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HEALTH TECHNOLOGY BRIEFING
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Atezolizumab in combination with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma

NIHRIO ID	24067	**NICE ID**	10217
Developer/Company	Roche Products Ltd	**UKPS ID**	652449

Licensing and market availability plans	Currently in phase II clinical trials

SUMMARY

Atezolizumab in combination with bevacizumab is currently in clinical development for the treatment of patients with an unresectable or advanced type of liver cancer called hepatocellular carcinoma (HCC) that have not received previous treatment. HCC is the most common type of liver cancer and occurs mainly in patients with underlying chronic liver disease and cirrhosis. Advanced or metastatic HCC occurs when the cancer has spread to lymph nodes or to other organs. Advanced unresectable HCC is often diagnosed late in life and has a poor prognosis. It is a debilitating condition with many distressing symptoms, including pain, digestive problems and weight loss.

If licensed, the combination of atezolizumab, that increases the ability of the immune system to attack the cancer cells and slows down disease progression, and bevacizumab that stops the development of tumour blood vessels in order to decrease tumour growth, can potentially provide patients with unresectable or advanced HCC with greater quality and length of life.

PROPOSED INDICATION

Unresectable or advanced hepatocellular carcinoma who have received no prior systemic therapy [a,1]

TECHNOLOGY

DESCRIPTION

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to programmed death-ligand 1 (PD-L1) and provides a dual blockade of the programme cell death protein 1 (PD-1) and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist. PD-L1 may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.[2]

Bevacizumab (Avastin) binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.[3]

Atezolizumab in combination with bevacizumab is in clinical development for the treatment of patients with unresectable or advanced hepatocellular carcinoma (HCC) who have received no prior systemic therapy. In the ongoing phase III clinical trial (NCT03434379) atezolizumab and bevacizumab are administered intravenously (IV) at 1200mg and at 15mg per kilogram respectively on day 1 of each 21 days cycle.[1]

INNOVATION AND/OR ADVANTAGES

Advanced HCC is a disease of high unmet medical need. Current treatment with multikinase inhibitor may have considerable toxicities. Single-agent inhibition of PD-L1/ PD-1 or VEGF signalling has only modest activity in HCC. Bevacizumab, when given with atezolizumab, may further enhance atezolizumab's efficacy by reversing VEGF-mediated immunosuppression and promoting T-cell infiltration into the tumour. Clinical benefit with atezolizumab in combination with bevacizumab has also been observed in phase III studies of patients with first line renal cell carcinoma and non-small cell lung cancer.[4,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The combination treatment of atezolizumab and bevacizumab does not currently have Marketing Authorisation in the EU/UK for any indication.

[a] Information provided by Roche Products Ltd

Atezolizumab as monotherapy is indicated for:[2]

- the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-containing chemotherapy, or who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5%.
- the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab.

Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous NSCLC. In patients with EGFR mutant or ALK-positive NSCLC, atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.[2]

The most common side effects with atezolizumab (which may affect more than 1 in 10 people) are tiredness, reduced appetite, nausea (feeling sick) and vomiting, difficulty breathing, diarrhoea, rash, fever, joint pain, weakness, itching, and urinary tract infection.[6,2]

Bevacizumab is licensed for the following indications:[3]

- in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum.
- in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status.
- in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate.
- in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.
- in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.
- in combination with interferon alfa-2a is indicated for first line treatment of adult patients with advanced and/or metastatic renal cell cancer.
- in combination with carboplatin and paclitaxel is indicated for the front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
- in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.
- in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

The most common side effects with bevacizumab are hypertension (high blood pressure), tiredness or asthenia (weakness), diarrhoea and abdominal (belly) pain. The most serious side effects are gastrointestinal perforation (hole in the gut wall), haemorrhage (bleeding) and arterial thromboembolism (blood clots in the arteries).[7,3]

In addition to HCC, the combination of atezolizumab and bevacizumab is also being explored through phase II and III clinical trials for advanced renal cell carcinoma.[8,9]

PATIENT GROUP

DISEASE BACKGROUND

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, which develops from the main liver cells, called hepatocytes.[10] Most patients with HCC have liver cirrhosis, which develops following long periods of chronic liver disease. Cirrhosis is characterised by a decrease in hepatocyte proliferation, indicating an exhaustion of the regenerative capacity of the liver, and results in an increase in fibrous tissue and a destruction of liver cells, which may ultimately lead to the development of cancerous nodules. Half of all cases of HCC are associated with hepatitis B virus infection, with a further 25% associated with hepatitis C virus. Other risk factors for developing HCC include: alcoholic liver disease, non-alcoholic steatohepatitis, intake of aflatoxin-contaminated food, diabetes and obesity.[11]

The symptoms of liver cancer may include: weight loss, a swollen abdomen, jaundice, loss of appetite over a period of a few weeks, being sick, feeling full or bloated after eating, even after a small meal, itching, a sudden worsening of health in somebody with known chronic hepatitis or cirrhosis, a high temperature and sweating.[12] HCC is usually diagnosed using a combination of blood tests (liver function tests, urea and electrolytes, tumour markers – particularly alpha fetoprotein), ultrasound, CT or MRI scans, biopsy (of liver tumour tissue) and laparoscopic investigation.[13]

The symptoms of HCC in addition to the side-effects of treatment may significantly impact the quality of life of individuals with the condition. Nine out of ten patients reported experiencing pain over their HCC treatment course in a qualitative analysis.[14]

CLINICAL NEED AND BURDEN OF DISEASE

In England, HCC accounts for up to 55% of all primary liver cancer diagnoses in men and up to 28% of diagnoses in women.[15] In England in 2017 there were a total of 4,975 registrations of newly diagnosed malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C.22)[16] applying the percentage above would equal to 2,736 newly diagnosed cases of HCC in men and up to 1,393 in women in England in 2017.

For the UK alone, the European age-standardised incidence rate of liver cancer is projected to increase in the next years from 11.6 per 100,000 in 2014 (equating to 5,520 observed cases) to 15.39 per 100,000 in 2035 (equating to 11,133 projected cases).[17] Meanwhile the European age-standardised mortality rate is projected to increase from 10.29 per 100,000 observed rate in 2014 to 16.26 per 100,000 by 2035.[18]

For England between 2012 and 2016 the persons age-standardised survival rate of adults with liver cancer was 36.7% at one year and 12.1% at five years.[19]

In England and Wales in 2017 there were 4,967 deaths recorded as underlying case malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22).[20] Hospital Episodes Statistics for the period 2017 to 2018 recorded 18,973 finished consultant episodes (FCEs), 12,812 admissions of which 5,817 were days cases for primary diagnosis malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22).[21]

The company has estimated an eligible patient population of 1,700 by 2020.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for HCC depends on the location and stage of the cancer, and how well the liver function is preserved. For people with more advanced disease treatment is palliative rather than curative. Treatment options include interventional procedures such as trans arterial chemoembolisation (using doxorubicin or cisplatin) or selective internal radiation therapy, and external beam radiotherapy. People for whom these treatments are not suitable, or those with metastatic disease, are treated with sorafenib or lenvatinib in the first line setting. Some people with HCC are treated with best supportive care.[15,22]

HCC can be treated with surgical resection, liver transplantation, trans-catheter arterial chemo-embolisation, percutaneous ablation, systemic drug treatment, and external beam or stereotactic radiotherapy.[23]

CURRENT TREATMENT OPTIONS

For people with advanced HCC that have not received previous treatment, the National Institute for Health and Care Excellence (NICE) recommends treatment with lenvatinib only for people with Child-Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Sorafenib is recommended as an option for treating advanced HCC only for people with Child-Pugh grade A liver impairment.[24,22]

PLACE OF TECHNOLOGY

If licenced for this indication, atezolizumab in combination with bevacizumab will offer an additional treatment option for people with untreated unresectable or advanced HCC and may potentially improve quality of life and survival outcomes (Progression Free Survival and Overall Survival).

CLINICAL TRIAL INFORMATION

Trial	**IMbrave150**, NCT03434379, EudraCT-2017-003691-31, **YO40245; adults aged 18 and over; atezolizumab in combination with bevacizumab *vs* sorafenib monotherapy; phase III**
Sponsor	Hoffmann-La Roche
Status	Ongoing

[b] Information provided by Roche Products Ltd on UK Pharma Scan

Source of Information	Trial registry[1,25]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled
Participants	n=480 (planned); aged 18 years and older; locally advanced or metastatic and/or unresectable Hepatocellular Carcinoma (HCC); no prior systemic therapy for HCC; at least one measurable untreated lesion; ECOG Performance Status of 0 or 1.
Schedule	Randomised to: • Experimental arm: Participants will receive Atezolizumab (administered by IV, 1200 mg on day 1 of each 21 day cycle) in combination with bevacizumab (administered by IV, 15 mg/kg on day 1 of each 21 day cycle) until unacceptable toxicity or loss of clinical benefit as determined by the investigator. • Active comparator arm: Sorafenib will be administered orally, 400 mg twice per day, on days 1-21 of each 21-day cycle, until unacceptable toxicity or loss of clinical benefit as determined by the investigator
Follow-up	Follow-up 4 years
Primary Outcomes	1. Overall Survival (OS) [Time Frame: Randomization to death from any cause, through the end of study (up to approximately 4 years)] 2. Progression Free Survival (PFS) as Determined by an Independent Review Facility (IRF) According to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 [Time Frame: Randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 4 years)]
Secondary Outcomes	1. Objective Response (OR) defined as complete response or partial response as determined by the Investigator according to RECIST V1.1 [Time Frame: From baseline until disease progression or death, whichever occurs first (approximately 4 years)] 2. Progression Free Survival (PFS) as Determined by the Investigator According to RECIST v1.1 [Time Frame: Randomization to the first occurrence of disease progression or death from any cause, whichever occurs first (up to approximately 4 years)] 3. Time to Progression (TTP) as Determined by an Investigator According to RECIST v1.1 [Time Frame: Randomization to first occurrence of disease progression (up to approximately 4 years)] 4. Duration of Response (DOR) as Determined by the Investigator According to RECIST v1.1 [Time Frame: From first occurrence of a documented objective response to disease progression or death. Following initiation of study treatment, assessed at baseline, every 6 weeks for the first 54 weeks, and every 9 weeks thereafter (up to approximately 4 years)] 5. OR defined as complete or partial response as Determined by an IRF According to RECIST v1.1 [Time Frame: From baseline until disease progression or death, whichever occurs first (approximately 4 years)] 6. TTP as Determined by an IRF According to RECIST v1.1 [Time Frame: Randomization to the first occurrence of disease progression through the end of study (up to approximately 4 years)] 7. DOR as Determined by an IRF According to RECIST v1.1 [Time Frame: From the first occurrence of a documented objective

	response until confirmed disease progression or death from any cause (whichever occurs first), through the end of study (up to approximately 4 years)] 8. OR defined as complete or partial response, as Determined by an IRF According to Hepatocellular Carcinoma Modified RECIST (HCC mRECIST) [Time Frame: From baseline until disease progression or death, whichever occurs first (approximately 4 years)] 9. PFS as Determined by an IRF According to HCC mRECIST [Time Frame: Randomization to first occurrence of disease progression or death from any cause (whichever occurs first), through the end of study (up to approximately 4 years)] 10. TTP as Determined by an IRF According to HCC mRECIST [Time Frame: Randomization to first occurrence of disease progression through the end of study (up to approximately 4 years)] 11. DOR as Determined by an IRF According to HCC mRECIST [Time Frame: Time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first) through the end of study (up to approximately 4 years)] 12. Time to Deterioration (TTD) in Patient-Reported GHS/QoL, physical functioning, and role functioning, as determined by European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire-Core 30 (QLQ-C30) Score [Time Frame: Randomization to first deterioration maintained for two consecutive assessments, or one assessment followed by death (from any cause) within 3 weeks from any cause, through 1 year after treatment discontinuation] 13. PFS as determined by the investigator according to RECIST v1.1 [Time Frame: Baseline Serum Alpha-Fetoprotein (AFP) Level (< 400 ng/mL or >/=400 ng/mL)] 14. Serum Concentration of Atezolizumab [Time Frame: Day 1 cycle 1, prior to infusion and 30 minutes post-infusion; Day 1 of cycles 2, 3, 4 , 8, 12 and 16 prior to infusion; at treatment discontinuation, through end of study (Approximately 4 years)] 15. Change from Baseline in Anti-Drug Antibodies (ADAs) to Atezolizumab [Time Frame: Day 1 cycle 1, prior to infusion; Day 1 of cycles 2, 3, 4 , 8, 12 and 16 prior to infusion; at treatment discontinuation, through end of study (Approximately 4 years)] 16. Percentage of Participants with Adverse Events [Time Frame: Baseline to end of study (approximately 4 years)] 17. PFS as Determined by an IRF According to RECIST v1.1 [Time Frame: Baseline Serum AFP Level (< 400 ng/mL or >/=400 ng/mL)] 18. OS [Time Frame: Baseline Serum AFP Level (< 400 ng/mL or >/= 400 ng/mL)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Nov 2020

ESTIMATED COST

The NHS indicative price of one vial of Tecentriq 1200mg/20ml concentrate for solution for infusion vials (atezolizumab 60mg per 1 ml) is £3,807.69.[26] A confidential Patient Access Scheme (PAS) is in place.[c]

The NHS indicative price of one vial of Avastin 100mg/4ml solution for infusion vials (bevacizumab 25mg per 1 ml) is £242.66 and one vial of Avastin 400mg/16ml solution for infusion vials (bevacizumab 25mg per 1 ml) is £924.40.[27] A confidential PAS is in place.[d]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal guidance in development. Nivolumab for untreated advanced hepatocellular carcinoma (ID1248). August 2020
- NICE Technology appraisal guidance. Lenvatinib for untreated advanced unresectable hepatocellular carcinoma (TA551). December 2018
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- NICE MedTech innovation briefing. TheraSphere for treating operable and inoperable hepatocellular carcinoma (MIB62). March 2016.
- Interventional procedures guidance (IPG460). Selective internal radiation therapy for primary hepatocellular carcinoma. July 2013
- Interventional procedures guidance (IPG214). Microwave ablation of hepatocellular carcinoma. March 2007
- Interventional procedures guidance (IPG2). Radiofrequency ablation of hepatocellular carcinoma. July 2003

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. Clinical Commissioning Policy: The use of Stereotactic Ablative Radiotherapy (SABR) as a treatment option for patients with Hepatocellular carcinoma or Cholangiocarcinoma. 16022/P. 2016

OTHER GUIDANCE

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- Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. 2017.[29]
- Barts Health NHS Trust, Royal Free London NHS Trust, and London Cancer North and East. Hepatic pancreatic and biliary (HPB) faculty clinical guideline: management of patients with hepatocellular carcinoma (HCC). 2014.[30]

[c] Information provided by Roche Products Ltd
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- The European Society of Medical Oncology. Hepatocellular carcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2012.[31]
- The European Association for the Study of the Liver (EASL) and the European Organization for Research and Treatment of Cancer (EORTC). Management of hepatocellular carcinoma, EASLEORTC clinical practice guidelines. 2012.[32]

ADDITIONAL INFORMATION

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