

Baseline OCT cyst morphology and 24-month treatment outcomes in diabetic macular oedema: the BOSPHERUS-DME Study Group

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Baseline OCT cyst morphology and 24-month treatment outcomes in diabetic macular oedema: the BOSPHERUS-DME Study Group

Running title: *Cyst Stage and Anti-VEGF Outcomes in DME*

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ABSTRACT

Background/Objectives: To evaluate the effect of baseline ESASO OCT-based cyst stage on 24-month outcomes in treatment-naïve diabetic cystoid macular oedema (CME) receiving anti-VEGF therapy.

Subjects/Methods: Multicentre retrospective cohort of 311 treatment-naïve eyes classified at baseline as ESASO Stage 1 (mild, n=94), 2 (moderate, n=99), or 3 (advanced, n=118). BCVA (logMAR) and central macular thickness (CMT) at baseline and 3, 6, 12, 18, and 24 months were analysed using linear mixed-effects models with a random intercept per eye. A sensitivity analysis adjusted the BCVA model for anti-VEGF agent and cumulative dexamethasone exposure.

Results: Stage 3 had worse baseline BCVA (0.744 vs. 0.537 and 0.570 logMAR; $p<0.0001$) and CMT (516 vs. 335 and 410 μm ; $p<0.0001$). All groups improved significantly. At 12 months, Stage 3 had the highest proportion of ≥ 3 -line gainers (42.4% vs. 21.3% and 25.3%; $p=0.012$). Between 18 and 24 months, Stage 3 showed a within-stage BCVA deterioration (+0.061 logMAR; 95% CI +0.005 to +0.116; $p=0.032$), while Stages 1 and 2 remained stable ($p=0.41$ and $p=0.96$). This decline persisted after adjusting for treatment exposure (+0.060 logMAR; $p=0.034$). Stage 3 required more dexamethasone implants (linear trend $p=0.009$) and more clinic visits by 24 months (11.7 vs. 9.9; $p=0.002$).

Conclusions: In advanced diabetic CME, anti-VEGF therapy produces substantial mid-term visual gains but is associated with a small, statistically significant late-phase BCVA decline between 18 and 24 months not attributable to treatment heterogeneity. Baseline ESASO cyst

staging may serve as a supportive prognostic marker alongside baseline BCVA, identifying eyes warranting closer monitoring; prospective validation is required.

Key Words: anti-vascular endothelial growth factor; cystoid macular oedema; dexamethasone implant; diabetic macular oedema; ESASO classification; intraretinal cysts; late deterioration; longitudinal analysis; mixed-effects model; real-world outcomes

Summary

What was known before

- Baseline OCT morphology influences the short-term anti-VEGF response in diabetic macular oedema (DME), but the long-term trajectory of advanced cystoid forms is poorly characterised in real-world care.
- Most DME outcome data come from randomised trials with mandated retreatment schedules that do not reflect routine clinical practice.
- The ESASO cyst staging system is validated for grading diabetic maculopathy, yet its prognostic value for late-phase outcomes has not been tested in a stage-stratified longitudinal cohort.

What this study adds

- Across 311 treatment-naïve eyes followed for 24 months, advanced (Stage 3) cystoid morphology showed a small but significant late-phase BCVA decline between 18 and 24 months, whereas milder stages remained stable.
- The decline persisted after adjustment for anti-VEGF agent and cumulative dexamethasone exposure, and Stage 3 eyes required multiple dexamethasone implants more than twice as often — indicating refractory baseline disease rather than treatment heterogeneity.
- ESASO stage independently predicted 24-month anatomical but not functional outcome, supporting its use alongside baseline BCVA to identify eyes warranting closer late-phase monitoring.

INTRODUCTION

Diabetic macular oedema (DME) is the leading cause of vision loss in working-age adults with diabetes.¹ Among its morphological subtypes, cystoid macular oedema (CME), characterised by confluent intraretinal fluid spaces in the inner nuclear and outer plexiform layers, is associated with greater structural damage and more refractory disease.^{2,3} The European School for Advanced Studies in Ophthalmology (ESASO) OCT grading system classifies DME-associated cystoid changes into three stages based on cyst size and foveal involvement.⁴

Although intravitreal anti-VEGF therapy remains the first-line treatment for centre-involving DME, long-term real-world outcomes in cystoid subgroups are poorly characterised, and most existing evidence derives from randomised trials with fixed retreatment protocols.^{5–7} Whether

visual recovery differs systematically by baseline cyst stage — and whether eyes with advanced cystoid morphology sustain their gains beyond 18 months — has not been examined in a large stage-stratified cohort. We previously demonstrated that aflibercept reduces intraretinal cyst diameter more effectively than ranibizumab (MARMASIA Study),⁷ highlighting the clinical relevance of cyst-specific OCT metrics.

In the present study, we used linear mixed-effects modelling to characterise stage-stratified BCVA and CMT trajectories over 24 months in a multicentre real-world cohort of treatment-naïve diabetic CME eyes and to explore whether the baseline ESASO stage is associated with late-phase functional outcomes independent of treatment exposure.

METHODS

Study Design. This retrospective, observational, multicentre cohort study (Report No. 6 of the BOSPHEUS-DME Study Group) included 23 retinal specialists from ten tertiary referral centres on the European side of Istanbul and in Kocaeli, Türkiye. Medical records of patients with diabetic cystoid macular oedema (CME) who received intravitreal anti-VEGF therapy between January 2019 and January 2023 were reviewed. Under national reimbursement policy, patients initiating anti-VEGF therapy for DME received three consecutive monthly intravitreal bevacizumab injections (1.25 mg/0.05 mL) as the loading phase, followed by a pro re nata (PRN) regimen. Retreatment decisions were based on disease activity (intraretinal or subretinal fluid on OCT, a reduction in BCVA of ≥ 1 Snellen line, or both) at the discretion of the treating physician; no standardised retreatment protocol was mandated across centres. Adjunctive or alternative therapies

(ranibizumab 0.5 mg/0.05 mL, aflibercept 2 mg/0.05 mL, or intravitreal dexamethasone implant [IDI; Ozurdex®, AbbVie-Allergan]) were administered at physician discretion. Ethics approval was obtained from the Kocaeli University Faculty of Medicine Ethics Committee (decision no: KÜ GOKAEK-2025/06/18; date: 13.03.2025; project: 2025/115). The study adhered to the Declaration of Helsinki and written informed consent was obtained from all participants.

Patients. Inclusion criteria: (1) age ≥ 18 years; (2) diabetic CME confirmed by spectral-domain OCT; (3) treatment-naïve status (no prior intravitreal pharmacotherapy of any kind for diabetic macular oedema or any other retinal pathology); (4) baseline ESASO OCT cyst stage grading at study entry; (5) baseline BCVA between 0.05 (20/22) and 1.30 (20/400) logMAR; and (6) minimum 24-month follow-up with at least four annual clinic visits. Eyes with prior vitreoretinal surgery, concurrent non-diabetic macular disease, or non-diabetic macular oedema were excluded, as were eyes undergoing pars plana vitrectomy during follow-up. Where both eyes met criteria, each was analysed individually.

Data Collection. At baseline and each follow-up visit, patients underwent comprehensive ophthalmological examination, including BCVA assessment using a Snellen chart (converted to logMAR), intraocular pressure measurement, slit-lamp biomicroscopy, dilated fundus examination, and OCT imaging. Follow-up data were extracted at 3, 6, 12, 18, and 24 months (± 2 -week window). OCT scans were obtained using one of the following devices: Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), Cirrus OCT (Zeiss, Dublin, CA, USA), RTVue-100 OCT (Optovue Inc., Fremont, CA, USA), DRI OCT Triton Plus (Topcon Inc., Tokyo, Japan), or Xephilio WF-OCT S1 (Canon Inc., Tokyo, Japan). All scans were centred on the foveola, and CMT (μm) was automatically calculated. BCVA, lens status, OCT parameters, intravitreal agent

administered, cumulative injection and visit counts, and procedure-related adverse events were recorded.

ESASO Classification. OCT features were classified according to the European School for Advanced Studies in Ophthalmology (ESASO) grading system for diabetic maculopathy, as previously described.⁴ Cyst stage was defined as: Stage 1 (mild)—small cysts confined to the inner nuclear layer without foveal involvement; Stage 2 (moderate)—moderate cysts with early foveal involvement; Stage 3 (advanced)—large confluent cysts with marked foveal involvement and outer retinal disruption. Additional OCT biomarkers recorded at baseline included subretinal fluid, disorganisation of the retinal inner layers (DRIL), ellipsoid zone integrity, hyperreflective foci, and vitreoretinal interface status. At each centre, every scan was independently graded by two retinal specialists masked to clinical outcomes; in cases of discordance, a third senior specialist adjudicated the final stage. Only adjudicated stages were included. The ESASO system has previously demonstrated good inter-rater reproducibility.⁴ Because ESASO staging relies on qualitative morphological features (cyst location, size, foveal involvement, and outer retinal disruption), it is largely independent of device-specific segmentation algorithms, although absolute CMT values obtained from different platforms may not be directly comparable.

Outcomes. The primary outcome was change in BCVA (logMAR) from baseline at 3, 6, 12, 18, and 24 months, analysed as a longitudinal trajectory. Secondary outcomes included CMT change, visual outcome categories (≥ 3 ETDRS-line gain, stability [< 3 -line change], ≥ 3 -line loss), cumulative clinic visit and intravitreal injection counts, adjunctive dexamethasone implant exposure (within-period rates by 0–6, 6–12, and 12–24 months; cumulative exposure by 24 months; multiple-implant requirement defined as ≥ 2 implants; mean implant count per eye; and

timing of the first implant among recipients), and CMT normalisation ($<300\text{ }\mu\text{m}$) at 24 months. Pre-specified exploratory outcomes included within-stage BCVA comparison between 18 and 24 months, baseline DRIL prevalence by stage, anti-VEGF agent distribution and treatment-switching patterns, and a sensitivity analysis evaluating whether stage-related differences in late-phase BCVA persisted after adjustment for treatment exposure.

Statistical Analysis. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean $\pm$ SD. To account for within-eye correlation across six timepoints (baseline, 3, 6, 12, 18, and 24 months), longitudinal BCVA and CMT data were analysed using linear mixed-effects models with a random intercept per eye, fitted by restricted maximum likelihood. Each model included ESASO cyst stage and timepoint (both categorical) and their interaction as fixed effects. Linear mixed-effects modelling was preferred over generalised estimating equations because the primary inference concerned within-eye longitudinal trajectories rather than population-averaged effects. Within- and between-stage contrasts, including the pre-specified 18-to-24-month BCVA comparison, were evaluated using Wald tests with two-sided p-values and 95% confidence intervals. A sensitivity analysis additionally adjusted the BCVA model for the anti-VEGF agent at each visit and cumulative dexamethasone exposure at that timepoint. Mixed-effects models accommodate intermittently missing observations under the missing-at-random assumption and thus permitted inclusion of all 311 eyes without imputation. Categorical outcomes were compared using chi-square tests, with linear-by-linear association tests for ordered stage trends. Baseline comparisons used one-way ANOVA with Bonferroni post-hoc correction for continuous variables and chi-square tests for categorical variables. Logistic regression identified independent predictors of ≥ 3 ETDRS-line BCVA gain at 12 months (baseline BCVA, cyst stage, baseline CMT, age). Effect sizes were

reported as Cohen's d and partial eta-squared. The intraclass correlation coefficient (ICC) was computed using mixed-effects models to quantify within-eye correlation. Normality of continuous variables was assessed using the Shapiro-Wilk test. To identify independent predictors of 24-month functional and anatomical outcomes, multivariable linear regression models were fitted with 24-month BCVA and 24-month CMT as continuous outcomes, adjusting for baseline BCVA, baseline CMT, ESASO cyst stage, cumulative injection and visit counts, cumulative dexamethasone implant count, and age. Multicollinearity was assessed using variance inflation factor (VIF) diagnostics, with all values below 2, indicating no problematic collinearity. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 311 eyes of 257 patients (mean age 60.7 ± 10.5 years; 54% male) were analysed: 94 Stage 1 (30.2%), 99 Stage 2 (31.8%), and 118 Stage 3 (37.9%). Age and sex did not differ between groups (both $p > 0.05$). Stage 3 had significantly worse baseline BCVA (0.744 ± 0.349 logMAR [20/110]) than Stage 2 (0.570 ± 0.316 [20/75]) and Stage 1 (0.537 ± 0.348 [20/70]) (ANOVA $F=11.84$, $p < 0.0001$; Cohen's $d=0.60$ and 0.52 vs. Stages 1 and 2). CMT showed a stepwise increase: 335 ± 81 μm (Stage 1), 410 ± 93 μm (Stage 2), and 516 ± 125 μm (Stage 3) (all pairwise $p < 0.0001$). Baseline characteristics are summarised in Table 1.

BCVA Trajectories Over 24 Months

Mixed-effects modelling demonstrated significant within-stage improvements from baseline in all groups. The intraclass correlation coefficient was 0.64 for BCVA, indicating substantial within-eye correlation and confirming the appropriateness of mixed-effects modelling. Stage 3 achieved its first significant improvement at 3 months ($\Delta = -0.114$ logMAR; 95% CI -0.169 to -0.058 ; $p < 0.001$), whereas Stage 1 reached significance at 6 months ($\Delta = -0.073$ logMAR; 95% CI -0.135 to -0.010 ; $p = 0.022$). Maximum BCVA gain occurred at 18 months in Stage 3 ($\Delta = -0.276$ logMAR; 95% CI -0.332 to -0.221 ; $p < 0.001$) and Stage 2 ($\Delta = -0.142$ logMAR; $p < 0.001$), and at 24 months in Stage 1 ($\Delta = -0.137$ logMAR; $p < 0.001$). Between-stage differences in BCVA were significant at baseline ($p < 0.0001$), 3 months ($p = 0.008$), 6 months ($p = 0.020$), and 24 months ($p = 0.010$ for Stage 3 vs. Stage 1), but not at 12 or 18 months, when Stage 3 partially closed the baseline gap ($p = 0.17$ and $p = 0.40$; Figure 1A).

Between 18 and 24 months, Stage 3 showed a small but statistically significant BCVA deterioration ($\Delta = +0.061$ logMAR; 95% CI $+0.005$ to $+0.116$; $p = 0.032$; approximately one ETDRS line), whereas Stage 1 continued to improve marginally ($\Delta = -0.026$ logMAR; $p = 0.41$) and Stage 2 remained stable ($\Delta = +0.002$ logMAR; $p = 0.96$). Final 24-month BCVA was 0.400 ± 0.327 logMAR (20/50) for Stage 1, 0.430 ± 0.356 (20/54) for Stage 2, and 0.529 ± 0.451 (20/68) for Stage 3 (Table 2, Figures 1A and 3A).

Sensitivity Analysis: Treatment-Adjusted Trajectories

To evaluate whether the late-phase BCVA decline in Stage 3 could be attributed to treatment exposure rather than baseline cyst morphology, the mixed-effects model was additionally adjusted for the anti-VEGF agent at each visit and cumulative dexamethasone exposure. The 18-to-24-month deterioration in Stage 3 remained essentially unchanged ($\Delta = +0.060$ logMAR; 95% CI

+0.005 to +0.116; $p=0.034$), as did contrasts in Stages 1 ($\Delta = -0.025$ logMAR; $p=0.43$) and 2 ($\Delta = -0.001$ logMAR; $p=0.98$). These results indicate that late-phase functional decline in Stage 3 is not explained by stage-related differences in anti-VEGF agent or corticosteroid use.

CMT Trajectories Over 24 Months

CMT decreased significantly from baseline in all stages, with the largest reductions in Stage 3 (Δ at 12 months = -178 μm ; 95% CI -200 to -156 ; $p<0.001$). By 12 months, between-stage CMT differences were no longer significant (Stage 3 vs. Stage 1, $\Delta = +23$ μm ; $p=0.15$) and remained non-significant at 18 months ($\Delta = +21$ μm ; $p=0.20$). A modest rebound was observed in Stage 3 between 18 and 24 months ($\Delta = +22$ μm ; 95% CI -0.3 to $+44$; $p=0.053$), paralleling the functional decline, whereas Stages 1 and 2 remained anatomically stable ($\Delta = -3$ μm , $p=0.83$ and $\Delta = 0$ μm , $p=0.98$). At 24 months, between-stage CMT differences had re-emerged (Stage 3 vs. Stage 1, $\Delta = +45$ μm ; $p=0.005$), although CMT normalisation rates (<300 μm) did not differ significantly (52.2% vs. 49.5% vs. 40.5% ; $p=0.20$). Data are presented in Table 2 and Figure 1B.

Visual Outcome Categories

The distribution of visual outcome categories differed significantly at 12 ($p=0.012$) and 18 months ($p=0.004$). At 12 months, Stage 3 had the highest proportion of ≥ 3 -line gainers (42.4% vs. 25.3% and 21.3%). Stage 3 also had the highest ≥ 3 -line loss rate at 18 months (10.2% vs. 7.4% in both other groups). At 24 months, distributions no longer differed significantly ($p=0.21$), although Stage 3 retained the highest absolute rates of both ≥ 3 -line gain (33.9%) and ≥ 3 -line loss (11.9%). Data are shown in Figure 3B and Supplementary Table S2.

Treatment Burden and Anti-VEGF Exposure

Cumulative visit and injection counts were comparable through 12 months (all $p > 0.10$) but diverged in the second year, with Stage 3 requiring significantly more visits (11.67 ± 4.04 vs. 9.94 ± 2.85 in Stage 1 at 24 months; $p = 0.002$; partial $\eta^2 = 0.041$) and more injections (10.13 ± 2.67 vs. 9.29 ± 3.14 ; $p = 0.047$). Adjunctive dexamethasone implant requirement was significantly higher in Stage 3 across multiple measures: within-period rates in the first year (0–6 months: 26.3% vs. 11.7% and 10.1%, $p = 0.002$; 6–12 months: 32.2% vs. 13.8% and 18.2%, $p = 0.003$), a persistent linear trend in the 12–24-month period (linear-by-linear $p = 0.034$), and cumulative exposure by 24 months (46.6% vs. 30.3% and 34.0%; χ^2 $p = 0.033$; linear-by-linear $p = 0.009$). Stage 3 eyes were more than twice as likely as Stages 1 or 2 to require multiple implants (35.6% vs. 13.8% and 19.2%; χ^2 $p = 0.0005$; linear-by-linear $p < 0.0001$), the mean number of implants per eye was substantially higher (1.15 ± 1.43 vs. 0.56 ± 0.95 and 0.65 ± 1.15 ; ANOVA $p = 0.0006$), and the first implant was administered earlier in Stage 3 (mean 9.9 vs. 12.2 and 12.8 months among recipients; 56.4% within 6 months). Data are shown in Figure 2B and Supplementary Table S1.

Treatment Heterogeneity Across Cyst Stages

To characterise real-world treatment patterns, anti-VEGF agent use and treatment switching were examined by stage at each follow-up visit. All groups initiated therapy with the mandated bevacizumab loading phase. Progressive switching toward aflibercept and ranibizumab was observed across all stages with similar trajectories. By month 24, aflibercept was the predominant agent in 32% of Stage 1, 40% of Stage 2, and 41% of Stage 3 eyes ($p = 0.18$). At least one treatment switch between the 3-month and 24-month visits occurred in 60.6% of Stage 1, 61.6% of Stage 2, and 73.7% of Stage 3 eyes (chi-square $p = 0.075$). Despite Stage 3 eyes receiving more frequent

treatment switches, greater aflibercept exposure, and more dexamethasone implants, this more intensive treatment did not prevent the late-phase BCVA decline, consistent with the unchanged effect estimate in the treatment-adjusted sensitivity analysis. Data are shown in Figure 2A.

Independent Predictors of 24-Month Outcomes

Multivariable linear regression identified baseline BCVA as the strongest independent predictor of 24-month BCVA ($B = +0.475$ logMAR per unit; 95% CI $+0.356$ to $+0.594$; $p < 0.001$), with cumulative dexamethasone implant count as a secondary independent predictor ($B = +0.048$ logMAR per implant; 95% CI $+0.013$ to $+0.082$; $p = 0.007$); ESASO cyst stage was not independently associated with 24-month BCVA ($p = 0.52$), consistent with its collinearity with baseline BCVA. In contrast, for 24-month CMT, both baseline CMT ($B = +0.539$ μm per baseline μm ; $p < 0.001$) and ESASO cyst stage remained independent predictors ($B = -32.3$ μm per stage; 95% CI -54.1 to -10.5 ; $p = 0.004$), indicating that eyes with more advanced cystoid morphology at baseline achieved greater absolute CMT reduction by 24 months, independent of baseline thickness. Anti-VEGF injection count, visit count, and age were not independent predictors in either model. Regression results are presented in Supplementary Table S4.

Predictors of ≥ 3 -Line Gain

In logistic regression ($n = 311$, events = 95), baseline BCVA was the strongest independent predictor of ≥ 3 -line BCVA gain at 12 months (OR 34.1 per 1-logMAR unit; 95% CI 14.0–83.2; $p < 0.0001$), reflecting the well-established floor effect. ESASO stage showed a trend toward independent significance (OR 1.49; 95% CI 0.97–2.27; $p = 0.068$), attenuated by collinearity with baseline

BCVA (Spearman $\rho=0.46$, $p<0.0001$). Univariate analysis confirmed a significant stage–gain association ($\rho=0.195$, $p=0.0006$). Regression results are presented in Supplementary Table S3.

DISCUSSION

This 10-centre, 24-month real-world cohort study provides five clinically relevant observations on the relationship between baseline ESASO cyst stage and anti-VEGF outcomes in diabetic CME. First, Stage 3 eyes enter treatment with significantly worse baseline vision (Cohen's $d \approx 0.60$ vs. Stage 1) and approximately 55% greater CMT, a disadvantage that persists at 24 months despite a higher treatment burden, consistent with known associations between Müller cell dysfunction, advanced cystoid morphology, outer retinal disruption, and photoreceptor loss.⁸⁻¹²

Second, despite this baseline disadvantage, Stage 3 achieved greater proportional gains at 12 and 18 months, with approximately twice the rate of ≥ 3 -line gain as Stage 1 (42.4% vs. 21.3%). This

floor-effect phenomenon reflects greater improvement potential from a worse baseline and parallels findings from randomised trials.^{13, 14}

Third, mixed-effects modelling identified a small but statistically significant within-stage BCVA deterioration in Stage 3 between 18 and 24 months ($\Delta = +0.061$ logMAR; 95% CI +0.005 to +0.116; $p=0.032$), approximately one ETDRS line, whereas Stages 1 and 2 remained stable. Importantly, this late-phase decline persisted essentially unchanged after adjustment for anti-VEGF agent and cumulative dexamethasone exposure ($\Delta = +0.060$ logMAR; $p=0.034$), indicating it was not attributable to stage-related differences in treatment selection. A modest parallel CMT rebound was observed in Stage 3 over the same interval (+22 μm ; $p=0.053$), suggesting subclinical anatomical re-accumulation rather than fully resolved oedema. This pattern is consistent with the Protocol T 5-year extension study, in which visual gains attenuated between years 2 and 5 despite stable central subfield thickness.¹⁵ Our findings are therefore hypothesis-generating: they identify advanced cystoid morphology as a candidate at-risk subgroup for the late-phase attrition of visual gains previously described only at the cohort level, requiring prospective confirmation.

The mechanisms underlying this decline are likely multifactorial: progressive Müller cell failure from sustained cyst-mediated mechanical stress may drive delayed functional decline even after anatomical resolution,^{9–12} compounded by cumulative photoreceptor attrition in the outer nuclear layer¹⁵ and persistent low-grade neuroinflammation sustaining vascular hyperpermeability—consistent with the higher dexamethasone requirement in Stage 3 and with prior inflammatory OCT biomarker reports.^{16–19}

Fourth, treatment heterogeneity was systematically characterised to address whether stage-related outcome differences might reflect treatment pathway rather than baseline morphology. Progressive

switching toward aflibercept and ranibizumab followed similar trajectories across stages, and Stage 3 eyes underwent treatment switching more often (74% vs. 61% and 62%) and received more frequent dexamethasone implants, indicating intensified rather than insufficient treatment; the timing and clinical implications of anti-VEGF switching in refractory DME have been examined in detail elsewhere in our group.²⁰

Adjunctive dexamethasone use showed a clear stage-dependent gradient: Stage 3 eyes were more than twice as likely to require multiple implants (35.6% vs. 13.8% and 19.2%; $p=0.0005$, linear-by-linear $p<0.0001$), and the first implant was administered earlier (mean 9.9 vs. 12.2 and 12.8 months). This pattern reinforces that higher implant use reflects the more refractory nature of advanced cystoid morphology rather than treatment preference.²¹ The mean 24-month injection count of 10.1 ± 2.7 in Stage 3 is consistent with real-world patterns.²² The IRIS Registry reported only 3.9 injections in the first year of anti-VEGF therapy for DME,²³ substantially fewer than trial protocols—a relative undertreatment that, combined with the disproportionate dexamethasone requirement, underscores the need for closer late-phase monitoring and individualised adjunctive strategies in advanced cystoid DME.²⁴

Dexamethasone implants carry well-recognised risks including cataract progression and ocular hypertension, and our findings should not be interpreted as advocating broader corticosteroid use, but as identifying advanced cystoid morphology as a signal that may justify earlier adjunctive therapy when anti-VEGF monotherapy fails.²⁵ Treatment decisions must remain individualised, balanced against newer agents (e.g. faricimab, high-dose 8-mg aflibercept) and treat-and-extend regimens not widely available in the present cohort.

In logistic regression (Supplementary Table S3), ESASO stage's non-independent effect (OR 1.49; $p=0.068$) reflects collinearity with baseline BCVA ($p=0.46$) rather than absence of prognostic value; univariable analysis confirmed a significant association ($p=0.195$, $p=0.0006$).

Multivariable linear regression models corroborated and extended these findings by demonstrating a structural-functional discordance in Stage 3 eyes. ESASO cyst stage remained an independent predictor of 24-month CMT reduction ($B = -32.3 \mu\text{m}$ per stage; $p=0.004$), indicating that advanced cystoid morphology retains anatomical treatment responsiveness even after adjustment for baseline thickness. However, ESASO stage was not independently associated with 24-month BCVA when baseline BCVA was included ($p=0.52$), and higher cumulative dexamethasone exposure was independently associated with worse 24-month BCVA ($B = +0.048 \text{ logMAR}$ per implant; $p=0.007$), likely reflecting reverse causation whereby more refractory eyes required more intensive adjunctive therapy. Together, these findings suggest that advanced cystoid morphology signals a functional vulnerability that persists despite favourable anatomical response — an observation that complements the long-term real-world outcomes previously reported by the BOPHORUS-DME Study Group.²⁶

Limitations inherent to the retrospective multicentre design include heterogeneity of anti-VEGF agents with progressive treatment switching and potential for selection and information bias. Similar CMT normalisation rates across groups ($p=0.20$) suggest that functional divergence at 24 months is not fully explained by gross anatomical differences, although the modest CMT rebound in Stage 3 indicates subclinical fluid re-accumulation may contribute. Baseline DRIL prevalence increased across stages (5.3%, 12.1%, 24.6%); independent contributions of DRIL and ellipsoid

zone integrity warrant dedicated analysis. Newer agents and treat-and-extend regimens were not widely used during the study period, limiting generalisability to contemporary paradigms. Finally, formal inter-grader agreement statistics could not be computed retrospectively because per-reader scores were not preserved once consensus was reached; the ESASO system has demonstrated good inter-rater reproducibility in its original validation cohort,⁴ and prospective studies should incorporate per-reader staging from the outset.

CONCLUSIONS

In this 24-month real-world cohort of treatment-naïve diabetic CME, the baseline ESASO cyst stage was associated with the trajectory of visual recovery under anti-VEGF therapy. Advanced (Stage 3) eyes achieved substantial mid-term gains but exhibited a small, statistically significant late-phase BCVA decline between 18 and 24 months that was not attributable to differences in anti-VEGF agent or adjunctive corticosteroid use. ESASO cyst staging may serve as a supportive prognostic marker, alongside baseline BCVA, for identifying eyes that may warrant closer late-phase monitoring and individualised treatment decisions. These observations are hypothesis-generating and warrant prospective validation, particularly in the context of newer-generation anti-VEGF agents and treatment-and-extension regimens.

Author Contributions

A.K., A.O., and V.L.K. were responsible for study conceptualisation, methodology, formal data analysis, and drafting of the original manuscript. A.K. coordinated the multicentre data integration, statistical modelling, figure preparation, and manuscript revision. M.A., M.E., I.K., N.S., A.C., G.K., D.Y., E.O.T., S.E., S.C.H., M.Ka., E.O., S.A.O., S.T.D., T.U., M.E.K., M.Oz., B.D., I.U.O., and M.H. contributed to patient identification, clinical data acquisition, OCT image grading, and validation of records at their respective centres. All authors contributed to interpretation of the findings, critical review of the manuscript for important intellectual content, and final approval of the version submitted for publication. All authors agree to be accountable for all aspects of the work and have read and approved the final manuscript.

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Competing Interests

The authors declare no competing interests.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data are not publicly available due to privacy restrictions of the participating institutions.

427 **Ethics Approval and Consent to Participate**

428 This study was approved by the Kocaeli University Faculty of Medicine Ethics Committee
429 (decision no: KÜ GOKAEK-2025/06/18; date: 13.03.2025; project: 2025/115) and was
430 conducted in accordance with the Declaration of Helsinki. Written informed consent was
431 obtained from all the participants.

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REFERENCES

1. Yau JW, Rogers SL, Kawasaki R, et al. Global prevalence and major risk factors of diabetic retinopathy. *Diabetes Care* 2012;35:556-564.
2. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic macular edema: pathogenesis and treatment. *Surv Ophthalmol* 2009;54:1-32.
3. Daruich A, Matet A, Moulin A, et al. Mechanisms of macular edema: beyond the surface. *Prog Retin Eye Res* 2018;63:20-68.
4. Panozzo G, Cicinelli MV, Augustin AJ, et al. An OCT-based grading of diabetic maculopathy proposed by an international expert panel: the ESASO classification. *Eur J Ophthalmol* 2020;30:8-18.
5. Nguyen QD, Brown DM, Marcus DM, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology* 2012;119:789-801.
6. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med* 2015;372:1193-1203.
7. Tokuc EO, Karabas VL, Sevik MO, et al. Efficacy of ranibizumab and aflibercept on reducing maximum diameter of largest cyst in diabetic cystoid macular edema: MARMASIA study group. *Eur J Ophthalmol* 2024. doi:10.1177/11206721241280737.
8. Bringmann A, Wiedemann P. Muller glial cells in retinal disease. *Ophthalmologica* 2012;227:1-19.
9. Ceklic L, Huf W, Ebner A, Zinkernagel MS. The impact of ganglion cell layer cysts in diabetic macular oedema treated with anti-VEGF. *Acta Ophthalmol* 2019;97:e1041-e1047.
10. Sophie R, Lu N, Campochiaro PA. Predictors of functional and anatomic outcomes in patients with diabetic macular edema treated with ranibizumab. *Ophthalmology* 2015;122:1395-1401.

- 459 11. Khoramnia R, Nguyen QD, Kertes PJ, Sararols Ramsay L, Vujosevic S, Anderesi M, Igwe
460 F, Eter N. Exploring the role of retinal fluid as a biomarker for the management of
461 diabetic macular oedema. *Eye (Lond)*. 2024 Jan;38(1):54-60.
- 462 12. Nakao S, Kusuhara S, Murakami T. Anti-VEGF therapy for the long-term management of
463 diabetic macular edema: a treat-to-target strategy based on macular morphology. *Graefes*
464 *Arch Clin Exp Ophthalmol* 2024;262(12):3749-3759.
- 465 13. Bressler SB, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, Wells JA 3rd; Diabetic Retinopathy
466 Clinical Research Network. Factors associated with changes in visual acuity and central
467 subfield thickness at 1 year after treatment for diabetic macular edema with ranibizumab.
468 *Arch Ophthalmol* 2012;130(9):1153-1161.
- 469 14. Bressler NM, Beaulieu WT, Glassman AR, et al. Persistent macular thickening following
470 intravitreal aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular
471 edema. *JAMA Ophthalmol* 2018;136:257-269.
- 472 15. Glassman AR, Wells JA 3rd, Josic K, Maguire MG, Antoszyk AN, Baker C, et al; DRCR Retina
473 Network. Five-year outcomes after initial aflibercept, bevacizumab, or ranibizumab treatment
474 for diabetic macular edema (Protocol T extension study). *Ophthalmology* 2020;127(9):1201-
475 1210.
- 476 16. Vujosevic S, Bini S, Midena G, Berton M, Pilotto E, Midena E. Hyperreflective intraretinal spots
477 in diabetics without and with nonproliferative diabetic retinopathy: an in vivo study using
478 spectral domain OCT. *J Diabetes Res* 2013;2013:491835.
- 479 17. Framme C, Schweizer P, Imesch M, Wolf S, Wolf-Schnurrbusch U. Behavior of SD-OCT-detected
480 hyperreflective foci in the retina of anti-VEGF-treated patients with diabetic macular edema.
481 *Invest Ophthalmol Vis Sci* 2012;53(9):5814-5818.

18. Bolz M, Schmidt-Erfurth U, Deak G, Mylonas G, Kriechbaum K, Scholda C; Diabetic Retinopathy Research Group Vienna. Optical coherence tomographic hyperreflective foci: a morphologic sign of lipid extravasation in diabetic macular edema. *Ophthalmology* 2009;116(5):914-920.
19. Vujosevic S, Torresin T, Bini S, Convento E, Pilotto E, Parrozzani R, et al. Imaging retinal inflammatory biomarkers after intravitreal steroid and anti-VEGF treatment in diabetic macular oedema. *Acta Ophthalmol* 2017;95(5):464-471.
20. Karataş G, Çakır A, Yıldız D, et al. Cost-effectiveness analysis of early versus late switching in treatment-naïve patients with refractory diabetic macular oedema in the Turkish population: real-world data from the BOSPHORUS-DME study group, report number 5. *Clin Exp Optom* 2026;1-10.
21. Zur D, Iglicki M, Busch C, Invernizzi A, Mariussi M, Loewenstein A, et al; International Retina Group. OCT biomarkers as functional outcome predictors in diabetic macular edema treated with dexamethasone implant. *Ophthalmology* 2018;125(2):267-275.
22. Ciulla TA, Bracha P, Pollack J, Williams DF. Real-world outcomes of anti-vascular endothelial growth factor therapy in diabetic macular edema in the United States. *Ophthalmol Retina* 2018;2(12):1179-1187.
23. Kuo BL, Tabano D, Garmo V, Kim E, Leng T, Hatfield M, et al. Long-term treatment patterns for diabetic macular edema: up to 6-year follow-up in the IRIS® Registry. *Ophthalmol Retina* 2024;8(11):1074-1082.
24. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica* 2017;237(4):185-222.

505 25. Boyer DS, Yoon YH, Belfort R Jr, Bandello F, Maturi RK, Augustin AJ, et al;
506 Ozurdex MEAD Study Group. Three-year, randomized, sham-controlled trial of
507 dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology
508 2014;121(10):1904-1914.

509 26. Özal E, Özkaya A, Arıcı M, et al . Intravitreal Anti-Vascular Endothelial Growth
510 Factor Therapy for Diabetic Macular Edema in Türkiye: 48-Month Data, BOSPHORUS-DME
511 Study Group Report No. 1. Turk J Ophthalmol. 2026 Feb 18;56(1):31-40.

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Table 1. Baseline Characteristics by ESASO Cyst Stage

Parameter	Stage 1 (n=94)	Stage 2 (n=99)	Stage 3 (n=118)	P
Age, years (mean ± SD)	62.1 ± 11.1	61.9 ± 9.8	58.6 ± 10.4	0.07
Male, n (%)	42 (44.7%)	49 (49.5%)	52 (44.1%)	0.64
BCVA, logMAR (mean ± SD)	0.54 ± 0.35	0.57 ± 0.32	0.74 ± 0.35	<0.0001*
CMT, µm (mean ± SD)	335 ± 81	410 ± 93	516 ± 125	<0.0001†

*Post-hoc (Bonferroni): Stage 3 vs. Stage 1, $p<0.001$; Stage 3 vs. Stage 2, $p<0.001$; Stage 1 vs. Stage 2, $p=1.0$.

†All CMT pairwise comparisons $p<0.0001$ (Bonferroni). BCVA, best-corrected visual acuity; CMT, central macular thickness; SD, standard deviation.

537 **Table 2. BCVA and CMT Trajectories Over 24 Months by ESASO Cyst Stage**

Stage	Timepoint	n	BCVA, logMAR (95% CI)	P vs. baseline	CMT, μm (95% CI)	P vs. baseline
Stage 1	Baseline	94	0.537 (0.463–0.610)	—	335 (312–359)	—
	3 mo	94	0.497 (0.424–0.570)	0.208	320 (297–343)	0.229
	6 mo	94	0.464 (0.391–0.537)	0.022	309 (285–332)	0.035
	12 mo	94	0.430 (0.356–0.503)	<0.001	315 (292–339)	0.117
	18 mo	94	0.426 (0.353–0.500)	<0.001	313 (290–337)	0.081
	24 mo	94	0.400 (0.327–0.473)	<0.001	311 (287–334)	0.051
Stage 2	Baseline	99	0.570 (0.499–0.641)	—	410 (387–433)	—
	3 mo	99	0.500 (0.429–0.572)	0.024	375 (352–398)	0.005
	6 mo	99	0.494 (0.422–0.565)	0.014	359 (336–382)	<0.001
	12 mo	99	0.443 (0.372–0.515)	<0.001	342 (319–364)	<0.001
	18 mo	99	0.428 (0.357–0.500)	<0.001	338 (316–361)	<0.001
	24 mo	99	0.430 (0.358–0.501)	<0.001	339 (316–362)	<0.001
Stage 3	Baseline	118	0.744 (0.679–0.810)	—	516 (496–537)	—
	3 mo	118	0.631 (0.565–0.696)	<0.001	400 (379–421)	<0.001
	6 mo	118	0.581 (0.515–0.646)	<0.001	389 (368–410)	<0.001
	12 mo	118	0.498 (0.433–0.564)	<0.001	338 (317–359)	<0.001
	18 mo	118	0.468 (0.403–0.534)	<0.001	334 (313–355)	<0.001

Stage	Timepoint	n	BCVA, logMAR (95% CI)	P vs. baseline	CMT, μm (95% CI)	P vs. baseline
	24 mo	118	0.529 (0.464–0.595)	<0.001	356 (335–377)	<0.001

Values are mixed-effects model–estimated marginal means with 95% confidence intervals. P values are from Wald tests of within-stage change from baseline.

Between-stage ANOVA p values: BCVA — baseline $p<0.0001$, 3 mo $p=0.012$, 6 mo $p=0.054$, 12 mo $p=0.28$, 18 mo $p=0.63$, 24 mo $p=0.038$; CMT — baseline $p<0.0001$, 3 mo $p<0.001$, 6 mo $p<0.001$, 12 mo $p=0.16$, 18 mo $p=0.22$, 24 mo $p=0.058$.

BCVA, best-corrected visual acuity; CI, confidence interval; CMT, central macular thickness.

555 Supplementary Material

556 **Supplementary Table S1. Treatment Burden and Dexamethasone Exposure by ESASO Cyst Stage**

Parameter	Stage 1 (n=94)	Stage 2 (n=99)	Stage 3 (n=118)	P
<i>Cumulative clinic visits (mean ± SD)</i>				
6 months	3.56 ± 1.09	3.64 ± 1.20	3.77 ± 1.34	0.45
12 months	5.78 ± 1.77	6.02 ± 2.12	6.39 ± 2.47	0.12
18 months	7.80 ± 2.23	8.19 ± 2.63	9.07 ± 3.20	0.003
24 months	9.94 ± 2.85	10.69 ± 3.34	11.67 ± 4.04	0.002
<i>Cumulative intravitreal injections (mean ± SD)</i>				
6 months	4.29 ± 0.89	4.31 ± 0.89	4.46 ± 1.07	0.37
12 months	6.11 ± 1.69	6.04 ± 1.53	6.45 ± 1.51	0.12
18 months	7.81 ± 2.41	7.83 ± 1.91	8.45 ± 2.15	0.045
24 months	9.29 ± 3.14	9.38 ± 2.39	10.13 ± 2.67	0.047
<i>Dexamethasone implant administration by period, n (%)</i>				
0–6 months	11 (11.7%)	10 (10.1%)	31 (26.3%)	0.002
6–12 months	13 (13.8%)	18 (18.2%)	38 (32.2%)	0.003
12–24 months	20 (21.3%)	24 (24.2%)	40 (33.9%)	0.091**
Cumulative by 24 months	32 (34.0%)	30 (30.3%)	55 (46.6%)	0.033*
<i>Burden of dexamethasone use (cumulative over 24 months)</i>				
≥2 DEX implants, n (%)	13 (13.8%)	19 (19.2%)	42 (35.6%)	<0.001***
Mean number of DEX implants per eye (± SD)	0.56 ± 0.95	0.65 ± 1.15	1.15 ± 1.43	0.0006†

Parameter	Stage 1 (n=94)	Stage 2 (n=99)	Stage 3 (n=118)	P
First DEX within 6 months among recipients, n/n (%)	11/32 (34.4%)	10/30 (33.3%)	31/55 (56.4%)	0.064

*Cumulative DEX by 24 months: linear-by-linear association across ordered stages, $p=0.009$.

**12–24-month period: χ^2 $p=0.091$; linear-by-linear association across ordered stages, $p=0.034$.

*** ≥ 2 DEX implants: linear-by-linear association across ordered stages, $p<0.0001$.

†Mean implant count: one-way ANOVA ($F=7.58$); Kruskal–Wallis $p=0.005$ confirms the result under non-parametric assumptions.

P values from one-way ANOVA (continuous) or chi-square (categorical). DEX, dexamethasone; SD, standard deviation.

Supplementary Table S2. Visual and Anatomical Outcomes by ESASO Cyst Stage

Outcome	Stage 1 (n=94)	Stage 2 (n=99)	Stage 3 (n=118)	P
Visual outcomes at 12 months, n (%)				
≥ 3 ETDRS-line gain	20 (21.3%)	25 (25.3%)	50 (42.4%)	0.012†
Stable (<3-line change)	67 (71.3%)	67 (67.7%)	60 (50.8%)	
≥ 3 -line loss	7 (7.4%)	7 (7.1%)	8 (6.8%)	
Visual outcomes at 24 months, n (%)				
≥ 3 -line gain	23 (24.5%)	26 (26.3%)	40 (33.9%)	0.21
Stable	64 (68.1%)	64 (64.6%)	64 (54.2%)	
≥ 3 -line loss	7 (7.4%)	9 (9.1%)	14 (11.9%)	
Anatomical outcome				

Outcome	Stage 1 (n=94)	Stage 2 (n=99)	Stage 3 (n=118)	P
CMT normalisation (<300 µm) at 24 months, n (%)	48 (52.2%)	49 (49.5%)	47 (40.5%)	0.20

#Overall distribution chi-square at 12 months: $p=0.012$; at 18 months (not shown): $p=0.004$.

P values from chi-square test. CMT, central macular thickness.

Supplementary Table S3. Logistic Regression — Predictors of ≥ 3 ETDRS-Line BCVA Gain at 12 Months

Variable	OR	95% CI	P	Spearman ρ
ESASO Cyst Stage	1.49	0.97–2.27	0.068	0.195*
Baseline BCVA (logMAR)	34.1	14.0–83.2	<0.0001	0.525*
Baseline CMT (µm)	0.999	0.996–1.001	0.31	0.164*
Age (years)	1.01	0.99–1.04	0.37	—

N=311; events=95. * $p<0.001$ for all Spearman correlations.

ESASO stage $p=0.068$ in the multivariable model reflects collinearity with baseline BCVA (Spearman $\rho=0.46$, $p<0.0001$); univariable association significant ($p=0.195$, $p=0.0006$).

OR for baseline BCVA expressed per 1-logMAR unit change; the magnitude reflects the floor effect. BCVA, best-corrected visual acuity; CI, confidence interval; CMT, central macular thickness; OR, odds ratio.

Supplementary Table S4. Multivariable Linear Regression for 24-Month Functional and Anatomical Outcomes

Variable	B	95% CI	P	VIF
Model 1: 24-month BCVA (logMAR) — $F(7,303)=13.76$, $p<0.001$, $R^2=0.24$				
Baseline BCVA (logMAR)	+0.475	+0.356 to +0.594	<0.001	1.16
Baseline CMT (μm)	-0.0001	-0.0005 to +0.0003	0.58	1.16
ESASO cyst stage	+0.020	-0.040 to +0.080	0.52	1.53
Cumulative injections	-0.008	-0.022 to +0.007	0.30	1.10
Cumulative visits	-0.005	-0.017 to +0.007	0.42	1.21
DEX implant count	+0.048	+0.013 to +0.082	0.007	1.65
Age (years)	+0.001	-0.003 to +0.004	0.71	1.07
Model 2: 24-month CMT (μm) — $F(7,299)=11.45$, $p<0.001$, $R^2=0.21$				
Baseline CMT (μm)	+0.539	+0.399 to +0.679	<0.001	1.16
Baseline BCVA (logMAR)	+4.93	-38.11 to +47.98	0.82	1.16
ESASO cyst stage	-32.32	-54.12 to -10.51	0.004	1.53
Cumulative injections	+0.10	-5.27 to +5.47	0.97	1.10
Cumulative visits	+3.33	-1.03 to +7.69	0.13	1.21
DEX implant count	+8.79	-3.66 to +21.24	0.17	1.65
Age (years)	+0.31	-1.07 to +1.68	0.66	1.07

Models fitted using ordinary least squares on the full analytic dataset (BCVA model N=311; CMT model N=307). Regression coefficients (B) are unstandardised.

588 *Multicollinearity assessed using variance inflation factors (VIF) after centring continuous predictors; all VIF values <2, indicating no problematic*
589 *collinearity.*

590 *B, unstandardised regression coefficient; BCVA, best-corrected visual acuity; CI, confidence interval; CMT, central macular thickness; DEX,*
591 *dexamethasone; VIF, variance inflation factor.*

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Figure Legends

Figure 1. Best-corrected visual acuity (BCVA, logMAR; Panel A) and central macular thickness (CMT, μm ; Panel B) trajectories over 24 months by ESASO cyst stage. Values are mixed-effects model–estimated marginal means with 95% confidence intervals (error bars and shaded ribbons). In Panel A, the y-axis is inverted so that lower values (better vision) appear higher on the plot. BCVA, best-corrected visual acuity; CMT, central macular thickness.

Figure 2. Cyst-stage effects on late-phase BCVA and treatment exposure. **(A)** Forest plot of within-stage BCVA change between 18 and 24 months from linear mixed-effects models, shown as unadjusted estimates (filled squares) and treatment-adjusted estimates (open diamonds) accounting for anti-VEGF agent administered at each visit and cumulative dexamethasone implant exposure. Stage 3 eyes showed a statistically significant late-phase BCVA decline that persisted after adjustment for treatment exposure, indicating that the deterioration is not attributable to stage-related differences in treatment selection. **(B)** Proportion of eyes receiving adjunctive dexamethasone (DEX) intravitreal implant during each follow-up period and cumulatively by 24 months. Stage 3 eyes received significantly more DEX implants in the first year and showed a significant linear trend across ordered stages (linear-by-linear association $p=0.009$).

Figure 3. Late-phase BCVA trajectory and visual outcome distribution by ESASO cyst stage. **(A)** Zoomed-in BCVA trajectory between 12 and 24 months, presented as mixed-effects model–estimated marginal means with 95% confidence interval ribbons. Stage 3 eyes showed a statistically significant within-stage BCVA deterioration between 18 and 24 months ($\Delta = +0.061$ logMAR; 95% CI +0.005 to +0.116; $p=0.032$), corresponding to approximately one ETDRS line.

628 The shaded red band marks the deterioration window. **(B)** Visual outcome distribution (≥ 3
629 ETDRS-line gain, stable, ≥ 3 -line loss) at 12 and 24 months by ESASO cyst stage. Between-
630 group distribution differed significantly at 12 months (χ^2 $p=0.012$), driven by the substantially
631 higher proportion of ≥ 3 -line gainers in Stage 3 (42.4%). At 24 months, the overall distribution no
632 longer differed significantly between stages (χ^2 $p=0.21$).

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Figures

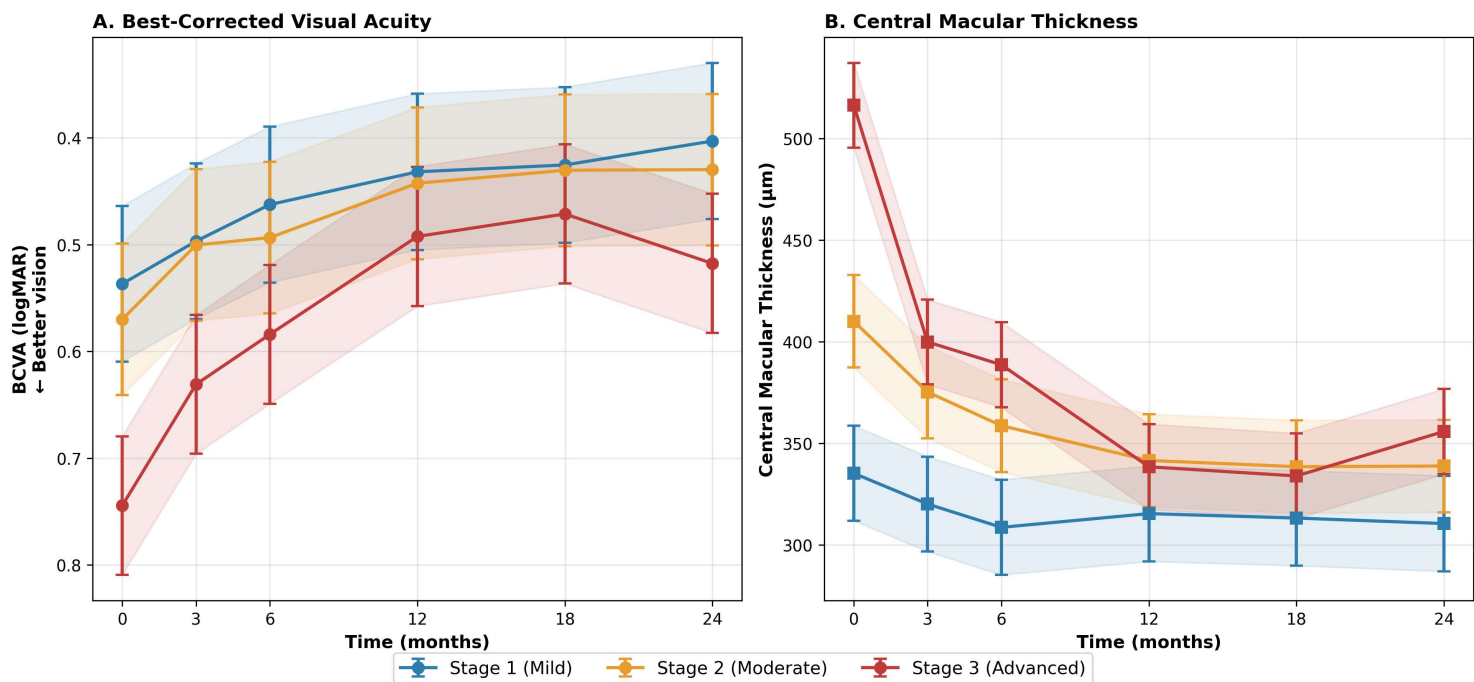


Figure 1

Best-corrected visual acuity (BCVA, logMAR; Panel A) and central macular thickness (CMT, μm ; Panel B) trajectories over 24 months by ESASO cyst stage. Values are mixed-effects model–estimated marginal means with 95% confidence intervals (error bars and shaded ribbons). In Panel A, the y-axis is inverted so that lower values (better vision) appear higher on the plot. BCVA, best-corrected visual acuity; CMT, central macular thickness.

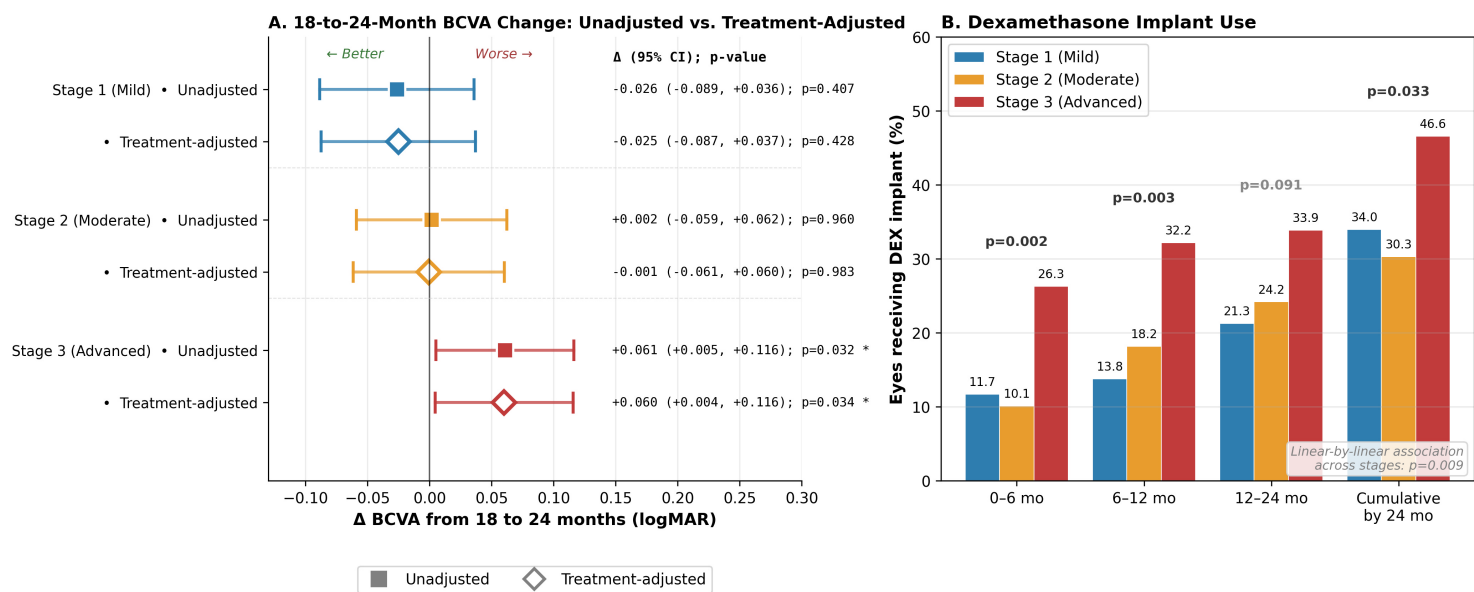


Figure 2

Cyst-stage effects on late-phase BCVA and treatment exposure. (A) Forest plot of within-stage BCVA change between 18 and 24 months from linear mixed-effects models, shown as unadjusted estimates (filled squares) and treatment-adjusted estimates (open diamonds) accounting for anti-VEGF agent administered at each visit and cumulative dexamethasone implant exposure. Stage 3 eyes showed a statistically significant late-phase BCVA decline that persisted after adjustment for treatment exposure, indicating that the deterioration is not attributable to stage-related differences in treatment selection. (B) Proportion of eyes receiving adjunctive dexamethasone (DEX) intravitreal implant during each follow-up period and cumulatively by 24 months. Stage 3 eyes received significantly more DEX implants in the first year and showed a significant linear trend across ordered stages (linear-by-linear association $p=0.009$).

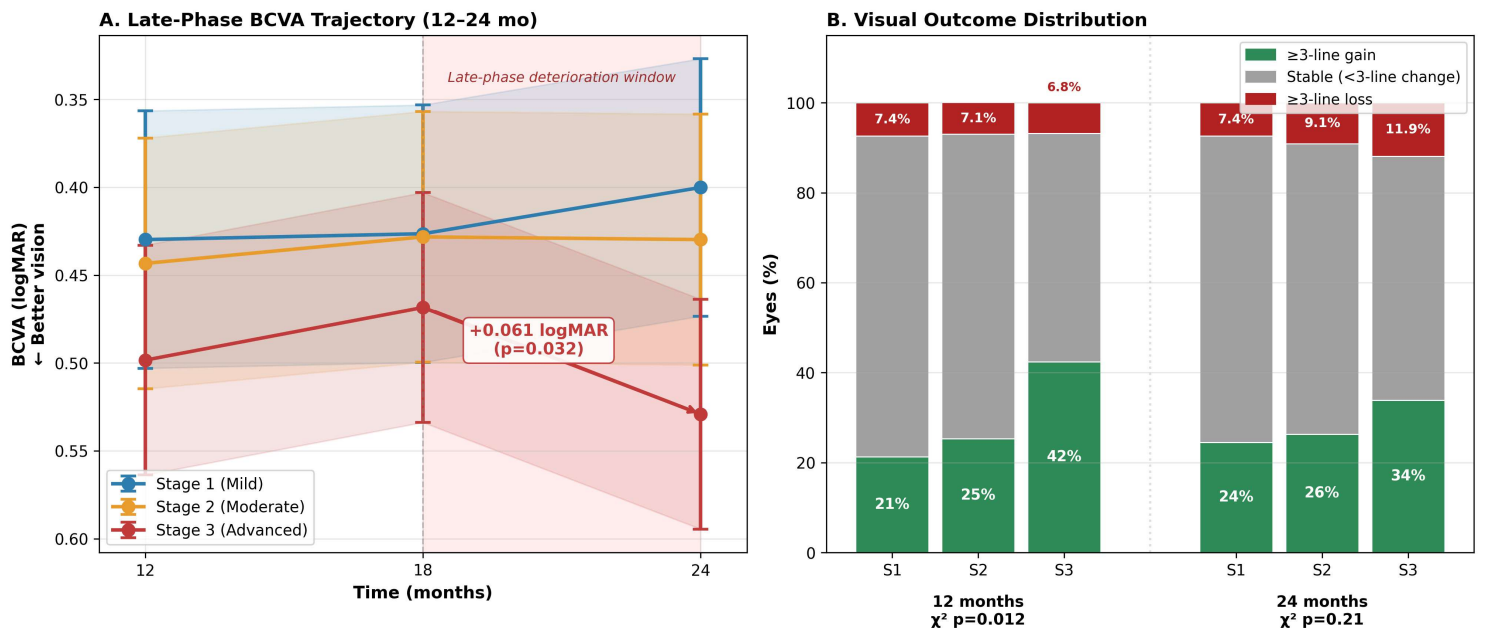


Figure 3

Best-corrected visual acuity (BCVA, logMAR; Panel A) and central macular thickness (CMT, μm ; Panel B) trajectories over 24 months by ESASO cyst stage. Values are mixed-effects model–estimated marginal means with 95% confidence intervals (error bars and shaded ribbons). In Panel A, the y-axis is inverted so that lower values (better vision) appear higher on the plot. BCVA, best-corrected visual acuity; CMT, central macular thickness.

Supplementary Files

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