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Pembrolizumab for advanced nonsmall cell lung cancer: Efficacy and safety in everyday clinical practice

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ABSTRACT

Objectives: While pembrolizumab improves overall survival (OS) in a subset of advanced nonsmall cell lung cancer (aNSCLC) patients (pts) in clinical trials, individuals with poor Eastern Cooperative Oncology Group performance status (ECOG PS) were excluded. Furthermore, some studies have identified a potential link between improved pt outcomes and development of immune related adverse events (irAE.) In a large provincial cohort, we studied the efficacy and safety of pembrolizumab for poor ECOG PS pts and whether irAE correlate with improved OS.

Materials and methods: aNSCLC pts treated with pembrolizumab between 06/2015 and 08/2018 at BC Cancer were retrospectively identified. Kaplan-Meier curves of OS from initiation of pembrolizumab were plotted. 3-, 6-, and 9- month landmark Kaplan-Meier analysis was performed and log-rank tests used to determine an association of irAE subtypes with OS. Multivariable logistic regression identified variables associated with grade ≥3 irAE within 3 months of pembrolizumab initiation.

Results: Of 190 pts, 74.2% were treatment naïve and 92.6% had PD-L1 expression ≥ 50%. Median OS in the 1st line and ≥2nd line settings were 24.3 months (95% CI, 9.7-not reached, NR) and 13.4 months (95% CI, 8.1-NR), respectively. Pts with ECOG PS 2/3 had lower median OS than if ECOG PS 0/1 (5.8 months vs. 16.7 months, $p < 0.0001$). In multivariable analysis, the odds of grade ≥ 3 irAE within 3 months was 6.3 fold higher if ECOG PS 2/3 versus 0/1 ($p = 0.05$). Development of pneumonitis at the 9 month landmark weakly correlated with decreased OS ($p = 0.09$).

Conclusion: In the studied cohort, ECOG PS 2/3 pts had a significantly lower OS and greater odds of experiencing high-grade irAE than if ECOG PS 0/1. Development of irAE did not result in improved OS. Randomized trials to determine benefit of pembrolizumab for poor ECOG PS pts are needed.

1. Introduction

Immune checkpoint inhibition has profoundly improved survival in a subset of patients with advanced nonsmall cell lung cancer (aNSCLC) [1–4]. As many as 68% of NSCLC tumors express programmed death ligand 1 (PD-L1); binding of PD-L1 to programmed death protein 1 (PD-1) on activated T cells prevents an antitumor immune response [4]. Pembrolizumab, a humanized IgG4 monoclonal antibody to PD-1, inhibits its interaction with PD-L1 [1]. As a first line treatment for aNSLC patients with a PD-L1 tumor proportion score (TPS) ≥ 50% not harbouring genomic tumor alterations (i.e., Epidermal Growth Factor Receptor (EGFR) mutation or Anaplastic Lymphoma Kinase (ALK) rearrangement), overall survival (OS) is significantly higher with pembrolizumab compared to platinum doublet chemotherapy [2,3] In patients who have progressed on platinum-based chemotherapy, pembrolizumab improves OS compared to docetaxel if the PD-L1 TPS

Abbreviations: ALK, anaplastic lymphoma kinase; CCI, Charlson comorbidity index; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, Epidermal growth factor receptor; Gr, grade; Ig, immunoglobulin; irAE, immune related adverse events; NR, not reached; NSCLC, Nonsmall cell lung cancer; OS, overall survival; PD-1, programmed death protein 1; PD-L1, programmed death protein ligand 1; PH, proportional hazard; TPS, tumor proportion score

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> 1% [4].

Randomized trials of pembrolizumab excluded patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 [1–4]. Nivolumab is a PD-1 antibody indicated for aNSCLC after progression on platinum-based doublet chemotherapy [5,6]; all pivotal trials of nivolumab included only ECOG PS ≤ 1 aNSCLC pts. As such, the magnitude of benefit of PD-1 antibodies in patients with ECOG PS 2 is unclear. Retrospective studies by Dudnik et al. and Lin et al of nivolumab utilized in aNSCLC as part of routine clinical practice both included a substantial number of patients with ECOG PS 2 (46% and 49%, respectively) [7,8]; OS in both studies was significantly worse in those with a poor ECOG PS (median OS 3.5 months and 0.8 months, respectively.) Little published data exists on the safety and efficacy of pembrolizumab for aNSCLC with ECOG PS ≥ 2.

PD-1 antibodies have a unique side-effect profile, termed immune related adverse events (irAE) [[9]]. The proportion of patients experiencing any grade irAE and severe irAE in KEYNOTE-024 were 29.2% and 9.7%, respectively [2]. While any organ can be effected, gastrointestinal, dermatologic, hepatic, and endocrine toxicities are most common. irAE must be recognized promptly and potentially treated with corticosteroids, immune modulating agents, or suspension of pembrolizumab based on the severity of irAE [[9]. The exact physiologic mechanisms spurring irAE might relate to: unmasking of underlying autoimmune diseases, molecular mimicry (similarity in tumor and host neoantigens), or organ damage from cytokine-induced inflammation [10].

A growing body of literature has, in general, correlated nivolumab-induced irAE with improved patient outcomes. In a prospective cohort study of 43 patients, Teraoka et al. noted progression free survival (PFS) to be higher amongst patients that developed irAE 2- and 6- weeks after starting nivolumab [11]. In contrast, another small prospective study of 38 aNSCLC patients did not find a correlation with irAE and PFS using landmark analysis at 60 days [12]. In a retrospective series, Haratani et al. observed an association between any irAE and dermatitis (but not endocrine irAE) and greater OS in nivolumab recipients using 6- week landmark analysis [13]. Similarly, an Italian based multicenter retrospective analysis found nivolumab treated aNSCLC patients who developed any irAE had improved OS utilizing 6- and 12- week landmark analysis [14]. It should be noted that other large retrospective series have observed poorer OS in nivolumab treated patients who developed particular irAE subtypes [15,16].

There are few studies correlating patient outcomes with irAE due to pembrolizumab in aNSCLC. KEYNOTE-001 is an international phase 1 trial of 495 pembrolizumab treated aNSCLC patients [1]. Based on retrospective review of 51 patients enrolled onto KEYNOTE-001 at Memorial Sloan Kettering Cancer Centre, Osario et al. observed a 71% improvement in OS amongst patients experiencing thyroid function abnormalities [17]. In a similar analysis, OS was greater for aNSCLC patients accrued at University of California, Los Angeles as part of KEYNOTE-001 who developed treatment related adverse events [18].

British Columbia (BC) is the westernmost province in Canada with a population of 4.8 million. In BC, pembrolizumab is publically funded as a first-line treatment for aNSCLC patients with a PD-L1 TPS ≥ 50% or after progression on platinum-based chemotherapy if PD-L1 TPS ≥ 1% through BC Cancer. We performed a multi-center retrospective analysis of all aNSCLC pts treated at BC Cancer center with pembrolizumab to investigate its efficacy in routine clinical practice, particularly to determine if the benefit persists when ECOG PS 2/3 at baseline. We also sought to evaluate the irAE profile of pembrolizumab and its association with OS utilizing landmark analysis.

2. Patients and methods

aNSCLC patients (7th edition UICC TNM classification: Stage IV or stage IIIB/recurrent disease not amenable to curative intent radiotherapy) treated with pembrolizumab at one of six BC Cancer centers between June 2015 and August 2018 were retrospectively identified. Chart review was conducted by three medical oncologists and subsequently by the first author to ensure consistency. Patient records were reviewed from initial lung cancer diagnosis until December 2018. The protocol was approved by the University of British Columbia Research Ethics Board.

Information abstracted from charts included: (1) Clinical characteristics at initiation of pembrolizumab. If ECOG PS was not stated explicitly, the reviewing oncologist made an estimate based on the clinical narrative. Also, Charlson Comorbidity Index (CCI) score was tabulated by the abstractor based on presence or absence of 19 medical conditions (aNSCLC not included as a 'solid metastatic tumor') listed in the initial medical oncology consultation note (2) Cancer histology and presence of EGFR mutation, ALK rearrangement, and PD-L1 TPS utilizing PD-L1 immunohistochemical 22c3 pharmDx assay (Dako North America, Inc., Carpentaria, CA) (3) Prior systemic therapy (4) Number of pembrolizumab doses administered (5) Development and management of irAE as identified by the treating healthcare practitioner (6) Grade of irAE (abstractor assigned grade as per Common Terminology Criteria for Adverse Events, version 4) (7) Receipt of radiotherapy within one year prior to initiation of pembrolizumab (8) Date of physician assessed progression (9) Post-pembrolizumab systemic therapy (10) Survival status at last follow-up.

At BC Cancer, patients on pembrolizumab are evaluated every 3 weeks for symptom review and blood work (including complete blood count, liver function tests, creatinine, amylase, thyroid stimulating hormone and morning cortisol). Protocol driven algorithms to treat irAE are to be followed by BC Cancer healthcare practitioners in order to standardize care [19].

2.1. Survival assessment

OS was calculated from date of first pembrolizumab dose until death from any cause or last follow-up. PFS was calculated as time from pembrolizumab initiation until tumor progression as determined by treating physician, death from any cause, or last follow-up (whichever occurred first.)

2.2. Statistical analysis

Clinical and disease characteristics were summarized as medians and ranges for continuous variables and as frequencies and percentages for categorical variables. Median follow-up times were computed (i) simply, as the median of all survival times (ignoring censoring), and (ii) by the reverse Kaplan-Meier method (REF) which provides an estimate of the potential follow-up [20]. The reverse Kaplan-Meier estimate of median follow-up time is computed as the Kaplan-Meier survival median where censoring/death indicators are reversed. Kaplan-Meier OS curves from initiation of pembrolizumab were generated and groups compared using the log-rank test. Univariable and multivariable Cox proportional hazard (PH) models were fitted to determine associations between demographic and clinical characteristics and survival outcomes. In these models, low grade (1,2) and high grade (≥3) irAE were included as time-dependent covariates since they were not known at the date of first pembrolizumab dose.

A multivariable logistic regression model was used to determine the odds of experiencing a high-grade irAE within 3 months of pembrolizumab initiation based on baseline characteristics. Included in this analysis were 160 patients; patients with follow-up less than 3 months who did not develop a grade ≥3 irAE were excluded from the logistic regression analysis.

Landmark analysis was utilized in order to minimize lead-time bias associated with time-dependent factors [21]. A landmark analysis includes patients 'in the risk set' at a set time point, excluding patients who died or were censored before this time point. Three-month landmark analysis included 159 patients (29 patients died and 2 were

censored prior to landmark) and outcomes for patients who developed a given irAE within 3 months of initiation of pembrolizumab were compared with those who did not. Similar 6-month (95 patients included, 59 patients died and 36 censored prior to landmark) and 9-month (55 patients included, 69 patients died and 66 censored prior to landmark) analyses were also performed. This method was used to obtain unbiased estimates since the irAE groups are determined during study follow-up rather than at time zero (time of initiation of pembrolizumab treatment.) Multiple landmarks over the course of six months were chosen due to the wide range in time to onset of pembrolizumab-induced irAE [22].

All p values were based on two sided hypotheses tests and those less than 0.05 were considered statistically significant. Statistical analyses were generated using R version 3.2.3 and R packages 'survival' version 2.40.1 and 'survminer' version 0.3.1 [23,24].

3. Results

3.1. Patients

A total of 190 patients received at least one dose of pembrolizumab between June 2015 to August 2018. All except two patients received the drug as routine clinical practice outside of a clinical trial. Baseline clinical and tumor characteristics at initiation of pembrolizumab are displayed in Table 1. Of note, 53% of patients were ≥70 years of age, 34% had ECOG PS ≥ 2 at baseline, 9% had liver metastases, and 14% brain metastases. 74.2% received pembrolizumab in the first-line setting while 25.8% had progressed on platinum-based doublet chemotherapy. EGFR mutation, ALK-rearrangement, and PD-L1 TPS immunohistochemistry results (all performed in a central laboratory) were available for all patients. 92.6% of tumors had PD-L1 TPS ≥ 50% while EGFR mutations were reported in 3.7% and ALK rearrangements in none. Radiation therapy was administered (most commonly for palliative intent) in 57.9% of cases within one year prior to starting pembrolizumab.

Table 1
Baseline Demographic, Tumor, and Treatment Characteristics.

Characteristic	Pembrolizumab n = 190
Age, median (range), years	70 (41-91)
Sex, n (% of pts)	
Males	97 (51.1)
Females	93 (48.9)
ECOG PS at initiation of pembrolizumab, n (% of pts)	
0/1	125 (65.8)
≥2	65 (34.2)
Histological subtype, n (% of pts)	
Squamous	42 (22.1)
Non-squamous	148 (77.9)
Smoking status, n (% of pts)	
Non-smoker	14 (7.4)
Current smoker	67 (35.3)
Former smoker	109 (57.4)
Tumor molecular aberration, n (% of pts)	
EGFR mutation	7 (3.7)
ALK rearrangement	0 (0.0)
PD-L1 staining n (% of pts)	
1-49%	14 (7.4)
≥50%	176 (92.6)
Brain metastases, n (% of pts)	26 (13.7)
Liver metastases, n (% of pts)	17 (8.9)
CCI score, median (range)	2 (0-11)
Stage IV at diagnosis, n (% of pts)	142 (74.7)
Prior adjuvant chemo, n (% of pts)	11 (5.8)
Any RT within 1 year prior to pembrolizumab, n (% of pts)	110 (57.9)
Treatment line, n (% of pts)	
First line	141 (74.2)
Second line	42 (22.1)
≥Third line	7 (3.7)
Number of PD-1 treatments, median (range)	7 (1-35)

Abbreviations: ALK= Anaplastic Lymphoma Kinase; CCI= Charlson comorbidity index; ECOG PS= Eastern Cooperative Oncology Group performance status; EGFR= epidermal growth factor receptor; n= number of patients; PD-L1= programmed death ligand 1; pts=patients; RT= radiotherapy.

3.2. Treatment

Pembrolizumab was administered at a dose of 2 mg/kg intravenous every 3 weeks to all patients. A median of 7 doses (range 1–35) were administered. Median duration of pembrolizumab treatment was 4.4 months (range 0.03–27 months). 41% of patients were still receiving pembrolizumab at the time of last follow-up.

3.3. Effectiveness

The median duration of follow-up for OS was 6.1 months (range 0.03–39.8) and 8.8 months by the reverse Kaplan-Meier method. At the time of last follow-up, 82 patients (43%) had died. The median PFS for the entire cohort was 3.7 months (95% CI, 2.8–4.3). Median OS for the whole cohort was 13.4 months (95% CI, 9.7–25.1) (Fig. 1); there was no statistically significant difference for median OS when pembrolizumab was delivered in the first-line setting (24.3 months; 95% CI, 9.7-not reached, NR) or after progression on platinum-based doublet chemotherapy (13.4 months; 95% CI, 8.1-NR, p = 0.97).

As shown in Fig. 2, median OS for patients with an ECOG PS ≤ 1 at baseline was 16.7 months (95% CI, 13.4- NR) compared to 5.8 months (95% CI, 4.8–11.4) if ECOG PS ≥ 2 (p < 0.0001). In the multivariate Cox proportional hazard regression analysis (Table 2), only ECOG PS at initiation of immunotherapy correlated significantly with overall survival (p < 0.001). Factors such as age (p = 0.73), sex (p = 0.63), smoking status (p = 0.42), CCI score (p = 0.75), histology (p = 0.54), presence of brain (p = 0.14) or liver (p = 0.42) metastases, line of treatment (p = 0.38), PD-L1 TPS (p = 0.14), development of low-grade (p = 0.31) or high-grade (p = 0.28) irAE, and radiotherapy within one year prior to initiation of pembrolizumab (p = 0.79) did not correlate with OS.

3.4. Safety

89 separate irAE were observed amongst the entire cohort; 8.4% of whole cohort experienced a grade 3 or 4 irAE (there were no treatment related deaths) (Table 3). Amongst the 66 patients who developed an irAE: 46 patients had 1 irAE, 17 patients developed two separate irAE, and 3 patients experienced three irAE subtypes. The most common irAE of any grade were dermatitis (observed in 10.5% of cohort), colitis (7.4% of cohort), hypothyroidism (6.8% of cohort), and pneumonitis (5.3% of cohort). Hepatitis and dermatitis were the most common high-grade irAE seen. 15.8% of the entire cohort required steroids to treat irAE while none needed immune modulatory agents such as infliximab. irAE management necessitated overnight hospitalization in 8 patients (4.2%). Treatment was temporarily interrupted in 12 patients (6.3%) due to irAE and discontinued in 23 patients (12.1%). There was no difference in median OS amongst patients who required treatment interruption (either delay or discontinuation) versus those receiving pembrolizumab continuously at the 3-month landmark (p = 0.75), 6-month landmark (p = 0.97), and 9-month landmark (p = 0.55).

Multivariable logistic regression analysis was performed to determine factors predicting irAE grade ≥3 within 3 months of starting pembrolizumab. Patients with an ECOG PS < 2 at initiation of pembrolizumab had 0.16 the odds of developing a severe irAE compared to those with an ECOG PS ≥ 2 (p = 0.05). Weaker associations were found with chances of developing high-grade irAE and CCI score < 3 (vs. ≥ 3, p = 0.06) and non-squamous histology (vs. squamous histology, p = 0.09). No statistically significant association on the odds of suffering a severe irAE at the 3-month landmark was found with age

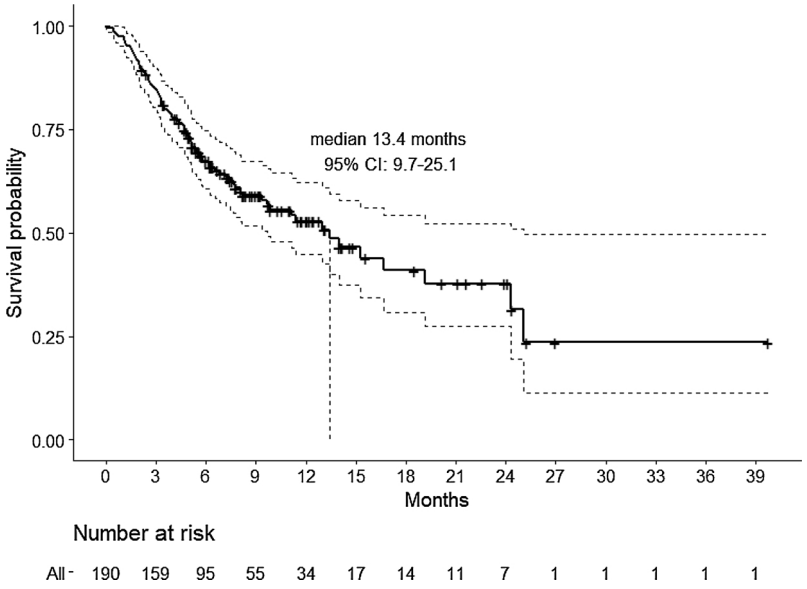

Fig. 1. Kaplan-Meier curves of overall survival for entire cohort of aNSCLC patients treated with pembrolizumab.

(p = 0.19), sex (p = 0.23), smoking status (p = 0.67), presence of liver metastases (p = 0.23), line of pembrolizumab (p = 0.21), and receipt of radiotherapy within 1 year prior to starting pembrolizumab (p = 0.32.)

3.5. Association of irAE and survival

At the 6-month landmark, development of arthralgia (versus absence of arthralgia) was weakly associated with lower OS (p = 0.08); however, only 4 patients experienced arthralgias by this time point. At the 9-month landmark, development of pneumonitis (versus absence of pneumonitis) was weakly associated with lower OS (p = 0.09). Otherwise, there was no association between any irAE or common irAE subtypes and OS at the 3-month and 6-month, and 9-month landmarks (Supplemental Table 1)

4. Discussion

We retrospectively analyzed 190 aNSCLC patients treated with pembrolizumab as part of routine practice, of whom 34.2% had an ECOG PS of 2 or 3. While treatment efficacy and incidence of irAE was generally similar to that observed in randomized clinical trials, patients with an ECOG PS ≥ 2 did poorly. Specifically, median OS was 10.9 months lower (5.8 months vs 16.7 months, p < 0.0001) and odds of experiencing a high-grade irAE at the 3 month landmark was 6.3 fold greater (p = 0.05) when comparing patients with ECOG PS 2/3 vs. 0/1.

When examined as a whole cohort, efficacy of pembrolizumab in this retrospective series is in line with randomized controlled trials. The median OS observed in KEYNOTE-024 (enrolled treatment naive aNSCLC patients with a PD-L1 TPS ≥ 50%) was 30.0 months (95% CI, 18.3-NR) [2]. In KEYNOTE-042 (frontline trial of PD-L1 positive aNSCLC pts) median OS in the subset of patients with PD-L1 TPS ≥ 50% was 20 months (95% CI, 15.4–24.9) [3]. Similarly, in this retrospective series (in which 92.6% had high PD-L1 expression) median OS for treatment naïve patients was 24.3 months (95% CI 9.7-NR). Regarding pembrolizumab in the second line setting, KEYNOTE-010 included PD-L1 positive aNSCLC patients who had progressed on platinum-based doublet chemotherapy [4]. The median OS of patients treated in

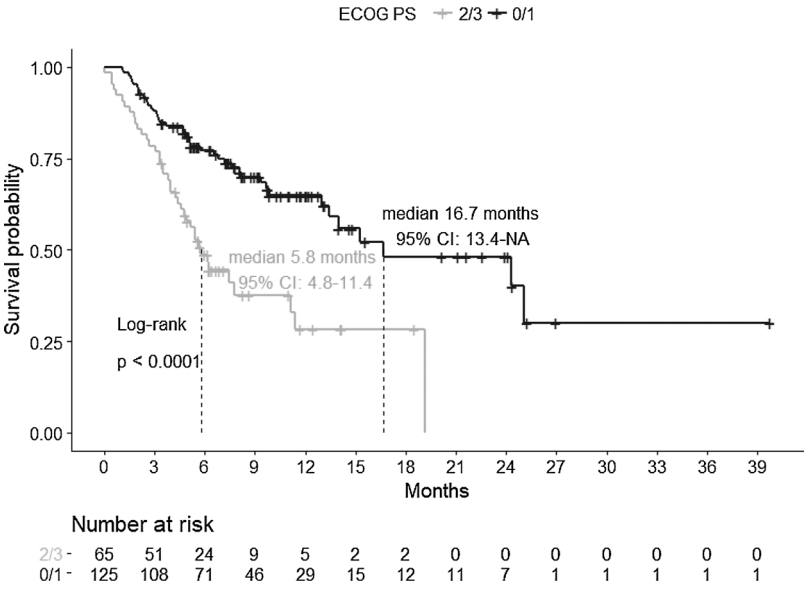

Fig. 2. Kaplan-Meier curves of overall survival based on ECOG PS at initiation of pembrolizumab.

Table 2
Multivariable Cox Proportional Hazard Regression Analysis on Overall Survival.

Variable	HR (95% CI)	P
Age (< 64 years vs. ≥ 64 years)	0.91 (0.53-1.57)	0.73
Sex (female vs. male)	0.89 (0.57-1.41)	0.63
Smoking status		
(current vs. non-smoker/former)	0.81 (0.49-1.34)	0.42
CCI score (< 3 vs. ≥ 3)	0.93 (0.58-1.48)	0.75
Histology (non-squamous vs. squamous)	0.84 (0.48-1.46)	0.54
ECOG PS (0/1 vs. 2/3)	0.37 (0.24-0.59)	< 0.001
Brain metastases (none vs. present)	0.61 (0.32-1.18)	0.14
Liver metastases (none vs. present)	0.75 (0.37-1.5)	0.42
Line of treatment (1^{st} vs. > 1^{st})	0.79 (0.46-1.35)	0.38
PDL1 TPS (≥50% vs. < 50%)	2.11 (0.78-5.76)	0.14
irAE		
Gr1/2 vs. no irAE	0.66 (0.29-1.48)	0.31
Gr≥3 vs. no irAE	0.33 (0.04-2.43)	0.28
RT within 1 year prior to first pembrolizumab dose	0.93 (0.57-1.54)	0.79

Abbreviations: CCI = Charlson comorbidity index; ECOG PS = Eastern Cooperative Oncology Group performance status; irAE = immune related adverse events; PD-L1 TPS = programmed death ligand 1 tumor proportion score; pts = patients; RT = radiotherapy.

Table 3
Distribution of Immune Related Adverse Events.

Immune related adverse event	Any grade n (%)	Grade 3 or 4 n (%)
All	66 (34.7)	16 (8.4)
Dermatitis	20 (10.5)	3 (1.6)
Colitis	14 (7.4)	2 (1.1)
Hypothyroidism	13 (6.8)	0 (0.0)
Pneumonitis	10 (5.3)	1 (0.5)
Hepatitis	7 (3.7)	4 (2.1)
Arthralgias	6 (3.2)	0 (0.0)
Nephritis	3 (1.6)	1 (0.5)
Neurologic	3 (1.6)	0 (0.0)
Hyperthyroidism	2 (1.1)	0 (0.0)
Polymyalgia rheumatica	2 (1.1)	0 (0.0)
Pericarditis	2 (1.1)	2 (1.1)
Cholangitis	1 (0.5)	0 (0.0)
Hypophysitis	1 (0.5)	0 (0.0)
Infusion reaction	1 (0.5)	0 (0.0)
Idiopathic thrombocytopenia purpura	1 (0.5)	1 (0.5)
Myocarditis	1 (0.5)	1 (0.5)
Neutropenia	1 (0.5)	1 (0.5)

Abbreviations: n = number of patients with irAE, % = number of patients who developed irAE/190.

KEYNOTE-010 with pembrolizumab 2 mg/kg every 3 weeks was 10.4 months (95% CI, 9.4–11.9); in our study, patients receiving pembrolizumab in the second line or greater demonstrated a median OS of 13.4 months (95% CI, 8.1-NR).

aNSCLC patients with ECOG PS ≥ 2 represent a substantial proportion of everyday clinical practice, yet are underrepresented in clinical trials. In the present cohort, 34.2% of patients had an ECOG PS of 2 or 3 at initiation of pembrolizumab. Analyzing data from two quality of life studies conducted in the United States of America, Lilenbaum et al. found 34% of lung cancer patients had an ECOG PS of 2–4 [25]. KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 required patients to have an ECOG PS of 0 or 1 at baseline [24]. The only prospective study in this patient population is a small phase II trial- Pembrolizumab in Performance Status 2 Nonsmall Cell Lung Cancer (PePS2) [26]. As per the abstract, 15 of 62 accrued patients had a PD-L1 TPS ≥ 50% and demonstrated a PFS was 8.5 months; 8% of all patients enrolled on the trial had an adverse event related to pembrolizumab.

Data from extended access programs (EAP) and retrospective series have observed lower OS amongst nivolumab treated aNSLC patients with ECOG PS 2 compared to those with an ECOG PS ≤ 1. A French EAP including 600 aNSCLC patients receiving nivolumab in the second line, found the median OS amongst patients with poor ECOG PS was less than half that observed in patients with good ECOG PS (3.6 months vs. 9.5 months, respectively) [27]. In Checkmate 153, a phase IIIB/IV study of nivolumab in aNSCLC, patients with an ECOG PS 2 had a lower one year OS than those with ECOG PS < 2 (23% vs. 46%, respectively) [28]. Large retrospective studies conducted in Israel and Japan both observed worse outcomes amongst ECOG PS 2 patients treated with nivolumab versus those with an ECOG PS ≤ 1 [7,29].

In this retrospective series, 92.6% of tumors expressed a PD-L1 TPS ≥ 50%. All immunohistochemical testing was completed at a central BC Cancer laboratory by lung pathologists using the same antibody. All tissue samples were obtained from either core biopsy or fine needle aspiration (not cytology) of the most accessible lesion. Since 74.7% of patients presented with incurable disease, deterioration of PD-L1 antigen in tumor bank samples was likely not an issue. In registration trials, the proportion of tumors with PD-L1 TPS ≥ 50% ranged from 23%–30% [1,2,4]. The high proportion of tumors with PD-L1 TPS ≥ 50% noted in our series likely reflects preferential use of front-line pembrolizumab when PD-L1 expression exceeds 50%.

The presence of liver or brain metastases are traditionally considered poor prognostic factors, yet neither was associated with OS in the present study on Cox PH regression modelling. In our series all patients with brain metastases were treated with either whole brain radiation or stereotactic radiosurgery. Golderberg et al. performed a phase II trial of metastatic melanoma and aNSCLC patients with asymptomatic brain metastases between 0.5–2 cm in size [30]. Amongst the 18 patients with aNSCLC patients (brain metastases untreated in 16 patients) the intracranial response rate was 33%. In the current study, it is possible that pembrolizumab treatment in addition to radiotherapy were able to control brain metastases such that extra-cranial disease limited survival. Regarding liver metastases, subgroup analysis of KEYNOTE-001 revealed that hepatic metastases were associated with lower PFS and response rates [31]. Mechanistic explanations for this phenomenon put forth by the authors include liver induced systemic tolerance. The discordant findings in our series might relate to the study cohort being predominately treatment naïve and having a high PD-L1 TPS, thereby increasing the likelihood of response to pembrolizumab.

The proportion of patients developing a severe irAE in this series was low (8.4%) and there were no treatment related deaths. Furthermore, only 8 patients required overnight hospitalization (of whom 1 required admission to an intensive care unit) to treat irAE. The pattern of irAE was, on the whole, consistent with that observed in the literature. As a notable exception, 2 patients in the present study developed grade 3 pericarditis; pembrolizumab induced cardiotoxicity (typically myocarditis) is a recognized but uncommon complication [32]. The proportion of patients requiring treatment discontinuation

due to irAE is inconsistently reported in clinical trials; in KEYNOTE-024, 7.1% of pembrolizumab treated patients had therapy discontinued due to an adverse event [2]. In a retrospective review of 482 patients treated at Memorial Sloane Kettering Cancer Center both on and outside of a clinical trial with PD-L1/PD-1 antibodies (10% received combination therapy with a CTLA-4 inhibitor), 6.9% needed treatment stopped permanently due to an irAE [33]. In the present series, 12.1% of patients had treatment discontinued due to irAE as documented specifically in clinic notes. While BC Cancer healthcare practitioners are supposed to follow irAE treatment algorithms, it is possible that pembrolizumab was discontinued prematurely with low grade irAE due to concern about potential future worsening.

In multivariate logistic regression analysis, ECOG PS of 2 or 3 significantly increased the odds ($p = 0.05$) of severe irAE within 3 months of initiation of pembrolizumab while a weaker association existed if CCI score < 3 (vs. ≥ 3, $p = 0.06$). It is important to note that in our series patients with a poor performance status demonstrated a median OS 10.9 months lower and odds of severe irAE 6.3 fold higher than those with a good performance status at initiation of pembrolizumab. This highlights the need for prospective clinic trials to determine the safety and efficacy of immunotherapy in this patient. The trend to association of severe irAE in patients with a CCI score < 3 (versus ≥ 3) is surprising. CCI has been identified as a poor prognostic factor in retrospective studies for patients with aNSCLC that are EGFR/ALK wildtype [34]. It is possible that individuals with multiple medical conditions have more frequent contact with a variety of healthcare practitioners and, as such, irAE would be detected earlier.

Multiple theories have been postulated to explain the physiologic mechanism of irAE. PD-1 inhibitors might modulate the humoral immune system to unmask latent auto-immunity [10]. For example, antithyroid antibodies (which can cause hyperthyroid conditions such Grave's disease) are present in 11% of the population, even though only 4% demonstrate abnormal thyroid function tests. In a retrospective review of aNSCLC patients enrolled onto KEYNOTE-001 at a single institution, Osario et al. observed that hypothyroidism developed in 80% of patients who had thyroid antibodies present at baseline, compared to 8% who did not [17]. The authors believe this finding consistent with auto-immune destruction of the thyroid gland.

Cross reactivity of tumor and self neoantigens (so-called molecular mimicry) has been postulated to explain skin toxicity due to nivolumab [35]. Hasan Ali et al. performed immunohistochemical staining (CD3, CD4+, and CD8+) from punch biopsy specimens of patients with aNSCLC who developed nivolumab induced dermatitis; 2 punch biopsies were obtained from patients with squamous tumors and 2 from patients with adenocarcinoma histology. The distribution of CD3 and CD8 + T cells was dependent on cancer subtype, with lymphocytes being more prominent above the basal cell membrane in patients with squamous histology, while patients with adenocarcinoma histology displayed more lymphocytes in the dermis. The authors hypothesize that molecular mimicry (i.e., similarities between antigens expressed on keratinocytes near the basal cell membrane and those present on squamous tumors) could account for skin toxicity in nivolumab treated aNSCLC patients.

In the present study, there was no association with OS and development of irAE with 3-, 6-, and 9-month landmark analysis. Landmark analysis was utilized in order to minimize lead- time bias associated with time-dependent factors. Studies involving nivolumab treated aNSCLC patients utilized landmarks within the first weeks of therapy [13,14,29]. However, median time of onset of pembrolizumab induced irAE can occur many months after treatment [22]; based on the product monograph, median time to onset of nephritis is 5.1 months (range 12 days to 12.8 months). Treatment cessation due to irAE has been suggested as a marker of immune activation due to immune checkpoint inhibition [36]. However, in this retrospective series there was no difference in median overall survival amongst patients needing treatment interruption and those receiving pembrolizumab continuously.

With respect to irAE subtypes, we observed a weak association between development of pneumonitis and lower OS at the 9-month landmark. Unlike previous studies with pembrolizumab, no association between dermatitis or thyroid changes and OS were noted in this study [17,37]. Regarding nivolumab induced pneumonitis, retrospective studies have shown conflicting results regarding this irAE and patients outcomes. In an observational retrospective series involving Japanese patients, Fujimoto et al. correlated pneumonitis with improved PFS [29]. In contrast, Suresh et al. found decreased OS using a Markov multi-state model amongst nivolumab recipients at an American institution [15]. The authors of the latter study suggest that comorbid pulmonary conditions (i.e., chronic obstructive pulmonary disease) might differ in patient populations and explain the disparate results.

Our study has some limitations. First, while all the healthcare practitioners prescribing pembrolizumab at BC Cancer are trained to follow irAE management algorithms, access to subspecialty support at smaller centres is often limited. Subspecialty care is imperative to ensure that irAE are treated adequately and that patients have access to immune modulating agents for severe adverse effects. Second, as knowledge of PD-L1 status is required to obtain access to pembrolizumab but not nivolumab, it is possible that patients who were too ill to undergo biopsy for immunohistochemical testing would preferentially receive nivolumab.

5. Conclusion

In this retrospective series, pembrolizumab provided the expected clinical benefit and toxicity profile, except amongst aNSCLC patients with poor ECOG PS. Furthermore, patients with an ECOG PS 2/3 (compared to ECOG PS 0/1 patients) experienced high odds developing irAE $\geq$ grade 3 from pembrolizumab. Careful consideration should be taken when contemplating pembrolizumab treatment for patients with a poor ECOG PS. Randomized clinical trials with ECOG PS 2/3 patients are required in order to determine the exact benefit of pembrolizumab compared to standard chemotherapy.

Conflict of interest

Dr. Doran Ksienski- honoraria for continuing medical education events from Merck Canada and Bristol Myers Squibb Canada. Unrestricted education grant received from AstraZeneca Canada

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.05.005.

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