A Real-World Retrospective Observational Study of Patients With Advanced/Recurrent Endometrial Cancer Across England

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Data Supplement

Supplemental Methods

Patients were required to have received treatment for advanced or recurrent endometrial cancer (EC; including surgery, radiotherapy, or anti-cancer medications) and to have no other active malignancy. Individuals with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage III or IV reported 180 days on either side of a primary EC diagnosis date were classified as having advanced EC. Patients with FIGO stage I or II reported 180 days either side of a primary EC diagnosis date, as well as a gap of more than 120 days between consecutive treatments for EC, were defined as having recurrent disease. A gap of 120 days was included to ensure the two treatments reflected distinct treatment events and were reflective of a new treatment following likely recurrence.

As shown in **Supplemental Fig. 1**, the cohort entry date for advanced EC was defined as the first primary diagnosis of advanced-stage EC, in which the first diagnosis for EC had a diagnosis order of one and in which a FIGO stage III or IV was also recorded within 180 days either side of the diagnosis date. As the date of staging can be missing in real-world data sources, patients who had a recorded stage but with a missing date were assumed that the stage was recorded within 180 days. The index date for patients with advanced EC was the initiation of EC treatment following the cohort entry date.

As shown in **Supplemental Fig. 2**, the index date for recurrent EC was the initiation of a treatment for EC that occurred more than 120 days from the first of any treatment for EC following the first primary diagnosis of early-stage EC, in which the first diagnosis for EC had a diagnosis order of one and in which a FIGO stage I or II was recorded within 180 days either side of the diagnosis date.

The time windows for each exclusion criterion, as well as the assessment window for covariates of interest relative to the index date, are provided in the red and blue boxes, respectively, in **Supplemental Figs 1** and **2**. The green arrow indicates the study observation period in which longitudinal assessments were carried out, including treatment pathways and overall survival.

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Most English electronic health records (EHRs) matured around 2015, which is depicted by a spike in records of new patients with a diagnosis of EC in the data (**Supplemental Fig. 3**).

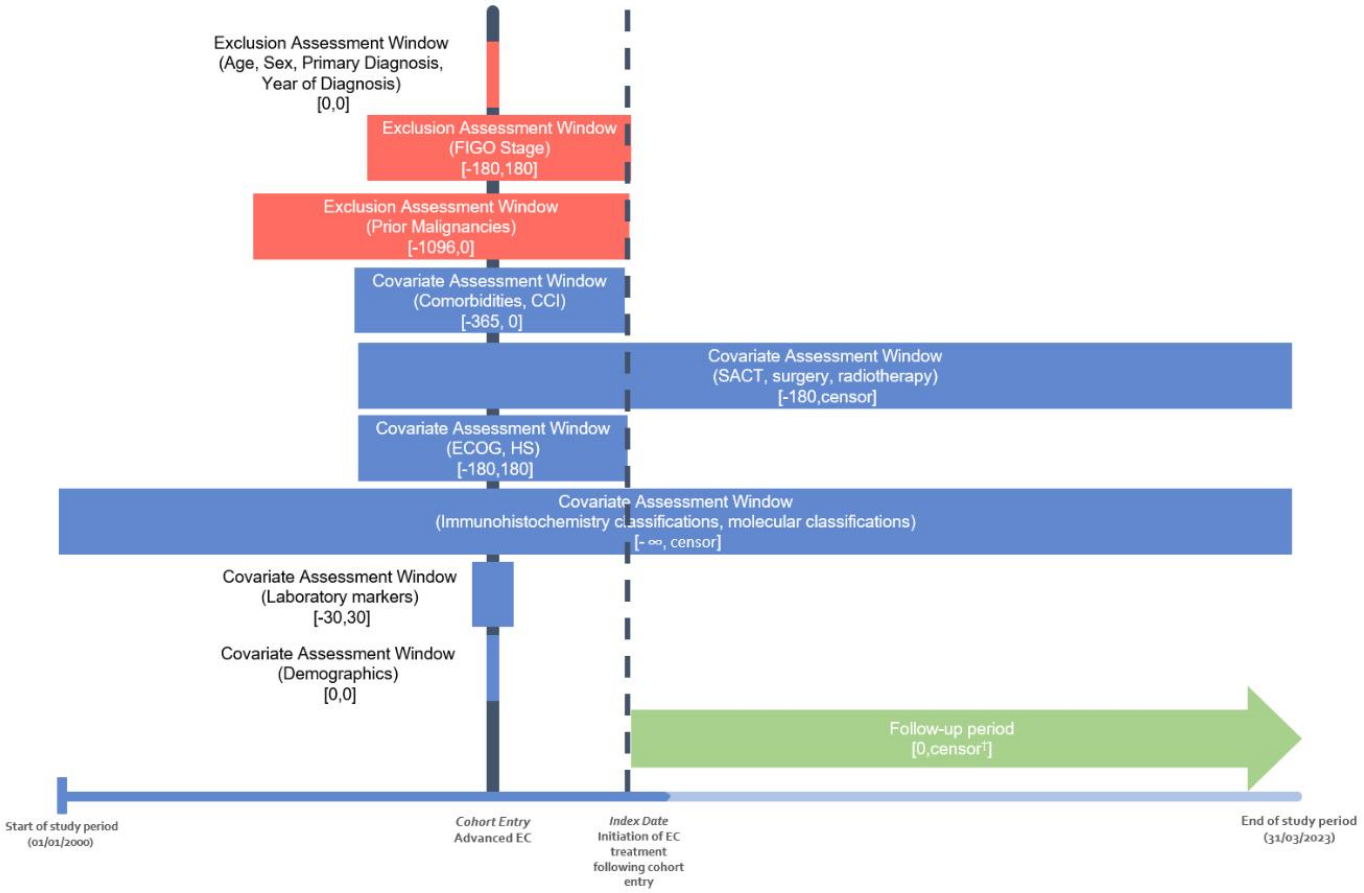
As a retrospective study of EHR, selection and information bias are likely to arise as data were not collected for research purposes, but as a representation of routine care in the secondary care National Health Service (NHS) setting. Treatment decisions and testing of patients reflect the decision-making of the treatment clinician at the trust. This may lead to systematic missing data as only those with more severe disease or where there is cause for concern may trigger care decisions; patients whose disease and treatment are more stable or with higher levels of functioning may be under-represented. As this study reflects both historical and current treatment practices, it is not expected that this bias affects the descriptive nature of the study results.

Line of therapy algorithm: A change in line of therapy was defined as either when a planned course of therapy was modified to include other treatment agents (alone or in combination) or when a planned period of observation of therapy is interrupted by a need

for additional treatment for the disease. In addition, changes in the dosage of drugs do not constitute a change in a line of therapy; therefore, this information is not considered when defining lines of therapy but is explored as part of the secondary analysis objectives. This definition forms the basis of the line of therapy derivation algorithm applied here.

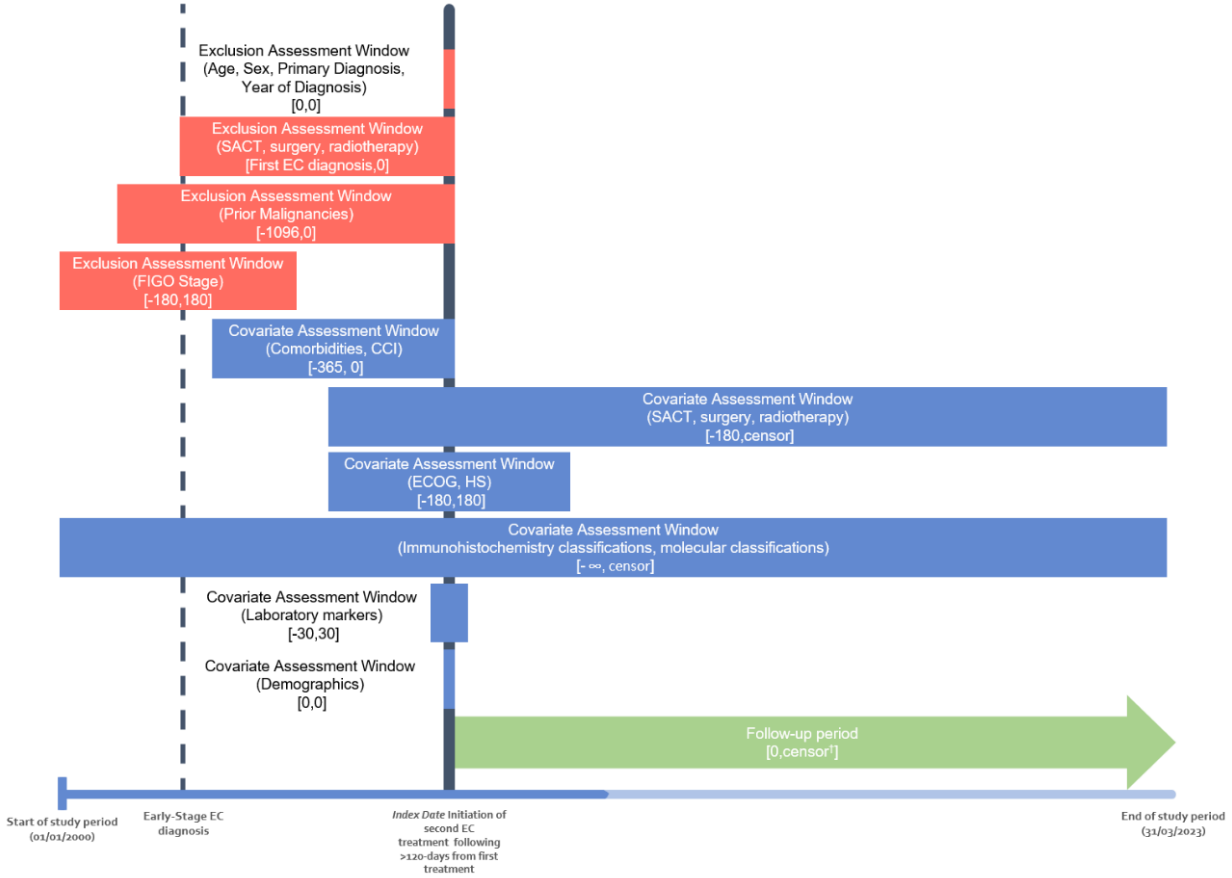
Chemotherapy data provided by partner institutions come in two forms: high-level summary data describing constituent therapeutic agents and a start and stop date, and low-level therapy administration data. In some cases, the high-level and low-level data conflict, or one aspect of the data is missing. Therefore, these two data sources must be consolidated to derive a set of start and stop dates, and therapeutic exposures for each individual in the full analysis set.

Supplemental Fig. 1. Study timeline for patients with advanced EC indicating study period, exclusion assessment windows, covariate assessment windows, and follow-up



>90-day period is only used for those patients with FIGO stage I or II at first diagnosis to determine recurrent EC.
†Patients were censored at either the end of the study period, defined as the date of data cut-off by each trust, at loss to follow-up, defined as the last recorded EHR if no recorded data are found 24 months prior to data cut-off, or at date of death for non-survival-based outcomes, whichever occurs soonest.
CCI Charlson Comorbidity Index; *EC* endometrial cancer; *ECOG* Eastern Cooperative Oncology Group; *EHR* electronic health record; *FIGO* Fédération Internationale de Gynécologie et d'Obstétrique; *HS* histological subtype; *SACT* systemic anti-cancer therapy.

Supplemental Fig. 2. Study timeline for patients with recurrent EC indicating study period, exclusion assessment windows, covariate assessment windows, and follow-up



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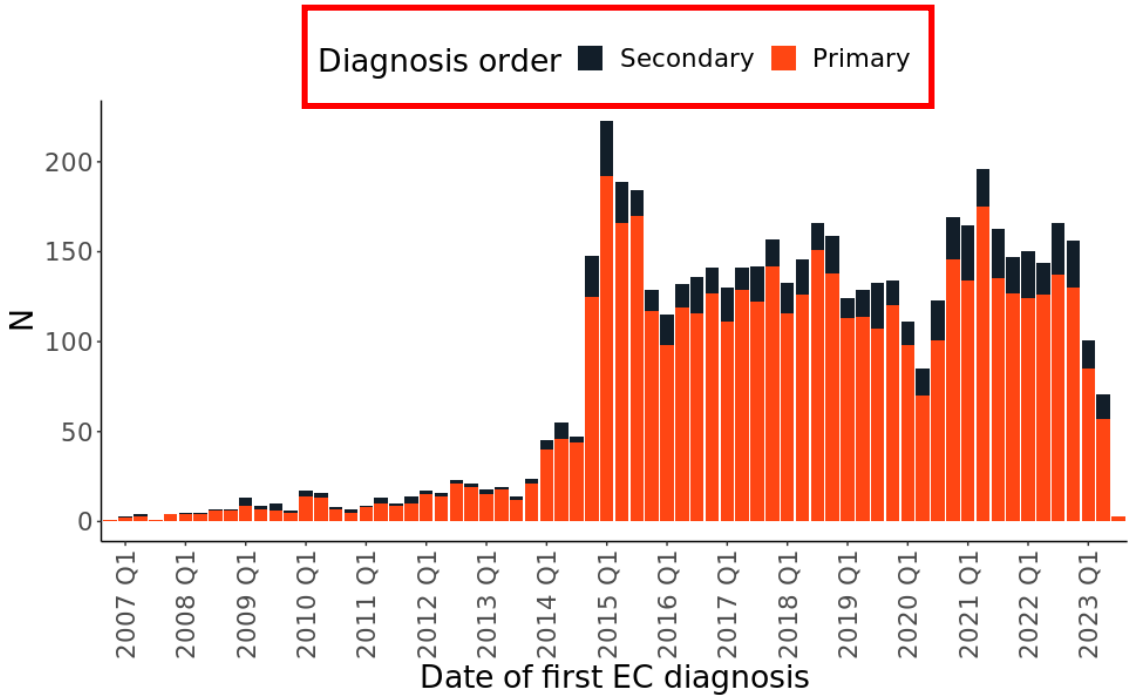
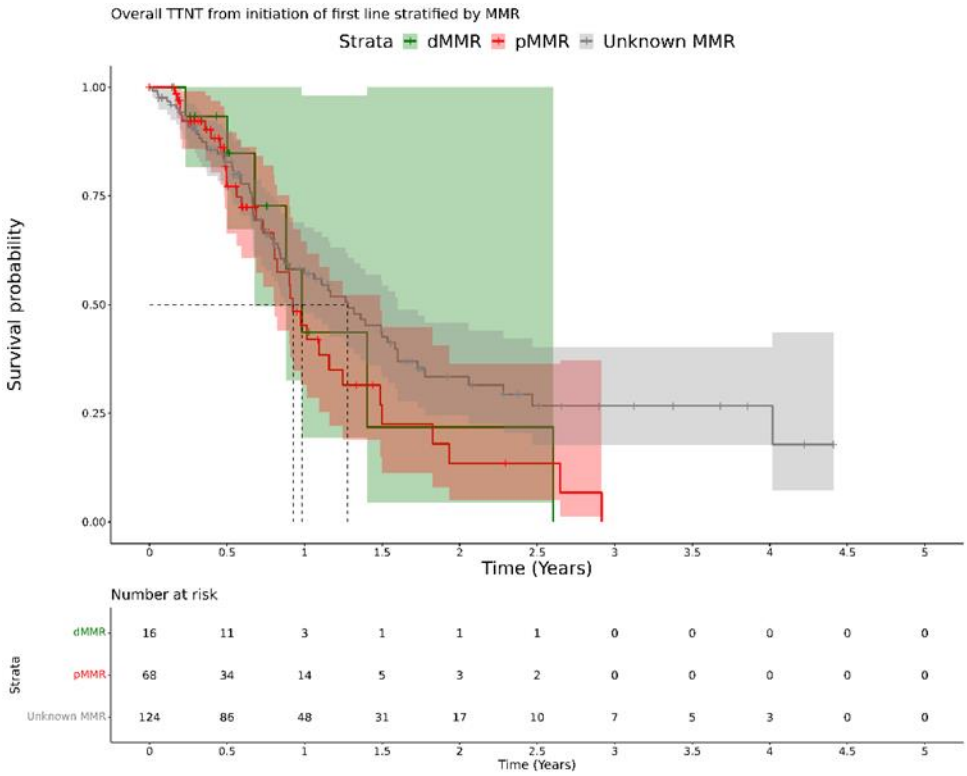
Supplemental Fig. 3. Distribution of the first recorded EC diagnoses available



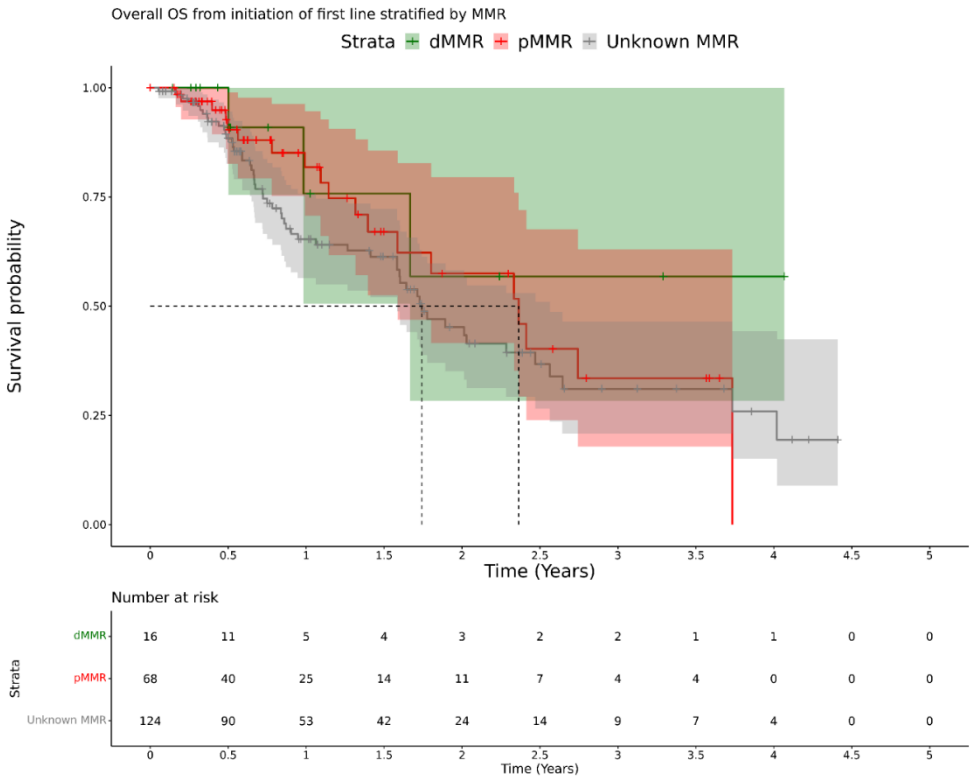
EC endometrial cancer; *Q* quarter.

Supplemental Fig. 4. TTNT following initiation of 1L therapy under sensitivity analysis stratified by MMR status



1L first line; *dMMR* mismatch repair-deficient; *MMR* mismatch repair; *MMRp* mismatch repair-proficient; *TTNT* time to next treatment.

Supplemental Fig. 5. OS following initiation of 1L therapy under sensitivity analysis, stratified by MMR status



1L first line; *dMMR* mismatch repair-deficient; *MMR* mismatch repair; *MMRp* mismatch repair-proficient; *OS* overall survival.

Supplemental Table 1. Summary of lines of therapy received by patients stratified by MMR status

	Regimen	*N* (% of cohort)	Duration of therapy (days), median (range)	Medication dose (mg), median (range)
Unknown MMR	**1L therapy**	310 (54.87)	105 (0–833)	–
	Carboplatin + paclitaxel	221 (71.29)	105 (0–224)	Carboplatin 500 (450–630), paclitaxel 264 (175–300)
	Carboplatin	40 (12.90)	78 (0–203)	Carboplatin 450 (400–500)
	Cisplatin + doxorubicin	10 (3.23)	120 (49–162)	–
	(Carboplatin → cisplatin) + paclitaxel	6 (1.94)	109 (62–150)	Carboplatin 700 (630–718.75), cisplatin 79 (70–100), paclitaxel 336 (270–336)
	Other	33 (10.65)	90 (0–833)	–
	1L of therapy maintenance	≤ 5	–	–
	Other	≤ 5	–	–
	2L therapy	69 (12.21)	63 (0–201)	–
	Cisplatin + doxorubicin	22 (31.88)	56 (0–201)	–
	Carboplatin + paclitaxel	12 (17.39)	87 (0–119)	Carboplatin 560 (450–612.5), paclitaxel 240 (135–300)
	Paclitaxel	10 (14.49)	70 (0–154)	Paclitaxel 108 (80–132)
	Carboplatin + liposomal doxorubicin	8 (11.59)	103 (0–162)	Carboplatin 500 (400–500), liposomal doxorubicin 30 (26–54)
	Carboplatin	6 (8.70)	78 (0–126)	Carboplatin 500 (365–500)
	Other	11 (15.94)	59 (0–169)	–
	2L of therapy maintenance	≤ 5	–	–
	Other	≤ 5	–	–
	3L therapy	11 (1.95)	107 (7–198)	–
	Other	11 (100.0)	107 (7– 198)	–
	3L of therapy maintenance	≤ 5	–	–
	Other	≤ 5	–	–

dMMR	**1L therapy**	19 (45.23)	107 (20–154)	–
	Carboplatin + paclitaxel	16 (84.21)	107 (48–154)	Carboplatin 630 (560–695), paclitaxel 270 (175–336)
	Other	3 (15.79)	112 (20–142)	–
	1L of therapy maintenance	≤ 5	–	–
	Other	≤ 5	–	–
	2L therapy	6 (14.29)	257 (0–719)	–
	Other	6 (100.0)	257 (0–719)	–
MMRp	**1L therapy**	85 (68.55)	105 (0–280)	–
	Carboplatin + paclitaxel	66 (77.65)	105 (0–280)	Carboplatin 500 (500–560), paclitaxel 270 (175–300)
	Other	19 (22.35)	98 (1–158)	–
	2L therapy	33 (26.61)	84 (0–189)	–
	Carboplatin + paclitaxel	12 (36.36)	68 (0–114)	Carboplatin 500 (300–560), paclitaxel 270 (216–336)
	Carboplatin + liposomal doxorubicin	9 (27.27)	140 (36–189)	Carboplatin 450 (450–560), liposomal doxorubicin 54 (30–54)
	Other	12 (36.36)	69 (0–161)	–
	3L therapy	14 (11.29)	58 (0–161)	–
	Paclitaxel	6 (42.86)	156 (0–161)	Paclitaxel 162 (80–162)
	Other	8 (57.14)	25 (0–141)	–

Regimens of 'Other' are pooled results for all regimens that contain ≤5 patients. Regimens containing a '→' imply the drug was swapped out during therapy.
1L first line; *2L* second line; *3L* third line; *dMMR* mismatch repair-deficient; *MMR* mismatch repair; *MMRp* mismatch repair-proficient.

Supplemental Table 2. Median time to event for TTNT from initiation of 1L or 2L therapy overall and by MMR status

	N	Total person-years	Events	Median time to event, years (95% CI)
1L treatment, total cohort	414	562.02	251	1.22 (1.02–1.37)
MMR status				
dMMR	19	21.19	10	1.17 (0.88–NR)
MMRp	85	88.94	46	1.03 (0.90–1.49)
Unknown MMR	310	451.89	195	1.26 (1.00–1.40)
2L treatment, total cohort	108	70.59	77	0.66 (0.62–0.82)
MMR status				
dMMR	6	12.01	≤ 5	NR
MMRp	33	18.60	21	0.78 (0.63–1.11)
Unknown MMR	69	39.98	55	0.63 (0.50–0.75)
1L treatment, sensitivity analysis	208	192.86	105	1.11 (0.90–1.49)
MMR status				
dMMR	16	11.72	7	0.98 (0.68–NR)
MMRp	68	48.44	33	0.93 (0.80–1.49)
Unknown MMR	124	132.70	65	1.28 (0.90–1.60)

1L first line; *2L* second line; *CI* confidence interval; *dMMR* mismatch repair-deficient; *MMR* mismatch repair; *MMRp* mismatch repair-proficient; *NR* not reached; *TTNT* time to next treatment.

Supplemental Table 3. The number of patients, total person-years, events, and median time to event for OS from initiation of 1L or 2L therapy overall and by MMR status

	N	Total person-years	Events	Median time to event, years (95% CI)
1L treatment, total cohort	414	654.10	215	1.80 (1.59–2.16)
MMR status				
dMMR	19	33.20	≤ 5	4.25 (1.67–NR)
MMRp	85	117.69	30	2.36 (2.10–4.05)
Unknown MMR	310	503.21	180	1.64 (1.32–1.98)
2L treatment, total cohort	108	92.09	72	0.75 (0.63–1.15)
MMR status				
dMMR	6	12.01	≤ 5	NR
MMRp	33	28.76	17	1.31 (0.63–NR)
Unknown MMR	69	51.33	54	0.65 (0.61–0.87)
1L treatment, sensitivity analysis	208	239.76	77	1.89 (1.64–2.56)
MMR status				
dMMR	16	17.5	3	NR (1.67–NR)
MMRp	68	71.02	19	2.36 (1.59–NR)
Unknown MMR	124	151.24	55	1.74 (1.58–2.56)

1L first line; *2L* second line; *CI* confidence interval; *dMMR* mismatch repair-deficient; *MMR* mismatch repair; *MMRp* mismatch repair-proficient; *NR* not reached; *OS* overall survival.