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

Colmenar Viejo (Madrid), a 12 de junio de 2018

De conformidad con lo previsto en el artículo 228 del Texto Refundido de la Ley de Mercado de Valores, por la presente se procede a comunicar el siguiente **HECHO RELEVANTE**:

"Se adjunta presentación corporativa en inglés que estará disponible también en la página web de la Compañía www.pharmamar.com."

June 2018

# 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

***Leader in development & commercialization of marine-inspired oncology drugs***

**Global integrated biotech developing marine-inspired and novel MoA oncology drugs.**

- From discovery to commercialization.

**Established oncology sales force in Europe.**

- Strong partners in the US (Janssen), Japan (Taiho) and Australia (STA).

**Late stage pipeline driving future value; 1 Phase III ongoing, other indications Phase II**

- **Zepsyre®** (lurbinectedin).

**Track record of operational excellence.**

- Revenue generating and cash flow.
- 2017 revenues €179mm; Q1 ‘18  €45mm
- C. €365market cap.
- €24mm in cash and cash equivalents (Q1 2018)
- Headquartered and traded in Madrid.

# YONDELIS® - COMMERCIAL EXPANSION WORLDWIDE

**Yondelis Sales 2017: €132,5MN**
EU (PHM): €85MN
ROW: €48MN

## PHM Territories /

- WESTERN EU.
- Scandinavia and Eastern EUROPE:
- Swedish Orphan Biovitrum Greece, Cyprus and Balkans: Genesis Pharma
- Sarcoma and ovarian cancer.

## Partner Territories /

USA and rest of the world (exclud. EU): Janssen.

- Sarcoma

## Partner Territories /

JAPAN / Taiho

- Sarcoma

## PharmaMar Subsidiaries /

# UNIQUE FULLY INTEGRATED PLATFORM

## *Discovery*

- Marine inspired products.
- Global expeditions.

## *Development*

- Molecule optimization.
- c.200,000 samples.
- Broad oncologic activity screening.

## *Chemistry*

- Patent protection.
- Synthesis.
- FDA approved production facility.

## *Clinical*

- Pre-clinical trials.
- Clinical trials.
- Post marketing trials.

## *Commercial*

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

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

# THE PLAN FOR GROWTH

## *Potential to commercialize new oncology products in more indications*

**Pharma Mar**

***TODAY***

- ***1 marketed product***
- ***2 indications***

**Zepsyre®**
**(Lurbinectedin)**

- *Small Cell Lung cancer.*

**Yondelis®**

- *Soft Tissue Sarcoma.*
- *R/R Ovarian Cancer (EU)*

**Pharma Mar**

***IN THE NEAR FUTURE***

- ***2 marketed products***

**PM184**
**PM14**

- *2 or more clinical products.*
- *Multiple indications.*

**Pharma Mar**

***FURTHER IN THE FUTURE***

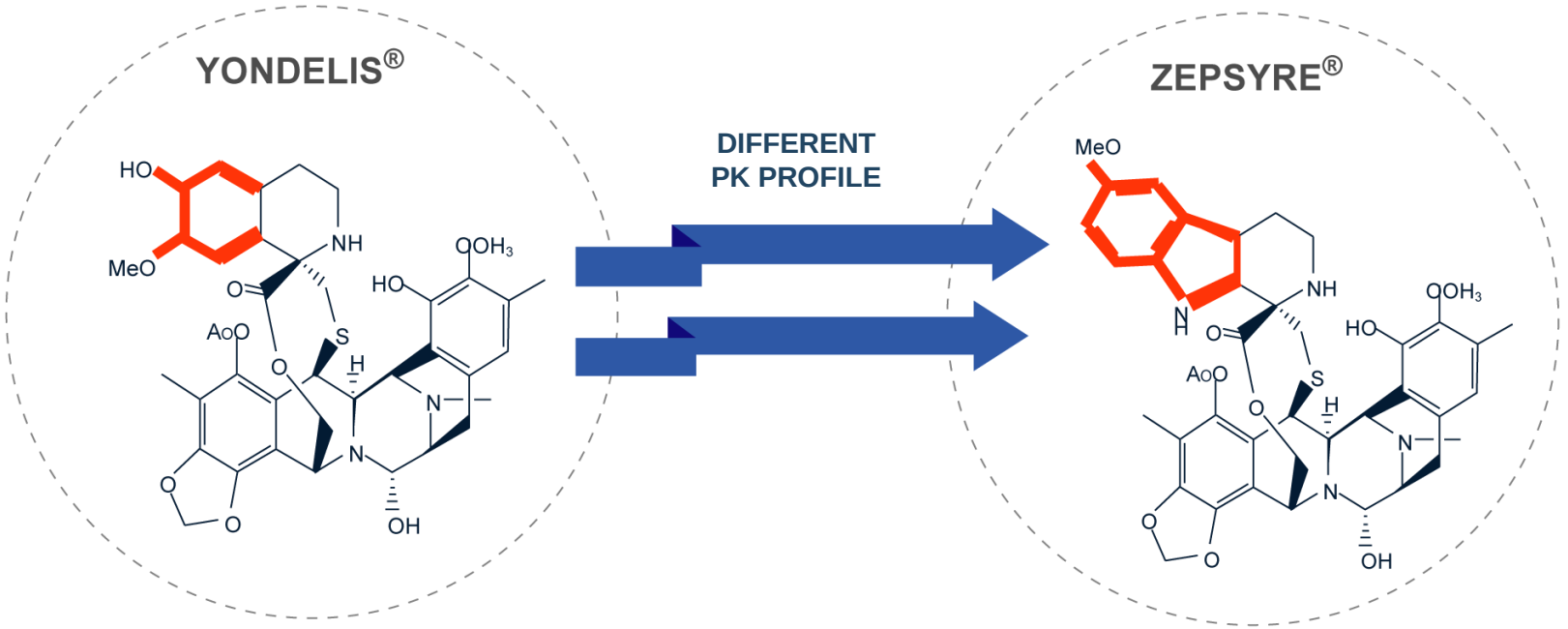
# OUR ONCOLOGY PORTFOLIO:

| | 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)<br>Taiho (Japan) | |
| | Ovarian Cancer 2nd/3rd line | Yondelis®+Doxil | EU/Others | | | | | |
| **Zepsyre®**<br>**Lurbinectedin** | SCLC Relapsed | Zepsyre®+Doxo | Global | | | | | 2H 2019 |
| | Basket trial | Single agent | Global | | | | | Ongoing |
| **PM184** | Colorectal Cancer 3rd line | Single agent | Global | | | | | FPI 1H '18 |
| | Solid tumors | Single agent and combinations | Global | | | | | Ongoing |
| **PM14** | Solid tumors | Single agent and combinations | Global | | | | | Ongoing |

# ZEPSYRE ® (Lurbinectedin)

***Key oncology compound– accelerating growth***

Zepsyre, a second generation Yondelis®, with improved PK, absorption and other attributes.




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

- 4x tolerated dose.
- 15x exposure at RD.
- Better therapeutic window.
- Oncology “office practice” friendly.

# MoA- ZEPSYRE® (Lurbinectedin)

## *Targeted transcription Inhibitor as a cancer therapeutic*

Zepsyre only affects activated transcription. Does not affect basal transcription*

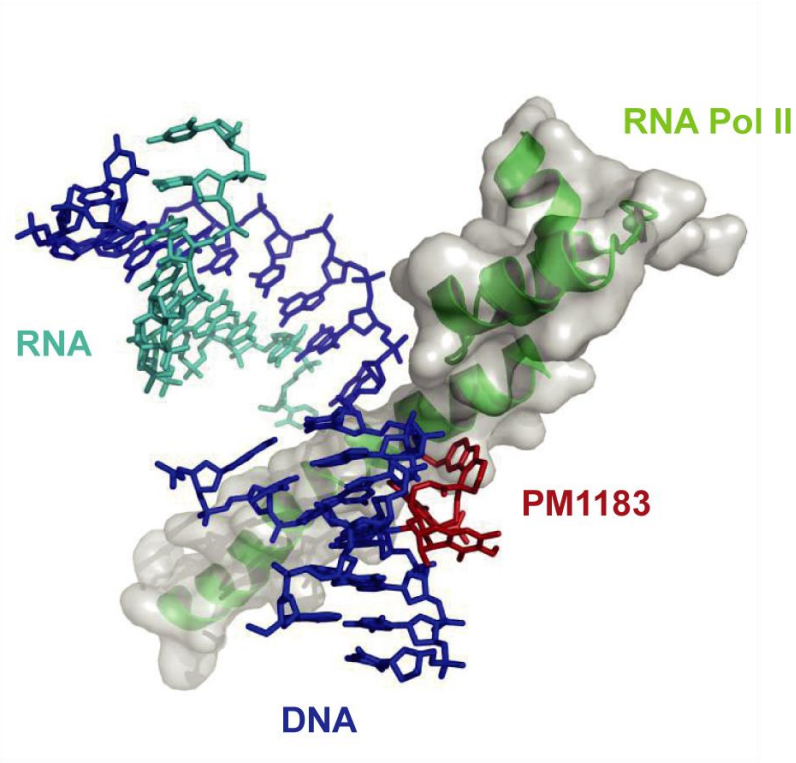
Generates double strand DNA breaks.

Some tumors are addicted to transcription (SCLC, Ovarian Cancer, etc...)

Effect on tumor microenvironment: Zepsyre inhibits the activated trans- cription of certain cytokines such as IL-6, IL-8, CCL2 and PTX3.

"Lurbinectedin...inhibits the transcription process through (i) its binding to CG-rich sequences, mainly located around promoters of protein-coding genes; (ii) the irreversible stalling of elongating RNA polymerase II (Pol II) on the DNA template and its specific degradation by the ubiquitin/protea- some machinery; and (iii) the generation of DNA breaks and subsequent apoptosis. The finding that inhibition of Pol II phosphorylation prevents its degradation and the formation of DNA breaks after drug treatment under- scores the connection between transcription elongation and DNA repair. "

Santamaria et al, Mol Cancer Ther. 2016 Oct;15(10):2399-2412.




*Source Molecular cancer Therapeutics 2016 Oct;15(10):2399-2412.

# PIPELINE- ZEPSYRE® (Lurbinectedin)

## *Development and commercial strategy*

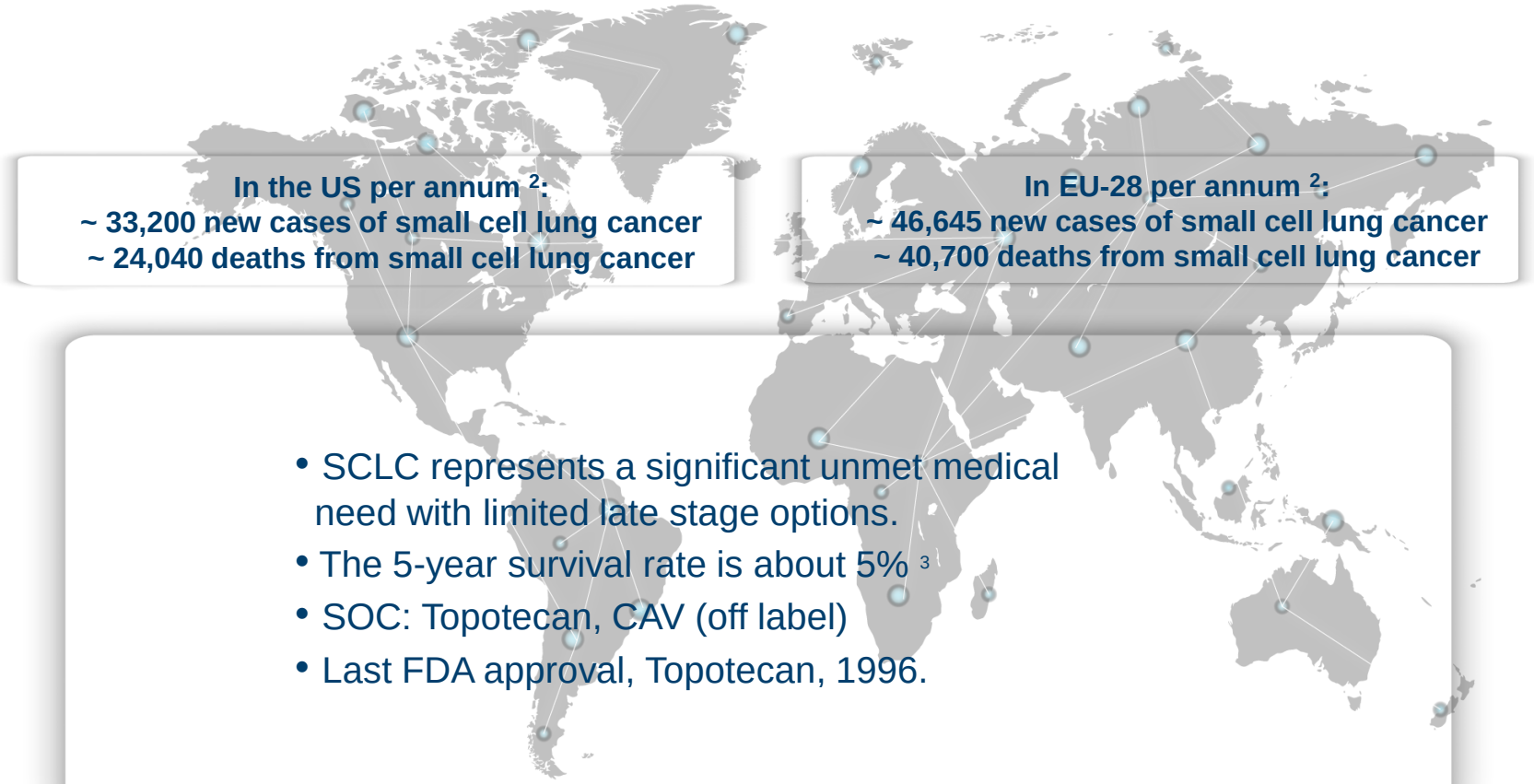
| Clinical Program / Indication | | Phase I | Phase II | Phase III | Market | Data timing |
|---|---|---|---|---|---|---|
| **ZEPSYRE®** | | | | | | |
| SCLC Relapsed | Combo Doxorubicin | | | | | 2H 2019 |
| Basket trial | Single agent | | | | | Ongoing |
| Combination Studies | Solid Tumors | | | | | Ongoing |

**Commercial Plans:**

- EU: Utilize existing Yondelis sales force
- US: Self commercialize; build out commercial infrastructure
- ROW: regional partnerships

# ZEPSYRE®: SMALL CELL LUNG CANCER (SCLC)

## *Market overview: Orphan Indication US/EU [1]*



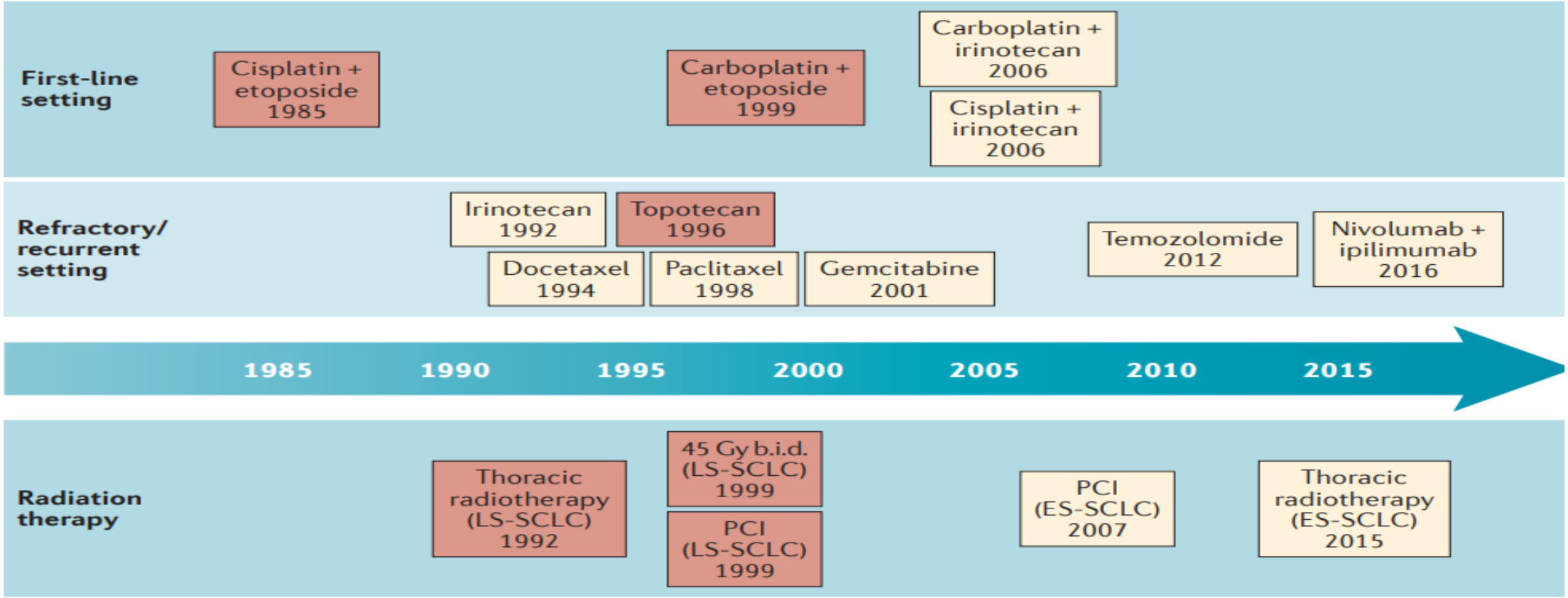
**In the US per annum [2]:**
**~ 33,200 new cases of small cell lung cancer**
**~ 24,040 deaths from small cell lung cancer**

**In EU-28 per annum [2]:**
**~ 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.
- The 5-year survival rate is about 5% [3]
- SOC: Topotecan, CAV (off label)
- Last FDA approval, Topotecan, 1996.

***Sources:***
1, 2 American Cancer Society, Decision Resources, Inc.
3 http://www.cancer.gov/types/lung/hp/small-cell-lung-treatment-pdq

# Small Cell Lung Cancer over the years[1]; it's not NSCLC!



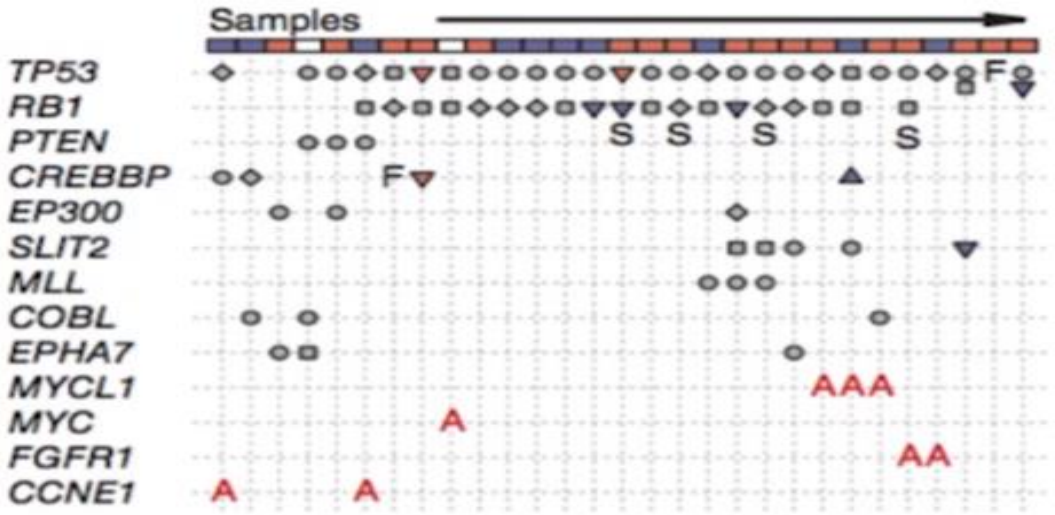

NSCLC

- Alkyliting
- Amtimetabolites
- Antiangiogenesis
- Microtubule
- IO
- EGFR
- TKI

CARBOplatin
GEMZAR
ALIMTA
AVASTIN
CYRAMZA
Abraxane
Taxol
TAXOTERE
OPDIVO
KEYTRUDA
TECENTRIQ
IMFINZI
IRESSA
Tarceva
TAGRISSO osimertinib
Portrazza
XALKORI
ALUNBRIG

*Source; Sabari et al, Clinical Oncology; September 2017*

# Why is SCLC so hard to target?

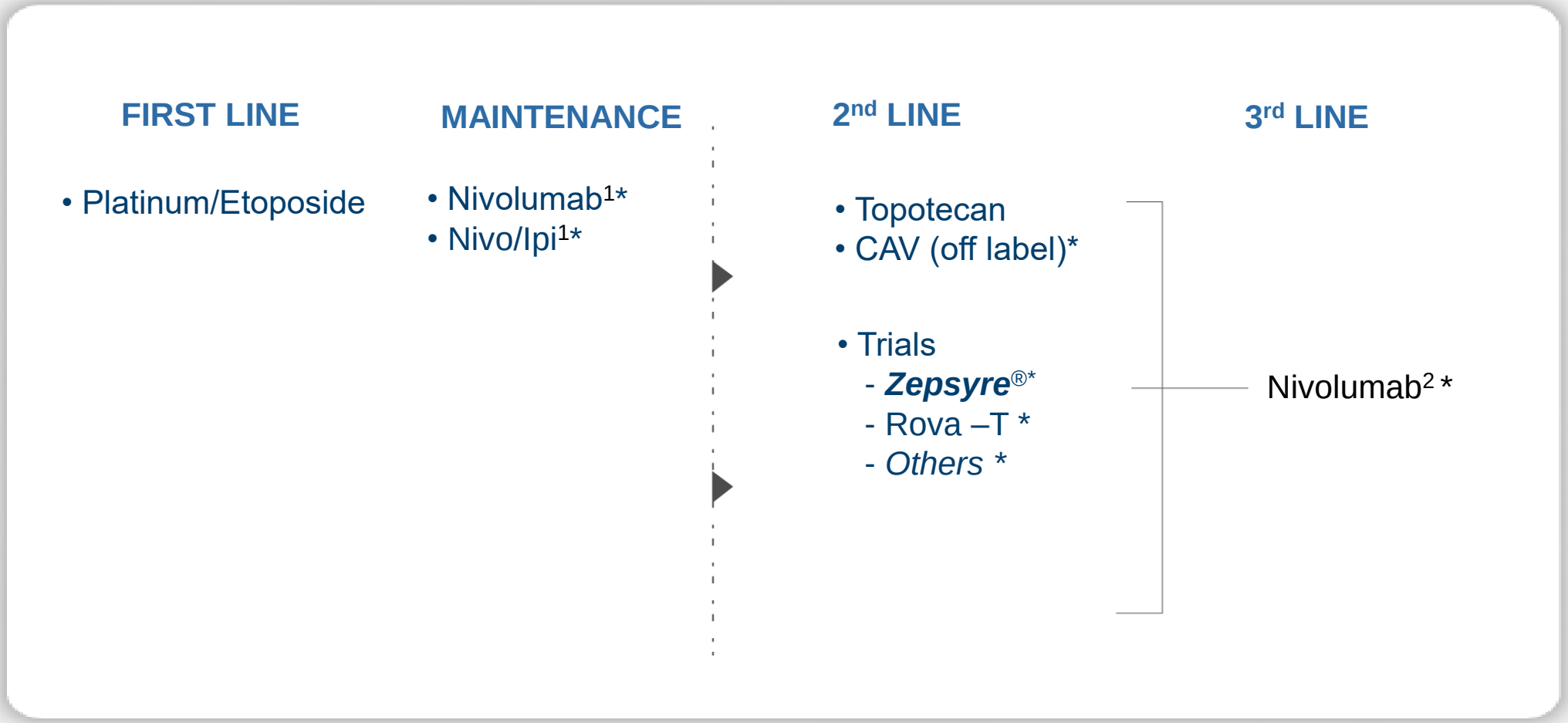



- Most common genomic alterations are in tumor suppressor genes
  - Turning off an "off switch" is a real challenge

Peifer et al Nature Genetics 2012

# ZEPSYRE®: SMALL CELL LUNG CANCER

## *Current and Emerging reatment paradigm*



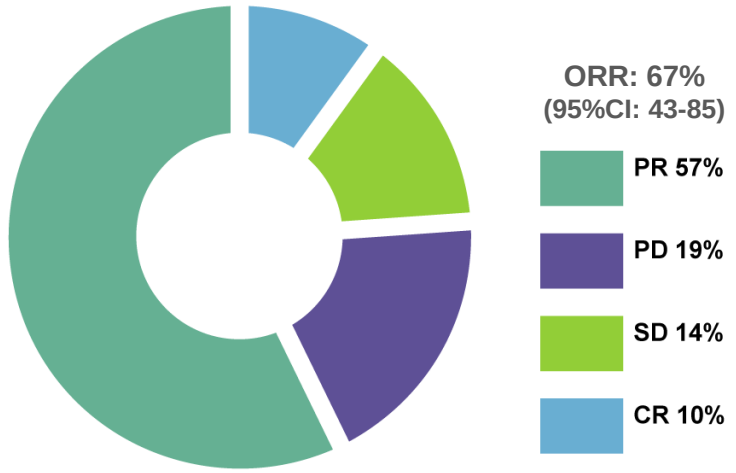

* Investigational drug or not aproved for this indication

1. Not approved; however both included in NCCN guidelines
2. Nivo filed for 3rd line SCLC with FDA; PDUFA August 6 2018

# ZEPSYRE®: PHASE I/II RELAPSED SMALL CELL LUNG CANCER

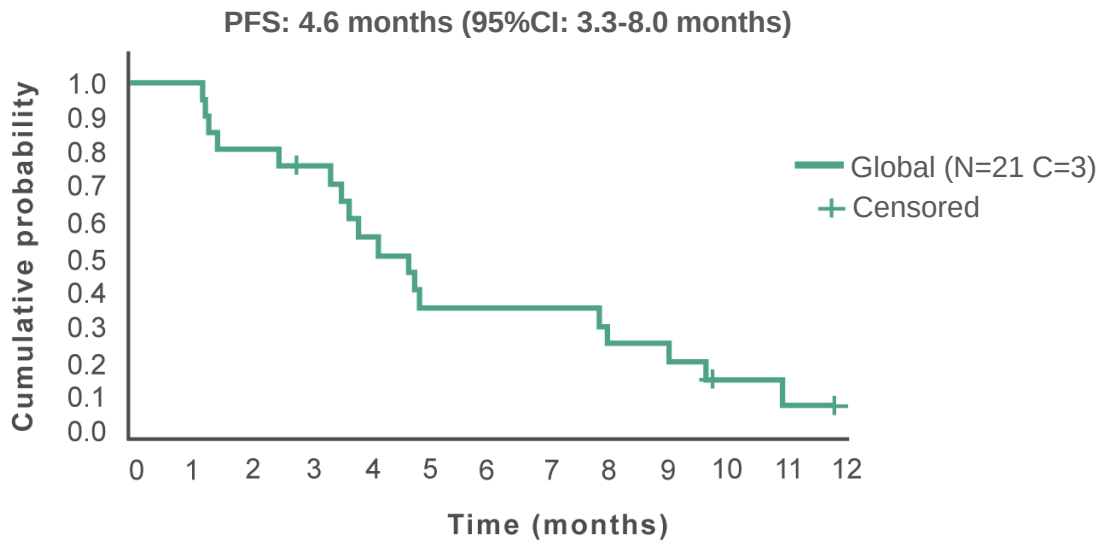
## *Cohort A: ASCO 2015 n=21*

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




M. Forster et al. ASCO 2015

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




Other examples ORR in SSLC:

- 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:

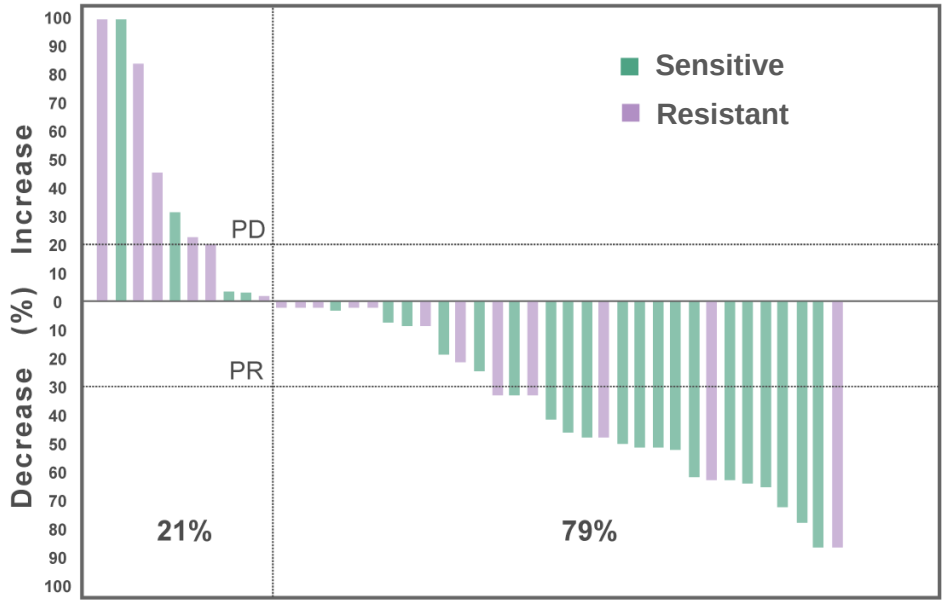
- CAV: 2.8 months
- Topotecan 3 months

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

# ZEPSYRE®: PHASE I/II 2nd LINE SMALL CELL LUNG CANCER

## *Combo and Monotherapy latest data*

| EFFICACY | | | |
|---|---|---|---|
| RESPONSE EVALUABLE PATIENTS | Lurbinectedin +DOX (q3wk) | | Lurbinectedin single-agent (q3wk) |
| | Cohort A L 3-5 mg FD D1 + DOX 50 mg/m² D1 (n=21) | Cohort B L 2 mg/m² D1 + DOX 40 mg/m² D1 (n=27) | L 3.2 mg/m² D1 n=61 |
| CR | 2 (10%) | 1 (4%) | - |
| PR | 12 (57%) | 9 (33%) | 24 (39%) |
| ORR | 14 (67%) | 10 (37%) | 24 (39%) |
| SD | 3 (14%) | 9 (33%) | 21 (34%) |
| PD | 4 (19%) | 8 (30%) | 16 (26%) |
| DCR | 17 (81%) | 19 (70%) | 45 (74%) |
| DOR (mo) | 4.5 | 5.2 | 6.2 |
| PFS (mo) CTFI >30d* | 4.7 | 5.3 | - |
| PFS (mo) Platinum-sensitive | 5.8 | 6.2 | n.a |
| PFS (mo) median | n.a | n.a | 4.1 |
| OS | n.a | n.a | 11.8 |




**Combined Cohorts A&B[1]**
**N=48**

**CR 6%**
**PR44%**
**ORR 50%**
**PFS 5.0m**

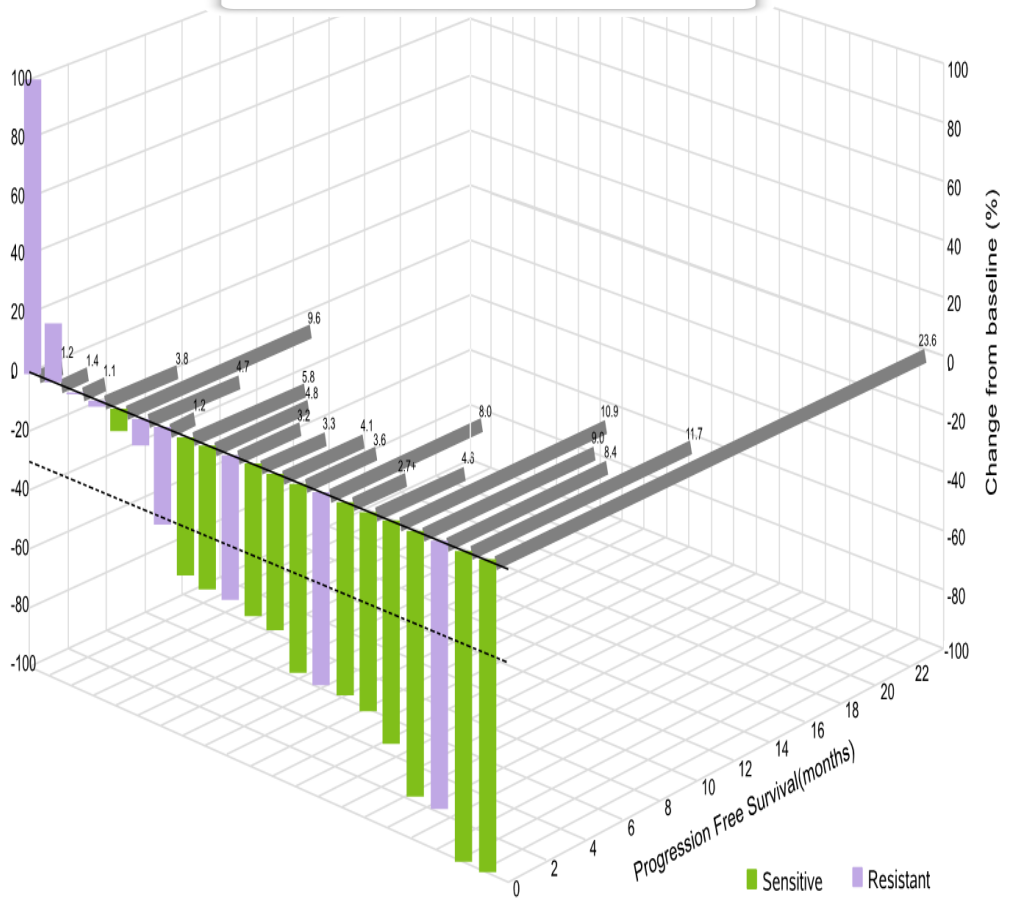
Phase III regimen and endpoint

1. Cohort A as ASCO 2015, Cohort B as ESMO 2017 and mono as ASCO 2018.

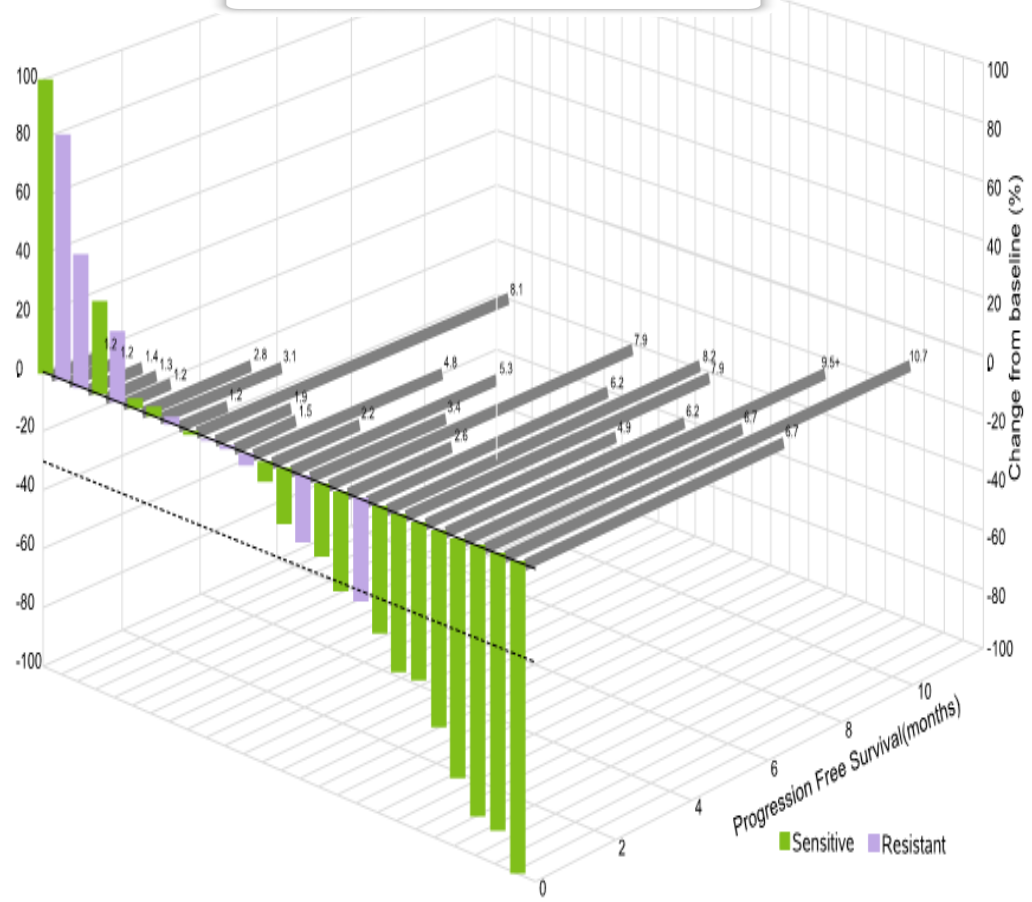
# ZEPSYRE®: PHASE I/II 2nd LINE SMALL CELL LUNG CANCER

*Cohorts A & B, maximal tumor reduction according to CTFI and PFS (n=21, 27)*

**PFS: 4.7m**
**Median DOR:4.5mo**




**PFS: 5.3m**
**Median DOR:5.2mo**



# WHAT DOES OVARIAN PHASE III TELL US RE SCLC?

**OVARIAN:**

- Drug is active
- Drug is tolerated
- Phase III BSA DOSE ~75% OF Phase II Fixed Dose
- Rescue G-CSF
- Weekly scanning
- Lab abnormalities grade 3-4 stat sig better for anemia, neutropenia, thrombocytopenia vs. control

**SCLC:**

- Monotherapy also shows activity, could offer alternative, especially for older/frailer or with cardio co-morbidities
- Phase III BSA DOSE ~90% OF Phase II Fixed Dose
- Prophylaxis G-CSF
- Bi-weekly scanning
- Data showing neutropenia inc. FN and thrombocytopenia are mainly early cycle, transient, and successfully managed with dose modifications/GCSF.

# NON HEAD-TO-HEAD COMPARISONS

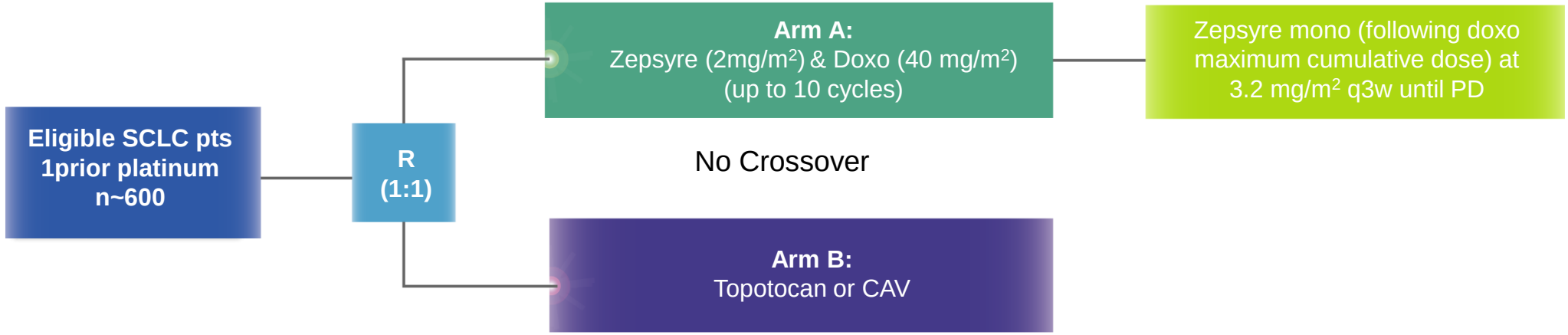
| | Cohort A, n=21 FD combo doxo | Cohort B, n=27 BSA combo doxo | Monotherapy n=61 | Topotecan label N=107 | CAV (from Topo label), n=104 |
|---|---|---|---|---|---|
| ORR | 67% | 37% | 39% | 24% | 18% |
| DCR | 81% | 70% | 74% | | |
| PFS CTFI>30d | 4.7m (CTFI>30d) | 5.3m (CTFI>30d) | 4.1m | 3.1m | 2.8m |
| OS | | World Lung 2018 | 11.8m | 5.8 | 5.7m |
| FN Gr 3-4 | 36% | 12% | 9% | 28% | 26% |
| Anemia Gr 3-4 | 46% | 25% | 6% | 42% | 20% |
| Thrombocytopenia G3-4 | 32% | 22% | 8% | 29% (G4) | 5% (G4) |
| Neutropenia G3-4 | 96%* | 93%* | 39%* | 70% (G4) | 72% (G4) |

* G-CSF give as rescue in 71%, 43% and 18% respectively, Phase III using prophylaxis

# ZEPSYRE®: PHASE III RELAPSED SMALL CELL LUNG CANCER

## *ATLANTIS Trial Design SCLC (Trial initiated August 2016); Anticipate data 2019*

- **Primary endpoint: median OS HR ≤ 0.75 with 90% power (10m vs. 7.5m)**
- **Key secondary endpoints:**
  - PFS
- **Registration Strategy**
  - Interim analysis passed @n=150 after 2 cycles (NOV'17).
  - Interim analysis passed @n=500 (May'18).
  - Trial supported by ongoing monotherapy trial (n=61 at ASCO 2018).
  - Trial will complete enrolment ~Q3 2018




Stratification by prior PD1/PDI-1 and brain mets.

# ZEPSYRE®: ATLANTIS TRIAL

***Change primary endpoint from PFS to OS***

- PharmaMar recently received the OS analysis for cohort B of the combo Phase I/II (submitted to IASLC World conference on Lung Cancer) which prompted the change
- Regulators prefer OS vs. surrogate endpoints, especially in an aggressive and fatal disease such as SCLC
- Greater chance of approval and uptake

- The change adds a modest ~6-8m to the data read out timing

# KEY IP AND BARRIERS TO ENTRY

- **Yondelis:**
  - EU: Sarcoma orphan expired 9/17,  ovarian orphan 2019, use 2022, formulation 2025#
  - US:  Sarcoma orphan 2022, formulation 2025#
  - Japan: Sarcoma orphan 2022, formulation 2025#. Ovarian 10 years from approval orphan
  - Manufacturing US/EU/Japan 2031
- **Zepsyre**
  - All indications orphan US/EU/JP (7/10/10yrs)
  - Composition 2024 (US)*, 2022 (EU)*
  - SCLC combo doxorubicin 2031
- **All indications:** Chemistry/synthesis/manufacturing know how

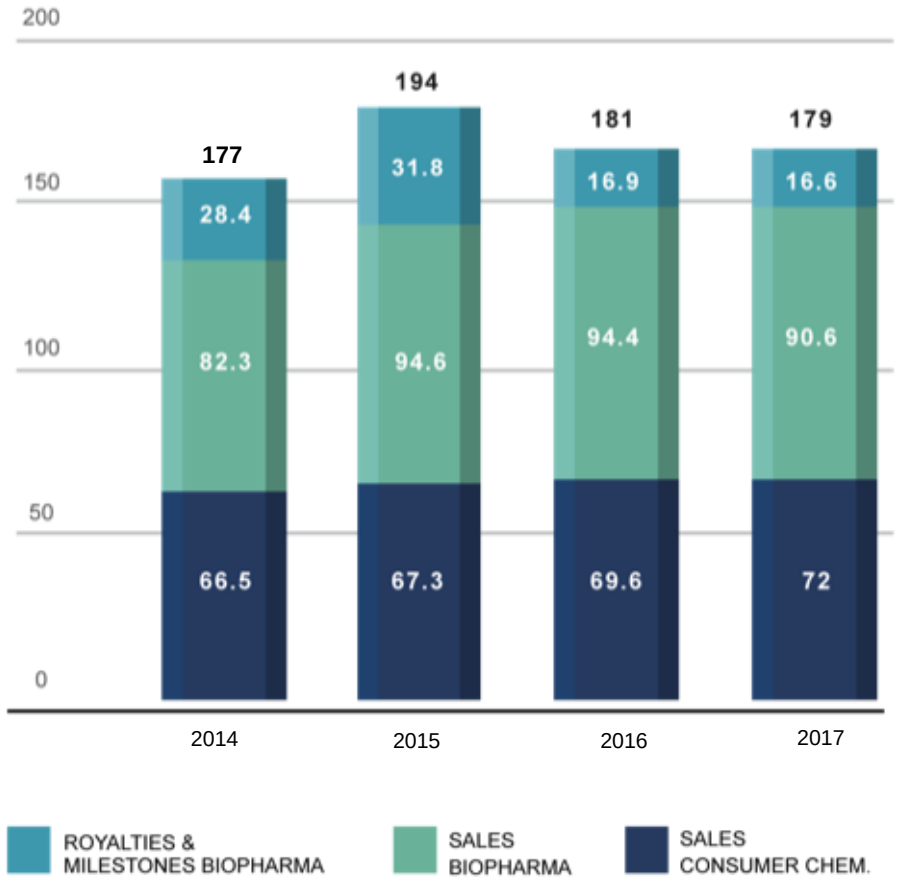
* Subject to potential patent term extension

# patent pending

# GROUP REVENUES AND R&D EXPENSES

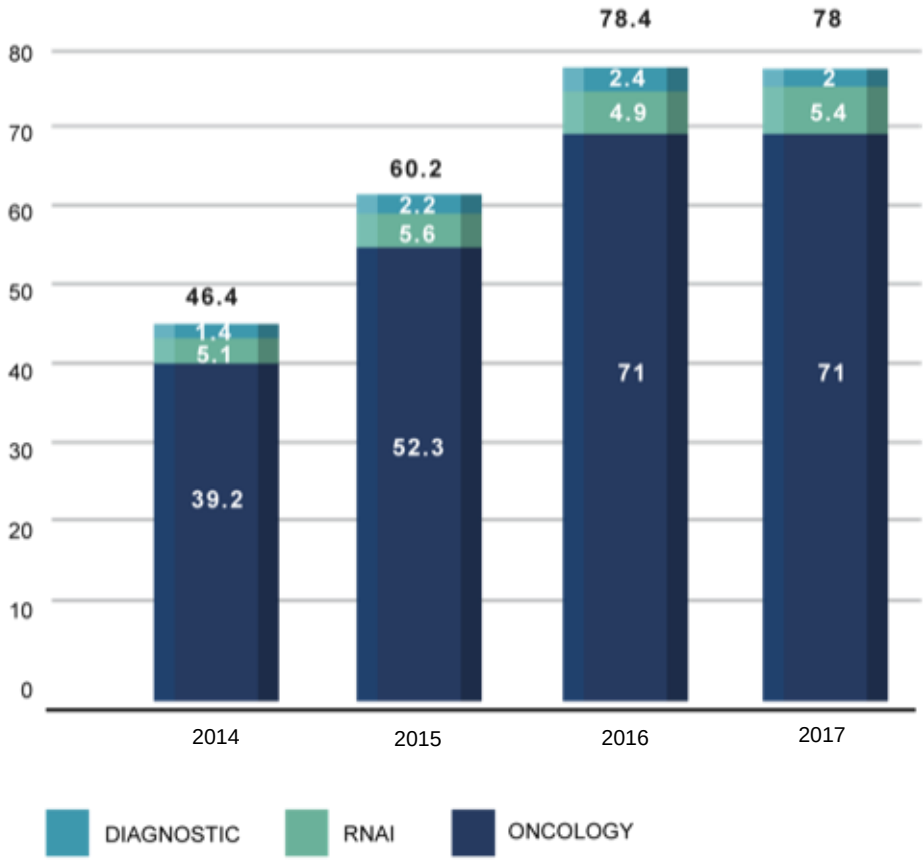
## Revenues

€ millions




## R&D

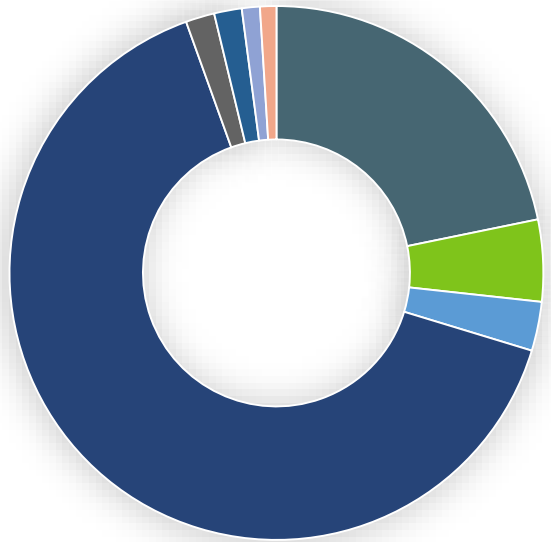
€ millions



# KEY FACTS AND CURRENT SHAREHOLDERS

## KEY FACTS

- Ticker: PHM SM
- Market Cap*: C. € 330 million
- 2017 Total Income: € 179 million
- 2017 EBITDA: € -7.4 million




Source: Bloomberg March 2nd 2018

# KEY EVENTS

***Transformative times for Pharma Mar; catalyst 2018***

- ✓ SCLC futility analysis
- ✓ Zepsyre® Phase III platinum-resistant ovarian cancer 1H ’18; *primary endpoint not met*
- ASCO Zepsyre® : Monotherapy SCLC, TiP ATLANTIS, Ewing’s sarcoma
- Zepsyre® SCLC ATLANTIS Phase III complete enrolment mid’ 18
- Zepsyre® PI/II cohort B OS data submitted to World Lung (September)
- Zepsyre® CORAIL ovarian submission to ESMO (October)
- Zepsyre® CORAIL OS data (Q4)
- Update(s) on Zepsyre SCLC monotherapy trial, ESMO and others
- Protocol finalization and initiation of combos with Keytruda and Tecentriq
- Zepsyre® ATLANTIS data (2H 19)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# CONTEXTUAL COMPARATIVE DATA, READING ACROSS TRIALS.

# STANDARD OF CARE FOR RELAPSED SMALL CELL LUNG CANCER

## *Competitive Landscape after first line treatment: Platinum/Etoposide*

| 2nd line | 3rd line | N | PFS (ORR%) | Notes |
|---|---|---|---|---|
| **Zepsyre/Doxo** | | **48** | **5.0 (50%)** | **ASCO 2015/ ESMO 2017** |
| Paclitaxel | | Literature | (29) | Nature Reviews Glisson,2011[1] |
| Topo | | Literature | 3.0 (24) | Glisson,2011[1] |
| CAV | | Literature | 2.8 (19) | Glisson,2011[1] |
| Nivo | Nivo | 98 | 1.4 (11) | ASCO 2016-7 ESMO 2017 |
| Nivo/Ipi | Nivo/Ipi | 61 | 2.6 (23) | ASCO 2016-7 ESMO 2017 |
| Pembro | Pembro | 24 | 1.9 (33) | ESMO 2017 |
| Pembro | Pembro | 45 | 1.4 (12) | ESMO 2017 |
| | Rova-T | 177 | (16) | 3rd line; "DLL 3 hgh" [2] |
| Rova-T | | 48 | 4.3 (38) | 2nd line; DLL3 "high" [2] |
| Sacituzumab | Saci | 50 | 3.7 (14) | "Heavily pre-treated" |

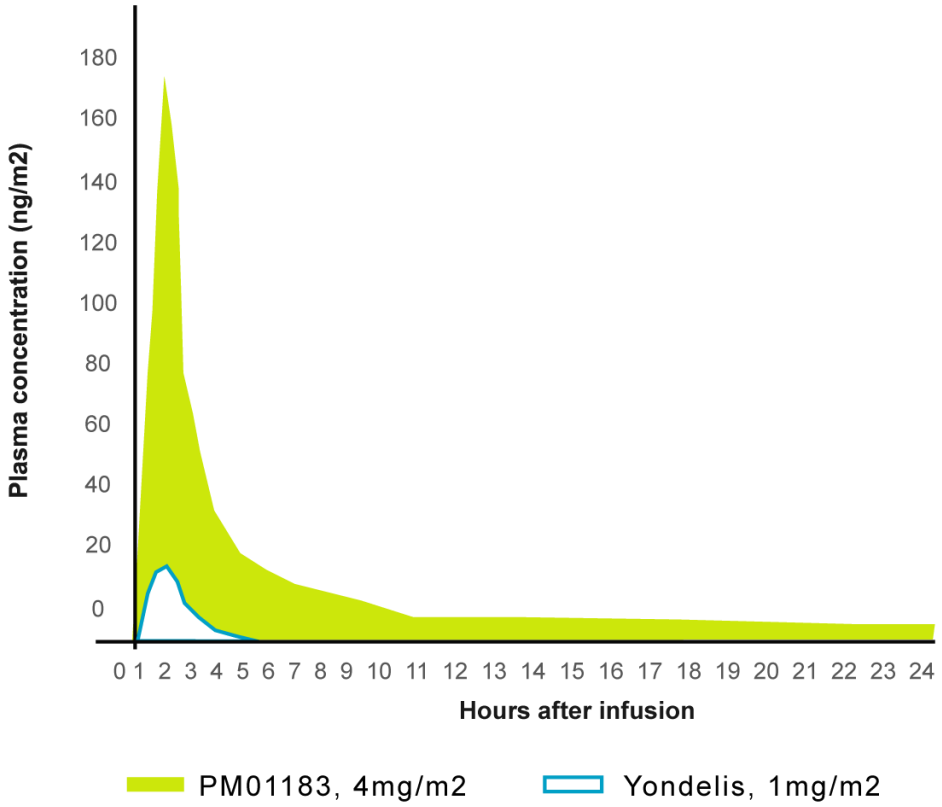
1. Source: Nature Reviews 2011;8:611-19. William N, Glisson, Lancet Oncology 6/4/16; Merck PR 12/6/16; Lancet Oncology 12/5/16
2. Source: AbbVie

# SCLC: A history of failure

| MoA | Drug | Study | Setting | N | Outcome |
|---|---|---|---|---|---|
| PARP | Olaparib | PII RDB vs. pbo | 2L | 220 | Inferior to pbo |
| PARP | Veliparib | PI/II +/- Cis/Etop | Extensive | 128 | PFS 6.1 vs. 5.5<br>OS 10.3m vs. 8.9m |
| Aurora | Alisertib | PII solids | Refractory | 48 | ORR 21% |
| Aurora | Alisertib | PII +/- paclitax | 2L | 178 | PFS 87d vs. 50d<br>OS 186d vs. 165d |
| RAD51 | Amuvantinib | PII + carbo/etop | R/R | 23 | CBR 12% |
| Wee1 | AZD1775 | Phase I +chemo | Refractory solids | 202 | ORR 10% |
| NOTCH | Tarextumab | PII+etop/plat | Naïve extensive | 145 | “No difference” |
| DLL3 | Rova-T | Open label PII | 3L | 349 | 16% ORR in “DLL3 high” |
| MoA | Drug | Study | Setting | N | Outcome |
| PARP | Olaparib | PII RDB vs. pbo | 2L | 220 | Inferior to pbo |
| PARP | Veliparib | PI/II +/- Cis/Etop | Extensive | 128 | PFS 6.1 vs. 5.5<br>OS 10.3m vs. 8.9m |

# ZEPSYRE® vs YONDELIS®

## Different pharmacological profile




## Better safety profile