Gynecologic Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Treatment patterns and real-world clinical outcomes in patients with advanced endometrial cancer who are microsatellite instability (MSI)-high or are mismatch repair deficient (dMMR) in the United States

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HIGHLIGHTS

- This study fills a gap in real-world outcomes in MSI-H/dMMR aEC patients with disease progression after systemic therapy.
- Most frequently administered 2 L treatments in patients were pembrolizumab (immunotherapy) and doxorubicin (chemotherapy).
- Patients who received pembrolizumab as 2LOT had rwPFS and OS outcomes comparable to those seen in clinical trials.
- Results approximate clinical trial results, showing survival benefits of pembrolizumab as 2LOT in real-world settings.

ARTICLE INFO

Article history:
Received 10 June 2022
Received in revised form 21 September 2022
Accepted 18 October 2022
Available online xxxx

Keywords:
Endometrial cancer
MSI-H/dMMR
Real-world data
Second-line treatment
Clinical outcomes
Immunotherapy

ABSTRACT

Objectives. Microsatellite instability-high (MSI-H) and deficient DNA mismatch repair (dMMR) status have emerged as actionable biomarkers for advanced endometrial cancer (aEC). The objective of this study was to assess clinical outcomes and treatment patterns among MSI-H/dMMR aEC patients who had disease progression following prior systemic therapy (FPST) in the US.

Methods. Endometrial Cancer Health Outcomes (ECHO) was a retrospective, medical chart review study of patients with MSI-H/dMMR aEC who had disease progression between 07/01/2016 and 12/31/2018 FPST and were not candidates for curative surgery. Data on patient demographics, clinical and treatment characteristics, and clinical outcomes were collected. Kaplan-Meier analyses were performed to estimate real-world progression-free survival (rwPFS) and overall survival (OS), stratified by drug class.

Results. A total of 124 eligible patients who initiated second-line chemotherapy ± bevacizumab or immunotherapy were included. Mean age was 61.4 years at aEC diagnosis and 86.3% of patients were stage IIIB-IV. Median rwPFS and OS were 4.0 months (95% CI: 2.0–9.0) and 7.0 months (95% CI: 5.0–18.0), respectively, among 21 patients who received chemotherapy ± bevacizumab, and 29.0 months (95% CI: 18.0-NE) and not reached (95% CI: 30.0-NA), respectively, among 103 patients who received immunotherapy. Most patients ($n = 92$) received pembrolizumab; among these patients, rwPFS and OS were 29.0 months (95% CI: 18.0-NE) and 30 months (95% CI: 30.0-NA), respectively.

Conclusions. Real-world evidence suggests that pembrolizumab monotherapy provides considerable clinical benefits and has become the standard of care for MSI-H/dMMR aEC patients FPST who are not candidates for curative surgery in real-world settings.

1. Background

Endometrial cancer (EC) is the most common malignancy of the female reproductive system in developed countries with a steady

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https://doi.org/10.1016/j.ygyno.2022.10.016

increase in incidence over the past few decades [1]. In the United States (US), the estimated incidence of EC in 2022 is 65,950 new cases with approximately 12,550 estimated deaths [1–7]. EC is commonly diagnosed among postmenopausal women, although women with key risk factors such as obesity, family history of EC, early menarche, late menopause, old age and infertility remain at higher risk for the disease [8]. Traditional treatment for EC has been a combination of therapies including surgery, radiotherapy, and/or chemotherapy, depending on disease stage [5]. EC diagnosed in patients at stage I or II (the majority of EC cases) is considered curable with a five-year survival rate of roughly 90% [6]. However, the 10%–13% of patients diagnosed with recurrent or advanced stage III–IV disease are difficult to treat and have poor prognosis [3,6,7].

The Cancer Genome Atlas Project (TCGA) identified specific types of EC tumors based on genomic characterization that have shown to be reliable prognostic biomarkers for this disease [9]. In patients with hormone sensitive Type I EC, the most common molecular alteration is microsatellite instability (MSI) [10]. It is caused by defects in the DNA mismatch repair (MMR) system, which is responsible for rectifying errors in and preserving the stability of DNA, specifically at DNA microsatellites [11]. Tumors with abnormal or missing MMR proteins are considered to be mismatch repair deficient (dMMR). If at least two of the standard DNA repeat sites used in microsatellite testing are altered or mutated, the tumor is also considered to be microsatellite instability-high (MSI-H). Given their mechanisms, overlap between dMMR tumor status and MSI-H tumor status is high (roughly 90–95%) and thus, the two statuses are interchangeable [1]. Classification of EC patients through these biomarkers allows for a more tailored understanding of the disease mechanisms and relevant treatment options based on tumor biomarker status. A meta-analysis of aEC patients diagnosed in the US reported a pooled estimate of 26% (95% CI, 23%–29%) MSI-H tumors and 25% (95% CI, 22%–28%) dMMR tumors, indicating that roughly a quarter of aEC patients may benefit from the availability of pembrolizumab and other immune checkpoint inhibitors as novel therapies [12].

Recent approval of treatments specific to tumor status has changed the treatment landscape for patients with recurrent or aEC [13–16]. In May 2017, the FDA granted accelerated approval for the use of pembrolizumab, an anti-PD-1 antibody, for patients with MSI-H/dMMR tumors. In March 2022, FDA granted regular approval for pembrolizumab as a single agent for the treatment of patients with advanced endometrial carcinoma (aEC) that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation. In September 2019, FDA approved the combination of pembrolizumab with lenvatinib for patients with non-MSI-H/mismatch repair proficient (pMMR) tumors [17,18]. Dostarlimab was also recently provided accelerated approval for treatment of patients with recurrent or aEC that is dMMR and with progression on or following a prior platinum-based therapy [19].

Guidelines from the National Comprehensive Cancer Network (NCCN) for recurrent, metastatic or high-risk disease EC patients recommend carboplatin/paclitaxel as the preferred therapy. NCCN guidelines for biomarker-directed second-line systemic therapy recommend pembrolizumab as the preferred therapy for aEC patients with MSI-H/dMMR tumors, and combination therapy of lenvatinib with pembrolizumab for non-MSI-H/pMMR tumors [5]. A recent systemic literature review of observational studies (2000−2020) of chemotherapy for recurrent or advanced EC (aEC) found that patients with treatment-free intervals of <6 months receiving traditional chemotherapies in later-line settings experienced poor outcomes including overall survival (median of 5.5–11.3 months) and progression-free survival (median of 2.0–3.2 months) [20].

Despite the increasing importance of tumor biomarkers and recent shifts in the treatment landscape and guidelines for aEC, there remains a lack of real-world evidence for MSI-H/dMMR aEC patients who are not candidates for curative surgery and/or have disease progression following prior systemic therapy and who are being treated with either chemotherapy or immunotherapy. The purpose of the Endometrial Cancer Health Outcomes (ECHO) study was to describe treatment patterns and real-world clinical outcomes in MSI-H/dMMR aEC patients who have progressed following prior systemic therapy in the US from mid-2016 to mid-2019.

2. Methods

2.1. Study design and eligibility criteria

The ECHO study was a multi-center, retrospective, medical chart review study conducted in the US. Physicians recruited to participate in the study were selected from the Definitive Healthcare National Database and represented a geographically dispersed sample of EC-treating oncologists (medical oncologist or gynecologic oncologist) in the US. Physicians provided de-identified data from eligible patients' medical records. The ECHO study was approved by the WCG institutional review board (IRB) (previously known as Western IRB/Copernicus Group), which granted the study a waiver from obtaining informed consent from patients.

Patient selection was conducted in two parts. In Part I, all patients managed by the participating oncologists who were ≥18 years of age, diagnosed with aEC between July 1, 2016 and December 31, 2018 and not candidates for curative surgery were eligible. These data were used to determine prevalence of MSI/MMR tumor testing in real-world clinical practice. Physicians reported MSI testing using a polymerase chain reaction test (categorized as MSI-H, MSI-low, or microsatellite instability stable) or MMR testing using an immunohistochemistry test (categorized as MLH1, MSH2, or MSH6). Details on methodology and results from Part I, including prevalence of MSI/MMR testing in aEC patients, have been previously presented [21].

In Part II, data were obtained for a subset of patients from Part I who met additional eligibility criteria: had a known MSI/MMR tumor status of MSI-H/dMMR; had received at least 1 systemic therapy after the diagnosis of aEC; had disease progression between July 1, 2016 and June 30, 2019; and were not enrolled in an EC clinical trial. Physicians completed a comprehensive patient case report form (CRF) for eligible patients based on information available from patient medical charts. Patients were excluded if they had any malignancy active within the previous 3 years except for locally curable cancers that had been cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix, or breast. This study focuses on patient characteristics, treatment patterns and outcomes from Part II of the study.

2.2. Data collection and study measures

Physicians provided de-identified patient data from medical records from diagnosis of EC until the last available patient follow-up for patients fulfilling all eligibility criteria. Data were entered into an electronic case report form (eCRF) via a secure online portal. Study measures in Part I included patient demographics and disease status (age, comorbidities, race, BMI, ECOG performance status, disease stage, histology), and MSI/MMR testing information (type of test, result).

Study measures in Part II included details on treatment (drugs, dosage, frequency, discontinuation) and real-world best overall response to treatment (rwORR). Treatment response to second-line of therapy (2LOT) was categorized as complete response (CR), partial response (PR), stable disease (SD) or disease progression. The rwORR consisted of CR and PR. Real-world progression-free survival (rwPFS) was measured from date of initiation of 2LOT until date of progression and defined as increase in tumor size, discontinuation of a line of therapy (LOT) due to disease progression, or death. Overall survival (OS) was estimated from date of initiation of 2LOT until date of death.

2.3. Statistical analysis

Categorical variables were summarized using the percentage and count in each category. Continuous variables were summarized using the summary statistics of mean and standard deviation and/or median and range, as appropriate. Time to event analyses such as OS and rwPFS were conducted using Kaplan-Meier analysis methods and were reported as median values and estimated probabilities of events at specific timepoints. For time to event outcomes, patients were censored at date of most recent patient follow-up/contact. All analyses were conducted using SAS Version 9.4.

Patients were further stratified by 2LOT drug class (chemotherapy and/or bevacizumab administered as mono- or combination therapy [chemotherapy ± bevacizumab] vs. immunotherapy), as well as by the most common 2LOT therapy agent administered for each drug class.

3. Results

3.1. Physician characteristics

A total of 48 physicians participated in this study. Physicians were primarily medical oncologists (77.1%), predominantly male (77.1%), <60 years of age (56.2%), and had been practicing for >10 years (68.8%). About 90% physicians practiced in an urban setting, 66.7% had a group practice and 95.8% practiced in a teaching/academic hospital.

3.2. Demographic and clinical characteristics in patients initiating second-line therapy

Medical chart data were abstracted from 124 eligible patients who met inclusion and exclusion criteria and who initiated second-line chemotherapy ± bevacizumab ($n = 21$) or immunotherapy ($n = 103$). The mean age was 61.4 years at aEC diagnosis, 78.2% were White/Caucasian and 12.9% were Black or African origin. The most prevalent comorbidity was diabetes (33.9%). At diagnosis, 86.3% were Stage IIIB-IV, 76.6% had ECOG status of 1 or 2, and more than half of the patients had endometroid carcinoma histology (Table 1).

Patient demographics and characteristics were similar across both the therapy agents and drug classes. Patients who received chemotherapy ± bevacizumab had a mean age of 61.9 years, 81.0% were White/Caucasian and 95.3% were Stage IIIB-IV at diagnosis, while patients who received immunotherapy had a mean age

Table 1
Patient demographic and clinical characteristics.

Characteristics	All (N = 124)	Chemotherapy ± Bevacizumab (*N* = 21)	Immunotherapy (N = 103)	Doxorubicin/doxorubicin liposomal monotherapy (*N* = 12)	Pembrolizumab (N = 92)
Age at aEC diagnosis					
Mean (SD)	61.4 (9.5)	61.9 (9.3)	61.2 (9.6)	60.4 (10.3)	61.1 (9.9)
Median (Q1 to Q3)	60.0 (54.5 to 68.0)	60.0 (56.0 to 69.0)	60.0 (53.0 to 68.0)	60.0 (52.5 to 68.5)	60.0 (53.0 to 68.0)
BMI at aEC diagnosis					
Mean (SD)	26.5 (5.2)	29.3 (8.6)	26.1 (4.5)	33.2 (14.3)	26.6 (4.4)
Median (Q1 to Q3)	25.7 (23.3 to 29.2)	26.6 (24.9 to 30.0)	25.2 (23.3 to 29.1)	28.2 (24.8 to 41.5)	25.9 (23.6 to 29.8)
Race, N (%)					
White	97 (78.2)	17 (81.0)	80 (77.7)	8 (66.7)	73 (79.3)
Black	16 (12.9)	4 (19.0)	12 (11.7)	4 (33.3)	11 (12.0)
Asian	7 (5.6)	0 (0.0)	7 (6.8)	0 (0.0)	6 (6.5)
Other	4 (3.2)	0 (0.0)	4 (3.9)	0 (0.0)	2 (2.2)
Ethnicity, N (%)					
Hispanic or Latino	26 (21.0)	6 (28.6)	20 (19.4)	3 (25.0)	18 (19.6)
Not Hispanic or Latino	98 (79.0)	15 (71.4)	83 (80.6)	9 (75.0)	74 (80.4)
Charlson Comorbidity Index					
Mean (SD)	1.4 (1.9)	0.8 (1.1)	1.5 (2.0)	0.6 (0.9)	1.4 (1.9)
Median (Q1 to Q3)	1.0 (0.0 to 2.0)	0.0 (0.0 to 2.0)	1.0 (0.0 to 2.0)	0.0 (0.0 to 1.5)	1.0 (0.0 to 2.0)
Disease Stage at diagnosis, N (%)					
IA	3 (2.4)	0 (0.0)	3 (2.9)	0 (0.0)	3 (3.3)
IB	2 (1.6)	0 (0.0)	2 (1.9)	0 (0.0)	2 (2.2)
II	10 (8.1)	0 (0.0)	10 (9.7)	0 (0.0)	9 (9.8)
Stage IIIA	2 (1.6)	1 (4.8)	1 (1.0)	1 (8.3)	1 (1.1)
Stage IIIB	8 (6.5)	1 (4.8)	7 (6.8)	0 (0.0)	6 (6.5)
Stage IIIC	13 (10.5)	2 (9.5)	11 (10.7)	0 (0.0)	11 (12.0)
IVA-T4, Any N, M0	7 (5.6)	1 (4.8)	6 (5.8)	0 (0.0)	6 (6.5)
IVB-Any T, Any N, M1	79 (63.7)	16 (76.2)	63 (61.2)	11 (91.7)	54 (58.7)
ECOG at initiation of 2LOT, N (%)					
0 = Fully active	20 (16.1)	2 (9.5)	18 (17.5)	0 (0.0)	18 (19.6)
1 = Restricted in physically strenuous activity	77 (62.1)	7 (33.3)	70 (68.0)	2 (16.7)	59 (64.1)
2 = Unable to carry out work activity	18 (14.5)	4 (19.0)	14 (13.6)	2 (16.7)	14 (15.2)
Histology, N (%)					
Clear Cell Carcinoma	19 (15.3)	2 (9.5)	17 (16.5)	1 (8.3)	16 (17.4)
Carcinosarcoma	3 (2.4)	1 (4.8)	2 (2.0)	1 (8.3)	1 (1.1)
Endometroid carcinoma	71 (57.3)	14 (66.7)	57 (55.3)	10 (83.3)	52 (56.5)
Undifferentiated Carcinoma/ Mixed cell tumors	3 (2.4)	0 (0.0)	3 (2.9)	0 (0.0)	3 (3.3)
Mucinous Carcinoma	8 (6.5)	2 (9.5)	6 (5.8)	0 (0.0)	4 (4.3)
Serous Carcinoma	20 (16.1)	2 (9.5)	18 (17.5)	0 (0.0)	16 (17.4)
Metastatic site, N (%)					
Distant lymph nodes	40 (32.3)	6 (28.6)	34 (33.0)	3 (25.0)	30 (32.6)
Lung	49 (39.5)	7 (33.3)	42 (40.8)	3 (25.0)	39 (42.4)
Bone	16 (12.9)	3 (14.3)	13 (12.6)	1 (8.3)	10 (10.9)
Liver	34 (27.4)	7 (33.3)	27 (26.2)	5 (41.7)	21 (22.8)
Other	10 (8.1)	1 (4.8)	9 (8.7)	1 (8.3)	9 (9.8)

Abbreviations: aEC, advanced endometrial cancer; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; SD, standard deviation.

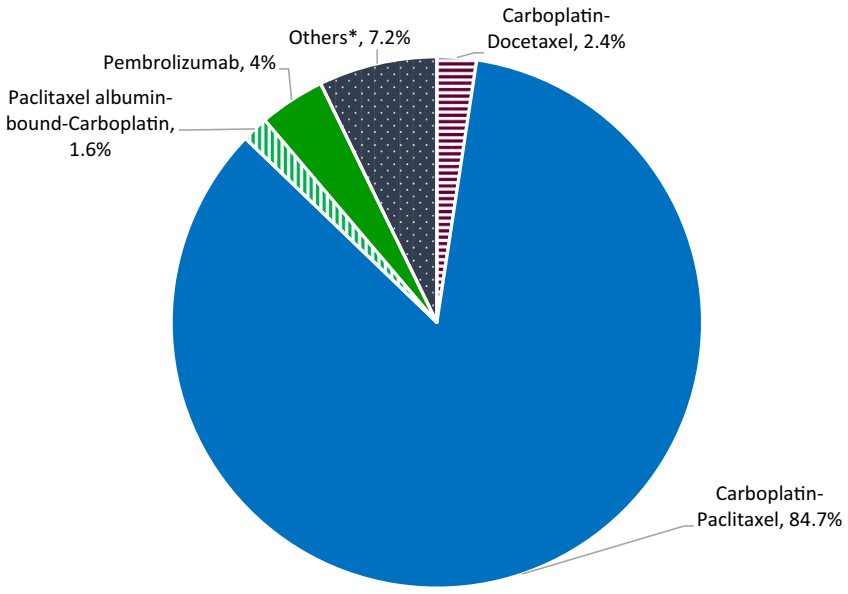

Fig. 1. Treatment distribution for first-line therapy agents in aEC patients with MSI-H/dMMR tumors ($n = 124$).
Others include: Carboplatin-docetaxel-bevacizumab, 0.8%; Carboplatin-paclitaxel-bevacizumab, 0.8%; Cisplatin, O.8%; Doxorubicin, 0.8%; Doxorubicin liposomal, 0.8%; Letrozole, 0.8%; Nivolumab-ipilimumab, 0.8%; Paclitaxel-carboplaOthers include: Carboplatin-docetaxel-bevacizumab, 0.8%; Carboplatin-paclitaxel-bevacizumab, 0.8%; Cisplatin, O.8%; Doxorubicin, 0.8%; Doxorubicin liposomal, 0.8%; Letrozole, 0.8%; Nivolumab-ipilimumab, 0.8%; Paclitaxel-carboplatin-docetaxel, 0.8%; Topotecan, 0.8% tin-docetaxel, 0.8%; Topotecan, 0.8%.

of 61.2 years, 77.7% were White/Caucasian and 84.5% were Stage IIIB-IV at diagnosis.

3.3. Treatment patterns

Of 124 patients, 84.7% ($n = 105$) were administered carboplatin/paclitaxel as first-line of therapy (1LOT) (Fig. 1). As 2LOT, among 21 (16.9%) patients that received chemotherapy ± bevacizumab, a majority (57.1%, $n = 12$) received doxorubicin/doxorubicin liposomal monotherapy. Of 103 (83.1%) patients that received immunotherapy, a majority (89.3%, $n = 92$) received pembrolizumab (Fig. 2). In all patients, the most common reason for treatment selection was efficacy or proven survival (70.2%), followed by biomarker test conducted (57.3%) and patient preference (18.5%). The most common reason for treatment selection in chemotherapy ± bevacizumab group was efficacy/proven survival (95.2%), meanwhile in the immunotherapy group it was biomarker test conducted (68.9%). Overall, <5% of patients required second-line dose changes. A total of 13.7% of patients also received radiation therapy, of which more than half received conventional external beam radiotherapy.

3.4. Treatment discontinuation

A total of 72 (58.1%) patients discontinued 2LOT after a median duration of 15 months (95% confidence interval [CI]: 11.0–25.0) from treatment initiation. In the chemotherapy ± bevacizumab group, 95.2% of patients discontinued after a median of 4 months (95% CI: 2.0–6.0), while in the immunotherapy group 50.5% of patients discontinued after a median of 21 months (95% CI: 15.0 – Not Estimable [NE]). Patients treated with doxorubicin/doxorubicin liposomal monotherapy discontinued after a median of 2 months (95% CI: 2.0–5.0), while those treated with pembrolizumab had a median time to discontinuation of 24 months (95% CI: 15.0 -NE) (Fig. 3).

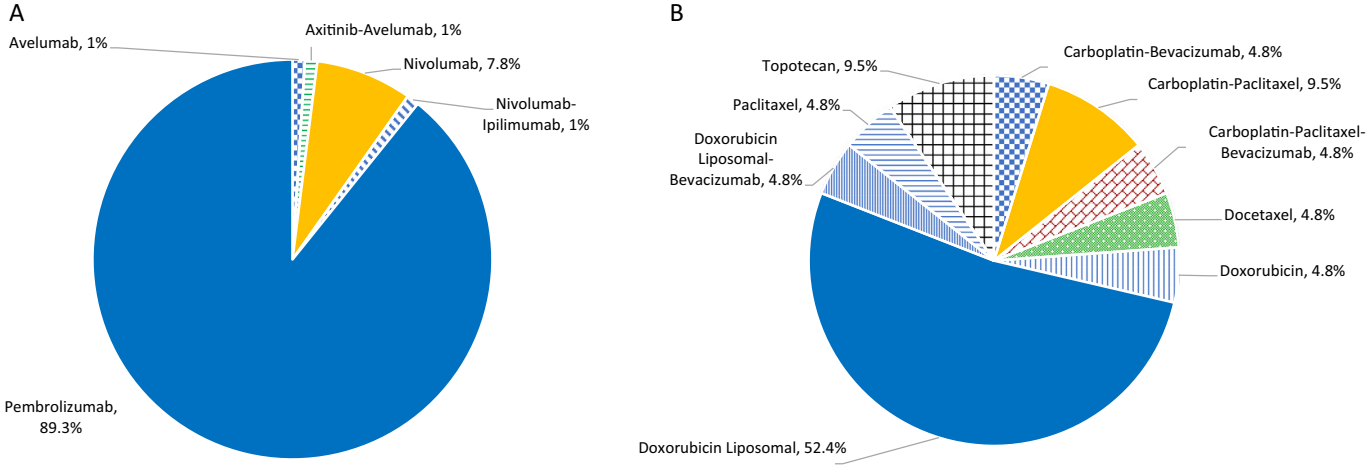

Fig. 2. Treatment distribution for second-line therapy agents in aEC patients with MSI-H/dMMR tumors (n = 124).
(A) 2L drug regimens and proportion of patients for immunotherapy (N = 103). (B) 2L drug regimens and proportion of patients for chemotherapy ± bevacizumab (N = 21).

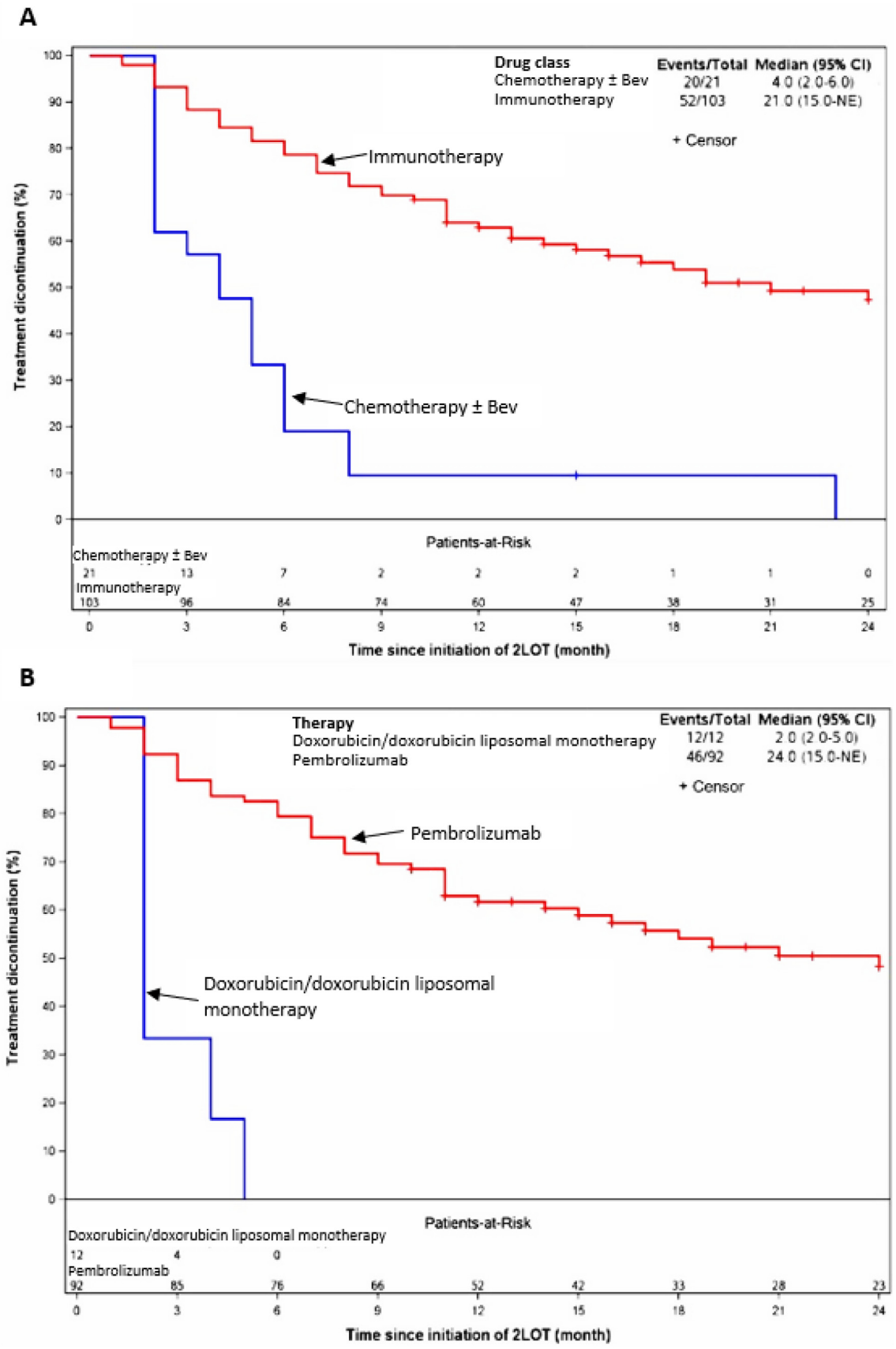

Fig. 3. Kaplan–Meier plot of time to treatment discontinuation in aEC patients with MSI-H/dMMR tumors by drug class (3A) and by therapy agent (3B) ($n = 124$).
Note: Bev: Bevacizumab, 2LOT: Second Line of Therapy.

The most common reason for treatment discontinuation was disease progression (62.5%), followed by patient choice/preference/refusal (15.3%), maximum clinical benefit (11.1%) and patient death (11.1%). The most common reason for treatment discontinuation was disease progression among both the chemotherapy ± bevacizumab group (80.0%) and the immunotherapy group (55.8%). Among patients who discontinued 2LOT, a total of 17 (23.6%) initiated a third line of therapy (3LOT). The most common 3LOT therapies were pembrolizumab (17.6%, $n = 3$) and bevacizumab (17.6%, n = 3).

3.5. Response to treatment

In 1LOT, the physician-reported rwORR (either CR or PR) was 72.6% ($n = 90$). The physician-reported rwORR in 2LOT was 23.8% (4.8% had CR and 19.0% had PR) in patients who received chemotherapy ± bevacizumab and was 78.6% (29.1% had CR and 49.5% had PR) in patients who received immunotherapy. No patients who received doxorubicin/doxorubicin liposomal monotherapy responded to treatment, while the rwORR was 80.4% in patients who received pembrolizumab. Among the 90 patients who had an overall response in 1LOT, 78.9% ($n = 71$) also responded to treatment in 2LOT.

In 2LOT, the median time to rwORR was 4 months among those who received chemotherapy ± bevacizumab and was 4 months among those who received immunotherapy. The median time to rwORR was 3 months among those who received pembrolizumab. Median duration of rwORR among patients who received chemotherapy ± bevacizumab was 4 months (95% CI: 4.0–14.0) and 26 months (95% CI: 26.0 – NE) among those who received immunotherapy. In the immunotherapy group, one patient's disease progression status was unknown and was excluded from the duration of response and disease progression analyses (in such analyses $n = 102$ for immunotherapy). Response was assessed based on the RECIST (78.2%), imRECIST (10.5%) and clinic assessment (10.5%) criteria.

3.6. Real-world progression-free survival

In 1LOT, the overall median rwPFS was estimated to be 10.0 months (95% CI: 7.0–12.0). In 2LOT, median rwPFS was estimated to be 4.0 months (95% CI: 2.0–9.0) for patients who received chemotherapy ± bevacizumab and 29.0 months (95% CI: 18.0 - NE) for patients who received immunotherapy. Median rwPFS was estimated to be 2.0 months (95% CI: 2.0–9.0) among those who received doxorubicin/doxorubicin liposomal monotherapy and 29.0 months (95% CI: 18.0 - NE) among those who received pembrolizumab. The estimated probabilities of rwPFS at 6, 12, and 24 months since the initiation of 2LOT in the chemotherapy ± bevacizumab group were 38.1%, 14.3%, and 0.0%, respectively, and in the immunotherapy group were 82.2%, 70.2%, and 53.5%, respectively. The estimated probabilities of rwPFS at 6, 12, and 24 months since the initiation of 2LOT in the doxorubicin/doxorubicin liposomal monotherapy group were 8.3%, 0.0%, and 0.0%, respectively, and in the pembrolizumab group were 83.4%, 69.9%, and 55.5%, respectively (Fig. 4).

3.7. Overall survival

Median OS was 7.0 months (95% CI: 5.0–18.0) in patients who received chemotherapy ± bevacizumab and was not reached (95% CI: 30.0 - NE) in patients who received immunotherapy. Median OS was 4.5 months (95% CI: 4.0–18.0) in patients who received doxorubicin/doxorubicin liposomal monotherapy and was 30.0 months (95% CI: 30.0 - NE) in patients who received pembrolizumab. The estimated probabilities of survival at 6, 12, and 24 months since the initiation of 2LOT in the chemotherapy ± bevacizumab group were 52.4%, 38.1%, and NA, respectively, and in the immunotherapy group were 93.2%, 78.0%, and 61.8%, respectively. The probabilities of survival at 6, 12, and 24 months since initiation of 2LOT in the doxorubicin/doxorubicin liposomal monotherapy group were 16.7%, 16.7%, and 0.0%, respectively, and in the pembrolizumab group were 93.4%, 77.4%, and 62.0%, respectively (Fig. 5).

4. Discussion

This is the first real-world, observational study conducted in the US using retrospective chart review data obtained from patients with aEC that is MSI-H/dMMR, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery. In the current literature, there is a lack of information on treatment outcomes in aEC patients based on MSI-tumor status. This study provides real-world evidence for the MSI-H/dMMR aEC population that can be used to understand the change in the treatment landscape due to approval of novel biomarker-specific therapies.

This study identified a total of 124 eligible aEC patients who received second-line chemotherapy ± bevacizumab or immunotherapy. The patients included in this study were relatively representative of the general aEC population in the US in terms of age and race [22]. At diagnosis, most patients were Stage IIIB-IV (86.3%) and a majority had an ECOG status of ≥1 (76.6%). More than half of the patients had endometroid carcinoma histology and exhibited a metastasis at diagnosis, with the lung being the most prevalent metastatic site (39.5%).

Our results show that in the first-line setting, almost 90% of patients initiated treatment with carboplatin/paclitaxel, consistent with the NCCN recommendations, indicating a consensus of 1LOT selection in clinical practice [5]. The current NCCN guidelines recommend use of pembrolizumab as the preferred regimen in the second-line setting for endometrial cancer patients with MSI-H/dMMR tumors. In our study, a majority (83.1%) initiated 2LOT with an immunotherapy, while 16.9% initiated with chemotherapy ± bevacizumab. In addition, there were 5 patients that had initiated second-line with a hormonal therapy that were not included in our analysis due to small sample size. This suggests that about 20% of patients were not treated with immunotherapy as second-line treatment. A subgroup analysis was conducted among the two most frequent drug regimens in the immunotherapy and chemotherapy ± bevacizumab groups. Among patients who received immunotherapy, the most frequent therapy was pembrolizumab monotherapy (89.3%) and among those who received chemotherapy ± bevacizumab, most received doxorubicin/doxorubicin liposomal monotherapy (57.1%). Physicians in the study noted that the primary reason for initiating pembrolizumab in the second-line setting was biomarker test conducted, followed by efficacy/proven survival. It was interesting to find that the most common reason for initiation of doxorubicin monotherapy was efficacy/proven survival, as this may indicate a lack of awareness of recent evidence and guidelines recommending the use of novel tumor-based therapies.

Overall, the MSI-H/dMMR patients in second-line settings had a median OS of 30.0 months and rwPFS of 19.0 months, indicating favorable clinical outcomes. There was a marked discrepancy depending on the treatment initiated in 2LOT. The median OS and rwPFS for patients initiating second-line therapy with pembrolizumab was 30.0 months (95% CI: 30.0 - NE) and 29.0 months (95% CI: 18.0 - NE) respectively, while in the doxorubicin/doxorubicin liposomal monotherapy group median OS and rwPFS were merely 4.5 months (95% CI: 4.0–18.0) and 2.0 months (95% CI: 2.0–9.0), respectively. Thus, those who received chemotherapy, particularly doxorubicin/doxorubicin liposomal monotherapy, demonstrated poor clinical outcomes.

Existing research from clinical trials supports the use of pembrolizumab for MSI-H/dMMR biomarker-specific treatment in patients with different solid tumors types such as EC. The KEYNOTE-158 trial was a phase II study that enrolled 79 MSI-H/dMMR aEC patients on second-line pembrolizumab (no comparators) and found an objective response rate of 48.0% (95% CI: 37.0–60.0); median PFS for these patients was 13.1 (95% CI: 4.3–34.4) months and OS was not reached (95% CI: 27.2 - NR) at end-point (disease progression and/or death) [23]. Our study

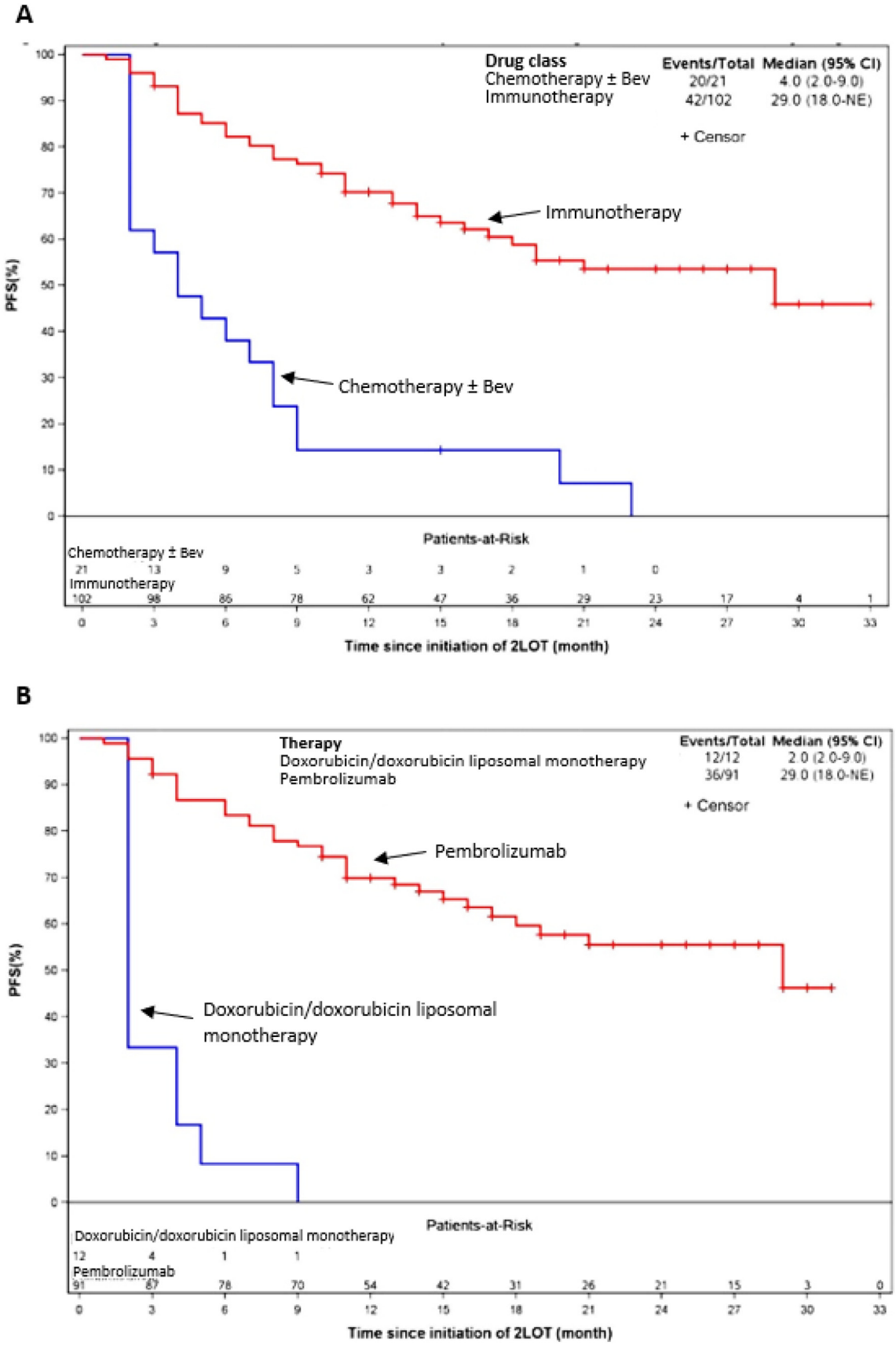

Fig. 4. Kaplan–Meier plot of real-world Progression-Free Survival (rwPFS) in aEC patients with MSI-high/dMMR tumors by drug class (4A) and by therapy agent (4B) ($n = 123$).
Note: PFS: Progression-free survival, Bev: Bevacizumab, 2LOT: Second Line of Therapy.

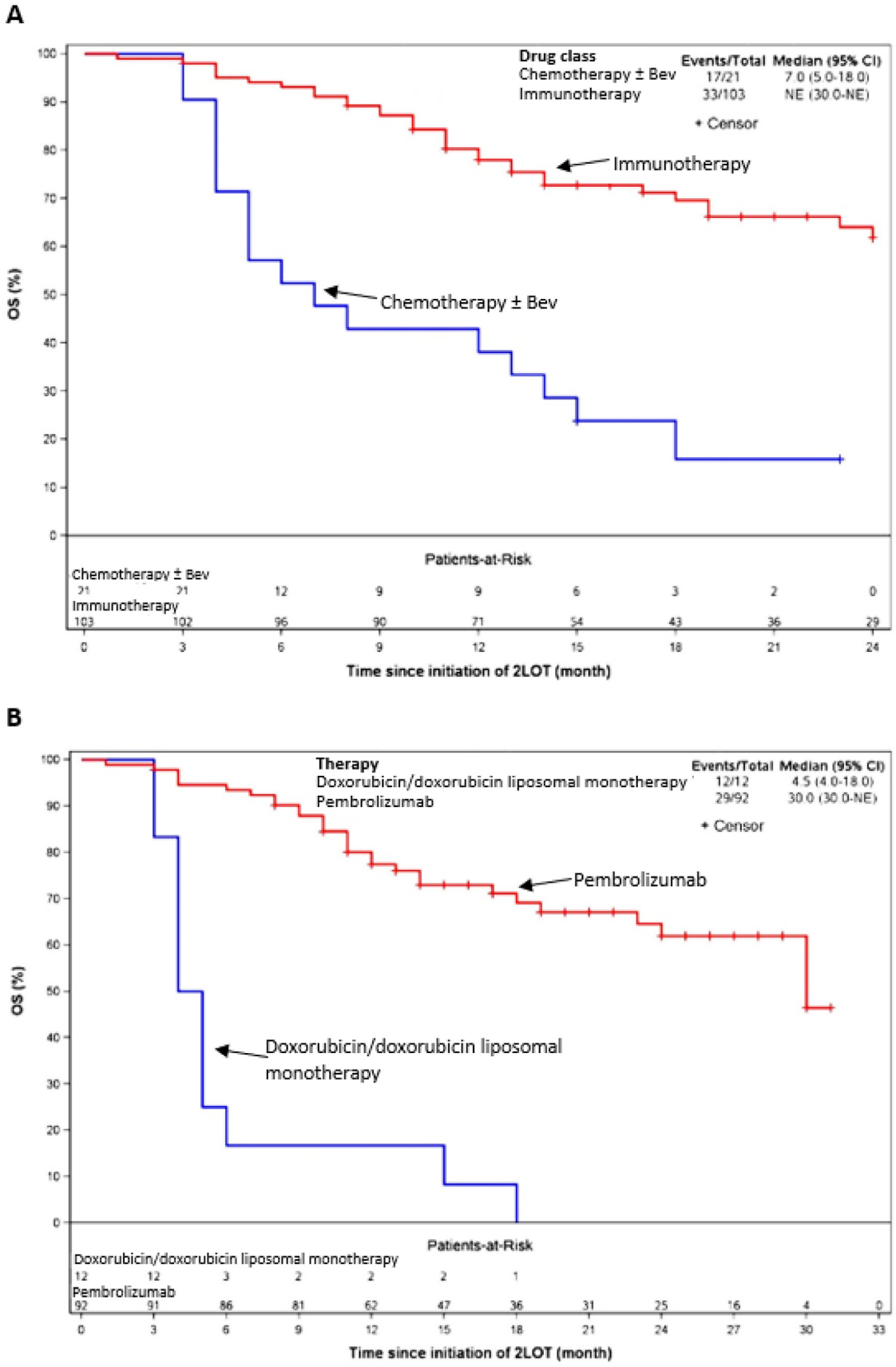

Fig. 5. Kaplan–Meier plot of Overall Survival (OS) in aEC patients with MSI-H/dMMR tumors by drug class (5A) and by therapy agent (5B) (n = 124).
Note: OS: Overall survival, Bev: Bevacizumab, 2LOT: Second Line of Therapy.

results corroborate the findings of KEYNOTE-158. In our study, rwORR was 69.4% overall and was 80.4% in patients with second-line therapy with pembrolizumab. The higher rwORR in our study could be attributable to differences in the availability of novel therapies due to the earlier enrollment period of KEYNOTE-158 compared to our study, relative to the May 2017 approval of pembrolizumab. Other attributable factors include adherence to guidelines in clinical practice when defining a response along with the inherent difference in the study design of randomized trials versus real-world clinical practice.

With over 80% of patients initiating immunotherapy primarily with pembrolizumab monotherapy, our study suggests that immunotherapy with pembrolizumab monotherapy has become the standard of care among patients with MSI-H/dMMR tumor status aEC in the US who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery. Our study finds a positive impact and potential real-world clinical benefit of tumor specific treatment of patients with MSI-H/dMMR aEC who progress following prior systemic therapy in the US. Results show favorable clinical outcomes such as higher OS and rwPFS among patients receiving immunotherapy as 2LOT while those receiving chemotherapy ± bevacizumab had comparatively poorer outcomes. While the relatively smaller sample size in patients initiating chemotherapy ± bevacizumab should be considered when interpreting the results, this study underlines the importance of treatment choice in determining the prognosis of these patients.

The efficacy of biomarker-specific therapies in improving the clinical outcomes in aEC patients has been well established. In the US, pembrolizumab was the first drug to have received an accelerated, tissue agnostic indication approval from the FDA in 2017 for patients with unresectable or MSI-H/dMMR solid tumors and in 2020 for tumor mutational burden-high (TMBH) patients who have progressed following prior treatment and who have no satisfactory alternative treatment options [24,25]. This was followed by the accelerated approval of the combination of pembrolizumab and lenvatinib in 2019 for treatment of patients with aEC that is not MSI-H or dMMR and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation, and more recently an accelerated approval for dostarlimab-gxly in 2021 for adult patients with dMMR recurrent or aEC (as determined by an FDA-approved test) that has progressed on or following a prior platinum-containing regimen [19,26] Pembrolizumab monotherapy and combination with lenvatinib have since received full approval of the FDA for MSI-H/dMMR and pMMR/not MSI-H populations, respectively [18]. Approvals of the novel, biomarker-specific therapy pembrolizumab have led to improved outcomes for aEC patients with MSI-H/dMMR tumors, as indicated by the findings of this study.

There are several limitations of this study. First, it is important to note this study was descriptive in nature and no hypothesis testing or controlling for patient characteristics were performed. Second, study results are subject to extraction or measurement error and there may be inconsistency in outcome measurement among physicians. We performed data validation to improve the accuracy and consistency of collected information. Third, the data extracted were limited by information available in the medical charts of the patients. Fourth, the interpretation of results is limited to patients diagnosed during the study period that were captured in our study population. We used random selection to mitigate potential selection bias and improve generalizability of the results to patients across US. Despite the limitations, this study has several strengths. Using a retrospective chart review provided an efficient, reliable, and verifiable method of data collection. Medical charts are often the best sources of information for the documentation of cancer treatments and clinical outcomes. In addition, this study design allowed for sufficient follow-up, which was crucial for studying subsequent lines of therapy and evaluating long-term outcomes such as overall survival. This study filled a gap in existing knowledge of current treatment patterns, clinical outcomes and resource utilization, addressing the recent landscape in real-world settings.

5. Conclusion

Findings of the ECHO retrospective chart review study suggest that patients with MSI-H/dMMR aEC who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery experience considerable benefits in survival and treatment response when treated with immunotherapy, especially pembrolizmab monotherapy. Real-world outcomes of pembrolizumab were comparable to those from clinical trials. Results suggest pembrolizumab has become the standard of care for this patient population in the US. There may be potential for clinical benefit through the adoption of this standard of care for MSI-H/dMMR aEC patients in other regions as well.

Declaration of Competing Interest

Sneha Kelkar, Shelby Corman & Nifasha Rusibamayila report support from Merck & Co., Inc. during the conduct of the study; and consulting fees from Merck & Co., Inc. Vimalanand Prabhu and Robert Orlowski are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co, Inc., Rahway, NJ, USA. Vimalanand Prabhu reports stock from Merck & Co., Inc., Rahway, NJ, USA; and other financial interests from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.. Cynthia Macahilig & Shardul Odak report support from RTI-Health Solutions during the conduct of the study. Robert Orlowski reports support from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA during the conduct of the study; patents with Merck & Co., Inc., Rahway, NJ, USA; and stock from Merck & Co., Inc., Rahway, NJ, USA. Linda Duska reports support from Merck & Co., Inc. during the conduct of the study; grants/contracts from Genentech/Roche, Cerulean/NextGen/(GOG 3008), AbbVie/(GOG 3005), Tesaro, Pfizer, GlaxoSmithKlein/Novartis, Morab, MorphoTek, Merck & Co., Inc., Aduro BioTech, Syndax, Ludwig, LEAP Therapeutics, Eisai, Lycera, Inovio, Advaxis, Mersana, Verastem, Ellipses, Corcept, Plexxicon, Constellation, Arch, Mirasol, and Quest Pharmtech; royalties from Elsevier and JB Learning; consulting fees from MorphoTek, Merck & Co., Inc., Genentech/Roche, Advance Medical, UpToDate, Parexel, State of California and ClearView Health Care; personal fees from expert review; and leadership/board roles in ASCO, National Cancer Institute and British Journal of OB/GYN.

Acknowledgements

This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing/editorial support provided by Rishi P Verma, MPH, from OPEN Health, Bethesda, MD, USA.

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