# Supplementary Table 1

| KRAS mutation | Drug | Drug status | NCT | Clinical trial | Link | Intervention | Ph |
|---|---|---|---|---|---|---|---|
| G12C | AMG 510 | Approved | NCT04625647 | Testing the Use of Targeted Treatment (AMG 510) for KRAS G12C Mutated Advanced Non-squamous Non-small Cell Lung Cancer (A Lung-MAP Treatment Trial) | https://clinicaltrials.gov/ct2/show/NCT04625647 | Sotorasib | 2 |
| | | | NCT04303780 | Study to Compare AMG 510 "Proposed INN Sotorasib" With Docetaxel in Non Small Cell Lung Cancer (NSCLC) (CodeBreak 200). | https://clinicaltrials.gov/ct2/show/NCT04303780 | Docetaxel | 3 |
| | | | NCT04667234 | Expanded Access of AMG 510 (Sotorasib) | https://www.clinicaltrials.gov/ct2/show/NCT04667234 | | |
| | MRTX849 | Investigational | NCT04685135 | Phase 3 Study of MRTX849 vs Docetaxel in Patients With Advanced Non-Small Cell Lung Cancer With KRAS G12C Mutation (KRYSTAL-12) | https://clinicaltrials.gov/ct2/show/NCT04685135 | Docetaxel | 3 |
| | | | NCT04613596 | Phase 2 Trial of MRTX849 Plus Pembrolizumab for NSCLC With KRAS G12C Mutation KRYSTAL-7 | https://clinicaltrials.gov/ct2/show/NCT04613596 | Pembrolizumab | 2 |
| | | | NCT04330664 | Phase 1/2 Study in Patients With Cancer Having a KRAS G12C Mutation KRYSTAL 2 | https://clinicaltrials.gov/ct2/show/NCT04330664 | TNO155 | 2 |
| | JNJ-74699157 | Investigational | NCT04006301 | First-in-Human Study of JNJ-74699157 in Participants With Tumors Harboring the KRAS G12C Mutation | https://clinicaltrials.gov/ct2/show/NCT04006301 | | 1 |
| | LY3499446 | Investigational | NCT04165031 | A Study of LY3499446 in Participants With Advanced Solid Tumors With KRAS G12C Mutation | https://clinicaltrials.gov/ct2/show/NCT04165031 | Abemaciclib Cetuximab Erlotinib Docetaxel | 2 |
| | GDC-6036 | Investigational | NCT04449874 | A Study to Evaluate the Safety. Pharmacokinetics. and Activity of GDC-6036 Alone or in Combination in Participants With Advanced or Metastatic Solid Tumors With a KRAS G12C Mutation | https://clinicaltrials.gov/ct2/show/NCT04449874 | Atezolizumab Cetuximab Bevacizumab Erlotinib | 1 |
| | JDQ443 | Investigational | NCT04699188 | Study of JDQ443 in Patients With Advanced Solid Tumors Harboring the KRAS G12C Mutation | https://clinicaltrials.gov/ct2/show/NCT04699188 | TNO155 Spartalizumab | 2 |
| | Cisplatin-Pemetrexed vs Carboplatin-Paclitaxel-Bevacizumab | Approved | NCT02743923 | Cisplatin-Pemetrexed Compared With Carboplatin-Paclitaxel-Bevacizumab in KRAS Mutated Non-small Cell Lung Cancer | https://clinicaltrials.gov/ct2/show/NCT02743923 | Carboplatin Paclitaxel Bevacizumab Pemetrexed Cisplatin | 3 |
| | V941 | Investigational | NCT03948763 | A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001) | https://clinicaltrials.gov/ct2/show/NCT03948763 | Pembrolizumab | 1 |
| G12D | Bortezomib | Approved | NCT01833143 | Bortezomib in KRAS-Mutant Non-Small Cell Lung Cancer in Never Smokers or Those With KRAS G12D | https://clinicaltrials.gov/ct2/show/NCT01833143 | Acyclovir | 2 |
| | ELI-002 | Investigational | NCT04853017 | A Study of ELI-002 in Subjects With KRAS Mutated Pancreatic Ductal Adenocarcinoma (PDAC) and Other Solid Tumor (AMPLIFY-201) | https://clinicaltrials.gov/ct2/show/NCT04853017 | | 2 |
| | V941 | Investigational | NCT03948763 | A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001) | https://clinicaltrials.gov/ct2/show/NCT03948763 | Pembrolizumab | 1 |
| | BCA101 | Investigational | NCT04429542 | Study of Safety and Tolerability of BCA101 Alone and in Combination With Pembrolizumab in Patients With EGFR-driven Advanced Solid Tumors | https://clinicaltrials.gov/ct2/show/NCT04429542 | Pembrolizumab | 1 |
| G12V | VS-6766 v. VS-6766 + Defactinib | Investigational | NCT04620330 | A Study of VS-6766 v. VS-6766 + Defactinib in Recurrent G12V or Other KRAS-Mutant Non-Small Cell Lung Cancer | https://www.clinicaltrials.gov/ct2/show/NCT04620330 | Defactinib | 2 |
| | Cisplatin-Pemetrexed vs Carboplatin-Paclitaxel-Bevacizumab | Approved | NCT02743923 | Cisplatin-Pemetrexed Compared With Carboplatin-Paclitaxel-Bevacizumab in KRAS Mutated Non-small Cell Lung Cancer | https://clinicaltrials.gov/ct2/show/NCT02743923 | Carboplatin Paclitaxel Bevacizumab Pemetrexed cisplatin | 3 |
| | V941 | Investigational | NCT03948763 | A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001) | https://clinicaltrials.gov/ct2/show/NCT03948763 | Pembrolizumab | 1 |
| G13D | BCA101 | Investigational | NCT04429542 | Study of Safety and Tolerability of BCA101 Alone and in Combination With Pembrolizumab in Patients With EGFR-driven Advanced Solid Tumors | https://clinicaltrials.gov/ct2/show/NCT04429542 | Pembrolizumab | 1 |
| | V941 | Investigational | NCT03948763 | A Study of mRNA-5671/V941 as Monotherapy and in Combination With Pembrolizumab (V941-001) | https://clinicaltrials.gov/ct2/show/NCT03948763 | Pembrolizumab | 1 |
| G12R | ELI-002 | Investigational | NCT04853017 | A Study of ELI-002 in Subjects With KRAS Mutated Pancreatic Ductal Adenocarcinoma (PDAC) and Other Solid Tumor (AMPLIFY-201) | https://clinicaltrials.gov/ct2/show/NCT04853017 | | 2 |

# Supplementary Table 2

## Downregulated Genes

- ❑ *VAV3*

  Exchange factor for GTP-binding proteins RhoA. RhoG and. to a lesser extent. Rac1. Binds physically to the nucleotide-free states of those GTPases. Plays an important role in angiogenesis. Its recruitment by phosphorylated EPHA2 is critical for EFNA1-induced RAC1 GTPase activation and vascular endothelial cell migration and assembly.

- ❑ *TFRC*

  Cellular uptake of iron occurs via receptor-mediated endocytosis of ligand-occupied transferrin receptor into specialized endosomes. Endosomal acidification leads to iron release. The apotransferrin-receptor complex is then recycled to the cell surface with a return to neutral pH and the concomitant loss of affinity of apotransferrin for its receptor. Positively regulates T and B cell proliferation through iron uptake. Acts as a lipid sensor that regulates mitochondrial fusion by regulating activation of the JNK pathway

- ❑ *TIAM1*

  This gene encodes a RAC1-specific guanine nucleotide exchange factor (GEF). GEFs mediate the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP). The binding of GTP induces a conformational change in RAC1 that allows downstream effectors to bind and transduce a signal. This gene thus regulates RAC1 signaling pathways that affect cell shape. migration. adhesion. growth. survival. and polarity. as well as influencing actin cytoskeletal formation. endocytosis. and membrane trafficking. This gene thus plays an important role in cell invasion. metastasis. and carcinogenesis. In addition to RAC1. the encoded protein activates additional Rho-like GTPases such as CDC42. RAC2. RAC3 and RHOA.

- ❑ *CDK6*

  The protein encoded by this gene is a member of the CMGC family of serine/threonine protein kinases. This kinase is a catalytic subunit of the protein kinase complex that is important for cell cycle G1 phase progression and G1/S transition. The activity of this kinase first appears in mid-G1 phase. which is controlled by the regulatory subunits including D-type cyclins and members of INK4 family of CDK inhibitors. This kinase. as well as CDK4. has been shown to phosphorylate. and thus regulate the activity of. tumor suppressor protein Rb

- ❑ *CD24*

  This gene encodes a sialoglycoprotein that is expressed on mature granulocytes and B cells and modulates growth and differentiation signals to these cells. The precursor protein is cleaved to a short 32 amino acid mature peptide which is anchored via a glycosyl phosphatidylinositol (GPI) link to the cell surface.

- ❑ *HDAC9*

  Responsible for the deacetylation of lysine residues on the N-terminal part of the core histones (H2A. H2B. H3 and H4). Histone deacetylation gives a tag for epigenetic repression and plays an important role in transcriptional regulation. cell cycle progression and developmental events. Isoform 3 lacks active site residues and therefore is catalytically inactive. Represses MEF2-dependent transcription by recruiting HDAC1 and/or HDAC3.

- ❑ *VTCN1*

  Negatively regulates T-cell-mediated immune response by inhibiting T-cell activation. proliferation. cytokine production and development of cytotoxicity. When expressed on the cell surface of tumor macrophages. plays an important role. together with regulatory T-cells (Treg). in the suppression of tumor-associated antigen-specific T-cell immunity. Involved in promoting epithelial cell transformation.

## Upregulated Genes

- ❑ *IRS2*

  Encodes the insulin receptor substrate 2. a cytoplasmic signaling molecule that mediates effects of insulin. insulin-like growth factor 1. and other cytokines by acting as a molecular adaptor between diverse receptor tyrosine kinases and downstream effectors. The product of this gene is phosphorylated by the insulin receptor tyrosine kinase upon receptor stimulation. as well as by an interleukin 4 receptor-associated kinase in response to IL4 treatment

- ❑ *SMOC1*

  Plays essential roles in both eye and limb development. Probable regulator of osteoblast differentiation.

- ❑ *HOPX*

  Atypical homeodomain protein which does not bind DNA and is required to modulate cardiac growth and development. Acts via its interaction with SRF. thereby modulating the expression of SRF-dependent cardiac-specific genes and cardiac development. Prevents SRF-dependent transcription either by inhibiting SRF binding to DNA or by recruiting histone deacetylase (HDAC) proteins that prevent transcription by SRF. May act as a tumor suppressor. Acts as a co-chaperone for HSPA1A and HSPA1B chaperone proteins and assists in chaperone-mediated protein refolding

- ❑ *KIT*

  This gene was initially identified as a homolog of the feline sarcoma viral oncogene v-kit and is often referred to as proto-oncogene c-Kit. The canonical form of this glycosylated transmembrane protein has an N-terminal extracellular region with five immunoglobulin-like domains. a transmembrane region. and an intracellular tyrosine kinase domain at the C-terminus. Upon activation by its cytokine ligand. stem cell factor (SCF). this protein phosphorylates multiple intracellular proteins that play a role in the proliferation. differentiation. migration and apoptosis of many cell types and thereby plays an important role in hematopoiesis. stem cell maintenance. gametogenesis. melanogenesis. and in mast cell development. migration and function.

- ❑ *PDE4D*

  The encoded protein has 3'.5'-cyclic-AMP phosphodiesterase activity and degrades cAMP. which acts as a signal transduction molecule in multiple cell types.

- ❑ *CRLF1*

  In complex with CLCF1. forms a heterodimeric neurotropic cytokine that plays a crucial role during neuronal development (Probable). May also play a regulatory role in the immune system.

# Supplementary Table 3

| SURFACEOME PROTEINS | | | | | |
|---|---|---|---|---|---|
| Gene | Mean expression in *K-RAS* mutant tumours (n=57) | Mean expression in *K-RAS* wildtype tumours (n=451) | FC | Direction | p-value |
| *TSPAN11* | 1812 | 763.14 | 2.37 | upregulated | 0.00041 |
| *CLDN10* | 1185.4 | 508.48 | 2.33 | upregulated | 9.75E-08 |
| *SLC26A9* | 3021.7 | 1446.85 | 2.09 | upregulated | 0.00984 |
| *SLC7A2* | 5828.09 | 3016.17 | 1.93 | upregulated | 0.00845 |
| *TREM1* | 2937.05 | 1608.93 | 1.83 | upregulated | 0.00899 |
| *SLC46A2* | 258.33 | 153.47 | 1.68 | upregulated | 0.000296 |
| *PCDHB11* | 229.33 | 136.59 | 1.68 | upregulated | 0.00107 |
| *CHL1* | 1565.28 | 942.56 | 1.66 | upregulated | 0.000161 |
| *SCN9A* | 549.39 | 340.24 | 1.61 | upregulated | 0.00507 |
| *PARM1* | 8012.47 | 5010.32 | 1.6 | upregulated | 0.000791 |
| *TMPRSS6* | 560.28 | 361.42 | 1.55 | upregulated | 0.0066 |
| *KIT* | 2971.02 | 1956.93 | 1.52 | upregulated | 0.00262 |

# Supplementary Table 4

| Gene | Kaplan-Meier Plotter Lung Adenocarcinoma | | | | | |
|---|---|---|---|---|---|---|
| | FP (N=443) | | | OS (N=672) | | |
| | Hazard Ratio | p-value | FDR | Hazard Ratio | p-value | FDR |
| *TSPAN11* | 0.58(0.38-0.87) | 0.008 | 50% | 0.73(0.57-0.93) | 0.012 | 50% |
| *CLDN10* | 1.56(1.13-2.16) | 0.0069 | 50% | 1.7(1.3-2.23) | 7.9e-05 | 3% |
| *SLC26A9* | 0.51(0.37 – 0.71) | 3.8e-05 | 1% | 0.56(0.42 – 0.74) | 5.3e-05 | 2% |
| *SLC7A2* | 0.42(0.3-0.58) | 5.8e-08 | 1% | 0.48(0.38-0.61) | 1.9e-09 | 1% |
| *TREM1* | 1.28(0.94-1.75) | 0.11 | 100% | 1.33(1.06-1.68) | 0.014 | 50% |
| *SLC46A2* | 0.58(0.38 – 0.87) | 0.0083 | 50% | 0.65(0.5 – 0.85) | 0.0016 | 50% |
| *PCDHB11* | 1.36(0.99-1.86) | 0.053 | 100% | 0.74(0.58-0.93) | 0.011 | 50% |
| *CHL1* | 0.56(0.41-0.77) | 0.00026 | 5% | 0.55(0.42-0.72) | 1.4e-05 | 1% |
| *SCN9A* | 0.65(0.45-0.92) | 0.015 | 50% | 0.69(0.53-0.9) | 0.0064 | 50% |
| *PARM1* | 0.4(0.28 – 0.55) | 1.8e-08 | 1% | 0.59(0.46-0.75) | 1.3e-05 | 1% |
| *TMPRSS6* | 1.56(1.13-2.16) | 0.0069 | 50% | 1.49(1.18-1.88) | 0.00073 | 20% |
| *KIT* | 0.45(0.33-0.62) | 3.6e-07 | 1% | 0.42(0.33-0.53) | 2.5e-13 | 1% |
| *CLDN10+TMPRSS6* | 1.77(1.27-2.46) | 6E-04 | 10% | 1.75(1.33-2.29) | 4.2e-05 | 2% |