Durvalumab (Imfinzi®) in combination with gemcitabine and cisplatin for the first-line treatment of unresectable or metastatic biliary tract cancer (BTC)

General information

Drug description [1]	Indication [2]
Durvalumab (Imfinzi®) is a fully human, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1).	Durvalumab (Imfinzi®) in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC.

Current treatment [3]

- **First-line treatment of advanced and metastatic BTC**
  - Cisplatin–gemcitabine is recommended as standard of care in the first-line setting for patients with a performance status of 0-1 (I, A).
  - The combination of cisplatin–gemcitabine with durvalumab should be considered in first-line BTC (I, A; ESMO-MCBS v1.1 score: 4; FDA approved, not EMA approved).
  - Oxaliplatin may be substituted for cisplatin when renal function is of concern (II, B).
  - Gemcitabine monotherapy may be used in patients with a PS of 2 (IV, B).

Regulatory status

EMA [1, 2]

Approval status for this indication: On 10 November 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Imfinzi®.

<u>The CHMP adopted a new indication to include first-line treatment of biliary tract cancer:</u>

- Imfinzi® in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC.

Other indications:

- Imfinzi® as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.
- Imfinzi® in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising epidermal growth factor receptor (EGFR) mutations or ALK positive mutations.
- Imfinzi® in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).
- Imfinzi® in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC)

✓ **Medicine under additional monitoring**

FDA [4, 5]

Approval status for this indication: On 2 September 2022, the FDA approved durvalumab (Imfinzi®) in combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic BTC.

- ✓ **Priority review**
- ✓ **Orphan drug designation**

Other indications: Imfinzi® is indicated:

- for the treatment of adult patients with unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
- in combination with tremelimumab-actl and platinum-based chemotherapy, for the treatment of adult patients with metastatic NSCLC with no sensitising EGFR mutations or anaplastic lymphoma kinase (ALK) genomic tumour aberrations.
- in combination with etoposide and either carboplatin or cisplatin, as first-line treatment of adult patients with ES-SCLC.
- in combination with tremelimumab-actl, for the treatment of adult patients with unresectable HCC

Costs

10 ml Imfinzi® concentrate for solution for infusion 50 mg/ml = **€ 3,026.24** (ex-factory price) [6].

Warnings and precautions [4]

- **Immune-mediated adverse reactions**
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis and renal dysfunction, solid organ transplant rejection, and immune-mediated pancreatitis.
    - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
    - Withhold or permanently discontinue based on severity and type of reaction.
- **Infusion-related reactions**
  - Interrupt, slow the rate of infusion, or permanently discontinue Imfinzi® based on the severity of the reaction.
- **Complications of allogeneic HSCT**
  - Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody.
- **Embryo-foetal toxicity**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and use of effective contraception.
- **Traceability**
  - In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.
- **Pneumonitis and radiation pneumonitis**
  - Radiation pneumonitis is frequently observed in patients receiving radiation therapy to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar. Patients should be monitored for signs and symptoms of pneumonitis or radiation pneumonitis.
  - Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended (please see product information).
- **Immune-mediated myocarditis**
  - Immune-mediated myocarditis, which can be fatal, occurred in patients receiving Imfinzi® or Imfinzi® in combination with tremelimumab.
  - Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in product information.
- **Disease-specific precaution (BTC)**
  - Cholangitis and biliary tract infections
    - Cholangitis and biliary tract infections are not uncommon in patients with advanced BTC. Patients with BTC (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter.

Study characteristics [3, 7]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
TOPAZ-1 NCT03875235	685 1:1	Durvalumab 1500 mg on day 1 of each cycle, in combination with gemcitabine (1000 mg/m²) and cisplatin (25 mg/m²),	Placebo on day 1 of each cycle, in combination with gemcitabine (1000 mg/m²) and cisplatin (25 mg/m²),	OS	**ongoing**[3], randomised, double-blind, placebo-controlled, global, phase 3 study	-	AstraZeneca	TOPAZ-1 trial [8]

[3] The TOPAZ-1 trial is currently ongoing; estimated study completion date is 03/2025.

		which were administered on days 1 and 8 of each cycle[1]	which were administered on days 1 and 8 of each cycle[2]					

Efficacy (I vs. C)	**Safety** (I vs. C)
Data cut-off 11 August 2021: **Median duration of follow-up**: 16.8 months (95% CI, 14.8-17.7) vs. 15.9 months (95% CI, 14.9-16.9) **Patients who had died as of data cut-off**: 58.1% vs. 65.7% **Median OS**: 12.8 months (95% CI, 11.1-14.0) vs. 11.5 months (95% CI, 10.1-12.5) **HR for OS**[4]: 0.80; 95% CI, 0.66-0.97; p=0.021 **Estimated OS rates at 12 months**: 54.1% (95% CI, 48.4-59.4) vs. 48.0% (95% CI, 42.4-53.4) **Estimated OS rates at 18 months**: 35.1% (95% CI, 29.1-41.2) vs. 25.6% (95% CI, 19.9-31.7) **Estimated OS rates at 24 months**: 24.9% (95% CI, 17.9-32.5) vs. 10.4% (95% CI, 4.7-18.8) **Median PFS**: 7.2 months (95% CI, 6.7-7.4) vs. 5.7 months (95% CI, 5.6-6.7) **HR for PFS**: 0.75 (95% CI, 0.63-0.89; p=0.001) **Investigator-assessed confirmed ORR** (sum of the rate of complete responses and partial responses in patients with measurable disease): 26.7% vs. 18.7%; odds ratio 1.60; 95% CI, 1.11-2.31 **Complete response**: 2.1% vs. 0.6% **Partial response**: 24.6% vs. 18.1% **Patients with continued response for ≥9 months**: 32.6% vs. 25.3% **Patients with continued response for ≥12 months**: 26.1% vs. 15.0% **Updated OS data (data cut-off 25 February 2022, median follow-up time 23.4 vs. 22.4 months) [9]:** **Median OS**: 12.9 months (11.6-14.1) vs. 11.3 months (10.1-12.5); HR 0.76; 95% CI, 0.64-0.91 **OS rates at 12 months, 18 months and 24 months**: 54.3% vs. 47.1%, 34.8% vs. 24.1% and 23.6% vs. 11.5%	**Data cut-off 11 August 2021** **Any grade AEs**: n=336/338 (99.4%) vs. n=338/342 (98.8%) **AEs grade 3 or 4**: n=256/338 (75.7%) vs. n=266/342 (77.8%) **Discontinuation of any treatment component due to AEs**: 13.0% vs. 15.2% **Deaths due to AEs:** n=12/338 (3.6%) vs. n=14/342 (4.1%) **Immune-mediated AEs**: 12.7% vs. 4.7% **Immune-mediated AEs grade 3 or 4**: 2.4% vs. 1.5% **Updated OS data (data cut-off 25 February 2022, median follow-up time 23.4 vs. 22.4 months) [8]:** **Grade 3/4 TRAEs**: 60.9% vs. 63.5% of pts **TRAEs leading to discontinuation of any study medication**: 8.9% vs. 11.4%

Patient-reported outcomes [10]

- The EORTC Quality of Life Questionnaire (QLQ)-C30 and BIL21 were administered at baseline and every cycle throughout treatment.
- Change from baseline to post-2 cycles and deterioration of HRQoL (≥10 points change) were analysed (data cut-off 22 March 2021).
- Compliance for QLQ was very high (>90%) at all time points.
- C30 global health status (GHS) scores remained stable at all time points and from baseline to post 2 cycles (mean change 2.66, 95% CI, -1.10–6.42), with greater improvements observed in patients with responder (a best response of CR or PR) (3.60, -1.27-8.47) compared to non-responder (stable disease or progressive disease, 0.66, -5.19-6.51).
- For the overall cohort, functioning scales also remained stable from baseline to post 2 cycles.
- Nausea/vomiting (8.4), dyspnea (7.28), constipation (9.24), financial difficulties (5.53) in C30 and eating (5.53), tiredness (5.42), treatment side effects (7.98) in BIL21 were worse at post 2 cycles.
- Pain (-7.14), diarrhoea (-4.48) in C30 and jaundice (-5.51), pain (-6.02) in BIL21 were improved and more improvement was shown in responder compared to non-responder.

[1] After completion of gemcitabine and cisplatin, 1500 mg of durvalumab or placebo monotherapy was administered once every 4 weeks until clinical or imaging (per RECIST v1.1) disease progression or until unacceptable toxicity, withdrawal of consent, or any other discontinuation criteria were met. Patients who were clinically stable at initial disease progression could continue to receive study treatment at the discretion of the investigator and patient.

[2] After completion of gemcitabine and cisplatin, 1500 mg of durvalumab or placebo monotherapy was administered once every 4 weeks until clinical or imaging (per RECIST v1.1) disease progression or until unacceptable toxicity, withdrawal of consent, or any other discontinuation criteria were met. Patients who were clinically stable at initial disease progression could continue to receive study treatment at the discretion of the investigator and patient.

[4] Since the trial reached statistical significance for the primary objective on the basis of the prespecified interim analysis, the sponsor was unblinded, and the results presented are to be considered the final, formal statistical analysis for OS. The TOPAZ-1 study is ongoing, allowing for further, exploratory follow-up analyses of OS.

❖ Regarding deterioration of C30 GHS, median deterioration-free survival (months was 4.14, 95% CI, 2.66-6.47) in all cohorts and there was no difference between responder (3.68) and non-responder (5.59, HR= 1.00; 95% CI, 0.62-1.61, p=0.997). There was no difference among 3 cohorts.

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2a	≤12 months	OS at 24 months: +23.3%	-	Increase in 2 year survival ≥10%	4	-	No differences	-	4
Adapted	NC	2a	≤12 months	OS at 24 months: +23.3%	-	Increase in 2 year survival ≥10%	4	-	No differences	-	4

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear	unclear	yes	unclear[5]	yes[6]	unclear

First published: 12/2022
Last updated: 04/2023

Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, BTC=biliary tract cancer; C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, EC-SCLC=extensive-stage small cell lung cancer, EGFR=epidermal growth factor receptor, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HCC=hepatocellular carcinoma, HSCT=haematopoietic stem cell transplantation, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NSCLC=non small cell lung cancer, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

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8. Do-Youn Oh, He AR, Shukui Qin, et al., Investigators ftT-. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evid 2022; 1 (8).

[5] The TOPAZ-1 trial is ongoing; currently, only interim analysis data is available.

[6] AstraZeneca sponsored the trial and collaborated with the steering committee on the trial design and collection, analysis, and interpretation of the data. Data analyses were completed by PHASTAR, London, United Kingdom, and AstraZeneca. Durvalumab was provided by AstraZeneca. An independent data monitoring committee reviewed unblinded safety data approximately every 6 months. The manuscript was prepared by the authors, with medical writing support funded by the sponsor.

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