One Wales Medicine Assessment Group summary of decision rationale

Medicine: **infliximab**
Indication: **treatment of grade 3–4 steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy (OW31)**
Meeting date: **11 August 2025**

Criteria	OWMAG opinion
Clinical effectiveness and safety	OWMAG note that there is limited clinical evidence available for infliximab for the treatment of grade 3–4 steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy and that no randomised controlled trials or comparative studies were identified. Evidence comes from systematic reviews, retrospective case series and case reports plus some real-world outcomes for [confidential information removed] patients with this condition treated with infliximab in NHS Wales. OWMAG acknowledge the paucity of data to inform comparisons between different second-line immunosuppressive therapy options for this indication. Taking the evidence as a whole, OWMAG note that just over half of patients (where an outcome was reported) showed a clinical response to infliximab, just over a quarter required additional immunosuppressants after infliximab and just under a quarter had no improvement in their myocarditis symptoms after treatment with infliximab. OWMAG note the limitations of the evidence and acknowledge that case reports are generally the lowest grade of evidence as they may be subject to selection bias, are difficult to compare, involve small patient numbers, differ in the amount of clinical information given and the outcomes reported, and so may not be generalisable to patients with this condition in Wales. They note that many of the case reports were for patients with multiple ICI-induced toxicities, which may have affected clinical outcomes, that many patients were treated with multiple immunosuppressive agents in addition to steroids making the relative benefit of infliximab difficult to ascertain, and that in some cases infliximab was given in circumstances not reflective of clinical practice in Wales. OWMAG acknowledge that published clinical guidelines, which mainly considered the same published clinical evidence, differ in their recommended second-line options, none of which are licensed for this indication in the UK. OWMAG note that all guideline recommendations on treatment options are based on low-quality evidence, mainly derived from clinical expert opinion and that clinical opinion can also be informed by preference and experience of using specific treatments.

	OWMAG note the evidence provided by clinical experts, both in the evidence summary report (ESR) and at the meeting, who report that patients who do not respond to intravenous corticosteroid treatment within 1–3 days require prompt and effective treatment with an additional immunosuppressant to prevent further deterioration. Current treatment options used in NHS Wales include mycophenolate mofetil (MMF) and tacrolimus. However, MMF takes a couple of weeks to have a clinical effect and tacrolimus requires extensive monitoring during dose titration, which is resource intensive and turnaround times may be up to a few days. Clinicians in Wales report they have experience and familiarity with using infliximab for myocarditis and some other ICI-induced toxicities and have had experienced positive clinical outcomes for the treatment of myocarditis with infliximab. Infliximab is fast-acting and does not require additional monitoring. OWMAG note that currently clinicians have to request infliximab on an individual patient basis through local processes which takes time and clinical resource; this can cause delay in initiating treatment and can be detrimental to patient outcomes as patients with this condition can deteriorate rapidly and prompt appropriate treatment is essential. Routine all-Wales access to infliximab will help standardise the treatment pathway in Wales, ensure equity and avoid delay in treatment which may lead to better patient outcomes. OWMAG note that all-Wales guidelines are currently in development by the National Immunotherapy Toxicity Sub-Group on the management of ICI-induced toxicities including myocarditis. OWMAG note that infliximab is contra-indicated in patients with moderate or severe heart failure (NYHA class III/IV) and that one small case series reported that patients who received infliximab for ICI-induced myocarditis were more likely to die from cardiovascular causes than other causes. However, OWMAG also note that another case series reported that none of the 23 patients who received infliximab for ICI-induced myocarditis developed worsening heart failure after infliximab administration in comparison to patients who did not receive infliximab. OWMAG acknowledge that the National Immunotherapy Toxicity Sub-Group advises that tocilizumab will be used in preference to infliximab for patients with an LVEF of below 40% (which may be indicative of heart failure). The clinical expert in attendance also stated that further doses of infliximab would not be given to patients who had not responded to the first dose of infliximab, in line with criteria set out in the starting and stopping criteria accompanying any recommendation for use. Taking into account the limited evidence available, the views of clinical experts and the safety considerations

	highlighted, OWMAG consider infliximab demonstrates some clinical effectiveness as a treatment option for this indication and that the benefits of its use outweigh the risks.
Cost-effectiveness	OWMAG note that no comparative cost-effectiveness evidence was identified for this use of infliximab, and in the absence of any comparative studies of infliximab for this indication, no cost effectiveness analyses were undertaken by AWTTC. OWMAG consider that the likely costs associated with using infliximab for this indication would be reasonable in considering the potential benefit gained from this intervention.
Budget impact	OWMAG consider the clinical estimate of patient numbers reported to be reasonable. However, the Group note the statement from the clinical expert that identification of myocarditis in affected patients is increasing and that use of ICI-treatments are likely to increase in future years, treatment-related toxicities including myocarditis are also likely to increase. Therefore, patient numbers may be expected to rise with an accompanying increase in budget impact. OWMAG note additional screening, monitoring and adverse event costs are excluded from the budget impact calculations both for infliximab and for comparator treatments. In particular, monitoring costs for tacrolimus titration may be considerable and the longer onset time for MMF to show clinical effect may mean patients remain in hospital for longer at significant cost. Clinicians indicate the faster clinical response time of infliximab mean patients can return home sooner and receive subsequent doses at home or as an outpatient. Based on outcome data provided by clinicians in Wales for patients treated with infliximab for grade 3–4 steroid-refractory myocarditis, OWMAG note that the degree of displacement of the comparator treatments, MMF and tacrolimus, is difficult to estimate at present. However, acquisition costs of both are low and so the impact of their displacement on the overall budget impact would be expected to be modest. Also, from the outcome data provided, OWMAG note that it's likely not all patients will receive three doses of infliximab; therefore the budget impact may be overestimated. OWMAG also acknowledge that the lack of comparative data between treatments means that any additional benefit from infliximab cannot be quantified and taken into account in budget impact calculations.

	OWMAG consider that the base case provided in the report is a reasonable estimate of the associated cost to NHS Wales.
Resource use	OWMAG note that infliximab is given by intravenous infusion in a healthcare setting whereas some comparator treatments are taken orally. However, due to the severity of the condition and the need for cardiac monitoring, patients with grade 3–4 ICI-induced myocarditis are likely to initially be hospital in-patients and so the addition of the first dose of infliximab to the treatment pathway is likely to have a low additional impact. It is expected that subsequent doses can be administered at home or as an outpatient. As previously mentioned, the use of infliximab may shorten hospital stay in comparison to patients receiving MMF. Infliximab does not need additional monitoring, in contrast to tacrolimus which requires blood trough concentration monitoring during dose titration.
Other factors	OWMAG acknowledges that myocarditis is a rare but a serious complication of ICI therapy. Myocarditis is potentially fatal and early assessment and intervention are key as patients with this condition can deteriorate rapidly. Whilst patients will generally accept significant toxicities in order to live longer, effective and early interventions are needed to improve patient quality of life and outcomes. OWMAG recognises that a standardised NHS Wales treatment pathway for myocarditis unresponsive to steroids will ensure that appropriate and swift second-line immunosuppression treatment can be given which will help avoid unnecessary long-term complications or death. Making infliximab routinely available for this group of patients will avoid potential delays in getting access, freeing up clinician time and enabling prompt and equitable access for patients across Wales. There are no licensed alternative treatment options routinely available.
Final recommendation	OWMAG recommend the use of infliximab for the treatment of grade 3–4 steroid-refractory myocarditis induced by immune checkpoint inhibitor (ICI) therapy. This recommendation is subject to the development of appropriate start/stop criteria.
Summary of rationale	There is some limited evidence to support the use of infliximab as a clinically effective option for the treatment of ICI induced grade 3-4 myocarditis, where symptoms have not responded to first-line immunosuppression with corticosteroids. There are no licensed alternative treatment options and some international guidelines recommend the

	use of infliximab for this indication. Clinicians in Wales also report positive outcomes for its use in the treatment of ICI-induced myocarditis that has not responded to first-line treatment with steroids. Allowing routine access to infliximab will help standardise the treatment pathway in Wales and may enable earlier initiation of treatment resulting in improved patient outcomes. Due to the known cardiovascular side effects associated with infliximab, clinicians in Wales propose using it only in patients who have a left ventricular ejection fraction (LVEF) of 40% or above. The review after 12 months will provide the number of patients who have received this treatment in Wales and more evidence on whether this is an effective treatment for this patient population.