MDM2 inhibitor milademetan: Safety profile and management of adverse events

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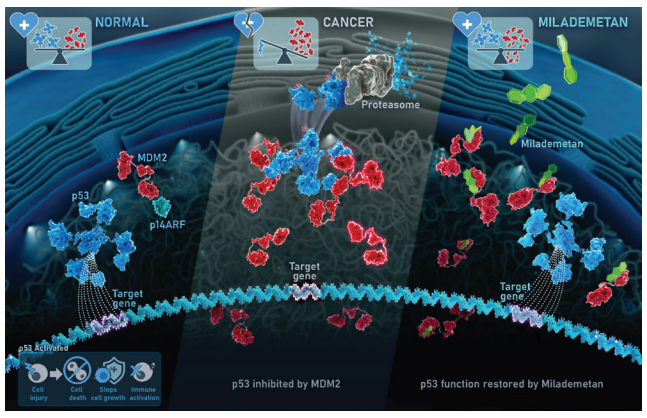
Background

- MDM2 inhibition is a viable therapeutic strategy in several malignancies.
- *MDM2* amplification is found in 3.5% to 7.0% of human cancers,[1,2] although there is currently no accepted copy number threshold for defining *MDM2* status.
- Multiple tumor types display *MDM2* amplification without *TP53* mutations.
- These include sarcomas, urothelial and bladder carcinomas, cholangiocarcinomas, and lung cancers.[1,2]

Milademetan

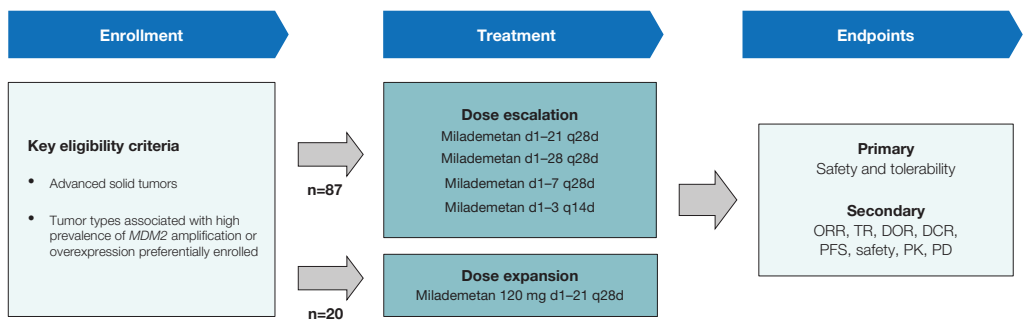
- Milademetan (RAIN-32) is a selective small-molecule inhibitor of the MDM2-p53 interaction and reactivates p53 to induce apoptosis of *TP53* wildtype malignant cells.[1]
- In a first-in-human phase 1 study (**U101**; NCT01877382), milademetan showed promising clinical activity in patients with dedifferentiated liposarcomas (DDLPS).[2]
- Two other studies of milademetan are in progress:
  - **MANTRA** (NCT04979442): a randomized phase 3 study of milademetan vs trabectedin in unresectable/metastatic DDLPS with progression on ≥1 prior systemic therapies (enrollment completed).
  - **MANTRA-2** (NCT05012397): a phase 2 basket study of milademetan in *MDM2*-amplified *TP53*-wildtype advanced solid tumors (currently enrolling).
- We present an overview of available milademetan safety data from phase 1 and 2 studies and guidance from MANTRA investigators on the management of key adverse events associated with milademetan.

Milademetan: Mechanism of action



- Selective small-molecule inhibitor of the MDM2-p53 interaction.
- Reactivates p53 to induce apoptosis of *TP53* wildtype malignant cells.

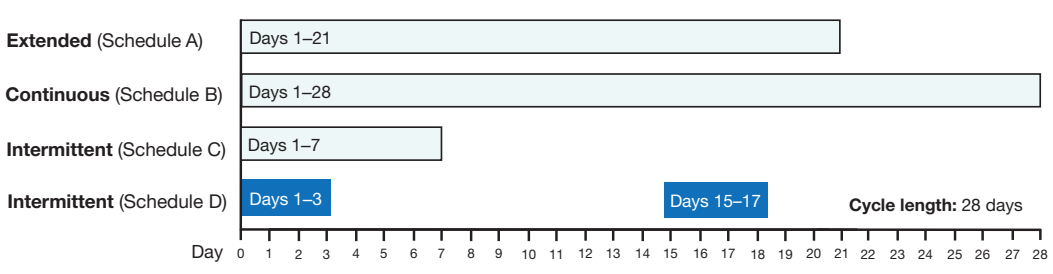
Phase 1 U101: Study design[4]



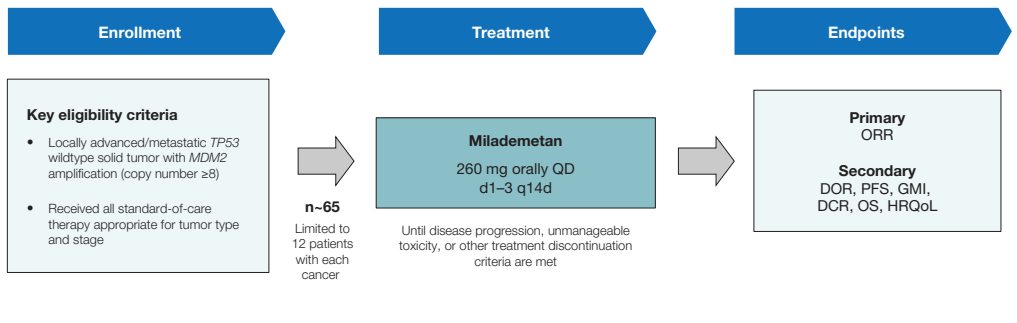
ClinicalTrials.gov Identifier: NCT05012397

DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; TR, time to response

Phase 1 U101: Study schedules[4]



MANTRA-2: Study design



ClinicalTrials.gov Identifier: NCT05012397

DCR, disease control rate; DOR, duration of response; GMI, growth modulation index; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival

Milademetan safety: Phase 1 and 2 studies

	Phase 1 (U101)[4]				Phase 2 (MANTRA-2)[a]	
	Other schedules[b] (n=78)		260 mg 3/14 days (n=20)		260 mg 3/14 days (n=15)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Hematological, n (%)						
Thrombocytopenia*	52 (67)	27 (35)	9 (45)	3 (15)	4 (27)	3 (20)
Anemia	33 (42)	14 (18)	4 (20)	0	1 (7)	0
Neutropenia	22 (29)	15 (19)	2 (10)	1 (5)	1 (7)	1 (7)
Sepsis from neutropenia	0	0	0	0	0	0
Non-hematological, n (%)						
Nausea	57 (73)	2 (3)	16 (80)	0	3 (20)	0
Vomiting	22 (28)	2 (3)	10 (50)	1 (5)	4 (27)	0
Diarrhea	26 (33)	0	5 (25)	0	2 (13)	0

Data are treatment-related AEs; *No episodes of bleeding reported.
[a]Data cutoff: 26 Oct 2022; [b]21/28 days (n=60); 28/28 days (n=9); 7/28 days (n=9).

Milademetan: Adverse event management strategies

- Management recommendations were based on feedback from nine MANTRA sites with clinical experience with milademetan.

Adverse event	Phase 1 (U101) incidence,[a] %	Management
Thrombocytopenia	45	• **Dose interruptions and reductions** were the preferred management option
Nausea/vomiting	80/50	• Perceived onset of nausea was acute in nature with a duration of 3–5 days post dosing • The patient experience with nausea and/or vomiting varied and required an **individualized approach** to anti-emetic treatment options • Use of **anti-emetic therapy** (i.e., 5HT-3 antagonists, benzodiazepines) was encouraged and was found to be beneficial • Use of **benzodiazepines** was reported to be helpful in patients with anticipatory and persistent nausea after common anti-emetic therapy

[a]All-grade treatment-related AEs from U101 phase 1 study (260 mg cohort).

Safety of MDM2 inhibitors currently studied in sarcomas

	Recommended dose schedules for solid tumors									
	Siremadlin[5] 120 mg d1+8/28 days		Navtemadlin[6] 240 mg 7/21 days		BI 907828[7] 45 mg 1/21 days		Milademetan 260 mg 3/14 days			
	(n=29)		(n=68)		(n=59)		Phase 1 (n=20)[3]		Phase 2 (n=15)[a]	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Hematological, %										
Thrombocytopenia	31[b]	14[b]	21	ND	36	19	45	15	27	20
Anemia	52	21	15	ND	24	10	20	0	7	0
Neutropenia	31	28	18	ND	41	20	10	5	7	7
Non-hematological, %										
Nausea	69	7	68	ND	66	7	80	0	20	0
Vomiting	41	3	47	ND	36	2	50	5	27	0
Diarrhea	17	0	68	ND	ND	ND	25	0	13	0

Data are treatment-related AEs; ND, no data available.
[a]Data cutoff: 26 Oct 2022; [b]Note: "Platelet count decreased" listed as a separate term (all-grade 31%; grade ≥3 10%).

Conclusions

- Milademetan has a well-established safety profile, mainly represented by thrombocytopenia and nausea, both of which are common MDM2 inhibitor class effects.
- Antiemetics, such as 5HT-3 antagonists and benzodiazepines, should be considered as prophylaxis for nausea/vomiting.
- An intermittent dosing schedule (3/14 days) mitigates the occurrence and severity of thrombocytopenia.
- Platelet transfusions and growth factors have limited utility in prolonged thrombocytopenia.
- Dose interruptions and dose reductions prevent unnecessary treatment withdrawal and are the preferred management options for thrombocytopenia.
- Results of the phase 3 MANTRA study are expected during the first half of 2023.

References

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Acknowledgements

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- This poster discusses the investigational use of the MDM2 inhibitor milademetan (RAIN-32) in patients with various solid tumors, including sarcomas.
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