COMBINATION THERAPY AND RELATED METHODS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Serial No.: 63/483,399, filed February 6, 2023, the entire contents of which is incorporated herein by reference.

1. FIELD

[0002] This disclosure relates to methods comprising the use of KRAS (*e.g.,* hKRAS) inhibitors in combination with an agent(s) that specifically binds to EGFR (*e.g.,* hEGFR) and TGFβ (*e.g.,* hTGFβ). The disclosure further relates to compositions and kits comprising the same.

2. BACKGROUND

[0003] KRAS is a small GTPase that regulates diverse cellular processes including *e.g.,* cell proliferation, survival, differentiation, and migration. KRAS cycles through a GTP-bound active state and a GDP-bound inactive state, with the cycling largely regulated by guanine nucleotide exchange factors. Active KRAS mediates its functional effects through downstream signaling pathways, *e.g.,* through the MAPK and PI3K kinases. KRAS variants comprising one or more amino acid modification (*e.g.,* amino acid substitutions (*e.g.,* single amino acid substitutions)) that impair hydrolyzation of GTP to GDP, hence permanently locking KRAS in an active state, have been reported in various cancers, including, *e.g.,* various solid tumors (*e.g.,* pancreatic, lung, colon, rectal, and colorectal cancers). These KRAS variant cancers are typically associated with increased tumorigenesis, aggressive disease, and poor prognosis.

3. SUMMARY

[0004] Described herein are, *inter alia*, methods of utilizing KRAS (*e.g.,* hKRAS) inhibitors in combination with an agent(s) that specifically binds to EGFR (*e.g.,* hEGFR) and TGFβ (*e.g.,* hTGFβ), including *e.g.,* methods of treating cancer, methods of inhibiting the KRAS (*e.g.,* hKRAS) pathway and the TGFβ (*e.g.,* hTGFβ) pathway, methods of restoring sensitivity of a cancer to a KRAS (*e.g.,* hKRAS) inhibitor, and methods of suppressing or preventing resistance of a cancer to a KRAS (*e.g.,* hKRAS) inhibitor, along with *e.g.,* diagnostic methods, combination regimens, combination compositions, pharmaceutical compositions, and kits.

[0004a] In one aspect, described herein is a use of (a) a kirsten rat sarcoma virus homolog

(KRAS) (e.g., human KRAS (hKRAS)) inhibitor in the manufacture of a first medicament; and use of (b) a fusion protein comprising: (i) a first moiety that specifically binds epidermal growth factor receptor (EGFR) (e.g., human EGFR (hEGFR)) operably connected to (ii) a second moiety that specifically binds transforming growth factor β (TGFβ) (e.g., human TGFβ (hTGFβ)), in the manufacture of a second medicament, wherein the first and second medicaments are to be used in a combination therapy to treat cancer in a subject.

[0005] In one example, described herein are methods of treating cancer in a subject in need thereof, the method comprising: administering to the subject (a) a kirsten rat sarcoma virus

homolog (KRAS) (*e.g.,* human KRAS (hKRAS)) inhibitor; in combination with (b) a fusion protein comprising: (i) a first moiety that specifically binds epidermal growth factor receptor (EGFR) (*e.g.,* human EGFR (hEGFR)) operably connected to (ii) a second moiety that specifically binds transforming growth factor β (TGFβ) (*e.g.,* human TGFβ (hTGFβ)), to thereby treat cancer in the subject in need thereof.

[0006] In one example, described herein are methods of treating a KRAS (*e.g.,* hKRAS) variant cancer in a subject in need thereof, the method comprising: (a) receiving test results showing that the KRAS (*e.g.,* hKRAS) variant cancer is resistant to a KRAS inhibitor; in combination with (b) administering to the subject the KRAS (*e.g.,* hKRAS) inhibitor; and a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby treat the KRAS (*e.g.,* hKRAS) variant cancer in the subject.

[0007] In one example, described herein are methods of treating a KRAS (*e.g.,* hKRAS) variant cancer in a subject in need thereof, the method comprising: (a) administering to the subject a KRAS (*e.g.,* hKRAS) inhibitor; (b) receiving testing results showing that the KRAS (*e.g.,* hKRAS) variant cancer has developed resistance to the KRAS (*e.g.,* hKRAS) inhibitor; and (c) administering to the subject the KRAS (*e.g.,* hKRAS) inhibitor; in combination with a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby treat the KRAS (*e.g.,* hKRAS) variant cancer in the subject.

[0008] In one example, described herein are methods of treating a KRAS (*e.g.,* hKRAS) variant cancer in a subject in need thereof, the method comprising: (a) determining that the KRAS (*e.g.,* hKRAS) variant cancer is resistant to a KRAS (*e.g.,* hKRAS) inhibitor; and (b) administering to the subject a KRAS (*e.g.,* hKRAS) inhibitor; in combination with a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby treat the KRAS (*e.g.,* hKRAS) variant cancer in the subject.

[0009] In one example, described herein are methods of delivering a KRAS (*e.g.,* hKRAS) inhibitor and a fusion protein to a subject in need thereof, the method comprising administering (a) a KRAS (*e.g.,* hKRAS) inhibitor; and (b) a fusion protein comprising: (i) a first moiety that specifically binds EGFR) (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby deliver the KRAS (*e.g.,* hKRAS) inhibitor and the fusion protein to the subject.

[0010] In one example, described herein are methods of inhibiting the KRAS (*e.g.,* hKRAS) pathway and the TGFβ (*e.g.,* hTGFβ) pathway in a subject in need thereof, the method comprising administering (a) a KRAS (*e.g.,* hKRAS) inhibitor; in combination with (b) a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby inhibit the KRAS (*e.g.,* hKRAS) pathway and the TGFβ (*e.g.,* hTGFβ) pathway in the subject.

[0011] In one example, described herein are methods of restoring sensitivity to a KRAS (*e.g.,* hKRAS) inhibitor in a subject in need thereof, the method comprising administering to the subject a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby restore sensitivity to a KRAS (*e.g.,* hKRAS) inhibitor in the subject.

[0012] In one example, described herein are methods of suppressing or preventing resistance to a KRAS (*e.g.,* hKRAS) inhibitor in a subject in need thereof, the method comprising administering to the subject (a) a KRAS (*e.g.,* hKRAS) inhibitor; in combination with (b) a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby suppress or prevent resistance to a KRAS (*e.g.,* hKRAS) inhibitor in the subject.

[0013] In one example, described herein are pharmaceutical compositions comprising (a) a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* a KRAS (*e.g.,* hKRAS) inhibitor described herein); and (b) a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ) (*e.g.,* a fusion protein described herein); and (c) a pharmaceutically acceptable excipient.

[0014] In one example, described herein are kits comprising a (ii) (a) a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* a KRAS (*e.g.,* hKRAS) inhibitor described herein), or a pharmaceutical composition thereof; and (b) a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ) (*e.g.,* a fusion protein described herein), or a pharmaceutical composition thereof; (ii) a pharmaceutical composition described herein; (iii) a combination regimen described herein; or (iv) a combination composition described herein.

[0015] For the sake of clarity, the following exemplary embodiments are applicable to each of the foregoing examples as if recited individually after each example.

[0016] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor and the fusion protein are administered in an amount and for a time sufficient to treat or prevent the cancer in the subject.

[0017] In some examples, the cancer is a KRAS (*e.g.,* hKRAS) variant cancer. In some examples, the cancer has been determined to contain a KRAS (*e.g.,* hKRAS) variant. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a KRAS (*e.g.,* hKRAS) activating amino acid modification (*e.g.,* substitution). In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification (*e.g.,* substitution) at amino acid position G12, G13, or Q61, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification (*e.g.,* substitution) at amino acid position G12 or G13, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G12S, G13D, or Q61H, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G12S, or G13D, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one of the following amino acid substitutions G12C, G12V, G12R, G12A, G12S, or G12D, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a G12C amino acid substitution, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0018] In some examples, the cancer is resistant to the KRAS (*e.g.,* hKRAS) inhibitor. In some examples, the cancer has been determined to be resistant to the KRAS (*e.g.,* hKRAS) inhibitor.

[0019] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has previously been administered to the subject. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has previously been administered to the subject in the absence of the fusion protein.

[0020] In some examples, the cancer cells overexpress EGFR (*e.g.,* hEGFR) relative to non-cancer cells. In some examples, the cancer cells have been determined to overexpress EGFR (*e.g.,* hEGFR) relative to non-cancer cells. In some examples, the cancer cells express an EGFR (*e.g.,* hEGFR) variant. In some examples, the cancer cells have been determined to express an EGFR (*e.g.,* hEGFR) variant. In some examples, the cancer cells overexpress hTGFβ (*e.g.,* hTGFβ) relative to non-cancer cells. In some examples, the cancer cells have been determined to overexpress TGFβ (*e.g.,* hTGFβ) relative to non-cancer cells.

[0021] In some examples, the cancer is local, locally advanced, or metastatic. In some examples, the cancer is a carcinoma (*e.g.,* adenocarcinoma, squamous cell carcinoma). In

some examples, the cancer is a lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma), colorectal cancer (*e.g.,* colorectal adenocarcinoma), pancreatic cancer (*e.g.,* pancreatic ductal adenocarcinoma), breast cancer (*e.g.,* invasive ductal carcinoma), stomach cancer (*e.g.,* stomach adenocarcinoma), endometrial cancer (*e.g.,* undifferentiated endometrial carcinoma), uterine cancer (*e.g.,* uterine endometrial carcinoma), testicular cancer (*e.g.,* testicular germ cell cancer), cervical cancer (*e.g.,* cervical squamous carcinoma), bile duct cancer (*e.g.,* cholangiocarcinoma), a myelodysplastic cancer, or esophageal cancer (*e.g.,* esophageal adenocarcinoma, gastroesophageal junction cancer). In some examples, the cancer is a lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma), colorectal cancer (*e.g.,* colorectal adenocarcinoma), or a pancreatic cancer (*e.g.,* pancreatic ductal adenocarcinoma). In some examples, the cancer is a non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma, colorectal adenocarcinoma, or pancreatic ductal adenocarcinoma.

[0022] In some examples, the subject has been previously administered a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* the KRAS (*e.g.,* hKRAS) inhibitor). In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has not been previously administered to the subject. In some examples, the subject has been previously administered a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* the KRAS (*e.g.,* hKRAS) inhibitor) and the cancer in the subject developed resistance to the KRAS (*e.g.,* hKRAS) inhibitor.

[0023] In some examples, the cancer in the subject is resistant to a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* the KRAS (*e.g.,* hKRAS) inhibitor).

[0024] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor is capable of selectively inhibiting a KRAS (*e.g.,* hKRAS) variant. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a KRAS (*e.g.,* hKRAS) activating amino acid modification. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification at amino acid position G12, G13, or Q61, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification at amino acid position G12 or G13, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G13D, or Q61H, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, or G13D, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS)

variant comprises any one of the following amino acid substitutions G12C, G12V, G12R, G12A, or G12D, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a G12C amino acid substitution, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0025] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises or consists of a small molecule, protein (*e.g.,* an antibody or functional fragment or variant thereof), nucleic acid, carbohydrate, a lipid, a metal, or a toxin. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises or consists of a small molecule. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises a KRAS (*e.g.,* hKRAS) inhibitor in Table 2. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises sotorasib (AMG-510).

[0026] In some examples, the first moiety comprises an antibody, or functional fragment or functional variant thereof. In some examples, the first moiety comprises a full-length antibody, a single chain variable fragment (scFv), a Fab, or a single domain antibody (sdAb). In some examples, the first moiety comprises a full-length antibody.

[0027] In some examples, the first moiety comprises a variable heavy chain (VH) region that comprises three complementarity determining regions: VH CDR1, VH CDR2, and VH CDR3; and a variable light chain (VL) region that comprises three complementarity determining regions: VL CDR1, VL CDR2, and VL CDR3.

[0028] In some examples, (a) the amino acid sequence of VH CDR1 comprises the amino acid sequence SEQ ID NO: 39, or the amino acid sequence of SEQ ID NO: 39 comprising 1, 2, or 3 amino acid modifications; (b) the amino acid sequence of VH CDR2 comprises the amino acid sequence SEQ ID NO: 40, or the amino acid sequence of SEQ ID NO: 40 comprising 1, 2, or 3 amino acid modifications; (c) the amino acid sequence of VH CDR3 comprises the amino acid sequence SEQ ID NO: 41, or the amino acid sequence of SEQ ID NO: 41 comprising 1, 2, or 3 amino acid modifications; and (d) the amino acid sequence of VL CDR1 comprises the amino acid sequence SEQ ID NO: 42, or the amino acid sequence of SEQ ID NO: 42 comprising 1, 2, or 3 amino acid modifications; (e) the amino acid sequence of VL CDR2 comprises the amino acid sequence SEQ ID NO: 43, or the amino acid sequence of SEQ ID NO: 43 comprising 1, 2, or 3 amino acid modifications; and (f)the amino acid sequence of VL CDR3 comprises the amino acid sequence SEQ ID NO: 44, or the amino acid sequence of SEQ ID NO: 44 comprising 1, 2, or 3 amino acid modifications.

[0029] In some examples, the VH region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45; and the VL region comprises an amino

acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46.

[0030] In some examples, the first moiety comprises a heavy chain (HC) and a light chain (LC), wherein the amino acid sequence of the HC is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 48; and the amino acid sequence of the LC is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49.

[0031] In some examples, the second moiety comprises an antibody, or functional fragment or functional variant thereof. In some examples, the second moiety comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')2, or a F(v).

[0032] In some examples, the second moiety comprises or consists of at least a portion of the extracellular domain (ECD) of a transforming growth factor-beta receptor (TGFβR) (*e.g.,* hTGFβR). In some examples, the second moiety comprises or consists of at least a portion of the ECD of transforming growth factor-beta receptor II (TGFβRII) (*e.g.,* hTGFβRII). In some examples, the second moiety comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII). In some examples, the amino acid sequence of the second moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73.

[0033] In some examples, the fusion protein comprises (iii) a third moiety that specifically binds TGFβ (*e.g.,* hTGFβ) and is operably connected to the first moiety.

[0034] In some examples, the third moiety comprises an antibody, or functional fragment or functional variant thereof. In some examples, the third moiety comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')2, or a F(v).

[0035] In some examples, the third moiety comprises or consists of at least a portion of the extracellular domain (ECD) of a TGFβR (*e.g.,* hTGFβR). In some examples, the third moiety comprises or consists of at least a portion of the ECD of TGFβRII (*e.g.,* hTGFβRII). In some examples, the third moiety comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII). In some examples, the amino acid sequence of the third moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid

sequence of SEQ ID NO: 72 or 73. In some examples, the amino acid sequence of the second moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73; and the amino acid sequence of the third moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73.

[0036] In some examples, the amino acid sequence of the second moiety is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the third moiety.

[0037] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first light chain.

[0038] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first heavy chain.

[0039] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first light chain and the N-terminus of the third moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the second light chain.

[0040] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first heavy chain and the N-terminus of the third moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the second heavy chain.

[0041] In some examples, the first moiety is directly operably connected to the second moiety. In some examples, the first moiety is indirectly operably connected to the second moiety. In some examples, the first moiety is indirectly operably connected to the second moiety through a first peptide linker. In some examples, the first peptide linker comprises or consists of glycine or glycine and serine amino acid residues. In some examples, the amino acid sequence of the first peptide linker comprises or consists of (a) the amino acid sequence of any one of SEQ ID NOS: 105-124; or (b) the amino acid sequence of any one of SEQ ID NOS: 105-124 comprising or consisting of 1, 2, or 3 amino acid modifications. In some examples, the amino acid sequence of the first peptide linker comprises or consists

of (a) the amino acid sequence of SEQ ID NO: 111; or (b) the amino acid sequence of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications.

[0042] In some examples, the first moiety is directly operably connected to the third moiety. In some examples, the first moiety is indirectly operably connected to the third moiety. In some examples, the first moiety is indirectly operably connected to the third moiety through a second peptide linker. In some examples, the second peptide linker comprises or consists of glycine or glycine and serine amino acid residues. In some examples, the amino acid sequence of the second peptide linker comprises or consists of (a) the amino acid sequence of any one of SEQ ID NO: 111; or (b) the amino acid sequence of any one of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications. In some examples, the amino acid sequence of the first peptide linker comprises or consists of (a) the amino acid sequence of SEQ ID NO: 111; or (b) the amino acid sequence of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications. In some examples, the amino acid sequence of the first peptide linker is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the second peptide linker.

[0043] In some examples, the amino acid sequence of the first peptide linker is 100% identical to the amino acid sequence of the second peptide linker.

[0044] In some examples, (a) the first moiety comprises or consists of a full-length antibody; (b) the second moiety comprises a comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII); (c) the third moiety comprises a comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII); (d) the second moiety is operably connected to the first moiety through a first peptide linker; and (e) the third moiety is operably connected to the first moiety through a second peptide linker.

[0045] In some examples, the N-terminus of the second moiety is operably connected to the C-terminus of the first light chain of the full-length antibody and the N-terminus of the third moiety is operably connected to the C-terminus of the second light chain of the full-length antibody.

[0046] In some examples, (a) (i) the amino acid sequence of VH CDR1 comprises the amino acid sequence SEQ ID NO: 39, or the amino acid sequence of SEQ ID NO: 39 comprising 1, 2, or 3 amino acid modifications, the amino acid sequence of VH CDR2 comprises the amino acid sequence SEQ ID NO: 40, or the amino acid sequence of SEQ ID NO: 40 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of VH CDR3 comprises the amino acid sequence SEQ ID NO: 41, or the amino acid sequence of SEQ ID

NO: 41 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of VL CDR1 comprises the amino acid sequence SEQ ID NO: 42, or the amino acid sequence of SEQ ID NO: 42 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of VL CDR2 comprises the amino acid sequence SEQ ID NO: 43, or the amino acid sequence of SEQ ID NO: 43 comprising 1, 2, or 3 amino acid modifications; and the amino acid sequence of VL CDR3 comprises the amino acid sequence SEQ ID NO: 44, or the amino acid sequence of SEQ ID NO: 44 comprising 1, 2, or 3 amino acid modifications; (ii) the VH region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45; and the VL region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45; and/or (iii) the amino acid sequence of the heavy chain of the full-length antibody is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 48; and wherein the amino acid sequence of the light chain of the full-length antibody is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49; (b) the amino acid sequence of the second moiety is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73; (c) the amino acid sequence of the third moiety is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73; (d) the amino acid sequence of the first peptide linker is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 111; and (e) the amino acid sequence of the second peptide linker is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 111.

[0047] In some examples, the fusion protein comprises: (a) a first polypeptide, wherein the amino acid sequence of the first polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 125; (b) a second polypeptide, wherein the amino acid sequence of the second polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO:

125; (c) a third polypeptide, wherein the amino acid sequence of the third polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 126; and (d) a fourth polypeptide, wherein the amino acid sequence of the fourth polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 126.

[0048] In one example, described herein are methods of treating a KRAS (*e.g.,* hKRAS) variant cancer in a subject in need thereof, the method comprising: (a) receiving test results showing that the KRAS (*e.g.,* hKRAS) variant cancer is resistant to a KRAS inhibitor; in combination with (b) administering to the subject the KRAS (*e.g.,* hKRAS) inhibitor; and a fusion protein comprising: (i) a first moiety that specifically binds EGFR (*e.g.,* hEGFR) operably connected to (ii) a second moiety that specifically binds TGFβ (*e.g.,* hTGFβ), to thereby treat the KRAS (*e.g.,* hKRAS) variant cancer in the subject.

[0049] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has been previously administered to the subject.

[0050] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor and the fusion protein are administered in an amount and for a time sufficient to treat the KRAS (*e.g.,* hKRAS) variant cancer in the subject.

[0051] In some examples, the cancer is a KRAS (*e.g.,* hKRAS) variant cancer.

[0052] In some examples, the cancer has been determined to contain a KRAS (*e.g.,* hKRAS) variant.

[0053] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a KRAS (*e.g.,* hKRAS) activating amino acid modification (*e.g.,* substitution).

[0054] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification (*e.g.,* substitution) at amino acid position G12, G13, or Q61, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0055] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification (*e.g.,* substitution) at amino acid position G12 or G13, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0056] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G12S, G13D, or Q61H, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0057] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G12S, or G13D, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0058] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one of the following amino acid substitutions G12C, G12V, G12R, G12A, G12S, or G12D, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0059] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a G12C amino acid substitution, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0060] In some examples, the cancer is resistant to the KRAS (*e.g.,* hKRAS) inhibitor. In some examples, the cancer has been determined to be resistant to the KRAS (*e.g.,* hKRAS) inhibitor.

[0061] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has previously been administered to the subject. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has previously been administered to the subject in the absence of the fusion protein.

[0062] In some examples, the cancer cells overexpress EGFR (*e.g.,* hEGFR) relative to non-cancer cells. In some examples, the cancer cells have been determined to overexpress EGFR (*e.g.,* hEGFR) relative to non-cancer cells. In some examples, the cancer cells express an EGFR (*e.g.,* hEGFR) variant. In some examples, the cancer cells have been determined to express an EGFR (*e.g.,* hEGFR) variant. In some examples, the cancer cells overexpress hTGFβ (*e.g.,* hTGFβ) relative to non-cancer cells. In some examples, the cancer cells have been determined to overexpress TGFβ (*e.g.,* hTGFβ) relative to non-cancer cells.

[0063] In some examples, the cancer is local, locally advanced, or metastatic.

[0064] In some examples, the cancer is a carcinoma (*e.g.,* adenocarcinoma, squamous cell carcinoma).

[0065] In some examples, the cancer is a lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma), colorectal cancer (*e.g.,* colorectal adenocarcinoma), pancreatic cancer (*e.g.,* pancreatic ductal adenocarcinoma), breast cancer (*e.g.,* invasive ductal carcinoma), stomach cancer (*e.g.,* stomach adenocarcinoma), endometrial cancer (*e.g.,* undifferentiated endometrial carcinoma), uterine cancer (*e.g.,* uterine endometrial carcinoma), testicular cancer (*e.g.,* testicular germ cell cancer), cervical cancer (*e.g.,* cervical squamous carcinoma), bile duct cancer (*e.g.,* cholangiocarcinoma), a myelodysplastic cancer, or esophageal cancer (*e.g.,* esophageal adenocarcinoma, gastroesophageal junction cancer).

[0066] In some examples, the cancer is a lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma), colorectal cancer (*e.g.,* colorectal adenocarcinoma), or a pancreatic cancer (*e.g.,* pancreatic ductal adenocarcinoma).

[0067] In some examples, the cancer is a non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma, colorectal adenocarcinoma, or pancreatic ductal adenocarcinoma.

[0068] In some examples, the subject has been previously administered a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* the KRAS (*e.g.,* hKRAS) inhibitor).

[0069] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor has not been previously administered to the subject. In some examples, the subject has been previously administered a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* the KRAS (*e.g.,* hKRAS) inhibitor) and the cancer in the subject developed resistance to the KRAS (*e.g.,* hKRAS) inhibitor.

[0070] In some examples, the cancer in the subject is resistant to a KRAS (*e.g.,* hKRAS) inhibitor (*e.g.,* the KRAS (*e.g.,* hKRAS) inhibitor).

[0071] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor is capable of selectively inhibiting a KRAS (*e.g.,* hKRAS) variant.

[0072] In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a KRAS (*e.g.,* hKRAS) activating amino acid modification. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification at amino acid position G12, G13, or Q61, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification at amino acid position G12 or G13, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G13D, or Q61H, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, or G13D, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises any one of the following amino acid substitutions G12C, G12V, G12R, G12A, or G12D, numbering relative to the amino acid sequence of SEQ ID NO: 3. In some examples, the KRAS (*e.g.,* hKRAS) variant comprises a G12C amino acid substitution, numbering relative to the amino acid sequence of SEQ ID NO: 3.

[0073] In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises or consists of a small molecule, protein (*e.g.,* an antibody or functional fragment or variant thereof), nucleic

acid, carbohydrate, a lipid, a metal, or a toxin. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises or consists of a small molecule. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises a KRAS (*e.g.,* hKRAS) inhibitor in Table 2. In some examples, the KRAS (*e.g.,* hKRAS) inhibitor comprises sotorasib (AMG-510).

[0074] In some examples, the first moiety comprises an antibody, or functional fragment or functional variant thereof. In some examples, the first moiety comprises a full-length antibody, a single chain variable fragment (scFv), a Fab, or a single domain antibody (sdAb). In some examples, the first moiety comprises a full-length antibody.

[0075] In some examples, the first moiety comprises a variable heavy chain (VH) region that comprises three complementarity determining regions: VH CDR1, VH CDR2, and VH CDR3; and a variable light chain (VL) region that comprises three complementarity determining regions: VL CDR1, VL CDR2, and VL CDR3.

[0076] In some examples, (a) the amino acid sequence of VH CDR1 comprises the amino acid sequence SEQ ID NO: 39, or the amino acid sequence of SEQ ID NO: 39 comprising 1, 2, or 3 amino acid modifications; (b) the amino acid sequence of VH CDR2 comprises the amino acid sequence SEQ ID NO: 40, or the amino acid sequence of SEQ ID NO: 40 comprising 1, 2, or 3 amino acid modifications; (c) the amino acid sequence of VH CDR3 comprises the amino acid sequence SEQ ID NO: 41, or the amino acid sequence of SEQ ID NO: 41 comprising 1, 2, or 3 amino acid modifications; and (d) the amino acid sequence of VL CDR1 comprises the amino acid sequence SEQ ID NO: 42, or the amino acid sequence of SEQ ID NO: 42 comprising 1, 2, or 3 amino acid modifications; (e) the amino acid sequence of VL CDR2 comprises the amino acid sequence SEQ ID NO: 43, or the amino acid sequence of SEQ ID NO: 43 comprising 1, 2, or 3 amino acid modifications; and (f)the amino acid sequence of VL CDR3 comprises the amino acid sequence SEQ ID NO: 44, or the amino acid sequence of SEQ ID NO: 44 comprising 1, 2, or 3 amino acid modifications.

[0077] In some examples, the VH region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45; and the VL region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46.

[0078] In some examples, the first moiety comprises a heavy chain (HC) and a light chain (LC), wherein the amino acid sequence of the HC is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 48; and the amino acid sequence of the LC is at least 85%, 86%,

87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49.

[0079] In some examples, the second moiety comprises an antibody, or functional fragment or functional variant thereof.

[0080] In some examples, the second moiety comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')2, or a F(v).

[0081] In some examples, the second moiety comprises or consists of at least a portion of the extracellular domain (ECD) of a transforming growth factor-beta receptor (TGFβR) (*e.g.,* hTGFβR). In some examples, the second moiety comprises or consists of at least a portion of the ECD of transforming growth factor-beta receptor II (TGFβRII) (*e.g.,* hTGFβRII). In some examples, the second moiety comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII). In some examples, the amino acid sequence of the second moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73.

[0082] In some examples, the fusion protein comprises (iii) a third moiety that specifically binds TGFβ (*e.g.,* hTGFβ) and is operably connected to the first moiety.

[0083] In some examples, the third moiety comprises an antibody, or functional fragment or functional variant thereof.

[0084] In some examples, the third moiety comprises a full-length antibody, a single chain variable fragment (scFv), a scFv2, a scFv-Fc, a Fab, a Fab', a F(ab')2, or a F(v).

[0085] In some examples, the third moiety comprises or consists of at least a portion of the extracellular domain (ECD) of a TGFβR (*e.g.,* hTGFβR). In some examples, the third moiety comprises or consists of at least a portion of the ECD of TGFβRII (*e.g.,* hTGFβRII). In some examples, the third moiety comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII). In some examples, the amino acid sequence of the third moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73. In some examples, the amino acid sequence of the second moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73; and the amino acid sequence of the third moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73.

[0086] In some examples, the amino acid sequence of the second moiety is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the third moiety.

[0087] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first light chain.

[0088] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first heavy chain.

[0089] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first light chain and the N-terminus of the third moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the second light chain.

[0090] In some examples, the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the first heavy chain and the N-terminus of the third moiety is operably connected (*e.g.,* optionally via a linker) to the C-terminus of the second heavy chain.

[0091] In some examples, the first moiety is directly operably connected to the second moiety. In some examples, the first moiety is indirectly operably connected to the second moiety. In some examples, the first moiety is indirectly operably connected to the second moiety through a first peptide linker. In some examples, the first peptide linker comprises or consists of glycine or glycine and serine amino acid residues. In some examples, the amino acid sequence of the first peptide linker comprises or consists of (a) the amino acid sequence of any one of SEQ ID NOS: 105-124; or (b) the amino acid sequence of any one of SEQ ID NOS: 105-124 comprising or consisting of 1, 2, or 3 amino acid modifications. In some examples, the amino acid sequence of the first peptide linker comprises or consists of (a) the amino acid sequence of SEQ ID NO: 111; or (b) the amino acid sequence of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications.

[0092] In some examples, the first moiety is directly operably connected to the third moiety.

[0093] In some examples, the first moiety is indirectly operably connected to the third moiety. In some examples, the first moiety is indirectly operably connected to the third

moiety through a second peptide linker. In some examples, the second peptide linker comprises or consists of glycine or glycine and serine amino acid residues. In some examples, the amino acid sequence of the second peptide linker comprises or consists of (a) the amino acid sequence of any one of SEQ ID NO: 111; or (b) the amino acid sequence of any one of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications. In some examples, the amino acid sequence of the first peptide linker comprises or consists of (a) the amino acid sequence of SEQ ID NO: 111; or (b) the amino acid sequence of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications. In some examples, the amino acid sequence of the first peptide linker is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of the second peptide linker.

[0094] In some examples, the amino acid sequence of the first peptide linker is 100% identical to the amino acid sequence of the second peptide linker.

[0095] In some examples, (a) the first moiety comprises or consists of a full-length antibody; (b) the second moiety comprises a comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII); (c) the third moiety comprises a comprises or consists of the ECD of TGFβRII (*e.g.,* hTGFβRII); (d) the second moiety is operably connected to the first moiety through a first peptide linker; and (e) the third moiety is operably connected to the first moiety through a second peptide linker.

[0096] In some examples, the N-terminus of the second moiety is operably connected to the C-terminus of the first light chain of the full-length antibody and the N-terminus of the third moiety is operably connected to the C-terminus of the second light chain of the full-length antibody.

[0097] In some examples, (a) (i) the amino acid sequence of VH CDR1 comprises the amino acid sequence SEQ ID NO: 39, or the amino acid sequence of SEQ ID NO: 39 comprising 1, 2, or 3 amino acid modifications, the amino acid sequence of VH CDR2 comprises the amino acid sequence SEQ ID NO: 40, or the amino acid sequence of SEQ ID NO: 40 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of VH CDR3 comprises the amino acid sequence SEQ ID NO: 41, or the amino acid sequence of SEQ ID NO: 41 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of VL CDR1 comprises the amino acid sequence SEQ ID NO: 42, or the amino acid sequence of SEQ ID NO: 42 comprising 1, 2, or 3 amino acid modifications; the amino acid sequence of VL CDR2 comprises the amino acid sequence SEQ ID NO: 43, or the amino acid sequence of SEQ ID NO: 43 comprising 1, 2, or 3 amino acid modifications; and the amino acid sequence of VL

CDR3 comprises the amino acid sequence SEQ ID NO: 44, or the amino acid sequence of SEQ ID NO: 44 comprising 1, 2, or 3 amino acid modifications; (ii) the VH region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45; and the VL region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46; and/or (iii) the amino acid sequence of the heavy chain of the full-length antibody is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 48; and wherein the amino acid sequence of the light chain of the full-length antibody is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49; (b) the amino acid sequence of the second moiety is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72; (c) the amino acid sequence of the third moiety is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72; (d) the amino acid sequence of the first peptide linker is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 111; and (e) the amino acid sequence of the second peptide linker is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 111.

[0098] In some examples, the fusion protein comprises: (a) a first polypeptide, wherein the amino acid sequence of the first polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 125; (b) a second polypeptide, wherein the amino acid sequence of the second polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 125; (c) a third polypeptide, wherein the amino acid sequence of the third polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 126; and (d) a fourth polypeptide, wherein the amino acid sequence of the fourth polypeptide comprises or consists of an amino acid sequence at least 85%, 86%,

CLAIMS

What is claimed is:

1. Use of (a) a kirsten rat sarcoma virus homolog (KRAS) (*e.g.,* human KRAS (hKRAS)) inhibitor in the manufacture of a first medicament; and use of (b) a fusion protein comprising: (i) a first moiety that specifically binds epidermal growth factor receptor (EGFR) (*e.g.,* human EGFR (hEGFR)) operably connected to (ii) a second moiety that specifically binds transforming growth factor β (TGFβ) (*e.g.,* human TGFβ (hTGFβ)), in the manufacture of a second medicament, wherein the first and second medicaments are to be used in a combination therapy to treat cancer in a subject.

2. The use of claim 1, wherein the cancer is a KRAS (*e.g.,* hKRAS) variant cancer.

3. The use of claim 2, wherein the KRAS (*e.g.,* hKRAS) variant comprises a KRAS (*e.g.,* hKRAS) activating amino acid modification (*e.g.,* substitution).

4. The use of claim 2 or 3, wherein the KRAS (*e.g.,* hKRAS) variant comprises an amino acid modification (*e.g.,* substitution) at amino acid position G12, G13, or Q61, numbering relative to the amino acid sequence of SEQ ID NO: 3.

5. The use of any one of claims 2-4, wherein the KRAS (*e.g.,* hKRAS) variant comprises any one or more of the following amino acid substitutions G12C, G12V, G12R, G12D, G12A, G12S, G13D, or Q61H, numbering relative to the amino acid sequence of SEQ ID NO: 3.

6. The use of any one of the preceding claims, wherein the cancer is a lung cancer (*e.g.,* non-small cell lung cancer (NSCLC), lung adenocarcinoma, lung squamous carcinoma), colorectal cancer (*e.g.,* colorectal adenocarcinoma), colon cancer (*e.g.,* colon adenocarcinoma), rectal cancer (*e.g.,* rectal adenocarcinoma), pancreatic cancer (*e.g.,* pancreatic ductal adenocarcinoma), breast cancer (*e.g.,* invasive ductal carcinoma), stomach cancer (*e.g.,* stomach adenocarcinoma), endometrial cancer (*e.g.,* undifferentiated endometrial carcinoma), uterine cancer (*e.g.,* uterine endometrial carcinoma), testicular cancer (*e.g.,* testicular germ cell cancer), cervical cancer (*e.g.,* cervical squamous carcinoma), bile duct cancer (*e.g.,* cholangiocarcinoma), a myelodysplastic cancer, or esophageal cancer (*e.g.,* esophageal adenocarcinoma, gastroesophageal junction cancer).

7. The use of any one of the preceding claims, wherein the KRAS (*e.g.,* hKRAS) inhibitor comprises a KRAS (*e.g.,* hKRAS) inhibitor in Table 2.

8. The use of any one of the preceding claims, wherein the KRAS (*e.g.,* hKRAS) inhibitor comprises sotorasib (AMG-510).

9. The use of any one of the preceding claims, wherein the first moiety comprises a full length antibody comprising a heavy chain comprising a variable heavy chain (VH) region that comprises three complementarity determining regions: VH CDR1, VH CDR2, and VH CDR3; and a light chain comprising a variable light chain (VL) region that comprises three complementarity determining regions: VL CDR1, VL CDR2, and VL CDR3, wherein

a) the amino acid sequence of VH CDR1 comprises the amino acid sequence SEQ ID NO: 39, or the amino acid sequence of SEQ ID NO: 39 comprising 1, 2, or 3 amino acid modifications;

b) the amino acid sequence of VH CDR2 comprises the amino acid sequence SEQ ID NO: 40, or the amino acid sequence of SEQ ID NO: 40 comprising 1, 2, or 3 amino acid modifications;

c) the amino acid sequence of VH CDR3 comprises the amino acid sequence SEQ ID NO: 41, or the amino acid sequence of SEQ ID NO: 41 comprising 1, 2, or 3 amino acid modifications; and

d) the amino acid sequence of VL CDR1 comprises the amino acid sequence SEQ ID NO: 42, or the amino acid sequence of SEQ ID NO: 42 comprising 1, 2, or 3 amino acid modifications;

e) the amino acid sequence of VL CDR2 comprises the amino acid sequence SEQ ID NO: 43, or the amino acid sequence of SEQ ID NO: 43 comprising 1, 2, or 3 amino acid modifications; and

f) the amino acid sequence of VL CDR3 comprises the amino acid sequence SEQ ID NO: 44, or the amino acid sequence of SEQ ID NO: 44 comprising 1, 2, or 3 amino acid modifications.

10. The use of claim 9, wherein the VH region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 45; and the VL region comprises an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 46.

11. The use of claim 9 or 10, wherein the amino acid sequence of the heavy chain is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 48; and the amino acid sequence of the light chain is at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%,

94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 49.

12. The use of any one of the preceding claims, wherein the second moiety comprises or consists of the ECD of human TGFβRII.

13. The use of any one of the preceding claims, wherein the amino acid sequence of the second moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73.

14. The use of any one of the preceding claims, wherein the fusion protein comprises (iii) a third moiety that comprises or consists of the ECD of human TGFβRII and is operably connected to the first moiety.

15. The use of claim 14, wherein the amino acid sequence of the third moiety comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 72 or 73.

16. The use of claim 14 or 15, wherein the first moiety comprises a full-length antibody and wherein the N-terminus of a second moiety is operably connected via a first peptide linker to the C-terminus of the first light chain; and the N-terminus of the third moiety is operably connected via a second peptide linker to the C-terminus of the second light chain.

17. The use of claim 16, wherein the amino acid sequence of the first peptide linker comprises or consists of (a) the amino acid sequence of SEQ ID NO: 111; or (b) the amino acid sequence of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications; and the amino acid sequence of the second peptide linker comprises or consists of (a) the amino acid sequence of any one of SEQ ID NO: 111; or (b) the amino acid sequence of any one of SEQ ID NO: 111 comprising or consisting of 1, 2, or 3 amino acid modifications.

18. The use of claim 16 or 17, wherein the amino acid sequence of the first peptide linker consists of the amino acid sequence of SEQ ID NO: 111; and the amino acid sequence of the second peptide linker consists of the amino acid sequence of SEQ ID NO: 111.

19. The use of any one of the preceding claims, wherein

(a) the first moiety consists of a full-length antibody comprising a first and second heavy chain; and a first and second light chain;

(b) the second moiety consists of the ECD of hTGFβRII;

(c) the third moiety consists of the ECD of hTGFβRII;

(d) the second moiety is operably connected to the C-terminus of the first light chain of the full-length antibody of the first moiety through a first peptide linker; and

(e) the third moiety is operably connected to the C-terminus of the second light chain of the full-length antibody of the first moiety through a second peptide linker.

20. The use of any one of the preceding claims, wherein the fusion protein comprises:

(a) a first polypeptide, wherein the amino acid sequence of the first polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 125;

(b) a second polypeptide, wherein the amino acid sequence of the second polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 125;

(c) a third polypeptide, wherein the amino acid sequence of the third polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 126; and

(d) a fourth polypeptide, wherein the amino acid sequence of the fourth polypeptide comprises or consists of an amino acid sequence at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 126.

21. The use of any one of the preceding claims, wherein the fusion protein comprises:

a) a first polypeptide, wherein the amino acid sequence of the first polypeptide consists of the amino acid sequence of SEQ ID NO: 125;
b) a second polypeptide, wherein the amino acid sequence of the second polypeptide consists of the amino acid sequence of SEQ ID NO: 125;
c) a third polypeptide, wherein the amino acid sequence of the third polypeptide consists of the amino acid sequence of SEQ ID NO: 126; and
d) a fourth polypeptide, wherein the amino acid sequence of the fourth polypeptide consists of the amino acid sequence of SEQ ID NO: 126.