Programa Cooperación Farma-Biotech

Jornada IIb: **Oncología**

Advanced PI3K inhibitors

cnio
Fundación
Centro Nacional
de Investigaciones
Oncológicas Carlos III

Madrid, 12 de mayo de 2011

CataloniaBIO
Associació catalana d'empreses de biotecnologia

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

GOBIERNO DE ESPAÑA
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The Institution and the Programme

• The CNIO (Centro Nacional de Investigaciones Oncológicas) Spanish National Cancer Research Centre, was constituted in 1998, under the direction of Dr. Barbacid, and was operative in 2003.

• Currently, it is recognized worldwide as a centre of excellence and reference in the field of cancer research.

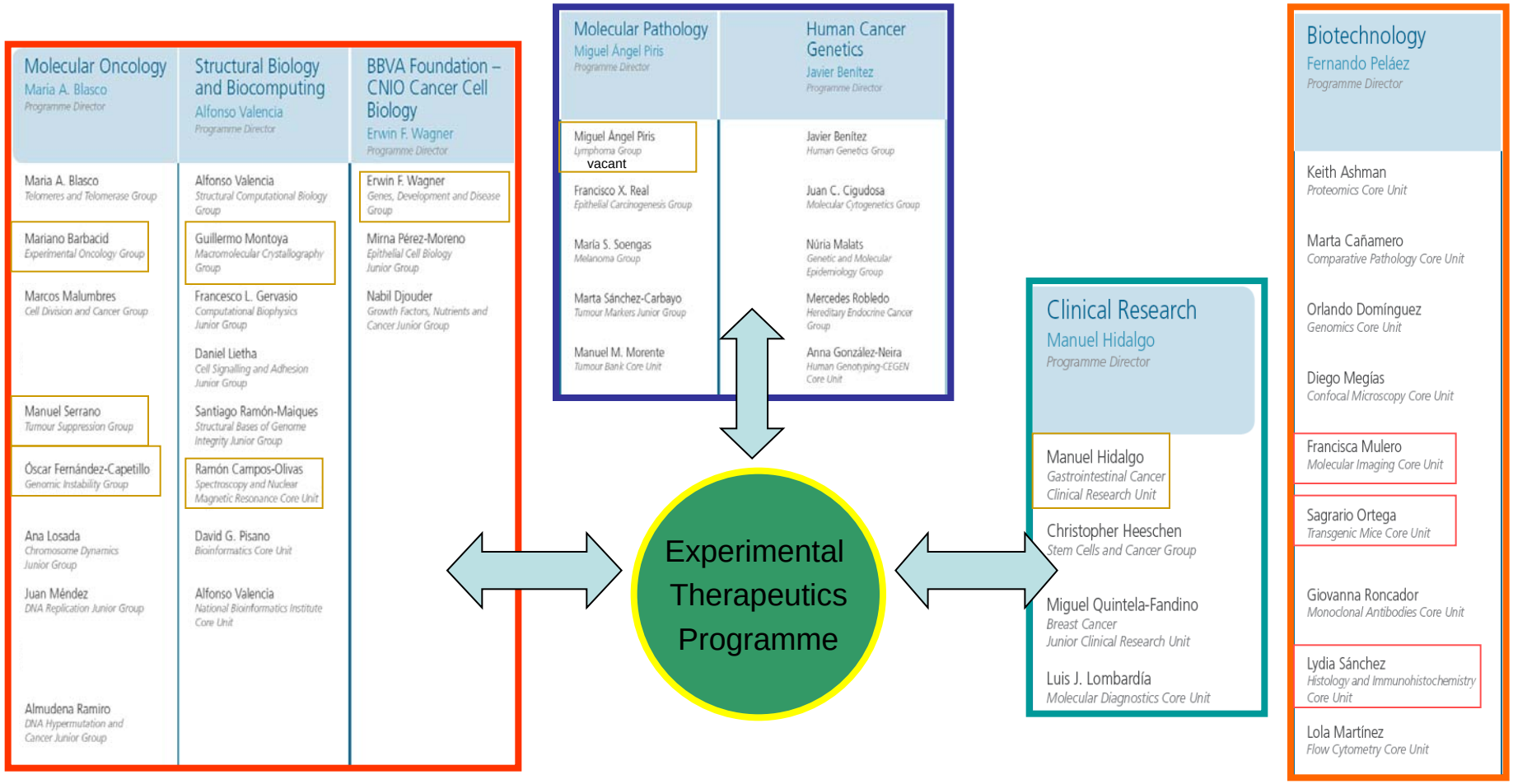
• The CNIO integrates basic, translational and applied research.

• The Experimental Therapeutics Programme started operations in 2005, with the set up of the labs, and was fully staffed by the end of 2007.

• The Programme is constituted by Medicinal Chemistry and Biology, with the objective of discovering new therapeutics for the treatment of cancer.

• The ultimate goal of “ETP” is to deliver new candidates for clinical development.

ETP: Drug Discovery in a Multidisciplinary Environment



Collaborations

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ETP: Structure and Capabilities

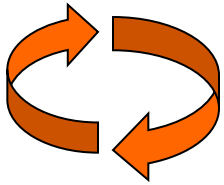
A Typical "Pharma Drug Discovery Platform"

Biology: 25 FTEs*

Med-Chem: 25FTEs*

HTS/Biochemistry/Cell pharmacology :

- Automated platform for HTS
- Development of biochemical assays for HTS.
- Screening of ETP compounds in several formats.
- In vitro ADME assays.
- Cellular assay development
- Target identification and validation



In vivo pharmacology and target validation:

- In vivo pharmacokinetics.
- Anti-tumour activity of new ETP compounds and its mechanism of action in xenografts models.
- Development of xenografts models.

- Characterization of ETP compounds in genetically engineered mouse (GEM) tumour models
- Validation of molecular targets of therapeutic interest in GEM tumor models.
- Development of GEMMs

Hit generation/finding and Optimization:

- Rational design based on med-chem expertise and computational chemistry approaches.
- Guided selection of HTS sets of compounds for HTS.
- Crystallography (in collaboration with GM group)
- Multi-factorial/early assessment of drug-likeness.

Compound synthesis:

- Modern and advanced synthetic methodologies.
- Analytical and purification systems to meet standard "pharma requirements" for ETP compounds.

Intelectual Property:

- Responsible for patenting strategy and process / Potter-Clarkson.
- FTO as priority.
- Databases for IP assessment.

Logistics: Creation and maintenance of data bases for compound flow and data management.

A team with "Pharma experience": Merck / J&J / GSK / Pharmamar / Boehringer/ Bayer/ Pharmacia/ Almirall…

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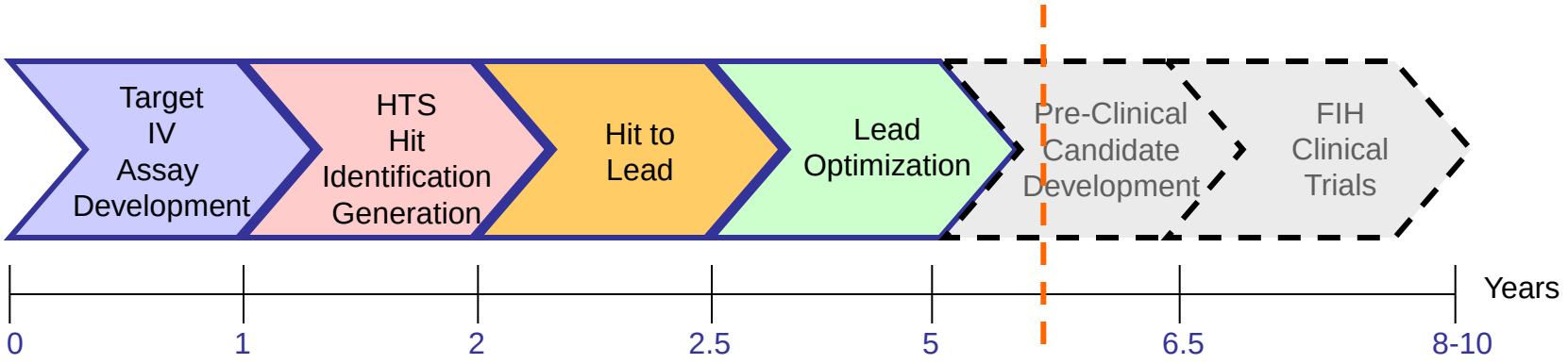
The Product / Therapeutic Focus: Targets and D-D Process

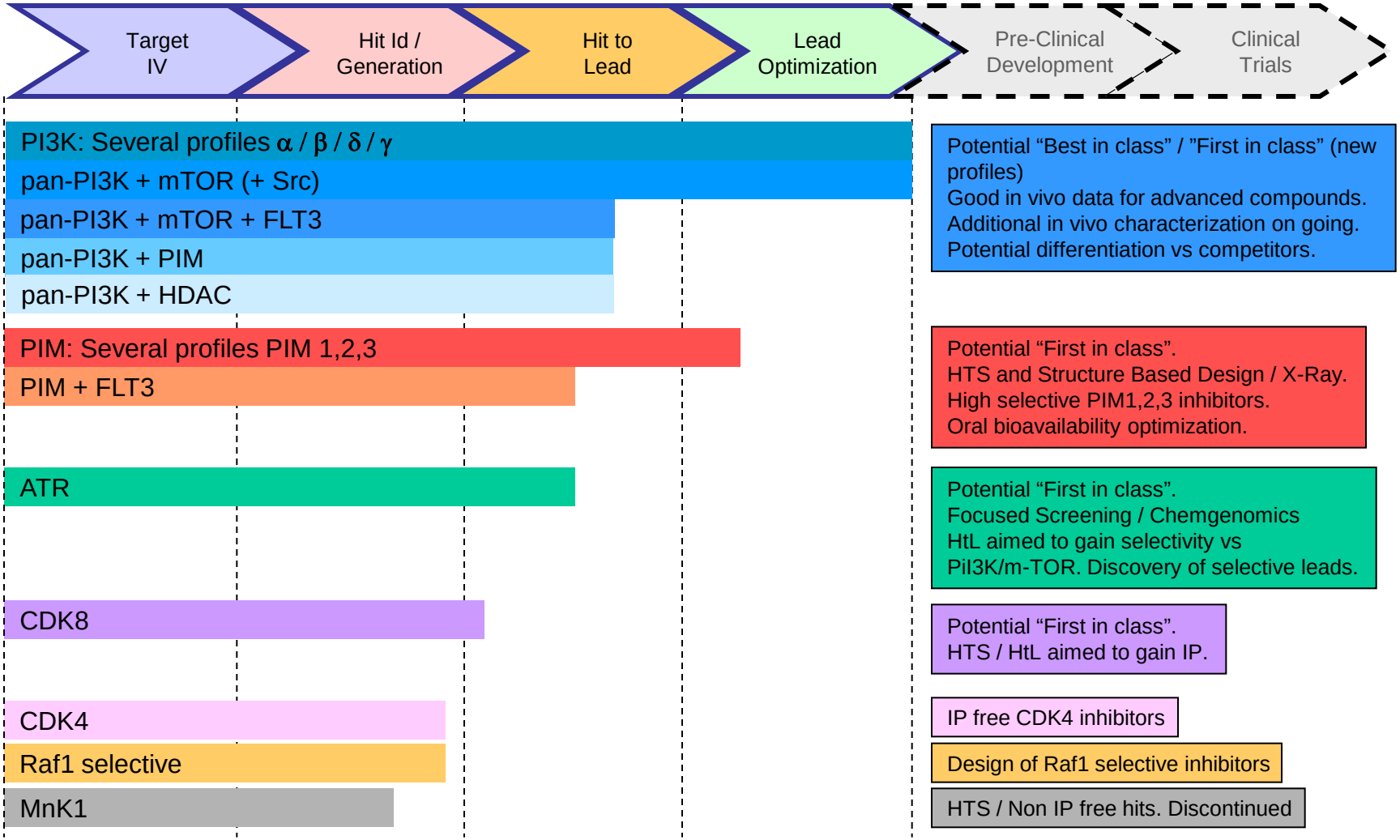
Target Selection:

- Currently, kinases, mutated and/or disregulated in cancer.
- Main drivers in cancer development and progression.
- Steering committee with members from different CNIO Programmes.
- Potential novel drugable targets from CNIO basic research.



- ETP activities up to candidate selection with optimal clinical profile in novel validated targets.
- Seek for partners/out-licensing opportunities at pre-clinical development level.
- Other highly innovative, targets may be partnered/commercialized much earlier…

The Product / Therapeutic Focus: ETP pipeline



The Product / Mechanism of Action: PI3K Inhibitors

PI3K Pathway Activation

- Phosphoinositide 3-kinase (PI3K) pathway are a family of lipid kinases.
- The PtdIns(3,4,5)P3, which is generated by activated class I PI3Ks is the key second messenger that drives several downstream signaling cascades (AKT phosphorylation) that regulate cell survival, proliferation, differentiation and angiogenesis.
- PI3K is present in 4 isoforms ($\alpha,\beta,\delta,\gamma$) α–isoform carries the majority of the signal in this pathway. The β-isoform is related to tumors with PTEN loos and δ and γ are restricted to hematopoietic cells.

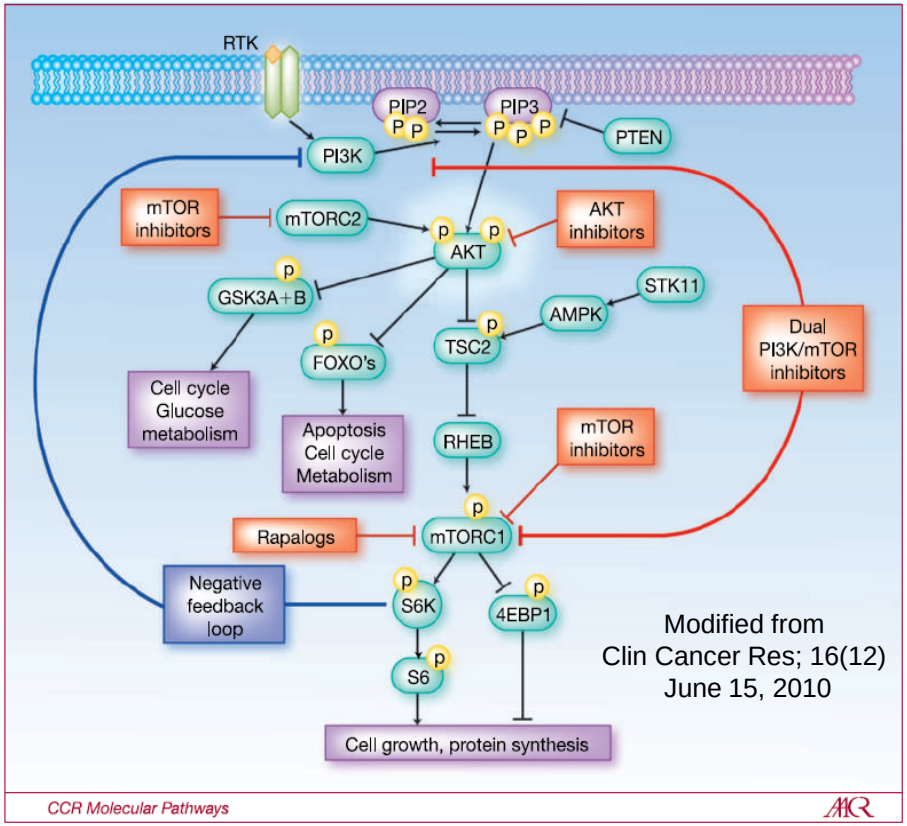


Fig. 1. Schematic of the PI3K pathway and main targets for therapeutic intervention. The PI3K pathway integrates growth factor stimulation (RTK) with the availability of nutrients (AMPK) and can be activated in cancer by amplification or mutation of upstream RTKs, such as HER2 and EGFR, by downstream activating mutations (e.g., *PIK3CA*) or by inactivating deletions or mutations (e.g., *PTEN*). The PI3K pathway can be inhibited by new cancer therapeutics at several levels, shown in red. A negative feedback pathway (blue) signals from S6K to PI3K and can be a cause of AKT-activation in response to mTORC1 inhibition.

The Product / Mechanism of Action: PI3K Inhibitors: PI3K Pathway and Genetic Alterations in Cancer

- Mutations to PIK3CA and PTEN are associated with resistance to conventional therapy.

- Mutations and amplification of p110-α are important in a broad type of cancers. Breast, colon, gastric. lung, ovarian. melanoma …

- Related pathways to PI3K also show genetic alterations in a variety of tumors e.g.
- EGFR glioma, breast, NSCL, colorectal.
- HER2/*neu*, breast, ovarian.
- Ras, pancreatic, lung, breast.
- bRaf, melanoma.
- ER, breast.
- Src, bowel, breast.
- Kit, GIST.

- Combinations with agents targeting such alterations will be beneficial.

The Product / Differential Features Facing the Market. Competitive Landscape /Conclusions from the Clinic.

Current clinical information indicates:

- There are 18 compounds in clinical phases I/II.

- PI3K inhibitors work well in combination, and not as single agents, with drugs that block related pathways, in particular the KRas/MAPK pathway.

- KRas mutations are associated with many of the deadliest cancers, including colorectal, lung and pancreatic.

- The general trend is to have an array of therapeutic options related to isoforms and dual profiles (PI3K and/or PI3K+ m-TOR)

C&EN April 11, 2011,Volume 89, Number 15, pp. 15 – 19. **PI3K At The Clinical Crossroads**

The Product / Differential Features Facing the Market.

Opportunities and Differentiating Factors vs Competitors

- PI3K inhibitors with new isoforms profiles.

Clinical studies will unveil bests relationships between profiles, combinations, and tumor types.

- Compounds with additional activities on top of PI3Ki.

Potential synergistic and/or beneficial activities in a single compound.

- PI3Ki with exquisite selectivity and ADMET profile for combination therapy.

Off-target selectivity.
Absolute clean profiles for CYP inhibition to avoid drug-drug interactions.
PI3K inhibitors with improved pharmacokinetics will impact therapeutic window: Efficacy / Toxicity.

The Product / Current Status of Development

Summary ETP-PI3K Inhibitors

Highly Potent, Selective, Drug-like, Orally Active Inhibitors with the following profiles (+ back-ups):

pan-PI3K inhibitors / Selective vs m-TOR.
PI3K $\alpha + \delta$ inhibitors / Selective vs m-TOR.
PI3K $\alpha + \delta + \gamma$ inhibitors / Selective vs m-TOR.
pan-PI3K inhibitors / m-TOR / (Src inhibition).

In vivo PoC and efficacy studies: done
Additional characterization in combination settings underway.

HtL/LO level (on going)

- PI3K $\alpha + \gamma$ inhibitors / Selective vs m-TOR.
- PI3K α / Selective vs m-TOR.
- PI3K + PIM.
- PI3K + HDAC.

Selected data for advanced compounds are disclosed in the following slides.

The Product / Current Status of Development

ETP-PI3K Inhibitors

- Profile:
  - PI3K α + δ inhibitors / Selective vs m-TOR.
  - Selective vs 288 kinase panel.
  - Clean CYP inhibition profile.

- Status: Advanced lead optimization.
- Back-up series /status: Yes / Early LO.
- IP: Patented.

- *In vivo* available data for representative compound(s):
  - PK (BALB/C mice).
  - Mechanisms of Action (MoA) in U87 human glioma xenograft.
  - Efficacy in A549 human NSCLC xenograft / HT-29-Luc xenograft.
  - Efficacy in SK-OV-3 xenograft /combination with docetaxel.
  - Efficacy Studies and MoA in Kras driven NSCLC GEMM.(PK/PD in tumor)
    - CT-PET Follow up.
  - Efficacy Studies Kras driven NSCLC GEMM / combination with MEKi.

The Product / Current Status of Development

Representative Compound: PI3K α + δ inhibitors / Selective vs m-TOR.

SERIES	STRUCT_ID	PI3K-ALFA HTRF; Ki app	PI3K-BETA HTRF; Ki app	PI3K-DELTA HTRF; Ki app	PI3K-GAMMA HTRF; Ki app	PI3K-ALFA E542 HTRF; Ki app	PI3K-ALFA E545 HTRF; Ki app	PI3K-ALFA E1047 HTRF; Ki app
Series 1	ETP-00046321	2.34E-09	1.70E-07	1.42E-08	1.79E-07	1.89E-09	1.77E-09	2.33E-09

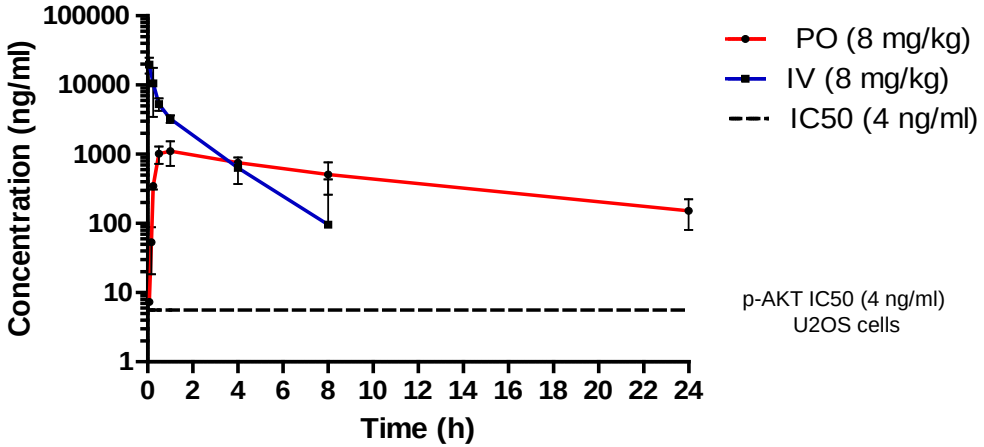
Selective in a 288 kinases pannel (ProQinase). mTOR IC50 > 1 uM; GDC-0941 aprox 300 nM

Differentiating Factor: α + δ profile

AKT-P(SER-473) LINE:U2OS;WB;IC50	CYP_1A2 10uM	CYP_2C19 10uM	CYP_2C9 10uM	CYP_2D6 10uM	CYP_3A4 10uM
8.35E-09	20	18	8	8	3

ETP-PI3Ki do not cross BBB

ETP-46321.-PLASMA PK (BALB/C MICE)

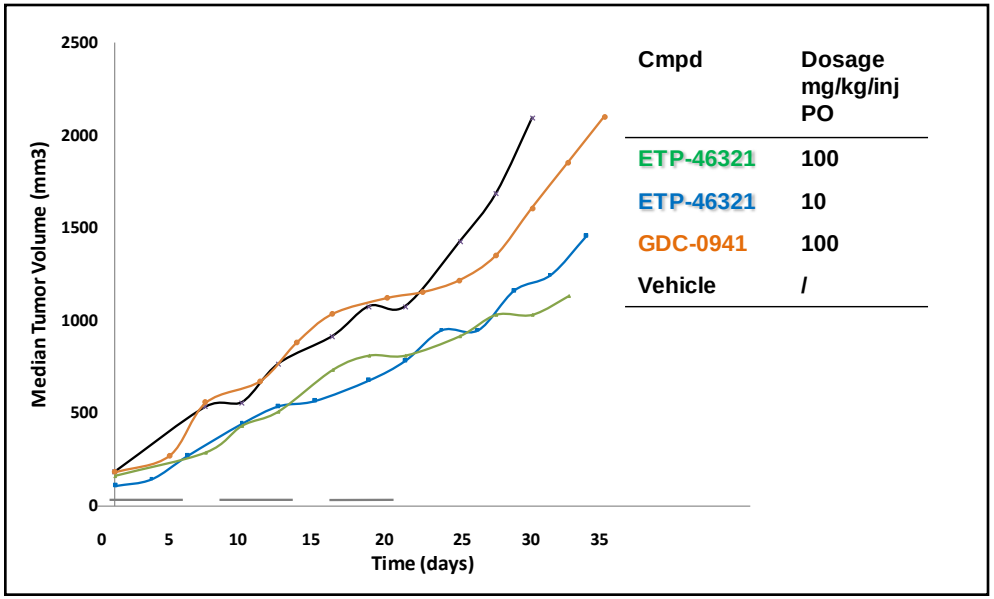


Parameter	I.V.	Oral
Oral bioavailability (%F)	-	88.6
Cmax (ng/ml)	-	1132.28
Tmax (h)	-	1
AUC (h x ng/ml)	14185.73	12573.51
$T_{1/2}$ (h)	1.36	8.38
Cl (L/h/kg)	0.56	-
Vd (L)	0.02	-
MRT (h)	1.43	8.16

The Product / Current Status of Development
ETP-46321.-In vivo Efficacy in human NSCLC A549 xenografts.

Compound (batch)	Dosage mg/kg/inj	Drug death (day of death)	Total dose (mg/kg)	Average body weight change in % at nadir (day of nadir)	Time for median tumor to reach 1500 mg in days	T-C in days
ETP-46321	100	0/5	1800	-4.5 (27)	51.5	12.9
	10	0/4	150	(+)	47.3	8.7
GDC-0941	100	0/3	1600	-0.5 (42)	44.2	5.6
Vehicle	/	0/7	/	-8 (32)	38.6	

Oral administrations, once daily, 5 days a week, for 3 weeks. Median tumor burden per group at the start of the therapy: 108-183 mg. T-C= Median time for treated (T) versus control (C) tumor groups to reach a predetermined size.

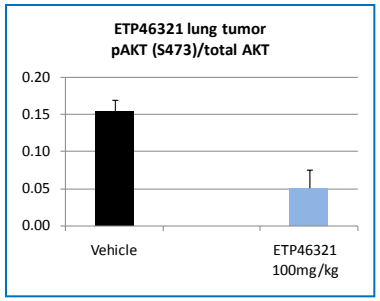


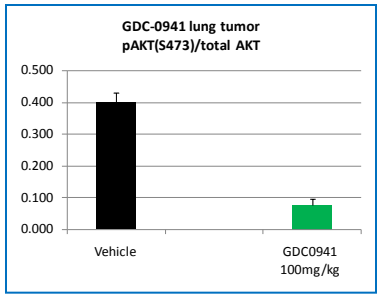
Compound well tolerated in repeated dosage.

DF: ETP-321 looks like more efficacious than reference GDC-0941 even at 10 mpk dose.

Mice bearing established tumors were given orally once daily, 5 days a week, for 3 weeks: ETP-46321 at 10 mg/kg (solution) or at 100 mg/kg (suspension), GDC-0941 at 100 mg/kg (suspension), or vehicle. Treatment duration is symbolized by horizontal lines. The curves represent the median tumor values of all groups.

The Product / Current Status of Development
ETP-46321.- MoA and Efficacy: Kras driven NSCLC Mouse Model.



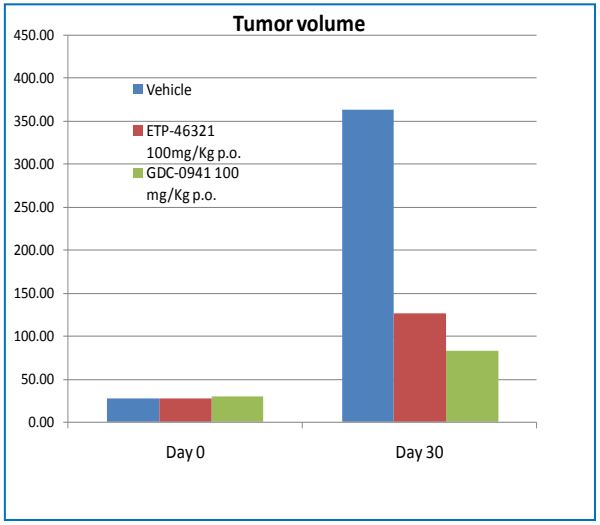


MoA study

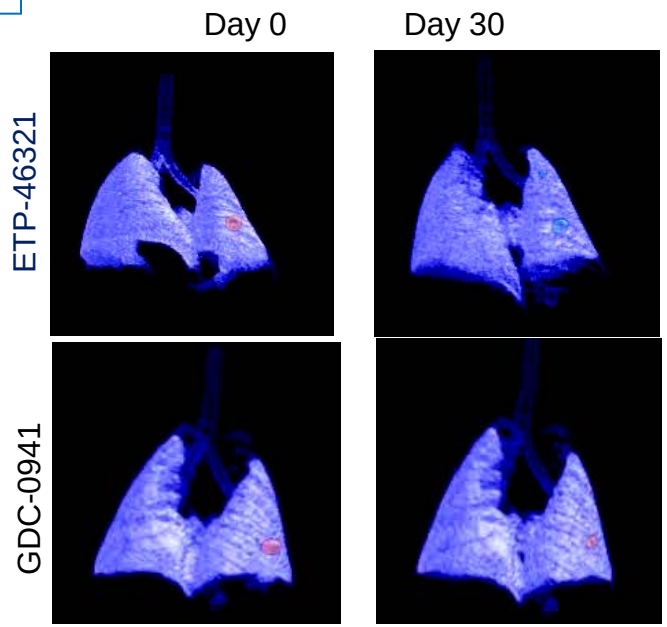
Group	Dose
ETP-46321	100 mg/kg p.o daily (suspension)
GDC 0941	100 mg/kg p.o daily (suspension)

Lung tumor samples were obtained 1 hour after a single administration and the effect of compounds on pAkt was evaluated by Western Blot. Results are expressed as an average ratio of pAkt vs. total Akt. Values are means ± s.d. Three animals per group.

Efficacy study: 30 days of treatment



Total tumor volumes of three mice in each treatment group at the beginning (Day 0) and at the end (Day 30) of treatment. t-student analysis demonstrates statistical significance *p<0.05 vs vehicle.



Three-dimensional reconstruction of CT-PET scans from representative mice treated either with GDC-0941 or ETP-46321 before and after 1 month of treatment. Red color shows ^{18} Fluorodeoxyglucose (FDG) measured by PET imaging.

CT-PET

Removal of the ^{18}(FDG) avidity of the tumor and reduction of tumor size

DF ?

Reduction of tumor size. Thre is still PET signal

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The Product / Current Status of Development

ETP-PI3K Inhibitors

- Profile:
  - PI3K α + δ + γ inhibitors / Selective vs m-TOR.
  - Selective vs 288 kinase panel.
  - Clean CYP inhibition profile.

- Status: Advanced lead optimization.

- Back-up series /status: Yes / LO.

- IP: Patented.

- *In vivo* available data for representative compound(s):

  - PK (BALB/C mice).
  - Mechanisms of Action (MoA) in U87 human glioma xenograft.
  - Efficacy in A549 human NSCLC xenograft.
  - Efficacy Studies Kras driven NSCLC GEMM / combination with MEKi.

The Product / Current Status of Development

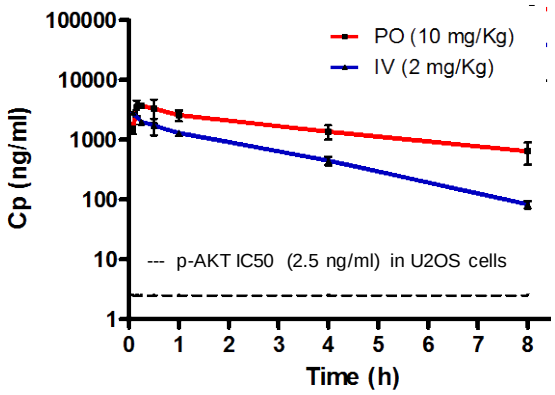
Representative Compounds: PI3K $\alpha + \delta + \gamma$ inhibitors / Selective vs m-TOR.

SERIES	STRUCT_ID	PI3K-ALFA HTRF; Ki app	PI3K-BETA HTRF; Ki app	PI3K-DELTA HTRF; Ki app	PI3K-GAMMA HTRF; Ki app	PI3K-ALFA E542 HTRF; Ki app	PI3K-ALFA E545 HTRF; Ki app	PI3K-ALFA E1047 HTRF; Ki app
Series 1	ETP-00046444	2.38E-09	2.12E-07	9.85E-09	8.40E-08	2.77E-09	1.73E-09	3.07E-09
Series 2	ETP-00047022	5.48E-09	5.80E-07	1.36E-08	5.80E-08			

ETP-46444 Selective in a 288 kinases pannel (ProQinase). mTOR IC50 > 1 uM.

STRUCT_ID	AKT-P(SER-473) LINE:U2OS;WB;IC50	CYP_1A2 10uM	CYP_2C19 10uM	CYP_2C9 10uM	CYP_2D6 10uM	CYP_3A4 10uM
ETP-00046444	5.00E-09	9	16	14	9	23
ETP-00047022	6.37E-08	13.7	21.7	13	0	15.9

ETP-46444.-PLASMA PHARMACOKINETIC PROFILE OF (BALB/C MICE)



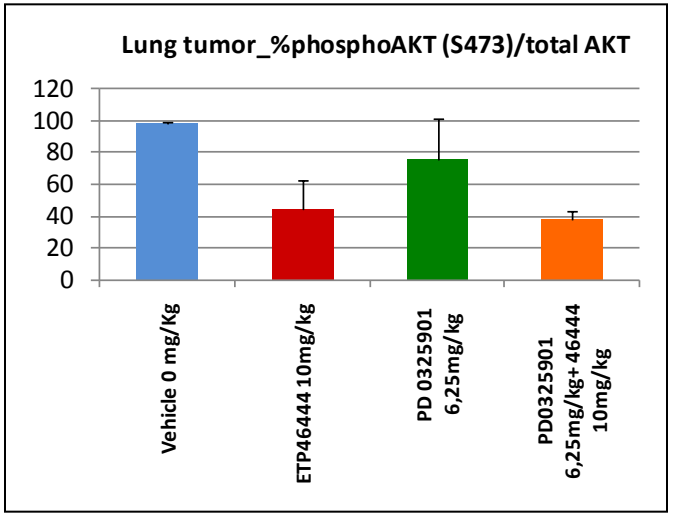
Parameter	I.V.	Oral
Oral bioavailability (%F)	-	61.8
Cmax (ng/ml)	-	3728.41
Tmax (h)	-	0.29
AUC (h x ng/ml)	5185.44	16020.84
$T_{1/2}$ (h)	0.9	1.45
Cl (L/h/kg)	0.39	-
Vd (L)	0.02	-
MRT (h)	2.33	4.80

Pharmacokinetic parameters estimated by fitting the experimental data to a bicompartmental model using Winnonlin software for analysis.

The Product / Current Status of Development
ETP-46444-MoA/Efficacy in Combination with MEKi: Kras driven NSCLC Model

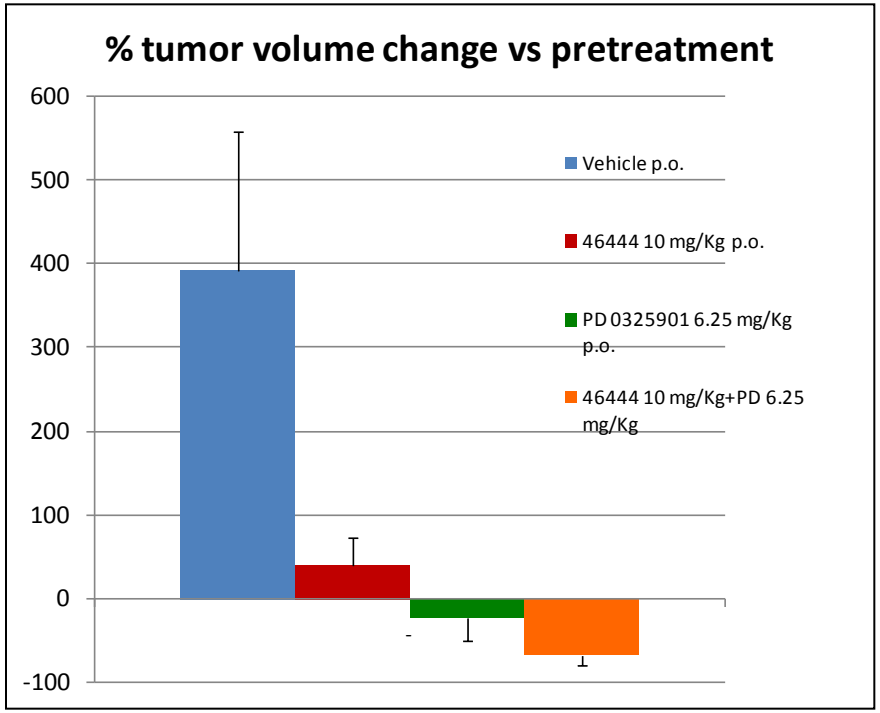
MoA

Group	Dose
ETP-46444	10 mg/kg p.o daily (solution)
PD0325901 (MEK inhibitor)	6.25 mg/kg p.o. daily
ETP-46444+PD0325901	10mg/kg + 6.25 mg/Kg p.o. daily



Lung tumor samples were obtained 1 hour after the last administration and the effect of compounds on pAkt was evaluated by Western Blot. Results are expressed as percentatge of pAkt vs. total Akt. Values are means ± s.d.

Efficacy Study: 3 weeks treatment



Tumor volumes in each treatment group after three weeks are shown as percentage of relative change in tumor volume compared to the starting volume at the beginning of the treatment. Zero and below zero values are considered no changes and a decrease (respectively) vs pretreatment volumes. These calculations are based on previous papers (Puyol, Cancer Cell 2010; Dankort; Nat Genet, 2009). Results are expressed as means ± sd. t-student analysis demonstrates statistical significance *p<0.05 vs vehicle # + p<0.05 vs. 46321 and PD groups. Four mice per group

The Product / Current Status of Development

ETP-PI3K Inhibitors

- Profile:
  - pan-PI3K inhibitors / m-TOR.
  - Highly selective vs 288 kinase panel.
  - Clean CYP inhibition profile and in vitro CV safety.
- Status: Advanced lead optimization.
- Back-up series /status: Yes / LO.
- IP: Patented.
- *In vivo* available data for representative compound(s):
  - PK (BALB/C mice).
  - Mechanism of action (MoA) in A549 human NSCLC xenograft.
  - Efficacy Studies and MoA in Kras driven NSCLC GEMM.
    - CT-PET Follow up.

The Product / Current Status of Development

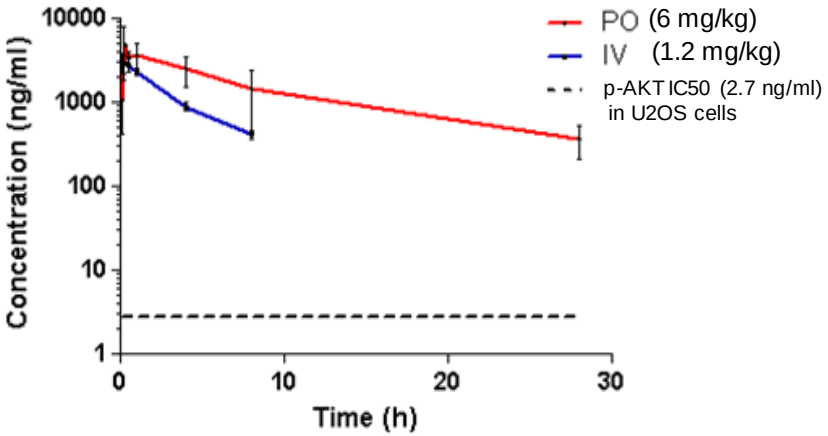
Representative Compounds: pan-PI3K inhibitor / m-TOR.

SERIES	STRUCT_ID	PI3K-ALFA HTRF; Ki app	PI3K-BETA HTRF; Ki app	PI3K-DELTA HTRF; Ki app	PI3K-GAMMA HTRF; Ki app	PI3K-ALFA E542 HTRF; Ki app	PI3K-ALFA E545 HTRF; Ki app	PI3K-ALFA E1047 HTRF; Ki app
Series 5	ETP-00047187	1.98E-10	3.64E-09	2.94E-10	7.60E-10	3.50E-10	2.00E-10	2.90E-10
Series 5	ETP-00047362	9.04E-11	1.92E-09	1.36E-10	2.64E-10			

STRUCT_ID	MTOR IC50	AKT-P(SER-473) U2OS;Elisa;EC50	CYP_1A2 IC50	CYP_2C19 IC50	CYP_2C9 IC50	CYP_2D6 IC50	CYP_3A4 IC50
ETP-00047362	7.42E-10	1.90E-09	3.01E-05	3.01E-05	5.95E-07	3.01E-05	7.06E-06
ETP-00047187	1.66E-09	2.91E-09	3.01E-05	3.01E-05	8.05E-06	3.01E-05	3.01E-05

Selective in a 288 kinases panel (ProQuinase) except for
Src (IC50 < 10 nM for ETP-47362)*
Src overexpression is related to invasion and metastasis. (DF?)

PLASMA PHARMACOKINETIC (BALB/C MICE)

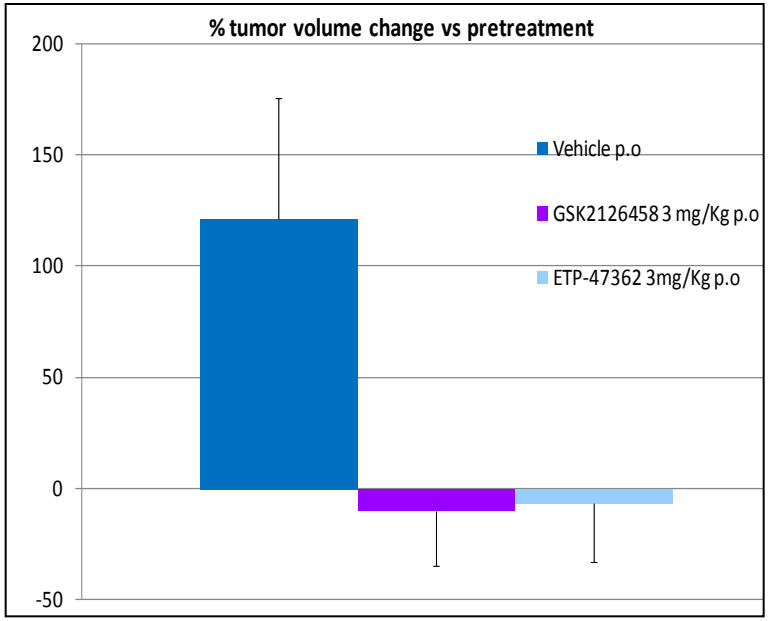


Oral bioavailability (%F)	-	73
Cmax (ng/ml)	-	4850.95
Tmax (h)	-	0.25
AUC (h x ng/ml)	11790.16	43014.83
$T_{1/2}$ (h)	2.41	-
Cl (L/h/kg)	0.11	-
Vd (L)	0.38	-
MRT (h)	3.47	10.88

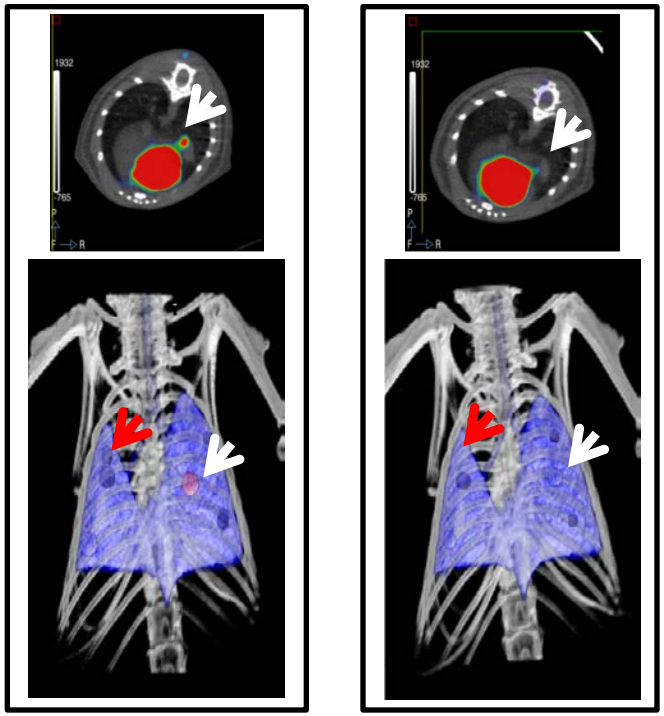
The Product / Current Status of Development

ETP-47362.- Efficacy Studies: Kras driven NSCLC Mouse Model.

Group	Dose	Group	Dose
ETP-47362	3 mg/kg p.o. daily	GSK -2126458	3 mg/kg p.o. daily



Tumor volumes in each treatment group after three weeks are shown as percentage of relative change in tumor volume compared to the starting volume at the beginning of the treatment. Zero and below zero values represent no changes and a decrease (respectively) vs pretreatment volumes. These calculations are based on previous papers (Puyol, Cancer Cell 2010; Dankort; Nat Genet, 2009).Results are expressed as means ± sd. t-student analysis demonstrates statistical significance *p<0.05 vs vehicle. Five mice per group



Computed tomography (CT) Positron Emission Tomography (PET) before and after treatment. White and red arrows on the scans indicate respectively PET response and tumor size. Red color shows ^{18} Fluorodeoxyglucose (FDG) measured by PET imaging. Dark blue color means tumor

The Product / IPR Protection

- Potter-Clarkson (UK) as advisor.

- ETP-PI3K inhibitors are protected by international patent applications (PCT).

- The chemical series are designed and protected to allow “Freedom to Operate” with the compounds.

- 9 applications have been filed:

  WO2010119264 / WO2010112874 / WO2011036461

  P43625EP. (Priority date: 22-Jan-2010)
  P46258EP. (Priority date: 05-May-2010)
  P43626EP. (Priority date: 13-May-2010)
  P46259EP. (Priority date: 11-Aug-2010)
  P46692EP. (Priority Date: 01-Oct-2010)
  P47390EP. (Priority date: 21-Oct-2010)

2 more applications under preparation

The Product: Pitfalls & Risks

• Risk for PI3K as a target is low.
The “expert reports” consider PI3K as of high value to be targeted in cancer therapy.

• “First in Class”: PI3Ki with new profiles.
The risk could be minimized with appropriated patient selection criteria in clinical trials.

• “Best in Class”: Compounds with improved properties for combination therapy.
The risk (low) could be attenuated with preclinical comparison vs reference compounds.

• We have:
Drug-like molecules with new isoforms/target profiles.
Good pharmacological properties and activity in vivo.
Back-ups for our advanced compounds.
Strong IP position.
Preliminary results: Similar/Superior performance vs references.
Additional in vivo data to better benchmark our compounds, on going.

• Regulatory preclinical safety package is key to progress ETP-PI3K inhibitors to Phase I.
Consider to partner at this stage or after “Safety-package” (1 year).

Availability for Cooperation

- Typical Licensing Agreement
- Co-Development Agreement.
- Research Funding with Options Agreement.
- We are open to other creative formula.

"We believe in our compounds and are committed to push them forward to the clinic"

Thanks for your attention !

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