Protocol Registration Receipt
03/19/2010

Efficacy and Safety Assessment of Oral LBH589 in Adult Patients With Advanced STM After Pre-treatment Failure (ESTIM-LBH)

This study is currently recruiting participants.
Verified by Centre Leon Berard, November 2009

Sponsor:	Centre Leon Berard
Collaborators:	Centre Leon Berard
Information provided by:	Centre Leon Berard
ClinicalTrials.gov Identifier:	

Purpose

The purpose of this study is to assess efficacy and safety of LBH589 - Panobinostat®, a potent HDACi, in patients with advanced STS who experiment disease progression after or during first-line chemotherapy. The rational is based on the observation of activity of deacetylase inhibitor (DACi) in several pre-clinical models of STS including Synovial sarcoma and Ewing sarcoma.

Condition	Intervention	Phase
Soft Tissue Sarcoma	Drug: 40 mg MWF	Phase 2

Study Type: Interventional
Study Design: Treatment, Single Group Assignment, Open Label, Non-Randomized, Active Control, Safety/Efficacy Study
Official Title: Efficacy and Safety Assessment of Oral LBH589 in Adult Patients With Advanced Soft Tissue Sarcoma After Pre-treatment Failure: an Open-label, Multicenter Phase II Study

Further study details as provided by Centre Leon Berard:

Primary Outcome Measure:

- To estimate the 3-months non progression rate associated with LBH 589. [Time Frame: by CT scan or MRI 6 weeks after inclusion, 3 months after inclusion and all the 3 months throughout the study according to the RECIST criteria and validated by a central review committee] [Designated as safety issue: No]

Secondary Outcome Measures:

- To estimate the progression-free survival (PFS) [Time Frame: by CT scan or MRI 6 weeks after inclusion, 3 months after inclusion and all the 3 months throughout the study according to the RECIST criteria and validated by a central review committee .] [Designated as safety issue: No]
- the time to disease progression (TTP) [Time Frame: by CT scan or MRI 6 weeks after inclusion, 3 months after inclusion and all the 3 months throughout the study according to the RECIST criteria and validated by a central review committee] [Designated as safety issue: No]
- the best objective response rate associated with LBH589 [Time Frame: by CT scan or MRI 6 weeks after inclusion, 3 months after inclusion and all the 3 months througout the study according to the RECIST criteria and validated by a central review committee] [Designated as safety issue: No]
- safety profile associated with 40 mg of LBH589 dosed 3 days per week every week [Time Frame: all the 4 weeks throughout the study by clinical examination] [Designated as safety issue: No]
- increases in acetylation and duration of increased acetylation in histones H3 and H4, and tubulin in Peripheral Blood Mononuclear Cells (PBMC) [Time Frame: day 1 and day 22] [Designated as safety issue: No]
- assess transcriptional activation of genes including p21 in PBMC, [Time Frame: day 1, day 32, day 61 and at the and of the study.] [Designated as safety issue: No]
- changes in Fetal Hemoglobin (HbF) levels in red blood cells, [Time Frame: Throughout the study] [Designated as safety issue: No]
- changes in markers of apoptosis (M30 and M65) in serum samples. [Time Frame: Day 1,day 8,day 15, day 32, day 61] [Designated as safety issue: No]
- To assess the plasmatic rate of the new oral formulation of LBH589 [Time Frame: day 1 and day 22] [Designated as safety issue: No]
- To assess the role of p53 mutational status in predicting the efficacy of LBH589 [Time Frame: at the begin of the study and at day 32] [Designated as safety issue: No]

Estimated Enrollment: 50
Study Start Date: January 2010
Estimated Study Completion Date: January 2013
Estimated Primary Completion Date: January 2012

Number of arms: 1
Intervention Details:

Drug: 40 mg MWF

40mg of LBH589, orally administered on Monday, Wednesday and Friday (MWF) on a weekly schedule, until tumor progression or unacceptable toxicity.

Despite surgical excision and radiation therapy, approximately 50% of patients treated for localised STS will experience local or distant relapse (52).

4.1. Recurrent STS : current therapeutic strategies Although some patients may be salvaged with surgery, chemotherapy using doxorubicin-based regimens is in most cases indicated for patients with recurrent STS.

Progression-free survival (PFS) is in most cases less than or equal to 6 months (53). Most patients die of their disease within 12-15 months following the diagnosis of advanced disease. Doxorubicin is considered as the standard of care in the first line setting for patients with locally advanced unresectable or metastatic STS. However, only 15-25% of these patients exhibit objective response following this chemotherapy while 30-35% experiment rapid disease progression. Doxorubicin-based combinations have resulted in an inconsistent increase in response rate but no survival advantage versus single-agent doxorubicin. After doxorubicin-based regimens failure, most agents, including other agents approved for the treatment of STS such as dacarbazine, ifosfamide and trabectedin, have shown very low response rates and short PFS. The only approved agent in this setting is trabectedin, which has shown prolonged stabilization in approximately 20% of patients at 6 months in several phase II trials (54;55). Gemcitabine-docetaxel combination, although not approved for the treatment of STS has shown interesting response rates in leiomyosarcomas, as well as other STS subtypes (56;57). Mechanisms of chemoresistance are poorly understood.

4.2. Place of LBH589 LBH589 is postulated to have activity in sarcomas by being able to arrest gene transcription through the inhibition of HDAC, to cause the misfolding of important proteins for sarcoma biology such as fusion proteins or overexpressed genes (HDM2, cdk4, AKT…) via the disruption of HSP90 functioning (58). Some mechanisms similar to leukemia-associated fusion proteins, which have been shown to recruit HDAC to repress hematopoietic differentiation, might be involved by some translocation-associated sarcomas. The SYT portion of the synovial sarcoma oncoprotein SYT-SSX interacts with trithorax-group proteins and binds directly to the mSin3A HDAC component (59). SSX associates with polycomb-group proteins, which involve HDAC activity to mediate transcriptional repression; thus, aberrant epigenetic changes in gene expression seem to be a central effect of the fusion oncoprotein in this disease (60). HDAC inhibitors have been effective against both synovial sarcoma and Ewing sarcoma in preclinical studies (61-63). Evidence has also been presented for growth inhibition and induction of differentiation in clear cell sarcoma (Nielsen TO, Vancouver Coastal Health Research Institute, Vancouver, Canada, unpublished data) and chondrosarcoma (64) by HDACi.

Data from the phase I study involving patients with advanced solid tumors indicate that the MWF every week schedule of LBH589 is pharmacodynamically and clinically active. Histone acetylation was detected in peripheral blood cells for up to 72 hours (the maximum duration between doses on the MWF every week schedule) in 50% of patients at the 20 mg and 30 mg doses and CR and PR were observed in two and three patients respectively, with cutaneous T-cell lymphoma (65). Grade 3 fatigue was the dose-limiting toxicity (DLT) in 2 patients treated at the 40 mg level and 1 patient treated at the 60 mg level. The 40 mg level seem to be tolerable and is felt to be the most likely to have activity in solid tumors.

After first-line chemotherapy failure, efficacy of therapeutic alternatives is limited. The purpose of this trial is therefore to investigate the efficacy, safety and tolerability of 40 mg of LBH589 given orally on a twice a week.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

INCLUSION CRITERIA

- Age ≥ 18 years.
- Histologically proven advanced metastatic or unresectable soft tissue sarcoma, excluding osteosarcoma.
- Prior treatment with a doxorubicin containing regimen whether in the adjuvant setting or for metastatic/advanced disease. If doxorubicin was given as adjuvant therapy patient may be included if

relapse occurs within a year of adjuvant therapy. If relapse occurs more than one year after the completion of adjuvant therapy, the patient must have received one prior regimen for metastatic disease. Patient may have received one or more previous line of therapy. Patients with sex cord tumors may be included after prior treatment with a platinum containing regimen (pretreatment with a doxorubicin containing regimen is not required for this patients subgroup).

- Patient has at least one site of measurable nodal disease at baseline ≥ 2.0 cm in the longest transverse diameter and clearly measurable in at least two perpendicular dimensions, as determined by CT scan (MRI is allowed only if CT scan can not be performed).
- ECOG performance status (PS) ≤ 2.
- Adequate haematological, liver and renal function:
    - Absolute Neutrophil Count (ANC) ≥ 1.5 G/L,
    - Hemoglobin ≥ 9 g/dL,
    - Platelets ≥ 100 G/L,
    - Total calcium (corrected for serum albumin) ≥ lower limit of normal (LLN) or correctable with supplements,
    - Magnesium ≥ LLN or correctable with supplements,
    - Potassium ≥ LLN or correctable with supplements,
    - Phosphorus ≥ LLN or correctable with supplements,
    - Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (or ≤ 5.0 x ULN if liver metastasis are present),
    - Serum bilirubin ≤ 1.5 x ULN,
    - Serum creatinine ≤ 1.5 x ULN,
    - If the serum creatinine is ≥ 1.5 x ULN, then a 24-hour creatinine clearance must be conducted and the result must be ≥ 50 mL/min.
- Clinical euthyroidy (patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism).
- Ability to swallow capsules or tablets.
- Life expectancy ≥ 12 weeks.
- Mandatory affiliation with health security insurance.
- Signed written informed consent.

EXCLUSION CRITERIA

- Prior treatment with any HDAC or HSP90 inhibitor drug.
- Unresolved toxicities (≥ Grade 1) from prior therapy that would, in the opinion of the investigator, compromise patient safety.
- Any of the following concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study:
    - Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
        - Left ventricular systolic function (LVEF) determined by MUGA scan or echocardiogram < center normal value,
        - Complete left bundle branch block,
        - Obligate use of a cardiac pacemaker,
        - Congenital long QT syndrome,
        - History or presence of ventricular tachyarrhythmia,

- Presence of unstable atrial fibrillation (ventricular response > 100bpm),
- Clinically significant resting bradycardia (< 50 bpm),
- Mean corrected QT interval (QTcF - n ≥ 3) ≥ 450 msec on screening ECG,
- Right bundle branch block + left anterior hemiblock (bifasicular block),
- Angina pectoris ≤ 3 months prior to starting study drug,
- Acute myocardial infarction (MI) ≤ 3 months prior to starting study drug,
- History or presence of acute coronary syndrome,
- Other clinically significant heart disease (e.g.: Congestive heart failure (CHF), uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen),

- Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of LBH589 (e.g.: ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or extensive small bowel resection),
- Other concurrent severe and/or uncontrolled medical conditions (e.g.: uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease) that could cause unacceptable safety risks or compromise compliance with the protocol.

- Current treatment with any of the medications listed in appendix 04, if the treatment cannot be discontinued or switched to a different medication prior to starting study drug. The medications listed in appendix 04 have a relative risk of prolonging the QT interval, or inducing Torsades de Pointes, or inhibit CYP3A4/5.
- Major surgery ≤ 2 weeks prior starting study drug or who have not recovered from side effects of such therapy.
- History of brain metastases.
- Absence of at least one metastatic lesion greater than or equal to 2cm on pretreatment CT scan or other radiographic imaging as defined in RECIST criteria (appendix 02).
- Systemic treatment with any anti-cancer drug, including any investigational drug that is administered on an intermittent schedule if the last dose has not been administered ≥ 4 weeks ago, or if the patient has not recovered from any ongoing toxicity prior to study enrolment.
- Systemic treatment with any anti-cancer drug, including investigational drug that is administered on a chronic dosing schedule (e.g.: daily dosing, every-other-day dosing, MWF weekly) if ≤ 5 half-lives elapsed since the last dose, or if the patient has not recovered from any ongoing toxicity prior to study enrolment.
- Women who are pregnant or breast feeding.
- Women of childbearing potential (WCBP) are excluded unless they have a negative serum pregnancy test ≤ 48 hours prior starting study treatment. All sexually active WCBP and male patients are excluded unless they agree to use adequate contraceptive methods (injectable or implantable hormonal contraceptive, tubal ligation, intra-uterine device, barrier contraceptive with spermacide, or vasectomized partner) throughout the study. Since the potential of LBH589 to induce CYP3A4 is unknown, patients who are using oral contraceptives should use another effective method of contraception.
- Current immunosuppressive syndrome.
- History of another malignancy that is currently clinically significant or currently requires active intervention.
- Refusal or inability to comply with the protocol or follow the instructions given to them by the clinic staff.

Contacts and Locations

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More Information

Publications:

Herman JG, Latif F, Weng Y, Lerman MI, Zbar B, Liu S, Samid D, Duan DS, Gnarra JR, Linehan WM, et al. Silencing of the VHL tumor-suppressor gene by DNA methylation in renal carcinoma. Proc Natl Acad Sci U S A. 1994 Oct 11;91(21):9700-4.

Szyf M. DNA methylation properties: consequences for pharmacology. Trends Pharmacol Sci. 1994 Jul;15(7):233-8. Review.

Herman JG, Merlo A, Mao L, Lapidus RG, Issa JP, Davidson NE, Sidransky D, Baylin SB. Inactivation of the CDKN2/p16/MTS1 gene is frequently associated with aberrant DNA methylation in all common human cancers. Cancer Res. 1995 Oct 15;55(20):4525-30.

Merlo A, Herman JG, Mao L, Lee DJ, Gabrielson E, Burger PC, Baylin SB, Sidransky D. 5' CpG island methylation is associated with transcriptional silencing of the tumour suppressor p16/CDKN2/MTS1 in human cancers. Nat Med. 1995 Jul;1(7):686-92.

Herman JG, Jen J, Merlo A, Baylin SB. Hypermethylation-associated inactivation indicates a tumor suppressor role for p15INK4B. Cancer Res. 1996 Feb 15;56(4):722-7.

Herman JG, Umar A, Polyak K, Graff JR, Ahuja N, Issa JP, Markowitz S, Willson JK, Hamilton SR, Kinzler KW, Kane MF, Kolodner RD, Vogelstein B, Kunkel TA, Baylin SB. Incidence and functional consequences of hMLH1 promoter hypermethylation in colorectal carcinoma. Proc Natl Acad Sci U S A. 1998 Jun 9;95(12):6870-5.

Cameron EE, Baylin SB, Herman JG. p15(INK4B) CpG island methylation in primary acute leukemia is heterogeneous and suggests density as a critical factor for transcriptional silencing. Blood. 1999 Oct 1;94(7):2445-51.

Gelmetti V, Zhang J, Fanelli M, Minucci S, Pelicci PG, Lazar MA. Aberrant recruitment of the nuclear receptor corepressor-histone deacetylase complex by the acute myeloid leukemia fusion partner ETO. Mol Cell Biol. 1998 Dec;18(12):7185-91.

Grignani F, De Matteis S, Nervi C, Tomassoni L, Gelmetti V, Cioce M, Fanelli M, Ruthardt M, Ferrara FF, Zamir I, Seiser C, Grignani F, Lazar MA, Minucci S, Pelicci PG. Fusion proteins of the retinoic acid receptor-alpha recruit histone deacetylase in promyelocytic leukaemia. Nature. 1998 Feb 19;391(6669):815-8.

Lin RJ, Nagy L, Inoue S, Shao W, Miller WH Jr, Evans RM. Role of the histone deacetylase complex in acute promyelocytic leukaemia. Nature. 1998 Feb 19;391(6669):811-4.

Redner RL, Wang J, Liu JM. Chromatin remodeling and leukemia: new therapeutic paradigms. Blood. 1999 Jul 15;94(2):417-28. Review. No abstract available.

Yoshida M, Nomura S, Beppu T. Effects of trichostatins on differentiation of murine erythroleukemia cells. Cancer Res. 1987 Jul 15;47(14):3688-91.

Yoshida M, Beppu T. Reversible arrest of proliferation of rat 3Y1 fibroblasts in both the G1 and G2 phases by trichostatin A. Exp Cell Res. 1988 Jul;177(1):122-31.

Itazaki H, Nagashima K, Sugita K, Yoshida H, Kawamura Y, Yasuda Y, Matsumoto K, Ishii K, Uotani N, Nakai H, et al. Isolation and structural elucidation of new cyclotetrapeptides, trapoxins A and B, having detransformation activities as antitumor agents. J Antibiot (Tokyo). 1990 Dec;43(12):1524-32.

Sugita K, Koizumi K, Yoshida H. Morphological reversion of sis-transformed NIH3T3 cells by trichostatin A. Cancer Res. 1992 Jan 1;52(1):168-72.

Hoshikawa Y, Kwon HJ, Yoshida M, Horinouchi S, Beppu T. Trichostatin A induces morphological changes and gelsolin expression by inhibiting histone deacetylase in human carcinoma cell lines. Exp Cell Res. 1994 Sep;214(1):189-97.

Medina V, Edmonds B, Young GP, James R, Appleton S, Zalewski PD. Induction of caspase-3 protease activity and apoptosis by butyrate and trichostatin A (inhibitors of histone deacetylase): dependence on protein synthesis and synergy with a mitochondrial/cytochrome c-dependent pathway. Cancer Res. 1997 Sep 1;57(17):3697-707.

Biggs JR, Kudlow JE, Kraft AS. The role of the transcription factor Sp1 in regulating the expression of the WAF1/CIP1 gene in U937 leukemic cells. J Biol Chem. 1996 Jan 12;271(2):901-6.

Nakano K, Mizuno T, Sowa Y, Orita T, Yoshino T, Okuyama Y, Fujita T, Ohtani-Fujita N, Matsukawa Y, Tokino T, Yamagishi H, Oka T, Nomura H, Sakai T. Butyrate activates the WAF1/Cip1 gene promoter through Sp1 sites in a p53-negative human colon cancer cell line. J Biol Chem. 1997 Aug 29;272(35):22199-206.

Sowa Y, Orita T, Minamikawa S, Nakano K, Mizuno T, Nomura H, Sakai T. Histone deacetylase inhibitor activates the WAF1/Cip1 gene promoter through the Sp1 sites. Biochem Biophys Res Commun. 1997 Dec 8;241(1):142-50.

Sambucetti LC, Fischer DD, Zabludoff S, Kwon PO, Chamberlin H, Trogani N, Xu H, Cohen D. Histone deacetylase inhibition selectively alters the activity and expression of cell cycle proteins leading to specific

chromatin acetylation and antiproliferative effects. J Biol Chem. 1999 Dec 3;274(49):34940-7.

Yu X, Guo ZS, Marcu MG, Neckers L, Nguyen DM, Chen GA, Schrump DS. Modulation of p53, ErbB1, ErbB2, and Raf-1 expression in lung cancer cells by depsipeptide FR901228. J Natl Cancer Inst. 2002 Apr 3;94(7):504-13.

Yu X, Guo ZS, Marcu MG, Neckers L, Nguyen DM, Chen GA, Schrump DS. Modulation of p53, ErbB1, ErbB2, and Raf-1 expression in lung cancer cells by depsipeptide FR901228. J Natl Cancer Inst. 2002 Apr 3;94(7):504-13.

Nimmanapalli R, Fuino L, Bali P, Gasparetto M, Glozak M, Tao J, Moscinski L, Smith C, Wu J, Jove R, Atadja P, Bhalla K. Histone deacetylase inhibitor LAQ824 both lowers expression and promotes proteasomal degradation of Bcr-Abl and induces apoptosis of imatinib mesylate-sensitive or -refractory chronic myelogenous leukemia-blast crisis cells. Cancer Res. 2003 Aug 15;63(16):5126-35.

Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. Nat Rev Cancer. 2005 Oct;5(10):761-72. Review.

Blagosklonny MV, Trostel S, Kayastha G, Demidenko ZN, Vassilev LT, Romanova LY, Bates S, Fojo T. Depletion of mutant p53 and cytotoxicity of histone deacetylase inhibitors. Cancer Res. 2005 Aug 15;65(16):7386-92.

Warrell RP Jr, He LZ, Richon V, Calleja E, Pandolfi PP. Therapeutic targeting of transcription in acute promyelocytic leukemia by use of an inhibitor of histone deacetylase. J Natl Cancer Inst. 1998 Nov 4;90(21):1621-5.

O'Connor OA, Heaney ML, Schwartz L, Richardson S, Willim R, MacGregor-Cortelli B, Curly T, Moskowitz C, Portlock C, Horwitz S, Zelenetz AD, Frankel S, Richon V, Marks P, Kelly WK. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. J Clin Oncol. 2006 Jan 1;24(1):166-73. Epub 2005 Dec 5.

Saito A, Yamashita T, Mariko Y, Nosaka Y, Tsuchiya K, Ando T, Suzuki T, Tsuruo T, Nakanishi O. A synthetic inhibitor of histone deacetylase, MS-27-275, with marked in vivo antitumor activity against human tumors. Proc Natl Acad Sci U S A. 1999 Apr 13;96(8):4592-7.

Piekarz RL, Robey R, Sandor V, Bakke S, Wilson WH, Dahmoush L, Kingma DM, Turner ML, Altemus R, Bates SE. Inhibitor of histone deacetylation, depsipeptide (FR901228), in the treatment of peripheral and cutaneous T-cell lymphoma: a case report. Blood. 2001 Nov 1;98(9):2865-8.

Parker C, Molife R, Karavasilis V, Reid A, Patterson SG, Riggs C et al. Romidepsin (FK228), a histone deacetylase inhibitor: Final results of a phase II study in metastatic hormone refractory prostate cancer (HRPC). J Clin Oncol (Meeting Abstracts) 2007;25:15507.

Rathkopf, D. E., Wong, B. Y., Ross, R. W., George, D. J., Picus, J., Sawyers, C. L., Chen, Y., Tanaka, E., Yang, W., Culver, K. W., and Scher, H. I. A phase I dose escalation study of oral panobinostat (LBH589) alone and in combination with IV docetaxel (Doc) and oral prednisone in castration-resistant prostate cancer (CRPC). 2008 Genitourinary Cancer Sympsium , abst. 171. 2008.

Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005 Aug 18;353(7):701-11. Review. No abstract available.

Helman LJ, Meltzer P. Mechanisms of sarcoma development. Nat Rev Cancer. 2003 Sep;3(9):685-94. Review.

Coindre JM, Terrier P, Bui NB, Bonichon F, Collin F, Le Doussal V, Mandard AM, Vilain MO, Jacquemier J, Duplay H, Sastre X, Barlier C, Henry-Amar M, Macé-Lesech J, Contesso G. Prognostic factors in adult patients with locally controlled soft tissue sarcoma. A study of 546 patients from the French Federation of Cancer Centers Sarcoma Group. J Clin Oncol. 1996 Mar;14(3):869-77.

Guillou L, Coindre JM, Bonichon F, Nguyen BB, Terrier P, Collin F, Vilain MO, Mandard AM, Le Doussal V, Leroux A, Jacquemier J, Duplay H, Sastre-Garau X, Costa J. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol. 1997 Jan;15(1):350-62.

Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchère D, Sastre X, Vilain MO, Bonichon F, N'Guyen Bui B. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer. 2001 May 15;91(10):1914-26.

Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchère D, Sastre X, Vilain MO, Bonichon F, N'Guyen Bui B. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer. 2001 May 15;91(10):1914-26.

Jebsen NL, Trovik CS, Bauer HC, Rydholm A, Monge OR, Hall KS et al. Radiotherapy to Improve Local Control Regardless of Surgical Margin and Malignancy Grade in Extremity and Trunk Wall Soft Tissue Sarcoma: A Scandinavian Sarcoma Group Study. Int.J.Radiat.Oncol.Biol.Phys. 2008;..

[No authors listed] Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997 Dec 6;350(9092):1647-54.

Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005 Aug 18;353(7):701-11. Review. No abstract available.

Woll PJ, Van GM, Hohenberger P, Le CA, Gronchi A, Hoekstra HJ et al. Adjuvant chemotherapy (CT) with doxorubicin and ifosfamide in resected soft tissue sarcoma (STS): Interim analysis of a randomised phase III trial. ASCO Meeting Abstracts 2007;25:10008.

Clark MA, Fisher C, Judson I, Thomas JM. Soft-tissue sarcomas in adults. N Engl J Med. 2005 Aug 18;353(7):701-11. Review. No abstract available.

[No authors listed] Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997 Dec 6;350(9092):1647-54.

Edmonson JH, Ryan LM, Blum RH, Brooks JS, Shiraki M, Frytak S, Parkinson DR. Randomized comparison

of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J Clin Oncol. 1993 Jul;11(7):1269-75.

Santoro A, Tursz T, Mouridsen H, Verweij J, Steward W, Somers R, Buesa J, Casali P, Spooner D, Rankin E, et al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcomas: a randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 1995 Jul;13(7):1537-45.

Prince HM, George DJ, Johnstone R, Williams-Truax R, Atadja P, Zhao C et al. LBH589, a novel histone deacetylase inhibitor (HDACi), treatment of patients with cutaneous T-cell lymphoma (CTCL). Changes in skin gene expression profiles related to clinical response following therapy. J Clin Oncol (Meeting Abstracts) 2006;24:7501.

Beck J, Fischer T, George D, Huber C, Calvo E, Atadja P et al. Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of ORAL LBH589B: A novel histone deacetylase (HDAC) inhibitor. J Clin Oncol (Meeting Abstracts) 2005;23:3148.

Beck J, Fischer T, Rowinsky E, Huber C, Mita M, Atadja P et al. Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of LBH589A: A novel histone deacetylase inhibitor. J Clin Oncol (Meeting Abstracts) 2004;22:3025.

[No authors listed] Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997 Dec 6;350(9092):1647-54.

Le Cesne A, Judson I, Crowther D, Rodenhuis S, Keizer HJ, Van Hoesel Q, Blay JY, Frisch J, Van Glabbeke M, Hermans C, Van Oosterom A, Tursz T, Verweij J. Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group. J Clin Oncol. 2000 Jul;18(14):2676-84.

Garcia-Carbonero R, Supko JG, Manola J, Seiden MV, Harmon D, Ryan DP, Quigley MT, Merriam P, Canniff J, Goss G, Matulonis U, Maki RG, Lopez T, Puchalski TA, Sancho MA, Gomez J, Guzman C, Jimeno J, Demetri GD. Phase II and pharmacokinetic study of ecteinascidin 743 in patients with progressive sarcomas of soft tissues refractory to chemotherapy. J Clin Oncol. 2004 Apr 15;22(8):1480-90.

Le Cesne A, Blay JY, Judson I, Van OA, Verweij J, Radford J 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;%20;23:576-84.

Bay JO, Ray-Coquard I, Fayette J, Leyvraz S, Cherix S, Piperno-Neumann S, Chevreau C, Isambert N, Brain E, Emile G, Le Cesne A, Cioffi A, Kwiatkowski F, Coindre JM, Bui NB, Peyrade F, Penel N, Blay JY; Groupe Sarcome Français. Docetaxel and gemcitabine combination in 133 advanced soft-tissue sarcomas: a retrospective analysis. Int J Cancer. 2006 Aug 1;119(3):706-11. Erratum in: Int J Cancer. 2007 Jan 15;120(2):450. Penel, Nicolas [added].

Hensley ML, Maki R, Venkatraman E, Geller G, Lovegren M, Aghajanian C, Sabbatini P, Tong W, Barakat R,

Spriggs DR. Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: results of a phase II trial. J Clin Oncol. 2002 Jun 15;20(12):2824-31.

Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. 2006 Sep;5(9):769-84. Review.

Ito T, Ouchida M, Ito S, Jitsumori Y, Morimoto Y, Ozaki T, Kawai A, Inoue H, Shimizu K. SYT, a partner of SYT-SSX oncoprotein in synovial sarcomas, interacts with mSin3A, a component of histone deacetylase complex. Lab Invest. 2004 Nov;84(11):1484-90.

Wunder JS, Nielsen TO, Maki RG, O'Sullivan B, Alman BA. Opportunities for improving the therapeutic ratio for patients with sarcoma. Lancet Oncol. 2007 Jun;8(6):513-24. Review. Erratum in: Lancet Oncol. 2007 Aug;8(8):670.

Kutko MC, Glick RD, Butler LM, Coffey DC, Rifkind RA, Marks PA, Richon VM, LaQuaglia MP. Histone deacetylase inhibitors induce growth suppression and cell death in human rhabdomyosarcoma in vitro. Clin Cancer Res. 2003 Nov 15;9(15):5749-55.

Ito T, Ouchida M, Ito S, Jitsumori Y, Morimoto Y, Ozaki T, Kawai A, Inoue H, Shimizu K. SYT, a partner of SYT-SSX oncoprotein in synovial sarcomas, interacts with mSin3A, a component of histone deacetylase complex. Lab Invest. 2004 Nov;84(11):1484-90.

Sakimura R, Tanaka K, Nakatani F, Matsunobu T, Li X, Hanada M, Okada T, Nakamura T, Matsumoto Y, Iwamoto Y. Antitumor effects of histone deacetylase inhibitor on Ewing's family tumors. Int J Cancer. 2005 Sep 20;116(5):784-92.

Prince HM, George D, Patnaik A, Mita M, Dugan M, Butterfoss D et al. Phase I study of oral LBH589, a novel deacetylase (DAC) inhibitor in advanced solid tumors and non-hodgkin's lymphoma. J Clin Oncol (Meeting Abstracts) 2007;25:3500. 66. A'Hern RP. Sample

A'Hern RP. Sample size tables for exact single-stage phase II designs. Stat Med. 2001 Mar 30;20(6):859-66.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.

Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst. 2000 Feb 2;92(3):205-16.

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