A novel platform for treating metastatic breast cancer

SELECTIVE ESTROGEN RECEPTOR DEGRADERS [SERDS] FOR TREATMENT OF ADVANCED BREAST CANCER

TECHNOLOGY:
THERAPEUTIC: ORALLY BIOAVAILABLE SERDS WITH BRAIN PENETRATION (SELECTIVE ESTROGEN RECEPTOR DEGRADERS)

INDICATION: METASTATIC BREAST CANCER TREATMENT INCLUDING BRAIN METASTASIS

Investigators: Debra Tonetti, Ph.D., Gregory Thatcher, Ph.D., Rui Xiong, Ph.D.

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Executive Summary

The Problem:

•The majority of breast cancer is treatable with endocrine therapy and CDK4/6 inhibitor; however, at least half of these cancers are refractory or develop resistance to therapy

•When endocrine therapy fails, chemotherapy, with its associated systemic toxicity, is the therapeutic option

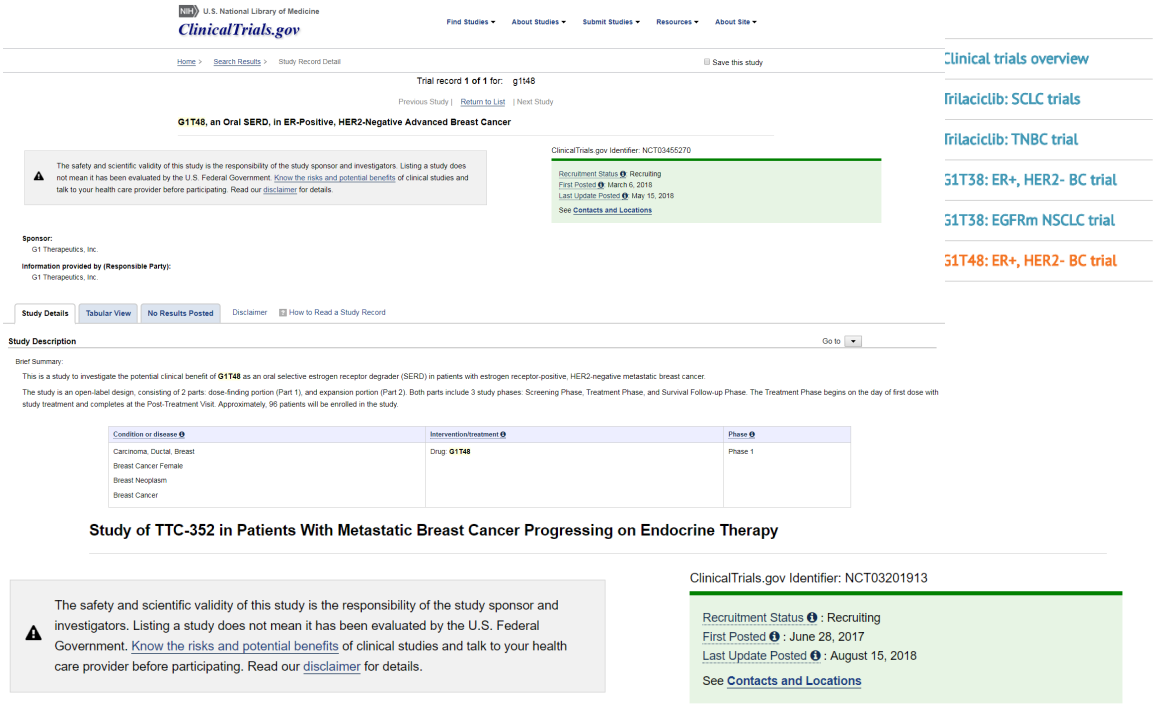
•10-15% endocrine-resistant breast cancer patients have brain metastasis

The Solution:

- Next generation SERDs developed from core compound G1T48 to deliver next generation SERD with brain penetration
- Treatment for TAM/AI-resistant breast cancer
- Strong potential for treatment in ER+ metastatic breast cancer
- Opportunity for combination with CDK4/6 inhibitors and PI3K inhibitors

Our established technology in developing SERDs and ER partial agonist

- **Licensed to G1 Therapeutics**
- **Currently in Phase 1/2 clinical trial**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Trial record 1 of 1 for: g1t48

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G1T48, an Oral SERD, in ER-Positive, HER2-Negative Advanced Breast Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03455270

Recruitment Status : Recruiting
First Posted : March 6, 2018
Last Update Posted : May 15, 2018
See Contacts and Locations

Sponsor:
G1 Therapeutics, Inc.

Information provided by (Responsible Party):
G1 Therapeutics, Inc.

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

Study Description

Go to

Brief Summary:

This is a study to investigate the potential clinical benefit of **G1T48** as an oral selective estrogen receptor degrader (SERD) in patients with estrogen receptor-positive, HER2-negative metastatic breast cancer.

The study is an open-label design, consisting of 2 parts: dose-finding portion (Part 1), and expansion portion (Part 2). Both parts include 3 study phases: Screening Phase, Treatment Phase, and Survival Follow-up Phase. The Treatment Phase begins on the day of first dose with study treatment and completes at the Post-Treatment Visit. Approximately, 96 patients will be enrolled in the study.

Condition or disease	Intervention/treatment	Phase
Carcinoma, Ductal, Breast Breast Cancer Female Breast Neoplasm Breast Cancer	Drug: G1T48	Phase 1

Study of TTC-352 in Patients With Metastatic Breast Cancer Progressing on Endocrine Therapy

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03201913

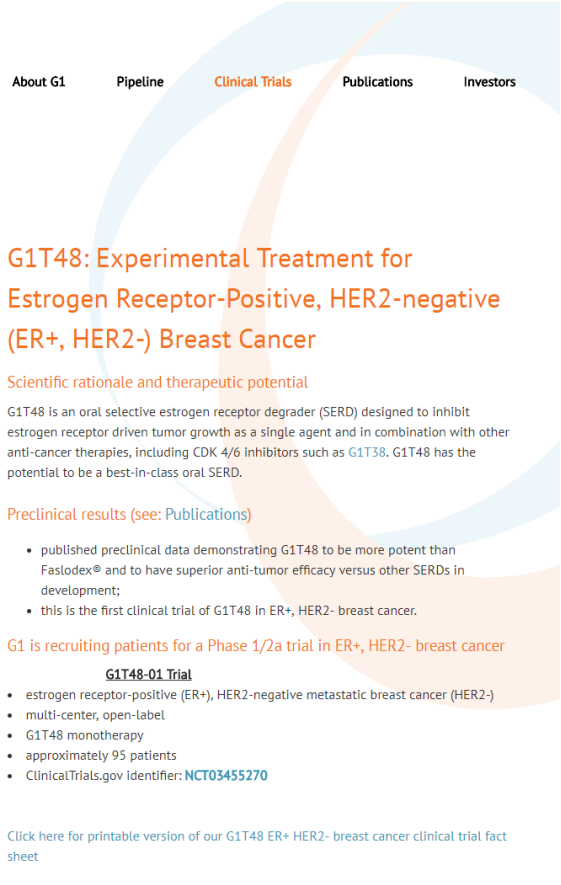
Recruitment Status : Recruiting
First Posted : June 28, 2017
Last Update Posted : August 15, 2018
See Contacts and Locations

Sponsor:
TTC Oncology, LLC

Information provided by (Responsible Party):
TTC Oncology, LLC

Clinical trials overview
Trilaciclib: SCLC trials
Trilaciclib: TNBC trial
G1T38: ER+, HER2- BC trial
G1T38: EGFRm NSCLC trial
G1T48: ER+, HER2- BC trial

- **Licensed to TTC Oncology**
- **Currently in Phase 1 clinical trial**


About G1 | Pipeline | Clinical Trials | Publications | Investors

G1T48: Experimental Treatment for Estrogen Receptor-Positive, HER2-negative (ER+, HER2-) Breast Cancer

Scientific rationale and therapeutic potential

G1T48 is an oral selective estrogen receptor degrader (SERD) designed to inhibit estrogen receptor driven tumor growth as a single agent and in combination with other anti-cancer therapies, including CDK 4/6 inhibitors such as G1T38. G1T48 has the potential to be a best-in-class oral SERD.

Preclinical results (see: Publications)

- published preclinical data demonstrating G1T48 to be more potent than Faslodex® and to have superior anti-tumor efficacy versus other SERDs in development;
- this is the first clinical trial of G1T48 in ER+, HER2- breast cancer.

G1 is recruiting patients for a Phase 1/2a trial in ER+, HER2- breast cancer

G1T48-01 Trial

- estrogen receptor-positive (ER+), HER2-negative metastatic breast cancer (HER2-)
- multi-center, open-label
- G1T48 monotherapy
- approximately 95 patients
- ClinicalTrials.gov identifier: NCT03455270

Click here for printable version of our G1T48 ER+ HER2- breast cancer clinical trial fact sheet

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SERDs Mechanism of Action

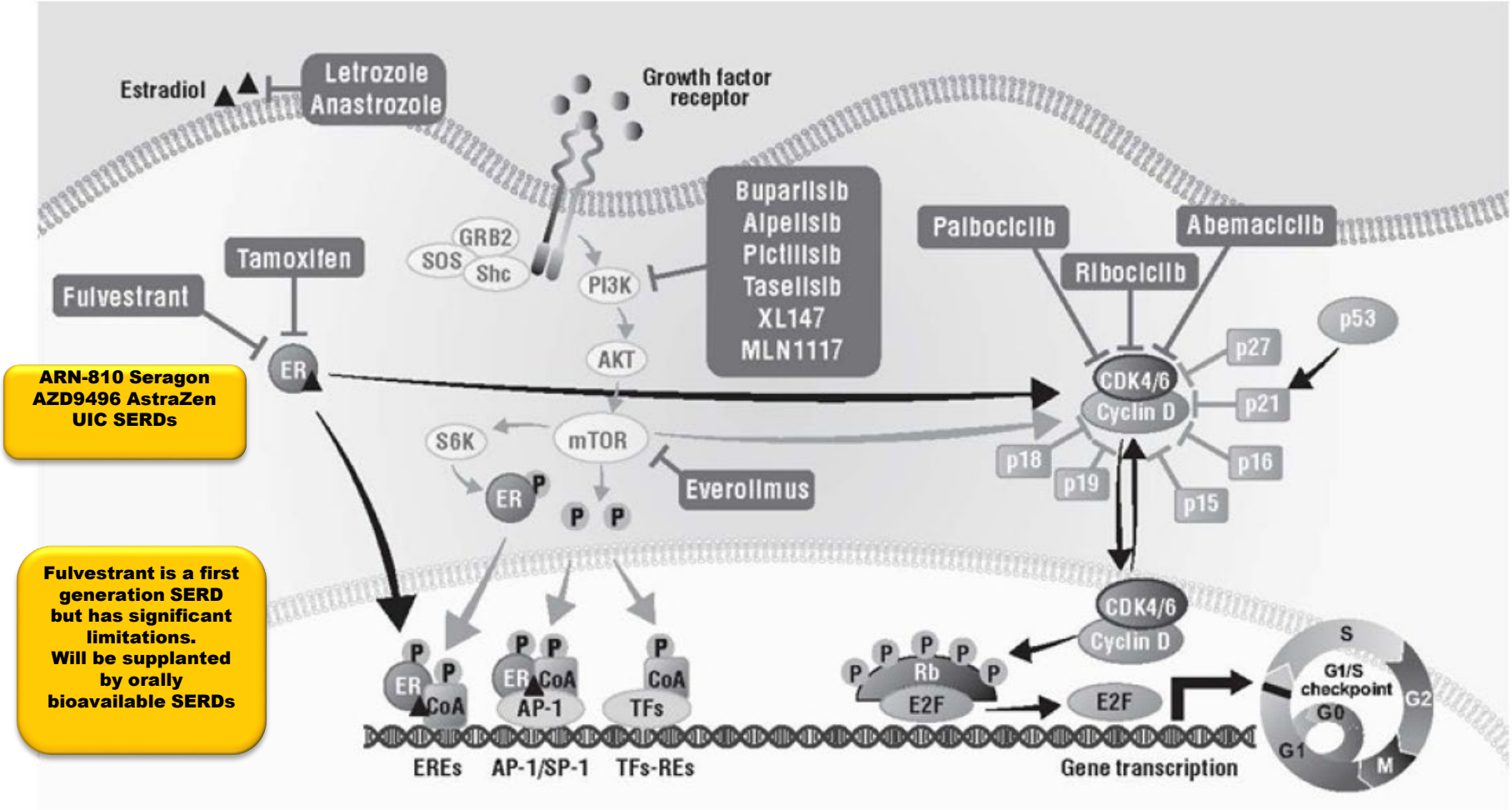
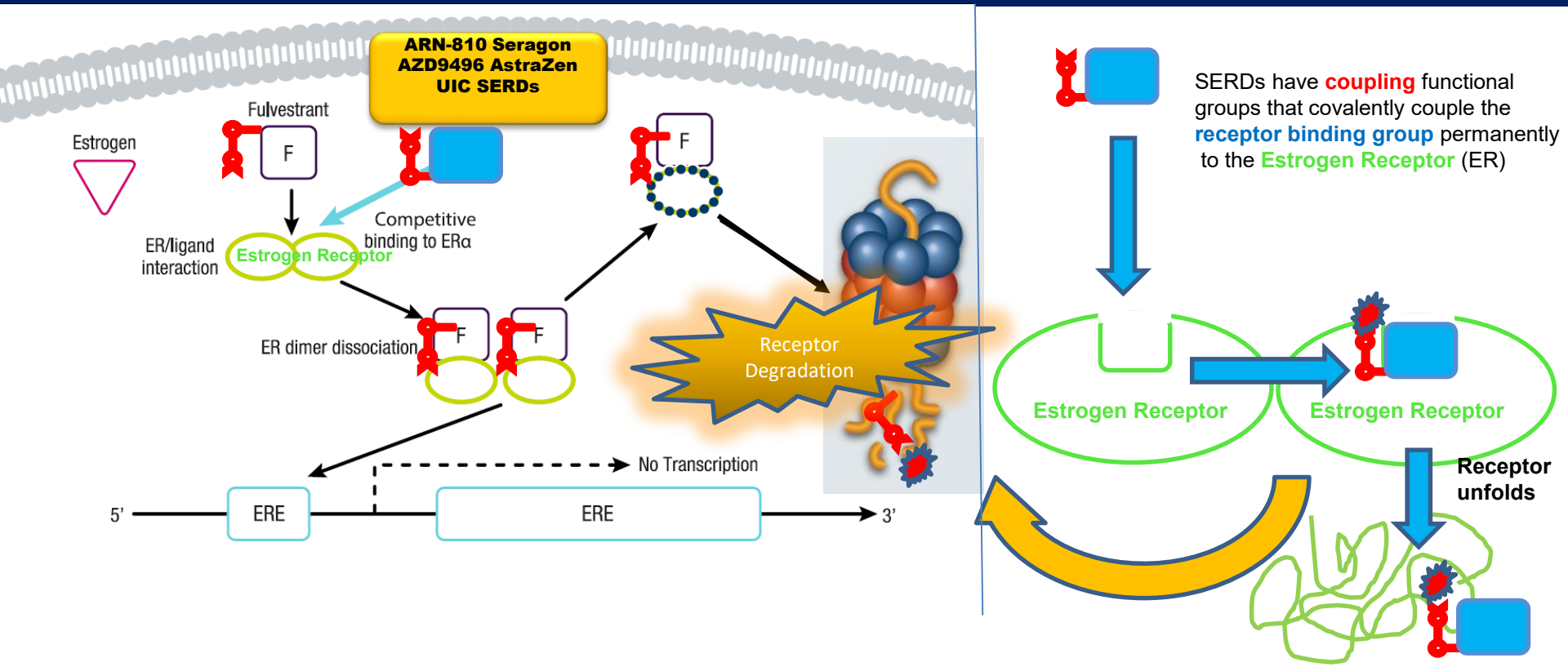


Figure 1. Targeting the cyclin D-CDK 4/6-INK4-Rb pathway. CDK, cyclin-dependent kinase; E2F, E2 transcription factor; ER, estrogen receptor; GRB2, growth factor receptor-bound protein 2; HR , hormone receptor-positive; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; Rb, retinoblastoma; RTK, receptor tyrosine kinase; S6K, S6 kinase.

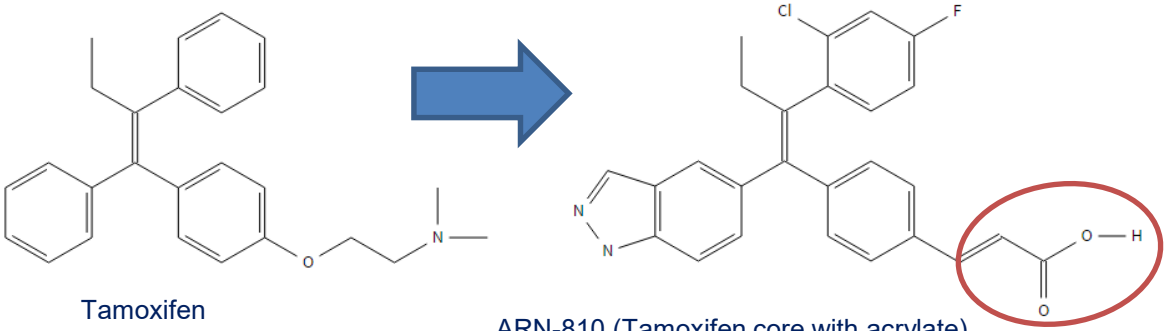
SERDs Mechanism of Action



Approximately 70% of all breast cancer tumors are **Estrogen Receptor** (ER) positive. The standard of care for these tumors typically use Tamoxifen therapy or Aromatase Inhibitor therapy to attempt to interfere with this nuclear receptor's function. When these options begin to fail, tumors become refractory to these treatments and the patients survival is severely impacted. Approximately 50% of the breast cancer population treated with standard of care approaches develop tumors that are Tamoxifen resistant. UIC scientists have developed a new core compound (TTC 352) that has the ability to drive the **Estrogen Receptor** out of the nucleus similar to how Xtandi (Enzalutamide) works on the Androgen Receptor. Modification of the core compound using a coupling domain has developed a highly potent series of SERDs with improved properties.

Next generation compounds:SERDS

Selective Estrogen Receptor Degraders/ Down-regulators



Tamoxifen

ARN-810 (Tamoxifen core with acrylate)

exome

all the information, none of the junk | biotech • healthcare • life sciences

SERDs covalently couple to Estrogen Receptors and lead to the degradation of the receptors

Seragon CEO Rich Heyman Is Going on Hiatus

DealB%k WITH FOUNDER ANDREW ROSS SORKIN

MERGERS & ACQUISITIONS | INVESTMENT BANKING | PRIVATE EQUITY | HEDGE FUNDS | I.P.O./

Roche to Pay Up to $1.7 Billion for Seragon Pharmaceuticals

By CHAD BRAY JULY 2, 2014 4:15 AM Comment

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The deal is the latest in an string of smaller acquisitions by Roche Group, based in Basel, Switzerland. Reuters

LONDON – The Swiss drug maker Roche Group said on Wednesday that it would pay up to $1.7 billion to acquire Seragon Pharmaceuticals, a privately held biotechnology firm focused on developing treatments for breast cancer.

Under the deal, Genentech, a unit of Roche based in San Francisco, will pay $725 million in cash, plus up to an additional $1 billion if Seragon's products reach certain milestones.

Roche to Pay Up to $1.7 Billion for Seragon Pharmaceuticals

By CHAD BRAY JULY 2, 2014 4:15 AM Comment

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Market competition

SERM/SEM	Stage	Company	Safety/Side Effects
ARN-810	Preclinical proven	Roche	
AZD 9496		Astrazeneca	
RAD-1901		Radius Health	
GDC-0927	Preclinical proven	Roche	
G1T48	Phase 1	G1 Therapeutics	
LSZ-102		Novartis	
D-0502		InventisBio	

Second generation Basic-amino SERDs

B-SERDs showed increased potency and more consistent suppression of ER signaling from in-house and outside data

Session PO.CH01.01 - Target Based Drug Discovery

1648 / 3 - Discovery and evolution of orally bioavailable selective estrogen receptor degraders for ER+ breast cancer: From GDC-0810 to GDC-0927

Add To My Itinerary

April 16, 2018, 8:00 AM - 12:00 PM | Section 30

Presenter/Authors

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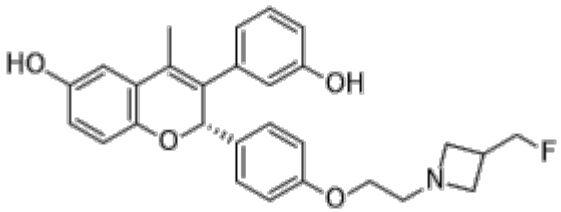
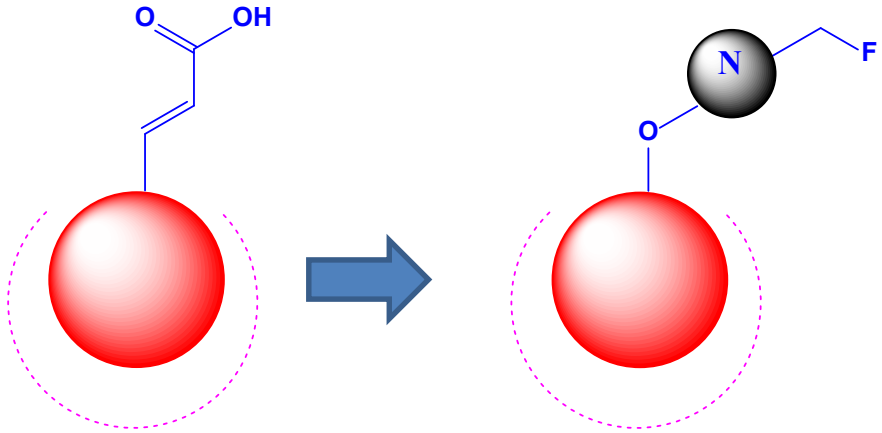
Abstract

Breast cancer is the most frequently diagnosed cancer among women and remains the second leading cause of cancer death in women. An estimated 70% of all breast cancers express estrogen receptor alpha (ERα); and endocrine therapies have validated ERα as a target for the treatment of breast cancer. Despite effective endocrine therapies, many patients eventually relapse and become resistant to standard of care treatments. Endocrine resistant tumors often remain dependent on ERα for growth and survival, as evidenced by their sensitivity to the selective estrogen receptor degrader (SERD), fulvestrant. However, fulvestrant may be limited in achieving maximal target occupancy due to pharmaceutical and pharmacokinetics properties which necessitates intramuscular route of administration. Consequently, SERDs with superior drug-like properties were sought to allow consistent and rapid achievement of maximal therapeutic exposure. GDC-0810 and GDC-0927 as first and second generation orally bioavailable SERDs were discovered through a prospective lead optimization on ERα degradation. The evolution from GDC-0810 to GDC-0927 will be described and provides new insights into ERα biology and biochemistry. By shifting away from the acrylic acid moiety in GDC-0810, GDC-0927 achieved increased potency and more consistent, complete suppression of ER signaling. Co-crystal structures of both GDC-0810 and GDC-0927 with ERα will be shared. Subsequent optimization of GDC-0927 resulting in improved pharmacokinetic properties will also be highlighted.



GDC-0927 (Genentech)
Poor bioavailability (1400 mg dose)

Second generation Basic-amino SERDs

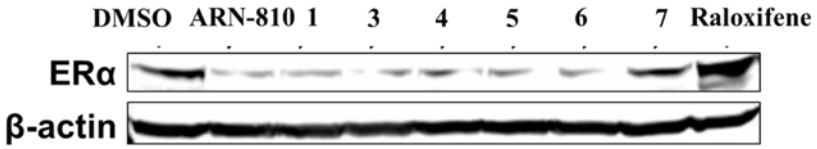


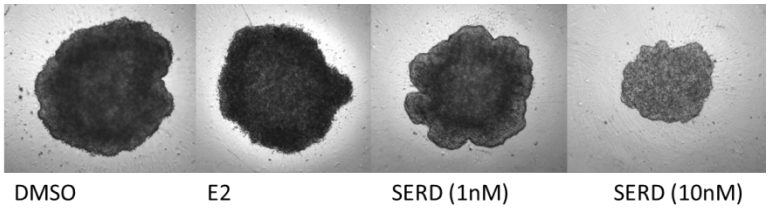
ER ligand-binding pocket

ER ligand-binding pocket

Combined with new deuterium technology to minimize metabolism

- **Verified ER degradation and efficacy in cell models**



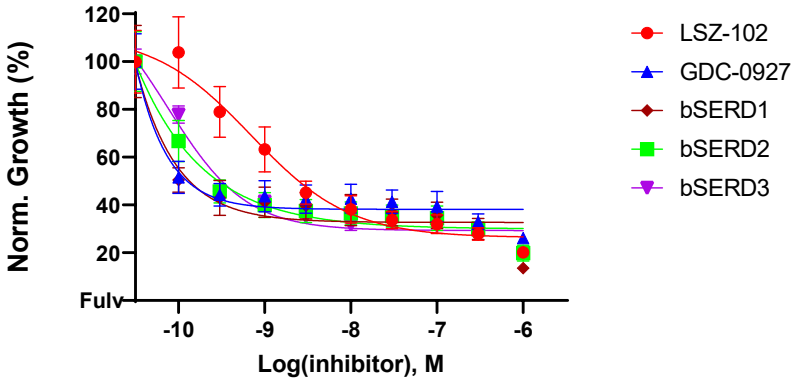


IC50 ~ 1nM in multiple treatment-resistant cell lines

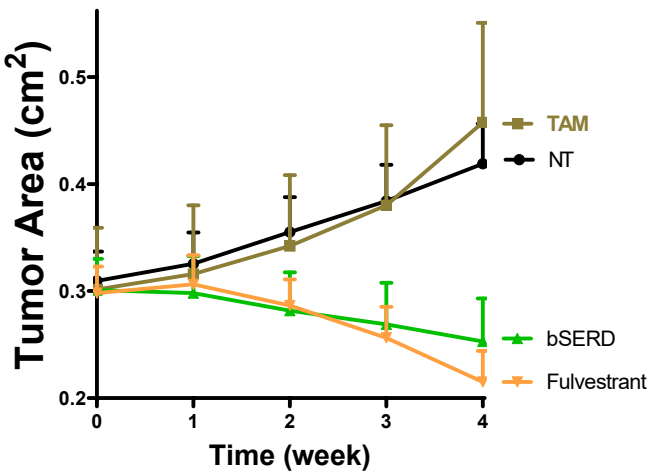
UIC Second generation Basic-amino SERDs

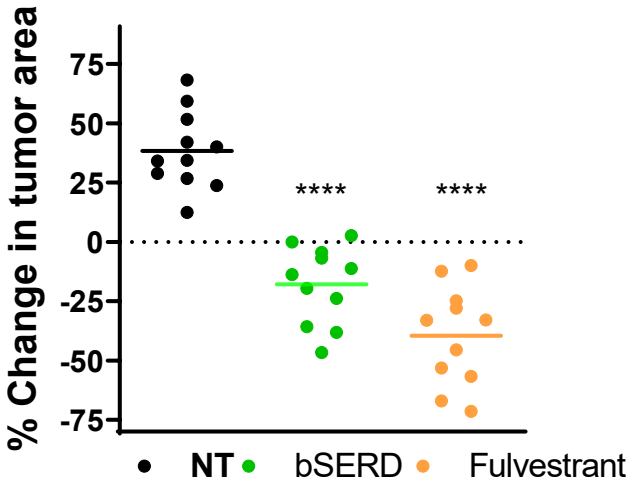
$T_{1/2}$ = 4.48 h
F = 22%
Cmax ratio (brain/plasma) = 1.54
Auc ratio (brain/plasma) = 1.26

P-glycoprotein substrate in MDCK-MDR1 Cell Line:
Efflux ratio = 0.46



Comparable activity with GDC-0927 and LSZ-102





100 mg/kg S.C. injection 5mg/mice

Evidence that cdk 4/6 inhibitors need adjunct therapy

Table 1.

Randomized phase II/III clinical trials of CDK4/6 inhibitors as first-line treatment of advanced ER-positive breast cancer.

	PALOMA-1	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7
Design	Phase II open-label	Phase III placebo control	Phase III placebo control	Phase III placebo control	Phase III placebo control in pre-/perimenopausal women
Treatment arms	Letrozole ± palbociclib	Letrozole ± palbociclib	Letrozole ± ribociclib	NSAI ± abemaciclib	Tamoxifen/NSAI + goserelin ± ribociclib
Patients, *n*	165	666	668	493	672
Median PFS (months)	20.2 *versus* 10.2	24.8 *versus* 14.5	25.3 *versus* 16	NR *versus* 14.7	23.8 *versus* 13
HR, 95% CI	0.49 (0.32 0.75)	0.58 (0.46–0.72)	0.56 (0.43–0.72)	0.54 (0.41–0.72)	0.55 (0.44–0.69)
ORR,* %	55 *versus* 39	55 *versus* 44	53 *versus* 37	59 *versus* 44	51 *versus* 36%
CBR (ITT), %	81 *versus* 58	85 *versus* 70	80 *versus* 73	78 *versus* 71.5	

*In patients with measurable disease at baseline.

CBR, clinical benefit rate; NR, not reached; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; PFS, progression-free survival.

Evidence that cdk 4/6 inhibitors need adjunct therapy

Table 2.

Major clinical trials of CDK4/6 inhibitors in patients with advanced ER-positive breast cancer who had previously progressed on endocrine therapy.

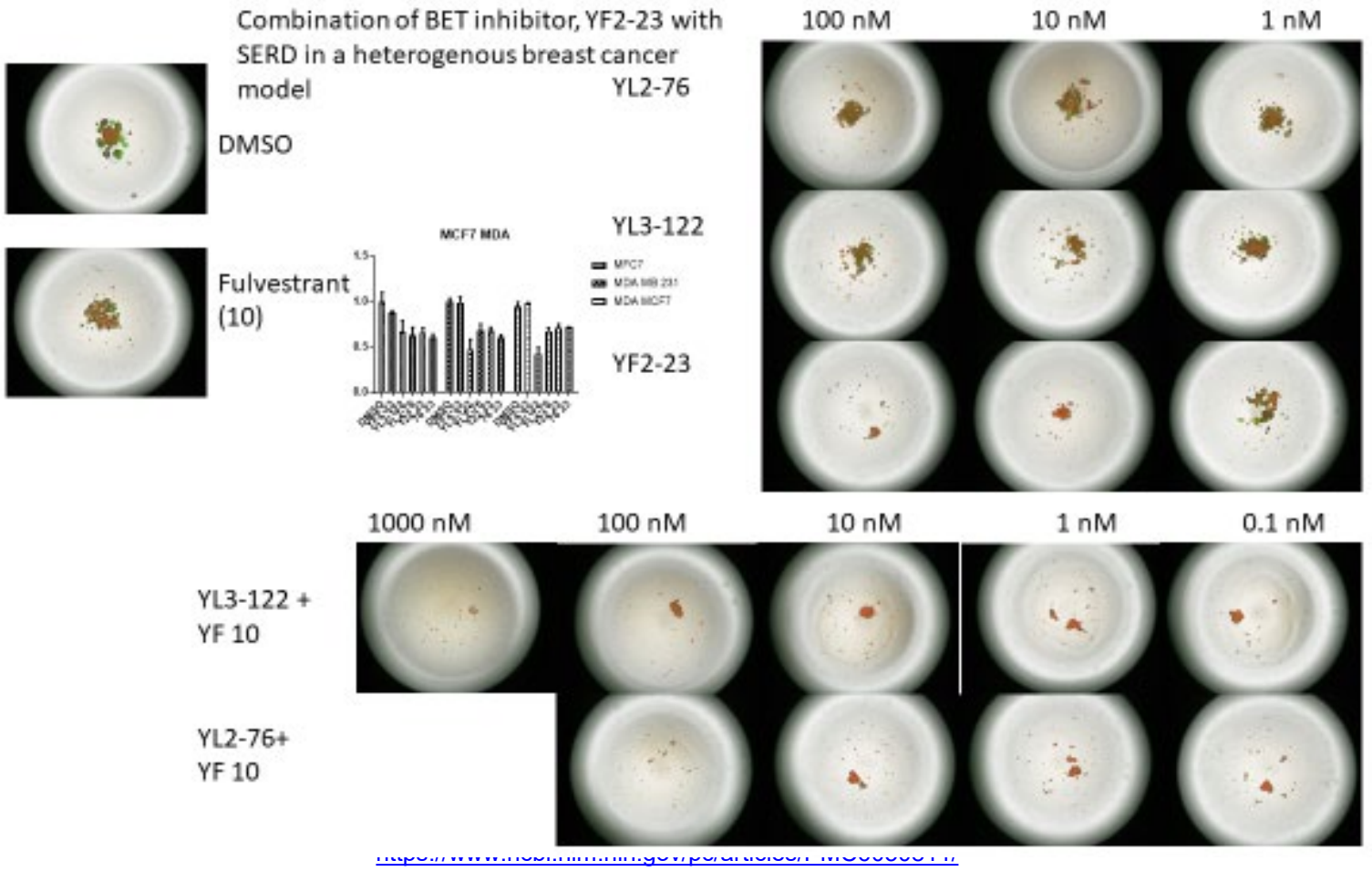
	PALOMA-3	MONARCH-2	MONALEESA-3*	MONARCH-1
Design	Phase III placebo control, second line	Phase III placebo control, second line	Phase III placebo control, second line	Phase II
Treatment arms	Fulvestrant ± palbociclib	Fulvestrant ± abemaciclib	Fulvestrant ± ribociclib	Abemaciclib monotherapy
Patients, *n*	521	669	725	132
Patient population	⩽1 prior CT for MBC; any line of previous ET in MBC	Previous CT for MBC not permitted; one line of previous ET in MBC		Progression on or after prior endocrine therapy; 1–2 lines prior CT for MBC
Median PFS, months	9.5 *versus* 4.6	16.4 *versus* 9.3		6.0
HR	0.46 (0.36–0.59)	0.55 (0.45–0.68)		
ORR (measurable disease), %	25 *versus* 11	48 *versus* 21		20
CBR (ITT), %	67 *versus* 40	72 *versus* 56		42.4

*Not yet reported.

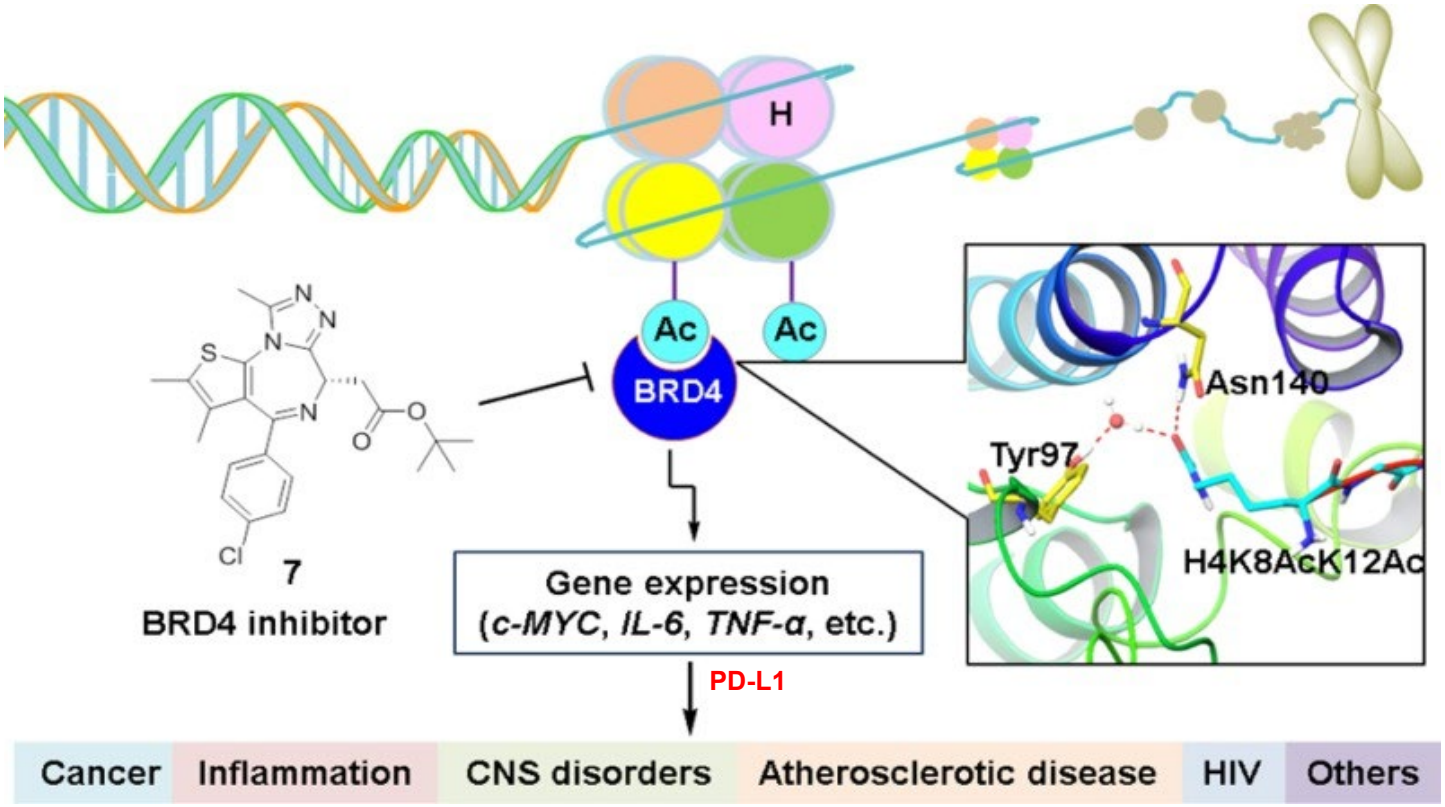
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6050811/

CBR, clinical benefit rate; CT, chemotherapy; ET, endocrine therapy; MBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival.

Combination Bromodomain inhibitors and SERDs



BET proteins is central transcriptional drivers

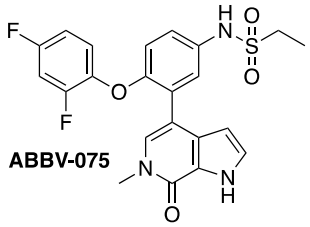


J Med Chem. 2017 Jun 8; 60(11): 4533–4558.

Front-running BET inhibitors are tested in multiple combinations for cancer therapy

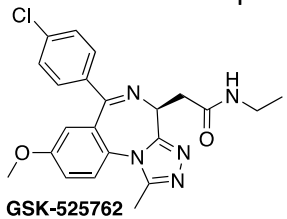
abbvie

ABBV-075 + Venetoclax (bcl2) for CLL



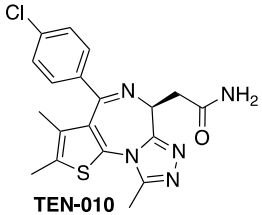
gsk

GSK525762 + fulvestrant for Breast cancer
GSK525762 + enzalutamide for prostate cacner



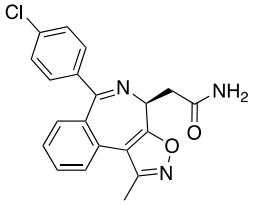
Roche

RO6870810 + Daratumumab (CD38)
RO6870810 + Atezolizumab (PDL1)



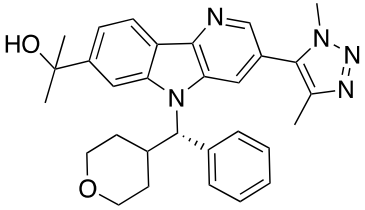
Constellation PHARMACEUTICALS

CPI-0610 + Ruxolitinib (JAK) for Myelofibrosis



Bristol-Myers Squibb

BMS-986158 + Nivolumab (PD1) in solid tumors

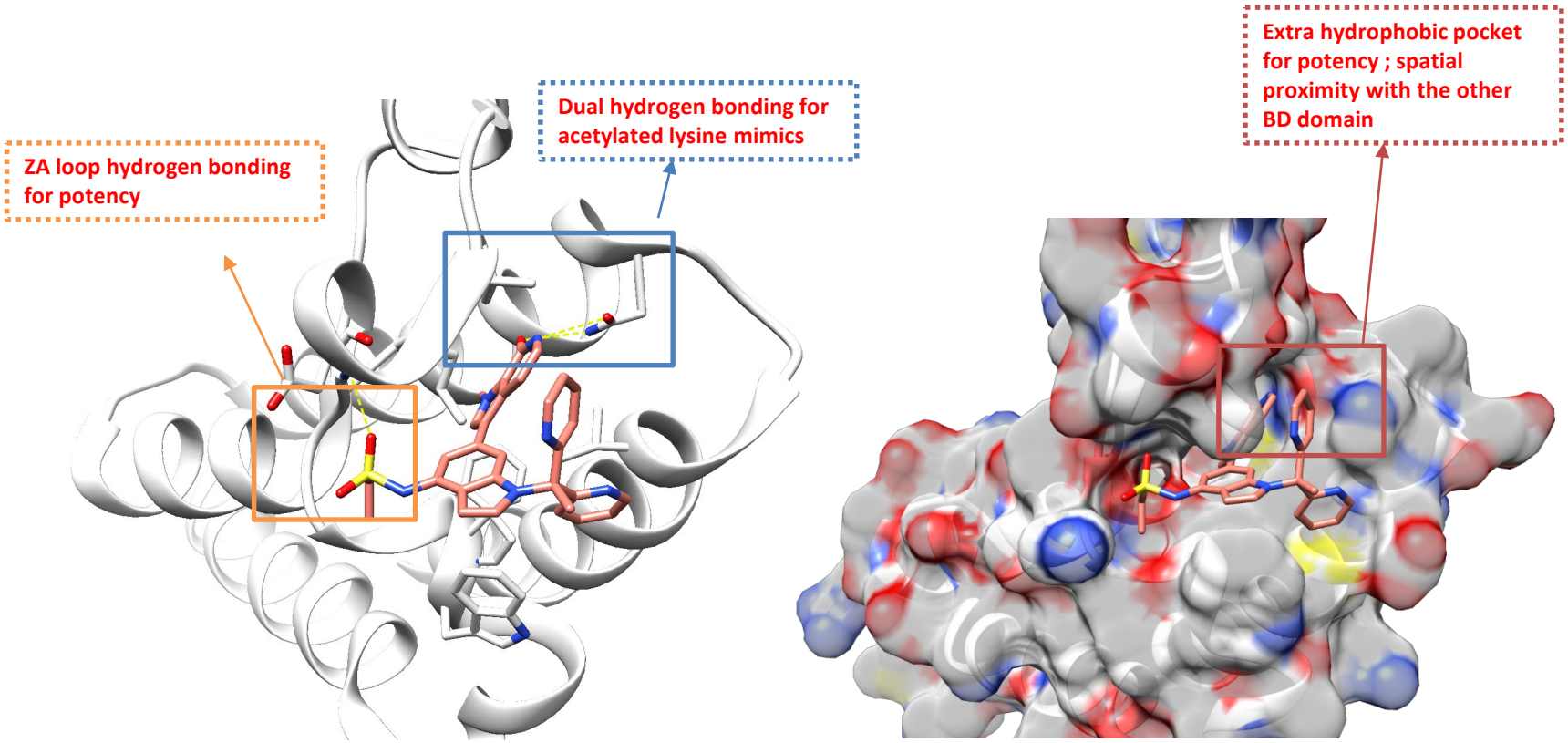


GILEAD

GS-5829 + fulvestrant for Breast cancer
GS-5829 + enzalutamide for prostate cacner

Initial clinical data looks promising with manageable thrombocytopenia

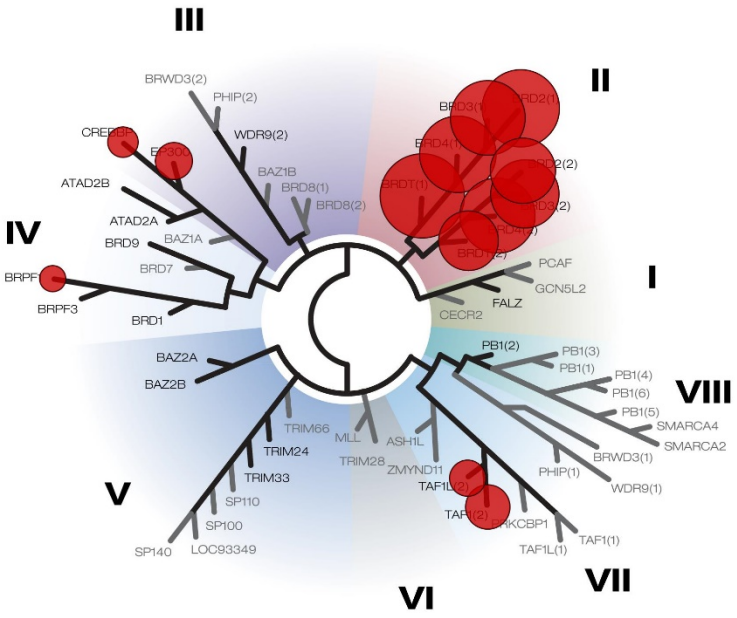
How YF-2-23was designed



Potent and selective against BET family

Bromodomain	YF-2-23 (nM)	JQ-1 (nM)
BRD2(BD1)	0.27	27
BRD2(BD2)	0.77	18
BRD2(BD1,2)	0.57	5.6
BRD3(BD1)	0.34	14
BRD3(BD2)	0.61	19
BRD3(BD1,2)	0.27	14
BRD4(BD1)	0.29	14
BRD4(BD2)	0.33	8.2
BRD4(BD1,2)	0.29	7.3
BRD4(full length,short-iso.)	0.1	11
BRDT(BD1)	0.14	47
BRDT(BD2)	1.4	35
BRDT(BD1,2)	0.23	46

50-100 fold more potent than bench mark JQ1



Data by DiscoverX

Pharmacokinetic profiles

Protein binding results of YF2-23.HCl in human plasma				
Compound ID	Species	% Bound	% Recovery	% Remaining at 6 hr
Ketoconazole	Human	98.35	88.07	88.92
YF2-23.HCl	Human	97.98	94.45	93.18

Test article	hERG IC_{50} [µM]
YF2-23.HCl	29.258
Dofetilide	0.015[(1)]

The solubility data of YF2-23.HCl and control compound diclofenac in PBS pH 7.4			
Compound ID	Solubility (µM)		
Progesterone	22.37		
YF2-23.HCl	73.43		

Pharmacokinetic profiles

Summary of YF2-23.HCl IV pharmacokinetic parameters			
IV Dose	5	mg/kg	
PK parameters		Unit	Mean
Cl_obs		mL/min/kg	25.5
$T_{1/2}$		h	1.95
C_0		ng/mL	10441
AUC_{last}		h*ng/mL	3208
AUC_{Inf}		h*ng/mL	3270
$AUC_{\_\%Extrap\_obs}$		%	1.89
MRT_{Inf}_obs		h	0.976
AUC_{last}/D		h*mg/mL	642
V_{ss}_obs		L/kg	1.49

Summary of YF2-23.HCl PO pharmacokinetic parameters			
PO Dose	30	mg/kg	
PK parameters		Unit	Mean
$T_{1/2}$		h	2.90
T_{max}		h	0.250
C_{max}		ng/mL	3090
AUC_{last}		h*ng/mL	9598
AUC_{Inf}		h*ng/mL	9620
$AUC_{\_\%Extrap\_obs}$		%	0.222
MRT_{Inf}_obs		h	3.20
AUC_{last}/D		h*mg/mL	320
F		%	49.0

Relative short half-life to reverse thrombocytopenia

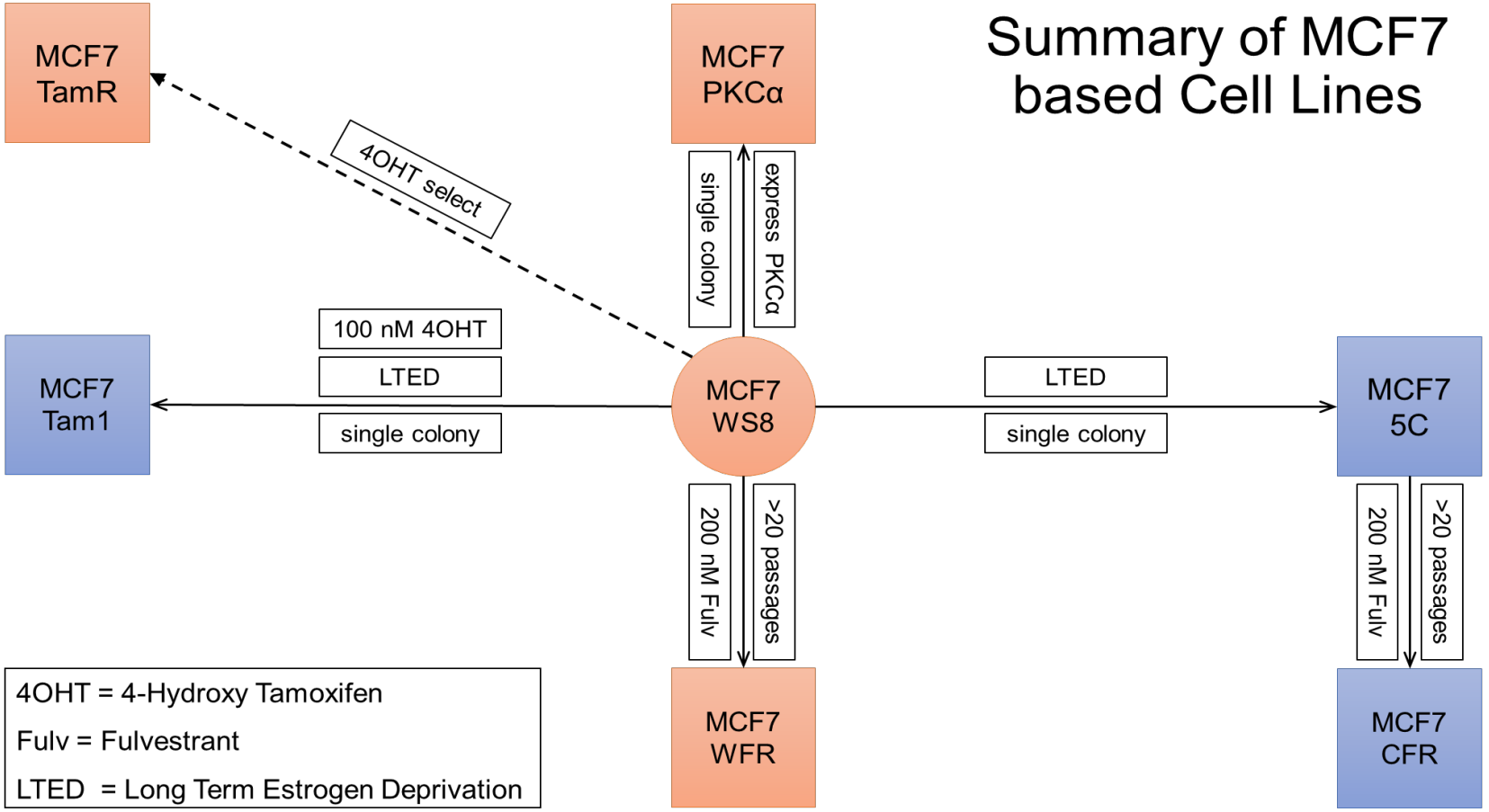
Pharmacokinetic profiles

Data Summary

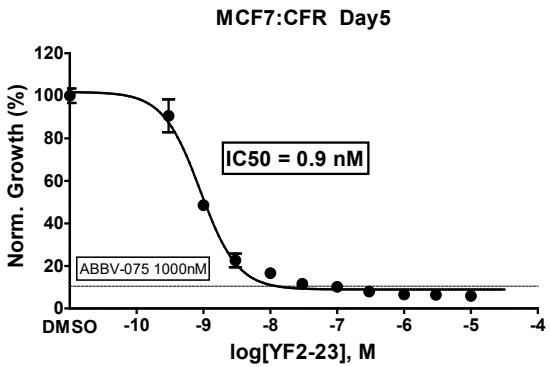
Table 1. Inhibition percentages for YF2-23.HCl and known inhibitors against CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4

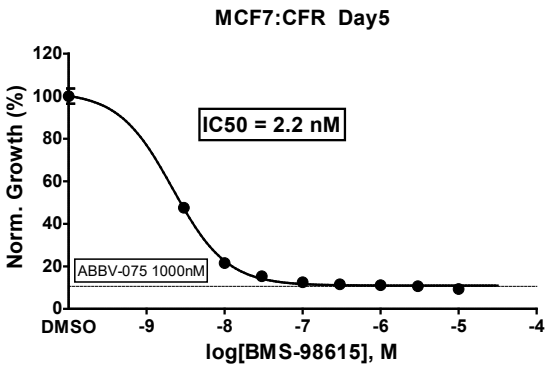
Compound	% Inhibition @ 10 µM							
	CYP1A2 (Phenacetin)	CYP2A6 (Coumarin)	CYP2C8 (Paclitaxel)	CYP2C9 (Tolbutamide)	CYP2C19 ((s)-Mephenytoin)	CYP2D6 (Dextromethorphan)	CYP3A4 (Midazolam)	CYP3A4 (Testosterone)
Furafylline	83.68	-	-	-	-	-	-	-
Tranylcypromine	-	98.19	-	-	-	-	-	-
Quercetin	-	-	80.89	-	-	-	-	-
Sulfaphenazole	-	-	-	87.68	-	-	-	-
(+)-N-3-Benzylnirvanol	-	-	-	-	96.83	-	-	-
Quindine	-	-	-	-	-	94.37	-	-
Ketoconazole	-	-	-	-	-	-	99.46	98.99
YF2-23.HCl	2.29	7.47	84.23	30.74	31.79	14.50	50.61	56.52

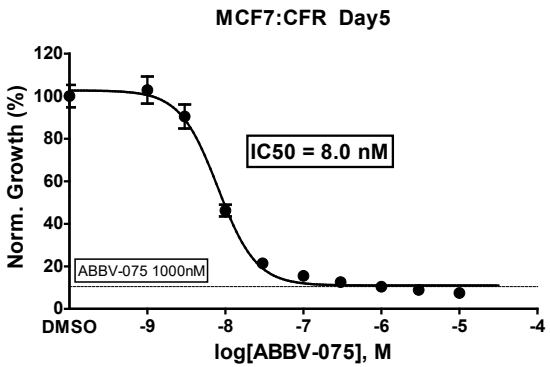
Systematic model of resistant breast cancer

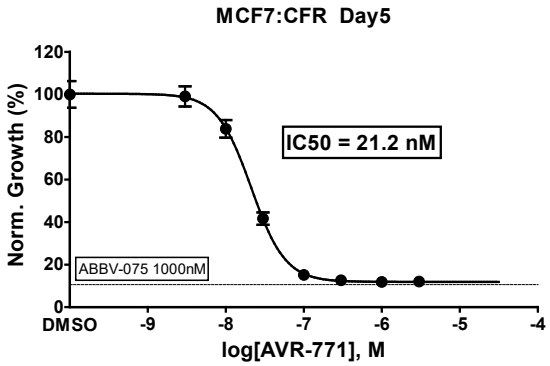


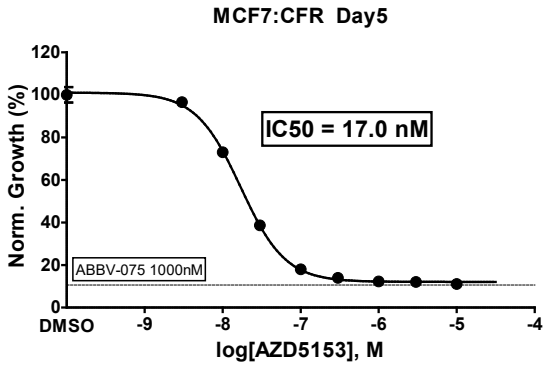
YF-2-23 displayed superior potency in 2D and 3D models

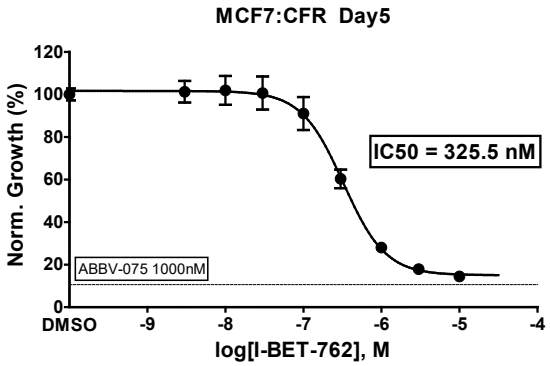






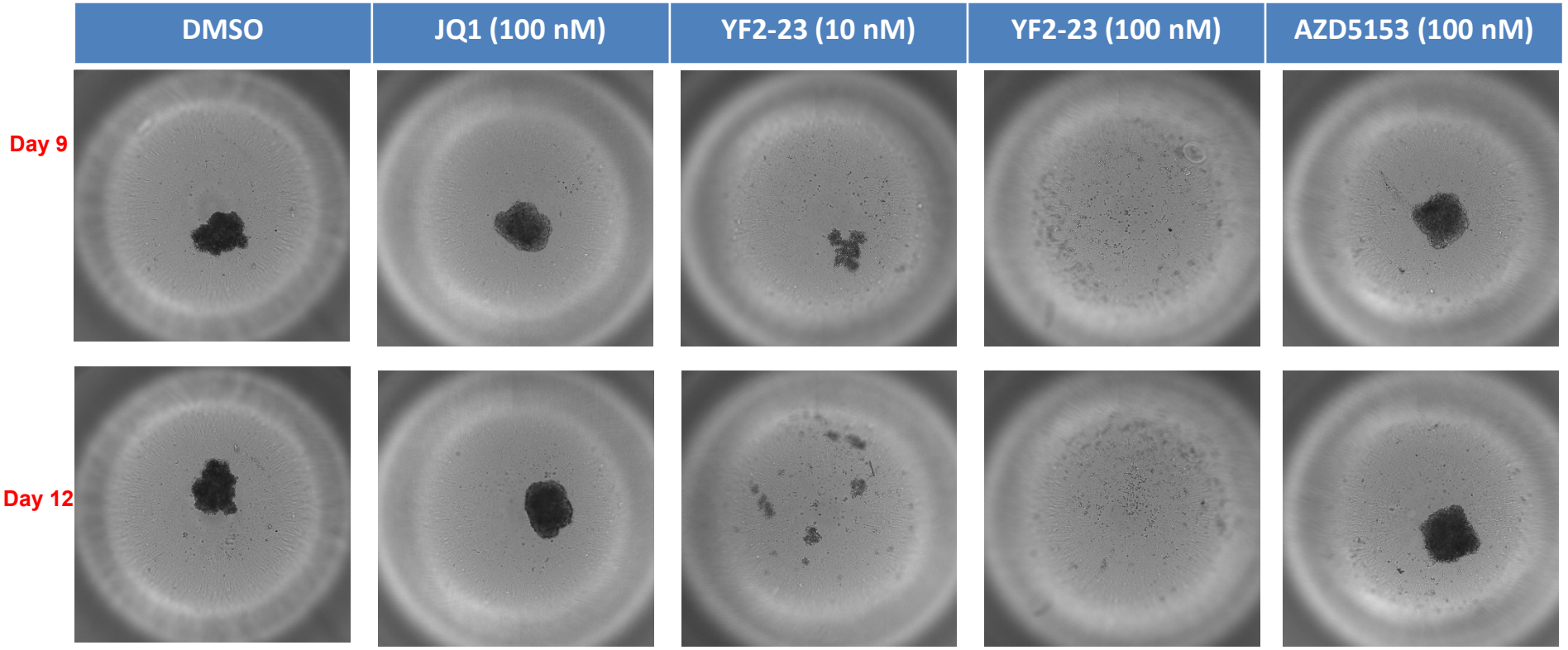






YF-2-23 exhibited excellent inhibitory activity over BMS-98615(BMS), ABBV-075 (Abbvie), AZD-5153 (Astrazeneca), AVR-771 (Arvinas) and iBET-762 (GSK525762, GSK) in fulvestrant-resistant MCF-7:CFR cells.

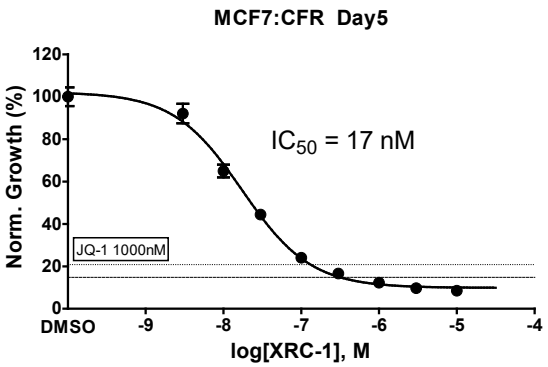
YF-2-23 displayed superior potency in 3D models



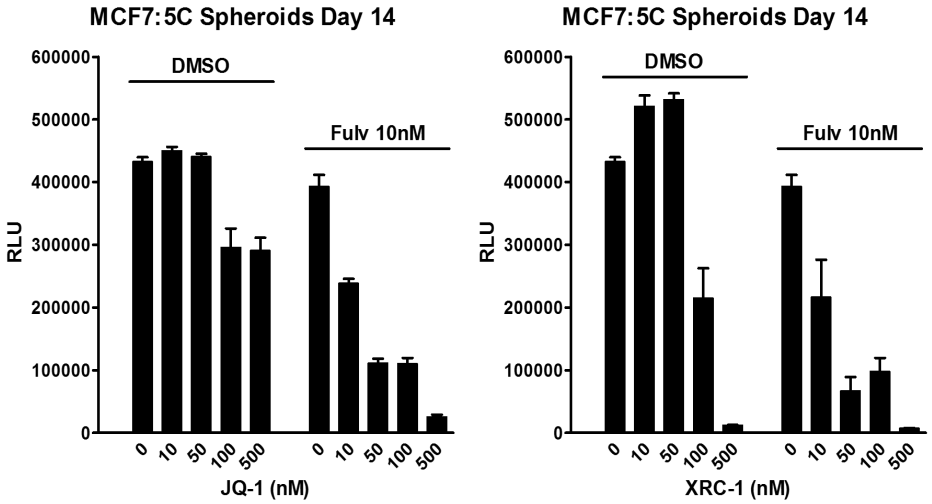
Representative wells from 96 well plates in fulvestrant-resistant ER+ MCF-7:CFR cells

Combination of BET inhibition with ER degraders for endocrine resistant Breast cancer

2D model

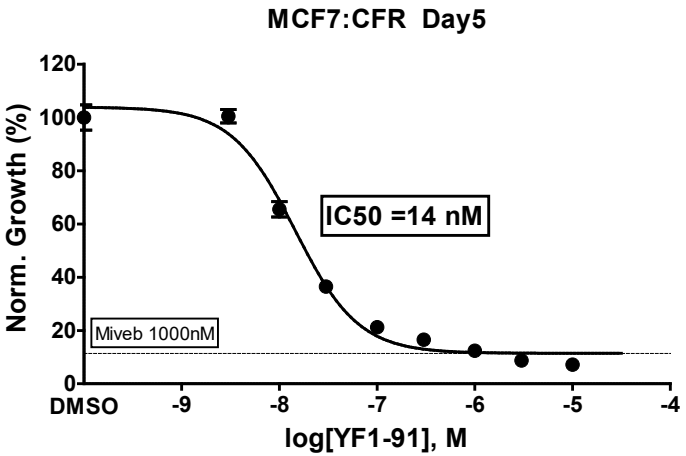


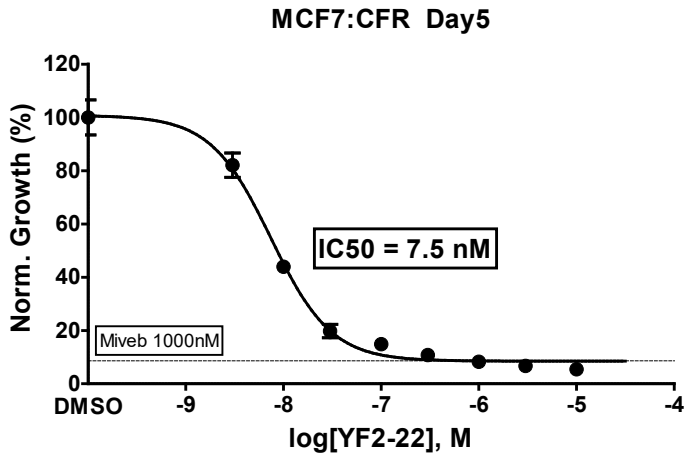
3D model

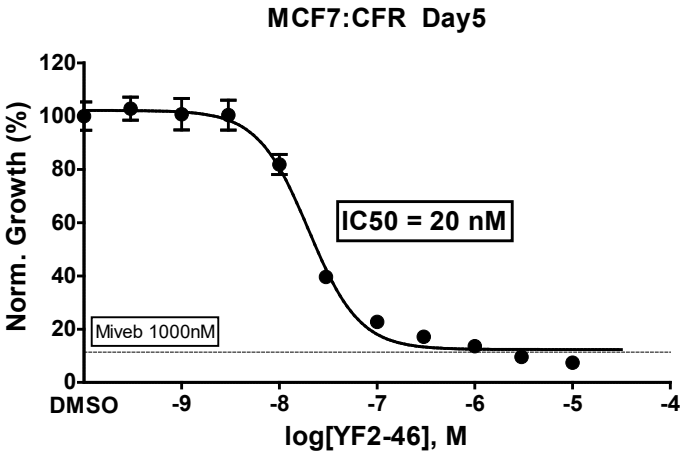


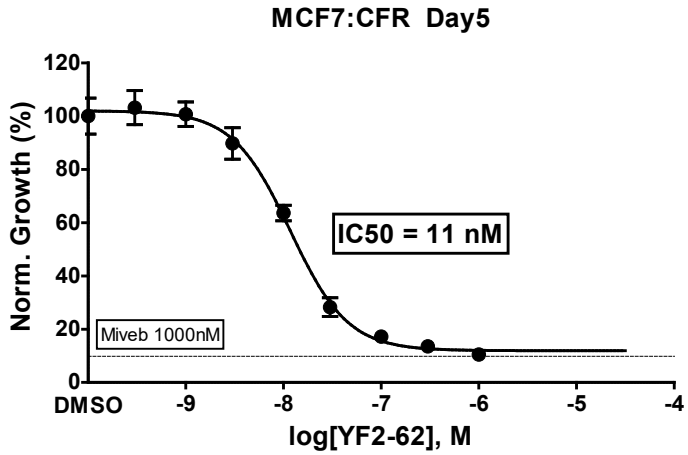
Comparison of combination treatment of non-oral, clinical SERD, fulvestrant in endocrine-resistant MCF-7:5C 3D spheroid model. A potent 1st generation BET inhibitor from our lab, XRC-1, was compared with JQ-1, demonstrating greater than additive efficacy in reducing spheroid growth.

Other backup compound in the library









Data from fulvestrant-resistant MCF-7:CFR cells.

Key Differentiation

- Unique design for three hydrogen-bonding interactions; utilizing spatial proximity of BD1 and BD2 to drive binding affinity
- Superior potency over competitors in 2D and 3D cell models: first-generation diazepine-based compound (eg. iBET-762, GSK); second-generation compound (eg. bivalent AZD5153, ABBV-075)
- Good and potentially differentiate PK for transient transcription suppression to attenuate side-effects
- No chiral center; scalable synthesis with minimum or no column purification for CMC

About The Investigators

Dr. Debra Tonetti

- Associate Professor in Biopharmaceutical Sciences at the UIC College of Pharmacy.
- Trained at Northwestern University focusing on SERM action and endocrine resistance with 18 years of experience in molecular signaling pathways in breast cancer.
- Extensive experience with breast cancer models using mouse xenografts and the first to report PKCα as a biomarker for TAM resistance.
- Oversees the PK and xenograft mouse experiments and coordinates with Dr Thatcher.
- Cofounder of TTC Oncology LLC with Greg Thatcher to develop SEM TTC-352

Dr. Gregory Thatcher

- Professor and Hans W Vahlteich Chair of Medicinal Chemistry at University of Illinois College of Pharmacy.
- Founding Director of campus-wide initiative UICentre (drug discovery @ UIC).
- Extensive experience in mechanistic and biological chemistry with a multidisciplinary approach to drug discovery.
- Over 120 publications in medicinal chemistry, chemical biology, and chemical toxicology as well as 20 issued patents.

Dr. Rui Xiong

- Research Assistant Professor in Biopharmaceutical Sciences at the UIC College of Pharmacy.
- Designer of TTC-352 and G1T48.

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