Programa Cooperación Farma-Biotech

Jornada II: **Oncología**

Early to mid-stage oncology developments: ATH001- Acadra®

Barcelona, 13 de abril de 2011

CataloniaBIO
Associació catalana d'empreses de biotecnologia

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

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Content

1. The Company: ADVANCELL S.A.

2. The Product: Acadra®

a) Therapeutic focus
b) Innovative mechanisms of action
c) Differential features facing the market
d) Current status of development
e) IPR protection
f) Pitfalls & Risks to be considered

3. Availability for cooperation

ADVANCELL, S.A.

Advancell is an emerging biopharmaceuticals company focused on the development of promising drug products with significant commercial potential

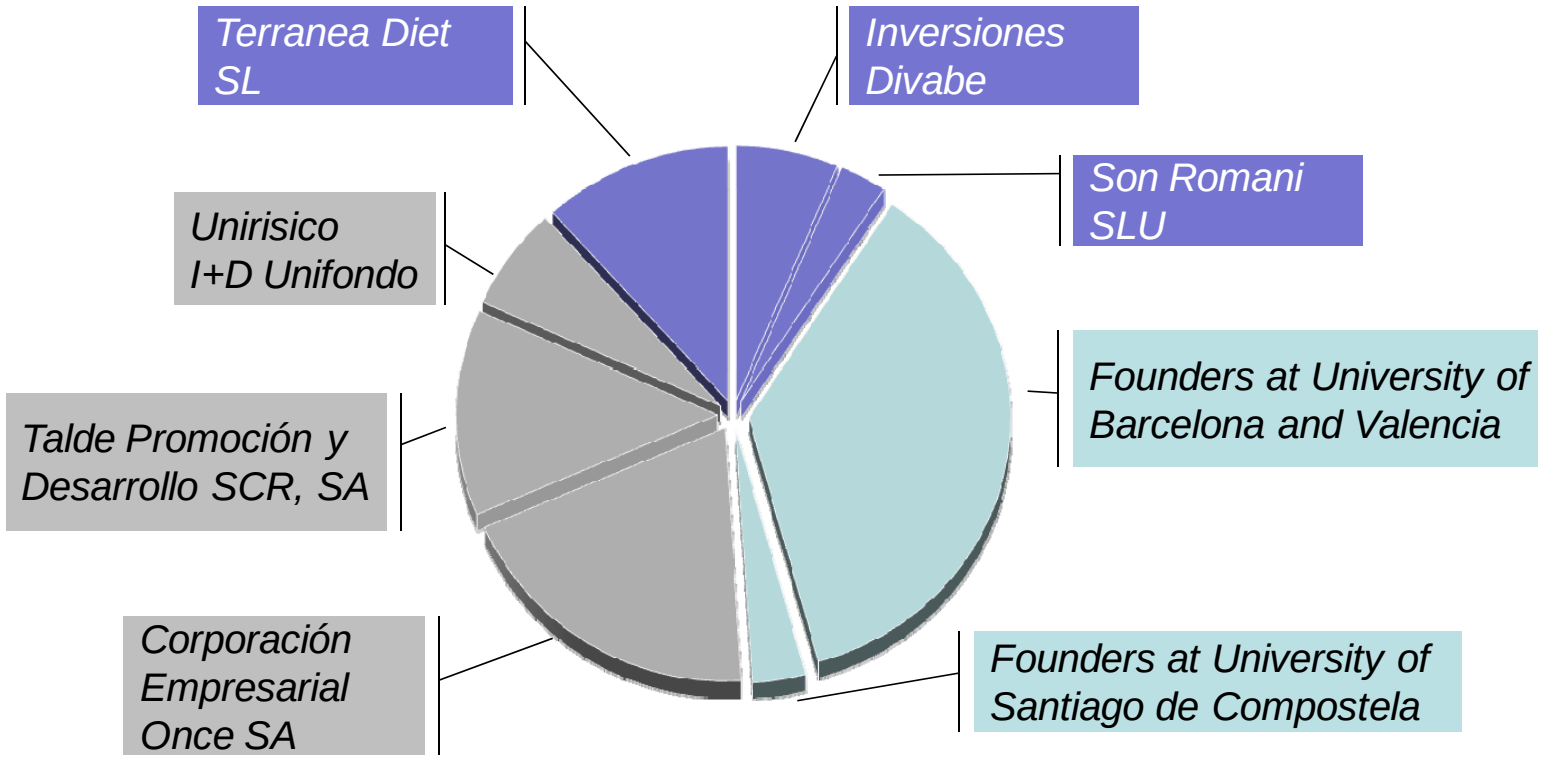
The Company generates proprietary drug candidates by:

- Identifying novel applications of known drugs (repositioning)
- Leveraging its nanosystems delivery technology (reformulation)

ADVANCELL, S.A.

- Privately held, Advancell is led by a competent Management and Board with significant financial and pharmaceutical experience and strong academic roots
- Employs 16 staff, 80% with advanced academic degrees
- Draws on the expertise of internationally renowned clinicians and scientists
- Partially funds R&D from internal cash flow and partnered projects

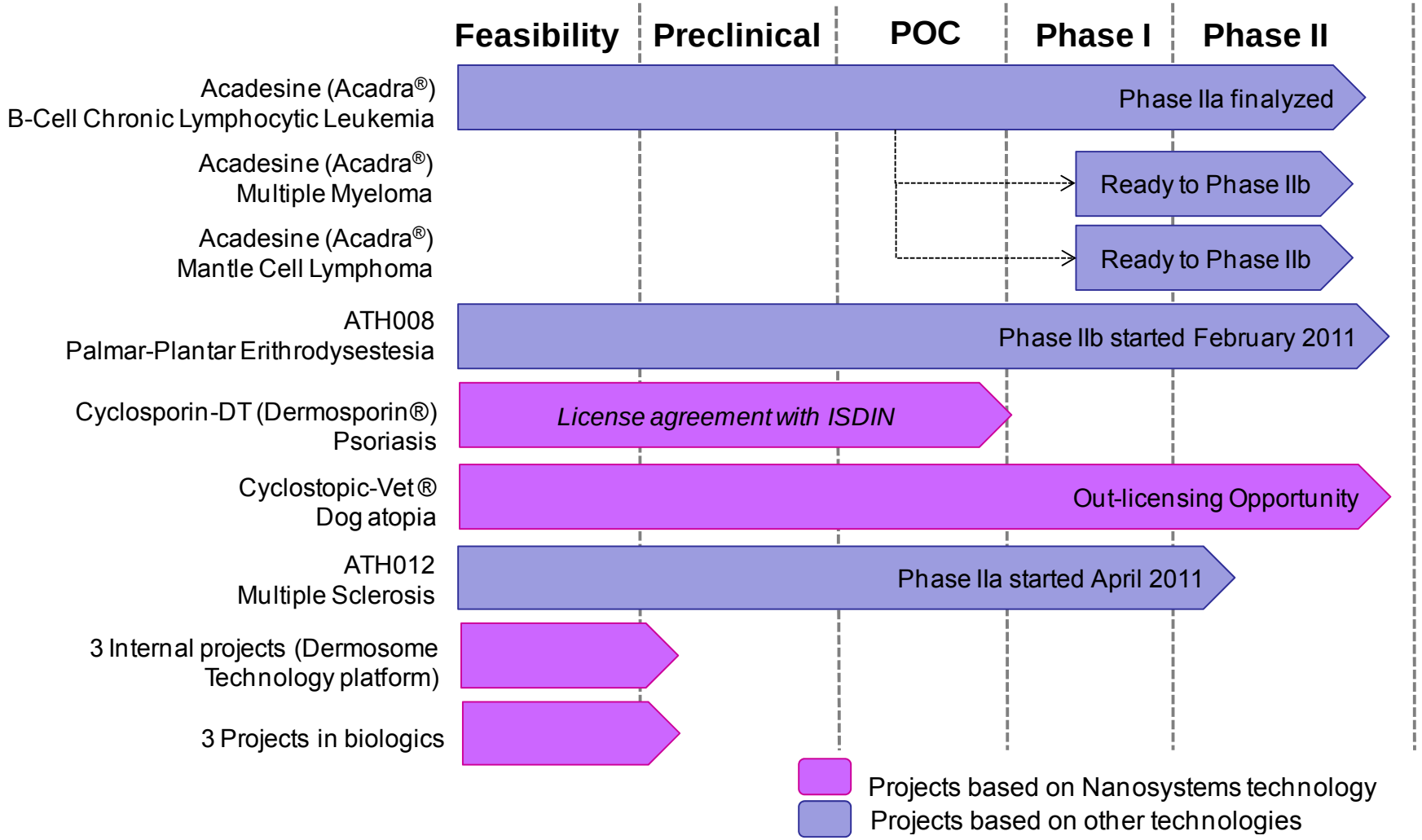
ADVANCELL - Shareholders



ADVANCELL - History

- Founded in 2001 as an spin-off from the University of Barcelona and Valencia offering ADME-Tox services and reagents
- In 2004, in-licensed a portfolio of patents in nanomedicine (USC) and a patent in oncology (UB)
- In 2006, first licensing agreement with ISDIN covering nanomedicine reformulation products for the treatment of skin diseases
- In 2008, clinical proof of concept for first nanomedicine product and entry of project Acadra® into phase IIa for CLL
- In 2010, successfully divested the Company's ADME-Tox service business and completed strategic transition focusing on the development of drug candidates for significant unmet medical needs

ADVANCELL – Pipeline 2011



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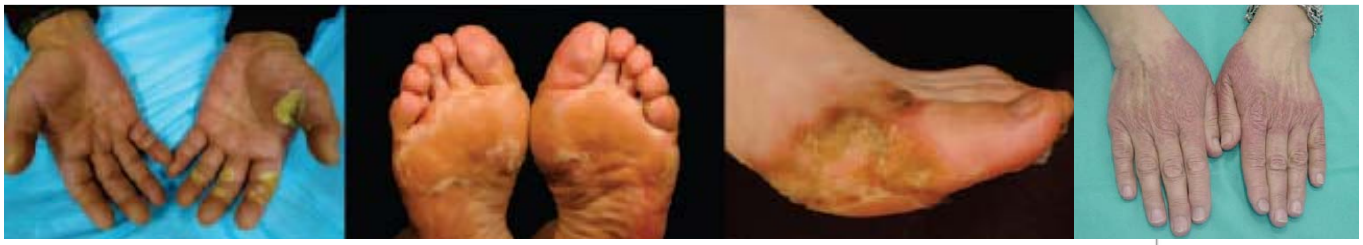
ATH008 for Hand-Foot Syndrome or PPES

- Hand-Foot Syndrome is a main cause of dose reduction and treatment interruption in chemotherapy with capecitabine (*Xeloda*®), 5-FU, doxorubicin (*Doxil*®), docetaxel (*Taxotere*®), paclitaxel and the new multikinase inhibitors sorafenib (*Nexavar*®) and sunitinib (*Sutent*®).
- ATH008 cream is a novel product for PPES
- Treatment market (>200M€) and prevention (>500M€) worldwide
- Clear unmet need (no drugs approved in the indication)
- Currently in Phase IIb development in EU
- A unique Phase III is needed to gain MAA in EU

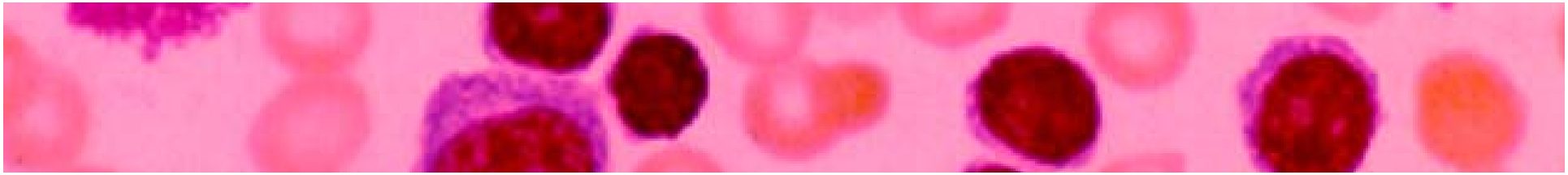


Acadra® for B-cell leukemia and lymphomas

Indication

Treatment of **leukemia and lymphoma of B-cell origin**

- Chronic Lymphocytic Leukemia (CLL)
- Multiple Myeloma (MM)
- Mantle Cell Lymphoma (MCL)
- Acute lymphoblastic Leukemia (ALL)
- Splenic Marginal Zone Lymphoma (SMZL)
- Potentially others



Acadra® for B-cell leukemia and lymphomas

Product

Acadra® is a **solution for IV infusion**.

Drug substance is the **small molecule** Acadesine.

Reprositioning strategy: the drug was developed up to Phase III to prevent ischemia during bypass surgery (early 90's). Good safety background. Never marketed.

New indication: B-cell neoplasms

Acadra® mechanism of action

Mechanism of Action*

Acadra's active form is **selectively accumulated in B-cells** causing an unbalance in nucleotide pools and activation of specific BH3 only proteins that lead to **apoptosis and cell cycle arrest**.

Selective for B cells, does not compromise T-cell immunity.

Independent of p53, ATM or other cytogenetic features. Works in cells resistant to current therapies.

** Campàs et al., Blood 2003; Campàs et al., Leukemia 2005; Coll-Mulet et al., Blood 2006; Santidrián et al., Blood 2010; Pairet et al., EHA 2010; Montraveta et al., ASH 2010*

Acadra® differential features facing the market

Acadra has a better risk/benefit profile than current drugs:

- Does not induce immunosupression nor myelosupression: selective for B-cells.
- Acadra is uniquely suited to replace drugs now widely used in combination therapy (esp. fludarabine) for 1st and 2nd line CLL and MM due to markedly better safety profile.
- Independent of p-53 (17p) or other genetic features. Works in cells resistant to other therapies.
- Acadra has potential in multiple patient sub-segments, 1st and 2nd line.

Acadra® differential features facing the market

Synergic effects with drugs in the indication:

- Synergic effects with anti-CD20 monoclonal antibodies (rituximab, ofatumumab, GA-101) without increasing toxicities.

- Synergic effect with bortezomib (Velcade®) and with lenalidomide (Revlimid®) in MM treatment without increasing toxicities.

Acadra is the optimal combination therapy for drugs that claim B-cell selectivity and p-53 independence

Acadra® current status of development

Drug substance and product

- ❑ Drug substance is the small molecule Acadesine
- ❑ Reliable drug substance supplier, batches up to >50kg.
- ❑ Drug product scaled-up to 200L batch size
- ❑ Stable for ≥ 36 months (ICH stability studies)
- ❑ To be diluted in sterile saline buffer for IV infusion

Acadra® current status of development

Pharmacology

- Antileukemic effect in more than 500 **primary samples** from CLL patients, independently of prognostic markers and cytogenetic profile.
- Antileukemic effect in blood cells and **bone marrow cell**s from CLL and SMZL patients.
- Inhibited tumor growth in a **MCL xenograft**. Synergic effects with anti-CD20 monoclonal antibodies.
- Inhibited tumor growth in a **MM xenograft**. Synergic effects with bortezomib (Velcade®) and lenalidomide (Revlimid®). Increased mice overall survival.

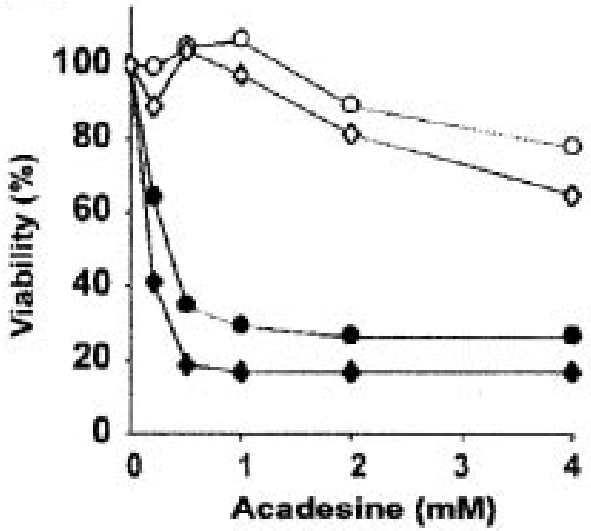
Non-clinical development

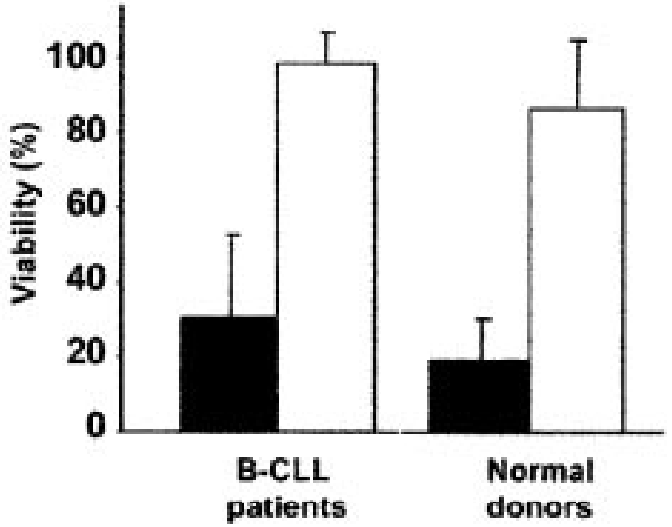
- Non-clinical safety package available (rat, dog)

Acadra® current status of development

Acadra ® is selective for B cells, does not affect T lymphocytes

Acadra active drug (ZMP) is selectively accumulated in B-cells. B-cells are sensitive to Acadra with an IC50 of 380 µM while T-cells are resistant at doses up to 3mM.



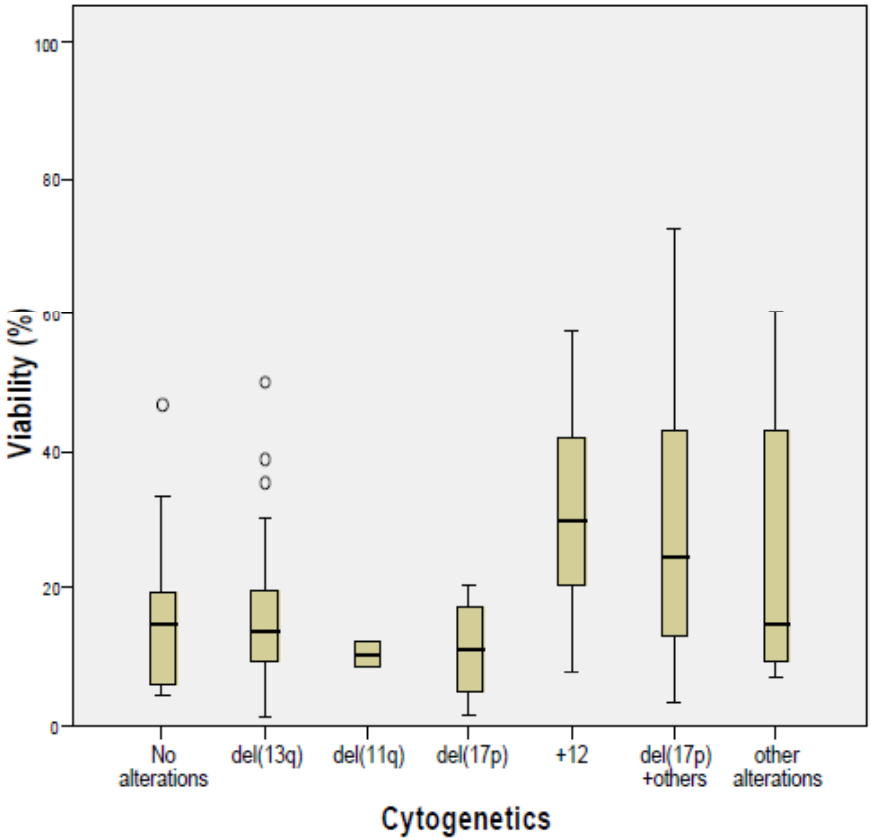


B-cells
T-cells

Campàs et al., Blood 2003

Acadra® current status of development

Acadra ® induces apoptosis in CLL cells *in vitro* despite p53 status



CLL cells from 93 CLL patient samples were cultured with 0.5mM Acadra for 24 hours.

CLL cells with del(17p) are as sensitive to Acadra than CLL with no cytogenetic alterations.

CLL cells with trisomy 12 alterations are less sensitive to 1 mM Acadra than cases without cytogenetic alterations or with del(13q) as a sole cytogenetic abnormality.

Campàs et al., Blood 2003
Coll-Mulet et al., Blood 2006
Pairet et al., EHA 2010 and ASH 2010

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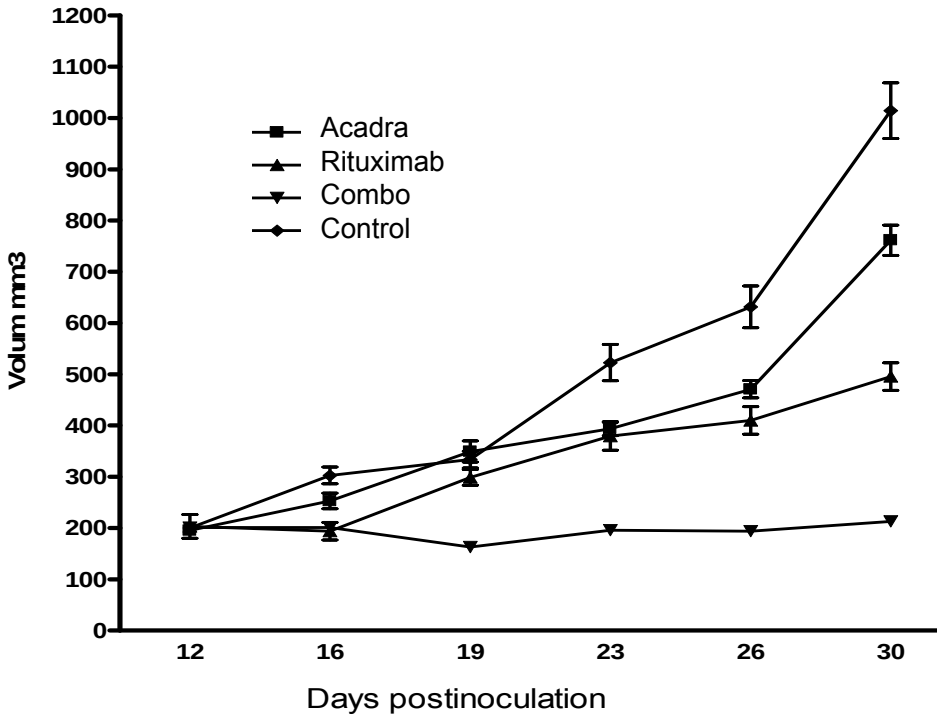
Acadra® current status of development

Acadra® synergic effect in combination with rituximab in a MCL xenograft from the human MCL cell line Jeko-1 (non-indolent MCL, p53 mutated)



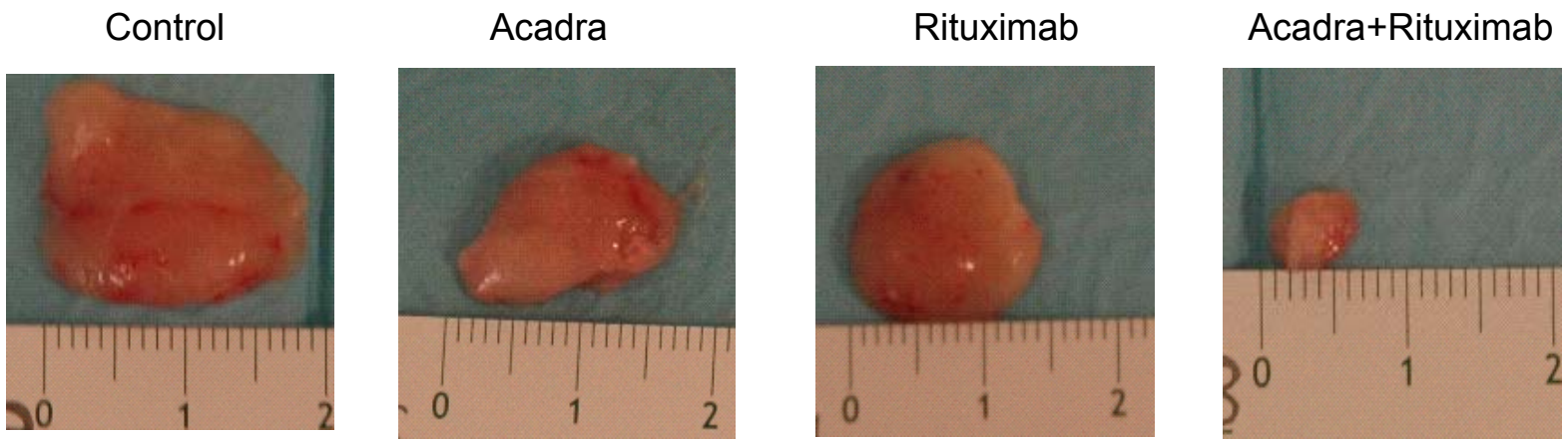
SCID mice were subcutaneously inoculated with Jeko-1 cells. At day 12 post-inoculation, mice were randomized and administered for 18 days with either 400 mg/kg Acadra 5 days weekly, Rituximab 10mg/kg weekly, both drugs or vehicle.

The combination was significantly more effective than Rituximab or Acadra monotherapy ($p<0.001$).

Montraveta et al., ASH 2010

Acadra® current status of development

Acadra® synergic effect in combination with rituximab in a MCL xenograft from the human MCL cell line Jeko-1 (non-indolent MCL, p53 mutated)

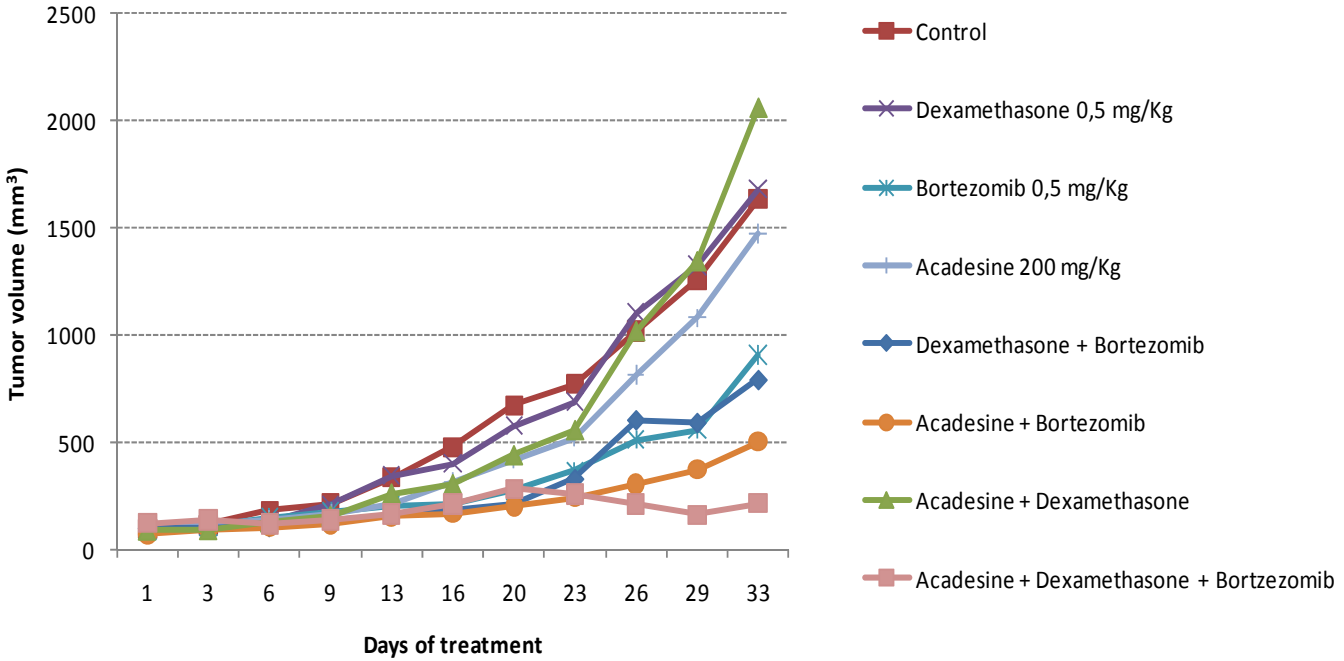


Montraveta et al., ASH 2010

Acadra® current status of development

Acadra® synergism with bortezomib and dexamethasone in a MM xenograft

Xenograft mice model inoculated with human MM1S cells. When the tumor reached a volume of 100 mm^3, mice were randomized and i.p. administered for 33 days with either 200mg/kg daily Acadra, 0.5 mg/kg daily bortezomib, 0,5 mg/kg twice a week dexamethasone, a combination of these drugs or PBS (control).



Hernández-García et al., ASH 2010

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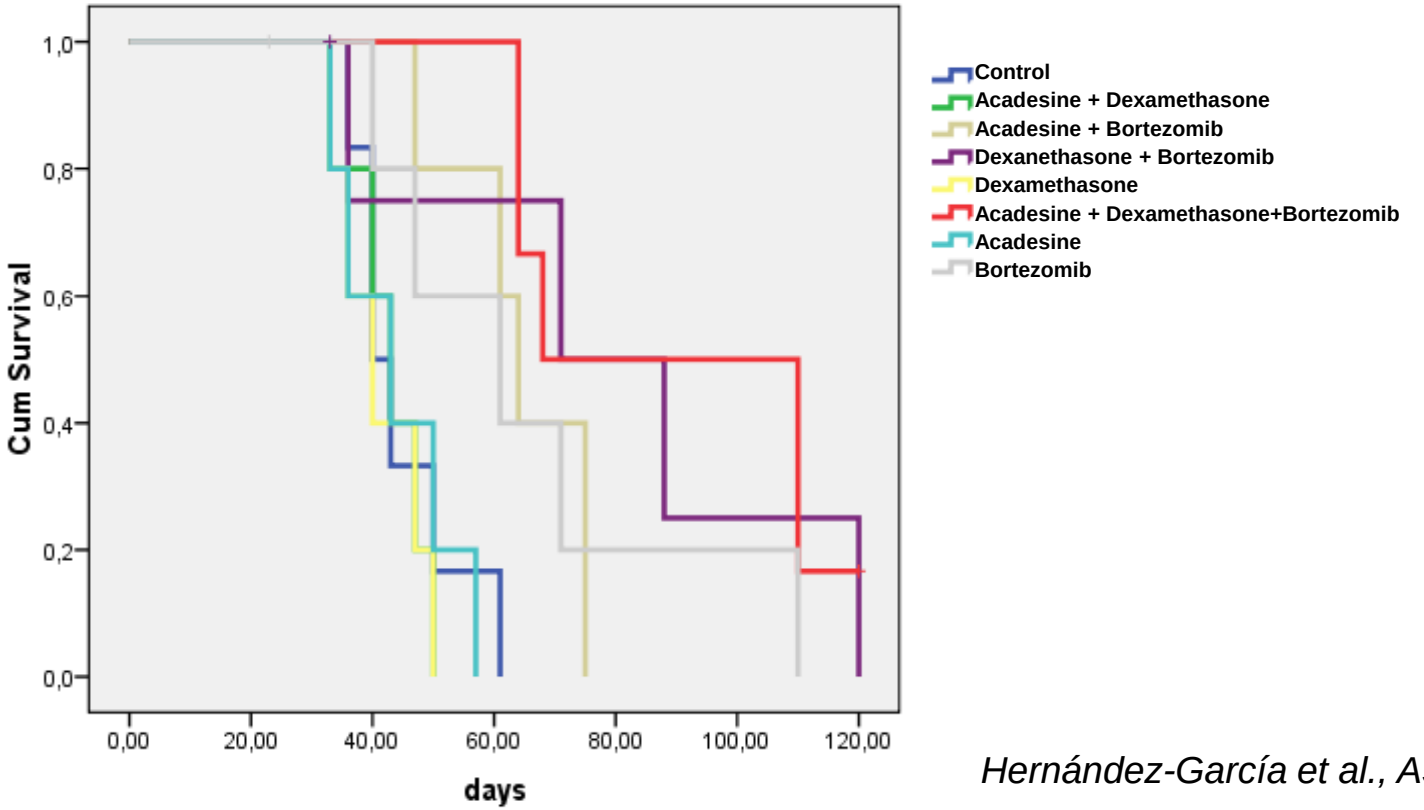
Acadra® current status of development

Acadra® increased mice overall survival, and this effect was potentiated in the combination with bortezomib and dexamethasone



Hernández-García et al., ASH 2010

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Acadra® current status of development

Phase IIa study in CLL

- **Completed Phase IIa Study** in resistant/refractory CLL patients showed very good safety profile at Optimal Biological Dose (OBD)
- 24 patients treated in EU (Belgium, France and Spain)
- OBD is the dose of Acadra that gives a maximum exposure to ZMP
- At OBD tumor burden is significantly reduced in both peripheral blood and lymphadenopathies (50-75% of reduction after 5 doses)

Acadra is ready for Phase IIb in CLL, MM, MCL, SMZL and ALL

Acadra® market and market exclusivity

Market exclusivity

Patents filed/granted in major markets. Expire ≥ 2023 (EU), 2025 (US)

Orphan Drug Status for CLL (EMA 2005; FDA 2011)

Other ODD applications *ongoing*

Market

Market well above 400M€ in CLL alone

Potentially moving to revenue well over €1 billion considering use in Multiple Myeloma, Mantle Cell Lymphoma and/or ALL

Acadra®: pitfalls and risks to consider

Risk	Risk Management
Composition of matter patents are old and have expired	o Good use patent protection o No other active patents in other indications, most have expired o Orphan Drug designations EU and FDA o Good supply agreements with suppliers
Strategy to market	Development to market needs to be **guided by indication and by combination strategies** for an optimal positioning in the market

Acadra® availability for cooperation

- Advancell is ready to partner the program.
- Formal contact with selected companies started February 2011.
- Partner will assume lead role in continued development and regulatory efforts to market.
- We seek a customary licensing transaction – upfront, milestones and royalty.
- Global rights still available (April 2011).

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Executive Vice-President

ADVANCELL