Erdafitinib (Balversa®) as monotherapy for the treatment of unresectable or metastatic urothelial carcinoma (UC)

General information [1]

Drug description

The active substance of Balversa® is erdafitinib, an antineoplastic protein kinase inhibitor that inhibits the fibroblast growth factor receptor (FGFR) tyrosine kinases. Deregulation of FGFR3 signalling has been implicated in the pathogenesis of urothelial cancer, and FGFR inhibition has shown antitumour activity in FGFR-expressing cells.

Indication

Balversa® as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting.

Incidence [2]

In Austria, in 2022, a total of 1,247 persons were newly diagnosed with bladder cancer. The age-standardised[1] incidence rate was 22.3/100,000 in men and 6.3/100,000 in women.

Current treatment [3]

The Onkopedia treatment recommendation for the treatment of metastatic urothelial carcinoma is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1]	FDA [4, 5]
Approval status for this indication: On 27 June 2024, the CHMP adopted a positive opinion, recommending granting a marketing authorisation for Balversa®. The full indication is: ❖ Balversa® as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting. Balversa® will be available as 3 mg, 4 mg and 5 mg film-coated tablets. **Other indications**: none	**Approval status for this indication**: On 19 January 2024, the FDA approved erdafitinib (Balversa®) for adult patients with locally advanced or metastatic UC with susceptible FGFR3 genetic alterations, as determined by an FDA-approved companion diagnostic test, whose disease has progressed on or after at least one line of prior systemic therapy. Limitations of Use: Balversa® is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy. ✓ Priority review **Other indications**: none

Manufacturer

Balversa® is manufactured by Janssen-Cilag International N.V.

Costs

Currently, there is no cost information available.

Warnings and precautions[2] [4]

❖ **Ocular disorders**

[1] European Standard Population 2013.

[2] Since there is currently no EMA EPAR available, chapter "Warnings and precautions" refers to FDA Label Information.

- Balversa® can cause central serous retinopathy/retinal pigment epithelial detachment.
- Perform monthly ophthalmological examinations during the first four months of treatment, every 3 months afterwards, and at any time for visual symptoms.
- Withhold Balversa® when central serous retinopathy/retinal pigment epithelial detachment occurs and permanently discontinue if it does not resolve within 4 weeks or if Grade 4 in severity.

❖ **Hyperphosphataemia**
- Increases in phosphate levels are a pharmacodynamic effect of Balversa®. Monitor for hyperphosphatemia and manage with dose modifications when required.

❖ **Embryo-foetal toxicity:**
- Can cause foetal harm. Advise patients of the potential risk to the foetus and to use effective contraception.

Study characteristics [6-9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
THOR NCT03390504	266 (1:1)	21-day cycles of oral **erdafitinib** (8 mg per day with a pharmacodynamically guided increase in the dose to 9 mg on day 14)	investigator's choice of **chemotherapy** (docetaxel 75 mg/m^2 of BSA IV over a 1-hour period or vinflunine at a dose of 320 mg/m^2 IV over a 20-minute period) every 3 weeks	OS	15.9 months	**ongoing**[3], randomised, open-label, multicentre, global phase 3 study	FGFR	Janssen Research and Development	THOR trial [8]

Inclusion criteria[4]

- ❖ Histologic demonstration of transitional cell carcinoma of the urothelium. Minor components (<50 % overall) of variant histology, such as glandular or squamous differentiation or evolution to more aggressive phenotypes such as sarcomatoid or micropapillary change, are acceptable.
- ❖ Metastatic or surgically unresectable urothelial cancer.
- ❖ Documented progression of disease is any progression that requires a change in treatment prior to randomisation.
- ❖ Cohort 1: Prior treatment with an anti-PD-(L) 1 agent as monotherapy or as combination therapy; no more than 2 prior lines of systemic treatment.
- ❖ Cohort 2: No prior treatment with an anti-PD-(L) 1 agent; only 1 line of prior systemic treatment. Subjects who received neoadjuvant or adjuvant chemotherapy and showed disease progression within 12 months of the last dose are considered to

Exclusion criteria

- ❖ Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to randomisation.
- ❖ Active malignancies (that is, requiring treatment change in the last 24 months). For exceptions, please see Trial Protocol.
- ❖ Symptomatic CNS metastases
- ❖ Received prior FGFR inhibitor treatment.
- ❖ Known allergies, hypersensitivity, or intolerance to erdafitinib or its excipients.
- ❖ Current central serous retinopathy or retinal pigment epithelial detachment of any grade.
- ❖ History of uncontrolled cardiovascular disease.
- ❖ Impaired wound healing capacity is defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

Patient characteristics at baseline (n=136 vs. n=130)

- ❖ Median age (range): 66 (32–85) vs. 69 (35–86) years
- ❖ Age group:
  - <65 years: 43.4% vs. 34.6%
  - ≥65 years: 56.6% vs. 65.4%
- ❖ Sex:
  - Male: 70.6% vs. 72.3%
  - Female: 29.4% vs. 27.7%
- ❖ Race:
  - White: 59.6% vs. 48.5%
  - Asian: 27.2% vs. 30.8%
  - Black: 0 vs. 0.8%
  - Multiple: 0 vs. 0.8%
  - Not reported: 13.2% vs. 19.2%
- ❖ Geographic region:
  - North America: 5.9% vs. 3.8%
  - Europe: 60.3% vs. 61.5%
  - Rest of the world: 33.8% vs. 34.6%
- ❖ Visceral metastasis:
  - Present: 74.3% vs. 74.6%
  - Absent: 25.7% vs. 25.4%

[3] THOR trial is currently ongoing; the estimated study completion date is 11/2026.
[4] For detailed in- and exclusion criteria, please see Trial Protocol.

have received systemic therapy in the metastatic setting. ❖ A woman of childbearing potential who is sexually active must have a negative pregnancy test at Screening (urine or serum). ❖ Participants must meet appropriate molecular eligibility criteria. ❖ ECOG PS Grade 0, 1, or 2. ❖ Adequate bone marrow, liver, and renal function		❖ ECOG performance-status score: • 0: 46.3% vs. 39.2% • 1: 44.9% vs. 50.8% • 2: 8.8% vs. 10.0% ❖ Primary tumour location: • Upper tract: 30.1% vs. 36.9% • Lower tract: 69.9% vs. 63.1% ❖ PD-1 or PD-L1 status • CPS <10: 93% vs. 86% • CPS ≥10: 7% vs. 14% ❖ FGFR alterations: • Mutation: 79.4% vs. 82.3% • Fusion: 18.4% vs. 14.6% • Mutation and fusion: 1.5% vs. 2.3% ❖ False positive result: 0.7% vs. 0.8% ❖ Previous lines of systemic therapy • 1: 33.1% vs. 25.4% • 2: 66.2% vs. 74.6% • 3: 0.7% vs. 0

Efficacy (I vs. C), interim analysis data[5]	**Safety** (I vs. C, n=135 vs. n=112), interim analysis data
Clinical cutoff date: 15 January 2023 **Median OS**: 12.1 months (95% CI, 10.3-16.4) vs. 7.8 months (95% CI, 6.5-11.1); estimated HR for death 0.64 (95% CI, 0.47-0.88); p=0.005 **Estimated percentage of patients alive at 6 months**: 85% (95% CI, 77-90) vs. 66% (95% CI, 56-74) **Estimated percentage of patients alive at 12 months:** 51% (95% CI, 41-60) vs. 38% (95% CI, 28-47) **Median PFS:** 5.6 months (95% CI, 4.4-5.7) vs. 2.7 months (95% CI, 1.8-3.7); estimated HR for progression or death 0.58 (95% CI, 0.44-0.78); p<0.001 **ORR:** 45.6% vs. 11.5%; relative benefit 3.94 (95% CI, 2.37-6.57); p<0.001 **CR**: 6.6% vs. 0.8% **PR**: 39.0% vs. 10.8% **Patients with a confirmed objective response by investigator assessment**: 35.3% vs. 8.5%; relative benefit 4.16 (95% CI, 2.27-7.64) **Median duration of response**: 4.9 months (95% CI, 3.8-7.5) vs. 5.6 months (95% CI, 2.1-6.0) **Subsequent anticancer therapy**: 32.4% vs. 36.9%	**AEs of any cause**: 98.5% vs. 97.3% **TRAEs of grade 3 or 4**: 45.9% vs. 46.4% **AEs leading to death**: 4.4% vs. 6.2% **TRAEs leading to death**: 0.7% vs. 5.4% **Treatment-related SAEs:** 13.3% vs. 24.1% **AEs of any cause leading to treatment discontinuation**: 14.1% vs. 17.9% **TRAEs leading to treatment discontinuation:** 8.1% vs. 13.4%

Patient-reported outcomes

According to the trial protocol, HRQoL, symptoms, functioning, and general well-being will be assessed using 3 patient-reported outcome measures: the FACT-BI, PGIS, and the EQ-5D-5L. Results are not available yet.

ESMO-MCBS version 1.1 [10]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

[5] After the interim analysis, the independent data monitoring committee made a recommendation to stop the trial, unblind the data, and **allow crossover** from chemotherapy to erdafitinib.

Original	NC	2A	≤12 months	OS: +4.3 months	0.64 (0.47-0.88)	HR≤0.65 AND gain ≥3months	4	-	NA	-	4
Adapted	NC	2A	≤12 months	OS: +4.3 months	0.64 (0.47-0.88)	HR≤0.65 AND gain ≥3months	4	+10.8% treatment-related SAEs	NA	-1[6]	3

Risk of bias (RCT) [11]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes high risk	-	no high risk	unclear[7] unclear risk	yes[8] high risk	unclear

Ongoing trials

NCT number/trial name	Description	Estimated study completion date
NCT03390504 / THOR	Please see above.	11/2026
NCT03473743	A phase 1b-2 study to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamics of various regimens of erdafitinib in subjects with metastatic or locally advanced UC.	06/2025
NCT04963153	Phase Ib trial of erdafitinib combined with enfortumab vedotin following platinum and PD1/L1 inhibitors for metastatic UC with FGFR2/3 genetic alterations.	09/2024

Available assessments

- No assessments were identified via NICE (assessment in progress), CDA-AMC (reimbursement review in progress), ICER, G-BA and NIHR.

Other aspects and conclusions

- In June 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Balversa®, indicated as monotherapy for the treatment of adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting. In January 2024, the **FDA approved** Balversa® for adult patients with locally advanced or metastatic UC with susceptible FGFR3 genetic alterations, as determined by an FDA-approved companion diagnostic test, whose disease has progressed on or after at least one line of prior systemic therapy.
- **THOR** (NCT03390504) is an **ongoing**, randomised, open-label, global phase 3 study of erdafitinib compared with chemotherapy in patients with metastatic UC with susceptible FGFR3/2 alterations
  who had progression after one or two previous treatments that included an anti–PD–1 or anti–PD-L1. Eligible patients were ≥18 years with metastatic or surgically unresectable UC and select FGFR3/2 alterations had an ECOG PS of 0-2. adequate organ function and progression during or after previous systemic therapy that included an anti–PD–1 or anti–PD-L1 agent and patients had received no more than two previous lines of treatment.
- The **primary endpoint** of THOR trial is OS. **Interim analysis** data showed that **median OS** was **significantly** longer with erdafitinib than with chemotherapy: 12.1 months vs. 7.8 months; HR for death 0.64; (95% CI, 0.47-0.88); p=0.005.
- Evaluation of patient-reported outcomes is planned; results are not available yet.
- The original and adapted **ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **4 and 3**, respectively.
- Due to the ongoing status of the trial, the **risk of bias** was considered **unclear**. However, the risk is increased by the open-label trial design and the industry-funded background of the trial.
- Besides THOR, no further phase 3 trial could be identified for the assessed indication.
- Considering the ongoing status of the THOR trial (only interim analysis data available) and the small number of patients, as well as the heterogeneous baseline characteristics of patients, the lack of patient-reported outcomes and further phase 3 data, it has to be stated that evidence for the assessed indication is currently rare.

First published: 07/2024

[6] Toxicity adjustment.
[7] The THOR trial is ongoing; currently, only interim analysis data is available.
[8] The trial was designed by the sponsor, with input from a protocol steering committee. Data from case-report forms were captured through data entry by trial center personnel in a sponsor database system. The first author, the last author, and the authors employed by the trial sponsor accessed and verified the raw data. All the authors had full access to all the data in the trial and were involved in the collection, analysis, or interpretation of the trial data; the writing of the manuscript; and approval of the final version of the manuscript. Writing assistance was funded by the sponsor.

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CR=complete response, CSR=central serous retinopathy, ECOG PS=Eastern Cooperative Oncology Group performance status, EMA=European Medicines Agency, EQ-5D-5L=European Quality of Life – 5 Dimensions-5 Levels, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-BI= Functional Assessment of Cancer Therapy – Bladder Cancer, FDA=Food and Drug Administration, FGFR=fibroblast growth factor receptor, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, Int.=intention, IV=intravenous, MG=median gain, n=number of patients, NA=not available, NICE=National Institute for Health Care Excellence, ORR=objective response rate, OS=overall survival, PD-1=anti–programmed cell death protein 1, PD-L1=anti–programmed death ligand 1, PE=primary endpoint, PFS=progression-free survival, PGIS=Patient-Global Impression of Severity, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TRAE=treatment-related adverse event, UC=urothelial carcinoma,

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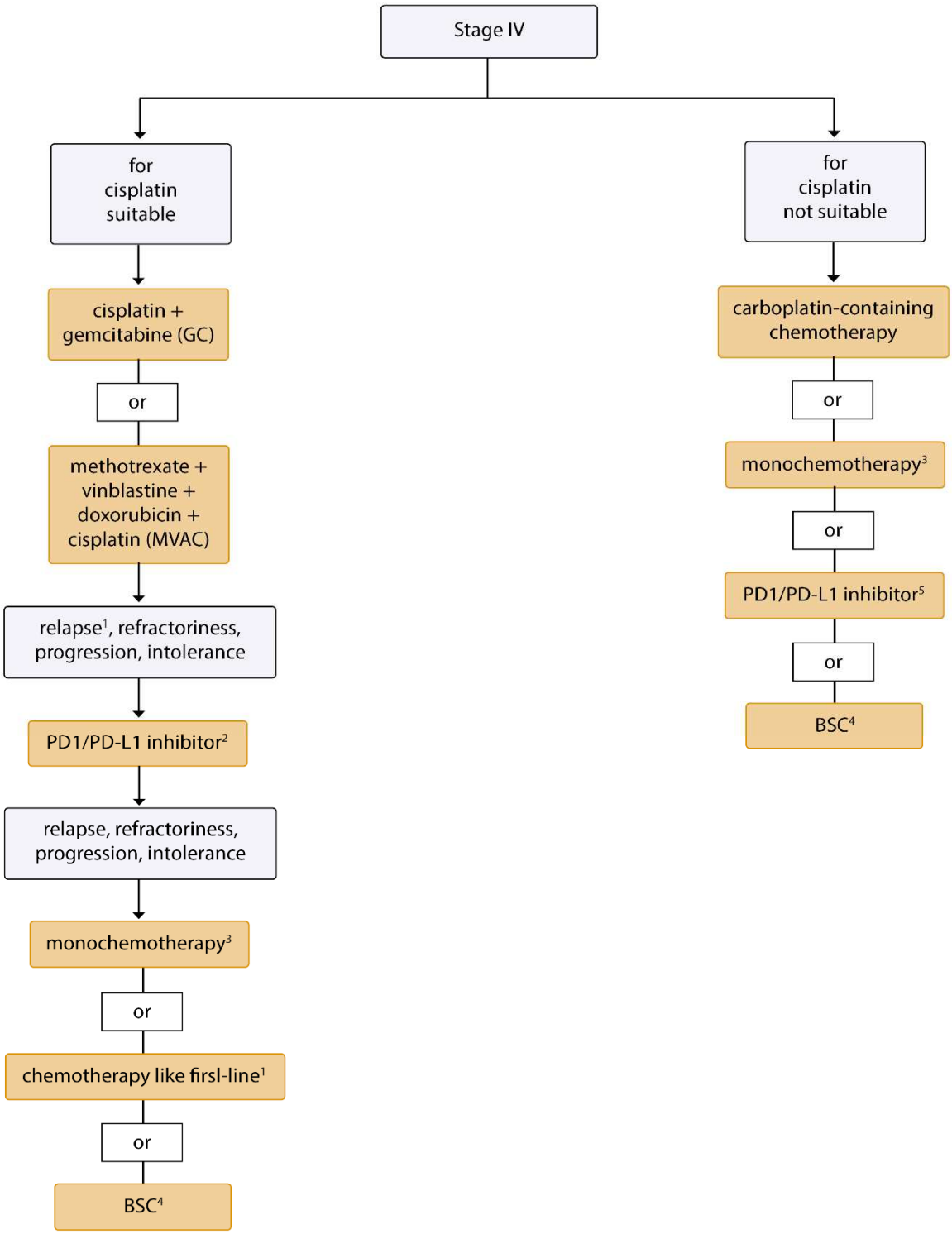
Appendix – Figure 1:



Legend:

curative therapy intention; palliative therapy intention;

[1] *With a remission duration >6 months, a repeat of the first-line therapy is also possible, depending on tolerability*

[2] *PD1/PD-L1 inhibitor: approved are atezolizumab, nivolumab, pembrolizumab*

[3] *Monochemotherapy: vinflunine, carboplatin, docetaxel, gemcitabine, paclitaxel*

[4] *BSC - Best Supportive Care*

[5] *PD1/PD-L1 inhibitor: if PD-L1 expression is positive (combined positive score, CPS): approved are pembrolizumab CPS ≥10%, atezolizumab PD-L1 ≥5%*