CT Application(s) Summary Report

- **Protocol title:** A Phase III, Randomized, Open-Label, Sponsor-Blinded, Multicenter Study of Durvalumab in Combination with Tremelimumab ± Lenvatinib Given Concurrently with Transarterial Chemoembolization (TACE) Compared to TACE Alone in Patients with Locoregional Hepatocellular Carcinoma (**EMERALD-3**)
- **Protocol code number:** D910VC00001
- ***Public Registry Number:*** Eudra-CT,021-003822-54
- **Version:** 3
- **Date:** 18 December 2024.

- **Investigational Medicinal Product being tested:**

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

- **Sponsor: AstraZeneca**
- **Indication:** Participants with locoregional HCC not amenable to curative therapy (eg, surgical resection, transplantation, or ablation).
- **Investigator's brochure (IB) (For Durvalumab)**

Version: V21
Date: 05 Aug 2025
Investigator's brochure (IB) For (Tremelimumab)
Version: 12
Date: 05 Dec.2024

- **Name of all Sites:**
  1. National Hepatology and Tropical Medicine Research Institute (NHTMRI).
  2. Egyptian liver Hospital
  3. National Liver institute, Menoufia university
- **Name of PI(s):**
  1. Dr. Mohamed El Kassas
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- **EDA approval date:**

- Initial Approval on Protocol version 1.0, Durvalumab IB edition 18, and Tremelimumab edition 10: 08/02/2024
- Approval on Protocol V 2.0: 08/02/2024
- Approval on Durvalumab IB edition 20 and Tremelimumab edition 11: 17/01/2025
- Approval on Protocol V3.0, Durvalumab IB edition 21, and Tremelimumab edition 12: 12/03/2026

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

❖ **Durvalumab**

➢ **In Vitro Pharmacology**

1-Durvalumab Binds Specifically to Human PD-L1 with High Affinity and Inhibits the Interaction of PD-L1 with PD-1 or CD80. The binding specificity of durvalumab for rhPD-L1 was confirmed by an ELISA. No specific binding to the related recombinant human proteins was detected. In addition, no binding to murine PD-L1 was detected.

The ability of durvalumab to inhibit the binding of rhPD-L1 to either rhPD-1 or rhCD80 durvalumab effectively blocks the binding of rhPD-L1 to both rhPD-1 and rhCD80. Based on this result, **durvalumab potently inhibits the binding of hPD-L1 to both its ligands, PD-1 and CD80.**

2-Durvalumab Overcomes PD-L1 Mediated Inhibition of Primary Human T-cells From Different Donors: Durvalumab specifically enhanced the proliferation of primary human CD3+ T cells from each of eight independent donors "**MedImmune Research Report ONC4736-0020",** whereas no enhancement was observed with control antibody. This suggests that sustaining a serum concentration of durvalumab above 3 µg/mL in patients would maximize the chance of observing activity.

3-Durvalumab Does Not Trigger Effector Function (lack both ADCC and CDC activities):

-Durvalumab and hIgG1 (a version of durvalumab with a wild type IgG1 Fc domain) were tested for NK cell CD16 receptor activation in a reporter gene bioassay that mechanistically is a relevant surrogate for ADCC activity. In this assay, durvalumab did not specifically induce reporter activity when reporter NK cells were incubated with a PD-L1 expressing target tumor cell line whereas hIgG1 did potently induce activity.

-Durvalumab and hIgG1 did not have any CDC activity at any concentration tested. The anti-CD20 antibody, which is active in CDC assays, was used as a positive control and demonstrated **dose-dependent CDC activity against the human CD20-expressing Daudi target B-cell line in the presence of human serum** but not with heat inactivated serum that lacks functional complement, thus supporting the validity of the CDC assay used to test durvalumab.

4-Durvalumab Does Not Induce Cytokine Release Alone or in Combination with Other Immunomodulatory Agents as it did not induce significant test article-specific cytokine release in human whole blood or PBMCs. Donors under the conditions tested "(MedImmune research reports ONC4736-0004, ONC4736-0017, BAS6383-02-BAR-HUMAN-CRA, and BAS9447-0002-Bar-Human-CRA; Eurofins Study OX-14/128-003), whereas positive control **anti-human CD3** antibodies induced substantial cytokine release.

- **In Vivo Pharmacology**

1-Durvalumab Inhibits the Growth of Human Tumors in Mice via an Immune-mediated Killing Mechanism (MedImmune Research Report ONC4736-0006):

Durvalumab **significantly inhibited growth of the pancreatic adenocarcinoma cell line**, HPAC, by up to **74%** as compared to the isotype-control antibody. Similarly, durvalumab inhibited growth of the **A375 melanoma** cell line by up to **77%** compared to the isotype-control antibody.

The HPAC or A375 tumor cell lines were implanted into non-obese diabetic/severe combined immunodeficient mice on Day 1 of the studies. When similar experiments were conducted without the co-implantation of human **T-cells**, no anti-tumor activity was observed. Therefore, **Durvalumab activity is dependent upon the presence of tumor-specific human T-cells, supporting a mechanism of enhanced immune-mediated tumor killing for durvalumab.**

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

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

-Animals were administered 0 (vehicle) or durvalumab IV on Day 1 and Days 15, 22, and 29 showed that the values of **increased in an approximately dose-proportional manner** demonstrating an 11.8-fold increase from 1.77±0.424 to 20.8±1.27 µg/mL over the 10-fold dose range. The AUC0-τ **increased in a greater than dose-proportional manner**, demonstrating a 38.2-fold increase from 2.10±0.165 to 80.3±14.7 µg·d/mL over the same dose range. A corresponding **decrease in the systemic CL** of durvalumab from 43.8±3.27 to 11.1±1.11 mL/d/kg was observed. These results suggest **nonlinear PK** of durvalumab in the dose range studied. This was likely due to saturable target-mediated CL, which is frequently observed for antibodies targeting membrane-bound targets. Following the last dose of durvalumab on Day 29, AUC0-τ increased by 105-fold (from 70.0±57.9 to 7370±7240 µg·d/mL) over the 10-fold dose range. All animals tested positive for the presence of ADA. However, considerable exposures were still achieved and pharmacodynamic effects (suppression of PD-L1) were maintained 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 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):

-Animals were administered 0 (vehicle) or durvalumab IV on Day 1 and 0 (vehicle) on Days 8, 15, 22, and 29. Following administration of the loading doses of durvalumab, serum concentrations of **durvalumab declined biphasically,** with a mean elimination half-life ranging from **5.9 to 6.8 days.**

Systemic CL of durvalumab was constant across the **3 dose levels** with the mean CL ranging from **6.1 to 7.5 mL/d/kg.** These elimination rates gave systemic exposures (AUC) of durvalumab that were linearly proportional to the **3 dose** levels. A similar dose-dependent increase was also observed in the **Cmax** of durvalumab. Systemic exposure of durvalumab following the final dose was likely affected by **ADA** in a small proportion of the animals. In the majority of animals, sustained exposures and pharmacodynamic effects were maintained throughout the study, with **AR** estimates **(based on AUCτ)** independent of dose and ranging from **1.1 to 1.7**.

N.B: No mentions for number of animals was mentioned in study report, AUC, CMAX aren't mentioned either.

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

Female cynomolgus monkeys received a **loading dose** (double the maintenance dose) of durvalumab by IV infusion upon confirmation of pregnancy on **GD20.**This was followed by weekly doses of durvalumab from **GD27** until delivery. Following the first durvalumab IV dose on **GD20**, mean systemic exposures in maternal animals increased dose proportionally.

Weekly **IV infusion** of durvalumab resulted in systemic accumulation towards a steady state attained by approximately **GD76.** Mean ARs based on **AUCτ** following dose **17 (GD132)** were **1.68** or **1.74** following repeat dosing. Serum durvalumab concentrations declined following cessation of treatment at parturition, with exposure to durvalumab was still detectable in maternal serum on **Days 28** and **56 pp**. Breast milk

collected from lactating mothers on **Day 28 pp** showed dose proportional excretion of durvalumab into milk. Exposure to durvalumab was generally associated with full suppression of **sPD-L1** from the first dose on **GD20** and throughout gestation. Despite a high number of animals tested positive for **ADA,** exposure to durvalumab was affected by the **ADA** formation in maternal animals.

In these animals, increased **ADA-mediated** serum **CL** of durvalumab was associated with a rebound of serum **sPD-L1 levels**. Serum samples collected from infants showed dose-proportional exposure to durvalumab on Day **1±1 pp**, with durvalumab serum concentrations declining with time and being non-quantifiable by Day **180±1 pp**. The gradual decline of serum durvalumab concentrations in infants resulted in corresponding increases in serum **sPD-L1** to control levels by Day **180±1 pp.**

- **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 group 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 animal 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- <u>Reproductive and Development Toxicity</u>

In the **GLP 13-week repeat-dose toxicity** study, no treatment-related effects were observed on either reproductive organ weights or microscopic histopathology in male or female animals.

In the study **ePPND**, was conducted in **cynomolgus monkeys**. In this study, **pregnant females** were dosed with durvalumab from confirmation of pregnancy **(GD20)** until natural delivery.

Two durvalumab-treated groups were included in the study, receiving either a loading dose of durvalumab by IV infusion on **GD20**, followed by weekly IV infusions until parturition.

Following birth, the development of the infants was monitored in a **6-month postnatal phase**, which included an assessment of immune competence in the infants by inclusion of a challenge with a **T cell-dependent antigen (KLH).**

Following IV administration, exposure to durvalumab was maintained in the majority of animals, despite a **high ADA incidence**, and was associated with full **sPD-L1** suppression.

Administration to maternal animals was associated with **placental transfer**, with durvalumab exposure detected in infants and associated with full sPD-L1 suppression up to **Day 56 pp**.

Dose-related **low-level secretion** of durvalumab was also detected in **breast milk collected on Day 28 pp**.

Following cessation of dosing at parturition, exposure to durvalumab gradually declined in both maternal animals and infants during the **6-month** postnatal phase, with durvalumab levels being undetectable and **sPD-L1** returning to baseline values by the end of the study **(Day 180±1 pp).**

Based on comparisons to concurrent control, durvalumab had an apparent effect on mid- and late-stage pregnancy losses, stillbirths or infants found dead, total pregnancy loss, and infant loss, without a clear trend in dose relationship. Pregnancy outcome parameters for the durvalumab-treated groups were within the normal range when compared to the test facility's historical control data set. 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.

➢ **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.

❖ **Tremelimumab**

➢ **In vitro studies**

1- Characterization of Tremelimumab

Tremelimumab specifically binds to **immobilized human CTLA-4-Ig**, to **CTLA-4** on activated human T cells, and to **CTLA-4-transfected cells**, it blocks binding of **CTLA-4-Ig** to **CD86-Ig.**

Binding studies demonstrated that tremelimumab displays **>500-fold** selectivity for human **CTLA-4-Ig** over human **CD28-Ig**, **CD86 Ig,** and **IgG1.**

2- T-cell cytokine enhancement

Human **PBMCs** or human whole blood cultures were stimulated with **staphylococcal enterotoxin A (SEA)** super-antigen in the presence of Tremelimumab or an isotype-matched control antibody. **IL-2 levels** in cell supernatants were then quantified by **(ELISA).** Addition of **Tremelimumab** enhanced the release of **IL-2** in cultures of **SEA-stimulated PBMCs** from **healthy donors** relative to an isotype-matched control antibody.

A second assay was developed, in addition to the **SEA assay**, which involved stimulation of **human T-cell blasts** with a **CD80/86-positive Raji** human B cell line for **72 hours. Tremelimumab** also enhanced production of **IL-2** and **IFN-γ** by human T-cell blasts in this assay.

These studies confirmed that tremelimumab was able to enhance T-cell responses to activation stimuli in healthy donors.

In cancer patients, the addition of Tremelimumab resulted in a concentration-dependent increase in release of IL-2 from PBMCs and whole blood from the majority of patients. About 10% of the normal and cancer subject whole blood samples tested did not show enhancement of IL-2 with tremelimumab, even though PBMC responses from the same donors were in the normal range.

In cancer patients, the addition of Tremelimumab resulted in a **concentration-dependent increase** in release of IL-2 from PBMCs and whole blood from the majority of patients. About 10% of the normal and cancer subject whole blood samples tested did not show enhancement of IL-2 with tremelimumab, even though PBMC responses from the same donors were in the normal range.

These findings support clinical testing of tremelimumab in a wide range of tumor types and different stages of disease.

3- Antibody-dependent cell-mediated cytotoxicity

Only 0.2% of isolated naïve human T cells expressed CTLA-4 on their cell surface as judged by flow cytometry. Incubation of naïve T cells with tremelimumab or anti-erythropoietin antibody followed by addition of IL-2-activated NK effector cells **did not significantly increase ADCC** (1% to 3% cytotoxicity). In contrast, a marked increase in cytotoxicity was observed when naïve target cells were incubated with the anti-human CD3 mouse IgG2a positive-control antibody. Target cell cytotoxicity increased as the effector-to-target ratios increased, reaching a maximum of 37% at the 25:1 ratio.

--**These data demonstrate that tremelimumab does not potentiate NK cell-mediated ADCC against CTLA-4 expressing T cells.**

4- Whole-blood Cytokine Release 05-CP-675,206

Cultures of human whole blood from **healthy donors** were incubated in the presence of **tremelimumab** or **anti-human CD3 antibody**, which was used as a positive control. When the **anti-CD3 antibody** was used at a concentration of **100 µg/mL**, average levels of **TNF-α, IL-6, and IL-1β** in cell supernatants were **1184, 1358, and 540 pg/mL,** respectively.

In contrast, incubation with **tremelimumab** resulted in levels of **TNF-α** and **IL-1β** below reliable levels of detection **(< 30 and < 8 pg/mL**, **respectively)** for all donors and in levels of **IL-6** below reliable levels of detection **(<6 pg/ml)** fordonors and an average of **22 pg/mL** in the remaining donors. When the anti-CD3 antibody was used at a concentration of **10 µg/mL**, average levels of **TNF-α, IL-6**, and **IL-1β** in cell supernatants were **1120, 350**, and **513 pg/mL**, respectively. Again, incubation with tremelimumab resulted in levels of all-**cytokines** that were near or below the reliable levels of detection.

Tremelimumab does not induce cytokine release in vitro.

5-Cytokine Release in Combination with durvalumab ONC4736-0017

Human whole blood from healthy donors was incubated for **24 hours** in the presence of anti-human CD3 or lipopolysaccharide-positive controls, and a combination of durvalumab and Tremelimumab.

Durvalumab and Tremelimumab were tested.

Following incubation, the levels of **IFN-γ, IL-2, IL-6, and TNF-α** were measured in culture supernatants.

As expected, anti-human CD3 and lipopolysaccharide-positive controls induced high concentrations of cytokines in human whole blood after 24-hour incubation in all conditions tested.

In contrast, **durvalumab and Tremelimumab, either alone or in combination, did not induce cytokine release** in blood from any donor.

6- **Cynomolgus monkey versus human CTLA-4 expression and reactivity with tremelimumab 14-CP-675,206**

Minimal expression of surface or intracellular **CTLA-4** was detected in unstimulated **CD3-positive T cells** from human or cynomolgus blood. The same cells stimulated for **72 hours** with **phytohemagglutinin** displayed comparable low surface staining.

Anti-CTLA-4 mAbs in excess generally displayed approximately **3-fold higher total binding** (surface plus intracellular) to **stimulated human CD3+ cells** than to stimulated cynomolgus cells as judged by median fluorescence intensities.

In both **cynomolgus monkey** and **human tissues** using a **tissue cross-reactivity assay**, **tremelimumab** bound similarly to a minority of **lymphocytes** in lymphoid tissues, including **tonsil**, **lymph nodes**, **spleen**, and **thymus**.

Whole blood from a **cynomolgus monkey** was stimulated with **SEA** superantigen in the presence of **tremelimumab** and assayed for **IL-2** enhancement as described for human whole blood. **Tremelimumab** reproducibly **enhanced IL-2** production in **SEA** superantigen-stimulated **cynomolgus whole blood cultures.** Concentration response profiles were generally comparable to those for **human blood**

These data together demonstrate that tremelimumab has comparable affinity for cynomolgus monkey **CTLA-4** relative to human **CTLA-4** and shows comparable effects in functional cell-based assays in both species.

- **In vivo study**

1- **Monotherapy efficacy of anti-mouse CTLA-4 in a murine fibrosarcoma syngeneic model**

A hamster anti-mouse CTLA-4 mAb (clone 9H10) was used to study the **antitumor activity** of an **anti-CTLA-4 mAb** in these models.

Syngeneic SA1N fibrosarcoma cells were injected subcutaneously into **A/J mice** on **Days 0, 3, and 6. Animals** were administered **9H10** or an **isotype-control antibody** by intraperitoneal injection at a dose level of **200 µg.** Treatment with **9H10** resulted in a **90%** reduction in average tumor size on **Day 28** compared to treatment with an isotype control antibody. Animals treated with **anti-CTLA-4 mAb** had no detectable tumors when followed for **60 days** and were resistant to **tumor rechallenge**.

Additional studies demonstrated a dose-dependent anti-tumor effect of **anti-CTLA-4 mAb** treatment. These studies demonstrate a significant anti-tumor effect for **anti-CTLA-4** in a mouse model of cancer and provide proof of principle for **anti-CTLA-4 antibodies** in cancer therapy.

2- Combination efficacy of anti-mouse CTLA-4 mAb with an anti-mouse PD-L1 mAb in a mouse colorectal cancer model

A surrogate **anti-mouse PD-L1** antibody clone **10F.9G2** was used in combination with mouse anti-**CTLA-4 (clone 9D9)** in a mouse syngeneic model of colon cancer. **Balb/c** mice were implanted subcutaneously with the **CT26** mouse colorectal cancer cell line. Animals were treated with either **anti-mouse PD-L1** clone **10F.9G2**, 9D9, **anti-mouse CTLA-4 clone** or the combination of **10F.9G2 and 9D9**.

All mice treated with an isotype control antibody demonstrated continuous tumour growth, with no mice surviving until the end of the study. Treatment with **10F.9G2** alone demonstrated some benefit, resulting in a tumour growth delay and complete regression in **25%** of mice.

Treatment with **9D9** alone also resulted in a tumour growth delay and complete regression in **50%** of mice. The combination of **10F.9G2** and **9D9** resulted in greatly increased activity with tumour regression observed in all mice treated

This data suggests that **CTLA-4 blockade differs mechanistically from PD-L1 blockade** and supports the testing of tremelimumab in combination with durvalumab in patients with cancer.

- **Non-clinical pharmacokinetics and drug metabolism**

A- Pharmacokinetics

The **PK** of tremelimumab was characterized in **cynomolgus monkeys** following IV administration of a single dose of both **clonally** and **non-clonally** derived tremelimumab. The PK of tremelimumab from both sources was characterized by **low plasma CL** and **small VSS** that is similar to plasma space, resulting in a **long mean t½ of 9.1 to 11 days**. **Differences** in the PK of tremelimumab generated from **clonal and non-clonal sources** were shown to be **not statistically significant.**

In addition, the observed primate antidrug antibody **(ADA)** responses appear to be similar between these 2 lots of tremelimumab.

B-Toxicokinetic

1- Single-dose Toxicokinetic

Systemic exposure Cmax and [AUC0-Tlast]) in cynomolgus monkeys receiving single IV doses of tremelimumab increased with dose **Tremelimumab PK was linear over the dose range studied**. There were no gender-related differences observed in drug exposure Tremelimumab PK was linear over the dose range studied. There were no gender-related differences observed in drug exposure.

2- Repeat-dose Toxicokinetics

In study **(DM2001-675206-006)** , A **1 Month** Intravenous Toxicity Study With 2-month Post-dose Observation in **Cynomolgus Monkeys** ,Systemic exposure **(mean Cmax and mean area under the plasma concentration-time curve from time 0 to 24 hours [AUC0-24])** in cynomolgus monkeys receiving weekly **IV doses** of tremelimumab increased from **first dose (Day 1)** to last dose **Group mean AUC0-tlast [Days 1 to 30]** of tremelimumab **were 69,500, 186,000 and 590,000 µg·hr/mL**. For animals followed through the observation period, the mean **AUC0-tlast [Days 1 to 105]** of tremelimumab **were 88,600, 210,000 and 775,000 µg·hr/mL.**

In Conclusion: There was a trend towards **higher mean Cmax and (AUC)** on **Day 29** as compared to **Day 1.** There were no gender-related differences observed in drug exposure, as measured by Cmax and AUC0-24 on Days 1 and 29. The monkeys developed ADA response to the human IgG2 mAb in all dose groups in the single-dose and 1-month toxicokinetic studies.

In the **6-month study (DM2004-675206-016), cynomolgus monkeys** received **once-weekly IV administration** of tremelimumab for **26 consecutive weeks** and at **50 mg/kg** for **7** consecutive weeks.

A 3-fold and a **10-fold** increase in dose on Day 1 resulted in a **2.9-** and **9.7**-fold increase in **Cmax**, and a **2.8**- and **9.6**-fold increase in **AUC0-24,** respectively.

On **Day 29,** a **3-** and **10-fold** increase in dose resulted in a **2.2-** and **8.7-fold** increase in Cmax, and a **1.8-** and **8.5-fold** increase in **AUC0-24**, respectively.

On **Day 176**, a **3-fold** increase in dose resulted in a **2.3-fold** increase in **Cmax** and a **2.0-fold** increase in **AUC0-24**.

Similarly, the weekly **(AUC from time 0 to 168 hours)** and monthly **(AUC from time 0 to Day 30)** exposures also increased with dose.

Following weekly administrations of **tremelimumab** for **6 months**, the mean exposures to **tremelimumab (Cmax and AUC0-24**) on **Days 29 and 176** were generally similar to those observed on **Day 1**.

The only exception was a **slight increase (1.6- to 1.7-fold)** of both **Cmax and AUC0-24** on **Day 29** compared to **Day 1 at tremelimumab**.

both **Cmax and AUC0-24** increased approximately **1.5-fold** on **Day 29** compared to **Day 1** following **5 weekly** administrations of **tremelimumab.**

Of the **28 animals** administered **tremelimumab** in the study, **7** animals had tremelimumab concentrations at the **LLOQ** at some point in the study and, hence, were tested for ADA. Anti-drug antibodies and neutralizing antibodies were detected in all **7 animals.**

In an **embryofoetal development study** (**DM2007- 675206-021**), the systemic exposures to tremelimumab, as assessed by mean Cmax and mean AUC0-24, increased with increasing dose on

Gestational Days (GDs) **20 and 48 following once weekly IV administration for 5 consecutive weeks to pregnant female cynomolgus monkeys.**

A 6-fold increase in dose of tremelimumab on **GD 20** resulted in a **6.2-** and **6.6-**fold increase in **Cmax** and **AUC0-24,** respectively.

On **GD 48**, a **6-fold** increase in dose of **tremelimumab** resulted in a **6.6-** and **6.5-fold** increase in **Cmax** and **AUC0-24**, respectively.

A **6-fold** increase in dose of **tremelimumab** resulted in a **5.9-fold** increase in cumulative **AUC** following **5** consecutive **weekly** treatments from time **0 on GD 20 to GD 49 (24 hours postdose on GD 48).**

Following weekly administrations of tremelimumab for **5 consecutive weeks,** there was a trend toward higher **mean Cmax** and **AUC0-24** on **GD 48** as compared to those on **GD 20.**

On **GD 48**, **Cmax** of tremelimumab groups were **1.2-** and **1.3-fold** higher from those on **GD 20**, respectively.

In conclusion, on GD 48, **AUC0-24** were **1.3-fold** higher from those on **GD 20.** During the treatment, the mean trough exposures to tremelimumab, as assessed by pre-dose exposures on **GD 27, 34, 41, and 48,** in animals were in the range of **40.6 to 75.9, 116 to 154, and 212 to 364 µg/mL**, respectively. Anti-tremelimumab antibodies were not evaluated in this study.

- **Toxicology**

1- Single dose toxicity

Single-dose toxicity of tremelimumab in cynomolgus monkeys was investigated in 2 studies ,**Study 00-1985-06 (non-GLP) and Study 99-1985-01 (GLP):**

Study 00-1985-06 was an initial assessment of **PK**, pharmacodynamics, and tolerability in the **cynomolgus monkey**. Comparable exposure was observed and pharmacodynamic activity of **tremelimumab** was demonstrated in the **ex vivo SEA assay,** where increased **IL-2 production** was detected from **0.5 h post** IV administration until the end of the study. Administration of **tremelimumab** had no effects on clinical signs, food consumption or bodyweight.

The aim of Study **99-1985-01** was to assess the local and systemic toxicity of tremelimumab in **cynomolgus monkeys** following a single IV dose of vehicle **(20 mM sodium acetate, 140 mM NaCl, 0.2 mg/ml, pH 5.5).** Scheduled necropsies of the vehicle control and **100 mg/kg** tremelimumab dose groups were conducted on **Day 106.** Administration of **tremelimumab** was associated with a dose-related exposure and increases in the incidence and frequency of diarrhoea or loose stool.

These changes were not associated with any effects on body weights or food consumption and not considered adverse. No additional effects of toxicological relevance were noted, with no gross macroscopic or microscopic pathology findings in animals after necropsy on **Day 106.**

2- Repeated-dose toxicity:

In the 1-month study **(00-1985-04), IV** administration of **tremelimumab** was associated with **intermittent diarrhoea** or **loose stool** in individual animals across all treated groups **during the dosing phase,** and in the **10-week** treatment-free period only in individual animals that had previously received **tremelimumab.** Consistent with its primary pharmacodynamics, administration of tremelimumab was also associated with reversible increases in the absolute number and/or percent of peripheral blood lymphocytes that correlated with increases in circulating **T cells and/or B cells.**

In histopathology, **tremelimumab** treatment was associated with periportal mononuclear cell infiltrates in the liver, which reversed in females but not in males after a **10-week** treatment-free period. Additional **histopathology** findings included **lymphoid hyperplasia** in the spleen and mesenteric lymph node, which was observed at all dose levels; these changes were considered consistent with the primary pharmacodynamics of tremelimumab and reversed or showed a trend towards reversal after a **10-week treatment-free period**.

In the **6 month study (2004-0150)**, IV administration of tremelimumab was associated with adverse clinical signs that included **persistent diarrhoea (requiring supportive care [fluid replacement therapy]** in **animals** at this dose) and **skin lesions (swollen eyelids; dry, cracked, scaly, or crusty skin; rash or reddened skin; scabbed areas and yellowish skin)** that led to suspension of dosing after **6 or 7 weekly doses**, and **termination** of all main study animals at this dose between **Day 49** and **77,** with the recovery animals at this dose assigned to a **new 99 day** treatment-free period. At **tremelimumab**, clinical signs generally occurred with lower incidence and reduced severity, with only one animal tremelimumab requiring supportive care due to **persistent diarrhoea.** Histopathology findings included **inflammation in the cecum and colon**, **mononuclear cell inflammation** in the skin, and **lymphoid hyperplasia in peripheral lymph nodes**.

In addition to these findings, dose-related increases in the incidence of mononuclear cell infiltration and inflammation in numerous lymphoid and non-lymphoid tissues were observed. These findings were considered consistent with the primary pharmacodynamic activity of tremelimumab and were generally reversible or showed a trend towards reversibility. Given that administration of tremelimumab was associated with adverse clinical signs **(persistent diarrhoea, skin lesions)** that required supportive care in animals**,** a **NOAEL** for tremelimumab was not identified in this study.

- **Reproductive and developmental toxicity**

Embryo-foetal development study with tremelimumab in cynomolgus monkeys (Study 2501-001; GLP)

After the final dose on **GD 48**, animals were maintained until **GD 100±1**, when caesarean sections were carried out and foetuses assessed.

There were no unscheduled deaths during the course of the study. In addition, there were no tremelimumab-mediated adverse effects on clinical signs, body weights, vaginal smears, placental weights and appearance, or abortion rates/prenatal losses in the pregnant dams. In the foetal assessments post-caesarean section, there were no effects of tremelimumab on foetal weights, or external, visceral and skeletal abnormalities, or weights of selected organs. Tremelimumab did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

➢ **Other toxicity studies**

Tissue cross-reactivity studies with tremelimumab in normal human (Study IM676; GLP) and cynomolgus monkey (Study IM645; GLP) tissues

Tremelimumab-specific staining was present in various lymphoid tissues, including tonsil, lymph nodes, spleen, and (non-involuted) thymus. Specific reactivity was also observed with rare to occasional lymphocytes in mucosal-associated lymphoid tissues, including submucosal lymphoid nodules in the gastrointestinal tract (colon, small intestine and/or stomach), in both species. Cells staining with tremelimumab were judged to be lymphocytes based on their typical morphology and location. Based on the above, tissue cross-reactivities observed were considered to be consistent with the immunohistochemical distribution of CTLA-4 in human tissues as reported in the literature.

- **Summary of previous clinical studies:**

***Durvalumab:**

As of 30 April 2025, **patients** received durvalumab in AstraZeneca/MedImmune-sponsored interventional studies across multiple tumor types and treatment settings. Some received monotherapy, received durvalumab + tremelimumab, and others received combination therapy with investigational and/or approved products. Additionally, **patients** were randomized and treated in sponsor-blinded or double-blinded studies.

➢ **Pharmacokinetics and Drug Metabolism in Humans**

Following the first IV dose, **durvalumab exhibited nonlinear pharmacokinetics** (due to saturable target-mediated clearance) and linear PK. AUC_{0-14} increased dose-proportionally and more than dose-proportionally, while Cmax increased dose-proportionally across the evaluated range. Steady state was reached at ~Week 16, with accumulation observed upon repeated dosing.

➢ **Pharmacodynamics**

Target engagement, assessed by serum sPD-L1, showed complete suppression, with patients achieving sustained suppression.

Two validated flow cytometry assays evaluated circulating lymphocytes in UC and NSCLC ~~(n=262)~~ patients. In UC, proliferating CD8+ T cells increased on Day 10 and Day 15, exceeding assay variability, although not statistically significant. In NSCLC, baseline-normalized proliferating CD4+ and CD8+ T cells increased on Day 10 and Day 15 following 10 mg/kg Q2W.

A modest but significant increase in B cells was observed at Day 99. No other lymphocyte subsets showed changes exceeding assay variability within the first 100 days.

Overall, findings demonstrate pharmacodynamic activity consistent with durvalumab's mechanism of action.

- **Immunogenicity**

ADA data were available for patients. **Overall, ADA prevalence was 5.3%**, and ADA incidence was 3.1, **ADA prevalence was 4.9%**, among these, it showed ≥4-fold titer increase. The treatment-emergent ADA incidence was 2.7%.

Anti-TM antibody was detected in patients (0.1%), with no impact on durvalumab or sPD-L1 concentrations. **No clear effect of ADA on safety was observed**; adverse events were comparable to those of ADA-negative patients, with no signals of immune complex disease. Among nAb-positive patients, no infusion reactions or hypersensitivity events were reported.

The impact of treatment-emergent ADA on efficacy in UC and NSCLC was not evaluable due to the low number of ADA-positive patients.

--Study D4190C00006 (Durvalumab + Tremelimumab):

PK data were available for durvalumab and tremelimumab from dose-escalation/expansion studies. Durvalumab and tremelimumab concentrations were quantified using ECL and ELISA methods, respectively.

Both agents showed approximately dose-proportional increases in exposure (Cmax and $AUC_{0–28}$) **across the evaluated dose ranges**. Accumulation following multiple dosing was consistent with first-dose PK parameters. Exposure profiles in combination were comparable to monotherapy, indicating **no PK interaction.**

- **Pharmacodynamics**

sPD-L1 data were available for **patients** receiving durvalumab in combination with tremelimumab. Target engagement, assessed via **free sPD-L1 suppression**, showed **complete suppression in almost all patients** across the evaluated dose range, with **no clear dose-dependent effect**.

Partial suppression was observed in **patients**: achieved complete suppression after repeated dosing, while remained partially suppressed at Day 29 and was **ADA-positive with PK impact**.

- **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 DCO: 16 Oct 2017 Study completed.	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 DCO: 11 Jan 2021 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.	Median PFS (BICR) was significantly longer with durvalumab treatment (16.8 months [95% CI: 13.0, 18.1])e compared with placebo (5.6 months [95%CI: 4.6, 7.8]); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; op<0.0001.	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

			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.	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.	16.2 months; hazard ratio 0.53; 95% CI, 0.41, 0.68).
	Study D4194C00006 PACIFIC 6 Primary DCO: 15 Jul 2021 Final DCO: 20 Mar 2023 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 DCO:1 Jun 2017 OS analysis DCO: 4 Oct 2018 Study completed	PD-L1 TC ≥25% Durvaluma b: 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%	Median PFS (BICR) was 4.7 months [95% CI: 3.1, 6.3]) compared with durvalumab VS chemotherapy (5.4 months [95% CI: 4.6, 5.8]); hazard ratio 0.87; 99.5% CI: 0.593, v1.285; p=0.324.	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.

			with chemotherapy.	The 12-month PFS rate was 32.3% with durvalumab vs 14.3% with chemotherapy.	
	Study D9102C00001 ORION DCO: 11 Jan 2021 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 DCO: 27 Oct 2022 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; hazard ratio: 0.77 (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)	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,	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).

		SoC: 266 (271 in the PD-L1 TC ≥25% LREM analysis set)		5.9) for the SoC arm; hazard ratio: 0.85 (95% CI: 0.704, 1.030; p=0.097).	
	Study D933YC00001 PACIFIC-5 DCO for PFS final analysis: 23 Jun 2024 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 vs13.8 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 DCO: 15 Jan 2024 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;	At the pre-planned interim PFS analysis, median PFS was 16.6 months (95% CI: 10.2, 28.2) for the durvalumab monotherapy	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).

			hazard ratio: 0.73; 95% CI: 0.569, 0.928; p = 0.01042.	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.	
	HNSCC				
	Study D4193C00001 HAWK DCO: 31 Mar 2017 DCO for OS extension period: 5 Oct 2018 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 DCO: 31 Mar 2017 DCO for OS extension period: 27 Aug 2018 Study completed	67 (PD-L1 negative)	Median OS was observed at 95% CI	Median PFS was 1.9 months (95% CI: 1.8, 2.8 months).	ORR at 12 months was 9.2% (6/65 patients; 95% CI: 3.5%, 19.02%).
	CD-ON-MEDI4736-1108 DCO: 16 Oct 2017 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). p	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 DCO: 10 Sept 2018 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 DCO: 16 Oct 2017 Study completed	201 (190 in the FAS)	Median OS was 10.5 months (95% CI: 6.9, 15.7); the OS rate at 24 months was 30.0% (95% CI: 21.1, 39.3).	Median PFS was 1.5 months (95% CI: 1.4d, 1.8), with a PFS rate of 13.7% at 18 months.	ORR (BICR) was 17.6% (35/199; 95% CI: 12.6, 23.6). PD-L1 high: 27.7% (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 DCO: 27 Jan 2020 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	40	Median OS was 13.2 months (95% CI: 6.3, 23.0); the OS	Median PFS was 2.7 months (95% CI: 1.4,	ORR (RECIST v1.1) was 10.0% (4/40; 95% CI: 2.8, 23.7).

	DCO: 16 Oct 2017 Study completed		rate at 24 months was 28.2% (95% CI: 14.3, 43.9).	5.3), with a PFS rate of 9.2% at 18 months.	Median DOR was 16.2 months.
	Study D4190C00022 DCO: 06 Nov 2020 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 DCO: 27 Aug 2021 Long-term 4-year follow-up DCO: 23 Jan 2023 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 (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).	Median PFS was 3.65 months (95% CI: 3.19, 3.75).	ORR was 17.0% (66/389; 95% CI: not reported).
	Other indications				
	CD-ON-MEDI4736-1108 DCO: 16 Oct 2017 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%	Median PFS ranged from 1.4 months in HNSCC, uveal melanoma, glioblastoma multiforme, and gastroesophageal cancer, to 5.4 months in microsatellite	ORR (RECIST v1.1), ranged from 0% in glioblastoma multiforme to 30.0% in nasopharyngeal carcinoma.

		CI: 12.4, not evaluable) in the microsatellite instability-high cancer cohort.	instability- high cancer.	

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 DCO: 19 Nov 2019 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 DOR of 24.4 weeks.71.6%. 7.2).	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.
		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	Median PFS (BICR) was 1.7 months (95% CI: 1.6, 2.6)	ORR (BICR) was 5.3% (2/38; 95% CI:

			patients with NSCLC) Median OS was 8.3 months; the OS rate at 12 months was 30.1%		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 DCO: 4 Oct 2018 Study completed	PD-L1 TC ≥25% durvalumab+ tremelimumab 163 Chemotherapy 162	Median OS was 11.9 months (95% CI: 9.0, 17.7) for the durvalumab+ tremelimumab arm and was 12.9 months (95% 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.	Median PFS (BICR) was 3.9 months [95% CI: 2.8, 5.0]) for the durvalumab +tremelimumab arm compared with chemotherapy (5.4 months [95% CI: 4.6, 5.8]); hazard ratio 1.05; 99.5% CI: 0.722, 1.534; p=0.705.) The 12-month PFS rate was 25.8% with durvalumab +tremelimumab vs 14.3% with chemotherapy.	ORR was 34.4% in the durvalumab +tremelimumab arm compared with 37.7% in the chemotherapy arm. Median DOR was not 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 DCO: 12 Mar 2021	331 Durvalumab + tremelimumab (75 mg Q3W, for 5 doses) + SoC chemotherapy (338 in the FAS) 331 SoC chemotherapy	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 arm alone arm; hazard ratio: 0.77 (95% CI: 0.650,	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 SoC chemotherapy alone arm; hazard ratio:	ORR was 46.3% (155/335; 95% CI: NR). Median DOR was 7.4 months.

	Long-term 4-year follow-up DCO: 11 Mar 2022 Long-term 5-year follow-up DCO: 24 Aug 2023 Study completed	(337 in the FAS)	0.916; p=0.00304). At the time of the 4-year follow-up, median OS was14.0 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 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).	0.72 (95% CI: 0.600, v0.860; p=0.00031).	
	UC				
	Study D4190C00010 DCO: 11 Apr 2018 OS analysis DCO: 13 Mar 2020 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 DCO:	340 Durvalumab + tremelimumab (75 mg Q4W,	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.

27 Jan 2020 Study completed	for up to 4 doses) (342 in the FAS)			
HCC				
Study D4190C00022 DCO: 06 Nov 2020 Study completed	Parts 1A and 1B 40 Durvalumab + tremelimumab (75 mg Q4W, for 4 doses) (40 in the FAS)	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 374 Durvalumab + single dose of tremelimumab (300 mg) (75 in the FAS)	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). Median DOR was 18.43 months.
	Parts 2A and 382 Durvalumab + tremelimumab (75 mg Q4W, for 4 doses) (84 in the FAS)	Median OS was observed with 95% CI	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 DCO: 27 Aug 2021 Long-term 4-year follow-up DCO: 23 Jan 2023	389 Durvalumab + A 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 the durvalumab + tremelimumab arm (95% CI: 14.2, 19.6) and was 13.8 months (95% CI: 12.3, 16.1) for	Median PFS was 3.78 months (95% CI: 3.68, 5.32).	ORR was 20.1% (79/393; 95% CI: NR).

Study completed		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).		
	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 DCO: 22 Jun 2020 Study completed	Arm A: 41	Median OS was 5.4 months (95% CI: 2.9, 7.2).	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: 31 Mar 2017 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 DCO:	71	In the IMT-naïve expansion cohorts (PD-L1 high and PD-L1 low/negative patients;	In the IMT-naïve expansion cohorts (PD-L1 high and PD-L1 low/negative patients;	ORs were observed only in the PD-L1 high cohort. ORR per investigator was

	8 Nov 2017 Study completed		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%.	n=42), 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%	20.0% (95% CI: 5.7%, 43.7%) in this cohort.
	Study D4193C00002 EAGLE DCO: 10 Sept 2018 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 DCO:	Dose-finding phase: 29 Dose-expansion	Median OS was 6.6 months (90% CI: 1.87, 15.77) for the A SARCOMA	Median PFS was 1.7 months (90% CI: 1.58, 1.91) for the SARCOMA cohort, and 1.7 months	In the SARCOMA cohort, no response was observed. In the STO cohort, one

28 Feb 2023 Study completed	phase (FAS): 21 (SARCOMA cohort: 11 STO cohort: 10)	cohort, and 6.9 months (90% CI: 1.61, NR) for the STO cohort.	(90% CI: 0.89, 2.76) for the STO cohort.	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 DCO: 24 Jul 2019 OS analysis DCO: 12 Mar 2021 Long-term 4-year follow-up DCO: 11 Mar 2022 Long-term 5-year follow-up DCO: 24 Aug 2023 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: 1v0.5, 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 arm alone; hazard	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).

			ratio: 0.84 (95% CI: 0.711, 0.990). At the time of the 5-yearfollow-up, median OS was 13.3 months (95% CI: 11.4, 14.7) for the durvalumab + 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 DCO: 14 Jan 2022 Final pCR and first interim EFS analysis DCO: 10 Nov 2022 Second interim EFS analysis: 10 May 2024 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 DCO: 11 Mar 2019 Final analysis	265 Durvalumab + chemotherapy (etoposide platinum [carboplatin or cisplatin]) (268 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	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)	ORR was 79.5% in the durvalumab + chemotherapy arm and 70.6% in the chemotherapy arm.	

	DCO: 27 Jan 2020 Long-term 3-year follow-up DCO: 22 Mar 2021 Study completed	266 Chemotherapy (269 in the FAS)	(95% CI: 9.3, 11.2) for the chemotherapy arm; hazard ratio: 0.73 (95% CI: 0.59, 0.91; p=0.0047). At the time of the final analysis, the median OS was observed 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; hazard ratio: 0.71	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 + chemotherapy arm and 2.9% for the chemotherapy arm.	

		(95% CI: 0.595, 0.858 p=0.0003).		
Study D419BR00018 ORIENTAL DCO: 31 Mar 2023 Study completed	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% (95% CI:52.8, 67.9) at 12 months.	Median PFS was 6.3 months (95% CI: 5.6, 6.5), with 17.6%patients alive and progression-free at 12 months (95% CI: 12.0, 24.1).	ORR was 76.4% (126/165; 3 CR and123 PR [95% CI: 69.1, 82.6]). Median DOR was 5.1 months (95% CI: 4.7, 5.7).
BTC				
Study D933AC00001 TOPAZ-1 Interim analysis 2 DCO: 11 Aug 2021) OS update analysis DCO: 25 Feb 2022 3-year update DCO: 23 Oct 2023 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, the median OS was 12.9 months (95% CI: 11.6,14.1) for the durvalumab + gemcitabine/ cisplatin group and A11.3 months (95% CI: 10.1, 12.5) for the placebo +gemcitabine	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).

		/cisplatin group; hazard ratio: 0.76 (95% CI: 0.64, 0.91). At the time of the 3-year update analysis, median OS was observed (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: 0.74 (95% CI: 0.63, 0.87).		
MPM				
Study D419KC00001 DREAM DCO: 30 Sep 2019 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.	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 DCO: 24 Apr 2020 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 DCO: 20 Jan 2022 OS analysis DCO: 03 Jul 2023 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 DUO-E DCO: 12 Apr 2023 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 chemotherapy (SoC + D) 49 SoC chemotherapy (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; hazard ratio: 0.77 (95% CI: 0.56, 1.07). dMMR subgroup Median OS for SoC + D was not preached vs 23.7 months (95% CI: 16.9, NR) in SoC arm with	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; hazard ratio: 0.71 (95% CI: 0.57, 0.89; p=0.003). dMMR subgroup Median PFS was not reached in the SoC + D arm compared in the SoC arm (hazard ratio 0.42;	<u>FAS (MMR any)</u> 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; hazard ratio: 0.71 (95% CI: 0.57, 0.89; p=0.003) <u>dMMR subgroup</u> Median PFS was not reached in the SoC + D arm compared in the SoC arm (hazard

		HR 0.34 (95% CI: 0.13, 0.79)	95% CI: 0.22, 0.80).	ratio 0.42; 95% CI: 0.22, 0.80).
Muscle-invasive bladder cancer				
Study D933RC00001 NIAGARA pCR final analysis DCO: 14 Jan 2022 Second interim EFS analysis DCO: 29 Apr 2024 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 DCO: 11 Jan 2021 Study completed	Durvalumab + olaparib: 134 (134 in the FAS) following initial therapy with SoC platinum-	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.

	based chemotherapy with durvalumab			
HCC				
Study D4190C00022 DCO: 06 Nov 2020 Study completed	Part 4 47 Durvalumab + bevacizumab (15 mg/kg 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 DCO: 11 Sep 2023 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 and (95% CI: 26.8, 35.8) 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; hazard ratio: 0.77 (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 28.8 months (95% CI: 24.2, 38.7) for the durvalumab + TACE arm and 30.5 months (95% CI: 26.8, 35.8) for the placebo + TACE arm.	Median PFS was 10.0 months for the durvalumab + TACE arm and 8.2 months for the placebo + TACE arm; hazard ratio: 0.94 (95%	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

			CI: 0.75, 1.19; p=0.638).	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 (SoC + D + O) 192 SoC chemotherapy (SoC)	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; 95% CI: 0.59, 0.99).	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.
Ovarian cancer				
Study D081RC00001 DUO-O DCO: 05 Dec 22	Non-tBRCAm 378 Durvalumab + olaparib +	Median OS was NR in the SoC + D + O arm and the SoC arm.	Median PFS was 24.2 months (95% CI: 22.7, 26.8) in the	ORR was 74.7% (222/297). Median DOR was 19.6 months.

	Final analysis for PFS/interim OS analysis DCO: 18 Sep 23 Study completed	bevacizumab + SoC chemotherapy (SoC + D + O) (378 in the FAS) 378 Bevacizumab + SoC chemotherapy (SoC) (378 in the FAS)	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 armo and 48.0 months (95% CI: 44.1, NR) in the SoC arm; hazard ratio: 0.95 (95% CI: 0.76, 1.20).	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).	
		Non-tBRCAm HRD-positive 140 Durvalumab + olaparib + bevacizumab + SoC chemotherapy (SoC + D + O) (140 in the FAS) 143 Bevacizumab + SoC chemotherapy	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 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	Median PFS was 37.3 months (95% CI: 29.8, 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	ORR was 83.7% (87/104). Median DOR was 29.1 months.

		(SoC) (143 in the FAS)	(95% CI: 0.51, 1.37).	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).	
		Non-tBRCAm 374 Durvalumab + bevacizumab + SoC chemotherapy (SoC + D) (374 in the FAS) 378 Bevacizumab + SoC chemotherapy (SoC) (378 in the FAS)	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 (95% CI: 44.1, NR) in the SoC arm; hazard ratio: 0.92 (95% CI: 0.73, 1.16).	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). 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).	ORR was 69.1% (199/288). Median DOR was 16.5 months.

	Other indications				
	Study D081KC00001 MEDIOLA Initial Stage DCO: 14 Jun 2019 Second Stage/final DCO: 17 Sep 2021 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-negative breast cancer): 34 Durvalumab + olaparib (30 in the FAS)	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).
		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	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%.

	cancer): 51 Durvalumab + olaparib (51 in the FAS)			
	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 months (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 ovarian cancer): 32 Durvalumab + olaparib (32 in the FAS)	At the Second Stage/final analysis, median OS was 26.1 months (95% CI: 18.7, NC).	At the Second Stage/final analysis, median PFS was 5.5 months (95% CI: 3.6, 7.5).	At the Second Stage/final analysis, ORR was 34.4% (11/32; 11 PR). DCR at 24 weeks was 28.1% (9/32).

- **Safety in Human:**

Pooled Monotherapy Data

Safety data have been pooled from a total of 9 durvalumab monotherapy studies:

Patients are included in this validated pooled data set. The durvalumab monotherapy pooled dataset includes patients with a number of solid tumor indications, including NSCLC, HNSCC, and UC.

- **The most common** TEAEs that were considered treatment-related by the investigators were **fatigue** ([13.0%]patients), **hypothyroidism** ([8.3%] patients), **diarrhoea** ([7.9%] patients), **pruritus** ([6.7%] patients), **nausea** ([6.6%] patients), **rash** ([6.4%] patients each), **decreased appetite** ([6.4%]patients), and **asthenia** ([5.0%] patients).
- **AEs of maximum** Grade 3 or higher considered related to durvalumab were reported in 11.3% patients and 9.7% patients had events of Grade 3, 0.9% patients had events of Grade 4 and 0.7% patients had Grade 5 (fatal) events.

- **Grade 5 events** considered related to durvalumab occurring in patient each were **brain natriuretic peptide increased, death, gastrointestinal hemorrhage, haemoptysis, hemorrhage, hepatic function abnormal, immune thrombocytopenia, inappropriate antidiuretic hormone secretion, mental status changes, pneumonia, pneumonia cytomegaloviral, radiation pneumonitis, respiratory distress, right ventricular failure and toxic cardiomyopathy.**

---SAEs:

- A total of 6.5% patients had **SAEs that** were considered **treatment-related** by the investigators. The most common were: **pneumonitis** (1.2% patients); **pneumonia** (0.3% patients); *diarrhoea* and **ILD** (0.2% patients each); **colitis** and **infusion related reaction** (0.2% patients each); **dyspnea** and **fatigue** (0.2% patients each); **radiation pneumonitis** (0.1% patients); and **acute kidney injury**, **adrenal insufficiency**, **AST increased**, **dehydration**, **hypothyroidism**, **nausea**, **nervous system disorder** and **thrombocytopenia** ([<0.1%]patients each.
- 9.4% patients discontinued from study treatment due to an AE.
- **The most common events leading to treatment discontinuation** were : pneumonitis (1.1% patients); pneumonia (0.6% patients); dyspnea (0.4% patients); general physical health deterioration (0.3% patients); ILD (0.2% patients), radiation pneumonitis (0.2% patients); and anemia, respiratory failure and sepsis (0.2% patients each); all other discontinuation events occurred in ≤4 patients.

--Immune-mediated Adverse Events – Durvalumab Monotherapy

In patients receiving durvalumab monotherapy, **immune-mediated pneumonitis** occurred in 3.1% patients, immune-mediated **hepatitis** occurred in 2.3% patients , immune-mediated **colitis or diarrhea** occurred in 1.9% patients, immune-mediated **hypothyroidism** occurred in 8.2% patients, immune-mediated **hyperthyroidism** occurred in 1.7% patients, immune-mediated **thyroiditis** occurred in 0.4% patients, immune-mediated **adrenal insufficiency** occurred in 0.5% patients, Grade 3 immune-mediated type 1 **diabetes mellitus** occurred in (<0.1%), patient immune-mediated **hypophysitis/hypopituitarism** occurred in patients (<0.1%), **immune-mediated nephritis** occurred in 0.4% patients, **immune-mediated rash or dermatitis** (including pemphigoid) occurred in 1.7% patients .

--Laboratory Data – Durvalumab Monotherapy:

Hepatic chemistry: The highest incidence (>20% of patients) of ≥1 grade shift from baseline was observed for **GGT, albumin, AST, ALP** and **ALT increased**. Any ≥2-grade worsening occurring in ≥5% patients were observed for albumin (11.5%) and GGT increased (10.1%). Any grade worsening to Grade 3 or 4 occurring in ≥5% patients was observed for GGT increased (8.9%).

Renal chemistry: 22.9% patients had ≥1 grade shift from baseline in **increased creatinine**. A total of 2.5% patients reported any ≥2-grade worsening in increased creatinine; 0.5% patients had any grade worsening to Grade 3 or 4.

Pancreatic chemistry: 23.7% patients had ≥1 grade **shift from baseline in amylase**. A total of 7.7% patients reported any ≥2-grade worsening in amylase; 5.7% patients had any grade worsening to Grade 3 or 4.

Other clinical chemistry: The highest incidence (>20% of patients) of ≥1 grade shift from baseline was observed for **hyperglycemia, hyperkalaemia, hypocalcaemia,** and **hyponatremia**. More than 5% of patients had a ≥2-grade worsening in hyperglycaemia (13.0%), hyponatremia (8.4%), and hyperkalaemia (5.1%). Any grade worsening to Grade 3 or 4 occurring in ≥5% patients was observed for hyponatremia (8.5%) and hyperglycaemia (5.0%).

Hematology: The highest incidence (>20% of patients) of ≥1 grade shift from baseline was observed for **hemoglobin and lymphocyte decrease**. More than 5% of patients had a ≥2-grade worsening in lymphocyte decreases (19.1%). Any grade worsening to Grade 3 or 4 occurring in ≥1% patients was observed for lymphocyte decrease (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.

PACIFIC: Incidence of Pneumonitis (Grouped Term) or Radiation Pneumonitis (Safety Analysis Set)

--Immune-mediated pneumonitis events in PACIFIC

The event of immune-mediated pneumonitis occurred in 9.9% patients in the durvalumab-treated group and 6.0% patients in the placebo group, including Grade 3 in 1.9% patients on durvalumab vs 2.6% patients on placebo, and Grade 5 in 0.8% patients on durvalumab vs 1.3% patients 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.

It was noted that the majority of patients who responded **achieved tumor 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 Q3W Chemotherapy Regimens**

The safety of a Q3W 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 Q3W 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 (14.6% patients), pruritus (14.3% patients), fatigue (13.0% patients), rash (10.4% patients), hypothyroidism (9.3% patients), decreased appetite (7.8% patients), nausea (7.2% patients), asthenia (5.4% patients), and hyperthyroidism (5.3% patients).

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

A total of 17.1% **patients 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 (2.3% patients); pneumonitis (1.8% patients); colitis (1.6% patients); adrenal insufficiency (0.6% patients); ILD (0.6% patients); pyrexia (0.65 patients); and pneumonia (0.5% patients).

A total of ~~17.0%~~ **patients** 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:**

Durvalumab Plus Tremelimumab T75+D Combination

In patients receiving tremelimumab in combination with durvalumab (T75+D immune-mediated pneumonitis occurred in 3.5% patients, immune-mediated hepatitis occurred in 3.0% patients, immune-mediated colitis or diarrhoea occurred in 5.7% patients, immune-mediated hypothyroidism occurred in 8.0% patients, immune-mediated hyperthyroidism occurred in 2.1% patients, immune-mediated adrenal insufficiency occurred in 1.1% patients, 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 ~~1.3%~~ patients, immune-mediated hepatitis occurred in 7.4% patients, immune-mediated colitis or diarrhoea occurred in 6.7% patients ,immune-mediated hypothyroidism occurred in 10.0% patients, immune-mediated hyperthyroidism occurred in 4.5% patients, immune-mediated thyroiditis occurred in 1.3% patients, immune-mediated adrenal insufficiency occurred in 1.3% patients ,immune-mediated Type 1 diabetes mellitus was not observed, immune-mediated hypophysitis/hypopituitarism occurred in 1.1% patients, immune-mediated nephritis occurred in 0.9% patients ,immune-mediated rash or dermatitis (including pemphigoid) occurred in 5.6% patients.

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 combinationcould 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, **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 32.1% patients. SAEs reported in ≥2% of patients were febrile neutropenia (4.5%) and pneumonia (2.3%). Six 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, 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 anemia (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 314 (92.9%) patients had AEs considered possibly related to any study medication. Overall, 73.7% patients reported maximum CTCAE Grade 3 or 4 AEs; 211 (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%); anemia (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 D081RC00001 (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 program; 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 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 of (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 30 mg/kg 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.

***Tremelimumab:**

Pharmacokinetics and drug metabolism in humans

1-Single-dose pharmacokinetics

Following single-dose administration in **Study A3671001**, tremelimumab showed **approximately dose-proportional increases in Cmax and AUC**, with **low clearance (0.132 mL/hour/kg)**, **small Vss (81.2 mL/kg)**, and a **long half-life (22.1 days)**, consistent with IgG2 characteristics.

In **Study A3671002**, tremelimumab exhibited a **biphasic PK profile** with similarly **low clearance (0.139 mL/hour/kg)**, **small Vss (78.1 mL/kg)**, and **long half-life (19.6 days)**.

2-Multiple-dose pharmacokinetics

With monthly dosing, there was a mean **26% increase** in exposure at steady state. Mean peak concentrations ranged from **309 to 472 µg/mL,** while **mean C-trough** ranged from **7 to 19 µg/mL.**

Neither peak nor Ctrough **changed significantly after multiple doses** of tremelimumab suggesting **minimal accumulation** of tremelimumab after multiple **Q90D doses.**

3-Population PK analysis

A **2-compartment linear model with first-order elimination** adequately described tremelimumab PK. Typical estimates were **CL ~0.2–0.26 L/day** and **central volume (V1) ~3.5–3.97 L**, with **modest inter-individual variability** (**CL: 22–31.8%; V1: 7–20.4%**).

Covariates: Clearance was higher in **males**, and in patients with **higher creatinine clearance, endogenous Ig levels, poorer baseline prognostic factors, higher body weight, and ECOG status**; V1 increased with **body weight and male sex**. No dose adjustment was required (**CL change <30%**).

Exposure: resulted in **sub-target exposure** for ~half of the dosing interval, with most patients below LLOQ at Day 90. In contrast, maintained exposure **at or above target levels** throughout the dosing interval. Overall, PK characteristics were **consistent with monoclonal antibodies without target-mediated elimination**.

Pharmacokinetics in combination studies

Study A3671025

A Phase I study (A3671025) evaluated the **safety and tolerability** of tremelimumab in combination with sunitinib in patients with **metastatic RCC.**

Because the expansion cohort was terminated early due to acute renal failure, only the **Cmax** values after the first dose were determined. The median (range; number of patients) **Cmax** of tremelimumab was **193 µg/mL (168 to 438 µg/mL) , 230 µg/mL (60 to 336 µg/mL), and 397 µg/mL (264 to 428 µg/mL).**

Overall, the PK of tremelimumab was **similar** between **melanoma and RCC populations**.

In 3 of the 4 patients who **developed serious renal events,** the **Cmax for tremelimumab was 251 µg/mL , 420 µg/mL , and 264 µg/mL .** No sample for PK analysis was collected from the 4th patient. Although the data are limited, the serious renal events did not appear to be associated with high tremelimumab concentrations.

Summary of PK data in Study D4880C00010 (tremelimumab monotherapy)

Following **Dose 1** of **tremelimumab**, **serum tremelimumab concentration reached the peak level** at the end of infusion and *afterward gradually decreased* with first order elimination rate. The geometric mean (GMean) (coefficient variable [CV]%) of total drug exposure over time (AUC0-t) after **Dose 1** of tremelimumab was 1850 (3.12) day·µg/mL**,** and the GMean (CV%) of serum tremelimumab (Cmin and Cmax) were 33.0 (35.2) and 183 (15.5) µg/mL, respectively. Time to reach maximum concentration **(Tmax)** was after the end of infusion **(0.051 day).**

After **Dose 2** of **tremelimumab**, serum tremelimumab concentration **dropped** to **trough level before Dose 2**. At steady state, the GMean (CV%) of the tremelimumab accumulation ratio RAC [Cmin] and RAC [Cmax] were 1.13 (20.5) and 1.34 (10.2), respectively. The GMean (CV%) of maximum and minimum tremelimumab serum concentration at steady state (Css min and Css max) were 44.4 (43.4) and 253 (14.0), respectively. The **Tmax** at steady state was **similar to that after the first dose**.

After Dose 1 of tremelimumab, **serum tremelimumab concentration reached** the peak level at the end of infusion. **Tremelimumab was detected in the serum before infusion of subsequent doses**. However,

no apparent accumulation was observed by comparing the GMean of the serum tremelimumab concentration at the end of infusion at **Week 25 to Week 1.**

- **Efficacy and safety in humans**
  - **Efficacy**

Association between exposure and survival in Phase I and II studies

For the **exposure-survival analysis**, data were divided into **high-** and **low-exposure** groups based on the median value of **AUC** (**103570 µg·hr/mL**). The **median OS** was **significantly longer** in the **high-AUC** group **(15.3 months)** versus the **low-AUC group (6.0 months).** This difference in **OS** corresponds to an **HR of 0.41; p<0.001** and the estimated survival rates in the **2** groups were **59%** versus **29%** at **1** year. **The highest exposure to tremelimumab as measured by AUC was associated with the longest survival.** Median **OS** was **24.3 months** in the highest-AUC quartile **(Q4),** but only **4.3 months** in the **lowest-AUC quartile (Q1).**

In the **highest-AUC quartile, 42%** of the patients received tremelimumab, **only 20%** had **ECOG** performance status of **1**, and 21% had LDH ≥upper limit of normal (ULN) at baseline, while in the **lowest-AUC quartile**, **only 10%** received tremelimumab, **56%** had **ECOG performance status of 1**, and 40% had LDH ≥ULN at baseline, besides having lower body weight

Cox proportional hazard regression modelling identified **LDH**, **ECOG** performance status, **C-reactive protein (CRP),** and **metastasis stage** as the **most significant baseline characteristics for increased OS** in the Phase II study (**A3671008**).

In order to adjust for the imbalance in these baseline variables between different AUC groups, a **Cox regression model** was fit stratified by **LDH**, **ECOG** performance status, and metastasis stage, with median **AUC**, **CRP**, and body weight included as covariates. The adjusted effect of AUC on **OS** in terms of **HR** was **statistically significant favoring higher AUC (p <0.001)**.

Association between exposure and survival in the Phase III study

Survival analysis of patients treated with tremelimumab in a **Phase III study** in melanoma (**A3671009**) showed **better OS in patients with higher exposure**. The median **OS** was **18.4 months** for the **high-AUC (≥123,665 µg·hour/mL)** group compared to **9.0 months** for the **low-AUC (<123,665 µg·hour/mL)** group **(HR 0.5, 95% CI: 0.38, 0.65; p <0.001)** Higher rates of **1-year survival (67% vs 56%)** were observed in the **high** versus **low AUC** groups, respectively.

- **Safety**

Frequent adverse events

In **Study D4880C00003 (DETERMINE; mesothelioma),** the following **most common AEs** (≥10% in the tremelimumab group) occurred **at a higher frequency** in the **tremelimumab 10 mg/kg group** compared with the **placebo group**: **diarrhoea** (47.1% vs 19.0%), **nausea** (28.2% vs 20.1%), **pruritus** (27.1% vs 7.9%), **rash** (20.8% vs 6.9%), **vomiting** (20.3% vs 11.6%) and **pyrexia** (16.3% vs 8.5%). In comparison, the following most common **AEs** occurred at a higher frequency in the **placebo group:** fatigue (24.2% vs 31.7%) and constipation (17.4% vs 28.0%). The following **most common AEs** occurred **at a similar frequency in both groups**: **dyspnoea** (31.8% vs 36.5%), **decreased appetite** (28.9% vs 24.3%), **cough** (17.6% vs 16.4%), **anaemia** (15.5% vs 12.2%), **asthenia** (14.5% vs 14.3%), **musculoskeletal chest pain** (13.4% vs 18.0%), **abdominal pain** (12.9% vs 13.2%), **weight decreased** (12.6% vs 9.0%) and **peripheral oedema** (10.3% vs 8.5%).

In the **TMMD** pool, at the dose of tremelimumab used in **Study D4880C00003 (DETERMINE),** a higher proportion of patients in the melanoma group had the **most common AEs (≥10% overall) of nausea** (48.5%), **fatigue** (56.1%), **pruritus** (42.4%), **decreased appetite** (40.9%), **rash** (37.9%), **vomiting** (37.9%) and **headache** (15.2%) compared with patients in the mesothelioma group. However, **fewer patients in this melanoma group had AEs of dyspnoea** (12.1%) compared with patients in the **mesothelioma group** (where **dyspnoea** occurred at higher frequency in placebo group).

In the **TST pool 15 mg/kg group, and overall, the proportion of patients who had the most common AEs (≥10% overall)** was either **similar or lower when compared** with the overall tremelimumab group in the **TMMD** pool.

Adverse events of ≥Grade 3

In Study **D4880C00003 (DETERMINE; mesothelioma),** the following **most common ≥Grade 3 AEs (≥5% in the tremelimumab group**) occurred **at a higher frequency** in the tremelimumab group compared with the **placebo group**: **diarrhoea** (15.3% vs 0.5%) and **colitis** (6.8% vs 0%). **Dyspnoea** was the only **≥Grade 3 AE** that occurred **at a higher frequency** in the placebo group (8.9% vs 14.3%). The frequencies of the remaining **≥Grade 3 AEs** were **similar** across both groups.

In the **TMMD pool**, at the dose of tremelimumab used in Study **D4880C00003 (DETERMINE), fewer patients in the melanoma** group had **≥Grade 3 AEs** of **dyspnoea** (1.5%) compared with patients in the mesothelioma group. The frequencies of the remaining **≥Grade 3 AEs** were **similar** across both indications, at this dose.

In the **TST pool**, the proportion of patients who had the most common **≥Grade 3 AEs** was either **similar or lower** when compared with the overall tremelimumab group in the TMMD pool.

Serious adverse events

- In Study **D4880C00003 (DETERMINE; mesothelioma)**, the following most common **SAEs (≥0.5% in the tremelimumab group)** occurred **at a higher frequency** in the tremelimumab 10 mg/kg group compared with the placebo group: **diarrhoea** (18.2% vs 0.5%) and **colitis (6.3% vs 0).** Dyspnoea was the only SAE that occurred at a higher frequency in the placebo group. The frequencies of the remaining **SAEs** were **similar** across **both** groups. The high rate of **SAEs** in the placebo group suggests **these events are related to disease progression or background rates for this patient population**.
- In the **TMMD** pool, at the dose of **tremelimumab** used in Study **D4880C00003 (DETERMINE**), the frequencies of SAEs were **similar** across both indications.
- In the **TST pool**, the proportion of patients who had the most common **SAEs** was either **similar or lower** when compared with the overall tremelimumab group in the TMMD pool.

Deaths

Adverse Events with Outcome of Death Occurring in > 1 Patient per Treatment Group: TMMD Pool:

The proportion of patients with an adverse event resulting in death was **9.5%** in the **mesothelioma tremelimumab** group versus **6.3%** = in the **mesothelioma placebo** group. In the **melanoma studies**, the corresponding percentages were **6.8%** for **Phase IIIb tremelimumab** versus **4.4%** for the **chemotherapy comparator**, and in **Phase I/IIc melanoma** the rates were **9.3%** for **tremelimumab 6.1%** for **tremelimumab ,** and **0.0%** for **tremelimumab**. The most common cause of death by **System Organ Class** in the total tremelimumab population was **Neoplasms benign, malignant and unspecified (including cysts and polyps)**, reported in **3.4% patients**, and the most common **Preferred Term** overall was **neoplasm progression**, reported in **3.0% patients**. Other notable fatal events by SOC/PT included **cardiac disorders** (**1.1% patients**), especially **myocardial infarction** (**0.3% patients**), **respiratory, thoracic and mediastinal disorders** (**1.1% patients**), including **dyspnoea** (**0.4% patients**) and **respiratory failure** (**0.2%patients**), as well as **infections and infestations** (**0.8% patients**) with **lung infection** (**0.3% patients**) and **gastrointestinal disorders** (**0.8% patients**) with **colitis** (**0.2% patients**). Overall, the pattern suggests that most fatal outcomes were driven primarily by **progression of the underlying malignancy**, with smaller contributions from cardiac, respiratory, infectious, and gastrointestinal causes.

In Study **D4880C00003 (DETERMINE; mesothelioma), 80.4%** of patients in the **tremelimumab** group compared with **81.5%** in the p**lacebo** group **died due to a number of causes**

Adverse events leading to discontinuation of investigational product

In **Study D4880C00003 (DETERMINE; mesothelioma), 27.4%** of patients in the **tremelimumab** compared with **5.3%** in the placebo group had an **AE leading to discontinuation of treatment. Diarrhoea (12.9% vs 0.5%)** was the **only AE leading to discontinuation** that occurred at a **higher frequency** in the **tremelimumab** compared with the placebo group. The frequencies of the remaining **AEs** leading to **discontinuation** were similar across both groups.

In the **TMMD pool**, there were **fewer AEs** leading to discontinuation in the **melanoma group.**

In the **TST pool** the proportion of patients who had **AEs** leading to discontinuation was lower than the **TMMD pool**

Adverse events of special interest

Diarrhoea, Colitis/enterocolitis, Dermatitis, Endocrinopathy, Hepatitis/hepatic toxicity, Pancreatitis, Neuropathy/neuromuscular toxicity, Pneumonitis/interstitial lung disease, Renal failure and nephritis and Hypersensitivity reaction/anaphylaxis/infusion reactions.

***Combination therapy (other than durvalumab) ***

- A total of **98.3% patients** experienced at least **1** event. Adverse events were most frequently reported in the **SOCs** of Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders. Adverse events reported in **>10%** of patients overall were **diarrhoea, nausea, fatigue**, **rash, decreased appetite, pruritus, vomiting, pyrexia, influenza-like illness, arthralgia, constipation, injection site reaction, thrombocytopenia, AST increased, peripheral oedema, ALT increased, back pain, dysgeusia, headache, dyspnoea, and cough.** Most of these events occurred at a higher rate with **tremelimumab+ sunitinib** compared with the other combinations.
- Of the patients who experienced **AEs, 62.9%** had **events of ≥Grade 3 severity.** The most frequently reported **≥Grade 3 AEs (in >3% of patients)** were **diarrhoea** (14.7%), **fatigue** (7.8%), **hypertension** (5.2%), **disease progression and dyspnoea** (4.3% each), and **nausea, ALT increased, lipase increased,** and **dehydration** (3.4% each). Adverse events were considered to be treatment related in **70.7% patients.**
- The most frequent treatment-related **AEs (occurring in >10% of patients)** were **diarrhoea** (44.0%), **pruritus** (25.0%), **fatigue** (24.1%), **rash** (23.3%), **nausea** (19.8%), **decreased appetite** (18.1%), **vomiting and pyrexia** (12.9% each), **and thrombocytopenia** (10.3%).
- Of note, thrombocytopenia was reported with **tremelimumab+ sunitinib and tremelimumab+ gemcitabine.**

Serious adverse events

The highest incidence of SAEs occurred with **tremelimumab+ sunitinib (53.6%**) and **tremelimumab+ PF 03512676 (52.4%). S**erious adverse events experienced by **>3%** of patients were **diarrhoea, pyrexia, dyspnoea, disease progression, dehydration,** and **acute renal failure.** Most of these events were **≥Grade 3** in severity **(diarrhoea** [6.0%], **disease progression** [4.3%], **dyspnoea** [3.4%], **dehydration and acute renal failure** [2.6% each]), except for the events of **pyrexia** that were all Grade 1 or 2 in severity. The acute renal failure events occurred in patients treated with **tremelimumab+ sunitinib** and in patient treated with **tremelimumab+ gemcitabine.**

Deaths

The highest frequency of **fatalities** was reported with **tremelimumab+ gemcitabine (82.4%) and tremelimumab+ PF 03512676 (71.4%).** The majority of the deaths occurred more than **90 days (27.6%) after and within 90 days (18.1%)** of the last dose of tremelimumab, and **4.3%** of deaths occurred within **60** days of study entry (defined as the date of randomization for randomized studies and start of study treatment for non-randomized studies). The cause of death was ascribed to **underlying disease** (39.7%), **unknown/missing** (4.3%), **other** (3.4%), or **investigational product** (0.9%).

- **Protocol:** A Phase III, Randomized, Open-Label, Sponsor-Blinded, Multicenter Study of Durvalumab in Combination with Tremelimumab ± Lenvatinib Given Concurrently with Transarterial Chemoembolization (TACE) Compared to TACE Alone in Patients with Locoregional Hepatocellular Carcinoma (EMERALD-3).

-Durvalumab is a human mAb of the immunoglobulin G 1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of cancer. The proposed MOA for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon-gamma (IFN-γ).

-**Tremelimumab** is a human immunoglobulin G2 mAb of the IgG2κ isotype that is directed against CTLA-4; CD152). The binding of CTLA-4 to its target ligands (CD80 and CD86) provides a negative regulatory signal, which limits T-cell activation and blocks the interaction of the co-stimulatory receptor CD28 with CD80 and CD86, thus limiting CD28-mediated T cell co-stimulation. Tremelimumab antagonizes the binding of CTLA-4 to its ligands and enhances human T-cell activation, as demonstrated by increased cytokine (IL-2, IFN-γ) production in vitro within whole blood or PBMC cultures. In addition, the blockade of CD80/86 binding to CTLA-4 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and the

induction of protective antitumor immunity. Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

-Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant, targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity. Therefore, AstraZeneca is also investigating the use of durvalumab plus tremelimumab combination therapy for the treatment of cancer.

-**Lenvatinib** is a multikinase inhibitor that targets several kinases including VEGF receptors (VEGFRs) 1 to 3, fibroblast growth factor receptors (FGFRs) 1 to 4, platelet-derived growth factor receptor, RET and KIT.

Phase: III

Objective(s):

Objectives	Endpoints / Variables
Primary	
To demonstrate superiority of durvalumab + tremelimumab + lenvatinib + TACE relative to TACE alone by assessment of PFS in participants with locoregional HCC.	PFS is defined as time from randomization until progression per RECIST 1.1 as assessed by BICR, or death due to any cause. The analysis will include all randomized participants, regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the HR of PFS
Key Secondary	
To demonstrate superiority of durvalumab + tremelimumab + TACE relative to TACE alone by assessment of PFS in participants with locoregional HCC.	OS is defined as time from randomization until the date of death due to any cause. The comparison will include all randomized participants, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
To demonstrate superiority of durvalumab + tremelimumab + TACE relative to TACE alone by assessment of OS in participants with locoregional HCC	PFS as defined above
To demonstrate superiority of durvalumab + tremelimumab + TACE relative to TACE alone by assessment of OS in participants with locoregional HCC	OS as defined above
Secondary	

To demonstrate the effectiveness of durvalumab + tremelimumab + lenvatinib + TACE relative to TACE alone and durvalumab + tremelimumab + TACE relative to TACE alone by assessment of PFS using mRECIST in participants with locoregional HCC	PFS as defined above, using mRECIST as assessed by BICR and by the investigator.
To demonstrate the effectiveness of durvalumab + tremelimumab + lenvatinib + TACE relative to TACE alone and durvalumab + tremelimumab + TACE relative to TACE alone by assessment of ORR, DCR, DoR, TTP, and PFS2 in participants with locoregional HCC	• ORR is defined as the proportion of participants who have a confirmed CR or PR, as determined by BICR per RECIST 1.1 and per mRECIST by BICR and by the investigator. The analysis will include all randomized participants with measurable disease at baseline. Data obtained from randomization up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR, regardless of whether the participant withdraws from therapy. Participants who go off treatment without a response or progression, receive a subsequent therapy, and then respond will not be included as responders in the ORR. The measure of interest is the odds ratio of the ORR. • DCR is defined as the percentage of participants who have a confirmed CR or PR or who have SD per RECIST 1.1 as assessed by BICR and per mRECIST assessed by BICR and by the investigator after randomization. Data obtained from randomization up until progression will be included in the assessment of DCR, regardless of whether the participant withdraws from therapy. Participants who receive a subsequent therapy prior to the data cutoff for analysis will not be considered to have disease control in the analysis. The analysis will include all randomized participants. The measure of interest is the DCR. • DoR is defined as the time from the date of first documented response until the date of documented progression per RECIST 1.1 as assessed by BICR and per mRECIST as assessed by BICR and by the investigator, or death due to any cause. The analysis will include all

	randomized participants with measurable disease at baseline who have a response, regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to progression. The measure of interest is the median DoR. • TTP is defined as the time from randomization to objective tumor progression per RECIST 1.1 as assessed by BICR and per mRECIST as assessed by BICR and by the investigator. The analysis will include all randomized participants, regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to RECIST 1.1 progression. The measure of interest is the median TTP. • Time from randomization to second progression or death (PFS2) is defined as the time from randomization to the earliest progression event (following the initial progression), subsequent to first subsequent therapy or death. The date of second progression will be recorded by the investigator in the eCRF and defined according to local standard clinical practice. The comparison will include all randomized participants, regardless of whether the participant withdraws from subsequent therapy and regardless of missed visits. The measure of interest is the HR of PFS2.
To assess time to deterioration in key HCC symptoms (abdominal swelling and diarrhea) and physical functioning in participants treated with durvalumab + tremelimumab + lenvatinib + TACE compared with TACE alone and durvalumab + tremelimumab + TACE compared with TACE alone in participants with locoregional HCC	• Time to deterioration of the EORTC QLQ-HCC18: single item symptoms (abdominal swelling and diarrhea) • Time to deterioration of the EORTC QLQ-C30 physical functioning scale and item library item
To assess the relationship between the progressive changes in AFP level and efficacy parameters in participants with locoregional HCC	
To assess the PK of durvalumab and tremelimumab	

To investigate the immunogenicity of durvalumab and tremelimumab	Presence of ADAs for durvalumab and tremelimumab (confirmatory results: positive or negative, titers)
	Safety
To assess the safety and tolerability of durvalumab + tremelimumab + lenvatinib + TACE as compared with TACE alone and durvalumab + tremelimumab + TACE as compared with TACE alone in participants with locoregional HCC.	Safety and tolerability will be evaluated in terms of AEs (per CTCAE Version 5.0), vital signs, clinical laboratory results, ECGs, and Child-Pugh score. Assessments related to AEs cover: Occurrence/frequency • Relationship to study intervention as assessed by investigator • CTCAE grade • Seriousness • Death • AEs leading to discontinuation of study intervention • AEs leading to interruption/delay of study intervention • Dose reductions of lenvatinib • AEs of special interest • Other significant AEs: hepatic and hemorrhagic events Vital signs parameters include systolic and diastolic blood pressure, and pulse rate as well as respiration rate and body temperature. Assessments cover: • Observed value • Absolute and percent change from baseline values over time • Clinically significant abnormalities over time . Laboratory parameters include clinical chemistry and hematology as well as urinalysis. A complete list of parameters is presented in Section 8.2.4. Assessments cover: • Observed value • Absolute and percent change from baseline values over time • Clinically significant abnormalities in laboratory parameters over time

	• Laboratory status, including change in abnormality (eg, low, normal, high) from baseline to maximum on-treatment value • Laboratory status, including change in abnormality (eg, low, normal, high) from baseline to minimum on-treatment value • Treatment-emergent changes in laboratory parameters • Change in proteinuria from baseline to maximum on treatment value ECG measurements include heart rate, RR, PR, QRS, and QT intervals. Derived variables cover QTcF. Assessments cover: • Observed value. • QTcF exceeding 450 ms at any time during treatment • Change in QTcF exceeding 30 ms at any time during treatment as compared to baseline. • Change in Child-Pugh score from baseline will be evaluated.

Rationale:

Hepatocellular carcinoma (HCC) is the fourth most common cause of death from cancer worldwide, accounting for approximately 8.2% of all cancer-related deaths globally. Treatment with TACE procedures achieve an initial tumor response in most patients with locoregional HCC but is limited by the extent of vascular access for catheterization near the tumor, the inability to reach micro-metastases outside of the embolization field, and reduction of liver functional reserve with repeated procedures. These limitations result in residual tumor cells, some of which may not be visualized radiographically.

Several immunosuppressive signaling pathways play an important role in HCC including programmed cell death-1 (PD-1), programmed cell death-ligand 1 (PD-L1), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), and vascular endothelial growth factor (VEGF). Targeting these pathways may potentially improve clinical outcomes by reversing the immunosuppressive environment of HCC and by stimulating host immunity against HCC. In addition, locoregional treatments for HCC, such as TACE, may alter the tumor microenvironment and serve as a primer for anti-PDL-1 and anti-VEGF systemic therapy. Clinical evidence supporting the inhibition of the PD-1/PD-L1, CTLA-4, or VEGF pathways or their combinations (±TACE) in HCC is supported by the following trials in unresectable HCC.

Overall benefit\ Risk:

Combination therapy in HCC has already shown impressive outcomes for patients in many clinical trials. First, the combination of PD-L1 pathway inhibition and CTLA-4 has already shown substantial efficacy in second-line advanced HCC in other studies. Second, the anti-angiogenesis TKI therapy Lenvatinib has an approval in 1st line HCC and continues to show promising outcomes in combination with immunotherapy or TACE in HCC. And the combinatorial efficacy of the proposed triplet regimen + TACE is supported by the MOAs of the respective components: 1) Lenvatinib enhances the anti-tumor immune response and blocks the blood supply to existing tumor tissue, hence preventing tumor growth and/or accelerating tumor necrosis (Lenvatinib also facilitates tumor antigen release); 2) TACE throughout the study will ensure patients continue to receive standard of care as a backbone of therapy and will provide additional release of neoantigen; and 3) the HCC cell kill provided by TACE and Lenvatinib should also stimulate the immune response in the tumor microenvironment, and this immune response can be enhanced by the CTLA-4 blockade with Tremelimumab, which primarily acts to promote new anti-tumor T-cell responses that can then be further strengthened by PD-L1 blockade with durvalumab. Consequently, the hypothesis for the potency of the triplet combination with TACE will be to provide upfront tumor killing, deep responses with Lenvatinib and TACE, and long-term tumor control delivered with Tremelimumab and durvalumab.

Design:

- A Phase III, Randomized, Open-Label, Sponsor-Blinded, Multicenter Study.

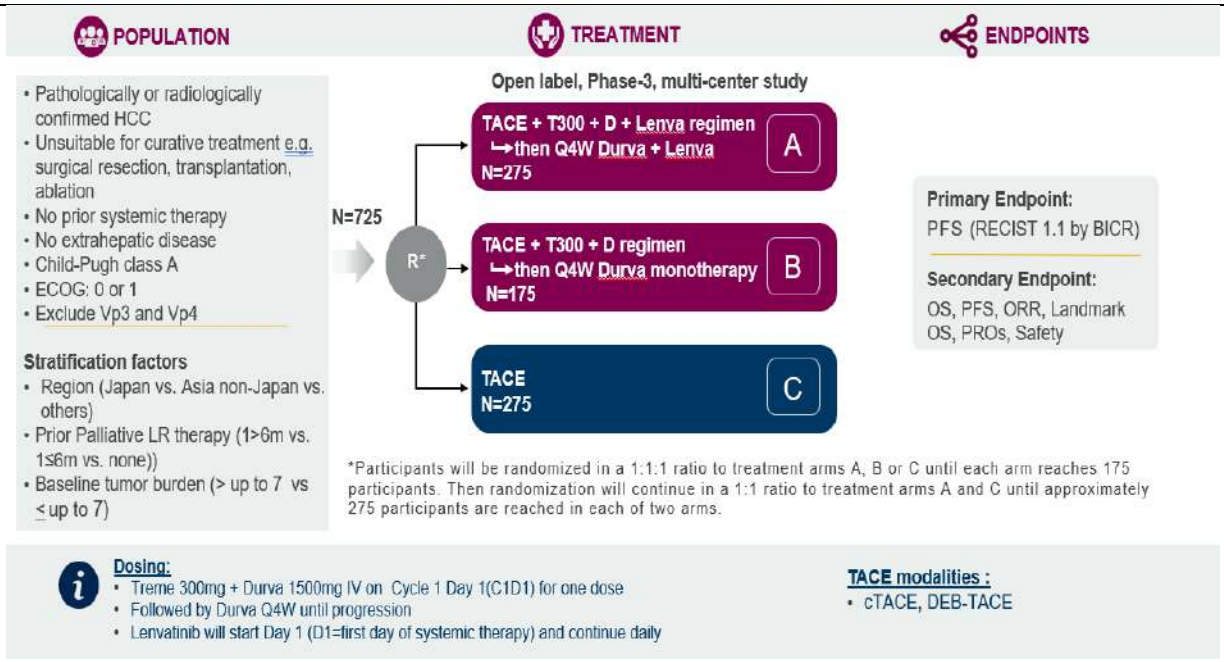
-Participants will be randomized in a **1:1:1** ratio to one of the following intervention groups:

- **Arm A**: Tremelimumab 300 mg (T300) + durvalumab 1500 mg + Lenvatinib 8 or 12 mg (per participant's body weight) on Cycle 1 Day 1, followed by durvalumab 1500 mg q4w + Lenvatinib once daily (dose may be subject to modification) + drug-eluting bead-Transarterial chemoembolization (DEB-TACE) or conventional Transarterial chemoembolization (cTACE)
- **Arm B**: T300 + durvalumab 1500 mg on Cycle 1 Day 1, followed by durvalumab 1500 mg q4w + DEB-TACE or cTACE
- **Arm C**: DEB-TACE or cTACE alone starting on Cycle 1 Day 1, followed by additional TACE procedures at the investigator's discretion

- Participants in Arm A and Arm B will receive 1500 mg durvalumab as an intravenous (IV) infusion q4w, starting on Cycle 1 Day 1 for up to a maximum of 36 months (**36 doses/cycles**), with the last administration on Cycle 36 Day 1, or until clinical progression (histopathological evidence from biopsy, cytological evidence, etc., for participants with unclear radiological progression), investigator-assessed mRECIST-defined radiological progression, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met.

-Participants in Arm A and Arm B will also receive a single dose of 300 mg Tremelimumab as an IV infusion on Cycle 1 Day 1.
-Participants in Arm A will also receive Lenvatinib 8 mg (for body weight < 60 kg) or 12 mg (for body weight ≥ 60 kg) orally once daily for up to a maximum of 36 months, with the last administration on Cycle 36 Day 28, or until clinical progression (histopathological evidence from biopsy, cytological evidence, etc., for participants with unclear radiological progression), investigator-assessed mRECIST-defined radiological progression , unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met .
-Participants in all study arms will receive treatment with TACE procedures using either the DEB-TACE or cTACE modality. The first TACE procedure should be performed after all screening assessments and randomization have been completed, and for Arms A and B, should start no earlier than 7 days following the first dose of durvalumab on Cycle 1 Day 1, and for Arm C, TACE should start within 7 days following randomization. Treatment with TACE procedures will continue per standard of care, and the interval and frequency are at the investigator's discretion. The entire tumor burden in the liver must be treated by TACE after randomization (before first RECIST assessment) if safe and feasible.
-**Randomization will be stratified** by:

- geographical region (Japan versus Asia without Japan versus rest of world)
- Prior palliative embolization before randomization (1 > 6 months versus 1 ≤ 6 months versus none), and
- Baseline tumor burden per the up-to-7 criteria (measured as the sum of the size of the largest tumor [in cm] and the number of tumors]: < 7 is within the criteria [ie, IN] versus > 7 is outside the criteria [ie, OUT]



-The target population of interest in this study **is participants with locoregional HCC not amenable to curative therapy** (eg, surgical resection, transplantation, or ablation). The participants will also have a Child-Pugh score of class A, a World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, have not received prior systemic anticancer therapy for HCC, have no extrahepatic disease, and no tumor thrombosis.

-Approximately 750 participants with locoregional HCC will be enrolled to achieve approximately **525 randomized participants** to study intervention.

-During the intervention period (ie, up to a maximum of 36 months), participants who are clinically stable may continue to receive durvalumab and Lenvatinib beyond mRECIST defined progression of disease (PD) as long as- they are continuing to show clinical benefit, as judged by the investigator.

-After study intervention discontinuation, all participants will undergo an end-of-treatment visit (within 3 days of discontinuation) and will be followed up for safety assessments 30, 60, and 90 days after their last dose of study intervention (ie, the safety follow-up visit).

- **Post trial benefit:**

As there is no proven benefit-risk profile of the study regimen(s), continuing treatment with the Investigational Products used on EMERALD-3 **cannot be considered as the combination is not yet an approved medicine by any regulatory authority**. Instead, all subjects will be able to complete up to 36

months. Furthermore, **AstraZeneca will continue to supply durvalumab, with or without Lenvatinib,** in the continued access phase of this study and after completion of this study and after completion of this study given the opinion of the investigator that the participant is benefitting or until the participant must be discontinued per the discontinuation criteria.

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

- **Abbreviation:**

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
AUC	Area under the curve
BICR	Blinded Independent Central Review
BTC	Biliary tract cancer
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Clearance
Cmax	Maximum observed concentration
CR	Complete response
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation

DCR	Disease control rate
DEB-TACE	Drug-eluting bead transarterial chemoembolization
DLT	Dose limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
EDA	Egyptian Drug Authority
ELISA	Enzyme-linked immunosorbent assay
EFS	Event-free survival
FAS	Full Analysis Set
GD	Gestational Day
GLP	Good Laboratory Practice
GGT	Gamma-glutamyl transferase
HCC	Hepatocellular carcinoma
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
ILD	Interstitial lung disease
I-O	Immuno-oncology
IV	Intravenous

KLH	Keyhole limpet hemocyanin
LDH	Lactate dehydrogenase
mITT	Modified Intent-to-Treat
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
pCR	Pathologic complete response
PD	Progression of disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
Q4W	Every 4 weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
SoC	Standard of Care

sPD-L1	Soluble programmed cell death-ligand 1
TACE	Transarterial chemoembolization
TEAE	Treatment-emergent adverse event
TTP	Time to progression
UC	Urothelial carcinoma
ULN	Upper limit of normal

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