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**Article**

# Docetaxel-oxaliplatin-capecitabine/5-fluorouracil (DOX/F) followed by docetaxel versus oxaliplatin-capecitabine/5-fluorouracil (CAPOX/FOLFOX) in HER2-negative advanced gastric cancers

Anant Ramaswamy, MD, DM,[1] Prabhat Bhargava, MD, DM,[1] Biswajit Dubashi, MD, DM,[2] Anuj Gupta, DNB,[3] Akhil Kapoor, MD, DM,[3] Sujay Srinivas, MD, DM,[1] Omshree Shetty, PhD,[4] Poonam Jadhav, BSC,[1] Veena Desai, MSC,[1] Vanita Noronha, MD, DM,[1] Amit Joshi, MD, DM,[1] Nandini Menon, DNB,[1] Vijay M. Patil, MD, DM,[5] Bal Krishna Mishra, MD,[3] Bipinesh Sansar, MD, DM,[3] Arpita Singh, MBBS,[3] Swapnil Patel, MS, MCh,[6] Satyendra Narayan Singh, MD,[7] Ipsita Dhal, MD,[8] Kunal Ranjan Vinayak, MD,[9] Vikash Pal, MSc,[3] Sarika Mandavkar, BSc,[1] Sadhana Kannan, BSc,[10] Deepali Chaugule, MSc,[1] Rajshree Patil, MPharm,[1] Manali Parulekar, BSc,[1] Chaitali Nashikkar, BAMS,[11] Suman Kumar Ankathi, MD,[12] Rajiv Kumar Kaushal, MD,[13] Aekta Shah, MD,[13] Prasanth Ganesan, MD, DM,[2] Smita Kayal, MD, DM,[2] Ramesh Ananthakrishnan, MD,[14] Noorzia Syed, MD,[1] Debdeep Samaddar, MD,[1] Venkatesh Kapu, MD,[1] Anokhi Shah, MD,[1] D. Kaaviya, BSc,[2] R. Suganiya, BSc,[2] Nirmala Devi Srinivasan, BSc,[2] Kumar Prabhash, MD, DM,[1] Vikas Ostwal, MD, DM[15,*]

[1]Department of Medical Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[2]Department of Medical Oncology, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
[3]Department of Medical Oncology, Homi Bhabha Cancer Hospital, Varanasi, India
[4]Department of Molecular Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[5]Consultant Medical Oncologist, P.D. Hinduja Hospital & Medical Research Centre, Mumbai, India
[6]Department of Surgical Oncology, Homi Bhabha Cancer Hospital, Varanasi, India
[7]Department of Radiology, Homi Bhabha Cancer Hospital, Varanasi, India
[8]Department of Pathology, Homi Bhabha Cancer Hospital, Varanasi, India
[9]Department of Palliative Medicine, Homi Bhabha Cancer Hospital, Varanasi, India
[10]Department of Statistics, Advanced Centre for Treatment, Research and Education in Cancer, Homi Bhabha National Institute (HBNI), Mumbai, India
[11]Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[12]Department of Radiodiagnosis, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[13]Department of Pathology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India
[14]Department of Radiodiagnosis, Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India
[15]Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute (HBNI), Mumbai, India

*__Correspondence to:__ Vikas Ostwal, MD, DM, Department of Medical Oncology, Tata Memorial Hospital, Homi Bhabha National Institute (HBNI), Dr Department Parel, Mumbai 400 012, India (e-mail: dr.vikas.ostwal@gmail.com).

## Abstract

**Background:** We evaluated whether the addition of docetaxel (D) to a combination comprising 5-fluorouracil/leucovorin (5-FU/LV) or capecitabine (C) plus oxaliplatin (O) (DOF/DOX) improved overall survival (OS) compared with 6 months of 5-fluorouracil (5-FU) or capecitabine in combination with oxaliplatin (FOLFOX/CAPOX) alone in advanced HER2-negative gastroesophageal junction and gastric adenocarcinomas (G/GEJ).

**Methods:** This study was an investigator-initiated, open-label, multi-institutional, randomized phase III trial in adult patients with HER2-negative advanced G/GEJs. The primary endpoint of the study was a comparison of median OS by Kaplan-Meier method. Next-generation sequencing was performed on tissue.

**Results:** Of the 324 patients randomly assigned between July 2020 and November 2022, 305 patients were evaluable for analysis (FOLFOX/CAPOX: 156; DOF/DOX: 149). With a median follow-up time of 19.2 months (95% Confidence Interval [CI] = 16.5 months to 21.9 months) for the entire cohort, the median OS was 10.1 months (95% CI = 9.2 to 10.9) for FOLFOX/CAPOX and 8.9 months (95% CI = 7.3 to 10.5) for DOF/DOX, and this difference was not statistically significant ($P = .70$). An increased proportion of grade 3 or grade 4 neutropenia (21% vs 3%; $P < .001$) and grade 2/3 neuropathy (17% vs 7%; $P = .005$) was seen in patients receiving DOF/DOX. Genomic profiling revealed a low incidence of microsatellite instability (1%) and a high incidence of *BRCA1* (8.4%) and *BRCA2* (7.5%) somatic alterations.

**Conclusion:** FOLFOX or CAPOX chemotherapy for 6 months remains one of the standards of care in advanced HER2-negative gastroesophageal junction and gastric adenocarcinomas, with no additional survival benefit seen with the addition of docetaxel. Genomic profiling of patients revealed a higher than previously known incidence of somatic BRCA alterations, which requires further evaluation.

CTRI (Clinical Trial Registry of India: CTRI/2020/03/023944).

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Patients with advanced gastric and gastroesophageal adenocarcinomas (G/GEJ) are usually treated with a range of doublet chemotherapeutic regimens, commonly comprising 5-fluorouracil (5-FU) or capecitabine in combination with oxaliplatin 5-fluorouracil (5-FU) or capecitabine in combination with oxaliplatin (FOLFOX/CAPOX). The addition of trastuzumab in HER2-positive tumors, zolbetuximab in Claudin-18.2-expressing tumors, and immune checkpoint inhibitors (ICIs) in high combined positive score (CPS) tumors to this doublet combination has resulted in clinically relevant improvements in overall survival in these specific subsets (1-4).

The addition of docetaxel to cisplatin and 5-fluorouracil-containing regimens (or similar doublet regimens) has improved survival compared with doublet regimens, but there is a marked associated increase in the incidence of chemotherapy-related adverse events; hence, there is equipoise with respect to the addition of a third chemotherapeutic agent in the management of G/GEJ (5-7). However, there are very limited data for or against the use of docetaxel in combination with FOLFOX/CAPOX in advanced G/GEJ, although the docetaxel-oxaliplatin-leucovorin-fluorouracil (DOF) and docetaxel-oxaliplatin-capecitabine (DOX) regimens have shown efficacy in retrospective datasets and small prospective studies (8-10).

Additionally, a less explored aspect of the management of advanced G/GEJ has been the optimal duration of systemic therapy. Unlike the well-established strategy of "Stop and Go" used in colorectal cancers, there is only one phase II study in G/GEJ that has shown that similar survivals can be obtained by considering a chemotherapy-free interval after 6 cycles of doublet chemotherapy (11). With this background, the investigators performed a randomized 2-arm multicenter phase III clinical trial to evaluate whether the addition of docetaxel to a combination of oxaliplatin and capecitabine or 5-fluorouracil for a duration of 4 months followed by docetaxel alone improves overall survival (OS) compared with FOLFOX or CAPOX for a maximal duration of 6 months in advanced gastric/gastroesophageal adenocarcinomas. An exploratory molecular analysis via next-generation sequencing (NGS) was also conducted in an attempt to identify genomic alterations in these patients and to classify patients in accordance with a modification of the Asian Cancer Research Group (ACRG) classification system.

# Methods

## Study design

This randomized, open-label, phase III study was conducted in adult patients with histologically proven metastatic or locally advanced unresectable adenocarcinoma of the gastroesophageal junction or stomach. The trial was conducted at Tata Memorial Center (TMC) in Mumbai, India; Homi Bhabha Cancer Hospital (HBCH) and Mahamana Pandit Madan Mohan Malaviya Cancer Centre (MPMMCC) in Varanasi; and Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry. The study was initially approved by the Institutional Ethics Committee of TMC and then by the Ethics Committee of the other institutions, and it was monitored by the Data Safety Monitoring Unit of the individual hospitals. All patients provided written informed consent. The trial was conducted according to the principles laid down by the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, Schedule Y (Drugs and Cosmetic Act, 1940), and the guidelines established by the Indian Council of Medical Research. The trial was registered at the Clinical Trials Registry of India (identifier: CTRI/2020/03/023944).

## Patient population

Adults aged 18 years and older with histologically proven metastatic or locally advanced unresectable adenocarcinoma of the gastroesophageal junction or stomach with adequate hematologic, hepatic, and renal function and Eastern Cooperative Oncology Group performance status of 2 or less were eligible for the study. Patients with HER2 positivity by immunohistochemistry (IHC) and in situ hybridization (ISH) evidence of HER2 amplification were excluded from the study. Full inclusion and exclusion criteria can be found in the protocol added as Supplementary Appendix 1 (available online). The study was approved by the Institutional Ethics Committee (IEC) with approval number IEC/0220/3392/001.

## Random assignment

Patients were randomly assigned 1:1 to Arm A (FOLFOX/CAPOX) or Arm B (DOX/DOF). Computer-generated block randomization was done by an independent biostatistician.

## Treatment protocol

Patients in Arm A received 1 of the 2 following treatment regimens: FOLFOX—oxaliplatin 85 mg/m$^2$ as an infusion over 2 hours and leucovorin 200 mg/m$^2$ as an infusion over 1 hour, both on day 1, and 5-fluorouracil 2400 mg/m$^2$ over 46 hours via an infusion pump every 2 weeks for a maximum of 12 cycles; or CAPOX—oxaliplatin 130 mg/m$^2$ as an infusion over 2 hours on day 1, and capecitabine at 2000 mg/m$^2$ per day in 2 divided doses for 14 days on, 1 week off every 3 weeks for a maximum of 8 cycles. Patients in Arm B received one of the two following treatment regimens: DOF—docetaxel 50 mg/m$^2$ as an infusion over 2 hours, oxaliplatin 85 mg/m$^2$ as an infusion over 2 hours and leucovorin 200 mg/m$^2$ as an infusion over 1 hour, all on day 1, and 5-fluorouracil 2400 mg/m$^2$ over 46 hours via an infusion pump every 2 weeks for a maximum of 8 cycles followed by continuation of chemotherapy with docetaxel 60 mg m$^2$ as an infusion over 2 hours every 3 weeks in case no evidence of disease progression after 8 cycles of chemotherapy or DOX—docetaxel 50 mg m$^2$ as an infusion over 2 hours and oxaliplatin 85 mg/m$^2$ as an infusion over 2 hours on day 1 along with capecitabine at 750 mg/m$^2$ per day in 2 divided doses for 14 days for a maximum of 8 cycles followed by continuation of chemotherapy with docetaxel 60 mg m$^2$ as an infusion over 2 hours every 3 weeks in case of no evidence of disease progression after 8 cycles of chemotherapy. The choice of 5-fluorouraacil or capecitabine-based therapy in either of the two arms was based on individual treating physician choice. Patients received antiemetics, growth factors, and other supportive care medications in accordance with institutional practice. Toxicity was managed according to the guidelines mentioned in the protocol. Clinical evaluation occurred before every chemotherapy cycle in both arms of the study. Response assessment was done using contrast-enhanced computed tomography (CECT) scans of the thorax, abdomen, and pelvis or 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) CT (FDG PET-CT) every 8 to 10 weeks in both arms of the study. Treatment in Arm A (FOLFOX/CAPOX) continued for a maximum of 6 months unless there was evidence of disease progression, unacceptable toxicity, or withdrawal of prior consent, whereas treatment in Arm B continued until disease progression, unacceptable toxicity, or withdrawal of consent. After disease

progression, therapy was at the discretion of the treating physician.

## Outcome measures

The primary objective was to compare the investigator-assessed overall survival (OS), measured from the date of random assignment to the date of death or last observation (censored). Secondary endpoints included progression-free survival (PFS), toxicity, response rate, and quality of life (QOL). PFS was measured from the time from enrollment to the time of disease progression or death, or to the date of last tumor assessment without any such event (censored observation). Toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 4.03. Adverse events were reported from the time of starting therapy to its cessation. The cause of adverse events and treatment was investigator-assessed, although all serious adverse events were reported to the Data Safety Monitoring Unit and independently assessed by them for causality and relatedness. The response rate in patients with one or more measurable lesions was calculated using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (12). In patients without one or more measurable lesions, responses were classified as follows: complete response (CR)—the disappearance of all baseline lesions; partial response (PR)—significant regression of lesions at the baseline; stable disease (SD)—no significant regression of baseline lesions and no new lesions; and progressive disease—the appearance of new lesions or a significant increase in baseline lesions. QOL was measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and STO22 forms. An exploratory endpoint was the performance of next-generation sequencing (NGS) on available biopsy specimens of patients enrolled in the study and the report of the different genetic alterations noted. An attempt was made to classify specimens based on the ACRG gastric cancer classification of gastric cancers, although identifying patients with the microsatellite stable-epithelial-to-mesenchymal transition (MSS-EMT) subtype was not feasible due to lack of antibodies to measure CDH1 loss of expression (13). Epstein-Barr virus (EBV)-encoded ribonucleic acid (RNA) in situ hybridization (ISH) (EBER-ISH) was additionally used for estimation of EBV positivity in biopsy specimens where feasible. A detailed description of the methods used for NGS and EBER-ISH is provided in Supplementary Appendix 2 (available online).

## Trial funding and oversight

The study was investigator-initiated. Both arms of the study were labeled as standards of care. The trial design, data collection, analysis, and interpretation were conducted by the study team. The study received educational grants from the Nag Foundation, intramural funding from the Tata Memorial Centre Research Administrative Council (TRAC), as well as funding from the Indian Cooperative Oncology Network (ICON) as part of a competitive funding opportunity. None of the organizations providing grants had any role in the trial design or analysis of the data. The study protocol was approved by the IECs in all the participating institutions, and it was regularly monitored by the Data Safety Monitoring Unit. Written informed consent was obtained from patients or their legal representatives before enrollment in the trial. The article was prepared solely by the authors, with no involvement of any funding agencies or organizations. The authors vouch for the accuracy of the data and the fidelity of the trial to the protocol.

## Statistical analysis

This study is designed as a phase III study that aims to compare 2 standard-of-care regimens in a randomized control trial. According to available evidence, the median OS of patients treated with CAPOX/FOLFOX ranges between 9 and 11 months. Similarly, the median OS of patients treated with docetaxel-based triplets (DOX or DOF) ranges between 14 and 18 months. Additionally, a retrospective analysis of patients treated with the DOX regimen followed by continuation of docetaxel in our institution showed a median OS of 15.3 months (8).

Based on these baseline assumptions for the purposes of sample size estimation, it was assumed that the median OS (mOS) with CAPOX/FOLFOX was 11 months, and a study with a power of 80% and a 2-sided alpha of 5% would require 324 patients (162 patients per arm) to show a superiority in terms of mOS of 5 months (16 months) with DOX/DOF by the log-rank test method. The study required a total of 211 events in the entire study for the analysis to be feasible with a hazard ratio of 0.68. A uniform accrual period of 38 months and a further 16 months of follow-up were considered, and a lost to follow-up rate of 10% patients per arm of the study was accounted for in the calculation of the sample size for the study.

As mandated by the IEC, an interim safety analysis was to be conducted after the accrual of 25% of patients (81 patients) in the entire sample size of the study. An unacceptable grade 3 to 4 adverse event rate of 70% in the first 2 months of therapy was considered the cutoff for the evaluation of safety in the study. The study would have to be terminated if 28 or more (≥70%) significant treatment-related grade 3 to 4 adverse events (per arm) occurred in the first 2 months of therapy. The adverse events included neutropenia, thrombocytopenia, febrile neutropenia, chemotherapy-induced nausea and vomiting (CINV), mucositis, diarrhea, and hand-foot syndrome (HFS). The IEC-mandated safety analysis was not meant to evaluate survival outcomes and did not require alpha splitting for the primary endpoint of the study. The results of the safety analysis are reported separately in Supplementary Appendix 3 (available online).

Efficacy outcomes and treatment-related adverse events are reported in patients who were enrolled, started on chemotherapy, and came for follow-up after administration of the first cycle of chemotherapy. Pretreatment characteristics and toxicities are presented using descriptive statistics. Toxicity results were tabulated to demonstrate the number of patients with the highest grade of toxicity in the 2 arms of the study. Asymptomatic laboratory abnormalities (predominantly grade 1 and grade 2 treatment-related adverse events), such as electrolyte derangements, elevated hepatic enzymes, neutropenia without infection, and thrombocytopenia without bleeding, were not considered clinically relevant by the study team and hence are not reported. Excluding these, all other adverse effects of grade 3 or greater were counted as serious, clinically relevant toxicities. Response rates and adverse event rates between the 2 arms were compared using the Pearson $\chi^2$ test or Fisher exact test. OS and PFS were estimated using the Kaplan-Meier method, and the 2 arms were compared using the log-rank test. Cox regression analysis was used to calculate the hazard ratio (HR) with its 95% confidence intervals (CIs). In a planned post hoc analysis, we evaluated the differential treatment effect between the 2 arms on the basis of various potential prognostic factors, including age (≤ vs > 60 years), location of primary tumor, presence of signet ring cancer, and Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or 1 vs 2). A linear mixed-effects

regression model was used to assess whether there were improvements and significant differences over time in QOL scores between Arm A (FOLFOX/CAPOX) and Arm B (DOX/DOF). Models included the treatment as a fixed effect and time × group as an interaction effect to account for correlation among repeated observations per participant. Estimated marginal means with a 95% CI were calculated for each time point for both groups.

# Results

## Patients

From July 15, 2020 through November 10, 2022, 455 patients were assessed for eligibility at 3 sites in India. Of these, 324 patients were concurrently randomly assigned to receive FOLFOX/CAPOX (161 patients) or DOF/DOX (163 patients); 305 patients were included in the final analysis for safety and efficacy (FOLFOX/CAPOX, 155 patients; DOX/DOF, 150 patients). Details of patient enrollment, allocation, therapy, and assessment are provided in Figure 1. The median follow-up for OS (time from concurrent random assignment of the last patient to last known date alive or death) was 19.2 months (95% CI = 16.5 months to 21.9 months) for the 305 patients included in the final analysis.

The patients' baseline characteristics were well balanced between the 2 arms of the study and are listed in Table 1. Notable characteristics include a significant proportion of patients with body and distal primary tumors (51%) and signet cell cancers (40%) and a small, but notable, proportion of patients with ECOG PS 2 (9%) and gastric outlet obstruction requiring an intervention (8%).

## Treatment

In Arm A, 62 patients (40%) received FOLFOX, whereas 93 patients (60%) received CAPOX. Eight-two patients (53%) in Arm A were able to complete the planned 6 months of therapy. Of the 73 patients (47%) who were unable to complete 6 months of chemotherapy, the most common reasons for noncompletion were disease progression in 58 patients (37%) and treatment-related side effects in 15 patients (10%).

In Arm B, 63 patients (42%) received DOF, whereas 87 patients (58%) received DOX. Of the 150 patients in Arm B, 73 patients (49%) completed 8 cycles of chemotherapy, did not have progressive disease, and went on to receive further maintenance monotherapy with docetaxel. The median number of doses of docetaxel received as maintenance therapy in this group of patients was 5 (range: 1-22). Overall, the most common reasons for treatment cessation in Arm B were disease progression in 106 patients (71%) and treatment-related adverse events in 12 patients (8%).

## Efficacy

The analysis of the primary endpoint of OS was performed after 246 events (FOLFOX/CAPOX, 130; DOX/DOF, 116) in the study. At the cutoff date for analysis on October 10, 2023, the primary endpoint of the study was not met. The median OS, 12-month OS, and 24-month OS for the FOLFOX/CAPOX arm was 10.1 months (95% CI = 9.23 months to 10.41 months), 38% (95% CI = 30.2% to 45.8%), and 6.6% (95% CI = 0.8% to 12.4%), whereas it was 8.9 months (95% CI = 7.28 months to 10.53 months), 34.6% (26.8% to 42.4%), and 16.7% (95% CI = 8.7% to 24.7% in the DOF/DOX arm, and there was no statistically significant difference between the 2 arms ($P = .70$) (Figure 2, A). As the proportional hazards

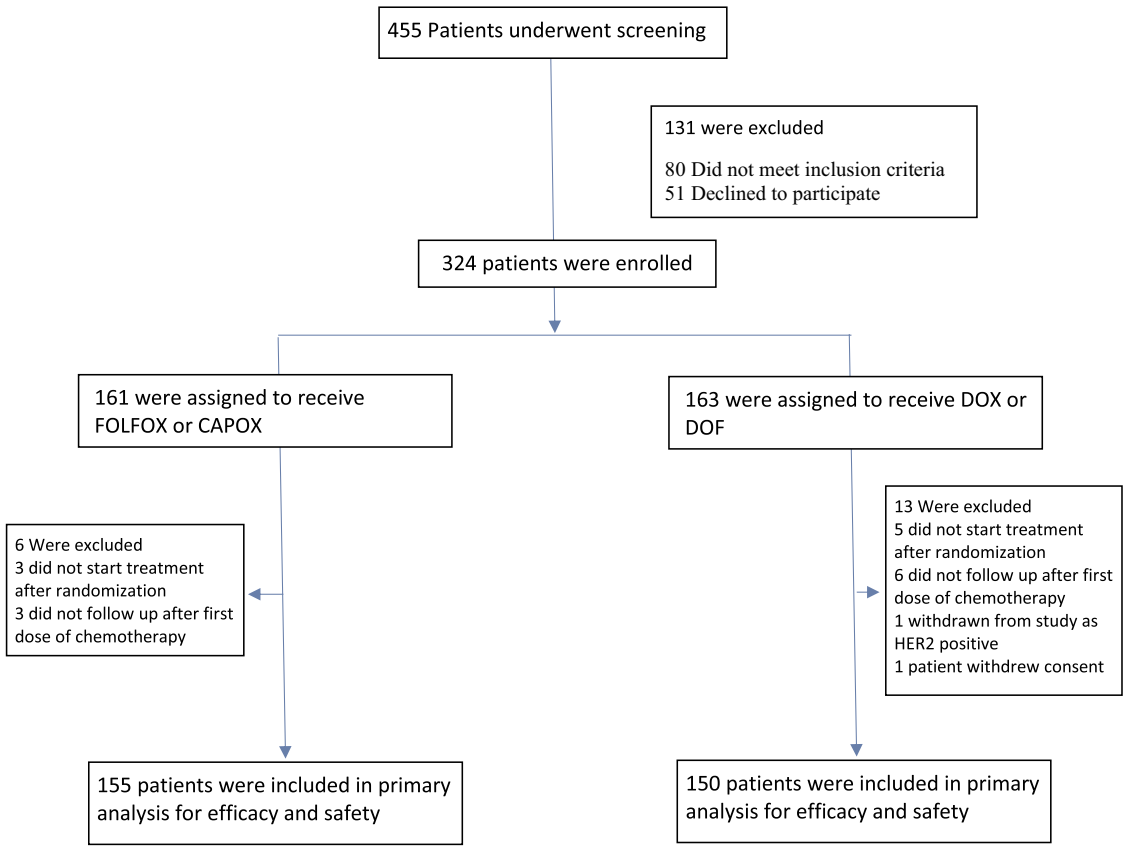



**Figure 1.** CONSORT diagram.

**Table 1.** Demographics and baseline clinical characteristics of analyzed patients

| Characteristics | No. of patients (%) | | |
|---|---|---|---|
| | Arm A (n = 155) | Arm B (n = 150) | Overall (305) |
| Age (years) | | | |
| Median | 49 | 50 | 49 |
| Range | 51 (19-70) | 52 (18-70) | 63 (18-70) |
| Sex, male | 108 (70) | 99 (66) | 207 (68) |
| Prior gastric surgery | 15 (10) | 20 (13) | 35 (11) |
| ECOG performance status[a] | | | |
| 0 | 6 (4) | 9(6) | 15 (5) |
| 1 | 133 (86) | 129 (86) | 262 (86) |
| 2 | 16 (10) | 12 (8) | 28 (9) |
| Presence of gastric outlet obstruction requiring intervention | 14 (9) | 11 (7) | 25 (8) |
| Primary tumor location at initial diagnosis | | | |
| Proximal | 68 (44) | 71 (47) | 139 (46) |
| Body and distal | 82 (53) | 75 (50) | 157 (51) |
| Linitis plastica | 4 (3) | 3 (2) | 9 (3) |
| Not identified | 1 (1) | 1 (1) | 2 (1) |
| Organs with metastases | | | |
| 1 | 125 (81) | 116 (77) | 241 (79) |
| ≥2 | 30 (19) | 34 (23) | 64 (21) |
| Site of metastases | | | |
| Liver | 50 (32) | 45 (30) | 95 (31) |
| Peritoneum | 81 (52) | 81 (54) | 162 (53) |
| Bone | 8 (5) | 11 (7) | 19 (6) |
| Lungs | 7 (5) | 10 (7) | 17 (6) |
| Degree of differentiation | | | |
| Well or moderately differentiated | 36 (23) | 42 (28) | 78 (26) |
| Poorly differentiated | 84 (54) | 82 (55) | 166 (54) |
| Not otherwise specified | 35 (23) | 26 (17) | 61 (20) |
| Signet ring cell carcinoma | 66 (43) | 57 (38) | 123 (40) |
| Treatment regimen | | | |
| 5-Fluorouracil containing | 62 (40) | 63 (42) | 125 (41) |
| Capecitabine containing | 93 (60) | 87 (58) | 180 (59) |

[a] ECOG = Eastern Oncology Cooperative Group.

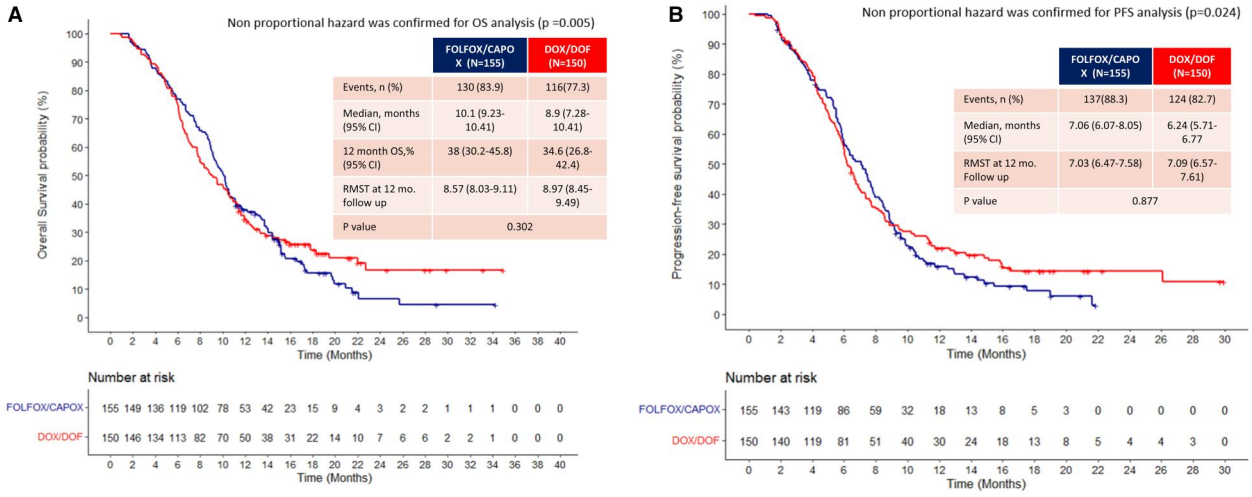



**Figure 2. A)** Kaplan-Meier curves for overall survival. **B)** Kaplan-Meier curves for progression-free survival. CAPOX = capecitabine-oxaliplatin; DOF = docetaxel-oxaliplatin-5-Fluorouracil-leucovorin; DOX = docetaxel-oxaliplatin-capecitabine; FOLFOX = 5-Fluorouracil-leucovorin-oxaliplatin; OS = overall survival; PFS = progression free survival; RMST = Restricted Mean Survival Time.

assumption was not met due to crossover of the overall survival curves, the restricted mean survival time (RMST) model was used to analyze the overall survival benefit difference. When using the RMST model, the RMST for OS was 8.97 months (95% CI = 8.45 months to 9.49 months) in the DOX/DOF group and 8.57 months (95% CI = 8.03 months to 9.11 months) in the FOLFOX/CAPOX group (RMST ratio: 0.956; 95% CI = 0.877 to 1.041; $P = .302$). The nonproportional hazard was confirmed for OS analysis ($P = .005$). The median OS for FOLFOX, CAPOX, DOX, and DOF individually was 9.8 months (95% CI = 8.27 months to 11.38 months), 10.2 months (95% CI = 9.31 months to 11.1 months), 9.5 months (95% CI = 7.09 months to 11.9 months), and 8.64 months (95% CI

= 6.74 months to 10.54 months), respectively. Planned post hoc analysis of factors influencing OS also did not show any differences between the 2 arms of the study in terms of OS (Supplementary Figure 1, available online).

Disease progression on first-line therapy was seen in 261 patients (FOLFOX/CAPOX, 137; DOX/DOF, 124) by the cutoff date for analysis. The median PFS and 12-month PFS for the FOLFOX/CAPOX arm were 7.06 months (95% CI = 6.08 months to 8.05 months) and 16% (95% CI = 9.8 months to 22.2 months), whereas it was 6.24 months (95% CI = 5.72 months to 6.77 months) and 21.9% (15.1% to 28.7%) in the DOF/DOX arm. There was no statistically significant difference in PFS between the 2 arms of the study ($P = .42$) (Figure 2, B). As the proportional hazards assumption was not met due to crossover of the PFS curves, the RMST model was used to analyze the PFS benefit difference. When using the RMST model, the restricted mean PFS time was 7.02 (95% CI = 6.47 months to 7.58 months) in the DOX/DOF group and 7.09 months (95% CI = 6.56 months to 7.61 months) in the FOLFOX/CAPOX group (RMST ratio: 0.99; 95% CI = 0.89 to 1.10; $P = .877$). The nonproportional hazard was confirmed for PFS analysis ($P = .024$). The median PFS for FOLFOX, CAPOX, DOX, and DOF individually was 7.5 months (95% CI = 5.76 months to 9.15 months), 6.7 months (95% CI = 5.31 months to 8.09 months), 6.1 months (95% CI = 5.5 months to 6.7 months), and 6.6 months (95% CI = 5.49 months to 7.78 months), respectively.

Radiological assessments for evaluation of response were available in 141 patients (91%) in Arm A, of whom 61% (n = 86) of patients had a response calculated by RECIST criteria. The best radiologic response achieved was partial remission (PR) in 75 patients (48.3%), stable disease (SD) in 51 patients (32.9%), and disease progression (PD) in 15 patients (9.6%). Radiological assessments for evaluation of response were available in 141 patients (94%) in Arm B, of whom 57% (n = 80) had a response calculated by RECIST. The best radiologic response achieved was complete remission in 1 patient (0.67%), PR in 66 patients (44%), stable disease (SD) in 51 patients (40.7%), and PD in 12 patients (8%). The objective response rates (CR plus PR) were not statistically different between the 2 arms in the study (48.3% vs 44.7%; $P = .389$).

## Treatment-related adverse events

Considering all toxicities, grade 3 or greater toxicities occurred in 51 patients (33%) in Arm A and 79 patients (53%) in Arm B, and this difference was statistically significant ($P < .001$). The grade 3 and grade 4 toxicities seen in an increased proportion in Arm B compared with Arm A were neutropenia (21% vs 3%; $P < .001$) and peripheral neuropathy (grade 2 and grade 3) (17% vs 7%; $P = .005$). The incidence of grade 2 and grade 3 hand-foot syndrome was increased in Arm B, but the difference did not approach statistical significance (9% vs 4%; $P = .054$) (Table 2).

## Special group—Patients with ECOG PS 2

Twenty-eight patients (Arm A—16 patients, Arm B—12 patients) in the entire cohort of the study presented with ECOG PS 2. The median PFS of patients in this group was statistically lower than patients with ECOG PS 0 or 1 (5.52 months [95% CI = 4.52 months to 6.52 months] vs 10.35 [95% CI = 4.94 months to 15.76 months] vs 6.54 [95% CI = 5.91 months to 7.17 months]; $P = .026$). Similarly, the median OS of patients in this group was also statistically lower than patients with ECOG PS 0 or 1 (6.93 months [95% CI = 4.8 months to 9.06 months] vs 17.02 months [95% CI = 6.6 months to 27.44 months] vs 9.53 months [95% CI = 8.69 months to 10.36 months]; $P = .002$).

**Table 2.** Summary of treatment related grade 3 and grade 4 adverse events

| | No. of patients (%) | | |
|---|---|---|---|
| **Characteristics** | **Arm A (n = 155)** | **Arm B (n = 150)** | **P** |
| Cumulative toxicities | 51 (33) | 79 (53) | <.001 |
| Hematological | | | |
| Anemia | 16 (10) | 14 (9) | .772 |
| Thrombocytopenia | 4 (3) | 3 (2) | .735 |
| Neutropenia | 8 (3) | 31 (21) | <.001 |
| Febrile neutropenia | 4 (3) | 7(5) | .329 |
| Non-hematological | | | |
| Non-neutropenic infection | 4 (3) | 3 (2) | .735 |
| CINV[a] | 8 (5) | 3 (2) | .139 |
| Diarrhea | 9 (6) | 10 (7) | .756 |
| Oral mucositis/stomatitis | 6 (4) | 6 (4) | .486 |
| Rise in aminotransferases | 6 (4) | 3 (2) | .334 |
| Peripheral neuropathy | 10 (7) | 25 (17) | .005 |
| Hand-foot syndrome | 6 (4) | 14 (9) | .054 |
| Fatigue | 10 (6) | 13 (9) | .464 |
| Dose modifications | 31 (20) | 33 (22) | .781 |

[a] CINV = chemotherapy induced nausea and vomiting.

Fourteen patients (50%) in this group experienced grade 3 or grade 4 treatment-related adverse events. None of the patients in either arm stopped treatment due to toxicities.

## Treatment post-progression

A total of 100 patients (32.7%) out of all patients in the study were offered second-line therapy post-progression or cessation of first-line therapy. A greater proportion of patients in Arm A received second-line therapy compared with patients in Arm B (60 [38.7%] vs 40 [26.7%]), but this difference did not reach statistical significance ($P = .07$). A detailed description of treatment regimens received by patients is given in Supplementary Table 1 (available online).

## Patient-reported outcomes

For patient-reported outcomes, compliance with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and EORTC QLQ-STO22 was evaluated as the proportion of patients completing at least one, two, or three questionnaires over the course of their treatment. The proportion of patients completing at least one, two, and three EORTC QLQ-C30 questionnaires was 100%, 78%, and 66%, whereas for the EORTC QLQ-STO22, the proportion of patients completing at least one, two, and three questionnaires was 100%, 80%, and 64%. There were no differences in QOL scores across the domains of the EORTC QLQ-C30 questionnaire between the 2 arms of the study (Figure 3, A-O). With regard to the domains evaluated in the EORTC QLQ-STO22 questionnaire, a markedly increased level of anxiety was noted by patients in Arm B, but this did not reach statistical significance ($P = .052$) (Supplementary Figure 2, A-D, available online).

## Exploratory analysis via next-generation sequencing and EBV status

A total of 107 patients' samples were available for analysis by NGS (Supplementary Figure 3, available online). In these 107 samples, 125 somatic alterations were detected. The common alterations were noted in *TP53* (56.1%), *BRCA2* (7.5%), and *BRCA1* (8.4%). A detailed analysis of the detected alterations is depicted in the Oncoprint map (Figure 4), and the classification of the alterations in accordance with Association for Molecular Pathology and ACMG recommendations is shown in

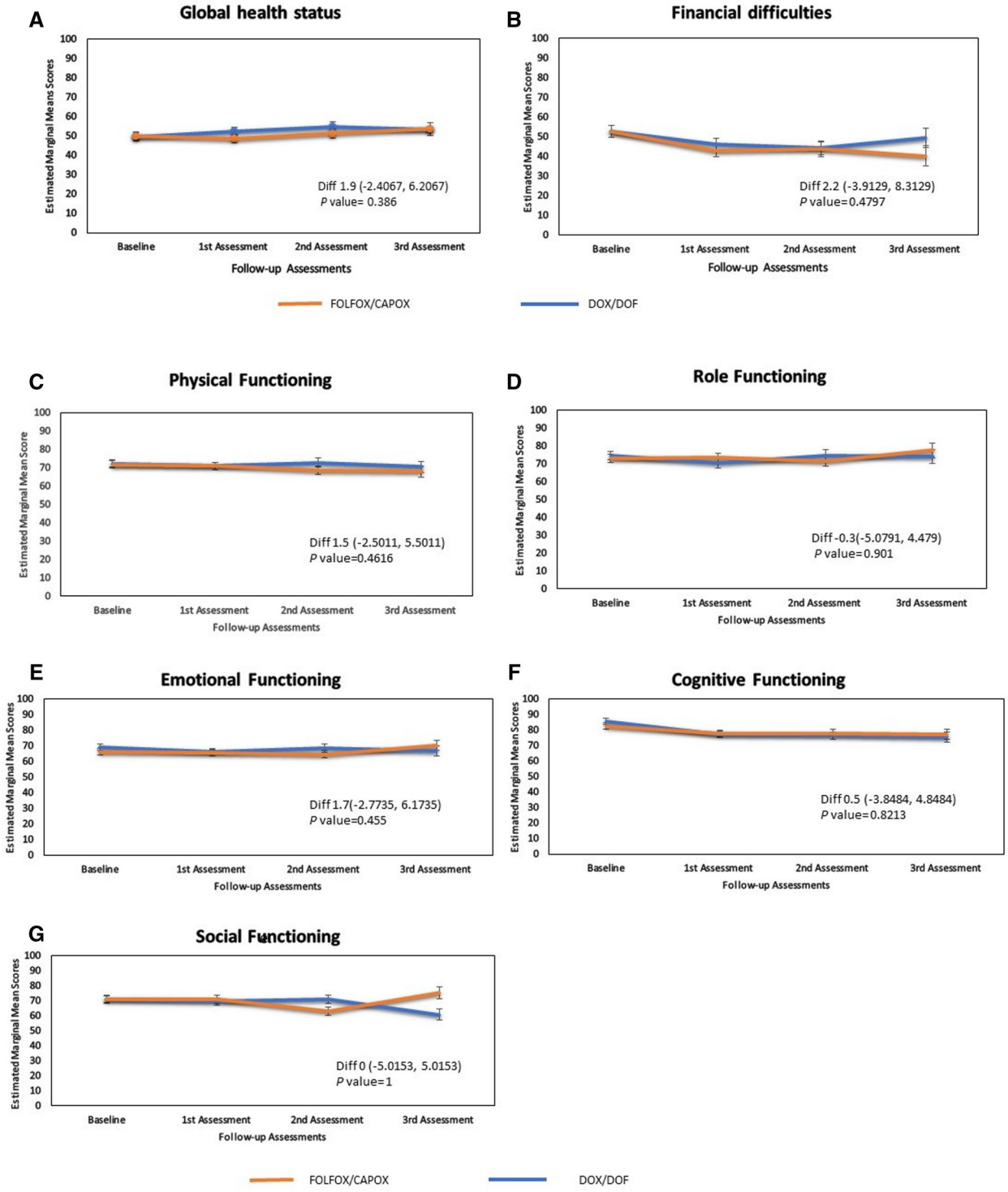
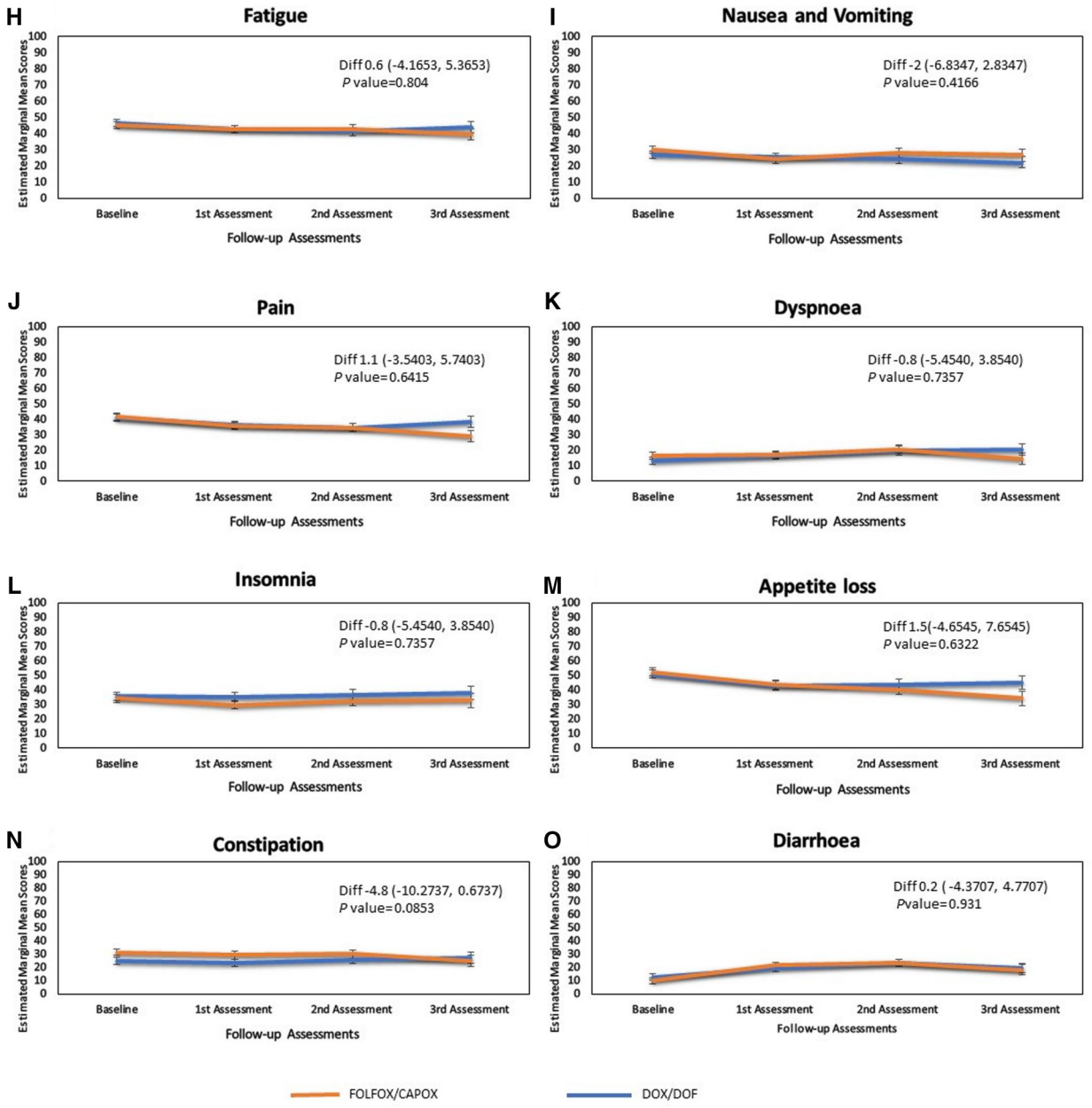



**Figure 3.** Patient-related outcomes as measured by EORTC QLQ-30.

Supplementary Table 2 (available online). The mutation map of the various TP53 alterations detected is shown in Supplementary Figure 4 (available online), and the alterations noted in BRCA1 and BRCA2 are detailed in Supplementary Figure 5, A and B (available online), respectively. The patients with BRCA mutations were similarly distributed between Arm A (17.3%) and Arm B (18.3%) with no differences in survival between patients with BRCA mutations and without BRCA mutations (mOS: 10.6 months vs 17.8 months; $P = .25$).

The modified ACRG classification was feasible for application in 99 patients (31%), and the proportion of patients was as follows: Microsatellite Stable and TP53 wild (MSS-TP53)—44 patients (44%), MSS-TP53 mutant—54 patients (54%), and Microsatellite intability high (MSI-H)—1 patient (1%). There were no statistical differences in median PFS (7 months vs 7.72 months; $P = .344$) or median OS (11.17 months vs 11.14 months; $P = .874$) between the patients classified as MSS-TP53 wild and MSS-TP53 mutant.




Longitudinal Analysis using a mixed-model approach of EORTC scores. The error bars are the standard errors of the estimates. The difference is calculated by subtracting the FOLFOX/CAPOX from the DOX/DOF; a positive difference represents a lower QOL for patients treated with FOLFOX/CAPOX and negative difference represents a lower QOL for patients in DOX/DOF group. All scores are corrected as per EORTC QLQ-C30 Scoring Manual (0-100). Diff - difference

QOL: Quality of Life.

**Figure 3.** (Continued).

Conduct of EBER-ISH was feasible in 82 of the 99 patients classified according to the modified ACRG system. EBER-ISH was positive in 6 patients (7%) and negative in the remaining 76 patients (93%). There were no statistical differences in median PFS (4.9 months vs 8 months; $P = .992$) or median OS (10.3 months vs 11.4 months; $P = .654$) between the patients classified as EBV positive and EBV negative, respectively. Characteristics of the groups classified by the modified ACRG as well as according to EBV status are provided in Table 3.

## Discussion

In this multi-institutional, investigator-initiated phase III randomized control trial evaluating advanced HER2-negative gastric/gastroesophageal junction adenocarcinomas (G/GEJ), the addition of docetaxel to a combination of oxaliplatin and capecitabine/5-fluorouracil (DOX/DOF) for a duration of 4 months followed by docetaxel alone did not improve OS compared with FOLFOX or CAPOX for a maximal duration of 6

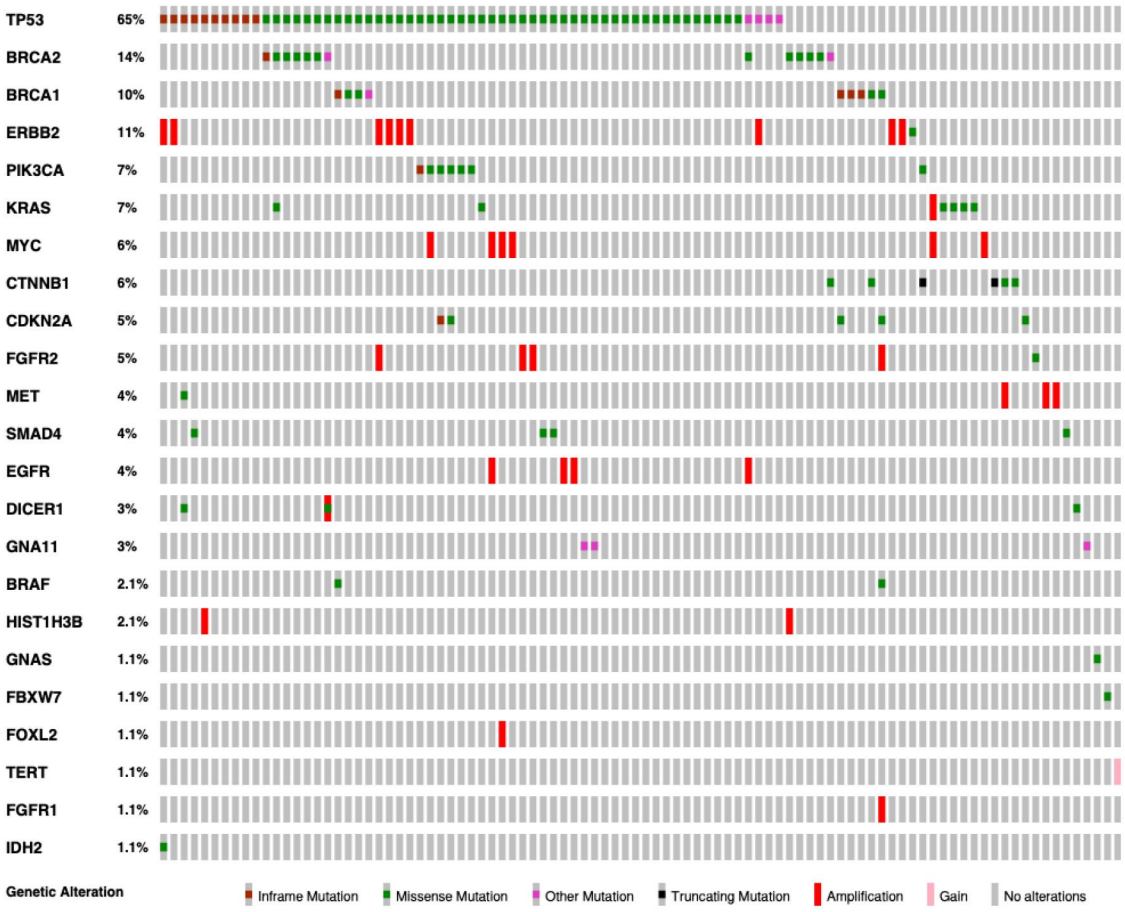



**Figure 4.** Oncoprint of alterations and Copy Number Variations (CNVs) detected among the study cohort.

**Table 3.** Classification of patients based on modified Asian Cancer Research Group (ACRG) system and EBV status

| | Number (%) | | | | |
|---|---|---|---|---|---|
| **Characteristics** | **MSS/TP53 mutant** | **MSS/TP53 wild** | **Characteristics** | **EBV positive** | **EBV negative** |
| Number of patients (n = 99) | 54 (55) | 44 (44) | Number of patients (n = 82) | 6 (7) | 76 (93) |
| Median age, years | 52 | 49 | Median age, years | 51 | 48 |
| Male sex | 28 (52) | 30 (68) | Male gender | 5 (83) | 50 (65) |
| Signet ring cancer | 13 (24) | 15 (34) | Signet ring cancer | 4 (67) | 24 (31) |
| Molecular alterations | | | Molecular alterations | | |
| *TP53* | 54 (100) | 0 | *TP53* | 6 (86) | 36 (47) |
| *KRAS* | 1 (2) | 3 (7) | *KRAS* | 0 | 5 (7) |
| *PIK3CA* | 5 (9) | 1 (2) | *PIK3CA* | 1 (14) | 5 (7) |
| *SMAD4* | 2 (4) | 1 (2) | *SMAD4* | 1 (14) | 1 (1) |
| Detection of copy number variants | 12 (22) | 10 (23) | Detection of copy number variants | 1 (14) | 19 (25) |
| mPFS (months) | 7.7 | 7.0 | mPFS (months) | 4.9 | 8.0 |
| mOS (months) | 11.14 | 11.17 | mOS (months) | 10.3 | 11.4 |

months. Additionally, the docetaxel-containing arm did not improve other clinically relevant endpoints such as response rates, patient-related outcomes (PROs), or PFS. To our knowledge, this is one of the first studies that has prospectively compared DOX/DOF to FOLFOX/CAPOX, besides partially answering the question of the optimal duration of treatment in this population.

The TAX-V325 trial was one of the first trials that showed a survival benefit (time to progression: 5.6 months vs 3.7 months; $P < .001$) for a triplet regimen (docetaxel-cisplatin-5-fluourouracil, DCF) as opposed to a standard doublet regimen (cisplatin-5-fluourouracil, CF), although the differences in OS were clinically marginal (9.2 months vs 8.6 months; $P = .02$), and there was a definite increase in clinically relevant toxicities (5). This approach further gained ground in view of other studies showing improved survival and the unequivocal survival advantages seen with FLOT in the perioperative setting (6,14). Despite such evidence, at least 4 large meta-analyses and network analyses tend to remain equivocal in their conclusions with regard to the benefits of adding docetaxel for various reasons, and this is likely why major guidelines continue to recommend a 5-FU/platinum combination as the first-line chemotherapy backbone in advanced G/GEJs (15-20). There are two important aspects to consider in this

scenario; first, these studies did not have a direct comparison between FOLFOX/CAPOX and a docetaxel-comprising regimen, and, second, none of these prospective studies included Indian patients with advanced G/GEJs.

Certain characteristics of the patients in this study deserve highlighting—for example, inclusion of patients with ECOG PS 2 and adequate end-organ function. Although such patients may have inferior survival outcomes compared with patients with ECOG PS 0 or 1, this study suggests that they can be included in trials safely with reasonable outcomes. Other characteristics include a patient cohort almost a decade younger than included in most published studies; a high proportion of patients with signet ring cancers (40%), a known prognostic factor for inferior outcomes; and a high proportion of distal gastric cancer primaries (51%), as opposed to the predominantly proximal location of cancers seen in recent clinical trials from other parts of the world. These variables suggest that the patient population in the study offers insights into the treatment of a gastric cancer population that is different when compared with patient cohorts from North America, Europe, and Southeast Asia.

The survivals seen in this study need to be evaluated from multiple viewpoints. The median PFS in both arms of the study and across the 4 regimens used in the study ranged from 6.0 to 7.5 months—barring the ATTRACTION-4 study and a few other phase II studies, a majority of phase III trials in G/GEJ adenocarcinomas have shown numerically similar PFS (or similar surrogate endpoints) (6,21,22). However, although the median OS for the FOLFOX/CAPOX arm is along expected lines (10.1 months), the median OS for the docetaxel-containing arm is surprisingly less than expected when compared with previously published data. Some of the possible clinical reasons for this variance could be a negative interaction between the variant clinical features of the patients in the study (primary distal cancers, increased proportion of signet ring cancers) and docetaxel, the increased treatment-related toxicities seen with a triplet chemotherapeutic regimen comprising docetaxel (as noted in this study), as well as the presence of unknown genomic biomarkers in the Indian context predicting for inferior outcomes with docetaxel. An important additional reason for the inferior performance of the docetaxel-containing arm is that a significantly lower than expected proportion of patients in this arm received second-line therapy compared with the FOLFOX/CAPOX arm (26.7% and 38%, respectively). This can be partially explained by the increased toxicities, especially cumulative toxicities such as neuropathy, seen in the docetaxel-containing arm that may have precluded patients from receiving further second-line treatment. Interestingly, despite the lack of differences in median PFS and median OS, there was an increased proportion of patients in the docetaxel-containing arm who were alive even at 2 years (16.7%) compared with the FOLFOX/CAPOX arm (6.6%). This suggests that a certain proportion of patients did benefit from the addition of docetaxel and maintenance, although this group needs to be evaluated further for clinical factors and biomarkers for prospective identification. There was also a suggestion of proximal cancers performing better with the docetaxel-containing arm, but this is likely due to chance as opposed to any biological rationale.

Another important aspect of this trial was to identify the appropriate duration of systemic therapy in advanced G/GEJ. This is crucial in these patients where a balance between reduction in disease-related symptoms and improved survival and treatment-related toxicities and potential detriment in QOL with continued treatment has to be achieved. Studies in a similar scenario of advanced colorectal cancers have suggested that appropriately timed treatment breaks do not hamper OS (23,24). Although comparing 4 months of intensive therapy and continued monotherapy as in the docetaxel arm with a fixed duration of 6 months of FOLFOX/CAPOX is not a wholly equivalent comparison, the results of this study do suggest that continuing treatment until disease progression does not significantly improve survival. This is further corroborated by the progression-free survivals in this study being similar to published data, wherein systemic therapy was allowed until disease progression or intolerable treatment-related adverse events. However, there are certain caveats to this assumption: this applies only to the administration of an intravenous chemotherapeutic agent such as docetaxel—whether other agents would have improved survival cannot be commented on; using an oral and potentially less toxic option such as capecitabine in either of the 2 arms of the study may have affected survivals—this was not explored in this study; continuing treatment with the usually well-tolerated immune checkpoint inhibitors, which may have continued therapeutic effect, would still be an option beyond 6 months of therapy.

Besides the lack of improved efficacy of the docetaxel-containing arm, there was an increased incidence of adverse events in this arm of the study. One of the major contributors to this increased toxicity was grade 2 and grade 3 neuropathy, besides other treatment-related adverse events, which is a major reason to consider the avoidance of prolonged periods of cytotoxic chemotherapy. The lack of a bolus 5-FU component in patients receiving FOLFOX and the usage of 2000 mg/m$^2$/day (as opposed to 2500 mg/m$^2$/day) of capecitabine in patients receiving CAPOX may have also contributed to the overall lower than expected incidences of grade 3 and grade 4 adverse events in the doublet arm of the study. Additionally, the lack of additional therapeutic efficacy was also noted in the PROs through the QOL assessments, and this is a major pointer toward a strong consideration of using FOLFOX/CAPOX as the standard (or standard backbone in combination with other treatment options) in patients with G/GEJ adenocarcinomas.

The exploratory studies in the trial highlight certain interesting insights into the genomic profile of Indian patients with G/GEJ cancers. Although the most common genetic alteration noted was TP53 alterations (63%), one of the highlights was the high proportion of patients with BRCA1 (8.4%) and BRCA2 (7.5%) alterations, which has not been well documented previously (25-27). Most previously published studies with respect to BRCA did not necessarily undergo multigene panel testing; thus, it is possible that some of the observed cases of gastric cancers were driven by pathogenic variants in genes increasing the risk of gastric cancers other than BRCA1/2, and this also explains the obvious lower frequency of BRCA1/BRCA2 mutation status in most of the studies reported. The available literature, although equivocal, suggests that BRCA2 is associated with an increased incidence of gastric cancers and that BRCA alterations may have a positive prognostic impact on outcomes in GC because of increased sensitivity to platinum-containing regimens (28). Such an interaction in terms of outcomes could not be ascertained in our study; however, the higher than expected incidence in the Indian population requires further evaluation, specifically with regard to whether they correlate with germline mutations of BRCA1 and BRCA2.

Within the confines of different methods of analysis as well as our inability to categorize patients into the MSS-EMT subtype, the key takeaway from our study in classifying patients according to modified ACRG subtypes is the low percentage of patients with MSI-H status (1%). This is at marked variance from internationally published data as well as the previously published

Indian data (13,29). A possible reason for this difference is that our study evaluated only patients with stage IV cancers as opposed to the patients in the ACRG database (resected specimens with an increased proportion of stage I-III cancers), and it is known that the incidence of MSI-H status decreases with increasing stage in gastric cancers (30). EBV-positive cancers were also seen in a slightly lower proportion than expected, especially compared with the results of the previously published Indian study—this can be partially explained by the different methods used in estimation of EBV positivity [(EBER-ISH vs IHC of Latent Membrane Protein (LMP)]. Lastly, there were no significant differences in survival between the MSS-TP53 wild-type and MSS-TP53 mutant cohorts as well as the EBV-positive and EBV-negative tumors—this is a possible reflection of the small numbers evaluated in this study.

Certain caveats in this study must be acknowledged. The effect size calculated for increased overall survival with the addition of docetaxel may have been larger than it should have been (approximately 45% relative increase in median OS); however, our assumptions were based on available data in advanced cancers as well as the remarkable increases in survival with the use of FLOT as perioperative therapy. The paradigm of intensive triplet chemotherapy for 4 months and continuing only docetaxel is based on published data from our institute and was used for sample size estimation as well—whether continuing the triplet chemotherapy until disease progression or intolerable toxicity might have altered survival outcomes is not known (8). Also, considering the increased proportion of adverse events such as neuropathy that was seen with docetaxel, continuing therapy with capecitabine or 5-FU/LV may have been a more viable treatment option as maintenance. However, this study was not designed to answer this question. Similarly, cessation of therapy after 6 months also might not be routine practice—most clinical trials as well as physicians in clinical practice consider continuation of systemic therapy until disease progression or increasing treatment-related adverse events. The study attempted to answer questions regarding the additional benefit of docetaxel as well as the optimum duration of therapy in G/GEJ cancers; however, the sample size estimation was not adequately powered to answer both questions individually and could have only answered an overall strategy of which treatment strategy was superior. A lower-than-expected proportion of patients receiving second-line therapy in comparison to data from recent trials is also a variance of note from recently published data.

In conclusion, the results of this study suggest that FOLFOX or CAPOX for a period of 6 months should continue to remain the standard chemotherapy backbone for patients with HER2-negative advanced gastric/gastroesophageal adenocarcinomas. The addition of docetaxel to this backbone as well as continuation of docetaxel is feasible but did not improve survival or patient-related outcomes. An increased incidence of somatic BRCA mutations and a low incidence of MSI was noted on exploratory genomic studies in the study population and bears further evaluation.

## Data availability

The data underlying this article cannot be shared due to privacy concerns of the patients enrolled in the study. Anonymized patient data can be shared on reasonable request after appropriate Institution Ethics Committee and regulatory approvals.

## Author contributions

Anant Ramaswamy, MD, DM (Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing), Deepali Chaugule, MPharm (Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing), Rajshree Patil, BSc (Investigation; Supervision; Writing—review & editing), Manali Parulekar, BSc (Data curation; Investigation; Resources; Supervision; Writing—review & editing), Chaitali Nashikkar, BHMS (Data curation; Investigation; Supervision; Writing—review & editing), Suman Kumar Ankathi, MD (Data curation; Investigation; Methodology; Writing—review & editing), Rajiv Kumar Kaushal, MD (Data curation; Investigation; Methodology; Supervision; Validation; Writing—review & editing), Aekta Shah, MD (Data curation; Investigation; Methodology; Writing—review & editing), Prasanth Ganesan, MD, DM (Investigation; Methodology; Supervision; Writing—review & editing), Smita Kayal, MD, DM (Investigation; Methodology; Supervision; Writing—review & editing), Ramesh Anantha Krishnan, MD (Investigation; Supervision; Writing—review & editing), Noorzia Syed, MD (Data curation; Investigation; Supervision; Writing—review & editing), Debdeep Samaddar, MD (Investigation; Project administration; Supervision; Writing—review & editing), Venkatesh Kapu, MD, DM (Data curation; Investigation; Methodology; Resources; Supervision; Writing—review & editing), Anokhi Shah, MD (Data curation; Investigation; Supervision; Writing—review & editing), D. Kaaviya, BSc (Investigation; Supervision; Writing—review & editing), R. Suganiya, BSc (Investigation; Methodology; Writing—review & editing), Nirmala Devi Srinivasan, BSc (Investigation; Methodology; Supervision; Writing—review & editing), Sadhana Kannan, BSc (Data curation; Formal analysis; Methodology; Validation; Writing—original draft; Writing—review & editing), Sarika Mandavkar, BSc (Data curation; Investigation; Methodology; Resources; Supervision; Validation; Writing—review & editing), Vikash Pal, BSc (Data curation; Investigation; Methodology; Supervision; Writing—review & editing), Kunal Ranjan Vinayak, MD (Investigation; Supervision; Writing—review & editing), Prabhat Bhargava, MD, DM (Data curation; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing—review & editing), Biswajit Dubashi, MD, DM (Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing—review & editing), Anuj Gupta, DNB (Data curation; Investigation; Methodology; Resources; Supervision; Writing—review & editing), Akhil Kapoor, MD, DM (Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Resources; Supervision; Writing—review & editing), Sujay Srinivas, MD, DM (Data curation; Formal analysis; Investigation; Software; Supervision; Writing—review & editing), Omshree Shetty, PhD (Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Writing—review & editing), Poonam Jadhav, BSc (Data curation; Investigation; Resources; Supervision; Writing—review & editing), Veena Desai, BSc (Data curation; Investigation; Supervision; Writing—review & editing), Kumar Prabhash, MD, DM (Data curation; Formal analysis; Investigation; Methodology; Resources; Supervision; Writing—original draft; Writing—review & editing), Vanita Noronha, MD (Data curation; Formal analysis; Investigation; Supervision; Writing—review & editing), Nandini

Menon, DNB (Investigation; Supervision; Writing—review & editing), Vijay Patil, MD, DM (Formal analysis; Investigation; Methodology; Supervision; Writing—review & editing), Bal Krishna Mishra, MD (Investigation; Methodology; Resources; Writing—review & editing), Bipinesh Sansar, MD, DM (Investigation; Supervision; Writing—review & editing), Arpita Singh, MBBS (Data curation; Investigation; Methodology; Writing—review & editing), Swapnil Patel, MS (Investigation; Methodology; Supervision; Writing—review & editing), Satyendra Narayan Singh, MD (Investigation; Methodology; Writing—review & editing), Ipsita Dhal, MD (Investigation; Methodology; Supervision; Writing—review & editing), Amit Joshi, MD, DM (Investigation; Methodology; Supervision; Writing—review & editing), Vikas Ostwal, MD, DM (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing—review & editing)

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## Conflicts of interest

None to report.

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