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NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

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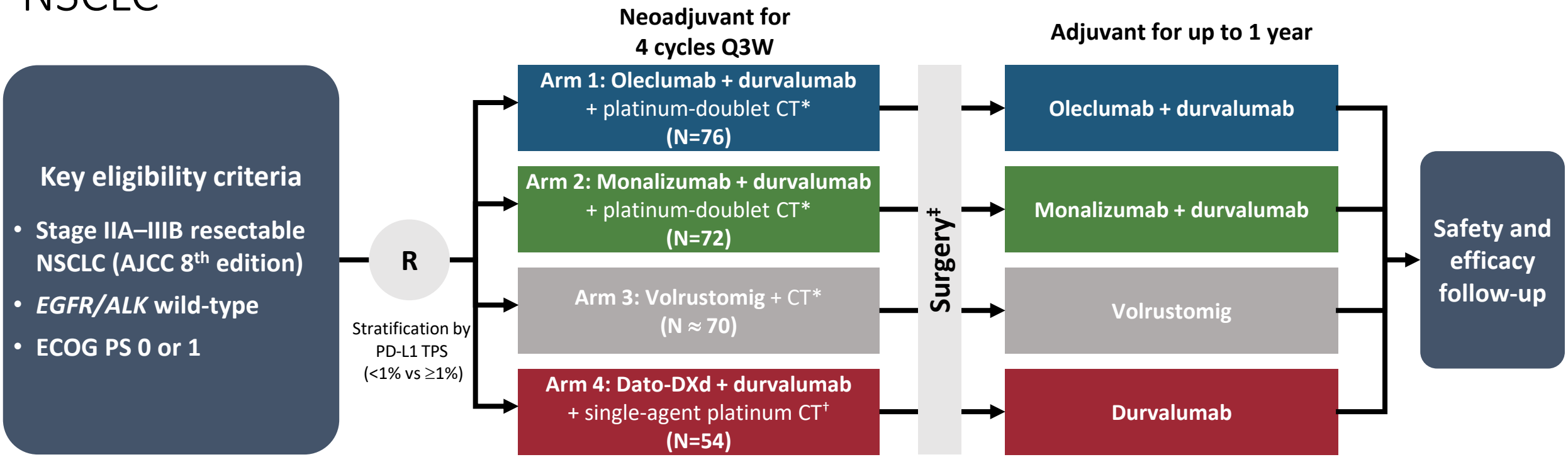
Background

- Durvalumab + oleclumab (anti-CD73) or monalizumab (anti-NKG2A) have demonstrated improved efficacy in COAST and NeoCOAST, two phase 2 studies in patients with early-phase NSCLC.[1,2]
- Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody drug conjugate, significantly improved PFS versus docetaxel in patients with locally advanced or metastatic NSCLC in the phase 3 TROPION-Lung01 study.[3]
- Perioperative anti-PD-(L)1 therapies + neoadjuvant CT have demonstrated improvements in EFS compared with CT alone, as reported by the phase 3 studies AEGEAN, KEYNOTE-671 and Checkmate 77T.[4–6]
- The phase 2 NeoCOAST-2 platform study (NCT05061550) is evaluating efficacy and tolerability of novel perioperative treatment combinations in patients with resectable NSCLC.

1. Herbst RS, et al. *J Clin Oncol* 2022;40:3383–93; 2. Cascone T, et al. *Cancer Discov* 2023;13;2394–411; 3. Ahn M-J, et al. *Ann Oncol* 2023;34;S1305–06; 4. Heymach JV, et al. *N Engl J Med* 2023;389;1672–84; 5. Wakelee H, et al. *N Engl J Med* 2023;389:491–503; 6. Cascone T, et al. *N Engl J Med* 2024;390:1756–69.
ADC, antibody drug conjugate; cCRT, concurrent chemoradiotherapy; CT, chemotherapy; EFS, event-free survival; mPR, major pathological response; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival.

NeoCOAST-2: open-label, multi-arm platform study in perioperative NSCLC



Primary endpoints
- pCR rate§
- Safety and tolerability

Key secondary endpoints
- mPR rate§ and EFS
- Feasibility to surgery

Statistical considerations
- This study was not powered to make direct statistical comparisons between arms.
- Descriptive statistics are summarised and presented.
- The primary intent was to look for preliminary efficacy signals by calculating pCR rates and their confidence intervals.

*Carboplatin + paclitaxel for squamous tumour histology, pemetrexed + cisplatin or carboplatin for non-squamous tumour histology. †Physician's choice of carboplatin or cisplatin. ‡Within 40 days of the last dose of neoadjuvant treatment. §Proportion of patients with no viable tumour cells and ≤10% residual viable tumour cells, respectively, in resected tumour specimen and sampled nodes at surgery.

CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; EFS, event-free survival; mPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; R, randomised; TPS, tumour proportion score.

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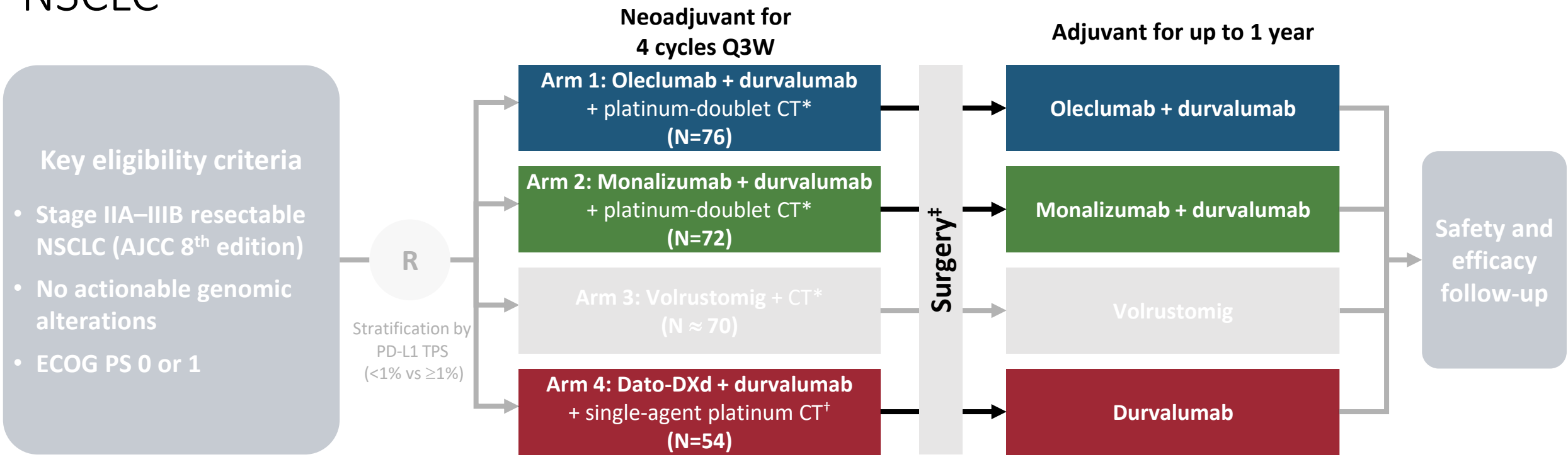

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Baseline patient characteristics were well balanced across arms

	Arm 1 Oleclumab + durvalumab + CT* N=76	Arm 2 Monalizumab + durvalumab + CT* N=72	Arm 4 Dato-DXd + durvalumab + CT* N=54
Median age, years (range)	66.5 (30–79)	66.0 (48–83)	65.0 (38–81)
Female/Male, n (%)	29 (38.2) / 47 (61.8)	29 (40.3) / 43 (59.7)	22 (40.7) / 32 (59.3)
Race, n (%)			
Asian	7 (9.2)	5 (6.9)	5 (9.3)
Black or African American	1 (1.3)	0	0
White	48 (63.2)	43 (59.7)	37 (68.5)
Not reported	20 (26.3)	24 (33.3)	12 (22.2)
ECOG PS 0/1, n (%)	45 (61.6) / 28 (38.4)†	49 (69.0) / 22 (31.0)‡	36 (66.7) / 18 (33.3)
PD-L1 <1% / PD-L1 ≥1% TPS, n (%)	24 (31.6) / 52 (68.4)	24 (33.3) / 48 (66.7)	13 (24.1) / 41 (75.9)
Stage, n (%)§			
IIA	7 (9.2)	7 (9.7)	2 (3.8)
IIB	16 (21.1)	19 (26.4)	13 (24.5)
IIIA	40 (52.6)	33 (45.8)	27 (50.9)
IIIB	13 (17.1)	13 (18.1)	11 (20.8)
Histology, n (%)			
Adenocarcinoma	50 (65.8)	46 (63.9)	33 (61.1)
Squamous cell carcinoma	24 (31.6)	20 (27.8)	17 (31.5)
Other	2 (2.6)	6 (8.3)	4 (7.4)

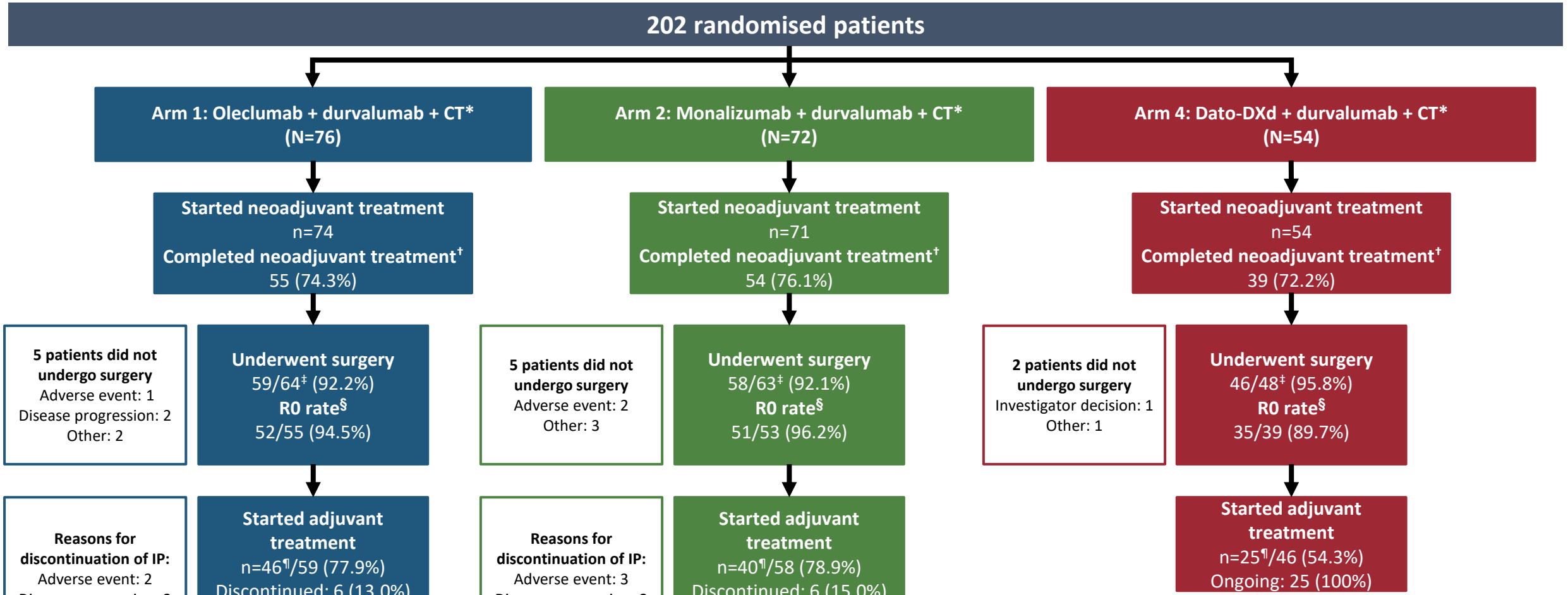
- Consistent with real-world practice, the majority of patients received carboplatin compared with cisplatin: 72%, 77%, and 87% of patients received carboplatin vs cisplatin in Arms 1, 2, and 4, respectively.

Data cut-off: 17 June 2024

*Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT; †Data missing for 3 patients; ‡Data missing for 1 patient; §Data missing for 1 patient in Arm 4.

CT, chemotherapy; D, durvalumab; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TPS, tumour proportion score.

Summary of treatment disposition and surgery

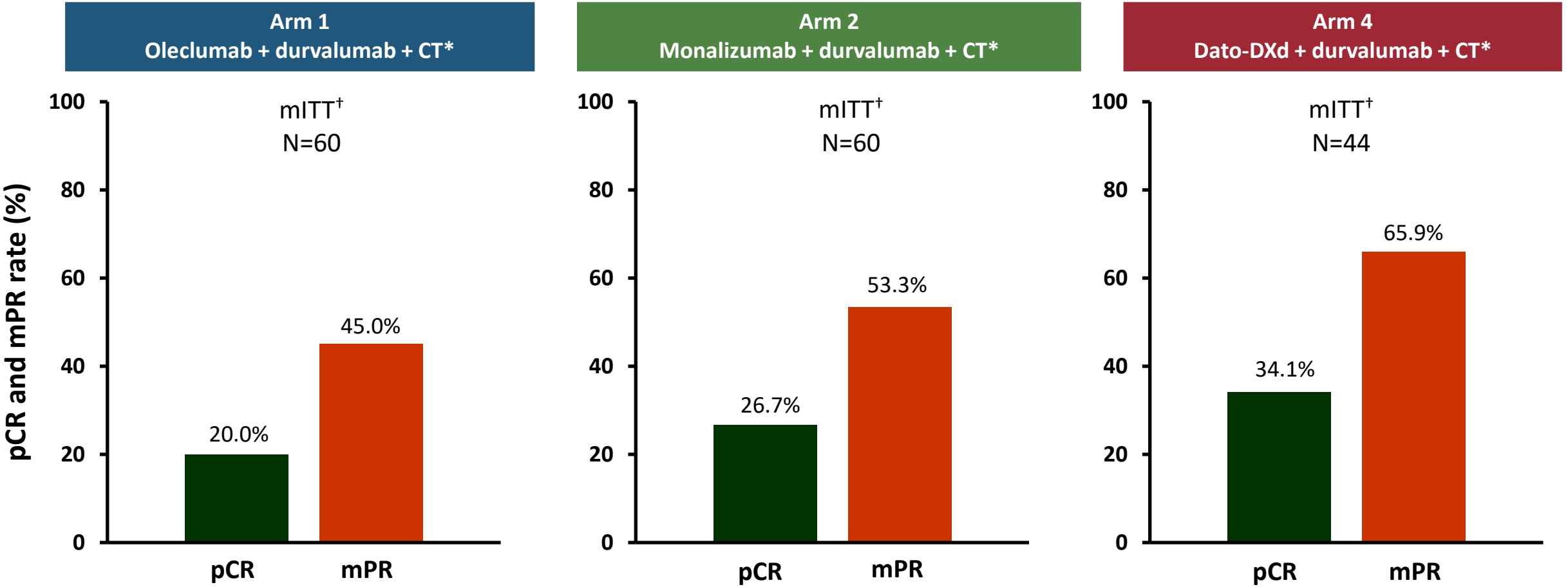


Data cut-off: 17 June 2024

Median (range) of number of adjuvant cycles completed per protocol in Arms 1, 2, and 4 are 6 (1–12), 7.5 (1–12) and 2 (1–6), respectively as of data cut-off. *Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT. †Completed 4 cycles of neoadjuvant treatment as per protocol. ‡Denominator includes patients who underwent surgery or were ineligible for surgery at data cut-off. §Margins are calculated from patients who completed surgery and had data available at data cut-off. ¶Numerator includes patients who underwent surgery and had enough follow-up time to start adjuvant treatment. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; IP, investigational product.

Cascone T| NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

NeoCOAST-2: pCR and mPR rates across treatment arms



Pathological assessment performed locally or centrally‡

Data cut-off: 17 June 2024

*Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT. †The mITT population includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at the data cut-off, including those who were unable to receive or complete surgery. Some patients who underwent surgery did not have pathology results available at data cut-off. ‡Blind independent pathological review was used where available; proportion of local results were Arm 1, 9/55 (16.3%); Arm 2: 6/55 (11%); Arm 4: 16/41 (39%). Denominator includes only those patients who had surgery and results available. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; mITT, modified intention-to-treat population; mPR, major pathological response; pCR, pathological complete response.

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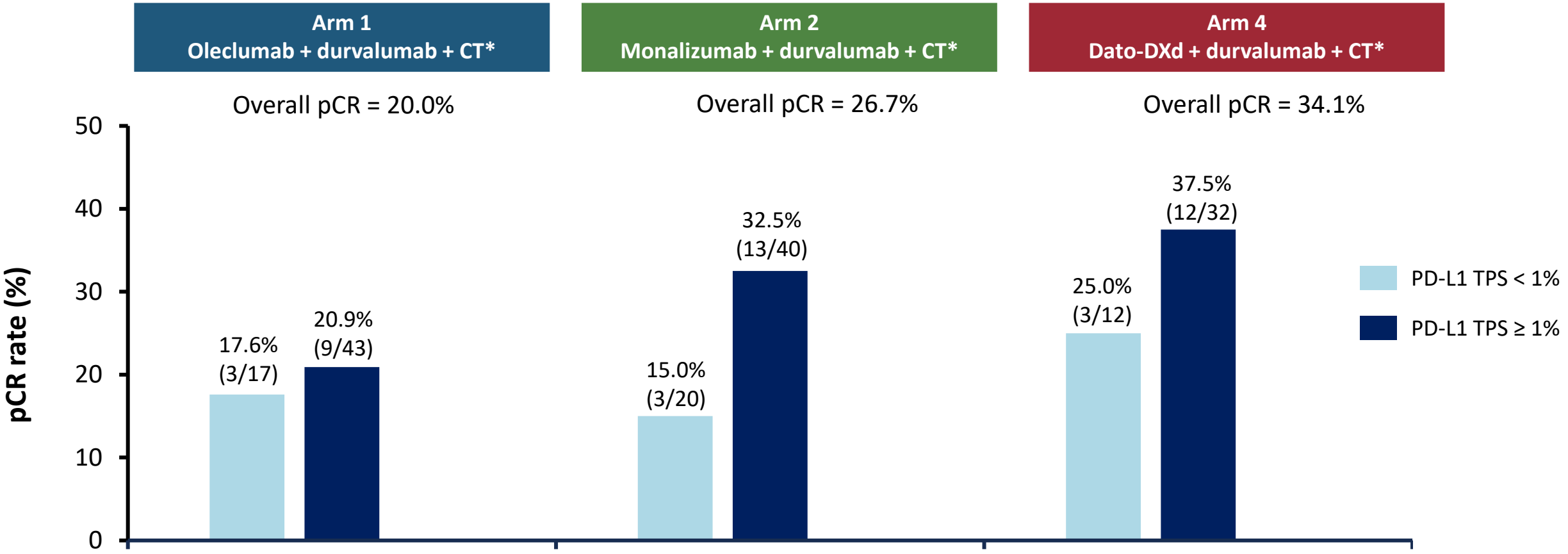
pCR rates across baseline PD-L1 positive and negative expression subgroups



Data cut-off: 17 June 2024

Based on the modified intention-to-treat population which includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at the DCO, including those who were unable to receive or complete surgery. Baseline PD-L1 status is assessed using central (Ventana SP263) or local testing (Ventana SP263, pharmDx 28-8, or pharmDx 22C3). Central results are reported for Arm 1, 12/60 (20%); Arm 2, 18/60 (30%); Arm 4, 13/44 (30%) patients. Local results are reported for all other patients.

In AEGEAN, pCR rates were 9.0%, 16.3% and 27.5% in PD-L1 <1%, PD-L1 1–49% and PD-L1 ≥50% subgroups, respectively (Heymach JV, et al. *N Engl J Med* 2023;389;1672–84).

*Arms 1 and 2 received platinum-doublet CT and Arm 4 received single-agent platinum CT.

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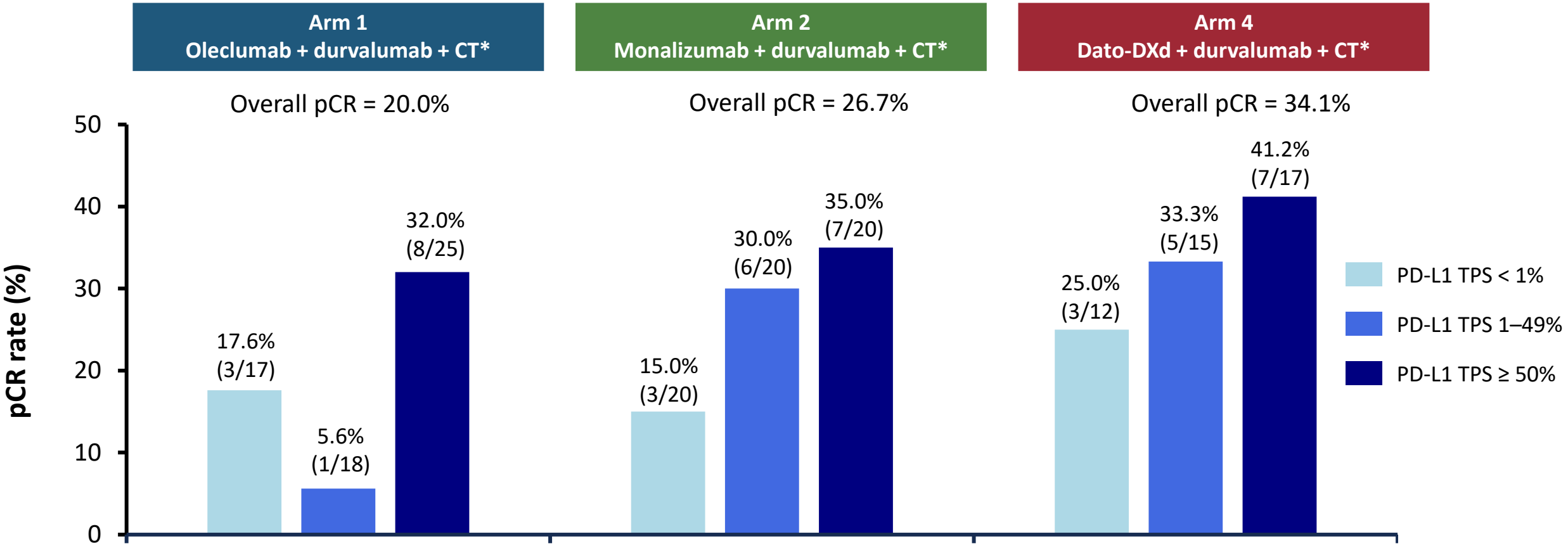

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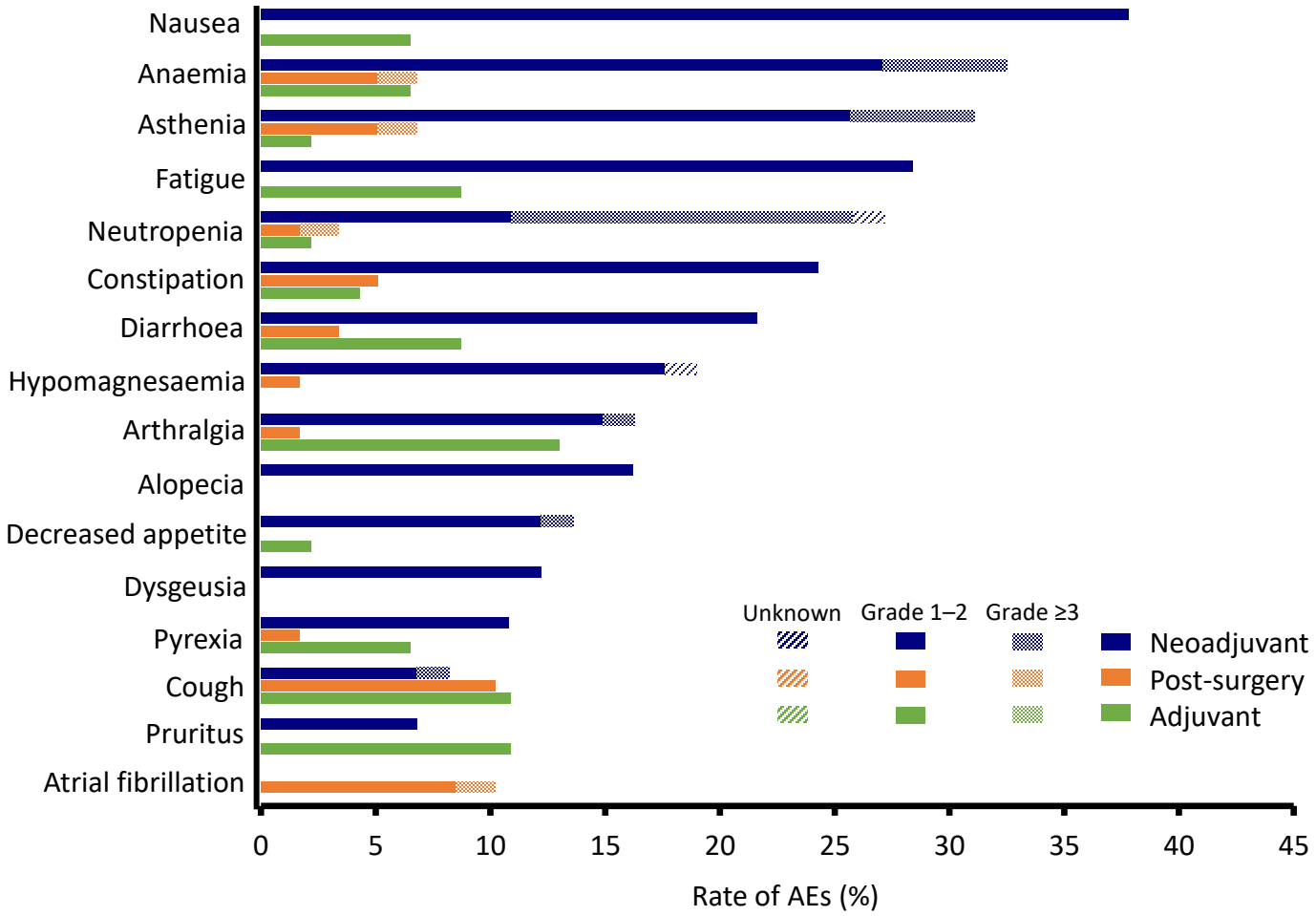
NeoCOAST-2: Safety profile of Arm 1 – Oleclumab + durvalumab + platinum-doublet CT

n (%)	Neoadjuvant N=74	Post-surgery N=59	Adjuvant N=46
Any TEAE	72 (97.3)	33 (55.9)	36 (78.3)
Any TRAE	70 (94.6)	3 (5.1)	29 (63.0)
Grade ≥3 TEAE	26 (35.1)	14 (23.7)	4 (8.7)
Grade ≥3 TRAE	23 (31.1)	0	2 (4.3)
AE leading to discontinuation	6 (8.1)	1 (1.7)	3 (6.5)
SAE	12 (16.2)	9 (15.3)	3 (6.5)
Any SAE with outcome of death	1 (1.4)*	2 (3.4)†	0

*Due to intestinal ischemia related to chemotherapy (carboplatin and paclitaxel).
†Both due to respiratory failure related to surgery; both patients had a lobectomy.

Any-grade TEAEs in ≥10% of patients from any treatment phase



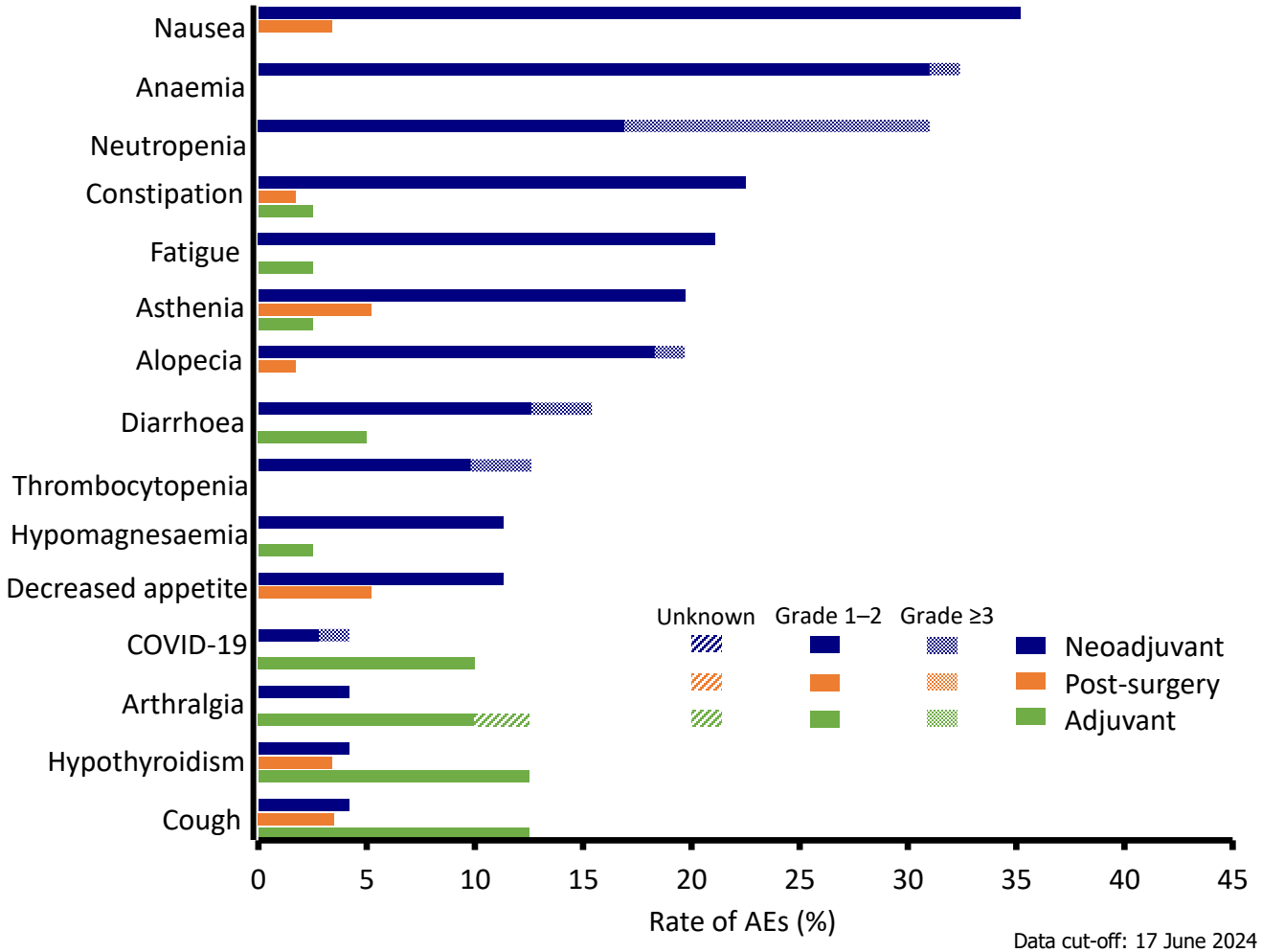
Data cut-off: 17 June 2024
The median (range) of number of adjuvant cycles completed per protocol in Arm 1 is 6 (1–12) as of data cut-off.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

NeoCOAST-2: Safety profile of Arm 2 – Monalizumab + durvalumab + platinum-doublet CT

n (%)	Neoadjuvant N=71	Post-surgery N=58	Adjuvant N=40
Any TEAE	70 (98.6)	36 (62.1)	29 (72.5)
Any TRAE	64 (90.1)	9 (15.5)	16 (40.0)
Grade ≥3 TEAE	29 (40.8)	14 (24.1)	8 (20.0)
Grade ≥3 TRAE	21 (29.6)	1 (1.7)	5 (12.5)
AE leading to discontinuation	9 (12.7)	0	3 (7.5)
SAE	12 (16.9)	14 (24.1)	5 (12.5)
Any SAE with outcome of death	0	3 (5.2)*	1 (2.5)†

*Due to sepsis (related to pneumonectomy), septic shock (related to lobectomy) and renal failure (related to bilobectomy).
†Due to cardiorespiratory arrest related to durvalumab and monalizumab.

Any-grade TEAEs in ≥10% of patients from any treatment phase



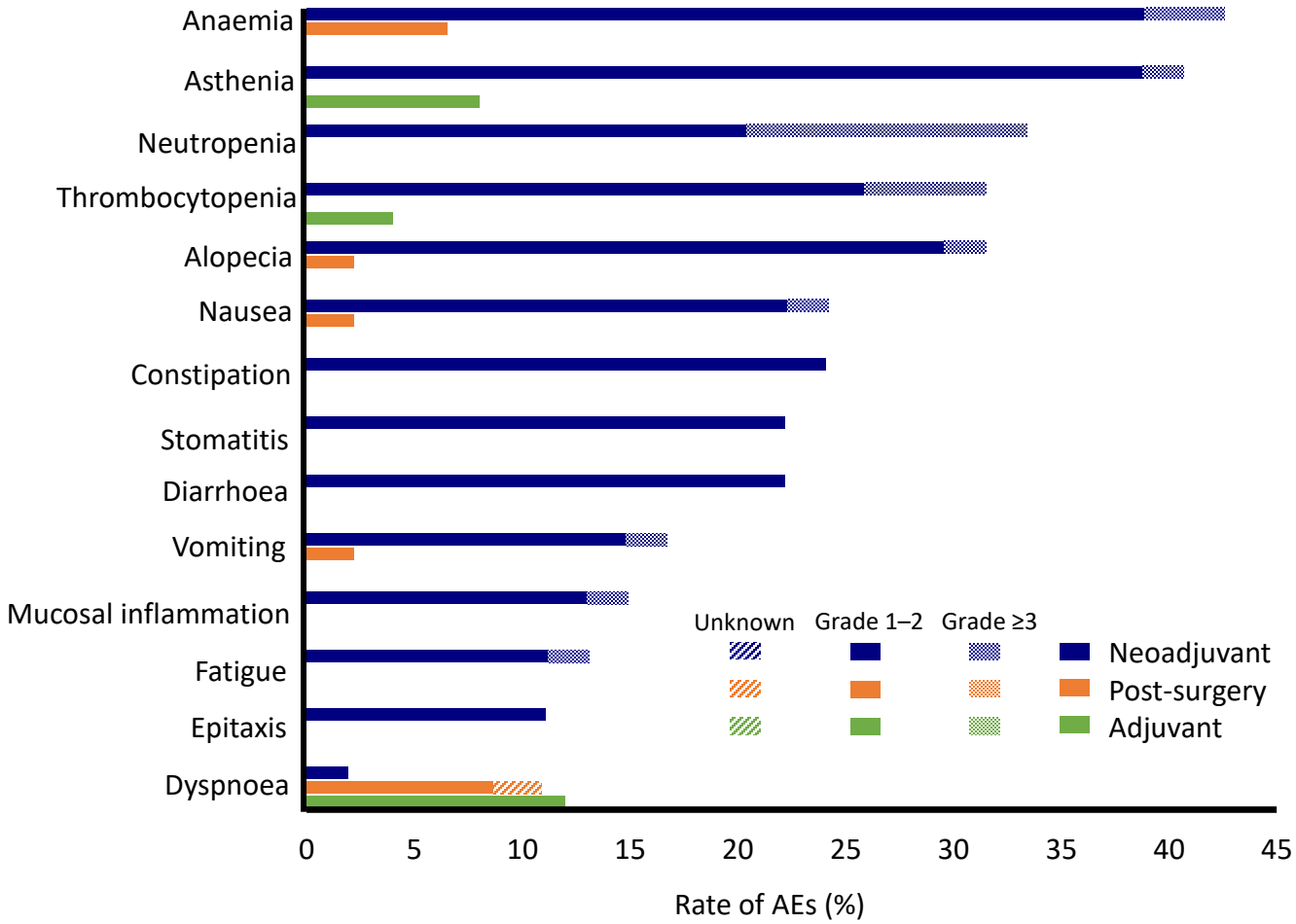
Data cut-off: 17 June 2024
The median (range) of number of adjuvant cycles completed per protocol in Arm 2 is 7.5 (1–12) as of data cut-off.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

NeoCOAST-2: Safety profile of Arm 4 – Dato-DXd + durvalumab + single-agent platinum CT

n (%)	Neoadjuvant N=54	Post-surgery N=46	Adjuvant N=25
Any TEAE	53 (98.1)	24 (52.2)	11 (44.0)
Any TRAE	52 (96.3)	6 (13.0)	5 (20.0)
Grade ≥3 TEAE	13 (24.1)	4 (8.7)	1 (4.0)
Grade ≥3 TRAE	10 (18.5)	0	0
AE leading to discontinuation	4 (7.4)	0	0
SAE	10 (18.5)	7 (15.2)	1 (4.0)
Any SAE with outcome of death	0	1 (2.2)*	0

*Due to idiopathic pulmonary fibrosis unrelated to treatment.†

Any-grade TEAEs in ≥10% of patients from any treatment phase



Data cut-off: 17 June 2024
The median (range) of number of adjuvant cycles completed per protocol in Arm 4 is 2 (1–6) as of data cut-off.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
†Unrelated per principal investigator, independent adjudication is pending.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- In this preliminary analysis of patients with early-stage resectable NSCLC, Dato-DXd + durvalumab + single-agent platinum CT showed highly promising pCR and mPR rates including in patients across all PD-L1 expression levels.
  - Oleclumab + durvalumab + CTx*: pCR rate 20.0% (95% CI; 10.8–32.3); mPR rate 45.0% (95% CI; 32.1–58.4)
  - Monalizumab + durvalumab + CTx*: pCR rate 26.7% (95% CI; 16.1–39.7); mPR rate 53.3% (95% CI; 40.0–66.3)
  - Dato-DXd + durvalumab + CT*: pCR rate 34.1% (95% CI; 20.5–49.9); mPR rate 65.9% (95% CI; 50.1–79.5)

- Treatments in all arms demonstrated a manageable safety profile and surgical rates comparable to currently approved regimens.[1–3]

- **This is the first global phase 2 study showing encouraging efficacy and manageable safety profile of an antibody drug conjugate in the neoadjuvant setting for patients with resectable NSCLC.**

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1. Wakelee H, et al. *New Engl J Med* 2023;389;491–503; 2. Forde PM, et al. *New Engl J Med* 2022;386;1973–85; 3. Heymach JV, et al. *New Engl J Med* 2023;389:1672–84.

CI, confidence interval; CT(x), chemotherapy(s); Dato-DXd, datopotamab deruxtecan; mPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response.

Acknowledgements

We thank all the patients, their families and caregivers, and all the investigators and their clinical and research team who participated in this study.

We dedicate this presentation to the memory of Ray Mager, Clinical Scientist at AstraZeneca, who worked extensively on this study and sadly passed away from brain cancer in August 2024.

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