MANTRA: A randomized, multicenter, phase 3 study of the MDM2 inhibitor miladametan (RAIN-32) versus trabectedin in patients with dedifferentiated liposarcoma

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Background

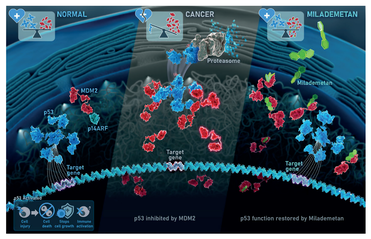
- Inactivation of tumor suppressor p53 is a common feature of human cancers:[1]
  - The two main mechanisms responsible for p53 pathway inactivation are *TP53* somatic mutations[2] and downregulation of wild-type p53 following interaction with regulatory proteins.[3]
  - Murine double minute 2 (MDM2), which promotes ubiquination and degradation of p53,[4,5] is the primary negative regulator of p53.
  - Overexpression of MDM2 via *MDM2* gene amplification or other mechanisms is observed in many cancers, notably dedifferentiated (DD) and well-differentiated (WD) liposarcomas.[6]
  - Multiplatform genetic analysis supports that 100% of patients with DD liposarcoma exhibit *MDM2* amplification coupled with wild-type *TP53* in 96% of cases.[7]
  - Inhibition of the MDM2-p53 interaction to restore p53 tumor suppressor activity is a logical therapeutic target in *TP53* wild-type, *MDM2*-dependent tumors.
- DD liposarcomas are relatively chemotherapy-resistant,[8] and systemic treatment options for patients with unresectable or metastatic disease are limited:
  - Anthracycline-based chemotherapy is standard first-line therapy, with trabectedin and eribulin recommended as second-line treatments for all histological subtypes of liposarcoma, including DD liposarcoma.[9]
  - No targeted therapies are approved for DD or WD liposarcoma with unique molecular features (e.g., *MDM2* amplification).

Miladametan: MDM2 inhibitor

- Miladametan is a potent, oral, inhibitor/disruptor of MDM2-p53 interaction[10] (see Figure 1), therefore reactivating p53 with an enhanced therapeutic index for the treatment of cancer.
- In preclinical studies, miladametan induced p53-dependent apoptosis in human cancer cell lines and demonstrated antitumor activity in xenograft models of tumors with functional, wild-type p53.[10]
- In a first-in-human phase 1 study (Clinicaltrials.gov: NCT01877382):
  - An intermittent schedule of miladametan (days 1–3 and 15–17 every 4 weeks) identified from PK-PD modeling studies[11] was found to mitigate dose-limiting myelosuppression while maintaining efficacy in advanced solid tumors.[12]
  - In patients with DD/WD liposarcoma, the median progression-free survival (PFS) with miladametan was 7.4 months (see Figure 2) when given at the recommended dose schedule (260 mg days 1–3 and 15–17 every 4 weeks).[12]
  - The efficacy demonstrated by miladametan in DD/WD liposarcoma[12] compared with prior studies of trabectedin and eribulin (median PFS ~2 months)[13,14] prompted the phase 3 MANTRA study.

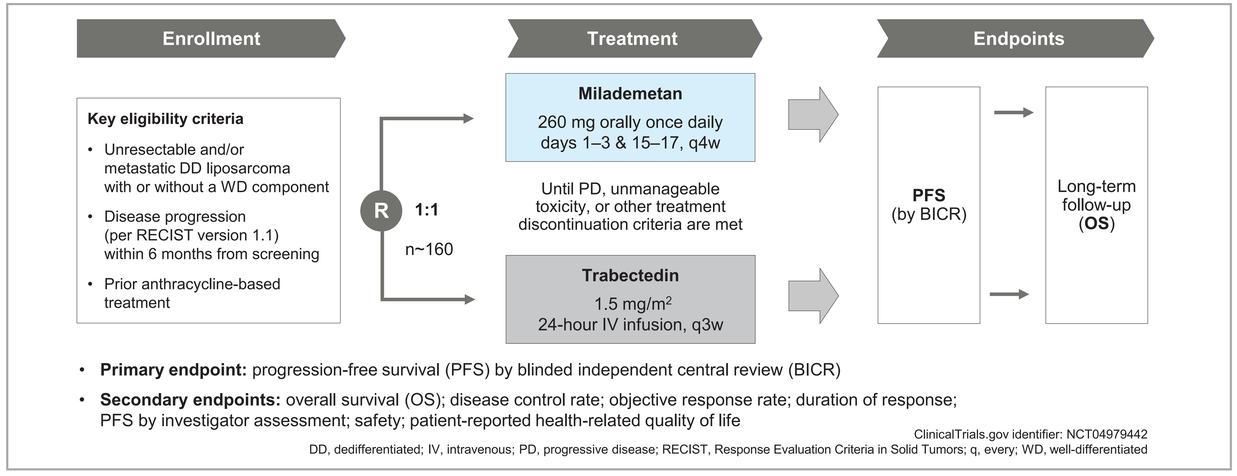
Figure 1: Miladametan proposed mechanism of action

- Wild-type p53 responds to normal cellular injury to protect against cancer via induction of cellular apoptosis or senescence.
- Mutated p53 is incapable of target gene binding and function.
- Dysregulated MDM2 can facilitate or support oncogenicity:
  - *MDM2* gene amplification.
  - MDM2 overexpression.
  - MDM2 regulator loss ($p14^{ARF}$ encoded by *CDKN2A*).
- As a disruptor of the MDM2-p53 interaction, miladametan restores / reactivates wild-type p53.



Source: Rain Therapeutics

MANTRA: Study design

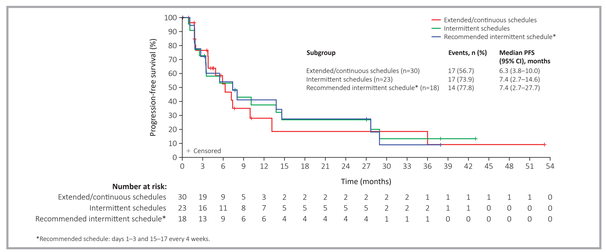


- **Primary endpoint:** progression-free survival (PFS) by blinded independent central review (BICR)
- **Secondary endpoints:** overall survival (OS); disease control rate; objective response rate; duration of response; PFS by investigator assessment; safety; patient-reported health-related quality of life

ClinicalTrials.gov identifier: NCT04979442

DD, dedifferentiated; IV, intravenous; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; q, every; WD, well-differentiated

Figure 2: Progression-free survival with miladametan by dosing schedule in patients with liposarcoma[12]



*Recommended schedule: days 1–3 and 15–17 every 4 weeks.

Study population

Abbreviated inclusion criteria
1. Male or female ≥18 years of age
2. Written informed consent provided
3. Histologically confirmed DD liposarcoma, with or without a WD component (WD/DD liposarcoma), by local pathologic review; central pathologic review will also be performed but is not required for inclusion
4. Documented advanced unresectable and/or metastatic WD/DD liposarcoma
5. Measurable tumor lesion(s) in accordance with RECIST version 1.1
6. Received 1 or more systemic cancer therapy regimens, including at least 1 anthracycline-based regimen, and had radiographic progressive disease (per RECIST version 1.1) within 6 months before the screening visit
7. Resolution of any clinically relevant toxic effects of prior chemotherapy, surgery, radiotherapy, or hormonal therapy
8. ECOG performance status of 0 or 1
9. Adequate bone marrow (platelet count ≥100 × 109/L; hemoglobin ≥9.0 g/dL; absolute neutrophil count ≥1.5 × 109/L), renal and hepatic function

Abbreviated exclusion criteria
1. Prior treatment with any MDM2 inhibitor or trabectedin
2. Other primary malignancies that have required systemic antineoplastic treatment within the previous 2 years, except for localized cancers that have apparently been cured and will not interfere with study outcomes
3. Gastrointestinal conditions that could affect the absorption of miladametan
4. Uncontrolled infection within last 7 days requiring intravenous antibiotics, antivirals, or antifungals
5. Known HIV infection or active hepatitis B or C infection
6. Untreated brain metastases
7. Does not meet minimum predefined washout periods for CYP3A4 inhibitors, CYP3A inducers, systemic anticancer therapy or immune checkpoint inhibitors before randomization
8. Major surgery ≤3 weeks from randomization
9. Curative-intent radiation therapy ≤4 weeks or palliative radiation therapy ≤2 weeks from randomization
10. Uncontrolled or significant cardiovascular disease
11. Pregnant or breastfeeding women or intends to become pregnant during the study
12. Concomitant medical condition that would interfere with the assessment of efficacy or increase the risk of toxicity

DD, dedifferentiated; ECOG, Eastern Cooperative Oncology Group; MDM2, murine double minute 2; RECIST, Response Evaluation Criteria in Solid Tumors; WD, well-differentiated

MANTRA study

- MANTRA (RAIN-3201; MilAdemetaN TRiAl) is a randomized, multicenter, open-label, phase 3 registration study.
- It is designed to evaluate the safety and efficacy of miladametan compared to trabectedin in patients with unresectable or metastatic DD liposarcoma that has been treated with 1 or more prior systemic therapies, including at least 1 anthracycline-based regimen, and has progressed (per RECIST version 1.1) within 6 months from screening.
- Trabectedin was chosen as the active control treatment because it is approved as a second-line therapy by the US FDA for patients with liposarcoma or leiomyosarcoma who have received a prior anthracycline-containing regimen.
- Based on the high frequencies of the appropriate genotype in DD liposarcoma (i.e. *TP53* wildtype, *MDM2*-amplified),[4] no prospective biomarker selection criteria are included in the study eligibility criteria; central pathologic review will be performed but not required for inclusion.

Study objectives/endpoints

Objectives	Endpoints
Primary	
Compare progression-free survival (PFS) in the miladametan and trabectedin arms	• PFS: time from randomization to earliest date of first objective documentation of radiographic disease progression (RECIST version 1.1) or death due to any cause, determined by blinded independent central review (BICR)
Secondary	
Compare the following efficacy measures in the miladametan and trabectedin arms: overall survival (OS); disease control rate (DCR); objective response rate (ORR); duration of response (DOR); PFS by investigator assessment	• OS: time from randomization to date of death by any cause • DCR: percentage of patients who achieve a complete response, partial response, or stable disease for ≥16 weeks • ORR: percentage of patients who achieve a confirmed complete response or partial response • DOR: time from date of first response to date of disease progression or death • PFS: time from randomization to earliest date of first objective documentation of radiographic disease progression (based on investigator assessment) or death due to any cause
Assess the safety profile of miladametan	• Adverse events graded according to NCI CTCAE version 5.0
Evaluate patient-reported outcomes from health economics and outcomes research	• Health-related quality of life evaluated using European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire, Core 30 (QLQ-C30)
Exploratory	
Explore molecular, cellular, and soluble markers in peripheral blood and/or tumor tissue that have possible relevance to the mechanism of action of, or response/ resistance to, miladametan treatment	• Tumor samples tested for genes in TP53 and MDM2 pathways • Other genomic tumor and circulating tumor DNA analyses may be done to understand patient response to therapy
Evaluate pharmacokinetics of miladametan and exposure-response relationships for efficacy and safety	• Blood samples for miladametan pharmacokinetic analyses will be collected in patients in the miladametan arm and correlated with response and safety parameters

NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors

Treatment

- Patients are randomly assigned (1:1) to receive miladametan (260 mg orally once daily on days 1–3 and 15–17 every 28 days) or trabectedin (1.5 mg/m^2 as a 24-hour intravenous infusion every 3 weeks):
  - Dose interruptions and reductions (without re-escalation) for miladametan due to certain adverse events are allowed.
  - Dose modification guidelines for trabectedin are per approved labeling.
  - Crossover was not permitted.
- Randomization is stratified by Eastern Cooperative Oncology Group performance status (0 or 1) and number of prior treatments for liposarcoma (≤2 or >2).
- Patients will receive study drug until reaching disease progression (as determined by the investigator), unacceptable toxicity, or until other treatment discontinuation criteria are met.
- Patients may be treated beyond tumor progression if they are experiencing clinical benefit based on investigator assessment in discussion with the Medical Monitor.

Assessments

- Tumor assessments by CT or MRI will be performed by both the investigator and a blinded central review committee; evaluation of tumor response will be based on RECIST version 1.1.
- Tumor response evaluations will be performed at screening, at the end of weeks 8, 16, 24, and 32, then every 12 weeks while the patient remains on study drug and any other time during the study as clinically indicated.
- All patients will be followed for documentation of disease progression and survival information (i.e. date and cause of death) and subsequent treatments (i.e. date/duration of treatment, response, and subsequent disease progression).
- Long-term follow-up will continue every 12 weeks until the endpoint of death, the patient is lost to follow-up, or for 24 months after the last patient enrolled, whichever comes first.

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- This poster discusses the investigational use of the MDM2 inhibitor miladametan (RAIN-32) in patients with DD liposarcoma.
- The presenting author, Mrinal M. Gounder, has the following financial relationships to disclose:
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