Sustained disease control with MDM2 inhibitor milademetan in patients with advanced dedifferentiated liposarcoma

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Disclosures: Mrinal Gounder

- Mrinal Gounder has the following financial relationships to disclose:
  - **Honoraria:** Medscape, More Health, Physicians Education Resource, touchIME
  - **Consulting or Advisory Role:** Athenex, Ayala, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Epizyme, Karyopharm, Rain, Springworks, Tracon, TYME Guidepoint, GLG, Third Bridge, Flatiron Health
  - **Patents, Royalties, Other Intellectual Property:** Wolters Kluwer, patents with MSKCC (GODDESS PRO)

Background

- p53 plays a central role in tumor suppression:[1]
  - p53 function is often compromised in tumor cells by *TP53*-inactivating mutations or overexpression of murine double minute 2 (MDM2), a key negative regulator[2]
  - MDM2 inhibition is a logical therapeutic approach for *MDM2*-amplified, *TP53* wild-type tumors, such as dedifferentiated liposarcomas (DDLPS)[3] and intimal sarcomas[4]
- Systemic treatment options for patients with unresectable or metastatic DDLPS are limited:
  - FDA-approved second-line agents – trabectedin and eribulin – have median progression-free survival (PFS) of ~2 months[5,6]
  - No targeted therapies are currently approved for this tumor type

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1. Lane DP. Nature 1992;358:15-6; 2. Nag S, et al. J Biomed Res 2013;27:254-71
3. TCGA Research Network Cell 2017;171:950-65; 4. Koelsche C, et al. Mod Pathol 2021;34:2122-9
5. Demetri GD, et al. J Clin Oncol 2017;35:3433-9; 6. Demetri GD, et al. J Clin Oncol 2016;34:786-93

Milademetan (RAIN-32): MDM2 inhibitor that restores p53 function

- Milademetan is a small-molecule MDM2 inhibitor that restores p53 function at nanomolar concentrations[7]
- Milademetan showed promising efficacy in patients with DDLPS in a first-in-human phase 1 study:[8]
  - The full article describing this study has been accepted for publication in *J Clin Oncol*
  - Median PFS with milademetan ranged from 6.3 to 7.4 months depending on the dosing schedule

Milademetan schedule	DDLPS (n=53)	
	N	Median PFS, months
Overall (any schedule)	53	7.2
Extended or continuous schedule	30	6.3
Intermittent schedule	23	7.4
Schedule recommended for future development (260 mg days 1–3 and 15–17 every 28 days)	16	7.4

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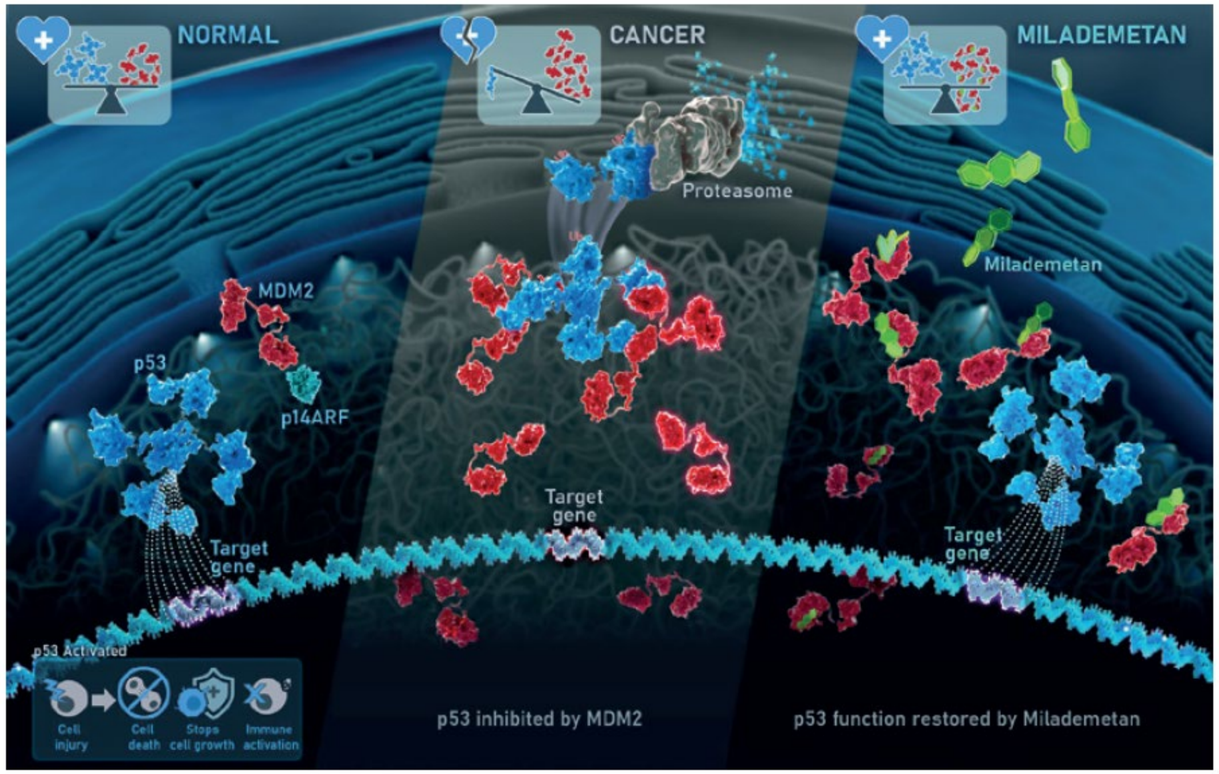
7. Ishizawa J, et al. Cancer Res 2018;78:2721-31; 8. Gounder et al. AACR-NCI-EORTC 2020

Mladememetan: 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 (p14ARF encoded by *CDKN2A*)
- As a disruptor of the MDM2-p53 interaction, mladememetan restores/reactivates wild-type p53



Source: Rain Therapeutics

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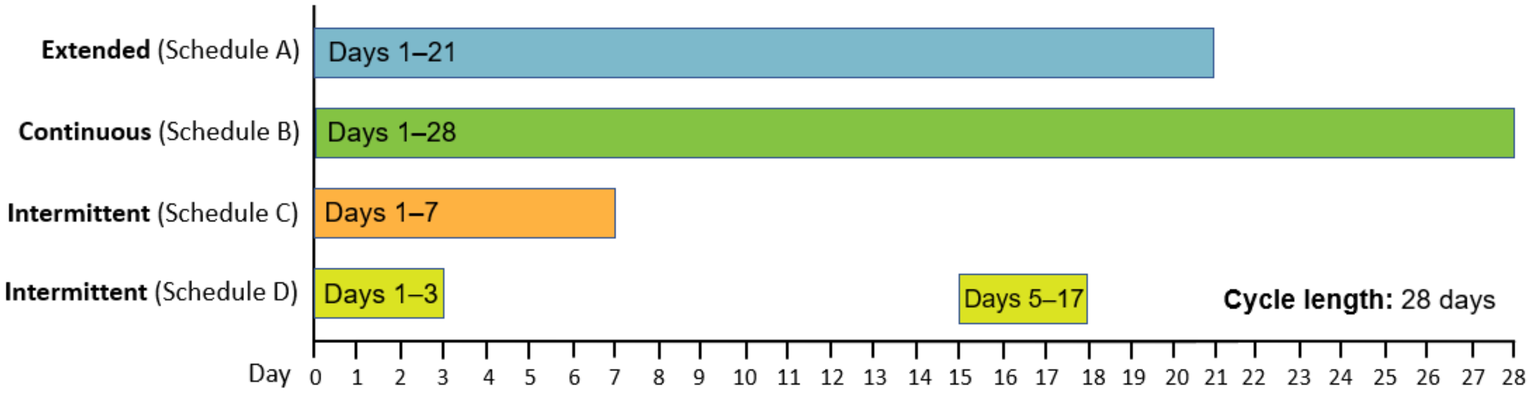
First-in-human phase 1 study of milademetan in patients with DDLPS (U101)

- In this study (ClinicalTrials.gov: NCT01877382), patients with DDLPS were preferentially enrolled:
  - Testing to determine *MDM2* amplification status was not required or collected
  - Confirmation of *TP53* status at screening was encouraged, but not required prior to milademetan dosing
- Miladametan was given orally once daily on a 28-day cycle according to four dosing schedules
- Study outcomes included tumor response (according to RECIST v1.1), PFS, and safety
- Here we describe a subset of 11 patients with DDLPS from this study who received miladametan (any schedule) for more than 12 months



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Baseline demographics (DDLPS): overall population vs patients receiving milademetan for >12 months

	DDLPS (n=53)	Milademetan >12 months (n=11)
Median age (range), years	62 (37–88)	62 (50–69)
Sex, n (%)		
Male	29 (55)	6 (55)
Female	24 (45)	5 (45)
ECOG performance status, n (%)		
0	23 (43)	4 (36)
1	30 (57)	7 (64)
Cancer stage, n (%)		
II	8 (15)	0
III	4 (8)	0
IV	40 (76)	11 (100)
Number of prior cancer therapies, n (%)		
0	17 (32)	6 (55)
1	7 (13)	1 (9)
2	8 (15)	3 (27)
3 or more	21 (40)	1 (9)

- Of 53 patients with DDLPS enrolled, 11 (20.8%) received milademetan for >12 months
- In this patient subset:
  - Ages ranged from 50–69 years
  - All patients had stage IV disease
  - Five patients had received prior systemic anticancer treatments, including:
    - Anthracyclines (n=2)
    - CDK4/6 inhibitors (n=2)

Outcomes in patients with DDLPS receiving miladametan for >12 months (n=11)

- Median duration of miladametan treatment was 28.6 (range 12.7–51.0) months
- Five patients (45.5%) received the dose schedule of miladametan recommended for future clinical development (i.e. 260 mg once daily on days 1–3 and 15–17/28 days)
- Two patients had a partial response, and nine patients had stable disease
- PFS times ranged from 10.2+ to 53.2 months
- Five patients continued treatment with miladametan via a post-trial access program

Outcomes by dosing schedule (n=11; DDLPS)

Patient	Schedule†	Milademetan dose, mg	Treatment duration, months	Best overall response	PFS, months
1	Extended	90	12.7	SD	10.2+
2¶		90	51.0	SD	53.2+
3		120	13.1	SD	13.1
4		120	36.3	SD	36.0
5¶	Intermittent	120	44.2	PR	43.0+
6	Intermittent	120	28.6	SD	28.9
7	Intermittent	260	14.4	SD	14.6
8		260	15.6	SD	13.8
9¶		260	26.9	PR	27.0+
10¶		260	29.1	SD	27.7
11¶		260	37.8	SD	37.9+

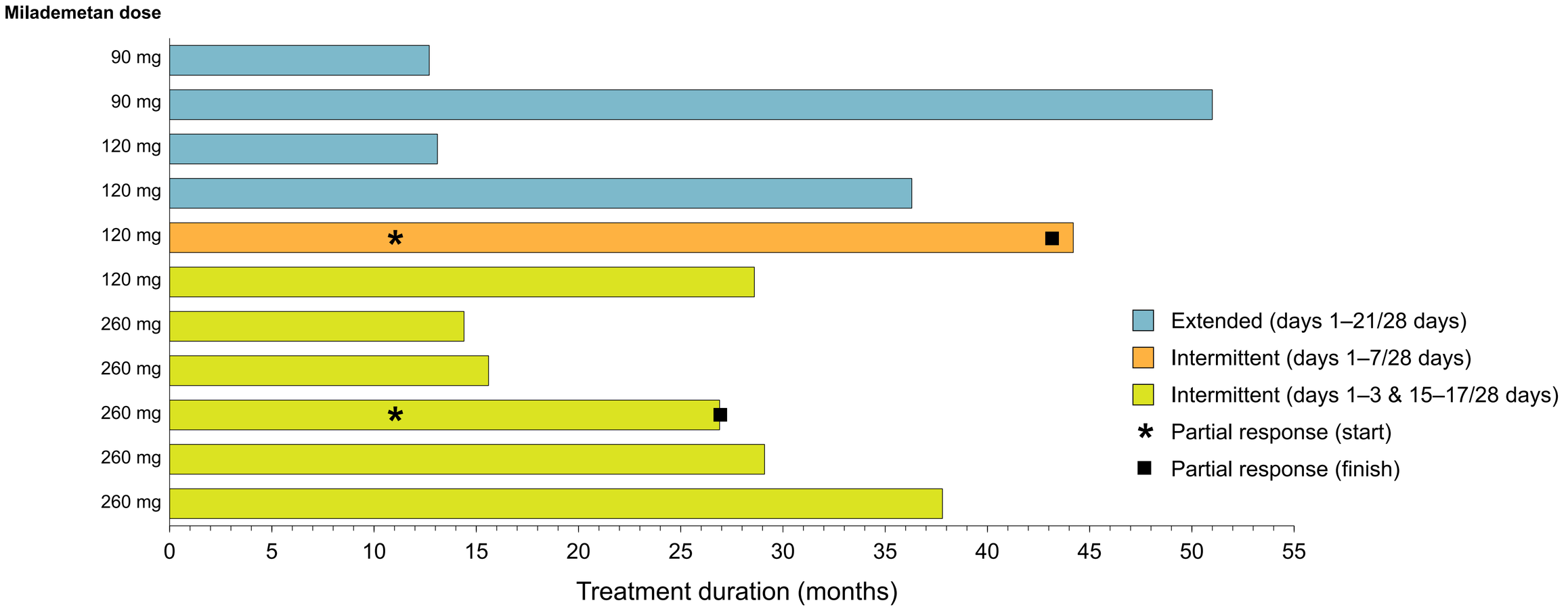
Recommended dose and schedule of milademetan

†Milademetan given once daily according to the following dosing schedules: extended (A: 21/28 days); continuous (B: 28/28 days); intermittent (C: 7/28 days; D: days 1–3 and 15–17/28 days)

+Indicates censored observations; ¶ Entered post-trial access program

PFS, progression-free survival; PR, partial response; SD, stable disease

Exposure to miladematan according to dosing schedule (n=11)



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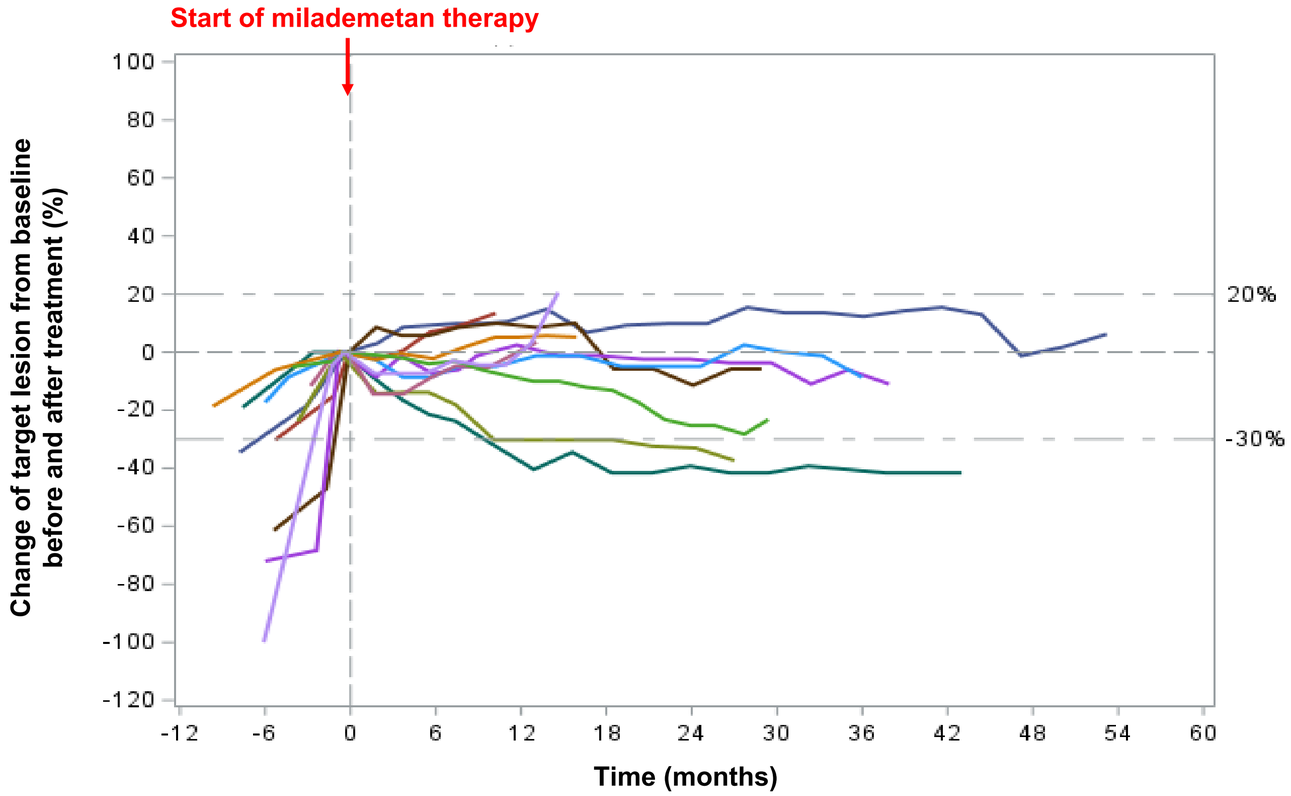
Mladememetan changes the growth kinetics of rapidly progressing patients with DDLPS (n=11)

- All patients showed clear tumor progression before study entry followed by sustained tumor suppression or shrinkage with mladememetan



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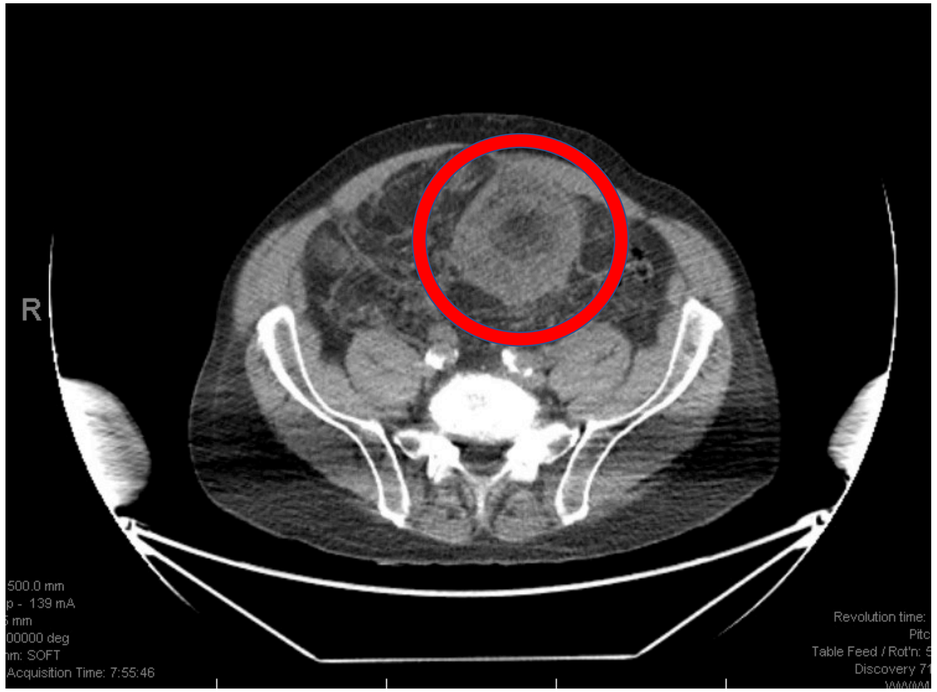
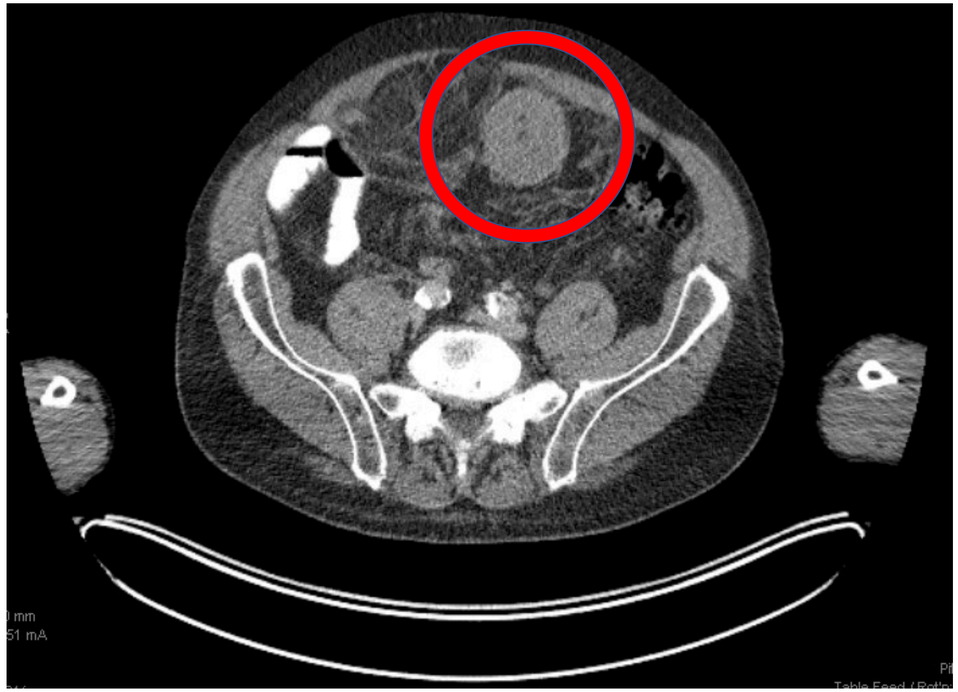
Case report: treatment-naïve DDLPS with PR

Baseline (Nov 2016)



Cycle 18 (Mar 2018)



- Male, white, 69 years of age, treatment-naïve DDLPS. Received milademetan 120 mg (schedule C, intermittent; days 1–7/28 days)
- Had a PR for 43 months with a maximum % change in tumor size of –41.7%
- Grade 2 thrombocytopenia during last cycle of treatment (temporary dose reduction but no dose change during further treatment
  Few Grade 1/2 hematologic toxicities. No Grade 3+ adverse events

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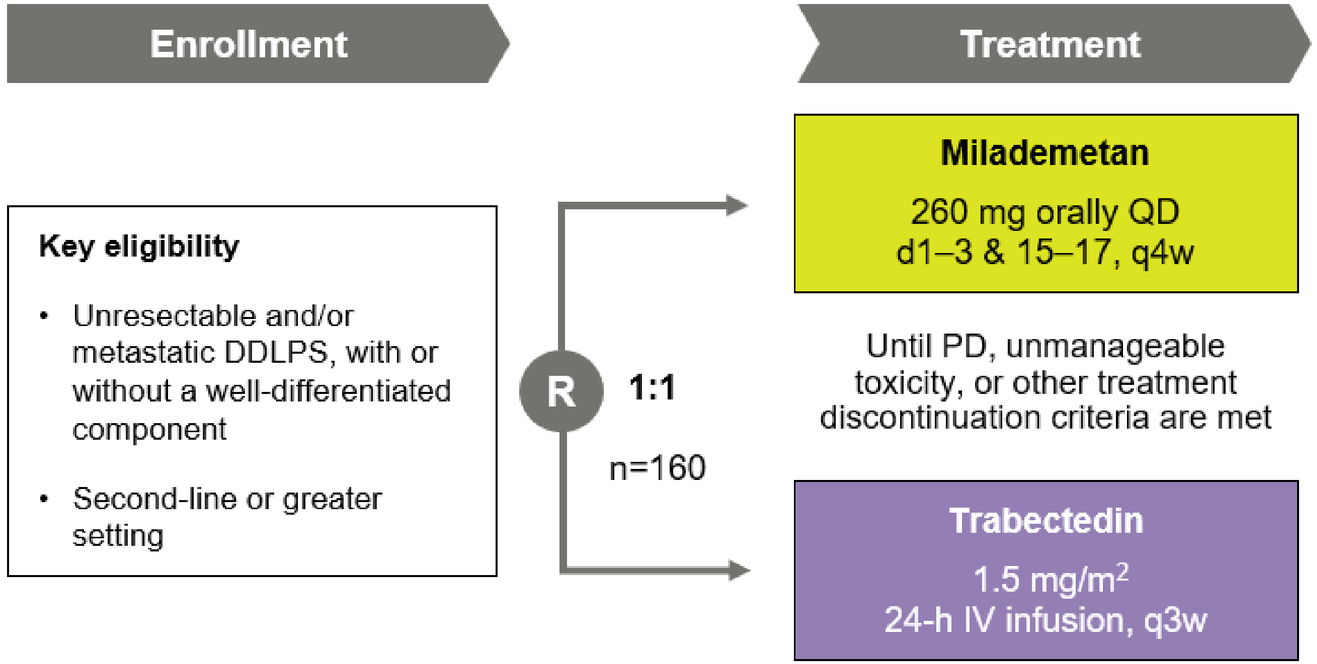
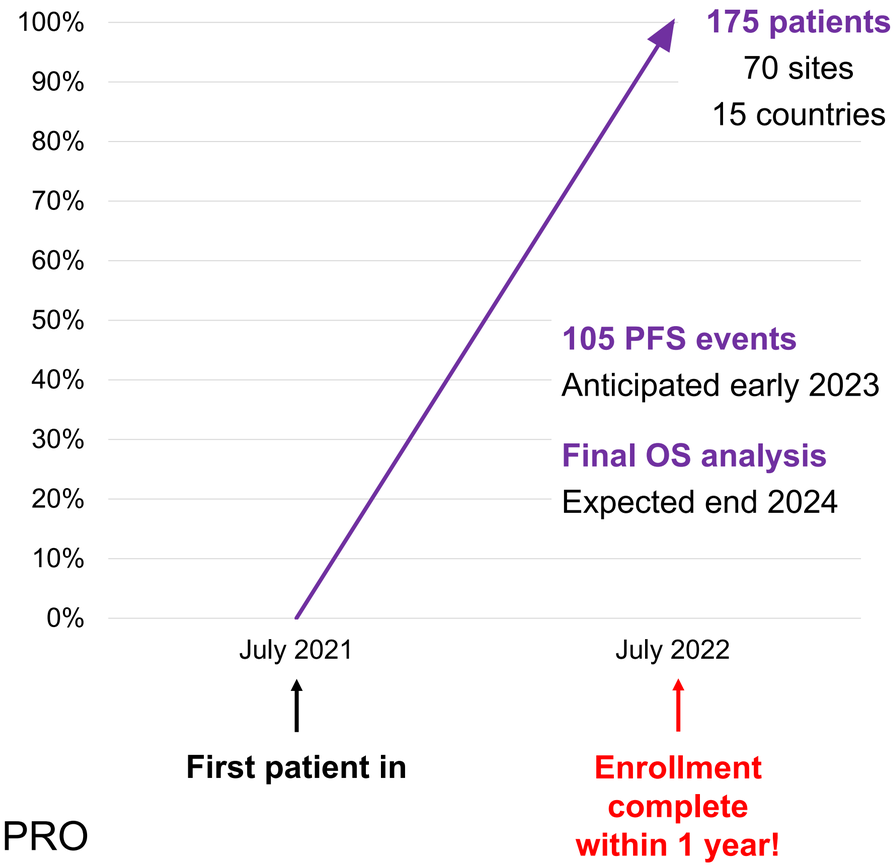
Long-term administration of miladematan was not associated with any unexpected adverse events

- Long-term administration of miladematan (any schedule) did not markedly increase the occurrence of hematologic or other adverse events
- There were very few grade ≥3 events and no reports of bleeding with miladematan

	DDLPS (n=53)		Miladematan >12 months (n=11)	
Treatment-related TEAE (≥20% of patients), n (%)	All grades	Grade ≥3	All grades	Grade ≥3
Any treatment-related TEAE	51 (96)	23 (43)	11 (100)	4 (36)
Nausea	42 (79)	1 (2)	11 (100)	0 (0)
Fatigue	28 (53)	3 (6)	7 (64)	0 (0)
Vomiting	20 (38)	2 (4)	8 (73)	1 (9)
Decreased appetite	18 (34)	0 (0)	5 (46)	0 (0)
Diarrhea	18 (34)	0 (0)	3 (27)	0 (0)
Thrombocytopenia	38 (72)	15 (28)	9 (82)	2 (18)
Leukopenia	19 (36)	2 (4)	5 (46)	1 (9)
Anemia	17 (32)	7 (13)	2 (18)	0 (0)
Neutropenia	12 (23)	7 (13)	5 (46)	3 (27)

MANTRA: pivotal phase 3 study has already completed enrollment





- **Primary endpoint:** PFS
- **Secondary endpoints:** OS, DCR, ORR, DOR, PFS (investigator), safety, PRO

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Conclusions and next steps

- Durable disease control of at least 12 months was seen in more than 20% of patients with advanced DDLPS following treatment with mirademetan:
  - 45% of these patients had received prior systemic anticancer treatments, including anthracyclines and CDK4/6 inhibitors
  - The recommended intermittent dose schedule of mirademetan (i.e. 260 mg once daily on days 1–3 and 15–17/28 days) was the most commonly used schedule in this patient subset
- Safety profile of mirademetan in patients treated for >12 months was consistent with the whole DDLPS population and there was no appreciable increase in occurrence of hematologic or other adverse events
- Findings from the whole DDLPS population will be published soon in *J Clin Oncol*
- The phase 3 registration trial (MANTRA) of mirademetan versus trabectedin in patients with pretreated DDLPS recently completed accrual

Acknowledgements

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