Pembrolizumab for the treatment of patients with early-stage triple-negative breast cancer

A case-based discussion ensuring clinical benefit while managing possible toxicity

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For many years, anthracycline- and taxane-based neoadjuvant chemotherapy has been the cornerstone of the treatment for patients with early-stage, triple negative breast cancer (TNBC).[1] More recently, however, the publication of the phase III KEYNOTE-522 study has changed this standard of care by introducing peri-operative pembrolizumab in the treatment paradigm for these patients.[2] In this trial, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab led to a statistically significant and clinically meaningful improvement in pathological complete response (pCR) and event-free survival (EFS) compared to neoadjuvant placebo plus chemotherapy followed by adjuvant placebo in patients with early-stage TNBC.[2] During the 2023 annual meeting of the European Society of Medical Oncology (ESMO), long-term results of this trial demonstrated an absolute EFS benefit of 9% for patients receiving pembrolizumab *vs.* placebo in this trial (5-year EFS rate: 81.3% *vs.* 72.3%; HR[95%CI]: 0.63[0.49-0.81]) (*Figure 1*).[3] The EFS benefit obtained with pembrolizumab was seen irrespective of disease stage, or nodal status and was observed regardless of the pCR status after neoadjuvant therapy.[3,4]

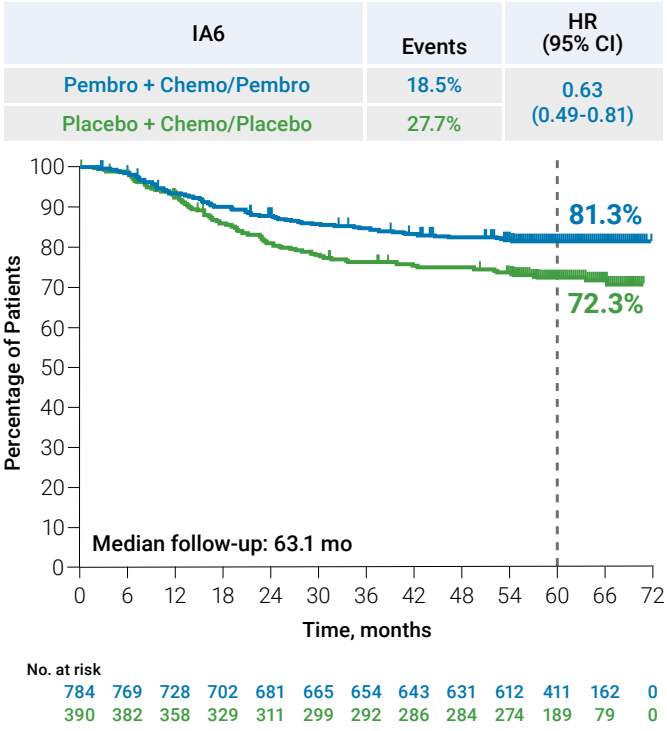

Figure 1. Event-free survival in the phase III KEYNOTE-522 study.[3]

"With close patient monitoring and sufficient vigilance for imAEs, most of these adverse events can be detected and managed in an early stage."

While KEYNOTE-522 provides convincing evidence on the efficacy of perioperative pembrolizumab in patients with early-stage TNBC, this treatment does come with a risk for the development of immune-mediated adverse events (imAEs), which can markedly complicate the management of your patient. This risk for imAEs requires careful consideration, especially in a curative setting, where the benefit-to-risk ratio is different than in patients with metastatic disease. However, with close patient monitoring and sufficient vigilance for imAEs, most of these adverse events can be detected and managed in an early stage. This avoids escalation and potential long-term burden from imAEs and allows patients with early-stage TNBC to reap the full benefit of perioperative pembrolizumab. To illustrate this, *Prof. Dr. Vibeke Kruse (VITAZ, Sint-Niklaas)* and *Dr. Aglaja De Pauw (University Hospital Ghent)* shared two real-life clinical cases.

CASE 1

A first patient case describes a 47-year-old woman presenting with a tumor in the left breast in October 2022. A diagnostic work-up revealed a TNBC with a largest diameter of 60 mm without nodal involvement (clinical stage: cT3N0).

Further imaging with a bone scintigraphy and a CT scan of the thorax and abdomen did not reveal any adenopathies or metastases. A cardiac evaluation of the patient showed a left-ventricular ejection fraction (LVEF) of 67%. During a multidisciplinary tumour board (MDT), it was decided to initiate neoadjuvant chemotherapy (paclitaxel and carboplatin followed by EC) in combination with pembrolizumab (KEYNOTE-522 regimen). Neoadjuvant therapy with paclitaxel-carboplatin (12x 1qw) and pembrolizumab (4x q3w) was started in November 2022. The treatment was well-tolerated, except for the development of a grade 1 polyneuropathy and a short hospitalization due to neutropenic fever following a urinary tract infection (controlled with antibiotics). After the 12th paclitaxel-carboplatin cycle, the chemotherapy backbone was changed to EC (4x q2w) with 2 additional cycles of pembrolizumab. During this treatment phase, an immunotherapy-related thyroiditis developed, evolving to hypothyroidism. An excellent response in the breast was seen and the MDT decided to proceed to surgery (tumorectomy left breast + sentinel lymph node dissection [SLND]). An analysis of the surgical samples showed that the patient was in pCR (no residual tumour tissue, no ductal carcinoma in situ [DCIS]) and did not have node involvement (TNM stage: ypT0ypN0sn). Subsequently, the patient received adjuvant radiotherapy followed by adjuvant pembrolizumab. In October 2023 (after 7 months of adjuvant pembrolizumab), the patient developed an immunotherapy-related gastritis (controlled with corticosteroids and a proton pump inhibitor) and an ileoscopy revealed an asymptomatic, microscopic colitis. As the patient had already completed the majority of the scheduled adjuvant therapy, it was decided to stop pembrolizumab at that time.

CASE 2

The second case consists of a 68-year-old woman who was diagnosed with a tumor in the left breast in June 2022. A biopsy of the tumor learned that it concerned a TNBC with a Ki-67-expression of 40%. Imaging with MRI revealed a 6.7 cm lesion, with eight level 1 and two level 2 axillary adenopathies that tested positive for tumour on cytology (stage cT3 N3a). There was no evidence for bone involvement on scintigraphy, while a CT scan of the thorax and abdomen showed several swollen lymph nodes in the axilla (no suggestions for metastasis). Finally, a cardiac evaluation showed a LVEF of 69%. After a MDT discussion, neoadjuvant chemotherapy (paclitaxel-carboplatin followed by EC) in combination with pembrolizumab as per KEYNOTE-522 was started in July 2022. The neoadjuvant treatment was well-tolerated except for some fatigue (grade 1) and grade 1 hematological toxicity. At the end of the neoadjuvant therapy, imaging showed no residual tumor in the breast and no axillary adenopathies. In December 2022, a left tumorectomy was performed in combination with an axillary-lymph node dissection (ALND). A pathological evaluation of the resected breast sample did not show any residual carcinoma but indicated extensive lymphovascular space invasion (LVSI) (as such, the patient did not have a pCR). An evaluation of 10 resected axillary lymph nodes showed one node with metastasis and fibrosis, one node with LVSI in the capsule and fibrosis, and 3 additional nodes with signs of fibrosis. Based on these findings, the pathological TNM stage was determined as ypT0 N1a. Subsequently, the patient was treated with adjuvant radiotherapy after which adjuvant pembrolizumab was started (in combination with zoledronic acid). Unfortunately, 1 month after the start of pembrolizumab (January 2023), the patient developed an immune-related colitis warranting a discontinuation of pembrolizumab and the initiation of corticosteroids. The colitis improved, but while tapering off the corticosteroids, an immunotherapy-related nephritis occurred in April 2023 (i.e., 3 months after stopping pembrolizumab). This second imAE was again treated with corticosteroids, but this time in combination with mycophenolate. In October 2023, 10 months after the surgery, a breast recurrence was observed, and the patient underwent a left mastectomy. An analysis of this resected sample revealed multiple foci, with extensive LVSI and a Ki-67 index of 80% (rpT3 rpNx).

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CASE 1 CASE 2

DISCUSSION

As these two clinical cases illustrate, the chance to improve patient outcomes with perioperative pembrolizumab in early stage TNBC can come at the cost of imAEs. In KEYNOTE-522, the incidence of imAEs was reported at 33.5% in the pembrolizumab arm, with about one out of eight patients (12.9%) experiencing a grade ≥3 imAEs (*vs.* 11.3% and 1.0% in the control arm).[2] As such, the rates of imAEs reported in this study are higher than what was seen with pembrolizumab-chemotherapy in metastatic TNBC patients (all grade: 26.5%, grade ≥3: 5.3%).[5] The most common imAEs observed in the pembrolizumab arm of KEYNOTE-522 consist of thyroid impairment (15.1% hypothyroidism & 5.2% hyperthyroidism), skin toxicities (5.7%), adrenal insufficiency (2.6%), pneumonitis (2.2%) and thyroiditis (2%).

An expert opinion

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By now we have been using the KEYNOTE-522 regimen for about three years. By combining the neoadjuvant chemotherapy with pembrolizumab we indeed see a higher incidence of (immune-related) adverse events (AEs), which sometimes requires us to discontinue the treatment and move ahead with the surgery. Also compared to the pembrolizumab-based regimen that is used in the metastatic setting, the KEYNOTE-522 regimen seems to be related with a bit more toxicity in clinical practice. The main reason for this is likely the more intensive chemotherapy backbone that is being used in the neoadjuvant setting. Despite this higher risk for AEs, however, there is a big desire among patients to receive immunotherapy which raises the level of 'toxicity acceptance' somewhat. In this respect, it is important to underscore that the treatment goes well in the majority of patients and that most imAEs are easy to manage. To facilitate an early detection of these imAEs, patient education and close monitoring is key, with a short line of contact between patients and their onconurse and/or treating physician. While we try to educate our patients on the early signsof treatment-related AEs, some of these toxicities are not easy to recognize.

This is particularly the case for hematological AEs and endocrinological imAEs. As such, not only patients need to be vigilant for the emergence of AEs, also physicians need to embrace a diligent patient monitoring. In my clinical practice we do a standard blood test at a weekly basis during the paclitaxel-carboplatin phase of the treatment, with a more elaborate evaluation (glucose, troponin, thyroid function, etc.) when pembrolizumab is given (i.e., every 3 weeks).

In the KEYNOTE-522 study, about one out of three patients experienced an imAE, reaching grade ≥3 in severity in about 13% of cases.[2,3] As a real-life patient population is less selected than a typical randomized controlled trial population, it should not come as a surprise that the incidence of imAEs is somewhat higher in clinical practice. As indicated in the article, early recognition of these imAEs is key to avoid serious complications. For me, patient education is the most important factor here. This education has to be more than a simple explanation of the possible side effects, but should include clear examples, with an emphasis that imAEs can occur in every organ and underscoring the need for a low threshold to get in touch with the treating physician or other healthcare providers, such as an onconurse or nurses in the day clinic. With respect to the latter, it is important that also the staff in the day clinic is well aware of the potential imAEs that can occur in patients receiving the KEYNOTE-522 regimen. While I try to maximize the use of pembrolizumab in the neoadjuvant phase of the treatment, I tend to have a lower threshold to discontinue pembrolizumab due to imAEs in the adjuvant phase, as there are no randomized data proving its effectiveness. This is especially the case in patients who obtained a pCR after neoadjuvant therapy.

In conclusion, with good patient education, a low threshold to reach out to healthcare providers and close patient monitoring by the treating physician, the KEYNOTE-522 regimen is a feasible treatment option for the majority of patients with early TNBC. Especially in the adjuvant phase of the treatment, the toxicity risk needs to be balanced against the expected clinical benefit for the individual patient.

While the majority of patients will not experience high-grade imAEs, the occurrence of such adverse events in a potentially curative setting has to be handled with utmost care. The latter is of particular importance in case of permanent or even life-threatening toxicities. While it is important to underscore that lethal imAEs are very rare, they can occur in patients receiving pembrolizumab.

For example, one patient in the pembrolizumab arm of KEYNOTE-522 died of an immune-mediated encephalitis while a second patient died following an immune-related pulmonary embolism. With more experience and a closer patient monitoring, these events could potentially have been prevented. In addition, also the chronicity of certain imAE (e.g., immune-related diabetes mellitus, certain endocrinopathies), requires careful attention and emphasizes the need for patient education facilitating an early recognition of these events. In this respect, a recent retrospective study in melanoma patients who received adjuvant anti-PD-1 therapy indicated that 43.2% of patients developed chronic imAEs (i.e., an imAEs persisting beyond 12 weeks after treatment discontinuation). While it is important to mention that most of these chronic imAEs were low grade (grade 1/2: 96.4%), this can still have an important impact on the quality of life (QoL) of patients.[6]

Importantly, while imAEs can be an important burden for patients, they may also indicate that the immunotherapy is working. In fact, several studies have indicated that the development of imAEs is associated with a clinical benefit.[7] Specifically for pembrolizumab, recent real-world data in early TNBC patients demonstrate that the emergence of imAEs is significantly correlated with the chance for a pCR after neoadjuvant therapy.[8]For most grade 1 imAEs, immune checkpoint inhibitor (ICI) therapy can generally be continued, with close monitoring of the patient. Exceptions to this consist of cardiac or neurological imAEs and endocrinopathies, which require special attention from the moment they are suspected. In case of a grade 2 imAEs, ICI therapy is generally interrupted, and corticosteroids (0.5-1mg/kg/day) are initiated. In patients developing a grade 3 imAEs, the ICI therapy needs to be stopped and high-dose corticosteroids (1-2 mg/kg/day) are required.

If the toxicity does not improve within the first 48-72 hours after the start of corticosteroids, an alternative immunosuppressant can be considered. When the toxicity resolves, or reverts to grade 1, ICI rechallenge can be considered. Especially after a grade 3 imAEs, the decision to resume ICI therapy needs to be based on a multidisciplinary discussion and requires close monitoring of the patient.[9] Reassuringly, data in the metastatic setting indicate that the use of corticosteroids to treat imAEs does not have a detrimental effect on the efficacy of the ICI.[10] In contrast, studies do suggest that the use of a second immunosuppressant has a negative impact on OS and should therefore be discussed within a multidisciplinary team.[11]

"To facilitate an early identification, of imAEs physicians should remain vigilant for signs of imAEs, during the pembrolizumab treatment and for an extended period of time thereafter."

CONCLUSIONS

KEYNOTE-522 provides convincing evidence on the efficacy of perioperative pembrolizumab in all patients with stage II or III TNBC. In clinical practice, careful patient monitoring is needed to early detect imAEs, especially in patients who present with concomitant diseases or comorbidities. To facilitate this early identification, physicians should remain vigilant for signs of imAEs, during the pembrolizumab treatment and for an extended period of time thereafter. In this respect, also a dedicated patient education on the recognition of imAEs is essential. In recent years, clear guidelines have been developed to manage imAEs and also the ever-increasing experience with imAEs makes that multidisciplinary tumor boards are generally able to adequately treat them.[12,13] When diagnosed early, (neo)adjuvant pembrolizumab can usually be continued, or re-initiated once the imAE has resolved, maximizing the potential benefit that pembrolizumab can offer to patients in this setting.

References:

1. *Garufi G, et al. Cancers (Basel) 2022;14(17):4064.*
2. *Schmid P, et al. N Engl J Med 2020;382(9):810-21.*
3. *Schmid P, et al. Presented at ESMO 2023; Abstract LBA18.*
4. *Schmid P, et al. Presented at SABCS 2023; Abstract LB01-01*
5. *Cortes J, et al. N Engl J Med 2022;387:217026.*
6. *Patrinely JR, et al. JAMA Oncol 2021;7(5):744-8.*
7. *Hsiechen D, et al. Oncoimmunology 2022;11(1):2017162.*
8. *Marhold M, et al. Oncoimmunology 2023;12(1):2275846.*
9. *Haanen J, et al. Ann Oncol 2022;33(12):1217-38.*
10. *Goodman R, et al. Clin Cancer Res 2023;29(14):2580-7.*
11. *Van Not O, et al. JAMA Oncol 2022;8(12):1794-801.*
12. *Haanen J, et al. Ann Oncol 2017;28(4):IV119-42.*
13. *Brahmer J, et al. J Clin Oncol 2018;36(17):1714-68.*

Abbreviations: *TNBC: triple-negative breast cancer; pCR: pathological complete response; EFS: Event-Free survival; vs: versus; HR: Hazard Ratio; CI: Confidence Interval; imAE(s): Immune-mediated Adverse Event(s); Prof.: Professor; Dr.: Doctor; mm: millimeter; CT scan: Computed Tomography scan; LVEF: Left-ventricular ejection fraction; MDT: Multidisciplinary tumour board; EC: Epirubicin Cyclophosphamide; q1w: every week; q3w: every 3 weeks; q2w: every 2 weeks; SLND: Sentinel lymph node dissection; DCIS: Ductal carcinoma in situ; ki-67: antigen Kiel 67; MRI: Magnetic resonance imaging; cm: centimeter; ALND: Axillary-lymph node dissection; LVSI: Lymphovascular space invasion; e.g.: for example; QoL: Quality of Life; ICI: Immune checkpoint inhibitor; OS: Overall survival; MD: Doctor of Medicine; PhD: Doctor of Philosophy in Medicine; i.e.: in other words.*

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1. NAME OF THE MEDICINAL PRODUCT KEYTRUDA 25 mg/ml concentrate for solution for infusion. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** One vial of 4 ml of concentrate contains 100 mg of pembrolizumab. Each ml of concentrate contains 25 mg of pembrolizumab. Pembrolizumab is a humanised monoclonal anti-programmed cell death1 (PD1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) 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 to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** *Melanoma* KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma. KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection (see section 5.1). *Nonsmall cell lung carcinoma (NSCLC) KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable nonsmall cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1).* KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (for selection criteria, see section 5.1). KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations. KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous nonsmall cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations. KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous nonsmall cell lung carcinoma in adults. KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic nonsmall cell lung carcinoma in adults whose tumours express PD-L1 with a ≥1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. *Classical Hodgkin lymphoma (cHL)* KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. *Urothelial carcinoma* KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1). KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see section 5.1). *Head and neck squamous cell carcinoma (HNSCC)* KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1). KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy (see section 5.1). *Renal cell carcinoma (RCC)* KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1). KEYTRUDA, in combination with lenvatinib, is indicated for the first line treatment of advanced renal cell carcinoma in adults (see section 5.1). KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, see section 5.1). *Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers: Colorectal cancer (CRC)* KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings: firstline treatment of metastatic colorectal cancer; treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidinebased combination therapy. *Non-colorectal cancers* KEYTRUDA as monotherapy is indicated for the treatment of the following MSIH or dMMR tumours in adults with: advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinumcontaining therapy in any setting and who are not candidates for curative surgery or radiation; unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. *Oesophageal carcinoma* KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus in adults whose tumours express PDL1 with a CPS ≥ 10 (see section 5.1). *Triplenegative breast cancer (TNBC)* KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or earlystage triplenegative breast cancer at high risk of recurrence (see section 5.1). KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triplenegative breast cancer in adults whose tumours express PDL1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease (see section 5.1). *Endometrial carcinoma (EC)* KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation. *Cervical cancer* KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PDL1 with a CPS ≥ 1. *Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma* KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1. KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PDL1 with a CPS ≥ 1. *Biliary tract carcinoma (BTC)* KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults**. 4.2 Posology and method of administration** Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer. PD-L1 testing If specified in the indication, patient selection for treatment with KEYTRUDA based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, 4.8 and 5.1). MSI/MMR testing If specified in the indication, patient selection for treatment with KEYTRUDA based on MSIH/dMMR tumour status should be confirmed by a validated test (see sections 4.1 and 5.1). Posology The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 3 years and older with cHL or patients aged 12 years and older with melanoma is 2 mg/kg bodyweight (bw) (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes. For use in combination, see the Summary of Product Characteristics (SmPC) for the concomitant therapies. Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication). Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. For the adjuvant treatment of melanoma, NSCLC, or RCC, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year. For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 4 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 13 doses of 200 mg every 3 weeks or 7 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment. For the neoadjuvant and adjuvant treatment of TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment. ***Dose delay or discontinuation (see also section 4.4)*** *No dose reductions of KEYTRUDA are recommended. KEYTRUDA should be withheld or discontinued to manage adverse reactions as described in Table 1. Table 1: Recommended treatment modifications for KEYTRUDA* ***Immune- mediated adverse reactions/Severity (Treatment modification)*** Pneumonitis: Grade 2 (Withhold until adverse reactions recover to Grades 0-1*), Grades 3 or 4, or recurrent Grade 2 (Permanently discontinue); Colitis: Grades 2 or 3 (Withhold until adverse reactions recover to Grades 0-1*), Grade 4 or recurrent Grade 3 (Permanently discontinue); Nephritis: Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN) (Withhold until adverse reactions recover to Grades 0-1*), Grade ≥ 3 with creatinine > 3 times ULN (Permanently discontinue); Endocrinopathies: Grade 2 adrenal insufficiency and hypophysitis (Withhold treatment until controlled by hormone replacement), Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis, Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis, Hyperthyroidism Grade ≥ 3 (Withhold until adverse reactions recover to Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.), Hypothyroidism (Hypothyroidism may be managed with replacement therapy without treatment interruption.); Hepatitis: NOTE: for RCC patients treated with pembrolizumab in combination with axitinib with liver enzyme elevations, see dosing guidelines following this table. Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN (Withhold until adverse reactions recover to Grades 0-1*), Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN (Permanently discontinue), In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week (Permanently discontinue); Skin reactions: Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (Withhold until adverse reactions recover to Grades 0-1*), Grade 4 or confirmed SJS or TEN (Permanently discontinue); Other immune-mediated adverse reactions: Based on severity and type of reaction (Grade 2 or Grade 3) (Withhold until adverse reactions recover to Grades 0-1*), Grades 3 or 4 myocarditis, Grades 3 or 4 encephalitis, Grades 3 or 4 Guillain-Barré syndrome (Permanently discontinue), Grade 4 or recurrent Grade 3 (Permanently discontinue). ***Infusion-related reactions:*** Grades 3 or 4 (Permanently discontinue). Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v.4). * If treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, or if corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks, KEYTRUDA should be permanently discontinued. The safety of re-initiating pembrolizumab therapy in patients previously experiencing immune-mediated myocarditis is not known. KEYTRUDA, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated adverse reactions, unless otherwise specified in Table 1. For Grade 4 haematological toxicity, only in patients with cHL, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1. ***KEYTRUDA in combination with axitinib in RCC*** For RCC patients treated with KEYTRUDA in combination with axitinib, see the SmPC regarding dosing of axitinib. When used in combination with pembrolizumab, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer (see section 5.1). *For liver enzyme elevations, in patients with RCC being treated with KEYTRUDA in combination with axitinib:* • If ALT or AST ≥ 3 times ULN but < 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered. If rechallenging with axitinib, dose reduction as per the axitinib SmPC may be considered. • If ALT or AST ≥ 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered. ***KEYTRUDA in combination with lenvatinib*** When used in combination with lenvatinib, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued in accordance with the instructions in the lenvatinib SmPC for combination with pembrolizumab. No dose reductions are recommended for KEYTRUDA. Patients treated with KEYTRUDA must be given the patient card and be informed about the risks of KEYTRUDA (see also package leaflet). ***Special populations Elderly*** No dose adjustment is necessary in patients ≥ 65 years (see sections 4.4 and 5.1). ***Renal impairment*** No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment (see sections 4.4 and 5.2). ***Hepatic impairment*** No dose adjustment is needed for patients with mild or moderate hepatic impairment. KEYTRUDA has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2). ***Paediatric population*** The safety and efficacy of KEYTRUDA in children below 18 years of age have not been established except in paediatric patients with melanoma or cHL. Currently available data are described in sections 4.8, 5.1 and 5.2. Method of administration KEYTRUDA is for intravenous use. It must be administered by infusion over 30 minutes. KEYTRUDA must not be administered as an intravenous push or bolus injection. When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first. For instructions on dilution of the medicinal product before administration, see section 6.6. **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.8 Undesirable effects** ***Summary of the safety profile*** Pembrolizumab is most commonly associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below). The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. *Pembrolizumab in monotherapy (see section 4.2)* The safety of pembrolizumab as monotherapy has been evaluated in 7,631 patients across tumour types and across four doses (2 mg/kg bw every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bw every 2 or 3 weeks) in clinical studies. In this patient population, the median observation time was 8.5 months (range: 1 day to 39 months) and the most frequent adverse reactions with pembrolizumab were fatigue (31%), diarrhoea (22%), and nausea (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-mediated adverse reactions and severe infusion-related reactions (see section 4.4). The incidences of immunemediated adverse reactions were 37% all Grades and 9% for Grades 35 for pembrolizumab monotherapy in the adjuvant setting and 25% all Grades and 6% for Grades 35 in the metastatic setting. No new immunemediated adverse reactions were identified in the adjuvant setting. *Pembrolizumab in combination with chemotherapy (see section 4.2)* When pembrolizumab is administered in combination, refer to the SmPC for the respective combination therapy components prior to initiation of treatment. The safety of pembrolizumab in combination with chemotherapy has been evaluated in 5 183 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw pembrolizumab every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (52%), nausea (52%), fatigue (35%), diarrhoea (33%), constipation (32%), vomiting (28%), decreased appetite (28%), neutrophil count decreased (27%) and neutropenia (25%). Incidences of Grades 35 adverse reactions in patients with NSCLC were 69% for pembrolizumab combination therapy and 61% for chemotherapy alone, in patients with HNSCC were 85% for pembrolizumab combination therapy and 84% for chemotherapy plus cetuximab, in patients with oesophageal carcinoma were 86% for pembrolizumab combination therapy and 83% for chemotherapy alone, in patients with TNBC were 80% for pembrolizumab combination therapy and 77% for chemotherapy alone, in patients with cervical cancer were 82% for pembrolizumab combination and 75% for chemotherapy, with or without bevacizumab, in patients with gastric cancer were 74% for pembrolizumab combination therapy (chemotherapy with or without trastuzumab) and 68% for chemotherapy with or without trastuzumab, and in patients with biliary tract carcinoma were 85% for pembrolizumab combination therapy and 84% for chemotherapy alone. *Pembrolizumab in combination with tyrosine kinase inhibitor (TKI) (see section 4.2)* When pembrolizumab is administered in combination with axitinib or lenvatinib, refer to the SmPC for axitinib or lenvatinib prior to initiation of treatment. For additional lenvatinib safety information related to advanced RCC see the SmPC for Kisplyx and for advanced EC see the SmPC for Lenvima. For additional axitinib safety information for elevated liver enzymes see also section 4.4. The safety of pembrolizumab in combination with axitinib or lenvatinib in advanced RCC, and in combination with lenvatinib in advanced EC has been evaluated in a total of 1,456 patients with advanced RCC or advanced EC receiving 200 mg pembrolizumab every 3 weeks with either axitinib 5 mg twice daily or lenvatinib 20 mg once daily in clinical studies, as appropriate. In these patient populations, the most frequent adverse reactions were diarrhoea (58%), hypertension (54%), hypothyroidism (46%), fatigue (41%), decreased appetite (40%), nausea (40%), arthralgia (30%), vomiting (28%), weight decreased (28%), dysphonia (28%), abdominal pain (28%), proteinuria (27%), palmar plantar erythrodysaesthesia syndrome (26%), rash (26%), stomatitis (25%), constipation (25%), musculoskeletal pain (23%), headache (23%) and cough (21%). Grades 3 5 adverse reactions in patients with RCC were 80% for pembrolizumab in combination with either axitinib or lenvatinib and 71% for sunitinib alone. In patients with EC, Grades 3-5 adverse reactions were 89% for pembrolizumab in combination with lenvatinib and 73% for chemotherapy alone. ***Tabulated summary of adverse reactions*** Adverse reactions observed in clinical studies of pembrolizumab as monotherapy or in combination with chemotherapy or other anti-tumour medicines or reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: 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); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Adverse reactions known to occur with pembrolizumab or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy. For additional safety information when pembrolizumab is administered in combination, refer to the SmPC for the respective combination therapy components. *Table 2: Adverse reactions in patients treated with pembrolizumab†:* Infections and infestations *Monotherapy:* Common: pneumonia, In *combination with chemotherapy:* Common: pneumonia, *In combination with axitinib or lenvatinib:* Very common: urinary tract infection; common: pneumonia. Blood and lymphatic system disorders *Monotherapy:* Very Common: anaemia; Common: thrombocytopenia, neutropenia, lymphopenia; Uncommon: leukopenia, immune thrombocytopenia, eosinophilia; Rare: haemophagocytic lymphohistiocytosis, haemolytic anaemia, pure red cell aplasia, In *combination with chemotherapy*: Very Common: anaemia, neutropenia, thrombocytopenia; Common: febrile neutropenia, leukopenia, lymphopenia; Uncommon: eosinophilia; Rare: haemolytic anaemia, immune thrombocytopenia, in *combination with axitinib or lenvatinib:* Very common: anaemia, Common: neutropenia, thrombocytopenia, lymphopenia, leukopenia; Uncommon: eosinophilia. Immune system disorders *Monotherapy:* Common: infusion-related reaction*; Uncommon: sarcoidosis; Not known: solid organ transplant rejection, *In combination with chemotherapy:* Common: infusion-related reaction*; Rare: sarcoidosis, *In combination with axitinib or lenvatinib:* Common: infusion-related reaction*. Endocrine disorders *Monotherapy:* Very Common: hypothyroidism*; Common: hyperthyroidism; Uncommon: adrenal insufficiency*, hypophysitis*, thyroiditis*; Rare: hypoparathyroidism, *In combination with chemotherapy:* Very Common: hypothyroidism*, Common:, adrenal insufficiency*, thyroiditis*, hyperthyroidism* Uncommon: hypophysitis*; Rare: hypoparathyroidism, *In combination with axitinib or lenvatinib:* Very common: hypothyroidism; Common: adrenal insufficiency*,

hyperthyroidism, thyroiditis*; Uncommon: hypophysitis*; Rare: hypoparathyroidism, Metabolism and nutrition disorders *Monotherapy:* Very Common: decreased appetite; Common: hyponatraemia, hypokalaemia, hypocalcaemia; Uncommon: type 1 diabetes mellitus*, *In combination with chemotherapy:* Very common: hypokalaemia, decreased appetite; Common: hyponatraemia, hypocalcaemia; Uncommon: type 1 diabetes mellitus*, *In combination with axitinib or lenvatinib* Very common: decreased appetite; Common: hyponatraemia, hypokalaemia, hypocalcaemia; Uncommon: type 1 diabetes mellitus*. Psychiatric disorders *Monotherapy:* Common: insomnia, *in combination with chemotherapy:* Very Common: insomnia, *in combination with axitinib or lenvatinib:* Common: insomnia. Nervous system disorders *Monotherapy:* Very Common: headache; Common: dizziness, neuropathy peripheral, lethargy, dysgeusia; Uncommon: myasthenic syndrome*, epilepsy; Rare: Guillain-Barré syndrome*, encephalitis*, myelitis*, optic neuritis, meningitis (aseptic) *, *in combination with chemotherapy:* Very common: neuropathy peripheral, headache; Common: dizziness, dysgeusia, lethargy; Uncommon: encephalitis*, epilepsy; Rare: myasthenic syndrome, Guillain-Barré Syndrome*, optic neuritis, *in combination with axitinib or lenvatinib:* Very common: headache; Common: dizziness, neuropathy peripheral, lethargy, dysgeusia; Uncommon: myasthenic syndrome*, encephalitis*; Rare: optic neuritis. Eye disorders *Monotherapy:* Common: dry eye; Uncommon: uveitis*; Rare: Vogt-Koyanagi-Harada syndrome, *In combination with chemotherapy:* Common: dry eye; Rare: uveitis*, *In combination with axitinib or lenvatinib:* Common: dry eye; Uncommon: uveitis*; Rare: Vogt-Koyanagi Harada-syndrome. Cardiac disorders *Monotherapy:* Common: cardiac arrhythmia‡ (including atrial fibrillation); Uncommon: myocarditis, pericardial effusion, pericarditis, *In combination with chemotherapy:* Common: cardiac arrhythmia‡ (including atrial fibrillation); Uncommon: myocarditis*, pericardial effusion, pericarditis, *In combination with axitinib or lenvatinib:* Common: cardiac arrhythmia‡ (including atrial fibrillation); Uncommon: myocarditis; pericardial effusion. Vascular disorders *Monotherapy:* Common: hypertension; Rare: vasculitis*, *In combination with chemotherapy:* Common: hypertension; Uncommon: vasculitis*, *In combination with axitinib or lenvatinib:* Very common: hypertension; Uncommon: vasculitis*. Respiratory, thoracic and mediastinal disorders *Monotherapy:* Very Common: dyspnoea, cough; Common: pneumonitis*, *In combination with chemotherapy:* Very common: dyspnoea, cough; Common: pneumonitis*, *In combination with axitinib or lenvatinib:* Very common: dyspnoea, cough; Common: pneumonitis*. Gastrointestinal disorders *Monotherapy:* Very common: diarrhoea, abdominal pain*, nausea, vomiting, constipation; Common: colitis*, dry mouth; Uncommon: pancreatitis*, gastritis*, gastrointestinal ulceration*; Rare: small intestinal perforation, *In combination with chemotherapy:* Very common: diarrhoea, vomiting, nausea, abdominal pain*, constipation; Common: colitis*, gastritis*, dry mouth; Uncommon: pancreatitis*, gastrointestinal ulceration*; Rare: small intestinal perforation; *In combination with axitinib or lenvatinib:* Very Common: diarrhoea, abdominal pain*, nausea, vomiting, constipation; Common: colitis*, pancreatitis*, gastritis*, dry mouth; Uncommon: gastrointestinal ulceration*; Rare: small intestinal perforation. Hepatobiliary disorders *Monotherapy:* Common: hepatitis*; Rare: cholangitis sclerosing, *In combination with chemotherapy:* Common: hepatitis*, Rare: cholangitis sclerosing*, *In combination with axitinib or lenvatinib:* Common: hepatitis*. Skin and subcutaneous tissue disorders *Monotherapy:* Very common: pruritus*, rash*; Common: severe skin reactions*, erythema, dermatitis, dry skin, vitiligo*, eczema, alopecia, dermatitis acneiform; Uncommon: psoriasis, lichenoid keratosis*, papule, hair colour changes; Rare: Stevens-Johnson syndrome, erythema nodosum, toxic epidermal necrolysis, *In combination with chemotherapy:* Very common: alopecia, pruritus*, rash*; Common: severe skin reactions*, erythema, dermatitis, dry skin, dermatitis acneiform, eczema; Uncommon: psoriasis, vitiligo*, papule; Rare: StevensJohnson syndrome, lichenoid keratosis*, erythema nodosum, hair colour changes, *In combination with axitinib or lenvatinib:* Very common: rash*, pruritus*; Common: severe skin reactions*, dermatitis, dry skin, erythema, dermatitis acneiform, alopecia; Uncommon: eczema, lichenoid keratosis*, psoriasis, vitiligo*, papule, hair colour changes; Rare: toxic epidermal necrolysis, Stevens Johnson syndrome. Musculoskeletal and connective tissue disorders *Monotherapy:* Very Common: musculoskeletal pain*, arthralgia; Common: myositis*, pain in extremity, arthritis* Uncommon: tenosynovitis*; Rare: Sjogren's syndrome, *In combination with chemotherapy:* Very Common: musculoskeletal pain*, arthralgia ; Common: myositis*, pain in extremity, arthritis*; Uncommon: tenosynovitis*; Rare: Sjogren's syndrome, *In combination with axitinib or lenvatinib:* Very common: arthralgia, musculoskeletal pain*, myositis*, pain in extremity; Common: arthritis*; Uncommon: tenosynovitis*; Rare: Sjogren's syndrome. Renal and urinary disorders *Monotherapy:* Uncommon: nephritis*; Rare: cystitis noninfective, *in combination with chemotherapy:* Common: acute kidney injury; Uncommon: nephritis*, cystitis noninfective, *in combination with axitinib or lenvatinib*: Common: nephritis*; Rare: cystitis noninfective. General disorders and administration site conditions *Monotherapy:* Very common: fatigue, asthenia, oedema*, pyrexia; Common: influenza like illness, chills, *In combination with chemotherapy:* Very common: fatigue, asthenia, pyrexia *; Common: oedema, influenza like illness, chills, *In combination with axitinib or lenvatinib:* Very common: fatigue, asthenia, oedema*, pyrexia, Common: influenza like illness, chills. Investigations *Monotherapy:* Common: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased, blood creatinine increased; Uncommon: amylase increased, *In combination with chemotherapy:* Very common: alanine aminotransferase increased, aspartate aminotransferase increased; Common: blood bilirubin increased, blood alkaline phosphatase increased, blood creatinine increased, hypercalcaemia; Uncommon: amylase increased, *In combination with axitinib or lenvatinib:* Very common: lipase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased; Common: amylase increased, blood bilirubin increased, blood alkaline phosphatase increased, hypercalcaemia. † Adverse reaction frequencies presented in Table 2 may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination. ‡Based upon a standard query including bradyarrhythmias and tachyarrhythmias. *The following terms represent a group of related events that describe a medical condition rather than a single event: infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion related hypersensitivity reaction, cytokine release syndrome and serum sickness); sarcoidosis (cutaneous sarcoidosis and pulmonary sarcoidosis); hypothyroidism (myxoedema, immune-mediated hypothyroidism and autoimmune hypothyroidism); adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute and secondary adrenocortical insufficiency); thyroiditis (autoimmune thyroiditis, silent thyroiditis, thyroid disorder, thyroiditis acute, and immune-mediated thyroiditis); hyperthyroidism (Basedow's disease); hypophysitis (hypopituitarism and lymphocytic hypophysitis); type 1 diabetes mellitus (diabetic ketoacidosis); myasthenic syndrome (myasthenia gravis, including exacerbation); encephalitis (autoimmune encephalitis and noninfective encephalitis); Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy); myelitis (including transverse myelitis); meningitis aseptic (meningitis and meningitis noninfective); uveitis (chorioretinitis, iritis and iridocyclitis); n. myocarditis (autoimmune myocarditis); vasculitis (central nervous system vasculitis, aortitis and giant cell arteritis); pneumonitis (interstitial lung disease, organising pneumonia, immune-mediated pneumonitis, immune-mediated lung disease and autoimmune lung disease); abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower); colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis, and immune-mediated enterocolitis); gastritis (gastritis erosive and gastritis haemorrhagic); pancreatitis (autoimmune pancreatitis, pancreatitis acute and immune-mediated pancreatitis); gastrointestinal ulceration (gastric ulcer and duodenal ulcer); hepatitis (autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis); cholangitis sclerosing (immune-mediated cholangitis); pruritus (urticaria, urticaria papular and pruritus genital); rash (rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash vesicular and genital rash); severe skin reactions (exfoliative rash, pemphigus, and Grade ≥ 3 of the following: cutaneous vasculitis, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, lichen planus, oral lichen planus, pemphigoid, pruritus, pruritus genital, rash, rash erythematous, rash maculopapular, rash pruritic, rash pustular, skin necrosis and toxic skin eruption); vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid); lichenoid keratosis (lichen planus and lichen sclerosus); musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis); cc. myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis); arthritis (joint swelling, polyarthritis, joint effusion, autoimmune arthritis and immune-mediated arthritis); tenosynovitis (tendonitis, synovitis and tendon pain); nephritis (autoimmune nephritis, immune-mediated nephritis, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome, glomerulonephritis, glomerulonephritis membranous and glomerulonephritis acute); oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema). ***Description of selected adverse reactions*** Data for the following immunemediated adverse reactions are based on patients who received pembrolizumab across four doses (2 mg/kg bw every 3 weeks, 10 mg/kg bw every 2 or 3 weeks, or 200 mg every 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4. *Immunemediated adverse reactions (see section 4.4)* Immunemediated pneumonitis Pneumonitis occurred in 324 (4.2%) patients, including Grade 2, 3, 4 or 5 cases in 143 (1.9%), 81 (1.1%), 19 (0.2%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.9 months (range: 2 days to 27.2 months). The median duration was 2.0 months (range: 1 day to 51.0+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (8.1%) than in patients who did not receive prior thoracic radiation (3.9%). Pneumonitis led to discontinuation of pembrolizumab in 131 (1.7%) patients. Pneumonitis resolved in 196 patients, 6 with sequelae. In patients with NSCLC, pneumonitis occurred in 230 (6.1%), including Grade 2, 3, 4 or 5 cases in 103 (2.7%), 63 (1.7%), 17 (0.4%) and 10 (0.3%), respectively. In patients with locally advanced or metastatic NSCLC, pneumonitis occurred in 8.9% with a history of prior thoracic radiation. In patients with cHL, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively. Immunemediated colitis Colitis occurred in 158 (2.1%) patients, including Grade 2, 3 or 4 cases in 49 (0.6%), 82 (1.1%) and 6 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4.3 months (range: 2 days to 24.3 months). The median duration was 1.1 month (range: 1 day to 45.2 months). Colitis led to discontinuation of pembrolizumab in 48 (0.6%) patients. Colitis resolved in 132 patients, 2 with sequelae. In patients with CRC treated with pembrolizumab as monotherapy (n=153), the incidence of colitis was 6.5% (all Grades) with 2.0% Grade 3 and 1.3% Grade 4. Immune-mediated hepatitis Hepatitis occurred in 80 (1.0%) patients, including Grade 2, 3 or 4 cases in 12 (0.2%), 55 (0.7%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.5 months (range: 8 days to 26.3 months). The median duration was 1.3 months (range: 1 day to 29.0+ months). Hepatitis led to discontinuation of pembrolizumab in 37 (0.5%) patients. Hepatitis resolved in 60 patients. Immune-mediated nephritis Nephritis occurred in 37 (0.5%) patients, including Grade 2, 3 or 4 cases in 11 (0.1%), 19 (0.2%) and 2 (< 0.1%) patients, respectively, receiving pembrolizumab as monotherapy. The median time to onset of nephritis was 4.2 months (range: 12 days to 21.4 months). The median duration was 3.3 months (range: 6 days to 28.2+ months). Nephritis led to discontinuation of pembrolizumab in 17 (0.2%) patients. Nephritis resolved in 25 patients, 5 with sequelae. In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=488), the incidence of nephritis was 1.4% (all Grades) with 0.8% Grade 3 and 0.4% Grade 4. Immune-mediated endocrinopathies Adrenal insufficiency occurred in 74 (1.0%) patients, including Grade 2, 3 or 4 cases in 34 (0.4%), 31 (0.4%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5.4 months (range: 1 day to 23.7 months). The median duration was not reached (range: 3 days to 40.1+ months). Adrenal insufficiency led to discontinuation of pembrolizumab in 13 (0.2%) patients. Adrenal insufficiency resolved in 28 patients, 11 with sequelae. Hypophysitis occurred in 52 (0.7%) patients, including Grade 2, 3 or 4 cases in 23 (0.3%), 24 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 5.9 months (range: 1 day to 17.7 months). The median duration was 3.6 months (range: 3 days to 48.1+ months). Hypophysitis led to discontinuation of pembrolizumab in 14 (0.2%) patients. Hypophysitis resolved in 23 patients, 8 with sequelae. Hyperthyroidism occurred in 394 (5.2%) patients, including Grade 2 or 3 cases in 108 (1.4%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range: 1 day to 23.2 months). The median duration was 1.6 months (range: 4 days to 43.1+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 4 (0.1%) patients. Hyperthyroidism resolved in 326 (82.7%) patients, 11 with sequelae. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2,060), the incidence of hyperthyroidism was 11.0%, the majority of which were Grade 1 or 2. Hypothyroidism occurred in 939 (12.3%) patients, including Grade 2 or 3 cases in 687 (9.0%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.4 months (range: 1 day to 25.9 months). The median duration was not reached (range: 2 days to 63.0+ months). Hypothyroidism led to discontinuation of pembrolizumab in 6 (0.1%) patients. Hypothyroidism resolved in 216 (23.0%) patients, 16 with sequelae. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In patients with HNSCC treated with pembrolizumab as monotherapy (n=909), the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with pembrolizumab in combination with platinum and 5-FU chemotherapy (n=276), the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients treated with pembrolizumab in combination with axitinib or lenvatinib (n=1,456), the incidence of hypothyroidism was 46.2% (all Grades) with 0.8% Grade 3 or 4. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2,060), the incidence of hypothyroidism was 18.5%, the majority of which were Grade 1 or 2. Immune-mediated skin adverse reactions Immunemediated severe skin reactions occurred in 130 (1.7%) patients, including Grade 2, 3, 4 or 5 cases in 11 (0.1%), 103 (1.3%), 1 (< 0.1%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.8 months (range: 2 days to 25.5 months). The median duration was 1.9 months (range: 1 day to 47.1+ months). Severe skin reactions led to discontinuation of pembrolizumab in 18 (0.2%) patients. Severe skin reactions resolved in 95 patients, 2 with sequelae. Rare cases of SJS and TEN, some of them with fatal outcome, have been observed (see sections 4.2 and 4.4). *Complications of allogeneic HSCT in cHL* Of 14 patients in KEYNOTE013 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients reported acute GVHD and 1 patient reported chronic GVHD, none of which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant. Of 32 patients in KEYNOTE087 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 16 patients reported acute GVHD and 7 patients reported chronic GVHD, two of which were fatal. No patients experienced hepatic VOD. No patients experienced engraftment syndrome post-transplant. Of 14 patients in KEYNOTE204 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant. *Elevated liver enzymes when pembrolizumab is combined with axitinib in RCC* In a clinical study of previously untreated patients with RCC receiving pembrolizumab in combination with axitinib, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT > 3 times ULN, and of those patients with recurrence of ALT > 3 times ULN, all recovered. There were no Grade 5 hepatic events. *Laboratory abnormalities In patients treated with pembrolizumab monotherapy*, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9.4% for lymphocytes decreased, 7.4% for sodium decreased, 5.8% for haemoglobin decreased, 5.3% for phosphate decreased, 5.3% for glucose increased, 3.3% for ALT increased, 3.1% for AST increased, 2.6% for alkaline phosphatase increased, 2.3% for potassium decreased, 2.1% for potassium increased, 1.9% for neutrophils decreased, 1.8% for platelets decreased, 1.8% for calcium increased, 1.7% for bilirubin increased, 1.5% for calcium decreased, 1.4% for albumin decreased, 1.3% for creatinine increased, 1.2% for glucose decreased, 0.8% for leucocytes decreased, 0.7% for magnesium increased, 0.5% for sodium increased, 0.4% for haemoglobin increased, and 0.2% for magnesium decreased. *In patients treated with pembrolizumab in combination with chemotherapy*, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 39.9% for neutrophils decreased, 25.5% for lymphocytes decreased, 23.3% for leucocytes decreased, 20.8% for haemoglobin decreased, 13.7% for platelets decreased, 10.4% for sodium decreased, 7.7% for potassium decreased, 7.3% for phosphate decreased, 5.7% for ALT increased, 5.5% for glucose increased, 5.3% for AST increased, 3.6% for bilirubin increased, 3.5% for calcium decreased, 3.4% for potassium increased, 3.1% for creatinine increased, 2.8% for alkaline phosphatase increased, 2.6% for albumin decreased, 1.7% for calcium increased, 1.0% for glucose decreased, 0.5% for sodium increased and 0.1% for haemoglobin increased. *In patients treated with pembrolizumab in combination with axitinib or lenvatinib*, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 23.0% for lipase increased (not measured in patients treated with pembrolizumab and axitinib), 12.0% for lymphocyte decreased, 11.4% for sodium decreased, 11.2% for amylase increased, 11.2% for triglycerides increased, 10.4% for ALT increased, 8.9% for AST increased, 7.8% for glucose increased, 6.8% for phosphate decreased, 6.1% for potassium decreased, 5.1% for potassium increased, 4.5% for cholesterol increased, 4.4% for creatinine increased, 4.2% for haemoglobin decreased, 4.0% for magnesium decreased, 3.5% for neutrophils decreased, 3.1% for alkaline phosphatase increased, 3.0% for platelets decreased, 2.8% for bilirubin increased, 2.2% for calcium decreased, 1.7% for white blood cells decreased, 1.6% for magnesium increased, 1.5% for prothrombin INR increased, 1.4% for glucose decreased, 1.2% for albumin decreased, 1.2% for calcium increased, 0.4% for sodium increased, and 0.1% for haemoglobin increased. ***Immunogenicity*** In clinical studies in patients treated with pembrolizumab 2 mg/kg bw every three weeks, 200 mg every three weeks, or 10 mg/kg bw every two or three weeks as monotherapy, 36 (1.8%) of 2,034 evaluable patients tested positive for treatmentemergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development. ***Paediatric population*** The safety of pembrolizumab as monotherapy has been evaluated in 161 paediatric patients aged 9 months to 17 years with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours at 2 mg/kg bw every 3 weeks in the Phase I/II study KEYNOTE-051. The cHL population (n=22) included patients 11 to 17 years of age. The safety profile in paediatric patients was generally similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia (33%), vomiting (30%), headache (26%), abdominal pain (22%), anaemia (21%), cough (21%) and constipation (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. Seventy-six (47.2%) patients had 1 or more Grades 3 to 5 adverse reactions of which 5 (3.1%) patients had 1 or more adverse reactions that resulted in death. The frequencies are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. Long-term safety data of pembrolizumab in adolescents with Stage IIB, IIC and III melanoma treated in the adjuvant setting are currently unavailable. ***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 via the national reporting system: **in Belgium:** Agence Fédérale des Médicaments et des Produits de Santé, www.afmps.be - Division Vigilance : Site internet: www.notifieruneffetindesirable.be, e-mail: adr@fagg-afmps.be, **in Luxembourg:** Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé. Site internet: www.guichet.lu/pharmacovigilance. **7. MARKETING AUTHORISATION HOLDER** Merck Sharp & Dohme B.V. Waarderweg 39. 2031 BN Haarlem. The Netherlands. **8. MARKETING AUTHORISATION NUMBER(S)** EU/1/15/1024/002 **9**. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 17 July 2015. Date of latest renewal: 24 March 2020**. 10. DATE OF REVISION OF THE TEXT** 03/2024. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. **DELIVERY**: on medical prescription.