

**Submitted By:**

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NCCN Guidelines® Panel: **Uterine Neoplasms**

Dear Panel Members,

On behalf of Eli Lilly and Company, we respectfully request the NCCN Uterine Neoplasms Guidelines Panel to review the enclosed data and consider inclusion of Lartruvo™ (olaratumab) in the NCCN Guidelines and Compendia.

**Specific Change:**

We request that the NCCN update the Clinical Practice Guidelines for Uterine Neoplasms and the Drugs & Biologics Compendium to list Lartruvo™ (olaratumab) in combination with doxorubicin as a therapy for patients with uterine sarcomas (uterine leiomyosarcoma [LMS] and endometrial stromal sarcoma).

**FDA Clearance:**

On October 19, 2016, the Food and Drug Administration (FDA) approved Lartruvo™ (olaratumab) in combination with doxorubicin for the treatment of adult patients with soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.<sup>2</sup> This indication is approved under accelerated approval based on results from a pivotal phase 2 clinical trial. A confirmatory phase 3 clinical trial has also completed accrual (study JGDJ, [NCT02451943](#)). Please see important safety information in the accompanying full prescribing information.

**Rationale:**

Lartruvo™ (olaratumab) in combination with doxorubicin was studied in a randomized, phase 2 clinical trial vs single-agent doxorubicin in 133 patients with STS not amenable to curative treatment with surgery or radiotherapy with a histologic type of sarcoma for which an anthracycline-containing regimen was appropriate (study JGDG, [NCT01185964](#)).<sup>2,5</sup> Lartruvo™ in combination with doxorubicin demonstrated a median overall survival (OS) of 26.5 months compared to 14.7 months for single-agent doxorubicin (hazard ratio [95% CI] of 0.52 [0.34, 0.79]; p<.05).<sup>2</sup> The most common histological subtype of STS in this study was LMS.<sup>2,5-6</sup>

The most common adverse reactions reported in at least 20% of patients receiving Lartruvo™ in combination with doxorubicin were nausea, fatigue, musculoskeletal pain, mucositis, alopecia, vomiting, diarrhea, decreased appetite, abdominal pain, neuropathy, and headache.<sup>5</sup> Infusion related reactions (IRRs) occurred in 13% of patients in the Lartruvo™ plus doxorubicin arm and 3% of patients in the single-agent doxorubicin arm.<sup>2</sup> The most common adverse reaction that resulted in permanent discontinuation of Lartruvo™ was IRR, which occurred in 3% of patients.<sup>2</sup> The most common laboratory abnormalities (≥20%) were lymphopenia, neutropenia, thrombocytopenia, hyperglycemia, elevated aPTT, hypokalemia, and hypophosphatemia; but neutropenia did not lead to an increase in febrile neutropenia events, hospital admissions, treatment discontinuations, or deaths.<sup>2,5</sup> A summary of cardiac toxicity event

terms excluding patients with unrelated peripheral edema, demonstrates that the prevalence of cardiac dysfunction was 8% with olaratumab plus doxorubicin and 6% with single-agent doxorubicin.<sup>5</sup> Clinicians should be aware that the potential for cumulative cardiotoxicity was mitigated by treating with dexrazoxane in cycles 5 to 8.<sup>5</sup>

A post hoc analysis of this study was performed to assess efficacy and safety of Lartruvo™ in combination with doxorubicin vs doxorubicin alone in patients with uterine LMS. Fifteen uterine LMS patients were identified by retrospective review of pathology and medical case reports. While small patient numbers preclude definitive conclusions, the uterine LMS patients achieved over a year of incremental improvement in median OS with Lartruvo™ in combination with doxorubicin compared to doxorubicin single-agent.<sup>6</sup> This result is consistent with the results in the non-uterine LMS subgroup and those previously reported in the phase 2 overall study population.<sup>2,6</sup> No improvement in PFS was demonstrated in the uterine LMS subgroup with the addition of Lartruvo™ to doxorubicin.<sup>6</sup> PFS and OS are summarized in Table 1 below for the phase 2 intent to treat, uterine LMS, and non-uterine LMS subgroups.<sup>2,6</sup> The safety profile of Lartruvo™ in combination with doxorubicin in the uterine LMS population was acceptable, manageable, and consistent with that previously reported from the overall study population.<sup>6</sup>

**Table 1. PFS and OS Results in ITT Population, Uterine LMS, and Non-Uterine LMS Subgroups (Phase 2)<sup>2,6</sup>**

	Phase 2 STS Trial <sup>2</sup>		Phase 2 STS Retrospective Analysis <sup>6</sup>			
	ITT Population		Uterine LMS		Non-Uterine LMS	
	OLA+DOX N=66	DOX N=67	OLA+DOX N=8	DOX N=7	OLA+DOX N=16	DOX N=20
<b>Median PFS, mo<sup>a</sup></b>	8.2	4.4	2.7	3.6	6.9	4.1
<b>HR (95% CI)<sup>b</sup></b>	0.74 (0.46-1.19)		0.93 (0.25-3.54)		0.71 (0.32-1.55)	
<b>Median OS, mo</b>	26.5	14.7	25.0	11.4	30.1	13.8
<b>HR (95% CI)<sup>b</sup></b>	0.52 (0.34-0.79)		0.61 (0.18-2.14)		0.43 (0.20-0.92)	

Abbreviations: DOX = doxorubicin; HR = hazard ratio; ITT = intent to treat; mo = months; LMS = leiomyosarcoma; N = number of treated patients; OLA = olaratumab; OS = overall survival; PFS = progression-free survival.

<sup>a</sup> Based on independent review

<sup>b</sup> Unstratified Cox model

A confirmatory phase 3 study to further test the efficacy of Lartruvo™ in combination with doxorubicin in advanced STS has completed enrollment and results are pending data maturity (study JGDG, [NCT01185964](https://clinicaltrials.gov/ct2/show/study/NCT01185964)). Additional uterine LMS patients are represented in the confirmatory trial and further analysis will be performed.

Lartruvo™ in combination with doxorubicin has received a Category 2A designation in the NCCN Guidelines for soft tissue sarcoma with an overall survival benefit of 11.8 months when compared to the recognized standard of care doxorubicin alone.<sup>2</sup> Recent literature has reported that patients with uterine sarcomas may be systematically treated with doxorubicin as a first-line chemotherapy option,<sup>1,3,4</sup> and demonstrate no difference in outcomes when compared to other soft tissue sarcomas.<sup>3</sup> However, the uterine neoplasm codes most often used by Gynecological Oncologists when treating STS are not included in the NCCN Compendia. This complicates the coding and reimbursement process for appropriately treated uterine LMS. We believe these codes include: C53.0, C54.0-C54.3, C54.8, C54.9, C55, C78.00-C78.02, and Z80.49.

**Resources:**

The following resources are submitted in support of this proposed change:

- [Lartruvo \[package insert\]. Indianapolis, IN: Eli Lilly and Company; 2017.](#)
- 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;388(10043):488-497. Accompanied by Supplementary appendix available at: [http://dx.doi.org/10.1016/S0140-6736\(16\)30587-6](http://dx.doi.org/10.1016/S0140-6736(16)30587-6).
- Van Tine BA, Peterson P, Shahir A, et al. An analysis of efficacy and safety of olaratumab + doxorubicin or doxorubicin alone in patients with uterine leiomyosarcoma: A retrospective assessment of the phase 1b/2 study JGDG. Presented at the Society of Gynecologic Oncology - 48th Annual Meeting on Women's Cancer; National Harbor, MD; March 12-15, 2017.

We appreciate the Panel's thorough consideration of Lilly's request that Lartruvo™ (olaratumab) in combination with doxorubicin be added to the treatment options for patients with appropriate uterine sarcomas.

Please do not hesitate to contact us with any questions.

Sincerely,

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**References:**

1. Dabgoor A, Seddon B, Gerrand C, et al. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res*. 2016; 6:20. doi: [10.1186/s13569-016-0060-4](https://doi.org/10.1186/s13569-016-0060-4).
2. [Lartruvo \[package insert\]. Indianapolis, IN: Eli Lilly and Company; 2017.](#)
3. Ray-Coquard I, Rizzo E, Blay JY, et al. Impact of chemotherapy in uterine sarcoma (UtS): review of 13 clinical trials from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG) involving advanced/metastatic UtS compared to other soft tissue sarcoma (STS) patients treated with first line chemotherapy. *Gynecologic Oncology*. 2016; 142(1):95-101. doi: [10.1016/j.ygyno.2016.05.016](https://doi.org/10.1016/j.ygyno.2016.05.016).
4. Reichardt P. The treatment of uterine sarcomas. *Ann Oncol*. 2012(23 Suppl 10):x151-7. doi: [10.1093/annonc/mds359](https://doi.org/10.1093/annonc/mds359).
5. 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;388(10043):488-497. Accompanied by Supplementary appendix available at: [http://dx.doi.org/10.1016/S0140-6736\(16\)30587-6](http://dx.doi.org/10.1016/S0140-6736(16)30587-6).
6. Van Tine BA, Peterson P, Shahir A, et al. An analysis of efficacy and safety of olaratumab + doxorubicin or doxorubicin alone in patients with uterine leiomyosarcoma: A retrospective assessment of the phase 1b/2 study JGDG. Presented at the Society of Gynecologic Oncology - 48th Annual Meeting on Women's Cancer; National Harbor, MD; March 12-15, 2017.