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 lillyloxooncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.
LOXO@LILLY AIMS TO CREATE MEDICINES THAT MAKE LIFE BETTER FOR ALL THOSE AFFECTED BY CANCER AROUND THE WORLD.

Bringing together the focus and spirit of a biotech with the scale, resources, and heritage of Lilly, our team is focused on rapidly delivering impactful new medicines for people with cancer. Our approach centers on creating oncology medicines that show early signs of clinical activity and will matter to patients.

To learn more about Loxo@Lilly’s commitment to people with cancer, please visit LillyLoxoOncologyPipeline.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 lillyloxooncologypipeline.com.

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

Loxo@Lilly is dedicated to developing and delivering innovative new medicines that will make a meaningful difference to cancer patients. Building on our work in cancer treatment, we are developing new medicines as fast as possible to help people living with cancer fight their disease. For us, this means putting an intense focus on the latest scientific advances and collaborating with doctors, other researchers, advocates, and payers to ensure our medicines bring value to people living with 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 lillyloxooncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.
## 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
- MONARCH plus, NCT02763566
  - Breast Cancer
- monarchE, NCT03155997
  - Breast Cancer
- CYCLONE 2, NCT03706365
  - Prostate Cancer
- CYCLONE 3, NCT05288166
  - Prostate Cancer
- postMONARCH, NCT05169567
  - Breast Cancer

### RET INHIBITOR
**SELPERCATINIB**
- LIBRETTO-531, NCT04211337
  - MTC
- LIBRETTO-431, NCT04194944
  - NSCLC
- LIBRETTO-432, NCT04819100
  - NSCLC

### SELECTIVE ER Degrader
**IMLUNESTRANT**
- EMBER-3, NCT04975308
  - Breast Cancer
- EMBER-4, NCT05514054
  - Breast Cancer

### VEGF RECEPTOR-2 ANTAGONIST
**RAMUCIRUMAB**
- RELAY, NCT02411448
  - NSCLC

---

## CANCER TYPE KEY
- **Breast**
- **Gastrointestinal**
- **Genitourinary**
- **Gynecologic**
- **Hematologic**
- **Lung**
- **Neurologic**
- **Other Solid Tumors**
- **Sarcoma**
- **Thyroid**

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 lillyloxooncologypipeline.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 2

<table>
<thead>
<tr>
<th>BTK INHIBITOR</th>
<th>KRAS G12C INHIBITOR</th>
<th>VEGF RECEPTOR-2 ANTAGONIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIRTOBRUTINIB</td>
<td>OLOMORASIB</td>
<td>RAMUCIRUMAB</td>
</tr>
<tr>
<td>BRUIN, NCT03740529</td>
<td>NCT04956640*</td>
<td>CAMPFIRE, NCT04145349</td>
</tr>
<tr>
<td>CLL/SLL or NHL</td>
<td>NSCLC, CRC, or Other Solid Tumors</td>
<td>Pediatric Cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CDK4/6 INHIBITOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABEMACICLIB</td>
</tr>
<tr>
<td>monarchHER, NCT02675231 Breast Cancer</td>
</tr>
<tr>
<td>Next MONARCH 1, NCT02747004 Breast Cancer</td>
</tr>
<tr>
<td>NCT03703466 Breast Cancer</td>
</tr>
<tr>
<td>NCT04238819 Pediatric Cancer or Other Solid Tumors</td>
</tr>
<tr>
<td>CAMPFIRE, NCT05440786 Sarcoma</td>
</tr>
</tbody>
</table>

### Cancer Type Key

- **Breast**
- **Gastrointestinal**
- **Genitourinary**
- **Gynecologic**
- **Hematologic**
- **Lung**
- **Neurologic**
- **Other Solid Tumors**
- **Sarcoma**
- **Thyroid**

*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 lillyloxooncologypipeline.com.

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

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

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.
FGFR3 INHIBITOR | LOXO-435

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.9-12,17 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.14,16

LOXO-435 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.16 LOXO-435 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.16

LOXO-435 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 lillyloxooncologypipeline.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%).

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

**NEXT-GENERATION RET INHIBITOR | LOXO-260**

Rearranged during transfection (*RET*) fusions have been identified in approximately 2% of non-small cell lung cancer, approximately 10% of papillary thyroid cancer, and less than 1% in other solid tumors including pancreatic and colorectal cancer. *RET* point mutations account for approximately 60% of medullary thyroid cancer. 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*.

Recently, resistance to targeted RET treatment has been described in the clinic with secondary solvent front mutations or other oncogenic pathway activations emerging. LOXO-260 is a selective small-molecule inhibitor of the *RET* receptor tyrosine kinase, developed to have activity against both solvent front and gatekeeper mutations, expressed alone or together, while maintaining the potency and selectivity of current selective RET inhibitors. LOXO-260 has demonstrated in vitro and in vivo activity as a selective inhibitor of both wild-type and oncogenic activated RET, including *RET* fusions, activating *RET* point mutations, and anticipated acquired resistant mutations.

**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 lillyloxooncologypipeline.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.)

**PI3Kα INHIBITOR | LOXO-783**

Phosphoinositide 3-kinase alpha (PI3Kα) H1047R mutations are activating oncogenic events that occur in ~15% of breast cancers and less commonly in other cancers. LOXO-783 is a potent, highly mutant-selective, brain-penetrant, allosteric small molecule PI3Kα H1047R inhibitor.

---

**LOXO-783** is being investigated in an open-label, multicenter, phase 1a/1b study in patients with PI3CA H1047R-mutant advanced breast cancer and other solid tumors.

**RET INHIBITOR | SELPERCATINIB**

Rearranged during transfection (RET) fusions have been identified in approximately 2% of non-small cell lung cancer,19,20 approximately 10% of papillary thyroid cancer,21,22 and less than 1% in other solid tumors including pancreatic and colorectal cancer.23,24 RET point mutations account for approximately 60% of medullary thyroid cancer.25,26 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.

---

**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.

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 lillyoxooncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.
SELECTIVE ER 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. Disruption of estrogen signaling by selective estrogen receptor degraders (SERDs) is one of the treatment options for 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.37,38

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

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.39-41

Ramucirumab is a human IgG1 monoclonal antibody receptor antagonist that has been shown in vitro 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.42,43

RAMUCIRUMAB is being investigated in clinical trials in patients with non-small cell lung cancer or pediatric 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 lillyloxooncologypipeline.com.

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


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 lillyloxooncologypipeline.com.

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

38. VandeKopple M, et al. ESMO Breast Cancer Annual Congress; May 11-13, 2023; Berlin, Germany. Abstract 41P.

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 lillyloxooncologypipeline.com.

This document was commissioned by Lilly Medical and is intended to be used by HCPs for medical, scientific, and educational purposes.
To learn more about Loxo@Lilly’s commitment to cancer research, please visit LillyLoxoOncologyPipeline.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 lillyloxooncologypipeline.com.

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