Lilly A MEDICINE COMPANY

CLINICAL DEVELOPMENT PROGRAM

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

Lilly

LILLY IS COMMITTED TO REDUCING BARRIERS AND MAKING LIFE BETTER FOR PEOPLE LIVING WITH CANCER.

Lilly is committed to the development of patient-tailored therapeutics that integrate disease and target biology with drug characteristics in order to optimize treatments for patients. Our multidisciplinary approach allows for the translation of molecular and cellular discoveries into clinically meaningful outcomes. Key to this approach is Lilly's extensive and growing catalog of biomarkers.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

CLINICAL DEVELOPMENT PIPELINE

PHASE 3

BTK INHIBITOR

PIRTOBRUTINIB

- BRUIN CLL-321, NCT04666038
  CLL/SLL
- BRUIN MCL-321, NCT04662255
  MCL
- BRUIN CLL-322, NCT04965493
  CLL/SLL
- BRUIN CLL-313, NCT05023980
  CLL/SLL
- BRUIN CLL-314, NCT05254743
  CLL/SLL

CDK4/6 INHIBITOR

ABEMACICLIB

- MONARCH 2, NCT02107703
  Breast Cancer
- MONARCH 3, NCT02246621
  Breast Cancer
- monarchE, NCT03155997
  Breast Cancer
- postMONARCH, NCT05169567
  Breast Cancer

KRAS G12C INHIBITOR

OLOMORASIB

- SUNRAY-01, NCT06119581
  NSCLC
- SUNRAY-02, NCT06890598
  NSCLC

RET INHIBITOR

SELPERCATINIB

- LIBRETTO-531, NCT04211337
  MTC
- LIBRETTO-431, NCT04194944
  NSCLC
- LIBRETTO-432, NCT04819100
  NSCLC

SELECTIVE ESTROGEN RECEPTOR DEGRADER

IMLUNESTRANT

- EMBER-3, NCT04975308
  Breast Cancer
- EMBER-4, NCT05514054
  Breast Cancer

VEGF RECEPTOR-2 ANTAGONIST

RAMUCIRUMAB

- RELAY, NCT02411448
  NSCLC

CANCER TYPE KEY

Breast · Genitourinary · Hematologic · Other Solid Tumors · Thyroid · Gastrointestinal · Gynecologic · Lung · Sarcoma

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

Lilly

CLINICAL DEVELOPMENT PIPELINE (cont.)

PHASE 2

BTK INHIBITOR

PIRTOBRUTINIB

BRUIN, NCT03740529

- CLL/SLL or NHL

BRUIN, NCT06588478

- CLL/SLL

CDK4/6 INHIBITOR

ABEMACICLIB

NCT04238819

- Pediatric Cancer or Other Solid Tumors

NCT06413706

- Other Solid Tumors

CAMPFIRE, NCT05440786

- Sarcoma

KRAS G12C INHIBITOR

OLOMORASIB

NCT04956640*

- NSCLC
- CRC
- Other Solid Tumors

RET INHIBITOR

SELPERCATINIB

LIBRETTO-001, NCT03157128

- NSCLC
- MTC, PTC
- Other Solid Tumors

LIBRETTO-121, NCT03899792

- Pediatric Cancer or Other Solid Tumors

VEGF RECEPTOR-2 ANTAGONIST

RAMUCIRUMAB

CAMPFIRE, NCT04145349

- Pediatric Cancer or Sarcoma

CANCER TYPE KEY

Breast · Genitourinary · Hematologic · Other Solid Tumors · Thyroid · Gastrointestinal · Gynecologic · Lung · Sarcoma

*This clinical trial is being conducted with one or more additional investigational molecules in the pipeline.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

CLINICAL DEVELOPMENT PIPELINE (cont.)

PHASE 1

FGFR3 INHIBITOR
LY3866288

NCT05614739

- Urothelial Cancer
- Other Solid Tumors

FRα ANTIBODY-DRUG CONJUGATE
LY4170156

NCT06400472

- Breast Cancer
- Gastrointestinal Cancer
- Gynecologic Cancer
- Lung Cancer

KRAS G12D INHIBITOR
LY3962673

MOONRAY-01, NCT06586515

- Gastrointestinal Cancer
- Lung Cancer
- Other Solid Tumors

NECTIN-4 ANTIBODY-DRUG CONJUGATE 1
LY4101174

EXCEED, NCT06238479

- Breast Cancer
- Gastrointestinal Cancer
- Genitourinary Cancer
- Gynecologic Cancer
- Lung Cancer
- Other Solid Tumors

PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) RADIOLIGAND
[Ac-255]-PSMA-62

ACCEL, NCT06229366

- Genitourinary

PAN-KRAS INHIBITOR
LY4066434

NCT06607185

- Gastrointestinal Cancer
- Lung Cancer
- Other Solid Tumors

NECTIN-4 ANTIBODY-DRUG CONJUGATE 2
LY4052031

NEXUS-01, NCT06465069

- Breast Cancer
- Gastrointestinal Cancer
- Genitourinary Cancer
- Gynecologic Cancer
- Lung Cancer
- Other Solid Tumors

SELECTIVE ESTROGEN RECEPTOR DEGRADER
IMLUNESTRANT

EMBER, NCT04188548*

- Breast Cancer
- Endometrial Cancer

SMARCA2 (BRM) INHIBITOR
LY4050784

NCT06561685

- Lung Cancer
- Other Solid Tumors

CANCER TYPE KEY

Breast · Genitourinary · Hematologic · Other Solid Tumors · Thyroid · Gastrointestinal · Gynecologic · Lung · Sarcoma

*This clinical trial is being conducted with one or more additional investigational molecules in the pipeline.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

CLINICAL DEVELOPMENT PIPELINE (cont.)

PHASE 1

PAN-MUTANT SELECTIVE PI3Kα INHIBITOR

LY4064809 (STX-478)

NCT05768139

- Breast Cancer
- Other Solid Tumors

PTK7 ANTIBODY-DRUG CONJUGATE

LY4175408

NCT07046923

- Gynecologic
- Breast Cancer
- Lung Cancer
- Other Solid Tumors

CANCER TYPE KEY

Breast · Genitourinary · Hematologic · Other Solid Tumors · Thyroid · Gastrointestinal · Gynecologic · Lung · Sarcoma

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT

BTK INHIBITOR | PIRTOBRUTINIB

Bruton's tyrosine kinase (BTK) is critical for the propagation of B-cell receptor signaling and is upregulated in many B-cell malignancies as compared with normal B cells. BTK inhibition, both in vitro and in vivo, decreases proliferation and survival signals.[1]

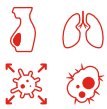
Pirtobrutinib is an investigational, oral, highly selective (in preclinical studies, over 300-fold more selective for BTK vs 98% of 370 non-BTK-kinases), non-covalent (reversible) BTK inhibitor.[2,3] It possesses nanomolar potency independent of BTK C481 status in enzyme and cell-based assays.[2-4] Pirtobrutinib has been shown in preclinical studies to reversibly bind BTK, have high target coverage regardless of BTK turnover rate, preserve activity in the presence of the C481 acquired resistance mutations, and predominantly avoid off-target kinases.[2]

PIRTOBRUTINIB is being investigated in clinical trials in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, and non-Hodgkin's lymphoma.

CDK4/6 INHIBITOR | ABEMACICLIB

Many human tumors acquire alterations which can lead to the activation of cyclin-dependent kinases (CDKs). These alterations include mutations that directly activate CDK4/6; gene amplifications, which increase expression of various protein activators such as D-type cyclins; as well as genetic losses, which reduce expression of protein inhibitors such as p16. These various mechanisms as well as loss of retinoblastoma (Rb) can lead to an enhanced proliferative potential by decreasing dependency on external growth factors and mitogenic signaling pathways, which are required to stimulate growth under normal conditions.[5,6]

Abemaciclib has been shown in vitro to be a selective ATP-competitive inhibitor of CDK4/6 kinase activity that prevents the phosphorylation and subsequent inactivation of the Rb tumor suppressor protein, thereby inducing G1 cell-cycle arrest and inhibition of cell proliferation.[7,8]



ABEMACICLIB is being investigated in clinical trials in patients with breast cancer, non-small cell lung cancer, pediatric cancers, or sarcoma.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

FGFR3 INHIBITOR | LY3866288

Fibroblast growth factor (FGF) receptor 3 (*FGFR3*) is a member of the highly conserved *FGFR* family of transmembrane receptors.[9-11] There are four FGF receptors, *FGFR1-4*, that each consist of an extracellular ligand-binding domain, transmembrane domain, and an intracellular tyrosine kinase domain.[10,11] Receptor dimerization induced upon binding of the extracellular domain with a high-affinity member of the *FGF* family of ligands leads to phosphorylation of the intracellular domain and phospholipase Cγ, *PI3K-AKT*, *RAS-MAPK-ERK*, and STAT pathways activation, playing a critical role in several biological and developmental processes.[9,11,12] *FGFR3* aberrations act as oncogenes across tumor types and have been identified in 15% to 20% of advanced urothelial bladder cancers, ~15% of uterine carcinosarcomas, ~5% of endometrial cancers, and less frequently (<5%) in other solid tumor malignancies.[10,11,13,14] Activating *FGFR3* alterations are diverse and include point mutations, fusions, amplifications, and overexpression.[9-12] Dysregulation of *FGFR3* promotes oncogenesis and tumor cell proliferation, migration, and survival.[9-12,15] Inhibition of oncogenic *FGFR3* shows clinical benefit in patients with advanced urothelial cancer; however, currently approved *FGFR* targeted therapies that are not specific to *FGFR3* demonstrate limited efficacy, dose-limiting off-target toxicities, and susceptibility to resistance mutations.[13, 15,16.]

LY3866288 is an isoform-selective *FGFR3* inhibitor that has shown antitumor activity across *FGFR3*-mutant in vivo preclinical models, with preserved potency against *FGFR3* gatekeeper resistance mutants.[14] LY3866288 spares *FGFR1* and *FGFR2* in preclinical in vivo models, with the goal of avoiding dose-limiting hyperphosphatemia and other clinical adverse events that drive chronic intolerance to pan-*FGFR* inhibitors.[14]

LY3866288 is being investigated in an open-label, multicenter, phase 1a/b study in patients with *FGFR3*-altered advanced urothelial carcinoma and other solid tumors.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

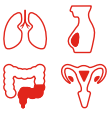
This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

FRα ANTIBODY-DRUG CONJUGATE | LY4170156

Folate receptor alpha (FRα) is a cell-surface glycoprotein encoded by the gene *FOLR1*. It binds to folic acid and reduced folates with high affinity.[17,18] Upon binding, the receptor-ligand complex is internalized via potocytosis and fused with a lysosome, releasing the folate for use in reactions.[18] The expression of FRα in non-malignant tissues is limited, whereas it is overexpressed in many solid tumors such as ovarian, non-small cell lung, and colorectal cancers, making the receptor an attractive therapeutic target for these indications.[17,19]

LY4170156 is an FRα-targeting antibody-drug conjugate (ADC) composed of an Fc-silenced, humanized IgG1 monoclonal antibody, a proprietary polysarcosine hydrophobicity masking agent with a dipeptide cleavable linker, and the topoisomerase I inhibitor payload exatecan. It has a drug-antibody ratio (DAR) of 8:1. In preclinical models, LY4170156 has shown activity against a range of FRα-expressing tumors, including low and moderate FRα-expressing ovarian tumors as well as other solid tumors.[19]



LY4170156 is being studied in ovarian and endometrial cancers, as well as other FRα-expressing solid tumors, in a phase 1 study.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

KRAS G12C INHIBITOR | OLOMORASIB

KRAS is the most common oncogene across all tumor types. KRAS G12C represents a KRAS mutation in patients with non-small cell lung cancer (14%), colorectal cancer (3%), and other solid tumors (1%-3%).[20]

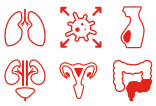
Olomorasib is a selective covalent inhibitor of KRAS G12C; in preclinical models, it shows activity as monotherapy and in combination with other anticancer therapies. It has pharmacokinetic properties supporting its advancement into clinical testing. Olomorasib has been shown in vitro to target a KRAS G12C mutation, thereby inhibiting mutant KRAS-dependent signaling.[21]

OLOMORASIB is being studied in patients with non-small cell lung cancer, colorectal cancer, or other solid tumors.

NECTIN-4 ANTIBODY-DRUG CONJUGATE 1 | LY4101174

Nectin-4 is a type I transmembrane protein and a member of the nectin glycoprotein family.[22] Nectin-4 is primarily expressed in the placenta during fetal development and is weakly expressed in some adult human tissues, such as skin.[22,23] Overexpression of Nectin-4 has been observed in several solid tumor types including urothelial, breast, cervix, lung, and ovarian cancers,[23,24] and is associated with promoting tumor proliferation and metastasis.[22] The higher expression of Nectin-4 in tumor cells compared to normal cells makes the protein an ideal target for tumor-specific delivery of cytotoxic agents via an antibody-drug conjugate (ADC).[22]

LY4101174 is a next-generation anti-Nectin-4 targeting ADC. It is comprised of a humanized IgG1 Fc-silent monoclonal Nectin-4 antibody linked to the topoisomerase I inhibitor, exatecan, via a maleimide-B-glucuronide poly-sarcosine linker with a homogeneous drug-antibody ratio (DAR) of 8:1. In preclinical in vivo models, LY4101174 has shown antitumor activity across a range of Nectin-4 expression levels including a Nectin-4 MMAE ADC resistant model.



LY4101174 is being investigated in a global open-label, multicenter, phase 1a/1b study in patients with advanced or metastatic urothelial carcinoma and select solid tumors.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

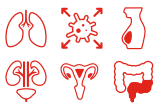
This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

NECTIN-4 ANTIBODY-DRUG CONJUGATE 2 | LY4052031

Nectin-4 is a type I transmembrane protein and a member of the nectin glycoprotein family.[22] Nectin-4 is primarily expressed in the placenta during fetal development and is weakly expressed in some adult human tissues, such as skin.[22,23] Overexpression of Nectin-4 has been observed in several solid tumor types including urothelial, breast, cervix, lung, and ovarian cancers,[23,24] and is associated with promoting tumor proliferation and metastasis.[22] The higher expression of Nectin-4 in tumor cells compared to normal cells makes the protein an ideal target for tumor specific delivery of cytotoxic agents via an antibody-drug conjugate (ADC).[22]

LY4052031 is a next-generation anti-Nectin-4 targeting ADC. It is comprised of a human IgG1 Fc-silent monoclonal Nectin-4 antibody linked to a novel camptothecin (topoisomerase I inhibitor) payload, via a cleavable linker with a homogeneous drug-antibody ratio (DAR) of 8:1. In preclinical in vivo models, LY4052031 has shown antitumor activity across a range of Nectin-4 expression levels, including a Nectin-4 MMAE ADC-resistant model.[25]



LY4052031 is being investigated in a global open-label, multicenter, phase 1a/1b study in patients with advanced or metastatic urothelial carcinoma and other select solid tumors.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

RET INHIBITOR | SELPERCATINIB

Rearranged during transfection (*RET*) fusions have been identified in approximately 2% of non-small cell lung cancer,[26, 27] approximately 10% of papillary thyroid cancer,[28,29] and less than 1% in other solid tumors including pancreatic and colorectal cancer.[30-32] *RET* point mutations account for approximately 60% of medullary thyroid cancer.[33-35] Cancers that harbor activating *RET* fusions or *RET* mutations depend primarily on this single constitutively activated kinase for their proliferation and survival. This dependency renders such tumors highly susceptible to small-molecule inhibitors targeting *RET*.

Selpercatinib is a selective, potent, CNS-active small-molecule inhibitor of RET. Selpercatinib possesses nanomolar potency against diverse *RET* alterations, including *RET* fusions, activating *RET* point mutations, and acquired resistance mutations. Selpercatinib has been shown in vitro and in vivo to exhibit specificity for *RET*, with limited activity against other tyrosine kinases.[36,37]

SELPERCATINIB is being investigated in clinical trials in patients with RET-associated medullary thyroid cancer, non-small cell lung cancer, papillary thyroid carcinoma, pediatric cancers, and other solid tumors.

SELECTIVE ESTROGEN RECEPTOR DEGRADER | IMLUNESTRANT

Estrogen signaling plays an important role in organ development and growth. In certain cancers, abnormal estrogen signaling via the estrogen receptor is a component of tumor growth.[38] Disruption of estrogen signaling by selective estrogen receptor degraders (SERDs) is being investigated in patients with estrogen-receptor-positive (ER+) cancers.

Imlunestrant is an orally available SERD that suppresses estrogen signaling and subsequently inhibits cell proliferation in ER-expressing tumor models.[38,40]

IMLUNESTRANT is being investigated in clinical trials in patients with ER+ breast cancer or endometrial cancer.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

VEGF RECEPTOR-2 ANTAGONIST | RAMUCIRUMAB

Angiogenesis is a tightly regulated, multiple-step process, which results in the formation of new blood vessels from preexisting vasculature and is an important component in the development and progression of malignant disease. Signaling by vascular endothelial growth factor (VEGF) receptor-2 in endothelial cells plays a role in inducing normal and pathologic angiogenesis and is activated by binding of ligands VEGF-A, VEGF-C, and VEGF-D.[41-43]

Ramucirumab is a human IgG1 monoclonal antibody receptor antagonist that has been shown in preclinical studies to bind to and block the activation of VEGF receptor-2 by preventing the binding of VEGF receptor ligands VEGF-A, VEGF-C, and VEGF-D.[44,45]

RAMUCIRUMAB is being investigated in clinical trials in patients with metastatic non-small cell lung cancer, biliary tract cancer, or pediatric sarcoma.

KRAS G12D INHIBITOR | LY3962673

KRAS is one of the most frequently mutated oncogenes.[46] Among the various KRAS mutations, G12D is the most prevalent, occurring in 37.0% of pancreatic cancer cases, 12.5% of colorectal cancer cases, and 4.9% of non-small cell lung cancer cases.[47] KRAS G12D mutations also confer a worse prognosis when compared to KRAS-wildtype tumors. [48,49]

LY3962673 is a selective, oral, non-covalent KRAS G12D inhibitor.[50] Scientists have observed preclinical dose-dependent tumor growth inhibition as monotherapy and in combination with other medicines.[50] LY3962673 is also selective against *HRAS*, KRAS, non-mutated KRAS, and other non-G12D-mutant KRAS.[51]

LY3962673 is being studied in patients with pancreatic cancer, colorectal cancer, non-small cell lung cancer, and other solid tumors with a KRAS G12D mutation.[52]

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

PAN-KRAS INHIBITOR | LY4066434

KRAS is among the most frequently mutated oncogenes with multiple subtypes conferring a worse clinical prognosis.[46,47,53] While KRAS G12C inhibitors have received regulatory approval in certain countries, a significant unmet need persists for other KRASmutant alleles, such as KRAS G12D, G12V, and G13D, which account for over 100,000 annual diagnoses in the United States alone.[46] Additionally, there are no selective targeted agents in clinical development for several less common KRAS mutations such as G12A and G12S.

LY4066434 is an oral, non-covalent, pan-KRAS inhibitor.[54] In preclinical studies, scientists have observed that LY4066434 inhibition includes, but is not limited to, KRAS G12D, G12V, G12C, G13D, G12A, and G12S. Inhibition also includes wildtype KRAS, while sparing *HRAS* and *NRAS*.[54]

LY4066434 is being studied in patients with pancreatic cancer, colorectal cancer, non-small cell lung cancer, and other solid tumors who have qualifying KRAS mutations.[55]

PROSTATE-SPECIFIC MEMBRANE ANTIGEN (PSMA) RADIOLIGAND

| [AC-225]-PSMA-62

Prostate-specific membrane antigen (PSMA) is a type II transmembrane protein that is weakly expressed in normal prostate tissue but strongly upregulated in prostate cancer.[56] PSMA expression increases with higher Gleason scores and further increases in metastatic disease and when resistance to androgen therapy emerges.[57,58] Upon binding to its ligand, PSMA internalizes, thereby facilitating endocytosis and intracellular accumulation of PSMA-targeted compounds.[59]

[Ac-225]-PSMA-62 is a next-generation PSMA-targeting radioligand comprised of the alpha-emitting radioisotope actinium-225, a chelating moiety, linker, and PSMA-62, a small peptide PSMA inhibitor. In nonclinical models, PSMA-62 showed high PSMA binding affinity, increased cellular internalization, and improved biodistribution, including high tumor retention and rapid renal clearance.[60]

[AC-225]-PSMA-62 is being studied in a Phase I/II clinical trial for patients with metastatic castration-resistant prostate cancer (mCRPC) and patients with oligometastatic hormone-sensitive prostate cancer (OmHSPC).

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

SMARCA2 (BRM) INHIBITOR | LY4050784

BAF (mSWI/SNF) is a chromatin remodeling complex comprised of multiprotein subunits. BAF requires either SMARCA2 (BRM) or SMARCA4 (BRG1), mutually exclusive ATPase subunits, for chromatin remodeling to occur. Inhibiting SMARCA2 in SMARCA4-deficient cancer is expected to cause synthetic lethality.[61] SMARCA4 mutations are observed in multiple tumor types, including up to 11% in non-small cell lung cancers.[62]

LY4050784 is a first-in-class, potent, selective, oral SMARCA2 (BRM) inhibitor with greater than 30-fold selectivity for SMARCA2 (BRM) over SMARCA4 (BRG1).[63] Preclinical models have demonstrated tumor regression or tumor growth inhibition in SMARCA4-mutant cell lines containing KRAS, TP53, STK11, and KEAP1.[63] The competitive pharmacokinetic properties and preclinical data support further advancements into clinical testing.

LY4050784 is being studied in clinical trials in patients with non-small cell lung cancer and other solid tumors.

PAN-MUTANT SELECTIVE PI3Kα INHIBITOR | LY4064809 (STX-478)

Phosphoinositide 3-kinase alpha (PI3Kα) molecules harboring activating *PIK3CA* mutations are oncogenic drivers found in approximately 40% of hormone receptor positive (HR+)/HER2-negative breast cancers and less commonly in other cancers.[64,65] The most common mutations include H1047R in the kinase domain, and E545K and E542K in the helical domain.[65,66] Alterations in the PI3K signaling pathway have been associated with endocrine therapy resistance in metastatic breast cancer.[67]

LY4064809 (STX-478) is a mutant-selective, allosteric PI3Kα inhibitor. It has shown preclinical activity in PI3Kα kinase and helical domain mutant driven breast cancer models.[68]

LY4064809 is being studied in patients with HR+ breast cancer and other solid tumors with *PIK3CA* mutations.[69]

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

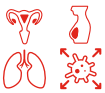
This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

MOLECULES IN CLINICAL DEVELOPMENT (cont.)

PTK7 ANTIBODY-DRUG CONJUGATE | LY4175408

Protein tyrosine kinase 7 (PTK7) is a catalytically inactive transmembrane receptor tyrosine kinase. It is implicated as a modulator of several signaling pathways, most notably Wnt.[70] PTK7 is highly expressed in primary tumors (eg, ovarian cancer, NSCLC, and triple-negative breast cancer) as well as in tumor-initiating cells (TICs).[71]

LY4175408 is a PTK7-targeting antibody-drug conjugate (ADC) composed of a fully human Fc-silenced IgG1 monoclonal antibody, a proprietary polysarcosine hydrophobicity masking agent with a cleavable linker, and the topoisomerase I inhibitor payload exatecan. It has a drug-antibody ratio (DAR) of 8:1. In preclinical models, LY4175408 has shown activity against a range of PTK7-expressing tumors, including low and moderate PTK7-expressing tumors.[72]



LY4175408 is being studied in a clinical trial in patients with non-small cell lung cancer, small cell lung cancer, endometrial cancer, and triple-negative breast cancer.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

REFERENCES

1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443.
2. Mato AR, et al. *Lancet*. 2021;397(10277):892-901.
3. Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216.
4. Gomez EB, et al. *Blood*. 2019;134(suppl 1):4644.
5. Kim JK, Diehl JA. *J Cell Physiol*. 2009;220(2):292-296.
6. Choi YJ, Anders L. *Oncogene*. 2014;33(15):1890-1903.
7. Dempsey JA, et al. AACR Annual Meeting; April 6-10, 2013; Washington, DC. Abstract LB122.
8. Gelbert LM, et al. *Invest New Drugs*. 2014;32(5):825-837.
9. Chen L, et al. *J Exp Clin Cancer Res*. 2021;40(1):345.
10. Krook MA, et al. *Br J Cancer*. 2021;124(5):880-892.
11. Katoh M. *Nat Rev Clin Oncol*. 2019;16(2):105-122.
12. Glaser AP, et al. *Nat Rev Urol*. 2017;14(4):215-229.
13. Helsten T, et al. *Clin Cancer Res.* 2016;22(1):259-267.
14. Ballard JA, et al. *Mol Cancer Ther*. 2021;20 (Suppl 12):P141.
15. Haugsten EM, et al. *Mol Cancer Res*. 2010;8(11):1439-1452.
16. Loriot Y, et al. *N Engl J Med*. 2019;381(4):338-348.
17. Bax HJ, et al. *Br J Cancer*. 2023;128(2):342-353.
18. Scaranti M, et al. *Nat Rev Clin Oncol*. 2020;17(6):349-359.
19. Viricel W, et al. *Cancer Res*. 2023;83 (suppl 7):1544.
20. Ji J, et al. *Onco Targets Ther*. 2022;15:747-756.
21. Peng SB, et al. *Cancer Res*. 2021;81 (suppl 13):1259.
22. Heath EI, Rosenberg JE. *Nat Rev Urol*. 2021;18(2):93-103.
23. Fares J, et al. Preclinical characterization of LY4101174, a next-generation antibody drug conjugate (ADC) targeting Nectin-4. Poster presented at: AACR-NCI-EORTC Annual Meeting; October 11-15, 2023; Boston, MA.
24. Challita-Eid PM, et al. *Cancer Res*. 2016;76(10):3003-3013.
25. Sagar D, et al. A next generation treatment for Nectin-4 positive cancers: preclinical characterization of LY4052031, an anti-Nectin-4 antibody, conjugated to a novel camptothecin payload. Presented at: AACR Annual Meeting; April 8, 2024; San Diego, CA.
26. Lipson D, et al. *Nat Med*. 2012;18(3):382-384.
27. Takeuchi K, et al. *Nat Med*. 2012;18(3):378-381.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

REFERENCES (cont.)

28. Drilon A, et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167.
29. Parimi V, et al. *NPJ Precis Oncol*. 2023;7(1):10.
30. Yang SR, et al. *Clin Cancer Res*. 2021;27(5):1316-1328.
31. Kohno T, et al. *Carcinogenesis*. 2020;41(2): 123-129.
32. Li AY, et al. *Cancer Treat Rev*. 2019;81:101911.
33. Hofstra RM, et al. *Nature*. 1994;367(6461): 375-376.
34. Agrawal N, et al. *J Clin Endocrinol Metab*. 2013;98(2):E364-E369.
35. Taccaliti A, et al. *Curr Genomics*. 2011;12(8):618-625.
36. Subbiah V, et al. *Ann Oncol*. 2018;29:1869-1876.
37. Drilon A, et al. LIBRETTO-001: A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RETaltered cancers. Presented at: ASCO Annual Meeting; June 1-5, 2018; Chicago, IL.
38. Lee HR, et al. *Int J Mol Med*. 2012;29:883-890.
39. Bhagwat SV, et al. *Cancer Res*. 2021;81(Suppl 13):1236.
40. VandeKopple M, et al. *ESMO Open*. 2023;8(Suppl 1):19.
41. Adams RH, Alitalo K. *Nat Rev Mol Cell Biol*. 2007;8(6):464-478.
42. Hicklin DJ, Ellis LM. *J Clin Oncol*. 2005;23(5):1011-1027.
43. Olsson AK, et al. *Nat Rev Mol Cell Biol*. 2006;7(5):359-371.
44. Lu D, et al. *J Biol Chem*. 2003;278(44):43496-43507.
45. Zhu Z, et al. *Leukemia*. 2003;17(3):604-611.
46. Kim D, et al. *Nature*. 2023; 619(7968):160-166.
47. Hofmann MH, et al. *Cancer Discov*. 2022;12(4):924-937.
48. Bournet B, et al. *Clin Transl Gastroenterol*. 2016;7(3):e157.
49. Ricciuti B, et al. *Ann Oncol*. 2022;33(10):1029-1040.
50. Gong X, et al. LY3962673, an oral, highly potent, mutant-selective, and non-covalent KRAS G12D inhibitor demonstrates robust anti-tumor activity in KRAS G12D models. Presented at: AACR Annual Meeting; April 5-10, 2024; San Diego, CA. Poster #3316.
51. Iyer C, et al. Preclinical characterization of LY3962673, an orally bioavailable, highly potent, and selective KRAS G12D inhibitor. Presented at: AACR-NCI-EORTC Annual Meeting; October 11-15, 2023; Boston, MA. Poster B115.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

REFERENCES (cont.)

52. A Phase 1a/1b Trial of LY3962673 in Participants With KRAS G12D-Mutant Solid tumors. ClinicalTrials.gov identifier: NCT06586515. Updated November 18, 2024. Accessed November 20, 2024. https://clinicaltrials.gov/study/NCT06586515
53. Zhu G, et al. *Mol Cancer*. 2021;20(1):143.
54. Prieto L, et al. Preclinical characterization of orally bioavailable, highly potent pan-KRAS inhibitors with selectivity over HRAS and NRAS. Presented at: AACR-NCI-EORTC Annual Meeting; October 11-15, 2023; Boston, MA. Poster B116.
55. A Phase 1a/1b Study of the Pan-KRAS Inhibitor LY4066434 in Participants With KRAS Mutant Solid Tumors. ClinicalTrials.gov identifier: NCT06607185. Updated November 12, 2024. Accessed November 20, 2024. https://clinicaltrials.gov/study/NCT06607185.
56. Silver DA, et al. *Clin Cancer Res*. 1997;3(1):81-85.
57. Kasperzyk JL, et al. *Cancer Epidemiol Biomarkers Prev*. 2013;22(12):2354-2363.
58. Meller B, et al. *EJNMMI Res*. 2015;5(1):66.
59. Rajasekaran SA, et al. *Mol Biol Cell*. 2003;14(12):4835–4845.
60. Vito A, et al. *Eur J Nucl Med Mol Imaging*. 2022;49(suppl 1):S440:EP-039.
61. Jancewicz I, et al. *Epigenetics Chromatin*. 2019;12(1):68.
62. Dagogo-Jack I, et al. *J Thorac Oncol*. 2020;15(5):766-776.
63. Lee JY, et al. Discovery of selective BRM (SMARCA2) ATPase inhibitors for the treatment of BRG1 (SMARCA4) mutant cancers. Presented at: AACR Annual Meeting; April 5-10, 2024; San Diego, CA.
64. Dirican E, et al. *Tumor Biol*. 2016;37(6):7033-7045.
65. Martinez-Saez O, et al. *Breast Cancer Res*. 2020;22(1):45.
66. Zhao L, Vogt PK. *Proc Natl Acad Sci U S A*. 2008;105(7):2652-2657.
67. Tokunaga E, et al. *Breast Cancer.* 2006;13(2):137-144.
68. Buckbinder L, et al. *Cancer Discov*. 2023;13(11):2432-2447.
69. First-in-Human Study of STX-478, a Mutant-Selective PI3Kα Inhibitor as Monotherapy and in Combination With Other Antineoplastic Agents in Participants With Advanced Solid Tumors. Clinicaltrials.gov Identifier: NCT05768139. Updated March 25, 2025. Accessed March 31, 2025. https://www.clinicaltrials.gov/study/NCT05768139
70. Dessaux C, et al. *Oncogene*. 2024;43(26):1973-1984.
71. Damelin M, et al. *Sci Transl Med*. 2017;9(372):eaag2611.
72. Sagar D, et al. Abstract presented at: EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; October 23-25, 2024; Barcelona, Spain. Abstract 520 LBA.

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

Lilly A MEDICINE COMPANY

To learn more about Lilly's commitment to cancer research, please visit **LillyOncologyPipeline.com**

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.

Pipeline information is current through April 2025.