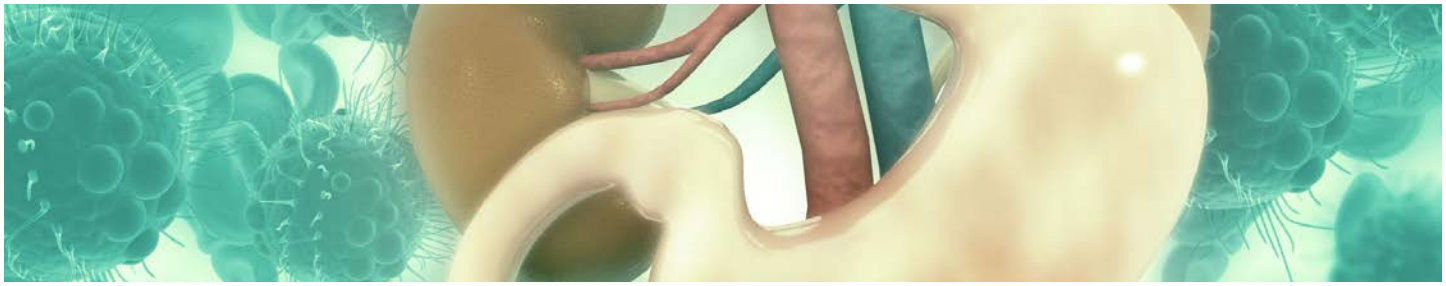


The expanding role of immunotherapy in the treatment of gastro-intestinal cancers

Practice-changing results with durvalumab-based therapy in patients with advanced hepatocellular and biliary tract cancer

Over the last decade, immunotherapy (IO) has changed the treatment landscape for many cancer types. Also in the management of gastrointestinal (GI) cancer, IO is becoming increasingly important. In this respect, two new IO indications in GI cancer were recently EMA approved and reimbursed in Belgium: durvalumab in combination with cisplatin and gemcitabine for the first line treatment of advanced biliary tract cancer (BTC) and dual IO therapy with a combination of tremelimumab and durvalumab as a first line treatment option for patients with advanced hepatocellular carcinoma (HCC). During the Belgian Group of Digestive Oncology (BGDO) session of the 2023 Belgian Week of gastroenterology, AstraZeneca organized a satellite symposium discussing the clinical basis for these new indications. During the symposium **Prof. Jeroen Dekervel (University Hospitals Leuven)** discussed the results of the **TOPAZ-1** trial, evaluating first line durvalumab plus gemcitabine/cisplatin in patients with advanced BTC after which **Prof. Ivan Borbath (Cliniques Universitaires Saint-Luc, Brussels)** turned the attention to HCC and discussed the results of the **HIMALAYA** study, assessing the potential of tremelimumab plus durvalumab in the first line setting of advanced HCC.

Durvalumab plus chemotherapy as new standard first-line treatment for advanced BTC

BTC is a highly aggressive and heterogeneous disease. This heterogeneity is amply illustrated by the marked differences in gene expression profiles of intrahepatic cholangiocarcinoma (iCCA), extrahepatic CCA (eCCA) and gallbladder cancer (GBC).[1] In BTC, treatment decisions are mainly steered by the operability of the tumour. Based on the results of the ABC-02 trial, the first-line standard of care (SoC) for patients with advanced unresectable BTC has consisted of gemcitabine and cisplatin (GemCis) since 2010.[2] In the ABC-02 study, GemCis was shown to provide a significant survival benefit over gemcitabine alone (11.7 *vs.* 8.1 months, respectively; HR: 0.64; p<0.001).[2,3] For patients with disease progression on or following first-line GemCis, the second-line treatment generally consists of 5-fluoruracil (5-FU) with oxaliplatin (FOLFOX) or with irinotecan or nanoliposomal irinotecan [nal-IRI] (FOLFIRI).[2]

In recent years, detailed genetic analyses of BTC have revealed recurrent oncogenic driver mutations in subgroups of BTC patients. In this, the main targetable aberrations in patients with iCCA consist of *IDH* and *FGFR,* while *HER2* aberrations are mainly encountered in eCCA and GBC tumours.[1] As a result of these findings, several clinical trials have successfully evaluated targeted therapies in specific subgroups of BTC patients. This includes the use of selective *FGFR* inhibitors (i.e., pemigatinib), inhibitors of *IDH* (i.e., ivosidinib) and dual *BRAF/MEK* targeting (i.e., dabrafenib-trametinib). For patients with advanced BTC harbouring a *HER2* mutation, promising responses have also been observed with a combination of pertuzumab and trastuzumab.[2] Until recently, the role of IO in the treatment of BTC was limited to patients with mismatch repair deficiency and/or a microsatellite instability high (MSI/dMMR) status. For this patient population and for patients with a high tumour mutational burden (≥10 mut/Mb), pembrolizumab is a valuable treatment option.[1,2]

In clinical practice, however, patients with targetable genetic alterations only represent a small portion of all patients presenting advanced BTC. For the majority of advanced BTC patients, the SoC first line treatment therefore remained GemCis for more than a decade. However, based on the recent publication of the results of the TOPAZ-1 trial, the role of IO in the management of BTC was dramatically expanded. TOPAZ-1 is the first global phase 3 study evaluating a combination of IO and GemCis as first-line treatment for patients with advanced BTC. In this trial, a total of 685 previously untreated, unresectable BTC patients were randomly assigned (1:1) to durvalumab or placebo, both combined with GemCis.[4] Of note, also patients

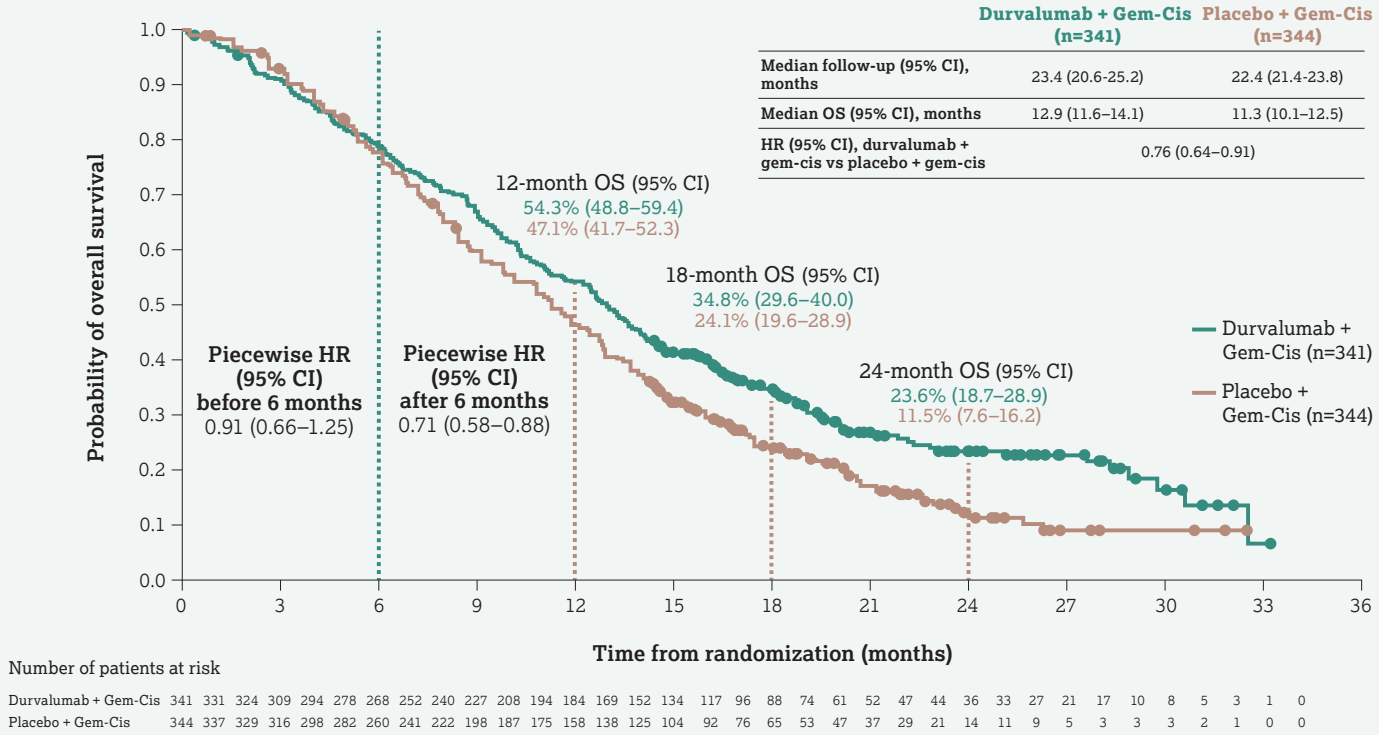


Figure 1. Updated overall survival results from the TOPAZ-1 trial.[6,7]

CI: confidence interval, Gem-Cis: gemcitabine-cisplatin, HR: hazard ratio, OS: overall survival.

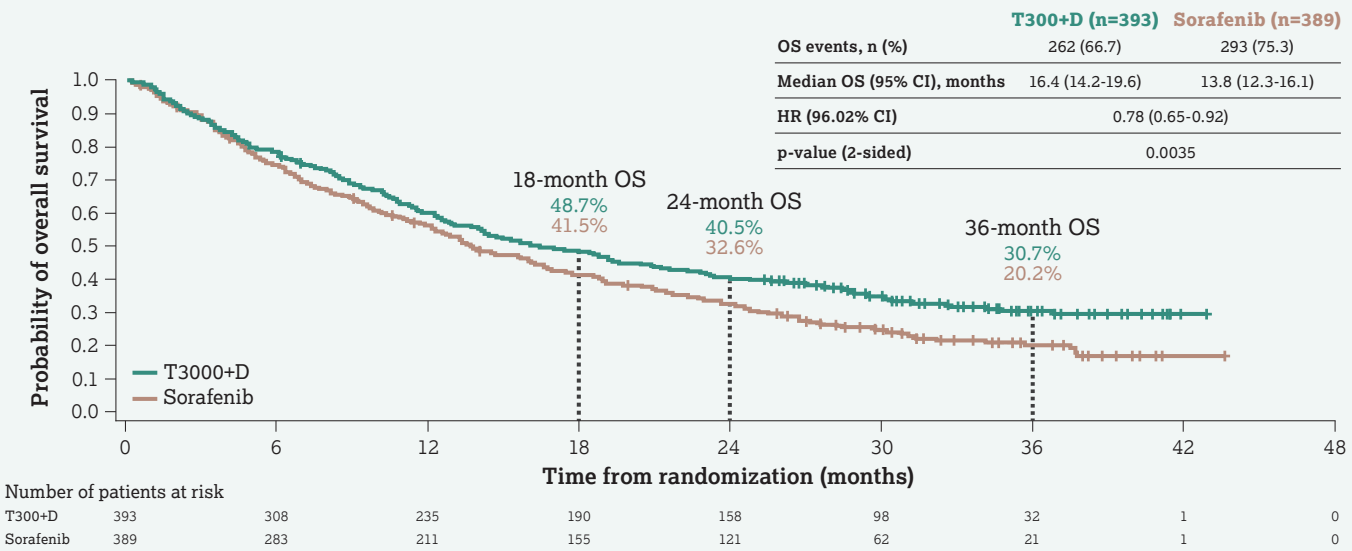
with disease recurrence within 6 months after surgery or completion of adjuvant therapy were eligible for the study. Patients were initially treated with GemCis in combination with durvalumab (1500 mg IV, q3w) or placebo for up to 8 cycles, followed by maintenance therapy with durvalumab (1500 mg IV, q4w) or placebo. The study showed that patients in the durvalumab + GemCis arm had a significantly longer median overall survival (OS, primary endpoint) than patients treated with placebo + GemCis (12.8 *vs.* 11.5 months; HR[95%CI]: 0.80[0.66-0.97]; p=0.021).[5] In an updated analysis of this trial with 6.5 months of additional follow-up, the HR for OS was further improved in favour of the durvalumab arm (HR[95%CI]: 0.76[0.64-0.91]) (*Figure 1*).[6,7] The continuously diverging Kaplan-Meier curves and the increasing difference in OS rate between the two treatment arms over time (34.8% *vs.* 24.1% at 18 months to 23.6% *vs.* 11.5% at 24 months) underscores the potential for a long-term benefit with durvalumab + GemCis in this setting.[6,7] Importantly, the OS benefit was shown to be consistent across all subgroups. Apart from improving OS, durvalumab + GemCis also significantly delayed disease progression compared to placebo + GemCis with a median progression-free survival (PFS) of 7.2 and 5.7 months, respectively. In addition, also the overall response rate (ORR, 26.7% *vs.* 18.7%) and duration of response (DoR, 6.4 *vs.* 6.2 months) were significantly better with durvalumab + GemCis than with placebo + GemCis.

Regarding safety, adding durvalumab to chemotherapy did not increase toxicity. The most common grade 3/4 treatment-related adverse events (AEs) in the durvalumab and placebo groups consisted of anaemia (23.7% *vs.* 22.5%), a neutrophil count decrease (21% *vs.* 25.7%) and neutropenia (20.1% *vs.* 21.1%).[8]

In summary, adding durvalumab to GemCis in first line advanced BTC significantly improves OS compared to GemCis alone, without increasing toxicity. In this, the increasing benefit in OS rate over time shows that a subgroup of patients derives a long-term benefit of this combination. As such, ***TOPAZ-1*** *provides compelling evidence to establish durvalumab + GemCis as the new standard of care in the first line treatment of patients with advanced BTC.*

Dual immunotherapy with tremelimumab and durvalumab as first line therapy for advanced HCC

The management of patients with HCC is based on the Barcelona Clinic Liver Cancer (BCLC) algorithm, which classifies HCC patients into five stages (0, A, B, C, and D) and allocates them to either curative or palliative therapy based on tumour status, liver function (Child-Pugh score) and performance status.[9] In addition to this, also the HCC aetiology (i.e., viral HCC [HBV or HCV], alcoholic fatty liver disease [AFLD] related HCC, HCC related to metabolic-related fatty liver disease [MAFLD]) can have an impact on the efficacy of certain treatment options and is often taken into consideration. In Europe, the development of HCC is primarily associated with alcohol consumption and HCV infections. This is also the case for the United States, but there we also see a rising incidence of MAFLD-related HCC. In contrast, in Asia and Africa, HCC primarily has a viral aetiology.[10]



Data cut-off: August 27, 2021. Median duration of follow-up was 33.18 (95% CI, 31.74-34.53) months for T300+D and 32.23 (95% CI, 30.42-33.71) months for sorafenib.
CI, confidence interval; HR, hazard ratio; OS, overall survival; T300+D, tremelimumab 300 mg x 1 dose + durvalumab 1500 mg Q4W.

Figure 2. Overall survival results from the HIMALAYA trial.[10,12]

CI: confidence interval, HR: hazard ratio, mo: months, OS: overall survival, T300 + D: tremelimumab 300 mg plus durvalumab.

The long-standing SoC first line treatment for patients with advanced HCC consisted of sorafenib. This picture changed a couple of years ago with the publication of the IMbrave150 data. In this trial, the combination of atezolizumab and bevacizumab (atezo/bev) was shown to significantly prolong the OS *vs.* sorafenib in patients with advanced HCC (median OS: 19.2 *vs.* 13.4 months (HR[95%CI]: 0.66[0.52-0.85];p=0.0009), establishing the combination of atezo/bev as the new SoC in this setting. Nevertheless, a subgroup analysis of this trial indicated an apparent lack of benefit for atezo/bev over sorafenib in the subgroup of patients with a non-viral HCC aetiology (HR:1.05).[11] In the quest for alternative treatment options for patients with advanced HCC, researchers evaluated dual immune checkpoint inhibition in this setting. In other tumour types, like melanoma or renal cell carcinoma, the combination of an anti-CTLA-4 and an anti-PD-(L)1 has shown to enhance the immune response against cancer cells through their complementary mechanisms resulting in long-term tumour responses. In fact, while anti-CTLA4 therapy can block the suppressive T-cell signalling in the lymph node, targeting PD-(L)1 inhibits immunosuppressive interactions in the tumour microenvironment. Based on this rationale, the phase 3 HIMALAYA trial evaluated the combination of tremelimumab (anti-CTLA-4) with durvalumab (anti-PD-L1) as first line treatment for patients with unresectable HCC (BCLC B and C).[12] In 2 arms of this study, patients were randomly assigned to receive a single dose of tremelimumab (300 mg) in combination with durvalumab (1500mg q4w) (STRIDE regimen) (N=393) or sorafenib monotherapy (N= 389).[12] In this study, the STRIDE regimen significantly improved the OS compared to sorafenib with a median OS of 16.4 and 13.8 months, respectively (HR[95%CI]: 0.78[0.65-0.92]; p=0.0035). The OS benefit of the STRIDE regimen was also reflected by the landmark OS analyses. At the 3 year landmark, this translated into an OS rate of 30.7% for STRIDE as compared to 20.3% with sorafenib (*Figure 2*). Importantly, the benefit of STRIDE over sorafenib was noted across most subgroups, including non-viral HCC variants, and irrespective of the level of PD-L1 expression.

Overall, the safety profile of STRIDE was manageable. Grade ≥3 haemorrhage was reported in 0.5 *vs.* 1.6% of the patients receiving STRIDE and sorafenib, respectively. In patients receiving STRIDE, immune-mediated events requiring an intervention with high-dose glucocorticoids or treatment discontinuation occurred in 21% and 5.7% of patients, respectively. The most common immune-mediated events with the IO-based therapy consisted of hepatic events, diarrhoea/colitis, and dermatitis/rash.

*In conclusion, the **HIMALAYA** trial revealed that the combination of single dose tremelimumab with 4-weekly dosing of durvalumab (the STRIDE regimen) prolongs OS compared to sorafenib in patients with advanced HCC, regardless of PD-L1 expression and HCC aetiology.[10] As such, the impressive results obtained with the STRIDE regimen in the HIMALAYA trial establish this regimen as a critical component of the first line treatment arsenal for patient with advanced HCC.*

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NSID XL-3403-Revision date 05/2023-LB Local code 733

ESSENTIAL INFORMATION ▼ 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 'Undesirable effects' for how to report adverse reactions. **1. NAME OF THE MEDICINAL PRODUCT** IMJUDO 20 mg/ml concentrate for solution for infusion. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Each mL of concentrate for solution for infusion contains 20 mg of tremelimumab. One vial of 1.25 ml of concentrate contains 25 mg of tremelimumab. One vial of 15 ml of concentrate contains 300 mg of tremelimumab. Tremelimumab is a human anti-CTLA-4 immunoglobulin G2 IgG2a monoclonal antibody produced in murine myeloma cells by recombinant DNA technology. For the full list of excipients, see section 'List of excipients' of the SmPC. **3. PHARMACEUTICAL FORM** Concentrate for solution for infusion (sterile concentrate). Clear to slightly opalescent, colourless to slightly yellow solution, free from or practically free from visible particles. The solution has a pH of approximately 5.5 and an osmolality of approximately 285 mOsm/kg. **4. CLINICAL PARTICULARS 4.1 Therapeutic indications** IMJUDO in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). **4.2 Posology and method of administration** Treatment must be initiated and supervised by a physician experienced in the treatment of cancer. Posology The recommended dose of IMJUDO is presented in Table 1. IMJUDO is administered as an intravenous infusion over 1 hour. **Table 1: Recommended dose of IMJUDO: Indication:** Advanced or unresectable HCC. **Recommended IMJUDO dosage:** IMJUDO 300 mg[a] as a single dose administered in combination with durvalumab 1500 mg[a] at Cycle 1/Day 1, followed by durvalumab monotherapy every 4 weeks. **Duration of Therapy:** Until disease progression or unacceptable toxicity. [a] For IMJUDO, HCC patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to IMJUDO 4 mg/kg until weight is greater than 40 kg. For durvalumab, patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to durvalumab 20 mg/kg until weight is greater than 30 kg. Dose escalation or reduction is not recommended during treatment with IMJUDO in combination with durvalumab. Treatment withholding or discontinuation may be required based on individual safety and tolerability. Guidelines for management of immune-mediated adverse reactions are described in Table 2 (see section 'Special warnings and precautions for use' of the SmPC). Refer also to the summary of product characteristics (SmPC) for durvalumab. **Table 2. Treatment modifications and management recommendations for IMJUDO in combination with durvalumab [Adverse reactions/Severity[a]/Treatment modification/ Corticosteroid treatment unless otherwise specified[b]]: Immune-mediated pneumonitis/interstitial lung disease:** Severity[a]: Grade 2; Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 or 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated hepatitis:** Severity[a]: ALT or AST > 3 - ≤ 5 x ULN or total bilirubin > 1.5 - ≤ 3 x ULN; Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 5 - ≤ 10 x ULN; Treatment modification: Withhold durvalumab and permanently discontinue IMJUDO (where appropriate); Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[d]; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 10 x ULN or total bilirubin > 3 x ULN; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)[e]:** Severity[a]: ALT or AST > 2.5 - ≤ 5 x BLV and ≤ 20 x ULN; Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 5 - 7 x BLV and ≤ 20 x ULN or concurrent ALT or AST 2.5 - 5 x BLV and ≤ 20 x ULN and total bilirubin > 1.5 - < 2 x ULN[d]; Treatment modification: Withhold durvalumab and permanently discontinue IMJUDO (where appropriate); Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 7 x BLV or > 20 x ULN whichever occurs first or bilirubin > 3 x ULN; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated colitis or diarrhoea:** Severity[a]: Grade 2; Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 or 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Intestinal perforation of ANY grade; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Consult a surgeon immediately if an intestinal perforation is suspected. **Immune-mediated hyperthyroidism, thyroiditis:** Severity[a]: Grade 2-4; Treatment modification: Withhold dose until clinically stable; Corticosteroid treatment unless otherwise specified[b]: Symptomatic management. **Immune-mediated hypothyroidism:** Severity[a]: Grade 2-4; Treatment modification: No changes; Corticosteroid treatment unless otherwise specified[b]: Initiate thyroid hormone replacement as clinically indicated. **Immune-mediated adrenal insufficiency, hypophysitis/hypopituitarism:** Severity[a]: Grade 2-4; Treatment modification: Withhold dose until clinically stable; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated. **Immune-mediated Type 1 diabetes mellitus:** Severity[a]: Grade 2-4; Treatment modification: No changes; Corticosteroid treatment unless otherwise specified[b]: Initiate treatment with insulin as clinically indicated. **Immune-mediated nephritis:** Severity[a]: Grade 2 with serum creatinine > 1.5-3 x (ULN or baseline); Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 with serum creatinine > 3 x baseline or > 3-6 x ULN; Grade 4 with serum creatinine > 6 x ULN; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated rash or dermatitis (including pemphigoid):** Severity[a]: Grade 2 for > 1 week or Grade 3; Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated myocarditis:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[f]. **Immune-mediated myositis/polymyositis:** Severity[a]: Grade 2 or 3; Treatment modification: Withhold dose[c,g]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Infusion-related reactions:** Severity[a]: Grade 1 or 2; Treatment modification: Interrupt or slow the rate of infusion; Corticosteroid treatment unless otherwise specified[b]: May consider pre-medications for prophylaxis of subsequent infusion reactions; Severity[a]: Grade 3 or 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines. **Immune-mediated myasthenia gravis:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated encephalitis:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Other immune-mediated adverse reactions[h]:** Severity[a]: Grade 2 or 3; Treatment modification: Withhold dose[c]; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified[b]: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Non-immune-mediated adverse reactions:** Severity[a]: Grade 2 and 3; Treatment modification: Withhold dose until ≤ Grade 1 or return to baseline; Severity[a]: Grade 4; Treatment modification: Permanently discontinue[i]. [a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value. [b] Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. Consider increasing dose of corticosteroids and/or using additional systemic immunosuppressants if there is worsening or no improvement. [c] After withholding, IMJUDO and/or durvalumab can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. IMJUDO and durvalumab should be permanently discontinued for recurrent Grade 3 adverse reactions, as applicable. [d] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations. [e] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement. [f] If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month. [g] Permanently discontinue IMJUDO and durvalumab if the adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency. [h] Includes immune thrombocytopenia and pancreatitis. [i] With the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue treatment should be based on accompanying clinical signs/symptoms and clinical judgment. For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. *Special populations Paediatric population* The safety and efficacy of IMJUDO in children and adolescents below 18 years of age have not been established. No data are available. *Elderly* No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 'Pharmacokinetic properties' of the SmPC). *Renal impairment* No dose adjustment of IMJUDO is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 'Pharmacokinetic properties' of the SmPC). *Hepatic impairment* No dose adjustment of IMJUDO is recommended for patients with mild or moderate hepatic impairment. IMJUDO has not been studied in patients with severe hepatic impairment (see section 'Pharmacokinetic properties' of the SmPC). Method of administration IMJUDO is for intravenous use. Administer IMJUDO prior to durvalumab on the same day. IMJUDO and durvalumab are administered as separate intravenous infusions. Refer to the SmPC for durvalumab administration information. For instructions on dilution of the medicinal product before administration, see section 'Special precautions for disposal and other handling' of the SmPC. **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 'List of Excipients' of the SmPC. **4.4 Undesirable effects** Summary of the safety profile The safety of tremelimumab 300 mg as a single dose in combination with durvalumab, is based on pooled data in 462 HCC patients (HCC pool) from the HIMALAYA Study and another study in HCC patients, Study 22. The most common (> 10%) adverse reactions were rash (32.5%), pruritus (25.5%), diarrhoea (25.3%), abdominal pain (19.7%), aspartate aminotransferase increased/alanine aminotransferase increased (18.0%), pyrexia (13.9%), hypothyroidism (13.0%), cough/productive cough (10.8%), oedema peripheral (10.4%) and lipase increased (10.0%) (see Table 3). The most common severe adverse reactions (NCI CTCAE Grade ≥ 3) are aspartate aminotransferase increased/alanine aminotransferase increased (8.9%), lipase increased (7.1%), amylase increased (4.3%) and diarrhoea (3.9%). The most common serious adverse reactions are colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%). The frequency of treatment discontinuation due to adverse reactions is 6.5%. The most common adverse reactions leading to treatment discontinuation are hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%). The severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life threatening and grade 5=death. Tabulated list of adverse reactions Table 3, unless otherwise stated, lists the incidence of adverse reactions (ADRs) in patients treated with tremelimumab 300 mg in combination with durvalumab in the HCC pool of 462 patients. Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the ADRs are presented in decreasing frequency. The corresponding frequency category for each ADR is defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness. **Table 3. Adverse reactions in patients with HCC treated with tremelimumab 300 mg in combination with durvalumab [Adverse Reaction/Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade/Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Infections and infestations:** Upper respiratory tract infections[a]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 39 (8.4%). Pneumonia[b]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 20 (4.3%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 6 (1.3%). Influenza: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 10 (2.2%). Dental and oral soft tissue infections[c]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 6 (1.3%). Oral candidiasis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 3 (0.6%). **Blood and lymphatic system disorders:** Immune thrombocytopenia[d]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. **Endocrine disorders:** Hypothyroidism[e]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 60 (13.0%). Hyperthyroidism[f]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 44 (9.5%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Thyroiditis[g]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 8 (1.7%). Adrenal insufficiency: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 6 (1.3%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Hypopituitarism/Hypophysitis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 4 (0.9%). Diabetes insipidus[a]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. Type 1 diabetes mellitus[a]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. **Nervous system disorders:** Myasthenia gravis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 2 (0.4%). Meningitis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 1 (0.2%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Guillain-Barré syndrome[a]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. Encephalitis[a]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. **Cardiac disorders:** Myocarditis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 2 (0.4%). **Respiratory, thoracic and mediastinal disorders:** Cough/Productive cough: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 50 (10.8%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Pneumonitis[h]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 11 (2.4%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Dysphonia: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 4 (0.9%). Interstitial lung disease: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 1 (0.2%). **Gastrointestinal disorders:** Diarrhoea: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 117 (25.3%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 18 (3.9%). Abdominal pain[i]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 91 (19.7%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 10 (2.2%). Lipase increased: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 46 (10.0%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 33 (7.1%). Amylase increased: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 41 (8.9%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 20 (4.3%). Colitis[j]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 16 (3.5%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 12 (2.6%). Pancreatitis[k]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 6 (1.3%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 3 (0.6%). Intestinal perforation[d]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. Large intestine perforation[d]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. **Hepatobiliary disorders:** Aspartate aminotransferase increased/ Alanine aminotransferase increased[l]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 83 (18.0%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 41 (8.9%). Hepatitis[m]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 23 (5.0%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 8 (1.7%). **Skin and subcutaneous tissue disorders:** Rash[n]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 150 (32.5%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Common: 14 (3.0%). Pruritus: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 118 (25.5%). Dermatitis[o]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 6 (1.3%). Night sweats: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 6 (1.3%). Pemphigoid: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 1 (0.2%). **Musculoskeletal and connective tissue disorders:** Myalgia: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 16 (3.5%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Myositis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 3 (0.6%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Polymyositis: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 1 (0.2%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). **Renal and urinary disorders:** Blood creatinine increased: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 21 (4.5%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 2 (0.4%). Dysuria: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 7 (1.5%). Nephritis[p]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Uncommon: 3 (0.6%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 2 (0.4%). Cystitis noninfective[d]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Not known. **General disorders and administration site conditions:** Pyrexia: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 64 (13.9%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 1 (0.2%). Oedema peripheral[b]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Very common: 48 (10.4%)/ [Tremelimumab 300 mg in combination with durvalumab (n=462)- Frequency of Grade 3-4]: Uncommon: 2 (0.4%). **Injury, poisoning and procedural complications:** Infusion-related reaction[r]: [Tremelimumab 300 mg in combination with durvalumab (n=462) - Frequency of any Grade]: Common: 6 (1.3%). [a] Includes nasopharyngitis, pharyngitis, rhinitis, tracheobronchitis and upper respiratory tract infection. [b] Includes pneumocystis jirovecii pneumonia and pneumonia. [c] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection. [d] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with durvalumab or durvalumab + tremelimumab in AstraZeneca-sponsored clinical studies. [e] Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism. [f] Includes blood thyroid stimulating hormone decreased and hyperthyroidism. [g] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute. [h] Includes immune-mediated pneumonitis and pneumonitis. [i] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain. [j] Includes colitis, enteritis and enterocolitis. [k] Includes pancreatitis and pancreatitis acute. [l] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased. [m] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity and immune-mediated hepatitis. [n] Includes eczema, erythema, rash, rash macular, rash maculo-papular, rash papular and rash pruritic. [o] Includes dermatitis and immune-mediated dermatitis. [p] Includes autoimmune nephritis and immune-mediated nephritis. [q] Includes oedema peripheral and peripheral swelling. [r] Includes infusion-related reaction and urticaria. Description of selected adverse reactions The data below reflects information for significant adverse reactions for tremelimumab 300 mg in combination with durvalumab in the HCC pool (n=462). *Immune mediated pneumonitis* In the HCC pool (n=462), immune mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). Six patients received systemic corticosteroids, and 5 of the 6 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients. *Immune mediated hepatitis* In the HCC pool (n=462), immune mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients. *Immune mediated colitis* In the HCC pool (n=462), immune mediated colitis or diarrhoea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients. Intestinal perforation was observed in patients receiving tremelimumab in combination with durvalumab (rare) in studies outside of the HCC pool. *Immune mediated endocrinopathies Immune-mediated hypothyroidism* In the HCC pool (n=462), immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapyincluding hormone replacement therapy . Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients. *Immune-mediated hyperthyroidism* In the HCC pool (n=462), immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic corticosteriods, and all of the four patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 patients. *Immune-mediated thyroiditis* In the HCC pool (n=462), immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy. Resolution occurred in 2 patients. *Immune-mediated adrenal insufficiency* In the HCC pool (n=462), immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 patients. *Immune-mediated type 1 diabetes mellitus* Immune-mediated type 1 diabetes mellitus was observed in patients receiving tremelimumab in combination with durvalumab (uncommon) in studies outside of the HCC pool. *Immune-mediated hypophysitis/hypopituitarism* In the HCC pool (n=462), immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients. *Immune mediated nephritis* In the HCC pool (n=462), immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 patients. Immune mediated rash In the HCC pool (n=462), immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patient. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 patients. Immunogenicity As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of tremelimumab is based on pooled data in 2075 patients who were treated with tremelimumab 75 mg or 1 mg/kg and evaluable for the presence of anti-drug antibodies (ADAs). Two-hundred fifty-two patients (12.1%) tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 10.0% (208/2075) patients. The presence of ADAs did not impact tremelimumab pharmacokinetics, and there was no apparent effect on efficacy and safety. In the HIMALAYA study, of the 182 patients who were treated with tremelimumab 300 mg as a single dose in combination with durvalumab and evaluable for the presence of ADAs against tremelimumab, 20 (11.0%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against tremelimumab were detected in 4.4% (8/182) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety. Elderly Data from HCCpatients 75 years of age or older are limited. 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: **Belgium** Federal Agency for Medicines and Health Products - FAMHP Department Vigilance, Postbus/Boîte Postale 97, 1000 BRUSSELS, Madou, Website: www.eenbijwerkingmelden.be / www.notifieruneffetindesirable.be, e-mail: adr@fagg.be / adr@afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy or Division de la pharmacie et des médicaments de la Direction de la santé, Site internet : www.guichet.lu/pharmacovigilance **5. MARKETING AUTHORISATION HOLDER** AstraZeneca AB, SE 151 85 Södertälje, Sweden **6. MARKETING AUTHORISATION NUMBER(S)** EU/1/22/1713/001 25 mg vial - EU/1/22/1713/002 300 mg vial **7. LEGAL STATUS DELIVERY** Medicinal product subject to medical prescription **8. DATE OF REVISION OF THE TEXT** 02/2023. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Ex-factory price excl. VAT
Price awaiting approval

ESSENTIAL INFORMATION. 1. NAME OF THE MEDICINAL PRODUCT. IMFINZI 50 mg/ml concentrate for solution for infusion. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION.** Each ml of concentrate for solution for infusion contains 50 mg of durvalumab. One vial of 2.4 ml of concentrate contains 120 mg of durvalumab. One vial of 10 ml of concentrate contains 500 mg of durvalumab. Durvalumab is produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology. For the full list of excipients, see section 'List of excipients' of the SmPC. **3. PHARMACEUTICAL FORM.** Concentrate for solution for infusion (sterile concentrate). Clear to opalescent, colourless to slightly yellow solution, free from visible particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 400 mOsm/kg. **4. CLINICAL PARTICULARS. 4.1 Therapeutic indications.** Non-Small Cell Lung Cancer (NSCLC). IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable non small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum based chemoradiation therapy (see section 'Pharmacodynamic properties' of the SmPC). IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. Small Cell Lung Cancer (SCLC). IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC). Biliary Tract Cancer (BTC). IMFINZI in combination with gemcitabine and cisplatin is indicated for the first line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). Hepatocellular Carcinoma (HCC). IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). **4.2 Posology and method of administration.** Treatment must be initiated and supervised by a physician experienced in the treatment of cancer. PD-L1 testing for patients with locally advanced NSCLC. Patients with locally advanced NSCLC should be evaluated for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 'Pharmacodynamic properties' of the SmPC). Posology. The recommended dose for IMFINZI monotherapy and IMFINZI combination therapy is presented in Table 1. IMFINZI is administered as an intravenous infusion over 1 hour. **Table 1. Recommended dose of IMFINZI monotherapy and combination therapy. Indication - Monotherapy: Locally Advanced NSCLC: Recommended IMFINZI dose:** 10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]; **Duration of therapy:** Until disease progression, unacceptable toxicity, or a maximum of 12 months[b]. **Indication - Combination therapy: Metastatic NSCLC: Recommended IMFINZI dose:** During platinum chemotherapy:1 500 mg[c] in combination with tremelimumab 75 mg[c,d] and platinum-based chemotherapy[e] every 3 weeks (21 days) for 4 cycles (12 weeks); Post-platinum chemotherapy: 1 500 mg every 4 weeks as monotherapy and histology-based pemetrexed maintenance[e,f] therapy every 4 weeks; A fifth dose of tremelimumab 75 mg[g,h] should be given at week 16 alongside IMFINZI; **Duration of therapy:** Until disease progression or unacceptable toxicity. **ES-SCLC: Recommended IMFINZI dose:** 1 500 mg[i] in combination with chemotherapy[e] every 3 weeks (21 days) for 4 cycles, followed by 1 500 mg every 4 weeks as monotherapy; **Duration of therapy:** Until disease progression or unacceptable toxicity. **BTC: Recommended IMFINZI dose:** 1 500 mg[j] in combination with chemotherapy[e] every 3 weeks (21 days) up to 8 cycles, followed by 1 500 mg every 4 weeks as monotherapy; **Duration of therapy:** Until disease progression or until unacceptable toxicity. **HCC: Recommended IMFINZI dose:** IMFINZI 1 500 mg[k] administered in combination with 300 mg[k] tremelimumab as a single dose at Cycle 1/Day 1, followed by IMFINZI as monotherapy every 4 weeks; **Duration of therapy:** Until disease progression or unacceptable toxicity. [a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg. [b] It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. [c] Metastatic NSCLC patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until weight is greater than 30 kg. Patients with a body weight of 34 kg or less must receive weight based dosing equivalent to tremelimumab 1 mg/kg until weight is greater than 34 kg. [d] When IMFINZI is administered in combination with tremelimumab and platinum-based chemotherapy, refer to the Summary of Product Characteristics (SmPC) for tremelimumab for dosing information. [e] When IMFINZI is administered in combination with chemotherapy, refer to the SmPC for etoposide, nab-paclitaxel, gemcitabine, pemetrexed and carboplatin or cisplatin for dosing information. [f] Consider maintenance administration of pemetrexed for patients with non-squamous tumours who received treatment with pemetrexed and carboplatin/cisplatin during the platinum-based chemotherapy stage. [g] In the case of dose delay(s), a fifth dose of tremelimumab can be given after Week 16, alongside IMFINZI. [h] If patients receive fewer than 4 cycles of platinum-based chemotherapy, the remaining cycles of tremelimumab (up to a total of 5) alongside IMFINZI should be given during the post-platinum chemotherapy phase. [i] ES-SCLC patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21 days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg. [j] BTC patients with a body weight of 36 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with chemotherapy dose every 3 weeks (21 days), followed by 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 36 kg. [k] HCC patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg until weight is greater than 30 kg. Patients with a body weight of 40 kg or less must receive weight-based dosing, equivalent to tremelimumab 4 mg/kg until weight is greater than 40 kg. Dose escalation or reduction is not recommended. Treatment withholding or discontinuation may be required based on individual safety and tolerability, see Table 2. Guidelines for management of immune-mediated adverse reactions are described in Table 2 (see section 'Special warnings and precautions for use' of the SmPC). When used in combination with tremelimumab refer also to the SmPC for tremelimumab. **Table 2. Treatment modifications and management recommendations for IMFINZI or IMFINZI in combination with tremelimumab [Adverse reactions/ Severity[a]/ Treatment modification/ Corticosteroid treatment unless otherwise specified]: Immune-mediated pneumonitis/interstitial lung disease:** Severity[a]: Grade 2; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 or 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated hepatitis:** Severity[a]: ALT or AST > 3 - ≤ 5 x ULN or total bilirubin > 1.5 - ≤ 3 x ULN; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 5 - ≤ 10 x ULN; Treatment modification: Withhold IMFINZI and permanently discontinue tremelimumab (where appropriate); Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[b]; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 10 x ULN or total bilirubin > 3 x ULN; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values)[c]:** Severity[a]: ALT or AST > 2.5 - ≤ 5 x BLV and ≤ 20 x ULN; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 5 - 7 x BLV and ≤ 20 x ULN or concurrent ALT or AST 2.5 - 5 x BLV and ≤ 20 x ULN and total bilirubin > 1.5 - < 2 x ULN[b]; Treatment modification: Withhold IMFINZI and permanently discontinue tremelimumab (where appropriate); Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: ALT or AST > 7 x BLV or > 20 ULN whichever occurs first or bilirubin > 3 X ULN; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated colitis or diarrhoea:** Severity[a]: Grade 2; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 for IMFINZI monotherapy; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 for IMFINZI + tremelimumab; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Intestinal perforation[d]:** Severity[a]: Any grade; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Consult a surgeon immediately if an intestinal perforation is suspected. **Immune-mediated hyperthyroidism, thyroiditis:** Severity[a]: Grade 2-4; Treatment modification: Withhold dose until clinically stable; Corticosteroid treatment unless otherwise specified: Symptomatic treatment, see section 'Undesirable effects'. **Immune-mediated hypothyroidism:** Severity[a]: Grade 2-4; Treatment modification: No changes; Corticosteroid treatment unless otherwise specified: Initiate thyroid hormone replacement as clinically indicated. **Immune-mediated adrenal insufficiency or hypophysitis/hypopituitarism:** Severity[a]: Grade 2-4; Treatment modification: Withhold dose until clinically stable; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated. **Immune-mediated type 1 diabetes mellitus:** Severity[a]: Grade 2-4; Treatment modification: No changes; Corticosteroid treatment unless otherwise specified: Initiate treatment with insulin as clinically indicated. **Immune-mediated nephritis:** Severity[a]: Grade 2 with serum creatinine > 1.5 - 3 x (ULN or baseline); Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 with serum creatinine > 3 x baseline or > 3 6 x ULN; Grade 4 with serum creatinine > 6 x ULN; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated rash or dermatitis (including pemphigoid):** Severity[a]: Grade 2 for > 1 week; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated myocarditis:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 2 to 4 mg/kg/day prednisone or equivalent followed by a taper[e]. **Immune-mediated myositis/polymyositis:** Severity[a]: Grade 2 or 3; Treatment modification: Withhold dose[f]; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Infusion-related reactions:** Severity[a]: Grade 1 or 2; Treatment modification: Interrupt or slow the rate of infusion; Corticosteroid treatment unless otherwise specified: May consider pre medications for prophylaxis of subsequent infusion reactions; Severity[a]: Grade 3 or 4; Treatment modification: Permanently discontinue. **Infection:** Severity[a]: Grade 3 or 4; Treatment modification: Withhold dose until clinically stable. **Immune-mediated myasthenia gravis:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated Myelitis transverse:** Severity[a]: Any grade; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated meningitis:** Severity[a]: Grade 2; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 3 or 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated encephalitis:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Immune-mediated Guillain-Barré syndrome:** Severity[a]: Grade 2-4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Other immune-mediated adverse reactions:** Severity[a]: Grade 2 or 3; Treatment modification: Withhold dose; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper; Severity[a]: Grade 4; Treatment modification: Permanently discontinue; Corticosteroid treatment unless otherwise specified: Initiate 1 to 2 mg/kg/day prednisone or equivalent followed by a taper. **Non-immune-mediated adverse reactions:** Severity[a]: Grade 2 and 3; Treatment modification: Withhold dose until ≤ Grade 1 or return to baseline; Severity[a]: Grade 4; Treatment modification: Permanently discontinue[g]. [a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value. [b] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations. [c] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement. [d] Adverse drug reaction is only associated with IMFINZI in combination with tremelimumab. [e] If no improvement within 2 to 3 days despite corticosteroids, promptly start additional immunosuppressive therapy. Upon resolution (Grade 0), corticosteroid taper should be initiated and continued over at least 1 month. [f] Permanently discontinue IMFINZI if adverse reaction does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency. [g] With the exception of Grade 4 laboratory abnormalities, about which the decision to discontinue should be based on accompanying clinical signs/symptoms and clinical judgment. For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. Based on the severity of the adverse reaction, IMFINZI and/or tremelimumab should be withheld and corticosteroids administered. Increasing dose of corticosteroids and/or using additional systemic immunosuppressants should be considered if there is worsening or no improvement. Upon improvement to ≤ Grade 1, corticosteroid taper should be initiated and continued over at least 1 month. After withhold, IMFINZI and/or tremelimumab can be resumed within 12 weeks if the adverse reactions improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. IMFINZI and tremelimumab should be permanently discontinued for recurrent Grade 3 (severe) immune-mediated adverse reactions and for any Grade 4 (life-threatening) immune-mediated adverse reactions, except for endocrinopathies that are controlled with replacement hormones. *Special populations. Elderly.* No dose adjustment is required for elderly patients (≥ 65 years of age) (see section 'Pharmacodynamic properties' of the SmPC). *Renal impairment.* No dose adjustment of IMFINZI is recommended in patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 'Pharmacokinetic properties' of the SmPC). *Hepatic impairment.* No dose adjustment of IMFINZI is recommended for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to draw conclusions on this population (see section 'Pharmacokinetic properties' of the SmPC). *Paediatric population.* The safety and efficacy of IMFINZI in children and adolescents aged below 18 years of age have not been established. No data are available. Method of administration. IMFINZI is for intravenous use. It is to be administered as an intravenous infusion solution over 1 hour (see section 'Special precautions for disposal and other handling' of the SmPC). For instructions on dilution of the medicinal product before administration, see section 'Special precautions for disposal and other handling' of the SmPC. *IMFINZI in combination with chemotherapy.* When IMFINZI is administered in combination with chemotherapy, administer IMFINZI prior to chemotherapy on the same day. *IMFINZI in combination with tremelimumab and platinum-based chemotherapy.* When IMFINZI is administered in combination with tremelimumab and platinum-based chemotherapy, tremelimumab is given first, followed by IMFINZI and then platinum-based chemotherapy on the same day of dosing. When IMFINZI is administered in combination with a fifth dose of tremelimumab and pemetrexed maintenance therapy at week 16, tremelimumab is given first, followed by IMFINZI and then pemetrexed maintenance therapy on the same day of dosing. IMFINZI, tremelimumab, and platinum-based chemotherapy are administered as separate intravenous infusions. IMFINZI and tremelimumab are each given over 1 hour. For platinum-based chemotherapy, refer to the SmPC for administration information. For pemetrexed maintenance therapy, refer to the SmPC for administration information. Separate infusion bags and filters for each infusion should be used. During cycle 1, tremelimumab is to be followed by IMFINZI starting approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Platinum-based chemotherapy infusion should start approximately 1 hour (maximum 2 hours) after the end of the IMFINZI infusion. If there are no clinically significant concerns during cycle 1, then at the physician's discretion, subsequent cycles of IMFINZI can be given immediately after tremelimumab and the time period between the end of the IMFINZI infusion and the start of chemotherapy can be reduced to 30 minutes. *IMFINZI in combination with tremelimumab.* When IMFINZI is administered in combination with tremelimumab, administer tremelimumab prior to IMFINZI on the same day. IMFINZI and tremelimumab are administered as separate intravenous infusions. Refer to the SmPC for tremelimumab dosing information. **4.3 Contraindications.** Hypersensitivity to the active substance(s) or to any of the excipients listed in section 'List of excipients' of the SmPC. **4.4 Undesirable effects.** Summary of the safety profile. *IMFINZI as monotherapy.* The safety of IMFINZI as monotherapy is based on pooled data in 3 006 patients across multiple tumour types. IMFINZI was administered at a dose of 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks. The most common (> 10%) adverse reactions were cough/productive cough (21.5%), diarrhoea (16.3%), rash (16.0%), pyrexia (13.8%), upper respiratory tract infections (13.5%), abdominal pain (12.7%), pruritus (10.8%), and hypothyroidism (10.1%). The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were pneumonia (3.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.3%). IMFINZI was discontinued due to adverse reactions in 3.6% of patients. The most common adverse reaction leading to treatment discontinuation was pneumonitis (1.1%) and pneumonia (0.8%). IMFINZI was delayed or interrupted due to adverse reactions in 13.7% of patients. The most common adverse reactions leading to dose delay or interruption were pneumonia (2.7%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.7%). *IMFINZI in combination with chemotherapy.* The safety of IMFINZI in combination with chemotherapy is based on pooled data in 603 patients from 2 studies (TOPAZ-1 and CASPIAN). The most common (> 10%) adverse reactions were neutropenia (53.1%), anaemia (43.9%), nausea (37.5%), fatigue (36.8%), thrombocytopenia (28.0%), constipation (25.4%), decreased appetite (22.6%), abdominal pain (18.4%), alopecia (18.4%), leukopenia (17.2%), vomiting (16.9%), pyrexia (15.1%), rash (14.8%), diarrhoea (13.8%), aspartate aminotransferase increased or alanine aminotransferase increased (10.9%), cough/productive cough (10.8%), and pruritus (10.4%).The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (35.2%), anaemia (17.4%), thrombocytopenia (11.1%), leukopenia (7.1%), fatigue (5.0%), febrile neutropenia (3.0%), aspartate aminotransferase increased or alanine aminotransferase increased (2.8%) and pneumonia (2.5%). IMFINZI was discontinued due to adverse reactions in 2.0% of patients. The most common adverse reaction leading to treatment discontinuation was fatigue (0.3%). IMFINZI was delayed or interrupted due to adverse reactions in 29.2% of patients. The most common adverse reactions leading to dose delay or interruption were neutropenia (17.1%), anaemia (3.8%), thrombocytopenia (4.3%), leukopenia (3.5%), fatigue (1.7%) and pyrexia (1.3). *IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy.* The safety of IMFINZI given in combination with tremelimumab 75 mg and chemotherapy is based on data in 330 patients with metastatic NSCLC. The most common (> 20%) adverse reactions were anaemia (49.7%), nausea (41.5%), neutropenia (41.2%), fatigue (36.1%), rash (25.8%), thrombocytopenia (24.5%) and diarrhoea (21.5%). The most common (> 2%) NCI CTCAE Grade ≥ 3 adverse reactions were neutropenia (23.9%), anaemia (20.6%), pneumonia (9.4%), thrombocytopenia (8.2%), leukopenia (5.5%), fatigue (5.2%), lipase increased (3.9%), amylase increased (3.6%), febrile neutropenia (2.4%), colitis (2.1%) and aspartate aminotransferase increased/alanine aminotransferase increased (2.1%). IMFINZI was discontinued due to adverse reactions in 8.5% of patients. The most common adverse reactions leading to treatment discontinuation were pneumonia (2.1%) and colitis (1.2%). IMFINZI was interrupted due to adverse reactions in 49.4% of patients. The most common adverse reactions leading to dose interruption were neutropenia (16.1%), anaemia (10.3%), thrombocytopenia (7.3%), leukopenia (5.8%), pneumonia (5.2%), aspartate aminotransferase increased/alanine aminotransferase increased (4.8%), colitis (3.3%) and pneumonitis (3.3%). *IMFINZI in combination with tremelimumab 300 mg.* The safety of IMFINZI given in combination with a single dose of tremelimumab 300 mg is based on pooled data (HCC pool) in 462 HCC patients from the HIMALAYA Study and another study in HCC patients, Study 22. The most common (> 10%) adverse reactions were rash (32.5%), pruritus (25.5%), diarrhoea (25.3%), abdominal pain (19.7%), aspartate aminotransferase increased/alanine aminotransferase increased (18.0%), pyrexia (13.9%), hypothyroidism (13.0%), cough/productive cough (10.8%), oedema peripheral (10.4%) and lipase increased (10.0%) (see Table 4). The most common severe adverse reactions (NCI CTCAE Grade ≥ 3) were aspartate aminotransferase increased/alanine aminotransferase increased (8.9%), lipase increased (7.1%), amylase increased (4.3%) and diarrhoea (3.9%). The most common serious adverse reactions were colitis (2.6%), diarrhoea (2.4%), pneumonia (2.2%), and hepatitis (1.7%). The frequency of treatment discontinuation due to adverse reactions was 6.5%. The most common adverse reactions leading to treatment discontinuation were hepatitis (1.5%) and aspartate aminotransferase increased/alanine aminotransferase increased (1.3%). The severity of adverse drug reactions was assessed based on the CTCAE, defining grade 1=mild, grade 2=moderate, grade 3=severe, grade 4=life threatening and grade 5=death. Tabulated list of adverse reactions. Table 3 lists the incidence of adverse reactions in the IMFINZI monotherapy pooled safety dataset (N=3 006) and in patients treated with IMFINZI in combination with chemotherapy (N=603). Unless otherwise stated, Table 4 lists the incidence of adverse reactions in patients treated with IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy in the POSEIDON study (N=330) and in patients treated with IMFINZI in combination with a single dose of tremelimumab 300 mg in the HCC pool (N=462). Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse reactions are presented in decreasing frequency. The corresponding frequency category for each ADR is 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); not known (cannot be estimated from available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. **Table 3. Adverse drug reactions in patients treated with IMFINZI [IMFINZI as monotherapy / IMFINZI in combination with chemotherapy]. Infections and infestations:** Very common: [IMFINZI as monotherapy:] Upper respiratory tract infections[a]. Common: [IMFINZI as monotherapy:] Pneumonia[b,c], Influenza, Oral candidiasis, Dental and oral soft tissue infections[d] / [IMFINZI in combination with chemotherapy:] Pneumonia[b,c], Upper respiratory tract infections[a]. Uncommon: [IMFINZI in combination with chemotherapy:] Oral candidiasis, Influenza, Dental and oral soft tissue infections[d]. **Blood and lymphatic system disorders:** Very Common: [IMFINZI in combination with chemotherapy:] Anaemia, Leukopenia[f], Neutropenia[f], Thrombocytopenia[dd]. Common: [IMFINZI in combination with chemotherapy:] Febrile neutropenia, Pancytopenia[c]. Rare: [IMFINZI as monotherapy:] Immune thrombocytopenia[z]. **Endocrine disorders:** Very common: [IMFINZI as monotherapy:] Hypothyroidism[e]. Common: [IMFINZI as monotherapy:] Hyperthyroidism[z] / [IMFINZI in combination with chemotherapy:] Adrenal insufficiency, Hyperthyroidism[z], Hypothyroidism[e]. Uncommon: [IMFINZI as monotherapy:] Thyroiditis[a], Adrenal insufficiency / [IMFINZI in combination with chemotherapy:] Thyroiditis[a], Type 1 diabetes mellitus. Rare: [IMFINZI as monotherapy:] Type 1 diabetes mellitus, Hypophysitis/Hypopituitarism, Diabetes insipidus. **Metabolism and nutrition disorders:** Very common: [IMFINZI in combination with chemotherapy:] Decreased appetite. **Nervous System Disorders:** Common: [IMFINZI in combination with chemotherapy:] Neuropathy peripheral[e]. Rare: [IMFINZI as monotherapy:] Myasthenia gravis[b], Meningitis[c]. Not known: [IMFINZI as monotherapy:] Noninfective encephalitis[z], Guillain-Barré syndrome, Myelitis transverse[aa]. **Cardiac disorders:** Rare: [IMFINZI as monotherapy:] Myocarditis. **Respiratory, thoracic and mediastinal disorders:** Very common: [IMFINZI as monotherapy:] Cough/Productive Cough / [IMFINZI in combination with chemotherapy:] Cough/Productive Cough. Common: [IMFINZI as monotherapy:] Pneumonitis[c], Dysphonia / [IMFINZI in combination with chemotherapy:] Pneumonitis. Uncommon: [IMFINZI as monotherapy:] Interstitial lung disease / [IMFINZI in combination with chemotherapy:] Interstitial lung disease, Dysphonia. **Gastrointestinal disorders:** Very common: [IMFINZI as monotherapy:] Diarrhoea, Abdominal pain[x] / [IMFINZI in combination with chemotherapy:] Diarrhoea, Abdominal pain[x], Constipation, Nausea, Vomiting. Common: [IMFINZI in combination with chemotherapy:] Stomatitis[v]. Uncommon: [IMFINZI as monotherapy:] Colitis[z], Pancreatitis[m] / [IMFINZI in combination with chemotherapy:] Colitis[z], Pancreatitis[m]. **Hepatobiliary disorders:** Very common: [IMFINZI in combination with chemotherapy:] Aspartate aminotransferase increased or Alanine aminotransferase increased[n]. Common: [IMFINZI as monotherapy:] Aspartate aminotransferase increased or Alanine aminotransferase increased[c,n] / [IMFINZI in combination with chemotherapy:] Hepatitis[c,o]. Uncommon: [IMFINZI as monotherapy:] Hepatitis[c,o]. **Skin and subcutaneous tissue disorders:** Very common: [IMFINZI as monotherapy:] Rash[p], Pruritus / [IMFINZI in combination with chemotherapy:] Rash[p], Alopecia, Pruritus. Common: [IMFINZI as monotherapy:] Night sweats / [IMFINZI in combination with chemotherapy:] Dermatitis. Uncommon: [IMFINZI as monotherapy:] Dermatitis, Psoriasis / [IMFINZI in combination with chemotherapy:] Pemphigoid[q], Night sweats, Psoriasis. Rare: [IMFINZI as monotherapy:] Pemphigoid[q]. **Musculoskeletal and connective tissue disorders:** Very common: [IMFINZI as monotherapy:] Arthralgia. Common: [IMFINZI as monotherapy:] Myalgia / [IMFINZI in combination with chemotherapy:] Myalgia, Arthralgia. Uncommon: [IMFINZI as monotherapy:] Myositis. Rare: [IMFINZI as monotherapy:] Polymyositis[r]. **Renal and urinary disorders:** Common: [IMFINZI as monotherapy:] Blood creatinine increased, Dysuria / [IMFINZI in combination with chemotherapy:] Blood creatinine increased, Dysuria. Uncommon: [IMFINZI as monotherapy:] Nephritis[s]. Rare: [IMFINZI as monotherapy:] Cystitis noninfective. **General disorders and administration site conditions:** Very common: [IMFINZI as monotherapy:] Pyrexia / [IMFINZI in combination with chemotherapy:] Pyrexia, Fatigue[w]. Common: [IMFINZI as monotherapy:] Peripheral oedema[t] / [IMFINZI in combination with chemotherapy:] Peripheral oedema[t]. **Injury, poisoning and procedural complications:** Common: [IMFINZI as monotherapy:] Infusion-related reaction[u] / [IMFINZI in combination with chemotherapy:] Infusion-related reaction[u]. Adverse reaction frequencies may not be fully attributed to durvalumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination. [a] includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection. [b] includes pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal, pneumonia streptococcal, candida pneumonia and pneumonia legionella. [c] including fatal outcome. [d] includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection. [e] includes autoimmune hypothyroidism, hypothyroidism, immune-mediated hypothyroidism, blood thyroid stimulating hormone increased. [f] includes hyperthyroidism, Basedow's disease, immune-mediated hyperthyroidism and blood thyroid stimulating hormone decreased. [g] includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute. [h] reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare, with no events at Grade > 2. [i] includes meningitis and noninfective meningitis. [j] reported frequency from ongoing AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare and includes two events of encephalitis, one was Grade 5 fatal (immune-mediated encephalitis) and one was Grade 2 (autoimmune encephalitis). [k] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain. [l] includes colitis, enteritis, enterocolitis, and proctitis. [m] includes pancreatitis and pancreatitis acute. [n] includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased. [o] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatic cytolysis, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis. [p] includes rash erythematous, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash. [q] includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing studies is uncommon. [r] polymyositis (fatal) was observed in a patient treated with IMFINZI from an ongoing sponsored clinical study outside of the pooled dataset: rare in any grade, rare in Grade 3 or 4 or 5. [s] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous. [t] includes oedema peripheral and peripheral swelling. [u] includes infusion-related reaction and urticaria with onset on the day of dosing or 1 day after dosing. [v] includes stomatitis and mucosal inflammation. [w] includes fatigue and asthenia. [x] includes neuropathy peripheral, paraesthesia and peripheral sensory neuropathy. [y] includes leukopenia and white blood cell count decreased. [z] includes neutropenia and neutrophil count decreased. [aa] includes thrombocytopenia and platelet count decreased. [bb] events were reported from post-marketing data. **Table 4. Adverse drug reactions in patients treated with IMFINZI in combination with tremelimumab [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy / IMFINZI in combination with tremelimumab 300 mg]. Infections and infestations:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Upper respiratory tract infections[a], Pneumonia[b]. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Influenza, Oral candidiasis / [IMFINZI in combination with tremelimumab 300 mg:] Upper respiratory tract infections[a], Pneumoniab, Influenza, Dental and oral soft tissue infections[c]. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Dental and oral soft tissue infections[c] / [IMFINZI in combination with tremelimumab 300 mg:] Oral candidiasis. **Blood and lymphatic system disorders:** Very Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Anaemia[d], Neutropenia[d,e], Thrombocytopenia[d,f], Leukopenia[d,g]. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Febrile neutropenia[d], Pancytopenia[d]. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Immune thrombocytopenia. Not known: [IMFINZI in combination with tremelimumab 300 mg:] Immune thrombocytopenia[h]. **Endocrine disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Hypothyroidism[i] / [IMFINZI

Ex-factory price excl. VAT		Reimbursed
500 mg/10 ml	€2.487,69	100%
120 mg/2,4 ml	€597,05	

in combination with tremelimumab 300 mg:] Hypothyroidism[r]. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Hyperthyroidism[r], Adrenal insufficiency, Hypopituitarism/ Hypophysitis, Thyroiditis[k] / [IMFINZI in combination with tremelimumab 300 mg:] Hyperthyroidism[r], Thyroiditis[k], Adrenal insufficiency. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Diabetes insipidus, Type 1 diabetes mellitus / [IMFINZI in combination with tremelimumab 300 mg:] Hypopituitarism/Hypophysitis. Not known: [IMFINZI in combination with tremelimumab 300 mg:] Diabetes insipidus[h], Type 1 diabetes mellitus[h]. **Metabolism and nutrition disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Decreased appetite[d]. **Nervous system disorders:** Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Neuropathy peripheral[d,l] / Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Encephalitis[m] / [IMFINZI in combination with tremelimumab 300 mg:] Myasthenia gravis, Meningitis. Not known: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Myasthenia gravis[n], Guillain-Barre syndrome[n], Meningitis[n] / [IMFINZI in combination with tremelimumab 300 mg:] Guillain-Barré syndrome[n], Encephalitis[n]. **Cardiac disorders:** Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Myocarditis[o] / [IMFINZI in combination with tremelimumab 300 mg:] Myocarditis. **Respiratory, thoracic, and mediastinal disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Cough/ Productive Cough / [IMFINZI in combination with tremelimumab 300 mg:] Cough/Productive cough. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Pneumonitis[p], Dysphonia / [IMFINZI in combination with tremelimumab 300 mg:] Pneumonitis[p]. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Interstitial lung disease / [IMFINZI in combination with tremelimumab 300 mg:] Dysphonia, Intersitial lung disease. **Gastrointestinal disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Nausea[d], Diarrhoea, Constipation[d], Vomiting[d] / [IMFINZI in combination with tremelimumab 300 mg:] Diarrhoea, Abdominal pain[q]. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Stomatitis[d,r], Amylase increased[m], Abdominal pain[q], Lipase increased[m], Colitis[s], Pancreatitis[t] / [IMFINZI in combination with tremelimumab 300 mg:] Lipase increased, Amylase increased, Colitis[s], Pancreatitis[t]. Not known: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Intestinal perforation[n], Large intestine perforation[n] / [IMFINZI in combination with tremelimumab 300 mg:] Intestinal perforation[h], Large intestinal perforation[h]. **Hepatobiliary disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Aspartate aminotransferase increased/Alanine aminotransferase increased[u] / [IMFINZI in combination with tremelimumab 300 mg:] Aspartate aminotransferase increased/Alanine aminotransferase increased[u]. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Hepatitis[v] / [IMFINZI in combination with tremelimumab 300 mg:] Hepatitis[v]. **Skin and subcutaneous tissue disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Alopecia[d], Rash[w], Pruritus / [IMFINZI in combination with tremelimumab 300 mg:] Rash[w], Pruritus. Common: [IMFINZI in combination with tremelimumab 300 mg:] Dermatitis[x], Night sweats. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Dermatitis, Night sweats, Pemphigoid / [IMFINZI in combination with tremelimumab 300 mg:] Pemphigoid. **Musculoskeletal and connective tissue disorders:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Arthralgia. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Myalgia / [IMFINZI in combination with tremelimumab 300 mg:] Myalgia. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Myositis, Polymyositis / [IMFINZI in combination with tremelimumab 300 mg:] Myositis, Polymyositis. **Renal and urinary disorders:** Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Blood creatinine increased, Dysuria / [IMFINZI in combination with tremelimumab 300 mg:] Blood creatinine increased, Dysuria. Uncommon: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Nephritis, Cystitis noninfective / [IMFINZI in combination with tremelimumab 300 mg:] Nephritis[y]. Not known: [IMFINZI in combination with tremelimumab 300 mg:] Cystitis noninfective[h]. **General disorders and administration site conditions:** Very common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Fatigue[d], Pyrexia / [IMFINZI in combination with tremelimumab 300 mg:] Pyrexia, Oedema peripheral[z]. Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Oedema peripheral[z]. **Injury, poisoning and procedural complications:** Common: [IMFINZI in combination with tremelimumab 75 mg and platinum-based chemotherapy:] Infusion-related reaction[aa] / [IMFINZI in combination with tremelimumab 300 mg:] Infusion-related reaction[aa]. [a] Includes laryngitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection. [b] Includes pneumocystis jirovecii pneumonia, pneumonia and pneumonia bacterial. [c] Includes periodontitis, pulpitis dental, tooth abscess and tooth infection. [d] Adverse reaction only applies to chemotherapy ADRs in the Poseidon study. [e] Includes neutropenia and neutrophil count decreased. [f] Includes platelet count decreased and thrombocytopenia. [g] Includes leukopenia and white blood cell count decreased. [h] Adverse reaction was not observed in the HCC pool, but was reported in patients treated with IMFINZI or IMFINZI+tremelimumab in AstraZeneca-sponsored clinical studies. [i] Includes blood thyroid stimulating hormone increased, hypothyroidism and immune-mediated hypothyroidism. [j] Includes blood thyroid stimulating hormone decreased and hyperthyroidism. [k] Includes autoimmune thyroiditis, immune-mediated thyroiditis, thyroiditis and thyroiditis subacute. [l] Includes neuropathy peripheral, parasthesia and peripheral sensory neuropathy. [m] Includes encephalitis and encephalitis autoimmune. [n] Adverse reaction was not observed in the POSEIDON study but was reported in patients treated with IMFINZI or IMFINZI+tremelimumab in clinical studies outside of the POSEIDON dataset. [o] Includes autoimmune myocarditis. [p] Includes immune-mediated pneumonitis and pneumonitis. [q] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain. [r] Includes mucosal inflammation and stomatitis. [s] Includes colitis, enteritis and enterocolitis. [t] Includes autoimmune pancreatitis, pancreatitis and pancreatitis acute. [u] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased and transaminases increased. [v] Includes autoimmune hepatitis, hepatitis, hepatocellular injury, hepatotoxicity, hepatitis acute and immune-mediated hepatitis. [w] Includes eczema, erythema, rash, rash macular, rash maculopapular, rash papular, rash pruritic and rash pustular. [x] Includes dermatitis and immune-mediated dermatitis. [y] Includes autoimmune nephritis and immune-mediated nephritis. [z] Includes oedema peripheral and peripheral swelling. [aa] Includes infusion-related reaction and urticaria. Description of selected adverse reactions. IMFINZI is associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy and/or treatment modifications. The data for the following immune-mediated adverse reactions reflect the IMFINZI monotherapy combined safety database of 3 006 patients which includes the PACIFIC Study and additional studies in patients with various solid tumours, in indications for which durvalumab is not approved. Across all studies, IMFINZI was administered at a dose of 10 mg/kg every 2 weeks, 20 mg/kg every 4 weeks or 1 500 mg every 3 or 4 weeks. Details for the significant adverse reactions for IMFINZI when given in combination with chemotherapy are presented if clinically relevant differences were noted in comparison to IMFINZI monotherapy. The data for the following immune-mediated adverse reactions are also based on 2 280 patients who received IMFINZI 20 mg/kg every 4 weeks in combination with tremelimumab 1 mg/kg or IMFINZI 1 500 mg in combination with tremelimumab 75 mg every 4 weeks. Details for the significant adverse reactions for IMFINZI when given in combination with tremelimumab and platinum-based chemotherapy are presented if clinically relevant differences were noted in comparison to IMFINZI in combination with tremelimumab. The data for the following immune-mediated adverse reactions also reflect the IMFINZI in combination with tremelimumab 300 mg combined safety database of 462 patients with HCC (the HCC pool). In these two studies, IMFINZI was administered at a dose of 1 500 mg in combination with tremelimumab 300 mg every 4 weeks. The management guidelines for these adverse reactions are described in section 'Posology and method of administration' and 'Special warnings and precautions for use' of the SmPC. *Immune-mediated pneumonitis.* In the combined safety database with IMFINZI monotherapy, (n=3 006 multiple tumour types), immune-mediated pneumonitis occurred in 92 (3.1%) patients, including Grade 3 in 25 (0.8%) patients, Grade 4 in 2 (< 0.1%) patients and Grade 5 in 6 (0.2%) patients. The median time to onset was 55 days (range: 2-785 days). Sixty-nine of the 92 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), 2 patients also received infliximab and 1 patient also received cyclosporine. IMFINZI was discontinued in 38 patients. Resolution occurred in 53 patients. Immune-mediated pneumonitis occurred more frequently in patients in the PACIFIC Study who had completed treatment with concurrent chemoradiation within 1 to 42 days prior to initiation of the study (9.9%), than in the other patients in the combined safety database (1.8%). In the PACIFIC Study, (n=475 in the IMFINZI arm, and n=234 in the placebo arm) immune-mediated pneumonitis occurred in 47 (9.9%) patients in the IMFINZI treated group and 14 (6.0%) patients in the placebo group, including Grade 3 in 9 (1.9%) patients on IMFINZI vs. 6 (2.6%) patients on placebo and Grade 5 (fatal) in 4 (0.8%) patients on IMFINZI vs. 3 (1.3%) patients on placebo. The median time to onset in the IMFINZI treated group was 46 days (range: 2-342 days) vs. 57 days (range: 26-253 days) in the placebo group. In the IMFINZI treated group, all patients received systemic corticosteroids, including 30 patients who received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 2 patients also received infliximab. In the placebo group, all patients received systemic corticosteroids, including 12 patients who received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received cyclophosphamide and tacrolimus. Resolution occurred for 29 patients in the IMFINZI treated group vs. 6 in placebo. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated pneumonitis occurred in 86 (3.8%) patients, including Grade 3 in 30 (1.3%) patients, Grade 4 in 1 (< 0.1%) patient, and Grade 5 (fatal) in 7 (0.3%) patients. The median time to onset was 57 days (range: 8 - 912 days). All patients received systemic corticosteroids and 79 of the 86 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Seven patients also received other immunosuppressants. Treatment was discontinued in 39 patients. Resolution occurred in 51 patients. In the HCC pool (n=462), immune-mediated pneumonitis occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient and Grade 5 (fatal) in 1 (0.2%) patient. The median time to onset was 29 days (range: 5-774 days). Six patients received systemic corticosteroids, and 5 of the 6 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received other immunosuppressants. Treatment was discontinued in 2 patients. Resolution occurred in 3 patients. *Immune-mediated hepatitis.* In the combined safety database with IMFINZI monotherapy, immune-mediated hepatitis occurred in 68 (2.3%) patients, including Grade 3 in 35 (1.2%) patients, Grade 4 in 6 (0.2%) patients and Grade 5 (fatal) in 4 (0.1%) patients. The median time to onset was 33 days (range: 3-333 days). Forty-five of the 68 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 31 patients. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated hepatitis occurred in 80 (3.5%) patients, including Grade 3 in 48 (2.1%) patients, Grade 4 in 8 (0.4%) patients and Grade 5 (fatal) in 2 (< 0.1%) patients. The median time to onset was 36 days (range: 1 - 533 days). All patients received systemic corticosteroids and 68 of the 80 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Eight patients also received other immunosuppressants. Treatment was discontinued in 27 patients. Resolution occurred in 47 patients. In the HCC pool (n=462), immune-mediated hepatitis occurred in 34 (7.4%) patients, including Grade 3 in 20 (4.3%) patients, Grade 4 in 1 (0.2%) patient and Grade 5 (fatal) in 3 (0.6%) patients. The median time to onset was 29 days (range: 13-313 days). All patients received systemic corticosteroids, and 32 of the 34 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Nine patients also received other immunosuppressants. Treatment was discontinued in 10 patients. Resolution occurred in 13 patients. *Immune-mediated colitis.* In the combined safety database with IMFINZI monotherapy, immune-mediated colitis or diarrhoea occurred in 58 (1.9%) patients, including Grade 3 in 9 (0.3%) patients and Grade 4 in 2 (< 0.1%) patients. The median time to onset was 70 days (range: 1-394 days). Thirty-eight of the 58 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient also received infliximab treatment and 1 patient also received mycophenolate. IMFINZI was discontinued in 9 patients. Resolution occurred in 43 patients. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated colitis or diarrhoea occurred in 167 (7.3%) patients, including Grade 3 in 76 (3.3%) patients and Grade 4 in 3 (0.1%) patients. The median time to onset was 57 days (range: 3 - 906 days). All patients received systemic corticosteroids and 151 of the 167 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty-two patients also received other immunosuppressants. Treatment was discontinued in 54 patients. Resolution occurred in 141 patients. Intestinal perforation and large intestine perforation were uncommonly reported in patients receiving IMFINZI in combination with tremelimumab. In the HCC pool (n=462), immune-mediated colitis or diarrhoea occurred in 31 (6.7%) patients, including Grade 3 in 17 (3.7%) patients. The median time to onset was 23 days (range: 2-479 days). All patients received systemic corticosteroids, and 28 of the 31 patients received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also received other immunosuppressants. Treatment was discontinued in 5 patients. Resolution occurred in 29 patients. Intestinal perforation was observed in patients receiving IMFINZI in combination with tremelimumab (rare) in studies outside of the HCC pool. *Immune-mediated endocrinopathies. Immune-mediated hypothyroidism.* In the combined safety database with IMFINZI monotherapy, immune-mediated hypothyroidism occurred in 245 (8.2%) patients, including Grade 3 in 4 (0.1%) patients. The median time to onset was 85 days (range: 1-562 days). Of the 245 patients, 240 patients received hormone replacement therapy and 6 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism. No patients discontinued IMFINZI due to immune-mediated hypothyroidism. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated hypothyroidism occurred in 209 (9.2%) patients, including Grade 3 in 6 (0.3%) patients. The median time to onset was 85 days (range: 1-624 days). Thirteen patients received systemic corticosteroids and 8 of the 13 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment discontinued in 3 patients. Resolution occurred in 52 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 25 patients or immune-mediated thyroiditis in 2 patients. In the HCC pool (n=462), immune-mediated hypothyroidism occurred in 46 (10.0%) patients. The median time to onset was 85 days (range: 26-763 days). One patient received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy. Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients. *Immune-mediated hyperthyroidism.* In the combined safety database with IMFINZI monotherapy, immune-mediated hyperthyroidism occurred in 50 (1.7%) patients, there were no Grade 3 or 4 cases. The median time to onset was 43 days (range: 1-196 days). Forty-six of the 50 patients received medical therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker or beta-blocker), 11 patients received systemic corticosteroids and 4 of the 11 patients received high-dose systemic corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated hyperthyroidism. Resolution occurred in 39 patients. Twenty patients experienced hypothyroidism following hyperthyroidism. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated hyperthyroidism occurred in 62 (2.7%) patients, including Grade 3 in 5 (0.2%) patients. The median time to onset was 33 days (range: 4-176 days). Eighteen patients received systemic coticosteroids, and 11 of the 18 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Fifty-three patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker or beta-blocker), One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 47 patients. In the HCC pool (n=462), immune-mediated hyperthyroidism occurred in 21 (4.5%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 30 days (range: 13-60 days). Four patients received systemic corticosteriods, and all of the four patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Twenty patients required other therapy (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). One patient discontinued treatment due to hyperthyroidism. Resolution occurred in 17 patients. *Immune-mediated thyroiditis.* In the combined safety database with IMFINZI monotherapy, immune-mediated thyroiditis occurred in 12 (0.4%) patients, including Grade 3 in 2 (< 0.1%) patients. The median time to onset was 49 days (range: 14-106 days). Of the 12 patients, 10 patients received hormone replacement therapy and 1 patient received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated thyroiditis. Three patients experienced hypothyroidism following thyroiditis. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated thyroiditis occurred in 15 (0.7%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 57 days (range: 22-141 days). Five patients received systemic corticosteroids and 2 of the 5 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Thirteen patients required other therapy including, hormone replacement therapy, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. No patients discontinued treatment due to immune-mediated thyroiditis. Resolution occurred in 5 patients. In the HCC pool (n=462), immune-mediated thyroiditis occurred in 6 (1.3%) patients. The median time to onset was 56 days (range: 7-84 days). Two patients received systemic corticosteroids, and 1 of the 2 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). All patients required other therapy including hormone replacement therapy. Resolution occurred in 2 patients. *Immune-mediated adrenal insufficiency.* In the combined safety database with IMFINZI monotherapy, immune-mediated adrenal insufficiency occurred in 14 (0.5%) patients, including Grade 3 in 3 (< 0.1%) patients. The median time to onset was 146 days (range: 20-547 days). All 14 patients received systemic corticosteroids; 4 of the 14 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). No patients discontinued IMFINZI due to immune-mediated adrenal insufficiency. Resolution occurred in 3 patients. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated adrenal insufficiency occurred in 33 (1.4%) patients, including Grade 3 in 16 (0.7%) patients and Grade 4 in 1 (< 0.1%) patient. The median time to onset was 105 days (range: 20-428 days). Thirty-two patients received systemic corticosteroids, and 10 of the 32 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in one patient. Resolution occurred in 11 patients. In the HCC pool (n=462), immune-mediated adrenal insufficiency occurred in 6 (1.3%) patients, including Grade 3 in 1 (0.2%) patient. The median time to onset was 64 days (range: 43-504 days). All patients received systemic corticosteroids, and 1 of the 6 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 2 patients. *Immune-mediated type 1 diabetes mellitus.* In the combined safety database with IMFINZI monotherapy, Grade 3 immune-mediated type 1 diabetes mellitus occurred in 1 (< 0.1%) patient. The time to onset was 43 days. This patient recovered with sequelae, required long-term insulin therapy and IMFINZI was permanently discontinued due to immune-mediated type 1 diabetes mellitus. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated type 1 diabetes mellitus occurred in 6 (0.3%) patients, including Grade 3 in 1 (< 0.1%) patient and Grade 4 in 2 (< 0.1%) patients. The median time to onset was 58 days (range: 7-220 days). All patients required insulin. Treatment was discontinued for 1 patient. Resolution occurred in 1 patient. *Immune-mediated hypophysitis/hypopituitarism.* In the combined safety database with IMFINZI monotherapy, immune-mediated hypophysitis/hypopituitarism occurred in 2 (< 0.1%) patients, both Grade 3. The time to onset for the events was 44 days and 50 days. Both patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and one patient discontinued IMFINZI due to immune-mediated hypophysitis/hypopituitarism. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset for the events was 123 days (range: 63-388 days). All patients received systemic corticosteroids and 8 of the 16 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Four patients also required endocrine therapy. Treatment was discontinued in 2 patients. Resolution occurred in 7 patients. In the HCC pool (n=462), immune-mediated hypophysitis/hypopituitarism occurred in 5 (1.1%) patients. The median time to onset for the events was 149 days (range: 27-242 days). Four patients received systemic corticosteroids, and 1 of the 4 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Three patients also required endocrine therapy. Resolution occurred in 2 patients. *Immune-mediated nephritis.* In the combined safety database with IMFINZI monotherapy, immune-mediated nephritis occurred in 14 (0.5%) patients, including Grade 3 in 2 (< 0.1%) patients. The median time to onset was 71 days (range: 4-393 days). Nine patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received mycophenolate. IMFINZI was discontinued in 5 patients. Resolution occurred in 8 patients. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated nephritis occurred in 9 (0.4%) patients, including Grade 3 in 1 (< 0.1%) patient. The median time to onset was 79 days (range: 39-183 days). All patients received systemic corticosteroids and 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 3 patients. Resolution occurred in 5 patients. In the HCC pool (n=462), immune-mediated nephritis occurred in 4 (0.9%) patients, including Grade 3 in 2 (0.4%) patients. The median time to onset was 53 days (range: 26-242 days). All patients received systemic corticosteroids, and 3 of the 4 received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 2 patients. Resolution occurred in 3 patients. *Immune-mediated rash.* In the combined safety database with IMFINZI monotherapy, immune-mediated rash or dermatitis (including pemphigoid) occurred in 50 (1.7%) patients, including Grade 3 in 12 (0.4%) patients. The median time to onset was 43 days (range: 4-333 days). Twenty-three of the 50 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). IMFINZI was discontinued in 3 patients. Resolution occurred in 32 patients. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), immune-mediated rash or dermatitis (including pemphigoid) occurred in 112 (4.9%) patients, including Grade 3 in 17 (0.7%) patients. The median time to onset was 35 days (range: 1-778 days). All patients received systemic corticosteroids, and 57 of the 112 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Treatment was discontinued in 10 patients. Resolution occurred in 65 patients. In the HCC pool (n=462), immune-mediated rash or dermatitis (including pemphigoid) occurred in 26 (5.6%) patients, including Grade 3 in 9 (1.9%) patients and Grade 4 in 1 (0.2%) patient. The median time to onset was 25 days (range: 2-933 days). All patients received systemic corticosteroids and 14 of the 26 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). One patient received other immunosuppressants. Treatment was discontinued in 3 patients. Resolution occurred in 19 patients. *Infusion-related reactions.* In the combined safety database with IMFINZI monotherapy, infusion-related reactions occurred in 49 (1.6%) patients, including Grade 3 in 5 (0.2%) patients. There were no Grade 4 or 5 events. In the combined safety database with IMFINZI in combination with tremelimumab (n=2 280), infusion-related reactions occurred in 45 (2.0%) patients, including Grade 3 in 2 (<0.1%) patients. There were no Grade 4 or 5 events. *Laboratory abnormalities.* In patients treated with durvalumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.4% for alanine aminotransferase increased, 3.6% for aspartate aminotransferase increased, 0.5% for blood creatinine increased, 5.7% for amylase increased and 5.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 18.8% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 18.1%. In patients treated with durvalumab 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: 6.4% for alanine aminotransferase increased, 6.5% for aspartate aminotransferase increased, 4.2% for blood creatinine increased, 6.4% for amylase increased, and 11.7% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 20.3% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 24.1%. In patients treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 6.2% for alanine aminotransferase increased, 5.2% for aspartate aminotransferase increased, 4.0% for blood creatinine increased, 9.4% for amylase increased and 13.6% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to > ULN was 24.8% and a TSH shift from baseline that was ≥ LLN to < LLN was 32.9%. In patients treated with IMFINZI in combination with tremelimumab, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.1% for alanine aminotransferase increased, 5.8% for aspartate aminotransferase, 1.0% for blood creatinine increased, 5.9% for amylase increased and 11.3% for lipase increased. The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to > ULN was 4.2% and a TSH shift from baseline that was ≥ LLN to < LLN was 17.2%. Immunogenicity. Immunogenicity of IMFINZI as monotherapy is based on pooled data in 2 280 patients who were treated with IMFINZI 10 mg/kg every 2 weeks, or 20 mg/kg every 4 weeks as a single-agent and evaluable for the presence of anti-drug antibodies (ADAs). Sixty-nine patients (3.0%) tested positive for treatment emergent ADAs. Neutralising antibodies (nAb) against durvalumab were detected in 0.5% (12/2 280) of patients. The presence of ADAs did not have a clinically relevant effect on safety. There are insufficient number of patients to determine ADA impact on efficacy. Based on population PK analysis, slightly lower exposure are expected in ADA-positive patients however, the reduction of PK exposure is less than 30% compared to a typical patient and is not considered clinically relevant. Across multiple phase III studies, in patients treated with IMFINZI in combination with other therapeutic agents, 0% to 10.1% of patients developed treatment-emergent ADAs. Neutralizing antibodies against durvalumab were detected in 0% to 1.7% of patients treated with IMFINZI in combination with other therapeutic agents. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety. Elderly. No overall differences in safety were reported between elderly (≥ 65 years) and younger patients. In studies PACIFIC, CASPIAN and TOPAZ-1 data on safety for patients 75 years and older are too limited to draw a conclusion on this population. In first line metastatic NSCLC patients in the POSEIDON study, some differences in safety were reported between elderly (≥ 65 years) and younger patients. The safety data from patients 75 years of age or older are limited to a total of 74 patients. There was a higher frequency of serious adverse reactions and discontinuation rate of any study treatment due to adverse reactions in 35 patients aged 75 years of age or older treated with IMFINZI in combination with tremelimumab and platinum-based chemotherapy (45.7% and 28.6%, respectively) relative to 39 patients aged 75 years of age or older who received platinum-based chemotherapy only (35.9% and 20.5%, respectively). 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: **Belgium:** Federal Agency for Medicines and Health Products - FAMHP, Department Vigilance, Postbus/Boîte Postale 97, 1000 BRUSSELS, Madou. Website: www.eenbijwerkingmelden.be / www.notifierueffetindesirable.be, e-mail: adr@fagg.be / adr@afmps.be. **Luxembourg:** Centre Régional de Pharmacovigilance de Nancy or Division de la pharmacie et des médicaments de la Direction de la santé. Site internet : www.guichet.lu/pharmacovigilance. **5. MARKETING AUTHORISATION HOLDER.** AstraZeneca AB, SE 151 85 Södertälje, Sweden. **6. MARKETING AUTHORISATION NUMBER(S).** EU/1/18/1322/002 120 mg vial. EU/1/18/1322/001 500 mg vial. **7. LEGAL STATUS DELIVERY.** Medicinal product subject to medical prescription. **8. DATE OF REVISION OF THE TEXT.** 04/2023. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.