Review Article

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# Current State of Immunotherapy With PD-1 Inhibitors for Solid Tumours

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## ABSTRACT

Cancer immunotherapy has become a successful treatment for many cancers. PD-1 inhibitors (Pembrolizumab, nivolumab) are immune checkpoint inhibitors. These agents use the body's own immune system to attack growing cancer cells. They are used in the treatment of a variety of cancers and have had the most success in the treatment of advanced and metastatic melanoma and non-small cell lung carcinoma, providing adequate overall response rate and overall survival benefit. Compared to chemotherapy, pembrolizumab and nivolumab are better tolerated by patients and common side effects include fatigue and decreased appetite. However, there are severe immune-related side effects associated with immunotherapy, including pneumonitis, which may cause patients to discontinue their treatment.

***Keywords:*** *Immunotherapy, Pembrolizumab, Nivolumab*

## Introduction

Cancer immunotherapy has been successful in recent years for treating a wide variety of cancers. Immune checkpoint inhibitors are a type of immunotherapy with promising results in clinical trials, particularly the PD-1 inhibitors, pembrolizumab and nivolumab. PD-1 inhibitors block the PD-1 receptor on the surface of T-lymphocytes, preventing the binding of inhibitory proteins produced by cancer cells, such as PD-L1 and PD-L2, thus allowing the body's own T-lymphocytes to attack the developing cancer cells. Pembrolizumab and nivolumab are indicated in the treatment of many cancers, including melanoma and non-small cell lung carcinoma (NSCLC).

## Recent Clinical Trials

Pembrolizumab was first approved by the Food and Drug Administration (FDA) in September 2014 for the treatment of advanced or unresectable melanoma due to success in the KEYNOTE-001 phase 1 trial.[1] Pembrolizumab given to patients at 2 mg/kg or 10 mg/kg resulted in adequate overall response rate assessed using RECIST 1.1 criteria. Nivolumab was then approved in December 2014 as a second-line treatment for melanoma due to success in the CheckMate 037 phase III trial.[2] More patients achieved the preset objective response when given 3 mg/kg infusion of nivolumab every 2 weeks compared to patients who received the available standard of care chemotherapy regimens. Both pembrolizumab and nivolumab are now approved as first line treatments of melanoma.

In a follow-up to the KEYNOTE-001 study, pembrolizumab provided overall survival benefit when used for the treatment of NSCLC with PD-L1 expression.[3] In the KEYNOTE-021 phase II trial it had success in treating NSCLC even in the absence of PD-L1 expression.[4] The CheckMate 017 phase III trial led to approval of nivolumab for metastatic squamous NSCLC previously treated with platinum-based chemotherapy[5] and the CheckMate 057 phase III trial led to approval for metastatic non-squamous NSCLC previously treated with platinum-based chemotherapy.[6] Pembrolizumab was confirmed as a first line treatment of metastatic NSCLC with ≥50% PD-L1 expression due to the results of the KEYNOTE-024 phase III trial[7] but nivolumab was not approved as a first line treatment due to the results of the CheckMate 026 phase III trial in which progression-free survival for patients on nivolumab was shorter than for patients being treated with chemotherapy.[8]

## Side Effects

The most common side effects of immunotherapy are side effects that are also common with chemotherapy. In the KEYNOTE-001 trial for melanoma, the most common side effect of treatment with pembrolizumab was fatigue. [1] In the CheckMate 017 trial for NSCLC, common side effects of nivolumab included fatigue and decreased appetite.[5]

Immunotherapy is generally better tolerated than chemotherapy because the common side effects occur less often in immunotherapy compared to chemotherapy. Pembrolizumab was compared to various chemotherapies in the KEYNOTE-002 phase II trial for melanoma and Grade 3-4 adverse events occurred in 11% of patients in

the 2 mg/kg pembrolizumab group, 14% of patients in the 10 mg/kg pembrolizumab group, and 26% of patients in the chemotherapy group. [9] In the CheckMate 037 trial for melanoma, 9% of patients treated with nivolumab experienced Grade ≥3 adverse events compared to 32% of patients in the chemotherapy group.[2]

There are potentially serious immune-mediated side effects from treatment with immunotherapy that do not occur as a result of treatment with chemotherapy. In the FDA approved test for treating NSCLC with pembrolizumab, there were various immune-mediated adverse events including pneumonitis, colitis, hypophysitis, and thyroid disorders and these occurred in 13% of patients.[10] In the CheckMate 017 trial for NSCLC, immune-mediated side effects included hypothyroidism, colitis, and pneumonitis. [5] Hypothyroidism and pneumonitis did not occur in any patients treated with docetaxel in this study. In a meta-analysis of randomized clinical trials for patients treated with nivolumab or pembrolizumab, a toxicity profile was established showing significant relative risk for getting hyperthyroidism or hypothyroidism.[11] There was also some risk of pneumonitis (pooled absolute risk of 2.65%).

The immune related side effects associated with pembrolizumab and nivolumab (such as colitis, pneumonitis, thyroid disorder, and hypophysitis) may be severe enough to discontinue the treatment. In the CheckMate 017 trial in which patients with NSCLC were treated with nivolumab, four patients discontinued treatment due to pneumonitis. [5]

**Table 1: Results of Early Clinical Trials with Pembrolizumab and Nivolumab**

| Name and phase | Agent | Indication (tumor type) | Number of enrolled pts and study groups | Primary endpoints | Results |
|---|---|---|---|---|---|
| KEYNOTE-001 Phase I | Pembrolizumab | Ipilimumab-refractory advanced melanoma | 173 patients, 2 mg/kg (n=89) and 10 mg/kg (n=84) | Overall Response Rate (ORR) | 26% at both doses |
| KEYNOTE-002 Phase II | Pembrolizumab vs. Chemotherapy | Ipilimumab-refractory advanced melanoma | 540 patients, 2 mg/kg (n=180), 10 mg/kg (n=181), chemo (n=179) | 6 month Progression-free survival (PFS) | 34% 2 mg/kg group, 38% 10 mg/kg group, 16% chemo group |
| KEYNOTE-001 Phase Ib | Pembrolizumab | Advanced NSCLC with PD-L1 expression | 550 patients, PD-L1 <1%, ≥1%, ≥50% | Overall Survival (OS) | Increased with increasing PD-L1 expression |
| KEYNOTE-021 Phase II | Pembrolizumab with Chemotherapy | Advanced non-squamous NSCLC | 123 patients, pembro plus chemo (n=60) and chemo (n=63) | Objective Response: Complete or partial response | 55% pembro plus chemo, 29% chemo |
| KEYNOTE-024 Phase III | Pembrolizumab vs. Chemotherapy | Advanced NSCLC with ≥50% PD-L1 expression | 305 patients, pembro group and chemo group | Median PFS | 10.3 months pembro, 6 months chemo |
| CheckMate 037 Phase III | Nivolumab vs. Chemotherapy | Ipilimumab-refractory advanced melanoma | 405 patients, nivo (n=272) and chemo (n=133) | Objective Response | 31.7% nivo, 10.6% chemo |
| CheckMate 017 Phase III | Nivolumab vs. Chemotherapy | Advanced squamous NSCLC | 272 patients, nivo group and chemo group | Median Overall Survival | 9.2 months nivo, 6 months chemo |
| CheckMate 057 Phase III | Nivolumab vs. Chemotherapy | Metastatic non-squamous NSCLC | 582 patients, nivo (n=292) and chemo (n=290) | Median Overall Survival | 12.2 months nivo, 9.4 months chemo |
| CheckMate 026 Phase III | Nivolumab vs. Chemotherapy | Stage IV or recurrent NSCLC | 423 patients, nivo group and chemo group | Median PFS | 4.2 months nivo, 5.9 months chemo |

**Table 2: Common Side Effects of Pembrolizumab and Nivolumab in Clinical Trials.**

| Side effect | Pembrolizumab, % (clinical trial) | Nivolumab |
|---|---|---|
| Fatigue | 33% 2 mg/kg group, 37% 10 mg/kg group (KEYNOTE-001)<br>23% 2 mg/kg group, 29% 10 mg/kg group (KEYNOTE-002)<br>10.4 % (KEYNOTE-024) | 16% (CheckMate 017)<br>16% (CheckMate 057)<br>21% (CheckMate 026) |
| Pruritus | 26% 2 mg/kg group, 19% 10 mg/kg group (KEYNOTE-001)<br>21% 2 mg/kg group, 23% 10 mg/kg group (KEYNOTE-002) | |
| Rash | 18% 2 mg/kg group, 18% 10 mg/kg group (KEYNOTE-001)<br>12% 2 mg/kg group, 10% 10 mg/kg group (KEYNOTE-002) | 10% (CheckMate 026) |
| Diarrhea | 8% 2 mg/kg group, 11% 10 mg/kg group (KEYNOTE-002)<br>14.3% (KEYNOTE-024) | 14% (CheckMate 026) |
| Fever | 10.4% (KEYNOTE-024) | |
| Decreased Appetite | | 11% (CheckMate 017)<br>10% (CheckMate 057)<br>12% (CheckMate 026) |
| Asthenia | | 10% (CheckMate 017)<br>10% (CheckMate 057) |
| Nausea | | 12% (CheckMate 057)<br>12% (CheckMate 026) |

**Table 3: Reasons for Discontinuation of Pembrolizmab and Nivolumab in Clinical Trials.**

| Reason | Pembrolizumab, % (clinical trial) | Nivolumab |
|---|---|---|
| Grade 1-4 adverse event, unspecified | 2% 2 mg/kg group, 7% 10 mg/kg group; diarrhea and pneumonitis common (KEYNOTE-002) 7.1%; diarrhea and pneumonitis common (KEYNOTE-024) | |
| Pneumonitis | | 2% (CheckMate 017)<br>1% (CheckMate 057)<br>1.1% (CheckMate 026) |
| Rash | | 1% (CheckMate 017) |
| Interstitial Lung Disease | | 1% (CheckMate 057) |

## Discussion

Immunotherapy and chemotherapy are both indicated for treatment of melanoma and NSCLC but they are significantly different when it comes to mechanism of action and side effects. Immunotherapy uses the body's own immune cells to fight against the tumour cells while chemotherapy poisons tumour cells to prevent cell division. Immunotherapy causes side effects less often than chemotherapy and the side effects tend to be less severe. Certain immune-related side effects occur more often with immunotherapy than chemotherapy and may not appear until months after initial treatment.

Upcoming clinical trials with immunotherapy will continue to explore overall survival and side effects compared to chemotherapy and real world reasons for discontinuation of treatment.

In the yet unpublished KEYNOTE-042 phase III trial, pembrolizumab was shown to be more effective than chemotherapy as a first line treatment for NSCLC with ≥1% PD-L1 expression.[12] Most patients treated with pembrolizumab had a longer median overall survival compared to chemotherapy, especially those with higher PD-L1 expression. The median overall survival for those with ≥50 PD-L1 expression was 20 months for patients treated with pembrolizumab compared to 12.2 months for patients treated with chemotherapy.

There is limited real world data of the reasons for discontinuation of immunotherapy. Possible reasons include completed treatment, patient choice, the treatment not being tolerated, disease progression, and death. When studying reasons patients cannot tolerate immunotherapy, special attention should be given to the unique immune-related side effects that are found with immunotherapy treatment but not with chemotherapy treatment.

## Conclusion

Pembrolizumab and Nivolumab are PD-1 inhibitors that allow the immune system to attack tumor cells. Immunotherapy with PD-1 inhibitors is currently used in the treatment of advanced melanoma and NSCLC, and other cancers. These agents have been proven in

clinical trials to be at least as effective for treating certain cancers as chemotherapy and they are more tolerable for patients. However, they can cause severe immune-related side effects that can lead to discontinuation of treatment. Better understanding of reasons of immunotherapy discontinuation will help us to optimize patient care in the future.

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