COLLEGE OF PHARMACY
UNIVERSITY OF UTAH

L. S. SKAGGS PHARMACY INSTITUTE

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EGFR INHIBITORS FOR APPROVED ONCOLOGIC DISORDERS

AFATINIB (GILOTRIF®)
AMIVANTAMAB (RYBREVANT®)
CETUXIMAB (ERBITUX®)
DACOMITINIB (VIZIMPRO®)
ERLOTINIB (TARCEVA®)
GEFITINIB (IRESSA®)
LAPATINIB (TYKERB®)
LAZERTINIB (LAZCLUZE®)
NECITUMUMAB (PORTRAZZA®)
NERATINIB (NERLYNX®)
OSIMERTINIB (TAGRISSO®)
PANITUMUMAB (VECTIBIX®)
VANDETANIB (CAPRELSA®)

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CONTENTS

Contents i

List of Figures iii

List of Tables iv

Abbreviations v

Executive Summary vii

1.0 Introduction 1

2.0 Methods 6

3.0 Mechanism of Action 7

4.0 Approved Indications 8

5.0 Special Populations 11

6.0 Disease Overview, Guideline Place-in-Therapy, And Direct Comparative Evidence 12

6.1 Breast Cancer 13

6.1.1 Guideline Recommendations for EGFR Inhibitors 14

6.1.2 Comparative RCTs for Approved EGFR Inhibitors for Breast Cancer 16

6.2 Colorectal Cancer (CRC) 17

6.2.1 Guideline Recommendations for EGFR Inhibitors 19

6.2.2 Comparative RCTs for Approved EGFR Inhibitors for mCRC 23

6.2.2.1 Subsequent-line therapy 23

6.3 Non-small Cell Lung Cancer (NSCLC) 24

6.3.1 Guideline Recommendations for EGFR Inhibitors 26

6.3.2 Comparative RCTs for Approved NSCLC Indications of EGFR Inhibitors 31

6.3.2.1 FIRST-LINE THERAPY 31

6.3.2.2 SUBSEQUENT THERAPY 33

6.4 Indications Unique to Vandetanib: Thyroid Cancer 35

6.4.1 Key NCCN Recommendations for EGFR Inhibitors 35

6.5 Indications Unique to Cetuximab: Squamous Cell Carcinoma of the Head and Neck (SCCHN) 37

6.5.1 Key NCCN Recommendations for EGFR Inhibitors 37

6.6 Indications Unique to Erlotinib: Pancreatic Cancer 41

6.6.1 Key NCCN Recommendations for EGFR Inhibitors 41

7.0 Off-label Uses 44

8.0 Safety 47

8.1 Safety information regarding EGFR-inhibitors indicated for NSCLC: afatinib, amivantamab, dacomitinib, erlotinib, gefitinib, lazertinib, necitumumab, osimertinib, ... 51

8.2 Safety information regarding EGFR-inhibitors indicated for mCRC: cetuximab, panitumumab 52

8.3 Safety information for EGFR-inhibitors indicated for breast cancer: lapatinib, neratinib 53

8.4 Additional safety information for other agents/indications 53

8.5 Drug-drug Interactions 54

References 56

Appendix A - Product Indications and Dosing 65

Appendix B - Literature Search 69

Appendix C - Publication Screening 74

Appendix D - Excluded Studies 75

LIST OF FIGURES

Appendix C, Figure 1. PRISMA Flow Chart[a] for Publication Screening 74

LIST OF TABLES

Table 1. EGFR Inhibitor Formulations Available in the United States 2

Table 2. EGFR Inhibitors by Indicated Disease State 3

Table 3. Mechanism of Action Information from Package Inserts 7

Table 4. EGFR Inhibitor Indications 9

Table 5. Renal and Hepatic Impairment Information 11

Table 6. EGFR Inhibitors, Approved Indications for Breast Cancer 14

Table 7. NCCN Breast Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024 15

Table 8. EGFR Inhibitors, Approved Indications for Colorectal Cancer 18

Table 9. NCCN Colorectal Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024 21

Table 10. EGFR Inhibitor Indications for Advanced Non-small Cell Lung Cancer 25

Table 11. NCCN Non-small Cell Lung Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2025 28

Table 12. NCCN Thyroid Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024 36

Table 13. Cetuximab Indications for Head and Neck Squamous Cell Carcinoma 37

Table 14. NCCN Head and Neck Cancers, EGFR Inhibitor Place-in-therapy, 2025 39

Table 15. NCCN Pancreatic Adenocarcinoma Guideline, EGFR Inhibitor Place-in-therapy, 2025 42

Table 16. Off-Label Uses of EGFR Inhibitors for Adults 45

Table 17. Labeled Warnings for EGFR Inhibitors 49

Table A1. EGFR Inhibitor Indications and Dosing 65

Table B1. Phased Literature Search Approach for Head-to-head SRs/RCTs 69

ABBREVIATIONS

5-FU	5-flurouracil
AEs	adverse events
anti-VEGF	vascular endothelial growth factor inhibitor
ASCO	American Society of Clinical Oncology
BBW	black box warning
BC	breast cancer
CAPEOX	oxaliplatin + capecitabine
CRC	colorectal cancer
dMMR	deficient mismatch repair
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
Ex	exon
Ex19del	exon 19 deletion
FOLFIRI	leucovorin + fluorouracil + irinotecan
FOLIRINOX	leucovorin + fluorouracil + irinotecan + oxaliplatin
FOLFOX	leucovorin + fluorouracil + oxaliplatin
FDA	US Food and Drug Administration
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
H-H	head-to-head
HIV	human immunodeficiency virus
HR	hazard ratio
ICIs	immune checkpoint inhibitors
IV	intravenous
LVEF	left ventricular ejection fraction
mCRC	metastatic colorectal cancer
MMR	mismatch repair
mRCC	metastatic renal cell carcinoma
MSI	microsatellite instability
MSS	microsatellite stable
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
OS	overall survival
PD-1	programmed cell death-1
PD-L1	programmed cell death 1 ligand
PDL	preferred drug list
PFS	progression free survival

pMMR	proficient mismatch repair
PS	performance status
RCTs	randomized controlled trials
SCCHN	squamous cell carcinoma of the head and neck
SRs	systematic reviews
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor
VTE	venous thromboembolism
WHO	World Health Organization
WT	wild type

EXECUTIVE SUMMARY

Background

Epidermal growth factor receptors (EGFRs) are transmembrane receptors located on epithelial cells. The EGFR signal-transduction pathway is implicated in the progression and survival of several cancers. EGFR inhibitors ultimately reduce the overly active EGFR-mediated pathway in susceptible cancers. Nine oral and 4 intravenous (IV) EGFR inhibitors are approved and available in the US: oral agents include afatinib (Gilotrif®), dacomitinib (Vizimpro®), erlotinib (Tarceva®), gefitinib (Iressa®), lapatinib (Tykerb®), lazertinib (Lazcluze®), neratinib (Nerlynx®), osimertinib (Tagrisso®), and vandetanib (Caprelsa®); and the IV agents are amivantamab (Rybrevant®), cetuximab (Erbitux®), necitumumab (Portrazza®), and panitumumab (Vectibix®). The IV agents are antibody-based therapies, whereas the oral agents are small-molecule drugs. Altogether, approved indications of EGFR inhibitors span 6 oncologic disorders including breast cancer (BC), metastatic colorectal cancer (mCRC), non-small cell lung cancer (NSCLC), pancreatic cancer, squamous cell carcinoma of the head and neck (SCCHN), and medullary thyroid cancer.[1-13] Most agents are approved for a single oncologic disorder; the exceptions are cetuximab and erlotinib, each approved for 2 oncologic diseases.

Of the cancers covered by EGFR-inhibitor approvals, 3 are subsets among the top ten broader cancer groups for the rate of new cancer cases in the US (per 2021 data):[14]

1st- **female breast cancer**, 134 case per 100,000 persons
3rd- **lung/bronchus cancers**, 49 per 100,000
4th- **colorectal cancer**, 36 per 100,000

Four rank among the top ten for cancer-related death rate (2022 data):

1st- lung/bronchus cancer, 30 per 100,000
3rd- female breast cancer, 19 per 100,000
4th- colorectal cancer, 13 per 100,000
5th- pancreatic cancer, 11 per 100,000

There are 3 disease states in common between 2 or more EGFR inhibitors with respect to FDA-approved indications: breast cancer (lapatinib, neratinib), mCRC (cetuximab, panitumumab), and NSCLC (afatinib, dacomitinib, erlotinib, gefitinib, lazertinib, and osimertinib, amivantamab, necitumumab). However, because approved indications are also specific to use as first- or second-line therapy, possible requirements for prior treatment, co-treatments, or other clinical characteristics (eg, genetic mutations or histology), *indications may not fully overlap*:

- **Breast cancer**: Lapatinib, in combination with letrozole, is approved for postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. Lapatinib and neratinib are approved in combination with capecitabine for subsequent-line therapy of advanced or metastatic HER2-positive breast cancer. Neratinib is also approved for adjuvant therapy of early-stage disease.[5,7]
- **mCRC:** Cetuximab and panitumumab, both IV agents, are approved for *first-line* treatment of KRAS wild-type (WT) mCRC, in combination with particular chemotherapy backbones. Each is also indicated for subsequent-line therapy after failing other chemotherapy-based, first-line regimens.

Additionally, cetuximab is indicated for BRAF V600F mutant mCRC, in combination with encorafenib.[3,12]

- **NSCLC**: Among the approved EGFR inhibitors for advanced NSCLC, most are oral agents with the exceptions of the IV agents, amivantamab and necitumumab. Most NSCLC indications are typically specified to particular EGFR mutations, which vary among agents (see **Table 10)**. For example, regarding first-line therapy, afatinib is approved for any amenable EGFR mutation;[9] however, it is typically not effective for exon (Ex) 20 insertion or T790M mutations.[15] Labeling for others specifies particular mutations: amivantamab is approved for Ex20 insertion, Ex19 deletion (Ex19del), or Ex21 L858R mutations; dacomitinib, erlotinib, lazertinib, and osimertinib are approved for Ex19del or Ex21 L858R mutations.[1,4,10,11,13] Lazertinib is approved only in combination with amivantamab[13]; otherwise, other EGFR inhibitors are approved as monotherapy or in combination with certain chemotherapy agents. Some EGFR inhibitors are additionally approved for subsequent-line therapy.[1,4,9,10] In addition to previously mentioned mutations, osimertinib is uniquely labeled for T790M mutation that arises after treatment with another EGFR therapy,[4] and amivantamab is uniquely/additionally indicated for disease progression following osimertinib treatment.[10] Necitumumab's indication is the exception, without specification to mutational status; it is generally indicated for metastatic squamous NSCLC,[6] yet it is not recommended by the National Comprehensive Cancer Network (NCCN) guideline as described below.[15]

Three agents are approved for disease states that no other EGFR inhibitors have as an approval: cetuximab for SCCHN, erlotinib for pancreatic cancer, and vandetanib for medullary thyroid cancer.[1,2,12] Product labeling (ie, package inserts) for all the reviewed agents describe that the safety and effectiveness have not been established in the pediatric population.

Table 16 of this report summarizes recognized off-label uses from Dynamed/Micromedex and Lexidrug medication-information compendia.

Guideline Recommendations

We reviewed treatment guidelines by the **National Comprehensive Cancer Network (NCCN)** for approved oncologic disorders of EGFR inhibitors; these guidelines are often updated multiple times a year. The place-in-therapy for EGFR inhibitors, according to NCCN-guideline recommendations, are summarized below with respect to overlapping indication areas:

- **Breast cancer** (BC; NCCN version 6.2024): For patients with advanced (ie, recurrent, unresectable local disease, or metastatic disease), HER2-positive BC and *indicated for endocrine therapy* (ie, with hormone receptor-positive disease), lapatinib is among NCCN-recommended regimens (combined with an aromatase inhibitor, with or without trastuzumab [a HER2 inhibitor]).[16] Several trastuzumab-containing regimens (in combination with endocrine therapy) are equally-preferred regimens to the lapatinib-based regimens. For patients with HER2-positive advanced disease *not indicated for endocrine therapy*, lapatinib and neratinib are among *fourth-line, subsequent regimens*, in combination with capecitabine, or in combination with trastuzumab (for lapatinib only). Earlier-line, NCCN-preferred regimens include (1) pertuzumab + trastuzumab + capecitabine as first line, (2) fam-trastuzumab deruxtecan-nxki (a trastuzumab-chemotherapy drug conjugate), as second line, and (3) tucatinib + trastuzumab + capecitabine as third line. In addition to lapatinib- or neratinib-

based fourth-line regimens, other fourth-line options include trastuzumab- or margetuximab-based regimens, or targeted therapy for unique mutations or biomarkers.[16]

- **Colorectal cancer** (CRC; NCCN version 5.2024): In the setting of *first-line* therapy for advanced or metastatic CRC, cetuximab- or panitumumab-based combination therapy is recommended only for *left-sided originating tumors that are also RAS wild-type*. Cetuximab or panitumumab are recommended in combination with chemotherapy; the NCCN considers these as equivalent choices (thus equally preferred) to IV bevacizumab (an anti-VEGF) + chemotherapy for first-line treatment of metastatic WT RAS/BRAF CRC, though bevacizumab is not restricted by tumor origination side (ie, can be used for right sided). Alternatively for first-line therapy, patients may be treated with chemotherapy-only regimens[*] (eg, FOLFIRI or FOLFOX or CAPEOX or FOLFIRINOX; which are equally preferred to the antibody-based regimens and can be used regardless of the tumor's origination side); or may be treated with less-intensive regimens if clinically indicated, such as cetuximab or panitumumab monotherapy.[17]

  Cetuximab- and panitumumab-based combination therapy can also be used for subsequent-line treatment of advanced or metastatic CRC, including BRAF V600E mutation-positive disease (must be used in combination with encorafenib), or KRAS G12C mutation-positive disease (must be used in combination with sotorasib or adagrasib).[17] The BRAF V600E and KRAS G12C mutational variants are technically off-label, NCCN-recommended uses for panitumumab, and the KRAS G12C variant is off-label for cetuximab. Although lapatinib does not have FDA-approval for mCRC, it is a recommended option, among others, for previously-treated, HER2-positive, RAS/BRAF WT, mCRC, in combination with trastuzumab.[17]

- **NSCLC** (NCCN version 1.2025): In general, EGFR inhibitors are recommended for EGFR mutation-positive NSCLC, with the exception of necitumumab, which the NCCN omits as an option altogether because of its toxicity, cost, and marginal benefit.[18] Osimertinib is recommended in many settings of treatment: as *adjuvant therapy of EGFR positive* (with ex19del or L858R mutation) completely resected disease (ie, for some cases of stage IB to stage III disease) or for locoregionally advanced inoperable disease following chemoradiation, and also for recurrent or metastatic EGFR-positive disease (a setting also applicable to other EGFR inhibitors/indications).[18]

  For metastatic disease (or for locally advanced/recurrent disease), osimertinib monotherapy is preferred for first-line systemic treatment of NSCLC with either of the two *common EGFR mutations* (Ex19del or Ex21-L858R, comprising 80%-85% of cases) or with *less common mutations* (Ex20-S768I, Ex21-L861Q, or Ex18-G719X; together comprising about 10% of EGFR mutations).[18] Afatinib, is an additional preferred first-line agent for the *less common mutations* (EGFR Ex20-S768I, Ex21-L861Q, and Ex18-G719X). Alternative first-line regimens for Ex19del or Ex21-L858R mutations are (a) osimertinib + chemotherapy or (b) amivantamab + lazertinib. Other EGFR inhibitors (afatinib, dacomitinib, erlotinib-based therapy, or gefitinib) are designated as "useful in certain circumstances" for the common EGFR mutations or as alternative options for the less common

[*] Chemotherapy-only regimens include CAPEOX (oxaliplatin + capecitabine), FOLFIRI (leucovorin + fluorouracil + irinotecan), FOLFOX (leucovorin + fluorouracil + oxaliplatin), and FOLFIRINOX (leucovorin + fluorouracil + irinotecan + oxaliplatin).

mutations. Osimertinib is also a subsequent-line option for EGFR T790M–positive metastatic disease following progression on erlotinib, afatinib, dacomitinib, or gefitinib. Amivantamab, in combination with chemotherapy, is a recommended option following progression on osimertinib.[18]

For EGFR Ex20 insertion mutations (comprising 4%-12% of EGFR-mutant cases, or about 2% of all NSCLC cases), amivantamab-based therapy is preferred for first-line treatment and is an option for disease progression after other first-line options (eg, immune checkpoint inhibitors and/or chemotherapy).[18]

The following points summarize select NCCN recommendations regarding disease states for which only one EGFR inhibitor is approved.

- In the setting of head and neck cancers, cetuximab-based regimens serve as *alternative* first-line systemic treatment options, among other options, or as subsequent-line regimens in a few scenarios. There are a variety of other first-line regimens, depending on the cancer location (nasopharyngeal vs. non-nasopharyngeal) and whether the patient is a candidate for radiation therapy (refer to section 6.5). For example, for locally advanced non-nasopharynx head and neck cancer[†], the preferred first-line systemic regimen is high-dose cisplatin with concurrent radiation therapy (considered the gold standard).[19]
- Generally, erlotinib plus gemcitabine is among *alternative* first-line systemic regimens recommended for locally advanced or metastatic pancreatic adenocarcinoma, or for subsequent-line therapy. Preferred first-line regimens are platinum- and/or gemcitabine-based combination regimens (refer to section 6.6).[20]
- For locally recurrent, unresectable, or metastatic medullary thyroid cancer, vandetanib or cabozantinib (an anti-VEGF agent) are among NCCN-preferred systemic therapy options. Vandetanib may also be considered for *off-label* treatment of radioactive iodine-refractory differentiated thyroid cancer when other approved therapies are not available, appropriate, or effective.[21]

Following a literature search for direct, comparative, randomized controlled trials (RCTs) of EGFR therapies for their FDA-indicated disease states in common, studies were found in the setting of *first-line* systemic therapy for NSCLC, while none were found in the setting of *first-line* systemic therapy for breast cancer (BC) or colorectal cancer (CRC). For these latter two cancers, only a few comparative studies are available in the setting of *subsequent-line therapy* for advanced BC (HER2-postive) or mCRC (WT RAS exon 2 disease). Overall, these findings are consistent with NCCN guidelines for the management of BC or CRC.

Head-to-head Comparisons

In the setting of NSCLC, 10 RCTs report comparative effectiveness for agents of interest used according to their FDA-approved indication for NSCLC, for certain EGFR mutations. Erlotinib and gefitinib, the first-generation agents, often served as the comparator; second- and third-generation EGFR inhibitors have not been compared to one another.[22-25] For *first-line therapy* of advanced NSCLC, particularly with the common mutations (*ex19del or Leu858R mutation),* 5 comparative studies are pertinent:

[†] According the NCCN treatment algorithm, it appears systemic therapy can be considered for squamous cell carcinoma along with other histologies, such as poorly differentiated, nonkeratinizing squamous cell, anaplastic (not thyroid), not otherwise specified, and possibly others.[18]

- An ongoing, phase 3 RCT comparing amivantamab + lazertinib vs. osimertinib (with 429 patients in each arm) so far has shown a significant improvement in median progression free survival (PFS) with the combination therapy (23.7 vs. 16.6 months, HR 0.70, P<0.001);[26] the final overall survival (OS) data is awaited.
- An open-label, phase 2b RCT (N=319) showed afatinib significantly improved median PFS (11.0 vs 10.9 months, HR 0.74, P=0.018) but not OS, compared to gefitinib; OS was similar with each agent.[27]
- A phase 3, open-label RCT (N=451) comparing dacomitinib vs. gefitinib found dacomitinib significantly improved median PFS (14.7 vs. 9.2 months; HR 0.59, P<0.0001) and median OS (34.1 vs. 26.8 months ; HR of 0.76, P = 0.044).[28]
- One phase 3, double-blinded RCT (N=556) demonstrated that osimertinib significantly improved PFS and OS outcomes versus the comparator arm of first-generation EGFR treatment, erlotinib or gefitinib: median PFS of 18.9 vs. 10.2 months, median OS of 38.6 vs. 31.8 months, and death HR of 0.80 (P=0.046) for osimertinib vs. first-generation agents, respectively.[29,30]
- One phase 3 and one small non-English RCT showed that erlotinib and gefitinib were comparable with respect to OS and/or PFS.[31,32]

Of the 4 publications addressing subsequent-line therapy for NSCLC, only 1 reported significant efficacy differences between agents: afatinib outperformed erlotinib for PFS and OS in the setting of subsequent-line treatment of *squamous cell* NSCLC.[33] Refer to section 6.3.2. for additional information.

In the setting of subsequent-line therapy for BC, one RCT (NALA, phase 3 study) compared neratinib versus lapatinib in treatment-experienced patients with advanced BC (having failed at least 2 prior HER2-directed therapies) and *not undergoing endocrine therapy*. At the primary cut-off assessment (median follow-up of 30 months), neratinib outperformed lapatinib (both in combination with capecitabine) for mean PFS (8.8 months vs. 6.6 months, HR = 0.76, p = 0.006), and performed similarly with respect to OS.[34] Refer to section 6.1.2 for additional information.

In the setting of mCRC, 2 comparative RCTs were found for *subsequent-line* therapy (ie, after prior treatment with first-line therapy) in populations with WT RAS exon 2 disease. These studies reported that panitumumab was non-inferior but not superior to cetuximab for respective primary endpoints of each study, ether OS or PFS.[35,36] Refer to section 6.2.2 for additional information.

Safety

Common adverse events (AEs) of EGFR inhibitors include **dermatologic reactions** and **diarrhea**, which occur in most treated patients with many of these agents. Except for neratinib, dermatologic toxicity is a labeled warning for all EGFR inhibitors; the warning for panitumumab is a black box warning (BBW) due to many events graded as severe (15% in a pivotal clinical study). Most EGFR inhibitors (except neratinib and necitumumab) have a warning regarding their association with **interstitial lung disease (ILD)**; cases were infrequent for most agents with the exception of a 56% ILD/pneumonitis incidence in osimertinib-treated patients particularly following treatment with platinum-based chemoradiation. Most agents have warnings regarding additional **soft tissue toxicities**: (a) ocular toxicity with afatinib, erlotinib, gefitinib, amivantamab + lazertinib, osimertinib, and panitumumab; (b) gastrointestinal perforation and/or hemorrhage risk with afatinib, erlotinib, gefitinib, and vandetanib; and (c) cutaneous vasculitis with osimertinib. Several have a warning regarding potential hepatotoxicity (as with afatinib, erlotinib,

gefitinib, lapatinib (BBW), neratinib, and vandetanib), or for unusual but serious cardiac events (ie, decreased LVEF with lapatinib, cardiomyopathy with osimertinib, cardiac failure with vandetanib, cardiac arrest [BBW] with cetuximab and necitumumab, and QTc prolongation with lapatinib, osimertinib and vandetanib [BBW]). The injectable antibodies have warnings regarding infusion-related reactions (BBW with cetuximab). All EGFR inhibitors have a warning regarding **embryofetal toxicity** and often have a recommendation for the use of effective contraception, as appropriate, during treatment and for a period after treatment discontinuation.

Unique warnings for one or two agents include acute renal failure with erlotinib and vandetanib; thromboembolic events with necitumumab and lazertinib + amivantamab (36% VTE incidence in the MARIPOSA clinical study [BBW]; thromboprophylaxis is now recommended with lazertinib + amivantamab therapy); hypomagnesemia (83% incidence) and electrolyte imbalances (BBW) with necitumumab; micro-angiopathic hemolytic anemia and thrombocytopenia with erlotinib; and aplastic anemia with osimertinib (with high incidences of leukopenia, neutropenia, and thrombocytopenia). Other warnings unique to vandetanib, also related to its anti-VEGF action, include impaired wound healing, hypertension, and a neurologic disorder called posterior reversable encephalopathy syndrome.

Utah Medicaid Preferred Drug List (PDL) Considerations

Because PDL-preference designations are foremost in steering prescribing decisions regarding the choice of *first-line* therapy among a drug class, the NCCN recommendations for *first-line therapy of the* reviewed oncologic disorders are the focus of this subsection.

In the setting of NSCLC, the mutational variant is a key factor that drives selection of therapy. For the most common EGFR mutational variants of NSCLC (Ex19del or Ex21-L858R; comprising 80%-85% of EGFR-mutant cases), the EGFR inhibitor class currently dominates NCCN-recommended, first-line options for metastatic disease (or recurrent advanced disease), with osimertinib as the preferred regimen, amivantamab + lazertinib as an alternative, and other EGFR agents designated as useful in certain circumstances (erlotinib, afatinib, gefitinib, or dacomitinib monotherapy; or erlotinib-based regimens). Osimertinib can alternatively be used as a subsequent-line therapy for EGFR T790M–positive metastatic disease that develops following first-line therapy with erlotinib, afatinib, dacomitinib, or gefitinib. Although there is one RCT showing benefits with the third-generation agent, osimertinib, over first-generation[‡] EGFR inhibitors for first-line therapy of NSCLC with the common EGFR mutations, there are no head-to-head RCTs between second-generation EGFR inhibitors and osimertinib. Some second- vs. first-generation comparisons have shown some benefits (eg, improved PFS and/or OS) with the second-generation agents.

For purposes of the PDL, at least one NCCN-recommended, first-line EGFR-inhibitor regimen for NSCLC with common EGFR-mutation variants could be considered for the designation of preferred status on the PDL. Particularly, given the guideline preferences, an NCCN-preferred (eg, osimertinib) or NCCN-alternative regimen (eg, amivantamab + lazertinib) could be considered for PDL-preferred status.

[‡] First generation EGFR inhibitors for NSCLC include erlotinib and gefitinib; second-generation agents are afatinib and dacomitinib; third generation agents include lazertinib and osimertinib

Regarding *first-line therapy* for advanced or metastatic CRC, there are many NCCN equally-recommended regimens. Patients may be treated with chemotherapy-only regimens (eg, FOLFIRI or FOLFOX or CAPEOX or FOLFIRINOX), or with a biologic (cetuximab or panitumumab, both EGFR inhibitors; or bevacizumab an anti-VEGF) added onto chemotherapy. Yet, in the setting of first-line treatment, the EGFR inhibitors, cetuximab and panitumumab, are recommended only for left-sided originating tumors that are RAS WT, whereas bevacizumab is not restricted based on origination side or RAS mutational status.

For purposes of the PDL, biologic-based regimens containing either cetuximab, panitumumab, or bevacizumab can be considered similarly effective for first-line treatment of left sided-originating, RAS WT, advanced or metastatic CRC; yet, it should also be considered that only bevacizumab-based therapy is recommended for first-line therapy of right sided-originating, RAS WT disease.

In the setting of *first-line* therapy for advanced, HER2-positive breast cancer that is *indicated for endocrine therapy* (ie, with hormone receptor-positive disease), lapatinib along with several trastuzumab-containing regimens are equally recommended options.[16] Trastuzumab is also recommended in earlier lines of therapy than lapatinib for other scenarios of advanced, HER2-positive breast cancer (eg, that are not indicated for endocrine therapy).

For purposes of the PDL, at least one NCCN-recommended first-line agent for HER2-positive disease can be considered for advanced breast cancer.

Because other chemotherapy regimens are equally preferrable or more preferrable to EGFR therapy according to the NCCN guidelines, in the setting of first-line treatment of advanced pancreatic cancer or for head and neck cancers, a specific recommendation for PDL designation of EGFR therapy with respect to those cancers is reserved. Because MTC is relatively uncommon, a particular recommendation for agent preference for MTC on the PDL is also reserved.

1.0 INTRODUCTION

Epidermal growth factor receptor (EGFR; ie, EGFR1) is a type of tyrosine kinase found on the surface of epithelial cells. Several cancers have over-expression of EGFR and/or over-activation of the receptor, playing a role in disease progression. The scope of this review focuses on **EGFR1 inhibitors**, commonly and more simply referred to as EGFR inhibitors (and pharmacologically classified[§] in Lexidrug as EGFR inhibitors). There are 13 EGFR inhibitors available in the US: 9 oral agents and 4 intravenous (IV) agents, as shown in **Table 1.** Three are available as generics (erlotinib, gefitinib, and lapatinib), while the remaining a currently available as brand only. Collectively, these products are approved for the treatment of 6 oncologic disorders including breast cancer, metastatic colorectal cancer (mCRC), head and neck squamous cell carcinoma (SCCHN), non-small cell lung cancer (NSCLC), pancreatic cancer, and thyroid cancer (**Table 2**). Except for cetuximab and erlotinib with approved indications for two oncologic disorders, most of these agents are individually approved for a single oncologic disease. The *IV* EGFR-inhibitors are antibody-based pharmaceuticals (ie, large molecular drugs), whereas the *oral* EGFR-inhibitors are small-molecule drugs.

Among EGFR-inhibitor indications, there are 3 FDA-indicated disease states in common between 2 or more agents: breast cancer, mCRC, and NSCLC.

- Agents approved for breast cancer: lapatinib and neratinib, both oral agents
- Agents approved for mCRC: cetuximab and panitumumab, both IV agents
- Agents approved for NSCLC: afatinib, amivantamab (IV agent), dacomitinib, erlotinib, gefitinib, lazertinib, necitumumab (IV agent), and osimertinib.

Because approved indications are also specific to use as first- or subsequent-line therapy, co-treatments, or other clinical characteristics, the indications may not fully overlap.[**] Package inserts for each agent describe that safety and efficacy have not been established in the pediatric population.

This review focuses on approved indications, the place-in-therapy for approved indications according to recent clinical guidelines (particularly those by the National Comprehensive Cancer Network [NCCN]), and labeled safety information of EGFR (ie, EGFR1) inhibitor products. Additionally, a literature search for direct, head-to-head comparative randomized controlled trial (RCT) information was conducted with respect to FDA-indicated disease states in common between the reviewed agents, to further inform decision-making regarding the Utah Medicaid Preferred Drug List (PDL).

Currently, the Utah Medicaid PDL does not preferentially classify the EGFR-inhibitors, with the exception of brand over generic specified for Tarceva (erlotinib) and Tykerb (lapatinib).

[§] EGFR inhibitors and HER2 inhibitors are classified more generally in Micromedex as Antineoplastic Agents and potentially subcategorized under immunologic as applicable.

[**] Refer to **Table A1** of Appendix A to view the applicable co-treatments (ie, treatment regimen) specified as part of the approved indication and recommended dose for each of these agents.

While there are other subcategories of receptors among the broad EGFR family and additional related medications pharmacologically classified as HER2-inhibitors (ie, EGFR2 inhibitors), for feasibility purposes, the review is limited primarily to EGFR1 therapy. Yet, because lapatinib and neratinib inhibit both EGFR1 and HER2, guideline recommendations addressing their place-in-therapy with respect to other HER2-directed options for breast cancer are included. Regarding mobocertinib, an EGFR inhibitor approved in the past but now withdrawn from the market (and its approval for NSCLC retracted in July 2024)[37] , this agent will also not be reviewed. The complex processes regarding diagnosis of the indicated cancers are also not reviewed. Yet, recommendations regarding pertinent biomarkers of these diseases are briefly addressed as they relate to pharmacotherapy decision-making.

Table 1 shows the available formulations of the FDA-approved EGFR inhibitors; **Table 2** lists agents by indicated disease state.

Table 1. EGFR Inhibitor Formulations Available in the United States

Oral Agents	afatinib (Gilotrif®): 20mg, 30 mg, and 40 mg tablets dacomitinib (Vizimpro®): 15 mg, 30 mg, and 45 mg tablets erlotinib (Tarceva®, and generic): 25 mg, 100 mg, and 150 mg tablets gefitinib (Iressa®, and generic): 250 mg tablets lapatinib (Tykerb®, and generic): 250 mg tablets lazertinib (Lazcluze®): 80 mg tablets (or 240 mg tablet as the mesylate salt) neratinib (Nerlynx®): 40 mg tablets osimertinib (Tagrisso®): 40 mg, and 80 mg tablets vandetanib (Caprelsa®): 100 mg, and 300 mg tablets
Intravenous Agents	amivantamab (Rybrevant®): 350 mg/7 mL (7 mL) cetuximab (Erbitux®): 100 mg/50 mL (50 mL); 200 mg/100 mL (100 mL) necitumumab (Portrazza®): 800 mg/50 mL (50 mL) panitumumab (Vectibix®): 100 mg/5 mL (5 mL); 400 mg/20 mL (20 mL)

Table 2. EGFR Inhibitors by Indicated Disease State[1-13]

Indication / Agent (Brand)	Breast cancer	Colorectal cancer, metastatic (mCRC)	Head and neck squamous cell carcinoma	Non-small cell lung cancer (NSCLC)	Pancreatic cancer	Thyroid cancer
Afatinib (Gilotrif)				X (first-line for metastatic, EGFR mutation-positive NSCLC, or subsequent-line for squamous NSCLC following platinum-based therapy)		
Amivantamab (Rybrevant)				X (locally advanced or metastatic NSCLC with EGFR exon 20 mutation, exon 19 deletion, or exon 21 L858R substitution; first-line or subsequent-line)		
Cetuximab (Erbitux)		X (BRAF V600E mutation-positive or KRAS wild-type, EGFR expressing disease)	X			
Dacomitinib (Vizimpro)				X (first-line for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations)		

Table 2. EGFR Inhibitors by Indicated Disease State[1-13]

Indication / Agent (Brand)	Breast cancer	Colorectal cancer, metastatic (mCRC)	Head and neck squamous cell carcinoma	Non-small cell lung cancer (NSCLC)	Pancreatic cancer	Thyroid cancer
Erlotinib (Tarceva)				X (for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations, any-line)	X (first-line for locally advanced, unresectable or metastatic disease)	
Gefitinib (Iressa)				X (first-line for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations)		
Lapatinib (Tykerb)	X (advanced or metastatic disease with HER2 overexpression)					
Lazertinib (Lazcluze)				X (first-line for NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations)		
Necitumumab (Portrazza)				X (metastatic, squamous NSCLC)		
Neratinib (Nerlynx)	X (for HER2-positive disease, as an adjuvant for early-stage disease, or for subsequent therapy of advanced or metastatic disease)					

Table 2. EGFR Inhibitors by Indicated Disease State[1-13]

Indication / Agent (Brand)	Breast cancer	Colorectal cancer, metastatic (mCRC)	Head and neck squamous cell carcinoma	Non-small cell lung cancer (NSCLC)	Pancreatic cancer	Thyroid cancer
Osimertinib (Tagrisso)				X (adjuvant treatment; first-line for locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations; or subsequent-line for metastatic EGFR T790M mutation-positive NSCLC)		
Panitumumab (Vectibix)		X				
Vandetanib (Caprelsa)						X (for locally advanced or metastatic medullary thyroid cancer)

2.0 METHODS

The National Comprehensive Cancer Network (NCCN) guidelines for EGFR approved indications were the focus of the review for the guideline information sections of this report. NCCN guidelines are often updated multiple times per year. Nonetheless, information from American Society of Clinical Oncology (ASCO) guidelines was also incorporated, particularly for indications where more than 1 EGFR therapy is approved.

For product prescribing information (ie, product labeling, package inserts), we searched the drug sponsor's website for each brand product if available, otherwise, Drugs@FDA and dailymed.nlm.nih.gov.

Literature Search for Comparative Evidence with Respect to Overlapping Approved Indications

Targeted search strategies were developed in a phased approach to identify systematic reviews (SRs) of randomized controlled trials (RCTs) for the reviewed agents respective to their FDA-approved indications in common. Overlapping indicated disease states among the reviewed products include breast cancer, colorectal cancer, and NSCLC. The phased approach incorporated searching and screening of most recently published SRs first, then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale described in Table B1 of Appendix B).

Recent SRs were searched for in Ovid-Medline (published from 2022–2024), and in Epistemonikos[††] (published from 2023–2024). Additional supplemental searches for individual RCTs were conducted in Ovid-Medline for first-line therapy of colorectal cancer and for EGFR mutation-positive NSCLC. Strategies in Ovid-Medline consisted of controlled vocabulary (ie, Medical Subject Headings [MeSH]) and keyword phrases for active ingredients and overlapping approved indications. Strategies in Epistemonikos consisted of keyword phrases with Boolean operators. A combination of independently derived filters was used to identify SRs in Ovid-Medline. Search filters for RCTs were applied using options referred to in the Cochrane Collaboration Handbook for SRs (Ovid-Medline[38] and Embase[39]). See **Appendix B** for search strategy details.

Screening: The lead author independently screened all search result records (titles/abstracts/full texts) for inclusion. **Appendix C** shows the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart for the literature screening process.

Inclusion and Exclusion Criteria for Comparative Evidence: Eligible reports were either SRs with RCTs of head-to-head parallel study arms, or individual RCTs, directly comparing 2 or more EGFR products listed in Table 1 with respect to overlapping approved indications. Direct, pair-wise meta-analysis data or inferential statistical results from individual RCTs with direct comparisons were eligible for inclusion. Moreover, there must be specification that the included population had the FDA-approved mutations for use of the product, where applicable. Additionally, for inclusion of data, agents must be used in accordance with the FDA approved regimen— which may entail a combination therapy for some products/indications. Refer to **Appendix D** for a list of excluded studies during full-text screening.

[††] Epistemonikos is a medical literature database consolidating SRs from Cochrane, Pubmed, Embase, CINAHL, and others.

3.0 MECHANISM OF ACTION

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is expressed on epithelial tissues.[12] In certain cancers this tyrosine kinase is overly active and/or overly expressed which propagates the cancer.[9,40] The reviewed agents inhibit EGFR (also known as EGFR-1), ultimately reducing associated downstream signaling transduction pathways that would otherwise stimulate tumor growth and survival. However, they are not specific for tumor cells and can affect non-tumor cells. Some of these agents may also affect other receptors (eg, MET [MET proto-oncogene, receptor], VEGFR [vascular endothelial growth factor receptor, HER2 [human epidermal growth factor receptor 2; ie, EGFR-2]) that are also relevant in the proliferation of certain cancers. **Table 3** summarizes the targeted receptors for each reviewed agent according to the mechanism of action section of product prescribing information.

Table 3. Mechanism of Action Information from Package Inserts

Agent (initial approval year)	**Inhibited Receptors**[a]	**Additional Information**
Oral Agents		
Erlotinib (2004)	EGFR	
Gefitinib (2003)	EGFR	Also inhibited IGF- and PDGF-mediated signaling in addition to EGF-mediated signaling
Lazertinib (2024)	EGFR	Only approved for use in combination with amivantamab
Lapatinib (2007)	EGFR, HER2	Approved for use in combination therapy only, with capecitabine or letrozole, depending on the indication
Afatinib (2013)	EGFR, HER2, and HER4	
Dacomitinib (2018)	EGFR, HER2, and HER4	Also has in-vitro inhibition activity at DDR-1, DDR-2, EPHA6, LCK, MNK1
Neratinib (2017)	EGFR, HER2, and HER4	
Vandetanib (2011)	EGFR, VEGFR	
Osimertinib (2015)	EGFR, HER2, HER3, HER4, ACK1, and BLK	
Intravenous Agents		
Cetuximab (2004)	EGFR	Recombinant human monoclonal antibody against EGFR
Panitumumab (2006)	EGFR	
Necitumumab (2015)	EGFR	
Amivantamab (2021)	EGFR, MET	Recombinant bispecific human antibody against EGFR and MET

Abbreviations: BLK, B lymphocyte kinase; DDR, discoidin domain receptor tyrosine kinase; EGFR, epidermal growth factor receptor; EPHA6, ephrin type-A receptor 6; HER, human epidermal growth factor receptor; IGF, insulin-like growth factor; LCK, lymphocyte cell-specific protein-tyrosine kinase; MET, MET proto-oncogene, receptor tyrosine kinase; MNK1, MAP kinase signal-integrating kinase 1; PDGF, platelet-derived growth factor; VEGFR, vascular endothelial growth factor receptor

[a] *There can be a variety of alias names for a given tyrosine kinase receptor; common alias names are as follows in parentheses: for EGFR (ErbB1, HER1, EGFR1); for HER2 (ErbB2, EGFR2); HER3 (ErbB3, EGFR3) HER4 (ErbB4, EGFR4)*[9,11,41,42]

4.0 APPROVED INDICATIONS

Table 4 shows the clinical scenarios for which the EGFR-inhibitors are indicated (ie, FDA-approval; including indication specifications regarding prior treatment, other clinical characteristics, and co-treatments as applicable). Approved indications encompass 6 oncologic disorders: breast cancer, metastatic colorectal cancer (mCRC), head and neck squamous cell carcinoma (SCCHN), non-small cell lung cancer (NSCLC), pancreatic cancer, and medullary thyroid cancer. Of the EGFR inhibitors, only cetuximab and erlotinib, are approved for more than 1 main oncologic disease (they each have 2 approved oncologic disease states). Oncologic disorders with more than 1 EGFR inhibitor approved for use include breast cancer, mCRC, and NSCLC. However, since approved indications are also specific to use as first- or second-line therapy, prior treatment, co-treatments, or other clinical characteristics (eg, genetic mutations or histology), *indications may not fully overlap*.

Two oral agents are approved for breast cancer: lapatinib is approved for postmenopausal women with hormone receptor-positive, HER2-positive metastatic breast cancer; furthermore, lapatinib or neratinib are approved for subsequent therapy of advanced or metastatic HER2-positive breast cancer. Neratinib is also approved for adjuvant therapy of early-stage disease.

Two intravenous agents are approved for mCRC: cetuximab and panitumumab are indicated for first-line treatment of KRAS wild-type (WT) mCRC, in combination with particular (but slightly different) chemotherapy backbones. Cetuximab and panitumumab are also approved for subsequent-line therapy after failing oxaliplatin- and irinotecan-based first-line regimens. Cetuximab is also indicated for BRAF V600F mutant disease, in combination with encorafenib.

Eight EGFR inhibitors are approved for NSCLC, with indications specified to particular EGFR mutations in most cases, with the exception of necitumumab (generally indicated for metastatic squamous NSCLC). Afatinib's indication for first-line therapy is also rather general: for *non-resistant* EGFR mutations but the clinical trials section of the package insert describes efficacy for exon 19 deletion or exon 21 L858R mutations. Additional agents are also indicated for first-line therapy for NSCLC with exon 19 deletion or exon 21 L858R substitution mutations: amivantamab, dacomitinib, erlotinib, gefitinib, and osimertinib. In addition, osimertinib is uniquely indicated for EGFR T790M mutation-positive NSCLC , which is a key mutation that renders resistance to the first- and second- generation EGFR inhibitors (ie, erlotinib, gefitinib, afatinib, and dacomitinib).[10,15] In additional to the previously mentioned indications, amivantamab is uniquely indicated for exon 20 insertion mutations, which are typically resistant to first- and second-generation EGFR inhibitors as well as osimertinib.[10,15,43]

Three agents have uniquely indicated disease states that no other EGFR inhibitors have: cetuximab for head and neck squamous cell carcinoma, erlotinib for pancreatic cancer, and vandetanib for medullary thyroid cancer.

Table 4. EGFR Inhibitor Indications[1-13]

Indicated Agent	Indicated Clinical Scenario
Breast cancer	
Lapatinib	○ In combination with capecitabine for advanced or metastatic breast cancer with overexpression of HER2 previously treated with chemotherapy including an anthracycline, a taxane, and trastuzumab ○ In combination with letrozole for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer with overexpression of HER2 (for whom hormonal therapy is indicated)
Neratinib	○ For extended adjuvant treatment of adults with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy ○ In combination with capecitabine, for adults with advanced or metastatic HER2-positive breast cancer who have received ≥2 prior anti-HER2 based regimens in the metastatic setting
Colorectal cancer, metastatic (mCRC)	
Cetuximab	For K-RAS wild-type, EGFR-expressing, mCRC: ○ First-line treatment, in combination with FOLFIRI ○ For disease refractory to irinotecan-based chemotherapy, in combination with irinotecan ○ As monotherapy after failing oxaliplatin- and irinotecan-based chemotherapy (or intolerance) For adults with BRAF V600E mutation-positive mCRC, in combination with encorafenib
Panitumumab	For K-RAS wild-type, mCRC: ○ First-line treatment, in combination with FOLFOX ○ As monotherapy following disease progression after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.
Non-small cell lung cancer (NSCLC)	
Afatinib	○ First-line treatment for metastatic NSCLC with non-resistant EGFR mutations ○ For progression of metastatic, squamous NSCLC following platinum-based chemotherapy
Amivantamab	○ First-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, in combination with carboplatin and pemetrexed ○ First-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with lazertinib ○ For adults with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, with disease progression on or after platinum-based chemotherapy; as monotherapy ○ For adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations and disease progression on or after treatment with an EGFR inhibitor; in combination with carboplatin and pemetrexed

Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, irinotecan; FOLFOX, fluorouracil, leucovorin, oxaliplatin; HER2, human epidermal growth factor receptor 2; K-RAS wild-type. wild-type in both KRAS and NRAS genes as determined by an FDA-approved test; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase

Table 4. EGFR Inhibitor Indications[1-13]

Indicated Agent	Indicated Clinical Scenario
Dacomitinib	First-line treatment for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Erlotinib	First-line, maintenance, or second- or greater-line therapy after progression following a prior chemotherapy regimen, for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Gefitinib	First-line for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Lazertinib	First-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with amivantamab
Necitumumab	First-line for metastatic squamous NSCLC, in combination with gemcitabine and cisplatin
Osimertinib	○ Adjuvant therapy after tumor resection in adults with NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations ○ First-line for adults with metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations ○ First-line for locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations, in combination with pemetrexed and platinum-based chemotherapy ○ Subsequent-line treatment for adults with metastatic EGFR T790M mutation-positive NSCLC with progression on or after EGFR TKI therapy
Head and neck squamous cell carcinoma	
Cetuximab	○ Locally or regionally advanced disease, in combination with radiation therapy ○ Recurrent locoregional disease or metastatic disease, in combination with platinum-based therapy with fluorouracil ○ Recurrent or metastatic disease with progression after platinum-based therapy
Pancreatic Cancer	
Erlotinib	First-line for locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine
Thyroid cancer	
Vandetanib	For symptomatic or progressive medullary thyroid cancer (unresectable locally advanced or metastatic disease)

Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, fluorouracil, leucovorin, irinotecan; FOLFOX, fluorouracil, leucovorin, oxaliplatin; HER2, human epidermal growth factor receptor 2; K-RAS wild-type. wild-type in both KRAS and NRAS genes as determined by an FDA-approved test; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase

5.0 SPECIAL POPULATIONS

Although EGFR inhibitors are not expressly contraindicated during **pregnancy**, their mechanism of action and findings from animal studies implicate that inhibition of epithelial cell development would cause fetal harm: "Disruption or depletion of EGFR in animal models results in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development."[6,10] Animal models have demonstrated embryotoxicity and increased loss of the fetus with EGFR inhibitors used at near therapeutic doses or even at subtherapeutic doses with some agents (eg, 0.2 times the therapeutic dose with afatinib and neratinib). Use of effective contraception is advised during treatment with EGFR inhibitors and for a period after their discontinuation (eg, at least 17 days after the last dose). Pregnant women should be warned of the potential risk of fetal harm.[1-12]

Product labeling (ie, package inserts) for the reviewed agents describe that their safety and efficacy have not been established in the **pediatric population. Table 5** provides hepatic and renal dose adjustment information for the reviewed agents.

Table 5. Renal and Hepatic Impairment Information[1-13]

Renal dose adjustments
• No dose adjustment required for mild to moderate impairment: afatinib, amivantamab, dacomitinib, lazertinib, osimertinib • No dose adjustment is recommended or specified in the labeling: cetuximab, erlotinib, gefitinib, lapatinib, necitumumab, neratinib, panitumumab
For moderate renal impairment:
Vandetanib: decrease the starting dose to 200 mg daily
For severe renal impairment:
Afatinib: dose reduce to 30 mg daily
Not recommended in severe impairment: vandetanib
The following agents have not been studied in end-stage, grade 5 renal impairment: afatinib, amivantamab, dacomitinib, gefitinib, lapatinib
Hepatic dose adjustments
• No adjustment specified in labeling based on pre-existing impairment: cetuximab, erlotinib, necitumumab, panitumumab • No dose adjustment needed with mild impairment: vandetanib • No dose adjustment needed for mild or moderate impairment: afatinib, dacomitinib, lapatinib, lazertinib, neratinib, osimertinib
For mild impairment:
Gefitinib: may consider dose reduction since exposure is increased
For moderate impairment:
Gefitinib: consider dose reduction since exposure is increased
Vandetanib: not recommended in moderate or severe hepatic impairment
For severe impairment:
Lapatinib: dose reduce to 750 mg daily if in combination with capecitabine; or to 1,000 mg daily if in combination with letrozole
Gefitinib: consider dose reduction since exposure is increased

Table 5. Renal and Hepatic Impairment Information[1-13]

Neratinib: dose reduce to 80 mg daily *Not recommended in severe hepatic impairment*: vandetanib *Has not been studied in severe hepatic impairment:* afatinib, lazertinib, osimertinib; amivantamab, necitumumab, panitumumab

6.0 DISEASE OVERVIEW, GUIDELINE PLACE-IN-THERAPY, AND DIRECT COMPARATIVE EVIDENCE

The following subsections are organized according to overlapping indicated disease states among the reviewed EGFR-inhibitors: breast cancer (Section 6.1), metastatic colorectal cancer (Section 6.2), and non-small cell lung cancer (Section 6.3). Thereafter, subsections address remaining approved indications that are unique to particular agents (applicable to vandetanib for thyroid cancer [Section 6.4], cetuximab for head and neck squamous cell carcinoma [Section 6.5], and erlotinib for pancreatic cancer [Section 6.6]).

National Comprehensive Cancer Network (NCCN) guidelines referenced in this report are as follows:

- Breast Cancer guideline (Version 6.2024)
- Colon Cancer guideline (Version 5.2024)
- NCCN Non-Small Cell Lung Cancer guideline (Version 11.2024; and Version 2.2025)
- Pancreatic Adenocarcinoma (Version 3.2024 and Version 1.2025)
- Thyroid Carcinoma guideline (Version 4.2024)
- Head and Neck Cancer guideline (Version 1.2025)

The NCCN guidelines categorize recommended regimens either as “preferred”, “other recommended”, or “useful in certain circumstances”; multiple regimen options may be listed in each recommendation category. Descriptions of each category are as follows:

- *Preferred*: interventions are preferrable “…based on superior efficacy, safety, and evidence; and, when appropriate, affordability."[17]
- *Other recommended*: interventions that are “…somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes,” relative to preferred options.[17]
- *Useful in certain circumstances*: “…may be used for selected patient populations…”[17] In addition to the reviewed drug class, the following drug classes are referred to in the following subsections when discussing recommended regimens:
- Antiangiogenic drugs, a broad pharmacologic class which includes certain **tyrosine kinase inhibitors** (**TKIs**; eg, sorafenib, lenvatinib, and cabozantinib) as well as anti-VEGF medications (eg, bevacizumab, ramucirumab, ziv-aflibercept).[44]
- **Immune check point inhibitors** (ICIs) include programmed cell death-1 (PD-1) receptor and PD-1 ligand (PD-L1) inhibitors (eg, nivolumab, pembrolizumab, durvalumab, dostarlimab, and atezolizumab); and inhibitors of cytotoxic T-lymphocyte-associated protein 4 (CTLA4; eg, tremelimumab and ipilimumab).[44]

6.1 Breast Cancer

Breast cancer is the leading cancer diagnosis in US females and the second leading for cancer-related deaths in females.[16] Estimated age-adjusted rates of new diagnoses or deaths by year in the US were as follows: breast cancer new diagnosis (in 2021), 134 per 100,000 women; and breast cancer-related deaths (in 2022), 19 per 100,000 women, in 2022.[45] Tangibly, about 1 in 8 US women will be diagnosed with invasive breast cancer during their lifetime and 1 in 43 will die from breast cancer.[46] The distribution of invasive breast cancer and deaths is primarily among women 50 years of age and older (84% of invasive cases and 91% of deaths).

Biomarkers guide pharmacotherapy decision-making for breast cancer. The NCCN recommends hormone-receptor testing (HR; ie, mutational characterization of estrogen receptors [ER] and progesterone receptors [PR]) for new primary or newly metastatic breast cancer, and at least ER testing for ductal carcinoma in situ (DCIS).[16] Additionally, mutational status regarding HER2 expression is central to guiding therapy decisions for invasive breast cancer.

The following bullets describe key molecular categories that influence treatment decisions:

- **ER status**: *ER-positive* status is defined as cancers with 1% or more of cells staining positive for ER expression. ER-positive disease is eligible for endocrine therapies[‡‡]; however, susceptibility to these treatments is more variable for invasive cancers with 1%–10% of cells with ER positivity (ie, ER-low-positive). *ER-negative* status is defined as cancers with <1% of positive staining cells for ER expression. These cancers generally do not benefit from endocrine therapies.[16]
- **PR testing** helps define the prognosis for breast cancer and serves as a control for potential false-negative ER results. Cancers with ER-negative, PR-positive results can be considered for endocrine therapies, yet this is based on limited data. PR-positive is defined as 1%–100% of cells staining positive for PR expression; PR negative is <1% of cells with PR expression.[16]
- **HER2 mutation status** is determined with immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). IHC detects HER2 prevalence on sampled cells. FISH testing determines the ratio of HER2 gene copies per chromosome 17; if the ratio is greater than 1, the gene is overly abundant. About 14% to 20% of breast cancer cases manifest HER2 overexpression (HER2 positive [HER2+]) and about half of these are also ER-and PR-positive (ie, HR positive [HR+]).[40,46]
- **BRCA 1/2 mutation status:** certain targeted therapies (eg, olaparib or talazoparib) may be indicated for this mutation depending on the clinical scenario.

Most breast cancer cases are luminal A subtype (68%; typically HR+/HER2-), which have a relatively slow progression and high response to hormone therapy.[46] The distribution of other subtypes is as follows: 10% as basal-like subtype (typically HR-/HER2-; ie, triple negative), 10% are the luminal B subtype (HR+/HER2+), and 4% are HR-/HER2+ (referred to as HER2 enriched); these latter subtypes are more aggressive relative to luminal A.[46] Based on the five year survival rates, triple-negative disease (ie, HR-/HER2-) is the most aggressive (77% 5-year survival); this subtype is twice as common in Black women versus other racial groups.[47] The second most aggressive is HER2 enriched (HR-/HER2+) disease (85% 5-year survival). Five-year survival rates for luminal A or B subtypes, with HR+ mutational status, are nearly

[‡‡] Endocrine therapies used in breast cancer include tamoxifen, aromatase inhibitors, elacestrant, and fluvestrant.

90% or higher.[46] Invasive breast cancer is prone to spread to the brain (occurring in about 30% of cases), especially with the molecular subtypes that are HER2+ or triple-negative.[48]

Two EGFR inhibitors are approved for the treatment of breast cancer, each with dual mechanisms of action (inhibition of EGFR and HER2): lapatinib and neratinib. There are also other FDA-approved HER2 inhibitors[§§]; however, because they are not considered EGFR1 inhibitors, they are not fully reviewed in this report. Nonetheless, they are included in the guideline section where there is an over-lapping recommended place-in-therapy with lapatinib or neratinib.

Both lapatinib and neratinib are approved for subsequent therapy of advanced or metastatic HER2-positive disease.[5,7] Neratinib is also approved for adjuvant therapy of early-stage disease. Both agents are taken orally on a daily basis, though, depending on the indication may be taken daily as part of a 3 week cycle with 1 week off.[5,7] Treatment regimens with these agents can confer a high pill burden being that 5 to 6 tablets are required per daily dose of either lapatinib or neratinib, along with the combined agent (eg, capecitabine, another 4-7 tablets per day). **Table 6** summarizes approved indications for the lapatinib and neratinib; Table 1 of Appendix A provides the recommended dosing.

Table 6. EGFR Inhibitors, Approved Indications for Breast Cancer[5,7]

Lapatinib	• For postmenopausal women with hormone receptor-positive, HER2-positive **metastatic** breast cancer in whom hormonal therapy is indicated; used in combination with letrozole • For **advanced or metastatic breast** cancer with overexpression of HER2, *previously treated* with chemotherapy including an anthracycline, a taxane, and trastuzumab
Neratinib	• For extended **adjuvant** treatment of adults with early-stage HER2-positive breast cancer, *to follow* adjuvant trastuzumab-based therapy • For adults with **advanced or metastatic** HER2-positive breast cancer *after receiving ≥2 prior anti-HER2 based regimens* for metastatic disease, in combination with capecitabine
Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2	

6.1.1 Guideline Recommendations for EGFR Inhibitors

The EGFR/HER2 inhibitors (neratinib and lapatinib) are used for the treatment of advanced recurrent/unresectable or invasive breast cancer, particularly for cancers that are *HER2-positive.* For patients with advanced or metastatic HER2-positive disease who are indicated for endocrine therapy (ie, with ER or PR positive disease), lapatinib is among NCCN-recommended, endocrine therapy-containing combination regimens (combined with an aromatase inhibitor, with or without trastuzumab).[16] Several trastuzumab-containing regimens (in combination with endocrine therapy) are additional, equally preferred regimens as to lapatinib-based regimens. Otherwise for patients with HER2-positive advanced disease *not indicated for endocrine therapy*, lapatinib and neratinib are among *fourth-line* regimens, in

[§§] Other HER2 inhibitors include trastuzumab and its biosimilars, trastuzumab-chemotherapy drug conjugates, margetuximab, pertuzumab, and tucatinib. Some of these agents (trastuzumab, ado-trastuzumab emtansine, and pertuzumab) are options in the preoperative and adjuvant setting, as well as the recurrent, unresectable setting. Additionally, fam-trastuzumab deruxtecan-nxki also has a place-in-therapy for second- or later-line treatment of *HER2-negative*, recurrent, unresectable disease with HER2 immunohistochemistry 1+ or 2+/in situ hybridization-negative molecular status.

combination with capecitabine, or in combination with trastuzumab (for lapatinib only); earlier-line regimens for this scenario comprise other HER2-inhibitors such as trastuzumab/biosimilars, trastuzumab-chemotherapy drug conjugates, pertuzumab, and tucatinib (refer to **Table 7**).[16]

In-line with its approved indications, the NCCN notes that neratinib can additionally be considered in the adjuvant setting for HR- and HER2-positive tumors after completion of adjuvant trastuzumab. There is also emerging evidence for the use of neratinib for HER2-negative, ER-positive invasive cancer previously treated with a cyclin dependent kinase (CDK) 4/6 inhibitor, but the guideline notes evidence is currently limited.

Table 7. NCCN Breast Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024[16,a]

A. Systemic Adjuvant Treatment for HR-positive, HER-2-positive Disease
• "Consider extended adjuvant **neratinib** *following adjuvant trastuzumab*-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence" (page 18; based on a phase 3 trial)
B. Systemic Therapy for Recurrent, Unresectable (Local or Regional) or Stage IV (M1) Disease

For **HER2-positive**, **ER and/or PR positive disease,** and postmenopausal women or premenopausal women receiving ovarian ablation or suppression (all are category 2A)
• aromatase inhibitor ± (**lapatinib** or trastuzumab)
• aromatase inhibitor **± lapatinib** + trastuzumab
• fulvestrant ± trastuzumab
• tamoxifen ± trastuzumab
• note: an FDA-approved biosimilar for trastuzumab is an acceptable substitute in applicable scenarios
For **HER2-positive, HR-positive or -negative** (category 2A, unless otherwise specified)
• *First line*: pertuzumab + trastuzumab + (docetaxel [category 1] or paclitaxel)
• *Second line*: fam-trastuzumab deruxtecan-nxki (T-Dxd, category 1)
• *Third line*:
  ○ tucatinib + trastuzumab + capecitabine (category 1)
  ○ ado-trastuzumab emtansine (T-DM1)
• *Fourth line and beyond* (unknown optimal sequence):
  ○ trastuzumab + docetaxel or vinorelbine
  ○ tastuzumab + paclitaxel ± carboplatin
  ○ capecitabine + (trastuzumab or **lapatinib or neratinib**)
  ○ trastuzumab + **lapatinib**
  ○ trastuzumab + other chemotherapy agents
  ○ margetuximab-cmkb + chemotherapy
  ○ targeted therapy options for other biomarkers such as PIK3CA, AKT1, ESR1, BRCA1 or 2, NTRK, TMB-H, or RET-fusion (refer to guideline)
• an FDA-approved biosimilar for trastuzumab is an acceptable substitute in applicable scenarios above

Table 7. NCCN Breast Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024[16,a]

Additional options for stage IV (M1) disease, based on emerging biomarkers

For ER-positive/**HER2-negative** disease, *previously treated* with a CDK4/6 inhibitor, favorable but limited data is emerging for use of the following regimens:

- **neratinib** ± fulvestrant (category 2B)
- **neratinib** ± trastuzumab/fulvestrant (category 2B)

Refer to guideline for additional regimens to treat **HER2-negative** disease

Abbreviations: BRCA, breast cancer susceptibility protein; CDK, cyclin dependent kinase; EGFR, epidermal growth factor receptor; ER, estrogen receptor status; HER2, human epidermal growth factor receptor 2; M1, distant metastasis; NCCN, National Comprehensive Cancer Network; PR, progesterone receptor status; TMB-H, tumor mutational burden-high

[a] *Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

The ASCO 2022 guideline is consistent with the NCCN in recommending the combination of trastuzumab plus pertuzumab and a taxane for first-line treatment of HER2+ advanced breast cancer; and reserving lapatinib- and neratinib-based regimens for third- or later-line therapy.[49] In the case of HER2-positive advanced disease with ER or PR positivity, the ASCO recommends considering endocrine therapy plus trastuzumab or lapatinib, or endocrine therapy alone.[49]

6.1.2 Comparative RCTs for Approved EGFR Inhibitors for Breast Cancer

Several recent systematic reviews (SRs)[49-52] cite 1 eligible comparative RCT (the NALA trial) between neratinib- and lapatinib-based therapy (each in combination with capecitabine) for the treatment of advanced HER2-positive breast cancer in the setting of *subsequent-line therapy* without endocrine therapy.

NALA was a multinational, open-label, phase 3 study RCT in patients treated with at least 2 prior HER2-directed regimens for advanced breast cancer.[34] Cases with brain metastasis were permitted for inclusion if they were in stable condition and non-symptomatic. Of the included patients (N=621) nearly all (99.7%) had prior treatment with trastuzumab, 54.3% had trastuzumab emtansine (T-DM1), and 42% had pertuzumab (not mutually exclusive due to combination regimens). Patients were randomized to either neratinib 240 mg daily plus capecitabine 1,500 mg/m^2 daily or to lapatinib 1,250 mg daily plus capecitabine 2,000 mg/m^2 daily; endocrine therapy was not allowed. The neratinib arm also received prophylactic antidiarrheal medication.[34]

Co-primary endpoints were progression free survival (PFS) and overall survival (OS; by blinded assessment). At the primary cut-off assessment (median follow-up of 29.9 months), neratinib outperformed lapatinib for PFS (mean PFS of 8.8 months vs. 6.6 months, HR = 0.76, p = 0.006). With respect to the OS, the trend favored neratinib but was not significant (mean OS of 24.0 months vs. 22.2 months, HR = 0.88, p = 0.21). Furthermore, significantly fewer patients in the neratinib arm required intervention for CNS metastasis. Regarding interaction tests for pertinent clinical covariates, hormone

receptor (HR) status and disease location had a significant effect on the PFS outcome: HR-negative status and non-visceral disease, independently, had more favorable responses to neratinib-based therapy compared to HR-positive or visceral disease, respectively.[34]

Numerically more lapatinib-treated patients (vs. neratinib-treated) had serious treatment-emergent adverse events (AEs; 34% vs. 30%) and discontinued treatment due to treatment-emergent AEs (18% vs. 14%). Although similar proportions of patients in each treatment arm experienced grade 3 or greater AEs (61% in each treatment arm), numerically more neratinib-treated patients experienced grade 3 or 4 diarrhea (24.4% vs 12.5%) even with anti-diarrheal prophylaxis, and numerically more lapatinib-treated patients experienced grade 3 or 4 palmar-plantar erythrodysesthesia (11.3% vs. 9.6%).[34]

6.2 Colorectal Cancer (CRC)

CRC was attributed to the 4th highest cancer incidence in the US (2021 age-adjusted rate of CRC: 36 per 100,000 people) and the 4th highest cancer-related death rate (after lung, prostate, and breast cancer; 2022 age-adjusted rate: 13 per 100,000 people). Utah rates are generally lower than national rates (age-adjusted incidence rate of CRC is 27).[45] Approximately 50-60% of CRC cases progress to metastatic disease, most often spreading to the liver and sometimes to the lungs.[17] The 5-year survival rate of unresectable metastatic CRC (mCRC) is 14%.[53,54] Risk factors for CRC include having a first-degree relative with CRC; a history of Lynch syndrome or inflammatory bowel disease; and possibly vitamin D deficiency, high red/processed meat consumption, high smoking or alcohol consumption, diabetes mellitus, metabolic syndrome, and obesity.[17]

Biomarkers guide pharmacotherapy decision-making for CRC treatment. The NCCN recommends for all patients with CRC to undergo tumor genotype assessment for RAS and BRAF mutations, as well as assessment for HER2 amplifications and mismatch repair (MMR) status (or microsatellite instability [MSI] or stability [MSS]).[17] It is recommended for molecular testing to be evaluated via broad molecular profiling with next-generation sequencing (NGS), since this genetic platform allows for identification of other rare actional driver mutations that can also influence treatment decisions (eg, POLE/POLD1, RET, and NTRK mutations).[17] The following bullets describe key mutational or molecular categories that influence treatment decisions:

- MMR deficiency (dMMR) and MSI refer to an endogenous DNA mismatch repair (MMR) system that insufficiently repairs DNA and can lead to accumulation of mutations.
    - MMR or MSI status testing is recommended to characterize all patients with colon cancer at diagnosis since appropriate treatment varies according to this histologic marker.[17] Cases without dMMR/MSI are referred to as proficient MRR (pMMR) or microsatellite stable (MSS). Cases with dMMR/MSI are further subcategorized as either MSI high (MSI-H) or MSI low (MSI-L) depending on the level of instability.
- RAS genetic mutations (genetic mutations in exon 2, 3, or 4 of KRAS or NRAS genes)
    - Testing for RAS mutations is recommended in all patients with mCRC.[17] Patients without mutation(s) are referred to as wild-type (WT) RAS.
        - Patients with RAS-related mutations (eg, in KRAS exons 2, 3, and 4; or NRAS exons 2, 3, and 4) should avoid anti-EGFR therapy unless part of a regimen targeting a KRAS G12C mutation per NCCN guidance[17]

    - As many as 40% of mCRC cases are reported to have KRAS mutations in codons 12 and 13, and of these, KRAS G12C comprised around 17% of cases[17]

- BRAF genetic mutation: genetic mutation of type V600E
    - Testing for BRAF mutation is recommended in all patients with mCRC[17]
    - An estimated 5-9% of mCRC cases are BRAF positive; generally, this mutation is limited to tumors without RAS mutations (ie, WT RAS).[17]
    - Cetuximab and panitumumab must be given with a BRAF inhibitor (encorafenib) in the presence of this BRAF mutation[17]
- HER2 positive: overexpression of the HER2 receptor
    - Testing is reserved to cases without RAS or BRAF mutations (ie, *wild-type* BRAF and *wild-type* RAS)[17]
    - Approximately 3% of CRC cases are HER2 positive
    - Anti-HER2 therapy is indicated in HER2-amplified tumors that are WT RAS/BRAF wild-type[17]
- POLE/POLD1 mutations
    - These refer to polymerase gene mutations that cause loss of function in subunits of the enzyme responsible for DNA proofreading/correction of mispaired bases during DNA replication.
    - POLE mutations occur in about 2% to 8% of CRC cases that are predominately MSS/pMMR; POLD1 mutations are extremely rare. Generally, patients with these mutations have a favorable prognosis and respond well to immune checkpoint inhibitors.[17]
- Other mutational biomarkers exist but present less frequently, such as NTRK fusions (<1% of CRC cases; may indicate treatment with entrectinib or larotrectinib), and RET fusions (<1% of cases; may indicate selpercatinib treatment).[17]

Monoclonal antibodies including EGFR inhibitors and vascular endothelial growth factor (VEGF) inhibitors (eg, bevacizumab) are approved and used for CRC. Two EGFR inhibitors are approved for the treatment of mCRC; however, their indications differ. Cetuximab is approved for the treatment of 2 histologic mCRC subtypes (K-RAS WT or BRAF V600E) and panitumumab is indicated for one subtype (K-RAS WT). Yet, there is supportive evidence for off-label use of both agents for additional mutational subtypes according to the NCCN guideline-recommended place in therapy as outlined in the following section. Both EGFR agents are administered IV on a biweekly interval, or on a weekly interval for cetuximab only. **Table 8** summarizes FDA-approved indications for cetuximab and panitumumab; Table 1 of Appendix A provides the recommended dosing.

Table 8. EGFR Inhibitors, Approved Indications for Colorectal Cancer[3,12]

Cetuximab	For **K-RAS wild-type, EGFR-expressing, mCRC**: • *First-line treatment*, in combination with FOLFIRI • For disease refractory to irinotecan-based chemotherapy, in combination with irinotecan • As monotherapy after failing oxaliplatin- and irinotecan-based chemotherapy (or intolerance) For adults with **BRAF V600E mutation-positive mCRC**, in combination with encorafenib

Table 8. EGFR Inhibitors, Approved Indications for Colorectal Cancer[3,12]

Panitumumab	For **K-RAS wild-type, mCRC**: • *First-line treatment*, in combination with FOLFOX • As monotherapy following disease progression after failing fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy.

Abbreviations: EGFR, epidermal growth factor receptor; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX, leucovorin + fluorouracil + oxaliplatin; mCRC, metastatic colorectal cancer

6.2.1 Guideline Recommendations for EGFR Inhibitors

Cetuximab and panitumumab are among NCCN-recommended, first-line and subsequent-line unresectable mCRC regimens, particularly for WT RAS/BRAF.[17] These therapies are often used in combination with a chemotherapy backbone[***]. In the setting of first-line treatment for mCRC, the location of the primary tumor (eg, left-sidedness) is a predictive factor of response to EGFR inhibitors. Only left sided-originating tumors (ie, from splenic flexure to rectum) are recommended for treatment with cetuximab or panitumumab in the setting of first-line treatment of metastatic disease, however, for subsequent therapy (ie, after failing a recommended first-line regimen), the tumor origination location is not a treatment restriction.[17]

According to the NCCN guideline, no comparative studies have been completed for cetuximab versus panitumumab in the setting of first-line therapy.[17] Rather, comparative studies are with respect to cetuximab- or panitumumab-based regimens versus bevacizumab-based regimens (an IV anti-VEGF therapy) for first-line therapy of mCRC. The NCCN guideline notes that currently, the options of either cetuximab, panitumumab, or bevacizumab added to chemotherapy are considered equivalent choices for first-line treatment of metastatic WT RAS/NRAS/BRAF mCRC (with pMMR/MSS).[17] Two non-inferiority, comparative RCTs are available in the setting of *subsequent-line therapy,* for panitumumab versus cetuximab, as described in the following section (6.2.2).

A regimen with cetuximab or panitumumab is among NCCN recommended options, for pMMR/MSS disease in the following settings[17]:

- *First-line* treatment of unresectable, WT RAS/BRAF, mCRC originating from the left side[†††] (with synchronous liver and/or lung metastases only); in combination with FOLFIRI or FOLFOX
- WT RAS/BRAF CRC (advanced or metastatic disease) with pMMR/MSS as part of an *initial* regimen or as part of subsequent therapy in patients with or without prior treatment with oxaliplatin-based therapy and/or irinotecan-based therapy. Patients with WT RAS/BRAF CRC plus dMMR/MSI-H or POLE/POLD1 mutation that is ineligible for or with progression on an immune checkpoint inhibitor[‡‡‡]

[***] Chemotherapy backbones are typically fluorouracil, leucovorin, oxaliplatin, and/or irinotecan-containing regimens. Abbreviations for certain chemotherapy backbones referred to in this section include: CAPEOX, oxaliplatin + capecitabine; FOLFIRI, leucovorin + fluorouracil + irinotecan; and FOLFOX, leucovorin + fluorouracil + oxaliplatin.

[†††] The left side of the colon is defined as to include the splenic flexure to the rectum for purposes of this recommendation.

[‡‡‡] Immune check point inhibitors for CRC include nivolumab ± ipilimumab, pembrolizumab, or dostarlimab-gxly.

are also eligible for cetuximab- or panitumumab-based initial- and subsequent-line therapy. See **Table 9** and/or guideline for clinical scenarios and recommended co-treatments.

- For unresectable, metachronous, mCRC *previously treated* with FOLFOX and CAPEOX within the past 12 months:
    - in combination with FOLFIRI or irinotecan for WT KRAS/BRAF disease
    - in combination with encorafenib for BRAF V600E-mutant disease (off-label use for panitumumab)
    - in combination with sotorasib or adagrasib for KRAS G12C-mutatnt disease (off-label use for cetuximab and panitumumab)

The dual HER2/EGFR inhibitor, lapatinib is recommended *off-label* in combination with trastuzumab for advanced or metastatic, HER2-positive tumors that are WT for RAS/BRAF.[17]

Table 9 summarizes NCCN treatment recommendations for EGFR-inhibitor-based treatment regimens for advanced or metastatic CRC. The NCCN 2024 guideline is the most recently published US guideline for the treatment of advanced CRC.

The 2023 ASCO guideline *preferred* anti-EGFR-based therapy (cetuximab or panitumumab in combination with doublet chemotherapy) over bevacizumab-based therapy for first-line treatment in patients with **left-sided, unresectable RAS WT mCRC** (with pMMR or MSS), based on meta-analysis data.[55] Anti-EGFR therapy was not recommended for RAS-mutant disease or as first-line treatment for right-sided RAS WT mCRC. For *right-sided RAS WT mCRC*, an anti-VEGF plus chemotherapy was recommended. The ASCO also recommended the combination of cetuximab plus encorafenib for previously-treated, BRAF V600E–mutant mCRC; the guideline's research question did not appear to consider panitumumab treatment for this mutation (different from the NCCN guideline). Unlike the NCCN guideline, there were no recommendations regarding lapatinib for any scenario, nor for anti-EGFR inhibitors for KRAS G12C-mutant mCRC.[55]

Table 9. NCCN Colorectal Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024[17,a]

Recommended regimens listed below containing cetuximab or panitumumab are rated as category 2A for level of evidence unless otherwise specified.[b]

A. Unresectable, mCRC with pMMR/MSS and with Synchronous Liver Only and/or Lung Only Metastases:

- Chemotherapy regimen options: FOLFIRI, FOLFOX, CAPEOX, or FOLFIRINOX
- Biologic + chemotherapy combination regimen options:
  - bevacizumab or approved biosimilar plus FOLFIRI, FOLFOX, CAPEOX, or FOLFIRINOX
  - **panitumumab or cetuximab** (both for KRAS/NRAS/BRAF WT and left-sided tumors only) plus FOLFIRI or FOLFOX

B. Unresectable Metachronous CRC Metastasis with pMMR/MSS *Previously Treated* with FOLFOX/CAPEOX within the Past 12 Months:

- Chemotherapy: FOLFIRI or irinotecan
- Biologic + chemotherapy:
  - bevacizumab (or approved biosimilar) plus FOLFIRI or irinotecan; bevacizumab is preferred over alternative similar anti-VEGF regimens with ziv-aflibercept or ramucirumab (plus FOLFIRI or irinotecan); preference is based on toxicity profiles and/or cost.
  - **cetuximab or panitumumab** (for KRAS/NRAS/BRAF WT) plus FOLFIRI or irinotecan
- Other targeted regimens:
  - **cetuximab or panitumumab** plus encorafenib for BRAF V600E mutation positive
  - **cetuximab or panitumumab** plus (sotorasib or adagrasib) for KRAS G12C mutation
  - trastuzumab + (pertuzumab, **lapatinib**, or tucatinib) for HER2-amplified and RAS/BRAF WT
  - fam-trastuzumab deruxtecan-nxkiss for HER2-amplified, IHC 3+

C. Systemic Initial or Continuation Therapy for Advanced or Metastatic CRC with Any of the Following:

a. pMMR/MSS CRC

b. Previously Treated mCRC with pMMR/MSS and with Synchronous Liver and/or Lung Metastases

c. dMMR/MSI-H or POLE/POLD1 Mutation that is Ineligible for or with Progression on an Immune Checkpoint Inhibitor

d. Unresectable Metachronous mCRC with pMMR/MSS Previously Untreated or Treated with FOLFOX/CAPEOX over 12 months Ago or with 5-FU/leucovorin or capecitabine:

Abbreviations: CAPEOX, oxaliplatin + capecitabine; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX; leucovorin + fluorouracil + oxaliplatin; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; IROX, oxaliplatin + irinotecan; mCRC, metastatic colorectal cancer; MSS, microsatellite stability; NCCN, National Comprehensive Cancer Network; pMMR, proficient mismatch repair; WT, wild-type

[a] *Recommended agents in alternative regimens depend on the presence of certain genetic markers (KRAS/NRAS/BRAF etc.); refer to full guideline for details on all recommended regimens and circumstances. In general, panitumumab or cetuximab are used for KRAS/NRAS/BRAF WT tumors; encorafenib added to an EGFR inhibitor is used for BRAF V600E mutation positive; fam-trastuzumab is used for HER2 amplified tumors that are also RAS/BRAF WT; NTRK inhibitors, larotrectinib and entrectinib, are active against NTRK fusion mutations; and selpercatinib is used for RET gene fusion-positive.*

[b] *Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

Table 9. NCCN Colorectal Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024[17,a]

- *Initial treatment*:
  Intensive Therapy Options
  - FOLFOX or CAPEOX or FOLFIRI or FOLFIRINOX
  - bevacizumab or approved biosimilar plus FOLFOX or CAPEOX or FOLFIRI or FOLFIRINOX
  - **cetuximab or panitumumab** (for KRAS/NRAS/BRAF WT and left-sided tumors only) + (FOLFOX or CAPEOX or FOLFIRI)

  Non-intensive Therapy Options
  - 5-FU +/- leucovorin +/- bevacizumab
  - capecitabine +/- bevacizumab
  - **cetuximab or panitumumab** monotherapy (only for KRAS/NRAS/BRAF WT and left-sided tumors; category 2B)
  - trastuzumab + (pertuzumab or **lapatinib** or tucatinib) for HER-2 amplified and RAS/BRAF WT tumors
- *Subsequent treatment;* refer to guideline for all optional regimens per mutational/biomarker status; only cetuximab or panitumumab regimens are listed:
  - **cetuximab or panitumumb** +/- irinotecan for KRAS/NRAS/BRAF WT
  - **cetuximab or panitumumb** + FOLFIRI for KRAS/NRAS/BRAF WT (for those without prior irinotecan treatment)
  - **cetuximab or panitumumb** + (FOLFOX or CAPEOX) for KRAS/NRAS/BRAF WT and prior irinotecan-based therapy without oxaliplatin
  - **cetuximab or panitumumb** + encorafenib for BRAF V600E mutation positive disease
  - **cetuximab or panitumumb** + (sotorasib or adagrasib) for KRAS G12C mutation positive disease

Abbreviations: CAPEOX, oxaliplatin + capecitabine; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; FOLFIRI, leucovorin + fluorouracil + irinotecan; FOLFOX; leucovorin + fluorouracil + oxaliplatin; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; IROX, oxaliplatin + irinotecan; mCRC, metastatic colorectal cancer; MSS, microsatellite stability; NCCN, National Comprehensive Cancer Network; pMMR, proficient mismatch repair; WT, wild-type

[a] *Recommended agents in alternative regimens depend on the presence of certain genetic markers (KRAS/NRAS/BRAF etc.); refer to full guideline for details on all recommended regimens and circumstances. In general, panitumumab or cetuximab are used for KRAS/NRAS/BRAF WT tumors; encorafenib added to an EGFR inhibitor is used for BRAF V600E mutation positive; fam-trastuzumab is used for HER2 amplified tumors that are also RAS/BRAF WT; NTRK inhibitors, larotrectinib and entrectinib, are active against NTRK fusion mutations; and selpercatinib is used for RET gene fusion-positive.*

[b] *Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

6.2.2 Comparative RCTs for Approved EGFR Inhibitors for mCRC

While comparative RCTs in the setting of first-line mCRC therapy have been performed for bevacizumab (an anti-VEGF monoclonal antibody) versus EGFR inhibitors, many recent SRs corroborate a lack of direct comparative RCTs between the EGFR inhibitors, cetuximab and panitumumab, for *first-line therapy* of advanced or metastatic mCRC.[56-62] Two comparative RCTs have been performed in the setting of *subsequent-line* therapy (ie, after prior treatment with first-line therapy).

6.2.2.1 Subsequent-line therapy

Based on 4 identified SRs, two direct comparative studies were identified in populations with prior failure on first-line therapy in patients with mCRC with **WT RAS exon 2**: Sakai et al (WJOG650G), and Price et al (ASPECCT).[59,60,63,64] Nonetheless, these studies did not appear to assess the mutational status of other pertinent RAS exons or the balance of those between treatment groups.[35,36]

ASPECCT was a multinational, open-label, noninferiority, phase 3 trial in 999 patients (as of July 2012) with metastatic disease who had failed chemotherapy.[35] Patients had prior failure or intolerance to treatment with oxaliplatin- and irinotecan-based chemotherapy, along with a thymidylate synthase inhibitor; about a quarter of patients had received chemotherapy plus bevacizumab. Panitumumab monotherapy (6 mg/kg every 2 weeks) was compared to cetuximab (400 mg/m^2 at initial dose, followed by 250 mg/m^2 every week). Panitumumab was *non-inferior* (but not superior) to cetuximab for the primary endpoint of overall survival (OS): median OS 10.4 vs. 10.0 months with panitumumab vs. cetuximab, respectively (HR 0.97, 95% CI 0.84 to 1.11). Overall progression free survival (PFS) was also similar between treatment groups, along with secondary patient-reported indices scores for health or symptoms (ie, EQ-5D Health Index Scale, the EQ Visual Analog Scale, and the FACT Colorectal Symptom Index). While the incidences of overall AEs along with grade 3 and 4 AEs were similar between treatments, grade 3/4 hypomagnesaemia was higher with panitumumab compared to cetuximab (7% vs 3%, respectively).[35]

The study by Sakai et al, was an open-label, phase 2 RCT including 120 patients in Japan.[36] Patients had unresectable KRAS exon 2 WT mCRC and had failed prior treatment with fluorouracil-, oxaliplatin-, and irinotecan-based chemotherapy (most also containing bevacizumab). Panitumumab 6 mg/kg every 2 weeks was compared to cetuximab (400 mg/m^2 at initial dose, followed by 250 mg/m^2 every week) both in combination with irinotecan. For the primary endpoint of median PFS, panitumumab was non-inferior to cetuximab (5.42 vs. 4.27 months, respectively; HR = 0.64, 95% CI 0.44 to 0.94, P <0.001 for non-inferiority), with the trend favoring panitumumab but superiority was not met. The median OS marginally favored panitumumab (14.85 vs. 11.53 months; HR 0.66, 95% CI 0.44 to 1.00, P = 0.050 for superiority). Grade 3 or 4 hypomagnesaemia occurred at a higher incidence in the panitumumab arm (17% vs. 7%), while grade 3 or worse leucopenia or neutropenia occurred more frequently with cetuximab. Authors noted that the prior ASPECCT trial also suggested a trend (but not significant) in favor of panitumumab over cetuximab for OS and PFS in subgroup analyses of patients previously treated with a bevacizumab-based regimen.[36]

6.3 Non-small Cell Lung Cancer (NSCLC)

Pulmonary cancer (lung and bronchus) is attributed to the leading cause of cancer-related death in the US (2022 age-adjusted rate: 30 per 100,000 people) but accounts for the 3rd highest cancer-diagnosis incidence rate (2021 age-adjusted rate: 49 per 100,000 people), following breast and prostate cancer.[45,65] Non-small cell lung cancer (NSCLC) is the primary type of lung cancer, accounting for approximately 81% of lung cancer cases. Small cell lung cancer is the second most prevalent type accounting for 14% of lung cancer cases.[53] Subcategories of NSCLC include adenocarcinoma (comprising about half of NSCLC cases; originating from mucus glands), squamous cell carcinoma (comprising about a third of NSCLC cases; originating from cells lining the airways and typically more aggressive), adenosquamous carcinoma, large cell carcinoma (about 2% of NSCLC cases; lacks features to define clear lineage), and other rarer forms (eg, sarcomatoid).[53] The overall, 5-year survival rate of NSCLC is 26%.[53]

In order to guide therapy decision-making, testing for certain genetic mutations and biomarkers are recommended for advanced or metastatic NSCLC with an adenocarcinoma component, large cell carcinoma, or NSCLC not otherwise specified (NOS).[65] Molecular and biomarker testing should include assessment for the following eleven markers: EGFR mutations, ALK, KRAS, ROS1, BRAF V600E, NTRK1/2/3 fusions, NRG1, MET exon 14 skipping mutation, RET, ERBB2 alterations (ie, HER2), and PD-L1 expression (an immuno-biomarker).[18] For advanced/metastatic NSCLC with *squamous cell* histologic type, these molecular tests are advised for consideration, rather than having strong recommendation as with the aforementioned histologies.[65] Potential limitations with molecular testing are long turnaround times for results, and that results may be limited by biopsy tissue specimen quality/quantity.[66] Thus, non-biomarker directed therapy *may be* started prior to receiving molecular testing results. Next-generation DNA sequencing is the preferred method to assess EGFR mutational variants. According to the NCCN NSCLC guideline, "…tumors that do not harbor a sensitizing EGFR mutation should not be treated with EGFR TKI in any line of therapy," (page 95, NCCN).[15]

Relevant to choosing EGFR-targeted therapies, the most commonly occurring EGFR mutations in NSCLC that are associated with responsiveness to certain EGFR inhibitors include exon 19 deletion (Ex19del; 45% of EGFR-mutation positive cases) and exon 21 L858R mutation (Ex21-p.L858R; 40% of EGFR-mutation positive cases).[15] EGFR mutations occurring less often but that are sensitive to certain EGFR inhibitors include exon 21 p.L861Q, exon 18 p.G719X, and exon 20 p.S768I mutations. EGFR exon 20 (Ex20) insertion mutations are diverse; most do not respond to traditional EGFR TKIs with exception of mutation Ex20 p.A763_Y764insFQEA and p.A763_Y764insLQEA as noted by the NCCN.[15] Yet, the only EGFR-based therapy in the NCCN treatment algorithm for ex20 insertion mutation is amivantamab.[18]

The EGFR mutation, p.T790M, is a common mutation that confers resistance to first- and second-generation EGFR inhibitors. In this case, newer agents (eg, osimertinib or amivantamab-based therapy) can typically be used for treatment. Thus, following progression on initial EGFR therapy, patients should be at least tested for p.T790M, and considered for testing of other specific potential resistance mutations (MET amplification, ERBB2 amplification) or broad genomic profiling.

Eight available EGFR inhibitors are approved for the treatment of advanced NSCLC: 6 oral agents (afatinib, dacomitinib, erlotinib, gefitinib, lazertinib, and osimertinib), and 2 IV agents (amivantamab, necitumumab). Nonetheless, indications differ regarding the cancer status (eg, localized and/or

metastatic), genetic mutational status, and prior and/or concurrent therapies. The small molecule, EGFR inhibitors are referred to a classical TKIs (tyrosine kinase inhibitors) and in the setting of NSCLC are often referred to and grouped according to "generation":[18]

- First generation TKIs: erlotinib, gefitinib
- Second generation TKIs: afatinib, dacomitinib
- Third generation TKIs: lazertinib, osimertinib

The oral agents are taken daily, while maintenance therapy with the IV agents is administered every 2-3 weeks for amivantamab depending on the indication, or on days 1 and 8 of each 3-week cycle for necitumumab. **Table 10** summarizes approved indications for the reviewed agents; Table 1 of Appendix A includes recommended dosing.

Table 10. EGFR Inhibitor Indications for Advanced Non-small Cell Lung Cancer[4,6,8-11]

Afatinib	• First-line treatment of **metastatic** NSCLC with non-resistant EGFR mutations • Treatment of **metastatic, squamous** NSCLC with disease progression on platinum-based chemotherapy
Amivantamab	• First-line treatment of adults with **locally advanced or metastatic** NSCLC with EGFR exon 20 insertion mutations, in combination with carboplatin and pemetrexed • First-line treatment of adults with **locally advanced or metastatic** NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with lazertinib • For adults with **locally advanced or metastatic** NSCLC with EGFR exon 20 insertion mutations, with disease progression on or after platinum-based chemotherapy; as monotherapy • For adults with **locally advanced or metastatic** NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations and disease progression on or after treatment with an EGFR inhibitor; in combination with carboplatin and pemetrexed
Dacomitinib	• First-line for **metastatic** NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Erlotinib	• First-line treatment, maintenance treatment, or for subsequent treatment (after progression on at least one prior chemotherapy) of **metastatic** NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations
Gefitinib	• First-line treatment of **metastatic** NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations
Lazertinib	• First-line treatment of adults with **locally advanced or metastatic** NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with amivantamab
Necitumumab	• First-line treatment of **metastatic squamous** NSCLC, in combination with gemcitabine and cisplatin

Table 10. EGFR Inhibitor Indications for Advanced Non-small Cell Lung Cancer[4,6,8-11]

Osimertinib	• For **adjuvant therapy** in adults (for up to 3 years) after NSCLC tumor resection, with EGFR exon 19 deletions or exon 21 L858R mutations • First-line treatment for adults with **metastatic** NSCLC and EGFR exon 19 deletions or exon 21 L858R mutations • First-line treatment for adults with **locally advanced or metastatic** NSCLC and EGFR exon 19 deletions or exon 21 L858R mutations, in combination with pemetrexed and platinum-based chemotherapy • For adults with **locally advanced, unresectable (stage III)** NSCLC (with EGFR exon 19 deletions or exon 21 L858R mutation) *without* progression during or following platinum-based chemoradiation therapy • For adults with **metastatic** EGFR T790M mutation-positive NSCLC with disease progression on or after EGFR therapy

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

6.3.1 Guideline Recommendations for EGFR Inhibitors

Treatment for early-stage NSCLC may include tumor resection and/or radiation therapy. For those treated with surgery, patients may also receive systemic therapies around the time of surgery such as immune checkpoint inhibitors, platinum-based chemotherapy, or targeted therapies to EGFR mutations (eg, osimertinib), PD-L1, or ALK rearrangements, as applicable. For example, osimertinib can be considered for completely resected stage IB–IIIA or stage IIIB (T3, N2) NSCLC with EGFR exon 19 deletion or exon 21 L858R mutations. For inoperable localized disease, therapy may involve chemoradiation therapy followed by adjuvant therapy with osimertinib if positive for EGFR ex19del or L858R mutations.

Treatment of metastatic disease (or locoregional advanced and recurrent disease): Targeted therapy is recommended for patients with actionable driver mutations in the setting of metastatic disease[§§§].[15] Similarly, for locally advanced/recurrent disease treatment eventually follows that for metastatic disease targeted to driver mutations as applicable. Osimertinib monotherapy is the preferred first-line agent for metastatic NSCLC with EGFR mutations including the two more common EGFR mutations, Ex19del and Ex21-L858R, and the less common mutations, Ex20-S768I, Ex21-L861Q, and Ex18-G719X (approximately 10% of EGFR mutations). Afatinib, is an additional preferred, first-line agent for EGFR Ex20-S768I, Ex21-L861Q, and Ex18-G719X mutations. Alternative first-line regimens for Ex19del or Ex21-L858R mutations are (a) osimertinib + chemotherapy or (b) amivantamab + lazertinib[****]; other EGFR inhibitors have been designated as useful in certain circumstances (dacomitinib, erlotinib, gefitinib, afatinib, or erlotinib with an anti-VEGF inhibitor). Alternative first-line regimens for the less common EGFR mutations (EGFR Ex20-S768I, Ex21-L861Q, or Ex18-G719X) include monotherapy with dacomitinib, erlotinib, or gefitinib.[15] In the setting of T790M-positive disease (ie, resistance mutation that develops

[§§§] Actionable drive mutations (ie, that guide choosing pharmacotherapy) include ALK rearrangements, EGFR activating mutations (except for exon 20 insertion mutation), ERBB2 mutations, KRAS p.G12C mutations, METex14 skipping, NTRK1/2/3 fusions, RET rearrangements, and ROS1 rearrangements.

[****] Notably, prophylactic anticoagulation is recommended to prevent venous thromboembolic events during treatment with the combination of amivantamab + lazertinib.

during EGFR first/second generation therapy), osimertinib can be considered. Amivantamab, in combination with chemotherapy is a recommended option following progression on osimertinib therapy. For disease that has progressed on osimertinib and amivantamab-based therapy, subsequent-line options include immune-checkpoint-inhibitors, chemotherapy, anti-VEGF-based therapy, or fam-trastuzumab.[15]

For EGFR exon 20 insertion mutation, amivantamab-based therapy is preferred for first-line treatment of non-squamous metastatic disease, and an option for disease progression after other previous therapies regardless of histology (adenocarcinoma or squamous cell). Alternatively for first-line therapy, patients with exon 20 insertion mutations can be treated similar to those without actionable driver mutations, for example with platinum-based chemotherapy (± various immunotherapies such as pembrolizumab or bevacizumab depending on the histology and the patient's performance status).[15]

Initiation of EGFR-targeted therapy is also recommended for patients who have these EGFR mutations discovered after performing a biopsy and were treated with non-targeted first-line systemic therapy. Initial therapy can be completed or interrupted before switching to an EGFR-targeted regimen. Refer to the guideline and **Table 11** regarding other regimens (not including EGFR inhibitors) targeted to other actionable driver mutations (eg, ALK rearrangement, ROS1, BRAF V600 E, NTRK gene fusion, MET exon 14 skipping mutation, RET rearrangement, ERBB2 HER2 mutation).[15]

Despite the broad approved indications that may span subsequent-line therapy for NSCLC in general, the NCCN recommends against erlotinib or afatinib as subsequent therapy for **squamous cell** NSCLC since there are several other options that appear more efficacious and safe for this histology. Additionally, the NCCN does not recommend necitumumab plus gemcitabine and cisplatin, for metastatic squamous cell NSCLC despite its approval for that indication, "…based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin plus gemcitabine" (page 164, NCCN).[15] Mobocertinib is also no longer recommended by the NCCN as it did not meet the phase 3 primary endpoint following FDA-accelerated approval, and as of 2023 is being phased out of the market.[15]

The 2024 ASCO guideline for metastatic NSLCL with actionable driver mutations is largely consistent with the NCCN guidelines with respect to EGFR place-in-therapy.[67,68] For example, like NCCN, the ASCO includes osimertinib monotherapy as a strong recommendation for first-line systemic therapy of disease with ex19del or ex21 L8585 mutations; alternative options (with weak recommendations) are osimertinib + chemotherapy or amivantamab + lazertinib.[68] Amivantamab plus chemotherapy is strongly recommended for NSCLC with either exon 20 insertion mutations (as first-line) or for those with disease progression on osimertinib (or other third generation agent). Afatinib is strongly recommended for the rarer EGFR mutations (G719X, L861Q, S768I; or osimertinib monotherapy, as weakly recommended).[67]

Table 11. NCCN Non-small Cell Lung Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2025[15,18,a,b]

A. Systemic Therapy Following Complete Surgical Resection of Tumors ≥4 cm or Node-positive	
For patients **with EGFR exon 19 deletion or exon 21 L858R mutations** who were previously treated with adjuvant chemotherapy or ineligible for platinum-based chemotherapy • **Osimertinib** 80 mg daily for 3 years (category 1)	
B. Adjuvant Therapy for Non-metastatic Disease After Definitive Chemoradiation Therapy	
For (a) unresectable stage IIIA (T4, N0-1), (b) unresectable superior sulcus tumor (T4, N0-1), (c) stage IIIB (T1-2, N3), (d) or stage IIIC (T3, N3), or (e) disease with mediastinal biopsy findings and T1-3, N1 or N2 nodes positive and M0 • **Osimertinib** (category 1) if EGFR exon 19 deletion of L858R mutation, or • Durvalumab (category 1) Consolidation therapy for patients with unresectable stage II/III NSCLC, PS 0–1, and no disease progression after definitive concurrent chemoradiation • **Osimertinib** 80 mg once daily until disease progression (category 1 for stage III; category 2A for Stage II) if EGFR exon 19 deletion or L858R9 • Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (for patients with a body weight of ≥30 kg; category 1 for stage III; category 2A for Stage II)	
C. Systemic Therapy for EGFR Exon 19 Deletion or Exon 21 L858R Mutation (for Metastatic Disease or Some Cases of Recurrent Locoregional Advanced Disease)	
First-line Therapy	
Preferred: • **Osimertinib** (category 1)	*Other recommended regimens:* • **Osimertinib** + pemetrexed + (cisplatin or carboplatin) (for nonsquamous disease; category 1) • **Amivantamab**-vmjw + **lazertinib** (category 1) *Useful in certain circumstances* • Any of the following monotherapies: **erlotinib, afatinib**, **dacomitinib, or gefitinib** (each category 1) • **Erlotinib** + (bevacizumab [for non-squamous histology] or ramucirumab) (category 2A)
Subsequent Therapy	
• **Osimertinib** (especially if T790M positive and not previously treated with osimertinib; category 1) • **Amivantamab** + carboplatin + pemetrexed (for nonsquamous disease following osimertinib treatment/progression; category 1)	

Abbreviations: PD-L1, programmed cell death 1 ligand; PS, performance status; NOS, not otherwise specified

[a] A bevacizumab FDA-approved biosimilar may be used as a substitute for bevacizumab in any of the applicable regimens specifying bevacizumab

[b] Refer to guideline for first-line treatment algorithms for other actionable-driver mutations (where IV anti-VEGF therapy is not included) (eg, EGFR S768I L861Q, and/or G719X mutations, EGFR exon 20 insertion, KRAS G12C mutation, ALK or ROS1 rearrangement, BRAF V600E)

Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.

Table 11. NCCN Non-small Cell Lung Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2025[15,18,a,b]

- **Afatinib** + **cetuximab** (category 2A)
- Refer to the full guideline for other non-EGFR-targeting systemic options after failing the EGFR-targeted treatment sequences; some examples are show in line-item "G".

D. Systemic Therapy for EGFR S768I, L861Q, and/or G719X Mutations (for Metastatic Disease or Some Cases of Recurrent Locoregional Advanced Disease)

First-line Therapy

Preferred; category 2A:	*Other recommended regimens; category 2A:*
• **Osimertinib** • **Afatinib**	• **Erlotinib** • **Gefitinib** • **Dacomitinib**

Subsequent-line Therapy

- **Osimertinib** (especially if T790M positive; category 1)
- **Afatinib** + **cetuximab** (category 2A)
- Refer to the full guideline for other non-EGFR-targeting systemic options after failing the EGFR-targeted treatment sequences; some examples are show in line-item "G".

E. EGFR Exon 20 Insertion Mutations (for Metastatic Disease or Some Cases of Recurrent Locoregional Advanced Disease)

First-line Therapy

- **Amivantamab** + carboplatin + pemetrexed (preferred for nonsquamous disease; category 1)
- *Other options for adenocarcinoma or squamous cell histology:* refer to full guideline for immunotherapy-based regimens, bevacizumab regimens, or chemotherapy-based regimens; some examples are shown in line item "I".

Subsequent Therapy

- **Amivantamab** (following prior treatment for general adenocarcinoma or squamous cell NSLCL; category 2A)
- *Following amaivantamab-containing therapy for nonsquamous disease:* can consider immune checkpoint inhibitors or chemotherapy-based regimens as outlined in guideline.
- Refer to the full guideline for other non-EGFR-targeting systemic options after failing the EGFR-targeted treatment sequences; some examples are show in line-item "G".

Abbreviations: PD-L1, programmed cell death 1 ligand; PS, performance status; NOS, not otherwise specified

[a] A bevacizumab FDA-approved biosimilar may be used as a substitute for bevacizumab in any of the applicable regimens specifying bevacizumab

[b] Refer to guideline for first-line treatment algorithms for other actionable-driver mutations (where IV anti-VEGF therapy is not included) (eg, EGFR S768I L861Q, and/or G719X mutations, EGFR exon 20 insertion, KRAS G12C mutation, ALK or ROS1 rearrangement, BRAF V600E)

Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.

Table 11. NCCN Non-small Cell Lung Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2025[15,18,a,b]

F. Targeted Regimen Examples for Other Actionable-Driver Mutations (for Metastatic Disease or Some Cases of Recurrent Locoregional Advanced Disease)		
KRAS G12C Mutation *For first-line therapy, treat according to PD-L1 algorithm* *Subsequent therapy*: sotorasib or adagrasib (category 2A) **ALK Rearrangement** *First-line preferred options, category 1*: alectinib, brigatinib, ensartinib, lorlatinib **NTRK1/2/3 Gene Fusion** *First-line/subsequent therapy*: larotrectinib, entrectinib, repotrectinib (category 2A) **RET Rearrangement** *First-line*: selpercatinib (category 1), pralsetinib (category 2A) *Subsequent therapy*: cabozantinib (category 2A)	**ROS1 Rearrangement** *First-line preferred options*: crizotinib, entrectinib, repotrectinib (category 2A) *Subsequent therapy options*: lorlatinib, entrectinib, repotrectinib **BRAF V600E Mutation** *First-line preferred options*: dabrafenib+trametinib, encorafenib+binimetinib (all category 2A); Useful in certain circumstances, dabrafenib or vemurafenib *Subsequent therapy*: dabrafenib + trametinib, encorafenib + binimetinib	**MET Exon 14 Skipping Mutation** *First-line therapy/Subsequent therapy*: capmatinib, tepotinib (category 2A); Useful in certain circumstances, crizotinib *Subsequent-line therapy following general (non-*mutational targeted) systemic treatment for advanced disease with the following: • **ERBB2 (HER2) mutation**: Fam-trastuzumab, deruxtecan-nxki, ado-trastuzumab emtansine (category 2A) • **NGR1 fusion mutation:** zenocutuzumab-zbco (category 2A)
G. Examples of Subsequent Line Therapies After Failure of EGFR-targeted Treatment Algorithms (selection is based on prior agents failed, refer to guideline for details)		
For Adenocarcinoma, Large Cell, and NOS NSCLC (and PS 0-2)		
Preferred; category 1: • Pembrolizumab/ (carboplatin or cisplatin)/ pemetrexed • Cemiplimab/pemetrexed/ (carboplatin or cisplatin) The above options are generally not used for patients with previous osimertinib + chemotherapy • nivolumab • pembrolizumab • atezolizumab	*Other recommended:* • Carboplatin/paclitaxel/ bevacizumab/ atezolizumab (category 1) • Nivolumab-based regimens • Tremelimumab-based regimens • See guideline for others	*Useful for scenarios with contraindications to PD-1 or PD-L1 inhibitors:* • Bevacizumab /carboplatin/ paclitaxel or pemetrexed • Bevacizumab/cisplatin/pemetrexed • Other platinum- or gemcitabine-based regimens

Abbreviations: PD-L1, programmed cell death 1 ligand; PS, performance status; NOS, not otherwise specified

[a] A bevacizumab FDA-approved biosimilar may be used as a substitute for bevacizumab in any of the applicable regimens specifying bevacizumab

[b] Refer to guideline for first-line treatment algorithms for other actionable-driver mutations (where IV anti-VEGF therapy is not included) (eg, EGFR S768I L861Q, and/or G719X mutations, EGFR exon 20 insertion, KRAS G12C mutation, ALK or ROS1 rearrangement, BRAF V600E)

Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.

6.3.2 *Comparative RCTs for Approved NSCLC Indications of EGFR Inhibitors*

Many recent SRs were identified that consolidate available head-to-head studies in NSCLC.[25,69-78] RCT publications were retrieved and study information was extracted most often from the primary study for completion of this section since head-to-head comparisons were too few for SR authors to perform direct-comparative meta-analyses. Eight primary publications (one reporting data from 2 RCTs) and 1 abstract account for ten comparative RCTs altogether for agents used as FDA-indicated (ie, for certain EGFR mutations). Erlotinib and/or gefitinib, the first-generation EGFR inhibitors, have often served as the drug of comparison for newer agents. According to several recent SRs, (2024 SR[22] and other corroborating SRs), second and third-generation EGFR inhibitors have not been compared to one another.[22-25,79] There is one comparison study for the third generation agents, lazertinib + amivantamab vs. osimertinib.[26]

In the setting of first-line therapy for advanced NSCLC with Ex19del or L858R mutations (the common EGFR mutations), 5 primary publications are pertinent. One partially open-label phase 3 RCT showed the combination of **amivantamab + lazertinib** outperformed **osimertinib** for median PFS.[26] One open-label, phase 2b RCT (N=319) showed **afatinib** improved PFS but not OS, compared to gefitinib (OS was similar with each agent). [27] A phase 3, open-label RCT (N=451) found improved PFS and OS outcomes with **dacomitinib** compared to gefitinib.[28] One phase 3, double-blinded RCT (N=556) demonstrated that **osimertinib** improved PFS and OS outcomes versus the comparator arm of first-generation EGFR inhibitors, erlotinib or gefitinib.[29] Data from one phase 3 and one small non-English RCT showed that **erlotinib and gefitinib** were comparable with respect to OS and/or PFS.[31,32]

For later-line therapy, 4 publications were pertinent. Of these, only 1 reported significant efficacy differences: afatinib outperformed erlotinib for PFS and OS in the setting of subsequent-line treatment of *squamous cell* NSCLC.[33]

6.3.2.1 FIRST-LINE THERAPY

Amivantamab + lazertinib vs. osimertinib

MARIPOSA (NCT04487080) is an international, phase 3 study in patients with previously untreated, locally advanced or metastatic NSCLC with Ex19del or L858R mutations.[26] Patients were randomized to amivantamab plus lazertinib[††††] (open-label arm; n=429), osimertinib (double-blinded arm; n=429), or lazertinib monotherapy (double-blinded arm; n=216). As of the data cutoff date with a median of 22 months of follow-up, an improvement in median PFS was demonstrated in favor of the combination arm compared to osimertinib (23.7 vs 16.6 months, respectively; HR 0.70, p=0.0002). At this time, the OS outcome remained immature, but the trend favored the combination regimen (though not a significant difference). The hazard ratio for PFS remained significantly in favor of the combination regimen over osimertinib regardless of brain metastasis history.

[††††] Dosages were as follows: lazertinib 240 mg daily; amivantamab based on weight, 1050 mg (for < 80 kg) or 1400 mg (for ≥ 80 kg) once a week for 4 weeks, then every 2 weeks from week 5 onward; osimertinib 80 mg daily. Because lazertinib monotherapy is not FDA-approved, we have not included results from this arm.

Treatment discontinuations due to AEs occurred more often in the combination regimen arm compared to osimertinib arm (35% vs. 14%, respectively).[26] While the overall incidence of venous thromboembolic (VTE) AEs was higher with amivantamab plus lazertinib (35%) vs. osimertinib (9%), events graded as moderate to severe occurred at similar rates among both arms. VTE prophylaxis was not used in this study, however, is now recommended, per lazertinib labeling.[13]

Notably, the NCCN has maintained preference for osimertinib over other options (such as amivantamab + lazertinib) for previously untreated, advanced or metastatic NSCLC with Ex19del or L858R mutations (per guideline version 1.2025).[18] The guideline's discussion section is currently being updated so does not yet provide the rationale; however, it could be that authors recognize challenges with the more complex regimen (with intravenous administration) plus the risk of thromboembolic events (or challenges with added prophylactic therapy that is now recommended with amivantamab + lazertinib) to sway the overall risk/benefit ratio in favor of osimertinib.

Osimertinib (third generation agent) vs. gefitinib or erlotinib (first-generation agents)

FLAURA (NCT02296125) was a multinational, double-bind, phase 3 RCT to compare first-line treatment with osimertinib 80 mg daily vs standard doses of gefitinib or erlotinib in adults (N= 556) with advanced or metastatic EGFR-mutation positive disease (exon19del or L858R).[29] At the primary endpoint assessment (median follow-up duration 16.2 months), osimertinib outperformed first-generation anti-EGFR treatment for median PFS (18.9 vs. 10.2 months, respectively; HR for disease progression or death 0.46, 95% CI 0.37 to 0.57, P<0.001). Benefits in PFS were consistently in favor of osimertinib for each subgroup assessment (eg, age, race, smoking history, CNS metastasis, WHO performance status 0 or 1, and EGFR mutation type exon19del or L858R). The final OS analysis (secondary endpoint) also favored osimertinib over the first-generation EGFR inhibitors: median OS of 38.6 months vs. 31.8 months, death HR 0.80, 95.05% CI 0.64 to 1.00, P=0.046).[30] At the primary endpoint analysis, grade 3 or worse AEs occurred less frequently with osimertinib vs. first-generation EGFR-inhibitors (34% vs. 45%). AEs of any grade that occurred more frequently with first-generation EGFRs and with greater than a 10% difference than in the osimertinib arm included rash or acne, and liver enzyme elevations.[29]

Afatinib (second-generation agent) vs. gefitinib (first-generation agent)

LUX Lung 7 (N=319) was a phase 2b, open-label, international RCT that compared afatinib 40 mg/day to gefitinib 250 mg/day for first-line treatment of NSCLC with Ex19del or L858R mutation.[80] Adults with stage IIIB (ineligible for surgery or radiotherapy) or IV (recurrent or metastatic) NSCLC adenocarcinoma were included. Co-primary endpoints were PFS, time to treatment failure (TTF), and OS. The median PFS and TTF were longer with afatinib compared to gefitinib (PFS: 11.0 months vs. 10.9 months, respectively; PFS HR 0.74, 95% CI 0.57 to 0.95, p=0.018);[80] however, OS was similar between both treatment arms.[27]

At the initial assessment for PFS (with median follow-up of 27.3 months), numerically more afatinib-treated patients experienced diarrhea (13% vs. 1%), rash or acne (9% vs. 3%), and serious treatment-related adverse events (11% vs. 4%), while more gefitinib-treated patients experienced liver enzyme elevation (9% vs. 0%). The same number of patients in each group discontinued therapy early due to AEs. Notably, 9% of afatinib-treated patients and 6% of gefitinib-treated patients had a fatal AE.[80]

Dacomitinib (second-generation agent) vs. gefitinib (first-generation agent)

ARCHER 1050 (N=451) was a phase 3, open-label, international RCT that compared dacomitinib 45 mg/day to gefitinib 250 mg/day for first-line treatment of adults with NSCLC of Ex19del or L858R mutation.[81] Brain metastases cases were excluded. Dacomitinib extended median PFS (primary endpoint) compared to gefitinib (14.7 vs. 9.2 months, respectively; HR 0.59, p<0·0001). The overall survival final analysis (at median follow-up 31.3 months) also showed a significant improvement with dacomitinib versus gefitinib (45% vs. 52% died; HR of 0.760, p = 0.044).[28]

At the PFS analysis timepoint (median of 22.1 months follow-up), grade 3 – 4 dermatitis acneiform occurred more often with dacomitinib compared to gefitinib (14% vs. 0%), along with diarrhea (8% vs. 1%). Yet, elevated alanine aminotransferase levels were more common with gefitinib (8% vs. 1%). Nine percent of dacomitinib-treated patients (vs. 4% of gefitinib-treated) experienced serious treatment-related AEs.[81]

Erlotinib (first-generation agent) vs gefitinib (first-generation agent)

A phase 3, open-label RCT (CTONG0901) compared erlotinib 150 mg/day to gefitinib 250 mg/day as *any line* of therapy in adults with locally advanced or metastatic NSCLC (stage IIIB or stage IV) and EGFR exon 19 or 21 mutations.[31] Included patients (N=256) were EGFR-TKI treatment naïve; 58% had exon 19 mutations and 42% had exon 21 mutations; and 65% of patients were receiving EGFR as first line therapy. Regarding the strata treated with EGFR inhibitors (n=165) as *first-line* systemic treatment, there were no significance differences between treatments for PFS, response rate (RR), or OS, but the numerical differences tended to favor erlotinib over gefitinib: PFS of 13.2 vs. 11.1 months and a median OS of 22.4 vs 20.7 month, respectively. In the total treated population (n=256), there were similar frequencies of Grade 3 or greater AEs in each treatment arm.[31]

Similarly, the abstract from a small RCT (available in Chinese language only, N=50) of untreated advanced EGFR-mutant NSCLC, reported no significant differences in PFS, objective response rate, or disease control rate following treatment with gefitinib versus erlotinib.[32]

6.3.2.2 SUBSEQUENT THERAPY

Afatinib vs. erlotinib

LUX Lung 8 (N=795) was a phase 3, open-label, international RCT that compared afatinib 40 mg/day to erlotinib 150 mg/day as subsequent treatment of advanced squamous cell NSCLC. Adults with stage IIIB or IV disease and progression after at least 4 cycles of platinum-based chemotherapy were included.[33] Afatinib outperformed erlotinib for the primary analysis endpoint for PFS (at median follow-up 6.7 months): PFS of 2.4 months vs 1.9 months, respectively; HR 0.82, 95% CI 0.68 to 1.00; P=0.043). At the later, overall survival analysis (with a median follow-up of 18.4 months), afatinib also significantly improved OS, PFS, and disease control compared to erlotinib: median OS was 7.9 months vs 6.8 months, HR 0.81, p=0.0077; median PFS was 2.6 months versus 1.9 months, HR 0.81, p=0·0103. Yet, the proportion of patients with an objective response were similar between groups. The proportion of patients with any grade 3 or higher AEs were also similar between groups (both 57%), though numerically more patients experienced treatment-related grade 3 diarrhea (10% vs 2%) or stomatitis (4% vs 0%) with afatinib; or grade 3 rash or acne with erlotinib (6% vs 10%).[33]

Dacomitinib vs. erlotinib

After accumulating evidence revealed that EGFR inhibitors were more effective for NSCLC with certain EGFR mutations, compared to WT disease or exon 20 insertion mutations, authors performed an exploratory pooled subgroup assessment for the subset of patients (n=100) with EGFR-mutant disease (eg, exon 19 or 21 activating mutations) from a phase 2 open-label RCT (A7471028) and a phase 3 double-blinded (ARCHER 1009) RCT to determine the descriptive comparison[‡‡‡‡] of dacomitinib 45 mg daily vs erlotinib 150 mg daily for second or third-line treatment. Included patients were adults with prior failure on chemotherapy but EGFR-treatment naive. For the exon19/21 subgroup, the median PFS appeared similar (p=0.146) but numerically longer with dacomitinib (14.6 months) compared to erlotinib (9.6 months). The same trends were observed regarding the median survival. Authors noted numerically more patients experiencing diarrhea and mucositis with dacomitinib versus erlotinib.[82]

Erlotinib vs. gefitinib, as any line of therapy

A phase 3 RCT (CTONG0901) compared erlotinib 150 mg daily vs. gefitinib 250 mg daily as any line of therapy in adults with locally advanced or metastatic NSCLC (stage IIIB or stage IV) and EGFR exon 19 or 21 mutations.[31] Included patients (N=256) were EGFR-TKI treatment naïve; 58% had exon 19 mutations and 42% had exon 21 mutations; and 35% of patients were receiving EGFR as second-line therapy. In the overall intent-to-treat population, there were no significant differences in PFS, OS, and response rate between treatment arms: the median PFS was 13.0 vs 10.4 months for erlotinib and gefitinib, respectively. Authors did not report results specific to the subsequent-line strata for any outcome. In the total treated population, there were similar frequencies of Grade 3 or greater AEs in each treatment arm.[31]

Erlotinib vs. gefitinib

A phase 3, open-label RCT (WJOG-5108L) to compare erlotinib 150 mg/day to gefitinib 250 mg/day was conducted in Japan and included adults with advanced NSCLC adenocarcinoma (stage IIIB or IV, or postoperative recurrence) previously treated with chemotherapy (but EGFR-TKI treatment naïve).[83] A stratification factor was EGFR-mutational status; 401 included patients (72% of the total included population) were EGFR mutation–positive, mostly L858R and Ex19del. Regardless of the EGFR mutation type, there were no significant differences in PFS, objective response rate, or disease control rate between gefitinib and erlotinib arms. Authors computed the overall worst-grade toxicity experienced per patient and found that gefitinib treatment tended to have a lower toxicity burden overall compared to erlotinib. Yet, the frequency of skin rash and elevation of T-bilirubin were significantly greater with erlotinib than with gefitinib, while liver enzyme elevations were more frequent with gefitinib.[83]

[‡‡‡‡] No multiplicity adjustment was applied for statistical comparisons; thus, authors describe that p-values produced were for descriptive purpose only and should be confirmed by another study.

6.4 Indications Unique to Vandetanib: Thyroid Cancer

Thyroid cancer, or carcinoma, is two to three times more common in people assigned female at birth.[21] Data from 2021 showed thyroid cancer was attributed to the 6th highest cancer-diagnosis rate in US females (age-adjusted rate: 18.5 per 100,000 women; 13 per 100,000 persons overall).[45] Histologic types of thyroid carcinoma include differentiated thyroid carcinoma (**DTC**; eg, papillary, follicular, and oncocytic), medullary thyroid carcinoma **(MTC**), and anaplastic thyroid cancer (ATC; an aggressive undifferentiated tumor). DTC accounts for most thyroid cancer cases in the US. Based on data between 2011 to 2015, papillary carcinoma (a differentiated type) was the most commonly diagnosed histology (90%), followed by other differentiated types (follicular, 4.5%; oncocytic, 1.8%), along with medullary carcinoma (**1.6%**), and anaplastic carcinoma (0.8%). DTC tends to have a favorable prognosis with treatment, and a 10-year survival rate between 90% to 95%. MTC has a high survival rate in stages I-III (5-year survival rate of 93%), but a low rate once in stage IV (5-year survival rate of 28%).[21]

Of the EGFR inhibitors, only vandetanib is approved for the treatment of thyroid cancer. It is indicated for unresectable, locally advanced or metastatic MTC, or for asymptomatic or slowly progressing disease (dosed as 300 mg once daily).

6.4.1 Key NCCN Recommendations for EGFR Inhibitors

The NCCN treatment of choice for thyroid carcinoma is surgery (for DTC and MTC), followed by radioactive iodine (RAI) therapy (for DTC only) or other ablative procedures (for DTC or MTC).[21] Generally, oral kinase inhibitors are reserved for patients with rapidly progressing and/or symptomatic disease rather than for indolent, asymptomatic disease.[21]

For locally recurrent, unresectable or metastatic **MTC**, vandetanib and cabozantinib (an anti-VEGF) are among NCCN preferred systemic therapy options; though, if the carcinoma is RET mutation positive, then selpercatinib or pralsetinib are the preferred agents.[21] The use of other agents off-label, such as sorafenib, sunitinib, lenvatinib, or pazopanib, can also be considered for symptomatic or progressing MTC if clinical trials and other approved systemic therapies are not available, appropriate, or effective.[21]

The use of vandetanib and other oral anti-VEGFs *off-label* for RAI-refractory **DTC** can also be considered if clinical trials and other approved systemic therapies are not available, appropriate, or effective.[21] **Table 12** summarizes the NCCN guideline treatment recommendations involving vandetanib for the treatment of thyroid cancer.

Table 12. NCCN Thyroid Cancer Guideline, EGFR Inhibitor Place-in-therapy, 2024[21,a]

Recommended regimens are rated as category 2A for level of evidence unless otherwise specified	
***Systemic Therapy for Progressive and/or Symptomatic DTC (<u>Papillary Carcinoma, Follicular Carcinoma, or Oncocytic Carcinomas</u>):* for unresectable locally recurrent/persistent disease, and/or disease with soft tissue, bone, or CNS metastasis not amenable to radioactive iodine therapy**	
Preferred • Lenvatinib (category 1)	*Other recommended* • Sorafenib (category 1)
Useful in Certain Circumstances • Cabozantinib, for progression after lenvatinib and/or sorafenib (category 1 for papillary carcinoma, 2A for follicular and oncocytic) • Larotrectinib, entrectinib, or repotrectinib for NTRK gene fusion-positive advanced solid tumors • Selpercatinib or pralsetinib RET mutation-positive tumors • Pembrolizumab for TMB-H (≥10 mut/Mb) tumors or for MSI-H or dMMR tumors that have progressed and exhausted alternative options • Dabrafenib + trametinib for BRAF V600E mutation and progression, lacking alternative treatment options • Other therapies are available and can be considered for progressive and/or symptomatic disease if clinical trials or other systemic therapies are not available or appropriate: ○ Eg, axitinib, everolimus, pazopanib, sunitinib, **vandetanib**, vemurafenib [BRAF positive, category 2B], or dabrafenib [BRAF positive, category 2B]	
***Systemic Therapy for Unresectable Recurrent or Persistent Locoregional MTC:* for symptomatic or progressing disease by RECIST Criteria**	
Preferred • **Vandetanib** (category 1) • Cabozantinib (category 1) • Selpercatinib for RET mutation-positive tumors (category 1) • Pralsetinib for RET mutation-positive tumors (category 2B)	*Useful in Certain Circumstances* • Pembrolizumab for TMB-H (≥10 mut/Mb) tumors or for MSI-H or dMMR tumors that have progressed and exhausted alternative options
Systemic Therapy for Unresectable Recurrent or Persistent MTC with Distant Metastases	
Preferred • **Vandetanib** (category 1) • Cabozantinib (category 1) • Selpercatinib for RET mutation-positive tumors (category 1) • Pralsetinib for RET mutation-positive tumors (category 2B)	*Other Regimens (for symptomatic or progressing disease)* • Sorafenib, sunitinib, lenvatinib, or pazopanib if a clinical trial or preferred options are not available or appropriate • Dacarbazine-based chemotherapy
Useful in Certain Circumstances • Pembrolizumab for TMB-H (≥10 mut/Mb) tumors or for MSI-H or dMMR tumors that have progressed and exhausted alternative options	

Abbreviations: dMMR, mismatch repair deficient; CNS, central nervous system; MoDTC, differentiated thyroid carcinoma; MSI-H, high microsatellite instability; MTC, medullary thyroid carcinoma; mut/MB, mutations/megabase; RECIST, Response Evaluation Criteria in Solid Tumors; TMB-H, tumor mutational burden-high

[a] Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with still uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus

6.5 Indications Unique to Cetuximab: Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Head and neck cancers include tumors originating from the oral cavity (and mucosal lip), pharynx, larynx, and paranasal sinuses, in additional to occult primary cancers where the origination location is undetermined.[19] About **3.6%** of new cancer cases in the US are attributed to oral cavity, pharyngeal, and laryngeal cancers. Most head and neck cancers (>90%) are *squamous cell* carcinomas. Risk factors include tobacco use, heavy alcohol use, and human papillomavirus (HPV) infection. Testing for HPV (via p16 immunohistochemistry) is required for all oropharynx cancers, as there are different treatment algorithms for HPV-positive vs. HPV-negative oropharynx disease. HPV-positive SCCHN generally has a more favorable response to treatment compared to HPV-negative disease. Epstein-Barr Virus (EBV) is a risk factor particularly for nasopharyngeal cancer, however, it is not necessary to screen for EBV since it does not have predictive value with respect to available treatment options.[19]

Of the EGFR inhibitors, only cetuximab has FDA approval for the treatment of SCCHN; approved indications are summarized in **Table 13**.

Table 13. Cetuximab Indications for Head and Neck Squamous Cell Carcinoma

- *For* locally or regionally advanced squamous cell carcinoma of the head and neck, in combination with radiation therapy
- For recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck, in combination with platinum-based therapy **with fluorouracil**
- For recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression *after* platinum-based therapy

6.5.1 Key NCCN Recommendations for EGFR Inhibitors

Treatment for early-stage, HPV-negative SCCHN may involve a single modality, either surgery or radiation therapy (RT). For cases unsuitable for surgery (eg, patients with locally or regionally advanced disease, metastatic disease, or unfit for or electing not to have the surgery), initial therapy may involve RT alone (generally for resectable cases) or in combination with **systemic chemotherapy**. The NCCN guideline describes that "…surgery is usually preferred for [early-stage/resectable] oral cavity and paranasal sinus cancers, while RT with or without chemotherapy is nearly always preferred for all stages of nasopharyngeal carcinoma (NPC) and more advanced stages of HPV-associated oropharyngeal cancer" (Pfister et al, page 147).[19] To guide systemic therapy-decision-making, newly diagnosed recurrent or metastatic SCCHN should also be tested for programmed death ligand 1 (PD-L1) expression and as needed for other actionable-driver mutations (eg, HER2) via next-generation sequencing.[19]

NCCN treatment algorithms and preferred regimens differ between the disease context of nasopharynx or non-nasopharynx-related SCCHN. Yet, regardless of these cancer subtypes, cetuximab-based therapy is not a *preferred* first-line regimen. Rather, cisplatin-based systemic therapy is preferred, while cetuximab-based regimens may serve as *alternative*, first-line options, among other options; or as subsequent-line regimens in a few scenarios. The NCCN guideline describes that high-dose cisplatin with concurrent RT is the most studied regimen, and is considered the gold standard, first-line systemic

therapy for locally advanced non-nasopharynx SCCHN. Because cetuximab + RT was inferior to cisplatin + RT for overall survival in three phase 3 trials of patients with HPV-positive, locally advanced squamous cell carcinoma of the oropharynx, the cetuximab + RT regimen is reserved as an alternative ("*useful in certain circumstances," category 2B)* to the preferred cisplatin + RT regimen (*category 1*).

Notably, the labeled indications for cetuximab do not reflect the entire scope of conditions where cetuximab is NCCN-recommended for SCCHN. Additional regimens/conditions included in the NCCN guideline that do not appear represented in the labeled indication are as follows:

- *For non-nasopharyngeal squamous cell carcinoma for which surgery or RT <u>are not options</u>:* the following cetuximab-containing regimens designated as *"other recommended"* or "*useful in certain circumstances*" for <u>first-line</u> treatment of advanced disease (ie, recurrent, unresectable, or metastatic):
    - cetuximab in combination with cisplatin, paclitaxel, or docetaxel
    - cetuximab in combination with carboplatin or cisplatin/docetaxel or paclitaxel
    - cetuximab monotherapy
    - cetuximab in combination with nivolumab or pembrolizumab
- *For advanced nasopharyngeal squamous cell carcinoma for which surgery or RT <u>are not options</u>:* cetuximab plus carboplatin is an alternative option (ie, *"other recommended"* option) for <u>first-line</u> systemic treatment .

Afatinib, another EGFR inhibitor, can be considered for <u>off-label use</u>, according to the NCCN, as a subsequent-line option for the treatment of non-nasopharyngeal cancer after progression on a platinum-based therapy.

Table 14 summarizes the NCCN guideline treatment recommendations involving EGFR inhibitors for head and neck cancer.

Table 14. NCCN Head and Neck Cancers, EGFR Inhibitor Place-in-therapy, 2025[19]

Recommended regimens are rated as category 2A for level of evidence unless otherwise specified

A. Nasopharyngeal Cancer: Recurrent, Unresectable Oligometastatic or Metastatic Disease; Systemic Treatment for when Radiotherapy or Surgery are Not Options

Preferred first-line regimens • cisplatin/gemcitabine + toripalimab-tpzi (category 1) *Preferred subsequent-line regimen* • topirpalimab-tpzi (after platinum therapy)	*Other recommended first-line regimens* • cisplatin + (5-FU, docetaxel, or paclitaxel) • cisplatin + gemcitabine (category 1) • cisplatin/gemcitabine/tislelizumab-jsgr (category 2B) • cisplatin/gemcitabine/PD-1 inhibitor (eg, pembrolizumab or nivolumab) • carboplatin + (**cetuximab**, docetaxel, paclitaxel, or gemcitabine) • Other monotherapy options: cisplatin, carboplatin, paclitaxel, docetaxel, 5-FU, methotrexate, gemcitabine, capecitabine *Other recommended subsequent-line regimens* • tislelizumab-jsgr (category 2B) • nivolumab (for previously treated, non-keratinizing disease; category 2B) • pembrolizumab (PD-L1–positive disease advanced disease; category 2B) • pembrolizumab (for TMB-H tumors)

B. Non-nasopharyngeal Cancer: Systemic Regimens in the Setting of Combined Radiotherapy
(for oral cavity, oropharynx, hypopharynx, larynx, ethmoid sinus, maxillary sinus, and occult primary cancers)

Primary Systemic Therapy + Concurrent RT *(ie, concurrent approach)*	***Induction/Sequential Systemic Therapy*** *(may not be as well-tolerated the concurrent therapy approach, which is generally more preferable)*	***Postoperative Systemic Therapy/RT***	***Systemic Therapy/RT Following Induction Therapy, or Combination Chemotherapy for Recurrent/Persistent Disease***
Preferred: • **high-dose cisplatin (category 1)** • carboplatin/infusional 5-FU (for cisplatin-ineligible patients; category 1) *Other Recommended Regimens* • weekly cisplatin (40 mg/m^2) • carboplatin/paclitaxel (category 2B) *Useful in Certain Circumstances*	*Preferred* • docetaxel/cisplatin/5-FU (category 1) *Other Recommended Regimens*	*For patients with high-risk adverse pathologic features following surgery.* *Preferred* • cisplatin (category 1 for high-risk non-oropharyngeal cancers)	*Preferred* • weekly carboplatin + concurrent RT • weekly cisplatin (category 2B) + concurrent RT *Useful in Certain Circumstances* • weekly **cetuximab** + concurrent RT

Abbreviations: 5-FU, fluorouracil; EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; PD-L1, programmed cell death 1 ligand; RT, radiation therapy; TMB-H, high tumor mutation burden

[a] Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with still uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.

Table 14. NCCN Head and Neck Cancers, EGFR Inhibitor Place-in-therapy, 2025[19]

• **cetuximab** (category 2B) • other options contain docetaxel, 5-FU, cisplatin, paclitaxel	• paclitaxel/cisplatin/infusional 5-FU *Useful in Certain Circumstances* • carboplatin/paclitaxel +/- **cetuxiumab** (category 2B)	*Useful in Certain Circumstances* • docetaxel • docetaxel/**cetuximab** (category 2B)	***Reirradiation + Concurrent Therapy*** *Preferred* • cisplatin + concurrent RT *Useful in Certain Circumstances* • (**cetuximab** or carboplatin or docetaxel)+ concurrent RT (category 2B)
C. Non-nasopharyngeal Cancer: Recurrent, Unresectable, or Metastatic Disease; Systemic Regimens for when Radiotherapy or Surgery are Not Options (for oral cavity, oropharynx, hypopharynx, larynx, ethmoid sinus, maxillary sinus, and occult primary cancers)			
Preferred First-line: pembrolizumab-containing regimens (see full guideline; category 1) Subsequent-line: nivolumab or pembrolizumab (if not previously used; category 1)	*Other Recommended Regimens, First-line or Subsequent-line Options* • **cetuximab/** (cisplatin or carboplatin)/5-FU (category 1) • cisplatin +/- **cetuximab** • cisplatin or carboplatin/docetaxel or paclitaxel • cisplatin or carboplatin/docetaxel or paclitaxel/**cetuximab** • cisplatin/5-FU • pembrolizumab/cisplatin or carboplatin/docetaxel or paclitaxel • carboplatin • paclitaxel or docetaxel • 5-FU • methotrexate • **cetuximab** • capecitabine • **afatinib** (subsequent-line only, and only for disease progression on or after platinum therapy; category 2B)		*Useful in Certain Circumstances, First-line or Subsequent-line Cetuximab-containing Regimens (refer to guideline for full list of other regimens in this category)* • **cetuximab**/nivolumab or pembrolizumab • **cetuximab**/paclitaxel or docetaxel
• Refer to the guideline for other regimens for the treatment of select ethmoid/maxillary sinus cancers, which do not include cetuximab			

Abbreviations: 5-FU, fluorouracil; EGFR, epidermal growth factor receptor; NCCN, National Comprehensive Cancer Network; PD-L1, programmed cell death 1 ligand; RT, radiation therapy; TMB-H, high tumor mutation burden

[a] *Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with still uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

6.6 Indications Unique to Erlotinib: Pancreatic Cancer

While pancreatic cancer only comprises about 3% of all cancer diagnoses, pancreatic cancer was the 5th leading cause of cancer-related death in the US in 2022.[14,84]. Ductal adenocarcinoma (and similar variants) is the most common histology (>90% of malignant cases).[85] Risk factors include smoking, heavy metal exposure, elevated BMI, chronic pancreatitis, type 2 diabetes, having 2 or more first-degree relatives with pancreatic cancer, and certain genetic disorders (eg, Peutz Jeghers syndrome, Lynch syndrome, Li-Fraumeni syndrome), among others.[84] Suggestive symptoms of the disease include continuous weight loss, jaundice, floating stools, pain, and GI symptoms (dyspepsia, nausea, vomiting) with or without pancreatitis.[85] At the time of diagnosis, only about 12% of cases are localized cancers. The 5-year survival rate, by location of disease, is 44% for localized disease, 16% for regional, and 3% for metastatic pancreatic cancer.[84]

Erlotinib is the only EGFR inhibitor FDA approved for the treatment of pancreatic cancer—for first-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine (dosed as 100 mg daily).

6.6.1 Key NCCN Recommendations for EGFR Inhibitors

NCCN treatment algorithms are provided according to performance status (ie, Eastern Cooperative Oncology Group [ECOG] Performance Status [PS]).[85] Testing for genetic mutation and molecular profiling is also recommended for advanced disease. Erlotinib is among treatment regimens for patients with good PS, which is defined as ECOG PS 0–1[§§§§], with good biliary drainage and adequate nutritional intake. Erlotinib, in combination with gemcitabine, is an *alternative-line* regimen (ie, secondary in preference to preferred options) for initial systemic treatment of locally advanced or metastatic pancreatic adenocarcinoma, or for subsequent-line therapy. Erlotinib is the only EGFR inhibitor NCCN recommended in the setting of pancreatic adenocarcinoma (see Table 15). Other treatment options for patients with good PS and locally advanced disease include chemotherapy , chemoradiation, and/or stereotactic body radiation therapy; for metastatic disease, there are also other chemotherapy options.[85]

[§§§§] ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0 is defined as being able to engage in all pre-disease performance/activity without restriction; ECOG PS of 1 is restriction in physically strenuous activity, however, with the patient still ambulatory and ably to perform light work.

Table 15. NCCN Pancreatic Adenocarcinoma Guideline, EGFR Inhibitor Place-in-therapy, 2025[20]

A. First-line systemic therapy for locally advanced disease (with PS 0-1)		
Preferred regimens, category 2A • FOLFIRINOX or modified FOLFIRINOX • gemcitabine + albumin-bound paclitaxel • NALIRIFOX If BRCA1/2 or PALB2 mutations are present: • FOLFIRINOX or modified FOLFIRINOX • gemcitabine + cisplatin	*Other recommended regimens, category 2A* • gemcitabine +/ (capecitabine or **erlotinib**) • fluoropyrimidine + oxaliplatin *Other recommended regimens, category 2B* • capecitabine +/- oxaliplatin • 5-FU + leucovorin + oxaliplatin • continuous infusion 5-FU • gemcitabine + albumin-bound paclitaxel + cisplatin • fixed-dose-rate gemcitabine, docetaxel, capecitabine	*Useful in certain circumstances, category 2A* Other TKIs • dabrafenib + trametinib (if BRAF V600E mutation-positive) • entrectinib or larotrectinib or repotrectinib (if NTRK gene fusion positive) • selpercatinib (if RET gene fusion positive) Refer to full guideline for additional types of treatment
B. First-line for metastatic disease (with PS 0-1)		
Preferred regimens: • FOLFIRINOX (category 1) or modified FOLFIRINOX (category 2A) • NALIRIFOX (category 1) • gemcitabine + albumin-bound paclitaxel (category 1) For BRCA1/2 or PALB2 mutations: • FOLFIRINOX (category 1) or modified FOLFIRINOX (category 2A) • gemcitabine + cisplatin (category 2A)	*Other recommended regimens:* *Category 1* • gemcitabine +/- **erlotinib** *Category 2A* • gemcitabine + capecitabine • gemcitabine + albumin-bound paclitaxel + cisplatin • fluoropyrimidine + oxaliplatin *Category 2B* • capecitabine + oxaliplatin • 5-FU + leucovorin + oxaliplatin • fixed-dose-rate gemcitabine, docetaxel, capecitabine	*Useful in certain circumstances"* • dabrafenib + trametinib (if BRAF V600E mutation-positive; category 2B) • entrectinib or larotrectinib or repotrectinib (if NTRK gene fusion positive, category 2A) • selpercatinib (if RET gene fusion positive, category 2A) • pembrolizumab (if MSI-H, dMMR, or TMB-H; category 2A)

Abbreviations: 5-FU, fluorouracil; dMMR, mismatch repair deficient; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; MSI-H, microsatellite instability- high; NALIRIFOX, liposomal irinotecan + *5-FU + leucovorin + oxaliplatin; NCCN, National Comprehensive Cancer Network; PS, performance status (based on the Eastern Cooperative Oncology Group classification; TMB-H, high tumor mutational burden*

[a] *Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with still uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

Table 15. NCCN Pancreatic Adenocarcinoma Guideline, EGFR Inhibitor Place-in-therapy, 2025[20]

C. Subsequent therapy for locally advanced/metastatic disease or for recurrent disease (with PS 0-1)
Preferred regimens, category 2A • entrectinib, larotrectinib, or repotrectinib (if NTRK gene fusion-positive) • pembrolizumabj (if MSI-H, dMMR, or TMB-H; and no prior immunotherapy) *Other recommended regimens:* • gemcitabine + **erlotinib** is an option, among others, if patient had prior fluoropyrimidine-based therapy (category 2A) • refer to the guideline for many other alternatives, depending on the clinical scenario (eg, prior treatment and mutation status) *Useful in certain circumstances:* • *erdafitinib (if FGFR mutations are present)* • *fam-trastuzumab deruxtecannxki (if HER2 positive)*

Abbreviations: 5-FU, fluorouracil; dMMR, mismatch repair deficient; FOLFIRINOX, leucovorin + fluorouracil + irinotecan + oxaliplatin; MSI-H, microsatellite instability- high; NALIRIFOX, liposomal irinotecan + *5-FU + leucovorin + oxaliplatin; NCCN, National Comprehensive Cancer Network; PS, performance status (based on the Eastern Cooperative Oncology Group classification; TMB-H, high tumor mutational burden*

[a] *Evidence/Consensus Category 1: recommendation is based upon high-level evidence and a uniform NCCN consensus; Category 2A is based upon lower-level evidence, but with still uniform NCCN consensus; Category 2B is based upon lower-level evidence, and majority consensus.*

7.0 OFF-LABEL USES

Table 16 compiles the class of recommendation for use and/or evidence ratings for drug-compendia recognized off-label uses (per Dynamed [a compendia incorporating Micromedex information] and Lexidrug). For some indications, Lexidrug provides extra detail regarding existence of an evidence-based clinical practice guideline in support of use (denoted as G in the table). Nonetheless, guidelines change frequently, and so even these compendia may not include an exhaustive list of all expert recognized uses. Additional off-label uses for agents that appear unaccounted for in these compendia and with an NCCN guideline recommendation in favor of use are as follows:

- Afatinib is specified as a subsequent-line option for the treatment of non-nasopharyngeal cancer after progression on a platinum-based therapy.[19]
- Axitinib monotherapy or in combination with avelumab: regarded as useful in certain circumstances for advanced salivary gland tumors where surgery or radiotherapy are not options.[86]
- Cetuximab for advanced mCRC with KRAS G12C mutation[17]
- Cetuximab plus afatinib for subsequent-line therapy for EGFR-mutation positive NSCLC and disease progression on first-line therapy
- Cetuximab (as monotherapy or in combination regimens, depending on the condition) for first-line treatment of advanced nasopharyngeal or non-nasopharyngeal squamous cell carcinoma disease for which surgery or RT are not options (refer to section 6.5)[19]
- Erlotinib as *subsequent therapy* for pancreatic adenocarcinoma[85]; the agent is FDA approved for first-line therapy, but NCCN also has erlotinib as an option for subsequent therapy.
- Panitumumab for advanced mCRC with BRAF V600E and KRAS G12C mutational variants[17]
- The use of vandetanib for RAI-refractory differentiated thyroid carcinoma (DTC) can be considered if clinical trials and other approved systemic therapies are not available, appropriate, or effective.[21]

Table 16. Off-Label Uses of EGFR Inhibitors for Adults

DynaMed (Micromedex)[a,b,87]	Lexidrug[b,c,88]
Afatinib	
Evidence favors efficacy (Category B): • Squamous cell carcinoma of head and neck, recurrent and/or metastatic disease, second-line following failure of platinum-based therapy (IIb; NCCN recognized treatment option[19])	None
Cetuximab	
Evidence favors efficacy (Category B): • Gastric cancer (IIb) • Cardio-esophageal junction of stomach malignant neoplasm (IIb) • mCRC, EGFR-expressing, after failure of both fluoropyrimidine- and oxaliplatin-based regimens; in combination with irinotecan (IIb) • mCRC, refractory, non-EGFR expressing disease (IIb) • Squamous cell carcinoma of head and neck, metastatic or recurrent disease, refractory to platinum-based therapy, as combination therapy (IIb)	• Squamous cell, advanced or metastatic penile cancer (LOE C) • Squamous cell, unresectable skin cancer (LOE B)
Erlotinib	
None	Papillary renal cell carcinoma, advanced (LOE B)
Lapatinib	
Evidence favors efficacy (Category B): • Metastatic breast cancer, HER2 overexpression, first-line (IIb) • Metastatic breast cancer, HER2 overexpression, refractory, monotherapy (IIb) • Inflammatory carcinoma of breast, HER2 overexpression, relapsed or refractory (IIb)	• mCRC, HER2 positive disease, with progression on conventional chemotherapy (LOE B; **G**) • Metastatic breast cancer, HER2 positive disease with: (a) previously untreated brain metastases (LOE B; **G**)

Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; LOE, level of evidence; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials

[a] Non-FDA uses were extracted from Dynamed (compiling Micromedex information) that were rated as "effective" or "evidence favors efficacy"; note that some off-label uses are viewable in the "In-depth Answers" view but not in the "Quick Answers" view of the database.

- *Micromedex Categories for Strength of Evidence: **Category A** is based on meta-analyses of homogenous RCT results, or multiple, well-designed RCTs with large patient population; **Category B** is based on data from meta-analyses of RCTs with either incongruent effect estimates, small populations, significant methodological flaws, or nonrandomized studies.*
- *Micromedex Strength of Recommendation: **IIa**, recommended in most cases; **IIb** recommended in some cases*

[b] All listed off-label uses are specified for the adult population

[c] Lexidrug Level of Evidence Definitions:

- *B - Evidence from RCT(s) with important limitations, or very strong evidence of some other research design. Estimate of effect may change with future evidence.*
- *C - Evidence from observational studies, unsystematic clinical experience, or from potentially flawed. Estimate of effect is uncertain.*
- *G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.*

Table 16. Off-Label Uses of EGFR Inhibitors for Adults

DynaMed (Micromedex)[a,b,87]	Lexidrug[b,c,88]
	(b) with progression on prior trastuzumab-containing therapy (LOE A; **G**)
Osimertinib	
None	• NSCLC, adenocarcinoma with leptomeningeal metastases, EGFR mutation positive (LOE B)
Panitumumab	
Evidence favors efficacy (Category B): • mCRC, wild-type KRAS mutation, second-line therapy following fluoropyrimidine-containing chemotherapy, in combination with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen)	• mCRC, KRAS wild-type, in combination with other chemotherapy agents (LOE **A**) • Cutaneous squamous cell carcinoma, unresectable, advanced or metastatic (LOE C, **G**)

Abbreviations: EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; LOE, level of evidence; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; RCTs, randomized controlled trials

[a] *Non-FDA uses were extracted from Dynamed (compiling Micromedex information) that were rated as "effective" or "evidence favors efficacy"; note that some off-label uses are viewable in the "In-depth Answers" view but not in the "Quick Answers" view of the database.*

- *Micromedex Categories for Strength of Evidence: **Category A** is based on meta-analyses of homogenous RCT results, or multiple, well-designed RCTs with large patient population; **Category B** is based on data from meta-analyses of RCTs with either incongruent effect estimates, small populations, significant methodological flaws, or nonrandomized studies.*
- *Micromedex Strength of Recommendation: **IIa**, recommended in most cases; **IIb** recommended in some cases*

[b] *All listed off-label uses are specified for the adult population*

[c] *Lexidrug Level of Evidence Definitions:*

- *B - Evidence from RCT(s) with important limitations, or very strong evidence of some other research design. Estimate of effect may change with future evidence.*
- *C - Evidence from observational studies, unsystematic clinical experience, or from potentially flawed. Estimate of effect is uncertain.*
- *G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.*

8.0 SAFETY

As a class, EGFR inhibitors commonly cause gastrointestinal adverse events, particularly **diarrhea** and **dermatologic** reactions (panitumumab has a black box warning [BBW] for severe events with a 15% incidence rate).

- *Diarrhea and/or acute renal failure:* Six of the oral EGFR inhibitors have labeled warnings regarding high rates of diarrhea observed in clinical studies, with some patients experiencing dehydration with or without renal impairment (some fatal). Grade 3-4 diarrhea occurred at the following rates: 16% with afatinib; 11% with dacomitinib, 3% with gefitinib, <10% with lapatinib, 40% with neratinib, and 11% with vandetanib. Diarrhea occurred at very high rates with some agents (96% with afatinib, 86% with dacomitinib, 50-60% with erlotinib, 64% with lapatinib, 95% with neratinib, 57% with vandetanib). Although there is not a formal warning for diarrhea with erlotinib, lazertinib, osimertinib, or with the IV agents (amivantamab, cetuximab, necitumumab, panitumumab), package inserts report diarrhea to be a common adverse reaction (occurring in >20% of treated patients). Moreover, package inserts for erlotinib and panitumumab include a warning for severe renal failure which may be proceeded by dehydration.
- *Severe dermatologic adverse AEs:* All reviewed EGFR inhibitors, except neratinib, have a warning for dermatologic AEs. Overall incidence rates of dermatologic reactions in clinical trials were high, but severe cases of bullous, exfoliative lesions, or other severe events were generally infrequent with the exception of a 15% incidence of dermatologic reactions experienced with panitumumab treatment. EGFR inhibitor therapy should be discontinued in the event of life-threatening bullous, blistering, or exfoliating skin lesions. Generally, in the event of grade 2 or higher dermatologic reactions, the medication should be withheld until resolution to grade 1 or less, and consideration can be given to resume the medication at a lower dose. Refer to package inserts for specific instructions for each medication per reaction.

All EGFR inhibitors have a warning regarding **embryofetal toxicity** and often a recommendation for the use of effective contraception as appropriate, during treatment and for a period after treatment discontinuation. Many of the EGFR inhibitors have been associated with unusual events of **interstitial lung disease (ILD)** and thus have a labeled warning; the exceptions without a labeled warning for ILD are neratinib and necitumumab. The incidence of ILD in clinical studies was relatively low across reviewed agents (eg <5% where explicitly reported) with exception of a 56% ILD/pneumonitis in osimertinib-treated patients who received prior treatment with platinum-based chemoradiation therapy.

- The onset of ILD symptoms can be highly variable, from days to months after drug initiation.[1] Patients should withhold treatment in the event of acute onset of new or progressive unexplained pulmonary symptoms until proper evaluation to rule out ILD; and discontinue therapy if ILD or pneumonitis is confirmed.

At least half of the reviewed agents have a warning regarding **ocular toxicity** (eg, keratitis, uveitis), **hepatotoxicity** (BBW for lapatinib), and/or **cardiovascular-related AEs** (eg, thromboembolic events (2 agents), QTc prolongation (3 agents; BBW for vandetanib), or cardiac dysfunction (5 agents; BBW for

cetuximab and necitumumab). The IV agents commonly cause **infusion-related reactions (IRR)** and carry labeled warnings (BBW for cetuximab). Elaboration of select drug-class effects are described below.

- *Ocular Toxicity:* Seven of the oral EGFR inhibitors have labeled warnings for ocular AEs such as keratits (and uveitis with amivantamab). Keratitis can lead to corneal ulceration or perforation. Therapy should be interrupted or discontinued if patients exhibit acute or worsening ocular disorders/symptoms, or if keratitis is suspected. Keratitis occurred infrequently (<1%) in pivotal trials with afatinib, amivantamab, and osimertinib monotherapies. With erlotinib, ocular disorders in general, occurred in 13-18% of patients, in clinical studies, which included decreased tear production, abnormal eyelash growth, keratoconjunctivitis sicca or keratitis. In addition to keratitis (0.1%) with gefitinib, blepharitis and dry eye (6.7%) were also reported. In the pivotal phase 3 trial with amivantamab + lazertinib ocular adverse AEs occurred in 16% of treated patients (0.7% had grade 3 or 4 events).

Table 17 compiles the labeled warnings/precautions for the reviewed EGFR inhibitors. Information regarding other warnings, along with the labeled common adverse events are described in the subsections to follow, with agents grouped by overlapping indication.

Table 17. Labeled Warnings for EGFR Inhibitors[1-13]

	Oral Agents									Intravenous Agents			
	Afatinib	Dacomitinib	Erlotinib	Gefitinib	Lapatinib	Lazertinib	Neratinib	Osimertinib	Vandetanib	Amivantamab	Cetuximab	Necitumumab	Panitumumab
Indications	NSCLC	NSCLC	NSCLC, PC	NSCLC	BC	NSCLC	BC	NSCLC	MTC	NSCLC	mCRC, SCCHN	NSCLC	mCRC
WARNINGS	***WARNINGS***									***WARNINGS***			
Embryo-fetal toxicity	X	X	X	X	X	X	X	X	X	X	X	X	X
Severe dermatologic AEs including exfoliative skin reactions	X (bullous)	X (plus rash)	X (bullous)	X (plus bullous)	X (SJS)	X	*NL, but rash is a common AE (18% in adjuvant treatment)*	X (SJS, EMM, TEN)	X	X (rash, TEN, AD)	X	X	X (photosensitivity; soft tissue toxicity; **BBW**)
Interstitial lung disease	X	X	X	X	X	X		X	X	X	X		X
Ocular toxicity	X (keratitis)		X (keratitis)	X (keratitis)		X		X (keratitis)		X (keratitis, uveitis)			X (keratitis)
Diarrhea	X	X	*NL but is a common AE (>20%)*	X	X	*NL but is a common AE (>20%)*	X	*NL but is a common AE (>20%)*	X	*NL but is a common AE (20%)*	*NL but is a common AE (25%)*	*NL but is a common AE (16%)*	*NL but is a common AE (>20%)*
Acute renal failure			X						X				X (when used with chemotherapy)
Bleeding risk	X (GI-perforation		X (GI perforation risk; CVA; hemorrhage risk when taking warfarin)	X (GI-perforation					X (hemorrhage risk)				
Thromboembolic events			X (CVA)			X (VTE; prophylactic anti-coagulation recommended)						X (venous and arterial events)	X (VTE when used with bevacizumab/chemo-therapy)
QTc prolongation					X			X	X (**BBW**, REMS)				
Cardiac dysfunction					X (decreased LVEF)			X (cardio-myopathy)	X (failure/ dysfunction)		X (cardiac arrest, **BBW**)	X (cardiac arrest **BBW**)	
Hypomagnesemia and accompanying electrolyte imbalances											X	X (**BBW**)	X
Hepatotoxicity	X		X	X	X (**BBW**)		X		X				
Infusion-related reactions										X	X (**BBW**)	X	X

Abbreviations: AE, adverse event; BBW, black box warning; BC, breast cancer; CVA, cerebrovascular accident; EMM, Erythema Multiforme Major; LVEF, left ventricular ejection fraction; mCRC, metastatic renal cell carcinoma; MTC, medullary thyroid cancer; NL, not labeled as a formal warning; NSCLC, non-small cell lung cancer; PC, pancreatic cancer; REMS, risk evaluation and mitigation strategy; SCCHN, squamous cell carcinoma of the head or neck; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrosis; VTE, venous thromboembolism

Table 17. Labeled Warnings for EGFR Inhibitors[1-13]

		Oral Agents								Intravenous Agents			
	Afatinib	Dacomitinib	Erlotinib	Gefitinib	Lapatinib	Lazertinib	Neratinib	Osimertinib	Vandetanib	Amivantamab	Cetuximab	Necitumumab	Panitumumab
Other Unique Warnings per Agent			Micro-angiopathic hemolytic anemia with thrombocytopenia					Cutaneous vasculitis Aplastic anemia	Impaired healing Ischemic CVA Hypertension Reversible Posterior Leukoencephalopathy Syndrome Thyroid dysfunction		lacks efficacy for Ras-mutant mCRC Increased toxicity when used in combination with radiation and cisplatin	Lacks efficacy for non-squamous NSCLC	Lacks efficacy for Ras-mutant mCRC

Abbreviations: AE, adverse event; BBW, black box warning; BC, breast cancer; CVA, cerebrovascular accident; EMM, Erythema Multiforme Major; LVEF, left ventricular ejection fraction; mCRC, metastatic renal cell carcinoma; MTC, medullary thyroid cancer; NL, not labeled as a formal warning; NSCLC, non-small cell lung cancer; PC, pancreatic cancer; REMS, risk evaluation and mitigation strategy; SCCHN, squamous cell carcinoma of the head or neck; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrosis; VTE, venous thromboembolism

8.1 Safety information regarding EGFR-inhibitors indicated for NSCLC: afatinib, amivantamab, dacomitinib, erlotinib, gefitinib, lazertinib, necitumumab, osimertinib,

The EGFR inhibitors indicated for NSCLC exert a high incidence of **dermatologic** adverse effects for which there are labeled warnings on all products. Common AEs also include **diarrhea** (labeled warning for some drugs) with all EGFR inhibitors and stomatitis with most agents. All EGFR inhibitors for NSCLC, except necitumumab, have a warning regarding their association with **ILD**; cases were infrequent with most agents with the exception of a 56% occurrence of ILD or pneumonitis in patients treated with osimertinib, particularly following treatment with platinum-based chemoradiation therapy. Most agents have warnings regarding other **soft tissue toxicities** aside from dermatologic: **ocular toxicity** (applies to all except for dacomitinib and necitumumab), gastrointestinal perforation[*****] (infrequent but serious events with afatinib, erlotinib, and gefitinib), and cutaneous vasculitis with osimertinib. Several have a warning for hepatotoxicity (as with afatinib, erlotinib, and gefitinib). Unique warnings for one or two agents include to acute renal failure with erlotinib; thromboembolic events with lazertinib + amivantamab (venous thromboembolism [VTE] incidence of 36%[†††††] in MARIPOSA clinical study) and necitumumab; QTc prolongation with osimertinib; rare events of cardiac arrest (BBW) with necitumumab; cardiomyopathy with osimertinib; cerebral vascular accident with erlotinib; hypomagnesemia (83% incidence) and electrolyte imbalances (BBW) with necitumumab; micro-angiopathic hemolytic anemia with thrombocytopenia with erlotinib; aplastic anemia with osimertinib (high incidence rates of leukopenia, neutropenia, and thrombocytopenia); and infusion-related reactions with the antibody therapies (amivantamab, necitumumab).

The most common adverse reactions listed in the package inserts (and reported in ≥20% of patients in a least one pivotal trial) are as follows:

- Afatinib monotherapy: diarrhea (75%-96%), rash/acneiform dermatitis (70%-90%), stomatitis (30%-71%), paronychia, dry skin, decreased appetite, nausea, vomiting, and pruritus.
- Amivantamab-containing therapy (regardless of a combined agent): rash (74%-86%), stomatitis, infusion-related reaction[‡‡‡‡‡] (IRR, 50%-66%), nausea, constipation, edema, fatigue
    - Additional common AEs, depending on the regimen:
        - Amivantamab monotherapy: paronychia, musculoskeletal pain, dyspnea, cough, and vomiting
        - Amivantamab plus carboplatin and pemetrexed: nail toxicity, decreased appetite, COVID-19, diarrhea, and vomiting.

[*****] The following factors may increase the risk of gastrointestinal (GI) perforation: concomitant anti-angiogenic agents, corticosteroids, NSAIDs, or taxane-based chemotherapy; or history of peptic ulceration or diverticular disease. Patients should be monitored for signs and symptoms of GI perforation and the drug discontinued in the event of Gl perforation.
[†††††] 10% of patients had Grade 3 events and 0.5% had grade 4 events; most cases occurred during the initial months of therapy.
[‡‡‡‡‡] IRR symptoms may entail dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting.

        - Amivantamab plus lazertinib: nail toxicity, musculoskeletal pain, venous thromboembolism (VTE, 36% in the MARIPOSA clinical trial), paresthesia, diarrhea, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, and ocular toxicity
- Dacomitinib: diarrhea (87%), rash (69%), paronychia, stomatitis (45%), decreased appetite and weight, dry skin, alopecia, cough, pruritus.
- Erlotinib, any-line of therapy for NSCLC: rash (75%-85%), diarrhea (54%-62%), anorexia or fatigue (each 52% in subsequently-line study), fatigue, dyspnea, and cough.
- Gefitinib: dermatologic reactions (47%), diarrhea (29%), increased liver enzymes (about 40%), proteinuria (35%)
- Lazertinib: refer to amivantamab + lazertinib, since lazertinib is indicated only in combination with amivantamab.
- Osimertinib-containing therapy (regardless of a combined agent): leukopenia (54%-88%), neutropenia (26%-85%), lymphopenia (44%-78%), thrombocytopenia (47%-85%), diarrhea (36%-58%), rash (39%-58%), nail toxicity
    - Additional common AEs, depending on the regimen:
        - Osimertinib monotherapy: anemia (59%), hyperglycemia, musculoskeletal pain, dry skin, stomatitis (32%), fatigue (21%), hypermagnesemia (30%), hyponatremia, increased liver enzymes
        - Osimertinib following platinum-based chemoradiation therapy: ILD/pneumonitis (56%), musculoskeletal pain (20%), cough and COVID-19.
        - Osimertinib plus pemetrexed and platinum-based chemotherapy: stomatitis (31%), dry skin, and increased blood creatinine (22%).
- Necitumumab: rash (44%), vomiting (29%) and hypomagnesemia (83%), hypokalemia (28%), hypocalcemia (36%), hypophosphatemia (31%)

8.2 Safety information regarding EGFR-inhibitors indicated for mCRC: cetuximab, panitumumab

Cetuximab and panitumumab cause a high burden of gastrointestinal AEs (eg, diarrhea, vomiting, constipation) and especially dermatologic events.[3,12] Both agents have labeled warnings for dermatologic toxicity—a BBW for panitumumab due to many events graded severe (15%). Additionally, panitumumab has warnings regarding soft tissue toxicity in general, ocular toxicity (some events of keratitis, ulcerative keratitis, and corneal perforation observed), and photosensitivity which can aggravate dermatologic reactions. Although fatigue is common with both agents, cetuximab seems to cause a very high incidence (91% in the monotherapy pivotal trial). Both agents have labeled warnings regarding (a) infrequent but serious cases of ILD, (b) hypomagnesemia and electrolyte imbalances (requires monitoring), and infusion-related reactions (BBW for cetuximab).[3,12] Cetuximab has a unique BBW warning regarding rare cases of cardiac arrest, but this was in the setting of combination treatment for SCCHN, with several cases having possible risk factors (eg, coronary artery disease, congestive heart failure).[12]

The most common adverse reactions listed in the package inserts (and reported in ≥20% of patients) are as follows[3,12]:

- Cetuximab monotherapy: dermatologic toxicity (rash [95%], dry skin, pruritus, nail toxicity), stomatitis (32%), fatigue (91%), fever, infection without neutropenia (38%), dyspnea, cough, pain, headache (38%), neuropathy (45%), insomnia, nausea (63%), constipation (53%), diarrhea (42%), and vomiting (40%).
- Cetuximab combined with chemotherapy (eg, FOLFIRI, or irinotecan): acne-like rash (86%-88%), stomatitis (31%), paronychia, diarrhea (66%-72%), nausea, anorexia (30%), asthenia (73% in one study), neutropenia (49%), and pyrexia.
- Cetuximab plus encorafenib: fatigue (51%), nausea (34%), diarrhea (33%), abdominal pain, vomiting (21%), decreased appetite, arthralgia, dermatitis acneiform (32%), rash (26%), and headache (20%).
- Panitumumab monotherapy: dermatologic reactions (90%; 15% were grade 3 or higher), paronychia, fatigue, nausea, and diarrhea (21%).
- Panitumumab plus FOLFOX chemotherapy: diarrhea (62%), stomatitis (27%), mucosal inflammation (25%), asthenia, paronychia, anorexia, hypomagnesemia (30%), hypokalemia (21%), rash (56%), acneiform dermatitis (32%), pruritus, and dry skin.

8.3 Safety information for EGFR-inhibitors indicated for breast cancer: lapatinib, neratinib

Lapatinib and neratinib are associated with a high burden of gastrointestinal AEs, particularly diarrhea which can be severe, requiring management with antidiarrheal agents, fluids/electrolyte replacement, and possible pause or discontinuation of therapy (labeled warning for both agents).[5,7] The package insert for neratinib suggests using premedication for diarrhea when not using a gradual dose escalation strategy. Both agents also have warnings regarding infrequent but potentially severe hepatotoxicity and the requirement for liver-enzyme monitoring (BBW for lapatinib). Lapatinib has several unique labeled warnings not carried by neratinib, regarding serious dermatologic adverse (eg, palmar-plantar erythrodysesthesia or other rash), and rare but severe cases of ILD, QTc prolongation, or cardiac dysfunction.[7] The most common adverse reactions listed in the package inserts (and reported in ≥15% of patients) are as follows[5,7]:

- Lapatinib plus capecitabine: diarrhea (65%), palmar-plantar erythrodysesthesia (53%), nausea, rash (28%), vomiting, fatigue, and mucosal inflammation (15%).
- Lapatinib plus letrozole: diarrhea (64%), rash (44%), nausea, and fatigue, and vomiting (17%).
- Neratinib monotherapy for adjuvant treatment (patients were not required to use antidiarrheal premedication in the pivotal trial[5]): diarrhea (95%), nausea, abdominal pain, vomiting, fatigue, and rash (18%).
- Neratinib plus capecitabine (patients were required to use antidiarrheal premedication[34]): diarrhea (83%), nausea, vomiting, decreased appetite, constipation, fatigue, and weight loss (20%).

8.4 Additional safety information for other agents/indications

Safety information for agent/indication groupings not already covered above include cetuximab for SCCHN, erlotinib for pancreatic cancer, and vandetanib for thyroid cancer.

A warning for cetuximab, particularly in the setting of SCCHN, is regarding infrequent events of cardiopulmonary arrest (2% incidence). Other applicable warnings for cetuximab, regardless of the indication (ie, that apply to both SCCHN and mCRC settings), are summarized in section 8.2.

Warnings for erlotinib, particularly in the setting of pancreatic cancer, include cerebrovascular accident (2.5% when used with gemcitabine), and increased risk of microangiopathic hemolytic anemia (1.4% when used with gemcitabine). Other applicable warnings for erlotinib, regardless of the indication (ie, that apply to both NSCLC and pancreatic cancer treatment), are summarized in section 8.1.

The anti-VEGF/EGFR inhibitor, vandetanib indicated for thyroid cancer, has several warnings in common with other anti-VEGF agents including those regarding impaired wound healing, severe bleeding events, hypertension, and a neurologic disorder called posterior reversable encephalopathy syndrome. As an EGFR inhibitor, vandetanib also has warnings in common with that class such as those regarding severe dermatologic reactions, diarrhea, association with ILD. Other unique warnings include risk of QTc prolongation (BBW), ischemic cerebrovascular events, and heart failure. Common adverse events occurring in >20% of vandetanib-treated patients and greater than in the placebo group included diarrhea/colitis, rash, acneiform dermatitis, hypertension, nausea, headache, upper respiratory tract infections, decreased appetite and abdominal pain.

8.5 Drug-drug Interactions

The following bullets briefly consolidate the most pertinent drug-drug interactions with the EGFR-inhibitors, as per labeling.

- EGFR inhibitors that can have compound QTc-prolongating effect with other QTc-prolongating drugs (conduct periodic monitoring, electrocardiograms and electrolytes, and weight risk/benefits): lapatinib, osimertinib, vandetanib
- EGFR inhibitors affected by P-glycoprotein (P-gp) inhibitors and inducers
    - Afatinib (must consider dose adjustments; eg, reduce dose with P-gp inhibitors), neratinib (avoid Pg-p and moderate CYP3A4 dual inhibitors)
- EGFR inhibitors affected by strong or moderate CYP3A4 inhibitors or inducers
    - Erlotinib (avoid concomitant use), gefitinib, lapatinib (avoid strong CYP3A4 inhibitors and inducers), lazertinib (avoid concomitant use), neratinib (avoid strong inhibitors and strong or moderate inducers), osimertinib (avoid strong inducers), vandetanib (avoid strong inducers)
- EGFR inhibitors affected by agents that increase gastric pH (decreases exposure); avoid use with proton pump inhibitors if possible and separate from H2-receptor antagonists
    - Dacomitinib, erlotinib, gefitinib, neratinib
- Cigarette smoking and CYP1A2 inducers decrease erlotinib exposure (avoid concomitant use if possible or consider done increase)
- Substrates of CYP3A4: lapatinib and lazertinib (increases exposure to such substrates)
- Substrates of CYP2C8: lapatinib (increases exposure to such substrates)
- Certain substrates of P-gp (eg, digoxin): lapatinib, neratinib (can increase exposure to substrate), vandetanib
- Substrates of CYP2D6: dacomitinib (increases exposure to CYP2D6 substrates)

- Substrates of BCRP (eg, rosuvastatin): lazertinib and osimertinib (increase exposure to such substrates)
- Substrates of OCT2 (eg, metformin): vandetanib (increases exposure to such substrates)
- Warfarin: Erlotinib can significantly increase INR (international normalized ratio) in patients on warfarin[1]

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2. Corporation G. CAPRELSA (vandetanib) tablet [Package Insert]. Cambridge, MA: Genzyme Corporation; April 2024. December 2022,

3. Vectibix (panitumumab) injection [Package Insert]. Thousand Oaks, CA: Amgen Inc.; August 2021.

4. Tagrisso (osimertinib) tablets [Package Insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; September 2024.

5. Nerlynx (neratinib) tablets [Package Insert]. Los Angeles, CA: Puma Biotechnology, Inc.; March 2022.

6. Portrazza (necitumumab) injection [Package Insert]. Indianapolis, IN: Eli Lilly and Company; November 2015.

7. Tykerb (lapatinib) tablets [Package Insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2022.

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10. Rybrevant (amivantamab-vmjw) injection [Package Insert]. Horsham, PA: Janssen Biotech, Inc.; September 2024.

11. Vizimpro (dacomitinib) tablet [Package Insert]. New York, NY: Pfizer Laboratories ; December 2020.

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APPENDIX A - PRODUCT INDICATIONS AND DOSING

Table A1. EGFR Inhibitor Indications and Dosing[a,]

Afatinib[9]
NSCLC • First-line treatment of metastatic NSCLC with non-resistant EGFR mutations   ○ The most common non-resistant mutations are exon 21 L858R substitutions and exon 19 deletions. • Treatment of metastatic, squamous NSCLC with disease progression on platinum-based chemotherapy *Dosage (oral):* 40 mg once daily; dose reduce in severe renal impairment
Amivantamab[10]
NSCLC • First-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, in combination with carboplatin and pemetrexed • First-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with lazertinib • For adults with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, with disease progression on or after platinum-based chemotherapy; as monotherapy • For adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations and disease progression on or after treatment with an EGFR inhibitor; in combination with carboplatin and pemetrexed *Dosage (intravenous)* • Dosing is weight-based (<80kg, or >80kg) and depends on whether use is as monotherapy or combination therapy; generally dosing range from 1400 mg to 2100 mg per weekly dose for 4 to 5 weeks, with the initial dose split over 2 days, and the following doses starting at week 7 administered every 2 to 3 weeks, depending on the treatment regimen.

Table A1. EGFR Inhibitor Indications and Dosing[a,]

Ceuximab[12]
Head and Neck Cancer
• Locally or regionally advanced squamous cell carcinoma of the head and neck, in combination with radiation therapy
• Recurrent locoregional disease or metastatic squamous cell carcinoma of the head and neck, in combination with platinum-based therapy with fluorouracil
• Recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy
Metastatic Colorectal Cancer
• First-line treatment for K-Ras wild-type, EGFR-expressing, metastatic colorectal cancer:
○ first-line treatment, in combination with FOLFIRI
○ refractory disease to irinotecan-based chemotherapy, in combination with irinotecan
○ as a monotherapy after failing (or intolerance to) oxaliplatin- and irinotecan-based chemotherapy
Dosage (intravenous)
• Premedicate with a histamine receptor antagonist
• *In a regimen with radiation therapy*: Initial dose: 400 mg/m^2 one week prior to initiating radiation therapy; followed by 250 mg/m^2 every week for the duration of radiation therapy (6–7 weeks)
• *As monotherapy or in combination with chemotherapy*:
○ Weekly: initial dose of 400 mg/m^2 and subsequent doses of 250 mg/m^2 infused once weekly
○ Biweekly: 500 mg/m^2 every two weeks
Dacomitinib[11]
NSCLC
• first-line for metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations
Dosage (oral): 45 mg once daily
Erlotinib[1]
NSCLC
• For first-line treatment, maintenance treatment for subsequent treatment (after progression on at least on prior chemotherapy) of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations
• *Dosage (oral)*: 150 mg, on an empty stomach, once daily

Table A1. EGFR Inhibitor Indications and Dosing[a,]

Erlotinib continued…

Pancreatic cancer

- First-line treatment for locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine
- *Dosage (oral)*: 100 mg once daily

Gefitinib[8]

NSCLC

- First-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations

Dosage (oral): 250 mg once daily

Lapatinib[7]

Breast Cancer

- For postmenopausal women with hormone receptor-positive, HER2-positive metastatic breast cancer in whom hormonal therapy is indicated:
    - Dosage (oral): 1,500 mg (6 tablets) once daily continuously, in combination with letrozole (2.5 mg once daily)
- For advanced or metastatic breast cancer with overexpression of HER2 *previously treated* with chemotherapy including an anthracycline, a taxane, and trastuzumab
    - Dosage (oral): 1,250 mg (5 tablets) once daily on Days 1-21 continuously, in combination with capecitabine (2,000 mg/m^2/day on days 1-14 in a repeating 21-day cycle)
- Modify dose for cardiac and other toxicities, severe hepatic impairment, diarrhea, and CYP3A4 drug interactions

Lazertinib[13]

NSCLC

- First-line treatment of adults with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, in combination with amivantamab
- Dosage (oral): 240 mg once daily

Necitumumab[6]

- First-line treatment of metastatic squamous NSCLC, in combination with gemcitabine and cisplatin

Dosage (intravenous): 800 mg (absolute dose) on Days 1 and 8 of each 3-week cycle

Table A1. EGFR Inhibitor Indications and Dosing[a,]

Neratinib[5]

Breast Cancer
• For extended adjuvant treatment of adults with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy
  ○ Dosage (oral): 240 mg (6 tablets) once daily, with food, continuously until disease recurrence for up to one year
• In combination with capecitabine, for adults with advanced or metastatic HER2-positive breast cancer *who have received ≥2 prior anti-HER2 based* regimens in the metastatic setting
  ○ Dosage (oral): 240 mg (6 tablets) once daily with food on days 1–21 of a 21-day cycle plus capecitabine (750 mg/m^2 orally twice daily on days 1–14 of 21-day cycle)
• Premedication for diarrhea when not using a 2-week dose escalation for neratinib (use loperamide; see package insert)
• In patients with *severe hepatic impairment,* reduce starting dose to 80 mg

Osimertinib[4]
NSCLC • For adjuvant therapy in adults (for up to 3 years) after NSCLC tumor resection, for disease with EGFR exon 19 deletions or exon 21 L858R mutations • First-line treatment for adults with metastatic NSCLC and EGFR exon 19 deletions or exon 21 L858R mutations • First-line treatment for adults with locally advanced or metastatic NSCLC and EGFR exon 19 deletions or exon 21 L858R mutations, in combination with pemetrexed and platinum-based chemotherapy • For adults with locally advanced, unresectable (stage III) NSCLC (with EGFR exon 19 deletions or exon 21 L858R mutation) *without* progression during or following platinum-based chemoradiation therapy • For adults with metastatic EGFR T790M mutation-positive NSCLC with disease progression on or after EGFR therapy Dosage (oral): 80 mg once daily, until disease progression or unacceptable toxicity
Panitumumab[3]
Metastatic Colorectal Cancer • First-line treatment for K-RAS wild-type disease**,** in combination with FOLFOX • As monotherapy following disease progression after failing fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy. Dosage (intravenous): 6 mg/kg every 14 days
Vandetanib[2]
Medullary thyroid cancer (symptomatic or progressive disease, locally advanced or metastatic) Dosage (oral): 300 mg once daily   ○ dose reduce in the event of severe toxicities or QTc interval prolongation; for moderate renal impairment, the starting dose is 200 mg

APPENDIX B - LITERATURE SEARCH

The phased literature search approach involved screening the most recently published SRs first, then refining the search to later publication years tailored to certain drugs/indications as needed (per the rationale described in **Table B1**). The search strategies for each literature search (A-D in Box 1) are included in the following subsections after the table.

Table B1. Phased Literature Search Approach for Head-to-head SRs/RCTs

A. SR Search in Ovid-Medline: EGFR Agents and Overlapping Indications (2022 onward)

- Searched with key words for anti-EGFR drugs plus key words and MESH terms for the 3 approved indications in common (ie, colorectal cancer, NSCLC, and breast cancer) from 2022 into 2024, September or October
- Updated SR search for NSCLC indication to December 2024.
- Identified SRs citing direct comparative RCTs for each indication

B. Targeted Supplemental SR Search in Epistemonikos (2023 onward)*:* the search was targeted to agents with overlapping NCCN guideline-recommended places-in-therapy for first-line treatment (ie, for NSCLC or CRC)

C. Supplemental RCT search in Ovid-Medline for Comparative Evidence in the Setting of First-Line Therapy

a. For CRC: searched from 2022 onward for cetuximab versus panitumumab (Liu et al systematic review searched from 2022 prior[60])
b. For NSCLC: searched 2024 publications for EGFR comparator studies for first-line therapy
    i. Supplemented SR searches: eg, Qureshi et al[77] searched to May 2024 for EGFR studies, Zhao et al searched to January 2024 for osimertinib studies; Li et al[89] searched to June 2023 for EGFR studies;

Abbreviations: CRC, colorectal cancer; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; SR, systematic review

A. Ovid Medline Searches for Disease States in Common, plus EGFR Agents

Colorectal Cancer, Systematic Reviews Search—Ovid Medline		
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **September 10 2024**		
#	*Search Lines*	*Results*
1	(cetuximab or panitumumab).ti,ab,kw,kf. or cetuximab/ or panitumumab/	10086
2	colorectal.ti,ab. or exp *Colorectal Neoplasms/	297191
3	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	605268
4	(Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	558574
5	3 or 4 (SR filter)	715631
6	1 and 2 and 5	252
	limit 7 to yr="**2022** -Current" (potential CRC SRs)	**43**

NSCLC, Systematic Reviews Search—Ovid Medline		
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **September 11 2024**		
#	*Search Lines*	*Results*
1	(afatinib or amivantamab or dacomitinib or erlotinib or gefitinib or necitumumab or osimertinib).ti,ab,kw,kf. or afatinib/ or amivantamab/ or dacomitinib/ or erlotinib/ or gefitinib/ or necitumumab/ or osimertinib/	18300
2	(non-small cell lung or nonsmall cell lung or NSCLC).ti,ab. or exp *Carcinoma, Non-Small-Cell Lung/	106103
3	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. or (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	716021
4	1 and 2 and 3	409
5	limit 4 to yr="**2022** -Current" (potential NSCLC SRs)	**100**

NSCLC, Systematic Review Search *Updated* —Ovid Medline

Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **December 9, 2024**		
#	*Search Lines*	*Results*
1	(afatinib or amivantamab or dacomitinib or erlotinib or gefitinib or necitumumab or osimertinib).ti,ab. or afatinib/ or amivantamab/ or dacomitinib/ or erlotinib/ or gefitinib/ or necitumumab/ or osimertinib/	18343
2	(non-small cell lung or nonsmall cell lung or lung-cancer).ti,ab. or exp *Carcinoma, Non-Small-Cell Lung/	228107
3	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. or (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	736434
4	1 and 2 and 3	424
5	limit 4 to yr="**2024 -Current**" (updated SR search)	**29**

Breast Cancer, Systematic Reviews Search—Ovid Medline		
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **October 21 2024**		
#	*Search Lines*	*Results*
1	(lapatinib or neratinib).ti,ab,kw,kf. or (lapatinib/ or neratinib/)	3882
2	(breast).ti,ab. or exp *Breast Neoplasms/	575138
3	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw. or (Medline or Embase or Pubmed or literature-search).ab. or (systematic-review or meta-analysis).pt.	725393
4	1 and 2 and 3	148
5	limit 4 to yr="**2022** -Current" (potential Breast Cancer SRs)	**27**

B. Targeted Epistemonikos Systematic Reviews Search: First-line Therapy Agents

- title:(colorectal OR colon OR non-small-cell-lung OR breast OR CRC OR mCRC OR NSCLC) OR abstract:(colorectal OR colon OR non-small-cell-lung OR breast OR CRC OR mCRC OR NSCLC) **AND** (title:(afatinib or GILOTRIF or amivantamab or RYBREVANT or dacomitinib or VIZIMPRO or erlotinib or TARCEVA or gefitinib or IRESSA or osimertinib or TAGRISSO or cetuximab or ERBITUX or panitumumab or VECTIBIX) OR abstract:(afatinib or GILOTRIF or amivantamab or RYBREVANT or dacomitinib or VIZIMPRO or erlotinib or TARCEVA or gefitinib or IRESSA or osimertinib or TAGRISSO or cetuximab or ERBITUX or panitumumab or VECTIBIX))
    - Results limited from *2023 onward* (searched on December 6, 2024): **28**

C. Ovid-Medline Supplemental RCT Search

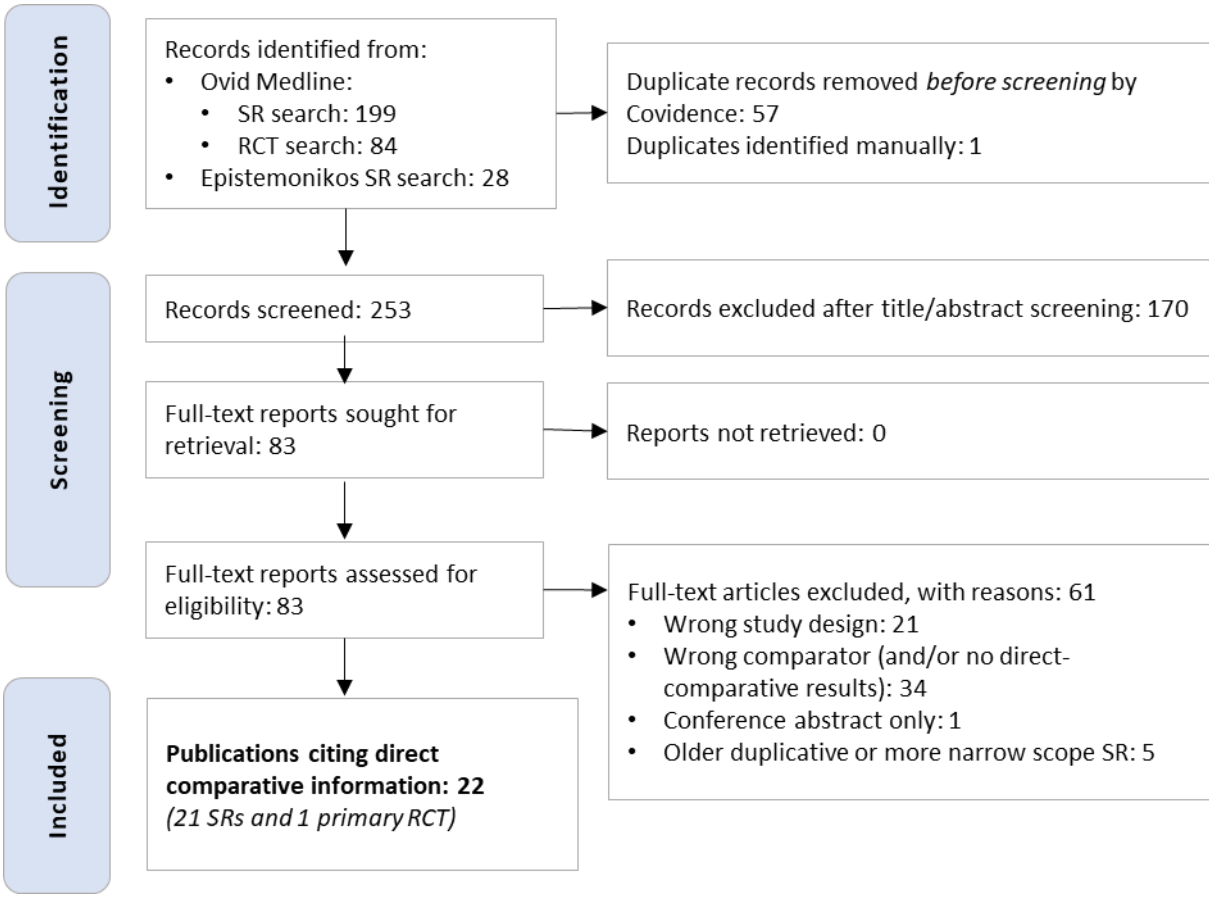
Colorectal Cancer, RCT Search—Ovid Medline		
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **December 8, 2024**		
#	*Search Lines*	*Results*
1	(cetuximab.ti,ab. or cetuximab/) and (panitumumab.ti,ab. or panitumumab/)	1285
2	colorectal.ti,ab. or exp *Colorectal Neoplasms/	301055
3	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1517445
4	1 and 2 and 3	174
5	limit 4 to yr="**2022** -Current" (potential CRC RCTs)	**18**

NSCLC, RCT Search—Ovid Medline		
Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to **December 10, 2024**		
#	*Search Lines*	*Results*
1	(afatinib or amivantamab or dacomitinib or erlotinib or gefitinib or necitumumab or osimertinib).ti,ab. or afatinib/ or amivantamab/ or dacomitinib/ or erlotinib/ or gefitinib/ or necitumumab/ or osimertinib/	18343
2	(non-small cell lung or nonsmall cell lung or lung-cancer).ti,ab. or exp *Carcinoma, Non-Small-Cell Lung/	228107
3	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1517873

4	1 and 2 and 3	1593
5	limit 4 to yr="2024 -Current"	66
6	(first-line or initial or naive or untreated).ti,ab.	1401697
7	5 and 6	**66**

APPENDIX C - PUBLICATION SCREENING

Appendix C, Figure 1. PRISMA Flow Chart[a] for Publication Screening



Abbreviations: H-H, head to head; RCT, randomized controlled trial; SR, systematic review

[a] Modified from Page et al. 2021[90]

Included Publications:

1 RCT for NSCLC (amivantamab + lazertinib vs. osimertinib) Cho et al 2024[26]

4 SRs showing 1 H-H RCT in the setting of previously-treated advanced breast cancer: Ji et al (2024)[51]; 2022 SRs: Giordano et al,[49] Simmons et al[50], and Wang et al[52]; plus 1 guideline by the ASCO[49]

4 SRs showing 2 H-H RCTs in the setting of previously-treated mCRC: 2 SRs from Jiang et al (2024)[63,64], Liu et al (2023)[60], Choi et al (2022)[59]

13 SRs showing 9 RCTs of interest for NSCLC:

- *2024 SRs: Favorito et al[70], Lasala et al[22], Li et al,[89] Qureshi (osimertinib, erlotinib, gefitinib)[77], Zhao et al (osimertinib)[91]; 2023 SRs: Alali et al[69], Jin et al (afatinib)[72], Lei et al (osimertinib)[24], Yang et al (dacomitinib)[25] ; 2022 SRs : Chen et al[92], Haeussler et al[93], Li et al[75], Qi et al[76]*

Additional SRs were identified but are duplicative and only address a smaller study cohort than the previously listed SRs.[94-99]

APPENDIX D - EXCLUDED STUDIES

Wrong Study Design

1. Adebayo AS, Agbaje K, Adesina SK, Olajubutu O. Colorectal Cancer: Disease Process, Current Treatment Options, and Future Perspectives. Pharmaceutics. 2023;15(11)
2. Bian DJH, Lazaratos A-M, Maritan SM, et al. Osimertinib is associated with improved outcomes in pre-treated non-small cell lung cancer leptomeningeal metastases: A systematic review and meta-analysiss. Heliyon. 2024;10(9): e29668.
3. Cai C, Luo Q, Liu Y, et al. The optimal first-line treatment for patients with left-sided RAS wild-type metastatic colorectal cancer: Double-drug regimen or triple-drug regimen therapy. Frontiers in pharmacology. 2022;13(101548923):1015510.
4. Chang H-C, Huang K-T, Tseng C-C, et al. Survival outcomes of east Asian patients with advanced non-small cell lung cancer treated with first-line EGFR tyrosine kinase inhibitors: A network meta-analysis of real-world evidence. Thoracic cancer. 2023;14(32):3217-3225.
5. Chang H-C, Wang C-C, Tseng C-C, et al. Do patient characteristics affect EGFR tyrosine kinase inhibitor treatment outcomes? A network meta-analysis of real-world survival outcomes of East Asian patients with advanced non-small cell lung cancer treated with first-line EGFR-TKIs. Thoracic cancer. 2023;14(32):3208-3216.
6. Felip E, Cho BC, Gutierrez V, et al. Amivantamab plus lazertinib versus osimertinib in first-line EGFR-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. Annals of oncology: official journal of the European Society for Medical Oncology. 2024;35(9):805-816.
7. Fukuda A, Okuma Y. From Rarity to Reality: Osimertinib's Promising Horizon in Treating Uncommon EGFR Mutations in Non-Small Cell Lung Cancer. Clinical cancer research: an official journal of the American Association for Cancer Research. 2024;30(15):3128-3136.
8. Greillier L, Gauvrit M, Paillaud E, et al. Targeted Therapy for Older Patients with Non-Small Cell Lung Cancer: Systematic Review and Guidelines from the French Society of Geriatric Oncology (SoFOG) and the French-Language Society of Pulmonology (SPLF)/French-Language Oncology Group (GOLF). Cancers. 2022;14(3)
9. Hunter Hall R, Wright CL, Hughes GK, et al. Assessing Patient Risk, Benefit, and Outcomes in Drug Development: Insights From Afatinib Clinical Trials Across Diverse Cancer Indications. Clinical therapeutics. 2024;46(6):e107-e113.
10. Kumar P, Mangla B, Javed S, Ahsan W, Musyuni P, Ahsan A, Aggarwal G. Gefitinib: An Updated Review of its Role in the Cancer Management, its Nanotechnological Interventions, Recent Patents and Clinical Trials. Recent patents on anti-cancer drug discovery. 2023;18(4):448-469.
11. Lazaratos A-M, Maritan SM, Quaiattini A, et al. Intrathecal trastuzumab versus alternate routes of delivery for HER2-targeted therapies in patients with HER2+ breast cancer leptomeningeal metastases. Breast (Edinburgh, Scotland). 2023;69(9213011):451-468.
12. Lee KH, Cho BC, Ahn M-J, et al. Lazertinib versus Gefitinib as First-Line Treatment for EGFR-mutated Locally Advanced or Metastatic NSCLC: LASER301 Korean Subset. Cancer research and treatment. 2024;56(1):48-60.
13. Pan J, Cai X, Cao Z, Pan J, Zheng H. Osimertinib in the Treatment of EGFR Mutation-Positive Advanced Non-Small Cell Lung Cancer: A Meta-Analysis. Pharmacology. 2023;108(1):8-16. doi:https://dx.doi.org/10.1159/000527321

14. Priantti JN, Vilbert M, Moraes FCA, et al. Safety and efficacy of osimertinib in patients with NSCLC and uncommon tumoral EGFR mutations: A systematic review and meta-analysis. J Clin Oncol. 2024;42(16)
15. Raimondi A, Nichetti F, Stahler A, et al. Optimal maintenance strategy following FOLFOX plus anti-EGFR induction therapy in patients with RAS wild type metastatic colorectal cancer: An individual patient data pooled analysis of randomised clinical trials. European journal of cancer (Oxford, England : 1990). 2023;190(arv, 9005373):112945.
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17. Sankarapandian V, Rajendran RL, Miruka CO, et al. A review on tyrosine kinase inhibitors for targeted breast cancer therapy. Pathology, research and practice. 2024;263(pbz, 7806109):155607.
18. Saoudi Gonzalez N, Ros J, Baraibar I, et al. Cetuximab as a Key Partner in Personalized Targeted Therapy for Metastatic Colorectal Cancer. Cancers. 2024;16(2)
19. Wang C, Zhao K, Hu S, Dong W, Gong Y, Li M, Xie C. Clinical outcomes of gefitinib and erlotinib in patients with NSCLC harboring uncommon EGFR mutations: A pooled analysis of 438 patients. Lung cancer (Amsterdam, Netherlands). 2022;172(b3u, 8800805):86-93.
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21. Xu, Ziyi et al. "Efficacy of First-Line Treatments in the Elderly and Non-Elderly Patients with Advanced Epidermal Growth Factor Receptor Mutated, Non-Small Cell Lung Cancer: A Network Meta-Analysis." *BMC cancer* 22.1 (2022): 514

Wrong Comparator

22. Bekaii-Saab TS, Lach K, Hsu L-I, et al. Impact of Anti-EGFR Therapies on HER2-Positive Metastatic Colorectal Cancer: A Systematic Literature Review and Meta-Analysis of Clinical Outcomes. The oncologist. 2023;28(10):885-893.
23. Li D, Li M, Li H, Shi P, Chen M, Yang T. The Use of Cytotoxic Drugs as First Line Chemotherapy for EGFR (+) Nonsquamous NSCLC: A Network Meta-Analysis. Disease markers. 2023;2023(dim, 8604127):5272125
24. Sakharkar P, Kurup S, Deb S, Assaad K, Gesinski D, Gayle EJ. Investigating the Efficacy of EGFR-TKIs and Anti-VEGFR Combination in Advanced Non-Small Cell Lung Cancer: A Meta-Analysis. Cancers. 2024;16(6)
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26. Tian W, Tan N, Ke J, et al. Adjuvant EGFR tyrosine kinase inhibitors for patients with resected EGFR-mutated non-small-cell lung cancer: a network meta-analysis. Future oncology (London, England). 2022;18(21):2695-2707.
27. Yoshino T, Hooda N, Younan D, et al. A meta-analysis of efficacy and safety data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in adult patients with RAS wild-type metastatic colorectal cancer by sidedness. European journal of cancer (Oxford, England : 1990). 2024;202(arv, 9005373):113975.
28. Zheng Y, Shen G, Zhang C, et al. Efficacy of anti-HER2 drugs in the treatment of patients with HER2-mutated cancers: a systematic review and meta-analysis. Clinical and experimental medicine. 2023;23(7):3205-3216.

No Head-to-head Comparisons or Outcome Results

29. Braicu V, Stelian P, Fulger L, et al. Impact of Systemic Treatments on Outcomes and Quality of Life in Patients with RAS-Positive Stage IV Colorectal Cancer: A Systematic Review. Diseases (Basel, Switzerland). 2024;12(4)
30. Cai Y-W, Shao Z-M, Yu K-D. Determining the Optimal (Neo)Adjuvant Regimen for Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer Regarding Survival Outcome: A Network Meta-Analysis. Frontiers in immunology. 2022;13(101560960):919369. doi:https://dx.doi.org/10.3389/fimmu.2022.919369
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33. Dong Y, Xu J, Sun B, Wang J, Wang Z. MET-Targeted Therapies and Clinical Outcomes: A Systematic Literature Review. Molecular diagnosis & therapy. 2022;26(2):203-227.
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42. Lian T, Zhang X. The Role of Tyrosine Kinase Inhibitors in Reduction of Mortality from Non-small Cell Lung Cancer: A Meta-analysis. Combinatorial chemistry & high throughput screening. 2023;26(5):928-937.

43. Liu A, Wang X, Wang L, et al. EGFR-TKIs or EGFR-TKIs combination treatments for untreated advanced EGFR-mutated NSCLC: a network meta-analysis. BMC cancer. 2024;24(1):1390. doi:10.1186/s12885-024-13168-8
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46. Papassotiriou I, Kapogiannatos A, Makatsoris C, et al. Efficacy and Safety of Amivantamab in Advanced or Metastatic EGFR-Mutant Non-Small Cell Lung Cancer: A Systematic Review. Journal of clinical medicine. 2024;13(18)
47. Perez, Edith A. et al. "Incidence of Adverse Events with Therapies Targeting HER2-Positive Metastatic Breast Cancer: A Literature Review." *Breast cancer research and treatment* 194.1 (2022): 1–11.
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52. Yang F, Zhang W, Shang X, et al. Comparison of the efficacy and safety of first-line treatments based on clinicopathological characteristics for patients with advanced epidermal growth factor receptor mutated non-small-cell lung cancer: A systematic review and network meta-analysis. Critical reviews in oncology/hematology. 2022;177(ago, 8916049):103760.
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55. Zhu Y, Liu C, Xu Z, et al. Front-line therapy for brain metastases and non-brain metastases in advanced epidermal growth factor receptor-mutated non-small cell lung cancer: a network meta-analysis. Chinese medical journal. 2023;136(21):2551-2561.

Set aside in lieu of a newer version or a more recent SR that includes a larger range of studies

56. Chan, Sik-Kwan, Horace Cheuk-Wai Choi, and Victor Ho-Fun Lee. "Overall Survival Benefits of First-Line Treatments for Asian Patients with Advanced Epidermal Growth Factor Receptor-Mutated NSCLC Harboring Exon 19 Deletion: A Systematic Review and Network Meta-Analysis." *Cancers* 14.14 (2022): 3362.

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Abstract Only

61. Priantti JN, Fujiwara Y, Aquino de Moraes FC, et al. Safety and Efficacy of Osimertinib in Patients With Non-Small-Cell Lung Cancer and Uncommon Tumoral Epidermal Growth Factor Receptor Mutations: A Systematic Review and Single-Arm Meta-Analysis. JCO precision oncology. 2024;8(101705370):e2400331.