Descriptive Analysis of first-line non-small cell Lung cancer treatment with Pembrolizumab in tumors expressing PD-L1 ≥ 50% in patients treated in five Québec's university teaching hospitals (DALP-First study)

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Introduction

Non-small cell lung cancer (NSCLC) is the most common type of thoracic cancers. Nearly half of patients are diagnosed when the disease is already at an advanced stage, most with metastatic disease. A significant number of patients diagnosed at an earlier stage will also eventually progress to metastatic disease. Of those patients who progress, approximately 25% will have tumor PD-L1 levels of 50% or greater.

Since the publication of the KEYNOTE-024 study, pembrolizumab has been accepted as first-line treatment for metastatic lung cancer in patients whose tumor expresses a PD-L1 level of 50% or more. The efficacy and safety data currently available for pembrolizumab in this indication come from two phase III studies, KEYNOTE-024 and KEYNOTE-042.

Since July 2017, pembrolizumab is authorized in Quebec in patients corresponding to the inclusion criteria of KEYNOTE-024. In the fall of 2018, CADTH and the PGTM recommended the use of weight-based capped dosing (WCD) for certain checkpoint inhibitors, including pembrolizumab (www.pgtm.qc.ca) and this guidance was subsequently accepted by INESSS (Quebec's provincial drug evaluation and health-technology assessments agency). This dosing strategy progressively replaced the fixed pembrolizumab 200 mg dose every 3 weeks (FD) in Quebec's health care institutions.

Methods

Objectives

- Describe and assess the real-world use of pembrolizumab in University teaching hospitals (UTH) in Quebec ;
- Assess progression-free survival (PFS), overall survival (OS) in an unselected population;
- Assess rate of immune-related adverse events (IRAE) causing delays or treatment interruptions;
- Compare outcomes between a FD (200 mg) and a WCD (2 mg/kg up to 200 mg) given every 3 weeks.

Participants

- A search identified patients who received pembrolizumab for first-line advanced or metastatic NSCLC between November 1st, 2017 and October 31st, 2019;
- Medical records of every patient were reviewed and followed until February 29th, 2020.

Method

- Retrospective descriptive analysis;
- Medical records, pharmacy and oncology nursing notes, laboratory results and any other useful documentation;
- Information collected on a standardized data collection sheet and entered into an Excel 2010 database;
- Continuous variables presented as means (standard deviation) if normally distributed or as median (interquartile range) otherwise

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

Results

A total of 279 patients received pembrolizumab for first-line advanced or metastatic NSCLC (129 men / 150 women) and were included in the analysis.
Median age: 68 [range: 34 to 94] – 123 patients (44.1%) were older than 70.
PD-L1 score was ≥ 50% in 276 patients, positive but < 50% in 2 and unknown in 1 patient.

Table 1. Patient characteristics

	Number of patients (%) (N = 279)
Lung cancer staging	
Metastatic	244 (87.5%)
Advanced (Stage III)	35 (12.5%)
ECOG PS score	
0 – 1	211 (75.7%)
> 1 - ≤ 2	37 (13.3%)
> 2	14 (5%)
Unknown	17 (6.1%)
Autoimmune disease	25 (9%)
Brain metastases	
Absence	197 (70.6%)
Presence:	63 (22.6%)
Treated and stable	52 (18.6%)
Untreated or unstable	10 (3.6%)
Unknown if treated or not	1 (0.4%)
Unknown / Not found in file	19 (6.8%)

Results (continued)

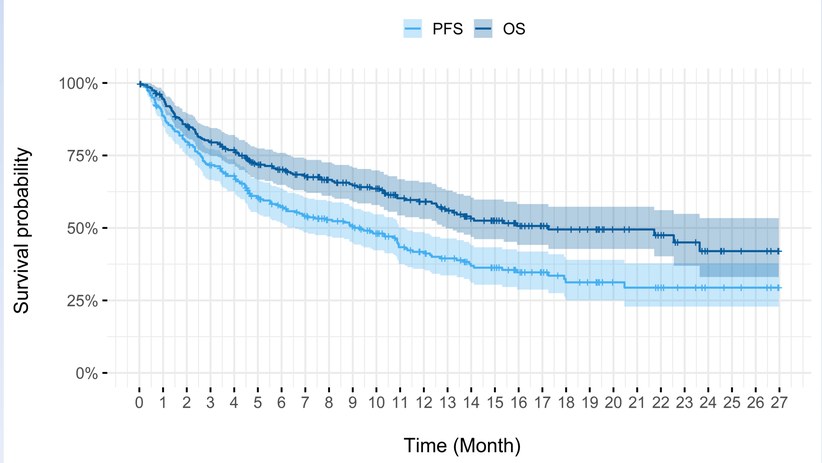
In this real-world population, median follow-up was 7.53 months (range, 0.03 to 26.84 months)
- WCD : 230 patients (82.4% of the population)
  - No patient changed to FD during treatment
- FD : 49 patients (17.6% of the population)
  - 13 patients changed to WCD during treatment

At the end of the follow-up period:
- Ongoing treatment: 76 patients (27.2%)
- Mean number of cycles received was 9.1 ± 8.5 (Median = 6; interquartile range = 2 to 13)
- 113 patients (40.5% of patients) received 4 cycles or less
- Median PFS : 9.4 months (95% CI, 6.6 to 11.2)
- Median OS: 17.3 months (95% CI, 12.9 to not reached)

Table 2: Estimated percentages of patients with no disease progression and alive

	% without progression	% alive
6 months	57.4	70.1
12 months	41.7	59.1
24 months	29.4	42.0

Figure 1: PFS and OS of the study population (N=279)



IRAE causing a treatment delay or interruption:
- All grade: 34.4% (96 IRAE in 77 of the 279 patients [27.6% of patient])
- Grade 3-4: 8.6% - half of which were colitis or other GI adverse events

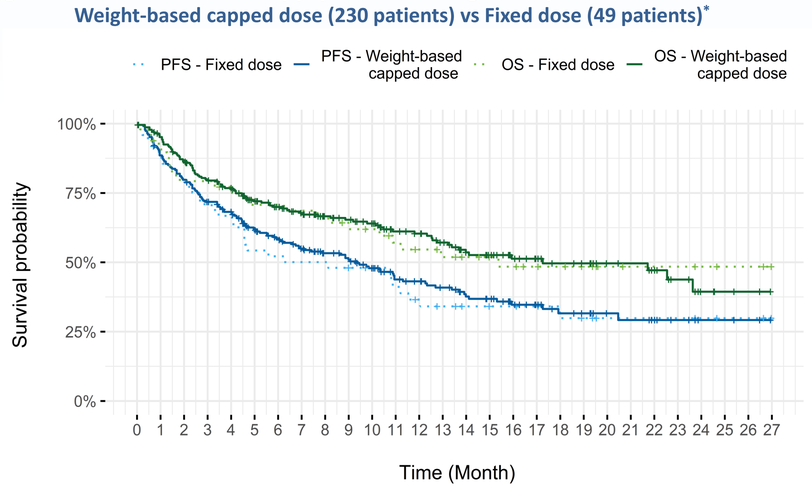
IRAE and other side effects were the main reasons for discontinuation in 44 patients (15.8 %). Median delay between the first pembrolizumab dose and occurrence of first IRAE causing a treatment delay or discontinuation: 15.4 weeks.

IRAE causing a treatment delay or discontinuation:
- Patients with autoimmune disease: 44% (11 of 25 patients)
- Patients with no history of autoimmune disease : 26% (66 of 254 patients)

Dosing strategy

Using a FD or a WCD:
- Did not have had an impact on patients' PFS or OS; (Figure 2).
  - PFS = 8.1 months with FD vs 9.4 months with WCD
  - OS = 15.4 months with vs 17.3 months with WCD
  - Cox regression model: hazard ratio for death of 0.97 between WCD vs FD (p = 0.88)
    - With adjustment for confounding factors (gender, smoking status, ECOG PS score and autoimmune disease), effect still non-significant.
- Did not have an impact on the presence of IRAE that caused delay or discontinuation
  - FD: 28.6% of patients had at least 1 IRAE (14 of 49 patients)
  - WCD: 27.4% of patients had at least 1 IRAE (63 of 230 patients)

Figure 2: PFS and OS of the study population with regards to pembrolizumab dose used – Weight-based capped dose (230 patients) vs Fixed dose (49 patients)*



*Effect favored WCD and remained non-significant [HR = 0.72 for OS (p = 0.17)] when patients that switched from FD to WCD were excluded

Results (continued)

Table 3: Number of pembrolizumab cycles received per dosing strategy

Number of cycles received	Fixed dose (FD) (n=49)	Weight-based capped dose (WCD)(n=230)
Mean ± standard deviation	9.3 ± 9.7	9.0 ± 8.2
Median	5	6
Range (Min – Max)	1 – 36	1 – 34
Interquartile range	2 – 14	2.25 – 13

Table 4: Comparison of PFS, OS, and IRAE of PGTM population with those of other studies on pembrolizumab as a first-line treatment of NSCLC in patients with a PD-L1 ≥ 50%

	PGTM	PEMBREIZH	KEYNOTE-024	KEYNOTE-042*
Number of patients	279	108	154	299
Median age (years)	68	67	64,5	63
ECOG PS 0 – 1	75.7%	76.9%	99.4%	100%
Brain metastases	22.6%	17.6%	11.7%	6%
PFS (Months) (95%CI)	9.4 (6.6 – 11.2)	10.1 (8.8 – NR)	10.3 (6.7 – NR)	7.1 (5.9 – 9.0)
OS (Months) (95%CI)	17.3 (12.9 – NR)	15.2 (13.9 –NR)	30.0 (18.3 – NR)	20.0 (15.4 – 24.9)
IRAE (All grade)	34.4%**	46.3%	73.4%	63%
IRAE (Grade 3 – 4)	8.6%	8%	9.7%	8%

Abreviations: NR – Not reached; IRAE – Immune related adverse events; PFS – Progression-free survival; OS – Overall survival
*Subgroup of patients with PD-L1 ≥50% ; **only IRAE causing delays or treatment interruptions were considered

Cost of treatment

Two key points were considered:
- Freshwater and al.: "doses of 200 mg and 2 mg/kg provide similar exposure distributions with no advantage to either dosing approach (…). These findings suggest that weight-based and fixed-dose regimens are appropriate for pembrolizumab".
- Goldstein and al.: "Personalized dosing of pembrolizumab may have the potential to save approximately $0.825 billion annually in the United States (24% of pembrolizumab cost), likely without impacting outcomes. This option should be considered for the first-line management of PD-L1-positive advanced lung cancer".

Use of WCD allowed savings of approximately $5.8 million CAN during the course of our study. (26% less than the cost had FD been given to every patient [16.4 millions $CAN instead of 22.3 millions $CAN]).

If all 279 patients had received WCD, the savings would have totalled $6.8 million CAN, representing 30% of the total cost, with efficacy results similar to those seen in KEYNOTE-024 and KEYNOTE-042.

Limitations

- Retrospective study
- Completeness of notes in patient medical files may vary between clinicians
- Small number of patients received FD compared to WCD

Conclusion

The results of KEYNOTE-024 have changed the landscape for advanced NSCLC patients with a PD-L1 score ≥ 50%. Monotherapy with pembrolizumab, and more recently with cemiplimab, is now the standard of care for first-line treatment of this population. The findings of this study support the effectiveness and safety of pembrolizumab in a real-world cohort of unselected advanced NSCLC patients with a PD-L1 score ≥ 50% with results similar to pivotal trials and other real-word studies.

Our analysis also shows that the use of a weight-based capped dose with pembrolizumab does not have a negative impact on patient outcomes and can optimize the use of precious financial resources for healthcare systems in a time of escalating oncology drug costs.

Acknowledgements

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