SUPPLEMENTARY MATERIALS

Additional details on safety endpoints: definitions of adverse events of potential interest (AEPI), adverse events of special interest (AESI), and immune-mediated adverse events (imAE)

As part of the safety evaluation, AESI, AEPIs and imAEs were assessed in all treatment arms. AESIs were defined as AEs with a likely inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab and requiring more frequent monitoring and/or interventions, such as corticosteroids, immunosuppressants, and/or endocrine therapy. AEPIs were defined as AEs that also had a potential inflammatory or immune-mediated pathophysiological basis resulting from the mechanism of action of durvalumab but were more likely to have occurred due to other pathophysiological mechanisms and, thus, the likelihood the event was inflammatory or immune-mediated in nature was not high and/or was most often or usually explained by the other causes. These AEs not routinely arising from an inflammatory or immune-mediated mechanism of action (typically quite general clinical terms that usually present from a multitude of other causes) were classified as AEPIs. AEs that were associated with drug exposure and were consistent with an immune-mediated mechanism of action, with no clear alternate etiology, were classified as imAEs. In addition to the events with an immune-mediated basis, infusion reactions and hypersensitivity/anaphylactic reactions were also considered to be AESIs but were not included in the imAE adjudication process, as these risks are common to mAb drugs, regardless of their mechanism of action.

SUPPLEMENTARY TABLES

Supplementary Table S1. Representativeness of study participants

Cancer type(s) / subtype(s) / stage(s) / condition	Resectable, early-stage (stage IA3-IIIA) non-small-cell lung cancer (NSCLC)
Considerations related to:	
Sex	A greater incidence of NSCLC has previously been reported in males than females in the USA. In the year 2000, respective incidence rates of NSCLC per 100,000 in males vs females were as follows – adenocarcinoma: 25.2 vs 18.7; large-cell carcinoma: 4.5 vs 2.4; and squamous-cell carcinoma: 20.3 vs 8.0 (1). However, the incidence in males has been declining over the last two decades. In 2020, the respective incidence rates per 100,000 in males and females were as follows – adenocarcinoma: 17.9 and 16.8; large-cell carcinoma: 0.5 and 0.3; squamous-cell carcinoma: 11.0 and 5.9 (1). Furthermore, in a recent retrospective analysis of the SEER database, 53% of 1.28 million patients diagnosed with NSCLC between 2010 and 2017 were male (2).
Age	The median age at diagnosis of lung cancer is approximately 63 years (3), while in NSCLC it is closer to 70 years (4). In a retrospective study, 67% of 1.28 million patients in the SEER database diagnosed with NSCLC in the USA between 2010 and 2017 were ≥65 years old (2).
Race/ethnicity	NSCLC is more common in White people than those of other ethnicities (5). Of 325,138 patients diagnosed with NSCLC between 2007 and 2018 in the USA, 75.2% were White and 12.1% were Black (5). The same study reported that, among men, the incidence (per 100,000) of NSCLC was highest in Black men, while in women, the incidence was highest among White women (5). Rates of NSCLC have declined across all races over the last two decades in the US (1).
Geography	An estimated 238,340 adults will be diagnosed with lung cancer in the USA in 2023 (6). NSCLC is the most common type of lung cancer in the USA, accounting for 81% of all lung cancer diagnoses (7). From 2010 to 2017, NSCLC incidence per 100,000 decreased from 46.4 to 40.9 (2).
Other considerations	In a 2016 retrospective analysis of patients with NSCLC in the USA, adenocarcinoma was the most common histology type, followed by squamous-cell carcinoma (2). Approximately 23% of all NSCLC patients were characterized as receiving no treatment, almost half (49.5%) received a single-modality treatment, and 27.7% received multiple treatments initially (2). The 5-year survival rate for NSCLC is 28% overall and 65% for patients with localized disease. However, around 70% of patients with NSCLC are diagnosed after disease has spread outside the lung (7).

	NSCLC occurs most often in patients who are current or former smokers, but does also occur in people who have never smoked (7). Around 90% of patients with stage III NSCLC are smokers or ex-smokers at the time of diagnosis (8). NSCLC incidence peaks in ages 80–84 in men, but in ages 75–79 in women (9).
Overall representativeness of this study	The median age of patients in our study is 67.5 years which is in line with the current literature (3,4). Our study consisted of a greater number of male patients (50) than female patients (34) which is aligned with previous reports showing a greater incidence of NSCLC in males than females (1). Adenocarcinoma was the most common subtype of NSCLC (60.7%) in our study, followed by squamous cell carcinoma (31%), which is consistent with previous reports (2). The vast majority (89.3%) of patients in our study were current or former smokers. This is reflective of real-world observations; 90% of NSCLC patients in a multi-study analysis were smokers (8). It should be acknowledged that this was a small study (N=84), thus impacting the potential representativeness of the NSCLC population.

References

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Supplementary Table S2. Efficacy summary (ITT population)

	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)	Total (N=84)
Pathologic responses					
MPR, n (%) [95% CI]	3 (11.1) [2.4, 29.2]	4 (19.0) [5.4, 41.9]	6 (30.0) [11.9, 54.3]	5 (31.3) [11.0, 58.7]	18 (21.4) [13.2, 31.7]
Rate difference with durva monotherapy, % [95% CI]	–	7.9 [-12.6, 28.5]	18.9 [-4.4, 42.2]	20.1 [-5.5, 45.8]	NA
pCR, n (%) [95% CI]	1 (3.7) [0.1, 19]	2 (9.5) [1.2, 30.4]	2 (10.0) [1.2, 31.7]	2 (12.5) [1.6, 38.3]	7 (8.3) [3.4, 16.4]
Rate difference with durva monotherapy, % [95% CI]	–	5.8 [-8.6, 20.3]	6.3 [-8.7, 21.2]	8.8 [-8.9, 26.5]	NA
Responses by RECIST v1.1*					
ORR, n (%) [95% CI]	2 (7.4) [0.9, 24.3]	1 (4.8) [0.1, 23.8]	3 (15.0) [3.2, 37.9]	1 (6.3) [0.2, 30.2]	7 (8.3) [3.4, 16.4]
Objective responses, n (%)					
CR	0	0	0	0	0
PR	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)	7 (8.3)
SD	22 (81.5)	17 (81.0)	15 (75.0)	14 (87.5)	68 (81.0)
PD	1 (3.7)	3 (14.3)	1 (5.0)	1 (6.3)	6 (7.1)
NE	1 (3.7)	0	1 (5.0)	0	2 (2.4)

*Responses were not confirmed as only one scan was done prior to surgery after patients started neoadjuvant treatment.

CI, confidence interval; CR, complete response; Danva, danvatirsen; Durva, durvalumab; ITT, intent-to-treat; Mona, monalizumab; MPR, major pathological response; NA, not applicable; NE, not evaluable; Ole, oleclumab; ORR, objective response rate; pCR, pathological complete response; progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Supplementary Table S3. Treatment-emergent AEs occurring in ≥10% of patients in any treatment arm (as-treated population)

Preferred term, n (%)	Durva (n=26)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Fatigue	6 (23.1)	4 (19.0)	2 (10.0)	3 (18.8)
Cough	1 (3.8)	3 (14.3)	1 (5.0)	2 (12.5)
Dyspnea	3 (11.5)*	1 (4.8)	0	3 (18.8)
Asthenia	3 (11.5)	3 (14.3)	0	0
Nausea	2 (7.7)	3 (14.3)	0	1 (6.3)
Pruritus	0	2 (9.5)	2 (10.0)	2 (12.5)
Procedural pain	5 (19.2)	0	0	0
Constipation	1 (3.8)	1 (4.8)	2 (10.0)	0
Alanine aminotransferase increase	1 (3.8)†	0	0	2 (12.5)‡
Decreased appetite	3 (11.5)	0	0	0
Paresthesia	0	0	1 (5.0)	2 (12.5)
Upper respiratory tract infection	0	1 (4.8)	2 (10.0)	0
Gastroesophageal reflux disease	0	0	0	2 (12.5)

*One patient had grade ≥3 dyspnea.

†Patient had grade ≥3 alanine aminotransferase increase.

‡One patient had grade ≥3 alanine aminotransferase increase.

Supplementary Table S4. Treatment-related AEs occurring in ≥5% of patients in any treatment arm (as-treated population)

Preferred term, n (%)	Durva (n=26)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)	Total (N=83)
Fatigue	3 (11.5)	2 (9.5)	2 (10.0)	2 (12.5)	9 (10.8)
Asthenia	2 (7.7)	3 (14.3)	0	0	5 (6.0)
Pruritus	0	2 (9.5)	2 (10.0)	1 (6.3)	5 (6.0)
Nausea	1 (3.8)	2 (9.5)	0	1 (6.3)	4 (4.8)
Pyrexia	0	2 (9.5)	1 (5.0)	0	3 (3.6)
Rash maculo-papular	0	1 (4.8)	1 (5.0)	1 (6.3)	3 (3.6)
Arthralgia	0	2 (9.5)	0	0	2 (2.4)
Constipation	0	1 (4.8)	1 (5.0)	0	2 (2.4)
Musculoskeletal pain	2 (7.7)	0	0	0	2 (2.4)
Paresthesia	0	0	1 (5.0)	1 (6.3)	2 (2.4)
Pneumonitis	1 (3.8)	0	1 (5.0)	0	2 (2.4)
Alanine aminotransferase increase	0	0	0	1 (6.3)	1 (1.2)
Aspartate aminotransferase increase	0	0	0	1 (6.3)	1 (1.2)
Dermatitis	0	0	0	1 (6.3)	1 (1.2)
Erthema	0	0	1 (5.0)	0	1 (1.2)
Hepatic enzyme increased	0	0	0	1 (6.3)	1 (1.2)
Hot flush	0	0	0	1 (6.3)	1 (1.2)
Muscular weakness	0	0	0	1 (6.3)	1 (1.2)
Neck pain	0	0	1 (5.0)	0	1 (1.2)
Neutrophil count decrease	0	0	0	1 (6.3)	1 (1.2)
Peripheral sensory neuropathy	0	0	1 (5.0)	0	1 (1.2)
Platelet count decreased	0	0	0	1 (6.3)	1 (1.2)
Procedural hemorrhage	0	0	0	1 (6.3)	1 (1.2)
Rash	0	0	1 (5.0)	0	1 (1.2)
Stomatitis	0	0	1 (5.0)	0	1 (1.2)
Thrombocytopenia	0	0	0	1 (6.3)	1 (1.2)

Supplementary Table S5. AESI/AEPI occurring in any patients in any treatment arm (as-treated population)

	AESI or AEPIs, n (%)			
	Durvalumab (n=26)	**Durvalumab + Oleclumab (n=21)**	**Durvalumab + Monalizumab (n=20)**	**Durvalumab + Danvatirsen (n=16)**
Any AE	7 (26.9)	11 (52.4)	6 (30.0)	7 (43.8)
Any AE Grade 3/4*	2 (7.7)	1 (4.8)	0	1 (6.3)
Any SAE[†]	2 (7.7)	1 (4.8)	0	0
Any AE with outcome death	0	0	0	0
AE possibly-related to treatment	3 (11.5)	9 (42.9)	6 (30.0)	5 (31.3)

*Grade ≥3 AESIs or AEPIs occurred in: one patient in the durvalumab monotherapy arm (Grade 4 alanine aminotransferase increase and Grade 4 aspartate aminotransferase increase); one patient in the durvalumab + oleclumab arm (Grade 3 diabetic ketoacidosis), and one patient in the durvalumab + danvatirsen arm (Grade 3 alanine aminotransferase increase).

[†]Serious AESIs or AEPIs occurred in two patients in the durvalumab monotherapy arm (Grade 3 pericarditis and grade 4 intestinal perforation) and in one patient in the durvalumab + oleclumab arm (Grade 3 diabetic ketoacidosis).

AE, adverse event; AEPI, adverse event of potential interest; AESI, adverse event of special interest; SAE, serious adverse event.

Supplementary Table S6. Baseline biomarker (CD73, HLA-E, NKG2A) association with response

n/N* (%)	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)	Total (N=84)
Overall MPR	3/27 (11)	4/21 (19)	6/20 (30)	5/16 (31)	18/84 (21)
Adenocarcinoma	0/18 (0)	4/14 (29)	3/11 (27)	4/8 (50)	11/51 (22)
LCC/Other	0/0 (0)	0/0 (0)	0/3 (0)	0/4 (0)	0/7 (0)
Squamous cell	3/9 (33)	0/7 (0)	3/6 (50)	1/4 (25)	7/26 (27)
Stage I/II	3/25 (12)	4/16 (25)	6/17 (35)	2/11 (18)	15/69 (22)
Stage III	0/2 (0)	0/5 (0)	0/3 (0)	3/5 (60)	3/15 (20)
PD-L1+ (≥1% tumor cells)	0/6 (0)	2/5 (40)	3/6 (50)	0/2 (0)	5/19 (26)
PD-L1- (<1% tumor cells)	0/3 (0)	1/6 (17)	0/2 (0)	0/5 (0)	1/16 (6)
PD-L1 NE	3/18 (17)	1/10 (10)	3/12 (25)	5/9 (56)	12/49 (25)
CD73 high (≥10% tumor cells)	0/8 (0)	3/5 (60)	2/4 (50)	0/1 (0)	5/18 (28)
CD73 low (<10% tumor cells)	0/1 (0)	0/6 (0)	1/5 (20)	0/6 (0)	1/18 (6)
CD73 NE	3/18 (17)	1/10 (10)	3/11 (27)	5/9 (56)	12/48 (25)
NKG2A[†] (≥median)	0/4 (0)	2/5 (40)	2/6 (33)	0/2 (0)	4/17 (24)
NKG2A (<median)	1/4 (25)	1/5 (20)	1/4 (25)	0/4 (0)	3/17 (14)
NKG2A NE	2/19 (11)	1/11 (9)	3/10 (30)	5/10 (50)	11/50 (22)
HLA-E[‡] (≥median)	1/6 (17)	3/6 (50)	0/3 (0)	1/4 (25)	5/19 (26)
HLA-E (<median)	1/4 (25)	0/7 (0)	3/5 (60)	0/3 (0)	4/19 (21)
HLA-E NE	1/17 (6)	1/8 (13)	3/12 (25)	4/9 (44)	9/46 (20)

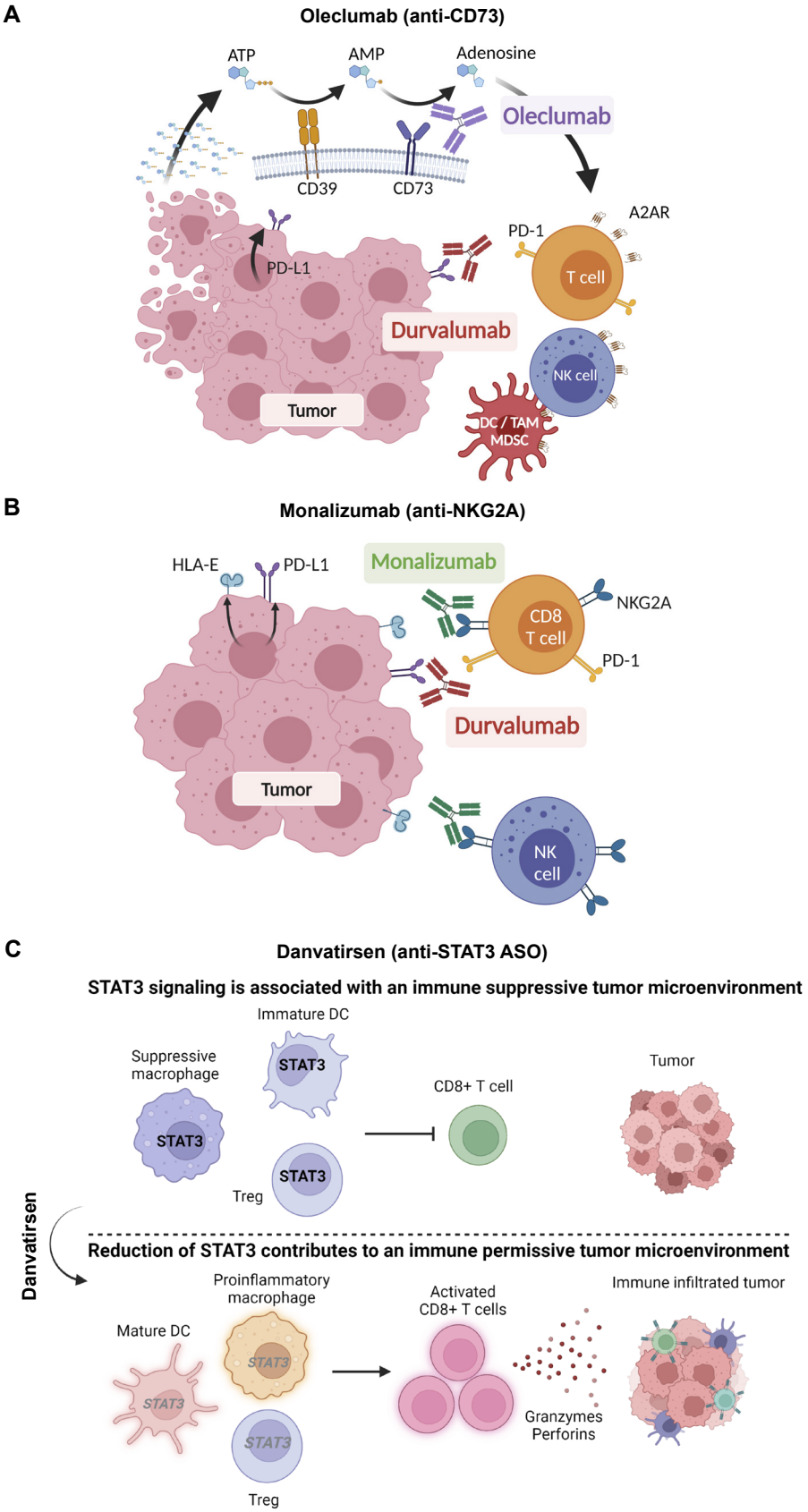
*Small sample sizes: baseline tissue mandatory for 50% of patients. [†]NKG2A positive cells/mm^2 in tumor center. [‡]HLA-E positive tumor cells.
CD73, cluster of differentiation 73; HLA-E, major histocompatibility complex E; LCC, large cell carcinoma; MPR, major pathological response; NE, not evaluable; NKG2A, NK group 2 member A; PD-L1, programmed cell death ligand-1

Supplementary Table S7. Tumor RNA sequencing - see additional supplementary file.

NeoCOAST
MS_Supplementary

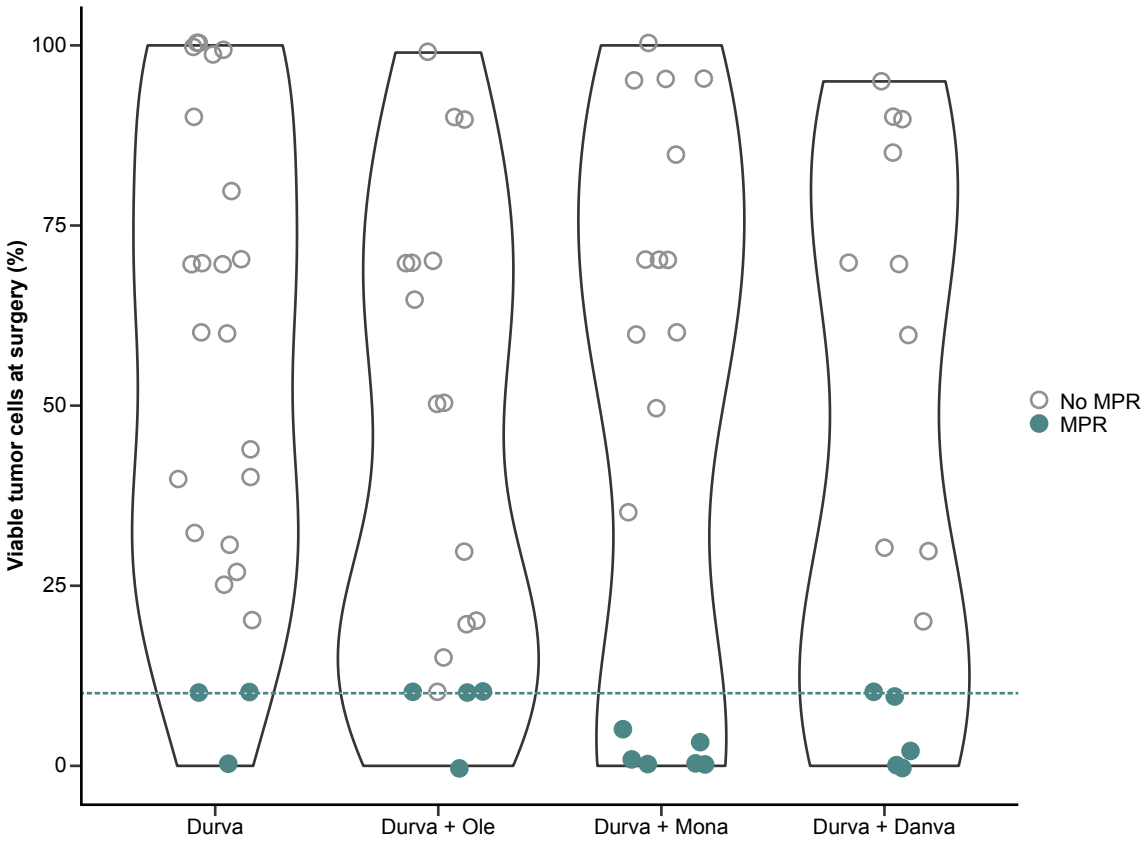
SUPPLEMENTARY FIGURES

Supplementary Figure S1



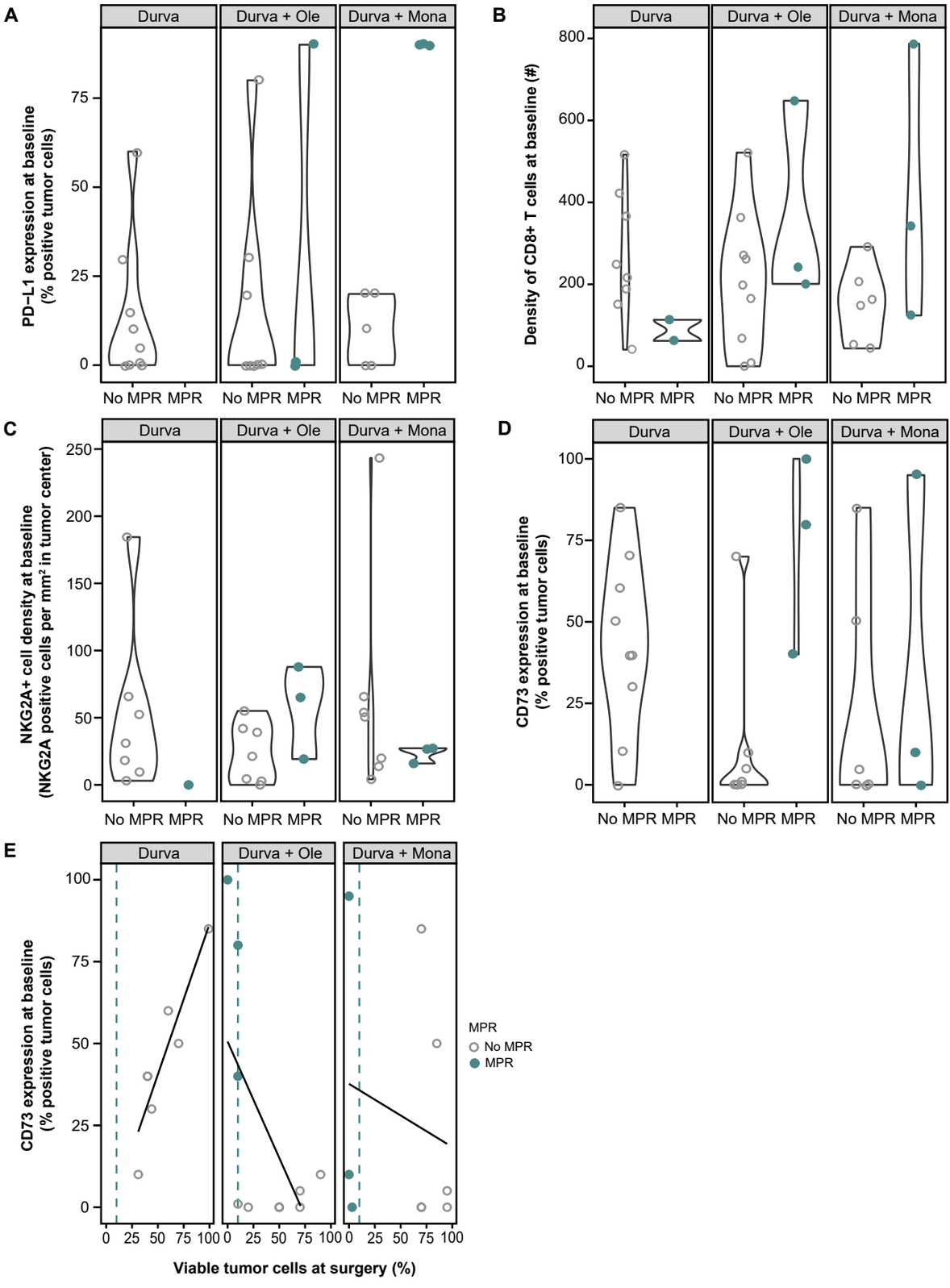
Supplementary Figure S1. Mechanisms of action for oleclumab (A) monalizumab (B), and danvatirsen (C)
A2AR, adenosine A2A receptor; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ASO, antisense oligonucleotide; CD, cluster of differentiation; DC, dendritic cell; HLA-E, major histocompatibility complex E; MDSC, myeloid-derived suppressor cell; NK, natural killer; NKG2A, NK group 2 member A; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; STAT3, signal transducer and activator of transcription 3; TAM, tumor-associated macrophage; Treg, T regulatory cell.

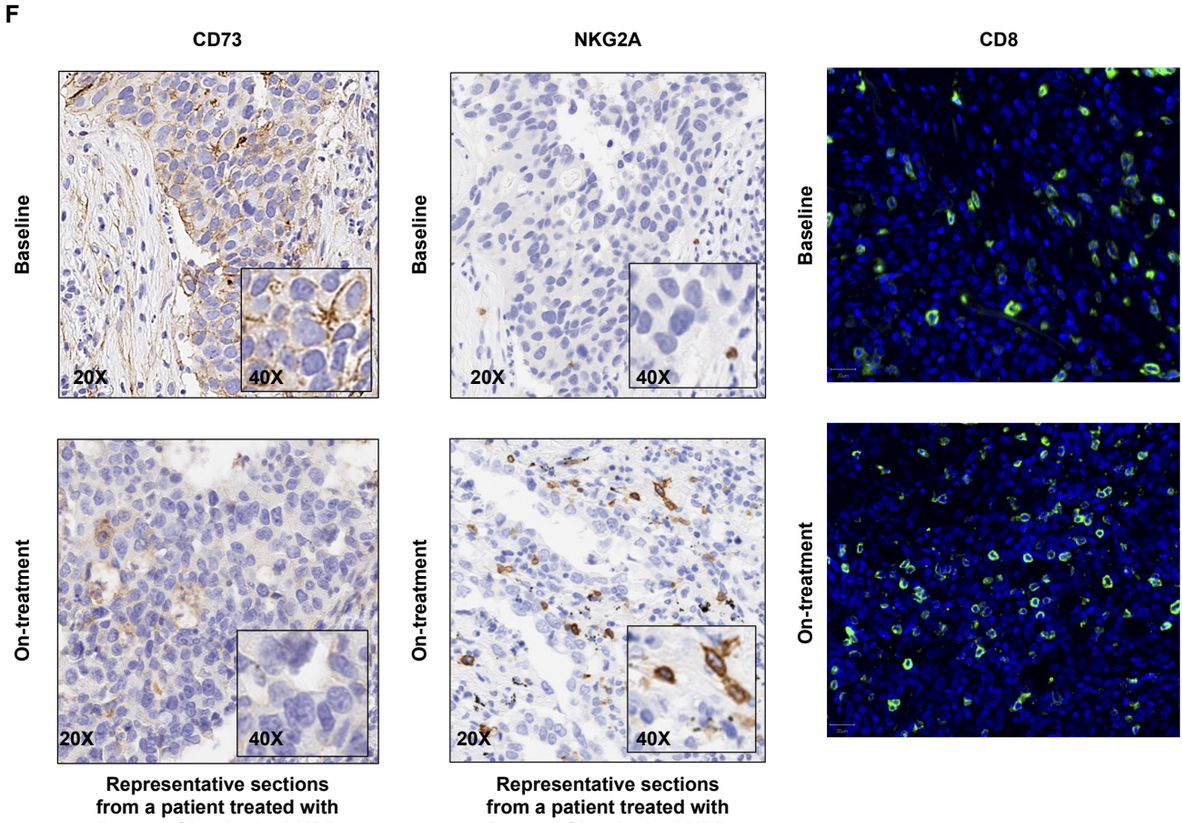
Supplementary Figure S2



Supplementary Figure S2. Violin plots with medians of percentage residual viable tumor cells (%RVT) in each arm Patients with a major pathological response (MPR) are indicated in closed teal circle; patients without MPR are indicated in open grey circle. Dashed line indicates threshold for MPR (RVT≤10%). Violin plots depicting density and distribution of RVT observed within and across each arm (durvalumab monotherapy arm: n=24; durvalumab + oleclumab arm: n=18; durvalumab + monalizumab arm: n=18; durvalumab + danvatirsen arm: n=15).

Supplementary Figure S3



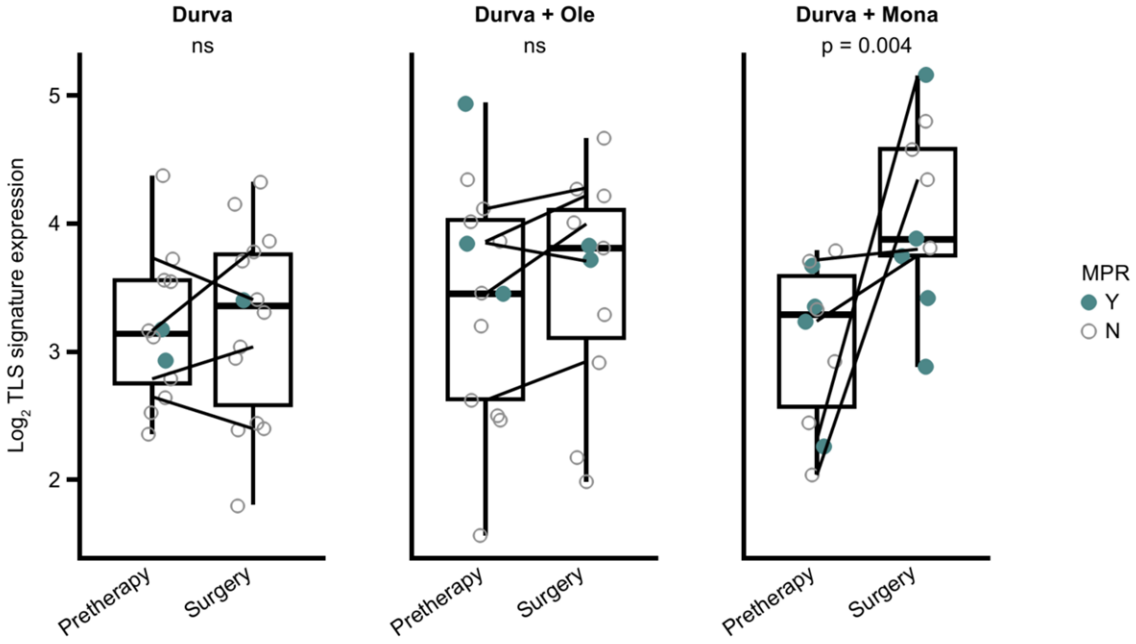


Supplementary Figure S3. Additional immunohistochemistry (IHC) biomarker to major pathological response (MPR) and representative images

Patients with MPR are indicated in closed teal circle; patients without MPR are indicated in open grey circle. Violin plots depicting density and distribution of cells in pre-therapy tumor tissues observed across patients with and without an MPR in each arm. **A,** PD-L1+ Tumor cells (SP263) (n=28). **B,** CD8+ T cell density (n=31) (SP239). **C,** NKG2A+ cell density (n=28) (AR9352). **D,** CD73+ tumor cells (n=29) (D7F9A). **E.** Correlation of CD73+ tumor cells with percentage residual viable tumor cells (%RVT) (n=26). **F,** Representative images from CD73, NKG2A and CD8. CD73 and NKG2A are from chromagenic assays; CD8 is from multiplex immunofluorescence assay. Sample numbers with IHC and percent viability measurements: CD8+ T cells at baseline n=31; PD-L1 at baseline n=25; CD73 at baseline n=26; NKG2A n=25. Sample numbers with IHC and MPR: PD-L1 n=28; CD73 n=29; NKG2A n=28; CD8 n=31.

Supplementary Figure S4. Calculation of gene signatures associated with tertiary lymphoid structure (TLS) formation from pretherapy and surgery tumor transcriptomes

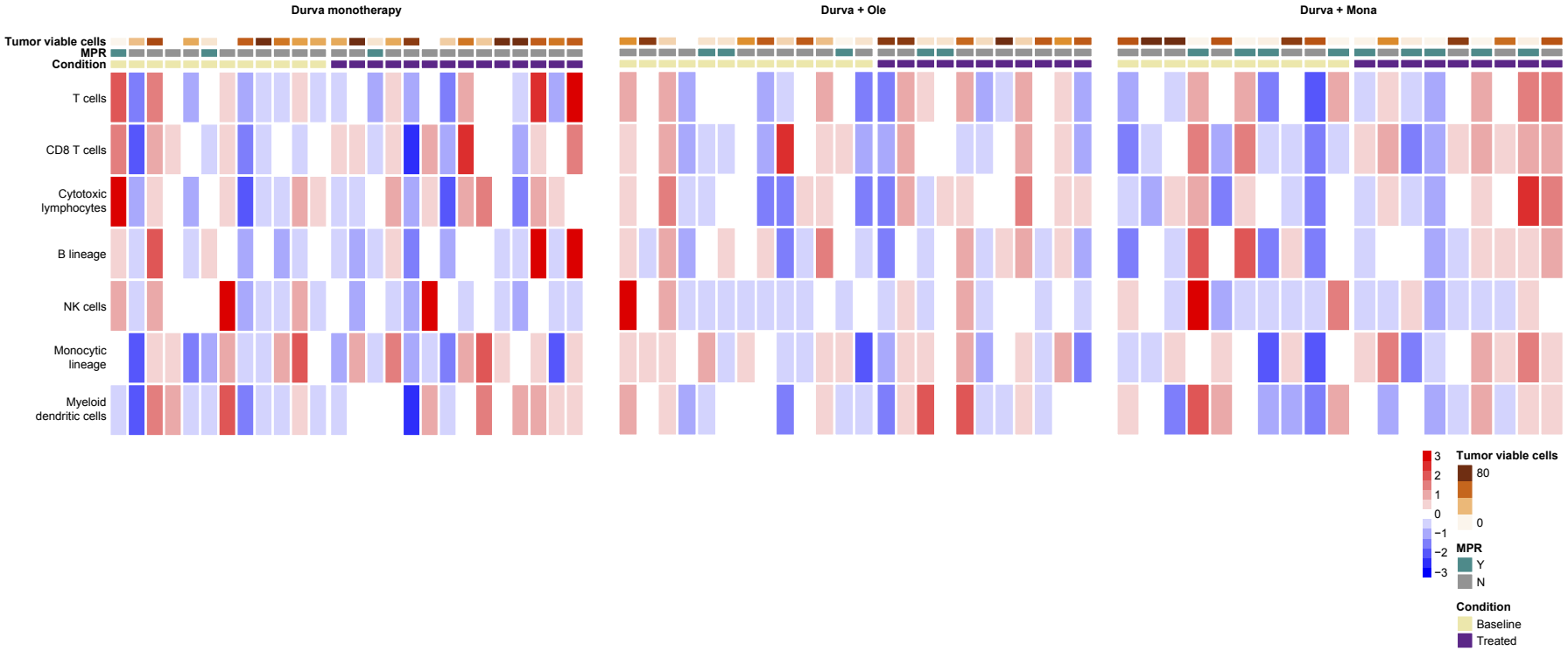
A TLS signature score was calculated as the mean expression of genes associated with TLS (Sautès-Fridman C, et al.). Wilcoxon-rank sum test identified significant upregulation of TLS signature in surgery samples compared to pretherapy in durvalumab + monalizumab. The y-axis scale is $\log_2$(TPM+1) where TPM is transcripts per million. Patients with major pathologic response (MPR) are indicated in closed teal circle; patients without MPR are indicated in open gray circle.



Reference

Sautès-Fridman C, Petitprez F, Calderaro J, Fridman WF. Tertiary lymphoid structures in the era of cancer immunotherapy. *Review Nat Rev Cancer.* 2019;19(6):307–325.

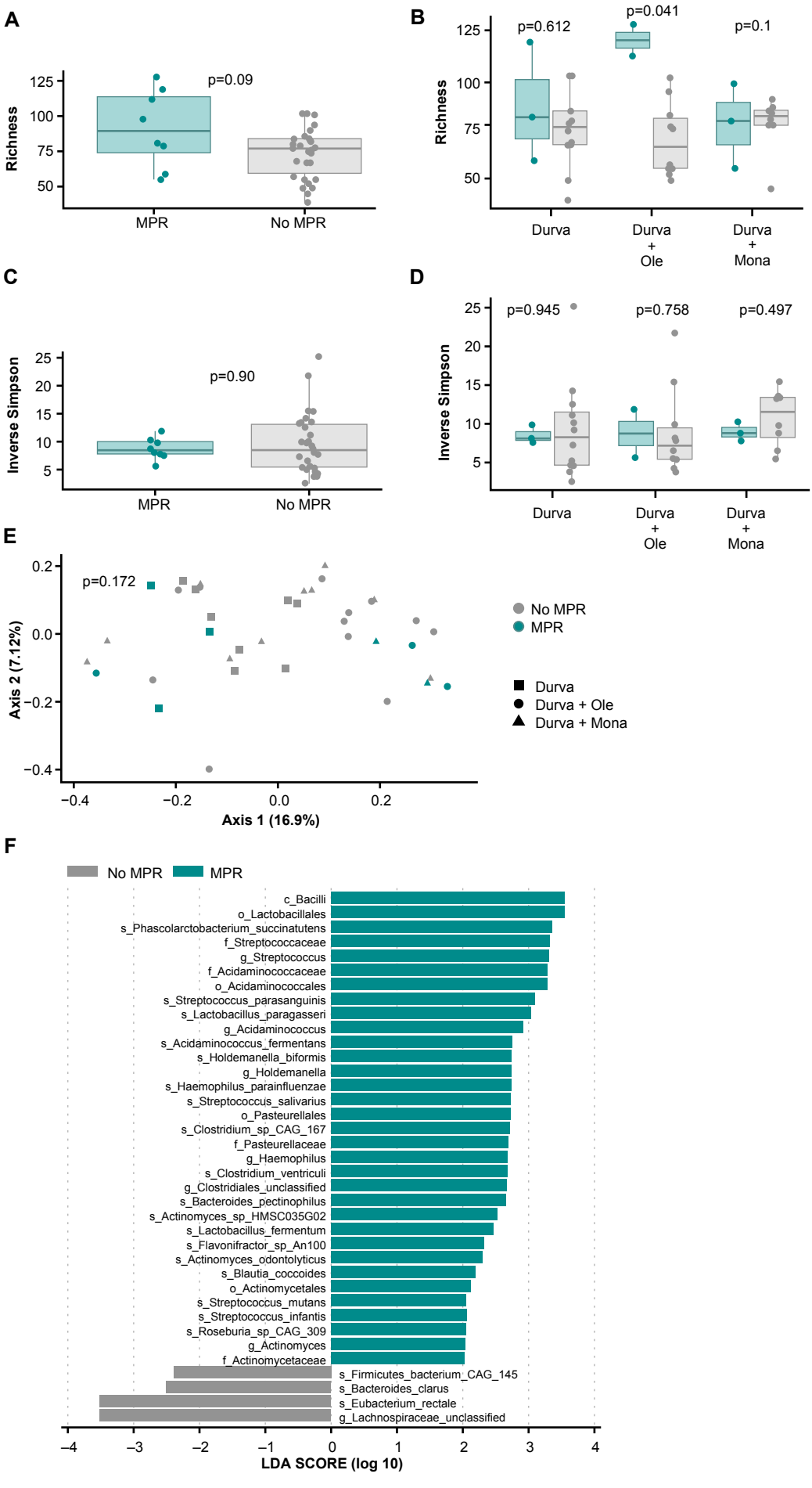
Supplementary Figure S5



Supplementary Figure S5. Changes in immune cell populations by deconvolution (MCP-counter)

Infiltration of immune populations were inferred using deconvolution software (MCP-counter) from bulk RNA sequencing of tumor tissue at pre-therapy and surgery for all patients with available samples (n=69), and compared with percentage residual viable tumor cells (%RVT), major pathological response (MPR), and time of collection.

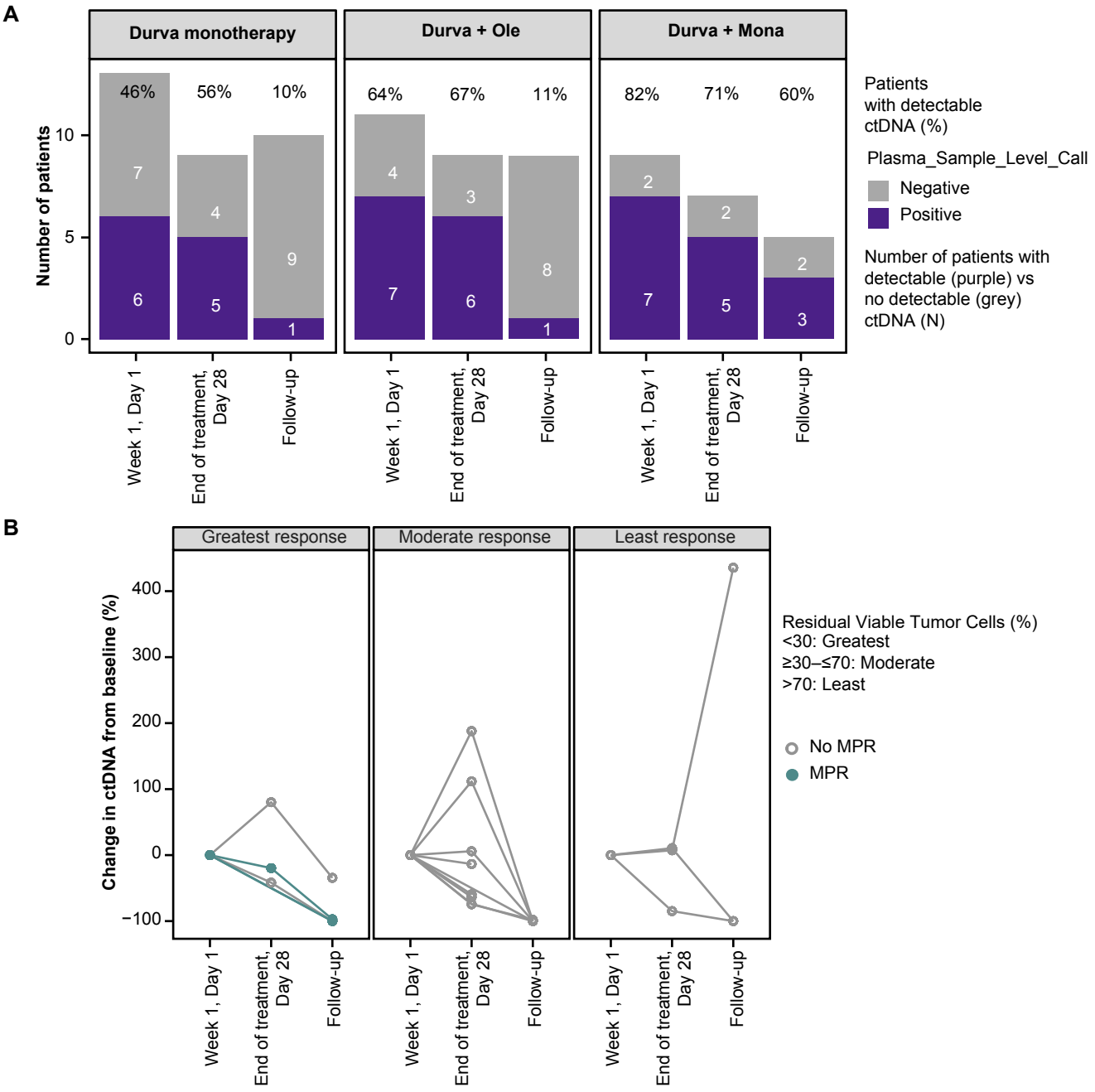
Supplementary Figure S6



Supplementary Figure S6. Stool microbiome richness and diversity, LEfSe correlates to major pathological response (MPR)

A, Richness of the stool microbiome across patients with MPR (n=8) and no MPR (n=30). **B,** Richness across patients with MPR and no MPR compared between arms (durvalumab arm: 3 MPR and 12 no MPR; durvalumab + oleclumab arm: 2 MPR and 10 no MPR; durvalumab + monalizumab arm: 3 MPR and 8 no MPR). **C,** Alpha-diversity measured by inverse Simpson index across patients with and without MPR. **D,** Alpha-diversity measured by inverse Simpson index compared across patients with and without MPR compared between arms. **E,** Ordination of beta-diversity distances (binary Jaccard) by principal coordinate analysis of all samples did not identify clustering of patients with or without MPR, or within each arm. **F,** Differential abundance analyses using LEfSe revealed a unique microbiome signature by MPR status. Taxa are ranked by logarithmic discriminant analysis (LDA) score, representing the effect size of each. MPR, major pathological response.

Supplementary Figure S7



MR response table

Timepoint	ctDNA response	Durva	Durva + Ole	Durva + Mona
Day 28	# MR/Total (%)	1/4 (25.0)	3/5 (60.0)	2/5 (40.0)
Follow up	# MR/Total (%)	5/6 (83.3)	5/5 (100)	3/4 (75.0)
Day 28	# Complete Clearance/Total (%)	0/4 (0)	0/5 (0)	0/5 (0)
Follow up	# Complete Clearance/Total (%)	5/6 (83.3)	4/5 (80.0)	1/4 (25.0)

Supplementary Figure S7. ctDNA dynamics

A, Number of patients with evaluable ctDNA samples at baseline (Week 1, Day 1; W1D1), end of treatment (Day 28) and follow up (Day 105). Samples with no detected ctDNA are grey and samples with detected ctDNA are purple. Numbers are depicted in the figure. **B,** For patients with detectable ctDNA at baseline (n=20), mean variant allele frequency (VAF) change from baseline to end of treatment (Day 28) to follow up (Day 105) evaluated between patients with 0–29% residual viable tumor cells (RVT) (greatest response), 30–70% RVT (moderate response), and 71–100% RVT (least response). MR, molecular response.