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HEALTH TECHNOLOGY BRIEFING
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Cabozantinib in combination with atezolizumab for advanced hepatocellular carcinoma –first line

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Developer/Company	Ipsen Ltd	**UKPS ID**	658945

Licensing and market availability plans	Pre-registration

SUMMARY

Cabozantinib in combination with atezolizumab is in clinical development for the treatment of advanced hepatocellular carcinoma (aHCC). HCC is the most common type of liver cancer and occurs mainly in patients with underlying chronic liver disease and cirrhosis. aHCC occurs when the cancer has spread to lymph nodes or other organs and is often diagnosed late in life with poor prognosis.

Oral cabozantinib is a tyrosine kinase inhibitor (TKI) that works by blocking the activity of enzymes known as tyrosine kinases which can be found in certain receptors in cancer cells. Intravenous atezolizumab is a monoclonal antibody, a type of protein designed to recognise and attach to a protein called PD-L1, which is present on many cancer cells. Their combination has shown promising antitumour activity and tolerability in patients with solid tumours including HCC. If licensed, cabozantinib in combination with atezolizumab will provide an additional first-line treatment option for patients with advanced HCC.

PROPOSED INDICATION

Cabozantinib in combination with atezolizumab versus sorafenib in adults with advanced HCC who have not received previous systemic anticancer therapy in the advanced HCC setting.[a]

TECHNOLOGY

DESCRIPTION

Cabozantinib (Cabometyx; XL-184) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.[1]

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 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.[5]

Cabozantinib in combination with atezolizumab is in clinical development for the first-line treatment of adults with advanced HCC. In the phase III trial (NCT03755791), patients will receive cabozantinib 40 mg orally once daily and atezolizumab 1200 mg intravenously once every 3 weeks. Overall treatment length not specified.[2]

INNOVATION AND/OR ADVANTAGES

Cabozantinib is a standard-of-care treatment option for patients with advanced HCC previously treated with sorafenib.[1] Preclinical and clinical evidence provides a strong scientific rationale for the combination of cabozantinib with atezolizumab and suggests the potential for a synergistic effect on tumour response. Early studies of these combinations have shown promising antitumor activity and tolerability in patients with solid tumours including HCC.[3] Clinical observations on circulating immune suppressive cells and immune effector cells in cancer patients suggest that cabozantinib promotes an immune-permissive microenvironment that may present an opportunity for synergistic effects from combined treatment with immune checkpoint inhibitors in tumour types including HCC.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Cabozantinib in combination with atezolizumab does not currently have Marketing Authorisation in the EU/UK for any indication.

[a] Indication taken from published clinical trial NCT03755791

Cabozantinib is currently licensed in the UK for the following indications as monotherapy:[5,6]

- Cabozantinib is indicated for the treatment of advanced renal cell carcinoma.
    - o in treatment-naïve adults with intermediate or poor risk
    - o in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

- Cabozantinib is indicated as monotherapy for the treatment of HCC in adults who have previously been treated with sorafenib.

- Cabozantinib is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Atezolizumab is currently licensed in the UK for the following indications:[7,8]

- As monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma:

    - after prior platinum-containing chemotherapy, or
    - who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression $\geqslant$ 5%

- As monotherapy for the treatment of adult patients with locally advanced or metastatic non-squamous non-small cell lung (NSCLC) after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving atezolizumab.

- In combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic 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

- In combination with nab-paclitaxel and carboplatin, for the first-line treatment of adult patients with metastatic non-squamous NSCLC who do not have EGFR mutant or ALK-positive NSCLC

- In combination with carboplatin and etoposide, for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)

- In combination with nab-paclitaxel is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer whose tumours have PD-L1 expression $\geqslant$ 1% and who have not received prior chemotherapy for metastatic disease.

Very common (affecting more than one in ten people) adverse reactions associated with the use of cabozantinib as a monotherapy include anaemia, thrombocytopenia, hypothyroidism, decreased appetite, hypomagnesaemia, hypokalaemia, hypoalbuminaemia, dysgeusia,

headache, dizziness, hypertension, haemorrhage, dysphonia, dyspnoea, cough, diarrhoea, nausea, Vomiting, stomatitis, constipation, abdominal pain, dyspepsia, up pain in extremity per abdominal pain, palmar-plantar erythrodysaesthesia syndrome, rash, fatigue, mucosal inflammation, asthenia, peripheral oedema, weight decreased, serum ALT increased, AST increased.[5]

Very common (affecting more than one in ten people) adverse reactions associated with the use of atezolizumab monotherapy include fatigue, decreased appetite, nausea, pyrexia, diarrhoea, cough, rash, dyspnoea, musculoskeletal pain, back pain, vomiting, pruritus, asthenia, arthralgia, urinary tract infection and headache.[9]

Cabozantinib in combination with atezolizumab is in phase III and II clinical development for the treatment of various cancer types including renal cell carcinoma, NSCLC, metastatic prostate cancer, prostate adenocarcinoma, neuroendocrine tumours, anaplastic thyroid cancer, adenocarcinoma, pheochromocytoma, paraganglioma, bladder cancer and various other locally advanced or metastatic solid tumours.[10]

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.[11] 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, and intake of aflatoxin-contaminated food, diabetes and obesity.[12]

HCC patients are frequently asymptomatic, and the appearance of symptoms can signal the development of severe disease. However, symptoms can appear early in patients with HCC due to chronic liver cancer.[13] The main 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, high temperature and sweating.[14] 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.[15]

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.[16]

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.[17] 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).[18] Applying the percentage for HCC 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, the European age-standardised incidence rate of liver cancer is projected to increase from 11 per 100,000 in 2014 (equating to 5,520 observed cases) to 15 per 100,000 in 2035 (equating to 11,133 projected cases).[19] Meanwhile, the European age-standardised mortality rate is projected to increase from 10 per 100,000 observed rate in 2014 to 16 per 100,000 by 2035.[20]

Hospital Episodes Statistics for England for the period 2018-2019 recorded 20,385 finished consultant episodes (FCEs), 13,536 admissions of which 6,267 were days cases and 62,937 FCE bed days for primary diagnosis malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22.0).[21]

In England and Wales in 2017 there were 4,967 deaths recorded for malignant neoplasm of the liver and intrahepatic bile ducts (ICD-10 code C.22.0) as the underlying cause.[22] Latest published survival statistics (patients diagnosed between 2013-2017) report a 1-year age-standardised net survival rate of 38.1% and a 5-year age-standardised net survival rate of 12.5% for patients with liver cancer.[23] In general, the survival rate is poor for HCC; once diagnosed overall survival rate is estimated to be 20 months for Barcelona Clinic Liver Cancer (BCLC) stage B, 11 months for BCLC stage C and <3 months for BCLC stage D.[24] The company has estimated an eligible patient population in the range of 1 per 50,000 and 25 per 100,000.[b]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment for HCC depends on the location and stage of cancer and how well the liver function is preserved. Commonly the Barcelona Clinic Liver Cancer (BCLC) staging system (stages 0, A, B, C and D) are used to assess the number and size of tumours in the liver as well as performance status and liver function.[25]

Patients with very early HCC (stage 0) are candidates for tumour resection or radiofrequency ablation. Early-stage HCC (stage A) can be treated with curative-intent radical therapies such as resection, liver transplantation, percutaneous ethanol injection, or radiofrequency ablation. Intermediate-stage HCC (stage B) is generally treated with transarterial chemoembolization.[26]

Advanced HCC (stage C) is treated with systemic agents. End-stage HCC (stage D) patients have survival of less than 3 months either due to poor liver function or very advanced HCC and may benefit from palliative care. Patients who fail or are not eligible for a certain treatment modality should be offered an alternative option within the same stage or the next BCLC stage.[26]

[b] Information provided by Ipsen Ltd on UK PharmaScan

CURRENT TREATMENT OPTIONS

Current first-line pharmacological treatment options for advanced hepatocellular carcinoma (HCC) patients include:[27]

- Atezolizumab plus bevacizumab is recommended as an option for treating advanced or unresectable HCC in adults who have not had previous systemic treatment only if:
  - they have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 and
  - the company provides it according to the commercial arrangement
- Lenvatinib as an option for untreated, advanced, unresectable hepatocellular carcinoma in adults only if they:
  - they have Child–Pugh grade A liver impairment and an ECOG performance status of 0 or 1 and
  - the company provides it according to the commercial arrangement
- Sorafenib as an option for treating advanced hepatocellular carcinoma only for people with Child-Pugh grade A liver impairment only if the company provides sorafenib within the agreed commercial access arrangement.

PLACE OF TECHNOLOGY

If licensed, cabozantinib in combination with atezolizumab will provide an additional first-line treatment for patients with advanced HCC in adults.

CLINICAL TRIAL INFORMATION

Trial	**COSMIC-312; NCT03755791; A Randomized, Controlled Phase 3 Study of Cabozantinib (XL184) in Combination With Atezolizumab Versus Sorafenib in Subjects With Advanced Hepatocellular Carcinoma Who Have Not Received Previous Systemic Anticancer Therapy** **Trial phase III:** Recruiting **Location(s):** EU (including UK), USA, Canada and other countries **Primary completion date:** August 2020
Trial design	Randomised, parallel assignment, open-label
Population	N= 740 (planned); HCC; BCLC-B and BCLC-C, not amenable to a curative treatment approach or locoregional therapy, child-Pugh A; 18 years and older
Intervention(s)	Cabozantinib 40 mg (once a day) + atezolizumab 1200 mg infusion (once every 3 weeks)
Comparator(s)	Sorafenib 400 mg (twice a day) Cabozantinib 60 mg (once a day)

Outcome(s)	Primary efficacy endpoints:[c] • Duration of progression free survival per RECIST 1.1, by Blinded Independent Radiology Committee (BIRC) for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib) • Duration of overall survival for the experimental arm (cabozantinib + atezolizumab) vs the control arm (sorafenib) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Cabozantinib is already marketed in the UK. The NHS indicative price for cabozantinib tablets is as follows:[28]

- Cabozantinib (20 mg, 40 mg and 60 mg) 30-tab pack costs £5,143.00

Atezolizumab is already marketed in the UK. The NHS indicative price for atezolizumab solution for infusion is as follows:[29]

- Atezolizumab 1200mg/20ml concentrate for solution for infusion (1 vial) costs £3,807.69
- Atezolizumab 840mg/14ml concentrate for solution for infusion (1 vial) costs £2,665.38

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Atezolizumab with bevacizumab for untreated unresectable or advanced hepatocellular carcinoma (ID1655). Expected publication date: 16 December 2020.
- NICE technology appraisal. Lenvatinib for untreated advanced hepatocellular carcinoma (TA551). December 2018.
- NICE technology appraisal. Sorafenib for treating advanced hepatocellular carcinoma (TA474). September 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for specialist liver disease service (children). E03/S(HSS)/d
- NHS England. 2013/14 NHS Standard Contract for Hepatobiliary and pancreas (adult). A02/S/a

[c] Information provided by Ipsen Ltd

OTHER GUIDANCE

- European Society for Medical Oncology (ESMO). eUpdate – Hepatocellular Carcinoma Treatment Recommendations. 2020.[30]
- European Society for Medical Oncology. Hepatocellular Carcinoma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. 2018.[31]
- European Association for the Study of Liver. Management of Hepatocellular Carcinoma guideline. 2018.[32]

ADDITIONAL INFORMATION

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