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Newcastle University

Health Technology Briefing
May 2022

Atezolizumab with bevacizumab for patients with resected or ablated hepatocellular carcinoma who are at high risk for disease recurrence

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28425	NICE ID: 10650	UKPS ID: 660129

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Atezolizumab and bevacizumab in combination is in clinical development for treating adults with high risk of hepatocellular carcinoma (HCC) coming back (recurring), after complete surgical removal (resection/ablation) of the affected tissue. HCC is the most common type of primary liver cancer, which affects men more than women, and is more likely to develop the older a person gets. Symptoms include weight loss, jaundice (yellowing of skin), itching, nausea (feeling sick), bloating of the abdomen, loss of appetite, feeling full after eating small amounts, abdomen pain and a lump on the right side of the abdomen. There are not currently any recommended treatment options for HCC patients to stop recurrence following surgical removal.

Atezolizumab is a monoclonal antibody, a type of protein designed to attach to a protein called program death-ligand 1 (PD-L1), which is present on many cancer cells. PD-L1 acts to switch off immune cells that would otherwise attack cancer cells. By attaching to PD-L1 and reducing its effects, atezolizumab increases the immune system's ability to attack cancer cells and thereby slow down progression of the disease. Bevacizumab binds to vascular endothelial growth factor (VEGF) to stop cancer cells from developing blood vessels that will help them grow, as such it halts tumour growth. Atezolizumab and bevacizumab are administered by infusion into the vein (intravenous). If licensed, a combination of atezolizumab and bevacizumab could provide the first treatment option to stop recurrence following surgical removal of HCC.

Proposed Indication

Adjuvant therapy for adult patients with completely resected or ablated HCC who are at high risk for disease recurrence.[1]

Technology

Description

Atezolizumab (Tecentriq) is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the 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. 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 and bevacizumab are currently in phase III clinical development for the adjuvant treatment of adults with completely resected or ablated HCC who are at high risk for disease recurrence. In the phase III clinical trial (NCT04102098, IMbrave050) patients receive 1200mg atezolizumab and 15mg/kg bevacizumab by intravenous (IV) infusion on Day 1 of each 21-day cycle.[1]

Key Innovation

While curative for some patients, resection and ablation are associated with high rates of recurrence. HCC is currently the only cancer with no proven adjuvant therapy after potentially curative resection.[4] If licensed atezolizumab and bevacizumab would offer the first treatment option for this population.

Regulatory & Development Status

Atezolizumab in combination with bevacizumab, paclitaxel and carboplatin is licensed in the UK for the first-line treatment of adults with metastatic, non-squamous non-small cell lung cancer (NSCLC). Atezolizumab in combination with bevacizumab is also licensed in the UK for the treatment of adults with advanced or unresectable HCC who have not received prior systemic therapy.[2]

Atezolizumab is licensed in the UK, both as a monotherapy and in combinations, for the treatment of adults with:[2]

- Locally advanced or metastatic urothelial carcinoma
- Early-stage NSCLC
- Metastatic NSCLC
- First-line treatment for extensive-stage small cell lung cancer
- Unresectable locally advanced or metastatic triple-negative breast cancer
- Advanced or unresectable HCC who have no received prior systemic therapy

Bevacizumab is licensed in the UK, both as a monotherapy and in combinations, for the treatment of adults with:[3]

- Metastatic carcinoma of the colon or rectum

- First-line treatment for metastatic breast cancer
- First-line treatment for unresectable, advanced or recurrent NSCLC
- First-line treatment for advanced and/or metastatic renal cancer
- First-line treatment for advanced epithelial ovarian, fallopian tube or primary peritoneal cancer
- Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
- Persistent, recurrent or metastatic carcinoma of the cervix

Atezolizumab in combination with bevacizumab is in phase II and III clinical development for appendix adenocarcinoma, rare solid tumours including human papillomavirus (HPV)-related carcinomas, head and neck neoplasms, and rectal cancer, amongst others.[5]

Patient Group

Disease Area and Clinical Need

HCC is the commonest type of primary liver cancer, affecting the main liver cells called hepatocytes.[6] Symptoms include weight loss, jaundice, itching, nausea, bloating of the abdomen, loss of appetite, feeling full after eating small amounts, abdomen pain and a lump on the right side of the abdomen.[7] It is more likely to develop in men than in women and becomes more common as a person ages.[6] Other risk factors of developing HCC include liver cirrhosis, smoking, being overweight or obese, excessive alcohol, non-alcoholic fatty liver disease, and infection with hepatitis viruses.[8]

In England, 2020-21, there were 7,736 finished consultant episodes (FCE) of malignant neoplasm of liver and intrahepatic bile ducts (ICD-10 code C22.0) resulting in 18,483 FCE bed days and 1,530 day cases.[9] In the UK, 2016-18, there were 5,635 deaths every year from liver cancer.[10]

There are no UK-wide statistics for liver cancer survival, however the following survival statistics (with treatment) are taken from the 2012 European Clinical Practice Guidelines for HCC:[11,12]

- Barcelona Clinic Liver Cancer (BCLC) stage 0 (very early stage; Child-Pugh A) – 70-90% will survive ≥5 years
- BCLC stage A (early stage; Child-Pugh A-B) – 50-70% will survive ≥5 years
- BCLC stage B (intermediate stage; Child-Pugh A-B) – Median survival 20 months
- BCLC stage C (advanced stage; Child-Pugh A-B) – Median survival 6-11 months

Recommended Treatment Options

Atezolizumab in combination with bevacizumab is indicated for the treatment of adult patients with advanced or unresectable HCC who have not received prior systemic therapy, however, there are currently no interventions recommended by NICE for HCC following surgical resection or ablation.[13]

Clinical Trial Information

Trial	**IMbrave050; NCT04102098; 2019-002491-14;** A Phase III, Multicenter, Randomized, Open-Label Study of Atezolizumab (Anti-PD-L1 Antibody) Plus Bevacizumab Versus Active Surveillance as Adjuvant Therapy in Patients With Hepatocellular Carcinoma at High Risk of Recurrence After Surgical Resection or Ablation **Phase III –** Active, not recruiting **Location(s):** 8 EU countries, Canada, United States, and other countries

	Primary completion date: September 2023
Trial Design	Randomised, open label treatment, parallel assignment
Population	N=668 (actual); ages 18 years and older; participants with a first diagnosis of HCC who have undergone either curative resection or ablation within 4-12 weeks prior to randomisation; high risk for HCC recurrence
Intervention(s)	• 1200mg atezolizumab administrated by intravenous (IV) infusion on Day 1 of each 21-day cycle. • 15mg/kg bevacizumab administrated by IV infusion on Day 1 of each 21-day cycle.
Comparator(s)	No intervention (active surveillance).
Outcome(s)	**Primary outcome measures:** Recurrence-Free Survival (RFS), as Determined by Independent Review Facility (IRF) [Time Frame: Baseline up to approximately 39 months] RFS is defined as the time from randomization to the first documented occurrence of intrahepatic or extrahepatic HCC as determined by an IRF, or death from any cause (whichever occurs first). See trial record for full list of outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Atezolizumab 1200mg/20ml concentrate for solution for infusion vial NHS indicative price is £3,807.69 (hospital only) and a 840mg/14ml concentrate for solution for infusion vial is £2665.38 (hospital only).[14]

Bevacizumab 100mg/4ml solution for infusion vial NHS indicative price is between £205.55 and £242.66 (hospital only).[15]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Pembrolizumab for adjuvant treatment of hepatocellular carcinoma (ID3994). Expected publication date TBC.
- NICE technology appraisal in development. Nivolumab for adjuvant treatment of high-risk hepatocellular carcinoma after liver resection or ablation (ID3858). Expected publication date: February 2024.

NHS England (Policy/Commissioning) Guidance

- 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.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.

Other Guidance

- The European Society of Medical Oncology (ESMO). Updated treatment recommendations for hepatocellular carcinoma (HCC) from the ESMO Clinical Practice Guidelines. 2021.[16]
- The European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. 2018.[17]
- The American Association for the Study of Liver Diseases (AASLD). AASLD guidelines for the treatment of hepatocellular carcinoma. 2018.[18]
- Hepatocellular Carcinoma: Therapeutic Guidelines and Medical Treatment. 2017.[19]

Additional Information

References

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