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ORIGINAL ARTICLE

Three versus six cycles of platinum-based chemotherapy followed by avelumab maintenance as first-line treatment for advanced urothelial cancer: the phase II DISCUS trial☆

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Available online 17 October 2025

Background: Six cycles of platinum-based chemotherapy followed by avelumab continues to be used in some circumstances in advanced/metastatic urothelial cancer (mUC). To investigate whether shorter chemotherapy duration improves quality of life (QoL) without worsening efficacy, this study compared three versus six cycles followed by avelumab.

Patients and methods: This randomized phase II trial compared three versus six cycles (3C arm versus 6C arm) of chemotherapy followed by avelumab in patients receiving first-line treatment for mUC. This trial had co-primary endpoints of patient-reported outcomes (PROs), defined as change from baseline to cycle 6 on the global health status/QoL score, and superior overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate, and safety. Here, we report the final PRO analysis and interim OS.

Results: A total of 267 patients were randomized (133 to 3C arm, 134 to 6C arm). Forty-two percent received gemcitabine/cisplatin and 58% gemcitabine/carboplatin. Seventy-eight percent and 40% of patients completed three and six cycles as allocated. Seventy-four percent of patients received avelumab in the 3C arm, versus 56% in the 6C arm. The mean QoL change between baseline and cycle 6 was 0 [95% confidence interval (CI) −5.9 to 5.2] in the 3C arm versus −8.5 (95% CI −14.1 to −2.9) in the 6C arm, with a significant difference favouring 3C (+8.5 points, 95% CI 0.7-16.3, $P = 0.016$). Improvement in PRO scores was observed in 41% (3C arm) versus 24% (6C arm) of patients. OS was not significant (18.9 months in both arms [hazard ratio (HR) 1.15, 95% CI 0.72-1.86, $P = 0.56$]. Median PFS was 8.0 months (95% CI 6.7-11.9 months) in the 3C arm versus 9.0 months (95% CI 6.9-12.7 months) in the 6C arm (HR 1.05, 95% CI 0.73-1.53). Median grade 3-4 treatment-related adverse events occurred in 11.9% (3C arm) versus 15.7% (6C arm).

Conclusions: Three cycles of chemotherapy followed by maintenance avelumab is associated with better QoL than six cycles. Randomized trials with patient-focused outcomes exploring shorter duration of therapy are feasible (NCT06892860).

Key words: cisplatin, carboplatin, avelumab, advanced urothelial cancer, maintenance, quality of life

INTRODUCTION

Advanced or metastatic urothelial cancer (mUC) remains a lethal disease for most patients.[1] Over the last few years, the first-line treatment landscape has changed dramatically, with major improvements not only in overall survival (OS) but also in the depth and durability of responses.[2]

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☆Note: This study was presented at the ESMO Congress 2025, 17-21 October 2025, Berlin, Germany.

Enfortumab vedotin plus pembrolizumab (EVP) is now the recommended standard of care in international guidelines.[3,4]

However, EVP is not yet universally available, and still today platinum-based chemotherapy is utilized in many countries. Currently, six cycles is considered optimal for historical reasons.[5] A significant number of patients have toxicity or progressive disease during the latter part of the chemotherapy treatment. Many miss an opportunity to start maintenance immune checkpoint inhibitor therapy.[6,7] Also, it is likely that this extended period of chemotherapy is associated with detrimental effects on quality of life (QoL) due to toxicity. This is concerning, particularly if the efficacy benefit of the extended treatment is uncertain. Therefore, we hypothesized that three rather than six cycles of platinum-based chemotherapy followed by maintenance avelumab will be better tolerated and potentially more efficacious.

The pivotal JAVELIN Bladder 100 trial measured OS only from the start of maintenance, excluding those who progressed on chemotherapy. As a result, the true survival benefit across the entire first-line population is less clear. A recent disease-modelling study estimated that while median OS reached 23.8 months in the JAVELIN trial, it is 15.9 months when measured from the initiation of first-line chemotherapy in an unselected population.[8] Prospective studies starting from induction of chemotherapy rather than from maintenance avelumab are needed to define the OS of the maintenance avelumab approach.

The DISCUS trial was designed to evaluate whether limiting induction to three instead of six cycles of platinum-based chemotherapy before maintenance avelumab could improve efficacy and QoL.

PATIENTS AND METHODS

Trial oversight

DISCUS (NCT06892860) is an ongoing, international, investigator-initiated study with Queen Mary University of London as the sponsor. It was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The design and conduct of the study was reviewed and approved by a trial steering committee with data monitoring committee responsibilities. The protocol was approved by the institutional review board/ethics committee at each site, and all patients provided written informed consent. All authors participated and approved the manuscript.

Patients

Patients with histologically confirmed, radiologically measurable, advanced or mUC, including those with a urothelial component in mixed histologies, who had not previously received systemic therapy for advanced disease were potentially eligible. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of two or less and adequate organ function. Patients were eligible regardless of whether they received prior perioperative treatment. Contraindication for platinum-based chemotherapy or avelumab and the presence of other malignancies were key exclusion criteria. Patients were required to have a creatine clearance >30 ml/min and cisplatin eligibility according to the Galsky criteria.

Trial design and treatment

This was an international (UK, France, Spain), open-label, randomized, phase II study with investigator-assessed progression-free survival (PFS) and 10-weekly cross-sectional imaging. Stratification factors included visceral metastasis and cisplatin eligibility. The 3C arm comprised three cycles of gemcitabine every 3 weeks (q3w) (1000 mg/m^2) on day (D) 1 and D8 + carboplatin [area under the curve (AUC) 4.5 or 5, as per local practice] on D1/cisplatin (70 mg/m^2) on D1 followed by maintenance avelumab (800 mg q2w). The 6C arm comprised six cycles of q3w gemcitabine (1000 mg/m^2) on D1 and D8 + carboplatin (AUC 4.5 or 5) on D1/cisplatin (70 mg/m^2) on D1 followed by maintenance avelumab (800 mg q2w). Up to six or three cycles were given (depending on the randomization) on a D1 and D8 3-weekly cycle. Treatment with avelumab (800 mg) was given 2-weekly until progression, unacceptable toxicity, or up to 2 years.

Patient-reported outcome (PRO) data were collected through use of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline, on D1 of cycle (C) 4 to C11, and every two cycles thereafter (C13D1, C15D1, C17D1, etc.) as well as on disease progression (PD)/treatment discontinuation. QoL questionnaires are only completed for a maximum of 1 year after randomization. The global health status (GHS)/QoL scale score was used for the primary endpoint and composed of 2 of the 30 items collected on the EORTC QLQ-C30. These questions were Q29 (How would you rate your overall health during the past week?) and Q30 (How would you rate your overall QoL during the past week?).

Endpoints

The primary endpoint was change in GHS/QoL scale scores from baseline to completion of six cycles of treatment. Patients who withdrew from treatment between the start of C4 and completion of C6 were included, provided an EORTC QLQ-C30 questionnaire is completed within 14 days from the date of withdrawal. If a patient did not complete the questionnaire at the completion of C6 or came off the study between the start of C4 and completion of C6 due to any reason and did not complete the EORTC QLQ-C30 questionnaire within 14 days after the date of withdrawal, their questionnaire at completion of C5 (C6D1) was used, if available. In the case that the questionnaire at completion of C5 (C6D1) was unavailable, the questionnaire at completion of C4 (C5D1) was used. This primary endpoint analysis is referred to as completion of C6 timepoint throughout.

The total score for the GHS/QoL was between 2 (very poor) and 14 (excellent). The scores were then linearly

transformed to a score from 0 to 100, giving a mean score. The primary endpoint compared the baseline score and a post-baseline score as described above. The mean difference in the two timepoints was calculated. In the DISCUS trial, a 9-point difference was considered statistically meaningful (see 'Statistical analysis' section).

OS was a co-primary endpoint with alpha allocation. The data presented here are an interim analysis. A final analysis will occur after 320 patients have been recruited (see 'Statistical analysis' section). Other secondary endpoints included (i) PROs for the whole EORTC QLQ-C30 questionnaire, (ii) GHS/QoL scale score time to deterioration (TTD) comparisons between arms, (iii) safety and tolerability, and (iv) efficacy. OS and investigator-assessed PFS, defined as the time from randomization to the first recurrence or death from any cause, were assessed using Kaplan—Meier and log-rank tests. Overall response rate (ORR) and duration of response were measured in both arms.

Adverse events (AEs) were measured [graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0] throughout treatment as well as on completion of six cycles of treatment.

Statistical analysis

Stata (version 18.0, StataCorp LLC, College Station, TX) was used for all statistical analyses. As observed in a similar setting, a 9-point improvement in the difference in GHS/QoL scale score change from baseline was proposed where the sample standard deviation of this change from baseline is assumed to be 26.9 (a pooled standard deviation calculated using results from the two arms analysed previously).[9] To detect a significant result at the 10% level (i.e. $\alpha = 0.1$) with 80% power (i.e. $1 - \beta = 0.80$), the total sample size required was 224 assessable patients (112 in each arm). All calculations for sample size were carried out using a two-sided two-sample equal variance *t*-test in the software package PASS version 16.0.1 (NCSS, LLC, Kaysville, UT). The primary endpoint analysis at 224 patients estimated QoL outcome with alpha spending of 98%. OS at this timepoint was estimated at 1% of the designated alpha. This study has a final OS analysis planned after 224 events from 320 patients.

RESULTS

Patient characteristics

Between January 2022 and August 2025, 346 patients were screened and 267 were randomized (133 to 3C arm, 134 to 6C arm; Figure 1). Baseline characteristics were balanced across the groups (Table 1). The median age was 71 years, 73% had an ECOG PS of 0, and 27% were female. Forty-two percent and 40% of patients in the 3C and 6C arms received gemcitabine/cisplatin, respectively. Seventy-four percent of patients received avelumab in the 3C arm, versus 56% in the 6C arm. Discontinuation of either drug for toxicity in the 3C and 6C arms occurred in 8% and 13%, respectively.

PRO analysis

A total of 99%, 70%, and 65% of patients completed an evaluable baseline, C4D1, and a subsequent QoL questionnaire for primary endpoint analysis, respectively (Figure 1). The mean GHS/QoL scores in the 3C and 6C arms were 63 (3C) and 67 (6C) at baseline versus 63 (3C) and 59 (6C) at completion of six cycles of treatment. The mean change in QoL with therapy for the 3C and 6C arms was 0.0 [95% confidence interval (CI) −5.9 to 5.2] and −8.5 (95% CI −14.1 to −2.9), respectively (Figure 2). The PRO difference between the arms significantly favoured the 3C arm by 8.5 (95% CI 0.7-16.3, $P = 0.016$) achieving the primary endpoint of the trial. This change in QoL did not meet the threshold of clinically meaningful change of 10 points, which is widely accepted.[9] However, it is a statistically significant change at the upper limit of the minimally important difference range of 5-10 points, which is also accepted to interpret changes in QLQ-C30 scores.[10]

Three cycles appear preferable to six cycles over multiple timepoints (Figure 3). Other secondary PRO endpoints are given in Table 2. Of note, 41% and 24% of patients showed an improvement in PRO scores in the 3C and 6C arms from baseline to C7D1 ($P < 0.05$). Time to significant deterioration was 4.8 months versus 3.5 months in the 3C and 6C arms, respectively (HR 0.81). There did not appear to be a long-term benefit in TTD with three cycles (95% CI 0.46-1.43) (Figure 4). Scores for all 30 questions of the EORTC QLQ-C30 also showed results similar to the two questions. A forest plot for the primary analysis is shown in Figure 5. Most of the difference between three and six cycles in terms of PRO scores was seen in the cisplatin group and patients with liver metastases.

Efficacy

The median OS was 18.9 months in both arms (HR 1.15, 95% CI 0.72-1.86, $P = 0.56$) (Figure 6). This failed to reach statistical significance. The median PFS in the 3C and 6C arms was 8.0 months (95% CI 6.7-11.9 months) versus 9.0 months (95% CI 6.9-12.7 months) (HR 1.05, 95% CI 0.73-1.53, $P = 0.79$) (Figure 7). The ORR was 24% in the 3C arm versus 27% in the 6C arm at completion of six cycles.

Subsequent systemic therapy was administered in 57% ($n = 30$) (3C arm) and 42% ($n = 28$) (6C arm) of patients with progression, most commonly antibody—drug conjugates (ADCs), immunotherapy, or chemotherapy. Further follow-up is required for data maturity.

Median duration of chemotherapy and avelumab was 1.7 months/3.7 months (3C arm) and 3.7 months/4.1 months (6C arm). The safety-assessable population consisted of 265 patients. Any-grade treatment-related AEs (TRAE) occurred in 86% (3C arm) and 90% (6C arm) of patients, with grade 3/4 TRAEs occurring in 40% (3C arm) and 54% (6C arm). The

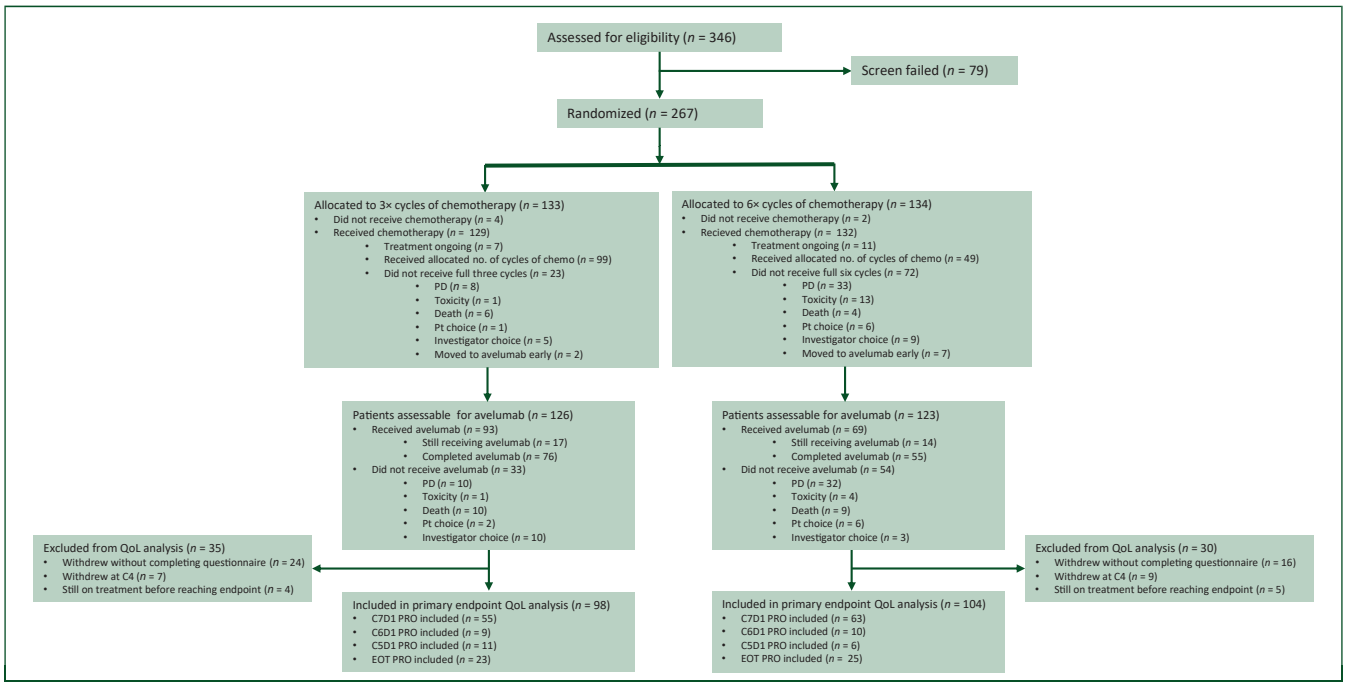

Figure 1. CONSORT diagram. This CONSORT diagram illustrates the flow of participants through each stage of the clinical trial.
C, cycle; CONSORT, Consolidated Standards of Reporting Trials; D, day; EOT, end of treatment; PD, disease progression; PRO, patient-reported outcome; Pt, patient; QoL, quality of life.

three most common TRAEs (any grade) in the two arms were nausea, neutropenia, and anaemia versus anaemia, nausea, and neutropenia in the 3C and 6C arms, respectively (Table 3). Fatal TRAEs occurred in 2% in the 3C arm and 0% in the 6C arm. Serious AEs occurred in 35% in the 3C arm and 37% in the 6C arm. AEs leading to discontinuation of chemotherapy in the 3C arm was 2%, and avelumab 4%. AEs leading to discontinuation of chemotherapy in the 6C arm was 10%, and avelumab 1%.

Table 1. Patient demographics and disease characteristics at baseline

	3C (n = 133)	6C (n = 134)	All patients (n = 267)
Age (years), median (range)	71 (45-89)	72 (44-91)	71 (44-91)
Age category (years), *n* (%)			
<65	36 (27)	37 (28)	73 (27)
≥65	97 (73)	97 (72)	194 (73)
Sex, *n* (%)			
Female	33 (25)	40 (30)	73 (27)
Male	100 (75)	94 (70)	194 (72)
Race, *n* (%)			
White	118 (89)	118 (88)	236 (88)
Not white	15 (11)	16 (12)	31 (12)
Liver metastasis, *n* (%)			
Present	25 (19)	25 (19)	50 (19)
Absent	108 (81)	109 (81)	217 (81)
ECOG, *n* (%)			
0	97 (73)	98 (73)	195 (73)
≥1	36 (27)	36 (27)	72 (27)
Chemotherapy received			
Cisplatin/gemcitabine	56 (42)	54 (40)	110 (42)
Carboplatin/gemcitabine	77 (58)	80 (60)	157 (59)

Values are presented as number (%) for categorical variables and median (interquartile range) for continuous variables unless otherwise indicated.
C, cycle; ECOG PS, Eastern Cooperative Oncology Group performance status.

DISCUSSION

A main shortcoming of this study is that EVP is now the standard of care. Nevertheless, there are still geographical regions where platinum chemotherapy is given. Also, EVP is not universally given where it is available. Also, platinum-based chemotherapy remains a standard of care after EVP. Therefore, determining the optimal number of cycles of chemotherapy remains relevant. Shortening the duration of systemic therapy is attractive in many cancer settings beyond bladder cancer. Demonstrating the feasibility of this trial design, which was completed in a timely manner, has broader implications. It may lead to new trials exploring shortened durations of targeted therapy or ADC therapy, both of which are currently recommended until progression of disease across a spectrum of cancers.

PRO was the primary endpoint of this study. The design was somewhat novel in that a selected specific time point and a key global outcome scores PRO from the validated EORTC questionnaire was selected. Results showed that three rather than six cycles of avelumab had comparatively better PROs at the time of completion of the six cycles of chemotherapy (0 versus −8.5 points difference compared with baseline). It is noteworthy that the difference between the two arms did not achieve the clinically meaningful 10-point threshold accepted by some,[10] although other publications suggest that a 5- to 10-point difference may be meaningful.[10,11] Also, most of the benefit appeared confined to the cisplatin subgroup of patients. It could reasonably be argued that the endpoint picked was at the time most likely to favour the 3C arm. However, with all of the uncertainty around the accuracy of PRO analysis with existing tools, showing any significant difference between arms was considered an important priority.

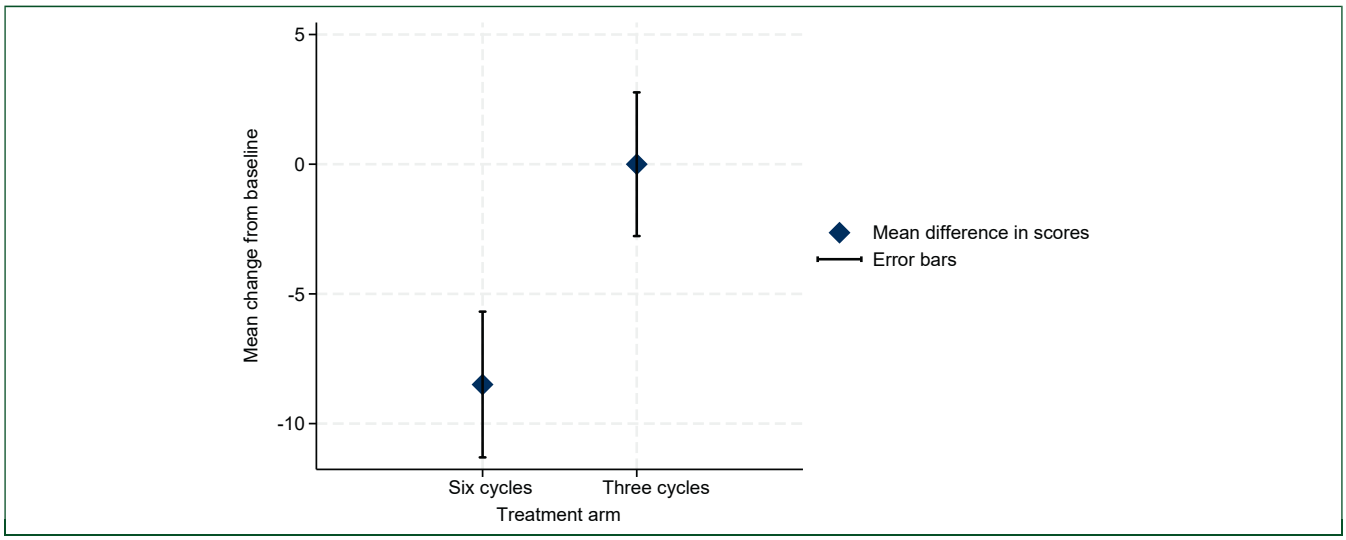

Figure 2. Mean change in global health status (GHS)/QoL (EORTC QLQ-C30) scores by treatment arm from baseline to completion of cycle 6. Dot plot of the mean difference change in standardized scores of GHS/QoL questions on QLQ-C30 questionnaire from baseline to primary endpoint analysis timepoint, with standard errors. GHS/QoL scale questions are only reported here, as per the primary endpoint of the trial. At completion of cycle 6, patients in the 3C arm reported a statistically significant improvement compared with the 6C arm ($P = 0.016$).
C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life.

Subsequent analysis measuring the proportion of patients who had an improvement in PROs showed similar superiority for the 3C arm (Figure 8). The effects in more longitudinal analysis such as TTD failed to show consistent superiority, suggesting that some effects are transient, but at no point did six cycles appear better tolerated.[6]

The AE profiles for the two arms were somewhat similar and likely reflect an apparent mismatch between reported TRAEs and their relevance on QoL. Novel TRAE and PRO assessment tools may be needed to address this inconsistency.

The PFS and OS data show that the control arm performs in a very similar way to predicted expectations in this setting.[7] Median OS of ∼18 months and PFS of 8 months in both arms were encouraging, but the 3C arm did not show superior OS as tested. Also, the study did not show non-inferiority using established methods; therefore, we cannot recommend switching to three cycles from six based

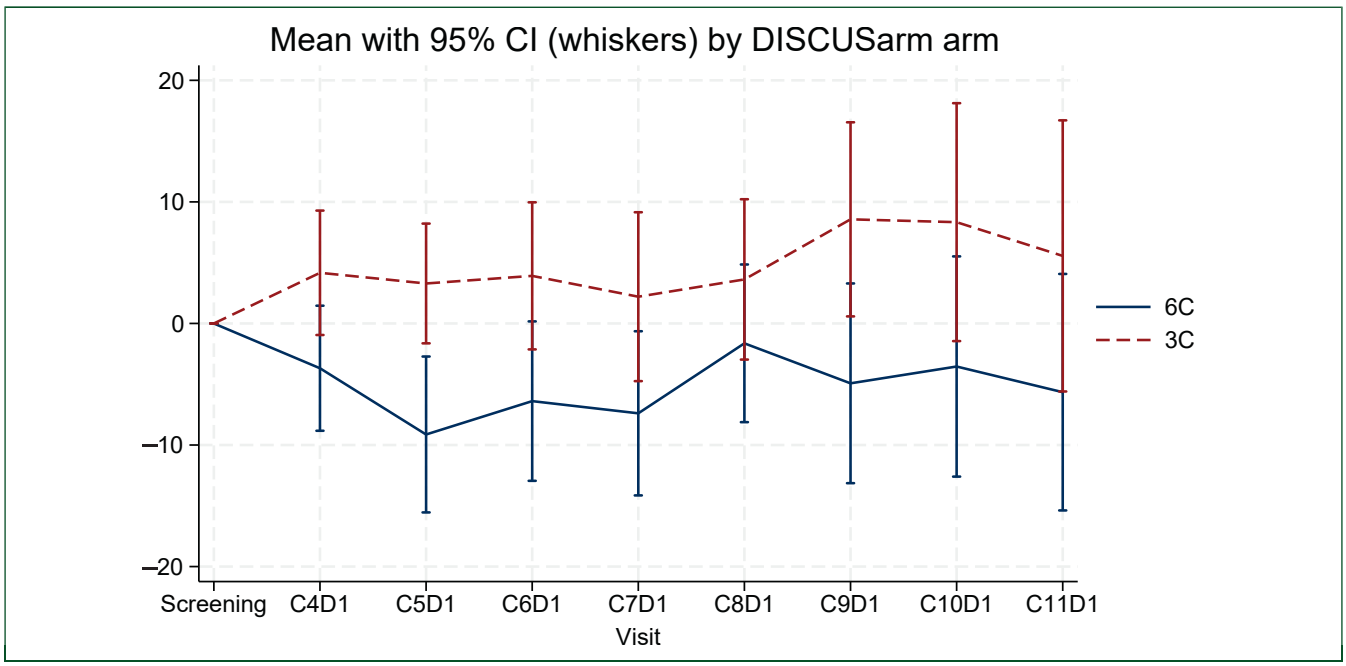

Figure 3. Mean change in global health status (GHS)/QoL (EORTC QLQ-C30) over time by treatment arm. Mean change in differences in GHS/QoL score from baseline for each timepoint to completion of cycle 10. Mean scores with 95% confident intervals are shown.
C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life.

Table 2. PRO endpoints

	Mean difference (3C arm) (95% CI)	Mean difference (6C arm) (95% CI)	Mean difference between the two arms (95% CI)	*P* value
GHS/QoL: primary endpoint				
Baseline versus completion of 4C, 5C, or 6C (primary endpoint analysis population) ($n = 202$)	0.0 (−5.9 to 5.2)	−8.5 (−14.1 to −2.9)	8.5 (0.7 to 16.3)	0.016
GHS/QoL: secondary endpoints				
Baseline versus completion 6C only ($n = 118$)	1.9 (−4.9 to 8.9)	−6.6 (−13.6 to 0.3)	8.6 (−1.1 to 18.3)	0.0417
Full EORTC QLQ-C30 secondary endpoints				
Baseline versus completion 4C, 5C, or 6C primary endpoint analysis population) ($n = 195$)	−0.1 (1.9 to 1.6)	−3.1 (4.6 to −1.7)	2.9 (0.8 to 5.2)	0.0044
Baseline versus completion 6C only ($n = 113$)	0.7 (−0.8 to 2.1)	−2.4 (−4.1 to −0.7)	3.0 (0.8 to 5.3)	0.0041

Summary of PRO endpoints. EORTC QLQ-C30 summary statistics for items by timepoint using paired *t*-test to assess significance of the mean change for linearly transformed scores. The minimally important difference (MID) range of 5-10 points is used to interpret clinically meaningful changes in QLQ-C30 scores.
C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS, global health status; PRO, patient-reported outcome; QoL, quality of life.

on similar efficacy. Demonstrating non-inferiority with existing methods often requires thousands of patients. This has attracted criticism and alternatives have been suggested.[12] More patients on the 3C arm received maintenance avelumab. This may result in better longer-term outcomes. Final OS analysis looking for superiority for the three cycles will occur after longer follow-up and additional patients are recruited.

Approximately half of the patients allocated to the 6C arm did not complete the full six cycles. Along with the PRO and efficacy data, this suggests that fewer than six cycles of platinum-based chemotherapy may be preferable for some patients. Four cycles of chemotherapy was allowed in the JAVELIN Bladder 100 trial and this may be attractive for those struggling with chemotherapy.

These data provide a benchmark on what efficacy outcomes can be expected from platinum-based chemotherapy and maintenance avelumab from the time of starting chemotherapy that could not be derived from the original JAVELIN Bladder 100 trial due to the study design.

Previous retrospective data from the avelumab JAVELIN Bladder 100 trial explored patients who received four versus six cycles of treatment in the study[8] and showed little difference in efficacy. However, efficacy data collection only started from the time of randomization and patient inclusion was subject to selection bias, making the

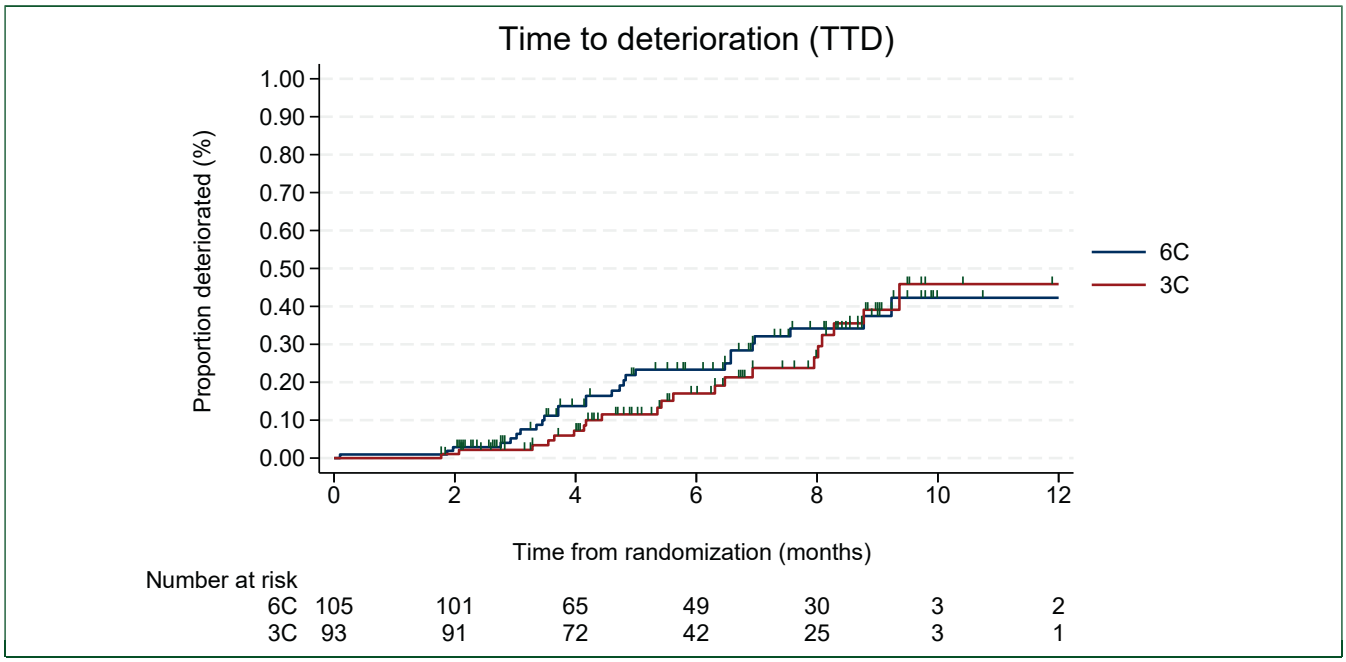

Figure 4. Kaplan–Meier curves for time to deterioration (TTD) in global health status/QoL (EORTC QLQ-C30) by treatment arm. TTD was defined as the time from randomization to the first clinically meaningful deterioration (≥10-point decrease from baseline) to completion of C10. Patients were censored at the last QoL assessment if no deterioration occurred. Vertical ticks indicate censored observations. Only patients with comparable post-baseline PROs were included. Hazard ratio 0.81, 95% confidence interval 0.46-1.43.
C, cycle; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; PRO, patient-reported outcome; QoL, quality of life.

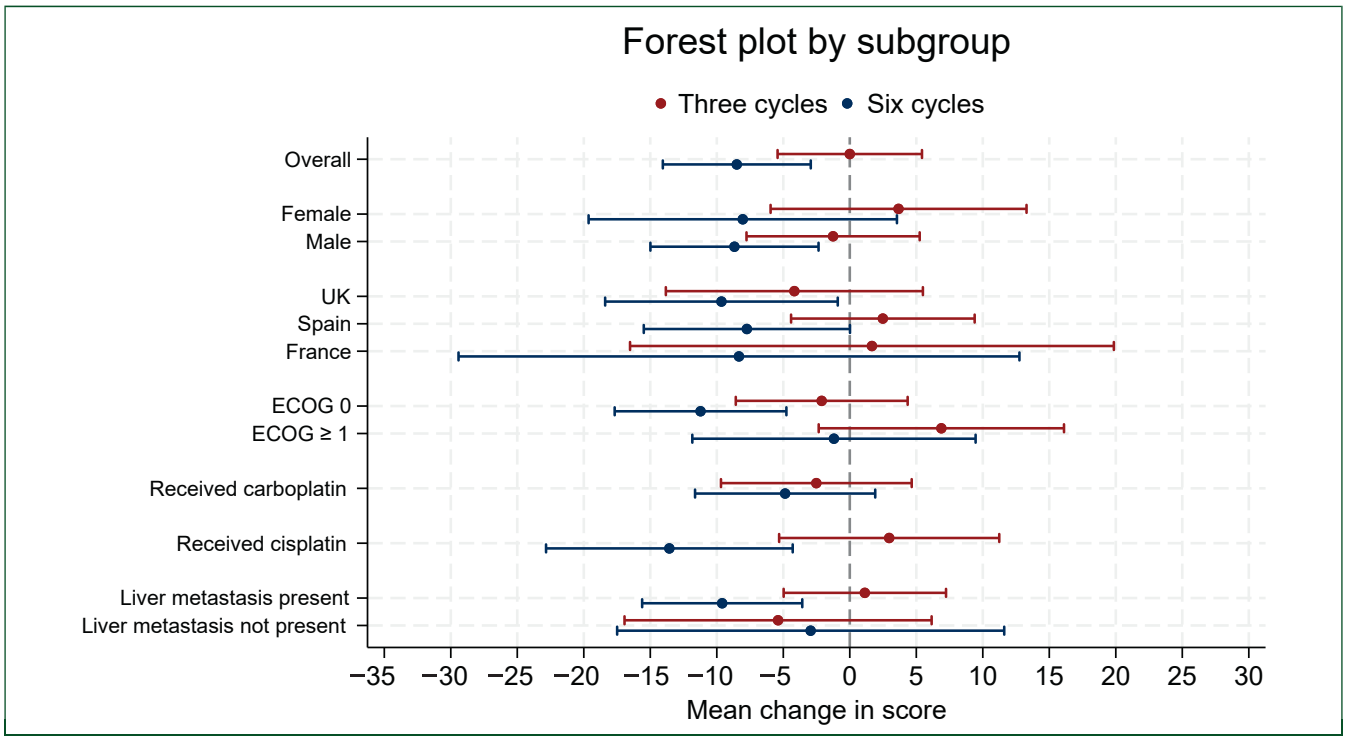

Figure 5. Subgroup effect on global health status/QoL (EORTC QLQ-C30). Forest plot of the analyses of mean change of GHS/QoL scores in all prespecified subgroups.
ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life.

analysis flawed. Also, retrospective data have compared four and six cycles of chemotherapy without avelumab with no apparent difference.[7] Once again we observed cisplatin-eligible patients performing somewhat better than their carboplatin counterparts, although the benefit was marginal (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.011). The true benefit of cisplatin against carboplatin in this setting remains debated but is becoming less relevant in the era of EVP.

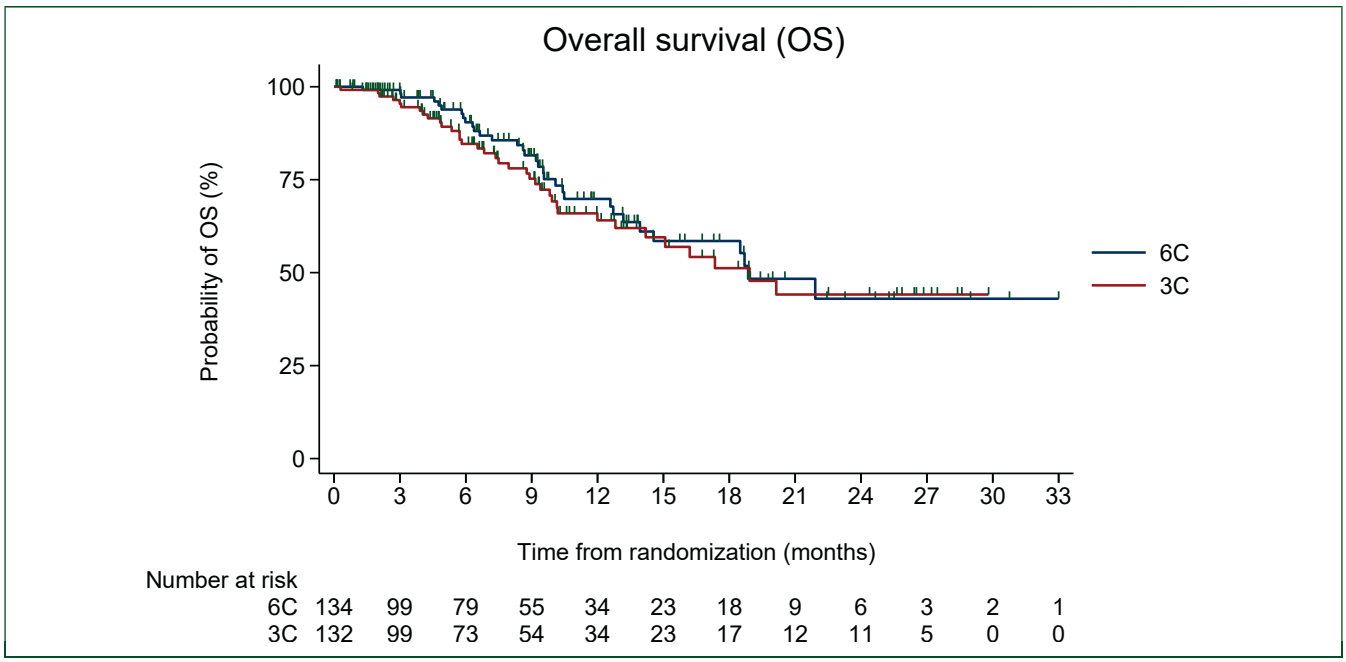

Figure 6. OS, Kaplan–Meier plot. Kaplan–Meier curves depict OS from randomization to death from any cause. Median OS was 18.9 months in both arms. The hazard ratio (HR) for death in the 3C arm was 1.15. Tick marks indicate censored observations.
C, cycle; CI, confidence interval; OS, overall survival.

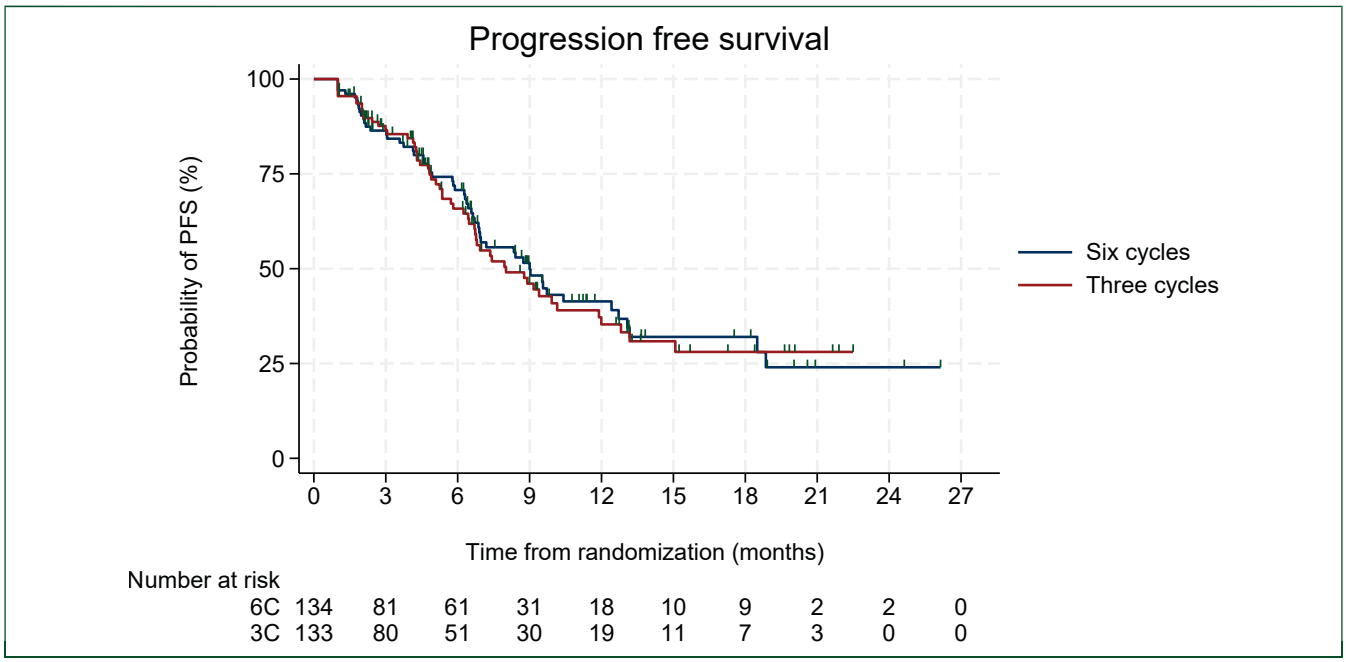

Figure 7. PFS, Kaplan–Meier plot. Kaplan–Meier curves depict PFS from randomization to radiological progression or death, whichever occurred first. Median PFS was 8.0 months in the 3C arm and 9.0 months in the 6C arm. Compared with the 6C arm, the hazard ratio in the 3C arm was 1.05. Tick marks indicate censored observations.
C, cycle; CI, confidence interval; PFS, progression-free survival.

Single-agent pembrolizumab has been seen as a standard of care for first-line mUC therapy in those patients who have a borderline PS.[10] This is partly because six cycles of platinum chemotherapy or EVP until progression (median number of cycles 12) has been seen as a large undertaking for those with a borderline PS. But results with single-agent pembrolizumab are suboptimal, due to a high proportion of individuals having early PD. The DISCUS approach, with only three chemotherapy cycles, switching to early avelumab, will be appealing to those who are uncertain about tolerability but desire an attempt at systemic therapy.

Limiting platinum-based chemotherapy to three cycles, followed by maintenance avelumab, is associated with better QoL at specific timepoints, but these benefits may not be durable. Longer follow-up is required for a clearer efficacy signal. Fewer than six cycles of chemotherapy may be attractive for some patients, particularly those struggling with toxicity. Randomized trials with patient-focused outcomes exploring shorter duration of therapy are feasible.

FUNDING

This work was supported by Merck (no grant number) (CrossRef Funder ID: 10.13039/100009945).

DISCLOSURE

TP reports grants or contracts from AstraZeneca, Roche, Bristol-Myers Squibb, Exelixis, Ipsen, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; consulting fees and honoraria from AstraZeneca, Bristol-Myers Squibb, Exelixis, Incyte, Ipsen, MSD,

Table 3. TRAEs by PT (treated population)

CTCAE v4.03 PT	3C arm		6C arm		Total (n = 1197)
	Grade 1/2 (n = 446)	Grade 3/4 (n = 72)	Grade 1/2 (n = 551)	Grade 3/4 (n = 128)	
Anaemia	29 (2)	7 (1)	42 (4)	26 (2)	104 (9)
Neutropenia	22 (2)	22 (2)	14 (1)	44 (4)	102 (9)
Nausea	42 (4)	2 (0)	50 (4)	2 (0)	96 (8)
Fatigue	35 (3)	1 (0)	37 (3)	1 (0)	74 (6)
Asthenia	30 (3)	0 (0)	31 (3)	4 (0)	65 (5)
Thrombocytopenia	9 (1)	9 (1)	21 (2)	17 (1)	56 (5)
Increased LFTs	17 (1)	3 (0)	22 (2)	4 (0)	46 (4)
Vomiting	16 (1)	0 (0)	22 (2)	2 (0)	40 (3)
Diarrhoea	17 (1)	1 (0)	19 (2)	0 (0)	37 (3)
Constipation	15 (1)	1 (0)	20 (2)	0 (0)	36 (3)

TRAEs have been grouped by PT related to any drug given. The total number of incidences (% of total incidences) of TRAEs is shown.
CTCAE, Common Terminology Criteria for Adverse Events; LFTs, liver function tests; PT, preferred term; TRAE, treatment-related adverse event.

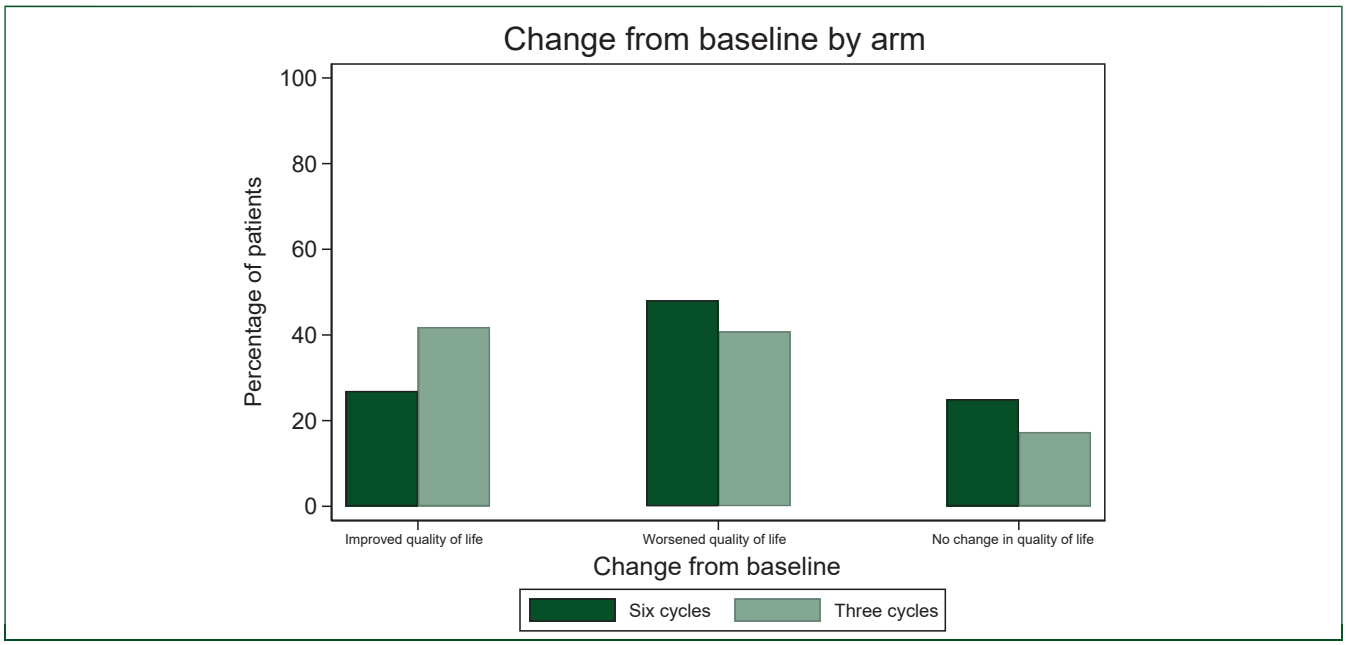

Figure 8. Change in global health status/QoL (EORTC QLQ-C30) by treatment arm from baseline. Bars represent the percentage of patients showing a decrease, increase, or no change in mean change from baseline in global health status/QoL scores at completion of cycle 6 for patients in each arm.
C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; QoL, quality of life.

Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, Eisai, Roche, Mashup, and Gilead Sciences; support for attending meetings and/or travel from Roche, Pfizer, MSD, AstraZeneca, Ipsen, Gilead Sciences, Astellas, and MSD; participation on a data safety monitoring board or advisory board for AstraZeneca, Roche, Bristol-Myers Squibb, Exelixis, Ipsen, MSD, Novartis, Pfizer, Seattle Genetics, Merck Serono, Astellas, Johnson & Johnson, and Eisai; and other financial interests from Novartis, Pfizer, AstraZeneca, Roche/Genentech, Eisai, and Merck. SAH has received research funding from CR UK, MRC/NIHR, UHB charities, CCC charities, North West Cancer Research, Yorkshire Cancer Research, Weston Park Cancer Charity, Bayer, Janssen, Boehringer Ingelheim, Eli Lilly, Roche; participated on advisory board or consultancy for Roche, MSD, AstraZeneca, BMS, Janssen, GSK, Astellas, Pfizer, Merck, Gilead, Boehringer Ingelheim. MAC has received speaker fees from AstraZeneca and BMS; has attended advisory boards for Astellas and MSD; has received speaker fees and attended an advisory board for Merck; and has received a grant from Janssen. IGC received honoraria as a speaker from Ipsen, and honoraria for travel and accommodation expenses from Ipsen. JMC declares consultant, advisory, or speaker roles for Ipsen, Roche, Pfizer, Sanofi, Janssen, and BMS, and has received research grants from Pfizer, Ipsen, and Roche. JP has received speaker fees and attended advisory boards for Astellas, MSD, Janssen, Roche, Eisai, Bayer, AstraZeneca, and Ipsen; has received grants and attended an advisory board for Merck; has received speaker fees from BMS; and has received speaker fees and grants and attended advisory boards for Gilead and Novartis. JM has participated in advisory boards for AstraZeneca, Bristol-Myers Squibb, Eisai, Merck-Pfizer, Ipsen, Astellas, Bayer, and received honoraria for meeting chair or conferences from Astellas, Bristol-Myers Squibb, Eisai, Pfizer, Ipsen, Merck, EUSA Pharma, and MSD. LMD has received honoraria from Janssen, Ipsen, Bayer, and Pfizer. RJ reports research support from Clovis, Astellas, Exelixis, AstraZeneca, and Roche, and honoraria from Clovis, Astellas, AstraZeneca, Roche, Ipsen, Bristol-Myers Squibb, Pfizer, Merck Serono, Merck Sharp Dohme, Janssen, Bayer, and Novartis. DC has received consulting or advisory role for Janssen Oncology, Roche/Genentech, Astellas Pharma, AstraZeneca, Pfizer, Novartis, Ipsen, Bristol-Myers Squibb, MSD Oncology, Bayer, Lilly, Sanofi, Pierre Fabre, Boehringer Ingelheim; research funding from Janssen Oncology; and travel, accommodations, expenses from Pfizer, Roche, Bristol-Myers Squibb, AstraZeneca Spain. ID has received research grant to institution from Roche, AstraZeneca; honoraria from Bristol-Myers Squibb, MSD, Ipsen, Roche-Genentech, Janssen, Astellas Pharma, EUSA Pharma, Bayer, Novartis, Gilead, Bayer; support for attending meetings and/or travel from Merck-Pfizer, Ipsen, Janssen, Bayer, AstraZeneca; serves on the advisory board for Bristol-Myers Squibb, MSD, Ipsen, Roche-Genentech, Astellas Pharma, EUSA Pharma, Bayer, Novartis, Eisai, Debio Pharma, Pharmacyclycs, Gilead. YL reports honoraria from AstraZeneca, Astellas Pharma, BMS, Gilead Sciences, Janssen, Roche, Merck KGaA, Merck Sharp & Dohme LLC, Pfizer, Sanofi Pasteur, Seagen, and Taiho Oncology; and travel accommodations/expenses from Astellas Pharma, AstraZeneca, BMS, Janssen, Merck KGaA, Merck Sharp & Dohme LLC, Pfizer, Roche, and Seagen. BS has received reimbursement for travel expenses from Genentech, Merck Sharp & Dohme (MSD), Pfizer, and Bristol-Myers Squibb (BMS); has received research funding from Roche, Genentech, Merck Sharp & Dohme, Pfizer, and Bristol-Myers

Squibb; and has received honoraria from Merck, Roche, Pfizer, Ellipses, Ipsen, and Janssen. FJS has received travel expenses from Merck and Eusa Pharma, and honoraria from Merck Sharp & Dohme. EG has received honoraria for speaker engagements, advisory roles, or funding of continuous medical education from Adacap, AMGEN, Angelini, Astellas, AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, Ipsen, ITM-Radiopharma, Janssen, Lexicon, Lilly, Merck KGaA, MSD, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, and Thermo Fisher Scientific. EG has received research grants from Pfizer, AstraZeneca, Astellas, and Lexicon Pharmaceuticals. All other authors have declared no conflicts of interest.

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