

Nivolumab – Pearls of Evidence

Abstract

Purpose: Nivolumab is one of the most extensively studied immune checkpoint inhibitors across various tumor types. In this narrative review, the current clinical efficacy and safety data of anti-programmed death-1 (PD-1) nivolumab for nonsmall cell lung cancer (NSCLC) and renal cell cancer (RCC) are elucidated. **Methods:** Systematic search was done on Pubmed, Medline, Embase, Web of Knowledge, and Cochrane Central through September 2016 for controlled prospective interventional studies of nivolumab across two indications - NSCLC and RCC. There was heterogeneity at all levels of abstraction; hence, author did not plan to provide a meta-analysis, but instead, a narrative elaboration of results structured around the conceptual frameworks. **Results:** Checkpoint receptor PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death-ligands 1 and 2, results in the downregulation of lymphocyte activation. Nivolumab is a fully human PD-1 immune checkpoint inhibitor. Nivolumab inhibits the interaction between PD-1 and its ligands and promotes immune responses including antitumor immune response and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. In 2013, the Food and Drug Administration granted fast track designation for nivolumab in NSCLC, RCC, and melanoma. **Conclusion:** The encouraging literature on nivolumab lends credibility to the promise of immune checkpoint blockade, not just in terms of its feasibility as an oncotherapeutic strategy but also as a key tool of the future in the therapeutic approaches against advanced cancers.

Keywords: *Immuno-oncology, nivolumab, nonsquamous cell lung carcinoma, programmed death-1 immune checkpoint inhibitor, renal cell carcinoma*

Introduction

Despite the advances in treatment options for cancer, there is a significant scope for improving clinical benefit for the existing standards of care which are dependent on line of therapy and/or histology. Some cancer patients are not eligible for targeted therapies and not all patients receiving targeted agents actually respond to it. Furthermore, conventional chemotherapy causes wide range of toxicities including bone marrow suppression.^[1]

The immune system plays a critical role in identifying and destroying abnormal cells in the body, including tumor cells. Tumor cells, however, use certain strategies to avoid recognition by the immune system, so as to grow unchecked.^[2] Among these, the one strategy that is most credulous in activation of a counterattack is “immune checkpoint activation.” Programmed death-1 (PD-1) immune checkpoint pathways are the most actively studied

pathway.^[3] Immuno-oncology agents target checkpoints within the cascade of immune regulatory molecules. Since these approaches directly target the patient’s immune system, they have the potential for utility across multiple tumor types.

The PD-1 receptor is expressed on activated T-cells, and the key ligands for this receptor are programmed death-ligands 1 (PD-L1) and 2 (PD-L2). PD-L1 is upregulated in many tumors. This overexpression helps tumor evade immune responses. Binding of ligands, PD-L1 or PD-L2 to PD-1 receptors inhibits T-cell activation and dampens antitumor immune responses. Thus, PD-1 receptor represents a logical target for cancer immunotherapy. This is a promising mechanism to stimulate the antitumor activity of the immune system, thereby improving therapeutic outcomes in cancer patients.^[4]

Currently, the various drugs being evaluated in this area are ipilimumab, nivolumab, and pembrolizumab. Nivolumab (Opdivo; Nivolumab BMS) was first PD-1 immune

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Pratishtha B Chaudhari

Department of Public Health,
NMMC Hospital, Navi Mumbai,
Maharashtra, India

Address for correspondence:
Dr. Pratishtha B Chaudhari,
NMMC Hospital, Navi Mumbai,
Maharashtra, India.
E-mail: pratishthabanga@gmail.com

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checkpoint inhibitor to be approved for use in advanced, squamous (SQ) non-small cell lung cancer (NSCLC) following prior chemotherapy. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody. It binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, thus releasing PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response.^[5]

Nivolumab is one of the most extensively studied immune checkpoint inhibitors across various tumor types and has anticancer activity against several tumor types, including melanoma, NSCLC, and renal cell cancer (RCC). Nivolumab monotherapy presents a favorable benefit-risk profile in patients with previously treated advanced or metastatic NSCLC as well as in patients with advanced or metastatic RCC.^[6]

Nivolumab is approved in the USA for the treatment of patients with metastatic SQ NSCLC which has shown progression on or after platinum-based chemotherapy and in the European Union (EU) for the treatment of adults with locally advanced or metastatic SQ NSCLC after prior chemotherapy treatment. Nivolumab is also approved in the USA and the EU for the treatment of advanced melanoma and in the USA for use in previously treated patients with advanced, non-SQ NSCLC. Several clinical trials are underway for other indications, such as the 1st line in RCC/NSCLC, glioblastoma multiforme, head and neck cancer, small cell lung cancer, gastrointestinal malignancies, and genitourinary malignancies.^[7]

Given the recent surge in research evaluating immuno-oncology molecules such as nivolumab and the growing list of indications that will actualize over the coming years, there is a need to bring together the existing evidence on current place of nivolumab. In this narrative review, the current clinical efficacy and safety data of anti-PD-1 nivolumab for cancer types relevant to India (NSCLC and RCC) are elucidated to appreciate the value of immune checkpoint blockade as a novel tool in the oncotherapeutic arsenal for advanced cancers.

Methods

Information sources

The reviewer conducted a systematic search for controlled prospective interventional studies of nivolumab across multiple indications - NSCLC and RCC. Author searched PubMed, Medline, Embase, Web of Knowledge, and Cochrane Central through September 2016. Furthermore, search on the metaRegister of Controlled Trials and the Clinical Trials Registry Platform to identify ongoing trials was performed. To identify additional studies, author reviewed reference lists of included articles and of systematic reviews. Search terms (exploded, all subheadings) used were: “Nivolumab,” “immuno-oncology,” “anti-PD-1,” “melanoma,” “NSCLC,” “RCC,” and “immune checkpoint

inhibitors.” The search was limited to studies in humans in English and was supplemented by handsearching reference lists in the identified papers.

Studies were eligible to be included if they were case-control or cohort studies (including those published as letters or abstracts) and provided adequate data to enable calculation of odds ratios and 95% confidence intervals (CIs). No restrictions were placed on the study population. The results of identified studies were classified as per indications in groups, efficacy and safety of nivolumab in melanoma, NSCLC, and RCC. There were three main points elucidated: efficacy, mechanism, and safety.

Study selection

One review author (PBC) independently assessed titles and abstracts identified by electronic literature searching to identify potentially qualified studies (screen 1). Any citation identified by either review author during screen 1 was selected for full-text review. The author assessed articles for inclusion using predefined inclusion and exclusion criteria (screen 2).

Data collection process

Author developed a standardized data extraction form using Google Forms to minimize data entry errors. The author piloted and revised the form to improve clarity. Author then independently extracted data on study design, key contextual factors, patient-important outcomes, results of these outcomes, and on design-specific risks for bias on studies.

Risk of bias in individual studies

Risk of bias of individual studies was assessed with component questions for risk of bias assessment dependent on the study design. For randomized controlled trials, author used the Cochrane risk of bias tool. Methodological components were decided separately for each study design that likely places a study at higher risk of bias. No attempt of any assessment of the risk of bias across studies was done.

Synthesis of Results

The characteristics of included studies were summarized by design and index test. There was heterogeneity at all levels of abstraction; hence, author did not plan to provide a meta-analysis, but instead, a narrative elaboration of results structured around the conceptual frameworks.

Nivolumab – molecule profile, pharmacokinetics, and programmed death

Nivolumab, a human monoclonal antibody, blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa that has a molecular mass of 146 kDa.

Wang *et al.* showed that nivolumab is bound to PD-1 with high affinity and specificity and effectively inhibits the interaction between PD-1 and its ligands. In addition, nivolumab can enhance T-cell reactivity at very low concentrations (~1.5 ng/mL) in the presence of a T-cell receptor stimulus but had no stimulatory effect in the absence of T-cell receptor stimulus. Specifically, there was not any significant release of inflammatory cytokines, including interferon (IFN)- γ , tumor necrosis factor-alpha, interleukin-2 (IL-2), IL-4, IL-6, or IL-10, from unstimulated whole blood after co-incubation with nivolumab, thus demonstrating that nivolumab does not cause nonspecific lymphocyte activation.^[8]

Injection nivolumab is a sterile, preservative-free, nonpyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. It is used for intravenous (IV) infusion which is supplied in single-dose vials. Each mL of nivolumab solution contains nivolumab 10 mg, mannitol, pentetic acid, polysorbate 80, sodium chloride, sodium citrate dihydrate, and water for injection, USP.^[9]

Nivolumab is expected to be cleared by proteolytic degradation through receptor-mediated endocytosis or nonspecific endocytosis mainly in hepatic or reticuloendothelial cells. It may be possible to speculate that nivolumab may exhibit target (PD-1)-mediated disposition, like other therapeutic proteins. This may constitute an interaction of the protein therapeutic with the pharmacological target receptor which is in a homeostatic equilibrium of synthesis and degradation. The metabolic pathway of nivolumab has not been characterized; however, it likely degrades through catabolic pathways into small peptides and amino acids in the same fashion as endogenous IgG. In addition, nivolumab is not expected to be metabolized by liver cytochrome P450 (CYP450) or other drug-metabolizing enzymes. In fact, due to the lack of cytokine modulation, nivolumab has no or low potential to modulate CYP enzymes, thus indicating a low risk of therapeutic protein-drug interactions.^[10]

Pharmacokinetics

Pharmacokinetic (PK) profile of nivolumab was well characterized using a population PK approach. The PK of single-agent nivolumab was analyzed in patients over a dose range of 0.1–20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% coefficient of variation) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state is 8.0 L (30.4%), and geometric mean elimination half-life ($t_{1/2}$) is 26.7 days (101%). The steady-state concentrations of nivolumab were reached by 12 weeks when given at 3 mg/kg every 2 weeks, and the systemic accumulation was observed to be approximately 3-fold. The exposure to nivolumab raised dose proportionally over the dose

range of 0.1–10 mg/kg administered every 2 weeks. A population PK analysis showed that the CL of nivolumab increased with increasing body weight, thereby supporting a weight-based dose. The population PK analysis showed that the following factors had no clinically important effects on the CL of nivolumab: age (29–87 years), gender, race, PD-L1 expression, tumor size, tumor type, renal impairment, baseline lactate dehydrogenase, and mild hepatic impairment.^[11]

Clinical evidence in nonsmall cell lung cancer

Lung cancer is a major health burden, with >1.6 million new cases diagnosed per year and leading to 1.3 million deaths per year. The GLOBOCAN report 2012 estimates the incidence of lung cancer in India to be about 70,000 in the adult population in both sexes. The estimated cancer mortality in India at all ages and in both sexes is 63,759.^[12]

Most cases of lung cancer (85%) are NSCLC, consisting of non-SQ (70%) and SQ (30%) histological subtypes, and half of patients present with incurable metastatic disease. Despite advances in treatment options for NSCLC, the incremental survival benefit for lung cancer remains modest. Long-term survival remains an elusive goal for the overwhelming majority of advanced NSCLC patients with 5-year survival being just 3.9%.^[13]

Looking at this high unmet need and the significant improvement in overall survival (OS) compared to standard second-line treatment (docetaxel) in both SQ and non-SQ histology NSCLC patients, nivolumab has been approved by the US Food and Drug Administration (US FDA) for metastatic SQ and non-SQ NSCLC in patients with progression on or after platinum-based chemotherapy.

Study CA209-017 (checkmate 017): Nivolumab versus docetaxel in previously treated nonsmall cell lung cancer (squamous only)

The phase III study CA209-017^[14] was a randomized (1:1), open-label study enrolling 272 patients with metastatic SQ NSCLC who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Patients received nivolumab ($n = 135$) administered IV at 3 mg/kg every 2 weeks or docetaxel ($n = 137$) administered IV at 75 mg/m² every 3 weeks. This study included patients regardless of their PD-L1 status. The trial excluded patients with autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis. The first tumor assessment was conducted 9 weeks after randomization and continued every 6 weeks thereafter. The primary efficacy outcome measure was OS.

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with docetaxel at the prespecified interim analysis.

Nivolumab in comparison with docetaxel demonstrated as follows:

- 41% reduction in risk of death (95% CI, 0.4, 0.8; $P = 0.00025$)
- 1-year OS rate of 42.1% (95% CI, 33.7, 50.3) for nivolumab versus 23.7% (95% CI, 16.9–31.1) for docetaxel
- 1-year progression-free survival (PFS) rate of 20.8% (95% CI, 14.0–28.4) for nivolumab versus 6.4% (95% CI, 2.9–11.8) for docetaxel
- Median OS of 9.2 months (95% CI, 7.3–13.3) for nivolumab versus 6.0 months (95% CI, 5.1–7.3) for docetaxel
- Nivolumab demonstrated superior benefit across all endpoints independent of PD-L1 expression
- Nivolumab monotherapy demonstrated a favorable safety profile as compared to docetaxel in patients with previously treated advanced or metastatic SQ NSCLC. Safety profile of nivolumab was consistent with expectations based on prior data in terms of the type, frequency, and severity of reported events, and no new safety concerns with nivolumab monotherapy treatment were identified.

Study CA209-063 (checkmate 063): Nivolumab in previously treated non-small cell lung cancer (squamous only)

The phase II study CA209-063^[15] evaluated nivolumab monotherapy in patients with advanced, refractory, SQ NSCLC. In this study, 117 patients with stage IIIB or IV SQ NSCLC who had received 2 or more prior systemic therapies and had the Eastern Cooperative Oncology Group performance status of 0 or 1 were included in the study. Patients ($N = 117$) received nivolumab 3 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. The major efficacy outcome measure was confirmed objective response rate (ORR) as measured by the Independent Review Committee (IRC) using the Response Evaluation Criteria in Solid Tumors (1.1). The first tumor assessment was conducted 8 weeks after the start of treatment and continued every 6 weeks thereafter.

Based on IRC review and with a minimum follow-up of at least 10 months on all patients, results showed as follows:

- Confirmed ORR (IRC assessed): 17 of 117 (14.5%; 95% CI, 8.7–22.2) patients, of which all were PRs; 13 of 17 (76.5%) patients with a confirmed response had ongoing responses (duration ranging from 1.9+ to 11.5+ months)
- Median OS: 8.1 (95% CI, 6.1–10.9) months
- OS rate at 1 year: 39% (95% CI, 30–48)
- Responses were observed across PD-L1 expression levels and patient subgroups (age, race, gender, performance status, region, and number of prior therapies).

Study CA209-057 (checkmate 057): Nivolumab versus docetaxel in previously treated nonsmall cell lung cancer (nonsquamous only)

CA209-057^[16] was a phase III randomized (1:1), open-label study of 582 patients with metastatic non-SQ NSCLC

who had experienced disease progression during or after one prior platinum doublet-based chemotherapy regimen. Appropriate prior targeted therapy in patients with known sensitizing epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation was allowed. Patients received nivolumab ($n = 292$) administered IV at 3 mg/kg every 2 weeks or docetaxel ($n = 290$) administered IV at 75 mg/m² every 3 weeks. The first tumor assessments were conducted 9 weeks after randomization and continued every 6 weeks thereafter. The major efficacy outcome measure was OS. In addition, prespecified analyses were conducted in subgroups defined by PD-L1 expression.

Nivolumab demonstrated a statistically significant improvement in OS compared with docetaxel at the prespecified interim analysis.

Nivolumab in comparison with docetaxel demonstrated:

- 28% lower risk of death (hazard ratio, 0.72; 95% CI, 0.60–0.88; $P < 0.001$)
- median OS of 12.2 months (95% CI, 9.7–15.1) with nivolumab in comparison to 9.4 months (95% CI, 8.1–10.7) with docetaxel,
- The OS rate at 1 year was 51% (95% CI, 45–56) with nivolumab and 39% (95% CI, 33–45) with docetaxel. At 18 months, the rate of OS was 39% (95% CI, 34–45) with nivolumab and 23% (95% CI, 19–28) with docetaxel
- The rate of PFS at 1 year was 19% (95% CI, 14–23) with nivolumab and 8% (95% CI, 5–12) with docetaxel
- Nivolumab was associated with longer OS, PFS, and higher ORR than docetaxel at the prespecified PD-L1 expression levels of 1% or higher, 5% or higher, and 10% or higher
- Nivolumab monotherapy demonstrated a favorable safety profile as compared to docetaxel in patients with previously treated advanced or metastatic non-SQ NSCLC. Safety profile of nivolumab was consistent with expectations based on prior data in terms of the type, frequency, and severity of reported events, and no new safety concerns with nivolumab monotherapy treatment were identified.

Study CA209-003: Nivolumab monotherapy in previously treated nonsmall cell lung cancer (squamous and nonsquamous)

Gettinger and Lynch and Sundar *et al.*^[17] reported outcomes for the NSCLC cohort ($n = 129$) from the CA209-003 trial, a phase I, open-label, multicenter, multidose, dose-escalation, cohort expansion study of nivolumab in patients with advanced cancers. Additional investigation included efficacy across tumor histologies. Patients received nivolumab 1, 3, or 10 mg/kg IV every 2 weeks in 8-week treatment cycles (4doses/cycle; maximum of 12 cycles; 96 weeks or until unacceptable toxicity).

- NSCLC cohort analysis across all dosage of nivolumab showed

- Confirmed ORR in 17.1% of patients (SQ 16.7% and non-SQ 17.6%)
- Median OS of 9.9 months (range 7.8–12.4 months); SQ 9.2 months (range 7.3–12.5 months) and non-SQ 10.1 months (range 5.7–13.7 months)
- 1-year OS of 42% (33–50); SQ 41% (27–54) and non-SQ 42% (30–53)
- 6-month PFS rate was 33% (25–42); SQ 41% (27–55) and non-SQ 29% (18–40).

Clinical evidence in renal cell carcinomas

In India, the incidence of RCC is 1.2/100,000 in males and 0.5/100,000 in females. Compared to the global trends where RCC is commonly seen in slightly older population, i.e., 50–70 years, in India, RCC is diagnosed in relatively younger population with the mean age of 52 years. Although the number of cases in Southeast Asia including India is on the lower side compared to rest of the world, the ratio of incidence to mortality is higher.^[18]

In developing countries like India, most of these patients present with large tumor burden, i.e., in advanced disease. About 20% to 30% of patients present with metastatic disease at diagnosis, and about one-third of patients undergoing nephrectomy for localized disease will develop metastases.

Systemic therapy comprising various chemotherapeutic agents and targeted therapies is the mainstay of treatment in advanced RCC. A number of targeted therapies have been approved for the treatment of advanced or metastatic RCC. These agents include vascular endothelial growth factor pathway inhibitors and mammalian target of rapamycin inhibitors. Selective advances in diagnosis, staging, and treatment of patients with RCC have resulted in improved survival of a selected group of patient and overall change in natural history of the disease; however, there is no satisfactory treatment exists for advanced RCC. The 5-year OS for patients with metastatic disease at presentation remains <20%.^[19]

RCC is considered a malignancy amenable to immune manipulation. Various immune-potentiating strategies have been applied to the treatment of RCC, but till date, cytokine therapy with IFN-alpha and IL-2 is the only ones that have had some degree of clinical success. Although everolimus and other agents have changed the therapeutic landscape for this disease, these treatments are associated with limited OS after a given agent is no longer effective. Looking at this high unmet need and the significant improvement in OS compared to standard second-line treatment (everolimus) in advanced RCC, nivolumab has been approved by the US FDA as a single agent is indicated for the treatment of patients with advanced RCC after prior therapy in adults.

The CA209-025^[20] was a randomized, open-label, phase III study of nivolumab comparing nivolumab with everolimus in patients with advanced or metastatic RCC who have

experienced disease progression during or after 1 or 2 prior antiangiogenic therapy regimens and no >3 total prior systemic treatment regimens. Patients had to have a Karnofsky performance score \geq 70%. This study included patients regardless of their PD-L1 status.

A total of 821 patients were randomized to receive either nivolumab 3 mg/kg ($n = 410$) administered IV over 60 min every 2 weeks or everolimus ($n = 411$) 10 mg daily, administered orally. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumor assessments were conducted 8 weeks after randomization and continued every 8 weeks thereafter for the 1st year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. The primary efficacy outcome measure was OS. Secondary efficacy assessments included investigator-assessed ORR and PFS.

The trial demonstrated a statistically significant improvement in OS for patients randomized to nivolumab as compared with everolimus at the prespecified interim analysis.

Nivolumab in comparison with everolimus demonstrated as follows:

- 27% reduction in risk of death; hazard ratio 0.73 (95% CI, 0.57–0.93; $P = 0.002$)
- 1-year OS rate of 76.0 (95% CI, 71.5, 79.9) for nivolumab versus 66.7% (95% CI, 61.8–71.0) for everolimus
- The median OS of 25.0 months in the nivolumab group and 19.6 months in the everolimus group.
- OS benefit was observed regardless of PD-L1 expression level.
- The median PFS was 4.6 months (95% CI, 3.7–5.4) in the nivolumab group and 4.4 months (95% CI, 3.7–5.5) in the everolimus group (hazard ratio, 0.88; 95% CI, 0.75–1.03; $P = 0.11$)
- Nivolumab had a safety profile consistent with that seen in other studies of this drug. Grade 3 or 4 treatment-related adverse events were less frequent with nivolumab than with everolimus, and treatment-related adverse events leading to discontinuation occurred in fewer patients in the nivolumab group than in the everolimus. Adverse events with nivolumab are manageable with treatment guidelines outlined in the prescribing information for nivolumab.

Conclusion

The encouraging literature on nivolumab lends credibility to the promise of immune checkpoint blockade, not just in terms of its feasibility as an oncotherapeutic strategy but also as a key tool of the future in the therapeutic approaches against advanced cancers. Since PD-L1 is a weak biomarker, it is difficult for the clinician to know in particular whether the patient will respond to nivolumab

therapy or not. This can lead to significant financial burden to the patient as immunotherapy is expensive. The way forward to leverage maximum benefits nivolumab may be to synergize both anti-PD-1 blockade with complementary targets in immune checkpoint pathways and other oncogenic signal transduction pathways. The US FDA has approved nivolumab for metastatic melanoma, NSCLC, and RCC. As more clinical data emerge globally, it is almost certain that approvals for nivolumab will be seen in other cancer therapeutic areas including lymphoma, hepatocellular carcinoma, and colorectal carcinoma.

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Conflicts of interest

There are no conflicts of interest.

References

- Davis C. Drugs, cancer and end-of-life care: A case study of pharmaceuticalization? *Soc Sci Med* 2015;131:207-14.
- Swann JB, Smyth MJ. Immune surveillance of tumors. *J Clin Invest* 2007;117:1137-46.
- Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-64.
- He J, Hu Y, Hu M, Li B. Development of PD-1/PD-L1 pathway in tumor immune microenvironment and treatment for non-small cell lung cancer. *Sci Rep* 2015;5:13110.
- Sundar R, Cho BC, Brahmer JR, Soo RA. Nivolumab in NSCLC: Latest evidence and clinical potential. *Ther Adv Med Oncol* 2015;7:85-96.
- Momtaz P, Postow MA. Immunologic checkpoints in cancer therapy: Focus on the programmed death-1 (PD-1) receptor pathway. *Pharmgenomics Pers Med* 2014;7:357-65.
- Available from: <https://www.clinicaltrials.gov/ct2/results?term=nivolumab&Search=Search>. [Last accessed on 2016 Oct 01].
- Wang C, Thudium KB, Han M, Wang XT, Huang H, Feingersh D, *et al.* *In vitro* characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and *in vivo* toxicology in non-human primates. *Cancer Immunol Res* 2014;2:846-56.
- Opdivo® (nivolumab) injection Prescribing Information. Princeton: Bristol-Myers Squibb Company; 2017.
- Nair S. Pharmacometrics and systems pharmacology of immune checkpoint inhibitor nivolumab in cancer translational medicine. *Adv Mod Oncol Res* 2016;2:18-31.
- Callahan MK, Wolchok JD. At the bedside: CTLA-4- and PD-1-blocking antibodies in cancer immunotherapy. *J Leukoc Biol* 2013;94:41-53.
- Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM, *et al.* Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893-917.
- Mandal SK, Singh TT, Sharma TD, Amrithalingam V. Clinico-pathology of lung cancer in a regional cancer center in Northeastern India. *Asian Pac J Cancer Prev* 2013;14:7277-81.
- Spigel DR, Reckamp KL, Rizvi NA, Poddubskaya E, West HJ, Eberhardt WE, *et al.* A phase III study (CheckMate 017) of nivolumab (anti programmed death-1) vs docetaxel in previously treated advanced or metastatic squamous (SQ) cell non-small-cell lung cancer (NSCLC). *J Clin Oncol (ASCO Annual Meeting)* 2015;33 (Suppl):abstr 8009.
- Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, *et al.* Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): A phase 2, single-arm trial. *Lancet Oncol* 2015;16:257-65.
- Paz-Ares L, Horn L, Borghaei H, Spigel DR, Steins M, Ready N, *et al.* Phase III, randomized trial (CheckMate 057) of nivolumab (NIVO) versus docetaxel (DOC) in advanced non-squamous cell (non-SQ) non-small cell lung cancer (NSCLC). *J Clin Oncol* 2015;33 Suppl:LBA109.
- Gettinger S, Lynch T. A decade of advances in treatment for advanced non-small cell lung cancer. *Clin Chest Med* 2011;32:839-51.
- GLOBOCAN; 2012. http://www.globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. [Last accessed on 2016 Nov 08].
- Bharthuar A. Metastatic renal cell carcinoma: Current scenario and future trends. *South Asian J Cancer* 2012;1:30-5.
- Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, *et al.* Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803-13.