

# Targeting the PD-1/PD-L1 axis for the treatment of non-small-cell lung cancer

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## ABSTRACT

Lung cancer is the leading cause of cancer-specific death among Canadians, with non-small-cell lung cancer (NSCLC) being the most common histologic variant. Despite advances in the understanding of the molecular biology of NSCLC, the survival rate for this malignancy is still poor. It is now understood that, to evade detection and immune clearance, NSCLC tumours overexpress the immunosuppressive checkpoint protein programmed death ligand 1 (PD-L1). Inhibiting the PD-1/PD-L1 axis with monoclonal antibodies has significantly changed the treatment landscape in NSCLC during the last 5 years. Despite evidence of clinical response in some patients, only approximately 20% of patients obtain any durable benefit, and many of the patients who do respond ultimately relapse with drug-resistant disease. The identification of patients who are most likely to benefit from such therapy is therefore important. In the present review, we cover the basics of the PD-1/PD-L1 axis and its clinical significance in NSCLC, biomarkers that are predictive of treatment response, relevant clinical trials of PD-1/PD-L1 blockade completed to date, and proposed mechanisms of acquired therapeutic resistance.

**Key Words** Lung cancer, NSCLC, immunotherapy, immune checkpoints, PD-1/PD-L1

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## INTRODUCTION

In 2017, it was estimated that lung cancer, the leading cause of cancer-specific death, would claim the lives of more than 21,000 Canadians<sup>1</sup>. Non-small-cell lung cancer (NSCLC), the most common histologic subtype, often presents as locally advanced or metastatic disease<sup>2</sup>. In the absence of an epidermal growth factor receptor (*EGFR*) mutation (present in approximately 50% of patients of Asian ethnicity and in 15% of white patients)<sup>3</sup> or an anaplastic lymphoma kinase (*ALK*) fusion (in <5% of the population)<sup>4</sup>, first-line platinum-based chemotherapy was, until recently, the standard of care. Despite improvements in systemic therapy, the survival rate for patients with stage IV disease is poor, with fewer than 5% living 5 years after diagnosis<sup>5</sup>. Novel therapeutic strategies are therefore desperately needed.

In the last decade, a paradigm shift has occurred in the understanding of the relationship between the immune system, cancer development, and subsequent disease progression. Avoiding immune destruction is now recognized as a “hallmark” of carcinogenesis<sup>6</sup>. Although the dysregulation of the host immune system in cancer is multifaceted and complex, aberrancies in the expression of immune checkpoints—namely, PD-1 and its cognate ligand PD-L1—have

risen to the forefront as a therapeutic target of interest. Monoclonal antibodies that target and inhibit the PD-1/PD-L1 axis have been associated with remarkable success in phase III clinical trials in a number of tumour histologies, ultimately leading Health Canada to approve those agents for melanoma<sup>7</sup>, renal cell carcinoma<sup>8</sup>, squamous cell carcinoma of the head and neck<sup>9</sup>, and NSCLC<sup>10–12</sup>. However, phase III clinical trials in NSCLC have uncovered two crucial issues connected with targeting this immunosuppressive axis: first, only approximately 20% of patients overall have any objective disease response to PD-1 axis blockade, and second, the median duration of response shows significant heterogeneity. It is therefore desirable to identify patients who would be optimal candidates to receive this immunotherapy and to understand what drives resistance in the patients who do respond.

Here, we summarize the current state of PD-1/PD-L1 axis targeting for the treatment of NSCLC as it pertains to the Canadian landscape. Because numerous clinical trials are currently evaluating these agents in combination with other chemotherapeutic and immunotherapeutic strategies, we hope to contextualize how PD-1/PD-L1 inhibition has solidified itself in the clinical arena as monotherapy. To that end, we highlight the evidence about predictive biomarkers

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of therapy response, summarize key clinical trials targeting the PD-1/PD-L1 axis in NSCLC that have been completed to date, and explore possible mechanisms of acquired resistance to these agents. It is also important to recognize that other immune checkpoint proteins—including CTLA-4, LAG-3, TIM-3, IDO, and OX40—are all of therapeutic interest in NSCLC, but because of a lack of current Health Canada approval are not discussed here.

## THE PD-1/PD-L1 AXIS: THE BASICS

To ensure that the adaptive immune system is capable of defending the host while maintaining self-tolerance and preventing autoimmunity, a delicate interplay between positive and negative regulatory signals is carried on. Although that regulation is multidimensional, one important aspect is the PD-1/PD-L1 axis. PD-1 is a type I transmembrane protein that is transcriptionally induced in activated T cells, B cells, and myeloid cells<sup>13</sup>. Its two ligands, PD-L1 and PD-L2<sup>14,15</sup>, are members of the B7 family of proteins and have a similar sequence homology<sup>16</sup>. The major role of PD-1 and its cognate ligands is to limit the activity of T cells in peripheral tissues during an inflammatory response and to limit autoimmunity<sup>14,17</sup>. That activity contrasts with the activity of cytotoxic CTLA-4, which is expressed exclusively on T cells to regulate the degree of their initial activation centrally (at the level of secondary lymphoid organs). As summarized by He *et al.*<sup>18</sup>, the PD-1/PD-L1 axis is immunosuppressive in a number of ways:

- Induction of apoptosis in activated T cells
- Facilitation of T-cell anergy and exhaustion
- Enhancement of the immunosuppressive function of regulatory T cells
- Limitation of T-cell proliferation
- Restraint of T-cell activation and production of interleukin-2

Specific to cancer, signalling through PD-1 can also prevent the conversion of CD8+ T memory cells into CD8+ central memory cells<sup>19</sup>, thus reducing long-term adaptive immune memory that might otherwise prevent future recurrent disease.

PD-1 is expressed on a large proportion of tumour-infiltrating lymphocytes (TILs) in varying tumour histologies, including carcinoma of the head and neck<sup>20</sup>, melanoma<sup>21</sup>, and NSCLC<sup>22</sup>. Not only do TILs within the tumour microenvironment express PD-1, but tumour cells themselves are also recognized to have a tendency to overexpress PD-L1 as a way to avoid immune detection<sup>23</sup>. Tumour PD-L1 expression is induced by a host of pro-inflammatory molecules, with interferon  $\gamma$  being the most potent inducer<sup>23,24</sup>. As activated type I T cells produce interferon  $\gamma$ , the tumour responds to infiltrating effector T cells by upregulating expression of PD-L1 and thus protecting itself from immune attack<sup>25</sup>. In this way, the PD-1/PD-L1 axis is a major contributor to “adaptive immune resistance” within the tumour microenvironment.

In contrast, tumoural regulation of PD-L1 expression can be driven through “innate immune resistance,” where-by expression is modulated through constitutive oncogenic

signalling pathways within the tumour cell. Aberrant ALK signalling, which is implicated in a subset of NSCLC patients, has been postulated to increase PD-L1 expression through STAT3 signalling<sup>26,27</sup>. Furthermore, epidermal growth factor receptor (EGFR) signalling through its cognate ligands has been implicated in the mediation of PD-L1 upregulation in NSCLC<sup>28</sup>, and other studies have demonstrated an association of PD-L1 overexpression with the presence of activating EGFR mutations<sup>29,30</sup>. Those data provide the rationale for future combinatorial therapy in NSCLC that uses agents targeting oncogenic drivers such as ALK and EGFR, and inhibitors of the PD-1/PD-L1 axis. However, it is interesting to note that retrospective analyses of clinical trials involving PD-1 axis inhibition have demonstrated low objective response rates in patients with mutated EGFR or ALK translocations<sup>31</sup>. Further studies are therefore needed to draw clinically meaningful conclusions about the implications of oncogenic driver mutations for PD-L1 expression in NSCLC and response to PD-1/PD-L1 axis blockade.

## THE CLINICAL SIGNIFICANCE OF PD-1/PD-L1 IN NSCLC

As discussed, the PD-1/PD-L1 axis is just one way in which NSCLC evades the immune system. In addition, it has long been acknowledged that most patients with NSCLC present with alterations in the counts of peripheral and tumour effector lymphocytes<sup>32</sup> and of immunosuppressive regulatory T cells<sup>33</sup>. From a clinical perspective, those data are interesting, because the levels of TILs<sup>34,35</sup> and regulatory T cells<sup>36,37</sup> have both been shown to be significant prognosticators of overall survival (OS) in patients with NSCLC.

In the same way, tumour expression of PD-L1 has been implicated as prognostic for OS. However, the data in the various studies are inconsistent. For example, studies by Mu *et al.*<sup>38</sup> and Zhang *et al.*<sup>39</sup> both found PD-L1 expression to be a poor prognosticator of OS, but that finding was not corroborated by other groups<sup>40,41</sup>. Two main meta-analyses have therefore been conducted to assess the clinical implications of tumour PD-L1 expression in NSCLC<sup>42,43</sup>.

Wang *et al.*<sup>42</sup>, analyzed six studies involving 1157 NSCLC patients. They found that PD-L1 expression was significantly associated with tumour differentiation [poorly differentiated vs. well-differentiated odds ratio (OR): 1.91; 95% confidence interval (CI): 1.33 to 2.75;  $p = 0.001$ ] and with poor patient OS (pooled HR: 1.75; 95% CI: 1.40 to 2.20;  $p < 0.001$ ). A second meta-analysis by Zhang *et al.*<sup>43</sup> analyzed forty-seven studies with a total of 11,444 patients having lung cancer of varying histology. Pooled results for all the histologic subtypes demonstrated that increased PD-L1 expression was associated with poor prognosis (HR: 1.40; 95% CI: 1.19 to 1.65;  $p < 0.001$ )—a result that was echoed in the subgroup analysis of NSCLC (HR: 1.26; 95% CI: 1.05 to 1.52;  $p = 0.01$ ). Further, their results indicated that PD-L1 expression was significantly associated with male sex (OR: 1.46; 95% CI: 1.24 to 1.71;  $p < 0.001$ ), a clinically relevant smoking history (OR: 1.57; 95% CI: 1.28 to 1.93;  $p < 0.001$ ), and EGFR wild-type status (OR: 0.61; 95% CI: 0.42 to 0.90;  $p = 0.01$ ).

Despite the fact that those two robust meta-analyses demonstrated a correlation of PD-L1 expression with poor OS in NSCLC, it remains important to recognize the variability

in that correlation between the individual studies. Possible contributing factors include variations in immunohistochemistry techniques and the antibody used, the cut-off used to determine PD-L1 positivity, the timing of tumour analysis (pre- or post-treatment), any prior treatments received, and variations in tumour histology. Those factors also have implications in the use of tumour PD-L1 expression as a predictive biomarker of response to PD-1/PD-L1 blockade, as will be discussed shortly.

## PREDICTIVE BIOMARKERS OF RESPONSE TO CHECKPOINT INHIBITION

In the age of targeted therapies, appropriate selection of patients for treatment is of crucial importance to lower costs, maximize efficacy, and avoid missed treatment opportunities. A prime example comes from the landmark phase III trial published by Mok *et al.*<sup>44</sup> that evaluated gefitinib against carboplatin–paclitaxel for the first-line treatment of advanced NSCLC. Their study demonstrated that, compared with carboplatin–paclitaxel, gefitinib was associated with superior progression-free survival (PFS) in patients who harboured an *EGFR* mutation, but with inferior PFS in the absence of a mutation—thus highlighting the importance of having a reliable predictive biomarker of treatment response. A biomarker with similar predictive ability could be useful for the optimal use of PD-1/PD-L1 inhibitors, which have been associated with heterogeneous responses in clinical trials completed to date<sup>10–12</sup>. Further, although those agents are generally regarded to be less toxic than traditional cytotoxic chemotherapy, their use is still associated with a small but serious risk of immune-mediated adverse events<sup>45</sup>. That risk, in conjunction with the substantial economic burden that these novel therapies impose<sup>46</sup>, makes identifying the patients most likely to benefit a priority. With respect to potential predictive biomarkers of treatment response to PD-1/PD-L1 inhibitors, the most mature data available relate to tumour PD-L1 expression and tumour mutational burden, which are reviewed next. Although not reviewed here, other potential predictive biomarkers are being investigated, including interferon gene signatures<sup>47,48</sup>, expression of class II major histocompatibility antigens<sup>49</sup>, the microbiome<sup>50,51</sup>, and on-treatment TIL accumulation<sup>52</sup>. However, in the context of NSCLC, those markers remain distant from routine clinical implementation.

### PD-L1 Expression

Almost all clinical studies of PD-1/PD-L1 modulating agents in NSCLC have investigated the possible correlation between tumour PD-L1 expression and therapeutic efficacy. Most of the studies have demonstrated that PD-L1 overexpression is associated with significantly higher objective response rates (ORRs)<sup>53–56</sup>, but others have not demonstrated the same correlation<sup>10,57</sup>.

Two recent meta-analyses have demonstrated a correlation between tumour PD-L1 expression and ORR to PD-1/PD-L1 inhibitors<sup>58,59</sup>. Passiglia *et al.*<sup>58</sup> analyzed seven studies with a total of 914 patients. Pooled analysis showed that the ORR was significantly higher in patients with PD-L1–positive tumours (>1% staining via immunohistochemistry) than in

patients with PD-L1–negative tumours (OR: 2.44; 95% CI: 1.61 to 3.68). The meta-analysis by Abdel-Rahman<sup>59</sup> included twelve studies with a total of 3790 patients. In patients treated with PD-1/PD-L1 inhibitors, the ORR was improved when patients had tumour PD-L1 expression exceeding 1% than when they had expression less than 1% (OR: 2.18; 95% CI: 1.45 to 3.29;  $p = 0.0002$ ). Furthermore, the OR increased as the PD-L1 cut-off value comparison was increased (>5% vs. <5%, >10% vs. <10%, and >50% vs. <50%). Taken together, those data suggest that tumour PD-L1 expression of more than 1% offers some benefit when NSCLC patients are treated with PD-1/PD-L1 inhibitors and that a possible dose–effect relationship might exist between the intensity of PD-L1 staining and ORR. However, it is currently unclear whether baseline tumour PD-L1 expression has any clinical relationship with the duration of treatment response.

Despite the role of tumour PD-L1 expression as a validated predictive biomarker of response to PD-1/PD-L1 inhibitors, relying solely on that expression is controversial. For example, the 4 PD-L1 antibodies commonly used as companion diagnostic tests for nivolumab (Dako 28-8 pharmDx: Dako Corporation, Glostrup, Denmark), pembrolizumab (Dako 22C3 pharmDx), atezolizumab (Ventana SP142: Ventana Medical Systems, Tucson, AZ, U.S.A.), and durvalumab (Ventana SP263) have shown variability in staining intensity and patterns. Studies are therefore underway to compare the reliability of the various assays. Early results from the phase I Blueprint PD-L1 IHC Assay Comparison Project<sup>60</sup> demonstrated that the percentage of PD-L1–stained tumour cells was comparable when using the 22C3, 28-8, and SP263 assays, but that the SP142 assay for atezolizumab resulted in fewer stained tumour cells overall. It is also important to note that the scoring system for the SP142 assay includes PD-L1–positive immune cells in addition to tumour cells. The authors of Blueprint I concluded that interchanging assays and cut-offs for positivity will lead to the misclassification of PD-L1 status for some patients, which could ultimately affect treatment decisions. More research in this area is needed if PD-L1 expression is to be reliably used when determining a patient's treatment eligibility.

Furthermore, even if consistency in PD-L1 testing is achieved, it is still important to consider that most clinical trials have demonstrated that a subset of PD-L1–negative patients will experience meaningful objective and durable responses to PD-1/PD-L1 inhibition. The question that remains is what is the definition of PD-L1–positive? PD-L1 can be expressed both by tumour cells and by immune cell populations within the tumour microenvironment, but the significance of that expression is currently unclear<sup>52</sup>. Further, PD-L1 is an inducible and dynamic biomarker, and thus should be considered differently from the more established oncologic predictive biomarkers such as *EGFR* and *ALK* mutations. For example, if PD-L1 expression is transiently elevated because of innate immune resistance rather than because of an antitumour immune response, disrupting the axis might not be effective, because there is no antitumour immune response to restore.

Finally, given that PD-L1 expression is dynamic, the expression level can potentially vary as a result of treatments. For example, it has been demonstrated that, in a subset of patients, tumour PD-L1 expression markedly

increases after treatment with the EGFR modulator gefitinib<sup>61</sup>. Because the ways in which various treatment modalities influence PD-L1 expression are currently unclear, future studies should evaluate the utility of tumour rebiopsy when using PD-L1 as a biomarker. It might therefore be necessary to view PD-L1 expression as a continuous variable rather than a binary one (that is, positive vs. negative) and to use it as one component of a broader predictive algorithm for PD-1/PD-L1 inhibitor response. As summarized by Grigg and Rizvi<sup>62</sup>, the findings from KEYNOTE-001<sup>54</sup> demonstrated that ORR trends were related to stratifications of PD-L1 positivity in the study patients. Having stringent cut-offs would increase the proportion of responders, but would fail to identify a substantial proportion of potential responders. A more lenient cut-off would increase the absolute number of responders, but decrease the predictive power of the biomarker. Uncovering other clinical or pathologic variables that could be predictive of treatment response will therefore be important.

### Global Tumour Mutational Burden

Early clinical studies of PD-1/PD-L1 inhibitors demonstrated the highest efficacy in melanoma and NSCLC<sup>63,64</sup>, two malignancies that are known to have a high rate of somatic mutations as a result of exposure to ultraviolet radiation and tobacco smoke respectively<sup>65,66</sup>. The mutations in the tumour cells produce “neoantigens” (tumour-specific T-cell epitopes), and T-cell reactivity against the neoantigens can be boosted by targeting PD-1/PD-L1 axis proteins. Studies have therefore been conducted to evaluate the correlation of mutational burden with the efficacy of PD-1/PD-L1 inhibitors.

A landmark paper by Rizvi *et al.*<sup>67</sup> demonstrated that a higher nonsynonymous mutation burden in tumours (defined as a level above the median burden of the cohort) was associated with an improved ORR (63% vs. 0%,  $p = 0.03$ ) and PFS (14.5 months vs. 3.7 months,  $p = 0.01$ ; HR: 0.19; 95% CI: 0.05 to 0.70) with pembrolizumab treatment. In addition, the efficacy of pembrolizumab correlated with neoantigen burden—a factor also associated with higher nonsynonymous mutation rates. The candidate neoantigen burden was significantly higher in patients who experienced a durable treatment benefit with pembrolizumab than in those who did not experience a durable benefit, and high candidate neoantigen burden was associated with improved PFS (14.5 months vs. 3.5 months,  $p = 0.002$ ). Furthermore, the authors demonstrated that, in patients with tumour PD-L1 expression of 1%–49%, a high nonsynonymous mutation burden was associated with a durable clinical response in 75% of patients, and a low burden was associated with a durable clinical response in only 11% of patients. Given that the sample sizes in the patient groups were small (4 and 9 respectively), larger-scale studies will be needed to determine if there are relations between PD-L1 intensity, mutational burden, and therapeutic response.

McGranahan *et al.*<sup>68</sup> found that high neoantigen burden and low neoantigen intratumoural heterogeneity in NSCLC are associated with significantly longer PFS. Compared with other tumours, tumours harbouring a large clonal neoantigen burden and low neoantigen heterogeneity were seen to have greater PD-L1 expression ( $p = 0.0017$ ). The

authors also demonstrated that, in certain patients with a poor response to PD-1 blockade, cytotoxic chemotherapy-induced subclonal neoantigens were enriched. Those data suggest that neoantigen heterogeneity, in addition to global neoantigen burden, might influence the therapeutic outcome of PD-1/PD-L1 inhibition.

### CLINICAL TRIALS OF PD-1/PD-L1 INHIBITORS

Numerous clinical trials have recently compared inhibitors of the PD-1/PD-L1 axis with traditional cytotoxic chemotherapies for the treatment of NSCLC (Table 1). Positive results from those trials ultimately led to Health Canada (HC) approval of 3 PD-1 inhibitors: nivolumab, pembrolizumab, and atezolizumab (Table 2). Durvalumab, another PD-L1 inhibitor, has recently shown promising results in clinical trials and will likely soon be under review for use in Canada.

#### Nivolumab

Nivolumab is a monoclonal antibody to PD-1 and has shown efficacy in NSCLC in multiple phase III clinical trials, ultimately leading to HC approval. The phase III clinical trials CheckMate 017<sup>10</sup> and CheckMate 057<sup>56</sup> showed the effectiveness of nivolumab (compared with docetaxel chemotherapy) as a second-line therapy in NSCLC. CheckMate 017 enrolled patients with advanced NSCLC of squamous cell histology. The median OS was 9.2 months with nivolumab (95% CI: 7.3 months to 13.3 months) compared with 6.0 months with docetaxel (95% CI: 5.1 months to 7.3 months). Further, the median PFS was 3.5 months with nivolumab compared with 2.8 months with docetaxel (HR: 0.62; 95% CI: 0.47 to 0.81;  $p < 0.001$ ). A 20% ORR was achieved in the nivolumab group, and no associations with PD-L1 tumour expression were observed in subgroup analyses. CheckMate 057 enrolled patients with advanced NSCLC of nonsquamous histology. Compared with docetaxel, nivolumab was associated with a significant improvement (OS: 12.2 months; response rate: 19%). Subgroup analyses demonstrated significant positive associations of tumour PD-L1 expression ( $\geq 5\%$ ) with both PFS and OS in the nivolumab treatment group. The reasons for the difference in PFS benefit and association with tumour PD-L1 expression in the two studies are not clear, but it has been postulated that the histology difference might be associated with mutational burden and tumour biology<sup>75</sup>.

In the multi-cohort phase I CheckMate 012 trial<sup>69</sup>, nivolumab was used as first-line monotherapy in advanced NSCLC. That approach resulted in an ORR of 23%, a median PFS of 3.6 months, and a median OS of 21.8 months. A nonsignificant association of improved response with 50% or greater PD-L1 expression in tumour cells in 12 patients was observed. Those 12 patients experienced a 50% response rate and 8.4 months of PFS. Those results led to the phase III clinical trials of nivolumab as first-line monotherapy for advanced NSCLC.

CheckMate 026<sup>70</sup> is the only completed phase III clinical trial that has evaluated nivolumab as first-line therapy. That trial compared nivolumab with a traditional platinum-based chemotherapy regimen in patients with advanced NSCLC who showed PD-L1 tumour cell expression of 5% or greater, with no EGFR mutation or ALK translocation.

**TABLE 1** Selected clinical trials of PD-1/PD-L1 inhibitors as monotherapy in non-small-cell lung cancer (NSCLC)

Trial name	Study drug	Phase	Indication	Population	Survival (months)		Response rate (%)
					Progression-free	Overall	
CheckMate 012 <sup>69</sup>	Nivolumab	I	First line	52 Advanced NSCLC	3.6	21.8	23 (PD-L1≥50%; 8.4)
CheckMate 017 <sup>10</sup>	Nivolumab	III	Second line	272 Advanced squamous NSCLC	4.2	9.2	20
	Docetaxel				3.5	6.0	9 (p=0.008)
CheckMate 057 <sup>56</sup>	Nivolumab	III	Second line	582 Advanced nonsquamous NSCLC	2.3	12.2	19
	Docetaxel				4.2	9.4	12 (p=0.02)
CheckMate 026 <sup>70</sup>	Nivolumab	III	First line	423 Advanced NSCLC, PD-L1-positive, no EGFR or ALK mutation	4.2	Not reported	Not reported
	Platinum-based chemotherapy (up to 6 cycles)				5.9	(HR: 0.72; p<0.001)	(p=0.02)
KEYNOTE 001 <sup>71</sup>	Pembrolizumab	I	Second line	495 Advanced NSCLC, PD-L1-positive, no EGFR mutation	3.7	12.0	19.4
KEYNOTE 010 <sup>12</sup>	Pembrolizumab (2 mg/kg)	II/III	Second line	1034 Advanced NSCLC, PD-L1-positive	3.9 vs. control	10.4 vs. control	18 vs. control
	Pembrolizumab (10 mg/kg)				(HR: 0.88; p=0.07)	(HR: 0.71; p=0.0008)	(p=0.0005)
	Docetaxel				4.0 vs. control	12.7 vs. control	18.5 vs. control
KEYNOTE 024 <sup>11</sup>	Pembrolizumab	III	First line	305 Advanced NSCLC, PD-L1-positive, no EGFR or ALK mutation	(HR: 0.79; p<0.004)	(HR: 0.61; p<0.0001)	(p=0.0002)
	Platinum-based chemotherapy (4-6 cycles)				vs. 2 mg/kg	vs. 2 mg/kg	
	Docetaxel				(HR: 1.09)	(HR: 1.17)	
KEYNOTE 024 <sup>11</sup>	Pembrolizumab	III	First line	305 Advanced NSCLC, PD-L1-positive, no EGFR or ALK mutation	4.0	8.5	9.3
	Platinum-based chemotherapy (4-6 cycles)				10.3	6-Month rate: 80.2%	44.8
	Docetaxel				6.0	6-Month rate: 72.4%	27.8
POPLAR <sup>48</sup>	Atezolizumab	II	Second line	287 Advanced NSCLC	(HR: 0.50; p<0.001)	(HR: 0.60; p=0.005)	
	Atezolizumab				2.7	12.6	15
	Docetaxel				3.0	9.7	15
OAK <sup>72</sup>	Atezolizumab	III	Second line	850 Advanced NSCLC	(HR: 0.94)	(HR: 0.73; p=0.04)	
	Atezolizumab				2.8	13.8	13.6
	Docetaxel				4.0	9.6	13.4
BIRCH <sup>73</sup>	Atezolizumab	II	First line	142 PD-L1-positive, 709 stage III NSCLC with ≥2 rounds of platinum-based chemotherapy and radiotherapy with no progression	(HR: 0.95; p=0.49)	(HR: 0.73; p=0.0003)	
	Durvalumab				7.3	13.8	13.6
	Placebo				16.8	23.2 <sup>a</sup>	28.4
PACIFIC <sup>74</sup>	Durvalumab	III	Second line (consolidation)	709 stage III NSCLC with ≥2 rounds of platinum-based chemotherapy and radiotherapy with no progression	5.6	14.6 <sup>a</sup>	16.0
	Placebo				(HR: 0.52; p<0.001)	(HR: 0.52; p<0.001)	(p<0.001)

<sup>a</sup> Death or distant metastasis.

**TABLE II** Canadian landscape of PD-1/PD-L1 inhibitors in non-small-cell lung cancer (NSCLC)

Drug	Indication	Approvals		Provincial funding
		Health Canada	pCODR	
Atezolizumab	Locally advanced or metastatic NSCLC with progression on or after systemic chemotherapy	6 Apr 2018	Under review	Not applicable
Nivolumab	Locally advanced or metastatic NSCLC with progression on or after systemic chemotherapy	26 Feb 2016	3 Jun 2016	Funded: BC, AB, SK, MB, ON, NS, NB, NL Under review: PEI
Pembrolizumab	Previously untreated metastatic NSCLC with tumour expression of PD-L1 and without sensitizing EGFR mutation or ALK translocation. Funding requested for TPS of PD-L1 ≥50%.	12 Jul 2017	23 Aug 2017	Funded: SK, MB, ON Under review: BC, AB, NS, NB, NL, PEI
Pembrolizumab	For treatment of metastatic NSCLC with tumour expression of PD-L1 and previous progression on or after systemic chemotherapy. Funding requested for TPS of PD-L1 ≥1%.	15 Apr 2016	3 Nov 2016	Funded: SK, MB, ON Under review: BC, AB, NS, NB, NL, PEI

TPS = tumour proportion score.

No significant differences in PFS or OS between the two study groups were observed. In the nivolumab group, the ORR was 26%, and the median PFS and OS were 4.2 months and 14.4 months respectively. In comparison, patients randomized to the control arm experienced a response rate of 33%, with a median PFS of 5.9 months and an OS of 13.2 months. The lack of a survival benefit was attributed partly to imbalances in post-discontinuation treatment (40% nivolumab vs. 60% control) and rates of strong PD-L1 expression (53.2% nivolumab vs. 74.1% control). Based on the negative results of the study, nivolumab has not been approved for first-line use in NSCLC.

**Pembrolizumab**

Pembrolizumab, another monoclonal antibody to PD-1, has been studied in multiple clinical trials that led to its approval by HC. The phase III KEYNOTE-010 trial<sup>12</sup> compared pembrolizumab monotherapy with docetaxel in advanced NSCLC. Pembrolizumab was given at 2 doses: 2 mg/kg and 10 mg/kg. The study enrolled NSCLC patients who had disease progression after platinum-based chemotherapy or tyrosine kinase inhibitors, and 1% or greater PD-L1 expression by tumour cells. The OS and ORR were significantly greater for both pembrolizumab groups than for the docetaxel group, but no significant difference in PFS between the two pembrolizumab groups was observed. The lower dose of pembrolizumab was associated with an ORR of 18%, a median PFS of 3.9 months, and a median OS of 10.4 months. The higher dose of pembrolizumab was associated with an ORR of 18.5%, a median PFS of 4.0 months, and a median OS of 12.7 months. No significant difference between the two pembrolizumab groups for any outcome and no significant associations in subgroup analysis were observed. The overall quality of the trial was considered moderate for all outcomes<sup>75</sup>.

In the phase I KEYNOTE-001 trial<sup>71</sup>, pembrolizumab was used as first-line monotherapy for advanced NSCLC. The result was an ORR of 24.8%, a median PFS of 6 months, and a median OS of 22.1 months. In patients having 50% or greater PD-L1 expression in tumour cells, median PFS increased to 12.5 months.

In the pivotal phase III KEYNOTE-024<sup>11</sup> trial, pembrolizumab monotherapy was compared with a platinum-based chemotherapy in the first line. The trial enrolled patients with advanced NSCLC having PD-L1 tumour cell expression of 50% or greater, no EGFR mutation or ALK translocation, and a life expectancy of more than 3 months. Based on a preplanned interim analysis, the trial was stopped early because of pembrolizumab superiority. The 10.3-month median PFS in the pembrolizumab group significantly exceeded the PFS in the platinum-based chemotherapy group. The estimated 80.2% 6-month survival and 44.8% response rate were also higher in the pembrolizumab group.

The heterogeneity in results between KEYNOTE-024 and CheckMate 026 might be attributable to differences in study design and inclusion criteria, including previous treatments, the PD-L1 biomarker test and expression level cut-off used, and intrinsic differences in biochemical efficacy between the PD-1 inhibitors<sup>76</sup>.

**Atezolizumab**

Atezolizumab, a monoclonal antibody to PD-L1, has been tested in multiple clinical trials that have led to its

approval by HC as a second-line therapy for advanced NSCLC. The phase II POPLAR trial<sup>48</sup> compared atezolizumab with docetaxel in the second-line setting. The trial enrolled patients with NSCLC who had progressed after platinum-based chemotherapy. In the atezolizumab group, os was significantly improved (HR: 0.69;  $p = 0.01$ ), with an ORR of 15%. No difference in median PFS was observed. Those results led to the associated phase III OAK trial<sup>72</sup>. The OAK trial made the same treatment comparison for patients with previously treated advanced NSCLC. The os was significantly greater in the atezolizumab group than in the docetaxel group, although no difference in PFS was observed. The atezolizumab group experienced a 13.6% ORR, a 2.8-month median PFS, and a 12.6-month median os. In subgroup analyses, even patients with less than 1% PD-L1 expression in tumour cells experienced better os (HR: 0.75;  $p = 0.02$ ). The overall quality of the evidence in the trials was considered moderate<sup>75</sup>.

The only trial to study atezolizumab as first-line therapy was the phase II BIRCH trial<sup>73</sup>. It enrolled 142 patients with previously untreated advanced NSCLC and tumour (or TIL) PD-L1 expression of 5% or greater. Results included a 25% ORR, a 7.3-month median PFS, and a 23.5-month median os.

### Durvalumab

Durvalumab is another monoclonal antibody to PD-L1 that has been studied in clinical trials, but that is not currently under HC review for use in Canada. A phase I clinical trial<sup>77</sup> evaluating durvalumab in 59 patients with treatment-naïve advanced NSCLC showed a 25% ORR that was not associated with histologic subtype. No PFS or os values were reported. The phase III PACIFIC trial<sup>74</sup> compared durvalumab as consolidation therapy with placebo in 709 patients with stage III NSCLC who had no disease progression after initial chemoradiotherapy. Patients treated with durvalumab consolidation therapy had a significantly greater ORR, PFS, and time until death or distant metastasis (28.4%, 16.8 months, and 23.2 months respectively). Development of new lesions and brain metastases was also significantly less frequent in the durvalumab group than in the placebo group. Within the durvalumab group, no difference in PFS was evident based on PD-L1 tumour cell expression with a threshold of 25%. The os data for the study have yet to be reported.

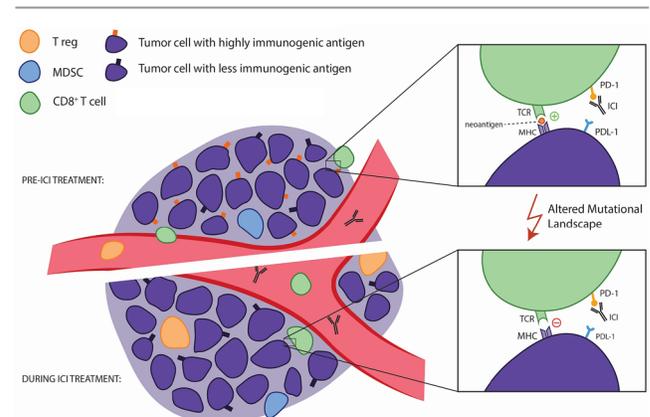
## THE CHALLENGE OF ACQUIRED RESISTANCE

Despite an objective clinical response to PD-1 axis blockade being obtained in approximately 20% of NSCLC patients, most patients will ultimately acquire drug resistance and subsequently experience disease progression<sup>53</sup>. However, the mechanisms that underpin acquired resistance to PD-1/PD-L1 inhibitors are poorly understood. Two proposed mechanisms that could contribute to the phenomenon are the evolution of the landscape of tumour neoantigens<sup>78</sup> and the upregulation of other immune checkpoint proteins that are independent of the PD-1/PD-L1 axis<sup>79</sup>.

A recent study by Anagnostou *et al.*<sup>78</sup> examined the evolving landscape of tumour neoantigens during the emergence of acquired resistance in patients with NSCLC

after initial response to immune checkpoint blockade with anti-PD-1 antibodies. They analyzed matched pre-treatment and resistant tumours, and identified genomic changes resulting in the loss of 7–18 putative mutation-associated neoantigens in resistant clones. They then generated peptides from the eliminated neoantigens that could elicit clonal T cell expansion in autologous T cell cultures—suggesting that those neoantigens could generate a functional immune response. Furthermore, they demonstrated that neoantigen loss occurred through the elimination of tumour subclones or through deletion of chromosomal regions with truncal alterations. Taken together, those data demonstrated for the first time that acquired resistance to PD-1 blockade could be a result of an evolving landscape of tumour mutations, some of which encode immunogenic neoantigens (Figure 1). The authors suggested that the putative neoantigens identified before and at the emergence of resistance could be leveraged to develop patient-specific vaccines and adoptive T cell transfer with engineered T cell receptor T cells.

In addition to the shifting landscape of neoantigens, upregulation of other immune checkpoint proteins can contribute to acquired resistance to PD-1 axis inhibition. Using two fully immunocompetent murine models of lung adenocarcinoma, Koyama *et al.*<sup>79</sup> observed the upregulation of TIM-3 in PD-1 antibody-bound T cells. Further, they showed that mice treated with a TIM-3–blocking antibody after failure of PD-1 blockade was associated with a survival advantage. To confirm that principle, they also analyzed tumour specimens from human patients, which showed similar TIM-3 upregulation in blocking antibody-bound T cells at the time of anti-PD-1 treatment failure. Hypothetically, the measurement of multiple immune checkpoints



**FIGURE 1** A possible mechanism for acquired resistance to PD-1 inhibition. Anagnostou and colleagues<sup>76</sup> discovered that acquired resistance to blockade of the PD-1/PD-L1 axis can potentially be explained by a shifting mutational landscape, which might cause the loss of neoantigens. That loss abrogates the ability of T cells in the tumour microenvironment to recognize the malignant cells as foreign, which renders therapy with PD-1 axis blockade ineffective. CD8+ T cells, regulatory T cells (T regs) and myeloid-derived suppressor cells (MDSCs) are all pictured here as part of the tumour microenvironment. ICI = immune checkpoint inhibitor; TCR = T cell receptor; MHC = major histocompatibility complex.

at time of biopsy could inform specific and personalized immunotherapeutic strategies. Ultimately, to develop beneficial therapeutic approaches, preclinical studies with larger sample sizes will be needed to better understand the dynamics and diversity of alternative immune checkpoint expression.

**SUMMARY AND FUTURE DIRECTIONS**

The last decade has uncovered the importance of targeting the PD-1/PD-L1 axis for the treatment of NSCLC. With HC approval now in place for the anti-PD-1 antibodies nivolumab, pembrolizumab, and atezolizumab, the clinical significance of blocking this immunosuppressive axis is clear. However, as things now stand, patient response to these therapeutics has substantial heterogeneity. No single biomarker has shown perfect reliability to date, and future studies will have to elucidate how administration of these agents can be optimized for patients. It remains to be seen whether future recipients will be selected based on a combination of currently studied clinicopathologic biomarkers or whether more predictive biomarkers will be found.

Furthermore, the scope of use of the PD-1/PD-L1 inhibitors will continue to evolve in coming years. The interim findings of the aforementioned PACIFIC trial<sup>74</sup> are certainly promising, and the hope is that its final results will lead to durvalumab being established as a safe and efficacious option for patients with nonresectable NSCLC after standard chemoradiotherapy. In addition, the ongoing phase III BR.31 trial (see NCT02273375 at <http://ClinicalTrials.gov>) led by the Canadian Cancer Trials Group, which is assessing the role of adjuvant immunotherapy in the postsurgical setting, has the potential to be practice-changing.

Although the present review has focused on the current landscape of PD-1/PD-L1 axis inhibitors as monotherapy, numerous trials are evaluating the use of those agents in a wide variety of combinations. Table III summarizes a selection of currently completed early-phase studies evaluating PD-1/PD-L1 axis blockade in combination with chemotherapy, radiotherapy, or other immune checkpoint inhibitors such as CTLA-4.

To summarize, despite room for optimization in the administration of PD-1/PD-L1 inhibitors and for combinatorial regimens to demonstrate superiority compared with monotherapy, it is important to recognize that, arguably, no bigger advance than the use of these inhibitors has yet occurred in the treatment of NSCLC. PD-1/PD-L1 inhibitors are extending the survival of patients with NSCLC and are doing so with less patient morbidity. We therefore look forward to the future and, hopefully, to continued improvement in NSCLC outcomes.

**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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**TABLE III** Selected clinical trials of PD-1/PD-L1 inhibitors as combination therapy non-small-cell lung cancer (NSCLC)

Study name	Drug	Phase	Treatment	Population	Survival (months)		Response rate (%)
					Progression-free	Overall	
CheckMate 012 <sup>80</sup>	Nivolumab 10 mg/kg with gemcitabine-cisplatin	I	First line	56 Advanced NSCLC	24-Week rate: 51%	2-year rate: 25%	33
	Nivolumab 10 mg/kg with pemetrexed-cisplatin			randomized based on histologic type	24-Week rate: 71%	2-year rate: 33%	47
	Nivolumab 10 mg/kg with paclitaxel-carboplatin				24-Week rate: 38%	2-year rate: 27%	47
	Nivolumab 5 mg/kg with paclitaxel-carboplatin				24-Week rate: 51%	2-year rate: 62%	43
CheckMate 012 <sup>81</sup>	Nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 12 weeks	I	First line	77 Advanced NSCLC	8.1	Not reached	38
	Nivolumab 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks				3.9	Not reached	47
KEYNOTE 021 <sup>82</sup>	Paclitaxel-carboplatin	I/II	First line	123 Advanced NSCLC, no EGFR or ALK mutation	8.9	20.9	32
	Pembrolizumab with paclitaxel-carboplatin				19.0	Not reached	57
					(HR: 0.54; p=0.0067) (HR: 0.59; p=0.0344)		
KEYNOTE 021 <sup>83</sup>	Pembrolizumab with pemetrexed-carboplatin	II	First line	123 Advanced nonsquamous NSCLC, no EGFR or ALK mutation	13.0	13	55
	Pemetrexed-carboplatin				8.9	14	29
					(HR: 0.53; p=0.01) (HR: 0.90; p=0.39)		
KEYNOTE 189 <sup>84</sup>	Pembrolizumab with pemetrexed-platinum agent	III	First line	616 Advanced nonsquamous NSCLC, no EGFR or ALK mutations	8.8	Not reached	48
	Pemetrexed-platinum agent				4.9	11.3	19
					(HR: 0.52; p<0.001) (HR: 0.49; p<0.001)		

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