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Response to first line platinum-based chemotherapy in mismatch repair deficient (MMRd)/ microsatellite instability high (MSI-high) endometrial carcinoma

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HIGHLIGHTS

- Approximately, 30% of primary endometrial cancers are MMRd/MSI-H.
- In this population, PD-1 and PDL-1 inhibitors therapy have shown response rates between 40 and 60%.
- However their response to 1st line platinum is unknown.
- We report that the response rate is similar to an all-comer population but PFS is shorter than expected.

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ABSTRACT

Background. Around 15% of metastatic endometrial carcinoma (EC) are MMRd/MSI-H improving response to immune checkpoint inhibitors (ICI). So far, few data existed considering the chemotherapy (CT) sensitivity in MMRd/MSI-H EC, especially response to first-line platinum-based treatment.

Patients and methods. We performed a multicentric retrospective analysis reporting the response to first line platinum CT in MMRd/MSI-H EC patients. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) with first line platinum-based CT.

Results. A total of 112 patients MMRd/MSI-H EC from 8 centers were identified. Median overall survival was 58.0 months (95% CI: 45.3–95.1). Among them, 78 patients received first line platinum CT in recurrent/metastatic setting. With a median follow up of 32.6 months (min: 0.03; max: 135.0), ORR and DCR (disease control rate) were 50% (95% CI: 38.5–61.5) and 68% (95% CI: 56.4–78.1), respectively. Median PFS and OS from first line platinum-based CT was 7.8 months (95% CI: 6.0–9.0) and 51.9 months (95% CI: 28.0-NE), respectively. Median PFS with ICI in second line ($n = 48$) was 10.7 months (95% CI: 3.4-NE) from ICI initiation.

Conclusion. ORR in first line metastatic MMRd/MSI-H EC is consistent with efficacy in an all comer metastatic EC population.

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1. Introduction

In contrast with most other solid malignant tumors, incidence and disease-related mortality of endometrial cancer (EC) is increasing, especially in developed countries. Whereas early-stage EC is associated with an excellent 5-year relative survival rate (96%), this rate decreases to 18% in patients with distant metastases [1,2]. At progression or initially, platinum chemotherapy with carboplatin and paclitaxel is currently the standard of care in first line for metastatic EC with an objective response rate (ORR) around 50–60%, a median progression-free survival (PFS) and an overall survival (OS) of 8 months and 15–20 months, respectively [3–6].

Mismatch repair (MMR) is a highly conserved mechanism responsible for restoring DNA integrity by correcting single-base mismatches and insertion-deletion loops that may occur during DNA replication. Deficiencies in MMR result in the accumulation of point mutations [7]. It is important to note that EC was recently shown to have the highest prevalence of MMRd/MSI-H tumors across 30 human cancer types [8–10]. MMRd/MSI-H tumors are secondary to a somatic or germline mutation in MMR genes (*MLH1, MSH2, MSH6, PMS2*), or more commonly to somatic epigenetic inactivation of the *MLH1* gene [11,12]. Approximately, 30% of primary and 15% of metastatic or recurrent ECs are MMRd/MSI-H [13,14,8].

The MMR/MSI status of the tumor is clearly predictive for benefit from immune checkpoint inhibitors (ICI) [15–17]. Early trials reported an unprecedent response rate and duration of response leading to an accelerated approval of pembrolizumab in all MMRd/MSI-H tumors (ie tumor agnostic) after failure of standard treatments by the U.S. Food and Drug Administration (FDA) [18–21]. In April 2021, the European Medicine Agency (EMA) approved another PD1 inhibitor, dostarlimab, for recurrent or metastatic MMRd/MSI-H EC progressing after platinum chemotherapy. Based on the final results of Garnet phase1/1b study, dostarlimab received the EMA approval [22]. In this population after platinum based chemotherapy, PD-1 inhibitors dostarlimab and pembrolizumab have shown response rates of 50%, with long duration of response [23,24]. In this setting, the expected response rate to second line chemotherapy in advanced EC is around 10% [25].

Thus, it is now well established that the best option after failure of first line carboplatin and paclitaxel is an ICI in MMRd/MSI-H EC. However, there is little data reporting the response to frontline carboplatin/paclitaxel in this population with advanced/metastatic disease. In localized EC, data from the recently completed PORTEC3 trial suggested that MMRd/MSI-H EC could derive no benefit from adjuvant platinum based chemotherapy [26,27]. The most frequent MMRd/MSI-H tumors after EC is colorectal carcinoma (CRC) and recent data has shown that ICI provided a significant improvement of PFS compared to chemotherapy in untreated patients with MSI-H metastatic CRC [19].

We conducted a multicentric retrospective study to describe ORR and PFS with first line platinum chemotherapy and subsequent immunotherapy in metastatic MMRd/MSI-H EC.

2. Methods

2.1. Patients

Patients with relapsed or metastatic MMRd/MSI-H EC treated with a first line of systemic therapy were identified via a multicenter retrospective review of electronic case records of metastatic EC patients treated in centers from the French national collaborative group, GINECO. Eligibility criteria included adult patients with relapsed, or metastatic EC not eligible to curative local treatment, and treated with first line systemic treatment. Patients in relapse could have received platinum chemotherapy in adjuvant setting. Standardized chart review collected date of diagnosis, age at diagnosis, date of initial local therapy, adjuvant treatment, date of first metastasis, type of metastatic site at initiation of systemic treatment, subsequent treatments and type. All patients had regular radiologic evaluation based on local practice. The response was determined locally according to the clinicians. Clinical (age, PS, histology, MMRd/MSI-H status, and survival data) were extracted from the database. The study was approved by a central ethics committee, and informed consent was obtained from patients.

2.2. Efficacy endpoints

The main endpoints were ORR and PFS under first line platinum-based chemotherapy in MMRd/MSI-H in relapsed or de novo metastatic EC (main analyses). These endpoints were also described in patients under subsequent ICI in second line and beyond (secondary analyses). Radiological evaluation was performed every 8–12 weeks and defined as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). ORR was defined by CR + PR and disease control rate (DCR) as CR + PR + SD. Response was determined by local assessment from the clinician, according to computed tomography (CT)-scanner evaluation or positron emission tomography CT (petCT) evaluation. PFS was defined as the time from the date of start of first line therapy to disease progression or death. OS was defined as the time from the date of start of first line therapy to death.

2.3. MMRd/MSI-H testing

The MMR/MSI status was determined locally according to one of the standard practices. Methods for determination included loss of 1 or 2 MMR protein expression by immunochemistry (IHC), or if 2 or more of five tumor repeat loci show instability by polymerase chain reaction (PCR) assay. In addition, depending on pattern of MMR protein loss or MSI status, age and/or family history a proportion of patients benefited from genetics consultation and germline analysis with blood test by a next generation sequencing panel to look for lynch syndrome. The MMRd/MSI status determination is detailed in supplementary table 1.

2.4. Statistical analysis

Patients' and tumor characteristics (age at diagnosis, Karnofsky Performance Scale (KPS), site of metastases, prior surgery or radiotherapy, histology, grade, and subsequent systemic treatment) were described (median and interquartile range [IQR] for continuous variables and frequency for categorical variables) for MMRd/MSI-H patients with relapsed or de novo metastatic EC. Median follow-up was estimated by using the reverse Kaplan-Meier method. Efficacy endpoints were analysed for MMRd/MSI-H EC patients treated by platinum chemotherapy as first line. The exact method was used to estimate the 95% confidence interval (CI) of ORR and DCR. PFS and OS were estimated by using the Kaplan-Meier method and median was reported with its 95% CI. The study cut-off date for the statistical analysis was December, 7th, 2020. Statistical analysis was performed by using SAS software 9.4 (SAS Institute).

3. Results

3.1. Metastatic MSI EC cohort description

3.1.1. Patients' and tumor characteristics

Between February 1st, 2018 and September 8th, 2020, we identified 112 MMRd/MSI-H patients with relapsed or de novo metastatic EC with a median follow-up of 33.9 months (range: 0.4–271.7) from the date of diagnosis of first relapse. Median age was 61 (42–90) years. Histology was endometrioïd in 88.4% (99/112) of patients, others included serous (4.5%), mixed tumors (4.5%), or clear cell (3%). Most tumors were grade 2 (44%, 49/112); 21% and 28.5% were grade 1 and 3, respectively according to former classification. Among the 112 patients, 25 (22%) were stage IV at diagnosis. Moreover, 63 (56%) had received prior adjuvant radiotherapy and 35 (31%) had received prior adjuvant chemotherapy.

The most frequent metastatic sites prior to chemotherapy initiation were nodes (60%) and peritoneum (28%). Other clinico-pathological characteristics are detailed in Table 1. Median OS for all metastatic MMRd/MSI-H EC patients was 58.0 months (95% CI: 45.3–95.1). Among these 112 patients, 97 received first line systemic treatment for metastatic disease (Fig. 1). Fifteen patients treated by upfront radio-chemotherapy (RCT) and surgery were excluded (non-evaluable for the response rate). First line treatment was mainly platinum based chemotherapy (78/97), but other systemic first line therapies included hormonal therapy ($n = 4$), non-platinum chemotherapy (n = 4) as well as immunotherapy with an anti-PD1/PDL1 alone ($n = 9$) or in combination with a CTLA4 ($n = 2$). (See Tables 2A and 2B.)

Among MMRd/MSI-H EC patients who were treated with platinum-based chemotherapy for primary treatment of metastatic disease ($n = 78$), 13 patients (16.7%) had received prior platinum-based therapy in the adjuvant setting. Regimens for metastatic disease included: platinum-based chemotherapy with carboplatin and paclitaxel in 89% ($n = 69$), platinum chemotherapy with pegylated doxorubicin or gemcitabine in 6% ($n = 5$) and 5% ($n = 4$) 183 received carboplatin as monotherapy. Moreover, 67 patients had tumors with loss of MMR proteins by IHC (86%) and in 14% MMRd/MSI-H status was determined by PCR. The most frequent protein loss was MLH1 by IHC in 76% of tumors (51/67) (Table 2). Genetic counseling and germline testing were performed in 45/78 (56%) and Lynch syndrome was confirmed in 11/78 (14%) patients.

3.1.2. Response to first line platinum in metastatic setting in MMRd/MSI-H EC ($n = 78$)

The median follow-up estimated from first line platinum in metastatic setting was 32.6 months (min: 0.03; max: 135.0). ORR and DCR was 50% (95% CI: 38.5–61.5) and 67.5% (95% CI: 56.4–78.1), respectively (Table 3). Sixty-eight (87.2%) patients have a progression event and 29 (37%) died. Median PFS and OS from first line platinum chemotherapy in metastatic setting was 7.8 months (95% CI: 6.0–9.0) and 51.9 months (95% 194 CI: 28.0-NE), respectively (Fig. 2A–B).

3.1.3. Response to ICI in MMRd/MSI-H EC ($n = 48$)

In terms of subsequent systemic therapies, 62% (48/78) received an ICI after chemotherapy failure, 31 in second line and 18 in third line and beyond; one patient received an ICI in monotherapy in second line and received an ICI combination as third line in a phase 1 trial. Subsequent therapy in second line was hormonotherapy ($n = 9$), chemotherapy ($n = 14$), others (n = 4 as targeted therapy in trials) and some patients ($n = 20$) were still in response at the study cut-off date. The ORR was 45.8% (95% CI: 31.4–60.8) and DCR was 66.7% (95% CI: 51.6–79.6) in patients receiving ICI in second line after platinum. Median PFS and OS under ICI were 10.7 months (95% CI: 3.4-NE) and 31.9 months (95% CI: 13.5-NE), respectively (Fig. 2C–D). Although 11 patients with MMRd/MSI-H who received first line ICI were not included for the primary endpoint analysis, outcome data was collected and ORR and DCR to ICI in first line were identical and equal to 54.5% (95% CI: 23.4–83.3) (6/11).

4. Discussion

In this study, we describe a large cohort of 78 MMRd/MSI-H EC treated with first line platinum-based chemotherapy in metastatic setting. The median PFS from first line platinum chemotherapy in metastatic setting was 7.8 months (95% CI: 6.0–9.0). ORR and DCR was 50% (95% CI: 38.5–61.5) and 67.5% (95% CI: 56.4–78.1), respectively (12% had a confirmed complete response). Currently, there is no clear evidence that MMR/MSI status in metastatic EC may predict differential benefit

Table 1
Patient's and tumor characteristics.

	Patient treated by platinum based chemotherapy $n = 78$ *n* (%)	All MSI-H patients $n = 112$
Age at diagnosis		
Median (IQR)	62 (42–90)	61 (42–90)
Germline testing for Lynch Syndrome		
Presence of a pathogen mutation	11 (14.1%)	13 (11.6%)
No pathogen mutation	34 (43.5%)	48 (42.8%)
Not done	33 (42.3%)	51 (45.5%)
Disease status prior to 1st line systemic therapy		
Stage IV	20 (25.6%)	25 (22.3%)
Recurrent/progression post-local treatment	58 (74.3%)	82 (73.2%)
NA	0	5 (4.5%)
Prior adjuvant treatment		
Platinum-based chemotherapy	13 (16.7%)	35 (31.2%)
Radiotherapy	40 (51.3%)	63 (56.2%)
Radio chemotherapy	11 (14.4%)	16 (14.2%)
Metastatic sites		
Node	52 (66.7%)	66 (59.0%)
Peritoneum	23 (29.4%)	30 (26.7%)
Lung	13 (16.7%)	29 (25.8%)
Liver	4 (5.1%)	7 (6.2%)
Bone	3 (3.8%)	5 (4.5%)
Brain	2 (2.5%)	3 (2.7%)
Histology		
Endometrioïd adenocarcinoma	69 (88.4%)	99 (88.4%)
Serous adenocarcinoma	4 (5.7%)	5 (4.5%)
Clear cell adenocarcinoma	2 (2.6%)	3 (2.7%)
At least 2 different subtypes	3 (4%)	5 (4.5%)
Missing	0 (0%)	0 (0.0%)
Grade		
Grade 1	17 (22.0)	24 (21.4%)
Grade 2	36 (46.7)	49 (43.7%)
Grade 3	21 (25.9)	32 (28.5%)
Missing for the grade	4 (5.1)	7 (6.2%)
Deaths	29 (37.1%)	37 (33.0%)

IQR: Interquartile range; FU: follow up.

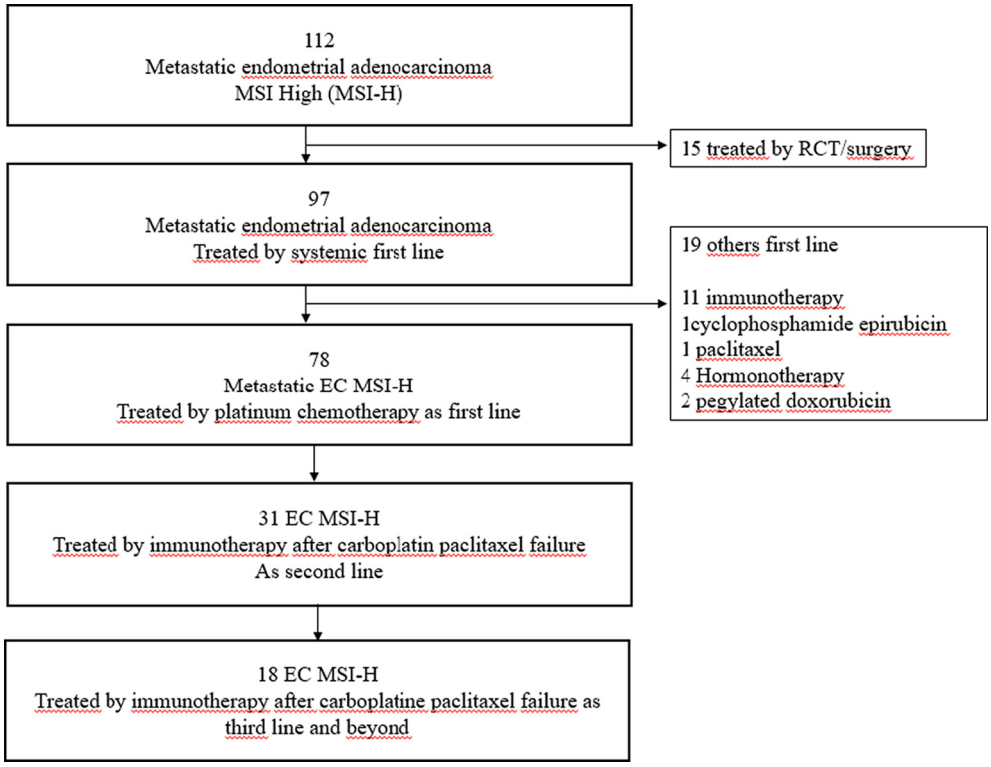

Fig. 1. Flowchart of the study.

from platinum chemotherapy. In EC, the prognostic value of MSI status is controversial [12]. Some studies in early stage have shown that MSI-H EC is associated with a more favorable outcome [28–30] even in tumors with high risk features according to PORTEC 3 trial results; whereas other data suggested worse prognosis [31–34]. Overall, the response rate observed in this retrospective cohort of MMRd/MSI-H EC is similar to the efficacy achieved with first line platinum in an all comer population of relapsed EC. Median PFS was 7.8 months in our cohort of MMRd/MSI-H which is comparable to that described in earlier trials of first line chemotherapy [3,4], investigating recurrent and/or stage IV de novo EC population (supplementary table 2). However, OS in our cohort of MMRd/MSI-H patients with stage IV or recurrent/progressive disease was longer with a median of 51.9 months from first line / 45.3 months from the diagnosis of metastatic disease than that described in previous studies (13–20 months) [3–5]. This could reflect increased benefit from subsequent therapies post-platinum progression especially ICI subsequent therapy. Indeed, among the 40% of patients who received ICI post-platinum, ORR and DCR was respectively 45.8% (95% CI: 31.4–60.8) and 66.7% (95% CI: 51.6–79.6); and PFS was longer under subsequent ICI than first line chemotherapy with a median of 10.7 months (95% CI: 3.4-NE). As none direct comparition was done, it is not possible to none compare benefits of the two therapies. The efficacy of ICI in our real life cohort is consistent with published data from trials in terms of response rate [20,24]. In the phase II KEYNOTE-158 study where pembrolizumab was given to patients with previously treated advanced non-colorectal MSI-H, ORR was 34.3% (95% CI: 28.3–40.8). But in MSI-H EC subgroup ($n = 49$), ORR was 57% (95% CI: 42.0–71.0), with 8 (16%) CR and 20 (41%) PR. Median duration of response DOR was not reached (NR; range, 3–27 months); and 26 (93%) of the 28 responses were ongoing after ≥9 months follow-up. Median follow-up duration was 24 months (range: 0.5–34) and median PFS was 26 months (95% CI: 5.0-NR) [23]. Given an unprecedented efficacy after failure of first line platinum, the FDA approved the anti PD1 pembrolizumab in recurrent/metastatic MSI-H ECs while the EMA recently approved dostarlimab in this post-platinum setting [35]. It is noteworthy that Miller et al., in the recent first line phase III trial of platinum chemotherapy in an all comer population, described similar ORR but a longer median PFS of 13 months and OS of 37 months [5]. However the sponsor amended inclusion criteria mid-trial to include patients with stage III disease (43% of patients) and those without measurable disease (>40% of patients). The improved survival was largely driven by patients with stage III or unmeasurable disease (OS = 11.3 months vs 20 months) [5].

Finally, according to our data, ORR of immunotherapy was quite consistent in first and subsequent line confirming that patients may benefit from immunotherapy regardless of line of systemic treatment. Although

Table 2A
MSI-H status patient's characteristics (n = 112).

Determination of MSI status by	n
IHC	110
RER	28
Tumoral NGS	7
Germline NGS	61

IHC: immunochemistry; RER: Replication ERor; NGS: next generation sequencing.

Table 2B
MSI status patient's characteristics IHC ($n = 112$).

IMMR protein loss of expression in IHC	All patients n = 112
MLH1, PMS2 extinction	71
MSH2 MSH6 extinction	17
MLH1, MSH2 extinction	1
MLH1, MSH6 extinction	1
Isolated MSH6 extinction	2
Isolated MLH1 extinction	9
Isolated PMS2 extinction	4
Missing expression of type of protein*	5
No extinction in IHC*	2

* Determination of MSI status was done according RER test.

Table 3
Efficacy results: response rate according to systemic first-line therapy.

Response rate	Patients treated by platinum-based chemotherapy * N (%)	Patients receiving by immune checkpoint blockers (ICI) in first line (L1), or at progression after platinum in second line (L2) and beyond	
	n = 78	L1**, n = 11	≥ L2, *n* = 48***
NE	11 (14.1%)	1 (9.1%)	3 (6.3%)
CR	9 (11.5%)	0 (0.0%)	6 (12.5%)
PR	30 (38.4%)	6 (54.5%)	16 (33.3%)
SD	14 (18%)	0 (0.0%)	10 (20.8%)
PD	14 (18%)	4 (36.4%)	14 (29.2%)
ORR	50.0% (95%CI: 38.5–61.5)	54.6% (95%CI: 23.4–83.3)	45.8% (95%CI: 31.4–60.8)
DCR	68.0% (95%CI: 56.4–78.1)	54.6% (95%CI: 23.4–83.3)	66.7% (95%CI: 51.6–79.6)

NE: non evaluable; CR: complete response; PR: partial response; SD: stable disease; PD: disease progression; ORR: objective response rate (CR + PR); DCR: disease control rate (CR + PR + SD).
* 3 patients received targeted therapy (PARPi or mTORi) with carboplatine paclitaxel as maintenance or in combination (clinical trials) in first line.
** Patients treated by immunotherapy in first line were not included in efficacy analysis, NB: among 11 patients, 2 patients received combination anti PD1 and Anti CTLA4 in first line setting.
*** 1 patient received immunotherapy in combination in third line after failure of antiPD1 as monotherapy in second line.

not included in the primary efficacy analysis, 11 patients received immunotherapy in first line and demonstrated an ORR of 54.5% (95% CI: 23.4–83.3), quite similar to the activity of platinum-based combination in first line. Whether first line ICI may improve tolerance and outcome for MSI-H EC is under investigation. The randomized DOMENICA trial is investigating efficacy of platinum chemotherapy versus ICI in first line in this population [36]. According to our data, platinum chemotherapy response rate is consistent in MSI-H EC population to the historical

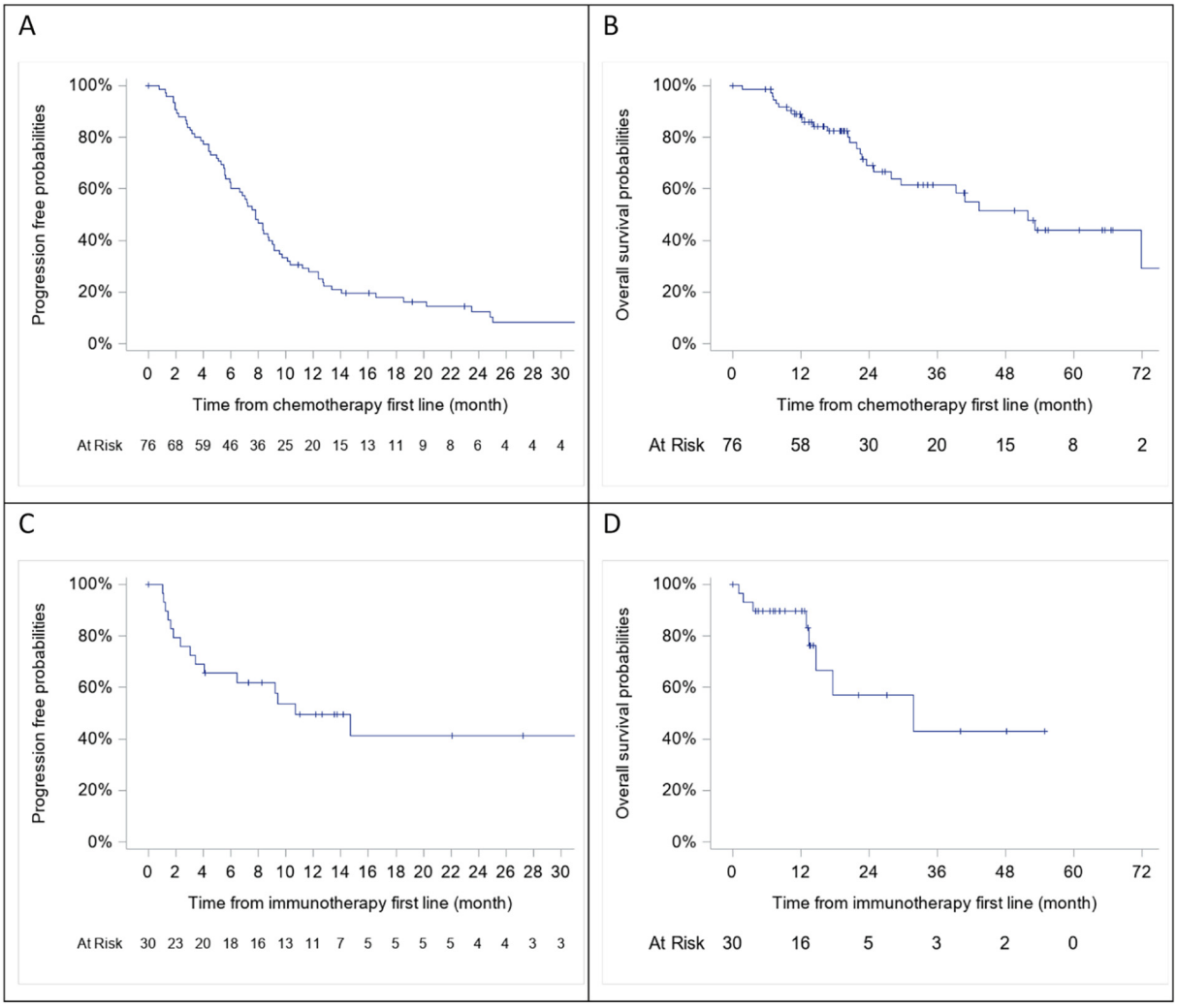

Fig. 2. Kaplan-Meier estimation of progression-free survival (A) and overall survival (B) in patients with platinum chemotherapy in first line setting and of progression-free survival (C) and overall survival (D) under ICI in second line setting.

activity reported in all comer EC population. Longer than expected OS in our metastatic/recurrent MMRd/MSI cohort may be attributable to subsequent ICI. When examining response rates, the ORR was 45.8% (95% CI: 31.4–60.8) in patients receiving ICI in second line after platinum chemotherapy in metastatic setting. This first exposure to ICI for this population MSI-H EC, probably lead to a more favorable relative response for ICI over platinum. Interestingly, median PFS in second line under ICI was longer than median PFS in first line. Longer PFS of ICI in second line may be linked to the small sample size; or it may reflect a priming effect of chemotherapy. Indeed chemotherapy mechanism leads to the stimulation of anticancer immunity either by initiating the release of immunostimulatory molecules from dying tumoral cells and by mediating off-target effects on immune cell populations [37]. Chemotherapy enhance tumor antigen presentation by upregulating the expression of tumor antigens themselves. For example, platinum chemotherapy is able to promote tumoral cells recognition and lysis, promote antitumor CD4 + T cell phenotype, and paclitaxel could increase dendritic cells activation and abrogate immunosuppressive Treg cells activity [38]. Randomized prospective trials are needed to address this question. Currently, the results of phase 3 trial ENGOT c93 trial comparing pembrolizumab with carboplatin plus paclitaxel in first dMMR advanced EC is still pending [39].

5. Conclusions

Recent advances in the molecular characterization of EC has led to significant advances in therapeutic strategies. In women with MMRd/MSI-H metastatic EC progressing after platinum, treatment with PD-1 or PDL-1 inhibitors results in unprecedented response rates between 40 and 60%. Our current retrospective study is the largest one describing benefit of first line platinum chemotherapy in MSI-H EC. Considering both ORR and PFS, platinum chemotherapy efficacy in metastatic MSI-H EC was consistent with efficacy in an all comers de novo metastatic/recurrent EC population. Together, our results provide some data in support of current trials investigating ICI as first line treatment compared to standard chemotherapy in MMRd/MSI-H EC.

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CRediT author statement

EC JA GLT AL: Conceptualization, Methodology, Software.

EC AL CG GLT Data curation, Writing- Original draft preparation.

EC GLT DC CG SP FJ SJ MP IRC MF FJ ND JSF PP JA AL: Visualization, Investigation.

EC AL JA GLT: Supervision.

EC AL JA CG Software, Validation.

EC GT DC SP EB FJ SJ MP IRC MF FJ ND JSF PP JA AL: Writing-Reviewing and Editing,

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Dr. Colomba has received honoraria (self and Institution) from AGSK, Eisai, Tesaro, Clovis Oncology, Tesaro, and IPSEN, Sanofi, BMS, Pfizer. She has served in a consulting or advisory role for IPSEN, MSD, EISAI, Clovis Oncology, Pfizer, and Tesaro; has received institutional research funding from IPSEN, and has been reimbursed for travel, accommodations, or other expenses by IPSEN, EISAI, Pfizer.

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G Le Teuff, Dr. Genestie, Dr. Coupez, Dr. De Percin, Dr. Brachet, Pr Joly, Dr. Sajous has no disclosure to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.11.029.

References

[1] L. Rahib, B.D. Smith, R. Aizenberg, A.B. Rosenzweig, J.M. Fleshman, L.M. Matrisian, Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States, Cancer Res. 74 (11) (2014) 2913–2921, https://doi.org/10.1158/0008-5472.CAN-14-0155.

[2] C. Eheman, S.J. Henley, R. Ballard-Barbash, et al., Annual report to the nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity, Cancer. 118 (9) (2012) 2338–2366, https://doi.org/10.1002/cncr.27514.

[3] M.A. Sovak, J. Dupont, M.L. Hensley, et al., Paclitaxel and carboplatin in the treatment of advanced or recurrent endometrial cancer: a large retrospective study, Int. J. Gynecol. Cancer 17 (1) (2007) 197–203, https://doi.org/10.1111/j.1525-1438.2006.00746.x.

[4] D. Pectasides, N. Xiros, G. Papaxoinis, et al., Carboplatin and paclitaxel in advanced or metastatic endometrial cancer, Gynecol. Oncol. 109 (2) (2008) 250–254, https://doi.org/10.1016/j.ygyno.2008.01.028.

[5] D.S. Miller, V.L. Filiaci, R.S. Mannel, et al., Carboplatin and paclitaxel for advanced endometrial Cancer: final overall survival and adverse event analysis of a phase III trial (NRG oncology/GOG0209), J. Clin. Oncol. 38 (33) (2020) 3841–3850, https://doi.org/10.1200/JCO.20.01076.

[6] H. Nomura, D. Aoki, F. Takahashi, et al., Randomized phase II study comparing docetaxel plus cisplatin, docetaxel plus carboplatin, and paclitaxel plus carboplatin in patients with advanced or recurrent endometrial carcinoma: a Japanese gynecologic oncology group study (JGOG2041), Ann. Oncol. 22 (3) (2011) 636–642, https://doi.org/10.1093/annonc/mdq401.

[7] L.A. Meyer, R.R. Broaddus, K.H. Lu, Endometrial cancer and lynch syndrome: clinical and pathologic considerations, Cancer Control 16 (1) (2009) 14–22, https://doi.org/10.1177/107327480901600103.

[8] Cancer Genome Atlas Research Network, C. Kandoth, N. Schultz, et al., Integrated genomic characterization of endometrial carcinoma, Nature. 497 (7447) (2013) 67–73, https://doi.org/10.1038/nature12113.

[9] R. Bonneville, M.A. Krook, E.A. Kautto, et al., Landscape of microsatellite instability across 39 Cancer types, JCO Precision Oncol. 1 (2017) 1–15, https://doi.org/10.1200/PO.17.00073.

[10] M. Kloor, Doeberitz M. von Knebel, The immune biology of microsatellite-unstable Cancer, Trends Cancer. 2 (3) (2016) 121–133, https://doi.org/10.1016/j.trecan.2016.02.004.
[11] A. Goel, C.N. Arnold, D. Niedzwiecki, et al., Characterization of sporadic colon cancer by patterns of genomic instability, Cancer Res. 63 (7) (2003) 1608–1614.
[12] I. Zighelboim, P.J. Goodfellow, F. Gao, et al., Microsatellite instability and epigenetic inactivation of MLH1 and outcome of patients with endometrial carcinomas of the endometrioid type, J. Clin. Oncol. 25 (15) (2007) 2042–2048, https://doi.org/10.1200/JCO.2006.08.2107.
[13] A. León-Castillo, S.M. de Boer, M.E. Powell, et al., Molecular classification of the PORTEC-3 trial for high-risk endometrial Cancer: impact on prognosis and benefit from adjuvant therapy, JCO. 38 (29) (2020) 3388–3397, https://doi.org/10.1200/JCO.20.00549.
[14] T.E. Soumerai, M.T.A. Donoghue, C. Bandlamudi, et al., Clinical utility of prospective molecular characterization in advanced endometrial Cancer, Clin. Cancer Res. 24 (23) (2018) 5939–5947, https://doi.org/10.1158/1078-0432.CCR-18-0412.
[15] L. Chang, M. Chang, H.M. Chang, F. Chang, Microsatellite instability: a predictive biomarker for Cancer immunotherapy, Appl. Immunohistochem. Mol. Morphol. 26 (2) (2018) e15–e21, https://doi.org/10.1097/PAI.0000000000000575.
[16] P. Zhao, L. Li, X. Jiang, Q. Li, Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy, J. Hematol. Oncol. 12 (1) (2019) 54, https://doi.org/10.1186/s13045-019-0738-1.
[17] L. Nebot-Bral, D. Brandao, L. Verlingue, et al., Hypermutated tumours in the era of immunotherapy: the paradigm of personalised medicine, Eur. J. Cancer 84 (2017) 290–303, https://doi.org/10.1016/j.ejca.2017.07.026.
[18] D.T. Le, T.W. Kim, E. Van Cutsem, et al., Phase II open-label study of Pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal Cancer: KEYNOTE-164, J. Clin. Oncol. 38 (1) (2020) 11–19, https://doi.org/10.1200/JCO.19.02107.
[19] T. André, K.K. Shiu, T.W. Kim, et al., Pembrolizumab in microsatellite-instability-high advanced colorectal Cancer, N. Engl. J. Med. 383 (23) (2020) 2207–2218, https://doi.org/10.1056/NEJMoa2017699.
[20] A. Marabelle, D.T. Le, P.A. Ascierto, et al., Efficacy of Pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient Cancer: results from the phase II KEYNOTE-158 study, J. Clin. Oncol. 38 (1) (2020) 1–10, https://doi.org/10.1200/JCO.19.02105.
[21] L.A. Diaz, D.T. Le, T. Yoshino, et al., KEYNOTE-177: phase 3, open-label, randomized study of first-line pembrolizumab (Pembro) versus investigator-choice chemotherapy for mismatch repair-deficient (dMMR) or microsatellite instability-high (MSI-H) metastatic colorectal carcinoma (mCRC), JCO. 36 (4_suppl) (2018) https://doi.org/10.1200/JCO.2018.36.4_suppl.TPS877 TPS877-TPS877.
[22] Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability–high tumors: A combined analysis of two cohorts in the GARNET studyJ. Clin. Oncol. Vol 39, issue 15 Supp 2021, Accessed February 17, 2022 https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.2564
[23] A. Oaknin, A.V. Tinker, L. Gilbert, et al., Clinical activity and safety of the anti-programmed death 1 monoclonal antibody Dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial Cancer: a nonrandomized phase 1 clinical trial, JAMA Oncol (2020) https://doi.org/10.1001/jamaoncol.2020.4515 Published online October 1.
[24] D. O'Malley, A. Marabelle, A.D. Jesus-Acosta, et al., Pembrolizumab in patients with MSI-H advanced endometrial cancer from the KEYNOTE-158 study, Ann. Oncol. 30 (2019) v425–v426, https://doi.org/10.1093/annonc/mdz250.052.
[25] V. Makker, M.L. Hensley, Q. Zhou, A. Iasonos, C.A. Aghajanian, Treatment of advanced or recurrent endometrial carcinoma with doxorubicin in patients progressing after paclitaxel/carboplatin: Memorial Sloan-Kettering Cancer Center experience from 1995 to 2009, Int. J. Gynecol. Cancer 23 (5) (2013) 929–934, https://doi.org/10.1097/IGC.0b013e3182915c20.
[26] S.M. de Boer, M.E. Powell, L. Mileshkin, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial, Lancet Oncol. 19 (3) (2018) 295–309, https://doi.org/10.1016/S1470-2045(18)30079-2.
[27] S.M. de Boer, M.E. Powell, L. Mileshkin, et al., Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial, Lancet Oncol. 20 (9) (2019) 1273–1285, https://doi.org/10.1016/S1470-2045(19)30395-X.
[28] J.B. Basil, P.J. Goodfellow, J.S. Rader, D.G. Mutch, T.J. Herzog, Clinical significance of microsatellite instability in endometrial carcinoma, Cancer. 89 (8) (2000) 1758–1764, https://doi.org/10.1002/1097-0142(20001015)89:8<1758::aid-cncr16>3.0.co;2-a.
[29] D. Kanopienė, G. Smailytė, J. Vidugirienė, J. Bacher, Impact of microsatellite instability on survival of endometrial cancer patients, Medicina (Kaunas). 50 (4) (2014) 216–221, https://doi.org/10.1016/j.medici.2014.09.002.
[30] D. Black, R.A. Soslow, D.A. Levine, et al., Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma, J. Clin. Oncol. 24 (11) (2006) 1745–1753, https://doi.org/10.1200/JCO.2005.04.1574.
[31] M.L. Cote, A. Kam, C.Y.Y. Chang, et al., A pilot study of microsatellite instability and endometrial cancer survival in white and African American women, Int. J. Gynecol. Pathol. 31 (1) (2012) 66–72, https://doi.org/10.1097/PGP.0b013e318224329e.
[32] H. Arabi, H. Guan, S. Kumar, et al., Impact of microsatellite instability (MSI) on survival in high grade endometrial carcinoma, Gynecol. Oncol. 113 (2) (2009) 153–158, https://doi.org/10.1016/j.ygyno.2009.02.004.
[33] H.J. Mackay, S. Gallinger, M.S. Tsao, et al., Prognostic value of microsatellite instability (MSI) and PTEN expression in women with endometrial cancer: results from studies of the NCIC clinical trials group (NCIC CTG), Eur. J. Cancer 46 (8) (2010) 1365–1373, https://doi.org/10.1016/j.ejca.2010.02.031.
[34] S. Fiumicino, A. Ercoli, G. Ferrandina, et al., Microsatellite instability is an independent indicator of recurrence in sporadic stage I-II endometrial adenocarcinoma, J. Clin. Oncol. 19 (4) (2001) 1008–1014, https://doi.org/10.1200/JCO.2001.19.4.1008.
[35] E.M. Francisco, Keytruda: Pending EC decision, European Medicines Agency, 2020 , Published December 10. Accessed January 17, 2021 https://www.ema.europa.eu/en/medicines/human/summaries-opinion/keytruda-1.
[36] ARCAGY/ GINECO GROUP, Randomized Phase III Trial in MMR Deficient Endometrial Cancer Patients Comparing Chemotherapy Alone Versus Dostarlimab in First Line Advanced/Metastatic Setting. clinicaltrials.gov, Accessed May 22, 2022 https://clinicaltrials.gov/ct2/show/NCT05201547 2022.
[37] L. Galluzzi, J. Humeau, A. Buqué, L. Zitvogel, G. Kroemer, Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors, Nat. Rev. Clin. Oncol. 17 (12) (2020) 725–741, https://doi.org/10.1038/s41571-020-0413-z.
[38] L.A. Emens, G. Middleton, The interplay of immunotherapy and chemotherapy: harnessing potential synergies, Cancer Immunol Res. 3 (5) (2015) 436–443, https://doi.org/10.1158/2326-6066.CIR-15-0064.
[39] Merck Sharp & Dohme LLC, A Phase 3 Randomized, Open-Label, Active-Comparator Controlled Clinical Study of Pembrolizumab Versus Platinum Doublet Chemotherapy in Participants With Mismatch Repair Deficient (DMMR) Advanced or Recurrent Endometrial Carcinoma in the First-Line Setting (KEYNOTE-C93/GOG-3064/ENGOT-En15), clinicaltrials.gov. Accessed May 22, 2022 https://clinicaltrials.gov/ct2/show/NCT05173987 2022.