AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence Status Report: nivolumab plus ipilimumab (OPDIVO® plus YERVOY®) for the neoadjuvant treatment of patients with resectable macroscopic stage III melanoma with ≥1 pathologically proven lymph node metastasis and up to 3 in-transit metastases **(OW35)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
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Key findings

Licence status
Nivolumab plus ipilimumab (OPDIVO® plus YERVOY®) is not licensed for neoadjuvant treatment of patients with resectable macroscopic stage III melanoma with ≥ 1 pathologically proven lymph node metastasis and up to 3 in-transit metastases; its use for this indication is off-label.

Clinical evidence
The clinical evidence supporting this treatment is primarily provided by the NADINA study (Blank et al. 2024), where 59% of patients treated with neoadjuvant therapy had a major pathological response, with an estimated 12-month recurrence-free survival and event-free survival of 95% and 84%, respectively. The adjuvant treatment arm of this study is considered comparable to current standard of care in Wales, therefore the evidence is considered generalisable.

Safety
No new safety signals have emerged for nivolumab plus ipilimumab for this indication.

Patient factors
Response rates did not differ significantly between BRAF V600 positive and wild-type patient subgroups. A major pathological response was achieved in 59% of patients and adjuvant therapy was not required, highlighting the potential treatment-sparing effect of this neoadjuvant therapy.

Cost effectiveness
No cost-effectiveness evidence was identified for this use of nivolumab plus ipilimumab, and no cost-effectiveness analyses have been undertaken for this indication.

Budget impact
The addition of neoadjuvant nivolumab plus ipilimumab is estimated to decrease the spend associated with this patient group in Wales by [commercial in confidence text removed] per year. This is based on an estimated uptake of 41 patients receiving treatment per year and assumes full displacement of comparator adjuvant treatment.

Impact on health and social care services
As patients achieving a major pathological response would not require adjuvant therapy, the number of outpatient clinic appointments would reduce. A baseline electrocardiogram, an additional computerised tomography (CT) scan prior to surgery, and additional pathology reporting post-surgery would be required for patients receiving neoadjuvant treatment.

Innovation and/or advantages
There are currently no UK-licensed neoadjuvant treatment options for this indication. The treatment is likely to reduce the treatment burden for patients, particularly for those achieving a major pathological response. A lower treatment burden benefits both the patient, and NHS Wales due to lower medicine acquisition, medicine administration, and healthcare resource costs.

Background

Melanoma is a type of skin cancer arising from melanocytes within the skin. In stage III melanoma, melanoma cells have spread into the skin, lymph vessels, or lymph glands[1]. In-transit metastases are melanoma cells that have spread more than 2 cm from the primary melanoma but not as far as the nearest lymph node[1].

The current treatment pathway for resectable macroscopic stage III melanoma in Wales is resection surgery, followed by adjuvant immunotherapy. The NHS Wales Cancer Network Immunotherapy Group (from here, the Group) identified an unmet clinical need for a neoadjuvant treatment option in NHS Wales, which would be treatment sparing for some patients. Therefore, neoadjuvant treatment with nivolumab plus ipilimumab was considered suitable for assessment though the One Wales medicines process.

Target group

The indication under consideration is resectable macroscopic stage III melanoma with ≥ 1 pathologically proven lymph node metastasis and up to 3 in-transit metastases in adults.

Marketing authorisation date: Not applicable, off-label

Nivolumab plus ipilimumab (OPDIVO® plus YERVOY®) is not licensed for the indication under consideration.

[Commercial in confidence text removed].

Dosing information

The neoadjuvant regimen proposed by the Group is 240 mg of nivolumab plus 80 mg of ipilimumab administered by intravenous infusion every three weeks for a total of

two cycles prior to surgery. For patients who achieve a complete/major pathological response, no further treatment is indicated after surgery. For patients who achieve a partial or non-pathological response, adjuvant treatment is indicated and is determined by the tumour's BRAF status.

For patients harbouring a BRAF wild-type tumour, the Group propose adjuvant treatment with 480 mg of nivolumab administered intravenously, or 1,200 mg of nivolumab administered sub-cutaneously, every 4 weeks for 11 cycles. For patients harbouring a BRAF V600 mutation-positive melanoma, adjuvant treatment with 150 mg of oral dabrafenib twice daily, plus 2 mg of oral trametinib once daily, for 46 weeks is proposed by the Group.

Both the neoadjuvant and adjuvant regimens are derived from the pivotal NADINA study[2]. The adjuvant treatment regimens' doses are consistent with their respective marketing authorisations[3-6].

Clinical background

Patients with malignant melanoma harbour either a BRAF V600 mutation-positive, or BRAF mutation wild type tumour. According to an NHS Wales clinician, 40% of the Welsh population harbour the BRAF V600 mutation. The tumour's BRAF mutation status is an important consideration in stage III melanoma, as it influences the adjuvant treatment options offered to patients.

General symptoms of advanced melanoma include weight loss, loss of appetite, and fatigue[7]. The five-year unstandardised net survival for stage III melanoma of the skin diagnoses in Wales between 2017-2021 was 77.7% (for people aged 15–99 years old)[8].

Nivolumab and ipilimumab are both immune checkpoint inhibitor (ICI) immunotherapies which are licensed to treat a range of different cancers, including melanoma[3,9]. The existing marketing authorisations are distinct from the indication under consideration.

ICI immunotherapy acts to enable T-cells to kill cancer cells. Nivolumab potentiates the anti-tumour response of T-cells by binding to the programmed death-1 (PD-1) protein. Ipilimumab binds to cytotoxic T lymphocyte antigen-4 (CTLA-4) which augments and prolongs the T-cell immune response[3,9].

Incidence/prevalence

Overall, the incidence of stage III melanoma gradually increased in Wales between 2011 and 2022[8]. In 2022, there were 1,170 new cases of melanoma of the skin recorded, of which 82 were stage III melanoma at diagnosis[8].

The Group estimate that 51 patients would be eligible for treatment with neoadjuvant nivolumab plus ipilimumab per year, and a treatment uptake of 80% (41 patients per year).

Current treatment options and relevant guidance

There are currently no UK-licensed treatment options for the neoadjuvant treatment of resectable stage III melanoma. The National Institute for Health and Care Excellence (NICE) recommends surgery followed by adjuvant treatment with nivolumab or pembrolizumab, or dabrafenib plus trametinib for BRAF mutation-positive patients[10].

Currently, treatment for resectable stage III melanoma in NHS Wales is surgery, followed by adjuvant therapy with either intravenous (IV) or sub-cutaneous (SC) nivolumab, IV pembrolizumab, or oral dabrafenib plus trametinib. Details of the regimens and the proportion of patients estimated to receive each regimen are outlined in Appendix 3.

In Scotland, the National Cancer Medicines Advisory Group (NCMAG) support the off-label use of nivolumab in combination with ipilimumab for the neoadjuvant treatment of resectable stage III melanoma[11]. In England, the use of off-label neoadjuvant plus adjuvant pembrolizumab treatment for patients with resectable stage III melanoma is under review[12]. In Wales, the Group consider the assessment of neoadjuvant nivolumab plus ipilimumab a higher priority than the pembrolizumab regimen, due to its potential to mitigate the need for adjuvant treatment in a large cohort of patients.

From an international standpoint, the European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO), The National Comprehensive Cancer Network® (NCCN), and the European Association of Dermato-Oncology (EADO) recommend both neoadjuvant treatment (followed by adjuvant treatment where required) and resection followed by adjuvant treatment for patients with resectable stage III melanoma[13-16]. The choice of neoadjuvant treatment varies between the international guidelines, but the two main options are either neoadjuvant treatment with nivolumab plus ipilimumab followed by adjuvant therapy post-surgery based on pathological response and BRAF V600 mutation status, or neoadjuvant plus adjuvant treatment post-surgery with pembrolizumab.

Summary of evidence on clinical effectiveness

The All Wales Therapeutics and Toxicology Centre (AWTTC) conducted a literature search during November 2025 to identify evidence concerning the use of nivolumab plus ipilimumab as neoadjuvant treatment for patients with resectable macroscopic stage III melanoma with ≥ 1 pathologically proven lymph node metastasis and up to 3 in-transit metastases.

Searches were performed using the Cochrane library, Central Register of Controlled Trials, EMBASE, MEDLINE and TRIP databases with the following search terms: nivolumab, OPDIVO, ipilimumab, YERVOY, melanoma, neoadjuvant therapy and resect(able). The primary outcomes were pathological response rate, overall survival, progression free survival, event free survival, overall response rate, adverse events/events, quality of life, and resource use.

A literature search identified 313 records which were assessed for eligibility, with 309 excluded following removal of duplicates and screening of title and abstracts. Following eligibility screening, 4 publications were included in the report. These

include the OpACIN study (with one 47-month follow-up study and the PRADO extension cohort) and the NADINA study (Blank et al. 2024)[2,17-19]. Any remaining records were excluded due to unsuitable study designs, small patient numbers, unclear outcome data or conference abstracts.

Of the included studies, the randomised controlled trial by Blank et al. 2024 was deemed the most relevant source of evidence pertinent to the indication in this report and was included in the main analysis. The remaining supporting studies supplement the findings of the NADINA study and are summarised in Appendix 2.

Efficacy

Blank et al. 2024 (NADINA Trial, NCT04949113) conducted a phase III, multicentred, open-label, controlled trial to compare neoadjuvant with adjuvant immunotherapy[2]. The neoadjuvant group comprised of 212 patients (median age of 60 years; range 22-84). The adjuvant group comprised of 211 patients (median age of 59 years; range 19-87). Baseline characteristics were balanced between the groups.

The neoadjuvant group received nivolumab 240 mg intravenously (IV) plus ipilimumab 80 mg IV every 3 weeks for 2 cycles, followed by surgery. Patients achieving a major pathological response did not receive adjuvant treatment. Patients achieving a partial or non-pathological response received adjuvant nivolumab 480 mg IV every 4 weeks for 11 cycles (BRAF wild-type) or adjuvant oral dabrafenib 150 mg twice daily plus trametinib 2 mg once daily for 46 weeks (BRAF V600 mutation-positive). The adjuvant group underwent surgery and received adjuvant treatment with nivolumab IV 480 mg every 4 weeks for 12 cycles, starting between week 6 and 12 (regardless of BRAF status).

The primary outcome was event-free survival (EFS): the time from randomisation to the occurrence of progression to unresectable melanoma before surgery, disease recurrence, or death due to melanoma or treatment. Results are given in Table 1.

At the time of data cutoff, the median duration of follow up was 10.6 months (interquartile range [IQR] 5.2 to 16.8) in the neoadjuvant group and 9.9 months (IQR 4.6 to 16.8) in the adjuvant group.

Table 1. Primary outcome from the NADINA study

	Neoadjuvant group (n = 212)	Adjuvant group (n = 211)
Number of events	28	72
Estimated 12-month EFS	83.7% (99.9% CI, 73.8 to 94.8)	57.2% (99.9% CI, 45.1 to 72.7)
Adjusted difference in restricted mean survival time	8.00 months (99.9% CI, 4.94 to 11.05; p < 0.001)	
Hazard ratio for progression, recurrence, or death	0.32; (99.9% CI, 0.15 to 0.66)	
EFS: event-free survival; CI: confidence interval		

The secondary outcomes were overall survival (OS), recurrence-free survival (RFS), distant metastasis–free survival (DMFS), pathological response, safety measures, and measures of health-related quality of life (HRQoL). Follow-up is ongoing for the

assessment of long-term EFS and DMFS, HRQoL, and OS, and outcomes have not yet been published in a peer-reviewed journal.

The pathological response rates and estimated 12-month RFS rates reported for the neoadjuvant group are outlined in Table 2. The assessment of pathological response was conducted according to the International Neoadjuvant Melanoma Consortium criteria by the local pathologist, followed by retrospective central review. A major pathological response (≤ 10% residual viable tumour) was achieved by 59% of patients with 47.2% achieving a pathological complete response (0% residual viable tumour) and 11.8% a pathological near-complete response.

Table 2. Pathological response rates to neoadjuvant arm reported in the NADINA study

Pathological response	Proportion of patients	Estimated 12-month recurrence free survival according to response
Major*	125 (59%)	95.1% (99.9% CI, 87.4 to 99.9)
Partial†	17 (8%)	76.1% (99.9% CI, 44.4 to 99.9)
Non-response§	56 (26.4%)	57.0% (99.9% CI, 33.3 to 97.6)
*≤ 10% residual viable tumour †11 to 50% residual viable tumour §>50% residual viable tumour		

Progression was reported in 2.4% of patients, and surgery was omitted or not yet performed in the remaining 4.2%.

BRAF mutation status did not appear to markedly influence EFS or pathological response. The estimated 12-month EFS was 83.5% (99.9% CI, 70.3 to 99.2) and 83.9% (99.9% CI, 70.1 to 99.9) in patients with a BRAF V600 mutation and BRAF wild-type melanoma, respectively. A major pathological response was achieved by 53.8% and 65.3% of patients with a BRAF V600 mutation and BRAF wild-type melanoma, respectively.

Safety

In the NADINA study, systemic treatment-related adverse events (AE) of grade 3 or higher occurred in 29.7% of patients in the neoadjuvant group compared to 14.7% of patients in the adjuvant group[2]. As 23.1% of patients in the neoadjuvant group experienced a systemic treatment-related AE of grade 3 or higher within the first 12 weeks, the AE was attributed to neoadjuvant treatment. Serious adverse events were reported in 36.3% of the neoadjuvant group compared to 24% of the adjuvant group[2].

Endocrinopathies related to systemic treatment occurred in 30.7% of the neoadjuvant group and in 9.9% the adjuvant group (all grades of AE). At the time of data cutoff, the events were ongoing in 25% of the neoadjuvant group and 7.5% of the adjuvant group. The most frequent ongoing events were hypothyroidism (in 11.3% and 6.5%, respectively) and adrenal insufficiency (in 7.1% and 1.2%, respectively)[2].

The most frequently reported systemic treatment-related grade 3 or higher AE in the neoadjuvant group were alanine aminotransferase (ALT) increased (4.7%), aspartate aminotransferase (AST) increased (4.2%), diarrhoea (3.8%), adrenal insufficiency (3.3%), and colitis (3.3%). These align with the AEs reported for the on-label use of

nivolumab plus ipilimumab for treating advanced melanoma, which uses a higher dose of ipilimumab. The respective Summaries of Product Characteristics (SmPC) for nivolumab and ipilimumab list increased ALT, increased AST, diarrhoea and hypothyroidism as very common adverse events (≥ 10%) when the medicines are administered together, with or without chemotherapy. Colitis and adrenal insufficiency are listed as common adverse events (≥ 1% to < 10%)[3,9].

Treatment discontinuation due to AE was reported in 9% of the neoadjuvant group and 14.4% in the adjuvant group[2]. Surgery was not performed in 3 patients in the neoadjuvant group due to toxic effects from treatment. No treatment-related deaths occurred in the neoadjuvant group, where one death occurred in the adjuvant group due to pneumonitis caused by nivolumab[2].

Overall, the adverse events observed in the NADINA study closely align with those described in the SmPCs, supporting the established safety profile of nivolumab plus ipilimumab therapy, with most toxicities being manageable and not resulting in treatment discontinuation.

Discussion

The primary outcome for the NADINA study was met, demonstrating that neoadjuvant nivolumab plus ipilimumab improved 12-month EFS compared to adjuvant nivolumab (83.7% versus 57.2%). Adjuvant treatment was not required in 59% of patients in the neoadjuvant group who achieved a major pathological response, and the estimated 12-month RFS was 95.1% for these patients. BRAF mutation status did not appear to markedly influence EFS or pathological response.

Median follow-up was approximately 10 months for the NADINA study, a relatively short duration. However, the findings align with the efficacy reported in the preceding OpACIN-neo and PRADO studies which are associated with longer follow up[17-19]. Although the preceding single-arm studies differ slightly in population and treatment regimens from NADINA (see Appendix 2 for details), there is sufficient comparability to provide supportive evidence for the treatment under consideration.

A major pathological response was achieved by 63.3% and 61% of applicable patients in the OpACIN-neo and PRADO studies, respectively[17-19]. The PRADO trial reported a 24-month RFS rate of 93%, 64% and 71% in patients who achieved a major, partial, and non-pathological response, respectively[17]. A survival update of the OpACIN-neo study reported an estimated 3-year EFS rate and RFS rate of 77% and 79%, respectively[19]. Unlike the NADINA and PRADO studies, the RFS analysis was not subdivided according to pathological response category.

The most frequently reported treatment-related grade 3-4 AEs reported in all three studies are consistent with the SmPC for nivolumab and ipilimumab. As per the NADINA study, the most frequently reported systemic treatment-related grade 3 or higher AE in the PRADO study were increased ALT (7%), increased AST (6%), diarrhoea (5%) and colitis (4%)[17]. In the OpACIN-NEO study, none of the grade 3 or higher immune-related AE were observed in more than one patient in the applicable treatment group, which included increased ALT, increased AST, and diarrhoea[18,19].

In the NADINA study, AEs were reported more often for the neoadjuvant treatment group compared to the adjuvant group. This finding aligns with nivolumab's SmPC, which reports that immune-related adverse reactions have occurred at higher

frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy.

Overall, favourable pathological response, EFS, and RFS rates reported in the NADINA and supporting studies suggests that neoadjuvant nivolumab plus ipilimumab is a clinically effective treatment for stage III melanoma. The consistency between the safety findings in the clinical studies and SmPC suggests that the off-label use of nivolumab plus ipilimumab is generally a tolerable treatment regimen.

Service impact

As adjuvant treatment can be omitted in patients who achieve a major pathological response, neoadjuvant nivolumab plus ipilimumab is likely to reduce the number of outpatient appointments required by the patient population.

The PRADO study showed that therapeutic lymph node dissection and adjuvant treatment could be omitted in patients who achieved a major pathological response following neoadjuvant treatment with nivolumab plus ipilimumab. The patient outcomes were encouraging, as reported above and in Appendix 2. Therefore, neoadjuvant nivolumab plus ipilimumab may offer further benefits to patients and the service in the future due to its potential to be surgery-sparing. A phase II study (NCT06754904) aims to investigate the surgery-sparing potential of neoadjuvant nivolumab and ipilimumab further, which is due to complete in 2032[20].

Due to the higher rates of grade 3–4 AEs that are associated with neoadjuvant treatment, there may be a greater rate of hospital admissions compared to standard of care (SOC) treatment. The budget impact of this, in addition to additional service requirements required by neoadjuvant treatment, are detailed in the budget impact section. Although neoadjuvant treatment is associated with a greater risk of grade 3–4 AEs in the short term, the treatment may reduce the longer-term burden of AEs associated with adjuvant treatment in patients who achieve a major pathological response.

Study design and generalisability to NHS Wales

The NADINA study is a phase III randomised controlled trial informed by the findings of the earlier OpACIN-neo and PRADO phase II studies[2]. Stratified randomisation of patients minimised selection bias and ensured that confounding factors were accounted for e.g. age or BRAF mutational status, giving the trial design good credibility. However, the ‘open-label’ design of this study increased the risk of performance and reporting bias among the patients and researchers.

The NADINA study compared neoadjuvant treatment with adjuvant nivolumab, administered intravenously. In NHS Wales, SOC adjuvant nivolumab is administered subcutaneously. However, due to the comparable pharmacokinetics, objective response rates and safety profile of nivolumab when given both intravenously and subcutaneously, it can be assumed that the findings are generalisable to the NHS Wales population who receive SOC adjuvant nivolumab treatment.

The NADINA study compares neoadjuvant treatment with adjuvant nivolumab. As clinicians estimate that only 10% of patients in NHS Wales currently receive SOC adjuvant nivolumab, with the remainder receiving pembrolizumab or dabrafenib plus trametinib, the generalisability of the findings to the wider NHS Wales population appears limited.

Although there are no published studies directly comparing the efficacy of each adjuvant treatment option, indirect comparisons suggest comparable effectiveness. Long-term follow up of the pivotal studies that supported the use of nivolumab and pembrolizumab in the adjuvant treatment of stage III melanoma (both BRAF-mutation positive and wild-type) reported similar RFS rates. A follow-up of the CheckMate 238 study reported a 4-year RFS rate of 51.7% (95% CI; 46.8 to 56.3, median follow-up 51.1 months, IQR 41.6 to 52.7) for nivolumab[21]. The KEYNOTE-054 follow-up reported a 5-year RFS rate of 55.4% (95% CI; 50.8 to 59.8, median follow-up 4.9 years) for pembrolizumab[22]. Furthermore, a propensity score matched survival analysis by Bloem et al. 2025 reported that no significant differences in outcomes were observed between patients with stage III BRAF-mutation positive melanoma treated with adjuvant immunotherapy versus dabrafenib plus trametinib[23]. Due to the likely comparable efficacy of the SOC adjuvant treatments prescribed in NHS Wales, it can be assumed that the findings of the NADINA study are generalisable to NHS Wales.

Patient organisation submissions

The patient organisation Melanoma Focus has provided a submission to support this assessment. The main points of the submission are listed below:

- Melanoma is a highly curable cancer if diagnosed at an early stage, however if the disease progresses to stage IV with the usual spread of the disease to lungs, liver, bone and/or brain, distressing symptoms may occur.
- It is therefore important to minimise the likelihood of patients with stage III melanoma from progressing to stage IV in order to increase patients' chances of survival or [improve] prognosis.
- The biggest fear for patients with stage III melanoma is their disease spreading to the brain, which causes significant anxiety. Caring for a loved one with melanoma can be emotionally draining as carers often have the same anxieties and fears. This is particularly concerning as there is often a considerable financial burden as many patients are economically active.
- The adjuvant treatments used routinely in the UK include pembrolizumab or nivolumab, which are immune checkpoint inhibitors, and dabrafenib in combination with trametinib, which is a targeted therapy treatment against the BRAF mutation that is present in about 40% of melanomas.
- The NADINA phase 3 neoadjuvant trial showed that by giving 2 cycles of ipilimumab and nivolumab prior to surgery in patients with high-risk stage 3 melanoma, the risk of the melanoma returning is reduced by an additional 28% after a median 9.9 month follow up.
- This study provided the option to stop treatment dependent upon response and 60% of patients did not require further adjuvant treatment, allowing patients to continue with their lives without the need for a year of treatment and the risk of further side effects.

Melanoma UK are another patient organisation who represent individuals affected by melanoma across the UK and were supportive of this assessment. Their submission states that patients with stage III melanoma voice concerns regarding limited treatment options and experience anxiety surrounding the risk of recurrence after surgery. From a patient perspective, access to effective neoadjuvant therapy would represent an important opportunity to improve long-term outcomes and reduce uncertainty that many patients experience.

Cost-effectiveness evidence

No cost-effectiveness evidence was identified for this indication. A cost effectiveness analysis was not undertaken by AWTTC.

Budget impact

In the absence of cost-effectiveness data and analysis, a comprehensive budget impact was undertaken which considered medicine acquisition, medicine administration, healthcare resource, and adverse event costs.

Treatment regimens for the proposed nivolumab plus ipilimumab neoadjuvant treatment and for SOC pathways are detailed in Appendix 3. Medicine acquisition costs were based on the confidential Patient Access Scheme (PAS) prices for each medicine. Treatment durations were informed by the NADINA study and validated with clinical expert opinion. The administration costs were based on the costs of delivering parenteral chemotherapy in line with the NHS England National Cost Data Publication[24].

Healthcare resource costs were sourced from the NHS England National Cost Data Publication. Clinical experts determined that a baseline electrocardiogram, an additional Computerised Tomography (CT) scan prior to surgery, and additional pathology reporting post-surgery would be required for patients receiving neoadjuvant treatment[24]. The cost of one consultant-led multi-professional attendance was included for each cycle in both the NHS Wales SOC and neoadjuvant treatment arms.

The AE costs comprised the most frequently reported systemic treatment-related grade 3 or higher AEs in the NADINA study: raised ALT, raised AST, diarrhoea, adrenal insufficiency, and colitis[2]. The cost of these adverse events for the adjuvant treatments was derived from the NADINA (nivolumab monotherapy and nivolumab plus ipilimumab), COMBI-AD (dabrafenib plus trametinib), and KEYNOTE-054 (pembrolizumab) studies, using the individual AE rates reported by each study[2,22,25]. The cost of a short, non-elective inpatient stay was considered appropriate to represent the adverse event costs (£753), which was sourced from the NHS England Cost Collection Index 2024/25[24].

Table 3 details the costs associated with each treatment regimen, per patient. Table 4 outlines the total cost the treatment under consideration and SOC treatment, according to the proportion of patients that are estimated to receive each treatment (as per clinician input and results of the NADINA study). Clinicians estimate that 51 patients will be eligible for treatment per annum. Of the eligible group, 41 patients (80%) are estimated to go on to receive treatment.

The NHS Healthcare Resource Group codes and associated costs that were used in the budget impact section are summarised in Appendix 4.

Table 3. Costs per patient, per regimen, per year

Intervention	Regimen	Cost per patient			
		Acquisition	Administration	Resource	Adverse event
Neoadjuvant treatment +/- adjuvant treatment according to response					
Neoadjuvant nivolumab plus ipilimumab	Nivolumab IV 240 mg plus ipilimumab IV 80 mg every three weeks for a total of 2 cycles	¶¶	£591	£909	£145
Neoadjuvant nivolumab plus ipilimumab plus adjuvant dabrafenib and trametinib	Neoadjuvant nivolumab IV 240 mg plus ipilimumab IV 80 mg every three weeks for a total of 2 cycles Adjuvant oral dabrafenib 150 mg twice daily plus trametinib 2 mg once daily for a total of 46 weeks	¶¶	£859	£3,230	£213
Neoadjuvant nivolumab plus ipilimumab plus adjuvant nivolumab monotherapy	Neoadjuvant nivolumab IV 240 mg plus ipilimumab IV 80 mg every three	¶¶	£3,747	£3,230	£191

Intervention	Regimen	Cost per patient			
	weeks for a total of 2 cycles Nivolumab IV 480 mg every 4 weeks for 11 cycles **or** nivolumab SC 1,200 mg every 4 weeks for 11 cycles				
Comparators – NHS Wales standard of care					
Adjuvant treatment - dabrafenib and trametinib	Oral dabrafenib 150 mg BD plus trametinib 2 mg OD every 4 weeks for 13 cycles	¶¶	£268	£2,840	£68
Adjuvant treatment - nivolumab monotherapy	1,200 mg SC every 4 weeks for 13 cycles	¶¶	£3,736	£2,840	£45
Adjuvant treatment – pembrolizumab monotherapy	400 mg IV every 6 weeks for 9 cycles	¶¶	£2,576	£1,996	£6.02
¶¶: commercial in confidence figure removed Sources for costs are outlined below. Acquisition: Patient Access Scheme prices. Excludes VAT. Administration: NHS England National Cost Collection Data Publication 2024/25[24]. Resource: NHS England National Cost Collection Data Publication 2024/25[24]. Adverse event: NHS England Cost Collection Index 2024/25 and adverse event rates from the following studies: NADINA, KEYNOTE-054, and COMBI-AD[2,22,24,25].					

Table 4. Costs per patient population, per regimen, per year

Intervention	Number of patients per year	Total cost per year
Neoadjuvant treatment according to response		
Neoadjuvant nivolumab plus ipilimumab	24	¶¶
Neoadjuvant nivolumab plus ipilimumab plus adjuvant dabrafenib and trametinib	11	¶¶
Neoadjuvant nivolumab plus ipilimumab plus adjuvant nivolumab monotherapy	6	¶¶
Total cost of treatment under consideration per year		¶¶
Comparators – SOC		
Adjuvant treatment - dabrafenib and trametinib	12	¶¶
Adjuvant treatment - nivolumab monotherapy	4	¶¶
Adjuvant treatment – pembrolizumab monotherapy	25	¶¶
Total cost of SOC treatment per year		¶¶
Annual cost difference		¶¶
¶¶: commercial in confidence figure removed Includes the following costs: medicines acquisition, medicines administration, adverse event management, and resource (where applicable). Calculations are based on 41 patients. Costs exclude VAT. Patient Access Scheme prices used.		

Table 5 outlines the total costs associated with SOC treatment and the treatment under consideration for eligible patients in NHS Wales. Table 5 highlights that the main source of cost saving is the avoidance of adjuvant treatment in 59% of patients receiving neoadjuvant treatment and the higher medicine acquisition cost of the NHS Wales SOC treatments.

Table 5. Comparison of costs for the treatment under consideration and its comparators

	Medicine acquisition	Medicine administration	Healthcare resource	Adverse event	Total costs (41 patients)
Neoadjuvant nivolumab plus ipilimumab	¶¶	£46,115	£76,726	£6,975	¶¶
NHS Wales SOC	¶¶	£82,560	£95,340	£1,144	¶¶
Cost difference	¶¶	£36,445	£18,614	-£5,831	¶¶(cost saving)

¶¶: commercial in confidence figure removed
Calculations are based on 41 patients.
Costs exclude VAT.
Patient Access Scheme prices used.
SOC: standard of care, as outlined in Appendix 3.

Discussion

The budget impact suggests that neoadjuvant treatment with nivolumab plus ipilimumab is expected to save [commercial in confidence text removed] per year. However, several assumptions and estimations have been made to inform the budget impact.

In line with NICE technology appraisals TA544 and TA684, it is assumed that the PAS prices will still apply to nivolumab, and dabrafenib plus trametinib for adjuvant treatment in patients who achieve a partial or non-response with neoadjuvant treatment.

Although AWTTC engaged with clinicians across Wales to ascertain current prescribing practices, the proportion of patients that are currently prescribed each NHS Wales SOC adjuvant regimen could be subject to variation. Similarly, the proportion of patents that are estimated to receive nivolumab monotherapy and dabrafenib plus trametinib following adjuvant treatment could be subject to variation, as they are derived from the NADINA study, rather than current practice in Wales. Variation in these proportions could either increase or decrease the budget impact. It is assumed that 100% of patients receive all doses of each regimen. It does not account for dose reductions or treatment interruptions, which could lower the budget impact.

The budget impact does not account for costs of any additional treatment that's required due to treatment failure or future recurrences, which would increase the budget impact.

The adverse effect costs assume fixed AE-specific rates for each regimen and a uniform cost per adverse effect. The COMBI-AD (dabrafenib plus trametinib), and KEYNOTE-054 (pembrolizumab) studies reported additional AEs to the five that were considered in the budget impact[22,25]. These AEs occurred at a higher or at

comparable frequencies to those considered in the budget impact (including rash, hypertension and pyrexia). However, these AE are less severe, and it is assumed that patients experiencing these AE would be less likely to require hospitalisation. Therefore, they were excluded from the calculation. However, it should be acknowledged that variation in the types of AE, their severity, and management could increase or decrease the budget impact.

The AE costs are subject to further uncertainty, as the pembrolizumab regimen in the KEYNOTE-054 differed slightly to the NHS Wales SOC regimen (a lower dose and higher frequency was used in the study). Additionally, the AE cost for neoadjuvant treatment is likely overestimated, as the reported AE were derived from the neoadjuvant arm where AE rates were not separated for patients requiring adjuvant treatment.

Genetic testing for BRAF variant status is a prerequisite for treatment with dabrafenib plus trametinib. As the test is routinely undertaken in NHS Wales, it is not considered an additional cost and has been excluded from the calculation.

In the NADINA study, surgery was not performed in 3 of the 212 patients in the neoadjuvant group due to toxic effects from treatment[2]. For this budget impact, it is assumed that 100% of patients (n = 41) receiving neoadjuvant treatment will undergo surgery. As surgery is indicated in both the proposed and SOC treatment pathways, surgery costs have been excluded from the calculation.

Although neoadjuvant nivolumab plus ipilimumab is not currently surgery-sparing, the literature suggests that it may be feasible for surgery to be safely omitted in patients achieving a major pathological response to neoadjuvant treatment, which would further reduce the budget impact of the treatment[17,20].

Equality and health impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that nivolumab plus ipilimumab will have a significant potential negative impact on people based on the protected characteristics of the Equality Act 2010.

Additional factors

Prescribing unlicensed medicines

Nivolumab plus ipilimumab is not licensed to treat this indication and is therefore ‘off label’. Providers should consult the relevant guidance on prescribing unlicensed medicines before any off-label medicines are prescribed.

Care has been taken to ensure the information is accurate and complete at the time of publication. However, the All Wales Therapeutics and Toxicology Centre (AWTTC) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC accept no liability in association with the use of its content. An Equality and Health Impact Assessment (EHIA) has been completed in relation to the medicine and has been published on the AWTTC website.

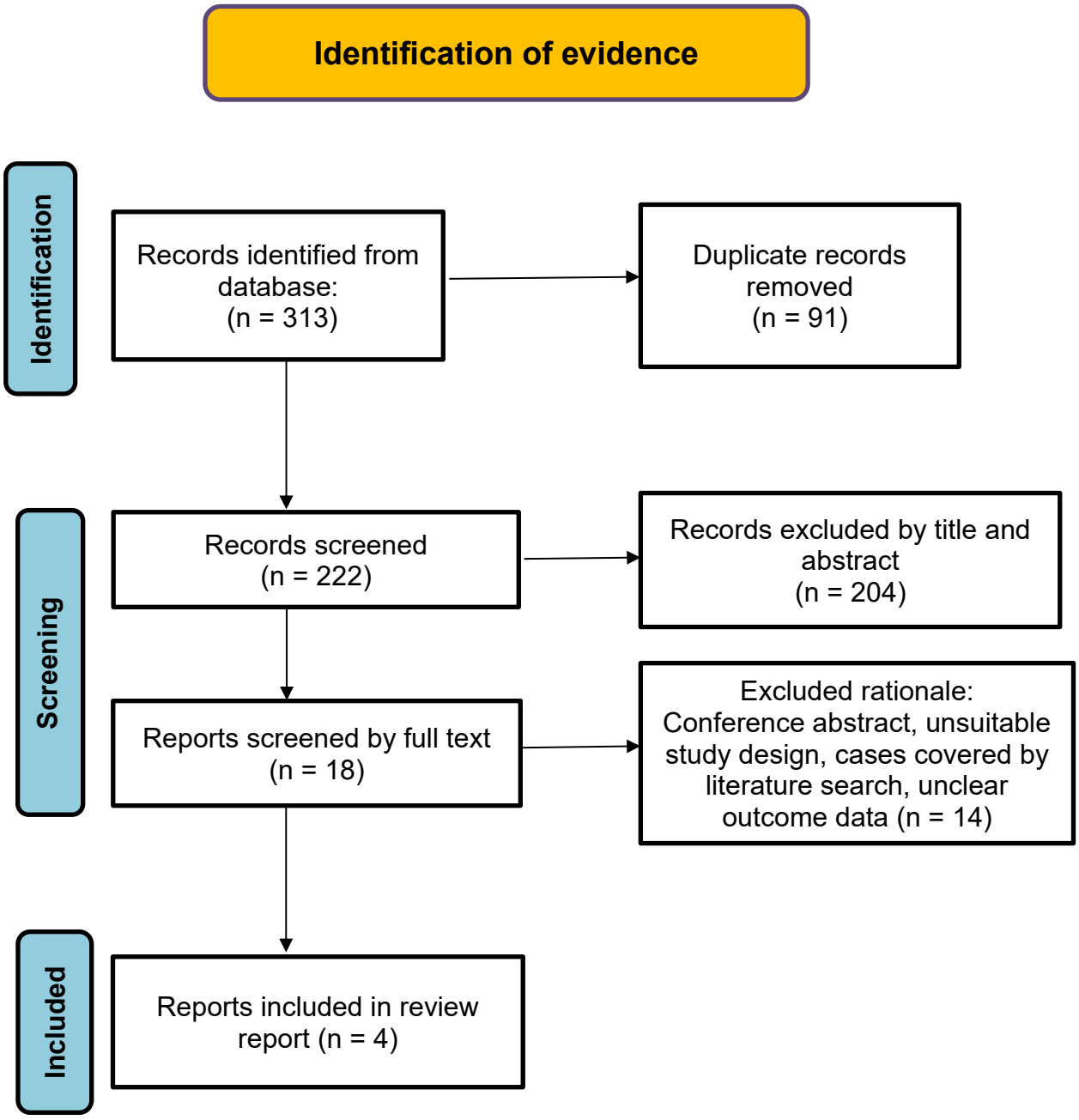
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Appendix 1. PRISMA flow diagram



Appendix 2. Supporting clinical trials

The table below summarises clinical trials that serve as supporting studies for this assessment. Although there are elements of the study design that do not fully align with this treatment under consideration, the evidence supplements the findings of the pivotal NADINA study.

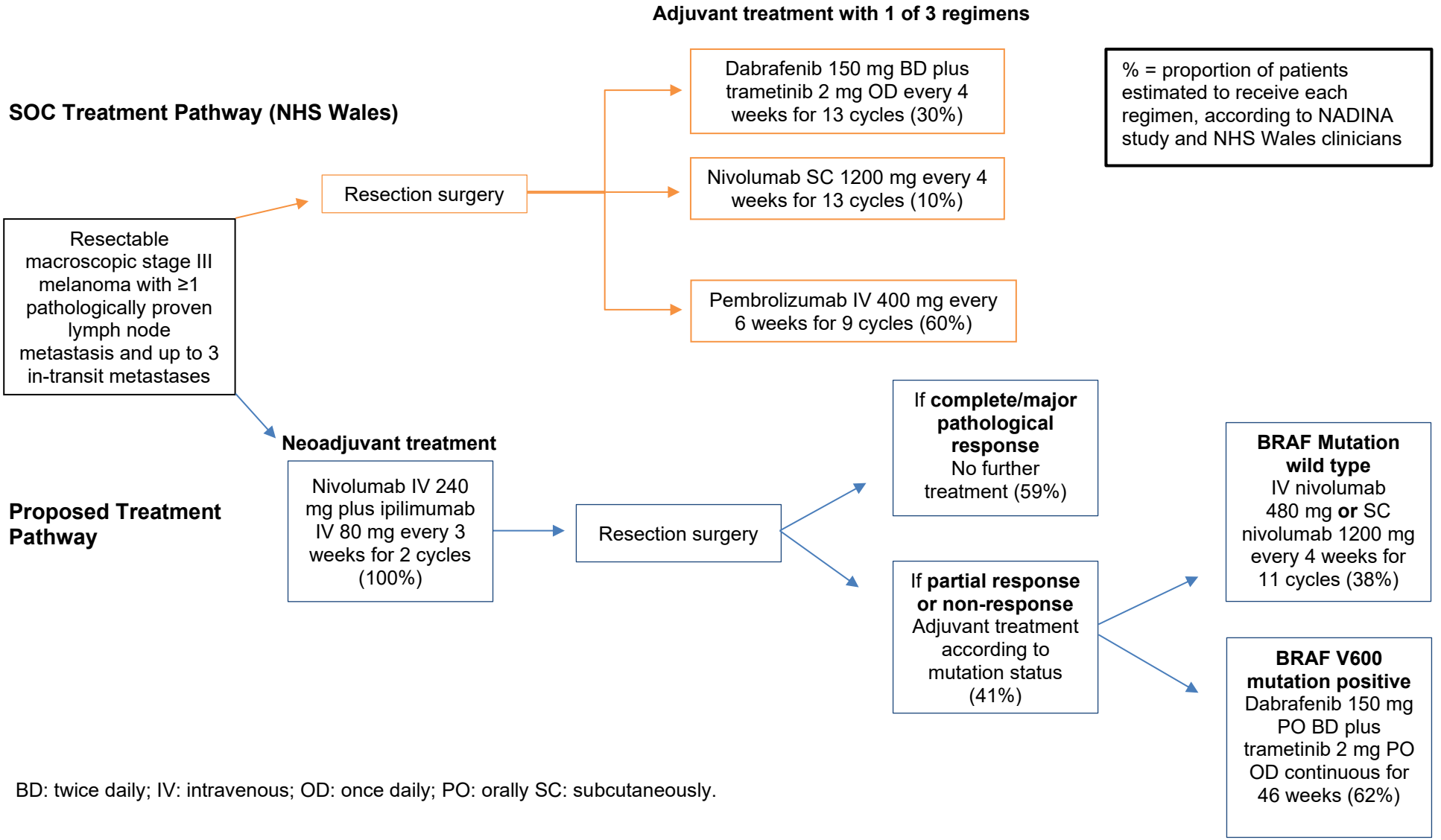
The trials include patients with resectable stage III melanoma with ≥1 lymph node metastasis and with a mutational status of either V600 BRAF positive or wild type. The table only reports data relating to patients that were treated with 2 cycles of neoadjuvant nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks for 2 cycles), which is comparable to the dose proposed by the Group. No adjuvant treatment was given to the patients whose outcome data is represented in the table.

A key difference to note is that the exclusion criteria for these studies included patients with in-transit metastasis within the last 6 months, whereas the treatment under consideration is for patients with up to 3 in-transit metastases.

Author (Year)	Study Design	Number of treated patients (age)	Number (%) patients achieving MPR	Longer-term outcomes	Safety	Key differences from current assessment
Rozeman et al (2019)[18]	OpACIN-Neo. Phase II multicentre, open-label, randomised controlled trial. 3 treatment arms in study: only group B reported as most relevant.	30 (≥ 18 years)	19 (63.3%)	Median follow-up 8.3 months: no relapse in patients achieving a MPR or pPR.	Within the first 12 weeks, grade 3–4 immune-related adverse events were observed in 6 (20%) patients.	<u>Both studies</u> Treatment dose (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg). Patients with a history of in-transit metastasis within last 6 month were excluded.
Versluis et al (2023)[19] 47 month follow-up			N/A	Estimated 3-year rates (not stratified by pathological response): RFS: 79% EFS: 77% DMFS: 86% OS: 93%		
Reijers et al (2022)[17]	PRADO extension cohort of OpACIN-Neo. Phase II, multicentre study. No blinding or randomisation.	99 (≥ 18 years)	60 (61%)	Estimated 24-month rates: MPR RFS: 93% MPR DMFS: 98% pPR RFS: 64% pPR DMFS: 64% pNR RFS: 71% pNR DMFS: 76%	Within the first 12 weeks, grade 3–4 immune-related adverse events were observed in 22 patients (22%; 95% CI; 14-32%).	<u>PRADO study</u> Surgery was not intended for patients achieving MPR following neoadjuvant treatment.

Author (Year)	Study Design	Number of treated patients (age)	Number (%) patients achieving MPR	Longer-term outcomes	Safety	Key differences from current assessment
Pathological response is assessed according to the International Neoadjuvant Melanoma Consortium (INMC) criteria. Major pathological response (MPR): ≤ 10% residual viable tumour which includes patients with a complete pathological response (pCR) (0% residual viable tumour) and those with a near-complete pathologic response (> 0% - ≤ 10% residual viable tumour). Pathological partial response (pPR): > 10% - ≤ 50% residual viable tumour. Pathologic non-response (pNR): > 50% residual viable tumour. BRAF: B-Raf proto-oncogene, serine/threonine kinase; DMFS: distant metastasis-free survival; EFS: event-free survival; IV: intravenous; OS: overall survival; RFS: recurrence-free survival; CI: confidence interval.						

Appendix 3. NHS Wales standard of care (SOC) and proposed treatment pathways



BD: twice daily; IV: intravenous; OD: once daily; PO: orally SC: subcutaneously.

Appendix 4. Costs used to inform the budget impact

The NHS Healthcare Resource Group (HRG) codes and associated costs utilised in the budget impact section of this report are summarised below[24].

Activity	HRG code	HRG code description	Cost
Administration of first cycle of nivolumab plus ipilimumab	SB13Z	Deliver more complex parenteral chemotherapy at first attendance*	£301
Administration of second cycle of nivolumab plus ipilimumab	SB15Z	Deliver subsequent elements of a chemotherapy cycle†	£290
Administration of first cycle of nivolumab monotherapy	SB12Z	Deliver simple parenteral chemotherapy at first attendance§	£256
Administration of subsequent cycles of nivolumab monotherapy	SB15Z	Deliver subsequent elements of a chemotherapy cycle	£290
Administration of dabrafenib plus trametinib	SB11Z	Deliver exclusively Oral Chemotherapy (outpatient) ¶	£268
Baseline electrocardiogram	EY51Z	Electrocardiogram Monitoring or Stress Testing, outpatient procedure	£175
Computerised Tomography scan	RD27Z	Computerised Tomography Scan of more than Three Areas, Outpatient imaging	£155
Pathology reporting	PATH02	Histopathology and histology	£60
Consultant-led multi-professional attendance, first attendance (all treatment arms)	WF02B	Multiprofessional non-admitted face-to-face attendance. First attendance, consultant-led (medical oncology)	£308
Consultant-led multi-professional attendance, subsequent attendances (all treatment arms)	WF02A	Multiprofessional non-admitted face-to-face attendance. Follow-up attendance, consultant-led (medical oncology)	£211

* Corresponds to 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle.
† Corresponds to the delivery of any pattern of outpatient chemotherapy regimen, other than the first attendance.
§ Corresponds to 30 minutes nurse time and 30 to 60 minutes chair time for the delivery of a complete cycle.
¶ Applied as an annual cost per patient that requires dabrafenib plus trametinib treatment.