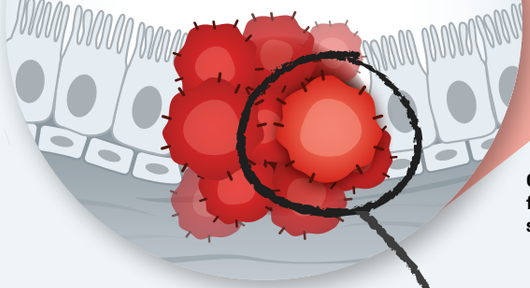
KRAS G12C IN NSCLC:

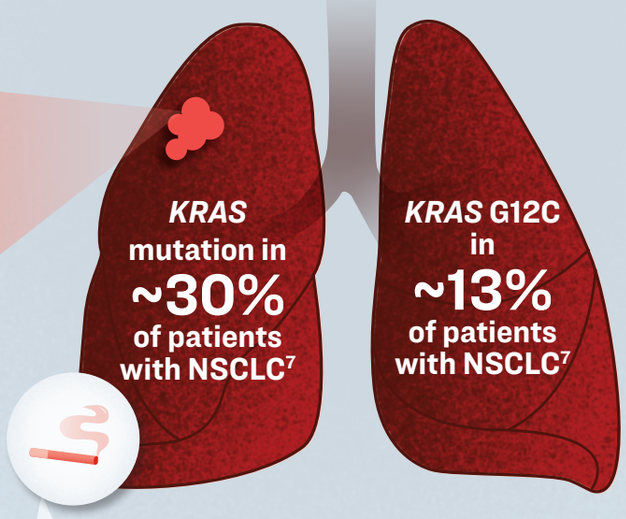
Not Your Usual Suspect

Patients with *KRAS* G12C–mutant NSCLC have **poor survival and PFS of 5 months**, and there is a **lack of targeted therapies in 1L.**[1,2]

KRAS G12C–mutant NSCLC has **unique features** compared to NSCLC with other oncogenic alterations.[2-6]

↑ TMB ↑ PD-L1 ↑ Sensitivity to immunotherapy | Co-mutations

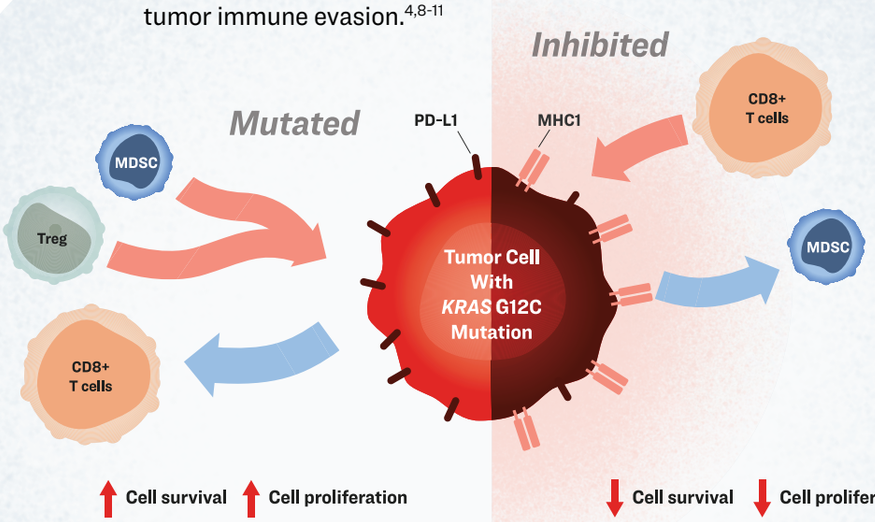




Correlated with former or current smoking history[3]

KRAS G12C drives oncogenesis and supports tumor immune evasion.[4,8-11]

KRAS G12C inhibition downregulates oncogenic signaling and enhances immunogenicity, immune cell infiltration, and antitumor response.[12-17]



Preclinical trials of KRAS G12C inhibitors **combined** with IO or chemotherapy show **additive or synergistic effect.**[12,18]

Ongoing Phase 3 trials are evaluating KRAS G12C inhibitors in combination with IO, chemotherapy, or chemoimmunotherapy in 1L treatment for advanced *KRAS* G12C–mutant NSCLC.[19-25]

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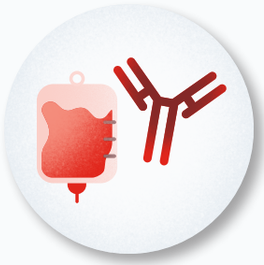
Poor Survival Outcomes With the Current SOC: Having Targeted Therapies in 1L Could Improve Outcomes in Patients With *KRAS* G12C–Mutant NSCLC



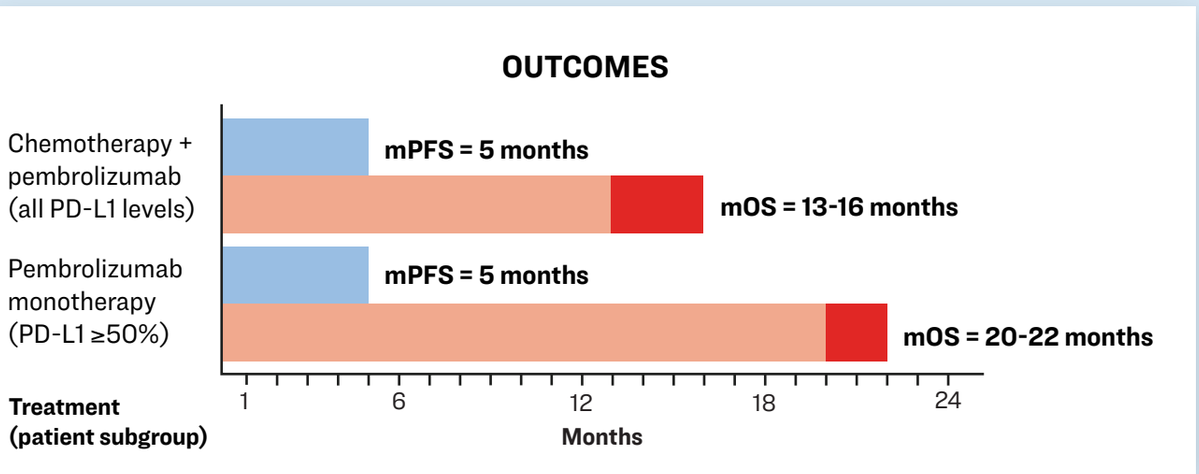
IO with or without chemotherapy remains the **SOC in 1L** for patients with *KRAS* G12C–mutant NSCLC, often guided by PD-L1 expression, with some exceptions. Currently available KRAS G12C inhibitors are only approved as **single agents for 2L and later settings.**[26]

Treatment recommendations are also guided by other patient and tumor factors that can influence outcomes to therapy.[1]

Better outcomes: nonsquamous cell carcinoma, no history of smoking, PD-L1 ≥1%.

Poorer outcomes: older age, PS ≥1, brain metastasis at 1L, *KEAP1* and *STK11* co-mutations.

Real-world evidence evaluating treatment patterns and clinical outcomes in 1L setting in patients with *KRAS* G12C–mutant advanced NSCLC in the US reported[1]:



Only **38%** advance to receive 2L

Effective and well-tolerated treatment remains an unmet need in 1L, as only **38%** of the patients who receive 1L therapy **advance to 2L therapy**, in part due to high disease burden, poor PS, and patient frailty/fitness.[1,27]

KRAS G12C Drives Oncogenesis and Supports Tumor Immune Evasion

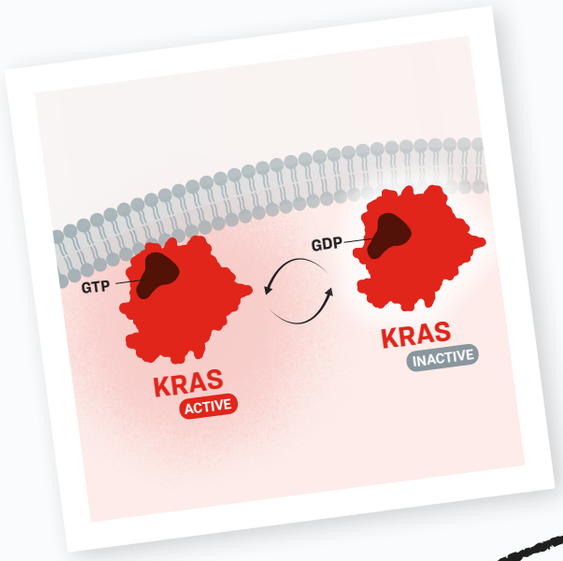


EXHIBIT A:

KRAS normally acts as an intracellular molecular switch, cycling between **inactive GDP-bound and active GTP-bound** states, to regulate downstream signaling pathways involved in normal cellular **proliferation, apoptosis, differentiation, and survival.**[7-9]

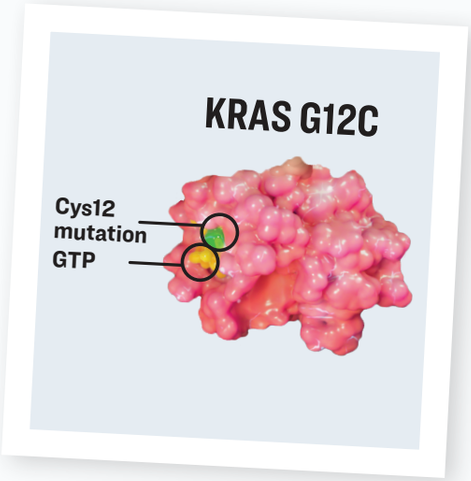
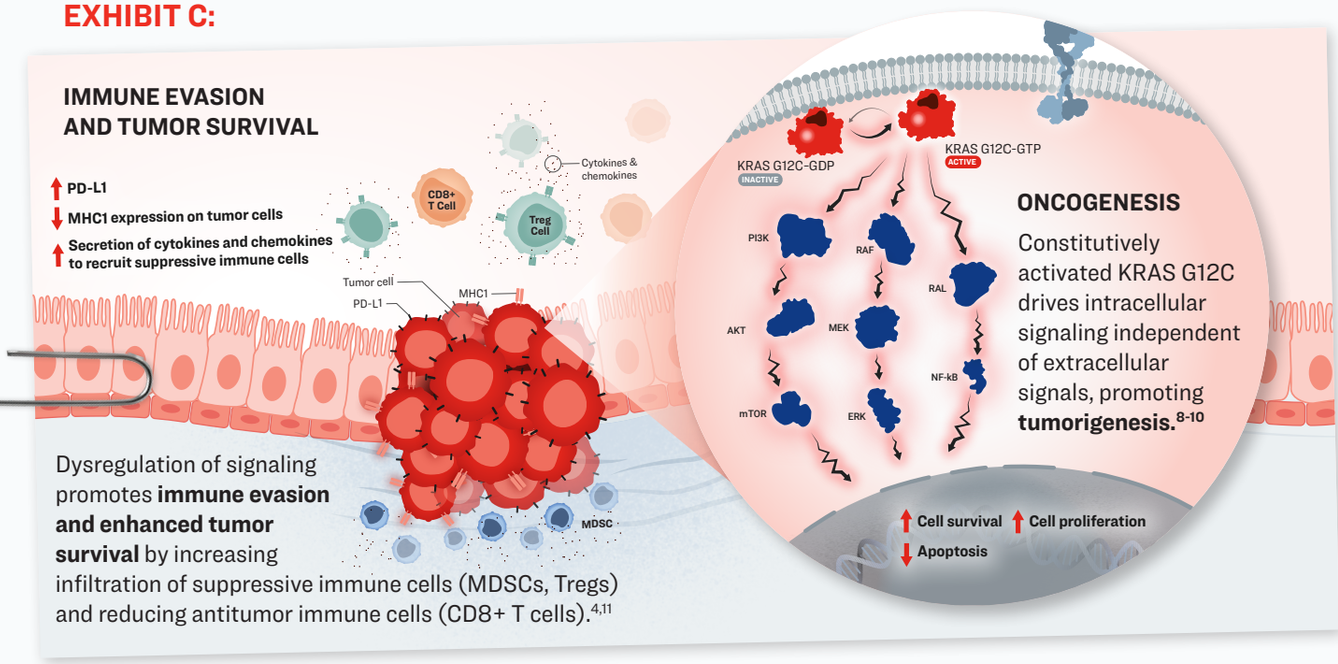


EXHIBIT B:

KRAS G12C is caused by a single base missense mutation in codon 12 of the *KRAS* gene, **substituting glycine with cysteine** in the KRAS protein. KRAS G12C **shifts cycling** of KRAS toward the GTP-bound active state by **blocking** GAP mediated **hydrolysis of GTP.**[7-10]

EXHIBIT C:



Dysregulation of signaling promotes **immune evasion and enhanced tumor survival** by increasing infiltration of suppressive immune cells (MDSCs, Tregs) and reducing antitumor immune cells (CD8+ T cells).[4,11]

additive or synergistic effect.[4,11]

KRAS G12C Inhibition Downregulates Oncogenesis and Restores Antitumor Immunity

EXHIBIT D:

Previously considered **undruggable**, a newly discovered **allosteric pocket** allows binding of KRAS G12C inhibitors, followed by locking of the protein in an **inactive GDP-bound state** through **covalent bond formation with cysteine.** Intrinsic hydrolysis of GTP to GDP, together with this binding and covalent bond formation, **suppresses downstream oncogenic signaling.**[8,9,10,28,*]

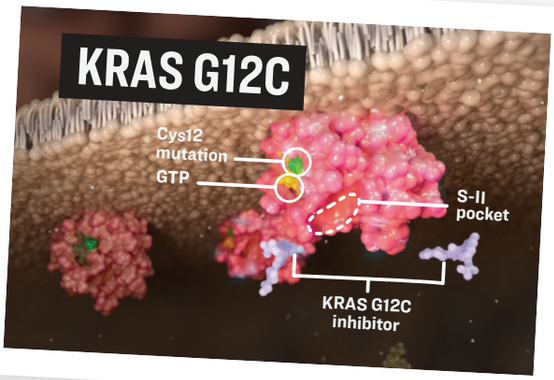
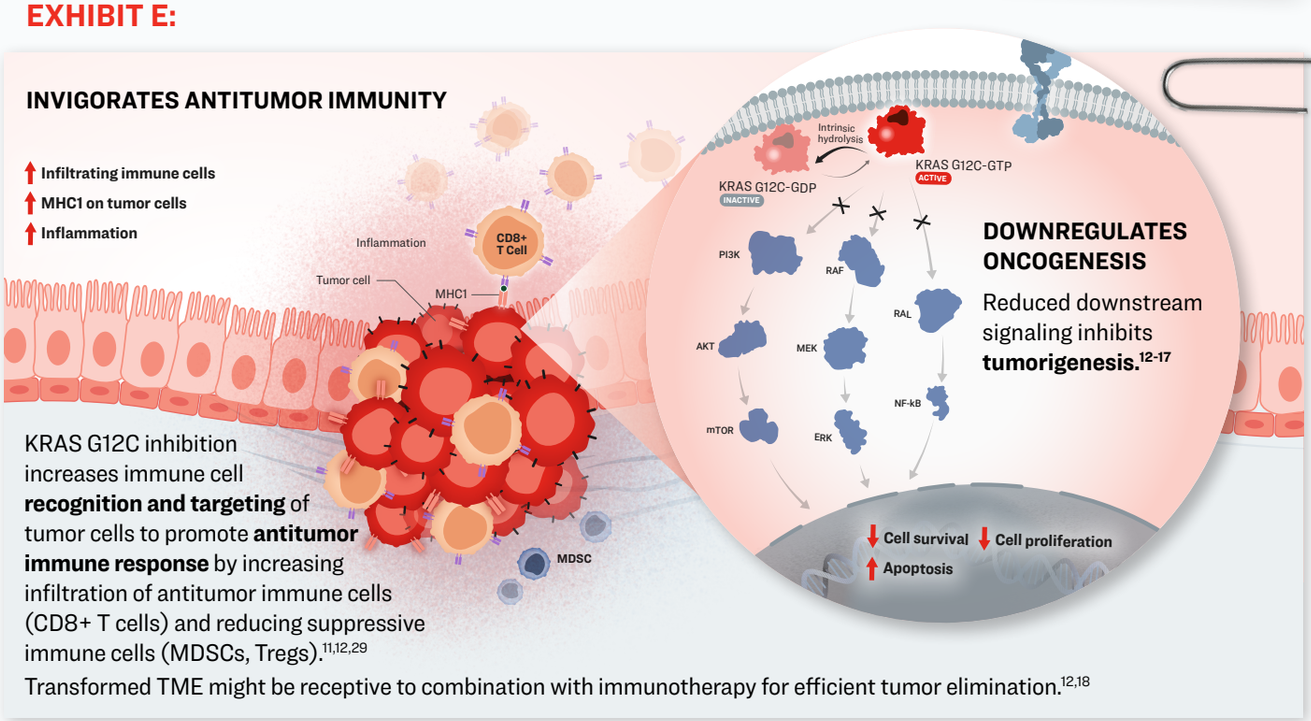


EXHIBIT E:



KRAS G12C inhibition increases immune cell **recognition and targeting** of tumor cells to promote **antitumor immune response** by increasing infiltration of antitumor immune cells (CD8+ T cells) and reducing suppressive immune cells (MDSCs, Tregs).[11,12,29]

Transformed TME might be receptive to combination with immunotherapy for efficient tumor elimination.[12,18]

EXHIBIT F:

Preclinical data show that KRAS G12C inhibitors **suppress the mutant protein** and may reverse immunosuppressive effects, acting **additively or synergistically** when combined with **IO or chemotherapy,** providing a rationale for using **combination therapy approach** in the clinical setting.[12,18]

Ongoing Phase 3 trials are evaluating KRAS G12C inhibitors in combination with IO, chemotherapy, or chemoimmunotherapy in 1L treatment for advanced *KRAS* G12C–mutant NSCLC.[19-25]

*Multiple mechanisms of KRAS G12C inhibition are under investigation.[8]

additive or synergistic effect.[18]

Abbreviations

1L = first-line; **2L** = second-line; **AKT** = protein kinase B; **CD** = cluster of differentiation; **ERK** = extracellular signal-regulated kinase; **GDP** = guanosine diphosphate; **GTP** = guanosine triphosphate; **IO** = immunotherapy; **KEAP1** = Kelch-like ECH-associated protein 1; **KRAS** = Kirsten rat sarcoma; **MDSC** = myeloid-derived suppressor cell; **MEK** = mitogen-activated protein kinase; **MHC** = major histocompatibility complex; **mOS** = median overall survival; **mPFS** = median progression-free survival; **mTOR** = mammalian target of rapamycin; **NF-kB** = nuclear factor-kB; **NSCLC** = non-small cell lung cancer; **PD-L1** = programmed death-ligand 1; **PI3K** = phosphoinositide 3-kinase; **PFS** = progression-free survival; **PS** = performance status; **RAF** = rapidly accelerated fibrosarcoma; **RAL** = Ras-like protein; **SOC** = standard of care; **STK11** = serine/threonine kinase 11; **TMB** = tumor mutational burden; **Treg** = regulatory T cell.

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