FRONTIER MEDICINES

Unlocking the Proteome to Deliver Next Generation Covalent Medicines

FRONTIER 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**
Pi3Kα-RAS breaker – IND 2H 2026	**FMC-242**
KRAS G12D ON+OFF – DC 1H 2026	**G12D**
Oncology & I&I discovery programs	

Value Creating Partnership with AbbVie

For Defined Undruggable Targets
– Since 2020

Backed by a strong investor syndicate

ARROWMARK PARTNERS · PCSC | Bio · DEEP TRACK CAPITAL · DEERFIELD Advancing Healthcare · DRIEHAUS CAPITAL MANAGEMENT · DROIA oncology ventures · Galápagos · MPM · RACAPITAL · SPHERA ASPIRE HIGHER · WOODLINE PARTNERS

Applying our collective experience to develop breakthrough medicines

Chris Varma, Ph.D.
Co-founder, Chair, and CEO

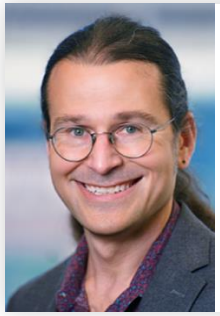
- **Co-founder & CEO:** Blueprint Medicines (acquired by Sanofi)
- **Co-founder:** Warp Drive Bio (acquired by Revolution Medicines)
- **Investor:** Flagship, Third Rock, MPM

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

Johannes Hermann, Ph.D.
Chief Technology Officer

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



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**

Gerardo Ubaghs
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**

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

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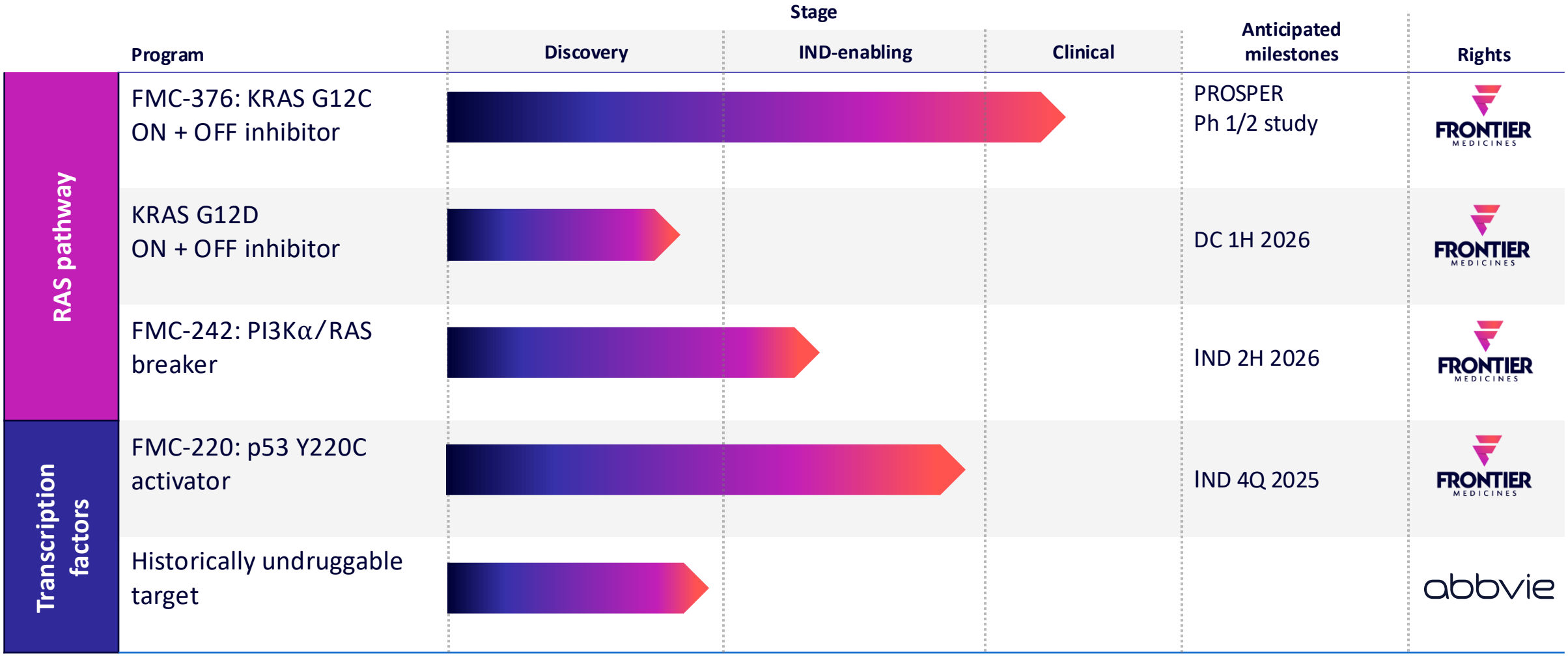
Clinical-stage precision pipeline: harnessing the Frontier™ Platform to deliver best-in-class covalent medicines



FMC-376

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

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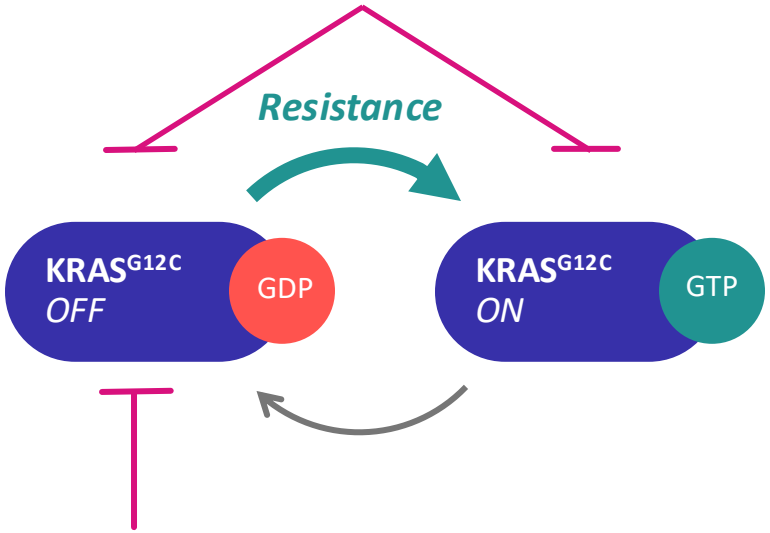
Blocking both ON and OFF KRAS G12C overcomes resistance

FMC-376



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 divarasib/sotorasib/ adagrasib resistant models

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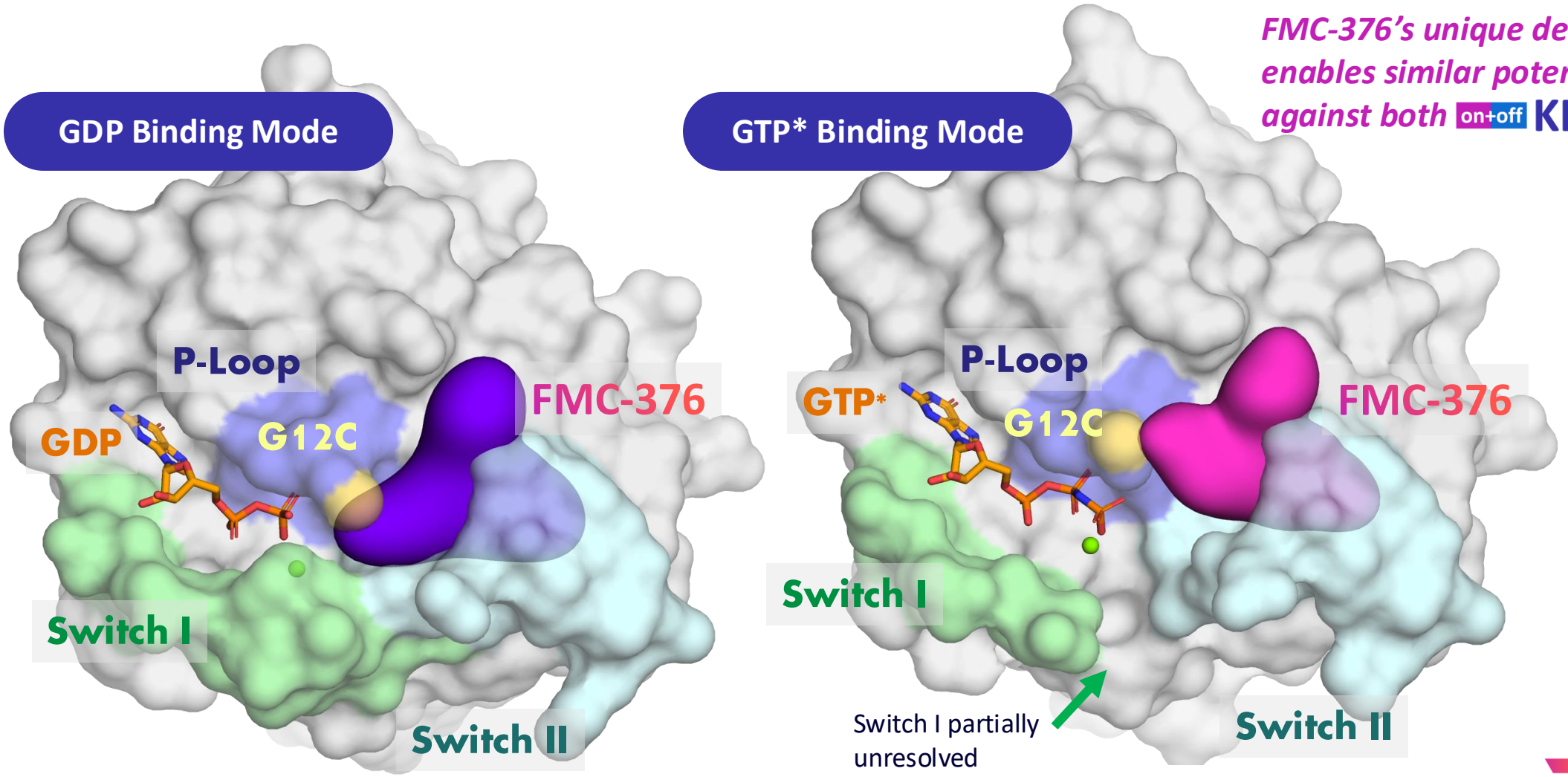
The Frontier™ Platform enabled FMC-376: the first small molecule adopting two low energy conformations

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



*GMP-PNP, G12C

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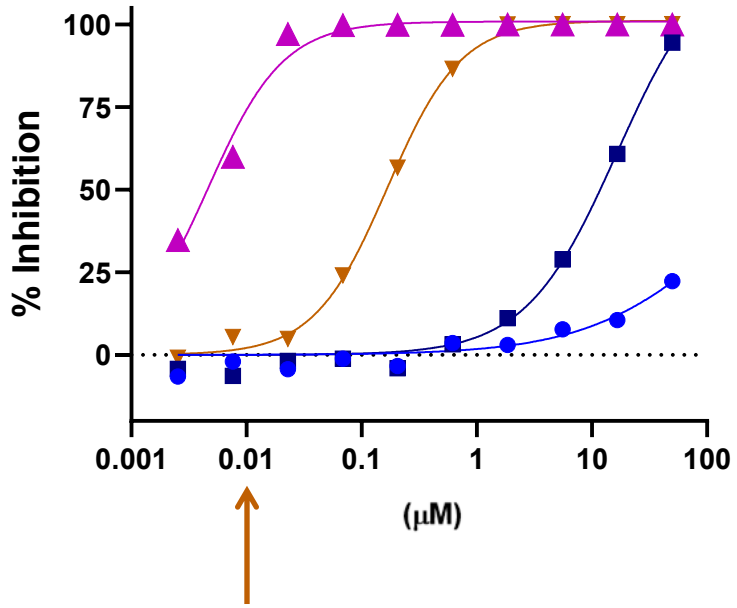
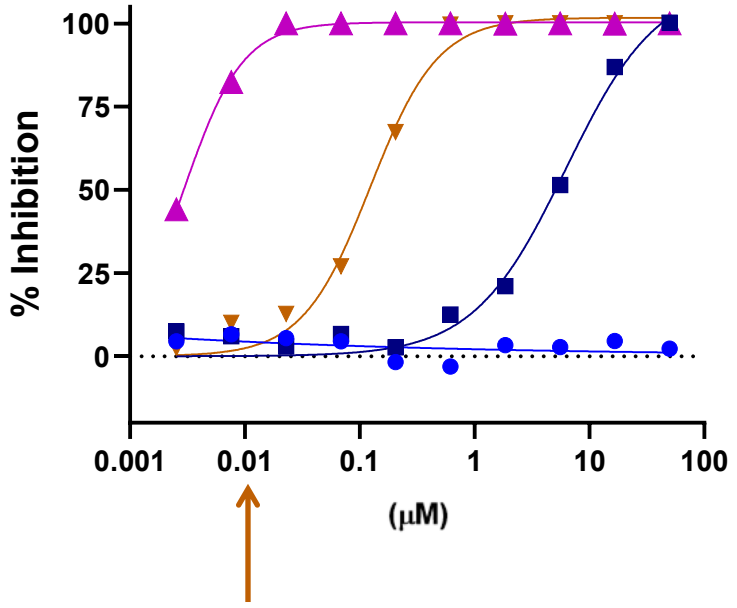
FMC-376 potently disrupts key effector protein interactions within our anticipated efficacious clinical dose range

RAF1 RBD binding



Maximum clinical exposure to divarasib

PI3Kα RBD binding

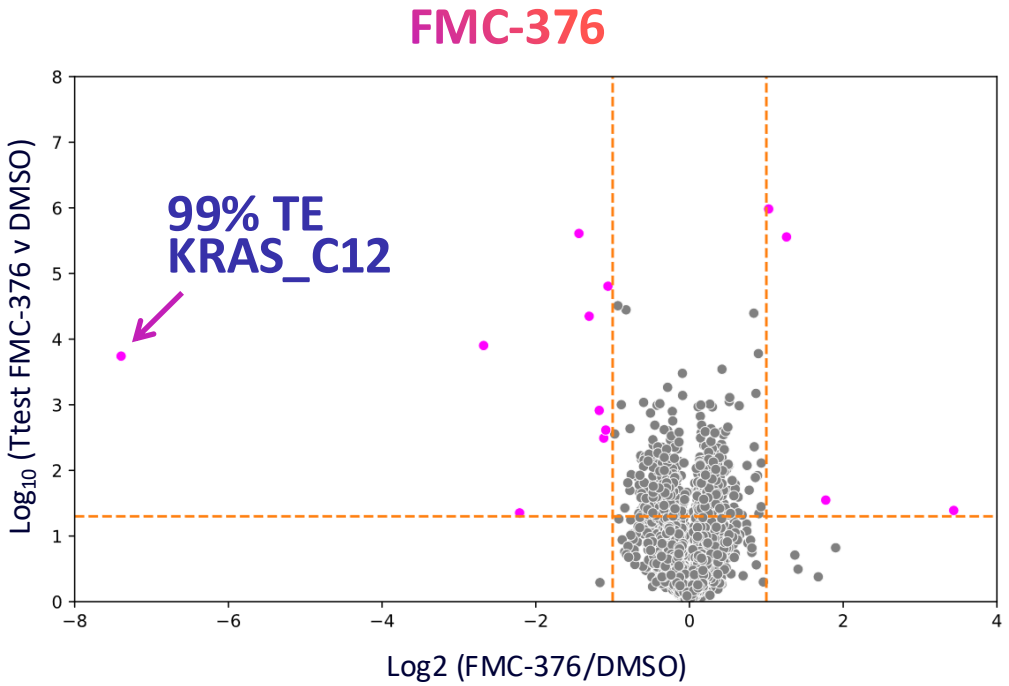


Maximum clinical exposure to divarasib

FMC-376
Adagrasib
Sotorasib
Divarasib

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

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

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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

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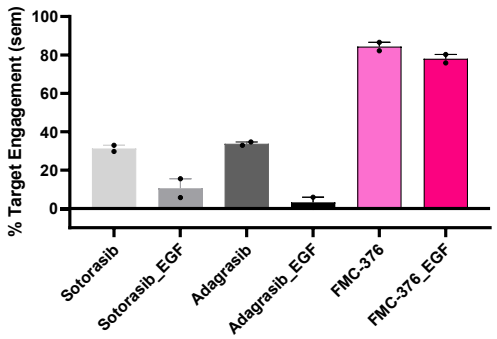
The Frontier™ Platform

FMC-376

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

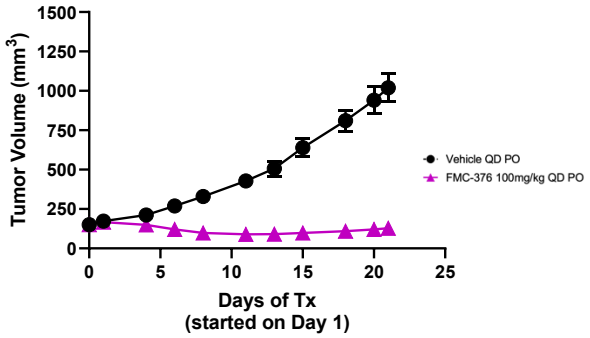
1. Adaptive resistance

FMC-376 target engagement -/+ EGF stimulation[1]

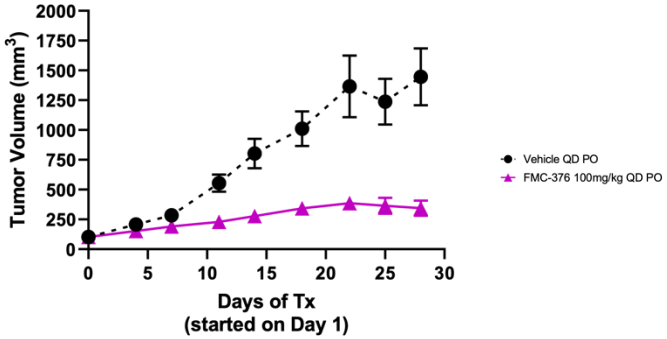


2. RTK amplification/fusions

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

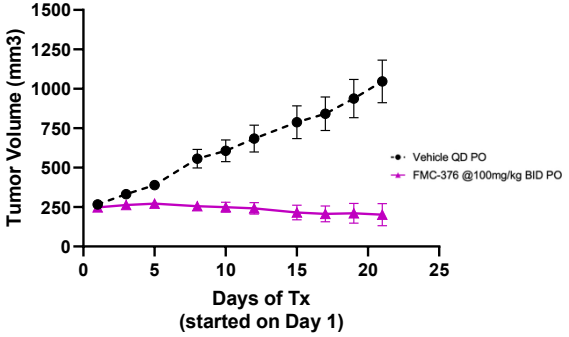


NSCLC PDX
KRAS^{G12C}, MET, BRCA1, NOTCH, MYC



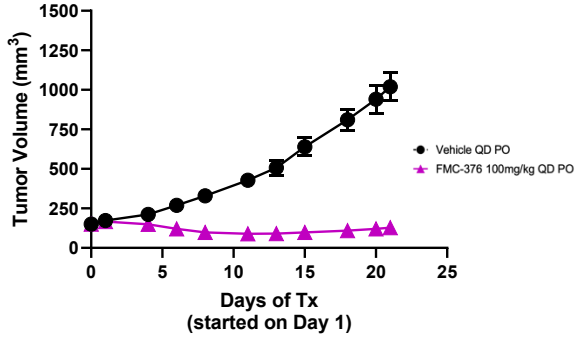
3. KRAS^{G12C} amplification

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



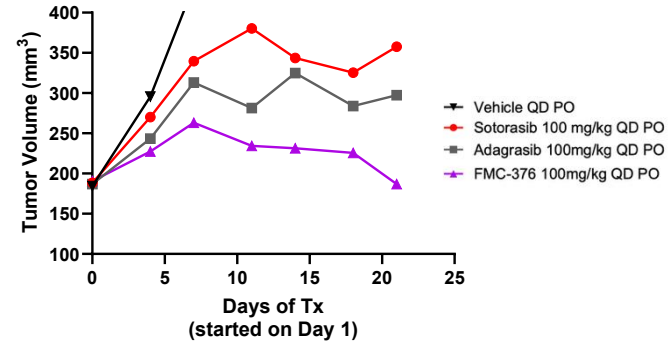
4. p53 mutation/deletion

NSCLC PDX
KRAS^{G12C}, p53



5. Innate resistance

NSCLC PDX
KRAS^{G12C}, KEAP1



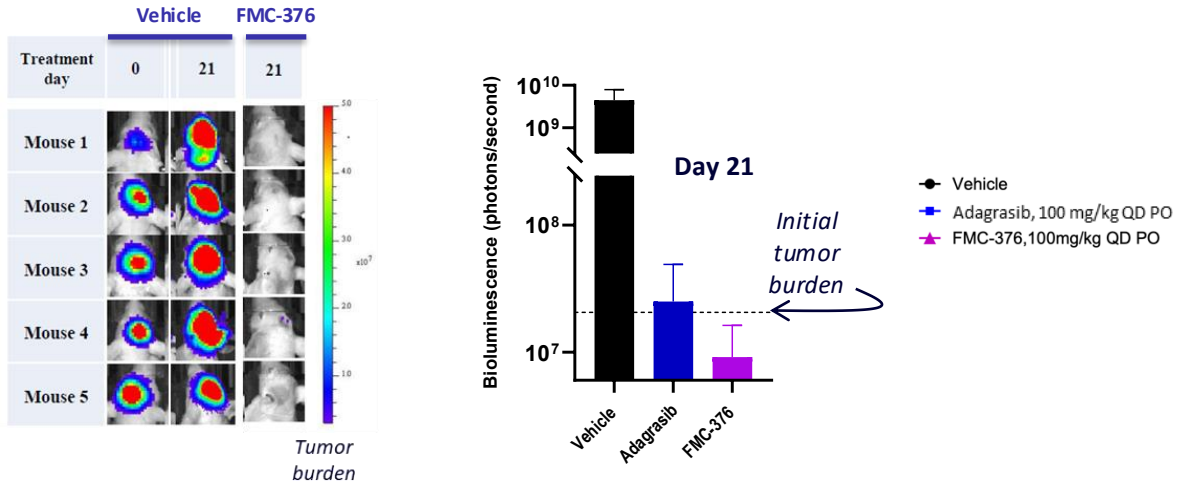
AACR 2023 AACR 2024

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

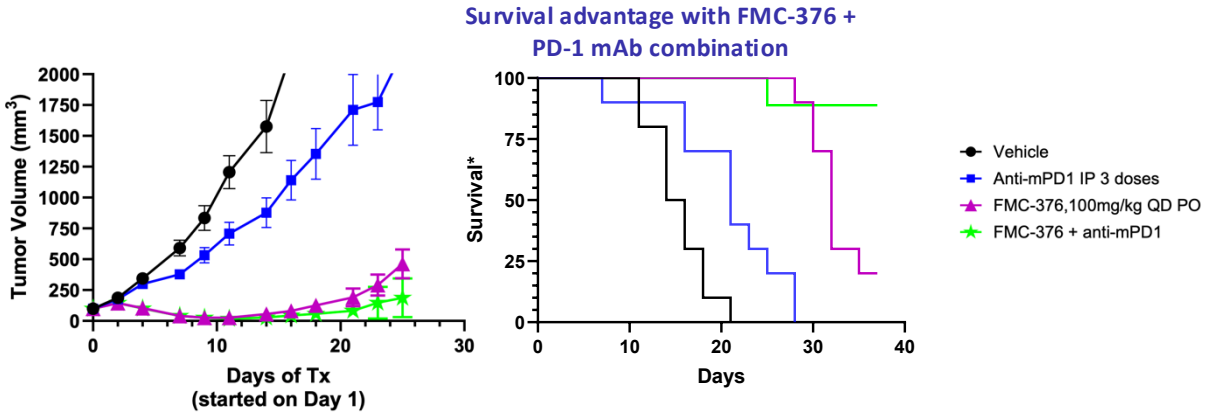
The FMC-376 difference:

- 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

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FMC-242

Exquisitely selective, allosteric inhibitor of PI3Kα-RAS PPI that spares normal enzymatic activity

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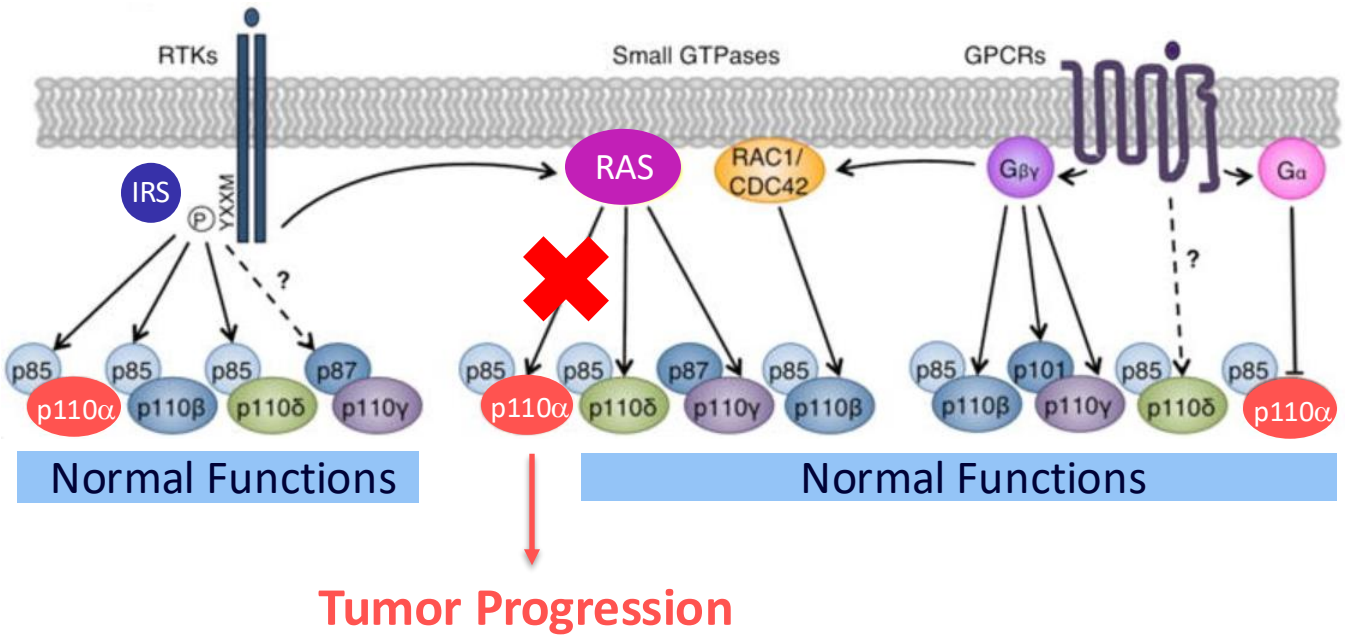
FMC-242 has the potential to become a foundational therapy targeting drug resistance in combination

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

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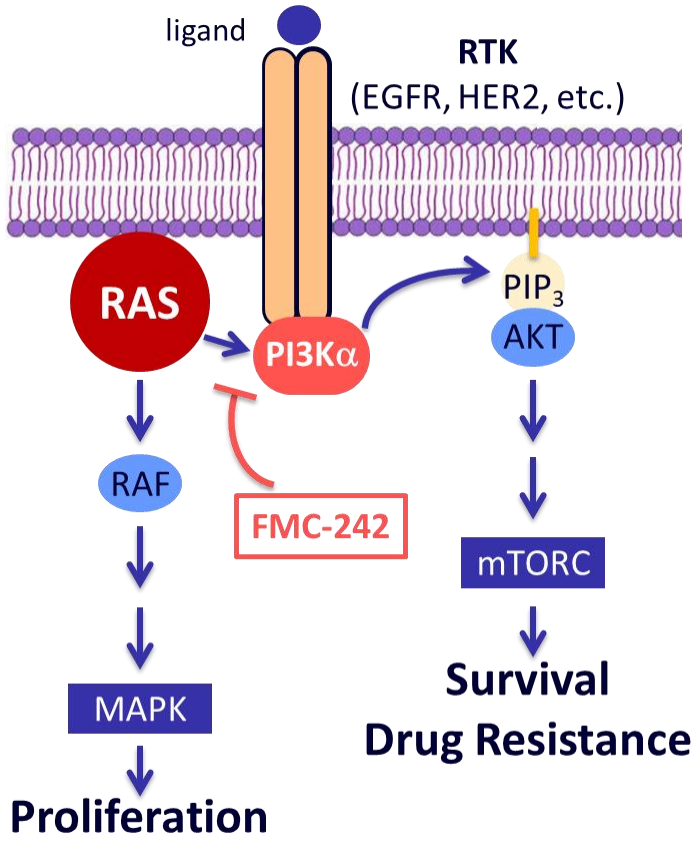
Selective inhibition of PI3Kα –RAS interaction provides broad mono- and combination therapeutic opportunities

PI3Kα 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

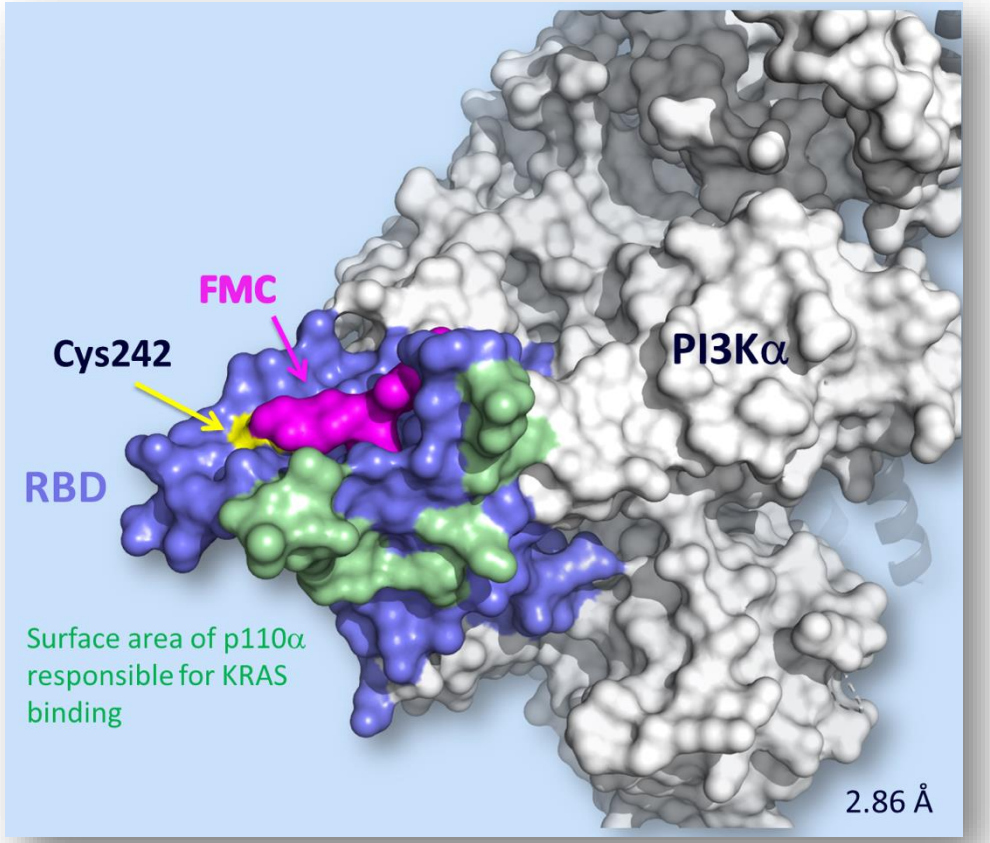
FMC-242 delivers selective allosteric inhibition of RAS binding

Cys242 is **covalently ligandable**

Cys242 provides **specificity within the PI3K family**

PI3Kα: SEQLKL**C**VLEYQGK
PI3Kβ: - - - - KEDEVSPYD
PI3Kδ: - - - - QPLVEQPED
PI3Kγ: SLMDIPESQSEQD

FMC-242 binding **disrupts RAS binding interface**



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All key complexes of PI3Kα / RAS are effectively inhibited

Protein-Protein Interaction can be broken across disease-relevant PI3Kα and RAS mutations

		A	B	C	D
		wt PI3Kα	**PI3Kα (H1047R)**	**PI3Kα (E542K)**	**PI3Kα (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

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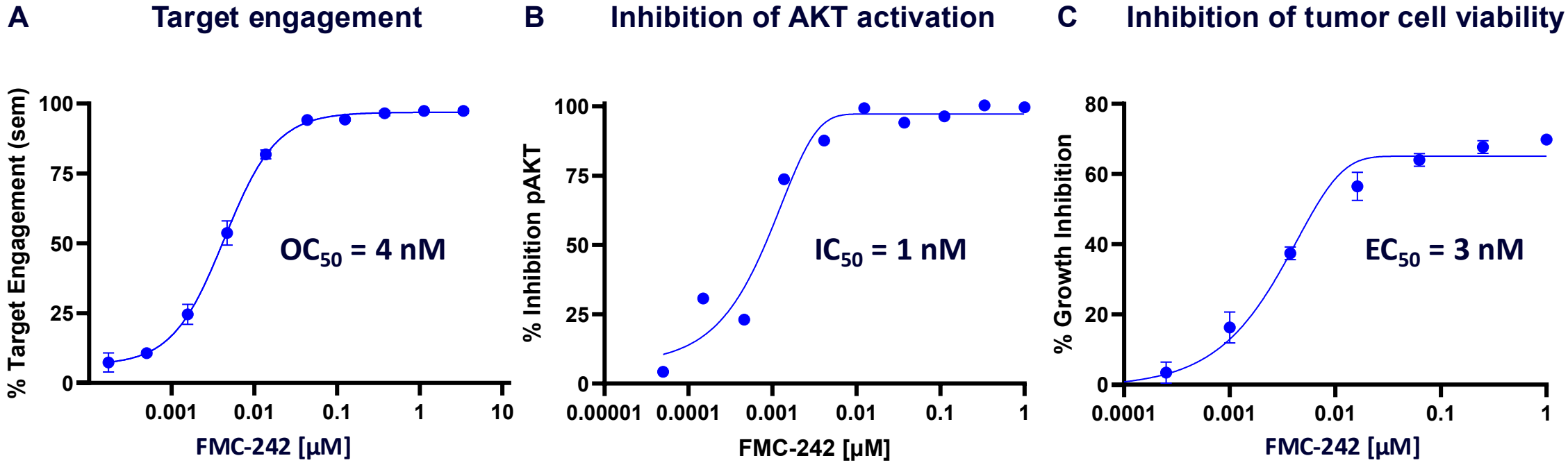
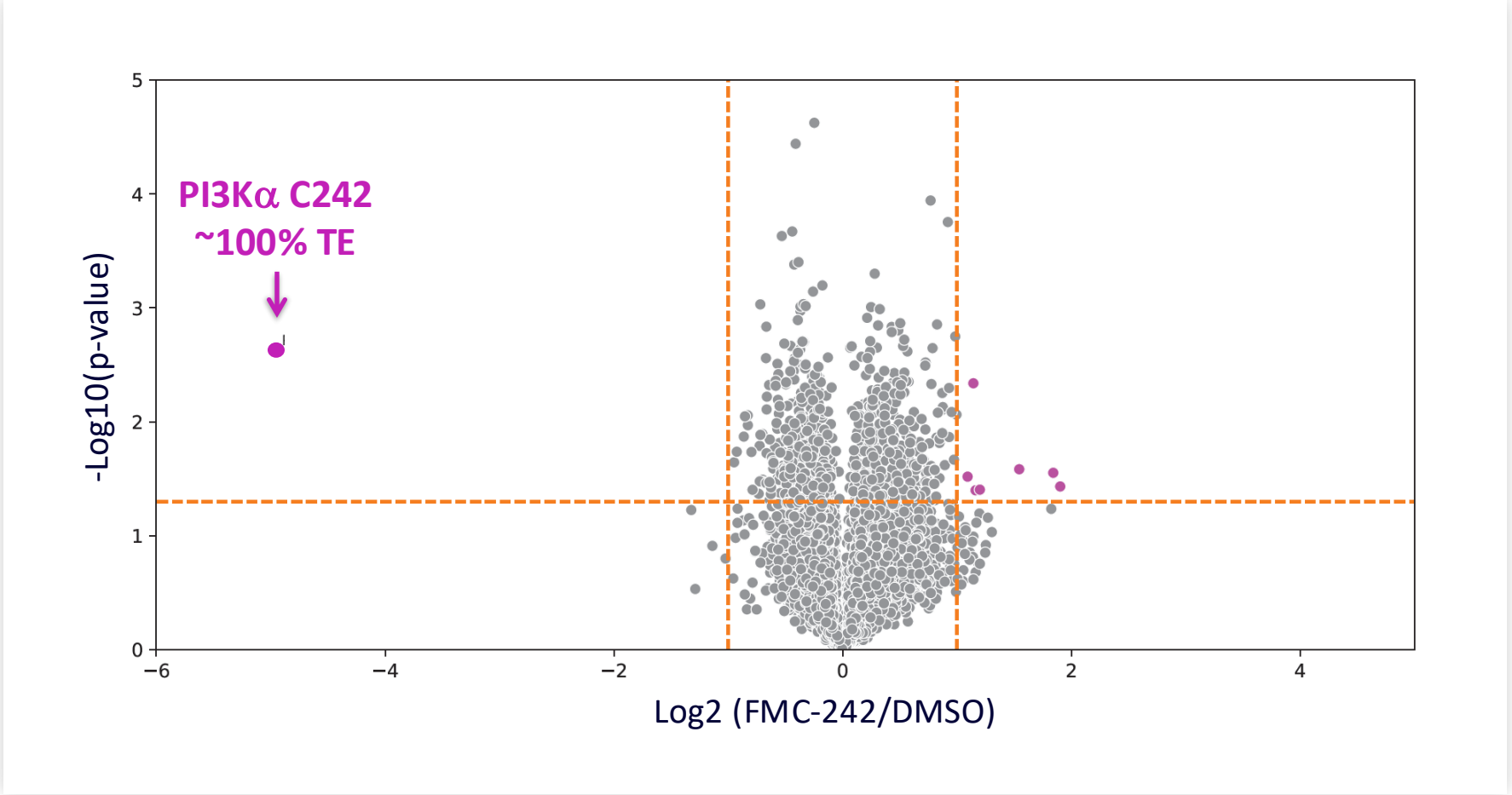
Covalent engagement of C242 inhibits AKT activation and tumor cell viability



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

FMC-242 achieves high selectivity across the proteome and complete target engagement of PI3Kα



Volcano plot depicting selectivity of FMC-242 after a 2 μM (465X the OC_{50}) 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)

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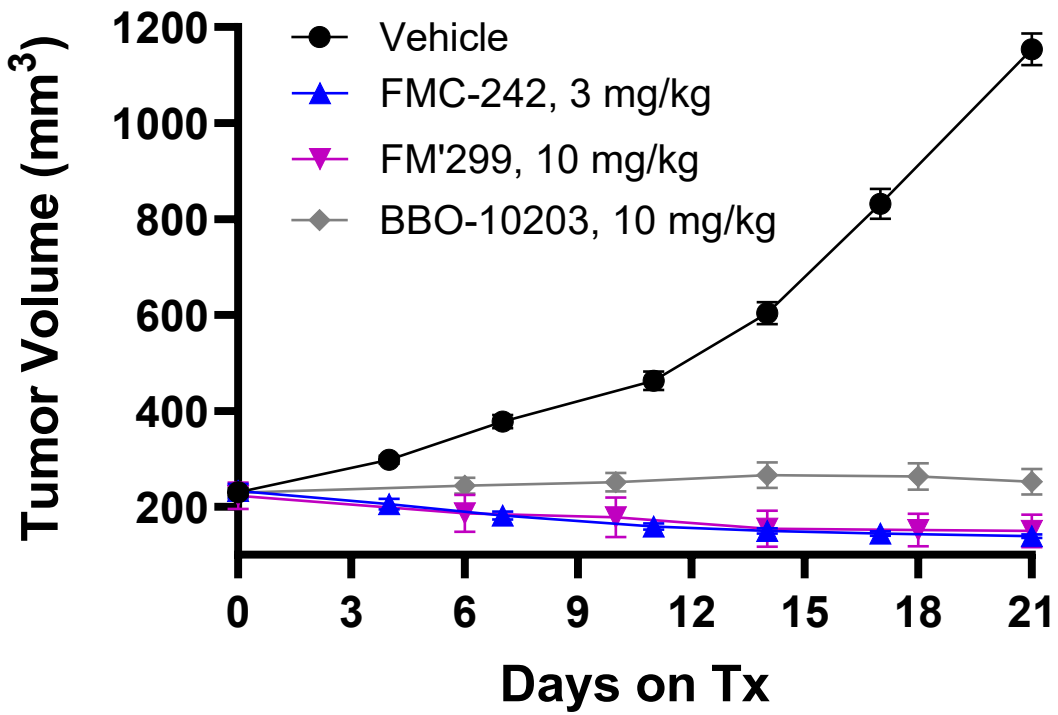
FMC-242 shows differentiated efficacy driving tumor regression at much lower dose

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



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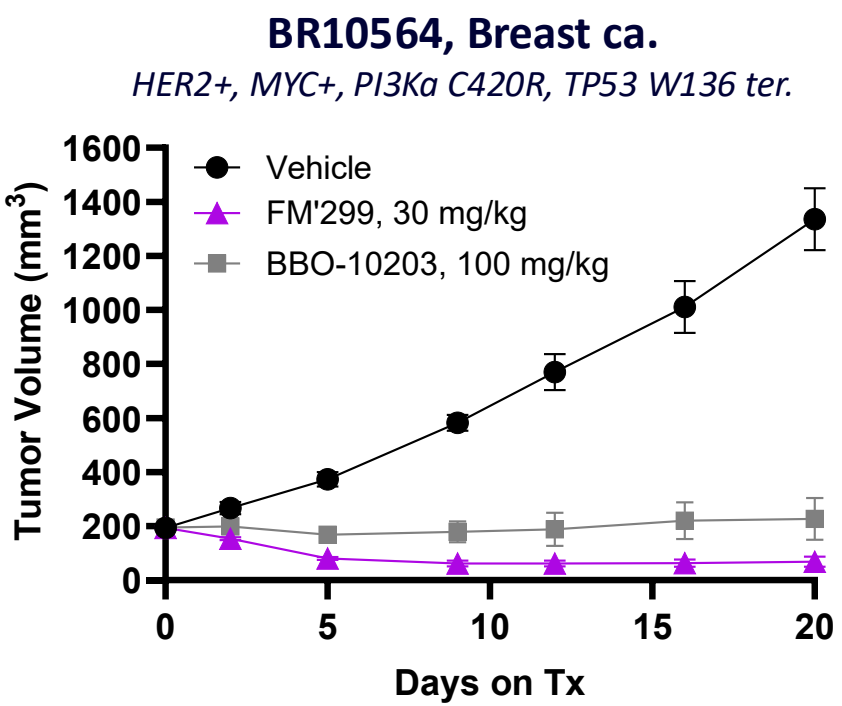
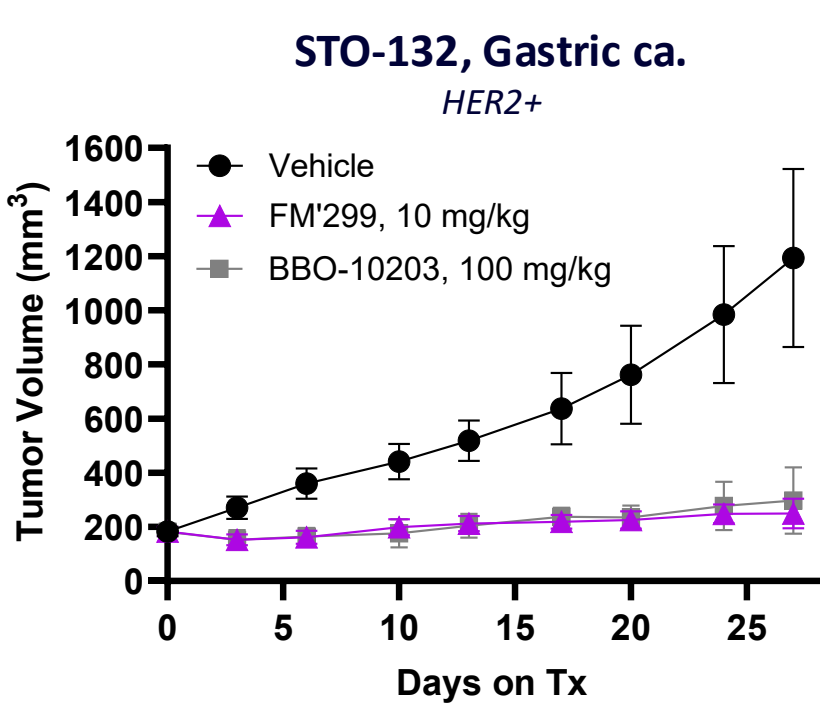
FMC PI3Kα-RAS breakers show strong single-agent activity in HER2+ PDX models





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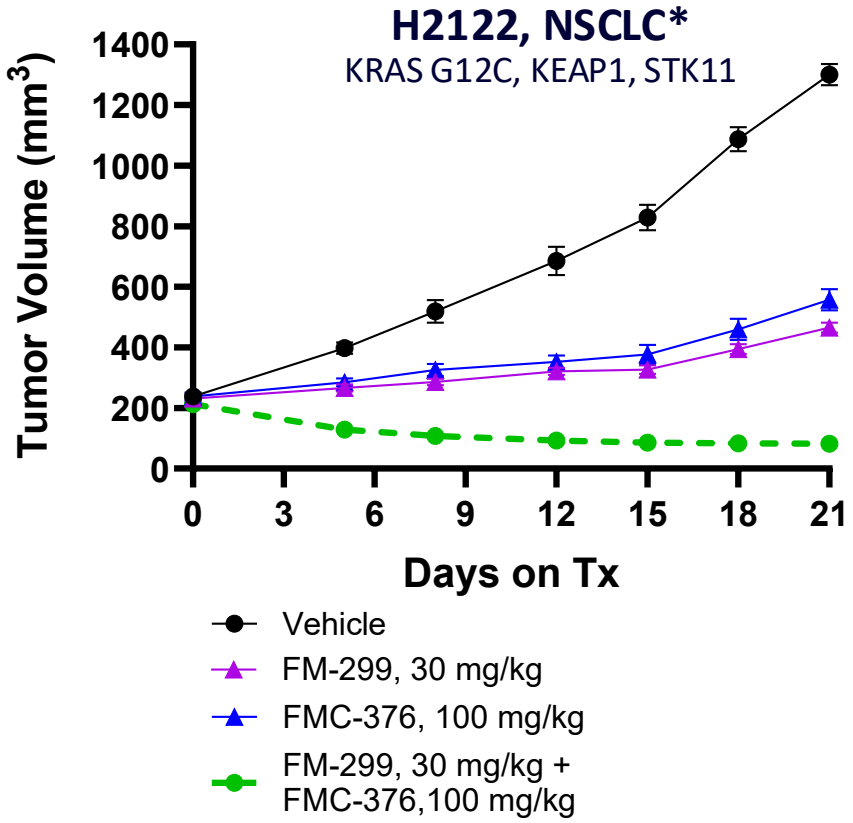
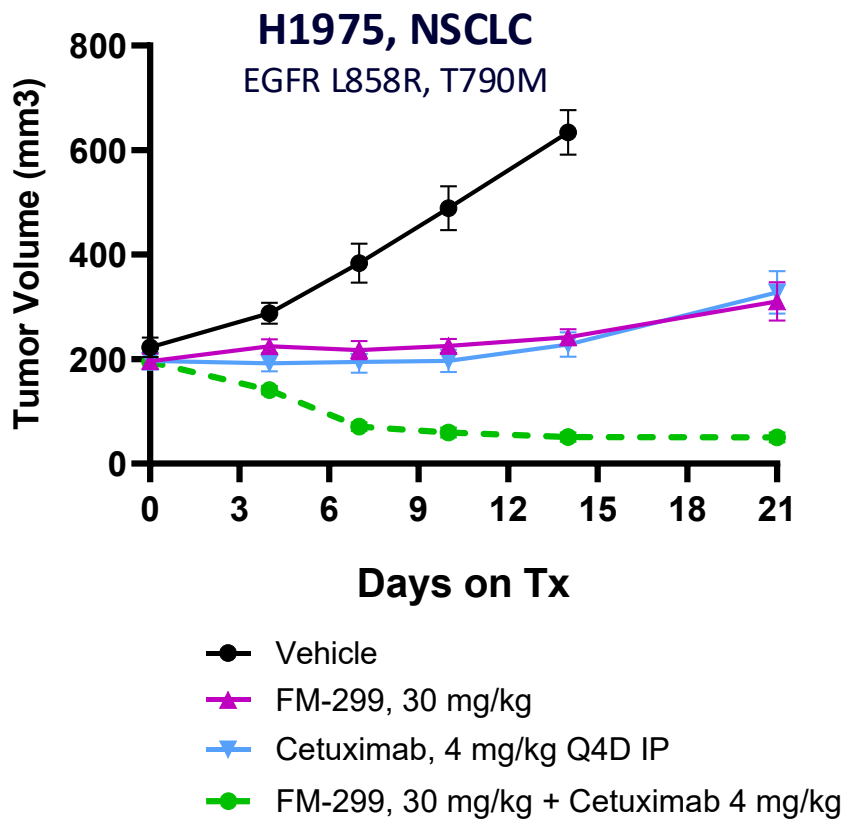
FMC PI3Kα-RAS breakers drive tumor regression in combination with KRAS and EGFR inhibitors

KRAS combination



EGFR combination



*KRAS inhibitor resistant model

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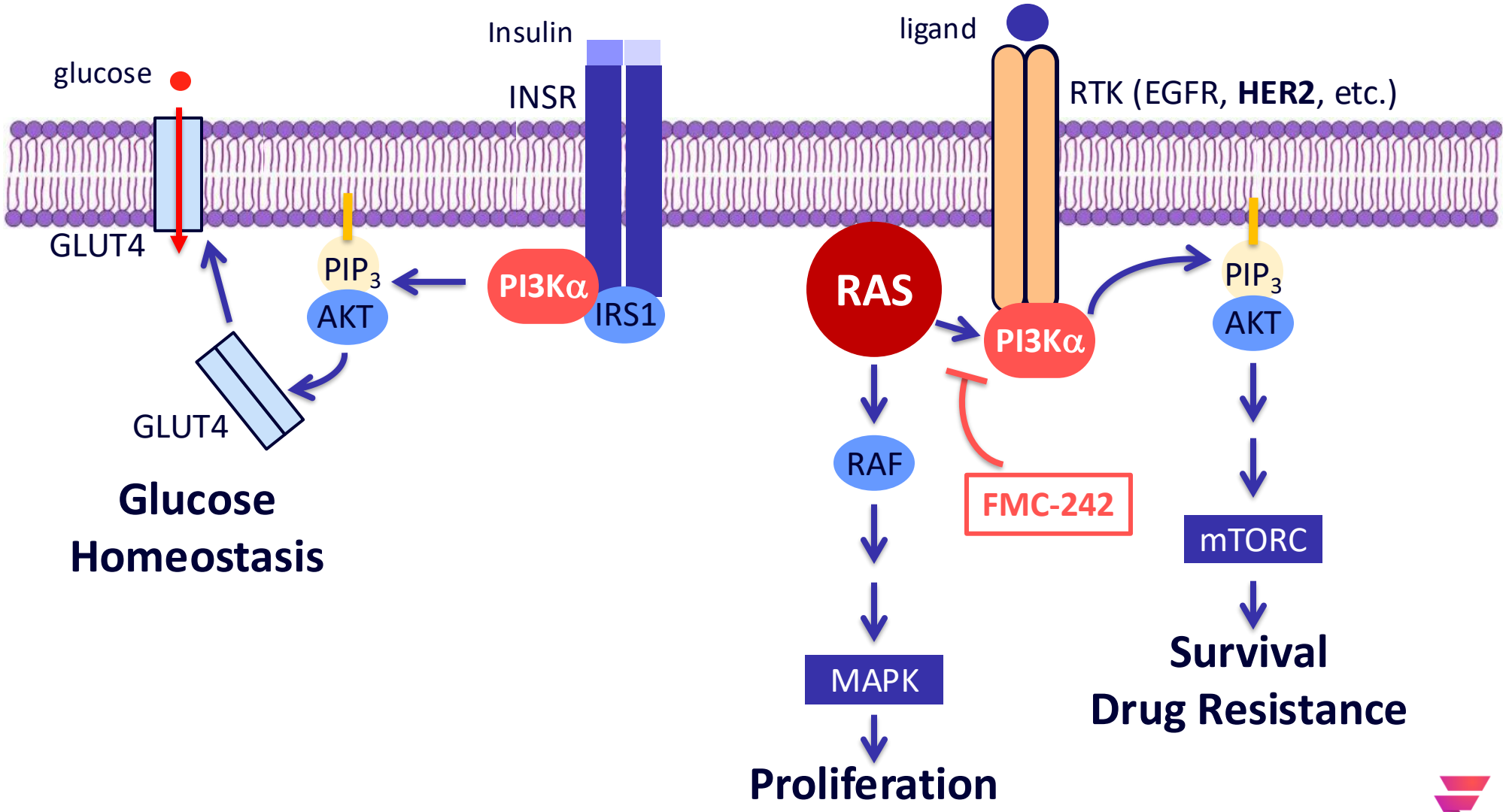
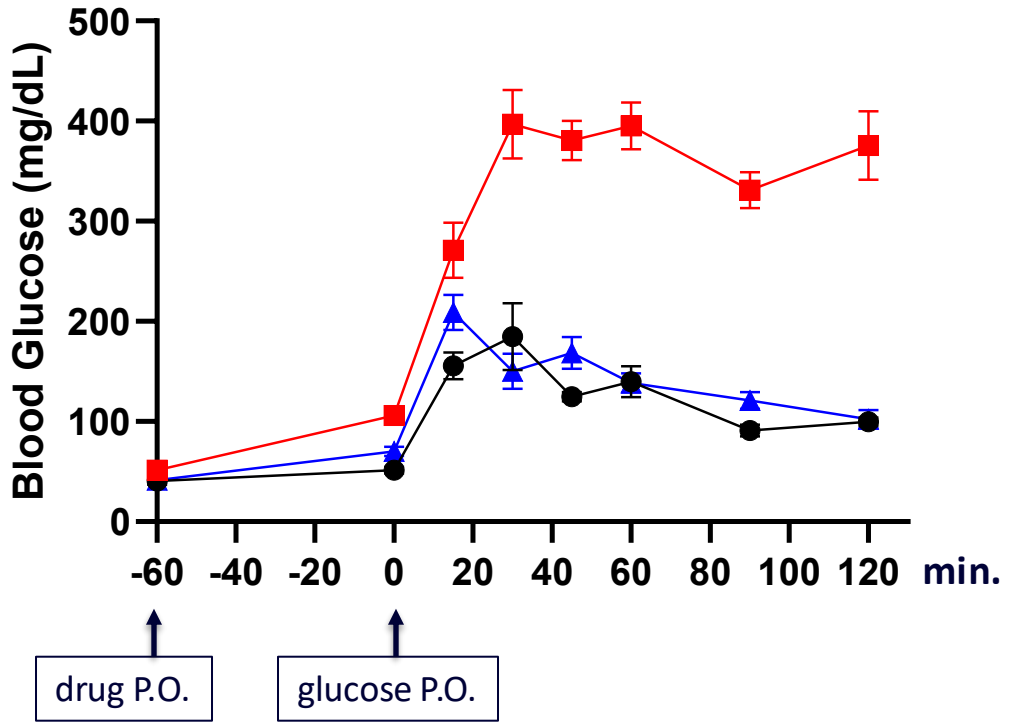
Inhibition of PI3Kα-RAS interactions spares normal PI3Kα function



FMC-242 does not disrupt normal glucose metabolism at ≥ 30x the efficacious dose

Oral Glucose Tolerance Text



FMC-242 a highly selective, covalent allosteric inhibitor of PI3Kα-RAS PPI that spares normal functions

PI3Kα-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**

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KRAS G12D

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

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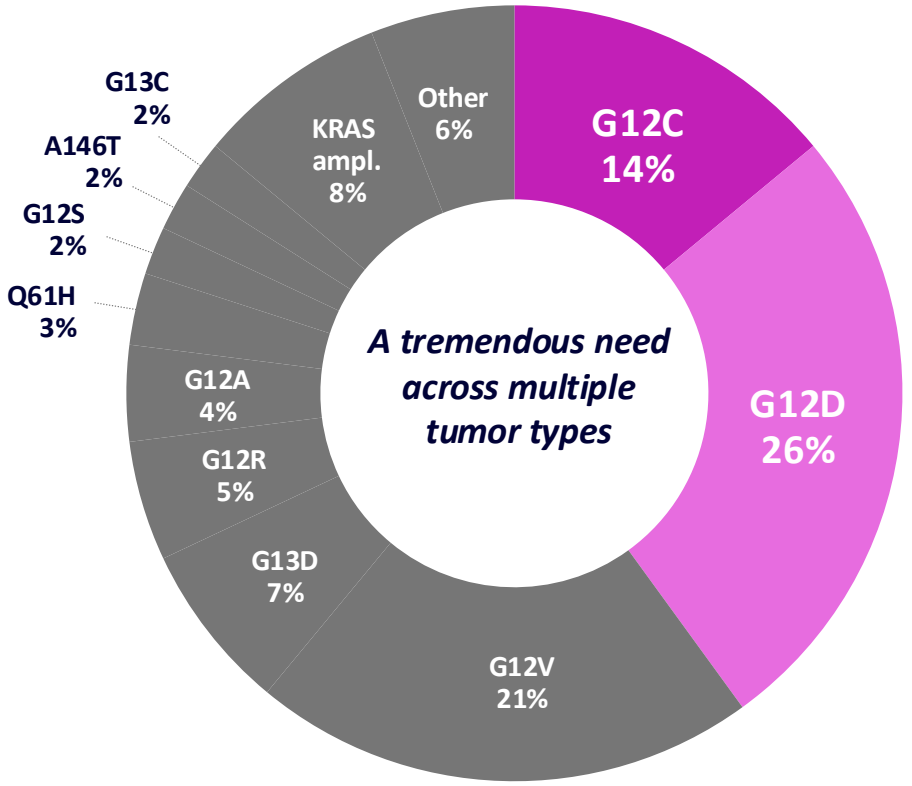
A targeted approach to conquer KRAS treatment

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.

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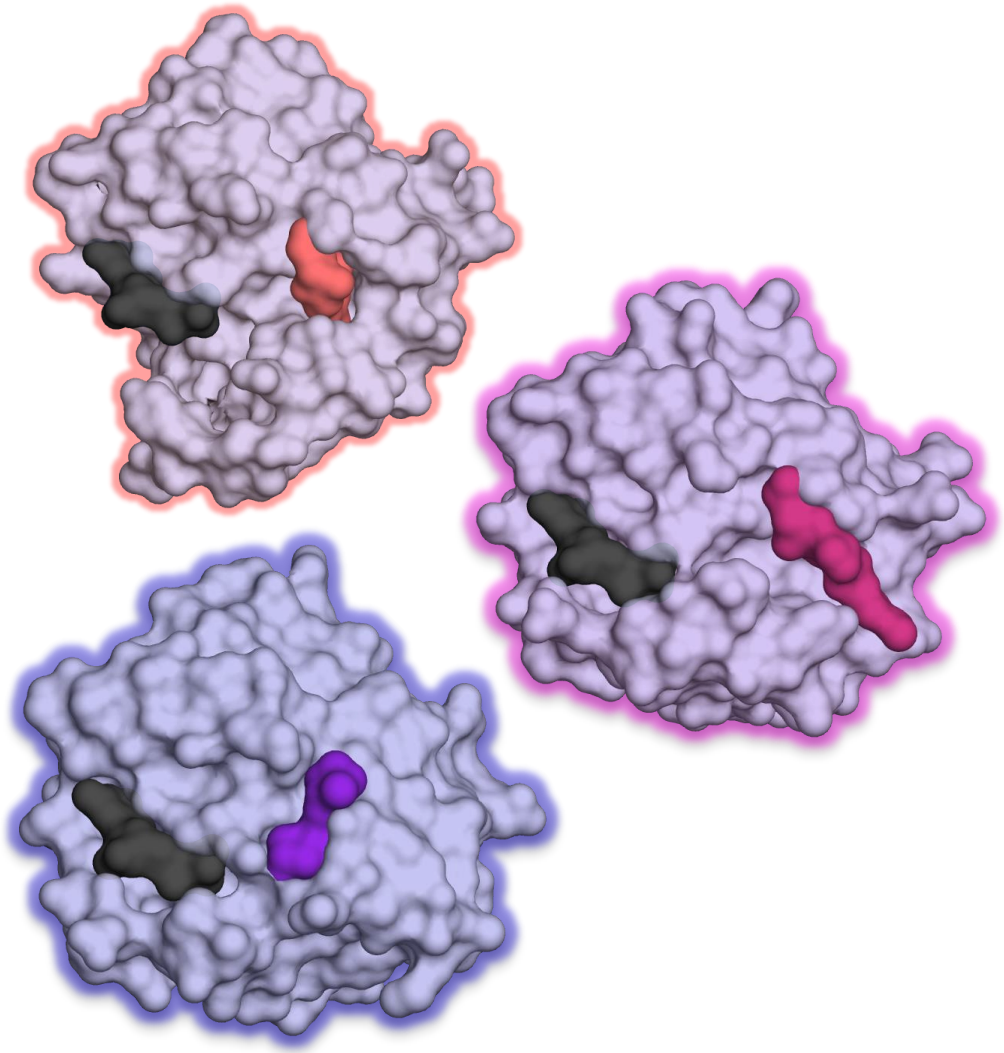
First in class covalent inhibitors of ON+OFF KRAS G12D



- **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

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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

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FMC-220

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

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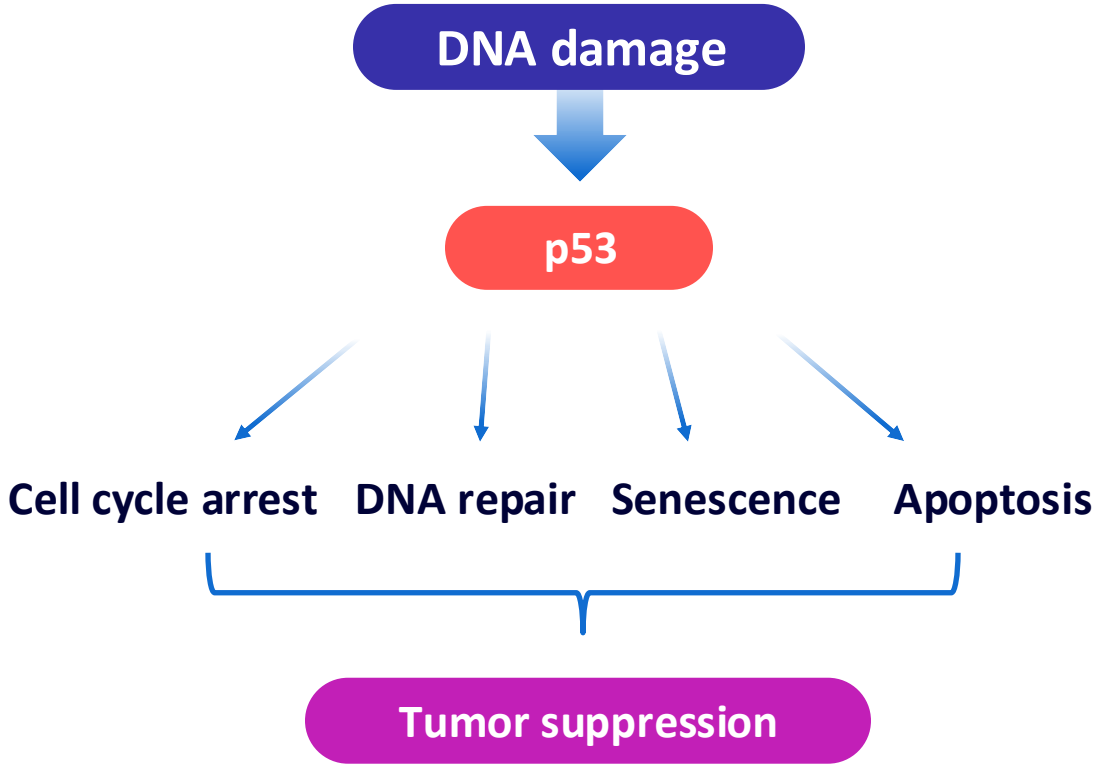
p53 Y220C is a clinically validated cancer driver

p53 is one of the most frequently mutated genes in human cancers[1]

- It is inactivated by mutation in ~50% of cancers[1]

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.

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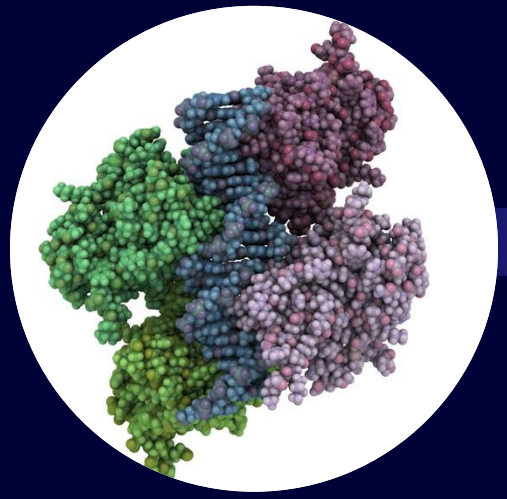
The Frontier™ Platform

FMC-220

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

>20 years



Non-covalent activators are limited

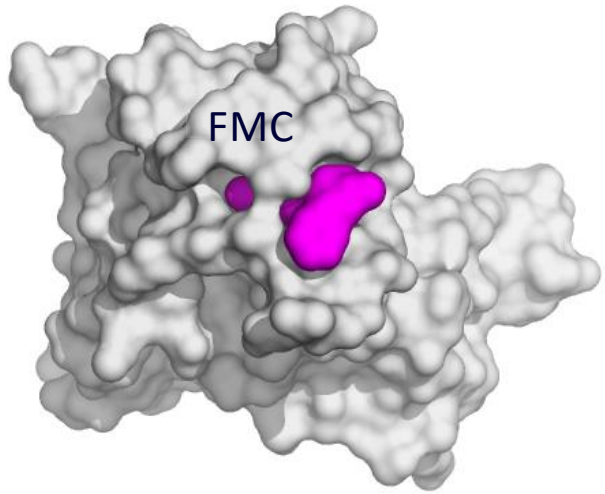
Applied

The Frontier™ Platform

Best-in-industry AI optimized chemoproteomics

FMC-220

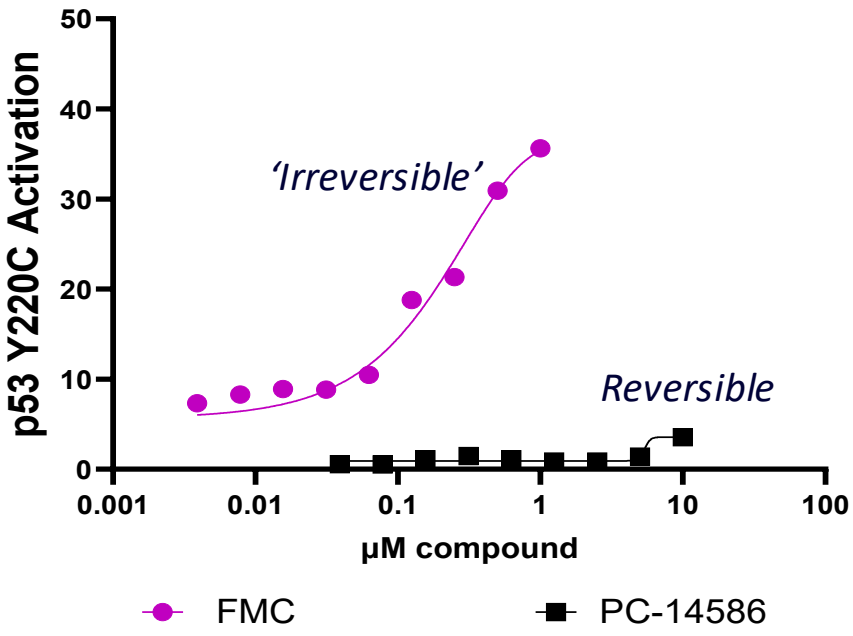
Rapidly progressed a potential best-in-class drug candidate

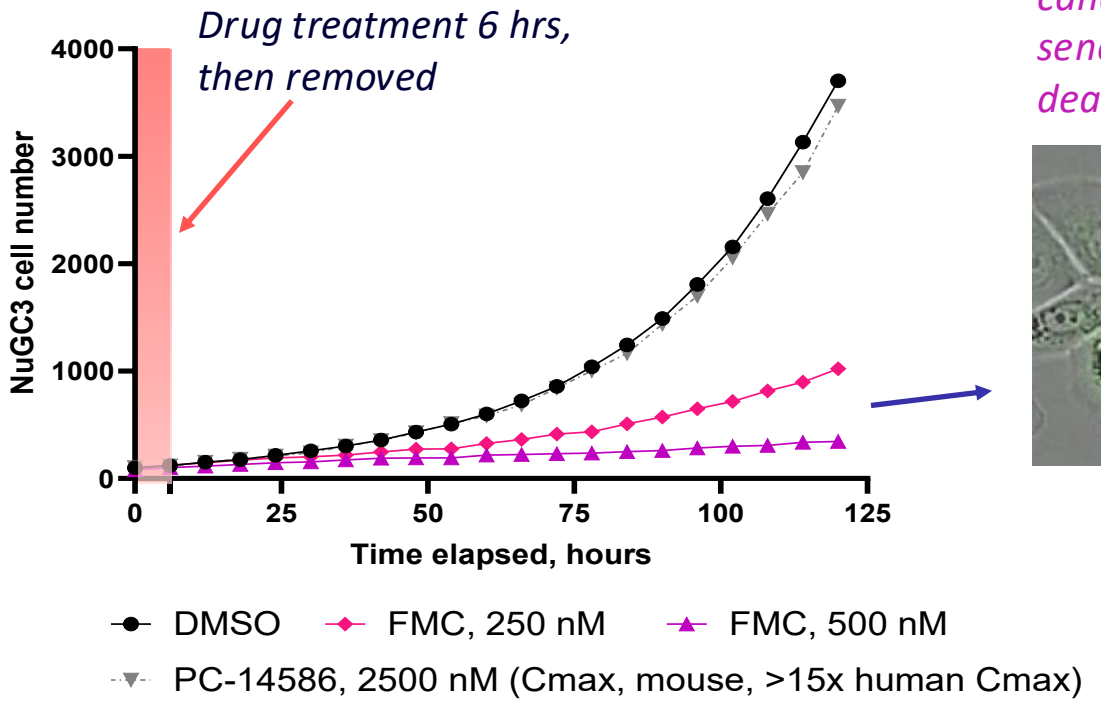


Enhanced potency,
Exquisite selectivity
Durable efficacy

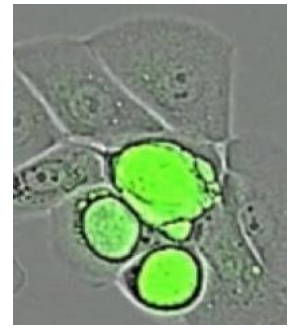
Differentiated covalent mechanism of action delivers potency with durability

Durable p53 response after drug wash-out (18 hrs) = **Durable anti-cancer effect that persists for 5 days and beyond**

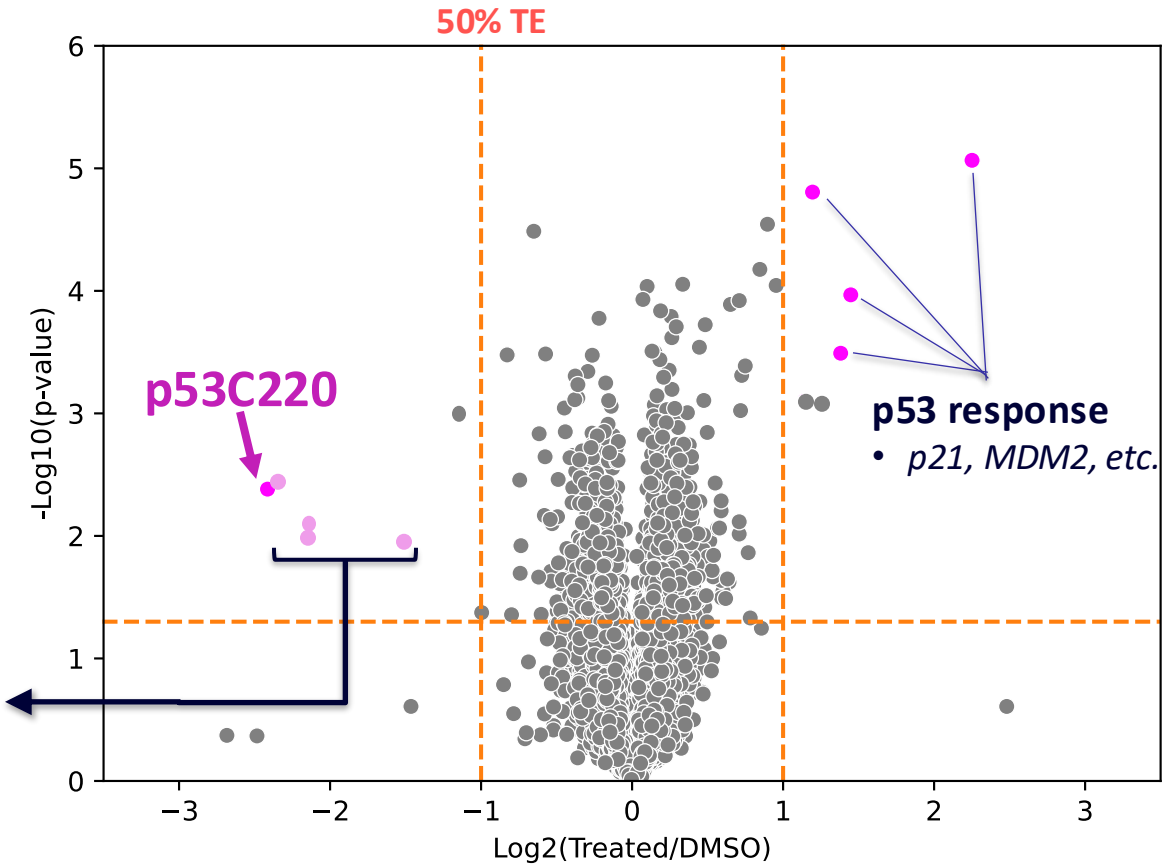




'Irreversible' anti-cancer phenotype, senescence and death



FMC-220 is exquisitely selective for p53 Y220C in cells

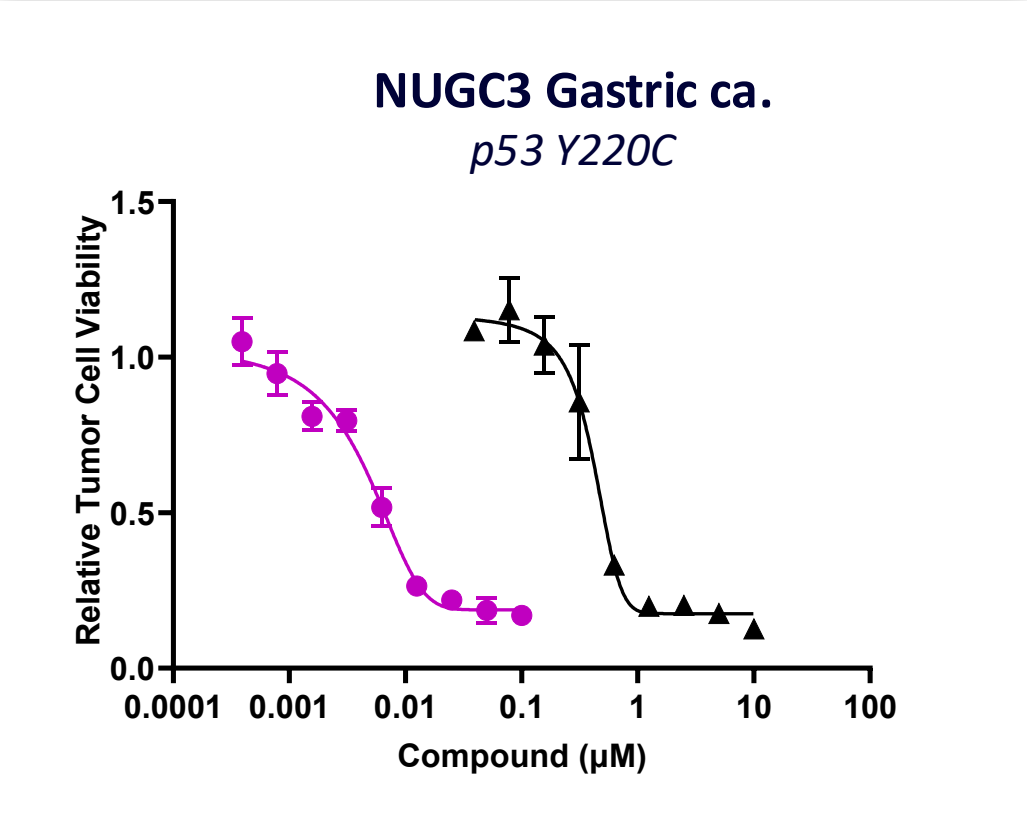


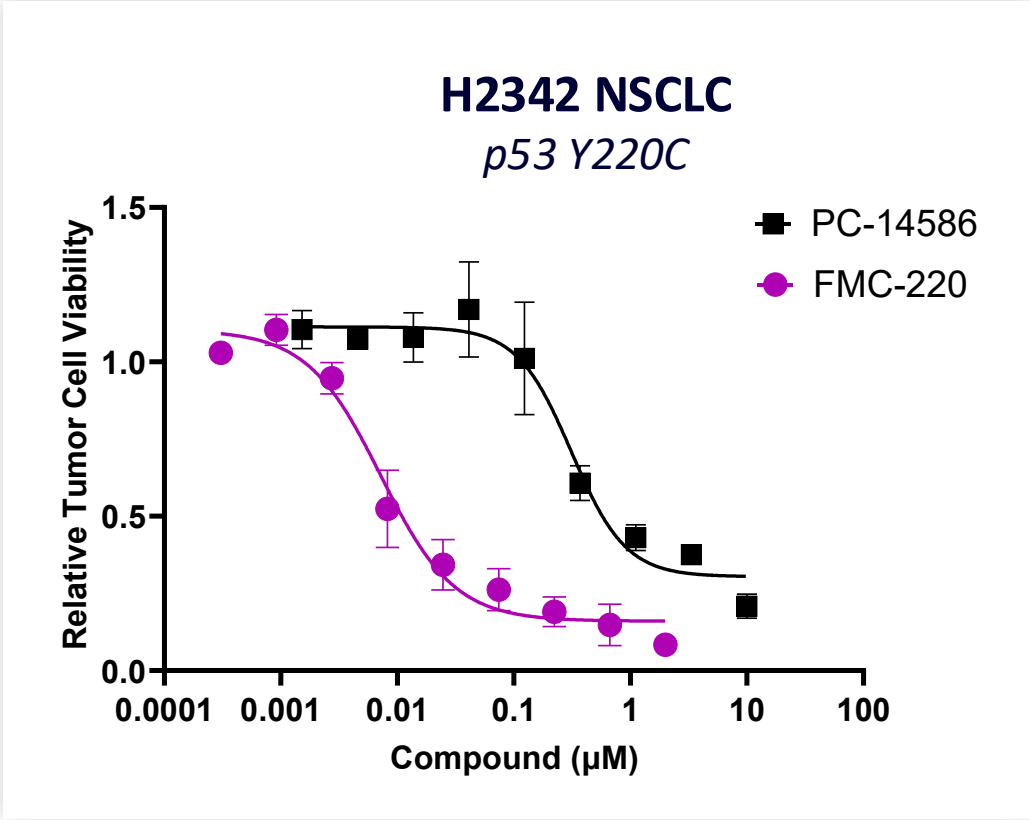
Due to stabilization and refolding of Y220C mutant protein

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





50-100X increased activity relative to PC-14586

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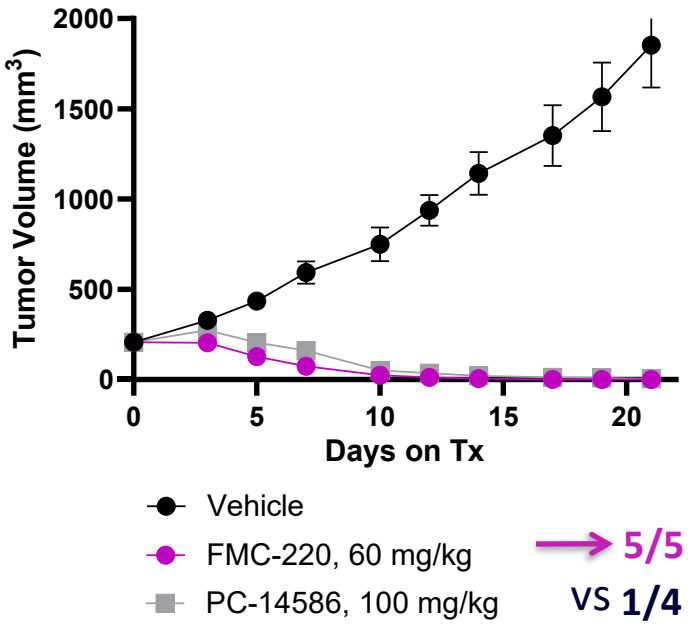
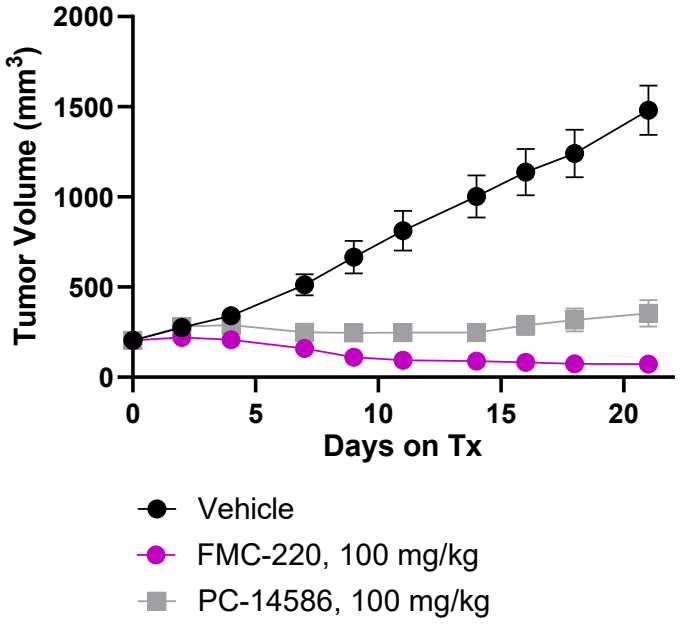
FMC-220 delivers tumor regression across PDX models

LU5269, SCLC
TP53Y220C, ATR, FLT3

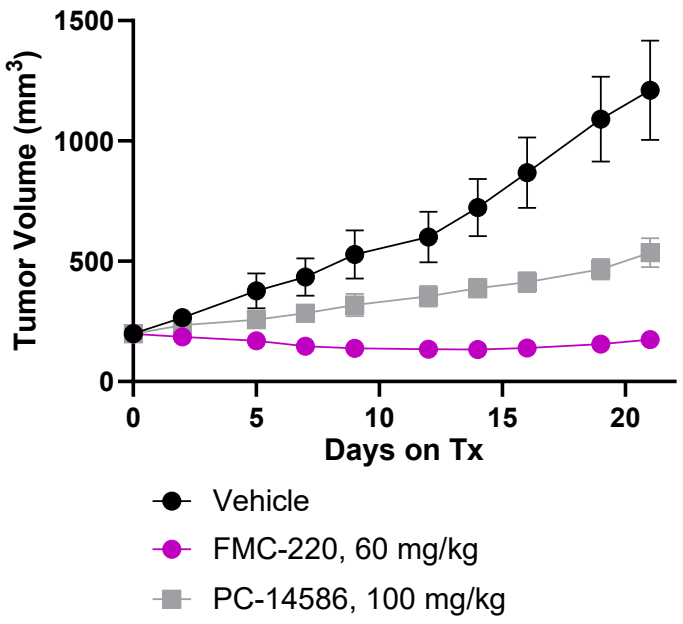


→ 5/5 CR
VS 1/4 CR

ES2411, Esophageal
TP53Y220C, APC, KEAP1, MYCamp



HN3537, HNSCC
TP53Y220C, SMARCA4, EP300, TSC2



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

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

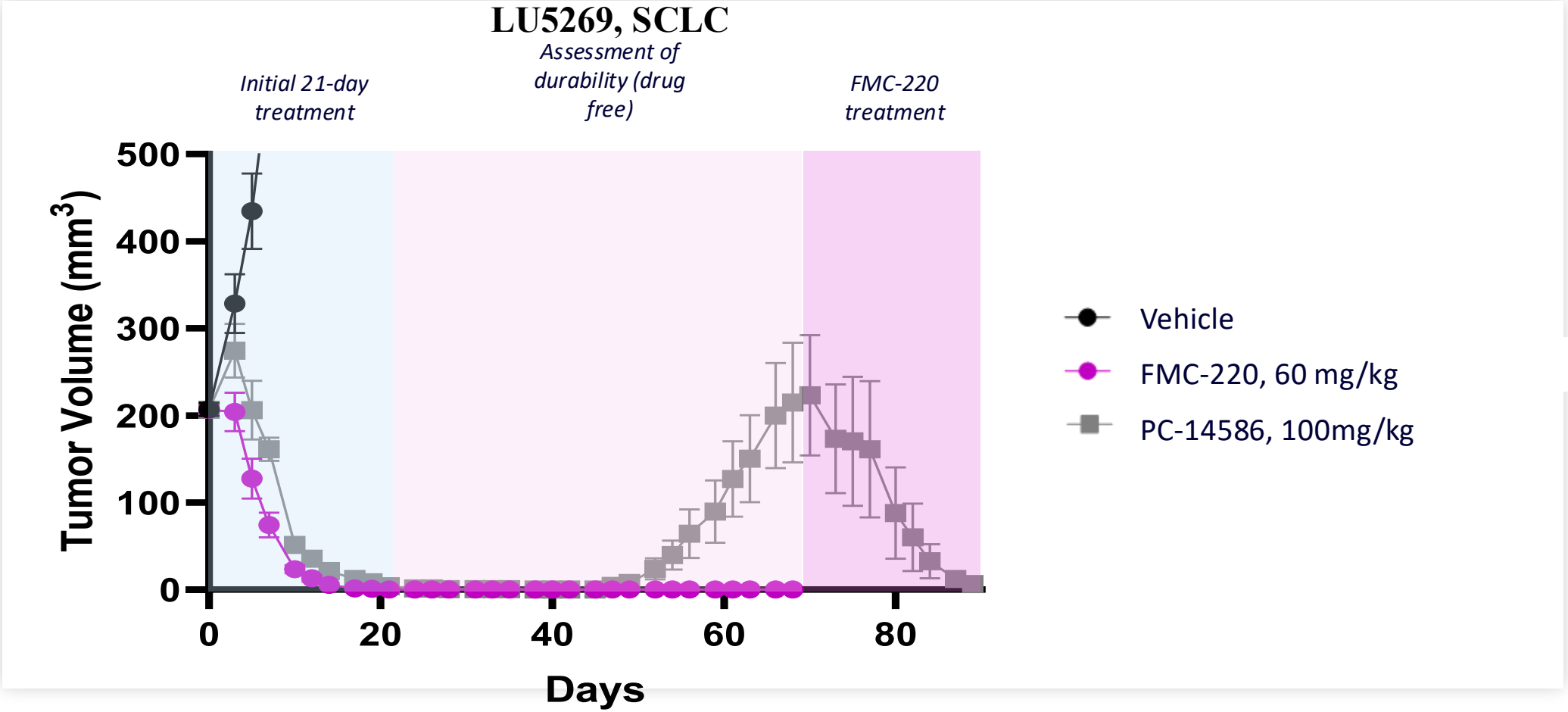

Figure 6: At the end of treatment (day 21), complete regression was achieved in all 5 mice in the FMC-220 treatment group, while only 1 out of 4 mice in the rezatapopt group was tumor free. Mice were monitored for tumor regrowth. All 5 mice in the FMC-220 group remained tumor free while the tumors in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

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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

FRONTIER MEDICINES

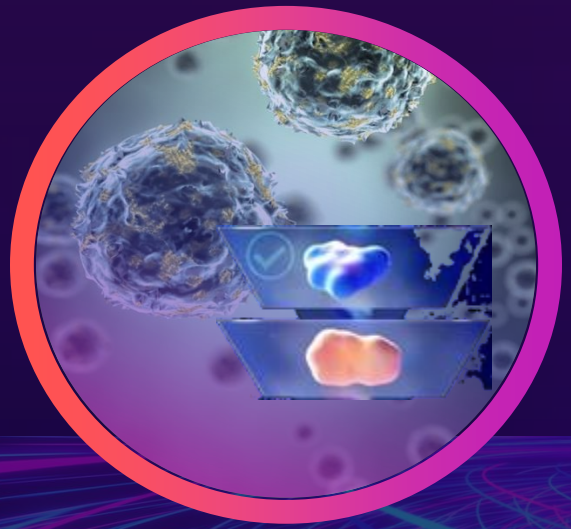
Inhibitors | **Novel E3 Engagers** | **Glue Discovery** | **Stabilizers/ Activators**

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

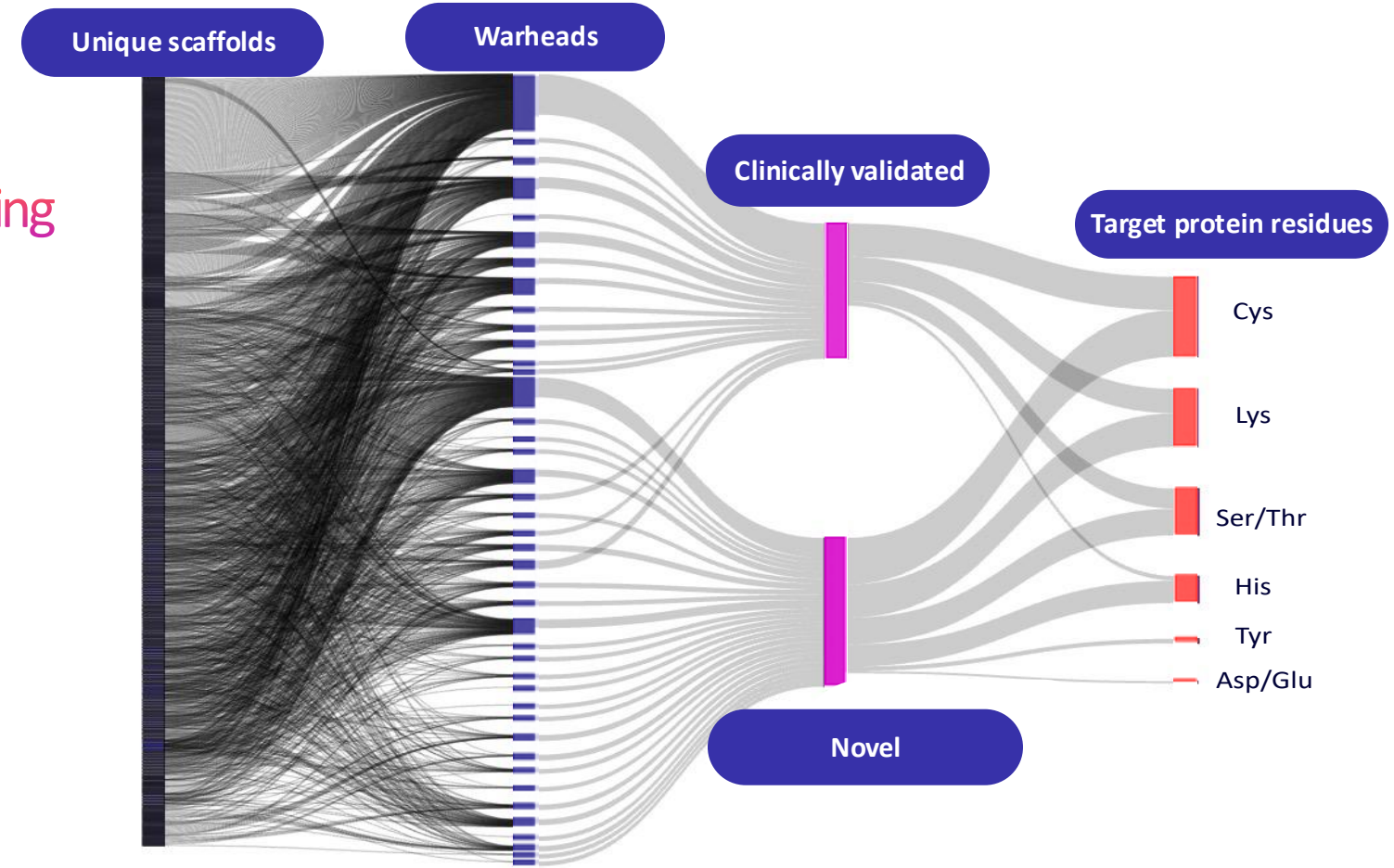
Covalent Library

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

>20,000 compounds and counting

40 warheads

Continually evolving through **AI** and **data**



Frontier library in Sankey flow diagram

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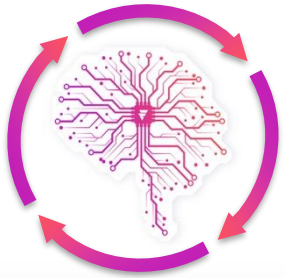
Covalent Library

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

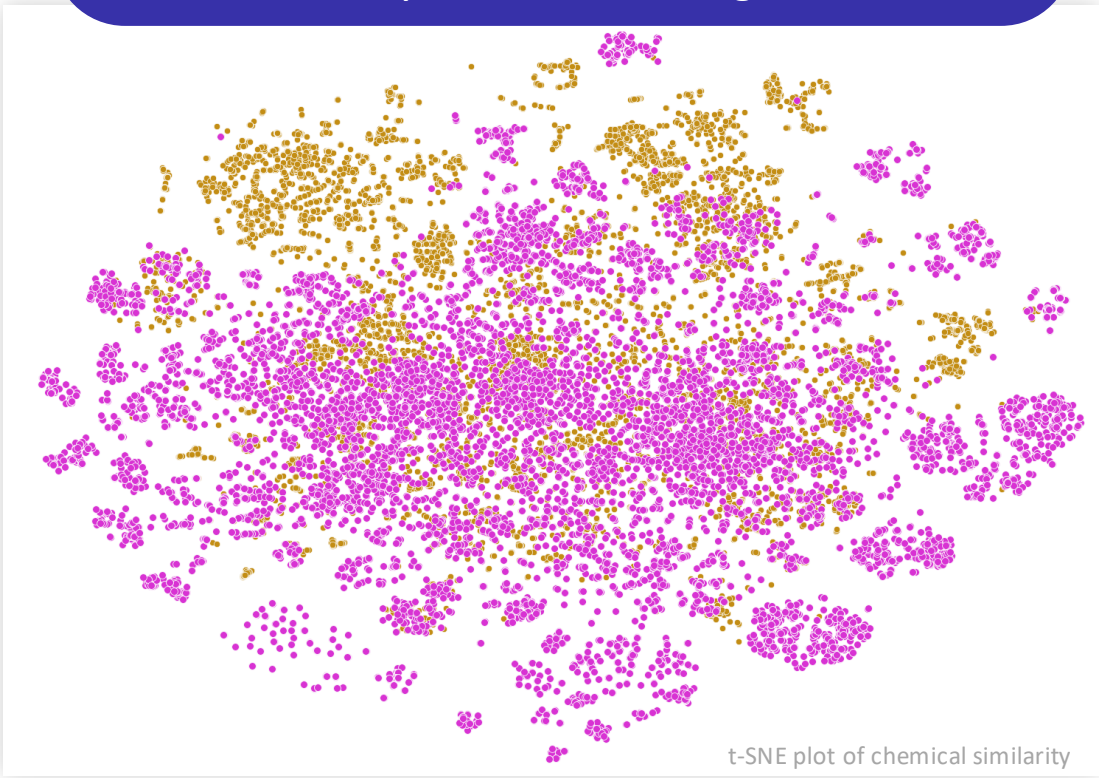


Continually evolving through **AI** and **data**

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

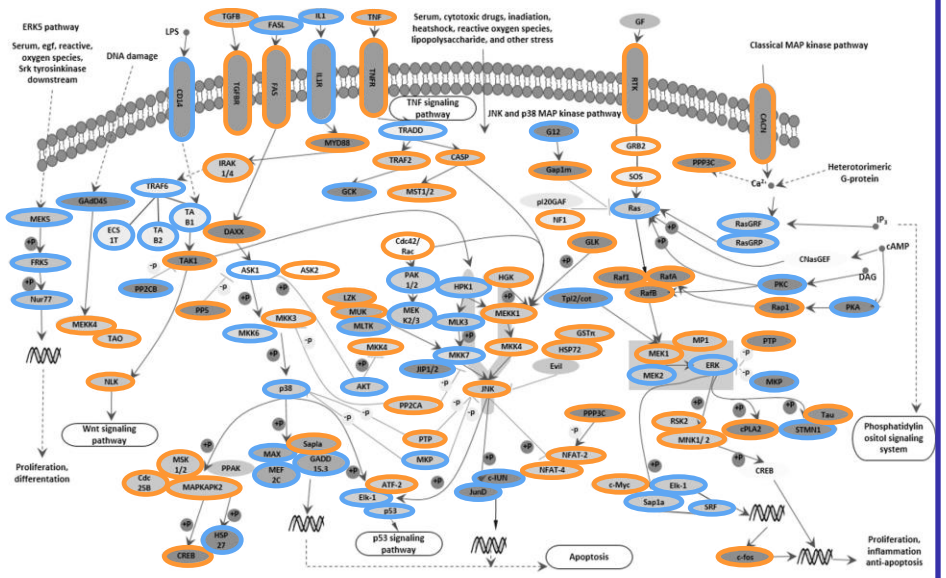
Comparison
Frontier library vs. commercial gold standard



Druggability Atlas™ in action: unlocking key disease pathways

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

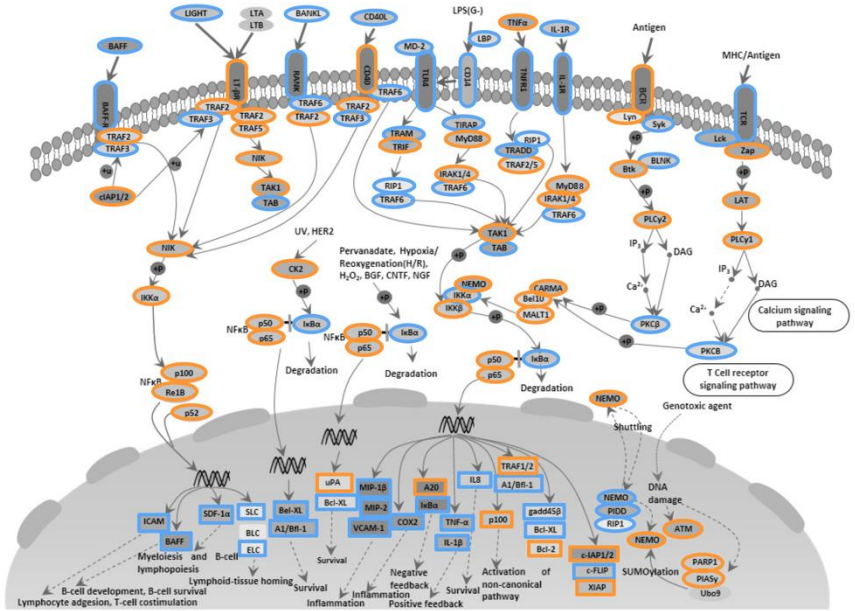
MAPK pathway



Binding Site **(96%)**

Library Hit **(62%)**

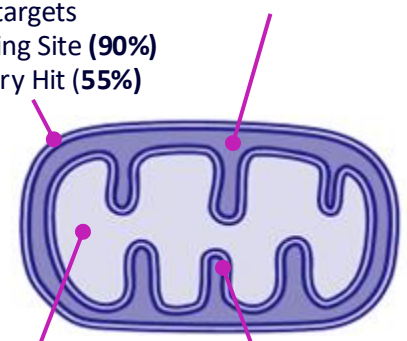
NF - κB Pathway



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%)**

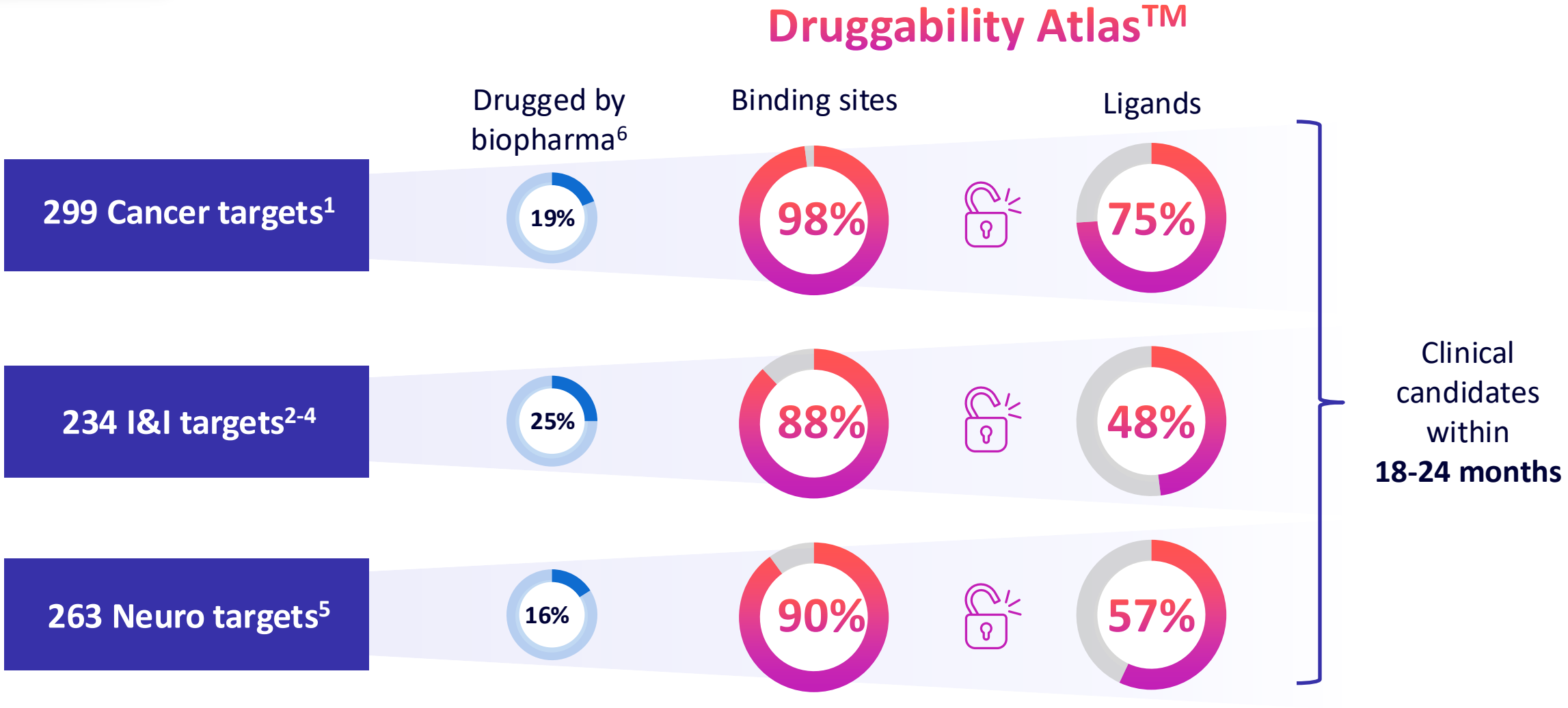
Matrix
522 Targets
Binding Site **(95%)**
Library Hit **(69%)**

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

Druggability Atlas™

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



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 MEDICINES

The Frontier™ Platform

Frontier technology fast forwards drug discovery

Conventional drug discovery

Make target protein
Clone
Express
Purify, test function

Screen
Estab. assay
Screen
Validate hits

Characterize hits
Structure
Binding site
Initial SAR

Improve hits
Potency
Selectivity
Function

Move into cells
Permeability
Selectivity
Cellular SAR

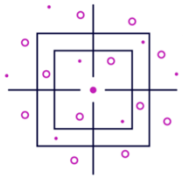
1 to 1.5 Years
May not have actionable chemistry

Med chem campaign
Potency
Selectivity
PK
Efficacy

3 to 5 Years
Clinical candidate

Frontier's time savings through tech

With Frontier ENABLEMENT



Druggability Atlas™

Day 0
Immediately actionable chemistry

- ✓ **Selective**
- ✓ **Known binding site**
- ✓ **Cell-permeable**
- ✓ **Initial cellular SAR**
- ✓ **Often functional activity**

Covalent AI™

With Frontier ACCELERATION

1.5 to 2 Years

Best-in-class clinical candidate

FRONTIER MEDICINES

FrontierMeds.com