A Phase 2 Study of the Polo-like Kinase 1 (PLK1) Inhibitor, Onvansertib, in Combination with Abiraterone in Patients with Abiraterone-Resistant Metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Background and Clinical Trial Rationale

Polo-like Kinase 1 (PLK1):

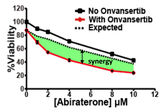
- is a serine/threonine kinase, master regulator of the cell-cycle progression[1]
- controls mitosis entry and progression
- is overexpressed in prostate cancer and linked to higher tumor grades[2]

Onvansertib:

- is an oral and highly-selective PLK1 inhibitor
- induces mitotic arrest and subsequently apoptosis in vitro and in vivo in preclinical models[3]
- is an oral drug with a short half-life (~24h), allowing for flexible dosing schedule[4]
- demonstrated safety and tolerability in solid tumors in a Phase 1 trial[4]

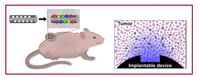
PLK1 inhibition + Abiraterone Demonstrates Synergy in CRPC models

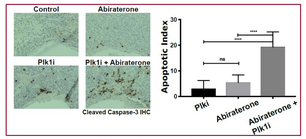
Synergy In Vitro in C4-2 Cells



Cell viability was measured with the CellTiterGlo assay 72h after treatment. The synergy was calculated based on the Bliss Independence model of drug additivity

Synergy In Vivo in C4-2 Xenograft Model



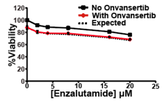


A tumor-implantable device containing multiple microwells generating drug gradients in C4-2 tumor-bearing mice was used. Fixed tumor sections adjacent to the microwells diffusing vehicle, Abi, PLK1i or Abi+ PLK1i were stained with cleaved-caspase 3 to detect apoptotic cells

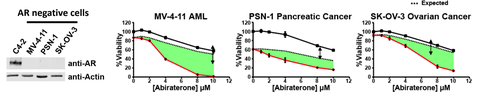
Synergy Between PLK1 Inhibition and Abiraterone is Independent of AR Signaling

- Onvansertib does not synergize with the AR antagonist enzalutamide
- Onvansertib synergizes with abiraterone in AR-negative non-prostate models

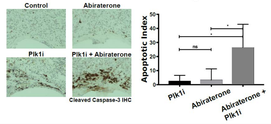
Onvansertib + Enzalutamide in C4-2 Cells



Synergy In Vitro in AR Negative Models



Synergy in vivo in an AR negative model (SK-OV-3)



Phase 2 Trial Design, Objectives and Enrollment (NCT03414034)

Trial Design: Phase 2 multi-center, open label trial in mCRPC

	Dosing Schedule	Duration	Efficacy Endpoint
Arm A n=24	Onvansertib 24 mg/m² Days 1-5 (21-day cycle) + Abi	4 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline
Arm B n=32	Onvansertib 18 mg/m² Days 1-5 (14-day cycle) + Abi	6 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline
Arm C n=32	Onvansertib 12 mg/m² Days 1-14 (21-day cycle) + Abi	4 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline

Enrollment as of September 23rd, 2020

Number of patients (N)	Arm A	Arm B	Arm C
Treated	24	11	4
Completing 12-weeks	14	8	0
Currently on Treatment	1	1	4

Eligibility Criteria: Initial signs of abiraterone resistance defined as 2 rising PSAs; one rise of ≥0.3 ng/mL separated by one week

Exclusion Criteria:

- Prior treatment with either enzalutamide or apalutamide
- Rapidly progressing disease or significant symptoms related to disease progression

Primary efficacy endpoint: Disease control evaluated as PSA decline or stabilization (PSA rise <25% over baseline) after 12 weeks of treatment

Secondary efficacy endpoint: Radiographic response per RECIST v1.1 criteria, time to PSA progression and time to radiographic response

Correlative studies: Analysis of circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) to identify response biomarkers

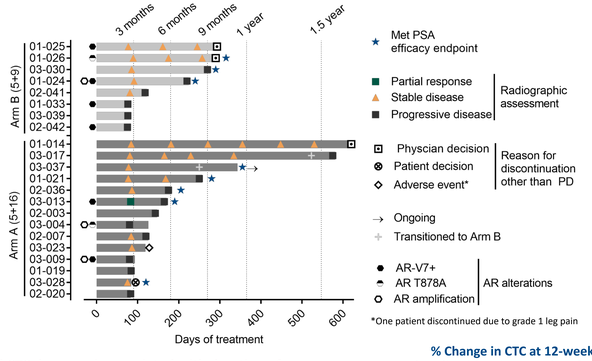
Efficacy

Efficacy Evaluation at 12-Weeks

	Arm A	Arm B
Evaluable for efficacy*	17	9
Completed 12-week treatment	14	8
Progressed within 12 weeks	3	1
Disease control**	5 (29%)	3 (33%)
Radiographic stable disease	9 (53%)	5 (55%)
Durable response (>7 months)	4 (23%)	4 (44%)

* Completed 12 weeks of treatment or progressed within 12 weeks
** Defined as PSA stabilization or decline (PSA rise <25% over baseline)

Clinical course of patients who completed 12 weeks of treatment



*One patient discontinued due to grade 1 leg pain

The combination shows efficacy in patients with AR alterations

AR mechanisms of resistance to abiraterone include the expression of the constitutively active AR splice variant AR-V7, the AR gain of function point mutation T878A and amplification of AR[5]

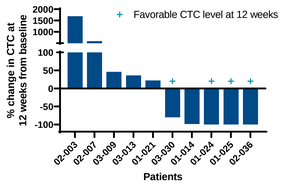
	n (%)
Patients evaluable for efficacy and with at least one AR alteration at baseline*	8
AR-V7+	6
AR T878A mutation	2
AR amplification	3
Disease control	3 (37%)
Radiographic stable disease	4 (50%)
Durable response (>7 months)	3 (37%)

*AR-V7 status was evaluated using the EPIC and Johns Hopkins University testing platforms. Genomic profiling of circulating tumor DNA was performed using Gardant360® test

Treatment-induced CTC decrease is associated with duration of response

- CTC count, reported as favorable or unfavorable (<5 versus ≥5 CTC/7.5mL of blood, respectively) is a prognostic factor for survival in CRPC and the conversion from unfavorable to favorable is associated with improved survival[6]
- At baseline, 27 (73%) of 37 patients had unfavorable CTC count; 10 were re-analyzed after 12 weeks of treatment:
  - 5 (50%) patients had a ≥80% CTC decrease, including 2 AR-V7+ patients
  - 4 (40%) patients converted from unfavorable to favorable CTC level, including 3 patients with no detectable CTC
  - Median time on treatment was 9.2 months for patients with decrease CTC (n=5) vs 4.9 months for patients with increase CTC (n=5)

% Change in CTC at 12-weeks vs baseline in patients with unfavorable CTC level at baseline



Baseline Characteristics and Safety

Baseline Characteristics

Total patients N=39	Median [range] or n (%)
Age, years	72 [54-87]
Nonwhite ethnicity	5 (13%)
ECOG	
0	34 (87%)
1	5 (13%)
Years since diagnosis	5 [1-18]
Grade groups 4 and 5	24 (62%)
De novo metastatic disease	13 (33%)
Presence of bone metastasis	33 (85%)
Presence of visceral metastasis	13 (33%)
Baseline PSA, ng/mL	12.5 [0.6-224]
AR-V7+ at baseline*	9 (23%)
Baseline CTC count per mL of blood**	2.2 [0-87]

ECOG: Eastern Cooperative Oncology Group, AR-V7: androgen receptor variant 7, CTC: circulating tumor cells
*AR-V7 status was evaluated using the EPIC and Johns Hopkins University testing platforms
**CTC count was performed by EPIC

Safety

- Safety lead-in was completed in Arm A at 24 mg/m², in Arm B at 18 mg/m² and in Arm C at 12 mg/m²
- Most frequent Grade 3 and 4 adverse events (AEs) were expected, on-target, reversible hematological (anemia, neutropenia, thrombocytopenia and WBC decrease), associated with the mechanism of action of onvansertib
- Hematological AEs were reversible and effectively managed by dose delay, dose reduction and/or growth factor support

Most Common Treatment-Emergent Adverse Events in Treated Patients (N=39)

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia	10	5	1		16
Thrombocytopenia	11	1		1	13
Fatigue	10	2			12
Neutropenia	1	1	7	3	12
Hypophosphatemia	3	3	4		10
WBC decrease	2	2	3	2	9
Back pain	2	3			5
Hypokalemia	3	1	1		5
Constipation	4	0			4
Nausea	3	1			4

WBC: white blood cells

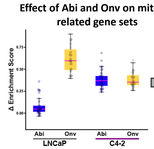
Identifying an Onvansertib-Abiraterone Response Gene Signature

Abiraterone (Abi) induces expression of mitotic-related genes in prostate cancer cells synergistic for onvansertib (Onv) and Abi

C4-2
Synergistic for Abi + Onv
LNCAP
Non synergistic for Abi + Onv

RNA-seq was performed to identify gene sets differentially regulated by Onv and Abi in synergistic vs non-synergistic cells

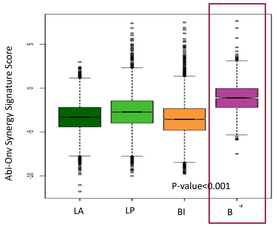
Analysis identified that Abi induces a synergy-specific gene expression signature dominated by mitosis-related gene sets



Based on the synergy-specific gene sets, we defined an Abi-Onv synergy gene signature mostly composed of mitosis-related genes

The Abi-Onv synergy gene signature is enriched in a basal molecular subtype

- Based on transcriptomic analysis of 32,000 prostate cancer specimens, Decipher Biosciences prostate subtyping classifier has characterized 4 molecular subtypes: Luminal A (LA), Luminal Proliferating (LP), Basal Immune (BI) and Basal (B)
- The Abi-Onv synergy gene signature was significantly enriched in the Basal subtype compared to the other subtypes (p<0.001)
- The Basal subtype represents ~1/3 of CRPC patients and is associated with lower responses to standard androgen deprivation therapy
- Hypothesis: patients with Basal subtype tumors may have a greater likelihood to response to the Abi-Onv combination



Determining the utility of tumor transcriptomic profiling to predict clinical response

Archived tissue (biopsy or prostatectomy) → RNA extraction → Gene expression profiling → Correlate clinical response with:

- Patient molecular subtype (e.g., Basal)
- Enrichment for the Abi-Onv synergy gene signature

Conclusions

- Onvansertib + abiraterone demonstrated safety across 3 different dosing schedules and AEs were effectively managed
- Across arms A and B, 26 patients were evaluable for efficacy: 8 (31%) achieved the primary endpoint (PSA stabilization), 14 (54%) had stable disease at 12 weeks and 8 (31%) had a durable response (>7months)
- Three of the 8 patients harboring AR alterations associated with abiraterone resistance achieved disease control and 4 had stable disease
- Onvansertib + abiraterone induced unfavorable-to-favorable CTC conversion, and this conversion was correlated with durable response
- We identified a gene signature associated with onvansertib and abiraterone synergy in prostate cancer cells that is significantly enriched in the basal molecular subtype of prostate cancer patients. The utility of primary tumor transcriptomic profiling to predict clinical response will be further explored

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