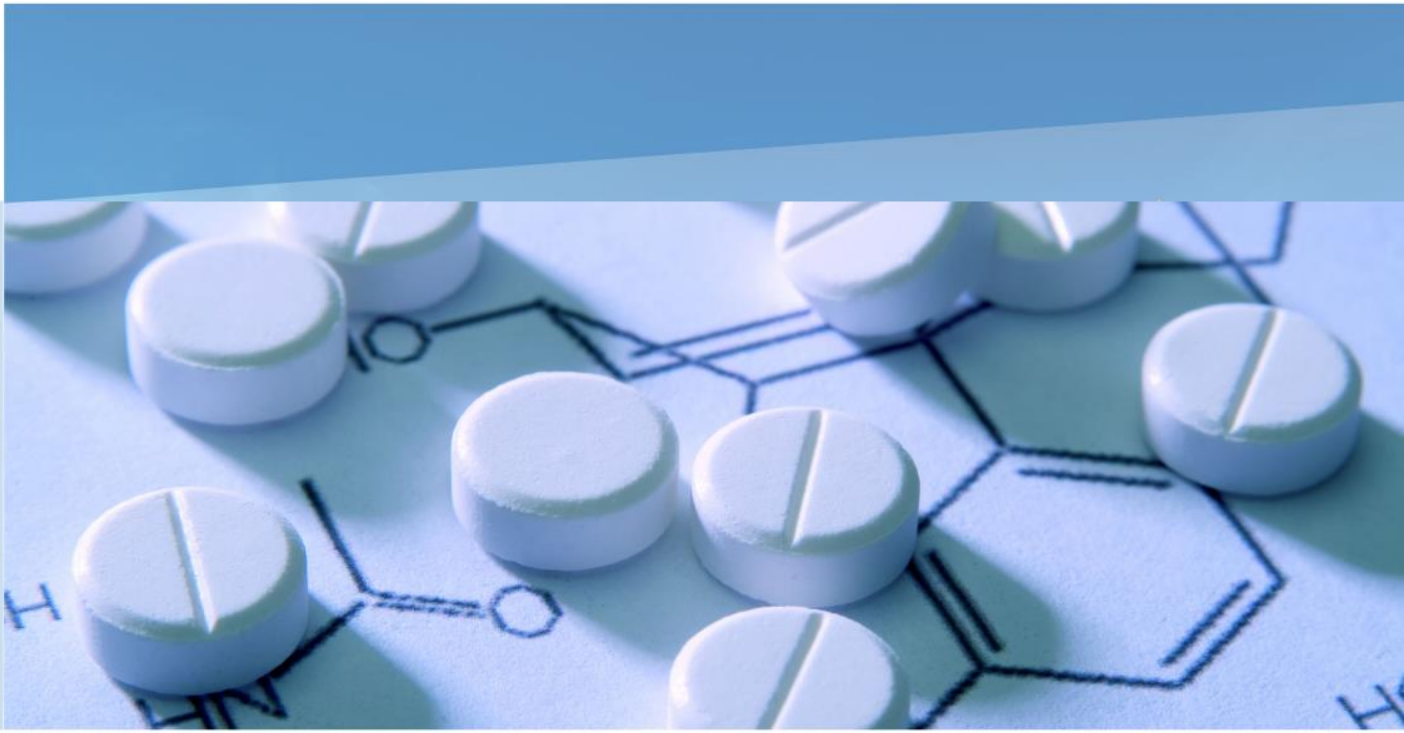
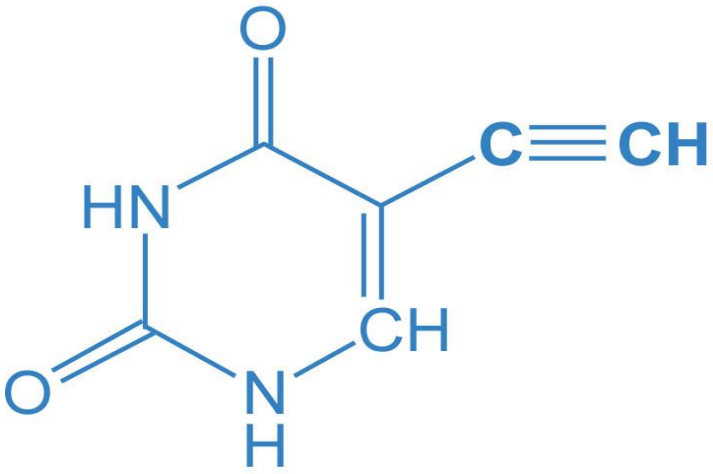
Eniluracil Summary



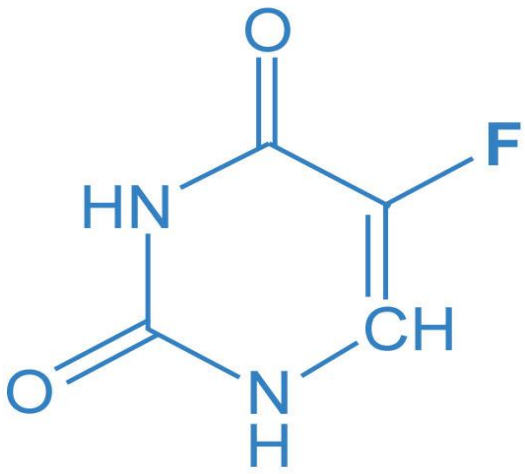
Product Candidate: Eniluracil (EU)

Oral Chemotherapy for Solid Tumors

- Irreversible inhibitor of DPD, the enzyme responsible for the rapid breakdown of 5-FU
- Developed as a potentiator of 5-FU in the 1990s by Burroughs Wellcome and then by GlaxoWellcome (now GSK)



Eniluracil
(5-Ethynyluracil)
(776C85)



5-Fluorouracil

Fluorouracil Market Overview

5-FU (5-Fluorouracil)

Discovered in 1957, widely available as generic

IV only

Principal uses: colorectal, breast, gastric, pancreatic, head and neck, ovarian and basal cell cancer

Used in combination with leucovorin, which improves 5-FU antitumor activity

Annual use: 500,000 patients in North America, millions worldwide

Xeloda® (capecitabine)

Oral, prodrug of 5-FU

On the market since 1998, expected generic in the US by 2013/2014

Principal uses: colorectal, breast and gastric cancer

Not used with leucovorin

Global Sales in 2012 of $1.6B 12% YOY growth, $634 MM US Sales, marketed by Roche

UFT® (tegafur-uracil)

Developed in Japan during the 1980s

Oral, combining uracil (competitive inhibitor of DPD) and tegafur (prodrug of 5-FU)

Approved in 50 countries, except the US

Principal uses: colorectal, breast, gastric, pancreatic, head and neck, liver, ovarian and basal cell cancer

Used in combination with leucovorin

Marketed by Merck Serono, Korea United and Taiho

Teysuno® (tegafur-gimeracil-oteracil-potassium)

Oral combination of tegafur (prodrug of 5-FU) plus 2 enzyme inhibitors: gimeracil and oteracil

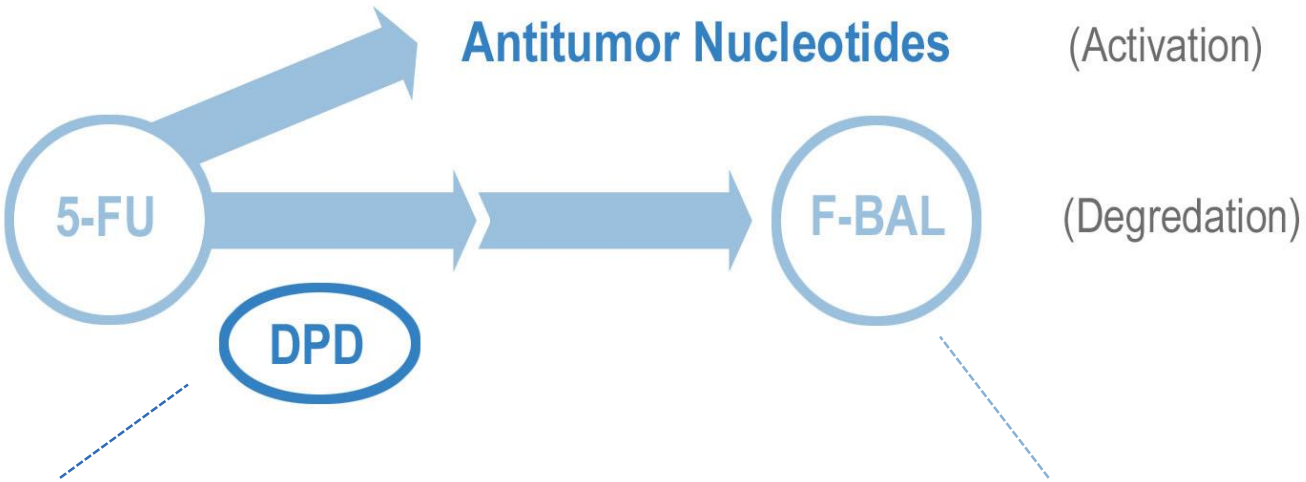
On the market since 1999 in Japan and since 2011 in Europe, marketed by Taiho

Principal uses: gastric, colorectal, head and neck, non-small cell lung, breast, pancreatic cancer

Not used with leucovorin

5-FU Metabolic Pathways

- 5-FU must be activated to kill cancer cells
- The enzyme, DPD, prevents activation and degrades 5-FU to F-BAL



DPD problems:

- Highly Variable levels
- Unpredictable 5-FU PK
- 5-FU $t_{1/2}$ = 10-20 min
- 5-FU MTD correlates with DPD

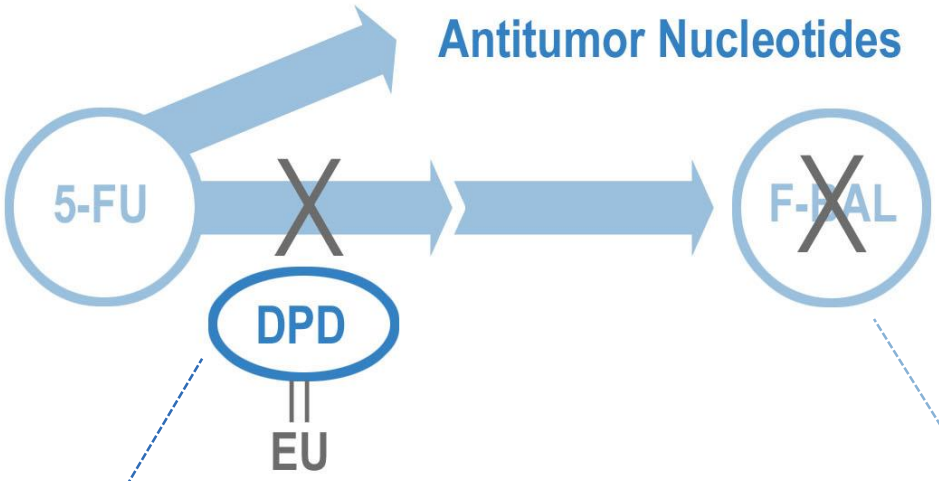
F-BAL problems:

- >80% of dose = F-BAL
- Decreases 5-FU Efficacy
- Neurotoxic
- Hand-foot syndrome (HFS) agent

(PK = pharmacokinetics; measurements of 5-FU in patient's blood. MTD = Maximum Tolerated Dose)

The Solution: EU Inactivates DPD

EU Eliminates **DPD** & **F-BAL** Problems



5-FU is not destroyed:

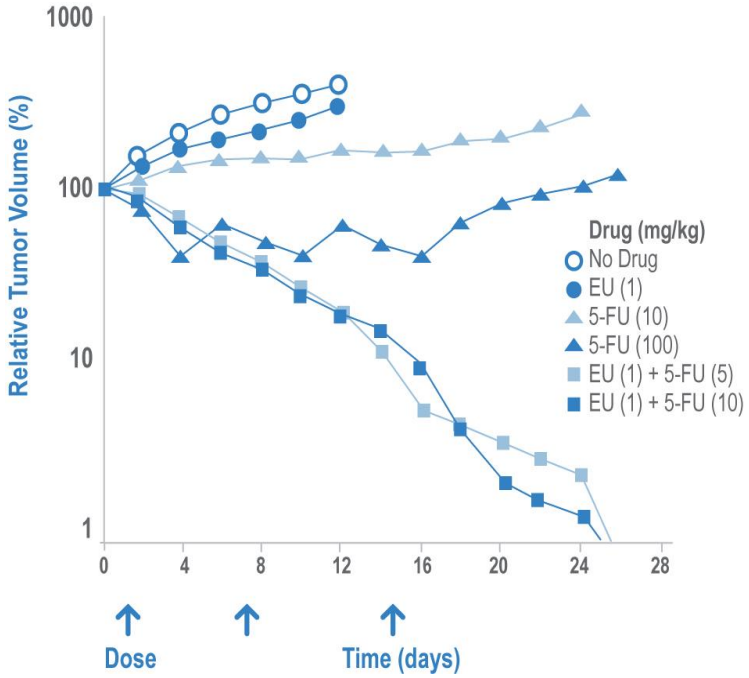
- Half-life = 5 hr.
- Highly predictable linear PK
- Oral dosing

F-BAL formation is minimal:

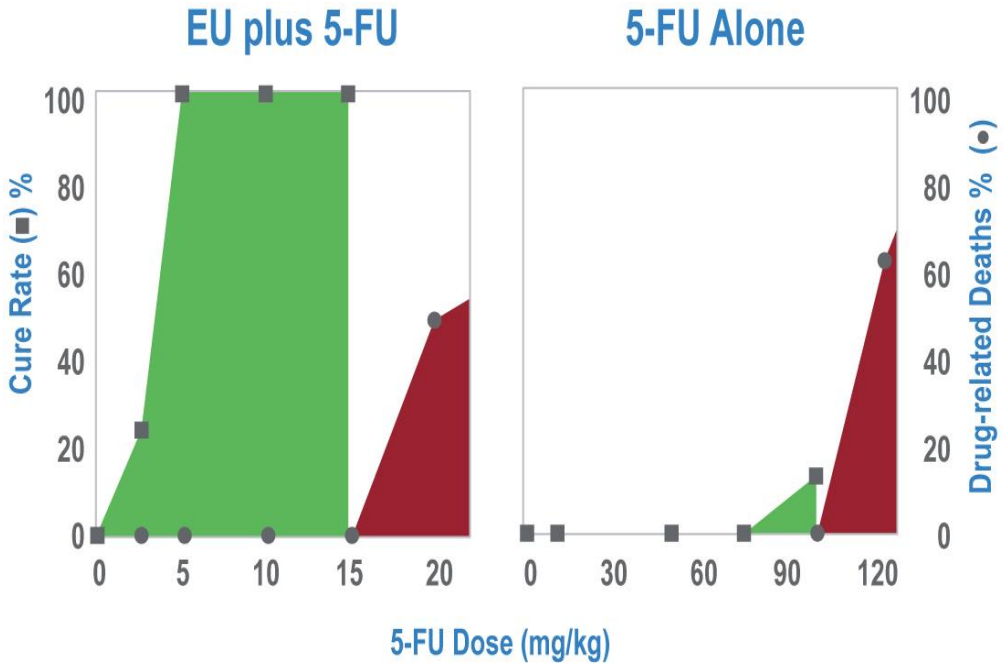
- No interference with efficacy
- Minimize neurotoxicity
- HFS is negligible

Burroughs Wellcome Preclinical Studies

Rats Bearing Advanced Colon Carcinoma



EU:5-FU ratio < 1:5



Cure Rate

EU/5-FU = **100**% 5-FU = **13%**

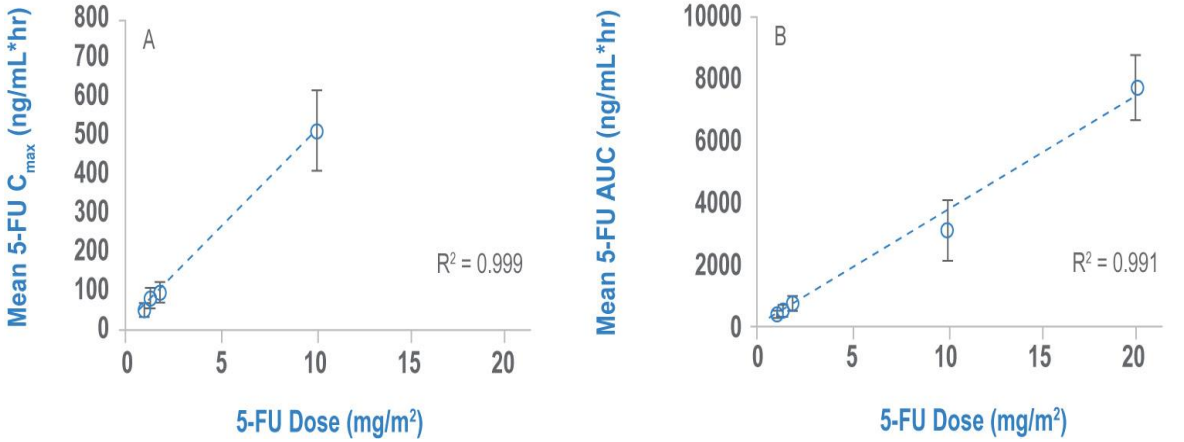
Therapeutic Index

EU/5-FU = **6** 5-FU = **1**

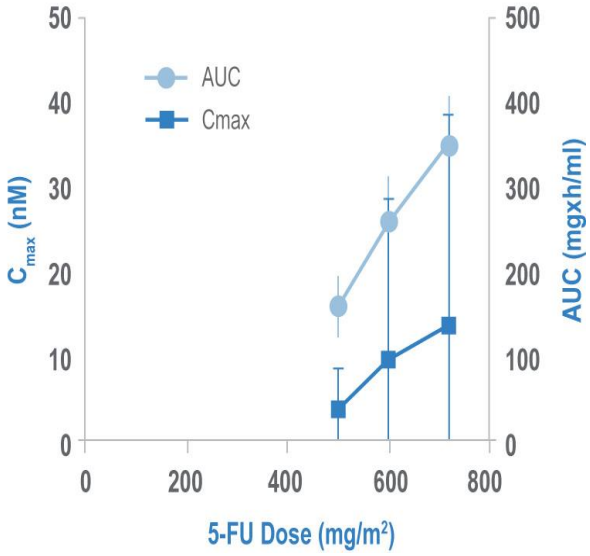
EU improves 5-FU antitumor activity and therapeutic index

EU Clear Advantages

5-FU Dose With EU*



5-FU Dose Without EU**



- Enable oral 5-FU dosing
  - 100% Oral Bioavailability
- Yield highly predictable 5-FU dosing

  (see above graphs oral 5-FU with EU *vs*. iv 5-FU)
- Decrease toxicity
  - Well tolerated, Negligible HFS
- Improve antitumor efficacy
  - Encouraging Preclinical and Phase I & II

*Source: Baker SD. Invest New Drugs 2000; 18:373-81

**Source: van Groeningen CJ, Pinedo HM, Heddes J, et al. Cancer Res 1988; 48:6956-61 (C_{max} & AUC are measurements of 5-FU in patient's blood)

GSK Pivotal CRC Phase III Results and MBC Phase II Results

FENNEC PHARMA

Results of the North American Pivotal Phase III Trial Colorectal Cancer

Treatment	PFS (weeks)	Survival (months)
EU (10 mg/m^2) + **5-FU** (1 mg/m^2) oral: every 12 hr for 28 days, then 7 days off	20.0	13.3
5-FU + Leucovorin iv: daily for 5 days	22.7	14.5

- Although considerably less toxic, oral **EU/5-FU** produced less antitumor activity than iv **5-FU/leucovorin**

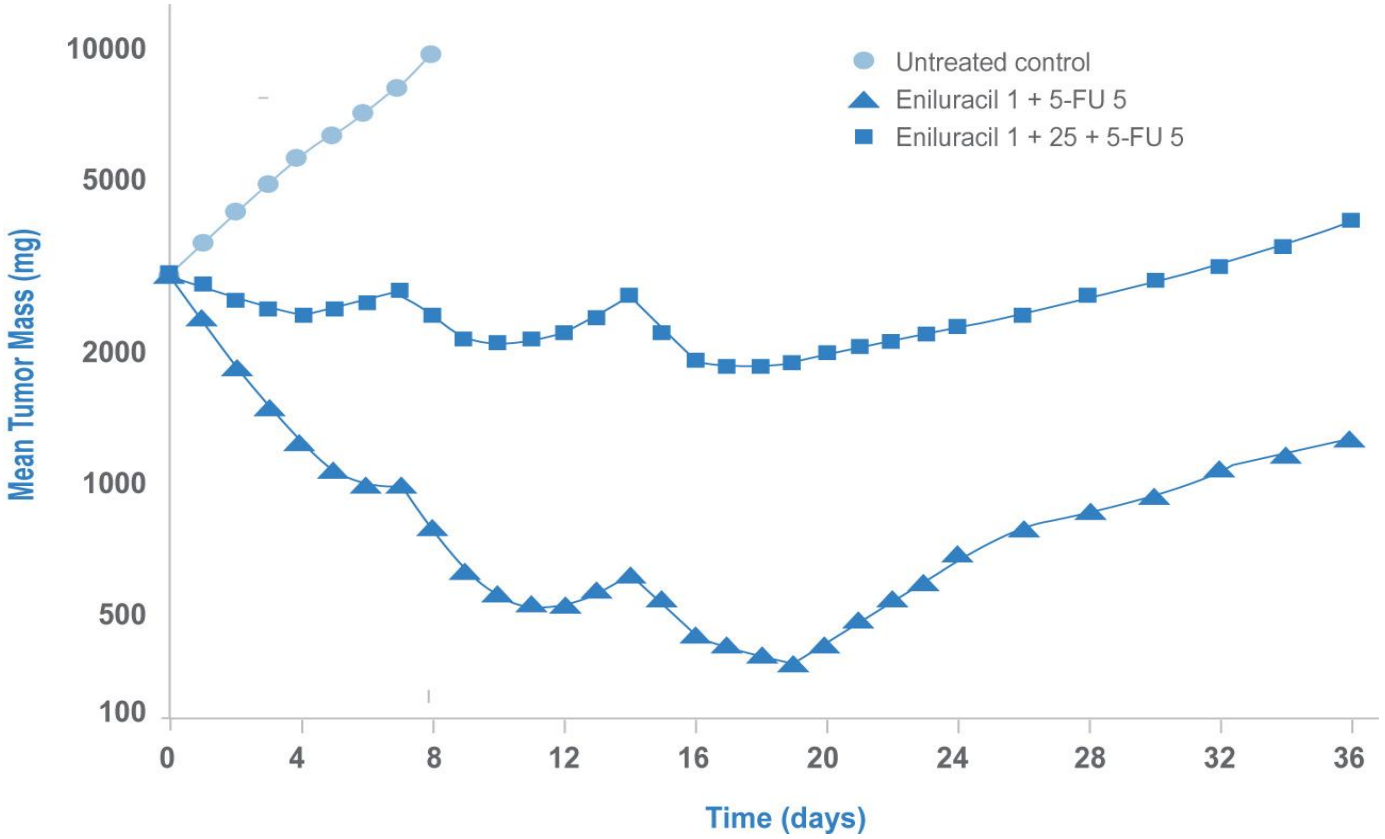
Phase II results in MBC patients already treated with anthracycline and taxane

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD n (%)	Median PFS (weeks)
EU (10 mg/m^2) + **5-FU** (1 mg/m^2) oral: every 12 hr for 28 days, then 7 days off	84	0 (0)	8 (10)	20 (24)	28 (34)	9.9

Could the weekly bid schedule that GSK used where the ratio of EU:5-FU is 10:1 have caused the problem?

High EU:5-FU Ratio Decreases Efficacy

Adherex licensed EU from GSK, based on the following study results of rats with large tumors:



EU:5-FU ratio

5:1 ratio excess EU present

<1:5 ratio excess EU avoided

A high ratio of EU to 5-FU was less effective than a low ratio

Data: Spector T, Cao, S. A Possible Cause and Remedy for the Clinical Failure of 5-Fluorouracil plus Eniluracil. Clinical Colorectal Cancer. 2010;9(1):52-4.

Adherex New Weekly Schedule: Avoids Excess EU when 5-FU is administered

FENNEC PHARMA

Dr. Grem's Phase I Weekly Schedule vs. Xeloda®'s Phase 2
in Advanced Colorectal Cancer Refractory to iv 5-FU/Lv

Outcome	EU/5-FU/Lv	Xeloda®
Treatment	20mg/29mg/m^2/30mg **weekly** for 3 weeks	1,250mg/m^2 **every 12 hr** for 14 days
Tumor Responses	**2/17**	**0/22**
Diarrhea total (*severe*)	**65** (*17*) **%**	**74** (*26*) **%**
Hand-Foot-Syndrome total (*severe*)	**0** (*0*) **%**	**87** (*13*) **%**

Eniluracil/5-FU/leucovorin: better efficacy and less toxicity than Xeloda®

This study established the correct 5-FU dose, without excess EU present

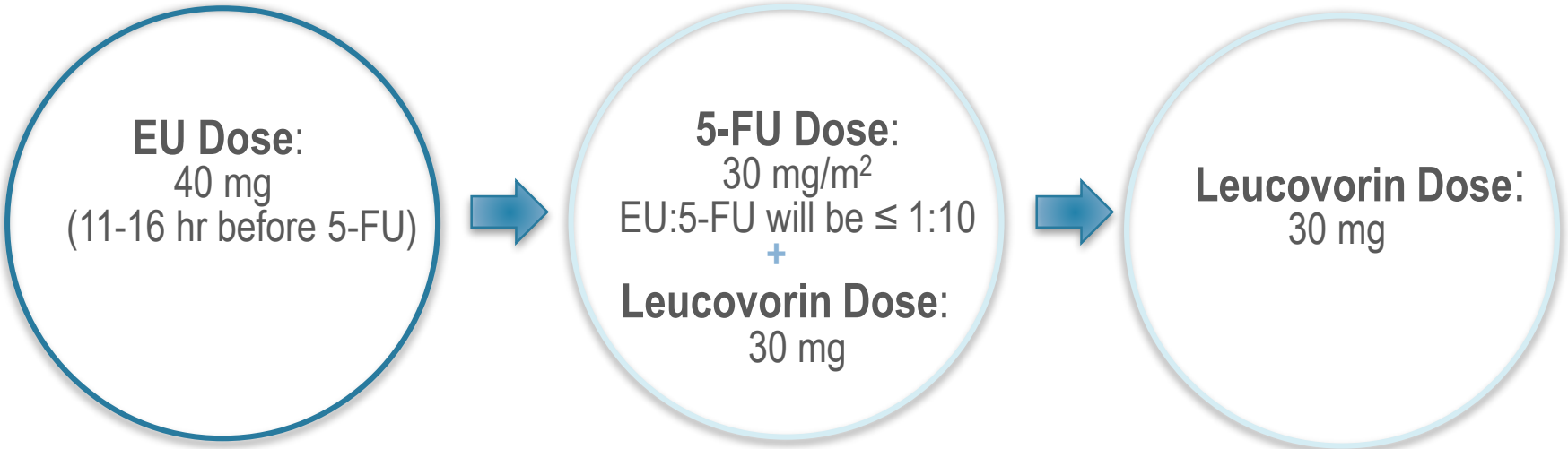
Phase II: Oral 5-FU Regimens Comparison in MBC

FENNEC PHARMA

Weekly EU/5-FU/Lv schedule (all oral regimen)

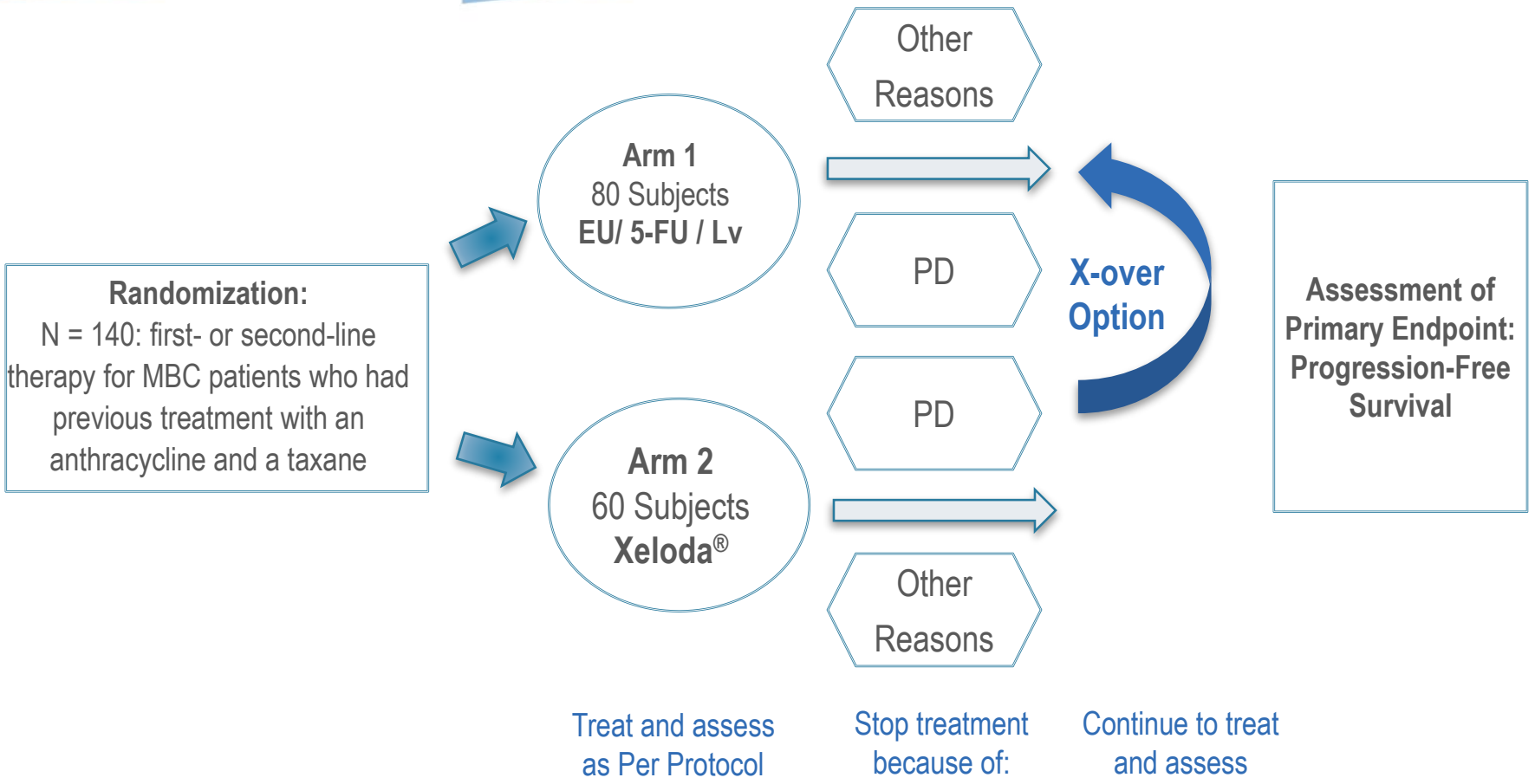
- Administers a higher EU dose to eliminate all DPD, including DPD in nervous tissue to minimize neurotoxicity. Allows excess EU to be cleared before dosing with 5-FU
- Administers 5-FU when the EU:5-FU ratio is very low to optimize efficacy
- Administers Lv with 5-FU and 24 hr afterwards to potentiate 5-FU efficacy
- Described in Adherex patents issued and pending worldwide, expiring from 2025 to 2029

Arm 1: Weekly Schedule: taken 3 weeks followed by 1 week interlude



Arm 2: 1000 mg/m^2 **Xeloda®** twice daily for 14 days followed by 7 days interlude

Phase II: Study Design



Arm 1: Eniluracil / 5-FU / leucovorin

Arm 2: Xeloda® (capecitabine)

X-over: Crossover Group Analyzed Separately

Interim Study Efficacy Results*

FENNEC PHARMA

Arm 1: EU/5-FU/Lv vs. Arm 2: **Xeloda®**

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD[1] n (%)	Median PFS (days)
EU/5-FU/Lv	74	1 (1)	18 (24)	38 (51)	57 (77)	125
Xeloda	61	0 (0)	18 (30)	27 (44)	45 (74)	126

Arm X: patients who failed **Xeloda®** and crossed over to take EU/5-FU/Lv

Arm	Evaluated patients	CR n (%)	PR n (%)	SD n (%)	CR + PR + SD[1] n (%)
Arm X (All Subjects)	21	0 (0)	3 (14)	9 (43)	12 (57)
Arm Xa (Refractory Xeloda®)[2]	10	0 (0)	3 (30)	6 (60)	9 (90)
Arm Xb (Non-Refractory Xeloda®)[3]	11	0 (0)	0 (0)	3 (27)	3 (27)

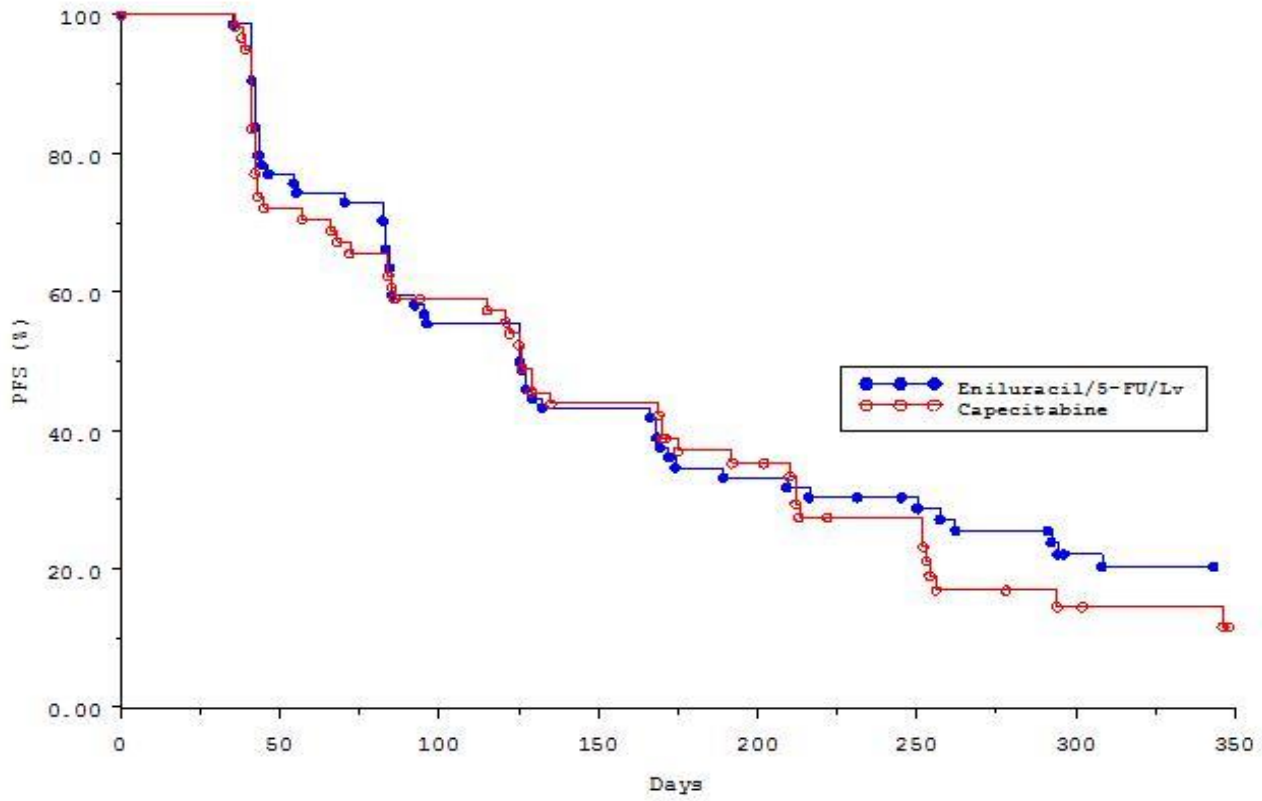
*All data cutoff as of March 30, 2013 for FDA meeting

1. Clinical benefit: CR=Complete Response, PR =Partial Response, SD=Stable Disease
2. Subjects who progressed (PD) on Arm 2 Xeloda at their first scan assessment, usually at day 45 in the study
3. Subjects who progressed (PD) on Arm 2 Xeloda after their first scan, or greater than day 45 in the study

Main Study PFS Interim Results

Arm 1: EU/5-FU/Lv vs. Arm 2: **Xeloda**® (capecitabine).

At the time of data cutoff, EU had at least 16 patients with PFS of greater than 250 days vs 8 patients for Xeloda



Unexpected Activity in Arm X

FENNEC PHARMA

Arm 2 Patients Who Rapidly Failed **Xeloda**® and Crossed Over to Take EU/5-FU/Lv in **Arm X**

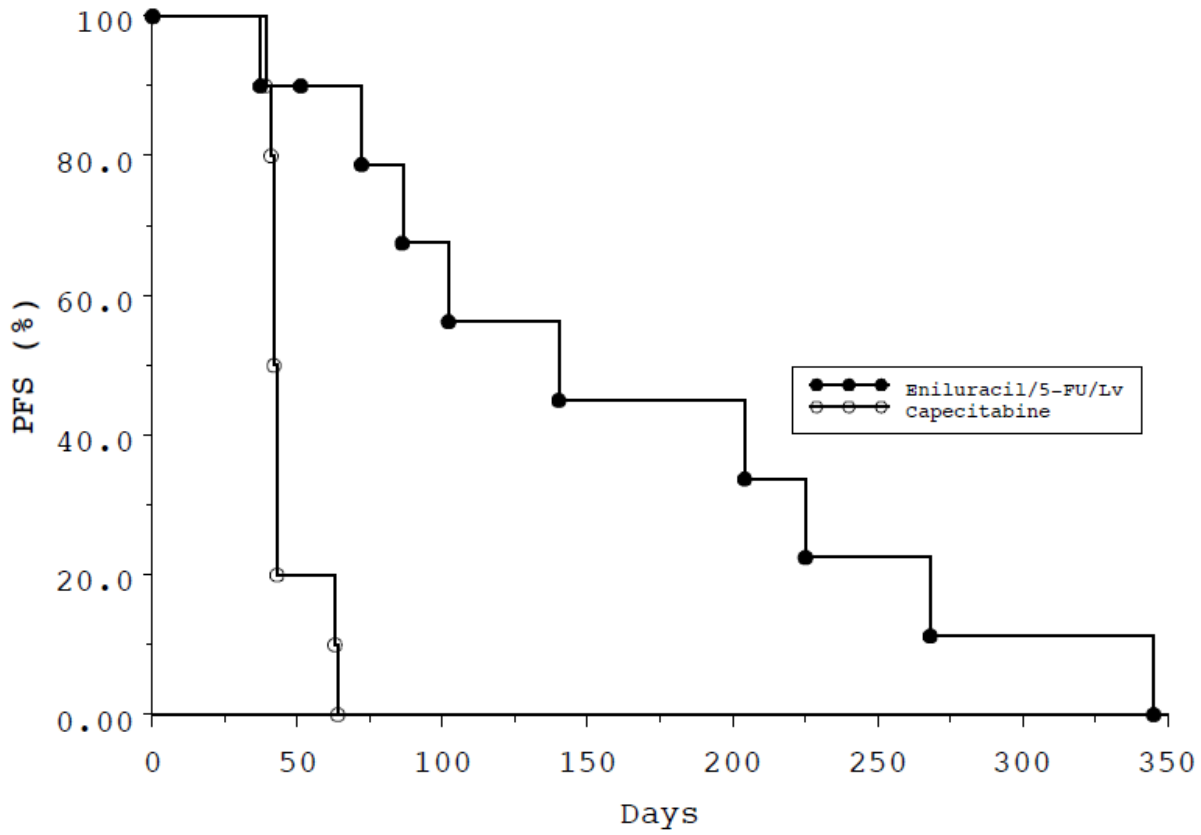
Patient	Arm 2: Xeloda		Arm Xa: EU/5-FU/Lv		Ratio PFS2:PFS1	Adjuvant/ Neoadjuvant 5-FU Treatment(s)
	PFS1 (Days)	Best Response	PFS2 (Days)	Best Response		
1	42	PD	37	PD	0.9	1
2	63	SD	51*	SD	0.8	1
3	42	PD	72	SD	1.7	1
4	64	SD	86	SD	1.3	0
5	43	PD	102	SD	2.4	1
6	42	PD	140	PR	3.3	2
7	43	PD	204	PR	4.7	0
8	41	PD	225	SD	5.5	2
9	39	PD	268	SD	6.9	1
10	43	PD	345	PR	8.0	1
	42.5 (median)		140 (median)		3.6 (median)	

*Patient withdrew from study to have surgery after a SD assessment

Crossover Arm PFS in Rapid Xeloda Failures

FENNEC PHARMA

Arm 2: **Xeloda**® (capecitabine) vs. Arm X: EU/5-FU/Lv



Triple Negative Patients in Arms 1, 2 and X

FENNEC PHARMA

Unexpected durable responses in triple negative patients

Patient	Arm 1: EU/5-FU/Lv		Arm 2: Xeloda		Arm X: Crossover	
	PFS1 (Days)	Best Response	PFS2 (Days)	Best Response	PFSX (Days)	Best Response
1	41*	SD	41	PD	34	PD
2	41	PD	41	PD	63	SD
3	44	PD	42	PD	79	SD
4	46	PD	42	PD	84	SD
5	82	PR	57	SD	124	PR
6	83	SD	72	SD	335	PR
7	125	SD	85	SD		
8	132	SD	169	SD		
9	168	SD	175	SD		
10	266	PR	742	PR		
	82.5 (median)		64.5 (median)		81.5 (median)	

*Patient withdrew from study after an SD assessment

Serious Adverse Events*

SAE Diagnosis	EU/5-FU/Lv	Xeloda	Arm X
Neutropenia	1		
Anemia	1		
Generalized tonic-clonic convulsions		1	
Brain Concussion	1		
Pulmonary edema or failure	1	1	
Pulmonary embolism	1		1
Metrorrhagia	1		
C. Difficile Diarrhea	1		
Urosepsis	3[a]		
Fractures	3		
Disease Progression	2	2	1
Acute pneumonia		1	
Total	15	5	2

*All data as of March 30, 2013
[a]All three events were in the same patient

Interim Adverse Events*

Adverse Event	Arm 1: EU/5-FU/Lv		Arm 2: Xeloda	
	All Grades N (%)	Grades 3&4 N (%)	All Grades N (%)	Grades 3&4 N (%)
Diarrhea	31 (42.5)	0 (0)	9 (16.4)	0 (0)
Asthenia	14 (19.2)	2 (2.7)	7(12.7)	1 (1.8)
Fatigue	13 (17.8)	2 (2.7)	2(3.6)	0 (0)
Hand-Foot Syndrome	9 (12.3)	0 (0)	17(32.7)	0 (0)
Elevated Bilirubin	8 (11.0)	0 (0)	3(5.5)	0 (0)
Dyspnea	4 (5.5)	0(0)	1(1.8)	0 (0)
Upper Abdominal Pain	3(4.1)	1(1.4)	1(1.8)	0 (0)
Mucositis	1(1.3)	0(0)	2(3.6)	0 (0)

*Patients were assessed 3 times per cycle in the EU/5-FU/Lv arm and only once per cycle in the Xeloda arm, which may account for the higher incidence of some of the findings in the EU/5-FU/Lv arm.

EU Clinical Benefit vs Xeloda®

The possible mechanisms for rapid **Xeloda®** failure and subsequent clinical benefit from EU/5-FU/Lv may include any of the following:

1. Low Xeloda® absorption (highly variable with possible extended lag periods)
2. Low or deficient levels of one or more of the three enzymes required to convert Xeloda® to 5-FU
3. Low intratumoral thymidine phosphorylase
4. Elevated DPD
5. Up to 85-fold swings in the diurnal variation of DPD levels
6. F-Bal interfering with the antitumor activity
7. Added benefit of leucovorin

EU/5-FU/Lv circumvents and/or eliminates problems 1-6 and enables the safer use of leucovorin because EU creates consistent and predictable 5-FU pharmacokinetics

EU Advantages Over Teysuno® and UFT®

DPD inhibitor (5-Chloro, 2,4- dihydroxypyridine) used in Teysuno® (S-1) is a simple competitive reversible inhibitor. Accordingly, it must be present when 5-FU is administered to inhibit 5-FU breakdown by DPD. Therefore, it is likely to interfere with the antitumor activity of 5-FU in a similar manner that excess eniluracil interfered in the GSK studies.

Because eniluracil is an irreversible inactivator of DPD, it can be separated and dosed the night before 5-FU and cleared from the body before 5-FU is given. Therefore, every patient DPD deficient, yet the DPD inhibitor is not present to interfere with 5-FU antitumor activity.

Because eniluracil eliminates all DPD, the 5-FU PK are remarkably consistent and predictable, thereby allowing the safe use of leucovorin to potentiate the antitumor activity of 5-FU.

In contrast, the variable conversion of the tegafur prodrug to 5-FU and its variable breakdown by DPD result in variable 5-FU PK from S-1, which render co-administration of leucovorin very risky.

UFT® has uracil as the DPD inhibitor. Uracil and thymine are the natural substrates for DPD. Uracil only inhibits as it is being degraded by DPD. It's a weak, reversible, alternative-substrate inhibitor that is metabolically depleted by DPD. Head-to-head in rats, EU/5-FU was considerably better than UFT.

FDA EOP 2 Meeting Summary

Interim Results indicate EU/5-FU/Lv regimen active and well tolerated in MBC

- FDA can not endorse a single arm pivotal trial in rapidly failed **Xeloda®** patients in MBC since there are other approved therapies available such as **Halaven®** and **Ixempra®**
- Discussed with Adherex the following development options in MBC:
  - One superiority study vs **Xeloda®** monotherapy for 1st or 2nd line therapy in metastatic setting for patients previously treated with an anthracycline and a taxane
  - One superiority study vs physician's drug of choice for patients who have previously received at least two chemotherapeutic regimens in metastatic setting and were previously treated with an anthracycline and a taxane
  - Two non inferiority studies vs physician's drug of choice for patients who have previously received at least two chemotherapeutic regimens in metastatic setting and were previously treated with an anthracycline and a taxane
- Adherex also must demonstrate the contribution of Leucovorin in future MBC studies, but not in colorectal cancer (CRC), where Leucovorin is approved
- Historical EU safety database supports future NDA filing
- FDA encourages Adherex to meet again and discuss a trial design for future Phase 3 study

EU Development Plan Forward

Future studies of EU/5-FU/Lv regimen in MBC require large number of patients

- EU/5-FU/Lv active and well tolerated in refractory iv 5-FU and Xeloda® populations
- Encouraging results from Dr. Grem Phase I study in mCRC and Adherex Phase II study in MBC
- Potential development options in mCRC:
  - EU/5-FU/Lv vs Xeloda® before or after Stivarga® (regorafenib) treatment
- Xeloda® not approved and not well tolerated in mCRC patients
- Patients have short expected overall survival making a smaller improvement more meaningful
- Possibly fast enrolling trial, could be done in the US
- Enthusiastic investigators, sites, CRO and PI have been identified
- A single Phase 3 adaptive trial could lead to approval
- Adherex is seeking a partnership to advance this plan forward