ABTL0812: first-in-class fully differentiated oral targeted anticancer compound causing cell death by autophagy

Madrid, 28 de noviembre de 2018

Content

1. The institution
2. The product
    a) Target indications
    b) Innovative mechanism of action
    c) Differential features facing the market
    d) Current status of development
    e) IPR protection
    f) Pitfalls & Risks to be considered
3. Partnering Opportunities

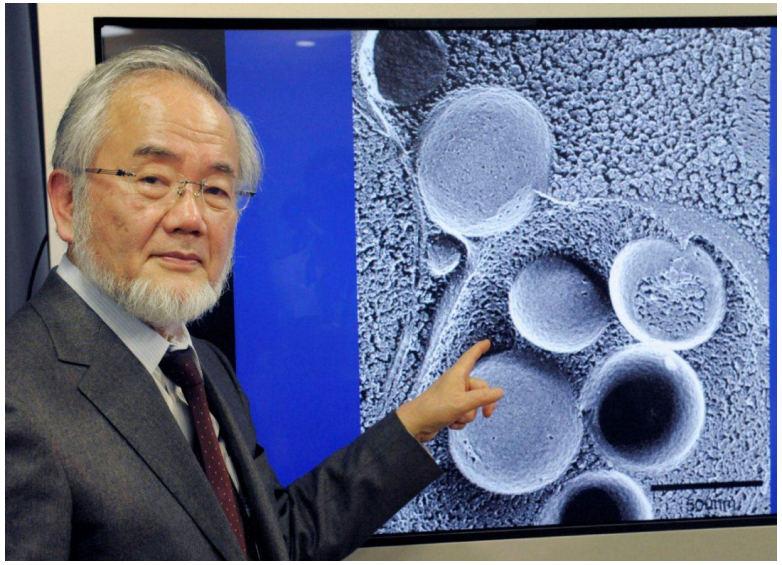
Content

1. **The institution**
2. The product
    a) Target indications
    b) Innovative mechanism of action
    c) Differential features facing the market
    d) Current status of development
    e) IPR protection
    f) Pitfalls & Risks to be considered
3. Partnering Opportunities

What do we do?

Running phase 2 clinical trials with the new anticancer drug ABTL0812 that kills cancer cells through **AUTOPHAGY**

The first anticancer drug using autophagy to control cancer - a significant breakthrough in oncology



Dr. Yoshinori Ohsumi was awarded with the 2016 Nobel Price for the discovery of autophagy

Who is who: Experienced management team

Carles Domènech, PhD
CEO & co-founder
- *Over 25 years of experience in Business Development and Licensing at Almirall and Lacer*
- *Director of Biotech Investments at a seed capital firm*
- *Cancer research for 8 years (CSIC and Memorial Sloan-Kettering Cancer Center)*

José Alfón, PhD
VP, Research and Development
- *Over 20 years of experience in the pharmaceutical industry*
- *Taking a drug from discovery to Phase 2 at Uriach and Palau Pharma*

Gemma Fierro, MSc
VP, Clinical and Regulatory Affairs
- *30 years of experience as Director Regulatory Affairs Spain at Bayer, Warner Chilcott and Procter & Gamble*

Vanessa Ruz, MSc
VP, Finance and Administration
- *10 years of experience in finance and administration of healthcare companies*
- *Prior CFO of Sevibe Cells*

An executive team that knows how to develop cancer drugs and how to partner with big pharma

Marc Cortal, MD
Director, Clinical Research
- *Over 10 years of experience in clinical trials as clinical investigator*
- *5 years of experience in the pharmaceutical industry*

Maria Jesús Guerrero
Director, Project Management
- *Over 20 years of experience in Project management*
- *Prior Southern Europe Director of United Biscuits*

Héctor Pérez-Montoyo, PhD
Director, Biological Research
- *Cancer research for 13 years (UT Southwestern Medical Center (TX), CIPF, Univ. Velencia and IDIBELL)*
- *PhD in the molecular pathophysiological mechanisms leading to autoimmunity and cancer development*

Marc Yeste, PhD
Director, Translational Research
- *Cancer research for 10 years (UB and Barts Cancer Institute (UK))*
- *PhD in apoptotic pathways involved in neuronal cell death*

Albert Marofa, MSc
Manager, Business Development and Licensing
- *4 years of experience in the pharmaceutical industry*
- *Prior Licensing Analyst at Thomson Reuters*

Who is who: Highly accomplished advisory board

Dr. Toni Pérez
Chairman, Clinical Advisory Board

- *Advisor for clinical development*
- *Formerly senior clinical development positions at Novartis Headquarters, Esteve, Almirall and Basilea Pharmaceuticals*

Dr. Jordi Rodón

- *Medical oncologist at the Department of Oncology at Vall d'Hebron Institute of Oncology VHIO.*
- *Chief of the Early Clinical Drug Development Group and Director of the Molecular Therapy Cancer Research Unit (UITM), at VHIO.*
- *Currently visitor investigator at MD Anderson Cancer Center.*

Dr. Pere Gascón

- *Previous Head of Oncology at Hospital Clínic de Barcelona*
- *Senior Consultant of Clinical Institute for Hemato-Oncologic (ICMHO) of Hospital Clínic de Barcelona*
- *Ptevious Head of the Hematology and Oncology Service at the New Jersey State Medical School*

José Miguel Lizcano, PhD
Chairman, Scientific Advisory Board

- *Professor and director of the Department of Biochemistry Institute of the Universitat Autònoma de Barcelona UAB*
- *Head and founder of the UAB Protein Kinases and Signal Transduction Laboratory*

Miguel F. Segura, PhD

- *Principal Investigator of the Laboratory of Neural Tumours at VHIO*
- *Researcher on epigenetic therapies and non-DNA-damaging agents for the treatment of nervous system tumours such as neuroblastoma*

Extensive KOL network build in Europe and United States

Where are we?

Content

1. The institution
2. **The product**
    a) Target indications
    b) Innovative mechanism of action
    c) Differential features facing the market
    d) Current status of development
    e) IPR protection
    f) Pitfalls & Risks to be considered
3. Partnering Opportunities

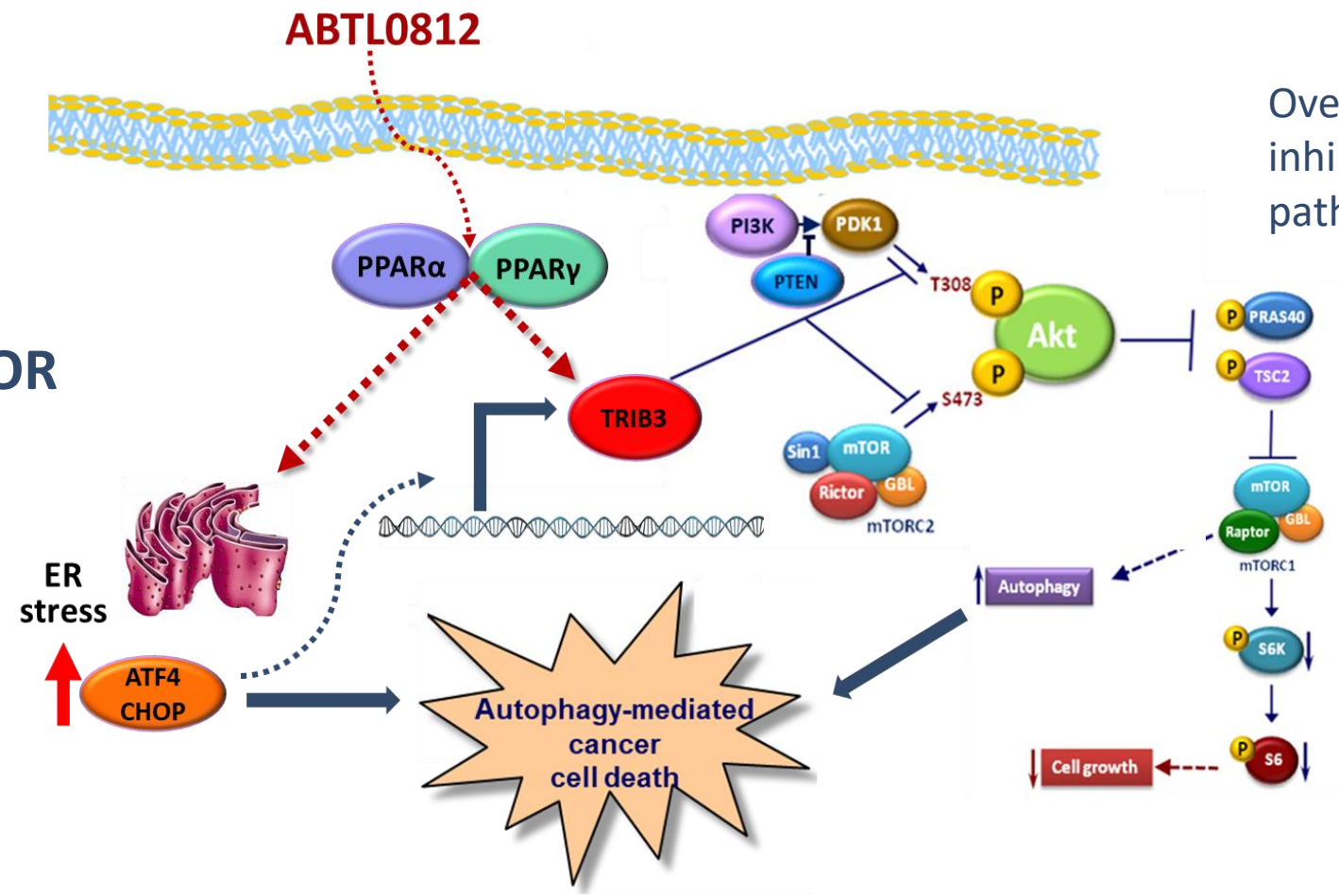
What do we do?

	EUROPE	USA (FDA)
Clinical Trials		
Endometrial and Lung cancer	CTA Approved in Sept 2016 (AEMPS, Spain) CTA Approved in Oct 2017 (ANSM, France)	IND Approved in Dec 2017
Pancreatic cancer *	CTA filing planned in France/Spain (May 2019)	Protocol approved in Jan 2018
Orphan Drug Designation (ODD)		
Neuroblastoma	Granted in Apr 2015	Granted in Aug 2015
Pancreatic cancer	Granted in Aug 2017	Granted in Nov 2016
Cholangiocarcinoma	Granted in Nov 2018	Granted in Sep 2018

* IND filed at Chinese FDA in Oct 2018

How does it work? Unique mechanism of action

Fully differentiated from PI3K/Akt/mTOR kinase inhibitors

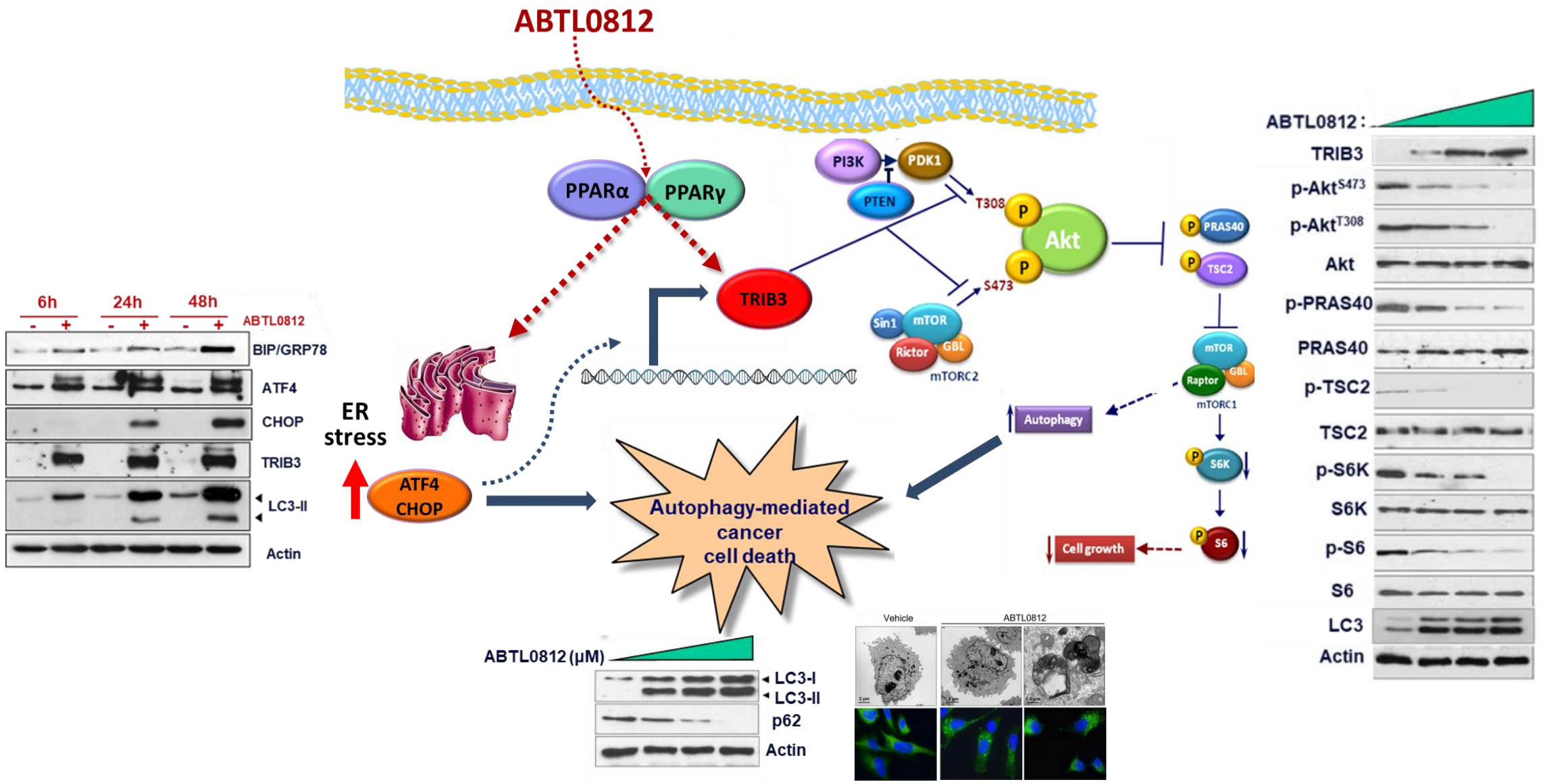


Overexpression of TRIB3 that inhibits the PI3K/Akt/mTOR pathway

ER-Stress

Robust Autophagy mediating cell-death in tumor cells

How does it work? Unique mechanism of action



How does it work? Unique mechanism of action

Erazo, et al. 2016

Clinical Cancer Research 22 (10): 2508–19

doi:10.1158/1078-0432.CCR-15-1808

Cancer Therapy: Preclinical

Clinical Cancer Research

The New Antitumor Drug ABTL0812 Inhibits the Akt/mTORC1 Axis by Upregulating Tribbles-3 Pseudokinase

Tatiana Erazo[1], Mar Lorente[2,3], Anna López-Plana[4], Pau Muñoz-Guardiola[1,5], Patricia Fernández-Nogueira[4], José A. García-Martínez[5], Paloma Bragado[4], Gemma Fuster[4], María Salazar[2], Jordi Espadaler[5], Javier Hernández-Losa[6], Jose Ramon Bayascas[7], Marc Cortal[5], Laura Vidal[8], Pedro Gascón[4,8], Mariana Gómez-Ferreria[5], José Alfón[5], Guillermo Velasco[2,3], Carles Domènech[5], and Jose M. Lizcano[1]

Abstract

Purpose: ABTL0812 is a novel first-in-class, small molecule which showed antiproliferative effect on tumor cells in phenotypic assays. Here we describe the mechanism of action of this antitumor drug, which is currently in clinical development.

Experimental Design: We investigated the effect of ABTL0812 on cancer cell death, proliferation, and modulation of intracellular signaling pathways, using human lung (A549) and pancreatic (MiaPaCa-2) cancer cells and tumor xenografts. To identify cellular targets, we performed *in silico* high-throughput screening comparing ABTL0812 chemical structure against ChEMBL15 database.

Results: ABTL0812 inhibited Akt/mTORC1 axis, resulting in impaired cancer cell proliferation and autophagy-mediated cell death. *In silico* screening led us to identify PPARs, PPARα and PPARγ as the cellular targets of ABTL0812. We showed that ABTL0812 activates both PPAR receptors, resulting in upregulation of Tribbles-3 pseudokinase (TRIB3) gene expression. Upregulated TRIB3 binds cellular Akt, preventing its activation by upstream kinases, resulting in Akt inhibition and suppression of the Akt/mTORC1 axis. Pharmacologic inhibition of PPARα/γ or TRIB3 silencing prevented ABTL0812-induced cell death. ABTL0812 treatment induced Akt inhibition in cancer cells, tumor xenografts, and peripheral blood mononuclear cells from patients enrolled in phase I/Ib first-in-human clinical trial.

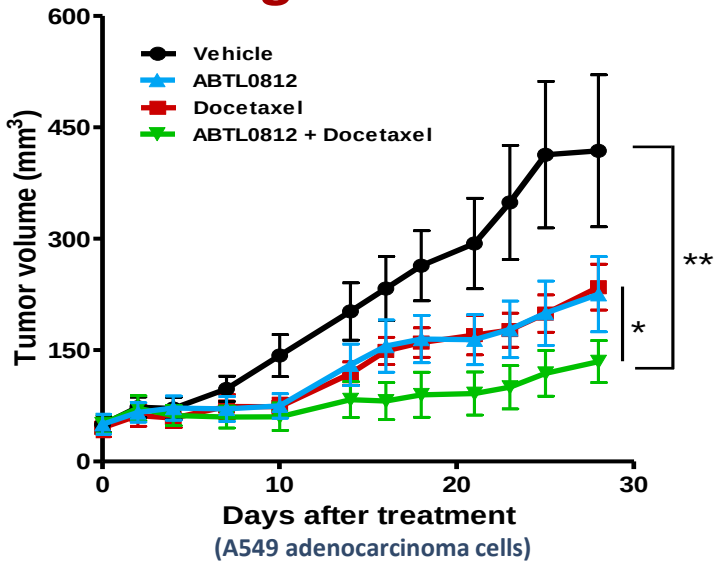
Conclusions: ABTL0812 has a unique and novel mechanism of action, that defines a new and drugable cellular route that links PPARs to Akt/mTORC1 axis, where TRIB3 pseudokinase plays a central role. Activation of this route (PPARα/γ-TRIB3-Akt-mTORC1) leads to autophagy-mediated cancer cell death. Given the low toxicity and high tolerability of ABTL0812, our results support further development of ABTL0812 as a promising anticancer therapy. *Clin Cancer Res; 1–12. ©2015 AACR.*

ABTL0812 unique preclinical profile

- Active in a broad range of human cancer cell lines
- High antitumor efficacy in xenografts as single agent
- Favorable safety profile (therapeutic margin 8.3)
- Synergy with chemotherapy: taxanes, platinum compounds and gemcitabine, without increasing toxicology
- Efficacy in resistant cell lines
- Superiority over other PI3K/Akt/mTOR pathway inhibitors in resistant cancer cells
- Active against cancer stem cell
- Inhibits metastasis formation
- Promising immunomodulatory effects
- Less probabilities of resistance than kinase inhibitors

Its efficacy - Efficacious as single agent and in combination

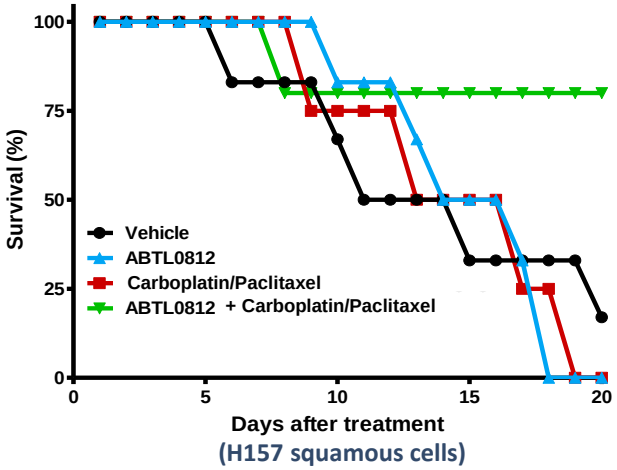
Lung Cancer



(A549 adenocarcinoma cells)

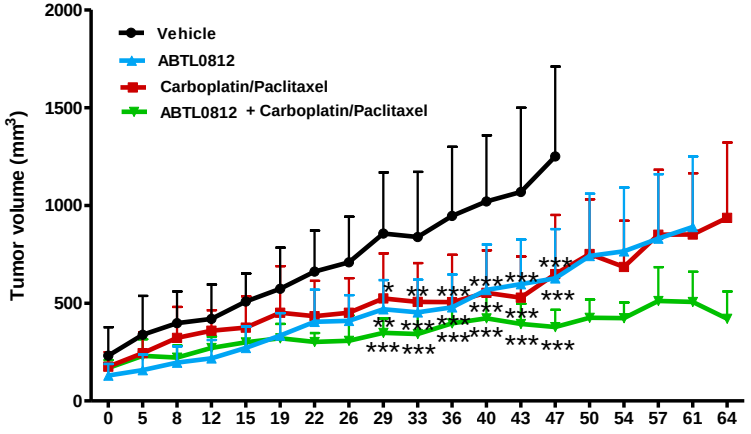
ABTL0812 shows efficacy similar to chemotherapy as single agent

ABTL0812 strongly potentiates chemotherapy in combination



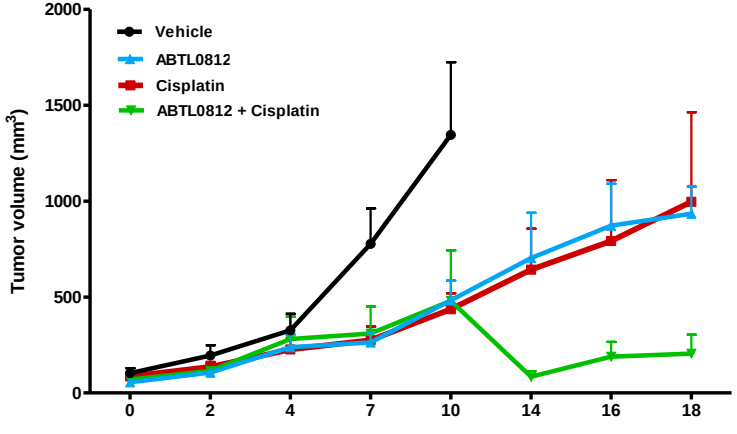
(H157 squamous cells)

Endometrial Cancer



(PDX)

Neuroblastoma

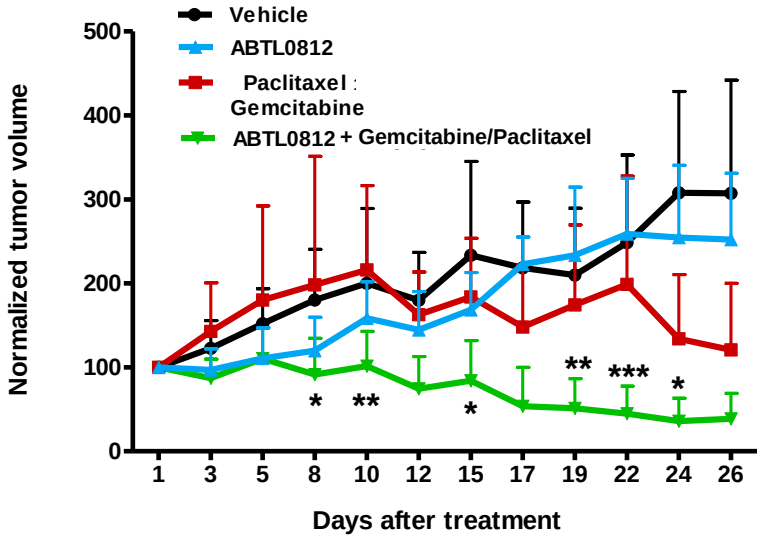


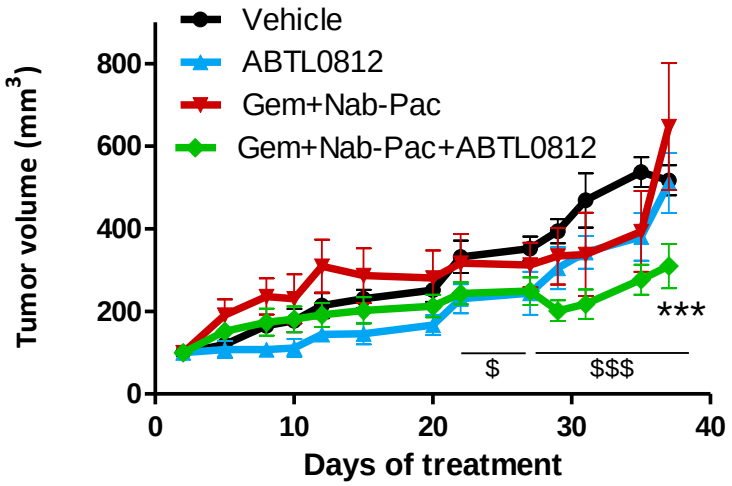
(SH-SY5Y cells)

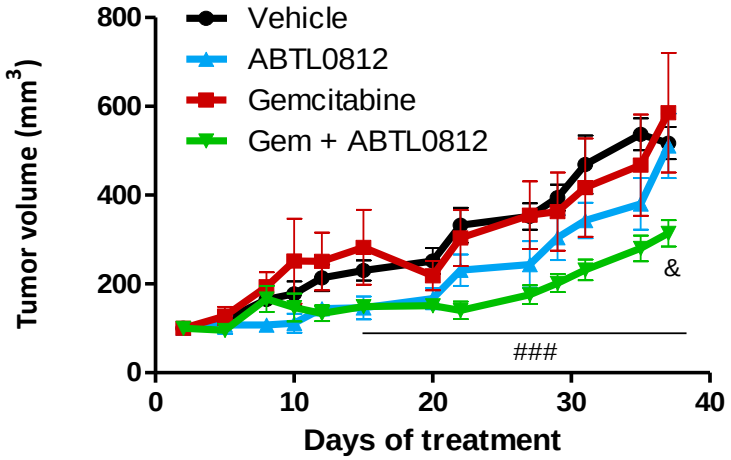
Its efficacy - Efficacious as single agent and in combination

Pancreatic cancer

ABTL0812 potentiates the antitumor activity of paclitaxel + gemcitabine chemotherapy and in Nab-paclitaxel + gemcitabine chemotherapy in pancreatic cancer xenografts (MiaPAca2)







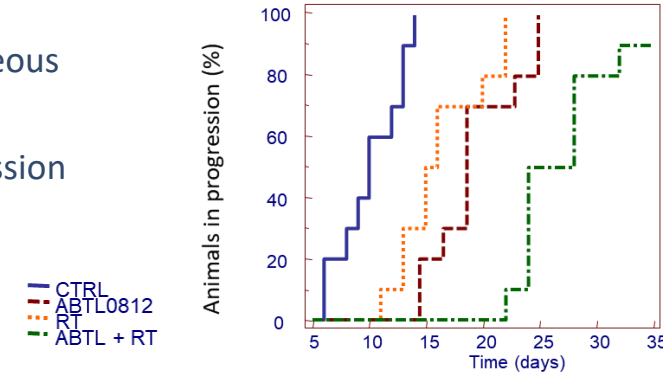
Its efficacy - Efficacious as single agent and in combination

Glioblastoma

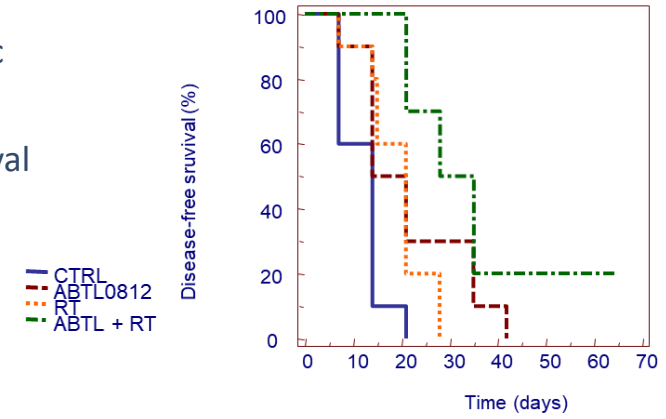
ABTL0812 efficacy to reduce xenograft glioblastoma tumors is similar to radiotherapy (RT)

The combination of ABTL0812 with RT increases efficacy compared to radiotherapy alone

U87MG subcutaneous xenograft model – Animals in progression

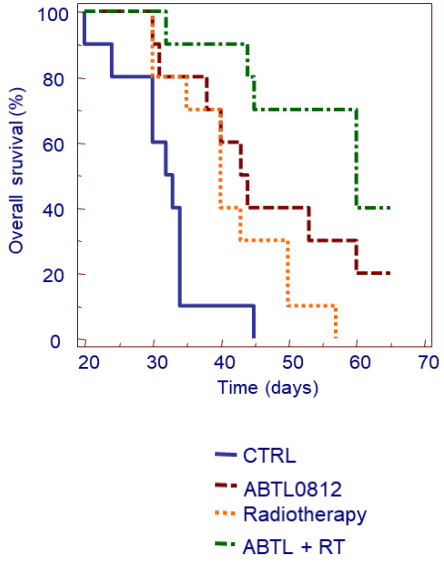


U87MG orthotopic xenograft model – Disease-free survival

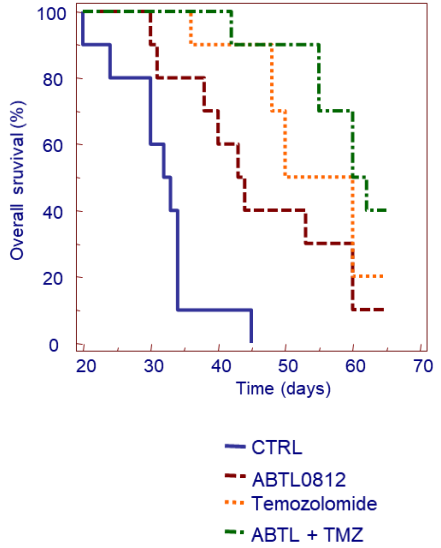


U87MG orthotopic xenograft model – Overall survival

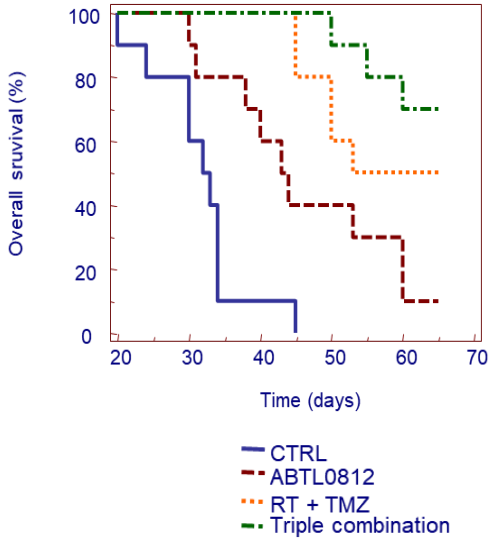
ABTL0812+ Radiotherapy



ABTL0812+ Temozolomide



ABTL0812+ RT/TMZ



Research and development collaborations

Autonomous University of Barcelona (UAB)

Institut Català d'Oncologia

Vall d'Hebron Research Institute

Vall d'Hebron Institut d'Oncologia

Università degli Studi dell'Aquila

IDIBAPS

Hospital Clínic de Barcelona

Universitat de Lleida

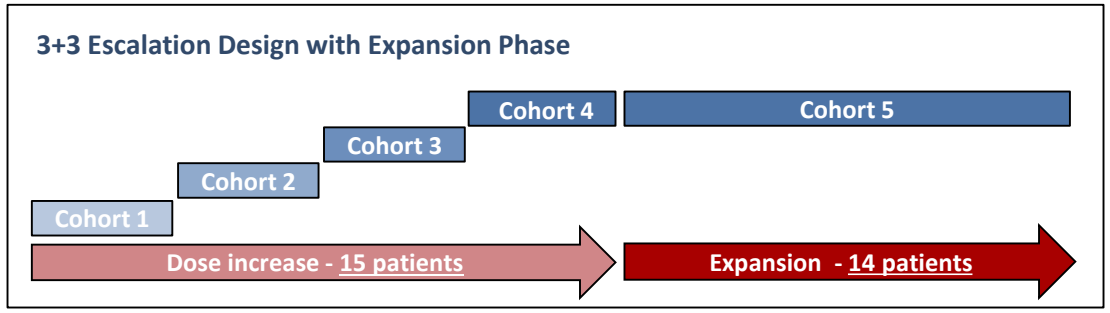
Universitat de Girona

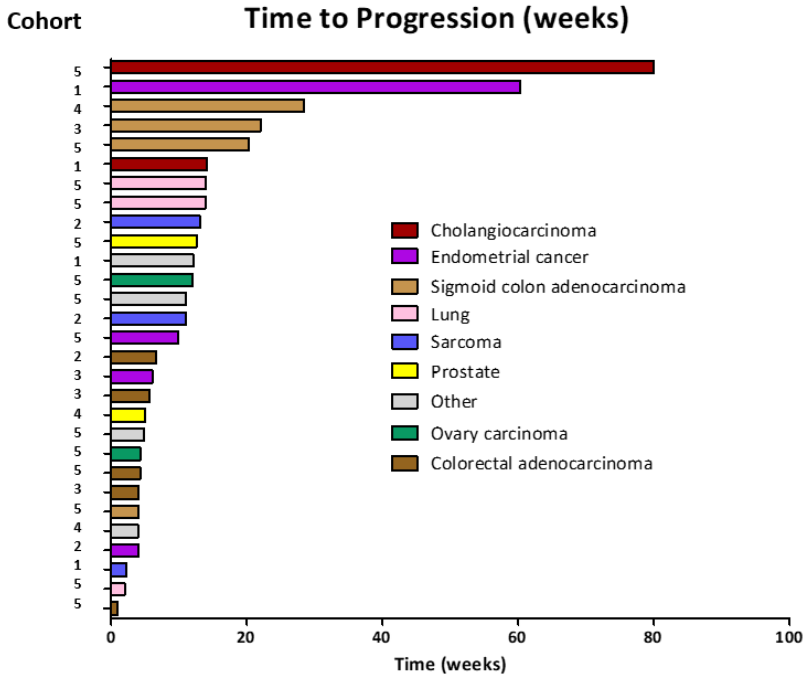
Universidad de Navarra

Phase 1/1b clinical trial – Design and results

ABTL0812 clinical phase 1/1b trial

- 29 patients with advanced solid tumors
- Best safety and tolerability
- Mild adverse events (no DLT)
- Better efficacy on biomarkers
- Recommended Phase 2 dose identified by PK/PD
- 90% inhibition of biomarkers
- Efficacy: 5 long-term disease stabilizations:
  - ✓ Sigmoid colon cancer: 5,6 & 7 months
  - ✓ Endometrial cancer: 14 months
  - ✓ Cholangiocarcinoma: 18 months
- Hospital Clinic Barcelona and Institut Català d'Oncologia





Phase 1/1b clinical trial – Mild adverse events

Extremely safe: Mild treatment related adverse events and no DLTs observed

Treatment-related adverse events (No. of patients [%])[b]				
Preferred term[a]	All cohorts n = 29			
	Grade 1-2		Grade 3-4	
	n	%	n	%
Asthenia	6	21		
Bronchitis			1	3
Cough	2	7		
Diarrhea	4	14	1	3
Edema peripheral			1	3
Hepatotoxicity			1	3
Nausea	7	24		
Oropharyngeal discomfort	5	17		
Pharyngeal inflammation	1	3	1	3
Rash maculopapular	1	3	1	3
Vomiting	5	17		

[a] MedDRA Preferred Terms, NCI-CTCAE v4.0 grading
[b] AEs were counted once for each patient, at the maximum severity reported

Much safer than direct PI3K/Akt/mTOR kinase inhibitors.

Outstanding safety profile in patients, conversely to what happens with direct PI3K inhibitors, some of them abandoned in advanced development because of non-acceptable adverse events.

Ongoing phase 2a clinical trial - Endometrial and NSCLC

Phase 1/2 as first-line therapy in endometrial cancer and squamous lung cancer in combination with chemotherapy (carboplatin + paclitaxel) with maintenance after chemotherapy

Chemo + ABTL0812 → **ABTL0812 single therapy** → 80 patients

Target Product Profile

Increasing the efficacy of chemotherapy → Increasing response rate
Avoiding resistance → Delaying relapse
Extremely safe → Making cancer a chronic disease

Preliminary Interim analysis endometrial cancer available

Final analysis endometrial cancer May 2019

Ongoing phase 2a clinical trial - Endometrial and NSCLC

Ability Pharma
real medicine for real life

Barcelona

VHIO

Vall d'Hebron Institute of Oncology

Paris

GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Lyon

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

Badalona, Girona, L'Hospitalet

ICO
Institut Català d'Oncologia

Marseille

INSTITUT
CENTRE REGIONAL DE LUTTE CONTRE LE CANCER
PAOLI-CALMETTES
PROVENCE - ALPES - CÔTE D'AZUR

Valencia

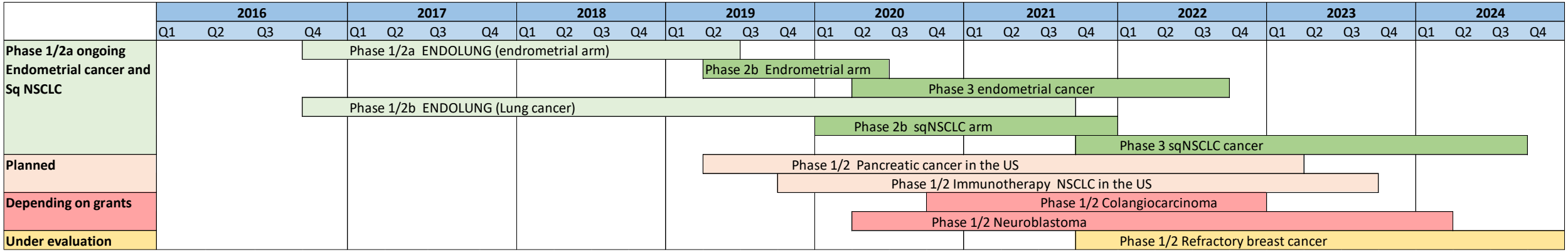
INCLIVA
Instituto de Investigación Sanitaria

Sevilla

Hospital Universitario Virgen del Rocío

Development plan - timelines

Planned clinical development plan until 2024



License agreement for Greater China

Partnered with SciClone Pharmaceuticals, Inc. for Greater China

BioSpace
Life Sciences News + Jobs

Ability Pharmaceuticals Enters Into A Licensing Agreement With **SciClone Pharmaceuticals, Inc. (SCLN)** For The Novel Anticancer Agent ABTL0812 For The China Market

5/11/2016 10:19:06 AM

- Collaboration Boosts Development of a Fully Differentiated Inhibitor of the PI3K/Akt/mTOR pathway.
- ABTL0812 is currently in Phase 2 Clinical Trials to Treat Lung and Endometrial Cancers.

BARCELONA, Catalonia, Spain- May 11th, 2016 – Ability Pharmaceuticals, SL today announced that the company has entered into an agreement with the NASDAQ-listed US company SciClone Pharmaceuticals, Inc. (SCLN) granting SciClone an exclusive license to develop and market the novel anticancer ABTL0812 in China and some adjacent territories.

Ability Pharma
real medicine for real life

SciClone® Pharmaceuticals

* US NASDAQ until 3Q2017. Acquired by a VC consortium led by GL Capital

Market potential

Potential sales ABTL0812 in 2026 (High scenario)

- Squamous non-small cell lung carcinoma:	180 M €	Market share 15%
- Non-small cell lung carcinoma (all types):	797 M €	Market share 15%
- Endometrial cancer:	397 M €	Market share 60%
- Pancreatic cancer:	114 M €	Market share 30%
- Brest cancer:	205 M €	Market share 17%
- Glioblastoma:	218 M €	Market share 90%
- Neuroblastoma:	150 M €	Market share 60%
- Cholangiocarcinoma:	200 M €	Market share 90%
Total sales:	**2261 M €**	

Based on very high scenario the sales could be over €3 billion in 2026

ABTL0812 also has high potential in pediatric indications

- Consortium with the Innovative Therapies for Children with Cancer group (ITCC)
- Orphan drug designation approved by EMA and FDA for Neuroblastoma
- Positive scientific advice from EMA

Positioning analysis performed by an external consulting firm:

AXIS PHARMA

Pitfalls & Risks

Risks minimized

- Intellectual property
  - ✓ Patented in main markets including Europe, US, Japan
- Clinical
  - ✓ ABTL0812 is already in phase 2 as a first in line therapy in combination
  - ✓ Signs of efficacy with no DLT already observed in phase 1
- Regulatory
  - ✓ Clinical trials approved by US FDA, Spain Medicines Agency and French Medicines Agency
  - ✓ Orphan Drug Status approved for neuroblastoma and pancreatic cancer and biliary tract cancers by FDA/EMA
- Technical
  - ✓ Preclinical studies demonstrating efficacy in many cancer types and resistant cancer cells
  - ✓ Toxicology studies have shown ABTL0812 is extremely safe
  - ✓ 100 Kg GMP production

Risks to be considered

- Clinical
  - ✓ Not obtaining enough clinical evidence in the indications being developed
  - ✓ Appearance of unexpected toxicities
- Technical
  - ✓ Bad taste of the current formulation
- Market
  - ✓ New treatment options

Content

1. The institution
2. The product
    a) Target indications
    b) Innovative mechanism of action
    c) Differential features facing the market
    d) Current status of development
    e) IPR protection
    f) Pitfalls & Risks to be considered
3. **Partnering Opportunities**

Key Takeaways

ABTL0812 is a novel first-in-class anticancer drug in phase 2, potentially active in many types of cancers with high unmeet needs

Looking for a Licensing agreement (territorial or worldwide)

Thank you!

ALBERT MAROFÀ (BD&L Manager)
albert.marofa@abilitypharma.com

www.abilitypharma.com