Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2349

atezolizumab (Tecentriq®) 1,200mg concentrate for solution for infusion

Roche Products Ltd.

04 June 2021

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 process

atezolizumab (Tecentriq®) is accepted for use within NHSScotland.

Indication under review: in combination with bevacizumab for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.

In a phase III study in patients with advanced or unresectable HCC who had not received prior systemic therapy, atezolizumab plus bevacizumab was associated with greater overall and progression-free survival compared with a multikinase inhibitor.

This advice applies only in the context of approved NHSScotland Patient Access Scheme (PAS) arrangements delivering the cost-effectiveness results upon which the decision was based, or PAS/ list prices that are equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

Atezolizumab, in combination with bevacizumab, is indicated for the treatment of adult patients with advanced or unresectable hepatocellular carcinoma (HCC) who have not received prior systemic therapy.[1]

Dosing Information

The recommended dose of atezolizumab is 1,200mg followed by bevacizumab 15mg/kg of body weight, administered by intravenous infusion every three weeks. The infusions must not be administered as an intravenous push or bolus. The initial dose of atezolizumab must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

It is recommended that patients are treated with atezolizumab until loss of clinical benefit or unmanageable toxicity.

Atezolizumab must be initiated and supervised by physicians experienced in the treatment of cancer. See SPC for further information.[1]

Product availability date

October 2020

Atezolizumab plus bevacizumab received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 18 June 2020.

Atezolizumab meets SMC end of life criteria for this indication.

Summary of evidence on comparative efficacy

Atezolizumab is a humanised immunoglobulin G1 (IgG1) monoclonal antibody that binds to programmed death-ligand 1 (PD-L1) and blocks its interactions with both the programmed death-1 (PD-1) and B7.1 receptors. This stops PD-L1/PD-1 mediated inhibition of the immune response. Bevacizumab interferes with the biological activity of vascular endothelial growth factor (VEGF) by binding to it and preventing interaction with its receptors on endothelial cells. Neutralisation of VEGF activity leads to inhibition of tumour growth.[1, 2]

The evidence to support the efficacy and safety of atezolizumab plus bevacizumab comes from IMbrave150, an international, randomised, open-label, phase III study. Adult patients with locally advanced, metastatic or unresectable HCC were recruited to the study provided that they had not received prior systemic therapy for liver cancer, had measurable disease (as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST 1.1]), had an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and Child–Pugh liver function class A.

Randomisation was stratified by geographic region (Asia excluding Japan versus rest of the world), macrovascular invasion or extrahepatic spread of disease (presence versus absence), baseline alpha-fetoprotein level (<400 versus ≥400ng/mL), and ECOG performance status (0 versus 1). Patients were randomised 2:1 to receive atezolizumab 1200mg IV infusions every 3 weeks plus bevacizumab 15mg/kg IV infusions every 3 weeks (n=336) or sorafenib 400mg oral twice per day (n=165). Treatment was to continue until unacceptable toxic effects occurred or there was loss of clinical benefit. Patients could continue treatment beyond RECIST 1.1 defined disease progression if the investigator observed evidence of clinical benefit and if there were no symptoms and signs indicating unequivocal disease progression. Patients in the atezolizumab/bevacizumab group who temporarily or permanently discontinued one agent could continue taking the other agent at the investigator's discretion.[3]

The co-primary outcomes were overall survival and progression-free survival (PFS). Overall survival was defined as the time from randomisation to death from any cause, and PFS was defined as the time from randomisation to disease progression according to RECIST 1.1, as assessed at an independent review facility, or death from any cause, whichever occurred first. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation.[3]

At the time of the primary PFS analysis (and first interim analysis for overall survival), atezolizumab plus bevacizumab was associated with significantly longer PFS and overall survival compared with sorafenib. A post hoc, descriptive analysis with longer follow-up (data-cut-off: 31 August 2020) was also provided by the submitting company.[4] See Table 1 for detailed results.

Table 1. Primary outcome results of IMBrave150 (ITT population).[3]

	Atezolizumab plus bevacizumab (n=336)	**Sorafenib (n=165)**	**Atezolizumab plus bevacizumab (n=336)**	**Sorafenib (n=165)**
Data cut-off:	**29 August 2019**		**31 August 2020**	
Median duration of follow-up	**8.6 months**		**15.6 months**	
Overall survival				
Number of events	96	65	280	
Median	NE	13.2 months	19.2 months	13.4 months
Hazard ratio (95% CI)	0.58 (0.42 to 0.79) p<0.001		0.66 (0.52 to 0.85)	
Overall survival at 6 months	85%	72%	-	-
Overall survival at 12 months	67%	55%	-	-
Overall survival at 18 months	-	-	52%	40%

Progression-free survival (IRF according to RECIST 1.1)				
Number of events	197	109	-	-
Median	6.8 months	4.3 months	-	-
Hazard ratio (95% CI)	0.59 (0.47 to 0.76) p<0.001		-	
PFS at 6 months	54%	37%	-	-

CI = confidence interval; IRF = independent review facility; PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1

Secondary outcomes included the objective response rate and the duration of response (the time from first documented complete or partial response to disease progression or death) and these were both improved with atezolizumab plus bevacizumab compared with sorafenib, as described in Table 2.[3]

Table 2. Secondary outcome results of IMBrave150.[3, 5]

	Atezolizumab plus bevacizumab (n=326)*	**Sorafenib (n=159)***	**Atezolizumab plus bevacizumab (n=326)***	**Sorafenib (n=159)***
Data cut-off:	**29 August 2019**		**31 August 2020**	
Median duration of follow-up	**8.6 months**		**15.6 months**	
Objective response rate (IRF according to RECIST 1.1)				
Confirmed objective response	27%	12%	30%	11%
Difference (95% CI)	15% (7.9 to 23) p<0.001		18%	
Complete response	5.5%	0	7.7%	0.6%
Partial response	22%	12%	22%	11%
Stable disease	46%	43%	44%	43%
Duration of confirmed response (IRF according to RECIST 1.1)				
Number of patients included in analysis	89	19	-	-
Number of patients no longer responding to treatment	12	6	-	-
Median time to loss of response	NE	6.3 months	18.1 months	14.9 months
Hazard ratio (95% CI)	0.23 (0.08 to 0.70)		-	
Proportion of patients still	88%	59%	-	-

responding to treatment at 6 months				

*Included are patients who presented with measurable disease according to the RECIST 1.1, as assessed at IRF.

CI = confidence interval; HCC = hepatocellular carcinoma; IRF = independent review facility; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours, version 1.1.

Patient reported outcomes were time to deterioration of quality of life, physical functioning, and role functioning, with deterioration being defined as a decrease from baseline of ≥10 points on the European Organisation for Research and Treatment of Cancer (EORTC) QLQ–C30 questionnaire maintained for two consecutive assessments or a decrease of ≥10 points in one assessment followed by death from any cause within 3 weeks. Compliance with the EORTC QLQ-C30 questionnaire (defined as completion of at least one question) in the ITT population was at least 93% from baseline until treatment cycle 17 (56 patients at week 51), and was at least 80% thereafter until treatment was discontinued. Treatment with atezolizumab plus bevacizumab delayed deterioration of quality of life (11.2 months versus 3.6 months), physical functioning (13.1 months versus 4.9 months), and role functioning (9.1 months versus 3.6 months) compared with sorafenib.[3]

The submitting company presented Bayesian network meta-analyses (NMA) to compare atezolizumab plus bevacizumab versus lenvatinib in adult patients with locally advanced or metastatic HCC who have received no prior systemic therapy for HCC. The treatments were compared indirectly via a common comparator (sorafenib) and three studies were included in the NMA (IMbrave150, REFLECT and Checkmate459). The reported outcomes of the analyses were PFS and overall survival. Hazard ratios for overall survival and PFS both favoured atezolizumab plus bevacizumab when compared with lenvatinib, although 95% credible intervals were wide and crossed one; overall survival HR = 0.63 (95% Credible interval [CrI]: 0.32 to 1.25); PFS HR = 0.91 (95% CrI: 0.23 to 3.65). The probability of atezolizumab plus bevacizumab performing better than lenvatinib was >90% in terms of overall survival and >60% for PFS.

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

Summary of evidence on comparative safety

In the IMBrave150 study at data cut-off August 2019, the median duration of treatment was 7.4 months with atezolizumab, 6.9 months with bevacizumab, and 2.8 months with sorafenib. Overall, the observed safety profile of atezolizumab plus bevacizumab in IMbrave150 reflected what has been previously observed for other indications. Adverse events (AEs) due to any cause were reported by 98% (323/329) of patients in the atezolizumab plus bevacizumab group and 99% (154/156) in the sorafenib group. In the atezolizumab plus bevacizumab group and sorafenib group respectively, patients reporting a grade 3/4 AE were 56% versus 55%, grade 5 AE 4.6%

versus 5.8%, serious AE 38% versus 31%, AE leading to dose modification or interruption of any study medicine 50% versus 61%, AE leading to withdrawal of any study medicine 16% versus 10%.[3]

The most frequently reported treatment related AEs of any grade with an incidence >10% in the atezolizumab plus bevacizumab group or the sorafenib group were: hypertension 30% versus 24%, fatigue 20% versus 19%, proteinuria 20% versus 7.1%, aspartate aminotransferase increase 20% versus 17%, pruritus 20% versus 9.6%, diarrhoea 19% versus 49%, decreased appetite 18% versus 24%, pyrexia 18% versus 9.6%, alanine aminotransferase increase 14% versus 9.0%, constipation 13% versus 14%, blood bilirubin increase 13% versus 14%, rash 12% versus 17%, abdominal pain 12% versus 17%, nausea 12% versus 16%, cough 12% versus 9.6%, infusion-related reaction 11% versus 0%, weight decrease 11% versus 9.6%, platelet count decrease 11% versus 12%, epistaxis 10% versus 4.5%, asthenia 6.7% versus 14%, alopecia 1.2% versus 14%, palmar-plantar erythrodysesthesia syndrome 0.9% versus 48%. A higher incidence of serious AEs was observed in the atezolizumab plus bevacizumab group; the main differences were related to gastrointestinal disorders, including bleeding (15% versus 12%) and infections (7.3% vs 1.9%).[3, 4]

Summary of clinical effectiveness issues

HCC is the most common form of liver cancer, and its incidence in Scotland is anticipated to rise. In most patients the disease is diagnosed at advanced stages when curative treatments, including resection, liver transplantation, and ablation, are no longer suitable. Prognosis is poor, with the median survival around 12 to 14 months for patients receiving current treatments.[6] Two treatments are available to adult patients with advanced or unresectable HCC who have received no prior systemic therapy: sorafenib (SMC 482/08) and lenvatinib (SMC 2138). Clinical experts consulted by SMC considered that atezolizumab plus bevacizumab fills an unmet need in this therapeutic area due to its efficacy compared with current treatments.

Progression free survival (assessed by independent review according to RECIST 1.1 criteria) was significantly improved with treatment with atezolizumab plus bevacizumab, with a median improvement of 2.5 months reported compared with sorafenib. For overall survival, interim analysis (data cut-off 19 August 2019) suggests a 42% improvement in favour of atezolizumab plus bevacizumab; at an informal later data cut-off (31 August 2020) the difference in survival between treatment groups was 5.8 months. Although the final analysis of overall survival is yet to be reported, and the data are immature at present, the magnitude of effect on both overall survival and PFS associated with atezolizumab plus bevacizumab is substantial and can be considered clinically meaningful. Secondary outcomes, overall response rate and duration of confirmed response, were also supportive. The European Medicines Agency (EMA) noted that efficacy may be negatively impacted by presence of anti-drug antibodies (ADA), or positively affected by positive PD-L1 expression, however no firm conclusions can be drawn at this time.[3]

There are some limitations to the evidence. IMbrave150 was an open-label study, which could potentially bias efficacy and safety outcomes. An independent review facility was used where possible to try to mitigate this potential for bias. There are possible generalisability issues with the

evidence to Scottish practice. There are very limited data available for atezolizumab plus bevacizumab in HCC patients with Child-Pugh B or C liver disease, no data in patients with ECOG performance status >1, and the population of IMbrave150 were also at a decreased risk of variceal bleeding compared to what might be expected of the population in Scotland. Furthermore, the proportion of patients from Asian regions excluding Japan (40%) and the proportion of patients with hepatitis B as the cause of HCC (48%) may not be reflective of the Scottish population. Lastly, a higher incidence of bleeding, including fatal bleeding, was observed in the atezolizumab plus bevacizumab group, despite selection criteria that aimed to exclude patients with high risk of gastrointestinal bleeding.[1, 3]

While IMbrave150 compared atezolizumab plus bevacizumab with sorafenib, there remains a lack of direct evidence compared with lenvatinib. Lenvatinib has been shown to be non-inferior to sorafenib in terms of overall survival, but was associated with a PFS benefit in the REFLECT study, and may be the treatment most likely to be displaced by atezolizumab plus bevacizumab.[6] There were some limitations of the indirect treatment comparison conducted by the submitting company. Firstly, not all data included in the NMA drawn from Checkmate459 could be confirmed, and the risk of bias in this study is unknown. A sensitivity analysis which removed the Checkmate459 study from the network was performed by the company and provided consistent results. There was heterogeneity across the included studies that could not be adjusted for, and the network formed was small, which may have limited statistical power. Credible intervals were wide and spanned 1, suggesting uncertainty in the results. PFS results were less convincing than the overall survival results, with only a >60% probability of atezolizumab plus bevacizumab being superior. Finally, the analyses did not assess safety or health-related quality of life outcomes, which may be clinically relevant when considering the risk/benefit of treatments. In conclusion, there may be a clinical benefit to treatment with atezolizumab plus bevacizumab over lenvatinib, but the aforementioned limitations mean that it is not certain.

Clinical experts consulted by SMC considered that atezolizumab plus bevacizumab is a therapeutic advancement due to its efficacy relative to current treatments, and would likely become standard of care for all patients deemed eligible for treatment, considering Child-Pugh grade and performance status. The introduction of atezolizumab plus bevacizumab is expected to have an impact on the service. As current treatments for HCC are oral, additional chair time would be required to accommodate the three weekly IV infusions for atezolizumab plus bevacizumab. Intravenous infusions are generally considered less convenient for patients than oral regimens.

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 atezolizumab (Tecentriq), as an end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Advanced unresectable HCC is a devastating condition that has a severe impact on patients and their families. Median life expectancy on currently available treatments is approximately 12 months. Patients can have symptoms such as weight loss, fatigue, ascites, abdominal discomfort, pain and nausea which can significantly impair quality of life as the condition progresses.

- There are only two treatment options for first-line advanced HCC. These treatments have limited efficacy and for some, cause severe side effects. Therefore there is a high unmet need in this setting. Atezolizumab and bevacizumab is the first immunotherapy combination to show a survival advantage over sorafenib, which has been standard of care for the last 10 years. Atezolizumab plus bevacizumab is likely to be the new standard of care treatment for these patients going forward.

- Patients who are treated with atezolizumab plus bevacizumab may live longer than with sorafenib, which is extremely important in advanced HCC when prognosis is so poor.

- There is evidence to suggest that quality of life is improved with atezolizumab plus bevacizumab when compared with current treatments. Even small improvements in quality of life could be life changing. If patients were able to remain independent for longer, this could also benefit family members/carers.

- Although there are potential downsides to treatment with atezolizumab plus bevacizumab (frequent hospital visits for IV administrations, side effects), patients are more than willing to tolerate these in return for the possibility of extended life and improved quality of life.

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 14% pharmaceutical company funding in the past two years, with none 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.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of atezolizumab plus bevacizumab for the treatment of adult patients with locally advanced or metastatic and/or unresectable HCC who have not received prior systemic treatment. The comparators of interest were sorafenib and lenvatinib, both of which are appropriate and relevant to clinical practice in Scotland, with lenvatinib being the preferred treatment option according to experts consulted by SMC.

The model is a partitioned survival model with three health states (PFS, progressed disease and death) and a time horizon of 20 years, although this was varied in sensitivity analysis between 5 and 15 years. Cycle length was weekly, likely to reflect treatment cycles of 21 days for both atezolizumab and bevacizumab.

Clinical data for the model were taken from the IMbrave150 trial comparing atezolizumab plus bevacizumab with sorafenib.[3] Lenvatinib estimates came from the hazard ratios resulting from the indirect treatment comparison. Trial data were extrapolated for each treatment for PFS and overall survival based on goodness of fit statistics, expert opinion from Scottish clinicians and consideration of visual fit. This was also the case for time to discontinuation except for lenvatinib where PFS had to be used as a proxy for time to discontinuation. The base case distributions used were log normal for PFS and OS (for the atezolizumab plus bevacizumab and sorafenib) and exponential extrapolation of the Kaplan-Meier distribution data for time to discontinuation from 14 months onwards (atezolizumab plus bevacizumab and sorafenib). Assumptions about the choice of distributions were tested in scenario analysis.

Utility values were available from EQ-5D-5L data collected for the IMbrave150 trial and cross-walked to EQ-5D-3L in order to apply UK tariff estimates to these data. Four methods were used to determine utilities and in the base case the company chose the proximity to death method which categorised patients into 4 groups depending on how close they were to death (≤ 5 weeks, >5 weeks but ≤15 weeks, >15 weeks but ≤30 weeks or >30 weeks) and whether or not they were on treatment. Utilities ranged from 0.64 to 0.80 on treatment and 0.37 to 0.71 off treatment. Other methods for applying health state utilities were also considered and the results applied in scenario analysis, including the use of separate utility scores within the PFS state but using pooled data for the post-progression state, and applying separate adverse event disutilities for events of severity grade 3 and above.

Resource use estimates included medicine acquisition costs and administration costs, which varied for atezolizumab plus bevacizumab due to the requirement for hospital administration of treatment whereas sorafenib and lenvatinib are oral therapies so this is not always required. The cost of subsequent treatments was also included but was difficult to account for because the treatments used in the main IMbrave150 study were not relevant to an NHS setting. In particular, regorafenib is only available as a second line treatment for patients following treatment with sorafenib, not lenvatinib or atezolizumab plus bevacizumab. The appropriateness of the use of

average costs of sorafenib, lenvatinib and regorafenib for subsequent tyrosine kinase inhibitors, and nivolumab costs as a proxy for subsequent immunotherapies is unclear.

The frequency of other resource use items was estimated by Scottish clinicians and routine sources were used to apply unit costs to these data. A one-off cost was applied to estimate terminal care costs, taken from the literature.

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 atezolizumab and bevacizumab. PAS discounts are in place for sorafenib and lenvatinib and these were included in the results used for decision-making by using estimates of the comparator PAS prices. The results presented do not take account of the PAS discounts for any medicines but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS prices for sorafenib and lenvatinib due to commercial confidentiality and competition law issues.

Base case results are provided in Table 3 using list prices for all medicines.

Table 3 – Base case results (list prices for all medicines)

Technologies	ICER (£/QALY)
Atezolizumab plus Bevacizumab	-
Sorafenib	£134,835
Lenvatinib	£86,875

LY = life year, QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

One way sensitivity analysis found the model to be sensitive to the discount rates for both benefits and costs, utilities off and on treatment for the period of time with the furthest proximity from death, and costs associated with post-progression survival. Probabilistic sensitivity analysis results at list price are provided in Table 4 and show greater variability for lenvatinib estimates than for sorafenib compared to the base case results. Selected scenario analysis estimates are provided at list for all medicines in Table 5.

Table 4 – Probabilistic Sensitivity Analysis results (at list prices for all medicines)

Technologies	ICER (£/QALY)
Atezolizumab plus Bevacizumab	-
Sorafenib	£136,598
Lenvatinib	£93,741

LY = life year, QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio

Table 5 – Scenario analyses (at list prices for all medicines)

Scenario	Scenario	ICER versus sorafenib	ICER versus lenvatinib
	Base case	£134,835	£86,875
1	5-year time horizon	£208,504	£151,095
2	Atezolizumab+Bevacizumab OS - Generalised Gamma	£141,784	£88,712
3	Atezolizumab+Bevacizumab OS - Log-logistic	£209,651	£99,375
4	Sorafenib OS - Generalised Gamma	£105,296	£86,875
5	Sorafenib OS - Log-logistic	£121,821	£86,875
6	Atezolizumab TTD - Exponential	£132,009	£84,302
7	Atezolizumab TTD - Weibull	£154,291	£104,441
8	Utilities: IMbrave150 (On/Off treatment)	£133,460	£86,701
9	Utilities: IMbrave150 (Off/On progression)	£131,829	£80,950
10	Utilities: IMbrave150 (Off/On progression)+ AE3+	£132,949	£83,189
11	Population: Asian patients (excluding Japan) are excluded	£151,122	£90,681
12	Combined analysis of 15 year time horizon, utilities:IMbrave150 (On/Off progression and Generalised Gamma for Atezolizumab+Bevacizumab OS	£145,744	£87,294
13	Removal of immunotherapies (and their costs) as a subsequent treatment option for sorafenib patients	£141,950	£92,821

QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio, OS = overall survival, PFS = progression-free survival, TTD = time to discontinuation

The main weaknesses with the analysis are:

- There are uncertainties associated with the estimation of long term treatment benefits over the 20 year horizon of the analysis. Median overall survival had not been reached at the time of data cut off in the IMBrave150 study and thus the OS data are immature. Sensitivity analysis did show variability in the ICERs when alternative approaches to extrapolating OS were used, or from the use of a shorter time horizon (Table 5, Scenarios 1-5). There is also uncertainty stemming from the Bayesian NMA in the comparison versus lenvatinib as this showed credible intervals that span 1 for both progression-free survival and overall survival.
- There may be some concerns regarding the generalisability of the clinical trial results to the Scottish population due to the strict inclusion criteria of the clinical trial regarding performance status, Child-Pugh grade and bleeding risk, as described in the clinical effectiveness section. In addition there may be differences in the aetiology of the origin of the disease in the study population versus the Scottish population. The submitting company provided an analysis (Scenario 11 in Table 5) where Asian patients (except those from Japan) were removed from the analysis.
- The company used a proximity to death approach to the estimation of utilities. While this was a reasonable method to use, the company did provide analysis using alternatives (Table 5, Scenarios 8-10). This was helpful it showing that the results were relatively stable when utilities were applied according to either the treatment or the progression status of the patient.

The Committee also considered the benefits of atezolizumab plus bevacizumab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission; and a substantial improvement in quality of life.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted atezolizumab plus bevacizumab for use in NHSScotland.

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

Additional information: guidelines and protocols

The European Society for Medical Oncology (ESMO) published Hepatocellular carcinoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up in 2018.[7] The guidance was subsequently update in 2019, 2020, and 2021 and makes the following relevant recommendations regarding the management of advanced disease:

Systemic therapies

- Sorafenib is the standard of care for patients with advanced HCC and those with intermediate-stage (BCLC B) disease not eligible for, or progressing despite, locoregional therapies. It is recommended in patients with well-preserved liver function and ECOG PS 0–2.
- Lenvatinib showed non-inferiority efficacy compared with sorafenib, and can be considered as first-line therapy in patients with advanced HCC without main portal vein invasion, clear bile duct invasion and ≥50% of tumour to total liver volume occupancy.

Immunotherapies

- In view of the positive results of the atezolizumab+bevacizumab combination, the regimen can be considered as first-line therapy.[7]

The European Association for the Study of the Liver (EASL) published Clinical practice guidelines: Management of hepatocellular carcinoma in 2018.[8] The guidance makes the following relevant recommendations regarding the management of advanced HCC:

Systemic therapies

- Sorafenib is the standard first-line systemic therapy for HCC. It is indicated for patients with well-preserved liver function (Child-Pugh A) and with advanced tumours (BCLC–C) or earlier stage tumours progressing upon or unsuitable for loco-regional therapies.
- Lenvatinib has been shown to be non-inferior to sorafenib and is also recommended in

first-line therapy for HCC given its approval. It is indicated for patients with well-preserved liver function (Child-Pugh A class), good performance status and with advanced tumours – BCLC-C without main portal vein invasion – or those tumours progressing upon or unsuitable for loco-regional therapies.

- There are no clinical or molecular biomarkers established to predict response to first or second-line systemic treatments.
- Regorafenib is recommended as second-line treatment for patients tolerating and progressing on sorafenib and with well-preserved liver function (Child-Pugh A class) and good performance status. Recently, Cabozantinib has shown survival benefits vs. placebo in this setting.

Immunotherapies

- Based on uncontrolled but promising data, immune therapy with nivolumab has received FDA approval in second-line treatment, pending phase III data for conventional approval. At present, the data are not mature enough to give a clear recommendation.[8]

Additional information: comparators

Sorafenib and lenvatinib.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per 3-week cycle (£)
Atezolizumab plus bevacizumab	Atezolizumab 1,200mg followed by bevacizumab 15mg/kg of body weight, administered by intravenous infusion every three weeks	£6,384

Costs from BNF online on 26 February 2021. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs assume body weight of 70kg for bevacizumab dose. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 105 patients eligible for treatment with atezolizumab in year 1 and 111 in year 5 and that 38 patients would receive treatment in year 1 rising to 78 patients in year 5.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to

estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

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

References

1. Roche Products Limited. Atezolizumab concentrate for solution for infusion (Tecentriq®). Summary of product characteristics. Electronic Medicines Compendium Last updated: 20/01/21.
2. Roche Products Limited. Bevacizumab 25mg/ml concentrate for solution for infusion (Avastin). Summary of product characteristics. Electronic Medicines Compendium Last updated: 22/01/21.
3. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY*, et al.* Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. New England journal of medicine. 2020;382(20):1894-905.
4. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y*, et al.* IMbrave150: Updated overall survival (OS) data from a global, randomized, open-label phase III study of atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in patients (pts) with unresectable hepatocellular carcinoma (HCC). Journal of Clinical Oncology. 2021;39(3_suppl):267.
5. European Public Assessment Report. Tecentriq (Atezolizumab). 23/10/2019, EMEA/H/C/004143. https://www.ema.europa.eu.
6. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F*, et al.* Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial.
7. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T*, et al.* Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv238-iv55. Epub 2018/10/05.
8. Galle PR, Forner A, Llovet JM, Mazzaferro V, Piscaglia F, Raoul J-L*, et al.* EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018;69(1):182-236.

This assessment is based on data submitted by the applicant company up to and including 16 April 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.