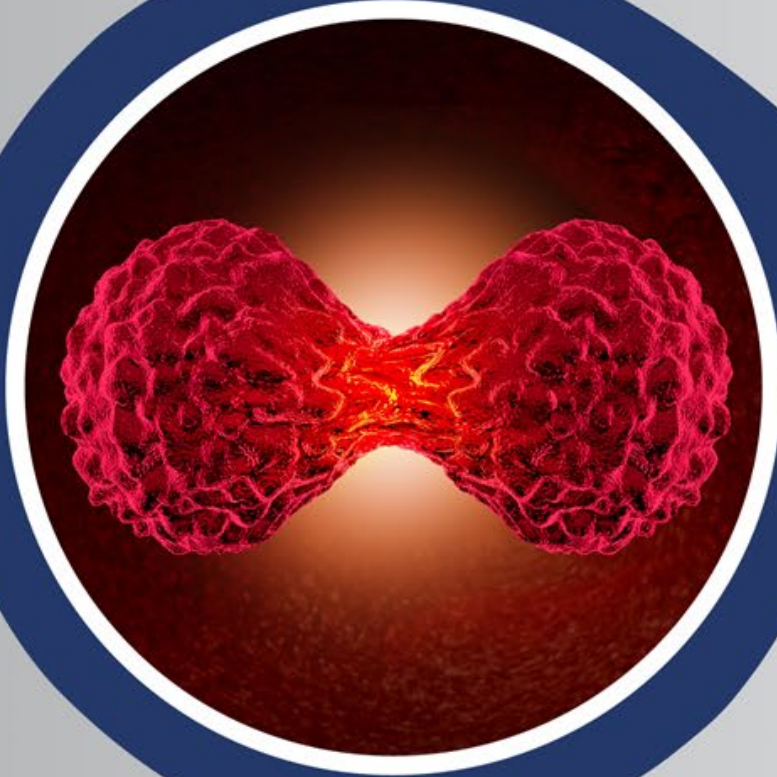




ONCTERNAL
therapeutics™



**Oncternal
R&D Day**

**Hematological
Malignancies and
Prostate Cancer**

Jan 25, 2022

New Science. New Cancer Therapies. New Hope.

Topics

Introduction

Heme Malignancies

- Lymphoma / MCL treatment overview
 - Oncternal Zilovertamab and ROR1 cell therapy program update
 - Q&A
-

Prostate Cancer

- Unmet needs in prostate cancer treatment
 - Oncternal ONCT-534 Dual-Action AR Inhibitor value proposition and other opportunities
 - Q&A
-

Wrap-up

Presented by

- Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics
-

- Michael Wang, MD (MD Anderson Cancer Center)
 - Oncternal Therapeutics Management
-

- Evan Yu, MD (Fred Hutchinson Cancer Research Center)
 - Oncternal Therapeutics Management
-

- Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

FORWARD-LOOKING STATEMENTS

This presentation contains forward-looking statements (including within the meaning of §21E of the U.S. Securities Exchange Act of 1934, as amended, and § 27A of the U.S. Securities Act of 1933, as amended). Forward-looking statements, which generally include statements regarding goals, plans, intentions and expectations, are based upon current beliefs and assumptions of Oncternal Therapeutics, Inc. (“Oncternal”) and are not guarantees of future performance. Statements that are not historical facts are forward-looking statements, and include statements regarding the expected timing for achieving key milestones, including the expected initiation of, and elements constituting, the ZILO-301 and ZILO-302 studies, the potential that the ZILO-301 study can serve as a registrational study, the potential enrollment timeline for zilovetamab prostate cancer studies, submission of an Investigational New Drug application for ONCT-808 and completing and announcing results of clinical trials of Oncternal’s other product candidates, the anticipated market potential, duration of patent coverage, ability to obtain and maintain favorable regulatory designations, and potential accelerated approval pathways for Oncternal’s product candidates and preclinical programs, Oncternal's estimated cash and cash equivalents as of December 31, 2021 and Oncternal’s anticipated cash runway.

All forward-looking statements are subject to risks and uncertainties, including risks and uncertainties inherent in Oncternal’s business, including risks associated with the clinical development and process for obtaining regulatory approval of Oncternal’s product candidates such as potential delays in the commencement, enrollment and completion of clinical trials; the risk that results seen in a case study of one patient likely will not predict the results seen in other patients in the clinical trial; the risk that interim results of a clinical trial do not predict final results and that one or more of the clinical outcomes may materially change as patient enrollment continues, following more comprehensive reviews of the data, as follow-up on the outcome of any particular patient continues, and as more patient data become available; potential changes in estimated cash and cash equivalents based on the completion of financial closing procedures and release of complete fourth quarter 2021 results; and other risks described in Oncternal’s filings with the U.S. Securities and Exchange Commission (“SEC”). Except as required by applicable law, Oncternal undertakes no obligation to revise or update any forward-looking statement. All forward-looking statements in this presentation are current only as of the date on which the statements were made. Additional factors that could cause actual results to differ materially from those expressed in the forward-looking statements are discussed in Oncternal’s filings with the SEC.

Zilovetamab, ONCT-216, ONCT-808, and ONCT-534 are investigational product candidates or preclinical programs that have not been approved by the U.S. Food and Drug Administration for any indication.

This presentation includes certain information obtained from trade and statistical services, third-party publications, and other sources. Oncternal has not independently verified such information and there can be no assurance as to its accuracy.

Hematological Malignancies

Zilovertamab – ROR1 monoclonal antibody

- Demonstrated clinical benefit of combination with ibrutinib in Phase 2 compared to historical ibrutinib monotherapy
- Expect MCL registrational study initiation in 2Q 2022

ONCT-808 – ROR1 CAR-T Cell Therapy

- Expect IND submission in mid 2022

ONCT-216 – ETS inhibitor – currently under investigation in a Phase 2 study in Ewing sarcoma, preclinical studies in both heme malignancies and prostate cancer underway

Prostate Cancer

ONCT-534 – Dual Action AR Inhibitor (DAARI)

- First-in-class MOA interacting with both N-terminal Domain and Ligand-Binding Domain of the androgen receptor inducing AR degradation
- Active preclinically against AR amplification, splice variant and LBD mutation models

Zilovertamab – ROR1 monoclonal antibody

- I-IND open for advanced prostate cancer

Topics	Presented by
Introduction	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics
<hr/>	
Heme Malignancies	
<ul style="list-style-type: none">• Lymphoma / MCL treatment overview• Oncternal Zilovertamab and ROR1 cell therapy program update• Q&A	<ul style="list-style-type: none">• Michael Wang, MD (MD Anderson Cancer Center)• Oncternal Therapeutics Management
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Prostate Cancer	
<ul style="list-style-type: none">• Unmet needs in prostate cancer treatment• Oncternal ONCT-534 Dual-Action AR Inhibitor value proposition and other opportunities• Q&A	<ul style="list-style-type: none">• Evan Yu, MD (Fred Hutchinson Cancer Research Center)• Oncternal Therapeutics Management
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Wrap-up	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

A landscape for Mantle Cell Lymphoma Treatment



THE UNIVERSITY OF TEXAS
**MD Anderson
Cancer Center**

Making Cancer History®

Michael Wang, MD

Puddin Clarke Endowed Professor

Department of Lymphoma and Myeloma

Department of Stem Cell Transplantation and Cellular
Therapy

Founding Director: MCL Program of Excellence

Disclosures

Consultancy

AstraZeneca
Bayer Healthcare
BeiGene
CSTone
DTRM Biopharma (Cayman) Limited
Epizyme
Genentech
InnoCare
Janssen
Juno
Kite Pharma
Loxo Oncology
Miltenyi Biomedicine GmbH
Oncternal
Pharmacyclics
VelosBio

Research Funding

Acerta Pharma
AstraZeneca
BeiGene
BioInvent
Celgene
Genentech
Innocare
Janssen
Juno
Kite Pharma
Lilly
Loxo Oncology
Molecular Templates
Oncternal
Pharmacyclics
VelosBio

Honoraria

Acerta Pharma	LLC TS Oncology
Anticancer Association	Miltenyi Biomedicine GmbH
AstraZeneca	Moffitt Cancer Center
BeiGene	Mumbai Hematology Group
BGICS	Newbridge Pharmaceuticals
CAHON	OMI
Chinese Medical Association	Pharmacyclics
Clinical Care Options	Physicians Education Resources (PER)
Dava Oncology	Scripps
Eastern Virginia Medical School	The First Affiliated Hospital of Zhejiang University
Epizyme	
Hebei Cancer Prevention Federation	
Imedex	
Janssen	
Kite Pharma	

Diagnosis of MCL - Immunophenotyping

- Important tool in differential diagnosis¹
- Immunophenotyping can be performed on:¹
 - Biopsy material
 - Blood
 - Bone marrow
- MCL has characteristic immunophenotype¹
 - Almost all cases positive for cyclin D1¹
 - Detected in nucleus of malignant cells¹

	IHC	FC
CD19		+
CD20	+	+
CD5	+	+
CD10	-	-
FMC7		+
CD23	-	-
Cyclin D1	+	
Bcl-6	-	
Bcl-2	+	
Slg		+ (bright)

IHC – immunohistochemistry
FC – flow cytometry

SOX11 and MCL

Overexpression of the transcription factor SOX11 has been described as a potential differential diagnostic marker in MCL.² SOX11 – not normally expressed in B-cells (and infrequently expressed in other B-cell malignancies) – is thought to play an oncogenic role in MCL development.^{3,4} Absence of SOX11 is characteristic of MCL that follows an indolent course.²

1. McKay, P., Leach, M., et al. (2012). *Br J Haematol.* **159**(4): 405-26.
2. Vose, J. (2012). *Am J Hematol.* **87**: 605-609.
3. Ferrando, A.A. (2013). *Blood.* 121(12): 2169-70.
4. Mozos, A., Royo, C., et al. (2009). *Haematologica.* 94(11): 1555-62.

Pathobiology of MCL (Wang et al, JCO)

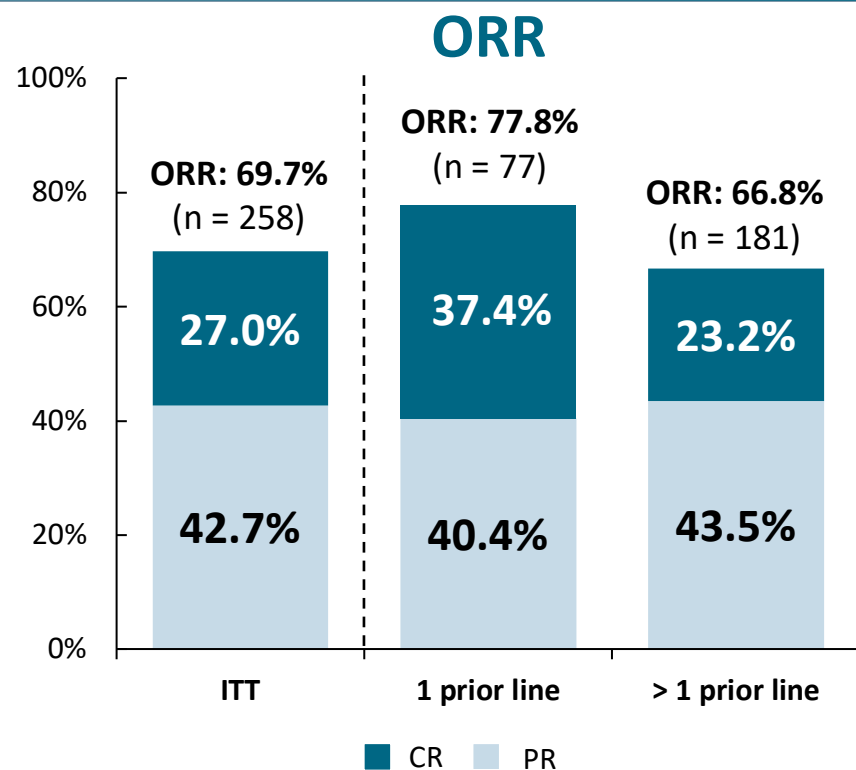
- **MKI67 gene (Ki-67) proliferation marker** was shown to be independently prognostic.
- **DNA repair genes** ATM, CCND1, and TP53 were confirmed as the most frequently recurrent somatic mutations.
- **Novel mutations** that affect the epigenetic modifiers WHSC1, MLL2, MEF2B, RB1, POT1, and SMARCA4A also were identified. Some of these may have prognostic significance in patients treated with ibrutinib because relative to patients who achieve durable remissions, those who exhibit primary ibrutinib resistance are more likely to carry mutations in epigenetic modifiers (WHSC1, MLL2, and CREBBP), proviral insertion in murine kinases, the mammalian target of rapamycin (mTOR) pathway, and oncogenes ERBB4 and BCL2.
- **NOTCH1/2 mutations** (reported in approximately 5% to 10% of patients with MCL) are associated with aggressive clinical behavior.
- **Tumor microenvironment** plays an important role in pathogenesis.

Median 3.5-Year Follow-up of Ibrutinib Treatment in Patients With Relapsed/Refractory Mantle Cell Lymphoma (MCL): a Pooled Analysis

Simon Rule,¹ Martin Dreyling,² Andre Goy,³ Georg Hess,⁴ Rebecca Auer,⁵ Brad Kahl,⁶ José-Ángel Hernandez-Rivas,⁷ Keqin Qi,⁸ Sanjay Deshpande,⁸ Lori Parisi,⁸ Michael Wang⁹

¹Department of Haematology, Plymouth University Medical School, Plymouth, UK; ²Department of Medicine III, Klinikum der Universität München, LMU, Munich, Germany; ³Department of Hematology & Oncology, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA; ⁴Department of Hematology, Oncology and Pneumology, University Medical School of the Johannes Gutenberg University, Mainz, Germany; ⁵Centre for Haemato-Oncology, Barts Cancer Institute, London, UK; ⁶Department of Medicine, Washington University, St. Louis, MO, USA; ⁷Hematology Department, Hospital Universitario Infanta Leonor, Madrid, Spain; ⁸Research & Development, Janssen, Raritan, NJ, USA; ⁹Department of Lymphoma/Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Overall Response and PFS/OS by Best Response



Median, Months (95% CI)	Best Response	
	CR (n = 100)	PR (n = 158)
PFS	NR (47.6-NE)	12.8 (10.4-16.7)
OS	NR (NE-NE)	25.4 (21.3-32.2)

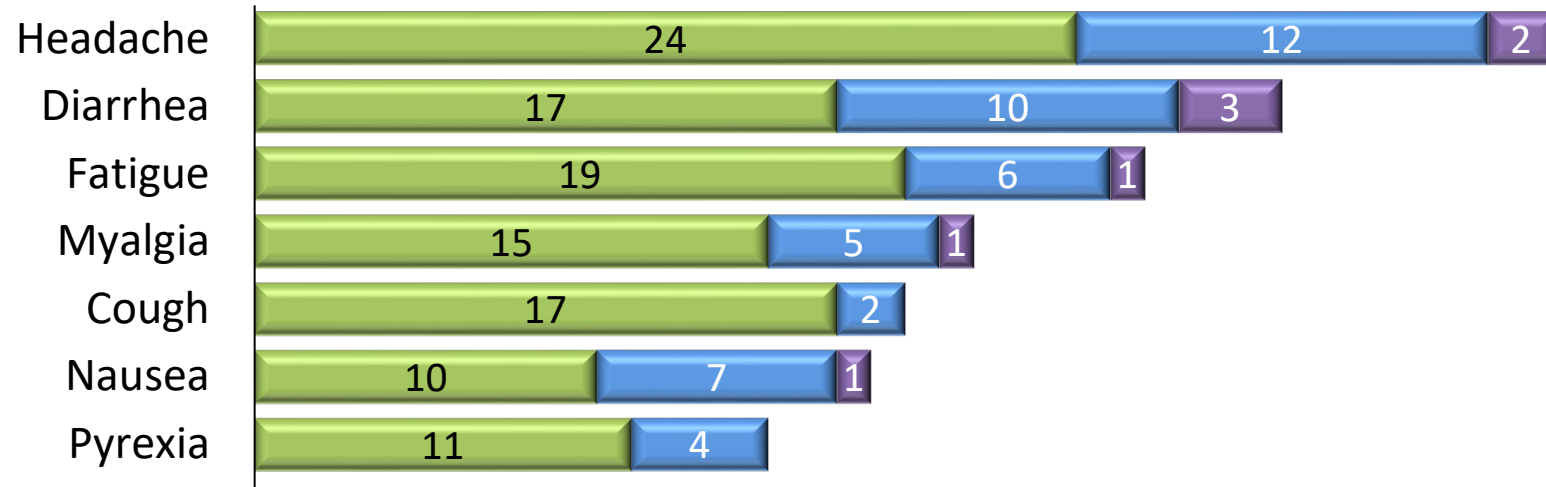
Kaplan-Meier estimate of median.

- CR rate was 37.4% in patients with 1 prior line of therapy
- Median PFS and OS were not reached in patients who achieved a CR (median follow-up 41 months)

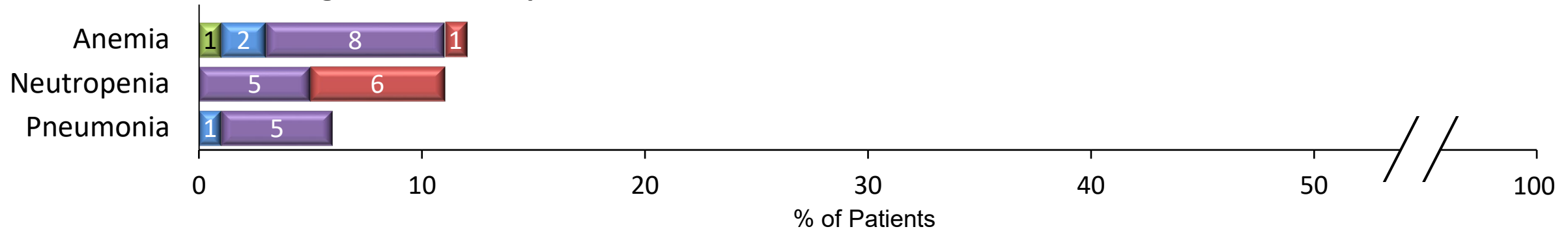
PR, partial response.

Most Common Adverse Events

AEs occurring in ≥15% of all patients



Grade ≥3 AEs occurring in ≥5% of all patients



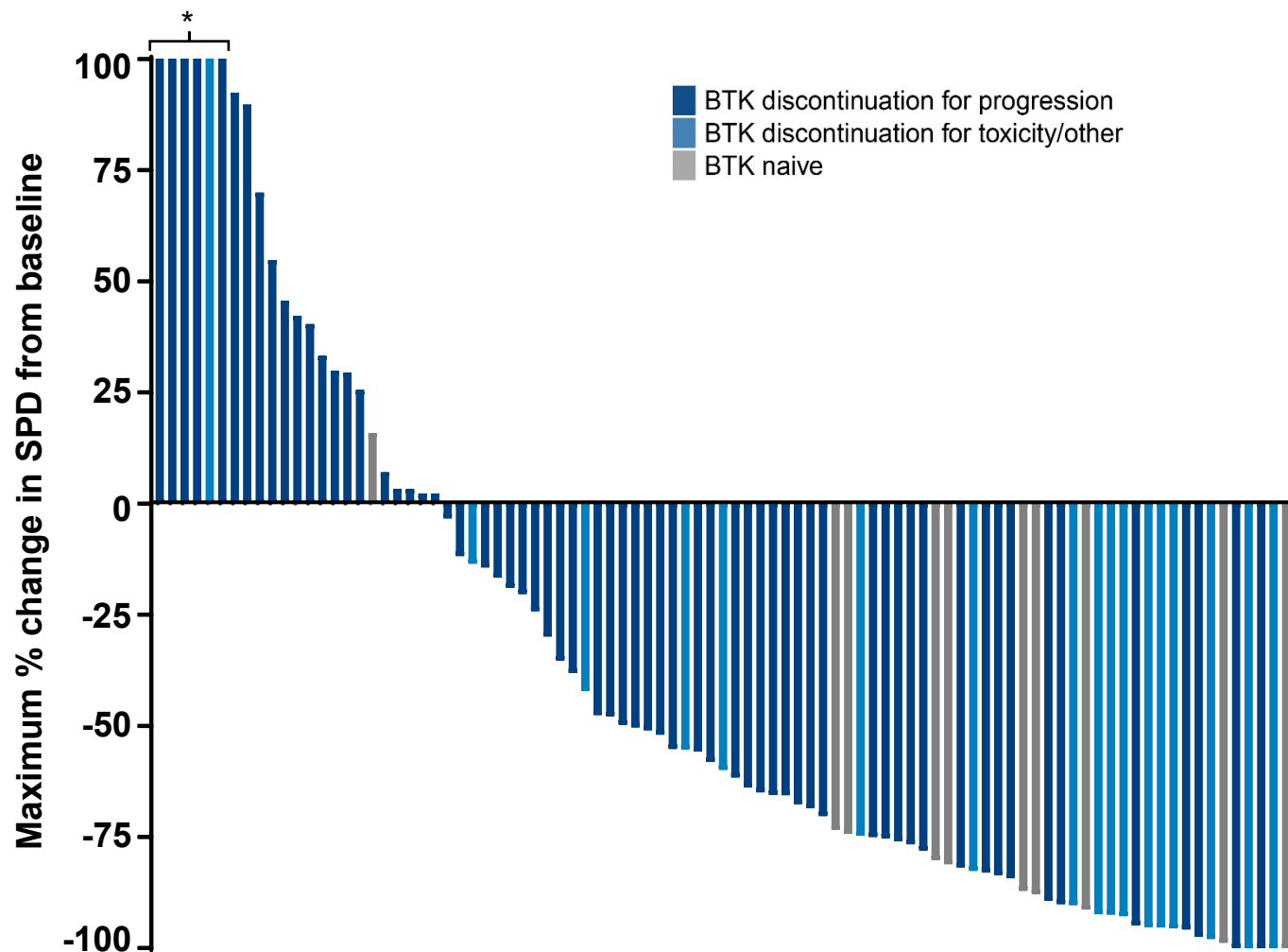
AE = adverse event.

Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

Michael L. Wang¹, Nirav N. Shah², Alvaro J. Alencar³, James N. Gerson⁴, Manish R. Patel⁵, Bitu Fakhri⁶, Wojciech Jurczak⁷, Xuan Tan⁸, Katharine Lewis⁸, Timothy Fenske², Catherine C. Coombs⁹, Ian W. Flinn¹⁰, David J. Lewis¹¹, Steven Le Gouill¹², M. Lia Palomba¹³, Jennifer A. Woyach¹⁴, John M. Pagel¹⁵, Nicole Lamanna¹⁶, Jonathon B. Cohen¹⁷, Minal A. Barve¹⁸, Paolo Ghia¹⁹, Toby A. Eyre²⁰, Pier Luigi Zinzani²¹, Chaitra S. Ujjani²², Youngil Koh²³, Koji Izutsu²⁴, Ewa Lech-Maranda²⁵, Constantine S. Tam²⁶, Suchitra Sundaram²⁷, Ming Yin²⁸, Binoj Nair²⁸, Donald E. Tsai²⁸, Minna Balbas²⁸, Anthony R. Mato¹³, Chan Y. Cheah⁸

¹Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX; ²Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI; ³Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, FL; ⁴Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; ⁵Florida Cancer Specialists / Sarah Cannon Research Institute, Sarasota, FL; ⁶Division of Hematology and Oncology, University of California, San Francisco, CA; ⁷Maria Skłodowska-Curie National Research Institute of Oncology, Krakow, Poland; ⁸Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; ⁹Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC; ¹⁰Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; ¹¹Plymouth Hospitals NHS Trust - Derriford Hospital, Plymouth, United Kingdom; ¹²Service d'hématologie clinique du CHU de Nantes, INSERM CRCINA Nantes-Angers, NeXT Université de Nantes, Nantes, France; ¹³Memorial Sloan Kettering Cancer Center, New York, NY; ¹⁴The Ohio State University Comprehensive Cancer Center, Columbus, OH; ¹⁵Center for Blood Disorders and Stem Cell Transplantation, Swedish Cancer Institute, Seattle, WA; ¹⁶Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; ¹⁷Winship Cancer Institute, Emory University, Atlanta, GA; ¹⁸Mary Crowley Cancer Research, Dallas, TX; ¹⁹Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, MI, Italy; ²⁰Churchill Cancer Center, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom; ²¹Institute of Hematology "Seràgnoli" University of Bologna, Bologna Italy; ²²Fred Hutchinson Cancer Research Center; ²³Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; ²⁴National Cancer Center Hospital, Tokyo, Japan; ²⁵Institute of Hematology and Transfusion Medicine, Warsaw, Poland; ²⁶Peter MacCallum Cancer Center, Royal Melbourne Hospital, and University of Melbourne, Melbourne, Australia; ²⁷Department of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; ²⁸Loxo Oncology at Lilly, Stamford, CT

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



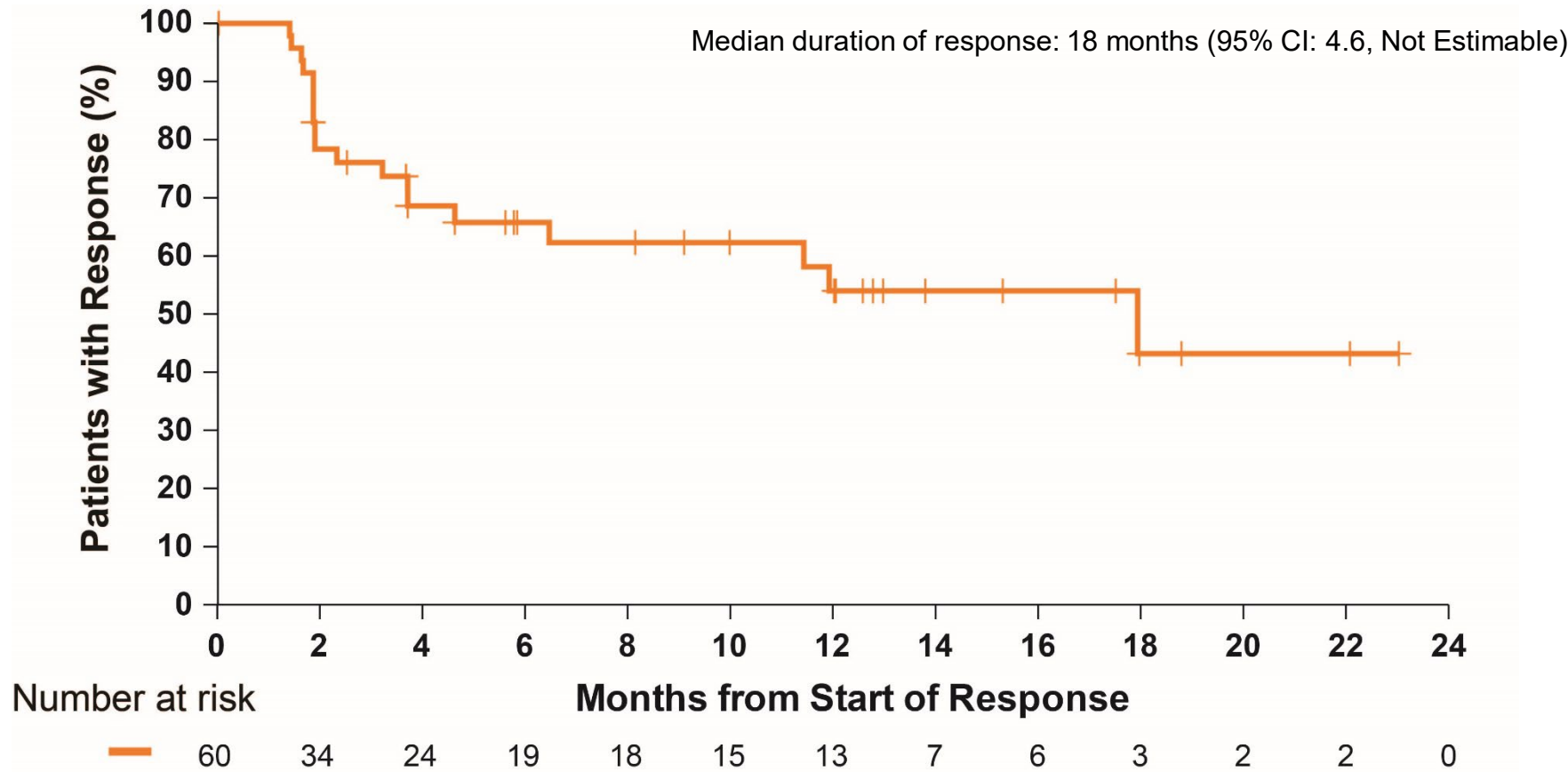
BTK Pre-Treated MCL Patients^a		n=100
Overall Response Rate^b, % (95% CI)	51% (41-61)	
Best Response		
CR, n (%)	25 (25)	
PR, n (%)	26 (26)	
SD, n (%)	16 (16)	
BTK Naive MCL Patients^a		n=11
Overall Response Rate^b, % (95% CI)	82% (48-98)	
Best Response		
CR, n (%)	2 (18)	
PR, n (%)	7 (64)	
SD, n (%)	1 (9)	

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. ^aEfficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. ^bORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia ^a	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest^b							
Bruising ^c	20%	2%	-	-	22%	-	15%
Rash ^d	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage ^e	5%	2%	1% ^g	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter ^f	-	1%	<1%	<1%	2% ^h	-	<1%

No DLTs reported and MTD not reached

96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. ^aAggregate of neutropenia and neutrophil count decreased. ^bAEs of special interest are those that were previously associated with covalent BTK inhibitors. ^cAggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. ^dAggregate of all preferred terms including rash. ^eAggregate of all preferred terms including hematoma or hemorrhage. ^fAggregate of atrial fibrillation and atrial flutter. ^gRepresents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. ^hOf 10 total afib/afflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

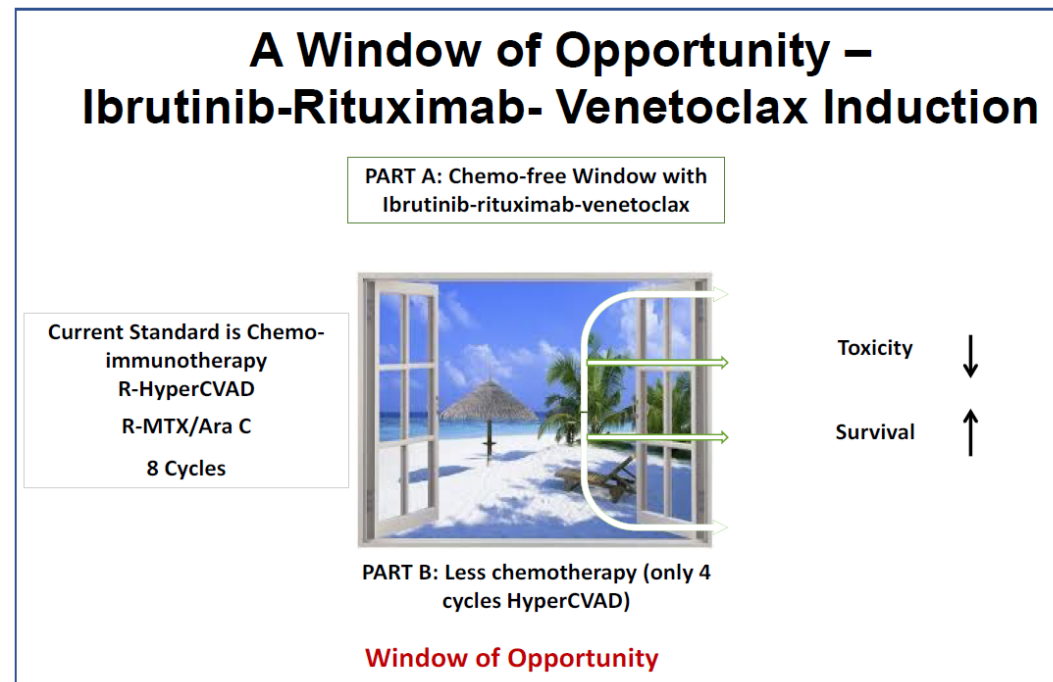
Ibrutinib plus rituximab and venetoclax (IRV) followed by risk-stratified observation or short course R HyperCVAD/MTX in young patients with previously untreated mantle cell lymphoma –phase-II WINDOW-2 clinical trial

Authors: Michael L. Wang¹, Preetesh Jain¹, Hun Ju Lee¹, Chi young Ok², Holly A. Hill¹, Lucy Navsaria¹, Rashmi Kanagal-Shamanna², Luis Malpica¹, Ranjit Nair¹, Swaminathan P. Iyer¹, Felipe Samaniego¹, Wendy Chen¹, Onyeka Oriabure¹, Lei Feng³, Selvi Thirumurthi⁴, David Santos⁵, Guilin Tang², Francisco Vega², Shaoying Li², Michelle Avellaneda¹, Maria Badillo¹ and Christopher Flowers¹

Institutions: ¹Departments of Lymphoma and Myeloma, ²Hematopathology, ³Biostatistics, ⁵Surgical Oncology, ⁴Gastroenterology
MD Anderson Cancer Center, Houston, Texas

Background

- Therefore, a risk stratified approach in W-2 study was adopted to use a triplet of IR+ Venetoclax as induction therapy followed by risk stratified chemo-immunotherapy.



CR Achieved

4 cycles of HyperCVAD/ MTX-AraC

High Risk

Ki-67 $\geq 50\%$ complex karyotype or FISH positive for del7p. MYC positive by FISH or $\geq 50\%$ by immunohistochemistry, mutations in the *TP53*, *NSD2* or in *NOTCH* genes, or largest tumor diameter >5 cm or blastoid/ pleomorphic histology or if they remain in PR after 12 cycles of part 1.

**Maintenance therapy R-Every other month:
I-Daily for up to 24 months
V- Daily for up to 24 months**

2 cycles of HyperCVAD/ MTX-AraC

Moderate Risk

Ki-67 31-49% and no features of High risk disease.
Tumor size 3-4.9cm.

**Maintenance therapy R-Every other month:
I-Daily for up to 24 months
V- Daily for up to 24 months**

No chemotherapy

Low Risk

Ki-67 $< 30\%$ and no risk features of High risk disease.
Tumor size < 3 cm.

**Maintenance therapy R-Every other month:
I-Daily for up to 24 months
V- Daily for up to 24 months**

Results

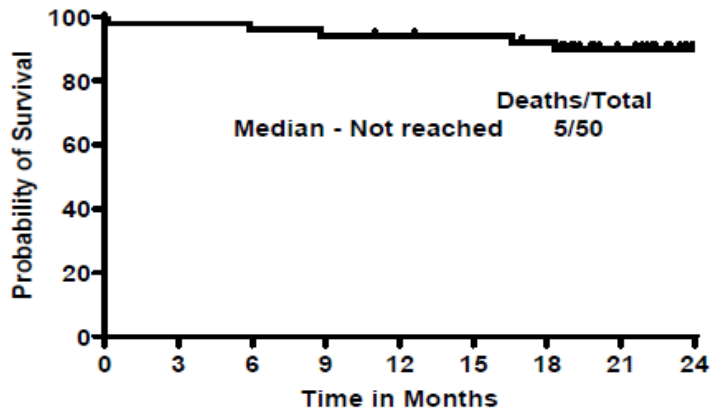
- 20 patients in high-risk group, 20 were in intermediate-risk group and 10 patients in low-risk group.
- High Ki-67 ($\geq 30\%$) in 18/50 (36%) patients. Eighteen (36%) had high and intermediate risk simplified MIPI scores. Six (12%) patients had aggressive MCL (blastoid/pleomorphic).
- Among the 24 *TP53* evaluable patients, eight (33%) had *TP53* aberrations (mutated and/or *TP53* deletion by FISH).

Results

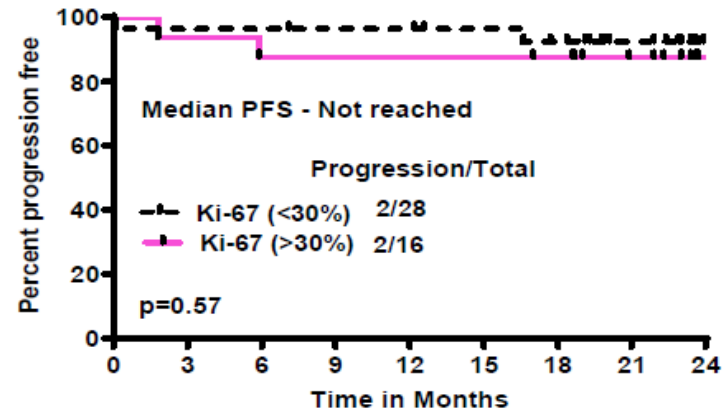
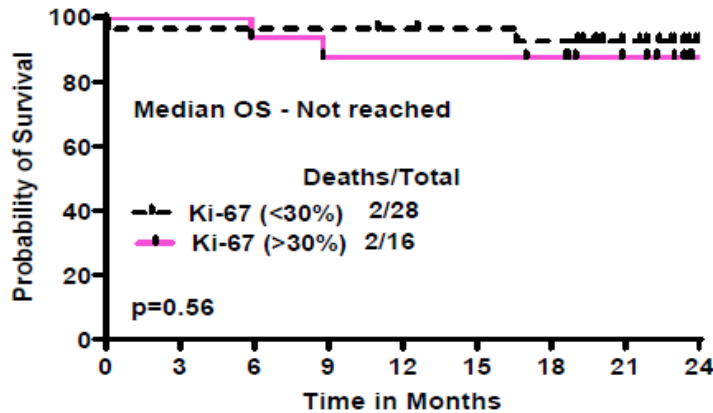
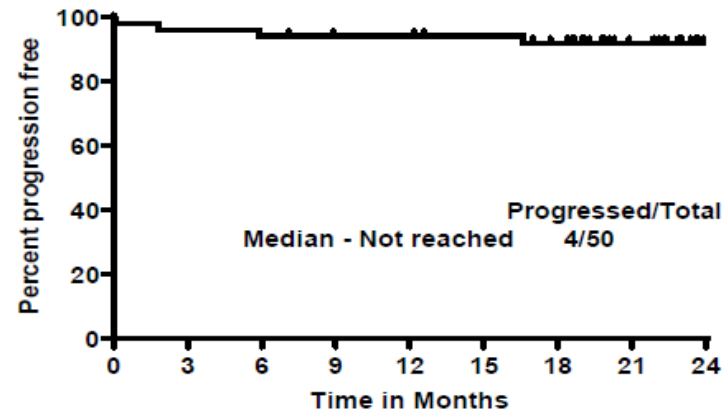
- Forty- eight patients received IRV.
- Best response to IRV was 96% and CR of 92%. After part 2, the best ORR remained unaltered, 96% (92% CR and 4% PR).
- The median number of cycles of triplet IRV to reach best response was 8cycles (range 2- 12).
- Fifteen patients (30%) did not receive part 2 chemotherapy, two patients (4%) received 1 cycle, 16 patients (32%) 2 cycles and 13 patients (26%) got 4 cycles of chemotherapy.

Time to Event Outcomes (median follow up 24 months)

OS



PFS

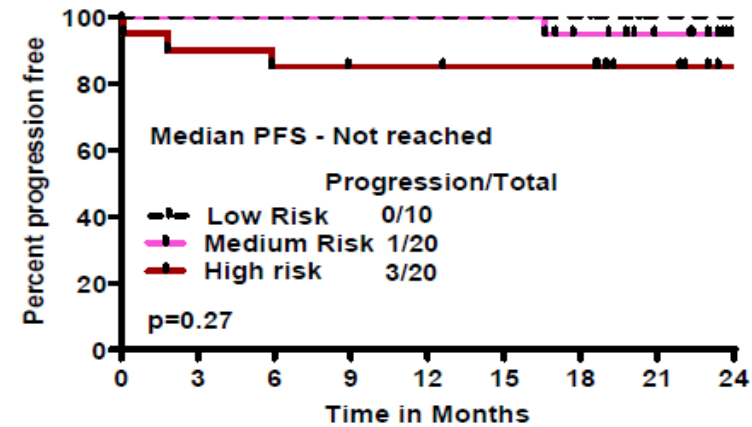
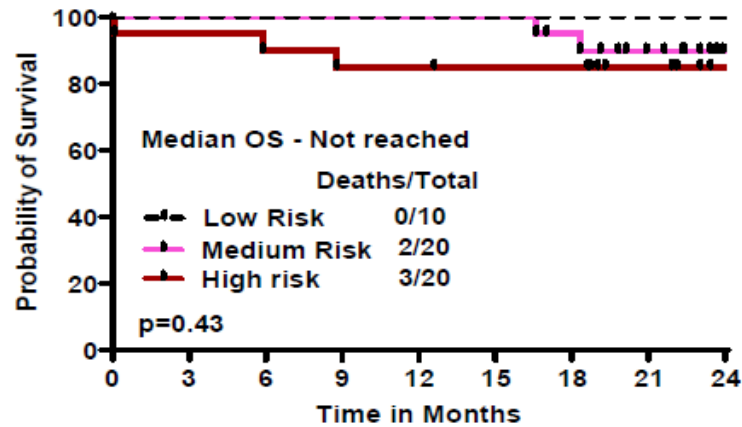
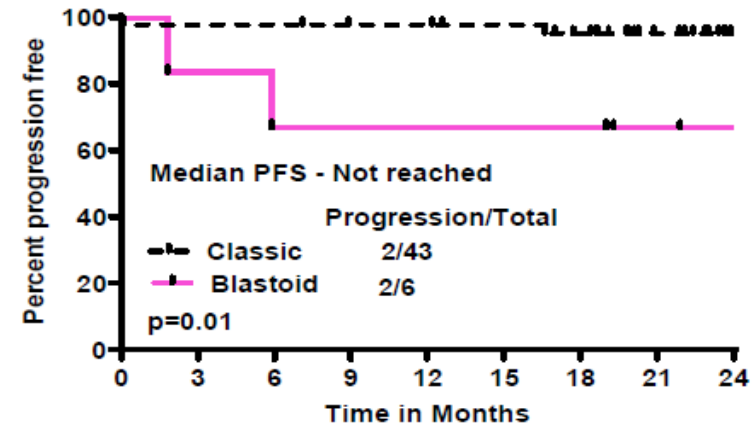
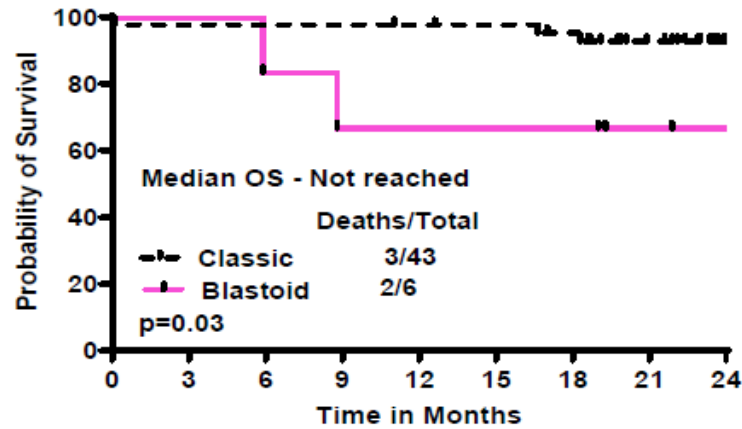


Wang et al, ASH, 2021

Time to Event Outcomes (median follow up 24 months)

OS

PFS



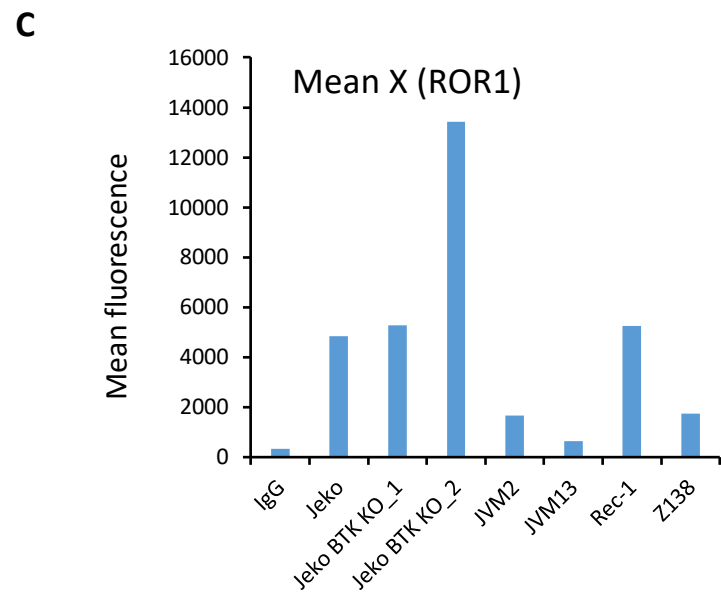
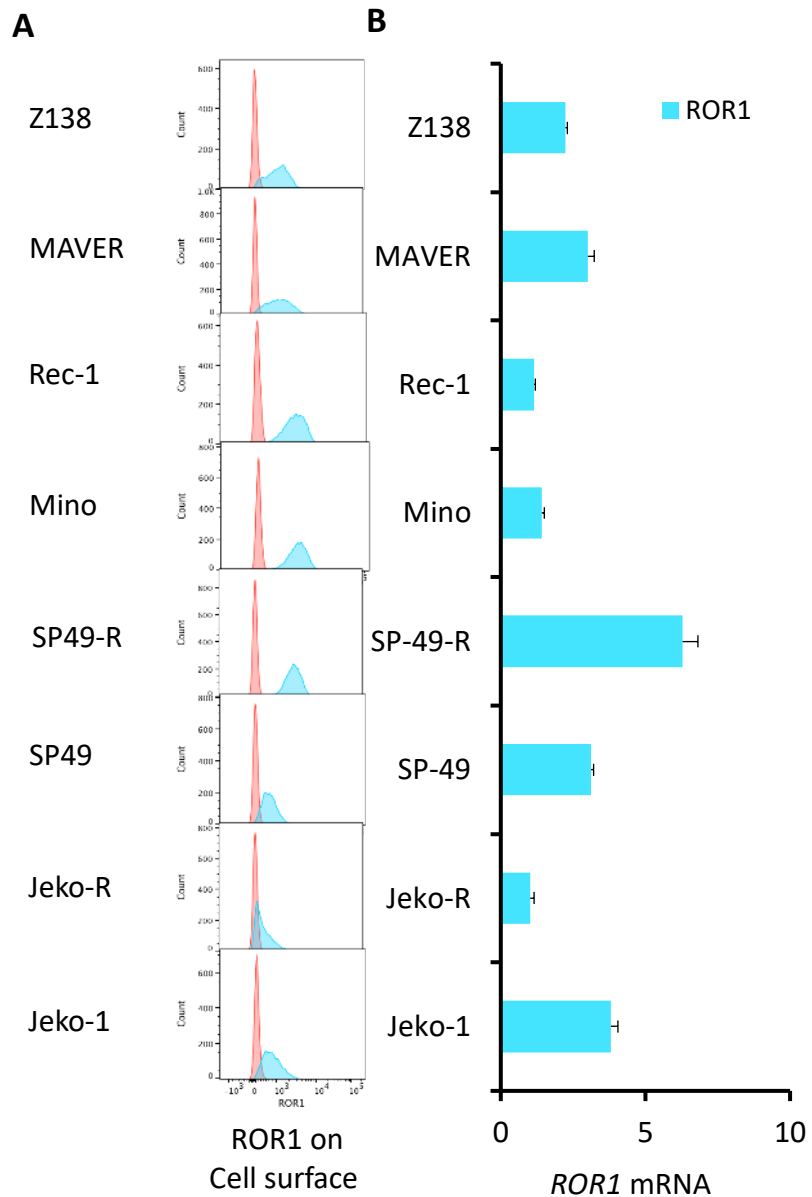
Conclusions

- Chemo-free ibrutinib-rituximab-venetoclax induced an unprecedented efficacy before chemo consolidation.
- Thirteen patients (26%) came off study –5 for adverse events, 3 for on study deaths, and 2 for patient choice, 2 patients lost to follow up and one for disease progression
- Overall, 5 patients died (3 on trial and 2 patients died off study, one due to progressive disease and another due to COVID pneumonia).
- WINDOW-2 approach suggests that patients with low risk MCL, may not need chemotherapy but further follow up is warranted
- Further studies on predictors of response, MRD and clonal evolution are ongoing and will be reported.

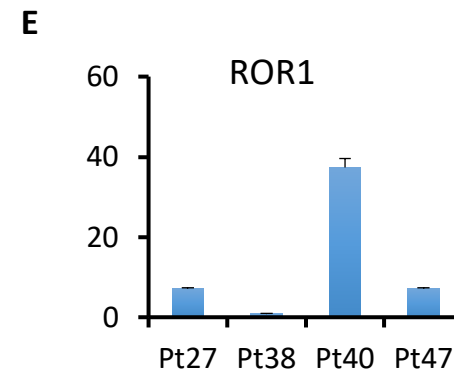
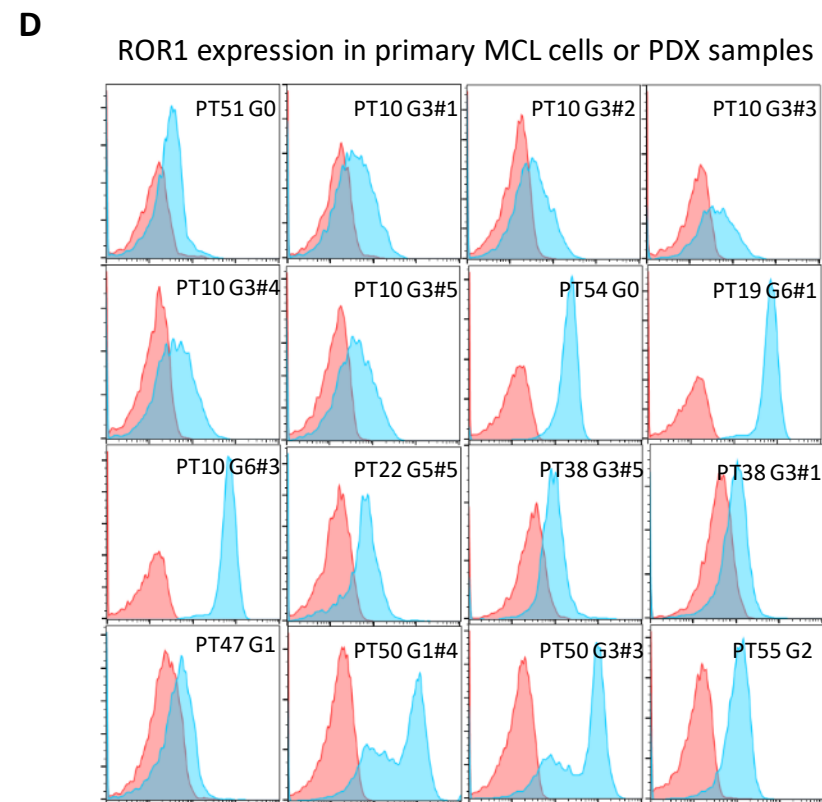
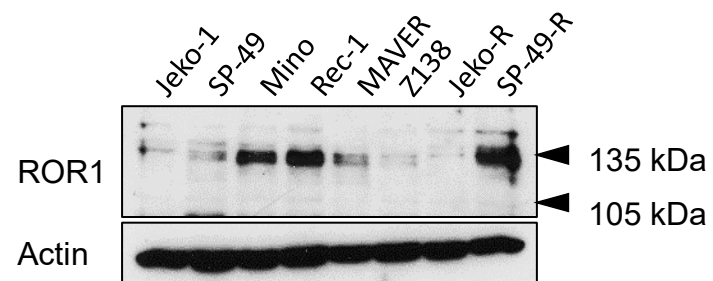
Zilovertamab Enhances Ibrutinib Cytotoxicity in MCL Cells

Vivian Jiang, Wang Lab

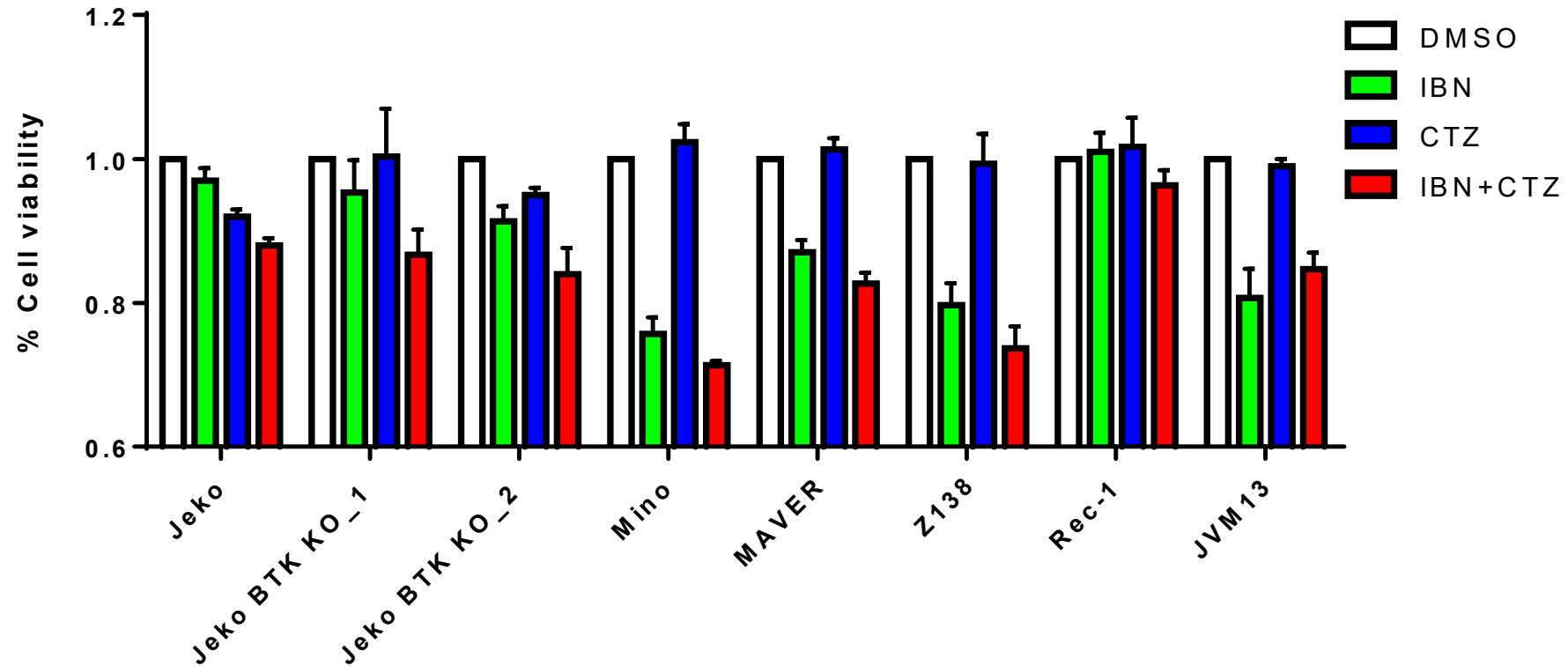
ROR1 expression in MCL cells



E ROR1 protein expression in MCL cell lines



Zilvertamab enhanced IBN induced-cytotoxicity in MCL cells



Treatment (24h)

- Low IBN: 1uM (Jeko), 0.5uM (Rec-1)
- High IBN: 10uM (Jeko BTK KO_1, Jeko BTK KO_2, Mino, MAVER, Z138, JVM13)
- Zilo: 2mg/ml

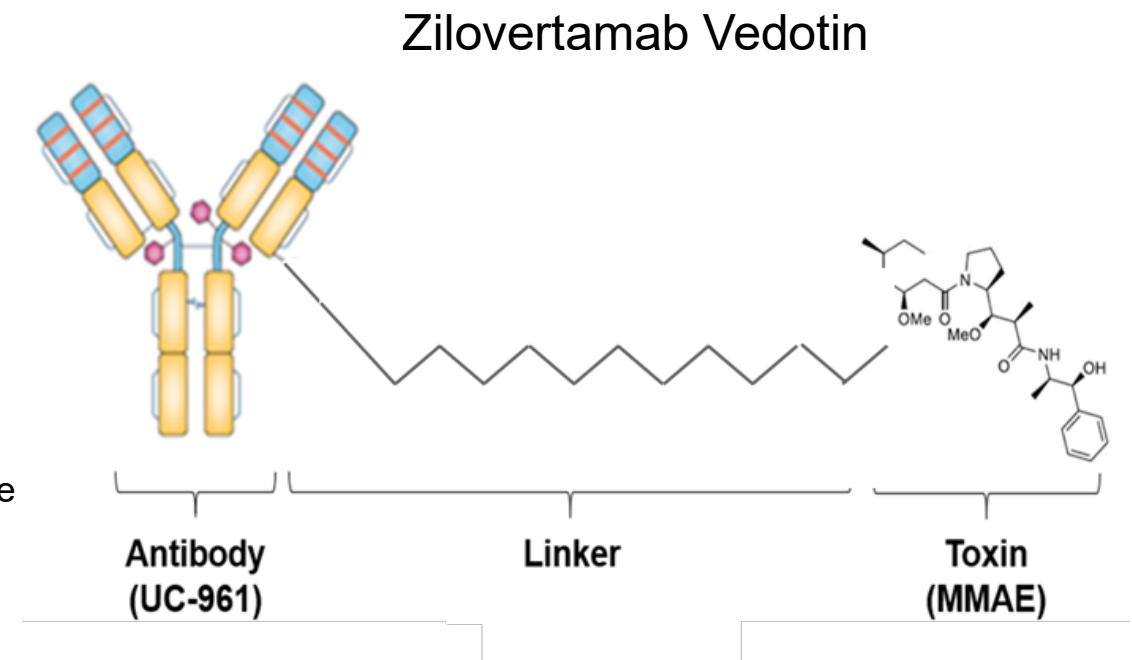
Phase 1 Dose Escalation and Cohort Expansion Study of the Anti-ROR1 Antibody-Drug Conjugate Zilovertamab Vedotin (MK-2140) for the Treatment of Non-Hodgkin Lymphoma

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ROR1 and Zilovertamab Vedotin

- ROR1 is an oncofetal protein important for embryonic development
 - Physiologic expression disappears before birth¹
 - Pathologic expression of ROR1 often reappears in aggressive hematologic and solid tumor cancers²
- ROR1 is present on the tumor cell surface and amenable to targeting with antibody-based therapeutics¹
- Zilovertamab vedotin (MK-2140) is an ADC of:
 - The humanized monoclonal antibody, UC-961, with no normal tissue cross-reactivity
 - A cleavable linker and the anti-microtubule toxin, MMAE³
- Binding to tumor cell ROR1 causes rapid internalization and lysosomal trafficking to deliver MMAE



All Cause Adverse Events of Special Interest in ≥ 4 Patients

All Patients N = 51		
Adverse Event, n (%)	Any Grade	Grade 3 or 4
Peripheral neuropathy ^a	25 (49.0)	4 (7.8)
Decreased neutrophil count	18 (35.3)	16 (31.4)
Decreased hemoglobin	10 (19.6)	8 (15.7)
Paraesthesia	5 (9.8)	0 (0)
Decreased platelet count	5 (9.8)	4 (7.8)
Febrile neutropenia	4 (7.8)	4 (7.8)
Infusion reactions	0	0
Tumor lysis syndrome	0	0

^aIncludes the preferred terms peripheral sensory neuropathy, peripheral neuropathy, peripheral motor neuropathy, and peripheral sensorimotor neuropathy.
Data cutoff: May 18, 2021.

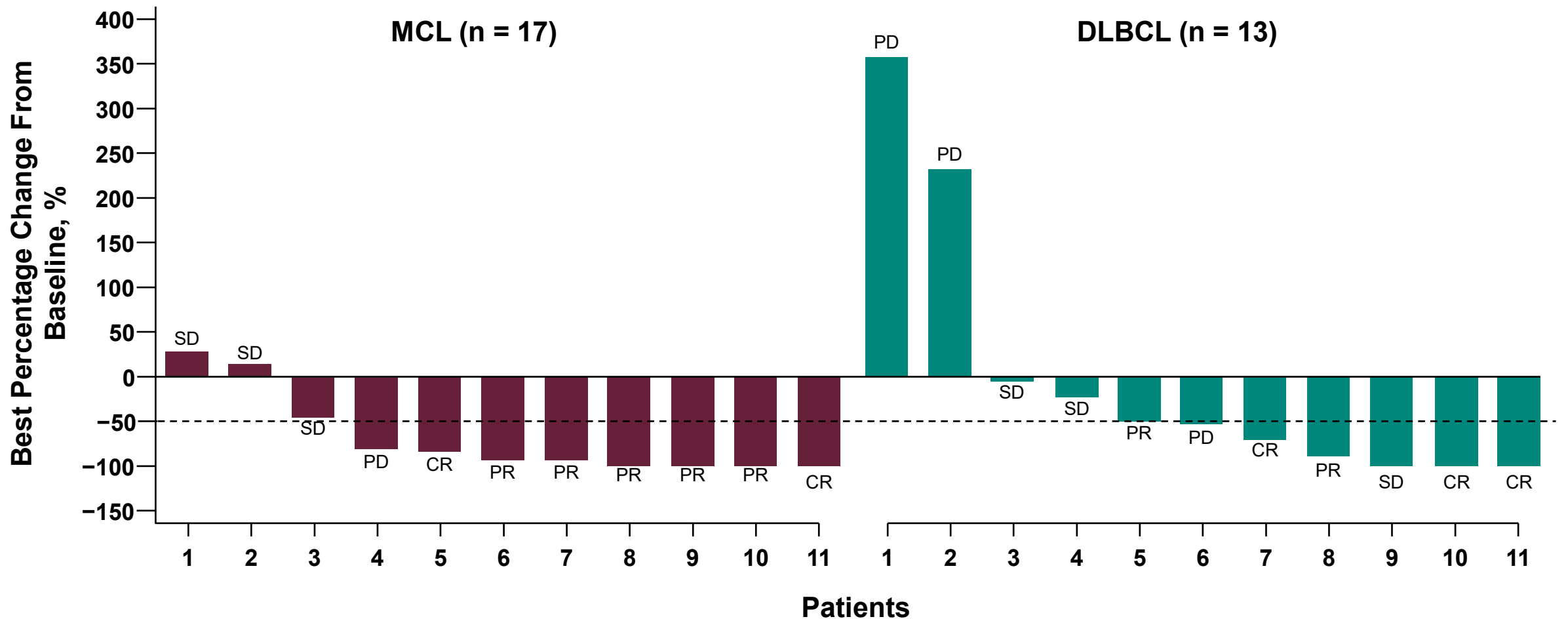
Objective Response Rate

	All Patients ^a N = 51	DLBCL n = 13	MCL n = 17	Prior CAR-T or CAR-NK n = 15
ORR, % (95% CI)	33.3 (20.8-47.9)	38.5 (13.9-68.4)	52.9 (27.8-77.0)	40.0 (16.3-67.7)
BOR, n (%)				
CR	5 (9.8)	3 (23.1)	2 (11.8)	2 (13.3)
PR	12 (23.5) ^b	2 (15.4)	7 (41.2)	4 (26.7)

^aPatients with CLL/SLL and AML did not achieve a response. ^bAt the time of data cutoff, 3 patients with RT experienced a partial response but only had 1 post-baseline assessment.

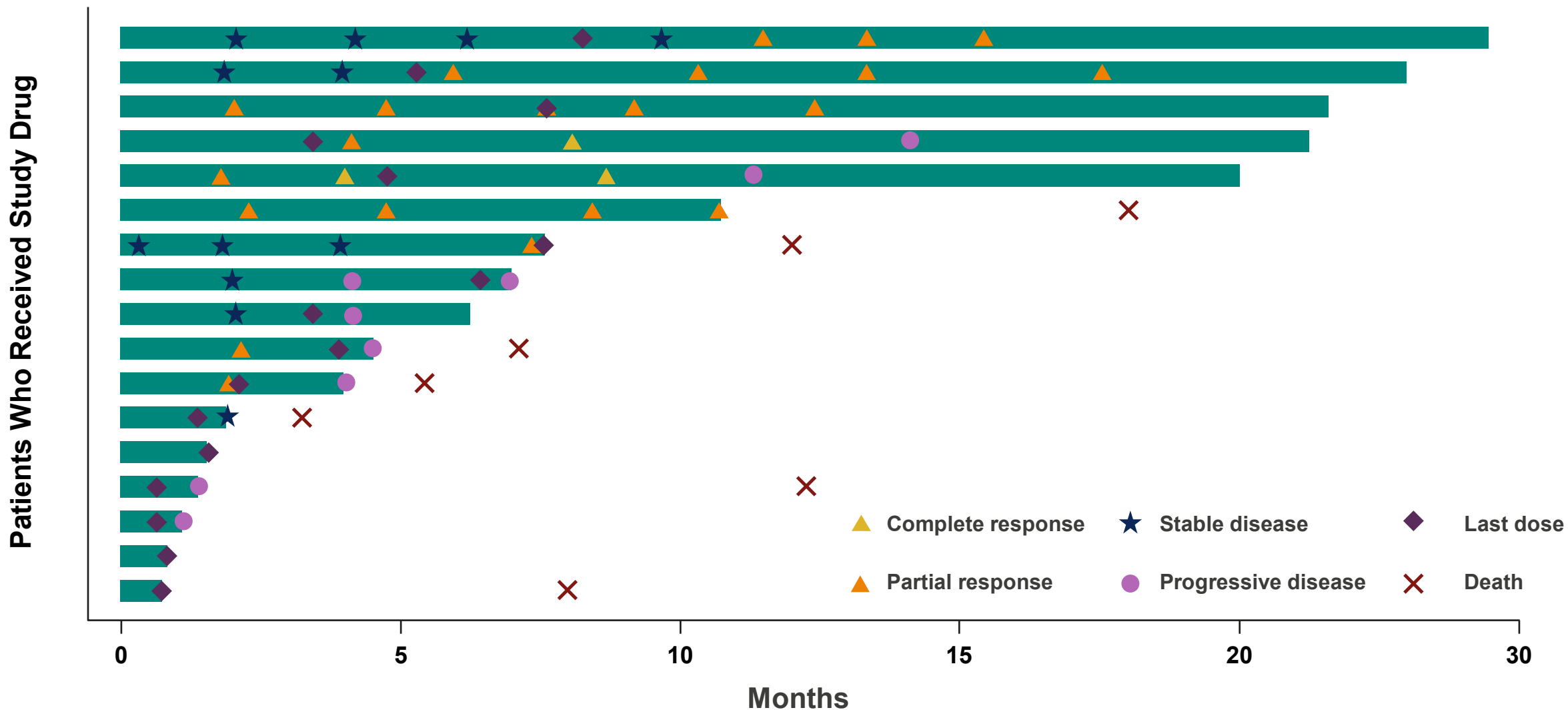
Data cutoff: May 18, 2021.

Percent Change From Baseline in Target Lesions^a



^aSix patients with MCL and 2 patients with DLBCL were excluded from this analysis as they didn't have evaluable postbaseline scans.
Data cutoff: May 18, 2021.

Time to Response and Response Duration: MCL



Summary and Conclusions

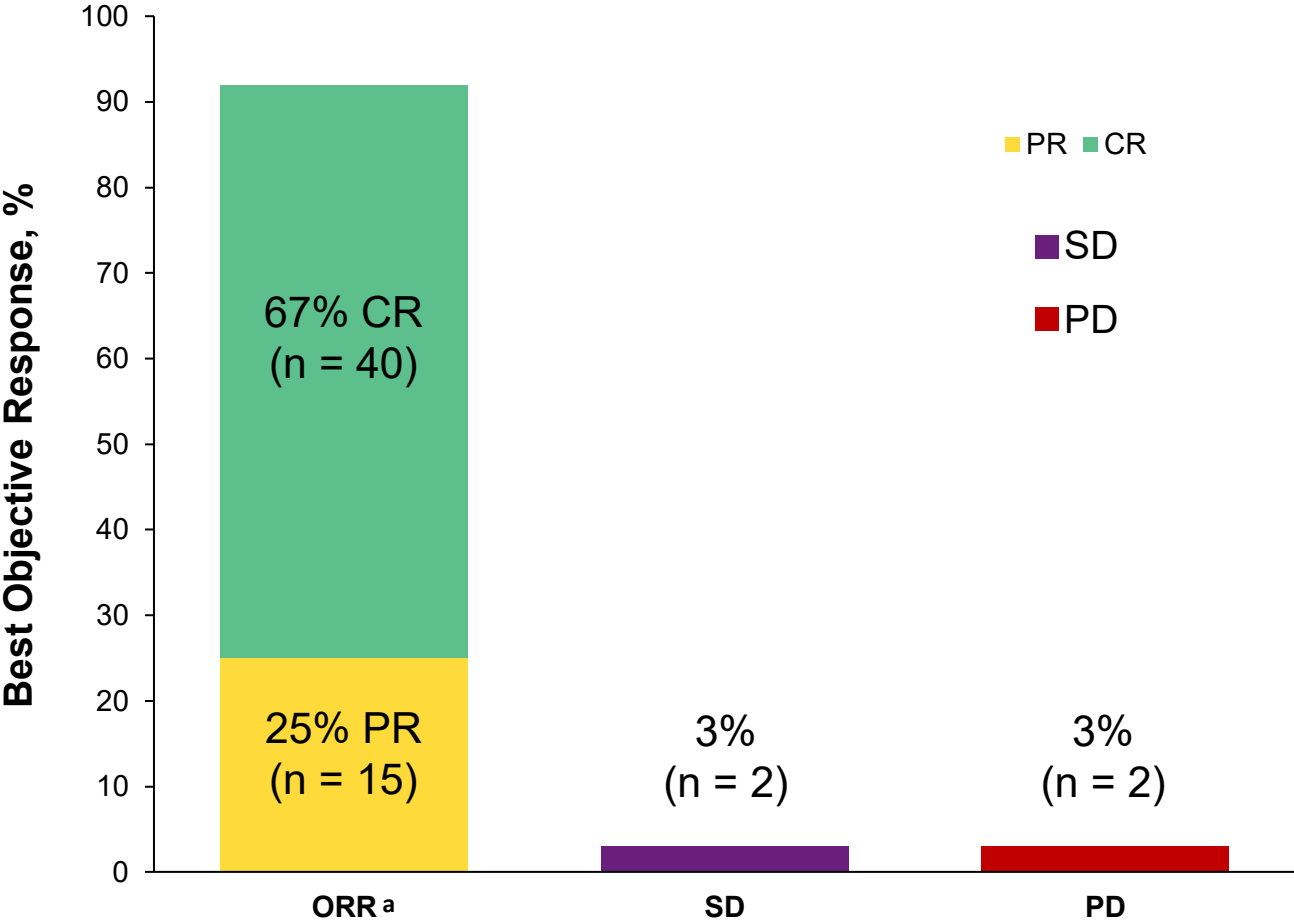
- The novel anti-ROR1 ADC zilovetamab vedotin was associated with a tolerable safety profile in schedule 1 of this study
 - Few dose-limiting toxicities observed up to the MTD of 2.5 mg/kg
 - The most common AEs were fatigue and neutropenia
 - GI AEs included nausea and diarrhea
 - The primary cumulative toxicity was peripheral neuropathy
 - No ROR-mediated toxicities (infusion reactions or tumor lysis syndrome) were observed
- Zilovetamab vedotin demonstrated clinical activity in patients with relapsed NHL
 - ORR was 38.5% for patients with DLBCL and 52.9% for patients with MCL
 - For patients who previously received CAR-T/CAR-NK, ORR was 40.0%
- Targeting the ROR1 pathway with zilovetamab vedotin is a promising therapeutic option for heavily pretreated patients with relapsed NHL

One-Year Follow-Up of ZUMA-2, the Multicenter, Registrational Study of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma

Michael L. Wang, MD¹; Javier Munoz, MD²; Andre Goy, MD³; Frederick L. Locke, MD⁴;
Caron A. Jacobson, MD⁵; Brian T. Hill, MD, PhD⁶; John M. Timmerman, MD⁷; Houston Holmes, MD⁸;
Samantha Jaglowski, MD⁹; Ian W. Flinn, MD, PhD¹⁰; Peter A. McSweeney, MD¹¹; David B. Miklos, MD, PhD¹²;
John M. Pagel, MD, PhD¹³; Marie José Kersten, MD, PhD¹⁴; Krimo Bouabdallah, MD¹⁵; Henry C.H. Fung, MD¹⁶;
Max S. Topp, MD¹⁷; Roch Houot, MD¹⁸; Amer Beitinjaneh, MD¹⁹; Weimin Peng, PhD²⁰; Lianqing Zheng, PhD²⁰;
John M. Rossi, MS²⁰; Swaminathan Murugappan, MD, PhD²⁰; Ioana Kloos, MD²⁰; and Patrick M. Reagan, MD²¹

¹The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ³John Theurer Cancer Center, Hackensack, NJ, USA; ⁴Moffitt Cancer Center, Tampa, FL, USA; ⁵Dana-Farber Cancer Institute, Boston, MA, USA; ⁶Cleveland Clinic Foundation, Cleveland, OH, USA; ⁷David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; ⁸Texas Oncology, Dallas, TX, USA; ⁹The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; ¹⁰Sarah Cannon Research Institute, Nashville, TN, USA; ¹¹Colorado Blood Cancer Institute, Denver, CO, USA; ¹²Stanford University School of Medicine, Stanford, CA, USA; ¹³Swedish Cancer Institute, Seattle, WA, USA; ¹⁴Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, on behalf of HOVON/LLPC; ¹⁵Hopital Haut Leveque, Pessac, France; ¹⁶Fox Chase Cancer Center, Philadelphia, PA, USA; ¹⁷Universitätsklinikum Würzburg, Würzburg, Germany; ¹⁸CHU Rennes, Rennes, France; ¹⁹University of Miami, Miami, FL, USA; ²⁰Kite, a Gilead Company, Santa Monica, CA, USA; and ²¹University of Rochester Medical Center, Rochester, NY, USA

ORR by IRRC Assessment Was 92% (95% CI, 82 – 97) and CR Rate Was 67% (95% CI, 53 – 78)



- At a median follow-up of 17.5 months (range, 12.3 – 37.6), 29 of 60 evaluable patients (48%) remain in ongoing responses
 - 28 of 40 patients who achieved CR (70%) remain in response
- The first 28 patients treated had a median follow-up of 32.3 months (range, 30.6 – 37.6)
 - 39% of patients remain in continued remission with no further therapy
- In all enrolled patients (N = 74), ORR was 84% (59% CR rate)

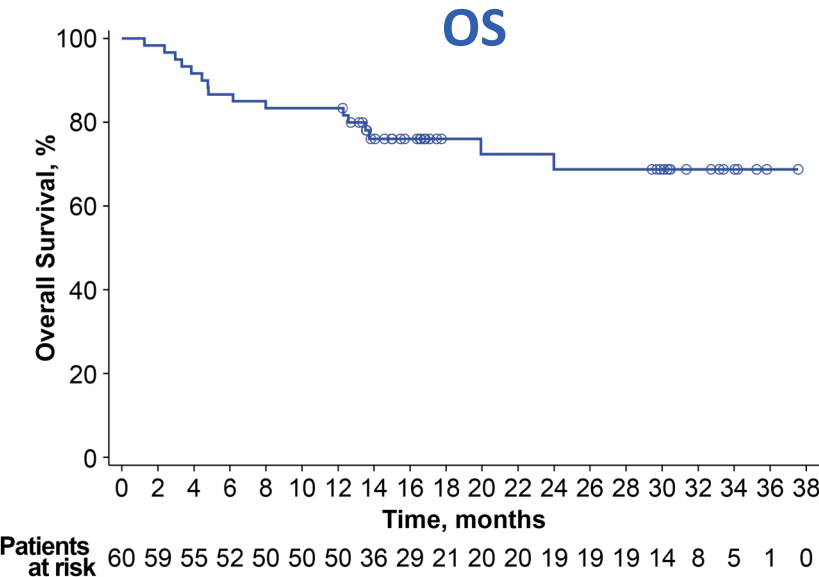
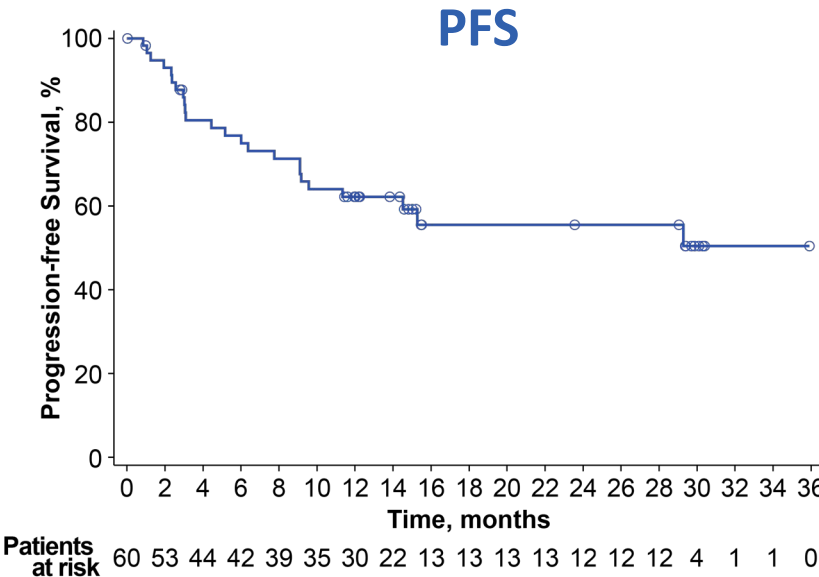
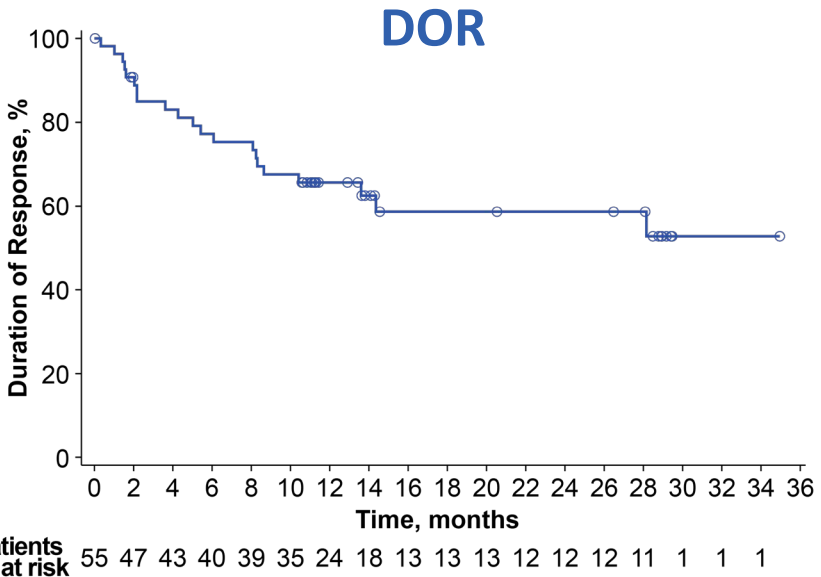
^a Assessed by an IRRC according to the Lugano Classification.¹ One patient was not evaluable.

1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response, Progression-Free Survival, and Overall Survival

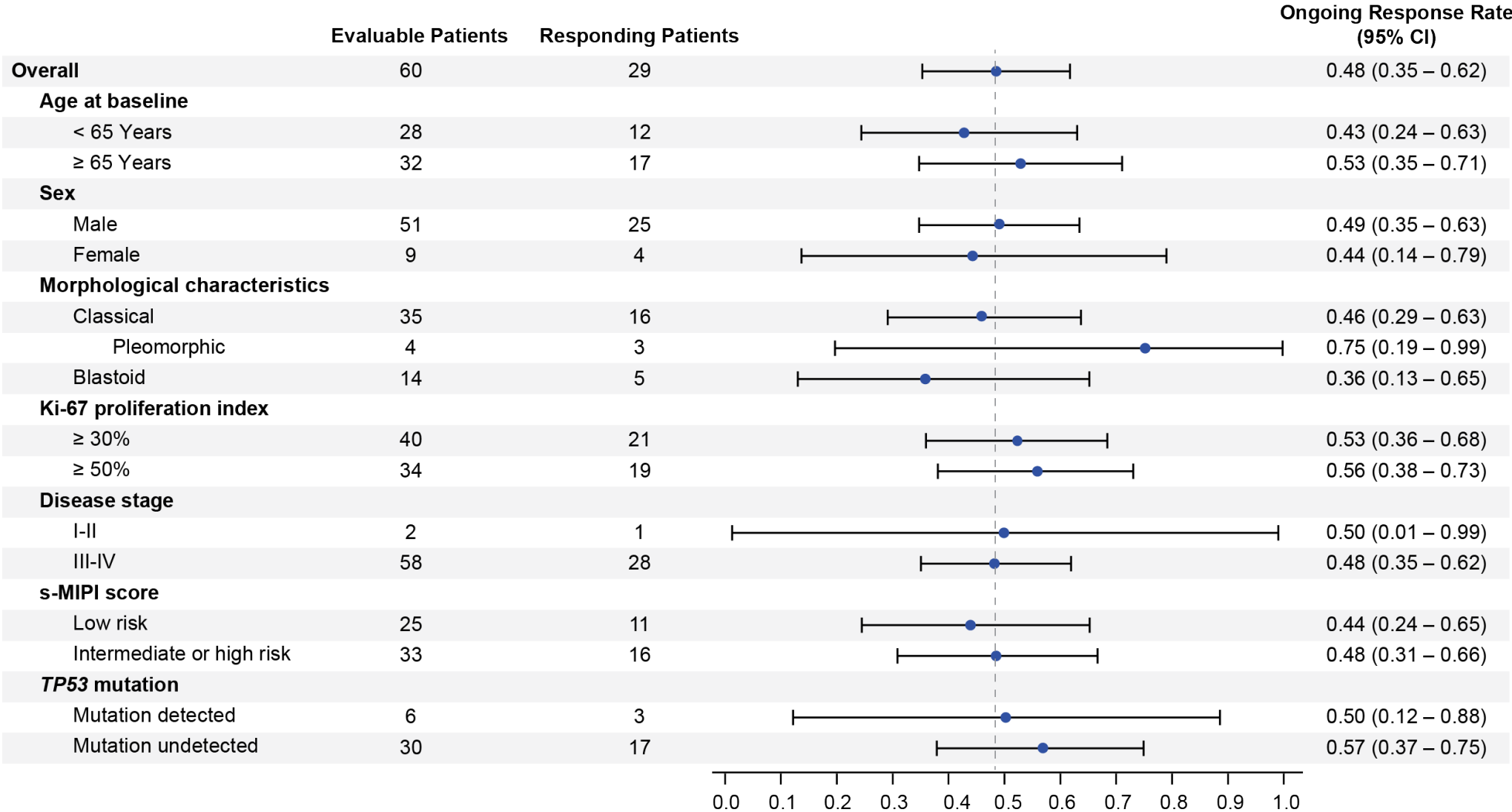
- The medians for DOR, PFS, and OS were not reached after a median follow-up of 17.5 months



	DOR		PFS		OS	
	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %	Median (95% CI), mo	15-Mo Rate (95% CI), %
Evaluable pts (N = 60)	NR (14 – NE) ^a	59 (43 – 72) ^a	NR (10 – NE)	59 (45 – 71)	NR (NE – NE)	76 (63 – 85)
Pts in CR (n = 40)	NR (14 – NE)	70 (49 – 83)	NR (15 – NE)	75 (57 – 87)	NR (NE – NE)	92 (76 – 97)
Pts in PR (n = 15)	2 (1 – 4)	24 (6 – 49)	3 (2 – 5)	24 (6 – 49)	13 (3 – NE)	47 (21 – 69)

^a Of 55 total responding patients.
 CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; PFS, progression-free survival; PR, partial response; pts, patients; OS, overall survival.

Ongoing Response Rate Was Consistent Across Adverse Prognostic Subgroups



s-MIPI, simplified Mantle Cell Lymphoma International Prognostic Index.

Adverse Events

AE, n (%) ^a	All Treated Patients (N = 68)			
	Present ≥ 3 Months Post-Infusion		Present ≥ 6 Months Post-Infusion	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any AE	55 (81)	33 (48)	49 (72)	25 (37)
Anemia	22 (32)	9 (13)	13 (19)	4 (6)
Neutropenia	20 (29)	16 (24)	14 (21)	11 (16)
Thrombocytopenia	20 (29)	14 (21)	14 (21)	9 (13)
White blood cell count decrease	16 (24)	9 (13)	12 (18)	6 (9)
Fatigue	10 (15)	0	10 (15)	0
Pneumonia	9 (13)	5 (7)	6 (9)	4 (6)
Cough	8 (12)	0	7 (10)	0
Hypogammaglobulinemia	8 (12)	0	7 (10)	0
Upper respiratory tract infection	7 (10)	2 (3)	5 (7)	1 (1)

AE, n (%)	All Treated Patients (N = 68)	
	Occurred Between Last DCO and Current DCO ^b	
	Any Grade	Grade ≥ 3
Any AE	13 (19)	9 (13)
Neutropenia	6 (9)	6 (9)
Infection	5 (7)	1 (1)
Anemia	3 (4)	1 (1)
Neurologic event	2 (3) ^c	1 (1)
Thrombocytopenia	2 (3)	2 (3)
CRS	0	0
Hypogammaglobulinemia	0	0
Tumor lysis syndrome	0	0

- No new safety signals were observed with additional follow-up
- No new CRS or new Grade 5 events occurred since the previous report

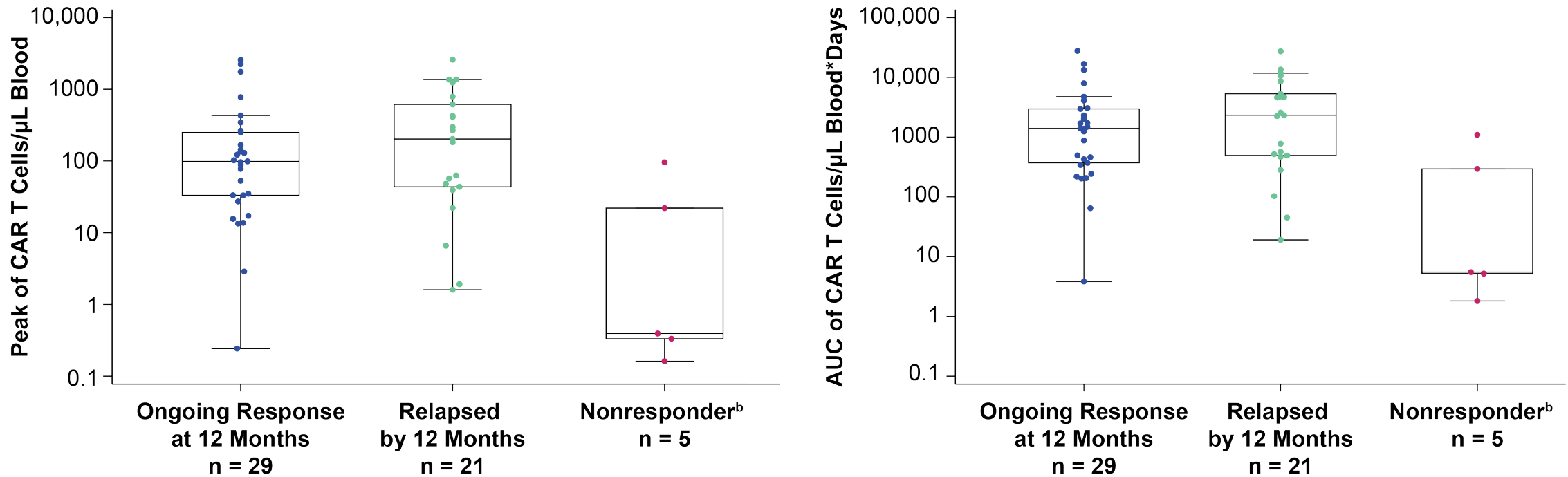
^a Includes AEs of any grade occurring in ≥ 10% of patients.

^b Includes all AEs that occurred after the primary analysis data cutoff date (July 24, 2019) and by the data cutoff date of the current analysis (December 31, 2019).

^c Grade 1 impaired balance (n = 1, Day 106); Grade 3 encephalopathy (n = 1, Day 397).

AE, adverse event; CRS, cytokine release syndrome; DCO, data cutoff.

Robust Expansion of CAR T Cells is Required to Achieve a Response to KTE-X19



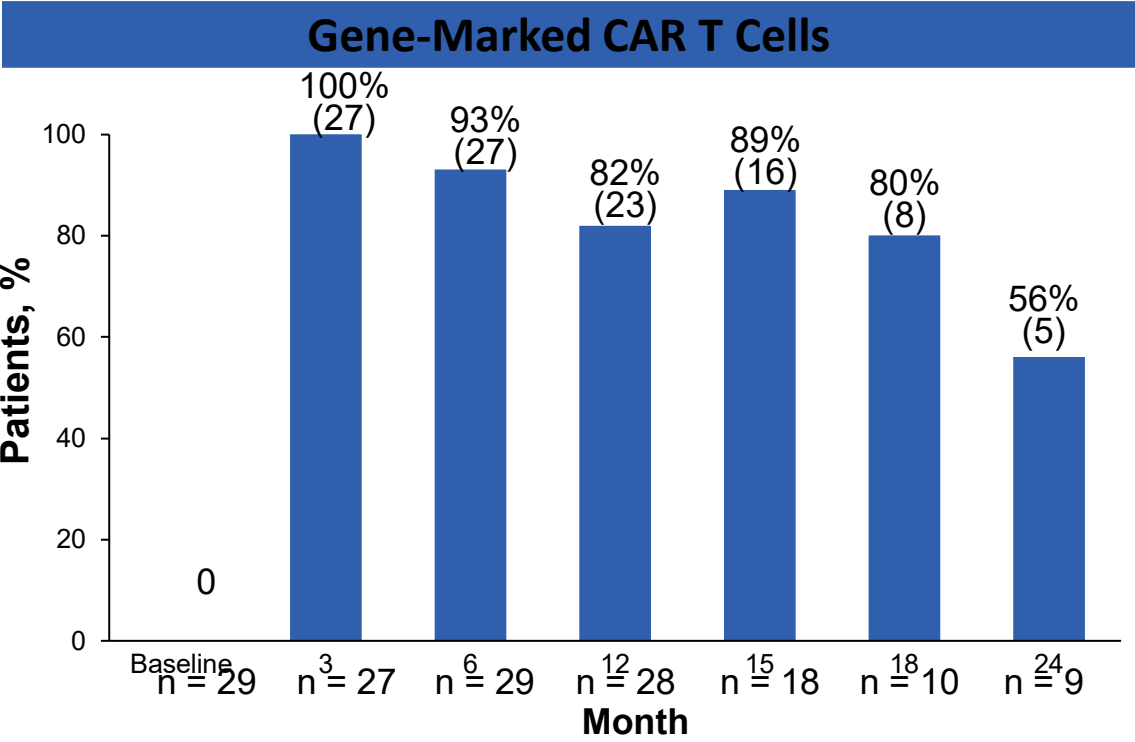
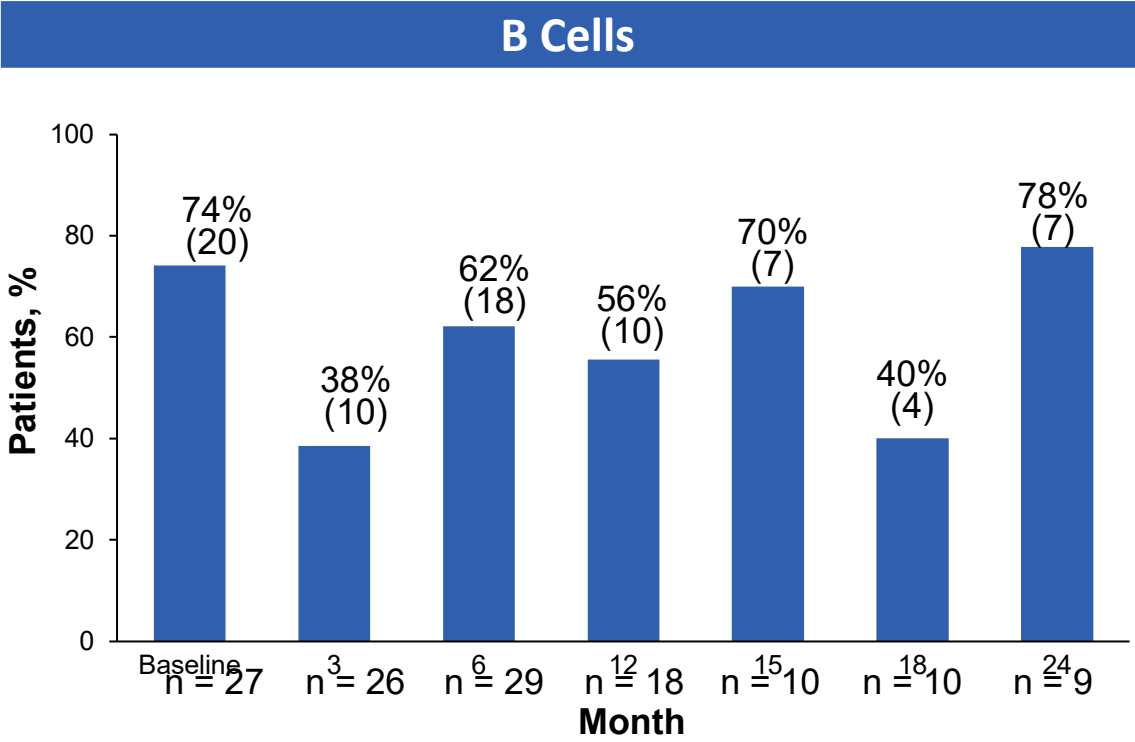
- Peak CAR T cell expansion^a was higher in patients with an ongoing response at 12 months or those who relapsed at 12 months compared with that in nonresponding patients
- Additional mechanistic studies are ongoing to further understand the observed

^a CAR T cell kinetics is related to Day 28 response and durability

^b Includes 2 patients with stable disease, 2 with progressive disease, and 1 who was not evaluable.

AUC, area under the curve; CAR, chimeric antigen receptor.

Detectable B Cells and CAR T Cells Over Time Among Patients With Ongoing Responses at 12 Months



- Of 57 efficacy-evaluable patients with data available at baseline, 48 (84%) had detectable B cells at baseline
- Among patients with ongoing responses at 12 months, recovery of B cells increased over time and gene-marked CAR T cells decreased over time
- No association between CAR T cell expansion measured within 2 weeks post-infusion and B cell aplasia was observed

CAR, chimeric antigen receptor.

Conclusions

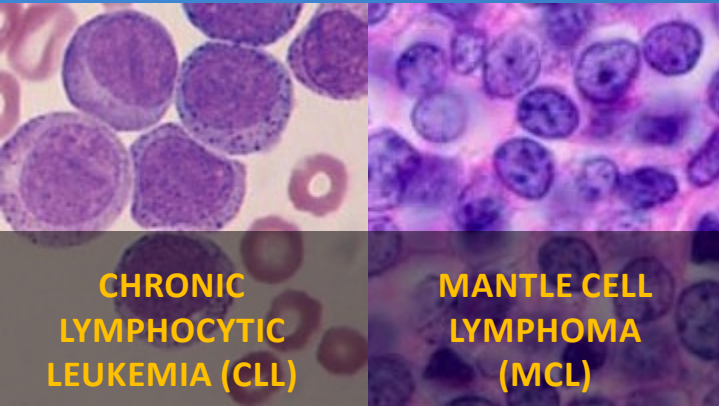
- At a median follow-up of 17.5 months, the ZUMA-2 study continues to show substantial and durable clinical benefit of KTE-X19 therapy in patients with R/R MCL
 - The ORR was 92% (67% CR rate), with ongoing durable responses in 48% of all efficacy-evaluable patients at the data cutoff date; 70% of patients who achieved CR remain in response
 - Ongoing response rates were largely consistent among patients with high-risk disease characteristics
 - Medians were not reached for DOR, PFS, or OS after a median 17.5 months
- KTE-X19 therapy resulted in a manageable safety profile with extended follow-up
 - AE rates decreased over time; no new safety signals were observed since the previous report
- The pharmacology findings in ZUMA-2 point to different mechanisms responsible for primary and secondary treatment failure in R/R MCL
 - We previously reported that most relapsed patients had detectable CD19 at relapse¹
 - In this analysis, elevated CAR T cell levels were observed in patients who are still in response and who initially responded, then relapsed, versus those in patients who failed to respond

1. Wang M, et al. *N Engl J Med*. 2020;382:1331-1342.

AE, adverse event; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory.

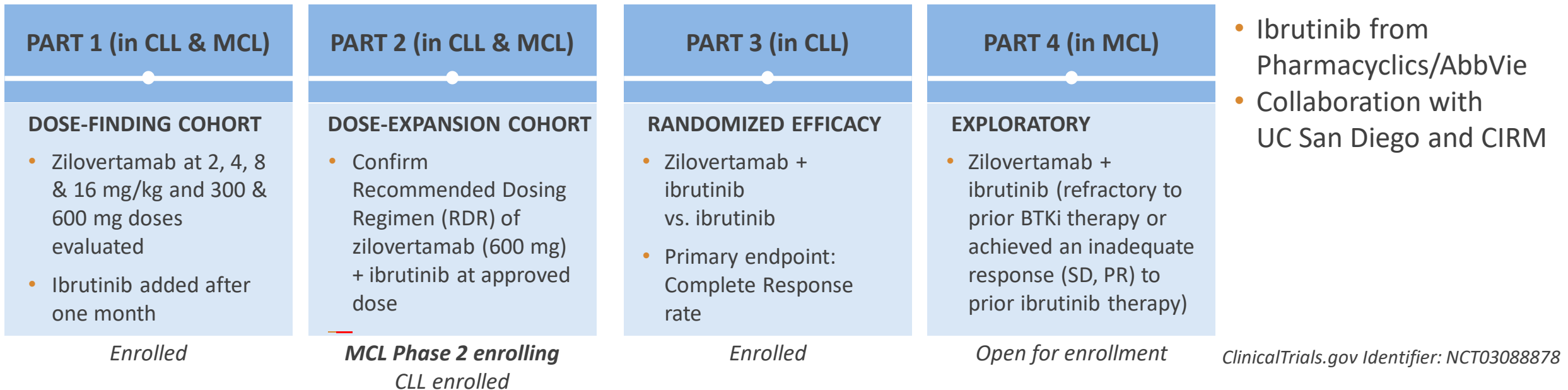
Topics	Presented by
Introduction	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics
Heme Malignancies <ul style="list-style-type: none">• Lymphoma / MCL treatment overview• Oncternal Zilovertamab and ROR1 cell therapy program update• Q&A	<ul style="list-style-type: none">• Michael Wang, MD (MD Anderson Cancer Center)• Salim Yazji, MD, CMO• Gunnar Kaufmann, PhD, CSO• Rajesh Krishnan, PhD, CTO
Prostate Cancer <ul style="list-style-type: none">• Unmet needs in prostate cancer treatment• Oncternal ONCT-534 Dual-Action AR Inhibitor value proposition and other opportunities• Q&A	<ul style="list-style-type: none">• Evan Yu, MD (Fred Hutchinson Cancer Research Center)• Oncternal Therapeutics Management
Wrap-up	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

CIRLL Trial (CIRM-0001) – Phase 1/2 Study of Zilovertamab and Ibrutinib in Patients with MCL and CLL



- ✓ Encouraging interim clinical data in MCL and CLL presented at ASH 2021
- ✓ Opened new treatment cohort in MCL patients who are refractory to prior BTK inhibitor treatment, or who had an inadequate response to ibrutinib

STUDY DESIGN

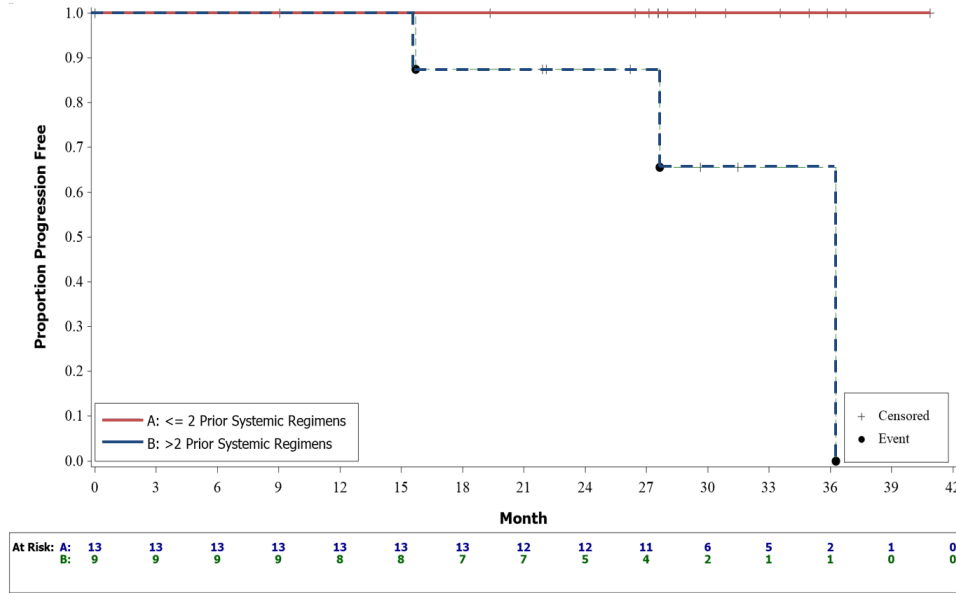


CIRLL = Cirmtuzumab and Ibrutinib targeting ROR1 for Leukemia and Lymphoma
CIRM = California Institute for Regenerative Medicine

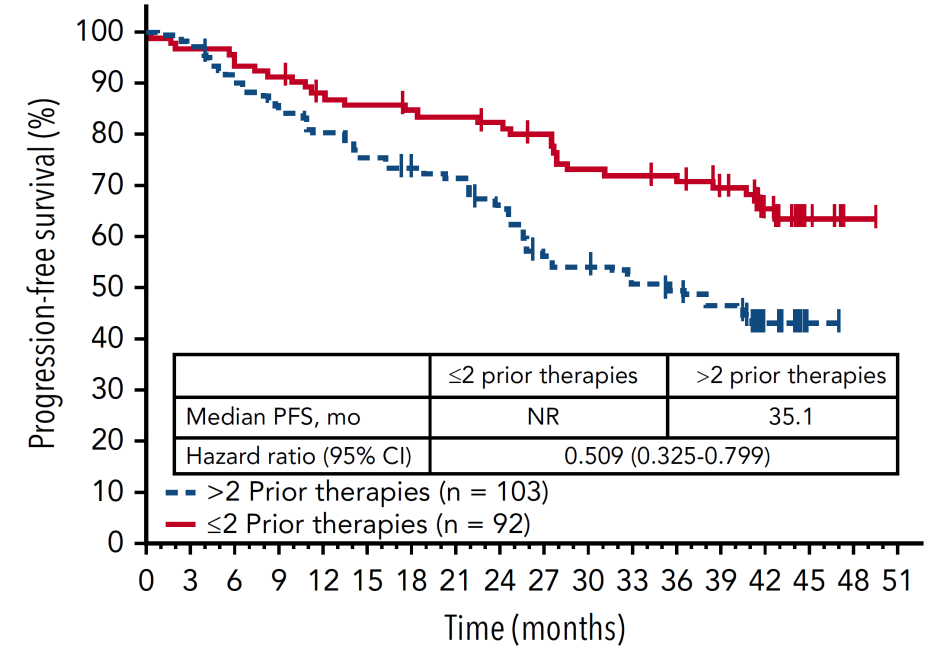
CLL: Encouraging landmark PFS based on number of prior lines of therapy

Zilovertamab + Ibrutinib Data Update at ASH 2021

**Zilovertamab + ibrutinib
(Oncternal Data Oct 2021)
PFS**



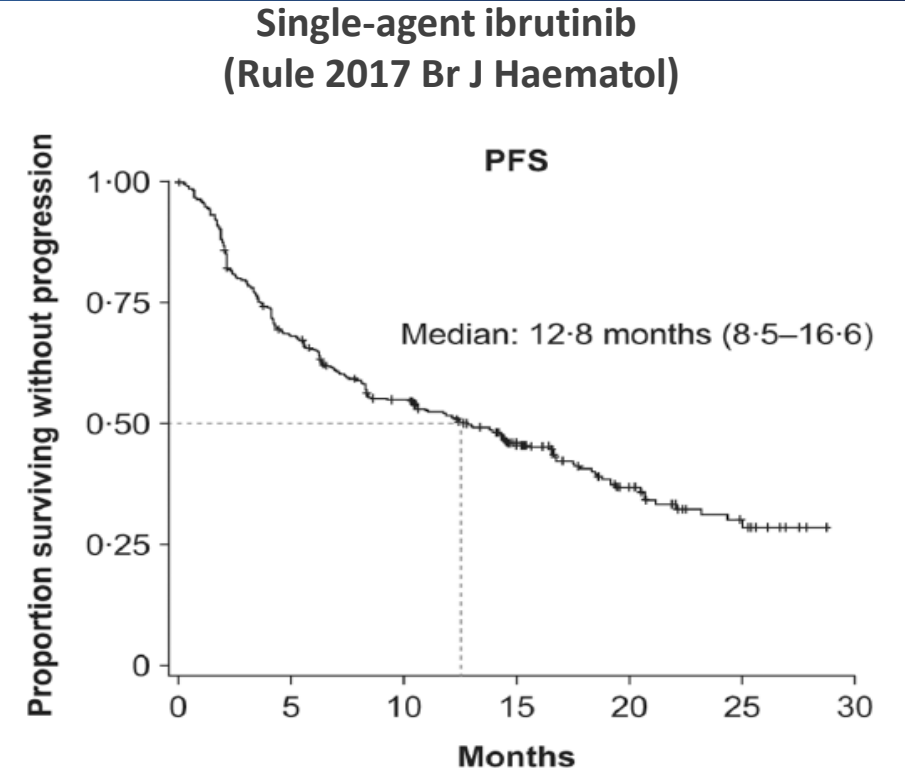
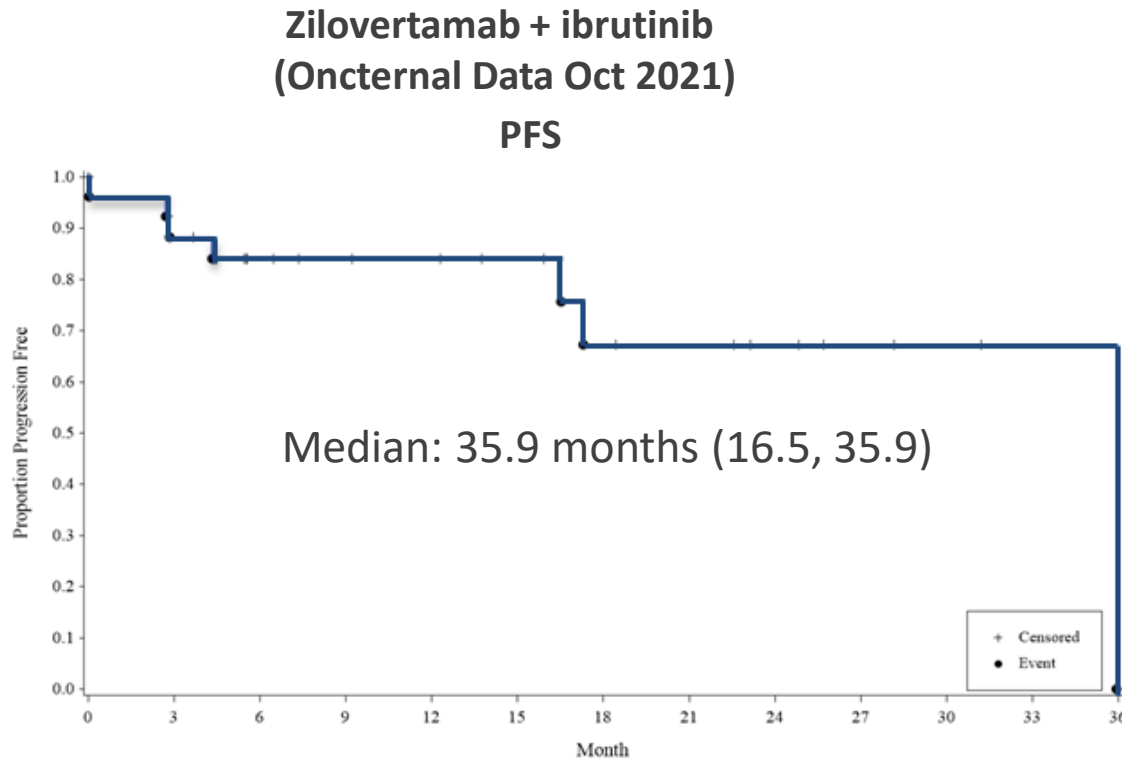
PFS by prior therapies from single-agent ibrutinib treatment in high-risk, relapsed patients with CLL (Byrd, Blood 2019)



PFS by Subtypes – Prior Systemic Therapy	Prior sys. therapy	Landmark PFS 24 months	Landmark PFS 36 months	Landmark PFS 24 months	Landmark PFS 36 months
	≤ 2	~100%	~100%	~85%	~75%
> 2	~85%	~65%	~65%	~50%	

R/R MCL: Compares Favorably to Historical Single-Agent Ibrutinib Data

Zilovertamab + Ibrutinib Data Update at ASH 2021

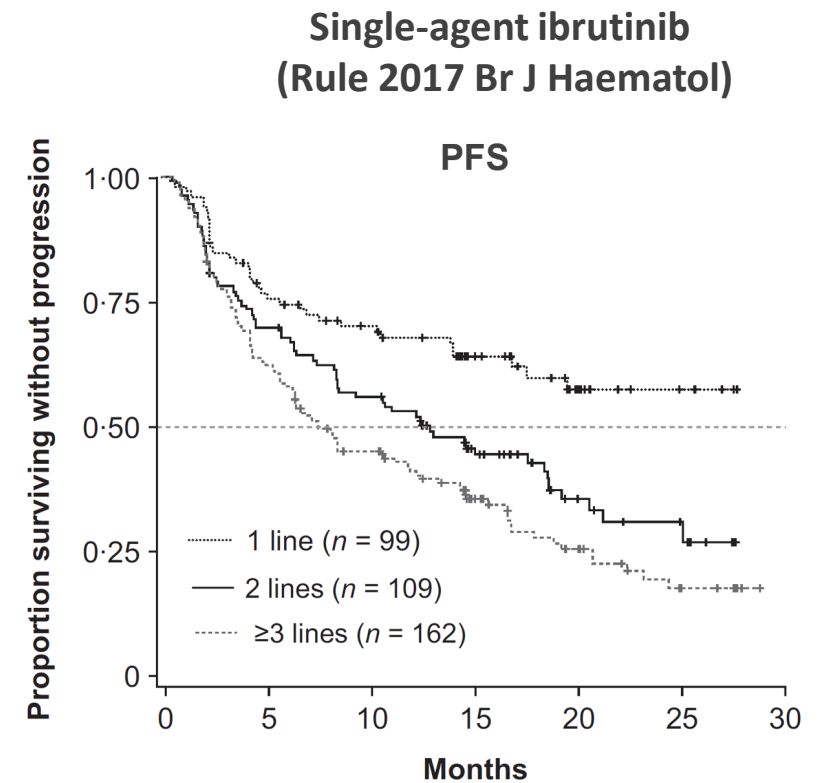
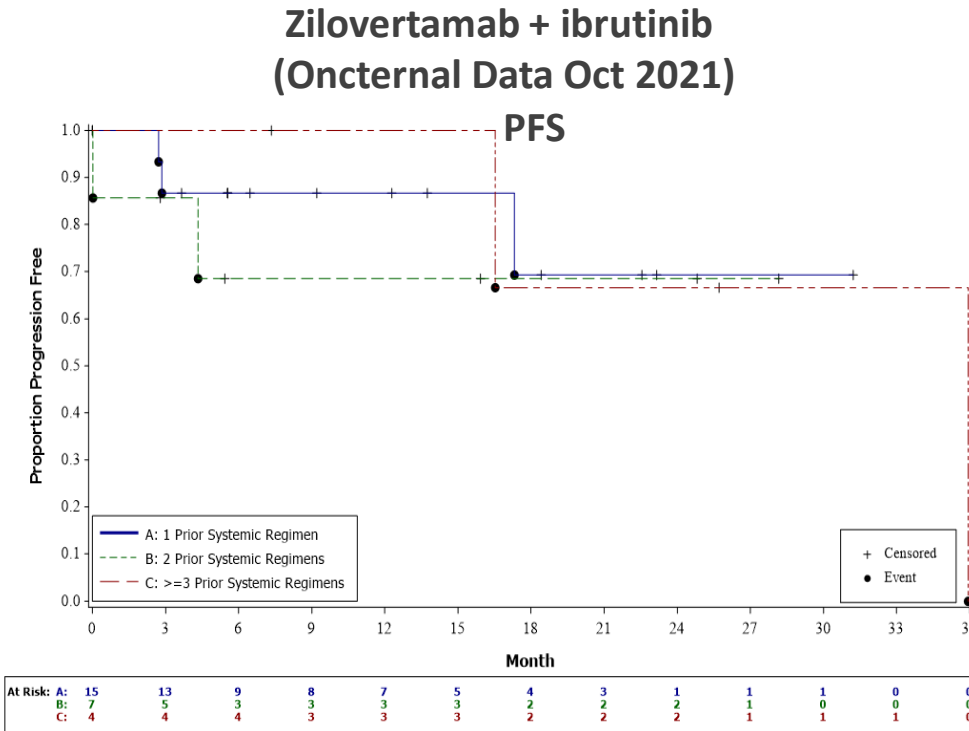


Baseline characteristics	Median follow-up	14.4 months	24-25 months
	Median PFS	35.9 months 95% CI: (16.5 – 35.9 months)	12.8 months. 95% CI: (8.5 – 16.6 months)
Clinical outcomes	ORR	80.8%	66%
	CR	34.6%	20%

Note: Data presented are from separate studies and such data may not be directly comparable due to differences in study protocols, conditions and patient populations. Accordingly, cross-trial comparisons may not be reliable predictors of the relative efficacy or other benefits of the combination of zilovertamab and ibrutinib compared to single-agent ibrutinib; NE= not estimable

R/R MCL: Encouraging PFS observed based on priorline of therapy compared to historical ibrutinib alone

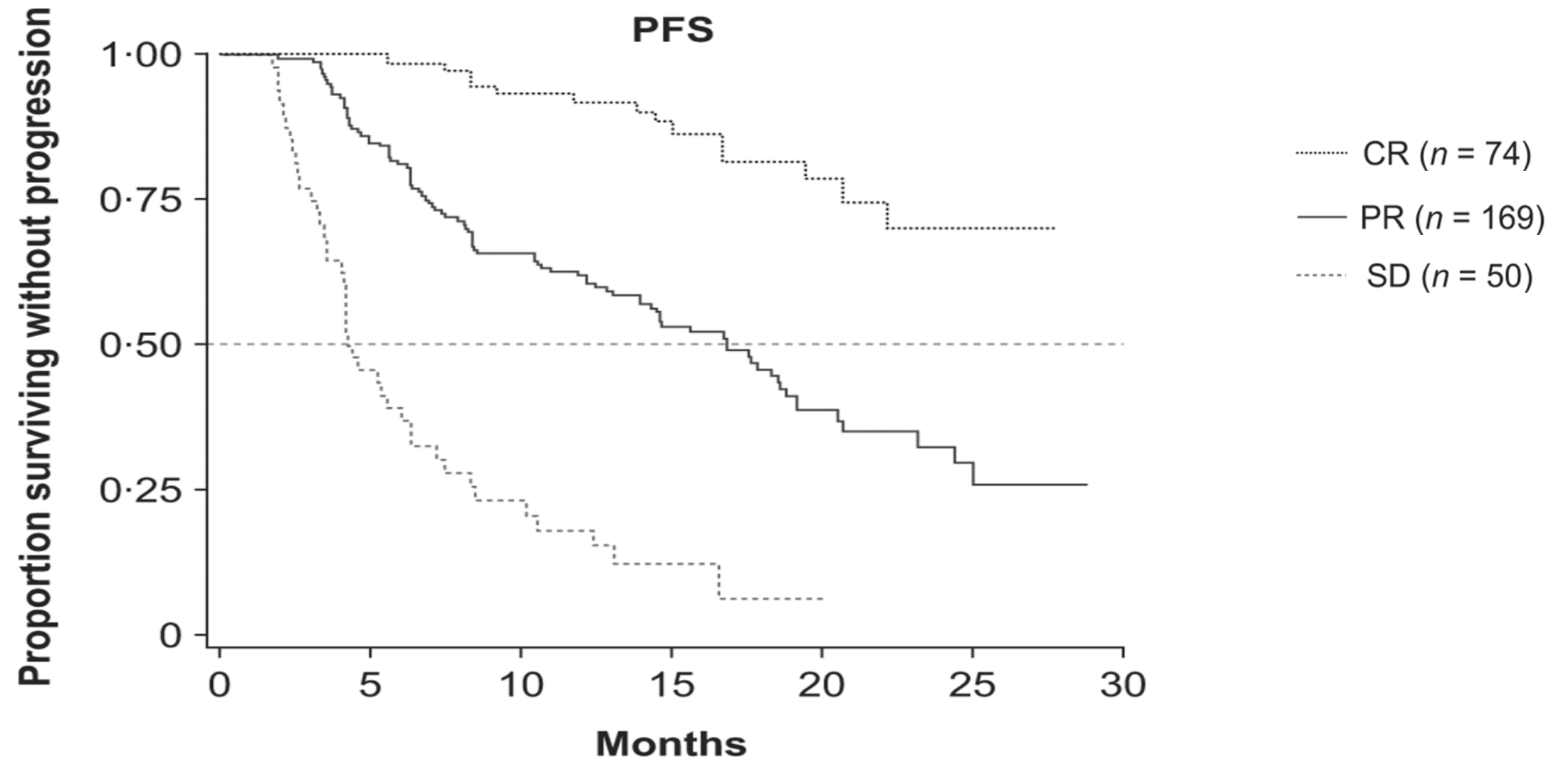
Zilovertamab + Ibrutinib Data Update at ASH 2021



PFS by Subtypes – Prior Systemic Therapy (months)	Prior sys. therapy	Zilovertamab + Ibrutinib PFS , median (95% CI)	Ibrutinib PFS median
	1	NR (17.3, NE)	NR
	2	NR (0.03, NE)	~12
	≥ 3	35.9 (16.5, 35.9)	~8

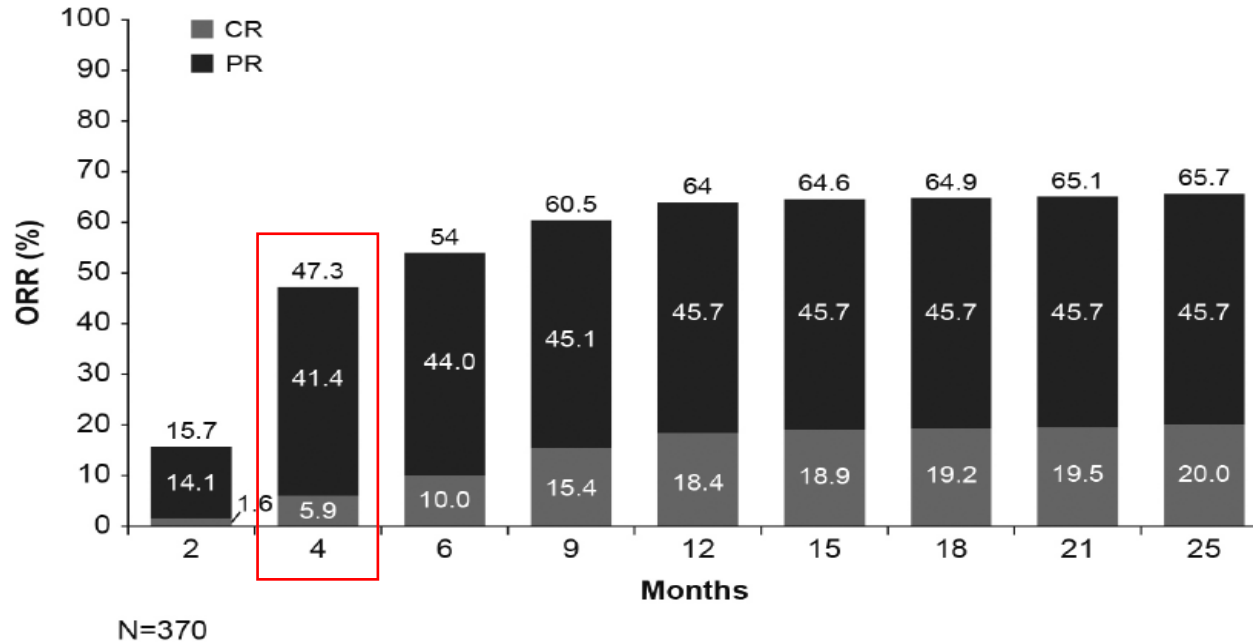
Note: Data presented are from separate studies and such data may not be directly comparable due to differences in study protocols, conditions and patient populations. Accordingly, cross-trial comparisons may not be reliable predictors of the relative efficacy or other benefits of the combination of zilovertamab and ibrutinib compared to single-agent ibrutinib; NE= not estimable

PFS by Best Response for Patients with R/R MCL on Single-Agent Ibrutinib



Rule Haematologica 2017: Meta-analysis of three studies of patients with relapsed/refractory MCL receiving ibrutinib as second or higher line of therapy ($n = 370$)

Best Response for Patients with R/R MCL on Single-Agent Ibrutinib



- Responses to Ibrutinib develop quickly in MCL
- At Month 4:
 - 6% of patients have CR
 - 41% of patients have PR
- After 4 months:
 - An additional 14% reach CR
 - An additional 5% reach PR
 - Only 18% additional ORR from Month 4-25

Rule Haematologica 2017: Meta-analysis of three studies of patients with relapsed/refractory MCL receiving ibrutinib as second or higher line of therapy. Best response observed by time, all patients (n = 370)

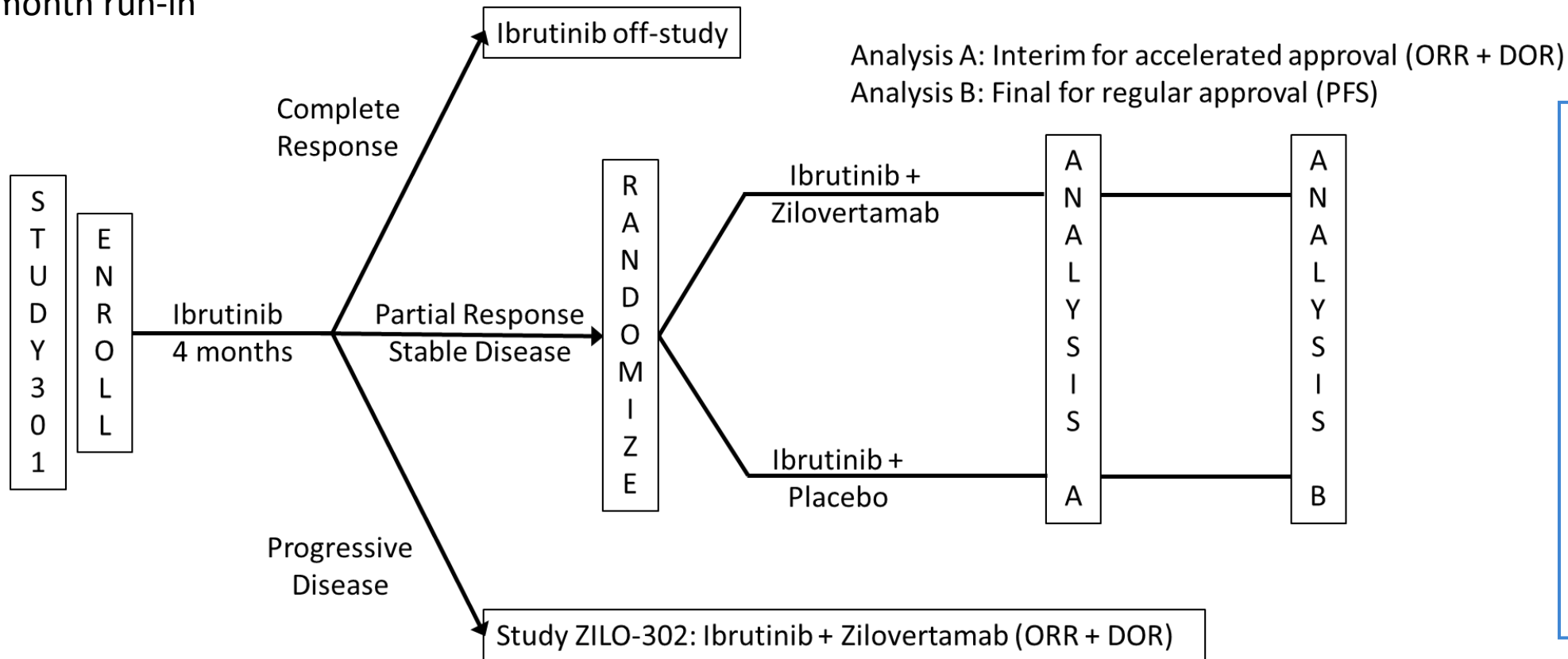
Successful End-of-Phase 2 FDA meeting

- Reached consensus on design and major details of Phase 3 superiority Study ZILO-301, to treat patients with R/R MCL with zilovertamab plus ibrutinib
- Positive feedback on the proposed key clinical and regulatory requirements of our development program for zilovertamab in MCL
- Agency previously provided positive feedback on the sufficiency of the preclinical and pharmacology studies of zilovertamab needed to support a BLA submission

Zilovertamab Registrational Study Plan

ZILO-301: Randomized, Double-blind, Placebo-controlled, Multi-center Phase 3 Study of Zilovertamab (A ROR1 Antibody) Plus Ibrutinib Versus Ibrutinib Plus Placebo in Patients with Relapsed or Refractory Mantle Cell Lymphoma

ZILO-302: Open-label companion study of zilovertamab plus ibrutinib for rescue of patient's refractory to ibrutinib during 4-month run-in



- Plan to randomize 250 patients
- Interim analysis ~2 years from first-patient-in (85% power)
- Final analysis ~3 years from first-patient-in (>90% power)

Global registrational study expected to be initiated in 2Q 2022

Oncternal's Two-Stage ROR1 Cell Therapy Development Strategy

1

ONCT-808 autologous ROR1 CAR-T cell therapy

- Quick path to demonstration of safety and efficacy
- Reduced technology risk: autologous CAR-T cells
- Reduced indication risk: B-cell malignancies, including failures to prior CD19 CAR-T cell therapy
- IND submission on track for submission in mid 2022



2

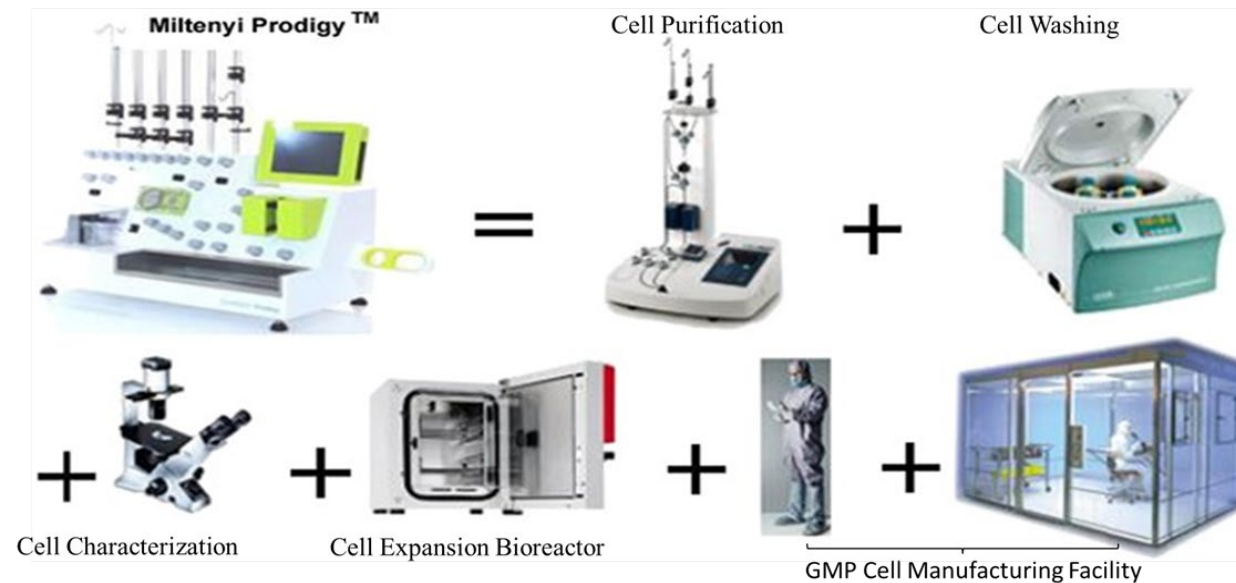
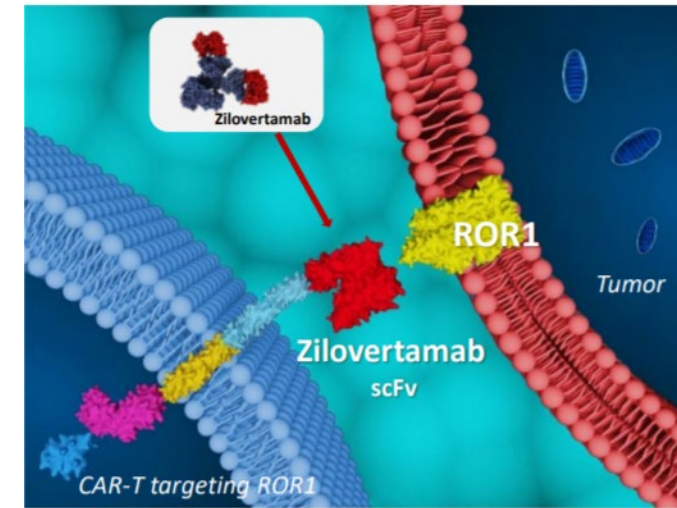
Next-generation allogeneic cell therapies targeting ROR1

- Incorporate technologies to overcome immunosuppression & CAR-T resistance
- Partnerships with Celularity and Karolinska Institutet
- Allogeneic CAR-T and CAR-NK cell therapies
- Hematologic and solid tumor indications

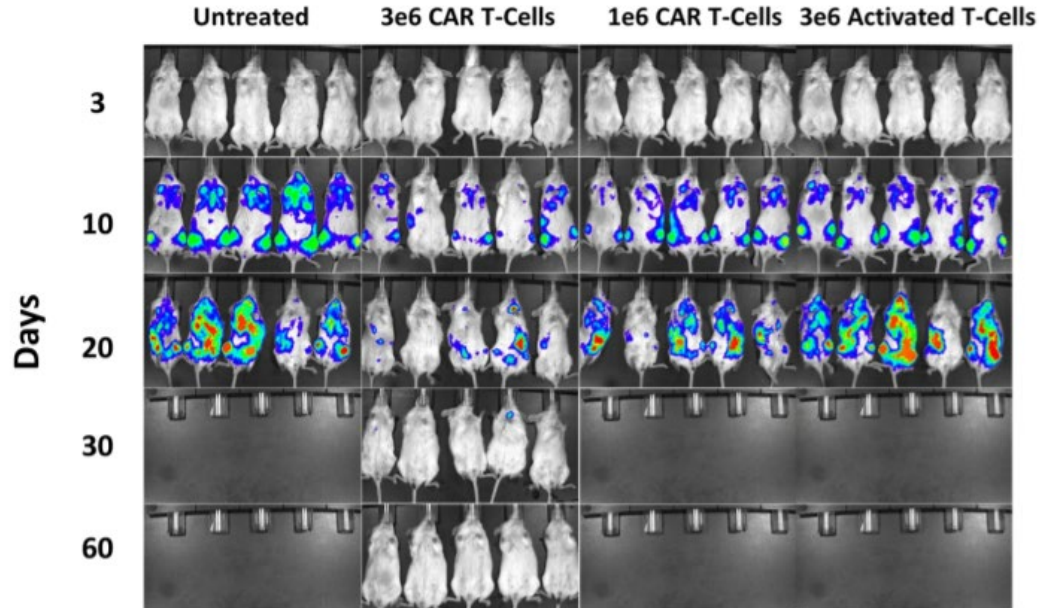


ONCT-808 CMC and Manufacturing Update

1. Lead ROR1 CAR construct optimized and selected with demonstrated high potency against ROR1+ cancer cell lines
2. Lentivirus production process confirmed with robust titers of greater than 1 E9 IFU/mL achieved
3. ROR1 CAR-T cell product process optimized and confirmed
 - Leveraging a flexible, closed fully-automated platform
 - One week production process post-activation
 - Greater than 2 billion CAR+ T cells produced with over 60% CAR+ expression
 - Majority of CAR T cells with juvenile phenotypes (CD4 and CD8 stem central memory T cells)

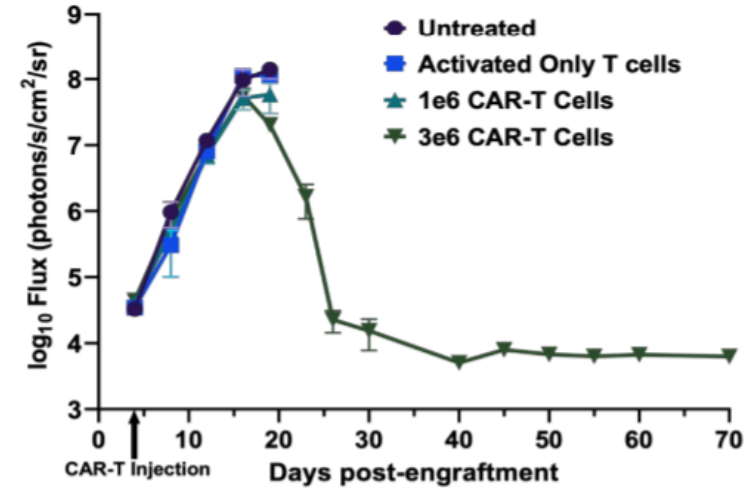


ONCT-808 Preclinical Update – Strong Anti-tumor Activity



Bioluminescence imaging of mice inoculated with MEC1-ROR1 cells and with ROR1 CAR T-cells. Animals treated with CAR-T cells had reduced disease burden compared to controls.

Prussak 2020 ASCO SITC



Bioluminescence imaging of MEC1-ROR1 cells following treatment with ROR1 CAR-T cells. Mice treated with 3e6 CAR-T reduced the leukemic burden to background levels by day 30 and controlled disease for remainder of study. Animals in the control groups (untreated, ATC or lower 1e6 dose) had to be sacrificed on day 20.

- Strong anti-tumor activity of ROR1 CAR-T cells demonstrated in CLL xenograft mouse model
- Additional IND-supporting in vivo studies are ongoing

Next-generation ROR1 Cell Therapy Effort Overview

Vision

- Off-the-shelf ROR1-targeting immune cell therapy for both liquid and solid malignancies

Mission

- Utilization of our potentially best-in-class ROR1 targeting moiety with:
 - Specific immune cell subsets or entire immune cell populations
 - Adult donor cells or stem cells
 - Fortified against tumor microenvironment
 - Dual targeting approaches to eliminate specific tumor cell populations

Current partnerships supporting next-generation ROR1 cell therapy efforts

- Karolinska Institutet R&D collaboration for CAR-T cell and CAR-NK cell therapies
- Celularity research collaboration with on allogeneic cell therapies

Topics	Presented by
Introduction	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics
Heme Malignancies <ul style="list-style-type: none">• Lymphoma / MCL treatment overview• Oncternal Zilovetamab and ROR1 cell therapy program update	<ul style="list-style-type: none">• Michael Wang, MD (MD Anderson Cancer Center)• Oncternal Therapeutics Management
<ul style="list-style-type: none">• Q&A	
Prostate Cancer <ul style="list-style-type: none">• Unmet needs in prostate cancer treatment• Oncternal ONCT-534 Dual-Action AR Inhibitor value proposition and other opportunities• Q&A	<ul style="list-style-type: none">• Evan Yu, MD (Fred Hutchinson Cancer Research Center)• Oncternal Therapeutics Management
Wrap-up	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

Topics	Presented by
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Metastatic Castration-Resistant Prostate Cancer: Present and Future

Evan Y. Yu, M.D

Professor of Medicine (Oncology)
University of Washington
Fred Hutchinson Cancer Research Center
January 25, 2022



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Cancer Care
Alliance**

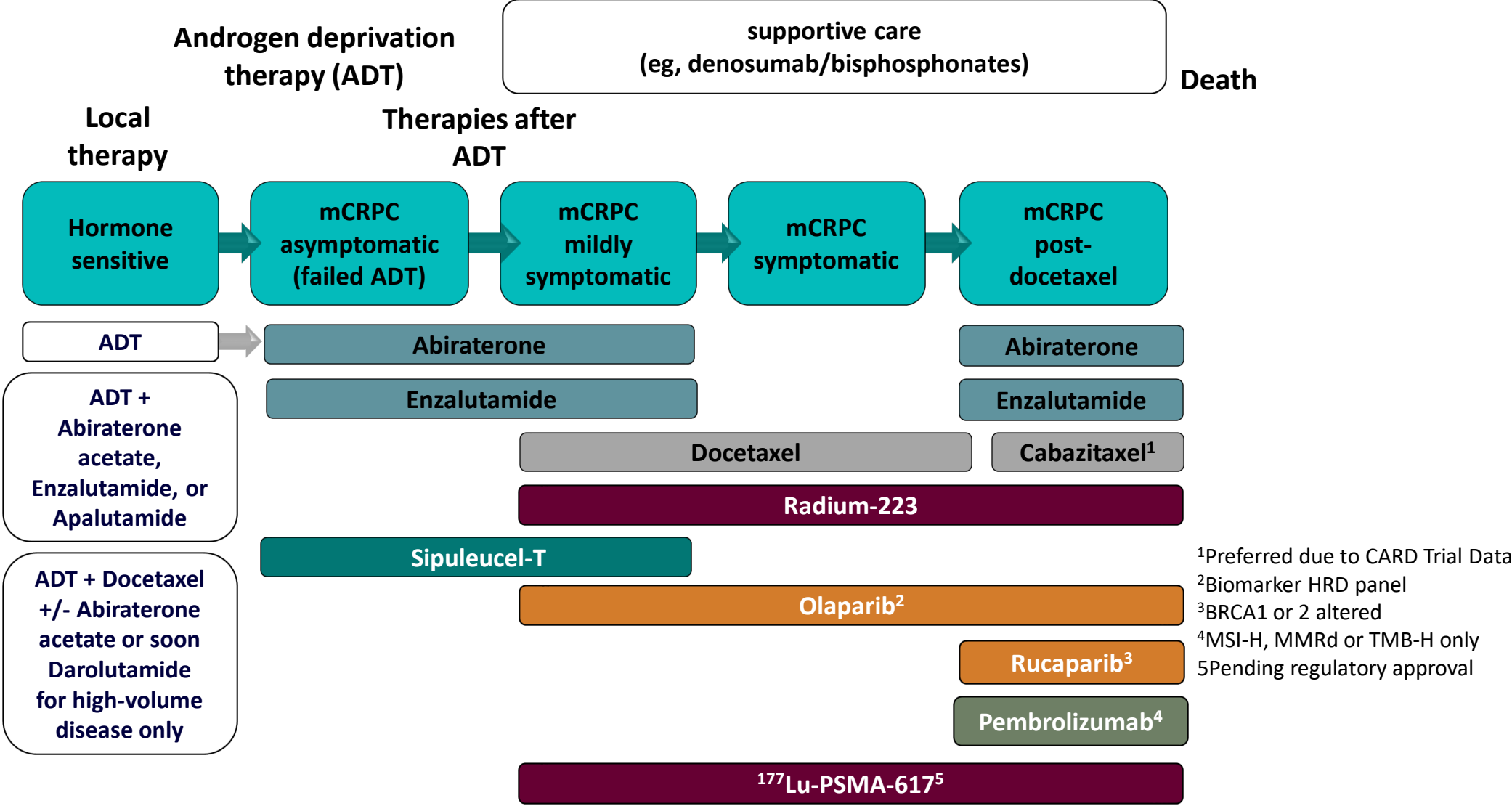
Disclosures

- Advisory/Consulting – Advanced Accelerator Applications (Novartis), Bayer, Janssen, Merck
- Research Funding to Institution – Bayer, Blue Earth, Daiichi-Sankyo, Dendreon, Lantheus, Merck, Seagen, Taiho

Discussion Topics

- Overview of metastatic castration-resistant prostate cancer
- Androgen/Androgen Receptor is a persistent driver in metastatic castration resistant prostate cancer
- Androgen Pathway Inhibitors – Abiraterone acetate and enzalutamide
- Mechanisms of AR resistance
- Trials

Summary of Treatment Options for Metastatic Prostate Cancer



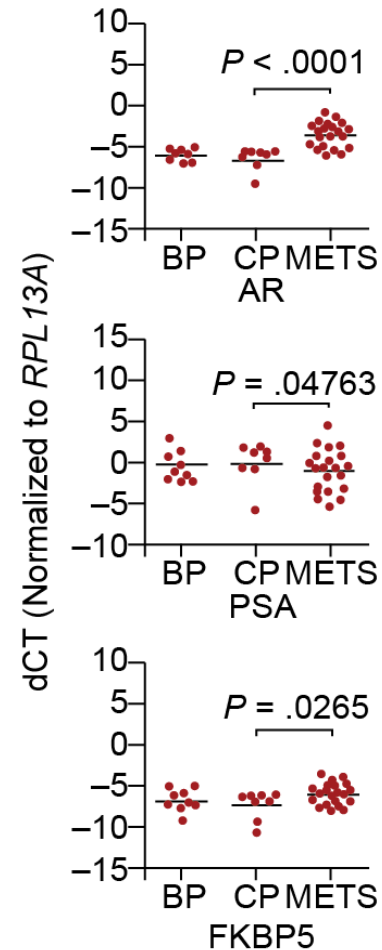
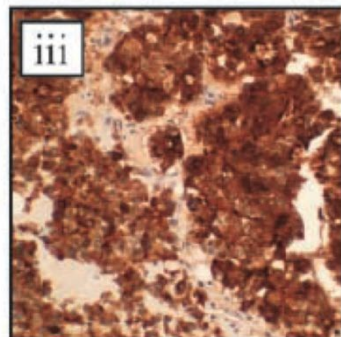
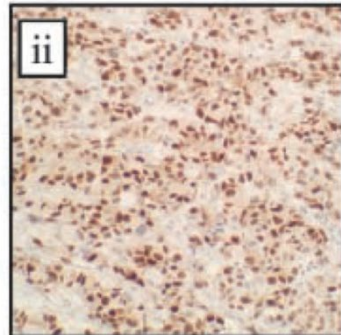
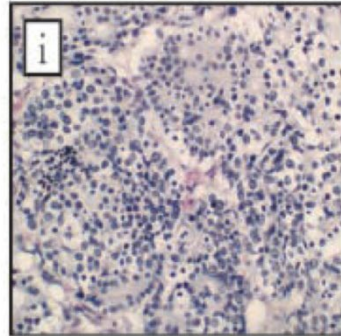
Androgen/AR Signaling is Active in Human Metastatic Castration-Resistant Prostate Cancer

Lymph node metastases¹

i: H&E

ii: Nuclear AR expression

iii: PSA stain with cytoplasmic PSA expression

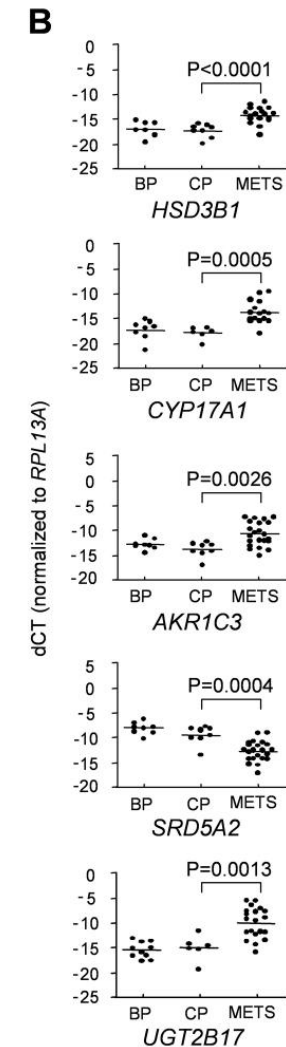
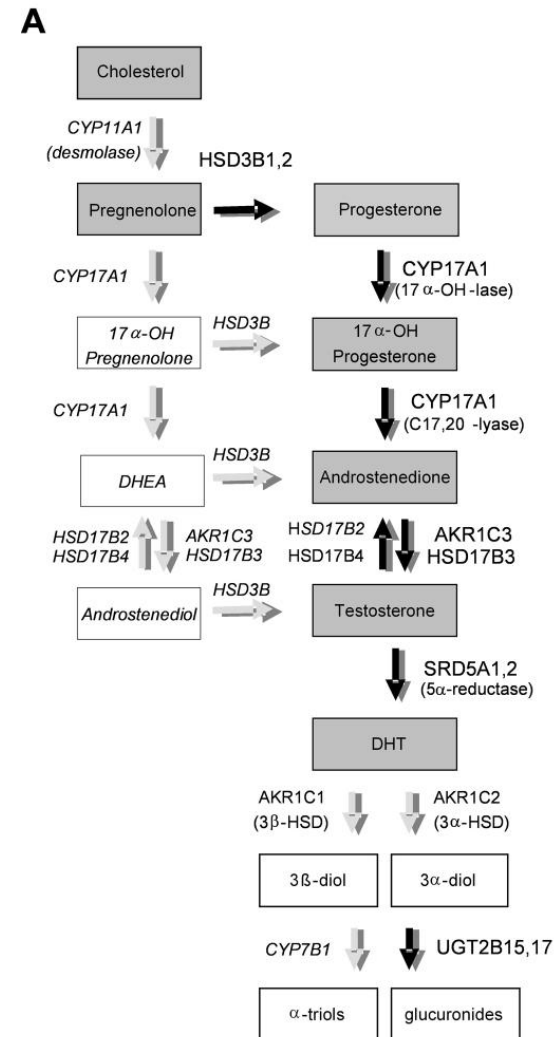
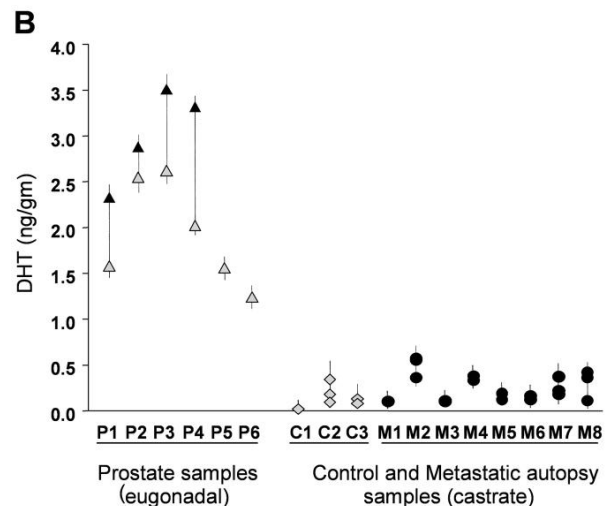
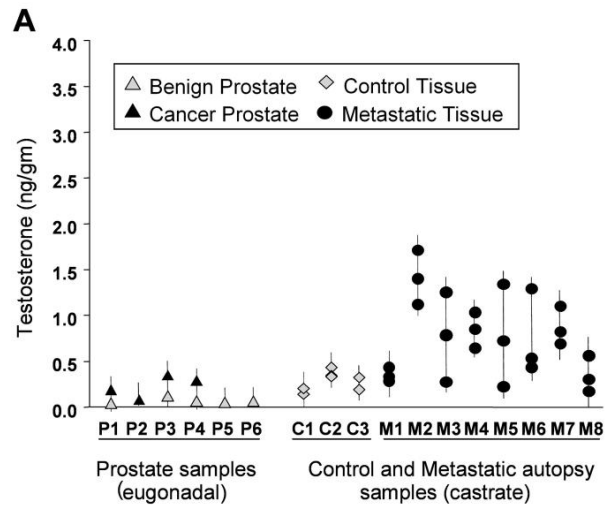


In a metastatic lymph node from a castration-resistant patient

- Androgen receptor expressed
- PSA expressed
- Androgen responsive genes expressed

AR: androgen receptor; BP: benign prostate; CP: cancer prostate; H&E: hematoxylin and eosin; METS: castration-resistant metastatic tumor.

Androgen Levels are Sustained in Metastatic Castration-Resistant Prostate Cancer



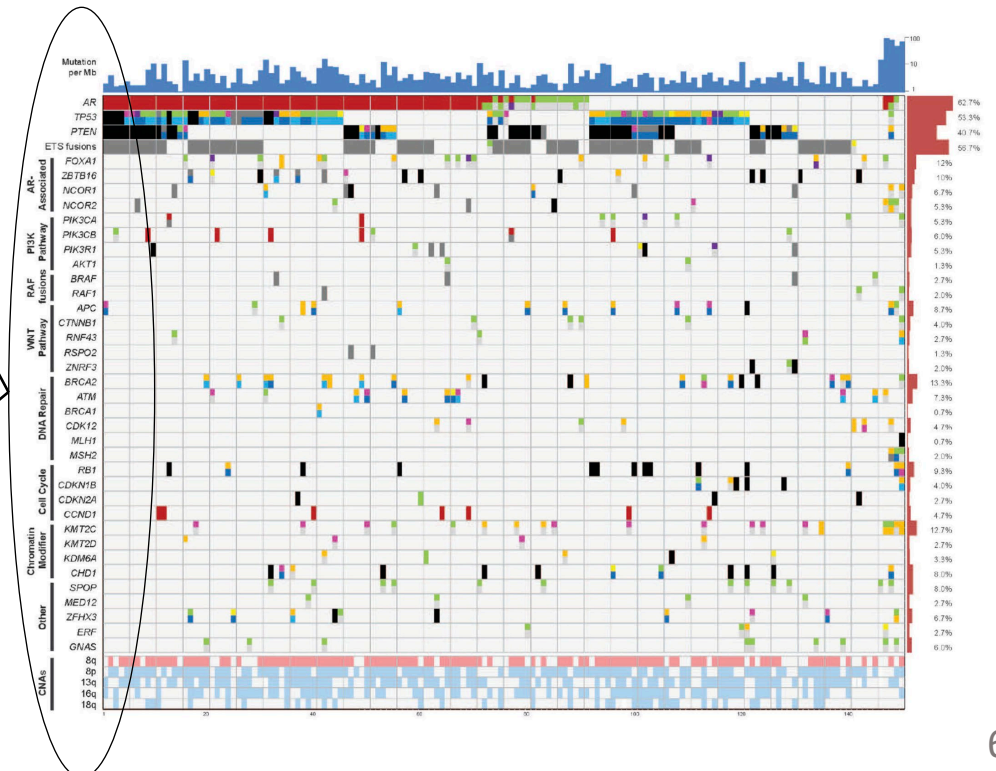
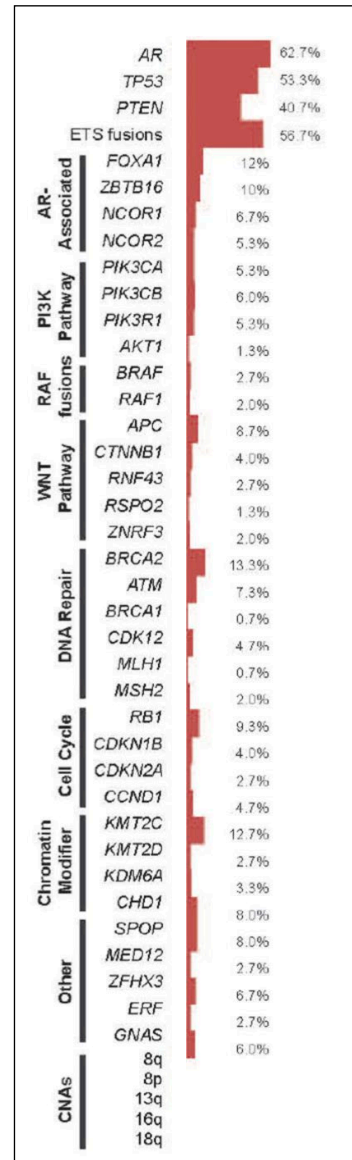
SU2C Sequencing of Metastatic Castration-Resistant Prostate Cancer Biopsies Supports AR Pathway as Top Driver

N=150 men with mCRPC

Whole exome and transcriptome sequencing

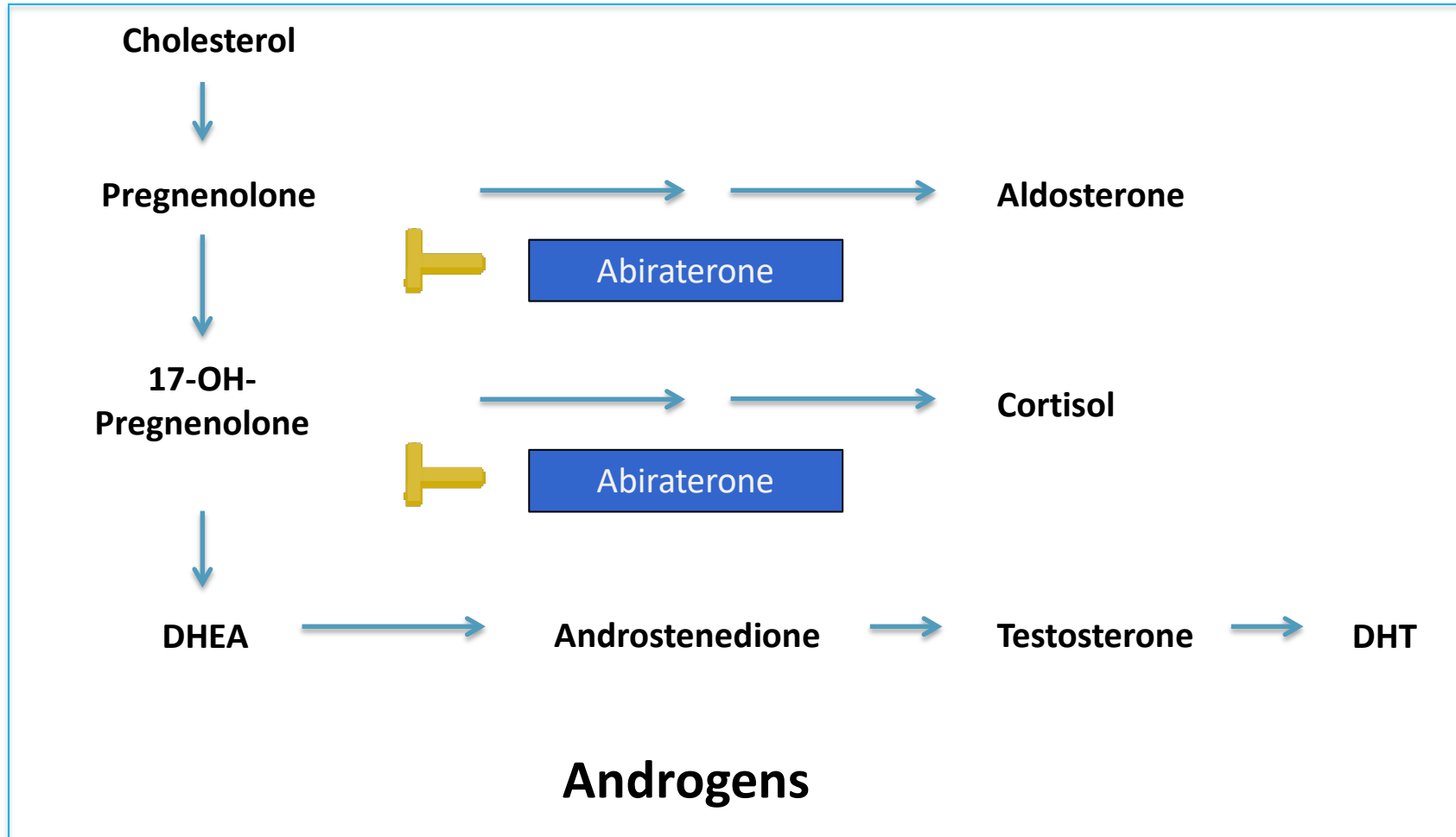
107/150 (71.3%) of cases harbored AR pathway aberrations

~50% of cases with AR amplification



Robinson, et al. *Cell*. 2015 May 21;161(5):1215-28

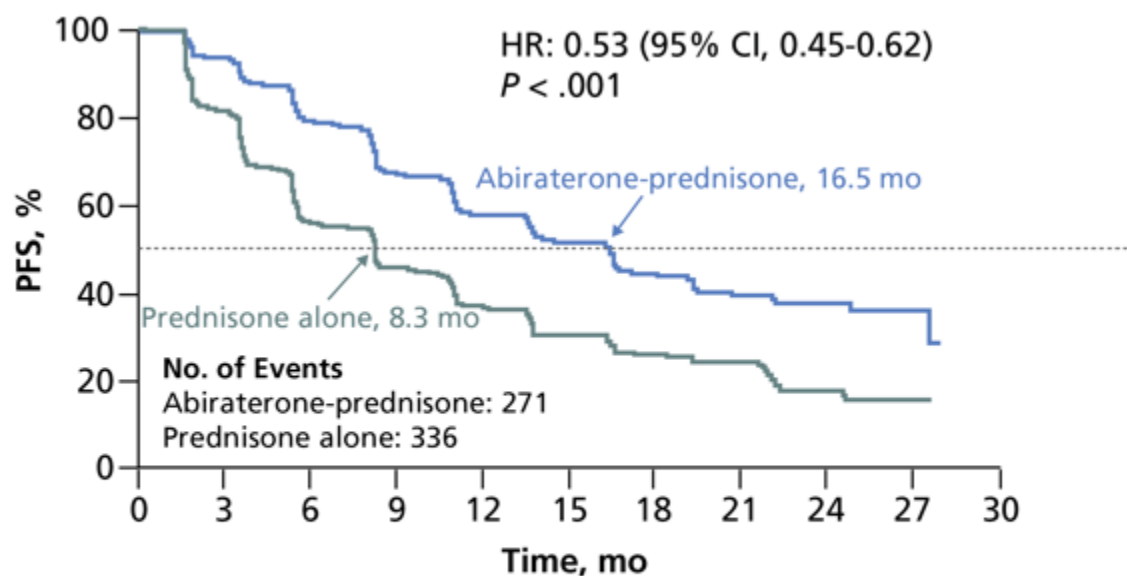
Abiraterone acetate: Mechanism of Action



1. De Bono JS et al. *N Engl J Med*. 2011;26:1995-2005. 2. Ryan et al. 2012 American Society of Clinical Oncology Annual Meeting (ASCO 2012). Abstract LBA4518.

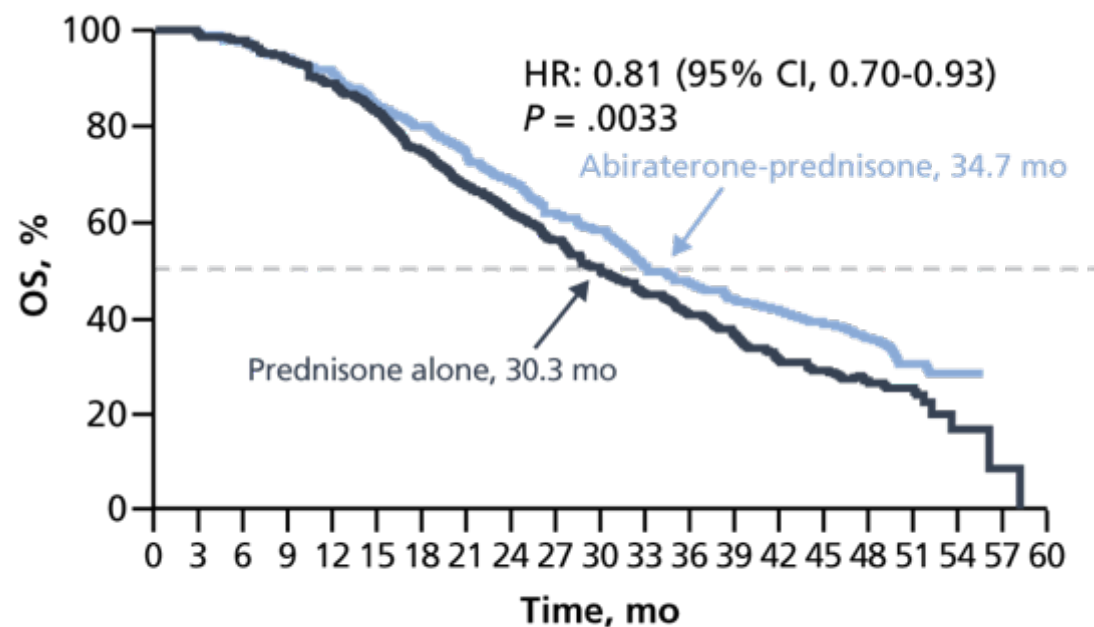
COU-AA-302 Abiraterone in pre-Chemotherapy Disease State

Radiographic PFS



No. at Risk	0	3	6	9	12	15	18	21	24	27	30
Abiraterone-prednisone	546	485	389	311	240	195	155	85	38	9	0
Prednisone alone	542	406	244	177	133	100	80	37	14	1	0

Overall Survival



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Abiraterone-prednisone	546	538	525	504	483	453	422	394	359	330	296	273	235	218	202	189	118	59	15	0	0
Prednisone alone	542	534	509	493	466	438	401	363	322	292	261	227	201	176	148	132	84	42	10	1	0

Ryan CJ et al. *N Engl J Med.* 2013;368:138-148.

Ryan CJ, Smith MR, Fizazi K, Miller K. 39th ESMO 2014. Abstract 7530

Enzalutamide is a Pure, Irreversible AR Antagonist

Enzalutamide improved OS and radiographic PFS in patients with mCRPC both pre-¹ and post-docetaxel²

1. AR Binding Affinity

- DHT ~ 5nM
- Bicalutamide ~160 nM
- MDV3100 ~35 nM

2. Nuclear Import

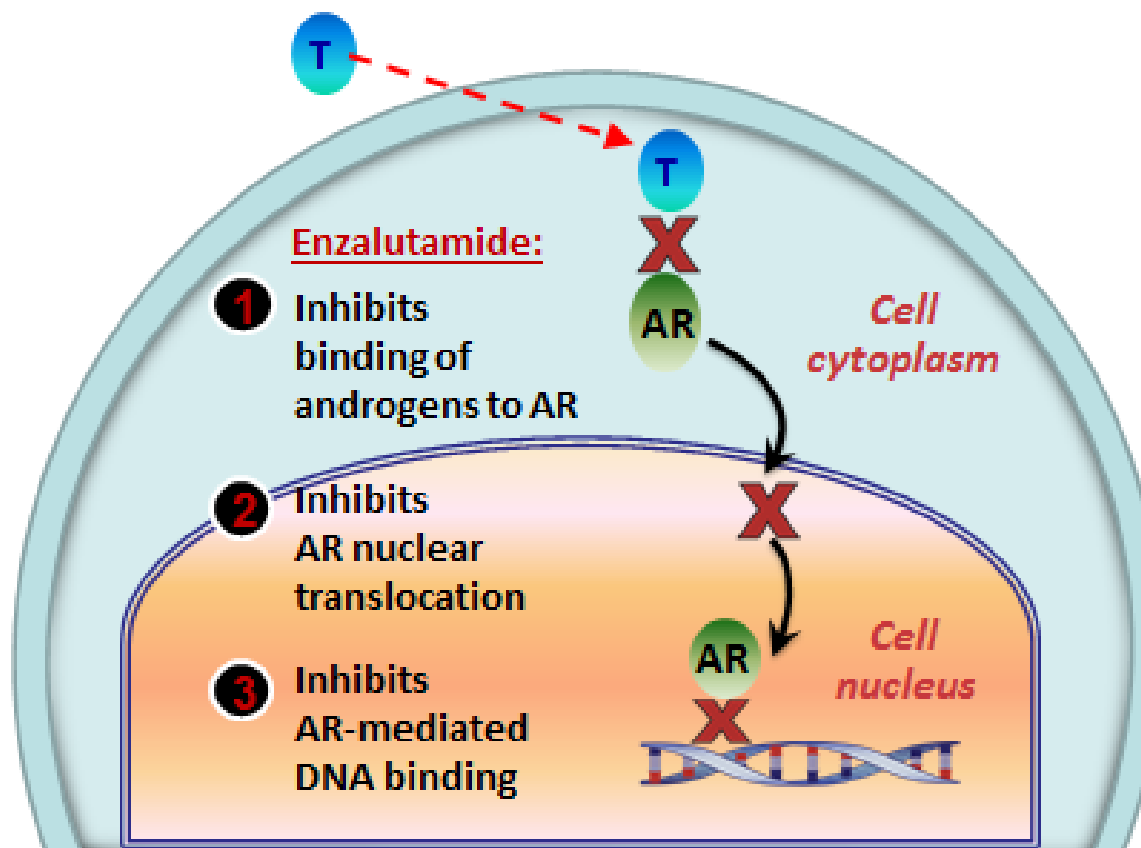
- DHT: +++++
- Bicalutamide: ++++
- MDV3100: ++

3. DNA Binding

- DHT: +++++
- Bicalutamide: ++
- MDV3100: -

4. Coactivator recruitment

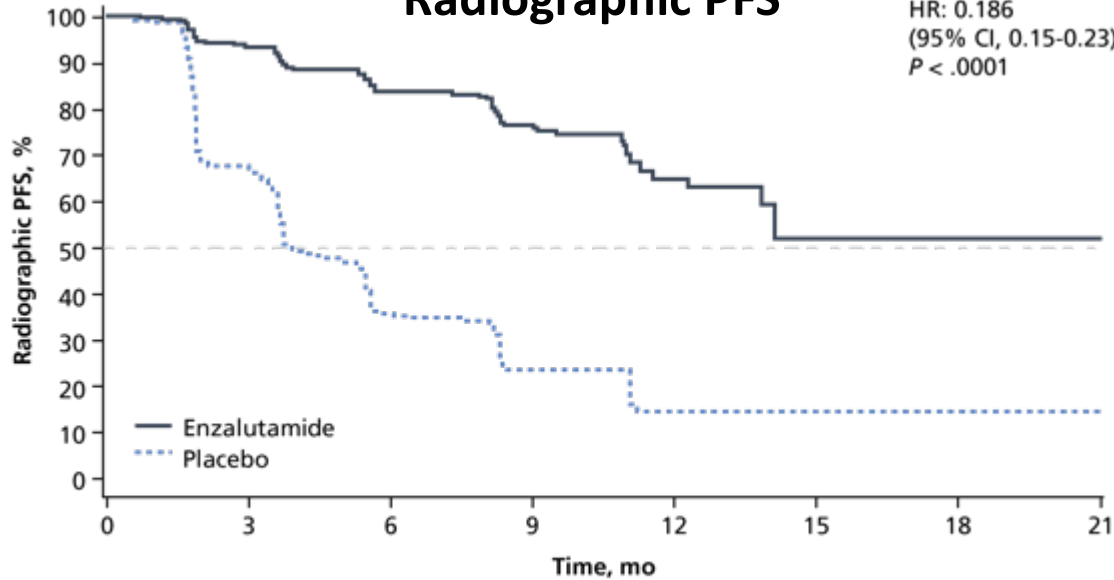
- DHT: +++++
- Bicalutamide: ++
- MDV3100: -



PREVAIL: Pre-chemotherapy Enzalutamide

Radiographic PFS

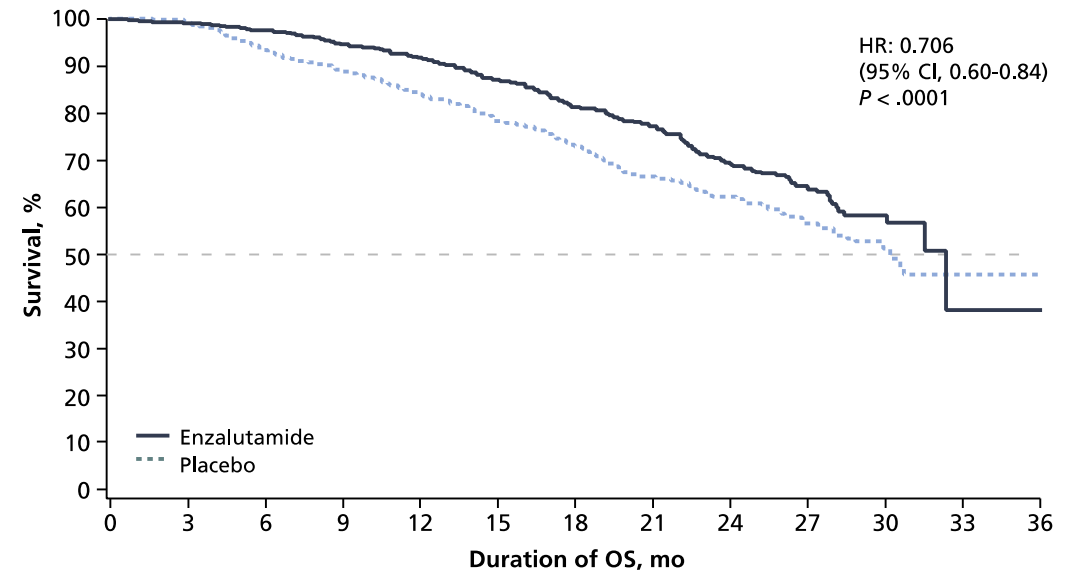
HR: 0.186
(95% CI, 0.15-0.23)
 $P < .0001$



No. at Risk		0	3	6	9	12	15	18	21
Enzalutamide	832	514	256	128	34	5	1	0	0
Placebo	801	305	79	20	5	0	0	0	0

Overall Survival

HR: 0.706
(95% CI, 0.60-0.84)
 $P < .0001$



No. at Risk		0	3	6	9	12	15	18	21	24	27	30	33	36
Enzalutamide	872	863	850	824	797	745	566	395	244	128	33	2	0	0
Placebo	845	835	781	744	701	644	484	328	213	102	27	2	0	0

Beer TM et al *N Engl J Med.* 2014;371:424-433.

Sequencing of Abiraterone and Enzalutamide

	Prior Docetaxel	N	PSA Decline ≥30%, %	PSA Decline ≥50%, %	Median TTP, mo	Median PFS, mo
Abiraterone after enzalutamide						
Noonan ¹	Y	27	11	4	NR	3.5
Loriot ²	Y	38	18	8	NR	2.7
Enzalutamide after abiraterone						
Schrader ³	Y	35	37	29	4.0 ^a	–
Bianchini ⁴	Y	39	41	13	2.2	2.8
Badrising ⁵	Y	61	46	21	4.0	2.8
Cheng ⁶	Y	122	39	26	–	–
Azad ⁷	Y	68	–	22	4.6	–
Cheng ⁶	N	28	40	36	–	–
Azad ⁷	N	47	–	26	6.6	–

^a Responders.

TTP: time to progression.

1. Noonan KL et al. *Ann Oncol.* 2013;24:1802-1807. 2. Loriot Y et al. *Ann Oncol.* 2013;24:1807-1812. 3. Schrader AJ et al. *Eur Urol.* 2014;65:30-36. 4. Bianchini D et al. *Eur J Cancer.* 2014;50:78-84. 5. Badrising S et al. *Cancer.* 2014;12:968-975. 6. Cheng HH et al. *Prostate Cancer Prostatic Dis* 2015; 18:122-7. 7. Azad AA et al. *Eur Urol.* 2015;67:23-29.

PLATO Trial: Abiraterone Post-PSA Progression on Enzalutamide

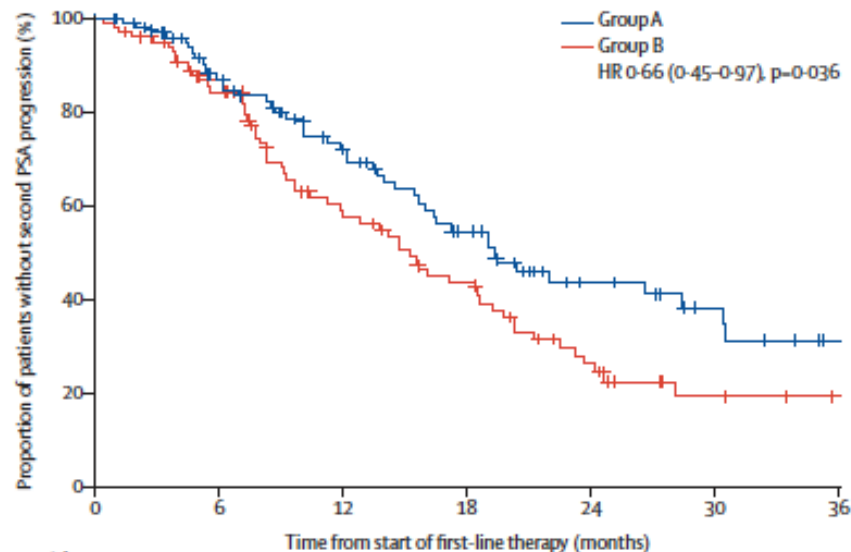
Endpoint	E+AA+P	Pbo+AA+P	Hazard Ratio (95% CI)
PFS, median	5.7 mos	5.6 mos	0.83 (0.61-1.12)
PFS event			
rPFS	38%	55%	
Clinical progression	25%	18%	
Death	2%	1%	
TTPP, median	2.8 mos	2.8 mos	0.87 (0.62-1.24)
PSA response rate	0.8%	2.5%	
rPFS, median	10.0 mos	7.0 mos	0.67 (0.47-0.94)
Adverse Event			
Back pain	21%	23%	
Hypertension	20%	7%	
Nausea	17%	9%	
Fatigue	14%	15%	

Median treatment duration = 5.6 mos

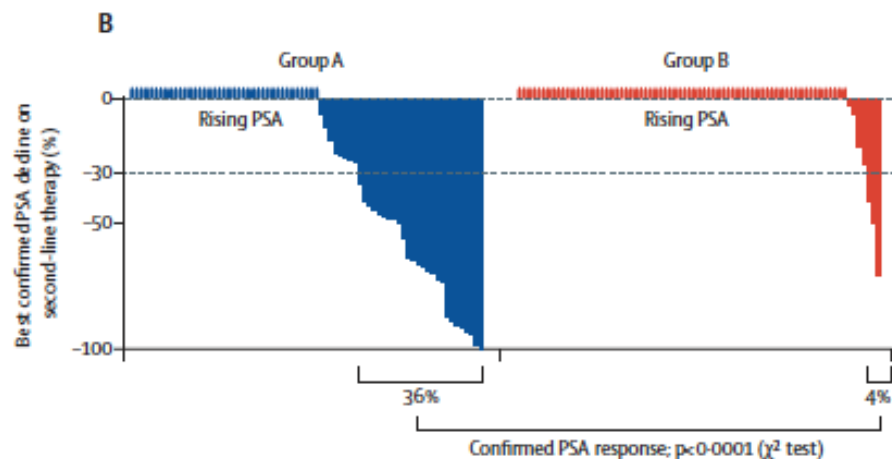
AA, abiraterone acetate; E, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; mos, months; P, prednisone; Pbo, placebo; PFS, progression free survival; PSA, prostate specific antigen; TTPP, time to PSA progression.

Sequencing of Abiraterone and Enzalutamide: Randomized Data

Group A: Abi -> Enza
Group B: Enza -> Abi



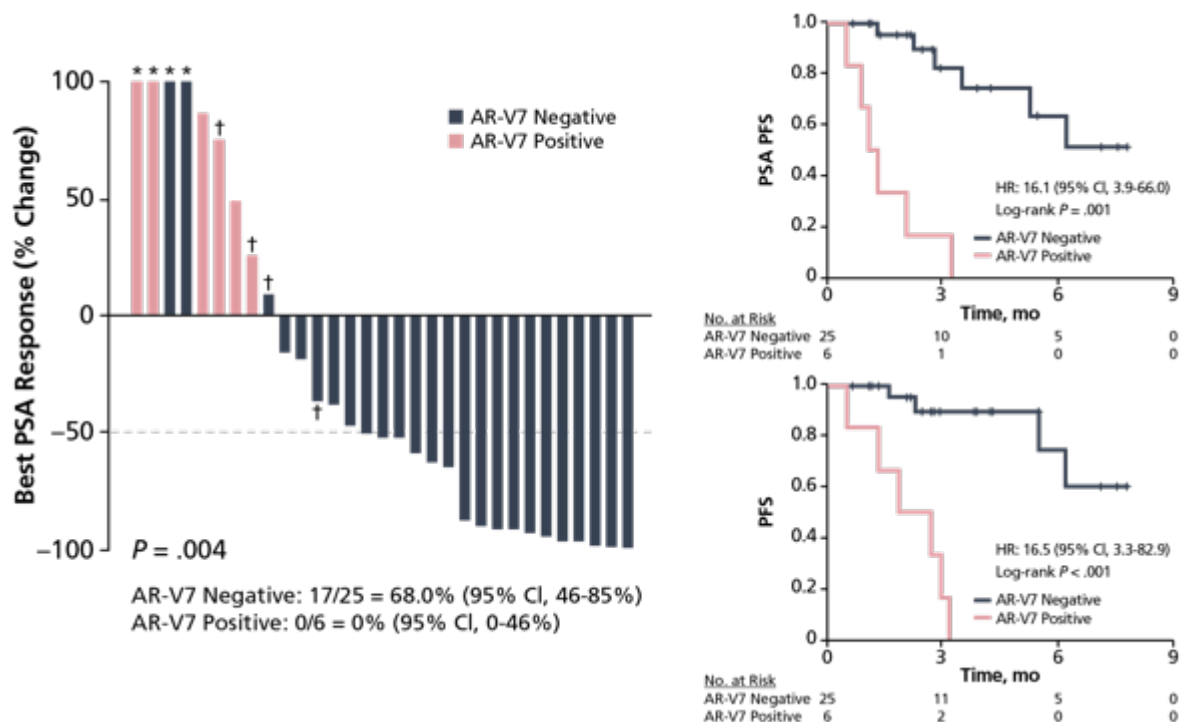
Number at risk (number censored)	0	6	12	18	24	30	36
Group A	76 (13)	53 (24)	34 (31)	18 (41)	11 (46)	5 (50)	
Group B	75 (11)	43 (22)	30 (25)	15 (29)	6 (35)	3 (38)	



Confirmed PSA30
response: Group A 36%
vs. Group B 4%

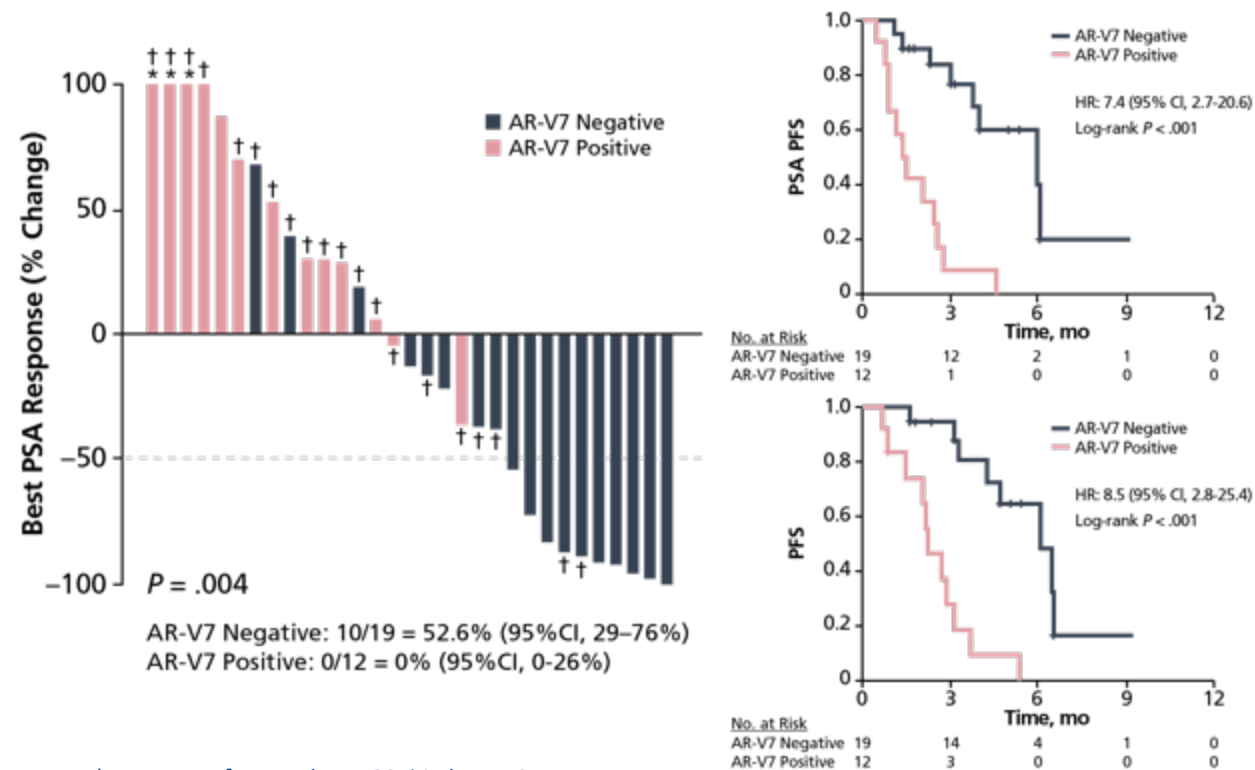
AR-v7 spliced variant detection from CTCs and Subsequent Response

Abiraterone



* Increase of more than 100% in best PSA response.
† Patients who had previously received enzalutamide.

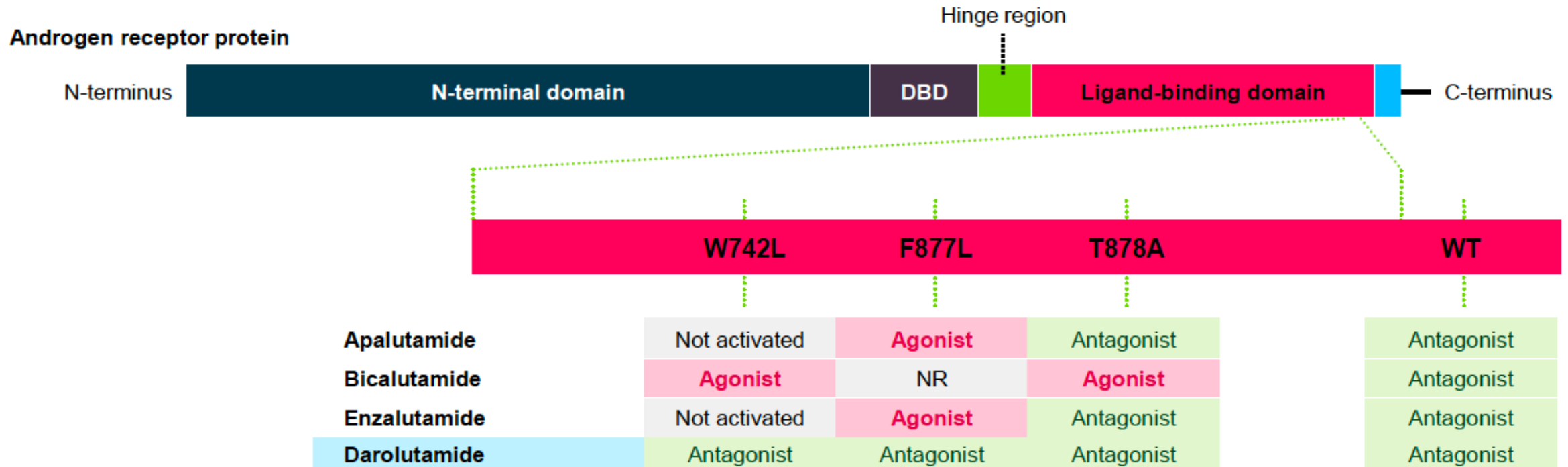
Enzalutamide



* Increase of more than 100% in best PSA response.
† Patients who had previously received abiraterone.

Antonarakis E et al. *N Engl J Med.* 2014;371:1028-1038.

AR Mutants



Galeterone was Supposed to do it All

- Selective CYP17 inhibitor
- Potent AR antagonist
- AR protein degradation
- Reduction in both full-length AR and AR-v7 spliced variant levels
- Activity against AR point mutation T878A and potentially F876L

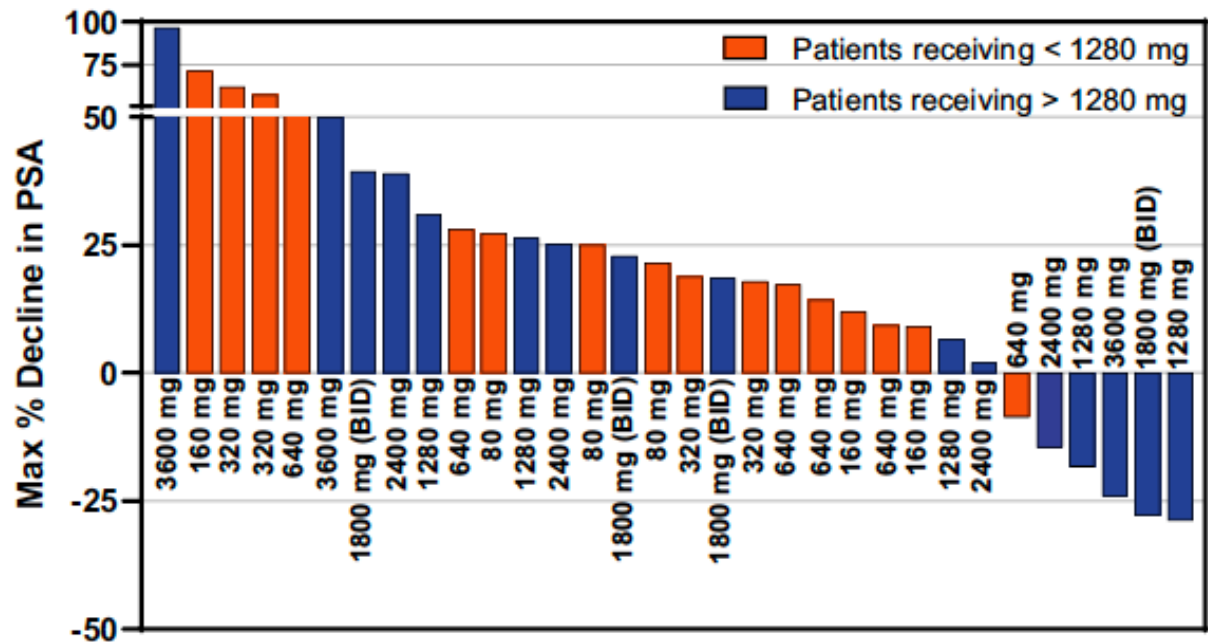
Jacoby D. J Clin Oncol 2013; Abstr 184.
Handratta VD, et al. J Med Chem 2005; 48:2972-84
Vasaitis T, et al. Mol Cancer Ther 2008; 7:2348-57.
Schayowitz A, et al. Mol Cancer Ther 2008; 7:121-32.
Purushottamachar P, et al. J Med Chem 2013; 56:4880-98.
Bruno RD, et al. Steroids 2011; 76:1268-79.
Kwegyir-Afful AK, et al. Oncotarget 2015; 6:27440-60.
AlNakouzi N, et al. AACR 2013; Abstr nr C89

Galeterone Randomized Phase 3 Trial

- Multicenter, randomized phase 3 trial in CTC mRNA AR-v7 positive enzalutamide-, abiraterone- and chemotherapy-naïve mCRPC to enzalutamide vs. galeterone (n=148 intended)
- 953 men were prescreened with 323 (34%) with detectable CTCs and 73/323 AR-v7 resulting in ARv7 prevalence of 8%
- 38 randomized to galeterone (n=19) vs. enzalutamide (n=19) with 35 dropping out before randomization
- Due to high censorship for rPFS, the DMC recommended early closure based on interim evidence the primary endpoint would not be met
- PSA50 values were galeterone 2/16 (13%) and enzalutamide 8/19 (42%)

Epi-506

- Targets N-terminal domain
- Phase 1 adaptive 3+3 escalation for patients with mCRPC who progressed on prior AR pathway inhibitor
- 28 patients enrolled into 7 dose cohorts
- 6 DLTs – grade 4 elevated amylase, grade 3 abdominal pain, grade 3 elevated ALT and grade 3 elevated AST
- Grade 2 nausea and grade 1 vomiting resulted in <75% of expected dose during DLT assessment period
- Early termination prior to reaching the MTD due to poor oral bioavailability



Maurice-Dror C, et al. Invest New Drugs 2021; epub.

ARV-110 Data

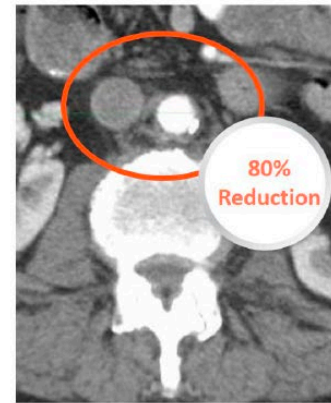
- ARV-110 orally bioavailable PROTAC
- Phase 1 in mCRPC patients who received 2 or more prior therapies, including enzalutamide and/or abiraterone
- 4 dosing levels to date of presentation
- 1 of 18 patients with DLT at 280 mg with grade 4 elevated AST/ALT and AKI
- Another patient and grade 3 AST/ALT that resolved off rosuvastatin that permitted retreatment with ARV-110
- 2 patients achieved confirmed PSA50, both at 140 mg

Petrylak DP, et al. J Clin Oncol 38, no. 15_suppl (May 20, 2020) 3500-3500.
 Snyder LB, AACR 2021 Virtual Meeting.
 Arvinas presentation at Prostate Cancer Foundation Scientific Retreat 2021.

Patient Characteristics	
PSA response	97% decline
RECIST response	80% reduction
Duration of ARV-110	18+ weeks ongoing
Biomarker status	AR H875Y and T878A mutations (associated with resistance to abiraterone or enzalutamide) ¹
Common prior therapies	Enzalutamide, Abiraterone, Bicalutamide
Other prior therapies	Provenge Cabazitaxel
History	Extensive disease involving adrenal gland, aortocaval nodes, multiple cone metastases

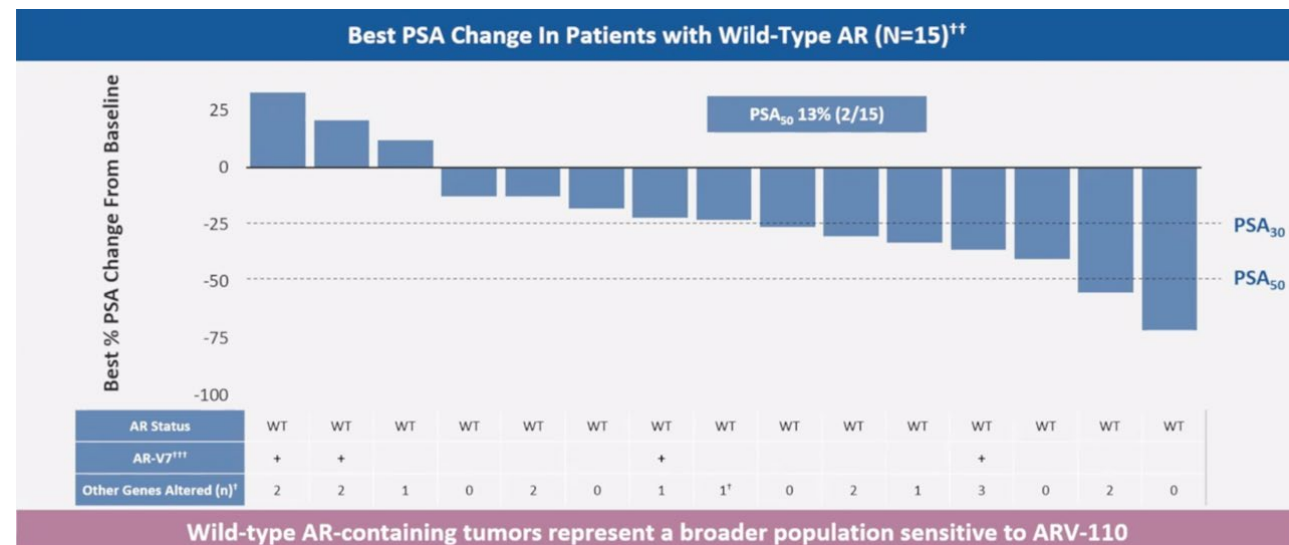


BASELINE CT SCAN
 Extensive retroperitoneal adenopathy compressing the inferior vena cava



AFTER 4 CYCLES
 Near complete regression of adenopathy

80% Reduction



Take Home Points

- Androgens and androgen receptor (AR) remain important targets in castration-resistant prostate cancer
- Abiraterone and enzalutamide are androgen pathway inhibitors that are highly efficacious but have many mechanisms of resistance that do not promote sequencing of these agents
- AR spliced variants and mutants are potential mechanisms of resistance post-AR pathway inhibitors
- Early novel AR targeted strategies, including N-terminal domain inhibitors and PROTACs, have met some efficacy and toxicity challenges
- New agents/strategies are necessary to fulfill this unmet need population

Thank you!
evanyu@uw.edu



Topics	Presented by
Introduction	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics
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Prostate Cancer	<ul style="list-style-type: none">• Evan Yu, MD (Fred Hutchinson Cancer Research Center)• Gunnar Kaufmann, PhD, CSO• Salim Yazji, MD, CMO
<ul style="list-style-type: none">• Unmet needs in prostate cancer treatment• Oncternal ONCT-534 Dual-Action AR Inhibitor value proposition and other opportunities• Q&A	
Wrap-up	<ul style="list-style-type: none">• Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

Unique Mechanism of Action (MOA)

- ONCT-534 binds to:
 - N-terminal Domain (NTD) and Ligand-Binding Domain (LBD)
 - induces AR degradation
- NTD binding relevant against splice-variants and LBD mutants
- AR antagonists (e.g. enzalutamide) and clinical-stage PROTACs bind to LBD only
- Potential in other AR-driven diseases:
 - AR⁺ triple negative breast cancer (LAR-TNBC)
 - non-oncology indications, e.g. Kennedy's disease (Spinal Bulbar Muscular Atrophy)

Strong Preclinical Activity

- In vitro antagonism and degradation:
 - full-length AR, LBD mutant AR, and AR-splice variants (SV)
- Strong in vivo activity against:
 - ENZA-resistant VCaP tumors (MDVR) in ***intact*** animals
 - ENZA-resistant AR-overexpressing LnCAP in ***intact*** animals
 - AR-splice variant 7 (AR-V7)-positive 22RV1
 - Strong anti-androgen activity in Hershberger studies

Drug-like Properties

- Conform to Lipinski's Rule of 5
- Facile synthesis
- Oral bioavailability

ONCT-534 chosen as clinical candidate

- ONCT-505 as back-up compound

IND-enabling activities (ongoing):

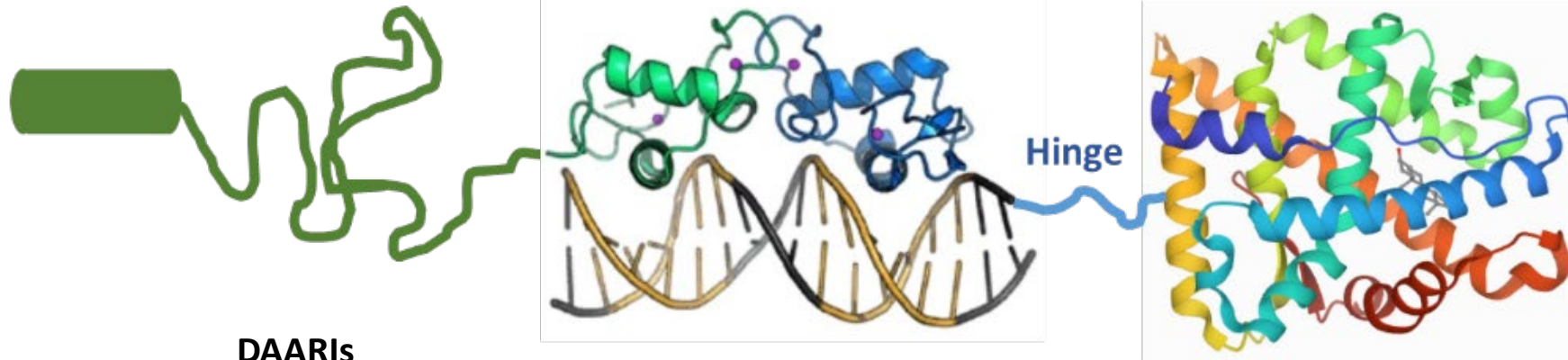
- Manufacturing process established and transferred to leading CDMO
 - GMP API batch (2H 2022)
- Oral dose drug product formulation
- PK and non-GLP toxicology studies
 - GLP toxicology studies (3Q 2022)

Overview of AR-targeting Therapeutic Modalities

N-terminal Domain (NTD)

DNA-binding Domain (DBD)

Ligand-binding Domain (LBD)



DAARIs
ANITEN

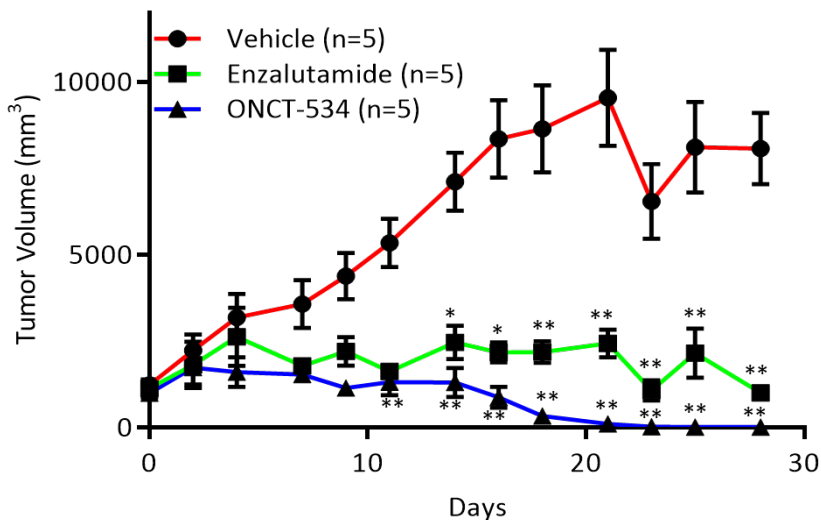
DAARIs
Enzalutamide
Apalutamide
Darolutamide
Bicalutamide
PROTACs

Evidence for DAARI NTD-binding:

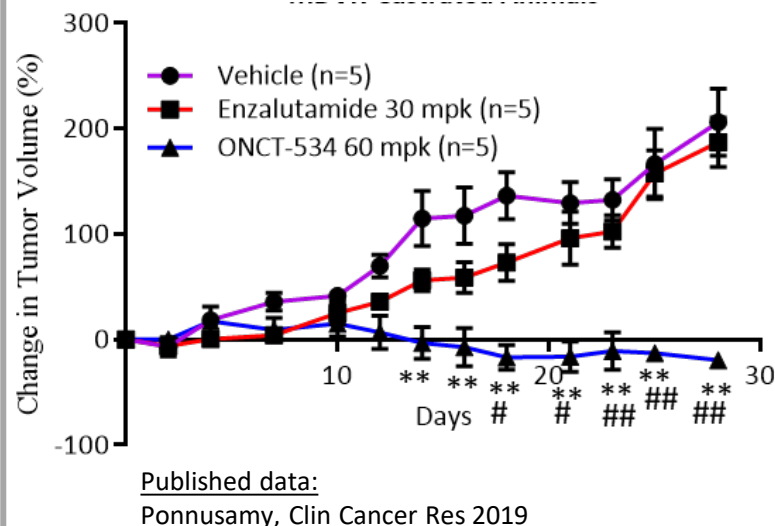
- Biophysical methods:
 - Fluorescence polarization
 - NMR
- Biochemical methods:
 - Covalent labeling
 - Protein engineering
- Functional studies using AR splice variant expressing cells

DAARIs exhibit strong AR-specific anti-tumor activity in preclinical model harboring different AR aberrations

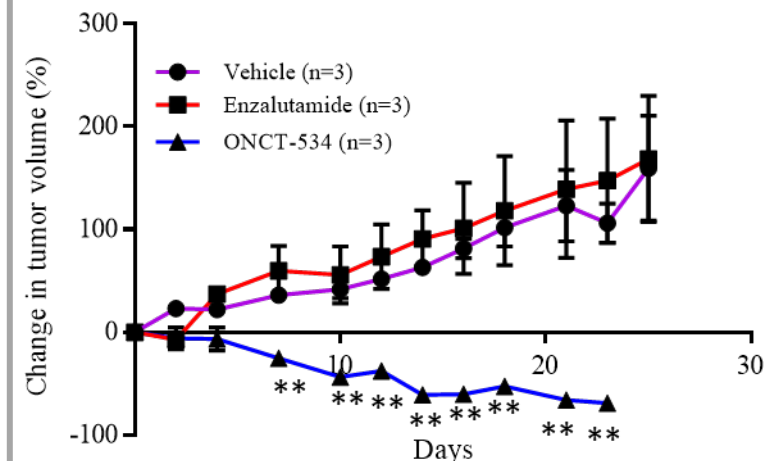
ENZA-sensitive: VCaP



ENZA-resistant: MDVR (castrated animals)



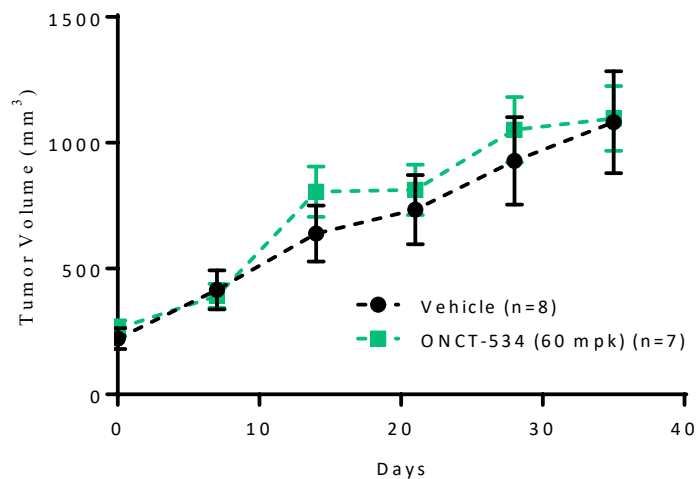
ENZA-resistant: MDVR (*intact* animals)



No activity in AR-independent model: PC3

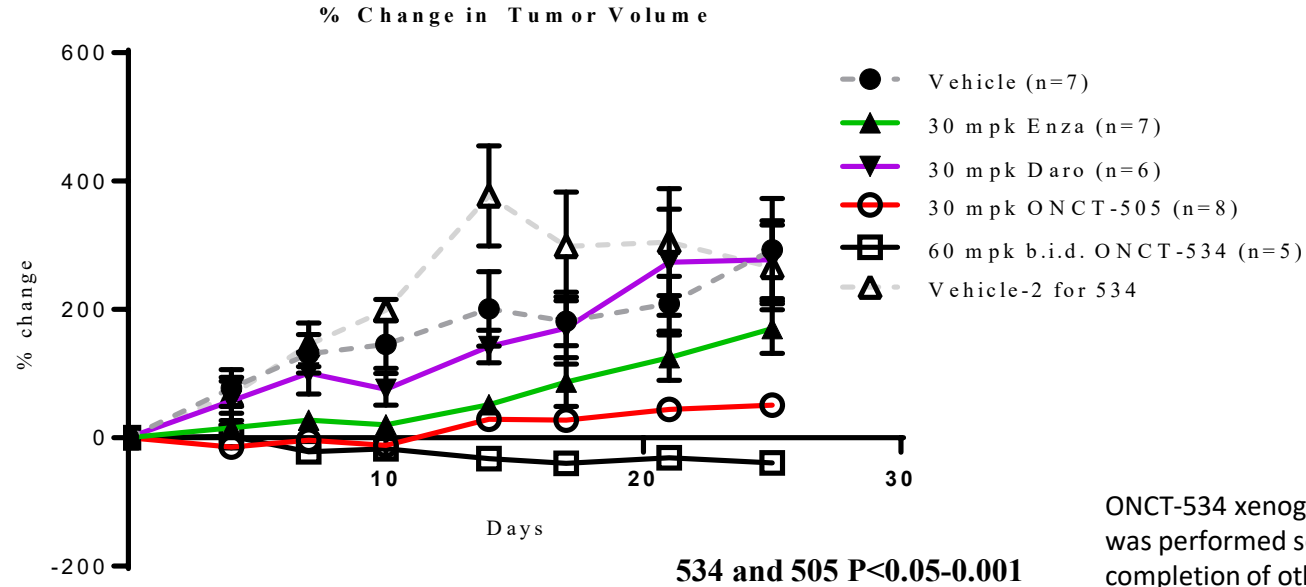
- demonstrating AR-specific anti-tumor activity

Tumor Volume (PC-3 Xenograft)



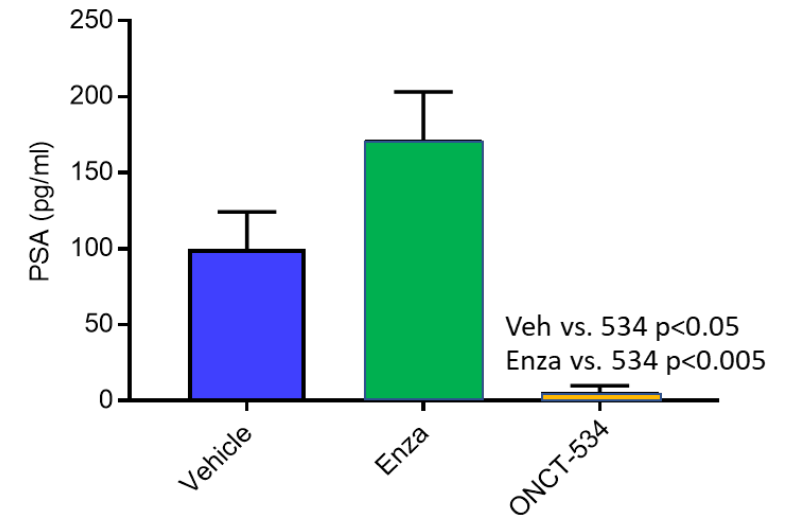
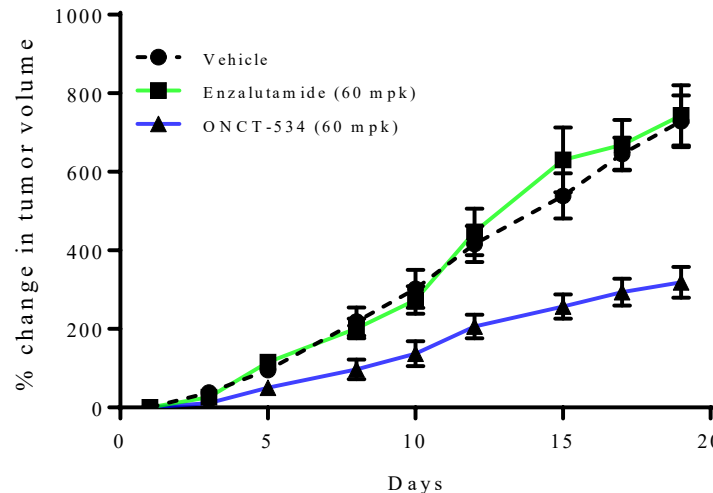
DAARIs exhibit strong anti-tumor activity in preclinical model harboring different AR aberrations

AR overexpression: LnCAP-AR (*intact* animals)



ONCT-534 xenograft (and corresponding vehicle) was performed separately a month after the completion of other groups.

AR-V7 splice variant: 22Rv1 (castrated animals)



ONCT-534 Potential Phase 1/2 Study Design

Phase 1 Portion:

- Sample size: N ~ 12-18 subjects
- Dose escalation 3+3 Design
- Patient Population: Relapsed/refractory mCRPC
- Primary endpoint:
 - Maximum tolerated dose (MTD) or
 - Recommended Phase 2 dose

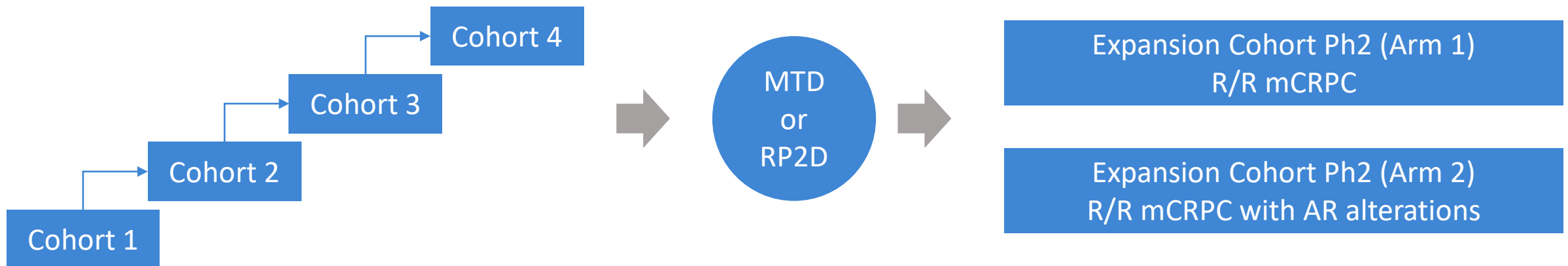
Phase 2 Portion:

Arm 1 expansion cohort

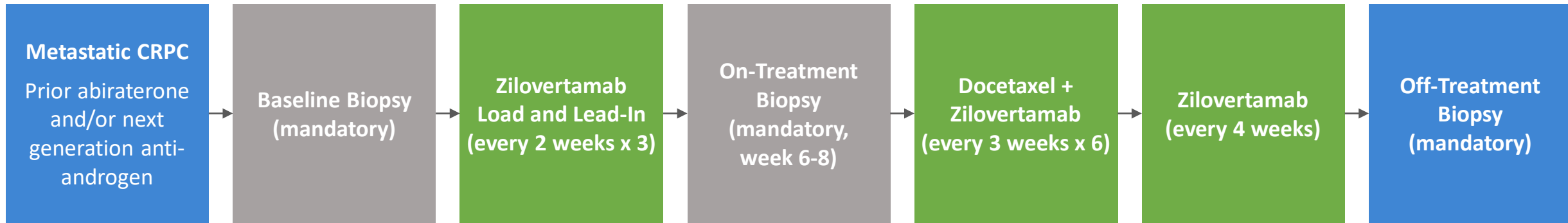
- Relapsed/refractory mCRPC
- Primary endpoint: PSA level

Arm 2 expansion cohort

- Relapsed/refractory mCRPC with AR alterations:
 - AR amplification
 - AR splice variant
 - T878, L702 & H875 mutation
- Primary endpoint: PSA level



Phase 1B IST Trial of Zilovertamab + Docetaxel in metastatic CRPC



Design: 3+3 dose escalation design with expansion (n=32)

Primary Endpoint: Determine the recommended phase 2 dose

Key Secondary Endpoint: Clinical benefit rate

Other Secondary Endpoints: ORR, PSA response rate, PFS, safety, tolerability

Anticipated Pipeline Milestones

Zilovetamab

- MCL global registrational Phase 3 Study Zilo-301 initiation **2Q 2022**
- MCL & CLL clinical data update for ongoing Phase 2 **2Q 2022**
- Prostate cancer mCRPC IST Phase 2 enrollment **mid 2022**
- HER2-negative breast cancer IST clinical data update **Fully Enrolled**

ONCT-808 ROR1 CAR-T cell therapy

- B-Cell malignancies IND submission **mid 2022**

ONCT-216

- Ewing sarcoma dose-intensive cohort interim data **4Q 2022**

ONCT-534

- Prostate cancer IND-enabling preclinical development **Ongoing**

Description	Ticker: ONCT (Nasdaq)
Cash & Cash Investments @ December 31, 2021 Cash Runway into mid-2023	\$90.8M
Debt	\$0M
Capitalization:	
Common Shares Outstanding	49.4M
Options / Warrants in the Money @ December 31, 2021 ⁽¹⁾	0.4M
Fully Diluted in the Money	49.8M
Non-Dilutive Support	
<ul style="list-style-type: none"> • CIRM Grant for CIRLL Study thru March 2022 	~\$14M
<ul style="list-style-type: none"> • Ibrutinib CTM for CIRLL Study 	Supply Agreement

(1) Excludes out-of-the-money stock options and warrants totaling ~10.3M
Oncternal R&D Day – January 25, 2022

Topics

Introduction

Presented by

- Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

Heme Malignancies

- Lymphoma / MCL treatment overview
- Oncternal Zilovetamab and ROR1 cell therapy program update
- Q&A

- Michael Wang, MD (MD Anderson Cancer Center)
- Oncternal Therapeutics Management

Prostate Cancer

- Unmet needs in prostate cancer treatment
- Oncternal ONCT-534 Dual-Action AR Inhibitor value proposition and other opportunities
- Q&A

- Evan Yu, MD (Fred Hutchinson Cancer Research Center)
- Oncternal Therapeutics Management

Wrap-up

- Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

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Wrap-up

Presented by

- Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

- Michael Wang, MD (MD Anderson Cancer Center)
- Oncternal Therapeutics Management

- Evan Yu, MD (Fred Hutchinson Cancer Research Center)
- Oncternal Therapeutics Management

- Jim Breitmeyer, MD, PhD CEO Oncternal Therapeutics

Hematological Malignancies

Zilovertamab – ROR1 monoclonal antibody

- Demonstrated clinical benefit of combination with ibrutinib compared to historical ibrutinib monotherapy
- Expect MCL registrational study initiation in 2Q 2022

ONCT-808 – ROR1 CAR-T Cell Therapy

- Expect IND submission in mid 2022

ONCT-216 – ETS inhibitor – currently under investigation in a Phase 2 study in Ewing sarcoma, preclinical studies in both heme malignancies and prostate cancer underway

Prostate Cancer

ONCT-534 – Dual Action AR Inhibitor (DAARI)

- First-in-class MOA interacting with both N-terminal Domain and Ligand-Binding Domain of the androgen receptor inducing AR degradation
- Active preclinically against AR amplification, splice variant and LBD mutation models

Zilovertamab – ROR1 monoclonal antibody

- IND open for advanced prostate cancer

ZILOVERTAMAB (FORMERLY CIRMTUZUMAB): POTENTIALLY FIRST-IN-CLASS MONOCLONAL ANTIBODY TARGETING ROR1

- Latest results for zilovertamab + ibrutinib in patients with MCL/CLL compare favorably to historical single-agent ibrutinib
- Agreement with U.S. FDA on Phase 3 registrational study design for the treatment of patients with R/R MCL

ONCT-808: AUTOLOGOUS CAR-T CELL THERAPY TARGETING ROR1

- IND-enabling activities supported by Lentigen (lentivirus manufacturing) and Miltenyi Biotec (process development)
- Research collaborations for next-gen allogeneic CAR-T and CAR-NK cell therapies with Karolinska Institutet & Celularity

ONCT-216 (FORMERLY TK216): TARGETED ETS INHIBITOR

- Two durable complete responses in patients with metastatic relapsed/refractory Ewing sarcoma in ongoing Phase 1/2
- Additional opportunities in ETS-driven tumor indications

ONCT-534 (FORMERLY GTX-534): DUAL-ACTION ANDROGEN RECEPTOR INHIBITOR (DAARI)

- Pre-clinical data in prostate cancer models suggest activity against tumors expressing androgen receptor splice variants

MULTIPLE DATA CATALYSTS

- Expected initiation of zilovertamab + ibrutinib global registrational Phase 3 Study ZILO-301 in 2Q 2022
- Clinical data updates in MCL, CLL, breast cancer and Ewing sarcoma
- ONCT-808 ROR1 CAR-T cell therapy IND submission planned in mid 2022