Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO326

Description

This policy is intended to encompass medications that are considered experimental and investigational based on the quality of evidence provided in the clinical trials.

Length of Authorization

- Initial: N/A
- Renewal: N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
adagrasib (Krazati®)	• Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation	600 mg tablets	60 tablets/30 days
avapritinib (Ayvakit™)	• Unresectable or metastatic Gastrointestinal Stromal Tumor with a PDGFRA exon 18 mutation • Advanced Systemic Mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm and mast cell leukemia	300 mg tablets	30 tablets/30 days
		200 mg tablets	
		100 mg tablets	
		50 mg tablets	
		25 mg tablets	
	• Indolent Systemic Mastocytosis	25 mg tablets	30 tablets/30 days
belzutifan (Welireg™)	• von Hippel-Lindau (VHL) disease associated with renal cell carcinoma (RCC), central nervous system (CNS), hemangioblastoma, or neuroendocrine tumors (pNET)	40 mg tablets	90 tablets/30 days
capmatinib (Tabrecta™)	• Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	200 mg tablets	112 tablets/28 days
		150 mg tablets	
futibatinib (Lytgobi®)	• Intrahepatic cholangiocarcinoma, advanced or metastatic, with FGFR2 fusion or rearrangement	12 mg dose pack (84 tablets of 4 mg)	84 tablets/28 days
		16 mg dose pack (112 tablets of 4 mg)	112 tablets/28 days
		20 mg dose pack	140 tablets/28 days

		(140 tablets of 4 mg)	
mobocertinib (Exkivity™)	• Metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy	40 mg capsules	120 capsules/30 days
pemigatinib (Pemazyre™)	• Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma in adults with FGFR2 fusions or rearrangements	13.5 mg tablet	14 tablets/21 days
		9 mg tablet	
		4.5 mg tablet	
	• Relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement.		30 tablets/30 days
pirtobrutinib (Jaypirca™)	• Relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two lines of systemic therapy including a BTKi • Chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) after at least two prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor	100mg tablets	60 tablets/30 days
		50 mg tablets	30 tablets/30 days
pralsetinib (Gavreto™)	• RET Fusion-Positive Non-Small Cell Lung Cancer • RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory	100 mg capsules	120 capsules/30 days
selpercatinib (Retevmo™)	• RET Fusion-Positive Non-Small Cell Lung Cancer • RET-Mutant Medullary Thyroid Cancer • RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory • RET Fusion-Positive Solid Tumors, locally advanced or metastatic	40 mg capsules	90 capsules/30 days
		80 mg capsules	60 capsules/30 days
		40 mg tablets	90 tablets/30 days
		80 mg tablets	60 tablets/30 days
		120 mg tablets	60 tablets/30 days
		160 mg tablets	60 tablets/30 days
sotorasib (Lumakras™)	• Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation	120 mg tablets	240 tablets/30 days
		320 mg tablets	60 tablets/30 days

tepotinib (Tepmetko)	• Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	225 mg tablets	60 tablets/30 days

Initial Evaluation

I. **All Medications listed in this policy** are considered investigational when used for all indications, including but not limited to, the following:
   A. adagrasib (Krazati)
      1. Non-Small Cell Lung cancer (NSCLC)
   B. avapritinib (Ayvakit)
      1. Gastrointestinal stromal tumor (GIST)
      2. Advanced systemic mastocytosis (AdvSM) [e.g., aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), mast cell leukemia (MCL)]
      3. Indolent systemic mastocytosis (ISM)
   C. belzutifan (Welireg)
      1. VHL-disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET)
   D. capmatinib (Tabrecta)
      1. Non-Small Cell Lung Cancer
   E. futibatinib (Lytgobi)
      1. Intrahepatic cholangiocarcinoma (iCCA)
   F. mobocertinib (Exkivity)
      1. Non-Small Cell Lung Cancer
   G. pemigatinib (Pemazyre)
      1. Cholangiocarcinoma
      2. Relapsed or refractory myeloid/lymphoid neoplasms (MLNs)
   H. pirtobrutinib (Jaypirca)
      1. Relapsed or refractory mantle cell lymphoma (R/R MCL)
      2. Chronic lymphocytic leukemia (CLL)
      3. Small lymphocytic lymphoma (SLL).
   I. pralsetinib (Gavreto)
      1. Non-Small Cell Lung Cancer (NSCLC)
      2. Thyroid Cancer
   J. selpercatinib (Retevmo)
      1. Non-Small Cell Lung Cancer (NSCLC)
      2. Thyroid Cancer

3. Other locally advanced or metastatic solid tumors with RET-fusion

K. sotorasib (Lumakras)
   1. Non-Small Cell Lung Cancer (NSCLC)

L. tepotinib (Tepmetko)
   1. Non-Small Cell Lung Cancer (NSCLC)

II. All Medications listed in this policy are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:

A. adagrasib (Krazati)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

B. avapritinib (Ayvakit)
   1. Gastrointestinal Stromal Tumor (GIST)
   2. Advanced systemic mastocytosis (AdvSM, ASM, SM-ANH, MCL)
   3. Non-advanced, indolent systemic mastocytosis (ISM)
   4. Non-advance, smoldering systemic mastocytosis (SMM)
   5. Soft tissue sarcoma
   6. Solid tumors with or without CKIT or PDGFRA mutations
   7. Acute myeloid leukemia (AML) with or without CKIT or PDGFRA mutations

C. belzutifan (Welireg)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

D. capmatinib (Tabrecta)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

E. futibatinib (Lytgobi)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

F. mobocertinib (Exkivity)
   1. being withdrawn from the market based on the outcome of the Phase 3 EXCLAIM-2 confirmatory trial in the setting of metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated Approval granted by the U.S. FDA nor the conditional marketing approvals granted in other countries. Takeda is working with the FDA towards the withdrawal of Exkivity from the U.S. market and will also withdrawal Exkivity globally where approved.

G. pemigatinib (Pemazyre)
   1. Has not been sufficiently studied for safety and efficacy for conditions other than cholangiocarcinoma and myeloid/lymphoid neoplasms to date. Cholangiocarcinoma

H. pirtobrutinib (Jaypirca)
   1. Pirtobrutinib (Jaypirca) used in combination with another oncology therapy

2. Mantle cell lymphoma (MCL)
   i. The efficacy of pirtobrutinib (Jaypirca) in patients with relapsed or refractory MCL was based on an open-label, single-arm, phase 1/2 clinical trial (BRUIN). The trial enrolled patients (N=120) with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor [ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa)]. Pirtobrutinib (Jaypirca) was administered as 200mg once a day. The primary efficacy outcome was objective response rate (ORR). Other measured outcomes included complete response (CR), partial response (PR), time to response, and duration of response. Pirtobrutinib (Jaypirca) showed an ORR of 50% (60) of patients. Fifteen (13%) achieved complete response with the remainder (38%) achieving partial response. Additionally, the time to response was 1.8 months (0.8-4.2) with a median duration of response of 8.3 months (5.7-NE).
   ii. The population was treatment experienced with a median of three prior lines of therapy, 93% having received two or more prior lines. All had previously received a BTKi containing regimen; other prior therapies being chemo-immunotherapy (88%), HSCT (20%), lenalidomide (18%), CAR-T therapy (9%).
   iii. The safety of pirtobrutinib (Jaypirca) was reported based on the pooled analyses from all cohorts in the phase 1/2 clinical trial. In the pooled safety population, the most common (≥ 20%) adverse reactions included decreased neutrophil count, hemoglobin, platelet count, lymphocyte count, as well as fatigue, musculoskeletal pain, bruising, and diarrhea. Severe adverse reactions specific to the MCL cohort occurred in 38% of patients which included pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). Dose reductions were seen in 4.7% of trial participants with therapy interruptions being needed in 32%. Nine percent of patients required permanent discontinuation. Fatal adverse reactions occurred in 7% of patients; most commonly due to infections (4.7%) including COVID-19 (3.1% of all patients). Current patient exposure to pirtobrutinib (Jaypirca) is limited to clinical trial participants; thus, the real-world safety profile and patient experience with this drug remain undefined. Based on a single-arm, open-label clinical trial in a small patient population, the overall safety profile of pirtobrutinib (Jaypirca) is largely unknown.
   iv. The quality of the evidence is considered low given the observational nature of the trial with an open-label study design and lack of a comparator arm. Additionally, there remains an unknown clinical impact on the overall survival and health-related quality of life measures. Although overall

response rate is an objective measure and may indicate the potential benefit of therapy, it does not predict long term outcomes such as overall survival.

v. As of March 2023, current third and subsequent line therapies for the treatment of R/R MCL are approved based on limited evidence. NCCN guideline directed therapies for third-line and beyond include brexucabtagene autoleucel (TECARTUS), pirtobrutinib (Jaypirca), and allogeneic HCT in eligible patients. Both CAR-T therapy and pirtobrutinib (Jaypirca) are FDA approved for R/R MCL under an accelerated approval pathway. Based on the limited available evidence, there is low confidence to direct to one therapy over another [i.e., brexucabtagene autoleucel (TECARTUS) versus pirtobrutinib (Jaypirca)].

vi. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for MCL note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with R/R MCL. Despite the accelerated FDA-approval, continued approval of pirtobrutinib (Jaypirca) as a subsequent-line treatment of MCL, remains contingent upon verification of clinical benefit in confirmatory trials. Additionally, an expanded access program via manufacturer, as part of the ongoing clinical studies of pirtobrutinib (Jaypirca), remains a practical option and an alternative path to treatment for qualifying patients.

3. Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL)

i. The efficacy of pirtobrutinib (Jaypirca) in patients with previously treated CLL/SLL was based on an open-label, single-arm, phase 1/2 arm of a larger clinical trial (BRUIN). The trial enrolled patients (N=108) with CLL/SLL after at least two lines of systemic therapy, including a BTK inhibitor [ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa)] and a BCL2 inhibitor. Pirtobrutinib (Jaypirca) was administered as 200mg once a day. The population was treatment experienced with a median of five prior lines of therapy (2-11). All had previously received a BTKi containing regimen [ibrutinib (Imbruvica) (97%), acalabrutinib (Calquence) (9%), zanubrutinib (Brukinsa) (0.9%)] and a BCL-2 inhibitor [venetoclax (Venclexta)].

ii. The primary efficacy outcome was objective response rate (ORR). Other measured outcomes included complete response (CR), partial response (PR), progression free survival (PFS), time to response, and duration of response.

Pirtobrutinib (Jaypirca) had an ORR of 70.0% (95% CI, 60.0 to 78.8) and 79.0% (95% CI, 69.7 to 86.5) when partial response with lymphocytosis was included. No patients in this subgroup were able to achieve a complete response. Additionally, the median time to response was 3.7 months (1.7-27.9) with a median duration of response of 12.2 months (9.3-14.7). Median PFS was 17 months.

iii. The most common adverse reactions (≥ 20%), excluding laboratory terms, were fatigue, bruising, cough, musculoskeletal pain, COVID-19, diarrhea, pneumonia, abdominal pain, dyspnea, hemorrhage, edema, nausea, pyrexia, and headache. Adverse events of special interest included infections (71%), bleeding (42.6%), and neutropenia (32.5%). The incidence of infection while on pirtobrutinib was higher than with other BTK inhibitors in this cancer type (71% vs 55.6%). Treatment-related adverse events led to dose reductions in 15 patients (4.7%) and permanent discontinuation of pirtobrutinib in nine patients (2.8%).

iv. In total, 18 patients died while receiving pirtobrutinib (Jaypirca). Two died from disease progression. The remaining 16 succumbed to other causes including coronavirus disease 2019 (Covid-19) or Covid-19–related pneumonia (8 patients), pneumonia or fungal pneumonia (2 patients), septic shock or shock (2 patients), and other causes (4 patients).

v. NCCN guidelines recommend use of pirtobrutinib (Jaypirca) for use in certain circumstances should there be resistance or intolerance to prior covalent BTKi therapy. Additionally, it remains as a therapy for relapsed or refractory disease after prior BTKi and venetoclax-based regimens. Use in the both of the settings above carry a category 2A recommendation. The FDA labeled indication specifically states pirtobrutinib (Jaypirca) is for use after therapy with a BTKi and BCL-2 inhibitor. Despite the accelerated FDA-approval, continued approval of pirtobrutinib (Jaypirca) as a subsequent-line treatment of CLL/SLL, remains contingent upon verification of clinical benefit in confirmatory trials.

vi. The quality of the evidence is considered low given the observational nature of the trial with an open-label study design and lack of a comparator arm. Additionally, there remains an unknown clinical impact on the overall survival and health-related quality of life measures. Although overall response rate is an objective measure and may indicate the potential benefit of therapy, it does not predict long term outcomes such as overall survival. Other outcomes measured including PFS may be considered the “gold standard” in this disease state, though other publications consider PFS an “unreliable survival surrogate” as patients with CLL/SLL have increased

comorbidities given it is a disease of the mostly elderly who generally succumb to other conditions without disease progression.

4. Waldenström macroglobulinemia
5. Marginal zone lymphoma
6. Chronic graft versus host disease

I. pralsetinib (Gavreto)
   1. Pralsetinib (Gavreto) in treatment of RET fusion-positive medullary thyroid cancer (MTC) is being withdrawn based on the confirmatory Phase III randomized AcceleRET study, which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated Approval granted by the U.S. FDA nor the conditional marketing approvals granted in other countries. Genetech is working with the FDA towards the withdrawal of this indication.
   2. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

J. selpercatinib (Retevmo)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

K. sotorasib (Lumakras)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

L. tepotinib (Tepmetko)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

adagrasib (Krazati)

I. Adagrasib (Krazati) is the second therapy FDA-approved for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It follows sotorasib (Lumakras), which received accelerated FDA approval in this setting, in 2021.
II. KRAS mutations account for up to 25% of mutations in NSCLC and are often associated with resistance to targeted therapies and generally poor patient outcomes in patients with cancer. KRAS G12C, a subset of KRAS mutations, accounts for about 13% of mutations in NSCLC.

III. Most patients with NSCLC including *KRAS*-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, and paclitaxel. Additionally, targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.

IV. Adagrasib (Krazati) is a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy and is indicated for patients 18 years of age and older.

V. The New Drug Application (NDA) for adagrasib (Krazati) for the treatment of NSCLC was based on results from a subset of participants (cohort A) in an open-label, Phase 1/2, single-arm trial (KRYSTAL-1). Patients (N=116) with KRAS G12C mutated NSCLC, who had disease progression after platinum-based chemotherapy and/ or immunotherapy received adagrasib (Krazati) 600 mg orally twice daily for a median 15.7 months. The primary efficacy outcome was Objective Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Adagrasib (Krazati) showed an ORR of 42.9% (95% CI; 33.5, 52.6), which included one patient (0.9%) complete response (CR) with remainder (n= 47) exhibiting partial responses. Additionally, participants in this cohort showed DoR of 8.5 months (95% CI; 6.2, 13.8), PFS 6.5 months (95% CI; 4.7, 8.4), and OS 12.6 months (95% CI; 9.2, 19.2).

VI. Based on the data from KRYSTAL-1 trial, the quality of the evidence to support efficacy of adagrasib (Krazati) is considered low at this time. Given the lack of comparator and single-arm open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy remains uncertain.

VII. The safety of adagrasib (Krazati) was based on drug exposure during the clinical trial (N=116). All participants reported any grade adverse reactions (AE) with 81.9% suffering a grade ≥ 3 AE. The most common AE included diarrhea, nausea and vomiting, fatigue, dyspnea, and increased creatinine and aspartate aminotransferase (AST). Anemia, hyponatremia, and dyspnea were reported as serious (grade ≥ 3) AE. Adagrasib (Krazati) led to 82.8% dose reduction or therapy interruptions, with 15.5% of patients requiring permanent discontinuation. Twenty (17.2%) patient deaths were reported during the trial, of which, two (1.7%) were ascribed as treatment-emergent (cardiac failure and pulmonary hemorrhage). Current patient exposure to adagrasib (Krazati) is limited to clinical trial participants; thus, the real-world safety profile and patient experience with this drug remain undefined. Based on a single-arm, open-label clinical trial in a small patient population, the overall safety profile of adagrasib (Krazati) is largely unknown.

VIII. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for adagrasib (Krazati) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, adagrasib (Krazati) is being studied as a combination regimen with other targeted therapies (e.g., MEK inhibitor, EGFR inhibitor, SHP2 inhibitor) for the treatment of NSCLC. These clinical trials are in early phases and as of October 2022, data is not available for review.

IX. Single-arm, open-label clinical trial may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with

patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

X. Targeted therapies for treatment of NSCLC have garnered interest in recent years and may be considered part of a paradigm shift in the management of NSCLC based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to current molecularly targeted therapies in lung cancer presents a major clinical challenge. Additionally, targeted therapy approach is also susceptible to failure due to escape mutations.

XI. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) have been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). The efficacy and safety of targeted agents such as adagrasib (Krazati) in comparison with, or in combination with, currently established regimens, have not been studied and remain unknown.

XII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, continued approval of adagrasib (Krazati) as a subsequent-line treatment of NSCLC, remains contingent upon verification of clinical benefit in confirmatory trials. Additionally, an expanded access program via manufacturer, as part of the ongoing clinical studies of adagrasib (Krazati), remains a practical option and an alternative path to treatment for qualifying patients.

avapritinib (Ayvakit)

I. Avapritinib (Ayvakit) is FDA-approved for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL), and adults with indolent systemic mastocytosis (ISM) whose symptoms are not adequately controlled by best supportive care (BSC).

II. Avapritinib (Ayvakit) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.

III. Avapritinib (Ayvakit) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication. Avapritinib (Ayvakit) has been studied when used in combination with BSC therapies (e.g., antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.) in patients with systemic mastocytosis.

IV. Due to the complex nature of treating any of the diagnoses listed above, treatment with avapritinib (Ayvakit) should be prescribed by, or in consultation with, an oncologist. When being requested for systemic mastocytosis, treatment may be prescribed by, an oncologist, allergist, immunologist gastroenterologist, or dermatologist.

V. **Gastrointestinal Stromal Tumors (GIST)**

a. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines state most PDGFRA mutations respond to imatinib (Gleevec), with the exception of PDGFRA D842V mutants, which do not respond to current TKI therapies [e.g. imatinib (Gleevec), sunitinib (Sutent), regorafenib (Stivarga)]. Avapritinib (Ayvakit) carries a category 2A recommendation as a preferred first line regimen for patients with unresectable, progressive, or metastatic GIST with a PDGFRA exon 18 mutations that are insensitive to imatinib (including PDGFRA D842V). Avapritinib (Ayvakit) is also listed under “useful in certain circumstances” as an additional treatment option after progression on approved therapies.

b. GIST tumors have the following mutation prevalence: 75%-80% are KIT mutated, 5%-10% are PDGFRA mutated, and 10%-15% do not express KIT or PDGFRA. PDGFRA D842V mutants make up 60% of all PDGFRA mutations.

c. In an international survey, imatinib (Gleevec) had a median progression free survival (PFS) of 2.8 months for patients with a D842V substitution and 28.5 months for patients with other PDGFRA mutations. In 46 months of follow-up, median overall survival was 14.7 months for patients with D842V substitutions and was not reached for patients with other PDGFRA mutations.

d. Avapritinib (Ayvakit) was FDA-approved off interim analysis of one Phase 1, open-label, single-arm trial (NAVIGATOR) in 43 patients with unresectable or metastatic GIST that is PDGFRA positive. Patients included had previously tried and failed one or more previous TKIs. The primary efficacy outcome was overall response rate (ORR), and at interim analysis, it was 84% (95% CI 69, 93), and 89% (95% CI 75, 97) for the PDGFRA exon 18 group, and PDGFRA D842V group, respectively. Secondary outcomes included duration of response (DOR), and PFS, which were only reported for the PDGFRA D842V group. DOR was 27.6 months (95% CI 14.3, 27.6), and median PFS was 29.5 months (95% CI not reported).

1. At trial completion, the ORR in the *PDGFRA* D842V population (n = 56), 91% (51/56 patients). The DOR was 27.6 months (95% CI: 17.6 – not

reached [NR]); the median PFS was 34.0 months (95% CI: 22.9 – NR); median OS was not reached.

e. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between drug use and patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.
f. The quality of the current evidence for avapritinib (Ayvakit) is considered low. The primary outcome, ORR, has not yet been correlated to clinically meaningful outcomes such as overall survival or quality of life parameters in GIST. The PFS result has unknown value due to the small sample size as well as the single arm, open-label design, and the medications significant safety profile. There is a lack of evidence indicated that avapritinib (Ayvakit) would provide a net health benefit for members.
g. Clinical trials initially started avapritinib (Ayvakit) at 400 mg daily but reduced the dose to 300 mg due to toxicity. Of the patients receiving 400 mg and 300 mg, 97% and 72% experienced AEs of grade ≥3 severity, respectively. There was no noted difference in efficacy between the 400 mg and 300 mg doses.
h. Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 22% permanent discontinuation rate due to intolerable adverse events.
i. Avapritinib (Ayvakit) has notable serious side effects for anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), vomiting (2%), acute kidney injury (2%), pneumonia (1%), and tumor hemorrhage (1%). Almost all patients experienced one AE (99%), with the most common AEs (>20%) being: edema, nausea, fatigue, cognitive impairment, vomiting, decreased appetite, diarrhea, increased lacrimation, abdominal pain, constipation, rash, dizziness, and hair color changes. There are no specific contraindications to using avapritinib (Ayvakit); however, warnings and precautions include: intracranial hemorrhage, central nervous system effects (e.g., cognitive impairment, dizziness, sleep disorders), and embryo-fetal toxicity.
j. The VOYAGER trial was a randomized, open-label, phase 3 clinical trial evaluating PFS, ORR, and OS of avapritinib (Ayvakit) against regorafenib (Stivarga) in patients with locally advanced unresectable or metastatic GIST. There was no significant difference in median PFS between avapritinib and regorafenib in patients with molecularly unselected, late-line GIST. In May 2020, the FDA issued a complete response letter stating that it will not approve a new drug application for avapritinib for use in the treatment of adult patients with unresectable or metastatic fourth-line GIST based on data from VOYAGER.

VI. **Advanced Systemic Mastocytosis (AdvSM)**

a. Systemic mastocytosis (SM) is a rare, clonal neoplastic proliferation of mast cells driven by the *KIT*D816V mutation, resulting in uncontrolled proliferation and activation of abnormal mast cells in various tissues, including skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes. Advanced systemic mastocytosis (AdvSM) accounts for approximately 5% of all SM cases and includes the following disease variants: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).
b. According to NCCN guidelines for systemic mastocytosis, as of May 2022, treatment options for AdvSM include cytoreductive therapy, allogenic HCT, and enrollment in clinical trials. Cytoreductive therapies include avapritinib, midostaurin, cladribine, imatinib, and peginterferon alfa-2a ± prednisone. The guidelines note the following treatment considerations for AdvSM, all with category 2A recommendations:
    1. Preferred regimens: Avapritinib and midostaurin
    2. Other recommended regimens: Cladribine for patients that may require when rapid debulking of disease. Peginterferon alfa-2a, has a cytostatic mechanism of action and may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction
    3. Useful in certain circumstance: Imatinib is FDA-approved for adult patients with ASM without the KIT D816V mutation (including wild-type) or with unknown mutational status. Imatinib included as a treatment option for patients with ASM (for KIT D816V mutation negative or unknown, WDSM, or if eosinophilia is present with FIP1L1-PDGFRA fusion gene may also be considered as another treatment option for patients diagnosed with ASM or SM-ANH.
c. Avapritinib (Ayvakit) was FDA-approved based on the data from one phase 1 (EXPLORER) and a prespecified interim analysis of the phase 2 (PATHFINDER) multicenter, single-arm, open-label clinical trials. Patients were considered evaluable if they had a confirmed diagnosis of AdvSM per World Health Organization (WHO) and met modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline. There were 48 evaluable patients in the EXPLORER trial and 32 patients in the PATHFINDER trial at interim analysis. The primary efficacy endpoint in the PATHFINDER trial was overall response rate (ORR), which was 75%. A favorable ORR was observed in the EXPLORER trial, which was 75% (95% CI, 62 – 86). Additional efficacy outcome measures included duration of response (DOR) and time to response; the median DOR for all evaluable patients was 38.3 months (95% CI, 19, not estimable) and time to response was 2.1 months.

d. A pooled efficacy and safety analysis from the EXPLORER and PATHFINDER trials compared avapritinib and best available therapy in patients with AdvSM who received ≥1 systemic therapy prior to avapritinib. The ORR in n=31 evaluable patients was 71% (95% CI: 52 – 86), including 19% with complete remission (CR)/CR with partial recovery of peripheral blood counts (CRh). Median OS was not reached (median follow-up 17.7 months). Median time to response was 2.3 months, median time to CR/CRh was 7.4 months. The median duration of response (DOR) was not reached. Median OS was significantly improved in patients treated with avapritinib (49.0 months [95% CI, 46.9 months–not estimable] vs. 26.8 months [95% CI, 18.2–39.7 months]; adjusted HR, 0.48; 95% CI, 0.29–0.79; P = .004). Data further demonstrated that avapritinib treatment was associated with improved OS compared to midostaurin (HR, 0.59; 95% CI, 0.36–0.97; P < .001) and cladribine (HR, 0.32; 95% CI, 0.15–0.67; P = .003). OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy. The efficacy of avapritinib in patients with AdvSM was established irrespective of prior therapies or S/A/R mutation status.
e. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.
f. Based on information from the EXPLORER and PATHFINDER trials, the quality of evidence is considered low at this time given the single-arm, open-label trial design and use of surrogate marker as the primary efficacy outcome. At this time, there is no correlation between ORR and clinically meaningful outcomes of morbidity and mortality or quality of life parameters. Therefore, the true efficacy of the medication remains unknown. The medication also has a significant safety profile that is under post-marketing review by the FDA. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members.
g. Avapritinib (Ayvakit) is associated with notable serious side effects, including anemia (5%), subdural hematoma (4%), pleural effusion, ascites and pneumonia (3% each), acute kidney injury, gastrointestinal hemorrhage, intracranial hemorrhage, encephalopathy, gastric hemorrhage, large intestine perforation, pyrexia, and vomiting (2% each). Grade ≥3 cytopenias occurred in up to one-quarter of patients and facial/periorbital edema (any grade) in one-half (3 percent grade ≥3 facial/periorbital edema). No new safety signals were observed during the clinical trials for AdvSM.
h. In patients with AdvSM, a platelet count must be performed prior to initiating therapy and every 2 weeks first the first 8 weeks of starting therapy. Thrombocytopenia is listed

as a warning/precaution for therapy when used in patients with AdvSM. Avapritinib (Ayvakit) is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.

i. The FDA has issued a post-marketing requirement to provide additional evaluation of the safety signals of intracranial hemorrhage and cognitive adverse reactions associated with avapritinib (Ayvakit), which can only be adequately assessed in clinical trials. This trial is anticipated to be submitted by 12/2021. The FDA has also issued a second post-marketing requirement to submit the completed phase 2 PATHFINDER trial data, which is anticipated to be completed 1/2026.

VII. **Non-advanced, indolent systemic mastocytosis (ISM)**

a. Indolent systemic mastocytosis (ISM) is defined as a rare, usually benign, chronic, form of systemic mastocytosis characterized by an abnormal accumulation of neoplastic mast cells mainly in the bone marrow, but also in other organs or tissues such as the skin. ISM accounts for more than 70% of all SM cases in published literature. One of the key diagnostic determinants that differentiates ISM from other SM subtypes includes absence of C-findings (are indicative of organ damage produced by mast cell infiltration via biopdy), no evidence of an associated hematologic neoplasm, low mast cell burden, and higher prevalence of skin lesions. Patients with ISM have a near-normal life expectancy, and ISM carries a low risk of progression with < 3% of patients progressing to a more severe form of systemic mastocytosis. The most common cause of death is disability or anaphylaxis.

b. Avapritinib (Ayvakit) is the first FDA-approved therapy for ISM. Approval was based on data from the randomized, double-blind, placebo-controlled part of the PIONEER trial, 141 patients received avapritinib (Ayvakit) 25 mg once daily + best supportive care (BSC) and 71 patients received placebo + BSC. The study included adults with an indolent SM diagnosis confirmed by central pathology review, and moderate-to-severe symptom burden despite an optimized regimen of BSC, which may include antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc. All patients were able to continue symptom-directed therapy throughout the trial and, following completion of the 24-week treatment period, had the option to receive avapritinib (Ayvakit) in an open-label extension study (HARBOR trial). The primary endpoint was the change in patient-reported disease symptoms as assessed by the ISM Symptom Assessment Form (ISM-SAF) total symptom score (TSS) Key secondary endpoints include mean change in individual symptom scores of ISM-SAF, change in most severe symptom score, QoL, and several biomarkers of mast cell burden. Avapritinib (Ayvakit) achieved a statistically significant improvement in TSS compared to placebo at 24 weeks (p=0.003) and demonstrated statistically significant differences all key secondary endpoints, observed with improvements in severe symptoms and across all symptoms measured by the ISM-SAF that deepened over time.

c. The most common treatment-related AEs were headache (8 %), nausea (6%), peripheral edema (6%), periorbital edema (6%), and dizziness (3%). Across treatment arms, most adverse events were mild to moderate in severity, and treatment-related AEs leading to discontinuations were low for both arms (< 2% each). No new safety signals were observed during the clinical trials for ISM.
d. Data from this trial are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. It is unclear whether avapritinib (Ayvakit) provides a clinically meaningful improvement in a condition that is already indolent. Furthermore, the NCCN guideline acknowledges that the IWG-MRT-ECNM response criteria were developed mainly for use in clinical trials and may not be widely used in clinical practice. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members with an already indolent form of SM.
e. The NCCN guidelines recommend observation or treating mast cell activation symptoms with best supportive care in patients with symptomatic ISM. The guidelines do not have any pharmacotherapies listed in their treatment algorithm for ISM nor have avapritinib (Ayvakit) noted as a potential therapy option for ISM. Furthermore, the NCCN guidelines encourages enrollment in well-designed clinical trials investigating novel therapeutic strategies regardless of SM type. As of May 2023, an expanded access program (EAP) (NCT04714086) for avapritinib for patients with ISM is available, which may provide access to therapy in lieu of clinical trial enrollment.

belzutifan (Welireg)

I. Belzutifan (Welireg) is the first systemic therapy FDA-approved for the treatment of adult patients with von Hippel-Lindau (VHL) disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. It is also the only orally administered drug indicated in this setting.
II. Von Hippel-Lindau syndrome (VHL) is a hereditary condition associated with tumors arising in multiple organs. VHL-related tumors include hemangioblastomas, which are blood vessel tumors of the brain, spinal cord, and retina. Patients with VHL also have an increased risk of developing clear cell renal cell carcinoma (cc-RCC), pheochromocytoma, or pancreatic neuroendocrine tumor (pNET). Initial features of VHL include kidney cysts, pancreatic cysts, epididymal cystadenomas, broad ligament cystadenomas, and endolymphatic sac tumors (ELST), which are tumors of the inner ear that may cause hearing loss.
III. Patients with VHL disease may present with cysts in any one or multiple organ systems. For example, it is possible for a patient to show radiographic presence of pNET or other neuroendocrine lesions without presence of kidney lesions. However, the prevalence data shows kidney lesions and cc-RCC as the most common progressive manifestation in VHL (up to 70% of cases). On the other hand, pNET, hemangioblastoma, pheochromocytoma may be prevalent between 5% and 30% of the VHL cases.

IV. Additionally, VHL disease associated tumors are slow growing in nature. Depending on the tumor type, natural evolution and progression for VHL tumors may be between four years to 10 years after onset. Onset of symptoms is mostly observed in adulthood with median age of onset 24 to 44 years of age.

V. VHL protein deactivation followed by HIF-2α buildup may be one of the key drivers to VHL-associated tumorigenesis. Unregulated levels of HIF-2α may stimulate several oncogenes associated with angiogenesis and tumor growth, leading to both benign and malignant tumors.

VI. The only way to diagnose VHL is with genetic testing. Nearly all patients with VHL will be found to have a genetic mutation in their *VHL* gene once tested. There are no universal guidelines regarding who should be screened for VHL. However, VHL should be suspected when a person has a family history of VHL.

VII. There are no FDA-approved systemic therapies for VHL associated tumors. Current standard of care (irrespective of tumor type at diagnosis) involves active surveillance, surgical resection when necessary (e.g., partial nephrectomy or ablation) and radiation (e.g., for spinal cord tumors). Active surveillance may involve radiographic imaging, biomarker screenings, and histological study. When tumors/cysts reach resectable mass (e.g., for RCC a 3 cm rule is followed), the patient may undergo resection. A patient may have to undergo multiple resections over lifetime. It is important to note that for initial manifestations, as well as lesions presenting later during life, surgical resection remains standard of care as long as the tumor/ lesions are determined to be benign.

VIII. For patients who progress to advanced carcinomas with metastatic potential, guideline recommended systemic therapies (e.g., tyrosine kinase inhibitors (TKI), vascular endothelial growth factor (VEGF) inhibitors) may be warranted as indicated for the tumor type and location. The National Comprehensive Cancer Network (NCCN) treatment guideline for kidney cancer (RCC) has included belzutifan (Welireg) as a Category 2A recommendation for systemic therapy for confirmed hereditary RCC associated with VHL disease. There are no treatment guidelines specific to the pharmacological management of the VHL disease.

IX. **Clinical Trial Data**:

- Belzutifan (Welireg) received FDA-approval based on an ongoing Phase 2, open-label, single-arm trial (Study004). Patients (N= 61) with VHL- associated cc-RCC (≥ 1 measurable localized tumor in the kidney and pancreas), received belzutifan (Welireg) 120 mg orally once a day for a median of 21.8 months. Primary efficacy outcome was Overall Response Rate (ORR) in RCC. Key secondary outcomes were ORR in non-RCC lesions, Progression-Free Survival (PFS), and Duration of Response (DoR). All participants were not candidates for immediate surgery and were naïve to chemotherapy. The study excluded patients with metastatic disease. Therapy with belzutifan (Welireg) for a median of 21.8 months showed 49.2% ORR (95% CI; 36.1, 62.3), all of which were partial responses (PR). DoR and PFS were not estimable currently. Additionally, patients with pancreatic lesions (n=61), pancreatic neuroendocrine tumors (pNET; n= 12), and CNS hemangioblastoma (n= 24) exhibited 77%, 83%, and 62% ORR, respectively.

- Belzutifan (Welireg) showed significant safety concerns with common adverse reactions (AE): anemia (90.2%), fatigue (65%), headache (41%), nausea (34%), and dyspnea (23%). Serious AE (grade 3, 14.8% patients) included anemia, fatigue, dyspnea and hypertension, pneumonitis, and elevation of liver enzymes. Although no contraindications are listed, the drug information includes warnings of serious anemia and hypoxia. Treatment during clinical trial led to 39% therapy interruptions, 13% dose reductions, 3.3% discontinuations, and one death. The real-world safety profile of belzutifan (Welireg) remains undetermined at this time.
- Additionally, a Phase 1, open-label, single arm clinical trial for belzutifan (Welireg) studied safety and efficacy of belzutifan (Welireg) in advanced cc-RCC. Enrolled patients in this trial had advanced cc-RCC with ECOG PS 1 through ≥ 3. All patients were treatment experienced (62% had ≥3 systemic therapies) with majority (91%) exposed to vascular endothelial growth factor (VEGF) inhibitors, along with mTOR inhibitors and checkpoint inhibitors. At median 27.7 months of follow-up, belzutifan (Welireg) treatment led to a 25% ORR (95%CI; 15, 39) in the cc-RCC cohort.

X. FDA-approval for belzutifan (Welireg) followed an accelerated approval pathway. Continued approval may be contingent upon verification of clinical benefits in confirmatory trials. Currently, clinical trials are underway for advanced cc-RCC as monotherapy as well as in combination with other oncolytic agents.

XI. Therapies based on targeting molecular pathways in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the pharmacological management of cancers. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Specifically, in the setting of VHL-associated tumors, this resistance may be associated with feedback activation of other downstream pathways such as vascular endothelial growth factor (VEGF), platelet derived growth factor receptor beta (PDGFRβ), and hypoxia inducible factor-1 (HIF-1) mediated oncogenesis. Thus, selective inhibition of HIF-2α (which is found mainly in renal cells) by belzutifan (Welireg) may not provide a clear path to complete suppression of VHL-associated tumors.

XII. Proposed place in therapy for belzutifan (Welireg) is as an initial (first-line) agent for the treatment of VHL associated tumors in patients, who do not require immediate surgery; and it may be considered an option to prolong progression to malignancy and/or surgery. However, available clinical data do not support clinically meaningful outcomes in mortality, quality of life, and morbidity (e.g., measurable reduction in the need for surgery, and/ or progression to malignancy). At this time, the quality of the available evidence is considered low. Although an acceptable surrogate marker in oncology, ORR does not establish true causal relation between the intervention and effect. Given the slow natural progression of VHL disease, lack of comparator, and open-label trial design, medication efficacy and true clinical value of belzutifan (Welireg) remains uncertain.

capmatinib (Tabrecta)

I. Capmatinib (Tabrecta) is the first therapy FDA-approved for NSCLC with a mutation that leads to MET 14 exon 14 skipping. Other therapies that may be used in this setting include tepotinib

(Tepmetko), crizotinib (Xalkori®), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., nivolumab, pembrolizumab); however, available data is limited and response in this population is generally poor.

II. Capmatinib (Tabrecta) is FDA-approved in the metastatic setting. It was evaluated in GEOMETRY mono-1, an open-label, Phase 2, multi-cohort, single-arm trial. Patients with METex14 skipping mutation or MET-amplified disease across various treatment settings (e.g., treatment naïve vs pretreated) were included. Initial FDA-approval under accelerated pathway, was based on those with METex14 skipping mutation only, Cohorts 4 and 5b. Cohort 4 patients were previously treated with one or two lines of therapy and Cohort 5b included treatment-naïve patients. Patients had MET-dysregulated advanced NSCLC, with absence of EGFR or ALK mutations. Full FDA approval was granted based on additional data from Cohorts 6 and 7. Cohort 6 patients were previously treated, with majority receiving one prior line of therapy and Cohort 7 patients were treatment naïve. Cohorts 6 and 7 included patients with METex14 skipping mutation.

III. Primary efficacy outcomes were Overall Response Rate (ORR) and Duration of Response (DoR). Secondary outcomes were Progression-free Survival (PFS) and Overall Survival (OS); however, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life. Capmatinib (Tabrecta) was FDA-approved under the accelerated approval pathway based on ORR and DoR. Conversion to regular FDA approval was based on additional ORR and DoR data for 63 patients as well as an additional 22 months of follow up. Despite receiving regular FDA approval, the medication efficacy continues to remain uncertain. There a several trials underway for NSCLC and other cancer types.

IV. The safety of capmatinib (Tabrecta) is based on patients from all cohorts (n=334). There were 37% of patients that were exposed to therapy for at least six months and 22% were exposed for at least one year. The most common adverse events include peripheral edema, nausea, fatigue, vomiting, dyspnea, and anorexia.

V. Serious adverse events occurred in 53% of patients and included dyspnea, pneumonia, pleural effusion, physical health deterioration, and peripheral edema. These events occurred in at least 2% of patients, and there was one case of fatal pneumonitis. There are no contraindications. Capmatinib (Tabrecta) showed a 54% dose interruption rate, a 23% dose reduction rate, and a 16% permanent discontinuation rate due to adverse events.

VI. As of January 2023, The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC with a mutation that leads to MET exon 14 skipping give capmatinib (Tabrecta) a Category 2A, preferred recommendation. Tepotinib (Tepmetko) is also a preferred, Category 2A recommended treatment option. Crizotinib (Xalkori) has a Category 2A recommendation, useful in certain circumstances. These circumstances are not defined in the guideline.

VII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged

as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

futibatinib (Lytgobi)

I. Futibatinib (Lytgobi) is a selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR), FDA-approved for adult patients with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring an FGFR2 fusion or other rearrangements. Futibatinib (Lytgobi) is a once-daily orally administered tablet.

II. Futibaitinib (Lytgobi) is the third FGFR2 inhibitor and joins infigratinib (Truseltiq) and pemigatinib (Pemazyre), which are indicated for previously treated patients with advanced or metastatic CCA. It should be noted that as of March 2023, infigratinib (Truseltiq) is scheduled to be withdrawn from the US market.

III. The FDA approval for futibatinib (Lytgobi) is limited only to the treatment of iCCA. On the other hand, pemigatinib (Pemazyre) carris a broader FDA-approved indication for the treatment of CCA (iCCA and eCCA). National Comprehensive Cancer Network (NCCN) guidelines have included Futibaitinib (Lytgobi) alongside pemigatinib (Pemazyre) and infigratinib (Truseltiq) as a subsequent-line therapy, useful in CCA with FGFR2 mutations (Category 2A).

IV. Futibaitinib (Lytgobi) was studied in an ongoing open-label, single-arm, multi-cohort phase 1/ 2 trial (N= 103). Patients with unresectable, advanced, or metastatic iCCA, who had received at least one prior platinum-based systemic therapy were administered futibatinib (Lytgobi) for a median of 9.1 months. At median follow-up, an objective response rate (ORR) of 41.7% (95% CI, 32, 52) was reported, with all participants reporting a partial response (PR). Additionally, a median PFS of 8.9 months and median OS of 20 months were observed.

V. Futibaitinib (Lytgobi) was FDA-approved under the accelerated approval pathway. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

VI. The quality of evidence is considered low due to single-arm, open-label study design with unknown impact on clinically meaningful outcomes such as morbidity, mortality, health-related quality-of-life, or symptom improvement in treated patients. OS remains an exploratory outcome due to the observational study design and requires confirmation in a subsequent clinical trial. Additionally, the efficacy of futibatinib (Lytgobi) in comparison with, as well as after progression on pemigatinib (Pemazyre) remains unknown.

VII. Most CCA patients present with advanced-stage or unresectable tumors at diagnosis, wherein platinum-based chemotherapy (cisplatin with gemcitabine and/ or durvalumab (Imfinzi)) remains the standard of care. For patients, who progress on the first-line therapy, FOLFOX is the preferred subsequent-line option, along with 5-fluorouracil (5-FU), capecitabine, and paclitaxel as alternatives. Targeted therapies may be considered as subsequent-line options based on the

presence of amenable mutations (e.g., entrectinib (Rozlytrek) and larotrectinib (Vitrakvi) for CCA with NTRK gene fusions).

VIII. Currently, there are other clinical trials (Phase 1b / 2) ongoing for futibatinib (Lytgobi) in the settings of metastatic breast cancer, cholangiocarcinoma, endometrial cancer, urothelial cancer etc. as a monotherapy as well as in combination with other agents (e.g., binimitinib, pembrolizumab). These clinical trials are in early phases and as of January 2023, data is not available for review.

IX. Single-arm, open-label clinical trial may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, Overall Response Rate (ORR), despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. ORR is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

X. Targeted therapies in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the management of CCA based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to current molecularly targeted therapies presents a major clinical challenge. Additionally, the targeted therapy approach is also susceptible to failure due to escape mutations. To date, the clinical data for FGFR2 inhibitors do not support robust conclusions regarding their safety, efficacy, and long-term impact on disease outcomes.

XI. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines note that the best management for any patient with cancer is in a clinical trial setting, and participation in a trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading healthcare facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced iCCA. Despite the accelerated FDA approval, continued approval of futibatinib (Lytgobi) as a subsequent-line treatment of iCCA, remains contingent upon verification of clinical benefit in confirmatory trials.

mobocertinib (Exkivity)

I. Mobocertinib (Exkivity) is an oral EGFR tyrosine kinase inhibitor (TKI) that is being evaluated for exon 20 insertion mutant-positive NSCLC (EGFRex20ins-NSCLC) in those that have had disease progression on platinum-based chemotherapy. This specific type of NSCLC is thought to account for 2-3% of NSCLC cases annually, and is more commonly seen in those that do not have a smoking history.

II. Mobocertinib (Exkivity) is the second therapy specifically FDA-approved for EGFRex20ins-NSCLC. Amivantamab-vmjw (Rybrevant), an IV human antibody, was FDA-approved in May 2021. Approval was based off of the Phase 1 CHYRSALIS trial, a single-arm, open-label trial in 81 patients that previously progressed on platinum chemotherapy.

III. Platinum-based chemotherapy is utilized first-line for this condition, and is considered standard of care. Mobocertinib (Exkivity) is the first TKI specifically FDA-approved for this mutation. Other EGFR TKIs (e.g., osimertinib [Tagrisso]) have been used in this setting off-label; however, most cases of EGFRex20ins-NSCLC are resistant to those therapies.

IV. Interim results of the Phase 1/2 trial are being used to support accelerated FDA-approval. Mobocertinib (Exkivity) was granted Priority Review, as well as Breakthrough Therapy, Fast Track and Orphan Drug designations. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Continued Phase 2, as well as Phase 3 trials are underway to assess safety and efficacy. Both of these therapies are expected to be utilized in the second-line treatment setting; however, given expected preference for the targeted indication – use in the first-line setting may appeal to patients and providers. Mobocertinib (Exkivity) is being evaluated in a Phase 3, open-label trial versus platinum-based chemotherapy in patients with advanced or metastatic EGFRex20ins-NSCLC. Per ClinicalTrials.gov, the study is recruiting; however, there have been potential pauses in recruitment due to futility analyses.

V. Mobocertinib (Exkivity) is being evaluated in a Phase 1/2, single-arm, open-label trial in 114 patients with metastatic EGFRex20ins-NSCLC that were previously treated with platinum chemotherapy. Interim results showed an overall response rate (ORR). Other trial outcomes include duration of response (DoR), and progression-free survival (PFS). The quality of the evidence is low given the open-label and single-arm trial design, and small sample size. True medication efficacy is unknown due to the observational nature of the data. Additionally, the endpoints evaluated have not been correlated with meaningful outcomes such as improved survival or quality of life. The results are similar to those seen for amivantamab-vmjw (Rybrevant). Use of this therapy in any treatment setting is considered experimental and investigational at this time given the unknown clinical benefit and ongoing clinical trials to evaluate safety and efficacy.

VI. The safety profile is based on the 114 patients that have received therapy to date. Treatment related adverse events (AE) occurred in 99% of patients. Common AE: diarrhea 91%, rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), vomiting (30%), increased creatinine (25%), stomatitis (24%), pruritus (21%). Grade 3-4 AE occurred in 47% and 49% of patients were documented to have serious AE. Dose reduction due to AE occurred in 25% of patients, and AE leading to treatment discontinued occurred in 17% of patients. One patient experienced cardiac failure, a TRAE leading to death. Given the observational nature of the data in a small population, the severity and extent of AE that are due to the drug versus the disease are unknown at this time.

VII. NCCN guidelines for advanced or metastatic EGFRex20ins-NSCLC recommend platinum-based combination chemotherapy for first-line treatment, this is a Category 1 recommendation. Mobocertinib (Exkivity) and amivantamab-vmjw (Rybrevant) have been added as subsequent therapy options (Category 2A recommendation). The recommendations are specific to patients with an ECOG score 0-2, and for those with PS 3-4, best supportive care is recommended (Category 2A recommendation). Clinical trials are highly encouraged for all settings. ASCO provides similar recommendations for platinum-based combination chemotherapy in the first-

line setting; however, have not been updated to include the targeted therapies. Guidelines do not recommend conventional EGFR TKIs for this mutation, and ASCO recommends platinum chemotherapy after progression on a conventional EGFR TKI if one was utilized.

VIII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC notes that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC.

emigatinib (Pemazyre)

Treatment of Cholangiocarcinoma

I. Pemigatinib (Pemazyre) is the first targeted therapy for cholangiocarcinoma that harbors FGFR2 fusions or rearrangements. Pemigatinib (Pemazyre) is a second-line chemotherapy option. Guideline preferred first line chemotherapy is gemcitabine and cisplatin, while second-line options include mFOLFOX, FOLFIRI, and regorafenib (Stivarga).

II. Pemigatinib (Pemazyre) was evaluated in FIGHT-202, an open-label, single-arm, multi-cohort Phase 2 trial. Patients (N=146) with locally advanced or metastatic CCA, previously treated with at least 1 chemotherapy were included. FDA approval was based on the overall response rate (ORR) in patients with FGFR2 gene fusion or rearrangements.

III. The primary efficacy endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

IV. Pemigatinib (Pemazyre) received accelerated approval from the FDA based on ORR and DOR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 3 trial underway to assess pemigatinib (Pemazyre) monotherapy versus gemcitabine + cisplatin in the first-line treatment of CCA with FGFR2 alterations.

V. The safety profile of pemigatinib (Pemazyre) was based on adverse reactions observed in all cohorts during CT (N=146). The most common adverse events (≥20% incidence) included hyperphosphatemia, alopecia, nausea, diarrhea, nail toxicity, back pain, fatigue, dysgeusia, dry eyes, and serous retinal detachment. There are no specific contraindications to pemigatinib (Pemazyre); however, warnings and precautions include: ocular toxicity, hyperphosphatemia, GI toxicity and renal function. Pemigatinib (Pemazyre) showed 9% treatment discontinuation rate, 14% dose reductions rate, and 42% dose interruption rate due to adverse events.

VI. As of January 2023, The National Comprehensive Cancer Network (NCCN) treatment guideline for hepatobiliary cancer has included pemigatinib (Pemazyre) as second-line treatment with a

Category 2A recommendation. Pemigatinib (Pemazyre) is useful in treatment of tumor with confirmed FGFR2 fusions or rearrangements, and which are refractory to first line chemotherapy.

Treatment of Myeloid/Lymphoid Neoplasms

VII. Myeloid/lymphoid neoplasms (MLNs) with FGFR1 rearrangement are rare hematologic malignancies included in the World Health Organization (WHO) major category "MLNs with eosinophilia and rearrangements of PDGFRA, PDGFRB, FGFR1, or with PCM1-JAK2." In this group of neoplasms the formation of a fusion gene, or (rarely) from a mutation, results in the expression of an aberrant tyrosine kinase. MLNs with FGFR1 rearrangement are an extremely rare and aggressive that impacts less than 1 in 100,000 people in the United States per year with less than 100 patients reported worldwide as of 2010.

VIII. In August 2022, pemigatinib (Pemazyre) was approved for adults with relapsed or refractory myeloid/lymphoid neoplasms (MLNs) with fibroblast growth factor receptor 1 (FGFR1) rearrangement. Approval was based on interim results from the Phase 2 FIGHT-203 trial. FIGHT-203 was a multicenter, open-label, single-arm trial including patients with relapsed or refractory MLNs with FGFR1 rearrangement.

IX. Adult participants (N=28) who were not candidates for stem cell transplantation or other disease modifying therapy along with confirmed MLN with 8p11 rearrangement known to lead FGFR1 activation were included in the study population. The primary outcome measure was complete response (CR) rate and was reported per the morphologic disease type. Of the 18 patients with chronic phase in the marrow with or without extramedullary disease (EMD), 14 achieved CR (78%; 95% CI: 52, 94). The median time-to-CR was 104 days (range, 44 to 435). The median duration was not reached (range: 1+ to 988+ days). Of the 4 patients with blast phase in the marrow with or without EMD, 2 achieved CR (duration: 1+ and 94 days). Of 3 patients with EMD only, 1 achieved a CR (duration: 64+ days). Secondary endpoints reported in the interim results included complete cytogenic response (CCyR). In all 28 patients (including 3 patients without evidence of morphologic disease), the CCyR rate was 79% (22/28; 95% CI: 59, 92). Progression free survival and overall survival are to be reported at trial conclusion.

X. The safety profile of pemigatinib (Pemazyre) was based on 34 patients. All patients experienced ≥ 1 treatment-emergent adverse event (TEAE). The most common any-grade hematologic TEAEs were anemia (35%), thrombocytopenia (12%), and neutropenia (3%). The most common nonhematologic TEAEs (any grade) were hyperphosphatemia (68%), alopecia (59%), and diarrhea (50%). Grade 3 and 4 TEAEs occurred in 85% of patients. Reported TEAEs led to treatment interruption in 65% of patients, dose reduction in 59% of patients, and discontinuation in 12% of patients.

XI. Based on the interim results posted trial does not offer OS or PFS data. Overall survival and progression free survival data is to be reported as the conclusion of the phase 2 trial. Interim results without OS data limit the applicability of this treatment outside of a clinical trial space. Current NCCN guidelines prefer to clinical trial, and now pemigatinib (Pemazyre), as first line. However, there is a caveat in the guidelines that early referral to allogeneic HCT should be

considered for eligible patients, since TKI therapy alone does not result in durable remissions. Given the lack of durability in TKI monotherapy, including pemigatinib (Pemazyre), the level of evidence is considered low.

XII. An FDA-approved test for detection of FGFR1 rearrangement in patients with relapsed or refractory myeloid/lymphoid neoplasm for selecting patients for treatment with pemigatinib (Pemazyre) is not available. However, FGFR 1 rearrangement can be detected with an 8p11 translocation on conventional cytogenetics and/or on break-apart fluorescence in situ hybridization testing (FISH).

pirtobrutinib (Jaypirca)

I. Pirtobrutinib (Jaypirca) is a non-covalent (i.e., reversable) Bruton Tyrosine Kinase inhibitor (BTKi), FDA-approved under an accelerated approval pathway for the treatment of relapsed or refractory mantle cell lymphoma (R/R MCL) after at least two lines of systemic therapy, including a BTKi. Additionally, pirtobrutinib (Jaypirca) was approved under an accelerated approval pathway for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) after at least two prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Continued approval of pirtobrutinib (Jaypirca) is contingent upon verification of clinical benefit in confirmatory trials.

II. Safety and efficacy of pirtobrutinib (Jaypirca) has not been established in a pediatric population.

III. Efficacy and safety of pirtobrutinib (Jaypirca) in combination with other oncology agents has not been evaluated by clinical trials.

IV. The diagnosis and management of MCL and CLL/SLL requires detailed clinical examination in combination with advanced testing. Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by an oncologist or hematologist is required.

pralsetinib (Gavreto)

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers.

II. Pralsetinib (Gavreto) was evaluated in one Phase 1/2, dose expansion and escalation, multi-cohort, open-label, single-arm trial. Interim results showed potential antitumor activity via overall response rate (ORR) and duration of response (DoR). The primary outcome is ORR, and the secondary outcomes include DoR and proportion of patients with DoR six months or greater.

III. For RET fusion-positive NSCLC: Patients with advanced or metastatic disease that were either treatment naïve (n=27) or progressed on platinum-based chemotherapy (n=87) were assessed. For RET-mutant MTC, patients were either treatment naïve (n=29) or progressed on cabozantinib (Cometriq) or vandetanib (Caprelsa) (n=55). All patients had progressed on standard of care for RET-fusion-positive TC (n=9).

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=87)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=9)**
ORR (%)	57% (46, 68)	60% (46, 73)	89% (52, 100)

CR (%)	5.7%	1.8%	0
PR (%)	52%	58%	89%
DoR (mo)	NR (15.2-NE)	NR (15.1, NE)	NR (NE, NE)
DoR ≥ 6 mo (%)	80%	79%	100%
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=27)**	**RET-Mutant MTC (n=29)**	**RET Fusion-Positive TC***
ORR (%)	70% (50, 86)	66% (46, 82)	N/A
CR (%)	11%	10%	
PR (%)	59%	55%	
DoR (mo)	9 (6.3-NE)	NR (NE, NE)	
DoR ≥ 6 mo (%)	58%	84%	

*All patients were refractory to standard therapy.

IV. The quality of the evidence is considered low given the open-label and single-arm trial design and small sample size; thus, true medication efficacy remains uncertain given the nature of observational data. Additionally, outcomes such as ORR and DoR have not been correlated with clinically meaningful outcomes such as improved survival or quality of life.

V. Phase 3 trial, AcceleRET, is planned to evaluate pralsetinib (Gavreto) in advanced or metastatic, RET fusion-positive NSCLC versus platinum-based chemotherapy. It will be evaluated in an open-label, randomized trial for first-line metastatic systemic therapy. Outcomes of interest include PFS, OS, time to intracranial progression, and quality of life. This international trial has a target enrollment of 250 patients, with an estimated completion date of November 2024.

VI. Pralsetinib (Gavreto) was initially approved under accelerated approval for RET fusion-positive NSCLC, advanced or metastatic. The conversion to regular approval was based on data from an additional 123 patients and 25 months of additional follow-up to assess durability of response. A total of 237 participants with locally advanced or metastatic RET fusion-positive NSCLC demonstrated an ORR of 78% (95% CI: 68, 85) with a median DOR of 13.4 months (95% CI: 9.4, 23.1). Among 130 patients previously treated with platinum-based chemotherapy, ORR was 63% (95% CI: 54, 71) with a median DOR of 38.8 months (95% CI: 14.8, not estimable). NCCN guidelines include pralsetinib (Gavreto) and selpercatinib (Retevmo) as preferred first-line and subsequent-line therapy (category 2a). Cabozantinib (Cometriq) is listed as useful in certain circumstances (category 2a) and vandetanib (Caprelsa) was recently removed as a treatment option.

VII. RET fusion-positive thyroid cancer: NCCN recommends radioactive iodine as first line therapy. In those not amenable to RAI, treatment options include selpercatinib (Retevmo) (category 1) and pralsetinib (category 2B).

VIII. Pralsetinib (Gavreto) was previously approved under an accelerated pathway for treatment of advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients aged 12 years and older. In June 2023, the manufacturer was unable to provide confirmatory MTC study results to fulfill the FDA post marketing requirement and voluntarily withdrawn this indication from the market. This decision is not based on efficacy or safety of pralsetinib and does not affect other approved indications.

IX. Safety data is based on a pooled population of 438 patients. Common adverse events (AE) that occurred ≥15% or more of the population: fatigue, constipation, musculoskeletal pain,

hypertension, edema, diarrhea, dry mouth, cough, and pneumonia. Serious AE that occurred ≥2%: pneumonia, sepsis, UTI, pyrexia, increased ALT/AST, and phosphatase, and decreased lymphocytes, neutrophils, hemoglobin, phosphate, calcium, sodium, and platelets. Fatal AE occurred in 5% of patients (pneumonia and sepsis) in the NSCLC cohort. Warnings and precautions: interstitial lung disease, hypertension, hepatotoxicity, hemorrhage, tumor lysis syndrome, impaired wound healing, and embryo-fetal toxicity.

X. Dose reductions due to AE occurred in up to 67% of patient, which varied by cohort. Dose reductions occurred in up to 44%, and permanent discontinuation rate in up to 15%. The true safety profile of pralsetinib (Gavreto) remains unknown given the observational evaluation.

XI. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents may remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for the treatment of majority of cancer types (e.g., NSCLC, cholangiocarcinoma, neuroendocrine, sarcoma) note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendations from NCCN, continued approval of selpercatinib (Retevmo) as a subsequent-line treatment of tumors harboring RET fusions in thyroid cancer refractory to radioactive iodine, remains contingent upon verification of clinical benefit in confirmatory trials.

selpercatinib (Retevmo)

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Selpercatinib (Retevmo) is the first FDA-approved therapy that targets RET alterations specifically.

II. Selpercatinib (Retevmo) is a kinase inhibitor of RET. It is FDA-approved for adults with metastatic RET fusion-positive non-small-cell lung cancer (NSCLC), advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients age 12 years and older, and advanced or metastatic RET fusion-positive thyroid cancer who are radioactive iodine (RAI)-refractory in patients age 12 years and older. As of September 2022, selpercatinib (Retevmo) also received accelerated approval for the treatment of adult patients with locally advanced or metastatic

solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.

III. RET fusion-positive NSCLC, advanced or metastatic: First-line treatment options include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (not FDA-approved for lung cancer) or combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed, and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine).

IV. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).

V. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, radioactive iodine (RAI) is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).

VI. **Clinical Trial in the setting of NSCLC, MTC, and Thyroid Cancer:**

- Selpercatinib (Retevmo) is being evaluated in one Phase 1/2, open-label, multi-cohort, single-arm trial in patients with RET abnormal, advanced solid tumors Interim results showed potential antitumor activity, based on objective response rate (ORR), in the three FDA-approved settings. Additional outcomes: progression-free survival (PFS) and overall survival (OS) at 12 months.
- RET fusion-positive NSCLC: Patients were advanced or metastatic, progressed on platinum-based chemotherapy or were systemic treatment naïve. Over half of pretreated patients also received anti-PD1/PD-L1 therapy (n=58).
- RET-mutant MTC: 98% had metastatic disease, and patients were previously treated with cabozantinib (Cometriq) and/or vandetanib (Caprelsa) or were treatment naïve to both. Ten patients were previously treated with platinum chemotherapy or anti-PD1/PD-L1 therapy.
- RET fusion-positive TC: Patients were not amenable to RAI therapy and may have been treated with lenvatinib (Lenvima) and/or sorafenib (Nexavar), or were naïve to both.

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=105)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=19)**
ORR (n)	67 (64%)	38 (69%)	15 (79%)
CR (n)	2 (2%)	5 (9%)	1 (5%)
PR (n)	65 (62%)	33 (60%)	14 (74%)
PFS (months)	16.5 (13.7-NE)	NE	20 (9.4-NE)
OS, 12 months (%)	88%	87%	NR
Clinical Efficacy in Treatment-Naïve Patients			

Outcome	RET Fusion+ NSCLC (n=39)	RET-Mutant MTC (n=88)	RET Fusion-Positive TC (n=8)
ORR (n)	33 (85%)	64 (73%)	8 (100%)
CR (n)	0	10 (11%)	1 (12.5%)
PR (n)	33 (85%)	54 (61%)	7 (87.5%)
PFS (months)	NE	23.6 (NE-NE)	NE
OS, 12 months (%)	NR	NR	NR

- For the treatment of RET-mutant medullary thyroid cancer and for RET-fusion positive thyroid cancer, selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway based on ORR. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. This therapy is being evaluated in multiple other clinical Phase 2 and Phase 3 trials. The quality of the evidence is considered low at this time given the open-label trial design and lack of comparator arm. Given the observational data, medication efficacy remains uncertain. Additionally, the medication has an unfavorable safety profile.
- As of June 2020, safety data are based on a pooled population in 702 patients, 65% were exposed for six months or greater, and 34% were exposed for over one year. Ninety-five percent of patients received 160 mg twice daily.

VII. **Clinical Trial in the setting solid tumors with RET-fusion:**

- Selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway for the treatment of adult patients with locally advanced or metastatic solid tumors with a RET gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options. This indication and FDA approval is based on an ongoing phase 1/ 2 single-arm, open-label clinical trial (basket trial, LIBRETT001). Selpercatinib (Retevmo) was administered to a tumor agnostic cohort of 41 patients with solid tumors harboring RET fusions, which consisted of following tumor types: pancreatic cancer (12), colon (10), salivary gland (4), sarcoma (3), unknown primary (3), breast (2), skin carcinoma (2), cholangiocarcinoma (2), xanthogranuloma (2), and carcinoid, ovarian, pulmonary sarcoma, rectal neuroendocrine, and small intestinal tumors (1 patient each). Majority of these patients were pre-treated and progressed after one to two lines of systemic therapies.
- At a median duration of follow-up 18.8 months, selpercatinib (Retevmo) reported a 43.9% (28.5 – 60.3) objective response rate (ORR) across all tumor types, as measured by a blinded independent committee review. When measuring the duration of response and progression-free survival outcomes, more than half of the patients were censored due to being lost to follow up. Due to the lack of causality of ORR with long-term clinically meaningful outcomes of morbidity and mortality, the quality of the current data is considered low. It is unknown if selpercatinib

(Retevmo) may provide true treatment benefit if and when tested in a larger comparator-controlled trial in the setting of solid tumors with RET fusions.
- Although the adverse reaction profile for selpercatinib (Retevmo) varied across participants with different tumor types, the basket trial did not provide significant safety signals other than those previously reported during the clinical trial in the setting of NSCLC and thyroid cancer.

VIII. Warnings and precautions: hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, impaired wound healing, and embryo-fetal toxicity. There are no contraindications. Serious adverse reactions occurred in 33% of patients. The most frequent was pneumonia. Fatal adverse reactions occurred in 3% of individuals due to sepsis (n=1), cardiac arrest (n=3), respiratory failure (N=3).

IX. Common adverse reactions (≥25%): increase liver enzymes, laboratory abnormalities (≥25% each, glucose, leukocytes, albumin, calcium, creatinine, alkaline phosphatase, platelets, cholesterol, sodium), dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation. Permanent discontinuation due to adverse reactions occurred in 5%, dose interruptions in 42%, and dose reduction in 31% of patients.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

XI. Targeted therapies in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the management of solid tumors based on histology and actionable mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Additionally, targeted therapy approach is also susceptible to failure due to acquired resistance and escape mutations.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents may remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for the treatment of majority of cancer types (e.g., NSCLC, cholangiocarcinoma, neuroendocrine, sarcoma) note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendations from NCCN, continued approval of selpercatinib (Retevmo) as a subsequent-line treatment of

tumors harboring RET fusions, remains contingent upon verification of clinical benefit in confirmatory trials.

sotorasib (Lumakras)

I. Sotorasib (Lumakras) is the first therapy FDA-approved for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It is also the first orally administered drug in this setting.
II. KRAS mutations account for up to 25% of mutations in NSCLC and are often associated with resistance to targeted therapies and generally poor patient outcomes in patients with cancer. KRAS G12C, a subset of KRAS mutations, accounts for about 13% of mutations in NSCLC.
III. Most patients with NSCLC including *KRAS*-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, paclitaxel. Additionally, targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.
IV. Sotorasib (Lumakras) received FDA-approval as a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy. The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC has given sotorasib (Lumakras) a Category 2A recommendation as a subsequent-line treatment for NSCLC harboring KRAS G12C mutation, after progression on or after conventional chemotherapy and / or immunotherapy.
V. Sotorasib (Lumakras) was evaluated in CodeBreak100, an ongoing Phase 1 / 2, open-label, single-arm trial. Patients (N=126) with KRAS G12C mutated NSCLC, who had disease progression after chemotherapy and/ or immunotherapy were included. All patients received sotorasib (Lumakras) 960 mg orally once a day for a median 15.3 months. Although this is an ongoing clinical trial with the goal to assess efficacy of sotorasib (Lumakras) for multiple oncological settings (NSCLC as well as other solid tumors harboring KRAS mutations), the FDA-approval for sotorasib (Lumakras) was based on outcomes from NSCLC cohort.
VI. The primary efficacy outcome for CodeBreak100 trial was Overall Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Sotorasib (Lumakras) showed an ORR of 37.1% (95% CI; 28.6, 46.2), which included 3.2% complete responses (CR) and 33.9% partial responses (PR). Additionally, participants in this cohort showed DoR of 11.1 months (95% CI; 6.9, NE), PFS 6.8 months (95% CI; 5.1, 8.2), and OS 12.5 months (95% CI; 10.0, NE).
VII. Based on the data from CodeBreak100 trial, the quality of the evidence to support efficacy of sotorasib (Lumakras) is considered low at this time. Given the lack of comparator and single-arm open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy remains uncertain.
VIII. The safety of sotorasib (Lumakras) was based on trial participants (n=126) exposed to therapy. The most common adverse events include diarrhea, nausea, fatigue, and aspartate

aminotransferase increase. Serious adverse events (grade 3 or higher) occurred in 42.1% patients and included dyspnea, pneumonitis, and elevation of liver enzymes. At this time, patient population and duration of exposure to sotorasib (Lumakras) are limited to clinical trial participants. Thus, real-world safety profile and patient experience with this drug remain undefined. Based on single-arm, open-label clinical trial in small sample population, the overall safety profile of sotorasib (Lumakras) is largely unknown; thus, it is unknown at this time if benefits of this medication outweigh the risks.

IX. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for sotorasib (Lumakras) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, sotorasib (Lumakras) is being studied as a combination regimen with other targeted therapies (e.g., MEK inhibitor, EGFR inhibitor, SHP2 inhibitor) for the treatment of NSCLC. These clinical trials are in early phases and data are not available for review.

X. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

XI. Targeted therapies for treatment of NSCLC have garnered interest in recent years and may be considered part of a paradigm shift in the management of NSCLC based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to current molecularly targeted therapies in lung cancer presents a major clinical challenge. Additionally, targeted therapy approach is also susceptible to failure due to escape mutations.

XII. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) has been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). Efficacy and safety of sotorasib (Lumakras) in comparison with, or in combination with, currently established regimens, has not been studied and remains unknown.

XIII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC notes that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, and category 2A recommendation from NCCN, continued approval of sotorasib (Lumakras) as a second-line

treatment of NSCLC, remains contingent upon verification of clinical benefit in confirmatory trials. As of August 2021, a Phase 3 randomized clinical trial (CodeBreak200) to assess efficacy and safety of sotorasib (Lumakras) in comparison with docetaxel, as a subsequent-line treatment for NSCLC, is underway. Additionally, expanded access program via manufacturer, as part of the ongoing clinical studies of sotorasib (Lumakras), remains a practical option and an alternative path to treatment for qualifying patients.

tepotinib (Tepmetko)

I. Tepotinib (Tepmetko) is a tyrosine kinase inhibitor that targets mesenchymal-epithelial transition (MET) and is currently being evaluated in Non-Small Cell Lung Cancer (NSCLC) that contains a mutation that leads to MET exon 14 skipping. The clinical trial dose is 500 mg orally once daily.

II. Tepotinib (Tepmetko) is the second therapy FDA-approved for this specific NSCLC mutation, joining capmatinib (Tabrecta). Other therapies that have been utilized in this setting include crizotinib (Xalkori), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., pembrolizumab); however, available data to support efficacy in this population is limited, and response to therapy is generally poor.

III. Place in therapy is likely to be in the advanced or metastatic setting based on the population being evaluated in the clinical trial, and may be utilized as first-line in these stages; however, given the limited safety and efficacy data to support its use, other therapies may be considered prior to tepotinib (Tepmetko). As of October 2020, the NCCN treatment guidelines had not yet included tepotinib (Tepmetko). Tepotinib (Tepmetko) is mentioned in the ESMO treatment guideline as a treatment option for this population, alongside capmatinib (Tabrecta) and investigational agent savolitinib.

IV. The pivotal trial for tepotinib (Tepmetko) is the VISION trial, which is an open-label, Phase 2, multi-cohort, single-arm, ongoing trial. Patients with MET exon 14 skipping mutations or MET-amplified disease across various treatment settings (e.g., treatment naïve vs. pretreated) were included in the trial. Patients were negative for EGFR mutations or ALK rearrangements, and those with brain metastases were allowed. Ninety-nine patients are being evaluated for efficacy, and the safety profile is based on 152 patients. The average patient age was 74 years, 97% had metastatic disease, 43% were treatment native in the advanced/metastatic setting, 33% received one prior therapy, and 11% had two or more prior therapies. Japanese patients were excluded, due to an ongoing trial specific to that population.

V. Objective response was seen in 46 patients (46%), all of which were partial responses. Duration of response was 11.1 months, progression-free survival was 8.5 months, overall survival 17.1 months, and EORTC-QLQ-LC13 cough symptom quality of life scores showed a 13-15 point reduction.

VI. Tepotinib (Tepmetko) was granted Breakthrough Therapy designation, Priority Review, and is being evaluated under FDA Real-Time Oncology Review (RTOR) pilot program – intended to be a

more efficient review process to bring safe and effective treatment to patients as early as possible. The application is supported by the results of the Phase 2, ongoing VISION study that has shown potential anti-tumor activity via response rate.

VII. True medication safety and efficacy of tepotinib (Tepmetko) remain unknown given the observational nature of the trial (i.e., lack of comparator arm and open-label study design).

VIII. Safety of tepotinib (Tepmetko) has been evaluated in 152 patients, with a median exposure of 6.9 months. Eighty-nine percent of patients experienced treatment related adverse events (AE). Common AE were peripheral edema (63%), nausea (26%), diarrhea (26%), creatinine increase (18%), hypoalbuminemia (16%), amylase increase (11%), lipase increase (9%), asthenia (8%), anorexia (8%), pleural effusion (8%), and alopecia (8%).

IX. Grade 3 or 4 AE occurred in 28% of patients, mainly peripheral edema and amylase and lipase increases. Serious AE's occurred in 15%, 11% permanently discontinued due to AE's overall, and 33% of patents had a dose reduction due to AE's. Peripheral edema was the most common reason for discontinuation or dose reduction. Sixteen percent of patients had dose reduction and 18% had dose interruption based on this AE alone. Twenty-one patients had an AE leading to death while on tepotinib (Tepmetko), one of which was due to interstitial lung disease determined as related to tepotinib (Tepmetko) therapy. Currently there is unknown clinical benefit/value of tepotinib (Tepmetko), and the safety risks are outweighing until further evidence is available to support safety and efficacy of tepotinib (Tepmetko). Of note, tepotinib (Tepmetko) is in several ongoing clinical trials alone and in combination with other chemotherapeutic agents for NSCLC.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

References

adagrasib (Krazati®)

1. Jänne PA, Riely GJ, et al. Adagrasib in Non-Small-Cell Lung Cancer Harboring a *KRASG12C* Mutation. N Engl J Med. 2022 Jul 14;387(2):120-131.
2. Takamasa K, Suda K, et al. KRAS Secondary Mutations That Confer Acquired Resistance to KRAS G12C Inhibitors, Sotorasib and Adagrasib, and Overcoming Strategies: Insights From In Vitro Experiments. J Thor Oncol. 2021 16 (8): 1321-1332.
3. Black RC, Khurshid H. NSCLC: an update of driver mutations, their role in pathogenesis and clinical significance. R I Med J. (2013). 2015; 98: 25-8.
4. Aggarwal S, Whipple S, Hsu H, et al. 1339P: Clinicopathological characteristics and treatment patterns observed in real-world care in patients with advanced non-small cell lung cancer (NSCLC) and KRAS G12C mutations in the Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB). *Ann Oncol*. 2020;31: S860.

5. Hayashi H, Okamoto I, Taguri M, Morita S, & Nakagawa K. Post-progression survival in patients with advanced non-small-cell lung cancer who receive second-line or third-line chemotherapy. *Clin Lung Cancer*. 2013; 14:261-266.
6. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V3.2022. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated March 16, 2022.

avapritinib (Ayvakit™)

1. Ayvakit [Prescribing Information]. Blueprint Medicines: Cambridge, MA. March 2023.
2. Ayvakit [Manufacturer e-dossier]. Blueprint Medicines: Cambridge, MA. June 2021.
3. National Comprehensive Cancer Network. NCCN Guidelines: Gastrointestinal Stromal Tumors. Version 1.2023. Accessed April 28, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf.
4. Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv68-iv78.
5. Heinrich M, Jones RL, von Mehren M, et al. Clinical Response to Avapritinib by RECIST and Choi Criteria in ≥4th Line and PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST). Presented at: Connective Tissue Oncology Society 2019 Annual Meeting. November 15, 2019; Tokyo, Japan.
6. Jones RL, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumors: Long-term efficacy and safety data from the NAVIGATOR phase 1 trial. European Journal of Cancer. 145(2021); 132-142.
7. Kang Y-K, George S, Jones RL, et al. Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: a randomized, open-label phase III study. J Clin Oncol. Published online August 3, 2021. doi:10.1200/JCO.21.00217
8. Blueprint Medicines receives complete response letter from FDA for avapritinib new drug application for the treatment of fourth-line gastrointestinal stromal tumor. News release. Blueprint Medicines. May 15, 2020. Accessed April 28, 2023. https://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-receives-complete-response-letter-fda
9. National Comprehensive Cancer Network. NCCN Guidelines: Systemic Mastocytosis. Version 2.2022. Accessed April 28, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf.
10. Gotlib J. Advanced systemic mastocytosis: Management and prognosis. In: Post T, ed. UpToDate. UpToDate; 2022. Accessed April 24, 2023. www.uptodate.com
11. DeAngelo DJ, et al. PATHFINDER: Interim Analysis of Avapritinib in Patients with Advanced Systemic Mastocytosis (AdvSM). Presented at the American Association for Cancer Research Annual Meeting. May 2021.
12. Radia DH, et al. Avapritinib induces responses in patients with advanced systemic mastocytosis (AdvSM), regardless of prior midostaurin therapy. Poster Presentation at BSH 2021 Virtual ASM. April 2021.
13. Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by *KIT/PDGFRA* mutations. *Sci Transl Med*. 2017;9(414):eaao1690. doi:10.1126/scitranslmed.aao1690
14. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia*. 2022;36(8):2108-2120. doi:10.1038/s41375-022-01615-z
15. Reiter A, Gotlib J, Álvarez-Twose I, et al. P1014: OVERALL SURVIVAL IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS RECEIVING AVAPRITINIB VERSUS MIDOSTAURIN OR CLADRIBINE. *Hemasphere*. 2022;6(Suppl):904-905. Published 2022 Jun 23. doi:10.1097/01.HS9.0000846924.89785.04
16. Reiter A, Schwaab J, DeAngelo DJ, et al. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. *Blood Adv*. 2022;6(21):5750-5762. doi:10.1182/bloodadvances.2022007539
17. DeAngelo DJ, Radia DH, George TI, et al. An updated analysis on safety and efficacy of avapritinib in patients with advanced systemic mastocytosis from the explorer clinical study: long-term efficacy and safety. *Blood*. 2022;140(Supplement 1):3932-3934.
18. Gotlib J, Schwaab J, Shomali W, et al. Proposed European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases (ECNM-AIM) Response Criteria in Advanced Systemic Mastocytosis. *J Allergy Clin Immunol Pract*. 2022;10(8):2025-2038.e1. doi:10.1016/j.jaip.2022.05.034

19. Hartmann K, Escribano L, Grattan C, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the european competence network on mastocytosis; the american academy of allergy, asthma & immunology; and the european academy of allergology and clinical immunology. Journal of Allergy and Clinical Immunology. 2016;137(1):35-45.
20. Weiler CR, Austen KF, Akin C, et al. Aaaai mast cell disorders committee work group report: mast cell activation syndrome (Mcas) diagnosis and management. Journal of Allergy and Clinical Immunology. 2019;144(4):883-896.
21. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2021;96(4):508-525. doi:10.1002/ajh.26118
22. Akin C. Indolent and smoldering systemic mastocytosis: Management and prognosis. In: Post T, ed. UpToDate. UpToDate; 2021. Accessed May 1, 2023. www.uptodate.com
23. Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, Versus Placebo in Patients With Indolent Systemic Mastocytosis (PIONEER). ClinicalTrials.gov identifier: NCT03731260. Updated September 20, 2022. Accessed May 1, 2023.
24. Study to Evaluate Efficacy and Safety of BLU-263 Versus Placebo in Patients With Indolent Systemic Mastocytosis (HARBOR). ClinicalTrials.gov identifier: NCT04910685. Updated April 6, 2023. Accessed May 1, 2023.
25. Akin C, Norregaard C, Roche M, Sullivan E, Siebenhaar F. Utility of a validated disease-specific measure to assess symptomology in patients with indolent systemic mastocytosis (ISM). Poster #220. Presented at the 2023 AAAAI Annual Meeting, February 24-27, 2023.
26. Castells M, Gotlib J, Henneke OE, et al. Detailed data from registrational PIONEER study demonstrate broad impact of AYVAKIT in patients with ISM. Powerpoint Presentation. Presented at the 2023 AAAAI Annual Meeting, February 27, 2023. https://ir.blueprintmedicines.com/static-files/60f73c28-4394-48e5-952a-e75a8d558250
27. Expanded Access Program (EAP) for Avapritinib. ClinicalTrials.gov identifier: NCT04714086. Updated November 17, 2022. Accessed May 1, 2023.

belzutifan (Welireg™)

7. Belzutifan (Welireg) [Prescribing Information]. Merck Sharp & Dohme Corp., Whitehouse Station, NJ. August 2021.
8. Srinivasan R, Donskov F, Iliopoulos O, et al. Phase 2 Study of Belzutifan (MK-6482), an Oral Hypoxia inducible Factor 2α Inhibitor, for Von Hippel-Lindau Disease–associated Clear Cell Renal Cell Carcinoma. Abstract #4555. Presented at: American Society of Clinical Oncology (ASCO); June 4-8, 2021; Virtual Meeting.
9. Jonasch E, Donskov F, Iliopoulos O, et al. Phase 2 study of the oral HIF-2α inhibitor MK-6482 for Von Hippel-Lindau disease-associated renal cell carcinoma. Abstract #5003. Presented at: American Society of Clinical Oncology (ASCO); May 29-31, 2020; Virtual Meeting.
10. NCCN Clinical practice Guidelines in Oncology for kidney cancer; V2.2022; updated September 8th, 2021.

capmatinib (Tabrecta™)

1. Tabrecta [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. August 2022.
2. Awad MM. Impaired c-Met receptor degradation mediated by MET exon 14 mutations in non-small-cell lung cancer. J Clin Oncol. 2016;34(8):879-881.
3. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of MET in lung cancer. Cancer Res. 2006;66(1):283-289.
4. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V1.2023. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated December 22, 2022.
5. Sabari JK, Montecalvo J, Chen R, et al. PD-L1 expression and response to immunotherapy in patients with MET exon 14-altered non-small cell lung cancers (NSCLC). Oral presentation presented at: American Society of Clinical Oncology (ASCO) Annual Meeting. June 2-6, 2017; Chicago, IL.
6. Drilon A, Clark J, Weiss J, et al. Updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. Abstract presented at: IASLC 19th World Conference on Lung Cancer. September 23-26, 2018.
7. Novartis. AMCP Formulary Dossier Version 4.1, Tabrecta (capmatinib). May 2020.
8. Novartis. Capmatinib (Tabrecta) METex14 Metastatic NSCLC Overview. January 2023.

futibatinib (Lytgobi®)

11. Goyal L, Meric-Bernstam F, Hollebeque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. J Clin Oncol 2022;40: Abstract 4009.
12. Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, Tran B, Kelley RK, Park JO, Javle M, He Y, Benhadji KA, Goyal L. Futibatinib, an Irreversible FGFR1-4 Inhibitor, in Patients with Advanced Solid Tumors Harboring *FGF*/*FGFR* Aberrations: A Phase I Dose-Expansion Study. Cancer Discov. 2022 Feb;12(2):402-415. doi: 10.1158/2159-8290.CD-21-0697. Epub 2021 Sep 22. PMID: 34551969.
13. Lytgobi. Package insert. Taiho Pharmaceutical Co. Ltd; September 2022.
14. National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 3.2022). NCCN. October 14, 2022. Accessed November 7, 2022. hepatobiliary.pdf (nccn.org)

mobocertinib (Exkivity™)

9. Riely GJ, Neal JW, Camidge DR, et al. Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with egfr exon 20 insertion mutations from a phase I/II trial. Cancer Discov. 2021;11(7):1688-1699.
10. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Non-Small Cell Lung cancer. V6.2021. Updated September 30,2021. Accessed October 6, 2021. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450
11. Hanna NH, Robinson AG, Temin S, et al. Therapy for stage iv non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol. 2021;39(9):1040-1091.
12. Rybrevant [Prescribing Information]. Janssen Pharmaceuticals. Horsham, PA. May 2021.
13. American Cancer Society. Treatment non-small cell lung cancer. Accessed August 23, 2021. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell.html.

pemigatinib (Pemazyre™)

1. Krasinskas A, Pawlik TM, et al. Distal bile duct. In: AJCC Cancer Staging Manual, 8th, Amin MB. (Ed), AJCC, Chicago 2017. p.317.
2. Aloia T, Pawlik TM, et al. Intrahepatic bile ducts. In: AJCC Cancer Staging Manual, 8th, Amin MB (Ed), AJCC, Chicago 2017. p.295.
3. Razumilava, N; Gores, GJ. "Cholangiocarcinoma". Lancet. 2014, 383, (9935): 68–79.
4. Patel N; Benipal B. 2019, Incidence of Cholangiocarcinoma in the USA from 2001 to 2015: A US Cancer Statistics Analysis of 50 States. Cureus. 2019;11(1): e3962.
5. Valle J, Wasan H, et al. Cisplatin plus gemcitabine vs gemcitabine for biliary tract cancer. N. Engl. J. Med. 2010; 362(14): 1273-81.
6. Blechacz B. Cholangiocarcinoma: Current Knowledge and New Developments. Gut Liver 2017; 11(1):13-26.
7. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. Nature Genetics 2015; 47: 1003-10.
8. Krook MA, Lenyo A, Wilberding M, et al. Efficacy of FGFR inhibitors and combination therapies for acquired resistance in FGFR2-fusion cholangiocarcinoma. Molecular Cancer Therapeutics 2020; 19: 847-57.
9. National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 3.2022). NCCN. October 14, 2022. Accessed October 26, 2022. hepatobiliary.pdf (nccn.org)
10. Abou-alfa GK et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicenter, open-label, phase 2 study. Lancet Oncol. 2020 May;21(5):671-684. (NCT02924376)
11. A study to evaluate the efficacy and safety of pemigatinib versus chemotherapy in unresectable or metastatic cholangiocarcinoma (FIGHT-302), clinicaltrials.gov; NCT03656536. https://clinicaltrials.gov/ct2/show/NCT03556536.
12. National Comprehensive Cancer Network. Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (Version 2.2022). NCCN. October 18, 2022. Accessed October 26, 2022.
13. Pemazyre. Package insert. Incyte Corporation; 2022.
14. Pemazyre (pemigatinib) product dossier. Incyte Corporation. September 14, 2022.
15. Gotlib J, Kiladjian JJ, Vannucchi A, et al. A Phase 2 Study of Pemigatinib (FIGHT-203; INCB054828) in Patients with Myeloid/Lymphoid Neoplasms (MLNs) with Fibroblast Growth Factor Receptor 1 (FGFR1) Rearrangement (MLN FGFR1). *Blood*. 2021; 138 (Supplement 1): 385. doi: https://doi.org/10.1182/blood-2021-148103

pirtobrutinib (Jaypirca™)

1. Jaypirca. Package Insert. Lilly USA LLC; January 2023.
2. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021;397(10277):892-901. doi:10.1016/S0140-6736(21)00224-5
3. National Comprehensive Cancer Network. B-Cell Lymphoma. NCCN. February 8, 2023. Accessed February 9, 2023. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
4. Cohen JB, Shah NN, Alencar AJ, et al. MCL-133 Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results From the Phase 1/2 BRUIN Study. Clin Lymphoma Myeloma Leuk. 2022;22 Suppl 2:S394-S395. doi:10.1016/S2152-2650(22)01569-5
5. Lilly. U.S. FDA Approves Jaypirca™ (pirtobrutinib), the First and Only Non-Covalent (Reversible) BTK Inhibitor, for Adult Patients with Relapsed or Refractory Mantle Cell Lymphoma After at Least Two Lines of Systemic Therapy, Including a BTK Inhibitor. Updated January 27, 2023. Accessed January 30, 2023.
6. Pirtobrutinib (Jaypirca) product dossier. Eli Lilly and Company. February 1, 2023.
7. Mato AR, Woyach JA, Brown JR, et al. Pirtobrutinib after a Covalent BTK Inhibitor in Chronic Lymphocytic Leukemia. N Engl J Med. 2023;389(1):33-44. doi:10.1056/NEJMoa2300696
8. National Comprehensive Cancer Network. B-Cell Lymphoma. NCCN. March 11, 2024. Accessed March 24, 2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
9. US Food and Drug Administration. FDA grants accelerated approval to pirtobrutinib for chronic lymphocytic leukemia and small lymphocytic lymphoma. FDA.gov. December 7, 2023. Accessed March 13, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pirtobrutinib-chronic-lymphocytic-leukemia-and-small-lymphocytic

pralsetinib (Gavreto™)

1. Gavreto (pralsetinib) [prescribing information]. South San Francisco, CA: Genentech Inc; June 2023.
2. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
3. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
4. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V2.2024. February 9, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
6. National Comprehensive Cancer Network. Thyroid Carcinoma Guidelines V1.2024. February 1, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
7. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.
8. FDA Approves Pralsetinib for Non-Small Cell Lung Cancer with RET Gene Fusions. FDA.gov, August 9, 2023.Available at https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-pralsetinib-non-small-cell-lung-cancer-ret-gene-fusions

selpercatinib (Retevmo™)

1. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
2. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
3. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
4. Guerra A, Sapio MR, Marotta V, Campanile E, Moretti MI, Deandrea M, et al. Prevalence of RET/PTC rearrangement in benign and malignant thyroid nodules and its clinical application. Endocr J. 2011;58(1):31-8.
5. Prasad ML, Vyas M, Horne MJ, Virk RK, Morotti R, Liu Z, et al. NTRK fusion oncogenes in pediatric papillary thyroid carcinoma in northeast United States. Cancer. 2016;122(7):1097-107.
6. Roy M, Chen H, Sippel RS. Current understanding and management of medullary thyroid cancer. Oncologist. 2013;18(10):1093-100.

7. Tappenden P, Carroll C, Hamilton J, Kaltenthaler E, Wong R, Wadsley J, et al. Cabozantinib and vandetanib for unresectable locally advanced or metastatic medullary thyroid cancer: a systematic review and economic model. Health Technol Assess. 2019 Feb;23(8):1-144.
8. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. RET aberrations in diverse cancers: next-generation sequencing of 4,871 patients. Clin Cancer Res. 2017 Apr;23(8):1988-97.
9. Sireci AN, Morosini D, Rothenberg S. Efficacy of immune checkpoint inhibition in RET fusion-positive non-small cell lung cancer patients (poster). Presented at the World Lung Cancer Conference; September 7-10, 2019. Barcelona, Spain. Available at: https://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf. Accessed February 28, 2020.
10. National Comprehensive Cancer Network. Thyroid Carcinoma Clinical Practice Guidelines V1.2020. June 12, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
11. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V6.2020. June 15, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
12. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol. 2022 Oct;23(10):1261-1273.

sotorasib (Lumakras™)

1. Lumakras [Prescribing Information]. Amgen Pharmaceuticals Inc., Thousand Oaks, CA. June 2021.
2. Skoulidis F, Li BT, Dy GK et al. Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation. N Engl J Med. 2021;384(25):2371-2381.
3. Black RC, Khurshid H. NSCLC: an update of driver mutations, their role in pathogenesis and clinical significance. R I Med J. (2013). 2015; 98: 25-8.
4. Aggarwal S, Whipple S, Hsu H, et al. 1339P: Clinicopathological characteristics and treatment patterns observed in real-world care in patients with advanced non-small cell lung cancer (NSCLC) and KRAS G12C mutations in the Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB). *Ann Oncol*. 2020;31: S860.
5. Hayashi H, Okamoto I, Taguri M, Morita S, & Nakagawa K. Post-progression survival in patients with advanced non-small-cell lung cancer who receive second-line or third-line chemotherapy. *Clin Lung Cancer*. 2013; 14:261-266.
6. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V5.2021. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated June 15, 2021.

tepotinib (Tepmetko)

1. Paik P.K., Felip E., Veillon R., et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med. 2020; 383(10): 931-943.
2. Tepmetko [Prescribing Information]. Merck KGaA. Darmstadt, Germany. February 2021.
3. Tabrecta [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. May 2020.
4. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of MET in lung cancer. Cancer Res. 2006;66(1):283-289.
5. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V8.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated September 15, 2020.
6. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

adagrasib (Krazati®)	
Policy Name	**Disease state**
sotorasib (Lumakras)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation

avapritinib (Ayvakit™)	
Policy Name	**Disease state**
regorafenib (Stivarga)	Gastrointestinal Stromal Tumors (GIST)
dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
ripretinib (Qinlock)	Gastrointestinal Stromal Tumors (GIST)
sunitinib (Sutent)	Gastrointestinal stromal tumors (GIST)
imatinib (Gleevec)	Gastrointestinal stromal tumors (GIST) Systemic mast cell disease (systemic mastocytosis)
midostaurin (Rydapt)	Systemic mast cell disease (aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia)
omalizumab (Xolair)	Systemic mastocytosis
belzutifan (Welireg™)	
Policy Name	**Disease state**
N/A	N/A
capmatinib (Tabrecta™)	
Policy Name	**Disease state**
tepotinib (Tepmetko)	Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping
futibatinib (Lytgobi®)	
Policy Name	**Disease state**
pemigatinib (Pemazyre)	Previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements
mobocertinib (Exkivity™)	
Policy Name	**Disease state**
pemigatinib (Pemazyre™)	
Policy Name	**Disease state**
erdafitinib (Balversa™)	Advanced or metastatic urothelial carcinoma FGFR3 or FGFR2 genetic alteration, second-line after platinum therapy progression
infigratinib (Truseltiq™)	Previously treated adults with unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable Hepatocellular Carcinoma
	Advanced Renal Cell Carcinoma
	Recurrent, High-risk or Metastatic Endometrial Carcinoma
	Locally Recurrent or Metastatic Progressive Thyroid Cancer
	Unresectable Liver Carcinoma
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with

	cytarabine/daunorubicin induction and cytarabine consolidation
ponatinib (Iclusig®)	CP-CML with resistance or intolerance to two prior kinase inhibitors
	AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated
	T315I-positive CML (any phase) or T315I-positive Ph+ ALL
pirtobrutinib (Jaypirca™)	
Policy Name	**Disease state**
acalabrutinib (Calquence®) Policy	Mantle cell lymphoma (previously treated)
	Chronic lymphocytic leukemia (CLL)
	Small lymphocytic lymphoma (SLL)
ibrutinib (IMBRUVICA®) Policy	Mantle cell lymphoma (previously treated)
	Marginal zone lymphoma (relapsed/refractory)
	Chronic graft-versus-host disease (refractory)
	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Waldenström macroglobulinemia
zanubrutinib (Brukinsa™) Policy	Mantle cell lymphoma
	Waldenström macroglobulinemia
	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen
venetoclax (Venclexta®) Policy	Chronic lymphocytic leukemia/Small lymphocytic lymphoma
	Acute myeloid leukemia
duvelisib (Copiktra®) Policy	Relapsed/refractory chronic lymphocytic leukemia (CLL)
	Relapsed/refractory small lymphocytic lymphoma (SLL)
idelalisib (Zydelig®) Policy	Relapsed Chronic Lymphocytic Leukemia (CLL)
lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®) Policy	Follicular lymphoma
	Mantle cell lymphoma
	Marginal zone lymphoma
	Multiple myeloma
	Multiple myeloma maintenance therapy following auto-HSCT
	Myelodysplastic syndromes
pralsetinib (Gavreto™)	
Policy Name	**Disease state**

selpercatinib (Retevmo)	RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory
cabozantinib (Cabometyx, Cometriq)	Progressive or metastatic medullary thyroid carcinoma
vandetanib (Caprelsa)	Locally advanced or metastatic medullary thyroid cancer
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	
selpercatinib (Retevmo™)	
Policy Name	**Disease state**
pralsetinib (Gavreto)	RET Fusion-Positive Non-Small Cell Lung Cancer
	RET-Mutant Medullary Thyroid Cancer
	RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory
sotorasib (Lumakras™)	
Policy Name	**Disease state**
sotorasib (Lumakras)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation
tepotinib (Tepmetko)	
Policy Name	**Disease state**
N/A	N/A

Policy Implementation/Update:

adagrasib (Krazati®)	
Action and Summary of Changes	**Date**
Policy created	11/2022
avapritinib (Ayvakit™)	
Action and Summary of Changes	**Date**
Added new indication of indolent systemic mastocytosis (ISM). Updated supporting evidence, E/I section, references for all indications. Added solid tumors and AML to E/I section. Added related policies section.	05/2023
Addition of new indication advanced systemic mastocytosis (AdvSM) and updated trial information for gastrointestinal stromal tumors (GIST)	10/2021
Policy created	05/2020
belzutifan (Welireg™)	
Action and Summary of Changes	**Date**
Policy created	11/2021
capmatinib (Tabrecta™)	
Action and Summary of Changes	**Date**
Added supporting evidence for regular FDA approval of capmatinib (Tabrecta) for the treatment of adults with metastatic NSCLC with METex14 skipping mutation, updated references, added related policies section.	02/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021

Policy created	08/2020
futibatinib (Lytgobi®)	
Action and Summary of Changes	**Date**
Policy created	02/2023
mobocertinib (Exkivity™)	
Action and Summary of Changes	**Date**
Updated from E/I to not medically necessary following withdrawal from U.S. market	**02/2024**
Policy created	11/2021
pemigatinib (Pemazyre™)	
Action and Summary of Changes	**Date**
Updated policy to include relapsed/ refractory MLNs with supporting evidence. Added SF criteria, updated references formatting, included related policies table.	01/2023
Policy created	06/2020
pirtobrutinib (Jaypirca™)	
Action and Summary of Changes	**Date**
Added SLL/CLL indication to E/I section with supporting evidence. Moved R/R MCL supporting evidence to E/I section. Updated related policies table.	4/2024
Policy created	05/2023
pralsetinib (Gavreto™)	
Action and Summary of Changes	**Date**
Updated supporting evidence to include extension study results to change FDA approval of pralsetinib (Gavreto) from accelerated to traditional in treatment of NSCLC and updated NCCN guideline recommendations. Moved RET-positive fusion MTC from covered indication to non-medically necessary due to withdrawn indication.	**3/2024**
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	02/2021
selpercatinib (Retevmo™)	
Action and Summary of Changes	**Date**
Added 120mg and 360mg tablets to the QL table and updated QL to 60/30. Updated QL for 40mg to 90/30	08/2024
Added tablet variation to the QL table	04/2024
Reviewed expanded indication for Retevmo for the treatment of RET-fusion positive solid tumors; added relevant supporting evidence	03/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	08/2020
sotorasib (Lumakras™)	
Action and Summary of Changes	**Date**
Policy created	11/2022
tepotinib (Tepmetko)	

Action and Summary of Changes	Date
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	02/2021