
# CORPORATE PRESENTATION

**January 2017**

# 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.

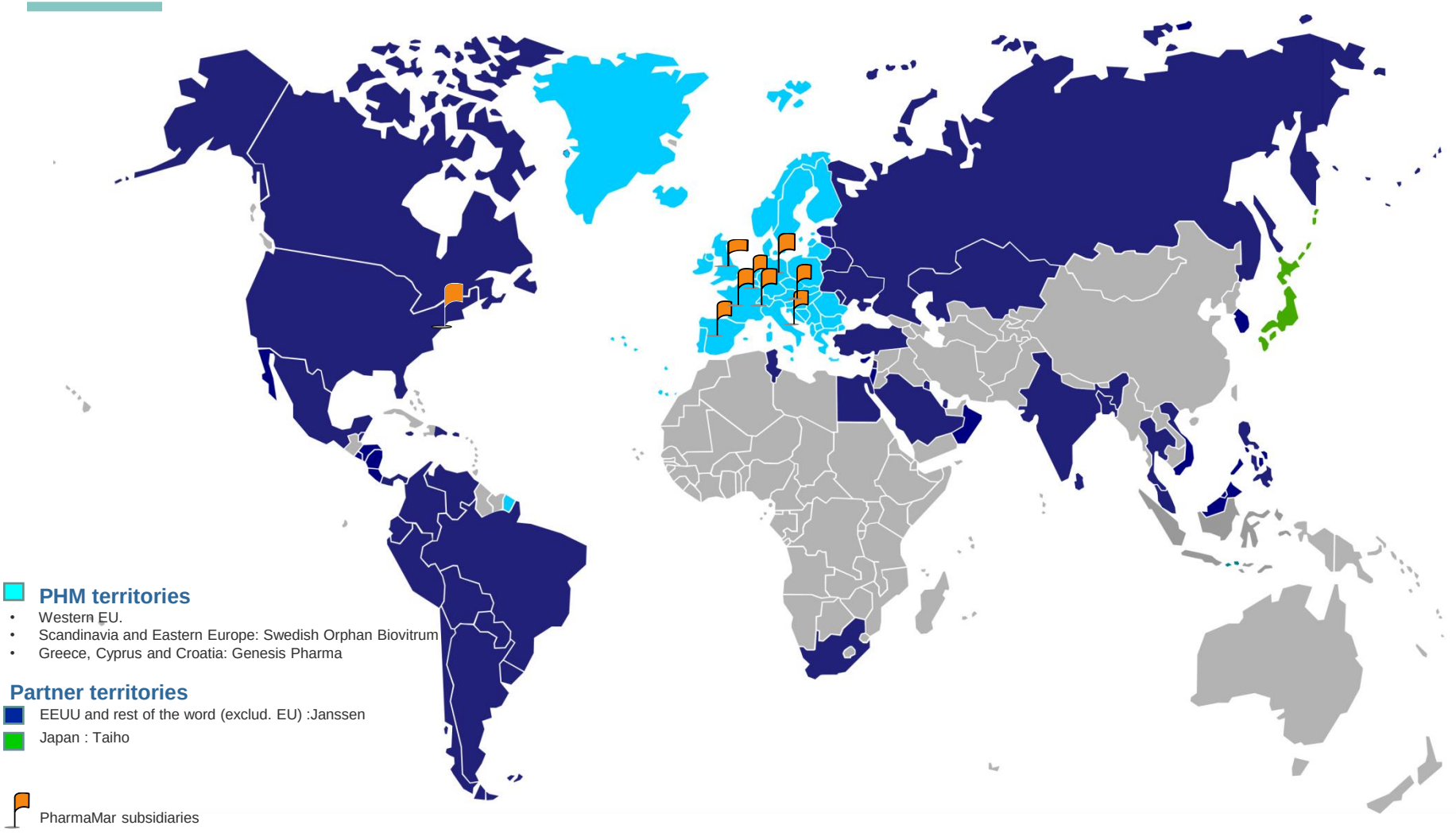
# Investment Highlights

## A leader in the development & commercialization of marine-derived oncology drugs

- **Multinational biotechnology company developing marine-derived and novel MoA oncology drugs**
  - Fully integrated biotechnology company – from discovery to commercialization
  - Highly productive R&D organization (1 approved drug and 2 in late stage development)
- **Established oncology sales force in Europe:**
  - Strong partners in the US (Janssen), Europe (Chugai), and Japan (Taiho, Chugai)
- **Late stage development pipeline driving future value**
  - Lurbinectedin (PM1183): Next generation Yondelis®
  - Aplidin®: Positive pivotal data in Multiple Myeloma with an EMA NDA filed in Sept 2016
- **Track record of operational excellence with a strong financial position**
  - Company with growing revenues and robust cash flow
  - Headquartered and traded in Madrid
  - C. €620m market cap (as of 12/21/16)
  - €63.5m in cash and cash equivalents (9 months 2016)*
  - €16m operating cash burn + debt service (9 months 2016)

* Proforma for Chugai Lurbinectedin partnership, €30mn upfront, announced Dec 22nd 2016

# Yondelis® - Commercial expansion worldwide



**PHM territories**

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

**Partner territories**

EEUU and rest of the word (exclud. EU) :Janssen

Japan : Taiho

PharmaMar subsidiaries

# Unique fully integrated platform

**Fully integrated capabilities**

**Marine expeditions** → **Sample library** → **Screening & Synthesis** → **Clinical Trials** → **Commercialization**

- Marine derived products
- Global expeditions

- New drug candidates
- Molecule optimization
- c.200,000 samples

- Patent protection
- Synthesis
- FDA approved production facility

- Pre-clinical trials
- Clinical trials
- Phase IV supportive trials

- Oncology-focused sales force in Europe (~ 65 people)
- Geographic licensing & partnering with experienced companies.

**Marine-derived compounds with novel mechanisms of action**

**Regulatory inspections passed from FDA, AEMPS,PMDA (US, Spain/EU, Japan)**

# 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

# A Balanced portfolio of product candidates

## Overview

| Clinical Program / Indication | | Phase I | Phase II | Phase III | Market | Partner | Data timing |
|---|---|---|---|---|---|---|---|
| **Yondelis®** | | | | | | | |
| Soft Tissue Sarcoma 2nd/3rd line | Single agent | EU, US, Japan | | | | J&J (US) Taiho (Japan) | |
| Ovarian Cancer 2nd/3rd line | Yondelis®+Doxil | EU/Others | | | | | |
| **Aplidin®** | | | | | | | |
| R/R multiple myeloma 4th line; | Aplidin® + Dexameth. | EU/Others | | | | Chugai/ Regionals | 2H´17 |
| R/R T-cell lymphoma (Pivotal) | Single agent | EU/Others | | | | | Ongoing |
| R/R multiple myeloma | Aplidin® + Bortezom+ Dexameth. | EU/Others | | | | | Ongoing |
| **Lurbinectedin (PM1183)** | | | | | | Chugai (Japan) | |
| Plat. Resistant ovarian cancer | Single agent | Global | | | | | 2H´17 |
| SCLC 2nd line | Lurbinec + Doxo | Global | | | | | 2019 |
| BRCA 1/2 Breast cancer | Single agent | Global | | | | | Initiating |
| Basket trial | Single agent | Global | | | | | Ongoing |
| Solid tumors | Combinations | Global | | | | | Ongoing |
| **PM184** | | | | | | | |
| Advanced Breast Cancer 3rd/4th line | Single agent | Global | | | | | Ongoing |
| Solid tumors | Single agent and combinations | Global | | | | | Ongoing |

# Pipeline – Lurbinectedin (PM1183)

## Targeted transcription Inhibitor as a cancer therapeutic

- Cancer cells aberrantly deregulate specific gene expression programs with critical functions in cell differentiation, proliferation and survival (Hoadley et al 2014)
- These altered gene programs in cancer cells have a striking dependence on continuous active transcription (transcription addiction)
- Lurbinectedin only affects activated transcription. Does not affect basal transcription*.
- Examples of tumors with transcription addiction:
  - Small Cell Lung Cancer (SCLC) cells are addicted to lineage-specific and proto-oncogenic transcription factors that support their growth (Christensen et al 2015)
  - Soft Tissue Sarcomas (STS) bearing translocations.
  - Effect on tumor microenvironment: Lurbinectedin inhibits the activated transcription of certain cytokines as IL-6, IL-8, CCL2 and PTX3

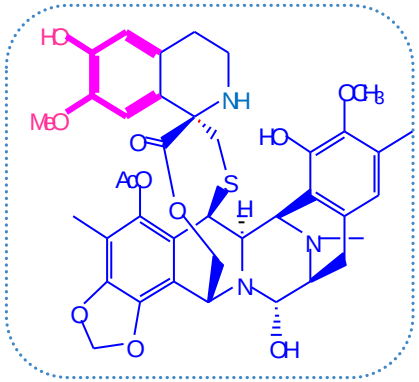
*** Source: Molecular Cancer Therapeutics 2016 Oct;15(10):2399-2412.** Lurbinectedin Specifically Triggers the Degradation of Phosphorylated RNA Polymerase II and the Formation of DNA Breaks in Cancer Cells.

# Lurbinectedin (PM1183):

## Key oncology compound – accelerating growth

**Lurbinectedin, a second generation Yondelis®, with improved PK and other attributes**

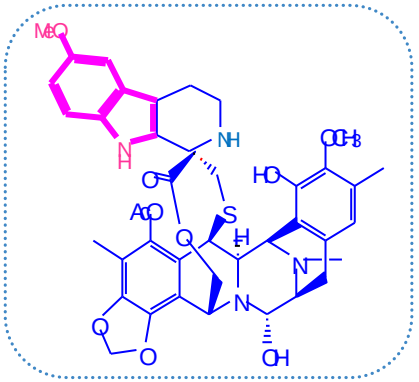
### YONDELIS®



- Lurbinectedin is administered as a 1h peripheral infusion versus 24h continuous central catheter infusion with Yondelis®.
- Lurbinectedin linear PK profile

**IMPROVED PK PROFILE**

### Lurbinectedin



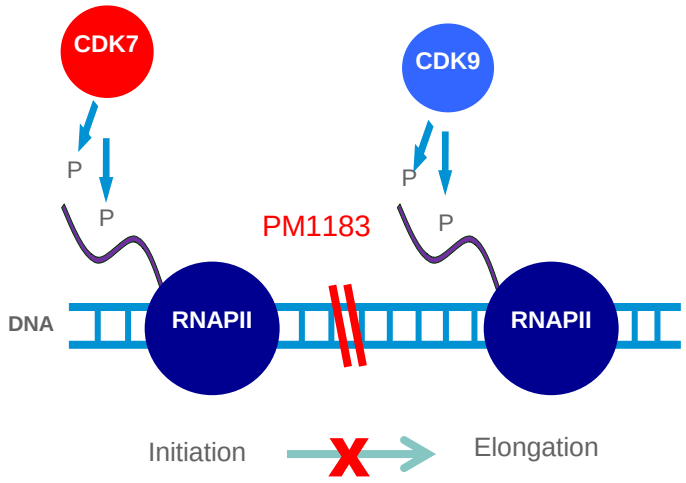
- 4x tolerated dose.
- 15x exposure at RD.
- Less toxicity
- More oncology “office practice” friendly.

# Pipeline – Lurbinectedin (PM1183)

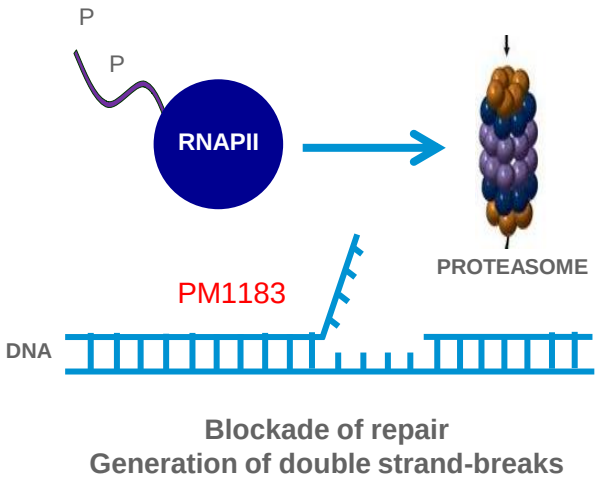
## Key oncology compound – accelerating growth

- **Inhibition of trans-activated transcription but not of basal transcription.**
- **Induction of the degradation of RNA Pol II but not of RNA Pol I or III.**

**RNA POL II INHIBITION**




**RNA POL II DEGRADATION**




**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.

# Pipeline – Lurbinectedin (PM1183)

## Development strategy

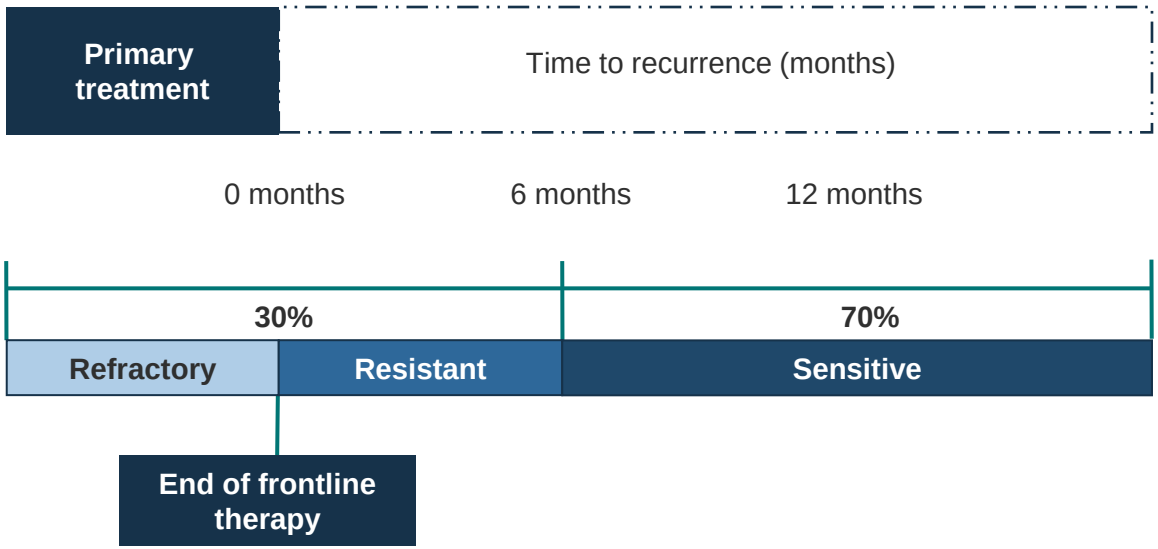
| CLINICAL PROGRAM/ INDICATION | | PHASE I | PHASE II | PHASE III | MARKET | PARTNERS |
|---|---|---|---|---|---|---|
| **Lurbinectedin PM1183®** | | | | | | **Chugai (Japan)** |
| **Plat. Resistant ovarian cancer** 2nd/3rd line | Single agent | | | | | |
| **SCLC** 2nd line | Combo Doxorubicin | | | | | |
| **BRCA2 Breast cancer*** 2nd/3rd line | Single agent | | | | | |
| **Basket Trial** | Single agent | | | | | |
| **Combination Studies** | Solid Tumors | | | | | |

* Subsequent to FDA meeting December 2016; subject to finalization in 2017

# Lurbinectedin – Platinum Resistant Ovarian Cancer

## Market overview: Orphan Indication US/EU

- ~ 250,000 WW  new cases of ovarian cancer
- ~ 150,000 WW  deaths from ovarian cancer
- Platinum resistant patients account for ~15% of all ovarian cancer patients
- 80% relapse after first line treatment with platinum




**Source:** Estimated ovarian cancer incidence and mortality, all ages. GLOBOCAN 2012 and PharmaMar market research studies

# Standard of care for Ovarian Cancer (per labels)

## Lurbinectedin: Competitive Landscape

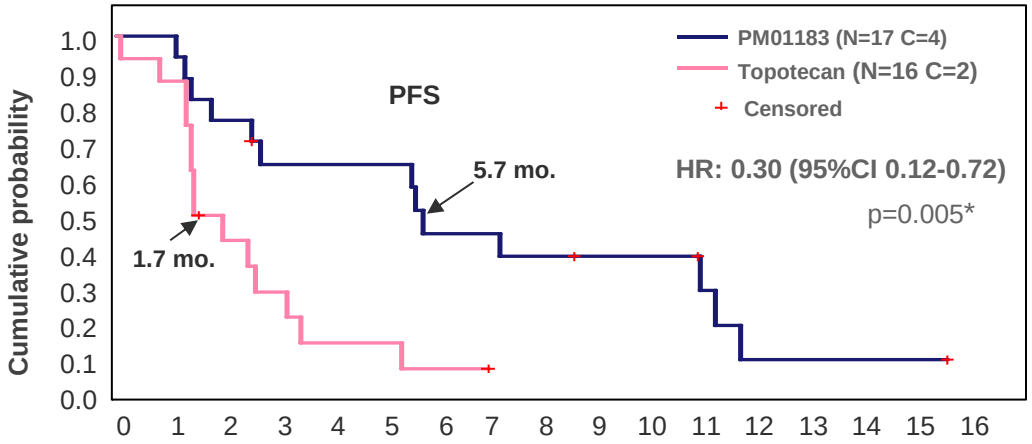
- PARP inhibitors work by blocking the action of poly (ADP-ribose) polymerase, a DNA repair enzyme; they are used after DNA damaging drugs which are *highlighted below*

| Front Line | Second line | 3L and beyond |
|---|---|---|
| ▪ *Platinum/* Taxane | **Sensitive**<br>▪ Same as 1L<br>▪ Yondelis/PLD (EU)<br>▪ Avastin<br>▪ Olaparib maintenance (EU)<br>**Resistant**<br>▪ *PLD*<br>▪ *Topotecan*<br>▪ **Lurbinectidin***<br>**Refractory**<br>▪ Same as resistant | ▪ Olaparib, (US) germline BRCAm, after 3 or more lines of chemo<br>▪ Rucaparib (US) BRCAm after 2 or more lines of chemo |

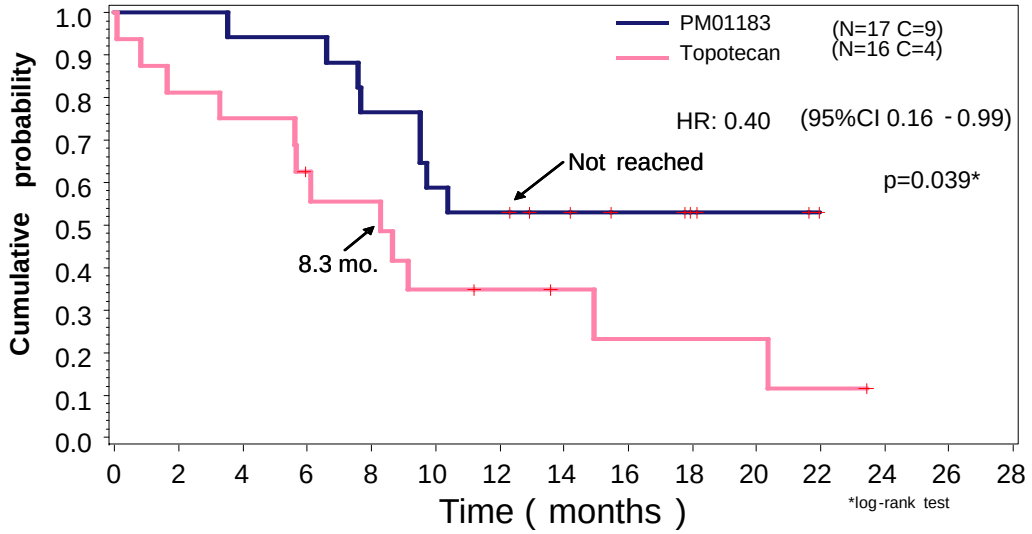
* Investigational drug; not approved

# Lurbinectedin:Phase II Platinum Resistant Ovarian Cancer

## Trial results




⊙ **Superior PFS**

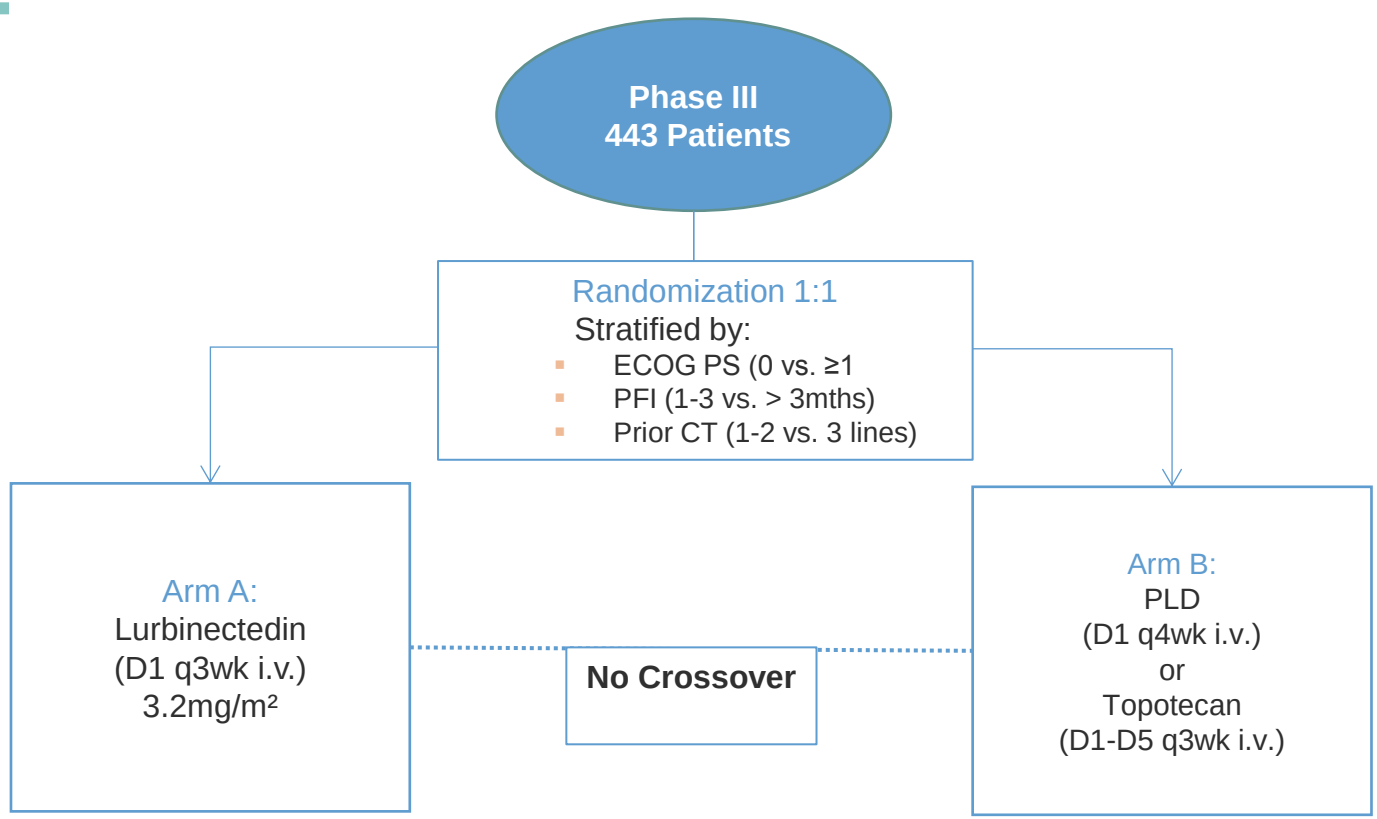



⊙ **Superior OS**

**Source: ASCO 2014** Poveda et al.

# Lurbinectedin:Phase III Platinum Resistant Ovarian Cancer

## CORAIL Trial Design




**Primary Endpoint: PFS, 90% power for HR=0.7; p=0.025 (one-sided)**

**Interim safety analysis: passed @ 80 patients**
**Interim analysis: @ 210 patients, summer ´16**

**Patient recruitment completed: October 2016; Data expected 2H17**

# Lurbinectedin: Small Cell Lung Cancer (SCLC)

## Market overview. Orphan Indication US/EU

### In the US per annum:

- ~ 33,200 new cases of small cell lung cancer
- ~ 24,040 deaths from small cell lung cancer (~ 27% of all cancer deaths)

### In EU-28 per annum:

- ~ 46,645 new cases of small cell lung cancer
- ~ 40,700 deaths from small cell lung cancer

- SCLC represents a significant unmet medical need with limited late stage options.
- SOC: Topotecan, CAV (off label)
- Last FDA approval, Topotecan, October 2007
- Last EMA approval, Topotecan, August 2009

**Source:** American Cancer Society, Decision Resources, Inc.

# Standard of care for Small Cell Lung Cancer

## Lurbinectedin: Competitive Landscape

- First line treatment. Platinum/Etoposide

| 2nd line | 3rd line | N | ORR (%) | Notes |
|---|---|---|---|---|
| **Lurbinectedin/Doxo** | | **21** | **67** | **ASCO 2015** |
| Paclitaxel | | Literature | 29 | Nature Reviews Glisson, 2011 |
| Topo | | Literature | 24 | Glisson, 2011 |
| CAV | | Literature | 19 | Glisson, 2011 |
| Nivo | Nivo | 98 | 11 | 2nd/3rd line |
| Nivo/Ipi | Nivo/Ipi | 61 | 25 | 2nd/3rd line |
| Pembro | Pembro | 24 | 33 | 'heavily pre-treated' |
| Rova-T | Rova-T | 61 | 18 | 2nd and 3rd line |
| Rova-T | Rova-T | 48 | 38 | DLL3 'high' |

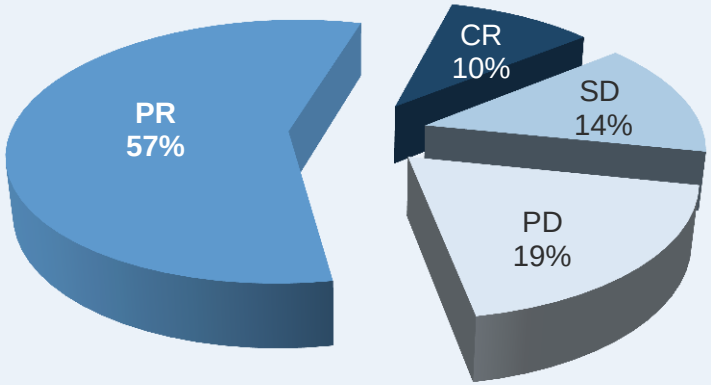
For information purposes, not head to head data

# Lurbinectedin: Phase I/II Small Cell Lung Cancer

## Trial results – Active treatment as second-line therapy with Doxorubicin

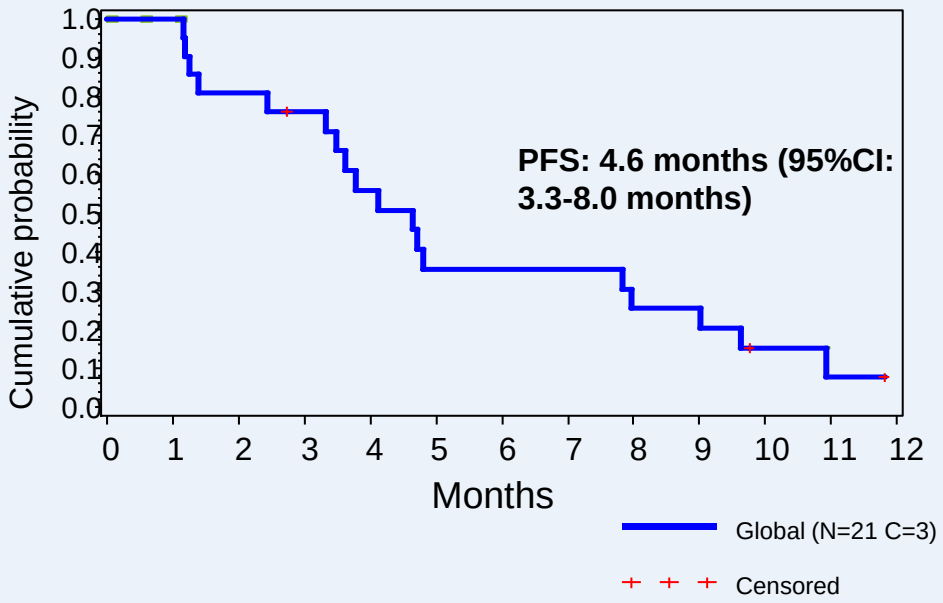
**Best RECIST v.1.1 overall response during treatment (n=21)**

**ORR: 67 %**
(95%CI: 43-85)




M. Forster et al. ASCO 2015

**Kaplan-Meier global PFS and according to CTFI (n=21)**




**Other examples ORR in SCLC:**

- **CAV 19%**
- **Topotecan 24%**
- **Paclitaxel 29%**
- **Gemcitabine 12%**
- **Vinorelbine 12%**

**Source: Nature Reviews 2011;8:611-19.** William N, Glisson

**PFS reported in registration Topotecan trial study :**

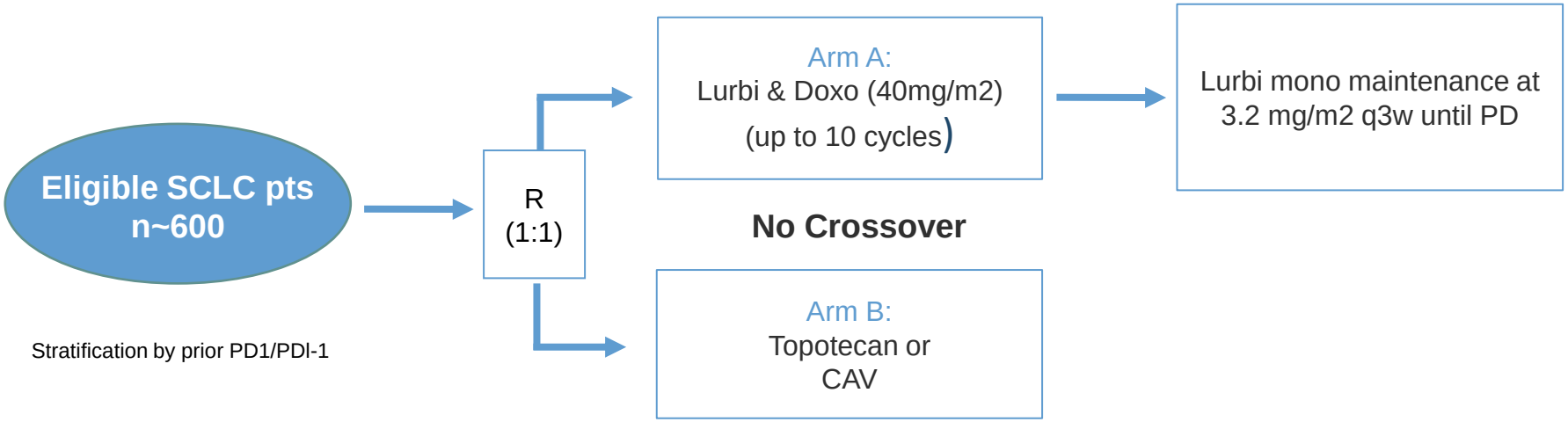
- **Topotecan : 3 months**
- **CAV : 2.8 months**

**Source: J Clin Oncol, 1999,** Von Pawel et al

# Lurbinectedin: Phase III 2nd line Small Cell Lung Cancer

## ATLANTIS Trial Design SCLC (Trial initiated August 2016)

- Primary endpoint: median PFS
  - HR≤ 0.7 in PFS with 90% power;
  - Futility analysis planned at n=150 events approximately
- Key secondary endpoints:
  - OS
- Registration Strategy
  - Trial supported by ongoing n=50 monotherapy trial
  - Factorial synergy supported by CAV control arm (includes **A**nthracycline ~ Doxo)

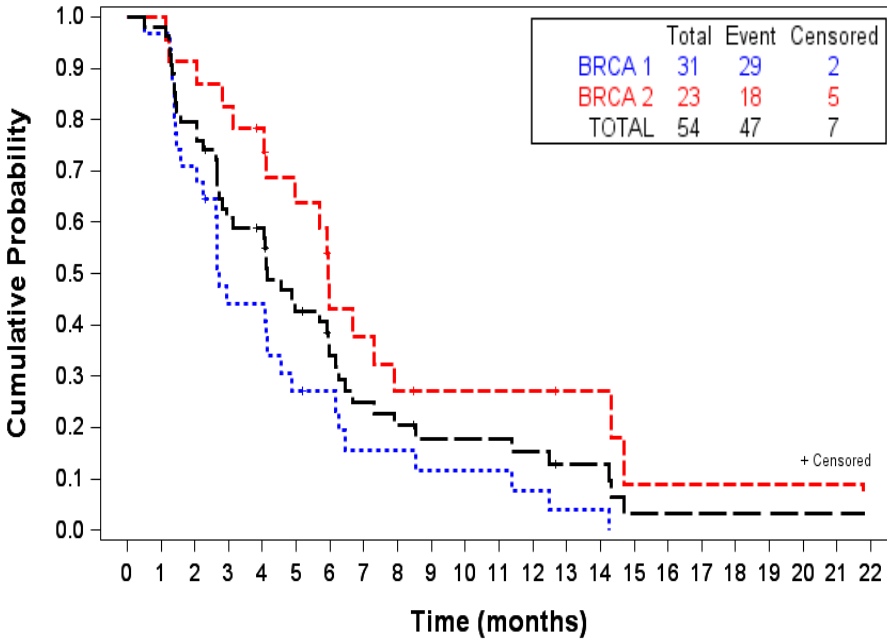


# Lurbinectedin: Phase IIb in BRCA 1/2- Breast Cancer

## Clinical efficacy: Progression Free Survival (PFS) and Overall Survival OS

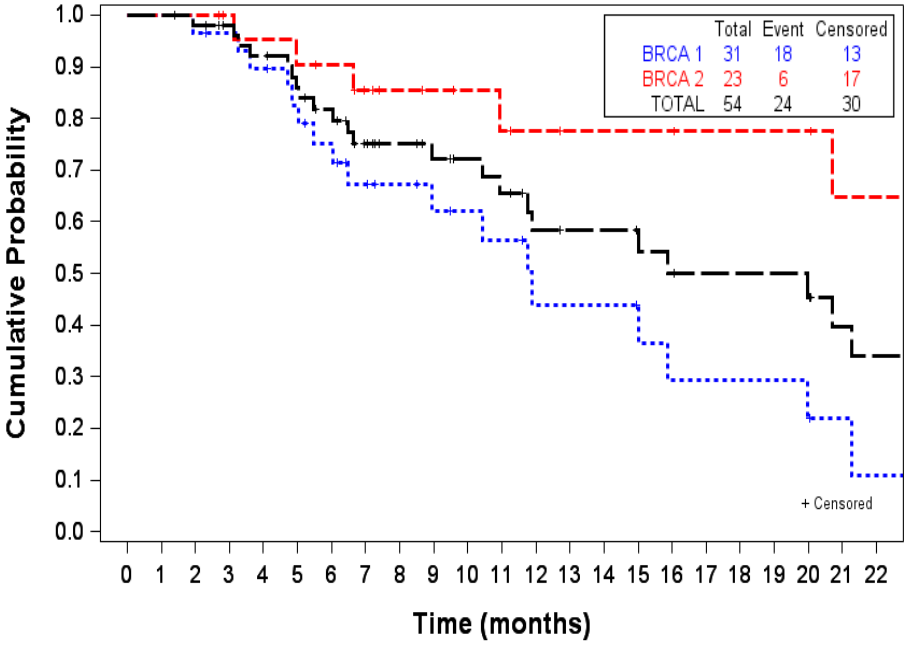
**Median PFS BRCA 1/2:**
**4.1 months 95% CI (2.8-5.9)**

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




**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)




**Source:** ESMO 2016

# Lurbinectedin – Phase IIb in BRCA 1/2- Breast Cancer

## 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) | 1/2 (n: 54) | 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) | **40.7%** (27,6-55,0) | **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) | **6.7 m** (3,0-13) | **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%) | 45 (83%) | 26 (79%) | 19 (90%) | 27 (87%) | 18 (78%) |
| **Clinical benefit (CR+PR+SD ≥ 3 mo)** | 19 (70%) | 14 (52%) | 14 (45%) | 19 (83%) | 33 (61%) | 29 (88%) | 14 (67%) | 21 (68%) | 12 (52%) |

* Includes 2 pts also HER-2 +

**Source:** ESMO 2016

# Lurbinectedin: Registrational trial BRCA 2- Breast Cancer

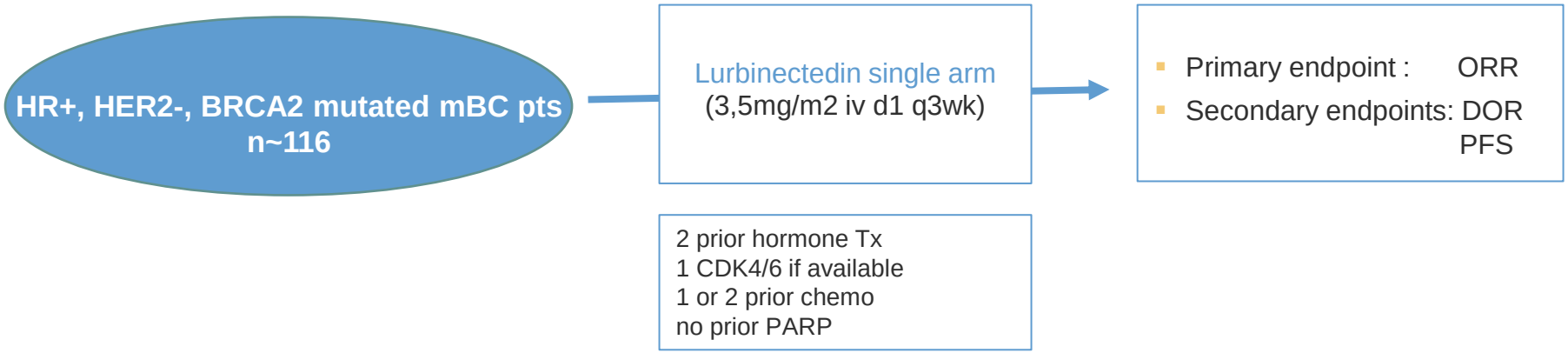
Subject to finalization and changes

## In the US per annum:

- ~ 10,300 new cases of BRCA 2- Breast cancer

## In the EU-28 per annum:

- ~ 14,500 new cases of BRCA 2- Breast cancer




**Expect to open first center 2H 2017**

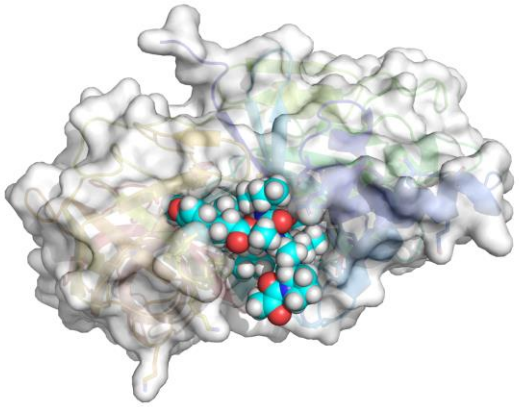
**Source:** US: seercancer.gov , EU28: Globocan2012, Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Andrew Tutt et al. Lancet 2010; 376: 235–44

# Pipeline - Aplidin®

## First in class drug with a novel mechanism of action

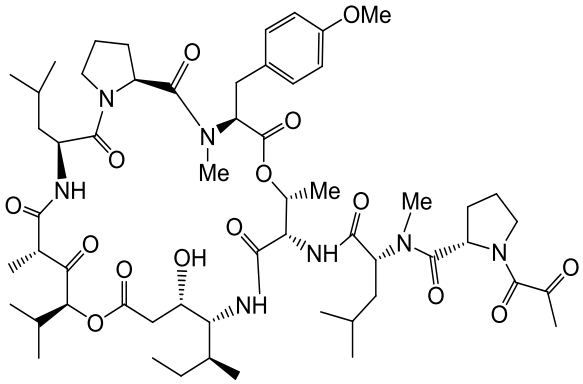
### *Aplidium albicans*

eEF1A2



Aplidin®

### PLITIDEPSIN




### MECHANISM OF ACTION

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

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

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

# Pipeline – Aplidin®

## First in class drug with a novel mechanism of action

| CLINICAL PROGRAM/ INDICATION | | PHASE I | PHASE II | PHASE III | REGISTRATION APPLICATION | MARKET | PARTNERS |
|---|---|---|---|---|---|---|---|
| **Aplidin®** | | | | | | | |
| **R/R multiple myel**oma 4th line; EU/others | Aplidin® + Dexameth | | | | | | CHUGAI |
| **R/R T-cell lymphoma** | Single agent | **(Pivotal)** | | | | | |
| **R/R multiple myeloma** | Aplidin® + Bortezomib+ Dexameth | | | | | | |

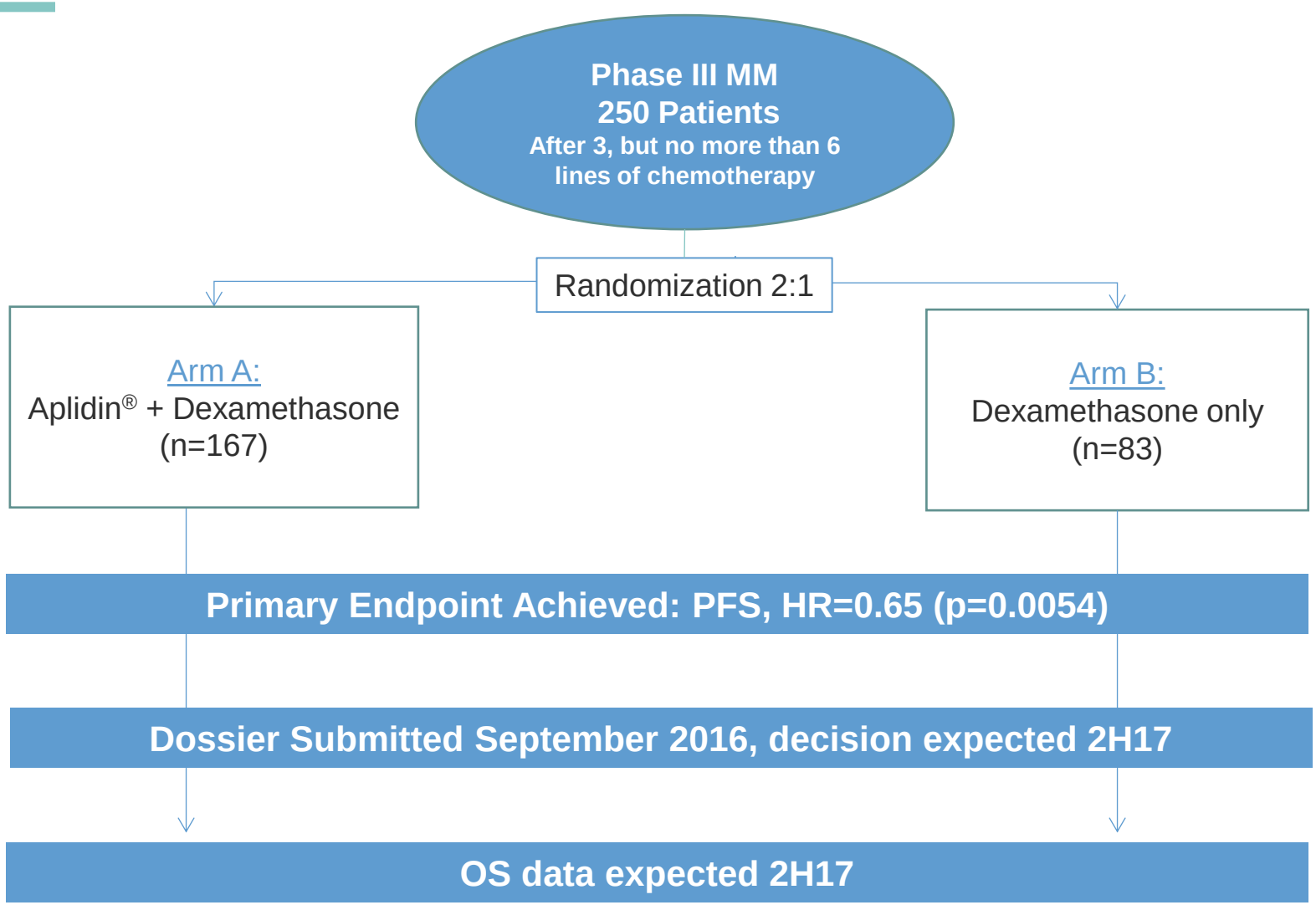
**Partnered with Roche's Chugai in 8 European countries** CHUGAI

**Other partners for Aplidin®** Specialised Therapeutics AUSTRALIA · TTY BIOPHARM 台灣東洋藥品 · BORYUNG pharm

**Commercial opportunity for Europe in M.M. estimated at c.€300mm**

# Aplidin® - ADMYRE Trial

## Phase III in Relapsed / Refractory Multiple Myeloma



# Key Events

## Transformative times for Pharma Mar; catalyst rich 2017

- ✓ Yondelis® approved in Japan for STS (9/2015); approved in the US for STS (10/2015)
- ✓ Lurbinectedin Phase III pivotal trial initiated for SCLC (Aug. 2016)
- ✓ Lurbinectedin interim activity analysis Phase III in platinum-resistant ovarian cancer (Aug`16)
- ✓ Aplidin® positive data for Phase III for multiple myeloma and dossier submitted (Sept. 2016)
- ✓ Lurbinectedin data for Phase II metastatic breast cancer (Sept. 2016)
- ✓ Lurbinectedin Phase III in platinum-resistant ovarian cancer: recruitment completed (Oct`16)
- ✓ Lurbinectedin license agreement in Japan (Chugai, Dec´16)
- Update Breast cancer trial, following FDA meeting
- Yondelis INNOVATYON (IST) interim analysis relapsed OC (2q´17)
- Aplidin® CHMP recommendation in multiple myeloma (2H 2017)
- Lurbinectedin Phase III data in platinum-resistant ovarian cancer (2H 2017)
- Aplidin® OS data Phase III for multiple myeloma expected 2H17
- Lurbinectedin potential start of Phase III BRCA
- Lurbinectedin expected publication of Phase II data as a single agent in SCLC

For more information: www.pharmamar.com