Descriptive Analysis of the Use of Pembrolizumab Alone or in Combination with Lenvatinib in the Treatment of Endometrial Cancer in Four University Hospitals in Quebec, Canada

Nathalie Letarte[1,5], Chantal Guévremont[2,5], Marc Simard[3,5], Sophie Fortier[2,5], Dr Laurence Bernard[2], Dr Raghu Rajan[2,5], Nicole Déry[3,5] and Ghislain Bérard[4,5]

1- CHUM, Montréal, Qc, Canada; 2- MUHC, Montréal, Qc, Canada; 3- CHU de Québec-Université Laval, Qc, Canada; 4- CIUSSS de l'Estrie - CHUS, Sherbrooke, Qc, Canada 5- Programme de gestion thérapeutique des médicaments (PGTM)

Introduction

Pembrolizumab in combination with lenvatinib (PEM-LEN) in mismatch repair proficient (pMMR) tumors is a new option in the treatment of endometrial cancer (EC), as demonstrated in KEYNOTE-775, and was approved by Quebec's Ministère de la Santé et des Services Sociaux in July 2023. The use of pembrolizumab (PEM) monotherapy in mismatch repair deficient / microsatellite instability – high (dMMR/MSI-H) tumors was studied in KEYNOTE-158 and approved for use in Quebec in February 2023. Both treatment options have been used prior to these approval dates due to early access programs.

Although PEM-LEN has demonstrated improvements in survival, toxicities are common. While some are manageable with supportive care, others could require dosage adjustments or treatment interruptions. These toxicities may have an impact on the efficacy of the treatment in clinical practice outside of the controlled environment of a clinical trial.

Methods

Objectives

- Describe and assess the real-world use of pembrolizumab with or without lenvatinib in the treatment of EC in 4 University teaching hospitals (UTH) in Quebec ;
- Assess the progression-free survival (PFS) and overall survival (OS) of these treatments in an unselected population ;
- Assess the rate of adverse events (AEs) causing treatment interruptions and discontinuations, and dose reductions for the PEM-LEN subgroup.

Participants

- Patients who received pembrolizumab with or without lenvatinib for the treatment of advanced, recurrent or metastatic EC between January 1st, 2020 and December 31st, 2022 were included in our study ;
- Data cut-off was September 30th, 2023.

Method (The complete protocol is available at: http://www.pgtm.qc.ca)

- Retrospective descriptive analysis ;
- Medical and pharmacy records were reviewed after institutional ethics board approval ;
- Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at CHU de QC-Université Laval ;
- Statistical analyses were performed using SPSS software.

Results

A total of 102 patients who received PEM-LEN or PEM for EC were included in the study. The total population was divided into 2 subgroups that were analyzed separately.

Table 1: Patient's characteristics

	PEM-LEN	PEM
Number of patients	84	18
Median follow-up (min – max)	9.7 months (1-46.1)	13.2 months (1.1-48.6)
Median age (min – max)	68.5 (47-87)	63.5 (35-77)
75 years old and above (%)	19 (22.6)	2 (11.1)
FIGO stage at diagnostic (n, %)[1]		
I-II	23 (27.4)	6 (33.3)
III-IV	59 (70.2)	12 (66.6)
ECOG (n, %)[2]		
0-1	78 (92.9)	15 (83.3)
2	1 (1.2)	2 (11.1)
Histology (n, %)		
Endometrioid	23 (27.4)	14 (77.8)
Serous	38 (45.2)	0
Clear cell	6 (7.1)	0
Carcinosarcoma	11 (13.1)	1 (5.6)
Mixed	4 (4.8)	1 (5.6)
Others[3]	2 (2.4)	2 (11.1)
Previous adjuvant pelvic radiotherapy (n, %)		
	37 (44)	8 (44.4)
Number of previous palliative treatments (excluding adjuvant treatment) (n, %)		
0	17 (20.2)	6 (33.3)
1	47 (56)	9 (50)
2	10 (11.9)	3 (16.7)
3 or more	10 (11.9)	0
MSI or MMR status[4]		
MSI-High / MMR deficient	2 (2.4)	18 (100)
MSS / MMR proficient	79 (94)	0

Unknown: [1] PEM-LEN: n = 2 (2.4 %); [2] PEM-LEN: n = 5 (6 %), PEM: n = 1 (5.6 %); [4] n = 3 (3.6 %)
[3] **Others**: PEM-LEN: Mullerian carcinoma with serous and clear cells, high grade adenocarcinoma with neuroendocrine differentiation; PEM: Mucinous, epidermoid
Abbreviations : FIGO : Fédération internationale de gynécologie et d'obstétrique; ECOG : Eastern Cooperative Oncology Group; MMR : Mismatch Repair; MSI : Microsatellite instability

Results – PEM-LEN combination subgroup

Efficacy

- Median number of cycles received was 7 (min - max: 1 - 37)
- Most common reasons for treatment discontinuation :
  - Progression : 60.3 %
  - Adverse events (PEM / LEN) : 16.2 % / 25.8 %
- 27 patients (32.9 %) received one or more subsequent lines of treatment

Table 2: Patient status at the end of study period (n = 84)

	Number of patients	%
Still on study treatment	22	26.2
Off study treatment – alive	21	25
Deceased	38	45.2
Lost to follow-up	3	3.6

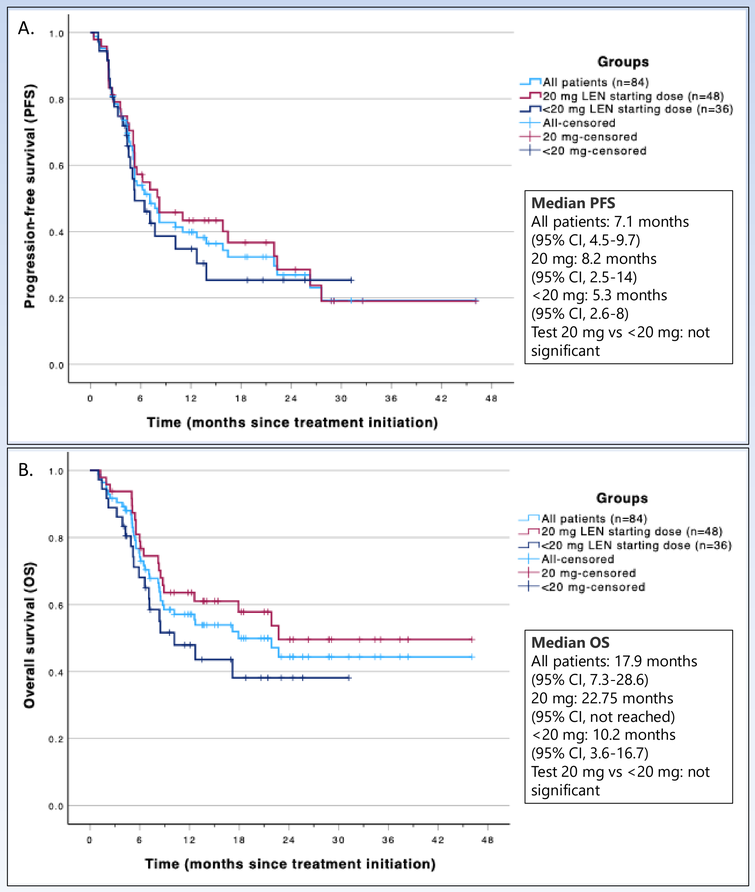

Figure 1. Progression-free survival (PFS) (panel A) and overall survival (OS) (panel B) analyses for the PEM-LEN group. Kaplan-Meier curves are presented for all patients (n=84), 20 mg LEN starting dose patients (n=48), and less than 20 mg LEN starting dose patients (n=36). For both PFS and OS, no statistical difference was observed between subgroups. Cox regressions have been performed for different parameters (age (less than 75 vs 75+), histology (non-endometrioid vs endometrioid), FIGO stage (I-II vs III-IV) and initial LEN dose (less than 20 mg vs 20 mg)). Only the endometroid subtype showed an improvement in PFS (HR 0.373, p=0.008) and OS (HR 0.387, p=0.035). A trend was observed towards a positive impact of LEN 20 mg starting dose on OS (HR 0.529, p=0.052).

Adverse events

- Thirty-six patients (42.9 %) started LEN at a reduced dose of less then 20 mg (29 patients started at 14 mg (34.5 %))
- LEN dose reductions were required in 66 patients (78.6 %) :
  - Time (days) before first dose reduction (associated with an AE) = median 25 (min - max : 2 - 420)
  - Median number of cycles received was 8.5 (min - max : 1 - 42)
  - 20 patients (30.3 %) were still on LEN treatment at the end of the study
- In the 18 patients who did not have a dose modification*:
  - Median number of cycles received was 3 (min - max: 0.19 - 9.7)
  - 2 patients (11.1 %) were still on treatment at the end of the study period

Table 3: LEN starting dose and toxicity parameters (n = 84)

		LEN starting dose	
		20 mg	Less than 20 mg
Number of patients	n (%)	48 (57.1 %)	36 (42.9 %)
Age	median (range)	68 (47-80)	70 (57-87)
Treatment interruption	n (range)	43 (1-6)	32 (1-8)
Treatment restarted	n (range)	39 (1-6)	24 (1-8)
Time (days) before first dose reduction (associated with an AE)	median (range)	31 (2-420)	21 (2-122)
Number of LEN dose reductions	0*	9 (18.8 %)	9 (25 %)
	1	8 (16.7 %)	14 (38.9 %)
	2	18 (37.5 %)	7 (19.4 %)
	3 and more	13 (27.1 %)	6 (16.7 %)
Treatment discontinuation	n (%)	11 (22.9 %)	15 (41.7 %)
Emergency consultation or hospitalization related to toxicity	n (%)	18 (37.5 %)	16 (44.4 %)

Results – PEM-LEN combination subgroup (cont'd)

Adverse events (cont'd)

- All 84 patients (100%) experienced at least one AE:
  - Each patient had a median of 6 AE (1-16)
  - The median time to first AE was 17.5 days (2-87)
  - 31 patients (36.9 %) had at least 1 AE of grade 3 (none had grade 4)
  - 32.4 % of AE led to a drug interruption (LEN or PEM or both)
  - 75 patients (89.3 %) had at least one treatment interruption
  - Treatments were restarted in 80.3 % of cases after a median of 14.9 days (2-174)

Table 4: Adverse events (AE) according to LEN starting dose

	20 mg (n = 48)		Less than 20 mg (n = 36)	
Time (days) before first AE (median (range))	18.5 (2-62)		15.0 (2-87)	
Most common AE	All grade	Grade 3	All grade	Grade 3
Hypertension	28 (58.3 %)	1 (2.1 %)	20 (55.6 %)	4 (11.1 %)
Hypothyroidism	25 (52.1 %)	0	15 (41.7 %)	0
Fatigue / Asthenia	19 (39.6 %)	0	13 (36.1 %)	1 (2.8 %)
Arthralgia / Myalgia	19 (39.6 %)	0	12 (33.3 %)	0
Diarrhea	17 (35.4 %)	0	10 (27.8 %)	1 (2.8 %)
Proteinuria	17 (35.4 %)	0	11 (30.6 %)	2 (5.6 %)
Number of patients with at least one grade 3 adverse event	17 (35.4 %)		14 (38.9 %)	

Results – PEM monotherapy subgroup

PFS and OS were 4.01 months (95% CI, 0-10.4) and 11.4 months (95% CI, 0-34.5), respectively, and AEs were seen in 14 (77.8 %) patients (grade 3 observed in 4 patients (22.2 %)).

Due to the small sample size (n = 18), more patients and data will be needed in this population before conclusions can be drawn about the real-world usefulness of PEM in dMMR/MSI-H EC.

Discussion

Makker et al. reported a median PFS and OS of 6.6 and 17.4 months, respectively for the pMMR population in patients receiving PEM-LEN (1). In this real-life study, the efficacy results are similar to the pivotal trial and other observational studies (3 - 6).

Time to first LEN dose reduction is short, but consistent with results from the literature. Also, considering that nearly half of the patients started at a reduced dose and that there were a large number of patients with a dose reduction, this reinforces the fact that proactive measures to promote LEN tolerance can be accomplished without a deleterious effect on efficacy.

In contrast, the PFS and OS results for the PEM monotherapy subgroup are somewhat inferior to the KEYNOTE-158 trial (median PFS of 13.1 months, median OS was not reached) (2); which could be partly explained by the small cohort size (n=18).

This non-randomized retrospective study may introduce some biases. For instance, completeness of notes in patient medical files may vary between clinicians. Also, reasons for initial LEN starting dose reduction were not captured. Clinicians may have prescribed a lower dose for less fit patients as suggested by a higher median age in the LEN less than 20 mg subgroup compared to the LEN 20 mg subgroup.

Conclusion

These findings support the use of the combination of PEM-LEN for pMMR tumors of EC in a real-world setting; PFS and OS are similar to previous studies. Side effects and need for dose reductions with LEN are major issues that need to be discussed with patients at the initiation of treatment for optimal management. As for PEM monotherapy subgroup in dMMR/MSI-H tumors, more real-world data are needed.

Acknowledgements

We would like to thank all the pharmacy students who participated in the data collection.

References

1. Makker V, Colombo N, Casado Herráez A, et al. for the Study 309–KEYNOTE-775 Investigators. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med 2022;386:437-448.
2. O'Malley DM, Bariani GM, Cassier PA, et al. Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. J Clin Oncol. 2022 Mar 1;40(7):752-761.
3. How JA, Patel S, Fellman B, et al. Toxicity and efficacy of the combination of pembrolizumab with recommended or reduced starting doses of lenvatinib for treatment of recurrent endometrial cancer. Gynecol Oncol. 2021 Jul;162(1):24-31.
4. Pawsey A, Mahalingam P, Senthivel N, et al. Real World Outcomes in Patients With Recurrent, Advanced, or Metastatic Endometrial Cancer Treated With Lenvatinib Plus Pembrolizumab. Clin Oncol (R Coll Radiol). 2025 Jan;37:103656.
5. Zammarrelli WA 3rd, Ma W, Espino K, et al. Adverse events and oncologic outcomes with combination lenvatinib and pembrolizumab for the treatment of recurrent endometrial cancer. Gynecol Oncol. 2023 Nov;178:27-35.
6. Kim J, Lee TK, Kim SI et al. Real-World experience of pembrolizumab and lenvatinib in recurrent endometrial cancer: A mulitcenter study in Korea. Gynecol Oncol 2022; 165:369-375.

Source of funding

This project was conducted in pharmacy departments and no outside funding was used.

Contact Information

For any question or additional information, contact: nathalie.letarte.chum@ssss.gouv.qc.ca

Programme de GESTION THÉRAPEUTIQUE des médicaments

SCAN ME

The pGTm is a joint initiative among Quebec's five university teaching hospitals

CHU de Québec Université Laval · Centre universitaire de santé McGill · McGill University Health Centre · CHUM Centre hospitalier de l'Université de Montréal · CHU Sainte-Justine Le centre hospitalier universitaire mère-enfant Université de Montréal · Centre intégré universitaire de santé et de services sociaux de l'Estrie – Centre hospitalier universitaire de Sherbrooke Québec