Toripalimab (Loqtorzi®) with cisplatin and paclitaxel for the first-line treatment of unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (OSCC)

General information [1]

Drug description

The active substance of Loqtorzi® is toripalimab, an antineoplastic agent. Toripalimab is a humanised IgG4 kappa monoclonal antibody that binds to programmed death receptor-1 (PD-1). It blocks the binding of programmed death ligand-1 (PD-L1) and PD-L2 to PD-1, thereby preventing the inhibition of immune responses via the PD-1 pathway, including anti-tumour immune responses.

Indication

Toripalimab (Loqtorzi®), in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC carcinoma.

Incidence [2]

In Austria, in 2022, a total of 362 men and 99 women were newly diagnosed with oesophageal cancer. The age-standardised[1] incidence rate was 8.3/100,000 in men and 2.0/100,000 in women.

Current treatment [3]

The Onkopedia treatment recommendation for the treatment of stage IV OSCC is displayed in Figure 1 of the Appendix.

Regulatory status

EMA [1]	FDA [4]
Approval status for this indication: On July 25 2024, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Loqtorzi® as follows: ❖ Loqtorzi®, in combination with cisplatin and paclitaxel, is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC. **Other indications**: ❖ Loqtorzi®, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma.	**Approval status for this indication**: not approved **Other indications**: Loqtorzi® is indicated: ❖ in combination with cisplatin and gemcitabine for first-line treatment of adults with metastatic or recurrent locally advanced nasopharyngeal carcinoma. ❖ as a single agent for the treatment of adults with recurrent unresectable or metastatic nasopharyngeal carcinoma with disease progression on or after platinum-containing chemotherapy.

Manufacturer

Loqtorzi® is manufactured by Coherus BioSciences, Inc.

Costs

Currently, there is no cost information available.

Warnings and precautions

Currently, there is no EMA EPAR available for Loqtorzi®.

Study characteristics [5, 6]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)

[1] European Standard Population 2013.

JUPITER-06 NCT03829969	514 (1:1)	toripalimab 240 mg IV + paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2)[2]	placebo + paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2)	**PFS** by BICR per RECIST v1.1 and **OS**, both in the ITT population	7.1 months	randomised, double-blind, placebo-controlled, phase 3 study	-	Shanghai Junshi Bioscience Co., Ltd.	JUPITER-06 trial [6]

Inclusion criteria[3]	Exclusion criteria	Patient characteristics at baseline (n=257 vs. n=257)
❖ Histologically or cytologically confirmed, locally advanced/relapsed or metastatic OSCC that cannot be eradicated. ❖ No prior systemic antitumor therapy for relapsed or metastatic tumours. ❖ No relapse in an interval of at least six months after the end of the last dose in the patients previously receiving adjuvant, neoadjuvant chemotherapy/radiotherapy/ chemoradiotherapy and radical therapy for non-metastatic disease. ❖ No risk of major haemorrhage or oesophageal fistula. ❖ Signed informed consent. ❖ Male or female aged 18 to 75 years. ❖ ECOG PS score of 0 or 1. ❖ Expected survival longer than three months. ❖ Agreement to provide a previously reserved tumour tissue specimen or biopsied tumour lesion tissue for biomarker analysis. ❖ ≥1 measurable lesion in accordance with RECIST 1.1 ❖ Adequate organ function as defined below: • Haematology: Neutrophil ≥1.5×10^9/L, haemoglobin ≥9 g/dL, and platelet ≥100×10^9/L; • Hepatic function: bilirubin ≤1.5× ULN, AST and ALT ≤2.5× ULN and ALP ≤3× ULN); albumin ≥3 g/dL;	❖ Active or untreated CNS metastasis was confirmed by CT or MRI at screening and previous radiological evaluation. ❖ Uncontrolled tumour-related pain. ❖ Uncontrolled pleural effusion, pericardial effusion, or ascites requiring repeated drainage. ❖ Uncontrollable or symptomatic hypercalcemia. ❖ History of malignant tumours, except oesophageal cancer, within five years prior to randomisation. ❖ Palliative radiotherapy within 28 days prior to enrolment or radiopharmaceutical therapy within eight weeks. ❖ Patients with bone metastasis of multiple vertebrae are prone to fractures, which puts the patient at risk of paraplegia, except for patients who are assessed by a specialist as stable and not in need of treatment. ❖ Patients with advanced cancer with metastasis to vital organs and who are at risk of developing life-threatening complications in the short term. ❖ Patients with known complete obstruction under endoscopy who require interventions or surgery to remove the obstruction and have undergone tracheal or oesophageal stenting. ❖ Patients who have a body mass index of <17.5, a body weight decrease of >10% within two months prior to the first dose of the study treatment, or severe malnutrition displayed by other indicators. ❖ Women who are pregnant, lactating, or plan to become pregnant during the study. ❖ History of severe allergy, anaphylactoid, or other hypersensitive reactions to chimeric or humanised antibody or fusion protein. ❖ Known allergy or hypersensitivity to the biological products manufactured from Chinese hamster ovary cells or any component of toripalimab. ❖ History of autoimmune disease. ❖ Patients with hypothyroidism but who receive stable-dose thyroid hormone replacement therapy can be enrolled in this study.	❖ Median age: 63.0 (range 20-75) vs. 62.0 (40-74) years ❖ Male gender: 84.4% vs. 85.6% ❖ Median baseline weight: 58.00 vs. 58.00 kg ❖ Baseline ECOG PS: • 0: 25.7% vs. 26.5% • 1: 74.3% vs. 73.5% ❖ Cigarette use: • Never a smoker: 36.2% vs. 32.7% • Former smoker: 12.8% vs. 17.9% • Current smoker: 51.0% vs. 49.4% ❖ Alcohol use: • Never a drinker: 43.2% vs. 35.8% • Former drinker: 7.0% vs. 9.3% • Current drinker: 49.8% vs. 54.9% ❖ Baseline metastasis status: • Locally advanced not amendable for curative therapy: 19.5% vs. 23.0% • Metastatic: 80.2% vs. 77.0% • Unknown: 0.4% vs. 0 ❖ Baseline clinical stage: • I/II: 1.2% vs. 1.6% • III: 8.6% vs. 9.7% • IV: 89.9% vs. 88.7%

[2] Chemotherapy phase: Regimens were given on Day 1 of each 3-week cycle. Chemotherapy was to continue until progressive disease, intolerable toxicity, withdrawal of consent, or a maximum of 6 cycles, whichever occurred first. Maintenance phase: toripalimab (240 mg) or placebo every 3 weeks until progressive disease, intolerable toxicity, withdrawal of consent or a maximum of 2 years of treatment. Crossover was not permitted as part of the study.

[3] For detailed in- and exclusion criteria, please see trial protocol.

- INR or prothrombin time or activated partial thromboplastin time ≤1.5× ULN;
- Renal function: Serum creatinine ≤1.5× ULN or estimated glomerular filtration rate by Cockcroft-Gault formula.

❖ Female patients who meet the following criteria are eligible:
- Female patients with no childbearing potential based on any of the following criteria:
  - o Hysterectomy performed
  - o Bilateral oophorectomy performed;
  - o Bilateral tubal ligation performed; or
  - o Postmenopausal (menopause ≥1 year).

❖ Female patients with childbearing potential who have a negative serum pregnancy test result at screening and use adequate contraceptive measures prior to the study until 60 days after the last dose of the investigational drug.

❖ Patients with type I diabetes whose blood glucose can be controlled through stable-dose insulin can be enrolled in this study.
❖ Patients with eczema, psoriasis, chronic lichen simplex, or cutaneous manifestations only of vitiligo are allowed to be enrolled in this study if they meet the conditions defined in trial protocol.
❖ History of idiopathic pulmonary fibrosis, organised pneumonia, drug-induced pneumonia, idiopathic pneumonia interstitial pneumonia, or evidence of active pneumonia found during chest CT screening scan.
❖ Patients with a positive test result of HIV.
❖ Patients with HBV (known HBV surface antigen and HBV DNA ≥1000 cps/mL or 200 IU/mL or ≥ULN at each study site) or HCV.
❖ Patients with active pulmonary tuberculosis.
❖ Serious infection within 28 days prior to randomisation
❖ Oral or IV antibiotics within 2 weeks prior to randomisation.
❖ Important cardiovascular diseases.
❖ Major surgery within 28 weeks prior to randomisation or expected major surgery during the study.
❖ Previous allogeneic bone marrow transplantation or solid organ transplantation.
❖ Previous immune checkpoint blocking therapy.
❖ Previous systemic immunostimulatory therapy within 2 weeks or 5 t1/2 prior to randomisation.
❖ Use of systemic immunosuppressive drugs within 2 weeks prior to randomisation.
❖ Patients receiving hematopoietic stimulating factors or blood transfusion within 2 weeks prior to randomisation.
❖ History of allergy to cisplatin, carboplatin, or other platinum-based compounds.
❖ Grade 2 or higher peripheral neuropathy according to the NCI CTCAE version 5.0.

- Not available: 0.4% vs. 0

❖ Site of tumour at initial diagnosis:
- Cervical oesophagus: 2.3% vs. 2.7%
- Upper thoracic oesophagus: 10.5% vs. 9.7%
- Middle thoracic oesophagus: 31.1% vs. 31.9%
- Lower thoracic oesophagus: 32.3% vs. 31.5%
- Esophagogastric junction: 3.9% vs. 1.9%
- Other: 19.8% vs. 22.2%

❖ PD-L1 status:
- CPS <1: 16.7% vs. 17.1%
- CPS ≥1: 78.2% vs. 77.8%
- CPS <10: 50.2% vs. 57.2%
- CPS ≥10: 44.7% vs. 37.7%
- Unknown: 5.1% vs. 5.1%

❖ Prior radiation therapy:
- Yes: 13.6% vs. 13.6%
- No: 86.4% vs. 86.4%

Efficacy (I vs. C)	**Safety** (I vs. C)
<u>Data cutoff date March 22 2021; median follow-up time 7.1 months</u> **Median PFS (final analysis):** 5.7 (95% CI, 5.6–7.0) vs. 5.5 (95% CI, 5.2–5.6) months; stratified HR for progression or death 0.58 (95% CI, 0.46–0.74; two-sided p< 0.0001) **1-year PFS rates**: 27.8% (95% CI, 20.4–35.8) vs. 6.1% (95% CI, 2.2–12.6) **HR for disease progression or death in the PD-L1 CPS ≥1 subgroup**: 0.58 (95% CI, 0.44–0.75) **HR for disease progression or death CPS <1 subgroup**: 0.66 (95% CI, 0.37–1.19) **HR for disease progression or death in the CPS≥10 subgroups**: 0.65 (95% CI, 0.45–0.92) and **HR for disease progression or death in the CPS<10 subgroups**: 0.56 (95% CI, 0.41–0.78) **Median PFS (investigator-assessed):** 7.0 (95% CI, 5.7–8.1) vs. 5.6 (95% CI, 5.5–5.8) months; stratified HR for progression or death of 0.58 (95% CI, 0.46–0.74; two-sided p< 0.0001). **1-year investigator-assessed PFS rates**: 27.6% (95% CI, 19.9–35.8) vs. 6.1% (95% CI, 2.4–12.1) **Median OS (interim analysis):** 17 (95% CI, 14.0-not reached) vs. 11 (95% CI, 10.4–12.6) months; stratified HR for death 0.58 (95% CI, 0.43–0.78; two-sided p=0.0004)	**Any TEAE:** 99.2% vs. 99.2% **Any TEAE related to study treatment**: 97.3% vs. 97.3 **Any TEAE related to toripalimab/placebo**: 71.2% vs. 61.5% **Any TEAE Grade ≥3**: 73.2% vs. 70.0% **Any TEAE Grade ≥3 related to study treatment**: 64.6% vs. 56.0% **Any TEAE Grade ≥3 related to toripalimab/placebo**: 23.7% vs. 13.2% **Any TEAEs resulting in death:** 8.2% vs. 8.2% **Any TEAEs resulting in death related to study treatment**: 0.4% vs. 1.2% **Any TEAEs resulting in death related to toripalimab/placebo**: 0.4% vs. 0.8% **Any SAE:** 36.2% vs. 28.8% **Any SAE related to study treatment**: 23.3% vs. 14.8% **Any SAE related to toripalimab/placebo**: 14.4% vs. 5.4% **Any TEAE leading to discontinuation of toripalimab/placebo**: 11.7% vs. 6.2%

1-year OS rates: 66.0% (95% CI, 57.5–73.2) vs. 43.7% (95% CI, 34.4–52.6) **ORR (by BICR in the ITT-population)**: 69.3% (95% CI, 63.2–74.8) vs. 52.1% (95% CI, 45.8–58.4, nominal p<0.0001) **DCR:** 89.1% (95% CI, 84.6–92.6) vs. 82.1% (95% CI, 76.9–86.6, nominal p=0.0206) (Table 2) **Median DoR by BICR**: 5.6 months (95% CI, 4.4–8.7) vs. 4.2 months (95% CI, 4.2–4.4); HR 0.58 (95% CI, 0.41–0.81; nominal p = 0.0014)	**Any TEAE leading to interruption of toripalimab/placebo**: 35.8% vs. 25.7% **Any immune-related AE**: 37.0% vs. 26.5% **Any immune-related AE with Grade ≥3:** 7.0% vs. 1.6% **Any infusion-related reaction**: 3.5% vs. 3.1%

Patient-reported outcomes

According to the trial protocol, evaluation of disease-related symptoms and HRQoL by the European Organisation for Research and Treatment of Cancer Quality of Life - Core Questionnaires 30 and QoL - Supplementary Scale for Oesophageal cancer 18 questionnaires was planned. Currently, results are not available.

ESMO-MCBS version 1.1 [7]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2A	>12 - ≤24 months	OS: +6 months	0.58 (0.43–0.78)	HR≤0.70 AND gain ≥5 months	4	-	NA	-	4
Adapted	NC	2A	>12 - ≤24 months	OS: +6 months	0.58 (0.43–0.78)	HR≤0.70 AND gain ≥5 months	4	+10.5% TEAEs grade ≥3 related to toripalimab/placebo +10.5% immune-related AEs	NA	-1[4]	3

Risk of bias (RCT) [8]

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 low risk	yes low risk	yes low risk	unclear[5] unclear risk	yes[6] high risk	unclear risk

Ongoing trials [9]

NCT number/trial name	Description	Estimated study completion date

No ongoing trials were identified for the assessed indication.

Available assessments

- In March 2023, NIHR published a Health Technology Briefing "Toripalimab in combination with paclitaxel and cisplatin for treating advanced or metastatic oesophageal squamous cell cancer without previous systemic chemotherapy" [10].
- No assessments were identified via NICE, ICER, CDA-AMC, G-BA.

Other aspects and conclusions

- In July 2024, the **CHMP adopted a positive opinion**, recommending the granting of a marketing authorisation for Loqtorzi® in combination with cisplatin and paclitaxel, which is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent, or metastatic OSCC. This indication has not been **approved by the FDA**.
- **JUPITER-06 (NCT03829969)** is a randomised, double-blind, placebo-controlled, phase 3, comparing the efficacy and safety of toripalimab plus paclitaxel+cisplatin vs. placebo plus paclitaxel+cisplatin as the first-line treatment for patients with advanced OESCC. Eligible patients were aged 18-75 years and had histologically or cytologically confirmed, locally advanced, recurrent, or metastatic OESCC that was not amendable for curative esophagectomy or definitive chemoradiation. Patients must have received either no prior systemic antitumor therapy for relapsed or metastatic disease or received (neo)adjuvant chemo(radio) therapy for non-metastatic disease and experienced relapse of disease following at least six months after the last dose of chemotherapy. Enrolled patients had to have an ECOG performance status of 0 or 1, a life expectancy of at least three months, adequate organ function, and at least one measurable lesion in accordance with RECIST v1.1. Exclusion criteria included the presence of malignant tumours except oesophagal cancer within five years prior to randomisation; active or untreated CNS metastasis; active or previous autoimmune or inflammatory disorders; prior use of immune checkpoint blockade, systemic immune-stimulators, and/or systemic immunosuppressive drugs.

[4] Toxicity adjustment.
[5] To date, not all results of predefined endpoints are available (2-year PFs and OS rates and QoL results are lacking).
[6] Industry-funded.

- **PFS and OS in the ITT-population** were the co-primary endpoints of the JUPITER-06 trial. **Median PFS** (final analysis) was 5.7 (95% CI, 5.6–7.0) vs. 5.5 (95% CI, 5.2–5.6) months; stratified HR for progression or death was 0.58 (95% CI, 0.46–0.74; two-sided p< 0.0001). **Median OS** (interim analysis) was 17 (95% CI, 14.0-not reached) vs. 11 (95% CI, 10.4–12.6) months; stratified HR for death was 0.58 (95% CI, 0.43–0.78; two-sided p=0.0004).
- Although determined as secondary efficacy objectives, the results of **patient-reported outcomes are currently unavailable**.
- The **original and adapted ESMO-MCBS** were applied, resulting in a final adjusted magnitude of clinical benefit of **4 and 3**, respectively.
- Since not all results for the predefined endpoints are currently available, the **risk of bias was considered unclear**. However, the risk is **increased** by the industry-funded background of the trial.
- No ongoing trials could be identified for the assessed indication.
- Final OS analysis and patient-reported outcome results are required to determine the role of toripalimab treatment in patients with advanced, recurrent, or metastatic oesophageal squamous cell carcinoma.

First published: 08/2024

Abbreviations: AE=adverse event, AJ=adjustment, ALP=alkaline phosphatase, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BICR=blinded independent central review, C=comparator, CDA-AMC=Canada´s Drug Agency, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, CT=computerized tomography, CTCAE=Common Terminology Criteria for Adverse Events, DNA=deoxyribonucleic acid, DoR=duration of response, ECOG PS =Eastern Cooperative Oncology Group Performance Status, EMA=European Medicines Agency, EPAR=European Public Assessment Report, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, ICER=Institute for Clinical and Economic Review, INR=International normalised ratio, Int.=intention, ITT=intention-to-treat, MG=median gain, MRI=magnetic resonance imaging, n=number of patients, NCI=National Cancer Institute, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health Research, OS=overall survival, OSCC=Oesophageal squamous cell carcinoma, PD-L1=programmed death receptor – ligand 1; PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, RECIST=Response Evaluation Criteria in Solid Tumors, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse events, ULN=upper limit of normal

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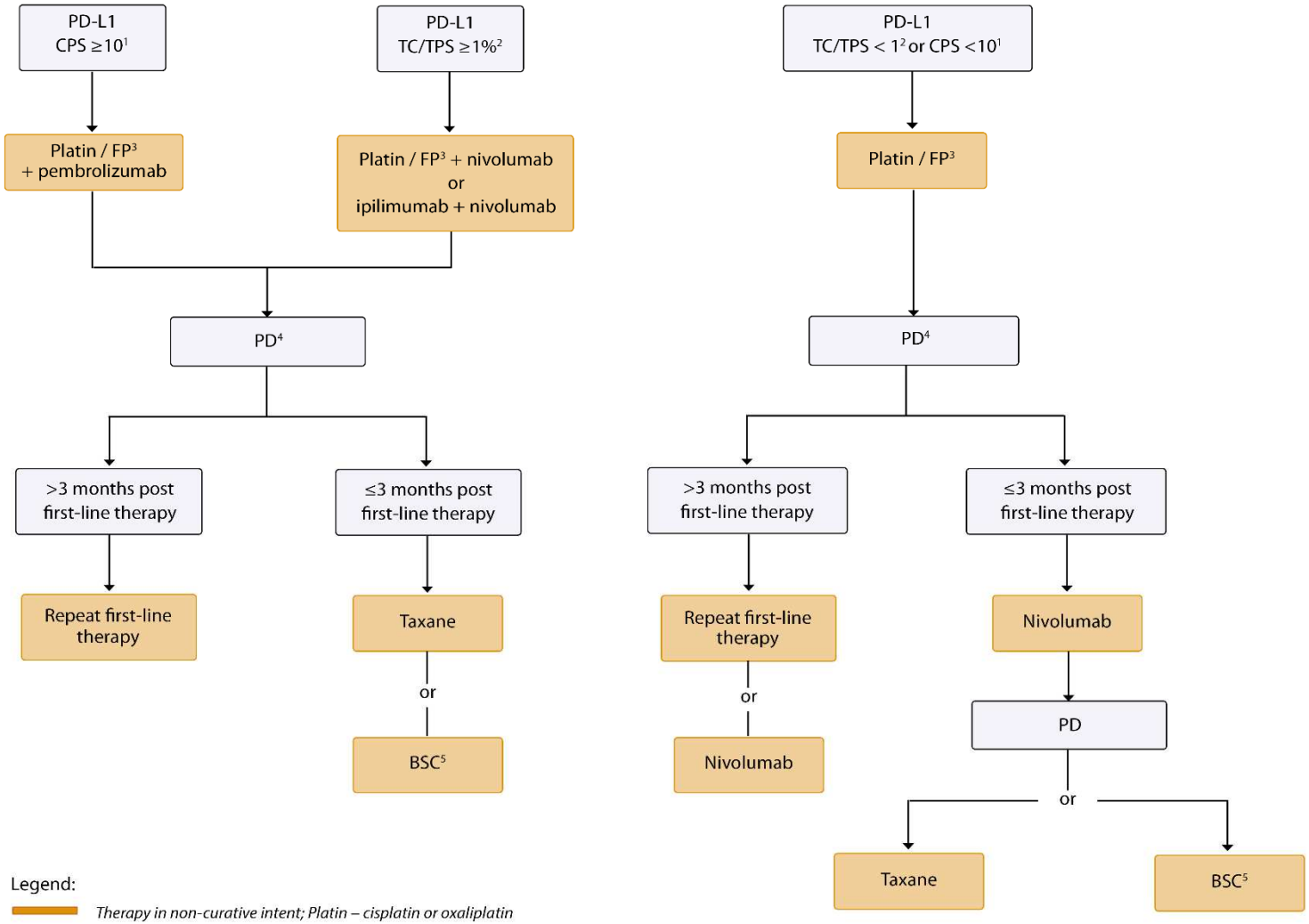
Appendix – Figure 1:



Legend:

Therapy in non-curative intent; Platin – cisplatin or oxaliplatin

[1] *CPS - Combined score of PD-L1 expression on tumor cells and immune cell infiltrate*
[2] *TC or TPS - number of PD-L1 positive tumor cells per 100 tumor cells*
[3] *FP - Fluoropyrimidine (5-fluorouracil + folinic acid, or capecitabine)*
[4] *PD - Progressive disease*
[5] *BSC - Best Supportive Care*