

# Circulating Tumor Cells and Prostate-Specific Antigen as Response Indicator Biomarkers in Chemotherapy-Naive Patients With Progressive Castration-Resistant Prostate Cancer Treated With MDV3100

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## BACKGROUND

- Availability of reliable indicators of treatment efficacy is a critical unmet need in drug development for castration-resistant prostate cancer (CRPC).
- Overexpression of the androgen receptor (AR) is frequent and believed to contribute to the progression of CRPC.<sup>1,2</sup>
- MDV3100 is a novel oral AR antagonist selected for activity against prostate cancer model systems with AR overexpression. MDV3100 has a novel mechanism that slows tumor growth and induces cell death in bicalutamide-resistant cancers via three complementary actions: MDV3100 blocks testosterone binding to the AR, impedes AR nuclear translocation, and inhibits binding to DNA. Preclinical data demonstrated that MDV3100 is superior to bicalutamide in each of these three actions.<sup>3</sup>
- MDV3100 induces an apoptotic response in xenograft models of bicalutamide-resistant prostate cancer.<sup>3</sup>
- Antitumor activity of MDV3100 was determined in a Phase 1-2 trial assessing post-therapy changes on prostate-specific antigen (PSA), circulating tumor cells (CTC), soft tissue disease, and bone metastases.<sup>4</sup>
- This poster explores a new PSA-based outcome measure in relation to CTC and time to radiographic progression.

- For this analysis, a "PSA response" was defined as 3 consecutive declines within 12 weeks of the start of treatment.
- CTC counts of <5 per 7.5 mL of blood were considered favorable and CTC counts of ≥5 per 7.5 mL of blood were considered unfavorable. A CTC response was defined at 12 weeks as favorable (F) or unfavorable (U).
- Time to radiographic progression was assessed using Prostate Cancer-Clinical Trials Working Group 2 (PCWG2) criteria.<sup>5</sup>
- 48 of 65 patients had CTC counts available at baseline and at 12 weeks of treatment and represent the evaluable patients for this analysis.
- Statistics:
  - Kaplan-Meier method was used to estimate the rate of radiographic progression.
  - The likelihood ratio test from the Cox proportional hazards model was used to determine the factors associated with time to radiographic progression.
  - The concordance probability estimate (CPE) was used to measure the predictive accuracy of the model.

## Patient Characteristics

TABLE 1. Key Inclusion and Exclusion Criteria

Inclusion criteria	
• Pathologic confirmation of prostatic adenocarcinoma	
• Serum testosterone level <50 ng/dL	
• Progressive disease defined as one or more of the following: <ul style="list-style-type: none"> <li>- Three rising PSA levels; screening PSA ≥2 ng/mL</li> <li>- Soft tissue progression by RECIST</li> <li>- Two or more new lesions on bone scan</li> </ul>	
Exclusion criteria	
• Metastases to brain or active epidural disease	
• History of another malignancy within the previous 5 years	
• Inadequate bone marrow, hepatic, or renal function	

TABLE 2. Demographics and Prior Therapy

	Patients
N	65
Age, years	68 (45-93)
PSA (ng/mL)	35 (2-335)
Treatment of primary tumor, n (%)	
Surgery	35 (54%)
Radiation	15 (23%)
No primary therapy	25 (38%)
Prior hormone therapy, n (%)	
1 line	11 (17%)
2 lines	17 (26%)
3 lines	19 (29%)
≥4 lines	18 (28%)
Ketoconazole	30 (46%)

TABLE 3. Distribution of Tumor Metastases

	Patients (N=65)
Soft tissue	37 (57%)
Evaluable by PCWG2 criteria <sup>5</sup>	25 (38%)
Bone	41 (63%)
Rising PSA only	6 (9%)

PCWG2, Prostate Cancer Clinical Trials Working Group 2.

## RESULTS

### PSA Changes

FIGURE 2. Waterfall Plot of Maximum PSA Change from Baseline

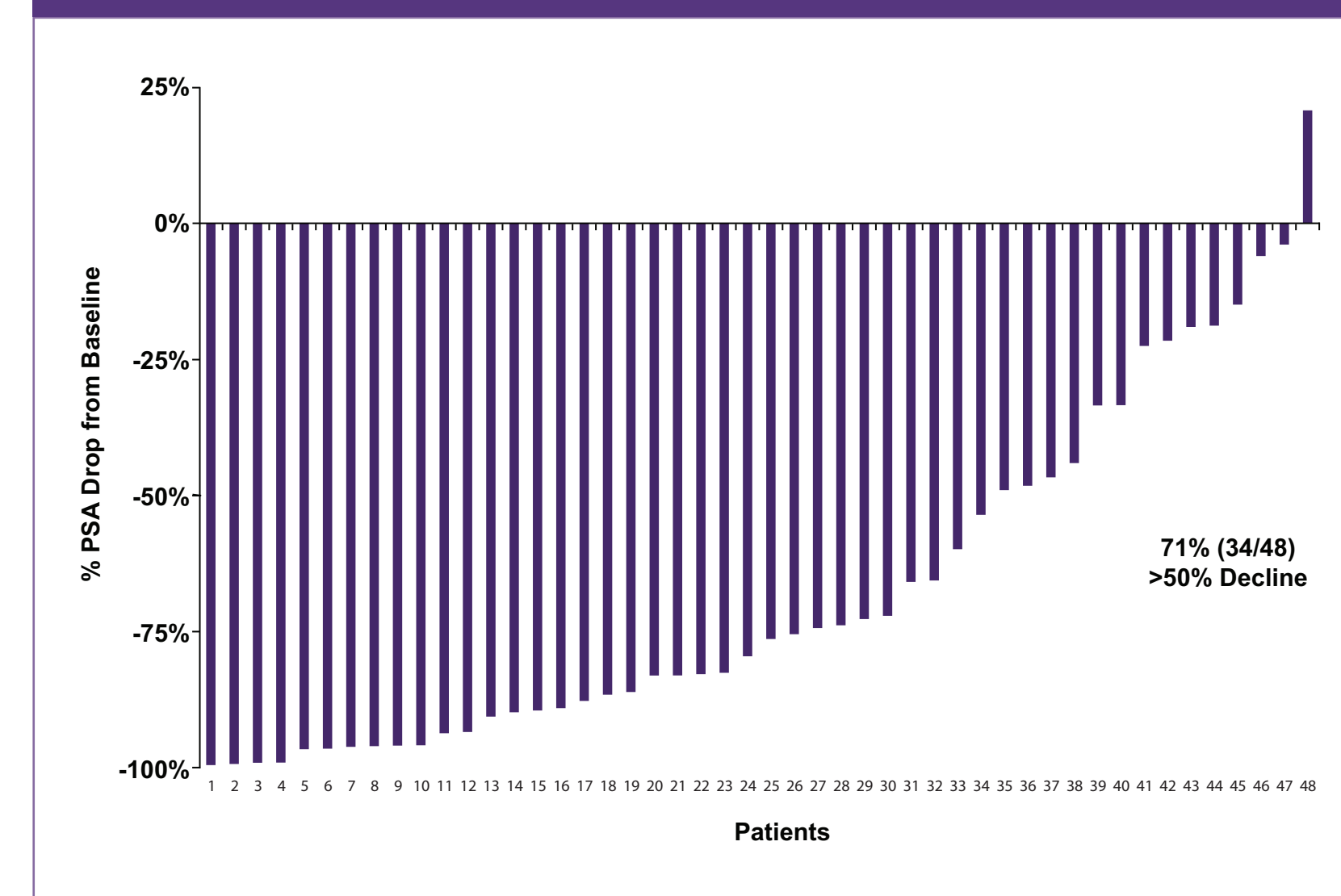
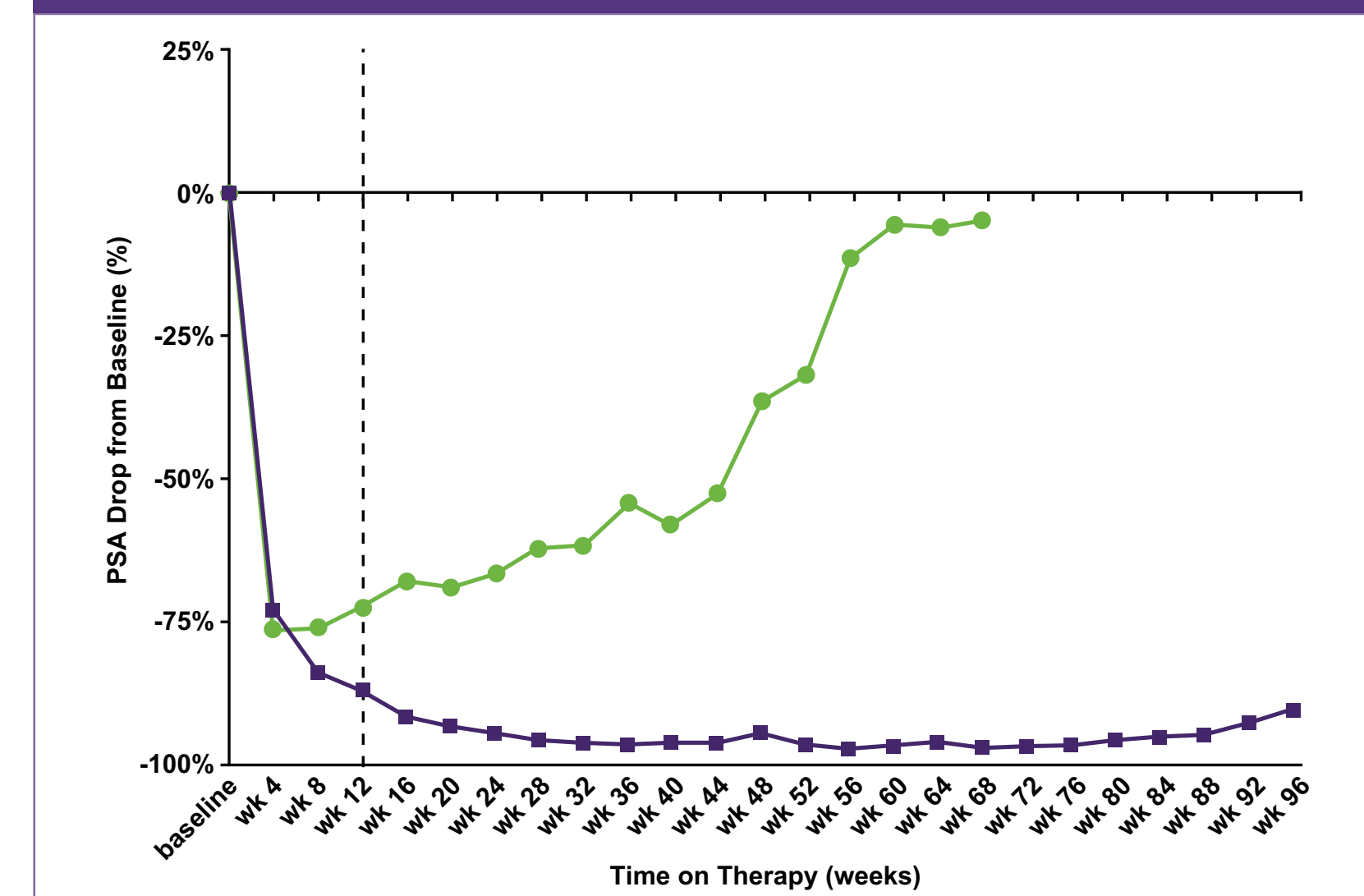


FIGURE 3. Example of a Patient With 3 Consecutive PSA Declines (Purple) and a Patient With <3 Consecutive PSA Declines (Green)



### CTC Changes

TABLE 4. CTC Counts at Baseline and Week 12

Baseline CTC	Week 12 CTC
< 5 CTC; N=38	< 5 ; N=36 (95%)
	≥ 5 ; N=2 (5%)
≥ 5 CTC; N=10	< 5 ; N=9 (90%)
	≥ 5 ; N=1 (10%)

### Time to Radiographic Progression

FIGURE 4. Radiographic Progression vs. 3 Consecutive PSA Declines

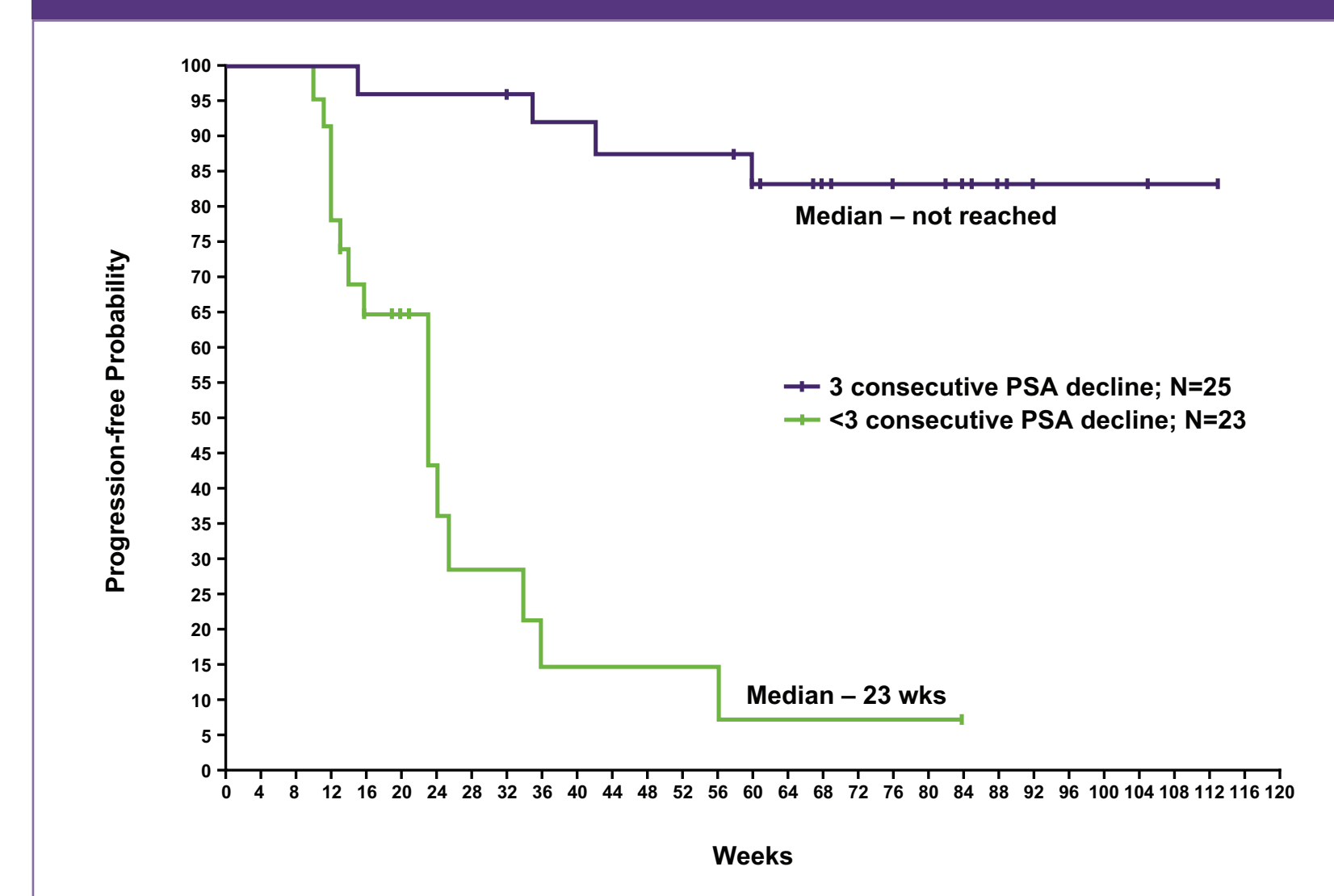
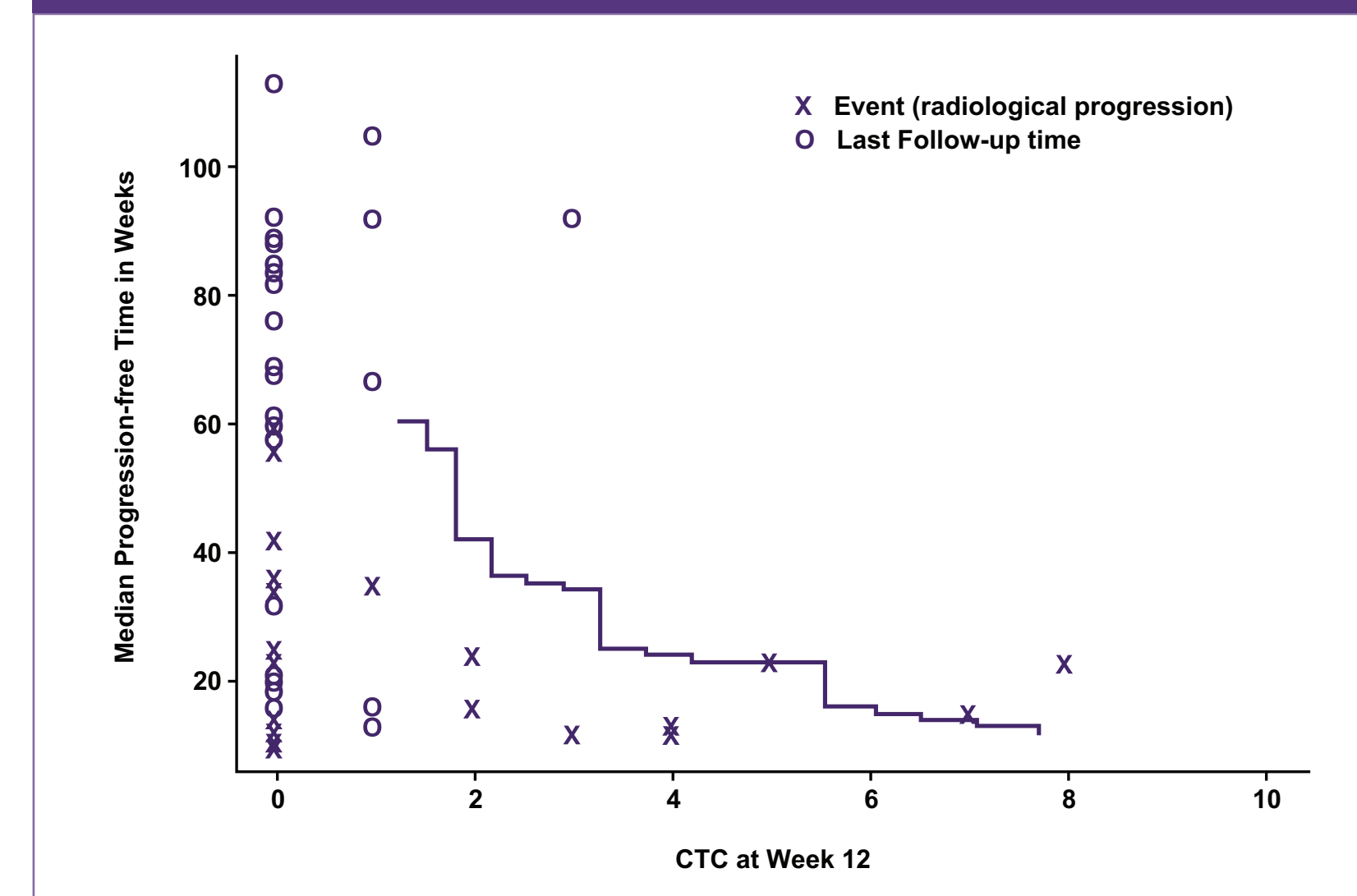


FIGURE 5. Radiographic Progression vs. CTC Count at Week 12



- Radiographic Progression Free probability at 12 months was 0.56 (95% CI: 0.43, 0.73) with a median follow-up of 13 months (2.4-26).
- PSA response and CTC enumeration at 12 weeks were significant predictors of time to radiographic progression ( $P < 0.001$ ).
- The concordance probability estimate (CPE) for joint model (CTC enumeration and PSA response) was 0.78, significantly higher than a model with each factor alone:
  - CTC at 12 weeks - CPE = 0.63
  - PSA response - CPE = 0.72

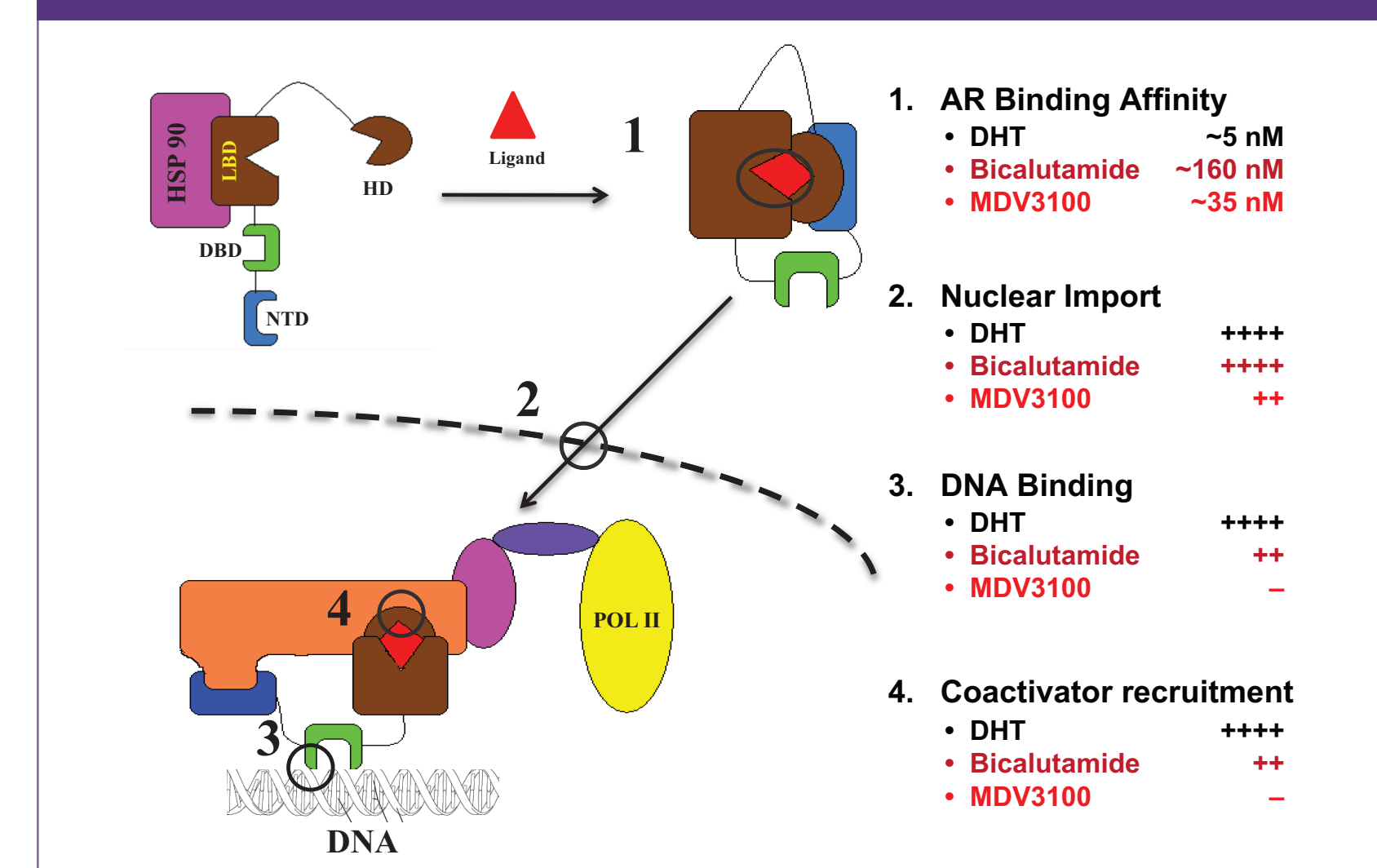
## CONCLUSIONS

- MDV3100 is active in advanced prostate cancer as demonstrated by PSA, CTC, and imaging.
- Sustained PSA declines are consistent with the observed preclinical apoptotic response.
- Both the PSA and CTC outcomes were associated with time to radiographic progression and may provide unique information.
- The joint model of CTC and PSA outcome was most predictive of time to radiographic progression.
- A Phase 3 placebo-controlled survival trial in post-chemotherapy CRPC patients is ongoing. The association of these biomarkers with clinical benefit will be tested prospectively in the Phase 3 trial.

## REFERENCES

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2. Scher HI, Buchanan G, Gerald W, Butler LM, Tilley WD. Targeting the androgen receptor: improving outcomes for castration-resistant prostate cancer. *Endocr Relat Cancer.* 2004;11:459-476.
3. Tran C, Ouk S, Clegg NJ, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science.* 2009;324:787-790.
4. Scher HI, Beer TM, Higano CS, et al. Antitumor activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet.* 2010;375:1437-1446.
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FIGURE 1. Effects of MDV3100 on the Androgen Receptor are Distinct From Bicalutamide



## METHODS

- This Phase 1-2 study was conducted at 5 centers in the United States.
- 65 chemotherapy-naive patients with progressive CRPC were treated at doses of 30 mg/day to 360 mg/day.
- PSA levels were measured monthly; CTC counts were assessed at baseline and at weeks 4 and 12 using the CellSearch assay.