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Requires Data Access? No

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Requires Data Access? Yes

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2024/05/SV_57KskaKADT3U9Aq-R_2lrGc0wur46SdgP.pdf
https://yoda.yale.edu/wp-content/uploads/2024/05/SV_57KskaKADT3U9Aq-R_84NkgHK0Uwsuvvv.pdf
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https://yoda.yale.edu/wp-content/uploads/2024/05/coi-form-ROM.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. NCT01343277 - ET743-SAR-3007 - A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma or Leiomyosarcoma
2. NCT00210665 - ET743-SAR-3002 - A Study to Provide Access to Trabectedin in Participants With Locally Advanced or Metastatic Soft Tissue Sarcoma Who Have Persistent or Recurrent Disease and Who Are Not Expected to Benefit From Currently Available Standard of Care Treatment
3. - ET-B-017-99 - Phase 2 study of ET-743 as second or third line therapy in advanced and/or metastatic soft tissue sarcoma patients
4. - ET-B-008-98 - Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients
5. NCT00579501 - ET-B-028-06 - Safety and Efficacy Study of Trabectedin for the Treatment of Localized Myxoid / Round Cell Liposarcoma
6. - ET-B-010-99 - Phase II clinical trial of ET-743 as 2nd or 3rd line treatment in patients with advanced stage and/or metastatic soft tissue sarcoma
7. NCT00060944 - ET743-STS-201 - A Randomized, Multicenter, Open-label Study of Yondelis (ET-743 Ecteinascidin) Administered by 2 Different Schedules (Weekly for 3 of 4 Weeks vs. q3 Weeks) in Subjects With Locally Advanced or Metastatic Liposarcoma or Leiomyosarcoma Following Treatment With an Anthracycline and Ifosfamide

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Pooled analysis of the efficacy of trabectedin in myxoid/round cell liposarcoma from trabectedin registrational and open access clinical trials

Narrative Summary:

The trabectedin trials were conducted in L-type sarcomas, which include leiomyosarcoma, and liposarcomas. Liposarcoma is composed of multiple genetically distinct subtypes: well differentiated/dedifferentiated liposarcoma, myxoid/round cell liposarcoma (MRCLS) and pleomorphic liposarcoma. MRCLS is the third most common type of liposarcoma. Efficacy in liposarcoma subtypes may differ, and the efficacy (ORR, DCR, TTR, DoR, PFS, Duration of SD, and OS) has not been comprehensively evaluated across the registrational and open access trabectedin trials. To better understand the efficacy of trabectedin within the patient population with MRCLS, this study would propose to evaluate specifically the efficacy in MRCLS across the trabectedin trials.

Scientific Abstract:

Background: Myxoid Round Cell Liposarcoma (MRCLS) is a subset of liposarcomas with limited treatment options. Most clinical trials do not report on this rare subgroup, thus efficacy for approved therapies such as trabectedin is uncertain.
Objective: Determine the treatment efficacy (ORR, DCR, TTR, DoR, PFS, duration of SD, and OS) of trabectedin within this rare MRCLS subgroup with advanced disease (unresectable or metastatic).
Study Design: Pooled analysis of all MRCLS patients treated within trabectedin clinical trials. Combination of MRCLS patients across these trials will allow for a larger individual patient dataset to more accurately estimate the efficacy of trabectedin in the treatment of advanced (locally unresectable or metastatic) MRCLS.
Participants: Any participant who received the standard trabectedin dosing (IV continuous infusion of

24 hours, 1.5 mg/m2 (with allowed dose reductions to 1.2 mg/m2 or 1.0 mg/m2), cycle length every 3 weeks) and has a confirmed diagnosis of advanced (locally unresectable or metastatic) MRCLS.
Primary Endpoint: ORR per RECIST v1.1
Secondary Endpoints: DCR, TTR, PFS, DoR, Duration of SD, and OS (where data available).
Statistical analysis: Appropriate descriptive statistics will be used to summarize demography, baseline characteristics, disease characteristics, anti-cancer therapy, disease burden and trabectedin exposure (where available). ORR and DCR will be reported with 2-sided 95% CI. TTR and duration of stable disease will be summarised descriptively. Time-to-event endpoints DOR, PFS and OS will be summarized using KM method.

Brief Project Background and Statement of Project Significance:

Soft tissue sarcomas are a group of rare tumors. There are ~12,000 to 13,000 soft tissue sarcomas diagnosed in the U.S. every year. One of the largest sub-groups is liposarcomas. However, this does not represent one disease. Liposarcoma is composed of several genetically distinct subtypes, specifically well differentiated, dedifferentiated, pleomorphic, and myxoid or myxoid round cell liposarcoma. Well and dedifferentiated liposarcoma are characterized by amplification of 12q including MDM2 and CDK4, whereas myxoid round cell liposarcoma is characterized by a translocation between DDIT3 and FUS or EWSR1. Given the rarity of these diseases clinical trials often examine subgroups together. For example, both the Eribulin (Demetri 2017) and Trabectedin (Demetri 2016) phase III clinical trials examined all L-type sarcomas (leiomyosarcoma and liposarcoma). The efficacy in each individual subgroup cannot necessarily be reported, particularly given the size of each specific subgroup. More recently clinical trials have been conducted for specific sarcoma subtypes. For example, Selinexor (Gounder 2022) was approved by the FDA specifically for well and dedifferentiated liposarcoma, and abemiciclib (NCT04967521) is being examined just in dedifferentiated liposarcoma. The lack of prior trials specifically for a sarcoma subtype or a subgroup analysis for a specific sarcoma subtype limit the ability to determine the standard of care efficacy for rare sarcoma subtypes that new agents must be compared against. In the case of trabectedin, which is approved for all types of leiomyosarcoma and liposarcoma, a sub-group analysis for each respective subtype is not available. For myxoid liposarcoma PFS of 5.6 months was reported with a HR of 0.41, though with a 95% confidence interval of 0.17 to 0.98. ORR and OS were not reported. A pooled analysis of the efficacy of trabectedin specifically in MRCLS across trials with trabectedin where MRCLS was included, will allow for determination of the efficacy of trabectedin in MRCLS across multiple efficacy parameters (ORR, TTR, DoR, DCR, PFS, duration of SD, and OS) [where data available]. This will provide a standard of care efficacy baseline against which all future therapy for MRCLS must be compared.

Specific Aims of the Project:

The aim of this project is to perform a pooled analysis of the efficacy of trabectedin in myxoid round cell liposarcoma. We will examine the efficacy across all trabectedin trials that enrolled MRCLS patients, who received the standard of care dosing of trabectedin (1.0 to 1.5 mg/m2 24 hours continuous infusion every 3 weeks). The objectives are to specifically report for MRCLS patients, ORR, DCR, TTR, DoR, PFS, and duration of SD based on RECIST v 1.1 response, and OS in the unresectable or metastatic setting (where data available). These clinical trial efficacy outcomes will provide a new baseline for trabectedin efficacy in MRCLS, to which any new therapy for MRCLS can be compared in the 2L+ setting for advanced or metastatic disease.

Study Design:

Other

Study Design Explanation:

We will conduct a pooled analysis for efficacy of trabectedin in MRCLS across clinical trials that include MRCLS and the established SoC dosing for trabectedin. These trials would include any of the trials that include patient with myxoid round cell liposarcoma, specifically: NCT01343277, A study of trabectedin or dacarbazine for the treatment of patients with advanced liposarcoma or

leiomyosarcoma; NCT00060944 A randomized, multicenter, open-label study of yondelis (ET-743 Ecteinascidin) administered by 2 different schedules (weekly for 3 of 4 weeks vs q3 weeks) in subjects with locally advanced or metastatic liposarcoma or leiomyosarcoma following treatment with an anthracycline and ifosfamide; NCT00210665 A study to provide access to trabectedin in participants with locally advanced or metastatic soft tissue sarcoma who have persistent or recurrent disease and who are not expected to benefit from currently available standard of care treatment; Phase II study of ecteinascidin-743 in advanced pretreated soft tissue sarcoma patients; Phase 2 study of ET-743 as second or third line therapy in advanced and/or metastatic soft tissue sarcomas patients; NCT00579501 Safety and efficacy study of trabectedin for the treatment of localized myxoid / round cell liposarcoma; Phase II clinical trial of ET-743 as 2nd or 3rd line treatment in patients with advanced stage and/or metastatic soft tissue sarcoma. The established dose of trabectedin is a 24 hour continue infusion given once every 3 weeks, with a starting dose of 1.5 mg/m2 and dose reductions allowed to 1.2 mg/m2 and 1.0 mg/m2. These trials may have included different dosing schema and different cycle lengths. The intent would be to examine the efficacy for those MRCLS patients who received the current standard of care dosing (24 hr continuous infusion 1.5 to 1.1 mg/m2) and cycle length (Q3 weeks) for MRCLS.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Other: Pooled efficacy analysis using only data from the YODA Project

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Inclusion Criteria:
Patient with a diagnosis of myxoid round cell liposarcoma (MRCLS)
Patients with advanced (locally unresectable or metastatic) disease
Patients that received trabectedin 24 hours continuous infusion
Patients that received trabectedin Q3 week cycle
Patients that received trabectedin with a dose of 1.5, 1.2, or 1.0 mg/m2

Exclusion Criteria:
All patients with a sarcoma diagnosis, other than MRCLS, will be excluded, such as diagnoses of leiomyosarcoma, pleomorphic liposarcoma, well differentiated or dedifferentiated liposarcoma, undifferentiated pleomorphic sarcoma
Patients that received trabectedin bolus infusion
Patients that received trabectedin Q4 weeks

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary Outcome Measure:

Objective Response (OR), defined as CR or PR according to RECIST v1.1, from first dose of trabectedin until documented disease progression will be based on confirmed (tumour) responses.

Secondary Outcome Measures:

Disease control, defined as participants with the following responses will be summarized: CR, PR, or SD >= 12 weeks, according to RECIST v1.1.

Time to Response (TTR) per RECIST v1.1, defined in responders, as the duration between the date of first dose of trabectedin and the initial date of the confirmed response.

Duration of Response (DoR) per RECIST v1.1, defined in responders as the duration from the initial date of the confirmed response to the earliest date of progressive disease (PD) or death due to any cause.

Progression-Free survival (PFS) per RECIST v1.1, defined as the interval between the date of first dose of trabectedin and the earliest date of disease progression or death due to any cause.

Duration of Stable disease (SD) per RECIST v1.1 defined as the interval between the initial date of the stable disease and the last date that stable disease is recorded.

Overall Survival (OS) defined as the duration between the date of first dose of trabectedin and date of death due to any cause.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Trabectedin (Current SOC dosing 1.5 to 1.0mg/m2 trabectedin Q3 week cycle 24hr continuous infusion)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Subgroups of interest are: age, race, sex, prior lines of therapy and other available relevant disease-specific subgroups. Subgroup analyses will only be performed if data available.

Statistical Analysis Plan:

Patient inclusion/exclusion:

Patients from the four selected studies (NCT01343277, NCT00060944, NCT00210665 and NCT00579501) who meet the inclusion criteria (defined above) will be included in the pooled efficacy analysis.

Subject disposition:

Subject disposition including the number of patients screened/enrolled, randomised and treated. Reasons for treatment discontinuation and study discontinuation will be displayed (where available).

Study population analyses:

Demography, baseline characteristics, disease characteristics at initial diagnosis, prior and on-study anti-cancer therapy, disease burden at baseline, and trabectedin exposure will be summarized (where available) using appropriate descriptive statistics.

Primary Outcome:

The primary outcome analysis population for efficacy will be participants who received at least one dose of trabectedin. Overall response rate (ORR) is defined as the percentage of participants with OR relative to the total number of participants in the analysis population, the corresponding Clopper-Pearson (exact binomial) 2-sided 95% confidence interval (CI) will also be provided.

Secondary Outcomes:

The secondary outcomes analysis population for efficacy will be participants who received at least one dose of trabectedin. Disease control rate (DCR) is defined as the percentage of participants with

CR, PR, or SD >= 12 weeks relative to the total number of participants in the analysis population, the corresponding Clopper-Pearson (exact binomial) 2-sided 95% confidence interval (CI) will also be provided. TTR will be summarized descriptively using median and quartiles in the subset of participants with a confirmed response of PR or CR. Time-to-event endpoints DOR, PFS and OS will be summarized and displayed graphically using Kaplan-Meier methodology to estimate the median, and the 25th and 75th percentiles if data warrant. Two-sided 95% CIs will be produced. Duration of SD will be summarized descriptively with median, minimum and maximum, also the number and percentage of patients with SD80

Given most clinical trials do not report on this rare subgroup and thus there is very limited published efficacy data available then it's critical that individual patient data (IPD) is used for this analysis to identify the subgroup of patients with advanced MRCLS who received current SOC trabectedin dosing. A pooled analysis opposed to a meta-analysis has been selected, however we do acknowledge that there could be differences between studies, such differences will be inspected and described in the report, and depending on the level of heterogeneity, alternative analysis methods may be used if required. Also to note, a systematic review is being carried out in parallel to identify if other e.g. unpublished data, is available in this patient population for possible inclusion in this research.

Software Used:

R, STATA

Project Timeline:

Key Milestones and timing:
Anticipated Project start date -- Late June 2024
Statistical Analysis Plan (Final) -- Q2 2025
Statistical Analysis -- Q2 2025
Provision of report describing results of the Research, which will take the form of an abstract, to Yale University -- Q2 2025
If accepted for presentation at a meeting for a clinical research society, provision of final poster to Yale University -- 4Q 2025
Provision of report describing results of the Research, which will take the form of a publication, to Yale University -- Q1 2026, at point of submission for publication
If accepted for publication, provision of final manuscript to Yale University - Upon expiration of the Data User Agreement between Yale University and Adaptimmune LLC

Dissemination Plan:

Trabectedin was approved for the treatment of 2nd line MRCLS in 2015. Since that time, engineered cell therapies have emerged (D'Angelo 2022, Hong 2023, Mackall 2017) as a potential treatment for this malignancy. As these novel cell therapies advance towards regulatory approval, sarcoma clinicians must critically evaluate the existing trabectedin safety and efficacy data in soft tissue sarcoma. The proposed study will support this identified need. Its conclusions will be summarized in two (2) reports; 1) Abstract for submission to the Connective Tissue Oncology Society, and 2) Publication for submission to a sarcoma-focused journal, such as Clinical Sarcoma Research, or SM Journal of Sarcoma Research.

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