



FRONTIER
MEDICINES

**Unlocking the Proteome to Deliver Next
Generation Covalent Medicines**

Accelerating best-in-class & first-in-class precision medicines

- Advancing and applying the **Frontier™ Platform for covalent drug discovery**, powered by chemoproteomics and AI
- **Strong management team** that collectively has discovered and developed **over 20 leading medicines**
- **Oversubscribed \$100M Series C in 2024** supports continued progress of clinical-stage pipeline

Wholly Owned Precision Medicines

KRAS G12C ON+OFF
– PROSPER Ph 1/2 Study

FMC-376

P53 Y220C activator
– IND 4Q 2025

FMC-220

Pi3K α -RAS breaker
– IND 2H 2026

FMC-242

KRAS G12D ON+OFF
– DC 1H 2026

G12D

Oncology & I&I discovery programs

Value Creating Partnership

For Defined Undruggable Targets
– Since 2020

Backed by a strong investor syndicate

Applying our collective experience to develop breakthrough medicines



Chris Varma, Ph.D.

Co-founder, Chair, and CEO

- **Co-founder & CEO:** Blueprint Medicines (acquired by Sanofi)
- **Co-founder:** Warp Drive Bio (acquired by Revolution Medicines)
- **Investor:** Flagship, Third Rock, MPM



Daniel Erlanson, Ph.D.

Chief Innovation Officer

- **Co-Founder:** Carmot Therapeutics (acquired by Roche)
- **Thought leader** in fragment-based drug discovery
- **>70 issued patents and publications**



Kevin Webster, Ph.D.

Chief Scientific Officer

- **VP of Oncology Research:** AstraZeneca
- **Head of Cell Cycle and Apoptosis discovery** at BMS
- **>20 programs delivered into development,** ranging from phase 1 to marketed



Gerardo Ubags

Chief Financial Officer

- **Managing Director:** Global Healthcare Investment Banking, BofA Securities
- **Focus:** biopharma & computationally-enabled drug development
- **Executed >\$100bn in M&A and >\$12bn in capital markets transactions**



Johannes Hermann, Ph.D.

Chief Technology Officer

- **Global Head, Data Science:** J&J Medical Devices Technology
- **Head, Machine Learning & Advanced Analytics:** Janssen



Aaron Weitzman, M.D.

Acting Chief Medical Officer

- **Served as CMO** at Tango
- **Led the development of novel anti-cancer agents,** advancing Arvinas' first PROTAC and Halda's first RIPTAC to first-in-human Phase 1 trials in solid tumors
- **Directed the development of cabozantinib (XL184)** at Exelixis

Clinical-stage precision pipeline: harnessing the Frontier™ Platform to deliver best-in-class covalent medicines

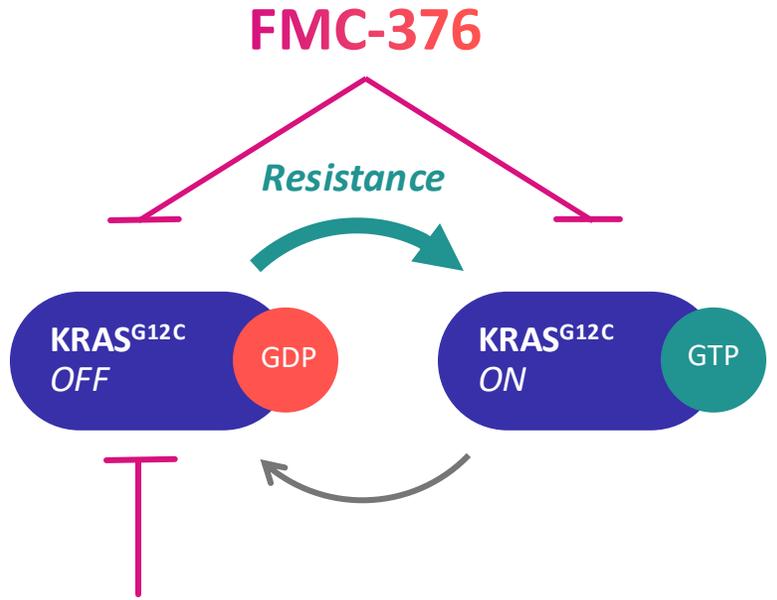


FMC-376

A covalent small-molecule dual inhibitor that **directly and rapidly blocks both on+off (active+inactive) KRAS^{G12C}** to surpass disease resistance



Blocking both ON and OFF KRAS G12C overcomes resistance



Sotorasib, adagrasib, and other OFF inhibitors
Significant rates of both innate and acquired resistance, majority shunting KRAS to activated state, e.g.:

- Adaptive resistance
- RTK amplification/ fusions
- KRAS^{G12C} amplification
- Loss of GAP function

FMC-376 advantages

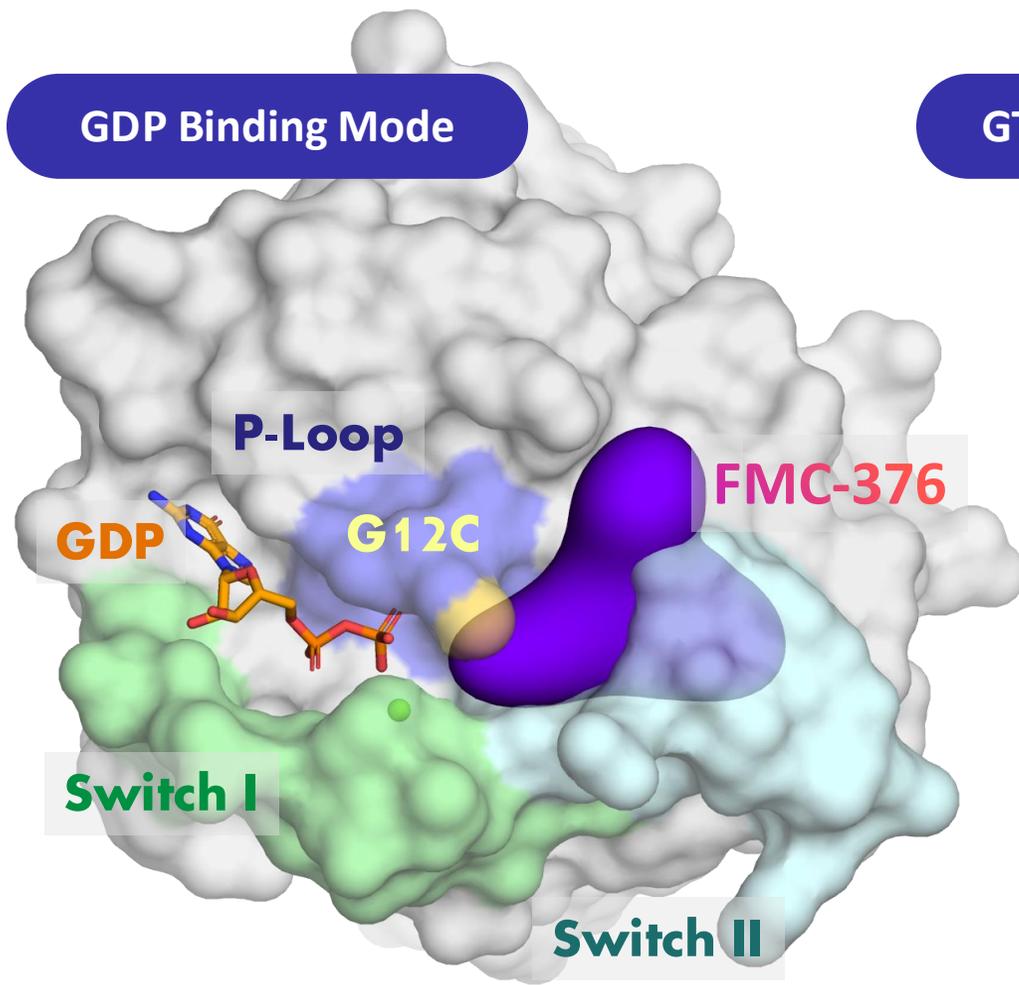
Direct dual inhibition that rapidly and completely blocks ON and OFF KRAS G12C

Retains potency in contexts of KRAS activation (e.g. KRAS amp, RTKs, ect.)

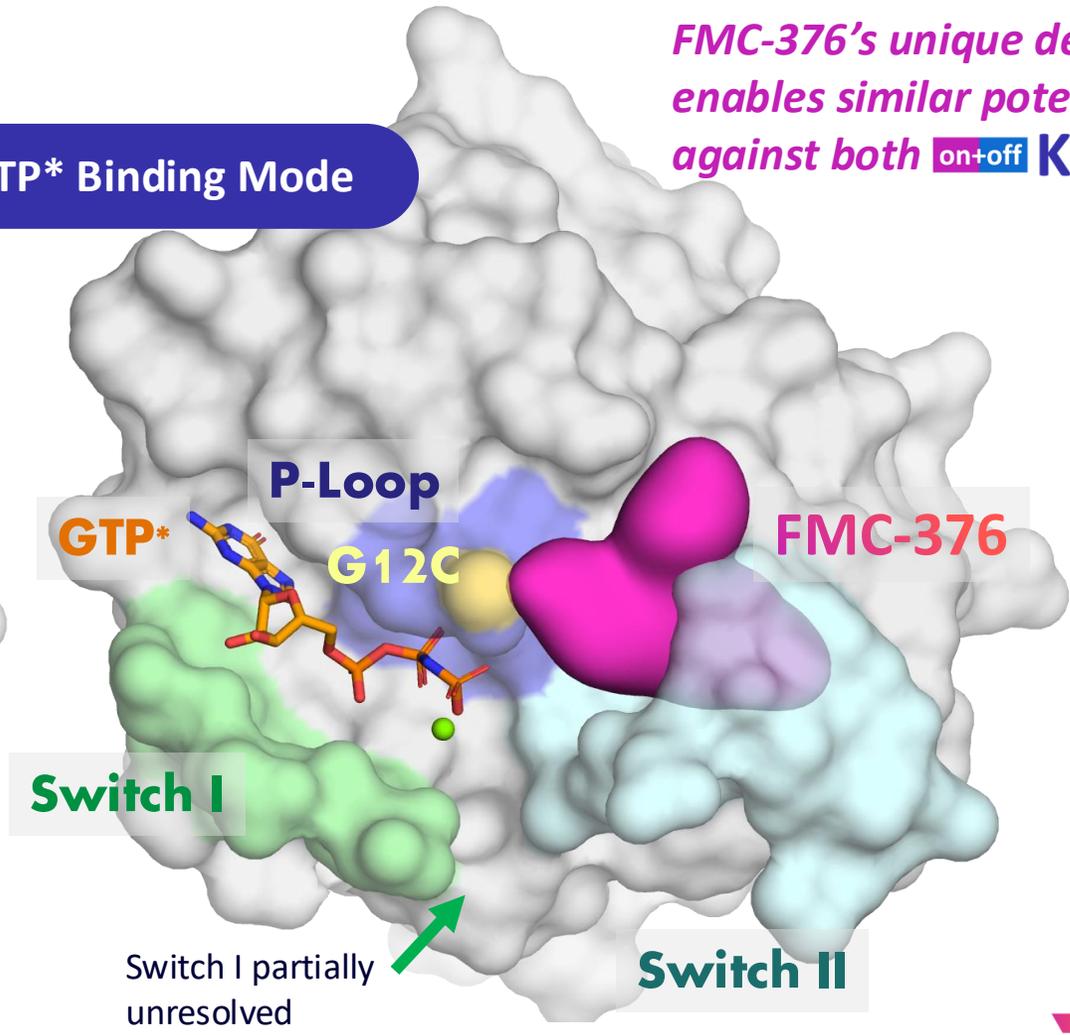
Effective in divarasil/sotorasil/ adagrasil resistant models

The Frontier™ Platform enabled FMC-376: the first small molecule adopting two low energy conformations

GDP Binding Mode



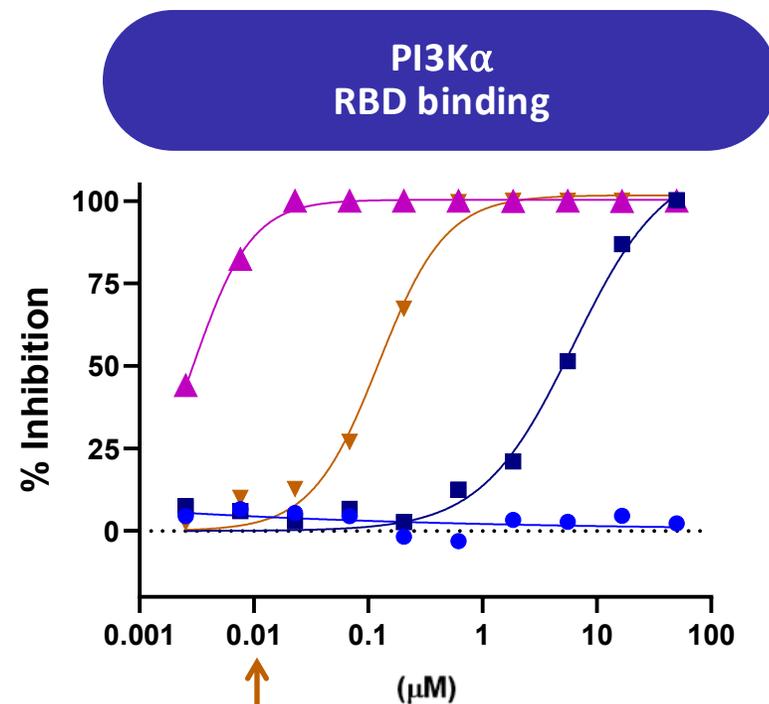
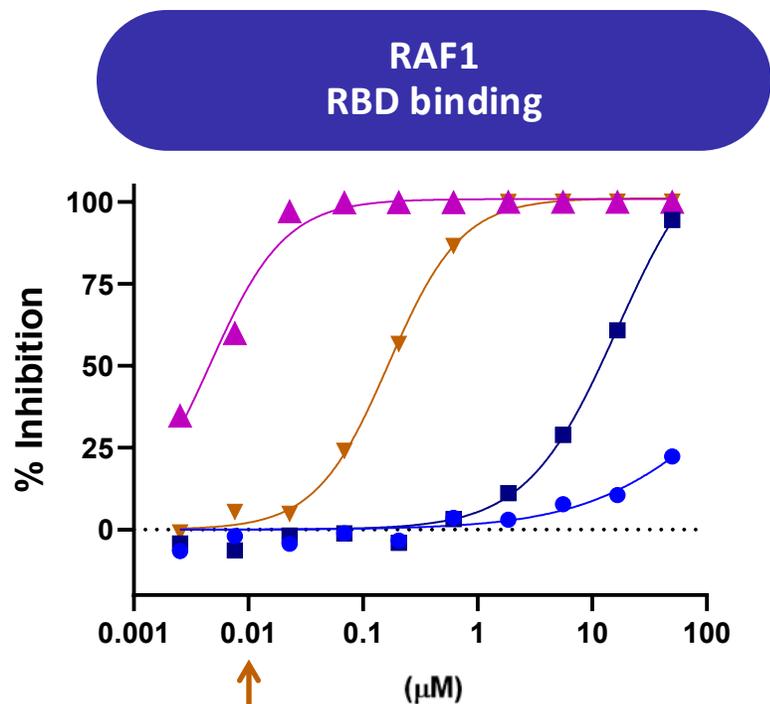
GTP* Binding Mode



FMC-376's unique design enables similar potency against both on+off KRAS^{G12C}

*GMP-PNP, G12C

FMC-376 potently disrupts key effector protein interactions within our anticipated efficacious clinical dose range



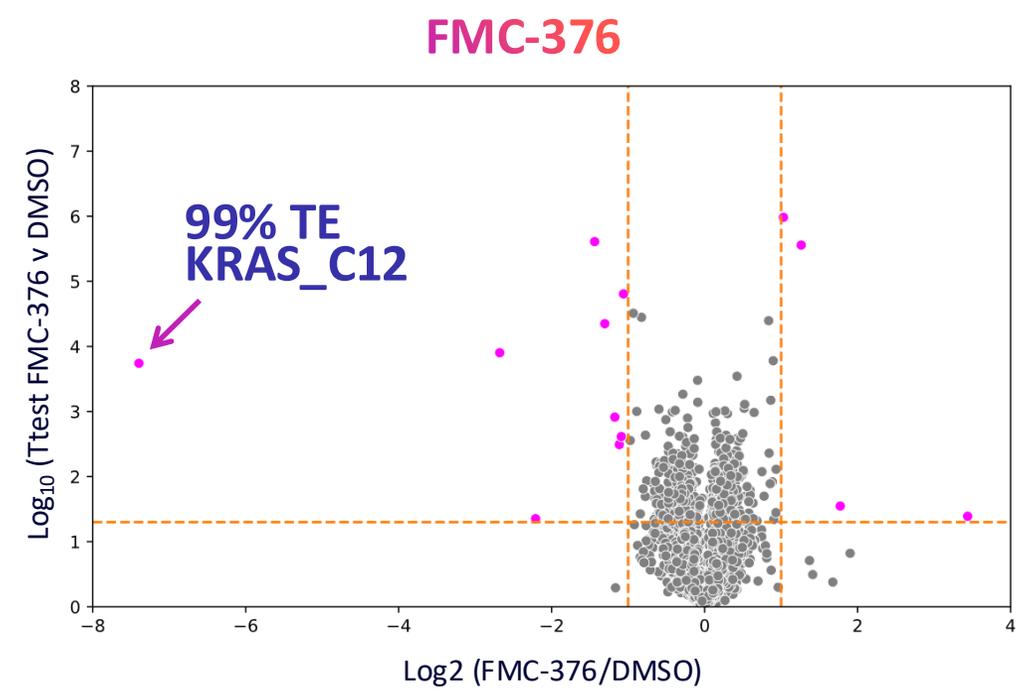
Divarasisib requires >10x the maximum clinically achievable dose to lightly touch key effector protein interactions

- ▲ FMC-376
- Adagrasib
- Sotorasib
- ▼ Divarasisib

Maximum clinical exposure to divarasisib

Maximum clinical exposure to divarasisib

FMC-376 delivers superior selectivity for KRAS^{G12C} in whole-cell screening



Best-in-class selectivity

MiaPACA-2, 4 hr. treatment with 1 uM drug, competitive isoTOP, significant- p-value < 0.05, log₂-fold change <-1 or >1

FMC-376 overcomes drivers of KRAS^{G12C} inhibitor resistance in NSCLC

Mechanisms of KRAS G12C inhibitor resistance in NSCLC*	% patients	FMC-376 activity
Adaptive resistance†	50%	
KRAS G12C / RTK / PI3Kα / NF1 / p53 / KEAP1 or other amplification/mutations	37.5%	
Secondary K, H, or NRAS / RAF / MEK / MAPK mutations	12.5%	

KRAS G12C inhibitor efficacy has been limited by the presence of either:

- Adaptive/compensatory signaling (ON-state )
- Secondary mutations

FMC-376 overcomes the majority of innate and acquired resistance mechanisms due to the ability to inhibit both ON and OFF states of KRAS G12C

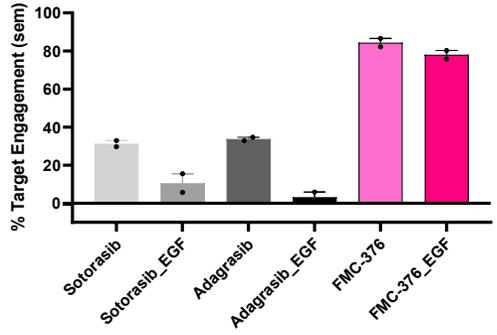
* *Cancer Discov* (2025) 15 (7): 1325–1349
 † Patients with no identified mutation

FMC-376 overcomes drivers of KRAS^{G12C} inhibitor resistance in NSCLC

FMC-376

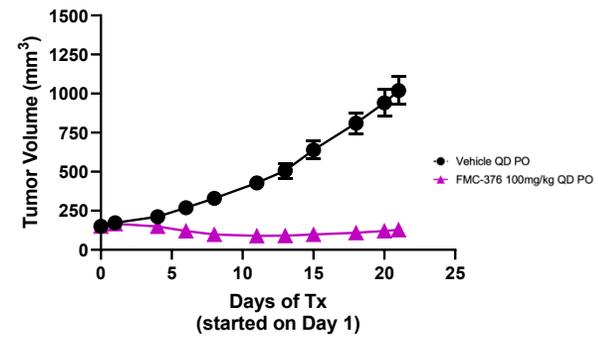
1. Adaptive resistance

FMC-376 target engagement +/- EGF stimulation¹

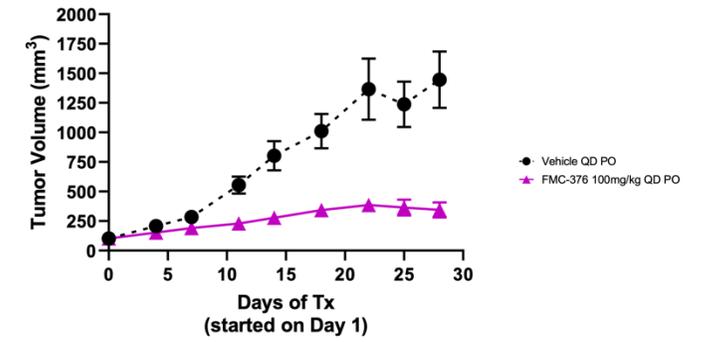


2. RTK amplification/fusions

NSCLC PDX
KRAS^{G12C}, EGFR amp, p53

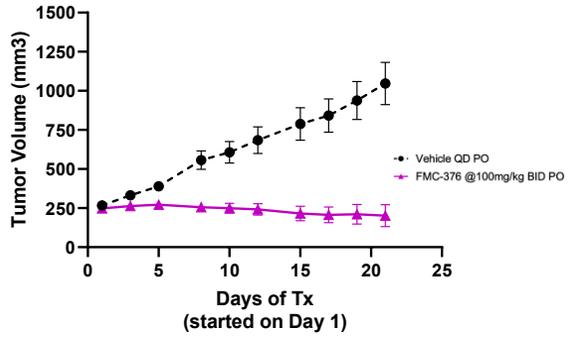


NSCLC PDX
KRAS^{G12C}, MET, BRCA1, NOTCH, MYC



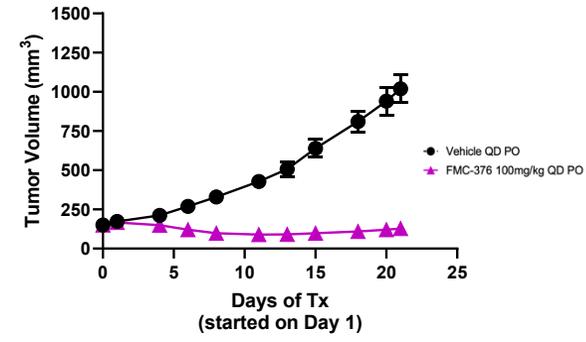
3. KRAS^{G12C} amplification

NSCLC PDX
KRAS^{G12C} amp (13 copies)



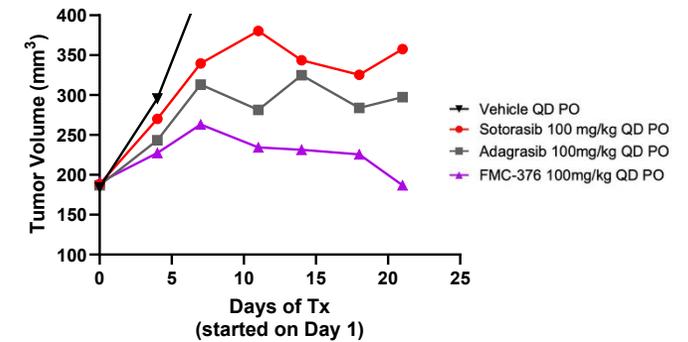
4. p53 mutation/deletion

NSCLC PDX
KRAS^{G12C}, p53



5. Innate resistance

NSCLC PDX
KRAS^{G12C}, KEAP1

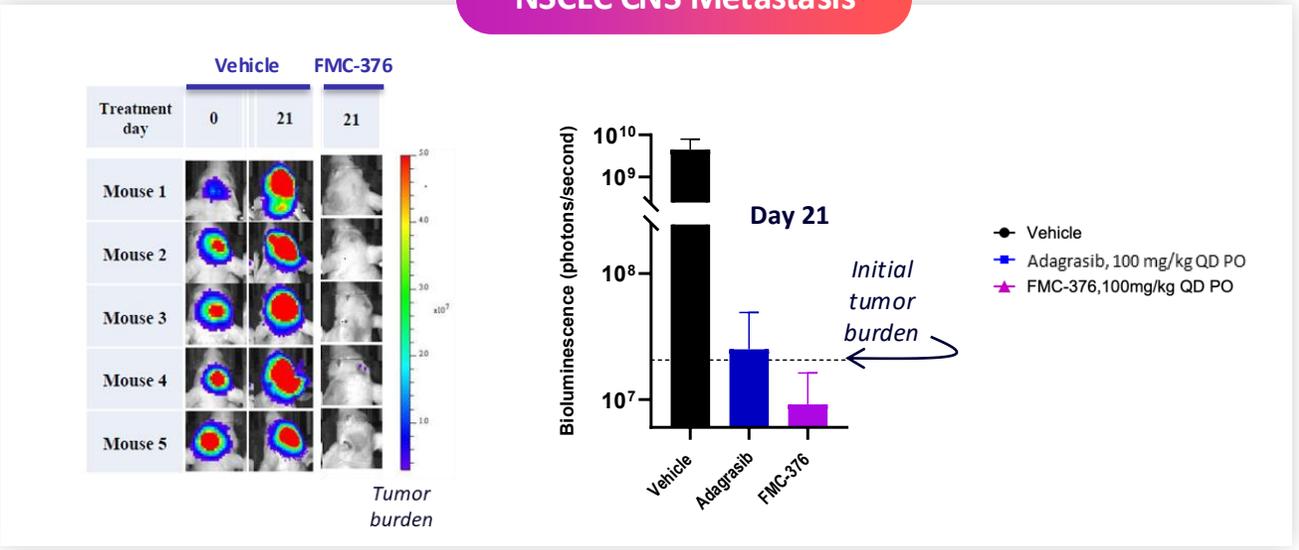


FMC-376 is optimized for development in 1L and 2+L KRAS G12C NSCLC patients

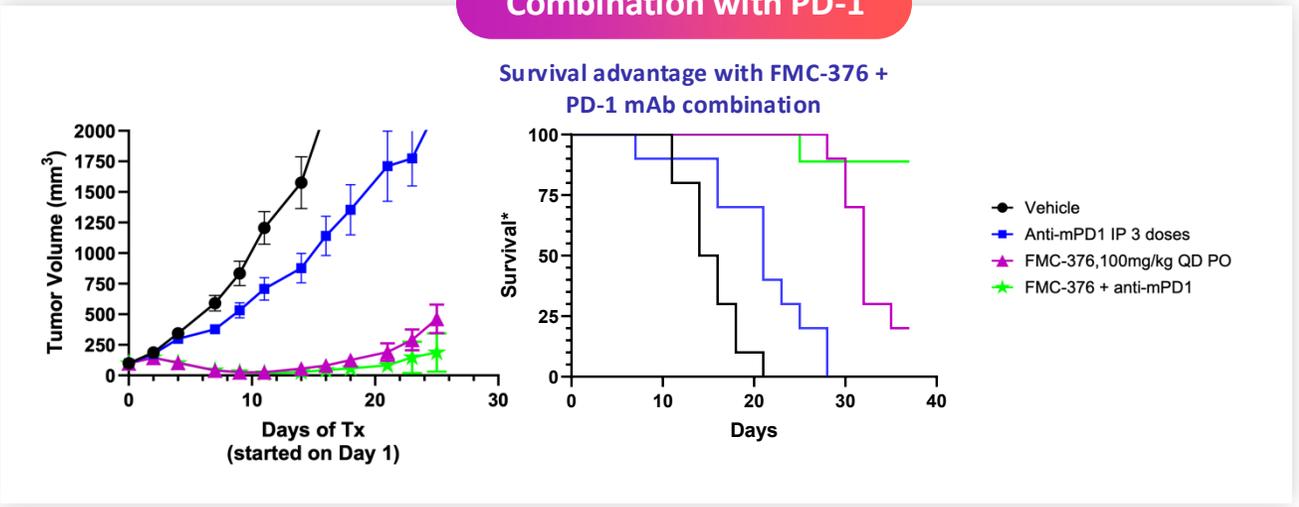
The FMC-376 difference:

- Broadly active across PDX models of NSCLC and in the presence of known drivers of clinical resistance
- Highly effective in a model of NSCLC CNS metastasis
- Increases survival in combination with immune checkpoint inhibition enabling front line NSCLC development strategies

NSCLC CNS Metastasis



Combination with PD-1



FMC-376: Delivering a best-in-class option to patients

The FMC-376 difference:

Rapidly and completely
shuts down

on+off KRAS^{G12C}

Addresses the majority
of known resistance
mechanisms;
effective in models of
CNS metastasis

Exquisitely selective
to support
monotherapy and
combination use

Ph 1/2 PROSPER trial actively recruiting

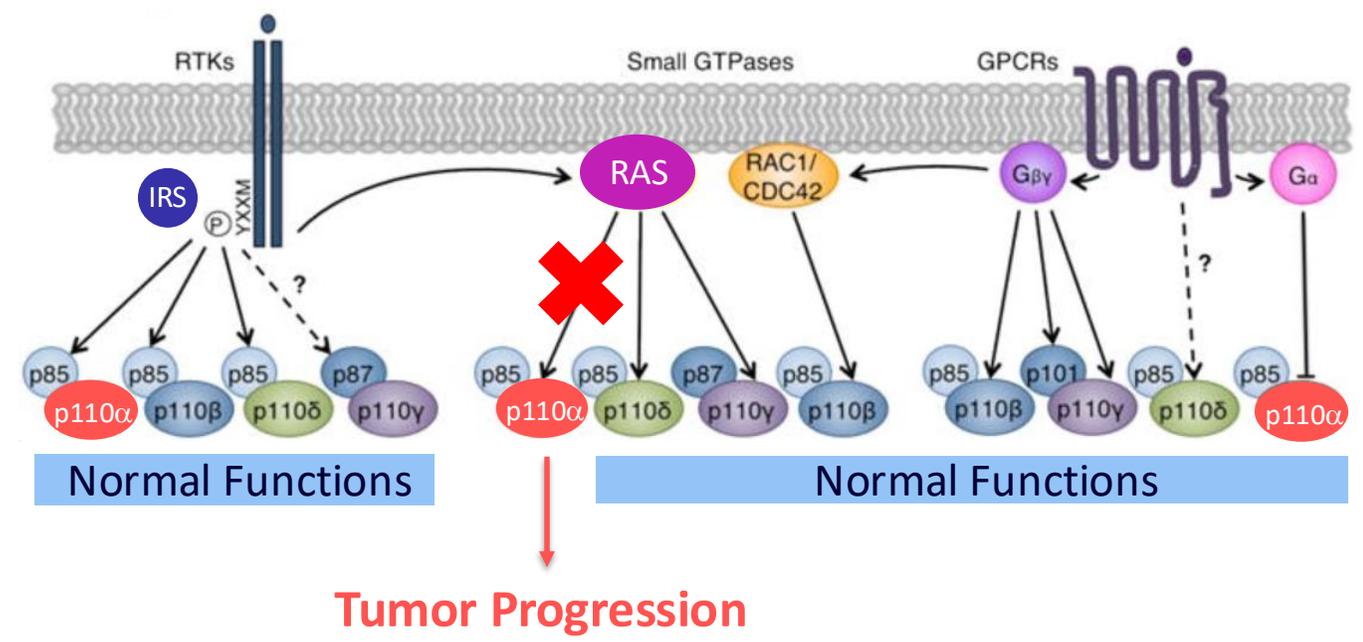
FMC-242

Exquisitely selective, allosteric inhibitor of PI3K α -RAS PPI that spares normal enzymatic activity



FMC-242 has the potential to become a foundational therapy targeting drug resistance in combination

Frontier™ Platform- identified site and covalent leads that deliver selective, allosteric inhibition of PI3Ka-RAS PPI while sparing normal functions



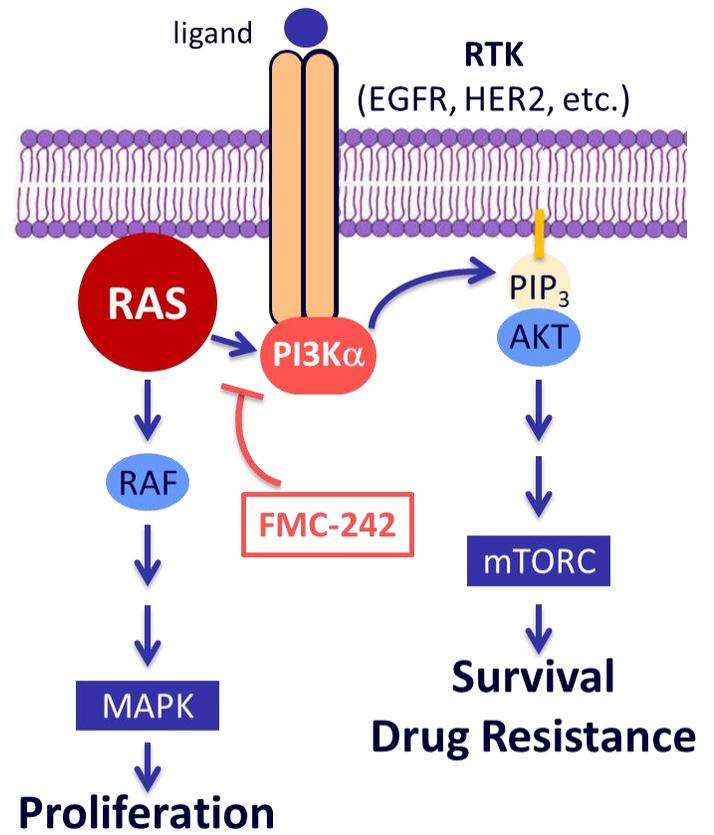
Selective inhibition of PI3Ka-RAS interaction delivers

- Monotherapy activity in tumors with RTK activation, RAS mutations, PI3Ka mutations
- In combination, overcomes resistance to targeted therapies including KRAS and EGFR
- Improved tolerability, e.g. spares glucose homeostasis

Adapted from- Vanhaesebroeck, B., et al. Nat Rev Mol Cell Biol 11, 329–341

Selective inhibition of PI3K α –RAS interaction provides broad mono- and combination therapeutic opportunities

PI3K α is an essential cofactor in both KRAS and RTK driven cancers



Monotherapy Strategies	Indications
Receptor Tyrosine Kinase (RTK) driven disease	50% CRC, 35% NSCLC, 20% BCa
KRAS mutant disease	14% of all cancers
PI3Ka mutant disease	~35% BCa
Drug Combination Strategies	Drugs
KRAS inhibitors	FMC-376, daraxonrasib, others
RTK inhibitors	Cetuximab, trastuzumab, osimertinib, others

FMC-242 delivers selective allosteric inhibition of RAS binding

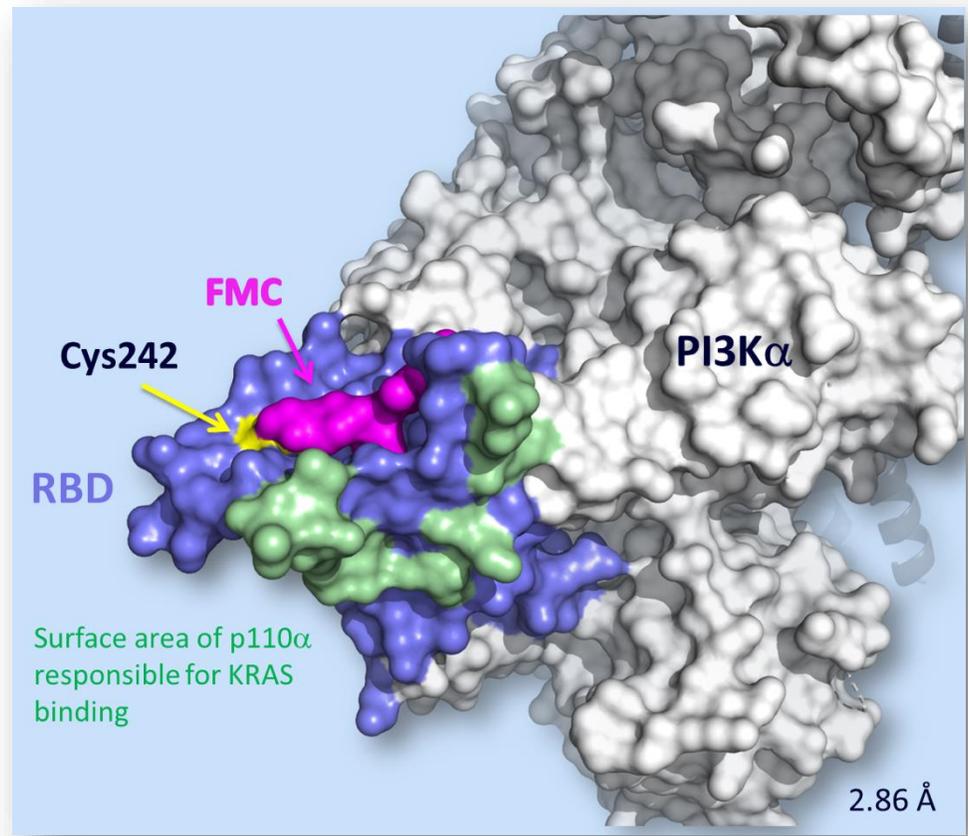
Cys242 is covalently ligandable



Cys242 provides specificity within the PI3K family

PI3Kα:	SEQLKLCVLEYQGK
PI3K β :	---- KEDEVSPYD
PI3K δ :	---- QPLVEQPED
PI3K γ :	SLMDIPESQSEQD

FMC-242 binding disrupts RAS binding interface



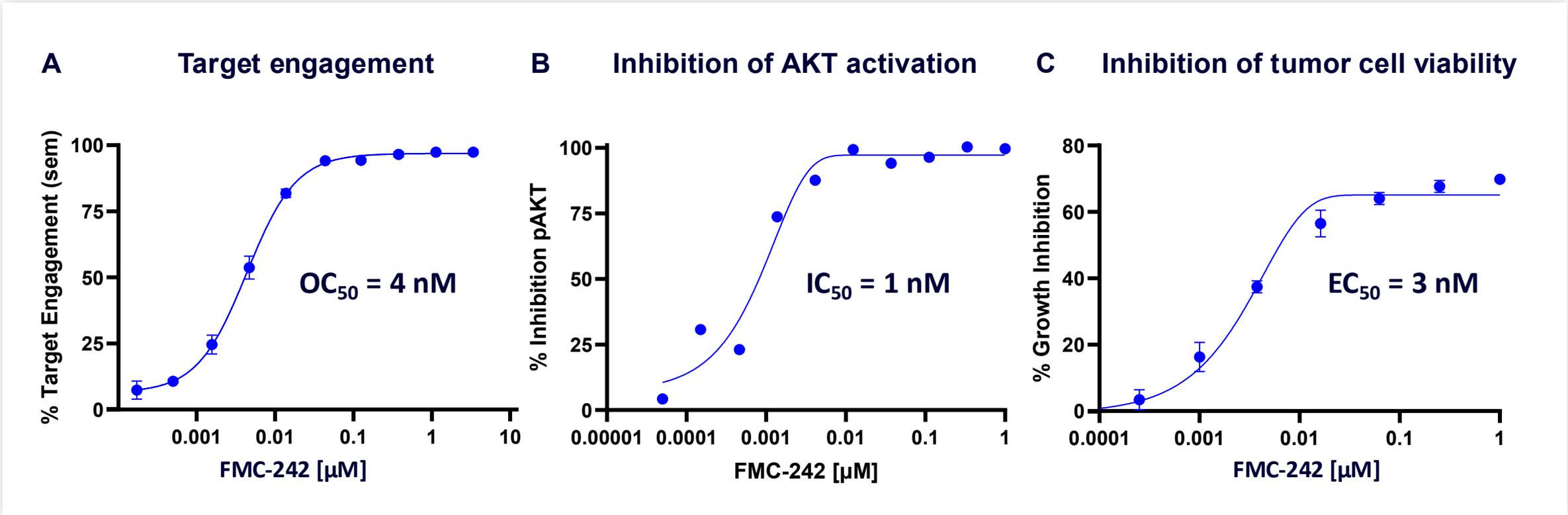
All key complexes of PI3K α / RAS are effectively inhibited

Protein-Protein Interaction can be broken across disease-relevant PI3K α and RAS mutations

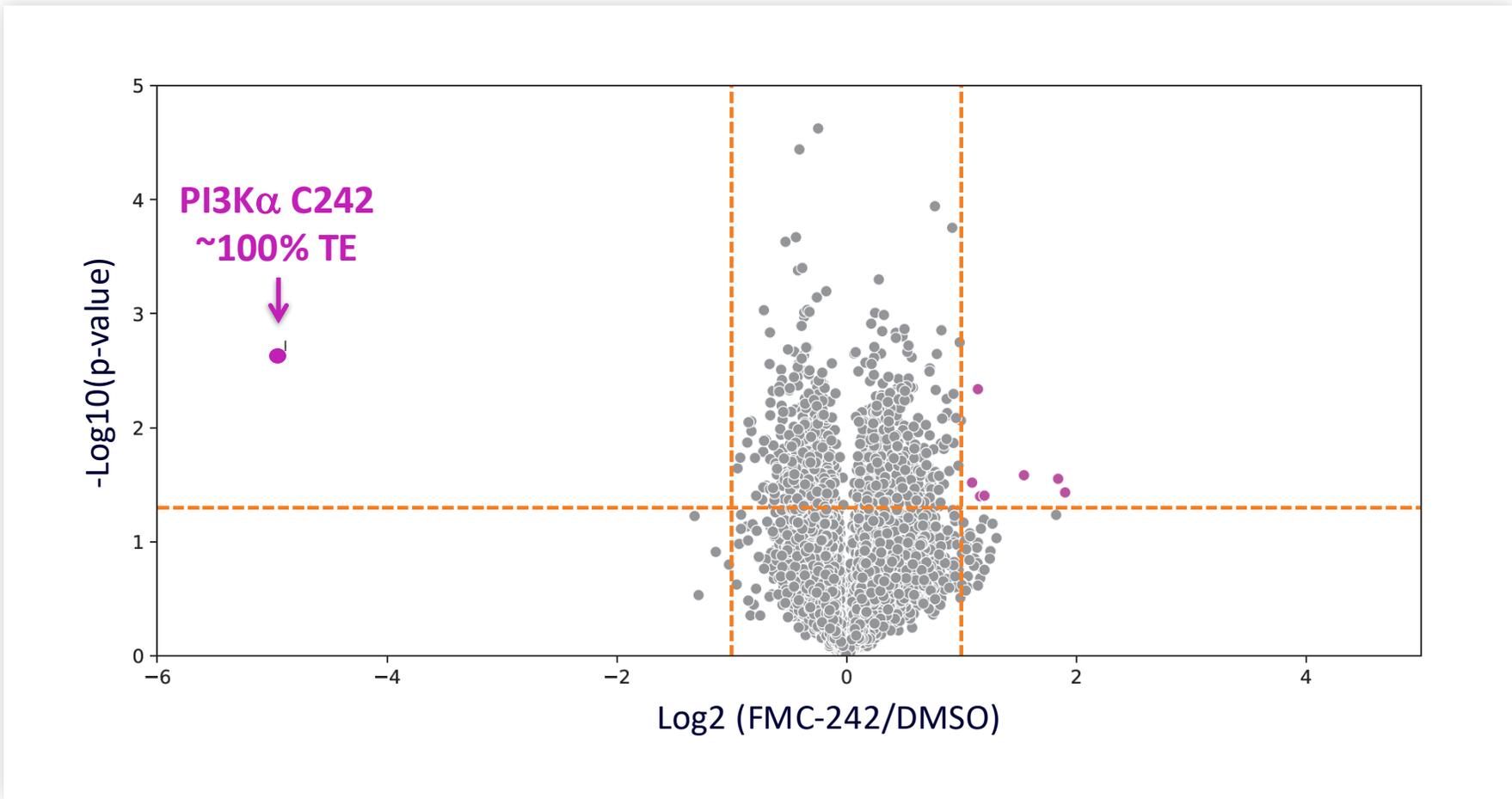
		A	B	C	D
		wt PI3K α	PI3K α (H1047R)	PI3K α (E542K)	PI3K α (E545K)
1	KRAS^{G12C}	✓	✓	✓	✓
2	KRAS^{G12D}	✓	✓	✓	✓
3	KRAS^{G12V}	✓	✓	✓	✓
4	wt KRAS	✓	✓	✓	✓
5	wt HRAS	✓	nt	nt	nt
6	wt NRAS	✓	nt	nt	nt

- Both the potency and extent of the PPI-inhibition hold up across pairings in the table

Covalent engagement of C242 inhibits AKT activation and tumor cell viability



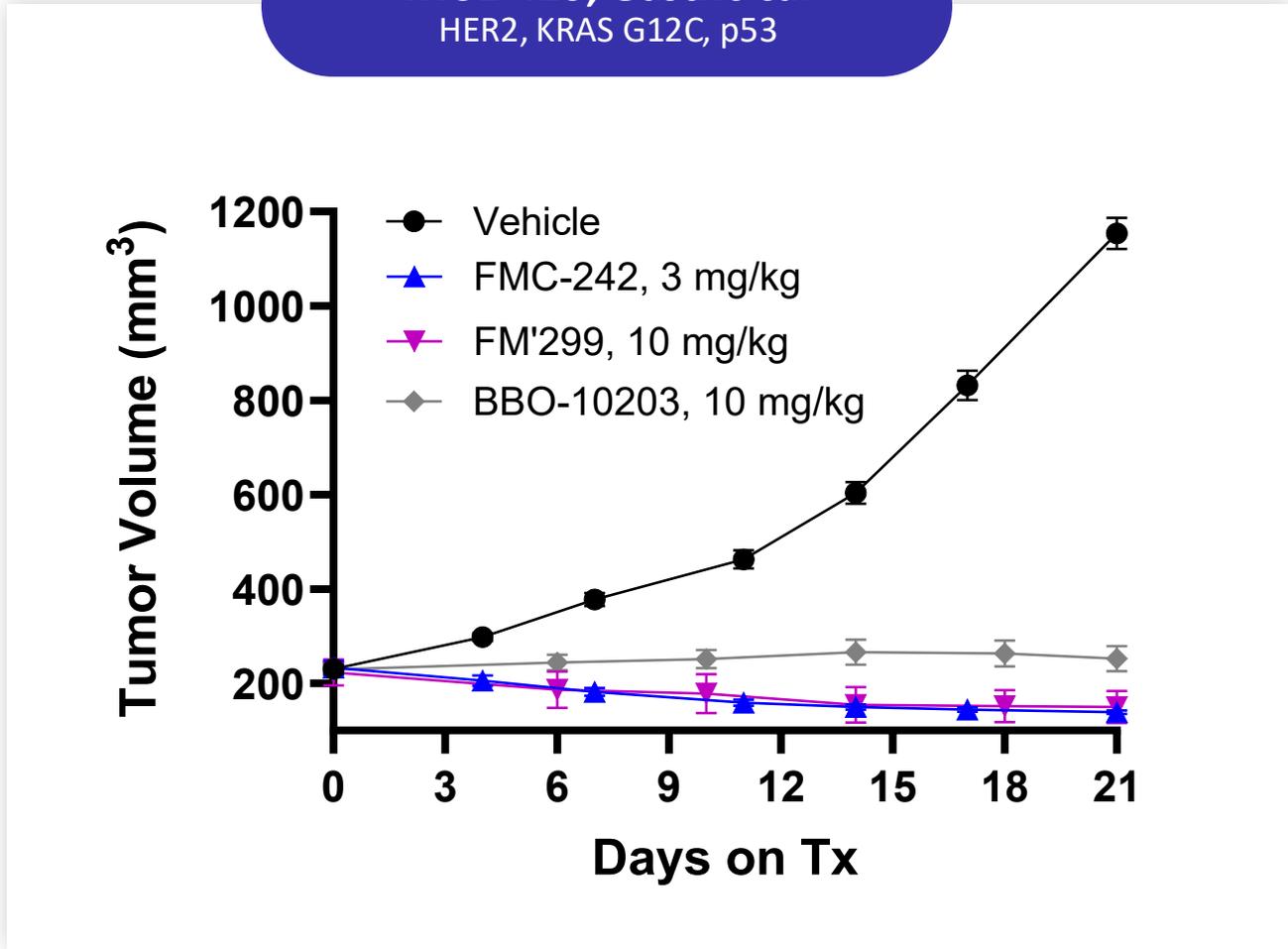
FMC-242 achieves high selectivity across the proteome and complete target engagement of PI3K α



Volcano plot depicting selectivity of FMC-242 after a 2 μ M (465X the OC₅₀) treatment for 2hrs in KYSE-410 cells. Orange dashed lines represent significance thresholds of a 2X fold change and a p-value of 0.05. Each dot represents a quantified cysteine (n = 22,620)

FMC-242 shows differentiated efficacy driving tumor regression at much lower dose

KYSE-410, Gastric ca.
HER2, KRAS G12C, p53

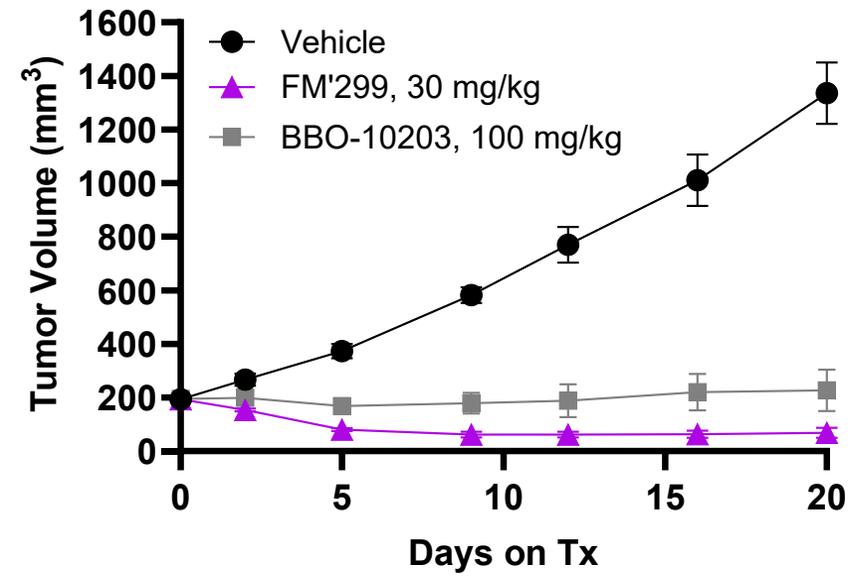


FMC PI3K α -RAS breakers show strong single-agent activity in HER2+ PDX models

FMC-242

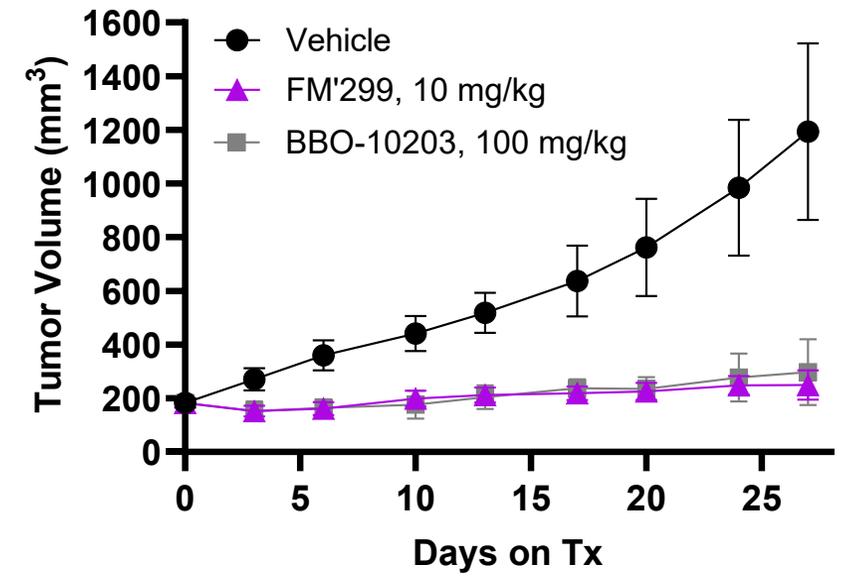
BR10564, Breast ca.

HER2+, MYC+, PI3K α C420R, TP53 W136 ter.



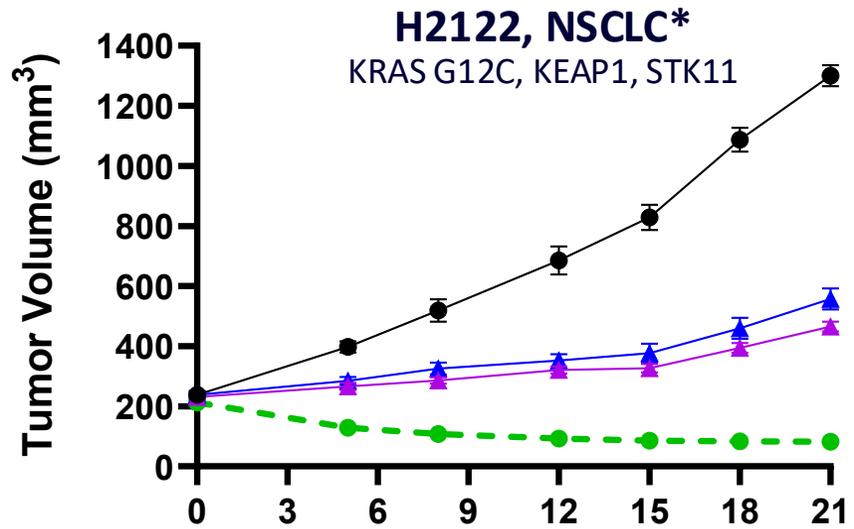
STO-132, Gastric ca.

HER2+



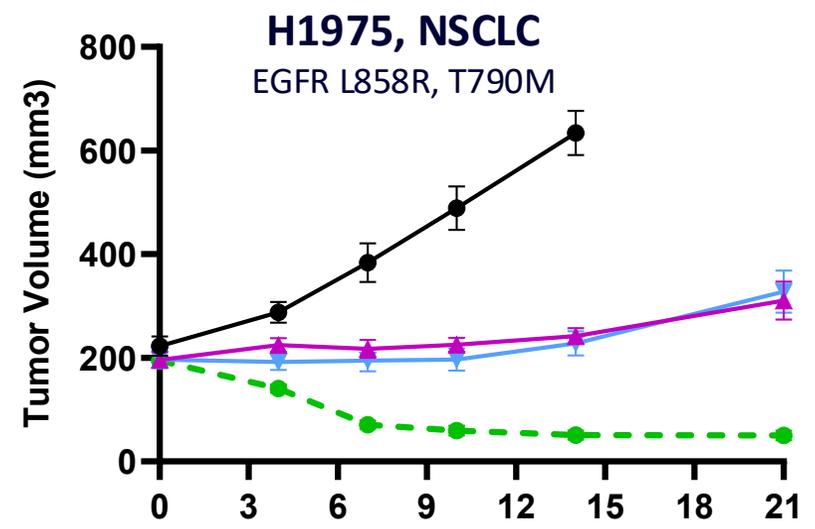
FMC PI3K α -RAS breakers drive tumor regression in combination with KRAS and EGFR inhibitors

KRAS combination



- Vehicle
- ▲ FM-299, 30 mg/kg
- ▲ FMC-376, 100 mg/kg
- FM-299, 30 mg/kg + FMC-376, 100 mg/kg

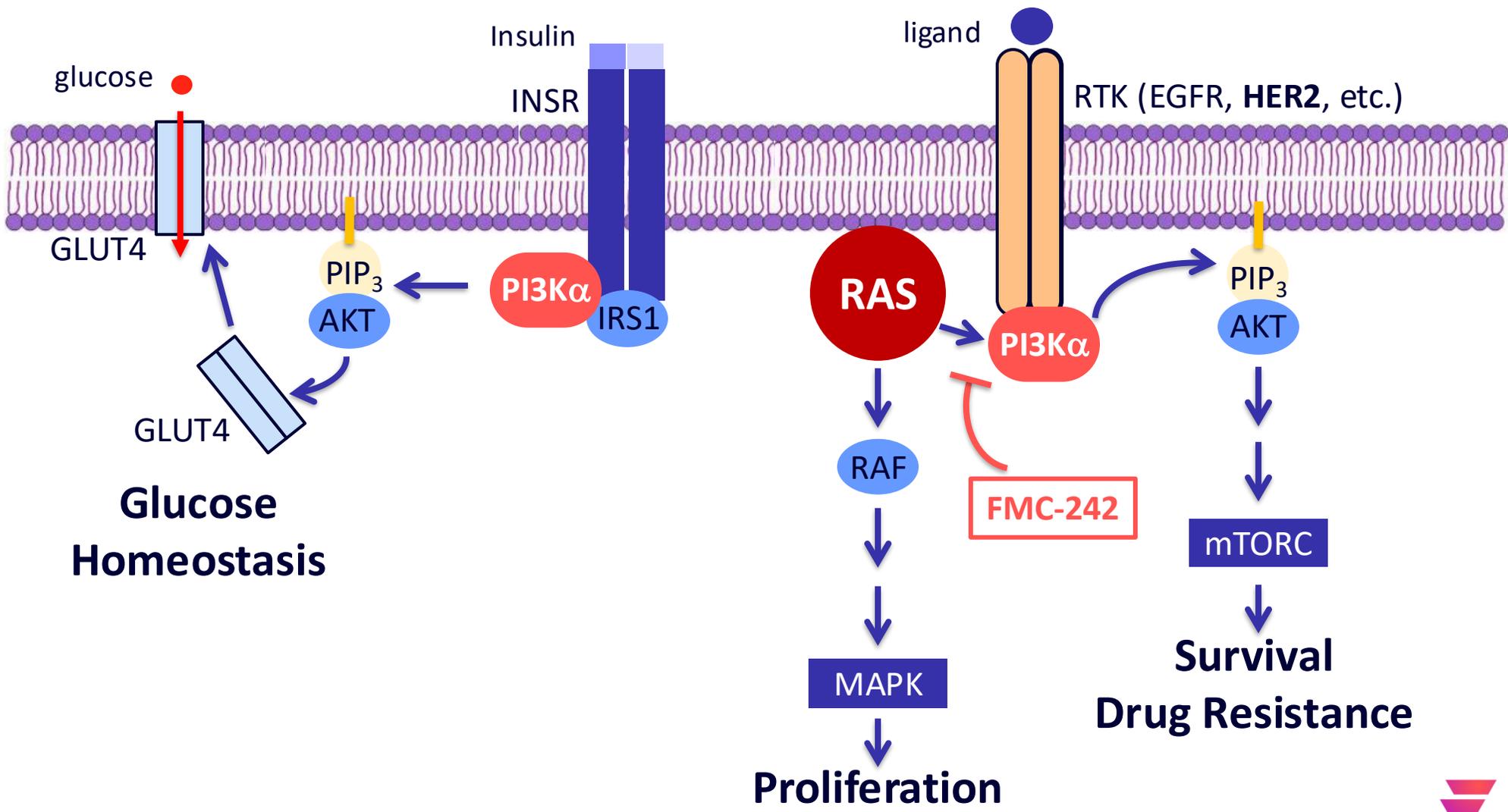
EGFR combination



- Vehicle
- ▲ FM-299, 30 mg/kg
- ▲ Cetuximab, 4 mg/kg Q4D IP
- FM-299, 30 mg/kg + Cetuximab 4 mg/kg

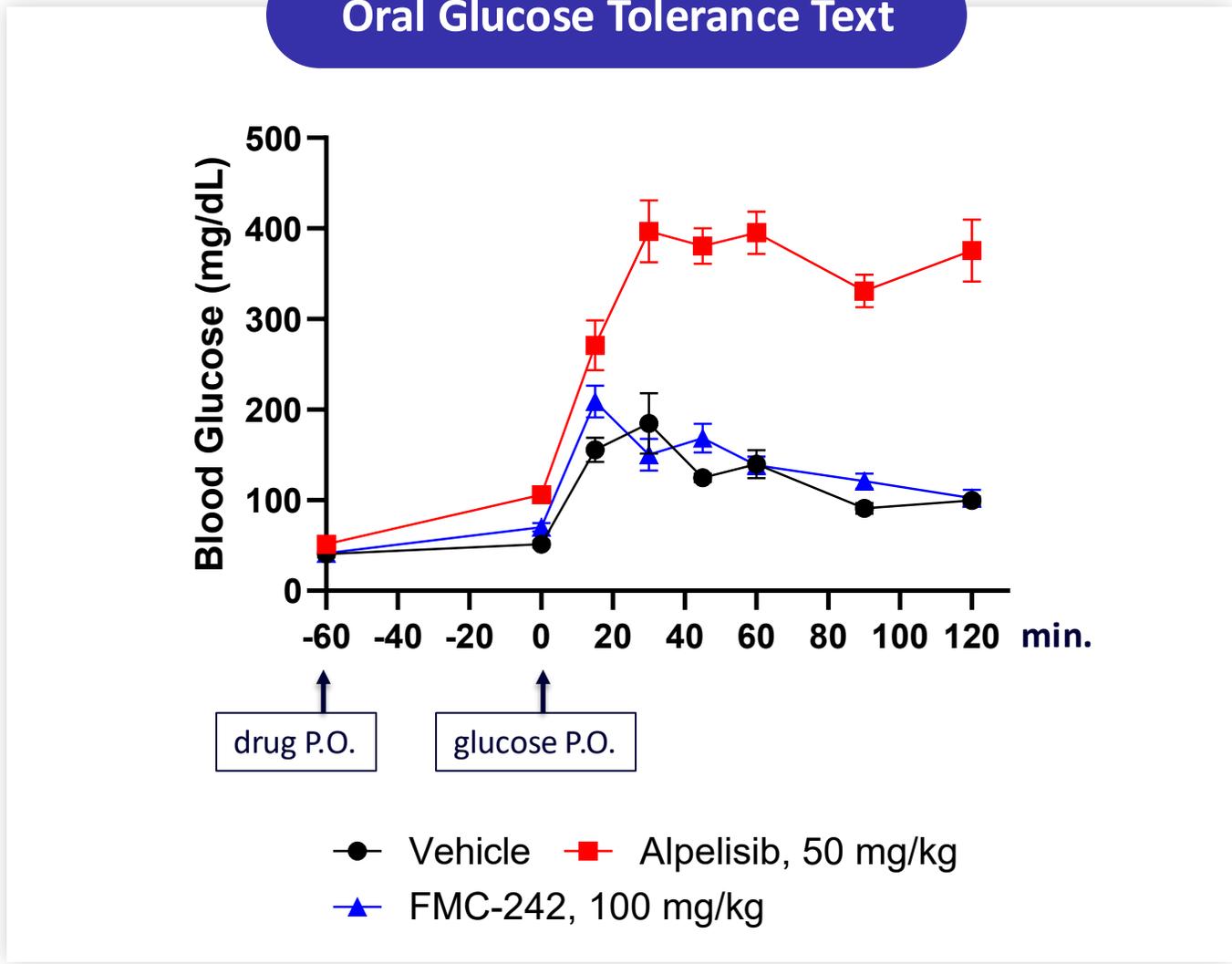
*KRAS inhibitor resistant model

Inhibition of PI3K α -RAS interactions spares normal PI3K α function



FMC-242 does not disrupt normal glucose metabolism at $\geq 30x$ the efficacious dose

Oral Glucose Tolerance Text



FMC-242 a highly selective, covalent allosteric inhibitor of PI3K α -RAS PPI that spares normal functions

PI3K α -RAS Breaker

Preclinical data show:

- ✓ Unprecedented potency
- ✓ Exceptional target coverage
- ✓ Broad inhibition of HER2+, EGFR, RAS mutant tumor cell viability
- ✓ Tumor regression
- ✓ CNS exposure
- ✓ Spares glucose metabolism
- ✓ Highly selective

KRAS G12D

A direct, selective, covalent inhibitor
of ON + OFF KRAS G12D to deliver
durable benefit for patients



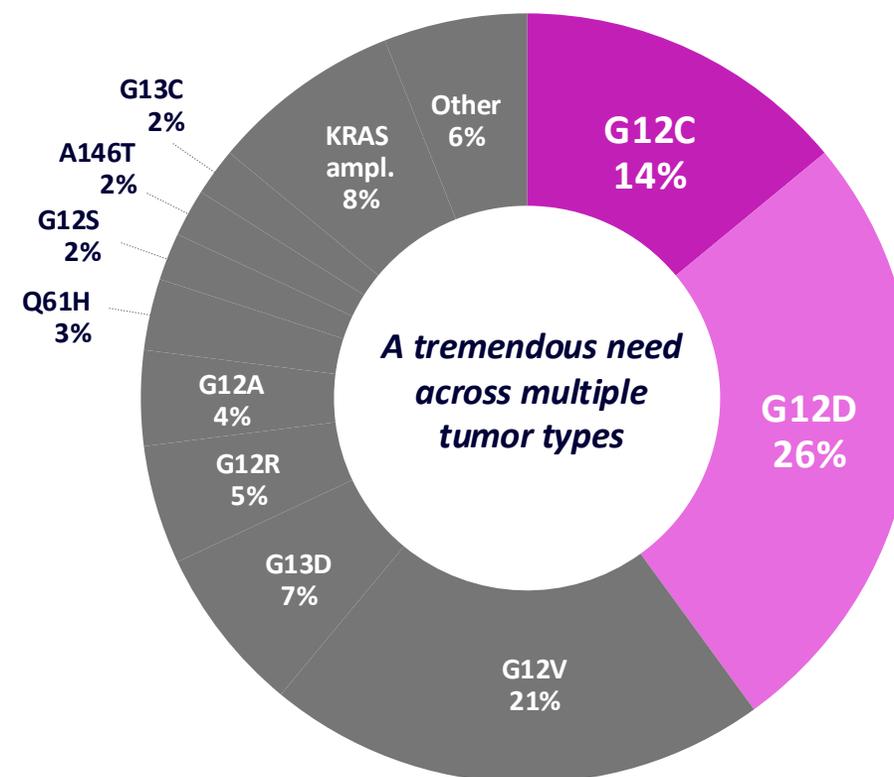
A targeted approach to conquer KRAS treatment

KRAS^{G12D}

is responsible for 55K+ new US cancers annually, including pancreatic, CRC and lung

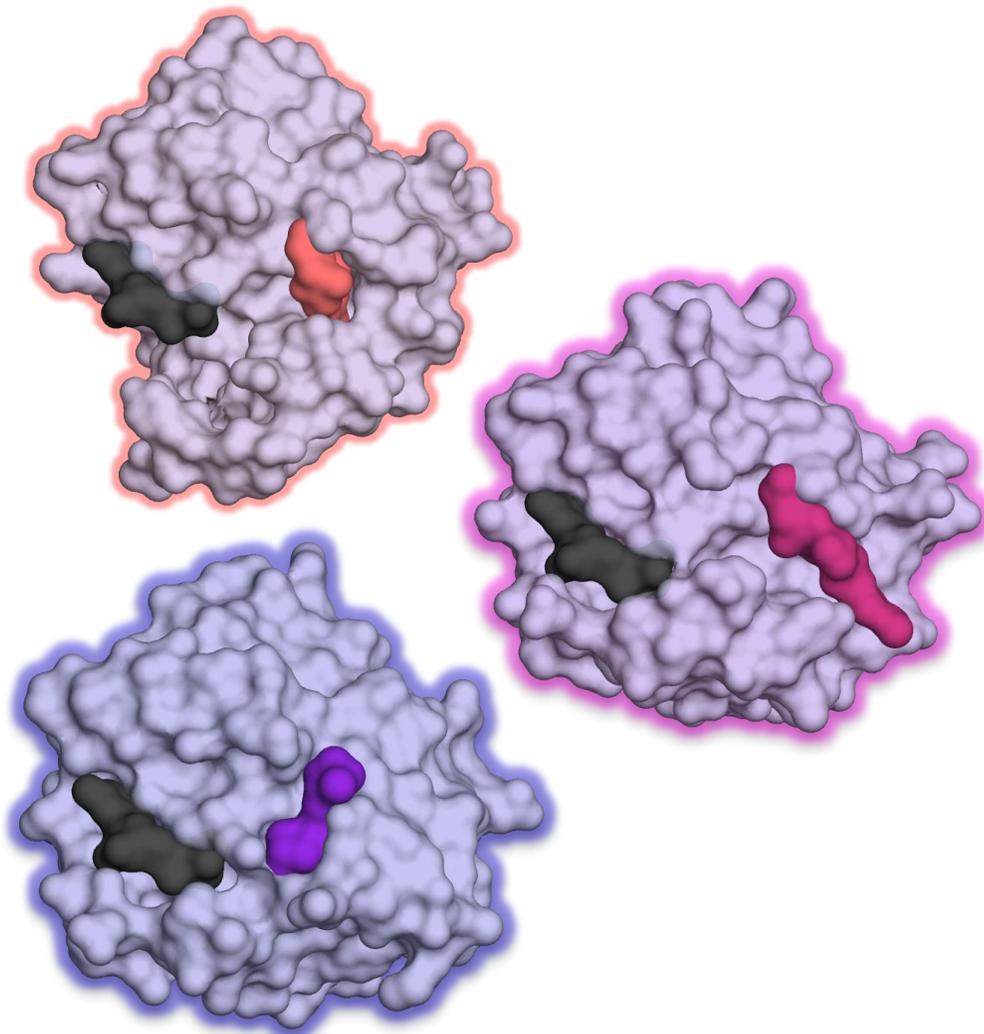
G12C and G12D combined compose 40% of KRAS mutations

Percentage patients, estimated



1 Data are based on projections using estimates of KRAS^{G12C} mutation frequency derived from <http://dx.doi.org/10.1016/j.trecan.2017.08.006>, DOI:10.1158/0008-5472.can-19-3682.

First in class covalent inhibitors of ON+OFF KRAS G12D



- **KRAS requires prolonged target engagement**
 - enabled by covalent chemistry
- **Frontier is the industry leader in covalent chemistries** > 40 warheads accessing novel amino acids, including Aspartic acid (D)
- **Deep structural understanding of KRAS**
 - > 100 high resolution KRAS-inhibitor structures solved, G12X, wt KRAS
- **Covalency delivers KRAS G12D selectivity** and targets ON+OFF

A direct, selective, covalent inhibitor of ON + OFF KRAS G12D to deliver durable benefit for patients

Differentiated covalent MOA	Benefit
Covalent engagement of 12D	Durable pathway suppression → deeper response
Improved selectivity vs wt KRAS/NRAS/HRAS	Tolerability as a mono and combination therapy
Inhibition of ON +OFF states of 12D	Rapid and durable pathway inhibition overcoming multiple drivers of clinical resistance
Optimized bioavailability, ADME and physical properties	High POS to achieve efficacious exposures in patients

FMC-220

A potential first and best-in-class,
covalent small-molecule p53^{Y220C}
activator



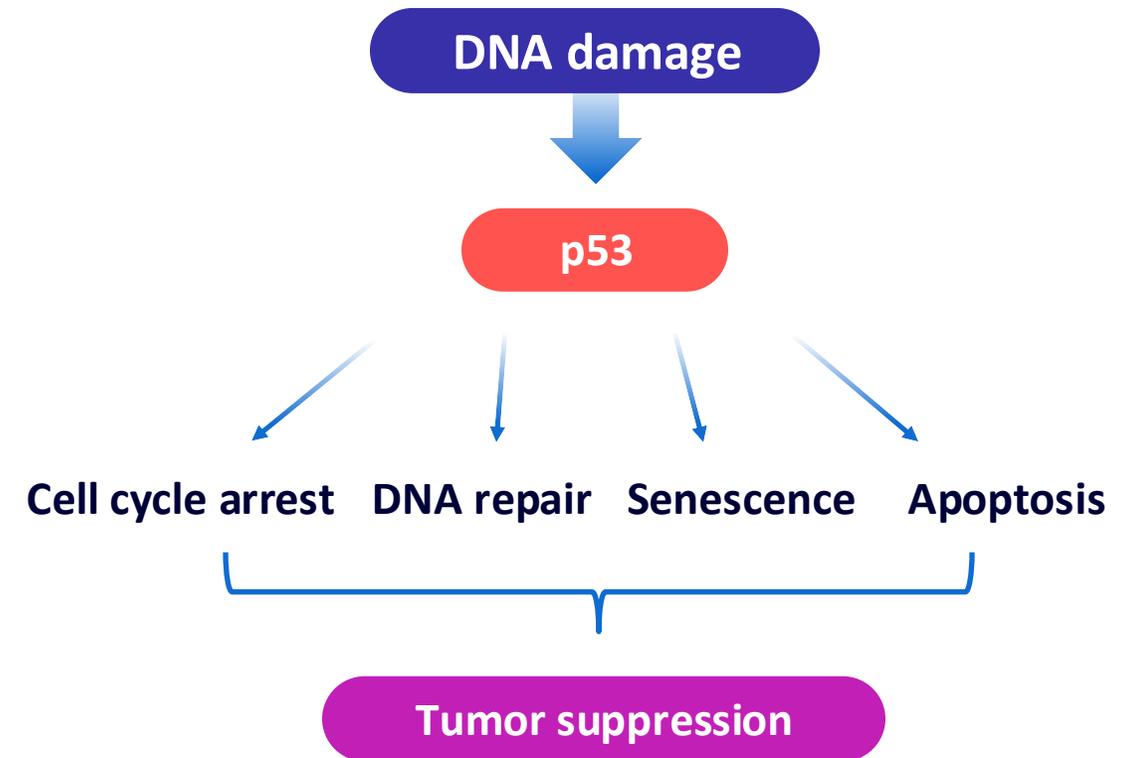
p53 Y220C is a clinically validated cancer driver

p53 is one of the most frequently mutated genes in human cancers¹

- It is inactivated by mutation in ~50% of cancers¹

p53 Y220C^{2,3}

- Key hot-spot missense mutation that destabilizes p53 leading to loss of function
- Affects ~1% of solid tumors including ovarian, breast, lung and others, ~ 125K new patients/year worldwide

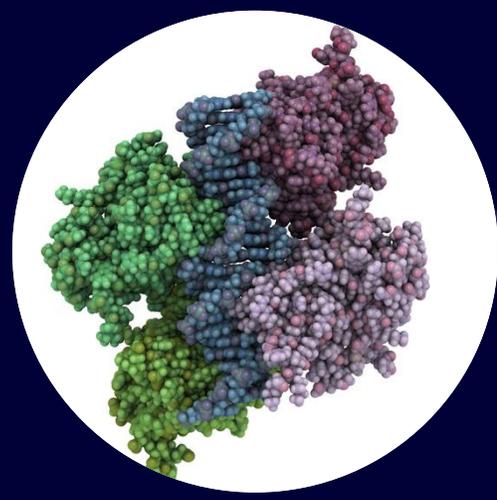


1. Wang H, et al. Signal Transduct Target Ther. 2023;8(1):92. 2. Balourdas DI, et al. Cell Death Dis. 2024;15(6):408. 3. Fallatah MMJ, et al. Trends Pharmacol Sci. 2023;44(5):274-289.

The Frontier™ Platform solved p53^{Y220C} with FMC-220, shattering the potency barrier

FMC-220

>20 years



Non-covalent activators are limited

Applied

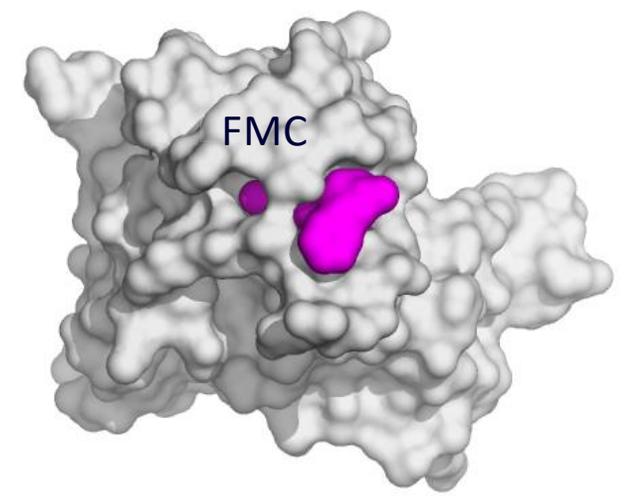
The Frontier™ Platform



Best-in-industry AI optimized chemoproteomics

FMC-220

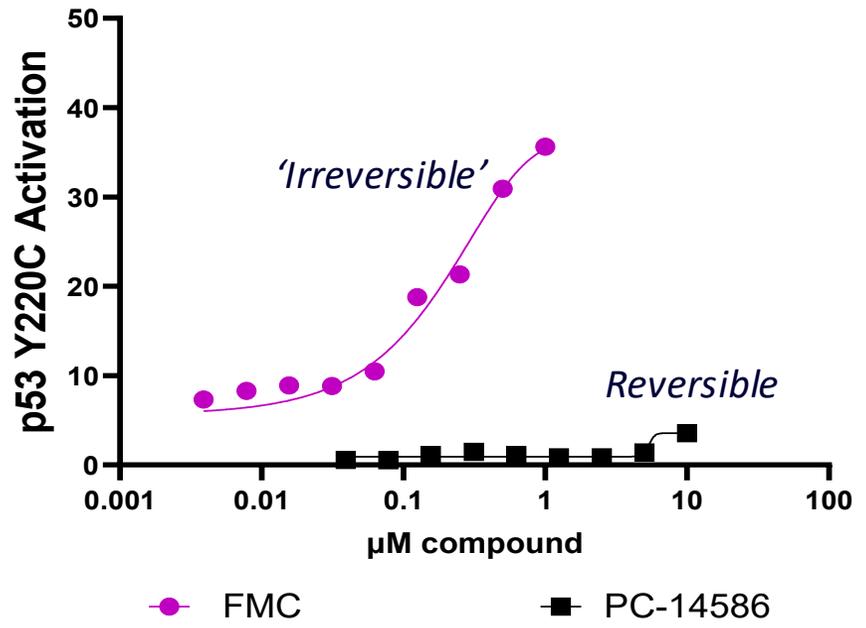
Rapidly progressed a potential best-in-class drug candidate



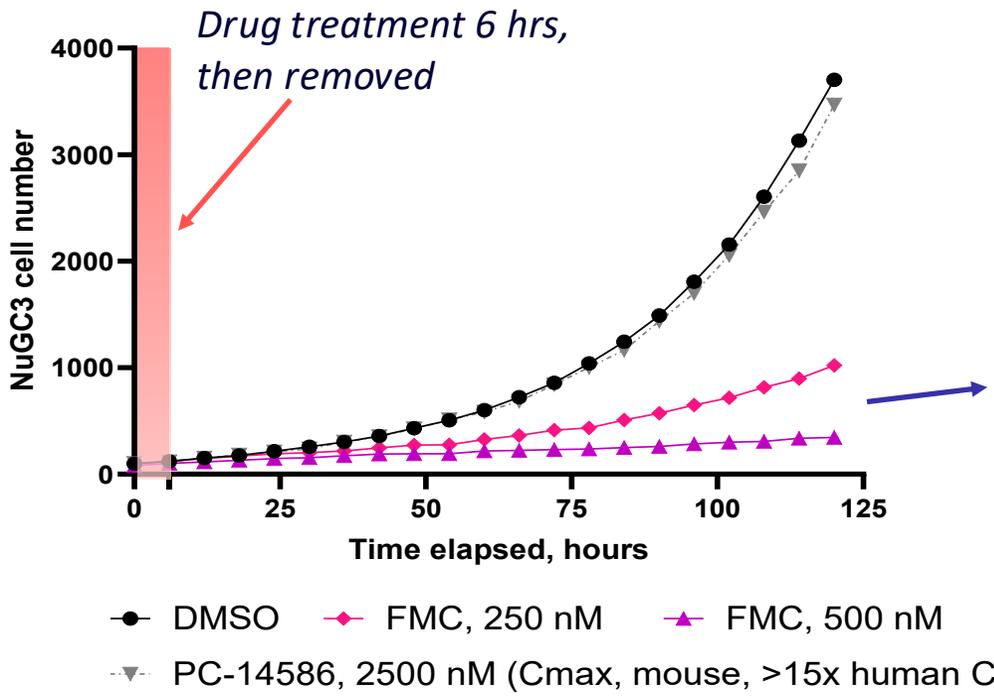
Enhanced potency,
Exquisite selectivity
Durable efficacy

Differentiated covalent mechanism of action delivers potency with durability

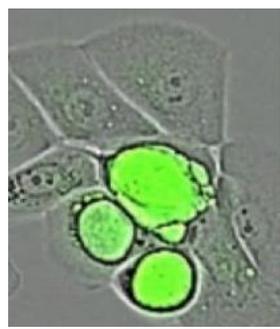
Durable p53 response after drug wash-out (18 hrs)



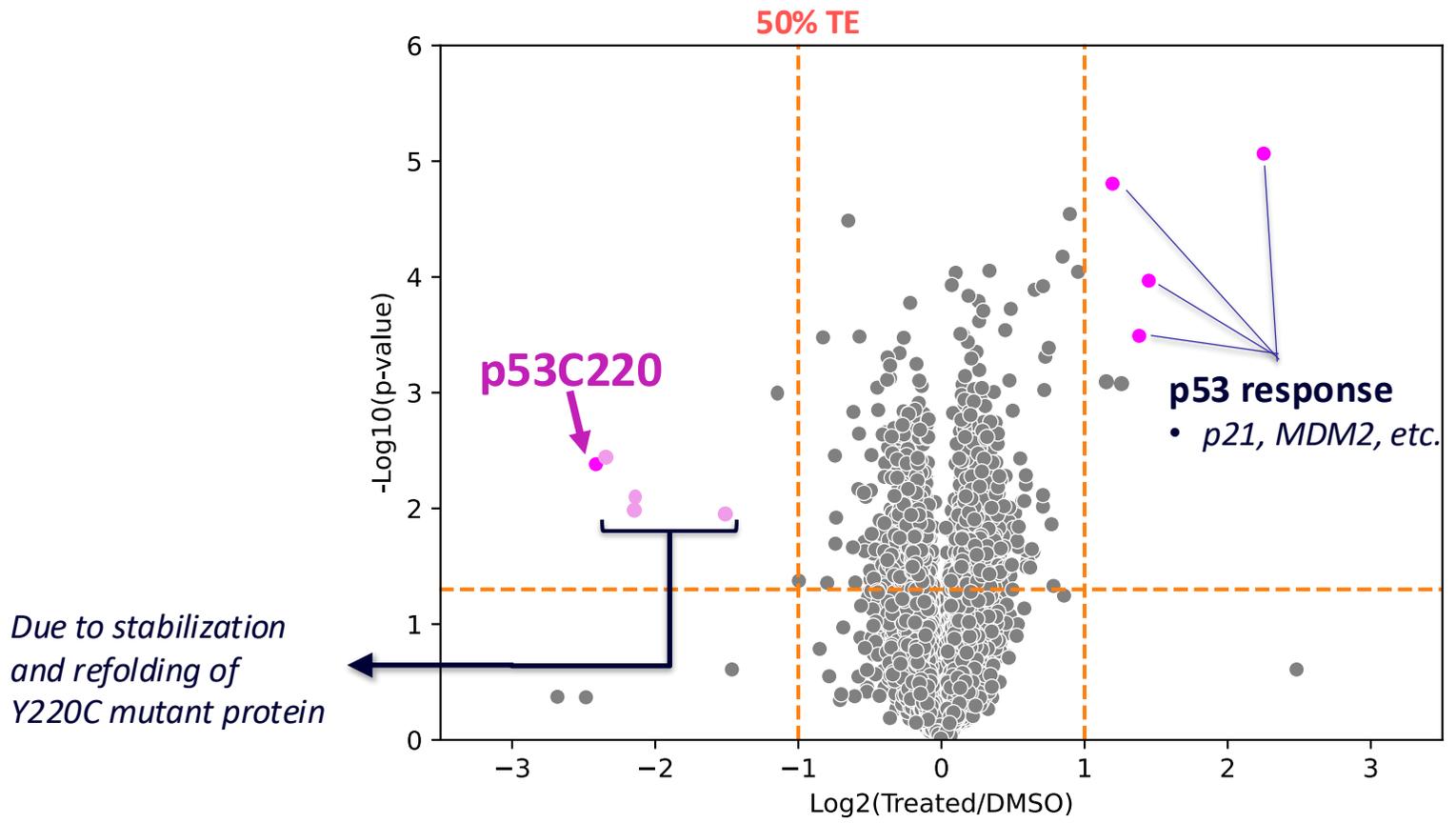
Durable anti-cancer effect that persists for 5 days and beyond



'Irreversible' anti-cancer phenotype, senescence and death



FMC-220 is exquisitely selective for p53 Y220C in cells

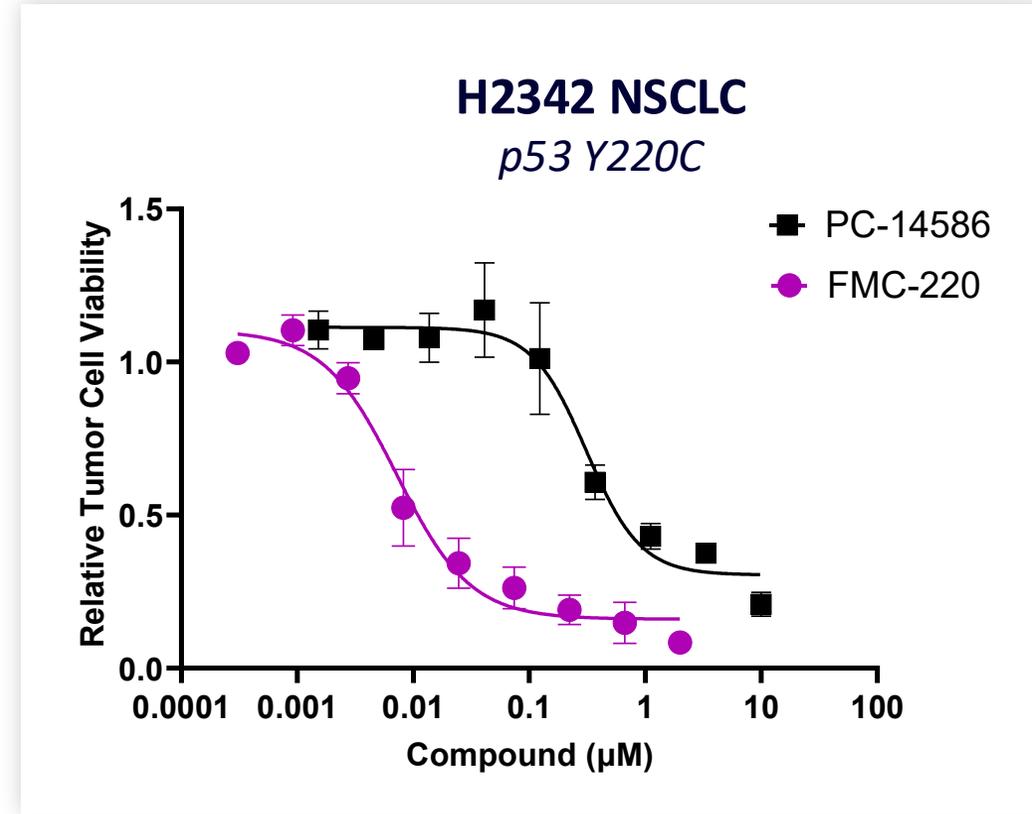
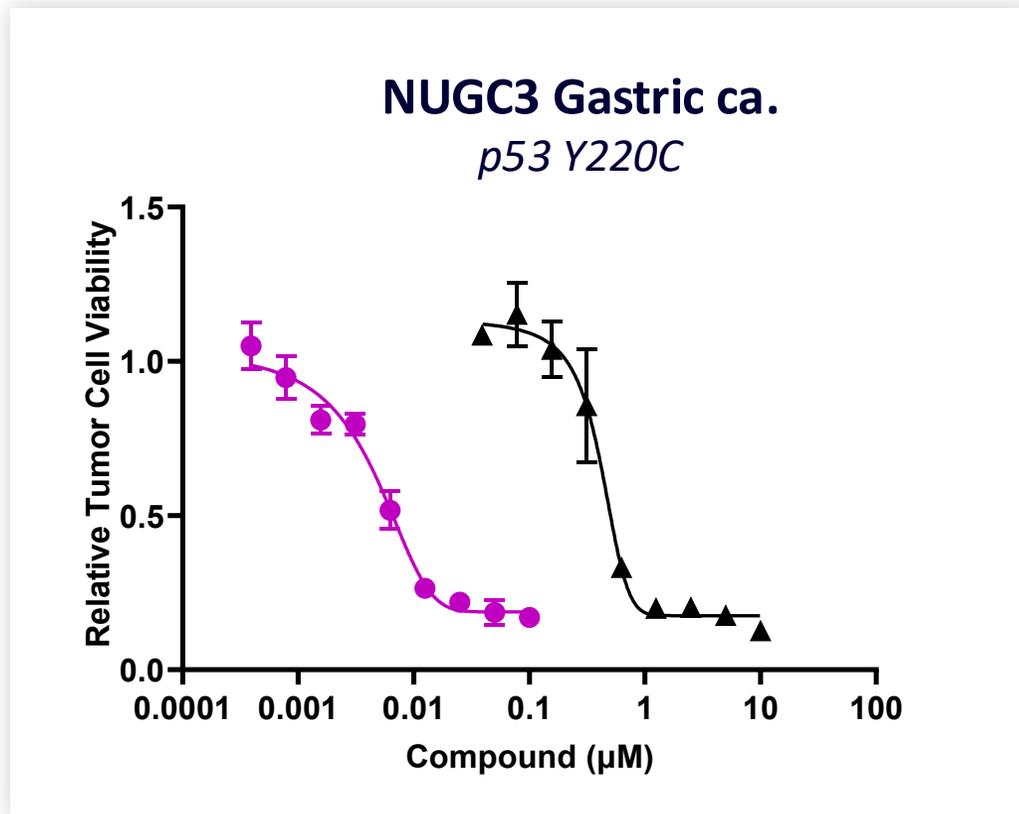


Cellular target engagement and selectivity was assessed using competitive isoTOP-ABPP. 4 hr treatment with 1 μM FMC-220, NUGC3 cells

Unprecedented inhibition of tumor cell proliferation

Potent induction of p53 response translates into superior anti-tumor activity across p53 Y220C mutant cell lines

FMC-220

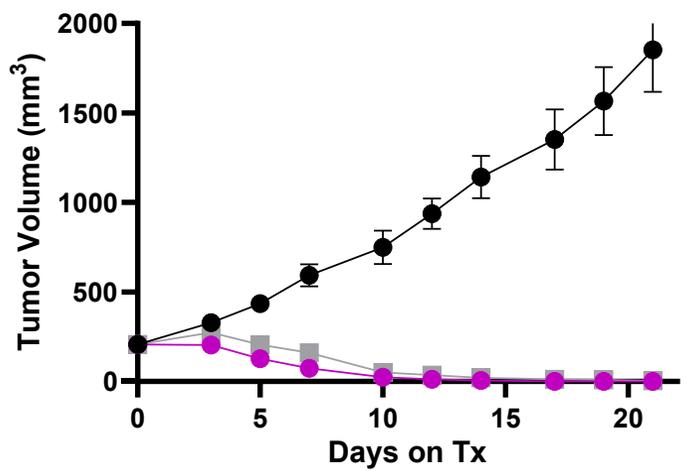


50-100X increased activity relative to PC-14586

FMC-220 delivers tumor regression across PDX models

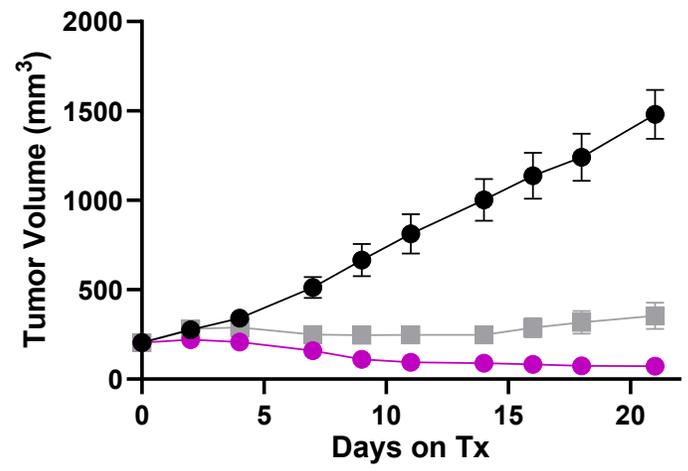
FMC-220

LU5269, SCLC
TP53Y220C, ATR, FLT3



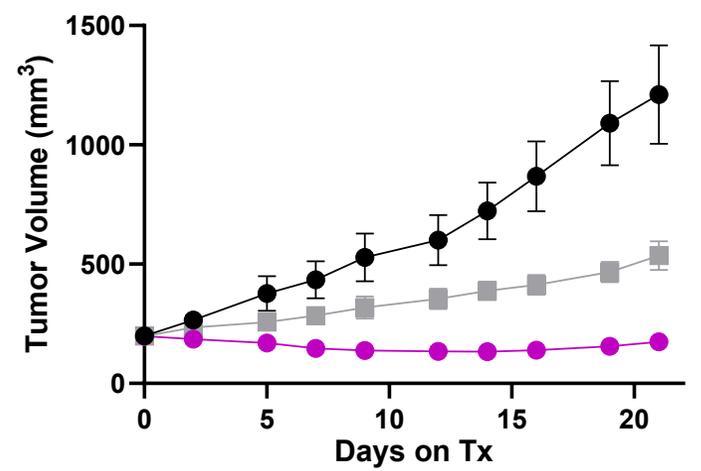
● Vehicle
● FMC-220, 60 mg/kg → **5/5 CR**
■ PC-14586, 100 mg/kg **VS 1/4 CR**

ES2411, Esophageal
TP53Y220C, APC, KEAP1, MYCamp



● Vehicle
● FMC-220, 100 mg/kg
■ PC-14586, 100 mg/kg

HN3537, HNSCC
TP53Y220C, SMARCA4, EP300, TSC2



● Vehicle
● FMC-220, 60 mg/kg
■ PC-14586, 100 mg/kg

FMC-220 delivers tumor regression regardless of histology or co-mutations

FMC-220 Delivers CRs in rezatapopt (PC-14586) relapsed PDX tumors

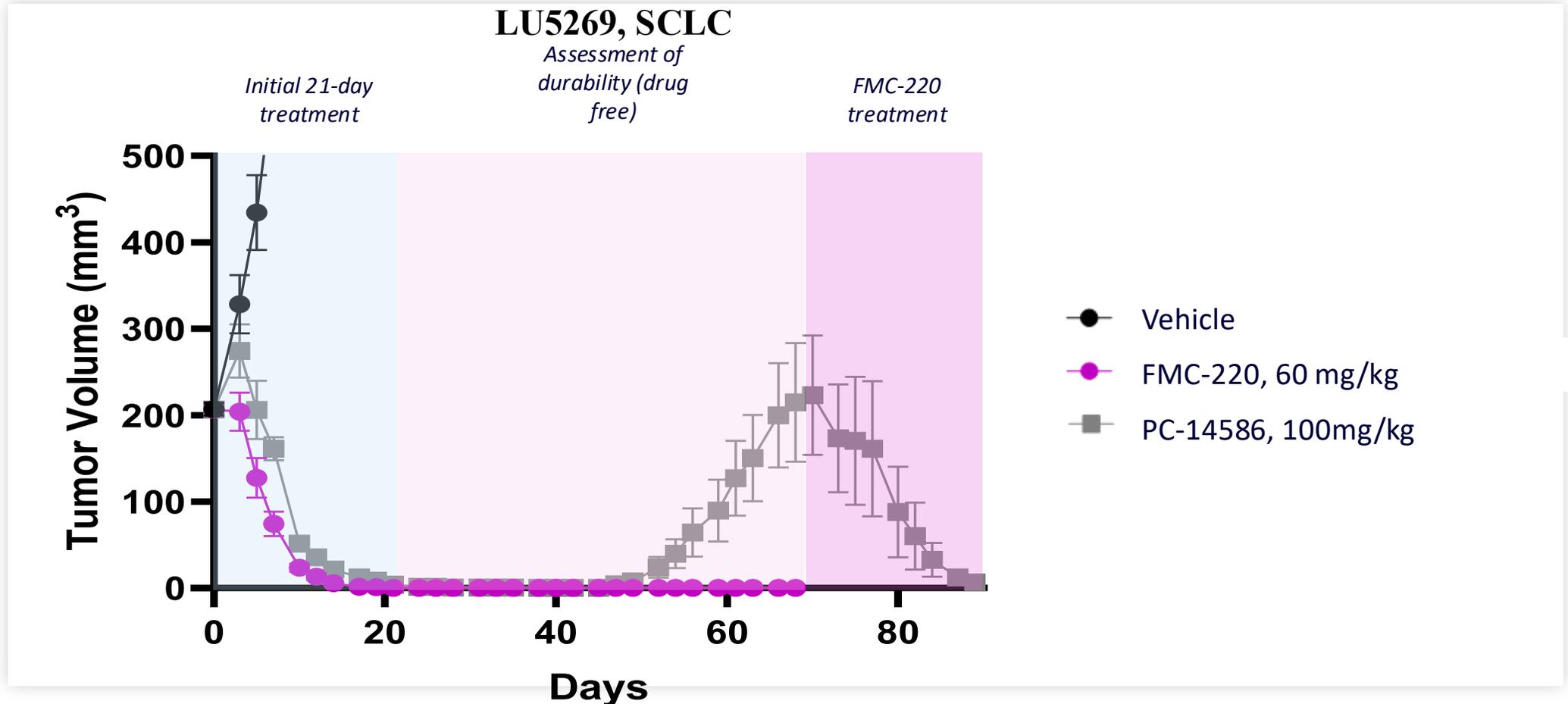


Figure 6: At the end of treatment (day 21), complete regression was achieved in all 5 mice in the FMC-220 treatment group, while only 1 out of 4 mice in the rezatapopt group was tumor free. Mice were monitored for tumor regrowth. All 5 mice in the FMC-220 group remained tumor free while the tumors in the rezatapopt group regrew. FMC-220 was able to completely inhibit the growth of relapsed tumors.

FMC-220 Summary

The Frontier Platform™ has enabled discovery of FMC-220, a first in class covalent activator of p53 Y220C

Covalent activation of p53 Y220C provides a positively differentiated mechanism of action that delivers:

- ~100-fold improvements in potency
- Durable pharmacology driving tumor cell senescence and death
- Activity across tumor histology's and \ in the presence of mutant KRAS
- Durable tumor regression
- **IND in 4Q 2025**

Duration drives a meaningful market opportunity

The FrontierTM Platform



Inhibitors

**Novel E3
Engagers**

**Glue
Discovery**

**Stabilizers/
Activators**

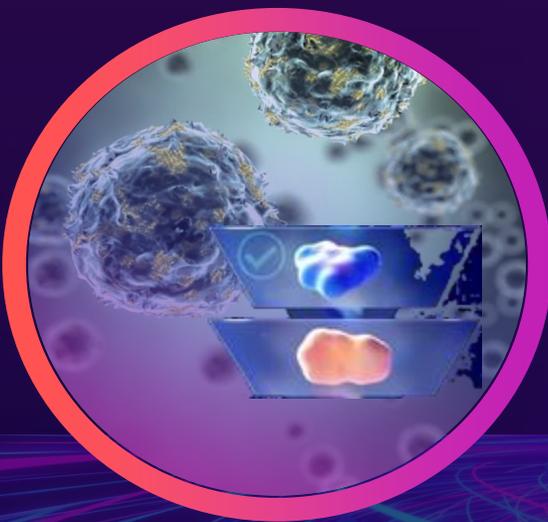
***Next generation of covalent based drug discovery
enabled by chemoproteomics and AI***

The Frontier™ Platform takes covalent drug discovery to the next level through AI enablement



AI optimized covalent library

Best in industry covalent library built in house



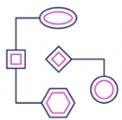
Mass spec screening in *living sets*

- >8,000 targets with library starting points
- Backbone of Druggability Atlas
- Largest covalent data set, enabling Covalent AI™



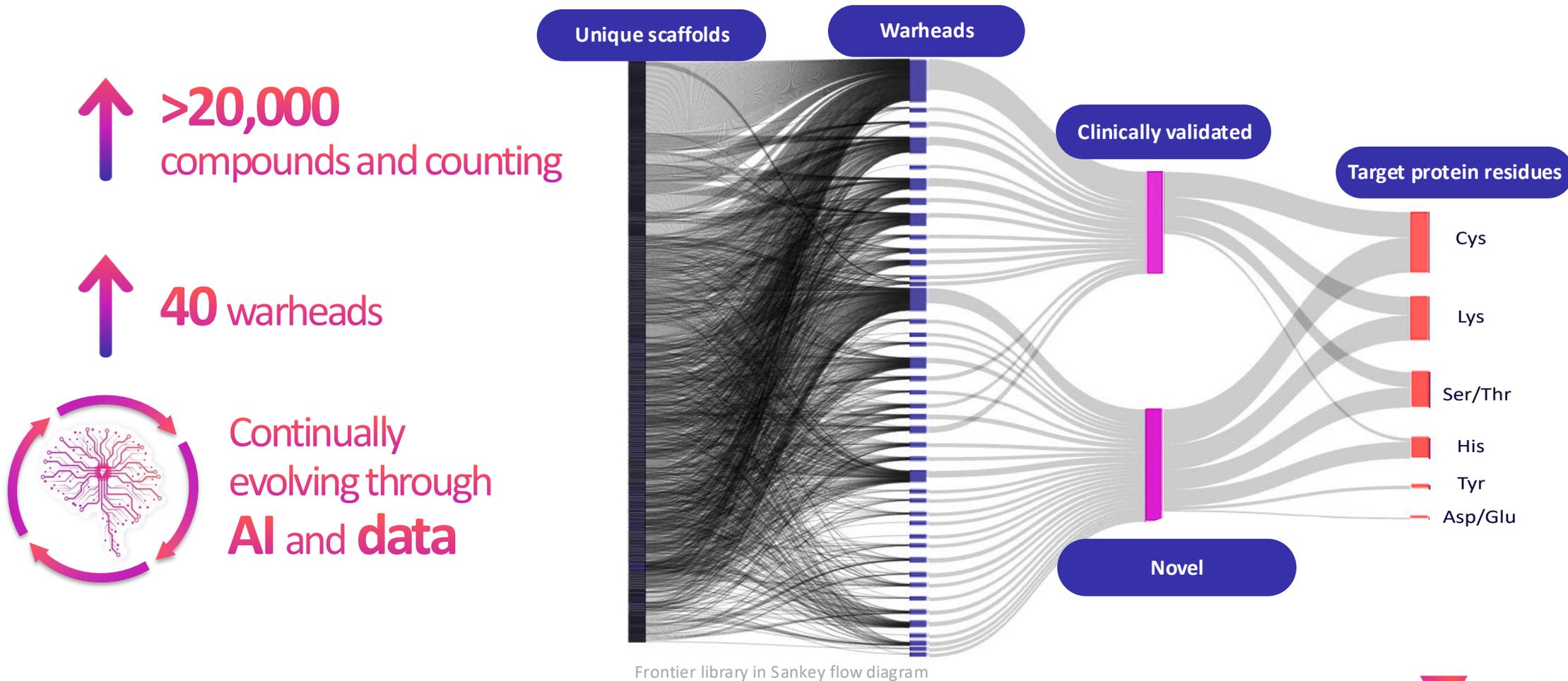
Covalent AI™ enabled acceleration

18-24 months to clinical candidate



Covalent
Library

In-house built, highly optimized covalent library provides quality small-molecules for undruggable targets

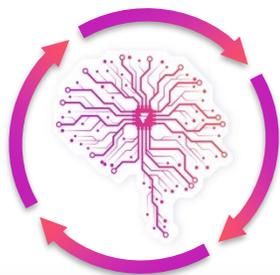


Frontier library in Sankey flow diagram



Covalent
Library

Driven by AI algorithms, Frontier's in-house library expands access into productive chemical space

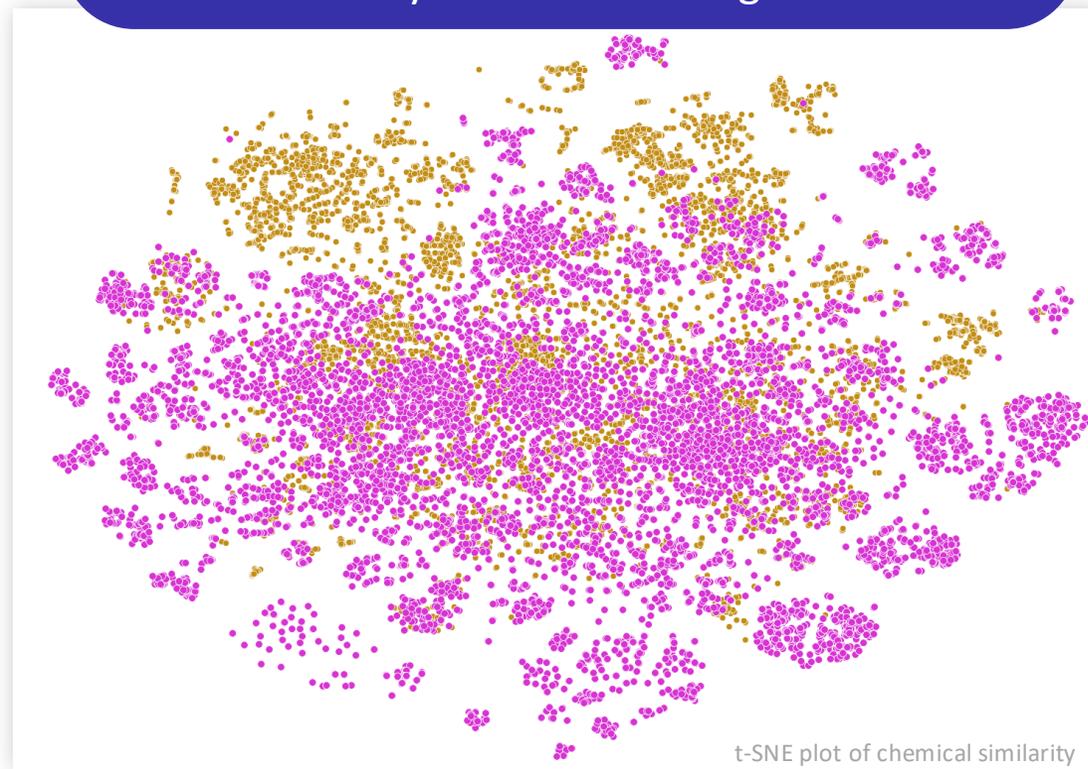


Continually
evolving through
AI and **data**

OUR IN-HOUSE BUILT LIBRARY:

- 1 Goes well beyond traditional libraries to expand access
- 2 Covers productive known chemical space
- 3 Avoids unattractive chemical space

Comparison Frontier library vs. commercial gold standard

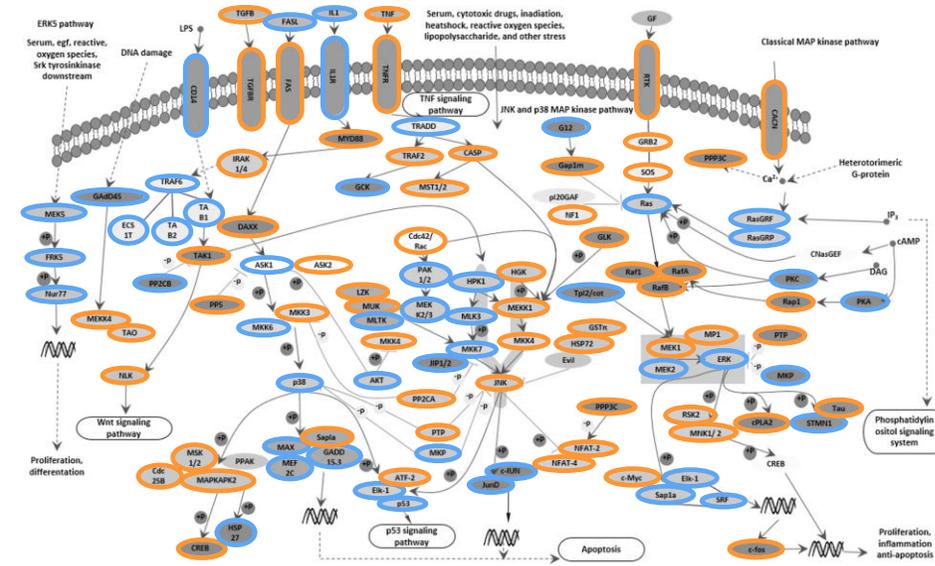


Commercial gold standard

Druggability Atlas™ in action: unlocking key disease pathways

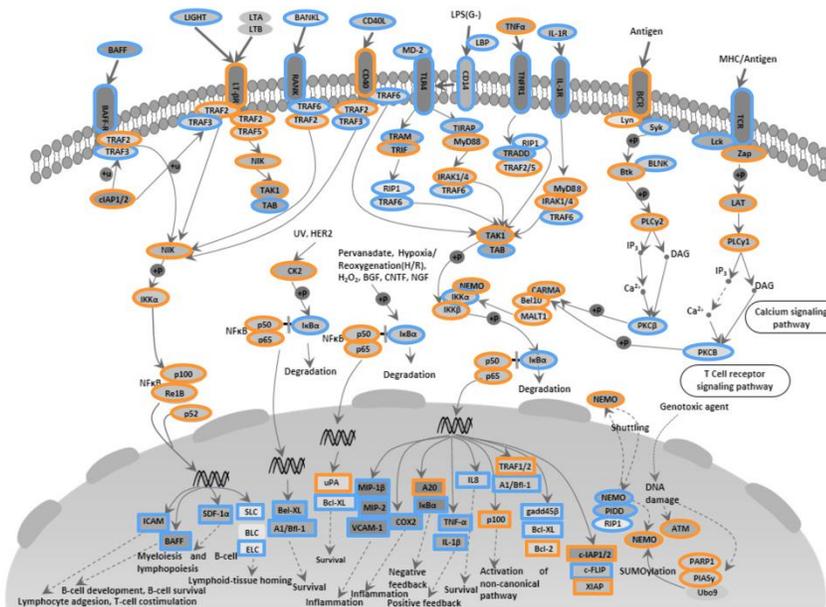
Small molecule starting points for targets in all pathways and cell compartments

MAPK pathway



○ Binding Site (96%)
○ Library Hit (62%)

NF - κB Pathway

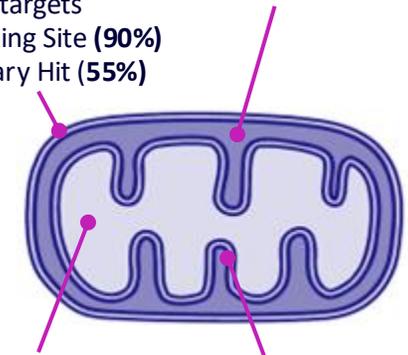


○ Binding Site (89%)
○ Library Hit (58%)

Mitochondria

Intermembrane Space
 49 Targets
 Binding Site (96%)
 Library Hit (73%)

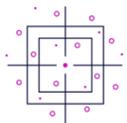
Outer Membrane
 112 targets
 Binding Site (90%)
 Library Hit (55%)



Matrix
 522 Targets
 Binding Site (95%)
 Library Hit (69%)

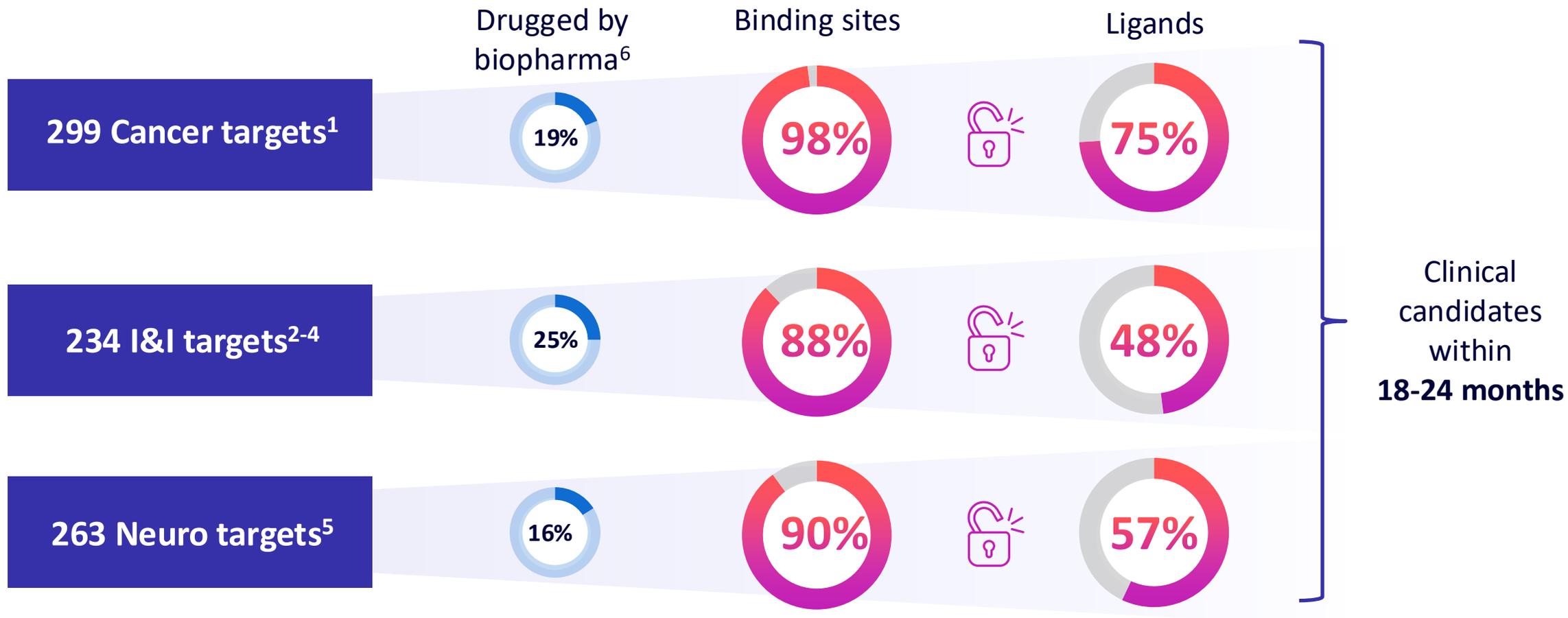
Inner Membrane
 356 Targets
 Binding Site (85%)
 Library Hit (38%)

Library hits are actionable chemical starting points
 Pathway images from <https://www.cusabio.com/pathway.html>



The Frontier™ Platform unlocks access to high-value targets across disease areas

Druggability Atlas™



¹ Bailey et al. 2018 *Cell*

² Kolkhir et al. 2023 *Nature Reviews Drug Discovery*

³ Fang et al. 2022 *Nucleic Acids Research*

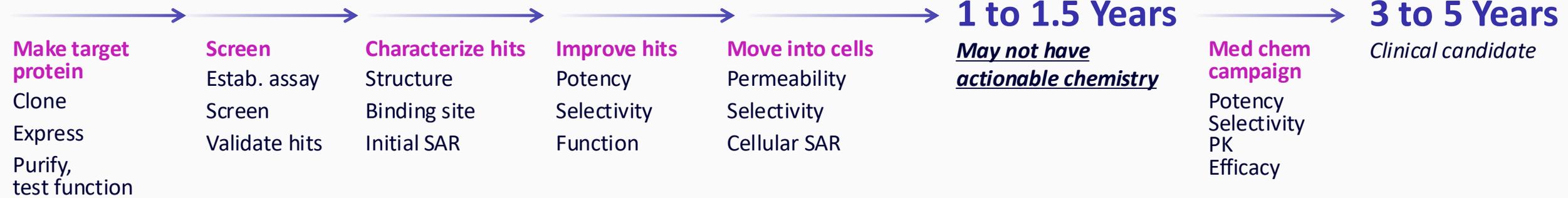
⁴ Grissa et al. 2022 *Diseases 2.0: Database*

⁵ Annotation by <https://www.uniprot.org/>

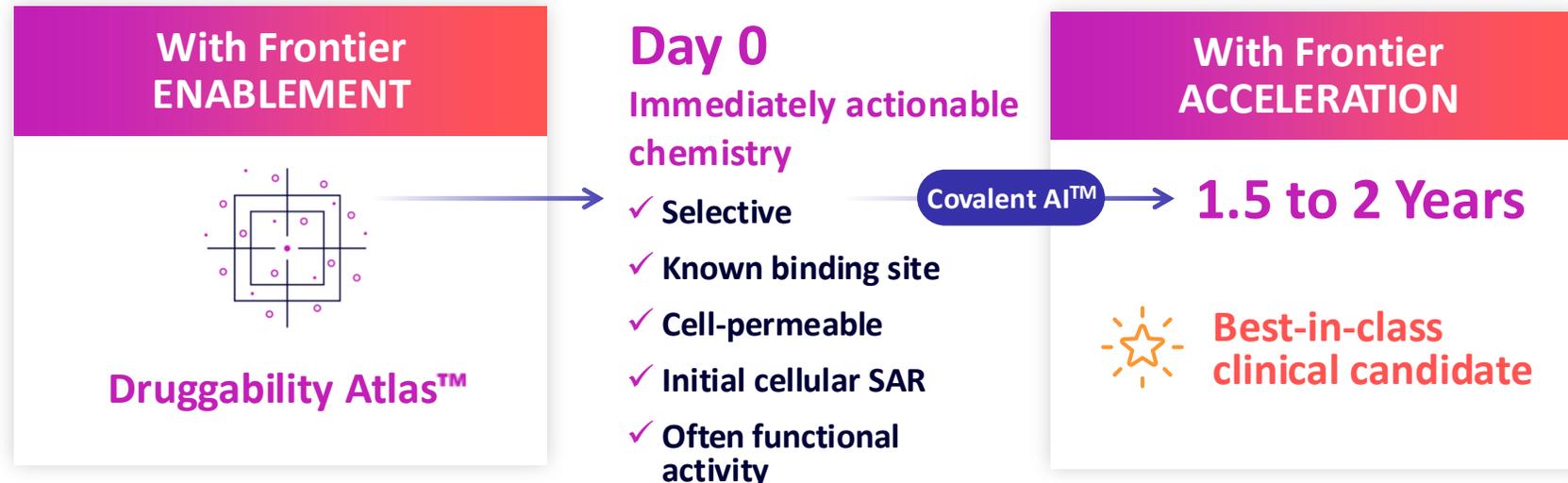
⁶ <https://www.ebi.ac.uk/chembl/>

Frontier technology fast forwards drug discovery

Conventional drug discovery



Frontier's time savings through tech



FrontierMeds.com