Comisión Nacional del Mercado de Valores
Att. Director del Área de Mercados
C/Edison núm. 4
28006 Madrid

Colmenar Viejo (Madrid), a 24 de abril de 2017

En relación con el Hecho Relevante nº 250382 de fecha 6 de abril de 2017 relativo a la celebración en el día de hoy en Nueva York de la jornada científica llamada "R&D Day" (10:30-13:30 ET; 16:30-19:30 CEST), adjunto le remitimos la documentación soporte de esta Presentación y que se publicará en el apartado de Calendario de eventos en la página web de la Compañía www.pharmamar.com.

La jornada podrá seguirse en directo a través del webcast que estará disponible en el mismo apartado de la página web de la Compañía. La grabación estará disponible durante treinta días en la página web de Pharma Mar.

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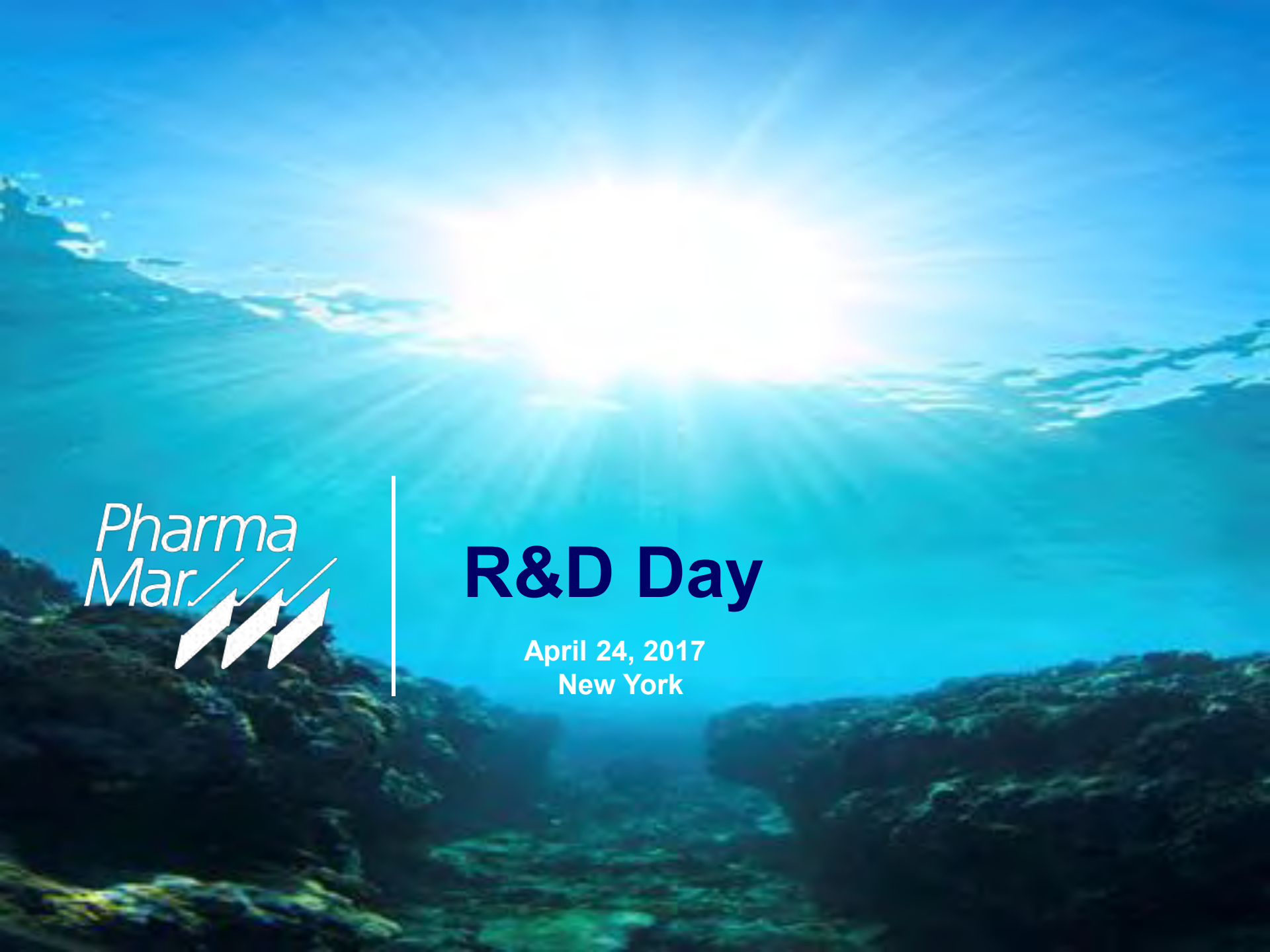
28770 Colmenar Viejo
(Madrid) Spain
www.pharmamar.com



R&D Day

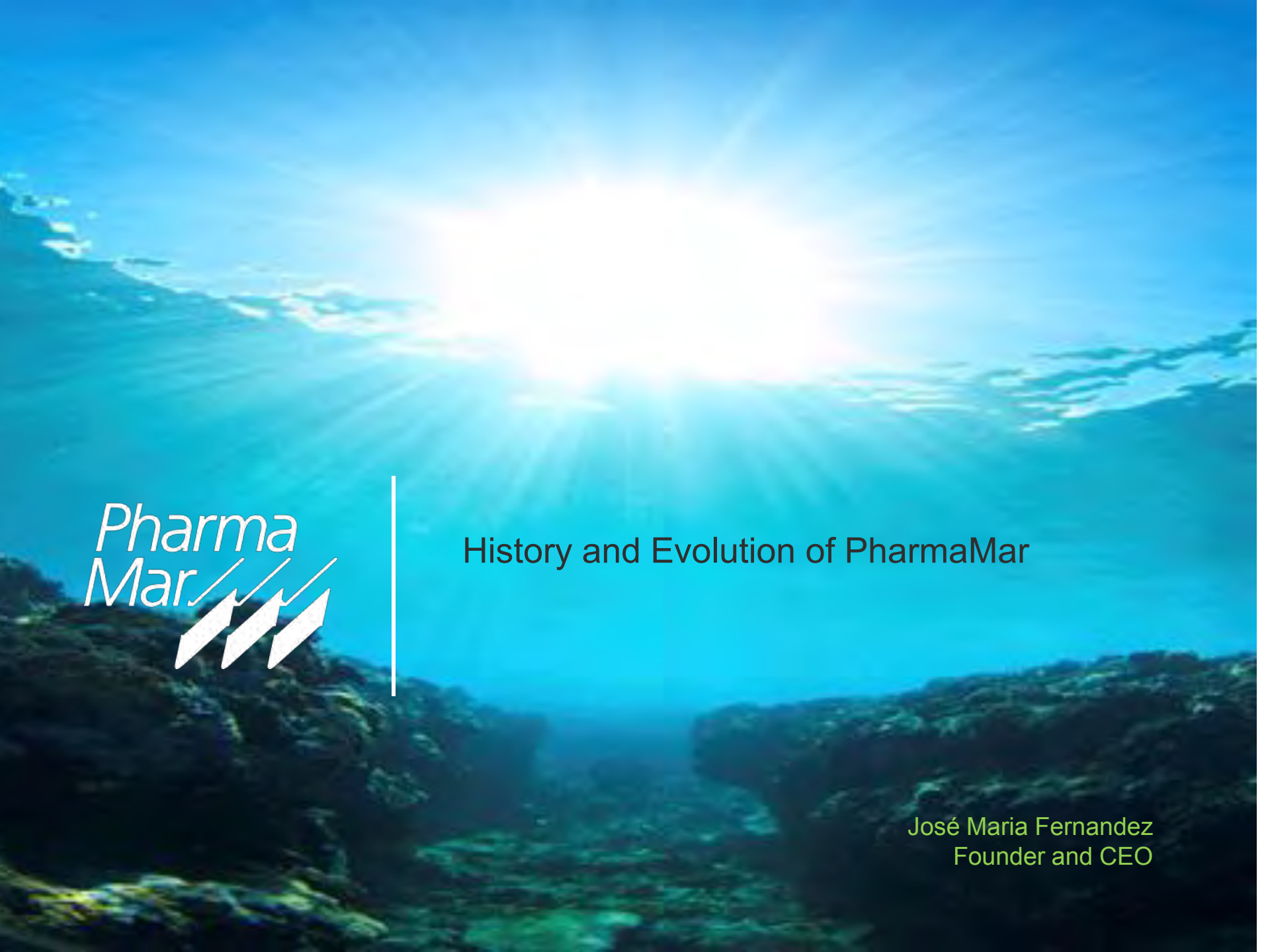
April 24, 2017
New York

Disclaimer

This document includes only summary information and is not intended to be comprehensive. This document includes "forward-looking statements" that are based on Management's current expectations. Factors that could cause future results to differ materially from such expectations include, but are not limited to: the success of the Company's research strategy; the applicability of discoveries made therein; the difficulties inherent in the development of pharmaceuticals, including uncertainties as to the timing and results of preclinical studies; delayed achievements of milestones; reliance on collaborators; uncertainty as to whether the Company's potential products will succeed in entering human clinical trials and uncertainty as to the results of such trials; uncertainty as to whether adequate reimbursement for these products will exist from the government, private healthcare insurers and third-party payers; and the uncertainties as to the extent of future government regulation of the pharmaceutical business. Therefore those statements involve risks and uncertainties beyond the Company's control and actual results may differ materially from those stated by such forward-looking statements. The Company expressly disclaims any obligation to review or update any forward-looking statements, contained in this document to reflect any change in the assumptions, events or circumstances on which such forward-looking statements are based unless so required by applicable law.

Agenda

- Introduction, José Luis Moreno
- History and Evolution of PharmaMar, José Maria Fernandez
- Current and Prospective Clinical Trials, Arturo Soto
- Dr. Martin Forster, UCL, Expert in Small Cell Lung Cancer
- Dr. Melinda Telli, Stanford, Expert in Hereditary Breast Cancers
- Mechanism of Action: Discussions on Lurbinectedin Mechanism of Action Compared to Yondelis, and Potential Synergy with IO and PARPs, Carlos Galmarini
- Sue Friedman, Executive Director FORCE, Patient Advocacy Women's Hereditary Cancers
- U.S. Commercial Plans and Infrastructure Build, Pascal Besman
- Strategy & Where PharmaMar Will Be in Five Years with the Head of Oncology, Luis Mora
- A Word on Financials, José Luis Moreno
- Wrap up, by Chairman, José Maria Fernandez



History and Evolution of PharmaMar

José Maria Fernandez
Founder and CEO

A Global Leader

- **Global leader in the development and commercialization of marine-derived oncology drugs**

Natural Products as Source Material for Approved Cancer Drugs

Taxus brevifolia

Paclitaxel:

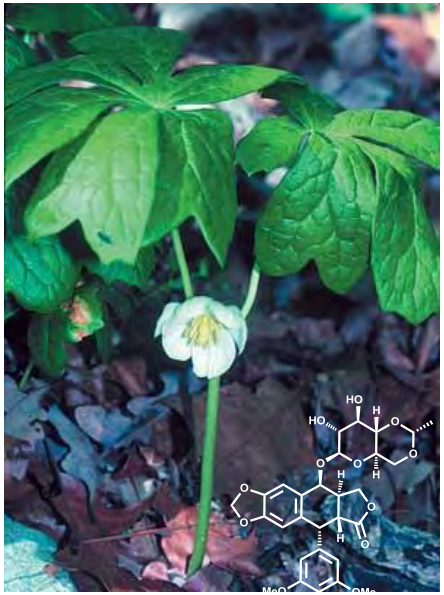
Breast cancer

Ovarian cancer

Lung cancer

Kaposi Sarcoma

Podophyllum peltatum



Etoposide

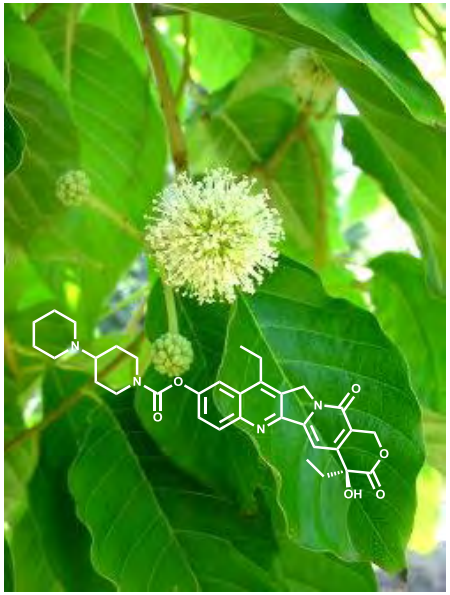
Lymphoma

Leukemia

Lung cancer

Breast cancer

Camptotheca acuminata

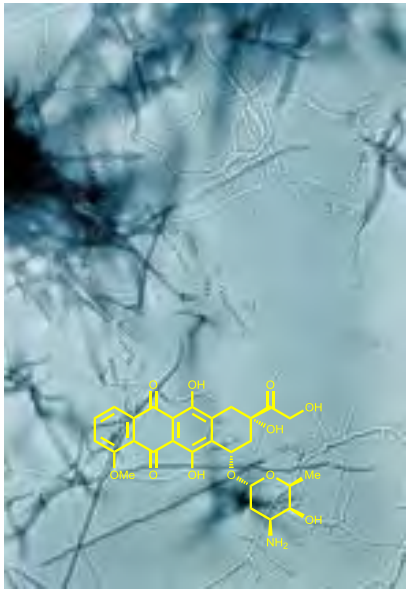


Irinotecan

Colon cancer

Lung cancer

Streptomyces peucetius



Doxorubicin:

Breast cancer

Lung cancer

Sarcoma

Ovarian cancer

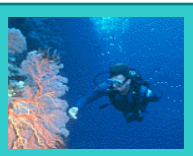
Leukemia

The Sea: Source of New Drugs

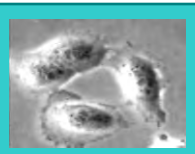
Life appeared 3,800 million years ago in the sea vs. 700 million years ago on land.

- ✓ **The sea occupies three quarters of our planet**
- ✓ **75-80% of living creatures live in the sea**

The Development Process...

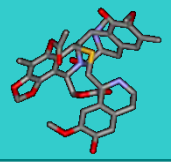


Marine Samples



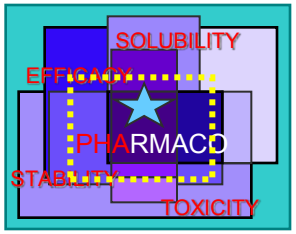
Primary Screening

New Molecules



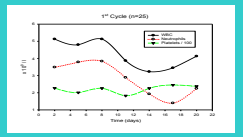
Animal Models

Analogs



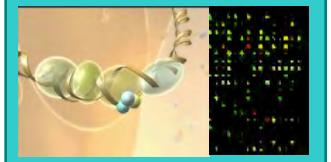
PRECLINICAL

Toxicity/ Pharmacokinetics



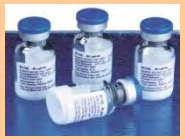
Synthesis

Mode of Action



CLINICAL

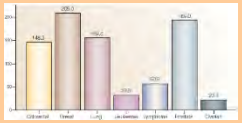
Phase I



Safety / Dose/ Pharmacokinetic

Phase II

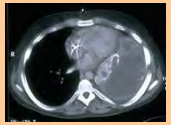
Activity/ Tumor type



Efficacy

Phase III

Randomized study



MARKET

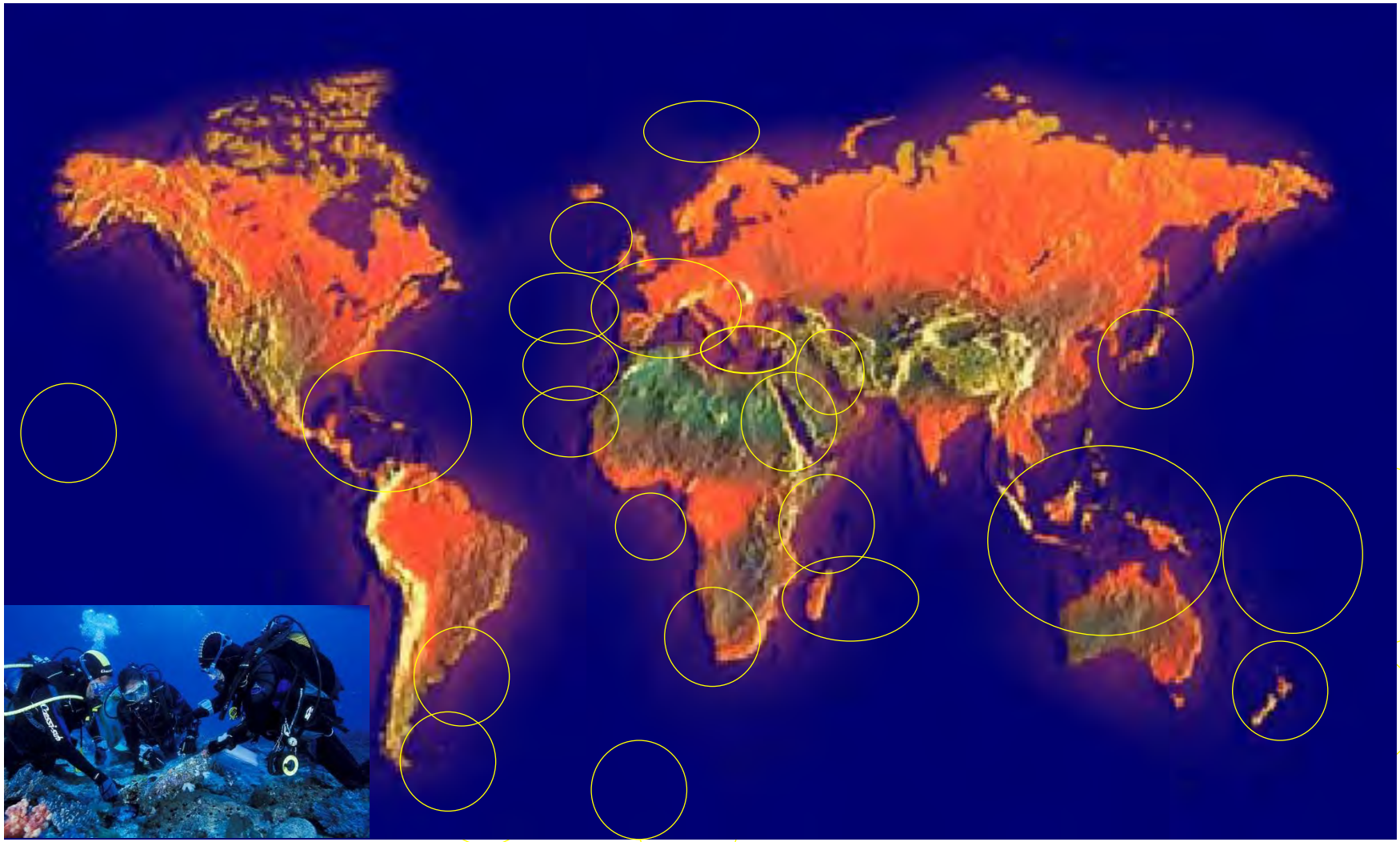
PATIENTS

NDA (US) *New Drug Approval*
MAA (UE) *Marketing Author. Applic.*

IND (US) Investigational New Drug
IMPD Investigational Medicinal Product Dossier
CTD Common Technical Document

Our Own Marine Divers Selectively Handpick Samples:

They comply with all supranational, international, and national laws and regulations.



PharmaMar's divers conduct ~8-12 expeditions annually.

Holds a Collection of 200,000 Marine Organisms

Trabectedin and Lurbinectedin MoA:

- ✓ **Inhibitors of transactivated transcription. Not affecting basal transcription.**

- ✓ **Housekeeping genes primarily use CpG dependent core promoters;**
- ✓ **Housekeeping genes are ubiquitously expressed in all cell types and constitute the basal transcriptome;**
- ✓ **Whereas the majority of tissue-specific genes (under transactivated transcription control) possess neither CpG islands not TATA-boxes in the core promoters.**

- ✓ **Trabectedin & lurbinectedin inhibit Pol II (not Pol I, not Pol III) at the elongation step of transcription.**

Source: Molecular Cancer Therapeutics 2016 Oct.; 15 (10): 2399-2412. Lurbinectedin Specifically Triggers the Degradation of Phosphorylated RNA Polymerase II and the Formation of DNA Breaks in Cancer Cells.

Clinical Activity in Tumors with Activated Transcription

- ✓ FUS-CHOP in Myxoid Liposarcomas
- ✓ EWS-FLI1 in Ewing's Sarcomas
- ✓ IRF1 in platinum-resistant ovarian cancer
- ✓ CDK7 in ovarian cancer
- ✓ NFkB controls cytokines { IL6, IL8, CCL2, CCL3, PTX3 } TAM ↑ Tumor microenvironment
- ✓ SCLC (tumor addicted to transcription)

Trabectedin and Lurbinectedin MoA

AMERICAN Scientist

Beating Cancers' Unexpected Vice: Transcription

Brian J. Abraham *Apr 10, 2015*

Cartoon by Tom Dunne.

Yondelis® First Indication

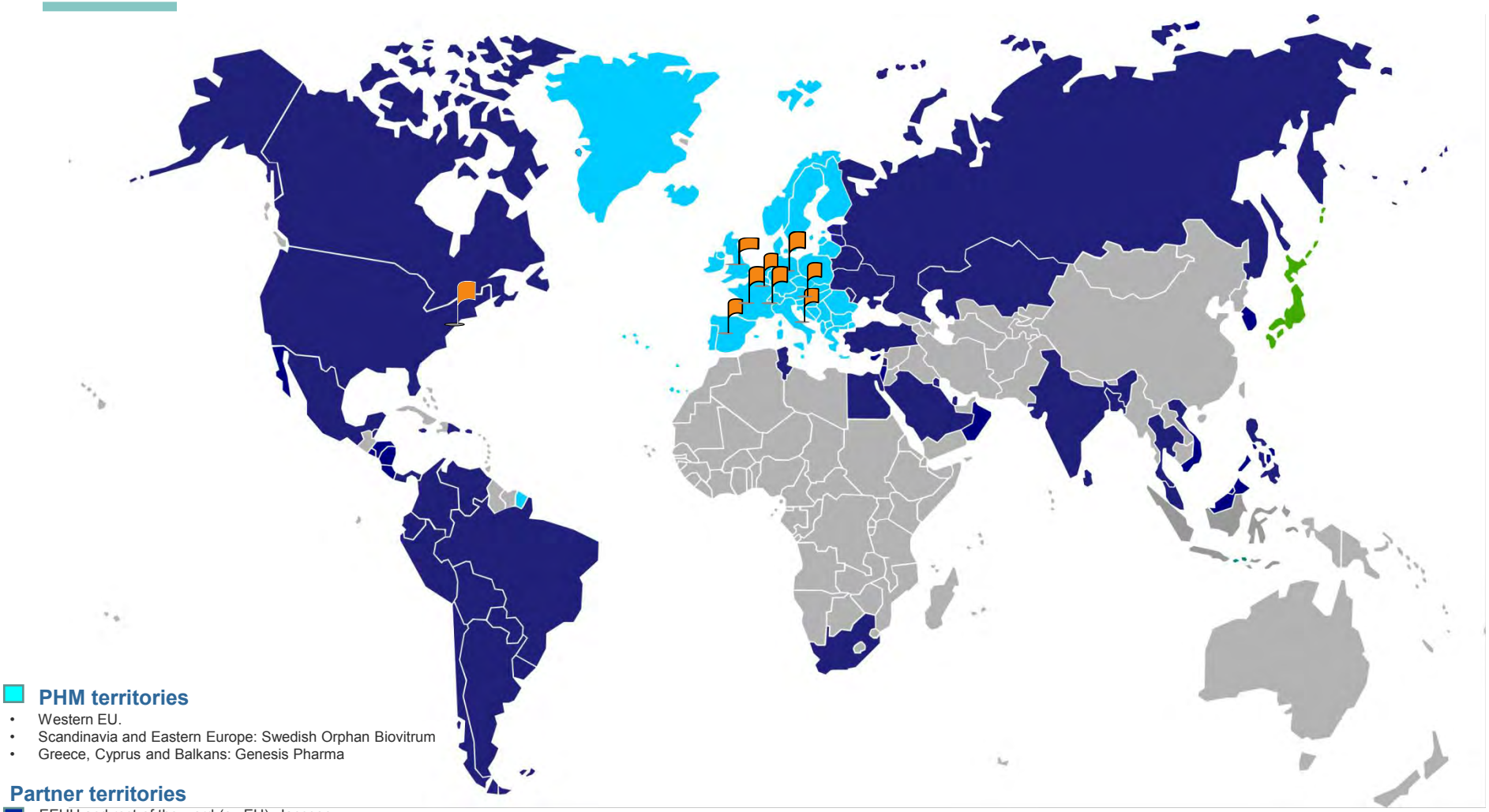
EMEA CHMP Positive Opinion

"Yondelis is indicated for the treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents.

Doc. Ref.: EMEA/CHMP/316962/London July 19th/2007

Yondelis®: A Proof of Concept

Commercial expansion worldwide with elite partners



PHM territories

- Western EU.
- Scandinavia and Eastern Europe: Swedish Orphan Biovitrum
- Greece, Cyprus and Balkans: Genesis Pharma

Partner territories

EEUU and rest of the word (ex EU) :Janssen

Japan: Taiho

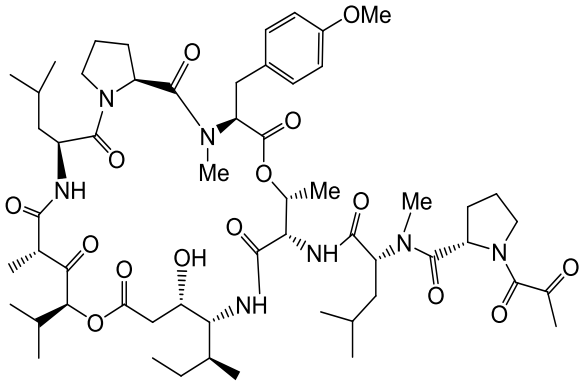
PharmaMar subsidiaries

MoA of Aplidin®

First in class drug with a novel mechanism of action

Aplidium albicans

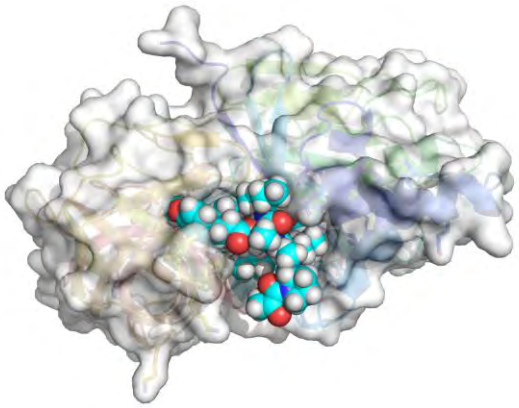
PLITIDEPSIN



MECHANISM OF ACTION

- Targets eEF1A2
- Proto-oncogene over-expressed in different tumor types e.g. multiple myeloma

eEF1A2



Aplidin®

- **Non-canonical functions of eEF1A2:**
  - Regulation of oxidative stress (e.g. peroxiredoxin-1, etc.)
  - Regulation of apoptosis (e.g. sphingosine-1 kinase)

Source: Scientific Reports. 2016 Oct 7;6:35100. Translation Elongation Factor eEF1A2 is a Novel Anticancer Target for the Marine Natural Product Plitidepsin.

The Plan for Growth

Potential to commercialize new oncology products in more indications

PharmaMar today

- 1 marketed product
- 2 indications

- **Yondelis®**
  - Soft Tissue Sarcoma
  - R/R Ovarian Cancer

PharmaMar tomorrow

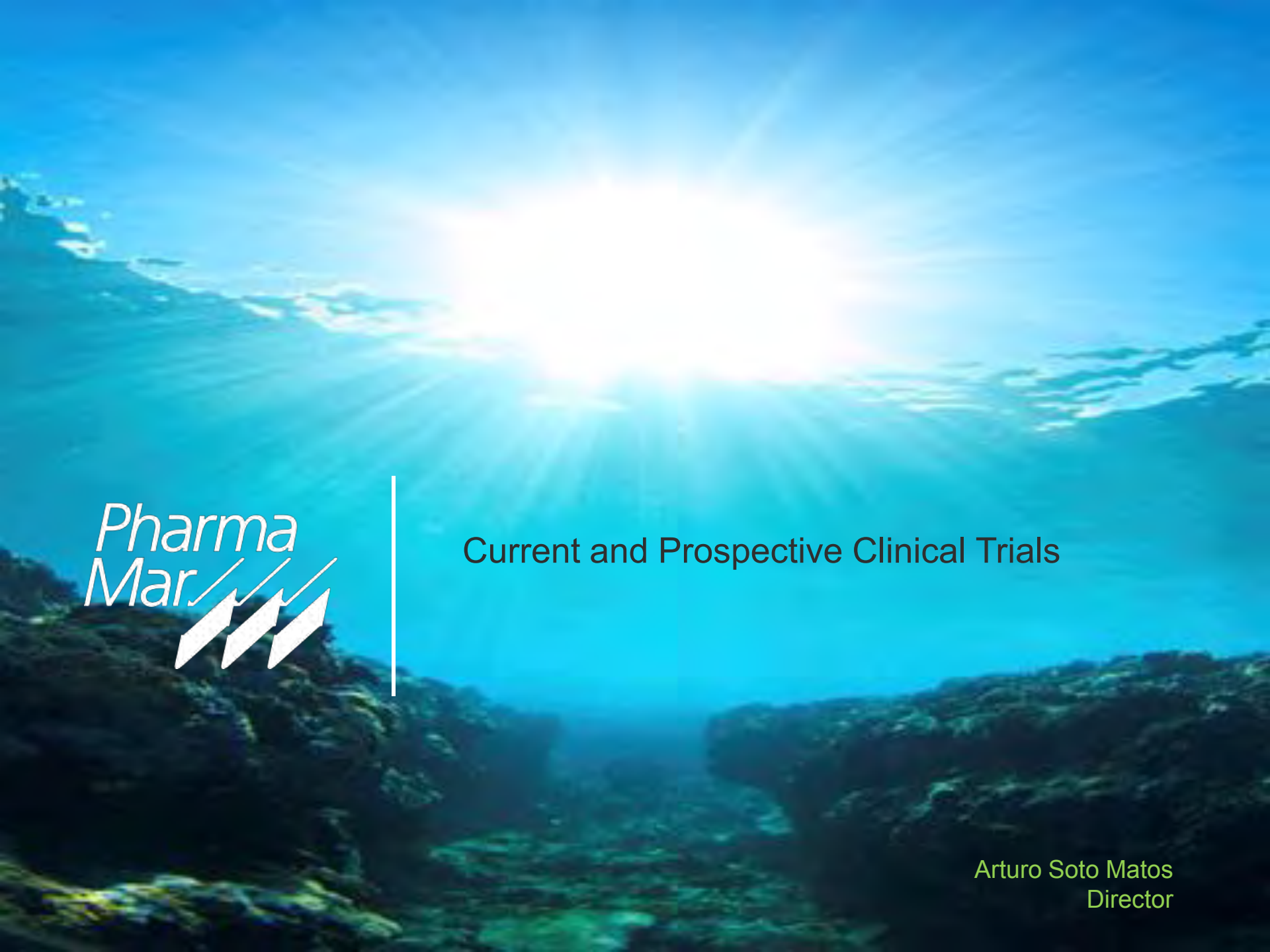
- 2 marketed products
- 3 indications

- **Aplidin®**
  - R/R multiple myeloma

PharmaMar in the near future

- 3 marketed products
- ≥ 5 indications

- **Lurbinectedin (PM1183)**
  - Small Cell Lung Cancer
  - Platinum resistant ovarian cancer
  - BRCA 2 breast cancer
  - Endometrial cancer



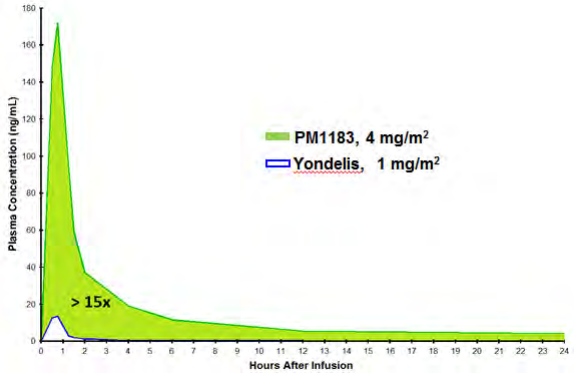
Current and Prospective Clinical Trials

Arturo Soto Matos
Director

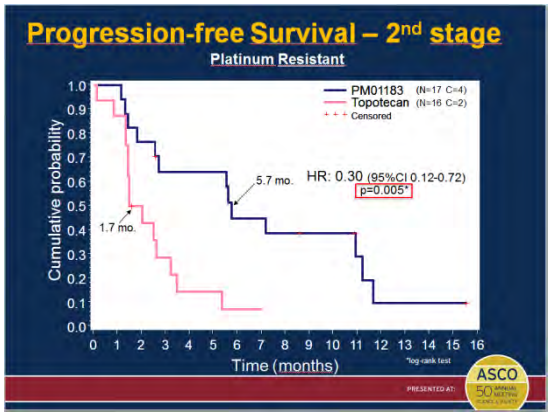
Lurbinectedin
Clinical Development

Lurbinectedin's Advantages over Trabectedin

- Different pharmacological profile



- Superior activity

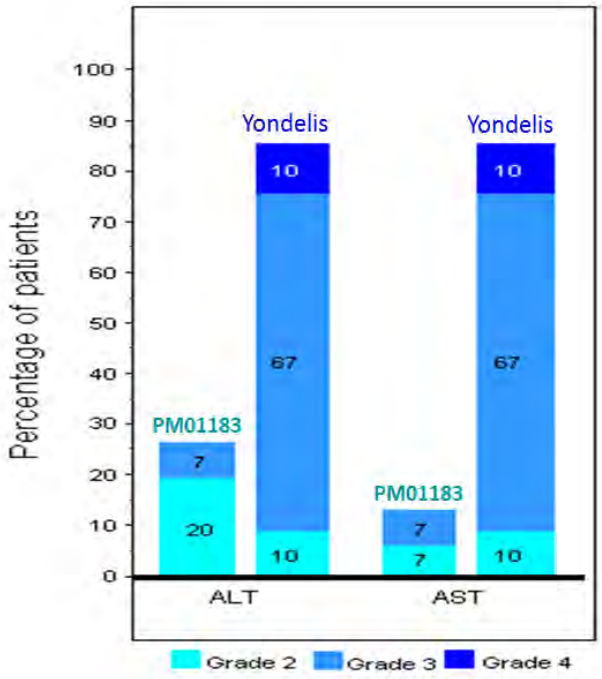


ORR in PROC

Yondelis 6%

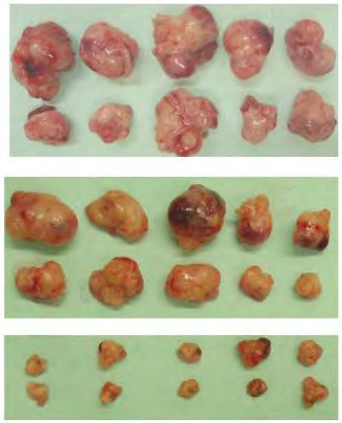
Lurbinectedin 30%

- Better safety profile



Pursued Indications

- PROC



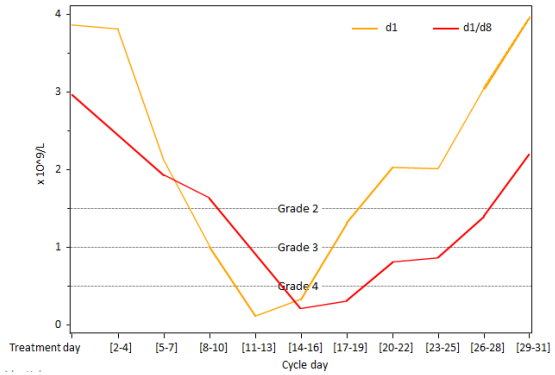
- SCLC & endometrial cancer

- BRCA2 mutated breast cancer

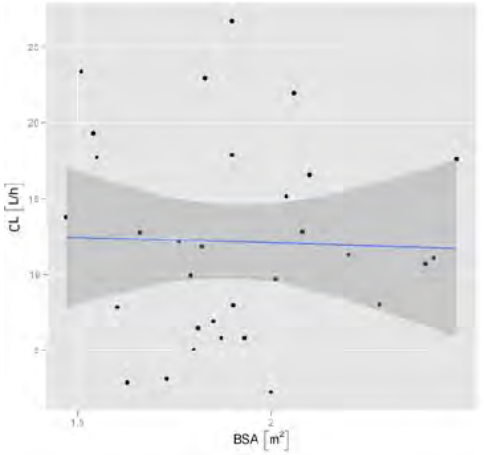
	Prior Platinum		BRCA		Hormone Status		Prior advanced CT lines	
	No (n: 27)	Yes (n: 27)	1 (n: 31)	2 (n: 23)	Triple Negative (n: 33)	HR+ (n: 21*)	0-1 (n: 31)	2-3 (n: 23)
ORR (95% CI)	56% (35.3-74.5)	26% (11.1-46.3)	26% (11.9-44.6)	61% (38.5-80.3)	36% (20.4-54.9)	48% (25.7-70.2)	52% (33.1-69.9)	26% (10.2-48.4)
Duration of Response (95% CI)	10.2 m (3.0-13.5)	5.9 m (2.8-12.8)	6.6 m (2.8-12.8)	6.7 m (3.4-13.5)	7.7 m (2.8-12.8)	6.7 m (2.8-13.4)	8.5 m (3.0-12.8)	3.4 m (2.8-20.5)
Disease control rate	25 (93%)	19 (70%)	23 (74%)	22 (96%)	26 (79%)	19 (90%)	27 (87%)	18 (78%)
Clinical benefit (CR+PR+SD ≥ 3 mo)	19 (70%)	14 (52%)	14 (45%)	19 (83%)	29 (88%)	14 (67%)	21 (68%)	12 (52%)

Dose & Schedule

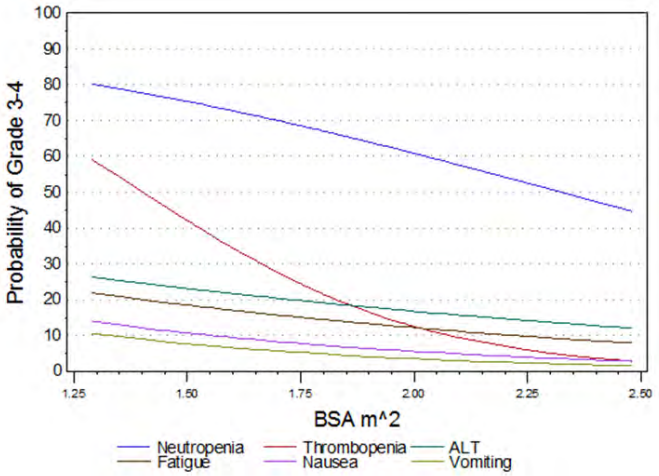
- 1h infusion D1 q3wk or D1&8 q3wk



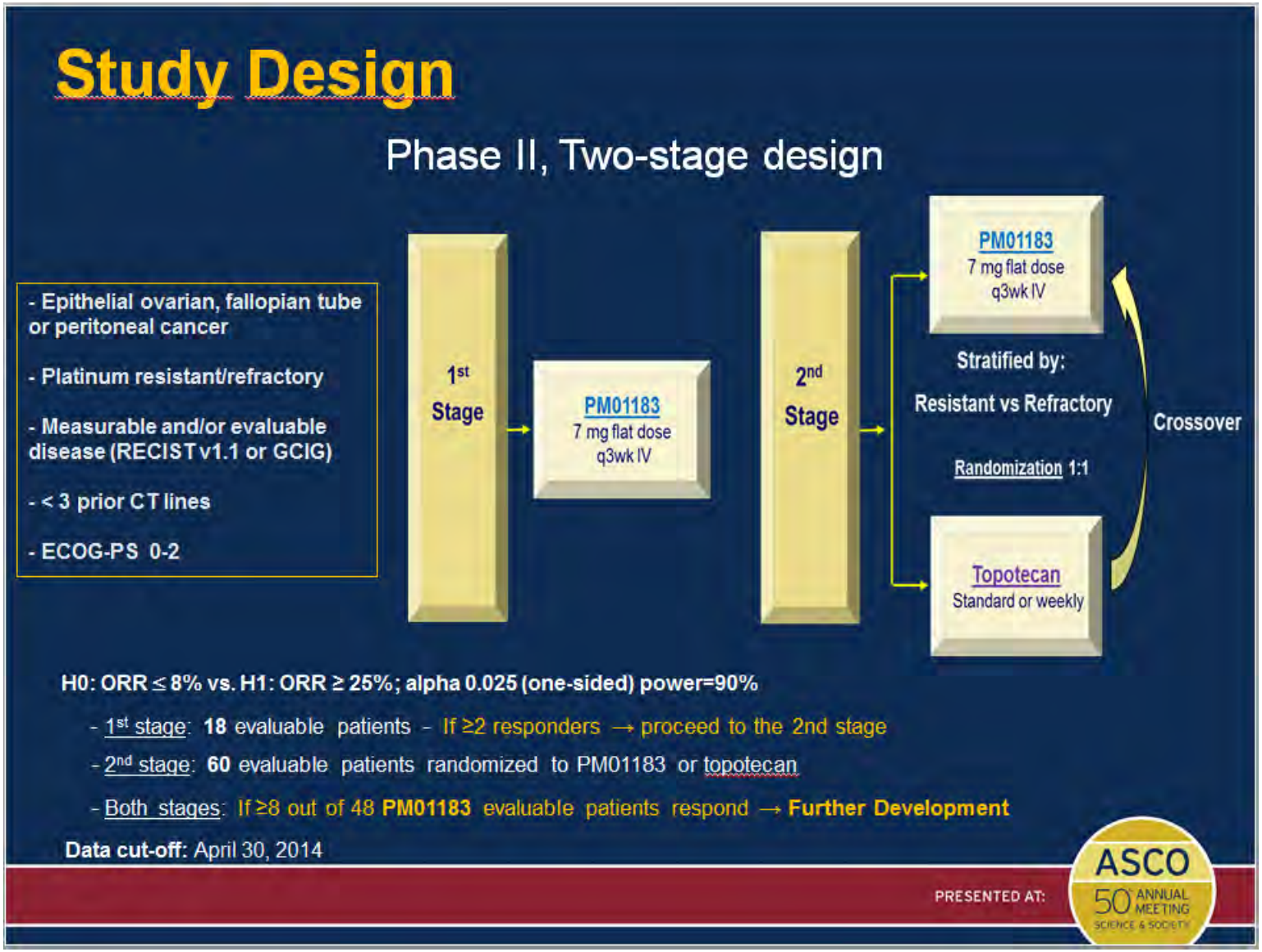
- RD: 4 mg/m² changed to 7 mg FD



- Pooled Phase II. Dose adjusted to:
  - Ovarian: 3,2 mg/m²
  - Breast: 3,5 mg/m²
  - SCLC & endometrial: 2 mg/m²



Lurbinectedin in Ovarian Cancer


Study Design
Phase II, Two-stage design
- Epithelial ovarian, fallopian tube or peritoneal cancer
- Platinum resistant/refractory
- Measurable and/or evaluable disease (RECIST v1.1 or GCIG)
- < 3 prior CT lines
- ECOG-PS 0-2
1st Stage
PM01183
7 mg flat dose
q3wk IV
2nd Stage
PM01183
7 mg flat dose
q3wk IV
Stratified by:
Resistant vs Refractory
Randomization 1:1
Topotecan
Standard or weekly
Crossover
H0: ORR ≤ 8% vs. H1: ORR ≥ 25%; alpha 0.025 (one-sided) power=90%
- 1st stage: 18 evaluable patients - If ≥2 responders → proceed to the 2nd stage
- 2nd stage: 60 evaluable patients randomized to PM01183 or topotecan
- Both stages: If ≥8 out of 48 PM01183 evaluable patients respond → Further Development
Data cut-off: April 30, 2014
PRESENTED AT:
ASCO
50 ANNUAL MEETING
SCIENCE & SOCIETY

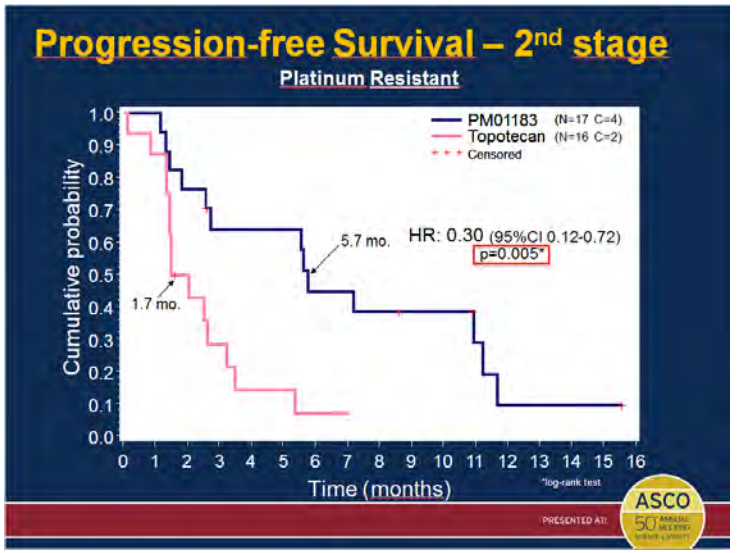
PROC

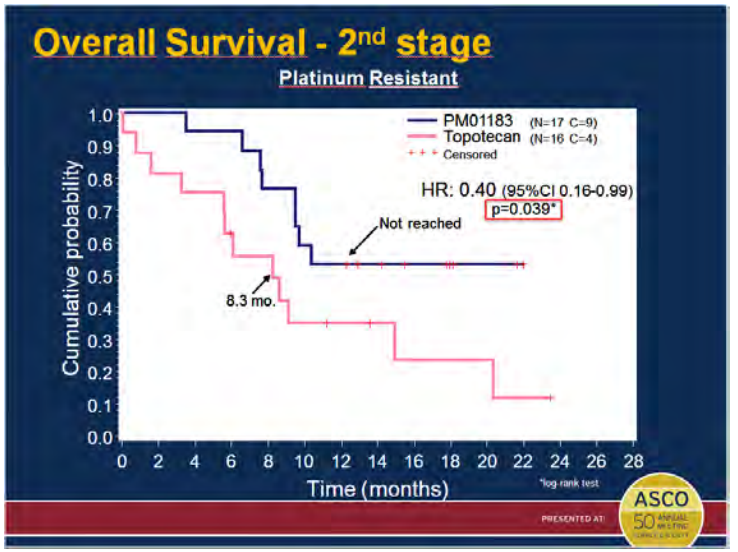
Overall Response Rate (ORR)

	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 50 ANNUAL MEETING

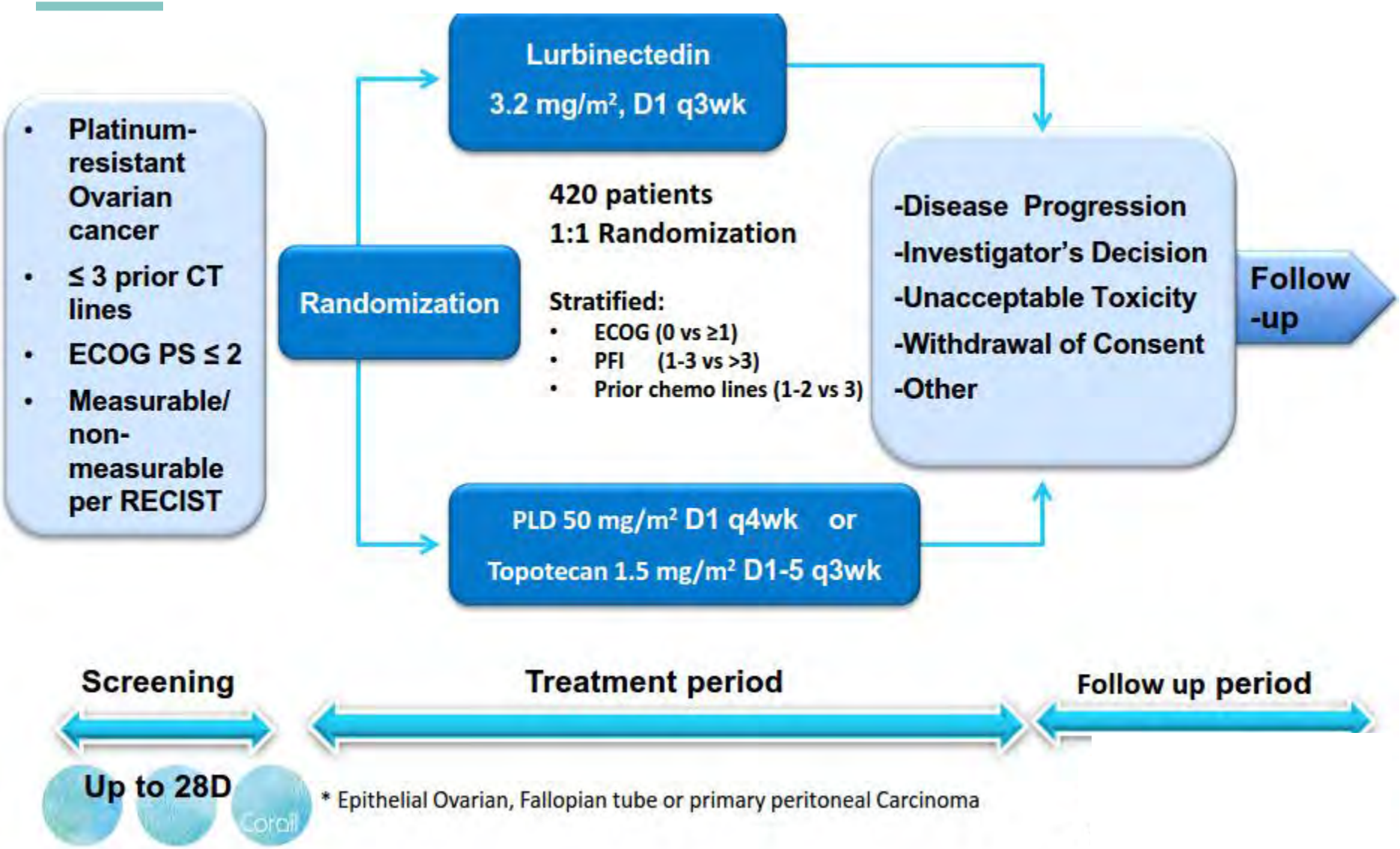




CORAIL

Phase III Randomized Clinical Trial of Lurbinectedin (PM01183) versus Pegylated Liposomal Doxorubicin or Topotecan in Patients with Platinum-resistant Ovarian Cancer

Study Design



Study Objectives and Endpoints

Primary

- To determine a difference in **Progression-Free Survival (PFS)** between lurbinectedin (PM01183) and PLD or topotecan in platinum-resistance ovarian cancer patient

  Endpoint: PFS according to RECIST v 1.1, as determined by the independent review committee

Secondary

- To evaluate Overall Survival (OS), anti-tumor activity, safety, PK and QoL

Exploratory

- Exploratory pharmacogenetic and pharmacogenomic sub-study

Statistical Assumptions

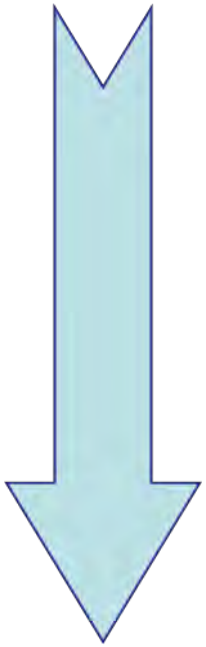
- The prospective assumptions are a 30% reduction in the relative risk of progression or death (HR=0.7) to be achieved with the experimental arm (PM01183), at a one-sided 2.5% significance level with at least 90% power, following exponential distributions and fulfilling the proportional hazard assumption. Median PFS with control arm is expected to be around 3.5 months. It is forecasted that an observed HR of approximately 0.8 will have enough power to reject the null hypothesis.

- Approximately 420 patients with platinum resistant ovarian cancer will be necessary to stratify and randomize at a 1:1 ratio over 18 months (~23 patients/month). **The required 332 PFS events are expected to occur around six months** after randomization of the last patient. Therefore, the IDMC meeting after the IRC review to test PFS is expected to occur about one year after randomization of the last patient.

Participating Sites and Timelines

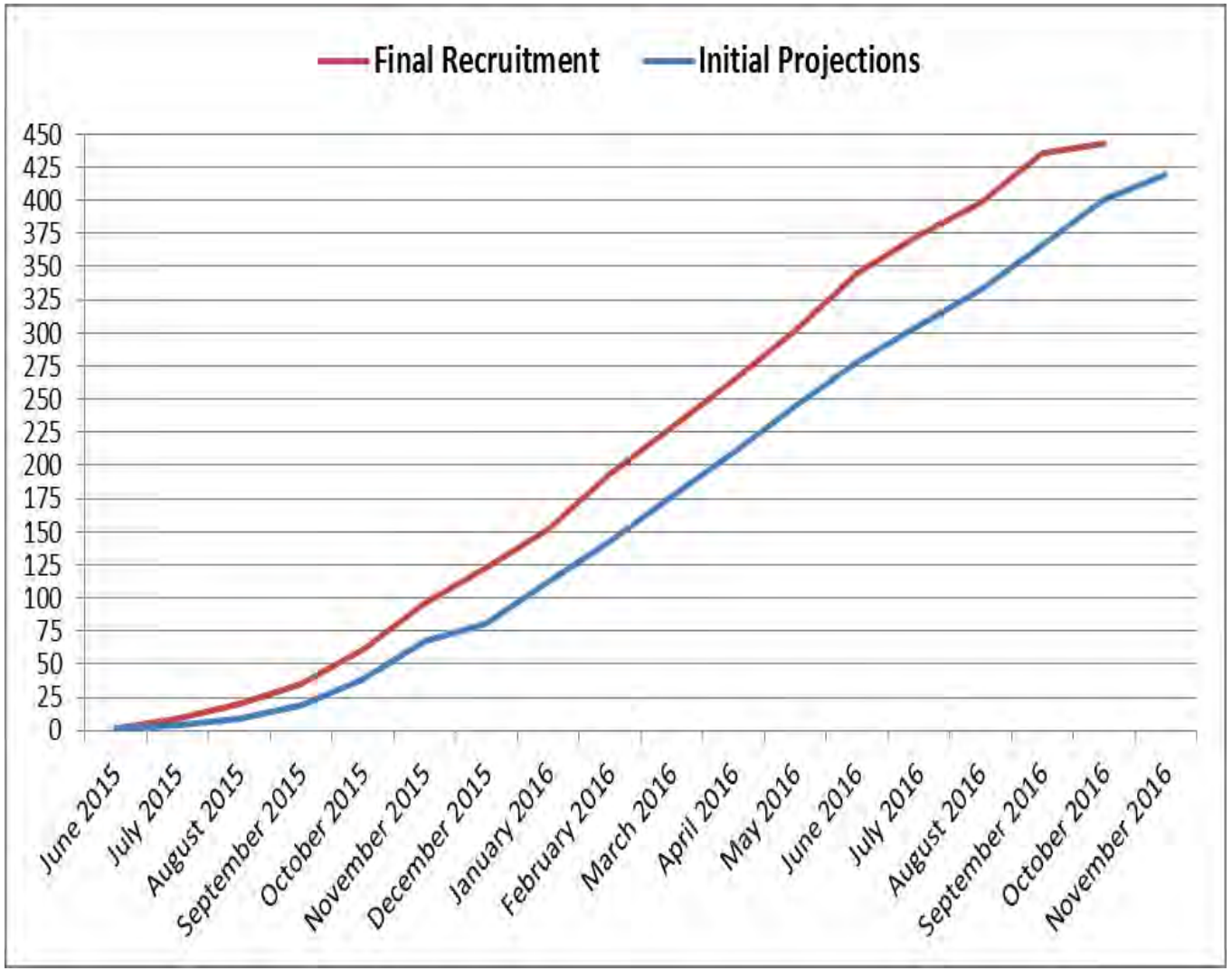
- **113 planned sites (13 countries) :**
  - North America (29 sites)
  - Europe (84 sites)

- **420 patients**



- **First patient in (FPI): June 2015**
- **Enrollment period: 18 months**
- **End of study: 24 months after randomization of the last patient (by Q4 2018)**

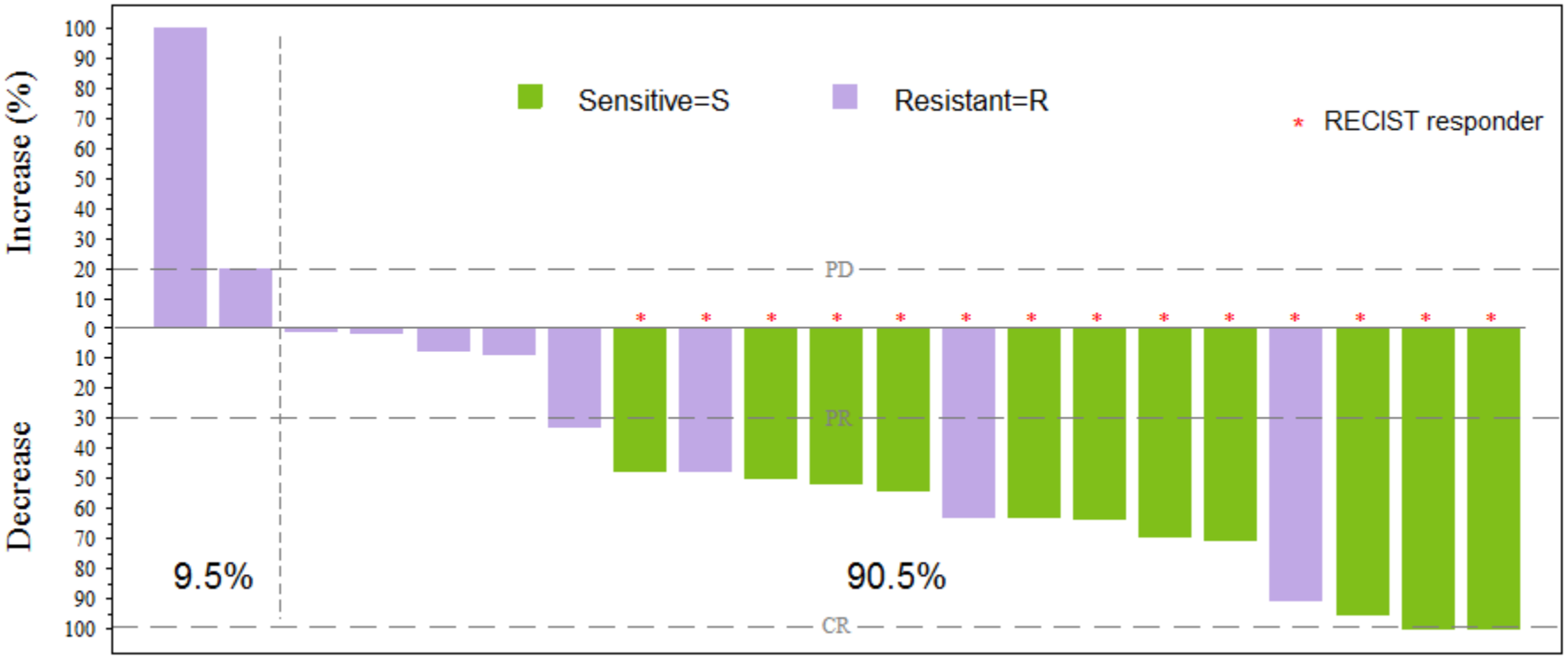
Recruitment



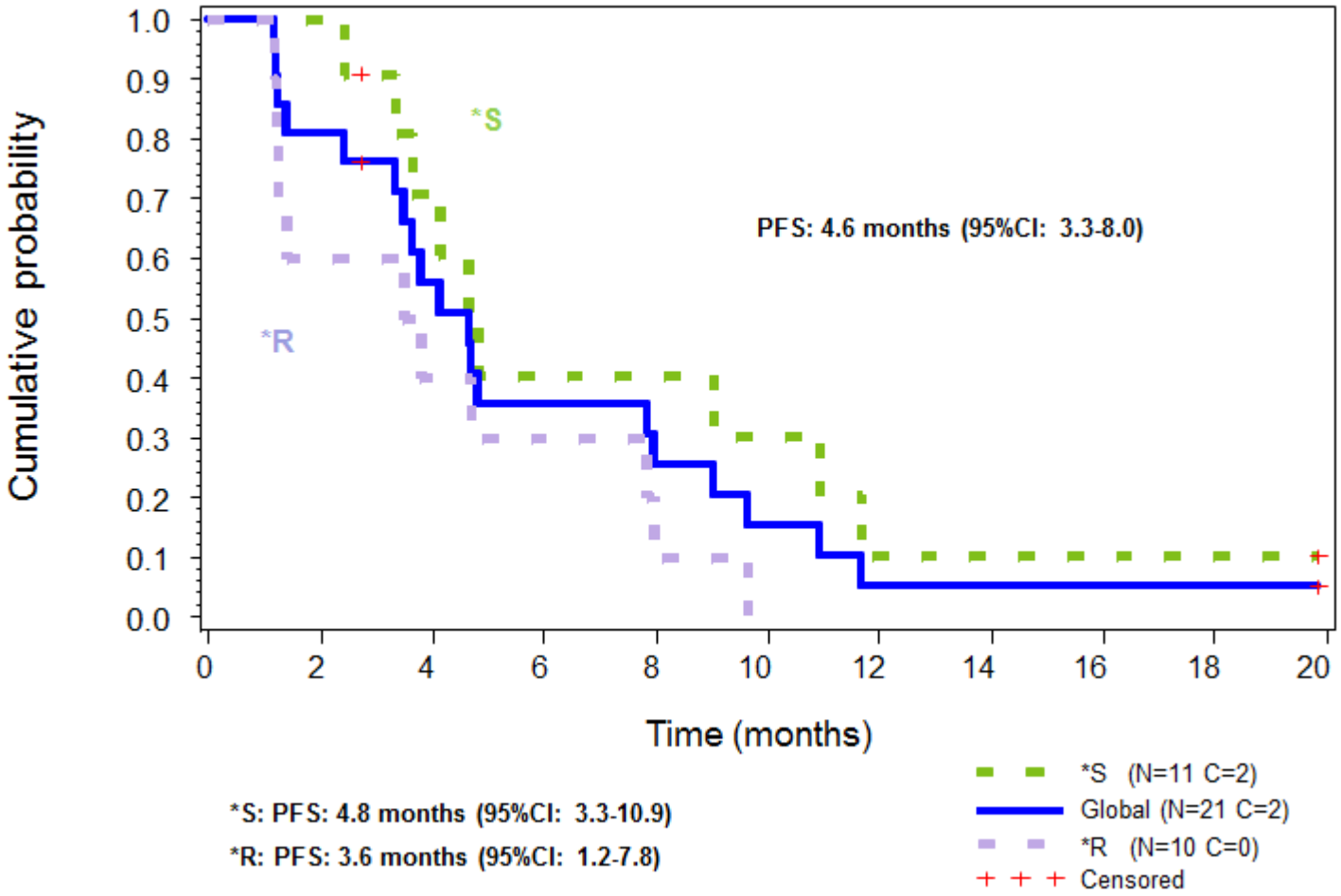
Target of 420 patients reached 2 months earlier than projected

Lurbinectedin in SCLC

Waterfall Plot SCLC 2nd Line



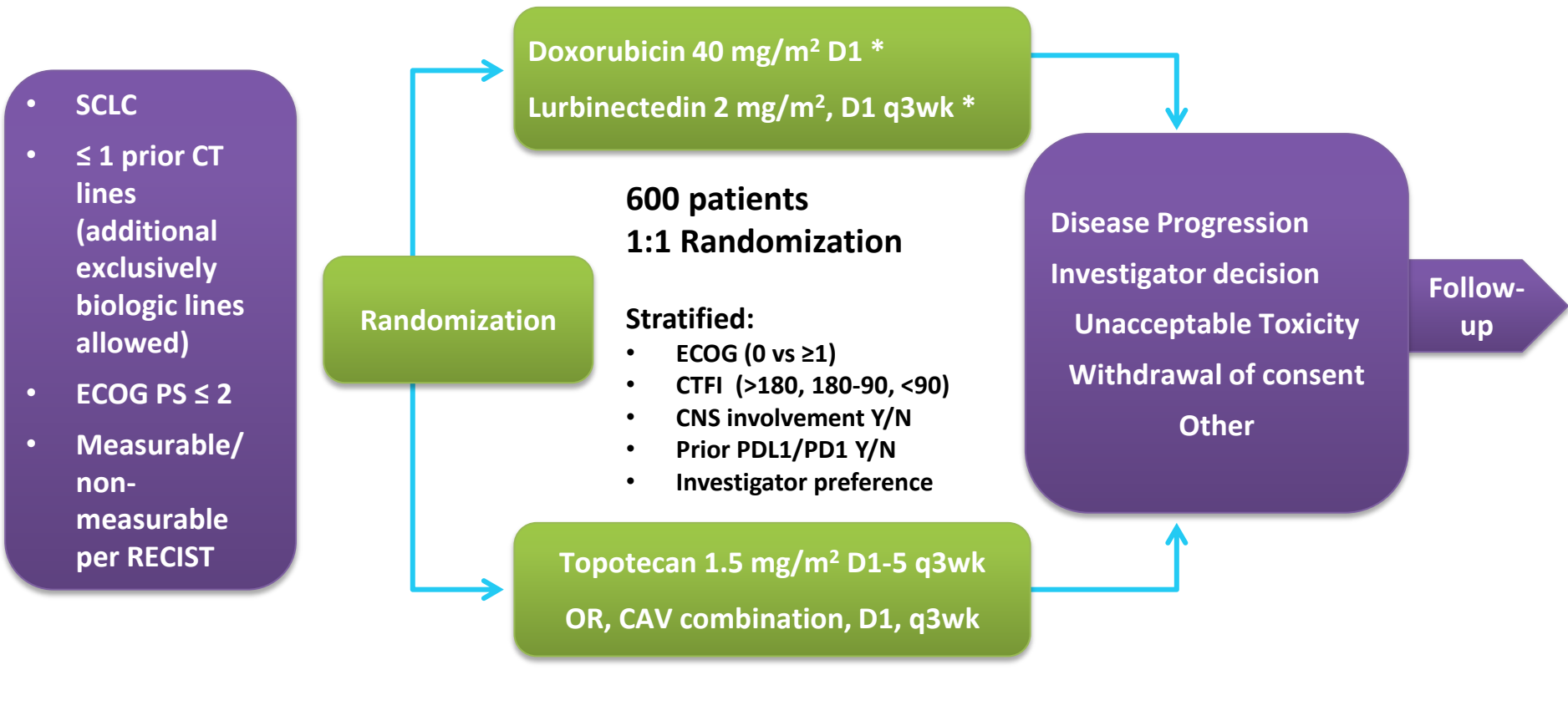
PFS


Cumulative probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
14
16
18
20
Time (months)
*S
*R
PFS: 4.6 months (95%CI: 3.3-8.0)
*S: PFS: 4.8 months (95%CI: 3.3-10.9)
*R: PFS: 3.6 months (95%CI: 1.2-7.8)
*S (N=11 C=2)
Global (N=21 C=2)
*R (N=10 C=0)
Censored

ATLANTIS STUDY

Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (Cy), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line

Study Design



* Maximum 10 cycles, Lurbinectedin to be continued at 3.2 **mg/m²**

Study Objectives

Primary Objective:

- Determine a difference in PFS between lurbinectedin (PM01183)/doxorubicin(DOX) and a control arm consisting of best Investigator's choice between cyclophosphamide(Cy), doxorubicin(DOX) and vincristine (VCR) (CAV) or topotecan

  ***MAIN ENDPOINT**:* PFS according to RECIST 1.1, as determined by the independent review committee

Secondary Objectives:

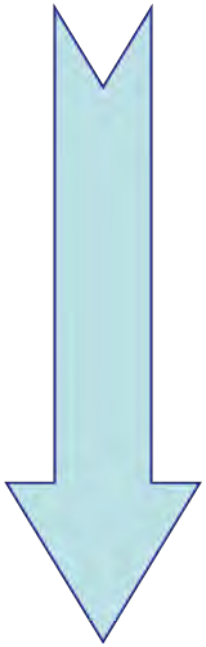
- Overall survival, OS rate at 12, 18 and 24 months
- PFS by Investigator's Assessment
- Antitumor activity: RECIST v.1.1
- Safety profile
- Patient-reported outcomes
- Pharmacokinetics
- PK/pharmacodynamic
- Pharmacogenetics of known polymorphisms (Experimental Arm)

Statistical Assumptions

- The prospective assumptions are a one-sided 2.5% significance level with at least 90% power and a ~25% decrease in the risk of progression or death to be achieved with the experimental arm (HR=0.745). PFS with either CAV or topotecan is expected to be ~3.5 months.
- To obtain the required 484 events, approximately 600 patients with SCLC who failed one prior platinum-containing chemotherapy line will be stratified and randomized at a 1:1 ratio. With the aforementioned prospective assumptions, recruitment is foreseen to be completed in 17 months, the IDMC meeting after the IRC review to test PFS is expected to occur about six months after randomization of the last patient, and for a final OS analysis a total study duration of about three years is planned.

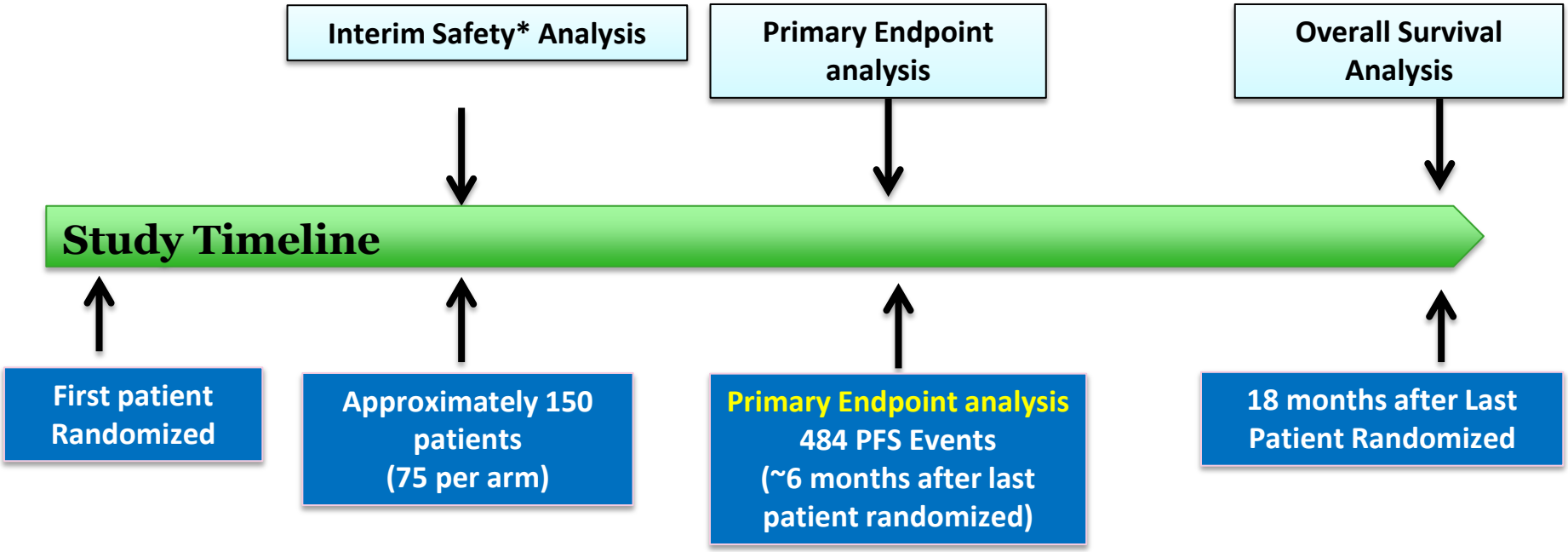
Participating Sites and Timelines

- **170 planned sites (20 countries) :**
  - North America (35 sites)
  - LATAM (15 sites)
  - Europe (107 sites)
  - MENA (13 sites)
- **600 patients**



- **First patient in (FPI): August 2016**
- **Enrollment period: 17 months**
- **End of study: 18 months after randomization of the last patient (by Q2 2019)**

Analysis Plan



* All patients treated with at least one dose of trial medication will be included in the safety evaluation.

Lurbinectedin in BRCA2 Breast Cancer

Anti-tumor activity of PM01183 (lurbinectedin) in *BRCA 1/2*-associated metastatic breast cancer patients: Results of a single-agent phase II trial

J. Balmaña[1], C. Cruz[1], B. Arun[2], M. Telli[3], J. Garber[4], S. Domchek[5], C. Fernandez[6], C. Kahatt[6], S. Szyldergemajn[6], A. Soto Matos[6], A. Perez de la Haza[6], J. Pérez Fidalgo[7], A. Lluch[7], S. Antolin[8], N. Tung[9], L. Vahdat[10], R. Lopez[11], S. Isakoff[12]

[1]Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]MD Anderson Cancer Center, Houston, USA; [3]Stanford University Medical Center, Stanford, USA; [4]Dana Farber Cancer Institute, Boston, USA; [5]University of Pennsylvania, Philadelphia, USA; [6]Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain; [7]Hospital Clínico de Valencia, Valencia, Spain; [8]Complejo Universitario Hospitalario La Coruña, La Coruña, Spain; [9]Beth Israel Deaconess Medical Center, Boston, USA; [10]Weill Cornell Medicine, New York, USA; [11]Complejo Hospitalario Universitario Santiago de Compostela, Santiago de Compostela, Spain; [12]Massachusetts General Hospital, Boston, USA.

COPENHAGEN 2016 ESMO congress

esmo

Focus on BRCA2

	Prior Platinum		BRCA		Hormone Status		Prior advanced CT lines	
	No (n: 27)	Yes (n: 27)	1 (n: 31)	2 (n: 23)	Triple Negative (n: 33)	HR+ (n: 21*)	0-1 (n: 31)	2-3 (n: 23)
ORR (95% CI)	**56%** (35.3-55.6)	**26%** (11.1-25.9)	**26%** (11.9-25.8)	**61%** (38.5-60.9)	**36%** (13.3-27.3)	**48%** (38.4-81.9)	**52%** (33.1-69.9)	**26%** (10.2-48.4)
Duration of Response (95% CI)	**10.2 m** (3.0-13.5)	**5.9 m** (2.8-12.8)	**6.6 m** (2.8-12.8)	**6.7 m** (3.4-13.5)	**7.7 m** (2.8-12.8)	**6.7 m** (2.8-13.4)	**8.5 m** (3.0-12.8)	**3.4 m** (2.8-20.5)
Disease control rate	25 (93%)	19 (70%)	23 (74%)	22 (96%)	26 (79%)	19 (90%)	27 (87%)	18 (78%)
Clinical benefit (CR+PR+SD ≥ 3 mo)	19 (70%)	14 (52%)	14 (45%)	19 (83%)	29 (88%)	14 (67%)	21 (68%)	12 (52%)

Pivotal Study: Design

- Multicenter, open-label, phase II clinical trial to confirm prior results of efficacy and safety observed with PM01183 administration in hormone-receptor positive/HER-2 negative with deleterious germline BRCA 2 MBC patients
- One hundred and sixteen evaluable patients hormone-receptor positive/HER-2 negative with deleterious germline BRCA2 mutation status will be enrolled
- The primary endpoint of the trial is ORR (confirmed response) per RECIST v.1.1 assessed by an IRC
- DOR by the IRC is included as a relevant secondary endpoint

Pivotal Study: Population

- MBC hormone-receptor positive/HER-2 negative with deleterious germline BRCA2 mutation
- Ductal or lobular carcinoma of the breast
- One or two prior advanced chemotherapy-containing regimens
- At least two endocrine-based regimens (including an approved CDK 4/6 inhibitor, in countries were available), unless they could have impending visceral crisis and would therefore not be appropriate for endocrine therapy

Pivotal Study: Statistical Assumptions

- The primary endpoint for this phase II study is ORR (confirmed response), also supported by a relevant DOR.
- Null hypothesis is set as 30% or less patients achieve a confirmed response ($p \leq 0.3$) *versus* the alternative hypothesis that 45% or more patients achieve a confirmed response ($p \geq 0.45$). One hundred and sixteen patients will be recruited to test the hypotheses. The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.1; hence, statistical power is 90%. With these assumptions, if the **number of responders is ≥ 46 out of 116 (≥ 39.7%)**, the null hypothesis will be rejected and the 95% lower limit of the binomial exact confidence interval will be > 30%.
- In case the null hypothesis is rejected, and in addition a median DOR ≥ 6 months is found, the clinical trial would have met its objectives and PM01183 could be considered as a new therapeutic option for hormone-receptor positive/HER-2 negative MBC patients with deleterious germline BRCA2 mutation.

Pivotal Study: Timelines

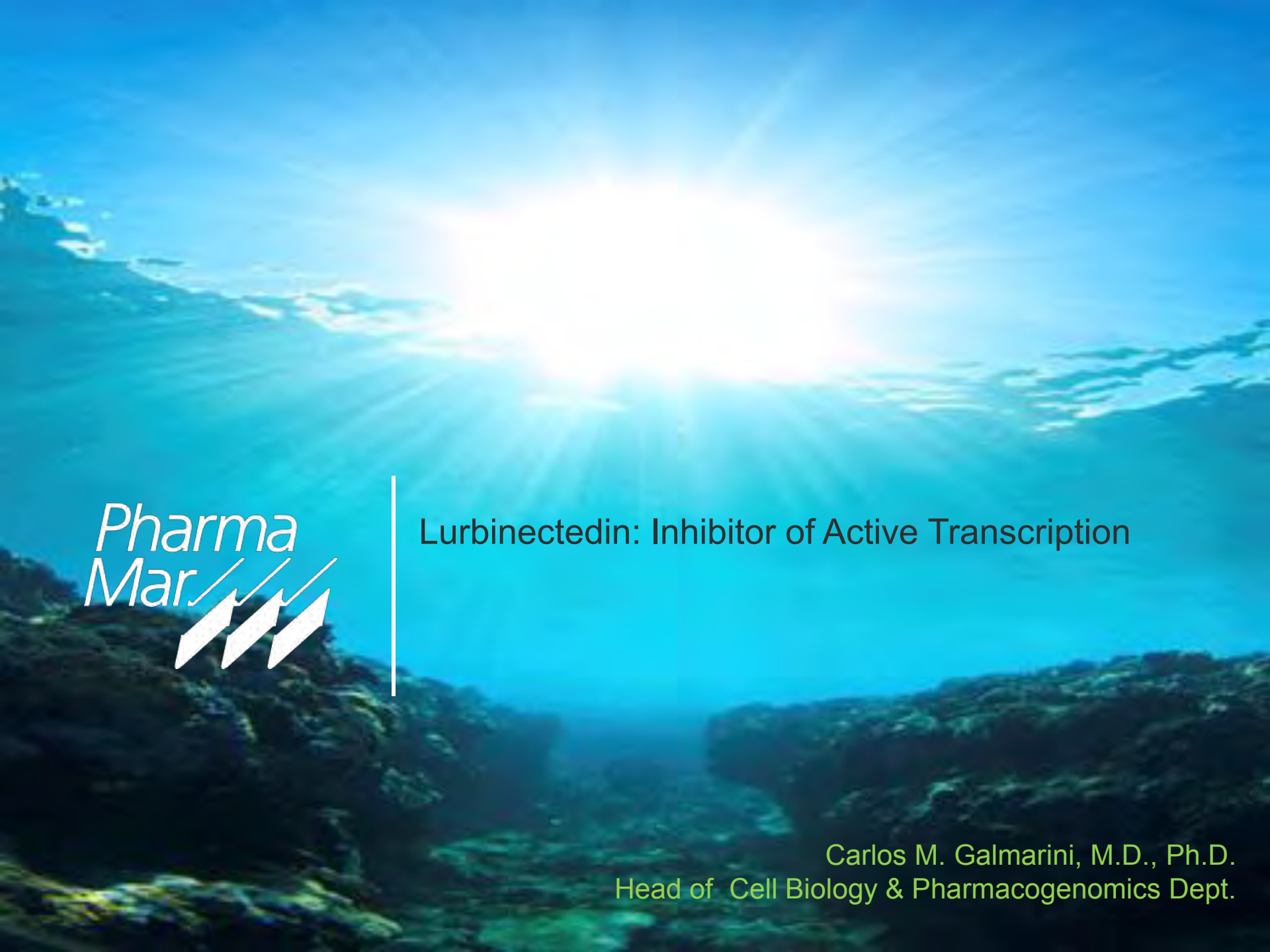
- First Patient In (expected) 4Q2017
- Recruitment period 24 months (dependent upon current CRO discussions)
- Readout primary endpoint: 6 months after the recruitment of the last patient
- End of study: 24 months after the recruitment of the last patient

Collaborations with Advocacy Groups to Enhance Awareness of Our BRCA2 Trial

BRCA2 mBC sees African-Americans' prevalence rate 3%; highest ethnic group for those available. SISTERS is a group of ~10k members, which has a 10-city conference tour* that aims at education, presentation of options, sharing of experiences, and overall support for the African-American breast cancer patient. We are proud sponsors and will be attending many of their meetings starting with the one in Memphis in May.

FORCE's mission is to improve the lives of individuals and families affected by hereditary breast, ovarian, and related cancers. Their main objectives are to educate, support, and provide resources to patients and families. Their community of patients, caregivers, and survivors has over 25,000 on its electronic mailing list. Majority of members have BRCA1/2 mutation, about 50/50.

* Source: http://ww5.komen.org/BreastCancer/InheritedGeneticMutations.html



Lurbinectedin: Inhibitor of Active Transcription

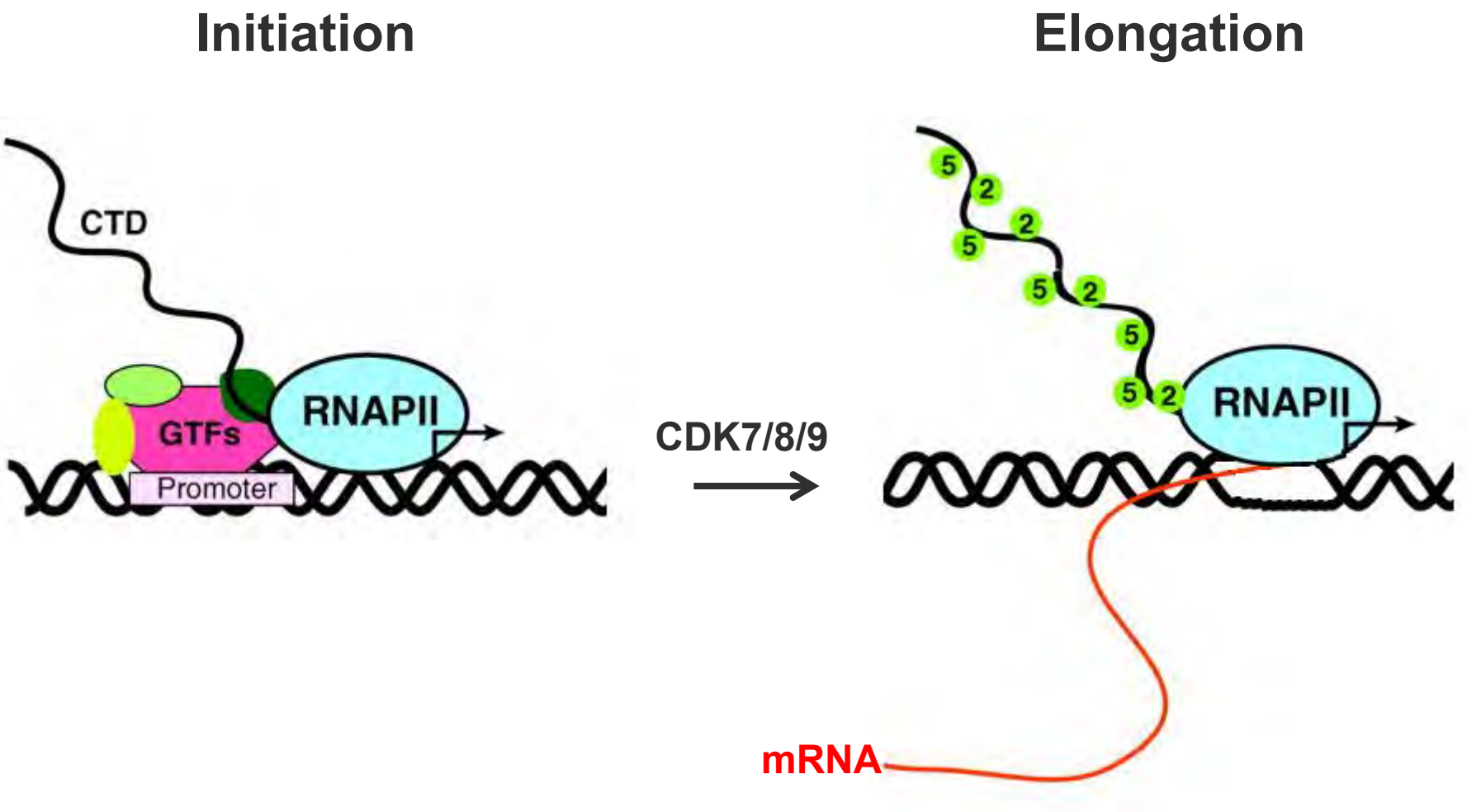
Carlos M. Galmarini, M.D., Ph.D.
Head of Cell Biology & Pharmacogenomics Dept.

Lurbinectedin: An Active Transcription Inhibitor

Topics for Discussion

- **Inhibition of Active Transcription**
- **Role of BRCA-2**
- **Tumor Microenvironment**

The Transcription Process

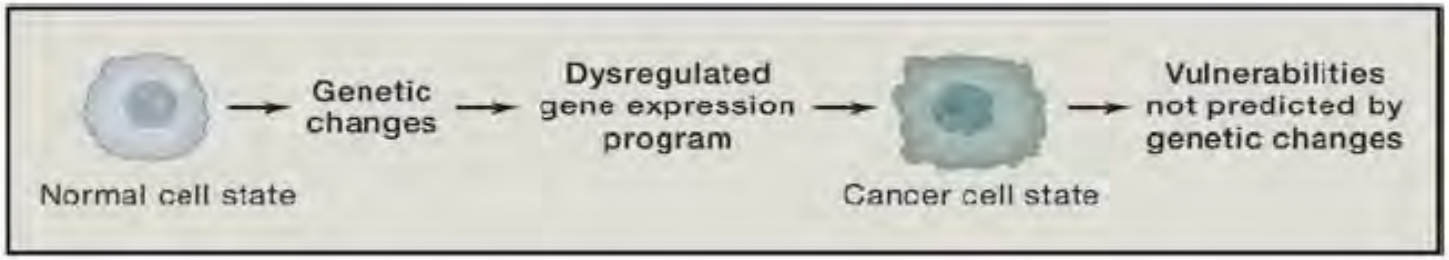


Leading Edge
Review

Cell

Transcriptional Addiction in Cancer

James E. Bradner,[1] Denes Hnisz,[2] and Richard A. Young[2,3,*]
[1]Novartis Institutes for Biomedical Research, 181 Massachusetts Avenue, Cambridge, MA 02139, USA
[2]Whitehead Institute for Biomedical Research, 9 Cambridge Center, Cambridge, MA 02142, USA
[3]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
*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)**

Examples of Tumors with Transcription Addiction

Translocation-Related Sarcomas

Fredrik Mertens,[a,1] Cristina R. Antonescu,[b,1] Peter Hohenberger,[c,1] Marc Ladanyi,[b,1] Piergiorgio Modena,[d,1] Maurizio D'Incalci,[e,1] Paolo G. Casali,[f,1] Massimo Aglietta,[g,2] and Thor Alvegård[h,2]

Semin Oncol 36:312-323. © 2009

Cancer Cell
Previews

Treating Transcriptional Addiction in Small Cell Lung Cancer

Arnaud Augert[1] and David MacPherson[1,*]
[1]Divisions of Human Biology and Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
*Correspondence: dmacpher@fhcrc.org
http://dx.doi.org/10.1016/j.ccell.2014.11.012

Article
Cell

CDK7-Dependent Transcriptional Addiction in Triple-Negative Breast Cancer

Wang et al., 2015, Cell 163, 174–186

Resource
Cell Reports

Phosphoproteomics of Primary Cells Reveals Druggable Kinase Signatures in Ovarian Cancer

Francavilla et al., 2017, Cell Reports 18, 3242–3256

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
*Correspondence: lee.kraus@utsouthwestern.edu
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,*]
*Correspondence: young@wi.mit.edu (R.A.Y.), kwong1@partners.org (K.-K.W.)
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,*]
[1]Stowers Institute for Medical Research, 1000 East 50th Street, Kansas City, MO 64110, USA
*Correspondence: ash@stowers.org
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,*]
[1]Divisions of Human Biology and Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
*Correspondence: dmacpher@fhcrc.org
http://dx.doi.org/10.1016/j.ccell.2014.11.012
Cancer Cell 26, December 8, 2014

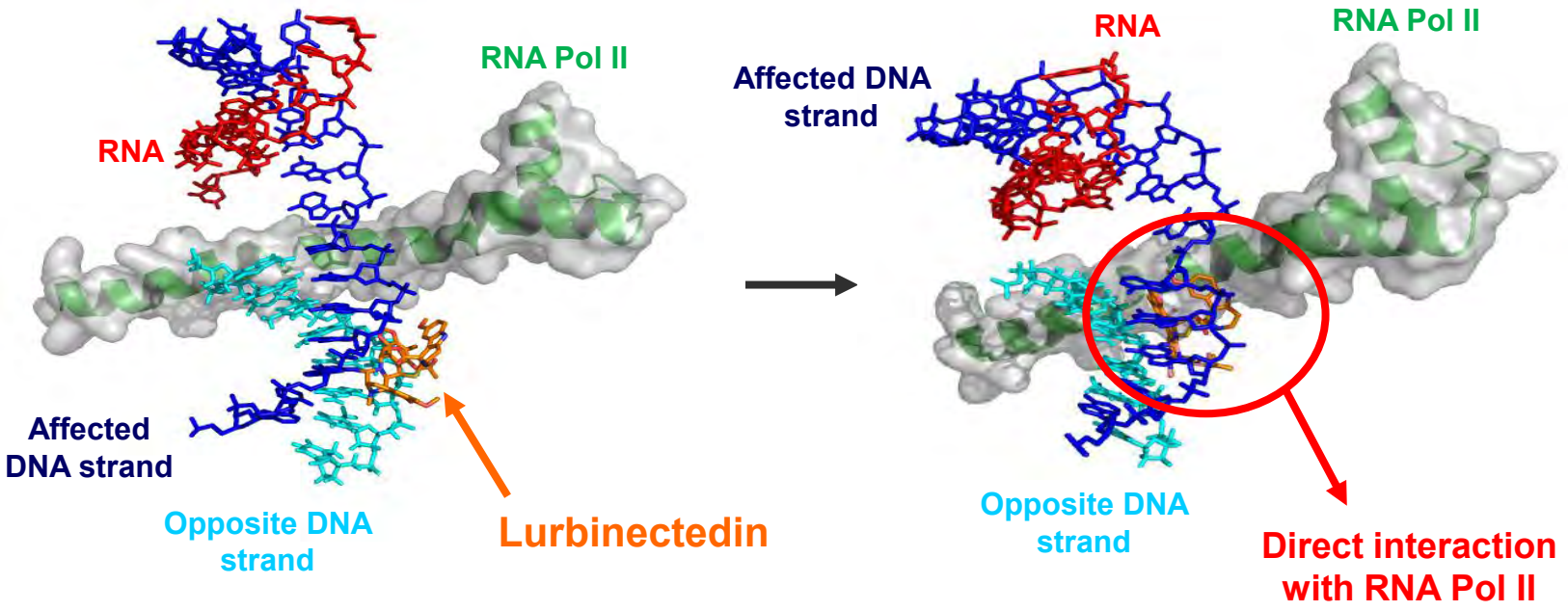
Small Molecule Therapeutics

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

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

LETTER

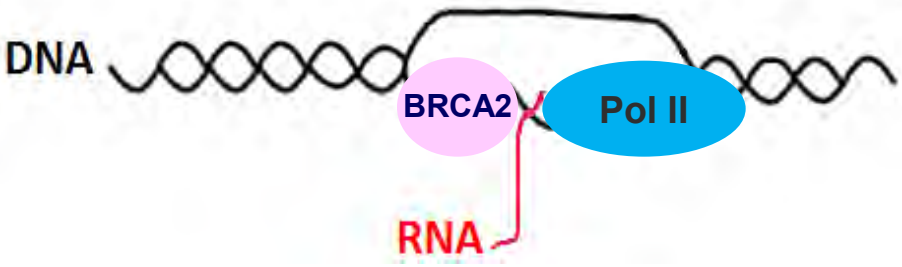
doi:10.1038/nature13374

BRCA2 prevents R-loop accumulation and associates with TREX-2 mRNA export factor PCID2

Vaibhav Bhatia[1], Sonia I. Barroso[1], María L. García-Rubio[1], Emanuela Tumini[1], Emilia Herrera-Moyano[1] & Andrés Aguilera[1]

Nature 2014 Jul 17;511(7509):362-5

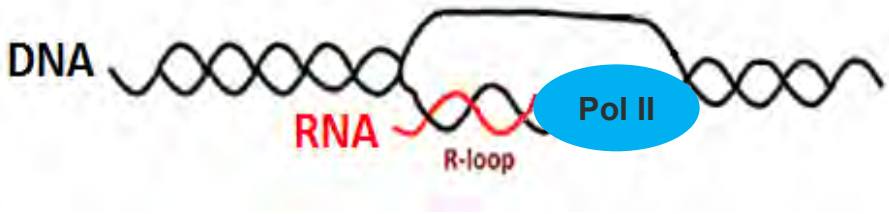
BRCA2-proficient cells



Prevention of R-loops

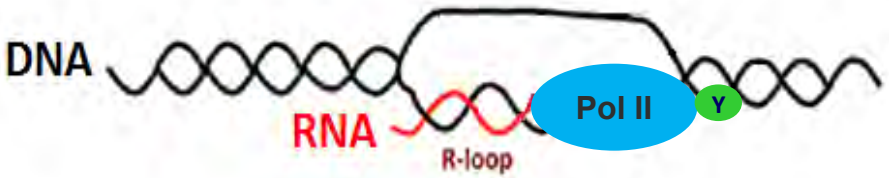
Maintenance of DNA integrity

BRCA2-mutated cells



Formation of R-loops

Accumulation of ds-DNA breaks



- **The resolution of transcription-replication conflicts mediated by R-loops requires the action of BRCA2/FANCD1**
- **Yondelis increases R-loop accummulation**
- **Yondelis induces DNA breaks that are partially R-loop dependent**

Aguilera et al, 2017

BRCA2-Mutated Cells

PARP inhibitors

Deficient HR

PARP inhibition

DNA damage

Synthetic Lethality

Cell death

Lurbinectedin

R-loops accumulation

Transcription inhibition

DNA damage

Synthetic Lethality

Cell death

Combinations with PARP inhibitors

Synergistic combination of lurbinectedin and PARP inhibitors in breast cancer cells
(Santamaría G, et al; Proc AACR 2014)

- **The combinations of PM1183 plus the PARP inhibitors Olaparib and Talazoparib were both synergistic and might be used to induce ¨artificial¨ synthetic lethality in breast cancer cell**
- **The synergistic interaction was observed in BRCA1/2 wt and mutant breast tumor cells**

Phase Ib/II study to evaluate the efficacy and tolerability of lurbinectedin in combination with olaparib in patients with advanced solid tumors
(Poveda A, et al; Ann Oncol 2016, 27:901TiP)

- **Phase Ib (escalation cohort): Patients with advanced or metastatic solid tumors without established standard therapeutic alternatives**
- **Phase-II (expansion cohort): Platinum-resistant ovarian cancer patients, triple-negative breast and endometrial cancer patients; endpoint : ORR perRECIST 1.1**
- **The combination of PM01183 and olaparib has shown a good safety profile**
- **Currently, undergoing extension of patients at DL4**

Tumors are organ-like structures

Developmental Cell *18*, June 15, 2010 ©2010

Developmental Cell
Review

Tumors as Organs: Complex Tissues that Interface with the Entire Organism

Mikala Egeblad,[1,*] Elizabeth S. Nakasone,[1,2] and Zena Werb[3,*]
[1]Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA
[2]Watson School of Biological Sciences, Cold Spring Harbor Laboratory, 1 Bungtown Road, Cold Spring Harbor, NY 11724, USA
[3]Department of Anatomy, University of California, 513 Parnassus Avenue, Box 0452, San Francisco, CA 94143, USA
*Correspondence: egeblad@cshl.edu (M.E.), zena.werb@ucsf.edu (Z.W.)
DOI 10.1016/j.devcel.2010.05.012

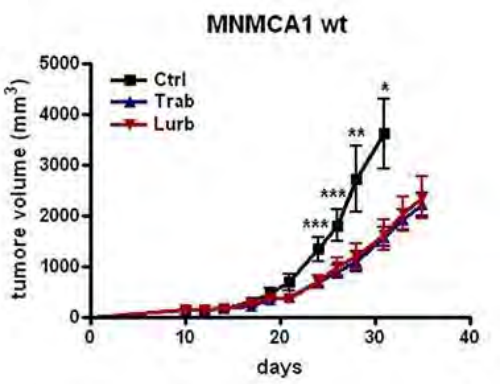
Cancer Cell
Article

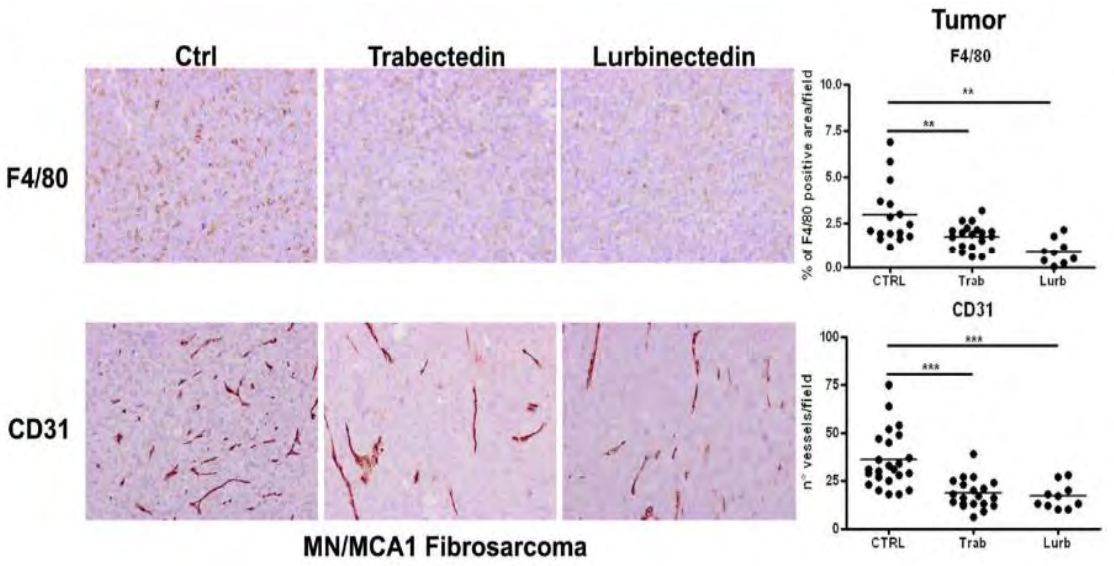
Role of Macrophage Targeting in the Antitumor Activity of Trabectedin

Giovanni Germano,[1] Roberta Frapolli,[2,10] Cristina Belgiovine,[1,10] Achille Anselmo,[1] Samantha Pesce,[1] Manuela Liguori,[1] Eugenio Erba,[2] Sarah Uboldi,[2] Massimo Zucchetti,[2] Fabio Pasqualini,[1] Manuela Nebuloni,[3] Nico van Rooijen,[5] Roberta Mortarini,[6] Luca Beltrame,[2] Sergio Marchini,[2] Ilaria Fuso Nerini,[2] Roberta Sanfilippo,[7] Paolo G. Casali,[7] Silvana Pilotti,[8] Carlos M. Galmarini,[9] Andrea Anichini,[6] Alberto Mantovani,[1,4] Maurizio D'Incalci,[2,*] and Paola Allavena[1,*]

Cancer Cell 23, 249–262, February 11, 2013

Lurbinectedin reduces TAMs and the production of inflammatory cytokines chemokines and angiogenic factors in preclinical models





- Tumor-associated macrophages (TAMs) elicit cancer-promoting inflammation and have been implicated in cancer progression, immune suppression, and resistance to therapies
- Selective depletion of TAMs
- Inhibition of the transcription of selected cytokines (e.g., CCL2, IL6, IL8, etc.) by TAMs abrogating their protumoral properties

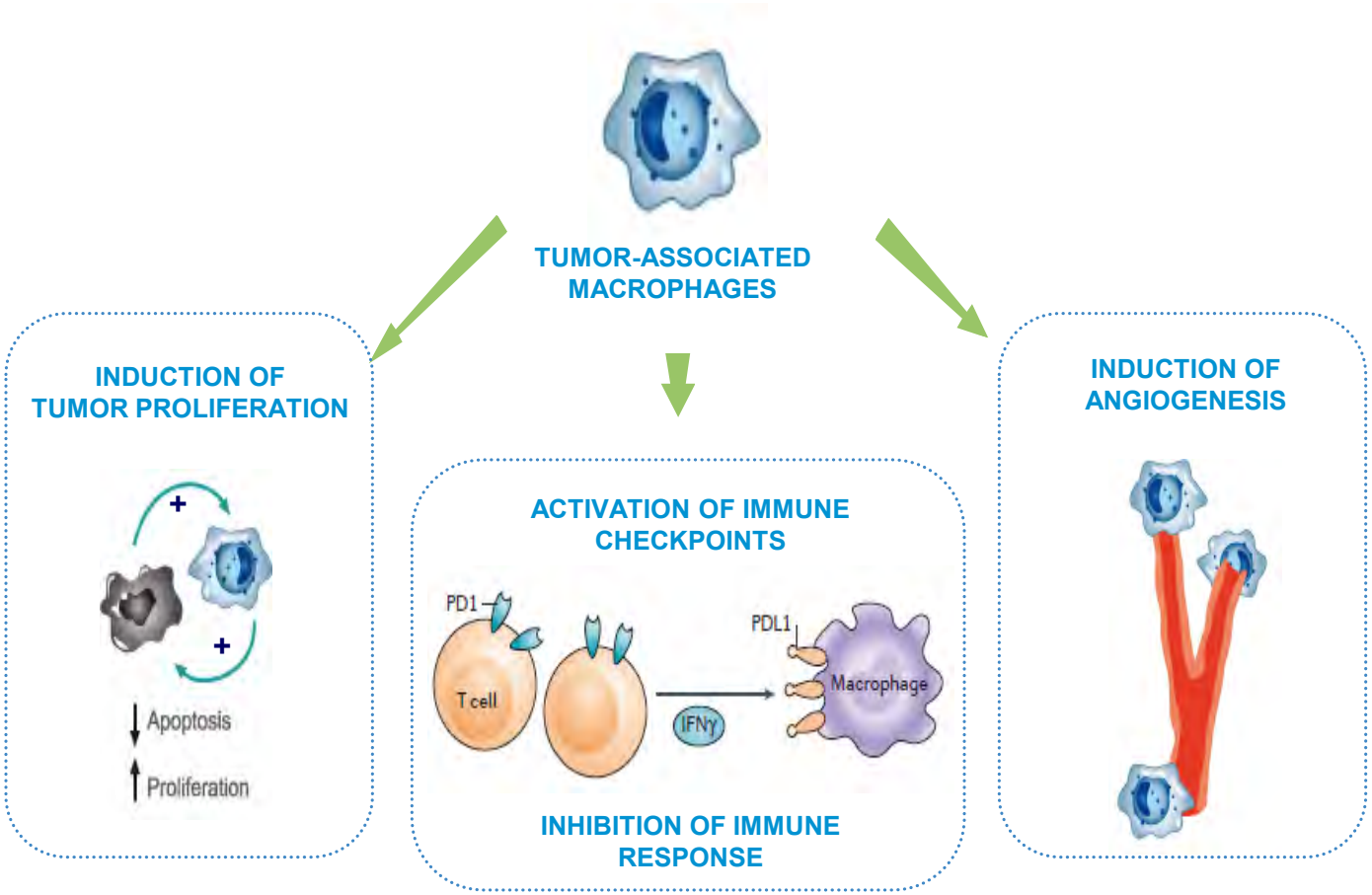
Allavena P, et. Al; Proc AACR 2016: A1284

Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology

Immunology in the clinic review series; focus on cancer: tumour-associated macrophages: undisputed stars of the inflammatory tumour microenvironment

P. Allavena* and A. Mantovani*†

2012, *Clinical and Experimental Immunology*, **167:** 195–205



Lurbinectedin - Summary

- ✓ Molecular Mechanism
- ❑ Inhibition of active transcription of protein-coding genes
- ❑ Degradation of RNA Pol II and subsequent induction of DNA breaks and apoptosis
- ✓ Effects on cancer cells
- ✓ Effects on tumor microenvironment
- ❑ Decrease in the number of TAMs
- ❑ Inhibition of the production of inflammatory mediators

U.S. Commercial Plans and Infrastructure Build

Pascal Besman
Chief Operating Officer

Commercializing and Building a Presence

- PharmaMar has a stated goal of commercializing Lurbinectedin itself in the U.S. market.
- PharmaMar has succeeded in navigating the commercial landscape in Europe involving multiple jurisdictions, languages, laws, reimbursements, etc.
- PharmaMar has already attracted elite partners in other jurisdictions: For Yondelis, Janssen in the U.S.; Taiho (Otsuka) in Japan; and for both Lurbinectedin and Aplidin in the EU, Chugai (Roche Group).
- PharmaMar is starting to increase its presence in the U.S. with investors, patients/care givers, and KOLs.
- Potential U.S. listing.

Positioning and Messaging Goals:

Three Buckets of Stakeholders

Investors

- Traditional IR ☑
- R&D Day ☑
- KOL calls ☑
- Analyst coverage ☑

Patients & Caregivers

- Social Media ☑
- KOL 'noise' ☑
- Public Relations ☑
- Patient Assoc. ☑

Oncologists

- Patient Push ☑
- Educ. resources ☑
- Med./CME mtgs ☑
- Add noisy KOLs ☑

Action Steps

- Refine our messaging, e.g., slide deck, website, ct.gov
- Hiring of KOL-investor focused PR firm
- Hiring oncology PR/strategic firm
- Initiate patient centric mBC campaign(s)
- Hire KOL(s)/social media expert consultant(s)
- Presence at a number of 2017 events
- Try and gain research coverage
- Start recruitment of commercial infrastructure

Refine Our Investor Messaging, e.g., Slide Deck, Website, ClinicalTrials.gov ✓

- Optimize our messaging as a 'global' biotech company. ✓
- Our investor presentations see all supporting documents, presentations, publications being placed on a stick drive, reinforcing our top shelf quality image. ✓
- Adding more videos including 'meet the professor' series for those seeking deeper science dive to YouTube and investor resources. 
- Hosting regular investor calls including call discussing the Chugai partnership and our first earnings call. ✓

Increase Specialty Media Coverage

- **What: Awareness PR campaign directed at MDs and patients. We will have a loud presence around key company events, such as start of BRCA2 pivotal trial.** ☑
- **Future campaigns to include PR in specialty media, social media, clinical trial spotlight, patient and oncologist educational resources, and media monitoring.** 

Appearing in the ASCO Edition of OncLive

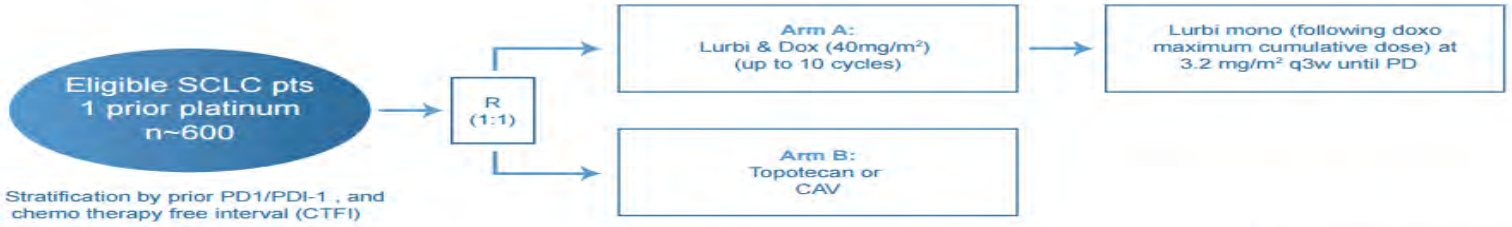
NOW ENROLLING

SMALL-CELL LUNG CANCER

ATLANTIS

Clinical Study of selective inhibitor of trans-activated RNA polymerase II transcription **Lurbinectedin** (Lurbi) in combination with doxorubicin in adult patients with Small-Cell Lung Cancer

ATLANTIS: Multicenter, international, randomized, Phase III trial of Lurbinectedin plus Doxorubicin (Dox) vs. Investigator's choice of Topotecan or CAV* in ECOG PS ≤ 2 Small Cell Lung Cancer patients with a CTFI**≥30d who have failed one prior platinum containing line, with a primary endpoint of progression-free survival (RECIST v.1.1; assessments every 6 weeks)



NCT02566993

* Cyclophosphamide, Doxorubicin, Vincristine
** Chemo therapy free interval

Caution: New Drug - Limited by Federal (or United States) law to investigational use.
The safety and efficacy of the investigational use of this product has not been determined. There is no guarantee that the investigational use listed will be filed with and/or approved for marketing by any regulatory agency.

Increase Patient and Care Giver Awareness

- What: Campaigns for patients, caregivers, and oncologists.
- We have added a 'patient resource' section to our website for myeloma, small cell lung and breast cancers that will also list our open clinical trials links.✓
- Finalized two patient advocacy collaborations for breast cancer ahead of opening up our phase III.✓ These will involve general awareness, education, support, etc.; and direct interested parties to clinicaltrials.gov and our protocols. Details from Sisters Network on next slide.
- We are finalizing  partnerships with various other patient advocacy and charitable groups to work with them for awareness, educational resources, etc., e.g., sponsoring an updated SCLC video library for G.R.A.C.E.✓

Sisters Network Inc.: A National African-American Breast Cancer Organization

- **BRCA2 mBC sees African Americans affected at a rate of 3:1 general population.**
- **SISTERS has a 10-city conference tour* aimed at the education/presentation of options, sharing of experiences, and overall support for the African-American breast cancer patient. We are sponsors and will be attendees.** ☑
- **Over 10,000 members with many others attending events.**
- **BRCA2 women ineligible for our pivotal trial will hopefully be made aware of our expanded access program.**

* Austin, Baton Rouge, Chicago, Hampton Roads VA, Greensboro, Houston, Memphis, Passaic NJ, Portland, Tampa.

Increase FDA, Academic, Industry, Government and Nonprofit Advocacy Visibility

AAADV
Accelerating Anticancer Agent Development and Validation

- Attending Accelerating Anticancer Agent Development and Validation (AAADV) workshop next week
- AAADV is a not-for-profit education initiative of the U.S. Food and Drug Administration, academic, industry and advocates focused on accelerating the development and delivery of cancer treatments to patients.

"AAADV not only impacts the rate at which oncology drugs are brought to market, but patients afflicted with cancer have been able to appreciate significant advances in their care and survival rates."

Richard Pazdur

Director, Office of Hematology and Oncology Drug Products
U.S. Food and Drug Administration Center for Drug Evaluation and Research

Exposure Re Drugs and Trials to KOLs

- KOL investor calls about our science and drugs.
- Hiring consultants who are KOLs *and* adept with social media. First one is hired, Jack West, M.D., ☑ a subeditor of JAMA oncology and *very* active on Twitter and other social media. Second consultant identified; likely signing in 2Q. 
- Having KOLs disclose their conflict of interest in consulting for us is great advertising; and since there is no pharma company that starts with "Q", we precede ROCHE.
- Participating and/or sponsoring CME is a great way to make KOL and community oncologist outreach. ☑
- KOL investor call slated for early May re Lurbinectedin.

Increase Exposure at Medical Meetings, CME Events, etc., (and Push for Publications of Data)

- We will be active in sponsoring meetings, giving talks, presenting posters, hosting symposia, arranging Lab Tours for the 3 Madrid meetings of 2017 (Imedex Lung, EHA, ESMO). ☑
- How: In addition to our presence at ASCO, EHA, and ESMO, we were/are a sponsor (and presenter) for all of the following events/entities: Imedex Lung, TAT (Paris), ELCC (Geneva), FORCE breast cancer (Orlando), Sisters Network Conference Tour, World Lung, and PER Lung Barcelona. ☑
- Attending other meetings such as Imedex SABCS Breast, SGO, EGOG, Imedex Lung NYC, SABCS to build up rapport and relationships. ☑
- It's already working; at Imedex SABCS (n~200), a presenter of talk on new drugs spent six minutes of his talk on Lurbinectedin at our urging by our being there. ☑

Goal: Start Process to Add a Commercial Officer, Medical Affairs, Market Access, BoD, and Oncology Board Members

- **CCO probably should be on board ~12-18 months before a potential launch.**
- **Medical Affairs and Market Access people have plenty to do ahead of a filing and launch.**
- **BoD and Oncology Board advisory additions ongoing.**

Strategy and Business Development

Luis Mora
Managing Director

The Plan for Growth

- **Today: 1 drug, 80 countries, 2 indications**
- **This year: 2 drugs, 3 indications**
- **In 2018/19: 3 drugs, 4 indications**
- **In 2020/21: 3 drugs, 5 indications**
- **A perpetual pipeline engine focused on the sea**

Business Development

- **Lurbinectedin: we partnered with Japan (~10% of world oncology market) for €30 million upfront, >€70 million developmental reimbursements and milestones, and double-digit royalty.**
- **We own 100% of other territories.**
- **Our EU sales force of ~80 total is a strategic asset for other oncology companies that need help selling in the EU.**
- **Our marine compound library of over 200,000 samples could be licensed out in non-oncology indications.**

The Long-Term View

- **Fully integrated from marine expeditions, discovery, screening, synthesis, pre-clinical work, clinical trials, manufacturing, and commercialization.**
- **Regulatory clearance and manufacturing inspections passed in the largest three jurisdictions (FDA, EMA, and PMDA).**
- **Commercial infrastructure being established in the U.S. market.**
- **Preside over a narrowing of the valuation gap compared with U.S. biotech companies.**

A Word on Financials

José Luis Moreno
Director of IR in Capital Markets

Year 2016 at a Glance: Financial Situation

- **Pro forma* cash and financial assets (current and non current): €60.5 million (€46.6mn in 2015)**
- **Net Debt 2016 €62 mn****
- **Total of €20mn in revolving credit available**
- **Operating cash-flow consumption 2016 €8.4mn**
- **Debt maturing in 2016 (€18mn) refinanced to long term (5-6 year terms)**

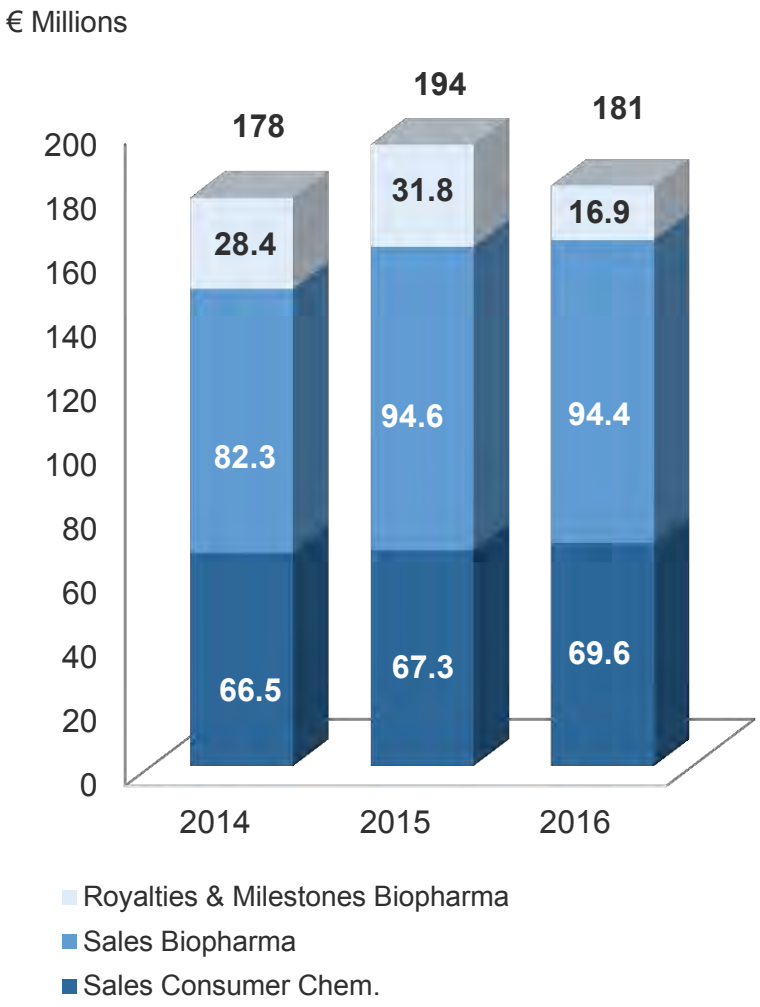
* Pro forma for Chugai-Lurbinectedin partnership, €30mn upfront (announced on December 22, 2016).
** (2016 Not pro-forma; without the effect of Chugai payment)

Cash Flow and Cash Position

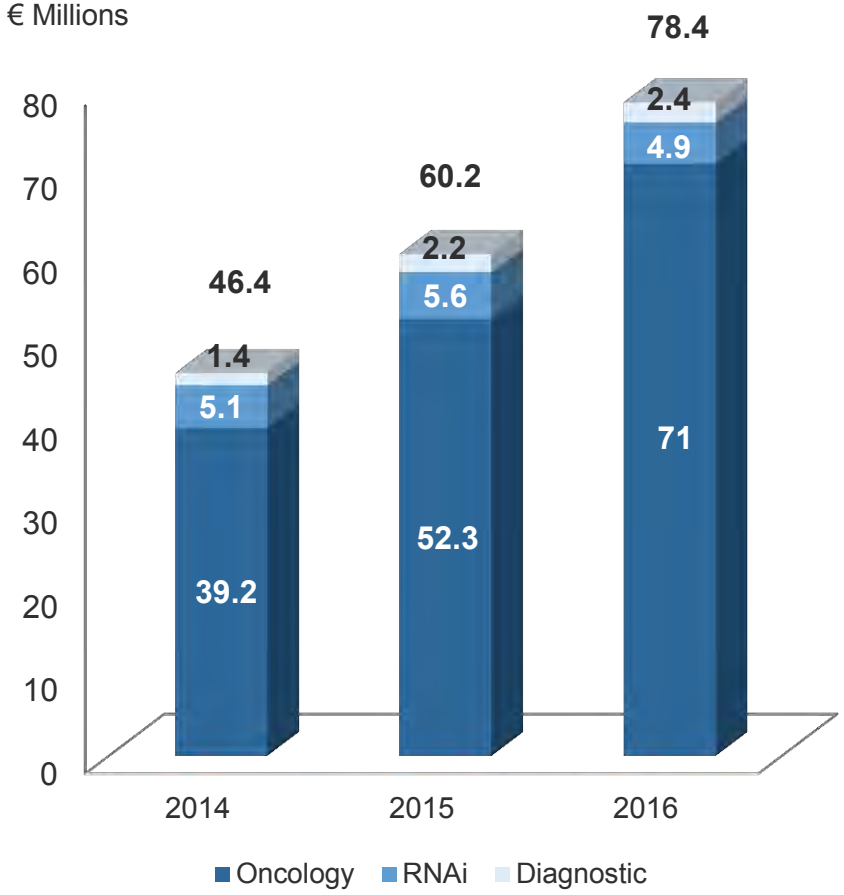
- **Operating Cash Flow 2016 €-8.4 mn**
- **Capex 2016 €-6.1 mn**
- **Debt maturing in 2016 refinanced to long term**
- **Cash Position:**
  - **Initial Cash & current financial assets 2016: €45.6 mn**
  - **Final Cash & current financial assets 2016: €32.4 mn**

Group Revenues and R&D Expenses

Revenues



R&D (Net)



Total Sales (Euros in Millions)

	2016	2015	Change
Oncology Sales (Yondelis)	**88,194**	**88,442**	-0.28%
Commercial Sales	86,680	80,677	7.44%
Sales Raw Material (API)	1,514	7,765	
Diagnostic Kits Sales	**6,180**	**6,202**	-0.35%
Sales Biopharmaceutical Area	**94,374**	**94,644**	**-0.29%**
Sales Consumer Chemical Area	**69,660**	**67,348**	**3.43%**
Xylazel	19,423	16,573	17.20%
Zelnova Zeltia	50,237	50,775	-1.06%
Total Sales	**164,034**	**161,992**	**1.26%**

Market cap of €750 million as of April 13, 2017.

Thank You

For more information visit: www.pharmamar.com

Combining Lurbinectedin and Doxorubicin
The UCLH Experience in Small Cell Lung Cancer

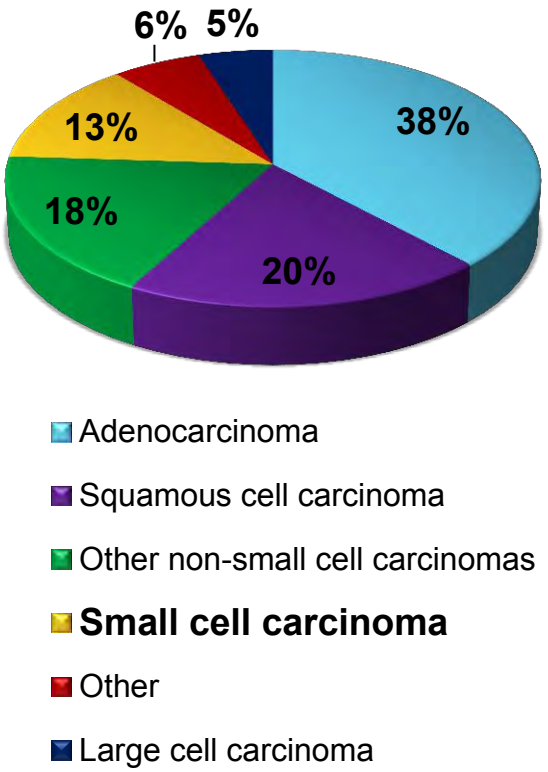
Dr Martin Forster MD PhD
Clinical Senior Lecturer in Experimental Cancer Medicine
Consultant in Medical Oncology
UCL Cancer Institute / UCLH, London, UK

CANCER RESEARCH UK | LUNG CANCER CENTRE OF EXCELLENCE

Pharmamar R&D Day
April 2017

Small Cell Lung Cancer (SCLC)

- Lung Cancer is the most common cancer across men and women globally and the highest cause of cancer mortality
- SCLC accounts for 10-15% of all lung cancer
- Strong association with tobacco use and associated co-morbidities
- ~30% present with ‘limited stage’ disease with only a proportion eligible for ‘radical intent’ treatment, chemo-radiation, associated with ~18 month survival
- >80% treated with palliative chemotherapy with median survival 9-11 months



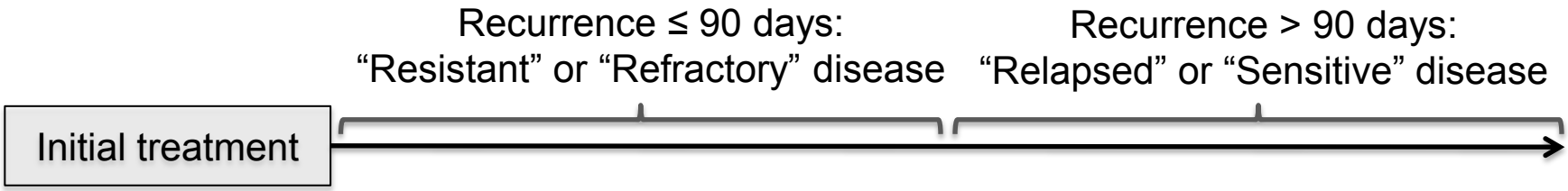
Jackman and Johnson, 2005

Extensive Stage SCLC: First-line therapy

- Combination chemotherapy with cisplatin / carboplatin and etoposide is the mainstay of first-line treatment
  - Response rates 60-70%
  - 4 to 6 cycles
  - Median progression free survival 2-3 months
  - 2-year overall survival < 5%
- Minimal improvement in first line therapy in decades
  - Cisplatin / Irinotecan demonstrated to be superior in Japanese population; not seen in study in Western population
  - Consolidation Thoracic Radiotherapy
  - Prophylactic Cranial Irradiation

Noda et al., NEJM 2002; Hanna et al., JCO 2006; Rossi et al., JCO 2012; Slotman et al., Lancet Onc 2015

Management of Recurrent Disease



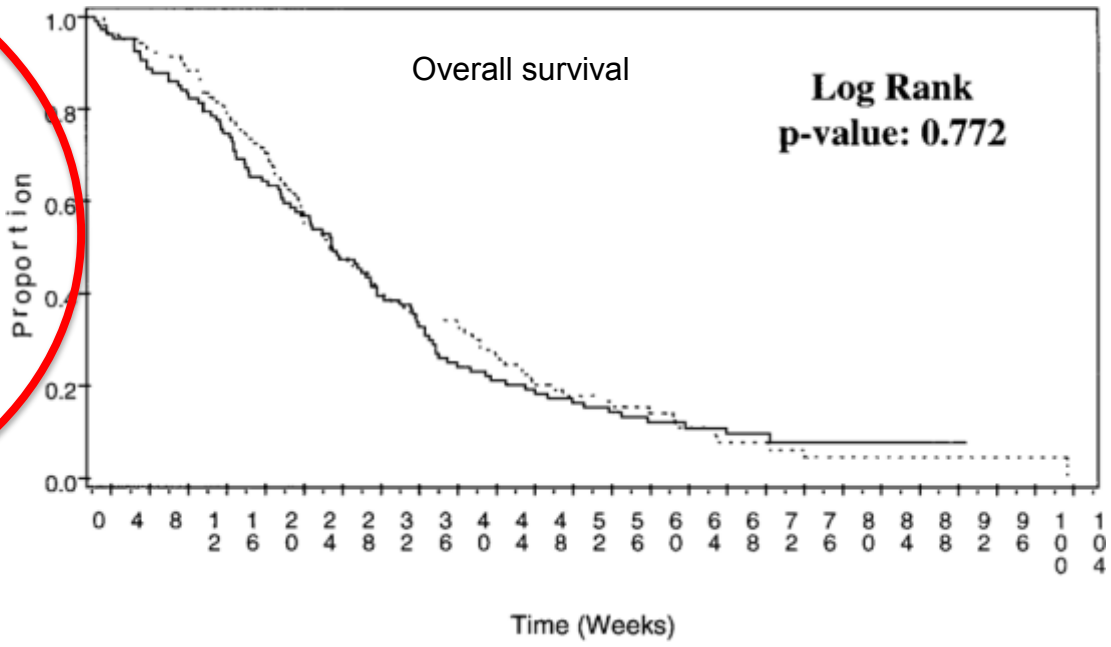
Topotecan as second-line therapy in SCLC

- Three open-label single-arm studies of IV topotecan days 1-5 q3 weekly showed response rates ranging 11% to 31% for 'sensitive' disease and 2% to 7% for 'resistant' disease
- Randomized phase 3 study of 211 patients receiving IV Topotecan vs CAV showed equivalent response rates, time to progression, and survival.

Ardizzoni et al., 1997; Von Pawel et al., 1999; NCCN guidelines v2.2017

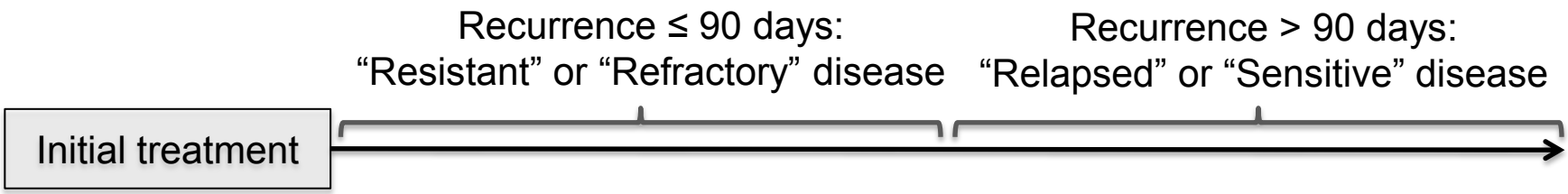
Topotecan vs CAV in second-line setting

- Randomized study in patients with relapse >60 days after completion of first-line therapy
  - Topotecan: 1.5 mg/m^2 IV daily days 1-5 Q21d vs CAV: Cyclophosphamide 1000 mg/m^2, Doxorubicin 45 mg/m^2, Vincristine 2 mg IV day 1 Q21d
- ORR
  - 24 vs 18%
- mTTP:
  - 13.3 vs 12.3 wks
- mOS:
  - 25.0 vs 24.7 wks



Von Pawel et al., JCO 1999

Management of Recurrent Disease



Topotecan is the only FDA- and EMA-approved second-line therapy in SCLC

- Randomized phase 3 study of 211 patients receiving IV Topotecan vs CAV showed equivalent response rates, time to progression, and survival
- Oral topotecan also improved survival compared to BSC

Oral and IV formulations approved by FDA and EMA

Ardizzoni et al., 1997; Von Pawel et al., 1999; O'Brien et al., 2006; NCCN guidelines v2.2017

Upcoming Interests – Immunotherapy

- Phase 3 Cisplatin & Etoposide +/- Ipilimumab

- Checkmate 032 - Phase 2 Nivolumab monotherapy vs Nivolumab plus Ipilimumab

	Nivolumab-3 (n = 98)	Nivolumab-1 + Ipilimumab-3 (n = 61)	Nivolumab-3 + Ipilimumab-1 (n = 54)
Objective response rate, % (n/N)			
Overall	**10 (10/98)**	**23 (14/61)**	**19 (10/54)**
Platinum-sensitive[a]	11 (6/55)	28 (7/25)	19 (4/21)
Platinum-resistant[a]	10 (3/30)	17 (4/23)	10 (2/21)

Antonia et al., Lancet Onc 2016; Reck et al.; JCO 2016

Upcoming Interests – DLL3 inhibitors

- Rovalpituzumab tesirine (Rova-T) – A delta-like protein 3 Antibody-Drug Conjugate
  - Phase 1 dose escalation study in SCLC (2nd or 3rd line therapy)
    - Maximum tolerated dose 0.4 mg/kg 3 weekly
    - Recommended phase II dose and schedule 0.3 mg/kg 6 weekly
    - 'Active' dose levels: 0·2 mg/kg or 0·4 mg/kg every 3 weeks or 0·3 mg/kg or 0·4 mg/kg every 6 weeks

	ORR (all patients) N=60	ORR (DLL3 +ve pts) N=26
Rova-T 'Active' dose levels	18% (11/60) PFS 2.8m OS 4.6m	38% (10/26) PFS 4.3m OS 5.8m

Rudin et al., Lancet Oncology 2016

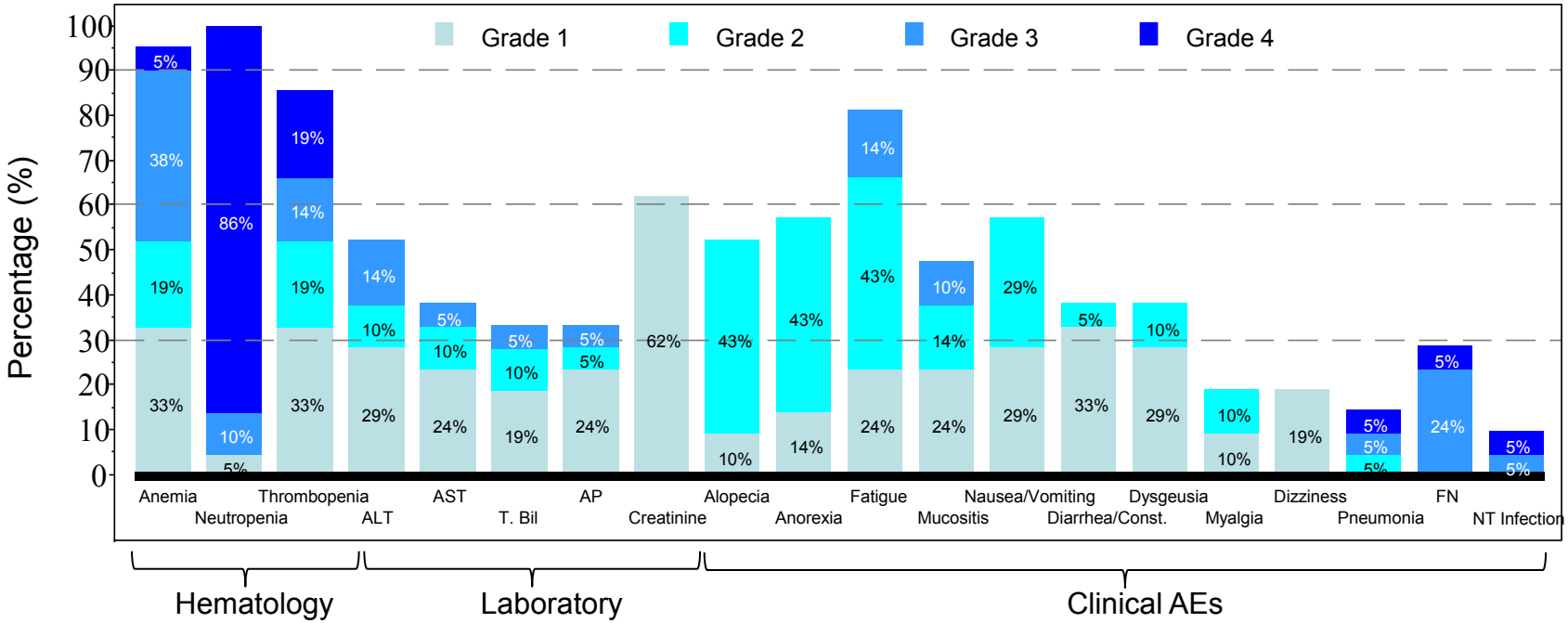
Upcoming Interests – Lurbinectedin & Doxorubicin

Lurbinectedin (PM1183) & Doxorubicin (DOX), as a possible new second-line therapy in Small Cell Lung Cancer (SCLC)

- Dose finding part of a Phase Ib study defined a recommended phase II dose of lurbinectedin 4.0 mg flat dose (FD) or 2.0 mg/m^2 + DOX 50 mg/m^2 both on day (D)1 every three weeks (q3w)
- Myelosuppression was dose-limiting regardless of colony stimulating factor (CSF) prophylaxis use
- After DOX withdrawal, treatment could continue with lurbinectedin alone, if clinically appropriate
- Compelling activity was observed during escalation phase with 5 of 7 evaluable 2nd line in SCLC pts (71%) having objective partial response (PR) as per RECIST v.1.1
- Thus, an expansion cohort of 20 2nd line SCLC pts was evaluated

Forster et al., ASCO 2015

Safety (n=21)



AEs, Adverse events; ALT, Alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; Const, constipation; FN, febrile neutropenia; NT, neutropenic; T Bil, Total bilirubin.

Neutropenia time course according to CSF prophylactic use or not (n=109 cycles)

	CSF (n=52)	No CSF (n=57)
Grade 4 neutropenia	25%	33%
Median day of grade 4 nadir (range)	8 (7-11)	14 (10-16)
Time to recovery to rechallenge, in days	4 (2-21)	4 (1-13)
Febrile neutropenia	7.7%	8.8%
Neutropenic infection	None	3.5%
Grade 4 thrombocytopenia	7.7%	None

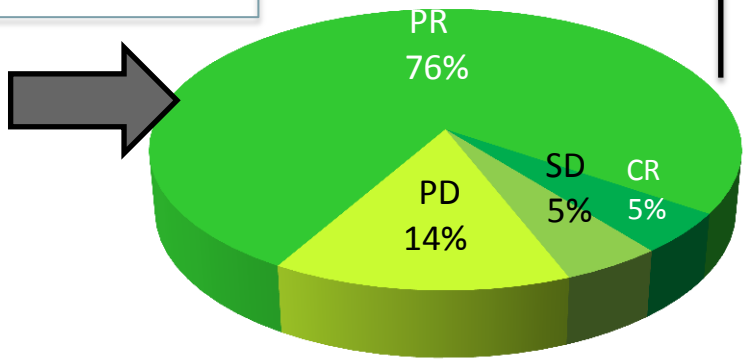
CSF, colony stimulating factor.

Forster et al., ASCO 2015

Efficacy

1st line Platinum-based combination

N=21



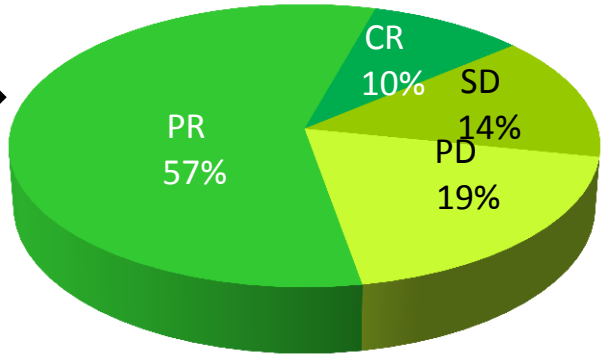
ORR
81%
95% CI: 58-95%

PD

median CTFI
3.1 months

2nd line Lurbinectedin /DOX

N=21

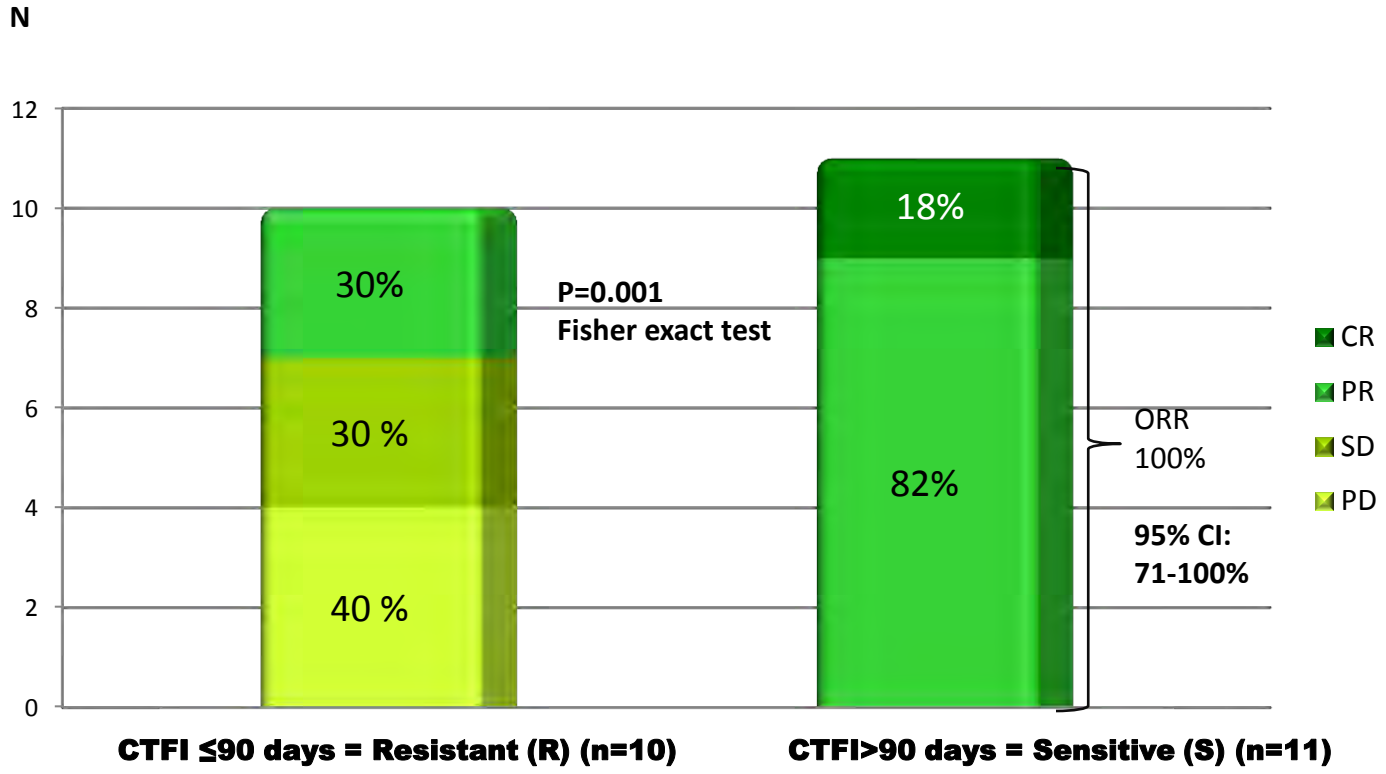


ORR
67%
95% CI: 43-85%

CI, confidence interval; CR, complete response; CTFI, chemotherapy-free interval; DOX, doxorubicin; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Forster et al., ASCO 2015

Best RECIST v.1.1 response according to chemotherapy free interval (CTFI)



Exceptional activity with significant but manageable toxicity led to a further expansion cohort of Lurbinectedin (2mg/m^2) and Doxorubicin (40mg/m^2) and plans for a randomised study

Forster et al., ASCO 2015

Patient Characteristics

- Dose escalating phase I study in patients with different tumour types
- 9 patients with metastatic small cell lung cancer treated at UCLH

Number of patients	9
Male	7
Female	2
Median Age	63 (58-78)

Lurbinectedin combination dose (mg)	**Dox (mg/m^2)**	**# patients**
3	50	1
4	50	3
5	50	1
$2mg/m^2$	40	4

# Lines prior systemic therapy	
0	0
1	9
2	0
Platinum Sensitivity	
Sensitive	6
Resistant	3
Platinum Free interval (weeks)	
Median	17
Range	8 to 55

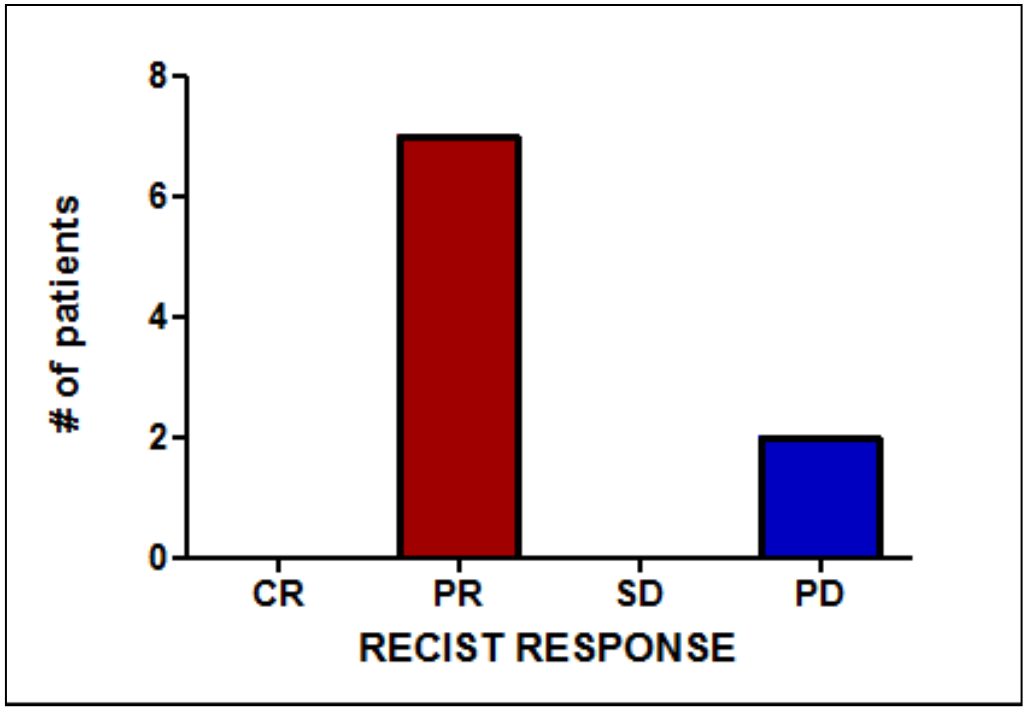
Toxicity

Patient #	PM Dose (mg)	Dox Dose (mg/m^2)	#Dox/PM combo	#PM single agent	DR in combo	DR single agent	Reason for DR
1*	3 mg	50	4	0	no	NA	
2	**3.5 mg**	**40**	**2**	**0**	**no**	**NA**	
3	**3.75 mg**	**40**	**6**	**2**	**no**	**yes**	G4 neut/ G3 plts
4	**3.75 mg**	**40**	**10**	**4**	**no**	**yes**	G4 neut/ G3 plts
5	4 mg	50	8	4	no	no	
6	**4 mg**	**40**	**2**	**0**	**no**	**NA**	
7	4 mg	50	8	7	yes	yes	G4 neut
8*	4 mg	50	4	0	no	no	
9**	5 mg	50	3	1	yes	yes	G4 neut

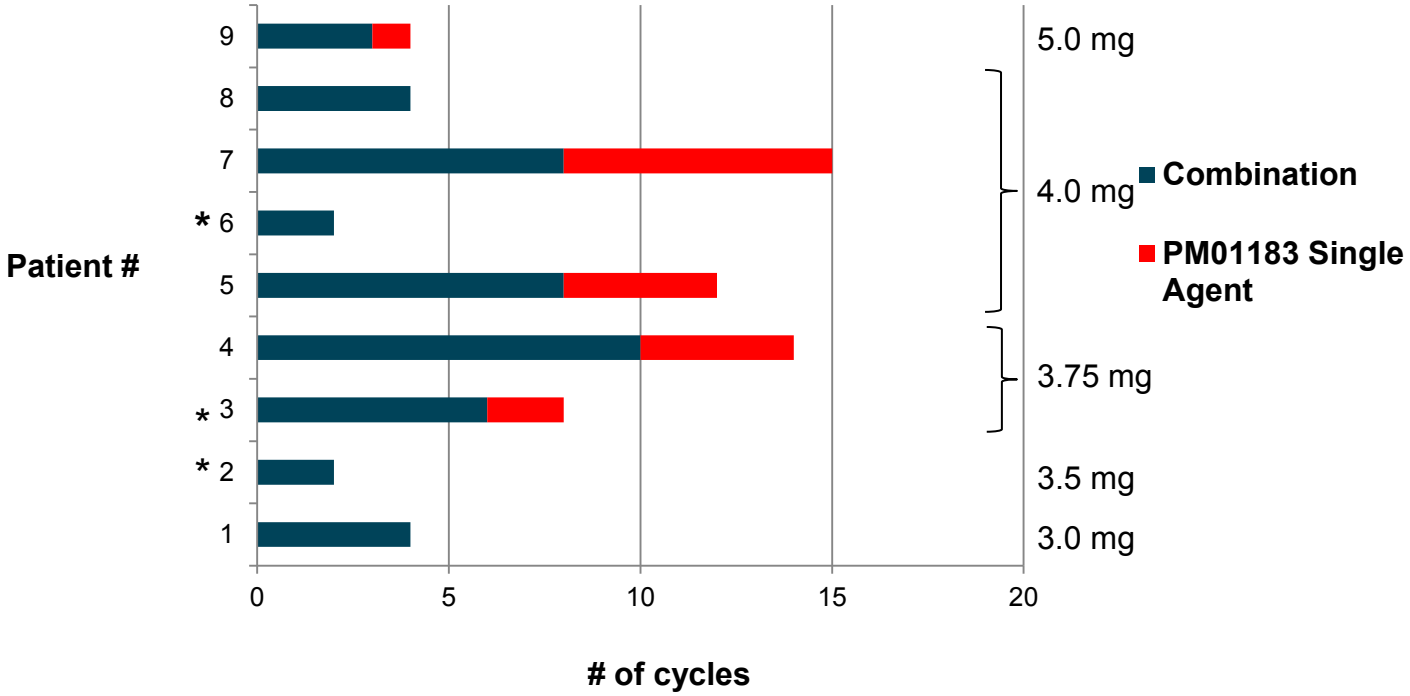
* Discontinued treatment due to fatigue / decline in PS without evidence of PD

** Discontinued treatment due to persistent pancytopenia despite dose reductions

Best Imaging Response



Treatment Duration



Median # cycles of Dox/Lurbinectedin = 4, range 2-10

Five patients on single agent lurbinectedin, median 4, range 1-7

Median # total cycles 4, mean 7.2, range 2-15

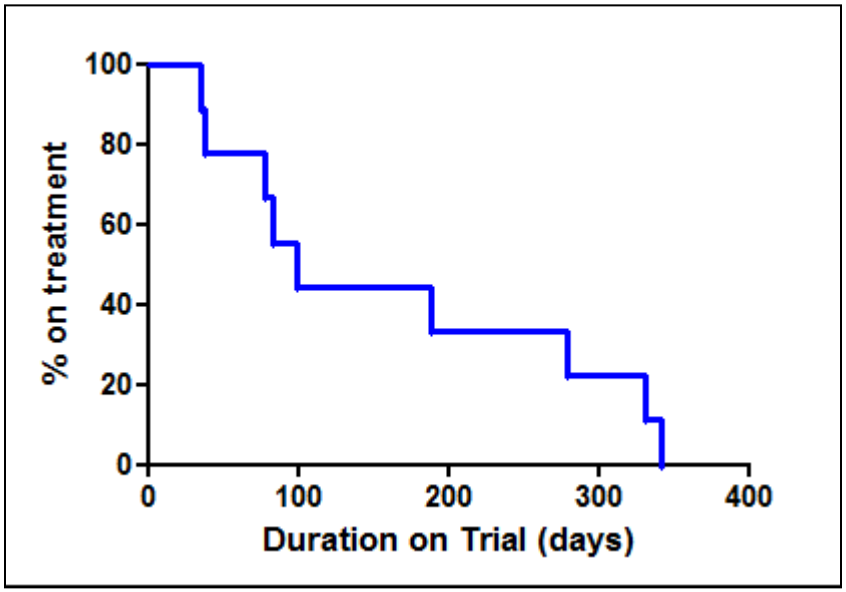
* Platinum refractory patients

Treatment Duration

Patient #	Dose PM	Dose Dox	#Dox/ PM	#PM single agent	Best response	Reason for discontinuation
1	3 mg	50 mg/m^2	4	0	PR	Pneumonia and decline in PS*
2	**3.5 mg**	**40 mg/m^2**	**2**	**0**	**PD**	**Disease Progression**
3	**3.75 mg**	**40 mg/m^2**	**6**	**2**	**PR**	**Disease Progression (Brain)**
4	**3.75 mg**	**40 mg/m^2**	**10**	**4**	**PR**	**Disease Progression (Brain)**
5	4 mg	50 mg/m^2	8	4	PR	Disease Progression
6	**4 mg**	**40 mg/m^2**	**2**	**0**	**PD**	**Disease Progression**
7	4 mg	50 mg/m^2	8	7	PR	Disease Progression
8	4 mg	50 mg/m^2	4	0	PR	Toxicity, fatigue and decline in PS**
9	5 mg	50 mg/m^2	3	1	PR	Persistent pancytopenia despite DR***

* PD 4 months after trial discontinuation
** Death 2 months after trial discontinuation
*** New brain mets 2 months after trial discontinuation

Duration on study drug



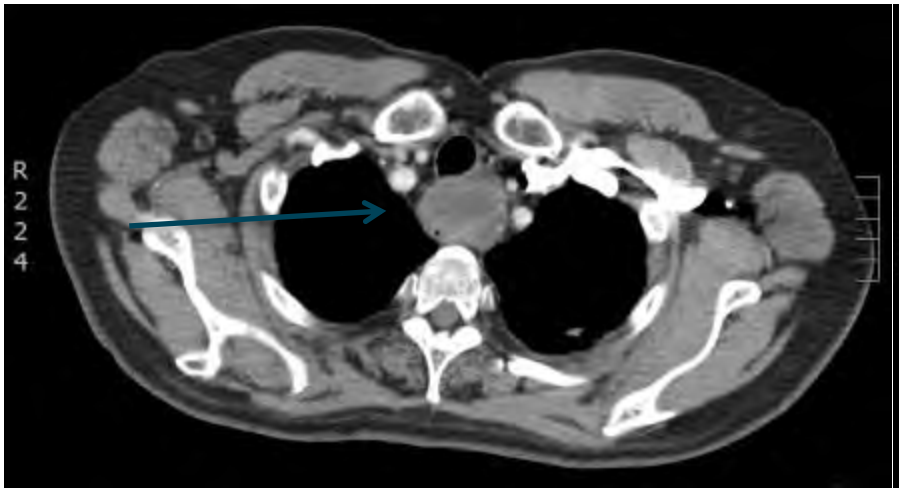
Median duration on IMP 99 days (35-341)

Patient JB

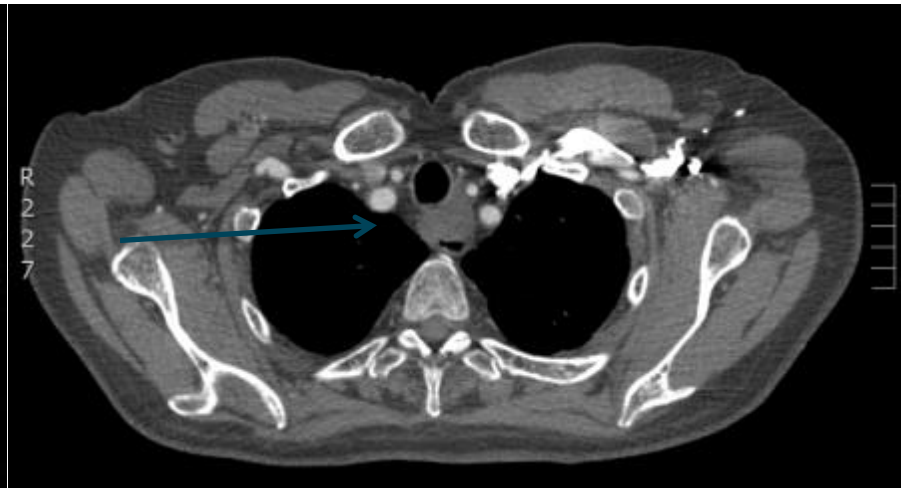
- 71 year old male
  - Ex smoker
  - COPD; CVD (TIAs); Depression
- April 2014 – T4N2M1b Extensive Stage Small Cell Lung Cancer with left suprahilar mass invading mediastinum, mediastinal LNs and a liver metastasis
- October 2014 – completed 6 cycles of carboplatin and etoposide with partial response
  - Had persisting respiratory symptoms and declined PCI but received palliative RT to left lung and mediastinum (20Gy in 5#) in Feb 2015
- March 2015 (~4 months PFI) developed disease progression in lungs and bone

- Referred to UCLH
  - Grade 1 cough; grade 1 SOB; grade 1 lethargy
  - ‘PS 1’
  - Intrathoracic disease (47mm mediastinal mass)
- May 2015 – commenced lurbinectedin 2mg/m^2 (3.75 mg) and doxorubicin 40mg/m^2
  - Minimal toxicity (G1 lethargy)
  - Partial response in June 2015 post 2 cycles (40% reduction in target lesions; 28mm)
- Incremental response until complete response of target lesion (post 4 cycles) and very good partial response of non target disease
- January 2016 – completed 10 cycles combination chemotherapy

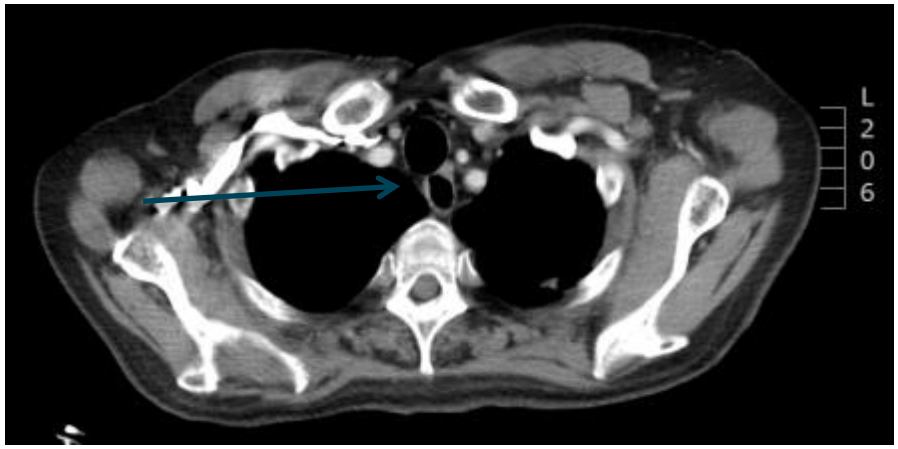
Baseline



Post 2 cycles



6 months



- Jan 2016 started onto single agent lurbinectedin (4mg/m^2; 7mg)
  - Dose reduced to 3mg/m^2 (5.25mg) due to pancytopenia after cycle 2
  - maintained PR on CT after 2 cycles
- April 2016 – complaining of blurred vision and unsteadiness
  - CT brain – multiple brain metastases
  - No extra-cranial progression
  - Off study
- April 2016 - RIP

Summary

- Tolerability across multiple dose levels driven by myelosuppression
  - Much better tolerated on expansion ‘phase III’ schedule
  - Side effects are manageable, with option for dose delays or modification if required
  - Maintenance monotherapy also feasible
- Very impressive responses
  - Some longer duration than with 1st line therapy!
- Phase III registration study ongoing with hopes to define a new standard second line SCLC treatment and improves outcomes for this patient population

Thanks

- UCLH CRF staff
  - Rebecca Kristeleit
  - Michael Flynn and other Clinical Fellows
  - David Leader and other research nurses
  - Aaron Clarke and other data managers
- NIHR UCH Clinical Research Facility
- Patients and their families

Any Questions?

Development of lurbinectedin in *BRCA2* mutation-associated breast cancer

Melinda Telli, M.D.

Stanford University School of Medicine

April 24, 2017

My background

- **Academic medical oncologist focused on breast cancer**
- **Interests in clinical development of novel treatment approaches for:**
  - **Hereditary breast cancer**
  - **Triple-negative breast cancer**
- **Pertinent appointments/memberships:**
  - **NCCN Breast Cancer Guidelines Panel**
  - **Komen Scholar**
  - **FORCE, Scientific Advisory Board Member**

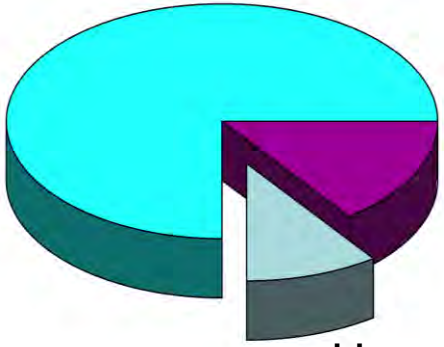
Talk Outline

- **Clinical features of hereditary breast cancer**
  - ***BRCA1***
  - ***BRCA2***
  - **Others**
- **Lurbinectedin in advanced *BRCA* mutated breast cancer**
- **Future landscape of *BRCA2* therapy**
- **Importance of hereditary cancer community advocacy**

Q & A will follow at the end of the presentations

Hereditary Breast and Ovarian Cancer

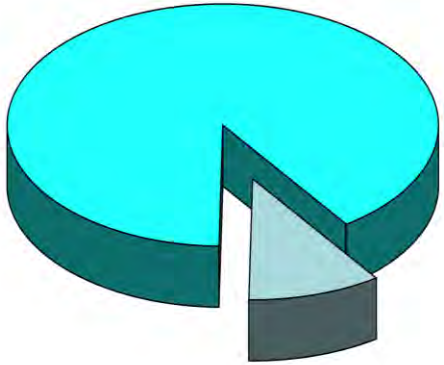
Breast



Family clusters: 15-20%

Hereditary: 5-10%

Ovarian



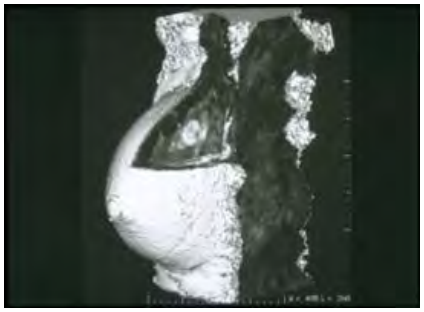
Hereditary: 10-15%

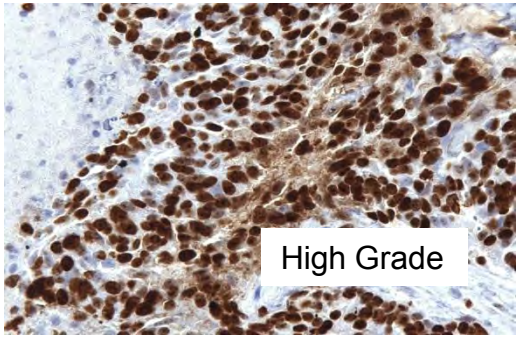
Most hereditary breast and ovarian cancers are due to germline *BRCA1* & *BRCA2* mutations

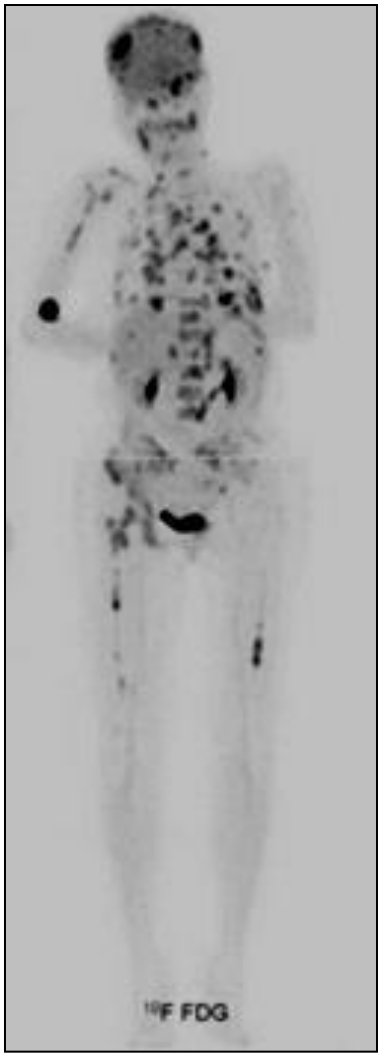
BRCA1 / BRCA2 Positive Breast Cancer

The Problem:

- Information from *BRCA1/2* testing does NOT guide treatment decisions at present
- Responses to standard therapies in carriers not well characterized
- PARP inhibitors active in advanced *BRCA*+ breast cancer, but no drugs approved
  - Landscape changing with expectation of olaparib approval in 2017
- Many patients with hereditary predisposition do not know it



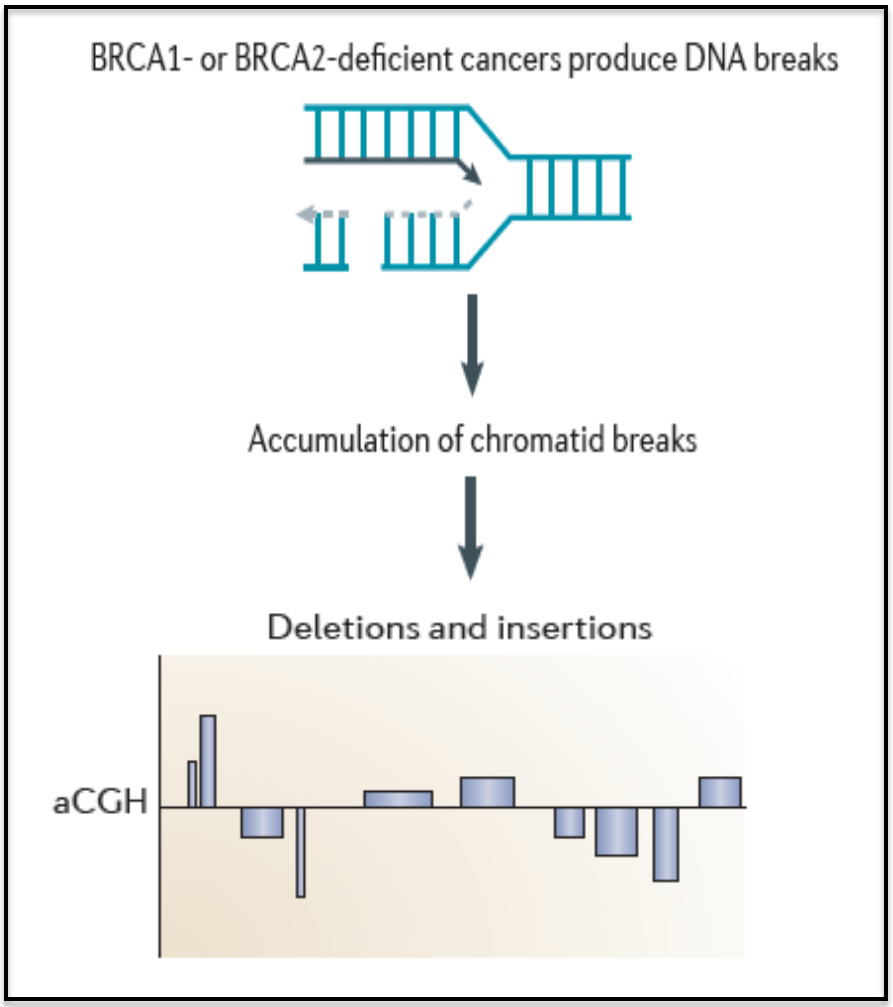




Clinical features of *BRCA1/2* mutated breast cancer

- ***BRCA1/2* mutated cancers are compromised in DNA repair resulting in genomic instability & higher grade features**
- **Majority of *BRCA1*+ tumors are triple-negative; majority of *BRCA2*+ are hormone receptor-positive**
  - **HER2 positivity is rare in both**
- ***BRCA1/2* mutated breast cancer continues to be treated systemically according to the same algorithm for the treatment of sporadic breast cancer**
- **Strong rationale for development of DNA damaging therapeutics in this disease**

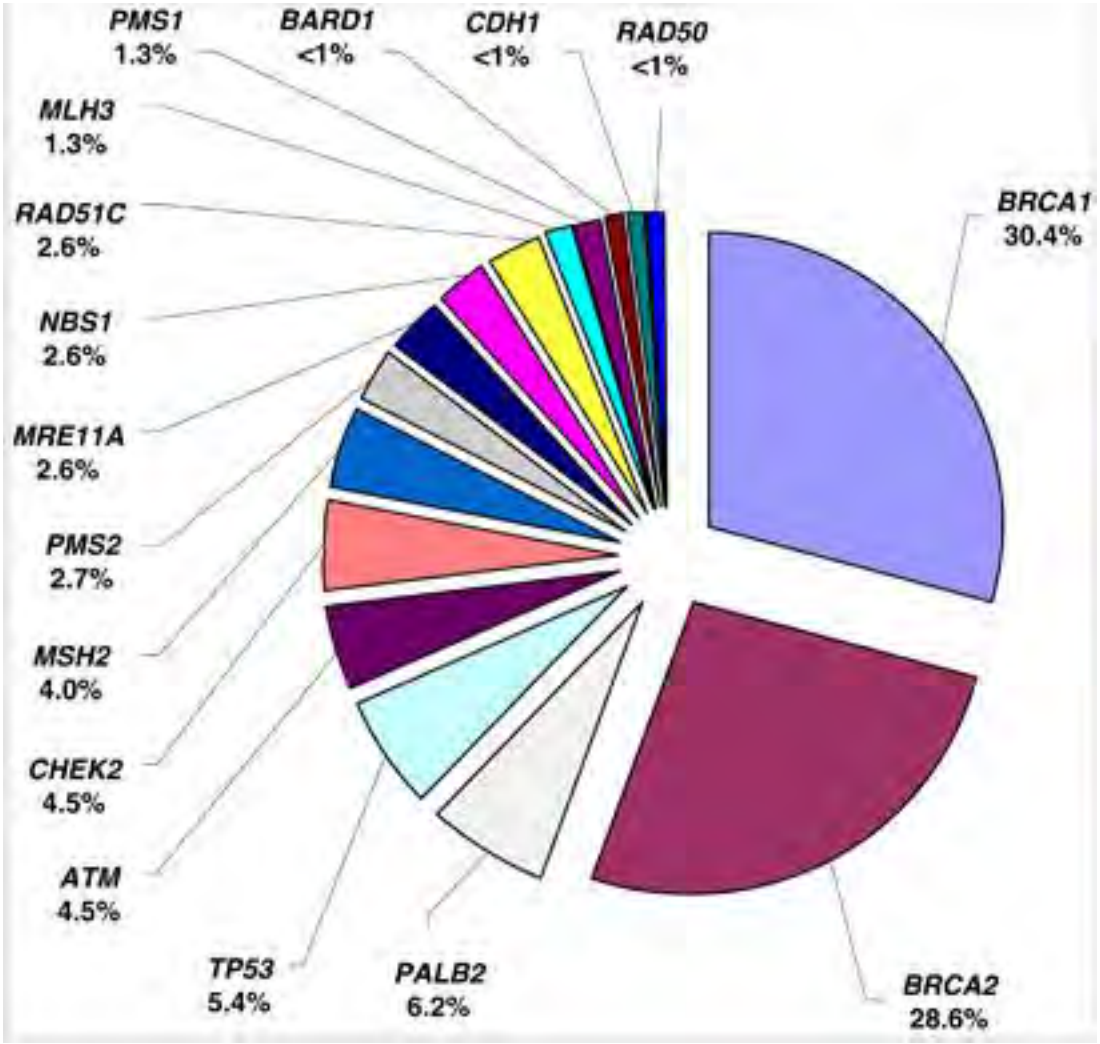
Homologous recombination (HR) DNA repair defects in breast cancer



Roy R, et al. Nat Rev Cancer. 2011 Dec 23;12(1):68-78

- **HR deficiency characterizes breast cancers in *BRCA1/2* mutation carriers**
  - **Due to loss of heterozygosity at *BRCA1* or *BRCA2***
- **Beyond *BRCA1/2*, there are other HR pathway genes implicated in hereditary breast cancer**
  - ***PALB2, ATM, CHEK2,* others**

HBOC: *BRCA1, BRCA2* and beyond



Castera L, et al. European journal of human genetics. 2014;22(11):1305 -1313

Case Scenario: *BRCA2*+ Breast Cancer

- **A 42 year-old woman presents with a clinical T2N1M0 Stage IIB high grade invasive ductal carcinoma**
  - **ER 90%, PR 20%, HER2 negative, Ki-67 50%**
- **Multiplex panel testing reveals a deleterious *BRCA2* mutation**
- **Treated with neoadjuvant AC-T chemotherapy, followed by oophorectomy and adjuvant aromatase inhibitor**
- **22 months later, she relapses with bone, nodal and lung metastases**
  - **Started on fulvestrant and palbociclib with progression at 8 months**
  - **Started on tamoxifen with rapid progression after 2 months**
  - **Recommended for clinical trial versus standard chemotherapy (capecitabine/taxane/carboplatin)**

Anti-tumor activity of PM01183 (lurbinectedin) in *BRCA 1/2*-associated metastatic breast cancer patients: Results of a single-agent phase II trial

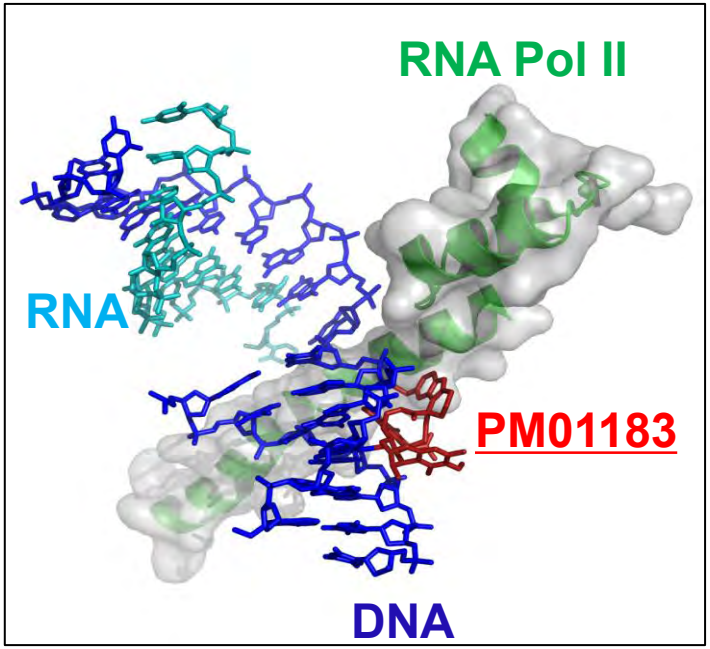
J. Balmaña[1], C. Cruz[1], B. Arun[2], M. Telli[3], J. Garber[4], S. Domchek[5], C. Fernandez[6], C. Kahatt[6], S. Szyldergemajn[6], A. Soto Matos[6], A. Perez de la Haza[6], J. Pérez Fidalgo[7], A. Lluch[7], S. Antolin[8], N. Tung[9], L. Vahdat[10], R. Lopez[11], S. Isakoff[12]

[1]Hospital Vall d'Hebron and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [2]MD Anderson Cancer Center, Houston, USA; [3]Stanford University Medical Center, Stanford, USA; [4]Dana Farber Cancer Institute, Boston, USA; [5]University of Pennsylvania, Philadelphia, USA; [6]Pharma Mar, S.A., Colmenar Viejo, Madrid, Spain;[7]Hospital Clínico de Valencia, Valencia, Spain; [8]Complejo Universitario Hospitalario La Coruña, La Coruña, Spain; [9]Beth Israel Deaconess Medical Center, Boston, USA; [10]Weill Cornell Medicine, New York, USA; [11]Complejo Hospitalario Universitario Santiago de Compostela, Santiago de Compostela, Spain; [12]Massachusetts General Hospital, Boston, USA.

Lurbinectedin

Lurbinectedin (PM01183) is a trabectedin analog with an unique mechanism of action *(1)*:

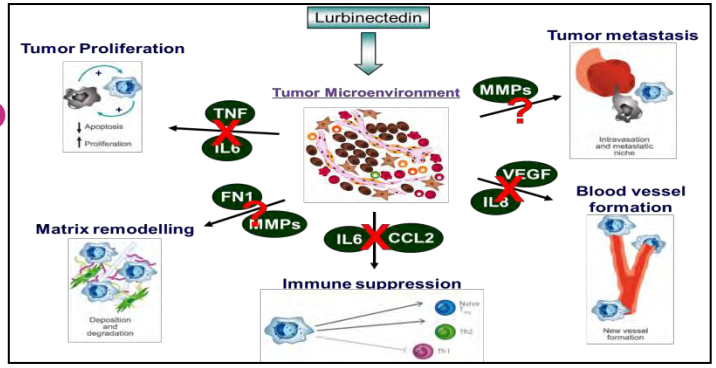
- ***Inhibits active transcription*** **(RNA Pol II blockade and degradation)**
- **Binds to CG-rich motifs**
- **Generates double strand DNA breaks**
- **Affects tumor microenvironment**



Deficient homologous recombination system favors PM01183-induced apoptosis *(2)*

Antitumor activity observed in patients resistant to platinum compounds *(3)*

Two Phase III trials are currently ongoing, one as a single agent in platinum resistant ovarian cancer, and one in combination with doxorubicin in 2nd line SCLC

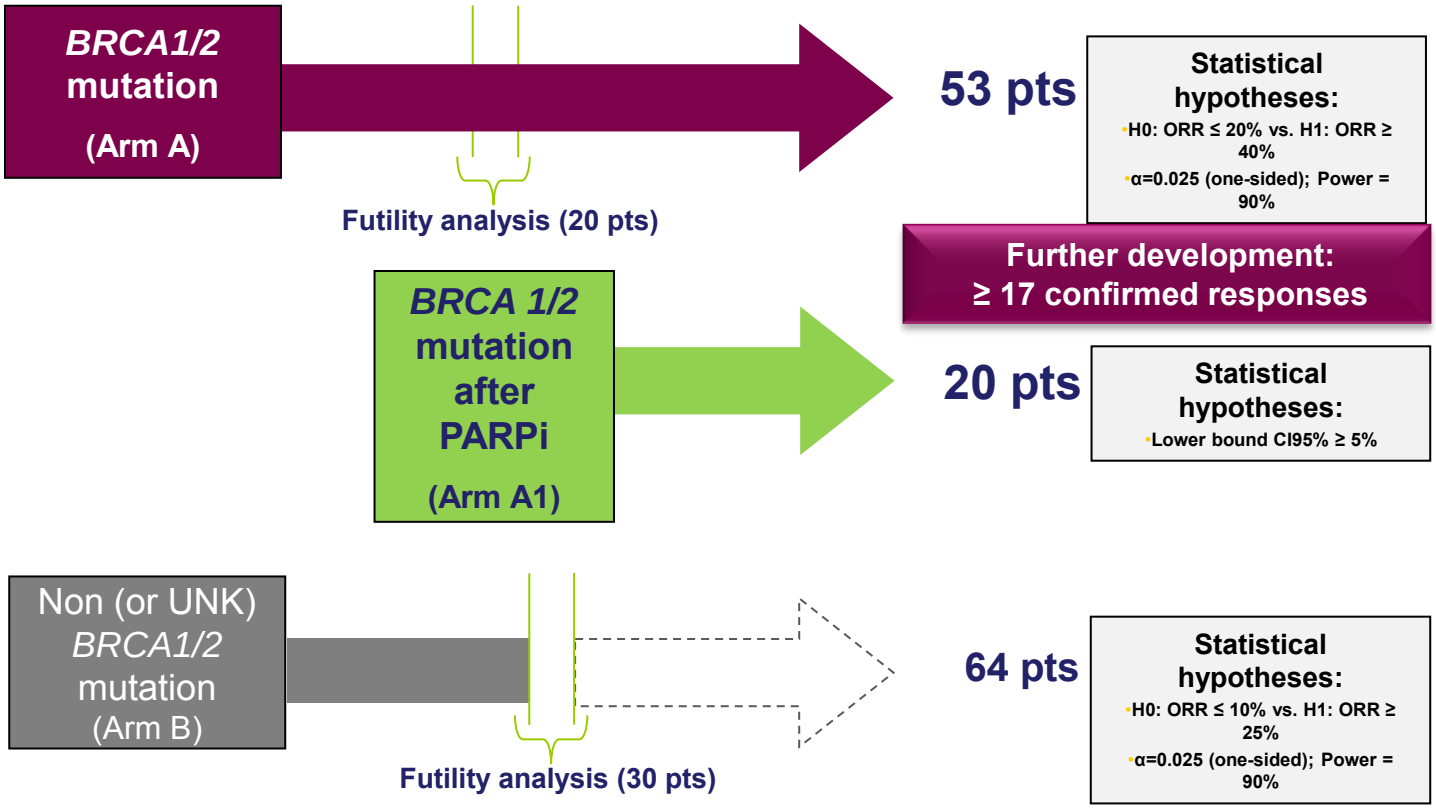


1. Santamaría G. et al, Mol Cancer Ther, 2016
2. Allavena P. et al, Proc AACR 2016
3. Poveda A. et al. ASCO 2014, oral presentation

Overview trial design and current status

MBC

- Ductal/Lobular
- Up to 3 prior advanced chemotherapy regimens
- PS: 0-1
- Asymptomatic, non steroid requiring CNS metastasis
- Measurable disease by RECIST v.1.1



Balmaña, SABCS 2014, poster P3-13-01
Cruz, ESMO 2016, abstract 1520O

Study Endpoints

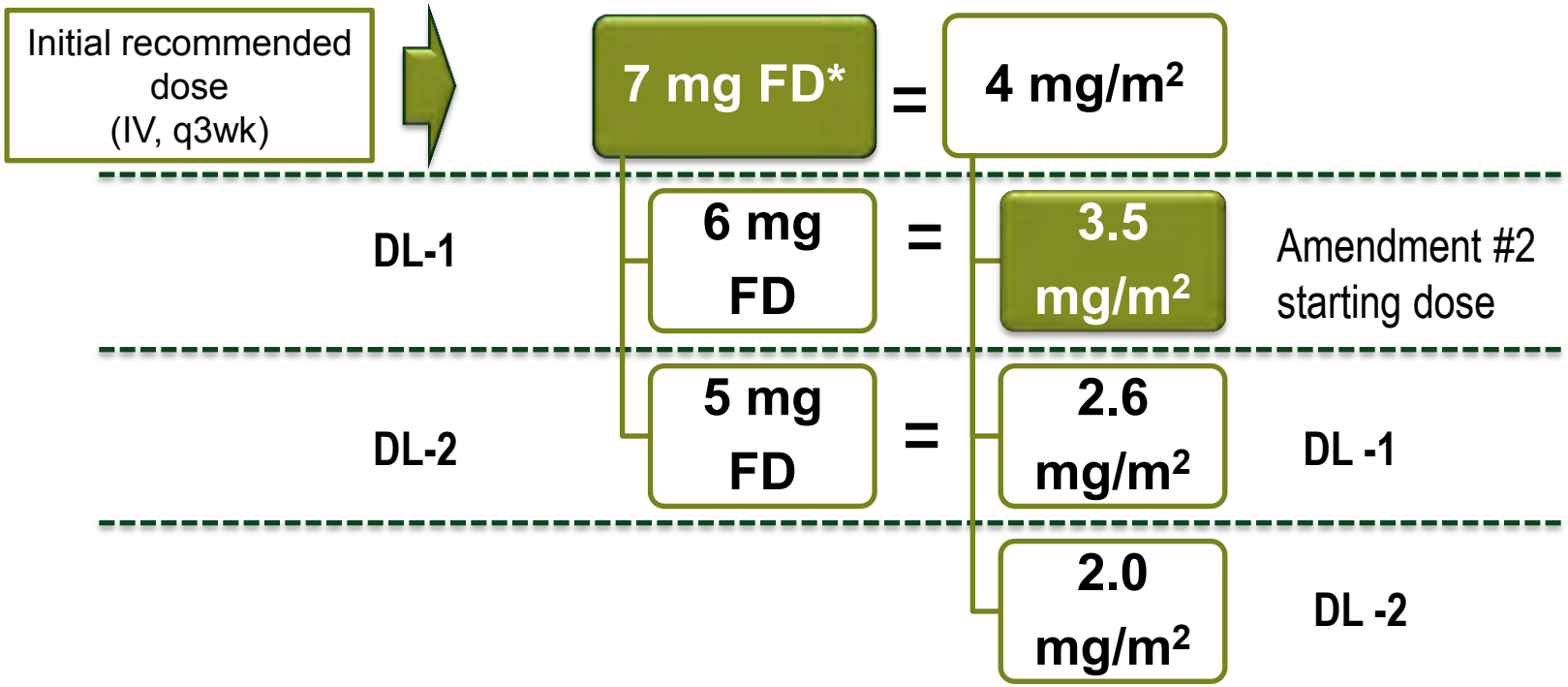
Primary endpoint:

- Overall confirmed response rate (ORR)

Secondary endpoints :

- Duration of response
- Clinical benefit (response or stable disease > 3 months)
- Exploratory ORR in specific MBC subpopulations
- PFS and one year-OS
- Safety profile
- Pharmacokinetics, pharmacodynamics and pharmacogenomics analysis

PM1183-B-003-11 Dosing



* FD: Fixed Dose

Patient Characteristics

		Patients (n: 54) (100%)	*BRCA1* (n: 31) (57%)	*BRCA2* (n: 23) (43%)
Age	Median (range)	**43 (29-73)**	40 (29-67)	55 (34-73)
PS	0/1	**31 (57%) / 23 (43%)**	15(48%) / 16(52%)	16(70%) / 7(30%)
Receptor Status	◆ Triple neg ◆ HR+ / HER2 - ◆ HER2+	**33 (61%)** **19 (35%)** **2 (4%)**	26 (84%) 5 (16%) -	7 (30%) **14 (61%)** 2 (9%)
Sites of Disease	-Liver -CNS	**28 (52%)** **3 (6%)**	12 (39%) 2 (7%)	**16 (70%)** 1 (4%)
	◆ ≥ 3 sites involved	**27 (50%)**	13 (42%)	**14 (61%)**
Prior Treatments	◆ Anthracyclines ◆ Taxanes ◆ Capecitabine ◆ Platinum ◆ PARP inhibitor	**43 (80%)** **47 (87%)** **18 (33%)** **27 (50%)** **9 (17%)**	28 (90%) 29 (94%) 6 (19%) 21 (67%) 4 (13%)	15 (65%) 18 (78%) 12 (52%) 6 (26%) 5 (22%)
	Advanced CT lines Median (range)	**1 (0-3)**	1 (0-3)	1 (0-3)

Safety - Most common related AEs

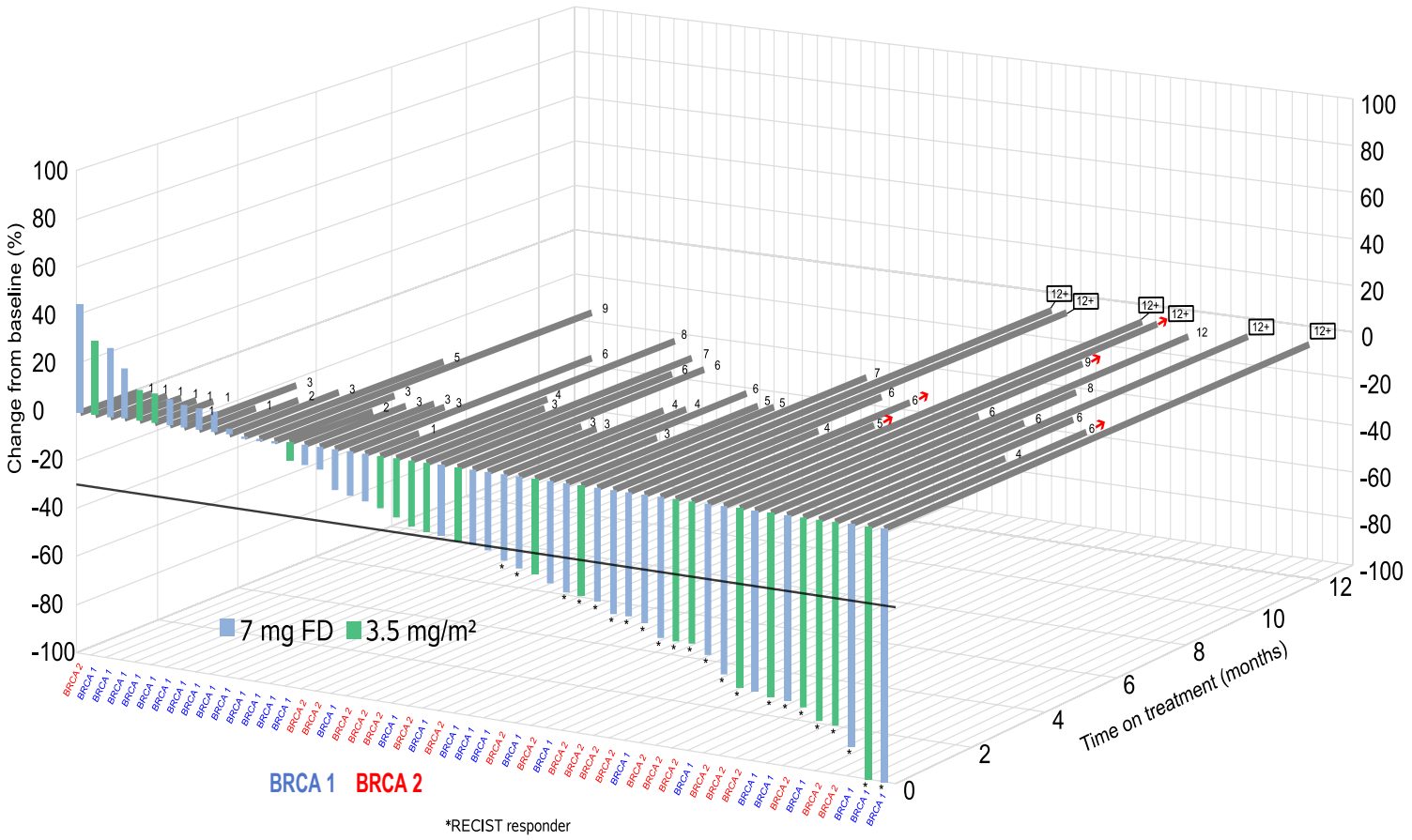
	7 mg FD (n: 35)			3.5 mg/m^2 (n: 19)		
	Grade 1-4	Grade 3	Grade 4	Grade 1-4	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any Related AE	**35 (100)**	**11 (31)**	**19 (54)**	**19 (100)**	**8 (42)**	**6 (32)**
Anemia	33 (94)	7 (20)	.	17 (90)	.	.
Fatigue	32 (91)	6 (17)	.	14 (74)	4 (21)	.
Neutrophil count decreased	31 (89)	**7 (20)**	**18 (51)**	13 (68)	**9 (47)**	**1 (5)**
Platelet count decreased	26 (74)	**1 (3)**	**8 (23)**	8 (42)	**1 (5)**	**.**
Transaminases increased	31 (89)	8 (23)	1 (3)	18 (95)	2 (11)	.
Nausea	28 (80)	3 (9)	.	15 (79)	1 (5)	.
Vomiting	17 (49)	2 (6)	.	7 (37)	1 (5)	.
Febrile neutropenia	10 (29)	**7 (20)**	**3 (9)**	1 (5)	**1 (5)**	**.**
Anorexia	8 (23)	1 (3)	.	2 (11)	.	.

Clinical efficacy: ORR

	PM01183
Treatment (n=54)	**7 mg FD (n=35) or 3.5 mg/m^2 (n=19) 1-h i.v. infusion, q3wk**
Best Overall Response (RECIST)	(n evaluable: 54 pts)
ORR (Confirmed Responses) (95%CI)	**22 (40.7%)** (27.6 - 55.0)
◆ CR ◆ PR ◆ SD* ◆ PD	**1** (1.9%) **21** (38.9%) 23* (42.6%) 9 (16.7%)
Median duration of response (95% CI)	6.7 months (3.0 -13.0)
Disease control rate (CR+PR+SD) n (%)	45 (83%)
Clinical benefit (CR+PR+SD ≥ 3 mo) n (%)	**33 (61%)**

* including 4 patients with unconfirmed PR

Waterfall - Sum of target lesions and time on treatment



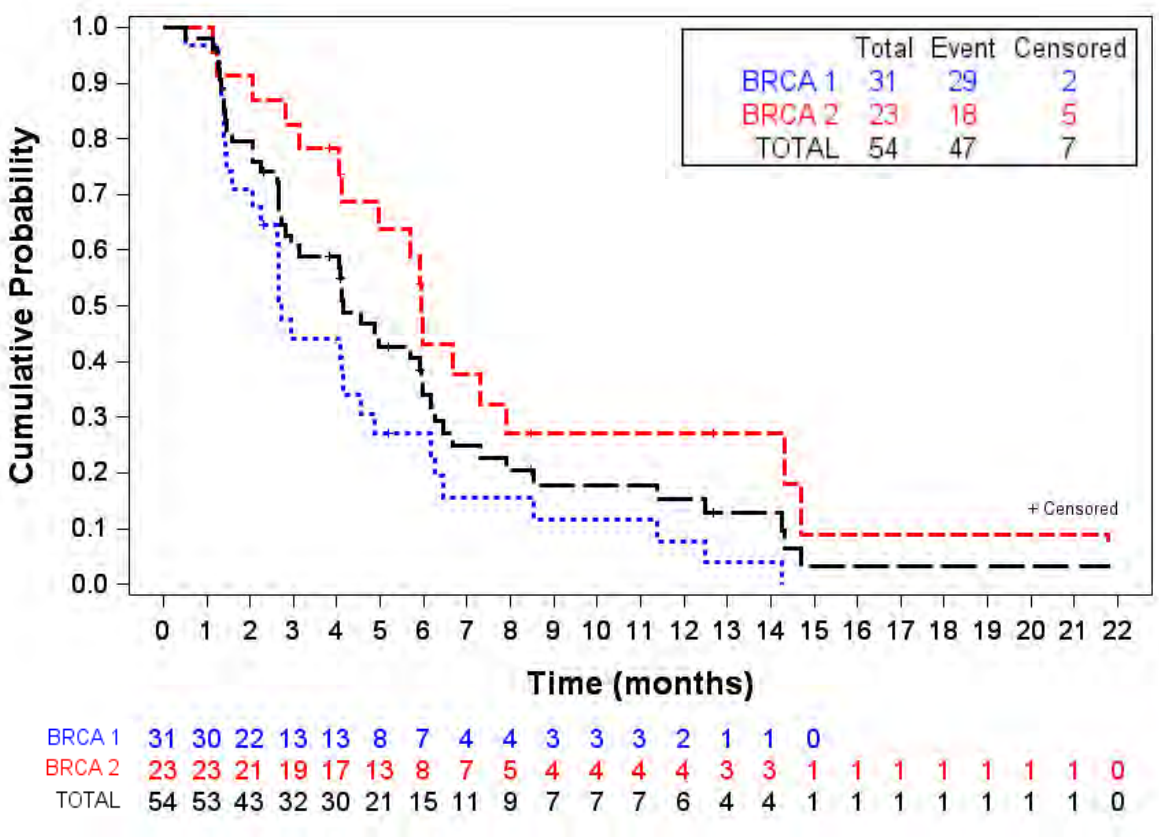
- 5 out of 22 responding patients had ongoing responses (→) at the time of data cutoff
- 7 patients had durable responses (> 10 months)
- Median number of cycles was 6 (1-24)

Best ORR in specific subpopulations

	Prior Platinum		BRCA		Hormone Status		Prior advanced CT lines	
	No (n: 27)	Yes (n: 27)	1 (n: 31)	2 (n: 23)	Triple Negative (n: 33)	HR+ (n: 21*)	0-1 (n: 31)	2-3 (n: 23)
ORR (95% CI)	**56%** (35.3-74.5)	**26%** (11.1-46.3)	**26%** (11.9-44.6)	**61%** **(38.5-80.3)**	**36%** (20.4-54.9)	**48%** (25.7-70.2)	**52%** (33.1-69.9)	**26%** (10.2-48.4)
Duration of Response (95% CI)	**10.2 m** (3.0-13.5)	**5.9 m** (2.8-12.8)	**6.6 m** (2.8-12.8)	**6.7 m** **(3.4-13.5)**	**7.7 m** (2.8-12.8)	**6.7 m** (2.8-13.4)	**8.5 m** (3.0-12.8)	**3.4 m** (2.8-20.5)
Disease control rate	25 (93%)	19 (70%)	23 (74%)	**22 (96%)**	26 (79%)	19 (90%)	27 (87%)	18 (78%)
Clinical benefit (CR+PR+SD ≥ 3 mo)	19 (70%)	14 (52%)	14 (45%)	**19 (83%)**	29 (88%)	14 (67%)	21 (68%)	12 (52%)

*** Including 2 patients also HER-2 +**

Progression-Free Survival

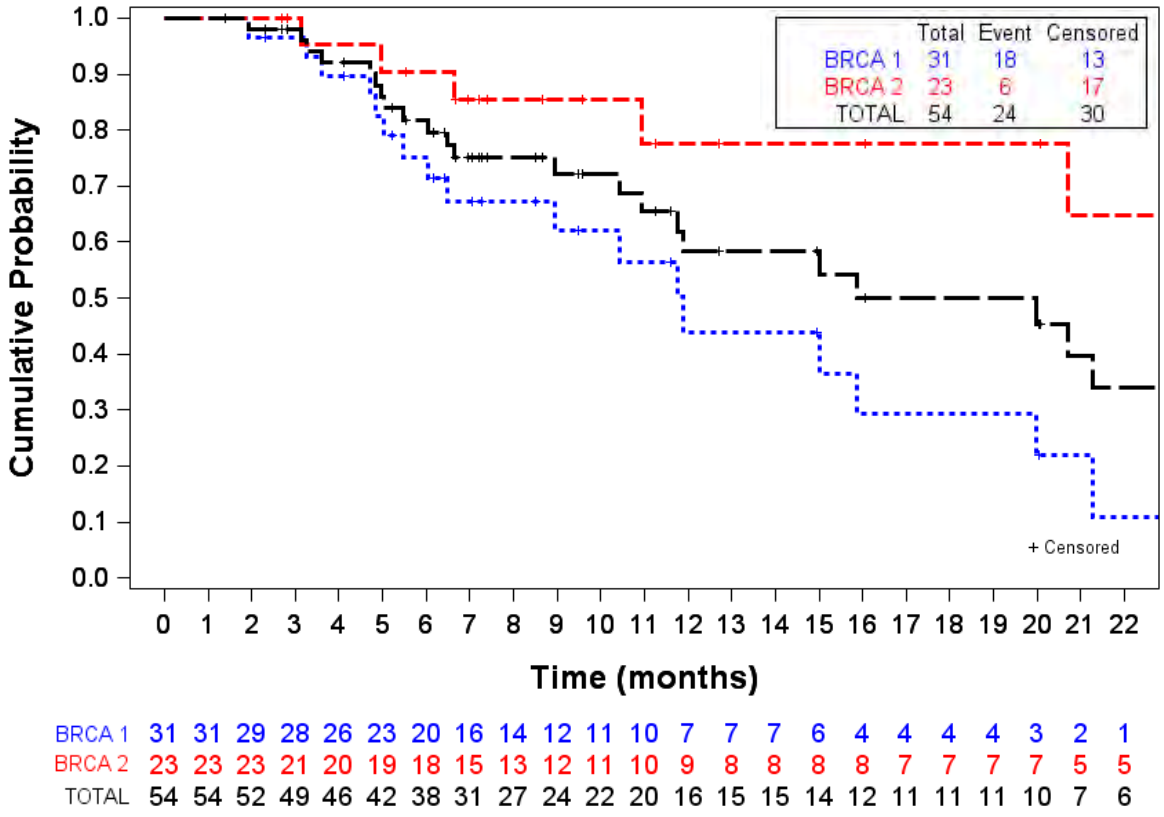


Median PFS BRCA 1/2:
4.1 months 95% CI (2.8-5.9)

BRCA 1: 2.7 95% CI (2.1-4.6)
BRCA 2: 5.9 95% CI (4.1-7.9)

p-value=0.0064

Overall Survival



Median OS BRCA 1/2:
20.0 months 95% CI (10.9-31.8)

BRCA 1: 11.8 95% CI (6.5-20.0)
BRCA 2: 31.8 95% CI (20.7-38.9)

p-value=0.0038

Take Away Thoughts

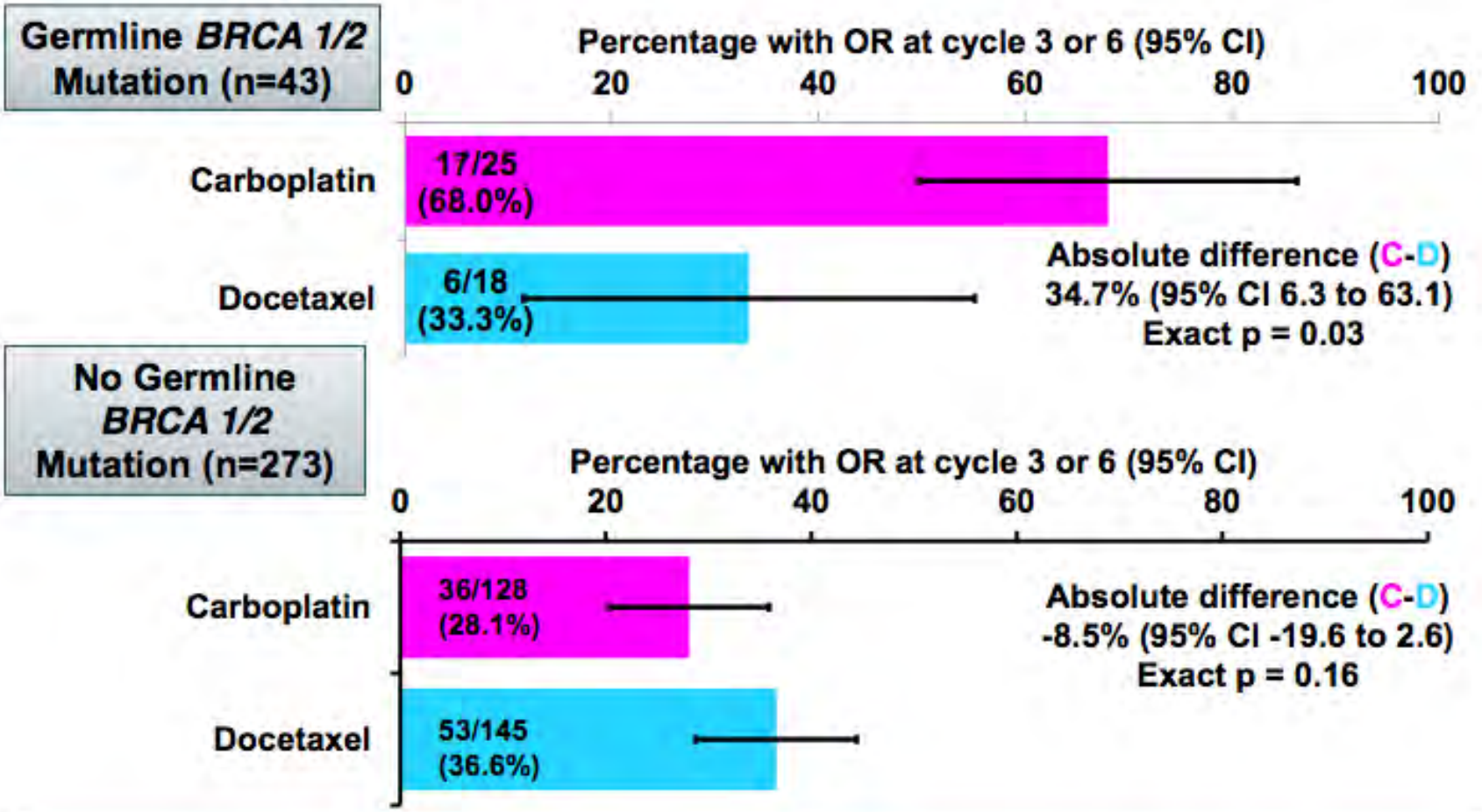
- **Lurbinectedin is active and well tolerated in patients with *BRCA1/2* mutated MBC**
  - **ORR: 40.7%**
  - **Significant activity observed in *BRCA2* patients**
- **Convenient 1 hour infusion every 3 weeks**
  - **Absence of alopecia, neuropathy**
  - **Myelosuppression manageable with growth factors**
- **Activity in platinum resistance important**
  - **PARP inhibitors have absent - minimal response rates in platinum resistance**

Current *BRCA2* Landscape

- **Endocrine therapy +/- CDK inhibitor initial therapy for relapsed ER+/HER2- MBC**
  - **My experience is that *BRCA2* mutated patients develop endocrine resistance more rapidly than sporadic disease though data on this is lacking**
- **Given rarity of HER2 positivity, HER2 treatment algorithms not generally applicable**
- **Cytotoxic chemotherapy:**
  - **TNT trial showed higher ORR with carboplatin vs. docetaxel in *BRCA1/2* mutated mTNBC**
  - **Limited uptake currently in ER+ disease**
- **PARP inhibitor approval expected this year**
  - **OlympiaD trial reached PFS endpoint per press release**

TNT Trial: Carboplatin vs. Docetaxel in Frontline mTNBC

Objective response – *BRCA 1/2* status



Olaparib in advanced *BRCA* mutant breast cancer: *Initial proof-of-concept*

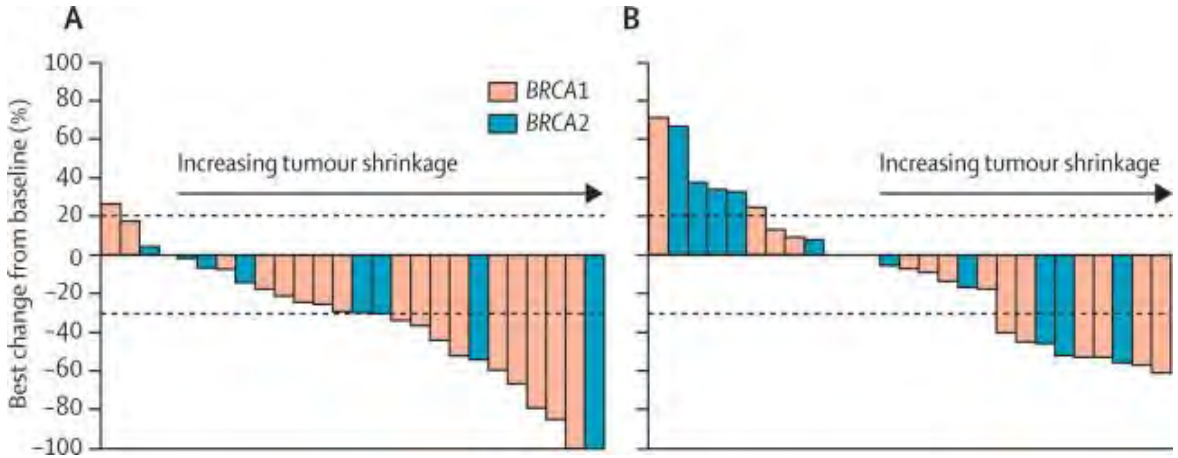
Olaparib: Superior activity at higher dose

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI).

400 mg po BID

100 mg po BID



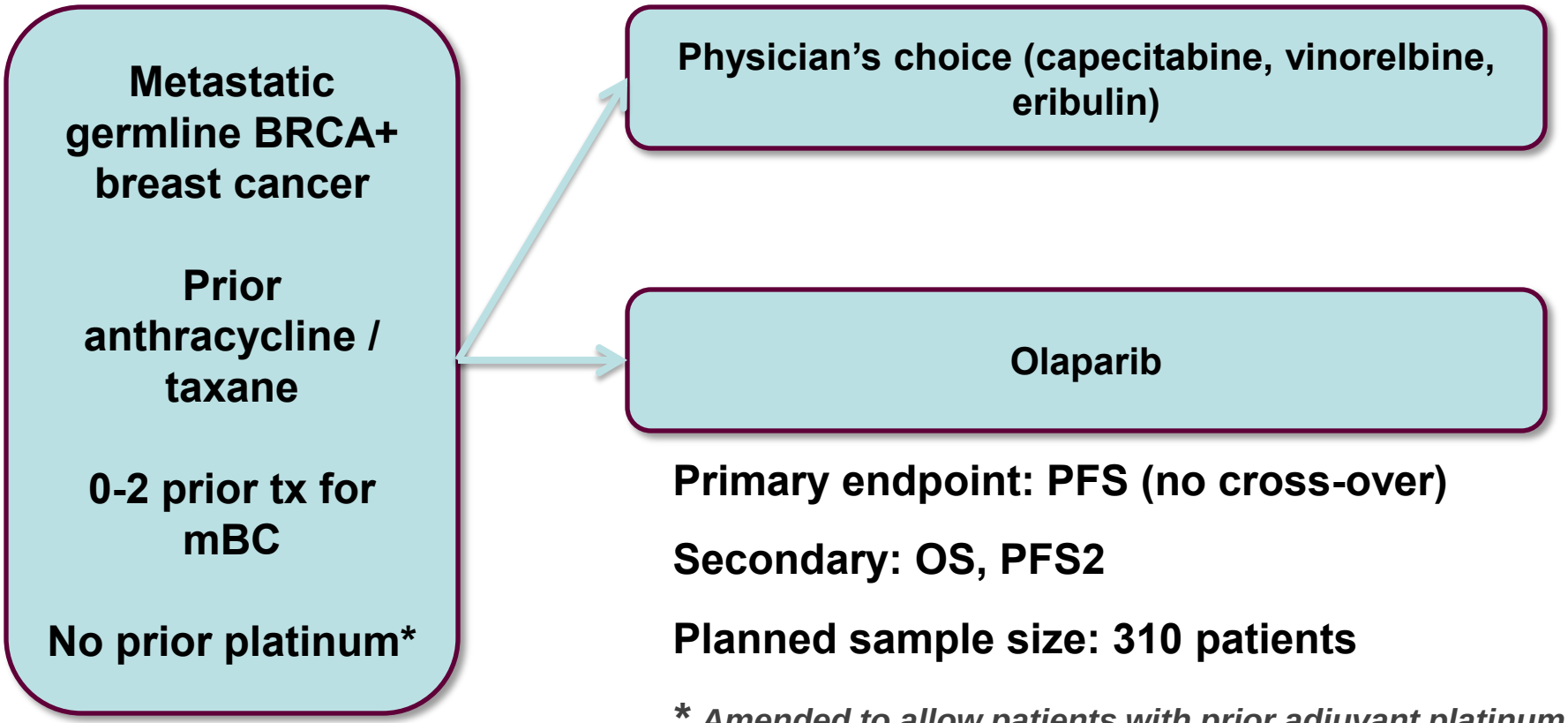
Tutt A. Lancet. Published online July 6, 2010

Responses in *BRCA 1/2* Carriers irrespective of subtype

	Olaparib 400 mg twice daily (n=27)			
	BRCA1 (n=18)	*BRCA2* (n=9)	Triple negative (n=13)	Non-triple negative (n=14)
Objective response	9 (50%)	2 (22%)	7 (54%)	4 (29%)
Complete response	1 (6%)	0	0	0
Partial response	8 (44%)	2 (22%)	7 (54%)	4 (29%)
Stable disease	7 (39%)	5 (56%)	4 (31%)	8 (57%)
Progressive disease	2 (11%)	2 (22%)	2 (15%)	2 (14%)
	Olaparib 100 mg twice daily (n=27)			
	BRCA1 (n=16)	*BRCA2* (n=11)	Triple negative (n=16)	Non-triple negative (n=11)
Objective response	3 (19%)	3 (27%)	4 (25%)	2 (18%)
Complete response	0	0	0	0
Partial response	3 (19%)	3 (27%)	4 (25%)	2 (18%)
Stable disease	9 (56%)	3 (27%)	7 (44%)	4 (36%)
Progressive disease	4 (25%)	5 (45%)	5 (31%)	5 (45%)

Tutt A. Lancet. Published online July 6, 2010

Phase III OLympiAD Trial (OLaparib in Advanced Disease)



Primary endpoint: PFS (no cross-over)

Secondary: OS, PFS2

Planned sample size: 310 patients

* *Amended to allow patients with prior adjuvant platinum or no progression on platinum in advanced setting*

Concluding Remarks

- **Lurbinectedin has significant activity in *BRCA1/2* mutant breast cancer**
- **ORRs higher in *BRCA2* compared with *BRCA1***
- **Provides rationale for development in *BRCA2* mutant MBC**
  - **Unmet clinical need exists in this space**
- **Given similarities with *BRCA2*+ MBC, potential role in *PALB2*+ MBC, others**

Concluding Remarks

- **Activity of lurbinectedin in platinum resistant disease of significant clinical interest**
  - Cross-resistance of platinum and PARPi will likely be clinically very significant
  - Evaluation of lurbinectedin in PARPi resistance ongoing

- **New clinical algorithms for specific treatment of hereditary breast cancers increasingly expected**
  - Development of additional active therapies beyond platinum chemotherapy and PARP inhibitors important
  - Optimal sequencing of these agents is a high priority

Importance of Advocacy

- **Facing Our Risk of Cancer Empowered (FORCE) is a leading national nonprofit dedicated to hereditary cancer**
- **Partnership with FORCE and other groups critical to disseminate information about active clinical trial and therapeutic options**
- **Credited with greatly increased awareness of hereditary breast cancer**

FORCE
Facing Our Risk of Cancer
EMPOWERED
www.facingourrisk.org

Thank you

FORCE

Facing Our Risk of Cancer Empowered (FORCE)

Mission Statement

Improve the Lives
of Individuals & Families
Affected
by Hereditary
Breast, Ovarian
& Related Cancers
(HBOC)

FORCE
Facing Our Risk of Cancer Empowered

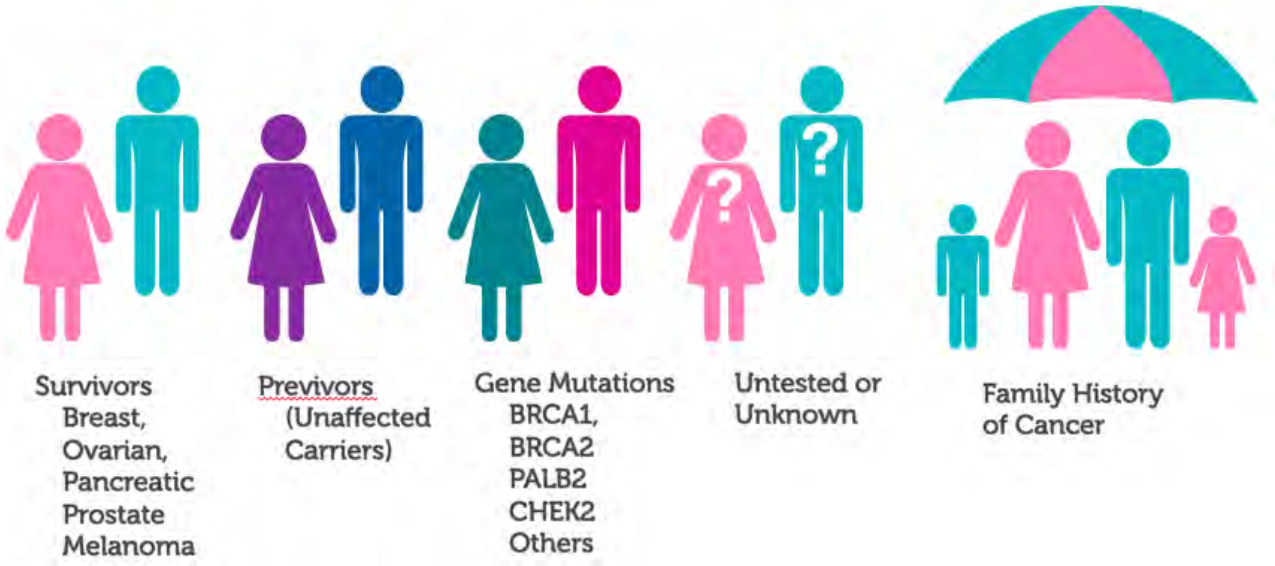
FORCE History and Experience

- Established in 1999 as the first national nonprofit organization for people affected by hereditary cancers
- Leader in legislative, regulatory and research advocacy on behalf of the hereditary cancer community
- Driving and promoting critical hereditary cancer research
- Comprehensive expert-reviewed information on hereditary cancers

FORCE
Facing Our Risk of Cancer Empowered

Who We Serve

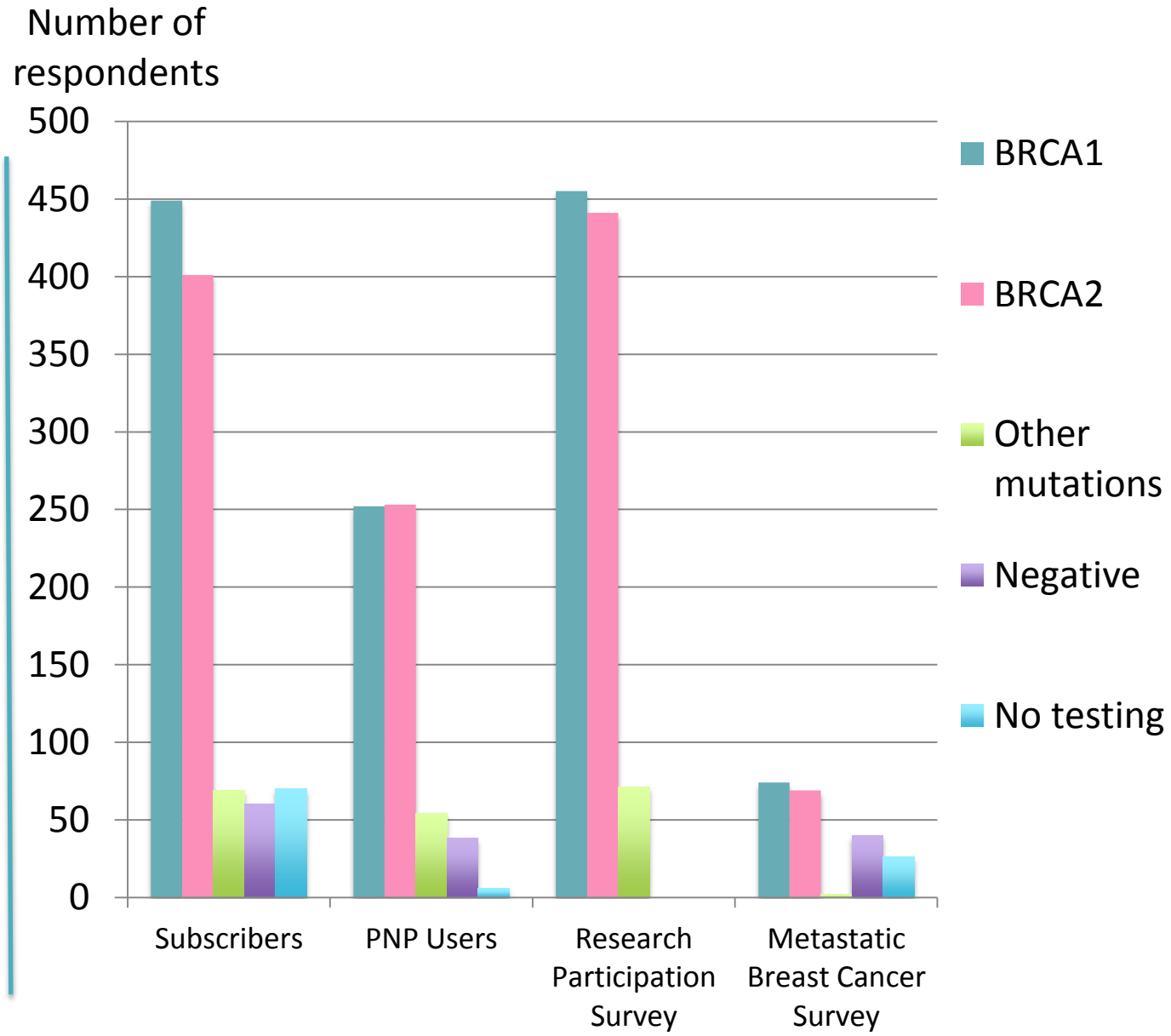
- FORCE is the only national nonprofit organization serving all people affected by hereditary breast, ovarian and related cancers.
- Our community includes people with a mutation in BRCA 1, BRCA 2, and newly-identified mutations like PALB2, ATM, and CHEK2.
- Our community includes cancer survivors and previvors.



FORCE
Facing Our Risk of Cancer Empowered

Who We Serve

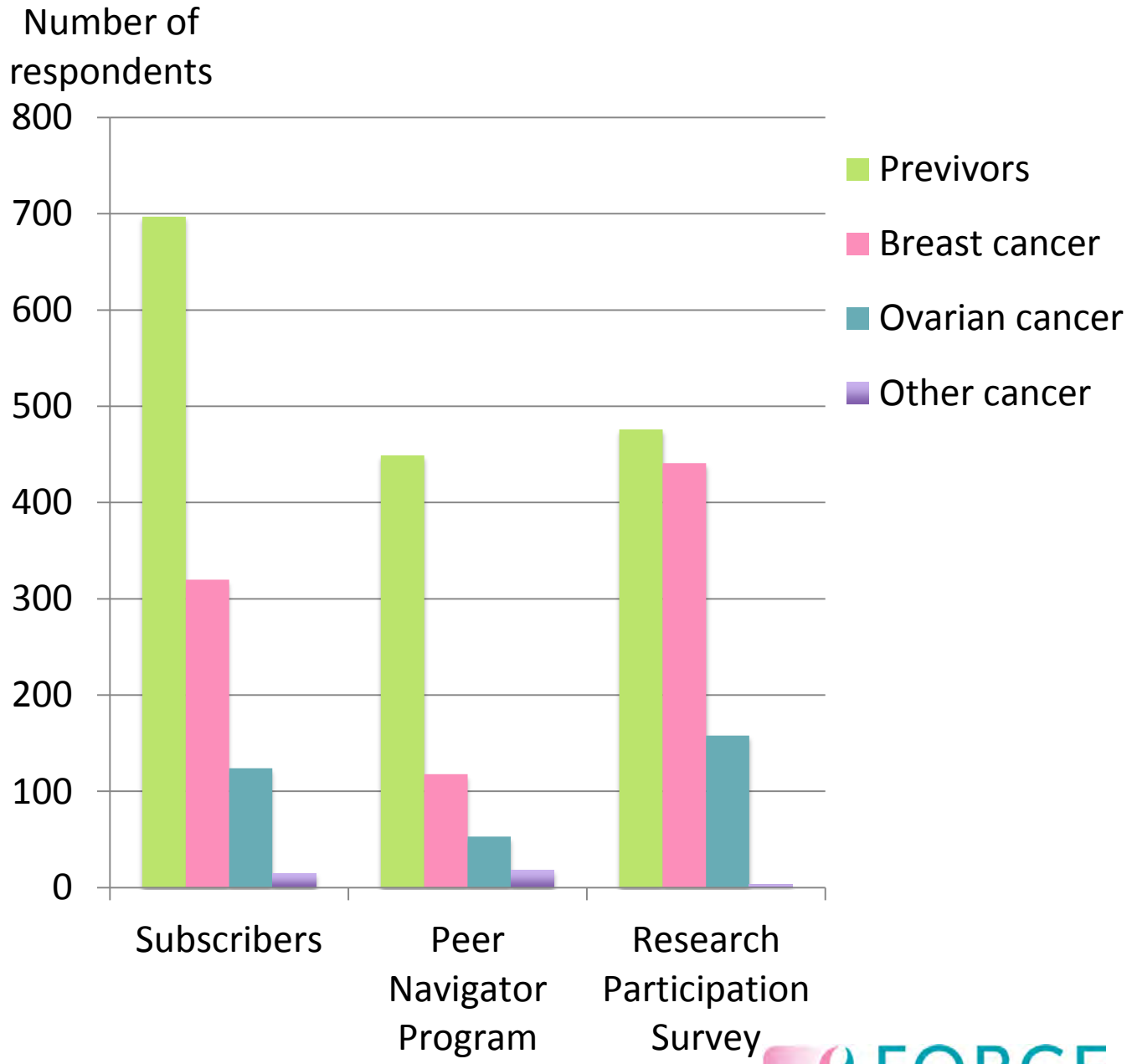
- Majority of members have BRCA1 or BRCA2 mutation
- Almost equal numbers of people with BRCA1 and BRCA2 mutations



FORCE
Facing Our Risk of Cancer Empowered

Who We Serve

- Majority of members are high risk
- Of members with cancer, majority have breast cancer



FORCE
Facing Our Risk of Cancer Empowered

FORCE Annual Reach

- Touching the lives of 440,000 people annually
- 341 trained volunteers
- 50 Outreach Groups in cities throughout the US held 263 in-person support meetings
- 28,000 mailing list subscribers and 30,000 Facebook likes
- Only national conference created *by* and *for* the hereditary cancer community

FORCE
Facing Our Risk of Cancer Empowered

Credible and Evidence Based

- Advisory Board Consists of World Experts in Hereditary Cancer, Genetics, Treatment, Prevention, detection & Policy
- Research Collaborations with Top Cancer Center & Academic Institutions.

USF UNIVERSITY OF SOUTH FLORIDA

UNIVERSITY OF PENNSYLVANIA Abramson Cancer Center

STANFORD CANCER INSTITUTE
Stanford University Medical Center
A NATIONAL CANCER INSTITUTE-DESIGNATED CANCER CENTER

City of Hope

MOFFITT CANCER CENTER

THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
Making Cancer History®

FORCE
Facing Our Risk of Cancer Empowered

Credible and Evidence Based

- Advisory Board Consists of World Experts in Hereditary Cancer, Genetics, Treatment, Prevention, detection & Policy
- Research Collaborations with Top Cancer Center & Academic Institutions.

DUKE CANCER INSTITUTE
A National Cancer Institute-designated Comprehensive Cancer Center

MEMORIAL SLOAN-KETTERING CANCER CENTER · ESTABLISHED 1884 ·

Georgetown | Lombardi
COMPREHENSIVE CANCER CENTER

CEDARS-SINAI

FRED HUTCHINSON CANCER RESEARCH CENTER
A LIFE OF SCIENCE

THE OHIO STATE UNIVERSITY The James

DANA-FARBER CANCER INSTITUTE

Advocacy Partnerships

- Partnerships with other organizations who share our goals

Advocacy Partnerships

- Partnerships with other organizations who share our goals

Pillars and Programs

Support

Education

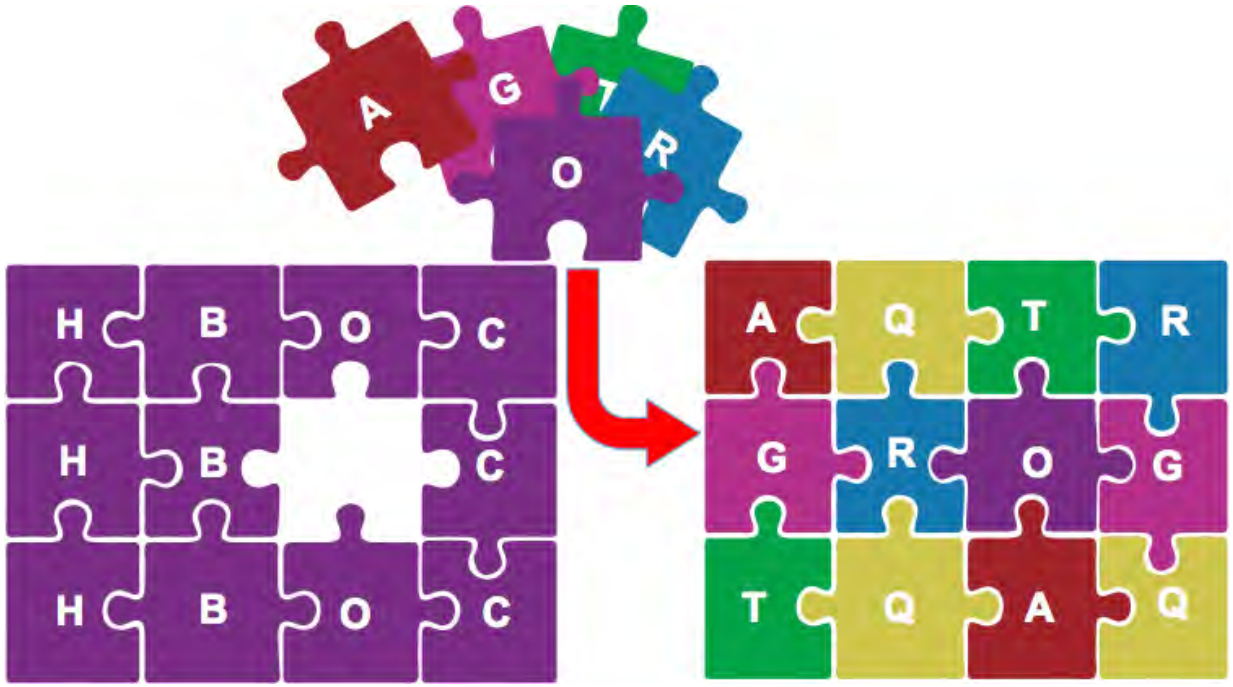
Advocacy

Research

FORCE
Facing Our Risk of Cancer Empowered

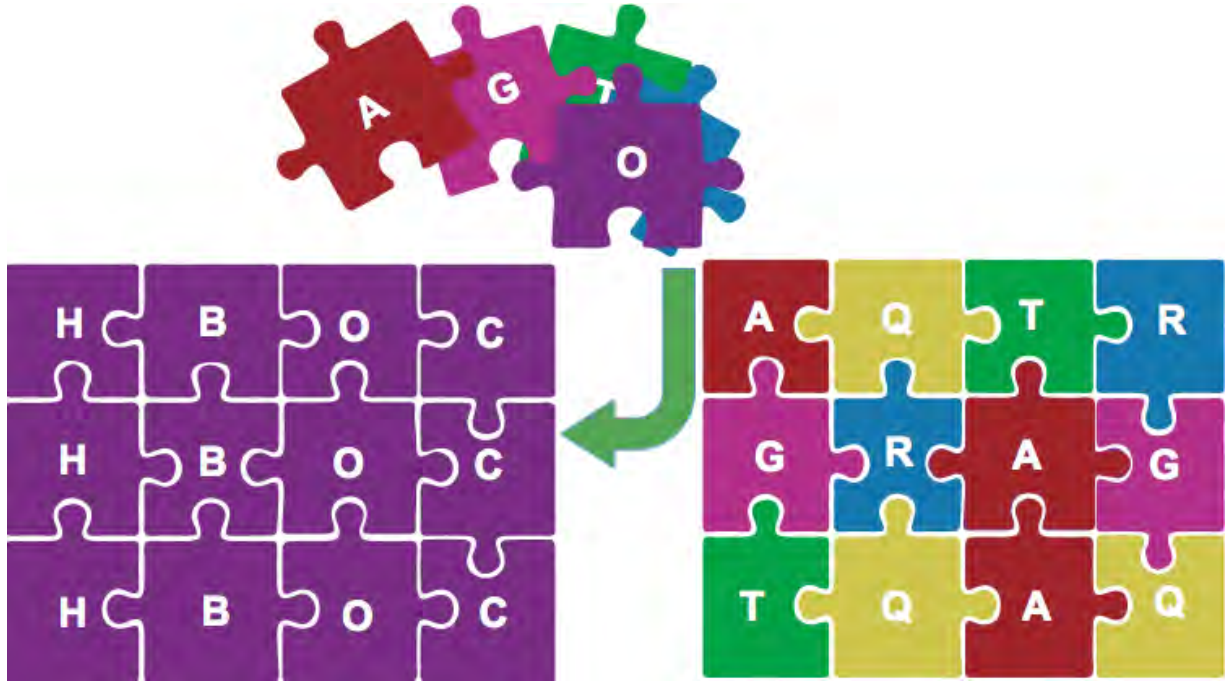
Challenges: HBOC Clinical Trials

- Studies compete for patients
- Finding and meeting eligibility criteria for research studies



Challenges: HBOC Clinical Trials

- Studies compete for patients
- Finding and meeting eligibility criteria for research studies



Challenges: HBOC Clinical Trials

- Patients rely on doctors to inform them. Doctors are unaware of studies and/or don't refer patients

"I wanted to start a clinical trial but my doctor just started me back on chemo last week."

"I just learned about a clinical trial but my doctor says we have treatment options and research is a last resort."

"My friend's doctor told her clinical trials were only for patients with no other options and put her on ineffectual chemotherapies. When her breast cancer recurred to her brain, she was ready for a clinical trial, but too sick to qualify. She died, leaving 2 young children motherless"

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FORCE Solution: Patient-Centered Approach

- Bring a real world perspective
- Understand patient barriers to research participation
- Articulate research priorities that improve health outcomes
- Identify the gaps in knowledge
- Trusted source of information

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Train Consumers to Participate in Research Process

- FORCE Research Advocacy Training (FRAT) Program
- Web-based training courses
- Consumers learn:
  - Research process
  - Research culture and language

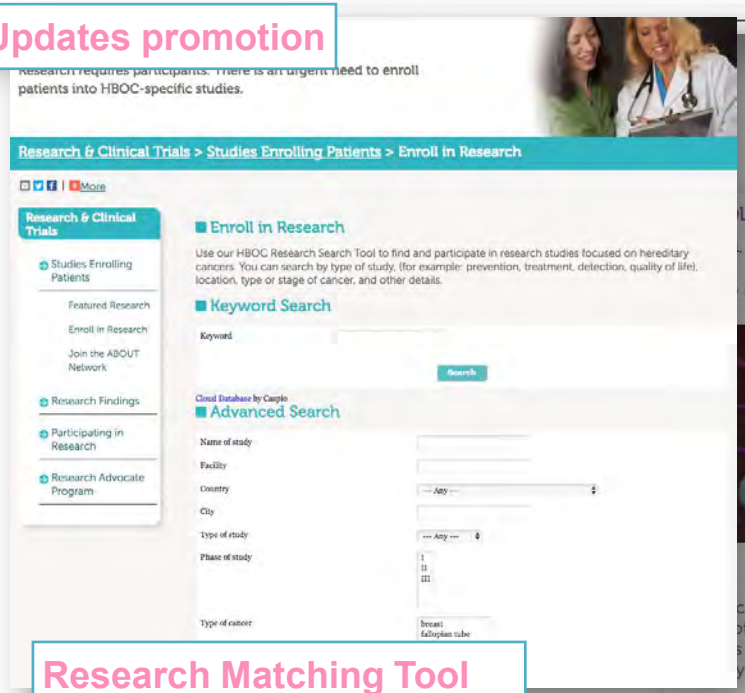
Promote Studies Directly to Patients

Study for Latina Women With a BRCA 1 or BRCA 2 Mutation

Are you a Latina with a BRCA1/2 mutation? If so, you can participate in a research study led by Georgetown University to learn about your thoughts on Risk Reduction Surgeries. Participants will be asked to participate in a 30-minute phone interview in Spanish or English (your preference) and will receive a $25 Target gift card. Contact Adriana Serrano at: 202-687-0806 or by email at: Adriana.Serrano@georgetown.edu

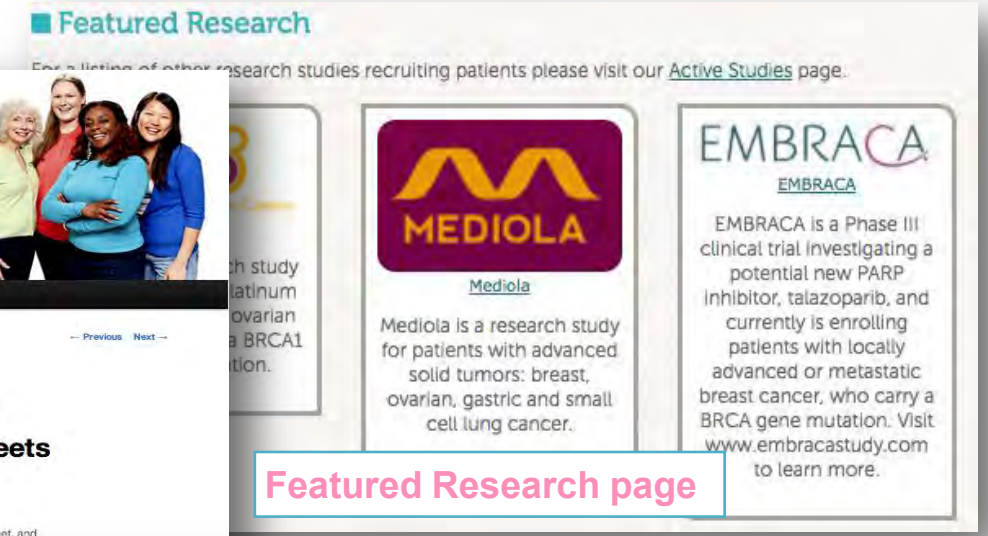
View Study Flier

Monthly Updates promotion



Research Matching Tool

Blog posts



Featured Research page

Facebook posts

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Build a Patient-Powered Research Network

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Build a Patient-Powered Research Network

Address Advocacy Issues that Impact Access

Advocacy

FORCE advocates for families facing hereditary breast and ovarian cancer in areas such as access to care, research funding, insurance, and privacy.

Advocacy > Current Issues

More

Newsflash

2/22/17
FORCE participated in NCI's "Approaches to Blue Ribbon Panel Recommendations: The Case of Lynch Syndrome" Workshop. More details...

2/21/17
FORCE submitted comments in support of Medicare coverage of comprehensive genetic profiling for patients with advanced ovarian cancer. Read more...

1/19/17
FDA launches Oncology Center of Excellence as part of the National Cancer Moonshot initiative.

12/21/16
The FDA approved AeroForm, a new tissue expander for women undergoing breast reconstruction. Learn more...

Current Issues

Hot Topic

Hereditary Cancer Health Care Report

President's Executive Order Provides Broad Directives That Could Weaken ACA

The day after his inauguration, one of Trump's first official actions as President was to sign an executive order to "minimize the unwarranted economic and regulatory burdens of the Affordable Care Act." Presidents use executive orders to give federal agencies direction on how to enforce laws. In this case, the order instructs the Department of Health and Human Services (HHS) and other agencies to use their existing powers to weaken ACA "to the maximum extent permitted by law."

In essence, the order changes nothing immediately. Most of the provisions in the ACA can't be changed by the president or HHS; they require action from Congress or a lengthy public comment period. Importantly, the executive order has no impact on coverage for those with preexisting conditions and other provisions outlined in ACA.

Read More

Election 2016 Update

Members of the FORCE community have reached out with questions and concerns about the implications of the recent election. See our statement on the impact of the 2016 election for people affected by hereditary cancer and our December 2016 blog to learn how the change in administration may affect you and your family. Stay tuned for updates in the coming months.

Have concerns about health insurance? Coverage for pre-existing conditions?

FORCE Supports Oral Chemotherapy Parity Initiatives

Oral chemotherapy is becoming more common and is the standard of care for many types of cancer. Oral treatment also accounts for about a third of the oncology development pipeline. Importantly, many oral anti-cancer medications do not have IV or injected alternatives, and are the only option for some patients. For this reason, these medications must be as affordable as their IV counterparts.

FDA Advisory Committee Meeting Blog

Current Articles | RSS Feed

Meeting Announcement - Olaparib

Posted by Eleanor Panico on Fri, Apr 25, 2014 @ 10:45 AM

June

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Pleas

will discuss new drug application
pplication submitted by
he proposed indication (use) for
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psed ovarian cancer (including
by an FDA-approved test, who are
therapy.

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ext meeting,

Lisa Schlager VP of Policy at FORCE testifies at FDA ODAC meeting.

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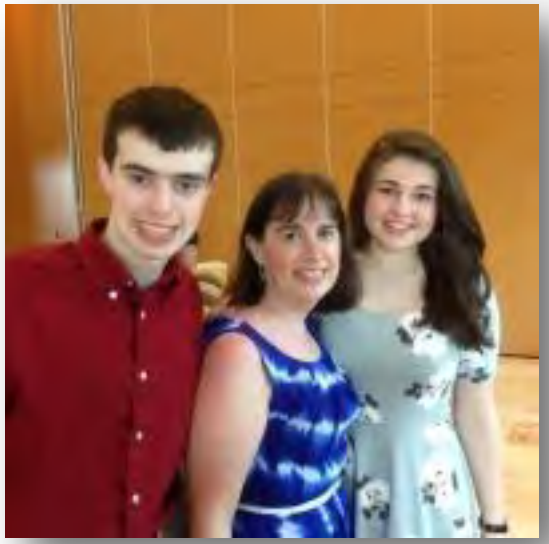
Why We Do This



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Thank You!

- Visit us: www.FacingOurRisk.Org
- Email us: info@facingourrisk.org
- Call us: 866-288-RISK (7475)
- Like us/follow us: (FacingOurRisk)

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