Cannabinoid agents for the treatment of multiple myeloma and related conditions

CONTENT

1. The Institutions & Current pipeline

2. The Product

a) Target Indications
b) Innovative aspects
c) Current status of development: PoC & trials already performed
d) Differential features facing the market & Business opportunities
e) IPR protection
f) Pitfalls & Risks to be considered

1. The Institution & Current pipeline

The **Institute of Biomedicine of Seville (IBiS)** is a comprehensive and multidisciplinary biomedical research facility focused on translational research on the most prevalent diseases

IBiS is supported by all the major regional and nation-wide research agencies in Andalusia and Spain

IBiS promotes the **transfer of knowledge** to the clinical setting

Hospital Universitario Virgen del Rocío is one of the largest university hospitals in Spain providing health coverage to over half million people and acts as a hospital of reference in some of its specialized areas.

1. The Institution & Current pipeline

Prof. José Antonio Pérez Simón

- **Director of the Department of Hematology and Hemotherapy at Virgen del Rocio / Virgen Macarena University Hospital and Head of the Cell Therapy and New Therapeutic Targets in Onco-hematology research group at IBiS.**

- Doctor of Medicine from the University of Salamanca, Prof. Pérez Simón did his training in Hematology in the University Hospital of Salamanca, where he worked before joining the Virgen del Rocio University Hospital. He also specialized at the Fred Hutchinson Cancer Research Center in Seattle (Washington, USA) and the Karolinska Institute in Stockholm (Sweden), so he was able to expand their knowledge in the field of transplantation (both in attendance and in research).

- His area of research is mostly focused on **Hematopoietic Stem Cell Transplantation and Cell Therapy**. In this field he has **> 140 manuscripts** in international prestigious journals, such as Blood, Leukemia, American Journal of Hematology and Cell Transplantation.

- **> 25 research projects** supported by national / international competitive grants.

1. The Institution & Current pipeline

PIPELINE 2014

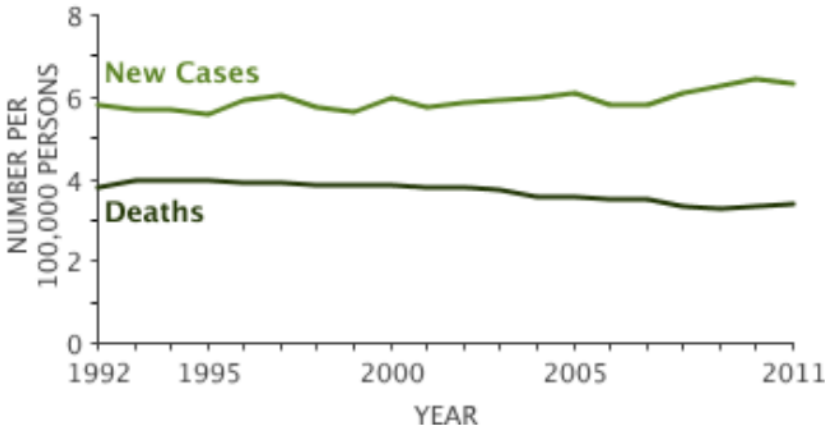
DIAGNOSTICS					
REFERENCE	TECHNOLOGY	THERAPEUTIC AREA	STAGE OF DEVELOPMENT		
			DESIGN	CLINICAL VALIDATION	SITE
FISEVI 120	METHOD FOR THE DIAGNOSIS OF NEUROMUSCULAR DISEASES	Musculoeskeletal disorders	▶▶▶▶▶	▶▶▶▶▶	EUROPE
FISEVI-13004/05	COMBINED GENETIC POLYMORPHISMS FOR PREDICTING THE RESPONSE TO TREATMENT IN PATIENTS INFECTED WITH HEPATITIS C VIRUS	Infectious diseases	▶▶▶▶▶	▶▶▶▶▶	EUROPE
FISEVI-133	METHOD AND DIAGNOSTIC KIT FOR PATIENTS SUFFERING CORD AND/OR LUNG CANCER	Oncology	▶▶▶▶▶	▶▶▶▶▶	EUROPE
FISEVI-124/13008	METHOD AND KIT FOR THE CHOICE OF TREATMENT & RESPONSE PREDICTION TO CHEMOTHERAPY IN COLORECTAL CANCER	Oncology	▶▶▶▶▶	▶▶▶▶▶	EUROPE

THERAPY						
REFERENCE	TECHNOLOGY	THERAPEUTIC AREA	STAGE OF DEVELOPMENT			
			RESEARCH	PRECLINICAL VALIDATION	CLINICAL VALIDATION	SITE
FISEVI-13002	AGENTS FOR THE TREATMENT OF MULTIPLE MYELOMA	Oncology	▶▶▶▶▶	▶▶▶▶▶	▷▷▷▷▷	EUROPE
FISEVI-121	METHOD FOR T-CELL SELECTION	Other (transplants)	▶▶▶▶▶	▶▶▶▶▶	▷▷▷▷▷	EUROPE
FISEVI 141	ANTI N-PROCALCITONIN ANTIBODIES FOR THE DIAGNOSIS AND TREATMENT OF DISEASES INVOLVING ALTERATION OF THE INFLAMMATORY RESPONSE, SUCH AS SPESIS AND LUNG INJURIES	Infectious diseases	▶▶▶▶▶	▶▶▶▶▶	▷▷▷▷▷	EUROPE
FISEVI-13020	ANTIDEPRESSANT-LIKE, NEUROPROTECTIIVE, AND ANTI--INFLAMMATORY EFFECTS MEDIATED BY IMMUNONEUTRALIZATION OF ENDOGENOUS AMINOPROCALCITONIN	Central Nervous System	▶▶▶▶▶	▶▶▶▶▶	▷▷▷▷▷	EUROPE
FRM 5	USE OF MESENCHYMAL CELLS TO MAINTAIN BLOOD CELL PRODUCTION	Other (transplants)	▶▶▶▶▶	▶▶▶▶▶	▷▷▷▷▷	EUROPE
FISEVI-13007	ANTITUMOR GENE THERAPY WITH NOS-3	Oncology	▶▶▶▶▶	▶▶▶▶▶	▷▷▷▷▷	EUROPE
FISEVI-13014	LYSOPHOSPHARTIDYLCHOLINE FOR THE DIRECT PROPHYLACTIC TREATMENT OF A NOSOCOMIAL INFECTION CAUSED BY *ACINETOBACTER BAUMANNII*	Infectious diseases	▶▶▶▶▶	▷▷▷▷▷	▷▷▷▷▷	EUROPE
FISEVI-13019	COMBINED COMPOSITIONS FOR THE TREATMENT OF ARTERIAL VASOSPASM	Cardiovascular system	▶▶▶▶▶	▷▷▷▷▷	▷▷▷▷▷	EUROPE

a) Target Indications

- **Multiple myeloma (MM)** develops in 6.1/ 100,000 people/ year with a mortality of 3.4/ 100,000 people/ year > **RARE DISEASE** but growing prevalence
- MM is the 2nd most prevalent blood cancer (10%) after non-Hodgkin's lymphoma, representing approx. 1% of all cancers and 2% of all cancer deaths.

Estimated New Cases in 2014	24,050
% of All New Cancer Cases	1.4%
Estimated Deaths in 2014	11,090
% of All Cancer Deaths	1.9%

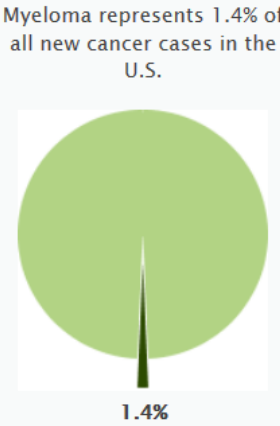


Source: US National Cancer Institute Statistics

a) Target Indications

- **Multiple myeloma (MM)** develops in 6.1/ 100,000 people/ year with a mortality of 3.4/ 100,000 people/ year > **RARE DISEASE** but growing prevalence
- MM is the 2nd most prevalent blood cancer (10%) after non-Hodgkin's lymphoma, representing approx. 1% of all cancers and 2% of all cancer deaths.

	Common Types of Cancer	Estimated New Cases 2014	Estimated Deaths 2014
1.	Prostate Cancer	233,000	29,480
2.	Breast Cancer (Female)	232,670	40,000
3.	Lung and Bronchus Cancer	224,210	159,260
4.	Colon and Rectum Cancer	136,830	50,310
5.	Melanoma of the Skin	76,100	9,710
6.	Bladder Cancer	74,690	15,580
7.	Non-Hodgkin Lymphoma	70,800	18,990
8.	Kidney and Renal Pelvis Cancer	63,920	13,860
9.	Thyroid Cancer	62,980	1,890
10.	Endometrial Cancer	52,630	8,590
	–	–	–
14.	**Myeloma**	**24,050**	**11,090**

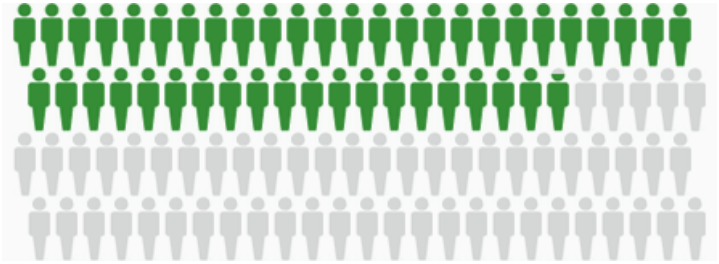


Source: US National Cancer Institute Statistics

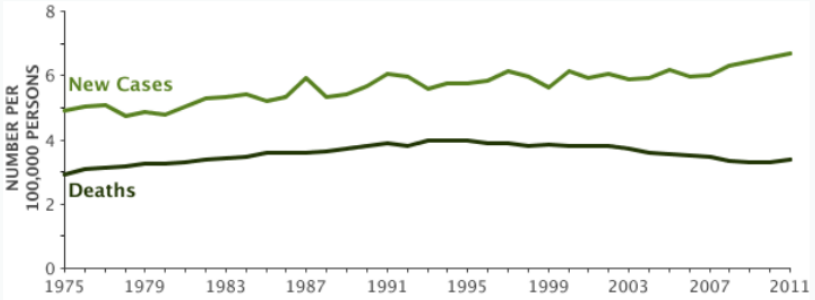
a) Target Indications

- MM is considered to be **incurable** but treatable > **Median survival is 3–4 years**, with conventional treatment, which may be extended to 5–7 years or longer with advanced treatments.

Percent Surviving 5 Years
44.9%
2004–2010



New Cases, Deaths and 5-Year Relative Survival View Data Table



Year	1975	1980	1985	1990	1994	1998	2002	2006
5-Year Relative Survival	26.3%	25.8%	27.0%	29.6%	30.7%	33.9%	39.5%	45.1%

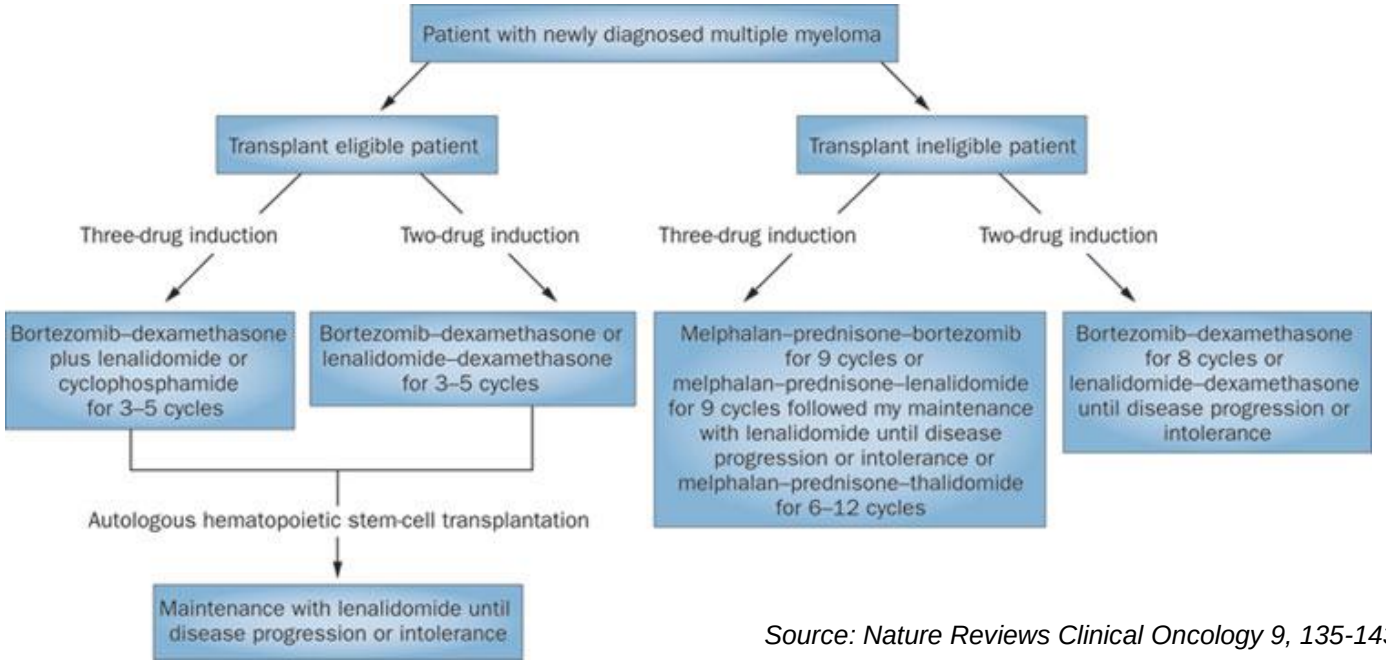
SEER 9 Incidence & U.S. Mortality 1975–2011, All Races, Both Sexes. Rates are Age-Adjusted.

Source: US National Cancer Institute Statistics

a) Target Indications

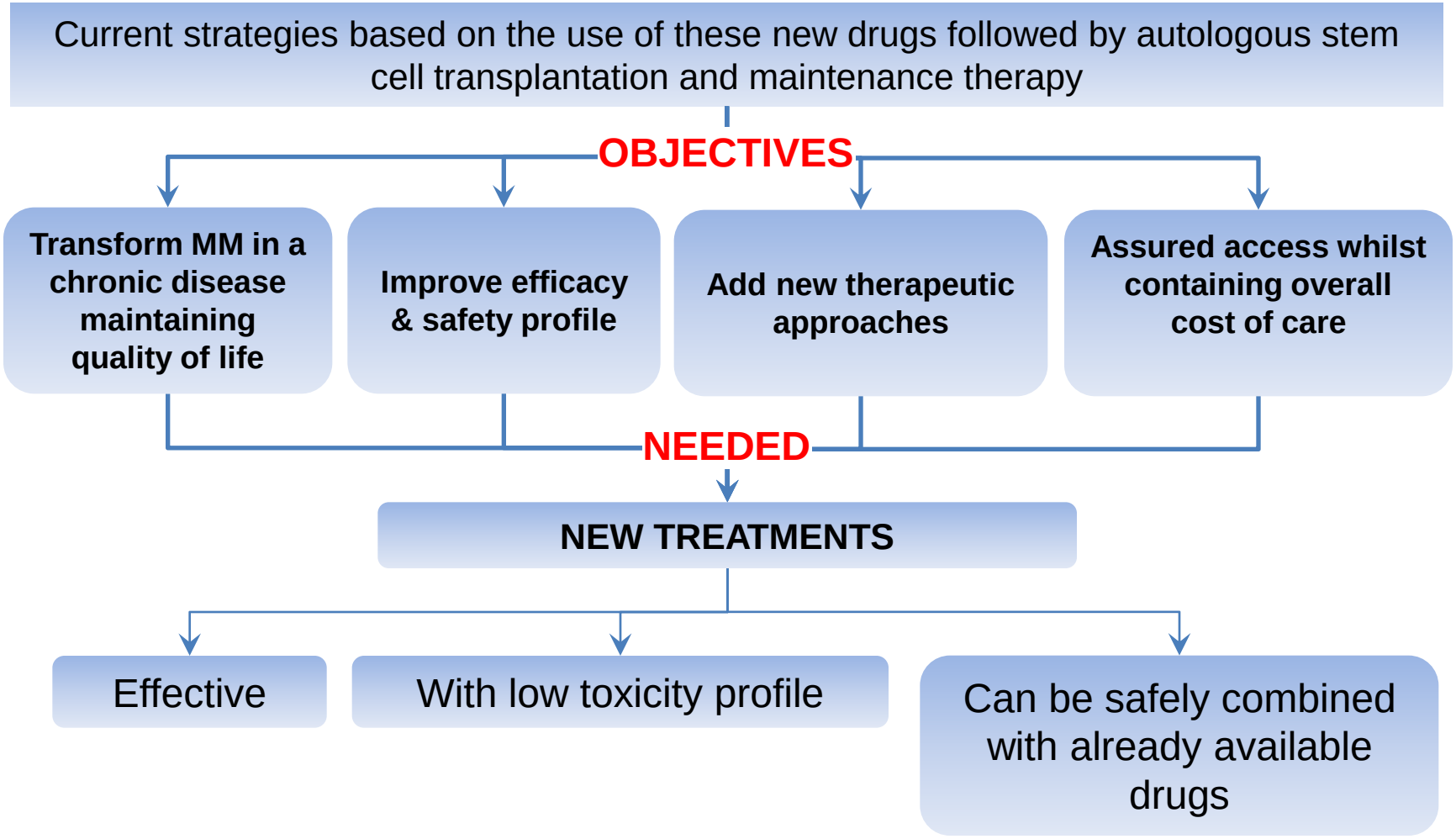
- Although new therapeutic regimens such as the proteasome inhibitor bortezomib and the immunomodulatory drugs thalidomide and lenalidomide have improved patient survival, **nearly all patients eventually relapse.**

Suggested approach to the treatment of patients with newly-diagnosed MM



Source: Nature Reviews Clinical Oncology 9, 135-143 (March 2012)

b) Innovative aspects



b) Innovative aspects

Current strategies based on the use of these new drugs followed by autologous stem cell transplantation and maintenance therapy

OBJECTIVES

- **Transform MM in a chronic disease maintaining quality of life**
- **Improve efficacy & safety profile**
- **Add new therapeutic approaches**
- **Assured access whilst containing overall cost of care**

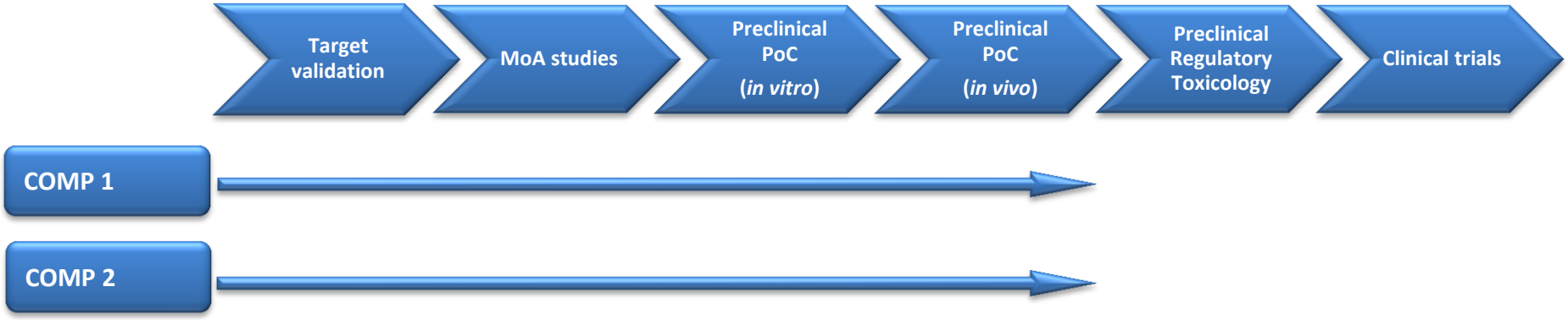
NEEDED

CANNABINOIDS

- **High cytotoxic effect in MM cells**.
- **Do not hamper viability of normal hematopoietic cells**.
- **Different types of cannabinoids** are currently being tested in several indications, some of them aimed to avoid chemotherapy-related toxicity.
- **Low toxicity profile** > Combined treatments & Induction or **maintenance therapy**.
- High number of **naturally available cannabinoids** & **well-defined chemical characteristics:** development platform of synthetic more specific & potent compounds.

c) Current status of development: PoC & trials already performed

COMPOUND 1	COMPOUND 2
Unspecific agonist of CB1 and CB2 cannabinoid receptors	**Specific CB2 agonist**



c) Current status of development: PoC & trials already performed

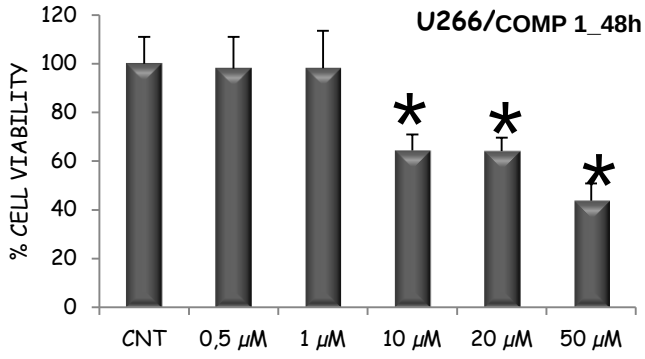
MECHANISM OF ACTION

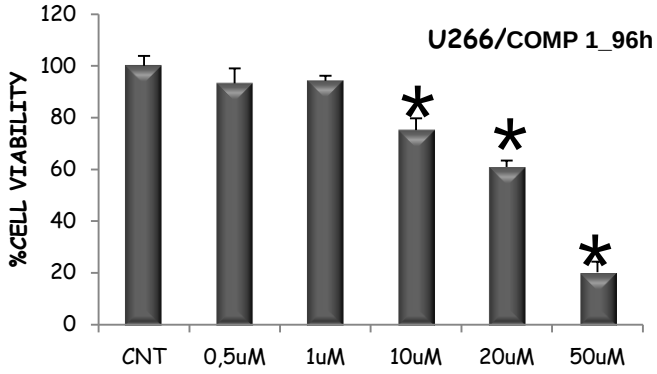
- Activation of caspase 8, 9, 3 and 2
- Inhibition of several MAP kinase pathways involved in myelomagenesis / cell proliferation and survival such as pAkT, pErK, among other pathways
- Modification of composition in cellular membranes of sphyngolipids involved in the control of cell viability, such as ceramides.

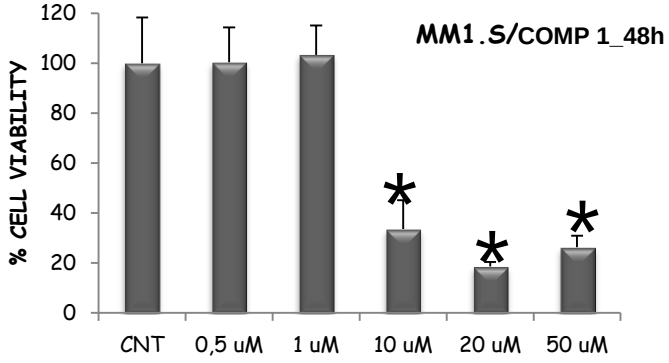
c) Current status of development: PoC & trials already performed

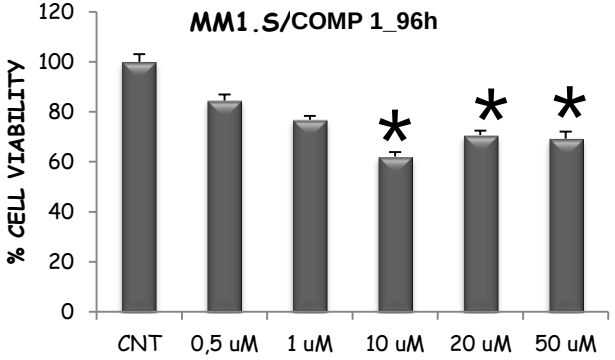
IN VITRO PoC

Dose-dependent inhibitory activity of viability





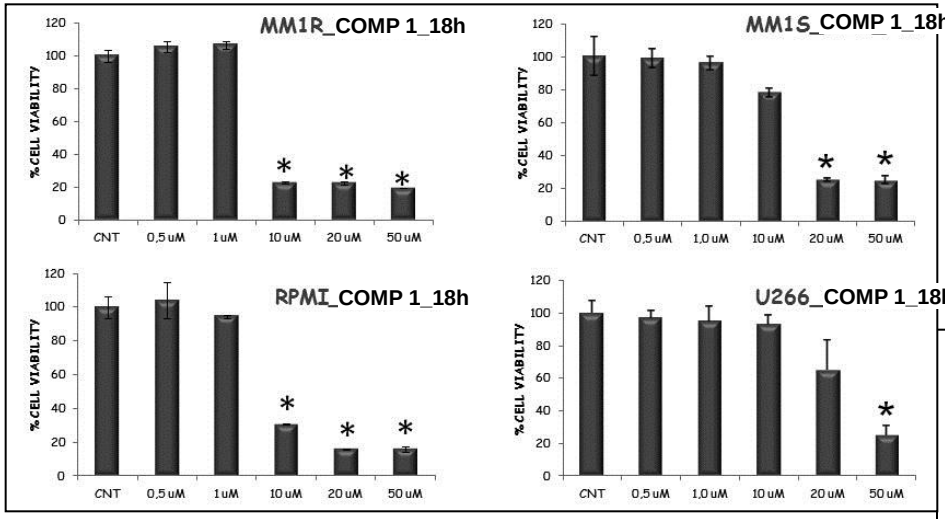


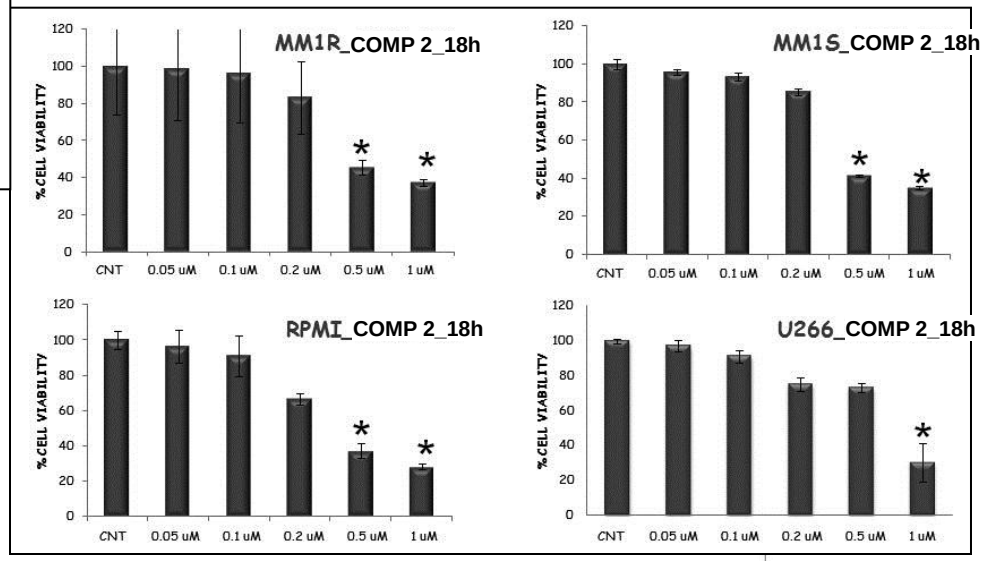


c) Current status of development: PoC & trials already performed

IN VITRO PoC

Dose-dependent inhibitory activity of viability

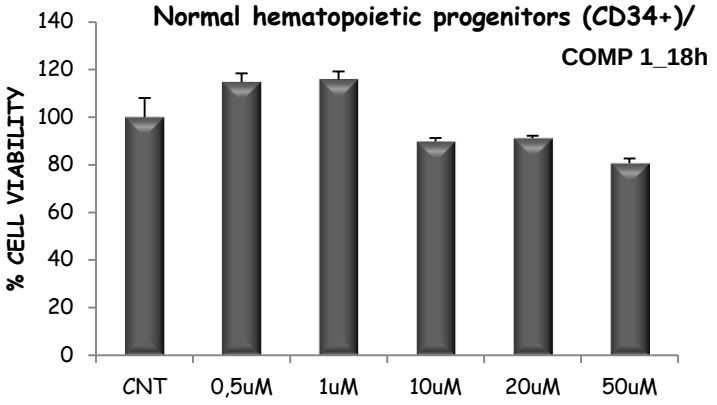


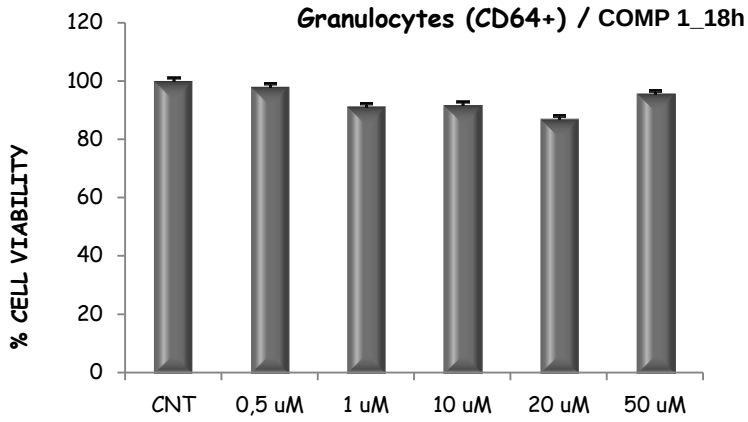


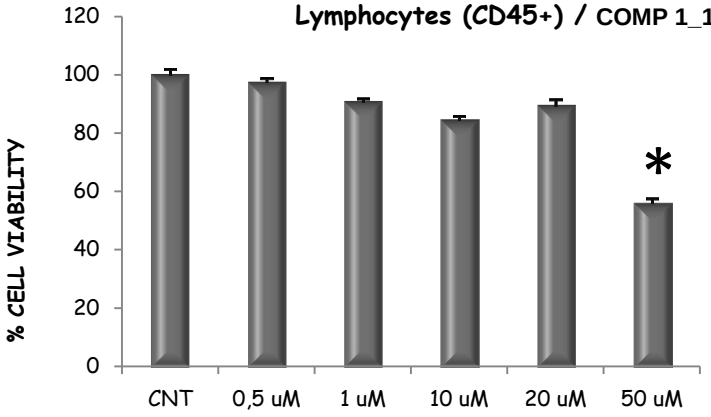
c) Current status of development: PoC & trials already performed

IN VITRO TOXICITY

Low toxicity profile



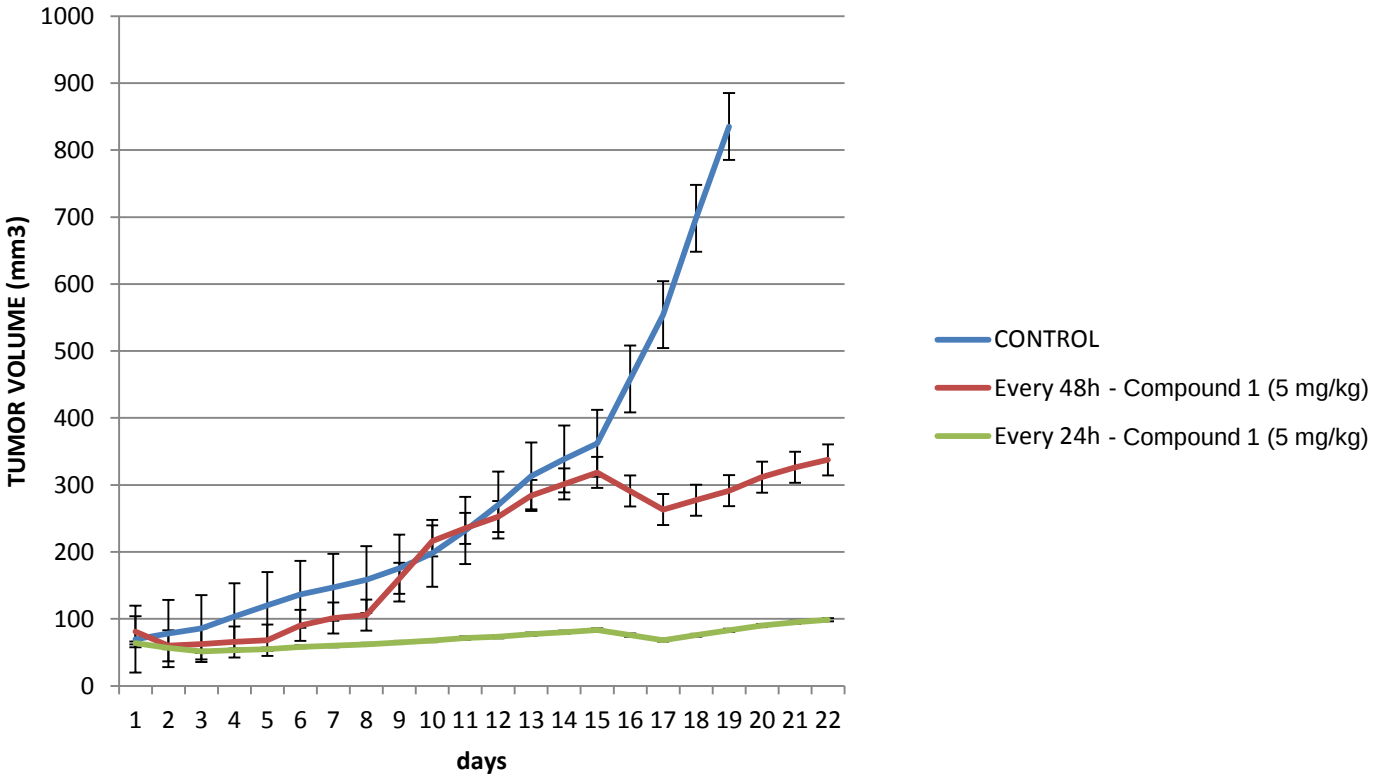




c) Current status of development: PoC & trials already performed

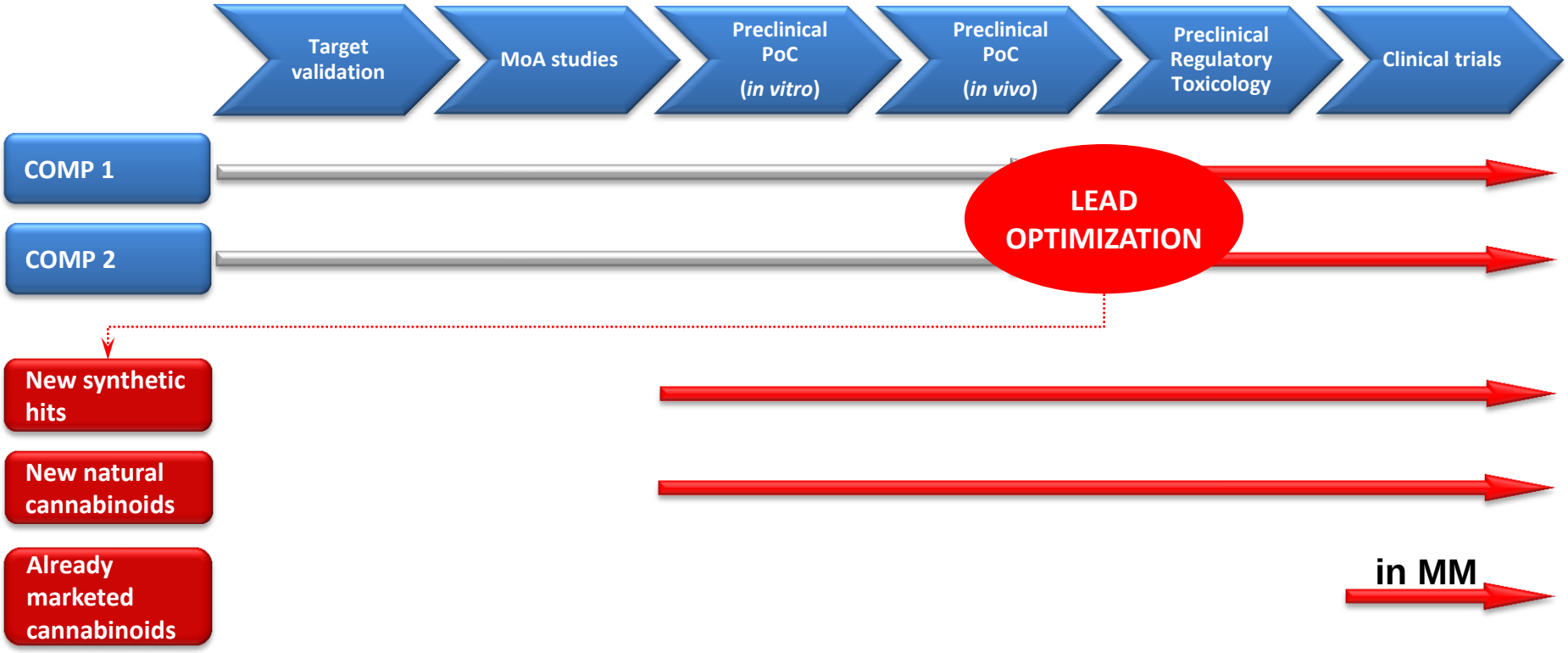
IN VIVO PoC

Able to COMPLETELLY ABOLISH already established tumor growth with COMPLETE regression of the tumor mass



c) Current status of development: PoC & trials already performed

NEXT STEPS OF DEVELOPMENT



d) Differential features facing the market & Business opportunities

EFFICACY

Not response to initial treatment

Growing although still LIMITED THERAPEUTIC ARSENAL: Challenging selection of optimal first-line regimen.

- Lenalidomide in first-line setting is currently not approved in any market.
- Lenalidomide–bortezomib–dexamethasone (RVD) therapy produces a complete or near-complete response only in 52% of newly diagnosed patients.
- RVD achieved responses in just 61% of patients with relapsed, refractory multiple myeloma who were often refractory to each of the three agents alone.

ALL PATIENTS INVARIABLY RELAPSE AFTER INITIAL TREATMENT STRATEGIES.

DRUG RESISTANCE

Drug resistance & relapse in the majority of patients

ROLE OF MAINTENANCE SETTING:

- **There is a role**
- **Nevertheless: toxicity remains a main issue**
- **Improvements in survival significant but still modest**
- **Growing costs for the Health System**

d) Differential features facing the market & Business opportunities

TOXICITY

Relevant treatment-related toxic effects

POTENTIAL CAPS ON EXTENDED DOSING DUE TO TOXICITY CONCERNS

- **Thalidomide >** Significant toxicities such as peripheral neuropathy, constipation and somnolence. High reported frequency of venous thromboembolism (VTE) (26%) when used in combination with high-dose dexamethasone.
- **Lenalidomide >** Significant toxicities such as neutropenia, VTE and risk of 2nd primary malignancies. At least threefold increased risk of clotting events in combination with high-dose glucocorticoids.
- **Bortezomib >** Peripheral neuropathy observed in approx. 40% of patients.

NEW APPROVED TREATMENTS

Optimum use remains to be elucidated

- **Carfilzomib > Inconvenient dosing schedule** (requires IV infusions on 2 consecutive days each week for the first three weeks of a 28-day cycle) & **Reimbursement issues** (authorized use only as last option).
- **Pomalidomide >** Boxed warning for **embryo-fetal toxicity** and **VTE**, only available through a restricted distribution system due to its **teratogenic potential**.

LARGER, RANDOMIZED CONTROLLED TRIALS ARE NECESSARY TO FURTHER ESTABLISH WHICH PATIENTS WILL BENEFIT FROM SPECIFIC REGIMENS

d) Differential features facing the market & Business opportunities

TOXICITY

Relevant treatment-related toxic effects

POTENTIAL CAPS ON EXTENDED DOSING DUE T TOXICITY CONCERNS

- **Thalidomide >** Significant toxicities such ripheral neuropathy, constipation and somnolence. Hig eported frequen enous thromboembolism (VTE) (26%) when used in co n with hi amethasone.
- lidomide oxi nd risk of 2nd primary nts in combination with

NEW APPROVED TREAT

Optimum use remains to be elucidated

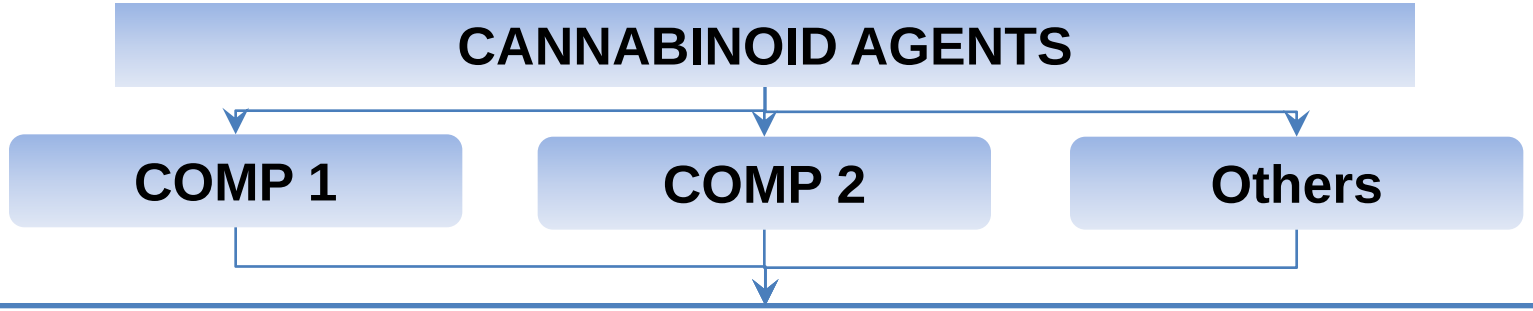
on 2 consecutive **ent issues**

- **Pom** and **VTE**, only available thr ti to its **potential**.

LARGER, RANDOM NTROLLED ARE NECESSARY FURTHER ESTABLISH WHICH PATIENTS W NEFIT FROM S FIC REGIMENS

BIGGEST CHALLENGE IN MM: HOW TO ACHIEVE RESPONSES WITHOUT SIGNIFICANTLY COMPROMISING QUALITY OF LIFE?

d) Differential features facing the market & Business opportunities

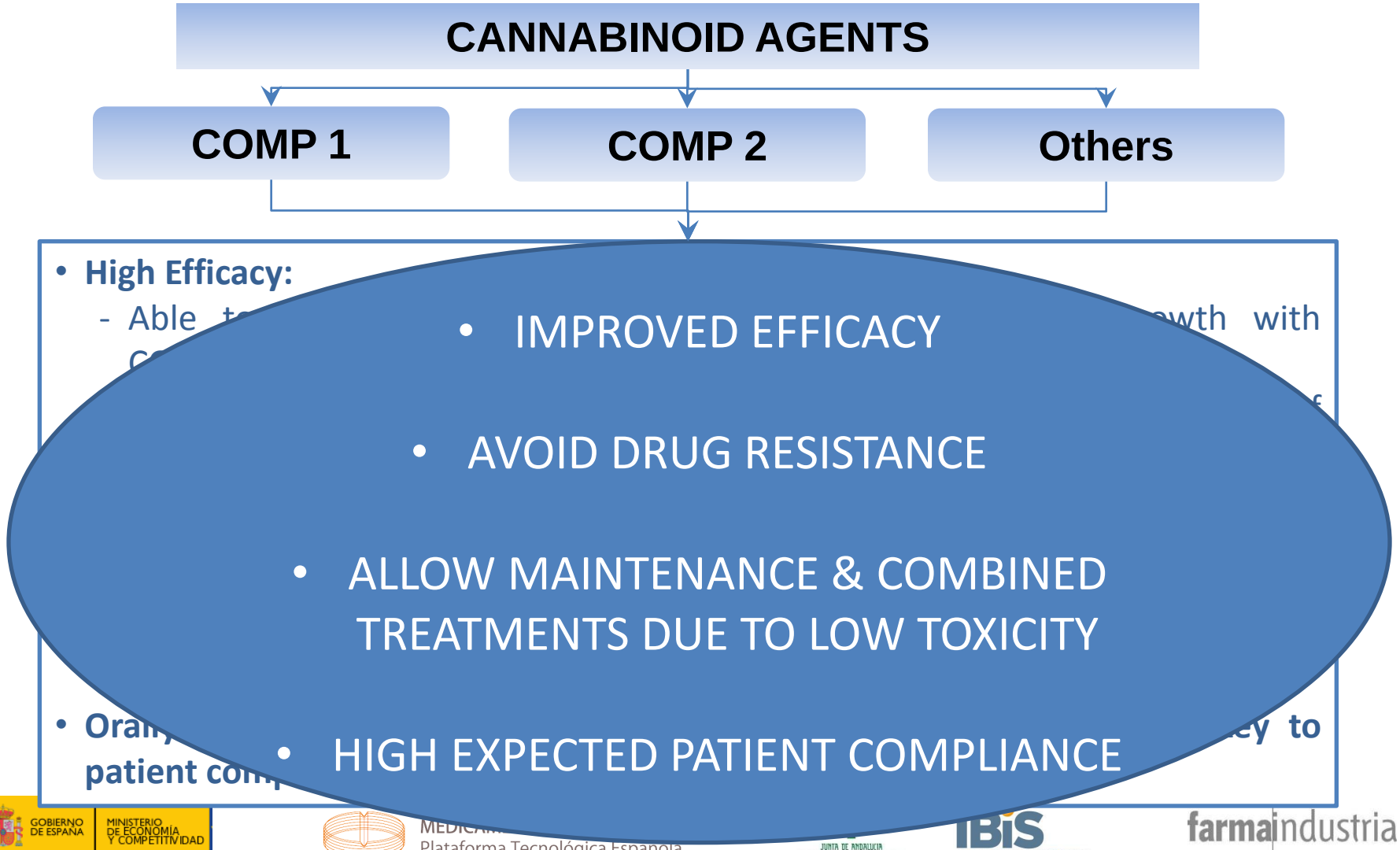


- **High Efficacy:**
  - Able to COMPLETELLY ABOLISH already stablished tumor growth with COMPLETE regression of the tumor mass in MM animal models.
  - High cytotoxic effect against MM cells whilst do not hamper viability of normal hematopoietic cells.

- **Low toxicity profile >** Do not hamper quality of life, especially if used as **maintenance therapy**, and can be **safely combined** with some of the already available drugs to treat this disease.

- **Orally available vs. IV administration (bortezomib & carfilzomib) > Key to patient compliance in maintenance therapy.**

d) Differential features facing the market & Business opportunities



d) Differential features facing the market & Business opportunities

BUSINESS & MARKET OPPORTUNITIES

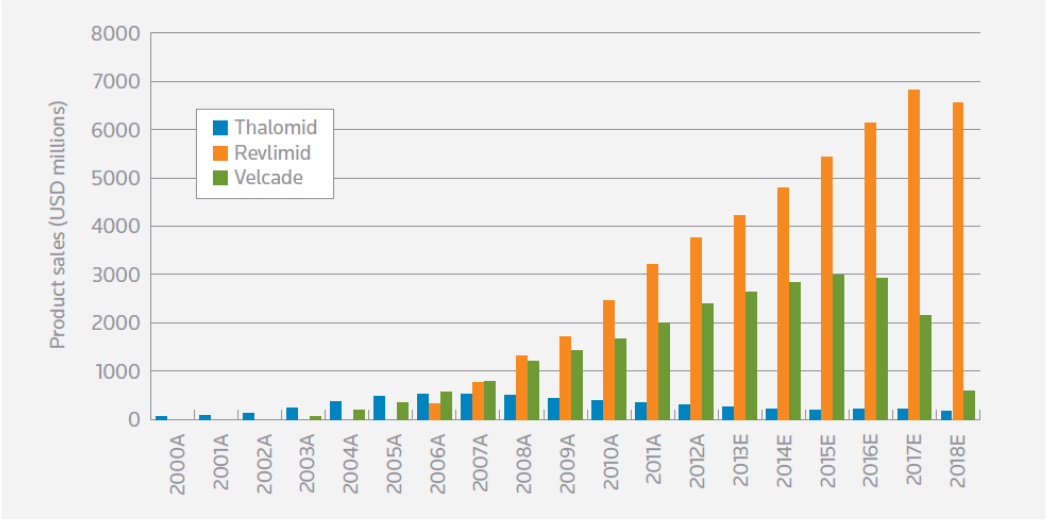
- Agents useful in the treatment of MM but also of **other monoclonal gammopathies** (plasma cell leukaemia, Waldeström macroglobulinaemia and amyloidosis).
- Regimens with **lower toxicity** are recommended for standard-risk patients to maximize quality of life.
- A program for synthetizing **new chemical analogs** to the original compound is being started.
- **Possible rapid advancement** from bench to the clinic, faster than as seen with bortezomib (progressed from first-in-human studies to US approval in 4.5 y).
- **Accelerated US approvals**, such as in carfilzomib or pomalidomide cases, in the space of 7 months.

d) Differential features facing the market & Business opportunities

BUSINESS & MARKET OPPORTUNITIES

- **Relapsed/ refractory setting >** Lack of a curative therapy and failure of currently available agents to induce long-term responses result in relapse in the vast majority of patients.
- **Maintenance therapy** > Lucrative opportunity (long-term treatments required).

- Growth prospects in MM are strong, with forecasts for the global market to grow from $7 billion in 2013 to **$15 billion by 2018** (Morningstar's analysis).



Source: Thomson Reuters. Spotlight on… Multiple Myeloma. Published May 2013

d) Differential features facing the market & Business opportunities

BUSINESS & MARKET OPPORTUNITIES

- **More than 560 deals related to MM** have been forged since 1986 (*Thomson Reuters Cortellis™ for Competitive Intelligence*).

DRUG	LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US $)*
daratumumab	Genmab	Janssen Biotech	Aug 2012	>~ 1.135 billion
elotuzumab	Facet Biotech	Bristol-Myers Squibb	Aug 2008	> 710 million
Kyprolis & oprozomib	Onyx Pharmaceuticals	Ono Pharmaceutical	Sep 2010	>~ 334 million

In early stage

In phase II

TABLE 3: SUMMARY OF SELECTED HIGH VALUE DEALS FOR STRATEGIC DRUGS OF FOCUS

*DRU*Approximate values based on the achievement of all milestones for the principal components included in the deal.*

DRUG	LICENSING COMPANY	PARTNER COMPANY	DEAL START DATE	DEAL VALUE (US $)*
INCB-18424	Incyte	Novartis	Nov 2009	> 1.310 billion
BHQ-880; BYM-338; HuCAL-based mAb (undisclosed indication), Novartis; LFG-316; LJM-716	Incyte	Novartis	May 2004	> 1.011 billion
dacetuzumab	Seattle Genetics	Genentech	Dec 2000	> 860 million

TABLE 4: SUMMARY OF HIGH VALUE AGREEMENTS FOR MULTIPLE MYELOMA

**Approximate values based on the achievement of all milestones for the principal components included in the deal.*

Source: Thomson Reuters. Spotlight on… Multiple Myeloma. Published May 2013

d) Differential features facing the market & Business opportunities

PARTNERING OPPORTUNITIES

- Looking for a partner interested in a **license and/or a collaboration agreement (First Option Agreement)** to further develop and exploit this innovative technology.

- Open to establishing partnerships for **co-development** of the technology before reaching the market and highly interested in applying to different funding calls, mainly to **Horizon 2020.**

e) IPR protection

PCT/ES2014/070491
(not published yet)

Filed in Jun 2014
(priority date: Jun 2013)

SECOND MEDICAL USE INVENTION

- **Use of a cannabionid agent**, or a composition comprising it, for the manufacture of a medicament for the prevention and/ or treatment of a monoclonal gammopathy, including multiple myeloma.
- **Use of the original assayed cannabinoid** compounds among others.
- **Use of a combined preparation** which comprises a cannabinoid agent and other active ingredient useful for the manufacture of a medicament for its combined administration, simultaneous or sequential, for the treatment of a monoclonal gammopathy, including multiple myeloma.

Entry into national phases expected by Dec 2015

e) IPR protection

PCT/ES2014/070491
(not published yet)

Filed in Jun 2014
(priority date: Jun 2013)

SECOND MEDICAL USE INVENTION

- **Use of a cannabionid agent**, or a composition comprising it, for the manufacture of a medicament for the prevention and/ or treatment of a monoclonal gammopathy, including multiple mye
- **Use of the original assayed cannabinoid** compo
- **Use of a combined preparation** which compr and other active ingredient useful for the manu for its combined administration, simultaneou treatment of a monoclonal gammopathy, includ

Entry into national phases expected

Possibility of
ORPHAN DRUG DESIGNATION

Benefit from a number of incentives, including ten-year market exclusivity (EU) once the medicine is on the market

f) Pitfalls & Risks to be considered

- Assayed cannabinoid compounds are known and available as biochemical reagents.
- A program for synthetizing new analogs is needed to get new chemical entities.
- Risks inherent to medicinal chemistry of lead optimization.
- Regulatory toxicology studies & Clinical trials to be performed.

THANK YOU!

CONTACT INFORMATION

- Prof. José Antonio Pérez Simón
  josea.perez.simon.sspa@juntadeandalucia.es
- Pablo Hervás Ballesteros
  Technology Transfer Unit (OTT-SSPA-FISEVI)
  pablo.hervas.exts@juntadeandalucia.es