HealthCare
The Power of Advanced Medicine

Molecular Targeted Therapies

Adult Oncology – Solid Tumors

Clinical Practice Guideline

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Executive Summary

Guideline Overview

This guideline contains evidence-based recommendations for the targeted therapies based on genetic testing of solid malignant tumors. It is heavily influenced by recommendations released by the National Comprehensive Cancer Network (NCCN) as well as local expert opinion.

Key Practice Recommendations

1. The UK Markey Cancer Center Molecular Tumor Board will be responsible for updating the clinical practice guideline document to reflect new evidence, changing practice trends, and expert opinion.
2. Establishes off-label therapy conditions for patients that are not eligible for a clinical trial specific for a molecular target locally or regionally, or an available basket trial.
3. Specific drug therapy recommendations have been provided for tumor type and molecular target and graded based on the level of evidence and strength of recommendation.

Companion Documents

cBioPortal Website
OncoKB Website

Pertinent UK Health Policies and Procedures

None

Patient Resources

My Cancer Genome

1. Scope

1.1. Disease/Condition(s): Solid Tumors, Cancer

1.2. Clinical Specialty: Medical Oncology, Pharmacy

1.3. Intended Users: Oncologists, Referring Oncologists, Pharmacist

1.4. CPG Objective(s): To outline evidence-based recommendations for targeted therapies in patients with cancer

1.5. Target population: Adult patients 18 years or older with solid tumor cancer

1.6. Interventions and Practices Considered: Targeted medication therapy

1.7. Major Outcomes Considered:

1. Percentage of patients who are clinical trial eligible for targeted therapies, percentage that enroll in clinical trials.
2. Progression free survival of patients referred to MCC MTB for treatment compared to patients who have not been referred
3. Progression free survival ratio of patients treated with targeted therapy based on the recommendation by the MCC MTB. The ratio will be calculated by the individual patient's progression free survival on current targeted therapy divided by the progression free survival on the regimen on which disease progression was experienced.

2. Methodology

2.1. Description of Methods Used to Collect/Select the Evidence:

Electronic database searches (i.e., PUBMED) were conducted by the workgroup members to collect evidence for review. Expert opinion, clinical experience, and regard for patient safety/experience were also considered during discussions of the evidence.

2.2. Methods Used to Assess the Quality and Strength of Evidence:

Evidence grading recommendations developed by external organizations (National Comprehensive Cancer Network [NCCN]) were maintained and adopted for use (Figure 1).

2.3. Rating Scheme for the Strength of Evidence:

Figure 1. NCCN Categories of Evidence and Consensus

Category	
1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

2.4. Description of Methods Used to Formulate Recommendations:

The interdisciplinary workgroup members agreed to adopt recommendations developed by external organizations (i.e., NCCN, OncoKB, BioPortal), and arrived at a consensus through discussion of the literature evidence and expert/institutional experiences to create the University of Kentucky Molecular Tumor Board Evidence Grading Scale (see Figure 2).

2.5. Rating Scheme for the Strength of the Evidence/Recommenations**:**

Figure 2. University of Kentucky, Markey Cancer Center, Molecular Tumor Board Evidence Grading Scale

Recommendation (based on color)	Evidence Level
FDA-indicated therapy; substantial evidence supporting use	Meta-analysis, RCTs, etc. OncoKB level 1
Off-label use; substantial evidence supporting use	Phase II studies and above OncoKB level 2 and above
Off-label use; low to moderate evidence supporting use; MTB recommends, clinical trial preferred	Phase I, case studies and reports OncoKB level 3 and below
Off-label; no evidence supporting use; enrollment in clinical trial recommended; report experience to MTB if used outside clinical trial	Little to no evidence (pre-clinical, animal/cellular models), mechanistically plausible
Not recommended	Phase II studies or above recommending against therapy

3. Introduction

Advances in technology have enabled routine molecular testing of malignant tumors, which may provide guidance in treatment decisions for some of the most common and fatal malignancies. This guideline provides evidence-based recommendations for approved and off-label use of molecular-targeted therapies for advanced malignant solid tumors.

4. Recommendations

4.1. Major Recommendations:

The Markey Cancer Center Molecular Tumor Board reserves the right to maintain the document to satisfy best clinical practices, emerging practice trends, and expert opinion. This document can be amended to add/remove conditions for off-label therapy by Markey Cancer Center Molecular Tumor Board (MCC MTB) co-chairs based on new evidence. Amendments will occur by the following process:

a) MTB collaborator or co-chair will nominate adding or removing a biomarker-off label therapy pair and submit a minimum of two primary research articles supporting its use, including at least one human clinical investigation. Additionally, a high-quality review article can be supplied.
b) At MTB journal club meeting the nominator or sponsoring co-chair will present evidence. Co-chairs will be responsible for identifying counter-evidence.
c) Decision will be made by agreement of co-chairs or, failing that, majority vote of co-chairs present.

Provisional approval is granted for drug-biomarker pairs when exceptionally strong preclinical data is available with FDA approved drugs, but clinical data on drug-biomarker pair beyond case reports or abstracts is unavailable.

Literature review is required for each subsequent MTB recommendation made under a provisional criterion. If the patient is not eligible or able to access a clinical trial specific for this molecular target (e.g. NCI-MATCH), off-label therapy may be recommended due to paucity of viable treatment options.

4.1.1 Conditions for Off-Label Therapy

Activating Oncogenes

<u>Direct pharmacologic inhibition of an activating oncogene mutation.</u>

This is adopted because of the broad evidence supporting the idea of oncogene addiction with concordant data from multiple models (cell lines, animal models) and human clinical evidence across multiple disease types.

Criteria for recommendation (all must apply):

a) Sequencing or genetic testing of tumor reveals an oncogenic mutation.
b) Any genetic sequencing testing is allowed, such as point mutation, indel, or translocation.
c) Amplification or overexpression is excluded.
d) The alteration must be known to activate an established oncogene.
e) An FDA-approved drug that inactivates oncogene function is available.

f) Antibodies used for oncogene overexpression are excluded (e.g. trastuzumab, cetuximab).
g) Single-agent targeted therapy is preferred, but on rare occasions combinations (including combinations of two off-label targeted agents that meet criteria) are allowed if appropriate rationale is provided under patient-specific regimen and safety is known.
h) The targeted agent is not known to be ineffective for this disease (e.g. BRAF inhibitors in colorectal cancer).

4.2 Recommendations for Selection of Targeted Agents Based on Tumor Type

4.2.1 Breast Cancer

Drug	BRCA	CCDN1	ER (ESR1)	HR	ERBB2 (HER2)	MSI-H*	PD-L1	PIK3CA	TMB^
Abemaciclib (Verzenio)		a		a					
Ado-trastuzumab emtansine (Kadcyla)					b				
Everolimus (Afinitor)			c	c				c	
Fulvestrant (Faslodex)			d						
Lapatinib (Tykerb)					e				
Neratinib (Nerlynx)					f				
Niraparib (Zejula)	g								
Olaparib (Lynparza)	h								
Palbociclib (Ibrance)		i		i					
Pembrolizumab (Keytruda)						j	j		j
Pertuzumab (Perjeta)					k				
Ribociclib (Kasqali)		l		l					
Rucaparib (Rubraca)	m								
Trastuzumab (Herceptin)					n				

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Abemaciclib: Abemaciclib is a CDK4/6 inhibitor approved in advanced breast cancer. The MONARCH 1 phase II trial investigated abemaciclib in women with HR-positive, HER2-negative, metastatic breast cancer who had progressed on endocrine therapy and at least one chemotherapy regimen.[1] The objective response rate was 19.7% with a clinical benefit rate of 42%. Median progression free survival (PFS) was 6 months and overall survival was 17.7 months.[1] The MONARCH II trial (phase III) randomized women with HR-positive, HER-2 negative, endocrine therapy-refractory, advanced breast cancer to receive either abemaciclib+fulvestrant or fulvestrant monotherapy.[2] The combination with abemaciclib increased the PFS over fulvestrant monotherapy (16.4 months versus 9.3 months, $p<0.001$). The objective response rate also favored the abemaciclib group (48.1% versus 21.3%).[2] Therefore, abemaciclib is recommended as systemic therapy in post-menopausal women with ER or PR-positive, HER2-negative advanced or metastatic disease.[3] (*NCCN Evidence Category 2A*)

b. Ado-trastuzumab emtansine: There is no persuasive evidence that combination regimens are superior to sequential single agents for recurrent or metastatic breast cancer.[3] Pertuzumab + trastuzumab + taxane (docetaxel or paclitaxel) remains the preferred first-line agent for HER2-positive disease based on improved overall survival compared to trastuzumab + taxane.[3] (*NCCN Evidence Category 1*) The MARIANNE trial demonstrated that ado-trastuzumab emtansine (T-DM1) and T-DM1 + pertuzumab were non-inferior.[4] Better tolerance and quality of life in the T-DM1 patients were noted compared to the trastuzumab + taxane group. Per the NCCN panel, T-DM1 is designated a first-line therapy that should be considered in those patients not suitable for the preferred treatment.[3-5] (*NCCN Evidence Category 2A*)
c. Everolimus: Everolimus is an inhibitor of mechanistic target of rapamycin (mTOR), thus having antiproliferative and antiangiogenic properties which may prove to be a useful therapeutic target. A combination of exemestane with everolimus can be considered for hormone-receptor positive advanced breast cancer patients who have disease progression within 12-months on non-steroidal aromatase inhibitors.[6-9] If there is disease progression while on exemestane + everolimus, there are no data to support an additional line of therapy with another everolimus regimen.[3] (*NCCN Evidence Category 2A)* Additionally, the activation of PIK3/AKT/mTOR pathway has been implicated in the hormone therapy resistance seen in breast and gynecologic cancers. In a phase I study of women with breast or gycecological cancers receiving hormonal therapy (anastrazole) with everolimus revealed 24% of the study subjects achieving stable disease for 6 months or longer.[10] It was noted in the responding patients, 75% of the group that had molecular testing also had at least one aberration in PIK3-AKT-mTOR pathway. Abnormalities in PIK3CA, PTEN (mutation or loss), and AKT are known to activate PIK3-AKT-mTOR pathway.[10] A phase II trial (GINECO) of post-menopausal women with HR-positive, HER2-negative, aromatase inhibitor-resistant, metastatic breast cancer randomized patients to receive either everolimus+tamoxifen or tamoxifen alone.[11] The clinical benefit rate favored the everolimus combination group (61% versus 42%) with a 46% in reisk reduction of disease production with the combination therapy. Additionally, tamoxifen+everolimus reduced the risk of death by 55%.[11] Therefore, combination of everolimus may be considered in combination with tamoxifen in post-menopausal, HER2-negative women with ER or PR-positive recurrent or stage IV breast cancer.[3] (*NCCN Evidence Category 2A*)
d. Fulvestrant: Fulvestrant, an estrogen receptor antagonist, is as effective as anastrozole in patients that failed prior endocrine treatment (e.g., tamoxifen).[12,13] The PALOMA-3 study compared palbociclib + fulvestrant versus fulvestrant monotherapy in women with HR-positive, HER2-negative advanced stage breast cancer who had failed prior endocrine treatment. There was nearly a 6-month advantage in progression free survival (PFS) in the combination group.[14,15] Therefore the recommendation is to offer palbociclib + fulvestrant to women (pre and post-menopausal) with HR-positive, HER2-negative metastatic breast cancer who have had disease progression on endocrine therapy.[3] (*NCCN Evidence Category 1*)
e. Lapatinib: Lapatinib is a multi-kinase inhibitor with activity against HER2 and EGFR. Lapatinib with capecitabine in HER2-positive recurrent or metastatic disease is recommended for those patients that have been previously exposed to trastuzumab.[16] (*NCCN Evidence Category 2A*) Lapatanib with an aromatase inhibitor (e.g., letrozole) had demonstrated increase in PFS compared to patients treated with letrozole alone (PFS 8.2 vs 3 months, respectively; p=) and remains an option for postmenopausal women with HR-positive and HER2-positive recurrent or advanced disease.[17] (*NCCN Evidence Category 2A*) Lapatinib has been investigated in HER2-positive breast cancer with disease progression on prior trastuzumab

therapy. The lapatinib + trastuzumab combination improved PFS when compared to lapatinib combination therapy.[18] An overall survival benefit of 4.5 months was detected in the lapatinib + trastuzumab dual therapy group over monotherapy with lapatinib.[19] Dual anti-HER2 blockade associated with trastuzumab + lapatinib or trastuzumab + pertuzumab has shown improvements pathologic complete response (pCR) when compared to chemotherapy + single anti-HER2 agent in the neoadjuvant setting.[20-22] The ALTTO trial failed to demonstrated disease-free survival (DFS) improvement in the adjuvant setting with dual anti-HER2 therapy when compared with trastuzumab alone. After a median follow-up of 4.5 years, the DFS rates were 86% for patients who received trastuzumab alone; 88% for patients treated with trastuzumab + lapatinib; and 87% for patients who received trastuzumab followed by lapatinib.[23] For postmenopausal women with HER2-positive disease, an aromatase inhibitor with lapatinib +/- trastuzumab remains an option for systemic therapy.[3] (*NCCN Evidence Category 2A*)
Lapatinib has been studied with combination capecitabine in previous untreated brain metastases from HER2-positive breast cancer. The LANDSCAPE trial was a phase-2 study of lapatinib + capecitabine in metastatic breast cancer patients with brain metastases not previously treated with brain radiation, lapatinib, or capecitabine. Of note, 93% of these patients were previously exposed to trastuzumab. Over 65% of patients receiving combination therapy with lapatinib + capecitabine had an objective CNS response at therapy, with the responders' time to progression delayed to a median of 6 months versus 2.8 months in the non-responder group.[24] Similar findings were reported in a multicenter retrospective investigation with nearly 70% of the patient group showing partial response or stable disease. Survival was increased from 12 months in the trastuzumab-based therapy compared to 19 months in the lapatinib + capecitabine group.[25]

f. Neratinib: Neratinib is a multi-kinase inhibitor with activity at HER2 and EGFR. A randomized, double blind, placebo controlled phase-3, multicenter (multi-continent) trial investigated neratinib in stage 1-3 HER2-positive breast cancer patients post-neoadjuvant and adjuvant trastuzumab up to 2 years before randomization. Neratinib for 12 months significantly improved 2-year invasive DFS when given after chemotherapy and trastuzumab-based adjuvant.[26] Adjuvant neratinib can be considered after adjuvant trastuzumab-containing therapy in patients with HR-positive disease with possible high risk of reoccurance.[3] (*NCCN Evidence Category 2A*)
g. Niraparib: Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor with activity in BRCA-mutated ovarian cancer. A phase I study investigated niraparib in a number of solid tumors. Of the group with identified BRCA-mutations, 50% of the breast cancer patients (n=4) had partial responses to niraparib treatment.[27] Although niraparib has not been extensively studied in breast cancer, it is plausible to anticipate some degree of niraparib activity in BRCA-positive breast cancer based on the activity of the drug in other BRCA-positive tumors (e.g., ovarian, prostate) and the activity of other PARP inhibitors (i.e., olaparib) in breast cancer.
h. Olaparib: Olaparib is a PARP inhibitor with activity against BRCA mutations. In phase III trial, olaparib was compared to standard chemotherapy in HER2-negative, BRCA-positive metastatic breast cancer and found favorable results with respect to PFS (7 versus 4.2 months, $p<0.001$), risk of disease progression (42% lower in olaparib group), and response rate (59.9% versus 28.8%).[28] It remains an monotherapy option for HER2-negative BRCA-positive tumors in metastatic breast cancer.[3] (*NCCN Evidence Category 2A*)

i. Palbociclib: Palbociclib is a CDK4/6 inhibitor approved in HER2-negative, advanced breast cancer. Palbociclib or ribociclib with letrozole or another aromatase inhibitor may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.[29,30] (*NCCN Evidence Category 1*) Palbociclib + fulvestrant is recommended for postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH-agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic endocrine therapy.[14,29] (*NCCN Evidence Category 1*) If there is disease progression while on a CDK4/6 inhibitor , there is no data to support an additional line of therapy with another CDK4/6 inhibitor regimen.[3]

j. Pembrolizumab: Pembrolizumab is an anti-programmed cell death-1 monoclonal antibody. Mismatch repair (MMR) deficiencies have been identified in a number of tumor types, providing another target for drug therapy.[31,32] Although breast cancer is not typically identified as an MMR deficient tumor, up to 2% of breast cancers have identified as such.[33] Pembrolizumab is an immune checkpoint inhibitor with antibodies for PD-1 that could be potentially effective in patients with MMR deficiency. Pembrolizumab has been shown to be highly responsive in other cancer types (e.g., melanoma, non-small cell lung cancer, etc.) with MMR deficiency and has earned FDA-approval for those indications, including microsatellite instability-high cancer that is unresectable or metastatic.[31,32] However, tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders ($p<0.0001$). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, $p=0.0086$). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, $p=0.0033$), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

k. Pertuzumab: Pertuzumab is a monoclonal antibody with activity against HER2, to be used in combination with other chemotherapeutic agents. The NCCN Panel recommends pertuzumab plus trastuzumab in combination with a taxane as a preferred option for first-line treatment of patients with HER2-positive metastatic breast cancer: pertuzumab + trastuzumab + docetaxel (*NCCN Evidence Category 1*) or pertuzumab + trastuzumab + paclitaxel.[3] (*NCCN Evidence Category 2A*) The NEOSPHERE trial that included patients with locally advanced, inflammatory, or early HER2-positive breast cancer discovered an increase in pCR with pertuzumab-containing regimens.[20,36] The NCCN Panel supports the use of pertuzumab-containing regimens pre-operatively in patients with HER2-positive, early-stage, inflammatory breast cancer.[3] (*NCCN Evidence Category 2A*) A multicenter, open-label, single-arm, phase II study reported pertuzumab + trastuzumab has activity and is well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab

therapy.[6] The NCCN panel recommends combination therapy with trastuzumab + pertuzumab with or without a cytotoxic agent (e.g., vinorelbine or taxane) in patients that have had disease progression on trastuzumab-based therapy.[3] (*NCCN Evidence Category 2A*)

l. Ribociclib: Ribociclib is a CDK4/6 inhibitor approved in HR-positive, HER2-negative, advanced breast cancer. Palbociclib or ribociclib with letrozole or another aromatase inhibitor may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.[29,30] (*NCCN Evidence Category 1*) Palbociclib + fulvestrant is recommended for postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH-agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic endocrine therapy.[14,29] (*NCCN Evidence Category 1*) If there is disease progression while on a CDK4/6 inhibitor) + letrozole, there are no data to support an additional line of therapy with another CDK4/6 inhibitor regimen.[3]

m. Rucaparib: Rucaparib is a PARP inhibitor with activity in patients with ovarian cancer and germline and/or somatic BRCA mutation. A phase II trial of rucaparib in BRCA 1/2-mutated, advanced breast or ovarian cancer reported a 2% objective response rate with intravenous rucaparib and 15% objective response rate with enteral rucaparib.[37] A phase I study investigated intravenous and oral rucaparib in combination with chemotherapy in advanced solid tumors.[38] Tumor response in the breast cancer cohort was reported as 1.2% achieving complete response, 10.6% achieving partial response, and 50.6% achieving stable disease.[38] Another phase I-II study investigated oral rucaparib in patients with germline BRCA solid tumors including breast cancer.[39] The overall objective response rate to rucaparib was 25%, with similar responses reported in the selective mutations (BRCA1 63.3% versus BRCA2 50%).[39] Although rucaparib has not been extensively studied in breast cancer, it is plausible to anticipate some degree of activity in BRCA-positive breast cancer based on the activity of the drug in other BRCA-positive tumors (e.g., ovarian) and the activity of other PARP inhibitors (i.e., olaparib) in breast cancer.

n. Trastuzumab: Trastuzumab is an anti-HER2 monoclonal antibody. All of the adjuvant trials of trastuzumab have demonstrated clinically significant improvements in PFS, and the combined analysis showed significant improvement in OS with the use of trastuzumab in patients with high-risk, HER2-positive breast cancer.[40-43] Therefore, regimens from each of these trials are included as trastuzumab-containing adjuvant regimen choices in the guideline. The benefits of trastuzumab are independent of ER status.[40,42] The NCCN Guidelines recommend a total of 12 months of adjuvant trastuzumab as the standard of care.[3] (*NCCN Evidence Category 1*) Shorter than 12-month duration has not been found to be as effective and longer than 12 months duration does not have any added benefit as it has been found to be as effective as the 12 months of trastuzumab therapy.[41,44]

4.2.2 Central Nervous System Tumors

Drug	EGFR	MSI-H*	PD-L1	PIK3CA	TMB^	VEGF
Bevacizumab (Avastin)						a
Erlotinib (Tarceva)	b					
Everolimus (Afinitor)				c		
Nivolumab (Opdivo)		d	d		d	
Sunitinib (Sutent)						e

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Bevacizumab: Bevacizumab is an anti-angiogenic monoclonal antibody and vascular endothelial growth factor inhibitor that is indicated in treatment of recurrent glioblastoma. Bevacizumab received accelerated approval in 2009 for recurrent glioblastoma based on two phase II studies. Patients with recurrent glioblastoma treated with bevacizumab with chemotherapy demonstrated similar progression free survival (PFS) at 6 months (38-50%).[45-47] Similar results in PFS were seen when bevacizumab monotherapy was compared to bevacizumab+irinotecan with estimated PFS rates of 42.6 and 50.3%, respectively.[45] The recommendation for bevacizumab is to be used as monotherapy or in combination with chemotherapy for recurrent anaplastic gliomas, glioblastomas, or intracranial and spinal ependymoma.[48] (*NCCN Evidence Category 2A*)

b. Erlotinib: Erlotinib is a small molecule tyrosine kinase inhibitor with activity against EGFR. A phase II trial of bevacizumab and erlotinib was investigated in patients with recurrent malignant glioma.[49] The 6-month PFS was achieved in 28% of the glioblastoma multiforme (GBM) cohort and in 44% in the anaplastic glioma group. The median overall survival in GBM patients was 42 weeks and 71 weeks in anaplastic glioma patients. However, the 6-month PFS did not differ from historical published reports of bevacizumab-based regimens in recurrent malignant gliomas.[49] In a small prospective study, ten patients with recurrent GBM status-post surgical resection and standard radiation and chemotherapy were assessed for tumor expression of EGFRvIII and MGMT promoter methylation, PTEN and VEGF.[50] Bevacizumab was given to patients with VEGF over expression, and EGFRvIII expresson earned those patients treatment with erlotinib. The overall response rate was 70%, with the bevacizumab+erlotinib group having 100% response and the erlotinib monotherapy group having 50% response rate. The overall median PFS was 8 months and overall survival was 9.5 months.[50] A phase I-II study of patients with recurrent malignant gliomas investigated erlotinib and temsirolimus combination therapy and reported 29% of glioblastoma patients and 12.5% of anaplastic glioma patients achieved stable disease.[51] The 6-month PFS was 12% in the GBM group and 8% in the anaplastic glioma cohort. The molecular analysis EGFRvIII expression and EGFR amplification did

not correlate with survival in this study. Additionally, the mTOR pathway appeared to increase the phospho-AKT signalling pathway, which may have contributed to the lack of anti-tumor activity in this study.[51] At this time, there appears to be an unclear role of erlotinib in successful treatment of recurrent malignant CNS tumors.

c. Everolimus: Everolimus is an inhibitor of mechanistic target of rapamycin (mTOR), thus having antiproliferative and antiangiogenic properties which may prove to be a useful therapeutic target. Abnormalities in PIK3CA, PTEN (mutation or loss), and AKT are known to activate PIK3-AKT-mTOR pathway.[10] A phase II study of treatment-naïve glioblastoma multiforme (GBM) patients initiated everolimus one week before radiation therapy and temozolomide therapy began, and then continued everolimus until disease progression.[52] The introduction of everolimus to this standard therapy did not prolong survival compared to historical controls, but did have a median PFS of 6.4 months and median overall survival of 15.8 months. In the cohort with MGMT hypermethylation, both PFS and overall survival were significantly longer compared to the non-MGMT tumor patients (p=0.018 and p=0.004, respectively). Everolimus sensitivity was evaluated through ^{18}FLT-PET imaging, pharmacokinetic analysis, and tumor genetics. Through imaging, 55% of the evaluated cohort were classified as non-responders and 45% as partial responders. There was no differences in serum concentrations of everolimus between the reponsers and non-responders (33.6 ng/mL versus 41.4 ng/mL, p=0.32). Additionally, the responder group was noted to have higher PTEN expression and lower AKT expression when compared to non-responders. Of note, the non-responders all had multiple abberations in the PIK3/AKT/mTOR pathway. From this study, the addition of everolimus to standard radiotherapy and temozolomide in GBM did not improve survival and did introduce additional toxicity.[52] The role of everolimus at this time has yet to be eludicated for CNS tumors.

d. Nivolumab: Nivolumab is an anti-PD-L1 monoclonal antibody and checkpoint inhibitor approved for use in multiple advanced/metastatic solid tumors, but not in tumors of the central nervous system (CNS). In a case report, two patients with recurrent glioblastoma multiforme and biallelic mismatch repair deficiency were treated with nivolumab. Those patients demonstrated disease regression by week 8 and 12 of therapy.[53] Both PD-L1 expression and mutational tumor burden (TMB) has been investigated for predictors of response to immunotherapy. Other solid tumor studies have reported response to immunotherapy with a median TMB of 19 mutations versus five mutations for non-responders (p<0.0001).[34] The PFS was also longer in the high TMB group (≥ 20 mutations) compared to the low to intermediate TMB groups (10 months versus 2.1 months, p=0.0033), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Specifically in CNS tumors, PD-1 and PD-L1 expression and grade IV gliomas were positively related, suggesting a possible biomarker target in this tumor type.[54] Another tumor molecular genetics database analysis discovered PD-1 was expressed on tumor-infiltrating lymphocytes (TIL) in 31.5% of cranial gliomas and PD-L1 on 6.1% of glioma tumors.[55] Low grade astrocytomas expressed PD-1 on lymphocytes 16.7% of the samples, wherease PD-L1 expression was not found in any tumors of oligodendroglial lineage. Due expression of PD-1 and PD-L1 occurred in 4.3% of the cases. There was no association found between the PD-1 or PD-L1 and expression of MGMT in GBM, but 38.4% of the GBM population had PD-1

expression with at least one other mutation (PTEN, TP53, IDH1, BRAF, or EGFR) and 4.7% had PD-L1 expression plus another mutation.[55] The significance of PD-1/PD-L1 expression and tumor mutation burden and response to immunotherapy remains unknown at this time in CNS tumors.

e. Sunitinib: Sunitinib is a small-molecule tyrosine kinase inhibitor that targets the VEGF receptor and platelet-derived growth factor receptor, both of which are abundant in meningioma. In a phase II trial in recurrent and progressive atypical and anaplastic meningioma treated with sunitinib, 42% of the cohort met PFS at 6 months with a median PFS 5.2 months and median overall survival 24.6 months. Patients with VEGF2-negative tumors had a median predicted PFS of 1.4 months versus 6.4 months in those with a positive mutation.[56] Because of this trial sunitinib is considered a systemic option for meningiomas.[48] (*NCCN Evidence Category 2B*)

4.2.3 Gastrointestinal Cancers (Colorectal, Gastrointestinal Stromal Tumors)

Drug	BRAF	ERBB2 (HER2)	EGFR	HRAS KRAS NRAS	KIT	MAP2K1 (MEK)	MSI-H*	PIK3	TMB^	VEGF
Bevacizumab (Avastin)										a
Cetuximab (Erbitux)			b	b						
Cobimetinib (Cotellic)						c				
Dasatinib (Sprycel)					d					
Everolimus (Afinitor)					e			e		
Imatinib (Gleevac)					f					
Lapatinib (Tykerb)		g								
Nilotinib (Tasigna)					h					
Nivolumab (Opdivo)							i		i	
Panitumumab (Vectibix)			j	j						
Pazopanib (Votrient)					k					
Pembrolizumab (Keytruda)							l		l	
Ramucirumab (Cyramza)										m
Regorafenib (Stivarga)	n				n					l
Sorafenib (Nexavar)					o					
Sunitinib (Sutent)					p					
Trametinib (Mekanist)						q				
Trastuzumab (Herceptin)		r								
Vemurafenib (Zelboraf)	s									
Ziv-aflibercept (Zaltrap)										t

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Bevacizumab: Bevacizumab is a monoclonal antibody with anti-VEGF activity and is approved in metastatic colorectal cancer. It is part of the core systemic therapy for initial management of metastatic colorectal disease. Bevacizumab has been studied with a number of systemic chemotherapy regimens (CapeOx, FOLFOX, FOLFIRI, 5-FU/LV, capecitabine, FOLFOXIRI) as first-line therapy in metastatic colorectal cancer. Meta-analyses have reported the addition of bevacizumab to these first-line cytotoxic treatments have resulted in improvement of overall survival and prolonged progression free survival (PFS) when compared to chemotherapy alone.[57,58] Irinotecan-based regimens with bevacizumab showed the greatest benefit to overall survival and PFS in the sub-analysis.[57,58] Although, the NCCN panel gives no preference to the choice of systemic chemotherapy, the addition of bevacizumab is recommended as the preferred first-line treatment option in metastatic

colorectal cancer in combination with chemotherapy.[59,60] (*NCCN Evidence Category 2A*) A meta-analysis of bevacizumab with cytotoxic regimens as second-line systemic therapy in patients with metastatic colorectal cancer reported favorable overall survival and PFS with the combination compared to chemotherapy alone.[61] The phase IV ARIES trial investigated the efficacy of bevacizumab as first- or second-line therapy in patients with metastatic colorectal cancer.[62] In patients who received bevacizumab therapy as first line, the median PFS was 10.2 months and median overall survival was 23.3 months. The second-line, bevacizumab-naïve treatment group had a median PFS of 8.1 months compared to the 7.6 months in the bevacizumab-exposed cohort, but conversely the median overall survival favored the bevacizumab-exposed cohort (19.8 versus 17.2 months).[62] Bevacizumab with chemotherapy has been compared to panitumumab with chemotherapy as first-line and second-line therapy. A meta-analysis found no difference in PFS between the groups (panitumumab 6-10.9 months versus bevacizumab 5.9-10.1 months, p=0.56), however the median overall survival favored the panitumumab cohorts (16.2-34.2 months versus 13.4-24.3 months, p=0.043).[63] Therefore, bevacizumab or panitumumab may be considered with chemotherapy for treatment of metastatic disease.[59,60] (*NCCN Evidence Category 2A*)

b. Cetuximab: Cetuximab is an anti-EGFR monoclonal antibody that is approved for KRAS-wild type, metastatic colorectal cancer. Evidence has demonstrated that tumors with KRAS, NRAS, and BRAF V600E mutations are not responsive or have poor response to cetuximab.[64-75] Because of these findings, cetuximab should be reserved for patient populations with wild-type RAS (KRAS or NRAS) and wild-type BRAF.[59,60,74,76,77] (*NCCN Evidence Category 2A*) Patients with right-sided tumors are unlikely to respond to first-line anti-EGFR therapy in metastatic disease.[78-81] Left-sided tumors can be considered for cetuximab in RAS-wild type disease.[59,60] (*NCCN Evidence Category 2A*) Meta-analyses have concluded the addition of first-line anti-EGFR monoclonal antibodies (cetuximab or panitumumab) in wild-type RAS tumors decreased the risk of death (19%, p=0.002) and increased resection rates (R0 resection rate 60%).[82,83] When anti-EGFR agents were compared to chemotherapy alone, first-line anti-EGFR monoclonal antibodies decreased the risk of death by 17% (p=0.07), and when compared to bevacizumab, anti-EGFR agents decreased the risk of death by 20% (p=0.003).[82] The median PFS with first-line EGFR decreased risk of progression by 23% (p=0.23), and this benefit was seen when EGFR inhibitors where compared to chemotherapy (p<0.001), but not when compared to bevacizumab (p=0.59).[72,82,83] Therefore, NCCN Panel recommends chemotherapy with the addition of cetuximab, panitumumab, or bevacizumab in the initial treatment of RAS wild-type, metastatic colorectal cancer.[59,60] (*NCCN Evidence Category 2A*) Combination therapy involving chemotherapy with anti-EGFRs (cetuximab or panitumumab) and anti-rVEGFs (bevacizumab) is not recommended based on the results of the PACCE and CAIRO2 trials as increased toxicity, shorter progression free survival (PFS), and lower quality of life scores were observed.[59,60,84,85] (*NCCN Evidence Category 2A*)

c. Cobimetinib: Cobimetinib is a MEK inhibitor that selectively inhibits MEK1 and MEK2, which is downstream from BRAF kinase. The BRAF V600E mutation has been reported in 8% of colorectal cancers and is thought to contribute to reactivation of the MEK/ERK signaling cascade.[86] Preclinical studies have investigated the combination of MEK inhibitors with cyclin-dependent-kinase inhibitors in BRAF V600E-positve colorectal tumors and have found enhanced apoptosis of cancer cells.[86] The MAP2K1 K57T mutation is also thought to be potential mechanism of resistance to EGFR inhibitors in colorectal cancer. This mutation is also associated with resistance to BRAF and MEK inhibitors. Preclinical studies have suggested that

combination treatment with BRAF and MEK inhibitors may help overcome MAP2K1 K57T-mutant colorectal cancer.[87] A phase I study investigated trametinib in a number of heavily treated solid tumor patients and reported no objective response in colorectal cancer patients.[88] However, other tumors harboring KRAS mutations (i.e. melanoma and NSCLC) observed objective responses (partial) with this exploratory treatment with tramatinib.[88] MEK inhibitor therapy in colorectal tumors has yet to supply the necessary evidence to garner recommendations for use in colorectal cancer.

d. Dasatinib: Dasatinib is a BCR-ABL tyrosine kinase inhibitor with activity against KIT and platelet derived growth factor receptor (PDGFR). A phase II investigated dasatinib in patients with imatinib- and sunitinib-resistant GIST.[89] The genotyping of the cohort revealed 47% with KIT (exon 9 or 11), 7% with PDGFR D842V, and 13% wild-type tumors. Treatment with dasatinib resulted with a median PFS of 2 months, with the wild type GIST having a prolong PFS of 8.4 months. The reported median overall survival of 19 months.[89] A phase II trial of TKI-naïve GIST patients receiving dasatinib reported a response rate of 67% at 4 weeks, and a PFS of 11.1 months.[90] The long-term data from the previous phase II trial of dasatinib described similar findings from the preliminary report, with a 74% response rate at 4 weeks, and a PFS of 13.6 months in patients with TKI-naïve GIST.[91] At this time, the NCCN Panel recommends dasatinib as a therapeutic option if failure of imatinib, sunitinib, or regorafenib occurs.[92] (*NCCN Evidence Category 2A*)

e. Everolimus: Everolimus is an inhibitor of mechanistic target of rapamycin (mTOR), thus having antiproliferative and antiangiogenic properties which may prove to be a useful therapeutic target. Everolimus will inhibit the PIK3/AKT/mTOR signaling pathway that is downstream from EGFR, KIT and platelet derived growth factor receptor A (PDGFRA). PIK3 mutation have been implicated in about 17% of colorectal cancers.[93] Specifically mutations in the p110a subunit of PIK3 activates the PIK3/AKT/mTOR in a number of tumor types. PIK3 mutations have been suggested as predictors of anti-EGFR therapy.[93,94] A prospective phase II trial investigated everolimus therapy in PIK3-amplified, PIK3-mutated, and PTEN-loss patients with solid tumors.[95] Unfortunately, everolimus therapy did not result in a complete or partial responses, but 40% of the study population experienced stable disease. The median PFS was 1.6 months with everolimus therapy.[95] Another phase II study trialed everolimus therapy in patients with heavily treated (bevacizumab, oxaliplatin, and irinotecan) metastatic colorectal cancers.[96] Disease control rates were modest in the two everolimus dosing regimens (weekly 31% and daily 32.4%). Both PFS and overall survival were similar, however those patients with wild-type KRAS tumors had a longer median overall survival ($p=0.0008$) and higher disease control rate ($p<0.035$).[96] At this time, the role of everolimus in treatment of colorectal cancer is not yet elucidated. Expression of KIT has been implicated in about 95% of GIST, with 80% having an activating mutation in the KIT receptor tyrosine kinase and 5-10% in PDFGRA, thus making this signaling pathway of interest for targeted therapies.[92,97-99] Preclinical data has suggested anti-tumor activity of mTOR inhibitors in GIST, especially when everolimus was used in combination with imatinib.[100] A phase I-II study of patients with GIST and failure on imatinib, sunitinib, or another tyrosine kinase inhibitor (TKI) therapy enrolled patients to receive both everolimus and imatinib.[101] The groups were stratified into cohorts with only previous imatinib exposure (strata 1) and previous imatinib plus sunitinib or other TKI exposure (strata 2). The median PFS was 1.9 months in strata I and a PFS of 3.5 months in strata II. However, overall survival was prolonged in the previous imatinib exposure group compared to strata II (14.9 months vs 10.7 months).[101]

Everolimus may be considered treatment of GIST in combination with a TKI (imatinib, sunitinib, and regorafenib).[92] (*NCCN Evidence Category 2A*)

f. Imatinib: Imatinib is a BCR-ABL tyrosine kinase inhibitor with activity at KIT, platelet derived growth factor receptor (PDGFR), and stem cell factor (SCF) that is indicated in GIST. A multi-center, open-label trial randomized KIT-expressing, unresectable or metastatic GIST to imatinib 400mg daily or 600mg daily.[102] Partial response was noted in 53.7% of the study group, with 27.9% achieving stable disease.[102] A 10-year follow-up trial of comparing imatinib 400mg daily to 800mg daily in patients with KIT-expressing, advanced GIST reported no difference in median PFS between the groups (400mg 1.7 years versus 800mg 2 year, p=0.18) and no difference in overall survival (3.9 years).[103] Imatinib 400mg once and twice daily regimens were compared in KIT-expressing, unresectable or metastatic GIST patients.[104] The PFS favored the twice daily imatinib group (p=0.026). Overall survival was similar between the treatment groups at both 1 year (daily 85% and twice daily 86%) and 2 years (69% and 74%).[104] Imatinib is the recommended therapeutic option for treatment of GIST. It is recommended as the primary therapy for KIT-expressing, unresectable or metastatic GIST.[92] (*NCCN Evidence Category 2A*) It is also recommended in primary GIST if systemic therapy is necessary before operative resection.[92] (*NCCN Evidence Category 1*)

g. Lapatinib: Lapatinib is a multi-kinase inhibitor with activity against HER2 and EGFR. Approximately 2-5% of metastatic colorectal cancer harbor somatic ERBB2 amplifications or activating mutations.[105] The HERACLES phase II trial investigated trastuzumab with lapatinib in treatment-refractory, KRAS-wild type, HER2-positive, metastatic colorectal cancer.[106] In this study, 30% of the cohort reported an objective response, with two patients achieving complete response, and 26% with partial responses, and 44% with stable disease.[106] The final analysis of the HERACLES trial observed a 70% disease control rate.[107] Early analysis are suggesting benefit of anti-HER2 therapies in metastatic colorectal cancer, however this evidence is still in the foundational stages

h. Nilotinib: Nilotinib is a BCR-ABL tyrosine kinase inhibitor with activity against KIT and platelet derived growth factor receptor (PDGFR). In a phase II trial, patients with imatinib- and sunitinib-resistant, advanced GIST were treated with nilotinib.[108] The median PFS was 12 weeks with 10% of the treated population achieving clinical response and 37% achieving stable disease. The median overall survival with nilotinib was 34 weeks.[108] Nilotinib was studied as third-line agent in patients with imatinib- and sunitinib-resistant GIST in a phase II trial.[109] At week 24, disease control was reported in 29% of the group, and 66% of the patients had six or more weeks of stable disease. The median PFS was 113 days with the overall survival reported at a median of 310 days.[109] Nilotinib was compared to best supportive care with or without imatinib or sunitinib in a phase III trial that included imatinib- and sunitinib-refractory advanced GIST.[110] There was no difference in PFS between the two groups (nilotinib 109 days versus supportive care 111 days, p=0.56). Overall survival did not differ significantly between the groups either (nilotinib 322 days versus supportive care 280 days, p=0.29). However, sub-analysis revealed patients with one prior regimen of imatinib and sunitinib had an improvement with nilotinib versus supportive care (405 days versus 280 days, p=0.02).[110] Nilotinib is recommend as a therapeutic option in advanced GIST if failure of imatinib, sunitinib, or regorafenib occurs.[92] (*NCCN Evidence Category 2A*)

i. Nivolumab: Nivolumab is an anti-programmed cell death-1 (PD-1) immune checkpoint inhibitor approved in mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) in numerous solid tumors. Lynch syndrome (germline dMMR)

has been identified in 2-4% cancer patients.[111,112] Additionally, somatic dMMR have been reported in 19-52% of colorectal cancer tumors, with MSI-high characterization in 3-6.5% of stage IV tumors.[113-117] The phase II CheckMate-142 study reported 69% of patients with disease control for 12 weeks or longer with treatment with nivolumab, a reported median PFS 14.3 months and 12-month overall survival of 73%.[118] Based on this data, the nivolumab is recommended in patients with metastatic dMMR colorectal tumors as second- or third-line therapy.[59,60] (*NCCN Evidence Category 2A*) Patients who are progressing with nivolumab therapy should not be offered pembrolizumab.[59,60] (*NCCN Evidence Category 2A*) Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders ($p<0.0001$). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, $p=0.0086$). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, $p=0.0033$), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

j. Panitumumab: Panitumumab is an anti-EGFR monoclonal antibody with approval in RAS-wild type, metastatic colorectal cancer. Evidence has demonstrated that KRAS, NRAS, and BRAF V600E mutations are not responsive or have poor response to panitumumab.[67,72,73,119] Because of these findings, panitumumab should be reserved for patient populations with wild-type RAS (KRAS or NRAS) and wild-type BRAF.[59,60,74,76] (*NCCN Evidence Category 2A*) Patients with right-sided tumors are unlikely to respond to first-line anti-EGFR therapy in metastatic disease.[78-81] Left-sided tumors can be considered for panitumumab in RAS-wild type disease.[59,60] (*NCCN Evidence Category 2A*) Meta-analyses have concluded the addition of first-line anti-EGFR monoclonal antibodies (cetuximab or panitumumab) in wild-type RAS tumors decreased the risk of death (19%, $p=0.002$) and increased resection rates (R0 resection rate 60%).[82,83] When anti-EGFR agents were compared to chemotherapy alone, first-line anti-EGFR monoclonal antibodies decreased the risk of death by 17% ($p=0.07$), and when compared to bevacizumab, anti-EGFR agents decreased the risk of death by 20% ($p=0.003$).[82] The median PFS with first-line EGFR decreased risk of progression by 23% ($p=0.23$), and this benefit was seen when EGFR inhibitors where compared to chemotherapy ($p<0.001$), but not when compared to bevacizumab ($p=0.59$).[72,82,83] Panitumumab or bevacizumab with chemotherapy has been compared as first-line and second-line therapy. A meta-analysis found no difference in PFS between the groups (panitumumab 6-10.9 months versus bevacizumab 5.9-10.1 months, $p=0.56$), however the median overall survival favored the panitumumab cohorts (16.2-34.2 months versus 13.4-24.3 months, $p=0.043$).[63] The SPIRITT phase II trial compared FOLFIRI and bevacizumab or FOLFIRI and panitumumab in oxaliplatin and bevacizumab-refractory, KRAS wild-type colorectal tumors.[120] No difference was found in PFS between the groups (bevacizumab 9.2 months versus

panitumumab 7.7 months, p=0.97), nor a difference in overall survival (bevacizumab 21.4 months versus panitumumab 18 months, p=0.75).[120] Therefore, NCCN Panel recommends chemotherapy with the addition of cetuximab, panitumumab, or bevacizumab in the initial treatment of RAS wild-type, metastatic colorectal cancer.[59,60] (*NCCN Evidence Category 2A*) Combination therapy involving chemotherapy with anti-EGFRs (cetuximab or panitumumab) and anti-rVEGFs (bevacizumab) is not recommended based on the results of the PACCE and CAIRO2 trials as increased toxicity, shorter progression free survival (PFS), and lower quality of life scores were observed.[59,60,84,85] (*NCCN Evidence Category 2A*)

k. Pazopanib: Pazopanib is a multi-tyrosine kinase inhibitor with VEGF, KIT, and PDGFR inhibiting properties. Pazopanib was investigated in a phase II trial in patients with imatinib- and sunitinib-refractory, advanced GIST.[121] The non-progression rate was reported at 17% with a median PFS was 1.9 months and median overall survival of 10.7 months.[121] In a larger, open-label phase II trial (PAZOGIST), patients with imatinib- and sunitinib-resistant, advanced GIST were randomized to pazopanib+best supportive care or best supportive care alone.[122] The reported median PFS was 3.4 months in pazopanib group and 2.3 months in the supportive care only cohort (p=0.03).(Mir 2016) Median overall survival favored the pazopanib treated group (17.8 months versus 12.9 months. As for the mutational analysis, 64% of the cohort had identified genetic aberrations. The pazopanib group had 10% with wild-type KIT/PDGFRA, and 5% of the supportive care cohort was identified as wild type. The pazopanib treated group with a KIT exon 11 mutation had a prolonged PFS compared to the supportive care group (p=0.09).[122] Pazopanib is a third-line therapeutic option in patients with imatinib and sunitinib-refractory advanced GIST.[92] (*NCCN Evidence Category 2A*)

l. Pembrolizumab: Pembrolizumab is an anti-PD-1 immune checkpoint inhibitor approved in dMMR and MSI-H in numerous solid tumors. Lynch syndrome (germline dMMR) has been identified in 2-4% cancer patients.[111,112] Additionally, somatic dMMR have been reported in 19-52% of colorectal cancer tumors, with MSI-H characterization in 3-6.5% of stage IV tumors.[113-117] A phase 2 study of patients with metastatic, treatment-refractory solid tumors found that 71% of study subjects with dMMR/MSI-H colorectal cancer responded to pembrolizumab therapy with an improvement in PFS (p<0.001) and overall survival (p<0.03) compared to MMR-proficient colorectal tumors.[32] Based on this data, the pembrolizumab is recommended in patients with metastatic dMMR colorectal tumors as second- or third-line therapy.[59,60] (*NCCN Evidence Category 2A*) Patients who are progressing with pembrolizumab therapy should not be offered pembrolizumab.[59,60] (*NCCN Evidence Category 2A*) Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders (p<0.0001). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, p=0.0086). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, p=0.0033), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on

these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

m. Ramucirumab: Ramucirumab is an anti-VEGF agent indicated in metastatic colorectal cancer in combination with FOLFIRI.[123,124] A phase III trial (RAISE) investigated second-line FOLFIRI with ramucirumab or placebo in metastatic colorectal cancer patients who had failed first-line bevacizumab, oxaliplatin, and a fluoropyrimidine.[123] Median overall survival was prolonged in the ramucirumab compared to placebo (13.3 versus 11.7 months, p=0.0219) as well as PFS (ramucirumab 5.7 months versus placebo 4.5 months, p<0.0005). In a sub-analysis, there was no difference in ramucirumab response based on presence or absence of KRAS mutation status or age below or at or above 65 years.[124] The NCCN Panel recommends ramucirumab with FOLFIRI or irinotecan as second-line therapy in metastatic colorectal cancer.[59,60] (*NCCN Evidence Category 2A*) No data is available to support ramucirumab use in patients that have progressed on FOLFIRI-bevacizumab nor is it preferred over bevacizumab in regards to cost.[59,60,125] (*NCCN Evidence Category 2A*)

n. Regorafenib: Regorafenib is a multi-kinase inhibitor with activity against VEGF, BRAF, KIT, and multiple others. In the phase III CORRECT trial, patients with previously treated metastatic colorectal cancer were treated with regorafenib or placebo.[126] The median overall survival was 6.4 months in the regorafenib group compared to 5 months in the placebo cohort with a similar PFS between both groups (regorafenib 1.9 months versus 1.7 months). Patients with colon cancer who received regorafenib had improved survival compared to those with rectal cancer, but similar effect on PFS in these cancer types.[126] The CONCUR phase III trial was conducted in patients with metastatic colorectal cancer who had disease progression with two previous treatments. The patients who received regorafenib had a favorable overall survival over the placebo group (8.8 months, versus 6.3 months).[127] Regorafenib is recommended as additional therapy in patients with chemotherapy-refractory metastatic colorectal cancer. No data is available to suggest the order of therapy, therefore may be given before or after trifluridine + tipiracil.[59,60] (*NCCN Evidence Category 2A*) Regorafenib is also indicated in unresectable or metastatic GIST. A multi-center, randomized, phase III trial (GRID) demonstrated the benefit of regorafenib in imatinib- and sunitinib-refractory, advanced GIST.[128] Regorafenib therapy prolonged PFS compared to placebo (4.8 months versus 0.9 months, p<0.0001). Placebo patients were allowed to crossover to regorafenib, and the calculated PFS for this group was 5 months. Additionally, patients with KIT mutations at exon 11 and 9 had favorable results with regorafenib compared to placebo. Overall survival did not differ between the regorafenib or placebo groups (p=0.199).[128] Regorafenib is the recommended treatment option for patients with GIST and progression on imatinib or sunitinib.[92] (*NCCN Evidence Category 2A*)

o. Sorafenib: Sorafenib is a multi-kinase inhibitor at BRAF kinases, VEGF, KIT, and RET kinase receptors. A multi-center phase II trial of imatinib- and sunitinib-resistant, KIT-expressing GIST tumors investigated sorafenib therapy.[129] Disease control rate (partial response + stable disease) was reported in 68% of the study subjects, with the primary sunitinib resistance cohort achieving disease control for at least 6 months in 32% of group.[129] The median PFS was 5.2 months and the median overall survival 11.6 months. KIT exon 11 mutations were discovered in 65% of the cohort, KIT exon 9 mutation in 15% and PDGFRA mutation in 4% of the tumors.[129] Another phase II trial investigated patients with imatinib- and sunitinib-refractory, metastatic GIST and treatment with sorafenib.[130] The achieved disease control rate was 65% with sorafenib therapy. The median PFS was 4.9 months and the median overall survival was 9.7 months. Patients who had received imatinib and

sunitinib only had better disease control compared those who received third-line nilotinib (p=0.0079). Of note, 55% of the patients harbored a KIT exon 11 mutation, 25% a KIT exon 9 mutation, 5% PDGFRA mutation and15% were wild-type GIST. Only 11% of the cohort without KIT exon 11 mutations had disease control at 24 weeks (p=0.035).[130] A retrospective analysis of sorafenib advance GIST that was previously treated with imatinib, sunitinib, and/or nilotinib revealed 57% of the cohort with disease stabilization with sorafenib therapy.[131] The PFS was 6.4 months in the overall cohort, and there was no difference in PFS whether sorafenib was used as third or fourth-line therapy (6 months versus 7.1 months, p=0.749). The median overall survival was 13.5 months, although there appeared to be a clinical difference between survival on third versus fourth-line sorafenib, although not statistically significant (17.9 months versus 11 months, p=0.299).[131] Sorafenib is recommend as a therapeutic option in advanced GIST if failure of imatinib, sunitinib, or regorafenib occurs.[92] (*NCCN Evidence Category 2A*)

p. Sunitinib: Sunitinib is a multi-kinase inhibitor with activity at VEGF, PDGFR, and RET indicated for treatment in GIST. A phase III study randomized patients with imatinib-resistant, advanced GIST to receive sunitinib or placebo.[132] The median time to tumor progression was 27.3 weeks in sunitinib group versus 6.4 weeks in the placebo group (p<0.0001) and the PFS was similar (24.1 weeks versus 6 weeks, p<0.0001). Overall survival also favored the sunitinib treated group compared to placebo (p=0.007). This study was unblinded after the interim analysis due to overwhelming success with sunitinib treatement.[132] Second-line sunitinib was compared to dose-escalated imatinib in advanced GIST patients who had progressed on first-line imatinib in a retrospective study.[133] Patients that received imatinib dose escalation or imatinib dose escalation followed by sunitinib therapy had better overall survival (37.5 months versus 16 months, p<0.0001) than compared to switching immediately to sunitinib after imatinib failure.[133] Sunitinib is recommended as second-line treatment after progression on or intolerance to first-line imatinib therapy.[92] (*NCCN Evidence Category 2A*)

q. Trametinib: Trametinib is a MEK inhibitor that reversibly and selectively inhibits MEK1 and MEK2, which is downstream from BRAF kinase. The BRAF V600E mutation has been reported in 8% of colorectal cancers and is thought to contribute to reactivation of the MEK/ERK signaling cascade.[86] Preclinical studies have investigated the combination of MEK inhibitors with cyclin-dependent-kinase inhibitors in BRAF V600E-positve colorectal tumors and have found enhanced apoptosis of cancer cells.[86] The MAP2K1 K57T mutation is also thought to be potential mechanism of resistance to EGFR inhibitors in colorectal cancer. This mutation is also associated with resistance to BRAF and MEK inhibitors. Preclinical studies have suggested that combination treatment with BRAF and MEK inhibitors may help overcome MAP2K1 K57T-mutant colorectal cancer.[87] A phase I study investigated trametinib in a number of heavily treated solid tumor patients and reported no objective response in colorectal cancer patients.[88] However, other tumors harboring KRAS mutations (i.e. melanoma and NSCLC) observed objective responses (partial) with this exploratory treatment with tramatinib.[88] MEK inhibitor therapy in colorectal tumors has yet to supply the necessary evidence to garner recommendations for use in colorectal cancer.

r. Trastuzumab: Trastuzumab is an anti-HER2 monoclonal antibody. Approximately 2-5% of metastatic colorectal cancer harbor somatic ERBB2 amplifications or activating mutations.[105] A case report observed success in achieving an improved performance status and reduced tumor burden for 12 months with treatment with trastuzumab, oxaliplatin, and capecitabine in a patient with sporadic rectal adenocarcinoma harboring ERBB2 amplification.[105] The HERACLES phase II trial investigated trastuzumab with lapatinib in treatment-refractory, KRAS-wild type, HER2-positive, metastatic colorectal cancer.[106] In this

study, 30% of the cohort reported an objective response, with one patient achieving complete response, and 26% with partial responses, and 44% with stable disease.[106] The final analysis of the HERACLES trial observed a 70% disease control rate.[107] Early analysis are suggesting benefit of anti-HER2 therapies in metastatic colorectal cancer; however, this evidence is still in the foundational stages.

s. Vemurafenib: Vemurafenib is a BRAF kinase inhibitor with proven activity against BRAF V600 mutations in melanoma. Interest in this anti-BRAF therapy has been awakened with the realization of 8-10% of colorectal cancers harboring BRAF mutations.[134] Pre-clinical investigation of vemurafenib therapy in combination with standard chemotherapy lead to enhanced antitumor efficacy.[134] A phase IB study of vemurafenib used in combination irinotecan and cetuximab in BRAF V600E-positive metastatic colorectal cancer reported a radiographic response in 35% of the patients and PFS of 7.7 months.[135] A phase II study of vemurafenib in BRAF-positive, metastatic colorectal cancer found a median PFS 2.1 months and median overall survival 7.7 months.[136] At this time, vemurafenib is recommended as second-line therapy (with irinotecan + cetuximab or panitumumab) in BRAF V600E mutation positive, advanced or metastatic colorectal cancer.[59,60] (*NCCN Evidence Category 2A*)

t. Ziv-aflibercept: Ziv-afilbercept is a VEGF inhibitor approved for combination therapy with FOLFIRI in patients with metastatic colorectal cancer. A phase III study (VELOUR) investigated ziv-aflibercept with FOLFIRI versus placebo with FOLFIRI in patients with metastatic colorectal cancer who had failed oxaliplatin-based therapy.[137] The reported median overall survival favored the ziv-aflibercept group (13.5 months versus 12 months, p=0.0032) and similarly a prolonged PFS in the ziv-aflibercept group (6.9 months versus 4.6 months, p<0.0001).[137] In a sub-analysis of the VELOUR study, the patients previously treated with bevacizumab displayed improvement in PFS and overall survival compared to the placebo arm (PFS: 6.9 months versus 3.9 months; OS: 12.5 months versus 11.7 months) and when compared to the cohort with no previous bevacizumab therapy the PFS and OS were similar in the ziv-aflibercept groups (PFS: p=0.5668; OS: p=0.1958).[138] Based on this data, ziv-aflibercept is recommended to be used as second-line treatment in combination with FOLFIRI (or irinotecan) in patients with metastatic disease.[59,60] (*NCCN Evidence Category 2A*)

4.2.4 Gynecological Cancers (Cervical, Ovarian, Uterine, Vulvar)

4.2.4.1 CERVICAL CANCER

Drug	VEGF	MSI-H*	TMB^
Bevacizumab (Avastin)	a		
Pembrolizumab (Keytruda)		b	b

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Bevacizumab: Bevacizumab is a monoclonal antibody targeted at the VEGF receptor. A phase III trial investigated the addition of bevacizumab in platinum-based (cisplatin+paclitaxel) and non-platinum-based (topotecan+placlitaxel) chemotherapy in women with metastatic, persistent, or recurrent cervical cancer.[139,140] Overall survival was similar between the bevacizumab and placebo cohorts in both chemotherapy groups, but the risk of disease progression was noted to be higher in the topotecan arms. However the addition of bevacizumab to either chemotherapy group prolonged the overall survival when compared to chemotherapy alone (17 months versus 13.3 months, p=0.004), and similar was true for progression free survival (PFS) in the bevacizumab arms (8.2 months versus 5.9 months, p=0.002).[139] In the final analysis of the same study, prolonged overall survival was maintained in the bevacizumab groups compared to chemotherapy alone (16.8 months versus 13.3 months, p=0.007).[140] Specifically, the groups that had not received pelvic irradiation had improved overall survival with bevacizumab therapy over chemotherapy alone (24.5 months versus 16.8 months, p=0.11). Bevacizumab-treated groups sustained the PFS advantage over chemotherapy alone as well (8.2 months versus 6 months, p=0.0002).[140] Based on these data, bevacizumab is preferred as part of first-line combination therapy with paclitaxel and either cisplatin or topotecan for treating persistent, recurrent, or metastatic cervical cancer.[141] (*NCCN Evidence Category 1*) Carboplatin and paclitaxel with bevacizumab may be considered as another option for first-line combination therapy in recurrent or metastatic cervical cancer.[141] (*NCCN Evidence Category 2A*) Bevacizumab has also been investigated as second or third-line treatment in recurrent cervical cancer. A phase II trial reported a median overall survival of 7.2 months and PFS of 3.4 months with bevacizumab monotherapy.[142] The NCCN Panel recommends bevacizumab as a second-line treatment option in recurrent or metastatic cervical disease.[141] (*NCCN Evidence Category 2B*)
b. Pembrolizumab: Pembrolizumab is an anti-PD-1 immune checkpoint inhibitor approved in mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) in many solid tumors. The KEYNOTE-028 trial assessed the safety and efficacy of pembrolizumab in PD-L1-positive solid tumors including cervical cancer (n=24).[143] Objective responses were appreciated in 17% of the group, with a median duration of response of 5.4 months. Target lesion diameters also decreased in 36% patients. The median PFS at 6 months and 12 months was 21% and 4%, respectively; overall survival rate at 6 months and 12 months

was 67% and 40%, respectively.[143] The NCCN Panel recommends pembrolizumab as second-line therapy in patients with identified dMMR or MSI-H cervical tumors and metastatic disease.[141] (*NCCN Evidence Category 2B*) Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders (p<0.0001). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, p=0.0086). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, p=0.0033), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

4.2.4.2 OVARIAN CANCER

Drug	BRCA	VEGF
Bevacizumab (Avastin)		c
Niraparib (Zejula)	d	
Olaparib (Lynparza)	e	
Pazopanib (Votrient)		f
Rucaparib (Rubraca)	g	

Footnotes:

c. Bevacizumab: Bevacizumab is a monoclonal antibody targeted at the VEGF receptor. Bevacizumab has been investigated for primary treatment of ovarian cancer. In the phase III randomized trial (GOG 0218), bevacizumab or placebo were randomized to patients with stage III or IV epithelial ovarian cancer also receiving carboplatin and paclitaxel.[144] Bevacizumab was given either as initial therapy (cycles 2-6) or throughout treatment (cycles 2-22). The median PFS was longer in the bevacizumab groups (initial group: 11.2 months; throughout group: 14.1 months) compared to placebo (10.3 months) and similar findings were reported with median overall survival (initial: 38.7 months; throughout: 39.7 months; placebo: 39.3 months), although none of these findings were statistically significant.[144] A phase III trial (ICON7) of first-line bevacizumab plus carboplatin and paclitaxel versus chemotherapy alone was conducted in high-risk or advance ovarian cancer patients.[145] The

bevacizumab+chemotherapy arm had a favorable PFS compared to standard chemotherapy (19 months versus 17.3 months, p=0.004).[145] The final analysis of this study reported a mean survival time of 45.5 months with bevacizumab and 44.6 months with chemotherapy alone (p=0.85).[146] Although benefit in PFS is seen with bevacizumab as first-line combination therapy, overall survival is equivocal to standard chemotherapy. Bevacizumab remains as an option to use in combination with carboplatin and paclitaxel as first-line therapy as described in the GOG 0218 and ICON7 trials.[147] (*NCCN Evidence Category 2B*) In a phase III trial (OCEANS), bevacizumab was compared to placebo in combination with gemcitabine and carboplatin in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer.[148] Patients randomized to bevacizumab had a longer PFS compared to placebo (12.4 months versus 8.4 months, p<0.0001). The overall response rate favored the bevacizumab treated group with 78.5% response reported compared to 57.4% in the placebo arm (p<0.0001).[148] The final analysis of OCEANS trial reported similar overall survival between the groups (bevacizumab 33.6 months versus placebo 32.9 months, p=0.65).[149] Another phase III trial (AURELIA) investigated bevacizumab with chemotherapy in women with platinum-resistant, recurrent ovarian cancer.[150] Bevacizumab with chemotherapy prolonged median PFS when compared to chemotherapy alone (6.7 months versus 3.4 months, p<0.001), and median overall survival favored the bevacizumab-treated arm (16.6 months versus 13.3 months, p=0.174).[150] A phase II trial of bevacizumab monotherapy in persistent or recurrent epithelial ovarian cancer of primary peritoneal cancer reported a median PFS of 4.7 months and median overall 17 months with bevacizumab as second or third-line treatment.[151] Bevacizumab was found have similar activity in a phase II study of platinum-resistant ovarian cancer or peritoneal serous cancer. Patients who received bevacizumab as second, third, or fourth-line treatment had a median PFS of 4.4 months and median overall survival of 10.7 months.[152] From this data, the use of bevacizumab is a preferred option in patients who have recurrent disease in women with either platinum-sensitive or platinum-resistant disease.[147] (*NCCN Evidence Category 2A*)

d. Niraparib: Niraparib is a PARP 1 and 2 inhibitor with activity at BRCA. In a phase III trial (NOVA), platinum-sensitive, recurrent ovarian cancer patients with and without a BRCA germline mutation were randomized to receive either niraparib or placebo.[153] The niraparib group had a longer median PFS than placebo (21 months versus 5.5 months, p<0.001) in the patient arm with germline BRCA mutation. Those without a germline BRCA mutation still had benefit with niraparib therapy over placebo (9.3 months versus 3.9 months, p<0.001).[153] Therefore, niraparib is recommended as maintenance therapy in ovarian cancer patients with platinum-sensitive disease.[147](*NCCN Evidence Category 2A*)
e. Olaparib: Olaparib is a small molecule PARP inhibitor with activity against BRCA mutations and approved for BRCA-mutated, advanced ovarian cancer. In a phase I trial, olaparib was given to BRCA 1/2-mutated ovarian cancer patients. An greater percent change in baseline tumor size and baseline CA-125 levels was reported in the platinum-sensitive cohort.[154] In a pooled study of monotherapy with olaparib in germline BRCA 1/2 mutant-relapsed ovarian cancer, 36% of the study subjects had response to olaparib, with 49% response to olaparib after 1-2 prior chemotherapy regimens, and 31% response after failure on three or more lines of chemotherapy.[155] The platinum-sensitive groups had a greater response rate than the platinum-resistant groups in all previous chemotherapy scenarios.[155] Platinum-sensitivity and olaparib efficacy was further

tested in the SOLO2/ENGOT-Ov21 phase III trial.[156] Patients with platinum-sensitive, BRCA 1/2-mutant, relapsed ovarian cancer were randomized to receive either olaparib or placebo as maintenance therapy. The olaparib arm had a PFS of 19.1 months compared to 5.5 months in the placebo arm (p<0.0001) Because of this study, olaparib is recommended for maintenance therapy in patients with ovarian cancer who have received 2 or more lines of chemotherapy.[147] (*NCCN Evidence Category 2A*) A phase II study described olaparib therapy in platinum-resistant ovarian cancer patients with germline BRCA1 and two mutations.[157] Patients who received olaparib experienced a 31% tumor response rate, with a median PFS of 7 months and median overall survival of 16.6 months.[157] This data supports the recommended use of olaparib in germline BRCA-positive, advanced ovarian cancer patients who have received 3 or more lines of chemotherapy.[147](*NCCN Evidence Category 2A*)

f. Pazopanib: Pazopanib is a multi-kinase inhibitor with activity against VEGF. A phase II trial of women with recurrent ovarian cancer after platinum therapy were treated with pazopanib.[158] Overall response rate was 18% in the treated group, with 31% having a response in CA-125 levels.[158] The MITO-11 study (phase II) investigated platinum-resistant or platinum-refractory ovarian cancer patients in an open label study of paclitaxel with or without pazopanib.[159] the PFS was longer in the combination group than with paclitaxel alone (6.3 months versus 3.5 months, p<0.0002). Overall survival favored the pazopanib+paclitaxel group as well (19.1 months versus 13.7 months, p=0.056).[159] Therefore, the recommendation for pazopanib is to be used in treatment of platinum-resistant disease.[147] (*NCCN Evidence Category 2A*) A phase III trial (AGO-OVAR16) enrolled women with stage II-IV epithelial ovarian , fallopian tube, or primary peritoneal cancer with stable disease after platinum+taxane-based chemotherapy on to maintenance therapy with pazopanib or placebo.[160] The median PFS favored the pazopanib group over placebo (17.9 months versus 12.3 months, p=0.0021), but there was no difference in overall survival (p=0.499). In a subgroup analysis, East-Asian women were found to have a less robust response to pazopanib therapy, although the prognostic factors did not reveal a rationale.[160] Another phase III trial explored the differing responses to pazopanib maintenance therapy in East Asian women with advance epithelial ovarian cancer.[161] East Asian women had poorer responses to pazopanib in median overall survival and PFS when compared to placebo, but the analysis did not identify any factors that would explain the discrepant results.[161] Pazopanib can be considered for recurrent therapy in the post-remission ovarian cancer population.[147] (*NCCN Evidence Category 2B*)

g. Rucaparib: Rucaparib is a PARP inhibitor approved in advanced ovarian cancer. A phase II trial of rucaparib in BRCA 1/2-mutated, advanced ovarian cancer reported a 2% objective response rate with intravenous rucaparib and 15% objective response rate with enteral rucaparib.[37] A phase I-II trial of rucaparib in germline BRCA 1/2-mutated ovarian cancer reported an objective response rate of 59% in this patient population.[39] Rucaparib was investigated in platinum-sensitive, recurrent, high-grade ovarian cancer in the ARIEL2 trial.[162] The objective response rate for the entire group was 57%, with median duration of response of 9.2 months. The median PFS with rucaparib in the BRCA-mutant sub-groups was noted to be 12.8 months versus a PFS of 5.7 months in the BRCA-wild type/loss of heterozygosity-high and 5.2 months in the BRCA-

wild/type/loss of heterozygosity-low groups.[162] Rucaparib is recommended as a single agent for treatment of recurrent, platinum-sensitive or resistant ovarian cancer with BRCA-mutations.[147](*NCCN Evidence Category 2A*)

4.2.4.3 UTERINE CANCER

Drug	MSI-H*	PTEN	TMB^	VEGF
Bevacizumab (Avastin)				h
Pazopanib (Votrient)				i
Pembrolizumab (Keytruda)	j		j	
Temsirolimus (Torisel)		k		

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

h. Bevacizumab: Bevacizumab is a monoclonal antibody targeted at the VEGF receptor. Bevacizumab was investigated in a phase II trial for women with recurrent or persistent endometrial cancer after receiving one or two cytotoxic chemotherapy regimens.[163] Objective response rate was reported in 13.5% of patients, and 40% of the study population was progression free for at least 6 months. The progression free survival (PFS) was 4.2 months and overall survival of 10.5 months in the bevacizumab treated patients.[163] In phase II study, bevacizumab was paired with temsirolimus in women with recurrent or persistent endometrial cancer after receiving one or two prior cytotoxic regimes.[164] This study reported had an objective response rate of 24.5% and median PFS of 5.6 months and overall survival of 16.9 months.[164] Bevacizumab may be considered as a single agent in patients who have progressed on previous cytotoxic regimens.[165] (*NCCN Evidence Category 2A*)

i. Pazopanib: Pazopanib is a multi-kinase inhibitor with activity against VEGF that is approved in advanced soft tissue sarcomas. A phase II study described the safety and efficacy of pazopanib patients with advanced or relapsed leiomyosarcoma and other soft tissue sarcomas after at least one standard chemotherapy regimen.[166] The reported median PFS was 3 months and median overall survival of 11.8 months with pazopanib thepary.[166] Similarly, the PALETTE trial (phase III) investigated pazopanib versus placebo in metastatic soft tissue sarcomas with progressive disease on standard chemotherapy.[167] The PFS in the pazopanib arm was 4.6 months versus 1.6 months in the placebo arm ($p<0.0001$). Overall survival slightly favored the pazopanib treated cohort, although the difference was not statistically significant (12.5 months versus 10.7 months, $p=0.25$).[167] This data supports the recommendation to consider pazopanib as single agent option in advanced or metastatic uterine cancer.[165] (*NCCN Evidence category 2A*)

j. Pembrolizumab: Pembrolizumab is an anti-PD-1 immune checkpoint inhibitor approved in mismatch repair deficiency (dMMR) and high microsatellite instability (MSI-H) in many solid tumors. The KEYNOTE-028 trial assessed the safety and efficacy of pembrolizumab in PD-L1-positive advance solid tumors including endometrial cancer (n=24).[168] Objective responses were appreciated in 13% of the group, with a median duration of response of 6.1 months. Target lesion diameters also decreased in 25% patients. The median PFS at study cut off was 1.8 months with PFS rates at 6 months and 12 months of 19% and 14.3%, respectively; overall survival rates at 6 months and 12 months were 67% and 51%, respectively.[168] Pembrolizumab is recommended as a single agent treatment option in patients with endometrial tumors with dMMR/MSI-H.[165] (*NCCN Evidence Category 2A*) Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders ($p<0.0001$). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, $p=0.0086$). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, $p=0.0033$), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

k. Temsirolimus: Temsirolimus is an mTOR kinase inhibitor that has an important role in inhibiting PI3K/Akt/mTOR signaling pathway responsible for neoplastic angiogenesis, protein translation, and cell cycle progression.[169] In a phase II study of women with recurrent endometrial cancer or metastatic, chemotherapy-naïve or treated endometrial cancer were assigned to receive temsirolimus.[169] The treatment-naïve cohort had partial response rate of 24% and stable disease reported in 69% of the group, with a median PFS of 7.3 months. The chemotherapy-treated cohort reported partial response in 4% and stable disease in 48% of the group, and a median PFS of 3.2 months.[169]In phase II study; bevacizumab was paired with temsirolimus in women with recurrent or persistent endometrial cancer after receiving one or two prior cytotoxic regimes.[164] This study reported had an objective response rate of 24.5% and median PFS of 5.6 months and overall survival of 16.9 months.[164] Temsirolimus may be considered as a single agent in patients who have progressed on previous cytotoxic regimens.[165] (*NCCN Evidence Category 2A*)

4.2.4.4 VULVAR CANCER

Drug	EGFR
Erlotinib (Tarceva)	I

Footnotes:

I. Erlotinib: Erlotinib is a tyrosine kinase inhibitor with anti-EGFR activity. A phase II trial of patients with squamous cell vulvar carcinomas evaluated the efficacy erlotinib.[170] Partial response was seen in 27.5% of the patients, and stable disease reported in 40% of the treated women, although the authors noted a short duration of response. EGFR gene amplification was described in 35.7% of the cohort, with three of the five partial responders having such amplification.[170] For treatment of advanced, recurrent, or metastatic disease, erlotinib remains a single-agent option in the difficult to treat scenario.[171] (*NCCN Evidence Category 2B*)

4.2.5 Melanoma

Drug	BRAF	KIT	MAP2K1 (MEK1)	MSI-H*	PD-L1	TMB^
Cobimetinib (Cotellic)			a			
Dabrafenib (Tafinlar)	b					
Imatinib (Gleevac)		c				
Nivolumab (Opdivo)				d	d	d
Pembrolizumab (Keytruda)				e	e	e
Trametinib (Mekinist)			f			
Vemurafenib (Zelboraf)	g					

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Cobimetinib: Cobimetinib is a MEK inhibitor approved for unresectable or metastatic melanoma with BRAF V600E or V600K mutation. It is considered as an option for first-line, systemic therapy for metastatic or unresectable disease when combined with vemurafenib, specifically when targeting BRAF V600 activating mutation. In a comparative trial of vemurafenib+cobimetinib and vemurafenib monotherapy, the combination had a higher (partial or complete) response rate (68% vs 45%, p<0.001), improved progression free survival (PFS) (9.9 vs 6.2 months, p<0.001) and improved overall survival (81% vs 73%, p=0.046).[172,173] Combination therapy with a BRAF inhibitor is preferred for first-line treatment of BRAF V600 activating tumors in metastatic or unresectable melanoma.[174] (*NCCN Evidence Category 1*)

b. Dabrafenib: Dabrafenib is a BRAF kinase inhibitor approved for metastatic or unresectable melanoma with BRAF V600E or K mutation. Dabrafenib has been investigated as monotherapy and in combination with a MEK inhibitor. A trial compared dabrafenib monotherapy to dacarbazine in patients with unresectable stage III or IV BRAF V600E-positive melanoma. Patients who received dabrafenib had a median PFS of 5.1 months compared to 2.7 months in the dacarbazine group (p<0.0001).[175] The BREAK-MB study investigated dabrafenib in patients with BRAF V600E or V600K melanoma with brain metastases who were either previously treated with local therapy for the metastases or treatment naïve. Dabrafenib-treated patients with the BRAF V600E mutation and who were treatment naïve to local therapy had a better overall intracranial response compared to the previously treated group (39.2% versus 30.8%). Similar results were seen in the BRAF V600K-treatment naïve group as well (22.2% versus 6.7%).[176] A randomized, double-blind, phase 3 study of dabrafenib+trametinib versus dabrafenib+placebo in BRAF V600-positive metastatic melanoma reported a median PFS in the dabrafenib+trametinib group of 11 months compared to the 8.8 months in the dabrafenib cohort (p=0.0004).[177] The combination dabrafenib+trametinib performed better than vemurafenib as first-line therapy in BRAF V600-positive metastatic melanoma

patients with a PFS of 11.4 months compared to the vemurafenib cohort PFS of 7.3 months (p<0.001).[178] In patients with stage III, resected melanoma with BRAF V600 mutation, the combination of dabrafenib+trametinib was found to increase the relapse-free survival rate (58% combination versus 39% placebo, p<0.001) and improve the 3-year overall survival rate (86% versus 77%, p=0.0006).[179] A recent investigation of long-term survival in patients on combination therapy reported a durable PFS response rate at four and 5-years since treatment randomization.[180] Therefore, combination therapy with BRAF/MEK inhibitors is recommended as first-line therapy in metastatic or unresectable disease with BRAF V600 mutation.[174] (*NCCN Evidence Category 1*) Combination therapy may also be considered as second line option if disease progression is present on immunotherapy and a BRAF V600 mutation is identified or as subsequent therapy if disease was previously stable on BRAF-targeted therapy but has progressed after more than 3 months off of therapy.[174] (*NCCN Evidence Category 2A*) Monotherapy with a BRAF-inhibitor is recommended only if the combination of BRAF/MEK inhibitor is contraindicated or if checkpoint inhibitors are not appropriate.[174] (*NCCN Evidence Category 2A*)

c. Imatinib: Imatinib is a tyrosine kinase inhibitor of the Bcr-Abl positive cell lines, as well as platelet-derived growth factor, stem cell factor, and c-KIT that has been studied in metastatic melanoma wit KIT mutations. In an open-label phase II trial, patients with advanced, unresectable melanoma with KIT aberrations (mutation or amplification) were given imatinib therapy.[181] The overall durable response rate was 16% with a median time to progression of 12 weeks, and median overall survival of 46.3 weeks. Patients that harbored both KIT mutation and amplification had a greater likelihood of response to imatinib compare those patients with only one alteration (36% versus 14%, p=0.35).[181] Another similar phase II trial, imatinib therapy was assessed in patients with metastatic melanoma with KIT mutations or amplifications.[182] The best overall response (complete and partial response) was reported in 29% of patients, with the 54% responders having only a KIT mutation and none having a KIT amplification. Fifty percent experienced disease control with the KIT mutated group having a more pronounced response than the KIT amplification group (76.9% versus 18.2%, p=0.01). The median PFS was 3.7 months, and no difference was found between the KIT status (mutated 3.9 months versus amplified 3.4 months, p=0.41). Overall survival was 12.5 months, and notably the patients with KIT mutation were on therapy longer than the KIT amplification cohort (p=0.01).[182] At this time, imatinib may be considered in second-line or subsequent therapy in metastatic or unresectable advanced melanoma with KIT mutations.[174] (*NCCN Evidence Category 2A*)

d. Nivolumab: Nivolumab is an anti-PD-L1 monoclonal antibody and checkpoint inhibitor that is approved in metastatic or unresectable melanoma, and as first-line combination therapy with ipilimumab for metastatic or unresectable melanoma. In treatment naïve patients with metastatic melanoma, comparing monotherapy with ipilimumab to the combination of nivolumab+ipilimumab had an improved objective response rate (61% versus 11%) with 22% achieving complete response with combination therapy (p<0.001).[183] Similarly, in a comparative trial of monotherapy with nivolumab or ipilimumab or the combination therapy in treatment naïve patients with metastatic melanoma found improved PFS in the nivolumab monotherapy and the combination therapy groups (6.9 months and 11.5 months, respectively) compared to ipilimumab (2.9 months). Patients with PD-1 ligand positive tumors had the longest PFS with combination therapy (14 months) and nivolumab monotherapy (14 months).[184] When followed out to 3-years after randomization, overall survival was greatest in the combination group (58%), followed by nivolumab cohort (52%), and then the ipilimumab monotherapy group (34%).[185]

Monotherapy with nivolumab was favored for higher objective response rates (72.9% and 42.1%, p<0.001) and longer PFS (5.1 months versus 2.2 months, p<0.001) compared to chemotherapy (dacarbazine) in treatment naïve patients with metastatic melanoma without a BRAF mutation.[186] In a study investigating treatment options for patients with disease progression after ipilimumab and BRAF inhibitors, nivolumab had a greater objective response rate than chemotherapy (31.7% versus 10.6%).[187] Nivolumab is the preferred adjuvant immunotherapy regimen over high-dose ipilimumab in Stage III melanoma.[174] (*NCCN Evidence Category 1*). Additionally, it is an adjuvant treatment option in previously treated, recurrent disease with incomplete resection.[174] (*NCCN Evidence Category 1*). It is first-line therapy in patients with metastatic or unresectable disease (*NCCN Evidence Category 1*) or a second or adjuvant agent in patients with disease progression on a BRAF inhibitor in metastatic or unresectable disease.[174] (*NCCN Evidence Category 2B*) Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (MTB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median melanoma TMB was found to be 10.5 mutations, which was above the median of the entire cohort (6 mutations). The responders to immunotherapy had a median MTB of 19 mutations versus five mutations for non-responders (p<0.0001). Melanoma patients treated with anti-PD-1/PD-L1 therapy had longer median PFS in the intermediate to high MTB group than the low MTB group (12.8 months versus 5.6 months, p=0.2075).[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

e. Pembrolizumab: Pembrolizumab is an anti-PD-L1 monoclonal antibody and checkpoint inhibitor that is approved in unresectable or metastatic melanoma and microsatellite instability high cancer. A phase I investigation of the treatment response in metastatic melanoma patients with and without PD-L1 tumor expression discovered that patients with PD-L1 expression had higher response rate and longer PFS, but there was suggestion that the PD-L1 negative tumors may also have a durable response.[188] A phase Ib study of pembrolizumab in patients with advanced or metastatic melanoma, the reported objective response rate was 33% and median PFS of 4 months. In the treatment naïve subgroup, an objective response rate of 45% and median PFS of 14 months.[189] In ipilimumab-refractory melanoma, pembrolizumab was compared to chemotherapy and found nearly double the improvement in PFS in the pembrolizumab groups.[190] Compared to ipilimumab, pembrolizumab therapy demonstrated a higher rate of 6-month PFS that ipilimumab therapy, and this response remained elevated through 24-months of follow-up.[191,192] Therefore, pembrolizumab is recommended an adjuvant treatment option in previously treated, recurrent disease (*NCCN Evidence Category 2B),* as well as first-line therapy in metastatic or unresectable disease.[174] (*NCCN Evidence Category 1*) Pembrolizumab has been shown to be highly responsive in other cancer types (e.g., melanoma, non-small cell lung cancer, etc.) with mismatch repair deficiency and has earned FDA-approval for those indications, including microsatellite instability-high cancer that is unresectable or metastatic.[31,32] However, tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (MTB) and associated response to immunotherapy in a wide variety of solid tumors.[34]

High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median melanoma TMB was found to be 10.5 mutations, which was above the median of the entire cohort (6 mutations). The responders to immunotherapy had a median MTB of 19 mutations versus five mutations for non-responders (p<0.0001). Melanoma patients treated with anti-PD-1/PD-L1 therapy had longer median PFS in the intermediate to high MTB group than the low MTB group (12.8 months versus 5.6 months, p=0.2075).[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

f. Trametinib: Trametinib is a MEK inhibitor approved in metastatic or unresectable melanoma with BRAF V600E or V600K mutation. In a comparative trial of trametinib to chemotherapy (dacarbazine or paclitaxel), trametinib was found to have a longer PFS (4.8 vs 1.5 months, p<0.0001) and overall survival at 6 months (81% vs 67%, p=0.01).[193] A randomized, double-blind, phase 3 study of dabrafenib+trametinib versus dabrafenib+placebo in BRAF V600-positive metastatic melanoma reported a median PFS in the dabrafenib+trametinib group of 11 months compared to the 8.8 months in the dabrafenib cohort (p=0.0004).[177] The combination dabrafenib+trametinib performed better than vemurafenib as first-line therapy in BRAF V600-positive metastatic melanoma patients with a PFS of 11.4 months compared to the vemurafenib cohort PFS of 7.3 months (p<0.001).[178] In patients with stage III, resected melanoma wit BRAF V600 mutation, the combination of dabrafenib+trametinib was found to increase the relapse-free survival rate (58% combination versus 39% placebo, p<0.001) and improve the 3-year overall survival rate (86% versus 77%, p=0.0006).[179] A recent investigation of long-term survival in patients on combination therapy reported a durable PFS response rate at four and 5-years since treatment randomization.[180] Therefore, combination therapy with BRAF/MEK inhibitors is recommended as first-line therapy in metastatic or unresectable disease with BRAF V600 mutation.[174] (*NCCN Evidence Category 1*) Combination therapy may also be considered as second line therapy if disease progression is present on immunotherapy and a BRAF V600 mutation is identified or as subsequent therapy if disease was previously stable on BRAF-targeted therapy but has progressed after more than 3 months off of therapy.[174] (*NCCN Evidence Category 2A*)

g. Vemurafenib: Vemurafenib is a BRAF kinase inhibitor approved for metastatic or unresectable melanoma with BRAF V600E mutation. A phase II trial investigated vemurafenib in patients with previously treated BRAF-positive melanoma and reported a 53% overall response rate and median PFS of 6.8 months.[194] When vemurafenib was compared to dacarbazine in patients with previously untreated, BRAF V600E-positive metastatic melanoma, the vemurafenib cohort had a 63% relative risk reduction in death and 74% reduction in risk of death or disease progression compared to chemotherapy.[195] In a follow-up study, vemurafenib sustained the advantage of longer overall survival than chemotherapy (13.6 versus 9.7 months, p=0.0008), and longer median PFS (6.9 versus 1.6 months, p<0.0001). A sub analysis of the V600E and V600K positive groups established a prolonged PFS with vemurafenib compared to chemotherapy.[196] In a comparative trial of vemurafenib+cobimetinib and vemurafenib monotherapy, the combination had a higher (partial or complete) response rate (68% vs 45%, p<0.001), improved progression free survival (PFS) (9.9 vs 6.2 months, p<0.001) and improved overall survival (81% vs 73%, p=0.046).[172,173] Combination therapy of vemurafenib with a MEK inhibitor is preferred for first-line treatment of

BRAF V600 activating tumors in metastatic or unresectable melanoma.[174] (*NCCN Evidence Category 1*) Combination therapy may also be considered as second line therapy if disease progression is present on immunotherapy and a BRAF V600 mutation is identified; similarly it may be considered as subsequent therapy if disease was previously stable on BRAF-targeted therapy but has progressed after more than 3 months off of therapy.[174] (*NCCN Evidence Category 2A*)

4.2.6 Non-Small Cell Lung Cancer

Drug	ALK	AKT1	BRCA	BRAF	EGFR	ERBB2 (HER2)	KRAS	MAP2K1 (MEK1)	MET	PD-L1	PIK3	PTEN	RET	ROS1	VEGF
Ado-trastuzumab emtansine (Kadcyla)						a									
Afatinib (Gilotrif)					b										
Alectinib (Alecensa)	c													c	
Atezolizumab (Tecentriq)										d					
Brigatinib (Alunbrig)	e														
Cabozantinib (Cometriq, Cabometyx)													f		
Ceritinib (Zykadia)	g													h	
Cetuximab (Erbitux)					h		h								
Crizotinib (Xalkori)	i								i					i	
Dabrafenib (Tafinlar)				j											
Erlotinib (Tarceva)					k										
Everolimus (Afinitor)		l			l		l				l	l			
Gefitinib (Iressa)					m										
Necitumamab (Portrazza)					n										
Niraparib (Zejula)			o												
Nivolumab (Opdivo)										p					
Olaparib (Lynparza)			q												
Osimertinib (Tagrisso)					r										
Pembrolizumab (Keytruda)										s					
Panitumumab (Vectibix)					t		t								
Ramucirumab (Cyramza)															u
Rucaparib (Rubraca)			v												
Trametinib (Mekinist)				w				w							
Trastuzumab (Herceptin)							x								
Vandetanib (Caprelsa)													y		
Vemurafenib (Zelboraf)				z											

Footnotes:

a. Ado-trastuzumab emtansine: Ado-trastuzumab emtansine (T-DM1) is an anti-HER2 antibody conjugated with a vinca alkaloid which is approved in HER2-positive metastatic breast cancer. However, HER2 mutations are present in up to 5% of NSCLC tumors.[197] Preclinical models have provided favorable results with T-DM1 use in HER2-expressing SCLC and may be an option to overcome trastuzumab resistance.[198] A case report has supported the use of T-DM1 in HER2-expressing lung

cancer; a phase II trial suggests that T-DM1 is has activity against HER2-mutant lung cancers with the report of 44% partial response rate and median progression free survivial of 5 months.[197,199,200] Ado-trastuzumab emanstine can be considered for targeted therapy in HER2-expressing lung tumors.[201] (*NCCN Evidence Category 2A*)

b. Afatinib: Afatinib is a tyrosine kinase inhibitor (TKI) and EGFR inhibitor approved for metastatic NSCLC with non-resistant EGFR mutations. A meta-analysis of first line treatment with EGFR TKI agents (afatinib, erlotinib, and gefitinib) in EFGR-positive advanced NSCLC reported higher tumor response rates and longer progression free survival (PFS) than chemotherapy alone.[202] The LUX-Lung 3 and LUX-Lung 6 studies of EGFR-positive lung adenosarcoma patients reported no overall survival benefit of afatinib over chemotherapy, but there was a survival benefit in the subgroup of patients with del19 EGFR mutations receiving afatinib.[203] Afatinib is recommend for first-line treatment of EGFR-mutation positive metastatic NSCLC prior to chemotherapy.[201] (*NCCN Evidence Category 1*) Afatinib may be used after completed or interrupted first-line therapy if EGFR mutation is discovered during chemotherapy.[201] (*NCCN Evidence Category 2A*) A combination of afatinib + cetuximab may be considered in patients who have had disease progression on EGFR TKI therapy.[201] (*NCCN Evidence Category 2A*)

c. Alectinib: Alectinib is an oral TKI that inhibits ALK rearrangements and has been found to be effective in crizotinib-refractory, ALK-positive NSCLC with and without CNS metastases.[204,205] Primary treatment with alectinib has shown superior efficacy and lower toxicity compared to crizotinib in patients with ALK-positive NSCLC.[206] Alectinib is recommended as first-line therapy or subsequent therapy in ALK-rearrangement advanced or metastatic NSCLC.[201] (*NCCN Evidence Category 2A*) It is also recommended as first-line therapy advanced or metastatic NSCLC with ROS1 rearrangement.[201] (*NCCN Evidence Category 2A*)

d. Atezolizumab: Atezolizumab is an anti-PD-L1 inhibitor and monoconal antibody. A phase 3 trial of atezolizumab versus docetaxel in previously platinum-treated NSCLC patients revealed improved survival in the atezolizumab group, regardless of the the PD-L1 expression status.[207] Atezolizumab is recommended as subsequent therapy in advanced or metastatic NSCLC with PD-L1 expression.[201] (*NCCN Evidence Category 2A*)

e. Brigatinib: Brigatinib is a second generation, dual TKI and ALK inihibitor approved in ALK-positive metastatic NSCLC. It has been shown to be effect in ALK-rearranged NSCLC and crizotinib-refractory ALK-positive NSCLC with and without brain metastases.[208,209] Brigatinib is recommended as subsequent therapy in ALK-positive, crizotinib-refractory advanced or metastatic NSCLC.[201] (*NCCN Evidence Category 2A*)

f. Cabozantinib: Cabozantinib is a multi-kinase inhibitor that targets MET, RET, ROS1, and VEGFR2, and may synergize with EGFR inhibition in NSCLC.[210] A case series of NSCLC patients with RET fusion-positive tumors had partial or complete response with cabozantinib treatment.[211] A phase II study of cabozantinib in advanced RET-rearranged NSCLC has over 28% response rate.[212] In the ECOG-ACRIN trial, EGFR-wild type, nonsquamous NSCLC patients were randomized to be given erlotinib, cabozantinib, or the combination. The cabozantinib and combination group had longer PFS compared to

monotherapy with erlotinib (greater than 4 vs 1.8 months).[213] Cabozantinib is remains as a treatment option of NSCLC with RET rearrangement.[201] (*NCCN Evidence Category 2A*)

g. Ceritinib: Ceritinib is a TKI that inhibits ALK and ROS1. Patients with ALK-rearranged NSCLC have responded to ceritinib therapy, regardless of ALK mutation status and previous crizotinib exposure.[214] The ASCEND-1 and ASCEND-4 trial have demonstrated the improvement of PFS in the first-line ceritinib treated group over platinum-based chemotherapy in ALK-rearranged NSCLC.[215,216] Ceritinib is recommended as first-line or subsequent therapy in ALK-rearrangement advanced or metastatic NSCLC.[201] (*NCCN Evidence Category 2A*) Ceritinib has been investigated in an open-label phase II trial of patients with advanced NSCLC with ROS1 rearrangements.[217] Patients who received ceritinib demonstrated an objective response rate of 62%, median PFS of 9.3 months, and overall survival of 24 months. In a subgroup analysis, the median PFS in crizotinib-naïve patients was 19.3 months.[217] Ceritinib may also be considered as first-line therapy in advanced or metastatic NSCLC with ROS1 rearrangement.[201,217] (*NCCN Evidence Category 2A*)

h. Cetuximab: Cetuximab is a EGFR inhibitor and monoclonal antibody with approved use in metastatic colorectal cancer (KRAS wild-type) and squamous cell head and neck cancer. The role of cetuximab in treatment of NSCLC is under investigation. Patients with EGFR-positive stage IIIB or IV NSCLC were randomized to platinum chemotherapy plus cetuximab or chemotherapy (cisplatin/venorelbine) alone and found to have longer survival in the cetuximab group (11.3 vs 10.1 months).[218] Furthermore, in the FLEX trial discovered patients with EGFR-high expressing advanced NSCLC had longer survival when given cetuximab compared chemotherapy alone (12 vs 9.6 months) but no benefit was found in low-EGFR exprssing tumors.[219] The NCCN group has removed the recommendation for cisplatin (or carboplatin) plus vinorelabine with or without cetuximab from the systemic therapy regimens due to toxicity reconcerns.[201] However, cetuximab place in therapy may be more appropriate in combination of afatinib + cetuximab in patients with EGFR T790M mutation who have had disease progression on EGFR TKI therapy.[201,220] (*NCCN Evidence Category 2A*)

i. Crizotinib: Crizotinib is a first generation TKI with inhibitory activities at ALK rearrangements, ROS1 rearrangements, and MET mutations. [221-223] In a study comparing crizotinib to standard chemotherapy in advanced ALK-positive NSCLC patients found crizotinib superior to chemotherapy in measures of PFS (7.7 mo vs 3 mo) and response rates (65% vs 20%, $p<0.001$).[224] The PROFILE 1014 trial confirmed that crizotinib was superior to standard first-line premetrexed+platinum chemotherapy in advanced ALK-positive NSCLC.[225] Crizotinib is recommended as first line therapy in ALK-rearrangement advanced or metastatic NSCLC, and as first line therapy in advanced or metastatic NSCLC with ROS1 rearrangement.[201] (*NCCN Evidence Category 2A*) In 4% of lung adenocarcinomas, MET exon skipping has been identified; thus this target is being investigated. [222,226-228]

j. Dabrafanib: Dabrafanib is a BRAF kinase inhibitor approved for use in metastatic NSCLC with BRAF V600E mutation.[229] The combination of dabrafanib+trametinib in metastatic stage 4, BRAF-positive NSCLC with progression on platinum-based chemotherapy had favorable results in a phase 2 trial.[230] Similarly, in a phase 2 trial of [231]untreated metastatic BRAF V600E mutated NSCLC, the dabrafanib+trametinib combination achieved clinically meaningful anti-tumor activity with 64% of the

enrolled having treatment response (complete 6% and partial 58%), and nearly 75% having disease control. The mediation duration of response was 15.2 months and PFS 14.6 months [231] Therefore, the combination of dabrafenib+trametinib is recommended as first-line and subesequent targeted therapy in advanced or metastatic NSCLC with BRAF V600E mutation.[201] (*NCCN Evidence Category 2A*)

k. Erlotinib: Erlotinib is a TKI which inhibitbs the EGFR-sensitizing mutaiton. In a meta-analysis of EFGR-positive advanced NSCLC, first-line treatment with erlotinib (or gefitinib or afatinib) have higher tumor response rates and higher PFS than chemotherapy alone.[202] Therefore, it is considered first-line therapy for EGFR-mutation positive NSCLC prior to chemotherapy.[201] (*NCCN Evidence Category 1*) However, erlotinib may be considered after completed first-line therapy or interrupt first-line therapy if EGFR mutation discovered during chemotherapy.[201] (*NCCN Evidence Category 2A*)

l. Everolimus: Everolimus is an inhibitor of mechanistic target of rapamycin (mTOR), thus having antiproliferative and antiangiogenic properties which may prove to be a useful therapeutic target. KRAS mutations are found in 15-25% of patients with lung adenocarcinoma, but currently no direct anti-KRAS therapies are available. However, targeting the downtream KRAS signaling pathway which includes mitogen-activated protein kinase (MAPK) signaling pathway (RAF-MEK-ERK) and PI3K pathway (PI3K-AKT-mTOR).[232] Everolimus is a plausible targeted treatment option for this mutation. A phase 1 study reported everolimus+erlotinib use as second- or third-line therapy in patients with advanced NSCLC, but the clinical effect was not robust (12% had partial/complete response; 37% had stable disease at 9 months).[233] A phase 2 study of everolimus+erlotinib in advanced NSCLC patients who have had at least one chemotherapy regimen found high toxicity rates (72%) outweighed the clinical benefit of this combination.[234] Phase 2 study of docetaxel+everolimus as salvage therapy in advanced NSCLC had a modest clinical benefit, but did not improve PFS or overall survival.[235] Another application of everolimus may be in TKI-resistant EGFR-expressing NSCLC. The EGFR T790M mutation is responsible for 60% of EGFR TKI resistance, and this mutation may also be found up to 30% in EGFR TKI-naïve patients. Case reports of anti-tumor activity with everolimus have been described in EGFR TKI-resistant, EGFR-positive NSCLC.[236]Additionally, the activation of PIK3/AKT/mTOR pathway has been implicated in the hormone therapy resistance seen in breast and gynecologic cancers. In a phase I study of women with breast or gycecological cancers receiving hormonal therapy (anastrazole) with everolimus revealed 24% of the study subjects achieving stable disease for 6 months or longer.[10] It was noted in the responding patients, 75% of the group that had molecular testing also had at least one aberration in PIK3-AKT-mTOR pathway. Abnormalities in PIK3CA, PTEN (mutation or loss), and AKT are known to activate PIK3-AKT-mTOR pathway.[10] Extrapolation of this data to molecular abberations found in other solid tumors may prove useful.

m. Gefitinib: Gefinitib is a TKI which inhibit EGFR sensitizing mutaitons and is approved in NSCLC with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. In a non-comparative trial, first-line gefitinib in Caucasian patients with EGFR-positive, advanced NSCLC was reported to be well tolerated and effective with nearly 70% objective response rate and 90% disease control rate.[237] The IPASS study reported that gefinitib was superior to carboplatin+paclitaxel in treatment-naïve patients with pulmonary adenosarcoma. There was a difference in PFS in all comers (gefitinib 24.9% vs chemotherapy 6.7%),

but the greatest benefit was found in the patients with EGFR mutation.[238] In a meta-analysis of EFGR-positive advanced NSCLC, first-line treatment with gefitinib (or erlotinib or afatinib) has higher tumor response rates and higher PFS than chemotherapy alone.[202] Therefore, gefitinib may be considered as first-line therapy if EGFR-sensitizing mutation is discovered.[201] (*NCCN Evidence Category 1*)

n. Necitumumab: Necitumumab is a monoclonal antibody with EGFR inhibition. The SQUIRE phase III trial randomized patients with stage IV squamous NSCLC to recieve either gemcitabine+cisplatin with or without necitumumab. The overall survival was noted to longer in the necitumumab group (11.5 months versys 9.9 months. However, grade 3 or worse adverse events were recorded more frequently in the necitumumab group (72% versus 38%).[239] The addition of necitumumab to cisplatin+gemcitabine is no longer recommended by the NCCN Panel due to limited efficacy and increased toxicity and cost.[201,240] (*NCCN Evidence Category 2A*)

o. Niraparib: Niraparib is an selective inhibitor for PARP-1 and PARP-2. A phase I trial demonstrated anti-tumor activity with niraparib in patients with BRCA1 or BRCA2 solid tumors, including NSCLC.[27]

p. Nivolumab: Nivolumab is a PD-1 immune checkpoint inhibitor monoclonal antibody which is indicated in a number of metastatic, microsatellite instability-high or mismatch repair deficient solid tumors, including NSCLC. In a phase 3 trial of nonsquamous NSCLC with disease progression after platinum chemotherapy doublet, patients were given nivolumab or doxetaxel. The median overall survival 12.2 months in the nivolumab groups versus 9.4 months in the doxetaxel group.[241] In advanced squamous NSCLC with disease progression during or after first-line chemotherapy, nivolumab was favored over doxetaxel due to longer median overall survival (9.2 months versus 6 months), and for improved response rate and longer PFS regardless of PD-L1 expression level.[242] In the phase III Checkmate 026 trial, first-line nivolumab was compared to platinum-based chemotherapy in patients with stage IV or recurrent NSCLC with a PD-L1 expression level of 1% or more.[243] Patients with PD-L1 expression level at 5% or above had a PFS of 5.9 months with chemotherapy and 4.2 months with nivolumab (p=0.25). Overal survival was similar between groups (nivolumab 14.4 months versus chemotherapy 13.2 months).[243] However, in a molecular sub-analysis of this trial, patients were categorized as high or low tumor mutation burden.[244] The group identified with high tumor mutation burden, the PFS was improved in the nivolumab group compared to chemotherapy (9.7 months versus 5.8 months) and similar results were seein in objective response rates (46.8% versus 28.3%).[244] A retrospective analysis of over 15,000 comprehensive genomic profiles of lung cancers revealed a median of 7.6 mutations, and 24% of cases had high tumor mutation burden (defined as ≥ 15 mutations).[245] High microsatellite instabilty was noted in 0.3% of the group with 97% of that group had high tumor burden. Conversely, of those patients with microsatellite stable tumors, 24% also were classified as high tumor burden.[245] Furthermore, another retrospective study analyzed the relationship between tumor burden and clinical response to immune checkpoint inhibitors in lung cancer. Patients with durable clinical response were more likely to have higher number of mutations than those who did not respond (p=0.0027).[246] More than 9 mutations were correlated with a longer PFS (p=0.015), although PD-L1 expression was not associated with tumor mutation burden.[246] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95%

sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted. At this time, nivolumab is recommended as subsequent therapy in advanced or metastatic NSCLC with progression on or after first-line chemotherapy.[201] (*NCCN Evidence Category 1*)

q. Olaparib: Olaparib is a PARP inhibitor with no FDA indication for NSCLC, but indicated in BRCA-positive ovarian cancer. NSCLC has highest mutation frequency in BRCA-1 of other solid tumors.[247] Monotherapy with olaparib has been investigated in a number of solid tumors (ovarian, breast, pancreatic, and prostate) with germline BRCA 1/2 mutations and noted to have favorable tumor response rates from 12.9-50%.[157] PARP inhibitors have shown some promise in radiosensitization in lung cancer in preclinical studies as well.[248]

r. Osimertinib: Osimertinib is a TKI with EGFR-sensitizing mutation and T790M inhibition which is FDA indicated in metastatic NSCLC with such mutations. When given to previously EGFR TKI treated patients with advance NSCLC, 61% of the patients with positive EGFR T790M mutation had tumor reponse with osimertinib therapy whereas only 21% of the study population without a confirmed mutation had tumor response to treatment.[249] The AURA-3 investigators reported improved efficacy with osimertinib monotherapy compared to platinium therapy with premetrexed in patients with EGFR T790M-positive advanced NSCLC after disease progression with first-line EGFR-TKI. This study reported longer median PFS in osimertinib (10.1 vs 4.4 months). Similarly, those with CNS disease, osimertnib was found to have longer median PFS of 8.5 vs 4.2 months.[250] Osimertinib is recommended as first line therapy for EGFR T790M-positive NSCLC patients, and in patients with symtomatic brain metasteses or with disease progression on erlotinib, gefitinib or afatanib.[201] (*NCCN Evidence Category 1*)

s. Panitumumab: Panitumumab is a EGFR inihibitor monoclonal antibody with and indication for treatment of RAS wild-type metastatic colon cancer. The CHAMP trial of advanded NSCLC with wild type KRAS mutation compared cisplatin+premetrexed with and without panitumumab. This phase 2 trial revealed little benefit in efficacy and quality of life, and increased toxicity in the panitumumab arm.[251] When studied as an adjuvant therapy to first-line carboplatin+premetrexed in advanced KRAS-wild type non-squamous NSCLC, the panitumumab was found to have little impact on efficacy and have increased toxicity.[252]

t. Pembrolizumab: Pembrolizumab is a PD-1 immune checkpoint inhibitor monoclonal antibody which is indicated in a number of metastatic solid tumors, including NSCLC. In open-label phase 2 trial reported that the combination of pembrolizumab + carboplatin + premetrexed as first-line therapy in advanced non-squamous NSCLC was well tolerated and had similar objective responses as chemotherapy alone.[253] Patients with at least 50% of tumor cells expressing PD-L1 without sensitizing mutation of EGFR or translocation of ALK who received pembrolizumab had a median PFS of 10.3 months to 6 months in the platinum-based chemotherapy group. Overall survival was also longer in the pembrolizumab group (80% vs 72.% at 6 months, p=0.005).[254] In patients with previously treated NSCLC, the introduction of pembrolizumab resulted in prolonged survival compared to the group receiving docetaxel. Patients with at least 1% PD-L1 expression receiving pembrolizumb experienced prolonged survival, with the greatest benefit seen in the overall survival of patients with 50% or more of their

tumors expressing PD-L1.[255] Pembrolizumab is recommended as first-line therapy for patients with advanced non-squamous or squamous NSCLC, with PD-L1 expression levels of 50% or more and with negative or unknown tests results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements.[201,254] (*NCCN Evidence Category 1*) A retrospective analysis of over 15,000 comprehensive genomic profiles of lung cancers revealed a median of 7.6 mutations, and 24% of cases had high tumor mutation burden (defined as ≥ 15 mutations).[245] High microsatellite instabilty was noted in 0.3% of the group with 97% of that group had high tumor burden. Conversely, of those patients with microsatellite stable tumors, 24% also were classified as high tumor burden.[245] Furthermore, another retrospective study analyzed the relationship between tumor burden and clinical response to immune checkpoint inhibitors in lung cancer. Patients with durable clinical response were more likely to have higher number of mutations than those who did not respond (p=0.0027).[246] More than 9 mutations were correlated with a longer PFS (p=0.015), although PD-L1 expression was not associated with tumor mutation burden.[246] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

u. Ramucirumab: Ramucirumab is a monoclonal antibody with VEGF activity indicated for the treatment of metastatic NSCLC in combination with doxetaxel. In randomized trial of progressive, metastatis NSCLC patients, ramucirumab+doxetaxal was compared to monotherapy with doxetaxel. The results of this trial found slightly higher median overall survival in the combination group (10.5 vs 9.1 months).[256] From the results of the REVEL trial, the combination of ramucirumab+doxetaxel is recommended in patients with metastatic NSCLC with disease progression on first-line chemotherapy.[201] (*NCCN Evidence Category 2A*)

v. Rucaparib: Rucaparib is a PARP inhibitor with no FDA indication for NSCLC, but indicated in BRCA-positive advanced ovarian cancer. NSCLC has highest mutation frequency in BRCA-1 of other solid tumors.[247] Pre-clinical data suggests that PARP inhibitors may play a role in suppressing lung tumor cellular growth.[257] PARP inhibitors have shown some promise in radiosensitization in lung cancer in preclinical studies as well.[248] Currently there are no active or planned investigations of rucaparib in NSCLC from query of www.clinicaltrials.gov [accessed 11/28/17].

w. Trametinib: Trametinib is a TKI with inhibitory activity at MEK 1 and MEK 2, which are down stream effectors of BRAF. Although the frequency of BRAF V600E mutation is low in NSCLC (1-2%), it appears to be a reasonable target.[231] The combination of dabrafanib+trametinib in metastatic stage IV, BRAF-positive NSCLC patients with previously treated and untreated tumors had favorable results.[230,231] In untreated metastatic BRAF V600E mutated NSCLC, the dabrafanib+trametinib combination achieved clinically meaningful anti-tumor activity with 64% of the enrolled having treatment response (complete 6% and partial 58%), and nearly 75% having disease control. The mediation duration of response was 15.2 months and PFS 14.6 months.[231] The combination of dabrafenib+trametinib is recommended as first-line and subesequent targeted therapy in advanced or metastatic NSCLC with BRAF V600E mutation.[201] (*NCCN Evidence Category 2A*)

x. Trastuzumab: Trastuzumab is a monoclonal antibody with anti-HER2 activity. HER2 mutations are described in up to 2% of NSCLC.[258] Patients with untreated stage IIIB/IV HER2-positive NSCLC received gemcitabine+cisplatin with or without trastuzumab. Both groups had similar response rates (36% trastuzumab versus 41% chemotherapy), median PFS (6.1 versus 7 months).[259] Trastuzumab is recommended as an additional targeted therapy in patients with HER2 mutations although a robust clinical benefit has not been described compared to chemotherapy alone.[201] (*NCCN Evidence Category 2B*)

y. Vandetanib: Vandetanib is a TKI with acitivity at EGFR, VEGF, and RET and approved in locally advanced or metastatic medullary thyroid cancer. An open-label, phase II study of recurrent of metastatic NSCLC with a RET rearrangement and disease progression on platinum-based chemotherapy found that vandetanib treated patients had a PFS of 4.5 months and overall survival of 11.6 months in the 14 month follow up period.[260] It is recommended for with RET rearrangements found in lung tumors.[201] (*NCCN Evidence Category 2A*)

z. Vemurafenib: Vemurafenib is a BRAF kinase inhibitor approved for BRAF-positive metastatic melanoma. In an investigation of non-melanoma solid tumors with BRAFV600-mutation, the NSCLC response rate was 42% and median PFS was 7.3 months.[261] A case report described intracranial disease regression in a patient with BRAF V600E-positive NSCLC with brain metastases.[262] Monotherapy with vemurafenib is recommended in patients with BRAF V600E mutation who do not tolerate combination therapy with dabrafenib+trametinib.[263] (*NCCN Evidence Category 2A*)

4.2.7 Prostate Cancer

Drug	BRCA	MSI-H*	PD-L1	TMB^
Nivolumab (Opdivo)			a	a
Niraparib (Zejula)	b			
Olaparib (Lynparza)	b			
Pembrolizumab (Keytruda)			c	

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Nivolumab: Nivolumab is an anti-PD-L1 monoclonal antibody and checkpoint inhibitor. Preclinical study of castration-resistant prostate cancer (CRPC) tumors revealed expression of PD-L1/2 in patients resistant to enzalutamide, thus increasing the interest of using anti-PD-L1 therapies.[264] Similarly, a review of advanced prostate cancer tumor mutations revealed 12% of the tumors with mismatch repair gene mutations and microsatellite instability.[265] A phase I study of nivolumab in a variety of advanced tumor types including CRPC was investigated, and no objective response was noted in the CRPC cohort.[266] However, a case report of a patient with locally advanced, castration-resistant prostate cancer who had failed four previous therapies trailed nivolumab monotherapy and had dramatic responses in PSA, tumor size, performance status.[267] PD-L1/PD-1 inhibitors have been shown to be highly responsive in other cancer types (e.g., melanoma, non-small cell lung cancer, etc.) with mismatch repair deficiency (MMR) deficiency and has earned FDA-approval for those indications, including microsatellite instability-high cancer that is unresectable or metastatic.[31,32] However, tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median MTB of 19 mutations versus five mutations for non-responders ($p<0.0001$). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, $p=0.0086$). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, $p=0.0033$), but there was no difference in overall survival.[34] One retrospective analysis estimated a TMB of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

b. Niraparib: Niraparib is a poly (ADP-ribose) polymerase (PARP) inhibitor with activity in BRCA-mutated ovarian cancer. A phase I study investigated niraparib in a number of solid tumors. Only one of the patients with sporadic CRPC had a BRCA mutation, and had disease progression after 49 days of niraparib therapy. However, 43% (n=9) of the patients with BRCA-

negative CRPC had stable disease, and the duration of response was a median of 254 days.[27] Although niraparib has not been extensively studied in prostate cancer, it is plausible to anticipate some degree of niraparib activity based on the activity of the drug in other BRCA-positive tumors (e.g., ovarian) and the activity of other PARP inhibitors (i.e., olaparib) in prostate cancer.

c. Olaparib: Olaparib is a PARP inhibitor agent with activity in BRCA-mutated cancer. Not indicated in prostate cancer. Recent data indicates that men with prostate cancer have germline DNA repair gene mutations (11.8%) with BRCA1/2, ATM and CHEK2 defects most commonly identified.[268] In a metastatic CRPC cohort, DNA repair mutations were identified in 22.7% of the patients with BRCA1/2 and ATM aberrations noted as most common.[269] A phase II trial in patients with metastatic, castration-resistant prostate cancer investigated reported that olaparib treated patients had 33% response rate. Similarly, 33% of the study cohort had aberrations in DNA-repair genes, with 88% of those patients having a response to olaparib. The most common DNA-repair gene defects were BRCA2 loss and ATM aberrations.[270] In another phase II study, patients with recurrent cancer and germline BRCA 1/2 mutations were enrolled to receive olaparib. The overall response rate to therapy was 26.2%, in which the prostate cancer cohort had 50% response rate to olaparib.[157]

d. Pembrolizumab: Pembrolizumab is an anti-PD-L1 monoclonal antibody and checkpoint inhibitor that is approved for microsatellite instability-high cancer. A review of advanced prostate cancer tumor mutations revealed 12% of the tumors with mismatch repair (MMR) gene mutations and microsatellite instability.[265] A recent interim analysis of a phase II study of pembrolizumab in CRPC patients with progression on enzalutamide was published. This small report demonstrated 30% had complete or partial responses, 30% had stable disease at week 30 and beyond, and 40% had no response to pembrolizumab.[271] Pembrolizumab is an immune checkpoint inhibitor with antibodies for PD-1 that could be potentially effective in patients with MMR deficiency. Pembrolizumab has been shown to be highly responsive in other cancer types (e.g., melanoma, non-small cell lung cancer, etc.) with MMR deficiency and has earned FDA-approval for those indications, including microsatellite instability-high cancer that is unresectable or metastatic.[31,32] However, tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median MTB of 19 mutations versus five mutations for non-responders ($p<0.0001$). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, $p=0.0086$). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, $p=0.0033$), but there was no difference in overall survival.[34] One retrospective analysis estimated a TMB of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

4.2.8 Renal Cell Carcinoma

Drug	EGFR	MET	MSI-H*	TMB^	VEGFR
Atezolizumab (Tecentriq)			a		
Axitinib (Inlyta)					b
Bevacizumab (Avastin)					c
Cabozantinib (Cabometyx)		d			d
Erlotinib (Tarceva)	e				
Everolimus (Afinitor)	f				
Lenvatinib (Lenvima)					g
Nivolumab (Opdivo)			h	h	
Pazopanib (Votrient)					i
Pembrolizumab (Keytruda)			j	h	
Sorafenib (Nexavar)					k
Sunitinib (Sutent)					l
Temsirolimus (Torisel)	m				

*MSI-H: microsatellite instability, high
^TMB: tumor mutation burden

Footnotes:

a. Atezolizumab: Atezolizumab is humanized monoclonal antibody and immune checkpoint inhibitor with activity at PD-L1. A phase I trial of metastatic renal cell carcinoma (clear cell and non-clear cell histology) treated with atezolizumab described a reasonable safety profile with this therapy and encouraging efficacy with median PFS 5.6 months, objective response rate of 15% and median overall survival of 28.9 months. Of note, the patients with less than 1% PD-LI tumor expression had lower PFS and overall survival comparatively.[272] Phase I and II trials are ongoing in order to delineate the role of atezolizumab in renal cell carcinoma therapy.

b. Axitinib: Axitinib is a tyrosine kinase inhibitor (TKI) and vascular endothelial growth factor (VEGF) inhibitor that is approved for treatment of advanced renal cell cancer. The AXIS trial compared axitinib and sorafenib as second-line treatment in patients with metastatic renal cell carcinoma. Overall survival did not differ between the cohorts (axitinib 20.1 months versus sorafenib 19.2 months, p=0.3744) but median progression free survival (PFS) favored the axitinib group (8.3 versus 5.7 months, p<0.0001).[273,274] A phase III trial of treatment-naïve, clear cell, metastatic renal cell carcinoma compared axitinib to sorafenib and found no difference in median PFS between the cohorts.[275] Due to these findings, axitinib is recommended as an option for first-line treatment in clear cell renal carcinoma.[276] (*NCCN Evidence Category 2A*) It is also recommended as an option for

subsequent therapy in relapsed or medically unresectable stage IV clear cell renal carcinoma.[276] (*NCCN Evidence Category 1*) For relapsed or medically unresectable stage IV non-clear cell renal cancer, axitinib may be considered as second-line systemic therapy.[276] *(NCCN Evidence Category 2A)*

c. Bevacizumab: Bevacizumab is an anti-angiogenic monoclonal antibody and vascular endothelial growth factor inhibitor that is approved for treatment of metastatic renal cell cancer. The AVOREN trial investigated interferon alfa-2a (IFN) compared to bevacizumab+IFN in patients with treatment naïve metastatic renal cell carcinoma patients. The median PFS was longer in the combination group (10.2 versus 5.4 months, p=0.0001) and the objective tumor response rate favored the combination cohort (30.6% versus 12.4%).[277] These results have led to the recommendation of bevacizumab with interferon alfa-2b as preferred first-line therapy in relapsed or medically unresectable stage IV clear cell renal cancer. [276] *(NCCN Evidence Category 1)* For relapsed or medically unresectable stage IV unresectable, non-clear cell renal cancer, bevacizumab may be considered for systemic therapy.[276] *(NCCN Evidence Category 2A)* A phase II study of progressive, metastatic clear cell renal cancer demonstrated that bevacizumab provided prolongation of time to progression of diseases when compared to placebo. Although there was not an overall survival benefit seen in this study, it is recommended as an option for subsequent therapy in relapsed or medically unresectable stage IV clear cell renal cancer.[276,278] *(NCCN Evidence Category 2B)* Additionally, the combination of bevacizumab with everolimus or erlotinib may be considered in patients with relapsed or medically unresectable stage IV non-clear cell, advanced papillary renal cell cancer.[276] *(NCCN Evidence Category 2A)*

d. Cabozantinib: Cabozantinib is a small molecule TKI with activity at VEGF receptor and MET. The phase III METEOR study investigated cabozantinib versus everolimus in patients with clear cell renal carcinoma and disease progression on VEGFR-TKI. The objective response rate was higher in the cabozantinib cohort (21% versus 5%, p<0.001) and the median PFS was prolonged in the cabozantinib group (7.4 versus 3.8 months).[279] In a prolonged follow-up study, the median overall survival favored cabozantinib over everolimus (21.4 versus 16.5 months, p<0.00026) and the median PFS was improved in the cabozantinib group.[280] Therefore cabozantinib is recommended as preferred subsequent therapy (over everolimus) in relapsed or unresectable stage IV clear cell renal cancer.[276] *(NCCN Evidence Category 1)* Cabozantinib is also recommended as first-line therapy in relapsed or medically unresectable stage IV clear cell renal carcinoma.[276] *(NCCN Evidence Category 2A)* For relapsed or unresectable stage IV non-clear cell renal cancer, cabozantinib may be considered for systemic therapy.[276] *(NCCN Evidence Category 2A)*

e. Erlotinib: Erlotinib is a TKI with epidermal growth factor receptor (EGFR) inhibitor activity. Patients with advanced papillary renal cell cancer were enrolled in a phase II study investigating the efficacy of erlotinib. Overall survival was 11% with a median overall survival time of 27 months. Erlotinib in this population resulted in a 64% disease control rate.[281] Therefore, erlotinib is recommend as a first-line agent for relapsed or medically unresectable stage IV non-clear cell renal cancer.[276] *(NCCN Evidence Category 2A)* Additionally, the combination of bevacizumab with everolimus or erlotinib may be considered in patients with relapsed or medically unresectable stage IV non-clear cell, advanced papillary renal cell cancer.[276] *(NCCN Evidence Category 2A)*

f. Everolimus: Everolimus is an mTOR kinase inhibitor approved for treatment of advanced renal cell cancer. The RECORD-1 phase III trial investigated everolimus versus placebo in patients with metastatic renal cell carcinoma with disease progression on VEGF targeted therapy (e.g., sunitinib, sorafenib). The study was halted early for significant differences between the groups, with the everolimus-treated cohort demonstrating prolonged PFS (four vs 1.9 months) and fewer progression events (37% versus 65%, p <0.0001).[282,283] The RECORD-4 trial confirmed everolimus as a viable second-line option after first-line sunitinib, other anti-VEGF agents, or cytokines in patients with metastatic clear-cell renal cell carcinoma. The overall median PFS was 7.8 months and medial overall survival of 23.8 months with everolimus.[284] Therefore, everolimus is recommended as an option for subsequent therapy in relapsed or unresectable stage IV clear cell renal cancer.[276] *(NCCN Evidence Category 2A)* Although everolimus and temsirolimus are both mTOR inhibitors, they are not interchangeable therapies. Everolimus role is as second-line therapy after anti-VEGFR TKI therapy in metastatic renal cell carcinoma as it has been found to have a decreased risk of death by 26% compared to temsirolimus (p=0.008).[285] However, monotherapy with everolimus in patients with refractory clear cell renal carcinoma is not recommended over monotherapy with nivolumab or cabozantinib. The CheckMate 025 trial compared nivolumab versus everolimus in previously treated advanced clear cell renal cell carcinoma patients. The nivolumab cohort had a 25-month median overall survival compared to 19.6 months in the everolimus group. The objective response rate was also higher in the nivolumab group (25% versus 5%, p<0.001), but there was no overall difference in median PFS (4.6 versus 4.4 months, p=0.11) [286] In a sub-analysis of demographic features and previous treatment exposure, nivolumab treatment favored everolimus in both survival benefit and objective response rate.[287] The phase III METEOR study investigated cabozantinib versus everolimus in patients with clear cell renal carcinoma and disease progression on VEGFR-TKI. The objective response rate was higher in the cabozantinib cohort (21% versus 5%, p<0.001) and the median PFS was prolonged in the cabozantinib group (7.4 versus 3.8 months).[279] In a prolonged follow-up study, the median overall survival favored cabozantinib over everolimus (21.4 versus 16.5 months, p<0.00026) and the median PFS was improved in the cabozantinib group.[280] Therefore, nivolumab or cabozantinib is recommended as preferred subsequent therapy (over everolimus) in relapsed or unresectable stage IV clear cell renal cancer.[276] *(NCCN Evidence Category 1)* A phase II trial compared everolimus to lenvatinib and the combination of everolimus+lenvatinib as second-line treatment in patients with metastatic clear cell renal cell carcinoma with previously retreated with anti-VEGF agent. The combination was found to prolong PFS when compared with everolimus (14.6 versus 5.5 months, p=0.0005).[288] Therefore, everolimus in combination with lenvatinib is also recommended as a preferred subsequent therapy in relapsed or medically unresectable stage IV clear cell renal cancer.[276] *(NCCN Evidence Category 1)* Similar to clear-cell histology, patients with relapsed or unresectable stage IV non-clear cell renal carcinoma may be considered for everolimus systemic therapy, a combination of lenvatinib and everolimus, or in the case of advanced papillary renal cell cancer, combination therapy of bevacizumab and everolimus may be considered.[276] (*NCCN Evidence Category 2A*)

g. Lenvatinib: Lenvatinib is a tyrosine kinase inhibitor and vascular endothelial growth factor (VEGF) inhibitor. A phase II trial compared everolimus with lenvatinib and the combination of everolimus and lenvatinib as second-line treatment in patients

with metastatic clear cell renal cell carcinoma with previously retreated with anti-VEGF agent. The combination was found to prolong PFS when compared with everolimus (14.6 versus 5.5 months, p=0.0005). Lenvatinib also prolonged PFS compared to everolimus (7.4 versus 5.5 months, p=0.048), but not when compared to the combination therapy (p=0.12).[288] Therefore, lenvatinib in combination with everolimus is recommended as a preferred subsequent therapy in relapsed or unresectable stage IV clear cell renal cancer.[276] (*NCCN Evidence Category 1*) Patients with relapsed or unresectable stage IV non-clear cell renal carcinoma may be considered the combination of lenvatinib and everolimus.[276] (*NCCN Evidence Category 2A*)

h. Nivolumab: Nivolumab is an anti-PD-L1 monoclonal antibody and checkpoint inhibitor with activity in renal cell carcinoma. The CheckMate 025 trial compared nivolumab versus everolimus in previously treated advanced clear cell renal cell carcinoma patients. The nivolumab cohort had a 25-month median overall survival compared to 19.6 months in the everolimus group. The objective response rate was also higher in the nivolumab group (25% versus 5%, p<0.001), but there was no overall difference in median PFS (4.6 versus 4.4 months, p=0.11) [286] In a sub-analysis of demographic features and previous treatment exposure, nivolumab treatment favored everolimus in both survival benefit and objective response rate.[287] Therefore, nivolumab is recommended as preferred subsequent therapy (over everolimus) in relapsed or unresectable stage IV clear cell renal cancer.[276] (*NCCN Evidence Category 1*) For relapsed or unresectable stage IV non-clear cell renal cancer, nivolumab may be considered for systemic therapy.[276] (*NCCN Evidence Category 2A*) Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders (p<0.0001). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, p=0.0086). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, p=0.0033), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

i. Pazopanib: Pazopanib is a multi-kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), as well as stem cell factor receptor (c-KIT) and has anti-angiogenesis activity. In a phase III placebo-controlled trial in metastatic renal cell carcinoma patients, pazopanib had prolonged median PFS in the overall group (9.2 versus 4.2 months, p<0.0001), prolonged median PFS in the treatment naïve group (11.1 versus 2.8 months, p<0.0001), and a better objective response rate than placebo (30% versus 3%, p<0.001).[289] However, in a follow-up study and final analysis, the difference in objective response rate was lost between pazopanib and placebo, although this may be confounded by the frequent crossover from placebo to pazopanib.[290] In the phase III COMPARZ study, pazopanib and

sunitinib were found to be similar in PFS and overall survival in patients with systemic treatment-naïve metastatic renal cell carcinoma.[291,292] Pazopanib was preferred over sunitinib for less side effects and overall quality of life.[291-293] Therefore, pazopanib is recommended as preferred first-line therapy in relapsed or unresectable stage IV clear cell renal cancer.[276] (*NCCN Evidence Category 1*) In small, phase II study of second-line pazopanib treatment in patients with advanced clear cell renal carcinoma and failure on first-line sunitinib or bevacizumab, the pazopanib-treated patients had a 27% objective response rate with a median PFS of 7.5 months and overall survival at 24 months of 43%.[294] Therefore, pazopanib is recommended as an option for subsequent therapy in relapsed or unresectable stage IV clear cell renal cancer.[276] (*NCCN Evidence Category 2A*) No published prospective trials describe the use of pazopanib in non-clear cell renal cell carcinoma, therefore the NCCN Kidney Panel extrapolated data and ultimately recommended that pazopanib may be considered for systemic therapy in relapsed or unresectable stage IV non-clear cell renal cancer.[276] (*NCCN Evidence Category 2A*)

j. Pembrolizumab: Pembrolizumab is an anti-PD-1 monoclonal antibody and checkpoint inhibitor approved for unresectable or metastatic microsatellite-high cancer. Mismatch repair deficiencies have been identified in a number of tumor types, providing another target for drug therapy.[31,32] Pembrolizumab has been shown to be highly responsive in other cancer types (e.g., melanoma, non-small cell lung cancer, etc.) with MMR deficiency and has earned FDA-approval for those indications, including microsatellite instability-high cancer that is unresectable or metastatic. Similarly, nivolumab, another immune checkpoint inhibitor has had great success in improving PFS in relapsed renal cell carcinoma. Phase I trials of pembrolizumab, as a neoadjuvant therapy in treatment naïve renal cell carcinoma and subsequent therapy in advanced cancers is underway. Tumor mutation burden is emerging as a possible predictor of immunotherapy response. A retrospective study of next-generation sequencing data assessed tumor mutational burden (TMB) and associated response to immunotherapy in a wide variety of solid tumors.[34] High TMB (≥20 mutations) was found in 25% of the patients, 32% had intermediate TMB (6-19 mutations) and 43% had low TMB (1-5 mutations). The median TMB for non-melanoma or non-NSCLC patients was found to be six mutations, which is the same as the median of the entire cohort. The responders to immunotherapy had a median TMB of 19 mutations versus five mutations for non-responders ($p<0.0001$). When excluding melanoma and NSCLC patients, the response rate favored immunotherapy in the high TMB group over the intermediate to low TMB group (40% versus 8%, $p=0.0086$). The PFS was also longer in the high TMB group as well (10 months versus 2.1 months, $p=0.0033$), but there was no difference in overall survival.[34] One retrospective analysis estimated a tumor burden of 8 mutations to yield a 95% sensitivity and 58% specificity for predicting a favorable response with immune checkpoint inhibitor therapy.[35] Based on these reports, tumor mutation burden may predict response in patients receiving immune checkpoint inhibitors, but further prospective investigation is warranted.

k. Sorafenib: Sorafenib is a small-molecule multikinase inhibitor with activity at VEGFR, PDGFR, c-KIT, and RET that is approved for treatment of advanced renal cell cancer. A phase II trial compared sorafenib and interferon alfa-2a in treatment-naïve, advanced renal carcinoma patients. The sorafenib cohort had greater tumor shrinkage (68.2 versus 39%) although no difference in median PFS between the groups was described (5.7 versus 5.6 months).[295] There appears to be a role for

sorafenib as first-line therapy in patients with relapsed or unresectable stage IV clear cell renal carcinoma.[276] (*NCCN Evidence Category 2A*) Patients with advanced non-clear cell renal carcinoma who received sorafenib had a clinical response, with 80% of the study group having stable disease for 8 weeks.[296] For relapsed or unresectable stage IV non-clear cell renal cancer, sorafenib may be considered for systemic therapy in treatment-naïve patients.[276] (*NCCN Evidence Category 2A*) In a phase III trial (TARGET), sorafenib has shown improved PFS compared to placebo (5.5 versus 2.8 months, p<0.01) in patients with advanced clear-cell renal cell carcinoma who had failed previous therapies.[297] The final analysis of the TARGET trial found no difference in overall survival between the sorafenib and placebo intention-to-treat group, however, there was much cross-over from placebo to sorafenib. When this was taken into account, the overall survival was improved in the sorafenib cohort (17.8 versus 14.3 months, p<0.029).[298] Patients with bevacizumab or sunitinib-refractory metastatic renal cell carcinoma were trialed on sorafenib. Patients experienced a 30% reduction in tumor burden and a median PFS of 4.4 months with subsequent sorafenib therapy.[299] However, in another phase II study of sunitinib-refractory metastatic renal cell carcinoma, sorafenib had modest efficacy with 9.6% of patients with partial responses observed, and 25% with some tumor reduction.[300] Therefore, sorafenib may be considered for subsequent therapy in renal cell carcinoma.[276] (*NCCN Evidence Category 2A*)

l. Sunitinib: Sunitinib is a small-molecule multikinase inhibitor that targets the VEGFR, PDGFR, and c-KIT. Sunitinib has been compared to interferon alfa in treatment-naïve patients with metastatic renal cell carcinoma. The efficacy and safety results favored sunitinib with a longer median PFS of 11 versus 5.5 months (p<0.001) and higher objective response rate (31% versus 6%, p<0.001), as well as a reported better quality of life in the sunitinib cohort (p<0.001).[301] A comparative study of pazopanib versus sunitinib as first-line therapy of metastatic renal cell carcinoma found no difference in overall survival between the groups (22.6 versus 22.3 months, p=0.65) and no difference in PFS in the cohorts (8.3 versus 8.4 months, p=0.17).[302] In the phase III COMPARZ study, pazopanib and sunitinib were found to be similar in PFS and overall survival in patients with systemic treatment-naïve metastatic renal cell carcinoma.[291,292] However, pazopanib was preferred over sunitinib due to less side effects and overall improved quality of life.[291-293] Therefore, sunitinib is recommended as preferred first-line therapy in relapsed or unresectable stage IV clear cell renal cancer.[276] (*NCCN Evidence Category 1*) Sunitinib as a second-line therapy option has been investigated in patients with metastatic clear-cell renal cell carcinoma with failure on cytokine therapy. A median PFS of 8.3 months and partial response in 34% was described in this cohort, attributing to the recommendation of sunitinib as an option for subsequent therapy in relapsed or unresectable stage IV clear cell renal cancer.[276,303] (*NCCN Evidence Category 2A*) In a phase II trial (ASPEN) in patients with metastatic non-clear cell kidney cancer, everolimus and sunitinib were compared in treatment-naïve patients. Sunitinib had prolonged PFS compared to the everolimus cohort (8.3 versus 5.6 months, p=0.16).[304] In a similar phase II trial (ESPN), results favored sunitinib over everolimus in median PFS (6.1 versus 4.1 months, p=0.6) and median overall survival (16.2 versus 14.9 months, p=0.18). Therefore, for relapsed or unresectable stage IV non-clear cell renal cancer, sunitinib is the preferred for systemic therapy.[276] (*NCCN Evidence Category 2A*) In both cellular histologies of renal cell carcinoma with sarcomatoid features, sunitinib can be

considered with gemcitabine.[276,305] (*NCCN Evidence Category 2B*)Sunitinib is also recommended as adjuvant therapy after nephrectomy in stage II or III renal cell carcinoma, although adjuvant treatment with VEGF TKIs (sorafenib and sunitinib) have not been shown to have survival benefit against placebo.[276,306] (*NCCN Evidence Category 2B*)

m. Temsirolimus: Temsirolimus is an intravenous mTOR kinase inhibitor approved in advanced renal cell carcinoma. In a phase III trial of treatment-naïve, poor-prognosis metastatic renal cell carcinoma patients, temsirolimus was compared to interferon alfa or combination therapy of both agents. The temsirolimus cohort had improved PFS and overall survival compared to monotherapy interferon (PFS 5.5 versus 3.1 months, p<0.001; overall survival 10.9 versus 7.3 months, p=0.008). However, the combination therapy did not perform much better than monotherapy interferon in PFS (4.7 versus 3.1 months) and overall survival (8.4 versus 7.3 months, p=0.7), thus suggesting temsirolimus monotherapy over interferon-based regimens in this patient population.[307] Temsirolimus with bevacizumab was compared to monotherapy sunitinib or standard combination bevacizumab+interferon in a phase II study (TORAVA trial). The median PFS favored the bevacizumab+interferon group over the temsirolimus group (16.8 versus 8.2 months), and as such the combination of temsirolimus and bevacizumab is not recommended as a first-line agent in metastatic renal cell carcinoma.[308] Temsirolimus is recommended as first-line therapy in relapsed or unresectable stage IV non-clear cell renal cancer with poor prognosis.[276] (*NCCN Evidence Category 1*) Predictors of short survival and poor prognosis include three or more of the following: lactate dehydrogenase level greater than 1.5 times the upper limit of normal, hemoglobin level less than the lower limit of normal, corrected serum calcium level above 10 mg/dL, less than one year of diagnosis to start of systemic therapy, Karnofsky performance score less than or equal to 70, and two of more sites of organ metastasis.[307] Temsirolimus can be considered in other prognostic groups of non-clear cell histology.[276] (*NCCN Evidence Category 2A*) Temsirolimus was investigated as second-line therapy versus sorafenib in patients with metastatic renal cell carcinoma and progression on sunitinib. There was no difference between the treatment arms for PFS (4.3 versus 3.9 months, p=0.19), however overall survival favored sorafenib (16.6 versus 12.3 months, p=0.01).[309] Because of this, temsirolimus remains an option for subsequent therapy in relapsed or unresectable stage IV clear cell renal cell carcinoma.[276] (*NCCN Evidence Category 2B*)

4.2.9 Thyroid Cancer

Drug	ALK	BRAF	EFGR	MAP2K1 (MEK)	RET	VEGF
Alectinib (Alecensa)	a					
Axitinib (Inlyta)						b
Cabozantinib (Cometriq)					c	c
Ceritinib (Zykadia)	d					
Crizotinib (Xalkori)	e					
Dabrafenib (Tafinlar)		f				
Everolimus (Afinitor)			g			
Lenvatinib (Lenvima)						h
Pazopanib (Voltrient)						i
Sorafenib (Nexavar)						j
Sunitnib (Sutent)						k
Trametinib (Mekinist)		l		l		
Vandetanib (Caprelsa)			m		m	m
Vemurafenib (Zelboraf)		n				

Footnotes:

a. Alectinib: Alectinib is an anaplastic lymphoma kinase (ALK) inhibitor with activity in ALK-positive non-small lung cancer. However, ALK gene fusions have been identified in up to 2% of papillary thyroid carcinoma patients, and may serve as a plausible target for ALK-inhibiting targeted therapy.[310-313] Investigations of the safety and effectiveness of ALK-inhibitors in thyroid carcinoma is in early phases of exploration.

b. Axitinib: Axitinib is a small-molecule tyrosine kinase inhibitor (TKI) and vascular endothelial growth factor (VEGF) inhibitor that has been utilized off-label in differentiated thyroid carcinoma. Patients with advance thyroid cancer of any histology and refractory or unable to receive radioactive iodide were to receive axitinib in a phase II trial.[314] These patients had an overall response rate of 30%, with 18/60 patients experiencing partial response and 23/60 patients experiencing stable disease for 16 or more weeks. The median progression free survival (PFS) 18.1 months.[314] In a long-term follow up of this phase II trial, the median PFS was 15 months, median duration or response was 21 months, and median overall survival was 35 months.[315] In another phase II trial of axitinib in advanced thyroid carcinoma patients who were refractory and unable to receive radioactive iodine, axitinib was found to have an overall objective response rate of 35% with a PFS of 16.1 months and

overall survival of 27.2 months.[316] Per NCCN recommendations, TKIs like axitinib may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

c. Cabozantinib: Cabozantinib is a small-molecule multikinase inhibitor with activity at VEGF receptor and RET that is approved in metastatic medullary thyroid carcinoma. In phase I study of cabozantinib for the treatment of patients with iodine refractory, differentiated thyroid cancer, 8/14 patients achieved partial response and 6/14 had stable disease with the duration of response ranging from 2-14.5 months.[318] In phase II trial of VEGFR targeted therapy-refractory and iodine-refractory, differentiated thyroid carcinoma patients, patients received cabozantinib. Ten of the analyzed 25 patients had partial response and 13/25 had stable disease on cabozantinib salvage therapy. The median PFS was 12.7 months and median overall survival was 34.7 months.[319] Per NCCN recommendations, small-molecule kinase inhibitors like cabozantinib may be trialed in progressive disease and in differentiated thyroid cancer if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*) In a phase III, placebo-controlled, randomized trial of patients with progressive metastatic medullary thyroid carcinoma, the cabozantinib group performed better in median PFS compared to placebo (11.2 versus 4 months, $p<0.001$). Similarly, the cabozantinib cohort had a higher response rate than placebo (28% versus 0%) regardless of the RET mutation status.[320] The NCCN Panel recommends cabozantinib for metastatic medullary thyroid carcinoma based on the phase III randomized trial.[317] (*NCCN Evidence Category 1*)

d. Ceritinib: Ceritinib is an ALK inhibitor with activity in ALK-positive non-small lung cancer. However, ALK gene fusions have been identified in up to 2% of papillary thyroid carcinoma patients, and may serve as a plausible target for ALK-inhibiting targeted therapy.[310-313] Investigations of the safety and effectiveness of ALK-inhibitors in thyroid carcinoma is in early phases of exploration.

e. Crizotinib: Crizotinib is an ALK inhibitor with activity in ALK-positive or ROS1-positive non-small lung cancer. However, ALK gene fusions have been identified in up to 2% of papillary thyroid carcinoma patients, and may serve as a plausible target for ALK-inhibiting targeted therapy.[310-313] A case report of crizotinib use in a patient with metastatic anaplastic papillary carcinoma described promising results with 90% of the pulmonary lesions responding at 3 and 6 months, and maintaining an excellent performance status 2 years after diagnosis.[321]

f. Dabrafenib: Dabrafenib is a targeted BRAF kinase inhibitor with activity at BRAF V600E and V600K mutations. Over half of papillary thyroid carcinomas have an aberration in the BRAF gene, with a single amino acid substitution at V600E accounting for 90% of those mutations.[322] Thus, BRAF kinase inhibitors have become of interest in the targeted treatment of thyroid cancers. In a phase I trial, patients with BRAF V600E-positive thyroid carcinoma received dabrafenib. Partial response was reported in 4/14 patients, and 7/14 patients with stable disease at study completion. The median PFS was 11.3 months.[323] In another study, ten patients with BRAF V600E-positive, iodine-refractory, metastatic papillary thyroid carcinomas received dabrafenib. Sixty percent of the patients experienced new radioiodine uptake after dabrafenib treatment. Four patients had stable disease and two has partial responses with dabrafenib.[324] An open label, phase II trial of dabrafenib+trametinib in locally advanced or metastatic BRAF V600E mutated anaplastic thyroid carcinoma reported a 69% overall response rate and

90% had a durable response at 12 months.[325] The 12-month PFS was 79% and 12-month duration of response was 80%, thus suggesting this combination therapy is a promising option for BRAF V600E-mutant anaplastic thyroid carcinoma.[325] Per NCCN recommendations, dabrafenib may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

g. Everolimus: Everolimus is an mTOR kinase inhibitor that may have some utility in thyroid carcinomas. In a phase II trial, patients with locally advanced or metastatic thyroid carcinomas (any histology) received a trial of everolimus.[326] Patients receiving everolimus had a disease control rate of 81%, with 76% patients having stable disease and 17% with progressive disease. The median PFS with everolimus therapy was 11.7 months.[326] Per NCCN recommendations, everolimus may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

h. Lenvatinib: Lenvatinib is a tyrosine kinase inhibitor with activity at VEGF receptors, fibroblast growth factor receptors, platelet-derived growth factor receptor, RET, and KIT. A phase II trial of advanced, radioiodine-refractory, differentiated thyroid cancer investigated lenvatinib therapy.[327] The median PFS was 12.6 months in the study group, with 50% of patients having an objective response rate. Patients with previous VEGF therapy exposure had a slightly higher rate of objective response (59%).[327] In the phase III SELECT trial, lenvatinib was compared to placebo in patients with radioiodine-refractory, differentiated thyroid cancer.[328] The median PFS was prolonged in the lenvatinib group (18.3 versus 3.6 months, $p<0.001$) with the lenvatinib group also having a greater response rate compared to placebo (64.8% versus 1.5%, $p<0.001$). The lenvatinib cohort maintained PFS benefits regardless of the baseline biomarkers and BRAF/RAS status.[329] However the median overall survival was not met in either group.[328] Lenvatinib is the preferred therapy in progressive radioiodine-refractory differentiated thyroid cancer.[317] (*NCCN Evidence Category 2A*) Lenvatinib has also been investigated as salvage therapy in patients with metastatic disease who have failed first-line sorafenib.[330] In a small, retrospective study, patients treated with another TKI (sunitinib, pazopanib, cabozantinib, lenvatinib, and vemurafenib) displayed partial responses in 41% and stable diseases in 59% of the study subjects. The median PFS was 11.4 months in the salvage group, which was longer than the median PFS of first-line sorafenib. Median overall survival was also prolonged in the salvage group compared to first-line sorafenib (58 versus 28 months, $p=0.013$). [330] Per NCCN recommendations, TKIs like lenvatinib may be trialed in progressive medullary thyroid cancer if failed vandetanib or cabozantinib, or if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

i. Pazopanib: Pazopanib is a small-molecule multi-kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), as well as stem cell factor receptor (c-KIT) and has anti-angiogenesis activity that has been utilized off-label in differentiated thyroid carcinoma. A phase II trial tested the efficacy of pazopanib in patients with metastatic and progressive differentiated thyroid carcinoma who had been refractory to radioactive iodine. Partial responses were reported in 49% of the cohort, and a calculated duration of response at 1 year in 65% of the responding group.[331] Per NCCN recommendations, TKIs like pazopanib may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

j. Sorafenib: Sorafenib is a small-molecule multikinase inhibitor with activity at VEGFR, PDGFR, c-KIT, and RET that is approved in treatment of differentiated thyroid cancer. A small study reported the use of sorafenib or sunitinib in metastatic, progressive, radioactive iodine-refractory, differentiated thyroid cancer. These patients demonstrated partial response in 20%, stable disease in 60%, and progressive disease in 20%. The median PFS was 19 months, and median overall survival at 2 years was 67%. Pulmonary lesions were more likely to have response to therapy than lymph nodes.[332] Sorafenib investigated in cohort of patients with metastatic or locally advanced, iodine-refractory differentiated thyroid carcinoma.[333] This phase II study reported an overall median PFS of 14.5 months; however, those patients with bone metastases fared worse in PFS compare to no bone metastases (11.7 versus 17.2 months, p=0.004).[333] A phase II study of sorafenib in iodine-refractory, advanced differentiated thyroid carcinoma reported a median PFS of 18 months and median overall survival of 34.5 months.[334] The DECISION trial was a randomized, placebo-controlled, phase III trial of patients with locally advanced or metastatic, iodine-refractory, differentiated thyroid carcinoma.[335] The median PFS favored the sorafenib group over placebo (10.8 versus 5.8 months, p<0.0001) and reduced the risk of progression by 41% in the sorafenib group. There was no difference in overall survival, and the median time to progression was 11.1 months with sorafenib versus 5.7 months with placebo (p<0.0001).[335] Sorafenib therapy in papillary thyroid carcinoma has been found to have anti-tumor activity in metastatic disease, with a median PFS of 15 months and 56% of the patients have stable disease at six months of therapy.[336] Similarly in metastatic medullary thyroid carcinomas, 14/16 patients with sporadic disease were reported to have stable disease, with a median PFS of 17.9 months.[337] Per NCCN recommendations, may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

k. Sunitinib: Sunitinib is a small-molecule multikinase inhibitor that targets the VEGFR, PDGFR, and c-KIT that has been utilized off-label in refractory thyroid carcinoma. A phase II study evaluated daily sunitinib in patients with iodine-refractory, differentiated or metastatic medullary thyroid carcinoma. Thirty-one percent of the patients achieved the objective response rate, with a median PFS of 12.8 months.[338] A small study reported the use of sorafenib or sunitinib in metastatic, progressive, radioactive iodine-refractory, differentiated thyroid cancer. These patients demonstrated partial response in 20%, stable disease in 60%, and progressive disease in 20%. The median PFS was 19 months, and median overall survival at 2 years was 67%. Pulmonary lesions were more likely to have response to therapy than lymph nodes. [332] Per NCCN recommendations, TKIs like sunitinib may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

l. Trametinib: Trametinib is a TKI with inhibitory activity at MEK 1 and MEK 2, which are down stream effectors of BRAF. The frequency of BRAF V600E mutation is significant in anaplastic thyroid carcinoma (20-50%).[325] An open label, phase II trial of dabrafenib+trametinib in locally advanced or metastatic BRAF V600E-mutated anaplastic thyroid carcinoma reported a 69% overall response rate and 90% had a durable response at 12 months.[325] The 12-month PFS was 79% and 12-month duration of response was 80%, thus suggesting this combination therapy is a promising option for BRAF V600E-mutant anaplastic thyroid carcinoma.[325]

m. Vandetanib: Vandetanib is a multikinase inhibitor with anti-EGFR and VEGF receptor activity approved in advanced and metastatic medullary thyroid cancer. A phase II trial examined vandetanib in patients with unresectable, locally advanced or metastatic medullary thyroid cancer and reported a 20% objective partial response, 53% had stable disease at 24 weeks, and a median PFS of 27.9 months. Notably, there was no associate with vandetanib response and RET germline mutation.[339] A placebo-controlled phase III trial of vandetanib in patients with advanced medullary thyroid carcinoma described a longer PFS in the vandetanib cohort over placebo (30.5 versus 19.3 months, $p<0.001$).[340] Based on the NCCN recommendations, vandetanib may be considered for recurrent or metastatic medullary thyroid carcinoma.[317] (*NCCN Evidence Category 1*) Another phase II trial in locally advanced or metastatic differentiated thyroid carcinoma compared vandetanib to placebo.[341] The primary analysis reported 72% of the vandetanib cohort and 84% of the placebo group had disease progression. The PFS was longer in the vandetanib group (11.1 versus 5.9 months, $p=0.017$), with the papillary thyroid cancer patients with a better PFS (16.2 months) than other histologies, but was not statistically significant.[341] Therefore, vandetanib may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

n. Vemurafenib: Vemurafenib is a targeted BRAF kinase inhibitor with activity at BRAF V600E mutations. Over half of papillary thyroid carcinomas have an aberration in the BRAF gene, with a single amino acid substitution at V600E accounting for 90% of those mutations.[322] Thus, BRAF kinase inhibitors have become of interest in the targeted treatment of thyroid cancers. In a phase I trial, vemurafenib was investigated in three patients with metastatic papillary thyroid cancer with the BRAFV600E mutation. One patient had a decrease in pulmonary lesions by 31%, with a response duration of 7.6 months, and time to progression at 11.7 months. Stable disease was described in the other two patients, and the time to progression was 11.4 and 13.2 months.[322] A phase II trial explored vemurafenib therapy in metastatic, iodine-refractory papillary thyroid cancer patients with BRAF V600E mutation. In the cohort that was kinase inhibitor-naïve, partial response was reported in 10/26 patients, and 9/26 patients achieved stable disease for 6 months. The median PFS was 18.2 months and the median duration of response was 16.5 months at the close of the study. The cohort with previous kinase inhibitor exposure experienced less of a response, with a median PFS of 8.9 months and median duration of response of 7.4 months.[342] Per NCCN recommendations, vemurafenib may be trialed in progressive disease if clinical trials or other therapy options are not available.[317] (*NCCN Evidence Category 2A*)

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6. UK HealthCare Implementation

Potential Benefits:
Following these guidelines should lead to decreased variation in targeted therapies recommended by oncology. The evidence base provided will allow informed decisions to be made on personalized treatment plans and optimal therapeutic management, which may result in improved cancer patient outcomes.

Potential Harms:
None identified.

Implementation Plan/Tools:
1. Guideline will be available on the UK Markey Cancer Center Molecular Tumor Board under "Guidance Documents" hyperlink.
2. Release of the guideline will be advertised at the 2nd Annual Precision Medicine Symposium: Advances in Immunotherapies (Lexington, KY; April 14, 2018).
3. Education and communication will be provided at 2nd Annual Precision Medicine Symposium: Advances in Immunotherapies (Lexington, KY; April 14, 2018) and the subsequent webinar posted on the Markey Cancer Center Molecular Tumor Board website.

7. Disclaimer

Clinical Practice Guidelines (CPG) are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This CPG outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.