

A Phase 2 Study of the Combination of PLK1 Inhibitor, Onvansertib, with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer

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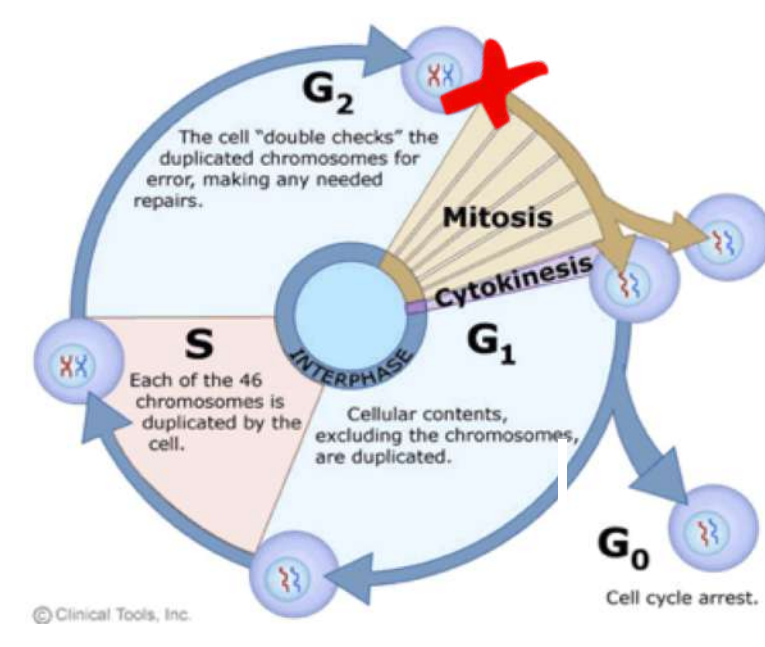
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Background

Polo-like Kinase 1 (PLK1):

- Serine/threonine kinase, master regulator of cell-cycle progression¹
- Controls G2/Mitosis (G2/M) checkpoint¹
- Inhibition of PLK1 causes mitotic arrest and subsequent cell death¹
- PLK1 is overexpressed in prostate cancer and linked to higher tumor grades²
- Emerging data demonstrates PLK1 is also a key regulator of cellular functions beyond mitosis that are essential for tumor growth
 - Biosynthesis of DNA
 - DNA Damage Response



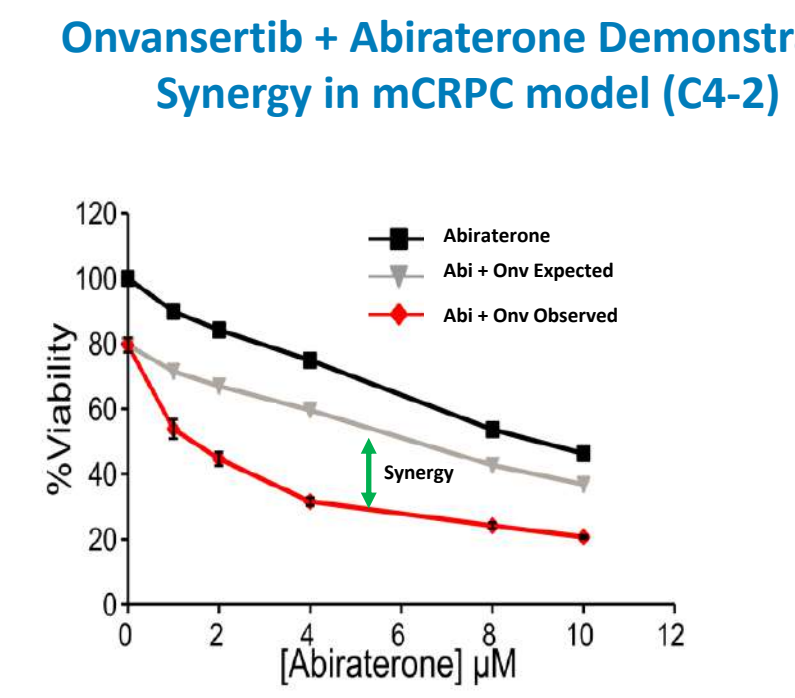
Onvansertib (also known as PCM-075 and NMS-1286937):

- First-in-class, third-generation, orally-bioavailable, highly-selective PLK1 inhibitor with a ~24-hour half-life
- Phase I study in solid tumors established the recommended phase 2 dose (RP2D) at 24 mg/m²

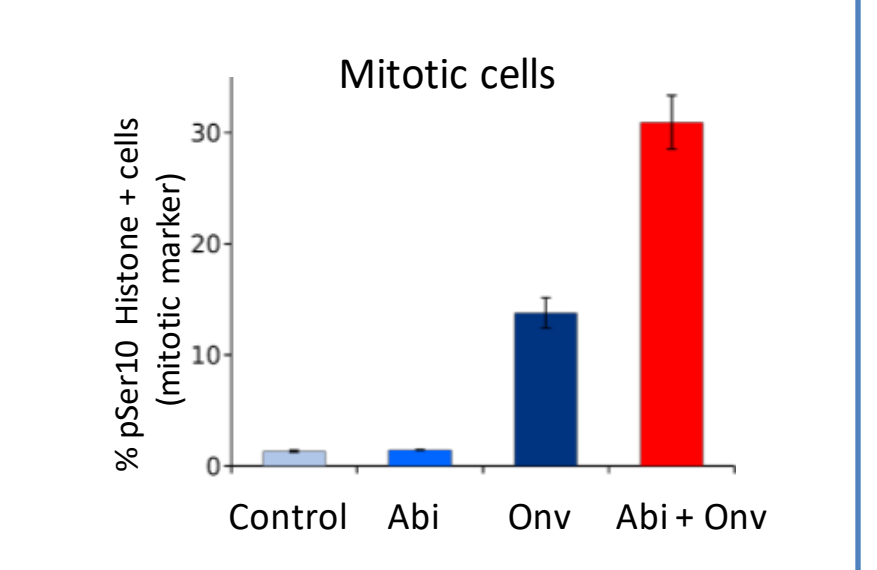


PLK Inhibitor Synergizes with Abiraterone in Preclinical Models

- Onvansertib induces synergistic cell death and mitotic arrest in combination with abiraterone in a castration-resistant prostate cancer (CRPC) model (C4-2)
- Combination of PLKi and abiraterone blocks tumor growth and PSA increase in a CRPC xenograft model³



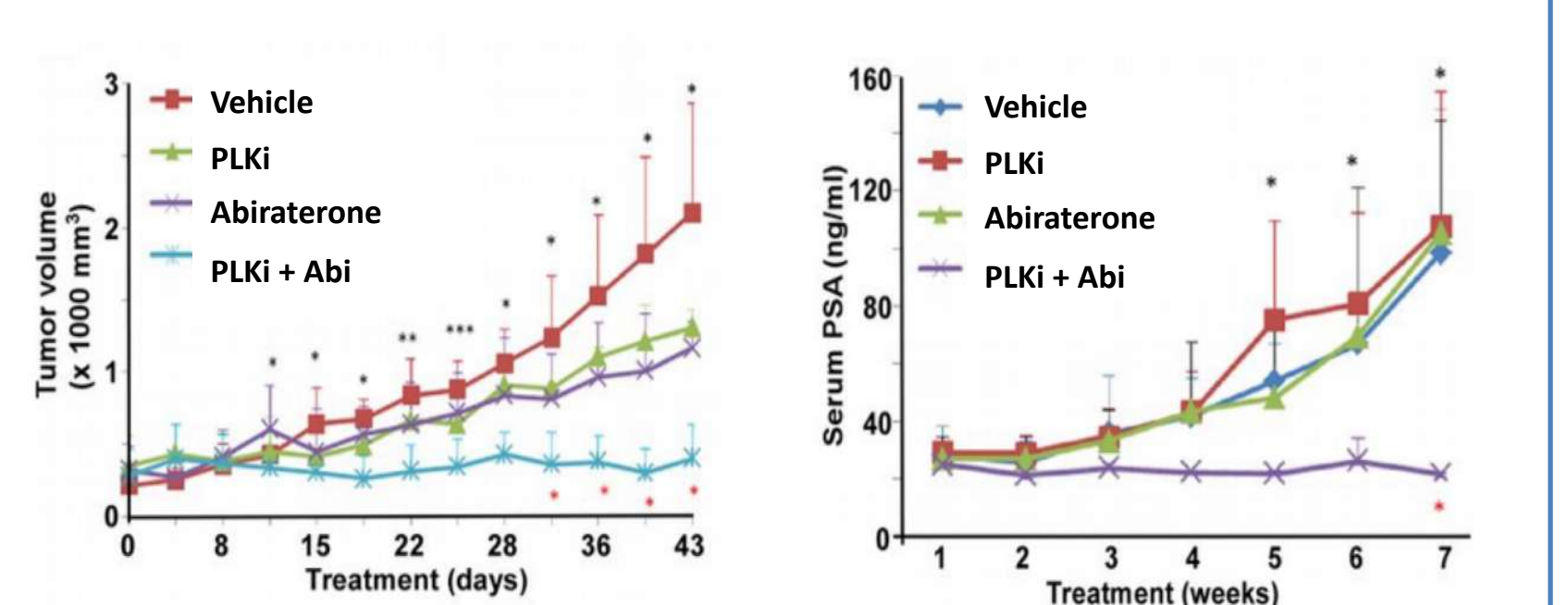
Onvansertib + Abiraterone Significantly Increase Mitotic Arrest



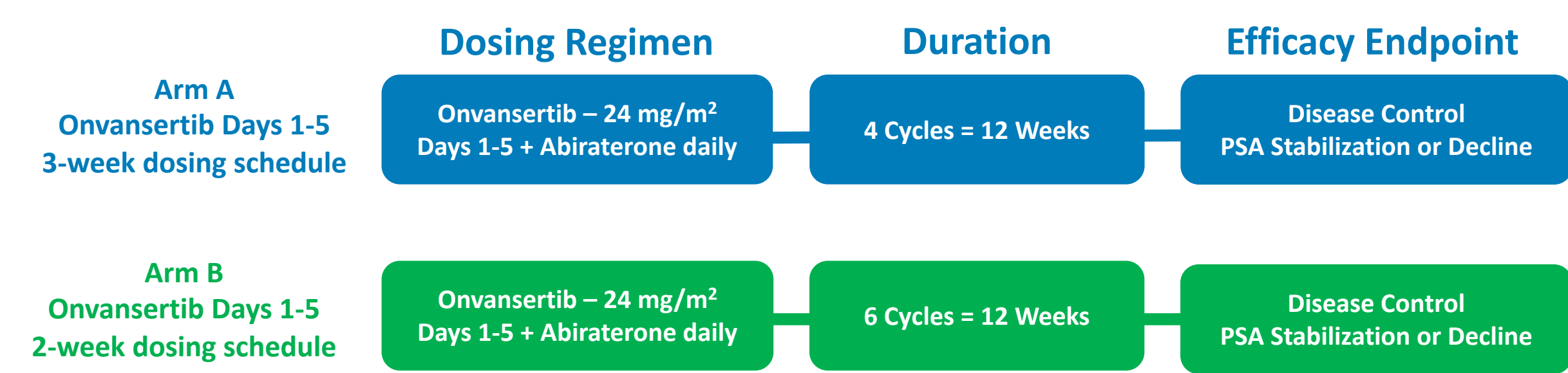
Androgen Receptor Variant 7 (AR-V7)

- AR-V7+ detection in CTCs is associated with abiraterone resistance⁴
- AR-V7+ has a shorter progression-free survival and overall survival in mCRPC intent-to-treat with abiraterone⁵
- Combination of abiraterone and PLK inhibitor (PLKi) reduces AR and AR-V7 protein expressions in CRPC cell lines³

PLK1 inhibitor and Abiraterone Blocks Tumor Growth and PSA Increase in an AR-V7 Positive CRPC Model (LuCaP35CR)



Phase 2 Trial (NCT03414034) Design and Objectives



Eligibility Criteria

- Inclusion:**
- First-line abiraterone treatment and response (in castration-sensitive or castration-resistant setting)
 - Initial signs of abiraterone resistance defined as 2 rising PSAs; one rise of ≥ 0.3 ng/mL and one confirmatory value not showing decline, separated by 1 week
- Exclusion:**
- Prior treatment with either enzalutamide or apalutamide
 - Rapidly progressive disease or significant symptoms related to disease progression

Efficacy Endpoints

- Disease control assessed by prostate-specific antigen (PSA) decline or stabilization pre- and post-treatment
- Changes in PSA relative to baseline following the addition of onvansertib to abiraterone
- Radiographic response following the addition of onvansertib to abiraterone
- Time to PSA and radiographic progression following the addition of onvansertib to abiraterone

Correlative Endpoints

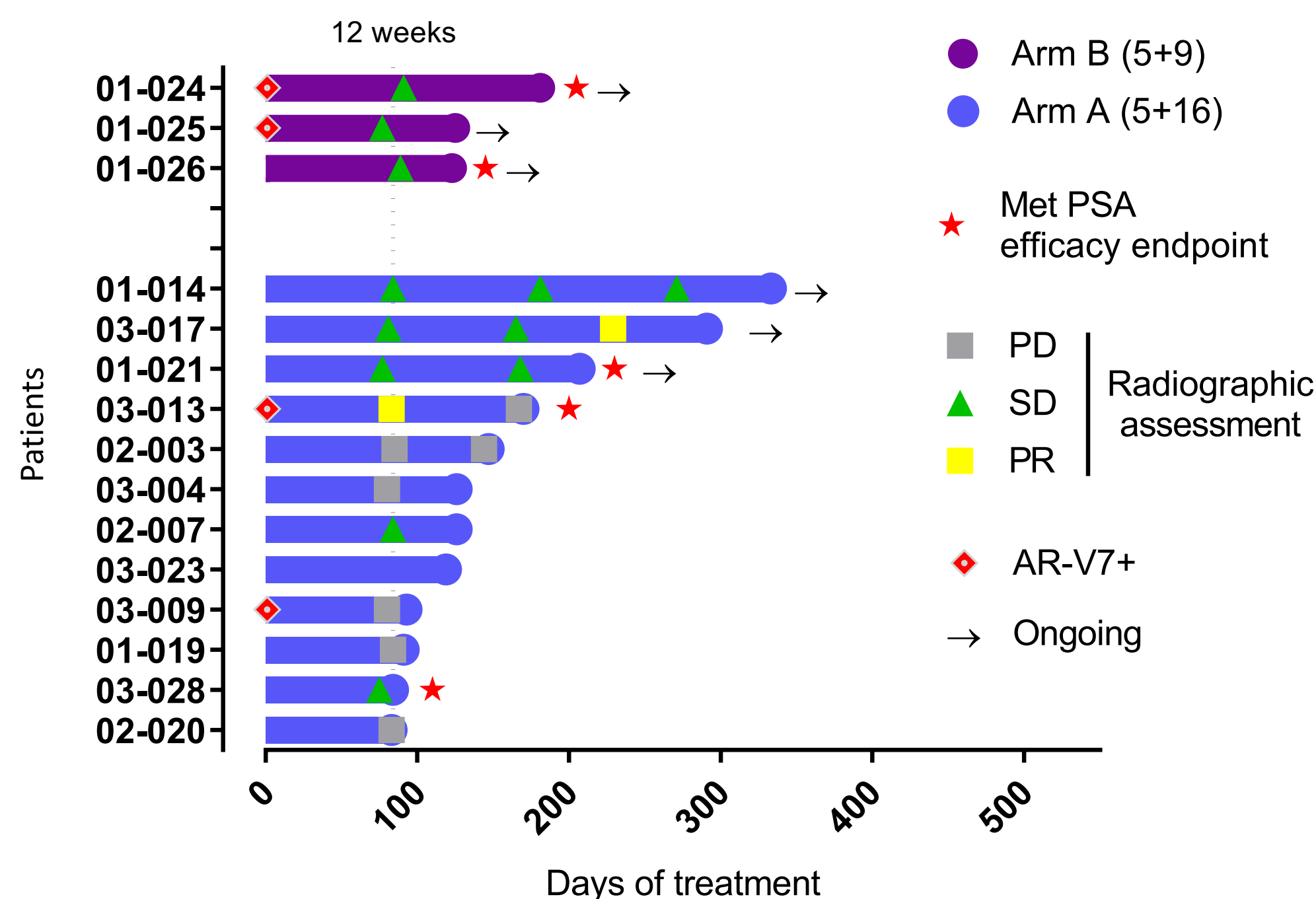
- Analysis of circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) to identify potential biomarkers of response
- Analysis of CTCs to assess AR-V7 status at baseline using the EPIC and Johns Hopkins University (JHU) testing platforms
- Analysis of ctDNA to identify genomic alterations

Enrollment Status (as of October 28th 2019):

	Number of patients (N)	Arm A	Arm B
Subjects Treated		24	6
Subjects Completing 12-weeks of Treatment		12	3
Subjects Currently on Treatment		6	5
AR-V7+ Subjects (Epic or JHU)		4	3

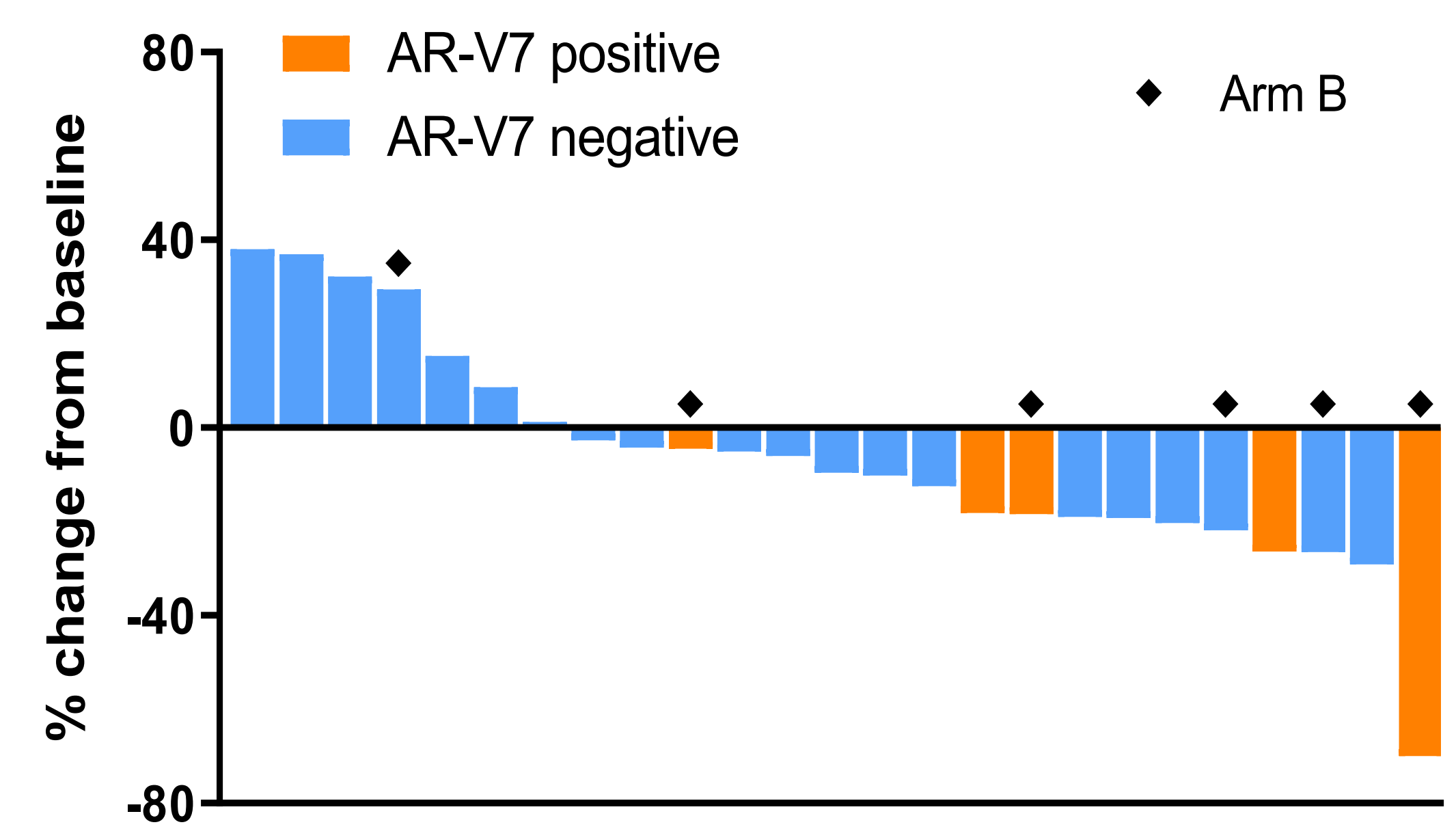
Efficacy in Abiraterone-Resistant Patients

Efficacy Observed in 60% of Patients Across Both Arms (A and B)



- 9 of 15 (60%) of patients achieved partial response (PR) or stable disease (SD) following 12 weeks of treatment with onvansertib + abiraterone. Response to treatment was evaluated based on PSA values (primary endpoint) and radiographic scans.
 - Arm B (n=3):**
 - 3 out of 3 patients had stable disease (SD) with 2 of 3 achieving primary efficacy endpoint; all patients remain on treatment (>120 days/>4 months)
 - 14-day dosing schedule (50% greater drug exposure to onvansertib) suggests that a shorter dosing schedule (vs Arm A) maximizes response to treatment
 - Arm A (n=12):**
 - 6 out of 12 patients had stable disease (SD) or partial response (PR) with 3 of 12 patients achieving the primary efficacy endpoint
 - 3 patients remain on treatment and have been on treatment for >200 days (>7 months)

72% of Patients Showing Decrease in PSA (Best PSA Response)



- 18 out of 25 (72%) of patients had decreases in PSA levels with the addition of onvansertib after 1 cycle of treatment
- Initial PSA stabilization or decrease was observed in all AR-V7 positive patients who completed at least 1 cycle of treatment (n=5)
- Among the AR-V7 positive patients who completed 12-weeks of treatment (n=4)
 - 3 of 4 patients had stable disease (SD) or partial response (PR) with 2 patients achieving the primary efficacy endpoint

Safety

Safety Assessment

- Safety lead-in was completed in Arm A at 24 mg/m² and is ongoing in Arm B at 18 mg/m²
- Most frequent AEs were expected, on-target hematological (anemia, neutropenia, thrombocytopenia and WBC decrease), associated with the mechanism of action of onvansertib
- Hematological AEs were easily and effectively managed by dose delay, dose reduction and/or growth factor support
- No unexpected, off-target toxicities have been reported in patients treated to-date

	AE reported in $\geq 10\%$ patients (N=30)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia	7	3	1		11
Neutropenia	1	1	6	3	11
Thrombocytopenia	8	1	0	1	10
WBC decrease	2	1	3	1	7
Hypophosphatemia	2	3	1		6
Fatigue	4				4
Alopecia	3				3
Back pain		3			3
Constipation	3				3
Creatine increase	3				3
Hypertension		1	2		3
Hypokalemia	1	1	1		3

Conclusions and Perspective

- Overall, across both arms (A and B), a 60% response (SD + PR) was observed (n=9/15) in patients evaluable for efficacy (completed 3 months of treatment); 72% of patients (n=18/25) had a decrease in PSA following 1 cycle of treatment; 6 patients remain on treatment for ≥ 4 months
- All 5 AR-V7 positive patients had a decrease in PSA following 1 cycle of treatment with onvansertib; efficacy (SD + PR) observed in 3 out of 4 patients
- In both arms (A and B) onvansertib in combination with abiraterone was safe and well-tolerated
- An alternative Arm C with a more continuous dosing schedule has been proposed (onvansertib 12 mg/m² on days 1-14 of a 21-day cycle) for safety and efficacy evaluation
- The addition of onvansertib to treatment in mCRPC patients with resistance to abiraterone (rising PSA) validates prior pre-clinical studies and shows promise as a new therapeutic option



References:

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