Cyramza® (ramucirumab)
(Intravenous)

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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Cyramza 100 mg/10 mL: 4 vials per 14 days
- Cyramza 500 mg/50 mL: 2 vials per 14 days

B. Max Units (per dose and over time) [HCPCS Unit]:

Gastric, Gastroesophageal, HCC, and Colorectal Cancer:
- 180 billable units every 14 days

NSCLC:
- 240 billable units every 14 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1]

- Patient does not have uncontrolled severe hypertension; **AND**
- Patient must not have had a surgical procedure within the preceding 28 days or have a surgical wound that has not fully healed; **AND**

Gastric, Esophageal, and Gastro-esophageal Junction Adenocarcinoma † Φ [1-3,5-7,14,17,2e,5e]

- Used as subsequent therapy after fluoropyrimidine- or platinum-containing chemotherapy; **AND**
- Used as a single agent OR in combination with paclitaxel; **AND**
    - Used for one of the following:

- Patient has unresectable locally advanced, recurrent, or metastatic disease; **OR**
- Used as palliative therapy for locoregional disease in patients who are not surgical candidates

Non-Small Cell Lung Cancer † [1,3,8,12,13,12e,13e,15e,35e,41e]

- Patient has recurrent, advanced, or metastatic disease; **AND**
  - Used as subsequent therapy following progression on a first-line cytotoxic regimen; **AND**
    - Used in combination with docetaxel; **AND**
    - Patient has not previously been treated with docetaxel or ramucirumab; **OR**
  - Used in combination with erlotinib for EGFR mutation-positive disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease, except for mediastinal lymph node recurrence with prior radiation therapy) ‡; **AND**
    - Used as first-line therapy; **AND**
      - Patient has EGFR exon 19 deletion or exon 21 L858R substitution mutations; **OR**
    - Used for continuation of therapy following disease progression on combination erlotinib and ramucirumab therapy for asymptomatic disease, symptomatic brain lesions, or symptomatic systemic limited metastases

Colorectal Adenocarcinoma † [1,3,9-11,17,18,25e,28e-30e]

- Will not be used in combination with an anti-EGFR agent (e.g., panitumumab or cetuximab); **AND**
- Used in combination with FOLFIRI (irinotecan, folinic acid/leucovorin, and 5-fluorouracil) for metastatic disease that progressed on or after therapy with bevacizumab, oxaliplatin and a fluoropyrimidine †; **OR**
- Used in combination with irinotecan; **AND**
  - Used as subsequent therapy for advanced or metastatic disease that progressed on or after therapy with bevacizumab, oxaliplatin and a fluoropyrimidine; **AND**
    - Patient has not previously been treated with irinotecan-based therapy

Hepatocellular Carcinoma (HCC) † Φ [1,3,4,16,31e-34e]

- Used as single agent therapy; **AND**
- Used as subsequent therapy for progressive disease; **AND**
- Patient has an alfa-fetoprotein (AFP) level of ≥ 400 ng/mL; **AND**
- Patient was previously treated with a tyrosine kinase inhibitor (e.g., sorafenib †, lenvatinib, etc.)

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendia recommended indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,3,13]

Authorizations can be renewed based on the following criteria:

- Patient continues to meet universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hemorrhage, arterial thromboembolic events, uncontrolled hypertension, infusion-related reactions, severe proteinuria (> 3g/24h)/nephrotic syndrome, gastrointestinal perforations, impaired wound healing, posterior reversible encephalopathy syndrome (PRES), thyroid dysfunction, worsening of pre-existing hepatic impairment, etc.

Non-Small Cell Lung Cancer (continuation of therapy in combination with erlotinib following disease progression):

- *Refer to Section III for criteria*

V. Dosage/Administration [1,12]

Indication	Dose
Gastric, gastroesophageal, hepatocellular carcinoma and colorectal cancer	8 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity
NSCLC	In combination with docetaxel: 10 mg/kg intravenously every 21 days until disease progression or unacceptable toxicity In combination with erlotinib: 10 mg/kg intravenously every 14 days until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9308 – Injection, ramucirumab, 5 mg: 1 billable unit = 5 mg

NDC:

- Cyramza 100 mg/10 mL solution, single dose vial: 00002-7669-xx
- Cyramza 500 mg/50 mL solution, single dose vial: 00002-7678-xx

VII. References (STANDARD)

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm duodenum
C17.1	Malignant neoplasm jejunum
C17.2	Malignant neoplasm ileum
C17.8	Malignant neoplasm of overlapping sites of small intestines
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of large intestines
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma

ICD-10	ICD-10 Description
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C78.00	Secondary malignant neoplasm of lung
C78.01	Secondary malignant neoplasm of lung
C78.02	Secondary malignant neoplasm of lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
D37.1	Neoplasm of uncertain behavior of stomach
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.028	Personal history of other malignant neoplasm of stomach
Z85.038	Personal history of malignant neoplasm of large intestine
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA):

Jurisdiction(s): J & M	**NCD/LCD/LCA Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate

Esophageal and Esophagogastric Junction Cancers:

Unresectable Locally Advanced, Recurrent or Metastatic Esophageal and Esophagogastric Junction Cancers – Second line or Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ramucirumab & Paclitaxel	1 preferred for gastric & EGJ adenocarcinoma 2A preferred for esophageal adenocarcinoma	YES (for gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy)	Phase 3 trial (RAINBOW)	Paclitaxel monotherapy	OS	Second-Line Therapy	OS benefit for Ramucirumab + Paclitaxel compared to patients receiving paclitaxel monotherapy as well as PFS and ORR.
Ramucirumab monotherapy	1 other for gastric & EGJ adenocarcinoma 2A for esophageal adenocarcinoma	YES Dosing: 8 mg/kg Q2 weeks until dx progression or unacceptable toxicity	Phase 3 (REGARD)	Placebo	OS	Second-Line therapy	OS benefit for Ramucirumab in patients with gastric or EGJ adenocarcinoma progressing after first line chemotherapy
Ramucirumab + FOLFIRI	2A	NO	Retrospective analysis	N/A	-----	Second-line	FOLFIRI plus ramucirumab is effective as second-line treatment of gastroesophageal adenocarcinoma after progression on first-line platinum and fluoropyrimidine.

Ramucirumab + irinotecan	2A	NO	Phase 3 (RINDBeRG), randomized	Irinotecan	OS	Third-line	Clinical trial is currently ongoing and data has not yet been reported.
Docetaxel monotherapy (Q3 weeks)	1-preferred	NO Approved for use in combo with cisplatin/5-FU as first line treatment for advanced dx	Phase 2 (two trials)-pts with locally advanced, metastatic, or recurrent dx	Docetaxel (weekly) & Gemzar	OR	Second-Line (also enrolled treatment naïve)	Docetaxel as single agent is active in both treatment naïve and previously treated patients with recurrent disease. (Addition of gemcitabine is well tolerated, but adds no efficacy)
Docetaxel monotherapy (Q3weeks)	1-preferred	NO	Phase 3, open-label, multi-center trial of pts 18 and older with advanced, adenocarcinoma of the oesophagus, oesophagogastric junction or stomach who progressed on or within 6 months of treatment with a platinum-fluoropyrimidine combination	Active symptom control	OS	Second-Line	Docetaxel is an appropriate second-line treatment for patients with oesophagogastric adenocarcinoma that is refractory to treatment with a platinum and fluoropyrimidine.
Paclitaxel monotherapy	1-preferred	NO	Phase 2, evaluate response rate, duration of response and toxicity in previously untreated pts with unresectable local-	-------	RR, Duration of response	-------	Paclitaxel is an active agent against adenocarcinoma and squamous cell carcinoma of the esophagus

			regional or metastatic carcinoma of the esophagus				COMMENTS: study enrolled previously untreated patients and not used as second line or subsequent therapy
Paclitaxel monotherapy	1-preferred	NO	Phase 2, evaluation of weekly paclitaxel in advanced esophageal cancer. Pts with prior tx for metastatic dx were excluded, however prior non-taxane chemo in the adjuvant or neo-adjuvant setting was permitted.	-------	RR	-------	Weekly paclitaxel has limited activity in esophageal cancer. The median survival, modest activity, and tolerance of therapy indicated that weekly paclitaxel may be an option in patients who are unable to tolerate combo chemo. COMMENTS: study enrolled previously untreated as well as those previously treated.
Paclitaxel monotherapy	1-preferred	NO	Phase 3 (WJOG 4007): Study comparing Irinotecan with paclitaxel in patients with advanced Gastric Cancer without severe peritoneal metastasis after failure of prior combo chemo using Fluoropyrimidine plus Platinum.	Irinotecan	OS	Second-Line	• No Statistically significant difference was observed between paclitaxel and irinotecan for OS. Therefore, both are reasonable second-line treatment options for advanced gastric cancer.

Irinotecan monotherapy	1-preferred	NO	Phase 2, study comparing biweekly irinotecan monotherapy or combo of irinotecan plus 5-FU/LV (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemo	mFOLFIRI	ORR	Second-Line	• CPT-11 monotherapy and mFOLFIRI appear to be equally active and tolerable as second-line chemotherapy for AGC • Addition of 5FU/LV to CPT-11 didn't significantly improve efficacy
Irinotecan monotherapy	1-preferred	NO	Phase 3, Survival advantage for irinotecan versus best-supportive care as second-line therapy in gastric cancer	BSC	OS	Second-Line	• Second-line Irinotecan showed a reduction in the hazard ratio for death compared to BSC COMMENTS: Not all data presented, study closed prematurely due to poor accrual
Irinotecan with 5-FU	2A-preferred	NO	RETRO REVIEW, of FOLFIRI a salvage chemo in patients with AGC previously treated with fluoropyrimidine, platinum and a taxane.	-------	ORR	Second-Line	• Bi-weekly irinotecan with 5-FU/LV has modest activity and tolerability in AGC patients
Irinotecan with 5-FU	2A-preferred	NO	Phase 2, study of Irinotecan and 5-FU in patients with primary refractory or relapsed	-------	ORR	Second-Line	• 5-FU/Irinotecan is a valuable regimen for second-line therapy of 5-FU/Platinum resistant oesophagogastric carcinoma.

			advanced oesophageal and gastric carcinoma				
Pembrolizumab	2A-preferred for second-line or subsequent therapy for MSI-H or dMMR tumors	YES	Phase 2, study to evaluate the clinical activity of pembrolizumab in progressive metastatic carcinoma with or without mismatch-repair deficiency.	-------	RR cohorts A and B, PFS cohort C	-------	• Mismatch-repair status predicted clinical benefit of immune checkpoint blockade with pembrolizumab
Pembrolizumab	2A- preferred for second-line or subsequent therapy for MSI-H or dMMR tumors	YES	Phase 2, study to further investigate dMMR response of solid tumors to PD-1 blockade	-------	RR	Second Line Therapy	• dMMR cancers also respond to PD-1 blockade • MMR deficiency appears to be a biomarker for predicting successful treatment outcomes for several solid tumors and a new therapeutic option for dMMR cancers

Non-Small Cell Lung Cancers:

EGFR mutation positive NSCLC – First line therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Erlotinib + ramucirumab	2A	No	Phase 3 (RELAY), randomized, double-blind, placebo-controlled	Erlotinib + placebo	PFS	First-line	• Ramucirumab plus erlotinib demonstrated superior progression-free survival compared with placebo plus erlotinib in patients with untreated EGFR-mutated metastatic NSCLC.
Osimertinib	1 preferred	Yes	Phase 3 (FLAURA),	Gefitinib or erlotinib	PFS	First-line	• Osimertinib showed efficacy in PFS superior to that of standard EGFR-TKIs in the first-line treatment of EGFR mutation-positive

			double-blind, randomized				advanced NSCLC, with a similar safety profile and lower rates of serious adverse events.
Afatinib	1 other	Yes	Phase 3 (LUX-Lung 3), randomized, multi-center, open-label	Cisplatin + pemetrexed	PFS	First-line	• Afatinib is associated with prolongation of PFS when compared with standard doublet chemotherapy in patients with advanced lung adenocarcinoma and EGFR mutations.
Gefitinib	1 other	Yes	Phase 4, open-label, single-arm	N/A	ORR	First-line	• First-line gefitinib was effective (ORR 69.8%) and well tolerated in patients with EGFR mutation-positive NSCLC.
Gefitinib	1 other	Yes	Phase 3 (IPASS), randomized	Carboplatin + paclitaxel	PFS	First-line	• Gefitinib is superior to carboplatin-paclitaxel as an initial treatment for pulmonary adenocarcinoma with an improvement in PFS and ORR.
Dacomitinib	1 other	Yes	Phase 3 (ARCHER 1050), randomized, multi-center, open-label	Gefitinib	PFS	First-line	• Dacomitinib significantly improved progression-free survival over gefitinib in first-line treatment of patients with EGFR-mutation-positive NSCLC.
Advanced or Metastatic Adenocarcinoma of the Lung and Squamous Cell Carcinoma of Lung – Subsequent Systemic Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Atezolizumab	1 preferred	YES Dosing: 1200 mg IV Q3 weeks until dx progression or unacceptable toxicity	Phase 2 trial (POPLAR), evaluated efficacy and safety of atezolizumab versus docetaxel in previously treated NSCLC (post-platinum chemotherapy)	Docetaxel monotherapy	OS	Subsequent Therapy	• Atezolizumab significantly improved survival compared with docetaxel in patients with previously treated NSCLC. • Improvement correlated with PD-L1 expression • Atezolizumab was well tolerated with a safety profile distinct from chemotherapy

Atezolizumab	1 preferred	YES	Phase 3 (OAK), study evaluating patients with squamous or non-squamous NSCLC who had received 1-2 previous chemo regimens (one or more platinum based tx) for Stage IIIB or IV disease.	Docetaxel monotherapy	OS	Second Line or Subsequent Therapy	• First randomized Phase 3 trial to report results of PD-L1 targeted therapy with atezolizumab resulting in clinically relevant OS versus docetaxel in previously treated NSCLC, regardless of PD-L1 expression or histology
Nivolumab	1 preferred	YES Dosing: 240 mg Q2 weeks or 480 mg Q4 weeks until dx progression or unacceptable toxicity	Phase 3, (CheckMate 057) evaluating patients with NSCLC who progressed during or after platinum-based doublet chemo to receive nivolumab or docetaxel 75 mg/m2	Docetaxel	OS	Second line or Subsequent Therapy	• Among patients with advanced non-squamous NSCLC that progressed during or after platinum-based chemo, OS is longer with nivolumab than docetaxel.
Nivolumab	1 preferred	YES	Phase 3, enrolled patients with advanced squamous cell NSCLC who had	Docetaxel	OS	Second line	• OS, RR, and PFS were significantly better with nivolumab than with docetaxel, regardless of PD-L1 expression. • PD-1 expression was neither prognostic nor predictive of benefit.

			disease progression during or after first-line chemotherapy.				
Nivolumab	1 preferred	YES	Phase 3 (CheckMate 017 and CheckMate 057), evaluated advanced NSCLC who had progression during or after prior platinum based chemo	Docetaxel	OS	Second Line or Subsequent Therapy	• Nivolumab provides long-term clinical benefit and favorable tolerability profile compared to docetaxel.
Nivolumab	1 preferred	YES	Phase 2, OS and Long-term safety of Nivolumab in patients with previously tx NSCLC	-------	OS	Second Line or Subsequent Therapy	• Nivolumab monotherapy provides durable response and encouraging survival rates in patients with heavily pre-treated NSCLC.
Pembrolizumab (2mg/kg or 10mg/kg)	1 preferred	YES for tumors that express PD-L1 (TPS ≥ 1%)	Phase 2/3 (KEYNOTE-010), assessed the efficacy of pembrolizumab for patients with previously platinum-treated, PD-L1-positive, advanced NSCLC	Docetaxel	OS PFS	Subsequent therapy	• Pembrolizumab prolongs overall survival in patients with previously treated, PD-L1-positive, advanced non-small-cell lung cancer.

Ramucirumab + Docetaxel	2A for first progression after initial therapy 2B for progression after subsequent therapy	YES In combo w/ docetaxel, is indicated for metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Dosing: 10 mg/kg Q21 days until dx progression or unacceptable toxicity	Phase 3 (REVEL), evaluation of ramucirumab and docetaxel compared to placebo as second-line treatment for patient with stage IV NSCLC after platinum based chemo.	Docetaxel/ placebo	OS	Second Line	• Ramucirumab plus docetaxel improves survival as second-line treatment of patients with stage IV NSCLC.
Docetaxel	2A	YES, single agent for locally advanced or metastatic NSCLC after platinum therapy failure Dosing: 75 mg/m2 Q3 weeks	Phase 3 (TAX 320), study of docetaxel monotherapy versus vinorelbine or Ifosfamide in patients with advanced NSCLC previously treated with platinum-containing regimens	Vinorelbine or Ifosfamide	OS	Second Line or Subsequent Therapy	• D75 Q3 weeks can offer clinically meaningful benefit with advanced NSCLC that has relapsed or progressed after platinum-based chemo.

Docetaxel	2A	YES	Phase 2, study of docetaxel monotherapy versus BSC in patients with advanced NSCLC previously treated with platinum-containing regimens	BSC	RR	Second line or Subsequent Therapy	• Treatment with docetaxel is associated with significant prolongation of survival at a dose of 75 mg/m2 the benefits of therapy, outweigh the risk.
Pemetrexed	2A for use in non-squamous dx only	YES, as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Dosing: 500 mg/m2 Q21 days until dx progression or unacceptable toxicity	Phase 3, Pemetrexed vs. Docetaxel in patients with NSCLC previously treated with chemotherapy	Docetaxel	OS	Second Line or Subsequent Therapy	• Treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with fewer side effects. ❖ Survival update for this study performed after 519 deaths, also found similar results
Gemcitabine	2A	NO	Phase 2, study to evaluate single-agent gemcitabine as second line treatment after previous chemo or radiotherapy	-------	Tumor response, toxicity and health-related quality of life (HRQL)	Second Line	• Gemcitabine as second-line treatment has modest anti-tumor activity, is well tolerated, may control tumor related symptoms, and improve HRQL in a significant minority of patients.

			in advanced NSCLC				
Gemcitabine	2A	NO	Phase 2, study to investigate the activity and toxicity of single agent gemcitabine in patients with advanced NSCLC after recurrence or failure of previous treatment with a platinum containing regimen.	-------	RR	Second Line	• Gemcitabine showed significant activity without relevant toxicity • Possible role for gemcitabine as second-line treatment in patients who had a previous response or achieved stable disease with a platinum-containing regimen.

Colorectal Cancer:

Colon Cancer – Subsequent Systemic Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Irinotecan + Oxaliplatin based chemo + bevacizumab	2A preferred	YES, in combo with fluoropyrimidine-irinotecan or oxaliplatin based chemo as 2nd line in pts who progressed on 1st line Avastin	Phase 3 (ML18147), study evaluating continuation of bevacizumab after first progression in mCRC after standard 1st-line bevacizumab based tx	Irinotecan/Oxaliplatin based chemo	OS	Second Line	• Maintenance VEGF inhibition with bevacizumab plus standard 2nd-line chemo beyond dx progression has benefit in mCRC.

		Dosing: 5 mg/kg Q2 weeks or 7.5 mg/kg Q3 weeks					
FOLFOX or FOLFIRI + bevacizumab	2A preferred	YES	Phase 3 (BEBYP), study to evaluate efficacy of continuing or reintroducing bevacizumab in combo with second-line chemo after progression to bevacizumab-based first line treatment	FOLFOX or FOLFIRI	PFS	Second Line	• Continuation or the re-introduction of bevacizumab with second-line chemo beyond first progression improves the outcome Comments: Study stopped premature out of consideration for the results of the ML18147 trial
FOLFIRI + bevacizumab	2A preferred	YES	Phase 3 (EAGLE), study to compare 2 doses of bevacizumab with FOLFIRI in 2nd line setting after 1st line therapy with bevacizumab plus oxaliplatin based tx	-------	OS, TTF, safety	Second Line	• Bevacizumab 10 mg/kg plus FOLFIRI as second-line didn't prolong PFS compared to bevacizumab 5 mg/kg plus FOLFIRI in patients with mCRC.
Irinotecan + Oxaliplatin based chemo + bevacizumab	2A preferred	YES	RETRO REVIEW, evaluation of the association between the continued use of bevacizumab beyond progression (BBP) and survival outcomes in mCRC	Irinotecan/Oxaliplatin based chemo	OS, post progression OS	Second Line	• BBP treatment is correlated with prolonged OS and ppOS in patients with mCRC.

			pts in the community setting.				
Irinotecan + Oxaliplatin based chemo + bevacizumab	2A preferred	YES	Observational cohort ARIES study analysis, examine association between exposure to bevacizumab after dx progression and post-progression survival in mCRC	-------	PPS (post progression survival)	Second Line	• Analysis supports the observation that bevacizumab exposure after disease progression is associated with longer PPS in mCRC.
FOLFIRI (Irinotecan) + ziv-aflibercept	2A	YES, in combo with FOLFIRI in pts with mCRC that is resistant to or has progressed on an oxaliplatin regimen	Phase 3 (VELOUR), study of aflibercept w/FOLFIRI in mCRC pts previously tx with oxaliplatin and some with bevacizumab	FOLFIRI + placebo	OS	Second Line	• Aflibercept in combination with FOLFIRI conferred a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin. • Activity only when given in combo with FOLFIRI or in FOLFIRI naïve patients
FOLFIRI (Irinotecan) + ziv-aflibercept	2A	YES	Phase 3 (VELOUR)-SUB-GROUP ANALYSIS, Aflibercept versus placebo in combination with FOLFIRI for tx of mCRC	FOLFIRI+ placebo	OS	Second Line	• Benefits of aflibercept in combo with FOLFIRI in pts with mCRC previously treated with oxaliplatin were maintained across the specific subgroups, including those with or without prior bevacizumab tx
FOLFIRI + ramucirumab	2A	YES, in combo with FOLFIRI for the tx of mCRC with dx progression on or after prior tx with bevacizumab,	Phase 3 (RAISE), study of ramucirumab + FOLIRI vs. placebo + FOLFIRI in patients with metastatic CRC that progressed during or after first-	FOLFIRI + placebo	OS	Second Line	• Ramucirumab + FOLFIRI significantly improved IS compared to placebo + FOLFIRI as second line tx for metastatic CRC. • No unexpected AEs and toxicity was manageable. • Activity only when given in combo with FOLFIRI or in FOLFIRI naïve patients

		oxaliplatin and fluoropyrimidine	line therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.				
Bevacizumab + FOLFIRI	2A (preferred after previous oxaliplatin- or fluoropyrimidine-based therapy without irinotecan or oxaliplatin)	Yes	Phase 2 (SPIRITT), randomized, multi-center	Panitumumab + FOLFIRI	PFS	Second-line after oxaliplatin-based therapy plus bevacizumab	• Panitumumab or bevacizumab with FOLFIRI as second-line treatment had efficacy similar in patients whose disease progressed during oxaliplatin-based chemotherapy with bevacizumab
Panitumumab + FOLFIRI	2A	No	Phase 3 (Study 181), randomized	FOLFIRI	PFS OS	Second-line	• Panitumumab plus FOLFIRI significantly improved PFS, however the improvement in OS was nonsignificant
Cetuximab + irinotecan	2A	Yes	Phase 3 (EPIC), multi-center, open-label	Irinotecan	OS	After fluoropyrimidine and oxaliplatin	• Cetuximab and irinotecan improved PFS and ORR versus irinotecan alone. OS was similar between study groups

Hepatocellular Carcinoma (HCC):

Subsequent Therapy							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Ramucirumab	1 (AFP ≥ 400 ng/mL only)	Yes (AFP ≥ 400 ng/mL only)	Phase 3 (REACH), randomized, double-blind, multi-center	Placebo	OS	Second-line after sorafenib	• In a subgroup analysis of second-line treatment of patients with advanced hepatocellular carcinoma with AFP ≥ 400 ng/mL, ramucirumab significantly improved survival over placebo.
Ramucirumab	1 (AFP ≥ 400 ng/mL only)	Yes (AFP ≥ 400 ng/mL only)	Phase 3 (REACH-2), randomized	Placebo	OS	Second-line after sorafenib	• REACH-2 met its primary endpoint, showing improved overall survival for ramucirumab compared with placebo in patients with hepatocellular carcinoma and α-fetoprotein

							concentrations of at least 400 ng/mL who had previously received sorafenib.
Regorafenib	1 (Child-Pugh Class A only)	Yes	Phase 3 (RESORCE), randomized, double-blind, placebo-controlled	Placebo	OS	Second-line after sorafenib (excluded prior treatment for HCC except sorafenib)	• Regorafenib demonstrated a survival benefit in HCC patients progressing on sorafenib treatment.
Cabozantinib	1 (Child-Pugh Class A only)	Yes (Child-Pugh Class A only)	Phase 3 (CELESTIAL), randomized, double-blind	Placebo	OS	Second or third-line after sorafenib	• Among patients with previously treated advanced hepatocellular carcinoma, treatment with cabozantinib resulted in longer overall survival and progression-free survival than placebo. The rate of high-grade adverse events in the cabozantinib group was approximately twice that observed in the placebo group.