical at this current time poses several challenges:

1. The impact of the COVID-19 pandemic has resulted in the slowdown of developmental work to establish NTRK testing capability in the genetics laboratory. RNA-based next-generation sequencing (NGS) is anticipated to be available for clinical use in the autumn of 2020 following validation of the technique; until then, testing will be performed using fluorescence in situ hybridization (FISH).

2. There is neither a defined diagnostic pathway nor a standard treatment pathway in existence for NTRK gene fusion positive tumours. Clinical pathways and staff education are required to ensure equity of access for patients across Wales, regardless of the geographical region in which they reside. There is also limited clinical experience in the use of such histology-independent drugs.

The All Wales Genomics-Oncology Group (AWGOG) has determined that given the above challenges, a 'phased implementation' of NTRK gene fusion genetic testing within Wales is required for patients who meet the eligibility criteria for treatment with larotrectinib and entrectinib. AWGOG includes representatives from the AWMGS, oncologists based at each of the adult cancer centres in Wales and the regional paediatric oncology service at UHW, pharmacy and histopathology services, the Welsh Health Specialised Services Committee (WHSCC) and the All Wales Therapeutics and Toxicology Centre (AWTTC) and All Wales Medicines Strategy Group (AWMSG).

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GENOMIC TESTING FOR NTRK GENE FUSIONS

The All Wales Genomics Laboratory will provide phased testing for the NTRK gene fusions for the following patients. A result should be returned to you within 10 working days from the time of the sample being received at the laboratory.

Phase 1
It is proposed that the first short introductory phase will be available from **July 2020** for patients in the following groups:

- Tumours with a high prevalence of NTRK gene fusions (>90%)
  [infantile fibrosarcoma, congenital mesoblastic nephroma, mammary analogue secretary carcinoma (MASC) of salivary glands, secretory breast cancer]
- Tumours with a NTRK gene fusion prevalence rate of 5-25%
  [gastrointestinal stromal tumours (GISTs), thyroid cancers, spitzoid neoplasms]
- Children aged 0-16 years with any solid tumour
- Teenagers aged 16-18 years with any solid tumour
- Young adults 18-25 years with any solid tumour

Phase 2
Phase 2 will commence in **October 2020** and will be extended to patients with more common cancer types which have a NTRK gene fusion prevalence rate of 2-5%

- Lung cancer
- Intrahepatic cholangiocarcinoma
- Brain cancers

Phase 3
By **January 2021**, access to NTRK gene fusion testing will be extended to all other patients with a diagnosis of any solid tumour type not cited in phases 1 and 2 (NTRK gene fusion prevalence rate of approximately <2%).

Sample Requirements:

NTRK gene fusion referral forms by FISH can be downloaded from the AWGL website: http://www.wales.nhs.uk/sites3/page.cfm?orgid=525&pid=19419. The request for NTRK gene fusion testing should be made directly to the pathology laboratory which stores the diagnostic histopathological specimen.

The histopathology laboratory should use the genetics Test Request Form and send the following:-
In phase 1: 6x 3-4 µm sections (singly mounted) on charged/adhesion slides for FISH testing
In phase 2 and 3: 5 x 10µM air dried unstained sections mounted on slides for the RNA-based NHS panel testing. SLIDES should be sent directly to the All Wales Genomic Laboratory.

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CLINICAL PATHWAY FOR NTRK FUSION TESTING

AWGOG is currently drafting a clinical guideline document detailing the NTRK fusion testing pathway, indications for treatment with TRK inhibitors and baseline and on-treatment monitoring requirements. The attached algorithm is a summary of this and the full guideline will be forwarded in due course.

Any queries about NTRK gene fusion service should be directed to:
Genetics Laboratory: Rhian White Rhian.White@wales.nhs.uk
South East (adults): Samantha Jane Cox (Velindre - Consultant) Samantha.Cox@wales.nhs.uk
Regional; South, Mid and West (children): Madeleine Adams (Cardiff and Vale UHB - Paediatric Oncology) Madeleine.Adams@wales.nhs.uk
South West: Mark Davies (Swansea Bay UHB - Oncology) Mark.Davies44@wales.nhs.uk
North: Pasquale Innominato (BCUHB - Cancer Services) Pasquale.Innominato@wales.nhs.uk

Please do not hesitate to see me should you wish to discuss this matter further.

Best wishes,

Sian M Morgan FRCPath
Consultant Clinical Scientist / Head of Laboratory
All Wales Genomics Labortaory