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A Phase II, Randomized, Double-blind Study of Sipuleucel-T Followed by IDO Pathway Inhibitor, Indoximod, or Placebo in the Treatment of Patients With Metastatic Castration-resistant Prostate Cancer

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BACKGROUND

- Prostate cancer is the most common solid tumor malignancy in men in the United States,[1] and androgen deprivation therapy, either through surgical or medical castration, is the standard treatment for metastatic or recurrent disease[2]
- Over time, castration-resistant disease often develops[2]; therefore, alternate treatment options are needed for this group of men with metastatic castration-resistant prostate cancer
- Sipuleucel-T (Provenge®) is the first therapeutic cancer vaccine approved in the United States and consists of peripheral blood mononuclear cells activated with a custom prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor fusion protein (PA2024)[3]
  - Sipuleucel-T has been shown to improve median overall survival by 3 to 4 months versus placebo in randomized, double-blind, phase III clinical trials and is very well tolerated, with mostly grade 2 side effects that are consistent with cytokine release[3,4]
- Tumor-mediated immune suppression by activation of inhibitory regulatory T cells poses a challenge for vaccine development[5-7]
- Indoleamine 2,3-dioxygenase (IDO) is a key immune-modulatory enzyme that degrades tryptophan to kynurenine[8,9]
  - The IDO pathway is a key counterregulatory mechanism that is exploited by tumors in order to prevent and defeat antitumor immunity
- Small-molecule inhibitors of the IDO pathway, such as indoximod (1-methyl-D-tryptophan), are an increasingly validated class of potential cancer therapeutics

OBJECTIVES

- The primary objective of this study was to assess whether inhibition of the IDO pathway by indoximod could augment the sipuleucel-T immune response
- Secondary objectives included assessment of safety and efficacy and improvements in health-related quality of life (HRQoL) while on therapy
- Preliminary results of this study are presented here

METHODS

Study Design

- This study was a randomized, double-blind, multi-institutional, phase II, therapeutic study of indoximod or placebo after the completion of standard of care sipuleucel-T in men with asymptomatic or minimally symptomatic metastatic prostate cancer that is castration resistant (hormone refractory)
- Following the completion of standard of care sipuleucel-T (ie, the day after the third and final sipuleucel-T infusion/leukapheresis), patients were randomized in a 1:1 ratio to receive either 2,400 mg/day of oral indoximod (twice daily) or an identically appearing placebo (twice daily) for 24 weeks, or until unacceptable toxicity or disease progression
- Patients were followed for both disease response until progression and survival for 2 years from study enrollment

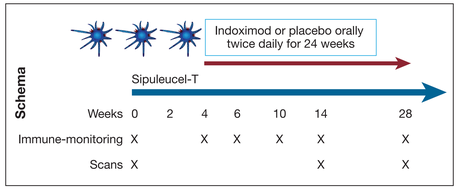
Key Eligibility Criteria

- Castration-resistant disease despite surgical or medical castration, as demonstrated by ≥1 of the following:
  - Prostate-specific antigen (PSA) progression (defined as 2 consecutive PSA measurements ≥14 days apart, ≥2.0 ng/mL, and ≥50% above the minimum PSA during castration therapy or above pretreatment value if no response)
  - Progression of measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST; ≥20% increase in the sum of the diameters of all target lesions or the development of any new lesions)
  - Progression of nonmeasureable disease based on imaging studies
- At study enrollment, serum PSA ≥2.0 ng/mL and castration levels of testosterone ≤50 ng/dL
- Planned standard of care treatment with sipuleucel-T
- Asymptomatic or minimally symptomatic disease, as demonstrated by an Eastern Cooperative Oncology Group performance status of 0 or 1, and no need for opiate pain medications to control cancer-induced pain/symptoms
- Adequate organ function within 14 days of study enrollment

Immune Endpoints

- Immune monitoring was performed throughout the study (**Figure 1**)
- Regulatory T cells, natural killer cells, T-cell subsets, myeloid-derived suppressor cells, and macrophages in the blood were measured by 8-color flow cytometry
- Immune response to PA2024 was measured by an enzyme-linked immunospot (ELISPOT) assay, an enzyme-linked immunosorbent assay (ELISA), and CD54 upregulation
- Ratio of kynurenine to tryptophan was assessed for IDO inhibition
- Optional paired biopsy (pretreatment and Week 14) to assess immune response in tissues with immunohistochemistry

Figure 1. Study schema.



Study Endpoints

- Primary endpoint: augmentation of T-cell activation to PA2024 as measured by ELISPOT at 14 weeks from first leukapheresis
- Secondary endpoints
  - Antibodies to PA2024 as measured by ELISA
  - Progression-free survival (PFS)
  - Objective response rate as defined by Prostate Cancer Working Group 2
  - Overall survival and survival at 2 years
  - Safety, tolerability, and pharmacokinetics
  - HRQoL
- Other assessments: measurement of circulating tumor cells

RESULTS

- Forty-six patients were enrolled and randomized to receive indoximod (n = 22) or placebo (n = 24)
- Patients were well balanced at baseline between the 2 treatment arms (**Table 1**)
- 40% of patients were able to complete 6 months of therapy in the indoximod arm as compared to 25% in the placebo arm, with fewer patients progressing in the indoximod arm
- No significant differences in adverse events were observed in patients receiving indoximod or placebo
- Fold change in PSA from baseline is trending lower in the indoximod arm (**Table 2**)

Table 1. Patient Demographic and Baseline Characteristics

	Placebo	Indoximod
Age, y	68.765	68.445
Median (range)	(58.06-85.47)	(49.34-89.64)
ECOG performance status, %		
0	79.17	68.18
1	20.83	31.82
PSA, g/mL	14	14.25
Median (range)	(2.26-50.6)	(2.46-211.86)

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

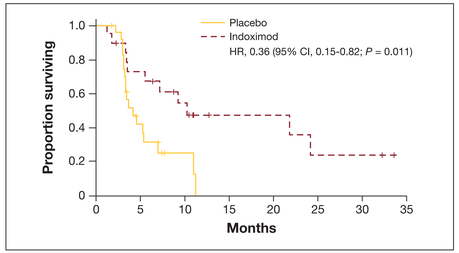
Table 2. Fold Change in PSA at Week 14 Compared to Baseline

	Placebo	Indoximod
Median	2.9	2.0
First quartile	1.4	1.3
Third quartile	5.4	3.7
Minimum	0.7	0.2
Maximum	12.2	7.7

PSA, prostate-specific antigen.

- Median radiographic PFS was 10.3 months in the indoximod arm compared to 4.1 months in the placebo arm, with a 64% improvement in the risk of progression (HR, 0.36; 95% CI, 0.15-0.82; $P = 0.011$; **Figure 2**)
  - PFS of 4.1 months in the placebo arm was similar to median time to objective disease progression in the sipuleucel-T arm (3.7 months) in the IMPACT study[3]

Figure 2. Radiographic PFS with indoximod versus placebo.



PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

CONCLUSIONS

- **Treatment with indoximod following sipuleucel-T is well tolerated and led to significant improvement in radiographic PFS**
- **No differences in augmentation of the immune response to PA2024, as measured by ELISPOT or ELISA, were observed between the 2 treatment arms, suggesting that this may not be the most informative biomarker for studying the IDO pathway**
- **This PFS improvement justifies a larger randomized study to confirm the results**

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References

1. American Cancer Society. Cancer facts & figures 2017. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html. Accessed May 9, 2017.
2. National Comprehensive Cancer Network. Prostate Cancer (Version 2.2017). https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed April 28, 2017.
3. Kantoff PW, et al. *N Engl J Med.* 2010;363(5):411-422.
4. Higano CS, et al. *Cancer.* 2009;115(16):3670-3679.
5. Colombo MP, Piconese S. *Nat Rev Cancer.* 2007;7(11):880-887.
6. Berinstein NL. *Vaccine.* 2007;25(suppl 2):B72-B88.
7. Copier J, et al. *Eur J Cancer.* 2009;45(8):1424-1431.
8. Prendergast GC. *Oncogene.* 2008;27(28):3889-3900.
9. Metz R, et al. *Oncoimmunology.* 2012;1(9):1460-1468.

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