

16th
CONGRESS
Lung **ON**
CANCER

BARCELONA
27 / 28
NOVEMBER 2025

Resistance pathways to RAS inhibition

With recognition to Miguel Angel Molina-Vila, Clara Mayo, Ana Giménez-Capitán, Jordi Bertrán-Alamillo, Elizabeth Martínez, Daniel Olmo, Kevin València-Clua, Jèssica González, Jordi Codony-Servat, Andrés Aguilar, Maria González-Gao

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CONFLICT OF INTEREST

I have no conflicts of interest to declare

Based on: Ebright, Dilly, Shaw and Aguirre. *Cancer Discov*, July 2025

Other reviews: *Molina-Arcas, Downward. Cancer Cell, March 2024; Singhal, Li, O'Reilly. Nature Medicine, April 2024*
Perurena, Situ, Cichowski. Nature Reviews Cancer, May 2024

Primary Resistance

Co-occurring baseline mutational patterns:

KRAS/LKB1, KEAP1, SMARCA4 and CDKN2A, TP53.

Acquired Resistance

- Multiple treatment-emergent mutations in CRC patients (*Riedl et al. Ann Oncol 2025*)
- Other KRAS mutations (R68S, H95D/Q/R and Y96C, prevents drug binding) or KRAS amplification
- RTK-RAS-MAPK activation (MAP2K1, NRAS); RTK amplification (EGFR, ERBB2, FGFR2, MET and NRTK1)
- IRE1 α , MYC amplification, EMT & histological transformation
- YAP/TAZ/TEAD signaling
- Claudin-18.2 (CLDN18.2 in the PDAC mouse model [zolbetuximab, CMG901] (*Dilly et al. Cancer Discov, 2024; Nakayama et al. Nat Rev Clin Oncol 2024*)
- MUC1 is upregulated by sotorasib & RMC-7977 in KRASG12C NSCLC, and by MRTX1133 in KRASG12D PDAC (*Araujo et al. Cancer Discov, 2024; Ozawa et al. CCR 2025*)
- *MUC1-HIF-1 α -spermidine/spermine N1-acetyltransferase 1 (SAT1)* (*Murthy et al. PNAS 2024*)

Conundrum – combinatory therapies (MOAs)- Preclinical studies (*Rosell et al. Critical Reviews in Oncology/Hematology 2024; Tanaka & Ebi. Cancer Science 2025*)

Skoulidis, Schuler. *Nature Medicine*, August 2025

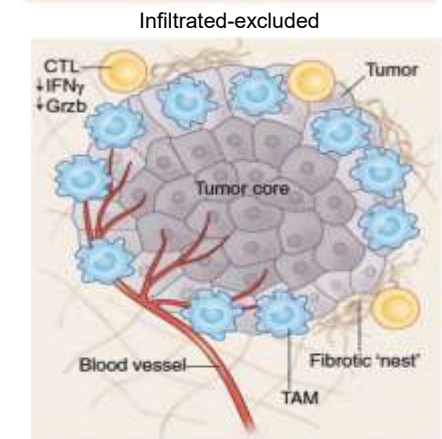
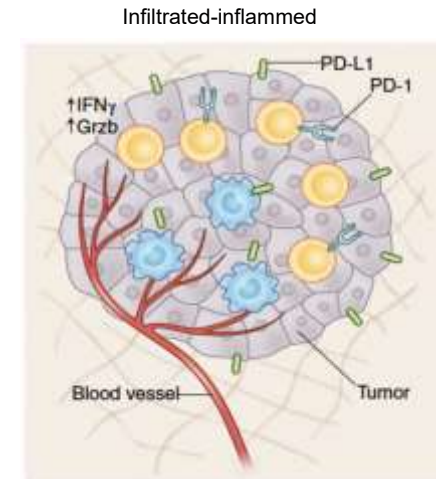
KP, KL and KC subtypes

KP- TP53 and 'hot' T cell-inflamed TME with high PD-L1

[PFS 7.75 mo vs 7.16 mo, sotorasib vs docetaxel]

KL- STK11, a 'cold' CD8-positive T cell-depleted TME with low PD-L1, KEAP1, elevated nuclear factor erythroid 2-related factor 2 (NRF2)

KC- Low TTF1, mucinous, NRF2 and CDKN2A/CDKN2B.



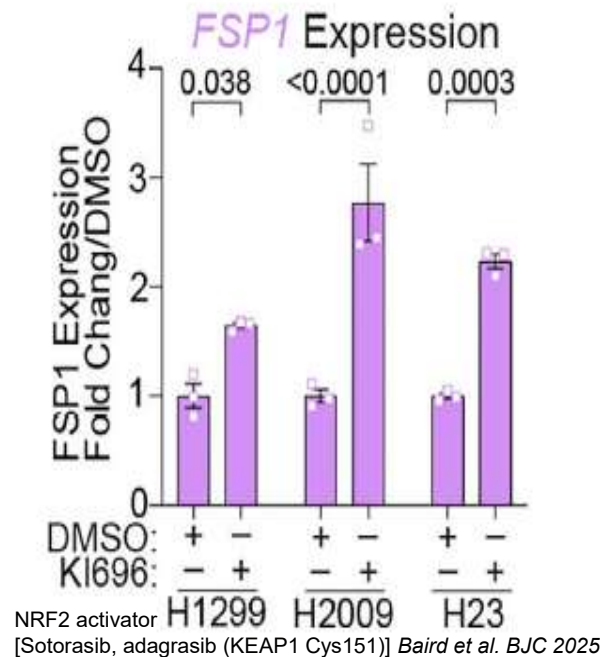
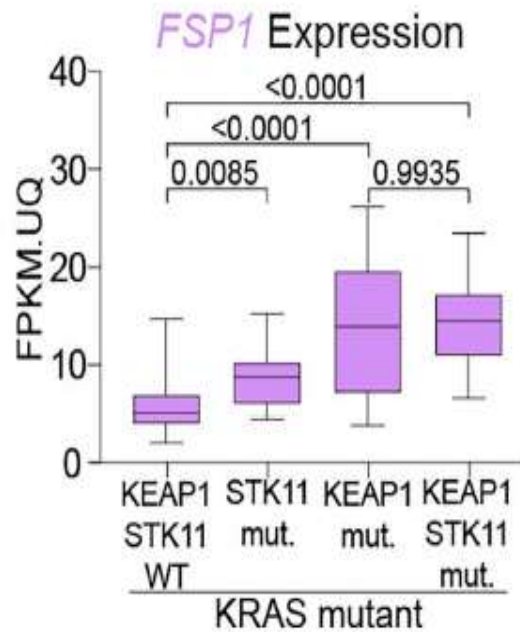
Binnewies et al. Nature Medicine 2018

- KRAS mutant-NSCLC is often accompanied by brain metastases at diagnosis.

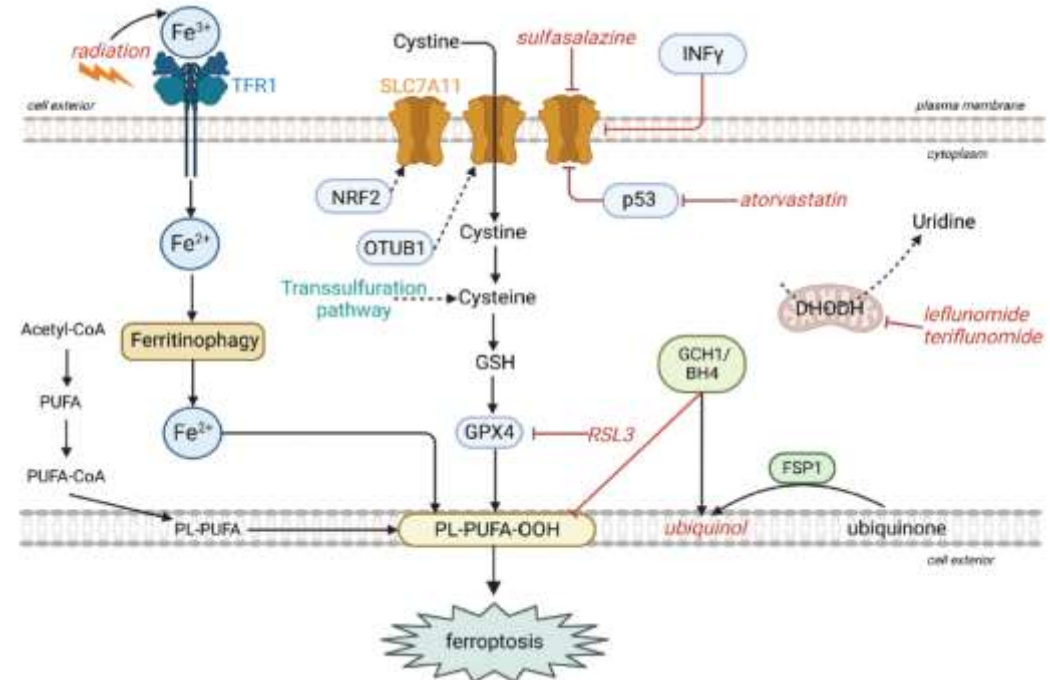
Stearoyl-CoA desaturase 1 (SCD1) is upregulated in microglia in lung-to brain metastases (*Chen et al. CDD 2025*). IGF2BP3 regulates SCD1 and FASN. FASN increases in leptomeningeal and brain metastases (*Li et al. CDD 2025*). Inhibition of SCD1 and CSF1R (pexidartinib) (*Ozawa et al. Mol Cancer Ther 2025*).

Bone metastases related to PRODH2-SLC7A11-IL8 axis (*Gong et al. Cancer Res 2025*).

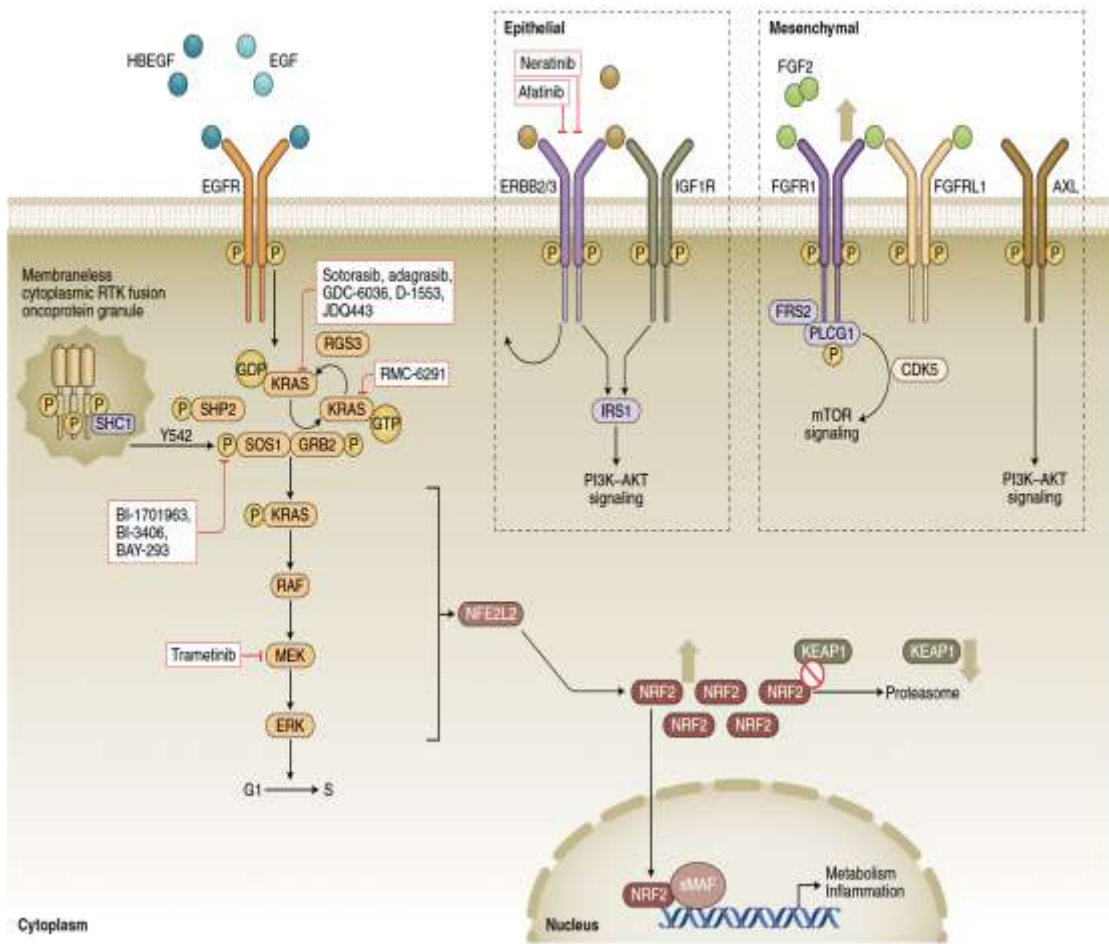
- Early adaptive resistance to KRASG12C compounds is observed in sensitive human KRASG12C lung cancer cell lines. KRAS cell lines are commonly de novo resistant.
- Solutions through the continuous application of scientific research - a burning need.



Wu et al. Nature, November 2025

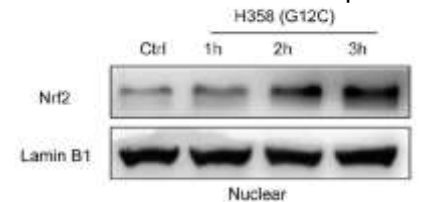


Rosell et al. Exp Rev Respir Med 2023



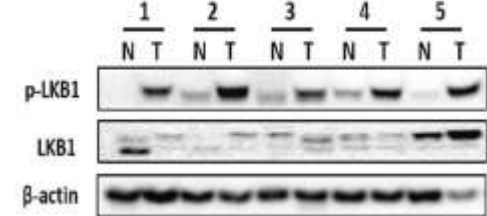
Rosell et al. Nature Cancer 2021

Kelch-like ECH-associated protein 1

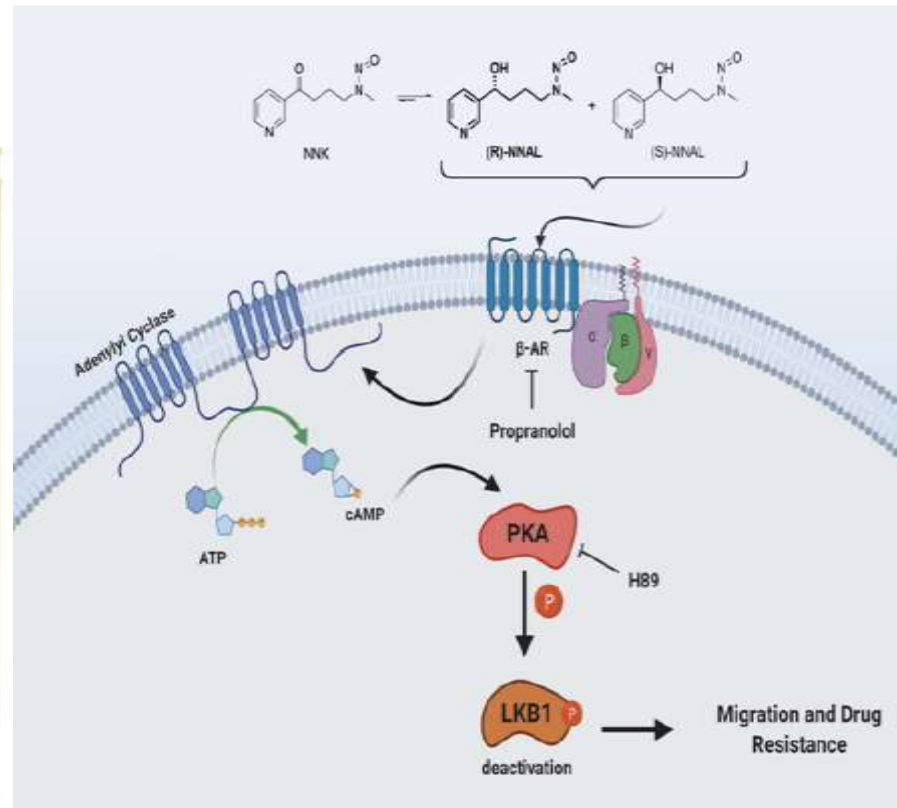


AMG510 modified KEAP1 Cys 288
Adagrasib inducer of NRF2 (KEAP1 Cys151)

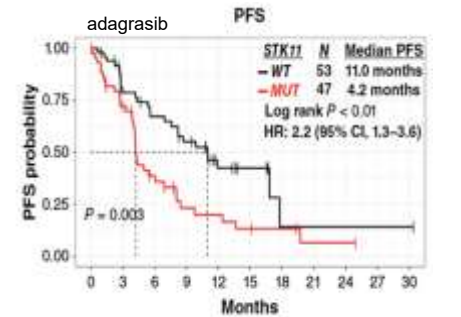
Wang et al. iScience 2023



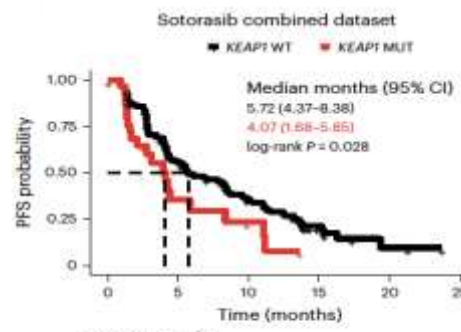
Bian et al. Oncogene 2022



Skoulidis, Schuler. Nature Medicine 2025

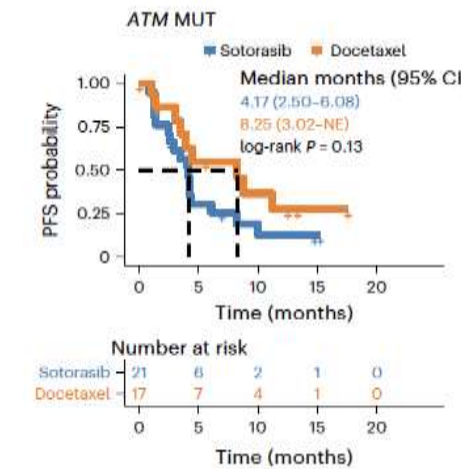
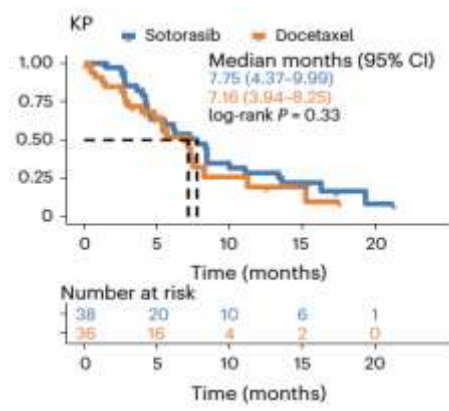
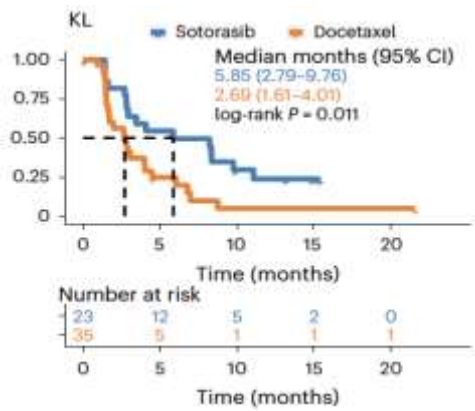


Negrao et al. CCR 2025



Number at risk

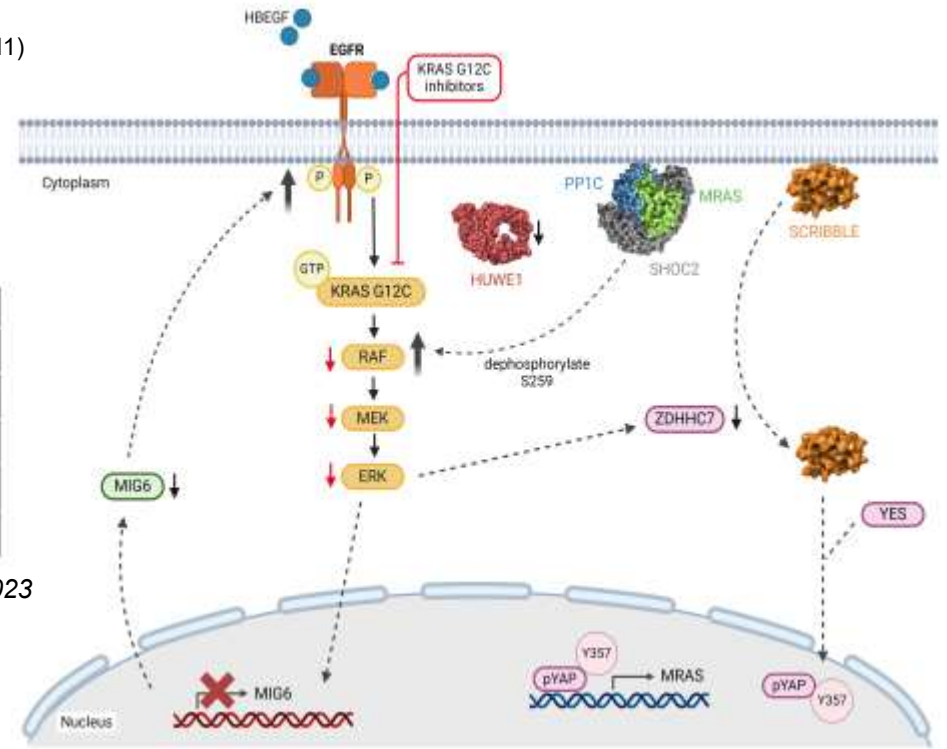
Time (months)	0	5	10	15	20	25
KEAP1 WT	175	87	49	12	2	0
KEAP1 MUT	30	7	3	0	0	0



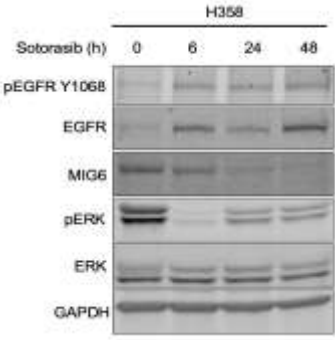
Number at risk

Time (months)	0	5	10	15	20
Sotorasib	21	6	2	1	0
Docetaxel	17	7	4	1	0

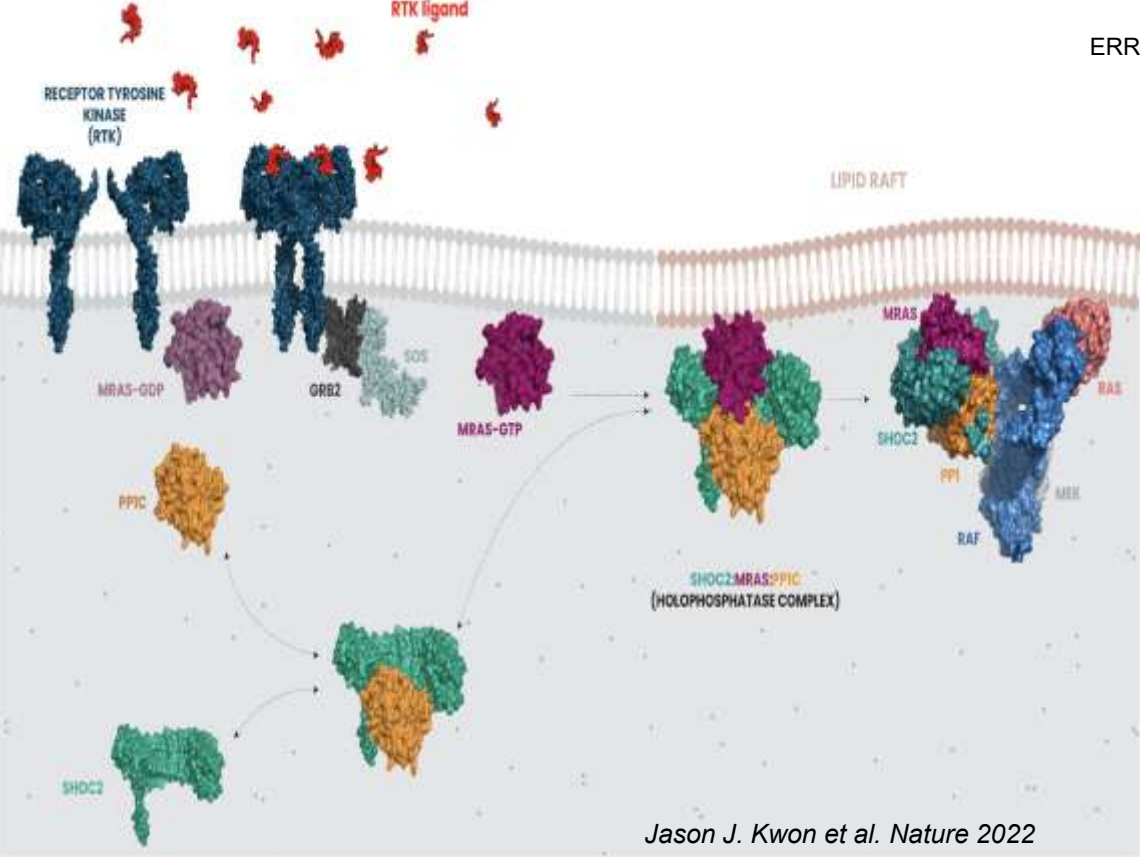
ERRB receptor feedback inhibitor 1 (ERRF1)



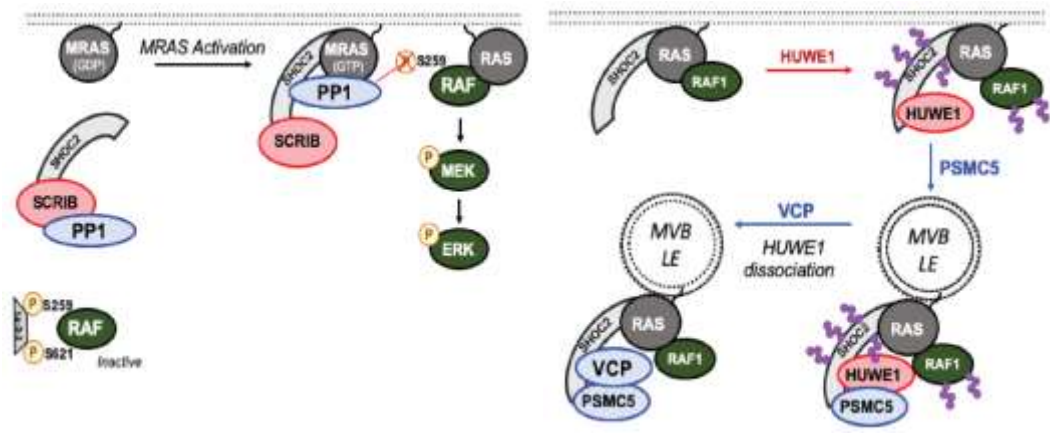
Rosell et al. Critical Reviews in Oncology/Hematology 2024



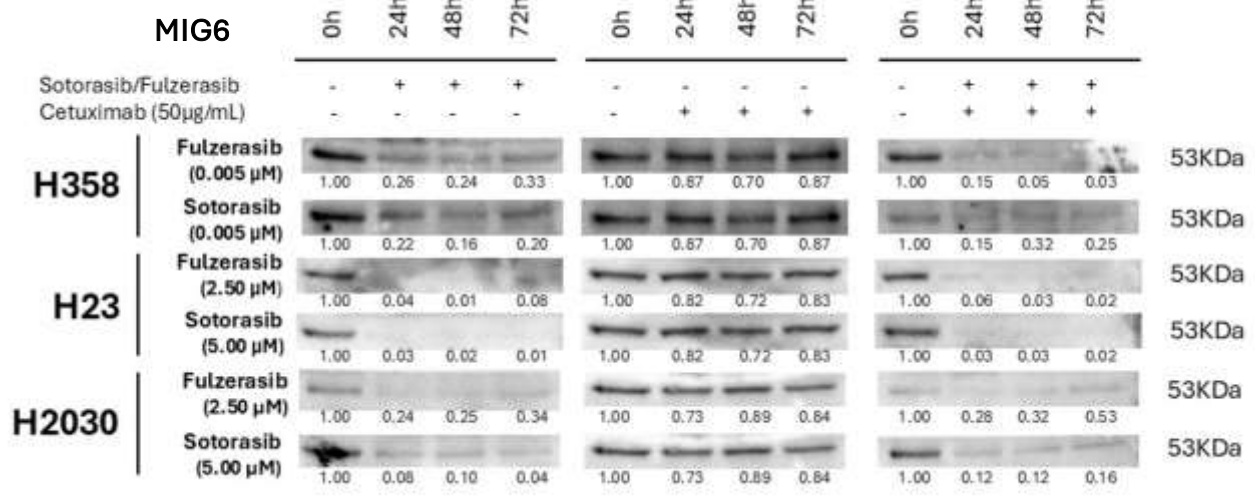
Chen et al. Mol Cancer Ther 2023



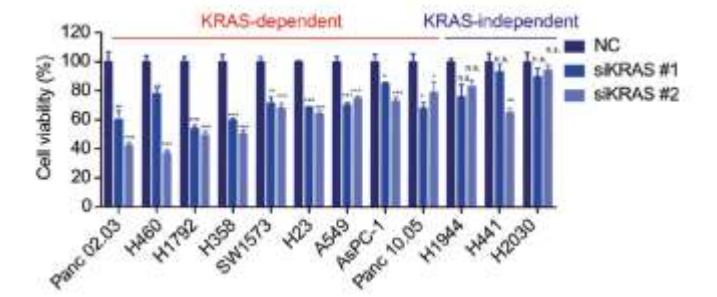
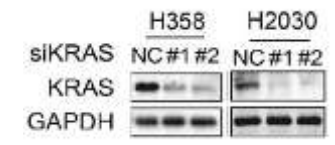
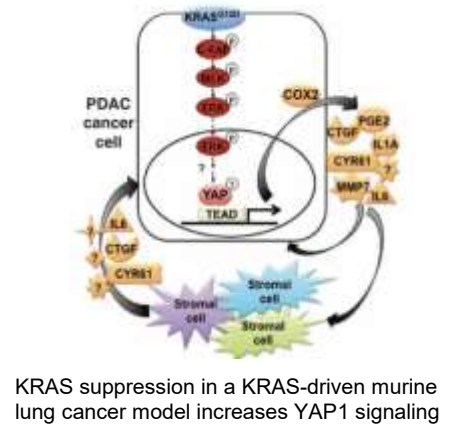
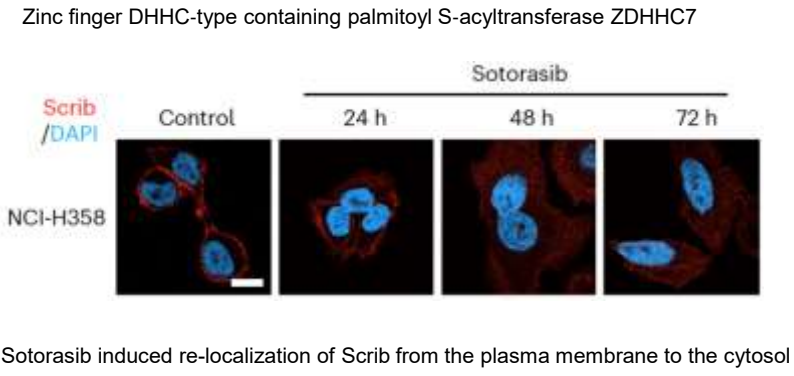
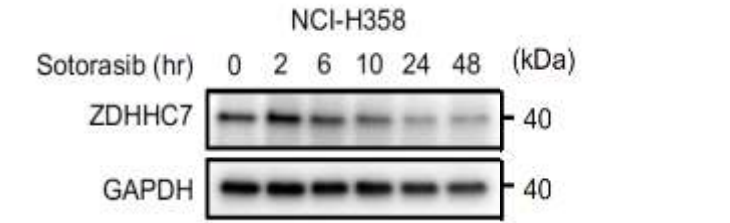
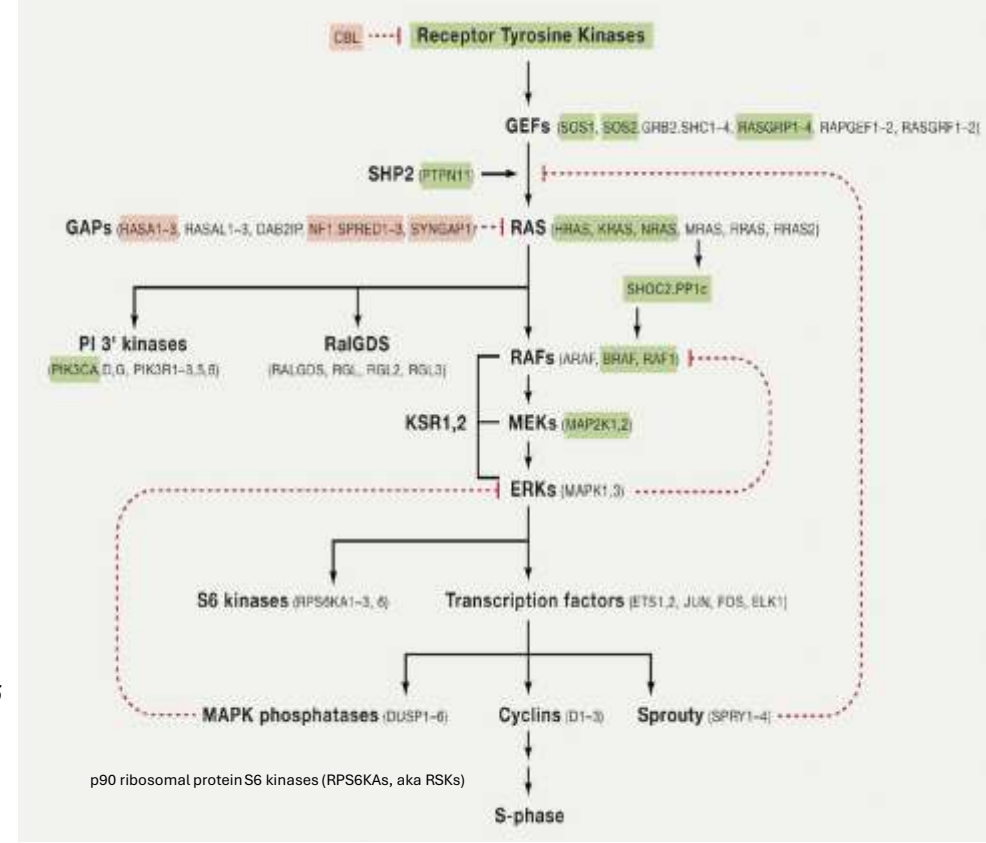
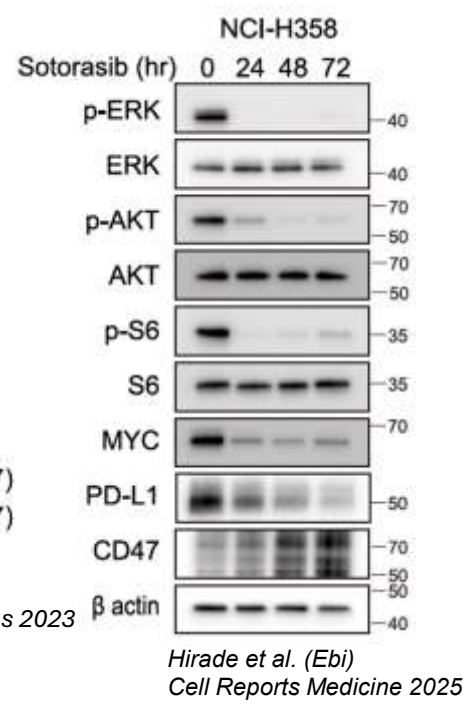
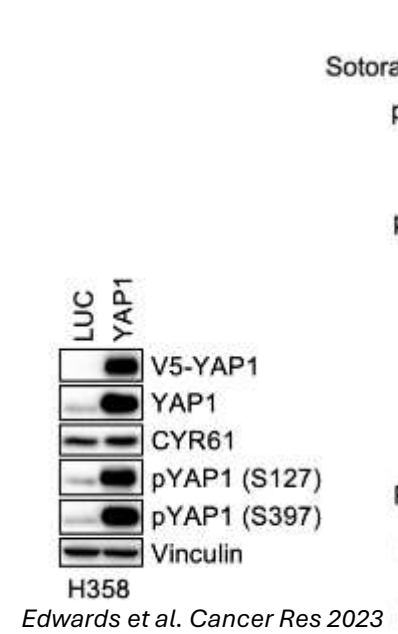
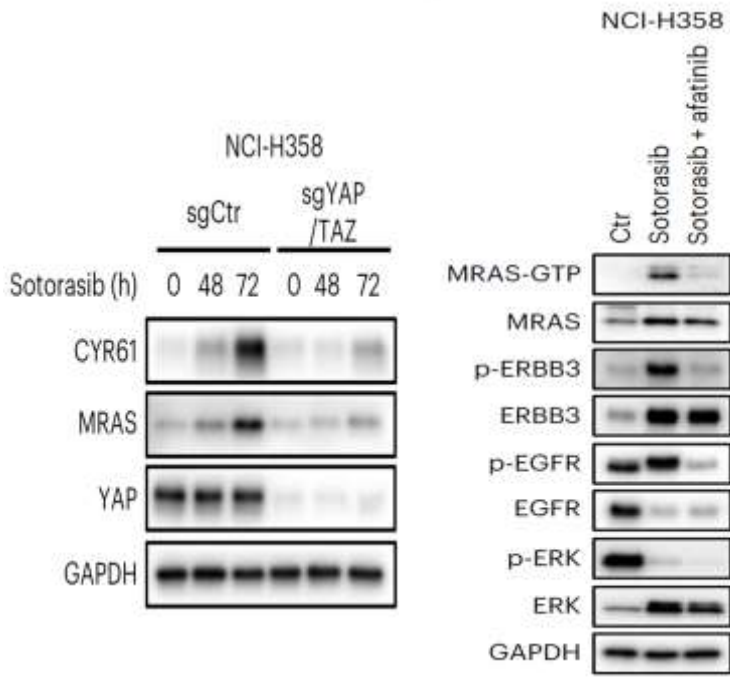
Jason J. Kwon et al. Nature 2022



Kwon & Hahn Mol Cell Biol 2021



Daniel Olmo

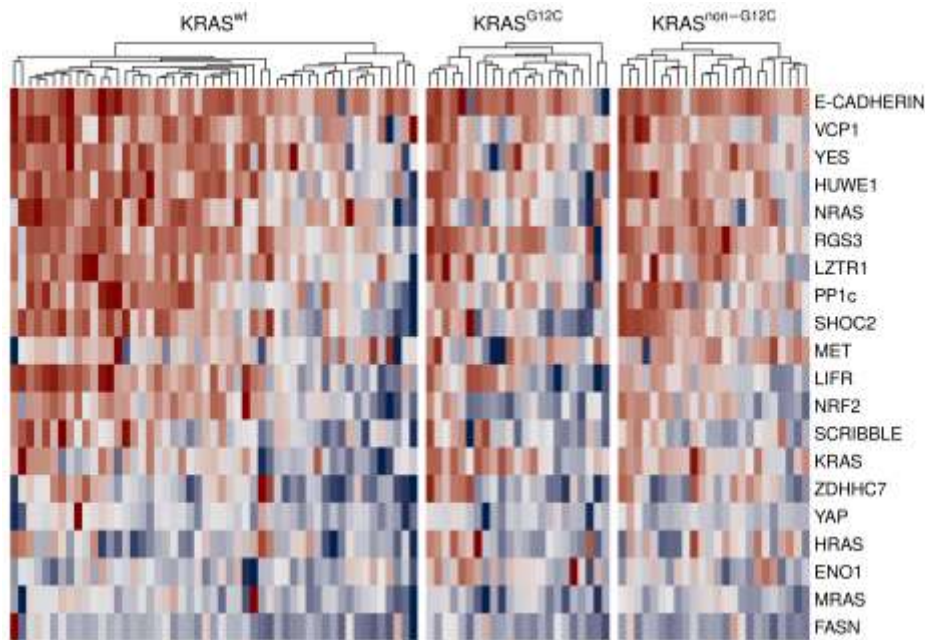


Adachi et al. (Ebi). Nat Cancer 2023

Zhang et al. Sci Signal 2014

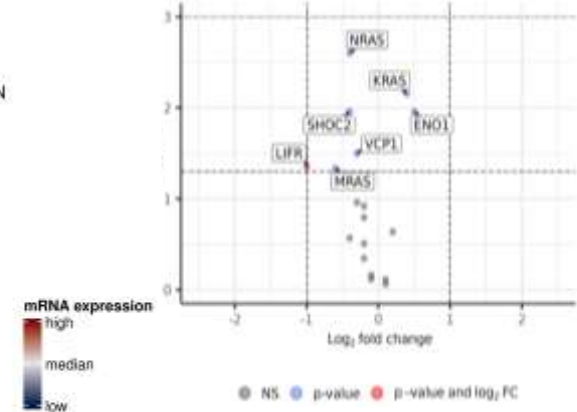
Chen et al. Acta Pharmacologica Sinica 2020

Heatmap for Gene Expression Analysis

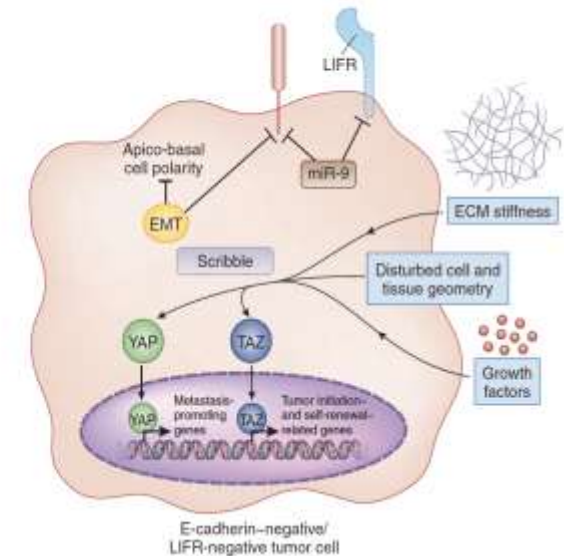
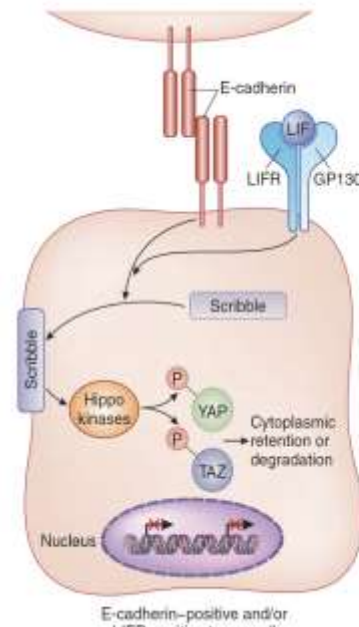


Ana Giménez-Capitán, Elizabeth Martínez

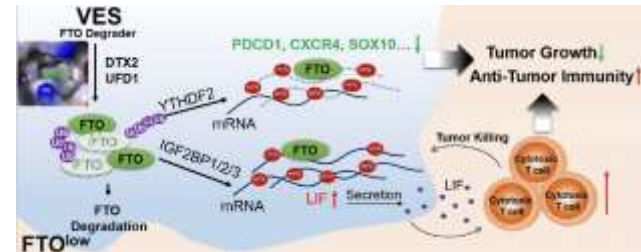
KRAS^{G12C} vs KRAS^{WT}



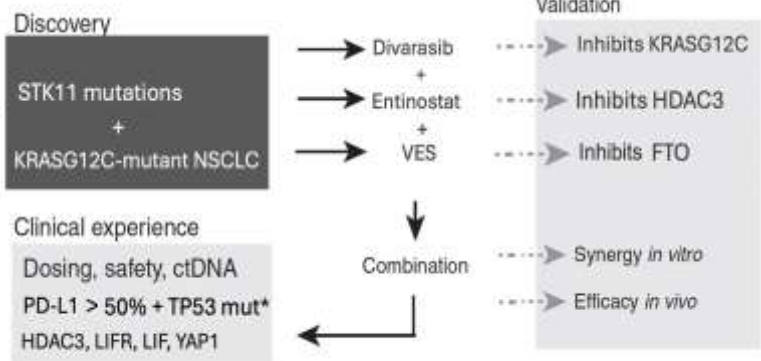
	p-value	KRAS ^{G12C}	KRAS ^{WT}
VCP1	0.032	Down-regulated	Up-regulated
NRAS	0.0025	Down-regulated	Up-regulated
ENO1	0.011	Up-regulated	Down-regulated
MRAS	0.046	Down-regulated	Up-regulated
LIFR	0.044	Down-regulated	Up-regulated
KRAS	0.007	Up-regulated	Down-regulated
SHOC2	0.011	Down-regulated	Up-regulated



Piccolo. Nat Med 2012

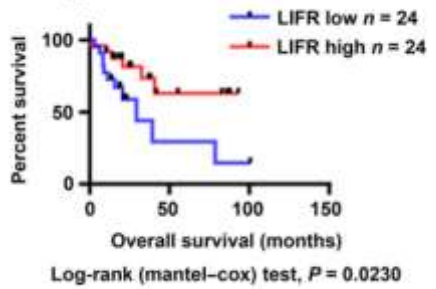


Cui et al. PNAS 2025



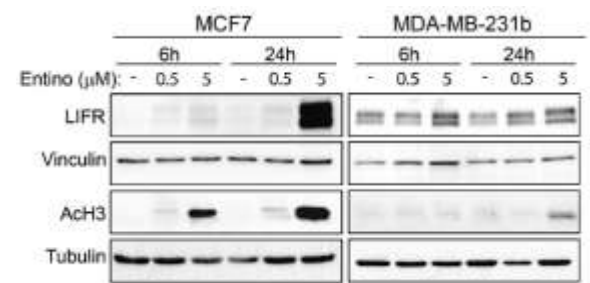
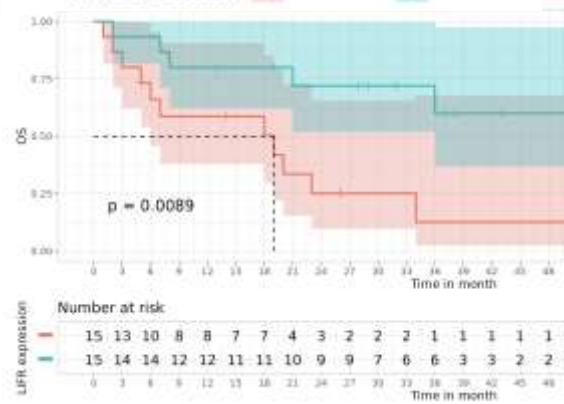
Rosell@

Lung adenocarcinoma with KRAS mutation



Liu et al. Mol Cancer Res 2021

LIFR expression



Clements et al. Oncogene 2021

*Divarasilb + entinostat + VES + atezolizumab

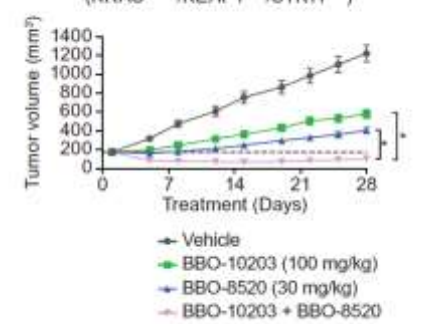
Compound	Company	Target	ON vs. OFF
Adagrasib (MRTX849)	Mirati/Bristol Myers Squibb	KRAS G12C	OFF
Sotorasib (AMG510)	Amgen	KRAS G12C	OFF
Divarasib (GDC-6036)	Roche/Genentech	KRAS G12C	OFF
Garsorasib (D-1553)	InventisBio	KRAS G12C	OFF
Glecirasib (JAB-21822)	Jacobio	KRAS G12C	OFF
MK-1084	Merck	KRAS G12C	OFF
Olomorasib (LY3537982)	Lilly	KRAS G12C	OFF
D3S-001	D3Bio	KRAS G12C	OFF
Fulzerasib (GFH925, IBI351)	GenFleet	KRAS G12C	OFF
ZG19018	Zelgen Biopharmaceuticals	KRAS G12C	OFF
Opnurasib (JDQ-443)	Novartis	KRAS G12C	OFF
BI-1823911	Boehringer Ingelheim	KRAS G12C	OFF
GH35	Suzhou Genhouse Bio	KRAS G12C	OFF
Elironrasib (RMC-6291)	Revolution Medicines	KRAS G12C	ON
FMC-376	Frontier Medicines	KRAS G12C	ON/OFF
BBO-8520	BridgeBio	KRAS G12C	OFF/ON
HS-10370	Hansoh	KRAS G12C	Undisclosed
HYP-209OPTSA	Sichuan Huiyu	KRAS G12C	Undisclosed
YL-15293	Shanghai YingLi	KRAS G12C	Undisclosed
BEBT-607	BeBetter Med	KRAS G12C	Undisclosed
BPI-421286	Betta Pharmaceuticals	KRAS G12C	Undisclosed
GEC255	GenEros Biopharma	KRAS G12C	Undisclosed
HBI-2438	HUYABIO	KRAS G12C	Undisclosed

Compound	Company	Target	ON vs. OFF
LY3962673	Lilly	KRAS G12D	OFF
Zoldonrasib (RMC-9805)	Revolution Medicines	KRAS G12D	ON
HRS-4642	Hengrui	KRAS G12D	OFF/ON
TSN1611	Tylgand	KRAS G12D	ON/OFF
VS-7375/GFH375	Verastem and GenFleet	KRAS G12D	ON/OFF
INCB161734	Incyte	KRAS G12D	ON/OFF
QTX3046	Quanta	KRAS G12D	OFF/ON
MRTX1133	Mirati/Bristol Myers Squibb	KRAS G12D	OFF/ON
RNK08954	Ranok Therapeutics	KRAS G12D	Undisclosed
GDC-7035	Roche/Genentech	KRAS G12D	Undisclosed
INCB186748	Incyte	KRAS G12D	Undisclosed
QLC1101	Qilu Pharmaceutical	KRAS G12D	Undisclosed
AZD0022	AstraZeneca	KRAS G12D	Undisclosed
ASP3082	Astellas	KRAS G12D	Undisclosed
ASP4396	Astellas	KRAS G12D	Undisclosed
PT0253	PAQ Therapeutics	KRAS G12D	Undisclosed

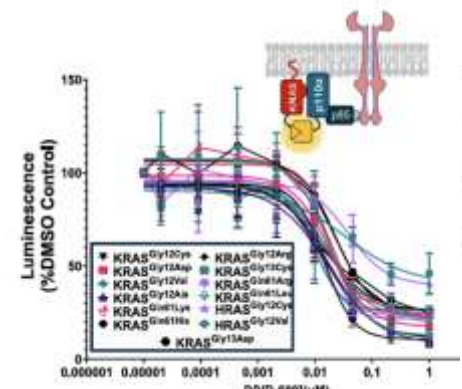
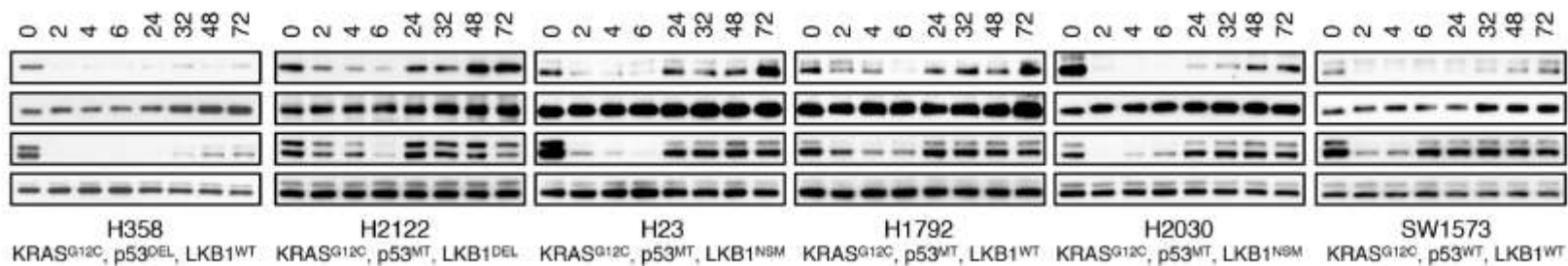
Compound	Company	Target	ON vs. OFF
BI-3706674	Boehringer Ingelheim	Pan-KRAS	OFF
LY4066434	Lilly	Pan-KRAS	OFF
ALTA-3263	Alterome	Pan-KRAS	ON
PF-07934040	Pfizer	Pan-KRAS	ON/OFF
BGB-53038	BeiGene	Pan-KRAS	Undisclosed
PF-07985045	Pfizer	Pan-KRAS	Undisclosed
QTX3034	Quanta	Pan-KRAS (G12D preferred)	OFF
QTX3544	Quanta	Pan-KRAS (G12V preferred)	OFF/ON
LUNA18	Chugai	Pan-RAS	OFF
Daraxonrasib (RMC-6236)	Revolution Medicines	Pan-RAS	ON
YL-17231/TEB-17231	Shanghai YingLi/280 Bio	Pan-RAS	Undisclosed

Richard Y. Ebright et al. Cancer Discov 2025

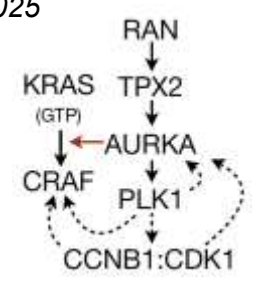
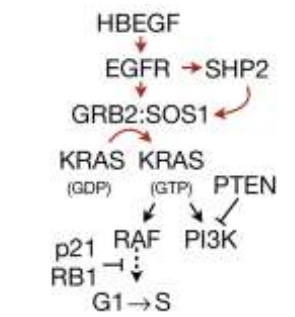
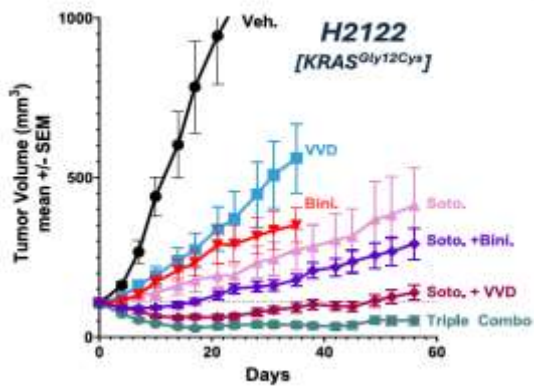
G12CI-Resistant Model NCI-H2122 NSCLC CDX (KRAS^{G12C}/KEAP1^{mut}/STK11^{mut})



Simanshu et al. Science 2025

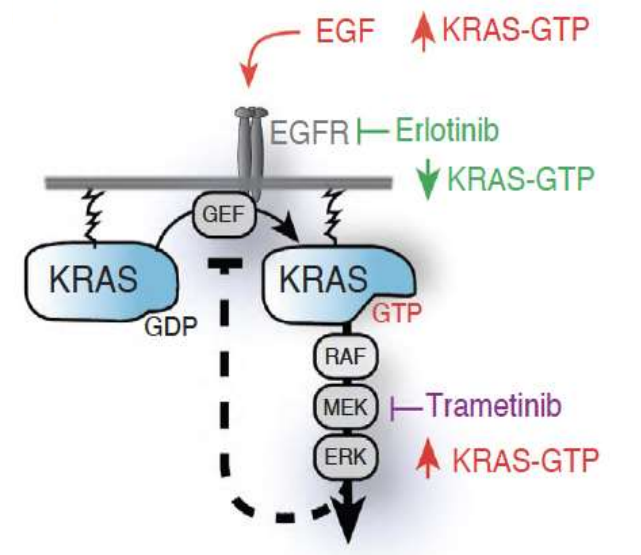
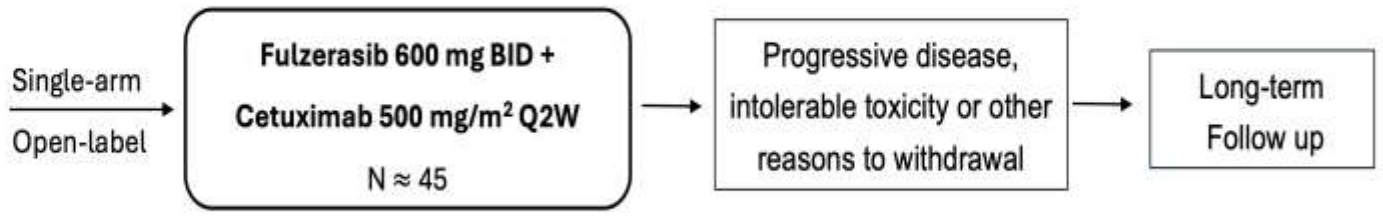


Klebba et al. Science 2025

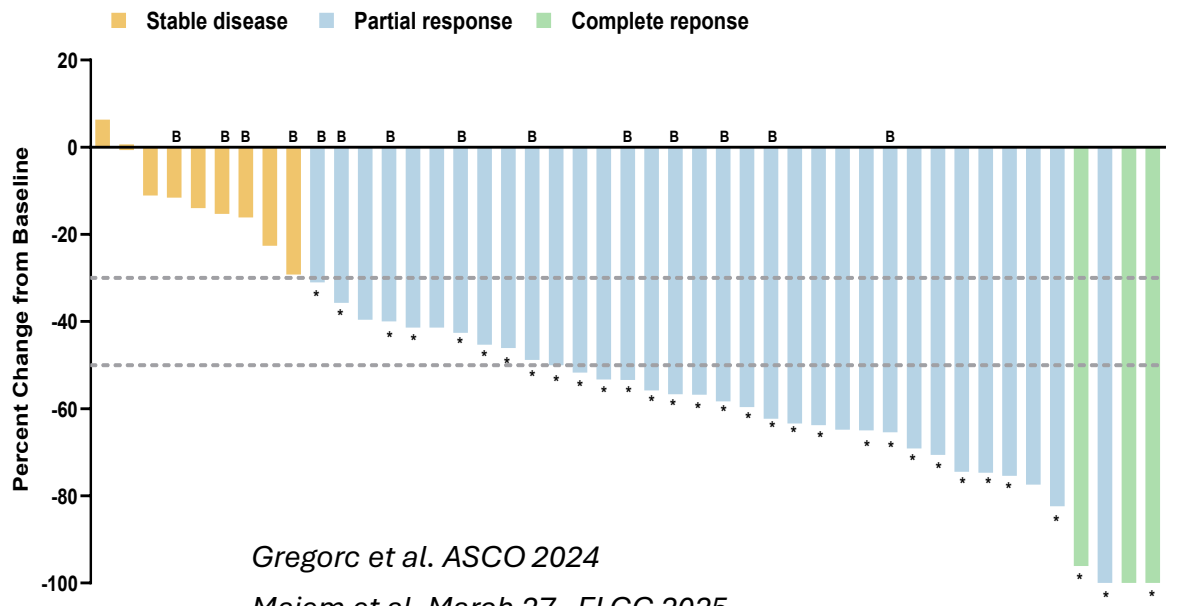


Jenny Y. Xue..., Piro Lito. Nature 2020

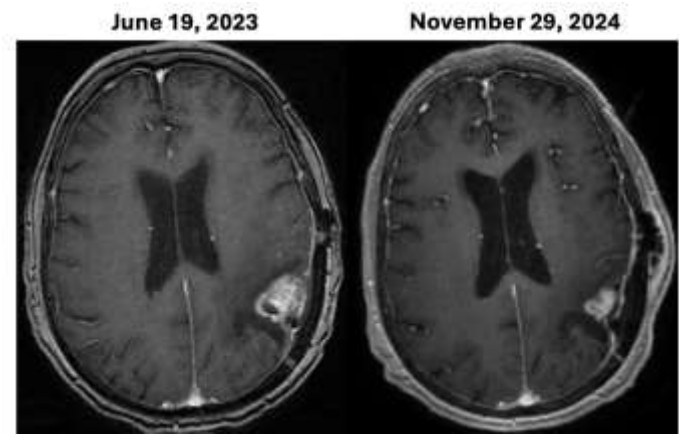
- Key eligibility criteria**
- Pathologically confirmed, advanced G12C KRAS mutated NSCLC*
 - Treatment naive
 - ECOG PS 0 - 1



Matthew P. Patricelli et al. *Cancer Discov* 2019

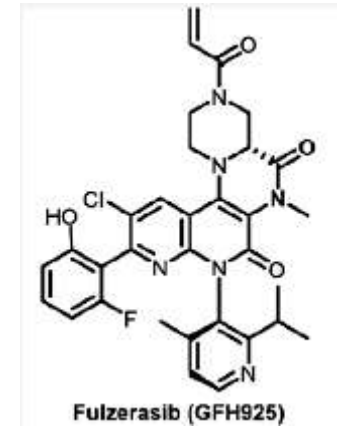


Gregorc et al. *ASCO* 2024
 Majem et al. *March 27, ELCC* 2025
 Manuscript under review



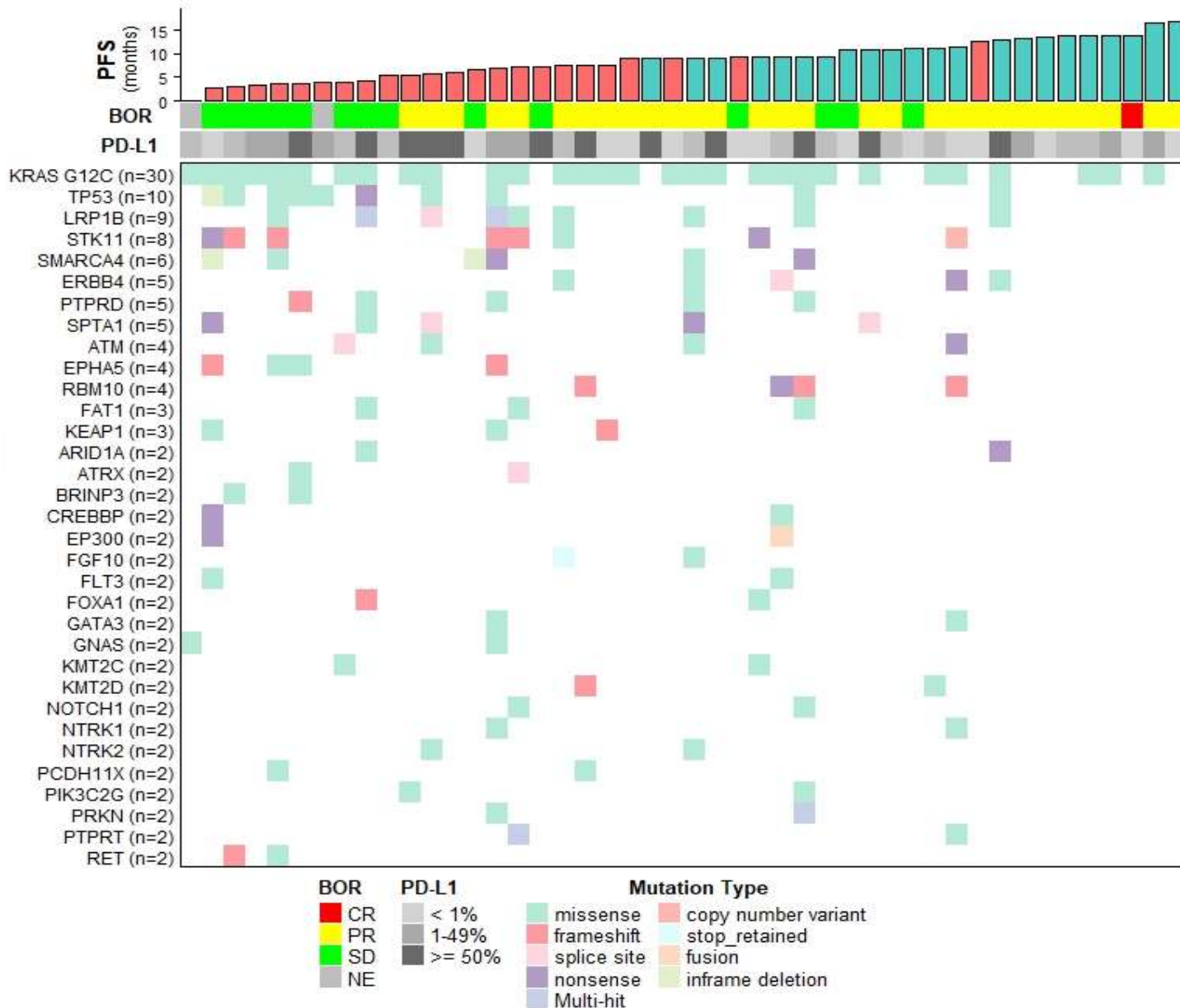
A 74-year-old woman with KRAS G12C LUAD with lung and brain metastases. July 4, 2023, starts KROCUS trial treatment PFS: 22 months +
 Courtesy of Dr. Andrés Aguilar

Cysteine Profiling of GFH925 in the NCI-H358



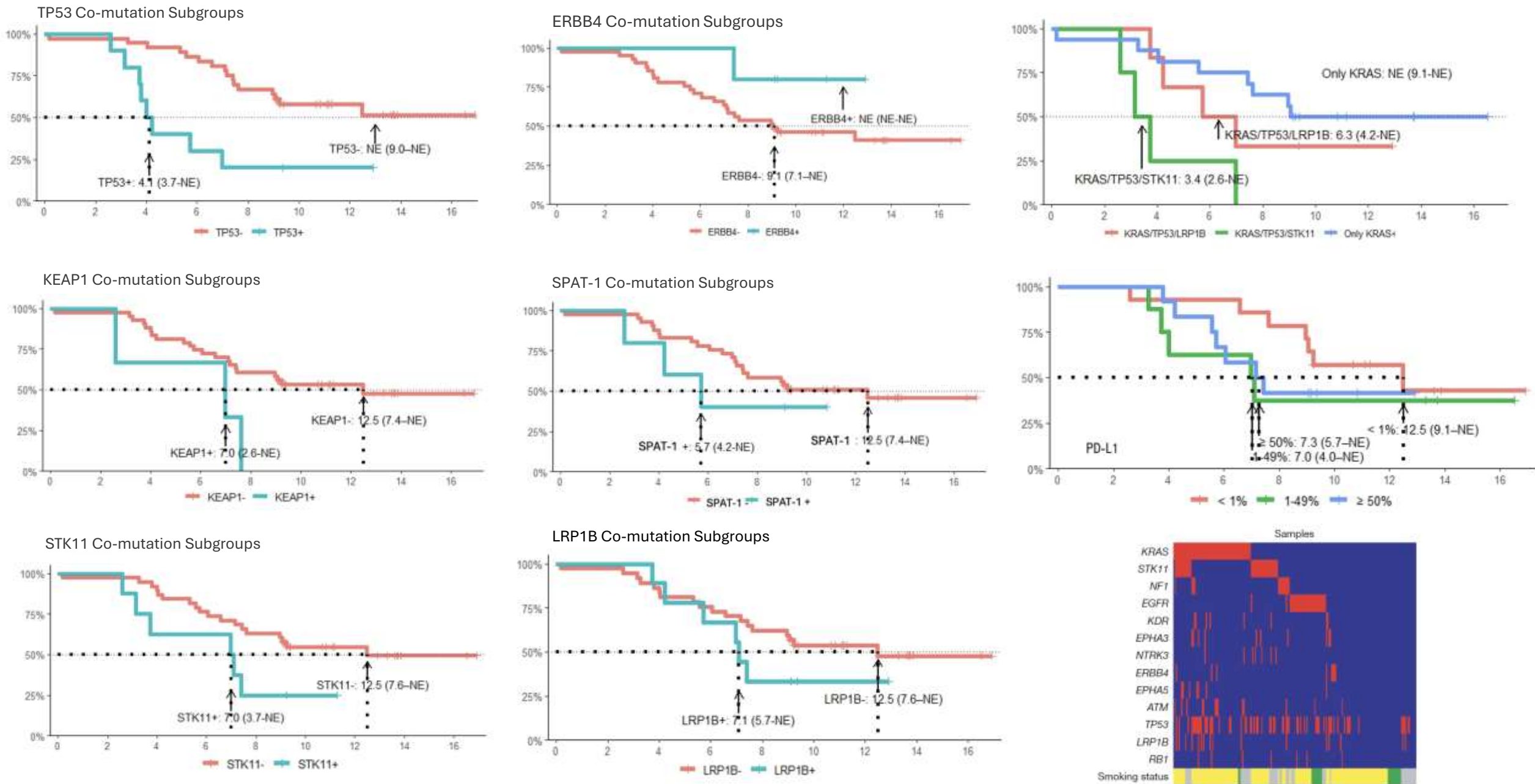
Four other proteins (RTN4, HMOX2, VDAC2, and RTN3) were found to be modified by GFH925
 Jiang et al. *J Med Chem*, 2025

Fulzerasib plus cetuximab in KRASG12C-mutant NSCLC (KROCUS)

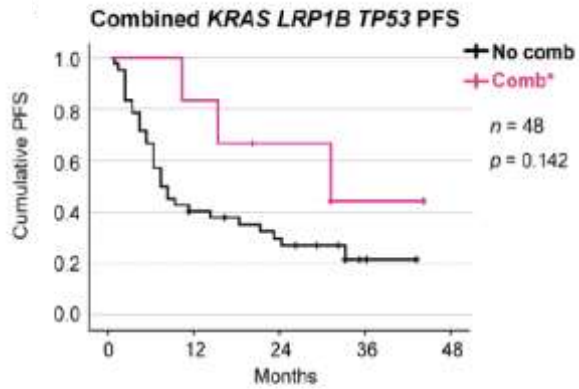


KRASG12C-mutant NSCLC (KROCUS trial)		Patients (n = 47)
Median age (range) - yr	68 (46, 87)	
Female Sex – no (%)	22 (46.8)	
Race – no. (%)†		
White	45 (95.7)	
Not reported	2 (4.3)	
Smoking status – no. (%)		
Never	2 (4.3)	
Former	34 (72.3)	
Current	11 (23.4)	
ECOG performance-status score – no. (%)‡		
0	21 (44.7)	
1	26 (55.3)	
Histological type – no. (%)		
Adenocarcinoma	46 (97.9)	
Large cell carcinoma	1 (2.1)	
Stage IV disease at screening – no. (%)	45 (95.7)	
Site of metastases – no. (%)		
Brain	16 (34.0)	
Bone	11 (23.4)	
Adrenal gland	9 (19.1)	
Previous therapy for nonmetastatic disease – no. (%)		
Thoracic radiotherapy	4 (8.5)	
Neoadjuvant therapy	1 (2.1)	
Adjuvant therapy	4 (8.5)	

PFS of fulzerasib plus cetuximab in KRASG12C-mutant NSCLC (KROCUS)

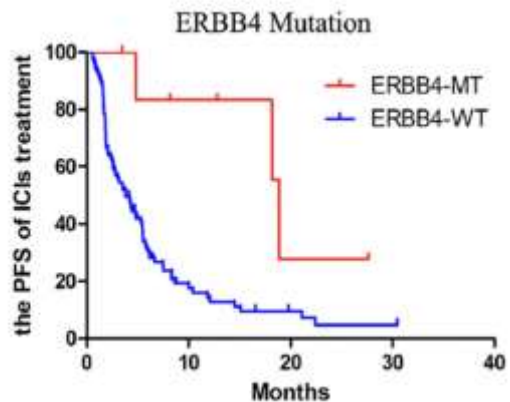


ICI outcomes in LUAD



No at risk	0	12	24	36	48	Median survival
No comb	42	16	7	1	1	7 months
Comb*	6	5	3	1	1	31 months

Eklund et al. *J Exp Clin Cancer Res* 2025

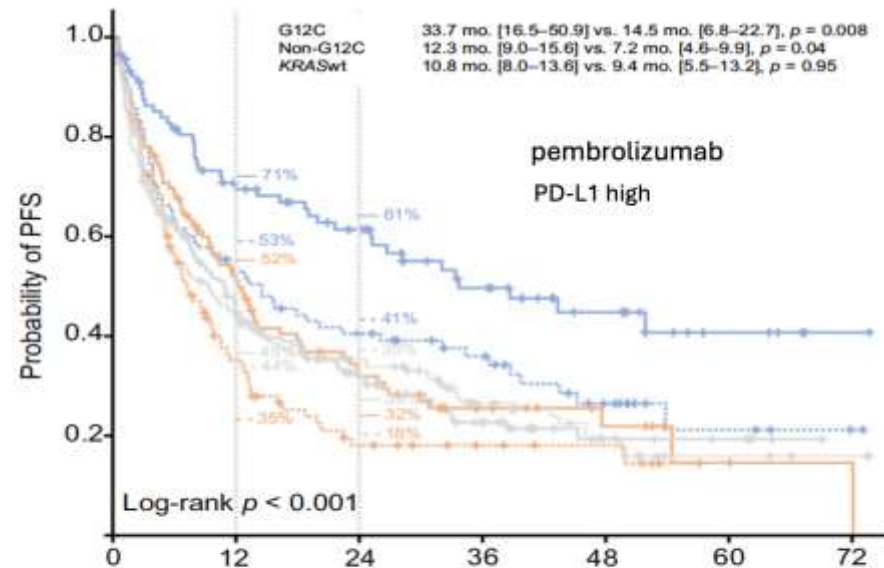


Xilin Hu et al. *Mol Med* 2021

Lung adenocarcinoma

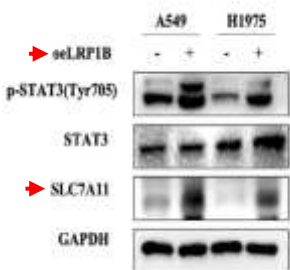
CIC co-occurring mutations (%)	
<i>TP53</i>	66.7
<i>KRAS</i>	34.7
<i>PTPRD</i>	36.0
<i>KEAP1</i>	28.0
<i>STK11</i>	26.0
<i>FAT1</i>	24.7
<i>EPHA1</i>	25.0
<i>EGFR</i>	23.8

Ballesteros-González et al. *EMBO Mol Med* 2025

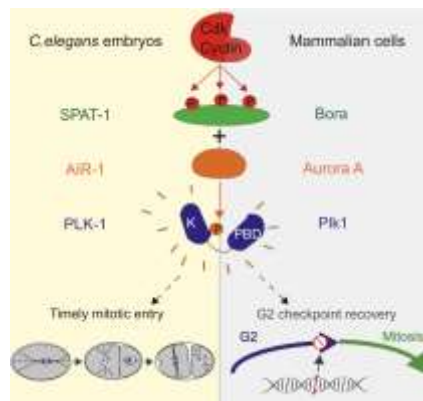


G12C/ <i>TP53</i> mut	90	56	42	27	15	5	1
G12C/ <i>TP53</i> wt	83	43	31	22	11	4	1
Non-G12C/ <i>TP53</i> mut	96	46	26	14	6	2	1
Non-G12C/ <i>TP53</i> wt	98	29	12	7	5		
<i>KRAS</i> wt/ <i>TP53</i> mut	171	71	40	21	7	5	
<i>KRAS</i> wt/ <i>TP53</i> wt	156	66	46	22	12	4	2

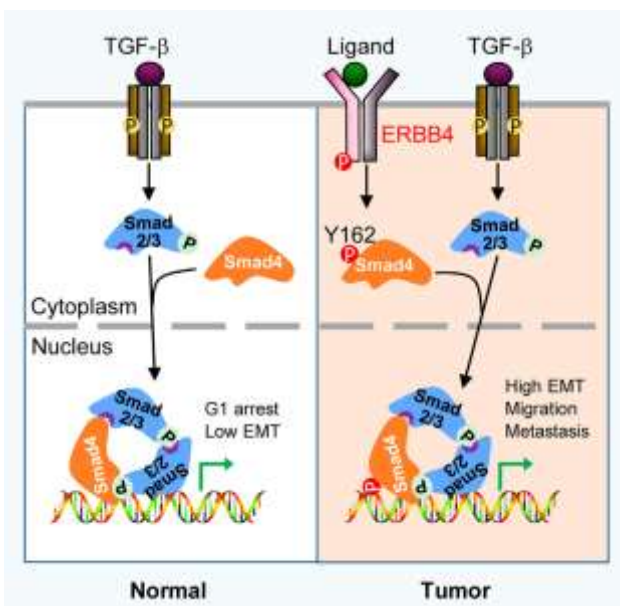
Philip Bischoff et al. *JTO* 2024



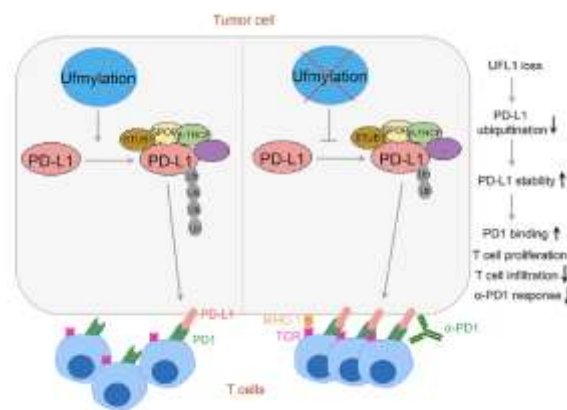
Ke et al. *Cancer Medicine* 2024



Thomas et al. *Cell Reports* 2016

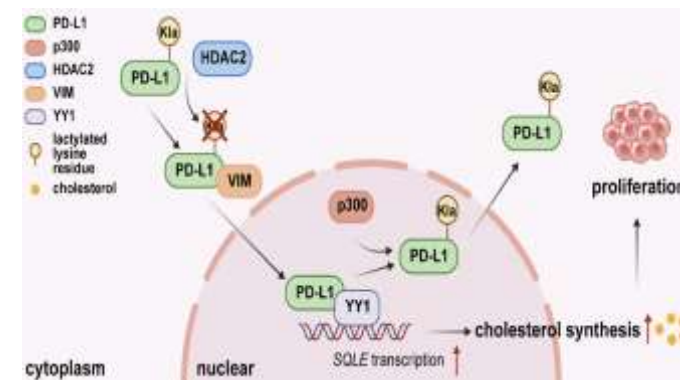


Luo et al. *Cell Reports* 2025



PD-L1 UFMylation via UFL1

Zhou et al. *PNAS* 2023



HDAC2 dependent delactylation of PD-L1 K189 promotes vimentin-mediated nuclear translocation of PD-L1.

Xue Wang et al. *Cancer Letters* 2025

↑IRE1α

Lu. Science 2023
Xue. Cell 2024
Luo. CDD 2025

Sen. Cancer Res 2025

Antonucci. Nature Cancer 2025

Selinexor —| nEZH2 [cEZH2 degrades DLC1]
XPO1

Chen. CDD 2025

Canon. Nature 2019
Dilly. Cancer Discovery 2024

Skoulidis. Nature Medicine 2025

STK11/KEAP1

medroxyprogesterone 17-
acetate (MTPA) as
a weak pan-AKR1Ci
[NRF2 regulates AKR1C,
AKR1C2 and AKR1C3]

Wohlhieter. Cell Reports 2020

KRASG12C/TP53mut/PD-L1 >50%

+/- LRP1B (lipoprotein receptor-related protein 1B)

Bischoff. JTO 2024; Eklund. Journal of Experimental and Clinical Research 2025

KRASG12C/STK11mut/KEAP1mut

SCD1 (stearoyl-CoA desaturase 1)

EZH2-NRF2 (nuclear factor erythroid-2 related factor 2)

EZH2 → ATOH8 → SCD1
(enhancer of zeste homolog 2)

EMT

SCD1-brain metastases

Chemotherapy synergy with KRAS inhibitors

docetaxel or carboplatin

ATMmut (16.5%)

Code Break 200

PFS 8.25 mo

vs

sotorasib 4.17 mo

NRF2

NSD2 [nuclear-receptor-binding SET domain containing-2]

Niemann-Pick c-like 1 (NPC1L1)
fibrinogen-like protein 1 (FGL1)

Wee inhibitors (Adavosertib)

CD47 inhibitors (IBI-188)

PFS > 33mo

pembrolizumab

+

KRASG12Ci
(olomorasib)

+

ebastine

+

entinostat

+

VES

+

docetaxel

Consider also
repurposing drugs

ezetimibe

+

aspirin

HDAC3

entinostat →

LIFR ↑

Vitamin E succinate →

LIF ↑

Scribble

↓ YAP1

Zoppoli. PNAS 2012

Nilsson et al. JTO, in press

Singh. PLOS Medicine 2016

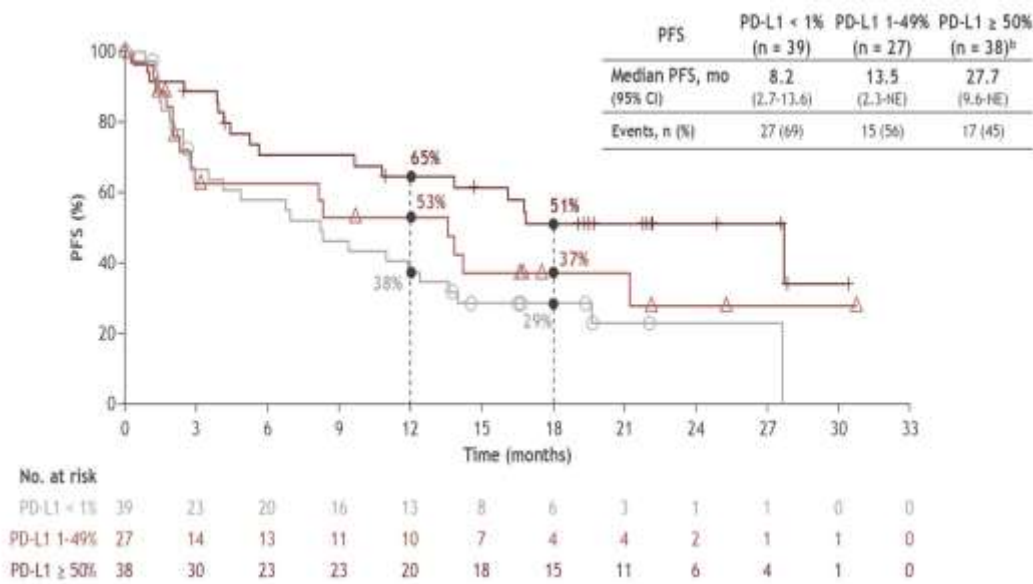
Jeong. Nature 2025

Zi. Innovation 2025

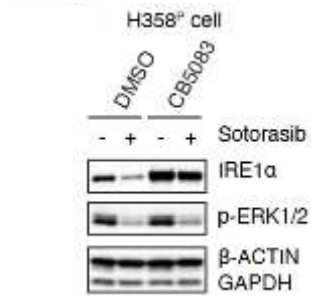
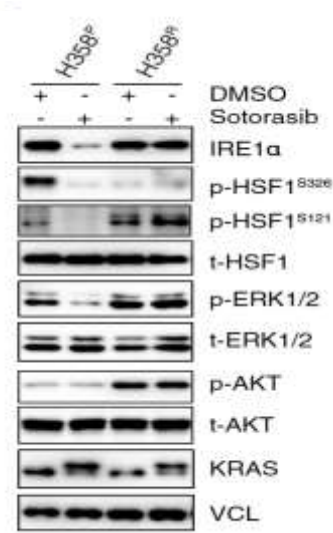
Zhou. CDD 2025

Hirade. Cell Reports Medicine 2025

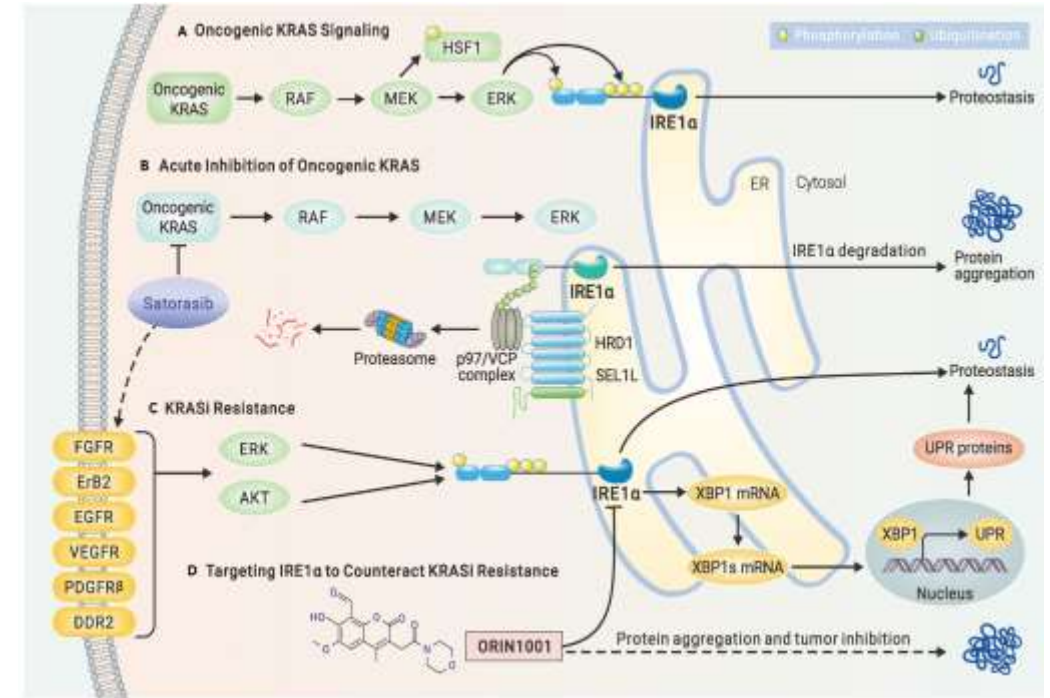
KRYSTAL-7: ADA + PEMBRO in 1L KRAS^{G12C} NSCLC



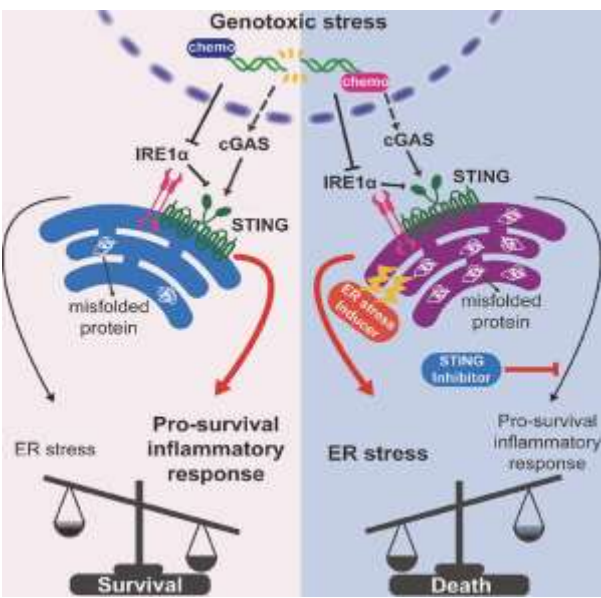
Jänne et al. ASCO 2025



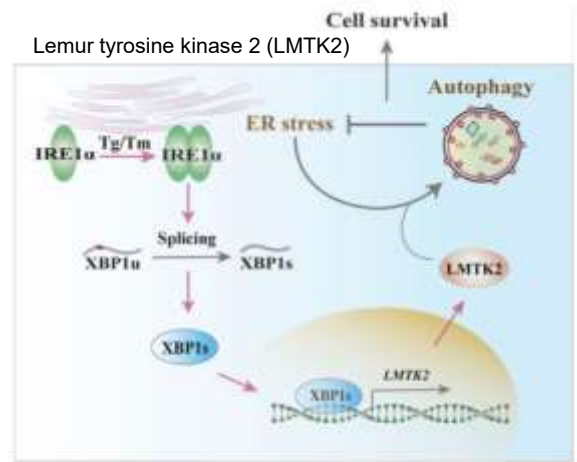
Lv et al. Science 2023



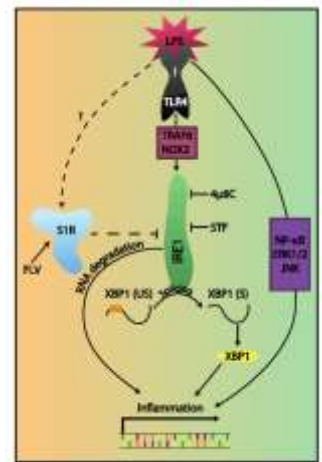
Song, Zhou & Westover. The Innovation, 2023



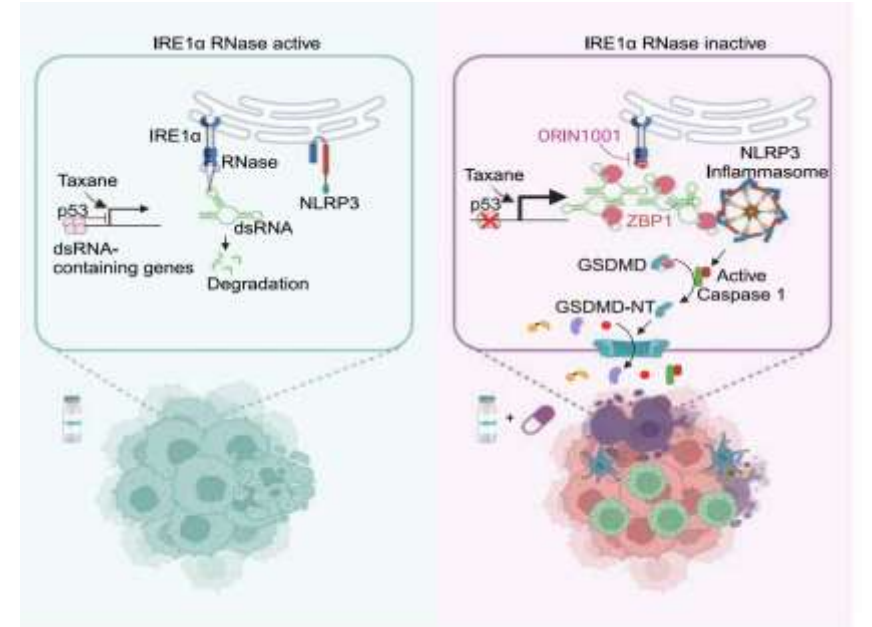
Luo et al. CDD 2025



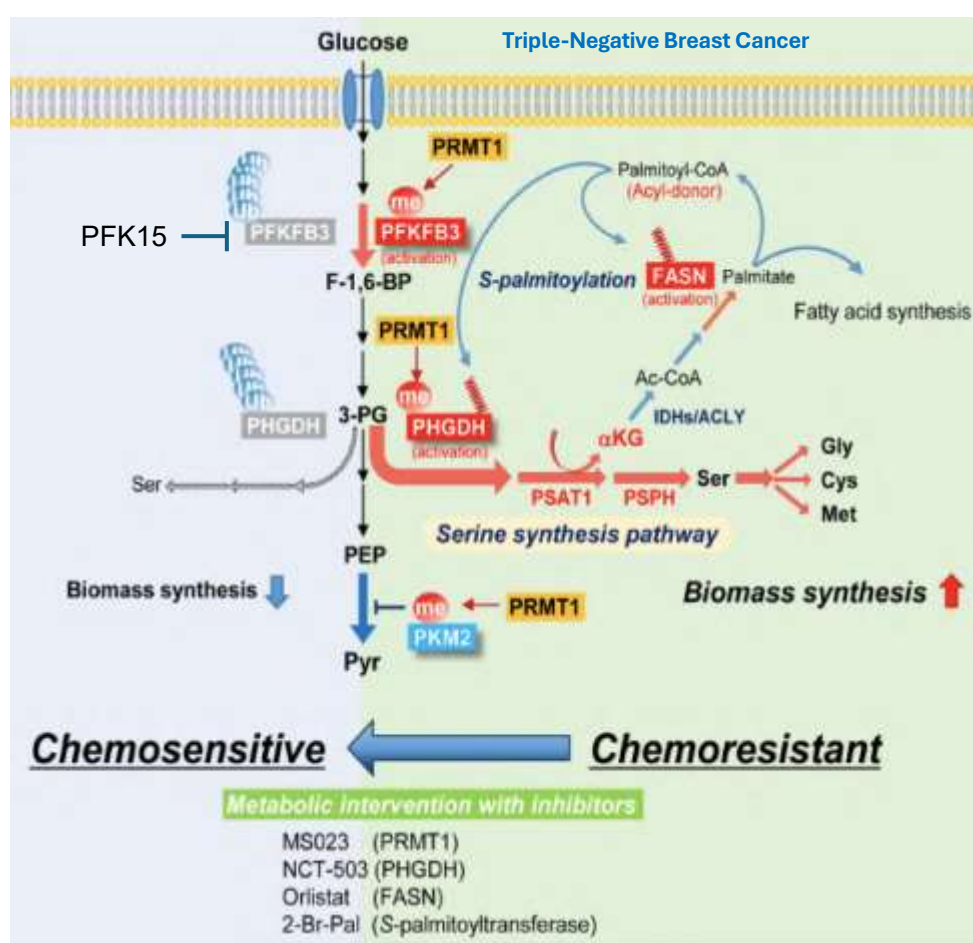
Lun et al. Cancer Letters, 2025



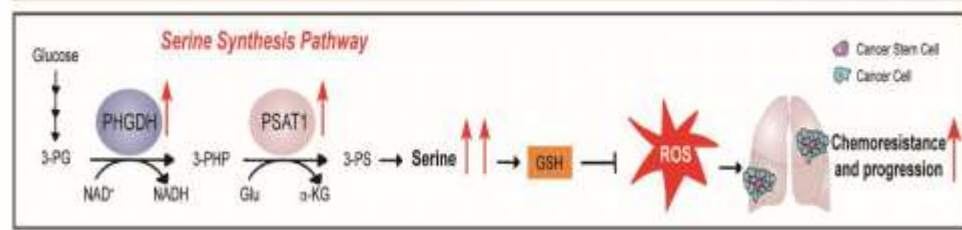
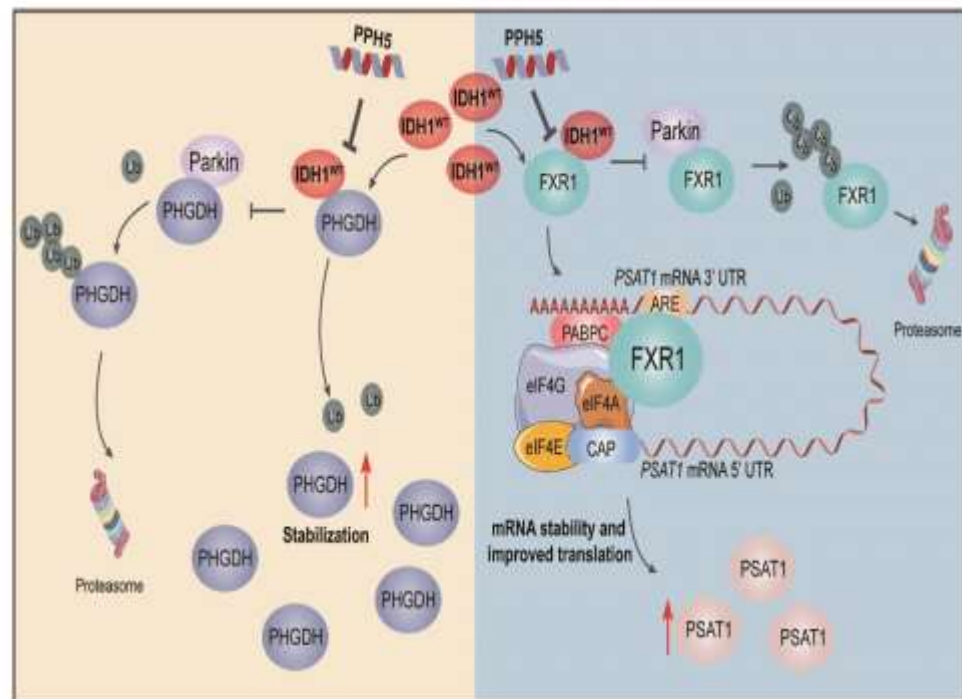
fluvoxamine
Rosen et al. Sci Transl Med 2019



Triple-Negative Breast Cancer
Xu et al. Cell 2024

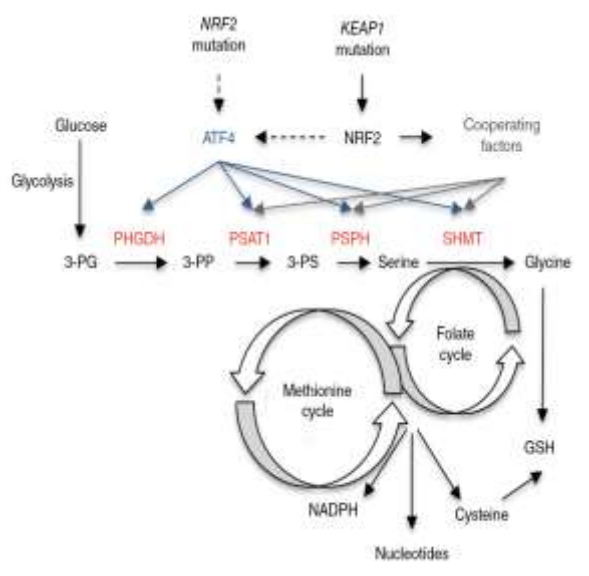


Yamamoto et al. Cancer Res 2024

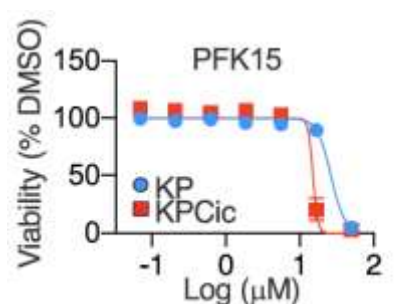


IDH1WT interacts with and stabilizes PHGDH and fragile X-related protein-1 (FXR1)

Cheng Zhang et al. Sci Transl Med 2023

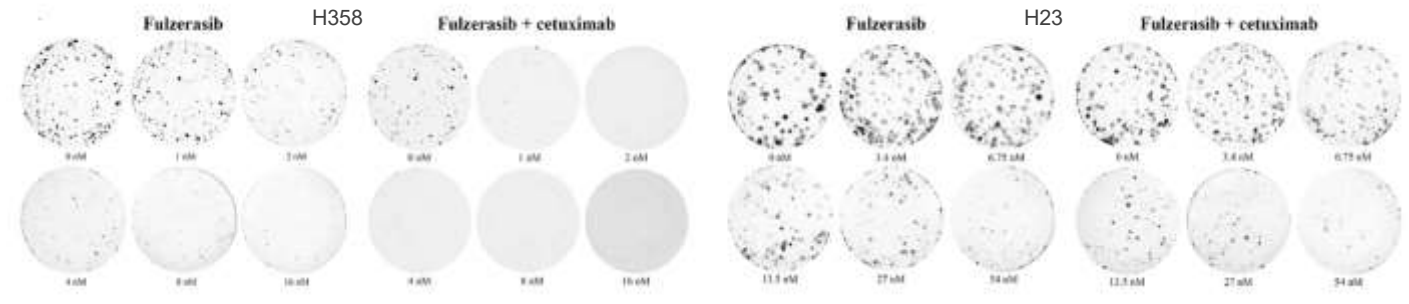


DeNicola et al. Nat Genet 2015

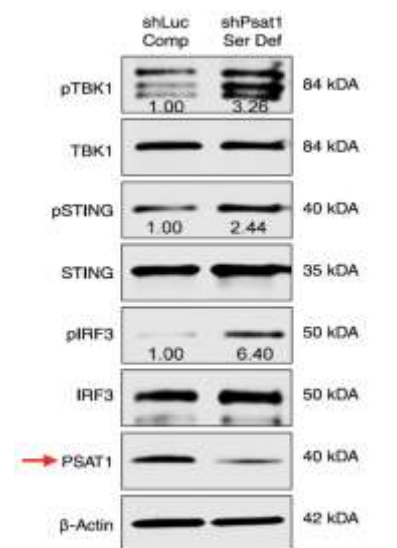


IC50 (μM)		
Drug	KP	KPCic
Quizartinib	>100	>100
Tx-1123	26.39	16.79
PFK15	26.43	15.05

Ballesteros-González et al. EMBO Mol Med, 2025



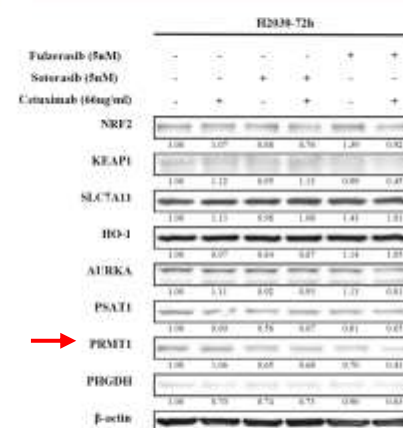
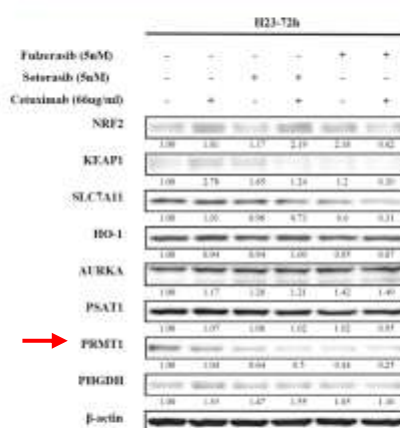
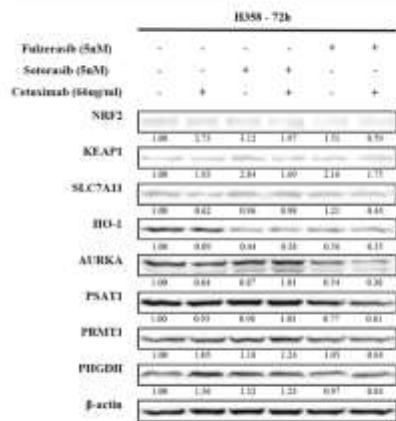
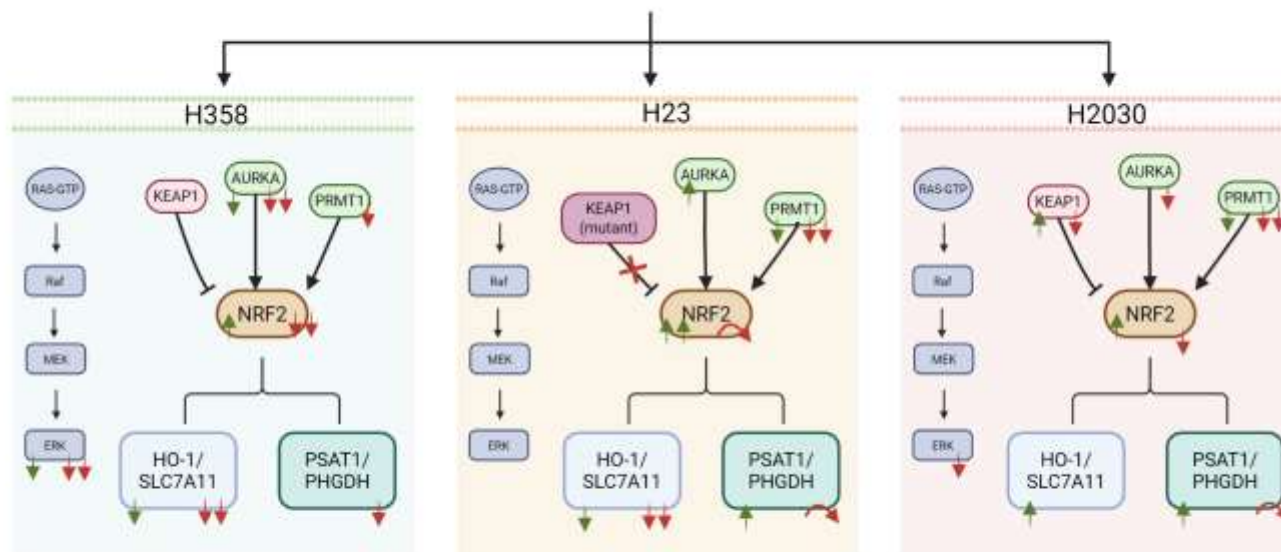
Mengxin Zhou et al. ESMO Congress, Berlin 2025



Saha et al. Cancer Res 2024

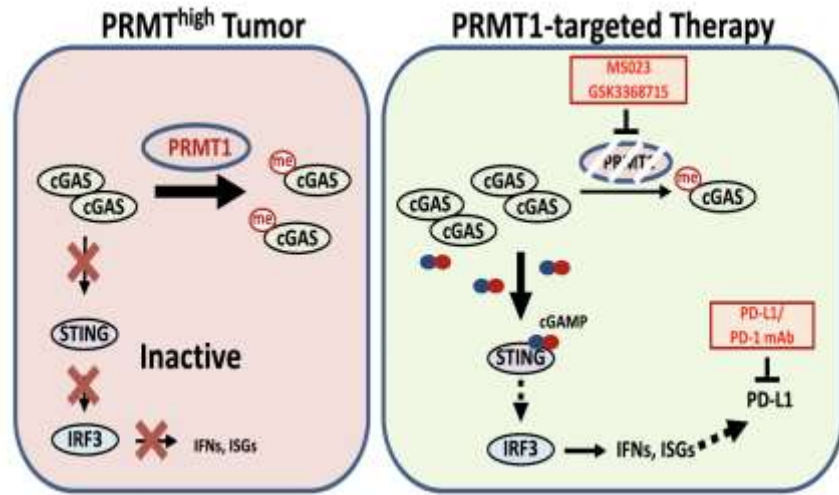
Visual Guide:

- **Treatment:** Green arrows (fulzerasib single-agent); Red arrows (fulzerasib-cetuximab combination)
- **Effect:** ↑/↓ (increase/decrease); ↻ (reverses mono-therapy-induced upregulation to baseline); Single-headed (moderate); Double-headed (strong)

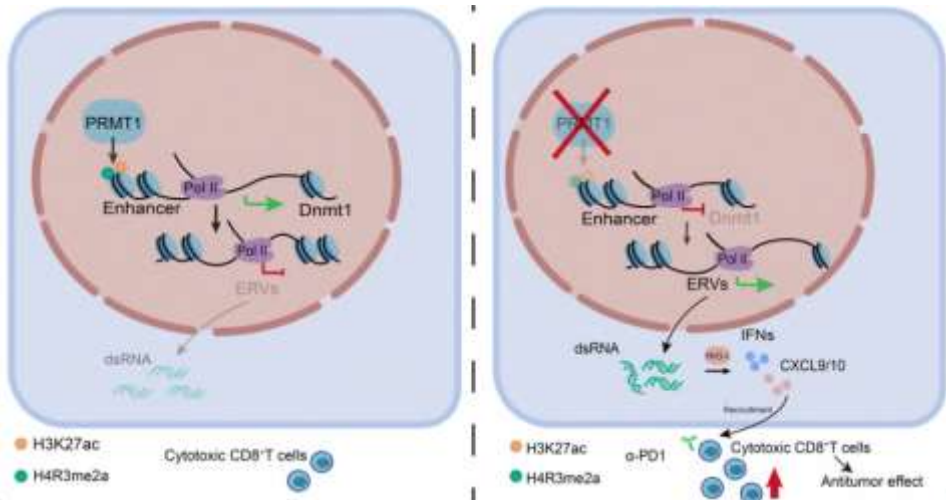
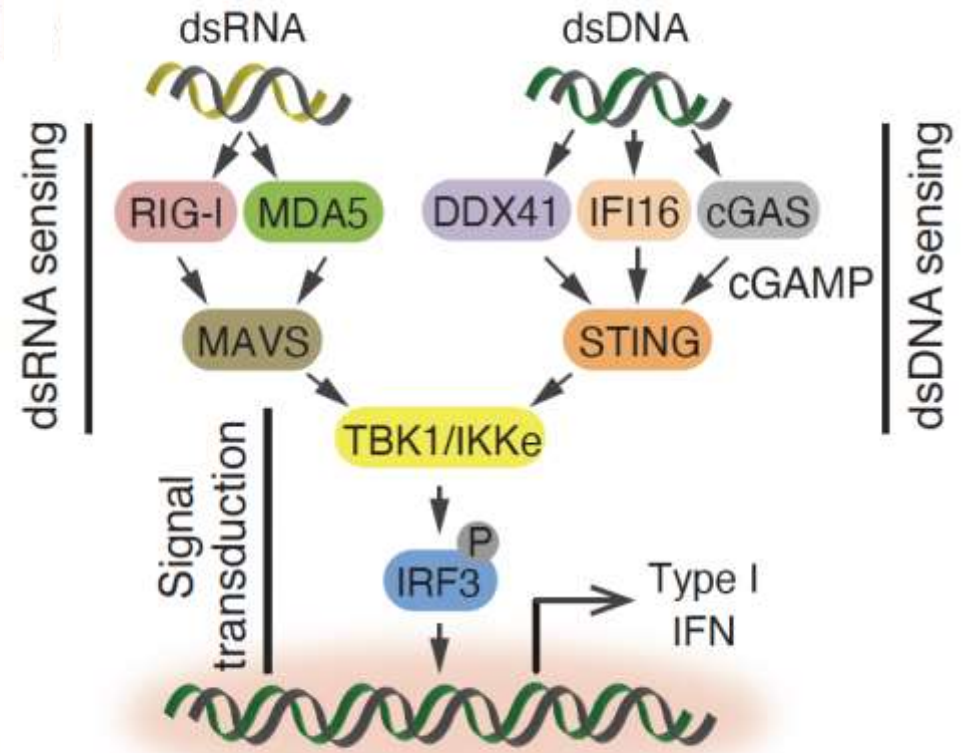


Colony formation inhibition

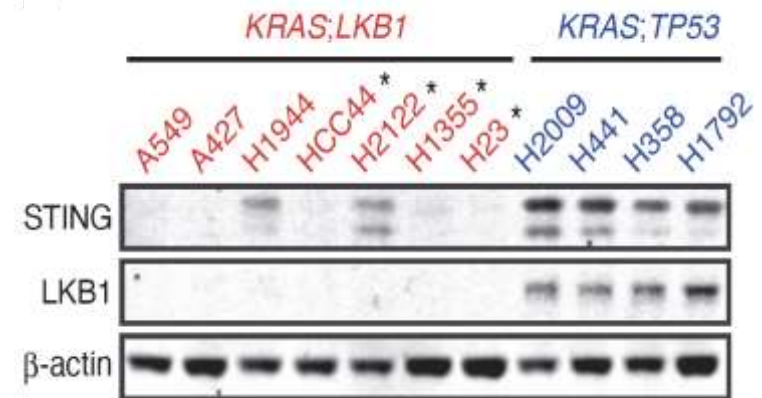
PRMT1 ablation increases PD-L1 expression



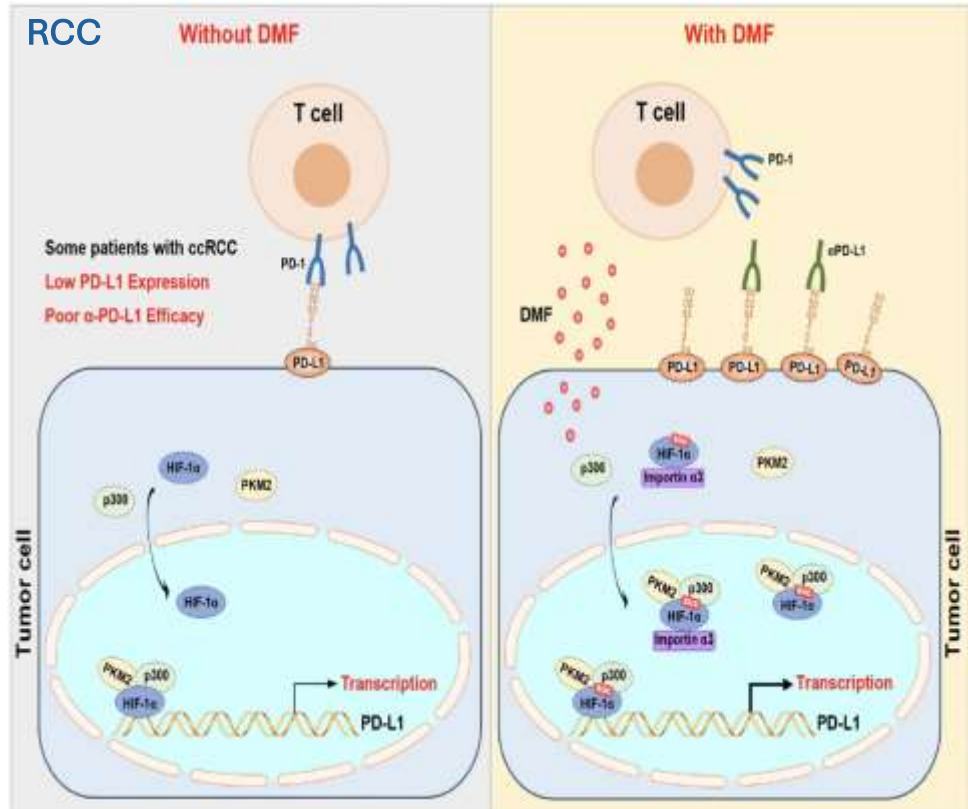
Jing Liu et al. (Wenyi Wei) Nat Commun 2023



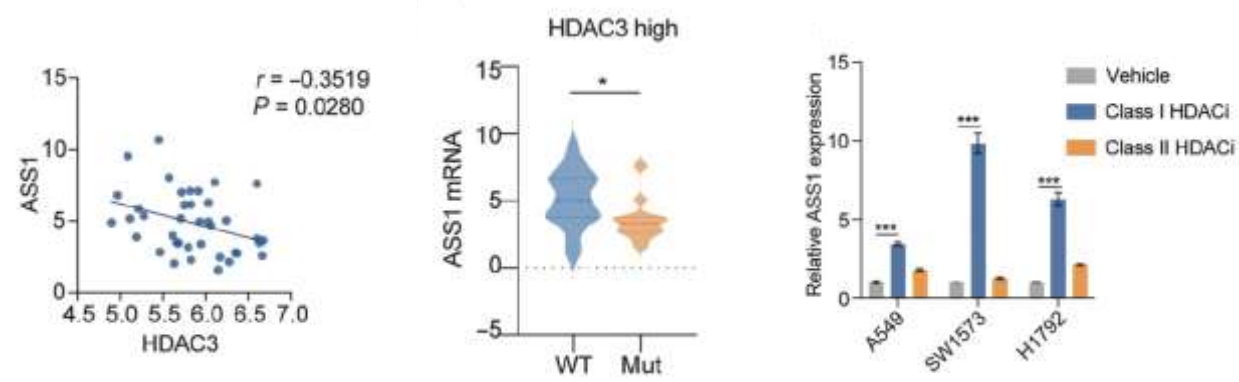
Hongru Tao et al. Cancer Res 2024



Kitajima, ... Barbie. Cancer Discovery 2019



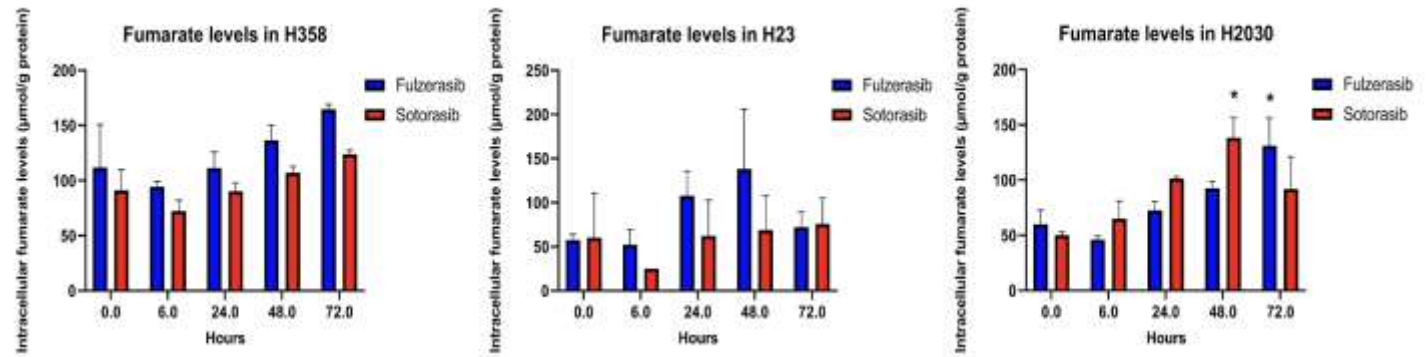
Yi Gao et al. Cell Death Disease 2025



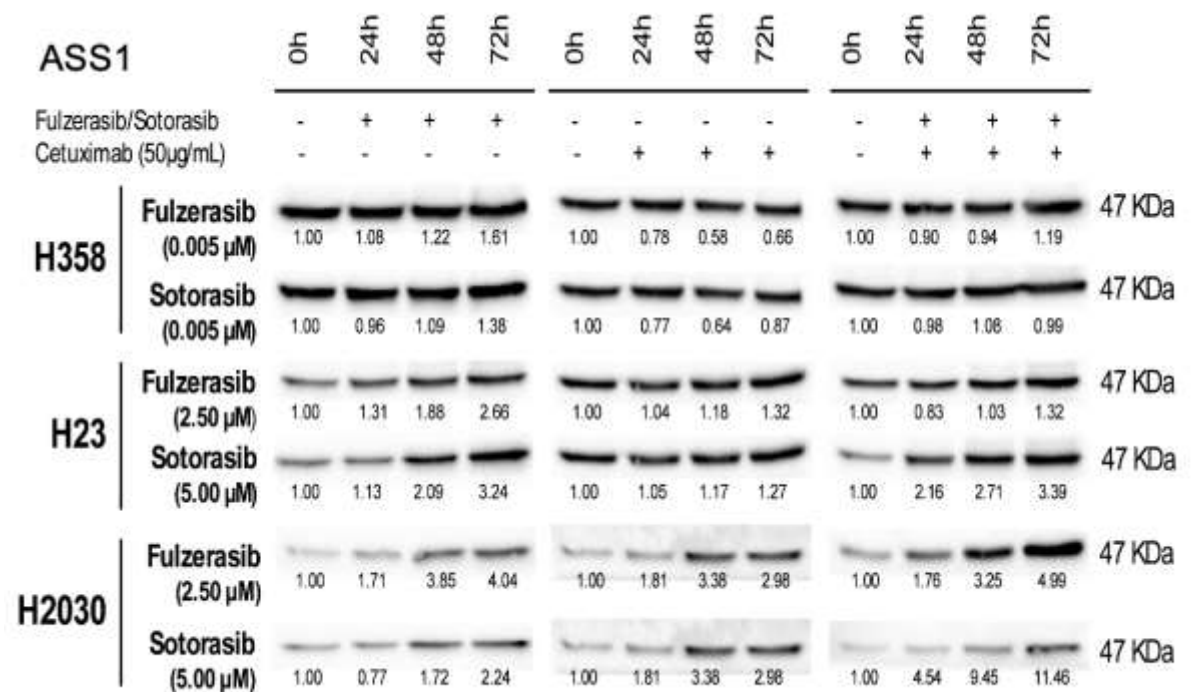
Gai et al. Cancer Res 2024

c-Myc, HIF-1α, SP4 and p53 activate ASS1

p53-activates ASS1, an intrinsic AKT repressor (Miyamoto et al. Sci Adv, 2017)



Argininosuccinate synthase 1 (ASS1)



Daniel Olmo et al. ESMO Congress Berlin, 2025

Exploring actionable therapeutic targets

1. HDAC3 mediates T cell exclusion from KRAS mutant NSCLC.

HDAC3 (2) inhibition increases (VEGFA) synergy with bevacizumab, unleashing CD8 + T cell infiltration + anti-PD-1 (MSS CRC)

McGuire et al. PNAS 2023, Eichner et al. Sci Adv 2023, Wang et al. Cancer Discovery 2025, Wang et al. Nat Med 2024.

Bispecific antibody ivonescimab (HARMONi-2) (*Xiong et al. Lancet 2025*)

2. Low LIFR in KRAS G12C NSCLC. HDAC inhibitors induce LIFR; VES therapy decreases LIF (leukemia inhibitory factor) mRNA decay.

LIFR/LIF opposes YAP1 activation (*Chen et al. Nat Med 2012*).

EZH2 inhibitors could recover ATOH8 and suppress SCD1.

EZH2 inhibitor synergistic with chidamide in T-cell lymphoma.

Clements et al. Oncogene 2021, Cui et al. PNAS 2024, Wu et al. CDD 2025.

[Ebastine, tazemetostat] (*Li et al. Mol Cancer Ther 2020, Gounder et al. Lancet Oncology 2020*)

3. PRMT1 inhibition activates interferon signaling and elevates tumor-infiltrating lymphocytes

Liu et al. Nat Commun 2023, Tao et al. Cancer Res 2023, Wang et al. CDD 2025

Cetuximab + fulzerasib decreases PRMT1 in KEAP1 and STK11 co-mutated KRASG12C cell lines.

Mengxin Zhou, Jordi Codony-Servat

4. Fumarate levels induce PDL1 expression

Gao et al. CDD 2025

Cetuximab + fulzerasib increase ASS1 and fumarate levels in KEAP1/STK11 co-mutated KRAS G12C cell lines.

Daniel Olmo, Miguel Ángel Molina-Vila

Pangaea Oncology, Dexeus University Hospital: bridging preclinical and clinical research

María González-Cao¹, Carlos Pedraz², Miguel Ángel Molina-Vila^{2*} and Rafael Rosell^{1,2*}

Molecular Cancer 2024



Clara Mayo, Ana Giménez-Capitán, Daniel Olmo-González, Miguel Ángel Molina-Vila



Mengxin Zhou, Jèssica González, Jordi Codony-Servat, Kevin València-Clua



Institut Germans Trias i Pujol, Badalona, Barcelona





Thank you and
congratulations to the
speakers and audience and
the Spanish Lung Cancer
Group

In collaboration with: Yu Wang, Haige Shen, Alan Zhu,
Yue Zhang, Yue Shen from Genfleet, Shanghai, China