Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2735

durvalumab concentrate for solution for infusion (Imfinzi®)

AstraZeneca

09 May 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life medicine process

durvalumab (Imfinzi®) is not recommended for use within NHSScotland.

Indication under review: In combination with tremelimumab for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC).

In an open-label phase III study durvalumab in combination with tremelimumab was associated with statistically significant improvements in overall survival compared with a multikinase inhibitor.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

The submitting company has indicated their intention to make a resubmission.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Durvalumab is a human monoclonal antibody which binds to programmed cell death ligand-1 (PD-L1) and inhibits the interaction of PD-L1 with PD-1 and CD80. This enhances anti-tumour immune responses and increases T-cell activation. For the indication under review, durvalumab is used in combination with tremelimumab, which is a human monoclonal antibody that blocks cytotoxic T lymphocyte-associated antigen (CTLA-4) interaction with its ligands, CD80 and CD86. This interaction enhances T-cell activation, proliferation, and anti-tumour activity. The recommended dose of durvalumab for the treatment of advanced HCC is 1,500 mg via intravenous infusion over one hour administered in combination with 300 mg of tremelimumab via intravenous infusion over one hour as a single dose at cycle 1/day 1, followed by durvalumab as monotherapy every four weeks. Treatment should be continued until disease progression or unacceptable toxicity. See Summary of Product Characteristics (SPC) for more details.[1, 2]

1.2. Disease background

The incidence of liver cancer is increasing worldwide and is the second most common cause of cancer death worldwide in men; incidence and mortality rates are two to three times higher among men than women and incidence increases with age, reaching a peak at 70 years. The main risk factors vary depending on region, but include chronic hepatitis B or C, aflatoxin-contaminated foods, heavy alcohol consumption, excess body weight, type 2 diabetes and smoking. HCC is the most common type of primary liver cancer. It typically develops and grows silently, which usually leads to late diagnosis. HCC is medically complex and difficult to treat, and consequently is associated with poor survival rates.[3, 4]

1.3. Treatment pathway and relevant comparators

For patients with advanced or unresectable HCC, who have not received prior systemic therapy and are not suitable for surgical or locoregional treatment options, the most commonly used treatment is atezolizumab in combination with bevacizumab (SMC2349). For those who have contraindications or decline intravenous therapy in favour of oral therapy, sorafenib (SMC482/08) and lenvatinib (SMC2138) are alternative first-line treatments; lenvatinib is the preferred oral option. Patients in areas of Scotland who live far away from treatment centres may be more likely to opt for oral treatment. NHS Scotland Cancer Medicines Outcome Programme (CMOP-PHS) data confirmed that atezolizumab plus bevacizumab is the most commonly used treatment, followed by lenvatinib.[5, 6]

1.4. Category for decision-making process

Eligibility for a PACE meeting

Durvalumab plus tremelimumab meets SMC end of life criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of durvalumab plus tremelimumab comes from the HIMALAYA study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant studies[3, 7]

Criteria	HIMALAYA
Study design	International, randomised, open-label, phase III study.
Eligible patients	• Age 18 years or older with histologically confirmed HCC. • No prior systemic therapy for HCC. • Ineligible for locoregional therapy for unresectable HCC. • Barcelona Clinic Liver Cancer stage B or C. • Child-Pugh Score class A. • ECOG performance status score of 0 or 1. • At least one measurable lesion per RECIST v1.1.
Treatments	Durvalumab 1,500 mg intravenously every four weeks plus one dose of tremelimumab 300 mg intravenously on day 1; durvalumab 1,500 mg intravenously every four weeks plus tremelimumab 75 mg intravenously every four weeks for four doses; monotherapy durvalumab 1,500 mg intravenously every four weeks; or sorafenib 400 mg orally twice daily. Treatment continued until progression, unacceptable toxicity, withdrawal of consent, or other discontinuation criteria were met. Patients could continue treatment after progression at the investigator's discretion. Patients receiving durvalumab plus tremelimumab (300 mg, one dose) who, per investigator opinion, were benefiting from treatment but had evidence of disease progression were eligible for retreatment one time with tremelimumab (300 mg) combined with durvalumab if they met the retreatment criteria. Based on phase II study data, the HIMALAYA study protocol was amended and enrolment to the durvalumab plus tremelimumab 75 mg group was closed and will not be discussed further.
Randomisation	Patients were randomised equally. Randomisation was stratified according to macrovascular invasion (yes or no), aetiology of liver disease (hepatitis B or C virus [but not both] or other/nonviral), and ECOG performance status (0 or 1).
Primary outcome	The primary outcome was overall survival (superiority), defined as time from date of randomisation until death from any cause, for durvalumab plus tremelimumab (one dose, 300 mg) versus sorafenib.
Secondary outcomes	OS (non-inferiority and superiority of durvalumab monotherapy versus sorafenib), OS rates (at 18, 24, and 36 months), PFS, ORR, DCR, DOR (for both comparisons durvalumab plus tremelimumab versus sorafenib and durvalumab monotherapy versus sorafenib).
Statistical analysis	Efficacy data were analysed in the ITT population, defined as all patients randomly assigned to durvalumab plus tremelimumab (one dose, 300 mg), durvalumab monotherapy, and sorafenib. The Lan

	DeMets approach was used to control for type I error for repeat testing of OS between durvalumab-tremelimumab versus sorafenib at interim and final analysis. OS (non-inferiority and superiority) between durvalumab monotherapy and sorafenib were also to be tested hierarchically if the primary outcome achieved statistical significance. If all OS analyses were successful, the alpha level was passed on to test three-year survival rates between durvalumab plus tremelimumab (one dose, 300 mg) and sorafenib. Other outcomes can be considered descriptive only.

Abbreviations: DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; ITT = intention-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1.

At the primary analysis data-cut (27 August 2021), durvalumab plus tremelimumab was associated with statistically significant improvements in overall survival versus sorafenib. A five-year overall survival update has also been published. See Table 2.2 for details.

Table 2.2. Results from HIMALAYA (ITT population).[3, 7, 8]

	Data-cut 27 August 2021		**Data-cut 01 March 2024**	
	Durvalumab plus tremelimumab (n=393)	**Sorafenib (n=389)**	**Durvalumab plus tremelimumab (n=393)**	**Sorafenib (n=389)**
Median follow-up	33.2 months	32.2 months	62.5 months	59.9 months
Primary outcome: overall survival				
Events	262	293	309	332
Median OS	16.4 months	13.8 months	-	-
HR (95% CI)	0.78 (0.65 to 0.93) p=0.0035		0.76 (0.65 to 0.89)	
OS rate at 36 months	31%	20%	-	-
OS rate at 60 months	-	-	20%	9.4%
Secondary outcome: progression-free survival (investigator-assessed, RECIST v1.1 criteria)				
Events	335	327	-	-
Median PFS	3.8 months	4.1 months	-	-
HR (95% CI)	0.90 (0.77 to 1.05)		-	
Secondary outcome: objective response rate (investigator-assessed, RECIST v1.1 criteria)				
Objective response	20%	5.1%	-	-
- CR	3.1%	0	-	-
- PR	17%	5.1%	-	-

Abbreviations: CI = confidence interval; CR = complete response; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response evaluation criteria in solid tumours version 1.1.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30 questionnaire and its HCC module (EORTC QLQ

HCC18). Median time to deterioration of patient-reported global health status or quality of life was 7.5 months for durvalumab plus tremelimumab and 5.7 months for sorafenib.[7]

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence, the submitting company conducted a Bayesian network meta-analysis (NMA) to compare the efficacy of durvalumab in combination with tremelimumab to atezolizumab plus bevacizumab, sorafenib, and lenvatinib. Details are summarised in Table 2.3.

Table 2.3. Summary of indirect treatment comparison

Criteria	Overview
Design	Bayesian NMA
Population	Adult patients with advanced or unresectable HCC
Comparators	Atezolizumab plus bevacizumab; lenvatinib; sorafenib
Studies included	HIMALAYA[7], IMbrave150[9, 10], REFLECT[11]
Outcomes	OS, PFS (Investigator assessed).
Results	Overall, OS and PFS comparisons (using a random effects model) between durvalumab plus tremelimumab and all other comparators had credible intervals that crossed one, so no evidence of a difference between treatments was identified.

Abbreviations: HCC = hepatocellular carcinoma; NMA = network meta-analysis; OS = Overall survival; PFS = progression-free survival.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the HIMALAYA study at data cut-off 27 August 2021, the median duration of treatment of durvalumab in the durvalumab plus tremelimumab group was 5.5 months and in the sorafenib group was 4.1 months. Any adverse event (AE) possibly related to any study treatment was reported by 76% (294/388) of patients in the durvalumab plus tremelimumab group and 85% (317/374) in the sorafenib group. In the respective groups, patients reporting a grade 3 or higher AE were 50% versus 52%, patients with a reported serious AE were 40% versus 30%, the proportion of patients who had an AE that led to dose interruptions or dose delay were 34% versus 48% and patients discontinuing therapy due to an AE was 14% versus 17%.[3]

The most frequently reported AEs of any grade with an incidence >10% in the durvalumab plus tremelimumab group versus the sorafenib group were: diarrhoea (26% versus 45%); abdominal pain (12% versus 17%); nausea (12% versus 14%); pruritus (23% versus 6.4%); rash (22% versus 14%); alopecia (0.5% versus 14%); palmar-plantar erythrodysaesthesia syndrome (0.8% versus 46%); aspartate aminotransferase increased (12% versus 6.4%); decreased appetite (17% versus 18%); asthenia (10% versus 12%); fatigue (17% versus 19%); pyrexia (13% versus 8.8%); insomnia (10% versus 4.3%); hypothyroidism (12% versus 4.3%); and hypertension (5.9% versus 18%). No treatment-related gastrointestinal or oesophageal varices haemorrhage events were observed with durvalumab plus tremelimumab. Pooled data of HIMALAYA and a phase II study reported immune-mediated AEs were more common with durvalumab plus tremelimumab when compared with the sorafenib treatment group in HIMALAYA (36% versus 7.5%); these were grade 3 or 4 in 13% and 2.4% of the patients, respectively.[3, 7]

Durvalumab plus tremelimumab is associated with a considerable toxicity profile. Many patients in HIMALAYA experienced grade 3, 4, or serious AEs, mostly related to diarrhoea and immune-mediated AEs. However, regulatory bodies noted that the rate of discontinuation was relatively low, and most AEs were manageable. Overall, the safety profile was considered comparable to that of sorafenib.[3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- HIMALAYA was a phase III study comparing durvalumab plus tremelimumab with a relevant active comparator, sorafenib.
- Durvalumab in combination with tremelimumab was associated with statistically significant and clinically meaningful improvements in overall survival compared with sorafenib; median overall survival was 16.4 months in the durvalumab plus tremelimumab group versus 13.8 months in the sorafenib group. These overall survival data can be considered mature and were further supported by additional data-cuts with longer follow-up (up to approximately 5 years) provided by the submitting company that indicated similar results.[7]
- Durvalumab plus tremelimumab has a different mechanism of action to currently available treatments, which may have benefits for some patients. VEGF inhibitors such as bevacizumab are associated with bleeding AEs. Clinical experts consulted by SMC and British Society of Gastroenterology HCC guidelines both note that the risk of variceal bleeding with durvalumab plus tremelimumab appears reduced compared with atezolizumab plus bevacizumab.[5]

4.2. Key uncertainties

- There are no direct data comparing durvalumab plus tremelimumab with atezolizumab plus bevacizumab, or lenvatinib. Therefore, a NMA of these comparisons was provided. The NMA had some limitations. There was variation in follow-up period time; the study of atezolizumab plus bevacizumab had shorter follow-up in particular. There was heterogeneity in patient characteristics, and some of these, such as disease aetiology, could be potential treatment effect modifiers.[9, 10] Safety and HRQoL outcomes were not assessed. Credible intervals were very wide suggesting uncertainty in the results. Lastly, the assumption of proportional hazards may have been violated for PFS comparisons, but may not have been violated for OS comparisons. Due to these limitations, the results of the NMA are uncertain.
- The selection criteria for patients in HIMALAYA are not reflective of the general population with advanced or unresectable HCC. Eligible patients had either mild or no symptoms related to HCC and/or liver cirrhosis (Eastern Cooperative Oncology Group [ECOG] performance status 0 or 1, Child-Pugh Class A, Barcelona Clinic Liver Cancer [BCLC] Stage C or B).[1, 3, 7]
- There may be some differences in the baseline characteristics of the study population of HIMALAYA compared with the relevant Scottish population. Almost half of the study

population were Asian, and a large proportion of the study had never used alcohol (approximately 40%) or were former users (approximately 45%). Roughly one third of patients had alpha-fetoprotein ≥400 ng/mL, suggesting that many patients in HIMALAYA had a favourable prognosis. Lastly, non-viral aetiology of HCC was reported in approximately 42% of patients; non-viral aetiology is potentially more common in Scotland. .[3]

- There were some limitations in the study methodology. HIMALAYA was an open-label study so may be prone to bias. Some secondary outcomes were not powered to detect statistical differences, were not adjusted for multiplicity, and radiological assessments were investigator-assessed. Therefore, secondary outcomes such as PFS, ORR, and HRQoL should be interpreted with caution. PFS and ORR data are further limited since the rate of possible pseudoprogression of HCC with PD-L1 (durvalumab) and CTLA-4 (tremelimumab) inhibition is unknown. In addition, randomisation was not stratified by geographic region, which may have introduced variability in local treatment practices that was unbalanced across treatment groups.[3, 7]
- The posology outlined in the SPC for durvalumab plus tremelimumab differs from the study. In HIMALAYA, patients randomised to durvalumab plus tremelimumab who were benefitting from treatment but had evidence of disease progression were eligible for retreatment with one additional dose of tremelimumab 300 mg. Thirty-one patients received this additional dose (approximately 8% of the durvalumab plus tremelimumab treatment group).[1, 7, 12]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that durvalumab plus tremelimumab fills an unmet need and is a therapeutic advancement for patients unable to receive atezolizumab plus bevacizumab.

4.4. Service implications

There may be advantages for both patients and the service since there are fewer overall intravenous administrations required for durvalumab plus tremelimumab when compared with atezolizumab plus bevacizumab. Durvalumab plus tremelimumab may be less convenient when compared with the oral treatments lenvatinib and sorafenib.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of durvalumab, as an end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Hepatocellular carcinoma (HCC) is a devastating cancer with a very poor prognosis and increasing incidence. It is commonly diagnosed alongside other liver conditions such as liver cirrhosis or hepatitis B which can bring additional complications. Patients live with uncertainty, hopelessness, and often stigma and isolation. Liver cancer is often diagnosed

too late for curative options. Patients report feeling extremely unwell, very tired, lethargic and weak. Symptoms include severe pain, itch, ascites (which can make it difficult to eat and even to breathe), anorexia, weight loss, and hepatic encephalopathy, which can make everyday activities such as conversation and staying awake difficult. Depression and anxiety are not uncommon. Patients with HCC are often relatively young who may have young families and working lives. Liver disease and liver cancer disproportionally affects the poorest in society. There are strong links with deprivation (including: homelessness, heavy alcohol and drug use, obesity).

- There are limited treatment options available. The most used first-line treatment is atezolizumab plus bevacizumab, which is not suitable for all patients. Patients with varices may be ineligible to receive atezolizumab plus bevacizumab. Patients who are not eligible for atezolizumab plus bevacizumab would not receive immunotherapy, and the other options of lenvatinib or sorafenib can be associated with significant toxicity and potentially limited efficacy. All currently available treatment options target VEGF (bevacizumab, lenvatinib, sorafenib). There are many patients with HCC who are not suitable for any available treatments due to contra-indications. Therefore, there is a high unmet need for a subset of patients.
- By widening the number of treatment options available, durvalumab plus tremelimumab can give patients hope and could positively impact their quality of life. It would provide an alternative immunotherapy option for patients with other co-morbidities who would otherwise not be eligible for immunotherapy and would improve access to treatment and survival for an incurable cancer.
- Durvalumab plus tremelimumab does not require an invasive, compulsory endoscopy before treatment, and there are less frequent infusions in comparison to atezolizumab plus bevacizumab. It is less burdensome for patients and family members/carers, freeing up time and money spent on travelling to appointments.
- The manageable toxicity of durvalumab plus tremelimumab could allow patients to continue to work throughout treatment.

Additional Patient and Carer Involvement

We received a patient group submission from the British Liver Trust which is a registered charity. The British Liver Trust has received 11% pharmaceutical company funding in the past two years, including from the submitting company. A representative from the British Liver Trust participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, which is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	40 years.
Population	Adult patients receiving first-line treatment for advanced or unresectable HCC.

Comparators	The three comparators were atezolizumab in combination with bevacizumab, sorafenib, and lenvatinib.
Model description	A three-state partitioned survival model was used, with mutually exclusive health states of progression free, progressed disease and death. Patients entered the model in the progression free health state, and progress through to progressed disease and to death.
Clinical data	OS, PFS, time to discontinuation (TTD), and adverse event rate data for durvalumab in combination with tremelimumab and sorafenib were from the HIMALAYA study. The OS data were from the updated analysis II (DCO: 1st March 2024), with PFS, TTD and adverse event rates from the primary analysis (DCO: 27th August 2021).[3, 7, 8] OS and PFS hazard ratios for atezolizumab in combination with bevacizumab versus sorafenib and lenvatinib versus sorafenib were drawn from the NMA. Adverse event rates for atezolizumab in combination with bevacizumab and lenvatinib were drawn from the IMbrave150 and REFLECT studies, respectively.[9-11]
Extrapolation	For durvalumab in combination with tremelimumab, OS was extrapolated using a normal 1 knot model, with sorafenib OS extrapolated using hazard 1 knot extrapolation. For atezolizumab in combination with bevacizumab, OS was extrapolated by applying the atezolizumab in combination with bevacizumab versus sorafenib OS hazard ratio to the sorafenib OS extrapolation. Lenvatinib and sorafenib OS efficacy was considered equivalent given non-inferior result of the REFLECT study, with a hazard ratio of 1 applied. Durvalumab in combination with tremelimumab PFS was extrapolated using a hazard 3 knot model, with sorafenib extrapolated using a hazard 2 knot model. Atezolizumab in combination with bevacizumab PFS was extrapolated by applying the atezolizumab with bevacizumab versus sorafenib PFS hazard ratio to the sorafenib PFS extrapolation. Lenvatinib PFS was extrapolated by applying the lenvatinib versus sorafenib PFS hazard to the sorafenib PFS extrapolation. Durvalumab TTD was extrapolated using a Weibull model, with sorafenib TTD extrapolated using a log-normal model. Durvalumab and sorafenib TTD was capped by OS to reflect post-progression treatment. TTD was for atezolizumab in combination with bevacizumab and lenvatinib TTD were assumed equal to their respective PFS extrapolations, due to no available TTD data.
Quality of life	Treatment-dependent utility values for durvalumab in combination with tremelimumab (0.812) and sorafenib (0.779) were derived from EQ-5D data from the HIMALAYA study. It was assumed that atezolizumab in combination with bevacizumab would have the same utility value as durvalumab in combination with tremelimumab of 0.812, and lenvatinib would have the same utility value as sorafenib of 0.779. Treatments retained the same utility values upon progression. Utility values were adjusted for age and sex.
Costs and resource use	Costs included in the model were medicine acquisition, administration, subsequent treatment costs, adverse events, healthcare resource use and end of life costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price for durvalumab. A PAS discount is in place for sorafenib, lenvatinib, atezolizumab, bevacizumab, cabozantinib, and regorafenib and these were included in the results used for decision-making by using estimates of the comparator PAS price. SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues.

6.2. Results

SMC considered results for decision-making that took into account all relevant PAS. SMC is unable to present these results due to competition law issues. Durvalumab plus tremelimumab was compared with atezolizumab plus bevacizumab, lenvatinib and sorafenib.

6.3. Sensitivity analyses

A range of sensitivity and scenario analyses were considered, and descriptions of these key scenarios are provided in Table 6.2 below.

Table 6.2 Selected scenario analyses

	Parameter	**Base case**	**Scenario**
	Base case	-	-
1a	Time Horizon	40 years	20 years
1b			10 years
2a	OS extrapolation – durvalumab in combination with tremelimumab	Normal 1 knot	Generalised gamma
2b			Hazard 1 Knot
2c			NMA OS HR
3a	OS extrapolation – sorafenib	Hazard 1 knot	Generalised gamma
3b			Odds 1 knot
4a	PFS extrapolation – durvalumab in combination with tremelimumab	Hazard 3 knots	Generalised gamma
4b			Hazard 2 knot
5a	PFS extrapolation – sorafenib	Hazard 2 knots	Log-normal
5b			Odds 1 knot
6	TTD cap (durvalumab and sorafenib)	OS Cap	PFS cap
7a	Atezolizumab with bevacizumab vs sorafenib OS HR	Mean	Lower bound
7b			HR=1
7c			Upper bound
8a	Atezolizumab with bevacizumab vs sorafenib PFS HR	Mean	Lower bound
8b			HR=1
8c			Upper bound

9a	Lenvatinib vs sorafenib PFS HR	Mean	Lower bound
9b			HR=1
9c			Upper bound
10	Lenvatinib vs sorafenib OS HR		NMA OS HR
11	Utilities	Treatment-dependent	Time-to-death
12	Tremelimumab retreatment	Excluded	Included
C1	7b, 8b and 9b	Base case	NMA PFS HRs =OS HRs = 1

Abbreviations: C = combined scenario; CIC = commercial in confidence; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; NMA = network meta-analysis; OS = overall survival; PFS = progression free survival; TTD = time to treatment discontinuation.

6.4. Key strengths

- The model structure was appropriate to capture disease progression for patients receiving treatment for HCC.
- Efficacy data for the model were sourced from the HIMALAYA study for durvalumab in combination with tremelimumab and sorafenib, a phase III RCT. OS data from the updated analysis II indicated maturity.
- A comprehensive selection of parameters was considered in one-way deterministic scenario analysis.

6.5. Key uncertainties

- There were uncertainties in the extrapolation of PFS and OS. Firstly, the PFS and OS hazard ratios from the NMA showed wide credible intervals, with the atezolizumab in combination with bevacizumab and lenvatinib ICERs sensitive to the bounds of these (Scenarios 7, 8, 9 and Combined Scenario 1). Secondly, the submitting company assessed the OS proportional hazards assumption in the HIMALAYA study for durvalumab in combination with tremelimumab versus sorafenib to be violated, but SMC statistical advisors noted that there did not appear to be strong supporting evidence. Therefore, a scenario applied the durvalumab in combination with tremelimumab versus sorafenib OS hazard ratio from the NMA (Scenario 2c). Thirdly, more conservative and plausible OS spline extrapolations were considered, which reduced the longer-term relative OS for durvalumab in combination with tremelimumab (Scenarios 2b and 3b). Finally, sorafenib was used as the reference treatment when applying PFS and OS hazard ratios. Using this approach, it was observed that the durvalumab in combination with tremelimumab PFS and OS extrapolations crossed and then exceeded the atezolizumab in combination with bevacizumab PFS and OS extrapolations after approximately 8 and 6 years, respectively. However, when considering durvalumab in combination with tremelimumab as the reference treatment, the NMA-reported PFS and OS hazard ratios showed point estimates that favoured atezolizumab in

combination with bevacizumab, with credible intervals suggesting no evidence of a difference between treatments. A scenario using durvalumab in combination with tremelimumab as the reference treatment for the PFS and OS hazard ratio-based extrapolations was requested from the submitting company but was not provided. However, a cost-minimisation analysis assuming equivalent efficacy between durvalumab in combination with tremelimumab and atezolizumab in combination with bevacizumab was presented and was considered by the Committee to be a relevant scenario for decision-making.

- The treatment-dependent utility values used in the economic model increased uncertainty in the economic results, as treatments retained the same utility values regardless of health state. Health state utility values showing a decline in the utility for progressed patients have been considered in previous SMC advice in HCC (SMC2349 atezolizumab and SMC2138 lenvatinib). As there was no decline in utility values following progression in this analysis, the QALYs gained from the longer-term OS improvements associated with durvalumab in combination with tremelimumab may be overestimated. In addition, it was assumed that atezolizumab in combination with bevacizumab would have the same utility value as durvalumab in combination with tremelimumab, and lenvatinib would have the same utility value as sorafenib. The submitting company did not provide further scenario analysis using health state-dependent utility values but instead provided a proximity to death utility approach where all treatments had the same utility values that decreased with proximity to death (Scenario 11).
- The extrapolation of TTD was subject to uncertainty, as there were inconsistent approaches used to TTD caps across treatment arms. However, a scenario was available applying PFS caps for TTD in all treatments (Scenario 6).
- The time horizon of 40 years used in the economic model was longer than those used in previous UK HTAs in advanced or unresectable HCC (SMC 482/08 sorafenib, SMC2138 lenvatinib, SMC2349 atezolizumab in combination with bevacizumab). Shortened time horizons of 20 and 10 years were therefore considered in scenario analysis (Scenario 1).
- Tremelimumab was administered as a priming single dose in combination with durvalumab at the start of the model as per the SPC. However, in HIMALAYA patients randomised to durvalumab plus tremelimumab who were benefitting from treatment but had evidence of disease progression were eligible for tremelimumab retreatment. Thirty-one patients received this additional dose (approximately 8% of the durvalumab plus tremelimumab treatment group). A scenario was provided to consider these additional costs (Scenario 12).

7. Conclusion

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept durvalumab for use in NHSScotland.

8. Guidelines and Protocols

British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults were published in 2024.[5]

European Society for Medical Oncology (ESMO) updated treatment recommendations for hepatocellular carcinoma from the ESMO Clinical Practice Guidelines (updated in 2021).[13]

9. Additional Information

9.1. Product availability date

June 2023

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 4-week cycle
Durvalumab plus tremelimumab	**Durvalumab 1,500 mg intravenously every four weeks** **Tremelimumab 300 mg intravenously on day 1 of cycle 1**	**First cycle: £28,008** **Subsequent cycles: £7,398**

Costs from BNF online on 31 January 2025. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 March 2025.

*Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.