ABSTRACT

Background Although PD-1 antibodies (PD1 Ab) are the standard of care for advanced non-small-cell lung cancer (aNSCLC), most patients will progress. We compared survival outcomes for patients with aNSCLC who received systemic therapy (st) after progression and for those who did not. Additionally, clinical characteristics that predicted receipt of st after PD1 Ab failure were evaluated.

Methods All patients with aNSCLC in British Columbia initiated on nivolumab or pembrolizumab between June 2015 and November 2017, with subsequent progression, were identified. Eligibility criteria for additional st included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 3 or less and survival for more than 30 days from the last PD1 Ab treatment. Post-progression survival (PPS) was assessed by landmark analysis. Baseline characteristics associated with PPS were identified by multivariable analysis.

Results Of 94 patients meeting the eligibility criteria, 33 received st after progression. In 75.6%, a PD1 Ab was received as first- or second-line treatment. The most common sts were erlotinib (36.4%) and docetaxel (27.3%). No statistically significant difference in median PPS was observed between patients who did and did not receive st within 30 days of their last PD1 Ab treatment (6.9 months vs. 3.6 months, log-rank p = 0.15.) In multivariable analysis, factors associated with increased PPS included an ECOG PS of 0 or 1 compared with 2 or 3 [hazard ratio (HR): 0.42; 95% confidence interval (CI): 0.24 to 0.73; p = 0.002] and any response compared with no response to PD1 Ab (HR: 0.54; 95% CI: 0.33 to 0.90; p = 0.02).

Conclusions In this cohort, only 35.1% of patients eligible for post–PD1 Ab therapy received st. Post-progression survival was not significantly affected by receipt of post-progression therapy. Prospective trials are needed to clarify the benefit of post–PD1 Ab treatments.

Key Words Pembrolizumab, nivolumab, non-small-cell lung cancer, immunotherapy, post-progression survival

INTRODUCTION

The PD-1 receptor antibodies (PD1 Ab) pembrolizumab and nivolumab have changed the treatment landscape in advanced non-small-cell lung cancer (aNSCLC). Compared with frontline platinum doublet chemotherapy, pembrolizumab improves overall survival (OS) in patients with aNSCLC showing PD-L1 expression of 50% or greater1,2. Pembrolizumab has also demonstrated superiority to docetaxel as a second-line treatment in patients with PD-L1–positive aNSCLC3. After a patient progresses on platinum-based chemotherapy, nivolumab, compared with docetaxel, confers an OS benefit regardless of PD-L1 expression4.5. Despite those remarkable therapeutic advances, most patients receiving PD1 Ab will progress.

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One approach to therapy after PD1 Ab failure is to offer additional systemic therapy (ST). In the pre-immunotherapy era, direct evidence supported the use of docetaxel or erlotinib in the third-line setting. In 2004, Hanna et al. conducted a randomized phase III trial of pemetrexed compared with docetaxel in patients progressing on a platinum doublet, demonstrating similar median OS results (8.3 months vs. 7.9 months). Pujol et al. subsequently observed a median OS of 9.6 months for patients in the pemetrexed arm who received docetaxel as a third-line treatment. In BR.21, erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), increased survival for patients with aNSCLC who had been treated with 1 or 2 lines of palliative chemotherapy compared with best supportive care alone (median OS: 6.7 and 4.7 months respectively). However, with the advent of routine screening for EGFR mutations, the benefit of erlotinib in EGFR wild-type tumours is uncertain.

There is potential for synergy between chemotherapy and checkpoint inhibitors in aNSCLC. When chemotherapy is administered before a checkpoint inhibitor, augmentation of the antitumour response is thought to occur through disruption of stroma, increased neoantigen processing, and suppression of regulatory T cells and myeloid-derived suppressor cells. As a frontline treatment, platinum-based chemotherapy combined with pembrolizumab, compared with chemotherapy alone, is associated with improved OS. That synergy could possibly persist when chemotherapy is given after a checkpoint inhibitor because of a “priming” effect on T cells or the long half-life of PD1 Abs. Indeed, a retrospective analysis of 28 patients conducted by Schwartsman et al. suggested an enhanced response to single-agent chemotherapy given after progression on PD1 Ab therapy. The objective response rate to single-agent chemotherapy in that cohort was 39%. Similarly, Yano et al. conducted a retrospective review of 26 patients who received systemic chemotherapy of EGFR TKI after progression on nivolumab and reported an objective response rate of 34.6% and post-progression survival (PPS) of 12.6 months [95% confidence interval (CI): 3.8 months to 14.7 months]. The authors of both studies postulate a chemosensitizing effect of antecedent immunotherapy.

BC Cancer consists of 6 centres across the province of British Columbia and provides publicly funded comprehensive care for a population of 4.8 million. BC Cancer medical oncologists who treat aNSCLC follow protocol-driven algorithms (http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols/lung) to ensure uniform delivery of care. In British Columbia, pembrolizumab is available as a first-line treatment for patients with aNSCLC and PD-L1 expression of 50% or greater and as a second-line treatment if PD-L1 expression is 1% or greater. Nivolumab can be used after progression on a platinum-based doublet regardless of PD-L1 expression.

However, with the advent of routine screening for EGFR mutations, the benefit of erlotinib in EGFR wild-type tumours is uncertain. There is potential for synergy between chemotherapy and checkpoint inhibitors in aNSCLC. When chemotherapy is administered before a checkpoint inhibitor, augmentation of the antitumour response is thought to occur through disruption of stroma, increased neoantigen processing, and suppression of regulatory T cells and myeloid-derived suppressor cells. As a frontline treatment, platinum-based chemotherapy combined with pembrolizumab, compared with chemotherapy alone, is associated with improved OS. That synergy could possibly persist when chemotherapy is given after a checkpoint inhibitor because of a “priming” effect on T cells or the long half-life of PD1 Abs. Indeed, a retrospective analysis of 28 patients conducted by Schwartsman et al. suggested an enhanced response to single-agent chemotherapy given after progression on PD1 Ab therapy. The objective response rate to single-agent chemotherapy in that cohort was 39%. Similarly, Yano et al. conducted a retrospective review of 26 patients who received systemic chemotherapy of EGFR TKI after progression on nivolumab and reported an objective response rate of 34.6% and post-progression survival (PPS) of 12.6 months [95% confidence interval (CI): 3.8 months to 14.7 months]. The authors of both studies postulate a chemosensitizing effect of antecedent immunotherapy.

BC Cancer protocols mandate cessation of PD1 Ab once definitive radiographic progression is demonstrated. Pseudoprogression (an uncommon imaging pattern in aNSCLC) describes an initial adverse change on imaging followed by radiographic response on subsequent imaging with radiographic response on subsequent imaging. At BC Cancer, if pseudoprogression is suspected, PD1 Ab can be continued, but persistent adverse radiographic change on successive computed tomography imaging over 6–10 weeks constitutes progressive disease21,22. In cases in which pseudoprogression was suspected, but later found to be true progression, date of progression was recorded as the date of the first computed tomography imaging showing adverse changes. In cases in which pseudoprogression was suspected and later confirmed, no progression was recorded.

METHODS

Data Collection

All patients with aNSCLC (stage IV, Union for International Cancer Control TNM classification, 7th edition; or recurrent nonresectable disease not amenable to curative-intent radiotherapy) treated with nivolumab or pembrolizumab at 1 of the 6 BC Cancer centres between June 2015 and November 2017 were identified (n = 271). Intravenous (IV) nivolumab was administered at 3 mg/kg every 2 weeks; IV pembrolizumab was administered at 2 mg/kg every 3 weeks. Chart reviews were conducted by 1 of 6 lung medical oncologists and subsequently by DK to ensure consistency. Patient records were reviewed from initial lung cancer diagnosis to December 2018. The protocol was approved by the University of British Columbia Research Ethics Board.

Clinical characteristics abstracted from the chart were the patient’s ECOG performance status (PS) at the time of progression on PD1 Ab; score on the Charlon comorbidity index at the time of initial consultation; cancer histology; presence of EGFR mutation and ALK rearrangement; PD-L1 expression by the immunohistochemical Dako 22C3 pharmDx assay (Dako North America, Carpinteria, CA, U.S.A.); number of PD1 Ab doses administered; development and management of immune-related adverse events (iRAEs) as identified by the treating health care practitioner; grade of the iRAEs (abstractor-assigned grade per the Common Terminology Criteria for Adverse Events, version 4); date of physician-assessed progression; post–PD1 Ab ST; and survival status at last follow-up.

Date of Progression on PD1 Ab

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Defining Eligibility for Post–PD1 Ab Treatments

To be considered eligible for post–PD1 Ab ST, these inclusion criteria were applied: physician-assessed progression on PD1 Ab; ECOG PS of 3 or less at the time of progression; and survival for more than 30 days from the last PD1 Ab dose. ATF and DK independently reviewed all patients who were no longer receiving PD1 Ab at last follow-up (n = 202) to determine those potentially suitable for additional treatment.

Survival Assessments

Overall survival was defined as the time from the first post–PD1 Ab treatment until death or last follow-up; progression-free survival (PFS) was measured from the date of post–PD1 Ab therapy initiation to date of failure on subsequent ST, last-follow-up, or death (whichever came
first). Post-progression survival was measured from the date of the last PD1 Ab treatment to death or last follow-up.

Statistical Analysis
Clinical and tumour characteristics are summarized using descriptive statistics. Categorical variables are reported as frequencies and percentages, and continuous variables, as median and ranges. Survival curves were generated using the Kaplan–Meier method and groups were compared using the log-rank test. Median follow-up was calculated in two ways: as the simple median of all survival times (ignoring censoring), and using the reverse Kaplan–Meier method, which provides an estimate of the potential follow-up. Univariable and multivariable Cox proportional hazard models with 1-month landmark analysis were used to determine associations between clinical characteristics and PPS. Patients were separated into groups based on whether they had received ST before the landmark time. Because the eligibility criteria had stipulated that patients must survive at least 30 days after the last PD1 Ab treatment, no patients were excluded from the landmark analysis. Univariable and multivariable logistic regression models were used to determine associations between clinical characteristics and receipt of post-progression therapy. Because of the low number of observed events, we used backward elimination for the multivariable analyses.

RESULTS
Patient Characteristics
All patients with NSCLC treated with either nivolumab or pembrolizumab were identified (n = 271). Within that cohort, 94 patients were deemed eligible for post-PD1 Ab treatment, but only 33 received ST after PD1 Ab failure (Figure 1). The remaining 177 patients were excluded because of ongoing PD1 Ab therapy (n = 69), poor ECOG PS or rapid clinical deterioration at progression (n = 91), no evidence of progression (n = 10), lost to follow-up (n = 6), or pursuit of medically assisted death (n = 1).

Table 1 reports the clinicopathologic characteristics of the patients deemed eligible for post-PD1 Ab treatment. Notably, median age at initiation of PD1 Ab was 65.5 years (range: 44–84 years), 46.8% were women, and 20.2% had squamous histology. Median score on the Charlson comorbidity index was 6 (range: 0–11), and at progression, 34.1% had EGFR mutation status, presence of brain or liver metastases, radiation before PD1 Ab treatment, and 9.6% discontinued treatment because of an iRAE (with subsequent progression).

Post-Progression Treatment Characteristics
Of 33 patients who received post-PD1 Ab treatment, 28 received 1 additional line of anti-cancer therapy, and 5 patients received 2 different lines (Figure 2). Median time from last PD1 Ab dose to next line of treatment was 0.6 months (range: 0.03–8.3 months). Systemic therapies after progression on PD1 Ab included erlotinib (n = 12), docetaxel (n = 9), pemetrexed (n = 7), platinum doublet (n = 5), vinorelbine (n = 2), cetuximab (n = 1), gefitinib (n = 1), and indoleamine-2,3-dioxygenase inhibitor with nivolumab on a clinical trial (n = 1). For all 33 patients, the median number of treatments delivered was 3 (range: 1–20), and median treatment duration was 1.7 months (range: 0.2–13.7 months; Figure 2). At last follow-up, only 1 patient was still receiving ST (docetaxel).

Survival After Progression on PD1 Ab Therapy
Median follow-up from the last dose of PD1 Ab therapy was 3.5 months (or 13.8 months if calculated by the reverse Kaplan–Meier method). For the patients who received additional ST, median PFS was 1.5 months (95% CI: 0.9 months to 2.8 months), and median OS was 6.1 months (95% CI: 2.8 months to 8.9 months). Using landmark analysis, the median PFS for patients who received additional ST within 30 days of the last PD1 Ab treatment was 6.9 months (95% CI: 3.5 months to 10.6 months); it was 3.6 months for patients who did not (95% CI: 3.0 months to 5.5 months; p = 0.15, Figure 3).

Factors associated with improved PFS in a univariable landmark analysis included ECOG PS at progression (ECOG 0/1 vs. 2/3 HR: 0.55; 95% CI: 0.33 to 0.90; p = 0.03) and response to PD1 Ab (nonprogression vs. progressive disease HR: 0.52; 95% CI: 0.32 to 0.86; p = 0.01; Table II). On multivariable landmark analysis, an ECOG PS of 0 or 1 (HR: 0.42; 95% CI: 0.24 to 0.73; p = 0.002) and response to PD1 Ab therapy (HR: 0.54; 95% CI: 0.33 to 0.90; p = 0.02) remained significant predictors of PPS (Table III).

Factors Associated with Receipt of Post-Progression Therapy
In univariable analysis, none of sex, age, ECOG PS, score on the Charlson comorbidity index, histology, smoking status, PD-L1 expression, EGFR mutation status, presence of brain or liver metastases, radiation before PD1 Ab treatment,
PD1 Ab treatment line, PD1 Ab treatment type, cessation of PD1 Ab because of an irAE, and investigator-determined best response was significantly associated with receipt of post-progression treatment (supplemental Table 1).

**TABLE 1** Baseline characteristics

| Variable                                      | Post-progression therapy |
|----------------------------------------------|--------------------------|
|                 | No       | Yes       |
| Patients (n)  | 61       | 33        |
| Sex [n (% women)] | 25 (41.0) | 19 (57.6) |
| Age at progression (years)                  |                        |
| Median   | 66.00    | 65.00     |
| Range    | 44.00–84.00 | 44.00–82.00 |
| ECOG PS at progression [n (%)]              |                        |
| 0–1     | 20 (32.8) | 12 (36.4) |
| 2–3     | 41 (67.2) | 21 (63.6) |
| Smoking status [n (%)]                      |                        |
| Current  | 14 (23.0) | 14 (42.4) |
| Former   | 34 (55.7) | 14 (42.4) |
| Nonsmoker| 13 (21.3) | 5 (15.2)  |
| Score on the CCI                            |                        |
| Median   | 6.00     | 6.00      |
| Range    | 0.00–11.00 | 0.00–11.00 |
| Histology [n (%)]                           |                        |
| Adenocarcinoma     | 50 (82.0) | 25 (75.8) |
| Squamous cell      | 11 (18.0) | 8 (24.2)  |
| PD-L1 status [n (%)]                         |                        |
| <1%        | 9 (14.8)  | 4 (12.1)  |
| 1–49%     | 9 (14.8)  | 5 (15.2)  |
| >50%      | 10 (16.4) | 6 (18.2)  |
| Unknown   | 33 (54.1) | 18 (54.5) |
| EGFR mutation [n (%)]                        |                        |
| 3 (4.9)    | 3 (9.1)   |
| ALK rearrangement [n (%)]                    |                        |
| 0 (0.0)    | 1 (3.0)   |
| Brain metastases before PD-1 Ab [n (%)]     |                        |
| 7 (11.5)   | 3 (9.1)   |
| Liver metastases before PD-1 Ab [n (%)]     |                        |
| 6 (9.8)    | 4 (12.1)  |
| Time from last PD-1 Ab to first post-progression Tx (months) | |
| Median     | —        | 0.59      |
| Range      | —        | 0.03–8.27 |

ECOG PS = Eastern Cooperative Oncology Group performance status; CCI = Charlson comorbidity index; Ab = monoclonal antibody; Tx = treatment; irAE = immune-related adverse event.

**FIGURE 2** Course of treatment for each patient. Chemo = chemotherapy.

**FIGURE 3** Post-progression survival after cessation of PD-1 monoclonal antibody (Ab) in 22 patients who received post-progression therapy and 72 patients who did not within 30 days of PD-1 Ab cessation.
DISCUSSION

In this retrospective analysis, only 35.1% of patients potentially eligible for further ST after progression on a PD1 Ab (good ECOG PS at progression and alive more than 30 days from the last PD1 Ab dose) actually received treatment. We did not observe a difference in survival between patients with aNSCLC who did and did not receive ST after PD1 Ab failure.

To our knowledge, no currently published phase III trials have explored the role of ST after progression on immunotherapy. The question of that role will become increasingly important with greater use of PD-1/-L1 antibody therapy either as monotherapy or in combination with chemotherapy as frontline treatment. The ongoing randomized double-blind placebo-controlled CANOPY-2 trial is testing docetaxel with or without interleukin-1β in patients with aNSCLC after progression on PD-1/-L1 antibody, platinum-based chemotherapy, and immunotherapy (see NCT03626545 at https://ClinicalTrials.gov/). Our series provides outcomes data for that patient population and a real-world comparison between patients who did and did not receive ST after progression on a PD1 Ab.

Compared with patients in other retrospective series, our group of patients with aNSCLC who received ST after PD1 Ab failure experienced modest survival outcomes. Specifically, for patients who received post-progression therapy, we observed a median PFS of 1.5 months (95% CI 0.67 to 2.91).

| TABLE II | Univariate landmark analysis of factors associated with post-progression survival after cessation of PD-1 monoclonal antibody |
|-----------|-------------------------------------------------------------------------------------------------------------------------------|
| Variable | Comparison | HR   | 95% CI          | p Value |
| Sex | Female vs. male | 0.76 | 0.47 to 1.21 | 0.24 |
| Age at initiation of PD-1 Ab Tx | <65 vs. ≥65 | 0.83 | 0.52 to 1.32 | 0.43 |
| ECOG PS at progression | 0/1 vs. 2/3 | 0.55 | 0.33 to 0.93 | 0.03 |
| Score on the CCI | <3 vs. ≥3 | 0.66 | 0.38 to 1.14 | 0.14 |
| Histology | Nonsquamous vs. squamous | 1.26 | 0.66 to 2.4 | 0.48 |
| Smoking status | Former or nonsmoker vs. current | 1.23 | 0.74 to 2.05 | 0.42 |
| PD-L1 staining | ≥50% vs. <50% or unknown | 1.47 | 0.78 to 2.74 | 0.23 |
| EGFR status | Positive vs. negative or unknown | 1.09 | 0.47 to 2.52 | 0.85 |
| ALK status | Positive vs. negative or unknown | 0.77 | 0.31 to 5.27 | 0.80 |
| Metastases before PD-1 Ab Tx | Brain: No vs. yes | 0.84 | 0.4 to 1.78 | 0.65 |
| | Liver: No vs. yes | 0.78 | 0.4 to 1.52 | 0.46 |
| Radiation before PD-1 Ab Tx | Yes vs. no | 1.2 | 0.73 to 1.97 | 0.48 |
| PD-1 Ab Tx type | Pembrolizumab vs. nivolumab | 1.09 | 0.55 to 2.14 | 0.81 |
| PD-1 Ab Tx line | First or second vs. ≥3rd | 1.54 | 0.88 to 2.69 | 0.13 |
| Cessation of PD-1 Ab Tx for an irAE | Permanent vs. temporary or no | 0.85 | 0.41 to 1.78 | 0.67 |
| Best response to PD1 Ab Tx | Response vs. no response | 0.52 | 0.32 to 0.86 | 0.01 |
| Post–PD1 systemic Tx | Yes vs. no | 0.67 | 0.38 to 1.16 | 0.15 |

HR = hazard ratio; CI = confidence interval; Ab = monoclonal antibody; Tx = treatment; ECOG PS = Eastern Cooperative Oncology Group performance status; CCI = Charlson comorbidity index; irAE = immune-related adverse event.

| TABLE III | Multivariate landmark analysis of factors influencing post-progression survival after cessation of PD-1 monoclonal antibody* |
|-----------|-------------------------------------------------------------------------------------------------------------------------------|
| Variable | Comparison | HR   | 95% CI          | p Value |
| Sex | Female vs. male | 0.64 | 0.39 to 1.03 | 0.07 |
| ECOG PS at progression | 0–1 vs. 2–3 | 0.42 | 0.24 to 0.73 | 0.002 |
| PD-1 Ab Tx line | 1st or 2nd vs. ≥3rd | 1.75 | 0.98 to 3.14 | 0.06 |
| Best response to PD1 Ab Tx | Response vs. no response | 0.54 | 0.33 to 0.9 | 0.02 |

| Variable | Comparison | HR | 95% CI | p Value |
|-----------|------------|----|--------|---------|
| Sex | Female vs. male | 0.64 | 0.39 to 1.03 | 0.07 |
| ECOG PS at progression | 0–1 vs. 2–3 | 0.42 | 0.24 to 0.73 | 0.002 |
| PD-1 Ab Tx line | 1st or 2nd vs. ≥3rd | 1.75 | 0.98 to 3.14 | 0.06 |
| Best response to PD1 Ab Tx | Response vs. no response | 0.54 | 0.33 to 0.9 | 0.02 |

HR = hazard ratio; CI = confidence interval; PPS = post-progression survival; ECOG PS = Eastern Cooperative Oncology Group performance status; NR = not reached; Ab = monoclonal antibody; Tx = treatment.

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* Reduced model by backward elimination.
either univariable or multivariable analysis. The low number of patients in our cohort receiving post-progression therapy might have limited our ability to identify those relationships. That small group could reflect the paucity of evidence available to guide decisions about subsequent anticancer therapy after failure of PD1 Ab. Only 35.1% of patients eligible for additional ST after progression on PD1 Ab actually received treatment. Low uptake of additional anticancer treatment might reflect patient preference, decline in functional status, or physician perception of modest benefit.

A limitation of the present study is its retrospective design, which increases the risk of survivor treatment selection bias. The number of patients receiving post-progression therapy was small, but reflects the reality of an emerging patient population. Second, the actual decision to pursue ST after progression on PD1 Ab is based on a detailed discussion of risk and benefits by treating physicians with patients; it is possible that certain aspects of those conversations were not documented in the charts.

CONCLUSIONS

Given the broadening landscape of options related to PD-1/-L1 antibodies (either alone or in combination with chemotherapy) for patients with treatment-naïve aNSCLC, post-immunotherapy ST will be more commonly used. Prior retrospective studies have suggested a survival benefit for patients receiving chemotherapy after Pd1 Ab therapy, which is postulated to be associated with a chemosensitizing effect. We compared survival outcomes for patients with aNSCLC who did and did not receive ST after progression on a PD1 Ab. In our retrospective study of 94 patients, only 35.1% received additional therapy after progression on a PD1 Ab. In contrast to findings in prior retrospective studies, PPS was not significantly affected by receipt of post-progression ST. That observation could be explained by the relatively high proportion of patients with wild-type EGFR in our study who received erlotinib after progression on PD1 Ab therapy. Post-progression chemotherapy could be considered for patients with good performance status, but additional data are required to clarify the benefit in this growing patient population.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Reck M, Rodriguez-Abreu D, Robinson AG, et al. on behalf of the KEYNOTE-024 investigators. Pembrolizumab versus chemotherapy for PD-L1–positive nonsmall cell lung cancer. N Engl J Med 2016;375:1823–33.
