ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

Tecentriq 1,200 mg concentrate for solution for infusion.

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each 20 mL vial of concentrate contains 1,200 mg atezolizumab*.

After dilution (see section 6.6), one mL of solution contains approximately 4.4 mg of atezolizumab.

*Atezolizumab is an Fc-engineered, humanised IgG1 anti-programmed death-ligand 1 (PD-L1) monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Concentrate for solution for infusion.

Clear, colourless to slightly yellowish liquid.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC):
• after prior platinum-containing chemotherapy, or
• who are considered cisplatin ineligible, and whose tumours have a PD-L1 expression ≥ 5% (see section 5.1).

Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1).

Tecentriq as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving Tecentriq (see section 5.1).

4.2 **Posology and method of administration**

Tecentriq must be initiated and supervised by physicians experienced in the treatment of cancer.
PD-L1 testing for patients with UC

Patients with previously untreated UC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology

*Tecentriq monotherapy*

The recommended dose of Tecentriq is 1,200 mg administered intravenously every three weeks.

*Tecentriq in combination therapy*

Please also refer to the full prescribing information for the combination products (see also section 5.1).

*1L non-squamous NSCLC*

*Tecentriq in combination with bevacizumab, paclitaxel, and carboplatin*

During the induction phase, the recommended dose of Tecentriq is 1,200 mg administered by intravenous infusion, followed by bevacizumab, paclitaxel, and then carboplatin every three weeks for four or six cycles.

The induction phase is followed by a maintenance phase without chemotherapy in which 1,200 mg Tecentriq followed by bevacizumab, is administered by intravenous infusion every three weeks.

*Duration of treatment*

It is recommended that patients are treated with Tecentriq until loss of clinical benefit (see section 5.1) or unmanageable toxicity.

*Delayed or missed doses*

If a planned dose of Tecentriq is missed, it should be administered as soon as possible. The schedule of administration must be adjusted to maintain a 3-week interval between doses.

*Dose modifications during treatment*

Dose reductions of Tecentriq are not recommended.
Dose delay or discontinuation (see also sections 4.4 and 4.8)

Table 1: Dose modification advice for Tecentriq

<table>
<thead>
<tr>
<th>Immune related adverse reaction</th>
<th>Severity</th>
<th>Treatment modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>Grade 2</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Grade 2: (ALT or AST &gt; 3 to 5 x upper limit of normal [ULN]) or blood bilirubin &gt; 1.5 to 3 x ULN)</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4: (ALT or AST &gt; 5 x ULN) or blood bilirubin &gt; 3 x ULN)</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Colitis</td>
<td>Grade 2 or 3 Diarrhoea (increase of ≥ 4 stools/day over baseline) or Symptomatic Colitis</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td>Grade 4 Diarrhoea or Colitis (life threatening; urgent intervention indicated)</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Hypothyroidism or hyperthyroidism</td>
<td>Symptomatic</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism: Treatment may be resumed when symptoms are controlled by thyroid replacement therapy and TSH levels are decreasing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism: Treatment may be resumed when symptoms are controlled by anti-thyroid medicinal product and thyroid function is improving</td>
<td></td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Symptomatic</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td>Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy</td>
<td></td>
</tr>
<tr>
<td>Immune related adverse reaction</td>
<td>Severity</td>
<td>Treatment modification</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>Grade 2 or 3</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and patient is stable on replacement therapy</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Type 1 diabetes mellitus</td>
<td>Grade 3 or 4 hyperglycaemia (fasting glucose &gt; 250 mg/dL or 13.9 mmol/L)</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when metabolic control is achieved on insulin replacement therapy</td>
</tr>
<tr>
<td>Infusion-related reactions</td>
<td>Grade 1 or 2</td>
<td>Reduce infusion rate or interrupt. Treatment may be resumed when the event is resolved</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Rash</td>
<td>Grade 3</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when rash is resolved and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome and Meningoencephalitis</td>
<td>All Grades</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Grade 3 or 4 serum amylase or lipase levels increased (&gt; 2 x ULN) or Grade 2 or 3 pancreatitis</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when serum amylase and lipase levels improve to Grade 0 or Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>Grade 4 or any grade of recurrent pancreatitis</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td>Immune related adverse reaction</td>
<td>Severity</td>
<td>Treatment modification</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>------------------------</td>
</tr>
<tr>
<td><strong>Myocarditis</strong></td>
<td>Grade 2</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when the symptoms improve to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>Grade 3 and 4</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td><strong>Nephritis</strong></td>
<td>Grade 2: (creatinine level &gt; 1.5 to 3.0 x baseline or &gt; 1.5 to 3.0 x ULN)</td>
<td>Withhold Tecentriq</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment may be resumed when the event improves to Grade 0 or Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4: (creatinine level &gt; 3.0 x baseline or &gt; 3.0 x ULN)</td>
<td>Permanently discontinue Tecentriq</td>
</tr>
<tr>
<td><strong>Other immune-related adverse reactions</strong></td>
<td>Grade 2 or Grade 3</td>
<td>Withhold until adverse reactions recover to Grade 0-1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day</td>
</tr>
<tr>
<td></td>
<td>Grade 4 or recurrent Grade 3</td>
<td>Permanently discontinue Tecentriq (except endocrinopathies controlled with replacement hormones)</td>
</tr>
</tbody>
</table>

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Event Version 4.0 (NCI-CTCAE v.4.).

Patients treated with Tecentriq must be given the Patient Alert Card and be informed about the risks of Tecentriq (see also package leaflet).

**Special populations**

**Paediatric population**  
The safety and efficacy of Tecentriq in children and adolescents aged below 18 years have not been established. No data are available.

**Elderly**  
Based on a population pharmacokinetic analysis, no dose adjustment of Tecentriq is required in patients ≥ 65 years of age (see sections 4.8 and 5.1).

**Asian patients**  
Due to increased hematologic toxicities observed in Asian patients in IMpower150, it is recommended that the starting dose of paclitaxel should be 175 mg/m² every three weeks.

**Renal impairment**  
Based on a population pharmacokinetic analysis, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

**Hepatic impairment**  
Based on a population pharmacokinetic analysis, no dose adjustment is required for patients with mild hepatic impairment. Tecentriq has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).
Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2
Patients with ECOG performance status ≥ 2 were excluded from the clinical trials in NSCLC and 2nd line UC (see sections 4.4 and 5.1).

Method of administration

Tecentriq is for intravenous use. The infusions must not be administered as an intravenous push or bolus.

The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

For instructions on dilution and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to atezolizumab or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Most immune-related adverse reactions occurring during treatment with atezolizumab were reversible with interruptions of atezolizumab and initiation of corticosteroids and/or supportive care. Immune-related adverse reactions affecting more than one body system have been observed. Immune-related adverse reactions with atezolizumab may occur after the last dose of atezolizumab.

For suspected immune-related adverse reactions, thorough evaluation to confirm aetiology or exclude other causes should be performed. Based on the severity of the adverse reaction, atezolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with systemic corticosteroid use, administration of other systemic immunosuppressants may be considered.

Atezolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reactions, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-related pneumonitis

Cases of pneumonitis, including fatal cases, have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis.

Treatment with atezolizumab should be withheld for Grade 2 pneumonitis, and 1 to 2 mg/kg/day prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 pneumonitis.

Immune-related hepatitis

Cases of hepatitis, some leading to fatal outcomes have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis.
Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be monitored prior to initiation of treatment, periodically during treatment with atezolizumab and as indicated based on clinical evaluation.

Treatment with atezolizumab should be withheld if Grade 2 event (ALT or AST > 3 to 5 x ULN or blood bilirubin > 1.5 to 3 x ULN) persists for more than 5 to 7 days, and 1 to 2 mg/kg/day of prednisone or equivalent should be started. If the event improves to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month.

Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or Grade 4 events (ALT or AST > 5.0 x ULN or blood bilirubin > 3 x ULN).

Immune-related colitis

Cases of diarrhoea or colitis have been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis.

Treatment with atezolizumab should be withheld for Grade 2 or 3 diarrhoea (increase of ≥ 4 stools/day over baseline) or colitis (symptomatic). For Grade 2 diarrhoea or colitis, if symptoms persist > 5 days or recur, treatment with 1 to 2 mg/kg/day prednisone or equivalent should be started. For Grade 3 diarrhoea or colitis, treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should be started. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 4 (life threatening; urgent intervention indicated) diarrhoea or colitis.

Immune-related endocrinopathies

Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, including diabetic ketoacidosis have been observed in clinical trials with atezolizumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies. Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Appropriate management of patients with abnormal thyroid function tests at baseline should be considered.

Asymptomatic patients with abnormal thyroid function tests can receive atezolizumab. For symptomatic hypothyroidism, atezolizumab should be withheld and thyroid hormone replacement should be initiated as needed. Isolated hypothyroidism may be managed with replacement therapy and without corticosteroids. For symptomatic hyperthyroidism, atezolizumab should be withheld and an anti-thyroid medicinal product should be initiated as needed. Treatment with atezolizumab may be resumed when symptoms are controlled and thyroid function is improving.

For symptomatic adrenal insufficiency, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required).

For Grade 2 or Grade 3 hypophysitis, atezolizumab should be withheld and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started, and hormone
replacement should be initiated as needed. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. If symptoms improve to ≤ Grade 1, corticosteroids should be tapered over ≥ 1 month. Treatment may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day and the patient is stable on replacement therapy (if required). Treatment with atezolizumab should be permanently discontinued for Grade 4 hypophysitis.

Treatment with insulin should be initiated for type 1 diabetes mellitus. For ≥ Grade 3 hyperglycaemia (fasting glucose > 250 mg/dL or 13.9 mmol/L), atezolizumab should be withheld. Treatment with atezolizumab may be resumed if metabolic control is achieved on insulin replacement therapy.

**Immune-related meningoencephalitis**

Meningoencephalitis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for clinical signs and symptoms of meningitis or encephalitis.

Treatment with atezolizumab must be permanently discontinued for any grade of meningitis or encephalitis. Treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow.

**Immune-related neuropathies**

Myasthenic syndrome/myasthenia gravis or Guillain-Barré syndrome, which may be life threatening, were observed in patients receiving atezolizumab. Patients should be monitored for symptoms of motor and sensory neuropathy.

Treatment with atezolizumab must be permanently discontinued for any grade of myasthenic syndrome / myasthenia gravis or Guillain-Barré syndrome. Initiation of systemic corticosteroids (at a dose of 1 to 2 mg/kg/day of prednisone or equivalent) should be considered.

**Immune-related pancreatitis**

Pancreatitis, including increases in serum amylase and lipase levels, has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be closely monitored for signs and symptoms that are suggestive of acute pancreatitis.

Treatment with atezolizumab should be withheld for ≥ Grade 3 serum amylase or lipase levels increased (> 2 x ULN), or Grade 2 or 3 pancreatitis, and treatment with intravenous corticosteroids (1 to 2 mg/kg/day methylprednisolone or equivalent) should be started. Once symptoms improve, treatment with 1 to 2 mg/kg/day of prednisone or equivalent should follow. Treatment with atezolizumab may be resumed when serum amylase and lipase levels improve to ≤ Grade 1 within 12 weeks, or symptoms of pancreatitis have resolved, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab should be permanently discontinued for Grade 4, or any grade of recurrent pancreatitis.

**Immune-related myocarditis**

Myocarditis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for signs and symptoms of myocarditis.

Treatment with atezolizumab should be withheld for Grade 2 myocarditis, and treatment with systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 myocarditis.
Immune-related nephritis

Nephritis has been observed in clinical trials with atezolizumab (see section 4.8). Patients should be monitored for changes in renal function.

Treatment with atezolizumab should be withheld for Grade 2 nephritis, and treatment with systemic corticosteroids at a dose of 1 to 2mg/kg/day of prednisone or equivalent should be started. Treatment with atezolizumab may be resumed if the event improves to ≤ Grade 1 within 12 weeks, and corticosteroids have been reduced to ≤ 10 mg prednisone or equivalent per day. Treatment with atezolizumab must be permanently discontinued for Grade 3 or 4 nephritis.

Infusion-related reactions

Infusion-related reactions have been observed in clinical trials with atezolizumab (see section 4.8).

The rate of infusion should be reduced or treatment should be interrupted in patients with Grade 1 or 2 infusion-related reactions. Atezolizumab should be permanently discontinued in patients with Grade 3 or 4 infusion-related reactions. Patients with Grade 1 or 2 infusion-related reactions may continue to receive atezolizumab with close monitoring; premedication with antipyretic and antihistamines may be considered.

Disease-specific precautions

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in metastatic non-squamous non-small cell lung cancer

Physicians should carefully consider the combined risks of the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin before initiating treatment (see section 4.8).

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: a history of autoimmune disease, history of pneumonitis, active brain metastasis, HIV, hepatitis B or hepatitis C infection. Patients who were administered a live, attenuated vaccine within 28 days prior to enrolment; systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal products within 2 weeks prior to study entry were excluded from clinical trials.

Patients with a baseline performance status ≥ 2 were excluded (apart from Study GO29293 [IMvigor210] Cohort 1 that enrolled patients with cisplatin ineligible urothelial carcinoma and allowed a baseline performance status ≥ 2) (see section 5.1).

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin

Patients with NSCLC that had clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging, were excluded from the pivotal clinical study IMpower150 after several cases of fatal pulmonary haemorrhage were observed, which is a known risk factor of treatment with bevacizumab.

In the absence of data, atezolizumab should be used with caution in these populations after careful evaluation of the balance of benefits and risks for the patient.

Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients with NSCLC who have progressed on erlotinib+bevacizumab

In study IMpower150, there are no data on the efficacy of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in EGFR+ patients who have progressed previously on erlotinib+bevacizumab.
Use of atezolizumab in urothelial carcinoma for previously untreated patients who are considered cisplatin ineligible

The baseline and prognostic disease characteristics of the IMvigor210 Cohort 1 study population were overall comparable to patients in the clinic who would be considered cisplatin ineligible but would be eligible for a carboplatin-based combination chemotherapy. There are insufficient data for the subgroup of patients that would be unfit for any chemotherapy; therefore atezolizumab should be used with caution in these patients, after careful consideration of the potential balance of risks and benefits on an individual basis.

Patient Alert Card

All prescribers of Tecentriq must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of Tecentriq therapy with the patient. The patient will be provided with the Patient Alert Card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with atezolizumab. Since atezolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting atezolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of atezolizumab. However, systemic corticosteroids or other immunosuppressants can be used to treat immune-related adverse reactions after starting atezolizumab (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and for 5 months after treatment with atezolizumab.

Pregnancy

There are no data from the use of atezolizumab in pregnant women. No developmental and reproductive studies were conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway in murine pregnancy models can lead to immune-related rejection of the developing foetus resulting in foetal death (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of atezolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth.

Human immunoglobulins G1 (IgG1) are known to cross the placental barrier and atezolizumab is an IgG1; therefore, atezolizumab has the potential to be transmitted from the mother to the developing foetus.

Atezolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with atezolizumab.
Breast-feeding

It is unknown whether atezolizumab is excreted in human milk. Atezolizumab is a monoclonal antibody and is expected to be present in the first milk and at low levels afterwards. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Tecentriq therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No clinical data are available on the possible effects of atezolizumab on fertility. No reproductive and development toxicity studies have been conducted with atezolizumab; however, based on the 26-week repeat dose toxicity study, atezolizumab had an effect on menstrual cycles at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose and was reversible (see section 5.3). There were no effects on the male reproductive organs.

4.7 Effects on ability to drive and use machines

Tecentriq has minor influence on the ability to drive and use machines. Patients experiencing fatigue should be advised not to drive and use machines until symptoms abate (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of atezolizumab as monotherapy is based on pooled data in 3,075 patients across multiple tumour types. The most common adverse reactions (≥10%) were fatigue (35.5%), decreased appetite (26.0%), nausea (23.7%), cough (20.7%), dyspnoea (20.7%), pyrexia (19.9%), diarrhoea (19.8%), rash (19.2%), back pain (15.3%), vomiting (15.3%), asthenia (14.8%), arthralgia (13.9%), pruritus (12.5%) and urinary tract infection (11.7%).

The safety of atezolizumab given in combination with paclitaxel and carboplatin, with or without bevacizumab, has been evaluated in 793 patients with metastatic NSCLC. The most common adverse reactions (≥20%) were peripheral neuropathy (42.6%), nausea (35.6%), anaemia (32.7%), neutropenia (32.4%), rash (29.8%), fatigue (29.6%), constipation (27.2%), decreased appetite (26.2%), diarrhoea (26.0%), thrombocytopenia (24.0%), arthralgia (23.8%).

Further details on serious adverse events are provided in Section 4.4 Warnings & Precautions.

Tabulated list of adverse reactions

The Adverse Drug Reactions (ADRs) are listed by MedDRA system organ class (SOC) and categories of frequency in Table 2 for atezolizumab given as monotherapy or as combination therapy. Adverse reactions known to occur with atezolizumab or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy. The following categories of frequency have been used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.
Table 2: Summary of adverse reactions occurring in patients treated with atezolizumab in clinical trials

<table>
<thead>
<tr>
<th>Atezolizumab monotherapy</th>
<th>Atezolizumab in combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>urinary tract infections&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>anaemia, thrombocytopenia&lt;sup&gt;b&lt;/sup&gt;, neutropenia&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Common</td>
<td>thrombocytopenia&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>hypersensitivity</td>
</tr>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>hypothyroidism&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Common</td>
<td>hypothyroidism&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uncommon</td>
<td>hyperthyroidism&lt;sup&gt;e&lt;/sup&gt;, diabetes mellitus&lt;sup&gt;f&lt;/sup&gt;, adrenal insufficiency&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rare</td>
<td>hypophysitis</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>decreased appetite, hypomagnesaemia</td>
</tr>
<tr>
<td>Common</td>
<td>hypokalaemia, hyponatremia</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very Common</td>
<td>peripheral neuropathy&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Guillain-Barré syndrome&lt;sup&gt;i&lt;/sup&gt;, meningoencephalitis&lt;sup&gt;j&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rare</td>
<td>myasthenic syndrome</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td>myocarditis&lt;sup&gt;k&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>hypotension</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>cough, dyspnoea, dyspnoea</td>
</tr>
<tr>
<td>Common</td>
<td>pneumonitis&lt;sup&gt;l&lt;/sup&gt;, hypoxia, nasal congestion</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>nausea, vomiting, diarrhoea&lt;sup&gt;m&lt;/sup&gt;, constipation</td>
</tr>
<tr>
<td>Common</td>
<td>abdominal pain, colitis&lt;sup&gt;n&lt;/sup&gt;, dysphagia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>pancreatitis&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
## Description of selected adverse reactions

The data below reflect information for significant adverse reactions for atezolizumab as monotherapy in clinical studies (see section 5.1). Details for the significant adverse reactions for atezolizumab when given in combination are presented if clinically relevant differences were noted in comparison to atezolizumab monotherapy. The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

### Atezolizumab monotherapy vs Atezolizumab in combination therapy

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>AST increased, ALT increased, hepatitis &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td>rash&lt;sup&gt;b&lt;/sup&gt;, pruritus</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>rash&lt;sup&gt;g&lt;/sup&gt;, pruritus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common</strong></td>
<td>arthralgia, back pain</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>musculoskeletal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal and urinary disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare</strong></td>
<td>nephritis&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td>pyrexia, fatigue, asthenia</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>infusion-related reaction&lt;sup&gt;i&lt;/sup&gt;, influenza like illness, chills</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes reports of urinary tract infection, cystitis, pyelonephritis, escherichia urinary tract infection, urinary tract infection bacterial, kidney infection, pyelonephritis acute, urinary tract infection fungal, urinary tract infection pseudomonal.

<sup>b</sup> Includes reports of thrombocytopenia and platelet count decreased.

<sup>c</sup> Includes reports of hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, autoimmune thyroiditis, blood thyroid stimulating hormone decreased, autoimmune hypothyroidism, euthyroid sick syndrome, myxoedema, thyroid function test abnormal, thyroiditis acute, thyroxine decreased, goitre.

<sup>d</sup> Includes reports of hyperthyroidism, endocrine ophthalmopathy, and exophthalmus.

<sup>e</sup> Includes reports of diabetes mellitus, type 1 diabetes mellitus, diabetic ketoacidosis and ketoacidosis.

<sup>f</sup> Includes reports of adrenal insufficiency and primary adrenal insufficiency.

<sup>g</sup> Includes reports of neurology peripheral, peripheral sensory neuropathy, polyneuropathy, herpes zoster, peripheral motor neuropathy, neuralgic amyotrophy, peripheral sensorimotor neuropathy, toxic neuropathy.

<sup>h</sup> Includes reports of Guillain-Barré syndrome and demyelinating polyneuropathy.

<sup>i</sup> Includes reports of oesophageal varices haemorrhage, varices oesophageal.

<sup>j</sup> Includes reports of pneumonitis, lung infiltration, bronchiolitis, interstitial lung disease, radiation pneumonitis.

<sup>k</sup> Includes reports of diarhoea, frequent bowel movements, and gastrointestinal hypermotility.

<sup>l</sup> Includes reports of colitis, autoimmune colitis, colitis ischaemic, colitis microscopic, colitis ulcerative.

<sup>m</sup> Includes reports of pancreatitis, pancreatitis acute, lipase increased and any lase increased.

<sup>n</sup> Includes reports of ascites, autoimmune hepatitis, hepatocellular injury, hepatitis, hepatitis acute, hepatotoxicity, liver disorder, drug-induced liver injury, hepatic failure, hepatic steatosis, hepatic lesion, oesophageal varices haemorrhage, varices oesophageal.

<sup>o</sup> Includes reports of acne, eczema, erythema, erythema of eyelid, erythema multiforme, generalised erythema, exfoliative rash, eyelid rash, folliculitis, furuncle, dermatitis, dermatitis acniform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, drug eruption, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash vesicular, seborrhoeic dermatitis, skin exfoliation, skin toxicity, skin ulcer, toxic epidermal necrolysis, toxic skin eruption, eczema infected.

<sup>p</sup> Includes report of Henoch-Schonlein Purpura nephritis.

<sup>q</sup> Includes infusion-related reaction and cytokine release syndrome.
**Immune-related pneumonitis**

Pneumonitis occurred in 2.8% (86/3,075) of patients who received atezolizumab monotherapy. Of the 86 patients, one experienced a fatal event. The median time to onset was 3.4 months (range 3 days to 20.5 months). The median duration was 1.4 months (range 1 day to 21.2+ months; + denotes a censored value). Pneumonitis led to discontinuation of atezolizumab in 12 (0.4%) patients. Pneumonitis requiring the use of corticosteroids occurred in 1.5% (45/3,075) of patients receiving atezolizumab monotherapy.

**Immune-related hepatitis**

Hepatitis occurred in 2.0% (62/3,075) of patients who received atezolizumab monotherapy. Of the 62 patients, two experienced a fatal event. The median time to onset was 1.5 months (range 6 days to 18.8 months). The median duration was 2.1 months (range 2 days to 22.0+ months; + denotes a censored value). Hepatitis led to discontinuation of atezolizumab in 6 (<0.2%) patients. Hepatitis requiring the use of corticosteroids occurred in 0.4% (12/3,075) of patients receiving atezolizumab monotherapy.

**Immune-related colitis**

Colitis occurred in 1.1% (34/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 4.7 months (range 15 days to 17.2 months). The median duration was 1.2 months (range 3 days to 17.8+ months; + denotes a censored value). Colitis led to discontinuation of atezolizumab in 8 (0.3%) patients. Colitis requiring the use of corticosteroids occurred in 0.6% (19/3,075) of patients receiving atezolizumab monotherapy.

**Immune-related endocrinopathies**

**Thyroid disorders**

Hypothyroidism occurred in 4.8% (149/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 4.9 months (range: 3 days to 31.3 months). Hyperthyroidism occurred in 0.9% (28/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 2.1 months (range 21 days to 15.7 months).

**Adrenal insufficiency**

Adrenal insufficiency occurred in 0.4% (12/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range: 3 days to 19 months). The median duration was 16.8 months (range: 1 day to 16.8 months). Adrenal insufficiency requiring the use of corticosteroids occurred in 0.3% (10/3,075) of patients receiving atezolizumab monotherapy.

**Hypophysitis**

Hypophysitis occurred in <0.1% (1/3,075) of patients who received atezolizumab monotherapy. The time to onset for this patient was 13.7 months and the patient required the use of corticosteroids.

Hypophysitis occurred in 0.8% (3/393) of patients who received atezolizumab with bevacizumab, paclitaxel, and carboplatin. The median time to onset was 7.7 months (range: 5.0 to 8.8 months). Two patients required the use of corticosteroids.

**Diabetes mellitus**

Diabetes mellitus occurred in 0.3% (10/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 3.6 months (range 3 days to 9.9 months). Diabetes mellitus led to the discontinuation of atezolizumab in 0.1% (3/3,075) patients.
**Immune-related meningoencephalitis**

Meningoencephalitis occurred in 0.4% (12/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 15 days (range: 1 day to 12.5 months). The median duration was 26 days (range 6 days to 14.5+ months; + denotes a censored value).

Meningoencephalitis requiring the use of corticosteroids occurred in 0.1% (4/3,075) of patients receiving atezolizumab and all four patients discontinued atezolizumab.

**Immune-related neuropathies**

Guillain-Barré syndrome and demyelinating polynuevropathy occurred in 0.2% (5/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 7 months (range: 18 days to 8.1 months). The median duration was 8.0 months (range 18 days to 8.3+ months; + denotes a censored value). Guillain-Barré syndrome led to discontinuation of atezolizumab in 1 patient (< 0.1%). Guillain-Barré syndrome requiring the use of corticosteroids occurred in < 0.1% (2/3,075) of patients receiving atezolizumab monotherapy.

**Myasthenic syndrome**

Myasthenia gravis occurred in < 0.1% (1/3,075) of patients who received atezolizumab monotherapy. The time to onset was 1.2 months.

**Immune-related pancreatitis**

Pancreatitis, including amylase increased and lipase increased, occurred in 0.5% (16/3,075) of patients who received atezolizumab monotherapy. The median time to onset was 5.5 months (range: 9 days to 16.9 months). The median duration was 28 days (range 3 days to 12.0+ months; + denotes a censored value). Pancreatitis led to the discontinuation of atezolizumab in 1 (< 0.1%) patient. Pancreatitis requiring the use of corticosteroids occurred in 0.1% (3/3,075) of patients receiving atezolizumab monotherapy.

**Immune-related myocarditis**

Myocarditis occurred in < 0.1% (2/8,000) of patients across all atezolizumab clinical trials in multiple tumour types and treatment combinations. The time to onset was 18 and 33 days. Both patients required corticosteroids and discontinued atezolizumab.

**Immune-related nephritis**

Nephritis occurred in < 0.1% (1/3,075) of patients who received atezolizumab. The time to onset was 13.1 months. The patient required corticosteroids and discontinued atezolizumab.

**Use of atezolizumab in combination with bevacizumab, paclitaxel and carboplatin**

In the first-line NSCLC study (IMpower150), an overall higher frequency of adverse events was observed in the four-drug regimen of atezolizumab, bevacizumab, paclitaxel, and carboplatin compared to atezolizumab, paclitaxel and carboplatin, including Grade 3 and 4 events (63.6% compared to 57.5%), Grade 5 events (6.1% compared to 2.5%), adverse events of special interest to atezolizumab (52.4% compared to 48.0%), as well as adverse events leading to withdrawal of any study treatment (33.8% compared to 13.3%). Nausea, diarrhoea, stomatitis, fatigue, pyrexia, mucosal inflammation, decreased appetite, weight decreased, hypertension and proteinuria were reported higher (≥5% difference) in patients receiving atezolizumab in combination with bevacizumab, paclitaxel and carboplatin. Other clinically significant adverse events which were observed more frequently in the atezolizumab, bevacizumab, paclitaxel, and carboplatin arm were epistaxis, haemoptysis, cerebrovascular accident, including fatal events.

**Immunogenicity**

In pooled assessment of studies IMvigor211 and OAK, 31.7% of patients tested positive for treatment-emergent anti-atezolizumab antibodies (ADAs) at one or more post-dose time points.

In study IMpower150, 36.4% of patients treated with atezolizumab, bevacizumab, paclitaxel and carboplatin tested positive for treatment-emergent ADAs at one or more time points. Overall, ADA
positivity by Week 4 appeared to have no clinically relevant impact on pharmacokinetics, efficacy or safety.

No data are available to allow conclusions to be drawn on possible effects of neutralising antibodies.

Elderly patients
No overall differences in safety were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab monotherapy. In study IMpower150, age ≥ 65 was associated with an increased risk of developing adverse events in patients receiving atezolizumab in combination with bevacizumab, carboplatin and paclitaxel. Data for patients ≥75 years of age are too limited to draw conclusions on this population (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with atezolizumab.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC

Mechanism of action

Programmed death-ligand 1 (PD-L1) may be expressed on tumour cells and/or tumour-infiltrating immune cells, and can contribute to the inhibition of the antitumour immune response in the tumour microenvironment. Binding of PD-L1 to the PD-1 and B7.1 receptors found on T-cells and antigen presenting cells suppresses cytotoxic T-cell activity, T-cell proliferation and cytokine production.

Atezolizumab is an Fc-engineered, humanised immunoglobulin G1 (IgG1) monoclonal antibody that directly binds to PD-L1 and provides a dual blockade of the PD-1 and B7.1 receptors, releasing PD-L1/PD-1 mediated inhibition of the immune response, including reactivating the antitumour immune response without inducing antibody-dependent cellular cytotoxicity. Atezolizumab spares the PD-L2/PD-1 interaction allowing PD-L2/PD-1 mediated inhibitory signals to persist.
Clinical efficacy and safety

Duration of treatment

Treatment with atezolizumab until loss of clinical benefit was permitted as defined by the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values [e.g., new or worsening hypercalcaemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumour progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be readily managed and stabilised by protocol-allowed medical interventions prior to repeat dosing
- Evidence of clinical benefit as assessed by the investigator

Patients with locally advanced or metastatic UC who are ineligible for cisplatin therapy were treated with atezolizumab until disease progression.

Urothelial carcinoma

IMvigor211 (GO29294): Randomised trial in locally advanced or metastatic UC patients previously treated with chemotherapy

A phase III, open-label, multi-center, international, randomised study, (IMvigor211), was conducted to evaluate the efficacy and safety of atezolizumab compared with chemotherapy (investigator’s choice of vinflunine, docetaxel, or paclitaxel) in patients with locally advanced or metastatic UC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease; active or corticosteroid-dependent brain metastases; administration of a live, attenuated vaccine within 28 days prior to enrolment; and administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 9 weeks for the first 54 weeks, and every 12 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 931 patients were enrolled. Patients were randomised (1:1) to receive either atezolizumab or chemotherapy. Randomisation was stratified by chemotherapy (vinflunine vs taxane), PD-L1 expression status on IC (< 5% vs ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no). Prognostic risk factors included time from prior chemotherapy of < 3 months, ECOG performance status > 0 and haemoglobin < 10 g/dL.

Atezolizumab was administered as a fixed dose of 1,200 mg by intravenous infusion every 3 weeks. No dose reduction of atezolizumab was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator or unacceptable toxicity. Vinflunine was administered 320 mg/m² by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Paclitaxel was administered 175 mg/m² by intravenous infusion over 3 hours on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. Docetaxel was administered 75 mg/m² by intravenous infusion on day 1 of each 3-week cycle until disease progression or unacceptable toxicity. For all treated patients, the median duration of treatment was 2.8 months for the atezolizumab arm, 2.1 months for the vinflunine and paclitaxel arms and 1.6 months for the docetaxel arm.
The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 67 years (range: 31 to 88), and 77.1% of patients were male. The majority of patients were white (72.1%), 53.9% of patients within the chemotherapy arm received vinflunine, 71.4% of patients had at least one poor prognostic risk factor and 28.8% had liver metastases at baseline. Baseline ECOG performance status was 0 (45.6%) or 1 (54.4%). Bladder was the primary tumour site for 71.1% of patients and 25.4% of patients had upper tract urothelial carcinoma. There were 24.2% of patients who received only prior platinum-containing adjuvant or neoadjuvant therapy and progressed within 12 months.

The primary efficacy endpoint for IMvigor211 is overall survival (OS). Secondary efficacy endpoints evaluated per investigator-assessed Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 are objective response rate (ORR), progression-free survival (PFS), and duration of response (DOR). Comparisons with respect to OS between the treatment arm and control arm within the IC2/3, IC1/2/3, and ITT (Intention-to-treat, i.e. all comers) populations were tested using a hierarchical fixed-sequence procedure based on a stratified log-rank test at two-sided level of 5% as follows: step 1) IC2/3 population; step 2) IC1/2/3 population; step 3) all comers population. OS results for each of steps 2 and 3 could be formally tested for statistical significance only if the result in the preceding step was statistically significant.

The median survival follow-up is 17 months. The primary analysis of study IMvigor211 did not meet its primary endpoint of OS. Atezolizumab did not demonstrate a statistically significant survival benefit compared to chemotherapy in patients with previously treated, locally advanced or metastatic urothelial carcinoma. Per the pre-specified hierarchical testing order, the IC2/3 population was tested first, with an OS HR of 0.87 (95% CI: 0.63, 1.21; median OS of 11.1 vs. 10.6 months for atezolizumab and chemotherapy respectively). The stratified log-rank p-value was 0.41 and therefore the results are considered not statistically significant in this population. As a consequence, no formal tests of statistical significance could be performed for OS in the IC1/2/3 or all comers populations, and results of those analyses would be considered exploratory. The key results in the all comers population are summarised in Table 3. The Kaplan-Meier curve for OS in the all comers population is presented in Figure 1.
Table 3: Summary of efficacy in all comers (IMvigor211)

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Atezolizumab (n = 467)</th>
<th>Chemotherapy (n = 464)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>324 (69.4%)</td>
<td>350 (75.4%)</td>
</tr>
<tr>
<td>Median time to events (months)</td>
<td>8.6</td>
<td>8.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.8, 9.6</td>
<td>7.2, 8.6</td>
</tr>
<tr>
<td>Stratified* hazard ratio (95% CI)</td>
<td>0.85 (0.73, 0.99)</td>
<td></td>
</tr>
<tr>
<td>12-month OS (%)**</td>
<td>39.2%</td>
<td>32.4%</td>
</tr>
<tr>
<td><strong>Secondary and exploratory endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator-assessed PFS (RECIST v1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events (%)</td>
<td>407 (87.2%)</td>
<td>410 (88.4%)</td>
</tr>
<tr>
<td>Median duration of PFS (months)</td>
<td>2.1</td>
<td>4.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.1, 2.2</td>
<td>3.4, 4.2</td>
</tr>
<tr>
<td>Stratified hazard ratio (95% CI)</td>
<td>1.10 (0.95, 1.26)</td>
<td></td>
</tr>
<tr>
<td>Investigator-assessed ORR (RECIST v1.1)</td>
<td>n = 462</td>
<td>n = 461</td>
</tr>
<tr>
<td>No. of confirmed responders (%)</td>
<td>62 (13.4%)</td>
<td>62 (13.4%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>10.45, 16.87</td>
<td>10.47, 16.91</td>
</tr>
<tr>
<td>No. of complete response (%)</td>
<td>16 (3.5%)</td>
<td>16 (3.5%)</td>
</tr>
<tr>
<td>No. of partial response (%)</td>
<td>46 (10.0%)</td>
<td>46 (10.0%)</td>
</tr>
<tr>
<td>No. of stable disease (%)</td>
<td>92 (19.9%)</td>
<td>162 (35.1%)</td>
</tr>
<tr>
<td>Investigator-assessed DOR (RECIST v1.1)</td>
<td>n = 62</td>
<td>n = 62</td>
</tr>
<tr>
<td>Median in months ***</td>
<td>21.7</td>
<td>7.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.0, 21.7</td>
<td>6.1, 10.3</td>
</tr>
</tbody>
</table>

CI = confidence interval; DOR = duration of response; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.
* An analysis of OS in the all comer population was performed based on the stratified log-rank test and the result is provided for descriptive purposes only (p = 0.0378); according to the pre-specified analysis hierarchy, the p-value for the OS analysis in the all comer population cannot be considered statistically significant.
† Stratified by chemotherapy (vinflunine vs taxane), status on IC (< 5% vs. ≥ 5%), number of prognostic risk factors (0 vs. 1-3), and liver metastases (yes vs. no).
** Based on Kaplan-Meier estimate
*** Responses were ongoing in 63% of responders in the atezolizumab arm and in 21% of responders in the chemotherapy arm.
Figure 1: Kaplan-Meier curve for overall survival (IMvigor211)

IMvigor210 (GO29293): Single-arm trial in previously untreated urothelial carcinoma patients who are ineligible for cisplatin therapy and in urothelial carcinoma patients previously treated with chemotherapy

A phase II, multi-centre, international, two-cohort, single-arm clinical trial, IMvigor210, was conducted in patients with locally advanced or metastatic UC (also known as urothelial bladder cancer).

The study enrolled a total of 438 patients and had two patient cohorts. Cohort 1 included previously untreated patients with locally advanced or metastatic UC who were ineligible or unfit for cisplatin-based chemotherapy or had disease progression at least 12 months after treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen. Cohort 2 included patients who received at least one platinum-based chemotherapy regimen for locally advanced or metastatic UC or had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.

In Cohort 1, 119 patients were treated with atezolizumab 1,200 mg by intravenous infusion every 3 weeks until disease progression. The median age was 73 years. Most patients were male (81%), and the majority of patients were White (91%).

Cohort 1 included 45 patients (38%) with ECOG performance status of 0, 50 patients (42%) with ECOG performance status of 1 and 24 patients (20%) with ECOG performance status of 2, 35 patients (29%) with no Bajorin risk factors (ECOG performance status ≥ 2 and visceral metastasis), 66 patients (56%) with one Bajorin risk factor and 18 patients (15%) with two Bajorin risk factors, 84 patients (71%) with impaired renal function (glomerular filtration rate [GFR] < 60 mL/min), and 25 patients (21%) with liver metastasis.

The primary efficacy endpoint for Cohort 1 was confirmed objective response rate (ORR) as assessed by an independent review facility (IRF) using RECIST v1.1.

The primary analysis was performed when all patients had at least 24 weeks of follow-up. Median duration of treatment was 15.0 weeks and median duration of survival follow-up was 8.5 months in all comers. Clinically relevant IRF-assessed ORRs per RECIST v1.1 were shown; however, when compared to a pre-specified historical control response rate of 10%, statistical significance was not reached for the primary endpoint. The confirmed ORRs per IRF-RECIST v1.1 were 21.9% (95% CI: 0.85 (0.73, 0.99).
9.3, 40.0) in patients with PD-L1 expression ≥ 5%, 18.8% (95% CI: 10.9, 29.0) in patients with PD-L1 expression ≥ 1%, and 19.3% (95% CI: 12.7, 27.6) in all comers. The median duration of response (DOR) was not reached in any PD-L1 expression subgroup or in all comers. OS was not mature with an event patient ratio of approximately 40%. Median OS for all patient subgroups (PD-L1 expression ≥ 5% and ≥ 1%) and in all comers was 10.6 months.

An updated analysis was performed with a median duration of survival follow-up of 17.2 months for Cohort 1 and is summarised in Table 4. The median DOR was not reached in any PD-L1 expression subgroup or in all comers.

### Table 4: Summary of updated efficacy (IMvigor210 Cohort 1)

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>PD-L1 expression of ≥ 5% in IC</th>
<th>PD-L1 expression of ≥ 1% in IC</th>
<th>All Comers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR (IRF-assessed; RECIST v1.1)</strong></td>
<td>n = 32</td>
<td>n = 80</td>
<td>n = 119</td>
</tr>
<tr>
<td>No. of Responders (%)</td>
<td>9 (28.1%)</td>
<td>19 (23.8%)</td>
<td>27 (22.7%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>13.8, 46.8</td>
<td>15.0, 34.6</td>
<td>15.5, 31.3</td>
</tr>
<tr>
<td>No. of complete response (%)</td>
<td>4 (12.5%)</td>
<td>8 (10.0%)</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(3.5, 29.0)</td>
<td>(4.4, 18.8)</td>
<td>(4.7, 15.9)</td>
</tr>
<tr>
<td>No. of partial response (%)</td>
<td>5 (15.6%)</td>
<td>11 (13.8%)</td>
<td>16 (13.4%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(5.3, 32.8)</td>
<td>(7.1, 23.3)</td>
<td>(7.9, 20.9)</td>
</tr>
<tr>
<td><strong>DOR (IRF-assessed; RECIST v1.1)</strong></td>
<td>n = 9</td>
<td>n = 19</td>
<td>n = 27</td>
</tr>
<tr>
<td>Patients with event (%)</td>
<td>3 (33.3%)</td>
<td>5 (26.3%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Median (months) (95% CI)</td>
<td>NE (11.1, NE)</td>
<td>NE (NE)</td>
<td>NE (14.1, NE)</td>
</tr>
<tr>
<td><strong>PFS (IRF-assessed; RECIST v1.1)</strong></td>
<td>n = 32</td>
<td>n = 80</td>
<td>n = 119</td>
</tr>
<tr>
<td>Patients with event (%)</td>
<td>24 (75.0%)</td>
<td>59 (73.8%)</td>
<td>88 (73.9%)</td>
</tr>
<tr>
<td>Median (months) (95% CI)</td>
<td>4.1 (2.3, 11.8)</td>
<td>2.9 (2.1, 5.4)</td>
<td>2.7 (2.1, 4.2)</td>
</tr>
<tr>
<td><strong>OS</strong></td>
<td>n = 32</td>
<td>n = 80</td>
<td>n = 119</td>
</tr>
<tr>
<td>Patients with event (%)</td>
<td>18 (56.3%)</td>
<td>42 (52.5%)</td>
<td>59 (49.6%)</td>
</tr>
<tr>
<td>Median (months) (95% CI)</td>
<td>12.3 (6.0, NE)</td>
<td>14.1 (9.2, NE)</td>
<td>15.9 (10.4, NE)</td>
</tr>
<tr>
<td>1-year OS rate (%)</td>
<td>52.4%</td>
<td>54.8%</td>
<td>57.2%</td>
</tr>
</tbody>
</table>

CI = confidence interval; DOR = duration of response; IC = tumour-infiltrating immune cells; IRF = independent review facility; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

In Cohort 2, the co-primary efficacy endpoints were confirmed ORR as assessed by an IRF using RECIST v1.1 and investigator-assessed ORR according to Modified RECIST (mRECIST) criteria. There were 310 patients treated with atezolizumab 1,200 mg by intravenous infusion every 3 weeks until loss of clinical benefit. The primary analysis of Cohort 2 was performed when all patients had at least 24 weeks of follow-up. The study met its co-primary endpoints in Cohort 2, demonstrating statistically significant ORRs per IRF-assessed RECIST v1.1 and investigator-assessed mRECIST compared to a pre-specified historical control response rate of 10%.

An analysis was also performed with a median duration of survival follow-up of 21.1 months for Cohort 2. The confirmed ORRs per IRF-RECIST v1.1 were 28.0% (95% CI: 19.5, 37.9) in patients with PD-L1 expression ≥ 5%, 19.3% (95% CI: 14.2, 25.4) in patients with PD-L1 expression ≥ 1%, and 15.8% (95% CI: 11.9, 20.4) in all comers. The confirmed ORR per investigator-assessed mRECIST was 29.0% (95% CI: 20.4, 38.9) in patients with PD-L1 expression ≥ 5%, 23.7% (95% CI: 18.1, 30.1) in patients with PD-L1 expression ≥ 1%, and 19.7% (95% CI: 15.4, 24.6) in all comers. The rate of complete response per IRF-RECIST v1.1 in the all comers population was 6.1% (95% CI: 3.7, 9.4). For Cohort 2, median DOR was not reached in any PD-L1 expression subgroup or in all comers.
comers, however was reached in patients with PD-L1 expression < 1% (13.3 months; 95% CI 4.2, NE). The OS rate at 12 month was 37% in all comers.

**IMvigor130 (WO30070): Phase III multi-center, randomized, placebo-controlled study of atezolizumab as monotherapy and in combination with platinum-based chemotherapy in patients with untreated locally advanced or metastatic urothelial carcinoma**

Based on an independent Data Monitoring Committee (iDMC) recommendation following an early review of survival data, accrual of patients on the atezolizumab monotherapy treatment arm whose tumours have a low PD-L1 expression (less than 5% of immune cells staining positive for PD-L1 by immunohistochemistry) was stopped after observing decreased overall survival for this subgroup. The iDMC did not recommend any change of therapy for patients who had already been randomized to and were receiving treatment in the monotherapy arm. No other changes were recommended.

**Non-small cell lung cancer**

**First-line treatment of non-small cell lung cancer**

**IMpower150 (GO29436): Randomised phase III trial in chemotherapy-naïve patients with metastatic non-squamous NSCLC, in combination with paclitaxel and carboplatin with or without bevacizumab**

A phase III, open-label, multicenter, international, randomised study, IMpower150, was conducted to evaluate the efficacy and safety of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, in chemotherapy-naïve patients with metastatic non-squamous NSCLC.

Patients were excluded if they had history of autoimmune disease, administration of a live, attenuated vaccine within 28 days prior to randomisation, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medications within 2 weeks prior to randomisation, active or untreated CNS metastases, clear tumour infiltration into the thoracic great vessels or clear cavitation of pulmonary lesions, as seen on imaging. Tumour assessments were conducted every 6 weeks for the first 48 weeks following Cycle 1, Day 1 and then every 9 weeks thereafter. Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC) and the results were used to define the PD-L1 expression subgroups for the analyses described below.

A total of 1,202 patients were enrolled and were randomised (1:1:1) to receive one of the treatment regimens described in Table 5. Randomization was stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC.
### Table 5: Intravenous treatment regimens (IMpower150)

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Induction (Four or Six 21-day cycles)</th>
<th>Maintenance (21-day cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Atezolizumab&lt;sup&gt;a&lt;/sup&gt; (1,200 mg) + paclitaxel (200 mg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;b,c&lt;/sup&gt; + carboplatin&lt;sup&gt;c&lt;/sup&gt; (AUC 6)</td>
<td>Atezolizumab&lt;sup&gt;a&lt;/sup&gt; (1,200 mg)</td>
</tr>
<tr>
<td>B</td>
<td>Atezolizumab&lt;sup&gt;a&lt;/sup&gt; (1,200 mg) + bevacizumab&lt;sup&gt;d&lt;/sup&gt; (15 mg/kg) + paclitaxel (200 mg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;b,c&lt;/sup&gt; + carboplatin&lt;sup&gt;c&lt;/sup&gt; (AUC 6)</td>
<td>Atezolizumab&lt;sup&gt;a&lt;/sup&gt; (1,200 mg) + bevacizumab&lt;sup&gt;d&lt;/sup&gt; (15 mg/kg)</td>
</tr>
<tr>
<td>C</td>
<td>Bevacizumab&lt;sup&gt;d&lt;/sup&gt; (15 mg/kg) + paclitaxel (200 mg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;b,c&lt;/sup&gt; + carboplatin&lt;sup&gt;c&lt;/sup&gt; (AUC 6)</td>
<td>Bevacizumab&lt;sup&gt;d&lt;/sup&gt; (15 mg/kg)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Atezolizumab is administered until loss of clinical benefit as assessed by the investigator

<sup>b</sup> The paclitaxel starting dose for patients of Asian race/ethnicity was 175 mg/m<sup>2</sup> due to higher overall level of haematologic toxicities in patients from Asian countries compared with those from non-Asian countries

<sup>c</sup> Paclitaxel and carboplatin are administered until completion of 4 or 6 cycles, or progressive disease, or unacceptable toxicity whichever occurs first

<sup>d</sup> Bevacizumab is administered until progressive disease or unacceptable toxicity

The demographics and baseline disease characteristics of the study population were well balanced between the treatment arms. The median age was 63 years (range: 31 to 90), and 60% of patients were male. The majority of patients were white (82%). Approximately 10% of patients had known EGFR mutation, 4% had known ALK rearrangements, 14% had liver metastasis at baseline, and most patients were current or previous smokers (80%). Baseline ECOG performance status was 0 (43%) or 1 (57%). 51% of patients’ tumours had PD-L1 expression of ≥ 1% TC or ≥ 1% IC and 49% of patients’ tumours had PD-L1 expression of < 1% TC and < 1% IC.

At the time of the final analysis for PFS, patients had a median follow up time of 15.3 months. The ITT population, including patients with EGFR mutations or ALK rearrangements who should have been previously treated with tyrosine kinase inhibitors, demonstrated clinically meaningful PFS improvement in Arm B as compared to Arm C (HR of 0.61, 95% CI: 0.52, 0.72; median PFS 8.3 vs. 6.8 months).

At the time of the interim OS analysis, patients had a median follow-up of 19.7 months. The key results from this analysis as well as from the updated PFS analysis in the ITT population are summarised in Tables 6 and 7. The Kaplan-Meier curve for OS in the ITT population is presented in Figure 2. Figure 3 summarises the results of OS in the ITT and PD-L1 subgroups. Updated PFS results are also presented in Figures 4 and 5.
Table 6: Summary of updated efficacy in the ITT population (IMpower150)

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Arm A (Atezolizumab + Paclitaxel + Carboplatin)</th>
<th>Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)</th>
<th>Arm C (Bevacizumab + Paclitaxel + Carboplatin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigator-assessed PFS (RECIST v1.1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 402</td>
<td>n = 400</td>
<td>n = 400</td>
<td></td>
</tr>
<tr>
<td>No. of events (%)</td>
<td>330 (82.1%)</td>
<td>291 (72.8%)</td>
<td>355 (88.8%)</td>
</tr>
<tr>
<td>Median duration of PFS (months)</td>
<td>6.7</td>
<td>8.4</td>
<td>6.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>(5.7, 6.9)</td>
<td>(8.0, 9.9)</td>
<td>(6.0, 7.0)</td>
</tr>
<tr>
<td>Stratified hazard ratio‡ (95% CI)</td>
<td>0.91 (0.78, 1.06)</td>
<td>0.59 (0.50, 0.69)</td>
<td>---</td>
</tr>
<tr>
<td>P-value †, ‡</td>
<td>0.2194</td>
<td>&lt; 0.0001</td>
<td>---</td>
</tr>
<tr>
<td>12-month PFS (%)</td>
<td>24</td>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td><strong>OS interim analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 402</td>
<td>n = 400</td>
<td>n = 400</td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>206 (51.2%)</td>
<td>192 (48.0%)</td>
<td>230 (57.5%)</td>
</tr>
<tr>
<td>Median time to events (months)</td>
<td>19.5</td>
<td>19.8</td>
<td>14.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>(16.3, 21.3)</td>
<td>(17.4, 24.2)</td>
<td>(13.4, 17.1)</td>
</tr>
<tr>
<td>Stratified hazard ratio‡ (95% CI)</td>
<td>0.85 (0.71, 1.03)</td>
<td>0.76 (0.63, 0.93)</td>
<td>---</td>
</tr>
<tr>
<td>P-value †, ‡</td>
<td>0.0083</td>
<td>0.006</td>
<td>---</td>
</tr>
<tr>
<td>6-month OS (%)</td>
<td>84</td>
<td>85</td>
<td>81</td>
</tr>
<tr>
<td>12-month OS (%)</td>
<td>66</td>
<td>68</td>
<td>61</td>
</tr>
<tr>
<td><strong>Investigator-assessed Overall Best Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 401</td>
<td>n = 397</td>
<td>n = 393</td>
<td></td>
</tr>
<tr>
<td>No. of responders (%)</td>
<td>163 (40.6%)</td>
<td>224 (56.4%)</td>
<td>158 (40.2%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(35.8, 45.6)</td>
<td>(51.4, 61.4)</td>
<td>(35.3, 45.2)</td>
</tr>
<tr>
<td>No. of complete response (%)</td>
<td>8 (2.0%)</td>
<td>11 (2.8%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>No. of partial response (%)</td>
<td>155 (38.7%)</td>
<td>213 (53.7%)</td>
<td>155 (39.4%)</td>
</tr>
<tr>
<td><strong>Investigator-assessed DOR (RECIST v1.1)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 163</td>
<td>n = 224</td>
<td>n = 158</td>
<td></td>
</tr>
<tr>
<td>Median in months</td>
<td>8.3</td>
<td>11.5</td>
<td>6.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>(7.1, 11.8)</td>
<td>(8.9, 15.7)</td>
<td>(5.5, 6.9)</td>
</tr>
</tbody>
</table>

‡ Stratified by sex, presence of liver metastases and PD-L1 tumour expression on TC and IC
^ The Arm C is the comparison group for all hazard ratios
* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018

PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.
CI = confidence interval; DOR = duration of response; OS = overall survival.
Table 7: Summary of updated efficacy for Arm A vs Arm B in the ITT population (IMpower150)

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Arm A (Atezolizumab + Paclitaxel + Carboplatin)</th>
<th>Arm B (Atezolizumab + Bevacizumab + Paclitaxel + Carboplatin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator-assessed PFS (RECIST v1.1)*</td>
<td>n = 402</td>
<td>n = 400</td>
</tr>
<tr>
<td>No. of events (%)</td>
<td>330 (82.1%)</td>
<td>291 (72.8%)</td>
</tr>
<tr>
<td>Median duration of PFS (months)</td>
<td>6.7</td>
<td>8.4</td>
</tr>
<tr>
<td>95% CI</td>
<td>(5.7, 6.9)</td>
<td>(8.0, 9.9)</td>
</tr>
<tr>
<td>Stratified hazard ratio‡ (95% CI) p-value</td>
<td>0.67 (0.57, 0.79)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>OS interim analysis*</td>
<td>n = 402</td>
<td>n = 400</td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>206 (51.2%)</td>
<td>192 (48.0%)</td>
</tr>
<tr>
<td>Median time to events (months)</td>
<td>19.5</td>
<td>19.8</td>
</tr>
<tr>
<td>95% CI</td>
<td>(16.3, 21.3)</td>
<td>(17.4, 24.2)</td>
</tr>
<tr>
<td>Stratified hazard ratio‡ (95% CI) p-value</td>
<td>0.90 (0.74, 1.10)</td>
<td>0.300</td>
</tr>
</tbody>
</table>

* Based on the stratified log-rank test
1 For informational purposes; in the ITT population, comparisons between Arm A and Arm B were not included in the pre-specified analysis hierarchy
2 Stratified by sex, presence of liver metastases and PD-L1 expression on TC and IC
* Updated PFS analysis and interim OS analysis at clinical cut-off 22 January 2018
§ The Arm A is the comparison group for all hazard ratios

Figure 2: Kaplan-Meier curve for overall survival in the ITT population (IMpower150)
Figure 3: Forest plot of overall survival by PD-L1 expression in the ITT population, Arm B vs C (IMpower150)

Figure 4: Kaplan-Meier curve for PFS in the ITT population (IMpower150)
Figure 5: Forest plot of progression free survival by PD-L1 expression in the ITT population, Arm B vs C (IMpower150)

In Arm B as compared to Arm C, pre-specified subgroup analyses from the interim OS analysis showed an OS improvement for patients with EGFR mutations or ALK rearrangements (hazard ratio [HR] of 0.54, 95% CI: 0.29, 1.03; median OS not reached vs. 17.5 months), and liver metastases (HR of 0.52, 95% CI: 0.33, 0.82; median OS 13.3 vs 9.4 months). PFS improvements were also shown in patients with EGFR mutations or ALK rearrangements (HR of 0.55, 95% CI: 0.35, 0.87; median PFS 10.0 vs. 6.1 months) and liver metastases (HR of 0.41, 95% CI: 0.26, 0.62; median PFS 8.2 vs. 5.4 months). OS results were similar for patients aged < 65 and ≥ 65 subgroups, respectively. Data for patients ≥ 75 years of age are too limited to draw conclusions on this population. For all subgroup analyses, formal statistical testing was not planned.

**Second-line treatment of non-small cell lung cancer**

**OAK (GO28915): Randomised phase III trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy**

A phase III, open-label, multi-center, international, randomised study, OAK, was conducted to evaluate the efficacy and safety of atezolizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen. This study excluded patients who had a history of autoimmune disease, active or corticosteroid-dependent brain metastases, administration of a live, attenuated vaccine within 28 days prior to enrolment, administration of systemic immunostimulatory agents within 4 weeks or systemic immunosuppressive medicinal product within 2 weeks prior to enrolment. Tumour assessments were conducted every 6 weeks for the first 36 weeks, and every 9 weeks thereafter. Tumour specimens were evaluated prospectively for PD-L1 expression on tumour cells (TC) and tumour-infiltrating immune cells (IC).

A total of 1,225 patients were enrolled and per the analysis plan the first 850 randomised patients were included in the primary efficacy analysis. Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens, and by histology. Patients were randomised (1:1) to receive either atezolizumab or docetaxel.

Atezolizumab was administered as a fixed dose of 1,200 mg by intravenous infusion every 3 weeks. No dose reduction was allowed. Patients were treated until loss of clinical benefit as assessed by the investigator. Docetaxel was administered 75 mg/m² by intravenous infusion on day 1 of each 3-week cycle until disease progression. For all treated patients, the median duration of treatment was 2.1 months for the docetaxel arm and 3.4 months for the atezolizumab arm.
The demographic and baseline disease characteristics of the primary analysis population were well balanced between the treatment arms. The median age was 64 years (range: 33 to 85), and 61% of patients were male. The majority of patients were white (70%). Approximately three-quarters of patients had non-squamous histology (74%), 10% had known EGFR mutation, 0.2% had known ALK rearrangements, 10% had CNS metastases at baseline, and most patients were current or previous smokers (82%). Baseline ECOG performance status was 0 (37%) or 1 (63%). Seventy five percent of patients received only one prior platinum-based therapeutic regimen.

The primary efficacy endpoint was OS. The key results of this study with a median survival follow-up of 21 months are summarised in Table 8. Kaplan-Meier curves for OS in the ITT population are presented in Figure 6. Figure 7 summarises the results of OS in the ITT and PD-L1 subgroups, demonstrating OS benefit with atezolizumab in all subgroups, including those with PD-L1 expression < 1% in TC and IC.

Table 8: Summary of efficacy in the primary analysis population (all comers)* (OAK)

<table>
<thead>
<tr>
<th>Efficacy endpoint</th>
<th>Atezolizumab (n = 425)</th>
<th>Docetaxel (n = 425)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths (%)</td>
<td>271 (64%)</td>
<td>298 (70%)</td>
</tr>
<tr>
<td>Median time to events (months)</td>
<td>13.8</td>
<td>9.6</td>
</tr>
<tr>
<td>95% CI</td>
<td>(11.8, 15.7)</td>
<td>(8.6, 11.2)</td>
</tr>
<tr>
<td>Stratified* hazard ratio (95% CI)</td>
<td>0.73 (0.62, 0.87)</td>
<td>0.95 (0.82, 1.10)</td>
</tr>
<tr>
<td>p-value**</td>
<td>0.0003</td>
<td>0.0003</td>
</tr>
<tr>
<td>12-month OS (%)***</td>
<td>218 (55%)</td>
<td>151 (41%)</td>
</tr>
<tr>
<td>18-month OS (%)***</td>
<td>157 (40%)</td>
<td>98 (27%)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator-assessed PFS (RECIST v1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of events (%)</td>
<td>380 (89%)</td>
<td>375 (88%)</td>
</tr>
<tr>
<td>Median duration of PFS (months)</td>
<td>2.8</td>
<td>4.0</td>
</tr>
<tr>
<td>95% CI</td>
<td>(2.6, 3.0)</td>
<td>(3.3, 4.2)</td>
</tr>
<tr>
<td>Stratified hazard ratio (95% CI)</td>
<td>0.95 (0.82, 1.10)</td>
<td>0.95 (0.82, 1.10)</td>
</tr>
<tr>
<td>Investigator-assessed ORR (RECIST v1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of responders (%)</td>
<td>58 (14%)</td>
<td>57 (13%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(10.5, 17.3)</td>
<td>(10.3, 17.0)</td>
</tr>
<tr>
<td>Investigator-assessed DOR (RECIST v1.1)</td>
<td>n = 58</td>
<td>n = 57</td>
</tr>
<tr>
<td>Median in months</td>
<td>16.3</td>
<td>6.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>(10.0, NE)</td>
<td>(4.9, 7.6)</td>
</tr>
</tbody>
</table>

CI = confidence interval; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours v1.1.

*The primary analysis population consists of the first 850 randomised patients

†Stratified by PD-L1 expression in tumour infiltrating immune cells, the number of prior chemotherapy regimens, and histology

** Based on the stratified log-rank test

*** Based on Kaplan-Meier estimates
An improvement in OS was observed with atezolizumab compared to docetaxel in both non-squamous NSCLC patients (hazard ratio [HR] of 0.73, 95% CI: 0.60, 0.89; median OS of 15.6 vs. 11.2 months for atezolizumab and docetaxel, respectively) and squamous NSCLC patients (HR of 0.73, 95% CI: 0.54, 0.98; median OS of 8.9 vs. 7.7 months for atezolizumab and docetaxel, respectively). The observed OS improvement was consistently demonstrated across subgroups of patients including those with brain metastases at baseline (HR of 0.54, 95% CI: 0.31, 0.94; median OS of 20.1 vs. 11.9 months for atezolizumab and docetaxel, respectively) and patients who were never smokers (HR of 0.71, 95% CI: 0.47, 1.08; median OS of 16.3 vs. 12.6 months for atezolizumab and docetaxel, respectively). However, patients with EGFR mutations did not show improved OS with atezolizumab.
compared to docetaxel (HR of 1.24, 95% CI: 0.71, 2.18; median OS of 10.5 vs. 16.2 months for atezolizumab and docetaxel, respectively).

Prolonged time to deterioration of patient-reported pain in chest as measured by the EORTC QLQ-LC13 was observed with atezolizumab compared to docetaxel (HR of 0.71, 95% CI: 0.49, 1.05; median not reached in either arm). The time to deterioration in other lung cancer symptoms (i.e. cough, dyspnoea, and arm/shoulder pain) as measured by the EORTC QLQ-LC13 was similar between atezolizumab and docetaxel. These results should be interpreted with caution due to the open-label design of the study.

**POPLAR (GO28753): Randomised phase II trial in locally advanced or metastatic NSCLC patients previously treated with chemotherapy**

A phase II, multi-centre, international, randomised, open-label, controlled study, POPLAR, was conducted in patients with locally advanced or metastatic NSCLC who progressed during or following a platinum-containing regimen, regardless of PD-L1 expression. The primary efficacy outcome was overall survival. A total of 287 patients were randomised 1:1 to receive either atezolizumab (1,200 mg by intravenous infusion every 3 weeks until loss of clinical benefit) or docetaxel (75 mg/m² by intravenous infusion on day 1 of each 3-week cycle until disease progression). Randomisation was stratified by PD-L1 expression status on IC, by the number of prior chemotherapy regimens and by histology. An updated analysis with a total of 200 deaths observed and a median survival follow-up of 22 months showed a median OS of 12.6 months in patients treated with atezolizumab, vs. 9.7 months in patients treated with docetaxel (HR of 0.69, 95% CI: 0.52, 0.92). ORR was 15.3% vs. 14.7% and median DOR was 18.6 months vs. 7.2 months for atezolizumab vs. docetaxel, respectively.

**Efficacy in elderly patients**

No overall differences in efficacy were observed between patients ≥ 65 years of age and younger patients receiving atezolizumab monotherapy. In study IMpower150, age ≥ 65 was associated with a diminished effect of atezolizumab in patients receiving atezolizumab in combination with carboplatin and paclitaxel. Data for patients ≥75 years of age are too limited to draw conclusions on this population.

**Paediatric population**

The European Medicines Agency has deferred the obligation to submit the results of studies with atezolizumab in all subsets of the paediatric population in the treatment of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (see section 4.2 for information on paediatric use).

**5.2 Pharmacokinetic properties**

Exposure to atezolizumab increased dose proportionally over the dose range 1 mg/kg to 20 mg/kg including the fixed dose 1,200 mg administered every 3 weeks. A population analysis that included 472 patients described atezolizumab pharmacokinetics for the dose range: 1 to 20 mg/kg with a linear two-compartment disposition model with first-order elimination. A population pharmacokinetic analysis suggests that steady-state is obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in area under the curve, maximum concentration and trough concentration was 1.91, 1.46 and 2.75-fold, respectively.

**Absorption**

Atezolizumab is administered as an intravenous infusion. There have been no studies performed with other routes of administration.
Distribution

A population pharmacokinetic analysis indicates that central compartment volume of distribution is 3.28 L and volume at steady-state is 6.91 L in the typical patient.

Biotransformation

The metabolism of atezolizumab has not been directly studied. Antibodies are cleared principally by catabolism.

Elimination

A population pharmacokinetic analysis indicates that the clearance of atezolizumab is 0.200 L/day and the typical terminal elimination half-life is 27 days.

Special populations

Based on population PK and exposure-response analyses age (21-89 years), region, ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG performance status have no effect on atezolizumab pharmacokinetics. Body weight, gender, positive ADA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended.

Elderly

No dedicated studies of atezolizumab have been conducted in elderly patients. The effect of age on the pharmacokinetics of atezolizumab was assessed in a population pharmacokinetic analysis. Age was not identified as a significant covariate influencing atezolizumab pharmacokinetics. Body weight, gender, positive ADA status, albumin levels and tumour burden have a statistically significant, but not clinically relevant effect on atezolizumab pharmacokinetics. No dose adjustments are recommended.

Paediatric population

No studies have been conducted to investigate the pharmacokinetics of atezolizumab in children or adolescents.

Renal impairment

No dedicated studies of atezolizumab have been conducted in patients with renal impairment. In the population pharmacokinetic analysis, no clinically important differences in the clearance of atezolizumab were found in patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m²; n=208) or, moderate (eGFR 30 to 59 mL/min/1.73 m²; n=116) renal impairment compared to patients with normal (eGFR greater than or equal to 90 mL/min/1.73 m²; n=140) renal function. Only a few patients had severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²; n=8) (see section 4.2). The effect of severe renal impairment on the pharmacokinetics of atezolizumab is unknown.

Hepatic impairment

No dedicated studies of atezolizumab have been conducted in patients with hepatic impairment. In the population pharmacokinetic analysis, there were no clinically important differences in the clearance of atezolizumab between patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin > 1.0 × to 1.5 × ULN and any AST, n= 71) and normal hepatic function (bilirubin and AST ≤ ULN, n = 401). No data are available in patients with either moderate or severe hepatic impairment. Hepatic impairment was defined by the National Cancer Institute (NCI) criteria of hepatic dysfunction.
(see section 4.2). The effect of moderate or severe hepatic impairment (bilirubin > 1.5 × to 3 × ULN and any AST or bilirubin > 3 × ULN and any AST) on the pharmacokinetics of atezolizumab is unknown.

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies have not been performed to establish the carcinogenic potential of atezolizumab.

Mutagenicity

Mutagenicity studies have not been performed to establish the mutagenic potential of atezolizumab. However, monoclonal antibodies are not expected to alter DNA or chromosomes.

Fertility

No fertility studies have been conducted with atezolizumab; however assessment of the cynomolgus monkey male and female reproductive organs was included in the chronic toxicity study. Weekly administration of atezolizumab to female monkeys at an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose caused an irregular menstrual cycle pattern and a lack of newly formed corpora lutea in the ovaries which were reversible. There was no effect on the male reproductive organs.

Teratogenicity

No reproductive or teratogenicity studies in animals have been conducted with atezolizumab. Animal studies have demonstrated that inhibition of the PD-L1/PD-1 pathway can lead to immune-related rejection of the developing foetus resulting in foetal death. Administration of atezolizumab could cause foetal harm, including embryo-foetal lethality.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
Glacial acetic acid
Sucrose
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years.
Diluted solution

Chemical and physical in-use stability has been demonstrated for no more than 24 hours at 2 °C to 8 °C or 24 hours at ≤ 30 °C from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C).

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass-vial with a butyl rubber stopper containing 20 mL of solution.

Pack of one vial.

6.6 Special precautions for disposal and other handling

Tecentriq does not contain any antimicrobial preservative and should be prepared by a healthcare professional using aseptic technique.

Do not shake.

Instructions for dilution

Twenty mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a 250 mL PVC, polyethylene (PE) or polyolefin infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, one mL of solution should contain approximately 4.4 mg of Tecentriq (1,200 mg/270 mL). The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately (see section 6.3).

Parenteral medicinal products should be inspected visually for particulates and discoloration prior to administration. If particulates or discoloration are observed, the solution should not be used.

No incompatibilities have been observed between Tecentriq and intravenous bags with product-contacting surfaces of polyvinyl chloride (PVC), polyethylene (PE) or polyolefin (PO). In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

Do not co-administer other medicinal products through the same infusion line.

Disposal

The release of Tecentriq in the environment should be minimised. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1220/001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 September 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

F. Hoffmann-La Roche AG
Grenzacherstrasse 124
4070 Basel
SWITZERLAND

Name and address of the manufacturer responsible for batch release

Roche Pharma AG
Emil-Barell-Strasse 1
79639 Grenzach-Whylen
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

Prior to launch of Tecentriq in each Member State the marketing authorisation holder (MAH) must agree about the content and format of the educational programme, including communication media,
distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness and providing information concerning the signs and symptoms of certain important identified risks of atezolizumab, including immune-related pneumonitis, hepatitis, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, neuropathies, meningoencephalitis, pancreatitis, and infusion related reactions, and how to manage them.

The MAH shall ensure that in each Member State where Tecentriq is marketed, all healthcare professionals and patients/carers who are expected to prescribe and use Tecentriq have access to/are provided with the following educational package:
- Physician educational material
- Patient Alert Card

The physician educational material should contain:
- The Summary of Product Characteristics
- Guide for healthcare professionals
- The Guide for healthcare professionals shall contain the following key elements:
  - Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility as applicable) of the following safety concerns associated with the use of Tecentriq:
    - Immune-Related Hepatitis
    - Immune-Related Pneumonitis
    - Immune-Related Colitis
    - Immune-Related Pancreatitis
    - Immune-Related Endocrinopathies (Type 1 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
    - Immune-Related Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis)
    - Immune-Related Meningoencephalitis
    - Immune-Related Myocarditis
    - Immune-Related Nephritis
    - Infusion-Related Reactions
  - Description of the signs and symptoms of immune-related adverse reactions.
  - Details on how to minimise the safety concerns through appropriate monitoring and management.
  - Reminder to distribute the patient alert card to all patients receiving treatment with Tecentriq and to advise them to show it to any healthcare professional who may treat them.
  - Reminder to educate patients/caregivers about the symptoms of immune-related adverse reactions and of the need to report them immediately to the physician.

The patient alert card shall contain the following key messages:
- Brief introduction to atezolizumab (indication and purpose of this tool)
- Information that atezolizumab can cause serious side effects during or after treatment, that need to be treated right away
- Description of the main signs and symptoms of the following safety concerns and reminder of the importance of notifying their treating physician immediately if symptoms occur, persist or worsen:
  - Immune-Related Hepatitis
  - Immune-Related Pneumonitis
  - Immune-Related Colitis
  - Immune-Related Pancreatitis
  - Immune-Related Endocrinopathies (Type 1 Diabetes Mellitus, Hypothyroidism, Hyperthyroidism, Adrenal Insufficiency and Hypophysitis)
- Immune-Related Neuropathies (Guillain-Barre Syndrome, Myasthenic Syndrome / Myasthenia Gravis)
- Immune-Related Meningoencephalitis
- Immune-Related Myocarditis
- Immune-Related Nephritis
- Infusion-Related Reactions

- Warning message for patients on the importance of consulting their doctor immediately in case they develop any of the listed signs and symptoms and on the important not attempting to treat themselves.
- Reminder to carry the Patient Alert Card at all times and to show it to all healthcare professionals that may treat them.
- The card should also prompt to enter contact details of the physician and include a warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tecentriq.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of atezolizumab for the treatment of patients with locally advanced or metastatic urothelial cancer, the MAH should submit the final OS results of study IMvigor210.</td>
<td>Submission of study results: 30 June 2019</td>
</tr>
<tr>
<td>Post-authorisation efficacy study (PAES): In order to evaluate the efficacy of atezolizumab monotherapy versus atezolizumab plus carboplatin/gemcitabine versus placebo plus cisplatin/gemcitabine in patients with locally advanced or metastatic urothelial cancer who are platinum–ineligible and –eligible patients, the MAH should submit the final CSR of study IMvigor130.</td>
<td>Submission of study results: 31 July 2021</td>
</tr>
</tbody>
</table>
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>OUTER CARTON</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tecentriq 1,200 mg concentrate for solution for infusion atezolizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each 20 mL vial of concentrate contains 1,200 mg atezolizumab</td>
</tr>
<tr>
<td>After dilution, 1 mL of solution contains approximately 4.4 mg of atezolizumab</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients: L-histidine, glacial acetic acid, sucrose, polysorbate 20, water for injections</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentrate for solution for infusion</td>
</tr>
<tr>
<td>1,200 mg/20 mL</td>
</tr>
<tr>
<td>1 vial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td>For intravenous use after dilution.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not shake the vial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>
9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Roche Registration GmbH
Emil-Barell-Strasse 1
79639 Grenzach-Wyhlen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1220/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Tecentriq 1,200 mg concentrate for solution for infusion
atezolizumab
Intravenous use

2. METHOD OF ADMINISTRATION

For intravenous use after dilution.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1,200 mg/20 mL

6. OTHER
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

Tecentriq 1,200 mg concentrate for solution for infusion
atezolizumab

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tecentriq is and what it is used for
2. What you need to know before you are given Tecentriq
3. How Tecentriq is given
4. Possible side effects
5. How to store Tecentriq
6. Contents of the pack and other information

1. What Tecentriq is and what it is used for

What Tecentriq is

Tecentriq is an anti-cancer medicine that contains the active substance atezolizumab. It belongs to a group of medicines called monoclonal antibodies. A monoclonal antibody is a type of protein designed to recognise and attach to a specific target in the body.

What Tecentriq is used for

Tecentriq is used to treat adults with:
- a cancer that affects the bladder and the urinary system, called urothelial carcinoma. It is used when this cancer has:
  - spread to other parts of the body
  - come back after previous treatment
  - or, if you cannot receive anticancer medicine (a chemotherapy called cisplatin), and your doctor has tested your cancer and found high levels of a specific protein in your body called programmed death-ligand 1 (PD-L1).
- a cancer that affects the lungs, called non-small cell lung cancer. It is used when this cancer is advanced. This means the lung cancer has:
  - spread to other parts of the body
  - come back after previous treatment.

If you have not received anticancer medicines before for advanced lung cancer, Tecentriq will be given to you in combination with bevacizumab and anticancer medicines (chemotherapies called paclitaxel and carboplatin). It is important that you also read the package leaflet for these medicines.
How Tecentriq works

Tecentriq works by attaching to a specific protein in your body called programmed death-ligand 1 (PD-L1). This protein suppresses the body’s immune (defense) system, thereby protecting cancer cells from being attacked by the immune cells. By attaching to the protein, Tecentriq helps your immune system to fight your cancer.

2. What you need to know before you are given Tecentriq

You must not be given Tecentriq if:

- you are allergic to atezolizumab or any of the other ingredients of this medicine (listed in section 6).

If you are not sure, talk to your doctor or nurse before you are given Tecentriq.

Warnings and precautions

Talk to your doctor or nurse before you are given Tecentriq if you:

- have an auto-immune disease (a condition where the body attacks its own cells)
- have been told that your cancer has spread to your brain
- have any history of inflammation of your lungs (called pneumonitis)
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have had serious side effects because of other antibody therapies that help your immune system to fight cancer
- have been given medicines to stimulate your immune system
- have been given medicines to suppress your immune system
- have been given a live, attenuated vaccine

If any of the above applies to you (or you are not sure), talk to your doctor or nurse before you are given Tecentriq.

Tecentriq may cause some side effects that you must tell your doctor about straight away. They may happen weeks or months after your last dose. Tell your doctor straight away if you notice any of the symptoms below:

- inflammation of the lung (pneumonitis): symptoms may include new or worsening cough, shortness of breath, and chest pain
- inflammation of the liver (hepatitis): symptoms may include yellowing of skin or eyes, nausea, vomiting, bleeding or bruising, dark urine, and stomach pain
- inflammation of the intestines (colitis): symptoms may include diarrhoea (watery, loose or soft stools), blood in stools, and stomach pain
- inflammation of the thyroid, adrenal glands and the pituitary gland (hypothyroidism, hyperthyroidism, adrenal insufficiency or hypophysitis): symptoms may include tiredness, weight loss, weight gain, change in mood, hair loss, constipation, dizziness, headaches, increased thirst, increased urination and changes in vision.
- type 1 diabetes, including acid in the blood produced from diabetes (diabetic ketoacidosis): symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, and feeling tired
- inflammation of the brain (encephalitis) or inflammation of the membrane around the spinal cord and brain (meningitis): symptoms may include neck stiffness, headache, fever, chills, vomiting, eye sensitivity to light, confusion and sleepiness
• inflammation or problems of the nerves (neuropathy): symptoms may include muscle weakness and numbness, tingling in hands and feet
• inflammation of the pancreas (pancreatitis): symptoms may include abdominal pain, nausea and vomiting
• inflammation of the heart muscle (myocarditis): symptoms may include shortness of breath, decreased exercise tolerance, feeling tired, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
• inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
• severe reactions associated with infusion (events occurring during the infusion or within one day of the infusion): may include fever, chills, shortness of breath and flushing.

If you notice any of the symptoms above, tell your doctor straight away.

Do not try to treat yourself with other medicines. Your doctor may:
• Give you other medicines to prevent complications and reduce symptoms.
• Delay giving your next dose of Tecentriq.
• Stop your treatment with Tecentriq.

Tests and checks

Before your treatment, your doctor will check your general health. You will also have blood tests during your treatment.

Children and adolescents

This medicine should not be given to children or adolescents below 18 years of age. This is because the effects of Tecentriq in this age group are not known.

Other medicines and Tecentriq

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Pregnancy and contraception

• Tell your doctor if you are pregnant, think you might be pregnant or are planning to become pregnant.
• You will not be given Tecentriq if you are pregnant unless your doctor considers it necessary. This is because the effect of Tecentriq in pregnant women is not known - it is possible that it could harm your unborn baby.
• If you could become pregnant, you must use effective contraception;
  - while you are being treated with Tecentriq and
  - for 5 months after the last dose.
• If you become pregnant while you are being treated with Tecentriq tell your doctor.

Breast-feeding

It is not known if Tecentriq gets into breast milk. Ask your doctor if you should stop breast-feeding or if you should stop treatment with Tecentriq.

Driving and using machines

Tecentriq has minor influence on your ability to drive and use machines. If you feel tired, do not drive or use machines until you feel better.
3. **How Tecentriq is given**

You will be given Tecentriq by a doctor experienced in cancer treatment in a hospital or clinic.

**How much Tecentriq is given**

The recommended dose is 1,200 milligrams (mg) every three weeks.

**How Tecentriq is given**

Tecentriq is given as a drip into a vein (an intravenous infusion).

Your first infusion will be given over 60 minutes.
- Your doctor will monitor you carefully during the first infusion.
- If you do not have an infusion reaction during the first infusion, the next infusions will be given to you over a period of 30 minutes.

**How long treatment lasts**

Your doctor will keep giving you Tecentriq until you no longer benefit from it. However, it may be stopped if the side effects become too much of a problem.

**If you miss a dose of Tecentriq**

If you miss an appointment, make another one straight away. For the treatment to be fully effective, it is very important to keep having the infusions.

**If you stop receiving Tecentriq**

Do not stop treatment with Tecentriq unless you have discussed this with your doctor. This is because stopping treatment may stop the effect of the medicine.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Tell your doctor straight away** if you notice any of the side effects below or if they get worse. They may happen weeks or months after your last dose. Do not try to treat yourself with other medicines: The following side effects have been reported in clinical trials with Tecentriq used alone:

**Very common:** may affect more than 1 in 10 people
- fever
- nausea
- vomiting
- feeling very tired with no energy (fatigue)
- lack of energy
- itching of the skin
- diarrhoea
- joint pain
- rash
- loss of appetite
- shortness of breath
• urinary tract infection
• back pain
• cough

**Common:** may affect up to 1 in 10 people
• inflammation of the lungs (pneumonitis)
• low oxygen levels, which may cause shortness of breath as a consequence of inflamed lungs (hypoxia)
• stomach pain
• inflammation of the liver
• elevated liver enzymes (shown in tests), which may be a sign of an inflamed liver
• difficulty swallowing
• blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia)
• low blood pressure (hypotension)
• underactive thyroid gland (hypothyroidism)
• allergic reaction (infusion-related reaction or hypersensitivity)
• flu-like illness
• pain in the muscles and bones.
• chills
• inflammation of the intestines
• low platelet count, which may make you more likely to bruise or bleed
• blocked nose (nasal congestion)

**Uncommon:** may affect up to 1 in 100 people
• inflammation of the pancreas
• numbness or paralysis, which may be signs of Guillain-Barré syndrome
• inflammation of the membrane around the spinal cord and brain
• low levels of adrenal hormones
• overactive thyroid gland (hyperthyroidism)
• type 1 diabetes

**Rare:** may affect up to 1 in 1,000 people
• inflammation of the heart muscle
• myasthenia gravis, an illness that can cause muscle weakness
• inflammation of the pituitary gland situated at the base of the brain
• inflammation of the kidneys

The following side effects have been reported in clinical trials when Tecentriq is given in combination with anticancer medicines:

**Very common:** may affect more than 1 in 10 people
• low number of red blood cells, which can cause tiredness and shortness of breath
• low white blood cell count with and without fever, which can increase the risk of infection
• low platelet count, which may make you more likely to bruise or bleed (thrombocytopenia)
• constipation
• low levels of magnesium, which can cause weakness and muscle cramping, numbness and pain in the arms and legs
• nerve damage resulting in possible numbness, pain, and/or loss of motor function (peripheral neuropathy)
• underactive thyroid gland (hypothyroidism)
• loss of appetite
• shortness of breath
• diarrhoea
• nausea
• itching of the skin
• rash
• joint pain
• feeling very tired with no energy (fatigue)
• fever

Common: may affect up to 1 in 10 people
• blood tests showing low levels of potassium (hypokalaemia) or sodium (hyponatremia)
• inflammation of the mouth or lips

If you notice any of the side effects above or if they get worse, tell your doctor straight away.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tecentriq

Tecentriq will be stored by the healthcare professionals at the hospital or clinic. The storage details are as follows:

• Keep this medicine out of the sight and reach of children.
• Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.
• Store in a refrigerator (2 °C - 8 °C). Do not freeze.
• Keep the vial in the outer carton in order to protect from light.
• The diluted solution should not be kept more than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature.
• Do not use if this medicine is cloudy, discoloured or contains particles

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help to protect the environment.

6. Contents of the pack and other information

What Tecentriq contains

• The active substance is atezolizumab. Each mL contains 60 mg of atezolizumab. Each vial contains 1,200 mg of atezolizumab (in 20 mL).
• The other ingredients are L-histidine, glacial acetic acid, sucrose, polysorbate 20 and water for injections.

What Tecentriq looks like and contents of the pack

Tecentriq is a concentrate for solution for infusion. It is a clear, colourless to slightly yellowish liquid.

Tecentriq is available in a pack containing 1 glass vial.
# Marketing Authorisation Holder

Roche Registration GmbH  
Emil-Barell-Strasse 1  
79639 Grenzach-Wyhlen  
Germany

## Manufacturer

Roche Pharma AG  
Emil-Barell-Strasse 1  
D-79639  
Grenzach-Wyhlen  
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

<table>
<thead>
<tr>
<th>Country</th>
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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu
The following information is intended for healthcare professionals only:

Instructions for dilution

Twenty mL of Tecentriq concentrate should be withdrawn from the vial and diluted into a 250 mL PVC, polyethylene (PE) or polyolefin infusion bag containing sodium chloride 9 mg/mL (0.9%) solution for injection. After dilution, one mL of solution should contain approximately 4.4 mg of Tecentriq (1,200 mg/270 mL). The bag should be gently inverted to mix the solution in order to avoid foaming. Once the infusion is prepared it should be administered immediately.

Parenteral medicinal products should be inspected visually for particulates and discoloration prior to administration. If particulates or discoloration are observed, the solution should not be used.

No incompatibilities have been observed between Tecentriq and intravenous bags with product-contacting surfaces of polyvinyl chloride (PVC), polyethylene (PE) or polyolefin (PO). In addition, no incompatibilities have been observed with in-line filter membranes composed of polyethersulfone or polysulfone, and infusion sets and other infusion aids composed of PVC, PE, polybutadiene, or polyetherurethane. The use of in-line filter membranes is optional.

Diluted solution

Chemical and physical in-use stability has been demonstrated for no more than 24 hours at 2 °C to 8 °C or 24 hours at ≤ 30 °C from the time of preparation.

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C or 8 hours at ambient temperature (≤ 25 °C)

Method of administration

Tecentriq is for intravenous use. Tecentriq infusions must not be administered as an intravenous push or bolus.

The initial dose of Tecentriq must be administered over 60 minutes. If the first infusion is tolerated all subsequent infusions may be administered over 30 minutes.

Do not co-administer other medicinal products through the same infusion line.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.