Report Imjudo® – Tremelimumab

Product & Mechanism of action

Substance: Tremelimumab

Brand Name: Imjudo®

Originator/licensee: AstraZeneca AB

Classification: NCE

ATC code: L01FX20

Orphan Status:
Eu: Yes
Us: Yes

Mechanism of action:
Tremelimumab is a monoclonal antibody that binds to CTLA-4, which is primarily expressed on the surface of activated T lymphocytes, and thus enhances T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced anti-tumour activity [1].

Authorized indications Licensing status

Authorized Indication:
EMA: Tremelimumab in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable HCC [1].

FDA: Tremelimumabis indicated in combination with durvalumab for the treatment of adult patients with unresectable HCC [2].

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
FDASpeed Approval Pathway: NO

ABBREVIATIONS:
AEs: Adverse Events
BCLC: Barcellona Clinic LiverCancer
CHMP: Committee for Medicinal Products for Human Use
CTLA-4: Cytotoxic T-Lymphocyte Antigen 4
ECOG: Eastern Cooperative Oncology Group
FDA: Food and Drugs Administration
HCC: hepatocellular carcinoma
HR: Hazard ratio
M.A.: Marketing Authorization
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 HIMALAYA study (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 receive durvalumab+tremelimumab (1,500 mg durvalumab in 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 4 weeks), or sorafenib (400 mg given orally twice daily). Randomization was stratified 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 disease progression or unacceptable toxicity, but it was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. The major efficacy outcome measure was OS between the durvalumab+tremelimumab arm and 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%), and anemia (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, musculoskeletal pain, 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% ofpts [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/medicines/human/summaries-opinion/imjudo
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761289Orig1s000Correctedlbl.pdf
3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761069s036lbl.pdf
4. https://clinicaltrials.gov (NCT03298451)
5. https://gallery.farmadati.it/
6. https://pubmed.ncbi.nlm.nih.gov/33479224/
7. https://www.ioveneto.it/pathology/tumore-del-fegato/
8. https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=Tremelimumab&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=1&phase=2&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=
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 of Imfinzi®, a single administration of 1,500mg would cost 7,894.77€ [5].The cost of Imjudo® is still not available.

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:
Tremelimumab has been approved, in combination with durvalumab, 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 treatments if the association atezolizumab + bevacizumab is contraindicated [6].

OTHER INDICATIONS IN DEVELOPMENT:
Phase 3: Head and neck cancer, bladder cancer, urothelial cancer, renal cell carcinoma, small cell lung cancer, solid tumours.
Phase 2: Thyroid cancer, mesothelioma, germ cell tumor , neuroendocrine tumors,gastric cancer, colorectal cancer, pancreatic cancer, esophageal adenocarcinoma, oropharyngeal cancer, breast cancer, endometrial cancer, Fallopian tube carcinoma, ovarian cancer, cervical cancer,prostate cancer, soft tissue sarcoma, sarcoma, peritoneal cancer, glioma[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

Issued on: