EC-70124 , a dual FLT3 -PIM inhibitor for the treatment of AML

Madrid, 28 de Noviembre de 2018

1. The Institution: EntreChem at a glance

- Founded in 2006, EntreChem **optimizes natural products for oncology.**
- Raised >9M€ of seed capital, public R&D funds and private partners.
- **STRATEGY**: select know anti-tumor **natural products** and expand their chemical space to **improve efficacy** and **reduce toxicity**.
- **TECHNOLOGY:** combinatorial biosynthesis, biocatalysis and **synthetic biology** to explore **new chemical space** not possible otherwise.

Francisco Morís, Ph.D.
Managing Director & Co-founder

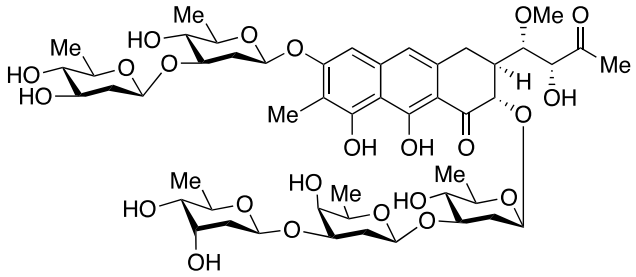
10 years track record in the US: TSRI, ThermoGen-MediChem-deCode, Bristol-Myers Squibb

Co-founded EntreChem in 2006

1. The Institution: Pipeline

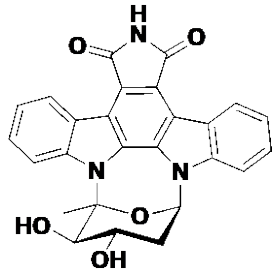
- Currently developing two lead compounds with **highly favorable preclinical data** :

  - **EC-8042**, novel in class transcription reprogramming agent for tumors with genomic instability .



EC-8042

  - **EC-70124**, next-generation Midostaurin for AML with superior metabolic and PPB profile.



EC-70124

EC-70124: dual Flt3-PIM inhibitor for the treatment of AML

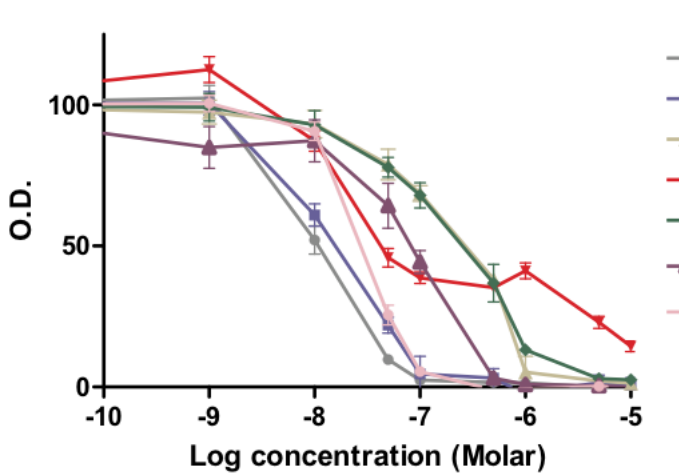
- **Indolocarbazoles** are a **promising class of anticancer compounds** (led by staurosporin) with a established safety record in clinical trials (midostaurin, UCN-01, becatecarin, edotecarin, enzastaurin, lestaurtinib).
- In April 2016, Novartis announced FDA approval of Midostaurin (Rydapt®) in Flt3-mutated AML patients.
- Patients treated with **PKC412 (midostaurin, RYDAPT®)** experienced a **23% improvement in overall survival,** a major advancement in the heavily underserved AML setting.
- EntreChem was able to create novel indolocarbazole compounds **with markedly improved properties** applying **proprietary technology** to combine biosynthesis genes for staurosporine and rebeccamycin.
- Modifications introduced include changes in the sugar moiety **which by classical medicinal chemistry methods would not have been possible.**

EC-70124 kinase profile vs Midostaurin

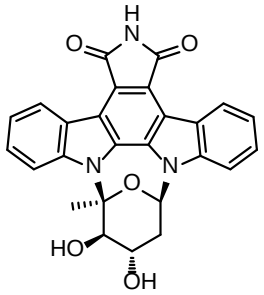
- Different profile based on affinity IC_{50} despite being close analogs → viability profile
- EC-70124 **more potent** on **relevant AML targets** Flt3, JAKs, PIMs and SYK

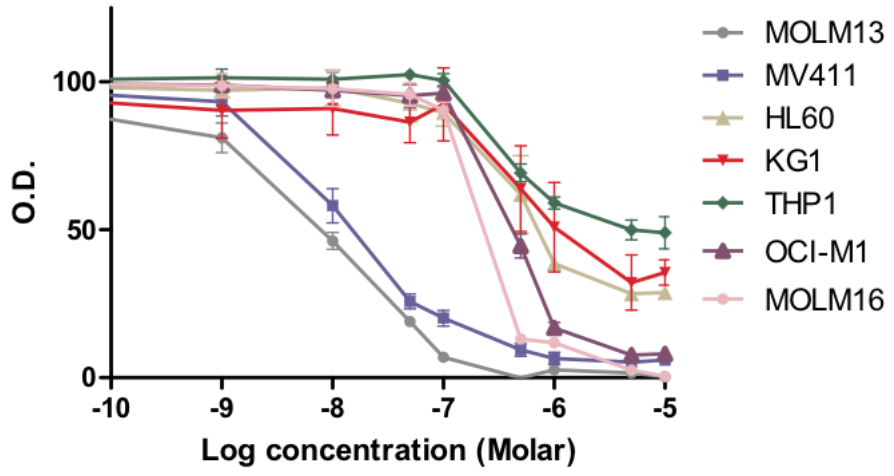
Kinase	Kd, nM	
	Midostaurin	EC-70124
FLT3	11	3.2
FLT3(ITD)	11	2.5
FLT3(D835H)	6.8	0.8
FLT3(D835Y)	15	1.1
FLT3(D835V)	2.2	0.8
FLT3(N841I)	6	1.4
FLT3(K663Q)	2	7
FLT3(R834Q)	12	11
FLT3 (ITD, D835V)	3.5	1.1
FLT3 (ITD, F691L)	5	1.2
JAK1	670	9.4
JAK2	94	2.5
JAK3	12	1.5
PDPK1	190	16
PIM1	560	2.9
PIM2	3100	3.1
PIM3	560	0.4
S6K1	1300	9.4
SYK	88	8

Assays run by Discoverex (formerly Ambit, USA)

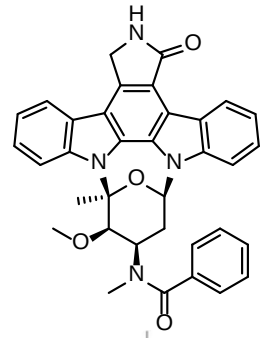


EC-70124



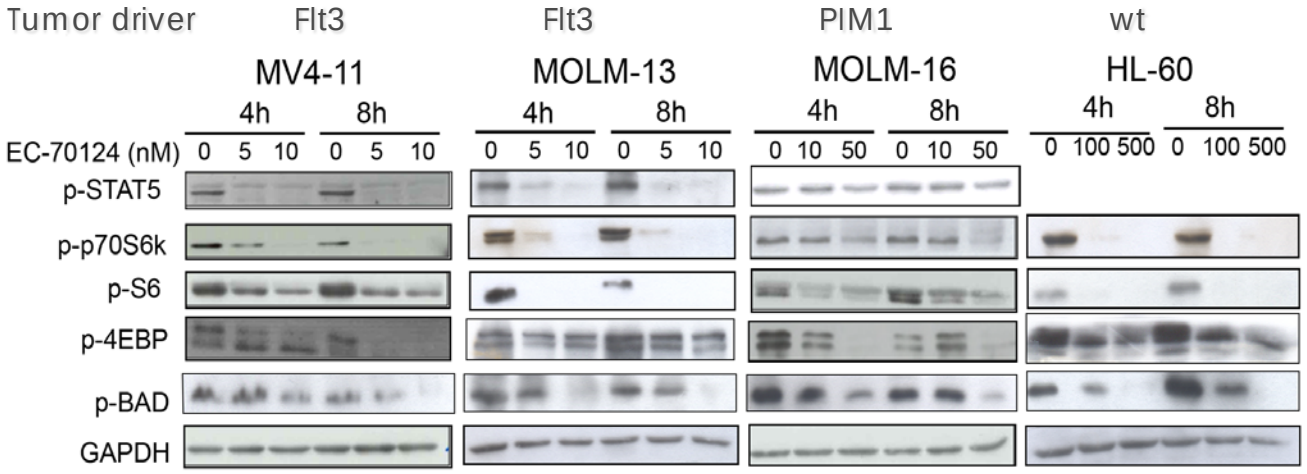


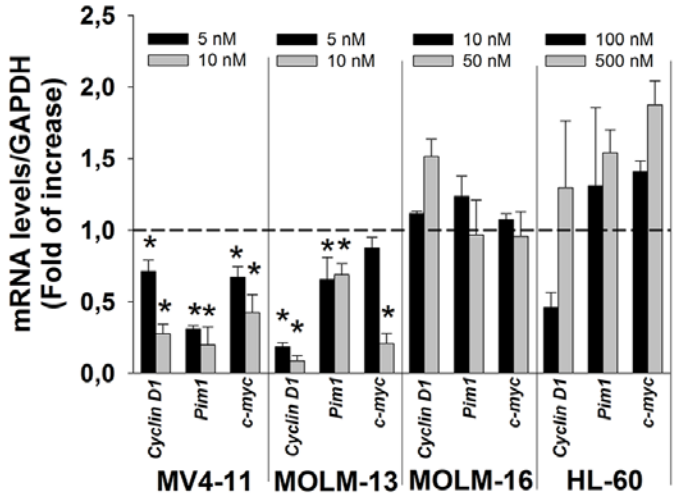
midostaurin



EC-70124 targets multiple key pathways in AML

- Flt3-ITD lines show strong STAT5 inhibiton (target of Flt3): phosphorylation and qPCR of STAT5 targets
- In all cell lines pBAD (PIM1 target) is inhibited by EC-70124, but not by midostaurin
- In all cell lines (including wt HL60) the mTOR-S6 pathway is inhibited

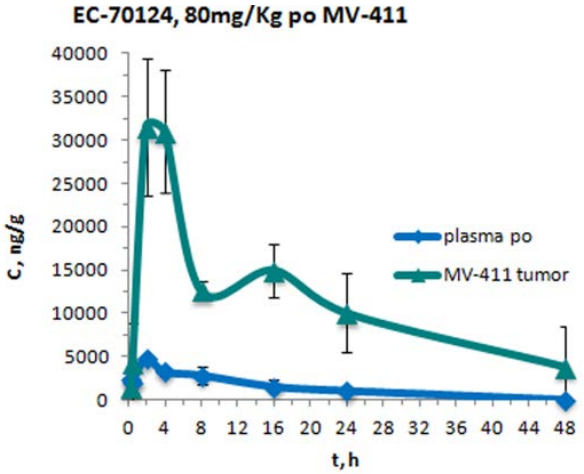


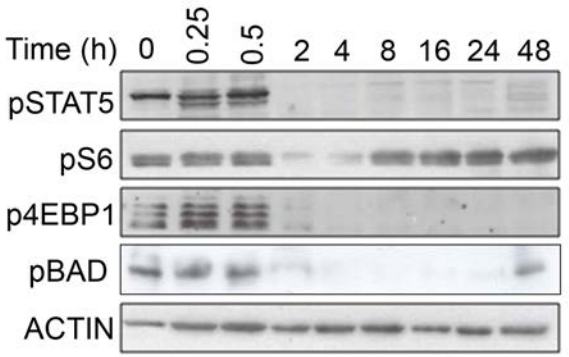


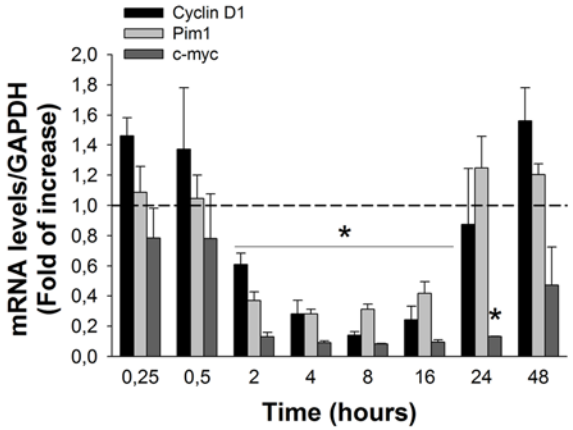
Puente-Moncada *et al*. Mol Cancer Ther. **2018** Mar;17(3):614-624

EC-70124 pharmacodynamic profile: same as in vitro

- Oral dose in mice bearing MV4-11 tumor shows high distribution to tumor tissue
- >100nM in plasma at 48h, 100x higher in tissue
- Main target pSTAT5 stays dephosphorylated at 48h
- mTOR downstream target pS6 recover early, but p4EBP1 response is sustained



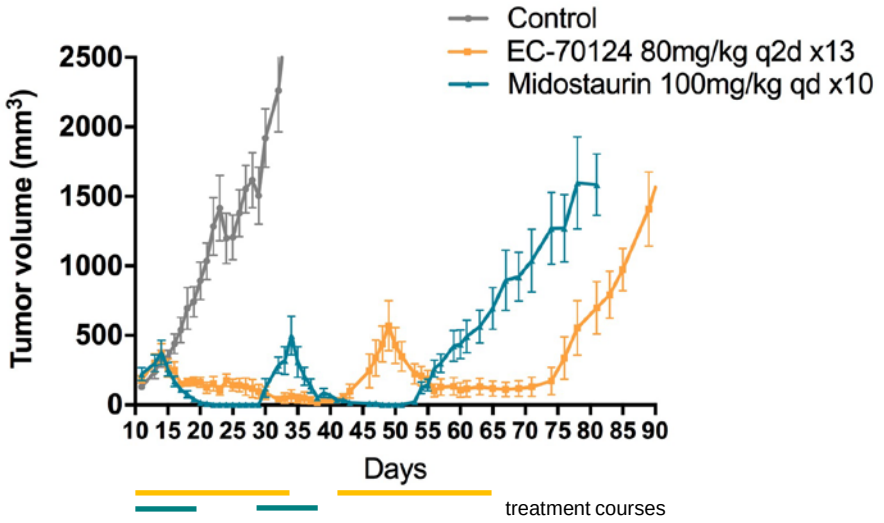


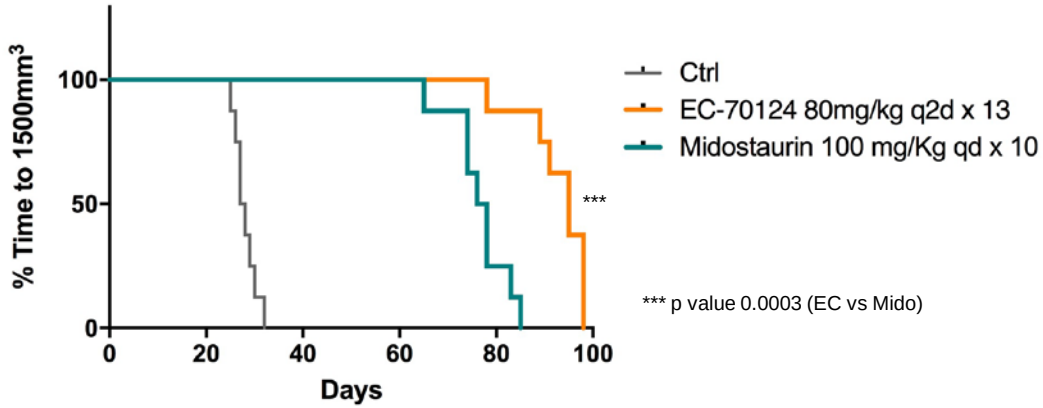


Puente-Moncada *et al*. Mol Cancer Ther. **2018** Mar;17(3):614-624

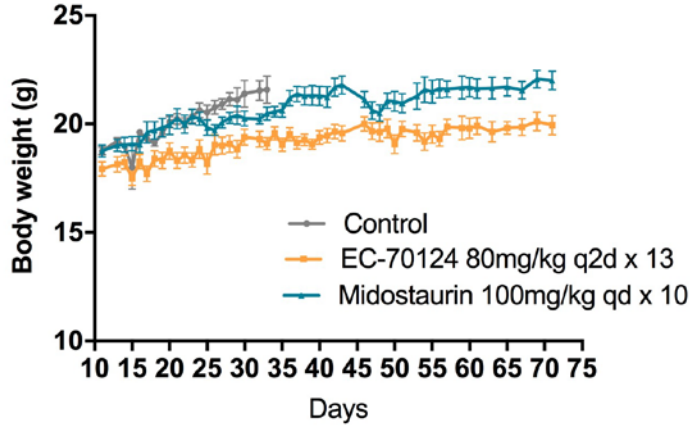
EC-70124 better survival than FDA approved Midostaurin

- MV4-11 xenograft in CB17 immunosuppressed mice
- Equivalent oral doses, 1g/Kg total dose per treatment course
- Both drugs cause 8/8 full regressions and one permanent cure
- Recurrence in 7/8 mice responds to a second course of drugs
- EC-70124 provides highly significant survival advantage at 2g/Kg total dose



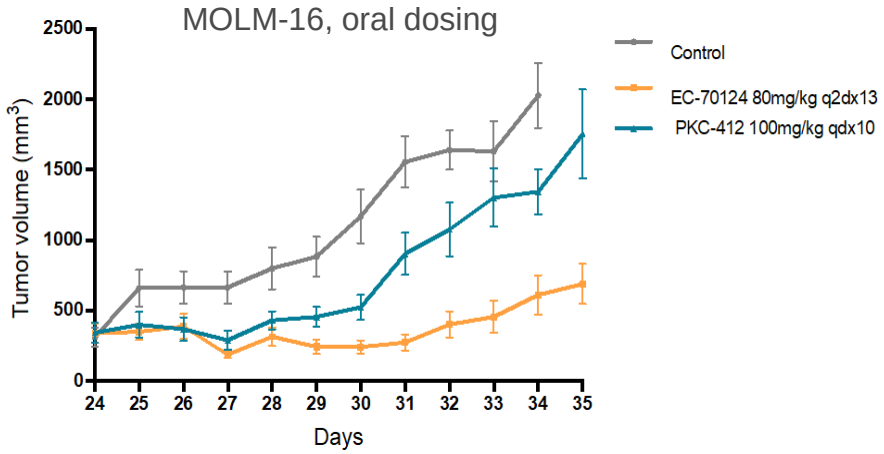


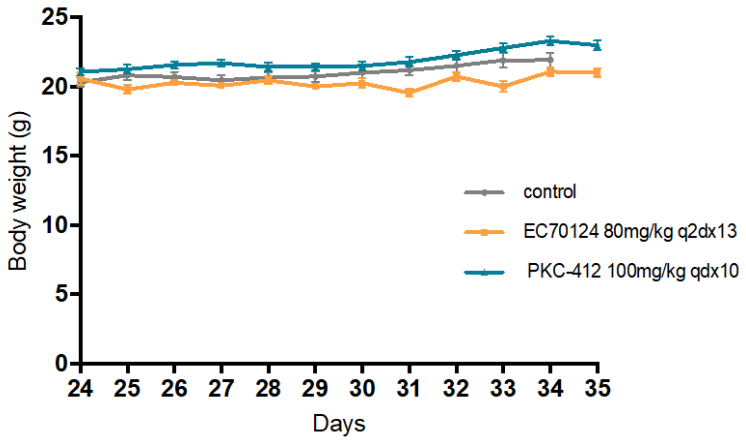
*** p value 0.0003 (EC vs Mido)



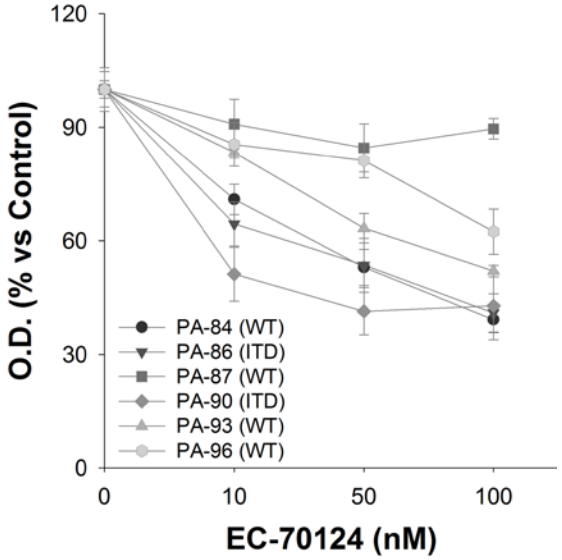
Puente-Moncada *et al*. Mol Cancer Ther. **2018** Mar;17(3):614-624

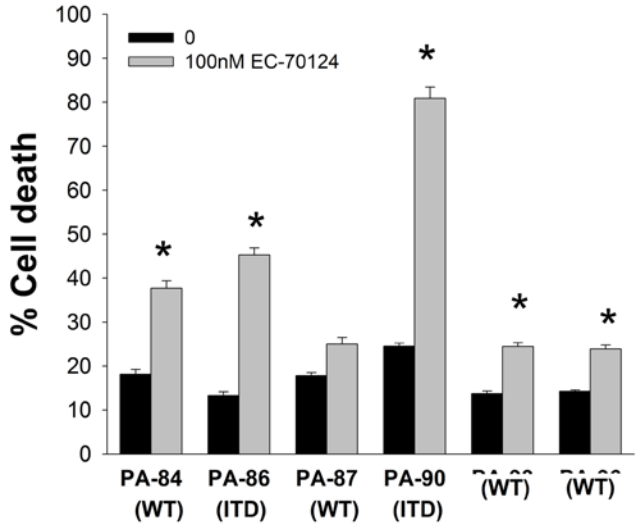
EC-70124 superior to midostaurin in AML not driven by Flt3





- EC-70124 superior to Midostaurin in murine models of PIM-driven AML (MOLM-16)
- *ex-vivo* AML specimens show EC-70124 activity in wt as well as in Flt3-ITD





Puente-Moncada *et al*. Mol Cancer Ther. **2018** Mar;17(3):614-624

AML - Pipeline Competition

- Midostaurin, the ***only natural product***, multi-targeted drug, in the clinical practice and the ***only one approved based on promising*** Phase III data

- EC-70124 better profile **represents a fast-follower approach** to Midostaurin

- NDAs under Revision:
  - **Quirzatinib** (Daichii, licensed from Ambit): resistance through mutation of Flt3 kinase domain
  - **Gilteritinib** (Astellas): resistance through mutation of Flt3 and others (NRAS)
  - In both cases resistance is rapid, so **survival benefit not comparable** to that of Midostaurin

- Other drugs struggling through advanced clinical trials or dropped from the pipeline
  - Volasertib (plk1 inhibitor), Crenolanib (dual FTL3- PDGFR), AZD1208 (pan PIM), sapacitabine (oral nucleoside analogue), CC-486 (DNA Methyl Transferase inhibitor, oral azacytidine)

EC-70124 vs Midostaurin key differences

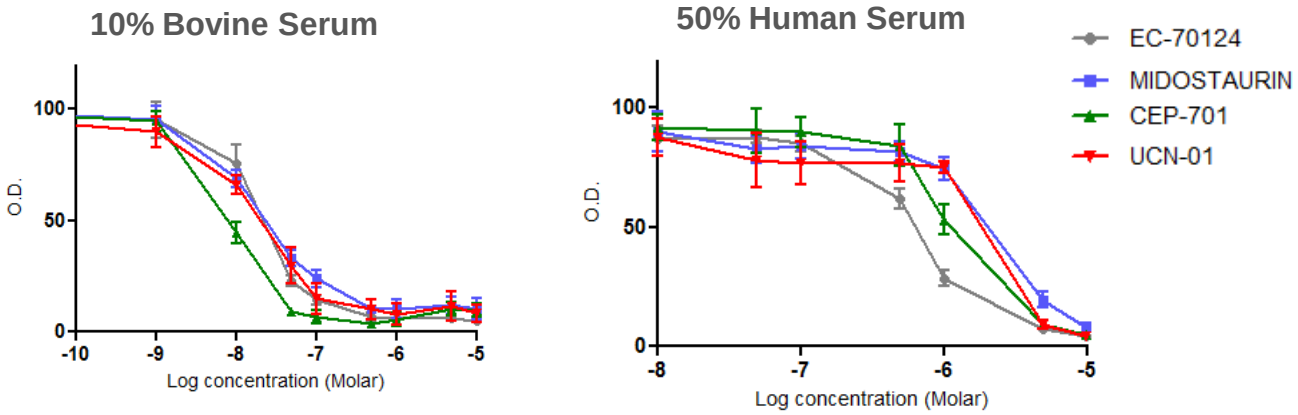
Parameter	Midostaurin	EC-70124
Selectivity Profile	Highly promiscuous, hitting also undesired targets like c-Kit	Much more **focused on AML-relevant targets** like Flt3, PIMs, VEGF2, and SYK
Protein Plasma Binding	High Protein Plasma Binding >99%	Unbound fraction **increased by a factor of 4** in comparison to midostaurin
Metabolic Stability	Metabolites detected in mice, 2 major metabolites (one accumulating) in humans	**Stable** in microsomal stability assays and *in vivo (mice, rats and dogs)*
***in vivo* Efficacy**	Limited to **Flt3-driven AML**, needs **combination with chemotherapy**	Potential to treat **both Flt3-ITD and other AMLs. Also potential for solid tumors** if human PK is at least similar to midostaurin

Species	EC-70124,fu*	PKC-412, fu*
Human	3.9	1.1
Rat	4.2	n.d.
Dog	3	n.d.

TRANSIL^{XL} high sensitivity binding kit.
** fu: fraction unbound*

Puente-Moncada *et al*. Mol Cancer Ther. **2018** Mar;17(3):614-624

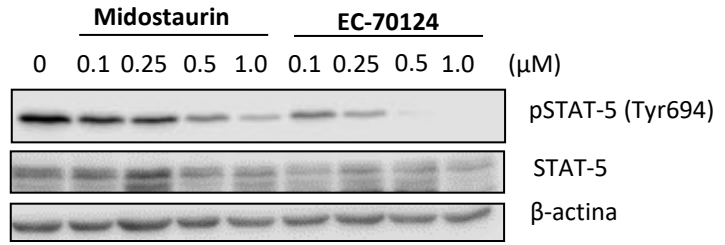
Functional assays show superior PPB profile of EC-70124



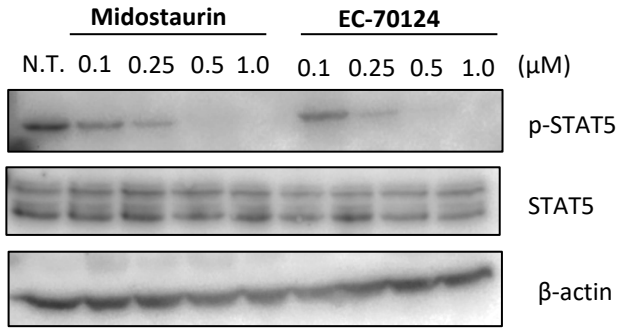
MOLM-13, IC50 (µM)				
% serum	EC-70124	Midostaurin	CEP-701	UCN-01
10% FBS	0.015 ± 0.005	0.016 ± 0.006	0.008 ± 0.0007	0.014 ±0.006
50% human serum	0.606 ± 0.036	2.160 ± 0.084	0.926 ± 0.176	2.010 ± 0.367
Ratio Human / 10%FBS	41	139	123	149
Human serum Ratio EC-70124 / others	1,0	**3,6**	1,5	3,3

Human vs Mice serum target inhibition by EC-70124 and midostaurin

human

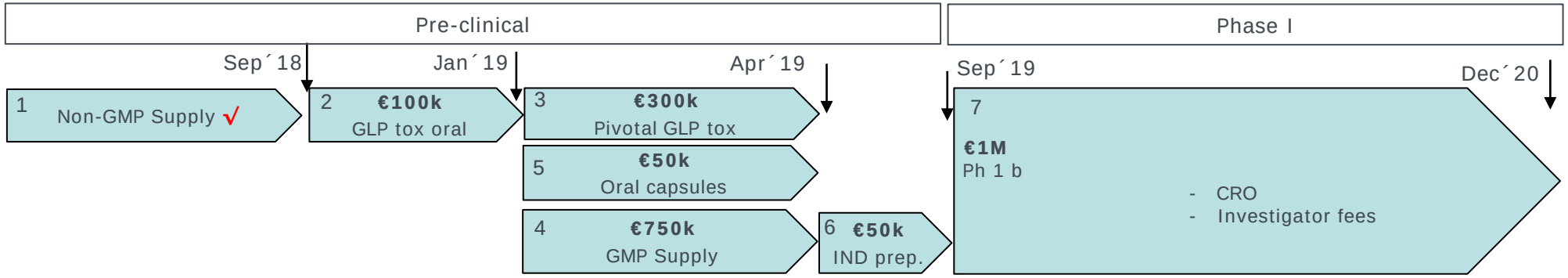


mouse



2. The Product d) Current status of development

EC-70124 Development: Next Steps



#	Step	Time	Cost	Suppliers profile	suppliers (clinical CROs not decided yet)
1	Non-GMP Supply	√	√	8000 L fermentation and downstream processing for isolation of non-GMP API	amri, KYMOS
2	2 week GLP oral tox	√	√	GLP certified Vivarium CRO + expert toxicology consultant	vivotecnia, SBQ, INNOQUA
3	28-days GLP oral tox	6 months	€400k	GLP certified Vivarium CRO + expert toxicology consultant	vivotecnia, SBQ, INNOQUA
4	GMP supply	6 months	€750k	Fermentation up to 3000L and downstream processing for isolation of API under GMP	amri, KYMOS, hjkfarma
5	Oral capsules	6 months	€50k	Define the capsule formulation	IDIFARMA, KYMOS, hjkfarma
6	IND prep.	3 month	€50k	Specialized consultants for IND filing	INNOQUA, hjkfarma
7	Phase 1	18 months	€2-3M	CRO to manage clinical trials	PIVOTAL, Cmed, SGS
	Total	**32 months**	**€3,2 - 4,2M**		

GOBIERNO DE ESPAÑA · MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

entrechem

farmaindustria

Phase I Strategy for EC-70124: value inflexion point

- The FIH trial will determine:
  - ✓ the Recommended Dose for a Phase 2 trial.
  - ✓ plasma levels (PK) for early assessment of the treatment potential:
    - ❑ Plasma levels **<15-20µM** → potential for selected tumors like Flt3-ITD AML
    - ❑ Plasma levels **>15-20µM** → potential for other AMLs, and solid tumors
- Unlike most drug development programs, **the value inflexion** point for EC-70124 resides in the Phase I data
  - ✓ Intrinsic potential to be the most bioavailable indolocarbazol ever in clinical trials

2. The Product e) IPR Protection

Strong IP position - Composition of Matter until 2028

Topic	Priority Date	Status
Indolocarbazole Rebeccamyicin genes *In-Licensed from UniOvi*	Oct 19, 2001	Granted on August 18, 2010 **EP1443113** Validated in ES, FR, GB, DE (All in force) Granted on June 26, 2012: **US 8,207,321** (in force)
Glycosylated Indolocarbazoles *In-Licensed from UniOvi* *EC-70124*	April 8, 2008	Granted on December 3, 2013: **US 8,598,132** (in force) Granted on March 15, 2017 **EP2277885** Validated in ES, FR, GB, DE and IT (All in force) Entry in National Phases in Europe Divisional EP17154953.8 Examination is in progress
70124 combinations in triple negative breast cancer 100% EntreChem	May 30, 2014	Granted on November 7, 2017: **US 9,808,469** (in force) Granted on Nov. 23, 2016. **EP14170596.2** Validated in DE, FR, GB, IT, ES (All in force)
70124 combinations in colon cancer 100% EntreChem	Sept 26, 2014	Entered regional/national Phases in EP and USA. Examination is in progress

- **Industrial secret**: a significant layer of protection is provided by EntreChem's **proprietary position** on the bacterial strain which is required for producing EC-70124.

- In addition to patent protection, EC-70124 is eligible for Orphan Drug Status in its lead indication AML, which confers a **market exclusivity of 10 years in Europe and Japan, and of 7 years in the US**.

Potential Pitfalls and Risks

1) *PK fails to reach levels similar to those of Midostaurin and other indolocarbazoles previously in clinical trials*

2) *GI toxicity limits the dose or forces a to non-optimal schedule*

3) *Unexpected toxicity not foreseen in preclinical studies*

3. Partnering Opportunities

Prefered scenario

- *Co-development until PoC in humans. Unmet disease, fast regulatory approval.*
  - *upfront fee + milestones*
- *From PoC until approval : EntreChem to provide CMC experitse + production*
  - *Royalties based on PoC results*

3. Partnering Opportunities

Final Summary

- **EC-70124** is a novel multi-targeted **kinase inhibitor from the same chemical class as Novartis midostaurin,** but with marked improvements in terms of **selectivity profile, protein plasma binding and metabolic stability**. It is the result of successful mining of new chemical space by applying proprietary technology.
- Based on strong in vitro and in vivo data, EntreChem has selected EC-70124 **as clinical development candidate** with **AML as lead indication** and FIH scheduled for 2019. Regulatory preclinical trials are underway.
- Further in vivo data indicate that in addition to AML, EC-70124 has potential in **glioblastoma, prostate, colorectal and triple-negative breast cancer**.
- EC-70124 **production is straightforward** through fermentation of a proprietary bacterial strain.

We are seeking for a partner to advance EC-70124 into the clinic, gain regulatory approval, and to commercialize the product on a regional or worldwide level.

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española

entrechem

farmaindustria