Halaven® (eribulin)
(Intravenous)

-E-

Document Number: MODA-0403

Last Review Date: 05/03/2021
Date of Origin: 01/07/2019
Dates Reviewed: 01/2019, 04/2019, 07/2019, 10/2019, 01/2020, 04/2020, 07/2020, 10/2020, 05/2021

I. Length of Authorization

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

II. Dosing Limits

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

- Halaven 1 mg/2 mL solution for injection: 8 vials every 21 days

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

- 80 billable units every 21 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

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

Breast Cancer † [1-3,7e,9e,14e,17e,18e]

- Patient has metastatic disease †; **AND**
  - Used as a single agent for patients who have previously received at least two chemotherapy regimens for the treatment of metastatic disease; **AND**
  - Prior therapy includes treatment with an anthracycline and a taxane in either the adjuvant or metastatic setting; **OR**
- Patient has recurrent or metastatic disease; **AND**
  - Used as a single agent for human epidermal growth factor receptor 2 (HER2)-negative disease in patients who have previously received therapy with an anthracycline and a taxane; **AND**
    - Disease is hormone receptor negative; **OR**
    - Disease is hormone receptor positive with visceral crisis or refractory to endocrine therapy; **OR**
  - Used with trastuzumab for HER2-positive as first-line therapy

Liposarcoma † [1,2,4,20e]

- Used as a single agent; **AND**
- Patient has unresectable or metastatic or recurrent disease; **AND**
- Patient has received prior anthracycline-based therapy (e.g., doxorubicin, 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]

Coverage can be renewed based on the following criteria:

- Patient continues to meet 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: severe QT-prolongation, severe neutropenia (ANC < 500/mm^3), peripheral neuropathy, etc.

V. Dosage/Administration [1,6]

Indication	Dose
All Indications	Administer 1.4 mg/m^2 , intravenously, on days 1 and 8, repeated every 21 days until disease progression or unacceptable toxicity

VI. Billing Code/Availability Information

HCPCS Code:

- J9179 – Injection, eribulin mesylate, 0.1 mg; 1 billable unit = 0.1mg

NDC:

- Halaven 1 mg/2 mL solution for injection: 62856-0389-xx

VII. References (STANDARD)

1. Halaven [package insert]. Woodcliff Lake, NJ; Eisai Inc; February 2021. Accessed April 2021.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) eribulin. National Comprehensive Cancer Network, 2021. The NCCN

Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2021.

3. Cortes J, O'Shaughnessy J, Loesch D, et al; EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. Lancet. 2011;377(9769):914-923.
4. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet. 2016 Apr 16;387(10028):1629-37. doi: 10.1016/S0140-6736(15)01283-0. Epub 2016 Feb 10.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Soft Tissue Sarcoma, Version 1.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed April 2021.
6. Schöffski P, Ray-Coquard IL, Cioffi A, et al. Activity of eribulin mesylate in patients with soft-tissue sarcoma: a phase 2 study in four independent histological subtypes. Lancet Oncol. 2011;12(11):1045-1052.

VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer, Version 3.2021. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. Accessed April 2021.

2e. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol. 2003 Feb 15;21(4):588-92.

3e. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol. 1999 Aug;17(8):2341-54.

4e. Seidman AD, Berry D, Cirrincione C, et al. Randomized Phase III Trial of Weekly Compared With Every-3-Weeks Paclitaxel for Metastatic Breast Cancer, With Trastuzumab for all HER-2 Overexpressors and Random Assignment to Trastuzumab or Not in HER-2 Nonoverexpressors: Final Results of Cancer and Leukemia Group B Protocol 9840. Journal of Clinical Oncology 2008 26:10, 1642-1649.

5e. Seidman AD, Tiersten A, Hudis C, et al. Phase II trial of paclitaxel by 3-hour infusion as initial and salvage chemotherapy for metastatic breast cancer. J Clin Oncol. 1995 Oct;13(10):2575-81.

6e. Bajetta E, Procopio G, Celio L, et al. Safety and Efficacy of Two Different Doses of Capecitabine in the Treatment of Advanced Breast Cancer in Older Women. Journal of Clinical Oncology 2005 23:10, 2155-2161.

7e. Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015 Feb 20;33(6):594-601. doi: 10.1200/JCO.2013.52.4892. Epub 2015 Jan 20.

8e. Twelves C, Awada A, Cortes J, et al. Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pretreated Patients with Advanced or Metastatic Breast Cancer. Breast Cancer (Auckl). 2016 Jun 28;10:77-84. doi: 10.4137/BCBCR.S39615. eCollection 2016.

9e. Baselga J, Cortés J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012 Jan 12;366(2):109-19. doi: 10.1056/NEJMoa1113216. Epub 2011 Dec 7.

10e. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015 Feb 19;372(8):724-34. doi: 10.1056/NEJMoa1413513.

11e. Datko FM, D'Andrea G, Dickler M, et al. Phase II study of pertuzumab, trastuzumab, and weekly paclitaxel in patients with HER2-overexpressing metastatic breast cancer (MBC). Journal of Clinical Oncology 2012 30:27_suppl, 134-134.

12e. Smyth LM, Iyengar NM, Chen MF, et al. Weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing metastatic breast cancer: overall survival and updated progression-free survival results from a phase II study. Breast Cancer Res Treat. 2016 Jul;158(1):91-97. doi: 10.1007/s10549-016-3851-7. Epub 2016 Jun 15.

13e. Ellis PA, Barrios CH, Eiermann W, et al. Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study. Journal of Clinical Oncology 2015 33:15_suppl, 507-507.

14e. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med. 2012 Nov 8;367(19):1783-91. doi: 10.1056/NEJMoa1209124. Epub 2012 Oct 1.

15e. Cameron D, Casey M, Oliva C, et al. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. Oncologist. 2010;15(9):924-34. doi: 10.1634/theoncologist.2009-0181. Epub 2010 Aug 24.

16e. Blackwell KL, Burstein HJ, Storniolo AM, et al. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-

positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol. 2012 Jul 20;30(21):2585-92. doi: 10.1200/JCO.2011.35.6725. Epub 2012 Jun 11.

17e. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol. 2009 Apr 20;27(12):1999-2006. doi: 10.1200/JCO.2008.19.6618. Epub 2009 Mar 16.

18e. Wilks S, Puhalla S, O'Shaughnessy J, et al. Phase 2, multicenter, single-arm study of eribulin mesylate with trastuzumab as first-line therapy for locally recurrent or metastatic HER2-positive breast cancer. Clin Breast Cancer. 2014 Dec;14(6):405-12. doi: 10.1016/j.clbc.2014.04.004. Epub 2014 Jun 2.

19e. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. J Clin Oncol. 2016 Mar 10;34(8):786-93.

20e. Demetri GD, Schöffski P, Grignani G, et al. Activity of Eribulin in Patients With Advanced Liposarcoma Demonstrated in a Subgroup Analysis From a Randomized Phase III Study of Eribulin Versus Dacarbazine. J Clin Oncol. 2017 Oct 20;35(30):3433-3439. doi: 10.1200/JCO.2016.71.6605. Epub 2017 Aug 30.

21e. Bui-Nguyen B, Butrynski JE, Penel N, et al. A phase IIb multicentre study comparing the efficacy of trabectedin to doxorubicin in patients with advanced or metastatic untreated soft tissue sarcoma: the TRUSTS trial. Eur J Cancer. 2015 Jul;51(10):1312-20.

22e. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. Lancet Oncol. 2014 Apr;15(4):415-23.

23e. Seddon B, Strauss SJ, Whelan J, et al. Gemcitabine and docetaxel versus doxorubicin as first-line treatment in previously untreated advanced unresectable or metastatic soft-tissue sarcomas (GeDDiS): a randomised controlled phase 3 trial. Lancet Oncol. 2017 Oct;18(10):1397-1410.

24e. Le Cesne A, Blay J-Y, Cupissol D, Italiano A, Delcambre C, Penel N, et al. Results of a prospective randomized phase III T-SAR trial comparing trabectedin vs best supportive care (BSC) in patients with pretreated advanced soft tissue sarcoma (ASTS) Ann Oncol. 2016;27(suppl 6):1396O.

25e. Le Cesne A, Blay JY, Judson I, et al. Phase II study of ET-743 in advanced soft tissue sarcomas: a European Organisation for the Research and Treatment of Cancer (EORTC) soft tissue and bone sarcoma group trial. J Clin Oncol. 2005 Jan 20;23(3):576-84.

26e. Kawai A, Araki N, Sugiura H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study. Lancet Oncol. 2015 Apr;16(4):406-16. doi: 10.1016/S1470-2045(15)70098-7. Epub 2015 Mar 18.

27e. Blay JY, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer. 2014 Apr;50(6):1137-47. doi: 10.1016/j.ejca.2014.01.012. Epub 2014 Feb 7.

28e. Baruchel S, Pappo A, Krailo M, et al. A phase 2 trial of trabectedin in children with recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas: a report from the Children's Oncology Group. Eur J Cancer. 2012 Mar;48(4):579-85. doi: 10.1016/j.ejca.2011.09.027. Epub 2011 Nov 14.

29e. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol. 2009 Nov 1;27(31):5182-8. doi: 10.1200/JCO.2009.22.3768. Epub 2009 Sep 21.

30e. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. J Clin Oncol. 2008 Nov 10;26(32):5269-74. doi: 10.1200/JCO.2008.17.3146. Epub 2008 Sep 22.

31e. Tap WD, Jones RL, Van Tine BA, et al. Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomised phase 2 trial. Lancet. 2016 Jul 30;388(10043):488-97. doi: 10.1016/S0140-6736(16)30587-6. Epub 2016 Jun 9.

32e. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol. 2013 Jan;24(1):257-63. doi: 10.1093/annonc/mds237. Epub 2012 Aug 21.

33e. Hawkins DS, Chi YY, Anderson JR, et al. Addition of Vincristine and Irinotecan to Vincristine, Dactinomycin, and Cyclophosphamide Does Not Improve Outcome for Intermediate-Risk Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. 2018 Sep 20;36(27):2770-2777. doi: 10.1200/JCO.2018.77.9694. Epub 2018 Aug 9.

34e. Kawai A, Araki N, Naito Y, et al. Phase 2 study of eribulin in patients with previously treated advanced or metastatic soft tissue sarcoma. Jpn J Clin Oncol. 2017 Feb 1;47(2):137-144. doi: 10.1093/jjco/hyw175.

35e. Pautier P, Floquet A, Penel N, et al. Randomized multicenter and stratified phase II study of gemcitabine alone versus gemcitabine and docetaxel in patients with metastatic or relapsed leiomyosarcomas: a Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) French Sarcoma Group Study (TAXOGEM study). Oncologist. 2012;17(9):1213-20. Epub 2012 Aug 20.

36e. Magellan Health, Magellan Rx Management. Halaven Clinical Literature Review Analysis. Last updated April 2021. Accessed April 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip
C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
C47.3	Malignant neoplasm of peripheral nerves of thorax
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including shoulder
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb
C49.12	Malignant neoplasm of connective and soft tissue of left lower limb
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C50.011	Malignant neoplasm of nipple and areola, right female breast
C50.012	Malignant neoplasm of nipple and areola, left female breast
C50.019	Malignant neoplasm of nipple and areola, unspecified female breast
C50.021	Malignant neoplasm of nipple and areola, right male breast
C50.022	Malignant neoplasm of nipple and areola, left male breast
C50.029	Malignant neoplasm of nipple and areola, unspecified male breast

ICD-10	ICD-10 Description
C50.111	Malignant neoplasm of central portion of right female breast
C50.112	Malignant neoplasm of central portion of left female breast
C50.119	Malignant neoplasm of central portion of unspecified female breast
C50.121	Malignant neoplasm of central portion of right male breast
C50.122	Malignant neoplasm of central portion of left male breast
C50.129	Malignant neoplasm of central portion of unspecified male breast
C50.211	Malignant neoplasm of upper-inner quadrant of right female breast
C50.212	Malignant neoplasm of upper-inner quadrant /of left female breast
C50.219	Malignant neoplasm of upper-inner quadrant of unspecified female breast
C50.221	Malignant neoplasm of upper-inner quadrant of right male breast
C50.222	Malignant neoplasm of upper-inner quadrant of left male breast
C50.229	Malignant neoplasm of upper-inner quadrant of unspecified male breast
C50.311	Malignant neoplasm of lower-inner quadrant of right female breast
C50.312	Malignant neoplasm of lower-inner quadrant of left female breast
C50.319	Malignant neoplasm of lower-inner quadrant of unspecified female breast
C50.321	Malignant neoplasm of lower-inner quadrant of right male breast
C50.322	Malignant neoplasm of lower-inner quadrant of left male breast
C50.329	Malignant neoplasm of lower-inner quadrant of unspecified male breast
C50.411	Malignant neoplasm of upper-outer quadrant of right female breast
C50.412	Malignant neoplasm of upper-outer quadrant of left female breast
C50.419	Malignant neoplasm of upper-outer quadrant of unspecified female breast
C50.421	Malignant neoplasm of upper-outer quadrant of right male breast
C50.422	Malignant neoplasm of upper-outer quadrant of left male breast
C50.429	Malignant neoplasm of upper-outer quadrant of unspecified male breast
C50.511	Malignant neoplasm of lower-outer quadrant of right female breast
C50.512	Malignant neoplasm of lower-outer quadrant of left female breast
C50.519	Malignant neoplasm of lower-outer quadrant of unspecified female breast
C50.521	Malignant neoplasm of lower-outer quadrant of right male breast
C50.522	Malignant neoplasm of lower-outer quadrant of left male breast
C50.529	Malignant neoplasm of lower-outer quadrant of unspecified male breast
C50.611	Malignant neoplasm of axillary tail of right female breast
C50.612	Malignant neoplasm of axillary tail of left female breast
C50.619	Malignant neoplasm of axillary tail of unspecified female breast
C50.621	Malignant neoplasm of axillary tail of right male breast
C50.622	Malignant neoplasm of axillary tail of left male breast
C50.629	Malignant neoplasm of axillary tail of unspecified male breast

ICD-10	ICD-10 Description
C50.811	Malignant neoplasm of overlapping sites of right female breast
C50.812	Malignant neoplasm of overlapping sites of left female breast
C50.819	Malignant neoplasm of overlapping sites of unspecified female breast
C50.821	Malignant neoplasm of overlapping sites of right male breast
C50.822	Malignant neoplasm of overlapping sites of left male breast
C50.829	Malignant neoplasm of overlapping sites of unspecified male breast
C50.911	Malignant neoplasm of unspecified site of right female breast
C50.912	Malignant neoplasm of unspecified site of left female breast
C50.919	Malignant neoplasm of unspecified site of unspecified female breast
C50.921	Malignant neoplasm of unspecified site of right male breast
C50.922	Malignant neoplasm of unspecified site of left male breast
C50.929	Malignant neoplasm of unspecified site of unspecified male breast

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): N/A

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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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; OR = odds ratio; TTF = time to treatment failure; PFR = progression free rate

Breast Cancer

Recurrent or Metastatic HER2-negative disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Doxorubicin	2A preferred	Yes	Phase 3	Paclitaxel vs. doxorubicin + paclitaxel (AT)	----------	First-line	• Combination of doxorubicin + paclitaxel resulted superior ORR and TTF however, did not improve survival compared to single agent doxorubicin therapy.
Doxorubicin	2A preferred	Yes	Phase 3, randomized	Docetaxel	----------	After previous alkylating agent-containing chemotherapy	• ORR was improved with docetaxel compared with doxorubicin however, no significant difference in TTP or OS.
Paclitaxel (every 3 weeks)	2A preferred	Yes (After failure of combination chemotherapy for metastatic disease or relapse within 6 months	Phase 3, randomized	Paclitaxel weekly	ORR	First- or second-line	• Weekly paclitaxel is more effective than every-3-week administration for metastatic breast cancer. • Weekly paclitaxel demonstrated an OS of 24 months.

		of adjuvant chemotherapy)					
Paclitaxel	2A preferred	Yes (After failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy)	Phase 2	N/A	----------	All lines of therapy	• Paclitaxel demonstrated an ORR 32% in first line therapy and an ORR 20.8% in subsequent therapy in patients with metastatic breast cancer.
Capecitabine	2A preferred	Yes (When resistant to paclitaxel/anthracycline-containing regimens or resistant to paclitaxel and not a candidate for further anthracycline therapy)	Phase 2, open-label	1,250mg/m^2 twice daily (standard) vs 1,000mg/m^2 twice daily	Safety	First-line and second-line	• Capecitabine is safe and effective in elderly breast cancer patients based on a low overall incidence of grade 3/4 toxicities and ORR of 36.7%.
Eribulin	2A preferred	Yes (After 2 or more chemotherapy regimens for metastatic disease. Prior therapy should have included an	Phase 3 (EMBRACE) open-label, randomized	Treatment of Physician's Choice (TPC) - any single agent chemotherapy, hormonal treatment or biological	OS	Third-line therapy or later (in patients with 2 or more prior treatments for advanced disease, including an anthracycline and taxane)	• OS was improved in eribulin compared to TPC.

		anthracycline and a taxane in either the adjuvant or metastatic setting.)		therapy approved for the treatment of cancer; or palliative treatment or radiotherapy			
Eribulin	2A preferred	Yes (After 2 or more chemotherapy regimens for metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.)	Phase 3, randomized Subgroup analysis	Capecitabine	OS and PFS	First-, second-, or third-line therapy for metastatic disease (in patients with prior anthracycline- and taxane-based therapy)	• Overall, eribulin was not shown to be superior to capecitabine with regard to OS or PFS. • In HER2-negative and triple-negative disease, OS advantage was observed with eribulin over capecitabine .
Recurrent or Metastatic HER2-positive disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Pertuzumab+ trastuzumab + docetaxel	1 preferred	Yes	Phase 3 (CLEOPATRA), randomized, double-blind, placebo-controlled	Docetaxel + trastuzumab+ placebo	PFS	First-line in metastatic breast cancer (patients with prior adjuvant or neoadjuvant therapy, with or without trastuzumab, must have an interval of at least 12 months between	• Pertuzumab group significantly prolonged PFS and OS compared to the placebo group.

			Second interim analysis			completion of the adjuvant or neoadjuvant therapy and the diagnosis of metastatic breast cancer)	
Pertuzumab+ trastuzumab + paclitaxel	2A preferred	No	Phase 2 Follow up analysis	N/A	PFS	First- or second-line in metastatic breast cancer	• Pertuzumab + trastuzumab + paclitaxel was associated with a favorable OS and PFS and offers an alternative to docetaxel-based therapy.
Ado-trastuzumab emtansine (T-DM1)	1 preferred second-line	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy)	Phase 3 (MARIANNE), randomized	(Docetaxel or paclitaxel)+ trastuzumab vs T-DM1 + pertuzumab (T-DM1 + P)	PFS Safety	First-line therapy in locally advanced or metastatic breast cancer with ≥ 6-month treatment-free interval since completion of adjuvant therapy	• No significant difference in PFS was observed between ado-trastuzumab-containing regimens and the control group. • T-DM1 is an effective and tolerable alternative first-line treatment for HER2-positive metastatic breast cancer.
Ado-trastuzumab emtansine (T-DM1)	1 preferred second-line	Yes (After prior trastuzumab and a taxane. Patients should have either received prior therapy for metastatic disease	Phase 3 (EMILIA), randomized, open-label	Lapatinib+ capecitabine	PFS OS Safety	Previous treatment with trastuzumab and a taxane (in any setting) • First-line with progression within 6-months after adjuvant therapy	• T-DM1 significantly prolonged PFS and OS with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane.

		or developed disease recurrence during or within 6 months of completing adjuvant therapy)				• Second-line therapy or later for locally advanced or metastatic disease	
Lapatinib+ capecitabine	2A other for third-line and beyond	Yes	Phase 3, randomized	Capecitabine alone	TTP	Second-line therapy or later after prior trastuzumab (metastatic setting) and prior treatment with an anthracycline and a taxane (metastatic or adjuvant setting)	• Lapatinib+ capecitabine demonstrated a significant benefit in TTP and a trend towards an improvement in OS compared to capecitabine alone.
Trastuzumab+ lapatinib	2A other for third-line and beyond	No	Phase III (EGF104900 Study), randomized, open-label	Lapatinib monotherapy	PFS	Second-line therapy or later after one or more prior trastuzumab-containing regimens for metastatic disease	• Modest improvement (3 weeks) in PFS with lapatinib+ trastuzumab versus lapatinib alone. • 4.5mon OS advantage with lapatinib+ trastuzumab in patients with pretreated HER2-positive metastatic breast cancer.
Trastuzumab+ capecitabine	2A other for third-line and beyond	No	Phase 3 (TBP), randomized	Capecitabine	TTP	After prior trastuzumab-based therapy (in adjuvant or metastatic setting)	• Continuing trastuzumab and adding capecitabine beyond trastuzumab progression showed a significant improvement in ORR and TTP compared with capecitabine alone. • However, difference in OS was not significant.

Trastuzumab+ eribulin	2A other for third-line and beyond	No	Phase 2, single-arm	N/A	ORR	First-line	• Because of the high ORR, prolonged PFS, and acceptable safety profile, trastuzumab+ eribulin is effective in treating recurrent or metastatic HER2-positive breast cancer.
Eribulin	None	Yes (After 2 or more chemotherapy regimens for metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.)	Phase 3 (EMBRACE) open-label, randomized	Treatment of Physician's Choice (TPC) - any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; or palliative treatment or radiotherapy	OS	Third-line therapy or later (in patients with 2 or more prior treatments for advanced disease, including an anthracycline and taxane)	• OS was improved in eribulin compared to TPC.
Eribulin	None	Yes (After 2 or more chemotherapy regimens for metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the	Phase 3, randomized Subgroup analysis	Capecitabine	OS and PFS	First-, second-, or third-line therapy for metastatic disease (in patients with prior anthracycline- and taxane-based therapy)	• Overall, eribulin was not shown to be superior to capecitabine with regard to OS or PFS. • In HER2-negative and triple-negative disease, OS advantage was observed with eribulin over capecitabine .

		adjuvant or metastatic setting.)					

Soft Tissue Sarcoma (STS):

Liposarcoma– Unresectable, metastatic, or recurrent disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Trabectedin	1	Yes	Phase 3 (T-SAR), randomized	Best supportive care (BSC)	PFS	Second-line therapy and later (including anthracycline)	• PFS benefit was demonstrated for trabectedin over BSC in both L-type and non-L-type pretreated advanced sarcoma. • Benefit seen most with L-type sarcomas .
Trabectedin	1	Yes	Phase 3, randomized open-label, active-controlled, parallel-group	Dacarbazine	OS	Third-line	• No difference in OS was observed between trabectedin and dacarbazine. • Trabectedin improved PFS versus dacarbazine.
Eribulin	1	Yes	Phase 2, non-randomized	N/A	PFS at 12 weeks	Second- or third-line (after one combination regimen or up to 2 single agents)	• Eribulin demonstrated clinical activity with a 12-week PFS of 31.6% in leiomyosarcoma, 46.9% in liposarcoma, and 19.2% in other sarcoma types.
Eribulin	1	Yes	Subgroup analysis of a phase 3, randomized open-label	Dacarbazine	OS	Third-line	• Eribulin improved liposarcoma OS versus dacarbazine. • PFS favored eribulin.

Generic regimens	2A						
Retroperitoneal/Intra-abdominal (unresectable or progressive disease) **and Extremity/Superficial Trunk, Head/Neck** (metastatic or recurrent disease)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Doxorubicin	2A	Yes	Phase 3, randomized, controlled	Doxorubicin + ifosfamide	OS	First-line therapy	• No significant difference in OS between groups.
Gemcitabine + docetaxel	2A	No	Phase 3 (GeDDiS), randomized, controlled	Doxorubicin	% of patients alive at 24 weeks	First-line therapy	• Gemcitabine+docetaxel failed to show superiority to doxorubicin in first-line therapy. • No difference in the proportion of patients alive at 24 weeks, PFS, and no significant difference in OS. • Also, no differential effect was evident in histological subtypes.
Trabectedin	2A	No	Phase 2b, randomized	Doxorubicin	PFS	First-line	• Trabectedin failed to show improvement in PFS versus doxorubicin in first-line therapy.
Trabectedin	2A	No	Phase 3 (T-SAR), randomized	Best supportive care (BSC)	PFS	Second-line therapy and later (including anthracycline)	• PFS benefit was demonstrated for trabectedin over BSC in both L-type and non-L-type pretreated advanced sarcoma. • Benefit seen most with L-type sarcomas.

Trabectedin	2A	No	Phase 2, non-randomized	N/A		Second- or third-line therapy	• Clinical activity of trabectedin was demonstrated based on TTP, PFS, and OS.
Eribulin	2A	No	Phase 2, open-label, multicenter, non-randomized	N/A		Second-line therapy and later	• Eribulin showed efficacy based on progression-free rate, PFS and OS.
Rhabdomyosarcoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Vincristine, dactinomycin, cyclophosphamide (VAC)	2A	Yes	Phase 3, randomized	VAC/V topotecan/ cyclophosphamide (TC)	FFS	First-line	• VAC/VTC does not significantly improve FFS nor OS versus VAC.
Vincristine, dactinomycin, cyclophosphamide (VAC)	2A	Yes	Phase 3, randomized	VAC alternating with vincristine & irinotecan (VI)	EFS	First-line	• Addition of VI to VAC did not improve EFS or OS for patients with intermediate-risk RMS.
Trabectedin	2A	No	Phase 2, randomized, open-label	Best supportive care	PFS	Second-line therapy and later	• PFS favored trabectedin in patients with translocation-related sarcomas.
Trabectedin	2A	No	Phase 3, randomized	Doxorubicin-based regimen	PFS	First-line therapy	• PFS and OS showed non-significant difference between arms in patients with translocation-related sarcomas.

							• Underpowered due to the high rate of censoring. • Study inclusion criteria did not include any rhabdomyosarcoma subtypes.
Trabectedin	2A	No	Phase 2	N/A		Second-line therapy and later	• Trabectedin did not demonstrate any significant evidence of activity in children with relapsed recurrent rhabdomyosarcoma, Ewing sarcoma and non-rhabdomyosarcoma soft tissue sarcomas.
Eribulin	2A (pleomor-phic)	No	No clinical literature to support use.				
Angiosarcoma							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Paclitaxel	2A	No	Phase 2 (ANGIOTAX)	N/A	PFS	All lines of therapy	• Demonstrated efficacy in patients with metastatic or unresectable angiosarcoma.
Bevacizumab	2A	No	Phase 2, open-label, single arm	N/A	PFS	All lines of therapy	• Bevacizumab demonstrated clinical activity based on partial response, stable disease, and TTP.
Trabectedin	2A	No	No clinical literature to support use.				
Eribulin	2A	No	No clinical literature to support use.				