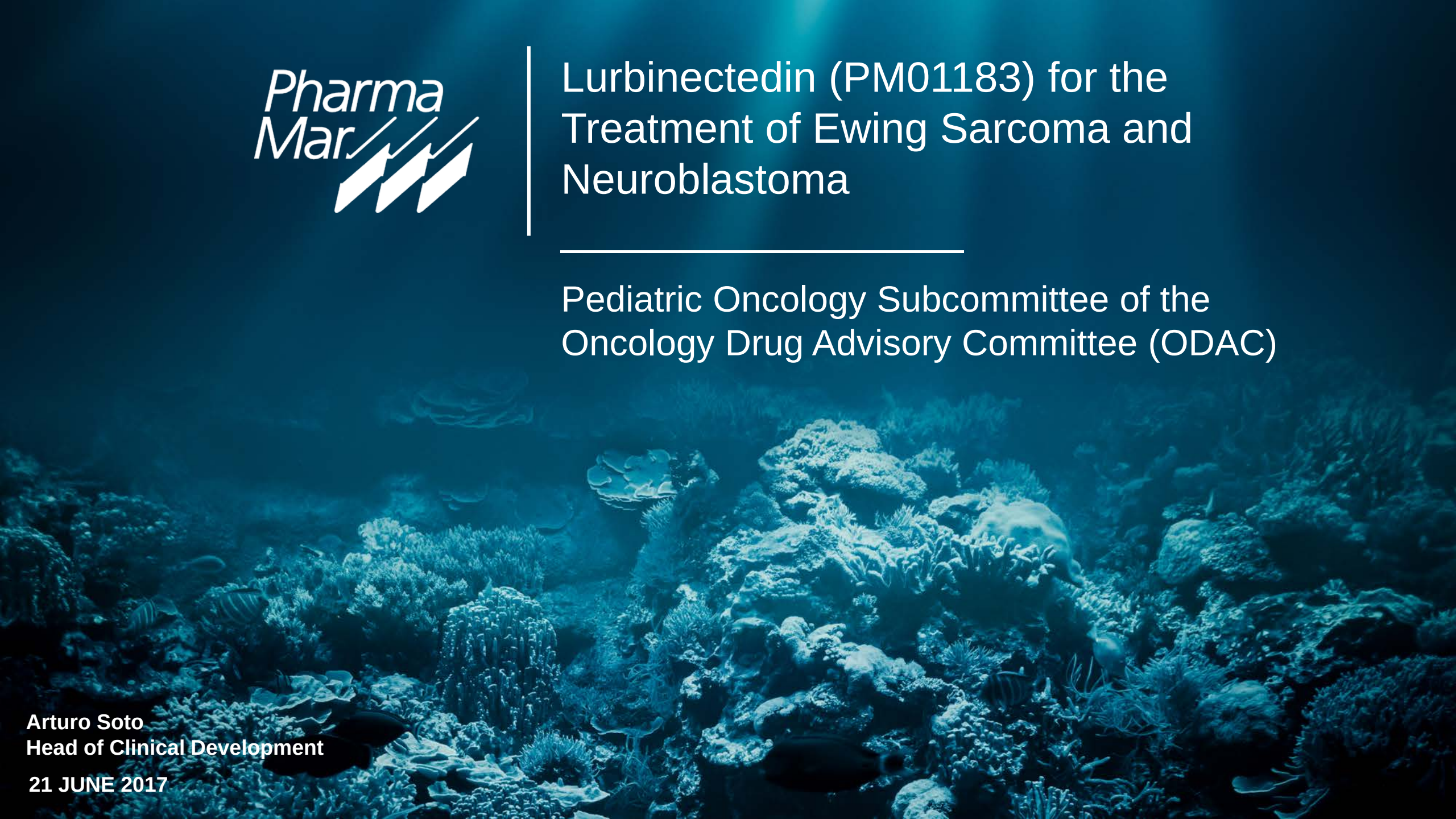
Lurbinectedin (PM01183) for the Treatment of Ewing Sarcoma and Neuroblastoma

Pediatric Oncology Subcommittee of the Oncology Drug Advisory Committee (ODAC)



Arturo Soto
Head of Clinical Development

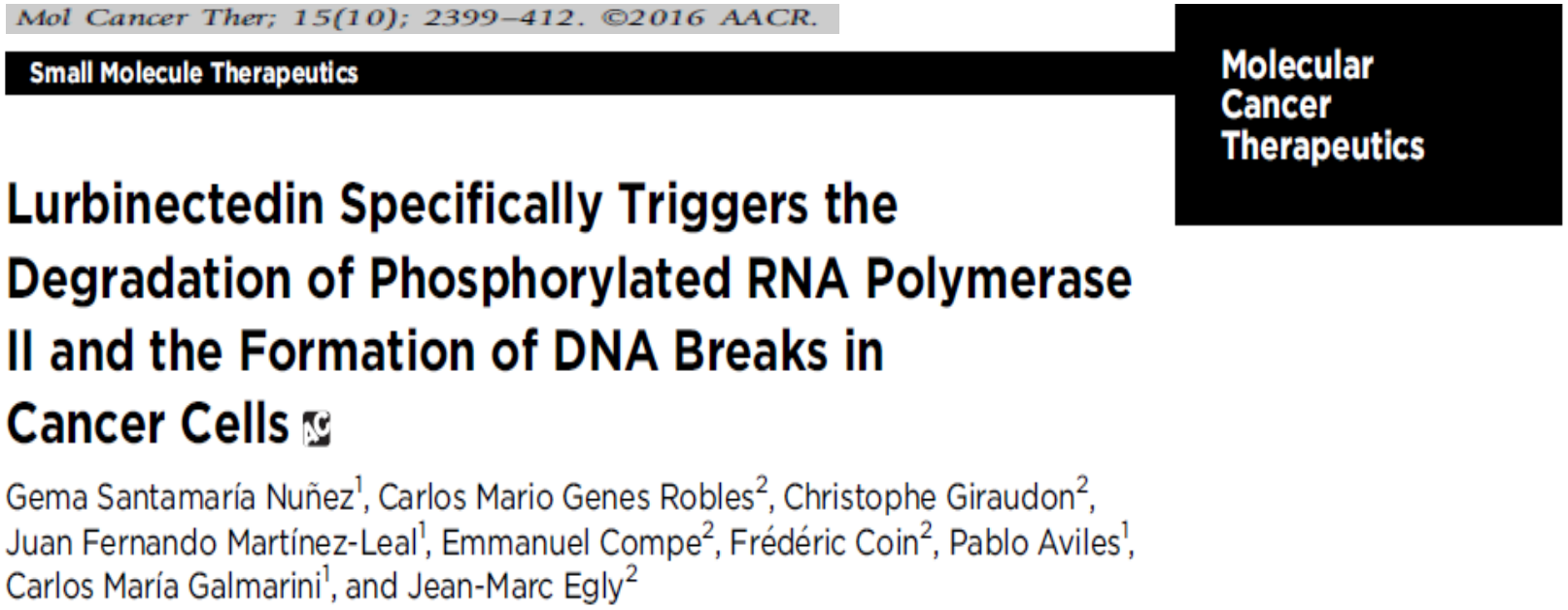
21 JUNE 2017

Agenda

- Mechanism of Action
- Regulatory History
- Preclinical data supporting clinical studies
- Clinical trials experience in adults
- Clinical trials with relevance to pediatrics, adolescents and young adults
- Proposed pediatric development plan
- Potential challenges for clinical development of lurbinectedin in pediatric indications

Lurbinectedin Mechanism of Action

Lurbinectedin: a transcription inhibitor



Mol Cancer Ther; 15(10); 2399–412. ©2016 AACR.

Small Molecule Therapeutics

Molecular Cancer Therapeutics

Lurbinectedin Specifically Triggers the Degradation of Phosphorylated RNA Polymerase II and the Formation of DNA Breaks in Cancer Cells

Gema Santamaría Nuñez[1], Carlos Mario Genes Robles[2], Christophe Giraudon[2], Juan Fernando Martínez-Leal[1], Emmanuel Compe[2], Frédéric Coin[2], Pablo Aviles[1], Carlos María Galmarini[1], and Jean-Marc Egly[2]

- **Stalling of elongating RNA Pol II and degradation by the ubiquitin/proteasome machinery**
- **Recruitment of XPF/ERCC1 and generation of DNA breaks**
- **Induction of apoptosis**

Leading Edge
Review

Cell

Transcriptional Addiction in Cancer

James E. Bradner,[1] Denes Hnisz,[2] and Richard A. Young[2,3,*]
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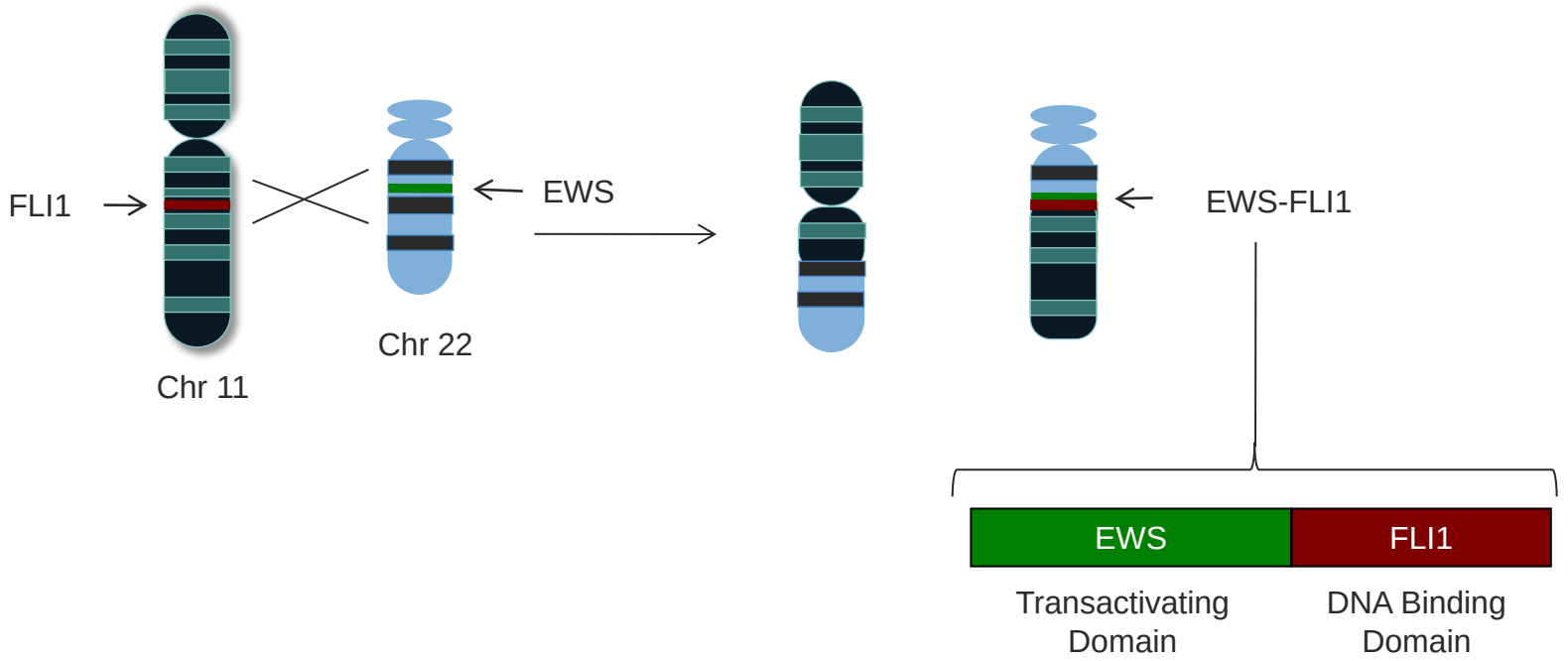
*Correspondence: young@wi.mit.edu
http://dx.doi.org/10.1016/j.cell.2016.12.013

- Cancer cells aberrantly deregulate specific gene expression programs with critical functions in cell differentiation, proliferation, and death
- These altered gene programs in cancer cells have a striking dependence on continuous active transcription (transcription addiction)

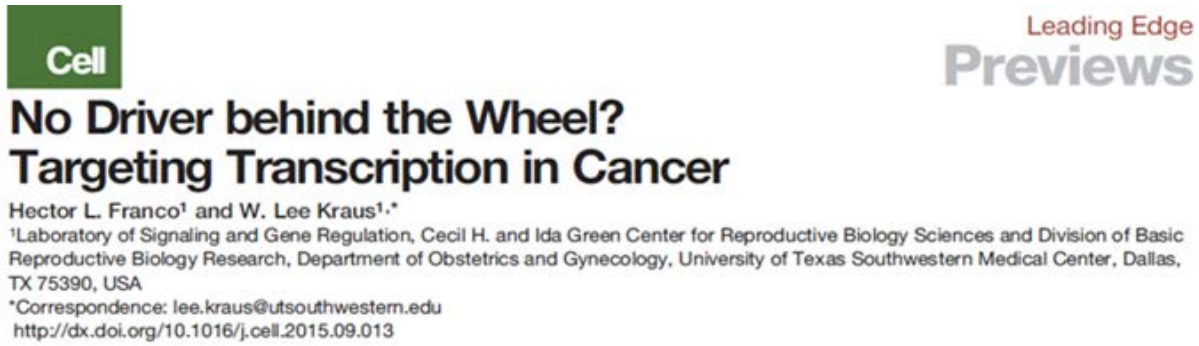
Transcription Dependency in Ewing Sarcoma



- EWS-FLI1 is a constitutively active transcription factor that is the hallmark of Ewing sarcoma
- EWS-FLI1 alters the expression of approximately 1000 genes
  - Mediate malignant transformation
  - Increased metastatic potential
  - Decreases thrombospondins to facilitate angiogenesis
  - Evasion of senescence
  - Directly or indirectly is anti-apoptosis

Fuchs FEBS Letters (2003); 104
Potikyan Cancer Res (2007) 67; 6675
Matsunobu Cancer Res (2006) 66: 803
Riggi Cancer Lett (2007) 254(10):1
Delattre (1992) Nature 359:1625

Transcription as a Valid Target in Oncology



Cell

Leading Edge
Previews

No Driver behind the Wheel? Targeting Transcription in Cancer

Hector L. Franco[1] and W. Lee Kraus[1,*]
[1]Laboratory of Signaling and Gene Regulation, Cecil H. and Ida Green Center for Reproductive Biology Sciences and Division of Basic Reproductive Biology Research, Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA
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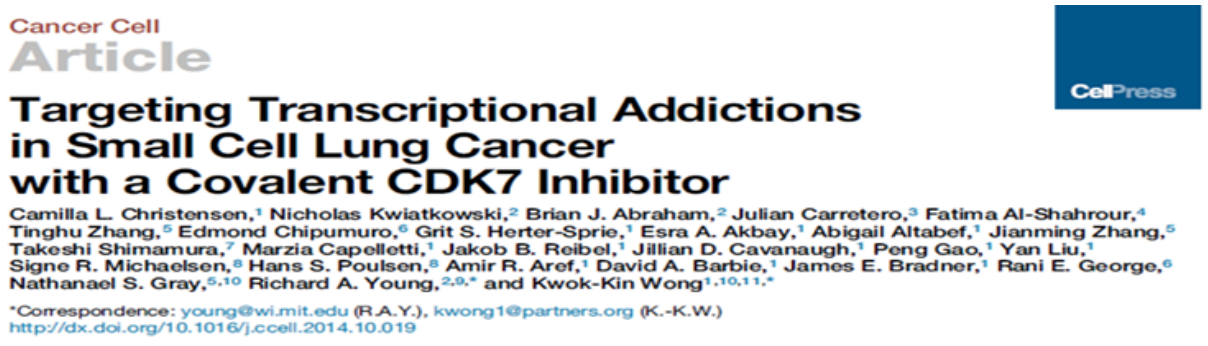
http://dx.doi.org/10.1016/j.cell.2015.09.013



Cancer Cell
Article

CellPress

Targeting Transcriptional Addictions in Small Cell Lung Cancer with a Covalent CDK7 Inhibitor

Camilla L. Christensen,[1] Nicholas Kwiatkowski,[2] Brian J. Abraham,[2] Julian Carretero,[3] Fatima Al-Shahrour,[4] Tinghu Zhang,[5] Edmond Chipumuro,[6] Grit S. Herter-Sprie,[1] Esra A. Akbay,[1] Abigail Altabef,[1] Jianming Zhang,[5] Takeshi Shimamura,[7] Marzia Capelletti,[1] Jakob B. Reibel,[1] Jillian D. Cavanaugh,[1] Peng Gao,[1] Yan Liu,[1] Signe R. Michaelsen,[8] Hans S. Poulsen,[8] Amir R. Aref,[1] David A. Barbie,[1] James E. Bradner,[1] Rani E. George,[6] Nathanael S. Gray,[5,10] Richard A. Young,[2,9,*] and Kwok-Kin Wong[1,10,11,*]
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http://dx.doi.org/10.1016/j.ccell.2014.10.019

CellPress

Cancer Cell
Previews

Inhibit Globally, Act Locally: CDK7 Inhibitors in Cancer Therapy

Kaixiang Cao[1] and Ali Shilatifard[1,*]
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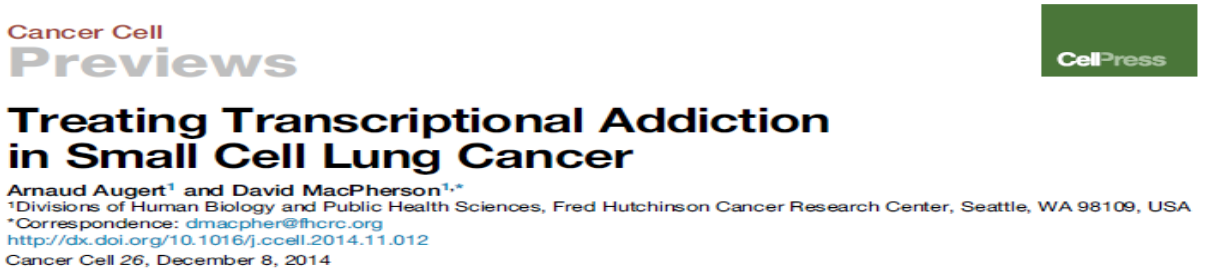
http://dx.doi.org/10.1016/j.ccr.2014.07.020



Cancer Cell
Previews

CellPress

Treating Transcriptional Addiction in Small Cell Lung Cancer

Arnaud Augert[1] and David MacPherson[1,*]
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http://dx.doi.org/10.1016/j.ccell.2014.11.012
Cancer Cell 26, December 8, 2014

Therapeutics, Targets, and Chemical Biology

Cancer Research

Lurbinectedin Inactivates the Ewing Sarcoma Oncoprotein EWS-FLI1 by Redistributing It within the Nucleus

Matt L. Harlow[1], Nichole Maloney[2], Joseph Roland[3], Maria Jose Guillen Navarro[4], Matthew K. Easton[5], Susan M. Kitchen-Goosen[5], Elissa A. Boguslawski[5], Zachary B. Madaj[5], Ben K. Johnson[5], Megan J. Bowman[5], Maurizio D'Incalci[6], Mary E. Winn[5], Lisa Turner[5], Galen Hostetter[5], Carlos María Galmarini[4], Pablo M. Aviles[4], and Patrick J. Grohar[2,5,7,8]

- **Degradation of Pol II by the ubiquitin/proteasome machinery**
- **Direct block in binding to its target genes**
- **Redistribution of EWS-FLI1 within the nucleus**

REGULATORY HISTORY:

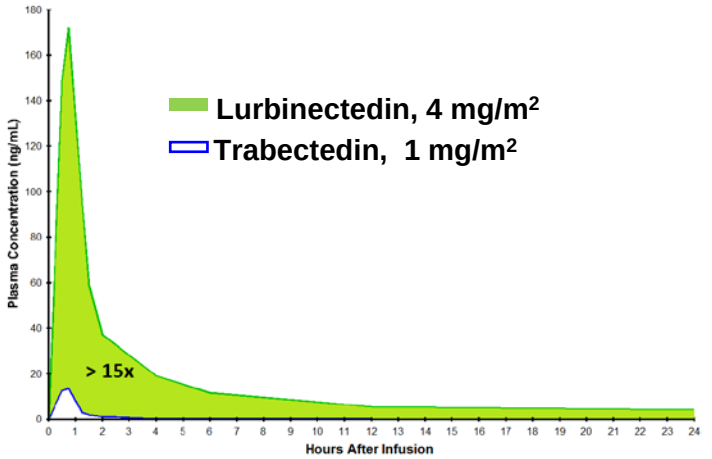
Lurbinectedin (PM01183) - IND Nr. 103556

REGULATORY APPLICATION:	DATE:
Initial Investigational New Drug (IND 103556) Application Clearance	January 16, 2009
Orphan Drug Designation US (Designation number: 12-3765; OD number: 099/12)	August 20, 2012
Orphan Drug Designation EU (EU/3/12/1053)	October 10, 2012.
Full **waiver** for the Initial Pediatric Study Plan (**Agreed iPSP**) for treatment of patients with extensive stage, small cell lung cancer (**SCLC**) that has progressed following platinum-containing chemotherapy.	October 11, 2016
Lurbinectedin is not currently approved for marketing in any country.	

Nonclinical Data

Pharmacokinetics

- Long terminal elimination half-life, slow plasma clearance and large volume of distribution in mice, rats, dogs and cynomolgus
- C_{max} and AUC are proportional to dose (up to MTD) either after single or repeated (up to 4 cycles) administration
- ^{14}C-lurbinectedin-related radioactivity is rapidly distributed in rats
  - Maximum concentration is observed in spleen, liver, lymph nodes, thyroid glands, lung, kidney and small intestine
  - Lowest radioactivity detected in brain and testes
  - Feces are the primary route of excretion in the rat (91% up to 168 h post-dose)
- Oxidative metabolism is very intensive, mainly dominated by CYP3A4
- Lurbinectedin is highly plasma protein bound

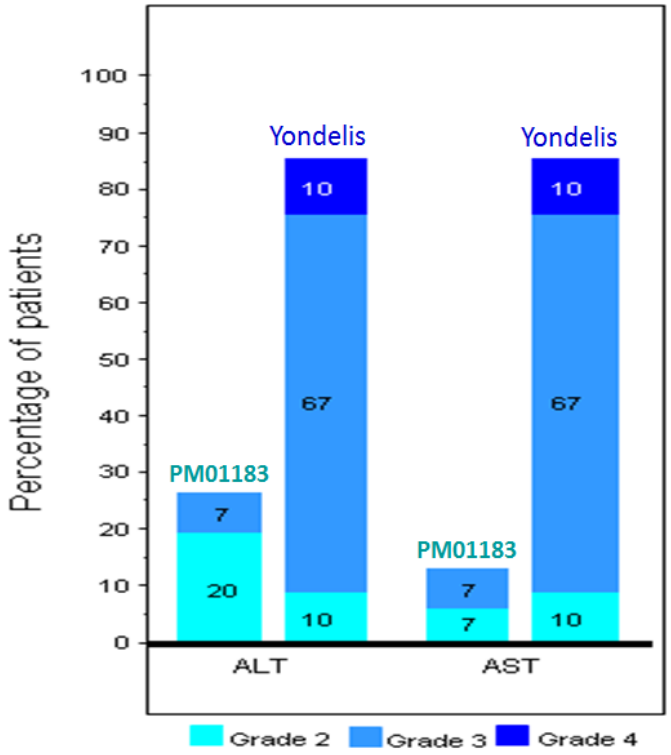


	AUC	HL
Lurbinectedin	706	60
Trabectedin	46	180

Nonclinical Data

Safety and Toxicology

- No concerns related to neurotoxicity, cardiovascular or respiratory functions
- Pivotal studies: up to 4 cycles in dogs; and to 8 cycles in rats and cynomolgus –ongoing–
- Clinical signs: transient body weight decreases, diarrhea and emesis
- Mortality related to bone marrow suppression, hepatic alterations and gastrointestinal events
- Reversible findings in the hematopoietic system: reduced reticulocytes and white blood cells, slight anemia, as well as bone marrow depletion and atrophy of the lymphoid system
- Hepatotoxicity: increase in liver function tests, hepatocellular necrosis and biliary damage
- Other target organs: gastrointestinal atrophy, adrenal glands (cortical hypertrophy) and kidneys (cortical tubular vacuolization)



Clinical Trials in Adult Patients with Cancer

Summary

- More than 1000 patients were treated with lurbinectedin in PharmaMar clinical trials
- The RD as single agent is 3.2 mg/m^2 and in combination from 1.1 to 2.2 mg/m^2
- Most relevant AE asociated with lurbinectedin are hematological, mainly dose dependent neutropenia
- Other AEs were mild to moderate gastrointestinal and fatigue
- Efficacy was observed in different tumor types with single agent and in combination

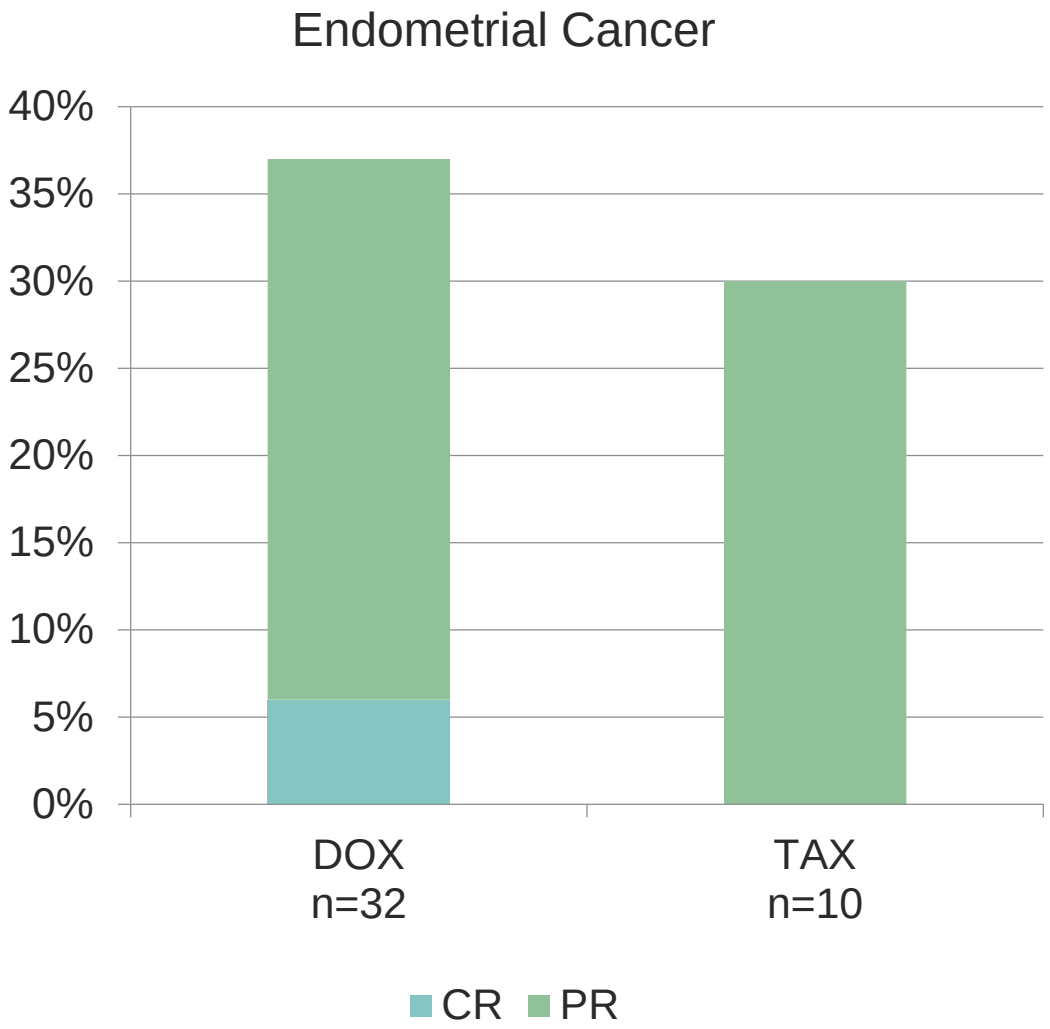
Clinical Trials in Adult Patients with Cancer

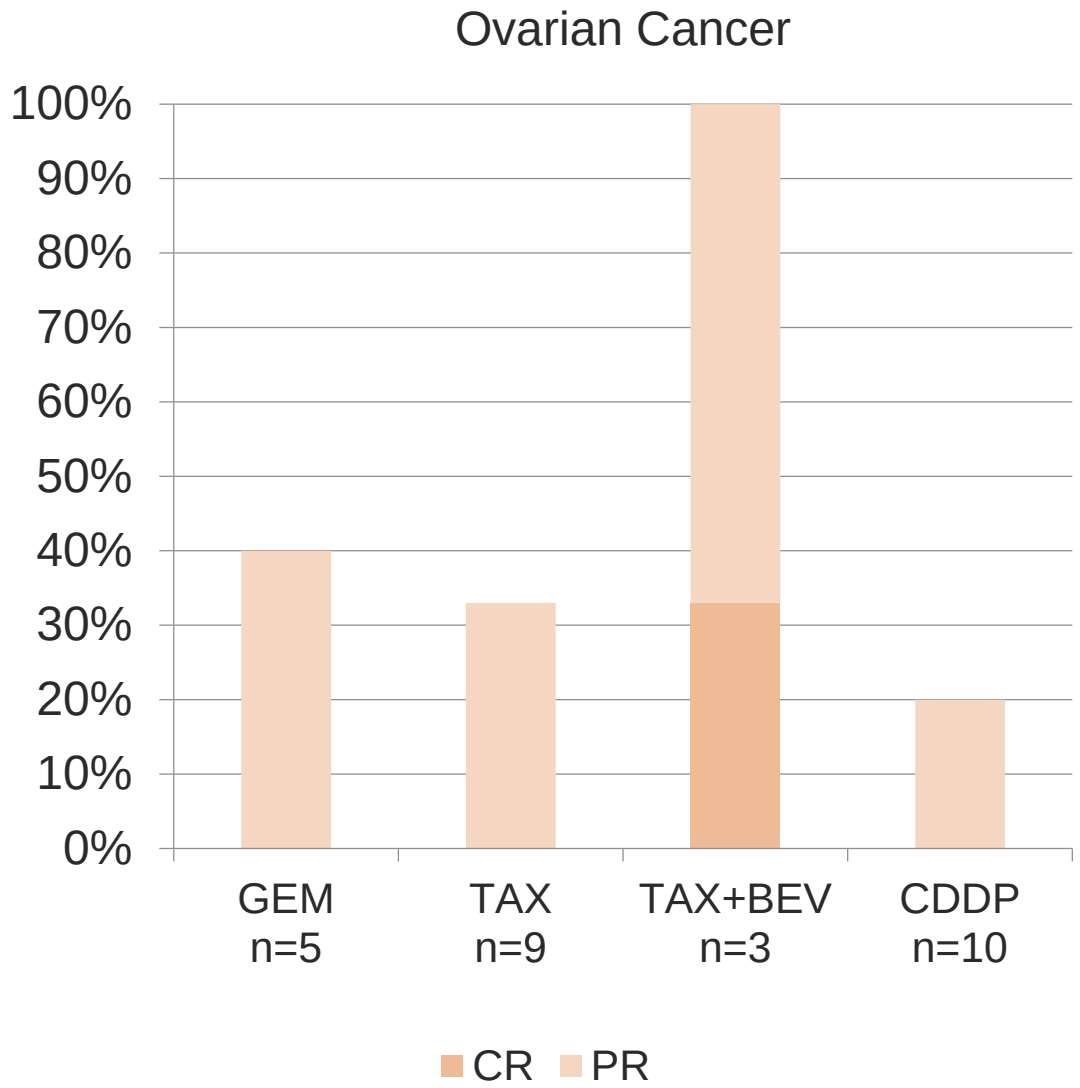
Single-agent
Phase 1 FIM
Day 1&8
Leukemia
Combination
Doxorubicin
Gemcitabine
Capecitabine
Paclitaxel
Paclitaxel + Bevacizumab
Cisplatin
Irinotecan

Non-randomized trials	
Pancreatic cancer	
Breast cancer	
Selected advanced solid tumors	
Randomized trials	
PRROC	Lurbinectedin
	Topotecan
NSCLC	Lurbinectedin
	Lurbinectedin+Gemcitabine
	Docetaxel
Phase III trials	
PROC	Lurbinectedin
	PLD or topotecan
SCLC	Lurbinectedin+Doxorubicin
	CAV or topotecan

Clinical Trials in Adult Patients with Cancer

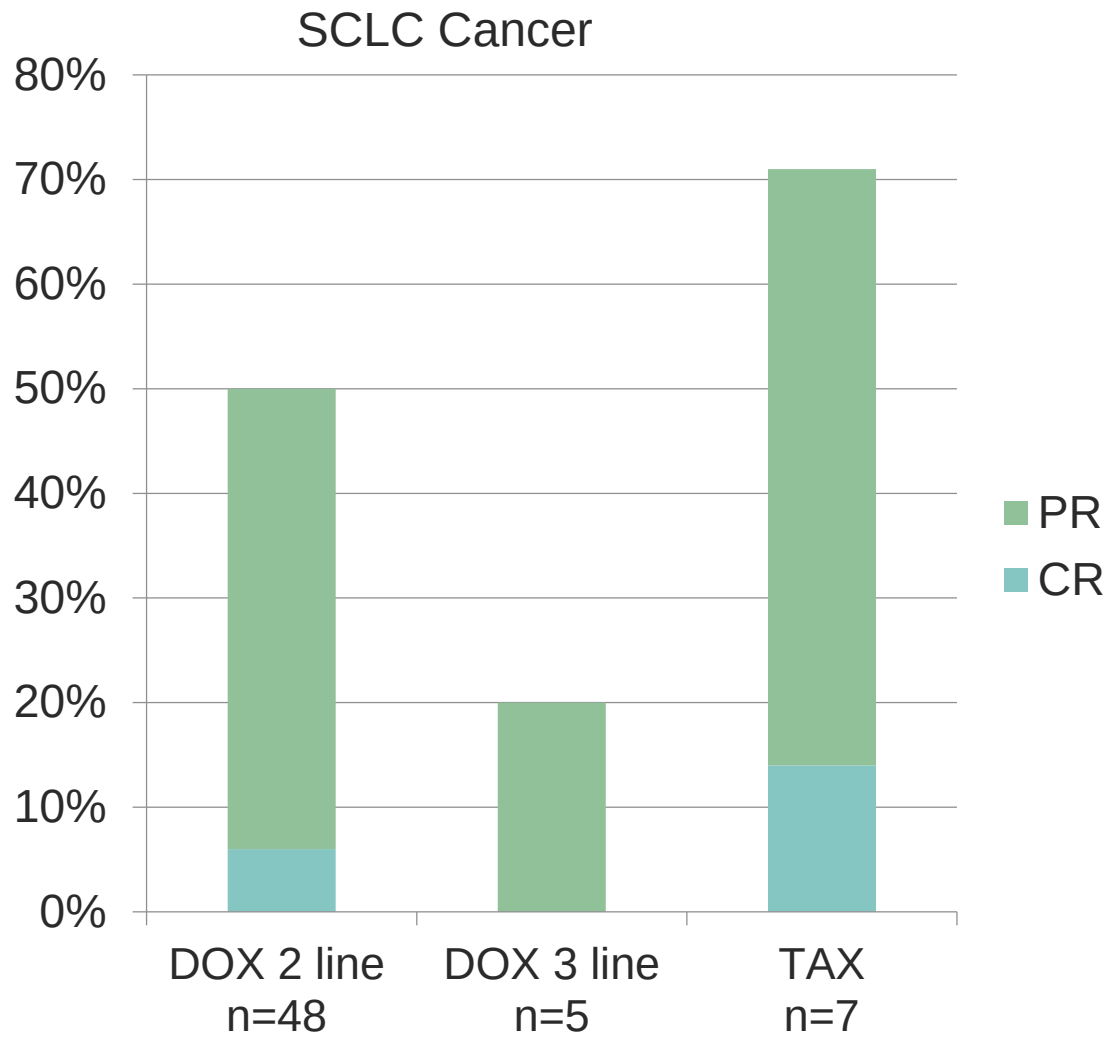
Efficacy in Endometrial and Ovarian Cancer from Phase I Studies in Combination

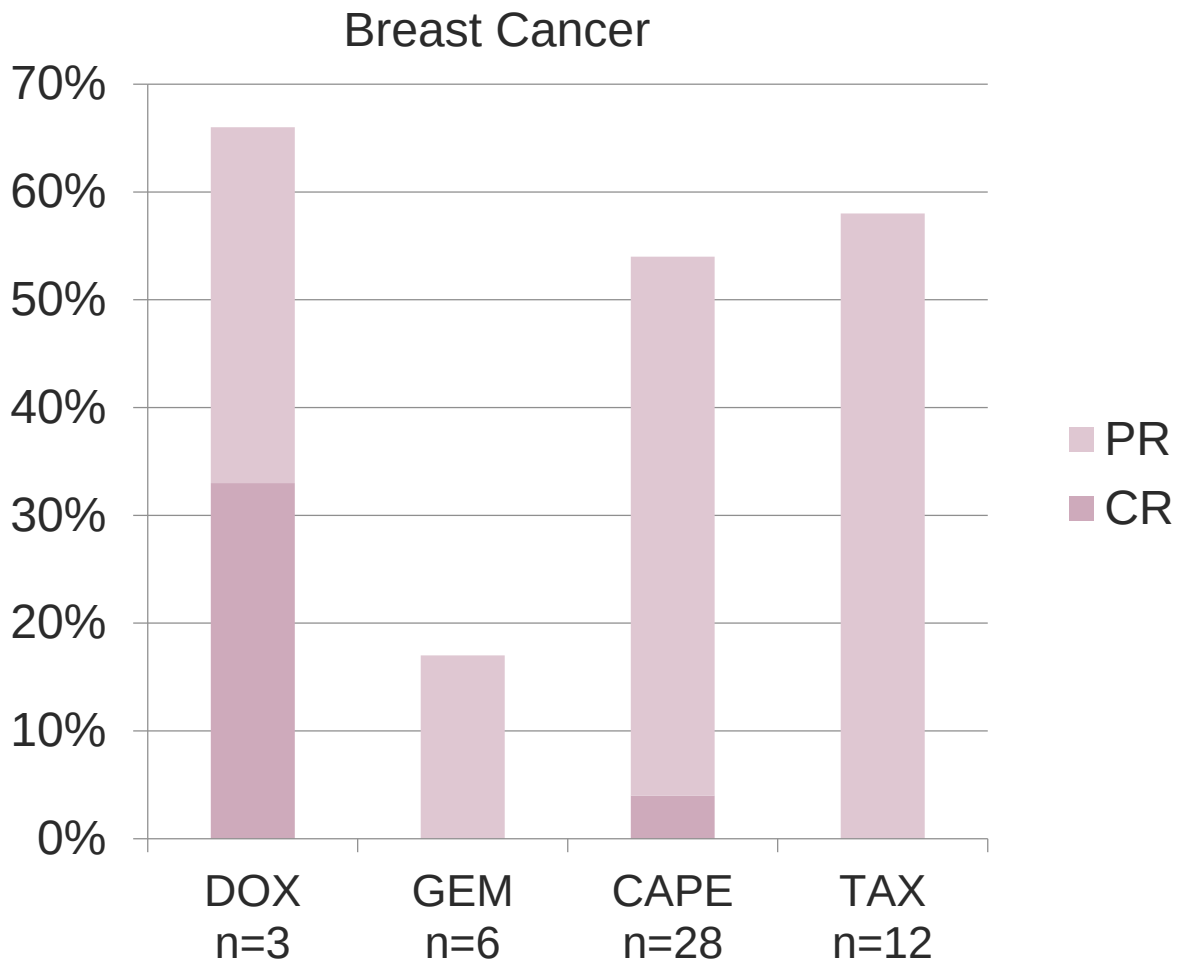




Clinical Trials in Adult Patients with Cancer

Efficacy in SCLC and MBC from Phase I Studies in Combination





Clinical Trials in Adult Patients with Cancer

Efficacy in Phase II single agent and single arm studies

Study Indication	Participant sites and countries	Evaluable patients	N pts	ORR % Conf RECIST v.1.1	Study status at cutoff
BRCA 1/2-associated or unselected MBC	11 Spain U.S.	BRCA+	54	41%	Recruitment completed
Selected advanced solid tumors	28 Belgium France Germany Italy Spain Sweden Switzerland U.K. U.S.	BRCA+ MBC	6	33%	Ongoing
		SCLC	23	26%	
		Endometrial	37	14%	
		EFT	**17**	**18%**	
		Biliary Tract	18	6%	
		NET	26	4%	

Efficacy in a randomized Phase II single agent study in PRROC

Overall Response Rate (ORR)

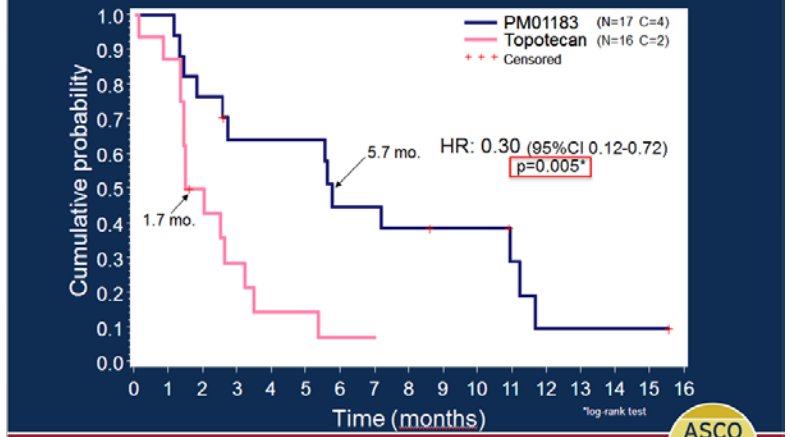
	PM01183		Topotecan	p-value
	Overall (1st & 2nd stage) n=52	Randomized (2nd stage) n=30	n=29	
ORR (n [%])				
CR	1 (2)	1 (3)	0 (0)	
PR	&10 (19)	4 (13)	0 (0)	
SD	26 (50)	14 (47)	15 (52)	
PD	15 (29)	11 (37)	14 (48)	
ORR (%) (95% CI)	**21 (11-35)**	17 (6-35)	0 (0-11)	0.006
- Platinum resistant	30 (16-49)	24 (7-50)	0 (0-21)	0.020
- Platinum refractory	5 (0-26)	8 (0-36)	0 (0-25)	1

&2 PRs by Rustin criteria

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Progression-free Survival – 2nd stage

Platinum Resistant



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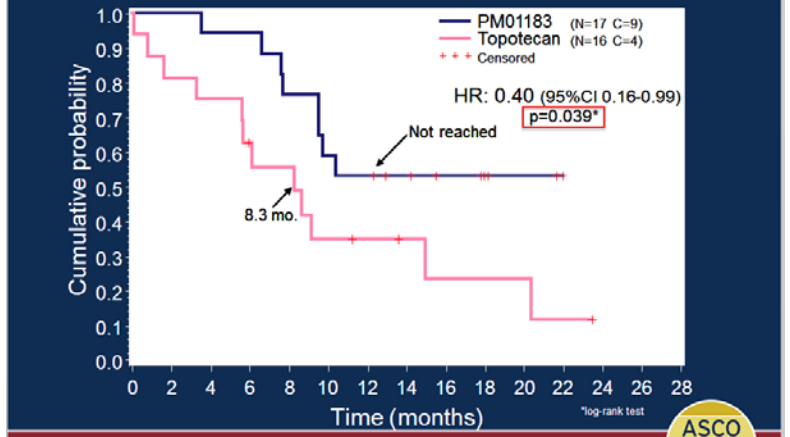
Overall Survival - 2nd stage

Platinum Resistant



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Clinical Trials in Adult Patients with Cancer

Safety: Adverse Events

SOC/MedDRA PT	NCI-CTCAE grade				Total (n=492)
	1	2	3	4	
	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment-related AEs or with unknown relationship					
Nausea	42 (8.5%)	40 (8.1%)	12 (2.4%)	.	94 (19.1%)
Vomiting	32 (6.5%)	32 (6.5%)	13 (2.6%)	.	77 (15.7%)
Fatigue	31 (6.3%)	36 (7.3%)	22 (4.5%)	.	89 (18.1%)
Diarrhea	14 (2.8%)	9 (1.8%)	.	.	23 (4.7%)
Constipation	13 (2.6%)	5 (1.0%)	.	.	18 (3.7%)
Alopecia	6 (1.2%)	3 (0.6%)	.	.	9 (1.8%)
Abdominal pain	3 (0.6%)	2 (0.4%)	.	.	5 (1.0%)
Abdominal pain upper	4 (0.8%)	1 (0.2%)	.	.	5 (1.0%)
Dyspnea	2 (0.4%)	.	3 (0.6%)	.	5 (1.0%)
Phlebitis	.	5 (1.0%)	.	.	5 (1.0%)
Stomatitis	4 (0.8%)	1 (0.2%)	.	.	5 (1.0%)

Clinical Trials in Adult Patients with Cancer

Safety: Laboratory Abnormalities

SOC/MedDRA PT	1 n (%)	2 n (%)	3 n (%)	4 n (%)	Total (n=492) n (%)
Hematological laboratory abnormalities					
Anemia	177 (36.0%)	176 (35.8%)	87 (17.7%)	.	440 (89.4%)
Leukopenia	62 (12.6%)	111 (22.6%)	124 (25.2%)	78 (15.9%)	375 (76.2%)
Neutropenia	22 (4.5%)	80 (16.3%)	89 (18.1%)	150 (30.5%)	341 (69.3%)
Thrombocytopenia	151 (30.7%)	41 (8.3%)	36 (7.3%)	49 (10.0%)	277 (56.3%)
Febrile neutropenia	.	.	30 (6.1%)	16 (3.3%)	46 (9.3%)
Biochemical laboratory abnormalities					
ALT increased	213 (43.3%)	62 (12.6%)	53 (10.8%)	3 (0.6%)	331 (67.3%)
AST increased	213 (43.3%)	34 (6.9%)	22 (4.5%)	3 (0.6%)	272 (55.3%)
Bilirubin increased	49 (10.0%)	21 (4.3%)	13 (2.6%)	3 (0.6%)	86 (17.5%)
Creatinine increased	38 (7.7%)	16 (3.3%)	10 (2.0%)	8 (1.6%)	72 (14.6%)

Clinical Trials with Relevance to Pediatrics

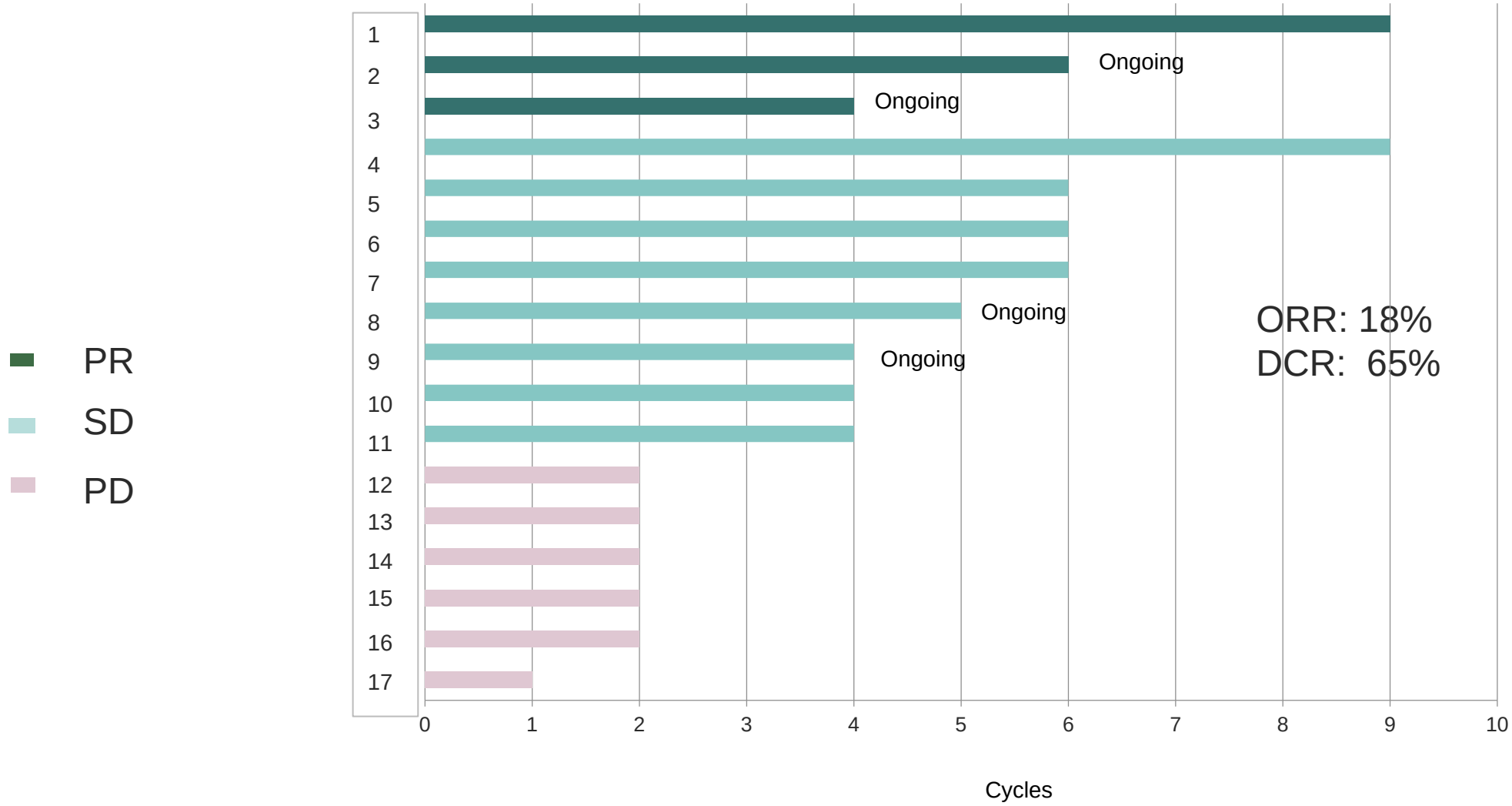
Ewing Sarcoma in Adults

Baseline Characteristics

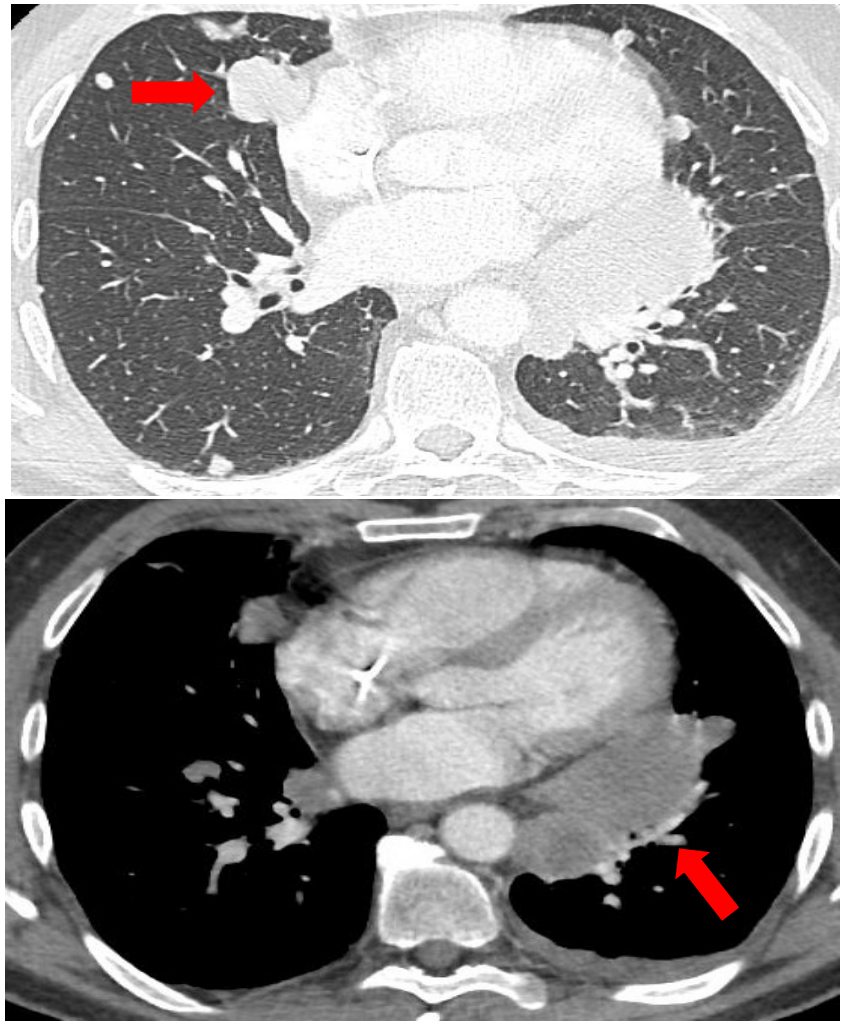
Baseline Characteristics		Ewing sarcoma n=22
Age years	Median range	30 (20-74)
Gender	M / F	14/8
ECOG PS	0/1/2	12/9/1
BSA m^2	Median range	1.9 (1.6-2.4)
Sites of disease involvement	< 3 / ≥ 3	16/6
Prior chemotherapy lines	1	5
	2	12
	>2	5

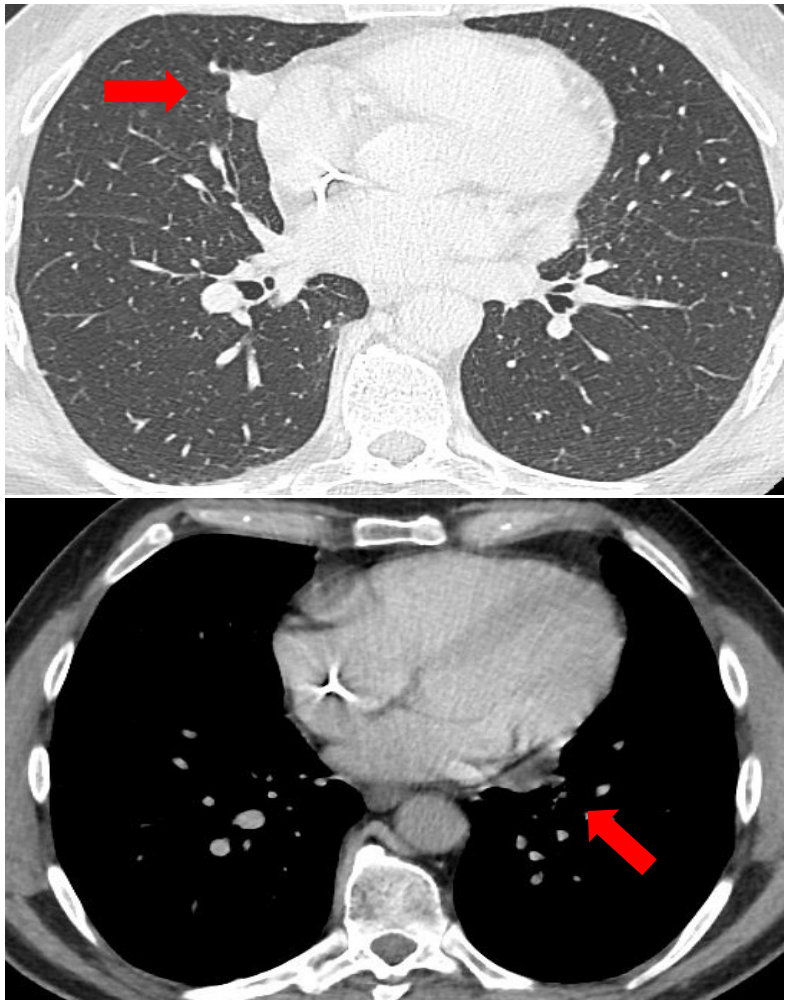
Ewing Sarcoma in Adults

Efficacy in 17 Evaluable Patients



54 years old
EWS of right femur, treated in 2015
Lurbinectedin as first line treatment (lung / pleural / mediastinal relapse)





Baseline (13/01/2017)

Post C2 Lurbinectedin (03/03/2017)

Rationale for the Development in Neuroblastoma

- No patients with neuroblastoma have been treated with lurbinectedin
- Amplification of the MYC family member, MYCN, is found in about 25% of cases and correlates with high-risk disease and poor prognosis
- MYCN protein, is a DNA binding transcription factor known to cause malignant transformation in both in vitro and in vivo tumor models

Proposed Pediatric Development Plan

Phase I
Pediatric
3+3 dose escalation

Based on:
MoA/target
Preclinical data
Studies in adults

Single Agent
Solid Tumors
RD
PK
Safety

Phase II Expansion cohort
Ewing
Neuroblastoma (MYCN+)
Other (efficacy signal)
Confirm RD

Randomized
Phase II
or
Phase III

Combination
Solid Tumors
RD
PK
Safety

Phase II Expansion cohort
Ewing
Neuroblastoma
Other (efficacy signal)
Confirm RD

Only children >2 years will be included initially. Once safety information for this subgroups is available to continue including pediatric population subgroups: infants and toddlers (28 days to 23 months) and term newborn infants (0 to 27 days) progressively

Potential Challenges for Clinical Development of lurbinectedin In Pediatric Indications

- Lurbinectedin is provided as a lyophilized drug product for solution for infusion for i.v. administration
  - The lubinectedin solution for infusion contains sucrose, sodium lactate and sodium chloride or glucose as excipients
  - Oral presentations for pediatric are precluded due to the very low permeability of lurbinectedin through oral mucosa and oral bioavailability below 5%
  - Lurbinectedin needs to be infused in a volume of at least 100 mL. The lower doses for pediatric population will require optimization of the lurbinectedin strength per vial and the infusion volumes to ensure accurate dose measurement, to reduce the risk of dosing errors and prevent subcutaneous lesions in case of extravasation
- Liver maturation
- Low penetration in CNS and testes

Thanks