Descriptive Analysis of Anti-PD-1 Use in Four Adult University Teaching Hospitals in Québec, Canada

Chantal Guévremont[1,6], Ghislain Bérard[2,6], Layal El Raichani[3], Nathalie Marcotte[4,6], Marie-Claude Michel[4,6], France Varin[3,6], Elaine Pelletier[5,6], Paul Farand[2,6], Louise Deschenes[4,6], Daniel Froment[3,6], Philippe Ovetchkine[5,6], Raghu Rajan[1,6] , Normand Blais[3] , Rahima Jamal[3] and Nathalie Letarte[3]

1- MUHC, Montréal, QC, Canada; 2- CIUSSS de l'Estrie - CHUS, Sherbrooke, QC, Canada; 3- CHUM, Montréal, QC, Canada; 4- CHU de Québec-Université Laval, QC, Canada; 5- CHU Sainte-Justine, Montréal, QC, Canada; 6- Programme de gestion thérapeutique des médicaments

Programme de **GESTION THÉRAPEUTIQUE** des médicaments

Introduction

The development of the field of immuno-oncology has revolutionized the treatment of cancer in recent years. Basic research has made it possible to better understand the interactions between the tumor and the patient's immune system as well as the mechanisms that increase the immunological reactions directed against tumor cells.

Since 2011, anti-PD-1 agents are used in the treatment of different cancer types in Québec, mostly through compassionate use programs at first then through provincial funding.

The efficacy and safety data currently available for anti-PD-1 drugs come mainly from phase III pivotal trials. Since their inclusion and exclusion criteria can be quite restrictive, the populations found in these trials may differ from the ones that clinicians are and will be asked to treat in real-world setting. A more objective overview of their use will allow clinicians to ensure that pembrolizumab or nivolumab immunotherapy remains the treatment of choice for their patients in terms of both efficacy and safety.

In April 2017, the Direction générale de cancérologie (now known as the Programme québécois de cancérologie), was concerned with the safety of immunotherapy in the real-world setting. They called upon institutions to keep a record of patients receiving immune checkpoint inhibitors to allow physicians and pharmacists to evaluate the use of these drugs and study their therapeutic results.

Methods

Objectives

- Describe and assess the real-world use of anti-PD-1 in various indications;
- Report overall survival (OS) and progression-free survival (PFS) in the different indications;
- Compare the PGTM real-world outcomes with the available literature (pivotal and observational studies) in the different indications;
- Describe immune related adverse events (IRAE) and their management.

Participants

- A search in the hospital pharmacy computer systems identified patients who received nivolumab or pembrolizumab between January 1st 2011 and October 31st 2017;
- Medical records of every patient who received nivolumab or pembrolizumab monotherapy between these dates were reviewed and followed until December 31st, 2017.

Methods

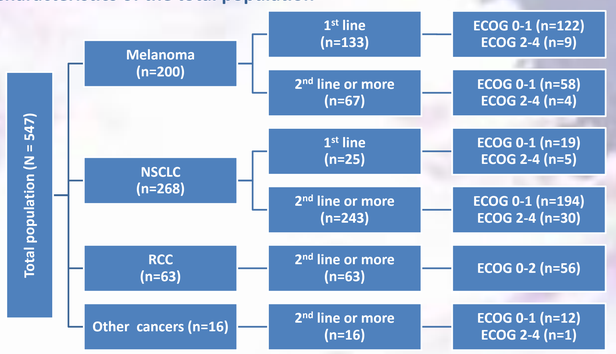
- Study design: retrospective descriptive analysis;
- Clinical data information sources: medical charts (paper or electronic), pharmacy and oncology nursing notes, laboratory results and any other useful documentation;
- Data management: Information was collected on a standardized data collection sheet and entered into an Excel database. Analysis were performed using Excel version 16.16.2 and SPSS version 25;
- Statistical analyses: Descriptive data are presented as mean ± SD, median (range) or %.

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

Results

During the study period, a total of 547 patients received an anti-PD-1 and were included in the study. Pembrolizumab or nivolumab were used in 200 melanoma, 268 non-small cell lung cancer (NSCLC), 63 renal cell carcinoma (RCC) and 16 patients with other cancers.

Figure 1. Characteristics of the total population



Melanoma (n = 200)

Table 1. Treatment status at data cut-off

		Pembrolizumab 1st line (n = 78)	Pembrolizumab 2nd line or more (n = 56*)	Nivolumab 1st line (n = 55)	Nivolumab 2nd line or more (n = 11**)
Median age (range)		69 (18 – 93)	59.5 (23 – 83)	68 (40 – 84)	67 (38 – 91)
Median weight (kg) (range)		80.5 (45 – 130)	78 (45 – 134)	76 (48 – 154)	88 (70 – 134)
Number of dose received	Mean Median Range	6.8 5 (1 – 23)	12 8 (1 – 36)	16.4 8 (1 – 57)	16.2 11 (5 – 50)
Treatment					
Ongoing		30 (39 %)	15 (27 %)	8 (15 %)	1 (9 %)
Discontinued		48 (61 %)	41 (73 %)	47 (86 %)	10 (91 %)
Treatment discontinuation					
Progression		30 (38 %)	26 (47 %)	26 (47 %)	4 (36 %)
Adverse event		5 (6 %)	5 (9 %)	10 (18 %)	2 (18 %)
Death of any cause		8 (10 %)	3 (5 %)	5 (9 %)	1 (9 %)
Patient decision		2 (3 %)	1 (2 %)	1 (2 %)	0
Complete response		1 (1 %)	3 (5 %)	2 (4 %)	1 (9 %)
Other		1 (1 %)	0	1 (2 %)	0
Unknown		1 (1 %)	3 (5 %)	2 (4 %)	2 (18 %)
Death of any cause at the end of study period		30 (39 %)	25 (45 %)	31 (56 %)	6 (55 %)

* 5 of these patients had also received 1st line nivolumab; ** 3 of these patients had also received 1st line nivolumab

Results (continued)

Non-small cell lung cancer (NSCLC) (n = 268)

Table 2. Treatment status at data cut-off

		Pembrolizumab 1st line (n = 25)	Pembrolizumab 2nd line or more (n = 61)	Nivolumab 2nd line or more (n = 182)
Median age (range)		63 (42 – 86)	68 (42 – 81)	65 (41 – 83)
Median weight (kg) (range)		68 (37 – 89)	68 (31 – 111)	70 (35 – 134)
Number of dose received	Mean Median Range	5 4 (1 – 18)	6 6 (1 – 17)	8.5 7 (1 – 63)
Treatment				
Ongoing		13 (52 %)	20 (33 %)	34 (19 %)
Discontinued		12 (48 %)	41 (67 %)	148 (81 %)
Treatment discontinuation				
Progression		7 (58 %)	24 (59 %)	97 (66 %)
Adverse event		2 (17 %)	3 (7 %)	31 (21 %)
Death of any cause		2 (17 %)	12 (29 %)	10 (7 %)
Patient decision		1 (8 %)	2 (5 %)	4 (3 %)
Complete response		0	0	2 (1 %)
Other		0	0	2 (1 %)
Unknown		0	0	2 (1 %)
Death of any cause at the end of study period		7 (28 %)	25 (41 %)	105 (58 %)

Renal cell carcinoma (RCC) (n = 63)

Table 3. Treatment status at data cut-off

		Nivolumab 2nd line or more (n = 63)
Median age (range)		67 (45 – 82)
Median weight (kg) (range)		79 (47 – 130)
Number of dose received	Mean Median Range	13.9 8 (1 – 47)
Treatment		
Ongoing		18 (29 %)
Discontinued		45 (71 %)
Treatment discontinuation		
Progression		31 (49 %)
Adverse event		9 (14 %)
Death of any cause		4 (6 %)
Patient decision		1 (2 %)
Death of any cause at the end of study period		24 (38 %)

General population

While PFS was comparable to pivotal and observational studies in most indications, OS results were more than double in pivotal trials for first line melanoma and NSCLC.

Table 4. Primary outcomes of the PGTM population compared to those of pivotal trials

	Indication	Drug	N	Median PFS PGTM (months)	Median PFS pivotal trial (months)	Median OS PGTM (months)	Median OS pivotal trial (months)
Melanoma	1st line	Pembro	78	5.8	8.4	12.5	32.7
	1st line	Nivo	55	8.8	5.1 & 6.9	17.4	NR & 36.4
	2nd + line	Pembro	56	7.7	3.4 & 5.4	18.4	15.9 & 13.4
	2nd + line	Nivo	11	5.7	3.1	34.8	15.7
NSCLC	1st line	Pembro	25	NR	6 & 10.3 & 7.1	10.4	16.2 & 30 & 20
	2nd + line	Pembro	61	6.0	3 & 3.9	11.5	9.3 & 10.4
	2nd + line	Nivo	182	4.4	2.3 & 3.5	8.6	12.2 & 9.2
RCC	2nd + line	Nivo	63	8.7	4.6	NR	25

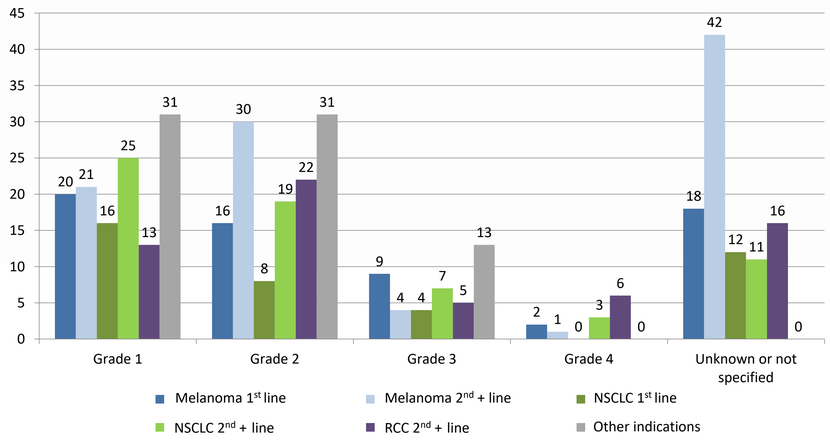
NR – Not reached

Immune-related adverse events (IRAE)

A total of 377 IRAE were seen in 243 patients (44 %). IRAE were similar in frequency for both pembrolizumab and nivolumab with 45 % and 43 % of patients respectively. Severity of IRAE was also similar between both drug. A total of 52 grade 3-4 IRAE were reported (14 % of all IRAE).

Of the 243 patients who experienced an IRAE, 161 (66 %) had 1 episode of IRAE, while 82 had 2 or more distinct episodes of IRAE (up to 7 in 2 patients).

Figure 2. Grade of IRAE by indication (%)



Results (continued)

Table 5. Incidence of total IRAE and grade 3 – 4 IRAE by type for all treatment indication

Type of IRAE	Total population (N = 547)			
	All grade		Grade 3 – 4	
	n	%	n	%
Total	**377**	**69**	**52**	**9.5**
Dermatologic	110	20.1	12	2.2
Gastro-intestinal	61	11.2	16	2.9
Pulmonary	38	6.9	5	0.9
Hepatic	32	5.9	9	1.6
Endocrine	103	18.8	0	0
Other	33	6	10	1.8

Twenty-nine patients (5 %) suffering from a pre-existing auto-immune condition received an anti-PD-1. In this group, 19 patients (66 %) experienced an IRAE (all grade) during the course of their treatment. Eight patients (28 %) presented a grade 3-4 IRAE, with two of these related to their pre-existing condition.

In accordance to most guidelines, grade 3-4 IRAE were managed mainly with corticosteroids, but prednisone doses were lower than those recommended in many patients and rate of retreatments was higher than expected. Prednisone dose at retreatment needs to be interpreted with caution in a retrospective setting without access to patients or their external pharmacy file/Dossier Santé Québec.

Table 6. Management of grade 3 – 4 IRAE by type for all treatment indication

Type of IRAE	Dermatologic (n = 12)	Gastro-intestinal (n = 16)	Pulmonary (n = 5)	Hepatic (n = 9)	Other (n = 10)
Median number of cycles before IRAE	7	7.5	7	2	2
Prednisone used as initial corticosteroid	9	12	4	7	6
Prednisone dose (mg/kg) (mean and median)	0.78 0.76	0.91 1	0.56 0.56	0.84 1	0.5 0.8
Prednisone dose at retreatment (median) (mg)	8.75	8	10	5	20
Other immunosuppresive agent received		Infliximab (4 patients)		MMF* (1 patient)	Infliximab (1 patient)
Retreatment after grade 3 - 4 IRAE	11	10	3	4	8

*MMF = Mycophenolate mofetil

Treatment discontinuation due to IRAE and other adverse events varied from 7 to 18 % depending on the indication. In melanoma, NSCLC and RCC, 182 patients received less than 12 weeks of treatment (up to 38 % of patients when divided by drug and indication) due to early progression, adverse events or death.

Table 7. Reason for early (≤ 12 weeks) treatment discontinuation

	n = 182 of the total 531 patients* (34.2 %)	
	Mean	Range
Adverse event (including IRAE)	6 %	0 – 10 %
Early progression	18.1 %	9 – 24 %
Death of any cause	6.6 %	1.8 – 10 %
Patient's decision	2.6 %	0 – 4 %
Unknown	1.1 %	0 – 4 %

* Information not collected for the 16 patients who received an anti-PD-1 for another indication

Discussion / Recommendations / Conclusion

- ECOG performance status were available 93 % of the time. They were compatible with reimbursement funding criteria for up to 90 % of the entire population studied. Poorer ECOG could be explained by the enrollment into compassionate programs. Criteria surrounding mutational status or PD-L1 level could also have been contaminated by these programs that were more permissive.
- Lower OS results when compared to the pivotal trial for some indications may be related to immature data (shorter follow-up durations). Patients with poorer ECOG score or having central nervous system metastasis and better access to subsequent therapies in other countries could also have contributed to these differences.
- More frequent in real-world setting, IRAE can be partly explained by patients' comorbidities. Pivotal and observational trial comparison could be hazardous since data collection differs frequently.
- Clinicians will need to ensure and document that the prednisone dose has reached 10 mg or less before retreatment after discussion with the patient.
- A closer clinical follow-up is recommended for the first three to four months of immunotherapy to allow a faster detection and management of IRAE.
- Patients with pre-existing auto-immune conditions should be clearly identified to allow for close monitoring, especially in the case of the appearance of IRAE.
- A codification system should be implemented specifically for IRAE in medical charts to facilitate their findings by archivists. Information regarding patients with grade 3-4 IRAE who often require hospitalization would be easily retrieved for further documentation in line with Vanessa's law.

Defining factors associated with better survival could optimize anti-PD-1 use. Closer follow-up of IRAE will be imperative at treatment onset and with combination therapy (dual immunotherapy or when combined with chemotherapy). Special considerations should be given to the monitoring of patients with pre-existing auto-immune disease treated with anti-PD-1.

References

KEYNOTE pivotal trials suite: **002** (Ribas et al, 2015 & Hamid et al, 2017), **006** (Robert et al, 2015 & 2019), **001** (Garon et al, 2015), **024** (Reck et al, 2016 & 2019), **042** (Mok et al, 2019), **010** (Herbst et al, 2016)
and **CHECKMATE** pivotal trials suite: **066** (Robert et al, 2015), **067** (Wolchok et al, 2017 & Hodi et al, 2018), **037** (Larkin et al, 2018), **057** (Borghaei et al, 2015), **017** (Brahmer et al, 2015), **025** (Motzer et al, 2015)

Contact Information

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

Le p**GT**m est une initiative des cinq centres hospitaliers universitaires du Québec

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