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Targeted Therapies for RAS-Mutant NSCLC

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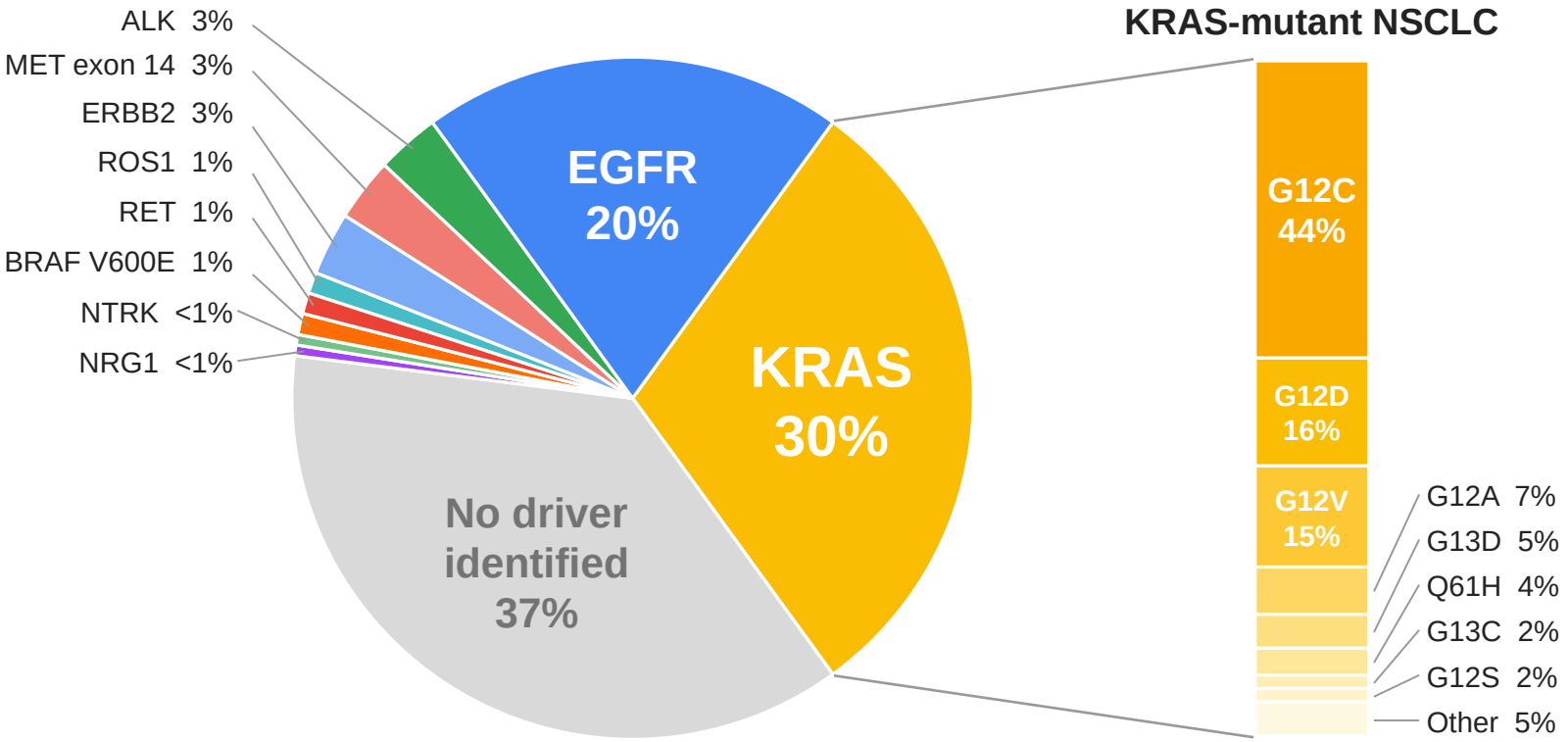
Memorial Sloan Kettering Cancer Center
Atlanta Lung 11/7/2026

Disclosures

The institution receives research support from Amgen and Eli Lilly for clinical research I conduct.

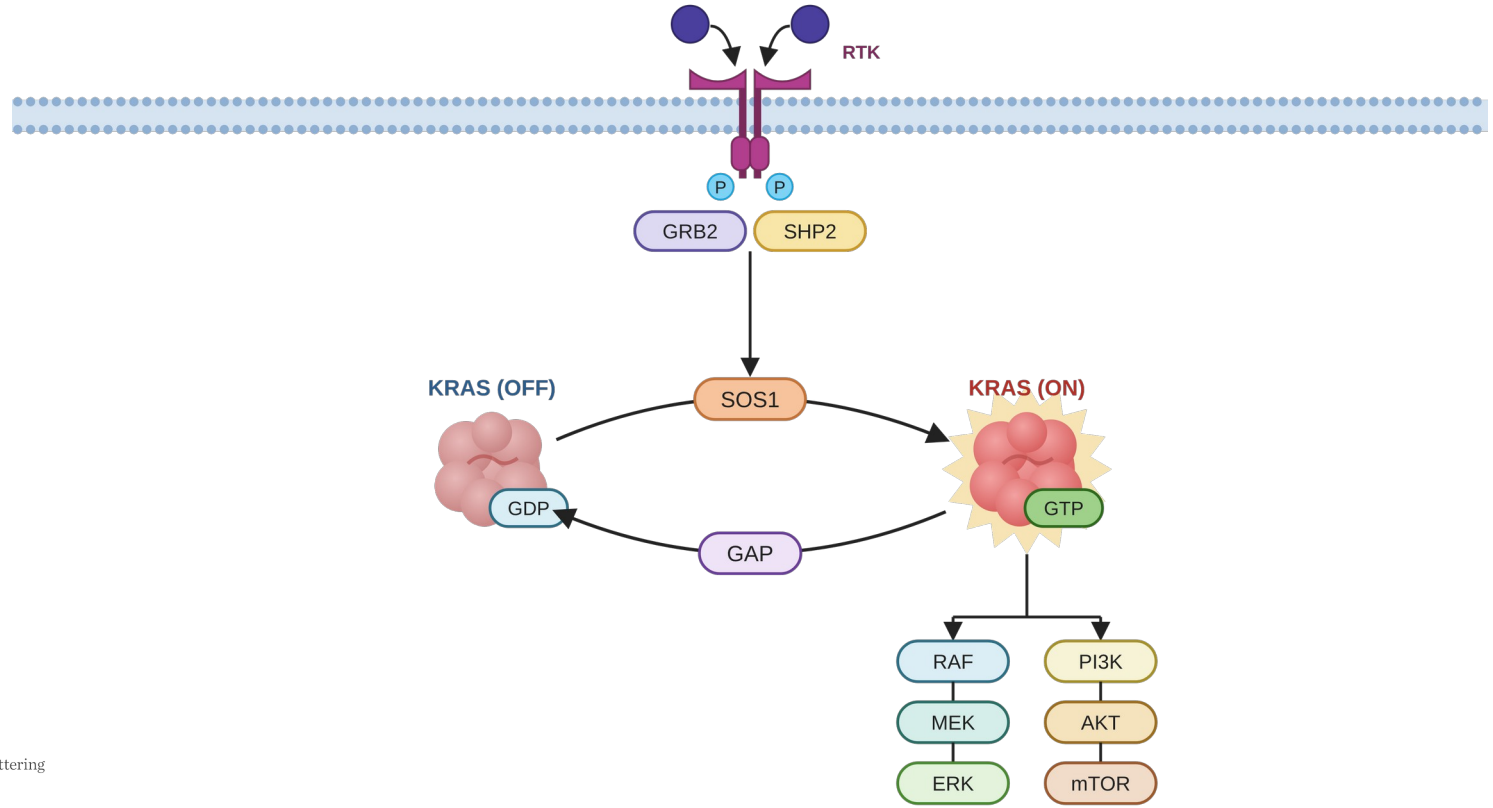
Oncogenic Drivers in Lung Adenocarcinoma



Adapted from Choudhury et al, Clin Cancer Res 2023; Arbour et al, Clin Cancer Res 2018

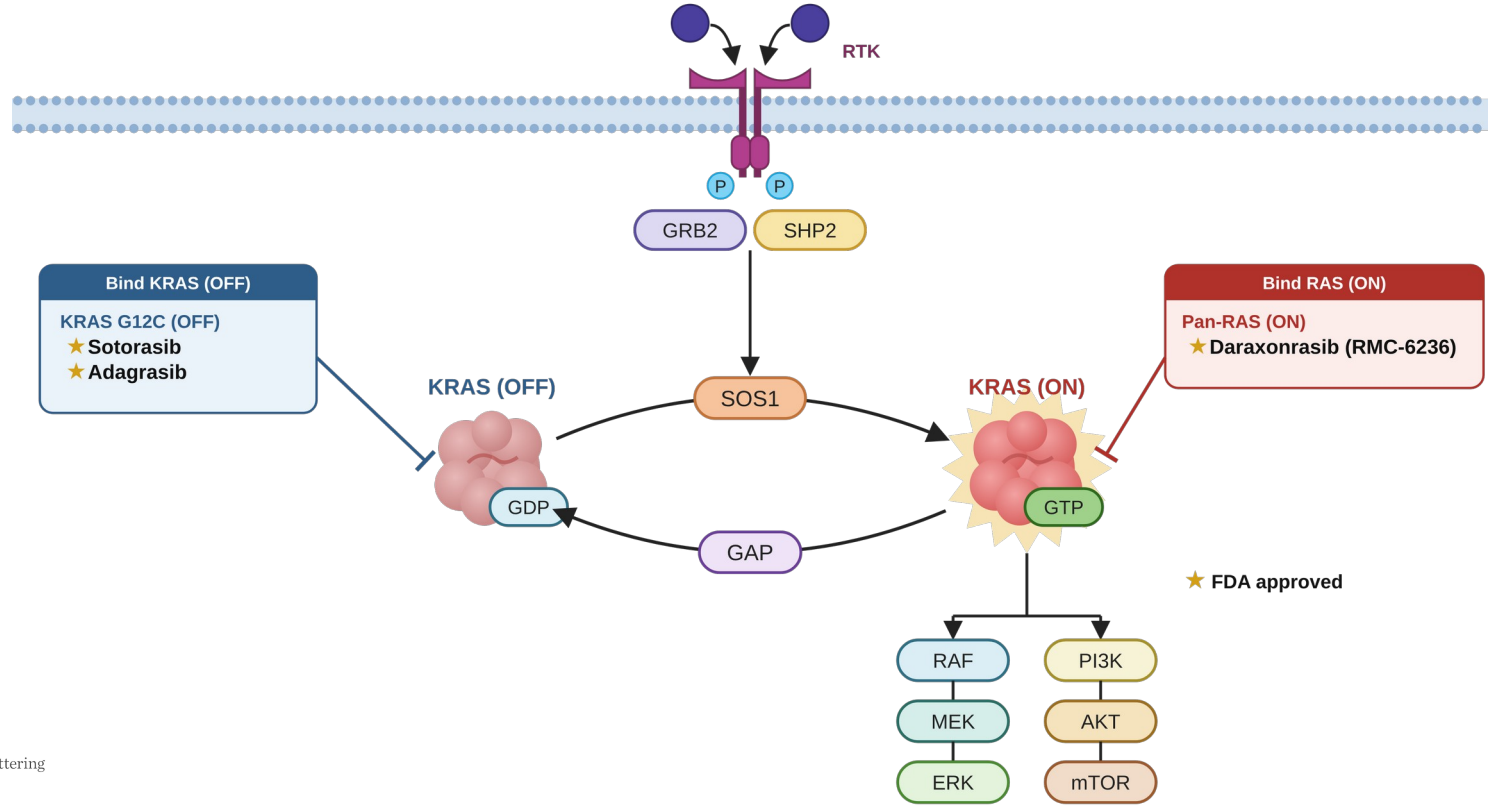
KRAS Cycles Between OFF and ON States

GDP-bound KRAS is inactive, GTP-bound KRAS engages effectors



FDA-Approved KRAS Targeted Therapy

Sotorasib and adagrasib bind KRAS G12C (OFF), daraxonrasib binds RAS (ON)



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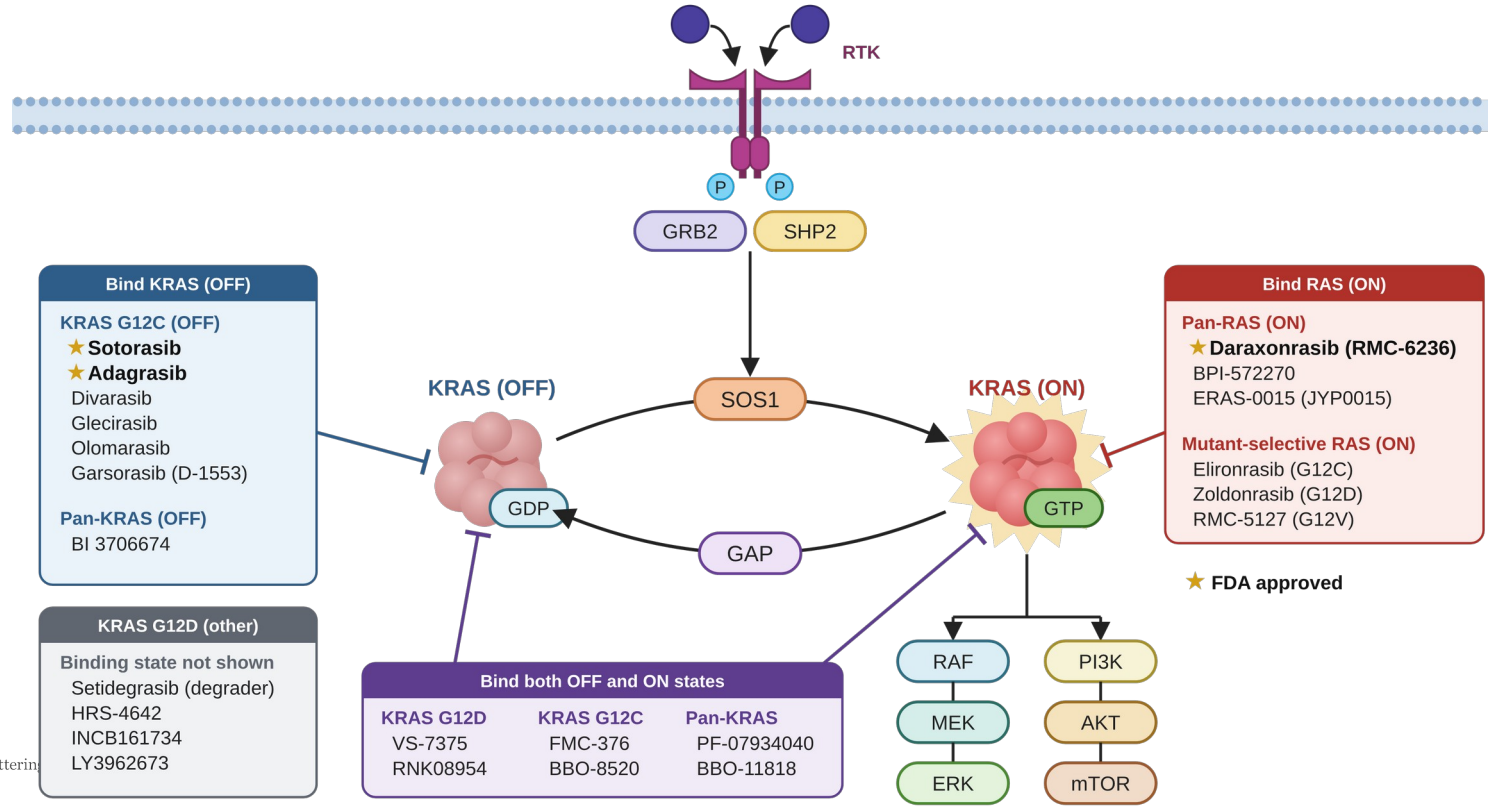
KRAS Targeted Therapy in 2026

Agents in active clinical development



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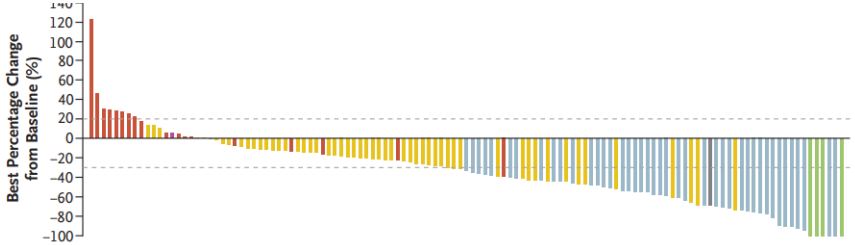
KRAS G12C Targeted Therapy Gained FDA Approval

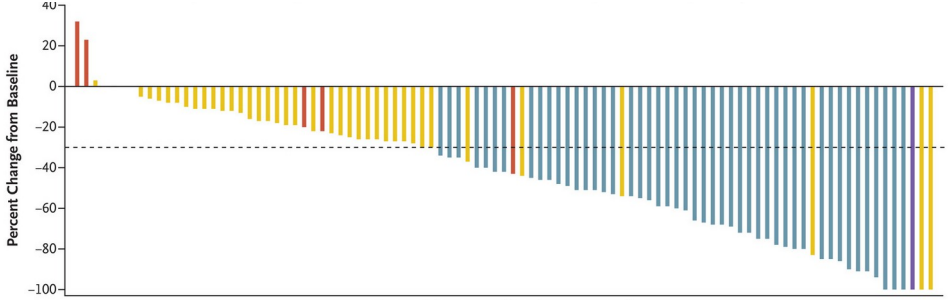
Phase 1/2 activity in previously treated KRAS G12C NSCLC

sotorasib



FDA grants accelerated approval to sotorasib for KRAS G12C mutated NSCLC

adagrasib



FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC

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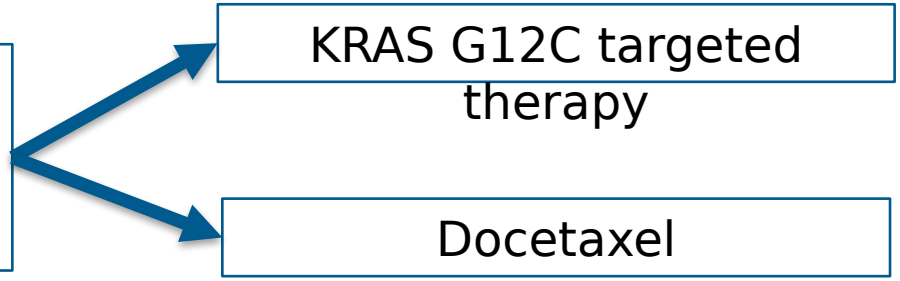
Skoulidis et al, NEJM 2021; Jänne et al, NEJM 2022

KRAS G12C Inhibitors vs Docetaxel

Randomized phase 3 trials: CodeBreaK 200 and KRYSTAL-12

- Recurrent/metastatic NSCLC
- Previous therapy with platinum-doublet and immunotherapy
- KRAS G12C



de Langen et al, Lancet 2023; Barlesi et al, Lancet 2025

G12C Inhibitors Improve RR and PFS vs Docetaxel

CodeBreaK 200 (sotorasib) and KRYSTAL-12 (adagrasib)

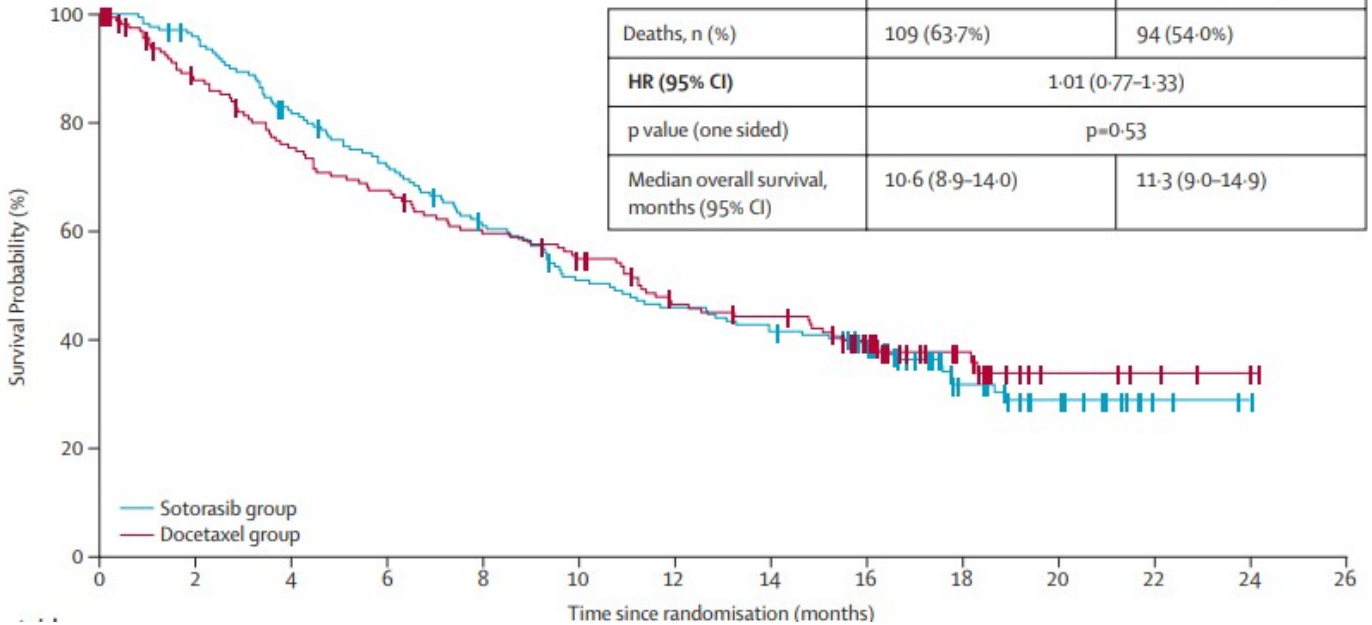
	RR	mPFS	PFS HR	P value
Sotorasib	**28%**	**5.6 months**	**0.66**	**P=0.0017**
Docetaxel	**13%**	**4.5 months**		
Adagrasib	**32%**	**5.5 months**	**0.58**	**P<0.0001**
Docetaxel	**9%**	**3.8 months**		

de Langen et al, Lancet 2023; Barlesi et al, Lancet 2025

Sotorasib Did Not Improve Overall Survival

CodeBreaK 200, sotorasib vs docetaxel

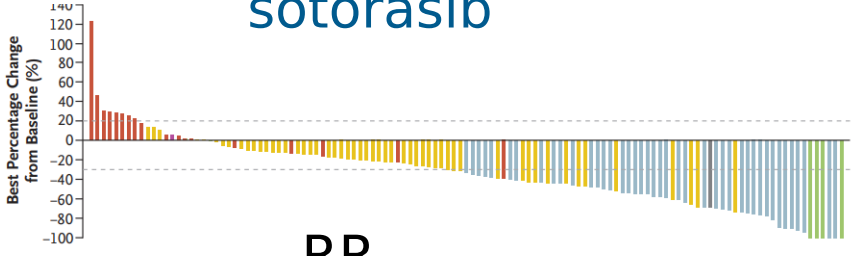
	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
Deaths, n (%)	109 (63·7%)	94 (54·0%)
HR (95% CI)	1·01 (0·77–1·33)	
p value (one sided)	p=0·53	
Median overall survival, months (95% CI)	10·6 (8·9–14·0)	11·3 (9·0–14·9)



de Langen et al, Lancet 2023

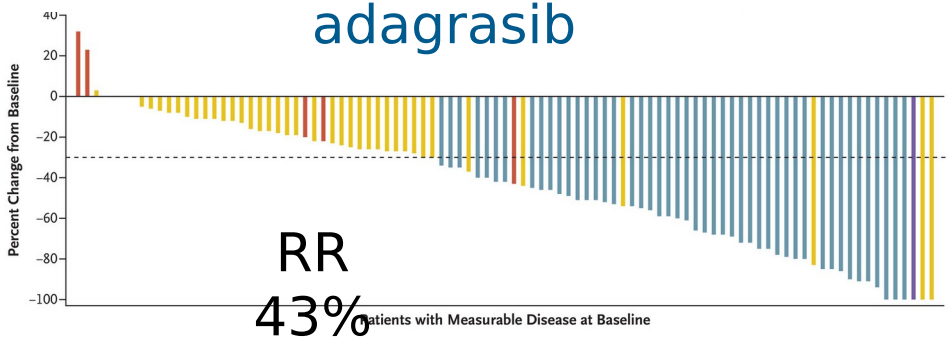
Targeting KRAS G12C

sotorasib



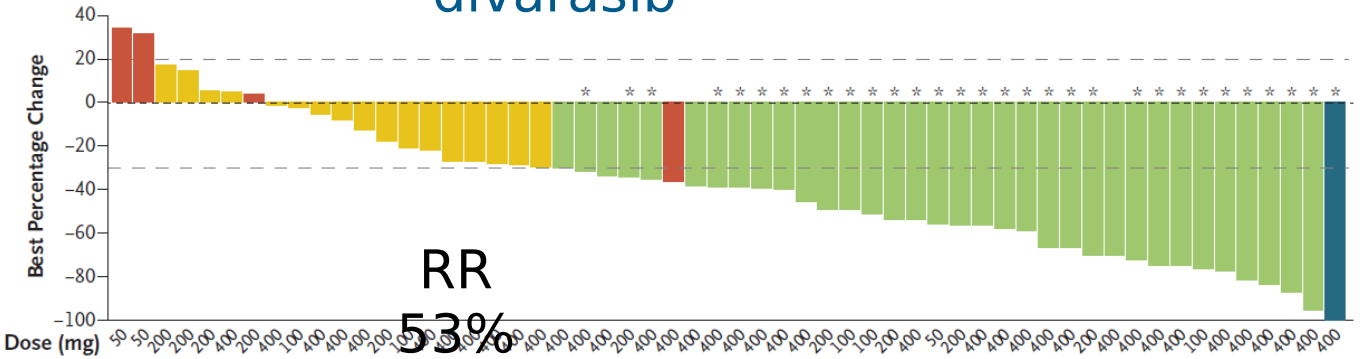
RR
37%

adagrasib



RR
43%

divarasib



RR
53%

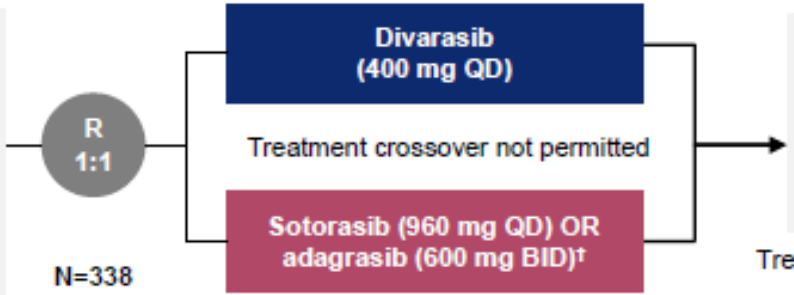
Skoulidis et al, NEJM 2021; Jänne et al, NEJM 2022; Sacher et al, NEJM 2023

Divarasib vs Sotorasib or Adagrasib

Krascendo 1, phase 3, previously treated KRAS G12C NSCLC

Key eligibility criteria

- KRAS G12C inhibitor naive
- ECOG PS 0–1
- Advanced *KRAS* G12C-mutated NSCLC
- ≥1 but ≤3 lines of prior systemic therapy, including platinum-based chemo and a PD-(L)1 inhibitor*
- Measurable disease per RECIST v1.1
- Patients with active, untreated CNS metastases were excluded



Stratification factors
- History of CNS metastases
- Intended choice of control arm KRAS G12C inhibitor†
- *KEAP1* mutation status‡

Primary endpoint
- PFS per BICR

Key secondary endpoints
- OS
- Confirmed ORR per BICR
- TTCD

Other secondary endpoints
- DoR per BICR
- Safety
- Other PROs

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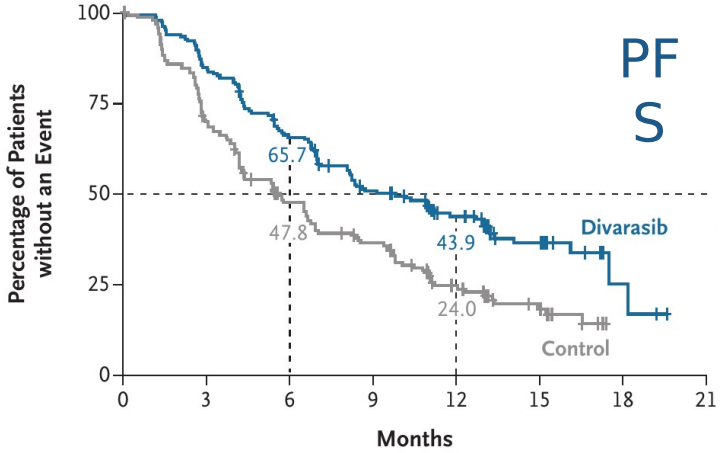
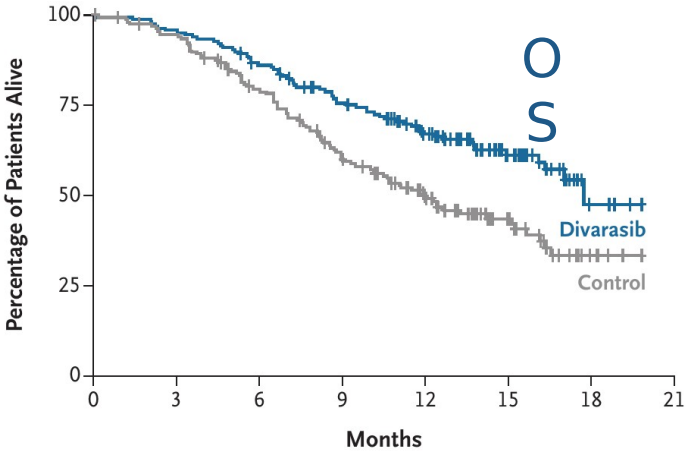
Skoulidis et al, NEJM 2026

Divarasib Improves PFS and OS over sotorasib/adagrasib

Krascendo 1, control sotorasib or adagrasib, PFS by BICR



No. at Risk								
Divarasib	167	142	108	80	53	27	3	0
Control	171	116	73	54	26	14	0	0



No. at Risk								
Divarasib	167	160	142	120	95	41	6	0
Control	171	159	128	94	65	31	6	0

Median PFS 9.8 vs 5.7 months, HR 0.58 (95% CI 0.44-0.76), P<0.001
Median OS 17.7 vs 12.0 months, HR 0.56 (95% CI 0.41-0.78), P<0.001

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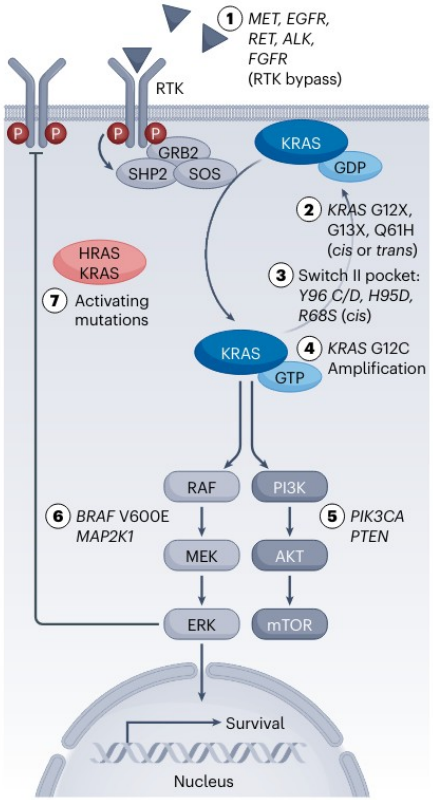
Skoulidis et al, NEJM 2026

Acquired Resistance to G12C Inhibitors

Mechanisms are diverse and often subclonal



Treatment-emergent alterations in 27 of 43 patients on sotorasib, including KRAS, NRAS, BRAF, EGFR, and MYC

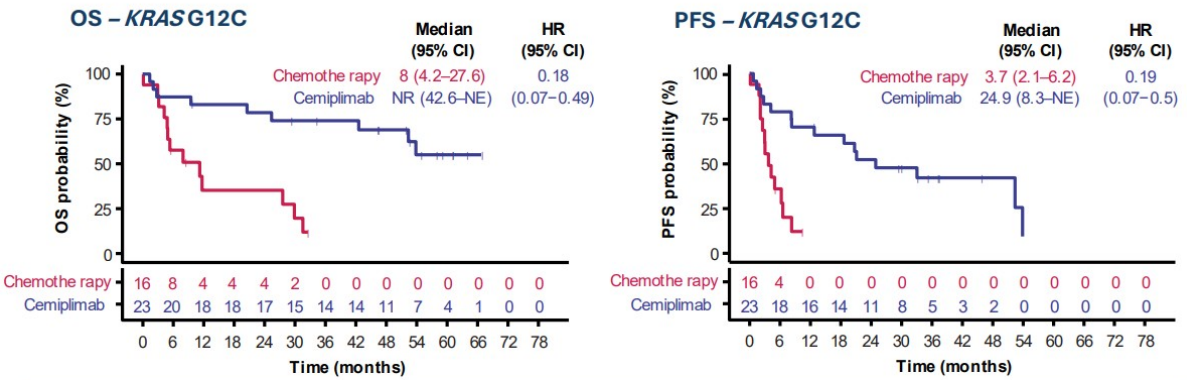
Singhal et al, Nat Med 2024; Zhao et al, Nature 2021

Can we bring to front line…add to IO?

IO Alone Can Work in KRAS G12C

EMPOWER-Lung 1 post hoc analysis, PD-L1 ≥50%

RESULTS: OS and PFS in the *KRAS*G12C subtype



***KRAS*G12C was associated with pronounced survival benefits from cemiplimab versus chemotherapy**

- **OS HR=0.18; PFS HR=0.19** (*KRAS* mutations with all subtypes: OS HR=0.46; PFS HR=0.31)
- **OS and PFS HRs were not affected by multivariable adjustments by sex, smoking status, or TMB**

Hypothesis-generating: cemiplimab n=23 vs chemotherapy n=16

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Gandara et al, WCLC 2026

Sotorasib can't be given with immune checkpoint inhibitors

	Soto+Atezo Concurrent (N=10)	Soto+Pembro Concurrent (N=19)
Safety, n (%)		
TRAE, any grade	9 (90)	17 (89)
TRAE, grade 3-4	6 (60)	15 (79)
Hepatotoxicity, Gr 3-4[a]	5 (50)	9 (47)
ALT increased	4 (40)	7 (37)
AST increased	5 (50)	5 (26)
TRAE leading to discontinuation of Sotorasib and/or IO	5 (50)	10 (53)
Number of treatment doses, max)		
Sotorasib	115.0 (22, 422)	82.0 (35, 791)
IO	3.5 (2, 21)	3.0 (2, 12)
Efficacy		
ORR, % (95% CI)	20[b] (3, 56)	32[d] (13, 57)
DCR, % (95% CI)	80 (44, 98)	90 (67, 99)
Median OS, (95% CI), months	11.5 (5.0, NE)	14.1 (6.2, 17.8)

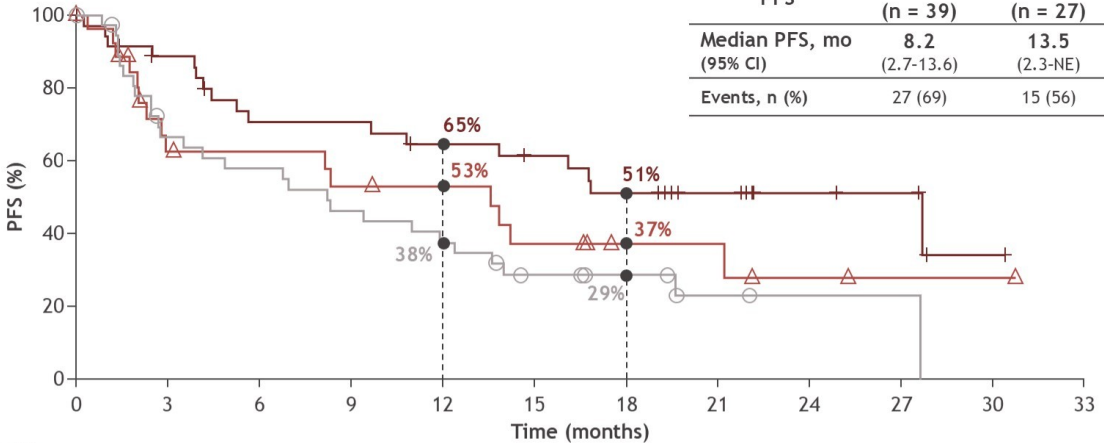
Modified from Li et al, WCLC 2022, Vienna

Adagrasib plus Pembrolizumab, PFS by PD-L1

KRYSTAL-7, first line

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

PFS according to PD-L1 status[a]



PFS	PD-L1 < 1% (n = 39)	PD-L1 1-49% (n = 27)	PD-L1 ≥ 50% (n = 38)[b]
Median PFS, mo (95% CI)	8.2 (2.7-13.6)	13.5 (2.3-NE)	27.7 (9.6-NE)
Events, n (%)	27 (69)	15 (56)	17 (45)

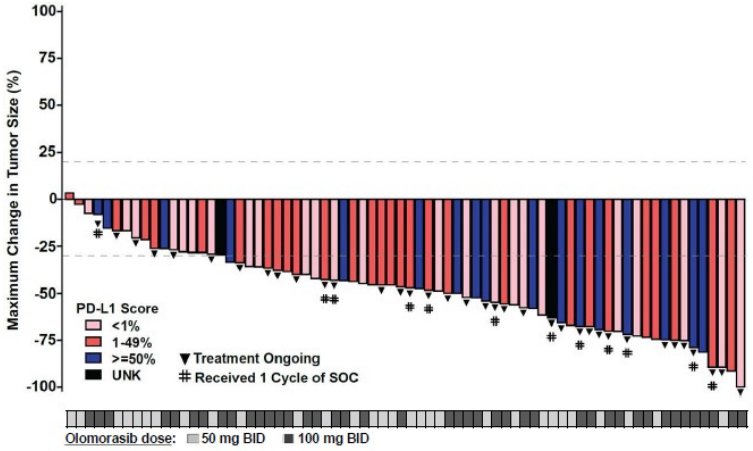
Median PFS 27.7 months with PD-L1 ≥50%

Jänne et al, ASCO 2025

Olomorasib + Pembrolizumab + Chemotherapy

First line

Efficacy of 1L Olomorasib + Pembrolizumab + Pemetrexed + Platinum



Olomorasib + Pembrolizumab + Pemetrexed + Platinum				
Efficacy Evaluable Patients[a]	All pts PD-L1 0-100% N = 77[b]	Pts with PD-L1 <1% N = 26	Pts with PD-L1 1-49% N = 31	Pts with PD-L1 ≥50% N = 18
ORR, (%) (95% CI)	61 (49.2, 72.0)	50 (29.9, 70.1)	68 (48.6, 83.3)	67 (41.0, 86.7)
BOR, n (%)				
CR	1 (1)	-	1 (3)	-
PR[b]	46 (60)	13 (50)	20 (65)	12 (67)
SD	22 (29)	9 (35)	8 (26)	5 (28)
PD	3 (4)	2 (8)	-	-
NE	5 (7)	2 (8)	2 (7)	1 (6)
DCR, (%) (95% CI)	90 (80.6, 95.4)	85 (65.1, 95.6)	94 (78.6, 99.2)	94 72.7, 99.9)

ORR 61% (n=77). Grade 3 AST increase in 9%.

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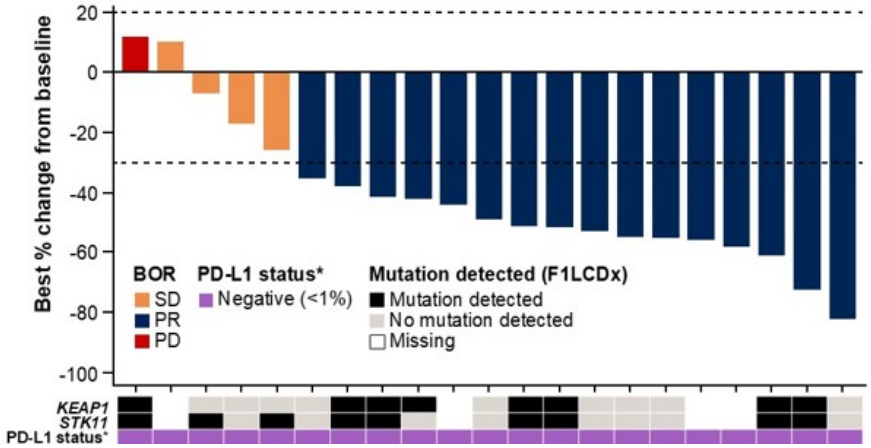
Negrao et al, WCLC 2025

Divarasib plus Pembrolizumab

First line, PD-L1 <1% cohort

PD-L1 negative cohort: Unconfirmed ORR



n (%) unless specified	Divarasib + pembrolizumab (N=23)
Unconfirmed† ORR [95% CI]	16 (69.6) [47.1–86.8]
CR	0
PR	16 (69.6)
SD	4 (17.4)
PD	1 (4.3)
Not evaluable/missing	2 (8.7)
Median time to first response, days (range)	40.5 (36–120)

Unconfirmed ORR 70% (n=23). Grade 3-4 TRAE in 65%.

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Skoulidis et al, ASCO 2026

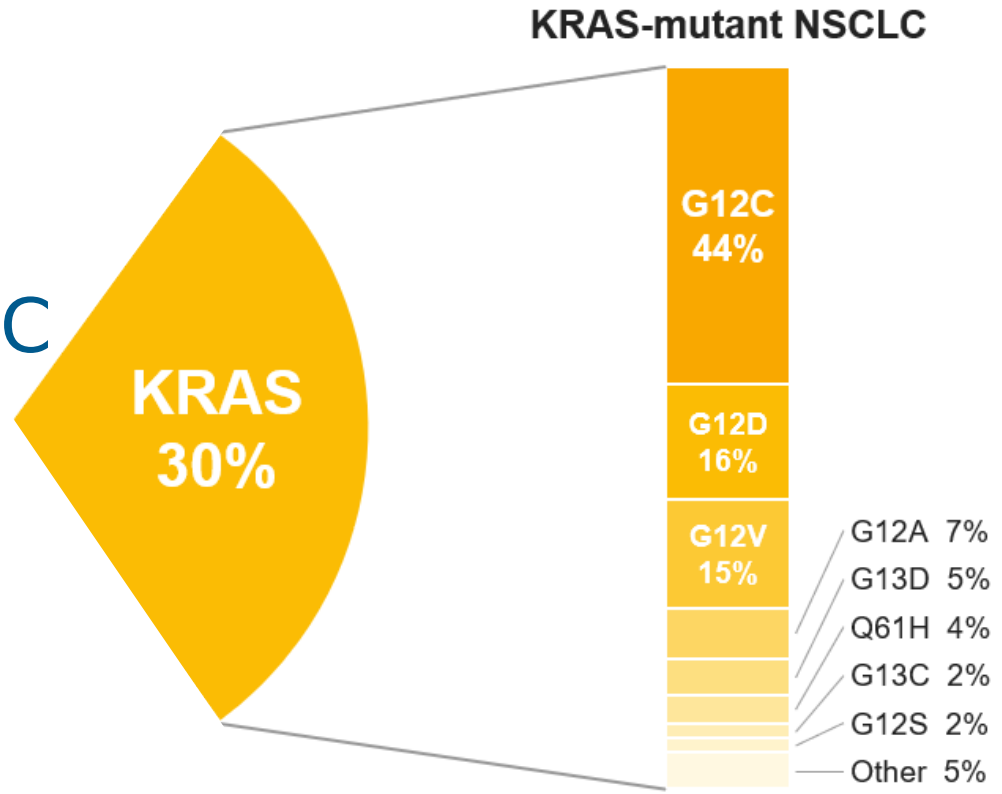
First-Line KRAS G12C Phase 3 Trials in NSCLC

Ongoing and recruiting

	Trial	Population	Experimental vs control
Sotorasib	CodeBreaK 202	PD-L1 <1%, nonsquamous	Sotorasib + carbo/pem vs pembro + carbo/pem
Adagrasib	KRYSTAL-7	PD-L1 ≥50%	Adagrasib + pembro vs pembro
	KRYSTAL-4	Any PD-L1, nonsquamous	Adagrasib vs placebo, each + pembro + plat/pem
Divarasib	Krascendo 2	Any PD-L1, nonsquamous	Divarasib + pembro vs pembro + plat/pem
Olomorasib	SUNRAY-01 (A)	PD-L1 ≥50%	Olomorasib vs placebo, each + pembro
	SUNRAY-01 (B)	Any PD-L1, nonsquamous	Olomorasib vs placebo, each + pembro + plat/pem
Calderasib	KANDLELIT-004	PD-L1 ≥50%	Calderasib vs placebo, each + pembro
	KANDLELIT-007	Any PD-L1, nonsquamous	Calderasib + pembro SC vs pembro SC + plat/pem
Garsorasib	NCT07174908	Nonsquamous (China)	Garsorasib + ifebemtinib (FAK) vs anti-PD-1 + plat/pem
Glecirasib	NCT06416410	Nonsquamous (China)	Glecirasib + sitneprotafib (SHP2) vs tislelizumab + carbo/pem

ClinicalTrials.gov, accessed November 2026

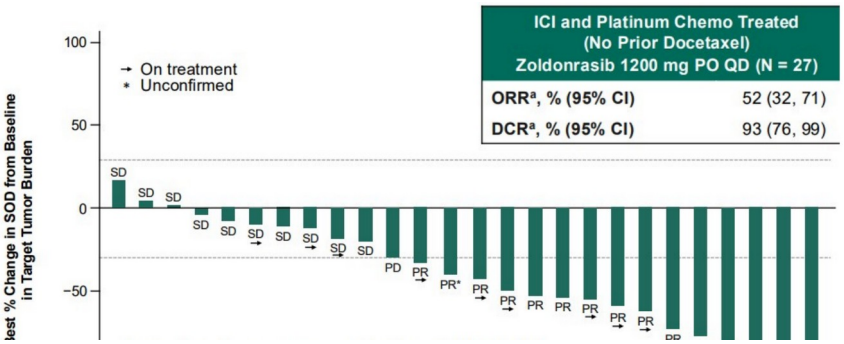
Beyond KRAS G12C



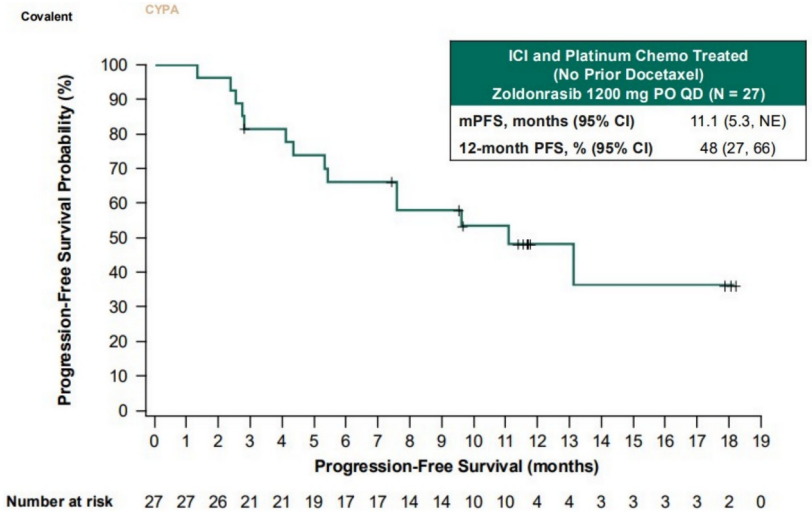
Zoldonrasib, a G12D RAS(ON) Inhibitor

After IO and platinum chemotherapy, 1200 mg daily (n=27)

Best response



Progression-free survival



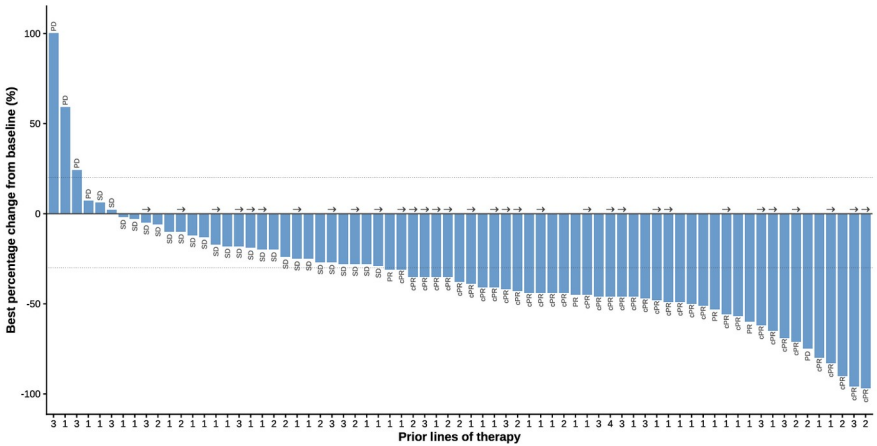
ORR 52%, median PFS 11.1 months

Riess et al, AACR 2026

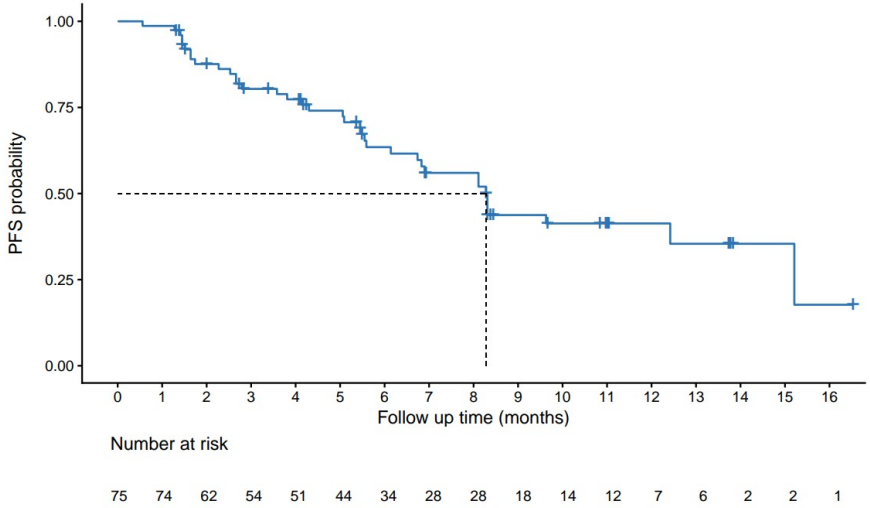
GFH375 (VS-7375), a G12D ON/OFF Inhibitor

Grade ≥3 hepatotoxicity 17% if ICI within 90 days (n=75)

Best response



Progression-free survival



Confirmed ORR 52%, median PFS 8.3 months

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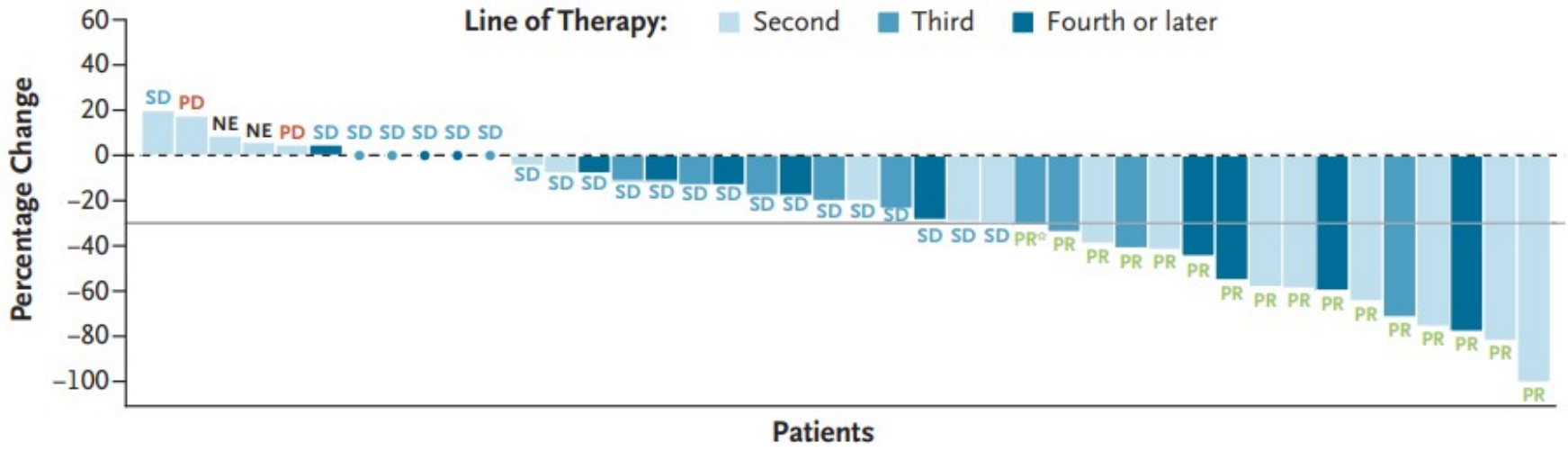
Li et al, WCLC 2026

Setidegrasib, a G12D Protein Degrader

Weekly IV, previously treated NSCLC



At 600 mg (n=45): ORR 36%, median PFS 8.3 months. Infusion reactions in 80%.

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Park et al, NEJM 2026

Daraxonrasib Improves PFS and OS in pancreas cancer

RAS data 202 … y tre … RAS G12 population

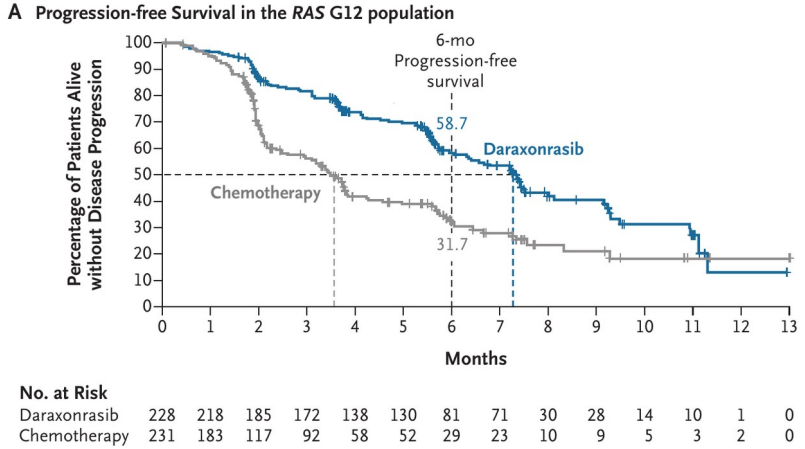
Metastatic PDAC
1 prior line of therapy
RAS G12, G13, Q61, or none identified

Daraxonrasib 300 mg daily (n=248)

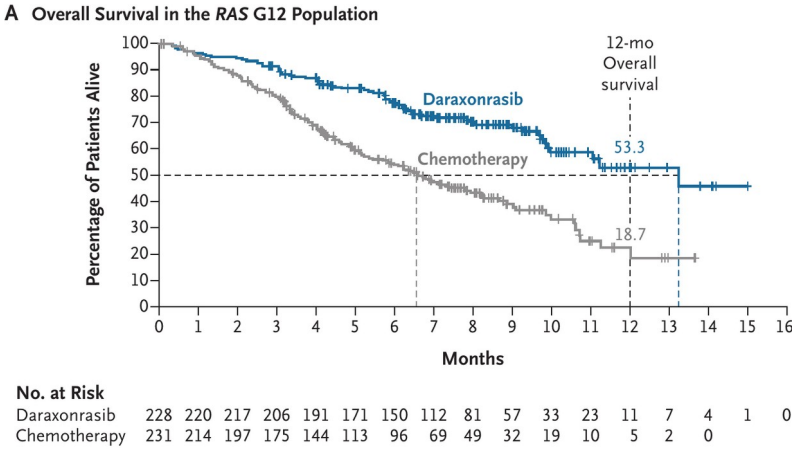
Investigator's choice chemo (n=252)

Dual primary endpoints:
OS and PFS (BICR) in the RAS G12 population

PFS 7.3 vs 3.5 mo, HR 0.45 (95% CI, 0.34-0.59)



OS 13.2 vs 6.6 mo, HR 0.40 (95% CI, 0.30-0.54)



O'Reilly et al, NEJM 2026

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Daraxonrasib Improves PFS and OS in pancreas cancer

RAS data 202 ... y tre ... RAS G12 population

Metastatic PDAC
1 prior line of therapy

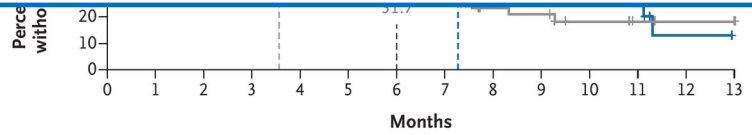
Daraxonrasib 300 mg daily
(n=248)

Dual primary endpoints:
OS and PFS (BICR) in the RAS

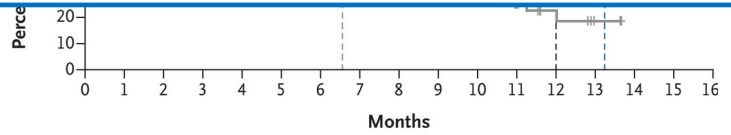
FDA NEWS RELEASE

FDA Approves First in Class Targeted Therapy for Metastatic Pancreatic Cancer

For Immediate Release: August 26, 2026



No. at Risk														
Daraxonrasib	228	218	185	172	138	130	81	71	30	28	14	10	1	0
Chemotherapy	231	183	117	92	58	52	29	23	10	9	5	3	2	0



No. at Risk																	
Daraxonrasib	228	220	217	206	191	171	150	112	81	57	33	23	11	7	4	1	0
Chemotherapy	231	214	197	175	144	113	96	69	49	32	19	10	5	2	0		

O'Reilly et al, NEJM 2026

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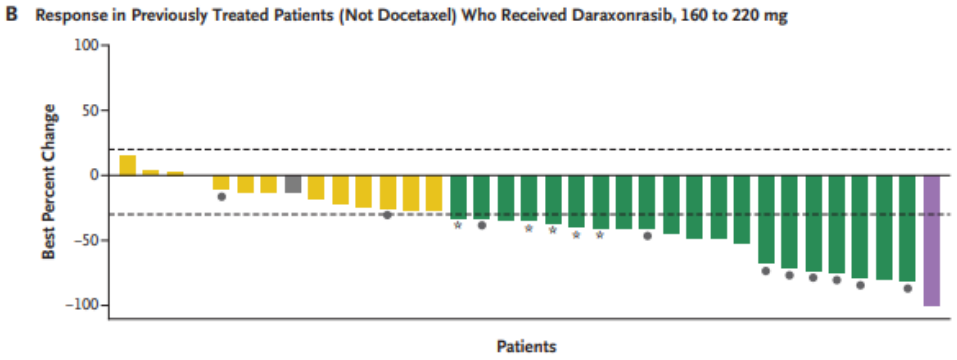
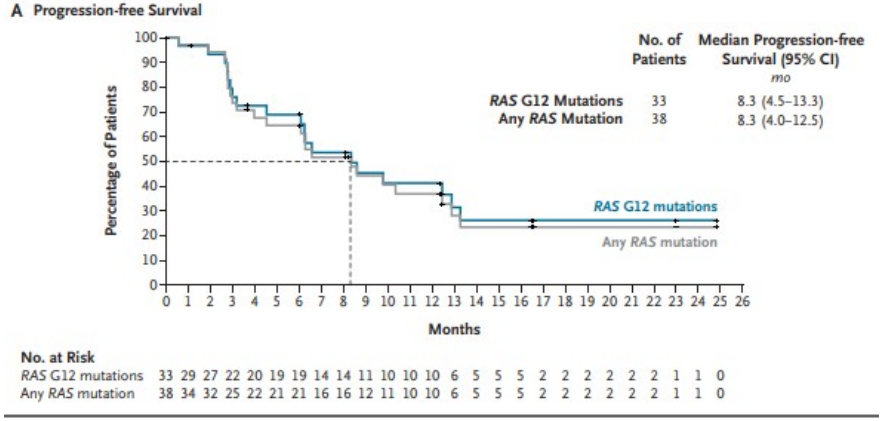
Daraxonrasib, a Pan-RAS(ON) Inhibitor

Previously treated RAS-mutant NSCLC, docetaxel naive, 160-220 mg (n=38)

Best response



Progression-free survival



ORR 42%, median PFS 8.3 months, median OS 16.0 months

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Arbour et al, NEJM 2026

Daraxonrasib Toxicity

Adverse events at 160-220 mg daily (n=59)

	Any grade	Grade ≥3
Rash	92%	8%
Diarrhea	68%	3%
Nausea	59%	2%
Vomiting	49%	8%
Mucositis or stomatitis	42%	0%

Phase 3 RASolve 301 (vs docetaxel) uses 200 mg daily

Arbour et al, NEJM 2026

Managing Daraxonrasib Toxicity

Off-label in NSCLC, FDA approved for pancreatic cancer

Rash: doxycycline or minocycline prophylaxis, topical steroids

Nausea and diarrhea early: ondansetron and loperamide from day 1

Mucositis: oral hygiene, dexamethasone rinses

Limit interruptions to 5-7 days, restage at 6 weeks

Summary

Nearly every KRAS mutation now has a targeted drug, approved or in trials

Sotorasib and adagrasib are FDA approved for KRAS G12C NSCLC. Divarasib improved PFS and OS over both but is not FDA-approved.

KRAS G12C targeted therapies are being studied in first line.

Daraxonrasib, FDA-approved for pancreatic cancer, has activity in KRAS mutant NSCLC.