Using Our Precision Medicine Strategy to Develop Oncology Drugs That Target Mitosis

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AUGUST 2018

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Strategy for Oncology Drug Development

- Taking a precision cancer medicine approach to develop Onvansertib (PCM-075)
- Leveraging a proven cancer target, PLK1
- Developing a first-in-class, 3rd generation PLK1 inhibitor
- Combining Onvansertib with already approved drugs
  - Phase 1b/2 trial of Onvansertib + cytarabine or decitabine in Acute Myeloid Leukemia (AML)
  - Phase 2 trial of Onvansertib + abiraterone acetate (Zytiga®)/prednisone in metastatic Castration-Resistant Prostate Cancer (mCRPC)

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Onvansertib – Pipeline Within a Molecule
Opportunities in Leukemias/Lymphomas and Solid Tumors

	Preclinical	Phase 1	Phase 2
Leukemias & Lymphomas	Acute Myeloid Leukemia – Orphan Drug Designation in the U.S. *Phase 1b/2 trial in combination with low-dose cytarabine (LDAC) or decitabine*		
	Non-Hodgkin Lymphoma		
	Metastatic Castration-Resistant Prostate *Phase 2 trial in combination with with abiraterone acetate (Zytiga®)/prednisone*		
Solid Tumor Cancers	Lung		
	Colon		
	Ovarian		
	Others (adrenocortical, sarcomas, head and neck, skin, liver, pancreatic, ampullary)		
	Triple Negative Breast		

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Licensed Drug Candidate from NMS
Onvansertib – Polo-like Kinase 1 (PLK1) Inhibitor

NERVIANO MEDICAL SCIENCES

Oncology Drug Discovery

- Largest oncology research and development company in Italy
- Developed anthracycline class of drugs (doxorubicin)
- Leader in protein kinase drug development (Polo-like Kinase Inhibitors)
- Identification and validation of molecular targets focused on driver oncogenes
- Excellent track record licensing innovative drugs to pharma/biotech companies including: Genentech (Roche), Ignyta (Roche), Novartis

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Developing Oncology Drugs That Target Mitosis

- Licensed global development and commercialization rights for Onvansertib
- Nerviano will continue manufacturing GMP API and finished drug
- Two active INDs in place with the FDA
- Financing in place to advance clinical trial program into mid-2019

IND = Investigational New Drug

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Leveraging a Proven Cancer Target

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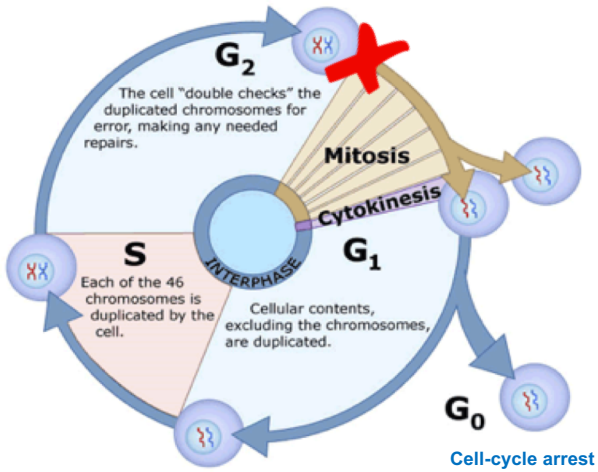
PLK1 – Established Target for Cancer Therapy

PLK1 Plays a Critical Role in Initiation, Maintenance and Completion of Mitosis



- Polo-like Kinase 1 (PLK1)
  - Belongs to a family of kinases (PLK1,2,3,4,5)
  - Dysfunction leads to cancer formation and progression
  - Over-expressed in dividing cancer cells
  - Inhibition leads to cancer cell death

[1]Liu et al- PLK1, A Potential Target for Cancer Therapy; Translational Oncology – Vol. 10 – pp. 22-32; February 2017

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PLK1 – Over-Expressed in Multiple Cancers

Publications

Over-Expression of PLK1 Observed in Numerous Cancers[1]	
Tumor Type	**PLK1 Fold Change Over-Expression**
AML	13.0
B-cell Lymphoma	56.3
Prostate	3.3
Adrenocortical	4.5
Lung Adeno	9.7
Lung Squamous	20.8
Breast	11.3
Esophageal	10.2
Stomach	4.8
Colon	2.5
Head & Neck	4.2
Pancreatic	2.2
Ovarian	31.7
Glioblastoma	12.4
Kidney	4.7
Liver	11.7
Uterine	21.3
Bladder	9.1

[1]Liu et al- PLK1, A Potential Target for Cancer Therapy; Translational Oncology – Vol. 10 – pp. 22-32; February 2017

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Developing Onvansertib
A First-in-Class, 3rd Generation PLK1

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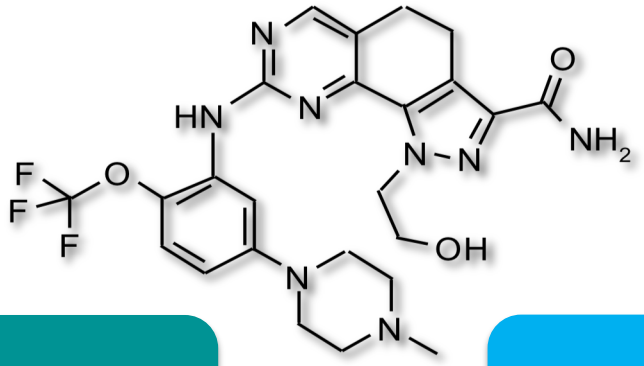
Onvansertib First-in-Class 3rd Generation PLK1

Best-in-Class Attributes

Highly Selective

Orally Available



Ideal Pharmacokinetics

Favorable Safety and Tolerability

Synergistic in Combination

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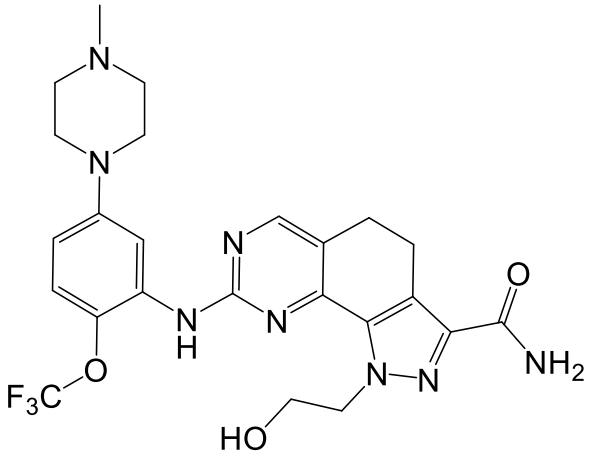
Onvansertib Intellectual Property



- Four worldwide patent families
  - Genus, Compound, Combinations, Salt
- Mature portfolio
  - Granted in most major jurisdictions
- Patent term 2030 plus up to 5 years extension

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Onvansertib – Highly-Selective Only for PLK1

Selective PLK1 Inhibitor

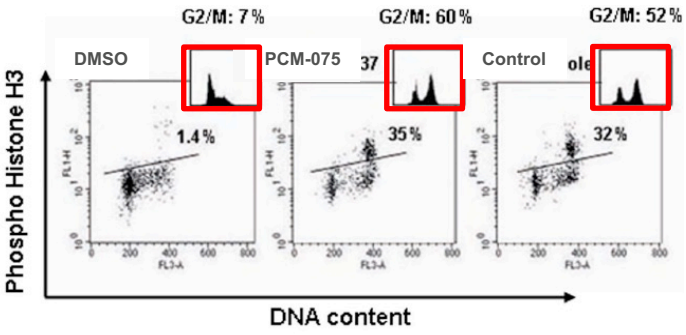
- Tested against >260 kinases
- PLK1 was the only active target (IC_{50} of 2nM)

PLK Member	Onvansertib IC50* (μM)
PLK1	0.002
PLK2	> 10
PLK3	> 10

Causes cancer cell death by G_2M arrest

- Onvansertib blocks cell division (mitosis)

AML-NS8 Patient-Derived Cells Treated with 200 nM Onvansertib for 24 Hrs[1]



[1]Data on File, Trovagene, Inc.

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Onvansertib Phase 1 Safety Trial[1]
Favorable First-in-Human Data

Phase 1 Dose Escalation Trial in Patients with Advanced or Metastatic Solid Tumors

Trial Design

Open-label dose escalation to assess safety and identify Phase 2 dose

19 patients administered Onvansertib orally, once daily for 5 consecutive days, every 21-days

Solid Tumors: colorectal, pancreatic, lung, sarcomas, hepatocellular, ampullary, prostate, ovarian, skin

Trial Results

1. Established safety and identified Phase 2 dose of 24 mg/m^2/day
2. 16 patients evaluable with 30% stable disease
3. Only mild to moderate side effects
4. No GI disorders, mucositis, or alopecia

[1]Weiss G et al., Phase I dose escalation study of NMS-1286937, an orally available Polo-like Kinase 1 inhibitor, in patients with advanced or metastatic solid tumors – Invest. New Drugs DOI 10.1007/s10637-017-0491-7

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Benefiting From Drug Class Experience

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Drawbacks Associated with 1st and 2nd Generation PLK Inhibitors

- Prior PLK inhibitors in development demonstrated significant clinical activity in combination with standard-of-care chemotherapy in AML
- Major drawbacks, unrelated to efficacy of the drug class, resulted in discontinuation of development

Non-Selective	panPLK inhibitors targeting both normal and tumor cells
Off-Target Toxicities	Serious adverse effects that are non-mechanism based
Sub-Optimal PK	Intravenous formulation; relatively long half-life
No Dosing/Schedule Flexibility	Fixed dose; no option to increase time between treatment
Lethal Infections	No mandated anti-infective propylaxis
No Biomarker Strategy	Inability to identify patients most likely to respond

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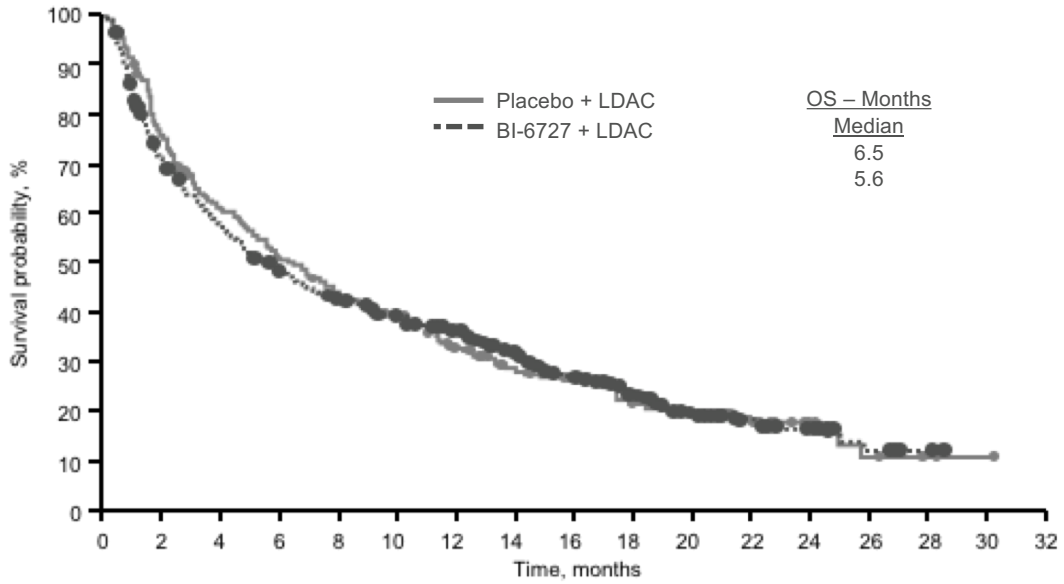
2nd Generation panPLKi (BI-6727)
Randomized Phase 3 Clinical Trial in AML

Overall Survival (OS) Analysis



- Increase in remission rate (CR + CRi)[1]:
  - 25.2% vs 16.8% (central assessment) – OR 1.659; p=0.071
  - 29.7% vs 19.2% (investigator assessment) – OR 1.757; p=0.034
- Negative OS trend (HR: 1.26; p=0.1129)

[1] https://www.boehringer-ingelheim.com/.../results-phase-iii-study-volasertib-treatment

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Onvansertib – First-in-Class, 3rd Generation PLK1 Addresses Drawbacks of 1st and 2nd Generation

- Onvansertib product profile and clinical development program effectively addresses drawbacks associated with 1st and 2nd generation PLK inhibitors

Highly-Selective	Selective only for PLK1 which is overexpressed in tumor cells
Safe and Well Tolerated	Only mild to moderate side effects reported
Ideal PK Properties	Orally administered and relatively short half-life of ~24 hours
Dosing and Treatment Schedule Flexibility	Dose individualized to patients based on weight and body surface area; flexibility to increase time between treatment
Proactive Infection Management	Protocol mandated prophylactic anti-infectives for all patients
Biomarker Strategy	Ability to identify patients most likely to respond to therapy

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Combination Therapy Approach

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Onvansertib Combination Therapy Strategy

- Cornerstone of precision cancer medicine
- Onvansertib has demonstrated synergy with targeted therapeutics and chemotherapy
- Enhanced efficacy (targets key pathways by synergy or additive effect)
- Reduces drug resistance, while providing therapeutic benefits

[1]Mokhtari, R et al - Combination Therapy in Combatting Cancer – Oncotarget, 2017, Vol. 8 (No. 23), pp: 38022-38043

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Onvansertib – Synergistic in Combination

- High PLK1 expression is associated with the most aggressive cancers
- Synergistic activity may enhance efficacy of standard-of-care therapies

Potentially Synergistic Drugs[1,2]
Abiraterone acetate
Bevacizumab
Bortezomib
Cisplatin
Cytarabine
Doxorubicin
FLT3 Inhibitors (Quizartinib)
Gemcitabine
HDAC Inhibitors (Belinostat)
Paclitaxel

Associated Cancers[2]
Leukemias/Lymphomas:
• Acute Myeloid Leukemia • Acute Lymphocytic Leukemia • Non-Hodgkin Leukemia • Multiple Myeloma
Solid Tumor Cancers
• Castration-Resistant Prostate • Adrenocortical Carcinoma • Triple Negative Breast • Sarcomas • Small Cell Lung • Colon

[1]Alphabetical order. [2]Preclinical data on file with PCM-075 and these combined therapeutics

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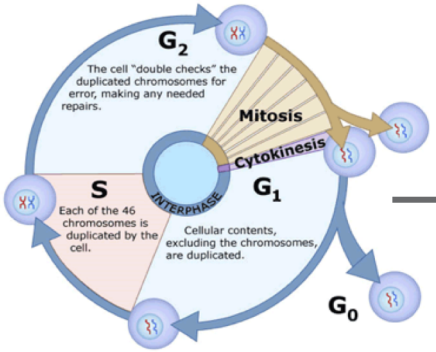
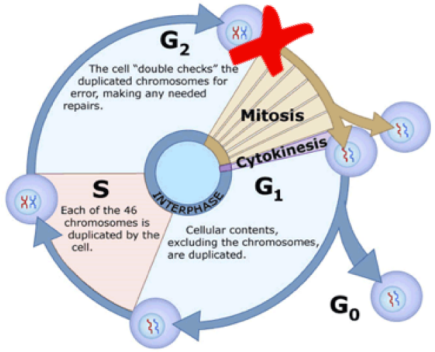
Onvansertib Rationale for Combination with DNA Damaging Agents[1,2]

DNA Damage Response (DDR) arrests cells at G2/M checkpoint

G2/M Arrest





Active PLK1

PLK1 Inhibited

Mitosis

1. Checkpoint adaptation
2. PLK1 inhibits DDR, induces mitotic entry for tumor cells & cell division

Cell Death

1. Keeps tumor cells in G2/M arrest leading to apoptosis
2. For cells that escape, mitosis is blocked, also leading to apoptosis

DNA Damaging Agents

- Cytarabine
- Doxorubicin
- Cisplatin

[1]van Vugt & Yaffe, Cell Cycle 2010 9:2097-2101; [2]van Vugt et al., 2010, PLoS 8:1-19

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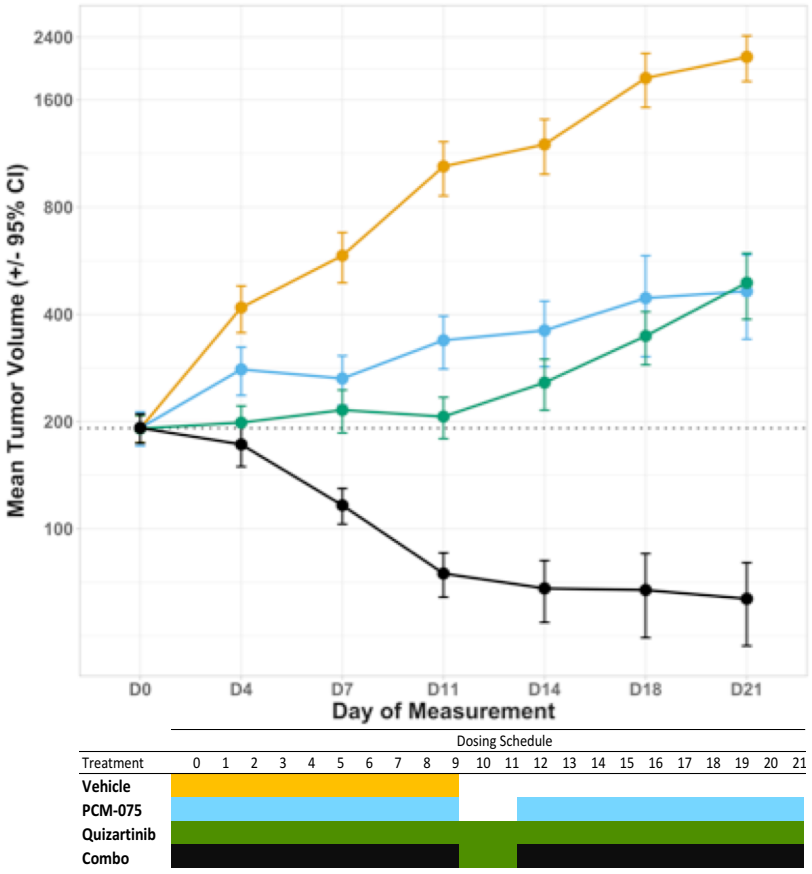
Onvansertib (PCM-075) + FLT3 Inhibitor
Acute Myeloid Leukemia (AML)

- 30% of AML patients have a FLT3 mutation[1]
- Quizartinib in Phase 3 clinical development[2]
- Combination of PCM-075 + quizartinib demonstrated:
  - 97% tumor growth inhibition
  - Regression in FLT3 AML xenograft model[3]

Evaluation of Efficacy of PCM-075 for MV-4-11 Human Acute Myeloid Leukemia (AML) Xenograft Model in NOD.SCID Mice



[1]Kindler et al, Blood 2010; 116:5089-10. [2]Stone et al, N Engl J Med 2017; 377:454-64.
[3]Data on File at Trovagene, Inc.

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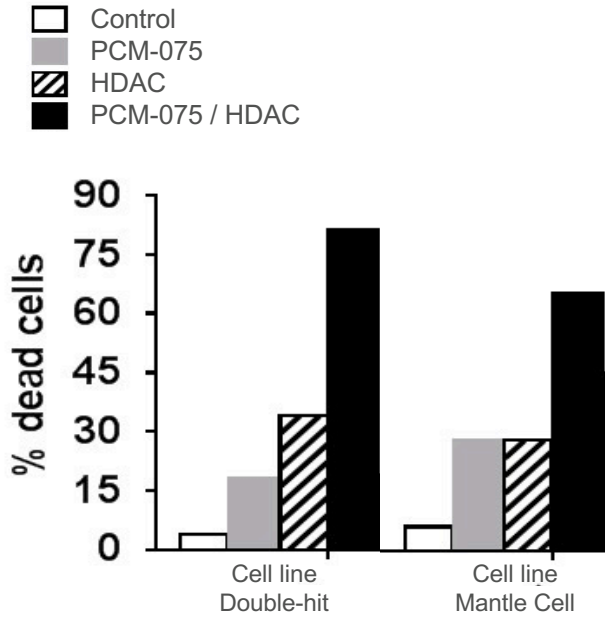
Onvansertib (PCM-075) + HDAC* Inhibitor
Non-Hodgkin Lymphoma (NHL)

- Aggressive NHL progresses rapidly; accounts for 60% of cases in the U.S.
- Demonstrated synergy of PCM-075 + HDAC inhibitor[3]
- Medical need to increase duration of HDAC inhibitor response

PCM-075 Combined with HDAC Inhibitor Reduces Survival of Double-Hit (DLBCL) and Mantle Cell Lymphoma Cell Lines[1]



HDAC inhibitors are approved for NHLs, peripheral and cutaneous t-cell

*HDAC – Histone Deacetylases

[1] Steven Grant, MD, Virginia Commonwealth University, Massey Cancer Center; [2]Unpublished Research Data; [3]Data on File

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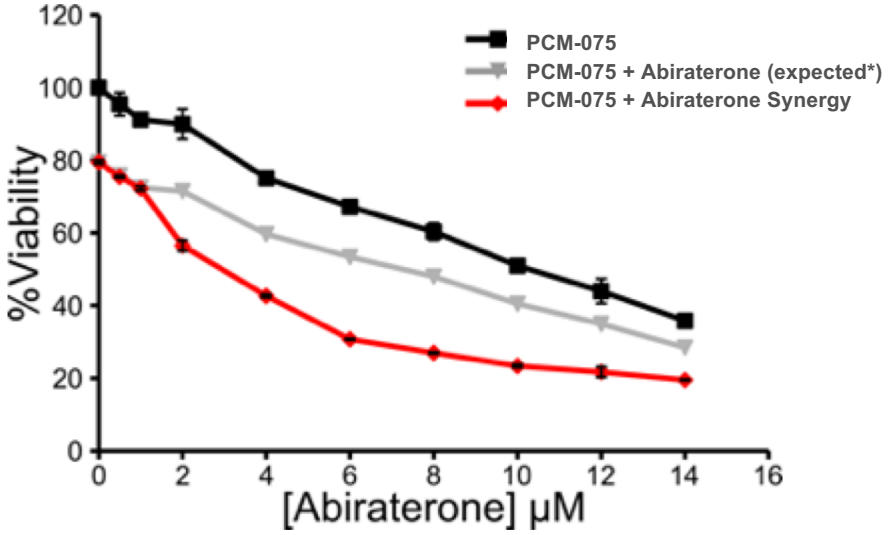
Onvansertib (PCM-075) + Abiraterone
Metastatic Castration-Resistant Prostate Cancer

- PCM-075 + abiraterone demonstrated synergy[1]
- Combination enhances PCM-075 mechanism of action[1]
- Medical need to increase duration of response to anti-androgen drugs

C4-2 Castration-Resistant Prostate Cancer Cells Increased Sensitivity to Abiraterone in the Presence of PCM-075



*Expected = the calculated value of the effect of the addition of each drug as calculated by Michael Yaffe, MD - MIT

[1]Yaffe, Michael, MD and Trovagene, 2017

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Onvansertib (PCM-075) Clinical Trials

Phase 1b/2 in Acute Myeloid Leukemia (AML)

Phase 2 in metastatic Castration-Resistant Prostate Cancer (mCRPC)

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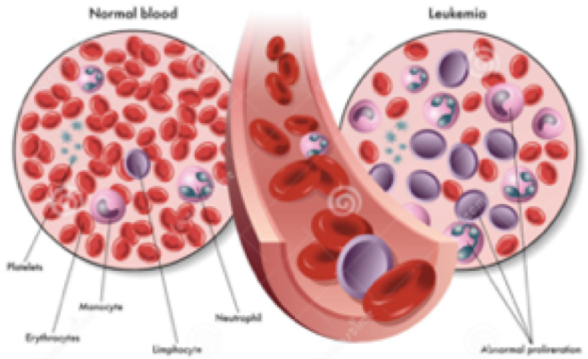
Acute Myeloid Leukemia[1]
Significant Need for New Treatment Options

- AML: aggressive hematologic malignancy of immature blood cells
- Incidence: 20,000* new cases and 10,400 deaths annually in the U.S.
- Prognosis: 5 year survival rate is 25%
- Treatment options vary based on patient condition / age, but can include:
  - Chemotherapy
  - Radiation
  - Stem cell transplant
- Genetically diverse landscape:
  - PLK1 selectivity presents opportunity across patient sub-populations

Acute Myeloid Leukemia



*Orphan Drug Designation granted by the FDA September 28, 2017; [1]National Cancer Institute SEER 2016

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Onvansertib (PCM-075) Scientific Rationale
Clinical Development in AML

- ***in-vitro* studies**[1]
  - High sensitivity of hematological tumor cell lines to PCM-075
- ***in-vitro and in-vivo* mode of action (MoA) studies**[2]
  - Xenograft model demonstrates dose dependent inhibition of PLK1 activity and G2/M arrest
- ***in-vivo* efficacy in AML xenograft models**[2]
  - Dose dependent efficacy of PCM-075 in
    - HL60 promyelocytic leukemia xenograft
    - Disseminated AML patient derived xenografts (AML-PS)
  - Combination of PCM-075 + cytarabine has greater survival than either agent alone (AML-PS)

[1]Source: Report No. N-0018670 Antiproliferative activity of NMS-1286937 in a panel of cell lines;[2]Valsasina et al., Mol Cancer Ther; 11(4) April 2012; [3]ClinicalTrials.gov, NCT03303339: PCM-075 in Combination With Either Low-dose Cytarabine or Decitabine in Adult Patients With Acute Myeloid Leukemia (AML) - Data-on-file, Trovagene 2018

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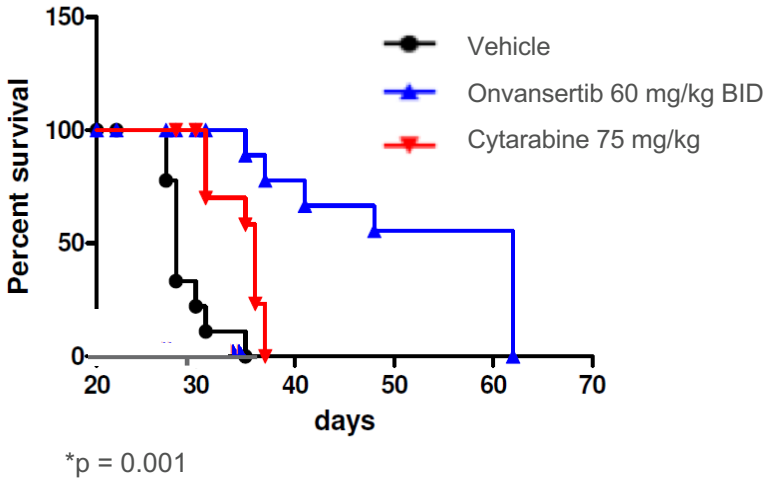
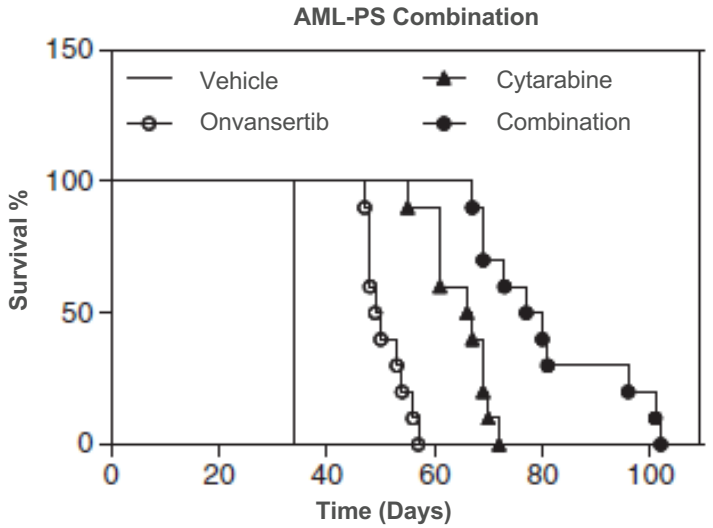
Onvansertib Comparative and Combination with Cytarabine in AML Models[1,2]

In Vivo Disseminated Leukemia Models



*p = 0.001

- Onvansertib 60 mg/kg BID (Days 1-2 with 5-day rest) + cytarabine 75 mg/kg IP Injection (Days 1-5 with 5-day rest)
- Onvansertib 120 mg/kg for 2 days repeated for 4 cycles with a 10-day rest



- Onvansertib 120 mg/kg for 2 days repeated for 4 cycles with a 10-day rest
- Cytarabine IP at 75mg/kg for 5 cycles of 5 consecutive days with 7-day rest
- The combination was given at the same schedule, doses, and routes of the single agents

- Onvansertib + cytarabine in combination showed increased survival compared to either agent alone

[1]Casolaro et al. (2013) PLOS One 8(3); [2]Valsasina et al. (2012), Mol Cancer Ther 11(4)

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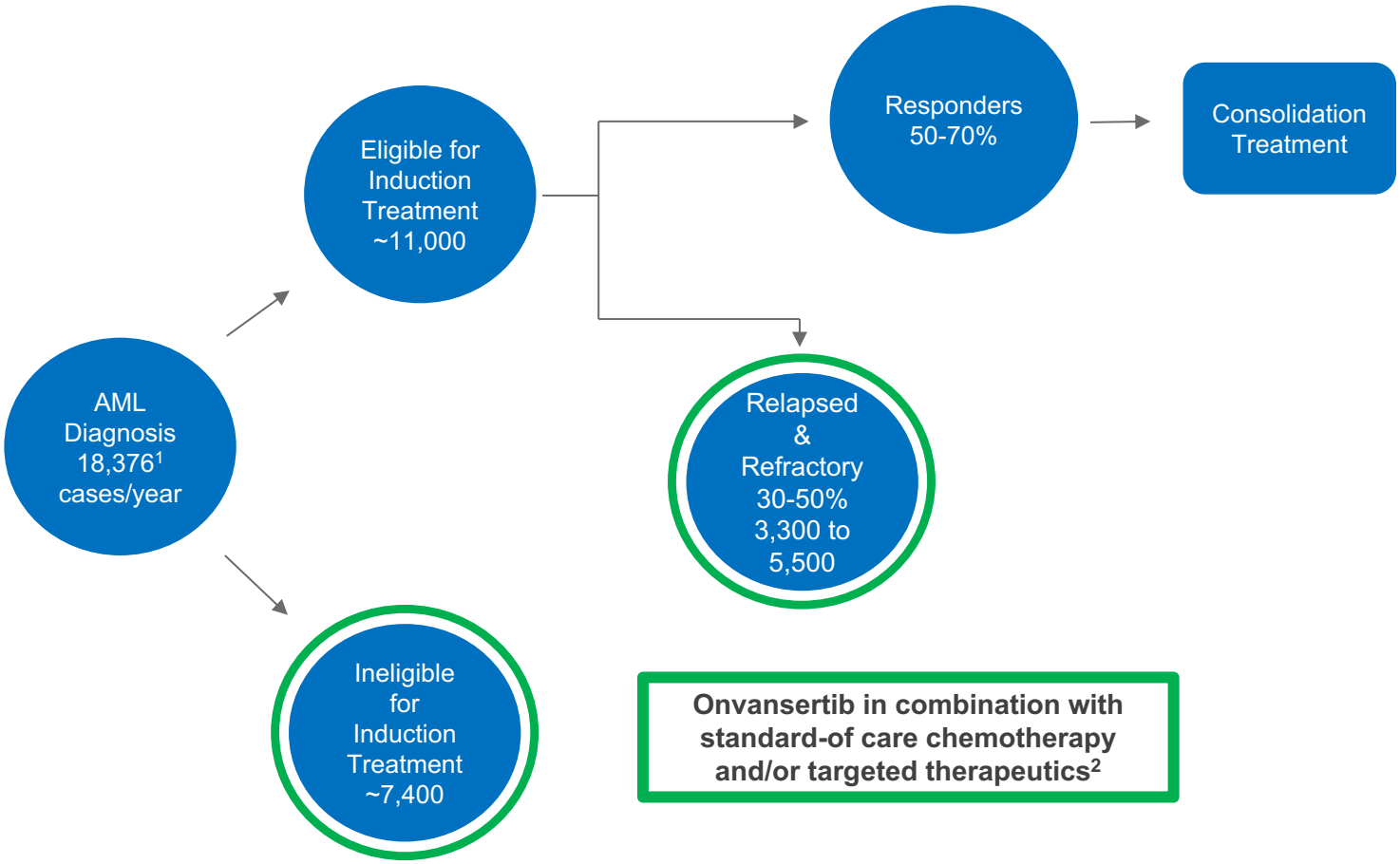
Onvansertib Positioning in AML
Patient Selection Algorithm



[1]Visser et al. (2012), Eur J Cancer (48). Estimated cases in EU27 per year; [2]e.g. Midostaurin for FLT3 mutation

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Ongoing Phase 1b/2 Clinical Trial in AML

Onvansertib in Combination with Either Low-Dose Cytarabine (LDAC) or Decitabine in Patients with Acute Myeloid Leukemia (AML)

Study Design:

- Dose escalation to identify recommended Phase 2 dose

Patient Population:

- Ineligible for induction therapy or relapsed/refractory disease

Treatment Cycle:

- Onvansertib administered orally on Days 1-5, in a flexible 21-28 day cycle

Safety Endpoints:

- Assess side effects, identify Phase 2 dose
- Compare combination regimens

Exploratory Endpoints:

- Evaluate pharmacodynamics and correlative biomarkers

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Ongoing Phase 1b/2 Clinical Trial in AML

Onvansertib in Combination with Either Low-Dose Cytarabine (LDAC) or Decitabine in Patients with Acute Myeloid Leukemia (AML)

Study Design:

- Assess safety and preliminary antitumor activity

Patient Population:

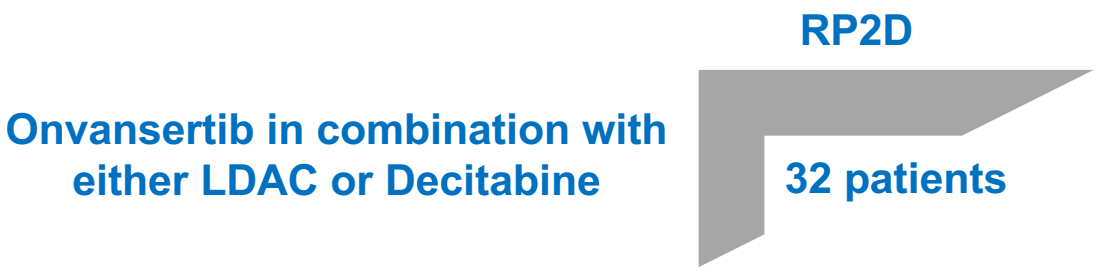
- Treatment naïve ineligible for induction therapy

Efficacy Endpoint:

- Rate of complete response (CR + CRi)

Exploratory Endpoints:

- Evaluation of pharmacodynamic and correlative biomarkers



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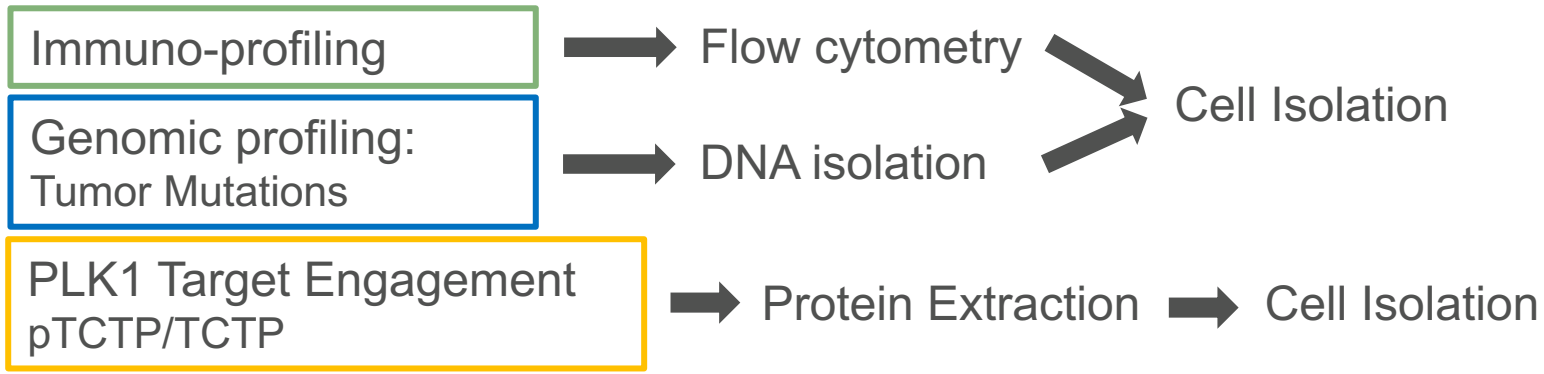
Biomarker Strategy in AML

- Biomarkers will be measured and correlated with pharmacokinetic drug levels to assess:
  - Treatment effects by measuring % blast cells in blood and bone marrow
  - Inhibition of PLK1 by Onvansertib (Target Engagement)
  - Correlating underlying tumor genetics with treatment response



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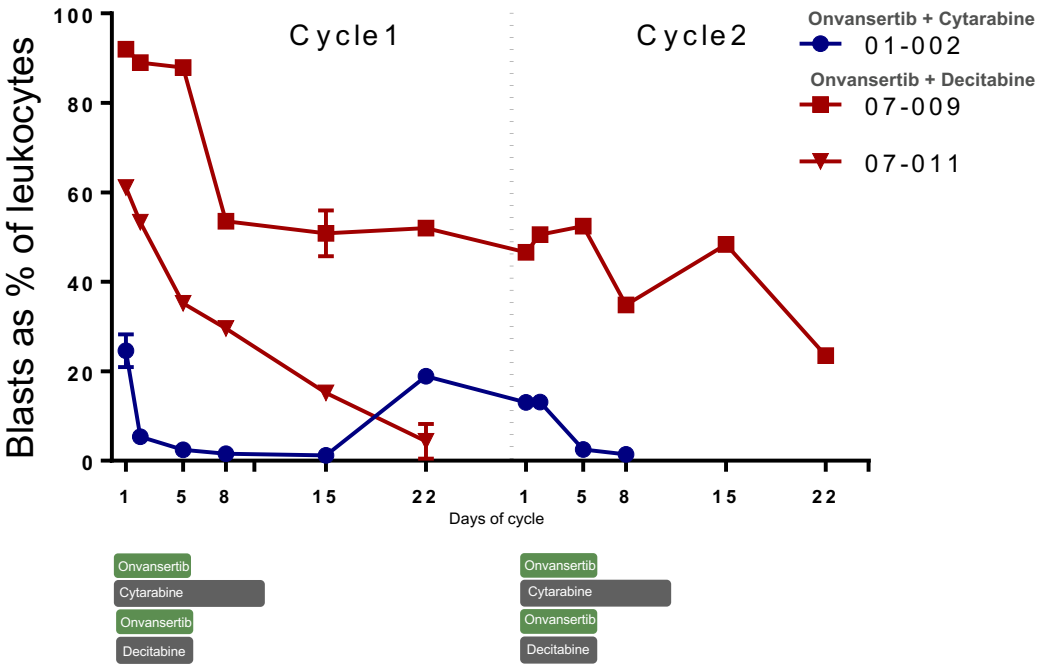
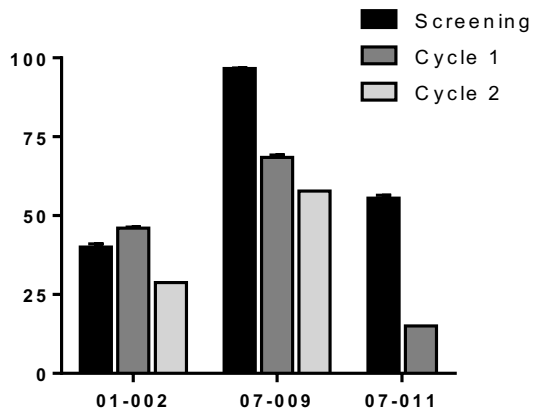
Immuno-Profiling:
Monitoring Leukemic Cells in Response to Treatment

% of Leukemic Cells in Blood



% of Leukemic Cells in Bone Marrow



- 3 of 6 patients treated with Onvansertib in combination with low-dose cytarabine (LDAC) or decitabine showed decreases in the percentage of blood leukemic cells
- Bone marrow analysis also showed a decrease in the percentage of leukemic cells for these 3 patients; with 2 patients (07-009 and 07-011) having decreases from 96% to 55% and 55% to 15%, respectively

[1]NCT03303339, ClinicalTrials.gov; "Onvansertib in Combination With Either Low-dose Cytarabine or Decitabine in Adult Patients With Acute Myeloid Leukemia (AML)

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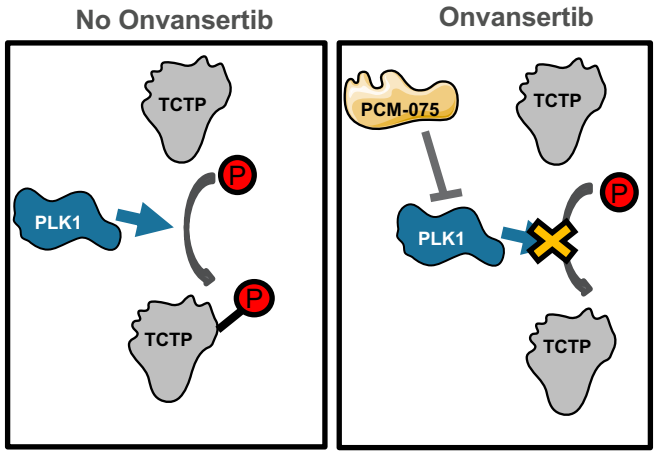
Target Engagement:
Monitoring PLK1 Inhibition Upon Treatment

The Translational Control Tumor Protein (TCTP) Identified as Specific Marker for PLK1 Activity In-Vivo[1]



- Onvansertib inhibits PLK1 kinase activity resulting in reduction in PLK1 substrates phosphorylation; Translational Control Tumor Protein (TCTP) is phosphorylated by PLK1

- PLK1 inhibition was assessed 3-hours following administration of Onvansertib at peak concentration (C_{max})

[1]Cusshi U. et al, Phosphorylation of TCTP as a Marker for Polo-like Kinase 1 Activity In Vivo – Anticancer Research December 2010 vol. 30 no. 12 pp. 4973-4985

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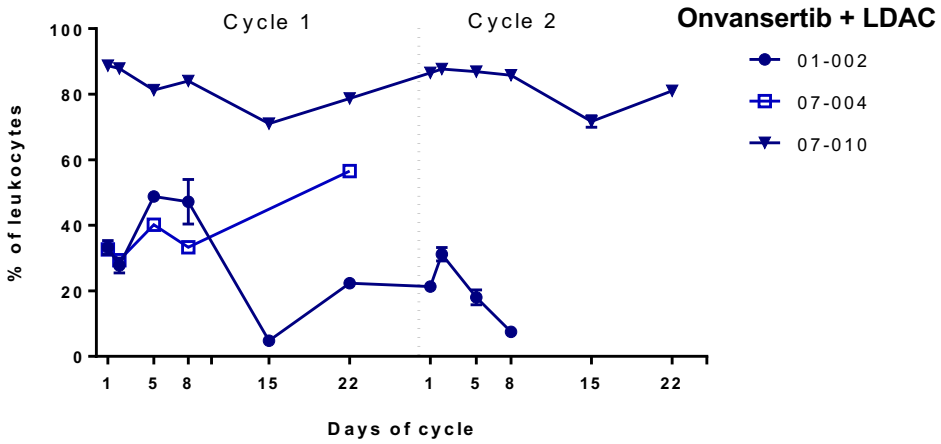
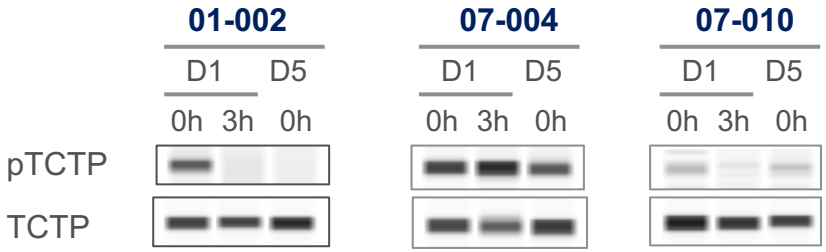
Correlation of Target Engagement and Treatment Response

% of Leukemic Cells in Blood

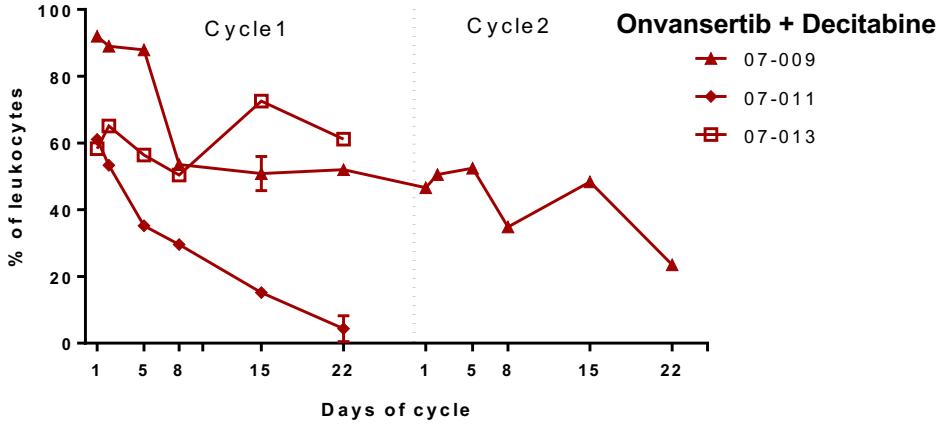


pTCTP status as a surrogate for PLK1 inhibition

Onvansertib 12mg/m^2 + LDAC

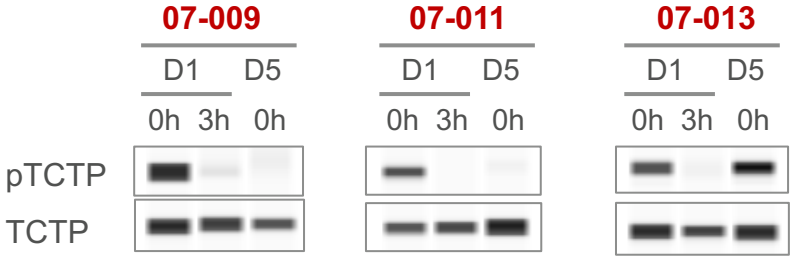


% of Leukemic Cells in Blood



pTCTP status as a surrogate for PLK1 inhibition

Onvansertib 12mg/m^2 + Decitabine



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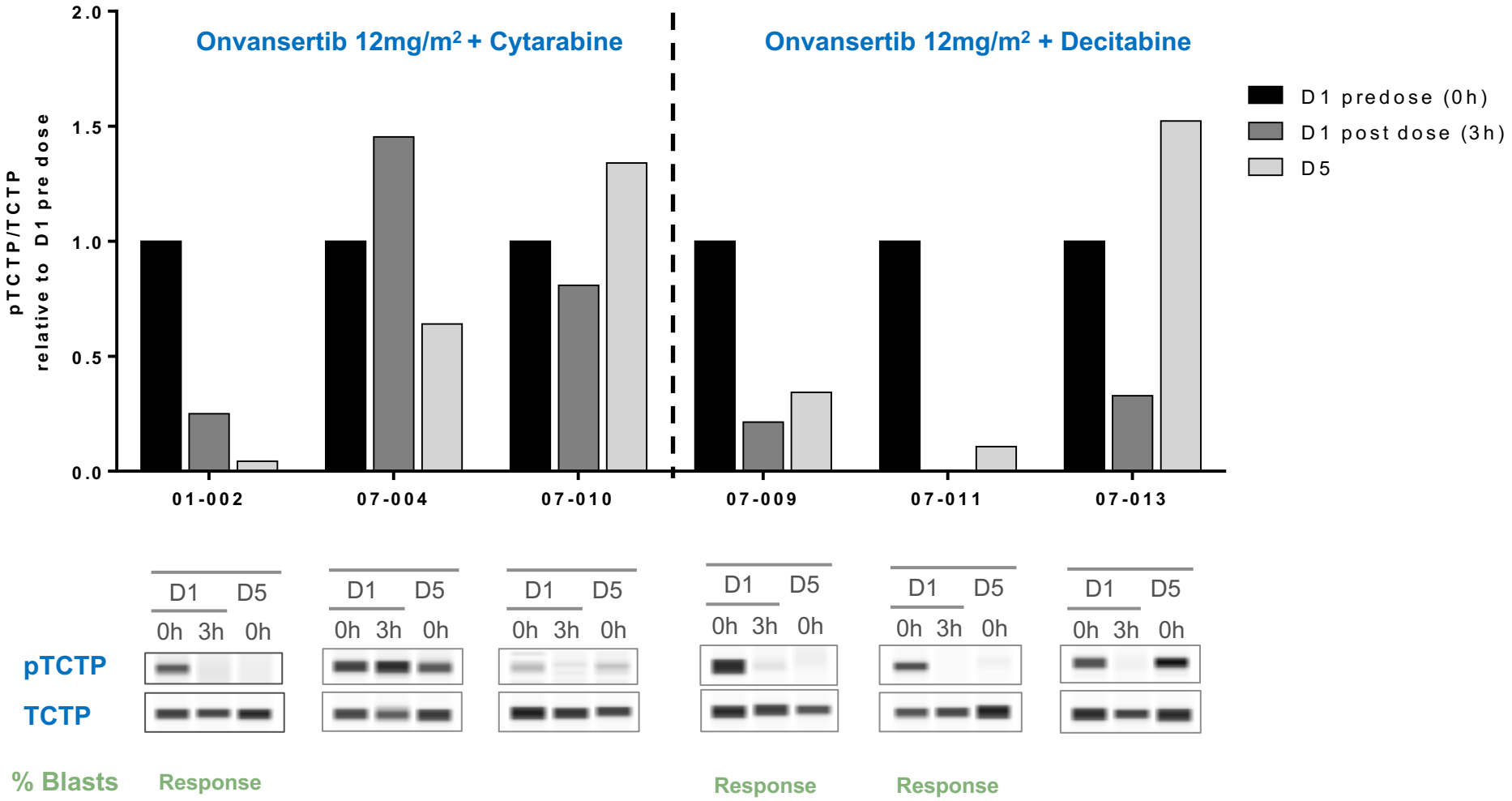
Summary of Target Engagement and Correlation to Treatment Response



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Predictive Response Strategy

Determining which Patients are Eligible for AML Trial

AML Patient

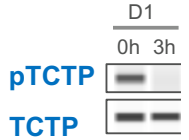
Pre-dose

Patient receives single dose Onvansertib

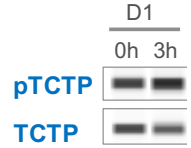
Assess target engagement of PLK1 by Onvansertib

3hr post-dose

Target Engagement Eligible Patient



NO Target Engagement Non-Eligible Patient



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Molecular Profiling and Patient Response in AML[1]

AML Genomic Subgroup	Frequency of Patients	Most Frequently Mutated Genes (%)	DNA Panel	RNA Panel
NPM1 mutation	27%	NPM1(100), DNMT3A(54), FLT3(39), NRAS(19), TET2(16), PTPN11(15)	X	
Mutated chromatin, RNA-splicing genes, or both	18%	RUNX1(39), MLLPTD(25), SRSF2(22), DNMT3A(20), ASXL1(17), STAG2(16), NRAS(16),TET2(15),FLT3ITD(15)	X	
TP53mutations, chromosomal aneuploidy, or both	13%	Complex karyotope(68), -5/5q(47), -7/7q(44), TP53(44), -17/17p(31), +8/8q(16)	X	X
inv(16)(p13.1q22) or t(16;16)(p13.1;q22);CBFB-MYH11	5%	inv(16) (100), NRAS(53), +8/8q(16), KIT(15), FLT3TKD(15)	X	X
biallelic CEBPA mutations	4%	CEBPAbiallelic(100), NRAS(30), WT1(21), GATA2(20)	X	
t(15;17)(q22;q12); PML-RARA	4%	t(15;17) (100), FLT3 ITD(35), WT1(17)	X	X
t(8;21)(q22;q22); RUNX1-RUNX1T1	4%	t(8;21) (100), KIT(38), -Y(33), -9q(18)	X	X
MLL fusion genes; t(x;11)(x;q23)	3%	t(x;11q23) (100), NRAS(23)	X	X
inv(3)(q21q26.2) or t(3;3)(q21;q26.2); GATA2,MECOM(EVI1)	1%	inv(3) (100), -7(85), KRAS(30), NRAS(30), PTPN11(30), ETV6(15), PHF6(15), SF3B1(15)	X	X
IDH2R172 mutations and no other class-defining lesions	1%	IDH2R172(100), DNMT3A(67), +8/8q(17)	X	
t(6;9)(p23;q34); DEK-NUP214	1%	t(6;9) (100), FLT3ITD(80), KRAS(20)	X	X

[1]Papaemmanuil et al. Genomic classification and prognosis in acute myeloid leukemia; NEJM 2016;374:2209-2221

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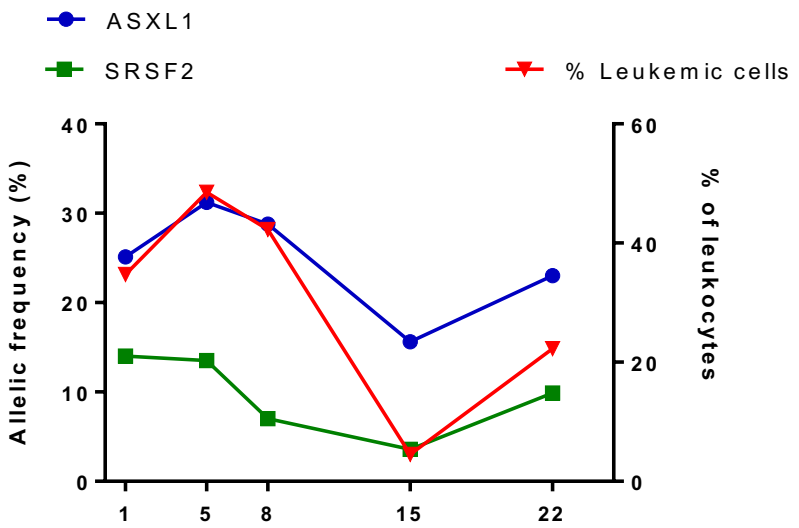
Genomic Profiling: Correlation of Mutation Detected in Blood and % Leukemic Cells

Patient	Mutations detected
01-002	ASXL1 c.1926_1927insG p.G646fs*12 SRSF2 c.284C>G p.P95R
07-004	TP53 c.955 A>T p.Lys319Ter
07-010	SRSF2 c.284C>G p.Pro95Arg RUNX1 c.511G>A p.Asp171Asn RUNX1 c.250A>C p.Thr84Pro TET2 c.3633T>A p.Cys1211Ter
07-009	SF3B1 c.1998G>T p.Lys666Asn FLT3 c.250G>T p.Asp835Tyr RUNX1 c.984_985delAG p.Ala329fs GATA2 c.829A>G p.Ser277Gly
07-011	TP53 c.773A>C p.Glu258Ala
07-013	PHF6 c.955C>T p.Arg319Ter GATA2 c.962T>C p.Leu321Pro

Mutations allelic frequencies and leukemic cells level in blood samples of patient 01-002



- Genomic analysis was performed on bone marrow and blood samples
- Mutations detected in bone marrow and blood were identical for all patients examined
- The mutation allelic frequencies detected in blood correlates with % of circulating leukemic cells

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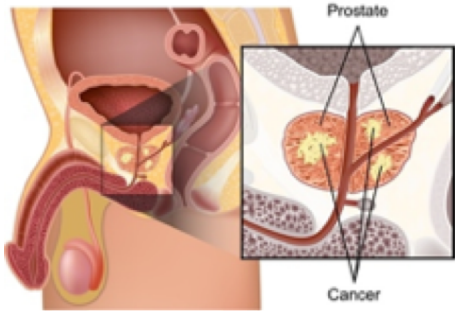
Metastatic Castration-Resistant Prostate Cancer
Opportunity to Increase Duration of Response to Therapy

- 25,000 men progress to metastatic prostate cancer resistant to standard androgen-deprivation therapy, anually[1]
  - Five-year survival rate of 37%[2]
  - Risk of metastases increases as the disease progresses; most common metastases are adrenal gland, bone, and lung[3]
- Treatments
  - Abiraterone acetate (Zytiga® – Johnson & Johnson) and prednisone
  - Enzalutamide (Xtandi® – Astellas/Pfizer)
  - Docetaxel (Docefrez, Taxotere) and prednisone
- Ongoing need to increase duration of response for mCRPC patients
  - Patients develop resistance to abiraterone and enzalutamide (within 9-15 months)[4] and do not respond well to subsequent therapies

Prostate Cancer



[1]2017 Annual Report on Prostate Disease – Harvard Health Publications; [2]GlobalData. Prostate Cancer—Global Drug Forecast and Market Analysis to 2023. Apr, 2015; [3] National Cancer Institute Metastatic cancer. Mar, 2013. Available at: http://www.cancer.gov/about-cancer/what-is-cancer/metastatic-fact-sheet; [4]GAntonarakis, Emmannel – Current Understanding of Resistance to Abiraterone and Enzalutamide in Advanced Prostate Cancer; Clinical Advances in Hematology & Oncology – May 2016 – Volume 14, Issue 5

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PLK1 and Abiraterone Acetate (Zytiga®)
Metastatic Castration-Resistant Prostate Cancer (mCRPC)

- All metastatic prostate cancer patients become castration-resistant
- PLK1 dependent microtubule dynamics promotes androgen receptor (AR) signaling[1,2]
- PLK1 inhibition improves abiraterone efficacy[3]
- Inhibition of PLK1 represses androgen signaling pathway[4]
- PLK1 inhibitors may add important therapeutic benefit for the treatment of castration-resistant prostate cancer patients[5]

[1]Xianzeng, Hou, Zhiguo, Li – PLK1-Dependent Microtubule Dynamics Promotes Androgen Receptor Signaling in Prostate Cancer; Prostate. 2013 September; 73(12): 1352–1363. doi:10.1002/pros.22683; [2] Arpaporn, Deeraksa, Jing, Pan - Plk1 is upregulated in androgen-insensitive prostate cancer cells and its inhibition leads to necroptosis; Oncogene. 2013 June 13; 32(24): 2973–2983. doi:10.1038/onc.2012.309; [3]Clemens, Thoma – Prostate Cancer: PLK-1 Inhibition Improves Abiraterone Efficacy; Nature Reviews Urology volume11, page603 (2014); [4]Zhang Z1, Chen L – Inhibition of PLK1 Represses Androgen Signaling Pathway in Castration-Resistant Prostate Cancer; Cell Cycle. 2015;14(13):2142-8. doi: 10.1080/15384101.2015.1041689; [5]Klaus, Strebhardt - Drugging Plk1: An attractive approach to inhibit androgen receptor signaling; Cell Cycle. 2015 Jul 18; 14(14): 2193–2194

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Ongoing Phase 2 Clinical Trial in mCRPC

Onvansertib in Combination with Zytiga® (abiraterone acetate)/Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Dosing Regimen	Duration	Evaluation
Onvansertib – 24 mg/m^2 Days 1-5 (21-Day Cycle) + Zytiga®/prednisone daily	4 Cycles = 12 Weeks	Disease Control based on PSA level

Study Design:

- Effect of combination therapy on increasing duration of response to abiraterone

Patient Population:

- Patients on abiraterone showing early signs of disease progression

Efficacy Endpoints:

- Disease control assessed by PSA decline or stabilization

Safety Endpoint:

- Safety of combination

Exploratory Endpoint:

- Evaluation of relevant biomarkers for correlation with patient response

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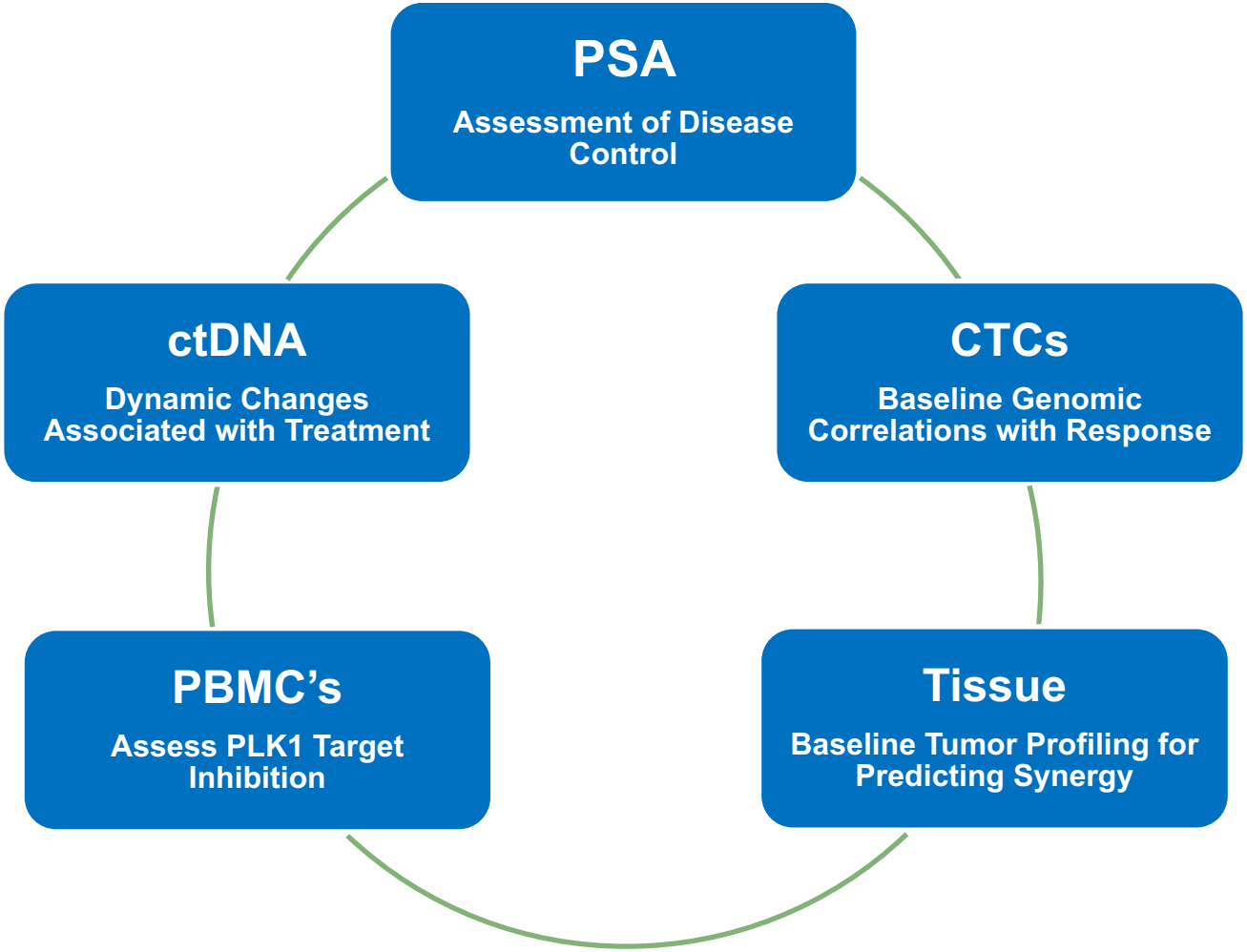
Biomarker Strategy in mCRPC



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PSA: NCCN Recommended Biomarker
Trial Eligibility and Efficacy for mCRPC[1]

- PSA is a validated biomarker assessing disease stability or progression
- Prostate Cancer Clinical Trials Working Group (PCWG)[1] has set criteria for the use of blood PSA levels:
  - Trial eligibility (defining progression)
  - Initial assessment of efficacy

[1]PCWG2: Sher et al, JCO, 2008, PCWG3: Sher et al, JCO, 2016

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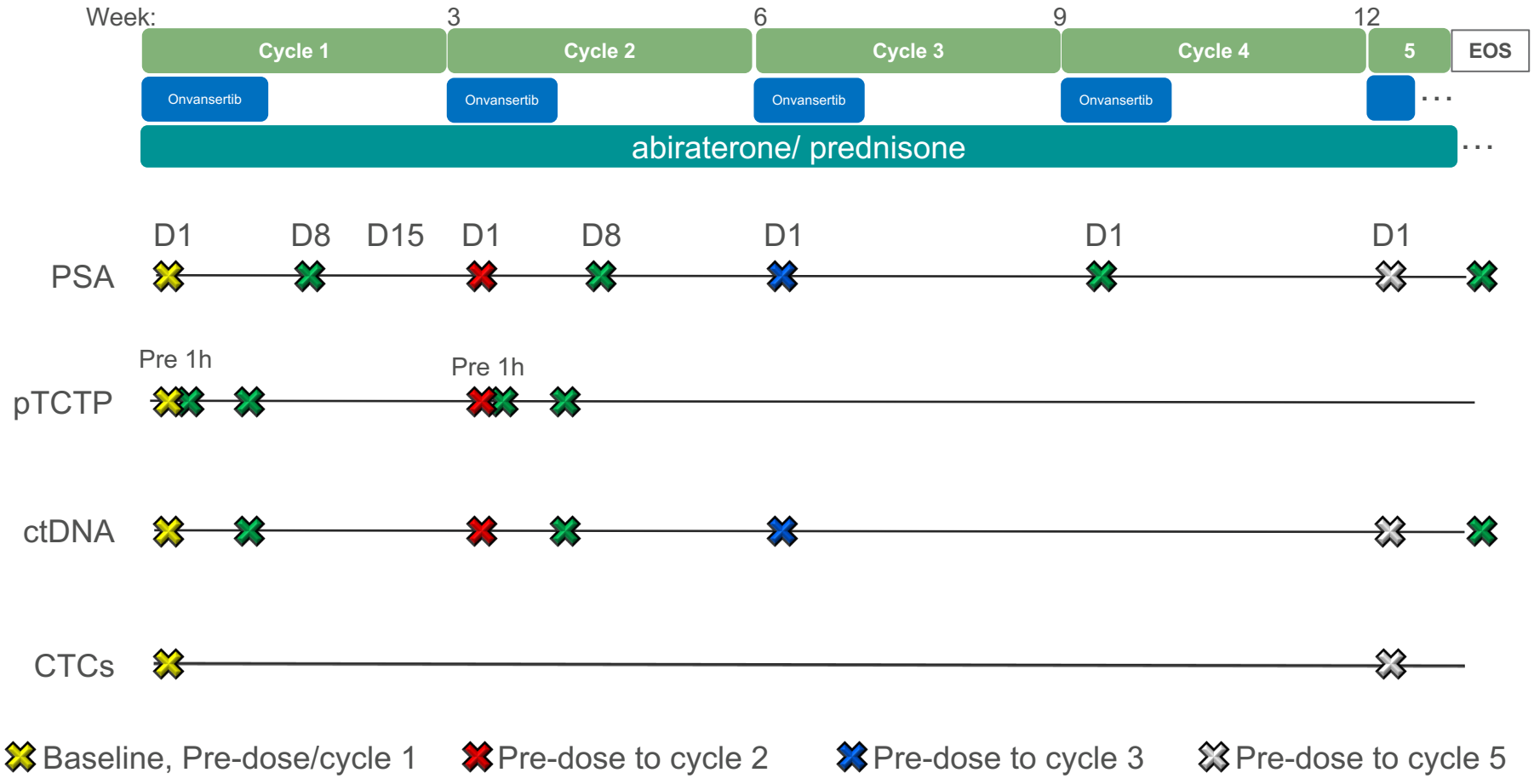
Biomarker Assessment Schedule



- Primary Endpoint: Proportion of patients achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression

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Summary

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Milestones
Significant Value Creation in 2018

	Q1 18	Q2 18	Q3 18	Q4 18
Phase 1b/2 AML Trial	AML Phase 1bTrial enrolling ✓	AACR Data Presentation ✓	EU Orphan Drug Designation ✓	ASH Data Presentation
	First Patient Completes Cycle ✓	Completion of 1st dosing cohort (cytarabine) ✓	Completion of 2nd dosing cohort	Phase 2 dose Identified
		Preliminary clinical safety and efficacy ✓	Initiation of 3rd dosing cohort in AML trial	Topline AML safety and efficacy data
Phase 2 mCRPC Trial	mCRPC Phase 2 Trial Clears FDA Review ✓	mCRPC Phase 2 trial sites activated ✓	3 safety lead-in patients enrolled	Continued enrollment in mCRPC trial
	ASCO GU Data Presentation ✓		Safety/efficacy on 3 lead-in patients	Continued efficacy data readouts

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Summary

- Precision Medicine Approach
- Leveraging a proven cancer target, PLK1
- Onvansertib – first-in-class, 3rd generation PLK1 inhibitor
- Synergy strategy – Onvansertib in combination with approved drugs

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ir@trovagene.com