Report Imfinzi®- durvalumab

Product & Mechanism of action

Substance: durvalumab

Brand Name: Imfinzi®

Originator/licensee: AstraZeneca AB

Classification: NI

ATC code: L01FF03

Orphan Status:
EU: No
US: Yes

Mechanism of action: Durvalumab is a fully human mABthatselectively blocks the interaction of PD-L1 with PD-1 and CD80. The blockade of PD-L1/PD-1 andPD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation[1].

Authorized indications Licensing status

Authorized Indication:
EMA:
Durvalumabin combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectableHCC [2].

FDA:
Imfinzi is indicated in combination with tremelimumab, for the treatment of adultpts with unresectable HCC [3].

Route of administration: IV

Licensing status
EU CHMP P.O. date: 15/12/2022
FDA M.A. date: 21/10/2022

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: No

ABBREVIATIONS:
AE: adverse event
BCLC: Barcellona Clinic Liver Cancer
CHMP: Committee for Medicinal Products for Human Use
ECOG: Eastern Cooperative Oncology Group
HCC: hepatocellular carcinoma
M.A.: marketing authorization
mAB: monoclonal antibody
OS: overall survival
P.O.: positive opinion
Pts: patients

Essential therapeutic features

Summary of clinical EFFICACY: The efficacy of durvalumab in combination with tremelimumab was evaluated in the HIMALAYAstudy (NCT03298451), a phase 3, randomized (1:1:1), open-label, multicenter study in pts with unresectable HCC. The study enrolled pts with BCLC Stage C or B (not eligible for locoregional therapy) and who had not received prior systemic treatment for HCC. Pts were randomized to receivedurvalumab+tremelimumab (1,500mg durvalumabin combination with tremelimumab as a one-time single IV infusion of 300 mg on the same day, followed by durvalumab every 4 weeks), durvalumab (1,500 mg every 4weeks), or sorafenib (400mg given orally twice daily). Randomization wasstratified by macrovascular invasion (yes or no), etiology of liver disease (hepatitis B virus vs hepatitis C virus vs others) and ECOG performance status (0 vs 1). Study treatment was given until diseaseprogression or unacceptable toxicity, but it was permitted beyond disease progression if the patient was clinically stable and derivingclinical benefit as determined by the investigator. The major efficacy outcome measure was OS between the durvalumab+tremelimumab armand the sorafenib arm. Efficacy interim results are presented in the following table [3]. The trial is still ongoing and recruiting pts [4].

	Durvalumab + tremelimumab(N=393)	Sorafenib (N=389)
Number of deaths (%)	262 (66.7)	293 (75.3)
Median OS (months) (95% CI)	16.4(14.2 - 19.6)	13.8(12.3 - 16.1)
HR (95% CI)	0.78 (0.66 - 0.92)	
p value for OS	0.0035	

Summary of clinical SAFETY: The safety of durvalumab in combination with tremelimumab was evaluated in a total of 388 pts in the HIMALAYA trial.Serious AEs occurred in 41% of pts who received durvalumab+tremelimumab. Serious AEs in >1% of pts included hemorrhage (6%), diarrhea(4%), sepsis (2.1%), pneumonia (2.1%), rash (1.5%), vomiting (1.3%), acute kidney injury (1.3%), andanemia (1.3%). Fatal adverse reactions occurred in 8% of pts, including death (1%), hemorrhage intracranial (0.5%), cardiac arrest (0.5%),pneumonitis (0.5%), hepatic failure (0.5%), and immune-mediated hepatitis (0.5%). The most common AEs (occurring in ≥ 20% of pts) were rash, diarrhea, fatigue, pruritis, musculoskeletalpain, and abdominal pain. Permanent discontinuation of treatment regimen due to an adverse reaction occurred in 14% of pts and dosage interruptions or delay of the treatment regimen due to an AE occurred in 35% of pts. [3]

Ongoing studies:
- ***For the same indication:***Yes
- ***For other indications:****Yes*

Discontinued studies (for the same indication): No

References:

1. https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf
2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/imfinzi-2
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s036lbl.pdf
4. https://clinicaltrials.gov/(NCT03298451)
5. https://gallery.farmadati.it/
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7. https://www.ioveneto.it/pathology/tumore-del-fegato/
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9. https://clinicaltrials.gov/ct2/results?cond=Advanced+Hepatocellular+Carcinoma&term=&cntry=&state=&city=&dist=&recrs=a&recrs=b&recrs=d&recrs=e&recrs=f&type=Intr&phase=2

NHS impact

Cost of therapy: Considering the ex-factory price (2,631.59€ forImfinzi® 50mg/mL 10mL, corresponding to 500mg of durvalumab), a single administration of 1,500mg would cost 7,894.77€. [5]

Epidemiology:HCC is the most common form of liver cancer and accounts for ~90% of cases [6].The European incidence of HCC is 7 cases per 100,000 inhabitants per year among males and 2 per 100,000 among females. In most cases, it occurs in an advanced stage [7].

POSSIBLE PLACE IN THERAPY: Durvalumab has been approved, in combination with tremelimumab, for the first-line treatment of advanced or unresectable HCC[2].Atezolizumab in combination with bevacizumab is also considered a first-line therapy for advanced or unresectable HCC.Sorafenib and lenvatinib are also considered first-line treatmentsif the associationatezolizumab + bevacizumab is contraindicated [6].

OTHER INDICATIONS IN DEVELOPMENT: Bladder cancer; Cervical cancer; Endometrial cancer; Fallopian tube cancer; Gastric cancer; Head and neck cancer; Liver cancer; Mesothelioma; Oesophageal cancer; Ovarian cancer; Peritoneal cancer; Renal cell carcinoma; Solid tumours; Triple negative breast cancer; Pancreatic cancer[8].

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:-

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:
Tislelizumab,Camrelizumab, Toripalimab, Nivolumab, Ipilimumab, Pembrolizumab, Nofazinlimab, Namodenoson, Icaritin, Anlotinib (Phase 3) [9].

*Service reorganization: Yes
*Possible off label use: Yes

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