NEW ZEALAND DATA SHEET

1. PRODUCT NAME

IMFINZI® 50 mg/mL, concentrated solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 50 mg of durvalumab.

One vial of 2.4 mL of concentrate contains 120 mg of durvalumab.

One vial of 10 mL of concentrate contains 500 mg of durvalumab.

Durvalumab is produced in mammalian (Chinese hamster ovary) cells by recombinant DNA technology.

For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Infusion, concentrate.

Sterile, preservative free, clear to opalescent and free from visible particles, colourless to slightly yellow, concentrated solution for infusion. The solution has a pH of approximately 6.0 and an osmolality of approximately 400 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Urothelial carcinoma

IMFINZI is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma who:

- have disease progression during or following platinum-containing chemotherapy.
- have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

This indication is approved based on objective response rate and duration of response in a single arm study. An improvement in survival or disease-related symptoms has not been established.

IMFINZI in combination with cisplatin-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adult patients with muscle invasive bladder cancer (MIBC).

Non-small cell lung cancer (NSCLC)

IMFINZI in combination with chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy after surgery, is indicated for the treatment of patients with resectable (tumours ≥ 4 cm and/or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

IMFINZI is indicated for the treatment of adult 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 chemotherapy is indicated for the treatment of patients with locally advanced or metastatic biliary tract cancer (BTC).

Endometrial Cancer

IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:

- IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
- IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).

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 administered in combination with other medicines, refer to the Data Sheet of the other medicines for further information.

Table 1 Recommended dosage of IMFINZI

Indication	Recommended IMFINZI dosage	Duration of Therapy
Monotherapy		
Urothelial Carcinoma	10 mg/kg every 2 weeks or 1500 mg every 4 weeks[a]	As long as clinical benefit is observed or until unacceptable toxicity
LS-SCLC	1500 mg[b] every 4 weeks	Until disease progression, unacceptable toxicity or a maximum of 24 months.

Indication	Recommended IMFINZI dosage	Duration of Therapy
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
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[d] in combination with chemotherapy every 3 weeks (21 days), followed by 1500 mg every 4 weeks as monotherapy	Until disease progression or until unacceptable toxicity
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 IMFINZI 1500 mg[e] every 4 weeks as monotherapy (dMMR patients) or in combination with olaparib 300 mg twice daily (pMMR patients)	Until disease progression or until 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

[a] Patients with a body weight of 30 kg or less must receive weight-based dosing, equivalent to IMFINZI 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks as monotherapy until weight increases to greater than 30 kg.

[b] 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.

[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 IMFINZI 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

[d] 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 IMFINZI every 3 weeks (21 days), followed by monotherapy at 20 mg/kg every 4 weeks until weight increases to greater than 30 kg.

[e] 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 is greater than 30 kg.

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 reactions. Permanently discontinue IMFINZI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3)

immune-mediated reactions 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 adverse reactions requiring specific management are summarized 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 adverse reactions

Adverse reactions	Severity[a]	IMFINZI treatment modification
Pneumonitis/interstitial lung disease	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Immune-mediated 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	Withhold dose
	ALT or AST > 10 x ULN OR total bilirubin x 3 ULN	Permanently discontinue
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN[b]	
Immune-mediated hepatitis with tumour involvement of the liver with abnormal baseline values[c]	ALT or AST > 2.5-≤ 5X BLV and ≤ 20 x ULN	Withhold dose
	ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent ALT or AST 2.5-5X BLV and ≤ 20XULN and total bilirubin > 1.5 - < 2 x ULN[b]	Withhold dose
	AST or ALT > 7 x BLV OR > 20 x ULN whichever occurs first OR bilirubin > 3 x ULN	Permanently discontinue
Colitis or diarrhoea	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue
	Intestinal perforation of 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

Adverse reactions	Severity[a]	IMFINZI treatment modification
	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[d]
	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
Immune-mediated myasthenia gravis	Grade 2-4	Permanently discontinue
Immune-mediated encephalitis	Grade 2-4	Permanently discontinue
Immune-mediated Guillain-Barré syndrome	Grade 2-4	Permanently discontinue
Pure red cell aplasia (PRCA)[f]	Any Grade	Permanently discontinue
Other immune-mediated adverse reactions[e]	Grade 2 or 3	Withhold dose
	Grade 4	Permanently discontinue

[a] Common Terminology Criteria for Adverse Events, version 4.03. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; BLV: baseline value.

[b] For patients with alternative cause follow the recommendations for AST or ALT increases without concurrent bilirubin elevations.

[c] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue durvalumab based on recommendations for hepatitis with no liver involvement.

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

[e] Includes immune thrombocytopenia, pancreatitis, immune-mediated arthritis, and uveitis.

[f] Adverse drug reaction is only associated when olaparib maintenance treatment is used in combination with IMFINZI, following treatment with IMFINZI in combination with platinum-based chemotherapy.

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

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

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

For intravenous administration.

IMFINZI in combination with chemotherapy

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

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 it needs to be stored, the total time from vial puncture to the start of administration 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.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

For suspected immune-mediated adverse reactions, adequate evaluation should be performed to confirm etiology or exclude alternate etiologies. Based on the severity of the adverse reaction, IMFINZI 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.

Immune-mediated adverse reactions

Immune checkpoint inhibitors, including durvalumab, can cause severe and fatal immune-mediated adverse reactions, which may involve any organ system. While immune-mediated reactions 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 adverse reactions 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).

Immune-mediated pneumonitis and radiation pneumonitis

Immune-mediated pneumonitis/interstitial lung disease, defined as requiring use of systemic corticosteroids and with no clear alternate etiology, including fatal cases, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 Undesirable Effects).

Pneumonitis is frequently observed in patients receiving radiation therapy 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 chemoradiation within 1 to 42 days prior to initiation of the 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 (3.4% vs 3.0%) and Grade 5 (1.1% vs 1.7%). See also Section 4.8 Undesirable Effects.

In the ADRIATIC Study, in patients who had completed treatment with chemoradiation 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.

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 – 2 mg/kg/day prednisone or equivalent should be initiated followed by a taper. For Grade 3 or 4 events, an initial dose of 2 – 4 mg/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.

Immune-mediated hepatitis

Immune-mediated hepatitis,* including a fatal case, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 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 1-2 mg/kg/day prednisone or equivalent followed by taper for all grades.

Immune-mediated colitis

Immune-mediated colitis* occurred in patients receiving durvalumab in clinical trials (see Section 4.8 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 1-2 mg/kg/day prednisone or equivalent followed by a taper for Grades 2-4. Consult a surgeon immediately if 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 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 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 1-2 mg/kg/day prednisone or equivalent followed by taper and a hormone replacement 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 Undesirable Effects). Patients should be monitored for clinical signs and symptoms of hypophysitis. 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 1-2 mg/kg/day prednisone or equivalent followed by taper and a 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 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 nephritis

Immune-mediated nephritis, defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 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 1-2 mg/kg/day prednisone or equivalent followed by taper for Grades 2-4.

Immune-mediated dermatological adverse reactions

Immune-mediated dermatitis (including pemphigoid), defined as requiring use of systemic corticosteroids and with no clear alternate aetiology, occurred in patients receiving durvalumab in clinical trials (see Section 4.8 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 1-2 mg/kg/day prednisone or equivalent followed by 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). 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 2-4 mg/kg/day prednisone or equivalent followed by 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 adverse reactions

Given the mechanism of action of durvalumab, other immune-mediated adverse reactions may occur. Other immune mediated adverse reactions are: aseptic meningitis, haemolytic anaemia, immune thrombocytopenia, myasthenia gravis, myelitis transverse, myositis, polymyositis, rhabdomyolysis, Guillain-Barré syndrome, pancreatitis, immune-mediated arthritis, encephalitis and ocular inflammatory toxicity, including uveitis and keratitis. Patients should be monitored for signs and symptoms of immune-mediated adverse reactions 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.

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 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.

Treatment-specific precaution

IMFINZI in combination with olaparib

Pure red cell aplasia (PRCA) (see section 4.8) was reported when olaparib was used in combination with IMFINZI in the maintenance phase, following treatment with IMFINZI in combination with platinum-based chemotherapy. If PRCA is confirmed, treatment with IMFINZI and olaparib should be discontinued.

Autoimmune hemolytic anaemia (AIHA) was reported when olaparib was used in combination with IMFINZI in the maintenance phase, following treatment with IMFINZI in combination with platinum-based chemotherapy. If AIHA is confirmed, treatment with IMFINZI and olaparib should be discontinued.

Efficacy in patients with PD-L1 expression <1%

Post-hoc analyses 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 sections 4.8 Undesirable Effects and 5.1 Pharmacological Properties).

Use in the elderly

No overall differences in safety or efficacy were observed between patients who were ≥ 65 years of age or who were ≥ 75 years of age compared to younger patients in study 1108 (urothelial carcinoma).

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 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 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 338 patients with BTC treated with IMFINZI in combination with chemotherapy, 158 (46.7%) 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 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. Of the 239 patients with endometrial cancer randomised to receive platinum-based chemotherapy + IMFINZI + olaparib, 104 (43.5%) patients were 65 years or older and 19 (7.9%) 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 533 patients with MIBC treated with IMFINZI in combination with chemotherapy, 275 (51.6%) 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.

Paediatric use

The safety and efficacy of durvalumab have not been established in patients younger than 18 years of age.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Durvalumab is an immunoglobulin and 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 chemotherapy was assessed in the CASPIAN study and no clinically meaningful PK drug-drug interaction was identified. Furthermore, in the DUO-E study, the exposure to durvalumab was similar in both treatment arms which indicates that there were no clinically meaningful PK drug-drug interactions between durvalumab and olaparib, although exposure to olaparib was not measured throughout the study.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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.

Breast-feeding

There is no information regarding the presence of durvalumab in human milk, the absorption and effects on the breastfed 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 breastfeed during treatment and for at least 3 months after the last dose.

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 23 times the exposure (based on AUC) in humans at the recommended clinical 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 UNDESIRABLE EFFECTS

Overall summary of adverse drug reactions

The safety of IMFINZI as monotherapy is based on pooled data in 3006 patients from 9 studies across multiple tumour types.

The most frequent adverse reactions were cough (21.5%), diarrhoea (16.3%) and rash (16.0%).

Tabulated list of adverse reactions

Table 3 lists the incidence of adverse reactions in the monotherapy safety dataset. Adverse drug reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse drug reactions are presented in decreasing frequency. Within each frequency grouping, adverse drug reactions 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); very rare (< 1/10,000); not determined (cannot be estimated from available data).

Table 3. Adverse drug reactions in patients treated with IMFINZI monotherapy

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
Respiratory, thoracic and mediastinal disorders	Cough/ Productive Cough	Very common	646 (21.5%)	Uncommon	11 (0.4%)
	Pneumonitis[a]	Common	114 (3.8%)	Uncommon	26 (0.9%)
	Dysphonia	Common	93 (3.1%)	Rare	2 (<0.1%)
	Interstitial lung disease	Uncommon	18 (0.6%)	Uncommon	4 (0.1%)
Hepatobiliary disorders	Aspartate aminotransferase increased or Alanine aminotransferase increased[a,b]	Common	244 (8.1%)	Common	69 (2.3%)
	Hepatitis[a,c]	Uncommon	25 (0.8%)	Uncommon	12 (0.4%)
Gastrointestinal disorders	Abdominal pain[d]	Very common	383 (12.7%)	Common	53 (1.8%)
	Diarrhoea	Very common	491 (16.3%)	Uncommon	19 (0.6%)
	Colitis[e]	Uncommon	28 (0.9%)	Uncommon	10 (0.3%)
	Pancreatitis[f]	Uncommon	6 (0.2%)	Uncommon	5 (0.17%)

System Organ Class	Adverse Drug Reaction	Frequency of any Grade		Frequency of Grade 3-4	
Eye disorders	Uveitis	Rare	1 (<0.1%)		0
Endocrine disorders	Hypothyroidism[g]	Very common	305 (10.1%)	Uncommon	5 (0.2%)
	Hyperthyroidism[h]	Common	137 (4.6%)	Rare	0
	Thyroiditis[i]	Uncommon	23 (0.8%)	Rare	2 (<0.1%)
	Adrenal insufficiency	Uncommon	18 (0.6%)	Rare	3 (<0.1%)
	Hypophysitis/ Hypopituitarism	Rare	2 (< 0.1%)	Rare	2 (< 0.1%)
	Type 1 diabetes mellitus	Rare	1 (< 0.1%)	Rare	1 (< 0.1%)
	Diabetes insipidus	Rare	1 (< 0.1%)	Rare	1 (< 0.1%)
Renal and urinary disorders	Blood creatinine increased	Common	105 (3.5%)	Rare	3 (<0.1%)
	Dysuria	Common	39 (1.3%)		0
	Nephritis[j]	Uncommon	9 (0.3%)	Rare	2 (< 0.1%)
Skin and subcutaneous tissue disorders	Rash[k]	Very common	480 (16.0%)	Uncommon	18 (0.6%)
	Pruritus[l]	Very common	325 (10.8%)	Rare	1 (< 0.1%)
	Night sweats	Common	47 (1.6%)	Rare	1 (< 0.1%)
	Dermatitis	Uncommon	22 (0.7%)	Rare	2 (< 0.1%)
	Pemphigoid[m]	Rare	3 (<0.1%)		0
Cardiac disorders	Myocarditis	Rare	1 (< 0.1%)	Rare	1 (<0.1%)
General disorders and administration site conditions	Pyrexia	Very common	414 (13.8%)	Uncommon	10 (0.3%)
	Oedema peripheral[n]	Common	291 (9.7%)	Uncommon	9 (0.3%)
Infections and infestations	Upper respiratory tract infections[o]	Very common	407 (13.5%)	Uncommon	6 (0.2%)
	Pneumonia[a,p]	Common	269 (8.9%)	Common	106 (3.5%)
	Oral candidiasis	Common	64 (2.1%)		0
	Dental and oral soft tissue infections[q]	Common	50 (1.7%)	Rare	1 (<0.1%)
	Influenza	Common	47 (1.6%)	Rare	2 (<0.1%)
Musculoskeletal and connective tissue disorders	Myalgia	Common	178 (5.9%)	Rare	2 (<0.1%)
	Myositis[r]	Uncommon	6 (0.2%)	Rare	1 (< 0.1%)
	Polymyositis[r]	Not determined[s]		Not determined[s]	
	Immune-mediated arthritis	Not determined[t]		Not determined[t]	
Nervous system disorders	Myasthenia gravis	Not determined[t]		Not determined[t]	
	Encephalitis	Not determined[u]		Not determined[u]	
	Guillain-Barré syndrome[a]	Not determined[t]		Not determined[t]	
Blood and lymphatic system disorders	Immune thrombocytopenia[a]	Rare	2 (<0.1%)	Rare	1 (<0.1%)
Injury, poisoning and procedural complications	Infusion related reaction[v]	Common	49 (1.6%)	Uncommon	5 (0.2%)

[a] Including fatal outcome.
[b] Includes alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, and transaminases increased.
[c] Includes hepatitis, autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatitis acute, hepatotoxicity and immune-mediated hepatitis.
[d] Includes abdominal pain, abdominal pain lower, abdominal pain upper, and flank pain.
[e] Includes colitis, enteritis, enterocolitis, and proctitis.

[f] Includes pancreatitis and pancreatitis acute
[g] Includes autoimmune hypothyroidism and hypothyroidism.
[h] Includes hyperthyroidism and Basedow's disease.
[i] Includes autoimmune thyroiditis, thyroiditis, and thyroiditis subacute.
[j] Includes autoimmune nephritis, tubulointerstitial nephritis, nephritis, glomerulonephritis and glomerulonephritis membranous.
[k] Includes rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, eczema and rash.
[l] Includes pruritus generalized and pruritus.
[m] Includes pemphigoid, dermatitis bullous and pemphigus. Reported frequency from completed and ongoing trials is uncommon.
[n] Includes oedema peripheral and peripheral swelling.
[o] Includes laryngitis, nasopharyngitis, peritonsillar abscess, pharyngitis, rhinitis, sinusitis, tonsillitis, tracheobronchitis, and upper respiratory tract infection.
[p] Includes lung infection, pneumocystis jirovecii pneumonia, pneumonia, candida pneumonia, pneumonia legionella, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia haemophilus, pneumonia pneumococcal and pneumonia streptococcal.
[q] Includes gingivitis, oral infection, periodontitis, pulpitis dental, tooth abscess and tooth infection.
[r] Includes rhabdomyolysis (as single medical concept with myositis/polymyositis).
[s] 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.
[t] Reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare.
[u] 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.
[v] Includes infusion related reaction and urticaria with onset on the day of dosing or 1 day after dosing.

Table 4 lists the incidence of laboratory abnormalities worsening from baseline in the IMFINZI monotherapy safety dataset.

Table 4. Laboratory abnormalities worsening from baseline occurring more frequently in IMFINZI-treated patients

Laboratory abnormalities	N	Any grade	Grade 3 or 4
Alanine aminotransferase increased	2866	813 (28.4%)	69 (2.4%)
Aspartate aminotransferase increased	2858	891 (31.2%)	102 (3.6%)
Blood creatinine increased	2804	642 (22.9%)	13 (0.5%)
TSH elevated >ULN and above baseline	3006	566 (18.8%)	NA
TSH decreased <LLN and below baseline	3006	545 (18.1%)	NA

ULN = upper limit of normal; LLN = lower limit of normal

The safety of IMFINZI in combination with chemotherapy in patients with ES-SCLC is based on data in 265 patients from the CASPIAN study, and was consistent with IMFINZI monotherapy and known chemotherapy safety profile.

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

The safety of IMFINZI in combination with chemotherapy in patients with BTC is based on data in 338 patients from the TOPAZ-1 study and was consistent with IMFINZI monotherapy and known chemotherapy safety profiles.

The safety of IMFINZI monotherapy in patients with LS-SCLC is based on data in 262 patients from the ADRIATIC study. The safety profile was consistent with IMFINZI monotherapy.

The safety of IMFINZI in combination with platinum-based chemotherapy followed by IMFINZI as monotherapy (N=235) or in combination with olaparib (N=238) is based on data in patients from the DUO-E (endometrial cancer) study. The safety profile was consistent with IMFINZI monotherapy and known olaparib and chemotherapy safety profiles, with PRCA identified as associated specifically when olaparib is added to IMFINZI in the maintenance phase.

The safety of IMFINZI in combination with chemotherapy 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.

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).

The management guidelines for these adverse reactions are described in sections 4.2 and 4.4.

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 chemoradiation within 1 to 42 days prior to initiation of the study (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 who received high dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and 1 patient also received cyclophosphamide and tacrolimus. Resolution occurred for 29 patients in the IMFINZI treated group vs 6 in placebo.

In the 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 chemoradiation 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%) 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.

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.

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.

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.

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.

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.

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.

Immune-mediated type 1 diabetes mellitus

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

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.

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.

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.

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.

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.

Nervous system disorders: Myelitis transverse

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s.

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC28

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.

Clinical Efficacy and Safety
Durvalumab doses of 10 mg/kg every 2 weeks, 1120 mg every 3 weeks or 1500 mg every 4 weeks were evaluated in UC, NSCLC, ES-SCLC and endometrial cancer clinical studies. Based on the modeling 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.

Urothelial carcinoma (UC)

Single-arm phase 2 study in patients with unresectable or metastatic UC after prior chemotherapy (Study 1108)

The efficacy of IMFINZI was evaluated in a phase 1/2 multi-cohort, open-label clinical trial (Study 1108).

The UC cohort of Study 1108 enrolled 201 patients with inoperable locally advanced or metastatic urothelial carcinoma (UC). Of these patients, 192 had disease progression on or after a platinum-based therapy (the 2L post-platinum cohort), including those whose disease had progressed within 12 months of receiving therapy in a neo-adjuvant or adjuvant setting. The trial excluded patients with a history of immunodeficiency; medical conditions that required systemic immunosuppression (not to exceed 10 mg per day of prednisone or equivalent); history of severe autoimmune disease; untreated CNS metastases; HIV; active tuberculosis, or hepatitis B or C infection.

All patients received IMFINZI 10 mg/kg via intravenous infusion every 2 weeks for up to 12 months or until unacceptable toxicity or confirmed disease progression. Tumour assessments were performed at Weeks 6, 12 and 16, then every 8 weeks for the first year and every 12 weeks thereafter. The primary efficacy endpoint was Objective Response Rate (ORR) according to RECIST v1.1 as assessed by Blinded Independent Central Review (BICR). Additional efficacy endpoints included Duration of Response (DoR) and Overall Survival (OS).

In the 2L post-platinum cohort, the median age was 67 years (range: 34 to 88), 71% were male, 70% were Caucasian, 67% had visceral metastasis (including 36% with liver metastasis), 12% had lymph-node-only metastasis, 32% had an ECOG performance status of 0, the remainder had an ECOG performance status of 1 and 44% of patients had a baseline creatinine clearance of <60 mL/min. Sixty-nine percent of patients received prior cisplatin, 29% had prior carboplatin and 36% received 2 or more prior lines of systemic therapy.

Tumour specimens were evaluated for PD-L1 expression on tumour cells (TC) and immune cells (IC) using the Ventana PD-L1 (SP263) Assay. All testing was performed prospectively at a central laboratory. Of the 192 2L+ post-platinum UC patients, 99 were classified as PD-L1 high (TC ≥ 25% or IC ≥ 25%), 80 as PD-L1 low/negative (TC < 25% and IC < 25%) and samples for 13 patients were inadequate for evaluation.

Table 5 summarises the efficacy results for the 2L+ post-platinum UC patients. The median duration of follow-up was 16.9 months (range: 0.4-37.7). In 36 patients who had received only neoadjuvant or adjuvant therapy prior to study entry, 27.8% responded.

Among the total 33 responding patients, 88% patients had ongoing responses of 6 months or longer and 64% had ongoing responses of 12 months or longer.

Table 5. Efficacy Results for Study 1108[a]

Parameter	2L+ Post-platinum UC		
	Total	**PD-L1 High (≥25%)**	**PD-L1 Low/Neg (<25%)**
	N=192	**N=99**	**N=80**
ORR, n (%) (95% CI)	33 (17.2) (12.1, 23.3)	27 (27.3) (18.8, 37.1)	4 (5.0) (1.4, 12.3)
CR, n (%)	11 (5.7)	8 (8.1)	2 (2.5)
PR, n (%)	22 (11.5)	19 (19.2)	2 (2.5)
Median DoR (95% CI)	NR (12.3, NE)	NR (8.2, NE)	12.25 (1.4, NE)
Median OS months (95% CI)	10.5 (6.6, 15.7)	19.8 (9.3, NE)	4.8 (3.1, 8.1)
OS at 12 months, % (95% CI)	46.1 (38.2, 53.5)	57.3 (46.1, 66.9)	28.0 (17.5, 39.6)
OS at 24 months, % (95% CI)	32.0 (22.9, 41.4)	43.9 (30.1, 57.0)	14.2 (6.0, 25.8)

[a] Median duration of follow up 16.9 months. All treated UC patients who had received prior platinum-based therapy, including those patients who progressed within 12 months of receiving therapy in a neo-adjuvant/ adjuvant setting.

CR = Complete Response; NE = Not Estimable; NR = Not Reached; CI = Confidence Interval

Exploratory PD-L1 subgroup analysis

An exploratory post-hoc analysis was conducted of the study 1108 results in UC patients by tumour cell (TC) and tumour-infiltrating immune cell (IC) PD-L1 expression with 'low' and 'high' defined at various cut-off levels (although the test was only validated at a cut-off of TC/IC 25% for this tumour type). The analysis showed a consistent trend of correlation between ORR and

PD-L1 expression (high versus low) at all cut-offs, more so for IC than for TC. There were no responses seen in patients who had both TC<1% and IC<1%.

Muscle invasive bladder cancer (MIBC) – NIAGARA Study

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 who were candidates for radical cystectomy and had not received prior systemic chemotherapy or immune-mediated therapy for the treatment of MIBC. The study excluded patients with pure non-urothelial histology, any small cell histology and primary non-bladder (i.e., 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 durvalumab 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 chemotherapy (Arm 1) or neoadjuvant chemotherapy alone (Arm 2):

- Arm 1 (IMFINZI + chemotherapy): IMFINZI 1500 mg + gemcitabine 1000 mg/m^2 and cisplatin 70 mg/m^2 every 3 weeks for 4 cycles prior to surgery, followed by IMFINZI 1500 mg every 4 weeks for up to 8 cycles after surgery, or
- Arm 2 (Chemotherapy): gemcitabine 1000 mg/m^2 and cisplatin 70 mg/m^2 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 endpoints were pathological complete response (pCR) by blinded central pathology review and event-free survival (EFS) which included blinded independent central review (BICR) assessment. The key secondary endpoint was overall survival (OS). Other secondary efficacy endpoints included proportion of patients who achieve <P2 per local pathology review, the proportion of patients who underwent radical cystectomy, metastasis-free survival (MFS), 24-month EFS, disease-free survival (DFS) and time from randomisation to second progression on subsequent therapy (PFS2).

The demographics and baseline disease characteristics were generally well-balanced between the 533 patients in Arm 1 and 530 patients in Arm 2. Baseline demographics were as follows: male (81.8%), age <65 years (46.9%), white (67%), 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 > T2N0a (59.7%), Regional lymph nodes N0 (94.5%) and N1 (5.5%), adequate renal function (81.1%) and borderline renal function (18.9%), and PD-L1 expression status high (73.1%) and low/negative (26.9%). 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%).

At a pre-specified interim analysis, the study demonstrated a statistically significant and clinically meaningful improvement in EFS in the IMFINZI + chemotherapy arm compared to the chemotherapy arm [HR = 0.68 (95% CI: 0.56, 0.82), p = <0.0001]. The study also demonstrated a statistically significant and clinically meaningful improvement in OS in the IMFINZI + chemotherapy arm compared to the chemotherapy arm [HR=0.75 (95% CI: 0.59, 0.93), p=0.0106]. A numerical improvement in pCR rates was observed in the IMFINZI + chemotherapy arm [Response rate = 37.3% (95% CI: 33.2, 41.6)] compared to the chemotherapy arm [Response rate = 27.5% (95% CI: 23.8, 31.6)]. See Table 6, Figure 1 and Figure 2.

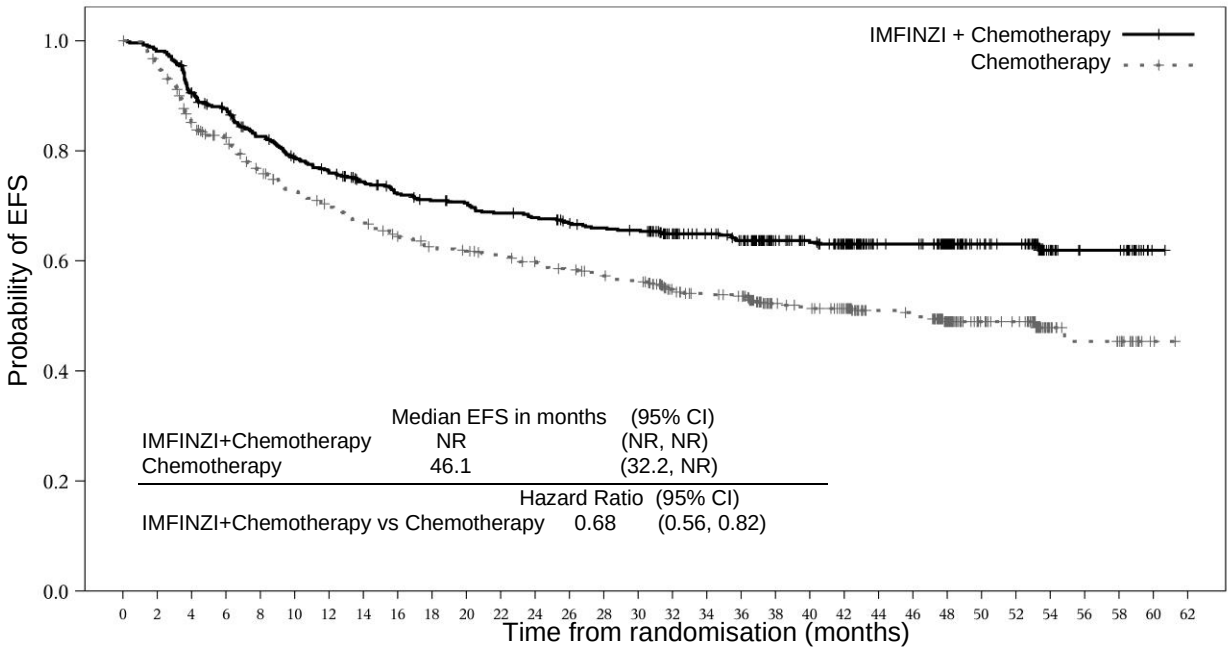
Table 6. Efficacy Results for the NIAGARA Study

	IMFINZI + chemotherapy (N=533)	**Chemotherapy (N = 530)**
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)
pCR[f]		
Number of patients with response	199	146
Response rate, % (95% CI)[g]	37.3 (33.2, 41.6)	27.5 (23.8, 31.6)
Odds ratio (95% CI)[h]	1.60 (1.23, 2.09)	
2-sided p-value[h,i]	0.0005	
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)
The proportion of patients who underwent radical cystectomy[a]		
Number of patients who underwent radical cystectomy	469	441
Radical cystectomy rate, % (95% CI)[g]	88.0 (84.9, 90.6)	83.2 (79.7, 86.3)
Odds ratio (95% CI)[h]	1.48 (1.05, 2.10)	
2-sided p-value[h,j]	0.0265	
Proportion of patients who achieved pathological response <P2 at cystectomy (FAS)[a]		
Number of patients who achieved < P2	265	215
Response rate, % (95% CI)[g]	49.7 (45.4, 54.0)	40.6 (36.4, 44.9)
Odds ratio (95% CI)[h]	1.47 (1.15, 1.88)	
2-sided p-value[h,j]	0.0024	
DFS in patients who underwent radical cystectomy and had an adjuvant baseline scan[a]		
Number of events (%)	78/352 (22.2)	102/337 (30.3)
Median DFS (months) (95% CI)[b]	NR (NR, NR)	NR (51.3, NR)
HR (95% CI)[c]	0.69 (0.51, 0.93)	
2-sided p-value[d,j]	0.0143	
PFS2[a]		
Number of PFS2 events (%)	138 (25.9)	171 (32.3)
Median PFS2 (months) (95% CI)[b]	NR (NR, NR)	NR (NR, NR)

	IMFINZI + chemotherapy (N=533)	Chemotherapy (N = 530)
HR (95% CI)[c]	0.76 (0.61, 0.95)	
2-sided p-value[d,j]	0.0155	
MFS[a]		
Number of events (%)	152 (28.5)	201 (37.9)
Median MFS (months) (95% CI)[b]	NR (NR, NR)	NR (NR, NR)
HR (95% CI)[c]	0.67 (0.54, 0.83)	
2-sided p-value[d,j]	0.0002	
MFS at 24 months (%) (95% CI)[b]	75.1 (71.0, 78.8)	65.1 (60.6, 69.3)

[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 with tumour stage [T2N0 vs. >T2N0], renal function [adequate vs. borderline], and PD-L1 status [high vs. low/negative] as stratification factors.
[d] Based on stratified log-rank test with tumour stage [T2N0 vs. >T2N0], renal function [adequate vs. borderline], and PD-L1 status [high vs. low/negative] as stratification factors.
[e] The boundary for declaring statistical significance for the primary efficacy endpoints pCR rate, 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. (pCR = 0.001, EFS = 0.0412, OS = 0.0154, 2-sided).
[f] Based on an updated, descriptive analysis of the primary endpoint. At the earlier pre-specified final analysis of pCR (DCO: 14 Jan 2022), a numerical improvement in pCR rates was observed in the IMFINZI + chemotherapy arm [Response rate = 33.8% (95% CI: 29.8, 38.0)] compared to the chemotherapy arm [Response rate = 25.8% (95% CI: 22.2, 29.8)] [Odds ratio 1.49 (95% CI: 1.14, 1.96), p = 0.0038].
[g] CI was calculated using the Clopper Pearson method.
[h] Obtained using logistic regression adjusted for the stratification factors (renal function [adequate vs. borderline], tumour stage [T2N0 vs. >T2N0] and PD-L1 status [high vs. low/negative] per IVRS).
[i] p-value is nominal.
[j] p-value is nominal as endpoint is not included in the multiple testing procedure.
CI = Confidence Interval, HR = Hazard Ratio, NR = Not Reached

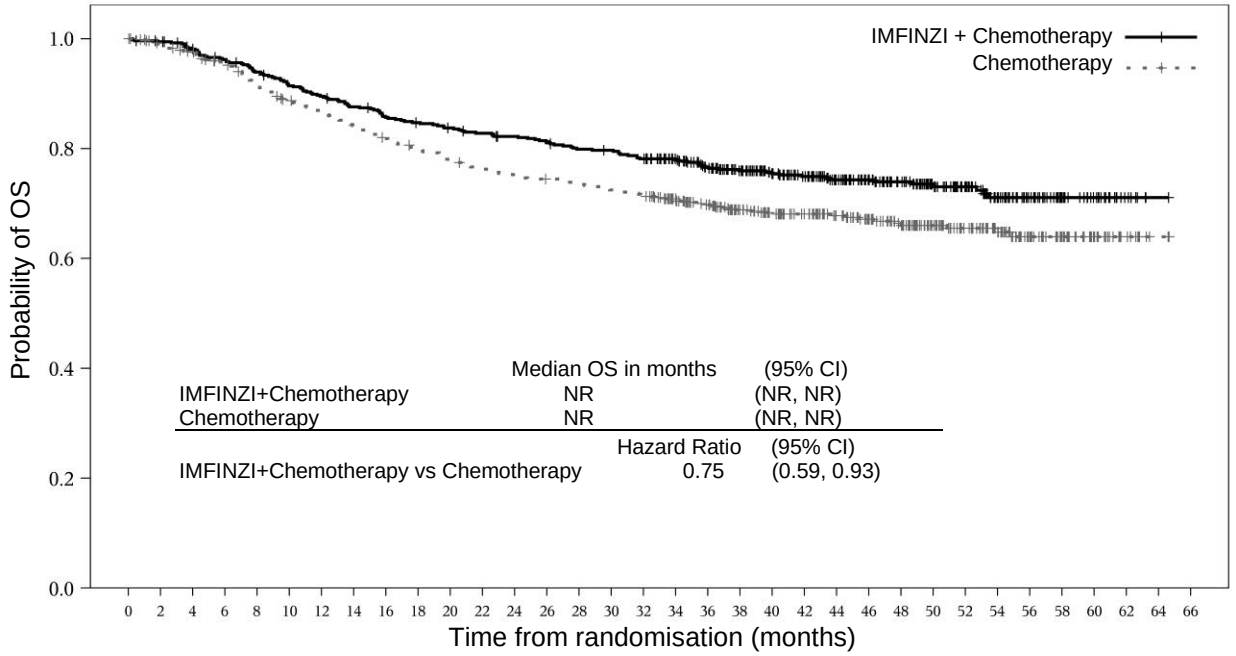
Figure 1. Kaplan-Meier Curve of EFS



Number of patients at risk:

IMFINZI+Chemotherapy	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
Chemotherapy	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 2. Kaplan-Meier Curve of OS



Number of patients at risk:

IMFINZI+Chemotherapy	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
Chemotherapy	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

Subgroup analysis

Improvements in EFS favouring patients in Arm 1 compared to patients in Arm 2 were consistent across pre-specified subgroups based on demographic and baseline disease characteristics. Improvements in OS favouring patients in Arm 1 compared to patients in Arm 2 were generally consistent across pre-specified subgroups based on demographic and baseline disease characteristics.

Patient Reported Outcomes (PRO)

Patient-reported symptoms, functioning, and health related quality of life (HRQoL) were collected using the EORTC QLQ-C30. The questionnaire was to be collected on Day 1 of every cycle and administered before discussion of disease progression and dosing. At baseline, patient-reported symptoms, functioning or HRQoL scores were comparable between the study arms. Overall, the PRO/HRQoL data was generally similar between treatment arms throughout the overall study period. Time to deterioration and change from baseline analyses were consistent with no detriment in symptoms, functioning and HRQoL per EORTC QLQC30 in Arm 1 compared to Arm 2.

Non-small cell lung cancer (NSCLC)

Locally advanced NSCLC (PACIFIC study)

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 radiation therapy within 1 to 42 days prior to initiation of study treatment and had an ECOG performance status 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 chemoradiation therapy, 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 chemoradiation therapy were retrospectively tested for PD-L1 expression on tumour cells (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 overall survival (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 Blinded Independent Central Review (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 a median follow-up of 34.2 months, IMFINZI continued to demonstrate improved OS and PFS compared to placebo (see Table 7 and Figure 3 and Figure 4).

Table 7. Efficacy Results for the PACIFIC Study (primary analysis and 5 year follow-up analysis)

	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		49.7% (45.0%, 54.2%)	36.3% (30.1%, 42.6%)
OS at 60 months (%) (95% CI)	NA		42.9% (38.2%, 47.4%)	33.4% (27.3%, 39.6%)

	Primary Analysis[a]		5 Year Follow-up Analysis[b]	
	IMFINZI (n = 476)	**Placebo (n = 237)**	**IMFINZI (n = 476)**	**Placebo (n = 237)**
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%)	55.7% (51.0%, 60.2%)	34.5% (28.3%, 40.8%)
PFS at 18 months (%) (95% CI)	44.2% (37.7%, 50.5%)	27.0% (19.9%, 34.5%)	49.1% (44.2%, 53.8%)	27.5% (21.6%, 33.6%)
PFS at 60 months (%) (95% CI)	NA	NA	33.1% (28.0%, 38.2%)	19.0% (13.6%, 25.2%)
Progression Free Survival 2[c] (PFS2)				
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	NA
p-value	p < 0.0001			

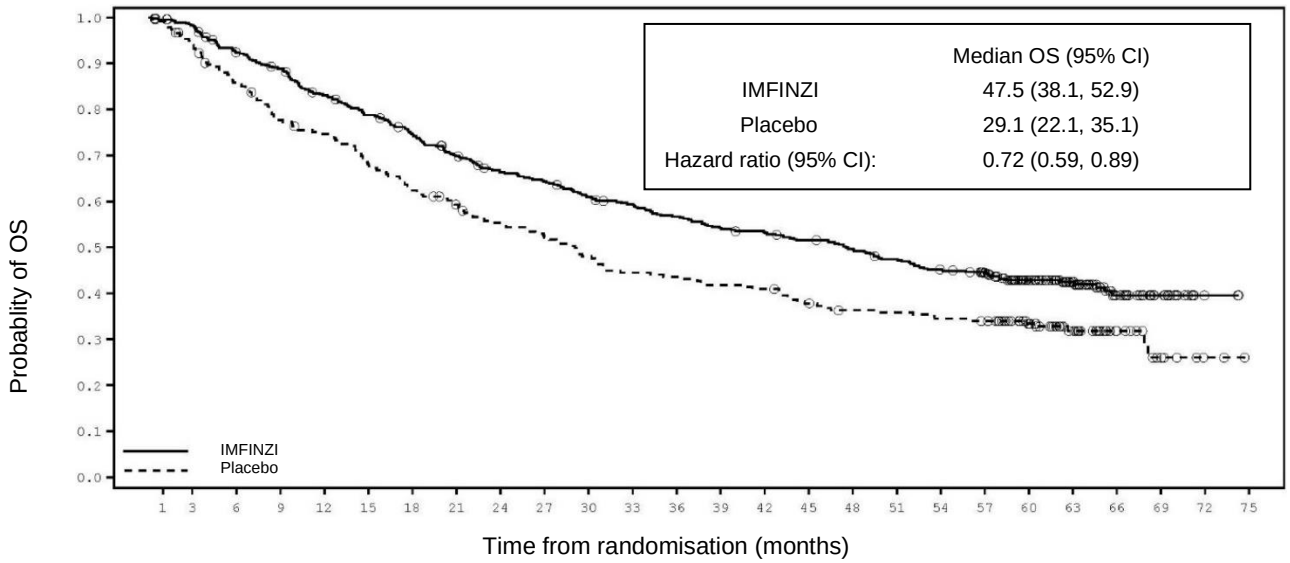
[a] Primary analysis of OS and PFS2 DoR at data cut-off 22 March 2018. Primary analysis of PFS at data cut-off 13 February 2017.

[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.

NR: Not Reached

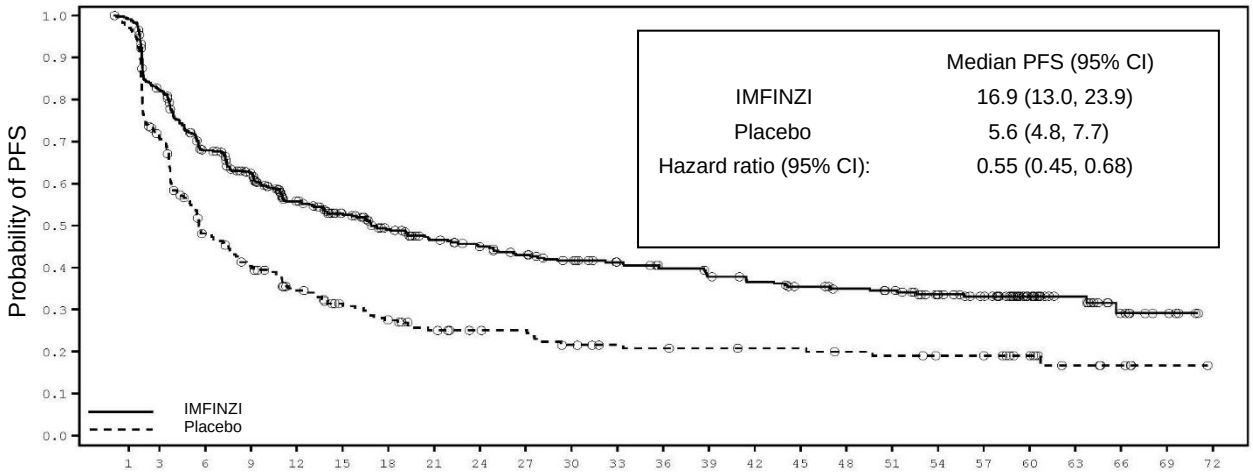
Figure 3. Kaplan-Meier curve of OS (PACIFIC study – DCO 11 Jan 2021)



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 4. Kaplan-Meier curve of PFS (PACIFIC study – DCO 11 Jan 2021)



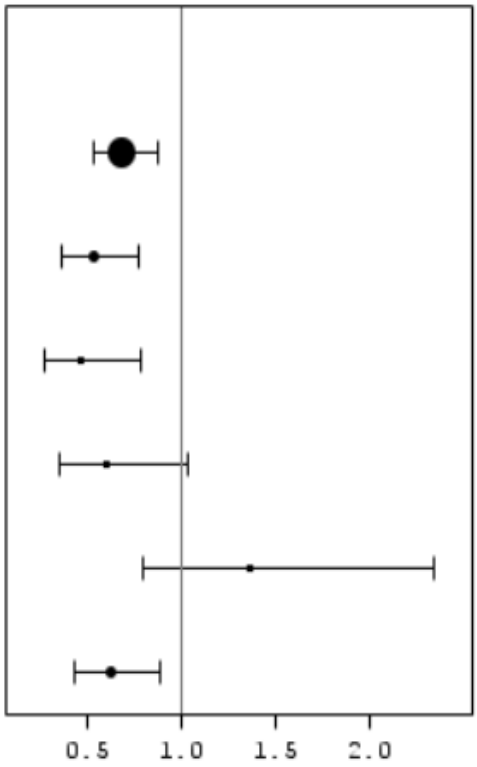
Number of patients at risk

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.

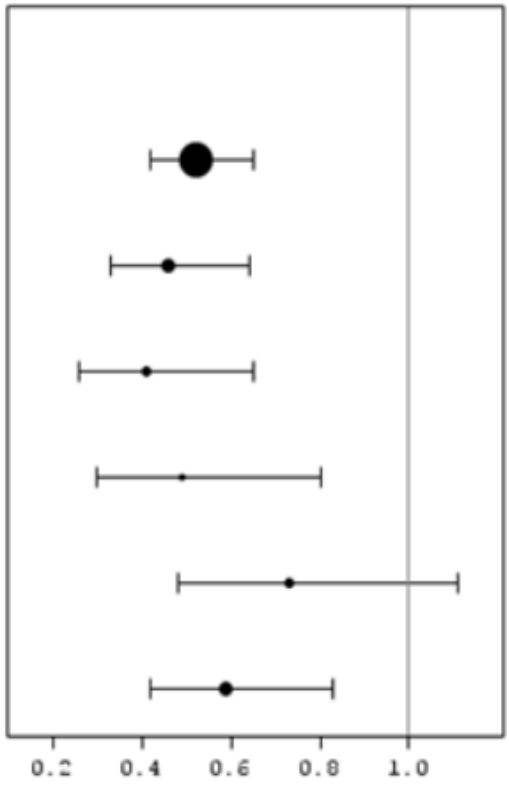
Post-hoc subgroup analysis by PD-L1 expression
Additional subgroup analyses were conducted to evaluate the efficacy by tumour PD-L1 expression (≥ 25%, 1-24%, ≥ 1%, < 1%) and for patients whose PD-L1 status could not be established (PD-L1 unknown). PFS and OS results are summarised in Figure 5 and Figure 6. 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 5. Forest plot of OS by PD-L1 expression (PACIFIC study)



	Events/N (%) IMFINZI	Placebo	HR (95% CI)
All Patients	183/476 (38.4%)	116/237 (48.9%)	0.68 (0.53, 0.87)
PD-L1 TC ≥ 1%	70/212 (33.0%)	45/91 (49.5%)	0.53 (0.36, 0.77)
PD-L1 TC ≥ 25%	37/115 (32.2%)	23/44 (52.3%)	0.46 (0.27, 0.78)
PD-L1 TC 1-24%	33/97 (34.0%)	22/47 (46.8%)	0.60 (0.35, 1.03)
PD-L1 TC < 1%	41/90 (45.6%)	19/58 (32.8%)	1.36 (0.79, 2.34)
PD-L1 Unknown	72/174 (41.4%)	52/88 (59.1%)	0.62 (0.43, 0.89)

Figure 6 Forest plot of PFS by PD-L1 expression (PACIFIC study)



	Events/N (%) IMFINZI	Placebo	HR (95% CI)
All Patients	214/476 (45.0%)	157/237 (66.2%)	0.52 (0.42, 0.65)
PD-L1 TC ≥ 1%	84/212 (39.6%)	59/91 (64.8%)	0.46 (0.33, 0.64)
PD-L1 TC ≥ 25%	48/115 (41.7%)	31/44 (70.5%)	0.41 (0.26, 0.65)
PD-L1 TC 1-24%	36/97 (37.1%)	28/47 (59.6%)	0.49 (0.30, 0.80)
PD-L1 TC < 1%	49/90 (54.4%)	40/58 (69.0%)	0.73 (0.48, 1.11)
PD-L1 Unknown	81/174 (46.6%)	58/88 (65.9%)	0.59 (0.42, 0.83)

Patient reported outcomes

Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC 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).

Resectable NSCLC – AEGEAN Study

AEGEAN was a randomized, double-blind, placebo-controlled, multicentre, Phase III study designed to evaluate the efficacy of IMFINZI in combination with 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/ECOG Performance status 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 (TC<1% vs. TC≥1%) status.

The AEGEAN study randomized 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.

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 PD, 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, DFS by BICR, and 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 (366 patients in Arm 1 and 374 patients in Arm 2 of the mITT set). 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.

In the mITT population there were 295 (80.6%) patients in Arm 1 who underwent curative intent surgery compared to 302 (80.7%) patients in Arm 2. There were 284 (77.6%) patients in Arm 1 who completed curative intent surgery compared to 287 (76.7%) patients in Arm 2. The resection margin status within the mITT population, who completed surgery, was (Arm 1 vs. Arm 2):

- R0 (no residual tumour): 94.7% vs. 91.3%
- R1 (microscopic residual tumour): 4.2% vs. 7.7%
- R2 (macroscopic residual tumour): 0.7% vs. 0.7%

The study demonstrated a statistically significant and clinically meaningful improvement in EFS [HR = 0.68 (95% CI: 0.53, 0.88), p = 0.003902] of the IMFINZI arm compared to the placebo arm. The study also demonstrated a statistically significant and meaningful improvement in pCR [Difference in proportions, 12.96% (95% CI: 8.67, 17.57)] of the IMFINZI arm compared to the placebo arm. See Table 8 and Figure 7.

At the primary (pre-specified) EFS analysis (DCO: 10 November 2022), with a maturity of 31.9% and a median EFS follow-up in censored patients of 11.7 months, the study demonstrated a statistically significant and clinically meaningful improvement in the IMFINZI arm compared to the placebo arm [HR=0.68 (95% CI: 0.53, 0.88), p=0.003902].

At the updated (pre-specified) EFS analysis (DCO: 10 May 2024), the median EFS follow-up in censored patients was 25.9 months. At this analysis, DFS was not statistically significant; however, a trend for improved DFS favouring the IMFINZI arm was observed [HR=0.66 (95% CI: 0.47, 0.92)]. OS was not formally tested for statistical significance; however, a trend for improved OS favouring the IMFINZI arm was observed [HR=0.89 (95% CI: 0.70, 1.14)].

Table 8: Efficacy Results for the AEGEAN Study (mITT)

	IMFINZI + chemotherapy (N=366)	**Placebo + chemotherapy (N = 374)**
EFS[a,b,e]		
Number of events, n (%)	124 (33.9)	165 (44.1)
Median EFS (95% CI) (months)	NR (42.3, NR)	30 (20.6, NR)

	IMFINZI + chemotherapy (N=366)	**Placebo + chemotherapy (N = 374)**
EFS at 12 months, % (95% CI)	73.3 (68.1, 77.7)	64.1 (58.7, 69.0)
EFS at 24 months, % (95% CI)	65.0 (59.4, 70.0)	54.4 (48.7, 59.6)
Hazard ratio (95% CI)	0.69 (0.55, 0.88)	
pCR[a,c,e]		
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)	
MPR[a,d,e]		
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 updated (pre-specified) EFS analysis (DCO: 10 May 2024) and pCR/MPR final analysis (DCO: 10 November 2022).

[b] Based on the primary (pre-specified) EFS analysis (DCO: 10 Nov 2022) with 31.9% EFS maturity, EFS was statistically significant (p=0.003902) compared to significance level of 0.9899%.

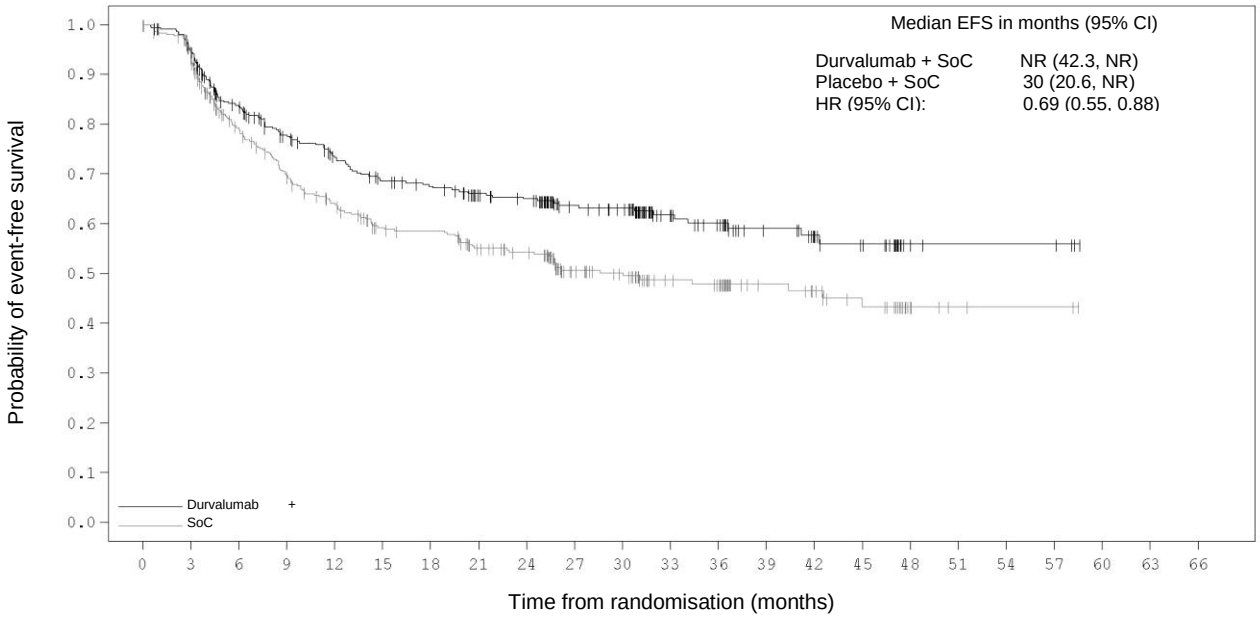
[c] Based on a pre-specified pCR interim analysis (DCO: 14 January 2022) in n =402, the pCR rate was statistically significant (p = 0.000036) compared to significance level of 0.0082%.

[d] 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%.

[e] 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 baseline 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).

Figure 7: Kaplan-Meier Curve of EFS (DCO: 10 May 2024)



Number of patients at risk

Durva + SoC	366	337	276	240	219	201	194	179	172	128	121	76	67	48	36	29	6	4	4	4	0	0	0
Placebo + SoC	374	338	261	225	201	176	172	151	142	93	83	57	53	36	32	25	8	3	2	2	0	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.

Patient Reported Outcomes (PRO)
Patient-reported symptoms, function, and health related quality of life (HRQoL) were collected using the EORTC QLQ-C30, complementary EORTC QLQ-LC13, and exploratory PGIS, EQ-5D-5L, and PRO-CTCAE. These questionnaires were administered before discussion of disease progression and dosing and collected on month 1, 2, 3, and 6 post last dose. Overall compliance rates were high at neoadjuvant baseline (>90%) in the IMFINZI in combination with chemotherapy arm and the placebo in combination with chemotherapy arm.

Overall, the PRO/HRQoL data was generally similar between treatment arms throughout the neoadjuvant period. The proportion of patients with a clinically meaningful (≥ 10 point change) improvement in EORTC QLQ-C30 GHS/QoL was similar over the neoadjuvant period (reported for approximately a quarter of patients in both treatment arms). Clinically meaningful changes (≥ 10 point from baseline) were observed in only two scales: worsening fatigue (EORTC QLQ-C30) in the D + CTx arm (12.57 points [D + CTx] vs 8.50 points [placebo + CTx]) and decreased coughing (EORTC QLQ-LC13) in the placebo + CTx arm (-9.26 points [D + CTx] vs -11.60 points [placebo + CTx).

In the adjuvant period, all PRO instruments (EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D/EQ-VAS, PGIS, and PRO-CTCAE) were administered at adjuvant baseline, the EORTC QLQ-C30 and PRO-CTCAE were administered every 4 weeks and the PGIS was administered at Weeks 20 and 44 during the adjuvant treatment period. Compliance rates were high (> 81%) in both arms at adjuvant baseline for all PRO instruments. For those instruments administered

beyond adjuvant baseline, the compliance rates remained high throughout the adjuvant period and were similar in both treatment arms.

Overall, the PRO/HRQoL data was generally similar between treatment arms throughout the adjuvant period. The proportions of patients with a meaningful improvement (defined as a ≥ 10 point improvement) in EORTC QLQ-C30 GHS/QoL was similar over the adjuvant period. The PRO/HRQoL at adjuvant baseline was either maintained or slightly improved (numerically) throughout the adjuvant period for both treatment arms. The proportion of patients with a clinically meaningful deterioration (defined as a ≥ 10-point worsening) were small (mostly < 20%) across GHS/QoL and functional domains during the adjuvant period and similar in both treatment arms, except for GHS/QoL in which the proportion of patients in the D + CTx arm with a meaningful deterioration were slightly (numerically) greater than those of the placebo + CTx arm.

Small Cell Lung Cancer (SCLC)

ADRIATIC Study

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 chemoradiation therapy. 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 chemoradiation, 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 chemoradiation therapy 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 versus 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.

Once 600 patients had been randomised across all three 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%), other (1.3%), Hispanic or Latino (4.2%), 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, the study demonstrated a statistically significant and clinically meaningful improvement in OS for IMFINZI compared with placebo [HR=0.73 (95% CI: 0.569, 0.928), p=0.01042]. The study also demonstrated a statistically significant and clinically meaningful improvement in PFS for IMFINZI compared with placebo [HR=0.76 (95% CI: 0.606, 0.950), p=0.01608]. See Table 9, and Figure 8 & Figure 9.

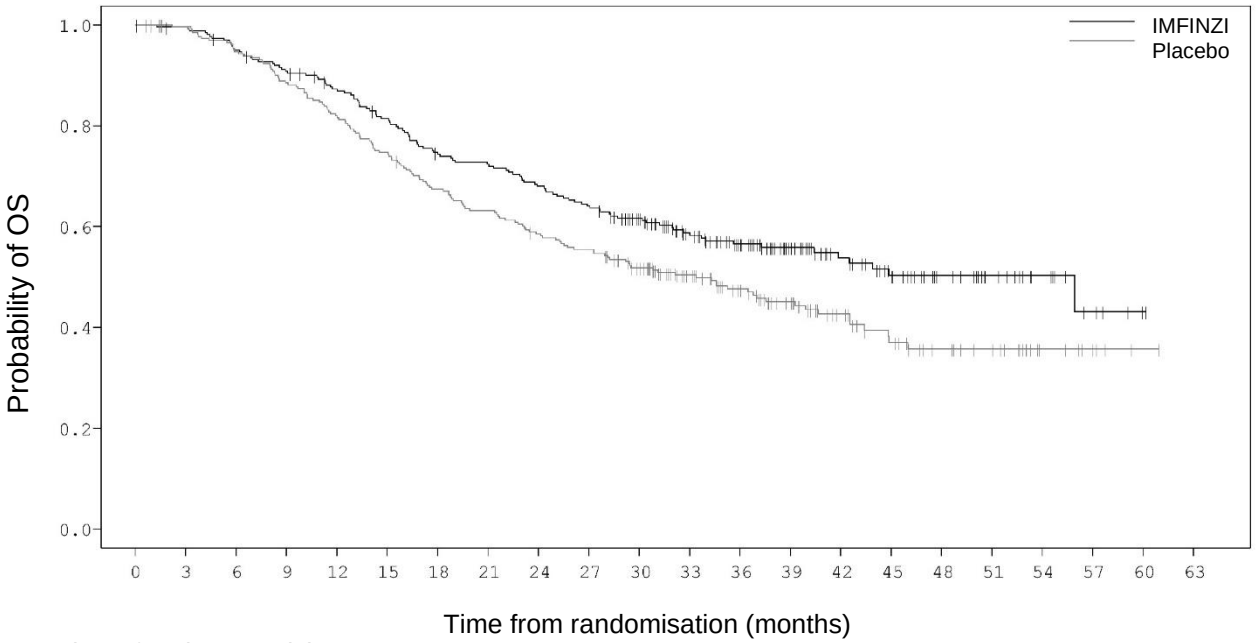
Table 9. Efficacy results for the ADRIATIC study

	Arm 1: IMFINZI (n=264)	**Arm 2: Placebo (n=266)**
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)
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)
ORR[e]		
ORR[g] n (%)	53/175 (30.3)	54/169 (32.0)
Complete Response n (%)	5 (2.9)	4 (2.4)

	Arm 1: IMFINZI (n=264)	**Arm 2: Placebo (n=266)**
Partial Response n (%)	48 (27.4)	50 (29.6)
Odds ratio (95% CI)	-1.2 (-11.0, 8.5)	
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 the IMFINZI arm and 37.24 months in the 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).

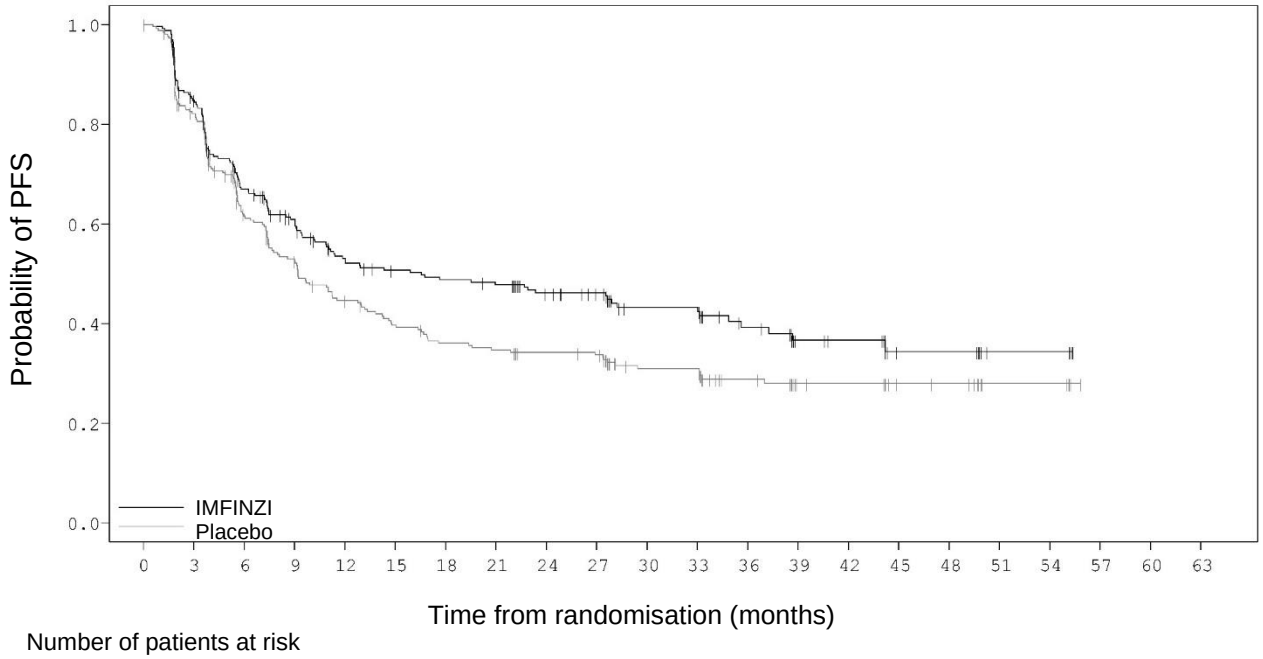
Figure 8. Kaplan-Meier Curve of OS for IMFINZI vs. placebo



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 9 Kaplan-Meier Curve of PFS for IMFINZI vs. placebo



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.

Patient Reported Outcomes

Patient-reported physical functioning and disease-related symptoms and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 and C30 scores were assessed at baseline, weekly for the first 8 weeks (LC13 only, C30 was assessed every 4 weeks), followed by every 4 weeks until completion of the treatment period or discontinuation of study drug due to toxicity or disease progression. At baseline, patient-reported physical functioning and symptoms were comparable between IMFINZI and placebo arms.

Throughout the duration of the study to Week 48, there was no clinically meaningful difference between IMFINZI and placebo arms in symptoms, functioning and HRQoL (as assessed by a difference of greater than or equal to 10 points).

CASPIAN Study

CASPIAN was a study designed to evaluate the efficacy of IMFINZI with or without tremelimumab in combination with etoposide and either carboplatin or cisplatin. CASPIAN was a randomized, open-label, multicentre study in 805 treatment naïve ES-SCLC patients with WHO/ECOG Performance status of 0 or 1, suitable 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 eligible. The study excluded patients with a history of chest radiation therapy; 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).

Patients were randomised 1:1:1 to receive:

- Arm 1: IMFINZI 1500 mg + tremelimumab 75 mg + etoposide and either carboplatin or cisplatin
- Arm 2: IMFINZI 1500 mg + etoposide and either carboplatin or cisplatin
- Arm 3: Either carboplatin (AUC 5 or 6 mg/mL/min) or cisplatin (75-80 mg/m2) on Day 1 and etoposide (80-100 mg/m2) intravenously on Days 1, 2, and 3 of each 21-day cycle for between 4 – 6 cycles.

For patients randomised to Arm 1 and 2, etoposide and either carboplatin or cisplatin was limited to 4 cycles on an every 3 week schedule 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 3, 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 3 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 Overall Survival (OS) of IMFINZI + chemotherapy (Arm 2) vs. chemotherapy alone (Arm 3) and IMFINZI + tremelimumab + chemotherapy (Arm 1) vs. chemotherapy alone (Arm 3). The key secondary endpoint was progression-free survival (PFS). Other secondary endpoints were Objective Response Rate (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 2) vs chemotherapy (Arm 3) met the efficacy boundary of the primary endpoint of OS. The results are summarised below.

The demographics and baseline disease characteristics were well balanced between the two study arms (268 patients in Arm 2 and 269 patients in Arm 3). 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. I n Arm 3, 56.8% of the patients received 6 cycles of chemotherapy and 7.8% of the patients received PCI.

At the primary analysis, the study demonstrated a statistically significant and clinically meaningful improvement in OS with IMFINZI + chemotherapy (Arm 2) vs. chemotherapy alone (Arm 3) [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) nominal p-value=0.0078].

In the long term follow-up analysis, with a median follow-up of 39.3 months, IMFINZI + etoposide + platinum (Arm 2) vs.etoposide + platinum (Arm 3) continued to demonstrate sustained improvement in OS. Results are presented in Table 10, Figure 10 and Figure 11.

Table 10. Efficacy Results for the CASPIAN Study

	Primary analysis		Long-term follow-up analysis[b]	
	Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)	**Arm 3: etoposide and either carboplatin or cisplatin (n=269)**	**Arm 2: IMFINZI + etoposide and either carboplatin or cisplatin (n=268)**	**Arm 3: etoposide and either carboplatin or cisplatin (n=269)**
Overall Survival (OS)				
Number of deaths (%)	155 (57.8)	181 (67.3)	221 (82.5)	248 (92.2)
Median OS (months) (95% CI)	13.0 (11.5, 14.8)	10.3 (9.3, 11.2)	12.9 (11.3, 14.7)	10.5 (9.3, 11.2)
HR (95% CI)[c]	0.73 (0.591, 0.909)		0.71 (0.595, 0.858)	
p-value[d]	0.0047			
OS at 12 months (%) (95% CI)	53.7 (47.4, 59.5)	39.8 (33.7, 45.8)	52.8 (46.6, 58.5)	39.3 (33.4, 45.1)
OS at 18 months (%) (95% CI)	33.9 (26.9, 41.0)	24.7 (18.4, 31.6)	32.0 (26.5, 37.7)	24.8 (19.7, 30.1)
OS at 24 months (95% CI)	NA	NA	22.9 (18.1, 28.2)	13.9 (10.1, 18.4)
OS at 36 months (%) (95% CI)	NA	NA	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)	NA	NA
Median PFS (months) (95% CI)	5.1 (4.7, 6.2)	5.4 (4.8, 6.2)	NA	NA
HR (95% CI)[c]	0.78 (0.645, 0.936)		NA	
p-value[e]	0.0078		NA	
PFS at 6 months (%) (95% CI)	45.4 (39.3, 51.3)	45.6 (39.3, 51.7)	NA	NA
PFS at 12 months (%) (95% CI)	17.5 (13.1, 22.5)	4.7 (2.4, 8.0)	NA	NA
Overall Response Rate (ORR)				
ORR n (%)[f]	182 (67.9)	155 (57.6)	NA	NA
Complete Response n (%)	6 (2.2)	2 (0.7)	NA	NA
Partial Response n (%)	176 (65.7)	153 (56.9)	NA	NA
Odds ratio (95% CI)[g]	1.56 (1.095, 2.218)		NA	
p-value[e]	0.0136		NA	
Duration of Response (DoR)				
Median DoR (months) (95% CI)[f]	5.1 (4.9, 5.3)	5.1 (4.8, 5.3)	NA	NA
DoR at 12 months (%)[f]	22.7	6.3	NA	NA

[a] Primary OS, PFS, ORR and DoR analysis at data cut-off 11 March 2019.
[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

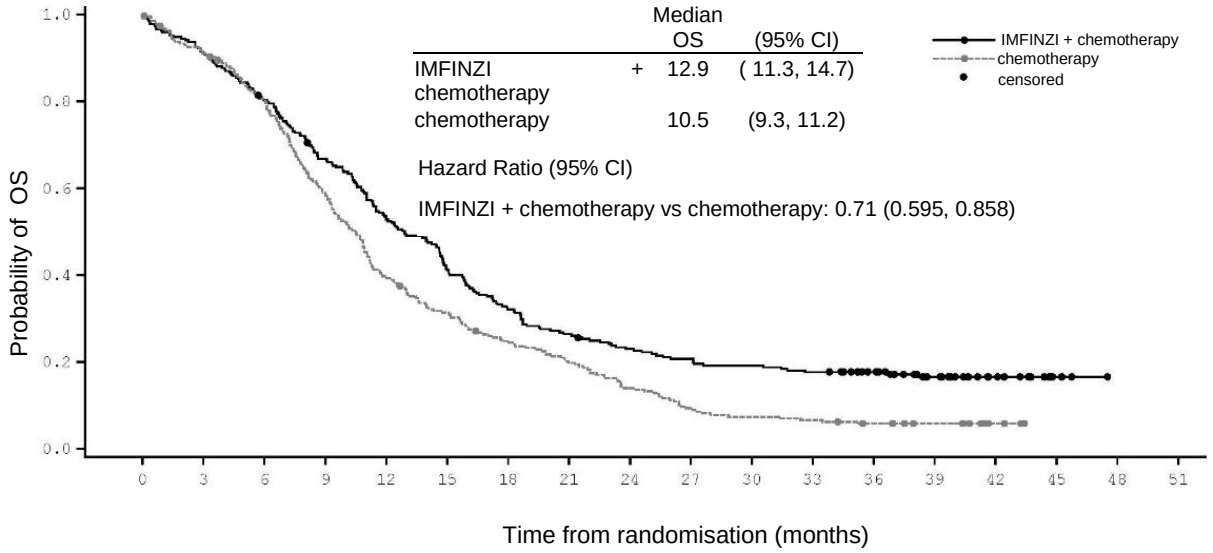
[d] Based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary with the actual number of events observed, the boundary for declaring statistical significance is 0.0178 (Lan◦and◦DeMets 1983).

[e] Nominal p-value. PFS was included in the Multiple Testing Procedure (MTP) hierarchy at the second level. It was not able to be tested within the MTP as both Arm 1 and Arm 2 were required to achieve statistical significance prior to stepping down to PFS. ORR was not included in the MTP.

[f] Confirmed Objective Response.

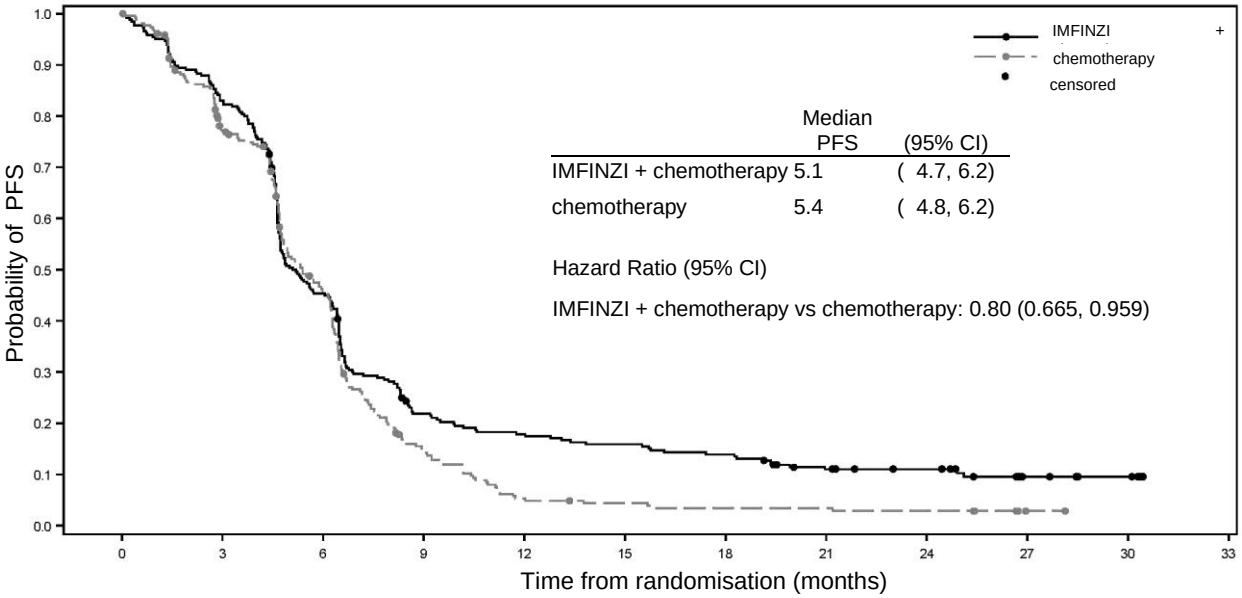
[g] The analysis was performed using a logistic regression model adjusting for planned platinum therapy in Cycle 1 (carboplatin or cisplatin) with 95% CI calculated by profile likelihood.

Figure 10. Kaplan-Meier curve of OS (DCO 22 March 2021)



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 11. Kaplan-Meier curve of PFS (DCO 27 Jan 2020)



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.

Patient Reported Outcomes
Patient-reported symptoms, function and health-related quality of life (HRQoL) were collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). Both questionnaires were administered up to second disease progression (PFS2) or death (whichever came first). At baseline, patient reported symptoms, functioning or HRQoL scores were comparable between the study arms. Compliance was 60% or higher over 84 weeks in IMFINZI + chemotherapy and 20 weeks in the chemotherapy only arm.

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

IMFINZI + chemotherapy demonstrated improvement by delaying time to deterioration in a broad range of patient-reported symptoms, function, and global health status/QoL compared to chemotherapy alone (seeTable 11 and Table 12).

Table 11. Delay in median time to deterioration in global health status/QoL and function (EORTC QLQ-C30)[a]

	Time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)
Global health status/QoL	8.4 vs. 7.2 0.81 (0.63, 1.05); p=0.1166
Physical	8.5 vs. 6.5 0.75 (0.58, 0.97); p=0.0276
Cognitive	8.4 vs. 6.0 0.61 (0.47, 0.78); p=<0.00001

	Time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)
Role	7.4 vs. 5.9 0.71 (0.55, 0.90); p=0.0059
Emotional	12.9 vs. 7.3 0.61 (0.46, 0.80); p=0.0003
Social	7.6 vs. 6.2 0.70 (0.55, 0.90); p=0.0048

[a] p-values for time to deterioration based on stratified log-rank test and were not adjusted for multiplicity

Table 12. Delay in median time to deterioration in symptoms (EORTC QLQ-C30 and QLQ-LC13)[a]

Symptom scale	Delay in time to deterioration (months) Arm 2 (N=261) vs. Arm 3 (N=260)
Coughing	9.3 vs. 7.7 0.78 (0.60, 1.03); p=0.0747
Dyspnoea (QLQ-C30)	9.0 vs. 7.4 0.75 (0.57, 0.99); p=0.0406
Dyspnoea (QLQ-LC13)	6.5 vs. 5.5 0.79 (0.63, 1.01); p=0.0578
Pain	7.8 vs. 6.7 0.79 (0.62, 1.02); p=0.0718
Chest pain	10.6 vs. 7.8 0.76 (0.58, 1.00); p=0.0464
Arm or shoulder pain	9.9 vs. 7.5 0.70 (0.54, 0.92); p=0.0088
Pain in other parts of body	7.8 vs. 6.4 0.72 (0.56, 0.92); p=0.0096
Fatigue	5.5 vs. 4.3 0.82 (0.65, 1.03); p=0.0835
Insomnia	8.6 vs. 7.3 0.75 (0.57, 0.98); p=0.0349
Appetite loss	8.3 vs. 6.6 0.70 (0.54, 0.90); p=0.0054
Constipation	11.1 vs. 7.3 0.65 (0.50, 0.86); p=0.0018
Diarrhoea	14.6 vs. 7.7 0.59 (0.44, 0.77); p=0.0002
Nausea/vomiting	8.4 vs. 6.6 0.80 (0.63, 1.03); p=0.0809
Haemoptysis	18.3 vs. 10.5 0.64 (0.47, 0.88); p=0.0049

[a] p-values for time to deterioration based on stratified log-rank test and were not adjusted for multiplicity

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.

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 performance status 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 83.6%. Results from this analysis are presented in Table 13 and Figure 12.

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 Table 13 and Figure 12.

Table 13. Efficacy Results for the TOPAZ-1 Study

	Primary Analysis[a]		Follow up Analysis[b]	
	IMFINZI + gemcitabine and cisplatin (n=341)	Placebo + gemcitabine and cisplatin (n=344)	IMFINZI + gemcitabine and cisplatin (n=341)	Placebo + gemcitabine and 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)	NA	NA
Median PFS (months) (95% CI)[c]	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)	NA	NA
HR (95% CI)[d]	0.75 (0.63, 0.89)		NA	
p-value[d,f]	0.001		NA	
PFS at 9 months (%) (95% CI)[c]	34.8 (29.6, 40.0)	24.6 (20.0, 29.5)	NA	NA
PFS at 12 months (%) (95% CI)[c]	16.0 (12.0, 20.6)	6.6 (4.1, 9.9)	NA	NA
Overall Response Rate (ORR)				
ORR n (%)[g]	91 (26.7)	64 (18.7)	NA	NA
Complete Response n (%)	7 (2.1)	2 (0.6)	NA	NA
Partial Response n (%)	84 (24.6)	62 (18.1)	NA	NA
Odds ratio (95 % CI)[h]	1.60 (1.11, 2.31)		NA	
p-value[h]	0.011		NA	
Duration of Response (DoR)[g]				
Median DoR (months) (95% CI)[c]	6.4 (5.9, 8.1)	6.2 (4.4, 7.3)	NA	NA
DoR at 9 months (%)[c]	32.6	25.3	NA	NA
DoR at 12 months (%)[c]	26.1	15.0	NA	NA

[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 tumor 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 tumor location. Nominal 2-sided p-value.

Figure 12. Kaplan-Meier curve of OS (DCO: 25 Feb 2022)

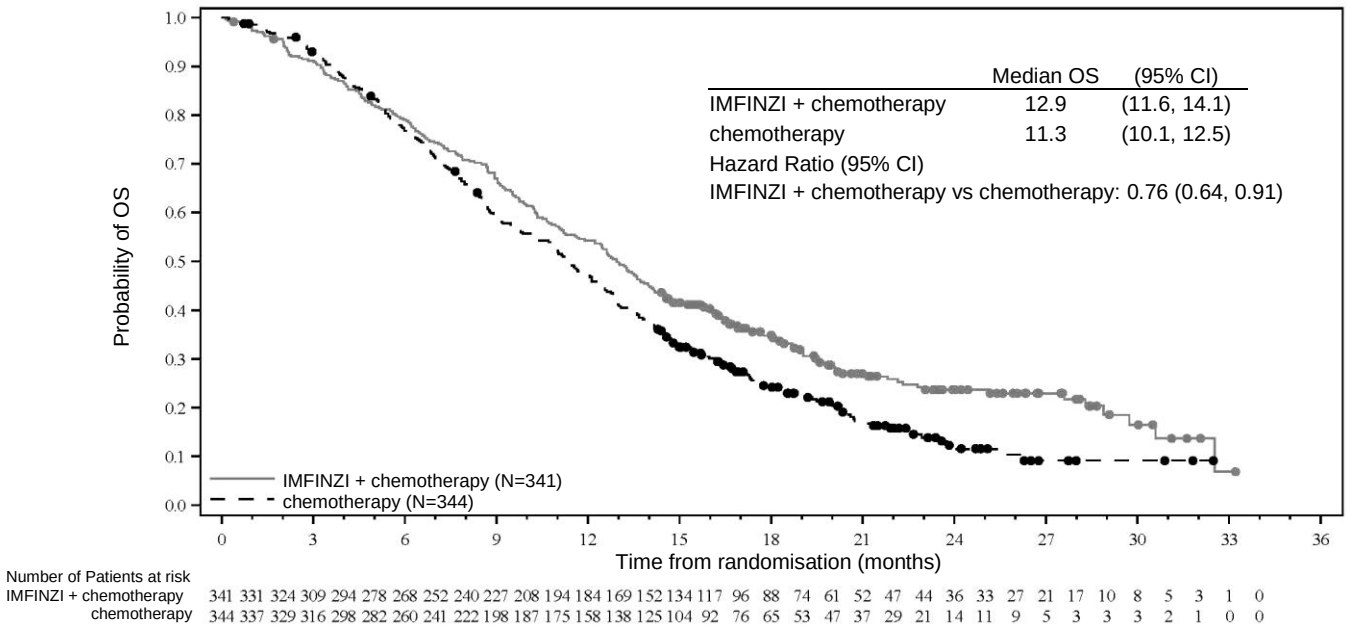
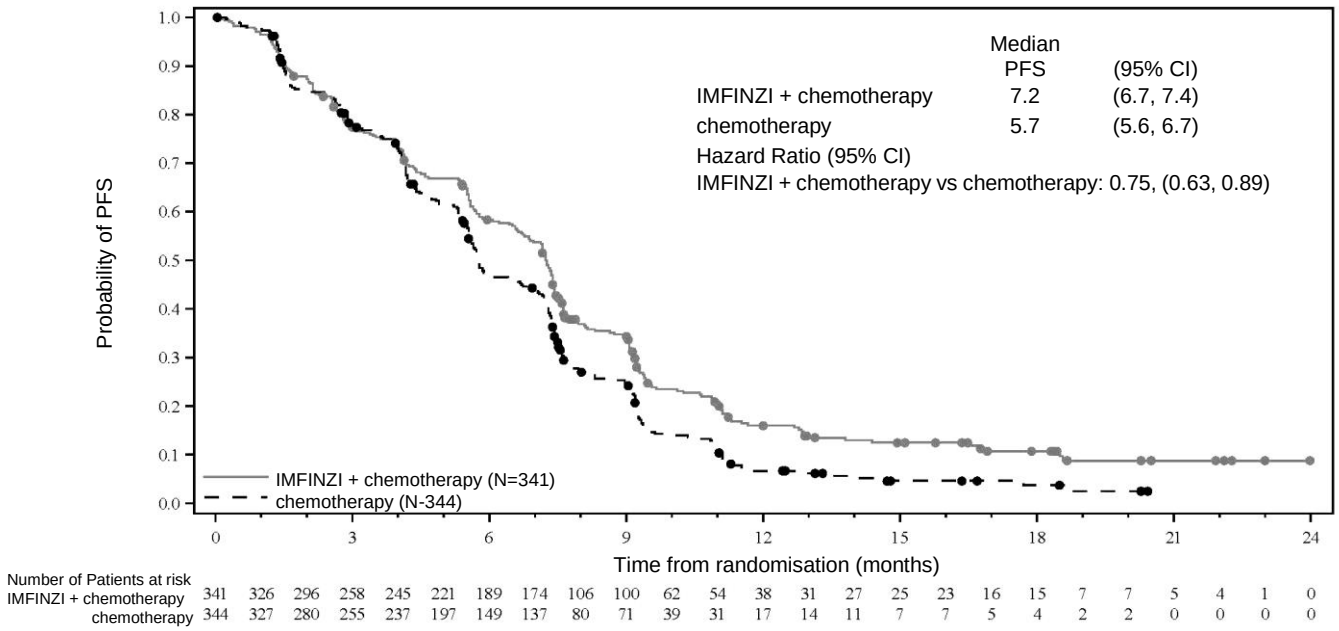


Figure 13. Kaplan-Meier curve of PFS (DCO: 11 Aug 2021)



Subgroup analysis

The improvements in OS and PFS in favour of patients receiving IMFINZI + chemotherapy compared to those receiving placebo + chemotherapy, were consistently observed across the

prespecified subgroups based on demographics, geographical region, primary tumour location, disease status, ECOG PS, and PD-L1 expression levels.

Patient-Reported Outcomes
Patient-reported symptoms, function and global health status/QoL (GHS/QoL) were collected using the EORTC QLQ-C30 and its biliary tract cancer module (EORTC QLQ-BIL21). At baseline, patient-reported symptoms, functioning and GHS/QoL scores were comparable between the study arms. Time to deterioration and change from baseline analyses were consistent with no detriment in symptoms, function and GHS/QoL per EORTC QLQ-C30 and EORTC QLQ-BIL21 in the IMFINZI + chemotherapy group compared to the placebo + chemotherapy group.

Endometrial Cancer – DUO-E Study

DUO-E was a randomised, multicentre, double-blind, placebo-controlled, Phase III study of first-line platinum-based chemotherapy in combination with IMFINZI, followed by IMFINZI with or without olaparib in patients with advanced or recurrent endometrial cancer. Patients had to have endometrial cancer in one of the following categories: newly diagnosed Stage III disease (measurable disease per RECIST v1.1 following surgery or diagnostic biopsy), newly diagnosed Stage IV disease (with or without disease following surgery or diagnostic biopsy), or recurrence of disease (measurable or non-measurable disease per RECIST v1.1) where the potential for cure by surgery alone or in combination is poor. 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 versus deficient), disease status (recurrent versus newly diagnosed), and geographic region (Asia versus rest of the world). Patients were randomised 1:1:1 to one of the following arms:

- **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.
- **Arm 3 (Platinum-based chemotherapy + IMFINZI + olaparib):** 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 300 mg olaparib tablets twice daily as maintenance treatment until disease progression.

Patients who discontinued either product (durvalumab/placebo or olaparib/placebo) for reasons other than disease progression could continue treatment with the other product if appropriate based on toxicity considerations and investigator discretion.

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 primary endpoint was PFS, determined by investigator assessment using RECIST v1.1. Secondary efficacy endpoints included OS, ORR and DoR.

The study demonstrated a statistically significant improvement in PFS in the ITT population, for patients treated with platinum-based chemotherapy + IMFINZI + olaparib compared to platinum-based chemotherapy [HR=0.55 (95% CI: 0.43, 0.69), p=<0.0001], and for patients treated with platinum-based chemotherapy + IMFINZI compared to platinum-based chemotherapy [HR=0.71 (95% CI: 0.57, 0.89), p=0.003]. At the time of PFS analysis, interim OS data were 28% mature with events in 199 of 718 patients.

Mismatch repair (MMR) status was determined centrally using an MMR immunohistochemistry panel assay. Of a total of 718 patients randomized in the study, 575 (80%) patients had MMR-proficient (pMMR) tumour status and 143 (20%) patients had MMR-deficient (dMMR) tumour status.

Patients with MMR-deficient (dMMR) endometrial cancer

Among patients with dMMR tumour status, demographic and baseline characteristics were generally well balanced between the treatment arms. Baseline demographics across all three arms were as follows: median age of 62 years (range: 34 to 85), 41% age 65 or older, 1.5% age 75 or older, 62% White, 29% Asian, and 2% Black or African American. Disease characteristics were as follows: ECOG PS of 0 (58%) or 1 (42%), 46% newly diagnosed and 54% recurrent disease. The histologic subtypes were endometrioid (83%), mixed epithelial (5%), serous (3%), carcinosarcoma (3%), undifferentiated (2%), and other (3%).

In patients with dMMR tumour status, the results are summarised in Table 14 and Figure 14. The median follow-up time for PFS in censored patients with dMMR tumour status was 15.5 months in the platinum-based chemotherapy + IMFINZI arm, and 10.2 months in the platinum-based chemotherapy arm. At the time of PFS analysis, interim OS data were 26% mature with events in 25 of 95 patients treated with platinum-based chemotherapy + IMFINZI and platinum-based chemotherapy.

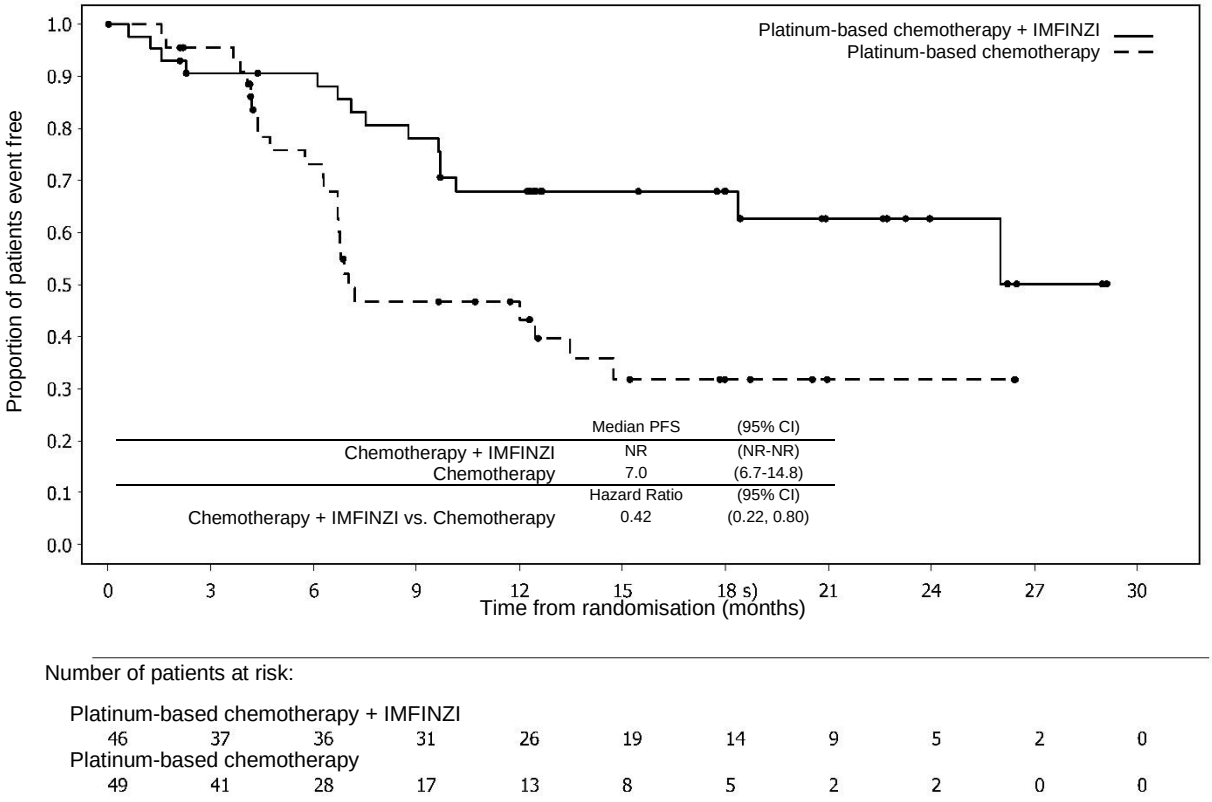
Table 14. Efficacy results for the DUO-E study (Patients with dMMR tumour status)

	Platinum-based chemotherapy + IMFINZI N=46	**Platinum-based chemotherapy N=49**
PFS[a,b]		
Number of events (%)	15 (32.6)	25 (51.0)
Median PFS (months) (95% CI)[c]	NR (NR, NR)	7.0 (6.7, 14.8)
HR (95% CI)	0.42 (0.22, 0.80)	-
OS[b]		
Number of events (%)	7 (15.2)	18 (36.7)
Median OS (months) (95% CI)[c]	NR (NR, NR)	23.7 (16.9, NR)
HR (95% CI)	0.34 (0.13, 0.79)	-
ORR[b]		
ORR[d] n (%)	30 (71.4)	17 (40.5)
DoR[b]		
Median DoR (months) (95% CI)[c]	NR (NR, NR)	10.5 (4.3, NR)

[a] Investigator assessed.
[b] Results are based on the first interim analysis (DCO: 12 April 2023).

[c] Calculated using the Kaplan-Meier technique.
[d] Response: Best objective response as confirmed complete response or partial response. Based on number of patients in treatment group with measurable disease at baseline (N=42 in platinum-based chemotherapy + IMFINZI arm, N=42 in platinum-based chemotherapy arm).
CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 14. Kaplan-Meier curve of PFS in DUO-E (Patients with dMMR tumour status)



Number of patients at risk:

Platinum-based chemotherapy + IMFINZI	46	37	36	31	26	19	14	9	5	2	0
Platinum-based chemotherapy	49	41	28	17	13	8	5	2	2	0	0

Patients with MMR-proficient (pMMR) endometrial cancer
Among patients with pMMR tumour status, demographic and baseline characteristics were generally well balanced between the treatment arms. Baseline demographics across all three arms were as follows: median age of 64 years (range: 22 to 86), 48% age 65 or older, 8.1% age 75 or older, 56% White, 30% Asian, and 6% Black or African American. Disease characteristics were as follows: ECOG PS of 0 (69%) or 1 (31%), 47% newly diagnosed and 53% recurrent disease. The histologic subtypes were endometrioid (54%), serous (26%), carcinosarcoma (8%), mixed epithelial (4%), clear cell (3%), undifferentiated (2%), mucinous (<1%), and other (3%).

Results in patients with pMMR tumour status are summarised in Table 15 and Figure 15. The median follow-up time in censored patients with pMMR tumour status was 15.2 months in the platinum-based chemotherapy + IMFINZI + olaparib arm, and 12.8 months in the platinum-based chemotherapy arm. At the time of PFS analysis, interim OS data were 29% mature with events in 110 of 383 patients treated with platinum-based chemotherapy + IMFINZI + olaparib and platinum-based chemotherapy.

Table 15. Efficacy results for the DUO-E Study (Patients with pMMR tumour status)

	Platinum-based chemotherapy + IMFINZI + olaparib N=191	**Platinum-based chemotherapy N=192**
PFS[a,b]		
Number of events (%)	108 (56.5)	148 (77.1)
Median PFS (months) (95% CI)[c]	15.0 (12.4, 18.0)	9.7 (9.2, 10.1)
HR (95% CI)	0.57 (0.44, 0.73)	-
OS[b]		
Number of events (%)	46 (24.1)	64 (33.3)
Median OS (months) (95% CI)[c]	NR (NR, NR)	25.9 (25.1, NR)
HR (95% CI)	0.69 (0.47, 1.00)	-
ORR[b]		
ORR[d] n (%)	90 (61.2)	92 (59.0)
DoR[b]		
Median DoR (months) (95% CI)[c]	18.7 (10.5, NR)	7.6 (7.1, 10.2)

[a] Investigator assessed.

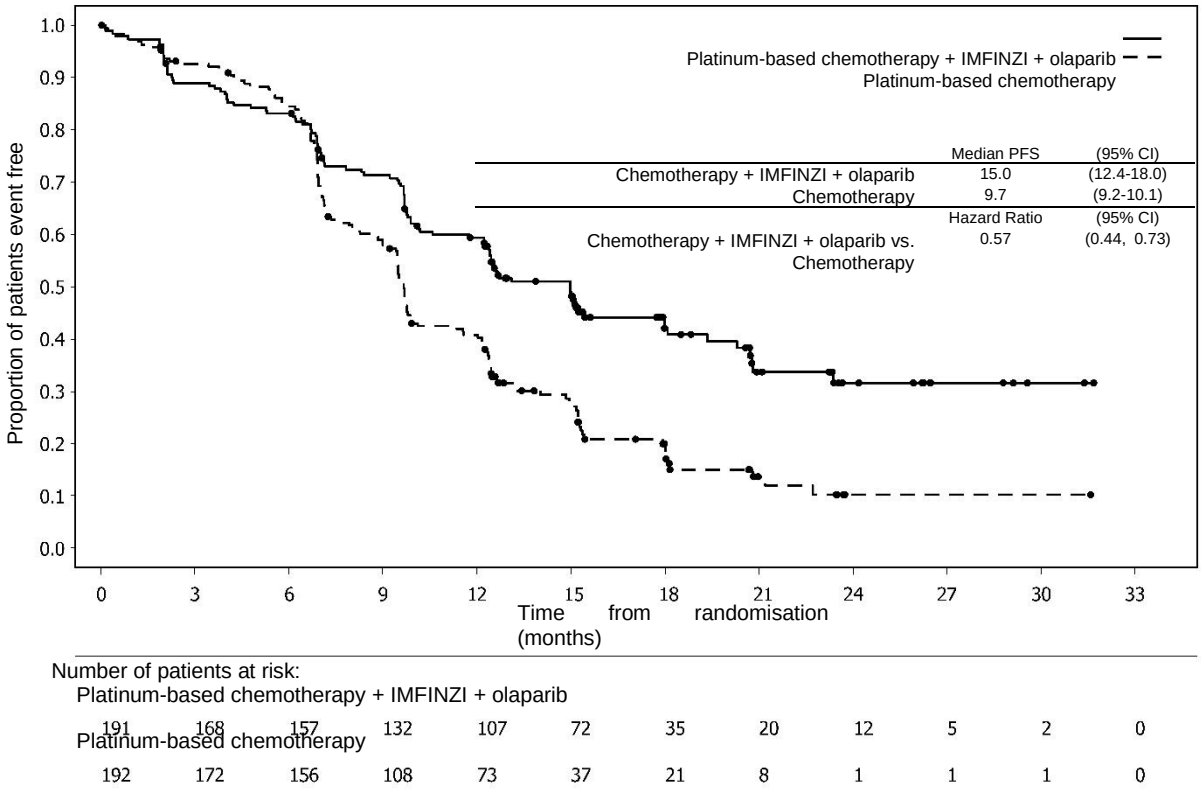
[b] Results are based on the first interim analysis (DCO: 12 April 2023).

[c] Calculated using the Kaplan-Meier technique.

[d] Response: Best objective response as confirmed complete response or partial response. Based on number of patients in treatment group with measurable disease at baseline (N=147 in platinum-based chemotherapy + IMFINZI + olaparib arm, N=156 in platinum-based chemotherapy arm).

CI=Confidence Interval, HR=Hazard Ratio, NR=Not Reached

Figure 15. Kaplan-Meier curve of PFS in DUO-E (Patients with pMMR tumour status)



Among patients with pMMR tumour status, the PFS HRs were 0.44 (95% CI: 0.31, 0.61) in patients with PD-L1 expression positive status (236/383; 62%) and 0.87 (95% CI: 0.59, 1.28) in patients with PD-L1 expression negative status (140/383; 37%), for the platinum-based chemotherapy + IMFINZI + olaparib arm compared to the platinum-based chemotherapy arm. PD-L1 expression positive was defined as tumour area positive (TAP) ≥ 1%.

Patient-Reported Outcomes
IMFINZI in combination with platinum-based chemotherapy followed by maintenance treatment with IMFINZI as monotherapy or in combination with olaparib when compared with platinum-based chemotherapy, had no detrimental effect on endometrial cancer/disease symptoms. Changes from baseline in a range of patient-reported symptoms, functions, and global health status/QoL were similar across the arms.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of durvalumab was assessed for both IMFINZI as a single agent, in combination with chemotherapy and in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib. There was no clinically meaningful difference between the PK of durvalumab as a single agent and in combination with chemotherapy or in combination with platinum-based chemotherapy followed by IMFINZI in combination with olaparib.

The pharmacokinetics of durvalumab was studied in 2903 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 1878 patients in the dose range of ≥ 10 mg/kg Q2W, 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 (t1/2), 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 (creatinine clearance (CrCl) 60 to 89 mL/min), moderate renal impairment (creatinine clearance (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) and 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 (bilirubin >3.0 x ULN and any AST) hepatic impairment 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.

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 a single-agent and evaluable for the presence of anti-drug antibodies (ADAs). Sixty nine patients (3.0%) tested positive for treatment-emergent ADAs. Neutralising antibodies 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. Neutralizing 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 chemotherapy and evaluable for the presence of ADAs, 0 (0%) patients tested positive for treatment-emergent ADAs. The impact of treatment-emergent ADA on pharmacokinetics and clinical safety of durvalumab was not evaluable as no patient samples tested positive for treatment-emergent durvalumab ADA.

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 neutralizing antibodies (2 patients each) to determine whether ADAs have an impact on pharmacokinetics and clinical safety of durvalumab.

In the DUO-E study, the number of the patients who were treated with platinum-based chemotherapy + IMFINZI (n=198) or platinum-based chemotherapy + IMFINZI + olaparib (n=207) and evaluable for the presence of ADAs, 2 (1.0%) patients tested positive for treatment-emergent ADAs in the platinum-based chemotherapy + IMFINZI arm and no patients tested positive for treatment-emergent ADAs in the platinum-based chemotherapy + IMFINZI + olaparib arm. Neutralizing antibodies against durvalumab were detected in 1 (0.5%) patient in the platinum-based chemotherapy + IMFINZI arm and 0 patients in the platinum-based chemotherapy + IMFINZI + olaparib arm. There were insufficient number of patients with treatment-emergent ADAs or neutralizing 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.

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.

Reproductive Toxicity

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 6 to 20 times higher than those observed in humans at the recommended clinical dose of 10 mg/kg (based on AUC). 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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- histidine
- histidine hydrochloride monohydrate
- trehalose dihydrate
- polysorbate 80
- water for injection.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

Unopened Vial: 36 months

Diluted Solution: IMFINZI does not contain a preservative. Administer infusion solution immediately once prepared. If infusion solution is not administered immediately and it needs to be stored, the total time from vial puncture to the start of administration 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.

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.

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

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 AND OTHER HANDLING

For dilution and administration instructions see Section 4.2 Dose and Method of Administration.

Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

AstraZeneca Limited
PO Box 87453
Meadowbank
Auckland 1742.
Telephone: 0800 684 432

9. DATE OF FIRST APPROVAL

10 October 2019

10. DATE OF REVISION OF THE TEXT

17 July 2025

IMFINZI is a registered trademark of the AstraZeneca group of companies.

VV-RIM-01437175 v16.0

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.1, 4.2, 4.8, 5.1, 5.2	New indication, dosing recommendation and clinical trial information (efficacy and safety including immunogenicity) for LS-SCLC.
4.4	Updates to Immune-mediated pneumonitis and Use in the elderly for LS-SCLC.
4.1, 4.2, 4.4, 4.8, 5.1, 5.2	New indication, dosing recommendation and clinical trial information (efficacy and safety including immunogenicity) for use in endometrial cancer (DUO-E study
4.4	Pure red cell aplasia (PRCA) and/or autoimmune haemolytic anaemia (AIHA) is added.
4.5	Sentence added regarding use with olaparib
4.1, 4.2, 4.4, 4.8 and 5.1	New muscle invasive bladder cancer indication and dosing, plus safety and efficacy associated with NIAGARA study.