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CT011

NeoCOAST: open-label, randomized, phase 2, multidrug platform study of neoadjuvant durvalumab alone or combined with novel agents in patients with resectable, early-stage non-small-cell lung cancer

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Disclosure Information

Tina Cascone

I have the following relevant financial relationships to disclose:

Commercial Interest	Relationship(s)
MedImmune/AstraZeneca	Advisory role/consultant and contracted institutional support/research
Bristol Myers Squibb	Advisory role/consultant and contracted institutional support/research
EMD Serono	Advisory role and contracted institutional support/research
Merck & Co.	Advisory role
Genentech	Advisory role
Arrowhead Pharmaceuticals	Advisory role
Society for Immunotherapy of Cancer, Roche, Medscape, PeerView, Bristol Myers Squibb	Speaker fees

- NeoCOAST Study Coordinating Principal Investigator
- This study was sponsored by AstraZeneca

NeoCOAST: Background

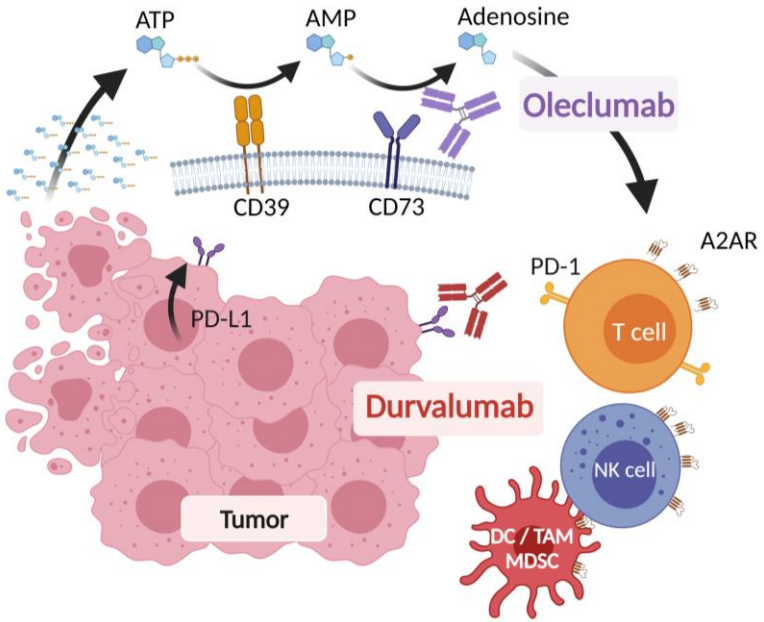
- Neoadjuvant therapy with PD-(L)1 inhibitors leads to pathological responses in patients with resectable NSCLC, both as monotherapy[1–4] and in combination with CTLA-4 inhibition.[5]
- In the phase 3 CheckMate-816 trial, PD-1 inhibition combined with platinum-based chemotherapy demonstrated superior efficacy vs chemotherapy alone in patients with resectable (Stage IB-IIIA) NSCLC.[6,7]
- In the phase 2 COAST trial (NCT03822351), the anti-PD-L1 mAb durvalumab[8] plus the anti-CD73 mAb oleclumab[9] or the anti-NKG2A mAb monalizumab[10] improved efficacy in patients with unresectable, Stage III NSCLC vs durvalumab alone.[11]
- NeoCOAST (NCT03794544) is a global, phase 2, open-label, multicenter, randomized, multidrug platform study of durvalumab alone or in combination with oleclumab, monalizumab, or the anti-STAT3 antisense oligonucleotide danvatirsen[12] as neoadjuvant therapy in patients with resectable, early-stage NSCLC.

CD73, cluster of differentiation 73; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; mAb, monoclonal antibody; NKG2A, NK group 2 member A; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death ligand-1; STAT3, signal transducer and activator of transcription 3

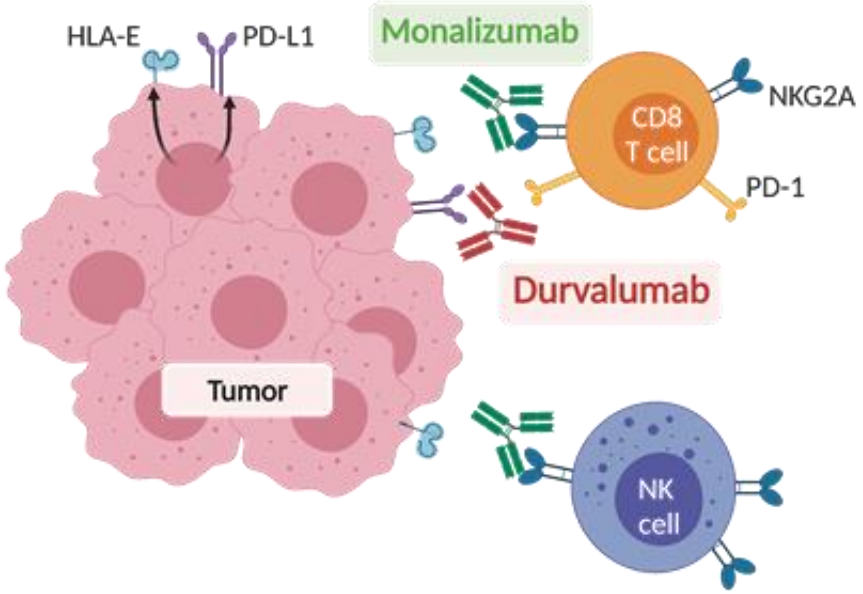
1. Forde PM, et al. N Engl J Med 2018;378:1976–86; 2. Lee JM, et al. WCLC 2020 (presentation PS01.05); 3. Gao S, et al. J Thorac Oncol 2020;15:816–26; 4. Tong BC, et al. J Thorac Cardiovasc Surg 2022;163:427–36; 5. Cascone T, et al. Nat Med 2021;27:504–14; 6. Forde PM, et al. Cancer Res 2021;81:abstract CT003; 7. Nivolumab US Prescribing Information. Accessed 18/03/2022; Available at: https://packageinserts.bms.com/pi/pi_opdivo.pdf 8. Stewart R, et al. Cancer Immunol Res 2015;3:1052–1062; 9. Hay CM, et al. OncoImmunology 2016;5:e1208875; 10. André P, et al. Cell 2018;175:1731–43.e13; 11. Martinez-Marti A, et al. Ann Oncol 2021;32(5 suppl):abstract LBA42; 12. Proia TA, et al. Clin Cancer Res 2020;26:6335–49.

NeoCOAST: Mechanism of action of novel agents

Oleclumab (anti-CD73)

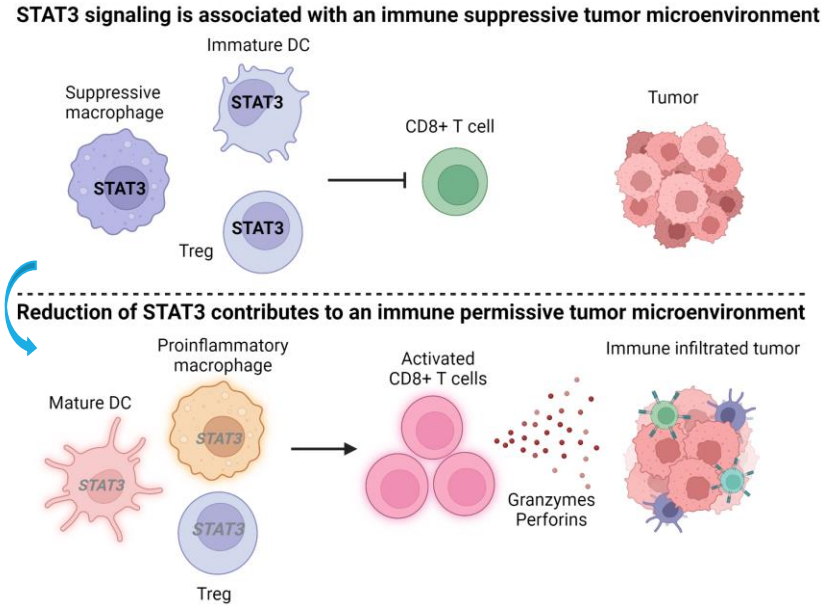


Monalizumab (anti-NKG2A)



Danvatirsen (anti-STAT3 ASO)

Danvatirsen



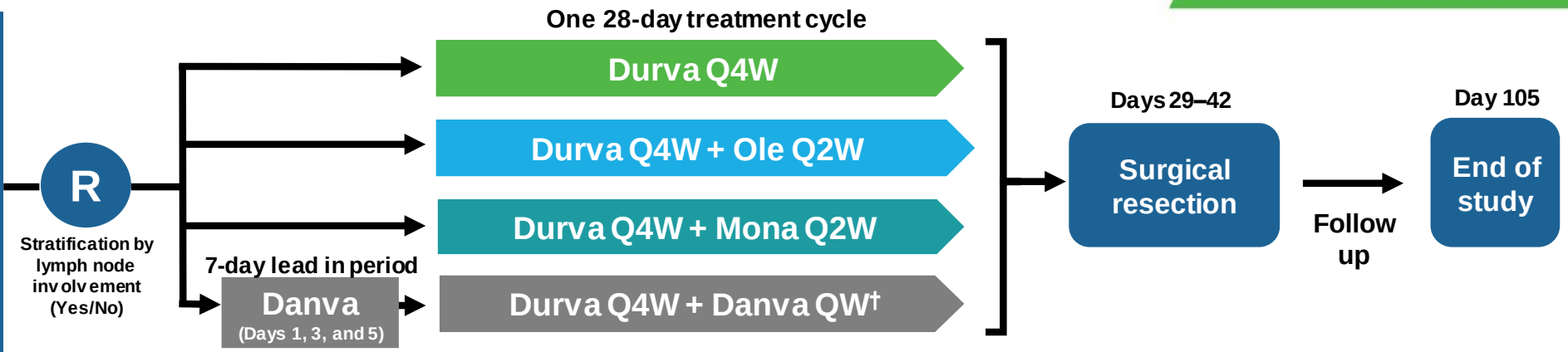
A2AR, adenosine A2A receptor; AMP, adenosine monophosphate; ATP, adenosine triphosphate; ASO, antisense oligonucleotide; CD, cluster of differentiation; DC, dendritic cell; HLA-E, major histocompatibility complex E; MDSC, myeloid-derived suppressor cell; NK, natural killer; NKG2A, NK group 2 member A; 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.

NeoCOAST: Study design and objectives

Key eligibility criteria:

- Stage I (>2cm) to IIIA NSCLC*
- Fully resectable
- ECOG PS 0 or 1
- No prior systemic therapy
- Adequate organ and marrow function

N=84



Endpoints:

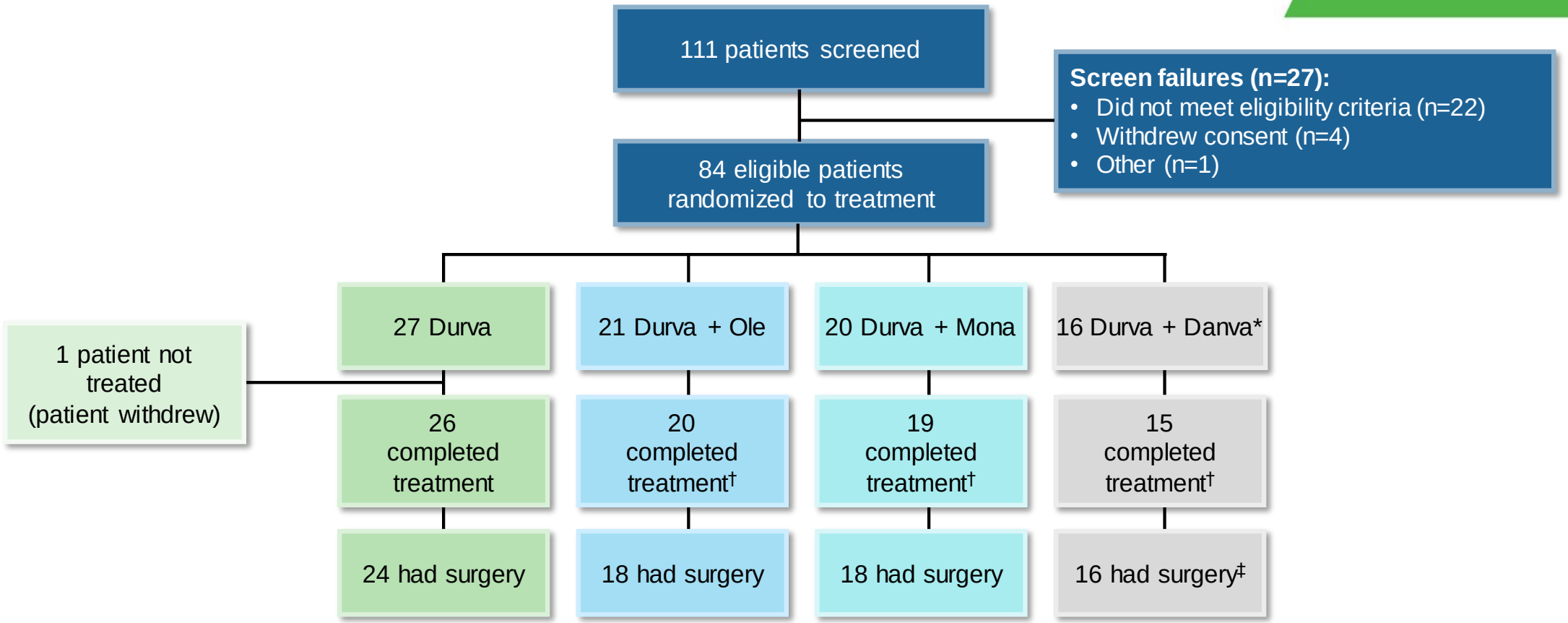
- **Primary**: MPR rate (proportion of patients with ≤10% residual viable tumor cells in resected tumor specimen and sampled nodes at surgery) per investigator assessment.
- **Secondary**: pCR rate (no viable tumor cells in resected tumor specimen or sampled nodes at surgery), safety and tolerability, feasibility of planned surgery, pharmacokinetics, and immunogenicity.
- **Exploratory**: Tumor, blood, and stool microbiome biomarkers; investigator-assessed best overall response and ORR (per RECIST v1.1).

Statistical analysis:

- Continuous variables were summarized using descriptive statistics; this study was not statistically powered to make explicit conclusions for any hypothesis test. The primary intent was to look for preliminary efficacy signals by calculating MPR rates and their confidence intervals.

*Per American Joint Committee on Cancer Staging, 8th edition.
†Danvatirsen arm was stopped early as the program was discontinued.
ECOG, Eastern Cooperative Oncology Group; MPR, major pathological response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; pCR, pathological complete response; PS, performance status; Q4W, once every 4 weeks; Q2W, once every 2 weeks; QW, every week; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

NeoCOAST: Patient enrollment and treatment disposition



- Between March 2019 and September 2020, 84 patients were randomized, 83 of whom received treatment.
- Clinical data cut-off: September 15, 2021

Totals are for the intention-to-treat population.
*Danvatirsen arm was stopped early as the program was discontinued.
†Patients who completed treatment with novel agent.
‡One patient did not receive all planned doses of danvatirsen but had surgery.

NeoCOAST: Baseline characteristics and demographics

	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Median age (range), years	67.0 (51–83)	65.0 (52–80)	64.5 (54–82)	71.5 (56–87)
Male, n (%)	14 (51.9)	12 (57.1)	14 (70.0)	10 (62.5)
Race, n (%)*				
White	23 (85.2)	20 (95.2)	19 (95.0)	13 (81.3)
Black or African American	3 (11.1)	1 (4.8)	1 (5.0)	0
Asian	1 (3.7)	0	0	1 (6.3)
Other	0	0	0	2 (12.5)
ECOG PS 0 / 1, n (%)	19 (73.1) / 7 (26.9)	12 (57.1) / 9 (42.9)	12 (60.0) / 8 (40.0)	10 (62.5) / 6 (37.5)
Histology type, n (%)				
Adenocarcinoma	18 (66.7)	14 (66.7)	11 (55.0)	8 (50.0)
Large cell carcinoma	0	0	2 (10.0)	1 (6.3)
Squamous cell carcinoma	9 (33.3)	7 (33.3)	6 (30.0)	4 (25.0)
Other	0	0	1 (5.0)	3 (18.8)
Ever smoked, n (%)	21 (77.8)	20 (95.2)	19 (95.0)	15 (93.8)
Disease stage at study entry, n (%)				
IA3	4 (14.8)	1 (4.8)	6 (30.0)	1 (6.3)
IB	7 (25.9)	4 (19.0)	2 (10.0)	1 (6.3)
IIA	3 (11.1)	4 (19.0)	1 (5.0)	2 (12.5)
IIB	11 (40.7)	7 (33.3)	8 (40.0)	7 (43.8)
IIIA	2 (7.4)	5 (23.8)	3 (15.0)	5 (31.3)
Lymph node involvement, n (%)	11 (40.7)	8 (38.1)	7 (35.0)	6 (37.5)
PD-L1 status, TC ≥1% / TC <1% / NE, n (%)	6 (22.2) / 3 (11.1) / 18 (66.7)	5 (23.8) / 6 (28.6) / 10 (47.6)	6 (30.0) / 2 (10.0) / 12 (60.0)	2 (12.5) / 5 (31.3) / 9 (56.3)

*Each race category counts patients who selected only that category.

ECOG, Eastern Cooperative Oncology Group; NE, not evaluable; PD-L1, programmed cell death ligand-1; PS, performance status; TC tumor cell.

NeoCOAST: Efficacy outcomes in the ITT population

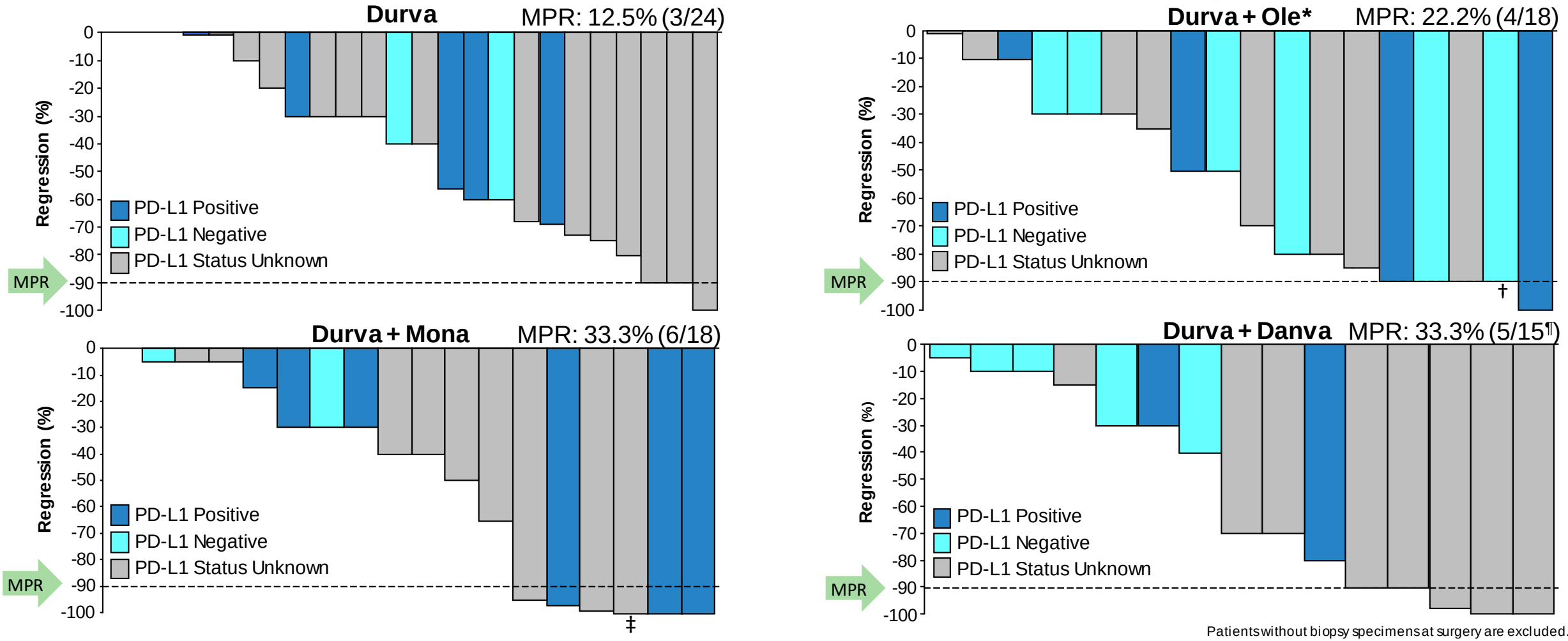
	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Pathologic responses				
MPR, n (%)	**3 (11.1)**	**4 (19.0)**	**6 (30.0)**	**5 (31.3)**
pCR, n (%)	1 (3.7)	2 (9.5)	2 (10.0)	2 (12.5)
Responses by RECIST v1.1				
ORR, n (%)	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)
Objective responses, n (%)				
PR	2 (7.4)	1 (4.8)	3 (15.0)	1 (6.3)
SD	22 (81.5)	17 (81.0)	15 (75.0)	14 (87.5)
PD	1 (3.7)	3 (14.3)	1 (5.0)	1 (6.3)
NE	1 (3.7)	0	1 (5.0)	0

- MPR and pCR rates in the durva arm were similar to published data for anti-PD-1/PD-L1 antibodies (MPR, 6.7–45%; pCR, 0–16.2%).[1–8]
  - Numerically higher MPR rates were observed across all combination arms, compared with a single dose of durva monotherapy.
  - No differences in pCR rates were observed between treatment arms.
  - No significant differences in ORR rates were observed between treatment arms.

ITT, Intention-to-treat; MPR, major pathological response; NE, not evaluable; ORR, objective response rate; pCR, pathological complete response; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

1. Forde PM, et al. N Engl J Med 2018;378:1976–86; 2. Gao S, et al. J Thorac Oncol 2020;15:816–26; 3. Lee JM, et al. WCLC 2020 (presentation PS01.05); 4. Altorki NK, et al. Lancet Oncol 2021;22:824–35; 5. Wislez M, et al. ESMO 2020 (presentation 1214O); 6. Tong BC, et al. J Thorac Cardiovasc Surg 2022;163:427–36; 7. Cascone T, et al. Nat Med 2021;27:504–14; 8. Besse B, et al. ESMO 2020 (presentation 1215O).

NeoCOAST: Pathological regression at surgery



Patients without biopsy specimens at surgery are excluded.

*One patient initially reported to have 10% viable tumor cells in primary tumor later determined by the investigator to have pCR;. †Patient determined not to have MPR after local evaluation of primary tumor and lymph nodes; ‡Patient reported to have 0% residual viable tumor cells in primary tumor but was later determined by investigator not to have pCR; ¶Of the 16 patients who underwent surgery, 1 patient was reclassified following a retrospective change in diagnosis.
MPR, major pathological response; PD-L1, programmed cell death ligand-1.

NeoCOAST: Safety summary in the as-treated population

Incidence, n (%)	Durva (n=26)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Any TEAE	18 (69.2)	19 (90.5)	15 (75.0)	13 (81.3)
Grade ≥3 TEAEs	5 (19.2)	3 (14.3)	2 (10.0)	5 (31.3)
Any TRAE	9 (34.6)	12 (57.1)	10 (50.0)	7 (43.8)
Grade ≥3 TRAEs	0	1 (4.8)	0	1 (6.3)
Serious TRAEs*	1 (3.8)	1 (4.8)	0	1 (6.3)
AEs leading to treatment discontinuation	0	1 (4.8)	1 (5.0)	1 (6.3)
Deaths†	0	0	0	1 (6.3)

- The safety profile in the durvalumab monotherapy arm was similar to previously published data for anti-PD-1/PD-L1 antibodies.[1–7]
- No new safety signals were identified with any of the combination regimens.
- Overall, 76/83 (91.6%) patients in the as-treated population completed surgery with no significant delay, of whom 72 completed surgery within 42 days, the protocol-defined time not considered to be a delay.
  - Of the seven patients who were unable to complete surgery, five had progressive or stage IV disease, one was lost to follow-up, and another had a serious AE of pneumonia and was no longer eligible for surgery.

*Serious TRAEs included one patient with immune-mediated arthritis in the durva arm; one patient with diabetic ketoacidosis in the durva + ole arm; and one patient with procedural hemorrhage in the durva + danva arm.
†Death in the durva + danva arm was due to an AE of bronchial anastomosis complication, deemed not to be related to either study drug.
AE, adverse event; PD-L1, programmed cell death ligand-1; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

1. Forde PM, et al. N Engl J Med 2018;378:1976–86; 2. Gao S, et al. J Thorac Oncol 2020;15:816–26; 3. Lee JM, et al. WCLC 2020 (presentation PS01.05; 4. Altorki NK, et al. Lancet Oncol 2021;22:824–35; 5. Wislez M, et al. ESMO 2020 (presentation 1214O); 6. Cascone T, et al. Nat Med 2021;27:504–14; 7. Besse B, et al. ESMO 2020 (presentation 1215O).

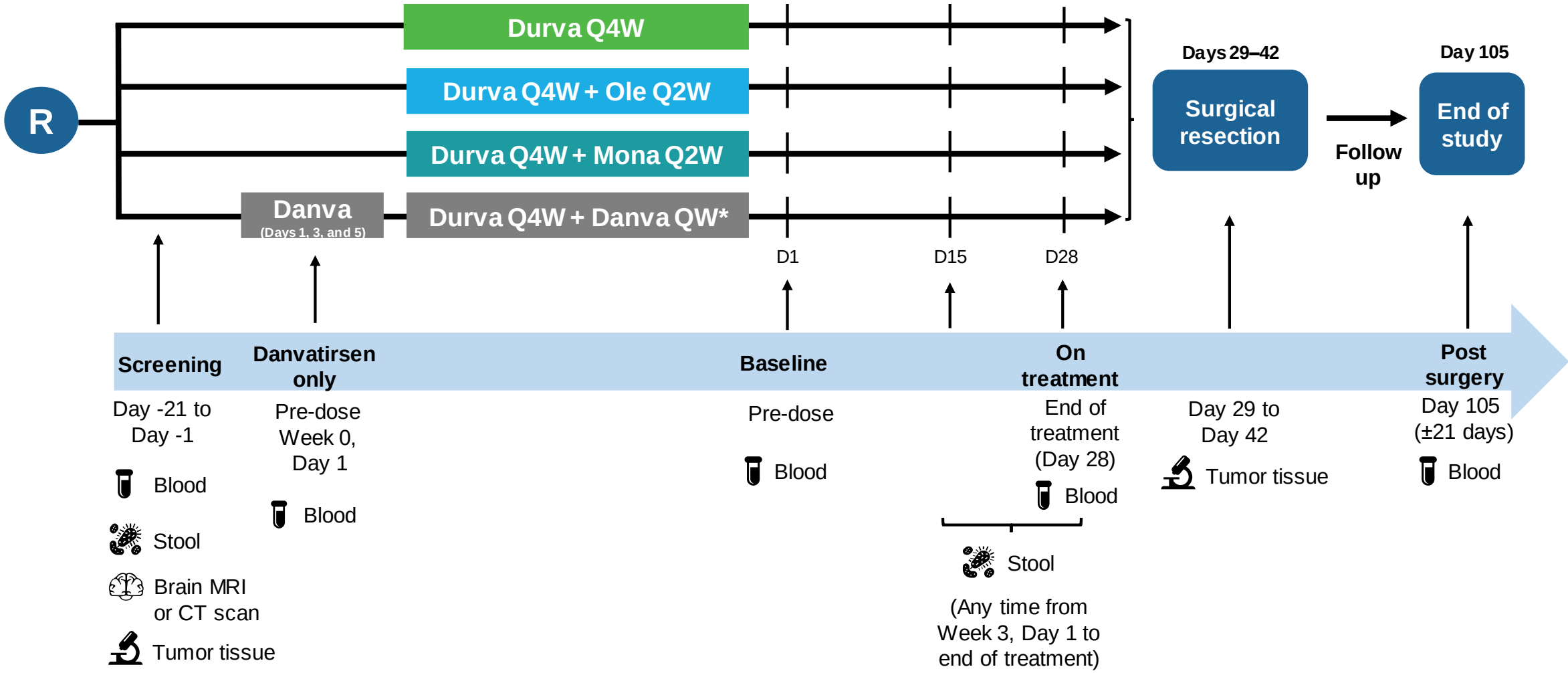
NeoCOAST: TEAEs occurring in ≥10% of patients in any arm in the as-treated population

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)

- Grade ≥3 TEAEs occurred in 5 (19.2%), 3 (14.3%), 2 (10.0%), and 5 (31.3%) patients in the durva, durva + ole, durva + mona, and durva + danva arms, respectively.

*One patient had grade ≥3 dyspnea.
†Patient had grade ≥3 alanine aminotransferase increase.
‡One patient had grade ≥3 alanine aminotransferase increase.
TEAE, treatment-emergent adverse event.

NeoCOAST: Translational assessments



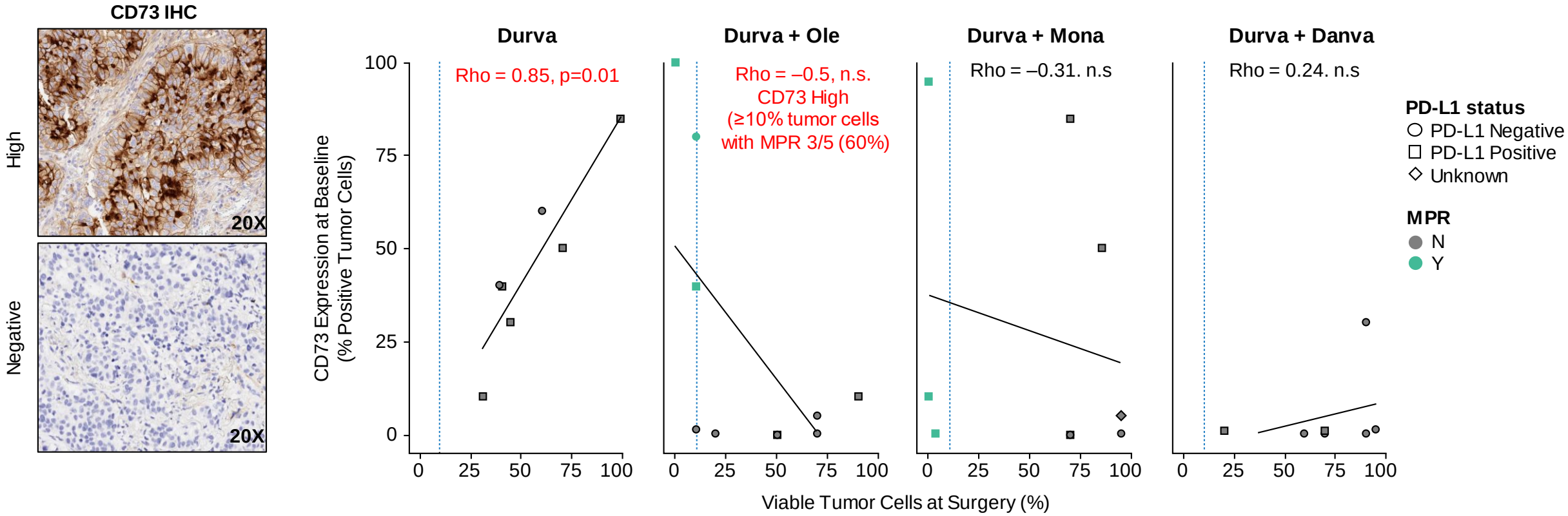
*Limited translational data were available for the durva + danva arm due to the treatment arm being discontinued and enrollment being halted early.

NeoCOAST: MPR by baseline clinical or biomarker characteristics

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

*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.

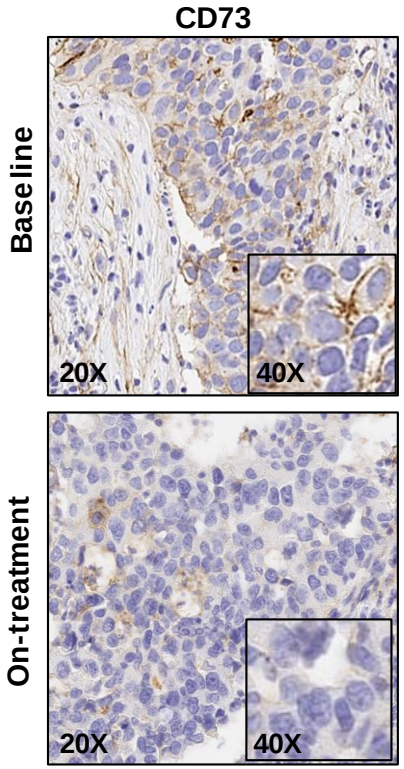
NeoCOAST: High baseline CD73 was associated with pathological response in the durva + ole arm



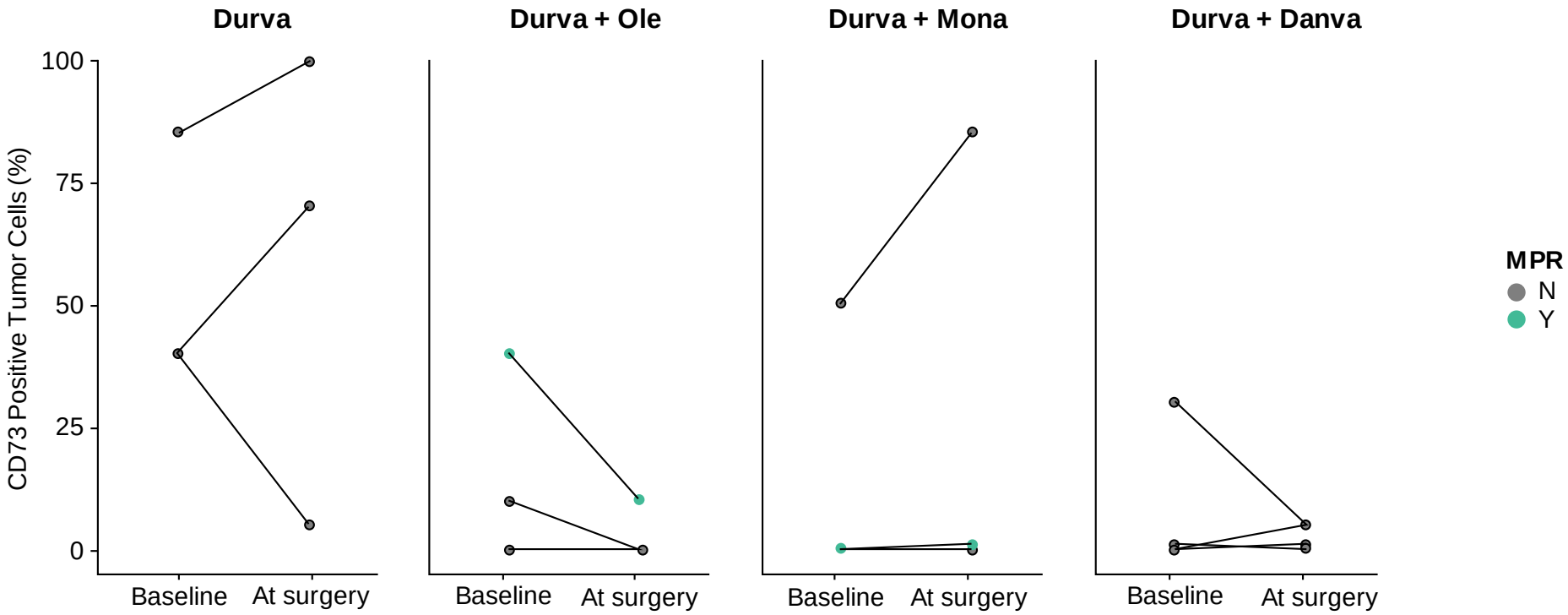
- High CD73 is associated with fewer viable tumor cells at surgery in the durva + ole arm, as expected based on the mechanism of action, but not in the durva arm.

CD73, cluster of differentiation 73; IHC, immunohistochemistry; n.s., not significant; MPR, major pathological response; PD-L1, programmed cell death ligand-1.

NeoCOAST: Durva + ole treatment resulted in decreased expression of CD73 on tumor cells



Representative sections from a patient treated with durva + ole who had MPR



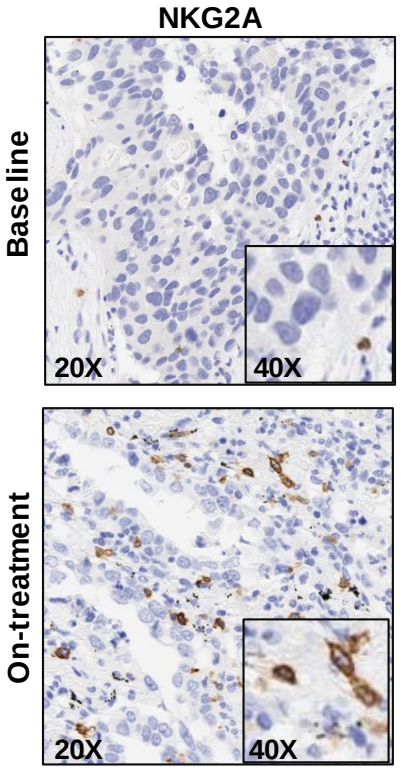
All arms, paired T-tests, n.s. All samples, unpaired T-test, n.s.

- Decrease in CD73 observed on treatment in the durva + ole arm (also observed in a previous study by Overman et al.[1]) but not in other arms.

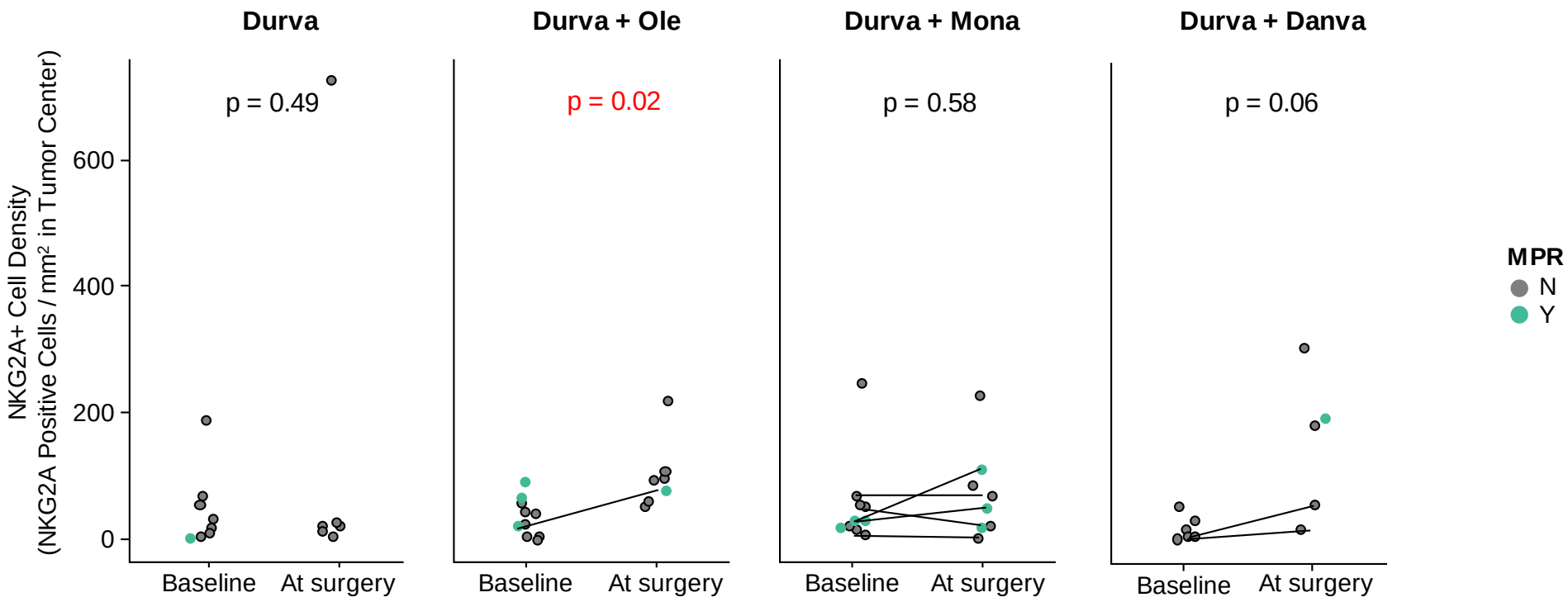
CD73, cluster of differentiation 73; MPR, major pathological response; n.s., not significant.

1. Overman M, et al. ASCO 2018 (poster P4123).

NeoCOAST: Durva + ole treatment resulted in increased effector immune cells in the tumor microenvironment



Representative sections from a patient treated with durva + ole who had MPR



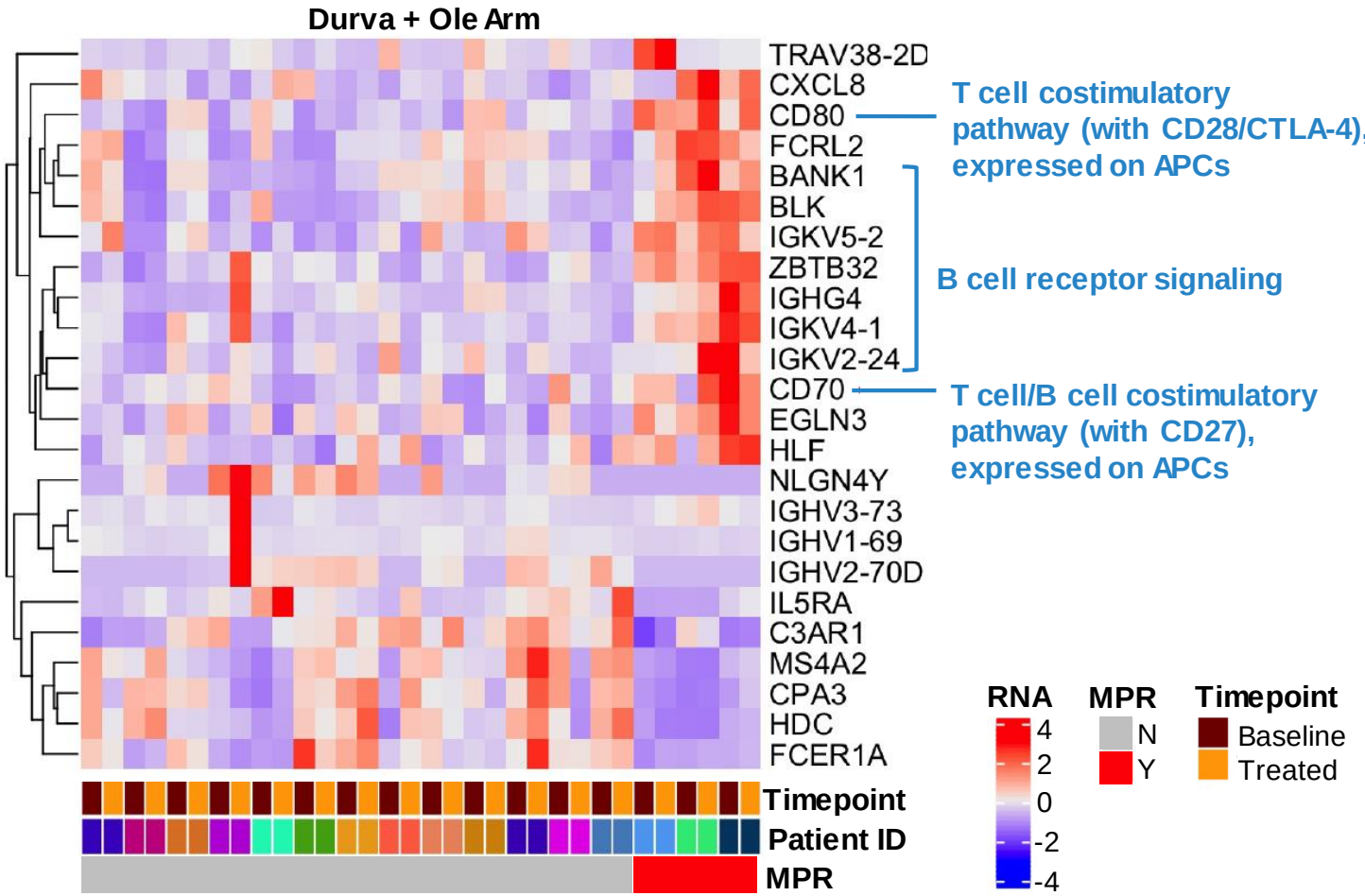
All arms, paired T-tests, n.s. All samples, unpaired T-test, n.s.

- Increase in NKG2A+ cell (NK cells, CD8 T cells) density in tumor center in durva + ole arm suggests increased infiltration of effector cells in the tumor microenvironment on treatment.

CD8, cluster of differentiation 8; MPR, major pathological response; NKG2A, NK group 2 member A; NK, natural killer; n.s., not significant.

NeoCOAST: In the durva + ole arm, patients with MPR have upregulation of genes involved in T- and B-cell activation in peripheral blood

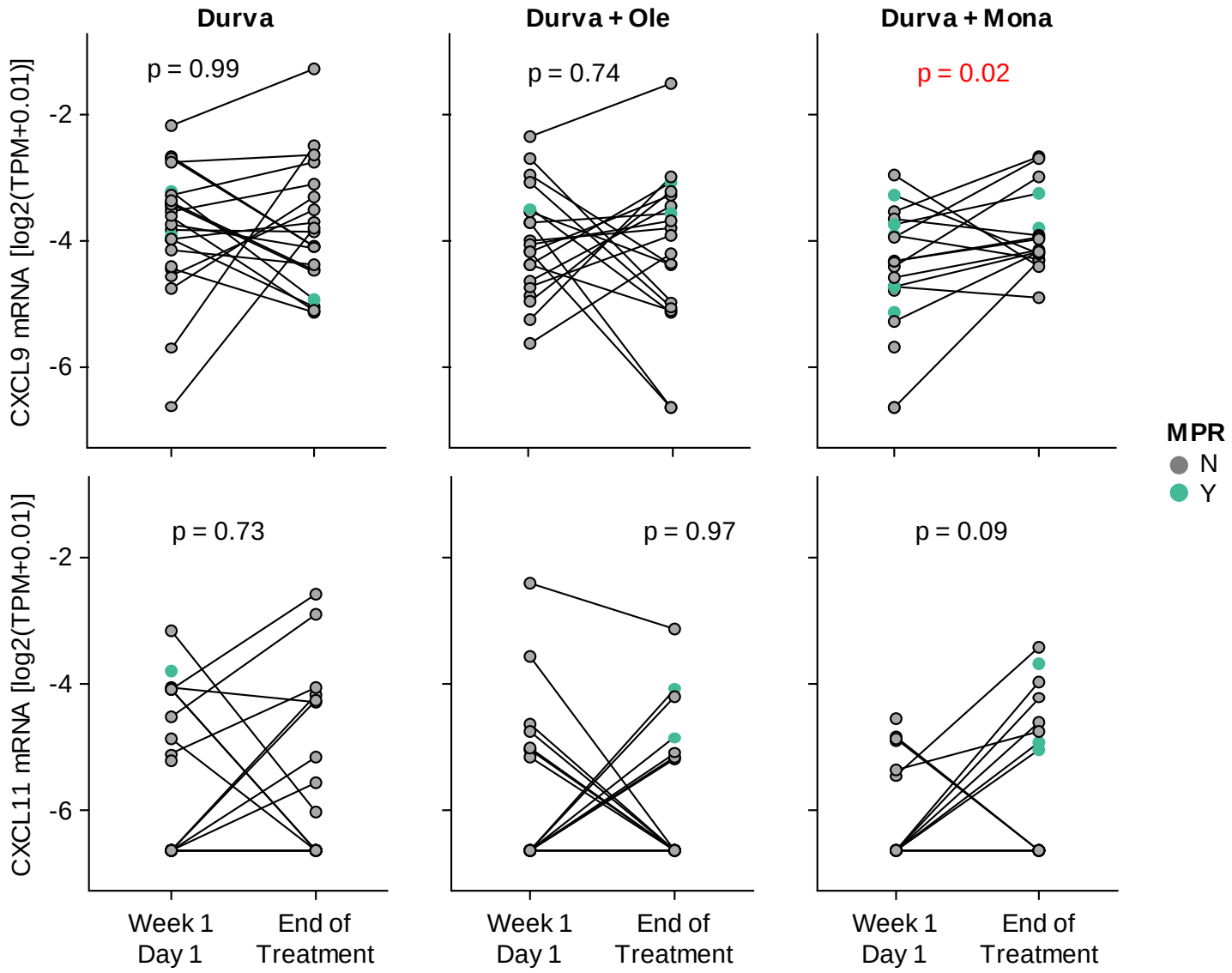
- Gene expression profiles were analyzed by whole transcriptome sequencing in peripheral blood at baseline (Week 1, Day 1) and end of treatment (Day 28).



- Differential expression between responders (MPR) vs non-responders (no MPR), identified significant upregulation of specific genes involved in B-cell activation, APCs, and T cell costimulatory pathways in the durva + ole arm, but not other arms.

APC, antigen presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T lymphocyte associated antigen-4; MPR, major pathological response.

NeoCOAST: Upregulation of CXCL9 and CXCL11 chemokines on treatment in the durva + mona arm



- CXCL9 and CXCL11 are IFN-γ inducible chemokines linked to NK & T cell recruitment.
- Both chemokines were upregulated in peripheral blood on treatment.

CXCL9, C-X-C motif chemokine ligand 9; CXCL11, C-X-C motif chemokine ligand 11; IFN-γ, interferon-gamma; NK, natural killer; TPM, transcript count per million.

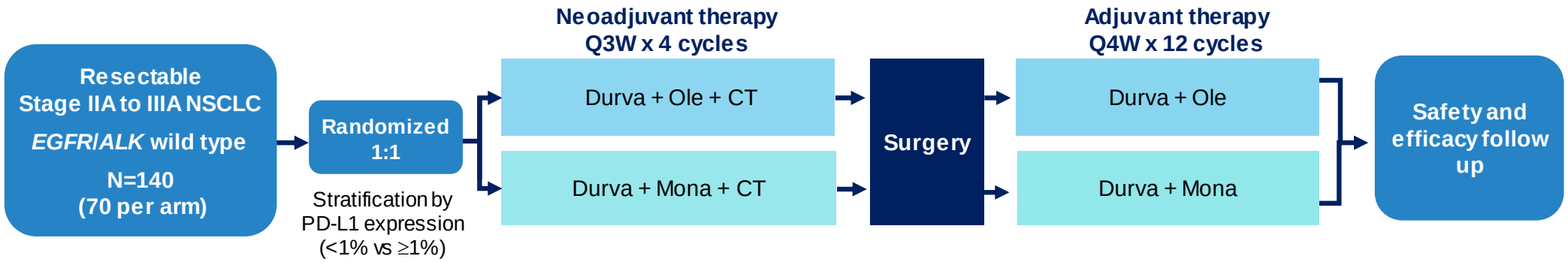
NeoCOAST: Conclusions

- A single cycle of neoadjuvant durva combined with ole, mona, or danva produced numerically improved MPR (19–31.3%) rates compared with durva alone (11.1%).
- MPR was associated with baseline tumor PD-L1 expression in durva plus ole or mona arms.
- Safety profiles were similar with combinations versus durva monotherapy.
- Patients with MPR who received neoadjuvant durva plus ole or mona had peripheral transcriptomic signatures related to immune cell function, suggesting that combined, multiple immune pathway inhibition may be superior to immune checkpoint inhibitor monotherapy.
- The use of a neoadjuvant platform trial design and surrogate endpoints facilitates the rapid generation of data to inform next-generation trials evaluating novel, immunotherapy-based, combination regimens in patients with early-stage resectable NSCLC.

MPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1.

NeoCOAST-2: Study design

NeoCOAST-2



- NeoCOAST-2 (NCT05061550) is a phase 2, randomized study of neoadjuvant durvalumab combined with chemotherapy and either ole or mona, followed by surgery and adjuvant durva plus ole or mona, in patients with resectable, Stage IIA–IIIA NSCLC.[1]
  - Primary endpoints: pCR, safety and tolerability
  - Secondary endpoints: EFS, DFS, OS, and ORR per RECIST v1.1; MPR; feasibility of surgery; pharmacokinetics; immunogenicity; baseline tumor PD-L1 expression; changes in ctDNA
  - Recruitment initiated in January 2022.

ALK, anaplastic large-cell lymphoma kinase; ctDNA, circulating tumor DNA; DFS, disease-free survival; EFS, event-free survival; EGFR, epidermal growth factor receptor; MPR, major pathological response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q3W, once every 3 weeks; Q4W, once every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Cascone T, et al. AACR 2022 (poster CT124).

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