AUSTRALIAN PRODUCT INFORMATION

IMFINZI®
(durvalumab)

1 NAME OF THE MEDICINE

Durvalumab

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of IMFINZI concentrated solution for infusion contains either 120 mg or 500 mg of durvalumab.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Sterile, preservative free, clear to opalescent and free from visible particles, colourless to slightly yellow, concentrated solution for infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Non-small cell lung cancer (NSCLC)

- IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of adults with resectable (tumours ≥4 cm and/or node positive) non-small cell lung cancer (NSCLC) and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.
- IMFINZI is indicated for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy (CRT).

Small cell lung cancer (SCLC)

- IMFINZI as monotherapy is indicated for the treatment of adult patients with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy (CRT).
- IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC).

Biliary tract cancer (BTC)

IMFINZI in combination with gemcitabine and cisplatin is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

Hepatocellular carcinoma (HCC)

IMFINZI in combination with tremelimumab is indicated for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC) who have not received prior treatment with a PD-1/PD-L1 inhibitor.

Endometrial cancer

IMFINZI in combination with carboplatin and paclitaxel, followed by IMFINZI monotherapy, is indicated for the first-line treatment of patients with primary advanced or recurrent endometrial cancer.

Bladder cancer

IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with muscle invasive bladder cancer (MIBC).

Gastric and gastroesophageal junction (GOJ) cancer (GC/GOJC)

IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of adults with resectable gastric or gastroesophageal junction adenocarcinoma.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose of IMFINZI depends on the indication as presented in Table 1. IMFINZI is administered as an intravenous infusion over 1 hour.

When IMFINZI is used in combination with other medicines, refer to the Product Information for the other medicines for their recommended dosing information. The studied medicines and doses are described in Section 5.1 Pharmacodynamic properties – Clinical trials.

The proposed combination should be administered and monitored under the supervision of physicians experienced with the use of immunotherapy.

Table 1 Recommended dosage of IMFINZI

Indication	Recommended IMFINZI dosage	Duration of therapy
Monotherapy		
Locally advanced NSCLC	10 mg/kg every 2 weeks or 1500 mg every 4 weeks [a]	For one year or until disease progression or unacceptable toxicity
LS-SCLC	1500 mg [b] every 4 weeks	Until disease progression or unacceptable toxicity or for a maximum of 24 months
Combination therapy		
Resectable NSCLC	1500 mg [c] in combination with chemotherapy every 3 weeks for up to 4 cycles prior to surgery, followed by 1500 mg monotherapy every 4 weeks for up to 12 cycles after surgery.	Until disease is deemed unresectable, recurrence, unacceptable toxicity, or a maximum of 12 cycles after surgery
ES-SCLC	1500 mg [d] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or unacceptable toxicity
BTC	1500 mg [e] in combination with gemcitabine and cisplatin every 3 weeks (21 days) for up to 8 cycles, followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity
uHCC	*Single Tremelimumab Regular Interval Durvalumab (STRIDE):* 300 mg tremelimumab as a single priming dose in combination with IMFINZI 1500 mg [f] at Cycle 1/Day 1, followed by IMFINZI as monotherapy every 4 weeks	Until disease progression or unacceptable toxicity

Indication	Recommended IMFINZI dosage	Duration of therapy
Endometrial cancer	1120 mg in combination with carboplatin and paclitaxel every 3 weeks (21 days) for a minimum of 4 and up to 6 cycles, followed by 1500 mg [g] every 4 weeks as monotherapy.	Until disease progression or unacceptable toxicity
MIBC	1500 mg [c] in combination with chemotherapy every 3 weeks (21 days) for 4 cycles prior to surgery, followed by 1500 mg [c] every 4 weeks as monotherapy for up to 8 cycles after surgery	Until disease progression that precludes definitive surgery, recurrence, unacceptable toxicity, or a maximum of 8 cycles after surgery
GC/GOJC	1500 mg [h] in combination with FLOT chemotherapy every 4 weeks for up to 2 cycles prior to surgery, followed by 1500 mg [h], with FLOT chemotherapy, every 4 weeks for up to 2 cycles and then as 1500 mg [h] monotherapy every 4 weeks for up to 10 cycles, for a total of up to 12 cycles after surgery	*Neoadjuvant phase*: until disease progression that precludes definitive surgery or unacceptable toxicity. *Adjuvant phase*: until progression or recurrence, unacceptable toxicity, or a maximum of 12 cycles after surgery

BTC biliary tract cancer; ES-SCLC extensive stage small cell lung cancer; FLOT chemotherapy (regimen of fluorouracil, leucovorin, oxaliplatin and docetaxel); GC/GOJC – gastric and gastroesophageal adenocarcinoma; LS-SCLC – limited stage small cell lung cancer; MIBC – muscle invasive bladder cancer; NSCLC - non-small cell lung cancer; uHCC unresectable hepatocellular carcinoma

[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 as monotherapy until weight increases to greater than 30 kg [locally advanced NSCLC].

[b] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg [LS-SCLC].

[c] 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 at 20 mg/kg every 3 weeks (21 days) prior to surgery, followed by monotherapy at 20 mg/kg every 4 weeks after surgery until weight increases to greater than 30 kg [resectable NSCLC; MIBC]

[d] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg in combination with chemotherapy every 3 weeks (21 days) for 4 cycles, followed by 10 mg/kg every 2 weeks as monotherapy until weight increases to greater than 30 kg. [ES-SCLC]

[e] Patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg in combination with gemcitabine and cisplatin doses every 3 weeks (21 days), followed by monotherapy at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg [BTC]

[f] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg and tremelimumab 4 mg/kg until weight increases to greater than 30 kg. [uHCC]

[g] Patients with a body weight of 30 kg or less during maintenance phase must receive weight-based dosing, equivalent to IMFINZI 20 mg/kg, until weight increases to greater than 30 kg [endometrial cancer]

[h] Patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg. In combination with FLOT chemotherapy or as monotherapy, dose at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg [GC/GOJC

It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

No dose reduction or escalation for IMFINZI is recommended. In general, withhold IMFINZI for severe (Grade 3) immune-mediated adverse drug reactions (ADR). Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated ADR, recurrent severe (Grade 3) immune-mediated ADR that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Immune-mediated ADR requiring specific management are summarised in Table 2. Refer to Section 4.4 Special warnings and precautions for use for further management recommendations, monitoring and evaluation information.

Table 2 Treatment modifications for IMFINZI or IMFINZI in combination with tremelimumab

Adverse drug reactions (ADR)	Severity [a]	Treatment modification
Pneumonitis / interstitial lung disease	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Hepatitis	ALT or AST >3-≤5 x ULN or total bilirubin >1.5-≤3 x ULN	Withhold dose
	ALT or AST >5 - ≤10 x ULN	
	Concurrent ALT or AST >3 x ULN and total bilirubin >2 x ULN [d]	Permanently discontinue
	ALT or AST >10 x ULN or total bilirubin >3 x ULN	
Hepatitis in HCC (or secondary tumour involvement of the liver with abnormal baseline values) [e]	ALT or AST >2.5-≤5 x BLV and ≤20 x ULN	Withhold dose
	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]	Withhold durvalumab and permanently discontinue tremelimumab
	ALT or AST >7 x BLV OR >20 x ULN whichever occurs first OR bilirubin >3 x ULN	Permanently discontinue
Colitis or diarrhoea	Grade 2	Withhold dose
	Grade 3 for IMFINZI monotherapy	Withhold dose
	Grade 3 for IMFINZI + tremelimumab	Permanently discontinue tremelimumab [f]
	Grade 4	Permanently discontinue
	Intestinal perforation ANY grade	Permanently discontinue
Endocrinopathies: Hyperthyroidism, thyroiditis	Grade 2-4	Withhold dose until clinically stable
Endocrinopathies: Hypothyroidism	Grade 2-4	No changes
Endocrinopathies: Adrenal insufficiency, hypophysitis / hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Endocrinopathies: Type 1 diabetes mellitus	Grade 2-4	No changes
Nephritis	Grade 2 with serum creatinine >1.5-3 x (ULN or baseline)	Withhold dose
	Grade 3 with serum creatinine >3 x baseline or >3-6 x ULN Grade 4 with serum creatinine >6 x ULN	Permanently discontinue
Rash or dermatitis (including pemphigoid)	Grade 2 for >1 week or Grade 3	Withhold dose
	Grade 4	Permanently discontinue
Myocarditis	Grade 2-4	Permanently discontinue
Myositis / polymyositis / rhabdomyolysis	Grade 2 or 3	Withhold dose [b]
	Grade 4	Permanently discontinue
Infusion-related reactions	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Infection	Grade 3 or 4	Withhold dose until clinically stable
Myasthenia gravis	Grade 2-4	Permanently discontinue
Myelitis transverse	Any grade	Permanently discontinue

Adverse drug reactions (ADR)	Severity [a]	Treatment modification
Encephalitis	Grade 2-4	Permanently discontinue
Guillain-Barré syndrome	Grade 2-4	Permanently discontinue
Other immune-mediated ADR [c]	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV - baseline value

[a] Common Terminology Criteria for Adverse Events, version 4.03

[b] Permanently discontinue IMFINZI if ADR does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.

[c] Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, uveitis and polymyalgia rheumatica.

[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] Permanently discontinue tremelimumab for Grade 3; however, treatment with durvalumab can be resumed once event has resolved

After withhold, IMFINZI can be resumed within 12 weeks if the ADR improved to ≤ Grade 1 and the corticosteroid dose has been reduced to ≤10 mg prednisone or equivalent per day. IMFINZI should be permanently discontinued for recurrent Grade 3 ADR, as applicable.

For non-immune-mediated ADR, withhold IMFINZI for Grade 2 and 3 ADR until ≤ Grade 1 or baseline. IMFINZI should be discontinued for Grade 4 ADR (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).

Special patient populations

Renal impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (see Section 5.2 Pharmacokinetic properties). Durvalumab has not been studied in subjects with severe renal impairment.

Hepatic impairment

Based on a population pharmacokinetic analysis, no dose adjustment is recommended for patients with mild or moderate hepatic impairment. IMFINZI has not been studied in patients with severe hepatic impairment. However, due to minor involvement of hepatic processes in the clearance of durvalumab, no difference in exposure is expected for these patients (see Section 5.2 Pharmacokinetic properties).

Use in paediatric patients

The safety and efficacy of durvalumab have not been established in patients younger than 18 years of age. Currently available data of IMFINZI in combination with tremelimumab are described in Sections 4.8 Adverse effects (undesirable effects) and 5.2 Pharmacokinetic properties but no dosing recommendations can be made.

Use in the elderly

No dose adjustment is required for elderly patients (≥65 years of age) (see Section 5.1 Pharmacodynamic properties - Clinical trials and Section 5.2 Pharmacokinetic properties).

Method of administration

Preparation of IMFINZI solution and infusion

Preparation of solution

IMFINZI is for single use in one patient only. Discard any residue.

IMFINZI is supplied as single-dose vials and does not contain any preservatives. Aseptic technique must be observed.

- Visually inspect drug product for particulate matter and discolouration. IMFINZI is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured or visible particles are observed. Do not shake the vial.
- Withdraw the required volume from the vial(s) of IMFINZI and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, or 5% Dextrose Injection. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL and 15 mg/mL. Do not freeze or shake the solution.
- Care must be taken to ensure the sterility of prepared solutions.
- Do not re-enter the vial after withdrawal of drug; only withdraw one dose per vial.
- Discard any unused portion left in the vial.
- No incompatibilities between IMFINZI and 9 g/L (0.9%) sodium chloride or 50 g/L (5%) dextrose in polyvinylchloride or polyolefin IV bags have been observed.

After preparation of infusion solution

IMFINZI does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and needs to be stored, the time from preparation should not exceed:

- 30 days at 2°C to 8°C and for up to
- 12 hours at room temperature (up to 25°C) from the time of preparation.

Administration of IMFINZI infusion solution

Administer infusion solution intravenously over 1 hour through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter.

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

IMFINZI in combination with chemotherapy

For resectable NSCLC, ES-SCLC, BTC, endometrial cancer, MIBC and resectable GC/GOJC when IMFINZI is administered in combination with chemotherapy, administer IMFINZI prior to chemotherapy on the same day.

IMFINZI in combination with tremelimumab

For uHCC, 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Refer to Section 4.2 Dose and method of administration Table 2 for recommended treatment modifications and management of adverse reactions.

Immune-mediated adverse drug reactions (ADR)

Immune checkpoint inhibitors, including durvalumab, can cause severe and fatal immune-mediated ADR, which may involve any organ system. While immune-mediated ADR usually manifest during treatment, they can also manifest after discontinuation. Early identification of such reactions and timely intervention are an important part of the safe use of durvalumab. In clinical trials, most immune-mediated ADR were reversible and managed with interruptions of durvalumab, administration of corticosteroids and/or supportive care. Patients should be monitored for signs and symptoms and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration) and further below.

For suspected immune-mediated ADR, adequate evaluation should be performed to confirm aetiology or exclude alternate aetiologies. Based on the severity of the ADR, IMFINZI or IMFINZI in combination with tremelimumab should be withheld or permanently discontinued. Treatment with corticosteroids or endocrine therapy should be initiated. For events requiring corticosteroid therapy, and 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.

Note: Use of * in the below sections indicates that the relevant term is defined as requiring use of systemic corticosteroids with no clear alternate aetiology.

Immune-mediated pneumonitis

Immune-mediated pneumonitis/interstitial lung disease*, including fatal cases, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). For Grade 2 events, an initial dose of 1-2mg/kg/day prednisone or equivalent should be initiated followed by a taper. For Grade 3 or 4 events, an initial dose of 2-4mg/kg/day methylprednisolone or equivalent (or in accordance with local immune-related adverse events management guidelines where these differ) should be initiated followed by a taper.

Pneumonitis and radiation pneumonitis

Radiation pneumonitis is frequently observed in patients receiving radiation therapy (RT) to the lung and the clinical presentation of pneumonitis and radiation pneumonitis is very similar.

In the PACIFIC study, in patients who had completed treatment with at least 2 cycles of concurrent CRT within 1 to 42 days prior to initiation of study treatment, pneumonitis or radiation pneumonitis occurred in 161 (33.9%) patients in the IMFINZI-treated group and 58 (24.8%) in the placebo group, including Grade 3 in 16 (3.4%) patients on IMFINZI vs 7 (3.0%) patients on placebo and Grade 5 in 5 (1.1%) patients on IMFINZI vs 4 (1.7%) patients on placebo. The median time to onset in the IMFINZI-treated group was 55 days (range: 1-406 days) vs. 55 days (range: 1-255 days) in the placebo group. See also Section 4.8 Adverse effects (undesirable effects).

In the ADRIATIC study, in patients who had completed treatment with CRT within 1 to 42 days prior to initiation of study treatment, pneumonitis or radiation pneumonitis occurred in 100 (38.2%) patients in the IMFINZI-treated group and 80 (30.2%) in the placebo group; including Grade 3 in 8 (3.1%) patients on IMFINZI vs 6 (2.3%) patients on placebo, and Grade 5 in 1 (0.4%) patient on IMFINZI vs 0 patients on placebo.

Immune-mediated hepatitis

Immune-mediated hepatitis*, including a fatal case, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for abnormal liver tests prior to each infusion, and as indicated based on clinical evaluation during and after discontinuation of treatment with durvalumab. Immune-mediated hepatitis should be managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered with an initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper for all grades.

Immune-mediated colitis

Immune-mediated colitis* occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for signs and symptoms of colitis (including diarrhoea) and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered at an initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper for Grades 2-4. Consult a surgeon immediately if an intestinal perforation of ANY grade is suspected.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism/hyperthyroidism/thyroiditis

Immune-mediated hypothyroidism, hyperthyroidism or thyroiditis have occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for abnormal thyroid function tests prior to and periodically during treatment and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). For immune-mediated hypothyroidism, initiate thyroid hormone replacement as clinically indicated for Grades 2-4. For immune-mediated hyperthyroidism/thyroiditis, symptomatic management can be implemented for Grades 2-4.

Immune-mediated adrenal insufficiency

Immune-mediated adrenal insufficiency occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for clinical signs and symptoms of adrenal insufficiency. For symptomatic adrenal insufficiency, patients should be managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered with an initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated for Grades 2-4.

Immune-mediated type 1 diabetes mellitus

Immune-mediated type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for clinical signs and symptoms of type 1 diabetes mellitus. For symptomatic type 1 diabetes mellitus, patients should be managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Treatment with insulin can be initiated as clinically indicated for Grades 2-4.

Immune-mediated hypophysitis/hypopituitarism

Immune-mediated hypophysitis/hypopituitarism occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for clinical signs and symptoms of hypophysitis or hypopituitarism. For symptomatic hypophysitis or hypopituitarism, patients should be managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered with an initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper and hormone replacement as clinically indicated for Grades 2-4.

Immune-mediated nephritis

Immune-mediated nephritis* occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for abnormal renal function tests prior to and periodically during treatment with durvalumab and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered with an initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper for Grades 2-4.

Immune-mediated dermatological adverse reactions

Immune-mediated dermatitis (including pemphigoid)* occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Adverse effects (undesirable effects)). Bullous dermatitis and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) have occurred with other products in this class. Patients should be monitored for signs and symptoms dermatitis (including rash) and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered with an initial dose of 1-2mg/kg/day prednisone or equivalent followed by a taper for Grade 2 >1 week or Grade 3 and 4.

Immune-mediated myocarditis

Immune-mediated myocarditis, which can be fatal, occurred in patients receiving IMFINZI or IMFINZI in combination with tremelimumab (see Section 4.8 Adverse effects (undesirable effects)). Patients should be monitored for signs and symptoms of immune-mediated myocarditis and managed as recommended in section 4.2. Corticosteroids should be administered with an initial dose of 2-4mg/kg/day prednisone or equivalent followed by a taper for Grades 2-4. 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.

Other immune mediated ADR

Given the mechanism of action of durvalumab, other immune-mediated ADR may occur. Other immune mediated ADR are: aseptic meningitis, haemolytic anaemia, immune thrombocytopenia, pancreatitis, encephalitis, myasthenia gravis, myelitis transverse, myositis, polymyositis, rhabdomyolysis, Guillain-Barré syndrome, immune-mediated arthritis, polymyalgia rheumatica and ocular inflammatory toxicity, including uveitis and keratitis. Patients should be monitored for signs and symptoms of immune-mediated ADR and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Corticosteroids should be administered with an initial dose of 1-2 mg/kg/day prednisone or equivalent followed by taper for Grades 2-4.

Also see Section 4.8 Adverse effects (undesirable effects), immune-mediated neurological adverse events in ongoing and completed trials.

Infusion-related reactions

Patients should be monitored for signs and symptoms of infusion-related reactions and managed as recommended in Table 2 (see Section 4.2 Dose and method of administration). Severe infusion related reactions have been reported in patients receiving durvalumab (see Section 4.8 Adverse effects (undesirable effects)). For Grade 1 or 2 severity, may consider pre-medications for prophylaxis of subsequent infusion reactions. For Grade 3 or 4, manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines and/or society guidelines.

Disease-specific precautions

Patients with pre-existing autoimmune disease (AID)

In patients with pre-existing AID, data from observational studies suggest that the risk of immune-mediated ADR following immune checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

Use of durvalumab in combination with chemotherapy (gemcitabine and cisplatin) in patients with resectable muscle-invasive bladder cancer

In the NIAGARA study, a higher overall incidence of venous thromboembolic events, including pulmonary embolism and thrombosis, was observed in patients treated with durvalumab in combination with chemotherapy (15.7%) compared to those receiving chemotherapy alone (10.5%). Fatal cases of pulmonary embolism have also been reported. The contributory role of IMFINZI in combination with chemotherapy (gemcitabine and cisplatin) in patients with resectable muscle-invasive bladder cancer has not been established.

Use of durvalumab in combination with FLOT chemotherapy in patients with resectable gastric or GOJ adenocarcinoma

In the MATTERHORN study, a higher overall incidence of pulmonary embolism was observed in patients treated with durvalumab in combination with FLOT chemotherapy (4.2%) compared to those receiving FLOT chemotherapy alone (1.9%). Fatal cases of pulmonary embolism have also been reported. Pulmonary embolism is a known ADR of oxaliplatin-containing regimens. The contributory role of IMFINZI in combination with FLOT chemotherapy in patients with resectable gastric or GOJ adenocarcinoma has not been established.

Efficacy in patients with PD-L1 expression <1%

Post-hoc analyses for locally advanced NSCLC suggest efficacy may be different for patients with PD-L1 <1%. Before initiating treatment, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the side effects of durvalumab (see Section 5.1 Pharmacodynamic properties - PACIFIC study).

Use in the elderly

No overall differences in safety were observed between patients treated with IMFINZI who were ≥ 65 years of age compared to younger patients in the PACIFIC study (NSCLC). Data from NSCLC patients 75 years of age or older are limited.

Of the 401 patients with resectable NSCLC treated with IMFINZI in combination with chemotherapy in the AEGEAN study, 209 (52%) patients were 65 years or older and 49 (12%) patients were 75 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 262 patients with LS-SCLC treated with IMFINZI, 103 (39.3%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 265 patients with ES-SCLC treated with IMFINZI in combination with chemotherapy, 101 (38%) patients were 65 years or older. There were no overall clinically meaningful differences in safety or effectiveness between patients ≥ 65 years of age and younger patients.

Of the 338 patients with BTC treated with IMFINZI in combination with chemotherapy, 158 (46.7%) patients were 65 years or older. No overall differences in safety or effectiveness were observed between patients ≥65 years of age and younger patients.

Of the 462 patients with uHCC treated with STRIDE, 173 (37.4%) patients were 65 years or older and 63 (13.6%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Of the 238 patients with endometrial cancer randomised to receive platinum-based chemotherapy + IMFINZI, 116 (48.7%) patients were 65 years or older and 29 (12.2%) patients were 75 years or older. There were no clinically meaningful differences in safety or efficacy between patients 65 years or older and younger patients.

Of the 530 patients with MIBC treated with IMFINZI in combination with gemcitabine and cisplatin in the NIAGARA study, 272 (51%) patients were 65 years or older, and 57 (11%) patients were 75 years or older. No overall differences in safety or effectiveness of IMFINZI have been observed between patients 65 years of age and older and younger adult patients.

Of the 475 patients with resectable GC/GOJC treated with IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, then as adjuvant IMFINZI monotherapy in the MATTERHORN study, 184 (38.7%) patients were 65 years or older and 37 (7.8%) patients were 75 years or older. There were no overall differences in safety or effectiveness between patients ≥65 years of age and younger patients.

Paediatric use

The safety and efficacy of durvalumab have not been established in patients younger than 18 years of age. Currently available data of IMFINZI in combination with tremelimumab are described in Sections 4.8 Adverse effects (undesirable effects) and 5.2 Pharmacokinetic properties but no dosing recommendations can be made.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Durvalumab is an immunoglobulin. The primary elimination pathways of durvalumab are protein catabolism via reticuloendothelial system or target mediated disposition, therefore no formal pharmacokinetic (PK) drug-drug interaction studies have been conducted since no metabolic drug-drug interactions are expected. PK drug-drug interaction between durvalumab and etoposide, and carboplatin or cisplatin was assessed in the CASPIAN study and no clinically meaningful PK drug-drug interaction between durvalumab and the chemotherapy was identified.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no data on the effects of durvalumab on fertility in humans. In repeat-dose toxicology studies of durvalumab up to 3 months duration in sexually mature cynomolgus monkeys, there were no notable effects on the male and female reproductive organs. These animals received weekly doses of durvalumab yielding 11 times the clinical exposure (based on AUC) at the clinical dose of 1500 mg every 3 weeks and 23 times at the clinical dose of 10 mg/kg every 2 weeks.

Use in pregnancy – Category D

There are no data on the use of durvalumab in pregnant women. Based on its mechanism of action, durvalumab has the potential to impact maintenance of pregnancy and may cause foetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier; therefore, durvalumab has the potential to be transmitted from the mother to the developing foetus. Durvalumab use is not recommended during pregnancy. Women of childbearing potential should use effective contraception during treatment and for at least 3 months after the last dose.

Animal data

As reported in the literature, the PD-1/PD-L1 pathway plays a central role in preserving pregnancy by maintaining maternal immune tolerance to the foetus. In mouse allogeneic pregnancy models, disruption of PD-L1 signalling was shown to result in an increase in foetal loss. The effects of durvalumab on prenatal and postnatal development were evaluated in reproduction studies in cynomolgus monkeys. Durvalumab was administered from the confirmation of pregnancy through delivery at exposure levels approximately 3 to 11 times the clinical exposure (based on AUC) at the clinical dose of 1500 mg every 3 weeks and 6 to 20 times at the clinical dose of 10 mg/kg every 2 weeks. Administration of durvalumab resulted in premature delivery, foetal loss (abortion and stillbirth) and increase in neonatal deaths compared to concurrent controls. Durvalumab was detected in infant serum on postpartum Day 1, indicating the presence of placental transfer of durvalumab. Based on its mechanism of action, foetal exposure to durvalumab may increase the risk of developing immune-mediated disorders or altering the normal immune response and immune-mediated disorders have been reported in PD-1 knockout mice.

Use in lactation

There is no information regarding the presence of durvalumab in human milk, the absorption and effects on the breast-fed infant, or the effects on milk production. Human IgG is excreted in human milk. In animal reproduction studies, administration of durvalumab to pregnant cynomolgus monkeys was associated with dose-related low-level excretion of durvalumab in breast milk and was associated with premature neonatal death compared to concurrent controls. Because of the potential for adverse reactions in breastfed infants from durvalumab, lactating women should be advised not to breast-feed during treatment and for at least 3 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Based on its pharmacodynamic properties, durvalumab is unlikely to affect the ability to drive and use machines. However, if patients experience adverse reactions affecting their ability to concentrate and react, they should be advised to use caution when driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Overall summary of adverse drug reactions (ADR)

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients from 9 studies 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 frequent (>10%) ADR 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%).

Tabulated list of adverse drug reactions (ADR)

Table 3 lists the incidence of ADR in the monotherapy safety dataset. ADR are listed according to system organ class (SOC) in MedDRA. Within each SOC, the ADR are presented in decreasing frequency. Within each frequency grouping, ADR are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each ADR is based on the CIOMS III convention and is defined as: very common (≥ 10%); common (≥ 1 to < 10%); uncommon (≥ 0.1 to < 1%); rare (≥ 0.01 to < 0.1%); very rare (< 0.01%); not determined (cannot be estimated from available data).

Table 3 ADR in patients treated with IMFINZI monotherapy

	IMFINZI monotherapy			
	Any grade (%)		Grade 3-4 (%)	
Infections and infestations				
Upper respiratory tract infections [a]	Very common	13.5	Uncommon	0.2
Pneumonia [b,c]	Common	8.9	Common	3.5
Oral candidiasis	Common	2.1		0
Dental and oral soft tissue infections [d]	Common	1.7	Rare	<0.1
Influenza	Common	1.6	Rare	<0.1
Blood and lymphatic system disorders				
Immune thrombocytopenia	Rare	<0.1	Rare	<0.1
Endocrine disorders				
Hypothyroidism [e]	Very common	10.1	Uncommon	0.2
Hyperthyroidism [f]	Common	4.6		0
Thyroiditis [g]	Uncommon	0.8	Rare	<0.1
Adrenal insufficiency	Uncommon	0.6	Rare	<0.1
Type 1 diabetes mellitus	Rare	<0.1	Rare	<0.1
Hypophysitis/hypopituitarism	Rare	<0.1	Rare	<0.1
Diabetes insipidus	Rare	<0.1	Rare	<0.1
Nervous system disorders				
Myasthenia gravis	Not determined [h]		Not determined [h]	
Encephalitis	Not determined [v]		Not determined [v]	
Guillain-Barré syndrome [c]	Not determined [h]		Not determined [h]	
Cardiac disorders				
Myocarditis	Rare	<0.1	Rare	<0.1
Respiratory, thoracic and mediastinal disorders				
Cough/productive Cough	Very common	21.5	Uncommon	0.4
Pneumonitis [c]	Common	3.8	Uncommon	0.9
Dysphonia	Common	3.1	Rare	<0.1
Interstitial lung disease	Uncommon	0.6	Uncommon	0.1
Gastrointestinal disorders				
Diarrhoea	Very common	16.3	Uncommon	0.6
Abdominal pain [i]	Very common	12.7	Common	1.8
Colitis [j]	Uncommon	0.9	Uncommon	0.3
Pancreatitis [u]	Uncommon	0.23	Uncommon	0.17
Hepatobiliary disorders				
AST increased or ALT increased [c,k]	Common	8.1	Common	2.3
Hepatitis [c,l]	Uncommon	0.8	Uncommon	0.4
Skin and subcutaneous tissue disorders				
Rash [m]	Very common	16.0	Uncommon	0.6
Pruritus [n]	Very common	10.8	Rare	<0.1
Night sweats	Common	1.6	Rare	<0.1
Dermatitis	Uncommon	0.7	Rare	<0.1
Psoriasis	Uncommon	0.8	Rare	<0.1
Pemphigoid [o]	Rare	<0.1		0

	IMFINZI monotherapy			
	Any grade (%)		Grade 3-4 (%)	
Musculoskeletal and connective tissue disorders				
Myalgia	Common	5.9	Rare	<0.1
Myositis [p]	Uncommon	0.2	Rare	<0.1
Polymyalgia rheumatica	Rare	-	-	-
Polymyositis [p]	Not determined [q]		Not determined [q]	
Immune mediated arthritis	Not determined [h]		Not determined [h]	
Eye disorders				
Uveitis	Rare	<0.1		0
Renal and urinary disorders				
Blood creatinine increased	Common	3.5	Rare	<0.1
Dysuria	Common	1.3		0
Nephritis [r]	Uncommon	0.3	Rare	<0.1
General disorders and administration site conditions				
Pyrexia	Very common	13.8	Uncommon	0.3
Peripheral oedema [s]	Common	9.7	Uncommon	0.3
Injury, poisoning and procedural complications				
Infusion related reaction [t]	Common	1.6	Uncommon	0.2

ALT – alanine aminotransferase; AST – aspartate aminotransferase

[a] includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis and upper respiratory tract infection.

[b] includes lung infection, 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.

[f] includes hyperthyroidism and Basedow's disease.

[g] includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.

[h] reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare.

[i] includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[j] includes colitis, enteritis, enterocolitis, and proctitis.

[k] includes ALT increased, AST increased, hepatic enzyme increased and transaminases increased.

[l] includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.

[m] includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.

[n] includes pruritus generalised and pruritus.

[o] includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing trials is uncommon.

[p] includes rhabdomyolysis (as single medical concept with myositis/polymyositis).

[q] 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.

[r] includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.

[s] includes oedema peripheral and peripheral swelling.

[t] includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

[u] includes pancreatitis and pancreatitis acute.

[v] 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) and one was Grade 2.

IMFINZI in combination with chemotherapy

Musculoskeletal and connective tissue disorders: Polymyalgia rheumatica [a] (rare)

[a] Not observed in the IMFINZI + chemotherapy pool, but observed in other AstraZeneca-sponsored clinical studies

Laboratory abnormalities

In patients treated with durvalumab monotherapy, the proportion of patients in the monotherapy pooled dataset 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 and 0.5% for blood creatinine increased. The proportion of patients who experienced a thyroid-stimulating hormone (TSH) shift from baseline that was ≤ upper limit of normal (ULN) to any grade > ULN was 18.8% and a TSH shift from baseline that was ≥ lower limit of normal (LLN) to any grade < LLN was 18.1%.

Tabulated list of adverse events in individual clinical studies

The data described below reflect exposure to IMFINZI as monotherapy, in patients with locally advanced, unresectable NSCLC (PACIFIC study) and LS-SCLC (ADRIATIC study), in combination with chemotherapy in patients with resectable NSCLC (AEGEAN study), ES-SCLC (CASPIAN study), BTC (TOPAZ-1 study), endometrial cancer (DUO-E study), MIBC (NIAGARA study) and resectable GC/GOJC (MATTERHORN study), and in combination with tremelimumab (STRIDE) in patients with uHCC (HIMALAYA study and Study 22).

Adverse events are listed according to MedDRA SOC. Within each SOC, the adverse events are presented in decreasing frequency.

Non-small cell lung cancer (NSCLC)

PACIFIC study (locally advanced NSCLC)

The safety of IMFINZI in patients with locally advanced NSCLC who completed concurrent platinum-based chemoradiotherapy within 42 days prior to initiation of study drug was evaluated in the PACIFIC study, a multicentre, randomised, double-blind, placebo-controlled study. A total of 475 patients received IMFINZI 10 mg/kg intravenously every 2 weeks. The study excluded patients who had disease progression following CRT, with active or prior autoimmune disease within 2 years of initiation of the study or with medical conditions that required systemic immunosuppression (see Section 5.1 Pharmacodynamic properties - Clinical trials).

The study population characteristics were: median age of 64 years (range: 23 to 90), 45% age 65 years or older, 70% male, 69% White, 27% Asian, 75% former smoker, 16% current smoker, and 51% had WHO performance status of 1. All patients received definitive RT as per protocol, of which 92% received a total radiation dose of 54 Gy to 66 Gy. The median duration of exposure to IMFINZI was 10 months (range: 0.2 to 12.6).

IMFINZI was discontinued due to adverse events in 15% of patients. The most common adverse events leading to IMFINZI discontinuation were pneumonitis or radiation pneumonitis in 6% of patients. Serious adverse events occurred in 29% of patients receiving IMFINZI. The most frequent serious adverse events reported in at least 2% of patients were pneumonitis or radiation pneumonitis (7%) and pneumonia (6%). Fatal pneumonitis or radiation pneumonitis and fatal pneumonia occurred in < 2% of patients and were similar across arms. The most common adverse events (occurring in ≥20% of patients) were cough, fatigue, pneumonitis or radiation pneumonitis, upper respiratory tract infections, dyspnoea and rash.

Table 4 summarises the adverse events that occurred in at least 10% of patients treated with IMFINZI.

Table 4 Treatment-emergent adverse events occurring in ≥10% of patients (PACIFIC)

Adverse event	IMFINZI N=475		Placebo [a] N=234	
	All grades (%)	Grades 3-4 (%)	All grades (%)	Grades 3-4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough/productive cough	40	0.6	30	0.4
Pneumonitis [b]/radiation pneumonitis	34	3.4	25	3.0
Dyspnoea [c]	25	1.5	25	2.6
Gastrointestinal disorders				
Diarrhoea	18	0.6	19	1.3
Abdominal pain [d]	10	0.4	6	0.4
Endocrine disorders				
Hypothyroidism [e]	12	0.2	1.7	0
Skin and subcutaneous tissue disorders				
Rash [f]	23	0.6	12	0
Pruritus [g]	12	0	6	0
General disorders and administration site conditions				
Fatigue [h]	34	0.8	32	1.3
Pyrexia	15	0.2	9	0
Infections				
Upper respiratory tract infections [i]	26	0.4	19	0
Pneumonia [j]	17	7	12	6

[a] The PACIFIC study was not designed to demonstrate statistically significant difference in adverse event rates for IMFINZI, as compared to placebo, for any specific adverse event listed in Table 4

[b] includes acute interstitial pneumonitis, interstitial lung disease, pneumonitis, pulmonary fibrosis

[c] includes dyspnoea and exertional dyspnoea

[d] includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain

[e] includes autoimmune hypothyroidism and hypothyroidism

[f] includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis

[g] includes pruritus generalised and pruritus

[h] includes asthenia and fatigue

[i] includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection

[j] includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, *pneumonia haemophilus*, *pneumonia klebsiella*, pneumonia necrotising, pneumonia pneumococcal, and pneumonia streptococcal

Other adverse events occurring in less than 10% of patients treated with IMFINZI were dysphonia, dysuria, night sweats, peripheral oedema, and increased susceptibility to infections.

AEGEAN study (resectable NSCLC)

The safety of IMFINZI in combination with chemotherapy as neoadjuvant treatment, is based on data in 401 patients from the AEGEAN (resectable NSCLC) study and was consistent with known IMFINZI monotherapy and known chemotherapy safety profiles.

See Section 5.1 Pharmacodynamic properties - Clinical trials for AEGEAN study design and patient population.

SAE occurred in 38% of patients receiving IMFINZI in combination with platinum-based chemotherapy. Fatal AEs occurred in 6% of patients receiving IMFINZI in combination with platinum-based chemotherapy including (in at least 2 patients), COVID-19 pneumonia, pneumonia, interstitial lung disease, COVID-19, sepsis and septic shock. Permanent discontinuation of IMFINZI due to an AE occurred in 12% of patients. AEs which required permanent discontinuation of IMFINZI (≥0.5%) were pneumonitis, rash, peripheral neuropathy, diarrhoea, increased alanine aminotransferase and immune mediated hepatitis.

Table 5 and Table 6 summarise the very common ADR and laboratory abnormalities in AEGEAN, respectively.

Table 5 Adverse drug reactions occurring in ≥10% of patients (AEGEAN)

Adverse drug reaction	IMFINZI with chemotherapy N=401		Placebo with chemotherapy N=398	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Endocrine disorders				
Hypothyroidism [a]	10.7	0	3.8	0
Gastrointestinal disorders				
Nausea	25.2	0.2	28.9	0.3
Constipation	24.9	0.2	21.1	0
Diarrhoea	13.0	0.7	12.3	0.8
Vomiting	11.2	0.7	10.6	1.0
General disorders and administration site conditions				
Fatigue [b]	24.7	0	24.6	1.5
Metabolism and nutrition disorders				
Decreased appetite	18.2	0.2	17.6	0.3
Nervous system disorders				
Peripheral neuropathy [c]	10.7	0.5	12.6	0.8
Respiratory, thoracic and mediastinal disorders				
Cough / productive cough	11.0	0	12.6	0
Skin and subcutaneous tissue disorders				
Rash [d]	18.7	0.5	13.1	0.3
Alopecia	17.2	0	15.8	0.3
Pruritus	11.7	0.2	5.5	0

[a] includes blood thyroid stimulating hormone increased and hypothyroidism

[b] includes fatigue and asthenia

[c] includes neuropathy peripheral, paraesthesia and peripheral sensory neuropathy

[d] includes eczema, erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular and rash pruritic

Table 6 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients (AEGEAN)

Laboratory Abnormality	IMFINZI with chemotherapy	Placebo with chemotherapy
	Grade [b] 3 or 4 (%)[c]	Grade [b] 3 or 4 (%) [c]
Chemistry		
Hyponatraemia	5.3	5.8
Hypomagnesaemia	2.8	3.6
Hypocalcaemia	3.3	4.5
Hypokalaemia	3.5	5.1

Laboratory Abnormality	IMFINZI with chemotherapy	Placebo with chemotherapy
	Grade [b] 3 or 4 (%)[c]	Grade [b] 3 or 4 (%) [c]
Hyperkalaemia	1.5	2.0
Creatinine increased	2.3	3.3
ALT increased	5.8	2.0
AST increased	3.5	1.8
GGT increased	4.7	2.1
Amylase increased	4.7	3.6
Lipase increased	4.9	6.9
Haematology		
Neutrophils decreased	24.3	27.4
Leukocytes decreased	11.5	10.8
Lymphocytes decreased	10.5	8.8
Haemoglobin decreased	9.8	8.5
Platelets decreased	6.8	7.5

ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyl transferase

[a] The frequency cut off is based on any grade change from baseline.

[b] Graded according to NCI CTCAE (Common Terminology Criteria for Adverse Event) version 5.0.

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI (range: 202 to 399) and placebo + chemotherapy (range: 212 to 398).

Neoadjuvant phase of AEGEAN

A total of 401 patients received at least 1 dose of IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment and 398 patients received at least 1 dose of placebo in combination with platinum-based chemotherapy as neoadjuvant treatment.

SAE occurred in 21% of patients who received IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment; the most frequent (≥1%) SAE were pneumonia, anaemia, myelosuppression, vomiting and neutropenia (1%). Fatal AE occurred in 2% of patients, including death due to COVID-19 pneumonia, sepsis, myocarditis, decreased appetite, haemoptysis and death not otherwise specified.

Permanent discontinuation of IMFINZI due to an AE occurred in 7% of patients who received IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment; the most frequent (≥0.5%) AE that led to permanent discontinuation of IMFINZI were peripheral sensory neuropathy and pneumonitis.

Of the 401 IMFINZI-treated patients and 398 placebo-treated patients who received neoadjuvant treatment, 2% and 1%, respectively, did not receive surgery due to AEs. The most frequent AE that led to cancellation of surgery in the IMFINZI arm were COVID-19 pneumonia, HIV infection, pneumonitis, prostate cancer, colon cancer, pruritus and colitis.

Of the 325 IMFINZI-treated patients who received surgery, 4% experienced delay of surgery (defined as on-study surgery occurring more than 40 days after the last dose of study treatment in the neoadjuvant period) due to AEs. Of the 326 placebo-treated patients who received surgery, 4% experienced delay of surgery due to AEs.

Of the 325 IMFINZI-treated patients who received surgery, 7% did not receive adjuvant treatment due to AEs. Of the 326 placebo-treated patients who received surgery, 6% did not receive adjuvant treatment due to AEs.

Adjuvant phase of AEGEAN

A total of 265 patients in the IMFINZI arm and 254 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received IMFINZI alone as adjuvant treatment, 13% experienced SAE. The most frequent SAE reported in >1% of patients were pneumonia and COVID-19. Four fatal AE occurred during the adjuvant phase of the study including COVID-19 pneumonia, pneumonia aspiration, interstitial lung disease and aortic aneurysm. Permanent discontinuation of adjuvant IMFINZI due to an AE occurred in 8% of patients. The most frequent (≥0.5%) AE that led to permanent discontinuation of adjuvant IMFINZI was rash.

Small cell lung cancer (SCLC)

ADRIATIC study (LS-SCLC)

The safety of IMFINZI as monotherapy in patients with LS-SCLC was based on data in 262 patients from the ADRIATIC study, with a median duration of exposure to IMFINZI of 9.2 months (range: 0.92 to 25). The safety profile was consistent with IMFINZI monotherapy.

See Section 5.1 Pharmacodynamic properties - Clinical trials for ADRIATIC study design and patient population.

Table 7 and Table 8 summarise the very common adverse events and laboratory abnormalities respectively that occurred in patients treated with IMFINZI in the ADRIATIC study.

Table 7 Adverse events occurring in ≥10% of patients (ADRIATIC)

Adverse events	**IMFINZI N=262**		**Placebo N=265**	
	Any grade (%)	**Grade 3-4 (%)**	**Any grade (%)**	**Grade 3-4 (%)**
Respiratory, thoracic and mediastinal disorders				
Pneumonitis or radiation pneumonitis [a]	38	3.1	30	2.6
Cough/productive cough	17	0	14	0
Dyspnoea [b]	11	0.4	7	0
General disorders				
Fatigue [c]	21	0.4	20	2.3
Skin and subcutaneous tissue disorders				
Rash [d]	18	0.4	11	0
Pruritus	13	0	7	0
Endocrine disorders				
Hypothyroidism [e]	17	0	4.9	0
Hyperthyroidism [f]	12	0	1.9	0
Metabolism and nutrition disorders				
Decreased appetite	17	0	13	0
Nervous system disorders				
Dizziness [g]	14	0	9	0
Infections and infestations				
Pneumonia [h]	13	3.1	9	4.2

Adverse events	IMFINZI N=262		Placebo N=265	
	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Nausea	13	0	11	0
Diarrhoea	11	1.9	8	0
Constipation	10	0	10	0

[a] Includes pneumonitis, immune-mediated lung disease, interstitial lung disease, radiation pneumonitis and lung radiation fibrosis.

[b] Includes dyspnoea and exertional dyspnoea.

[c] Includes fatigue and asthenia.

[d] Includes dermatitis, acneiform dermatitis, eczema, rash, maculo-papular rash, papular rash, pruritic rash and skin exfoliation.

[e] Includes hypothyroidism, increased blood thyroid stimulating hormone and decreased thyroxine free.

[f] Includes hyperthyroidism, decreased blood thyroid stimulating hormone, increased thyroxine free, increased thyroxine, increased tri-iodothyronine free and increased tri-iodothyronine.

[g] Includes dizziness, postural dizziness, vertigo and positional vertigo

[h] Includes pneumonia, atypical pneumonia, lower respiratory tract infection, bacterial pneumonia, pneumocystis jirovecii pneumonia, legionella pneumonia and viral pneumonia.

Table 8 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients (ADRIATIC)

Laboratory abnormality [b]	IMFINZI (n=262) [c]	Placebo (n=265) [d]
	Grade 3 or 4 (%)	Grade 3 or 4 (%)
Chemistry		
ALT increased	2.3	2.3
AST increased	2.3	1.5
Hypocalcaemia	0	0.8
Creatinine increased	0	0.8
GGT increased	6.6	2.9
Hyperglycaemia	3.2	1.5
Potassium increased	1.2	0.8
Sodium decreased	5.4	6.2
Haematology		
Leukocytes decreased	0.4	1.1
Lymphocytes decreased	10.5	9.5

ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyl transferase

[a] The frequency cut off is based on any grade change from baseline.

[b] Graded according to NCI CTCAE version 4.03.

[c] The denominator used to calculate the rate varied from 63 to 259 based on the number of patients with a baseline value and at least one post-treatment value.

[d] The denominator used to calculate the rate varied from 65 to 262 based on the number of patients with a baseline value and at least one post-treatment value.

CASPIAN study (ES-SCLC)

The safety of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC was evaluated in CASPIAN, a randomised, open-label, multicentre, active-controlled trial. A total of 265 patients received IMFINZI 1500 mg in combination with chemotherapy every 3 weeks for 4 cycles followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity. The trial excluded patients with active or prior autoimmune disease or with medical conditions that required systemic corticosteroids or immunosuppressants (see Section 5.1 Pharmacodynamic properties – Clinical trials).

Among 266 patients receiving chemotherapy alone, 57% of the patients received 6 cycles of chemotherapy and 8% of the patients received PCI after chemotherapy.

IMFINZI was discontinued due to adverse reactions in 7% of the patients receiving IMFINZI plus chemotherapy. These include pneumonitis, hepatotoxicity, neurotoxicity, sepsis, diabetic ketoacidosis and pancytopenia (1 patient each). Serious adverse reactions occurred in 31% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse reactions reported in at least 1% of patients were febrile neutropenia (4.5%), pneumonia (2.3%), anaemia (1.9%), pancytopenia (1.5%), pneumonitis (1.1%) and COPD (1.1%). Fatal adverse reactions occurred in 4.9% of patients receiving IMFINZI plus chemotherapy. These include pancytopenia, sepsis, septic shock, pulmonary artery thrombosis, pulmonary embolism, and hepatitis (1 patient each) and sudden death (2 patients). The most common adverse reactions (occurring in ≥ 20% of patients) were nausea, fatigue/asthenia and alopecia.

Table 9 summarises the adverse reactions that occurred in patients treated with IMFINZI plus chemotherapy.

Table 9 Adverse events occurring in ≥10% of patients (CASPIAN)

Adverse events	IMFINZI with etoposide and either carboplatin or cisplatin N = 265		Etoposide and either carboplatin or cisplatin N = 266	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
Respiratory, thoracic and mediastinal disorders				
Cough/productive cough	15	0.8	9	0
Gastrointestinal disorders				
Nausea	34	0.4	34	1.9
Constipation	17	0.8	19	0
Vomiting	15	0	17	1.1
Diarrhoea	10	1.1	11	1.1
Endocrine disorders				
Hyperthyroidism [a]	10	0	0.4	0
Skin and subcutaneous tissue disorders				
Alopecia	31	1.1	34	0.8
Rash [b]	11	0	6	0
General disorders and administration site conditions				
Fatigue/asthenia	32	3.4	32	2.3
Metabolism and nutrition disorders				
Decreased appetite	18	0.8	17	0.8

[a] Includes hyperthyroidism and Basedow's disease

[b] Includes rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema, rash and dermatitis

Table 10 summarises the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 10 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients (CASPIAN)

Laboratory Abnormality	IMFINZI with etoposide and carboplatin or cisplatin	Etoposide and carboplatin or cisplatin
	Grade [b] 3 or 4 (%) [c]	Grade [b] 3 or 4 (%) [c]
Chemistry		
Hyponatraemia	11	13
Hypomagnesemia	11	6
Hyperglycaemia	5	5
Alkaline phosphatase increased	4.9	3.5
ALT increased	4.9	2.7
AST increased	4.6	1.2
Hypocalcaemia	3.5	2.4
Blood creatinine increased	3.4	1.1
Hyperkalaemia	1.5	3.1
TSH decreased < LLN and ≥ LLN at baseline	NA	NA
Haematology		
Neutropenia	41	48
Lymphopenia	14	13
Anaemia	13	22
Thrombocytopenia	12	15

ALT – alanine aminotransferase; AST – aspartate aminotransferase; TSH – thyroid-stimulating hormone; LLN - lower limit of normal

[a] The frequency cut off is based on any grade change from baseline

[b] Graded according to NCI CTCAE version 4.03

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI (range: 258 to 263) and chemotherapy (range: 253 to 262) except magnesium IMFINZI + chemotherapy (18) and chemotherapy (16)

The proportion of patients who experienced a TSH shift from baseline that was ≤ ULN to any grade > ULN was 17.7% and a TSH shift from baseline that was ≥ LLN to any grade < LLN was 31.3%.

Biliary tract cancer (BTC)

TOPAZ-1 study

The safety of IMFINZI in combination with gemcitabine and cisplatin in locally advanced or metastatic BTC was evaluated in TOPAZ-1, a randomised, double-blind, placebo-controlled, multicentre trial. Safety data are available for the 680 patients, of which 338 patients received IMFINZI 1500 mg in combination with chemotherapy every 3 weeks up to 8 cycles followed by IMFINZI 1500 mg every 4 weeks until disease progression or unacceptable toxicity.

The trial excluded patients with active or prior documented autoimmune or inflammatory disorders, HIV infection or active infections, including tuberculosis or hepatitis C (see Section 5.1 Pharmacodynamic properties - Clinical trials).

IMFINZI was discontinued due to adverse events in 6.2% of the patients receiving IMFINZI plus chemotherapy. The most frequently reported adverse events resulting in discontinuation were sepsis (3 patients) and ischaemic stroke (2 patients). The remaining adverse events were dispersed across system organ classes and reported in 1 patient each. Serious adverse events occurred in 47.3% of patients receiving IMFINZI plus chemotherapy. The most frequent serious adverse events reported in at least 2% of patients were cholangitis (7.4%), pyrexia (3.8%), anaemia (3.6%), sepsis (3.3%) and acute kidney injury (2.4%). Fatal adverse events occurred in 3.6% of patients receiving

IMFINZI plus chemotherapy. These include sepsis, ischaemic stroke, upper gastrointestinal haemorrhage (reported in 2 patients each). The most common adverse events (occurring in ≥20% of patients) were nausea, constipation, abdominal pain, fatigue, pyrexia, decreased appetite, anaemia, neutropenia, neutrophil count decreased and platelet count decreased.

Table 11 summarises the adverse events that occurred in ≥10% of patients treated with IMFINZI plus chemotherapy.

Table 11 Adverse events occurring in ≥10% of patients on IMFINZI (TOPAZ-1)

Adverse event	IMFINZI with gemcitabine and cisplatin N = 338		Placebo with gemcitabine and cisplatin N = 342	
	All grades [a] (%)	Grade [a] 3-4 (%)	All grades [a] (%)	Grade [a] 3-4 (%)
Gastrointestinal disorders				
Nausea	40	1.5	34	1.8
Constipation	32	0.6	29	0.3
Abdominal pain [b]	24	0.6	23	2.9
Vomiting	18	1.5	18	2.0
Diarrhoea	17	1.2	15	1.8
General disorders and administration site conditions				
Fatigue [c]	39	6.2	39	5.6
Pyrexia	20	1.5	16	0.6
Metabolism and nutrition disorders				
Decreased appetite	26	2.1	23	0.9
Skin and subcutaneous tissue disorders				
Rash [d]	18	0.9	12	0
Pruritus	11	0	8	0

[a] Graded according to NCI CTCAE version 5.0

[b] Includes abdominal pain, abdominal pain lower, abdominal pain upper and flank pain.

[c] Includes fatigue and asthenia.

[d] Includes rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, rash erythematous, eczema, erythema and rash.

Table 12 summarises the laboratory abnormalities that occurred in at least 20% of patients treated with IMFINZI plus chemotherapy.

Table 12 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients (TOPAZ-1)

Laboratory abnormality	IMFINZI with gemcitabine & cisplatin	Placebo with gemcitabine & cisplatin
	Grade [b] 3 or 4 (%)	Grade [b] 3 or 4 (%)
Chemistry		
Hyponatraemia	18	13
GGT increased	12	13
Hyperbilirubinemia	9.6	13.5
Hypokalaemia	7.8	4.4
AST increased	7.5	7.9
ALT increased	6.6	6.2
Blood creatinine increased	5.1	2.1
Hypomagnesemia	4.5	2.2

Laboratory abnormality	IMFINZI with gemcitabine & cisplatin	Placebo with gemcitabine & cisplatin
	Grade [b] 3 or 4 (%)	Grade [b] 3 or 4 (%)
Hypoalbuminemia	3.6	2.9
Hyperkalaemia	2.1	2.1
Alkaline phosphatase increased	1.8	3.8
Hypocalcaemia	1.8	2.4
Haematology		
Neutropenia	48	49
Anaemia	31	28
Leukopenia	28	28
Lymphopenia	23	15
Thrombocytopenia	18	18

ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyl transferase

[a] The frequency cut off is based on any grade change from baseline

[b] Graded according to NCI CTCAE version 5.0. Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI + Gem/Cis (range: 312 to 335) and Placebo + Gem/Cis (range: 319 to 341).

Hepatocellular carcinoma (HCC)

HIMALAYA study and Study 22

A total of 462 patients with uHCC received STRIDE in two studies: HIMALAYA (N=388), a randomised, open-label, multicentre study and Study 22 (N=74), an open-label, multi-part, multicentre study. The patients were treated as long as clinical benefit was observed or until unacceptable toxicity.

The studies excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented GI bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders (see Section 5.1 Pharmacodynamic properties - Clinical trials).

In the two studies combined (HCC pool), the median duration of exposure to STRIDE was 20 weeks (range: 2 to 185). STRIDE was discontinued due to adverse events in 63 (13.6%) patients. The most common adverse events leading to treatment discontinuation were pneumonitis, colitis, diarrhoea and AST increased. Serious adverse events occurred in 40.9% of patients. The most frequent serious adverse events reported in at least ≥2% of patients were pneumonitis, colitis and diarrhoea. The most common adverse events (occurring in ≥20% of patients) were rash, pruritus and diarrhoea.

Table 13 summarises the adverse events that occurred in patients treated with STRIDE in the HIMALAYA study.

Table 13 Adverse events occurring in ≥10% of patients in the STRIDE treatment arm (regardless of causality) (HIMALAYA)

Adverse events	STRIDE (N=388)		Sorafenib (N=374)	
	All grades (%)	Grade 3-4 (%)	All grades (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhoea	26.5	4.4	44.7	4.3
Abdominal pain	11.9	1.3	16.8	3.2
Nausea	12.1	0	14.2	0
Skin and subcutaneous tissue disorders				
Pruritus	22.9	0	6.4	0.3
Rash	22.4	1.5	13.6	1.1
Metabolism and nutrition disorders				
Decreased appetite	17.0	1.3	17.9	0.8
General disorders and administration site conditions				
Asthenia	10.1	1.8	11.8	2.7
Fatigue	17.0	2.1	19.0	2.9
Pyrexia	12.9	0.3	8.8	0
Psychiatric disorders				
Insomnia	10.3	0.3	4.3	0
Endocrine disorders				
Hypothyroidism	12.1	0	4.3	0

STRIDE – *Single Tremelimumab Regular Interval Durvalumab*

Table 14 summarises the laboratory abnormalities that occurred patients treated with STRIDE in the HIMALAYA study.

Table 14 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients treated with STRIDE (HIMALAYA)

Laboratory abnormality	STRIDE		Sorafenib	
	Any grade [b] (%)[c]	Grade 3 [b] or 4 (%)[c]	Any grade [b] (%)[c]	Grade 3 [b] or 4 (%)[c]
Chemistry				
AST increased	63.1	26.8	54.6	21.1
ALT increased	56.2	17.8	52.6	12.2
Sodium decreased	46.0	15.3	39.8	11.1
Bilirubin increased	41.4	8.2	47.4	10.5
Alkaline phosphatase increased	41.2	8.3	44.4	5.4
Glucose increased	38.9	13.5	29.1	3.7
Calcium decreased	33.5	0	43.0	0.3
Albumin decreased	31.3	0.5	37.1	1.7
Potassium increased	28.4	3.8	21.3	2.6
Creatinine increased	20.9	1.3	14.8	0.9
Haematology				
Haemoglobin decreased	51.6	4.8	40.3	6.0
Lymphocytes decreased	41.4	11.1	39.3	10.0
Platelets decreased	28.8	1.6	34.7	3.1

Laboratory abnormality	STRIDE		Sorafenib	
	Any grade [b] (%)[c]	Grade 3 [b] or 4 (%)[c]	Any grade [b] (%)[c]	Grade 3 [b] or 4 (%)[c]
Leukocytes decreased	20.2	0.8	30.1	1.1

ALT – alanine aminotransferase; AST – aspartate aminotransferase; STRIDE – *Single Tremelimumab Regular Interval Durvalumab*

[a] The frequency cut-off is based on any grade change from baseline for STRIDE.

[b] Graded according to NCI CTCAE version 4.03.

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI with tremelimumab (range: 367-378) and sorafenib (range: 344-352).

Table 15 summarises the adverse events that occurred in patients treated with STRIDE in Study 22.

Table 15 Adverse events occurring in ≥10% of patients in the STRIDE treatment arm (regardless of causality) (Study 22)

Adverse events	STRIDE (N=74)	
	All grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders		
Pruritus	39.2	0
Rash	37.8	4.1
Hepatobiliary disorders		
Ascites	13.5	5.4
General disorders and administration site conditions		
Fatigue	23.0	4.1
Pyrexia	18.9	0
Oedema peripheral	16.2	0
Respiratory, thoracic and mediastinal disorders		
Cough	20.3	1.4
Gastrointestinal disorders		
Diarrhoea	18.9	1.4
Amylase increased	16.2	8.1
Lipase increased	16.2	12.2
Abdominal pain	16.2	4.1
Nausea	13.5	0
Constipation	12.2	0
Abdominal distension	10.8	1.4
Vomiting	10.8	0
Metabolism and nutrition disorders		
Decreased appetite	13.5	0
Endocrine disorders		
Hypothyroidism	10.8	0
Musculoskeletal and connective tissue disorders		
Arthralgia	10.8	0

STRIDE – *Single Tremelimumab Regular Interval Durvalumab*

Table 16 summarises the laboratory abnormalities that occurred patients treated with STRIDE in Study 22.

Table 16 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients treated with STRIDE (Study 22)

Laboratory abnormality	STRIDE	
	Any grade [b] (%) [c]	Grade 3 [b] or 4 (%) [c]
Chemistry		
Creatinine increased	91.5	4.2
AST increased	63.4	26.8
ALT increased	60.6	18.3
Glucose increased	56.3	19.7
Albumin decreased	53.5	0
Sodium decreased	50.7	9.9
Alkaline phosphatase increased	36.6	5.6
Bilirubin increased	33.8	5.6
Calcium decreased	29.6	1.4
Haematology		
Lymphocytes decreased	48.1	19.2
Haemoglobin decreased	42.3	8.5
Platelets decreased	32.4	0
Leukocytes decreased	23.9	1.4

ALT – alanine aminotransferase; AST – aspartate aminotransferase; STRIDE – *Single Tremelimumab Regular Interval Durvalumab*

[a] The frequency cut-off is based on any grade change from baseline for STRIDE.

[b] Graded according to NCI CTCAE version 4.03.

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI with tremelimumab (range: 52-71).

Endometrial cancer

DUO-E study

The safety of IMFINZI in combination with carboplatin and paclitaxel followed by IMFINZI as monotherapy (N=235) is based on data in patients from the DUO-E (endometrial cancer) study. The safety profile was consistent with IMFINZI monotherapy and chemotherapy safety profiles.

Table 17 and Table 18 summarise the very common adverse drug reactions (ADR) and laboratory abnormalities in DUO-E, respectively. Refer to the Product Information for carboplatin and paclitaxel for additional information about ADR.

Table 17 Very common adverse drug reactions (ADR) occurring in ≥10% of patients treated with IMFINZI in combination with carboplatin or paclitaxel followed by IMFINZI as monotherapy (DUO-E)

Adverse drug reactions (by SOC)	Percentage (%) of patients			
	CT + IMFINZI [a] (n=235)		CT (n=236)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Blood and lymphatic system disorders (see also laboratory anomalies table below)				
Anaemia [b]	47.2	16.2	54.2	14.8
Neutropenia [b]	32.3	19.1	38.6	20.8
Thrombocytopenia [b]	28.1	6.8	22.0	4.7
Leukopenia [b]	17.0	4.7	19.1	5.5

Adverse drug reactions (by SOC)	Percentage (%) of patients			
	CT + IMFINZI [a] (n=235)		CT (n=236)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine disorders				
Hypothyroidism [c]	16.6	0	4.7	0
Gastrointestinal disorders				
Nausea [b]	40.9	0.4	44.5	1.3
Constipation [b]	27.2	0.9	34.3	2.1
Diarrhoea	31.5	1.7	28.0	2.5
Vomiting [b]	20.9	1.7	18.2	1.3
Abdominal pain [d]	25.1	0.4	25.0	1.3
General disorders and administration site conditions				
Fatigue [b]	43.0	3.4	44.5	3.0
Peripheral oedema [e]	15.3	0.9	11.4	0.4
Metabolism and nutrition disorders				
Decreased appetite [b]	17.9	0	19.5	0
Musculoskeletal and connective tissue disorders				
Myalgia	13.6	0	18.6	0.4
Nervous system disorders				
Neuropathy peripheral [b]	53.6	1.3	58.5	3.0
Respiratory, thoracic and mediastinal disorders				
Cough / productive cough	15.7	0	12.3	0
Skin and subcutaneous tissue disorders				
Alopecia [b]	50.2	0	50.0	0
Rash [b,f]	26.4	1.7	20.3	1.3
Pruritus	15.3	0	12.3	0

CT – chemotherapy (carboplatin and paclitaxel); SOC – system order class

[a] Overall study of induction treatment with up to six 21-day cycles with carboplatin and paclitaxel in combination with IMFINZI, followed by maintenance treatment with IMFINZI as monotherapy.

[b] Known ADR of chemotherapy in the DUO-E study

[c] Includes blood thyroid stimulating hormone increased and hypothyroidism.

[d] Includes abdominal pain, abdominal pain lower, flank pain and abdominal pain upper.

[e] Includes peripheral oedema and peripheral swelling.

[f] Includes eczema, erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic and rash pustular.

Table 18 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients (DUO-E)

Laboratory abnormality	Grade 3 or 4 [b] (percentage (%)[c] of patients)	
	CT + IMFINZI	CT
Chemistry		
Hyponatremia	5.6	4.8
Hypomagnesemia	3.3	1.9
Hypermagnesemia	2.3	0.9
Hypokalaemia	3.9	1.7
Creatinine increased	0.4	1.7
ALT increased	3.5	1.3

Laboratory abnormality	Grade 3 or 4 [b] (percentage (%)[c] of patients)	
	CT + IMFINZI	CT
AST increased	3.0	0.4
GGT increased	4.7	2.9
Alkaline phosphatase increased	0.4	0.4
Haematology		
Neutrophils decreased	22.5	23.3
Leukocytes decreased	15.2	15.6
Lymphocytes decreased	11.4	15.9
Haemoglobin decreased	16.9	14.3
Platelets decreased	8.7	5.6

CT – chemotherapy (carboplatin and paclitaxel); ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyl transferase

[a] The frequency cut-off is based on any grade change from baseline.

[b] Graded according to NCI CTCAE version 5.0

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: chemotherapy + IMFINZI (range: 202 to 231) and chemotherapy (range: 205 to 231)

Bladder cancer

NIAGARA (muscle invasive bladder cancer)

The safety of IMFINZI in combination with neoadjuvant gemcitabine and cisplatin followed by surgery and continued IMFINZI treatment as adjuvant monotherapy in patients with MIBC is based on data in 530 patients from the NIAGARA study and was consistent with IMFINZI monotherapy and known chemotherapy safety profiles.

See Section 5.1 Pharmacodynamic properties - Clinical trials for NIAGARA study design and patient population.

The median duration of exposure to IMFINZI 1500 mg every 3 weeks in the neoadjuvant phase was 12 weeks (range: 1 to 84 weeks). The median duration of exposure to IMFINZI 1500 mg every 4 weeks in the adjuvant phase was 32 weeks (range: 2 to 50 weeks).

Table 19 and Table 20 summarise the very common adverse events and laboratory abnormalities in NIAGARA, respectively.

Table 19 Adverse events occurring in ≥10% of patients in the IMFINZI in combination with gemcitabine and cisplatin arm (regardless of causality) (NIAGARA)

Adverse event (by SOC)	IMFINZI with gemcitabine & cisplatin N = 530		gemcitabine & cisplatin N = 526	
	Any grade [a] (%)	Grade [a] 3-4 (%)	Any grade [a] (%)	Grade [a] 3-4 (%)
Gastrointestinal disorders				
Nausea [c]	54	1.5	48	1
Constipation [c]	39	0.8	39	0.8
Diarrhoea [c]	21	1.5	14	0.4
Abdominal pain [b,c]	20	0.9	13	1
Vomiting [b,c]	20	0.9	19	0.2
Endocrine disorders				
Hypothyroidism [b,c]	13	0.4	2.3	0

Adverse event (by SOC)	IMFINZI with gemcitabine & cisplatin N = 530		gemcitabine & cisplatin N = 526	
	Any grade [a] (%)	Grade [a] 3-4 (%)	Any grade [a] (%)	Grade [a] 3-4 (%)
Nervous system disorders				
Neuropathy peripheral [b,c]	16	0.2	14	0
Headache [b]	11	0	11	0
Dizziness [b]	11	0	10	0.2
Skin and subcutaneous tissue disorders				
Rash [b,c]	23	1.3	12	0.6
Pruritus [c]	15	0	7	0
General disorders and administration site conditions				
Fatigue [b,c]	52	2.3	49	3
Pyrexia [b,c]	22	0.4	17	0
Oedema [b]	13	0.4	13	0
Metabolism and nutrition disorders				
Decreased appetite [c]	27	0.6	25	0.6
Vascular disorders				
Hypertension [b]	12	4.5	9	2.9
Haemorrhage [b]	11	0.9	10	2.1

SOC - system organ class

[a] Graded according to NCI CTCAE version 5

[b] Includes multiple similar terms

[c] Adverse drug reaction (very common)

Table 20 Select laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients in the IMFINZI in combination with gemcitabine and cisplatin arm (NIAGARA)

Laboratory abnormality	IMFINZI with gemcitabine and cisplatin	Gemcitabine and cisplatin
	Grade [b] 3 or 4 (%)[c]	Grade [b] 3 or 4 (%) [c]
Chemistry		
Blood creatinine increased	9	7
Sodium decreased	9	10
Potassium increased	4.2	4.4
ALT increased	2.3	4.0
Magnesium decreased	1.9	2.3
AST increased	1.5	2.1
Calcium decreased	1.3	1.2
Alkaline phosphatase increased	0.8	0.4
Haematology		
Neutrophils decreased	31	34
Haemoglobin decreased	13	13
Lymphocytes decreased	10	8
Platelets decreased	6	7

ALT – alanine aminotransferase; AST – aspartate aminotransferase

[a] The frequency cut off is based on any grade change from baseline.

[b] Graded according to NCI CTCAE version 5

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI + gemcitabine and cisplatin (range: 482 to 528) and gemcitabine and cisplatin (range: 467 to 521).

Neoadjuvant phase of NIAGARA

A total of 530 patients received at least 1 dose of IMFINZI in combination with chemotherapy as neoadjuvant treatment in the IMFINZI treatment arm, and 526 patients received at least 1 dose of chemotherapy as neoadjuvant treatment in the chemotherapy treatment arm.

Serious adverse events occurred in 24% of patients who received IMFINZI in combination with chemotherapy; the most frequent (≥1%) serious adverse events were pulmonary embolism (1.9%), febrile neutropenia (1.5%), acute kidney injury (1.3%), thrombocytopenia (1.3%), urinary tract infection (1.3%) and pneumonia (1.3%). Fatal adverse events occurred in 1.1% of patients including sepsis (0.2%), myocardial infarction (0.2%) and pulmonary embolism (0.2%). . One fatal adverse event of pneumonia was reported in 1 (0.2%) patient in the post-surgery phase before adjuvant treatment started.

Permanent discontinuation of IMFINZI due to an adverse event in the neoadjuvant phase occurred in 9% of patients while receiving IMFINZI in combination with chemotherapy. The most frequent (≥0.5%) adverse events that led to permanent discontinuation of IMFINZI were blood creatinine increased (0.9%), neutropenia (0.6%), acute kidney injury (0.6%), asthenia (0.6%) and fatigue (0.6%).

Of the 530 patients in the IMFINZI treatment arm and 526 patients in the chemotherapy treatment arm who received neoadjuvant treatment, 1 (0.2%) patient in each treatment arm did not receive surgery due to adverse event. The adverse events that led to cancellation of surgery in the IMFINZI treatment arm was interstitial lung disease (ILD).

Of the 469 patients in the IMFINZI treatment arm who underwent radical cystectomy, 4 (0.8%) patients experienced delay of surgery (defined as occurring more than 56 days after the last dose of neoadjuvant treatment) due to adverse events. Of the 446 patients in the chemotherapy treatment arm who underwent radical cystectomy, 1 (0.2%) patient experienced delay of surgery due to adverse events.

Adjuvant phase of NIAGARA

A total of 383 patients (72%) in the IMFINZI treatment arm received at least 1 dose of adjuvant treatment.

Serious adverse events occurred in 26% of patients receiving IMFINZI as adjuvant treatment. The most frequent serious adverse events (occurring in ≥1% of patients) were urinary tract infection (7%), acute kidney injury (3.7%), hydronephrosis (2.1%), pyelonephritis (2.1%), urosepsis (1.8%) and sepsis (1.6%). Fatal adverse events occurred in 1.8% of patients, including COVID-19 (0.3%), severe acute respiratory syndrome (0.3%), cardiopulmonary failure (0.3%), gastrointestinal haemorrhage (0.3%) and chronic hepatic failure (0.3%).

Permanent discontinuation of adjuvant IMFINZI due to an adverse event occurred in 5% of patients. The most frequent (≥0.5%) adverse events that led to permanent discontinuation of adjuvant IMFINZI were nephritis (0.8%), fatigue (0.5%), diarrhoea (0.5%), decreased appetite (0.5%) and pneumonitis (0.5%).

Gastric and gastroesophageal junction (GOJ) cancer (GC/GOJC)

MATTERHORN study (resectable gastric and GOJ adenocarcinoma)

The safety of IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, in patients with GC/GOJC was evaluated in the MATTERHORN study. See Section 5.1 Pharmacodynamic properties - Clinical trials for MATTERHORN study design and patient population.

Safety data are available for 944 patients who received IMFINZI in combination with FLOT chemotherapy (n=475) or placebo in combination with FLOT chemotherapy (n=469). The median duration of exposure to IMFINZI 1500 mg every 4 weeks in the neoadjuvant phase was 8 weeks (range: 1.4 to 8.7 weeks). The median duration of exposure to IMFINZI 1500 mg every 4 weeks in the adjuvant phase was 48 weeks (range: 1.9 to 50.1 weeks). The safety profile was consistent with IMFINZI monotherapy and the known FLOT chemotherapy safety profiles.

Table 21 and Table 22 summarise the adverse reactions (≥10%) and laboratory abnormalities respectively that occurred in patients treated with IMFINZI in combination with FLOT chemotherapy in the MATTERHORN study.

Table 21 Adverse reactions occurring in ≥10% of patients in the IMFINZI in combination with FLOT chemotherapy arm (MATTERHORN)

Adverse reaction	IMFINZI + FLOT chemotherapy N=475		Placebo + FLOT chemotherapy N=469	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Diarrhoea [a,b]	64	8	59	7
Nausea [b]	51	2.5	51	1.5
Vomiting [a,b]	26	2.1	26	3
Abdominal pain [a,b]	27	2.3	29	1.3
Stomatitis [a,b]	20	1.1	15	0.6
Constipation [b]	16	0	17	0.9
Dysphagia	10	1.5	8	1.5
General disorders and administration site conditions				
Fatigue [a,b]	47	5	45	5
Pyrexia [a, b]	20	0.8	16	1.3
Metabolism and nutrition disorders				
Decreased appetite [a,b]	31	3.2	30	2.1
Nervous system disorders				
Peripheral neuropathy [a,b]	51	3.6	47	2.3
Dysgeusia [a]	19	0	15	0
Skin and subcutaneous tissue disorders				
Alopecia [b]	31	0	32	0
Rash [a,b]	30	1.5	20	0.4
Pruritus [a,b]	11	0	5	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [a]	21	1.5	19	0.6
Infections and infestations				
COVID-19 [a]	19	1.7	16	0.6
Pneumonia [a,b]	11	3.8	10	4.3

Adverse reaction	IMFINZI + FLOT chemotherapy N=475		Placebo + FLOT chemotherapy N=469	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
Investigations				
Weight decreased	15	2.1	19	3.4
Vascular disorders				
Haemorrhage [a]	14	2.5	15	2.8
Respiratory, thoracic and mediastinal disorders				
Cough [a,b]	10	0	10	0

[a] Includes multiple similar terms (as per FDA requirements)

[b] Very common ADR

FLOT chemotherapy (regimen of fluorouracil, leucovorin, oxaliplatin and docetaxel)
Source: FDA approved PI

Table 22 Laboratory abnormalities worsening from baseline occurring in ≥20% [a] of patients in the IMFINZI in combination with FLOT chemotherapy arm(MATTERHORN)

Laboratory abnormality	Grade 3 or 4 [b] (percentage (%)[c] of patients)	
	IMFINZI + FLOT chemotherapy N=475	Placebo + FLOT chemotherapy N=469
Chemistry		
AST increased	6	6
ALT increased	7	6
GGT increased	10	6
Lipase increased	16	15
Alkaline phosphatase increased	3.2	1.5
Hypocalcaemia	0.8	2.6
Amylase increased	6	4.5
Hypokalaemia	8	8
Hyponatremia	4.4	4.7
Hypoalbuminaemia	1.5	0.2
Hyperkalaemia	0.6	1.3
Haematology		
Leukocytes decreased	14	17
Neutrophils decreased	41	44
Haemoglobin decreased	7	8
Lymphocytes decreased	13	13
Platelets decreased	1.1	1.9

ALT – alanine aminotransferase; AST – aspartate aminotransferase; FLOT chemotherapy (regimen of fluorouracil, leucovorin, oxaliplatin and docetaxel); GGT – gamma glutamyl transferase

[a] The frequency cut-off is based on any grade change from baseline.

[b] Graded according to NCI CTCAE version 5.0

[c] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: IMFINZI + FLOT chemotherapy (range: 444 to 472) and FLOT chemotherapy (range: 443 to 468)

Source: FDA approved PI

Safety profile by phase of treatment

Table 23 Safety profile by phase of treatment (MATTERHORN)

Treatment phase	IMFINZI + FLOT chemotherapy	Placebo + FLOT chemotherapy
Neoadjuvant phase		
Number of patients	475	469
Serious adverse events (%)	21	18
Deaths during treatment-emergent period (%)	1.9	1.7
Permanent discontinuation of IMFINZI or placebo (%)	2.5	2.1
No surgery due to adverse event (%)	0.6	0.4
Delay in surgery due to adverse event (%)	2.3	2.6
Adjuvant phase		
Number of patients	365	351
Serious adverse events (%)	29	26
Deaths during treatment-emergent period (%)	2.2	2.6
Permanent discontinuation of IMFINZI or placebo (%)	7	4.6
Adjuvant phase (IMFINZI as monotherapy)		
Number of patients	345	331
Serious adverse events (%)	14	15
Deaths during Treatment-emergent period (%)	1.7	2.4
Permanent discontinuation of IMFINZI or placebo (%)	6	2.7

Source: FDA approved PI

Serious adverse drug reactions (≥2%) in the IMFINZI arm were diarrhoea (2.5%) during the neoadjuvant phase, and pneumonia (2.5%) in the adjuvant phase.

Deaths (≥2 patients) in the IMFINZI arm were septic shock (0.6%) and acute coronary syndrome (0.4%) during the neoadjuvant phase; gastrointestinal perforation (0.5%) and COVID-19 (0.5%) during adjuvant phase; and gastrointestinal perforation (0.6%) and COVID-19 (0.6%) in the monotherapy adjuvant phase.

Permanent discontinuation of IMFINZI (≥2 patients) due an adverse event in the IMFINZI arm were nephritis (0.4%) during the neoadjuvant phase; hepatitis (1.1%), pneumonitis (1.1%), rash (0.8%), musculoskeletal pain (0.5%) and renal failure (0.5%) during adjuvant phase; and hepatitis (0.9%), pneumonitis (0.9%), musculoskeletal pain (0.6%) and renal failure (0.6%) during the monotherapy adjuvant phase.

Description of selected adverse reactions

The data below reflect information for significant adverse reactions for IMFINZI as monotherapy in the pooled safety dataset across tumour types (n=3006) and IMFINZI in combination with tremelimumab (75 mg every 4 weeks) in the pooled safety dataset across tumour types (n=2280; pan-tumour pool) and STRIDE in the HCC pool (n=462). Significant adverse reactions for IMFINZI when given in combination with etoposide and carboplatin or cisplatin in the CASPIAN study were consistent with IMFINZI monotherapy and did not present clinically relevant differences. No new adverse reactions were identified for IMFINZI when given in combination with gemcitabine and cisplatin in the TOPAZ-1 study.

The management guidelines for these adverse reactions are described in Sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

Immune-mediated pneumonitis

In patients receiving IMFINZI monotherapy, 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 CRT within 1 to 42 days prior to initiation of study treatment (9.9%), compared to 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, 30 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day), and 2 patients also received infliximab. In the placebo group, 12 patients 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 ADRIATIC study in patients with LS-SCLC (n=262 in the IMFINZI arm and n=265 in the placebo arm), who had completed treatment with CRT within 1 to 42 days prior to initiation of study treatment, immune-mediated pneumonitis occurred in 31 (11.8%) patients in the IMFINZI-treated group and 8 (3.0%) patients in the placebo group, including Grade 3 in 5 (1.9%) patients on IMFINZI vs 1 (0.4%) patient on placebo, and Grade 5 in 1 (0.4%) patient on IMFINZI. The median time to onset in the IMFINZI-treated group was 55 days (range: 1-375 days) vs 65.5 days (range: 24-124 days) in the placebo group. In the IMFINZI-treated group, 25 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received infliximab. In the placebo group, 7 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Resolution occurred in 18 patients in the IMFINZI-treated group vs 3 in placebo.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, immune-mediated pneumonitis occurred in in 86 (3.8%) patients, including Grade 3 in 30 (1.3%) patients, Grade 4 in 1 (<0.1%) patient, and Grade 5 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.

HCC pool

In patients receiving STRIDE, 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 patients receiving IMFINZI monotherapy, immune-mediated hepatitis occurred in 67 (2.2%) patients, including Grade 3 in 35 (1.2%) patients, Grade 4 in 6 (0.2%) and Grade 5 in 4 (0.1%) patients. The median time to onset was 36 days (range: 3-333 days). Forty-four of the 67 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 29 patients.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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 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.

HCC pool

In patients receiving STRIDE, 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 patients receiving 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 one patient also received mycophenolate treatment. IMFINZI was discontinued in 9 patients. Resolution occurred in 43 patients.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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 was observed in patients receiving IMFINZI in combination with tremelimumab.

HCC pool

In patients receiving STRIDE, 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 not observed in patients receiving STRIDE.

Immune-mediated endocrinopathies

Immune-mediated hypothyroidism

In patients receiving 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, 6 patients received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day) for immune-mediated hypothyroidism followed by hormone replacement. No patients discontinued IMFINZI due to immune-mediated hypothyroidism. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 20 patients or immune-mediated thyroiditis in 3 patients.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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 patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day). Two-hundred and five patients required endocrine therapy. Treatment was 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.

HCC pool

In patients receiving STRIDE, 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 (thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker). Resolution occurred in 6 patients. Immune-mediated hypothyroidism was preceded by immune-mediated hyperthyroidism in 4 patients.

Immune-mediated hyperthyroidism

In patients receiving 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: 1-253 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.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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 corticosteroids, 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). Treatment was discontinued in 1 patient. Resolution occurred in 47 patients.

HCC pool

In patients receiving STRIDE, 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 corticosteroids, 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 patients receiving 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, 1 patient received high-dose corticosteroids (at least 40 mg prednisone or equivalent per day). One patient discontinued IMFINZI due to immune-mediated thyroiditis.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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). Thirteen 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.

HCC pool

In patients receiving STRIDE, 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, thiamazole, carbimazole, propylthiouracil, perchlorate, calcium channel blocker, or beta-blocker. Resolution occurred in 2 patients.

Immune-mediated adrenal insufficiency

In patients receiving 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.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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). Seven patients required endocrine therapy. Treatment was discontinued in 1 patient. Resolution occurred in 11 patients.

HCC pool

In patients receiving STRIDE, 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 patients receiving IMFINZI monotherapy, Grade 3 immune-mediate type 1 diabetes mellitus occurred in 1 (<0.1%) patient. The time to onset was 43 days. This patient required long-term insulin therapy and IMFINZI was permanently discontinued due to immune-mediated type 1 diabetes mellitus.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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 in 1 patient. Resolution occurred in 1 patient.

HCC pool

In patients receiving STRIDE, immune-mediated type 1 diabetes mellitus was not observed.

Immune-mediated hypophysitis/hypopituitarism

In patients receiving 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.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, immune-mediated hypophysitis/hypopituitarism occurred in 16 (0.7%) patients, including Grade 3 in 8 (0.4%) patients. The median time to onset 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.

HCC pool

In patients receiving STRIDE, 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 patients receiving 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.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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.

HCC pool

In patients receiving STRIDE, 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 patients receiving 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-four 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 31 patients.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, 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.

HCC pool

In patients receiving STRIDE, 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.

Immune-mediated neurological adverse events in ongoing and completed trials

Meningitis

Infusion-related reactions

In patients receiving 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.

IMFINZI + tremelimumab pan-tumour pool

In patients receiving IMFINZI in combination with tremelimumab, infusion-related reactions occurred in 45 patients (2.0%), including Grade 3 in 2 (<0.1%) patients. There were no Grade 4 or 5 events.

HCC pool

In patients receiving STRIDE, infusion-related reactions occurred in 13 (2.8%) patients.

Immune checkpoint inhibitor class effects

There have been cases of the following ADR reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with durvalumab: pancreatic exocrine insufficiency, haemophagocytic lymphohistiocytosis (HLH), aplastic anaemia.

Adverse drug reactions in patients with IMFINZI:

- As monotherapy - coeliac disease (rare)
- In combination with chemotherapy - coeliac disease (rare)
- In combination with tremelimumab - coeliac disease (rare)

Paediatrics and adolescents

The safety of IMFINZI in combination with tremelimumab in paediatric and adolescents aged less than 18 years has not been established. No new safety signals were observed in a clinical study evaluating 50 paediatric patients (<18 years), relative to the known safety profiles of IMFINZI and tremelimumab in adults. Of the 50 patients enrolled in the study, 42 received IMFINZI in combination with tremelimumab and 8 received IMFINZI only (see Section 5.2 Pharmacokinetic properties).

Post-marketing experience

The following adverse events have been identified during post-approval use of IMFINZI. Because these adverse events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic disorders: Autoimmune haemolytic anaemia

General disorders and administration site conditions: Systemic inflammatory response syndrome

Musculoskeletal and connective tissue disorders: Sjögren's syndrome, tenosynovitis, polymyalgia rheumatica

Nervous system disorders: Myelitis transverse

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no specific treatment in the event of durvalumab overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Expression of programmed cell death ligand-1 (PD-L1) protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. PD-L1 expression can be induced by inflammatory signals (e.g. IFN-gamma) and can be expressed on both tumour cells and tumour-associated immune cells in tumour microenvironment. PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80 (B7.1). By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, proliferation, and cytokine production.

Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 (B7.1). Durvalumab does not induce antibody dependent cell-mediated cytotoxicity (ADCC). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses. These antitumour responses may result in tumour elimination.

In preclinical studies, PD-L1 blockade by durvalumab led to increased T-cell activation and decreased tumour size in xenograft mouse models of human melanoma and/or pancreatic cancer cells as well as mouse syngeneic colorectal cancer.

The combination of durvalumab, a PD-L1 inhibitor, and tremelimumab, a CTLA-4 inhibitor functions to enhance anti-tumour T-cell activation and function at multiple stages of the immune response, maximizing anti-tumour immunity.

Clinical trials

Durvalumab doses of 10 mg/kg every 2 weeks, 1120 mg every 3 weeks or 1500 mg every 4 weeks were evaluated in NSCLC, ES-SCLC and endometrial cancer clinical studies. Based on the modelling and simulation of exposure, exposure-safety relationships and exposure-efficacy data comparisons, there are no anticipated clinically significant differences in efficacy and safety between durvalumab doses of 10 mg/kg every 2 weeks, 1120 mg every 3 weeks or 1500 mg every 4 weeks.

Non-small cell lung cancer (NSCLC)

AEGEAN study (resectable NSCLC)

AEGEAN was a randomised, double-blind, placebo-controlled, multicentre, Phase III study designed to evaluate the efficacy of IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, then continued as IMFINZI monotherapy after surgery, in patients with resectable NSCLC (Stage IIA to select Stage IIIB [AJCC, 8th edition]). The study enrolled previously untreated patients with documented squamous or non-squamous NSCLC and no prior exposure to immune-mediated therapy, a WHO/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and at least one RECIST 1.1 target lesion. Prior to randomisation, patients had tumour PD-L1 expression status confirmed using the Ventana PD-L1 (SP263) Assay.

The study excluded patients with active or prior documented autoimmune disease, or use of immunosuppressive medication within 14 days of the first dose of durvalumab. The study population for efficacy analysis (modified intent-to-treat [mITT]) excluded patients with known EGFR mutations or ALK rearrangements.

Randomisation was stratified by disease stage (Stage II vs. Stage III) and by PD-L1 expression on tumour cells (TC; TC<1% vs TC≥1%) status.

The AEGEAN study randomised 802 patients in a 1:1 ratio to receive perioperative IMFINZI (Arm 1) or placebo (Arm 2) in combination with neoadjuvant chemotherapy. Crossover between the study arms was not permitted. Efficacy analysis was conducted based on 740 patients in the mITT population.

- *Arm 1:* IMFINZI 1500 mg + chemotherapy every 3 weeks for up to 4 cycles prior to surgery, followed by IMFINZI 1500 mg every 4 weeks for up to 12 cycles after surgery
- *Arm 2:* Placebo + chemotherapy every 3 weeks for up to 4 cycles prior to surgery, followed by Placebo every 4 weeks for up to 12 cycles after surgery.

Patients who had surgical resection with R0 or R1 margins, and a post-surgical scan, were eligible to continue to adjuvant treatment. Following surgery, eligible patients started durvalumab or placebo treatment as soon as clinically feasible.

A RECIST 1.1 tumour assessment was performed at baseline, and upon completion of the neoadjuvant period (prior to surgery). The first post-surgical CT/MRI scan of the chest and abdomen (including the entire liver and both adrenals) was acquired 5 weeks ±2 weeks after surgery and prior to, but as close as possible to the start of adjuvant therapy. Tumour assessments were then conducted every 12 weeks (relative to the date of surgery) until week 48, every 24 weeks (relative to the date of surgery) until week 192 (approximately 4 years), and then every 48 weeks (relative to the date of surgery) thereafter until RECIST 1.1 defined radiological progressive disease, consent withdrawal, or death.

Survival assessments were conducted at month 2, 3, and 4 following treatment discontinuation and then every 2 months until month 12 followed by every 3 months.

The primary endpoints of the study were pathological complete response (pCR) by blinded central pathology review, and event-free survival (EFS) by Blinded Independent Central Review (BICR) assessment. The key secondary endpoints were major pathological response (MPR) by blinded central pathology review, disease free survival (DFS) by BICR, and overall survival (OS). Other secondary efficacy objectives included were EFS (PD-L1-TC ≥1% analysis set), pCR (PD-L1-TC ≥1% analysis set) and Patient Reported Outcomes (PRO).

At the planned interim analysis of pCR, the study met its prespecified boundary for declaring statistical significance for pCR and MPR. Subsequently, at the first planned interim analysis of EFS, the study met its prespecified boundary for declaring statistical significance for EFS.

The demographics and baseline disease characteristics were well balanced between the two study arms. Baseline demographics and disease characteristics of the population for efficacy analysis (mITT) were as follows: male (71.6%), female (28.4%), age ≥ 65 years (51.6%), median age 65 years (range: 30 to 88), WHO/ECOG PS 0 (68.4%), WHO/ECOG PS 1 (31.6), White (53.6%), Asian (41.5%), Black or African American (0.9%), American Indian or Alaska Native (1.4%), Other Race (2.6%), Hispanic or Latino (16.1%), Not Hispanic or Latino (83.9%). current or past smokers (85.5%), never smoker (14.5%), squamous histology (48.6%) and non-squamous histology (50.7%), Stage II (28.4%), Stage III (71.6%), PD-L1 expression status TC ≥1% (66.6%), PD-L1 expression status TC <1% (33.4%) . The demographics and baseline characteristics for the mITT population were similar to the ITT population except for the absence of patients with known EGFR mutations or ALK rearrangements.

Table 24 provides the curative intent surgery details for the mITT population.

Table 24 Curative intent surgery details (AEGEAN mITT population)

	IMFINZI + chemotherapy (N=366)	Placebo + chemotherapy (N = 374)
Curative intent surgery		
Patients who underwent surgery, n (%)	295 (80.6%)	302 (80.7%)
Patients who completed surgery, n (%)	284 (77.6%)	287 (76.7%)
Resection margin status, % of patients who completed surgery		
RO (no residual tumour)	94.7%	91.3%
R1 (microscopic residual tumour)	4.2%	7.7%
R2 (macroscopic residual tumour)	0.7%	0.7%

[a] DCO: 10 November 2022

The study demonstrated a statistically significant and clinically meaningful improvement in EFS of the IMFINZI arm compared to the placebo arm. The study also demonstrated a statistically significant and meaningful improvement in pCR of the IMFINZI arm compared to the placebo arm. OS data were not mature at the time of EFS analysis. See Table 25 and Figure 1.

Table 25 Efficacy results (AEGEAN mITT population)

	IMFINZI+chemotherapy (N=366)	Placebo+chemotherapy (N = 374)
Event free survival (EFS) [a]		
Number of events, n (%)	98 (26.8)	138 (36.9)
Median EFS (months) (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
EFS at 12 months, % (95% CI)	73.4 (67.9, 78.1)	64.5 (58.8, 69.6)
EFS at 24 months, % (95% CI)	63.3 (56.1, 69.6)	52.4 (45.4, 59.0)
HR (95% CI)	0.68 (0.53, 0.88)	
2-sided p-value[d]	0.003902	
Pathological complete response (pCR) [a,b,d]		
Number of patients with response	63	16
Response rate, % (95% CI)	17.21 (13.49, 21.48)	4.28 (2.46, 6.85)
Difference in proportions, % (95% CI)	12.96 (8.67, 17.57)	
Major pathological response (MPR) [a,c,d]		
Number of patients with response	122	46
Response rate, % (95% CI)	33.33 (28.52, 38.42)	12.30 (9.15, 16.06)
Difference in proportions, % (95% CI)	21.03 (15.14, 26.93)	

[a] Results are based on planned EFS interim analysis and pCR/MPR final analysis (DCO: 10 November 2022) which occurred 46.3 months after study initiation.

[b] Based on a pre-specified pCR interim analysis (DCO: 14 January 2022) in n =402, the pCR rate was statistically significant (p = 0.000036) compared to significance level of 0.0082%.

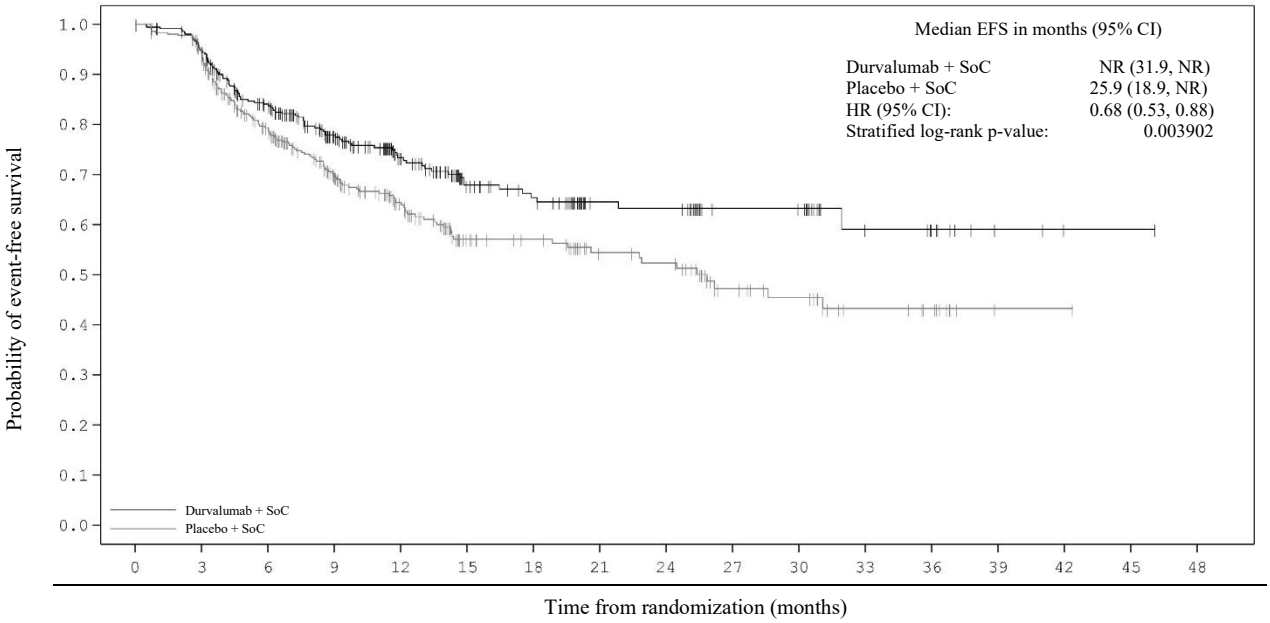
[c] Based on a pre-specified MPR interim analysis (DCO: 14 January 2022) in n=402, the MPR rate was statistically significant (p= 0.000002) compared to significance level of 0.0082%.

[d] The 2-sided p-value for pCR and MPR was calculated based on a stratified CMH test. The 2-sided p-value for EFS was calculated based on a stratified log-rank test. Stratification factors include PD-L1 and disease stage.

The boundary for declaring statistical significance for each of the efficacy endpoints were determined by a Lan-DeMets alpha spending function that approximates an O'Brien Fleming approach (EFS = 0.9899%, pCR = 0.0082%, MPR = 0.0082%, 2-sided).

HR – hazard ratio; CI – confidence interval; NR – not reached

Figure 1 Kaplan-Meier curve of EFS (AEGEAN; DCO 10 November 2022)



Number of patients at risk

Durva + SoC	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
Placebo + SoC	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

Subgroup analysis

The improvement in EFS and pCR favouring patients in Arm 1 compared to patients in Arm 2 were consistently observed across prespecified subgroups based on demographic and baseline disease characteristics, histology and planned chemotherapy.

PACIFIC study (locally advanced NSCLC)

The efficacy of IMFINZI was evaluated in the PACIFIC study, a randomised, double-blind, placebo-controlled, multicentre study in 713 patients with histologically or cytologically confirmed locally advanced, unresectable NSCLC. Patients had completed at least 2 cycles of definitive platinum-based chemotherapy with RT within 1 to 42 days prior to initiation of study treatment and had an ECOG PS of 0 or 1. Ninety-two percent of patients had received a total dose of 54 to 66 Gy of radiation. The study excluded patients who had progressed following CRT, patients with prior exposure to any anti-PD-1 or anti-PD-L1 antibody, patients with active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression (except physiological dose of systemic corticosteroids); active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI. Patients were randomised 2:1 to receive 10 mg/kg IMFINZI (n=476) or 10 mg/kg placebo (n=237) via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Randomisation was stratified by gender, age (<65 years vs ≥65 years) and smoking status (smoker vs non- smoker). Patients with disease control at 12 months were given the option to be re-treated upon disease progression. Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter.

Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, archival tumour tissue specimens taken prior to CRT were retrospectively tested for PD-L1 expression on TC using the VENTANA PD-L1 (SP263) IHC assay. Of the 713 patients randomised, 63% of patients provided a tissue sample of sufficient quality and quantity to determine PD-L1 expression and 37% were unknown.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics of the overall study population were as follows: male (70%), age ≥65 years (45%), white (69%), Asian (27%), other (4%), current smoker (16%), past-smoker (75%), and never smoker (9%), WHO/ECOG PS 0 (49%), WHO/ECOG PS 1 (51%). Disease characteristics were as follows: Stage IIIA (53%), Stage IIIB (45%), histological sub-groups of squamous (46%), non-squamous (54%). Of 451 patients with PD L1 expression available, 67% were TC ≥1% [PD-L1 TC 1-24% (32%), PD L1 TC ≥25% (35%)] and 33% were TC <1%.

The two primary endpoints of the study were progression-free survival (PFS) and OS of IMFINZI vs. placebo. Secondary efficacy endpoints included PFS at 12 months (PFS 12) and 18 months (PFS 18) from randomisation and Time from Randomisation to Second Progression (PFS2). PFS was assessed by BICR according to RECIST 1.1.

At the primary analysis, the study demonstrated a statistically significant improvement in PFS and OS in the IMFINZI-treated group compared with the placebo group. In the 5-year follow-up analysis, with median follow-up of 34.2 months, IMFINZI continued to demonstrate improved OS and PFS compared to placebo (see Table 26 and Figure 2 and Figure 3).

Table 26 Efficacy results for the primary analysis and 5-year follow-up analysis (PACIFIC)

	Primary analysis [a]		**5-year follow-up analysis [b]**	
	IMFINZI (n= 476)	**Placebo (n= 237)**	**IMFINZI (n=476)**	**Placebo (n=237)**
Overall survival (OS)				
Number of deaths (%)	183 (38.4%)	116 (48.9%)	264 (55.5%)	155 (65.4%)
Median (months) (95% CI)	NR (34.7, NR)	28.7 (22.9, NR)	47.5 (38.1, 52.9)	29.1 (22.1, 35.1)
HR (95% CI)	0.68 (0.53, 0.87)		0.72 (0.59, 0.89)	
2- sided p-value	0.00251		-	
OS at 24 months (%) (95% CI)	66.3% (61.7%, 70.4%)	55.6% (48.9%, 61.8%)	66.3% (61.8%, 70.4%)	55.3% (48.6%, 61.4%)
p-value	0.005		-	
OS at 48 months (%) (95% CI)	NA	NA	49.7% (45.0%, 54.2%)	36.3% (30.1%, 42.6%)
OS at 60 months (%) (95% CI)	NA	NA	42.9% (38.2%, 47.4%)	33.4% (27.3%, 39.6%)
Progression free survival (PFS)				
Number of events (%)	214 (45.0%)	157 (66.2%)	268 (56.3%)	175 (73.8%)
Median PFS (months) (95% CI)	16.8 (13.0, 18.1)	5.6 (4.6, 7.8)	16.9 (13.0, 23.9)	5.6 (4.8, 7.7)
HR (95% CI)	0.52 (0.42, 0.65)		0.55 (0.45, 0.68)	
p-value	p < 0.0001		-	
PFS at 12 months (%) (95% CI)	55.9% (51.0%, 60.4%)	35.3% (29.0%, 41.7%)		
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)		
PFS at 24 months (%) (95% CI)	NA	NA	45.0% (40.1%, 49.8%)	25.1% (19.3%, 31.2%)
PFS at 36 months (%) (95% CI)	NA	NA	39.7% (34.7%, 44.7%)	20.8% (15.3%, 26.9%)
PFS at 48 months (%) (95% CI)	NA	NA	35.0% (29.9%, 40.1%)	19.9% (14.4%, 26.1%)

	Primary analysis [a]		5-year follow-up analysis [b]	
	IMFINZI (n= 476)	**Placebo (n= 237)**	**IMFINZI (n=476)**	**Placebo (n=237)**
PFS at 60 months (%) (95% CI)	NA	NA	33.1% (28.0%, 38.2%)	19.0% (13.6%, 25.2%)
PFS2 [c]				
Median PFS2 (months) (95% CI)	28.3 (25.1, 34.7)	17.1 (14.5, 20.7)	NA	NA
HR (95% CI)	0.58 (0.46, 0.73)		NA	
p-value	p < 0.0001		NA	

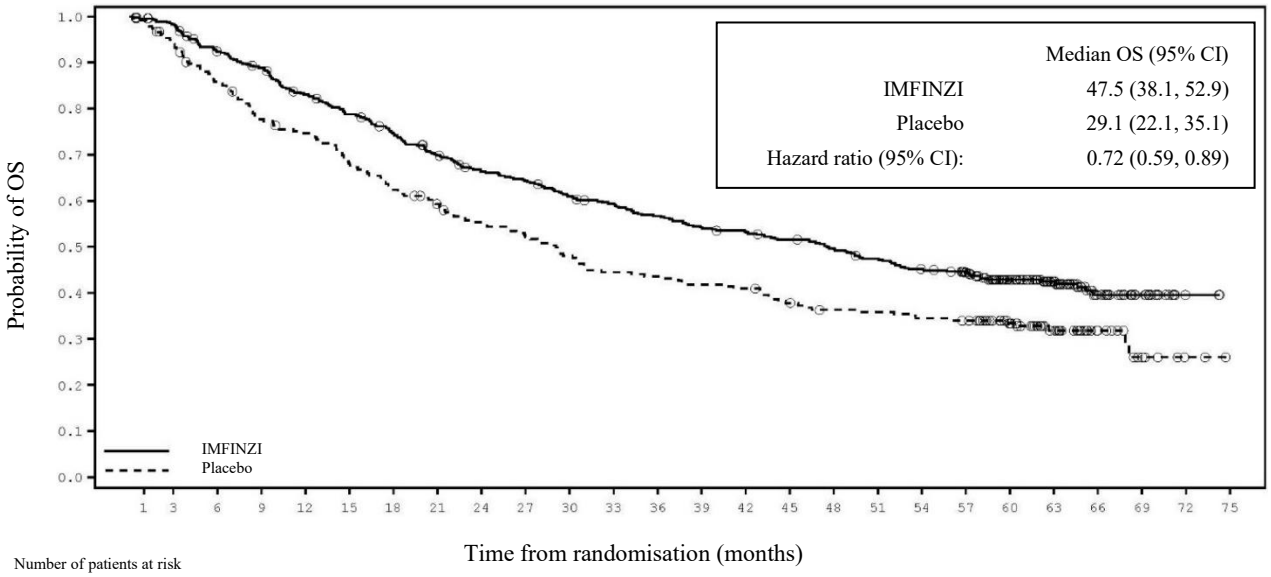
[a] Primary analysis of OS and PFS2 at data-cut-off 22 March 2018. Primary analysis of PFS at data cut-off 13 February 2017.

[b] Follow-up OS and PFS analysis at data cut-off 11 January 2021

[c] PFS2 is defined as the time from the date of randomisation until the date of second progression (defined by local standard clinical practice) or death.

HR – hazard ratio; CI - confidence interval; NR - not reached

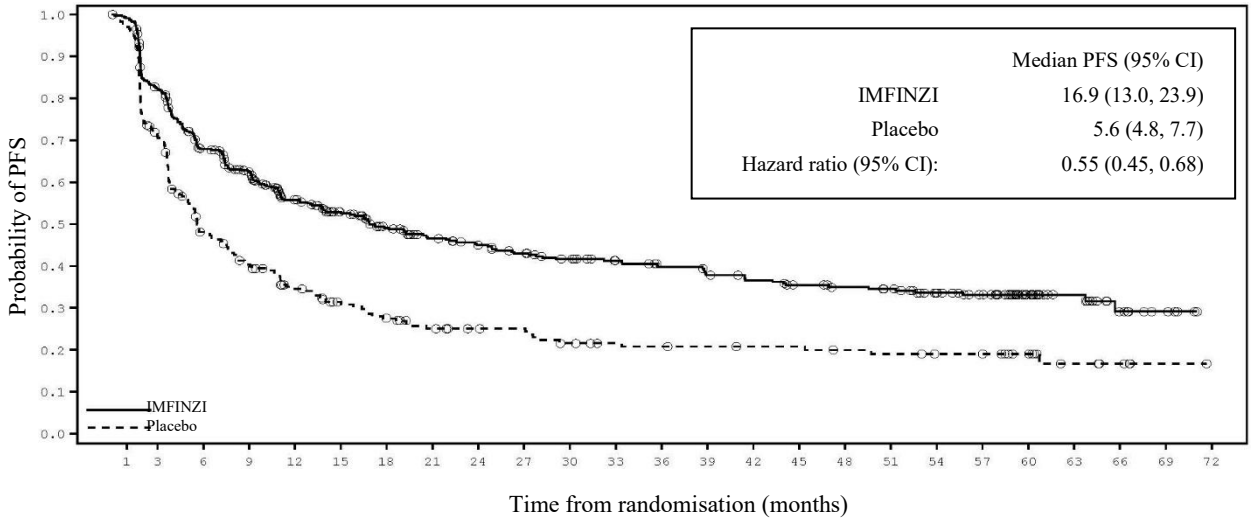
Figure 2 Kaplan-Meier curve of OS (PACIFIC; DCO 11 January 2021)



Number of patients at risk

Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63	66	69	72	75
IMFINZI	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	10	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Figure 3 Kaplan-Meier curve of PFS (PACIFIC; DCO 11 January 2021)



Number of patients at risk

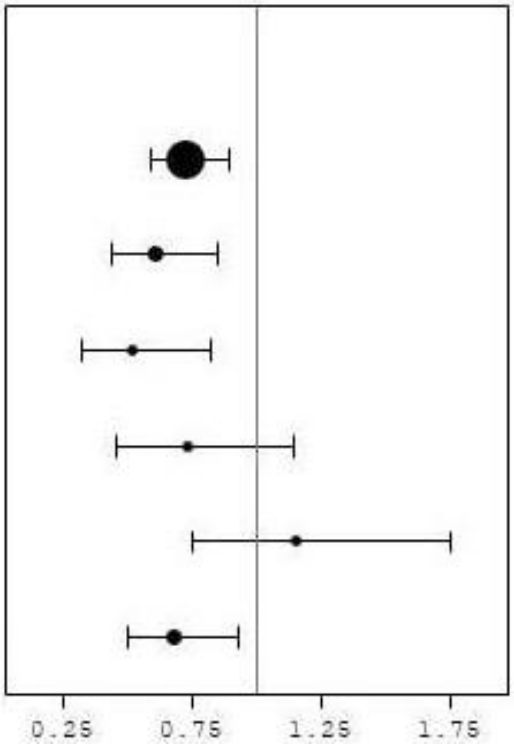
Month	0	3	6	9	12	15	18	21	24	27	30	33	36	42	45	48	51	54	57	60	63	66	69	72
IMFINZI	476	377	301	267	215	190	165	147	137	128	119	110	103	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	24	24	22	21	19	19	14	6	4	1	0

The improvements in PFS and OS in favour of patients receiving IMFINZI compared to those receiving placebo were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history, EGFR mutation status and histology. ALK mutation status was not analysed in this study.

Post-hoc subgroup analysis by PD-L1 expression

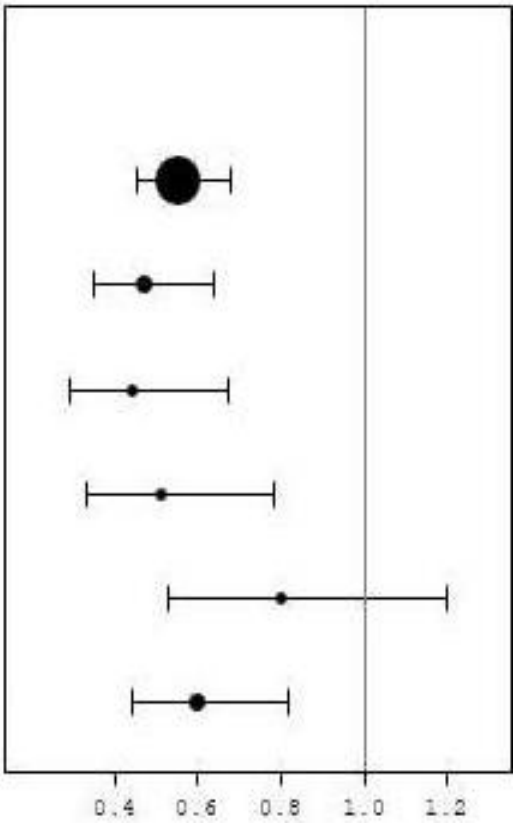
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥25%, 1-24%, ≥1%, <1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). OS and PFS results from the 5-year follow-up are summarised in Figure 4 and Figure 5. Overall the safety profile of durvalumab in PD-L1 TC ≥1% subgroup was consistent with the intent to treat population, as was the PD-L1 TC <1% subgroup.

Figure 4 Forest plot of OS by PD-L1 expression (PACIFIC)



	Events/N (%)	
	IMFINZI	**Placebo**
All Patients	264/476 (55.5%)	155/237 (65.4%)
PD-L1 TC ≥ 1%	103/212 (48.6%)	56/91 (61.5%)
PD-L1 TC ≥ 25%	51/115 (44.3%)	27/44 (61.4%)
PD-L1 TC 1-24%	52/97 (53.6%)	29/47 (61.7%)
PD-L1 TC < 1%	59/90 (65.6%)	35/58 (60.3%)
PD-L1 Unknown	102/174 (58.6%)	64/88 (72.7%)

Figure 5 Forest plot of PFS by PD-L1 expression (PACIFIC)



	Events/N (%)	
	IMFINZI	**Placebo**
All Patients	268/476 (56.3%)	175/237 (73.8%)
PD-L1 TC ≥ 1%	111/212 (52.4%)	69/91 (75.8%)
PD-L1 TC ≥ 25%	61/115 (53.0%)	33/44 (75.0%)
PD-L1 TC 1-24%	50/97 (51.5%)	36/47 (76.6%)
PD-L1 TC < 1%	55/90 (61.1%)	41/58 (70.7%)
PD-L1 Unknown	102/174 (58.6%)	65/88 (73.9%)

Patient reported outcomes

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of life questionnaire (QLQ) QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 and C30 were assessed at baseline and every 4 weeks for the first 8 weeks, then every 8 weeks until completion of the treatment period or discontinuation of study drug due to toxicity or disease progression. Compliance was similar between the IMFINZI and placebo treatment groups (83% vs 85.1% overall of evaluable forms completed).

At baseline, no differences in patient reported symptoms, function or HRQoL were observed between IMFINZI and placebo groups. Throughout the duration of the study to week 48, there was no clinically meaningful difference between IMFINZI and placebo groups in symptoms, functioning and HRQoL (as assessed by a difference of greater than or equal to 10 points).

Small cell lung cancer (SCLC)

ADRIATIC study (LS-SCLC)

ADRIATIC was a study designed to evaluate the efficacy of IMFINZI with or without tremelimumab. ADRIATIC was a randomised, double-blind, placebo-controlled multicentre study in 730 patients with histologically or cytologically confirmed LS-SCLC (Stage I to III according to AJCC, 8th edition) who had not progressed following concurrent CRT. Patients who were Stage I or II had to be medically inoperable as determined by the investigator. Patients completed 4 cycles of definitive platinum-based CRT, 60-66 Gy once daily (QD) over 6 weeks or 45 Gy twice daily (BID) over 3 weeks, within 1 to 42 days prior to the first dose of study treatment. Prophylactic cranial irradiation (PCI) could be delivered at the discretion of the investigator after CRT and within 1 to 42 days prior to the first dose of study treatment.

The study excluded patients with active or prior documented autoimmune disease within 5 years of initiation of the study; a history of active primary immunodeficiency; a history of Grade ≥2 pneumonitis or active tuberculosis or hepatitis B or C or HIV infection and patients with active interstitial lung disease. Patients with mixed SCLC and NSCLC histology were also excluded.

Randomisation was stratified by stage (I/II versus III) and receipt of PCI (yes vs no). Patients were randomised 1:1:1 to receive:

- *Arm 1*: IMFINZI 1500 mg + placebo every 4 weeks for 4 cycles, followed by IMFINZI 1500 mg every 4 weeks.
- *Arm 2:* Placebo + a second placebo every 4 weeks for 4 cycles, followed by a single placebo every 4 weeks.
- *Arm 3*: IMFINZI 1500 mg + tremelimumab 75 mg every 4 weeks for 4 cycles, followed by IMFINZI 1500 mg every 4 weeks (Information not included in Product Information. Analysis of data pending).

Once 600 patients had been randomised across all 3 arms, subsequent patients were randomised 1:1 to either Arm 1 or 2, and received either IMFINZI 1500 mg every 4 weeks or placebo every 4 weeks.

Treatment continued until disease progression, until unacceptable toxicity, or for a maximum of 24 months. Tumour assessments were conducted every 8 weeks for the first 72 weeks, then every 12 weeks up to 96 weeks, and then every 24 weeks thereafter.

The demographics and baseline disease characteristics were well balanced between study arms. Baseline demographics and disease characteristics of the IMFINZI and placebo arms were as follows: male (69.1%), age ≥ 65 years (39.2%), White (50.4%), Black or African-American (0.8%), Asian (47.5%), Hispanic or Latino (4.2%), other (1.3%), current smoker (22.3%), past-smoker (68.5%), never smoker (9.2%), WHO/ECOG PS 0 (48.7%), WHO/ECOG PS 1 (51.3%), Stage I (3.6%), Stage II (9.1%), Stage III (87.4%).

Prior to randomisation, all patients received platinum-based chemotherapy (66.2% cisplatin-etoposide, 33.8% carboplatin-etoposide); 72.1% of patients received RT QD (of which 92.4% received ≥60 - ≤66 Gy QD); 27.9% received RT BID (of which 96.6% received 45 Gy BID) and 53.8% patients received PCI. Response to CRT was as follows: complete response (12.3%), partial response (73.8%), stable disease (14.0%).

The dual primary endpoints of the study were OS and PFS of IMFINZI vs placebo. Secondary efficacy endpoints included ORR of IMFINZI vs placebo. PFS and ORR were assessed by BICR according to RECIST v1.1.

At a planned interim analysis (Data cut-off (DCO): 15 January 2024), the study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS for IMFINZI compared with placebo. See Table 27 and Figure 6 and Figure 7.

Table 27 Efficacy results (ADRIATIC; DCO 15 January 2024)

	Arm 1: IMFINZI (n=264)	**Arm 2: Placebo (n=266)**
Overall survival (OS) [a]		
Number of deaths (%)	115 (43.6)	146 (54.9)
Median OS (months) (95% CI) [b]	55.9 (37.3, NR)	33.4 (25.5, 39.9)
HR (95% CI) [c]	0.73 (0.569, 0.928)	
p-value [d]	0.01042	
OS at 24 months (%) (95% CI) [b]	68.0 (61.9, 73.3)	58.5 (52.3, 64.3)
OS at 36 months (%) (95% CI) [b]	56.5 (50.0, 62.5)	47.6 (41.3, 53.7)
Progression free survival (PFS) [e]		
Number of events (%)	139 (52.7)	169 (63.5)
Median PFS (months) (95% CI) [b]	16.6 (10.2, 28.2)	9.2 (7.4, 12.9)
HR (95% CI) [f]	0.76 (0.606, 0.950)	
p-value [d]	0.01608	
PFS at 18 months (%) (95% CI) [b]	48.8 (42.2, 55.0)	36.1 (29.9, 42.2)
PFS at 24 months (%) (95% CI) [b]	46.2 (39.6, 52.5)	34.2 (28.2, 40.3)
Overall response rate (ORR) [e]		
ORR [g] n (%)	53/175 (30.3)	54/169 (32.0)
Complete Response n (%)	5 (2.9)	4 (2.4)
Partial Response n (%)	48 (27.4)	50 (29.6)
Odds ratio (95% CI)	-1.2 (-11.0, 8.5)	
Duration of response (DoR)		
Median DoR [b,e] (months) (95% CI)	33.0 (22.4, NR)	27.7 (9.6, NR)
Proportion of patients in response at 12 months [b,e] (%) (95% CI)	73.7 (59.0, 83.8)	60.3 (44.5, 72.9)
Proportion of patients in response at 18 months [b,e] (%) (95% CI)	71.5 (56.6, 82.0)	55.2 (39.4, 68.5)

[a] Median duration of OS follow-up in censored patients was 37.19 months in IMFINZI arm and 37.24 months in placebo arm.

[b] Calculated using the Kaplan Meier technique. CI for median derived based on Brookmeyer-Crowley method.

[c] The analysis for HR was performed using a stratified Cox proportional hazards model and the 2 sided p-value is based on a stratified log-rank test, both are adjusted for receipt of PCI.

[d] p-value based on the results from the pre-planned interim analysis. Based on a Lan-DeMets alpha spending function O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for OS was 0.01679 for a 4.5% overall alpha and for PFS was 0.02805 for a 5% overall alpha (Lan◦and◦DeMets 1983).

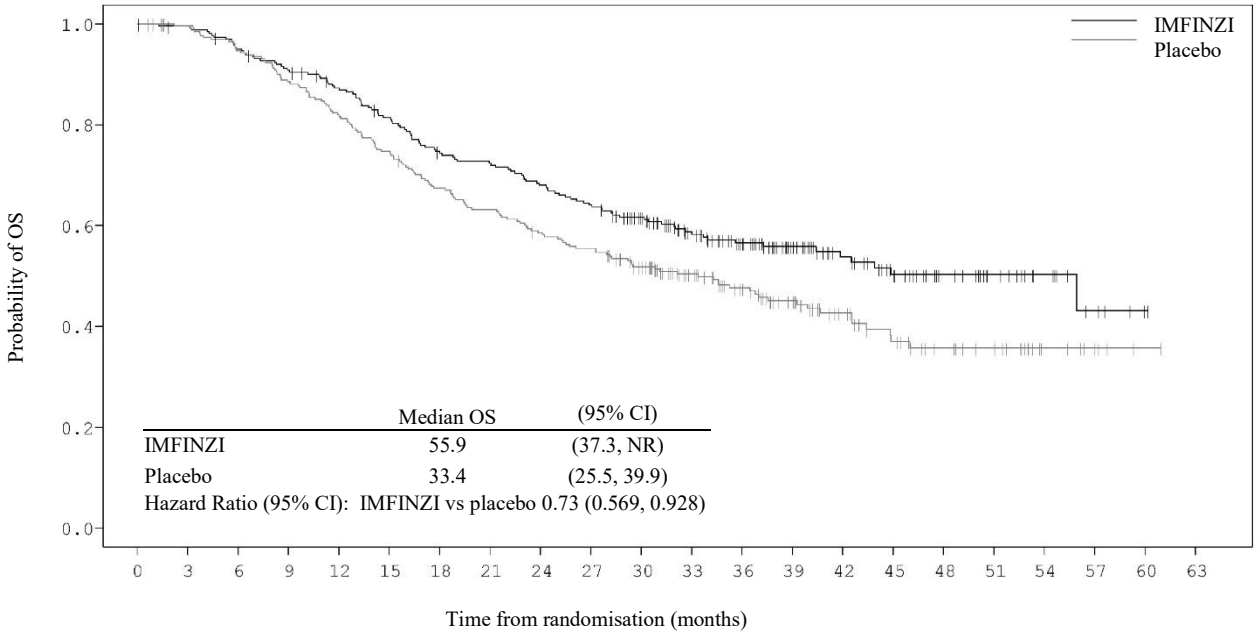
[e] Assessed by BICR according to RECIST v1.1.

[f] The analysis for HR was performed using a stratified Cox proportional hazards model and the 2 sided p-value is based on a stratified log-rank test, both are adjusted for TNM stage and receipt of PCI.

[g] Based on sub-group of full analysis set with measurable disease at baseline according to RECIST v1.1; IMFINZI (n=175), placebo (n=169).

HR – hazard ratio; CI - confidence interval

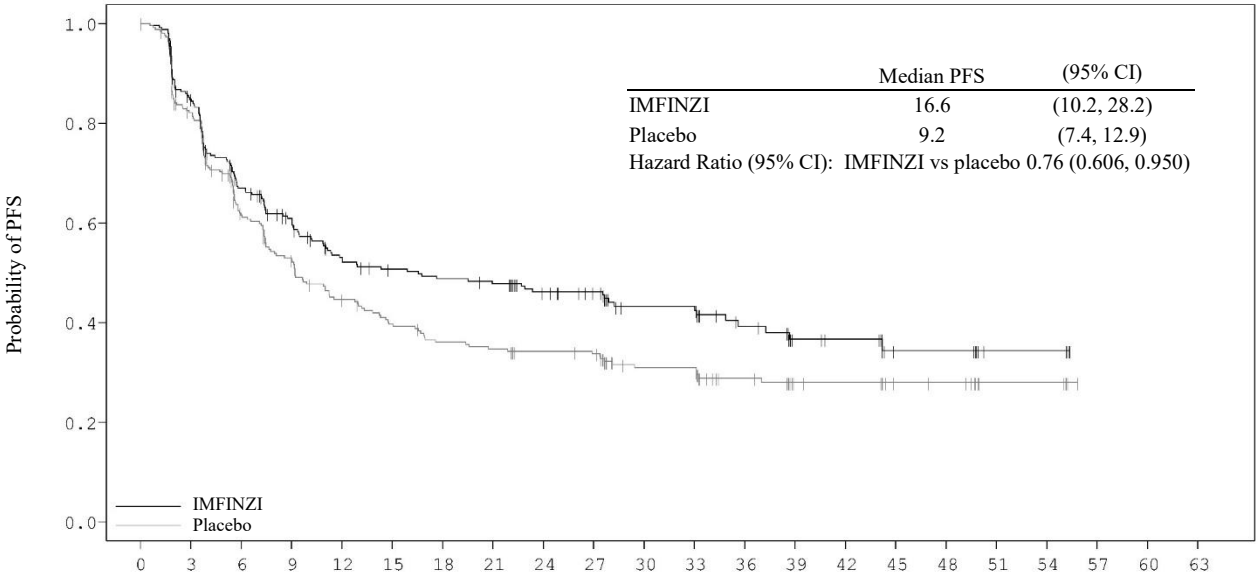
Figure 6 Kaplan-Meier curve of OS (ADRIATIC; DCO 15 January 2024)



Number of patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
IMFINZI	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

Figure 7 Kaplan-Meier curve of PFS (ADRIATIC; DCO 15 January 2024)



Number of patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60	63
IMFINZI	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

The improvements in OS and PFS in favour of patients receiving IMFINZI compared to those receiving placebo were generally consistent across predefined subgroups analysed.

CASPIAN study (ES-SCLC)

The efficacy of IMFINZI in combination with etoposide and either carboplatin or cisplatin in previously untreated ES-SCLC patients was investigated in CASPIAN, a randomised, open-label, multicentre study in treatment naïve ES-SCLC patients with WHO/ECOG PS of 0 or 1. Patients in the trial were eligible to receive a platinum-based chemotherapy regimen as first-line treatment for SCLC, with life expectancy ≥12 weeks, at least one target lesion by RECIST 1.1 and adequate organ and bone marrow function. Patients with asymptomatic or treated brain metastases were permitted. The study excluded patients with a history of chest RT; a history of active primary immunodeficiency; autoimmune disorders including paraneoplastic syndrome (PNS); active or prior documented autoimmune or inflammatory disorders; use of systemic immunosuppressants within 14 days before the first dose of the treatment except physiological dose of systemic corticosteroids; active tuberculosis or hepatitis B or C or HIV infection; or patients receiving live attenuated vaccine within 30 days before or after the start of IMFINZI.

Randomisation was stratified by the planned platinum-based therapy in cycle 1 (carboplatin or cisplatin).

The evaluation of efficacy for ES-SCLC relied on comparison between:

- *Arm 1:* IMFINZI 1500 mg + etoposide (80-100 mg/m^2) and either carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m^2)
- *Arm 2:* Either carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m^2) on Day 1 and etoposide (80-100 mg/m^2) intravenously on Days 1, 2, and 3 of each 21-day cycle for between 4 and 6 cycles.

For patients randomised to Arm 1, etoposide and either carboplatin or cisplatin was limited to 4 cycles every 3 weeks subsequent to randomisation. IMFINZI monotherapy continued until disease progression or unacceptable toxicity. Administration of IMFINZI monotherapy was permitted beyond disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.

Patients randomised to Arm 2, were permitted to receive a total of up to 6 cycles of etoposide and either carboplatin or cisplatin. After completion of chemotherapy, prophylactic cranial irradiation (PCI) was permitted only in Arm 2 per investigator discretion.

Tumour assessments were conducted at Week 6 and Week 12 from the date of randomisation, and then every 8 weeks until confirmed objective disease progression. Survival assessments were conducted every 2 months following treatment discontinuation.

The primary endpoints of the study were OS of IMFINZI + chemotherapy (Arm 1) vs. chemotherapy alone (Arm 2). The key secondary endpoint was PFS. Other secondary endpoints were ORR, OS and PFS landmarks and Patient Reported Outcomes (PRO). PFS and ORR were assessed using Investigator assessments according to RECIST v1.1.

At a planned interim (primary) analysis, IMFINZI + chemotherapy (Arm 1) vs chemotherapy (Arm 2) met the efficacy boundary of the primary endpoint of OS and at a planned follow-up OS analysis IMFINZI + chemotherapy (Arm 1) vs chemotherapy (Arm 2) continued to demonstrate improved OS. The results are summarised below.

The demographics and baseline disease characteristics were well balanced between the study arms (268 patients in Arm 1 and 269 patients in Arm 2). Baseline demographics of the overall study population were as follows: male (69.6%), age ≥65 years (39.6%), median age 63 years (range: 28 to 82 years), white (83.8%), Asian (14.5%), black or African American (0.9%), other (0.6 %), non-Hispanic or Latino (96.1%), current or past-smoker (93.1%), never smoker (6.9%), WHO/ECOG PS 0 (35.2%), WHO/ECOG PS 1 (64.8%), Stage IV 90.3%, 24.6% of the patients received cisplatin and 74.1% of the patients received carboplatin. In Arm 1, 1.1% of the patients received ≥5 cycles of chemotherapy and 0.4% of the patients received ≥6 cycles of chemotherapy based on etoposide exposure. In Arm 2, 62.8% of the patients received ≥5 treatment cycles, 56.8% of the patients received the maximum of 6 treatment cycles based on etoposide exposure and 7.8% of the patients received PCI after chemotherapy.

At the planned interim (primary) analysis (DCO 11 March 2019) the study demonstrated a statistically significant and clinically meaningful improvement in OS at the planned interim analysis with IMFINZI + chemotherapy (Arm 1) vs. chemotherapy alone (Arm 2) [HR=0.73 (95% CI: 0.591, 0.909), p=0.0047]. IMFINZI + chemotherapy demonstrated an improvement in PFS vs. chemotherapy alone [HR=0.78 (95% CI: 0.645, 0.936)].

In the planned final OS analysis (median: 25.1 months; DCO 27 January 2020), the median OS for Arm 1 and Arm 2 was consistent with the OS primary analysis.

In the long-term follow-up analysis, with a median follow-up of 39.3 months (DCO 22 March 2021), IMFINZI + etoposide + platinum (Arm 1) vs. etoposide + platinum (Arm 2) continued to demonstrate sustained improvement in OS.

Results for the final analysis and follow-up analysis are presented in Table 28. Kaplan-Meier curves for the long-term follow-up OS and the final analysis PFS are presented in Figure 8 and Figure 9.

Table 28 Efficacy results for final analysis and long-term follow-up analysis (CASPIAN)

	Final analysis [a]		Long-term follow-up analysis [b]	
	IMFINZI + etoposide & carboplatin or cisplatin (n=268)	**etoposide & carboplatin or cisplatin (n=269)**	**IMFINZI + etoposide & carboplatin or cisplatin (n=268)**	**etoposide & carboplatin or cisplatin (n=269)**
Overall survival (OS)				
Number of deaths (%)	210 (78.4)	231 (85.9)	221 (82.5)	248 (92.2)
Median OS (months) (95% CI)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)
HR (95% CI)[c]	0.75 (0.625, 0.910)		0.71 (0.595, 0.858)	
p-value [d]	0.0032		0.0003	
OS at 12 months (%) (95% CI)	52.8 (46.6, 58.5)	39.3 (33.4, 45.1)	52.8 (46.6, 58.5)	39.3 (33.4, 45.1)
OS at 18 months (%) (95% CI)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)
OS at 24 months (%) (95% CI)	22.2 (17.3, 27.5)	14.4 (10.3, 19.2)	22.9 (18.1, 28.2)	13.9 (10.1, 18.4)
OS at 36 months (%) (95% CI)	N/A	N/A	17.6 (13.3, 22.4)	5.8 (3.4, 9.1)
Progression free survival (PFS)				
Number of events (%)	226 (84.3)	233 (86.6)	N/A	N/A
Median PFS (months) (95% CI)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)	N/A	N/A
HR (95% CI) [c]	0.78 (0.645, 0.936)		NA	
PFS at 6 months (%) (95% CI)	45.4 (39.3, 51.3)	45.6 (39.3, 51.7)	N/A	N/A
PFS at 12 months (%) (95% CI)	17.5 (13.1, 22.5)	4.7 (2.4, 8.0)	N/A	N/A
PFS at 18 months (%) (95% CI)	13.9 (10.0, 18.4)	3.4 (1.6, 6.4)	N/A	N/A
PFS at 24 months (%) (95% CI)	11.0 (7.5, 15.2)	2.9 (1.2, 5.8)	N/A	N/A
Objective response rate (ORR) [e]				
ORR n (%)	182 (67.9)	156 (58.0)	N/A	N/A
Complete response n (%)	7 (2.6)	2 (0.7)	N/A	N/A
Partial response n (%)	175 (65.3)	154 (57.2)	N/A	N/A
Odds ratio (95% CI) [f]	1.53 (1.078, 2.185)		-	
Duration of response (DoR) [e]				
Median DoR (months) (95% CI)	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)	N/A	N/A
DoR at 12 months (%)	23.2	7.3	N/A	N/A
DoR at 24 months (%)	13.5	3.9	N/A	N/A

[a] Final OS analysis at clinical cut-off 27 January 2020.

[b] Long-term survival analysis at data cut-off 22 March 2021. RECIST data were not collected at this follow up DCO

[c] The analysis was performed using the stratified log-rank test, adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin), and using the rank tests of association approach.

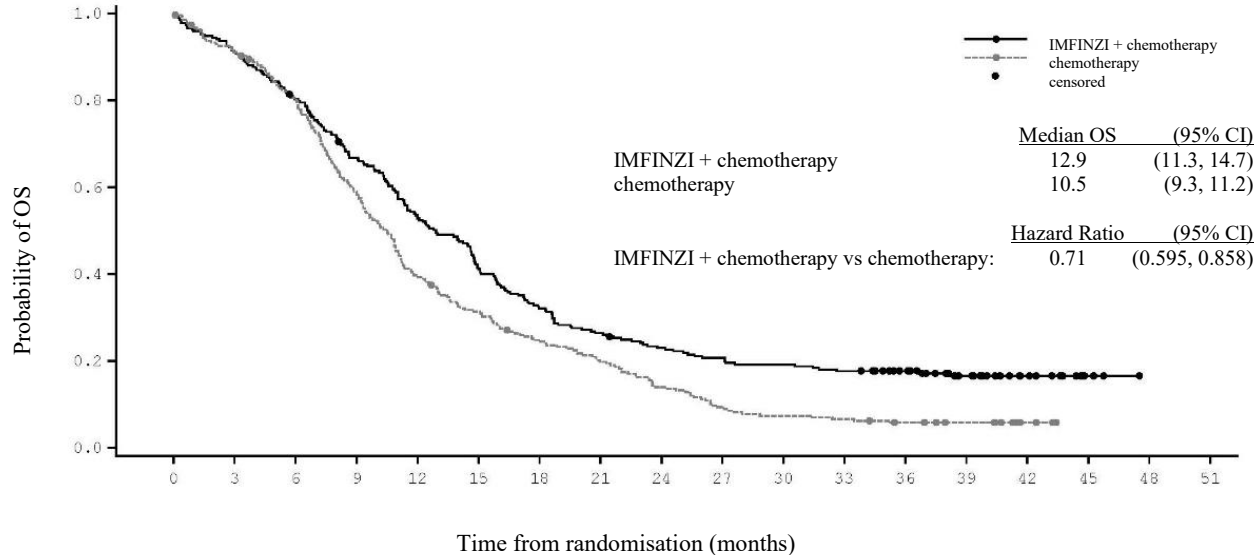
[d] At the primary analysis (data cut-off 11 March 2019) the OS p-value was 0.0047, which met the boundary for declaring statistical significance of 0.0178 for a 4% overall 2-sided alpha, based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed.

[e] Confirmed objective response.

[f] The analysis was performed using a logistic regression model adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) with 95% CI calculated by profile likelihood.

HR – hazard ration; CI - confidence interval

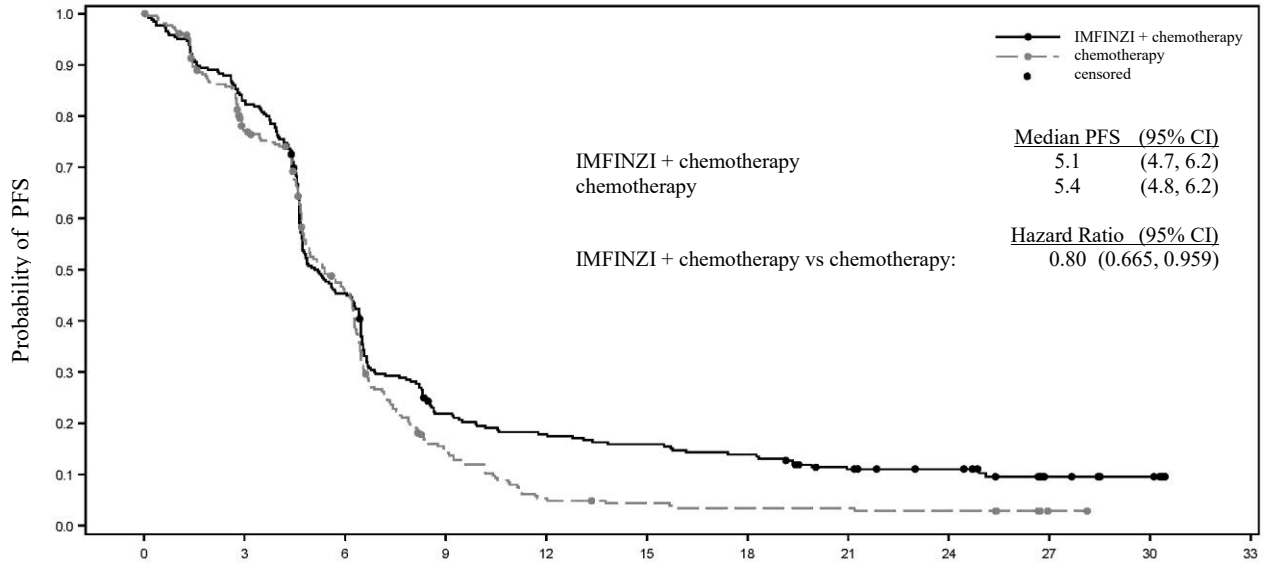
Figure 8 Kaplan-Meier curve of OS (CASPIAN; DCO 22 March 2021)



Time from randomisation (months)

Number of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
IMFINZI + chemotherapy	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
chemotherapy	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Figure 9 Kaplan-Meier curve of PFS (CASPIAN; DCO 27 January 2020)



Time from randomisation (months)

Number of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33
IMFINZI + chemotherapy	268	220	119	55	45	40	35	24	18	8	5	0
chemotherapy	269	194	110	33	12	9	7	7	6	1	0	0

Subgroup analysis

The improvements in OS in favour of patients receiving IMFINZI + chemotherapy compared to those receiving chemotherapy alone, were consistently observed across the prespecified subgroups based on demographics, geographical region, carboplatin or cisplatin use and disease characteristics.

Change from baseline in lung cancer symptoms over 12 months (mixed model for repeated measures)

IMFINZI + chemotherapy improved appetite loss by demonstrating a statistically significant difference in mean change from baseline versus chemotherapy alone during the overall time period from randomisation until 12 months (Estimated mean difference -4.5; 99% CI -9.04, -0.04; p=0.009). Both treatment arms demonstrated numerical symptom reduction in cough, chest pain, dyspnoea and fatigue over the same time period.

Patient-reported outcome results should be interpreted in the context of the open-label study design.

In the exploratory subgroup analyses of OS based on the planned platinum chemotherapy received at cycle 1, the HR was 0.70 (95% CI 0.55, 0.89) in patients who received carboplatin, and the HR was 0.88 (95% CI 0.55, 1.41) in patients who received cisplatin.

Biliary tract carcinoma (BTC)

TOPAZ-1 study

TOPAZ-1 was a study designed to evaluate the efficacy of IMFINZI in combination with gemcitabine and cisplatin. TOPAZ-1 was a randomised, double-blind, placebo-controlled, multicentre study in 685 patients with histologically confirmed locally advanced or metastatic BTC and ECOG PS of 0 or 1. Patients who developed recurrent disease more than 6 months after surgery and/or completion of adjuvant therapy were included. Patients must have had at least one target lesion by RECIST v1.1 and adequate organ and bone marrow function.

The study excluded patients with ampullary carcinoma, active or prior documented autoimmune or inflammatory disorders, HIV infection or active infections, including tuberculosis or hepatitis C or patients with current or prior use of immunosuppressive medication within 14 days before the first dose of IMFINZI.

Randomisation was stratified by disease status and primary tumour location.

Patients were randomised 1:1 to receive:

- *Arm 1:* IMFINZI 1500 mg administered intravenously on Day 1+ gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by IMFINZI 1500 mg every 4 weeks as long as clinical benefit is observed or until unacceptable toxicity, or
- *Arm 2:* Placebo administered intravenously on Day 1+ gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 (each administered on Days 1 and 8) every 3 weeks (21 days) for up to 8 cycles, followed by placebo every 4 weeks as long as clinical benefit is observed or until unacceptable toxicity.

Tumour assessments were conducted every 6 weeks for the first 24 weeks after the date of randomisation, and then every 8 weeks until confirmed objective disease progression.

The primary endpoint of the study was OS and the key secondary endpoint was PFS. Other secondary endpoints were ORR, DoR and PRO. PFS, ORR and DoR were Investigator assessed according to RECIST v1.1.

The demographics and baseline disease characteristics were well balanced between the two study arms (341 patients in Arm 1 and 344 patients in Arm 2). Baseline demographics of the overall study population were as follows: male (50.4%), age <65 years (53.3%), white (37.2%), Asian (56.4%), black or African American (2.0%), other (4.2%), non-Hispanic or Latino (93.1%), ECOG PS 0 (49.1%) vs PS 1 (50.9%), primary tumour location (intrahepatic cholangiocarcinoma (55.9%),

extrahepatic cholangiocarcinoma (19.1%) and gallbladder cancer (25.0%), disease status recurrent (19.1%) vs. initially unresectable (80.7%), metastatic (86.0%) vs. locally advanced (13.9%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS and PFS at a pre-planned interim (primary) analysis. The results in OS were [HR=0.80, (95% CI: 0.66, 0.97), p=0.021] and in PFS [HR=0.75, (95% CI: 0.63, 0.89), p=0.001]. The maturity for OS was 61.9% and the maturity for PFS was 83.64%. Results from this analysis are presented in Table 29 and Figure 11.

An additional OS analysis was performed 6.5 months after the interim analysis with an OS maturity of 76.9%. The observed treatment effect was consistent with the interim analysis. The OS HR was 0.76 (95% CI: 0.64, 0.91) and median survival was 12.9 months (95% CI: 11.6, 14.1) for the IMFINZI + gemcitabine and cisplatin arm. Results from this analysis are presented in the Table 29 and Figure 10.

Table 29 Efficacy results for the primary analysis and follow-up analysis (TOPAZ-1)

	Primary analysis [a]		**Follow-up analysis [b]**	
	IMFINZI + gemcitabine & cisplatin (n=341)	**Placebo + gemcitabine & cisplatin (n=344)**	**IMFINZI + gemcitabine & cisplatin (n=341)**	**Placebo + gemcitabine & cisplatin (n=344)**
Overall survival (OS)				
Number of deaths (%)	198 (58.1)	226 (65.7)	248 (72.7)	279(81.1)
Median OS (months) (95% CI) [c]	12.8 (11.1, 14)	11.5 (10.1, 12.5)	12.9 (11.6,14.1)	11.3 (10.1,12.5)
HR (95% CI) [d]	0.80 (0.66, 0.97)		0.76 (0.64, 0.91)	
p-value [d, e]	0.021		-	
OS at 12 months (%) (95% CI)[c]	54.1 (48.4, 59.4)	48 (42.4, 53.4)	54.3 (48.8, 59.4)	47.1 (41.7, 52.3)
OS at 18 months (%) (95% CI)[c]	35.1 (29.1, 41.2)	25.6 (19.9, 31.7)	34.8 (29.6, 40.0)	24.1 (19.6, 28.9)
OS at 24 months (%) (95% CI)[c]	24.9 (17.9, 32.5)	10.4 (4.7, 18.8)	23.6 (18.7, 28.9)	11.5 (7.6, 16.2)
Progression free survival (PFS)				
Number of events (%)	276 (80.9)	297 (86.3)	N/A	N/A
Median PFS (months) (95% CI) [c]	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)	N/A	N/A
HR (95% CI) [d]	0.75 (0.63, 0.89)		N/A	
p-value [d, f]	0.001		N/A	
PFS at 9 months (%) (95% CI) [c]	34.8 (29.6, 40.0)	24.6 (20.0, 29.5)	N/A	N/A
PFS at 12 months (%) (95% CI) [c]	16.0 (12.0, 20.6)	6.6 (4.1, 9.9)	N/A	N/A
Objective response rate (ORR) n (%) [g]	91 (26.7)	64 (18.7)	N/A	N/A
Complete Response n (%)	7 (2.1)	2 (0.6)	N/A	N/A
Partial Response n (%)	84 (24.6)	62 (18.1)	N/A	N/A
Odds ratio (95% CI) [h]	1.60 (1.11, 2.31)		N/A	
p-value [h]	0.011		N/A	
Duration of response (DoR)				
Median DoR (months) (95% CI) [c]	6.4 (5.9, 8.1)	6.2 (4.4, 7.3)	N/A	N/A
DoR at 9 months (%) [c]	32.6	25.3	N/A	N/A
DoR at 12 months (%) [c]	26.1	15.0	N/A	N/A

[a] Final OS, PFS, ORR and DoR analysis at data cut-off 11 Aug 2021.

[b] Follow-up OS analysis at data cut-off 25 Feb 2022

[c] Calculated using the Kaplan-Meier technique. CI for median derived based on Brookmeyer-Crowley method.

[d] The analysis for HR was performed using a stratified Cox proportional hazards model and 2-sided p-value is based on a stratified log-rank test, both are adjusted for disease status and primary tumour location.

[e] p-value based on the results from the pre-planned interim (primary) analysis. Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary for OS and the actual number of events observed, the boundary for declaring statistical significance was 0.03 for an 4.9% overall alpha (Lan◦and◦DeMets 1983).

[f] p-value based on the results from the pre-planned interim (primary) analysis. Based on a Lan-DeMets alpha spending function with Pocock type boundary and the actual number of events observed, the boundary for declaring statistical significance was 0.0481 for an 4.9% overall alpha (Lan and DeMets 1983).

[g] Confirmed objective response by Investigator per RECIST 1.1. Based on patients with measurable disease at baseline IMFINZI + gemcitabine and cisplatin (n = 341), Placebo + gemcitabine and cisplatin (n = 343).

[h] The analysis was performed using a stratified CMH test with factors for disease status and tumour location. Nominal 2-sided p-value

HR – Hazard ratio; CI – Confidence interval; N/A – not applicable

Figure 10 Kaplan-Meier curve of OS (TOPAZ-1; DCO 25 February 2022)

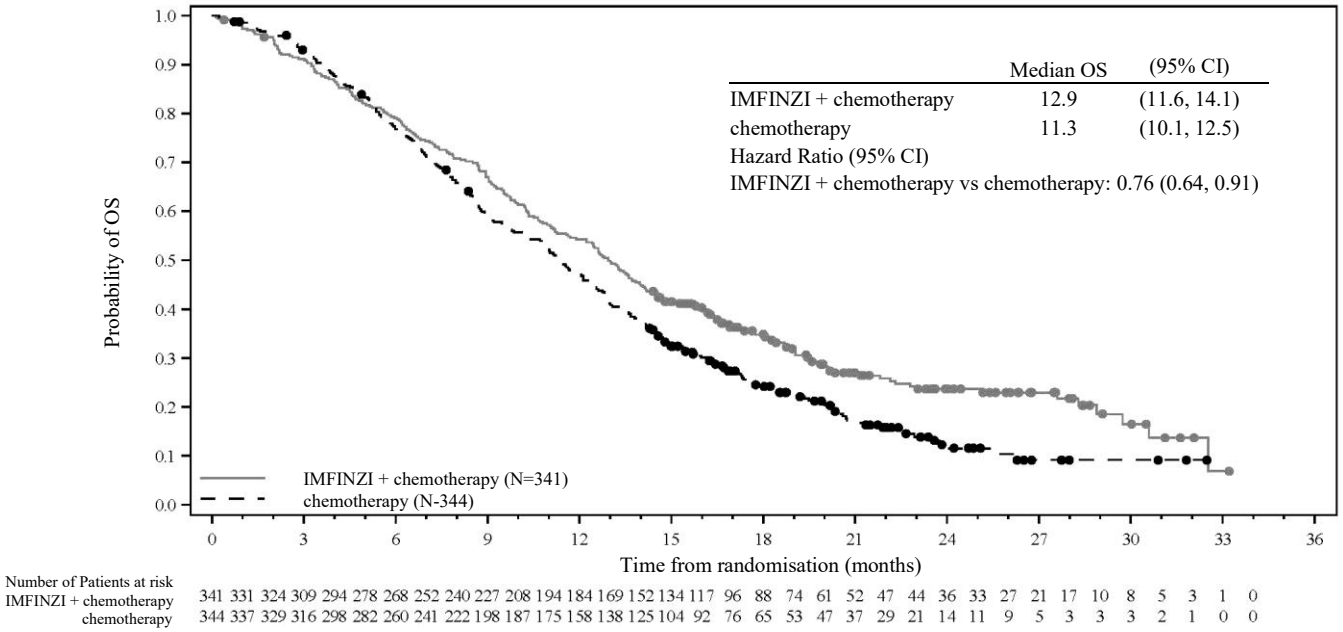
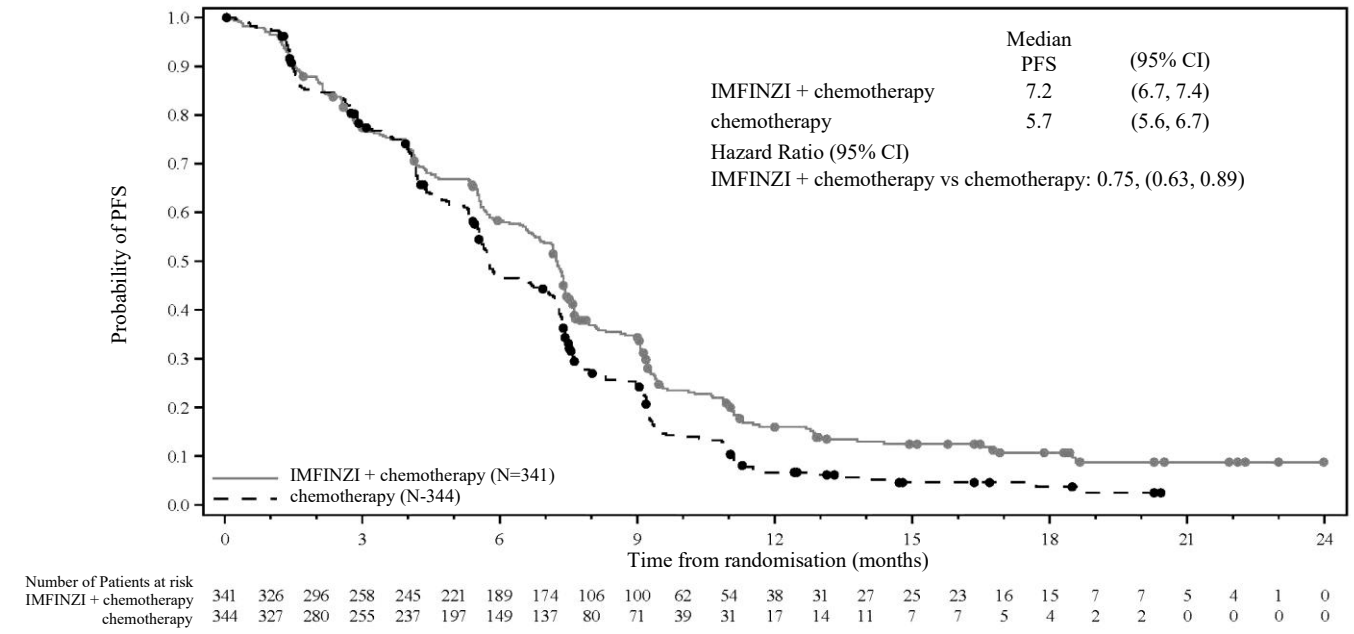


Figure 11 Kaplan-Meier curve of PFS (TOPAZ-1; DCO 11 August 2021)



Hepatocellular carcinoma (HCC)

HIMALAYA study (uHCC)

The efficacy of STRIDE was evaluated in the HIMALAYA study, a randomised, open-label, multicentre study in patients with confirmed uHCC who did not receive prior systemic treatment for HCC. The study included patients with BCLC Stage C or B (not eligible for locoregional therapy) and Child-Pugh Score Class A.

The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented GI bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders.

Patients with oesophageal varices were included except those with active or prior documented GI bleeding within 12 months prior to study entry.

Randomisation was stratified by macrovascular invasion (MVI) (yes vs no), aetiology of liver disease (confirmed hepatitis B virus vs confirmed hepatitis C virus vs others) and ECOG PS (0 vs 1).

The HIMALAYA study randomised 1171 patients 1:1:1 to receive:

- IMFINZI: durvalumab 1500 mg every 4 weeks
- STRIDE: tremelimumab 300 mg as a single priming dose + IMFINZI 1500 mg; followed by IMFINZI 1500 mg every 4 weeks
- Sorafenib (S) 400 mg twice daily

Treatment continued as long as clinical benefit was observed or until unacceptable toxicity. Patients in all arms could continue to receive treatment after evidence of disease progression if, in the Investigator's opinion, they were benefiting from study drug and met all inclusion and exclusion criteria for treatment beyond progression. In addition, patients in the STRIDE arm who continued treatment beyond progression were allowed to be rechallenged once with an additional single dose of tremelimumab 300 mg after cycle five of IMFINZI. Of the 182 patients enrolled to the STRIDE arm who received IMFINZI beyond progression, the median OS was 19.5 months (95% CI: 15.4, 23.4). Of the 30 patients who were enrolled to the STRIDE arm who were rechallenged with tremelimumab, the median OS was 30.4 months (95% CI: 23.4, NR).

Tumour assessments were conducted every 8 weeks for the first 12 months and then every 12 weeks thereafter. Survival assessments were conducted every month for the first 3 months following treatment discontinuation and then every 2 months.

The primary endpoint was OS for STRIDE vs sorafenib. The key secondary objective was OS for non-inferiority based on the comparison of IMFINZI vs. sorafenib. Key secondary endpoints were Investigator assessed PFS, ORR and DoR according to RECIST v1.1. PROs were also assessed.

The demographics and baseline disease characteristics were generally representative for patients with uHCC. The baseline demographics of the overall study population were as follows: male (83.7%), age <65 years (50.4%), white (44.6%), Asian (50.7%), black or African American (1.7%), other (2.3%), ECOG PS 0 (62.6%); Child-Pugh Class score A (99.5%), macrovascular invasion (25.2%), extrahepatic spread (53.4%), viral aetiology; hepatitis B (30.6%), hepatitis C (27.2%), uninfected (42.2%).

The study demonstrated a statistically significant and clinically meaningful improvement in OS with STRIDE vs sorafenib [HR=0.78 [95% CI 0.66, 0.92]; p=0.0035]. The study also met the key secondary objective of OS non-inferiority of IMFINZI to sorafenib with the upper limit of the 95.67% CI being below the pre-specified non-inferiority margin of 1.08. See Table 30 and Figure 12.

Table 30 Results for primary and key secondary efficacy endpoints for STRIDE vs sorafenib and IMFINZI vs sorafenib (HIMALAYA)

	STRIDE (n=393)	Sorafenib (n=389)	IMFINZI (n=389)
Follow up duration (months)			
Median follow up	33.2	32.2	32.6
Range	(31.7–34.5)	(30.4–33.7)	(31.6–33.7)
Overall survival (OS)			
Number of deaths (%)	262 (66.7)	293 (75.3)	280 (72.0)
Median OS (months) (95% CI)	16.4 (14.2-19.6)	13.8 (12.3-16.1)	16.6 (14.1-19.1)
HR (95% CI)	0.78 (0.66, 0.92)		-
p-value [a]	0.0035		-
HR (95% CI)	-	0.86 (0.73, 1.02)	
p-value [b]	-	0.0674	
OS at 12 months (%) (95% CI)	60.2 (55.2 - 64.9)	56.2 (51.0 - 61.0)	59.3 (54.2-64.0)
OS at 18 months (%) (95% CI)	48.7 (43.6-53.5)	41.5 (36.5-46.4)	47.4 (42.4-52.3)
OS at 24 months (%) (95% CI)	40.5 (35.6-45.3)	32.6 (27.9-37.4)	39.6 (34.8-44.5)
OS at 36 months (%) (95% CI)	30.7 (25.8-35.7)	20.2 (15.8-25.1)	24.7 (20.0-29.8)
p-value	0.0029		0.1926
Number of patients treated beyond progression	182	192	188
Progression free survival (PFS)			
Number of events (%)	335 (85.2)	327 (84.1)	345 (88.7)
Median PFS (months) (95% CI)	3.78 (3.68-5.32)	4.07 (3.75-5.49)	3.65 (3.19-3.75)
HR (95% CI)	0.90 (0.77 - 1.05)		-
p-value [c]	0.1625		-
HR (95% CI)	-	1.02 (0.88 - 1.19)	
p-value [c]	-	0.7736	
Objective response rate (ORR)			
ORR n (%) [c,d]	79 (20.1)	20 (5.1)	66 (17.0)
Complete response n (%)	12 (3.1)	0	6 (1.5)
Partial response n (%)	67 (17.0)	20 (5.1)	60 (15.4)
Odds ratio 95% CI	4.69 (2.85, 8.04)		3.8 (2.3, 6.6)
p-value	<0.0001 [c]		<0.0001 [c]
Duration of response (DoR)			
Median DoR (months)	22.3	18.4	16.8
Sample size (n)	79	20	66
% with duration ≥6 months	82.3	78.9	81.8
% with duration ≥12 months	65.8	63.2	57.8

[a] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for STRIDE vs sorafenib was 0.0398 (Lan◦and◦DeMets 1983).

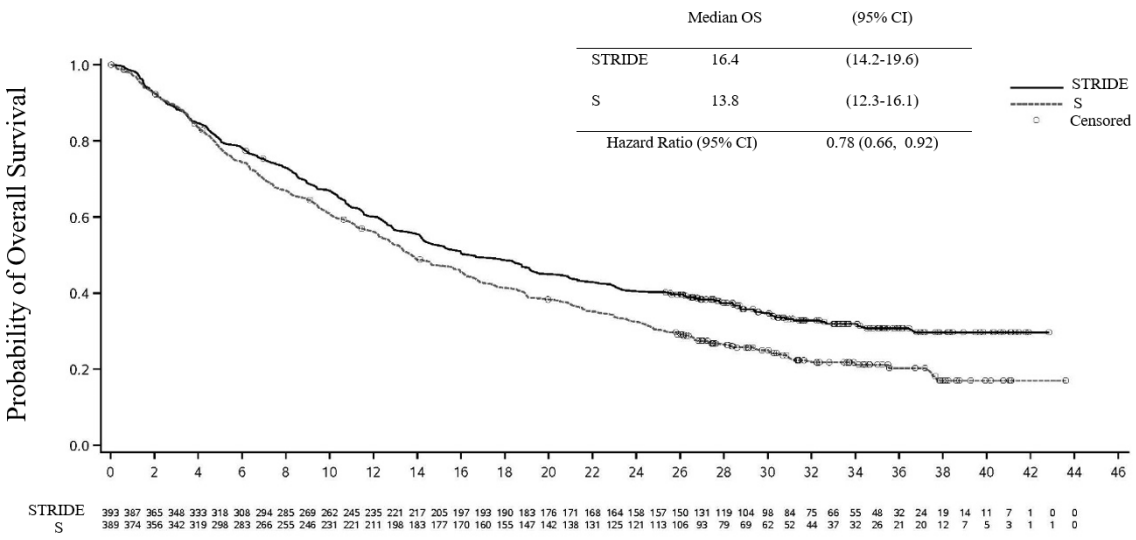
[b] p-value is for the superiority test of IMFINZI vs S. Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary and the actual number of events observed, the boundary for declaring statistical significance for IMFINZI vs S was 0.0433 (Lan◦and◦DeMets 1983).

[c] Nominal p-value. PFS and ORR were not included in the Multiple Testing Procedure (MTP).

[d] Confirmed complete response.

HR – Hazard ratio, CI -Confidence interval

Figure 12 Kaplan-Meier curve of OS (HIMALAYA)



Patient reported outcomes

Patient-reported symptoms, function and HRQoL were collected using the EORTC QLQ-C30 and its HCC module (EORTC QLQ-HCC18). At baseline, patient-reported symptoms, functioning or HRQoL scores were comparable between the study arms.

Delay in time to deterioration of symptoms, functioning and global health status/QoL:

STRIDE vs. sorafenib demonstrated a clinically meaningful improvement by delaying time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared to sorafenib. Longer time to deterioration (median in months) was observed in the STRIDE arm compared to S for the following symptoms: Global Health Status (7.5 vs 5.7 months, HR 0.76, p=0.0306); physical functioning (12.9 vs 7.4 months, HR 0.68; p=0.0020), fatigue (7.4 vs 5.4 months, HR 0.71; p=0.0026), nausea (25.0 vs 11.0 months, HR 0.65; p=0.0033), appetite loss (12.6 vs 6.9 months, HR 0.59; p<0.0001), abdominal pain (16.8 vs 8.9 months, HR 0.61; p=0.0008) and abdominal swelling (20.9 vs 11.1 months, HR 0.74; p=0.0431).

Change from baseline in patient-reported symptoms (mixed model for repeated measures):

STRIDE improved patient-reported HRQoL functioning and diarrhoea by demonstrating a nominal difference and clinically meaningful mean change from baseline vs. sorafenib from randomisation until 8 months (Estimated mean difference at 8 months: -18.5 (95% CI: -23.24, -13.84) and p-value: <0.0001).

Patient-reported outcome results should be interpreted in the context of the open-label study design.

Study 22 (uHCC)

The safety and efficacy of STRIDE was evaluated in Study 22, an open-label, uncontrolled, multi-part Phase I/II study involving 433 immunotherapy-naïve patients with uHCC. Of the 75 patients who received the STRIDE treatment regimen (tremelimumab 300 mg as a single priming dose + IMFINZI 1500 mg; followed by IMFINZI 1500 mg every 4 weeks), more than a quarter received STRIDE as first line of systemic therapy (73.3% had received prior systemic therapy with sorafenib/other VEGFR TKI). The higher percentage of patients alive and in survival follow-up (including those still receiving study treatment) in the STRIDE treatment arm (30.7%) compared to the other treatment arms (IMFINZI monotherapy and two additional tremelimumab arms; ranging from 17.4% to 19.2%) at DCO was more likely indicative of the data in the STRIDE treatment arm being less mature than that in the other 3 treatment arms as enrolment in the STRIDE safety run-in treatment arm (Part 2B) began approximately 8 months after the start of the other 3 treatment arms (in Part 2A).

The study included patients with BCLC Stage C or B (not eligible for locoregional therapy), ECOG PS of 0 or 1 and Child-Pugh Score Class A.

The study excluded patients with co-infection of viral hepatitis B and hepatitis C; active or prior documented GI bleeding within 12 months; ascites requiring non-pharmacologic intervention within 6 months; hepatic encephalopathy within 12 months before the start of treatment; active or prior documented autoimmune or inflammatory disorders.

Treatment continued as long as clinical benefit was observed or until unacceptable toxicity. Patients who completed the assigned dosing cycles and were benefiting from study drug in the Investigator's opinion and subsequently had evidence of disease progression during the IMFINZI monotherapy phase could be rechallenged with tremelimumab 300 mg.

Tumour assessments were conducted every 8 weeks.

The primary objective was safety and tolerability. Key secondary endpoints included OS, ORR and DoR. ORR, DoR and PFS were based on Investigator assessments and BICR according to RECIST 1.1.

The baseline demographics of the study population (STRIDE) were as follows: male (86.7%); age <65 years (45.3%), white (36.0%); Asian (58.7%); black or African American (5.3%); other (0%), ECOG PS 0 (61.3%), Child-Pugh Class/Score A/5 (68.0%), Child-Pugh Class/Score A/6 (30.7%), macrovascular invasion (21.3%); extrahepatic spread (70.7%), viral aetiology; hepatitis B (36.0%), hepatitis C (28.0%), uninfected (36.0%); prior systemic therapy (73.3%).

Efficacy results for the STRIDE and IMFINZI monotherapy treatment arms only are shown in Table 31. Results from the other two tremelimumab arms have not been provided.

Table 31 Efficacy results for STRIDE and IMFINZI monotherapy treatment arms (Study 22) [a]

	STRIDE (n=75)	**IMFINZI monotherapy [d] (n=104)**
Objective response rate (ORR)		
ORR n (%) [b,c]	18 (24.0)	12 (11.5)
95% CI	14.9, 35.3	6.1, 19.3
Duration of response (DoR)[b]		
Median DoR (months) (95% CI)	18.4 (5.6, 24.0)	15.0 (8.5, NR)
% with duration ≥6 months	71.8	83.3

	STRIDE (n=75)	IMFINZI monotherapy [d] (n=104)
% with duration ≥12 months	64.6	56.3
Overall survival (OS)		
Number of deaths (%)	49 (65.3)	78 (75.0)
Median OS (months) (95% CI)	17.05 (10.6-22.8)	12.9 (8.7-16.8)
OS at 12 months (%) (95% CI)	57.6 (45.5-68.0)	50.4 (40.3-59.7)
OS at 18 months (%) (95% CI)	47.8 (35.9-58.7)	34.0 (24.9-43.3)
OS at 24 months (%) (95% CI)	38.3 (26.9-49.6)	26.2 (17.9-35.3)

[a] DCO of Final analysis: 6 Nov 2020.

[b] Confirmed by BICR per RECIST v1.1.

[c] Confirmed complete response.

[d] durvalumab 1500 mg every 4 weeks

NR - Not reached; CI - Confidence interval

Endometrial cancer

DUO-E study

DUO-E was a randomised, multicentre, double-blind, placebo-controlled, Phase III study of first-line platinum-based chemotherapy (carboplatin plus paclitaxel) in combination with IMFINZI, followed by maintenance IMFINZI in patients with advanced or recurrent endometrial cancer. For patients with recurrent disease, prior chemotherapy was allowed only if it was administered in the adjuvant setting and there was at least 12 months from the date of last dose of chemotherapy administered to the date of subsequent relapse. The study included patients with epithelial endometrial carcinomas of all histologies, including carcinosarcomas. Patients with endometrial sarcoma were excluded.

Randomisation was stratified by tumour tissue's mismatch repair (MMR) status (proficient (pMMR) versus deficient (dMMR)), disease status (recurrent versus newly diagnosed) and geographic region (Asia versus rest of the world). Patients were randomised 1:1:1 across three treatment arms, including the following two:

- *Arm 1 (Platinum-based chemotherapy):*
  Platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks for a maximum of 6 cycles with durvalumab placebo every 3 weeks. Following completion of chemotherapy treatment, patients without objective disease progression received durvalumab placebo every 4 weeks and olaparib placebo tablets twice daily as maintenance treatment until disease progression.
- *Arm 2 (Platinum-based chemotherapy + IMFINZI):*
  Platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks for a maximum of 6 cycles with 1120 mg IMFINZI every 3 weeks. Following completion of chemotherapy treatment, patients without objective disease progression received 1500 mg durvalumab every 4 weeks with olaparib placebo tablets twice daily as maintenance treatment until disease progression.

Treatment was continued until RECIST v1.1-defined progression of disease or unacceptable toxicity. Assessment of tumour status was performed every 9 weeks for the first 18 weeks relative to randomisation and every 12 weeks thereafter.

The demographics and baseline disease characteristics were generally well balanced between the three study arms (241 patients in Arm 1, 238 patients in Arm 2 and 239 patients in Arm 3). Baseline demographics were as follows: age ≥ 65 years (47%), median age of 64 years (range: 22 to 86 years), white (57%), Asian (30%), Black (5%) and other (4%). Disease characteristics were as follows: WHO/ECOG PS 0 (67%) vs. PS 1 (33%), 47% newly diagnosed and 53% recurrent disease. The histologic subtypes were endometrioid (60%), serous (21%), carcinosarcoma (7%), mixed epithelial (4%), clear cell (3%), undifferentiated (2%), mucinous (<1%) and other (3%).

MMR status was determined centrally using an MMR immunohistochemistry panel assay. Of a total of 479 patients randomised to Arm 1 and Arm 2, 384 (~80%) patients had pMMR tumour status and 95 (~20%) patients had dMMR tumour status. Demographics and baseline characteristics in the MMR-based subgroups were similar to the overall study population.

The primary endpoint was PFS, determined by investigator assessment using RECIST 1.1. Secondary efficacy endpoints included OS, ORR and DoR.

Key results for DUO-E are summarised in Table 32, Figure 13, Figure 14 and Figure 15. The study demonstrated a statistically significant improvement in PFS in the ITT population for patients treated with platinum-based chemotherapy + IMFINZI compared to platinum-based chemotherapy alone, however, the benefit is clearer for patients with dMMR tumours. Results by BICR assessment were not meaningfully different from those by investigator assessment. For the ITT, the median follow-up time in censored patients was 15.4 months in the platinum-based chemotherapy + IMFINZI arm and 12.6 months in the platinum-based chemotherapy arm. At the time of PFS analysis, interim OS data were 31% mature and a significant difference between arms had not been demonstrated in the ITT (see Table 32).

Table 32 Efficacy results (DUO-E ITT population and MMR-based subgroups)

	ITT		dMMR subgroup		pMMR subgroup	
	CT + IMFINZI	**CT**	**CT + IMFINZI**	**CT**	**CT + IMFINZI**	**CT**
Size of population	238	241	46	49	192	192
Progression free survival (PFS) [a] (DCO: 12 April 2023)						
Number of events (%)	139 (58.4)	173 (71.8)	15 (32.6)	25 (51.0)	124 (64.6)	148 (77.1)
Median [b] PFS (months) (95% CI)	10.2 (9.7-14.7)	9.6 (9.0-9.9)	NR (NR-NR)	7.0 (6.7-14.8)	9.9 (9.4-12.5)	9.7 (9.2-10.1)
HR [c] (95% CI)	0.71 (0.57-0.89)		0.42 (0.22-0.80)		0.77 (0.60-0.97)	
p-value [d]	0.003		-		-	
Overall survival (OS) (DCO: 12 Apr 2023)						
Number of events (%)	65 (27.3)	82 (34.0)	7 (15.2)	18 (36.7)	58 (30.2)	64 (33.3)
Median [b] OS (months) (95% CI)	NR (NR, NR)	25.9 (23.9, NR)	NR (NR-NR)	23.7 (16.9-NR)	NR (NR-NR)	25.9 (25.1-NR)
HR [c] (95% CI)	0.77 (0.56-1.07)		0.34 (0.13-0.79)		0.91 (0.64-1.30)	
p-value [d,e]	0.120 (NS)		-		-	
Objective response rate (ORR) (DCO: 12 Apr 2023)						
ORR [f] n/N (%)	125/202 (61.9)	109/198 (55.1)	30/42 (71.4)	17/42 (40.5)	95/160 (59.4)	92/165 (59.0)
Complete response n (%)	26 (12.9)	19 (9.6)	12 (28.6)	4 (9.5)	14 (8.8)	15 (9.6)
Partial response n (%)	99 (49.0)	90 (45.5)	18 (42.9)	13 (31.0)	81 (50.6)	77 (49.4)
Duration of response (DoR) (DCO: 12 Apr 2023)						
Median [b] DoR (months) (95% CI)	13.1 (10.4-NR)	7.7 (7.4-10.3)	NR (NR, NR)	10.5 (4.3, NR)	10.6 (7.7, 13.1)	7.6 (7.1, 10.2)

[a] Investigator assessed.

[b] Calculated using the Kaplan-Meier technique.

[c] A HR less than 1 favours the chemotherapy + IMFINZI arm vs chemotherapy.

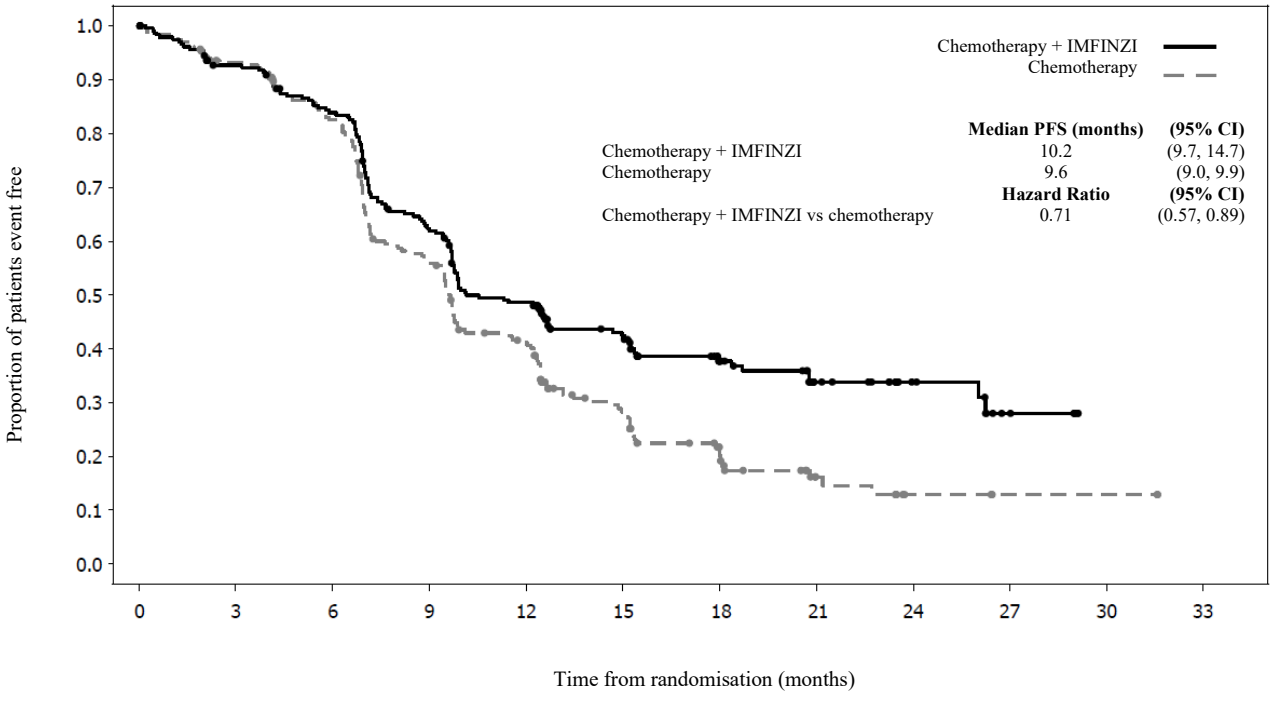
[d] p-value calculated using a log-rank test

[e] Not significant at a two-sided significance level of 0.0011 for chemotherapy + IMFINZI arm vs chemotherapy.

[f] Response: Best objective response as confirmed complete response or partial response.

HR – hazard ratio; CI - confidence interval, CT – chemotherapy with carboplatin and paclitaxel; dMMR – mismatch repair deficient; ITT – intention to treat; NR - not reached, NS - not significant; pMMR – mismatch repair proficient

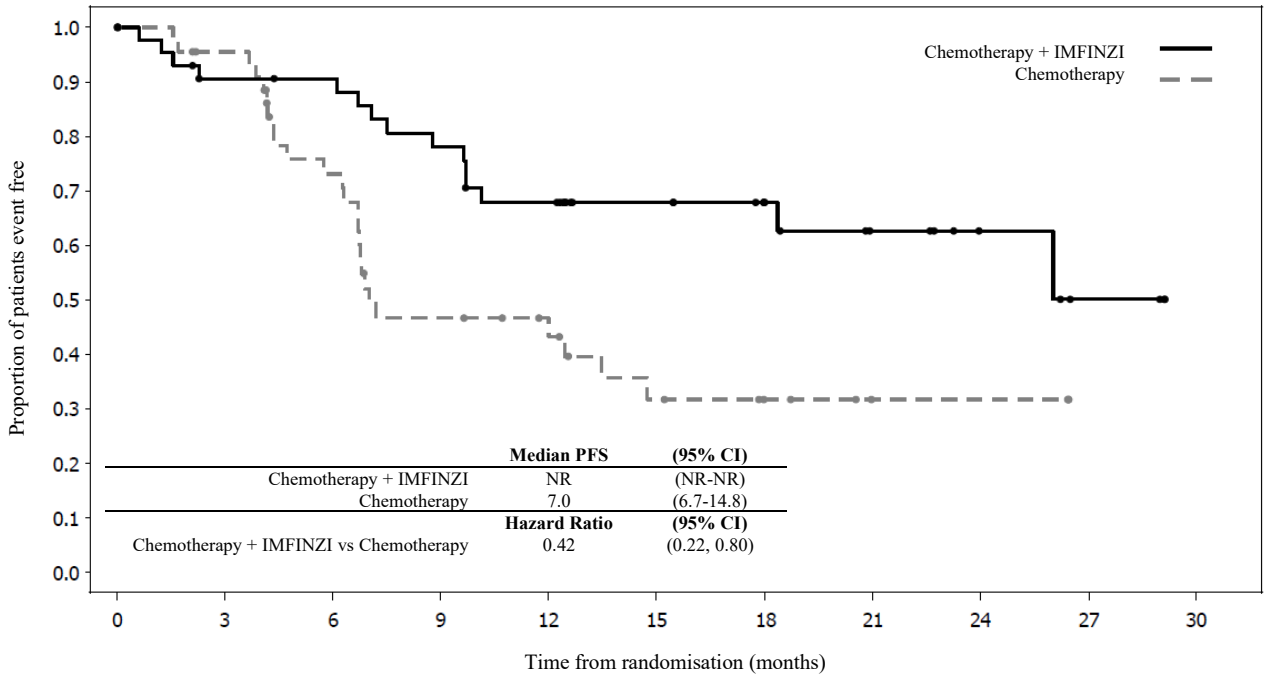
Figure 13 Kaplan-Meier curve of PFS (DUO-E ITT population; DCO 12 April 2023)



Number of patients at risk:

Chemotherapy + IMFINZI	238	211	188	138	105	69	45	26	13	5	0	0
Chemotherapy	241	213	184	125	86	45	26	10	3	1	1	0

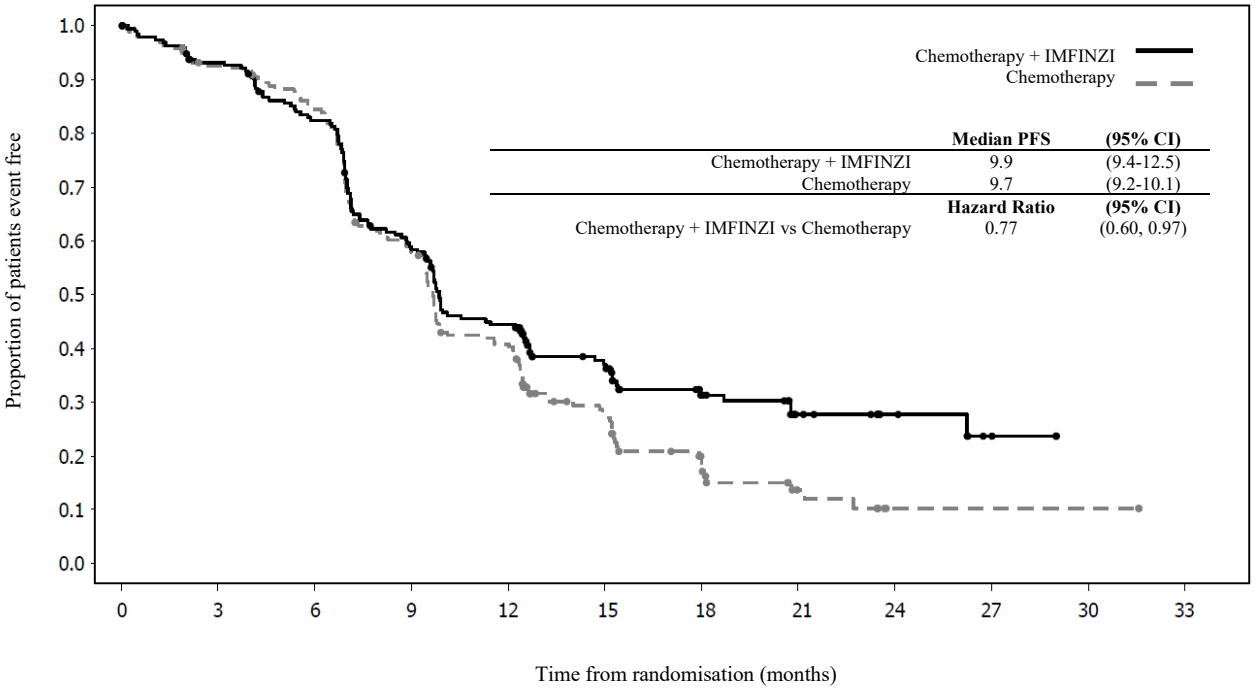
Figure 14 Kaplan-Meier curve of PFS (DUO-E dMMR subgroup; DCO 12 April 2023)



Number of patients at risk:

Chemotherapy + IMFINZI	46	37	36	31	26	19	14	9	5	2	0
Chemotherapy	49	41	28	17	13	8	5	2	2	0	0

Figure 15 Kaplan-Meier curve of PFS (DUO-E pMMR subgroup; DCO 12 April 2023)



Number of patients at risk:

Chemotherapy + IMFINZI	192	174	152	107	79	50	31	17	8	3	0	0
Chemotherapy	192	172	156	108	73	37	21	8	1	1	1	0

Bladder cancer

NIAGARA (muscle invasive bladder cancer)

NIAGARA was a randomised, open-label, multicentre Phase III study designed to evaluate the efficacy of neoadjuvant IMFINZI in combination with gemcitabine and cisplatin followed by adjuvant IMFINZI monotherapy in patients with MIBC. The study randomised 1063 patients with MIBC who were candidates for radical cystectomy and had not received prior systemic chemotherapy or immune-mediated therapy. The study excluded patients with pure non-urothelial histology, any small cell histology and primary non-bladder (ie ureter, urethral or renal pelvis) cancer of the urothelium, active or prior documented autoimmune disease, active tuberculosis or hepatitis B or C or HIV infection, or use of immuno-suppressive medication within 14 days of the first dose of IMFINZI except systemic corticosteroids when used at physiological doses or as premedication.

Randomisation was stratified by clinical tumour stage T2N0 vs >T2N0 (including T2N1, T3 and T4a), renal function (adequate renal function: creatinine clearance [CrCl] ≥60 mL/min vs borderline renal function: CrCl ≥40 mL/min to <60 mL/min) and PD-L1 expression (high vs low/negative) status.

Patients were randomised 1:1 to receive perioperative IMFINZI with neoadjuvant gemcitabine and cisplatin or neoadjuvant gemcitabine and cisplatin alone:

- *Arm 1:* IMFINZI 1500 mg + gemcitabine 1000 mg/m^2 and cisplatin 70 mg/m^2 on Day 1, then gemcitabine 1000 mg/m^2 on Day 8, every 3 weeks for 4 cycles prior to surgery, followed by IMFINZI 1500 mg every 4 weeks for up to 8 cycles after surgery
- *Arm 2:* gemcitabine 1000 mg/m^2 and cisplatin 70 mg/m^2 on Day 1, then gemcitabine 1000 mg/m^2 on Day 8, every 3 weeks for 4 cycles prior to surgery, without post-surgery treatment.

Patients with borderline renal function received split dose cisplatin of 35 mg/m^2 on days 1 and 8 of each cycle.

A RECIST 1.1 tumour assessment was performed at baseline and upon completion of neoadjuvant therapy (prior to surgery). After surgery, RECIST 1.1 tumour assessments were performed every 12 weeks for the first 24 months, then every 24 weeks for 36 months, and then every 52 weeks thereafter until progression, the end of study or death.

The primary endpoint was EFS by BICR assessment and the key secondary endpoint was OS.

The demographics and baseline disease characteristics were generally well-balanced between the 533 patients in the IMFINZI + gemcitabine and cisplatin arm and 530 patients in the gemcitabine and cisplatin arm. Baseline demographics were as follows: male (81.8%), age <65 years (46.9%), white (67.0%), Asian (27.9%), black or African American (0.9%), other (0.8%), Hispanic or Latino (8.0%) and ECOG PS 0 (78.4%) vs PS 1 (21.6%). Disease characteristics were as follows: tumour stage T2N0 (40.3%) and >T2N0 (59.7%), regional lymph nodes N0 (94.5%) and N1 (5.5%), adequate renal function (81.1%) and borderline renal function (18.9%). The histologic subtypes included urothelial carcinoma (84.5%), urothelial carcinoma with squamous differentiation (8.2%), urothelial carcinoma with variant histology (5.0%) and urothelial carcinoma with glandular differentiation (2.4%).

In the overall population, 469 (88%) patients in the IMFINZI plus gemcitabine and cisplatin arm and 441 (83%) patients in the gemcitabine and cisplatin arm underwent radical cystectomy.

At a pre-specified interim analysis (IA; DCO 29 April 2024), the study demonstrated a statistically significant improvement in EFS and OS in the IMFINZI + gemcitabine and cisplatin arm compared to the gemcitabine and cisplatin arm. The trial was not designed to isolate the effect of IMFINZI in each phase (neoadjuvant or adjuvant) of treatment. See Table 33, Figure 16 and Figure 17.

Table 33 Efficacy results (NIAGARA)

	IMFINZI + gemcitabine and cisplatin (n=533)	**Gemcitabine and cisplatin (n=530)**
Event free survival (EFS) [a]		
Number of events (%)	187 (35.1)	246 (46.4)
Median EFS (months) (95% CI) [b]	NR (NR, NR)	46.1 (32.2, NR)
HR (95% CI)[c]	0.68 (0.56, 0.82)	
2-sided p-value [d,e]	<0.0001	
EFS at 24 months (%) (95% CI) [b]	67.8 (63.6, 71.7)	59.8 (55.4, 64.0)
Overall survival (OS) [a]		
Number of events (%)	136 (25.5)	169 (31.9)
Median OS (months) (95% CI) [b]	NR (NR, NR)	NR (NR, NR)
HR (95% CI) [c]	0.75 (0.59, 0.93)	
2-sided p-value [d,e]	0.0106	
OS at 24 months (%) (95% CI) [b]	82.2 (78.7, 85.2)	75.2 (71.3, 78.8)

CI - confidence interval; FAS - full analysis set; HR – hazard ratio; NR - not reached

[a] Results are based on a pre-specified interim analysis (DCO: 29 April 2024) which occurred 68 months after study initiation

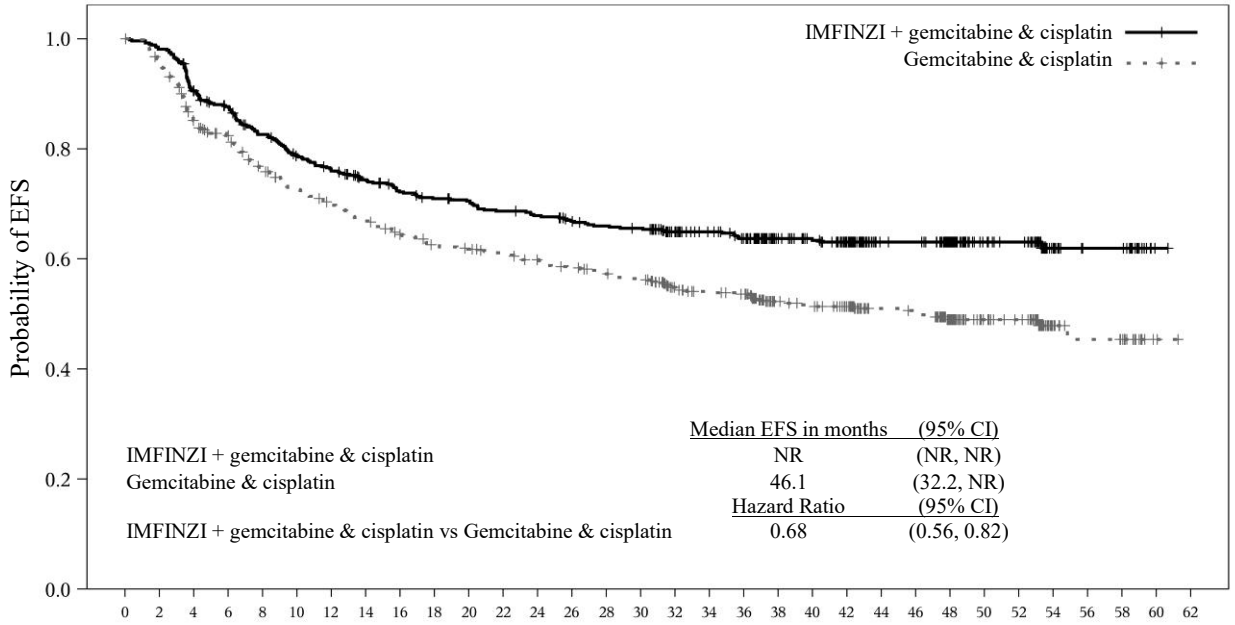
[b] Calculated using the Kaplan-Meier technique

[c] Based on stratified Cox proportional hazard model

[d] Based on stratified log-rank test

[e] The boundary for declaring statistical significance for the primary efficacy endpoint EFS and the key secondary endpoint OS were determined by a multiple test procedure with an alpha-exhaustive recycling strategy. Alpha allocated to EFS and OS at the interim analysis was based on a Lan-DeMets alpha spending function with O'Brien Fleming approach. (EFS=0.0412, OS= 0.0154, 2-sided).

Figure 16 Kaplan-Meier curve of EFS (NIAGARA; DCO 29 April 2024)

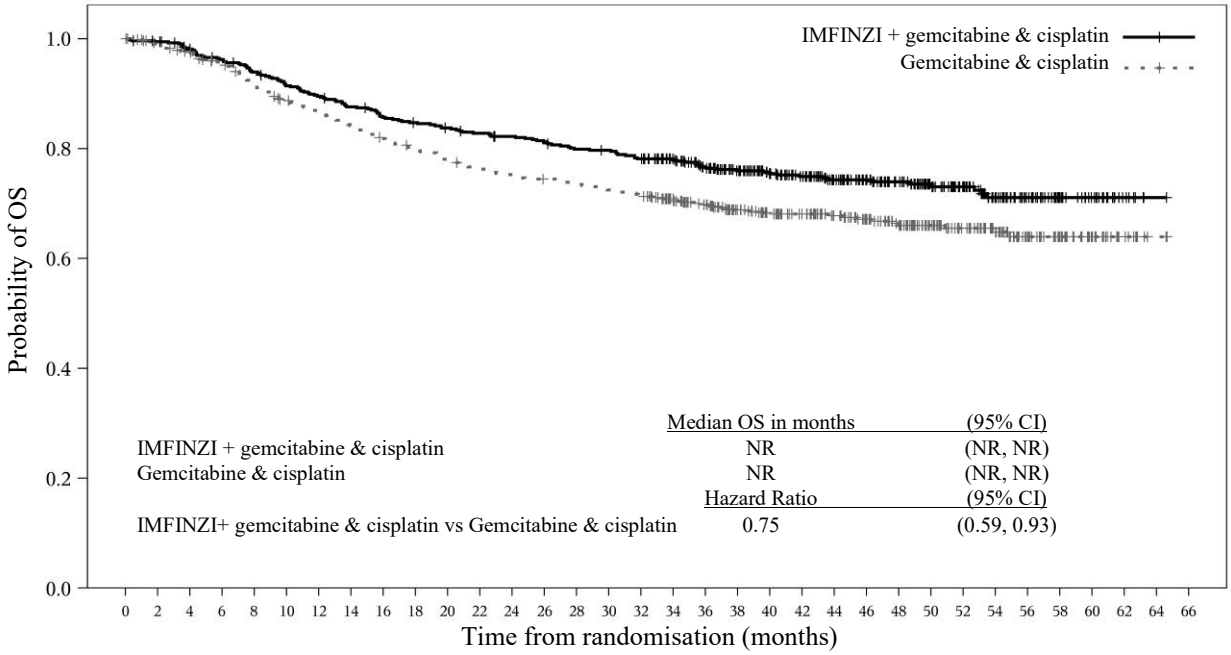


	Median EFS in months	(95% CI)
IMFINZI + gemcitabine & cisplatin	NR	(NR, NR)
Gemcitabine & cisplatin	46.1	(32.2, NR)
	Hazard Ratio	(95% CI)
IMFINZI + gemcitabine & cisplatin vs Gemcitabine & cisplatin	0.68	(0.56, 0.82)

Number of patients at risk:

IMFINZI+ gemcitabine & cisplatin	533	519	475	454	424	401	386	370	356	348	344	335	330	321	315	312	282	269	255	214	202	180	141	140	115	86	81	32	20	20	1	0
Gemcitabine & cisplatin	530	498	437	416	381	358	343	328	313	300	296	288	281	273	264	259	228	219	214	177	172	159	132	129	94	69	62	24	18	16	2	0

Figure 17 Kaplan-Meier curve of OS (NIAGARA; DCO 29 April 2024)



	Median OS in months	(95% CI)
IMFINZI + gemcitabine & cisplatin	NR	(NR, NR)
Gemcitabine & cisplatin	NR	(NR, NR)
	Hazard Ratio	(95% CI)
IMFINZI+ gemcitabine & cisplatin vs Gemcitabine & cisplatin	0.75	(0.59, 0.93)

Number of patients at risk:

IMFINZI+ gemcitabine & cisplatin	533	528	517	505	492	478	468	457	446	440	434	428	423	418	410	408	400	375	349	321	295	271	238	207	182	152	125	96	68	34	21	7	1	0
Gemcitabine & cisplatin	530	516	507	490	467	450	438	425	413	402	392	383	378	373	368	363	358	334	311	281	259	239	215	194	174	141	113	90	60	38	21	10	2	0

Gastric and gastroesophageal junction (GOJ) cancer (GC/GOJC)

MATTERHORN study (resectable gastric and GOJ adenocarcinoma)

MATTERHORN was a randomised, double-blind, placebo-controlled, multicentre, Phase III study designed to evaluate the efficacy of IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, in patients with resectable gastric or GOJ adenocarcinoma (Stage II to IVA [AJCC, 8th edition]). The study enrolled previously untreated patients with GC/GOJC, with no prior exposure to immune-mediated therapy and WHO/ECOG PS of 0 or 1. Patients were enrolled regardless of PD-L1 expression level and prior to randomisation, patients had their tumour PD-L1 expression status confirmed using the Ventana PD-L1 (SP263) assay. The study excluded patients with active or prior documented autoimmune or inflammatory disorders, or use of immunosuppressive medication within 14 days of the first dose of IMFINZI.

Randomisation was stratified by geographical region (Asia vs non-Asia), clinical lymph node status (positive vs negative) and PD-L1 expression status (Tumour Area Positivity (TAP) <1% vs TAP ≥1%).

Patients were randomised in a 1:1 ratio to one of the following treatment arms. Crossover between the study arms was not permitted.

- *Arm 1 (IMFINZI arm):* IMFINZI 1500 mg on Day 1 + FLOT chemotherapy on Days 1 and 15 every 4 weeks for 4 cycles (1 dose of IMFINZI and 2 doses of FLOT per cycle; 2 cycles in the neoadjuvant phase + 2 cycles in the adjuvant phase) followed by IMFINZI 1500 mg on Day 1 every 4 weeks for up to 10 additional cycles post-surgery for a total of 12 cycles (1 dose per cycle)
- *Arm 2 (placebo arm):* Placebo on Day 1 + FLOT chemotherapy on Days 1 and 15 every 4 weeks for 4 cycles (1 dose of placebo and 2 doses of FLOT per cycle; 2 cycles in the neoadjuvant phase + 2 cycles in the adjuvant phase) followed by placebo on Day 1 every 4 weeks for up to 10 additional cycles post-surgery for a total of 12 cycles (1 dose per cycle)

Patients in either the neoadjuvant or adjuvant phase who discontinued FLOT chemotherapy due to reasons other than disease progression or recurrence could, based on investigator discretion, continue treatment with IMFINZI monotherapy as described above.

A baseline RECIST 1.1 tumour assessment was performed prior to the start of neoadjuvant therapy, with a follow-up scan prior to surgery within 4 weeks after the final chemotherapy dose. An adjuvant baseline scan was performed no sooner than 4 weeks after surgery and before starting the adjuvant treatment. Tumour assessments were conducted every 12 weeks (relative to the adjuvant baseline scan) for 2 years, then every 24 weeks until RECIST 1.1 defined radiological progression, consent withdrawal or death.

The primary endpoint of the study was EFS by BICR assessment. The key secondary endpoints were OS and pCR rate by blinded central pathology review. Other secondary efficacy objectives included PROs.

The demographics and baseline disease characteristics were generally well balanced between the two study arms (474 patients in the IMFINZI arm and 474 patients in the placebo arm). The baseline demographics of the overall population were as follows: male (71.9%), age ≥65 years (41.4%), median age 62 years (range: 26 to 84), white (67.8%), Asian (20.4%), black or African American (1.1%), American Indian or Alaska Native (4.0%), other race (1.7%), not Hispanic or Latino (80.0%), WHO/ECOG PS 0 (74.2%) vs PS 1 (25.8%). Disease characteristics were as follows: Stage II (29.4%), Stage III (61.7%), Stage IVA (8.8%), gastric (67.5%), GOJ (32.5%), Siewert type 1 (10.4%), Siewert type 2 (14.8%), Siewert type 3 (7.3%), intestinal type (50.9%), diffuse type (26.3%), indeterminate type (22.8%), clinical lymph node status positive (70.4%), clinical lymph node status negative (29.2%), PD-L1 expression status TAP ≥1% (90.0%), PD-L1 expression status TAP <1% (10.0%).

There were 431 (90.9%) patients in the IMFINZI arm who attempted curative intent surgery compared to 428 (90.3%) patients in the placebo arm.

In a prespecified interim analysis the study demonstrated a statistically significant improvement in EFS for the IMFINZI arm compared to the placebo arm. The study also demonstrated a statistically significant improvement in pCR rate for the IMFINZI arm compared to the placebo arm. At the final OS analysis, the study demonstrated a statistically significant improvement in OS for the IMFINZI arm compared to the placebo arm. The study was not designed to isolate the effect of IMFINZI in each phase (neoadjuvant or adjuvant) of treatment. See Table 34, Figure 18 and Figure 19.

Table 34 Efficacy results (MATTERHORN)

	IMFINZI+FLOT chemotherapy (N=474)	**Placebo+FLOT chemotherapy (N = 474)**
Event free survival (EFS) [a]		
Number of events, n (%)	167 (35.2)	218 (46.0)
Median EFS (months) (95% CI) [b]	NR (40.7, NR)	32.8 (27.9, NR)
HR (95% CI) [c]	0.71 (0.58, 0.86)	
2-sided p-value [d, e]	<0.001	
EFS at 24 months, % (95% CI)	67.4 (62.9, 71.6)	58.5 (53.8, 63.0)
Overall survival (OS) [f]		
Number of deaths, n (%)	160 (33.8)	192 (40.5)
Median OS (months) (95% CI) [b]	NR (NR, NR)	NR (NR, NR)
HR (95% CI) [c]	0.78 (0.63, 0.96)	
2-sided p-value [d, g]	0.021	
OS at 24 months, % (95% CI)	75.5 (71.3, 79.1)	70.4 (66.0, 74.3)
OS at 36 months, % (95% CI)	68.6 (64.2, 72.6)	61.9 (57.3, 66.2)
Pathological complete response (pCR) [h]		
Number of patients with response, n	91	34
Response rate, % (95% CI) [i]	19.2 (15.7, 23.0)	7.2 (5.0, 9.9)
Odds ratio, % (95% CI)	3.08 (2.0, 4.7)	
2-sided p-value [j, k]	<0.001	

[a] Results are based on an EFS pre-specified interim analysis (DCO: 20 December 2024)

[b] Calculated using the Kaplan-Meier technique

[c] Based on stratified Cox proportional hazards model stratified by geographical region, clinical lymph node status and PD-L1 expression status at randomisation. A HR <1 favours IMFINZI. CI calculated using the profile likelihood approach

[d] Based on stratified log-rank test adjusting for geographic region, clinical lymph node status and PD-L1 expression status at randomisation

[e] Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary calculated using the actual number of events at DCO, the boundary for declaring statistical significance of EFS was 0.0239 for an overall alpha of 5% (2-sided).

[f] Results are based on an OS final analysis (DCO: 1 September 2025)

[g] An alpha of 4.99% (2-sided) was allocated to the final analysis of OS, corresponding to a boundary for declaring statistical significance of 0.0499.

[h] Results are based on pCR final analysis (DCO: 1 February 2023)

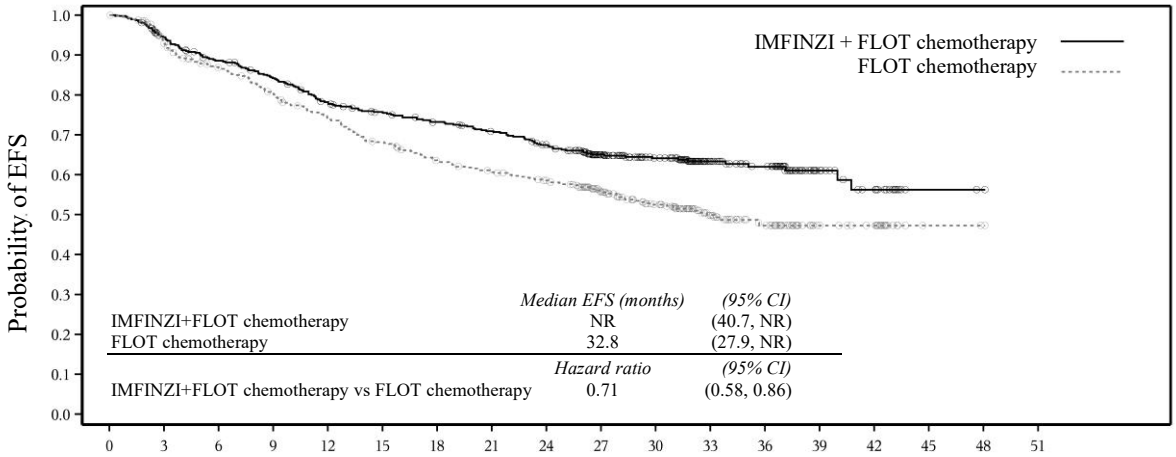
[i] CI was calculated using the Clopper Pearson method

[j] A fixed alpha of 0.1% (2-sided) was allocated to the analysis of pCR rate, corresponding to a p-value boundary for declaring statistical significance of 0.001

[k] Based on a stratified Cochran-Mantel-Haenszel test adjusting for geographic region, clinical lymph node status and PD-L1 expression status at randomisation

CI=Confidence interval, FLOT chemotherapy (regimen of fluorouracil, leucovorin, oxaliplatin and docetaxel); HR=Hazard ratio; NR – not reached

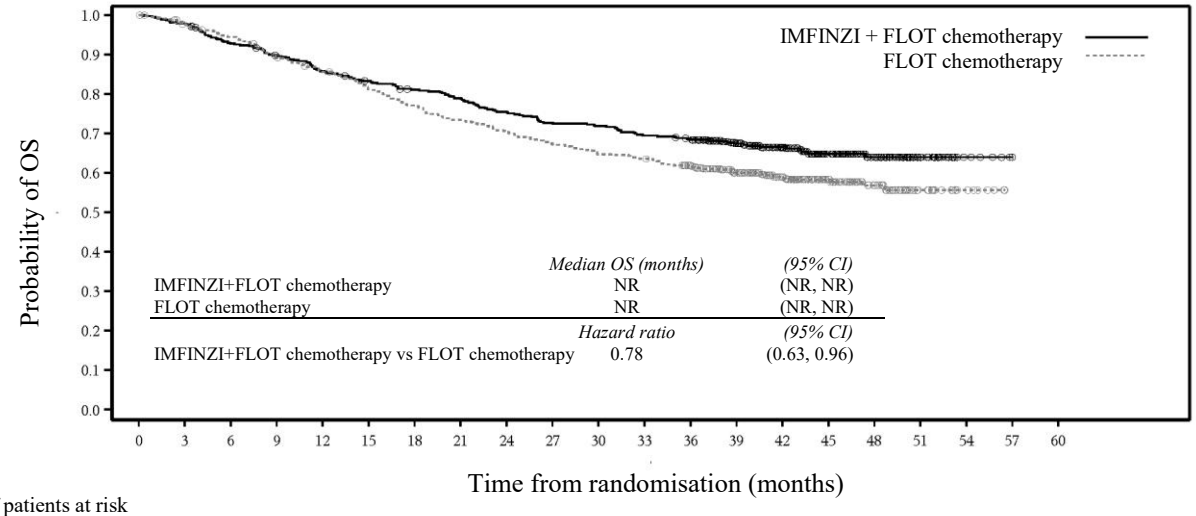
Figure 18 Kaplan-Meier curve of EFS (MATTERHORN; DCO 20 December 2024)



Number of patients at risk

IMFINZI+FLOT chemotherapy	474	436	404	381	351	334	320	307	288	234	187	107	88	33	20	2	1	0	474/167
FLOT chemotherapy	474	429	392	360	329	302	278	264	249	202	160	89	65	26	21	2	1	0	474/218

Figure 19 Kaplan-Meier curve of OS (MATTERHORN; DCO 1 September 2025)



Number of patients at risk

IMFINZI+FLOT chemotherapy	474	464	438	422	403	389	377	367	351	338	334	323	316	255	182	112	71	29	6	1	0	474/160
FLOT chemotherapy	474	457	439	414	395	374	355	338	324	310	298	293	278	221	167	99	61	23	7	0	0	474/192

Subgroup analysis

Improvement in EFS favouring patients in the IMFINZI arm compared to patients in the placebo arm was consistently observed across all pre-specified subgroups based on demographic and baseline disease characteristics, including sex, age, geographic region, primary tumour location, clinical lymph node status, ECOG PS and PD-L1 expression.

Patient reported outcomes (PRO)

Overall, EORTC QLQ-C30 and the gastric cancer module (EORTC QLQ-STO22 + IL38) results show that treatment with IMFINZI + FLOT chemotherapy did not adversely affect patient function and symptom burden. The proportion of patients reporting PRO-Common Terminology Criteria for Adverse Events (PRO-CTCAE) items was comparable across treatment arms, suggesting that both treatments were similarly well-tolerated from the patients' perspective.

5.2 PHARMACOKINETIC PROPERTIES

The PK of durvalumab was assessed for IMFINZI as monotherapy, in combination with chemotherapy (etoposide and carboplatin or cisplatin), in combination with tremelimumab and platinum-based chemotherapy, and in combination with platinum-based chemotherapy followed by IMFINZI. There was no clinically meaningful difference between the PK of durvalumab as monotherapy or in any of the assessed combinations.

The PK of IMFINZI was studied in patients with solid tumours with doses ranging from 0.1 to 20 mg/kg administered once every two, three or four weeks.

Distribution

PK exposure increased more than dose-proportionally (non-linear PK) at doses <3 mg/kg and dose proportionally (linear PK) at doses ≥3 mg/kg. Steady state was achieved at approximately 16 weeks. Based on population PK analysis that included patients in the dose range of 10 mg/kg every 2 weeks (Q2W), 15 mg/kg every 3 weeks (Q3W) and 20 mg/kg every 4 weeks (Q4W), the steady state volume of distribution (Vss) was 5.64 L.

Excretion

Durvalumab clearance (CL) decreased over time resulting in a geometric mean steady state clearance (CLss) of 8.16 mL/h at Day 365; the decrease in CLss was not considered clinically relevant. The terminal half-life ($t_{½}$), based on baseline CL, was approximately 18 days.

Special populations

Age (19–96 years), body weight (34-149 kg), gender, positive anti-drug antibody (ADA) status, albumin levels, LDH levels, creatinine levels, soluble PD-L1, tumour type, race, mild renal impairment (CrCl: 60 to 89 mL/min), moderate renal impairment (CrCl: 30 to 59 mL/min), mild hepatic impairment (bilirubin ≤ ULN and AST > ULN or bilirubin >1.0 to 1.5 × ULN and any AST) moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST) or ECOG/WHO status had no clinically significant effect on the pharmacokinetics of durvalumab.

The effect of severe renal impairment (CrCl: 15 to 29 mL/min) or severe hepatic impairment (bilirubin >3.0 x ULN and any AST) on the pharmacokinetics of durvalumab is unknown; however, as IgG monoclonal antibodies are not primarily cleared via hepatic pathways, a change in hepatic function is not expected to influence durvalumab exposure.

Paediatric and adolescents

The PK of durvalumab in combination with tremelimumab was evaluated in a study of 50 paediatric patients with an age range from 1 to 17 years, in Study D419EC00001. Patients received either durvalumab 20 mg/kg in combination with tremelimumab 1 mg/kg or durvalumab 30 mg/kg in combination with tremelimumab 1 mg/kg intravenously every 4 weeks for 4 cycles, followed by durvalumab as monotherapy every 4 weeks. Based on population PK analysis, durvalumab systemic exposure in paediatric patients ≥35 kg receiving durvalumab 20 mg/kg every 4 weeks was similar to exposure in adults receiving durvalumab 20 mg/kg every 4 weeks, whereas in paediatric patients (≥35 kg) receiving durvalumab 30 mg/kg every 4 weeks, exposure was approximately 1.5-fold higher compared to exposure in adults receiving durvalumab 20 mg/kg every 4 weeks. In paediatric patients <35 kg receiving durvalumab 30 mg/kg every 4 weeks, the systemic exposure was similar to exposure in adults receiving durvalumab 20 mg/kg every 4 weeks.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Immunogenicity of IMFINZI as monotherapy is based on pooled data in 2280 patients who were treated with IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy and evaluable for the presence of anti-drug antibodies (ADAs). Sixty-nine patients (3.0%) tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 0.5% (12/2280) patients. The presence of ADAs did not have a clinically relevant effect on pharmacokinetics, pharmacodynamics or safety.

In the AEGEAN study, of the 375 patients who were treated with IMFINZI 1500 mg in combination with chemotherapy every 3 weeks prior to surgery, followed by IMFINZI 1500 mg every 4 weeks following surgery, and were evaluable for the presence of ADAs, 25 (6.7%) patients tested positive for treatment emergent ADAs. Neutralising antibodies against durvalumab were detected in 2 patients (0.5%). The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety of IMFINZI.

In the ADRIATIC study, of the 206 patients who were treated with IMFINZI monotherapy and evaluable for the presence of ADAs, 7 (3.4%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 1% (2/206) patients. The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety.

In the CASPIAN study, of the 201 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with etoposide, and carboplatin or cisplatin and evaluable for the presence of ADAs, 0 (0%) patients tested positive for treatment-emergent ADAs.

In the TOPAZ-1 study, of the 240 patients who were treated with IMFINZI 1500 mg every 3 weeks in combination with chemotherapy, followed by IMFINZI 1500 mg every 4 weeks and evaluable for the presence of ADAs, 2 (0.8%) patients tested positive for treatment-emergent ADAs. There were insufficient numbers of patients with treatment emergent ADAs or neutralising antibodies (2 patients each) to determine whether ADAs have an impact on pharmacokinetics and clinical safety of durvalumab.

In the HIMALAYA study, of the 294 patients who were treated with STRIDE and evaluable for the presence of ADAs, 9 (3.1%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 1.7% (5/294) patients. The presence of ADAs did not have an apparent effect on pharmacokinetics or safety.

In the DUO-E study, the number of the patients who were treated with platinum-based chemotherapy + IMFINZI (n=198) and evaluable for the presence of ADAs, 2 (1.0%) patients tested positive for treatment-emergent ADAs in the platinum-based chemotherapy + IMFINZI arm.

Neutralising antibodies against durvalumab were detected in 1 (0.5%) patient in the platinum-based chemotherapy + IMFINZI arm. There were insufficient number of patients with treatment-emergent ADAs or neutralising antibodies to determine whether ADAs have an impact on pharmacokinetics or safety of durvalumab.

In the NIAGARA study, of the 453 patients who were treated with IMFINZI 1500 mg in combination with chemotherapy every 3 weeks prior to surgery followed by IMFINZI 1500 mg every 4 weeks following surgery and were evaluable for the presence of ADAs, 8 (1.8%) patients tested positive for treatment-emergent ADAs. Neutralising antibodies against durvalumab were detected in 6 (1.3%) patients. The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety.

In the MATTERHORN study, of the 441 patients who were treated with IMFINZI 1500 mg in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, then continued as adjuvant IMFINZI monotherapy, and were evaluable for the presence of ADAs, 40 (9.1%) patients tested positive for treatment emergent ADAs. Neutralising antibodies against durvalumab were detected in 2 patients (0.5%). The presence of ADAs did not have an apparent effect on the pharmacokinetics or safety of IMFINZI.

Immunogenicity assay results are highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications and underlying disease.

For these reasons, comparison of incidence of antibodies to IMFINZI with the incidence of antibodies to other products may be misleading.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of durvalumab has not been evaluated. As a large protein molecule, durvalumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of durvalumab has not been evaluated.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

IMFINZI concentrated solution for infusion contains the following excipients: histidine, histidine hydrochloride monohydrate, trehalose dihydrate, polysorbate 80 and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store unopened vials under refrigeration at 2°C to 8°C in the original carton to protect from light. Do not freeze. Do not shake.

6.5 NATURE AND CONTENTS OF CONTAINER

10 mL of concentrated solution for infusion in a 10 mL Type 1 glass vial with an elastomeric stopper and a white flip-off aluminium seal containing 500 mg durvalumab. Pack size of 1 vial.

2.4 mL of concentrated solution for infusion in a 10 mL Type 1 glass vial with an elastomeric stopper and a grey flip-off aluminium seal containing 120 mg durvalumab. Pack size of 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Durvalumab is a human immunoglobulin (IgG1κ) monoclonal antibody.

CAS number: 1428935-60-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4).

8 SPONSOR

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9 DATE OF FIRST APPROVAL

2 October 2018

10 DATE OF REVISION

29 January 2026

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8. 5.1, 5.2	New indication, dosing recommendation and clinical trial information (MATTERHORN efficacy and safety including elderly and immunogenicity) for perioperative treatment of gastric and GOJ adenocarcinoma
various	Editorial changes

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