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Platform study of neoadjuvant durvalumab (anti-PD-L1) alone or combined with oleclumab (anti-CD73), monalizumab (anti-NKG2A), or danvatirsen (anti-STAT3) in patients with resectable, early-stage non-small-cell lung cancer: pharmacodynamic correlates and ctDNA dynamics in the NeoCOAST study

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Declaration of interests

Jonathan Spicer, MD

- Speaker fees: AstraZeneca, Bristol Myers Squibb, Merck, and Novartis.
- Advisory board: AstraZeneca, Bristol Myers Squibb, Chemocentryx, Merck, Novartis, Protalix Biotherapeutics, and Roche.
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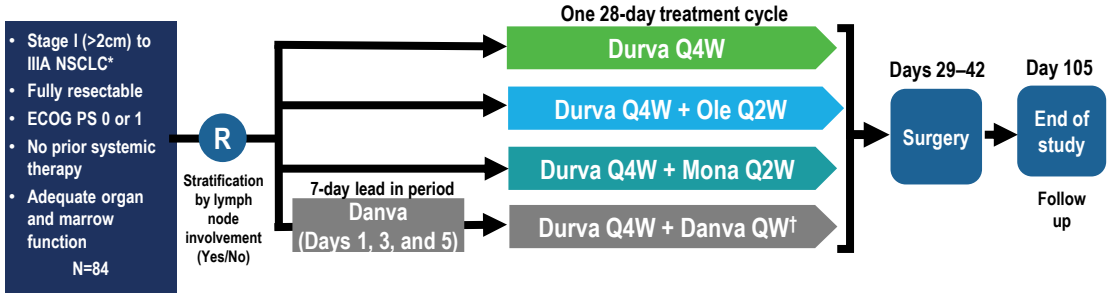
NeoCOAST: Neoadjuvant durvalumab +/– novel agents in resectable, early-stage (I [>2cm] to IIIA) NSCLC



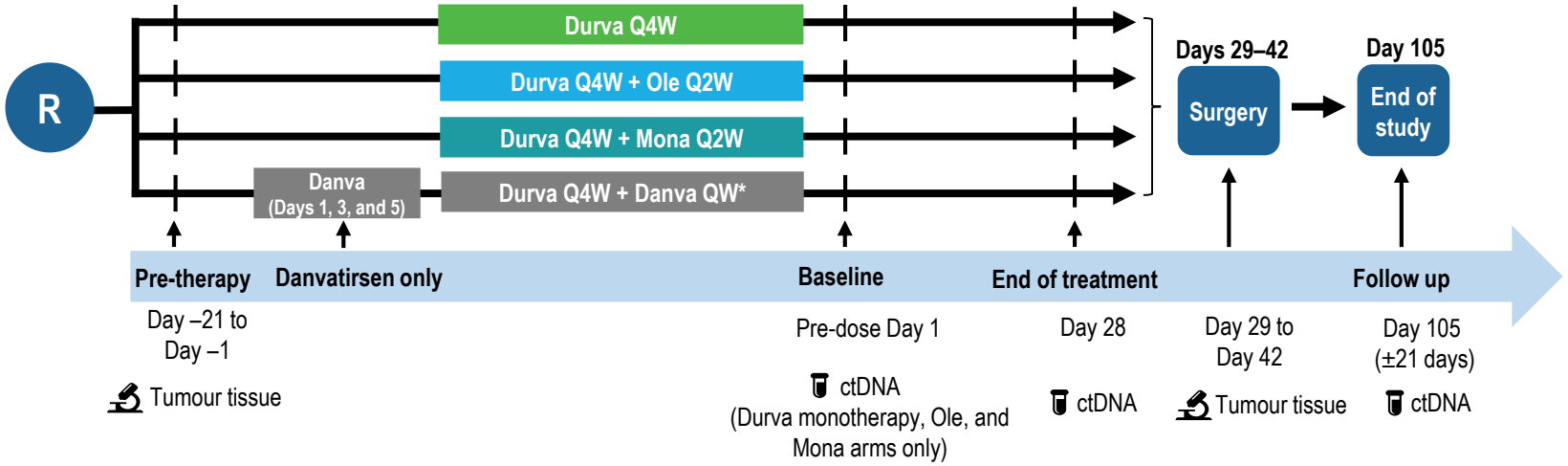
	Durva (n=27)	Durva + Ole (n=21)	Durva + Mona (n=20)	Durva + Danva (n=16)
Overall MPR (n/N, %)	3/27 (11%)	4/21 (19%)	6/20 (30%)	5/16 (31%)
PD-L1+	0/6 (0%)	2/5 (40%)	3/6 (50%)	0/2 (0%)
PD-L1–	0/3 (0%)	1/6 (16.7%)	0/2 (0%)	0/5 (0%)
PD-L1 NE	3/18 (17%)	1/10 (10%)	3/12 (25%)	5/9 (56%)

- Primary endpoint: MPR rate (proportion of patients with ≤10% residual viable tumour cells in resected tumour specimen and sampled nodes at surgery) per investigator assessment.
- A **single cycle of** neoadjuvant durva combined with ole, mona, or danva produced numerically improved MPR rates (19–31.3%) compared with durva alone (11.1%).[1]
- MPR was associated with baseline tumour PD-L1 expression in durva + ole and durva + mona arms.

*Per American Joint Committee on Cancer Staging, 8th edition. †Danvatirsen arm was stopped early as the program was discontinued.
ctDNA, circulating tumour DNA; ECOG, Eastern Cooperative Oncology Group; MPR, major pathological response; NE, not evaluable; NSCLC, non-small-cell lung cancer; PD-L1, programmed cell death ligand-1; 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; TMB, tumour mutational burden.

1. Cascone T, et al. AACR 2022 (presentation CT011).

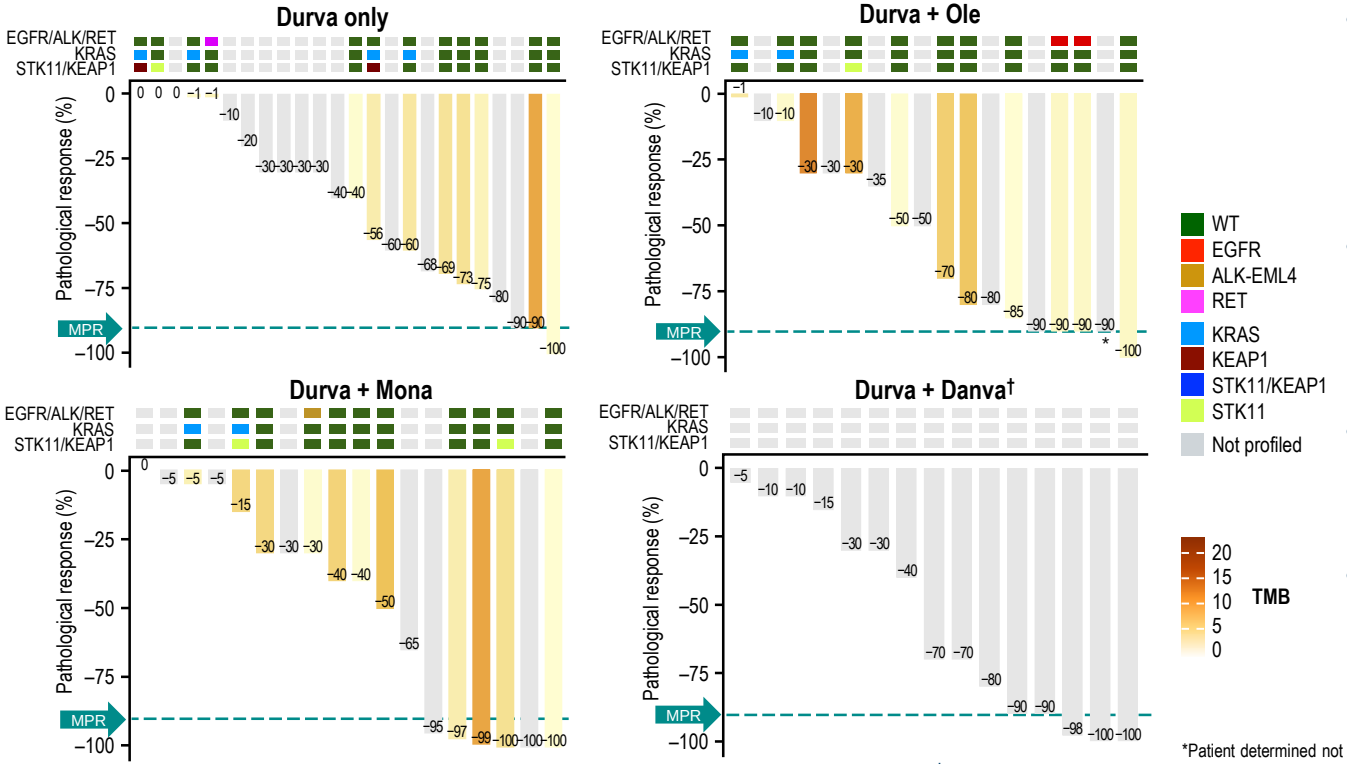
NeoCOAST: Translational assessments



- Blood and tumour samples were collected for exploratory translational analyses, including assessment of somatic tumour alterations and TMB, ctDNA dynamics, and gene expression profiling.

*Danvatirsen arm was stopped early as the program was discontinued.
ctDNA, circulating tumour DNA; Q4W, once every 4 weeks; Q2W, once every 2 weeks; QW, every week; TMB, tumour mutational burden.

Pathological regressions at surgery, and association with somatic tumour alterations and TMB



- TMB and somatic tumour alterations were profiled from tumour DNA and matched blood DNA by whole exome sequencing‡.
- TMB ranged 0.11–22.02 Mut/MB and was not correlated with percentage viable tumour cells at surgery (Rho: 0.19, p > 0.05).
- Among patients with an MPR, 2 had *EGFR* driver mutations (both durva + ole arm).
- *KRAS*, *STK11*, *RET* and *ALK* alterations were most commonly observed in patients without an MPR.

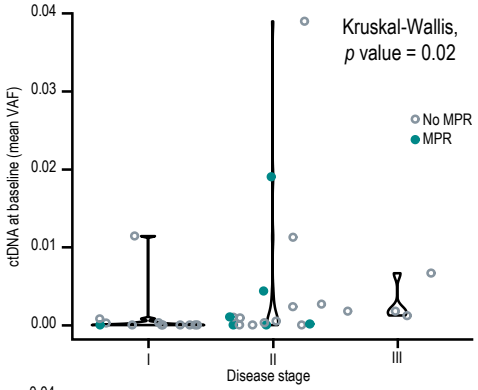
*Patient determined not to have MPR after local evaluation of primary tumour and lymph nodes

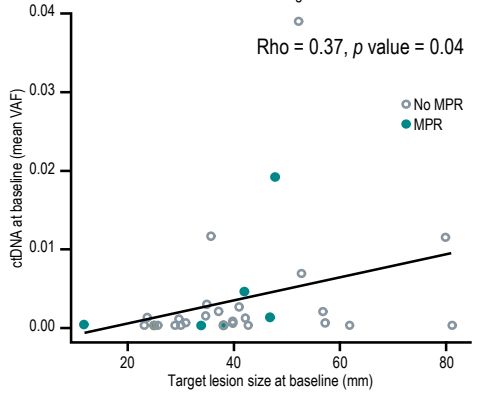
†Durva + danva analyses were limited as danva was stopped early and the program discontinued due to Sponsor decision

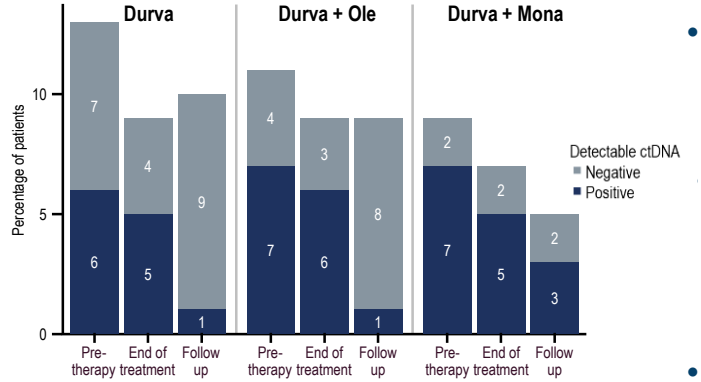
‡TMB and somatic alterations are from pre-therapy or surgery tumour tissue for patients with sufficient available tissue and/or DNA yield (N=34).

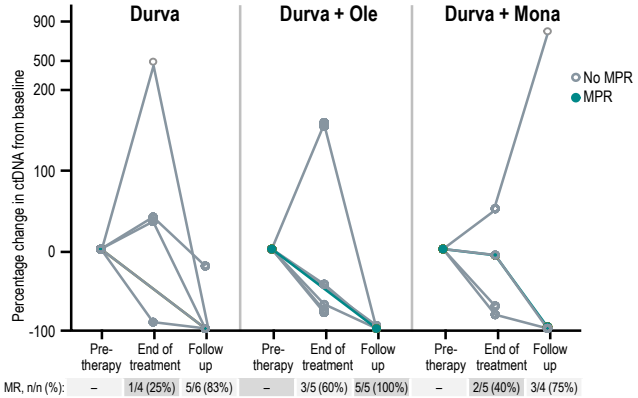
MPR, major pathological response; TMB, tumour mutational burden; WT, wild type..

Baseline ctDNA VAF was associated with disease stage and tumour size, on-treatment ctDNA reductions were observed





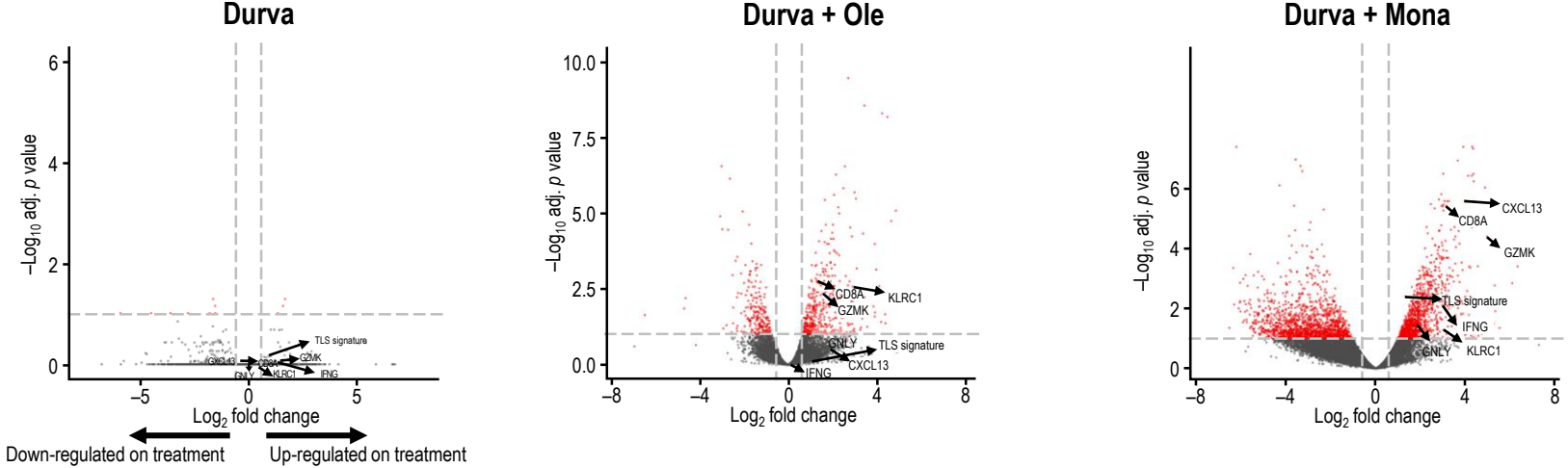




- ctDNA was profiled using a tumour-informed, personalized panel of genes tracked in longitudinal blood samples (Signatera).
- ctDNA at baseline (mean VAF) was increased in patients with Stage II–III disease compared with Stage I, and higher in patients with larger tumours.
- Overall, the number of patients with detectable ctDNA in peripheral blood decreased at end of treatment and post-surgery, compared with baseline.
- Molecular responses by ctDNA (≥50% ΔVAF from baseline) were observed in 25–60% of patients per arm after treatment, and 75–100% post-surgery, and included patients without an MPR.

ctDNA, circulating tumour DNA; MPR, major pathological response; MR, molecular response; VAF, variant allele frequency.

Evaluation of gene expression between tumours pre-therapy and at surgery reveals signatures of intratumoural immune activation



- Whole transcriptome RNA-sequencing was performed from tumour tissue collected pre-therapy and at surgery for all patients, where both samples were available.
- Expression of genes and gene signatures associated with NK cells (*KLRC1*, *GNLY*), CD8 T cells (*CD8A*, *GZMK*), cytotoxicity (*IFNG*, *GZMK*), tertiary lymphoid structures, and lymphocyte recruitment (*CXCL13*) demonstrated greater increases with durva + ole and durva + mona, than with durva alone.

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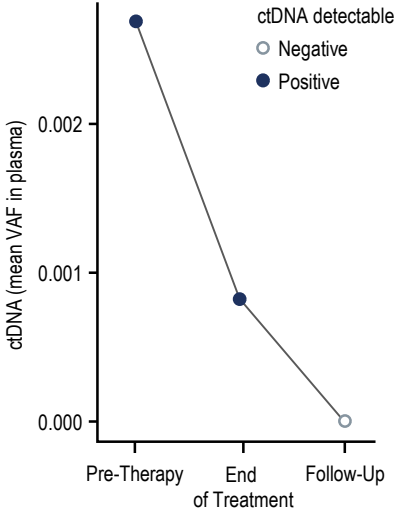
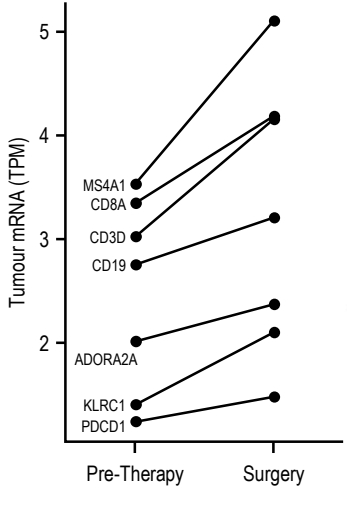
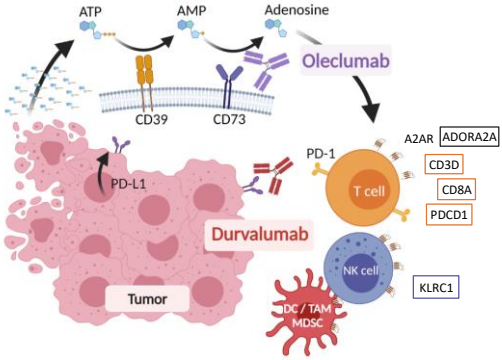
Patients with major pathological response out of total sample pairs: durva, 0/4; durva + ole, 1/5; durva + mona, 2/4.
NK, natural killer; TLS, tertiary lymphoid structures.

Case study: patient treated with durva + ole with pharmacodynamic evidence of intratumoural immune activation

- Patient characteristics: 63F, former smoker, Stage IIB, squamous cell carcinoma.
- Stable disease by RECIST v1.1, 50% viable tumour cells at surgery.
- ctDNA dynamics revealed molecular response at end of treatment, and complete clearance post-surgery.
- Increased PD-L1+ TC and CD8 T-cell density at surgery compared with pre-therapy.
- As assessed by tumour mRNA, T and NK cell genes, adenosine A2a receptor, and B cell markers (MS4A1/CD20, CD19) increased at surgery compared with pre-therapy, consistent with mechanism of action of ole.







IHC Biomarker	Pre-therapy	Surgery	Δ
PD-L1+ TC (%)	20%	90%	↑350%
CD73+ TC (%)	0%	0%	0%
CD8 T cell density (#)	521	711	↑36%

CD, cluster of differentiation; ctDNA, circulating tumour DNA; IHC, immunohistochemistry; NK, natural killer; PD-L1, programmed cell death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumour cell; TPM, transcripts per million; VAF, variant allele frequency.

Summary and conclusions

- A single cycle of neoadjuvant durva combined with ole, mona, or danva produced numerically improved MPR rates (19–31.3%) compared with durva alone (11.1%).
- Pathological regressions were not associated with TMB.
- Molecular responses by ctDNA were observed in 25–60% of patients per arm after treatment, and 75–100% of patients post-surgery, including those without an MPR.
- Pharmacodynamic responses by intratumoural mRNA show greater increases in immune activation genes with durva + ole and durva + mona than with durva alone.
- Further translational analyses of durva combined with ole or mona will be carried out as part of NeoCOAST-2 (NCT05061550), a Phase 2 study of neoadjuvant durva 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]

ctDNA, circulating tumour DNA; MPR, major pathological response; TMB, tumour mutational burden.

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

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