*KRAS*G12C: A Unique Oncogenic Driver in NSCLC

Lilly

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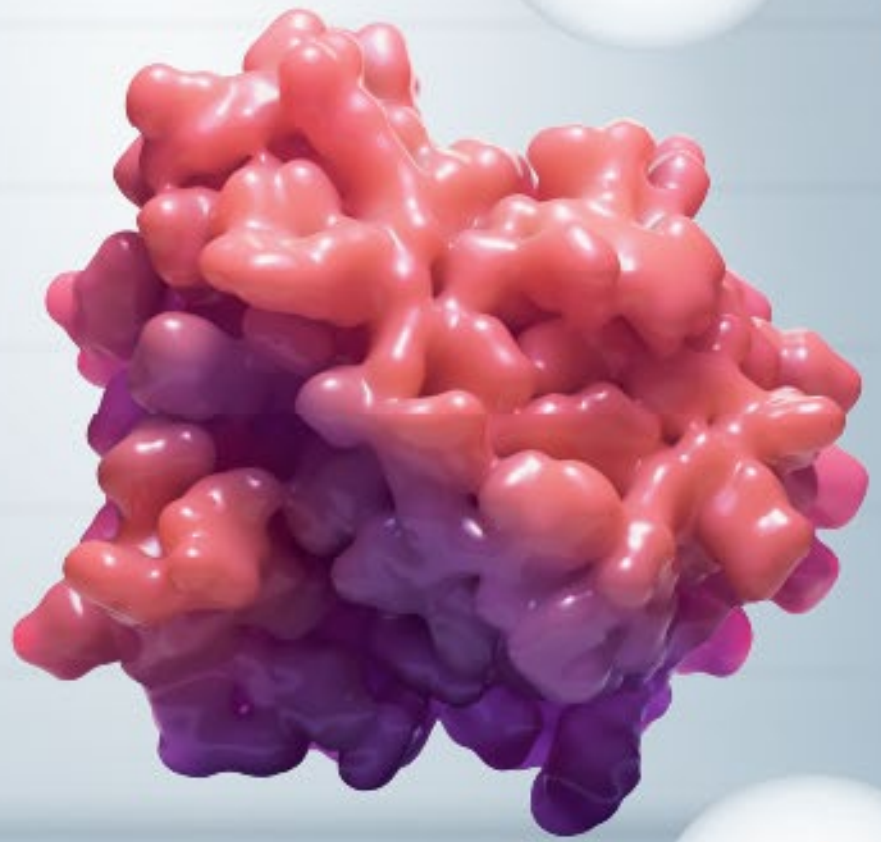
*KRAS*G12C–Mutant NSCLC

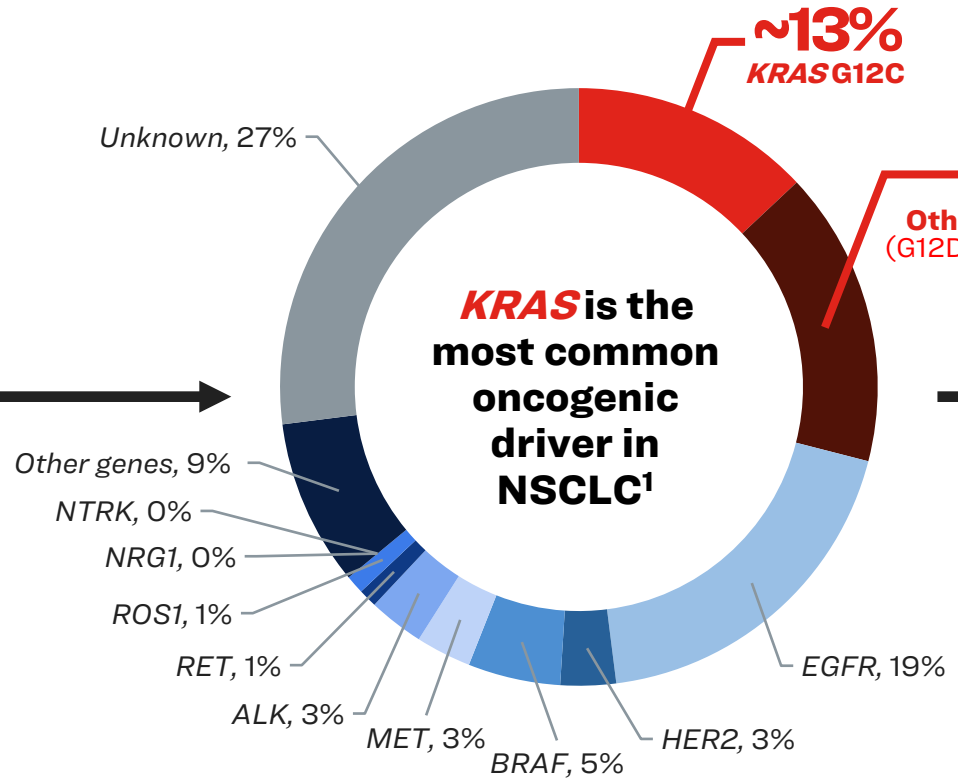
Is Unique and Is Associated With Poor Prognosis



KRAS G12C Is a Prevalent Oncogenic Driver Mutation in Non-small Cell Lung Cancer[1,2]

~85%
NSCLC

Non-small cell lung cancer accounts for ~80%-85% of all lung cancers[3]



KRAS mutations are predominantly found in lung adenocarcinoma **(1 in 4 people)** and are also found in squamous cell carcinoma[1,4]

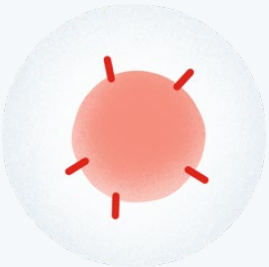
~13% of patients with NSCLC have the *KRAS* G12C mutation[1]

KRAS G12C Is Different

Patients with *KRAS* G12C–mutant NSCLC are a heterogenous population who typically exhibit a **unique** profile, with **distinct clinical features** and **tumor characteristics:**

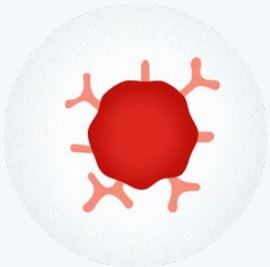
Current or former **smoking history**[5]

- Correlated with **smoking pack-years** in people with current and previous smoking history[6]
- Early tobacco exposure causes **irreversible DNA damage** with no significant reduction seen after smoking cessation[6]



Higher **programmed death-ligand 1 (PD-L1) levels**[2,7,8]

- Compared to NSCLC tumors with other oncogenic drivers or *KRAS* wild-type (WT) tumors[2,7]
- PD-L1 expression often **guides treatment decisions** for *KRAS* G12C–mutant NSCLC, unlike with other oncogenic driver alterations[9,10]



Elevated **tumor mutational burden (TMB)**[2,11]

- Compared with *EGFR, ALK, RET,* and *HER2* tumors that have **a low TMB**[12-14]
- Enables increased **neoantigen expression** on the cell surface to attract immune cells[15]
- Strongly correlated with **smoking history**[15]

KRAS G12C Is Different

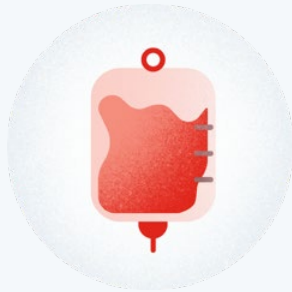
Patients with *KRAS* G12C–mutant NSCLC are a heterogenous population who typically exhibit a **unique** profile, with **distinct clinical features** and **tumor characteristics:**

***KRAS* G12C vs oncogenic drivers**

***KRAS* variants in NSCLC**

Co-mutations
including *STK11*, *KEAP1*, *TP53*, *LRP1B*, and *SMARCA4*[5]

- Co-mutations appear to influence the **tumor microenvironment (TME) and impact treatment response**[15-17]
- While *STK11* and *KEAP1* are associated with poor prognosis, the predictive value of co-mutations are unknown[15-17]



Higher sensitivity to **immunotherapy**[8,15]

- An **inflamed TME** resulting from elevated tumor-infiltrating lymphocytes (TILs), immunogenicity, and elevated TMB may facilitate an enhanced response to immunotherapy[7,8,15]
- Certain co-mutations, including *TP53*, *STK11*, and *KEAP1* may lead to heterogenous response[7,8,15]

KRAS G12C Is Different From Other Oncogenic Drivers in NSCLC

	EGFR mutation	*KRAS* G12C mutation	*ALK* rearrangement	*MET* ex14 mutation	*HER2* mutation	*RET* rearrangement	*BRAF* V600E mutation	*ROS1* rearrangement	*NTRK1/2/3* gene fusion	*NRG1* gene fusion
Incidence in NSCLC	21%[19]	13%[1]	5%[19]	4%[20]	2%[19]	2%[19]	2%[21]	2%[19]	1%[19]	<1%[22]
Associated with smoking history	No[19]	Yes[23]	No[19,24]	No[20]	No[1]	No[24]	Yes[1]	No[19,24]	No[24]	No[25]
TMB[14,*]	Low[13]	Intermediate[12]	Low[13]	Low/ Intermediate[26]	Low[13]	Low[13]	Low[13]	Low[13]	Intermediate[27]	Low[25]
Sensitivity to immunotherapy (objective response rate)	12%[28,†]	67%[15,‡]	0%[28,†]	17%[26,¶]	7%[28,†]	6%[28,†]	25%[14,§]	17%[28,†]	Unknown	20%[25,‖]
Targeted therapy approved in first-line NSCLC	Yes[22]	No[22,#]	Yes[22]	Yes[22]	No[22]	Yes[22]	Yes[22]	Yes[22]	Yes[22]	No[22]

KRAS G12C–mutant NSCLC

- Is prevalent and is strongly correlated with **smoking history**[23]
- Is associated with **intermediate TMB** and **increased sensitivity to immunotherapy**[12,15]
- **Lacks** approved targeted therapy in first-line, but there are ongoing Phase 3 trials evaluating targeted therapies in the first-line setting[22,29]

*TMB-high ≥20 muts/Mb, TMB-intermediate = 6 to 19 muts/Mb, TMB-low ≤5 muts/Mb.[14]
†Retrospective study in *EGFR* (n = 125), *ALK* (n = 23), *HER2* (n = 29), *RET* (n = 16), *ROS1* (n = 7) patients receiving immunotherapy.[28]
‡Subgroup analysis on 12 patients with a *KRAS* G12C–mutant NSCLC treated with immunotherapy alone.[15]
¶Retrospective analysis on 24 patients treated with single or combination immunotherapy in first-line, second-line, or third-line treatment.[26]
§Retrospective study with 21 patients in the *BRAF* V600E group with only 12 of these patients being treated and evaluated following immunotherapy.[14]
‖Retrospective analysis with only 5 patients being treated with single-agent immunotherapy.[25]
#Ongoing Phase 3 trials.[29]

KRAS G12C Is the Most Prevalent *KRAS* Variant in NSCLC

	***KRAS* G12C mutation**	***KRAS* G12D mutation**	***KRAS* G12V mutation**
Incidence in NSCLC	13%[1]	4%[30]	3%[31]
Associated with smoking history	Yes[23]	No[30]	Yes[31]
TMB[14,*]	Intermediate[12]	Intermediate[12]	Intermediate[12]
Sensitivity to immunotherapy (objective response rate)	67%[15,†]	16%[30,‡]	67%[31,¶]
Targeted therapy approved in first-line NSCLC	No[22,#]	No[9]	No[9]

- Both *KRAS* G12D and *KRAS* G12V mutations can be found in **gastrointestinal cancers** such as colorectal cancer[2]
- *KRAS* G12D mutation is also common in **pancreatic ductal adenocarcinoma and endometrial cancers**[2]
- *KRAS* G12V mutation is also common in **breast cancer**[2]
- Unlike *KRAS* G12D mutation, *KRAS* G12C and *KRAS* G12V mutations are correlated with **smoking history** and **sensitivity to immunotherapy in NSCLC**[15,23,31]

*TMB-high ≥20 muts/Mb, TMB-intermediate = 6 to 19 muts/Mb, TMB-low ≤5 muts/Mb.[14]
†Subgroup analysis on 12 patients with a *KRAS* G12C–mutant NSCLC treated with immunotherapy alone.[15]
‡Based on clinical outcomes to PD-L1 blockade alone in 538 patients with *KRAS* G12D–mutant NSCLC.[30]
¶Real-world analysis on a subgroup of 13 patients with *KRAS* G12V–mutant NSCLC treated with immunotherapy alone.[31]
#Ongoing Phase 3 trials.[29]

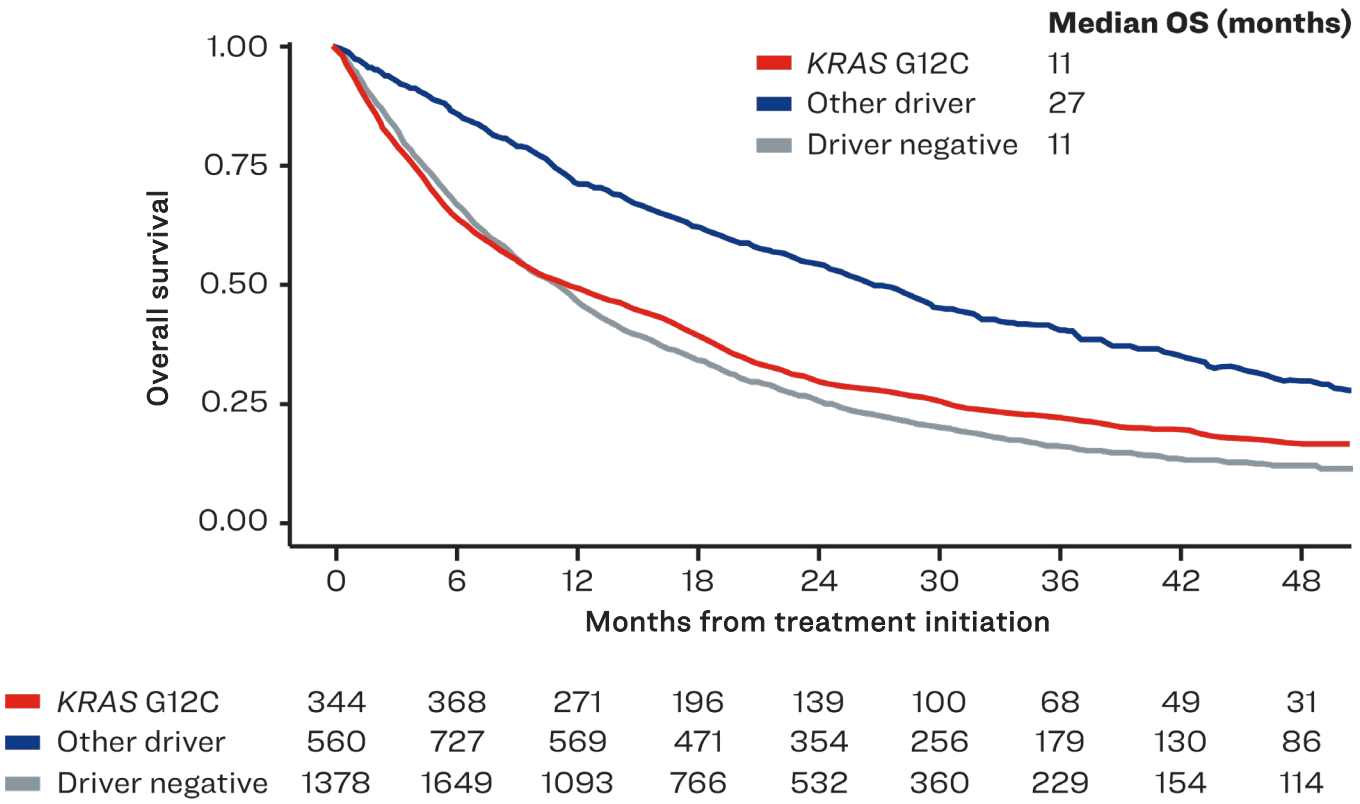
KRAS G12C–Mutant NSCLC Is Associated With Poor Prognosis[2]

Real-world differences in median overall survival (mOS):

11 months
in patients with *KRAS* G12C–mutant NSCLC

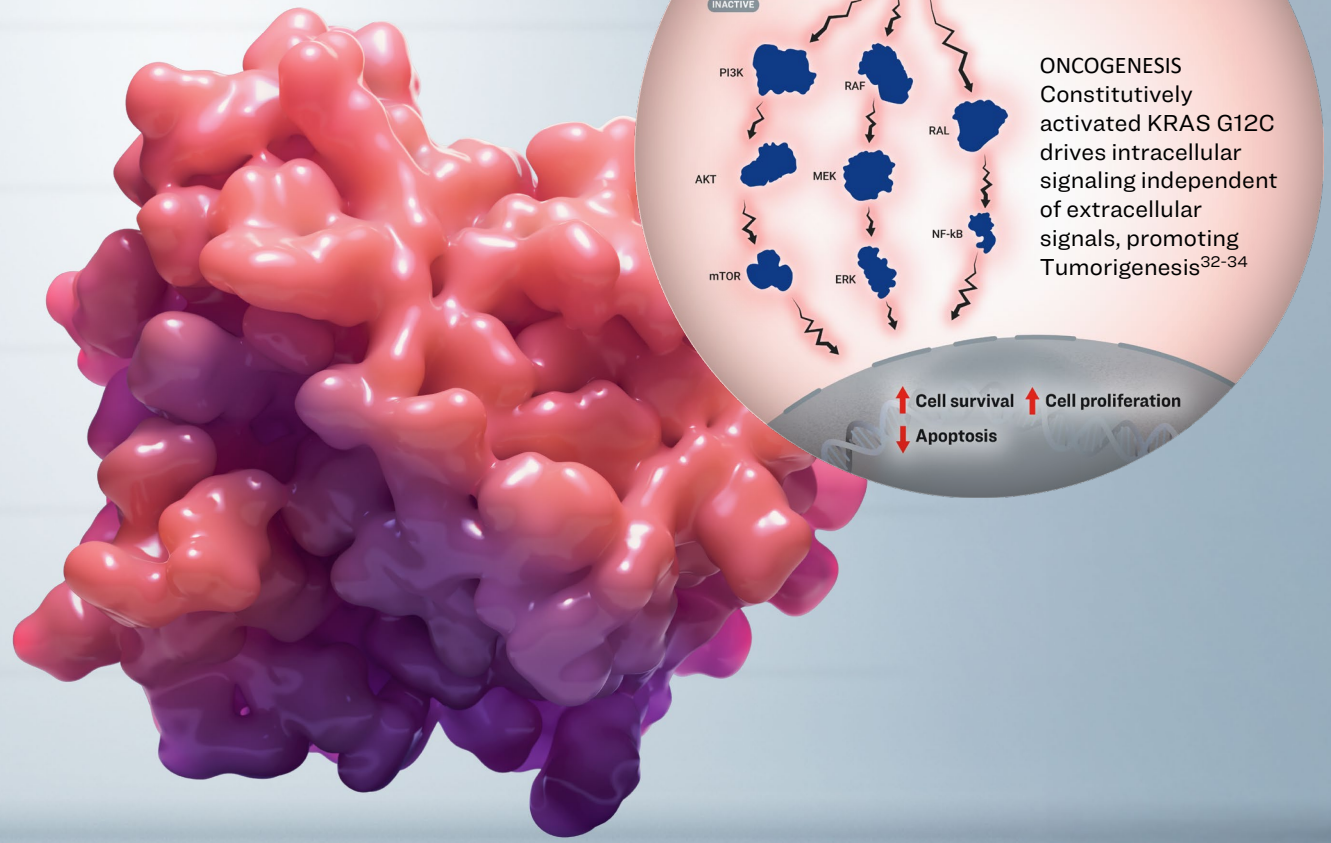
27 months
in patients with targetable driver alteration in NSCLC

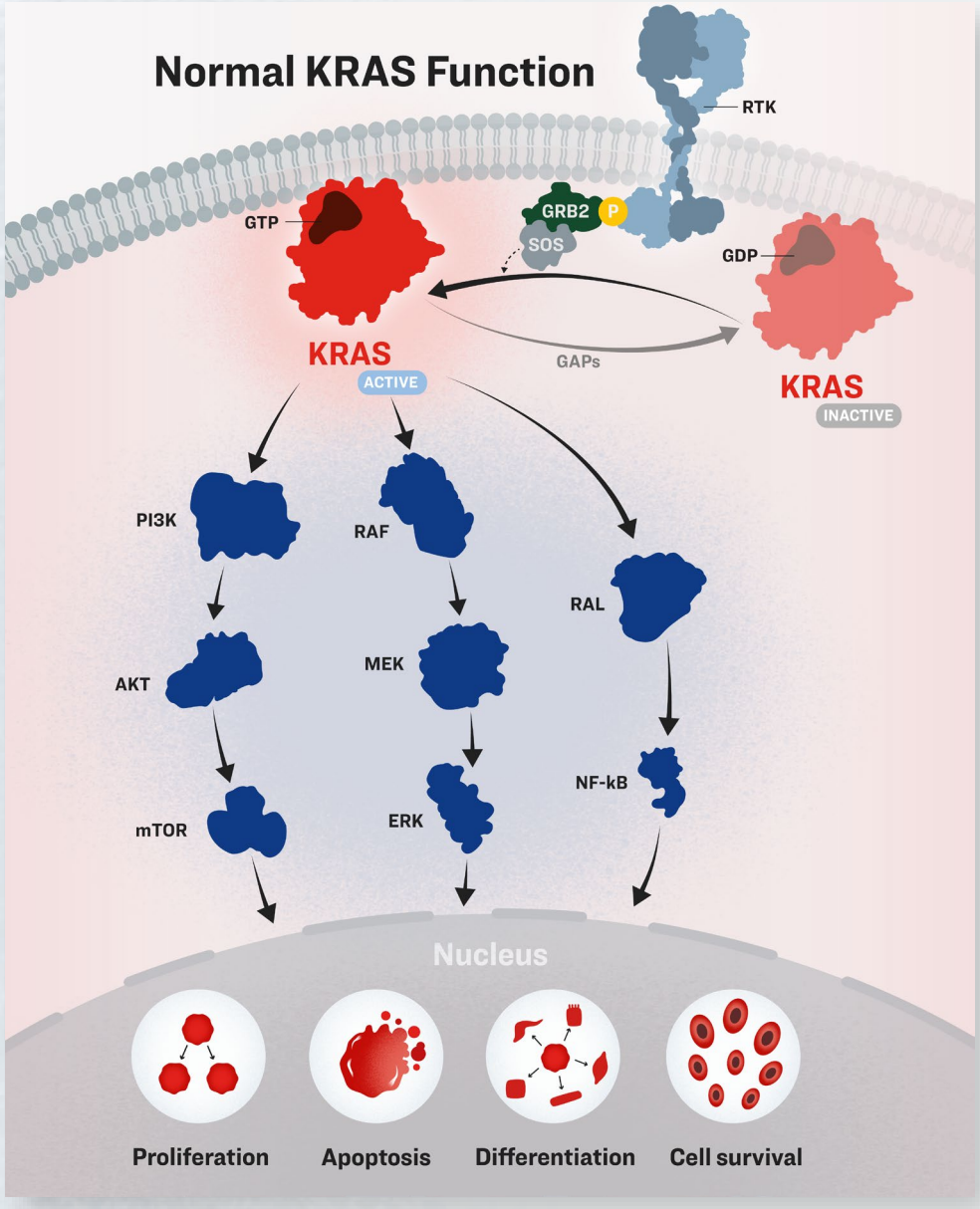
First-line treatment outcomes in *KRAS* G12C–mutant NSCLC lag behind oncogenic drivers (eg, *EGFR* and *ALK*) with approved targeted therapies.[2]



Kaplan–Meier curve shows real-world overall survival (rwOS) data generated through analysis of Flatiron Health–Foundation Medicine NSCLC clinico-genomic database (FH-FMI CGDB) for patients with advanced NSCLC harboring driver alterations.[2]

KRASG12C Drives Oncogenesis and Supports Immune Evasion





KRAS Is an Intracellular Molecule That Regulates Normal Cellular Processes[32]

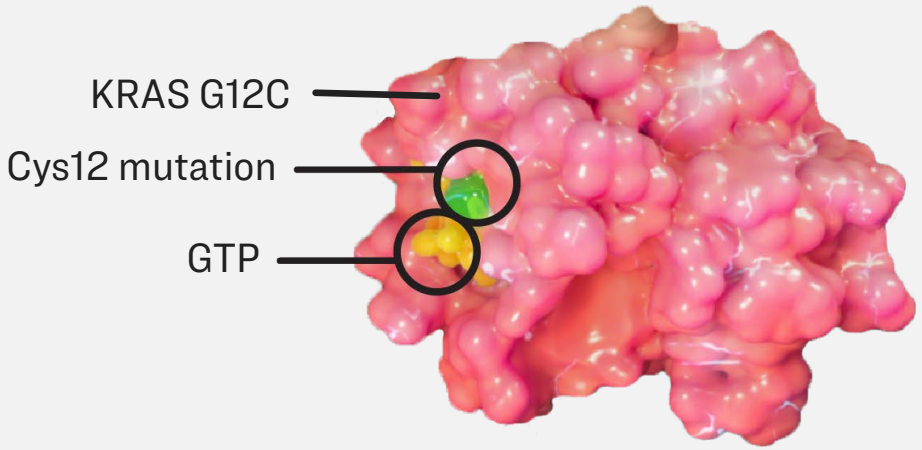
KRAS normally acts as an intracellular molecular switch, **cycling between inactive guanosine diphosphate (GDP)–bound and active guanosine triphosphate (GTP)–bound states.**[32]

Ligand binding to **receptor tyrosine kinase (RTK)** leads to[32,33]:

- Conformational changes and recruitment of **guanine nucleotide exchange factors (GEFs),** such as SOS1/2
- **GEFs** promoting **GTP binding to KRAS** to activate it
- **GTPase-activating proteins (GAPs)** together with **intrinsic GTPase activity** of KRAS mediating **GTP hydrolysis to GDP,** bringing KRAS back to its inactive state

GTP-bound activated KRAS transduces downstream signaling pathways involved in **normal cellular proliferation, apoptosis, differentiation, and survival.**[1,32,33]

KRAS G12C Mutation Leads to Constitutive Activation of the Mutated Protein[32]



KRAS G12C: Single base missense mutation in exon 2 codon 12 where glycine is substituted with cysteine[1,33,34]

Glycine-to-cysteine substitution impacts GTP hydrolysis by blocking[32-34]:

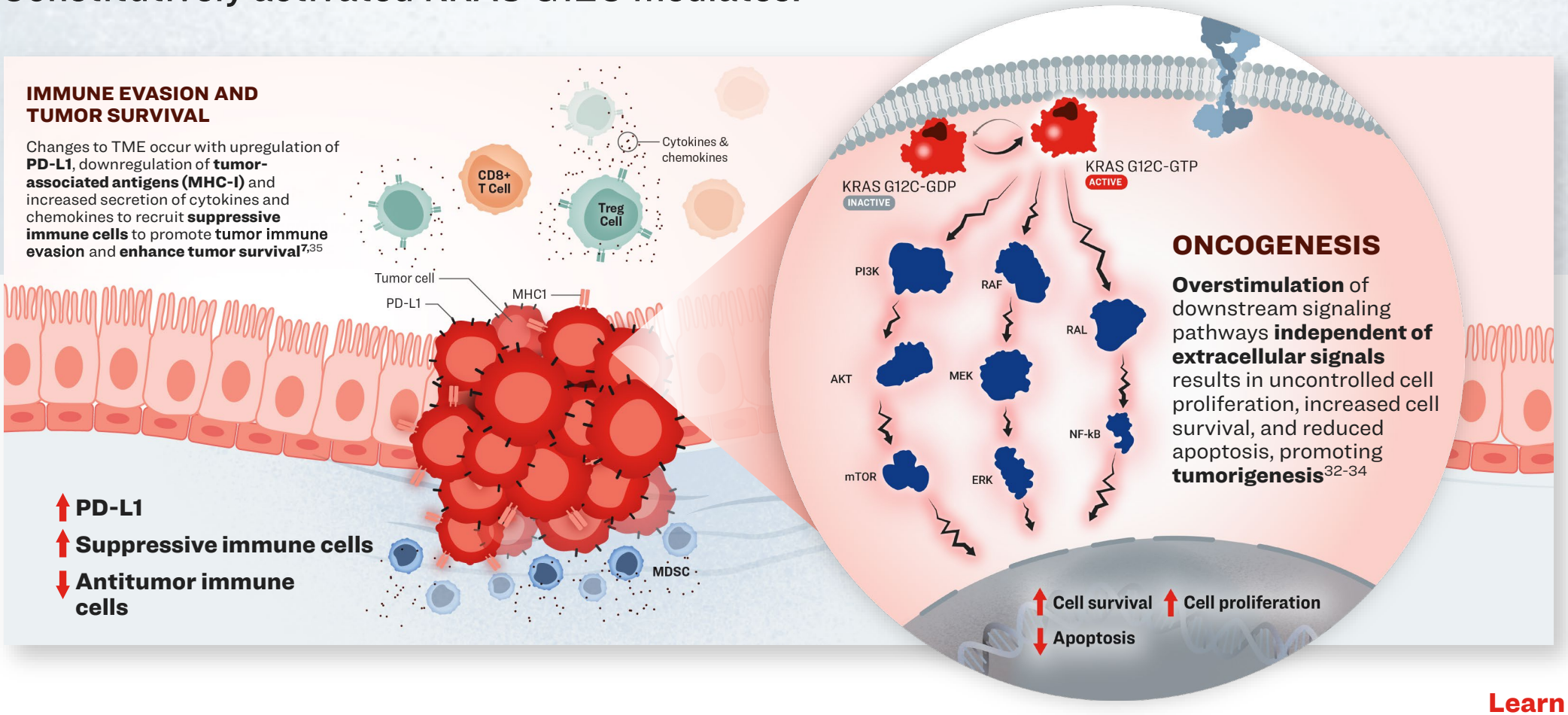
- Normal self-regulation of KRAS (intrinsic hydrolysis)
- External regulation provided by GTPase-activating (GAP) proteins

Prolonged GTP binding keeps **KRAS G12C persistently active,** continuously driving downstream signaling rather than acting as a controlled switch.[32-34]

Some cycling between the GTP- and GDP-bound state does continue to occur.[32-34]

KRAS G12C Drives Oncogenesis and Supports Tumor Immune Evasion[34,35]

Constitutively activated KRAS G12C mediates:



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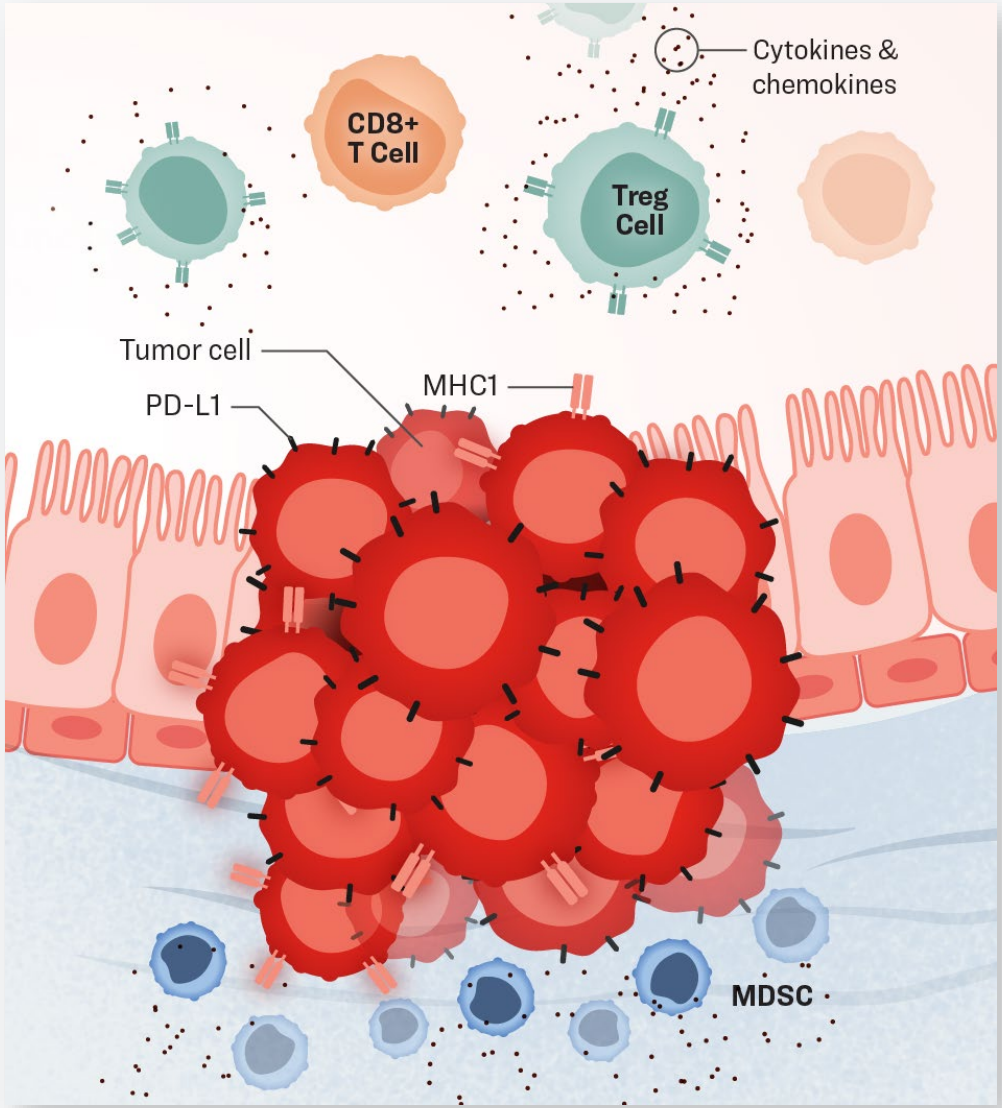
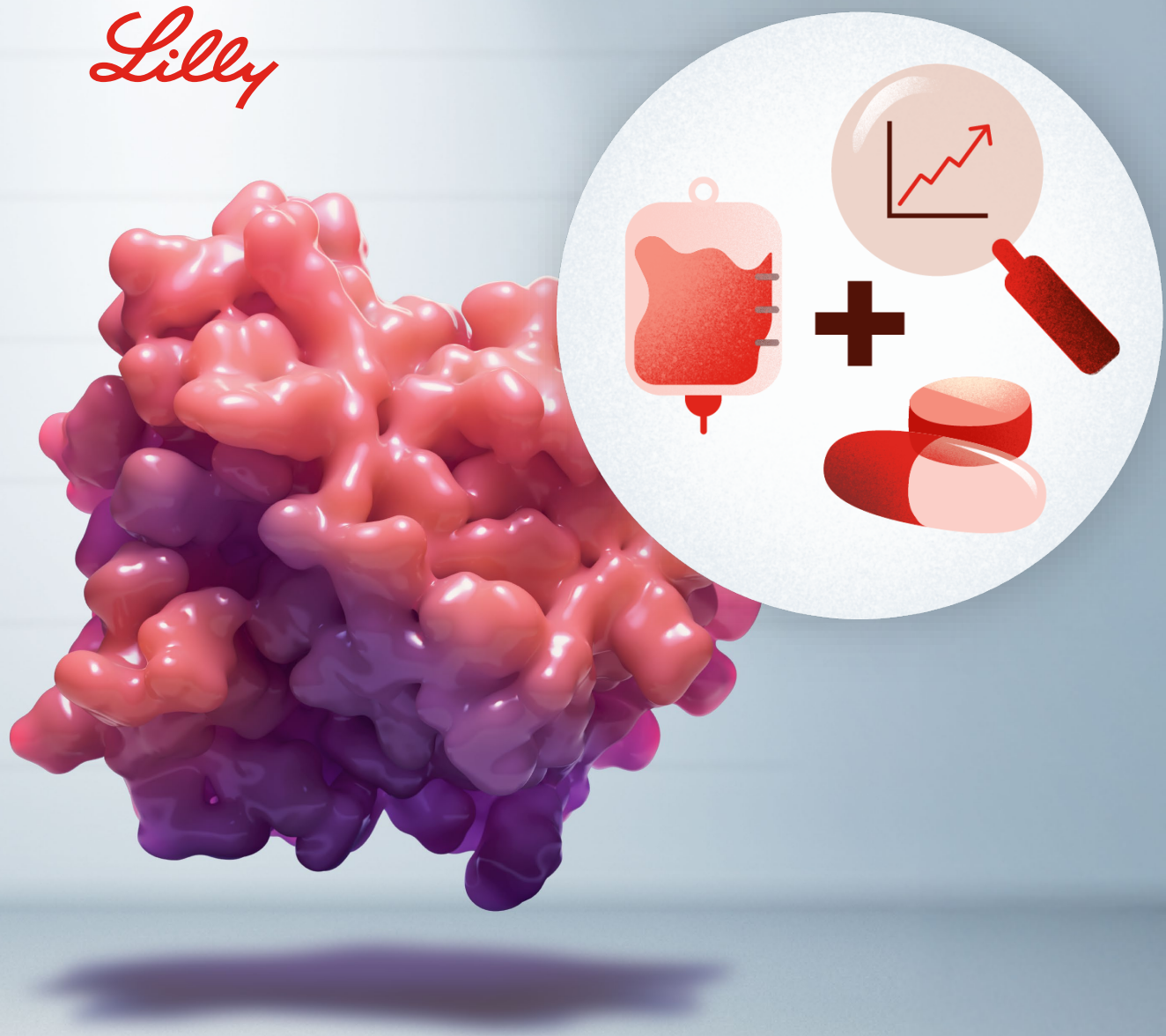


KRAS G12C Mediates Complex Interplay Between Different Immune Cells in the TME to Facilitate Tumor Immune Evasion[35]

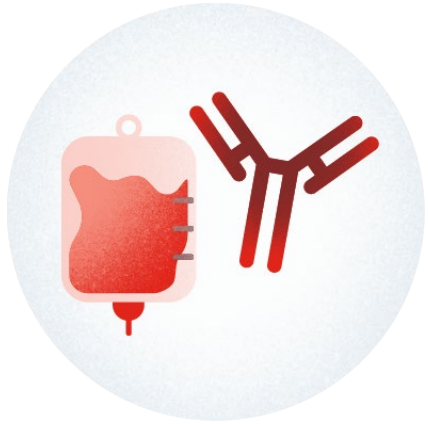
Effects of *KRAS* G12C mutation on the TME[7,8,35]:

- **Reduction** in tumor-infiltrating and cytotoxic T cells
- **Recruitment** of myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs)—**immune suppressive cells**
- **Reprogramming** of stromal cells into immunosuppressive secretory cells
- **Disruption of innate immunity** through neutrophil recruitment, promoting inflammation
- **Reduction of tumor-associated antigen presentation** (MHC-I) to avoid T-cell detection

Emerging First-Line Combination Strategies for *KRAS*G12C–Mutant NSCLC



Treatment-Related Decisions in the First-Line Setting Are Often Guided by Patient and Tumor Characteristics[17]



Immunotherapy with or without chemotherapy is the current **standard of care (SOC)** in *KRAS* G12C–mutant NSCLC, often guided by PD-L1 levels.[9,10]

Treatment-related decisions are typically based on **patient and tumor characteristics** that are associated with better/worse overall survival outcomes to the available therapy options[17]:

Better outcomes associated with

- Nonsquamous cell carcinoma
- No history of smoking
- PD-L1 ≥1%

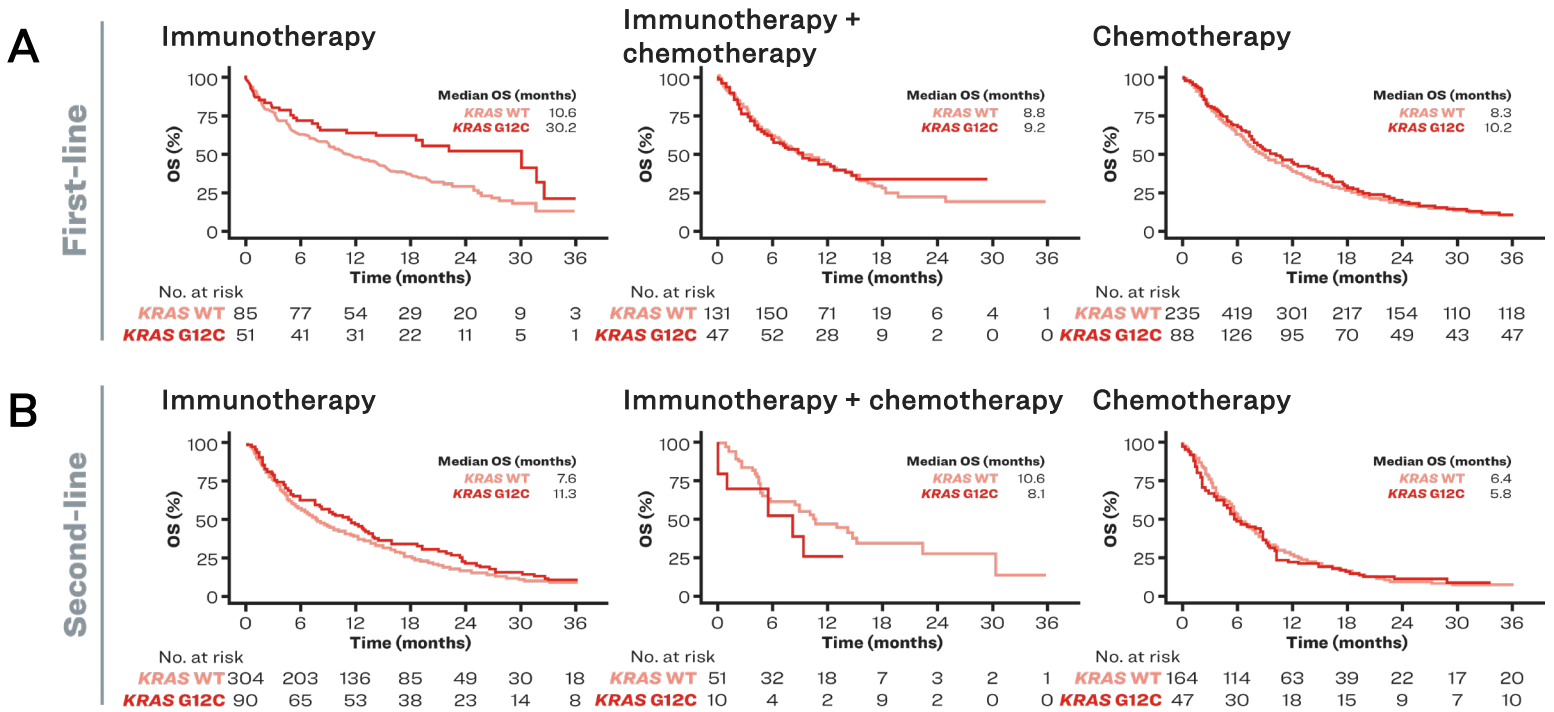
Poorer outcomes associated with

- Older age
- Performance status (PS) ≥1
- Brain metastasis at first-line setting
- *KEAP1* and *STK11* co-mutations

Patients with *KRAS* G12C–Mutant NSCLC Are More Responsive to Immunotherapy Alone Compared to Patients with *KRAS* WT Tumors in First-Line Treatment[18]

Real-world evidence shows that patients with *KRAS* G12C–mutant NSCLC have a mOS that is[18]:

- **Numerically longer** than in patients with *KRAS* WT tumors when receiving **immunotherapy alone in first-line treatment**
- **Comparable** to patients with *KRAS* WT tumors when receiving **immunotherapy + chemotherapy or chemotherapy alone with first-line or second-line treatment**



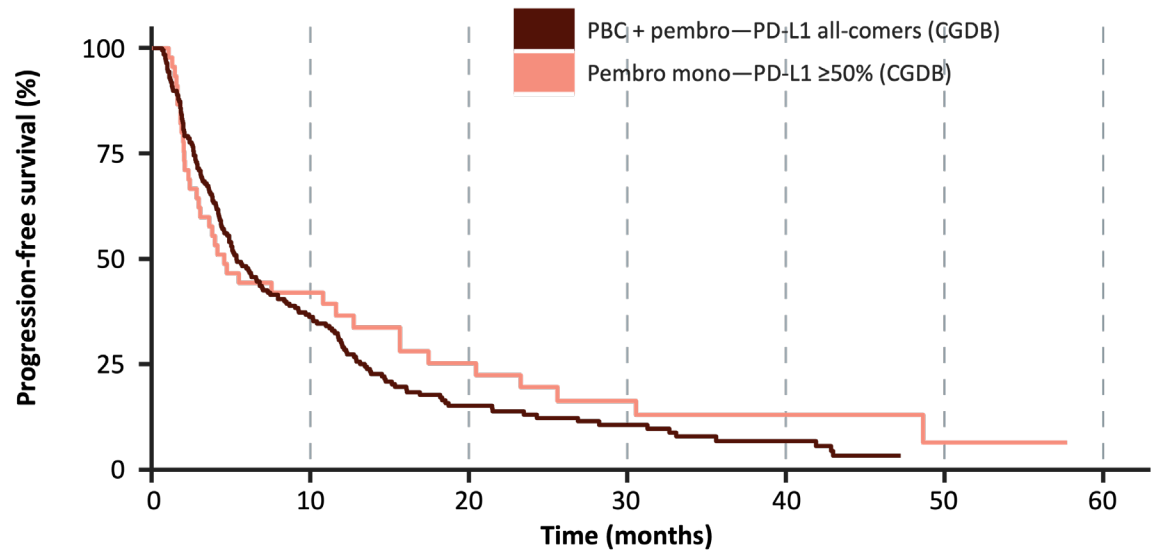
Kaplan–Meier curves show effect of *KRAS* mutational status on OS by treatment in **(A)** the first-line (n = 1798; adjusted by age, sex, race, cancer type, PD-L1, any metastasis, TMB, and histology) and **(B)** the second-line (n = 1016; adjusted by age, sex, race, cancer type, PD-L1, any metastasis, TMB, histology, and drug category in the first-line).

Poor Progression-Free Survival (PFS) With Current Standard of Care in Patients With *KRAS* G12C–Mutant NSCLC[17]

In a retrospective, real-world study evaluating treatment patterns and clinical outcomes in patients with *KRAS* G12C–mutant advanced NSCLC in the US[17,*]:

- Most patients had **advanced disease** at diagnosis
- **~25% of patients had documented brain metastasis** at initiation of first-line treatment
- Most common first-line treatment:
  - Platinum-based chemotherapy + pembrolizumab in PD-L1 all-comers
  - Pembrolizumab monotherapy in PD-L1 ≥50%

PFS outcomes by first-line treatment type in patients with *KRAS* G12C–mutant NSCLC*



Median PFS was 5 months irrespective of the first-line treatment regimen in patients with *KRAS* G12C–mutant NSCLC.[†,‡]

*Using data from US-based, electronic health record–derived (EHR) deidentified Flatiron Health Research Database and Flatiron Health–Foundation Medicine NSCLC Clinico-Genomic Database (FH-FMI CGDB).
[†]Median PFS (mPFS) outcomes were evaluated in other subgroups as well.[17]
[‡]PFS and overall survival (OS) outcomes are similar to other studies.[18,36-53]

Poor OS With Current Standard of Care in Patients With *KRAS* G12C–Mutant NSCLC[17]

Real-world differences in **median overall survival (mOS)** in the first-line setting in patients with *KRAS* G12C–mutant NSCLC[17,*,†,‡]:

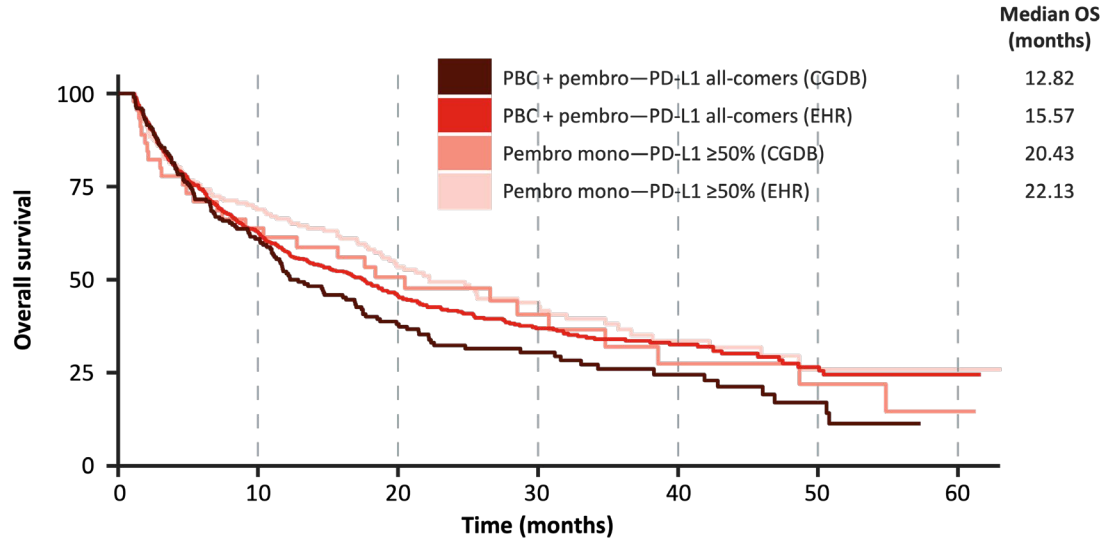
13-16 months

in PD-L1 all-comers treated with platinum-based chemotherapy + pembrolizumab

20-22 months

in PD-L1 ≥50% treated with pembrolizumab monotherapy

OS outcomes by first-line treatment type in patients with *KRAS* G12C–mutant NSCLC*



No. at risk				
PBC + pembro—PD-L1 all-comers (CGDB)	206	56	16	0
PBC + pembro—PD-L1 all-comers (EHR)	571	183	52	4
Pembro mono—PD-L1 ≥50% (CGDB)	46	17	7	1
Pembro mono—PD-L1 ≥50% (EHR)	177	67	21	2

Only 38% of patients who receive first-line therapy **advance to second-line therapy**, in part due to:

- High disease burden
- Poor performance status
- Patient frailty/fitness

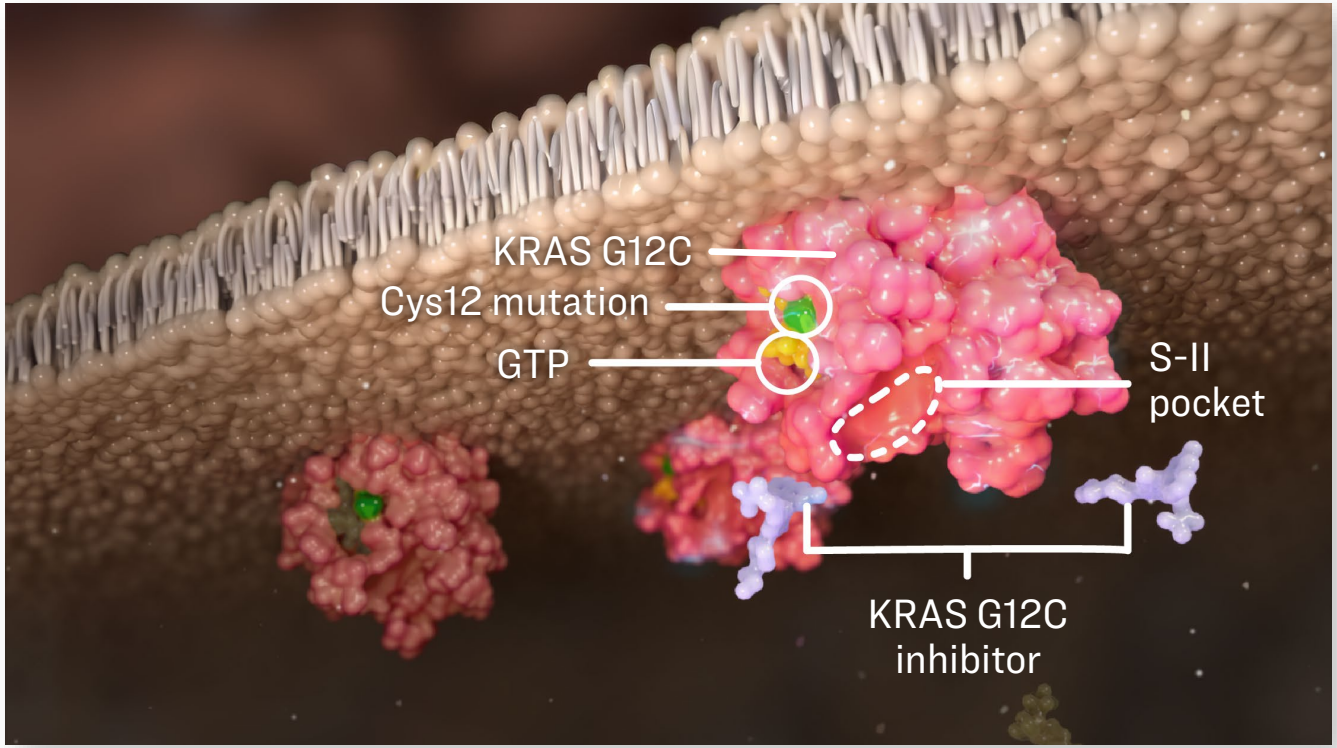
Effective and well-tolerated treatment remains an unmet need in first-line treatment.[17,54]

*Using data from US-based, electronic health record–derived (EHR) deidentified Flatiron Health Research Database and Flatiron Health–Foundation Medicine NSCLC Clinico-Genomic Database (FH-FMI CGDB).
†mOS outcomes were evaluated in other subgroups as well.[17]
‡PFS and OS outcomes are similar to other studies.[18,36-53]

Previously Considered "Undruggable," KRAS G12C Is Currently Targetable and Has Approved Targeted Inhibitors in 2L and Later Settings[10,32]

Discovery of the switch-II pocket (S-IIP), an **allosteric pocket** adjacent to the mutant cysteine residue, resolved the "undruggability" challenge.[32,33,55]

- Cysteine amino acid induces a **structural reconfiguration,** creating a **new pocket** beneath the switch-II domain (absent in the WT protein)
- Unique pocket enabled the design of **covalent inhibitors** that **specifically bind KRAS G12C**, sparing the WT protein
- **Several molecules/therapies** with different mechanisms of inhibiting mutated KRAS G12C protein are being investigated



KRAS G12C Inhibition Downregulates Oncogenesis and Promotes Restoration of Antitumor Immunity[15]

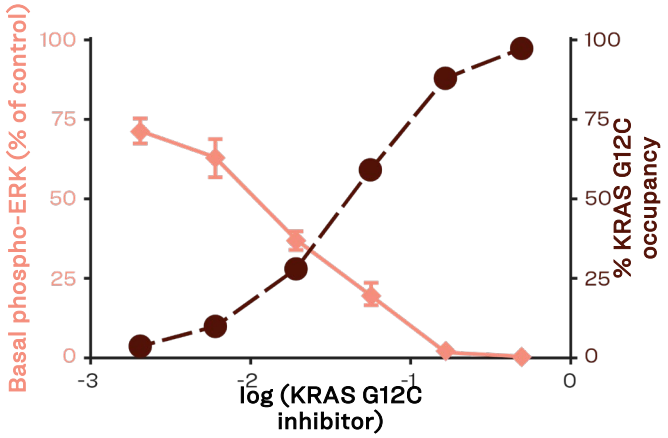
In preclinical studies, KRAS G12C inhibition reduces oncogenic signaling and reverses some of the immunosuppressive effects in the TME.[15,56-61]

Reduced tumor growth | **Increased antitumor immunity**

Tap to toggle

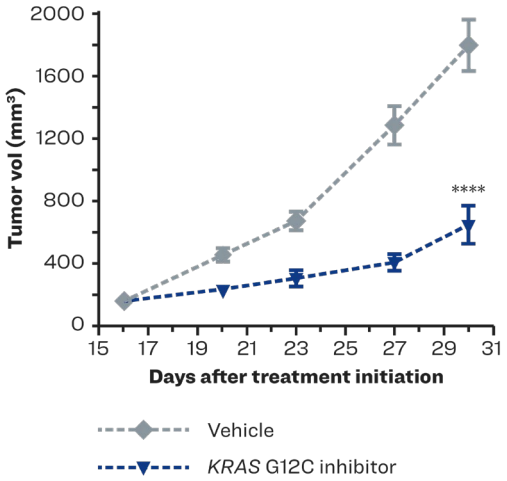
Reduces downstream signaling mediated by RAF/ERK pathway

Significantly inhibits basal phosphorylation of ERK1/2 (phospho-ERK) and reaches near maximal KRAS G12C occupancy in a *KRAS* G12C–mutant cell model.[61]



Restricts tumor cell growth

Reduces tumor growth in *KRAS* G12C–mutant NSCLC patient-derived xenograft (PDX) models.[61]



Reduced downstream oncogenic signaling **downregulates cell proliferation, survival, and tumor growth,** leading to **tumor regression.**[56-61]

****p < .0001 compared with vehicle; repeated measures ANOVA followed by Dunnett's multiple comparison test.

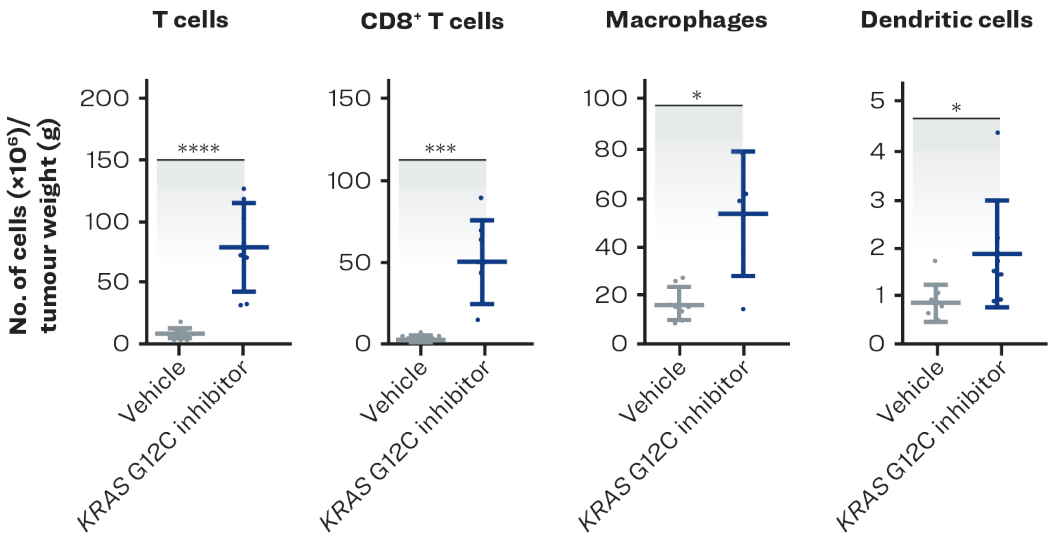
KRAS G12C Inhibition Downregulates Oncogenesis and Promotes Restoration of Antitumor Immunity[15]

In preclinical studies, KRAS G12C inhibition reduces oncogenic signaling and reverses some of the immunosuppressive effects in the TME.[15,56-61]

Reduced tumor growth | **Increased antitumor immunity**

Tap to toggle

KRAS G12C inhibition induces a proinflammatory TME that promotes **immune cell recognition, infiltration, and targeting of tumor cells**, leading to **antitumor immune response**.[15,61]



KRAS G12C inhibition increases levels of cytotoxic T cells, macrophages, and dendritic cells shown in CT-26 KRAS G12C tumors immunophenotyped by flow cytometry.[61]

****p < .0001 , *** p < .001, * p < .05; one-way ANOVA followed by Tukey's test.

KRAS G12C Inhibitors May Be Additive or Synergistic When Combined With Immunotherapy or Chemotherapy[61,62]

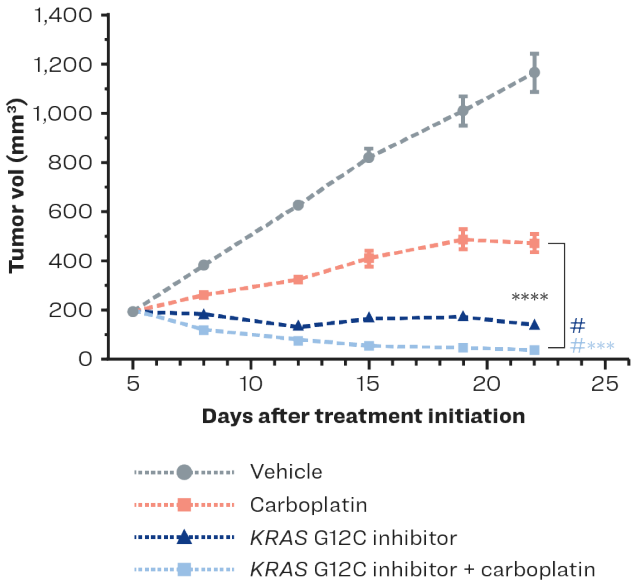
Preclinical data show that KRAS G12C inhibitors combined with immunotherapy or chemotherapy promote tumor immune evasion and enhance the ability of the immune system to target and eliminate tumor cells.[61,62]

Reduced tumor growth | **Increased antitumor immunity**

Tap to toggle

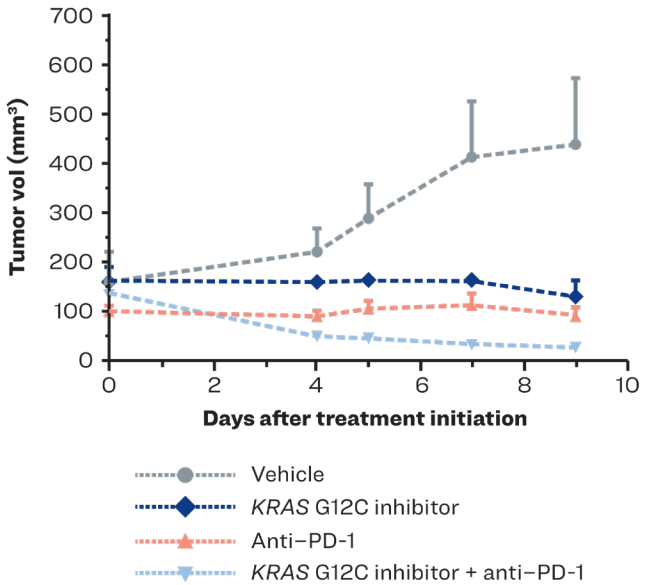
Combination treatment KRAS G12C inhibitor with carboplatin significantly inhibited tumor growth

Data is compared to KRAS G12C inhibition or carboplatin alone in *KRAS* G12C–mutant NCI-H358 tumors in mice.[61]



Combination treatment KRAS G12C inhibitor with PD-1 inhibitor delayed tumor growth

Data is compared to KRAS G12C or PD-1 inhibition alone in *KRAS* G12C–mutant NSCLC PDX model LU-01–0361.[62]



****p < .0001 for treatment group compared with vehicle; *** p ≤ .001 for combination treatment compared with the single agent; p values were determined by repeated-measures ANOVA followed by Dunnett's multiple-comparison test; #p < .001 regression by two-sided Student's t-test.

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Reduced tumor growth | **Increased antitumor immunity**

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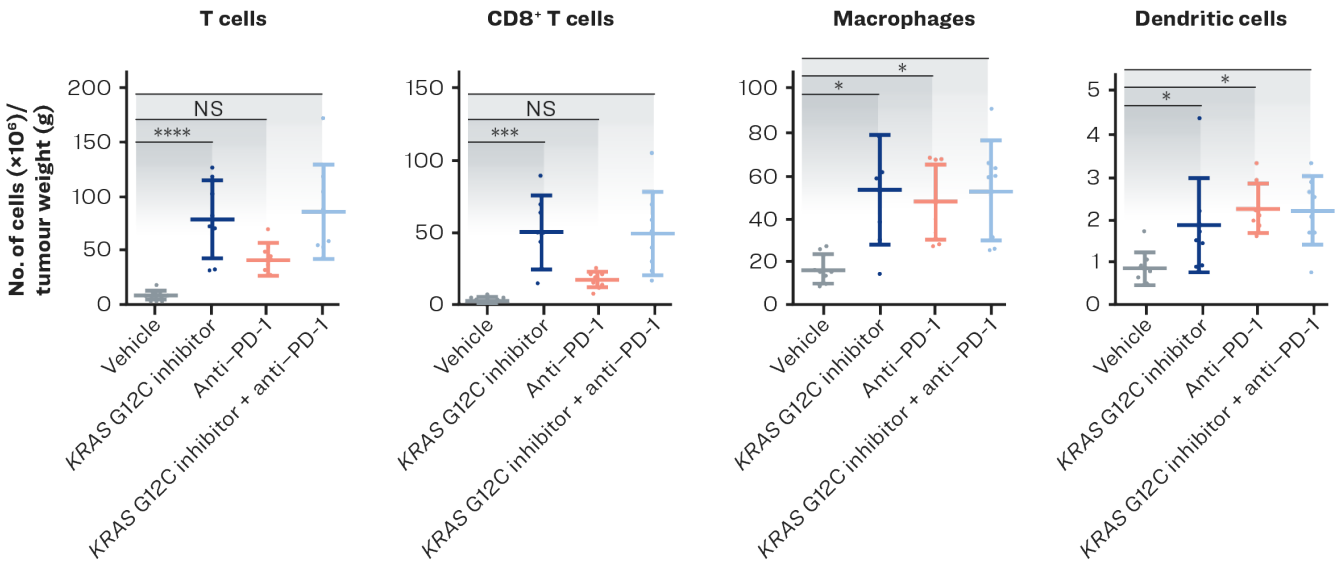


KRAS G12C inhibition alone and combination treatment of KRAS G12C inhibitor with anti–PD-1 increase levels of cytotoxic T cells, macrophages, and dendritic cells shown in CT-26 KRAS G12C tumors immunophenotyped by flow cytometry.[61]

****p < .0001 , *** p < .001, * p < .05; one-way ANOVA followed by Tukey's test.

KRAS G12C Inhibitors Show a Manageable Safety Profile When Combined With Immunotherapy, Chemotherapy, or Chemoimmunotherapy in First-Line Treatment of *KRAS* G12C–Mutant NSCLC[63-67]

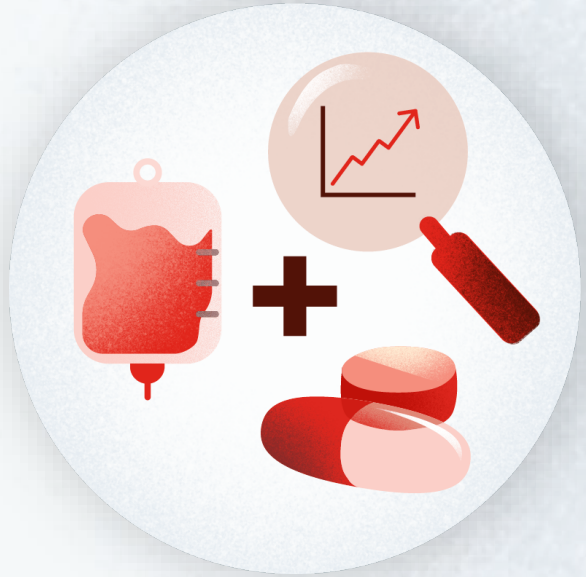
Early Phase 1-2 data demonstrate that KRAS G12C inhibitors combined with immunotherapy, chemotherapy, or chemoimmunotherapy can lead to[63-68]:

Safety profile

- **Treatment-related adverse events (TRAEs)** Grade ≥3 observed in 33%-65% of the patients
- **TRAEs leading to discontinuation** in ≥1 drugs in 4%-22% of the patients

Efficacy

- **Objective response rate (ORR)** of 40%-74%
- **Disease control rate (DCR)** of 80%-100%
- **Low rate of** central nervous system failure



Disclaimer: The safety and efficacy of the **molecules/agents** and uses under investigation have not been established. There is no guarantee that pipeline molecules will receive regulatory approval and become commercially available for the uses being investigated. The information provided about new disease states being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please **visit https://www.lilly.com/discovery/clinicaldevelopment-pipeline** or **lillyoncologypipeline.com**

KRAS G12C Inhibitor Combinations With Immunotherapy, Chemotherapy, or Chemoimmunotherapy Are Being Evaluated

Ongoing Phase 3 trials will validate our understanding of integrating KRAS G12C inhibitors with standard-of-care treatments in the first-line setting for advanced *KRAS* G12C–mutant NSCLC.[69-75,*]

KRYSTAL-7

NCT04613596

KRAS G12C inhibitor + pembro	Pembro

PD-L1 ≥50

KANDLELIT-004

NCT06345729

KRAS G12C inhibitor + pembro	Pembro

PD-L1 ≥50

SUNRAY-01 Part A | SUNRAY-01 Part B

NCT06119581

KRAS G12C inhibitor + pembro	Pembro	KRAS G12C inhibitor + pembro + chemo	Pembro + chemo

PD-L1 ≥50 | **PD-L1 all-comers**

KRYSTAL-4

NCT06875310

KRAS G12C inhibitor + pembro + chemo	Pembro + chemo

PD-L1 all-comers

KRASCENDO-2

NCT06793215

KRAS G12C inhibitor + pembro	Pembro + chemo

PD-L1 all-comers

KANDLELIT-007

NCT07190248

KRAS G12C inhibitor + sc pembro	Sc pembro + chemo

PD-L1 all-comers

CodeBreak 202

NCT05920356

KRAS G12C inhibitor + chemo	Pembro + chemo

PD-L1 negative

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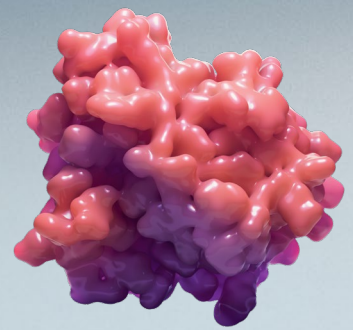
*Information up to date as of November 4, 2025.

Scan the QR Codes to Learn More

About *KRAS* G12C–mutant NSCLC

About emerging combination strategies for first-line treatment of *KRAS* G12C–mutant NSCLC



Abbreviations

1L = first-line; **2L** = second-line; **AKT** = protein kinase B; **ALK** = anaplastic lymphoma kinase; ANOVA = analysis of variance; **BRAF** = B-rapidly accelerated fibrosarcoma; **CD** = cluster of differentiation; **CGDB** = Clinico-Genomic Database; **DCR** = disease control rate; **EGFR** = epidermal growth factor receptor; **EHR** = electronic health record-derived; **ERK** = extracellular signal-regulated kinase; **FH-FMI CGDB** = Flatiron Health–Foundation Medicine NSCLC clinico-genomic database; **GAP** = GTPase-activating; **GDP** = guanosine diphosphate; **GEF** = guanine nucleotide exchange factor; **GRB2** = growth factor receptor-bound protein 2; **GTP** = guanosine triphosphate; **HER2** = human epidermal growth factor receptor 2; **KEAP1 =** Kelch-like ECH-associated protein 1; **KRAS** = Kirsten rat sarcoma; **LRP1B** = low-density lipoprotein receptor-related protein 1B; **MAPK** = mitogen-activated kinase; **Mb** = megabase; **MDSC** = myeloid-derived suppressor cell; **MEK** = mitogen-activated protein kinase; **MET** = mesenchymal-epithelial transition; **METex14** = mesenchymal-epithelial transition exon 14; **MHC** = major histocompatibility complex; **mOS** = median overall survival; **mTOR** = mammalian target of rapamycin; **muts** = mutations; **NF-kB** = nuclear factor-kB; **NRG1** = neuregulin 1; **NS** = not significant; **NSCLC** = non-small cell lung cancer; **NTRK** = neurotrophic tyrosine receptor kinase; **ORR** = objective response rate; **OS** = overall survival; **P** = phosphorylation; **PBC** = platinum-based chemotherapy; **PD-1** = programmed death 1; **PD-L1** = programmed death-ligand 1; **PDX** = patient-derived xenograft; **PFS** = progression-free survival; **PI3K** = phosphoinositide 3-kinase; **PS** = performance status; **RAF** = rapidly accelerated fibrosarcoma; **RAL** = Ras-like protein; **RET** = rearranged during transfection; **ROS1** = ROS proto-oncogene 1; **RTK** = receptor tyrosine kinase; **rwOS** = real-world overall survival; **S-IIP** = switch-II pocket; **SOC** = standard of care; **SOS** = Son of Sevenless; **SMARCA4** = SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4; **STK11 =** serine/threonine kinase 11; **TIL** = tumor infiltrating lymphocytes; **TMB** = tumor mutational burden; **TME** = tumor microenvironment; **TP53** = tumor protein p53; **TRAE** = treatment-related adverse events; **Treg** = regulatory T cells; **WT** = wild-type.

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