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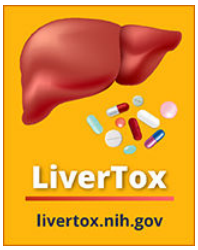


Trabectedin

Updated: November 22, 2022.

OVERVIEW

Introduction

Trabectedin is a natural product derived from the Caribbean sea squirt which has antineoplastic activity and is used to treat soft tissue sarcoma. Trabectedin therapy is associated with a high rate of transient serum enzyme elevations during treatment and with occasional instances of clinically apparent liver injury with jaundice.

Background

Trabectedin (tra bek' te din) is a novel antineoplastic agent initially derived from extracts of the Caribbean sea squirt, Ecteinascidia turbinata or mangrove tunicate. It was the first drug to be isolated from a sea animal. Trabectedin binds to the minor groove of DNA, allowing for alkylation of guanine and resulting in DNA damage. Biosynthesis of the active product allowed for clinical trials of trabectedin which demonstrated evidence of cytotoxic activity against soft tissue sarcomas. Trabectedin was approved for use in the United States in 2014 as therapy of advanced, refractory liposarcoma and leiomyosarcoma. Trabectedin is given intravenously and is available as 1 mg of lyophilized powder in single use vials under the brand name Yondelis. The typical dose is 1.5 mg/m^2 body surface area as a 24 hour infusion every 3 weeks. It is usually given after premedication with 20 mg of dexamethasone. Side effects are common and include bone marrow suppression, nausea, vomiting, diarrhea, anorexia, fatigue, peripheral edema, dyspnea, and headache. Serious adverse events include neutropenic sepsis, rhabdomyolysis, cardiomyopathy, capillary leak syndrome, and embryo-fetal toxicity. Lurbinectedin, a synthetic derivative of trabectedin with similar antineoplastic activity and adverse event profile, was approved for use in small cell lung cancer in 2020.

Hepatotoxicity

Elevations in serum aminotransferase levels arise in almost all patients treated with trabectedin and elevations above 5 times the upper limit of normal occur 20% to 50% of patients. Pretreatment with dexamethasone appears to decrease the degree and frequency of enzyme elevations. The elevations arise within 2 to 5 days of the intravenous infusion, rise to maximal levels between 5 and 9 days and generally fall to baseline values within 3 to 4 weeks. Minor elevations in serum alkaline phosphatase and bilirubin are also common. However, clinically apparent liver injury with jaundice from trabectedin is rare. On the other hand, patients with underlying liver disease appear to be at increased risk for septicemia and multiorgan failure, and monitoring of liver tests before and during therapy is recommended. The liver injury typically mimics acute decompensation of an underlying cirrhosis with modest elevations in serum enzymes and worsening jaundice and hepatic synthetic dysfunction. Immunoallergic and autoimmune features are uncommon. Fatalities are generally due to sepsis and multiorgan failure.

Likelihood score: C[HD] (probable cause of clinically apparent liver injury, generally in the setting of preexisting liver disease and use of high doses).

Mechanism of Injury

The transient serum aminotransferase elevations that occur with trabectedin therapy are most likely due to direct hepatotoxicity. Trabectedin is extensively metabolized by the hepatic cytochrome P450 system, predominantly CYP 3A4, and is susceptible to drug-drug interactions with agents that induce or inhibit CYP 3A activity.

Outcome and Management

The severity of liver injury from trabectedin ranges from mild elevations in liver enzymes to marked aminotransferase elevations to clinically apparent liver injury with jaundice and hepatic failure. Most severe cases occur in patients with preexisting liver disease. For these reasons, patients should be monitored with routine liver tests before and during therapy and therapy delayed or stopped if liver test abnormalities persist. In animal models, hepatotoxicity is lessened by pretreatment with dexamethasone and pretreatment with 20 mg of dexamethasone 30 minutes before each infusion is recommended.

Drug Class: Antineoplastic Agents, Alkylating Agents

Other Drugs in Same Class: Lurbinectedin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Trabectedin – Yondelis®

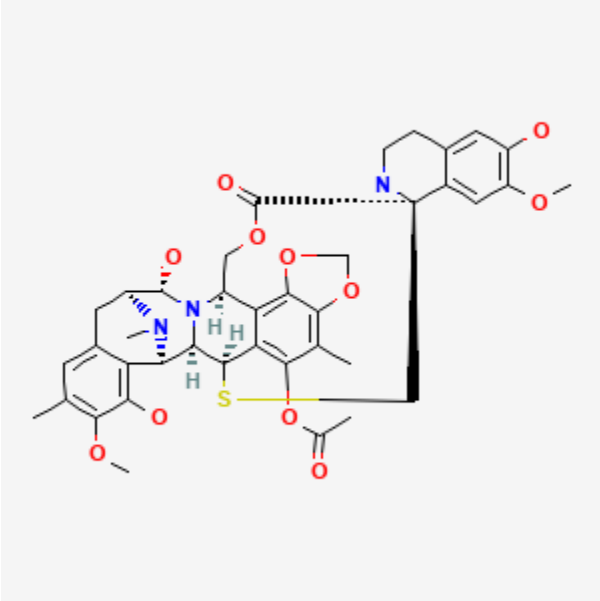
DRUG CLASS

Antineoplastic Agents, Alkylating Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Trabectedin	114899-77-3	C39-H43-N3-O11-S	

ANNOTATED BIBLIOGRAPHY

References updated: 22 November 2022

Zimmerman HJ. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999 before the availability of trabectedin).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 541-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; trabectedin is listed as causing serum enzyme elevations and rare instances of liver failure when given in high doses).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Trabectedin. Cytotoxic agents. Chemotherapy of neoplastic diseases. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1194.

(Textbook of pharmacology and therapeutics).

Brain EG. Safety and efficacy of ET-743: the French experience. Anticancer Drugs. 2002;13 Suppl 1:S11–4.

(Among 54 patients with advanced, refractory soft tissue sarcoma treated with trabectedin [1500 μg/m^2 intravenously every 3 weeks], 3 [6%] had a partial response, and side effects included asymptomatic and reversible neutropenia and aminotransferase elevations in 60% of patients and 2 cases of rhabdomyolysis).

van Kesteren Ch, de Vooght MMM, López-Lázaro L, Mathôt RA, Schellens JH, Jimeno JM, Beijnen JH. Yondelis (trabectedin, ET-743): the development of an anticancer agent of marine origin. Anticancer Drugs. 2003;14:487–502. PubMed PMID: 12960733.

(Review of the development, chemistry, mode of action and preclinical and clinical studies of trabectedin suggests that it acts by binding to the minor groove of DNA, thereby interfering with transcription factor binding to DNA and blocking transcription).

Yovine A, Riofrio M, Blay JY, Brain E, Alexandre J, Kahatt C, Taamma A, et al. Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol. 2004;22:890–9. PubMed PMID: 14990645.

(Among 54 patients with advanced, refractory soft tissue sarcoma treated with trabectedin [1-20 cycles], 6 had a partial or minor response, and side effects included ALT or AST elevations above 5 times ULN in 50% of patients with 2 treatment related deaths, one from rhabdomyolysis and one from febrile neutropenia which resulted in decompensation of a preexisting alcoholic cirrhosis).

Beumer JH, Schellens JH, Beijnen JH. Hepatotoxicity and metabolism of trabectedin: a literature review. Pharmacol Res. 2005;51:391–8. PubMed PMID: 15749453.

(Review of trabectedin hepatotoxicity in preclinical and clinical studies; mentions that hepatotoxicity is seen in mice, rats, dogs, and rhesus monkeys and is partially abrogated by dexamethasone pretreatment; the ALT elevations in humans start to rise 2-5 days after an infusion, reach at maximum at 5-9 days, and resolve within 4 weeks, the abnormalities often lessening with repeated cycles).

Le Cesne A, Blay JY, Judson I, Van Oosterom A, Verweij J, Radford J, Lorigan P, 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;23:576–84. PubMed PMID: 15659504.

(Among 104 patients with soft tissue or bone sarcoma treated with trabectedin [1500 mg/m^2 every 3 weeks], ALT elevations above 5 times ULN arose in 45%, bilirubin elevations in 42%, Alk P in 63% and neutropenia in 52%, while 4 patients died usually of multiorgan failure, but correlating best with preexisting liver abnormalities, particularly any elevation in Alk P).

Grosso F, Dileo P, Sanfilippo R, Stacchiotti S, Bertulli R, Piovesan C, Jimeno J, et al. Steroid premedication markedly reduces liver and bone marrow toxicity of trabectedin in advanced sarcoma. Eur J Cancer. 2006;42:1484–90. PubMed PMID: 16737808.

(Among 54 patients with advanced, refractory sarcomas treated with trabectedin, 31 did and 23 did not receive pretreatment with oral dexamethasone [4 mg twice daily for the 24 hours before infusions], and adverse events were less with pretreatment including aminotransferase elevations [above 5 times ULN] in 2% vs 34%, neutropenia in 2% vs 24% and thrombocytopenia in none vs 25%, while objective response rates and progression free survival appeared unaffected).

Krasner CN, McMeekin DS, Chan S, Braly PS, Renshaw FG, Kaye S, Provencher DM, et al. A Phase II study of trabectedin single agent in patients with recurrent ovarian cancer previously treated with platinum-based regimens. Br J Cancer. 2007;97:1618–24. PubMed PMID: 18000504.

(Among 147 women with recurrent ovarian carcinoma after platinum based therapy who were treated with trabectedin [0.58 mg/m^2 every week], ALT elevations occurred in 28% and were above 5 times ULN in 11%, but all were self-limited in course).

Demetri GD, Chawla SP, von Mehren M, Ritch P, Baker LH, Blay JY, Hande KR, et al. Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules. J Clin Oncol. 2009;27:4188–96. PubMed PMID: 19652065.

(Among 270 patients with advanced or metastatic, refractory soft tissue sarcoma treated with 1 of 2 regimens of trabectedin [weekly or every 3rd week], response rates were higher with every 3 week dosing as were adverse events including ALT elevations above 5 times ULN [45% vs 9%], but there were no instances of hepatic failure).

Pick AM, Nystrom KK. Fatal hepatic and renal toxicity as a complication of trabectedin therapy for radiation-induced sarcoma. J Oncol Pharm Pract. 2010;16:269–72. PubMed PMID: 20015930.

(79 year old man with sarcoma developed progressive renal and hepatic failure 1 week after a 2nd [every 3 weeks] intravenous infusion of trabectedin [bilirubin initially 2.4 and rising to 12 mg/dL, ALT 73 to 502 U/L, Alk P 473 U/L] and dying 3 weeks later [no autopsy]).

Fayette J, Boyle H, Chabaud S, Favier B, Engel C, Cassier P, Thiesse P, et al. Efficacy of trabectedin for advanced sarcomas in clinical trials versus compassionate use programs: analysis of 92 patients treated in a single institution. Anticancer Drugs. 2010;21:113–9. PubMed PMID: 19887935.

(Among 92 patients with advanced sarcoma treated with trabectedin [1.5 mg/m^2 every 3 weeks], adverse events included ALT or AST elevations above 5 times ULN in 37%, but no "toxic deaths" occurred).

Le Cesne A, Yovine A, Blay JY, Delaloge S, Maki RG, Misset JL, et al. A retrospective pooled analysis of trabectedin safety in 1,132 patients with solid tumors treated in phase II clinical trials. Invest New Drugs. 2012;30:1193–202. PubMed PMID: 21484250.

(Among 1132 patients treated with trabectedin in various regimens in 19 trials, common side effects including nausea [65%], fatigue [58%], neutropenia [69%], ALT elevations [91%], ALT elevations above 5 times ULN [44%] and bilirubin elevations [21%]).

Baruchel S, Pappo A, Krailo M, Baker KS, Wu B, Villaluna D, Lee-Scott 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;48:579–85. PubMed PMID: 22088484.

(Among 50 children with recurrent sarcomas who were treated with trabectedin [1.3 or 1.5 mg/m^2 every 3 weeks], only one patient had a partial response and 3 others had stable disease, while adverse events were common including ALT elevations above 5 times ULN in 32%, but all were asymptomatic and resolved without dose adjustment).

Monk BJ, Blessing JA, Street DG, Muller CY, Burke JJ, Hensley ML. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a gynecologic oncology group study. Gynecol Oncol. 2012;124:48–52. PubMed PMID: 21996263.

(Among 20 women with advanced uterine leiomyosarcoma treated with 2-29 cycles of trabectedin, the progression free survival rate was 5.8 months and adverse events included ALT elevations in 55% which were above 5 times ULN in 10%).

Laurenty AP, Thomas F, Chatelut E, Bétrian S, Le Guellec C, Hennebelle I, Le Guellec S, et al. Irreversible hepatotoxicity after administration of trabectedin to a pleiomorphic sarcoma patient with a rare ABCC2 polymorphism: a case report. Pharmacogenomics. 2013;14:1389–96. PubMed PMID: 24024892.

(66 year old man with pleiomorphic sarcoma developed liver injury 3 weeks after a second infusion of trabectedin [bilirubin 0.5 mg/dL, ALT 7 times ULN, Alk P 5 times ULN], with subsequent slow rise of bilirubin to 9.5 mg/dL and persistently high Alk P], liver biopsy showing cholangitis and jaundice persisting until his death from metastatic sarcoma 10 months later).

Ploner F, Lamm W, Schur S, Eisterer W, Kühr T, Lindorfer A, Tinchon C, et al. The Austrian experience with trabectedin in non-selected patients with metastatic soft tissue sarcoma (STS). J Cancer Res Clin Oncol. 2013;139:1337–42. PubMed PMID: 23666164.

(Among 101 adult Austrian patients with metastatic soft tissue sarcoma treated with trabectedin, the extent and severity of toxicity "were low and manageable", including ALT elevations in 25% with values above 5 times ULN in 3%).

Samuels BL, Chawla S, Patel S, von Mehren M, Hamm J, Kaiser PE, Schuetze S, et al. Clinical outcomes and safety with trabectedin therapy in patients with advanced soft tissue sarcomas following failure of prior chemotherapy: results of a worldwide expanded access program study. Ann Oncol. 2013;24:1703–9. PubMed PMID: 23385197.

(Among 1895 adults with advanced soft tissue sarcomas treated with trabectedin [1.5 mg/m^2 every 3 weeks], best results were achieved in leiomyosarcoma and liposarcoma, while ALT elevations arose in 19% and were above 5 times ULN in 11%; no mention of clinically apparent liver injury, although 23 patients [1%] died of suspected drug related complications).

Vincenzi B, Stumbo L, Maltese G, Cerbone L, Spalato Ceruso M, Badalamenti G, Santini D, et al. Lack of correlation between liver tests abnormalities and trabectedin efficacy in the treatment of soft tissue sarcoma: a retrospective study. Sci Rep. 2015;5:12077. PubMed PMID: 26235506.

(Among 113 patients with advanced sarcoma treated with trabectedin in 3 Italian oncology centers, 40% developed ALT or AST elevations above 5 times ULN, and retrospective analyses found no associations between ALT elevations and tumor response or progression free or overall survival).

Bui-Nguyen B, Butrynski JE, Penel N, Blay JY, Isambert N, Milhem M, Kerst JM, et al. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC/STBSG) and the Sarcoma Alliance for Research through Collaboration (SARC). 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;51:1312–20. PubMed PMID: 25912752.

(Among 133 patients with soft tissue sarcoma treated with trabectedin [as 3 or 24 hour infusions] vs doxorubicin [standard therapy], median progression free survival was less with trabectedin [2.8 and 3.1 vs 5.5 months] and side effects were more common, requiring discontinuation in 15% and 20% vs 3% and with ALT elevations above 5 times ULN in 67% and 49% vs 2.5%]).

Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka 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;16:406–16. PubMed PMID: 25795406.

(Among 76 Japanese patients with advanced sarcoma treated with trabectedin [1.2 mg/m^2 every 3 weeks] vs supportive case, median progression-free survival was 5.6 vs 0.9 months and adverse events included nausea [89% vs 8%], anorexia [53% vs 5%], neutropenia [83% vs 0%] and elevated ALT [67% vs 0%]).

Schack LH, Mouritsen LS, Elowsson C, Krarup-Hansen A, Safwat A. The Danish experience with trabectedin treatment for metastatic sarcoma: Importance of hyponatremia. Acta Oncol. 2015;54:34–40. PubMed PMID: 25263179.

(Among 117 patients with metastatic sarcoma treated with trabectedin in 3 oncology centers in Denmark, adverse events were frequent including 22% with "elevated liver enzymes" and there were 3 deaths, all related to severe infections).

Martin-Broto J, Pousa AL, de Las Peñas R, García Del Muro X, Gutierrez A, Martinez-Trufero J, Cruz J, et al. Randomized phase II study of trabectedin and doxorubicin compared with doxorubicin alone as first-line treatment in patients with advanced soft tissue sarcomas: a Spanish group for research on sarcoma study. J Clin Oncol. 2016;34:2294–302. PubMed PMID: 27185843.

(Among 115 patients with soft tissue sarcoma treated with doxorubicin with or without trabectedin [1.1 mg/m^2 every 3 weeks], progression-free survival was minimally longer with the combination [5.7 vs 5.5 months] and adverse events were more frequent including ALT elevations [71% vs 14%] and those greater than 5 times ULN [19% vs none]).

In brief: Two drugs for soft-tissue sarcoma. Med Lett Drugs Ther. 2016;58(1494):e62. PubMed PMID: 27148925.

(Concise summary of the mechanism of action, efficacy and safety of trabectedin and eribulin shortly after their approval in the US as therapy of soft tissue sarcoma; mentions that trabectedin therapy is associated with serum aminotransferase elevations).

Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, Milhem M, 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;34:786–93. PubMed PMID: 26371143.

(Among 518 patients with metastatic lipo- or leiomyosarcoma treated with trabectedin vs dacarbazine, progression-free survival was longer with trabectedin [4.2 vs 1.5 months], but overall survival similar [12.4 vs 12.9 months], while ALT elevations arose in 45% vs 6% and were above 5 times ULN in 26% vs 1%).

Angarita FA, Cannell AJ, Abdul Razak AR, Dickson BC, Blackstein ME. Trabectedin for inoperable or recurrent soft tissue sarcoma in adult patients: a retrospective cohort study. BMC Cancer. 2016;16:30. PubMed PMID: 26786213.

(Among 77 adults with advanced soft tissue sarcoma treated with trabectedin, elevations in liver enzymes occurred in 26% of subjects including values above 5 times ULN in 19%, but there were no serious liver related adverse events and two deaths attributed to therapy were both due to rhabdomyolysis).

Barone A, Chi DC, Theoret MR, Chen H, He K, Kufrin D, Helms WS, et al. FDA approval summary: trabectedin for unresectable or metastatic liposarcoma or leiomyosarcoma following an anthracycline-containing regimen. Clin Cancer Res. 2017;23:7448–7453. PubMed PMID: 28774898.

(FDA description of the clinical results of trabectedin therapy that led to its approval for soft tissue sarcomas in 2015, which was based upon a single, randomized active controlled trial in 518 patients in which median progression-free survival was 4.2 months with trabectedin vs 1.5 months with dacarbazine; serious adverse events included anaphylaxis, neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy and local tissue necrosis from extravasation during intravenous therapy).

Kobayashi H, Iwata S, Wakamatsu T, Hayakawa K, Yonemoto T, Wasa J, Oka H, et al. Efficacy and safety of trabectedin for patients with unresectable and relapsed soft-tissue sarcoma in Japan: A Japanese Musculoskeletal Oncology Group study. Cancer. 2020;126:1253–1263. PubMed PMID: 31825533.

(Among 140 Japanese patients with soft tissue sarcomas treated with trabectedin [1.2 mg/m^2 every 3 weeks] and enrolled in a postmarketing study of safety, 96% had an adverse event, and ALT or AST elevations arose in 89 [64%] which were above 5 times ULN in 53 [38%], but there were no deaths from liver failure).

Palmerini E, Sanfilippo R, Grignani G, Buonadonna A, Romanini A, Badalamenti G, Ferraresi V, et al. Trabectedin for patients with advanced soft tissue sarcoma: a non-interventional, retrospective, multicenter study of the Italian Sarcoma Group. Cancers (Basel). 2021;13:1053. PubMed PMID: 33801399.

(Among 512 patients with advanced soft tissue sarcoma treated with trabectedin in 20 Italian centers, median survival was 21.6 months and adverse events included bone marrow toxicity in 61% and ALT or AST elevations in 22%, but there were no deaths attributed to therapy and no mention of clinically apparent liver injury).

Cortinovis D, Grosso F, Carlucci L, Zucali PA, Pasello G, Tiseo M, Sperandi F, et al; ATREUS investigators. Trabectedin in malignant pleural mesothelioma: results from the multicentre, single arm, phase II ATREUS Study. Clin Lung Cancer. 2021;22:361–370.e3. PubMed PMID: 32732073.

(Among 132 patients with malignant pleural mesothelioma treated with trabectedin [1.1 or 1.3 mg/m^2 intravenously every 3 weeks], the clinical efficacy was described as "modest" and "at the expense of relevant liver toxicity", with ALT or AST elevations above 5 times ULN arising in 59% of patients and contributing to death from multiorgan failure in one).

Le Cesne A, Blay JY, Cupissol D, Italiano A, Delcambre C, Penel N, Isambert N, et al. A randomized phase III trial comparing trabectedin to best supportive care in patients with pre-treated soft tissue sarcoma: T-SAR, a French Sarcoma Group trial. Ann Oncol. 2021;32:1034–1044. PubMed PMID: 33932507.

(Among 103 patients with advanced soft tissue sarcoma treated with trabectedin or standard therapy in 16 French centers, the median progression-free survival was longer with trabectedin [3.1 vs 1. 5 months], and 33% of patients developed ALT or AST elevations above 5 times ULN, although there were no deaths due to liver injury and no mention of clinically apparent liver injury).

Lorusso D, Pignata S, Tamberi S, Mangili G, Bologna A, Nicoloso MS, Giolitto S, et al. Efficacy and safety of trabectedin for the treatment of advanced uterine or ovarian carcinosarcoma: Results of a phase II multicenter clinical trial (MITO-26). Gynecol Oncol. 2022:S0090-8258(22)01851-0. Epub ahead of print.

(Among 45 women with advanced refractory ovarian or uterine carcinoma treated with trabectedin [1.3 mg/m^2 every 3 weeks], the objective response rate was only 12% and ALT or AST elevations above 3 times ULN arose in 14%, none rising above 5 times ULN and all ultimately resolving).

Chaigneau L, Jary M, Nerich V, Hervieu A, Aubry S, Charon Barra C, Meynard G, et al. Real-world experience of efficacy and safety of trabectedin in patients with soft tissue sarcoma: a bicentric retrospective analysis. Oncology. 2022 Oct 25. Epub ahead of print.

(Among 126 patients with advanced soft tissue sarcoma treated with trabectedin in 2 French centers between 2002 and 2019, overall median survival was 12.3 months with disease control in 46% of patients, while "adverse events were manageable", GGT elevations arising in 83% [above 5 times ULN in 27%], and with 4 deaths due to therapy, 3 with rhabdomyolysis and 1 with febrile neutropenia).