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# Circulating tumor DNA dynamics and treatment responses in chemotherapy-ineligible patients with unresectable Stage III NSCLC from the phase 2 DUART trial

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# DECLARATION OF INTERESTS

**Andrea R. Filippi**

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**Participation on a steering committee:** AstraZeneca, EORTC

**Membership:** ESMO, ESTRO, IASLC

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# Background

- In the phase 2 DUART trial (NCT04249362), consolidation durvalumab after RT showed encouraging antitumor activity among chemotherapy-ineligible patients with unresectable Stage III NSCLC.[1]
- ctDNA has been proposed as a potential prognostic biomarker for patients with locally-advanced, unresectable NSCLC who receive CRT.[2–5]
- For chemotherapy-ineligible patients, ctDNA dynamics may allow early identification of patients who may benefit from escalation of treatment after RT.[6]
- Here, we report exploratory ctDNA analyses from DUART.
- Results from these exploratory analyses should be interpreted with caution given small sample sizes.



ctDNA, circulating tumor DNA; CRT, chemoradiotherapy; NSCLC, non-small-cell lung cancer; RT, radiotherapy

1. Filippi AR, et al. *Ann Oncol* 2023;34 (supplement 2):S1302 (Presented at ESMO 2023).
2. Moding EJ, et al. *Nat Cancer* 2020;1:176–183.
3. Wang Y, et al. *J National Cancer Center* 2024;4:177–187.
4. Yang Y, et al. *Int J Rad Onc Biology and Physics* 2021;111:S91–92.
5. Nielsen LR, et al. *Cancer Treatment and Res Comm* 2024;39:100802.
6. Jun S, et al. *J Thorac Oncol* 2024;Jul 5:S1556-0864(24)00664-6.

# DUART: a phase 2, open-label, multicenter, international study

**Primary endpoint:** Incidence of grade 3/4 PRAEs* within 6 months of durvalumab initiation

**Secondary endpoints:** PFS†, ORR, DoR (all investigator assessed; RECIST v1.1), OS†, and safety

**Patient Population**
- Unresectable Stage III NSCLC
- Ineligible for CT per investigator assessment
- RT alone as primary treatment per local SoC
- No biomarker selection
- ECOG PS 0–2

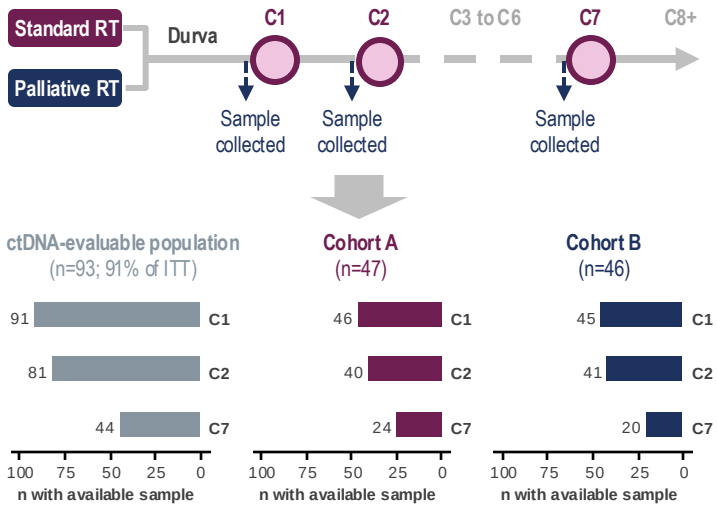
**Cohort A**
Standard RT‡
60 Gy ± 10% or equivalent BED

**Cohort B**
Palliative RT‡
40 to <54 Gy or equivalent BED

**Durvalumab**
1500mg Q4W
up to 12 months§
**N=102**

Study enrolment
(SD or better)

**ctDNA was assessed at pre-specified timepoints via a targeted methylation-based test (GRAIL)**

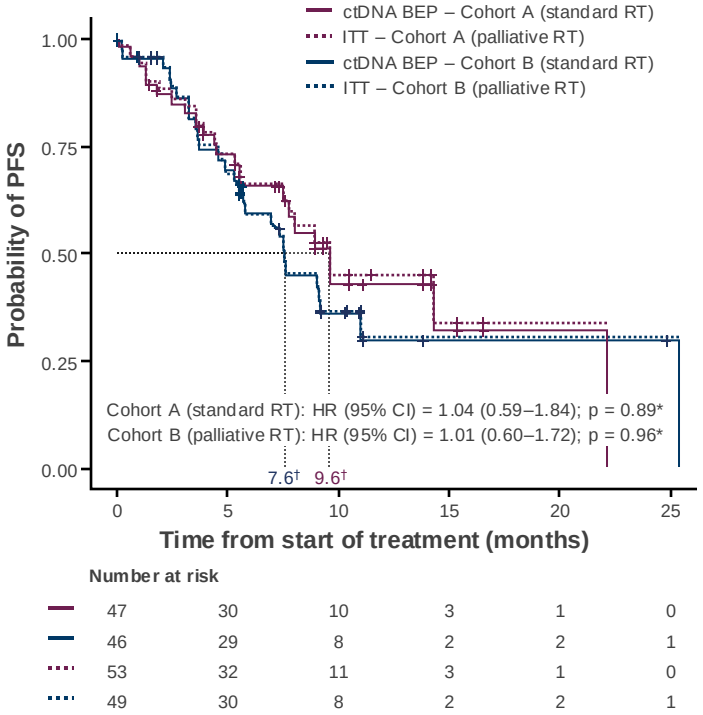



**ctDNA status was determined by GRAIL's Research Use Only (RUO) technology solution**

*PRAE is alternative nomenclature for a treatment-related adverse event and is used here to align with the case report form used to collect investigators' responses.
†PFS and OS were analysed using the Kaplan-Meier method to estimate medians, landmark rates, and associated 95% CIs.
‡RT must have been completed within 6 weeks (42 days) prior to the first dose of durvalumab.
§Or until disease progression, unacceptable toxicity or consent withdrawal. Durvalumab could also be administered for longer than the planned 12-month treatment period, per investigator assessment.
BED, biologically effective dose; CX, durvalumab Cycle X; CI, confidence interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; Gy, Gray (unit of ionizing radiation); ITT, intention-to-treat population; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRAE, adverse event possibly related to treatment; Q4W, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

# The ctDNA-evaluable population was generally similar to the ITT population

| Baseline Characteristics | Subgroup | Cohort A (standard RT) | | Cohort B (palliative RT) | |
|---|---|---|---|---|---|
| | | ctDNA BEP (n=47) | ITT (n=53) | ctDNA BEP (n=46) | ITT (n=49) |
| Age, y | Median (range) | 75.0 (43.0, 86.0) | 76.0 (43.0, 86.0) | 81.0 (56.0, 87.0) | 81.0 (56.0, 87.0) |
| Sex, n (%) | Male | 34 (72.3) | 38 (71.7) | 34 (73.9) | 35 (71.4) |
| | Female | 13 (27.7) | 15 (28.3) | 12 (26.1) | 14 (28.6) |
| Race, n (%) | White | 41 (87.2) | 46 (86.8) | 42 (91.3) | 45 (91.8) |
| | Other | 1 (2.1) | 1 (1.9) | 0 (0) | 0 (0) |
| ECOG PS, n (%) | 0 | 11 (23.4) | 12 (22.6) | 6 (13.0) | 7 (14.3) |
| | 1 | 34 (72.3) | 38 (71.7) | 35 (76.1) | 36 (73.5) |
| | 2 | 2 (4.3) | 2 (3.8) | 5 (10.9) | 6 (12.2) |
| Disease Stage, n (%) | Stage IIIA | 27 (57.4) | 32 (60.4) | 29 (63.0) | 30 (61.2) |
| | Stage IIIB | 18 (38.3) | 18 (34.0) | 13 (28.3) | 15 (30.6) |
| | Stage IIIC | 2 (4.3) | 3 (5.7) | 3 (6.5) | 3 (6.1) |
| Histology, n (%) | Adenocarcinoma | 16 (34.0) | 19 (35.8) | 15 (32.6) | 16 (32.7) |
| | Squamous | 28 (59.6) | 31 (58.5) | 26 (56.5) | 27 (55.1) |
| PD-L1 TC, n (%) | <1% | 15 (31.9) | 16 (30.2) | 17 (37.0) | 17 (34.7) |
| | 1-49% | 12 (25.5) | 14 (26.4) | 10 (21.7) | 10 (20.4) |
| | ≥50% | 5 (10.6) | 6 (11.3) | 7 (15.2) | 8 (16.3) |
| Smoking status, n (%) | Current | 8 (17.0) | 11 (20.8) | 9 (19.6) | 10 (20.4) |
| | Former | 34 (72.3) | 35 (66.0) | 33 (71.7) | 34 (69.4) |
| | Never | 5 (10.6) | 7 (13.2) | 4 (8.7) | 5 (10.2) |

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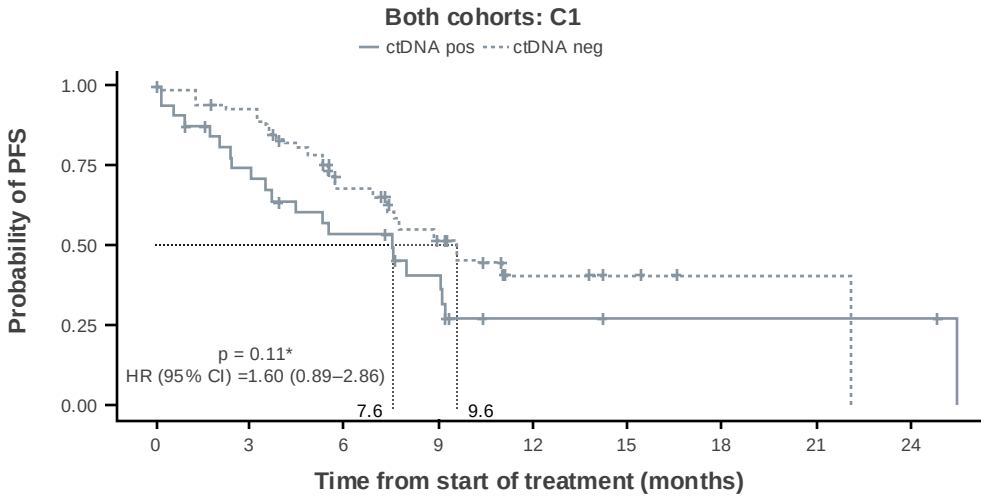
*Exploratory analysis, nominal p values presented, not adjusted for multiple analysis. HRs calculated with the corresponding ITT cohort as the reference.
†Median PFS was the same for the ITT and ctDNA BEP populations.
Efficacy comparisons were made via Cox proportional hazards model with p-values estimated via log-rank test.
BEP, biomarker-evaluable population; CI, confidence interval; HR, hazard ratio; PD-L1 TC, programmed cell death ligand-1 tumor cell expression; y, years

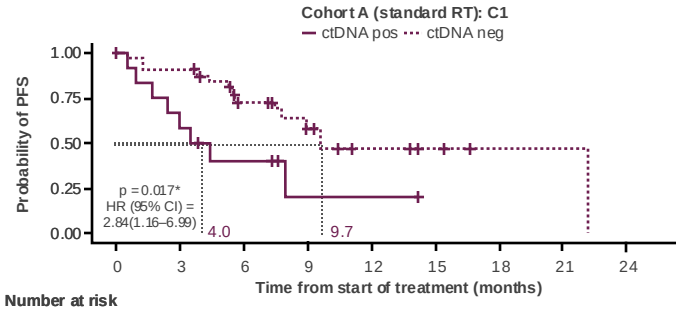
# Detectable ctDNA at C1 (immediately prior to the start of durvalumab) was associated with a trend toward decreased PFS




Number at risk

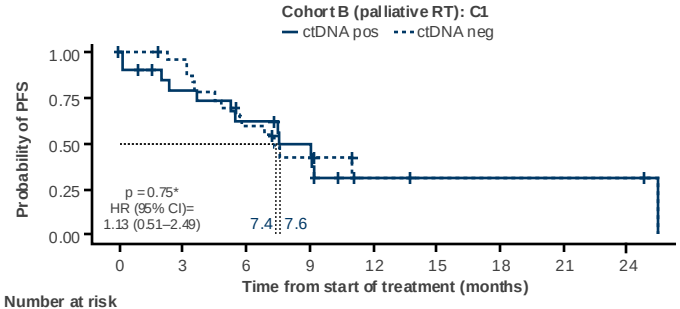
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ctDNA pos | 32 | 22 | 15 | 9 | 3 | 2 | 2 | 2 | 2 |
| ctDNA neg | 59 | 51 | 31 | 18 | 7 | 3 | 1 | 1 | 0 |

- The proportion of patients with detectable ctDNA at C1 (35.2% †) was numerically higher after palliative (44.4% †) vs standard (26.1% †) RT.




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ctDNA pos | 12 | 8 | 4 | 1 | 1 | 0 | 0 | 0 | 0 |
| ctDNA neg | 34 | 29 | 19 | 11 | 6 | 3 | 1 | 1 | 0 |




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ctDNA pos | 20 | 14 | 11 | 8 | 2 | 2 | 2 | 2 | 2 |
| ctDNA neg | 25 | 22 | 12 | 7 | 1 | 0 | 0 | 0 | 0 |

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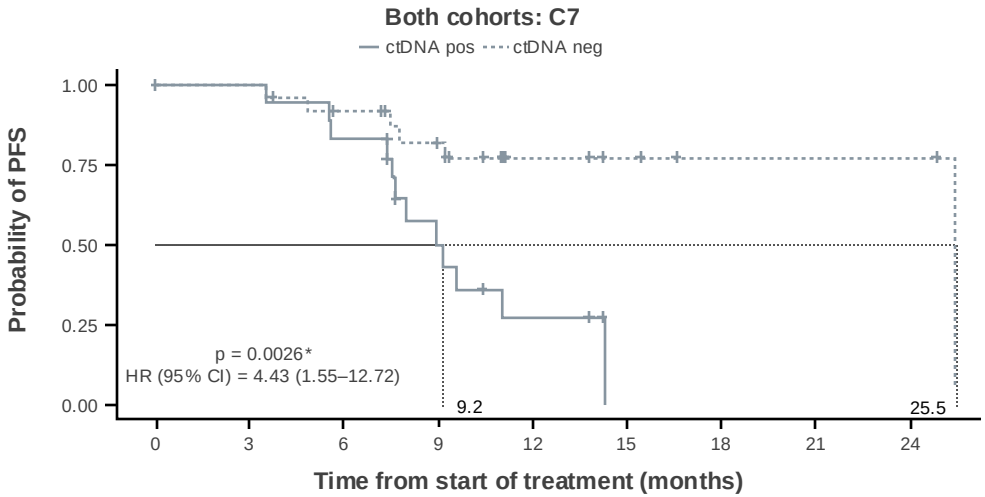
*Exploratory analysis, nominal p values presented, not adjusted for multiple analysis. HRs calculated with the corresponding ctDNA-negative population as the reference.
†Percentages based on the number of patients with evaluable ctDNA samples at the corresponding timepoint.
Efficacy comparisons were made via Cox proportional hazards model with p-values estimated via log-rank test.
neg, negative; OS, overall survival; pos, positive

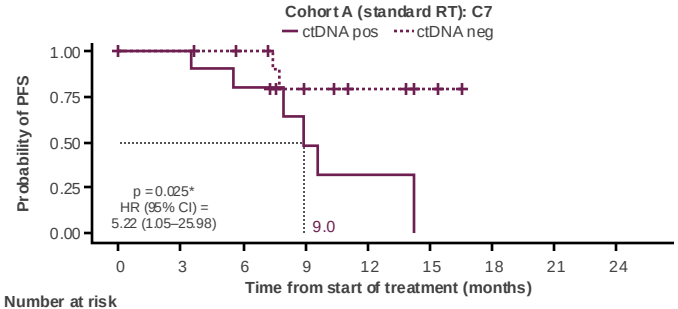
# Detectable ctDNA at C7 was associated with shorter PFS




Number at risk

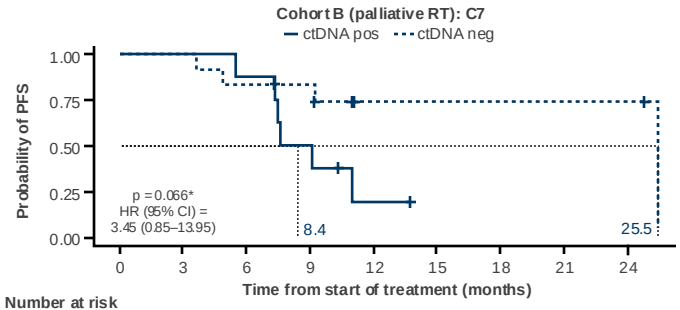
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ctDNA pos | 18 | 18 | 15 | 7 | 3 | 0 | 0 | 0 | 0 |
| ctDNA neg | 26 | 25 | 21 | 16 | 7 | 4 | 2 | 2 | 2 |

- The proportion of patients with detectable ctDNA at C7 (40.9%†) was similar after palliative (40.0%†) vs standard (41.7%†) RT.




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ctDNA pos | 10 | 10 | 8 | 3 | 2 | 0 | 0 | 0 | 0 |
| ctDNA neg | 14 | 13 | 11 | 7 | 5 | 2 | 0 | 0 | 0 |




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ctDNA pos | 8 | 8 | 7 | 4 | 1 | 0 | 0 | 0 | 0 |
| ctDNA neg | 12 | 12 | 10 | 9 | 2 | 2 | 2 | 2 | 2 |

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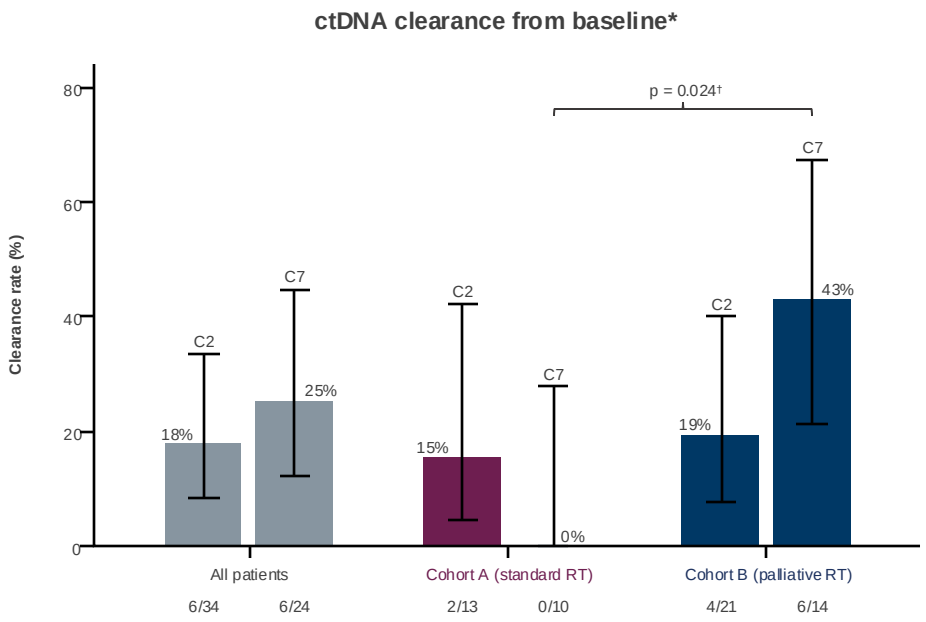
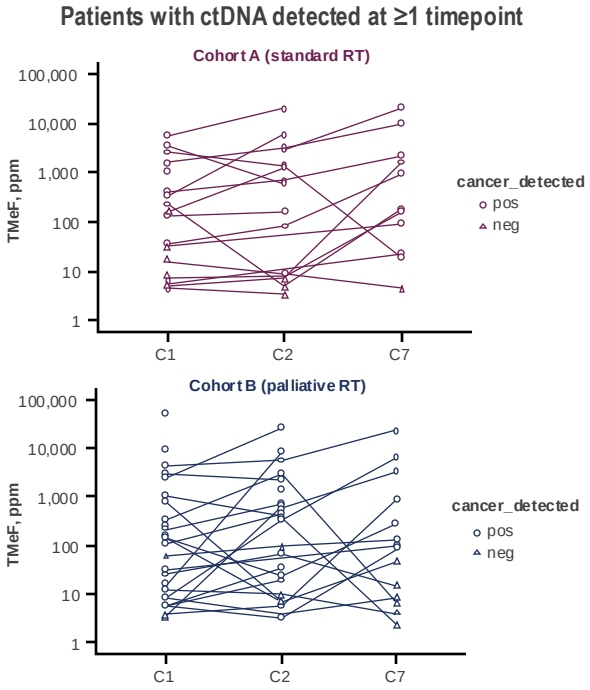
*Exploratory analysis, nominal p values presented, not adjusted for multiple analysis. HRs calculated with the corresponding ctDNA-negative population as the reference.
†Percentages based on the number of patients with evaluable ctDNA samples at the corresponding timepoint.
Efficacy comparisons were made via Cox proportional hazards model with p-values estimated via log-rank test.

# During durvalumab treatment, ctDNA clearance was similar between cohorts at C2 and higher among patients receiving palliative (vs standard) RT at C7




*The denominator for each value is all patients with either clearance or non-clearance. Clearance defined as ctDNA detected at baseline (C1) and not detected on treatment (C2 or C7). Non-clearance is defined as ctDNA detected on treatment (C2 or C7) regardless of baseline ctDNA status. Further details are available in the supplemental slides.
†Fisher's exact test. Exploratory analysis, nominal p values presented, not adjusted for multiple analysis.
ppm, parts per million; TMeF, tumor methylated fraction

# Conclusions

- In DUART, detectable ctDNA after RT (i.e., at C1) did not clearly associate with prognosis, though there was a trend toward decreased PFS among patients with detectable ctDNA at C1.
- However, the presence of detectable ctDNA later during consolidation (i.e., at C7) was associated with shorter PFS irrespective of RT dose.
- Subgroup analyses suggested:
    - An association between PFS and ctDNA status at C1 in patients receiving standard RT.
    - A higher rate of ctDNA clearance during durvalumab treatment among patients receiving palliative vs standard RT.
- Durvalumab after RT can lead to complete molecular responses.
- In future trials, ctDNA monitoring could help identify patients who may benefit from more intensive treatment.
- Further ctDNA analyses from patients enrolled in the DUART trial are planned.

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