CT Application(s) Summary Report

- **Protocol title:** Phase III, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Durvalumab Monotherapy or in Combination with Bevacizumab as Adjuvant Therapy in Patients with Hepatocellular Carcinoma Who Are at High Risk of Recurrence After Curative Hepatic Resection or Ablation (**EMERALD-2**).
- **Protocol code number:** D910DC00001

Public Registry Number: **EudraCT Number:**2018-004105-85, **EU CT Number:** 2023-507689-26-00

- **Version:**4.0
- **Date:** 22 April 2024

- **Investigational Medicinal Product being tested:**

Biological	■	**Pharmaceutical**	☐	**Innovative**	☐
Herbal medicine	☐	**Medical device**	☐		

- **Sponsor: AstraZeneca**
- **Indication:** Patients with Hepatocellular Carcinoma Who Are at High Risk of Recurrence after Curative Hepatic Resection or Ablation.
- **Investigator's brochure (IB) (For Durvalumab)**

Version: V21
Date: 05 Aug 2025

- **Name of all Sites:**
  - Alexandria University- CRC.
  - National Liver Institute-Menoufya University.
  - National Hepatology & Tropical Medicine Research Institute.
  - Air Force specialized Hospital.
  - Assuit University Hospital.
- **Name of PI(s):**
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- **EDA approval date:**
  - Initial Approval Amendment 1 (Protocol version 3.0):15/12/2021.
  - Protocol version 4.0, approved on 26/01/2025.
  - Durvalimab IB V20 date 29 July 2024 approved on 15/01/2025.
  - Durvalimab IB V21 dated 01 August 2025, approved on 27/01/2026.

- **Summary of pre-clinical studies:**

❖ **Durvalumab**

Durvalumab is a human monoclonal antibody immunotherapy that targets programmed death-ligand 1 (PD-L1). It is classified as an immune checkpoint inhibitor and is marketed under the brand name Imfinzi by AstraZeneca. Durvalumab enhances antitumor immune responses by blocking the interaction between PD-L1 and the PD-1/CD80 receptors on T cells, thereby restoring T-cell mediated immune activity against cancer cells.

Durvalumab selectively binds to PD-L1 expressed on tumor cells and immune cells within the tumor microenvironment. By inhibiting PD-L1 interaction with PD-1 and CD80, it prevents immune evasion by tumor cells and promotes activation and proliferation of cytotoxic T lymphocytes capable of targeting malignant cells.

➢ **In Vitro Pharmacology**

1-Durvalumab demonstrated high specificity for human PD-L1, as confirmed by ELISA, with no detectable binding to related proteins and no binding to murine PD-L1. Functionally, durvalumab effectively inhibited the interaction of PD-L1 with its ligands.

Overall, the following results confirm that durvalumab potently and specifically blocks PD-L1 binding to both PD-1 and CD80.

2-Durvalumab enhanced the proliferation of primary human $CD3^+$ T cells across eight independent donors (MedImmune Research Report ONC4736-0020), whereas no enhancement was observed with the control antibody.

These findings suggest that maintaining serum concentrations of durvalumab above 3 µg/mL may maximize the likelihood of observing biological activity.

3-Durvalumab does not trigger effector functions, demonstrating lack of both ADCC and CDC activities. In an NK cell CD16 reporter gene bioassay (a surrogate for ADCC), durvalumab did not induce reporter activity in PD-L1–expressing tumor cells, whereas hIgG1 (wild-type Fc version) showed potent activation.

Additionally, neither durvalumab nor hIgG1 exhibited any CDC activity at any tested concentration. In contrast, the anti-CD20 antibody demonstrated dose-dependent CDC activity against the Daudi CD20-expressing B-cell line in the presence of human serum, but not with heat-inactivated serum, confirming assay validity.

4-Durvalumab did not induce significant cytokine release, either alone or in combination with other immunomodulatory agents, in human whole blood or PBMCs across multiple donors (MedImmune research reports ONC4736-0004, ONC4736-0017, BAS6383-02-BAR-HUMAN-CRA, BAS9447-0002-Bar-Human-CRA; Eurofins Study OX-14/128-003).
In contrast, anti-human CD3 antibody induced substantial cytokine release, confirming the sensitivity and validity of the assay conditions.

- **In Vivo Pharmacology**

1-Durvalumab demonstrated significant inhibition of tumor growth in mouse models via an immune-mediated mechanism (MedImmune Research Report ONC4736-0006). Tumor growth inhibition reached up to 74% in the pancreatic adenocarcinoma HPAC cell line and up to 77% in the A375 melanoma cell line compared to the isotype-control antibody.
In vivo studies using non-obese diabetic/severe combined immunodeficient mice showed that antitumor activity was observed only when human T-cells were co-implanted with tumor cells; no activity was detected in their absence.
These findings indicate that durvalumab's antitumor effect is dependent on the presence of tumor-specific human T-cells, supporting an immune-mediated mechanism of action.

- **Non-clinical Pharmacokinetics and Drug Metabolism**

1-A PK/Pharmacodynamic and DRF Toxicity Study of Durvalumab in Cynomolgus Monkeys (Study 302833; Non-GLP):

-Durvalumab exhibited nonlinear pharmacokinetics across the evaluated dose range.
Following IV administration (on Day 1 and on Days 15, 22, and 29), exposure increased in an approximately dose-proportional manner, with concentrations rising **11.8-fold** from **1.77±0.424 to 20.8±1.27 µg/mL** over a 10-fold dose range. However, $AUC_{0-\tau}$ increased in a greater than dose-proportional manner, showing a **38.2-fold** increase from **2.10±0.165 to 80.3±14.7 µg·d/mL**, accompanied by a decrease in systemic clearance from **43.8±3.27 to 11.1±1.11 mL/d/kg**.
These findings indicate nonlinear PK, likely due to saturable target-mediated clearance, consistent with antibodies targeting membrane-bound proteins.

After the final dose on Day 29, $AUC_{0-\tau}$ increased by **105-fold** (from **70.0±57.9 to 7370±7240 µg·d/mL**) over the same dose range. Anti-drug antibodies (ADA) were detected in all animals.

Despite ADA presence, substantial exposure levels were maintained, and pharmacodynamic activity (PD-L1 suppression) persisted throughout the study.

2-A Subcutaneous Single Dose PK, Pharmacodynamic and Tolerability Study in the Cynomolgus Monkey (8401540; GLP)

-Male monkeys were administered a single SC dose of durvalumab on Day 1 (0 mg/kg [vehicle], or a single IV dose of durvalumab showed that the single SC or IV dose of durvalumab resulted in a**pproximately dose proportional exposure and full suppression of sPD-L1 24 hours post dose**.

The **single administration was associated with the induction of ADA**, which in individual animals affected the duration of exposure and/or sPD-L1 suppression, with the duration of sPD-L1 suppression showing dose dependency.

-Bioavailability of durvalumab when administered subcutaneously ranged from approximately 34% to 58%.

3-Four-week Repeat-dose Toxicity Study of Durvalumab in Cynomolgus Monkeys with an Eight-week Treatment-free Period (Study VMM0008; GLP):

Durvalumab showed biphasic decline in serum concentrations following IV loading doses with a mean elimination half-life ranging from **5.9 to 6.8 days**.

Systemic clearance (CL) remained consistent across dose levels, ranging from **6.1 to 7.5 mL/d/kg**, resulting in systemic exposures (AUC) that were linearly proportional to dose. A corresponding dose-dependent increase in **Cmax** was also observed.

Following repeated dosing, systemic exposure after the final dose was slightly affected by anti-drug antibodies (ADA) in a small proportion of animals.

However, in the majority of animals, sustained exposure and pharmacodynamic effects were maintained throughout the study, with accumulation ratio (AR, based on AUCτ) independent of dose and ranging from **1.1 to 1.7**.

4-Enhanced Pre- and Postnatal Development Study of Durvalumab in Cynomolgus Monkeys (Study 8291365; GLP)

- Durvalumab demonstrated dose-proportional systemic exposure in pregnant female cynomolgus monkeys following an initial IV loading dose on GD20, followed by weekly doses from GD27 until delivery.

- Repeated dosing resulted in systemic accumulation, with steady state achieved by approximately **GD76**, and mean accumulation ratios (AR, based on AUCτ) of **1.68** and **1.74** after dose 17 (GD132).
- Following parturition, serum concentrations declined but remained detectable up to **Days 28 and 56 postpartum**, with dose-proportional excretion observed in breast milk on **Day 28 postpartum**.
- Durvalumab exposure was associated with full suppression of sPD-L1 from the first dose on GD20 and throughout gestation. Although anti-drug antibodies (ADA) were detected, where increased ADA-mediated clearance was associated with rebound of sPD-L1 levels.
- In infants, serum concentrations showed dose-proportional exposure at **Day 1±1 postpartum**, followed by gradual decline to non-quantifiable levels by **Day 180±1 postpartum**, with corresponding recovery of sPD-L1 levels to control values.

➢ **Toxicology**

1- Single Dose Toxicity

Non-GLP Repeat-dose Toxicity Study

- **Nonlinear PK** was observed consistent with target-mediated drug disposition.
- This correlated with **dose-dependent pharmacodynamics**, as assessed by suppression of **sPD-L1** and occupancy of **membrane PD-L1** on various leukocyte subsets.
- In animals treated with durvalumab, non-dose-related decreases in **KLH-specific IgM and IgG** antibody responses were observed after primary immunization compared to controls.
- These effects were not considered adverse as quantifiable primary antibody responses were still mounted
- Based on these findings the **NOAEL** for durvalumab in this study was considered to be the highest dose tested.

2- GLP Repeat-dose Toxicity Studies

Two GLP repeat-dose IV toxicity studies were conducted with durvalumab in **cynomolgus monkeys**, a **4-week (Study VMM0008)** and a **13-week (Study VMM0033)** repeat-dose toxicity study.

In both GLP repeat-dose studies a loading dose was administered by **30 min IV infusion** on Day 1, and followed by **4 or 13 weekly doses.**

Control animals received weekly IV infusions with vehicle

In both studies, the majority of animals tested positive for **ADA,** however, exposure to durvalumab was largely maintained and serum levels of **sPD-L1** were generally fully suppressed within **24 hours** following the first administration of durvalumab and throughout the dosing period.

In the **4-week repeat dose** toxicity study, a single animal presented with clinical signs, loss of exposure and sPD-L1 suppression and pathology findings consistent with ADA-linked anaphylaxis.

No other durvalumab-related adverse effects were noted in any of the animals.

In the **13-week repeat-dose** toxicity study, no durvalumab-related effects were observed on any endpoint investigated.

In conclusion ADA immune complex deposition in the **4-week repeat-dose toxicity study**, weekly IV infusion of durvalumab to cynomolgus monkeys for **4 or 13 weeks** was not associated with any adverse effects. The **NOAEL** for durvalumab in these studies was therefore considered to be the highest dose tested in these studies.

3- Reproductive and Development Toxicity

Durvalumab showed no treatment-related effects on reproductive organ weights or microscopic histopathology in male or female animals in a GLP 13-week repeat-dose toxicity study.

In an enhanced pre- and postnatal development (ePPND) study in cynomolgus monkeys, pregnant females were administered durvalumab from GD20 until delivery, receiving loading doses followed by weekly doses. Infant development was monitored over a **6-month postnatal period**, including assessment of immune competence using a T cell-dependent antigen (KLH).

Systemic exposure to durvalumab was maintained in most animals despite a high incidence of ADA and was associated with full suppression of sPD-L1. Placental transfer was observed, with detectable exposure in infants and sustained sPD-L1 suppression up to **Day 56 postpartum**, along with low-level, dose-related excretion into breast milk at **Day 28 postpartum**.

Following cessation of dosing at parturition, durvalumab exposure declined gradually in both maternal animals and infants, becoming undetectable by **Day 180±1 postpartum**, with sPD-L1 returning to baseline levels.

Compared to concurrent controls, durvalumab was associated with increased mid- and late-stage pregnancy loss, stillbirths, infant mortality, and premature delivery, without a clear dose-response relationship. However, these outcomes were within the range of historical control data.

Overall, IV administration of durvalumab during pregnancy was associated with adverse pregnancy outcomes (including fetal loss and premature neonatal death) in the absence of maternal toxicity, with no effects observed relative to historical controls.

- **Special Studies**

1-Tissue Cross-reactivity Studies with Durvalumab (Study 20014789, Study 20014791; GLP)

In the **human tissues** examined, durvalumab-specific staining was present in the membrane and cytoplasm of **mononuclear cells** and **trophoblastic epithelium**, and in the cytoplasm of pituitary epithelium.

In the cynomolgus monkey tissues examined, durvalumab-specific staining was present in the membrane and cytoplasm of mononuclear cells, fallopian tube epithelium, and trophoblastic epithelium.

In conclusion, IV administration of durvalumab to pregnant cynomolgus monkeys from GD20 until parturition was associated with increased premature delivery, foetal loss, and premature neonatal death, but not with maternal toxicity, compared to concurrent controls. No effects of durvalumab were noted compared to historical controls.

- **Summary of previous clinical studies:**

Patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of disease and lines of therapy. Of these, patients received durvalumab monotherapy, patients received durvalumab in combination with tremelimumab, and patients received durvalumab or durvalumab plus tremelimumab in combination with an investigational and/or an approved product. Patients have been randomized and treated to the various treatment/comparator arms in sponsor blinded and/or double-blinded studies.

- **Pharmacokinetics and Drug Metabolism in Humans**

Following the first IV dose, durvalumab exhibited **nonlinear PK** likely due to saturable target-mediated CL and exhibited **linear PK**. Mean (±standard deviation [std dev] serum concentration-time profiles stratified by dose. The **AUC0-14** increased dose-proportionally**,** likely due to saturable target-mediated CL. **Cmax increased in a dose-proportional manner** within the dose range examined. The **steady state** was achieved at approximately **Week 16. Accumulation of durvalumab was observed following repeated dosing**.

- **Pharmacodynamics**

- Durvalumab demonstrated robust target engagement, with complete suppression of sPD-L1 observed, approximately 97% of subjects achieved sustained sPD-L1 suppression throughout the dosing interval, with comparable suppression across regimens.
- Pharmacodynamic effects were evaluated using flow cytometry-based assays in UC and NSCLC patients. In UC patients, administration of durvalumab resulted in increases in proliferating $CD8^+$ T cells on Day 10 and Day 15 exceeding the assay variability range, although not statistically significant.

- In NSCLC patients, increases in baseline-normalized proliferating T cells were observed following 10 mg/kg Q2W dosing, with $CD4^+$ $Ki67^+$ cells at Day 10 and Day 15 and $CD8^+$ $Ki67^+$ cells at Day 10 and Day 15.
- Additionally, modest but statistically significant increases in B cells were observed at Day 99. No other lymphocyte populations showed changes exceeding assay variability during the first 100 days.
- Overall, these findings demonstrate pharmacodynamic activity consistent with the mechanism of action of durvalumab.

➢ **Immunogenicity**

- Durvalumab showed low immunogenicity in an ADA-evaluable population of patients.
- The overall ADA prevalence was 5.3%, while the incidence of treatment-emergent ADA was 3.1%. In the 10 mg/kg Q2W group, ADA prevalence was 4.9%, with an ADA incidence of 2.7%. Among ADA-positive patients, Some were positive at baseline only, Some at both baseline and post-baseline, and (0.1%) patient showed a ≥4-fold increase in pre-existing ADA titers.
- Anti-TM antibodies were detected in (0.1%) patients, with no apparent impact on durvalumab or sPD-L1 serum concentrations.
- Safety analyses indicated no clear association between ADA development and adverse events (AEs), serious adverse events (SAEs), or immune complex–related events. The safety profile in ADA-positive patients was comparable to that of ADA-negative patients. Additionally, none of the nAb-positive patients experienced treatment-emergent AEs suggestive of infusion reactions or hypersensitivity.
- The impact of treatment-emergent ADA on clinical efficacy in UC and NSCLC patients was not evaluable due to the low number of ADA-positive cases.

--Study D4190C00006 (Durvalumab + Tremelimumab):

- Durvalumab and Tremelimumab pharmacokinetics were evaluated in patients, across dose-escalation and expansion phases.
- Durvalumab was administered **Q4W** or **Q2W** in combination with tremelimumab **Q4W.** PK analyses were conducted using **ECL** (durvalumab) and **ELISA** (tremelimumab) assays in human serum.
- Both agents demonstrated approximately dose-proportional increases in exposure (**Cmax and $AUC_{0–28}$**) across the evaluated dose ranges.
- Following multiple dosing, accumulation was consistent with first-dose PK parameters. Importantly, PK profiles of both durvalumab and tremelimumab in combination were comparable to their respective monotherapy data, indicating **no pharmacokinetic interaction** between the two agents.

➢ **Pharmacodynamics**

- Durvalumab target engagement, assessed by suppression of free sPD-L1, was evaluated in **patients** receiving combination therapy with Tremelimumab across dose-escalation and expansion phases.
- Complete sPD-L1 suppression was observed in **almost all patients** across the dose range of **durvalumab Q4W or Q2W** in combination with tremelimumab.
- A small number of patients showed partial suppression at certain time points, including:
- **Patients** (at **durvalumab + tremelimumab** and **durvalumab + tremelimumab**) who later achieved complete suppression after repeated dosing
- **Patients** (at **durvalumab + tremelimumab**) who showed partial suppression on Day 29 and was ADA-positive with an associated impact on PK.
- No clear dose-dependent effect on sPD-L1 suppression was observed across the evaluated dose range.

➢ **Safety and Efficacy in Humans**

❖ **Efficacy Summaries for Monotherapy Studies or Studies with Monotherapy Arm:**

Study ID	Exposure (no of patients)	OS data	PFS data	ORR/DOR and other efficacy endpoints
NSCLC				
CD-ON-MEDI4736-1108	302 (275 in the FAS)	Median OS: 12.4 months (95% CI: 9.3, 15.2). PD-L1 high (TC ≥25%): 16.4 months PD L1 low/neg (TC <25%): 7.6 months. Median OS was 21.0, 11.8, and 9.3 months in the 1L, 2L, and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6% (95% CI: 23.9, 35.5) and higher in the PD-L1 high (35.9%) vs the PD L1 low/negative (22.2%) subgroup.	Median PFS was 2.1 months (95% CI: 1.5, 2.6), with PFS rate of 12.7% at 18 months.	ORR (BICR) was 15.3% (42/275; 95% CI: 11.2, 20.1). PD-L1 high: 21.8% (32/147; 95% CI: 15.4, 29.3); PD L1 low/neg: 6.4% (7/109; 95% CI: 2.6, 12.8). ORR was 25.9%, 14.3%, and 11.5% in the 1L, 2L, and 3L+ cohorts, respectively. Median DOR was 17.74 months.

Study D4191C00001 PACIFIC PFS DCO: 13 Feb 2017 OS follow-up analysis DCO: 31 Jan 2019 Long-term 5-year follow-up Study completed	Durvalumab: 476 Placebo: 237	Median OS was not reached (NR) for the durvalumab arm (95% CI: 38.4, NR) and was 29.1 months (95% CI: 22.1, 35.1) for the placebo arm; hazard ratio 0.69; 95% CI: 0.55, 0.86. The 36 month OS rate was 57.0% (95% CI: 52.3, 61.4) with durvalumab vs 43.5% (95% CI: 37.0, 49.9) with placebo. At the time of the 5-year follow-up, median OS was 47.5 months for the durvalumab arm (95% CI: 38.1, 52.9) and was 29.1 months (95% CI: 22.1, 35.1) for the placebo arm; hazard ratio 0.72; 95% CI: 0.59, 0.89.	Median PFS (BICR) was significantly longer with durvalumab treatment (16.8 months [95% CI: 13.0, 18.1]) compared with placebo (5.6 months [95% CI: 4.6, 7.8]); hazard ratio 0.52; 98.9% CI: 0.39, 0.70;p<0.0001. At the time of the 5-year follow-up, median PFS (BICR) with durvalumab treatment was 16.9 months (95% CI: 13.0, 23.9) and with placebo was 5.6 months (95% CI: 4.8, 7.7); hazard ratio 0.55; 95% CI: 0.45, 0.68.	ORR was 30.0% (95% CI: 25.79, 34.53) in the durvalumab group compared with 17.8% (95% CI: 12.95, 23.65) in the placebo group. Median DOR was not reached with durvalumab (95% CI, 27.4 months, NR) vs 18.4 months (95% CI, 6.7, 24.5) with placebo. The median time to death or distant metastasis was longer with durvalumab than with placebo (28.3 months vs 16.2 months; hazard ratio 0.53; 95% CI, 0.41, 0.68).
Study D4194C00006 PACIFIC 6 Primary DCO: 15 Jul 2021 Study completed	117	A Median OS was 25.0 months (95% CI: 24.97, NC). At the time of the final DCO, median OS was 39.0 months (95% CI: 30.59, NC).	Median PFS was 10.9 months (95% CI: 7.33, 15.64). At the time of the final DCO, median PFS was 13.1 months (95% CI: 7.36, 19.91).	ORR was 17.1% (20/114; 95% CI: 11.1, 25.8). Median DOR was not reached. At the time of the final DCO, ORR was 20.5% (24/114; 95% CI: 13.6, 29.0). Median DOR was not reached.

Study D419AC00001 MYSTIC PFS OS analysis Study completed	PD-L1 TC ≥25% Durvalumab: 163 Chemo-therapy: 162	Median OS was 16.3 months (95% CI: 12.2, 20.8) for the durvalumab arm and 12.9 months (95% CI: 10.5, 15.0) for the chemotherapy arm; hazard ratio 0.76; 97.54% CI, 0.564, 1.019; p=0.036). The 24-month OS rate was 38.3% with durvalumab vs 22.7% with chemotherapy.	Median PFS (BICR) was 4.7 months [95% CI: 3.1, 6.3]) compared with chemotherapy (5.4 months [95% CI: 4.6, 5.8]); hazard ratio 0.87; 99.5% CI: 0.593, v1.285; p=0.324. The 12-month PFS rate was 32.3% with durvalumab vs 14.3% with chemotherapy.	ORR was 35.6% in the durvalumab arm compared with 37.7% in the chemotherapy arm. Median DOR was not reached with durvalumab vs 4.4 months with chemotherapy. The % of patients remaining in response at 12 months was 61.3% in the durvalumab arm and 18.0% in the chemotherapy arm.
Study D9102C00001 ORION Study completed	Durvalumab + placebo: 134 (135 in the FAS) following initial therapy with SoC platinum-based chemotherapy with durvalumab	Median OS was not reached (95% CI: 11.8, NR).	Median PFS was 5.3 months (95% CI: 3.7, 5.8).	ORR was 13.7%, the median DOR was not reached.
Study D419AC00002 PEARL Study completed	Durvalumab: 335 (335 in the FAS) SoC: 327 (334 in the FAS)	Median OS was 14.6 months (95% CI: 12.2, 16.9) for the durvalumab arm and 12.8 months (95% CI: 10.1, 14.7) for the SoC arm; hazard ratio: 0.84 (95% CI: 0.706, 0.989; p=0.037).	Median PFS was 5.4 months (95% CI: 4.2, 5.7) for the durvalumab arm and 4.8 months (95% CI: 4.3, 5.6) for the SoC arm; (95% CI: 0.650, 0.916; p=0.003).	ORR was 37.6% (95% CI: 32.4, 43.0) for the durvalumab arm and 37.4% (95% CI: 32.2, 42.9) for the SoC arm. Median DOR was 11.9 months (durvalumab) and 4.2 months (SoC).

	PD-L1 TC ≥25% LREM Durvalumab: 278 (278 in the PD-L1 TC ≥25% LREM analysis set) SoC: 266 (271 in the PD-L1 TC ≥25% LREM analysis set)	Median OS was 14.6 months (95% CI: 12.6, 17.2) for the durvalumab arm and 15.0 months (95% CI: 13.1, 16.8) for the SoC arm; hazard ratio: 0.96 (95% CI: 0.793, 1.151; p=0.628).	Median PFS was 5.5 months (95% CI: 4.4, 6.4) for the durvalumab arm and 5.6 months (95% CI: 4.8, 5.9) for the SoC arm; hazard ratio: 0.85 (95% CI: 0.704, 1.030; p=0.097).	ORR was 38.5% (95% CI: 32.7, 44.5) for the durvalumab arm and 40.2% (95% CI: 34.3, 46.3) for the SoC arm. Median DOR was 11.6 months (durvalumab) and 4.2 months (SoC).
Study D933YC00001 PACIFIC-5 Study completed	Global cohort Durvalumab: 251 (252 in the mITT) Placebo: 128 (129 in the mITT)	At the first OS interim analysis, median OS was 38.3 months (95% CI: 28.9, 42.8) for the durvalumab arm vs 32.5 months (95% CI: 20.6, 40.4) in the placebo arm; hazard ratio: 0.87 (95% CI: 0.656, 1.166; p = 0.346)	Median PFS was 14.0 months (95% CI: 10.9, 18.0) for the durvalumab arm vs 6.5 months (95% CI: 5.4, 13.8) for the placebo arm; hazard ratio: 0.75 (95% CI: 0.578, 0.986; p = 0.038).	ORR (BICR) was 27.6% for durvalumab arm vs 20.7% for the placebo arm; odds ratio: 1.51 (95% CI: 0.891, 2.607; p = 0.128). Median DOR was NR (durvalumab) and 37.6 months (placebo).
	China cohort Durvalumab: 131 (131 in the mITT) Placebo: 65 (66 in the mITT)	At the first OS interim analysis, median OS was NR (95% CI: 42.6, NR) for the durvalumab arm vs 40.4 months (95% CI: 29.5, NR) in the placebo arm; hazard ratio: 0.87 (95% CI: 0.553, 1.386; p = 0.536).	Median PFS was 22.0 months (95% CI: 13.8, 33.2) for the durvalumab arm vs 13.8 months (95% CI: 5.6, 22.3) for the placebo arm; hazard ratio: 0.74 (95% CI: 0.498, 1.104; p = 0.132).	ORR (BICR) was 32.7% for durvalumab arm vs 20.3% for the placebo arm; odds ratio: 1.94 (95% CI: 0.936, 4.229; p = 0.076). Median DOR was 29.5 months (durvalumab) and 11.6 months (placebo).

SCLC				
Study D933QC00001 ADRIATIC Study completed	Durvalumab: 263 (264 in the FAS) Placebo: 265 (266 in the FAS)	At the first interim OS analysis, median OS was 55.9 months (95% CI:37.3, NR) for thep durvalumab monotherapy arm vs 33.4 months (95% CI: 25.p5, 39.9) for the placebo arm; hazard ratio: 0.73; 95% CI: 0.569, 0.928; p = 0.01042.	At the pre-planned interim PFS analysis, median PFS was 16.6 months (95% CI: 10.2, 28.2) for the durvalumab monotherapy arm vs 9.2 months (95% CI: 7.4, 12.9) for the placebo arm; hazard ratio: 0.76; 95% CI: 0.606, 0.950; p = 0.01608.	ORR (unconfirmed responses, BICR) was 30.3% in the durvalumab monotherapy arm vs 32.0% in the placebo arm. Median DOR was 33.0 months (durvalumab) and 27.7 months (placebo).
HNSCC				
Study D4193C00001 HAWK Study completed	112 (PD-L1 high)	Median OS was 7.2 months (95% CI: 5.0, 10.1 months).	Median PFS was 2.1 months (95% CI: 1.9, 3.7 months).	ORR (BICR) was 16.2% (95% CI: 9.9%, 24.4%). ORRs were generally consistent across subgroups, except for subgroups based on HPV status; ORR in HPV-positive patients was numerically higher (29.4% [95% CI: 15.1%, 47.5%]) than ORR in HPV-negative patients (10.9% [95% CI: 4.5%, 21.3%]).
Study D4193C00003 CONDOR	67 (PD-L1 negative)	Median OS was observed (95% CI: 4.0).	Median PFS was 1.9 months (95% CI: 1.8, 2.8	ORR at 12 months was 9.2% (6/65 patients; 95% CI: 3.5%, 19.02%).

Study completed			months).	
CD-ON-MEDI4736-1108 Study completed	62 (55 in the FAS)	Median OS was 8.4 months (95% CI: 5.7, 12.3); the OS rate at 24 months was 24.2% (95% CI: 12.5, 38.0).	Median PFS was 1.4 months (95% CI: 1.4, 1.5), with a PFS rate of 7.2% at 18 months.	ORR (BICR) was 7.3% (4/55; 95% CI: 2.0, 17.6). PD-L1 high: 16.7% (3/18; 95% CI: 3.6, 41.1); PD-L1 low/neg: 2.9% (1/35; 95% CI: 0.1, 14.9). Median DOR was 12.37 months.
Study D4193C00002 EAGLE Study completed	Durvalumab: 240 SoC:249	Median OS was 7.6 months for the durvalumab monotherapy arm vs 8.3 months for the SoC arm; hazard ratio: 0.88; 95% CI: 0.72, 1.08; p=0.1993.	Median PFS was 2.1 months for the durvalumab monotherapy arm vs 3.7 months for the SoC arm.	ORR was 17.9% in the durvalumab monotherapy arm and 17.3% in the SoC arm. Median DOR was 12.9 (durvalumab) and 3.7 (SoC) months. The proportions of patients who remained in response at 12 months were 53.6% (durvalumab) and 5.8% (SoC). Only patients in the durvalumab arm (6 patients) had a complete response compared to none in the SoC arm.
UC				
CD-ON-MEDI4736-1108	201 (190 in the FAS)	Median OS was 10.5 months (95% CI: 6.9, 15.7); the OS rate at 24 months was	Median PFS was 1.5 months (95% CI: 1.4d, 1.8),	ORR (BICR) was 17.6% (35/199; 95% CI: 12.6, 23.6). PD-L1 high: 27.7%

Study completed		30.0% (95% CI: 21.1, 39.3).	with a PFS rate of 13.7% at 18 months.	(28/101; 95% CI: 19.3, 37.5); PD-L1 low/neg: 5.9% (5/85; 95% CI:1.9, 13.2). Median DOR not yet reached (range 2.7 to 25.7+ months).
Study D419BC00001 DANUBE Study completed	PD-L1 TC ≥25% 208 (209 in the FAS)	Median OS was 14.4 months (95% CI: 10.4, 17.3).	Median PFS was 2.4 months (95% CI: 1.9, 3.7).	ORR was 27.8% (58/209). Median DOR was 18.5 months
	345 (346 in the FAS)	Median OS was 13.2 months (95% CI: 10.3, 15.0).	Median PFS was 2.3 months (95% CI: 1.9, 3.5).	ORR was 25.7% (89/346). Median DOR was 9.3 months
HCC				
CD-ON-MEDI4736-1108 Study completed	40	Median OS was 13.2 months (95% CI: 6.3, 23.0); the OS rate at 24 months was 28.2% (95% CI: 14.3, 43.9).	Median PFS was 2.7 months (95% CI: 1.4, 5.3), with a PFS rate of 9.2% at 18 months.	ORR (RECIST v1.1) was 10.0% (4/40; 95% CI: 2.8, 23.7). Median DOR was 16.2 months.
Study D4190C00022 Study completed	101 (104 in the FAS)	Median OS was 12.91 months (95% CI: 8.74, 16.79).	Median PFS was 2.07 months (95% CI: 1.84,2.86).	ORR (BICR) was 11.5% (12/104; 95% CI: 6.1, 19.3). Median DOR was 14.95 months.
Study D419CC00002 HIMALAYA Long-term 4-year follow-up Study completed	386 (389 in the FAS)	Median OS was 16.56 months (95% CI: 14.06,19.12). At the time of the 4-year follow-up, median OS was 16.6 months for the durvalumab arm (95% CI: 14.1, 19.1) and was 13.8 months (95% CI: 12.3, 16.1) for the sorafenib arm; hazard ratio 0.86; 95% CI: 0.74, 1.01	Median PFS was 3.65 months (95% CI: 3.19,3.75).	ORR was 17.0% (66/389; 95% CI: not reported).

		(Sangro et al 2024). The OS rate at 48 months was 19.3% in the durvalumab arm and 15.1% in the sorafenib arm (Sangro et al 2024).		
Other indications				
CD-ON-MEDI4736-1108 Study completed	Range: 10 to 62	Median OS was reached in all cohorts except the advanced cutaneous melanoma cohort, and ranged between 4.9 months (95% CI: 2.6, 9.1) in the gastroesophageal cancer cohort to 24.1 months (95% CI: 12.4, not evaluable) in the microsatellite instability-high cancer cohort.	Median PFS ranged from 1.4 months in HNSCC, uveal melanoma, glioblastoma multiforme, and gastroesophageal cancer, to 5.4 months in microsatellite instability- high cancer.	ORR (RECIST v1.1), ranged from 0% in glioblastoma multiforme to 30.0% in nasopharyngeal carcinoma.

➢ **Efficacy Summaries for Durvalumab + Tremelimumab Studies**

Study ID	Exposure (no of patients)	OS data	PFS data	ORR/DOR and other efficacy endpoints
NSCLC				
Study D4190C00006 Study completed	Cohort A:45 Cohort B co-admin: 19 Cohort B sequential: 213 Cohort C refractory:38 Cohort C relapsed: 40	**Cohort A (treatment-naive NSCLC selected by PD-L1 status)** Median OS was 22.1 months; Median PFS (per investigator) ORR was 15.6% (7/45; 95% CI: 6.5, the OS rate at 12 months of was 3.5 months (95% CI: 1.7, 29.5). Median	Median PFS (per investigator) was 3.5 months (95% CI: 1.7, 7.2).	ORR was 15.6% (7/45; 95% CI: 6.5, 29.5). Median DOR of 24.4 weeks.

			DOR of 24.4 weeks. 71.6%. 7.2).		
			Cohort B co-administration (immunotherapy-naïve, 1L, or 2L patients with NSCLC) Median OS was 7.6 months; the OS rate at 12 months of 38.5%	Median PFS (per investigator) was 2.8 months (95% CI: 1.6, 4.7).	No objective responses were observed. Best overall response of SD for 9 of the 19 patients (DCR, 47.4%; 95% CI: 24.4, 71.1).
			Cohort B sequential administration (2L patients with non-squamous NSCLC) Median OS was 14.3 months; the OS rate at 12 months was 53.7%	Median PFS (BICR) was 3.5 months (95% CI: 1.7, 3.6).	ORR (BICR) was 16.9% (36/213; 95% CI: 12.1, 22.6). Median DOR was 123 weeks.
			Cohort C refractory (immunotherapy-pretreated, 2L to 4L patients with NSCLC) Median OS was 8.3 months; the OS rate at 12 months was 30.1%	Median PFS (BICR) was 1.7 months (95% CI: 1.6, 2.6)	ORR (BICR) was 5.3% (2/38; 95% CI: 0.6, 17.7). Median DOR was not reached.
			Cohort C relapsed (immunotherapy-pretreated, 2L to 4L patients with NSCLC) Median OS was 8.5 months; the OS rate at 12 months was 38.6%.	Median PFS (BICR) was 2.0 months (95% CI: 1.6, 3.1).	No objective responses (BICR) were observed. Best overall response of SD for 16 of the 40 patients (DCR, 40.0%; 95% CI: 24.9, 56.7).
	Study D419AC00001 MYSTIC PFS DCO: 1 Jun 2017 OS analysis Study completed	PD-L1 TC ≥25% durvalumab+ tremelimumb 163 Chemotherapy162	Median OS was 11.9 months (95% CI: 9.0, 17.7) for the durvalumab +tremelimumab arm and was 12.9 months (95%	Median PFS (BICR) was 3.9 months [95% CI: 2.8, 5.0]) for the durvalumab+tremelimumab arm compared with	ORR was 34.4% in the durvalumab+tremelimumab arm compared with 37.7% in the chemotherapy arm. Median DOR was not

			CI: 10.5, 15.0) for the chemotherapy arm; hazard ratio 0.85; 98.77% CI, 0.611, 1.173; p=0.202). The 24-month OS rate was 35.4% with durvalumab +tremelimumab vs 22.7% with chemotherapy.	chemotherapy d (5.4 months [95% CI: 4.6, 5.8]); hazard ratio 1.05; 99.5% CI: 0.722, 1.534; p=0.705. v The 12-month PFS rate was 25.8% with durvalumab +tremelimumab vs 14.3% with chemotherapy.	reached with durvalumab +tremelimumab vs 4.4 months with chemotherapy. The % of patients remaining in response at 12 months was 54.9% in the durvalumab +tremelimumab arm and 18.0% in the chemotherapy arm.
	Study D419MC00004 POSEIDON PFS DCO: 24 Jul 2019 OS analysis Long-term 4-year follow-up Long-term 5-year follow-up Study completed	331 Durvalumab + tremelimumab (75 mg, for 5 doses) + SoC chemotherapy (338 in the FAS) 331 SoC chemotherapy (337 in the FAS)	Median OS was 14.0 months (95% CI: 11.7, 16.1) for the durvalumab + tremelimumab + SoC chemotherapy arm and 11.7 months (95% CI: 10.5, 13.1) for the SoC chemotherapy alone arm (95% CI: 0.650, 0.916; p=0.00304). At the time of the 4-year follow-up, median OS was 14.0 months (95% CI: 11.7, 16.1) for the durvalumab + tremelimumab + SoC chemotherapy arm and 11.7 months (95% CI: 10.5, 13.1) for the SoC chemotherapy alone arm; hazard ratio: 0.75 (95% CI: 0.631, 0.882) At the time of the 5-year follow-up, median OS	Median PFS was 6.2 months (95% CI: 5.0, 6.5) for the durvalumab + tremelimumab + SoC chemotherapy arm and 4.8 months (95% CI: 4.6, 5.8) for the SoeC chemotherapy alone arm; hazard ratio: 0.72 (95% CI: 0.600,v 0.860; p=0.00031).	ORR was 46.3% (155/335; 95% CI: NR). Median DOR was 7.4 months.

		was 14.0 months (95% CI: 11.7, 16.1) for the durvalumab +tremelimumab + SoC chemotherapy arm and 11.6 months (95% CI: 10.5, 13.1) for the SoC chemotherapy alone arm; hazard ratio: 0.76 (95% CI: 0.642, 0.893).		
UC				
Study D4190C00010 OS analysis Study completed	168	Median OS was 9.6 months (95% CI: 8.0, 13.0).	Median PFS was 1.9 months (95% CI: 1.8, 3.4).	ORR was 20.8% which included 6 patients with CR. Patients with TC or IC ≥25% had numerically higher ORRs than those with TC or IC <25% (29.4% vs 15.1%).
Study D419BC00001 DANUBE Study completed	340 Durvalumab + tremelimumab (75 mg Q4W, for up to 4 doses) (342 in the FAS)	Median OS was 15.1 months (95% CI: 13.1, 18.0).	Median PFS was 3.7 months (95% CI: 3.4, 3.8).	ORR was 36.3% (124/342). Median DOR was 11.1 months.
HCC				
Study D4190C00022 Study completed	Parts 1A and 1B 40 Durvalumab + tremelimumab (75 mg Q4W, for 4 doses) (40 in the FAS)	A Median OS was 12.58 months (95% CI: 6.87, 20.99).	Median PFS was 3.52 months.	ORR was 20.0% (8/40; 95% CI: 9.1, 35.6). Median DOR was 16.66 months.
	Parts 2B and 3 74 Durvalumab + single dose of	Median OS was 17.05 months (95% CI: 10.55, 22.83).	Median PFS was 2.17 months (95% CI: 1.91, 5.42).	ORR (BICR) was 24.0% (18/75; 95% CI: 14.9, 35.3).

		tremelimumab (300 mg) (75 in the FAS)			Median DOR was 18.43 months.
		Parts 2A and 3 82 Durvalumab + tremelimumab (75 mg Q4W, for 4 doses) (84 in the FAS)	Median was observed (95% CI: 8.38, 14.95).	Median PFS was 1.87 months (95% CI: 1.77, 2.53).	ORR (BICR) was 9.5% (8/84; 95% CI: 4.2, 17.9). Median DOR was 13.21 months.
	Study D419CC00002 HIMALAYA Long-term 4-year follow-up Study completed	389 Durvalumab + single dose of tremelimumab (300 mg) (393 in the FAS)	Median OS was 16.43 months (95% CI: 14.16, 19.58). At the time of the 4-year follow-up, median OS was 16.4 months for pthe durvalumab + tremelimumab arm (95% CI: 14.2, 19.6) and was 13.8 months (95% CI: 12.3, 16.1) for the sorafenib arm; hazard ratio: 0.78 (95% CI: 0.67, 0.92) (Sangro et al 2024). The OS rate at 48 months was 25.2% in the durvalumab + tremelimumab arm and 15.1% in the sorafenib arm (Sangro et al 2024).	Median PFS was 3.78 months (95% CI: 3.68, 5.32).	ORR was 20.1% (79/393; 95% CI: NR).
		153 Durvalumab + tremelimumab (75 mg Q4W, for 4 doses) (153 in the FAS)	Median OS was 16.36 months (95% CI: 12.39, 19.65).	Median PFS was 3.65 months (95% CI: 2.79, 4.86).	ORR was 17.0% (26/153; 95% CI: NR).

SCLC				
Study D419QC00002 BALTIC Study completed	Arm A: 41	Median OS was 5.4 months (95% CI: 2.9, 7.2).	Median PFS was observed (95% CI: 1.8, 1.9) and the PFS rate at 6 months was 13.1%.	Confirmed ORR was 7.3% (95% CI: 1.5, 19.9). The DCR at 12 weeks was 26.8%.
HNSCC				
Study D4193C00003 CONDOR DCO for OS extension period: 27 Aug 2018 Study completed	133 (PD-L1 negative)	Median OS was 7.6 months (95% CI: 4.9, 10.6 months).	Median PFS was 2.0 months (95% CI: 1.9, 2.1 months).	ORR at 12 months was 7.8% (10/129 patients; 95% CI: 3.8%, 13.79%).
Study D4190C00011 Study completed	71	In the IMT-naïve expansion cohorts (PD-L1 high and PD-L1 low/negative patients; n=42), median OS was 11.0 months (95% CI: 5.2, 14.7) and OS rate at 12 months was 43.8%. In the PD-L1 high and low/ negative cohorts median OS was 5.2 and 14 months, respectively. In the IMT-pretreated cohort, median OS was 7.1 months (95% CI: 4.6, 10.1), OS rate at 12 months was 21.3%.	In the IMT-naïve expansion cohorts (PD-L1 high and PD-L1 low/negative patients; n=42), and PFS rate at 12 months was 7.5%. In the IMT pretreated cohort, median PFS was 2.5 months (95% CI: 1.8, 3.6) and PFS rate at 9 months was 0.0%	ORs were observed only in the PD-L1 high cohort. ORR per investigator was 20.0% (95% CI: 5.7%, 43.7%) in this cohort.

Study D4193C00002 EAGLE Study completed	Durvalumab + tremelimumab: 247 SoC:249	Median OS was 6.5 months for durvalumab + tremelimumab vs 8.3 months for the SoC arm; hazard ratio: 1.04; 95% CI: 0.85, 1.26; p=0.7624.	Median PFS was 2.0 months for durvalumab + tremelimumab vs 3.7 months for the SoC arm.	ORR was 18.2% in the durvalumab + tremelimumab arm and 17.3% in the SoC arm. Median DOR was 7.4 (durvalumab + tremelimumab) and 3.7 (SoC) months. The proportions of patients who remained in response at 12 months were 37.8% (durvalumab + tremelimumab) and 5.8% (SoC). Only patients in the durvalumab + tremelimumab arm (6 patients) had a complete response compared to none in the SoC group.
Other indications				
Study D419EC00001 Study completed	Dose-finding phase: 29 Dose-expansion phase (FAS): 21 (SARCOMA cohort: 11 STO cohort: 10)	Median OS was 6.6 months (90% CI: 1.87, 15.77) for the A SARCOMA cohort, and 6.9 months (90% CI: 1.61, NR) for the STO cohort.	Median PFS was 1.7 months (90% CI: 1.58, 1.91) for the ARCOMA cohort, and 1.7 months (90% CI: 0.89, 2.76) for the STO cohort.	In the SARCOMA cohort, no response was observed In the STO cohort, one response was observed. Confirmed ORR was 5% (1 of 20 evaluable patients).

➢ **Efficacy Summaries for Durvalumab + Chemotherapy Agent Studies**

Study ID	Exposure (no of patients)	OS data	PFS data	ORR/DOR and other efficacy endpoints

	NSCLC				
	Study D419MC00004 POSEIDON PFS OS analysis Long-term 4-year follow-up Long-term 5-year follow-up Study completed	335 Durvalumab + SoC chemotherapy (338 in the FAS) 331 SoC chemotherapy (337 in the FAS)	Median OS was 13.3 months (95% CI: 11.4, 14.7) for the durvalumab + SoC chemotherapy arm and 11.7 months (95% CI:1v 0.5, 13.1) for the SoC chemotherapy alone arm; hazard ratio: 0.86 (95% CI: 0.724, 1.016; p=0.07581). At the time of the 4-year follow-up, median OS was 13.3 months (95% CI: 11.4, 14.7) for the durvalumab + SoC chemotherapy arm and 11.7 months (95% CI: 10.5, 13.1) for the SoC chemotherapy alone arm; hazard ratio: 0.84 (95% CI: 0.711, 0.990). At the time of the 5-year follow-up, median OS was 13.3 months (95% CI: 11.4, 14.7) for the durvalumab +	Median PFS was 5.5 months (95% CI: 4.7, 6.5) for the durvalumab + SoC chemotherapy arm and 4.8 months (95% CI: 4.6, 5.8) for the SoC chemotherapy alone arm; hazard ratio: 0.74 (95% CI: 0.620, 0.885; p=0.00093).	ORR was 48.5% (160/330; 95% CI: NR).

			SoC chemotherapy arm and 11.6 months (95% CI: 10.5, 13.1) for the SoC chemotherapy alone arm; hazard ratio: 0.84 (95% CI: 0.717, 0.995).		
	Study D9106C00001 AEGEAN Interim pCR analysis Final pCR and first interim EFS analysis Second interim EFS analysis Study completed	400 Durvalumab + chemotherapy (196 in the interim mITT cohort at the interim pCR analysis; 366 in the mITT population at the first interim EFS analysis) 402 Placebo + chemotherapy (206 in the interim mITT cohort at the interim pCR analysis; 374 in the mITT population at the first interim EFS analysis)	At the second interim EFS analysis, the median OS was NR in the durvalumab + chemotherapy arm and was 53.2 months in the placebo + chemotherapy arm; hazard ratio 0.89 (95% CI: 0.70,1.14).	NA	At the interim pCR analysis, the pCR rate was 17.86% (95% CI: 12.76, 23.95) in the durvalumab + chemotherapy arm and 4.85% (95% CI: 2.35, 8.75) in the placebo + chemotherapy arm. At the time of the final pCR analysis, the pCR rate was 17.21% (95% CI: 13.49, 21.48) in the durvalumab + chemotherapy arm and 4.28% (95% CI: 2.46, 6.85) in the placebo + chemotherapy arm. At the time of the first interim EFS analysis, median EFS was NR in the durvalumab +

					chemotherapy arm and 25.9 months in the placebo + chemotherapy arm; hazard ratio: 0.68 (95% CI: 0.53, 0.88; p=0.0039). At the time of the second interim EFS analysis, median EFS was NR in the durvalumab + chemotherapy arm and 30.0 months in the placebo + chemotherapy arm; hazard ratio: 0.69 (95% CI: 0.55, 0.88).
	SCLC				
	Study D419QC00001 CASPIAN Interim analysis Final analysis DCO: 27 Jan 2020 Long-term 3-year follow-up Study completed	265 Durvalumab + chemotherapy (etoposide platinum [carboplatin or cisplatin]) (268 in theFAS) 266 Chemotherapy (269 in the FAS)	At the time of the interim analysis, the median OS was 13.0 months (95% CI: 11.5, 14.8) for the durvalumab + chemotherapy arm and 10.3 months (95% CI: 9.3, 11.2) for the chemotherapy arm; hazard ratio: 0.73 (95% CI: 0.59, 0.91; p=0.0047).	Median PFS was 5.1 months (95% CI: 4.7, 6.2) for the durvalumab + chemotherapy arm and 5.4 months (95% CI: 4.8, 6.2) for the chemotherapy arm; hazard ratio: 0.8 (95% CI: 0.67, 0.96; p=0.0157). The 24-month PFS rate was 11.0% for the durvalumab +	ORR was 79.5% in the durvalumab + chemotherapy arm and 70.6% in the chemotherapy arm.

			At the time of the final analysis, for the durvalumab + chemotherapy arm and for the chemotherapy arm; hazard ratio: 0.75 (95% CI: 0.625, 0.910; p=0.0032). The 24-month OS rate was 22.2% for the durvalumab +chemotherapy arm and 14.4% for the chemotherapy arm. At the time of the 3-year long-term follow-up, median OS was 12.9 months (95% CI) for the durvalumab +chemotherapy arm and 10.5 months (95% CI: 9.3, 11.2) for the chemotherapy arm; (95% CI: 0.595, 0.858 p=0.0003).	chemotherapy arm and 2.9% for the chemotherapy arm.	
	Study D419BR00018 ORIENTAL	165 Durvalumab + etoposide + cisplatin or carboplatin	Median OS was 14.8 months (95% CI: 13.2, 16.0), with an OS rate of 60.8%	Median PFS was 6.3 months (95% CI: 5.6, 6.5), with 17.6% patients alive and	ORR was 76.4% (126/165; 3 CR and123 PR [95% CI: 69.1, 82.6]). Median DOR was

	Study completed		(95% CI: 52.8, 67.9) at 12 months.	progression-free at 12 months (95% CI: 12.0,24.1).	5.1 months (95% CI: 4.7, 5.7).
	BTC				
	Study D933AC00001 TOPAZ-1 Study completed	338 Durvalumab + gemcitabine/cisplatin (341 in FAS)342 Placebo + gemcitabine/cisplatin (344 in the FAS)	Median OS was 12.8 months (95% CI: 11.1, 14.0) for the durvalumab + gemcitabine/cisplatin group and 11.5 months (95% CI: 10.1, 12.5) for the placebo +gemcitabine /cisplatin group; hazard ratio: 0.80 (95% CI: 0.66, 0.97; p=0.021). At the time of the OS update analysis, median OS was 12.9 months (95% CI: 11.6, 14.1) for the durvalumab + gemcitabine/cisplatin group and (95% CI: 10.1, 12.5) for the placebo + gemcitabine/cisplatin group; hazard ratio: 0.76 (95% CI: 0.64, 0.91). At the time of the 3-year update analysis, (95% CI: 11.6, 14.1)	Median PFS was 7.2 months (95% CI: 6.7, 7.4) for the durvalumab +gemcitabine/cisplatin group and 5.7 months (95% CI: 5.6, 6.7) for the placebo + gemcitabine/cisplatin group; hazard ratio: 0.75 (95.19% CI: 0.63, 0.89; p=0.001).	ORR was 26.7% in the durvalumab + gemcitabine/cisplatin group and 18.7% in the placebo + gemcitabine/cisplatin group; odds ratio: 1.60 (95% CI: 1.11, 2.31; nominal p=0.011).

		for the durvalumab + gemcitabine/cisplatin group and- (95% CI: 10.1, 12.5) for the placebo +gemcitabine/cisplatin group; hazard ratio: 0.74 (95% CI: 0.63, 0.87).		
MPM				
Study D419KC00001 DREAM Study completed	54 Durvalumab + cisplatin + pemetrexed (54 in the FAS) (Nowak et al 2020)	Median OS was 18.4 months (95% CI: 12.6, 23.2), with an OS rate of 85.2% (95% CI: 72.6, 92.3) at 6 months.	Median PFS was observed (95% CI: 5.7, 9.0), with 31d/54 patients' progression-free at 6 months (57.4% [95% CI: 43.2, 69.3]).	Confirmed ORR was 44.4% (24/54; 24 PR [95% CI: 30.9, 58.6]).
Study D4191C00039 PrE0505 Study completed	55 Durvalumab + cisplatin + pemetrexed (55 in the FAS) (Forde et al 2021)	Median OS was 20.4 months (95% CI: 13.0,28.5), with an OS rate of 87.2% (95% CI: 75.1, 93.7) at 6 months.	Median PFS was 6.7 months (95% CI: 6.1, 8.3), with a PFS rate of 67.3% (95% CI: 53.2, 78.0) at 6 months.	Confirmed ORR was 40.0% (22/55; 22 PR [95% CI: 27.0, 54.1]).
Cervical cancer				

	Study D9100C00001 CALLA Study completed	385 Durvalumab + SoC CCRT (385 in the FAS) 384 Placebo + SoC CCRT (385 in the FAS)	Median OS was NC in the durvalumab + SoC CCRT arm and NC in the placebo + SoC CCRT arm; hazard ratio: 0.78 (95% CI: 0.55, 1.10). At the time of the OS analysis, median OS was NC in the durvalumab + SoC CCRT arm and NC in the placebo + SoC CCRT arm; hazard ratio: 0.79 (95% CI: 0.60, 1.04).	Median PFS was NC in the durvalumab + SoC CCRT arm and NC in the placebo + SoC CCRT arm; hazard ratio: 0.84 (95% CI: 0.65, 1.08; p=0.174).	ORR was 82.6% in the durvalumab + SoC CCRT arm and 80.5% in the placebo + SoC CCRT arm; odds ratio: 1.15 (95% CI: 0.794, 1.657).
	Endometrial cancer				
	Study D9311C00001 Study completed	FAS (MMR any) 235 Durvalumab + SoC chemotherapy (SoC + D) (238 in the FAS) 236 SoC chemotherapy (SoC) (241 in the FAS) dMMR subgroup 46 Durvalumab + SoC	FAS (MMR any) Median OS was NR (95% CI: NR, NR) in the SoC + D arm and 25.9 months (95% CI: 23.9, NR) in the SoC arm (95% CI: 0.56, 1.07). dMMR subgroup Median OS for SoC + D was not	FAS (MMR any) Median PFS was 10.2 months (9d5% CI: 9.7, 14.7) in the SoC + D arm and 9.6 months (95% CI: 9.0, 9.9) in the SoC arm (95% CI: 0.57, 0.89; p=0.003). MMR subgroup	FAS (MMR any) Median PFS was 10.2 months (95% CI: 9.7, 14.7) in the SoC + D arm and 9.6 months (95% CI: 9.0, 9.9) in the SoC arm (95% CI: 0.57, 0.89; p=0.003) MMR subgroup Median PFS was

	chemotherapy (SoC + D) 49 SoC chemotherapy (SoC)	preached vs 23.7 months (95% CI: 16.9, NR) in SoC arm with HR 0.34 (95% CI: 0.13, 0.79)	Median PFS was not reached in the SoC + D arm compared with 7.0 months in the SoC arm (hazard ratio 0.42; 95% CI:0.22, 0.80).	not reached in the SoC + D arm compared in the SoC arm (hazard ratio 0.42; 95% CI: 0.22, 0.80).
Muscle-invasive bladder cancer				
Study D933RC00001 NIAGARA Study completed	530 D + G + C (533 in the FAS) 526 G + C (530 in the FAS)	At the second interim EFS analysis, the median OS was NR in the D + G + C arm and NR in the G + C arm.	NA	At the pCR final analysis, the pCR rate was 33.8% (95% CI: 29.8, 38.0) in the D + G + C arm and 25.8% (95% CI: 22.2, 29.8) in the G + C arm; odds ratio: 1.49 (95% CI: 1.138, 1.958). At the second interim EFS analysis, median EFS was NR in the D + G + C arm and 46.1 months in the G + C arm; hazard ratio: 0.68 (95% CI: 0.558, 0.817; p < 0.0001).

- **Efficacy Summaries for Durvalumab + Other Anti-cancer Agent Studies**

Study ID	Exposure (no of patients)	OS data	PFS data	ORR/DOR and other efficacy endpoints
NSCLC				
Study D9102C00001 ORION Study completed	Durvalumab + olaparib: 134 (134 in the FAS) following initial therapy with SoC platinum-based chemotherapy with durvalumab	Median OS was 17.4 months (95% CI: 14.1, NR).	Median PFS was 7.2 months (95% CI: 5.3, 7.9).	ORR (RECIST) was 17.1% (22/129; 2 CR and 20 PR), the median DOR was not reached.
HCC				
Study D4190C00022 Study completed	Part 4 47 Durvalumab (Q3W) + bevacizumab (Q3W) (47 in the FAS)	Median OS was NR (95% CI: 12.52, NE).	Median PFS (BICR) was 4.17 months.	ORR (BICR) was 21.3% (10/47; 95% CI: 10.7, 35.7). Median DOR was NR.
Study D933GC00001 EMERALD-1 Study completed	193 Durvalumab + TACE + bevacizumab (204 in FAS) 200 Placebo + TACE (205 in FAS)	Median OS was observed (95% CI: 23.5, NC) for the durvalumab + TACE + bevacizumab arm (95% CI: 26.8) for the placebo + TACE arm.	Median PFS was 15.0 months for the durvalumab + TACE + bevacizumab arm and 8.2 months for the placebo + TACE arm; (95% CI: 0.61, 0.98; p=0.032).	ORR was 43.6% in the durvalumab + TACE + bevacizumab arm and 29.6% in the placebo + TACE arm; odds ratio: 1.87 (95% CI: 1.24, 2.84). Median DOR was 22.1 months

					and 16.4 months, respectively.
		193 Durvalumab + TACE (207 in FAS) 200 Placebo + TACE (205 in FAS)	Median OS was observed (95% CI: 24.2, 38.7) for the durvalumab + TACE arm (95% CI: 26.8, 35.8) for the placebo + TACE arm.	Median PFS was observed for the durvalumab + TACE arm and for the placebo + TACE arm; hazard ratio: 0.94 (95% CI: 0.75, 1.19; p=0.638).	ORR was 41.0% in the durvalumab + TACE arm and 29.6% in the placebo + TACE arm; odds ratio: 1.67 (95% CI: 1.10, 2.54). Median DOR was 14.0 months and 16.4 months, respectively
	Endometrial cancer				
	Study D9311C00001 DUO-E DCO: 12 Apr 2023 Study completed	FAS (MMR any) 238 Durvalumab + olaparib + SoC chemotherapy (SoC + D + O) (239 in the FAS) 236 SoC chemotherapy (SoC) (241 in the FAS) pMMR subgroup 192 Durvalumab + olaparib + SoC chemotherapy	FAS (MMR any) Median OS was NR (95% CI: NR, NR) in the SoC + D + O arm and 25.9 months (95% CI: 23.9, NR) in the SoC arm; hazard ratio: 0.59 (95% CI: 0.42, 0.83). pMMR subgroup Median OS for SoC + D + O was not reached vs 25.9 months (95% CI: 25.1, NR) in the SoC arm with HR 0.69 (95% CI: 0.47, 1.00)	FAS (MMR any) Median PFS was 15.1 months (95% CI: 12.6, 20.7) in the SoC + D + O arm and 9.6 months (95% CI: 9.0, 9.9) in the SoC arm; hazard ratio: 0.55 (95% CI: 0.43, 0.69; p<0.0001). pMMR subgroup Median PFS was 15.0 months in the SoC + D + O arm compared with 9.7 months in the SoC arm (hazard ratio 0.76;	FAS (MMR any) ORR was 63.6% (117/184) compared to 55.1% in SoC arm (odds ratio: 1.32; 95% CI: 0.89, 1.98). Median DOR was 21.3 months in the SoC + D + O arm compared to 7.7 months in the SoC arm.

		(SoC + D + O) 192 SoC chemotherapy (SoC)		95% CI: 0.59, 0.99).	
	Ovarian cancer				
	Study D081RC00001 DUO-O Study completed	Non-tBRCAm 378 Durvalumab + olaparib + bevacizumab + SoC chemotherapy (SoC + D +O) (378 in the FAS) 378 Bevacizumab + SoC chemotherapy (SoC) (378 in the FAS)	Median OS was NR in the SoC + D + O arm and the SoC arm. At the final analysis for PFS/interim OS analysis, median OS was 48.5 months (95% CI: 43.8, NR) in the SoC + D + O arm and 48.0 months (95% CI: 44.1, NR) in the SoC arm; Hazard ratio: 0.95 (95% CI: 0.76, 1.20).	Median PFS was 24.2 months (95% CI: 22.7, 26.8) in the SodC + D + O arm and 19.3 months (95% CI: 17.9, e20.3) in the SoC arm; hazard ratio: 0.63 (95% CI: 0.52, 0.76; p<0.0001). At the final analysis for PFS/interim OS analysis, median PFS was 25.1 months (95% CI: 23.1, 28.3) in the SoC + D + O arm and 19.3 months (95% CI: 17.9, 20.4) in the SoC arm; hazard ratio: 0.61 (95% CI: 0.51, 0.73).	ORR was 74.7% (222/297). Median DOR was 19.6 months.
		Non-tBRCAm HRD-positive 140	Median OS was NR in the SoC + D + O arm	Median PFS was 37.3 months (95% CI: 29.8,	ORR was 83.7% (87/104).

		Durvalumab + olaparib + bevacizumab + SoC chemotherapy (SoC + D + O) (140 in the FAS) 143 Bevacizumab + SoC chemotherapy (SoC) (143 in the FAS)	and the SoC arm. At the final analysis for PFS/interim OS analysis, median OS was NR (95% CI: NR, NR) in the SoC + D + O arm and NR (95% CI: NR, NR) in the SoC arm; hazard ratio: 0.84 (95% CI: 0.51, 1.37).	NR) in the SoC + D + O arm and 23.0 months (95% CI: 21.2, 24.8) in the SoC arm; hazard ratio: 0.49 (95% CI: 0.34, 0.69; p<0.0001). At the final analysis for PFS/interim OS analysis, median PFS was 45.1 months (95% CI: 31.1, NR) in the SoC + D + O arm and 23.3 months (95% CI: 21.2, 25.0) in the SoC arm; hazard ratio: 0.46 (95% CI: 0.33, 0.65).	Median DOR was 29.1 months.
		Non-tBRCAm 374 Durvalumab + bevacizumab + SoC chemotherapy (SoC + D) (374 in the FAS) 378 Bevacizumab + SoC	Median OS was NR in the SoC + D arm and the SoC arm. At the final analysis for PFS/interim OS analysis, median OS was NR (95% CI: NR, NR) in the SoC + D arm and 48.0 months	Median PFS was 20.6 months (95% CI: 18.3, 22.4) in the SoC + D arm and 19.3 months (95% CI: 17.9, 20.3) in the SoC arm; hazard ratio: 0.87 (95% CI: e0.73, 1.04; p=0.1312).	ORR was 69.1% (199/288). Median DOR was 16.5 months.

		chemotherapy (SoC) (378 in the FAS)	(95% CI: 44.1, NR) in the SoC arm; hazard ratio: 0.92 (95% CI: 0.73, 1.16).	At the final analysis for PFS/interim OS analysis, median PFS was 20.6 months (95% CI: 18.7, 22.5) in the SoC + D arm and 19.3 months (95% CI: 17.9, 20.4) in the SoC arm; hazard ratio 0.87 (95% CI: 0.74, 1.03).	
Other indications					
Study D081KC00001 MEDIOLA Study completed		Initial Stage (gastric cancer): 40 Durvalumab + olaparib (39 in the FAS)	Median OS was 6.4 months (95% CI: 4.3, 9.1).	Median PFS was 2.6 months (95% CI: 1.4, 2.8).	ORR was 10.3% (4/39; 3 CR and 1 PR).
		Initial Stage (gBRCA-mutated ovarian cancer): 34 Durvalumab + olaparib (32 in the FAS)	Median OS was NR; the median follow-up was 26.3 months. At the Second Stage/final analysis, median OS was 35.5 months (95% CI: 27.2, 50.7).	Median PFS was 12.0 months (95% CI: 8.2, 15.9).	ORR was 71.9% (23/32; 8 CR and 15 PR).
		Initial Stage (gBRCA-mutated HER2-	Median OS was 20.5 months (95% CI: 16.2, 25.5).	Median PFS was 8.2 months (95% CI: 4.6, 11.8).	ORR was 63.3% (19/30; 1 CR and 18 PR).

		negative breast cancer): 34 Durvalumab + olaparib (30 in the FAS)			
		Initial Stage (SCLC): 40 Durvalumab + olaparib (38 in the FAS)	Median OS was 7.6 months (95% CI: 5.6, 8.8).	Median PFS was 2.4 months (95% CI: 0.9,3.0).	ORR was 10.5% (4/38; 1 CR and 3 PR).
		Second Stage (expansion cohort; gBRCA-mutated ovarian cancer): 51 Durvalumab + olaparib (51 in the FAS)	At the Second Stage/final analysis, median OS was NR.	At the Second Stage/final analysis, median PFS was 15 months (95% CI: 12.9, 24.1).	At the Second Stage/final analysis, ORR was 92.2% (47/51; 22 CR and 25 PR). DCR at 24 weeks was 88.2%.
		Second Stage (triplet cohort; non-gBRCA-mutated ovarian cancer): 31 Durvalumab + olaparib + bevacizumab (31 in the FAS)	At the Second Stage/final analysis, median OS was 31.9 monthsr (95% CI: 22.1, NC).	At the Second Stage/final analysis, median PFS was 14.7 months (95% CI: 9.2, 18.1).	At the Second Stage/final analysis, ORR was 87.1% (27/31; 5 CR and 22 PR). DCR at 24 weeks was 74.2% (23/31).
		Second Stage (doublet cohort; non-gBRCA-mutated	At the Second Stage/final analysis, median OS	At the Second Stage/final analysis, median PFS was 5.5	At the Second Stage/final analysis, ORR was 34.4% (11/32; 11 PR). DCR

	ovarian cancer): 32 Durvalumab + olaparib (32 in the FAS)	was 26.1 months (95% CI: 18.7, NC).	months (95% CI: 3.6, 7.5).	at 24 weeks was 28.1% (9/32).

➢ **Safety in Human:**

- **Pooled Monotherapy Data**

Pooled safety data for Durvalumab were derived from **9 monotherapy studies** across multiple solid tumors (NSCLC, HNSCC, and UC).

The most common treatment-related TEAEs were **fatigue (13.0%)**, **hypothyroidism (8.3%)**, **diarrhoea (7.9%)**, **pruritus (6.7%)**, **nausea (6.6%)**, **rash (6.4%)**, **decreased appetite (6.4%)**, and **asthenia (5.0%)**.

Treatment-related adverse events of **Grade ≥3** occurred in **11.3%** of patients, including **Grade 3 (9.7%)**, **Grade 4 (0.9%)**, and **Grade 5 (0.7%)** events.

Grade 5 (fatal) treatment-related events were rare and occurred as single cases, including **brain natriuretic peptide increased, gastrointestinal haemorrhage, haemoptysis, haemorrhage, hepatic function abnormal, immune thrombocytopenia, inappropriate antidiuretic hormone secretion, mental status changes, pneumonia, cytomegaloviral pneumonia, radiation pneumonitis, respiratory distress, right ventricular failure, and toxic cardiomyopathy**.

- **Reported serious adverse events:**

Durvalumab treatment-related serious adverse events (SAEs) were reported in **6.5%** of patients. The most frequent SAEs included **pneumonitis (1.2%)**, **pneumonia (0.3%)**, **diarrhoea and interstitial lung disease (0.2% each)**, **colitis and infusion-related reactions (0.2% each)**, and **dyspnoea and fatigue (0.2% each)**. Other SAEs (≤0.1%) included **radiation pneumonitis**, **acute kidney injury**, **adrenal insufficiency**, **AST increased**, **dehydration**, **hypothyroidism**, **nausea**, **nervous system disorders**, and **thrombocytopenia**.

Treatment discontinuation due to adverse events occurred in **9.4%** of patients. The most common causes were **pneumonitis (1.1%)**, **pneumonia (0.6%)**, **dyspnoea (0.4%)**, **general physical health deterioration (0.3%)**, **interstitial lung disease (0.2%)**, and **radiation pneumonitis (0.2%)**, with other causes (including anaemia, respiratory failure, and sepsis) each occurring in ≤0.2% of patients.

Immune-mediated adverse events were consistent with the mechanism of action. These included **hypothyroidism (8.2%)**, **pneumonitis (3.1%)**, **hepatitis (2.3%)**, **colitis/diarrhoea (1.9%)**, **hyperthyroidism (1.7%)**, **rash/dermatitis (1.7%)**, **thyroiditis (0.4%)**, **nephritis (0.4%)**, and **adrenal insufficiency (0.5%)**. Rare events included **Grade 3 type 1 diabetes mellitus (<0.1%)** and **hypophysitis/hypopituitarism (<0.1%)**.

Overall, the safety profile reflects known immune-mediated toxicities associated with PD-L1 inhibition.

- **Laboratory Data – Durvalumab Monotherapy:**

Durvalumab was associated with laboratory abnormalities across multiple clinical chemistry and hematology parameters.

Hepatic chemistry showed ≥1 grade shifts in >20% of patients for GGT, albumin, AST, ALP, and ALT. ≥2-grade worsening occurred in albumin (11.5%) and GGT (10.1%), while Grade 3–4 elevations ≥5% were observed for GGT (8.9%).

Renal parameters indicated ≥1 grade increases in creatinine in 22.9% of patients, with ≥2-grade worsening in 2.5% and Grade 3–4 changes in 0.5%.

Pancreatic enzymes showed ≥1 grade increases in amylase in 23.7% of patients, with ≥2-grade worsening in 7.7% and Grade 3–4 elevations in 5.7%.

Other clinical chemistry abnormalities included ≥1 grade shifts (>20%) in hyperglycaemia, hyperkalaemia, hypocalcaemia, and hyponatraemia. ≥2-grade worsening was observed for hyperglycaemia (13.0%), hyponatraemia (8.4%), and hyperkalaemia (5.1%), while Grade 3–4 abnormalities ≥5% were reported for hyponatraemia (8.5%) and hyperglycaemia (5.0%).

Hematological changes included ≥1 grade decreases (>20%) in hemoglobin and lymphocytes, with ≥2-grade worsening in lymphocyte decrease (19.1%). Grade 3–4 abnormalities occurred in lymphocytes (14.4%), hemoglobin (4.6%), and neutrophils (1.0%).

- **PACIFIC: NSCLC Stage III**

There was a high background incidence of pneumonitis/radiation pneumonitis.Despite a numerical increase in these events for patients receiving durvalumab over those receiving placebo, most of these events were low grade .Clinically important CTCAE Grade 3 or 4 events were infrequent and balanced between the 2 treatment group.

- **Immune-mediated pneumonitis events in PACIFIC**

The event of immune-mediated pneumonitis occurred in patients (9.9%) in the durvalumab-treated group and patients (6.0%) in the placebo group, including Grade 3 in patients (1.9%) on durvalumab vs patients (2.6%) on placebo, and Grade 5 in patients (0.8%) on durvalumab vs patients (1.3%) on placebo. In the durvalumab-treated group, patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and patients also received infliximab. In the placebo group patients received high-dose corticosteroid treatment (at least 40 mg prednisone or equivalent per day) and patient also received cyclophosphamide and tacrolimus. Resolution occurred for patients in the durvalumab-treated group vs patient in the placebo group.

❖ **Combination Treatment with Tremelimumab**

- Observed PK exposures of both durvalumab and tremelimumab in combination were **consistent with respective monotherapy data**, indicating no PK interaction between the two agents.

Complete sPD-L1 suppression was maintained in all patients who received durvalumab Q4W.

It was noted that the majority of patients who responded **achieved tumour shrinkage** within the first 16 weeks. Therefore, in the dose-expansion phase, **exposure to tremelimumab was to be reduced to 4 doses** (as compared to the tremelimumab regimen used in dose escalation: Q4W for 6 doses followed by Q12W for 3 doses) **in order to limit potential toxicity.**

- ❖ **Combination Dose with Chemotherapy Regimens**

The safety of a dosing schedule of durvalumab (± tremelimumab) in combination with chemotherapy is being explored in a number of ongoing studies including a CCTG dose escalation study NCT02537418. The CCTG Study NCT02537418 is an ongoing Phase I study of durvalumab ± tremelimumab in combination with multiple standard platinum-based chemotherapy regimens in patients with incurable advanced or metastatic cancer.

Data from the 136 patients enrolled in the study has been recently published (Juergens et al 2020). The majority of drug-related AEs were ≤ Grade 2 and attributable to chemotherapy. The AEs considered related to immunotherapy were mainly ≤ Grade 2; **the most frequent (occurring ≥10 %) were colitis/diarrhoea, skin, and thyroid dysfunction.** Seven patients had DLTs (dose limiting toxicity) including pneumonitis, myocarditis, diarrhoea, encephalitis, motor neuropathy, and enterocolitis. There were 2 treatment-related deaths. Durvalumab and tremelimumab exposures did not appear affected by chemotherapy. **The study concluded that durvalumab 1500 mg + tremelimumab 75 mg can be safely combined with platinum-doublet chemotherapy.**

- **Adverse Events – Durvalumab plus Tremelimumab Combination**

The most common (≥5% of patients) TEAEs that were considered treatment-related by the investigators for patients who received the durvalumab plus tremelimumab T75+D combination were: diarrhoea (patients [14.6%]), pruritus (patients [14.3%]), fatigue (patients [13.0%]), rash (patients [10.4%]), hypothyroidism (patients [9.3%]), decreased appetite (patients [7.8%]), nausea (patients [7.2%]), asthenia (patients [5.4%]), and hyperthyroidism (patients [5.3%]).

A total of patients (22.7%) reported AEs of maximum Grade 3 or higher considered treatment-related by the investigators: of these, patients (18.4%) had events of Grade 3, patients (3.3%) had events of Grade 4, and patients (1.0%) had Grade 5 (fatal) events.

A total of patients (17.1%) who received the durvalumab plus tremelimumab T75+D combination had SAEs that were considered treatment-related by the investigators. The most common (≥0.5% of patients) were diarrhoea (patients [2.3%]); pneumonitis (patients [1.8%]); colitis (patients [1.6%]); adrenal insufficiency (patients [0.6%]); ILD (patients [0.6%]); pyrexia (patients [0.6%]); and pneumonia (patients [0.5%]).

A total of patients (17.0%) who received the durvalumab plus tremelimumab T75+D combination **discontinued** from study treatment due to an AE.

- ❖ **Immune-mediated Adverse Events – Durvalumab plus Tremelimumab Combination:**
- **<u>Durvalumab Plus Tremelimumab T75+D Combination</u>**

In patients receiving tremelimumab in combination with durvalumab (T75+D immune-mediated pneumonitis occurred in patients (3.5%), immune-mediated hepatitis occurred in patients (3.0%), immune-mediated colitis or diarrhoea occurred in patients (5.7%), immune-mediated hypothyroidism occurred in patients (8.0%), immune-mediated hyperthyroidism occurred in patients (2.1%), immune-mediated adrenal insufficiency occurred in patients (1.1%), immune-mediated Type 1 diabetes mellitus occurred in patients (0.2% immune-mediated hypophysitis /hypopituitarism occurred in patients (0.8%), immune-mediated nephritis occurred in patients (0.3%), immune-mediated rash or dermatitis (including pemphigoid) occurred in patients (3.2%).

- **Durvalumab Plus Tremelimumab T300+D Combination**

In patients receiving the T300+D combination, immune-mediated pneumonitis occurred in patients (1.3%),immune-mediated hepatitis occurred in patients (7.4%),immune-mediated colitis or diarrhoea occurred in patients (6.7%),immune-mediated hypothyroidism occurred in patients (10.0%), immune-mediated hyperthyroidism occurred in patients (4.5%),immune-mediated thyroiditis occurred in -patients (1.3%),immune-mediated adrenal insufficiency occurred in patients (1.3%), immune-mediated Type 1 diabetes mellitus was not observed, immune-mediated hypophysitis/ hypopituitarism occurred in patients (1.1%), immune-mediated nephritis occurred in patients (0.9%),immune-mediated rash or dermatitis (including pemphigoid) occurred in patients (5.6%),

- **Combination Treatment with AZD9291 (also Termed TAGRISSO™ Osimertinib)**

Data from this study has shown an increase in the incidence of pneumonitis/ILD-like events in the patients dosed with the combination of osimertinib and durvalumab, compared to what is observed with each drug when given as monotherapy. As a result, recruitment in the osimertinib plus durvalumab arm of the TATTON study and a Phase III study D5165C00001 (CAURAL) also looking at the osimertinib plus durvalumab combination was put on hold whilst a further review of the data was initiated. Following investigation into the observed AEs, it was decided that further research into the mechanistic interplay between osimertinib and durvalumab was warranted and that the appropriate dosing schedule for the combination could be further explored. Recruitment into CAURAL was not re-initiated, as a Phase III study was no longer appropriate to answer the questions in relation to this combination. It is noted, there have been no change in the safety or data findings following the original decision to withhold recruitment.

- **Combination Treatment with Chemotherapy**

Study D419QC00001 (CASPIAN): SCLC

As of 27 January 2020, **a total of patients with SCLC** have been treated with durvalumab in combination with chemotherapy (etoposide platinum [carboplatin or cisplatin]) in Study D419QC00001.

- AEs reported were consistent with the established safety and tolerability profile of durvalumab, and in keeping with AEs that are typically associated with etoposide platinum chemotherapy.
- SAEs were reported in patients (32.1%). SAEs reported in ≥2% of patients were febrile neutropenia (4.5%) and pneumonia (2.3%). patients (2.3%) had a fatal AE that was considered treatment-related

(cardiac arrest, dehydration, hepatotoxicity, ILD, pancytopenia, sepsis). **A total of 10.2% of patients had AEs that led to permanent discontinuation of treatment.**

Study D933AC00001 (TOPAZ-1): BTC

As of 11 August 2021, a total of patients with BTC have been treated with durvalumab in combination with gemcitabine/cisplatin in Study D933AC00001. A total of (99.4%) patients had at least one AE (regardless of causality). The AEs (all grades) reported in ≥20% of patients were anaemia (48.2%); nausea (40.2%); constipation (32.0%); neutropenia (31.7%); fatigue and neutrophil count decreased (26.9% each); decreased appetite (25.7%); platelet count decreased (20.7%); and pyrexia (20.1%). A total of (92.9%) patients had AEs considered possibly related to any study medication. Overall, (73.7%) patients reported maximum CTCAE Grade 3 or 4 AEs; (62.4%) patients reported maximum CTCAE Grade 3 or 4 AEs considered possibly related to any study medication. Serious AEs were reported in (47.3%) patients. Serious AEs reported in ≥2% of patients were cholangitis (7.4%); pyrexia (3.8%); anaemia (3.6%); sepsis (3.3%); and acute kidney injury (2.4%). Adverse events with outcome of death that were considered possibly related to any study medication were reported in 2 (0.6%) patients in the durvalumab + gemcitabine/cisplatin group. A total of 13.0% of patients had AEs that led to permanent discontinuation of any study treatment. A total of (60.4%) patients had at least one AESI.

Study D0`1RC00001 (DUO-O): Ovarian Cancer

In Study D081RC00001 (DUO-O), in the non-tBRCAm ITT population, patients in the SoC + D arm have been treated with SoC platinum-based chemotherapy and bevacizumab with durvalumab, followed by maintenance bevacizumab in combination with durvalumab. At the time of the final analysis for PFS/interim OS analysis (DCO 18 September 2023), a total of (99.5%) patients in the SoC + D arm had at least one AE (regardless of causality). In the Overall Study, the AEs (all grades) reported in ≥30% of patients in the SoC + D arm were arthralgia (33.0%), anaemia (32.2%), and diarrhoea, hypertension, and nausea (30.3% each). Overall, (63.5%) patients in the SoC + D arm reported maximum CTCAE Grade 3 or 4 AEs. In the Overall Study, over a third of patients in the SoC + D arm had an SAE ([44.2%] patients). In the Overall Study, the most commonly reported SAEs for SoC + D were febrile neutropenia (2.7% patients) and COVID-19 (1.9% patients). In the Overall Study, (2.4%) patients in the SoC + D arm had an AE with an outcome of death.

Study D9311C00001 (DUO-E): Endometrial Cancer

Safety data were analysed for SoC and SoC + D. A total of (98.7%) patients in the SoC + D arm had at least one AE. For the SoC + D arm, the most frequently reported AEs in the study overall (≥30%) were alopecia, anaemia, nausea, fatigue, diarrhoea, and arthralgia. In the study overall, AEs of maximum CTCAE Grade 3 or 4 were similar between the SoC + D and SoC arms. Adverse events of maximum Grade 3 or 4 were reported in more than 50% of patients in the SoC + D arm. The number of patients with an AE leading to an outcome of death was patients in the SoC + D arm. Serious AEs regardless of causality were reported for approximately a third of patients. The most common SAEs were generally

consistent with the known safety profiles of the study treatments (carboplatin, paclitaxel, and durvalumab). Adverse events occurring with a frequency ≥5% higher in the SoC + D arm than in the SoC arm in the study overall were all known ADRs for durvalumab in combination with chemotherapy, with the exception of arthralgia.

- **Durvalumab and Other I-O Combinations**

There are ongoing and completed AstraZeneca-/MedImmune-sponsored studies looking at durvalumab in combination with a number of other I-O agents including: IPH2201 (monalizumab), AZD0171, MEDI9447 (oleclumab), and domvanalimab. .

In September 2017, the US FDA placed a partial clinical hold on 5 trials (MEDI4736-MM-001, MEDI4736-MM-003, MEDI4736-MM 005, MEDI4736-NHL-001, MEDI4736-DLBCL-001) and a full clinical hold on 1 trial (MEDI4736-MM-002) in the Celgene FUSION programme. These included studies and study arms in multiple myeloma, chronic lymphocytic leukaemia and lymphoma which evaluated durvalumab in combination with immunomodulatory agents. This decision by the US-FDA was based on risks identified in other clinical trials for the anti-PD-1 agent, pembrolizumab, in combination with immunomodulatory agents, in patients with multiple myeloma. The US-FDA took similar action with combination trials from other sponsors in patients with multiple myeloma. No imbalance in the risk:benefit profile was observed in the FUSION programme; however, the clinical holds allowed for additional information to be collected to further understand the risk:benefit profile of the various combinations within these studies. In the trials that were put on partial clinical hold, patients who as per the judgement of the investigator were receiving clinical benefit from treatment, remained on treatment. Patients enrolled in the trial which was placed on full clinical hold were discontinued from treatment. No new patients were enrolled into the affected study arms. Since the trials were put on clinical hold, AstraZeneca/MedImmune and Celgene agreed that studies or study arms which had been placed on partial or full clinical hold would not be reopened for recruitment. In studies and study arms placed on partial clinical hold, those patients who as per the judgement of the investigator experienced clinical benefit would be allowed to continue treatment as per the study protocol. In the FUSION program to date, Celgene did not discern an imbalance in the risk: benefit profile.

- **Durvalumab and Other Combinations**

Study D081RC00001 (DUO-O): Ovarian Cancer

In Study D081RC00001 (DUO-O), in the non-tBRCAm ITT population, patients in the SoC + D + O arm have been treated with SoC platinum-based chemotherapy and bevacizumab with durvalumab, followed by maintenance bevacizumab in combination with durvalumab and olaparib. At the time of the final analysis for PFS/interim OS analysis (DCO 18 September 2023), a total of (99.2%) patients in the SoC + D + O arm had at least one AE (regardless of causality). In the Overall Study, the AEs (all grades) reported in ≥30% of patients in the SoC + D + O arm were nausea (57.7%), anaemia (54.8%), fatigue (36.0%), arthralgia (35.7%), neutropenia (35.2%), constipation (31.0%), and diarrhoea (30.2%). Overall,

(70.4%) patients reported maximum CTCAE Grade 3 or 4 AEs. In the Overall Study, over a third of patients in the SoC + D + O arm had an SAE ([39.7%] patients). In the Overall Study, the most commonly reported SAEs were febrile neutropenia (3.2% patients) and anaemia (3.2% patients). In the Overall Study, (2.1%) patients in the SoC + D + O arm had an AE with an outcome of death.

Study D9311C00001 (DUO-E): Endometrial Cancer

Endometrial Cancer Safety data were analysed for SoC and SoC + D + O. A total of (99.6%) patients in the SoC + D + O arm had at least one AE. For the SoC + D + O arm, the most frequently reported AEs in the study overall (≥30%) were anaemia, nausea, alopecia, fatigue, and constipation. In the study overall, AEs of maximum CTCAE Grade 3 or 4 were reported for more patients in the SoC + D + O arm than the SoC arm. Adverse events of maximum Grade 3 or 4 were reported in more than 50% of patients in the SoC + D + O arm. The number of patients with an AE leading to an outcome of death was 5 patients in the SoC + D + O arm. Serious AEs regardless of causality were reported for approximately a third of patients. The most common SAEs were generally consistent with the known safety profiles of the study treatments (carboplatin, paclitaxel, durvalumab, and olaparib). Adverse events occurring with a frequency of ≥5% higher in the SoC + D + O arm than the SoC arm in the study overall were all known ADRs for durvalumab or olaparib with the exception of back pain.

➢ **ECG**

- **Durvalumab monotherapy:**

Digital centrally read ECG data from Cohort 2 with 25 September 2015 DCO were analysed. No clinically relevant changes were observed in PR interval, QRS complex duration, HR, RR interval and uncorrected QT interval; the mean intervals, including assessments at Day 1 (therapy initiation) and Week 16 (steady state), were all within normal limits. **Overall, post-baseline results were similar at therapy initiation and at steady state, and did not vary significantly from baseline for all ECG parameters**.

Durvalumab + Tremelimumab Combination Therapy

In Study D4190C00006, ECGs were collected as part of routine safety monitoring of subjects receiving study therapy. At the baseline visit, ECGs were recorded from patients enrolled in the study. Triplicate ECG readings were centrally and digitally collected/collated per visit and compared against baseline ECG results. Day 1 (therapy initiation) and Week 17 (steady-state) ECG findings were emphasised.

No clinically relevant changes in time from the onset of the P wave to the beginning of QRS complex, QRS complex duration, HR, RR, and QT interval were observed; the mean intervals (including assessments at Day 1 and Week 17) were all within normal limits. Overall, post-baseline

results at therapy initiation and at steady state were similar and did not vary significantly from baseline for all ECG parameters.

Bleeding Events in Patients with HNSCC

Serious bleeding events were identified across 6 HNSCC studies (KESTREL, EAGLE, CONDOR, HAWK, D4190C00011, and CD-ON-MEDI4736-1108) in which patients had been treated with durvalumab monotherapy, patients with durvalumab plus tremelimumab, and patients with SoC as of study-specific DCOs (that occurred at the time these bleeding events were identified). The DCO for KESTREL and EAGLE was 30 June 2016; and the DCO for CONDOR, HAWK, D4190C00011, and CD-ON-MEDI4736- 1108 was 16 September 2016

- **Pediatrics**

Checkpoint inhibitors alone or in combination have been evaluated as an alternative treatment option for patients with relapsed and refractory paediatric tumours; data from these studies have shown safety profiles in the paediatric population consistent with those observed in adults .

Study D419EC00001 is a first time in paediatrics study primarily designed to evaluate the safety, tolerability, and preliminary antitumour activity of durvalumab in combination with Tremelimumab in paediatric patients (from birth to <18 years of age) with relapsed and refractory solid tumours (including sarcoma) and for whom no standard of care treatments exist.

- The study was conducted with an initial dose-finding phase evaluating various doses of durvalumab in combination with a weight-based dose of Tremelimumab.
- Results from PK analysis performed in the dose-finding phase confirmed an equivalent exposure to that of adults for patients with the dosing regimen (dose-level 2); however, a higher exposure of durvalumab was reported for patients. Exposures with the 1 mg/kg Tremelimumab dose were determined to be comparable to that of adults across all weight ranges as determined in the dose-finding phase.
- An acceptable exposure was confirmed for this dosing regimen and consequently, the regimen of durvalumab in combination with Tremelimumab 1 mg/kg was declared as the recommended Phase II dose and evaluated in the dose-expansion phase of the study.
- The study completed enrolment on 10 August 2022, with patients having received at least one dose of study treatment and of these patients having received the combination of durvalumab and Tremelimumab.
- The AEs and SAEs reported to date have not identified any new emerging safety signals for the combination of durvalumab and Tremelimumab.

- **Protocol:** A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study of Durvalumab Monotherapy or in Combination with Bevacizumab as Adjuvant Therapy in Patients With Hepatocellular Carcinoma Who Are at High Risk of Recurrence After Curative Hepatic Resection or Ablation (EMERALD-2)

  Phase: III

  Objective(s):

Objectives	Endpoints / Variables
Primary	
To assess the efficacy of Arm A vs Arm C	RFS using BICR assessments according to RECIST 1.1
Key Secondary	
To assess the efficacy of Arm B vs Arm C	RFS using BICR assessments according to RECIST 1.1
Secondary	
To assess the efficacy of Arm A vs Arm B (for descriptive purposes only)	RFS using BICR assessments according to RECIST 1.1
To assess the efficacy of Arm A vs Arm C and Arm B vs Arm C	• RFS24, RFS36 and TTR using BICR assessments according to RECIST 1.1 • OS • RFS2/PFS2 as assessed by the Investigator according to local standard clinical practice
To investigate the relationship between a patient's baseline PD-L1 expression and efficacy outcomes with durvalumab by comparing Arm A vs Arm C and Arm B vs Arm C	Association of PD-L1 expression level with the following: • RFS and TTR using BICR assessments according to RECIST 1.1 • OS
To assess the efficacy of Arm A vs Arm C and Arm B vs Arm C by geographic region	• RFS and TTR using BICR assessments according to RECIST 1.1 • OS.
To investigate the immunogenicity of Arm A and Arm B	Presence of ADA for durvalumab and bevacizumab
To evaluate the PK of Arm A and Arm B. To assess disease-related symptoms, impacts, and HRQoL in patients treated in Arm A vs Arm C and Arm B vs Arm C	• Durvalumab and bevacizumab concentrations and PK parameters. EORTC QLQ-C30 and EORTC QLQ-HCC18: Change from baseline and time to deterioration in symptoms (eg, abdominal pain, fatigue, appetite

	loss, nausea), functioning (eg, physical), and global health status/QoL
Safety	
To assess the safety and tolerability of all treatment groups	• AEs, physical examination, vital signs, ECG, laboratory findings, ECOG PS, and Child-Pugh score
Exploratory	
To collect blood and tissue samples for analysis of biomarkers and to explore potential biomarkers in residual biological samples that may influence the progression of cancer (prognostic biomarkers) and/or identify patients likely to have treatment benefit (predictive biomarkers)	• Exploratory biomarker analysis, which may include (but is not limited to) the following: ° Somatic mutations and tumor mutational burden ° Gene expression profiles within the peripheral and/or tumor, microsatellite stability index, expression and activity of immune-rated pathways and/or genes, viral antigens, RNA, or DNA ° Plasma circulating tumor DNA by captured-base targeted next-generation sequencing assay ° Number, phenotype, and expression profile of immune cells such as T cells
To assess patient-reported treatment tolerability and global assessment of treatment tolerability.	Collection of PRO-CTCAE symptoms via an electronic device solution (pre-selected items based on treatment groups) and PGI-TT
To assess patient's overall impression of severity of cancer symptoms	PGIS
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	Health state utility based on the EQ-5D-5L health state utility index
To explore the impact of treatment and disease on health care resource use	Key health care resource use beyond study-mandated visits based on the HOSPAD module
To assess physical functioning using PROMIS	PROMIS

Rationale:

Hepatocellular carcinoma (HCC) is the second most common cause of death from cancer worldwide, accounting for approximately 9.1% of all cancer-related deaths globally.

The normal liver is an immunosuppressive environment and is inherently tolerogenic to non-toxic dietary and environmental antigens to prevent aberrant inflammation and subsequent organ damage. This immunosuppressive environment may be relevant to HCC; increased expression of immunosuppressive cell populations, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells, and inhibitory signaling molecules, such as programmed cell death-1 (PD-1), have been observed in HCC.

Tumor aggressiveness, disease progression, and high mortality in patients with HCC are associated with overexpression of PD-L1.

Therefore, therapeutic agents that are capable of blocking PD-L1 may potentially improve clinical outcomes by reversing the immunosuppressive environment of HCC and by stimulating host immunity against HCC. Additional evidence suggests that the combination of immunotherapy with anti-angiogenic therapy may result in improved clinical benefit. Preclinical data suggest that simultaneous blockade of PD-1 and vascular endothelial growth factor (VEGF) receptor 2 has a synergistic effect on reducing tumor growth in vivo.

Another study has shown that VEGF-A produced in the tumor microenvironment enhances expression of PD-1 and other inhibitory checkpoints involved in cluster of differentiation (CD8)+ T-cell exhaustion, which could be reverted by anti-angiogenic agents targeting VEGF-A.

It has also been shown that PD-L1 expression is upregulated under hypoxia in some cancer cell lines through a hypoxia-inducible factor-dependent mechanism.

These studies support that a synergistic anti-tumor effect on dual blockade of PD-L1 and VEGF pathways is possible. Modulating the immunosuppressive microenvironment with PD-L1 blockade (eg, monoclonal antibodies [mAbs] such as durvalumab and atezolizumab) in combination with VEGF inhibitors may provide a unique therapeutic strategy, particularly in targeting aggressive tumors.

Preliminary clinical data from non-AstraZeneca-sponsored studies in patients with HCC support that co-inhibition of PD-L1 with either VEGF-A (mAb) or vascular endothelial growth factor receptor (VEGFR; tyrosine kinase inhibitor [TKI]) results in potentially synergistic efficacy in the context of an acceptable safety profile.

In a non-AstraZeneca-sponsored study (NCT02715531), bevacizumab intravenous in combination with atezolizumab showed a 34% objective response rate (ORR; 23 responses out of 68 efficacy-evaluable patients) in patients with first-line (1L) advanced HCC naïve to systemic treatment.

Additionally, a response rate of 42.3% was reported in 26 patients receiving lenvatinib and pembrolizumab.

The safety profile of these combination regimens was manageable and predictable. Taken together, these data suggest that the addition of durvalumab and VEGF inhibitor therapy may enhance anti-tumor immune responses to produce significant and consistent clinical benefit in patients with HCC after curative hepatic resection or ablation. In combination, durvalumab and VEGF inhibitor therapy may further enhance anti-tumor activity by stimulating host immunity (ie, promote dendritic cell maturation, T-cell infiltration, etc) to produce significant clinical benefit in patients with HCC after curative hepatic resection or ablation.

Overall benefit\ Risk:

After curative-intent resection or ablation, overall recurrence rate exceeds 70% at 5 years. Currently, no adjuvant therapy is recommended or approved in HCC after curative resection or ablation. Therefore, this is a patient population with high unmet medical need for adjuvant treatment options.
The PD-1 and PD-L1 pathways play an important role in HCC, indicating therapeutic agents that are capable of blocking PD-L1 may potentially improve clinical outcomes by reversing the immunosuppressive environment of HCC and by stimulating host immunity against HCC).
In the Phase I/II Study 1108, durvalumab therapy showed early and durable clinical activity and manageable safety in patients with HCC with an ORR of 10.0% (4 responses; 95% CI: 2.8% to 23.7%) and a median OS of 13.2 months (95% CI: 6.3 to 23.0 months; data on file). Preclinical as well as recent clinical data support the synergistic anti-tumor effect of PD-L1 inhibition combined with VEGF inhibition. Preliminary data from a Phase Ib study of patients with 1L HCC treated with atezolizumab and bevacizumab showed promising clinical activity, with a confirmed ORR of 34% .
These data indicate further evaluation of durvalumab therapy in combination with VEGF inhibitor therapy in patients with HCC after curative resection or ablation. The preliminary safety of durvalumab in combination with bevacizumab has been established and is generally well tolerated. The scientific rationale and evidence provided above suggest an effective systemic therapy, such as checkpoint inhibitors with or without VEGF inhibitors, may enhance anti-tumor immune responses to produce significant and consistent clinical benefit in patients with HCC after curative resection or ablation. Therefore, the overall benefit/risk assessment supports the proposed study to evaluate the efficacy and safety of durvalumab, with or without a VEGF inhibitor, in HCC patients after curative resection or ablation.

Design:

- This is a Phase III, randomized, double-blind, placebo-controlled, multi-center, global study to assess the efficacy and safety of durvalumab in combination with bevacizumab or durvalumab monotherapy or placebo as adjuvant therapy.
- This study will be conducted in patients with HCC who are at high risk of recurrence after curative hepatic resection or ablation. Citing approximate numbers, this study will screen patients in 23 countries. patients who will be randomized in a 1:1:1 ratio to one of the following treatment groups:
  - Arm A: Durvalumab + bevacizumab 15 mg/kg (Q3W).
  - Arm B: Durvalumab + bevacizumab placebo (Q3W) .
  - Arm C: Durvalumab placebo + bevacizumab placebo (Q3W).
- Eligibility will be limited to patients with histologically or cytologically confirmed HCC, or radiologically confirmed HCC for patients undergoing ablation, who have successfully completed

curative therapy (resection or ablation). Prior systemic anticancer therapy for HCC (eg, anti-VEGF, anti-PD-1, anti-PD-L1, anti-CTLA-4) will not be permitted.

- **Recommendation &/ or Questions & Answers: N.A**

- **Abbreviation:**

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AR	Accumulation ratio
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCτ	area under the concentration-time curve during the dosing interval
B7-H1	B7 homolog 1 (also referred to as PD-L1)
BICR	Blinded independent central review
BTC	Biliary tract cancer
CD	cluster of differentiation
CDC	Complement-dependent cytotoxicity

CI	Confidence interval
CL	Systemic clearance
Cmax	Maximum observed concentration (at steady state)
CR	Complete response
CRC	Clinical research centre
CT	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
D + G + C	Neoadjuvant durvalumab plus gemcitabine and cisplatin prior to radical cystectomy, followed by adjuvant durvalumab monotherapy (treatment arm)
DLBCL	DLBCL diffuse large B-cell lymphoma
DLT	DLT dose-limiting toxicity
dMMR	deficient mismatch repair
DOR	Duration of response
DRF	dose range-finding
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDA	Egyptian Drug Authority
EFS	Event-free survival
ELISA	Enzyme-linked immunosorbent assay
EU	EU European Union

FAS	Full analysis set
GD	Gestational day
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard Ratio
IB	Investigator's Brochure
IC	Immune cell
ILD	Interstitial lung disease
IV	Intravenous
KD	Dissociation constant
KLH	Keyhole limpet hemocyanin
mITT	Modified intent-to-treat
N.A	Not Applicable
nAb	Neutralizing antibody
NK	Natural Killer
NOAEL	No Observed Adverse Effect Level
NR	Not Reached
NSCLC	Non-small cell lung cancer

ORR	Objective response rate
OS	Overall survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic complete response
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand-1
PFS	Progression-free survival
PI	Principle Investigator
PK	Pharmacokinetics
PR	Partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
RECIST	Response Evaluation Criteria in Solid Tumors
rcynoPD-L1	rcynoPD-L1
rhPD-L1	rhPD-L1
RFS	Recurrence-free survival
SAE	Serious adverse event
SCLC	Small cell lung cancer
sPD-L1	Soluble programmed cell death ligand-1
SEM	Standard Error of Mean

SoC	Standard of care
TC	Tumor cell
TEAE	Treatment-emergent adverse event
TMG	Toxicity Management Guidelines
TTR	Time to recurrence
UC	Urothelial carcinoma
V	Version
VEGF	Vascular endothelial growth factor

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