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DPYD-Guided Dosing of Metronomic Capecitabine Plus Vinorelbine in Metastatic Human Epidermal Growth Factor Receptor 2–Negative Breast Cancer: A Real-World Retrospective Study

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DOI https://doi.org/10.1200/PO-26-00273

ABSTRACT

PURPOSE Metronomic chemotherapy with oral capecitabine + vinorelbine (Cape + VNL) provides synergistic cytostatic activity and antiangiogenic and immunomodulatory effects, potentially offering prolonged disease control with limited toxicity in HER2-negative metastatic breast cancer (MBC). However, efficacy in the real-world (RW) setting, especially in late lines, and the impact of dihydropyrimidine dehydrogenase (*DPYD*) polymorphisms on dose reduction and safety remain limited.

METHODS In this retrospective study, 200 patients with human epidermal growth factor receptor 2 (HER2)–negative MBC were treated at the ASST Cremona Hospital (2015-2023) with metronomic Cape (1000 mg twice daily, in normal metabolizers; 500 mg twice daily, in *DPYD* variant carriers) + VNL (20 mg/day, once daily, 5-days-on/2-days-off). All patients underwent pretreatment *DPYD* genotyping and dose adjustment. Treatment was administered in the second-to-fourth setting. The primary end point was time-to-next treatment or death (TNTD); secondary end points included overall survival (OS), disease control rate (DCR) ≥24 weeks, overall response rate (ORR), safety, and genotype-toxicity correlations.

RESULTS The median age was 61 years, and *DPYD* variants were present in 14.5% of patients; 34%, 41%, and 25% received therapy as second-, third-, and fourth-line treatment. The median TNTD was 22.0 weeks, and the OS was 64.0 weeks. The DCR was 38.5%, and the ORR was 22.0%. Efficacy was comparable between *DPYD* variant carriers and normal metabolizers (all *P* values > .05). In later lines, Eastern Cooperative Oncology Group performance status 2 and >2 metastatic sites were independent negative prognostic factors (all values $P < .05$). Overall, 7.5% grade 3 toxicities occurred, especially in variant carriers without dose reduction and grade 4-5 events.

CONCLUSION These RW data suggest that metronomic Cape + VNL may represent a clinically active and manageable option in heavily pretreated HER2-negative MBC. Our findings support prospective evaluation of *DPYD*-guided dose individualization as a strategy to optimize the benefit-risk balance of fluoropyrimidine-based metronomic regimens.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Accepted June 24, 2026
Published August 7, 2026

JCO Precis Oncol 10:e2600273
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INTRODUCTION

Metastatic breast cancer (MBC) remains a leading cause of cancer-related mortality in women, with a median overall survival (mOS) of approximately 30-40 months despite therapeutic advances.[1,2] Although targeted agents, immunotherapy, and novel endocrine treatments (ETs) have improved outcomes, most patients with hormone receptor–positive/human epidermal growth factor receptor 2 (HER2)–negative and triple-negative breast cancer (TNBC) ultimately require chemotherapy.[3] Conventional chemotherapy administered at maximum tolerated doses (MTD) is often limited by cumulative toxicity, resistance, and deterioration in quality of life (QoL).[4] These limitations have driven interest in

CONTEXT

Key Objective

Could a dihydropyrimidine dehydrogenase (*DPYD*)–guided dose individualization strategy optimize the risk-benefit balance of metronomic capecitabine-vinorelbine combination in patients with human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC)?

Knowledge Generated

In this retrospective real-world analysis of 200 patients, metronomic capecitabine-vinorelbine achieved a median TNTD of 22.0 weeks, a median OS of 64.0 weeks, a DCR of 38.5%, and an objective response rate of 22.0% in patients with HER2-negative MBC. Efficacy outcomes were comparable between *DPYD* variant carriers receiving reduced-dose capecitabine and normal metabolizers receiving the full metronomic dose although grade ≥3 toxicities were more frequent among *DPYD* variant carriers.

Relevance

To our knowledge, this study provides the first evidence that *DPYD*-guided capecitabine dose reduction may be clinically valuable even in metronomic capecitabine–based regimens, potentially reducing severe toxicity while preserving activity and efficacy. These findings support the prospective evaluation of preemptive *DPYD*-guided dosing strategies for metronomic capecitabine-vinorelbine in pretreated HER2-negative MBC.

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metronomic chemotherapy (MCT), which involves continuous low-dose administration without prolonged breaks.[5,6] MCT exhibits anticancer activity primarily through antiangiogenic effects, modulation of the tumor microenvironment, and enhancement of antitumor immunity.[7-11] Capecitabine (Cape) and vinorelbine (VNL) are particularly attractive for metronomic administration because of their oral availability, favorable safety profiles, and complementary mechanisms of action.[12-15] However, large, randomized phase III trials are lacking, and robust real-world (RW) data remain limited. A critical issue in Cape therapy is the interpatient variability in drug metabolism because of dihydropyrimidine dehydrogenase (*DPYD*) genetic polymorphisms,[16] which can be responsible for severe adverse events (AEs) in 10%-30% of patients receiving standard doses and up to 1% of treatment-related deaths.[17-20] Prospective studies have shown that *DPYD*-guided dosing reduces severe toxicity from 73% to 28% without compromising efficacy.[21,22] However, the impact of *DPYD*-guided dosing in metronomic Cape regimens has not been systematically evaluated. We performed a large RW analysis in patients with MBC treated in later-line settings to assess the efficacy and safety of metronomic Cape + VNL and determine the effect of *DPYD* genotype–guided dosing on safety, activity, and efficacy.

METHODS

Study Design and Patient Population

This retrospective observational study included women with histologically confirmed MBC treated at the Breast Unit of the Cremona Hospital, Italy, between January 2015 and December 2023. Eligible patients were 18 years and older, had HER2-negative MBC, completed pretreatment *DPYD* genotyping, and received metronomic Cape + VNL for at least 4 weeks, with sufficient available data to assess the primary end point. All data were retrieved from institutional electronic medical records.

DPYD Variant Screening, Classification, and Scoring

Four *DPYD* variants were systematically screened, according to local and international recommendations.[2,23,24] Patients were classified as normal metabolizers (NM), intermediate metabolizers (IM) and poor metabolizers (PM), using the activity score system recommended by CPIC 2018/2022 guidelines.[23]

Study Treatment

Patients classified as *DPYD* NM received Cape 2,000 mg/day (1,000 mg twice daily), administered continuously, combined with VNL 20 mg/day on a 5-days-on/2-days-off schedule. *DPYD* IM received a prophylactically reduced starting dose of Cape 1,000 mg/day (500 mg twice daily), administered continuously, with the same VNL schedule. Heterozygous c.1236G>A carriers (13 patients) were treated with a 50% Cape dose reduction. PM were excluded as per the institutional protocol.

Study Objectives, End Points, and Assessments

The primary objective was to determine the efficacy of metronomic Cape + VNL in a RW setting, in general and according to *DPYD* status, in terms of RW time-to-next treatment or death (TNTD).[25] TNTD is an established RW end point formally recommended among time-to-event

measures for RW oncology analyses.[26] Secondary objectives included (1) RW overall survival (OS),[26] (2) disease control rate (DCR) at 24 weeks and objective response rate (ORR), and (3) safety. The radiologic imaging assessment was reperformed retrospectively according to RECIST 1.1 criteria.[27] AEs graded according to NCI-CTCAE v5.0 criteria were retrieved from patients' charts.

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics. Pearson's chi-square test compared DCR and ORR across subgroups. Time-to-event outcomes were estimated using the Kaplan-Meier method and compared with the log-rank test. Univariate Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% CIs to identify potential prognostic factors. Variables with $P < .10$ in univariate analysis were entered into multivariate Cox models. Logistic regression was used to estimate odds ratios (ORs) for grade ≥3 toxicity. Efficacy and activity outcomes were estimated in the overall population and prespecified subgroups of interest, namely, *DPYD* metabolizer status, treatment line, endocrine receptor status, metastatic burden, visceral involvement, Eastern Cooperative Oncology Group (ECOG) performance status (PS), and age. All tests were two-sided, with $P < .05$ considered statistically significant. To account for multiplicity across the prespecified subgroup analyses, a false discovery rate correction was applied using the Benjamini-Hochberg (BH) procedure. Statistical analyses were performed using SPSS Statistics v29.0.

Full methods are reported in Data Supplement materials.

Ethic Declarations

The study was conducted in accordance with the Declaration of Helsinki and approved by the ASST of Cremona Ethics Committee (IRB No. 499/10/2025); written informed consent was waived because of the retrospective, anonymized nature of the analysis.

RESULTS

Patient and Disease Characteristics

Overall, 249 women with HER2-negative MBC were included. Forty-nine did not meet eligibility criteria, either because of lack of sufficient data (71.4%) to assess the primary end point or lack of *DPYD* genotyping data (28.6%). To assess the potential impact of these exclusions, a sensitivity analysis comparing available baseline characteristics between included (n = 200) and excluded (n = 49) patients was performed. No statistically significant differences were identified in age, ECOG PS, surrogate molecular subtype, histotype, metastatic burden, grade, or treatment line distribution (Data Supplement, Table S1).

The median age at MCT initiation was 61 years (range, 35-84 years). The ECOG PS was mostly (84.0%) 0-1. Most patients (71.5%) had hormone receptor–positive/HER2-negative disease, whereas 28.5% had TNBC. Ductal carcinoma represented 82.5% of histologic subtypes, and tumor grade was three in 51.5% of cases. Visceral metastases were present in 79.5% of cases, with the liver being the most frequent site (53.5%). At baseline, 54.0% had >2 sites involved. Brain metastases were present in 9.0% of patients at treatment initiation. The median time from initial MBC diagnosis to MCT initiation was 3.8 years (range, 0.9-11.0 years), reflecting the heavily pretreated nature of this cohort. Sixty-eight patients (34.0%) received Cape + VNL as second-line treatment, 82 patients (41.0%) received Cape + VNL as third-line treatment, and 50 patients (25.0%) received Cape + VNL as fourth-line treatment. Detailed baseline study cohort characteristics are reported in Table 1. *DPYD* genotyping was successfully completed for all 200 patients before treatment initiation. Baseline characteristics were well-balanced between *DPYD* NM and variant carriers (IM and PM), with no significant differences in age, ECOG PS, surrogate molecular subtype, metastatic burden, or treatment line distribution (Data Supplement, Table S2). The distribution of *DPYD* variants and predicted metabolizer phenotypes is presented in Figure 1, along with variant allele frequencies and initial Cape dose.

In terms of prior systemic treatments, expected differences were observed according to surrogate subtypes although the population was overall heavily pretreated (Data Supplement, Tables S2 and S3).

RW TNTD

The median follow-up for the overall study cohort was 45.0 weeks (95% CI 40.0-52.0), with a median TNTD (mTNTD) of 22.0 weeks (95% CI, 19.0 to 25.0 weeks; Fig 2) and a 6-month TNTD rate of 41.5% (95% CI, 34.6 to 48.7). At data cutoff (December 31, 2023), 28 patients (14.0%) were still on treatment. When comparing patients according to the *DPYD* variant, no significant difference was observed in TNTD ($P = .580$, Fig 2, Data Supplement, Table S4). The 6-month TNTD rates were 41.8% (95% CI, 43.1 to 49.3) and 37.9% (95% CI, 20.7 to 57.7), respectively. Sensitivity analysis excluding c.1236G>A heterozygous carriers (n = 4) who received full-dose Cape yielded similar results ($P = .620$).

TNTD differed significantly by treatment line ($P = .003$), worsening from second- to fourth-line treatment (Fig 2). This trend was observed in both *DPYD* metabolizer groups without significant interaction ($P = .760$). No visceral metastases ($P = .007$), ECOG PS 0-1 ($P = .001$), and ≤2 metastatic sites ($P < .001$) were associated with more favorable TNTD (Data Supplement, Table S5). TNTD did not significantly differ by age and subtype (Data Supplement, Fig S1). In the multivariable model, further treatment lines, >2 metastatic

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TABLE 1. Baseline Study Cohort Characteristics

Characteristic	No. (%) or Median (min-max range)
Age at treatment initiation, years	61 (35-84)
Age groups, years	
≥70	58 (29.0)
<65	117 (58.5)
≥65	83 (41.5)
ECOG PS	
0-1	168 (84.0)
2	32 (16.0)
Surrogate subtypes	
Hormone receptor–positive/HER2-negative	143 (71.5)
TNBC	57 (28.5)
Histology	
Invasive ductal carcinoma	165 (82.5)
Invasive lobular carcinoma	24 (12.0)
Other	11 (5.5)
Tumor grade	
Grade 2	76 (38.0)
Grade 3	103 (51.5)
Unknown	21 (10.5)
Metastatic sites	
Liver	107 (53.5)
Lung	94 (47.0)
Bone	89 (44.5)
Lymph nodes	76 (38.0)
Brain	18 (9.0)
Other	42 (21.0)
No. of metastatic sites	
≤2 sites	92 (46.0)
>2 sites	108 (54.0)
Visceral metastases	
Present	159 (79.5)
Absent	41 (20.5)
Line of therapy	
Second line	68 (34.0)
Third line	82 (41.0)
Fourth line	50 (25.0)
Time from MBC diagnosis to treatment, years	3.8 (0.9-11.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; max, maximum; min, minimum; PS, performance status; TNBC, triple negative breast cancer.

sites, and ECOG PS two retained an independent negative prognostic value (Fig 3).

RW OS

The median OS for the entire cohort was 64.0 weeks (95% CI, 48.0 to 80.0 weeks; Fig 2), with a 1-year OS rate of 54.5% (95% CI, 47.3 to 61.5). At data cutoff, 64 patients (32.0%) were still alive. OS did not differ significantly between *DPYD* NM and variant carriers (log-rank $P = .520$). The median OS was 65.0 weeks (95% CI, 49.0 to 81.0) in NM versus 58.0 weeks (95% CI, 38.0 to 78.0) in *DPYD* variant carriers (Data Supplement, Table S4). The 1-year OS rates were 55.0% (95% CI, 47.2 to 62.3) and 51.7% (95% CI, 32.5 to 70.6), respectively.

OS analyses in subgroups of interest showed that ≤2 metastatic sites ($P = .002$), no visceral metastases ($P = .018$), and ECOG PS 0-1 ($P < .001$) were associated with more favorable OS (Data Supplement, Table S5). No significant differences were observed according to age and subtype (Data Supplement, Fig S2). When retaining significant prognostic variables in the multivariable analysis, further treatment lines, >2 metastatic sites, and ECOG PS two retained an independent negative association with OS in patients treated with Cape + VNL (Fig 3).

Activity Outcomes

The overall DCR at 24 weeks was 38.5% (95% CI, 31.7 to 45.6), with an ORR of 22.0% (95% CI, 16.5 to 28.4), without complete responses (CR). Progressive disease (PD) as best response occurred in 73 patients (36.5%). DCR at 24 weeks and ORR did not differ significantly ($P = .940$ and $P = .850$) between NM and *DPYD* variant carriers (Data Supplement, Table S4).

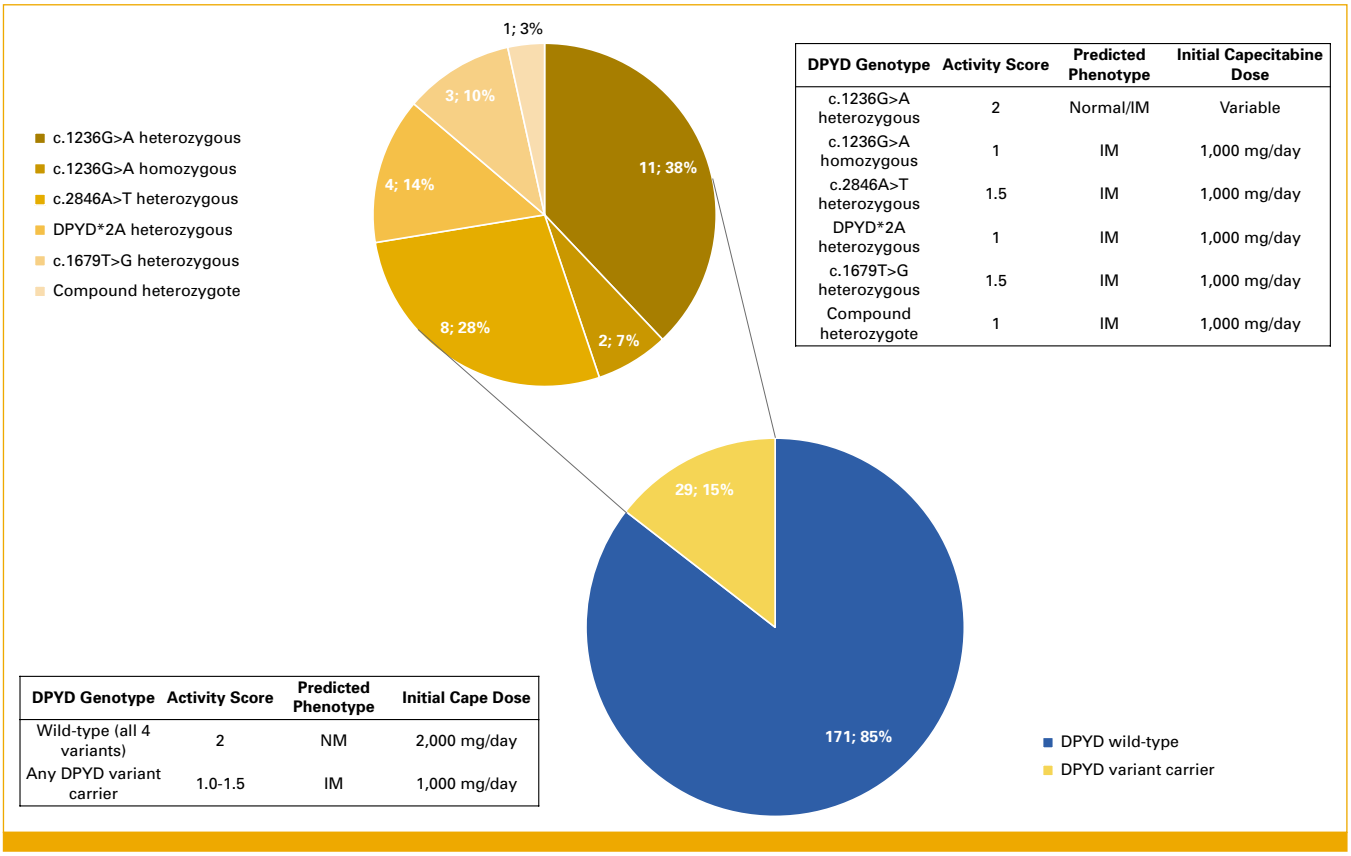
DCR varied significantly by treatment line across the overall study cohort, from 45.6% (95% CI, 33.5 to 58.1) to 37.8% (95% CI, 27.3 to 49.2) and 28.0% (95% CI, 16.2 to 42.5) in second-, third-, and fourth-line treatment, respectively ($P = .042$). Consistently, the ORR was 27.9% (95% CI, 17.7 to 40.2), 20.7% (95% CI, 12.6 to 31.1), and 16.0% (95% CI, 7.2 to 29.1) for the second-, third-, and fourth-line settings, respectively ($P = .031$). This gradient was observed consistently in both *DPYD* NM and variant carriers (not shown). However, after BH adjustment, treatment lines lost significant association with both DCR and ORR (Data Supplement, Table S5).

Subgroup analysis by HR status revealed no statistically significant difference in DCR between hormone receptor–positive/HER2-negative disease and TNBC ($P = .350$). This pattern was consistent across *DPYD* metabolizer groups (not shown). Patients with ≤2 metastatic sites achieved significantly higher DCR versus those with >2 sites (48.9% [95% CI, 38.3 to 59.6] *v* 29.6% [95% CI, 21.2 to 39.2], $P = .005$; Data Supplement, Table S5). This prognostic factor remained significant in both *DPYD* subgroups. The presence of visceral metastases did not significantly affect DCR ($P = .420$).

Safety and Tolerability

The metronomic regimen demonstrated excellent tolerability throughout the study period (Table 2). AEs were predominantly grade 1-2 across the overall cohort. Only 15

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DPYD Genotype	Activity Score	Predicted Phenotype	Initial Capecitabine Dose
c.1236G>A heterozygous	2	Normal/IM	Variable
c.1236G>A homozygous	1	IM	1,000 mg/day
c.2846A>T heterozygous	1.5	IM	1,000 mg/day
DPYD*2A heterozygous	1	IM	1,000 mg/day
c.1679T>G heterozygous	1.5	IM	1,000 mg/day
Compound heterozygote	1	IM	1,000 mg/day

DPYD Genotype	Activity Score	Predicted Phenotype	Initial Cape Dose
Wild-type (all 4 variants)	2	NM	2,000 mg/day
Any DPYD variant carrier	1.0-1.5	IM	1,000 mg/day

FIG 1. DPYD polymorphism distribution, predicted phenotypes, and initial capecitabine dose. Distribution of DPYD variants and predicted metabolizer phenotypes along with variant allele frequencies and initial Cape dose. In NM wild-type patients initial Cape dose was 1,000 mg twice daily (2,000 mg/day), while for IM variant carriers was 500 mg twice daily (1,000 mg/day). Cape, capecitabine; *DPYD*, dihydropyrimidine dehydrogenase; IM, intermediate metabolizer; NM, normal metabolizer.

patients (7.5%) experienced grade ≥3 toxicity requiring treatment interruption or additional dose reduction beyond the initial *DPYD*-guided adjustment and already reduced dosing schedule of MCT. The most frequently reported all-grade AEs were fatigue (29.0%), nausea/vomiting (23.5%), diarrhea (18.0%), neutropenia (16.5%), and hand-foot syndrome (12.5%). Among hematologic toxicities, grade 3-4 neutropenia occurred in 2.5% of patients, requiring treatment interruption and granulocyte colony-stimulating factor (G-CSF) support in 60.0% of cases. Grade 3 anemia was observed in 1.0% of patients and was managed with red blood cell transfusion. No cases of febrile neutropenia or grade 4 thrombocytopenia were reported (Table 2). No treatment-related deaths occurred during the study period. The incidence of grade ≥3 toxicity did not differ significantly according to age ($P = .350$), with a similar proportion of dose reductions ($P = .410$). Toxicity profiles did not differ significantly across treatment lines ($P = .62$ for grade ≥3 toxicity).

Despite receiving 50% reduced capecitabine doses, *DPYD* variant carriers experienced higher rates of grade ≥3 toxicity compared with NM receiving standard metronomic doses (20.7% *v* 5.3%, OR, 4.64 [95% CI, 1.52 to 14.18]; $P = .006$). A quasi-significant association with higher rates of grade ≥3 diarrhea was also observed in *DPYD* variant carriers (OR, 6.17, $P = .051$). No other relevant differences were observed, and no grade 4-5 toxicities occurred in *DPYD* variant carriers who received preemptively reduced doses (Data Supplement, Tables S5 and S6).

Treatment discontinuation because of AEs was required in 5 NM (2.9%) and 4 *DPYD* variant carriers (13.8%; $P = .009$). Toxicity-based dose reductions were required in 19 (11.1%) NM versus 8 (27.6%) *DPYD* variant carriers ($P = .014$).

More safety results are reported in Data Supplement materials.

DISCUSSION

We conducted a comprehensive RW analysis of 200 patients with HER2-negative MBC treated with metronomic Cape + VNL in second-, third-, or fourth-line treatment. With a median TNTD and OS of 22.0 and 60.0 weeks, a 24-week DCR of 38.5%, and an ORR of 22.0%, this regimen showed clinically meaningful activity in this retrospective heavily pretreated population. Previous phase II studies reported DCRs of 35%-45% and a median progression-free survival (PFS) of 4-6 months.[28,29] The VICTOR-1 trial showed good

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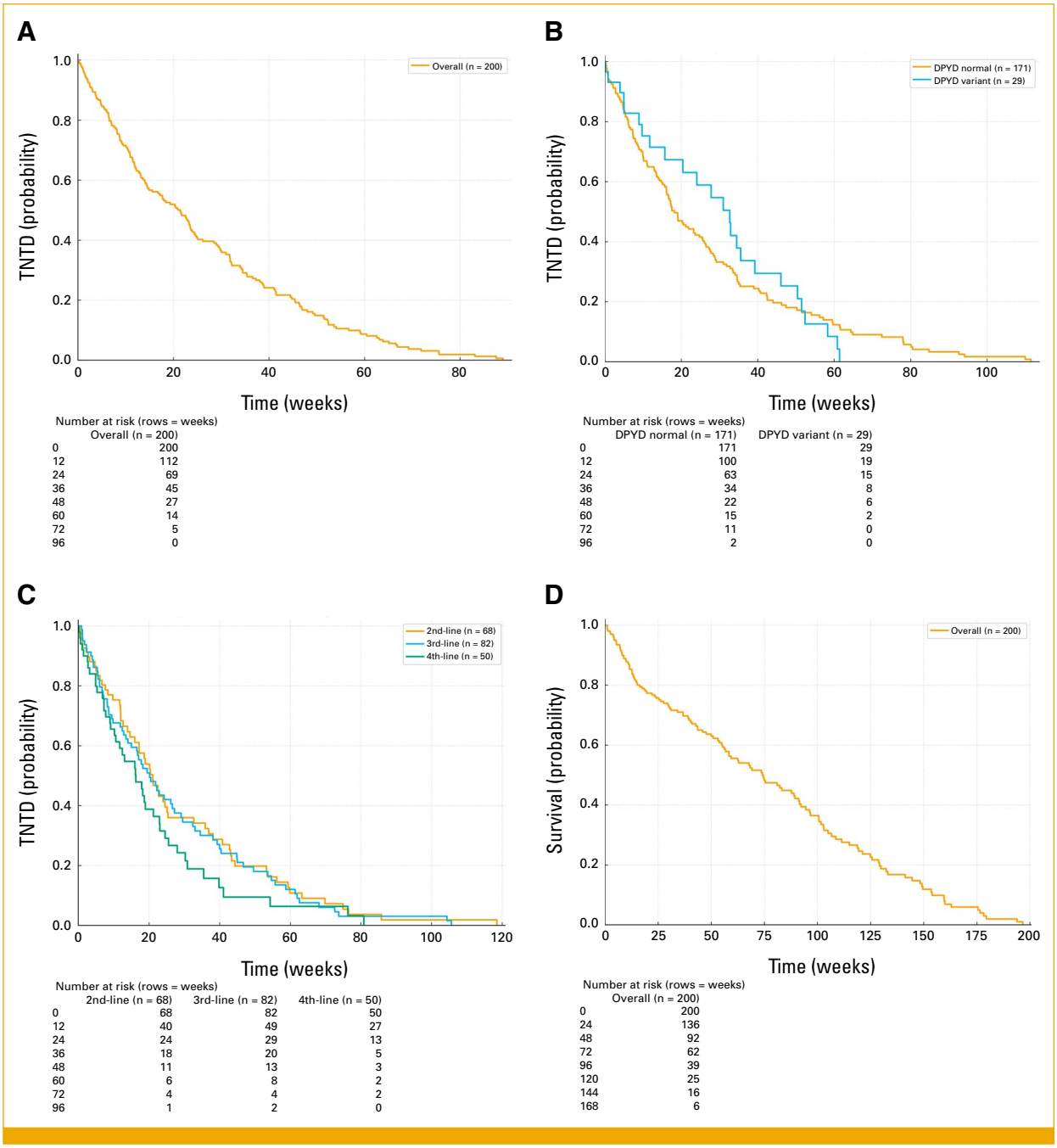


FIG 2. Kaplan-Meier curves of main survival analyses. Kaplan-Meier curves for TNTD (A) in the entire study cohort, (B) in patients according to *DPYD* status (wild-type *DPYD* and *DPYD* variants), and (C) among patients who received different treatment lines and OS in (D) the entire study cohort. *DPYD*, dihydropyrimidine dehydrogenase; OS, overall survival; TNTD, time to next treatment or death.

tolerability and a clinical benefit rate of 67% in elderly patients,[30] whereas the multicenter VICTOR-6 study reported a median PFS of 5.5-6.5 months with acceptable toxicity.[17] Our findings appeared broadly consistent with these data and with other metronomic Cape–based regimens.[19] As expected, efficacy outcomes declined across treatment lines, likely reflecting progressive treatment resistance and increasing disease burden. Nevertheless, even in later lines, the observed TNTD and OS remained numerically comparable with outcomes reported with eribulin or single-agent VNL in similar settings[20,31-33], although indirect cross-trial comparisons and the retrospective nature of our study warrant cautious interpretation.

A novel aspect of this study is the observation that *DPYD* variant carriers receiving prophylactic Cape dose reductions showed efficacy outcomes broadly similar to *DPYD* NM receiving standard metronomic doses. Although exploratory, these findings may support the hypothesis that continuous low-dose exposure, rather than peak drug concentrations, contributes substantially to the activity of metronomic regimens.[34] They also raise the possibility that genotype-

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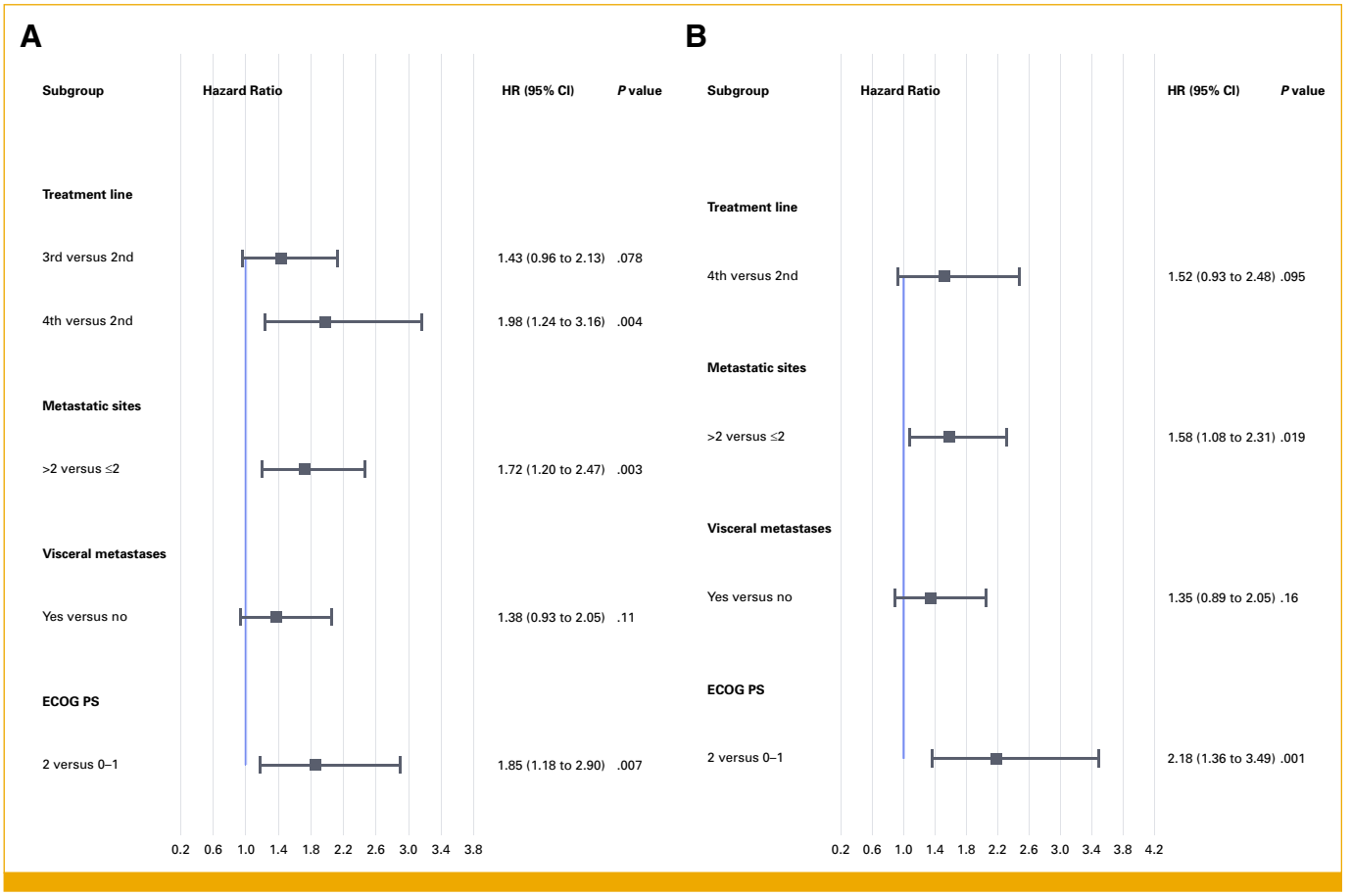


FIG 3. Forest plot of TNTD and OS multivariable analyses. (A) TNTD multivariable analysis including variables with $P < .10$ in univariate analysis. (B) OS multivariable analysis including variables with $P < .10$ in univariate analysis. -, negative; HR, hazard ratio; OS, overall survival; PS, performance status; TNTD, time to next treatment or death.

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guided dosing could help achieve adequate systemic 5-FU exposure despite reduced administered doses in patients with impaired fluoropyrimidine metabolism.[35] In this context, our results may provide RW support for current CPIC and EMA recommendations regarding preemptive *DPYD* testing and dose individualization,[23,24] also with metronomic Cape administration. Prospective validation is warranted.

Despite up-front dose reduction, *DPYD* variant carriers still experienced higher rates of grade ≥3 toxicity than NM, suggesting that dose adjustment may mitigate but not completely eliminate fluoropyrimidine-related toxicity risk. Nevertheless, the overall incidence of grade ≥3 AEs remained relatively low compared with historical reports for standard-dose Cape or Cape-docetaxel regimens.[36,37] The low rates of severe neutropenia, the absence of febrile neutropenia or treatment-related deaths, and the observed tolerability in patients 70 years and older may support the feasibility of continuous low-dose administration with *DPYD*-guided dose individualization, including in elderly or frail populations.[38]

In the hormone receptor–positive cohort, most patients were heavily pretreated with prior ET-based regimens, including CDK4/6-inhibitor combinations, and received Cape + VNL in third or later lines after prior chemotherapy exposure. In this setting, the lack of major outcome differences between hormone receptor–positive/HER2-negative disease and TNBC may potentially reflect endocrine resistance and reduced estrogen dependence. In line with this hypothesis, prior studies suggested that CDK4/6-inhibitor exposure may induce shifts toward less luminal and more chemotherapy-sensitive subtypes, including HER2-enriched disease,[39] whereas nonluminal tumors appeared less enriched for *ESR1* mutations.[40] Metronomic Cape + VNL was associated with a clinically meaningful DCR that may potentially delay the need for more intensive therapies while preserving QoL. Although cross-trial comparisons should be interpreted with caution, the observed TNTD appeared numerically comparable with outcomes reported with antibody-drug conjugates (ADCs) such as sacituzumab govitecan or datopotamab deruxtecan in heavily pretreated populations.[41,42] Given its favorable tolerability profile, this regimen may represent a potential option for patients wishing to avoid alopecia, severe myelosuppression, or other toxicities associated with conventional chemotherapy or ADCs.

TABLE 2. Adverse Events in the Overall Study Cohort

Adverse Events	Any Grade, No. (%)	Grade 1-2, No. (%)	Grade 3, No. (%)	Grade 4-5, No. (%)
Hematologic				
Neutropenia	33 (16.5)	28 (14.0)	5 (2.5)	0 (0)
Anemia	29 (14.5)	27 (13.5)	2 (1.0)	0 (0)
Thrombocytopenia	12 (6.0)	12 (6.0)	0 (0)	0 (0)
Febrile neutropenia	0 (0)	—	0 (0)	0 (0)
Gastrointestinal				
Nausea/vomiting	47 (23.5)	44 (22.0)	3 (1.5)	0 (0)
Diarrhea	36 (18.0)	32 (16.0)	4 (2.0)	0 (0)
Mucositis/stomatitis	14 (7.0)	14 (7.0)	0 (0)	0 (0)
Dermatologic				
Hand-foot syndrome	25 (12.5)	24 (12.0)	1 (0.5)	0 (0)
Constitutional				
Fatigue	58 (29.0)	56 (28.0)	2 (1.0)	0 (0)
Neurologic				
Peripheral neuropathy	9 (4.5)	9 (4.5)	0 (0)	0 (0)
Hepatic				
Transaminase elevation	11 (5.5)	11 (5.5)	0 (0)	0 (0)

NOTE. All % calculated for the total number of included patients (N = 200).

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Among patients with TNBC, the observed median TNTD of 19.0 weeks and the DCR of 33.3% may suggest potential clinical activity in a population with limited treatment options after prior chemotherapy and ADCs.[43] Given prior platinum exposure in 31.6% of patients, metronomic Cape + VNL could represent a feasible nonplatinum alternative, with outcomes appearing numerically comparable with those reported with eribulin.[20,33] Better outcomes were observed among patients treated in earlier lines, with lower metastatic burden, the absence of visceral disease, and ECOG PS 0-1, suggesting that patients with less aggressive disease biology may derive greater benefit from prolonged MCT. *DPYD* genotype did not appear to significantly interact with these prognostic factors although these exploratory findings require prospective validation.

Our study must be interpreted in the context of several limitations inherent to its retrospective single-center design. Moreover, we screened only the four most common *DPYD* variants recommended by international guidelines. These variants account for 20%-35% of deficiency cases, meaning that additional rare variants or variants outside coding regions might have been missed. The lack of uniform molecular profiling for actionable genomic alterations such as *BRCA1/2*, *ESR1*, *PIK3CA*, or PD-L1 status limits our ability to detect whether these features predict a differential response to metronomic therapy. In the modern treatment landscape, patients harboring these alterations would preferentially receive targeted therapies or immunotherapy rather than chemotherapy. Importantly, our study cohort includes patients who had not been previously treated with ADCs. This is an important caveat as ADCs are already the standard of care starting from the second-line setting and are quickly replacing first-line chemotherapy options in TNBC and in selected hormone receptor–positive/HER2-negative cases.[44-48] Moreover, as a single-center Italian study, our findings may not fully generalize to populations with different genetic backgrounds (*DPYD* variant frequencies vary across ethnicities) or practice patterns. In addition, our results do not allow us to draw definitive conclusions when numerically comparing the performance of the Cape + VNL regimen with that of other single or multiagent treatments. The use of TNTD rather than PFS as the primary end point, while pragmatically justified by the study design, represents an additional limitation: TNTD may be subject to informative censoring if treatment is changed for reasons other than disease progression (eg, toxicity or patient preference), potentially underestimating or overestimating treatment duration. In addition, the exclusion of approximately 20% of the screened cohort because of insufficient follow-up or missing genotyping data represents a potential source of selection bias. To note, the sensitivity analysis comparing baseline characteristics of included and excluded patients showed no statistically significant differences although a residual risk of optimistic bias cannot be entirely ruled out. Finally, while multiple subgroup comparisons performed in this study increased the risk of type I error, most significant results were confirmed after BH *P* value correction. In any case, all subgroup findings should be interpreted as exploratory.

Despite its limitations, to our knowledge, this study represents the largest cohort evaluating metronomic Cape + VNL and the first to systematically explore the potential impact of *DPYD*-guided dosing in this setting. The consistency of our findings with the prior literature, together with

systematic *DPYD* genotyping and detailed safety assessment, extends the available evidence to heavily pretreated HER2-negative MBC populations often under-represented in clinical trials.

Overall, this retrospective single-center analysis suggests that metronomic Cape + VNL could represent a feasible and manageable treatment option, whereas the similar efficacy outcomes observed between *DPYD* variant carriers receiving reduced doses and NM may provide preliminary support for preemptive *DPYD*-guided dose individualization. However, given the retrospective, single-arm design, these findings should be interpreted with caution and no definitive conclusions regarding comparative efficacy with alternative regimens can be drawn. Prospective studies are warranted to further evaluate these observations and to explore combinations with targeted therapies or immunotherapy.[7,21,22,24,49-53]

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SUPPORT

Supported by Novartis (honoraria for educational events/materials, advisory fees, and research grant), Astra-Zeneca (honoraria for educational events/materials and advisory fees), Pfizer (honoraria for educational events/materials, advisory fees, and research grant), Lilly (honoraria for educational events/materials and advisory fees), Roche (honoraria for educational events/materials, advisory fees, and travel expenses), Daiichi-Sankyo (honoraria for educational events/materials), and Myriad (research grant) (to D. Generali) and by the European Society for Medical Oncology (ESMO) through an ESMO Research Fellowship—Translational (to Dr. G. Di Grazia). Any views, opinions, findings, conclusions, or recommendations expressed in this material are those solely of the authors and do not necessarily reflect those of ESMO. It must also be noted that this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. All remaining authors have no relevant financial or nonfinancial interests to disclose.

DATA SHARING STATEMENT

A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/PO-26-00273.
The data sets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Honoraria: AstraZeneca, Daiichi Sankyo/Astra Zeneca, Lilly, MSD, Novartis, Menarini Group, Pfizer, Exact Sciences, Gilead Sciences
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Speakers' Bureau: AstraZeneca/Daiichi Sankyo, Exact Sciences, Lilly, MSD, Gilead Sciences, Menarini Group, Novartis, Pfizer, Roche
Research Funding: Daiichi Sankyo/Astra Zeneca (Inst)

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Travel, Accommodations, Expenses: AstraZeneca/Daiichi Sankyo, Lilly, Novartis, Roche, Pfizer, Gilead Sciences

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Travel, Accommodations, Expenses: Novartis, Roche, Pfizer

No other potential conflicts of interest were reported.

ACKNOWLEDGMENT

The authors express sincere gratitude to all clinicians, nurses, pharmacists, and data managers of the Breast Unit, ASST of Cremona, for their dedication to patient care and meticulous data collection that made this analysis possible. We thank the patients and their families for their continued trust in our care. Dr F. Schettini is supported by a Juan Rodés clinician scientist contract from the Instituto de Salud Carlos III (JR24/00024). Dr. G. Di Grazia is supported by a European Society for Medical Oncology (ESMO) Research Fellowship - Translational. Any views, findings, conclusions or recommendations expressed in this material are those solely of the authors and do not necessarily reflect those of ESMO.

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