BARCELONA 2024 ESMO congress

Circulating Tumour DNA (ctDNA) Clearance With Neoadjuvant Durvalumab (D) + Tremelimumab (T) + Enfortumab Vedotin (EV) for Cisplatin-Ineligible Muscle-Invasive Bladder Cancer (MIBC) From the Safety Run-in Cohort of the Phase 3 VOLGA Trial

Alexandra Drakaki,[1] Thomas Powles,[2] Ying Wang,[3] Manojkumar Bupathi,[4] Monika Joshi,[5] Mark Fleming,[6] Alfonso Gómez de Liaño,[7] Rafael Morales-Barrera,[8] Roberto Pili,[9] Suliman Boulos,[10] Yashaswi Shrestha[11]

[1]Division of Hematology/Oncology, David Geffen School of Medicine, Los Angeles, CA, USA; [2]Genitourinary Oncology, Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Oncology Data Science, AstraZeneca, Waltham, MA, USA; 4Medical Oncology, Rocky Mountain Cancer Centers, Littleton, CO, USA; [5]Department of Medicine/Division of Hematology and Oncology, Penn State Cancer Institute, Hershey, PA, USA; [6]US Oncology Research, Virginia Oncology Associates, Norfolk, VA, USA; [7]Medical Oncology, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas, Spain; [8]Medical Oncology Department, Vall d'Hebron Institute of Oncology and University Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain; [9]Division of Hematology/Oncology, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY, USA; [10]Oncology, AstraZeneca, Cambridge, UK; [11]Translational Medicine, AstraZeneca USA, Gaithersburg, MD, USA

1970MO

Presenter: Alexandra Drakaki, MD, PhD, UCLA, USA

Disclosures

Alexandra Drakaki

I have the following relevant financial relationships to disclose:

- Advisory: AstraZeneca, BMS, Daiichi, EMD Serono, Exelixis, Infinity, Janssen, Merck, PACT Pharma, Roche/Genentech, Seagen,
- Stocks/shares: Athos Therapeutics
- Research funding: Acrivon, Adcentrix, Allogene, Arcus, BMS, Infinity, Kite Pharma, Loxo, Merck, Roche, Seattle Genetics
- Steering committee member: AstraZeneca

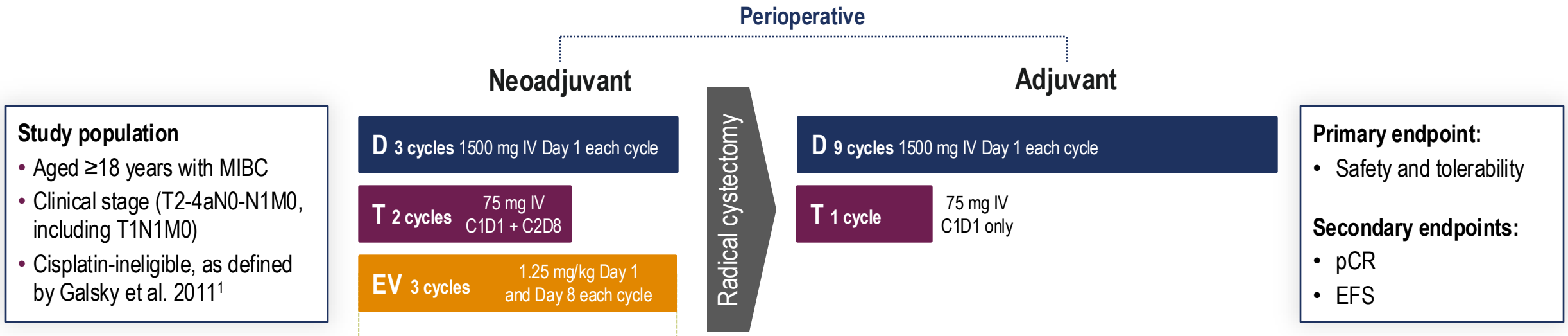
Background

- VOLGA is the first Phase 3, randomised, open-label, global study examining the novel combinations of durvalumab (anti-PD-L1) + tremelimumab (anti-CTLA-4) + enfortumab vedotin (EV; anti-nectin-4 ADC) or durvalumab + EV vs standard of care for cisplatin-ineligible MIBC
- Results from the VOLGA safety run-in cohort have been reported previously[1]
  - pCR in 6/17 patients, pathologic non-muscle invasive response in 9/17 patients
  - The safety profile was manageable; most common TRAEs were fatigue, maculopapular rash, dysgeusia, dry mouth, and pruritus
- Emerging data suggest that ctDNA may potentially help predict treatment benefit in patients with MIBC[2]
- **Here, we report an exploratory analysis of ctDNA in the VOLGA safety run-in cohort and potential association with pathological response at radical cystectomy and event-free survival**

ADC, antibody drug conjugate; ctDNA, circulating tumour DNA; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; MIBC, muscle-invasive bladder cancer; pCR, pathologic complete response; PD-L1, programmed cell death ligand-1; TRAE, treatment-related adverse event.

1. Powles T, et al. European Multidisciplinary Congress on Urological Cancers (EMUC). 2022; Poster LP166. 2. Kapriniotis K, et al. *Biomedicines*. 2024;12:921.

VOLGA safety run-in design and ctDNA analysis



ctDNA analysis

Baseline plasma sample

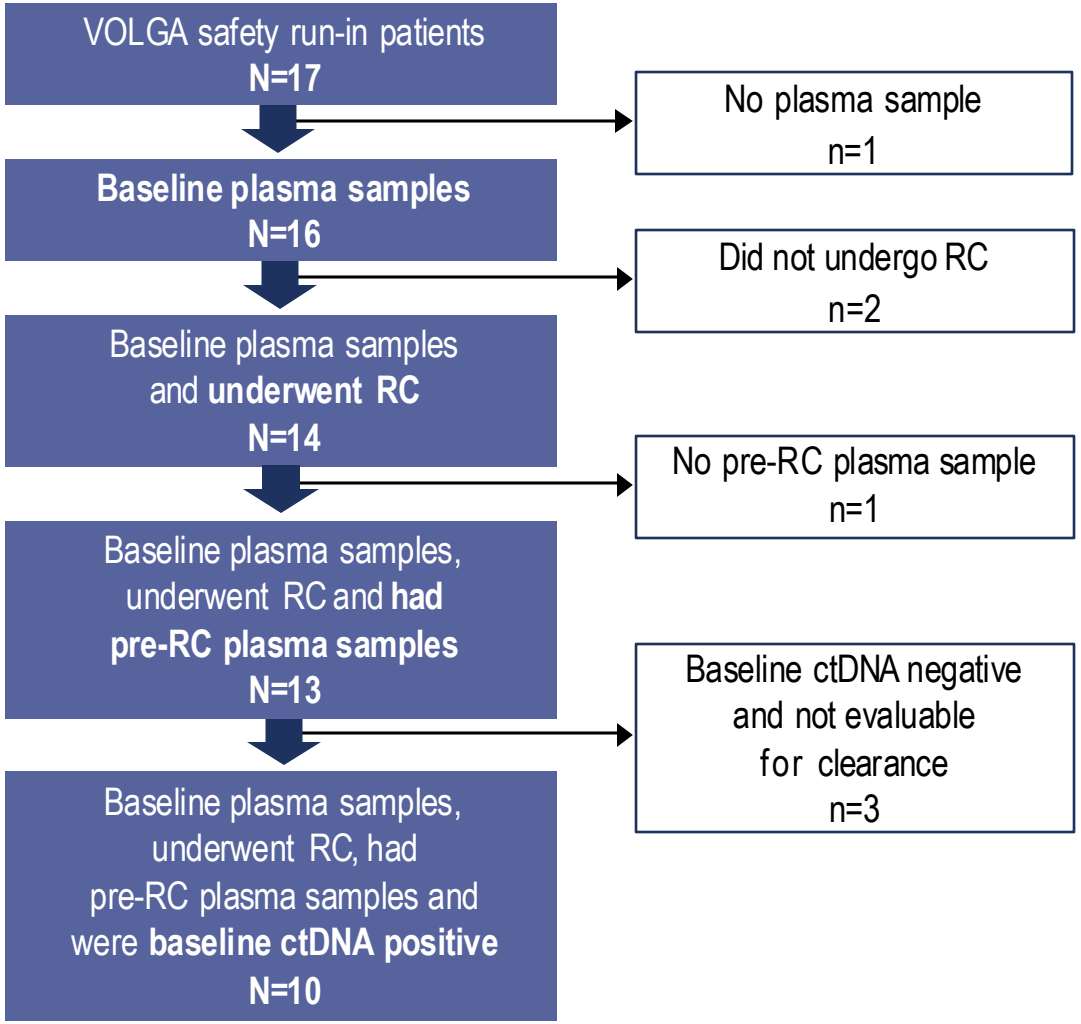
Pre-RC plasma sample (or Cycle 3, Day 1 sample)

- Cell-free DNA from plasma samples was assessed using GRAIL's Research Use Only (RUO) technology solution which detects methylation indicative of tumour DNA (GRAIL, Inc.)[2]
  - Cancer score cutoff: the exact choice of threshold is governed by the specificity parameter of the GRAIL's algorithm; for this analysis, a specificity threshold of 98% was chosen, meaning 98% of non-cancer samples in a held-out calibration set would be correctly identified as negative for ctDNA[2]
- ctDNA detection at baseline and pre-RC were evaluated for association with pathologic assessment at RC and EFS

ClinicalTrials.gov, NCT04960709.
ctDNA, circulating tumour DNA; C1D1, Cycle 1 Day 1; C2D8, Cycle 2 Day 8; D, durvalumab; EFS, event-free survival; EV, enfortumab vedotin; IV, intravenous; MIBC, muscle-invasive bladder cancer; pCR, pathologic complete response; RC, radical cystectomy; T, tremelimumab.
1. Galsky MD, et al. *Lancet Oncol.* 2011;12:211–214; 2 Desai M, et al. American Association for Cancer Research (AACR). 2023; Poster LB297.

ctDNA analysis populations

ctDNA populations



Patient treatment

- The safety run-in cohort included 17 patients – all received at least one dose of neoadjuvant durvalumab + tremelimumab + EV
- A total of 13 patients completed the 3 cycles of neoadjuvant treatment
- 14 patients underwent RC

GRAIL platform quality control

- A total of 66 of 69 plasma samples (95.6%) across baseline, pre-RC, and post-RC time points passed GRAIL's ctDNA processing quality control check

ctDNA, circulating tumour DNA; EV, enfortumab vedotin; pCR, pathologic complete response; RC, radical cystectomy.

ctDNA analysis patient-level summary

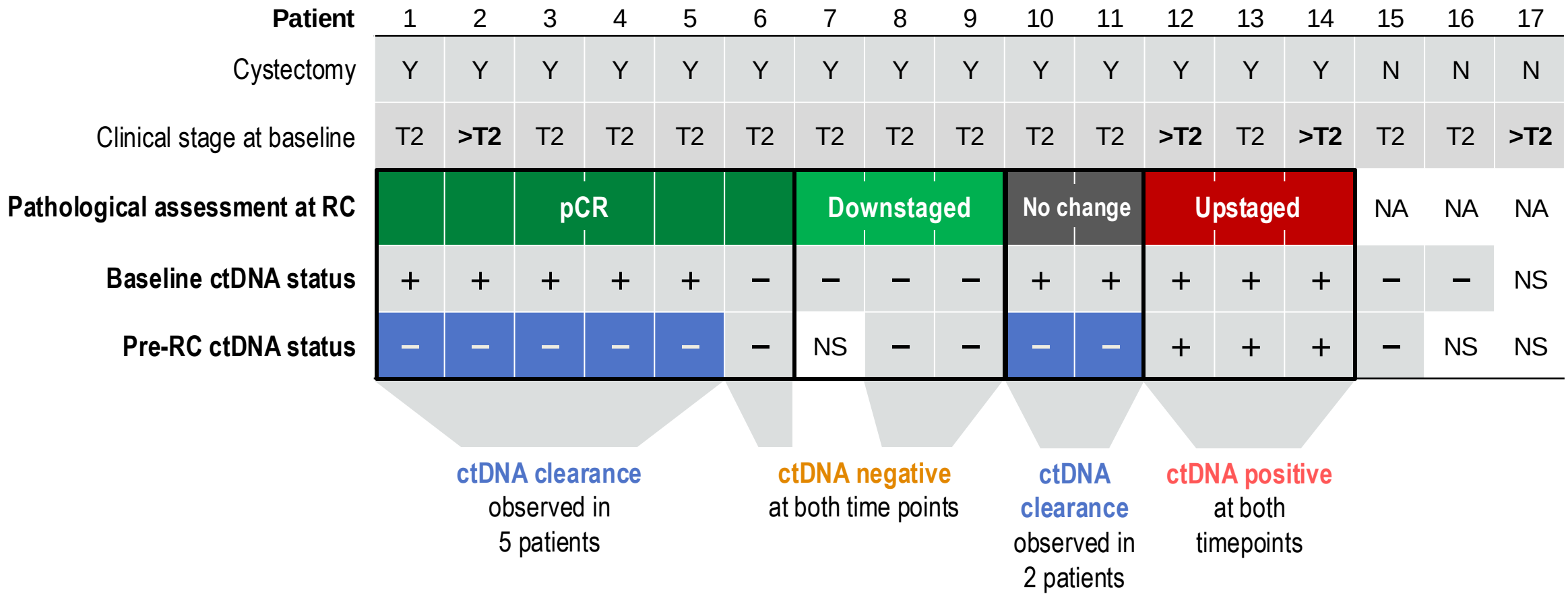
Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Cystectomy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N
Clinical stage at baseline	T2	**>T2**	T2	T2	T2	T2	T2	T2	T2	T2	T2	**>T2**	T2	**>T2**	T2	T2	**>T2**
Pathological assessment at RC			**pCR**			**Downstaged**				**No change**		**Upstaged**			NA	NA	NA
Baseline ctDNA status	+	+	+	+	+	−	−	−	−	+	+	+	+	+	−	−	NS
Pre-RC ctDNA status	−	−	−	−	−	−	NS	−	−	−	−	+	+	+	−	NS	NS

ctDNA clearance

- At baseline, the overall ctDNA-positive rate was 62.5% (10/16 patients) and the overall ctDNA-negative rate was 37.5% (6/16 patients)
- After neoadjuvant treatment, the pre-RC ctDNA-negative rate was 78.6% (11/14 patients)
- A total of **7 out of 10 patients had ctDNA clearance** (baseline ctDNA positive, then pre-RC ctDNA negative)

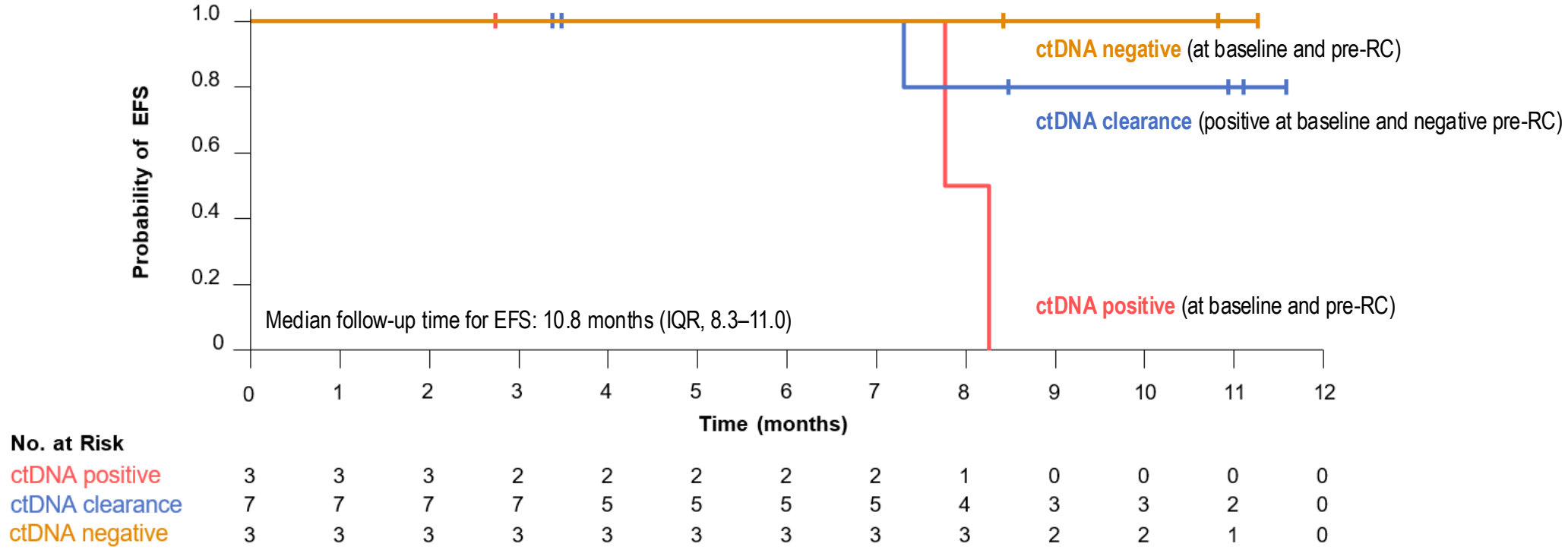
ctDNA, circulating tumour DNA; pCR, pathologic complete response; N, no (to RC); NA, not available; NS, no sample; Y, yes (to RC); RC, radical cystectomy.

ctDNA analysis by pathological assessment group



ctDNA, circulating tumour DNA; pCR, pathologic complete response; N, no (to RC); NA, not available; NS, no sample; Y, yes (to RC); RC, radical cystectomy.

ctDNA clearance and its association with EFS



- EFS was assessed in 13 patients who completed RC; 10 were ctDNA-positive at baseline, and 3 were ctDNA-negative at baseline
- **Longer EFS was observed in the ctDNA clearance and ctDNA negative groups compared with the ctDNA positive group**

EFS was defined as the time from randomization to the first occurrence of any of the following events: recurrence of disease post-radical cystectomy, progression in patients who did not receive radical cystectomy, or death due to any cause. The "survival" package (R version 4.1.2) was used for EFS analysis. The log method was used to calculate confidence intervals, the Efron approximation was used for tie handling, and *P*-values were from log-rank tests.
CI, confidence interval; ctDNA, circulating tumour DNA; IQR, interquartile range; mEFS, median event-free survival; neg, negative; NR, not reached; pos, positive.

Conclusions

- In a small safety run-in cohort of the VOLGA study, clearance of plasma ctDNA during the neoadjuvant phase was associated with a favourable outcome in cisplatin-ineligible patients with MIBC treated with durvalumab + tremelimumab + EV
- This exploratory analysis supports ctDNA as a potential biomarker to help inform treatment decisions in MIBC in the future
    - We are continuing to collect samples for ctDNA analysis in the main VOLGA trial
- The GRAIL RUO technology solution had a high quality-control pass rate for ctDNA assessment of plasma samples from patients with MIBC

ctDNA, circulating tumour DNA; EV, enfortumab vedotin; MIBC, muscle-invasive bladder cancer; RUO, research use only.

Thank you

The authors would like to thank the patients, their families, and caregivers, without whose participation and support this trial would not have been possible, as well as the global VOLGA investigators.

Scan the QR code to access:

- Plain language summary
- Slide presentation

Acknowledgements

Medical writing support, which was in accordance with Good Publication Practice guidelines, was provided by Lewis Cawkwell of Parexel International, United Kingdom, and was funded by AstraZeneca.

The VOLGA study was funded by AstraZeneca.