MILADEMETAN (DS-3032B OR RAIN-32), AN ORAL MDM2 INHIBITOR, IN WELL-DIFFERENTIATED/DEDIFFERENTIATED LIPOSARCOMA: RESULTS FROM A PHASE 1 STUDY IN PATIENTS WITH SOLID TUMORS OR LYMPHOMAS

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Disclosures

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p53 is the most commonly mutated protein across cancer

Missense/inactivating mutations in TP53 are most common

Several additional mechanisms of WT p53 inactivation exist – one such mechanism is MDM2 overexpression
• Milademetan (DS-3032b or RAIN-32)
  – Orally bioavailable
  – Demonstrated antitumor activity in preclinical studies

• This first-in-human phase 1 trial (NCT01877382) evaluated milademetan in patients with advanced solid tumors or lymphomas

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MDM2 Amplification ~ 17% Across All Cancers

- MDM2 amplification is a hallmark of well/dedifferentiated liposarcoma (WD/DD LPS)

Liposarcoma (LPS) accounts for approximately 15 - 20% of adult soft tissue sarcomas¹-⁴.

Well-differentiated/dedifferentiated LPS (WD/DD) LPS is characterized by MDM2 gene amplification in up to 100% of cases¹.

Current therapies for WD/DD LPS include anthracycline-based regimens, eribulin, and trabectedin⁵,⁶.

No targeted therapies are currently approved for WD/DD LPS.

Inhibition of MDM2 is a rational approach to WD/DD LPS.

LPS: Subtypes and Frequency⁷-¹¹
Trial Design – First in Human

**Primary endpoints:**
Safety, MTD, PK, PD

**Secondary endpoints:**
Tumor response

**Key inclusion criteria**
- R/R advanced solid tumors or lymphoma
- Age ≥18 years
- ECOG PS 0 or 1
- Adequate bone marrow, renal, hepatic, and blood-clotting function
- Consent to undergo TP53 genotyping

**Key exclusion criteria**
- KNOWN - TP53 mutation, insertion, or deletion

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**Dose Escalation**

**Schedule A: QD 21/28**
- 15 mg n = 3
- 30 mg n = 1
- 60 mg n = 1
- 120 mg n = 3
- 240 mg n = 2
- 90 mg (LPS) n = 15

**Schedule B: QD 28/28**
- 120 mg n = 3
- 160 mg n = 5

**Schedule C: QD 7/28 (Intermittent)**
- 120 mg n = 6
- 200 mg n = 3

**Schedule D: QD 3/14 x 2 (Intermittent)**
- 120 mg n = 3
- 200 mg n = 3
- 260 mg n = 20
- 340 mg n = 3

Amp, amplification; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRM, modified continuous reassessment method; MTD, maximum tolerated dose; R/R, relapsed/refractory.


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## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Cohorts (N = 107)</th>
<th>Patients with LPS (n = 53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), y</strong></td>
<td>61 (25-88)</td>
<td>62.0 (37-88)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td>Male 54 (50.5)</td>
<td>29 (54.7)</td>
</tr>
<tr>
<td><strong>Cancer type, n (%)</strong></td>
<td>WD/DD LPS (MDM2 amp)</td>
<td>53 (49.5)</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma (MDM2 amp)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Intimal sarcoma (MDM2 amp)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Synovial sarcoma (MDM2 amp)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td></td>
<td>Leiomyosarcoma</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>44 (41.1)</td>
</tr>
<tr>
<td><strong>Cancer stage at entry, n (%)</strong></td>
<td>13 (12.1)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td></td>
<td>92 (85.9)</td>
<td>44 (83.0)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td>0 43 (40.2)</td>
<td>23 (43.4)</td>
</tr>
<tr>
<td></td>
<td>1 64 (59.8)</td>
<td>30 (56.6)</td>
</tr>
<tr>
<td><strong>No. of prior cancer therapies, n (%)</strong></td>
<td>17 (15.9)</td>
<td>17 (32.1)</td>
</tr>
<tr>
<td></td>
<td>10 (9.3)</td>
<td>7 (13.2)</td>
</tr>
<tr>
<td></td>
<td>14 (13.1)</td>
<td>8 (15.1)</td>
</tr>
<tr>
<td>≥3</td>
<td>66 (61.7)</td>
<td>21 (39.6)</td>
</tr>
<tr>
<td><strong>TP53 mutation status, n (%)</strong></td>
<td>83 (77.6)</td>
<td>40 (75.5)</td>
</tr>
<tr>
<td></td>
<td>Wild type</td>
<td>Inactivating mutation 1 (0.9)</td>
</tr>
<tr>
<td></td>
<td>Indeterminate/unknown</td>
<td>23 (21.5)</td>
</tr>
</tbody>
</table>

Half of the patients had WD/DD LPS

The majority of patients received ≥2 prior therapies

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Milademetan Dosing Shows Linear PK

• Plasma $C_{\text{max}}$ (and AUC) of milademetan increased in a dose-dependent manner following single doses from 15 mg to 340 mg$^1$
• Median $T_{\text{max}}$ was approximately 3 hours
Activation of p53: Upregulation of MIC-1

- Milademetan dose/exposure-dependent increase in cellular levels of p53 determines the apoptotic vs cell cycle arrest response (PUMA, BAX, p21, etc).
- MIC-1/GDF15 is a secreted p53 downstream gene product that can be measured as a PD biomarker for p53 activation.


MIC-1 = macrophage inhibitory cytokine 1; PD = pharmacodynamic.
Pharmacodynamics: Increase in Serum MIC-1 Signals p53 Reactivation

Fold change of serum MIC-1 from baseline, mean – INTERMITTENT Schedule D (QD 3/14×2)

AUC, area under the concentration–time curve; C, cycle; C\(_{\text{max}}\), maximal concentration; D, day; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; T\(_{\text{max}}\), time to peak concentration.

Intermittent Dosing of Milademetan Markedly Improves Toxicity Profile

Select Drug-Related TEAEs of Interest

<table>
<thead>
<tr>
<th>System Organ Class, Preferred Term, n (%)</th>
<th>Schedule A, B, and C CONTINUOUS (n = 78)</th>
<th>Schedule D INTERMITTENT (n = 29)</th>
<th>Schedule D INTERMITTENT (260mg) (n=20)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
<td>All Grades</td>
</tr>
<tr>
<td>All drug-related TEAEs</td>
<td>74 (94.9)</td>
<td>43 (55.1)</td>
<td>25 (86.2)</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>52 (66.7)</td>
<td>27 (34.6)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>33 (42.3)</td>
<td>14 (17.9)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10 (12.8)</td>
<td>8 (10.3)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (73.1)</td>
<td>2 (2.6)</td>
<td>20 (69.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (28.2)</td>
<td>2 (2.6)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (33.3)</td>
<td>0</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (46.2)</td>
<td>3 (3.8)</td>
<td>12 (41.4)</td>
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- Milademetan 260 mg QD 3/14 has been chosen as the dose to develop further
Milademetan Was Effective in Patients With All Solid Tumors

**Response (All Patients)**

<table>
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<th>N = 107</th>
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<tr>
<td><strong>Best Overall Response, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>SD</td>
<td>56 (52.3)</td>
</tr>
<tr>
<td>PD</td>
<td>29 (27.1)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>17 (15.9)</td>
</tr>
<tr>
<td><strong>ORR (CR+PR), n (%)</strong></td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.5 – 10.6</td>
</tr>
<tr>
<td><strong>DCR (CR+PR+SD), n (%)</strong></td>
<td>49 (45.8)</td>
</tr>
<tr>
<td>95% CI</td>
<td>36.1 – 55.7</td>
</tr>
</tbody>
</table>

**Best % change in SoD from baseline**

**Continuous**

Schedule A: 90, 80, 70, 60, 50, 40, 30, 20, 10, 0

Schedule B: 105, 90, 75, 60, 45, 30, 15, 0

**Intermittent**

Schedule C: 75, 60, 45, 30, 15, 10, 5, 0

Schedule D: 90, 80, 70, 60, 50, 40, 30, 20, 10, 0

5 PRs include 3 confirmed PRs (LPS) and 2 unconfirmed PRs (non-LPS)

**DCR LPS vs non-LPS, % (95% CI)**

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<tbody>
<tr>
<td>WD/DD LPS (n = 53)</td>
<td>58.5% (44.1, 71.9)</td>
</tr>
<tr>
<td>Non-LPS (n = 34)</td>
<td>32.4% (17.4, 50.5)</td>
</tr>
</tbody>
</table>

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.

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A notable shift in the tumor growth curves was seen with milademetan, demonstrating its antitumor activity in WD/DD LPS.

Median (95% CI) duration of stable disease was 59.9 (15.1 to NR) weeks.

Percent Change in Sum of Diameters From Baseline in Target Lesions Prior to and During Milademetan Therapy in Patients With LPS.

Percent change
-120
-100
-80
-60
-40
-20
0
+20%
30%

Percent change
-120
-100
-80
-60
-40
-20
0
+20%

Month
-20 -15 -10 -5 0 5 10 15 20 25 30 35 40 45 50

NR, not reported.

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Patients With Liposarcoma Achieved Long Duration of Therapy

- Patients were able to interrupt milademetan dose and continue therapy

- 5 patients ongoing >2 years

**Treatment Duration and Dose Interruption (≥ 2 Weeks) by Dosing Schedule**

- Dose interruption starts
- Dose interruption ends
- Continues to extension phase

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In patients treated on intermittent schedule D at ≤260 mg, median PFS was 8.0 months.
Conclusions

• Milademetan given on an intermittent schedule (260 mg, QD 3/14) had a markedly improved safety profile compared with continuous dosing schedules
• Efficacy of milademetan was observed with a prolonged PFS of 8.0 months in patients with WD/DD LPS that was progressing on prior therapy
• Further evaluation of milademetan (RAIN-32) in WD/DD LPS is planned
• Tumor shrinkage and objective responses were also observed in selected non-LPS patients with \textit{MDM2} gene amplification, indicating potential for agnostic clinical trial using biomarker selection

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Acknowledgments

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