

Circulating Tumor Cells and Prostate-Specific Antigen as Response Indicator Biomarkers in Patients With Progressive Castration-Resistant Prostate Cancer Treated With MDV3100: Toward the Development of a Biomarker Basket

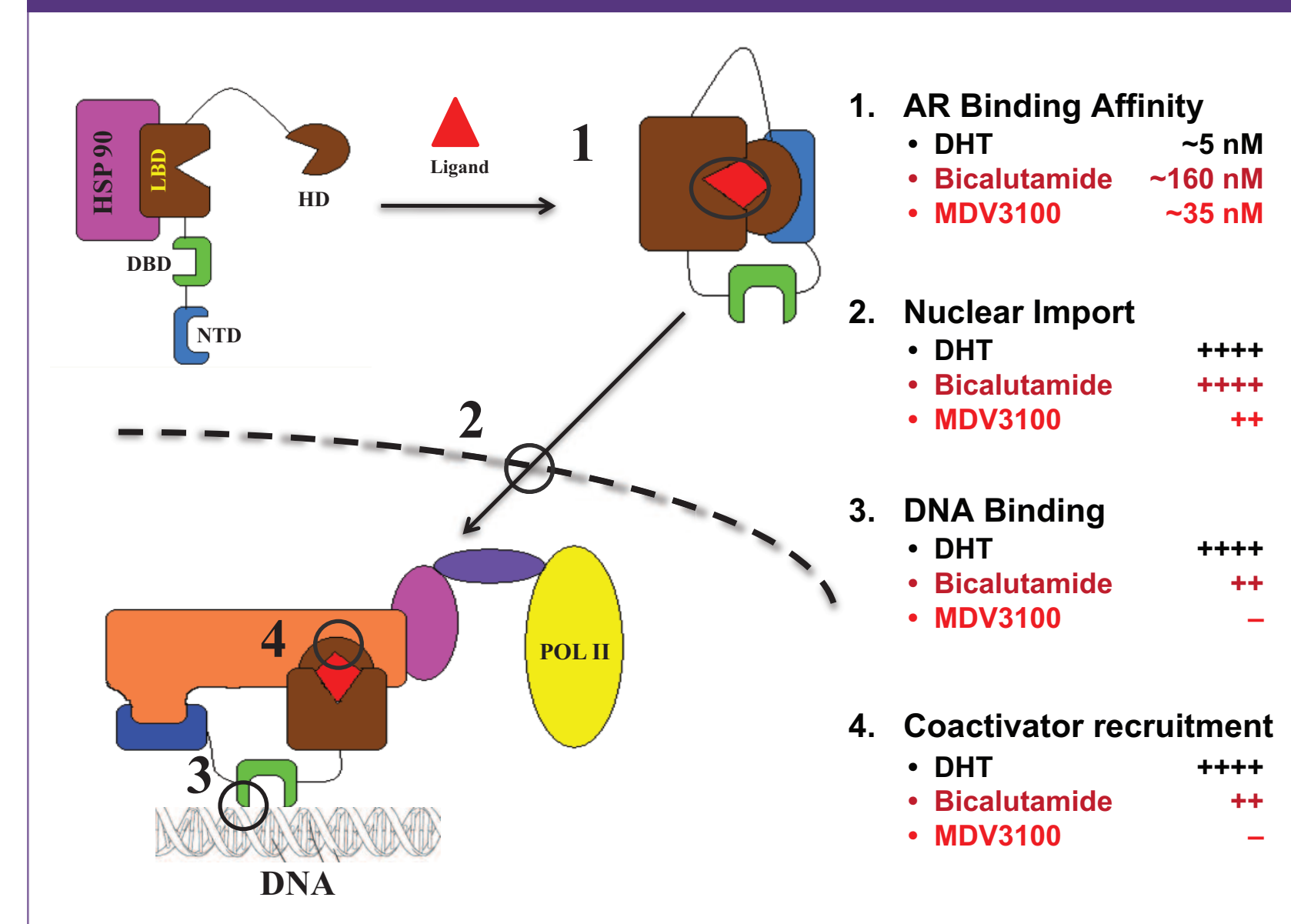
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BACKGROUND

- 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 has been linked to the progression of CRPC.^{1,2}
- MDV3100 is a novel AR antagonist selected for activity against prostate cancer model systems with AR overexpression. Unlike bicalutamide, MDV3100 also inhibits AR function by blocking nuclear translocation and DNA binding of AR, and has no known agonist activity in the setting of AR overexpression.³
- MDV3100 induces an apoptotic response in xenograft models of bicalutamide-resistant prostate cancer.³
- Antitumor activity of MDV3100 was determined in a Phase 1-2 trial assessing post-therapy changes on prostate-specific antigen (PSA), circulating tumor cell (CTC) count, soft tissue disease, and bone metastases.
- We explored a new PSA-based outcome measure, based on the effects of the drug in model systems in relation to CTC and time to radiographic progression.

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.
- 140 patients with progressive CRPC were treated at doses of 30 mg/day to 600 mg/day.
- Monthly PSA levels, CTC counts at baseline, week 4 and week 12, and bone and soft tissue imaging every 12 weeks were assessed.
 - For this analysis, a "PSA response" was defined as 3 consecutive declines within 12 weeks of the start of treatment.

- CTC enumeration was performed with the FDA-cleared CellSearch assay in a Clinical Laboratories Improvement Amendments (CLIA)-certified laboratory. CTC counts of <5 per 7.5 mL of blood at week 12 were considered favorable (F) and CTC counts of ≥5 per 7.5 mL of blood were considered unfavorable (U).
- Time to radiographic progression was assessed using Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria.⁴

- The association of the individual biomarkers to radiographic progression and the concordance rates between biomarkers were examined using a 12-week landmark time analysis.
- 105 of 140 patients reached the 12-week landmark. Of these, 96 patients were evaluable for CTC response as they had CTC counts pre- and post-treatment.

Patient Characteristics

TABLE 1. Key Inclusion and Exclusion Criteria

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

TABLE 2. Demographics and Prior Therapy

	Patients
N	140
Age, years	68 (44–93)
PSA (ng/mL)	50 (2–2,159)
Treatment of primary tumor, n (%)	
Surgery	42 (30%)
Radiation	37 (26%)
No primary therapy	61 (44%)
Prior hormone therapy, n (%)	
1 line	32 (23%)
2 lines	42 (30%)
3 lines	37 (26%)
≥4 lines	29 (21%)
Ketoconazole	63 (45%)
Prior Chemotherapy, n (%)	
None	65 (46%)
Any	75 (54%)

TABLE 3. Distribution of Tumor Metastases

	Patients (N=140)
Soft tissue	92 (66%)
Evaluable by PCWG2 criteria ⁴	59 (42%)
Bone	109 (78%)
Rising PSA only	7 (5%)

Sixty eight patients had both bone and soft tissue disease. PCWG2, Prostate Cancer Clinical Trials Working Group 2.

RESULTS

PSA Changes

FIGURE 2. Waterfall Plot of Week 12 PSA Change from Baseline

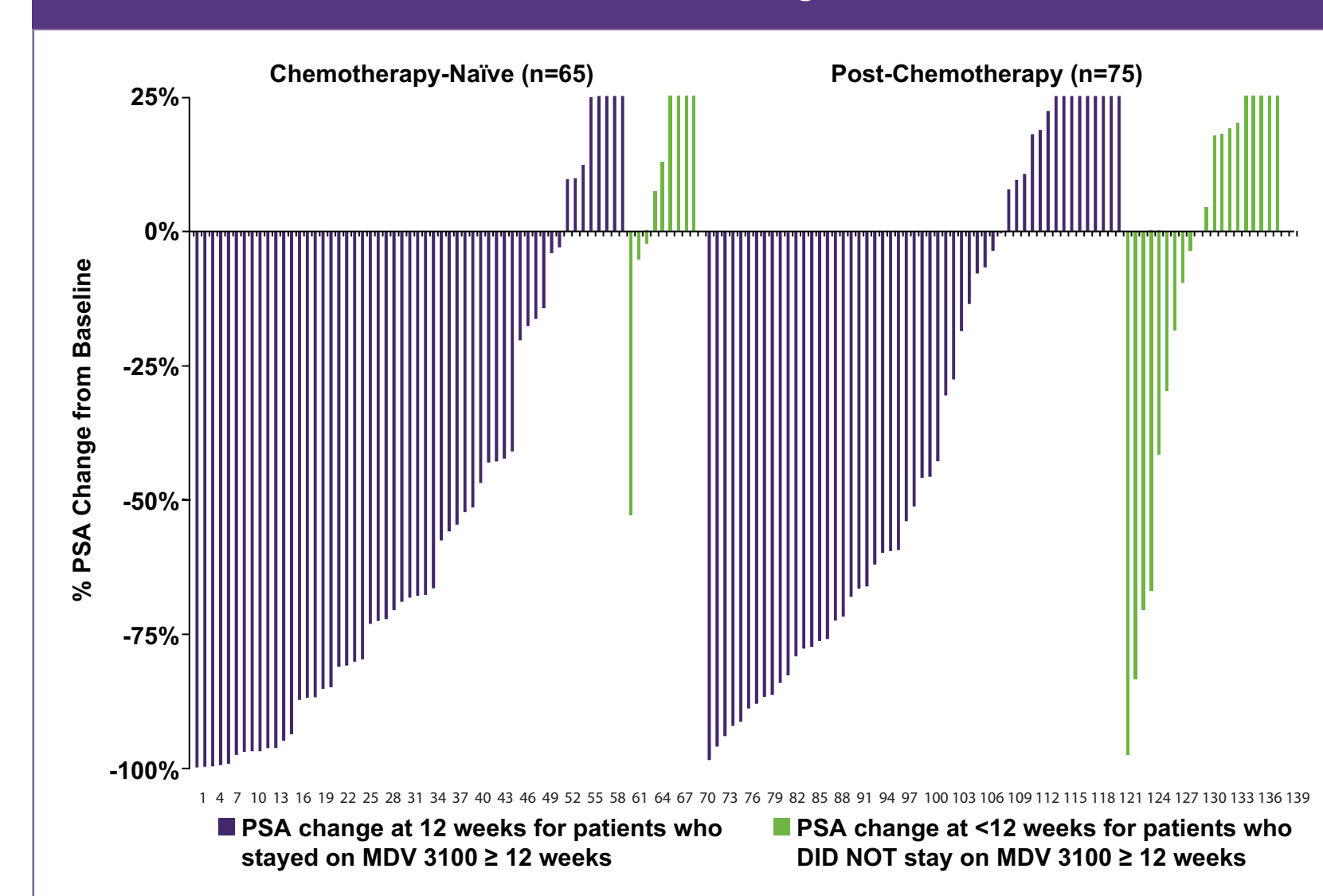
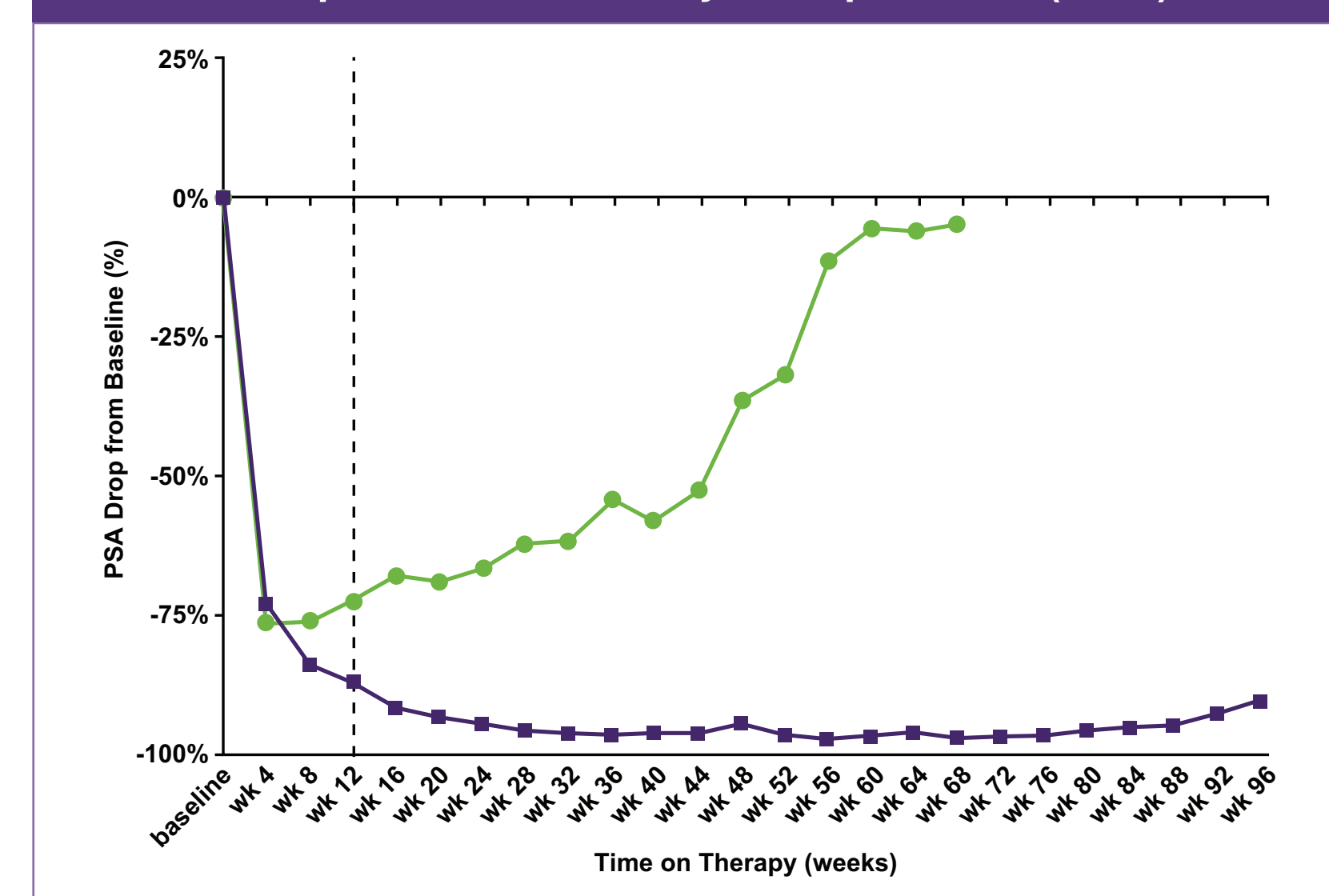


FIGURE 3. Examples of Two Response Types: Rapid Sustained Decline (Purple) and Rapid Decline Followed by Slow Upward Drift (Green)



Time to Radiographic Progression

FIGURE 4. Time to Radiographic Progression by PSA Response

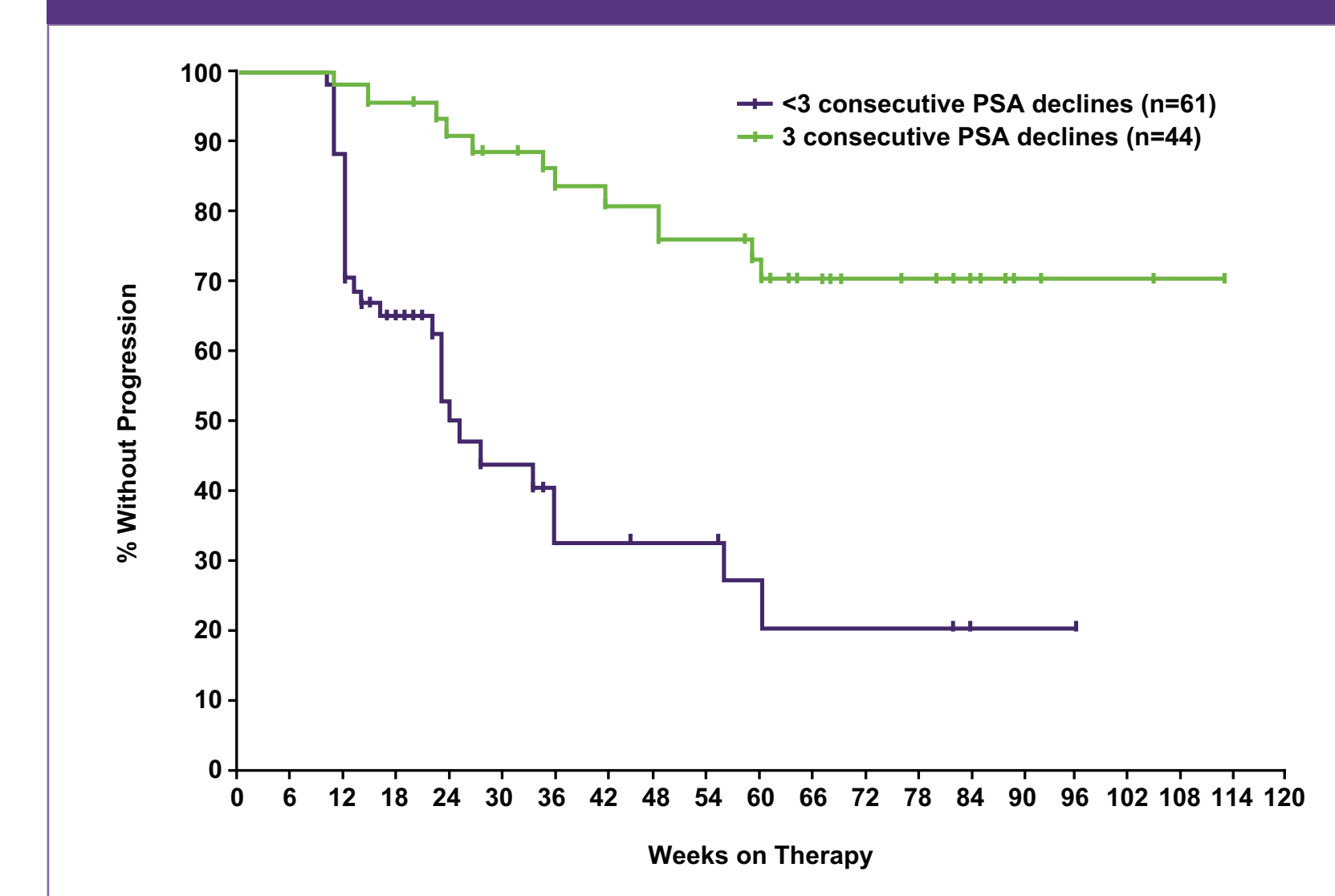


FIGURE 5. Time to Radiographic Progression by CTC Response

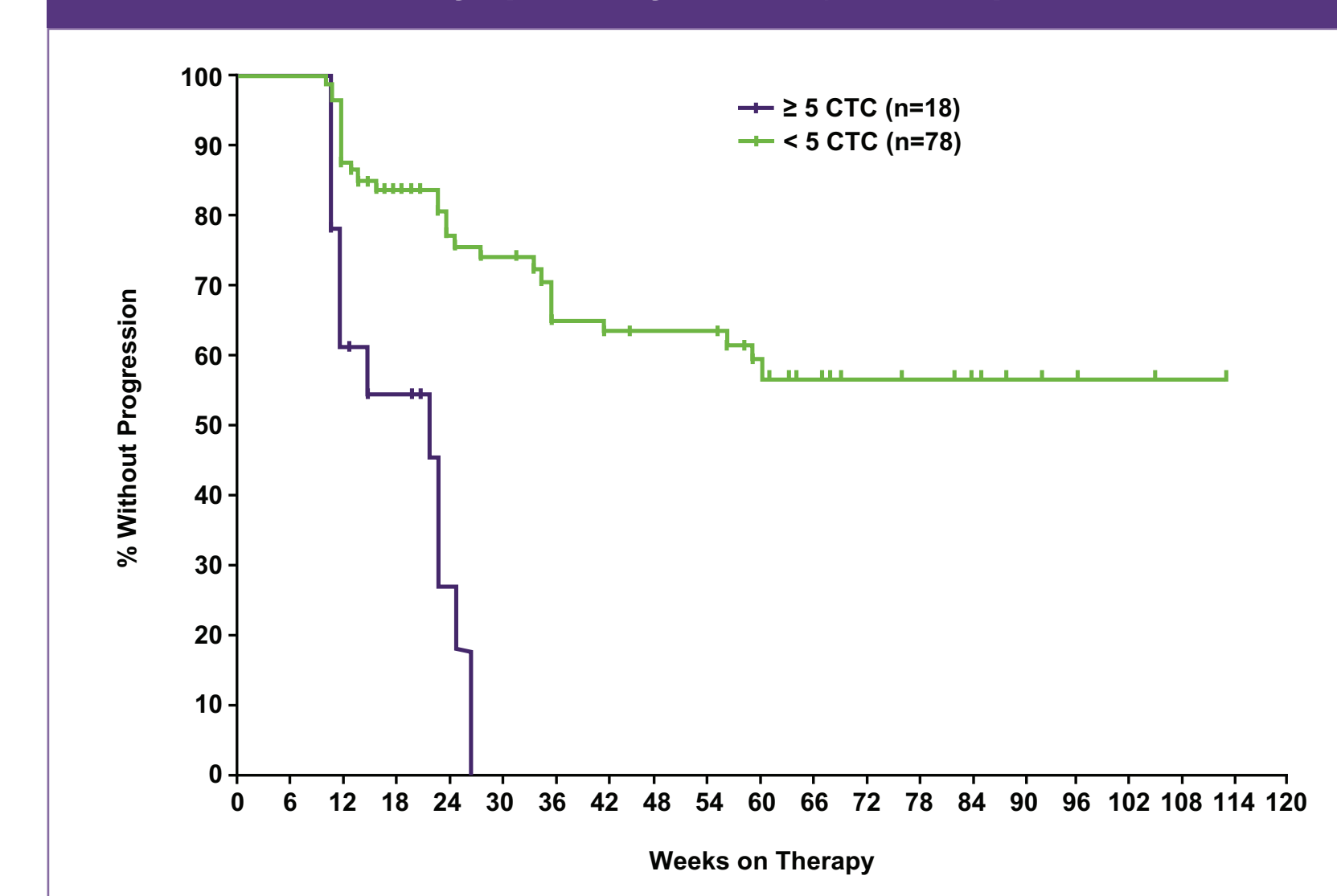


TABLE 4. "PSA Response" and CTC Number in Relation to the Time to Radiographic Progression

3 consecutive PSA declines (n=44)	Not reached
<3 consecutive PSA declines (n=61)	25 weeks
CTC response – favorable (n=78)	Not reached
No CTC response – unfavorable (n=18)	22 weeks

Concordance Between PSA and CTC

- There was nominal agreement (48% discordance) between CTC and PSA (Kappa 0.15), as presented in Table 5.

TABLE 5. Concordance Between PSA and CTC

PSA response	CTC response		
	CTC evaluable	F (< 5)	U (≥ 5)
Total (n=105)	96	78	18
Responders (n=44)	38	35	3
Non-responders (n=61)	58	43	15

PSA response was defined as 3 consecutive declines within 12 weeks of the start of treatment.

CONCLUSIONS

- MDV3100 is active in advanced prostate cancer before and after chemotherapy as demonstrated by PSA, imaging, and CTC counts.
- A "PSA response," defined as three progressive declines from baseline, was modestly associated with CTC changes.
- Both the PSA and CTC outcomes were associated with time to radiographic progression and may provide unique information.
- A Phase 3 placebo-controlled survival trial in post-chemotherapy CRPC patients is ongoing. The association of these and other biomarkers with clinical benefit will be tested prospectively in the Phase 3 trial.

REFERENCES

1. Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nat Med.* 2004;10:33-39.
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, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26:1148-1159.