COLUMBIA UNIVERSITY MEDICAL CENTER

Randomized Phase 1b/2 Study of Nivolumab or Nivolumab Plus BMS-986253 in Combination With Intermittent Androgen Deprivation Therapy in Men With Hormone-Sensitive Prostate Cancer

NCT03689699

July 12, 2023

NCI·CC

A Cancer Center Designated by the National Cancer Institute

INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

Prostate cancer is a major contributor to cancer morbidity and mortality in men (Jemal A et al, 2017). Treatment of localized disease typically involves either surgery or radiation. However, a significant number of men treated with definitive local therapy will eventually have PSA recurrence and develop clinical metastases (Roehl KA et al, 2004). Although some patients will demonstrate clear metastatic disease on imaging, a significant number of men will only have biochemical recurrence (BCR) with a rising PSA (Freedland SJ et al 2005).

Androgen deprivation therapy (ADT) can lead to rapid disease control for men with metastatic or non-metastatic hormone-sensitive prostate cancer. However, ADT is associated with significant side effects including decreased libido, increased fat mass, insulin resistance and osteoporosis (Litwin MS et al, 2017). Intermittent ADT (IADT) which has been shown to be non-inferior to continuous ADT allows for reduced ADT exposure (Crook JM et al 2012; Magnan S et al 2015; Klotz L et al 2017). However, the ADT free interval typically decreases with each cycle of IADT and all men will eventually progress to a castration-resistant state (Crook JM et al 2012). Therefore, developing novel strategies to prolong the ADT free interval and allow for recovery of testosterone while maintaining adequate disease control are essential to improving outcomes for prostate cancer patients.

Immunotherapy has shown mixed efficacy in prostate cancer to date. Although Sipuleucel T (Sip-T), an autologous cancer vaccine, can improve overall survival in castration-resistant prostate cancer (CRPC), other immunotherapy approaches like checkpoint blockade have been relatively unsuccessful when tested in patients with CRPC. However, it is becoming increasingly clear that the immune tumor microenvironment changes dramatically during disease progression and in response to ADT. For example initially ADT induces thymic output of T-cells with subsequent tumor infiltration (Drake CG et al, 2005). However, with prolonged ADT and disease progression a more immunosuppressive tumor microenvironment develops with increased regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) (Drake et al, 2005; Gannon PO et al, 2009). Recent data from Antonarakis et al also demonstrated that sequencing immunotherapy with Sipuleucel-T prior to ADT elicits a more robust immune response than ADT followed by Sipuleucel-T (Antonarakis et al, 2017). However, whether checkpoint blockade in combination with standard ADT can lead to more effective disease control and less exposure to ADT exposure for patients with less advanced hormone-sensitive disease remains unknown. In addition, data from our group and others have identified infiltration of PMN-MDSCs through increased production of IL-8 as an important mechanism of immune resistance in prostate cancer. In particular, pre-clinical data demonstrate a process by which ADT leads to secretion of IL-8 and attraction of PMN-MDSCs, thereby promoting immune resistance (Gannon PO et al, 2010; Drake lab unpublished data). Therefore, adding IL-8 targeted therapy to checkpoint blockade and ADT could further enhance anti-tumor immunity and offer patients with prostate cancer the potential to develop durable immune responses.

This is a two-arm, multicenter, phase 1b/2 study to assess the efficacy of immunotherapy with either Nivolumab (anti-PD-1) or Nivolumab plus BMS-986253 combined with ADT using Degarelix (LHRH antagonist) for men with hormone-sensitive prostate cancer and a rising PSA (30 patients per group), with a primary endpoint of rate of PSA recurrence 12 months after completion of therapy. We hypothesize that immunotherapy with either Nivolumab alone or Nivolumab plus BMS-986253 combined with Degarelix will decrease the percentage of men with hormonse-sensitive prostate cancer and a rising PSA who have PSA recurrence 12 months after completion of therapy from 50% (historical reference; McKay RR et al, 2016) to 25%. Baseline and on-treatment biopsies will be obtained for a subgroup of patients with biopsy accessible lesions in each group to characterize the immune effects of therapy.

STUDY OBJECTIVES

Primary Objective

- Determine the rate of PSA recurrence defined as a PSA >0.2ng/ml for radical prostatectomy patients or PSA >2.0ng/ml for patients who received other primary therapies (e.g. radiation, cryotherapy, brachytherapy) at a time point of 10 months after start of therapy.

- Determine the safety and tolerability of either nivolumab or nivolumab plus BMS-986253 in combination with degarelix in men with hormone-sensitive prostate cancer.

Secondary Objectives

- To assess the relapse-free survival (RFS) after recovery of testosterone with relapse defined as a PSA >0.2ng/ml for radical prostatectomy patients or PSA >2.0ng/ml for patients who received other primary therapies and recovery of testosterone defined as a testosterone (>150ng/dl).

- Determine the % change in PSA to immunotherapy by comparing the PSA prior to and following 8 weeks of immunotherapy and before initiation of ADT.

Exploratory Objectives

- To assess the anti-tumor immune response
    - Quantification of CD8 T cell, CD4 T cell, Treg, CD8/Treg, CD4/Treg, PMN-MDSC and other immune cell populations in a subset of patients (at least 10 per arm) with tumor specimens before and after treatment by immunohistochemistry (IHC). Immune cell density and proximity will also be assessed using polychromatic immunofluorescence.
    - Quantification a range of immunologic markers in a subset of patients (at least 10 per arm) with tumor specimens before and after treatment.
    - Quantification of tumor cell apoptosis by TUNEL and caspase-3 staining.
    - Quantification of circulating IL-8 and other cytokines before and after treatment and correlation with response to therapy.
    - Quantification of circulating PMN-MDSCs and other immune cell populations before and after treatment and correlation with response to therapy.

- Assess whether treatment can induce an increased IgG response to tumor antigens (epitope spreading) by comparing pre- and post-treatment sera.
- Assess the DNA or RNA-related molecular characteristics of tumor specimens and correlate with response to treatment (if adequate tissue available).

INVESTIGATIONAL AGENTS

Nivolumab

Pharmaceutical and Therapeutic Background

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death‑ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). Nivolumab is also now FDA-approved for treatment at a dose of 480mg every 4 weeks as a 30 minute infusion (US, Mar-2018). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies, and as single-dose monotherapy for the treatment of sepsis.

BMS-986253

Pharmaceutical and Therapeutic Background

BMS-986253 (also known as Humax-IL8 and formerly referred to as Humax-Inflam) is a fully human immunoglobulin subclass G1 kappa monoclonal antibody (mAb) directed against IL-8, also known as CXCL8. IL-8 is a well-described proinflammatory cytokine that has immunosuppressive and protumoral effects in the tumor microenvironment. BMS-986253 potently binds free IL-8. Disruption of the IL-8:CXCR1/2 signaling axis may inhibit recruitment of immunosuppressive myeloid-derived suppressor cells (MDSCs) to the tumor microenvironment, reduce cancer stem cell (CSC) renewal, reverse epithelial mesenchymal transition (EMT), and inhibit angiogenesis, all of which are important mechanisms for cancer-induced immunosuppression, tumor recurrence, and metastasis.

The drug was initially investigated for the treatment of inflammatory skin diseases under the name Humax-Inflam. HuMax-Inflam was in a Phase 1/2 dose-escalation, safety, and efficacy trial in patients with palmoplantar pustulosis (PPP). The antibody demonstrated a tolerable profile and sign of activity based on a reduced inflammation index at doses up to 8 mg/kg weekly.

Subsequently, the product is now being developed for the treatment of cancer under the product code BMS-986253. The clinical development strategy for BMS-986253 as an anticancer agent will be in combination with other therapeutic approaches such as immune checkpoint inhibitors.

The transition from hybridoma-derived to Chinese hamster ovary (CHO) cell-derived BMS-986253 was accomplished by the cloning and expression of the heavy and light chains of the antibody cDNAs in CHO cells to produce BMS-986253. A comparability exercise between CHO cell-derived material and hybridoma material has not revealed any significant differences in antigen-binding fragment (Fab) to IL-8 and other critical quality attributes, but has demonstrated a more complete processing and decreased heterogeneity in isoelectric point with the CHO cell-derived BMS-986253. Based on molecular characterization, the main difference between the hybridoma-derived and CHO cell-derived materials is glycosylation patterns. The transition from hybridoma-derived to Chinese hamster ovary (CHO) cell-derived BMS-986253 was accomplished by the cloning and expression of the heavy and light chains of the antibody cDNAs in CHO cells to produce BMS-986253. A comparability exercise between CHO cell-derived material and hybridoma material has not revealed any significant differences in antigen-binding fragment (Fab) to IL-8 and other critical quality attributes, but has demonstrated a more complete processing and decreased heterogeneity in isoelectric point with the CHO cell-derived BMS-986253. Based on molecular characterization, the main difference between the hybridoma-derived and CHO cell-derived materials is glycosylation patterns.

BMS-986253 was tested as monotherapy in 15 participants with advanced solid tumors (Study CA027-001) and demonstrated a tolerable profile at doses up to 32 mg/kg. Of these 15 participants, 11 had a best overall response of stable disease (SD) and 4 had a best overall response of progressive disease. In an ongoing Phase 1/2a study of BMS-986253 in combination with nivolumab in advanced cancers, safety data from the first 8 participants suggest that the drug combination is well tolerated.

The clinical development strategy for BMS-986253 as an anti-cancer agent will be in combination with other therapeutic approaches such as immune checkpoint inhibitors. It is hypothesized that inhibition of MDSC and neutrophil tumor infiltration, reduction of CSC renewal, and reversal of cancer cell EMT driven by anti-IL-8 disruption of the IL-8:CXCR1/2 signaling axis will further sensitize IL-8 producing tumors to other therapeutic approaches such as immune checkpoint blockade.

STUDY DESIGN

General Design

This is a multi-center, two-arm, open-label, phase 1b/2 study evaluating the anti-tumor effect of either Nivolumab alone or Nivolumab plus BMS-986253 with androgen deprivation therapy using Degarelix in men with hormone-sensitive prostate cancer and a rising PSA. Patients will be recruited from outpatient clinics at participating sites and randomized to either Nivolumab alone (Arm A) or Nivolumab plus BMS-986253 (Arm B).

Study Interventions: Eligible patients in Arm A will receive Nivolumab every 4 weeks for 2 doses and then Nivolumab + Degarelix every 4 weeks x 4 doses. Eligible patients in Arm B will receive Nivolumab every 4 weeks x2 doses + BMS-986253 every 2 weeks x 4 doses and then

Nivolumab every 4 weeks x 4 doses + BMS-986253 every 2 weeks x 8 doses + Degarelix every 4 weeks x 4 doses.

Schedule of Evaluations: During treatment patients will have safety assessments including routine bloodwork and physical examinations at each visit. (See **Section 12** for detailed study evaluations and the study schedule). Safety evaluations will also occur until 100 days after the last treatment doses.

The primary endpoint will be evaluated by assessing the PSA 10 months after start of therapy. PSA and serum testosterone will be checked monthly during treatment (+/- 3 days), the end of treatment visit (+/- 1 week), every 2 months (+/- 1 week) or until progression of disease during year 1 of follow up and every 3 months (+/- 1 month) or until progression of disease during year 2 of follow up. Sera, whole blood and CBC with differential will be collected for immunoassays at initiation of immunotherapy, at initiation of degarelix, end of treatment visit and 10, 14 and 18 month (+/- 1 week). Patients will also have CT or MRI scans (chest, abdomen and pelvis) and bone scan at screening, end of treatment and 10 months after start of therapy. Toxicity evaluation will utilize CTCAE v5.0 criteria.

Duration of Treatment: Subjects will receive treatment for a total of 6 months or intolerable toxicity or side effects.

Duration of Follow up: Toxicity and laboratory tests will be graded using the NCI CTCAE v5.0 scoring system. Adverse events will be assessed continuously during the study and for 100 days after the last dose of treatment. In addition, patients will have PSA, serum testosterone checked every 2 months (+/- 1 week) or until progression of disease for year 1 of follow up and every 3 months (+/- 1 month) or until progression of disease for year 2 of follow up. Sera, PMBCs and CBC with differential will be collected for immunoassays collected at end of treatment visit and 10, 14 and 18 months following start of therapy. Patients will also need to have imaging done at end of treatment visit and 10 months after start of therapy. Subjects who are removed from the study for reasons other than progression of disease will be followed every 2 months to evaluate disease status and survival while the study remains open.

Number of Subjects

The study will include a total of approximately 30 patients per arm to achieve at least 23 evaluable patients per arm. This study design yields at least 80% power to detect a PSA recurrence rate of 25% at 10 months after start of therapy (compared to the null hypothesis of 50%) at a significance level of 5%. Accounting for a dropout rate of 20%, we will plan to enroll a total of 30 patients per arm.

TREATMENT PLAN

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**

BMS-986253*	No specific premedications or precautions	2400mg	IV over 120 minutes (+/- 10 minutes) **before** Nivolumab	Days 1, 15 of each cycle	4 weeks (28 days)
Nivolumab	No specific premedications or precautions	480mg	IV over 30 minutes **(**-5 minutes/+10 minutes) **after** BMS-986253	Day 1 of each cycle	
Degarelix	No specific premedications or precautions	240mg loading dose (cycle 3), 80mg (cycle 4-6)	SQ **after** BMS-986253 and Nivolumab	Day 1 of each cycle	

* For patients weighing less than 35 kg BMS-986253 should be infused over 180 minutes. .

MEASUREMENT OF EFFECT

Biochemical Response/Progression

All participants who complete study requirements after treatment with androgen deprivation therapy using Degarelix with either Nivolumab alone or Nivolumab plus BMS- 986253 will follow-up until they reach PSA relapse defined as at least two serial rises in PSA (≥2 weeks apart) with PSA >0.2ng/ml for radical prostatectomy patients or PSA >2.0ng/ml for patients who received other primary therapies (e.g. radiation cryotherapy, brachytherapy).

Radiographic Progression

Radiographic progression will be defined as the appearance of new lesions for men who initially have biochemically recurrent, non-metastatic disease. For men with metastatic disease at baseline, Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) will be used for soft tissue lesions and Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria will be used for osseus disease

STATISTICAL CONSIDERATIONS

Study Design and Sample Size

This is a multicenter, 2-arm phase 1b/2 trial to evaluate the activity of Nivolumab or Nivolumab plus BMS-986253 with IADT using Degarelix in men with hormone sensitive prostate cancer with a rising PSA. The primary endpoints of this trial is rate of PSA recurrence 10 months after start of therapy. Within the context of this proposed trial, we will target a decrease in post-therapy PSA recurrence at 10 months of 25% compared to a historical recurrence rate of 50% with intermittent ADT alone. Probabilities of type I and type II error will be set at 0.05 and 0.2 respectively. The study will include a total of 23 evaluable patients per arm. This study design yields at least 80% power to detect a PSA recurrence rate of 25% at 10 months after start of therapy (compared to the null hypothesis of 50%) at a significance level of 5%. Accounting for a dropout rate of 20%, we will plan to enroll a total of 30 patients per arm.

Study Endpoints

We will use one-sided binomial tests to compare the post-therapy PSA recurrence rate in each arm with the historical recurrence rate of 50%. To compare the secondary outcomes between the two arms, Kaplan-Meier estimators and log-rank tests will be used to compare time-to-event variables (e.g., time to PSA recurrence, time to recovery of testosterone, and time to next anti-cancer treatment); Chi-squared tests will be used to compare incidence rates (e.g., incidence of metastases); t-tests will be used to compare continuous measurements (e.g., changes immune cell density and proximity). We will set the nominal significance level at 5%. Only patients undergoing randomization to the treatment arms will be used for comparison between the treatment arms.

Analysis Populations

Intention-to-treat population

All patients who meet eligibility criteria and receive at least one dose of the study drug will be included in the analysis of the primary and secondary endpoints, even if there are subsequent protocol deviations.

Safety population

All patients enrolled in the study will be included in the safety analysis population and considered evaluable for toxicity from the time of their first dose of the study drug(s). Patients never receiving any of the study drugs will not be included in this analysis. Demographic and baseline characteristics for the safety population will be summarized by number and percent for categorical data and by descriptive statistics for continuous data.

REFERENCES

1. Alfaro C, Sanmamed MF, Rodríguez-Ruiz ME, et al. Interleukin-8 in cancer pathogenesis, treatment and follow-up. Cancer Treatment Reviews 2017;60:24-31.

2. Antonarakis ES, Trock BJ, Feng Z, et al. The natural history of metastatic progression in men with PSA-recurrent prostate cancer after radical prostatectomy: long-term follow-up. BJU Int 2012; 109: 32-39.

3. Antonarakis ES, Kibel AS, Yu EY, et al. Sequencing of sipuleucel-T and androgen deprivation therapy in men with hormone-sensitive biochemically recurrent prostate cancer: a phase II randomized trial. Clin Can Res. 2017; 23(10):2451-2459.

4. Antonarakis ES, Zahurak M, Schaeffer EM et al, Neoadjuvant randomized trial of degarelix (Deg) +/- cyclophosphamide/GVAX (Cy/GVAX) in men with high-risk prostate cancer (PCa) undergoing radical prostatectomy (RP). Journal of Clinical Oncology 2017 35:15_suppl, 5077-5077

5. Attard G, Reid AH, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. J Clin Oncol 2008;26:4563-4571.

6. Bander, N.H., et al., MHC class I and II expression in prostate carcinoma and modulation by interferon-alpha and -gamma. Prostate, 1997. 33(4): p. 233-9.

7. Beer TM, Kwon ED, Drake CG, et al. Randomized, double-blind, phase III trial of ipilimumab versus placebo in asymptomatic or minimally symptomatic patients with metastatic chemotherapy-naïve castration-resistant prostate cancer. J Clin Oncol. 2017;35:40–47.

8. Berthold DR, Pond GR, Soban F, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol 2008; 26: 242-245.

9. Brusa, D., et al., Circulating immunosuppressive cells of prostate cancer patients before and after radical prostatectomy: profile comparison. Int J Urol, 2013. 20(10): p. 971-8.

10. Crook JM, O'Callaghan CJ, Duncan G, et al. Intermittent Androgen Suppression for Rising PSA Level after Radiotherapy. New England Journal of Medicine 2012;367:895-903.

11. D'Amico AV, Schultz D, Loffredo M, et al. Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for clinically localized prostate cancer. JAMA 2000; 284: 1280-1283.

12. Drake CG. Prostate cancer as a model for tumour immunotherapy. Nat Rev Immunol, 2010. 10(8): p. 580-93.

13. Drake, C.G., et al., *Androgen ablation mitigates tolerance to a prostate/prostate cancer-restricted antigen.* Cancer Cell, 2005. **7**(3): p. 239-49.

14. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med2011;364:1995-2005.

15. Fernando, RI, et al. IL-8 signaling plays a critical role in the epithelial-mesenchymal transition of human carcinoma cells. Cancer Res, 2011; 71(15):5296-306.

16. Freedland SJ, Humphreys EB, Mangold LA, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. J Clin Oncol 2007; 25: 1765-1771.

17. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer–specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294:433-9

18. Gannon PO, Poisson AO, Delvoye N, Lapointe R, Mes-Masson A-M, Saad F. Characterization of the intra-prostatic immune cell infiltration in androgen-deprived prostate cancer patients. Journal of Immunological Methods 2009;348:9-17

19. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975–2014, Featuring Survival. JNCI: Journal of the National Cancer Institute 2017;109:djx030-djx.

20. Kantoff, P.W., et al., *Sipuleucel-T immunotherapy for castration-resistant prostate cancer.* N Engl J Med, 2010. **363**(5): p. 411-22.

21. Klotz L, Loblaw A, Siemens R, Ouellette P, Kapoor A, Saad F. PD37-01 FOUR VS TEN MONTHS OF INDUCTION ADT FOR INTERMITTENT THERAPY: A PROSPECTIVE CURC RANDOMIZED TRIAL. The Journal of Urology;197:e673-e4.

22. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends Immunol 2016;37:208-20

23. Kwon ED, Drake CG, Scher HI, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184 043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. 2014;15:700–712.

24. Lawrence, M.S., et al., Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature, 2013. 499(7457): p. 214-218.

25. Le DT, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017 Jul;357(6349):409-413.

26. Litwin MS, Tan H. The diagnosis and treatment of prostate cancer: A review. JAMA 2017;317:2532-42.

27. Longo DL. New therapies for castration-resistant prostate cancer. N Engl J Med. 2010 Jul 29;363(5):479-81.

28. Lopez-Bujanda Z, Drake CG. Myeloid-derived cells in prostate cancer progression: phenotype and prospective therapies. Journal of Leukocyte Biology 2017;102:393-406.

29. McKay RR, Zurita AJ, Werner L, et al. A randomized phase II trial of short-course androgen deprivation therapy with or without bevacizumab for patients with recurrent prostate cancer after definitive local therapy. J Clin Oncol. 2016:34:1913-1920.

30. Magnan S, Zarychanski R, Pilote L, et al. Intermittent vs continuous androgen deprivation therapy for prostate cancer: A systematic review and meta-analysis. JAMA Oncology 2015;1:1261-9.

31. Martin AM, Nirschl TR, Nirschl CJ, et al. Paucity of PD-L1 expression in prostate cancer: innate and adaptive immune resistance. Prostate Cancer Prostatic Dis. 2015;18:325–332.

32. Mercader M, Bodner BK, Moser MT, et al. T cell infiltration of the prostate induced by androgen withdrawal in patients with prostate cancer. Proc Natl Acad Sci U S A 2001;98:14565-70.

33. Nonclinical Study Report: Medarex Study No. MDX1106-025-R. In vitro characterization of a fully human anti-PD-1 monoclonal antibody. Bristol-Myers Squibb Company; 2007. Document Control No.930046580.

34. Nonclinical Study Report: Medarex Study No. MDX1106-028-R. Binding and blocking characteristics of chimeric anti-mouse PD-1 antibody, 4H2. Bristol-Myers Squibb Company; 2007. Document Control No. 930046578.

35. Nonclinical Study Report: Medarex Study No. 1106-0042-R. Effect of MDX-1106 on recall antigen-activated T-cell secretion of interferongamma in vitro. Bristol-Myers Squibb Company; 2006. Document Control No. 930046579.

36. Nonclinical Study Report: Medarex Study No. MDX1106-001 (Sierra Study No. SUV00006). Cellular and humoral immune response analysis report: an investigative repeat-dose toxicity and efficacy study of MDX-010, 4C5, and 5H1 in combination with HBsAG, DNP Ficoll, and SKMel-3 immunostimulants following three monthly administrations. Bristol-Myers Squibb Company; 2006. Document Control No. 930039656.

37. Nonclinical Study Report: Study No. SUV00027. A single-dose pharmacokinetic study of MDX-1106 administered by intravenous injection to cynomolgus monkeys. Bristol-Myers Squibb Company; 2009. Document Control No. 930039664.

38. Amendment 2 to Nonclinical Study Report: Study No. SUV00027. A single-dose pharmacokinetic study of MDX-1106 administered by intravenous injection to cynomolgus monkeys. Bristol-Myers Squibb Company; 2011. Document Control No. 930039664.

39. Nonclinical Study Report: Study No. SUV00025/MDX1106-024-R. A 30-day toxicity study of MDX-1106 administered by once weekly intravenous injection to cynomolgus monkeys, followed by an approximate 4-week recovery period. Bristol-Myers Squibb Company; 2006. Document Control No. 930039682.

40. O'Donnell A, Judson I, Dowsett M, et al. Hormonal impact of the 17alpha-hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer.Br J Cancer 2004;90:2317-2325.

41. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; 281: 1591-1597.

42. Pritchard CC, Mateo J, Walsh MF et al. Inherited DNA-repair gene mutations in men with metastatic prostate cancer. N Engl J Med. 2016 Aug;375(5):443-453.

43. Qazi BS, Tang K, Qazi A, et al. Recent advances in underlying pathologies provide insight into interleukin-8 expression-mediated inflammation and angiogenesis. Int J Inflam. 2011.

44. Roehl KA, Han M, Ramos CG, Antenor JA, Catalona WJ. Cancer progression and survival rates following anatomical radical retropubic prostatectomy in 3,478 consecutive patients: long-term results. J Urol 2004;172:910-4.

45. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med2013;368:138-148.

46. Sanda, M.G., et al., Molecular characterization of defective antigen processing in human prostate cancer. J Natl Cancer Inst, 1995. 87(4): p. 280-5.

47. Santegoets SJ, Stam AG, Lougheed SM, et al. Myeloid derived suppressor and dendritic cell subsets are related to clinical outcome in prostate cancer patients treated with prostate GVAX and ipilimumab. Journal for ImmunoTherapy of Cancer 2014;2:31.

48. Scher HI, Beer TM, Higano CS, et al. Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study.Lancet 2010;375:1437-1446.

49. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187-1197.

50. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012 Jan Feb;62(1):10-29. doi: 10.3322/caac.20138. Epub 2012 Jan 4.

51. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004; 351: 1502-1512.

52. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med. 2012;366:2443–2454.

53. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009 May 8;324(5928):787-90.

54. Varn FS, Wang Y, Mullins DW, Fiering S, Cheng C. Systematic Pan-Cancer Analysis Reveals Immune Cell Interactions in the Tumor Microenvironment. Cancer Res 2017;77:1271-82.\

55. Zhao, X., et al., *Abstract CT101: A model-based exposure-response (E-R) assessment of a nivolumab (NIVO) 4-weekly (Q4W) dosing schedule across multiple tumor types.* Cancer Research, 2017. **77**(13 Supplement): p. CT101-CT101.