MSAC Application 1750

Testing of tumour tissue to detect IDH1 mutations in patients with cholangiocarcinoma to determine eligibility for ivosidenib on the PBS

Application for MBS eligible service or health technology

MSAC Application Number:
1750

Application title:
Testing of tumour tissue to detect IDH1 mutations in patients with cholangiocarcinoma to determine eligibility for ivosidenib on the PBS

Submitting organisation:
Servier Laboratories (Aust.) Pty. Ltd.

Submitting organisation ABN:
54004838500

Application description

Succinct description of the medical condition/s:
Cholangiocarcinoma (CCA) is a rare cancer arising from the intrahepatic or extrahepatic biliary epithelium (Rare Cancers Australia 2022). Patients diagnosed with cholangiocarcinoma in Western countries are generally over 65 years of age (approximately 65% of diagnosed cholangiocarcinoma patients). CCA is an aggressive cancer, with 5-year survival around 2% when diagnosed in the advanced stage (Cancer Council Australia 2022, Cancer.Net 2022). Various genetic markers have been identified in CCA; however, there is no standard genetic testing currently conducted in Australia. Isocitrate dehydrogenase (IDH) is an essential metabolic enzyme for cellular respiration in the tricarboxylic acid cycle (Boscoe, Rolland et al. 2019). Mutations in the IDH gene can lead to the increased conversion of α-ketoglutarate to D-2-hydroxyglutarate (D-2HG), which acts as an oncometabolite, promoting tumour proliferation and metastasis development through several pathways (Salati, Caputo et al. 2020).

Succinct description of the service or health technology:
The proposed medical service is testing of tumour tissue in adult patients with locally advanced or metastatic CCA to detect IDH1 mutations to determine eligibility for PBS-subsidised Tibsovo® (ivosidenib). Ivosidenib is an oral, potent, and reversible selective inhibitor of the IDH1 mutant protein, making it a highly targeted therapeutic candidate for treating patients with CCA that harbours an IDH1 mutation.

This application does not nominate a specific methodology for IDH1 testing; however, it is anticipated most pathology laboratories will utilise pyrosequencing, polymerase chain reaction (PCR) or next-generation sequencing (NGS) panels to detect IDH1 mutations in adult patients with locally advanced or metastatic CCA.

Application contact details

Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?
Applicant

Are you applying on behalf of an organisation, or as an individual?
Organisation

Is the applicant organisation the organisation you are representing in the HPP today?
Yes

Application details

Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prostheses List?
Yes

Which list/schedule will the other health technologies be listed on?
Pharmaceutical Benefits Scheme

Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?
New

Please select any relevant MBS items.
-

What is the type of service or health technology?
Investigative

Please select the type of investigative health technology:
Molecular diagnostic tests

Please select the type of molecular diagnostics health technology:
Single gene assay

PICO Set

<u>IDH1 test of CCA tumour tissue to determine eligibility for ivosidenib on the PBS</u>

State the purpose(s) of the health technology for this PICO set and provide a rationale:
-

Purpose category:
Diagnosis / sub-classification

Purpose description:
To establish a diagnosis or disease (sub)classification in symptomatic or affected patients

Population

Describe the population in which the proposed health technology is intended to be used:
Cholangiocarcinoma (CCA) is a rare cancer that encompasses all tumours originating from the epithelium of the bile duct. Bile ducts are a group of thin tubes that carry bile (a digestive fluid) from the liver and gallbladder into the intestines (Rare Cancers Australia 2022). CCA can be categorised into two types (Brindley, Bachini et al. 2021):

- intrahepatic CCA (iCCA) – this type of cancer forms in the bile ducts inside the liver.
- extrahepatic CCA (eCCA) – this type of cancer forms in the bile ducts outside the liver. Extrahepatic cancer can be further distinguished by which region the cancer can form:
  - perihilar CCA: this type of cancer that is found in the hilum region the area where the right and left bile ducts exit the liver and join to form the common hepatic duct.
  - distal CCA: this type of cancer is found in the distal region and is made up of common bile duct which passes through the pancreas and ends in the small intestine.

Although CCA is an uncommon disease, the global incidence of CCA has been rising in recent years (Khan, Emadossadaty et al. 2012, Rizvi, Khan et al. 2018) owing to an increase in the underlying risk factors for the disease. Globally, the incidence of CCA is estimated to be between 0.3-6 cases per 100,000 people (Banales, Marin et al. 2020). The true incidence of iCCA and eCCA is unclear, owing to misclassification between the two types in many national databases (Khan, Tavolari et al. 2019). It is estimated that ~1,161 new cases of CCA were diagnosed in Australia in 2022, based on data from the Australian Institute of Health and Welfare (AIHW) (Australian Institute of Health and Welfare 2022).

Isocitrate dehydrogenases (IDH) are essential metabolic enzymes for cellular respiration in the tricarboxylic acid cycle (Boscoe, Rolland et al. 2019). A mutation in the IDH gene leads to the increased conversion of α-ketoglutarate to D-2-hydroxyglutarate (D-2HG), which acts as an oncometabolite, promoting tumour proliferation and metastasis development through several pathways, such as DNA methylation and activation of vascular endothelial growth factors (VEGFs) (Salati, Caputo et al. 2020). The two main subtypes of IDH are IDH1 and IDH2.

In the early stages of CCA, patients are often asymptomatic, hence they often present with advanced disease (Blechacz, Komuta et al. 2011, Brindley, Bachini et al. 2021). Symptomatic patients will vary in clinical presentation depending on the location of the tumour and growth pattern (Blechacz, Komuta et al. 2011). Patients diagnosed with iCCA often present asymptomatically during early stages of disease but will later develop symptoms such as abdominal pain or uncommonly, jaundice during progression into advanced stage. Patients diagnosed with eCCA typically present with painless jaundice owing to the underlying biliary obstruction (Brindley, Bachini et al. 2021). The general symptoms of CCA are consistent with the clinical presentation for biliary obstruction i.e. jaundice, pale stool, dark urine and pruritus. Other common symptoms can include, abdominal pain, malaise, weight loss, fatigue, fever, cachexia and night sweats (Blechacz 2017, Brindley, Bachini et al. 2021).

CCA is among the most challenging cancers to treat and is often associated with poor prognosis both in the early and advanced stages due to its silent clinical character. The 5-year survival of CCA is around 2% if diagnosed in the advanced stage (Cancer.Net 2022). The current treatment landscape for CCA is generalised to broad biliary tract cancer, with limited second-line treatment options available. Hence, there is a significant clinical need for new targeted treatments. Although IDH1 mutations have been found in CCA, there is no standard genetic screening tests currently available in Australia.

Search and select the most applicable medical condition terminology (SNOMED CT):
Cholangiocarcinoma of biliary tract

Intervention

Name of the proposed health technology:
Test: Tumour tissue testing for IDH1 gene mutations. Treatment: TIBSOVO® (ivosidenib)

Comparator

Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:

Test: As testing for IDH1 mutation is not currently funded for CCA patients, the comparator would be 'no testing'.

Treatment: The standard care for previously treated patients with locally advanced or metastatic CCA without an actionable genetic target (such as IDH1) is palliative care, or combination chemotherapy (FOLFOX, FOLFIRI). Based on data from the TOPAZ-1 study, up to 40% of patients are expected to receive second-line treatment with combination chemotherapy, while the majority of patients are currently expected to receive palliative care. Proportionally fewer patients are expected to received third-line treatment with combination chemotherapy. As such, no treatment/palliative care is expected to be the primary treatment comparator for this submission.

Outcomes

Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:
As a result of a positive IDH1 tumour tissue test, a change in clinical management would occur. Patients who harbour an IDH1 mutation would be eligible to receive ivosidenib on the PBS, resulting in improved health outcomes such as increased progression-free survival, overall survival and maintenance of quality of life.

Test outcomes
Trial based (evidentiary standard) analytical performance:

- Sensitivity
- Specificity
- Positivity predictive value (PPV)
- Negative predictive value (NPV)

Clinical utility of test:

Treatment effect modification of ivosidenib in patients with locally-advanced or metastatic CCA positive with an IDH1 mutation.

Other test-related considerations:

- Test turn-around time
- Estimated number of patients being tested
- Number needed to test
- Cost of testing per patient

Drug outcomes
-

Safety outcomes:
Safety and tolerability of ivosidenib treatment assessed by adverse events, physical examinations, laboratory findings, and vital signs.

Clinical effectiveness outcomes:
- Progression-free survival (PFS)
- Overall survival (OS)
- Adverse events (AEs)
- Health-related quality of life (HRQoL)

The ClarIDHy trial (n=185) investigated the efficacy and safety of ivosidenib in IDH1 mutation in patients with locally advanced or metastatic CCA who had experienced disease progression

on prior therapy. The results of the study found that treatment with ivosidenib was associated with significantly improved progression-free survival (PFS) compared to placebo (median PFS for ivosidenib 2.7 months vs 1.4 months with placebo; HR 0·37; 95% CI 0·25–0·54; one-sided p<0·0001). Treatment with ivosidenib was associated with significantly improved OS after adjustment for treatment switching (median OS for ivosidenib 10.3 months vs 5.1 months with placebo; HR 0.49; 95% CI 0.34-0.7; one-sided p < 0.01). Overall, the study showed that in CCA patients with an IDH1 mutation, ivosidenib significantly improves PFS and OS, while maintaining quality of life.

Proposed MBS item

Proposed Item AAAAA

MBS item number:
73372

Proposed category:
PATHOLOGY SERVICES

Proposed group:
GENETICS

Proposed item descriptor:
Analysis of tumour tissue, as requested by a specialist or consultant physician, that:

- Is for a patient with histologically confirmed locally advanced or metastatic cholangiocarcinoma,
- Is for the identification of IDH1 pathological variant status,
- To determine eligibility for PBS-subsidised ivosidenib

Applicable only once per lifetime

Proposed MBS fee:
$340.00

Indicate the overall cost per patient of providing the proposed health technology:
$340.00

Please specify any anticipated out of pocket costs:
$0.00

Provide details and explain:
N/A

How is the technology/service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):
Currently, there is no public funding for diagnostic tests for IDH1mutations in CCA patients. Research funding is available through the MoST program or other research programs. Testing is often self-funded by patients if they are not enrolled in a clinical trial.

Claims

In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?
Superior

Please state what the overall claim is, and provide a rationale:
Tumour tissue testing to determine IDH1 status, followed by targeted treatment with ivosidenib is superior to no genetic testing and untargeted care in patients with locally advanced or metastatic CCA.

In patients with locally advanced or metastatic CCA harbouring an IDH1 mutation , ivosidenib has been shown to significantly improve health outcomes compared to treatment with placebo (Abou-Alfa, Macarulla et al. 2020, Zhu, Macarulla et al. 2021). The ClarIDHy trial was an international, multicentre, randomised double-blinded placebo-controlled trial that investigated the efficacy and safety of ivosidenib in patients with IDH1 mutated locally advanced or metastatic CCA who had received at least one previous line of chemotherapy. 185 participants were assessed to be eligible and enrolled in the study and were randomly assigned (2:1) to receive 500mg of either ivosidenib or matched placebo. The primary endpoint was progression-free survival, followed by the key secondary endpoints of overall survival, health-related quality of life and safety. Patients were allowed to cross-over into the intervention arm after disease progression in the placebo arm – resulting in 70% of patients in the placebo arm crossed over and receiving ivosidenib. The results of the study found that treatment with ivosidenib was associated with significantly improved progression free survival (PFS) (median PFS for ivosidenib 2.7 months vs 1.4 months with placebo; HR: 0.37; 95% CI 0.25-0.54; one-sided p = <0.0001). For overall survival (OS), when adjusted for crossover, the study showed that treatment with ivosidenib was associated with significantly improved OS. After adjustment for treatment switching (median OS for ivosidenib 10.3 months vs 5.1 months with placebo (HR 0.49; 95% CI 0.34-0.70; one-sided p<0.01). Overall, ivosidenib was well tolerated with low rates of treatment discontinuation or dose reductions.

Estimated utilisation

Estimate the prevalence and/or incidence of the proposed population:
Cholangiocarcinoma is a rare cancer with limited accuracy on the actual number of diagnosed cases. The true incidence of iCCA and eCCA is unclear, owing to the extensive misclassification of intrahepatic and extrahepatic CCA in many national databases (Khan, Tavolari et al. 2019). The Australian Institute for Health and Welfare (AIHW) publishes Australian incidence data classified based on ICD 10 codes. eCCA is classified under ICD 10 code C24.0 (extrahepatic biliary tract cancers) and data is available for the incidence of this subgroup alone. The AIHW predicted that 425 new cases of eCCA would be diagnosed in 2022 (Australian Institute of Health and Welfare 2022).

iCCA is categorised as a primary liver cancer, and incidence for this subgroup is not readily available. Based on actual incidence data from 2013, it is estimated 25.3% of primary liver cancers are iCCA (Australian Institute of Health and Welfare 2018). The AIHW estimated that 2,905 new cases of primary liver cancer would be diagnosed in Australia in 2022 (Australian Institute of Health and Welfare 2022). Therefore, it is estimated 736 new iCCA diagnoses were reported in 2022. (i.e. ~25.3% of 2,905).

Overall, the estimated incidence of new cases of CCA in Australia in 2022 was calculated to be 1,161 patients (736+425).

Provide the percentage uptake of the proposed health technology by the proposed population:

Year 1 estimated uptake(%)

[redacted]

Year 2 estimated uptake(%):

[redacted]

Year 3 estimated uptake(%):

[redacted]

Year 3 estimated uptake(%):

[redacted]

Estimate the number of patients who will utilise the proposed technology for the first full year:

[redacted]

Optionally, provide details:
Not all patents with locally advanced or metastatic cancer will be subject to IDH1 testing based on the health status of the patient, availability of biopsy material or patients in clinical trials.

Will the technology be needed more than once per patient?

No, once only

Consultation

List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the health technology/service:

- Omico
- The Royal College of Pathologists of Australasia (RCPA)

List all appropriate professional bodies / organisations representing the group(s) of health professionals who request the health technology/service:

- Clinical Oncology Society of Australia (COSA)
- Omico
- Private Cancer Physicians of Australia (PCPA)
- The Medical Oncology Group of Australia (MOGA)
- The Royal College of Pathologists of Australasia (RCPA)

List all appropriate professional bodies / organisations representing the group(s) of health professionals that may be impacted by the health technology/service:

- Omico
- Private Cancer Physicians of Australia (PCPA)
- The Australasian Gastro-Intestinal Trials Group (AGITG)
- The Medical Oncology Group of Australia (MOGA)
- The Royal College of Pathologists of Australasia (RCPA)

List the patient and consumer advocacy organisations or individuals relevant to the proposed health technology:

- Cholangiocarcinoma Foundation Australia
- GI Cancer Institute
- Pancare
- Rare Cancers Australia

List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed service or health technology:
-

Regulatory information

Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?
No

Codependent details

Will a submission be made to the Pharmaceutical Benefits Advisory Committee (PBAC)?
Yes

Please provide a rationale for the codependency and indicate how the proposed PBS restriction would reference the intervention(s) proposed for MSAC consideration:
It is proposed that all patients diagnosed with locally advanced or metastatic CCA will be eligible to undergo testing for IDH1 mutation, regardless of CCA subtype classification (iCCA or eCCA).

Patients who test positive to an IDH1 mutation would then be eligible for access to PBS-subsidised ivosidenib, following disease progression. The test is proposed to occur at diagnosis of CCA (rather than following progression) to avoid delays in receiving treatment with ivosidenib.

[redacted]