One Wales Medicine Assessment Group summary of decision rationale

Medicine: **Dabrafenib and trametinib**
Indication: **Treatment of inoperable BRAF V600E variant anaplastic thyroid cancer**
Meeting date: **18 March 2024**

Criteria	OWMAG opinion
Clinical effectiveness and safety	OWMAG note that the main clinical effectiveness evidence for the use of dabrafenib plus trametinib to treat BRAF V600E variant anaplastic thyroid cancer (ATC) is from the open-label ROAR phase II study. This study demonstrated clinical benefit of dabrafenib and trametinib treatment in the advanced/metastatic ATC population. An updated analysis of results after 4 years showed an investigator-assessed overall response rate of 56% in 36 patients which included 3 complete responses and 17 partial responses; an additional 11 patients had stable disease. Median progression-free survival (PFS) was 6.7 months and median overall survival (OS) was 14.5 months. OWMAG notes that the published median OS for patients with unresectable ATC receiving supportive care only is 2 months. OWMAG also note that in Wales, the main comparator is palliative chemotherapy with carboplatin and paclitaxel and that the published overall response rate and median PFS are 16% and 3.1 months for this treatment. OWMAG acknowledge, however, that patient numbers in the ROAR study were small, thus increasing the uncertainty in the results and the lack of a comparator study makes it hard to assess relative effectiveness compared to other treatments. Real world evidence for 4 retrospective reviews was also considered and OWMAG note reports of complete and partial responses to treatment with dabrafenib and trametinib, in some cases allowing for resection of the tumour. However, OWMAG acknowledge these studies were of small numbers of patients and had different criteria for including patients. OWMAG note that no new safety signals have been observed for the use of dabrafenib and trametinib to treat ATC. OWMAG consider that the evidence provided demonstrates clinical effectiveness for using dabrafenib and trametinib to treat BRAF V600E variant anaplastic

	thyroid cancer for those patients unsuitable for surgical resection. Therefore, OWMAG consider that there is sufficient clinical effectiveness evidence to support the use of off-label dabrafenib and trametinib to treat inoperable BRAF V600E variant anaplastic thyroid cancer.
Cost-effectiveness	There is no published cost-effectiveness evidence available for dabrafenib and trametinib for this indication. In the absence of any cost effectiveness analyses OWMAG considered the clinical effectiveness, quality of life (QoL) and safety data to help inform a more general value for the intervention. OWMAG note from both published evidence and from submissions received from two patient organisations that the rapid growth of the neck tumour and the impact of this on speech, swallowing and breathing plus the associated pain have a significant impact on day-to-day QoL. OWMAG note the evidence from real-world studies where the resection of the tumour can improve the QoL in patients with ATC. OWMAG acknowledge that the reduction in tumour size in response to treatment with dabrafenib plus trametinib, which may enable resection in some cases, may offer health gains to this patient cohort. A cost comparison assessment was undertaken in the meeting. OWMAG consider that treatment with dabrafenib and trametinib is likely to be both more effective and more costly than standard treatment with chemotherapy and therefore, this treatment combination is likely to sit in the right-hand upper quadrant of the cost effectiveness plane. OWMAG acknowledge that ATC is a very rare disease with an incidence of 1-2 cases per million each year and that all Wales pathology data indicate that 5-10 cases of ATC are diagnosed each year in Wales. OWMAG also acknowledge that the disease significantly shortens life and severely impairs quality of life and, once inoperable there are no satisfactory treatment options. On consideration of these factors OWMAG consider it is likely that dabrafenib plus trametinib would be considered cost effective when compared to chemotherapy.
Budget impact	OWMAG consider the clinical estimate of patient numbers reported to be reasonable. The group acknowledge that whilst a net budget impact range has been calculated accounting for displacement of the most common

	comparator treatment given in Wales which is palliative chemotherapy, the estimated annual medicine acquisition costs of dabrafenib plus trametinib are likely to be a better reflection of budget impact. This is because clinicians state that in practice, many patients with unresectable ATC are not fit enough or opt not to have palliative treatment and, of those that do, most can only tolerate 1–2 cycles of chemotherapy. The group note that additional monitoring and adverse event costs have not been included in the budget impact indicating that resource costs may be higher. OWMAG note that the genetic testing of biopsy samples for the BRAF variant is a prerequisite for treatment of ATC with dabrafenib plus trametinib and that this is not included in the BI calculations as this service is provided as standard by the All Wales Medical Genomics Service. OWMAG consider that the base case ranges (between [commercial in confidence text removed] per year for 2-5 patients) provided in the report are reasonable estimates of the associated cost to NHS Wales. This range takes in to consideration no use of chemotherapy and the full 6 cycles of chemotherapy. The rationale for including both ranges is that some patients are either too poorly to receive chemotherapy, decline treatment with chemotherapy or have only 1-2 cycles of chemotherapy. Based on the costs provided, OWMAG consider the budget impact to be reasonable value for money for NHS Wales.
Other factors	OWMAG acknowledge that patients with inoperable BRAF variant ATC have limited treatment options and usually receive supportive care. OWMAG note the patient perspectives as outlined in the submissions received from the British Thyroid Foundation and the Thyroid Cancer Support Group Wales and acknowledge the fast-growing and aggressive nature of ATC and that the associated symptoms are physically challenging, painful and distressing and significantly affect quality of life. OWMAG note that the combination of dabrafenib and trametinib is routinely commissioned by NHS England to treat inoperable BRAF variant ATC and is also supported for use in NHS Scotland for this patient cohort. OWMAG also note that the European Society of Clinical Oncology (ESMO) and American Thyroid Association (ATA) both recommend using the combination of dabrafenib and trametinib to treat locally advanced or metastatic unresectable ATC if the BRAF V600E variant is present.

	OWMAG acknowledge that there may be additional resource use associated with this treatment in terms of testing, monitoring and the potential for surgical intervention.
Final recommendation	OWMAG recommend the use of dabrafenib and trametinib as an off-label treatment of inoperable BRAF V600E variant anaplastic thyroid cancer. This recommendation is subject to the development of appropriate start/stop criteria.
Summary of rationale	There is some clinical evidence to support the use of dabrafenib and trametinib as an off-label treatment of inoperable BRAF V600E variant anaplastic thyroid cancer. OWMAG are of the opinion that, the use of dabrafenib and trametinib treatment offers this patient cohort increased survival and consider the associated cost to be a reasonable use of NHS resources. Real world data will be captured to assess the benefit of this treatment for this cohort of patients.