



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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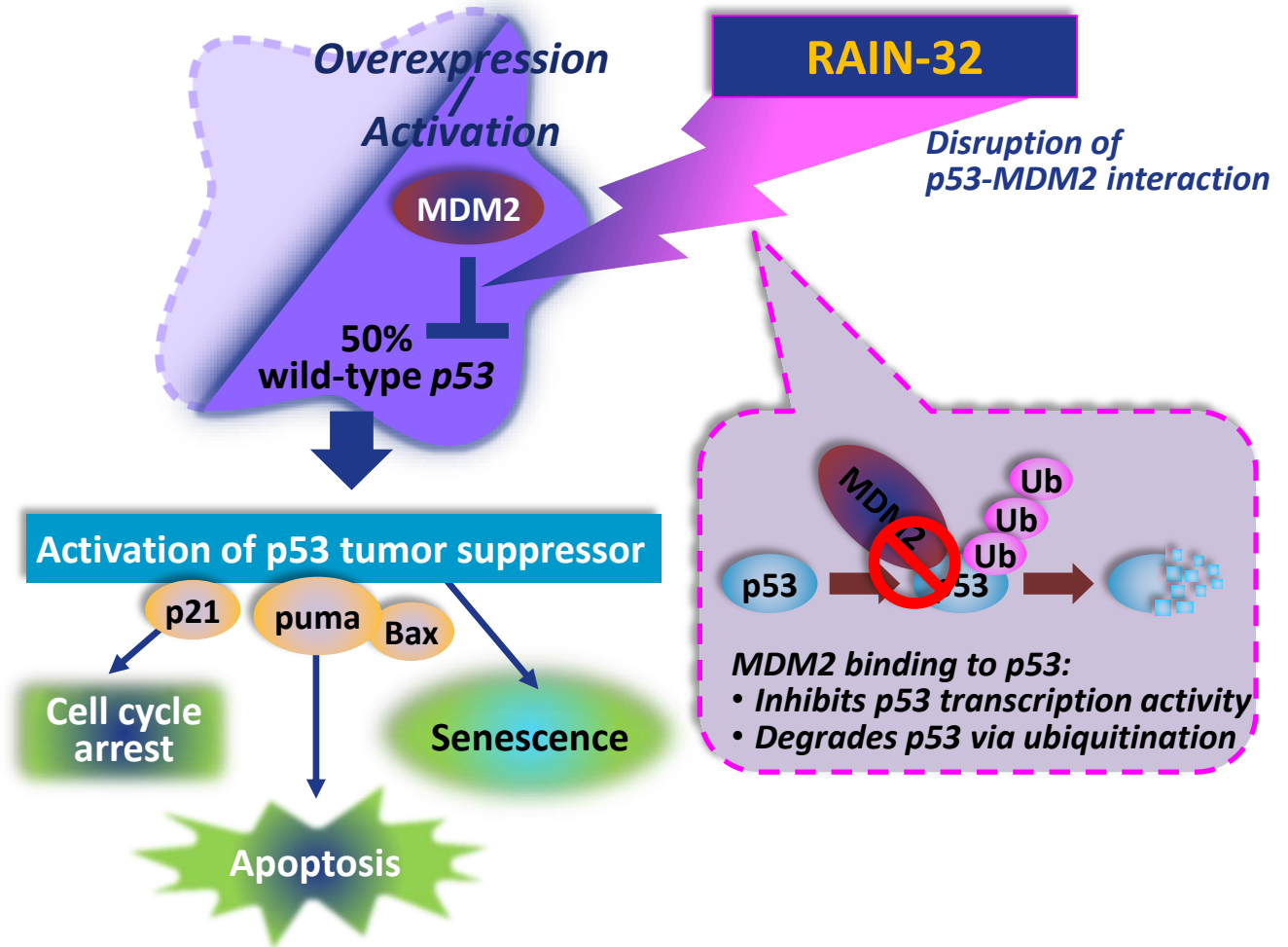
- Dr Gounder participated in advisory boards and also received sponsored research support from Daiichi Sankyo

MDM2 Overexpression Can Inactivate p53

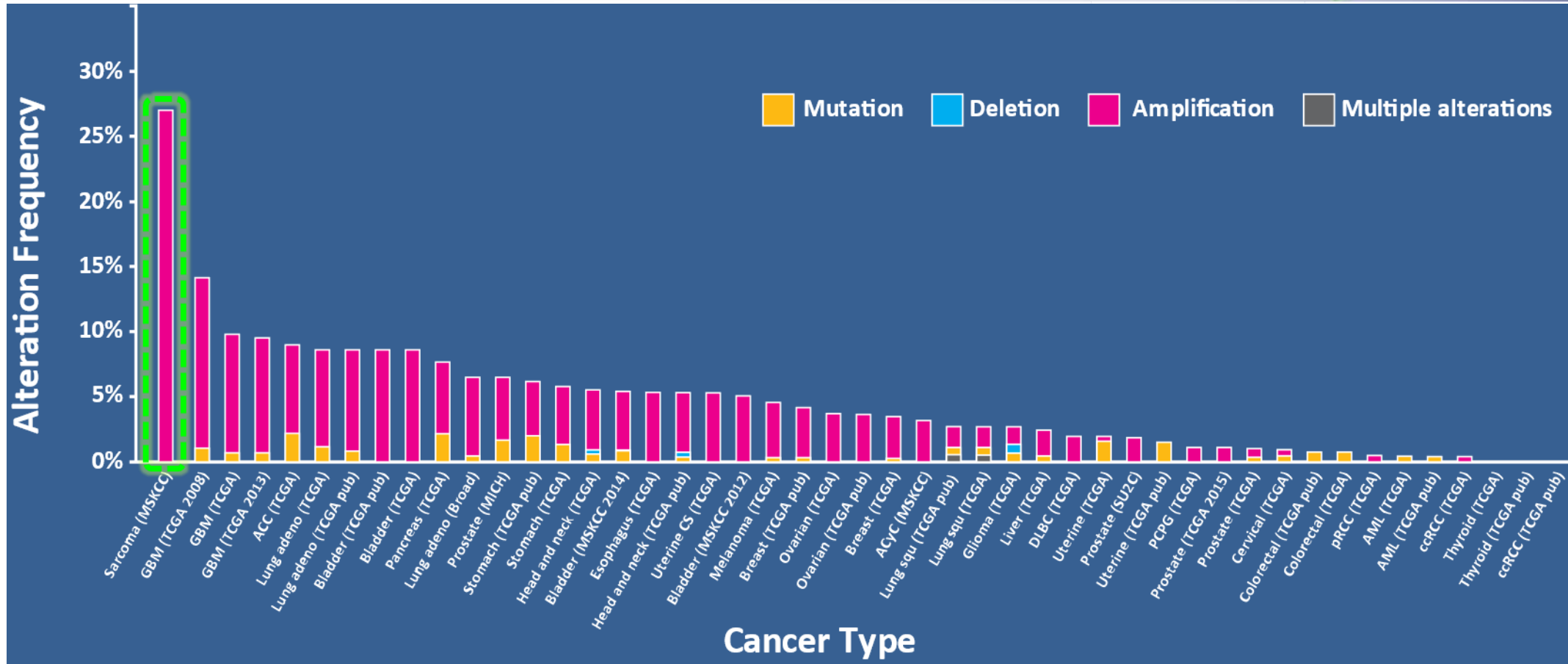
- p53 is the most commonly mutated protein across cancer¹
- Missense/inactivating mutations in *TP53* are most common
- Several additional mechanisms of WT p53 inactivation exist – one such mechanism is MDM2 overexpression¹

Milademetan Inhibits the p53-MDM2 Interaction

- 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



MDM2 Amplification ~ 17% Across All Cancers



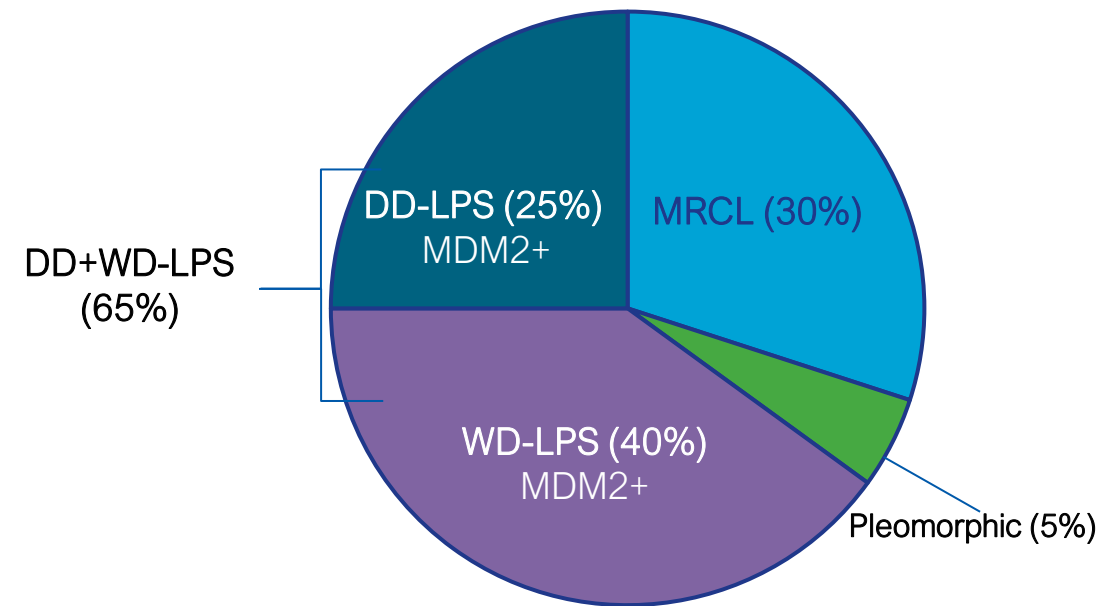
- MDM2 amplification is a hallmark of well/dedifferentiated liposarcoma (WD/DD LPS)

MDM2 Gene Amp: A Hallmark of 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 trabectedin^{5,6}
- 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



MRCL, myxoid round cell liposarcoma

1. Asano, N. *et al. Oncotarget*. 2017;8:12941-12952. 2. Ducimetière F, et al. *PLoS One*. 2011;6:e20224-e20294. 3. Kim HS, et al. *BMC Cancer*. 2009;9:1-8. 4. Kim YJ, et al. *Lab Invest*. 2019; doi:10.1038/s41374-019-0263-4. 5. Eribulin (HALAVEN) [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2016. 6. Trabectedin (YONDELIS) [package insert], Horsham, PA; Janssen Products; 2015. 7. Manji GA, Schwartz GK. *J Oncol Pract*. 2016;12(3):221-227. 8. Nassif NA, et al. *F1000Res*. 2016;5:2907. 9. Maki RG. *Ann Oncol*. 2012;23(suppl_9):abstract 93IN. 10. Crago AM et al. *Surg. Oncol. Clin. N. Am.* 2016;25(4):761-773. 11. Katz D, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:925-938.

Trial Design – First in Human

Primary endpoints:

Safety, MTD, PK, PD

Secondary endpoints:

Tumor response

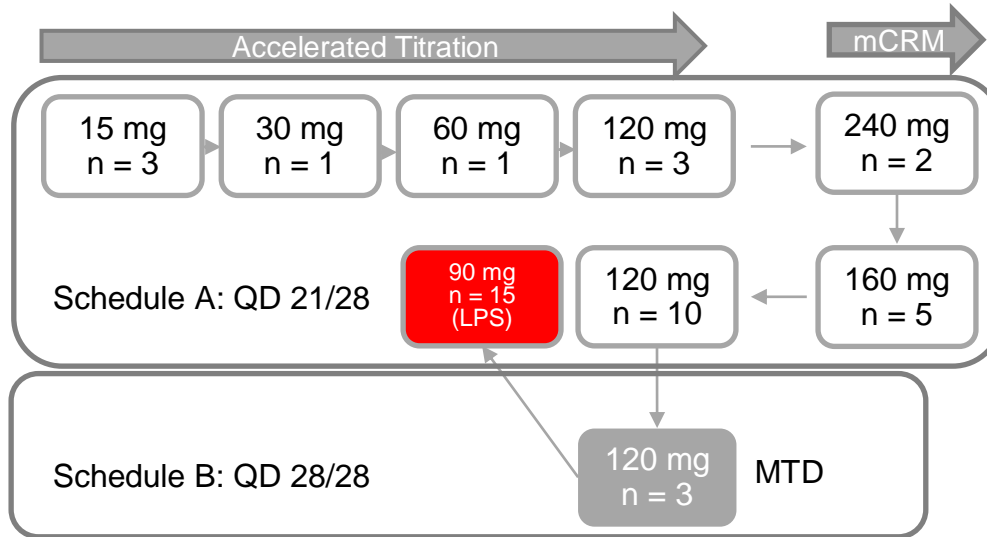
Key inclusion criteria

- 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

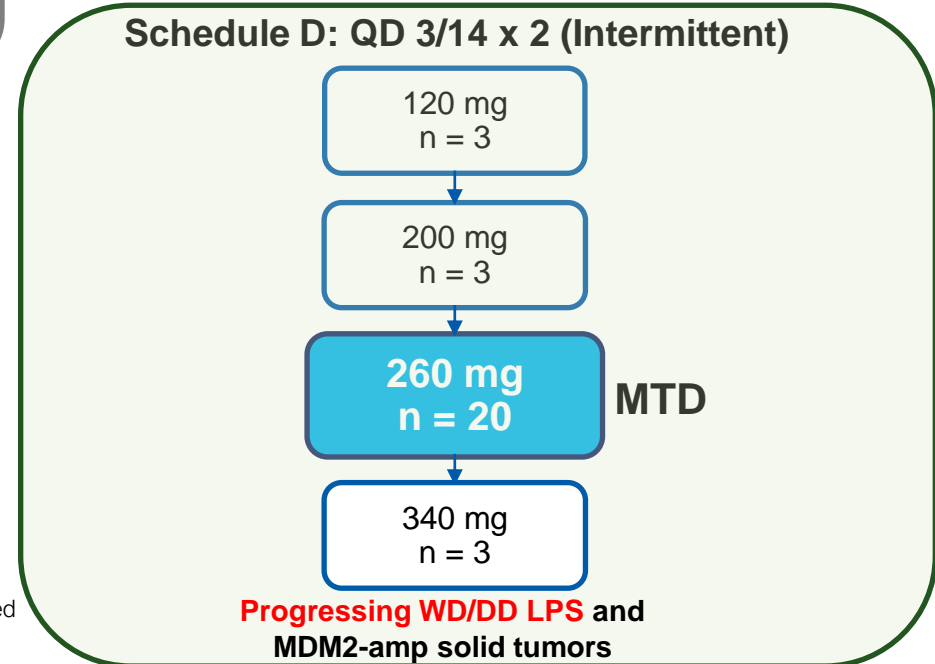
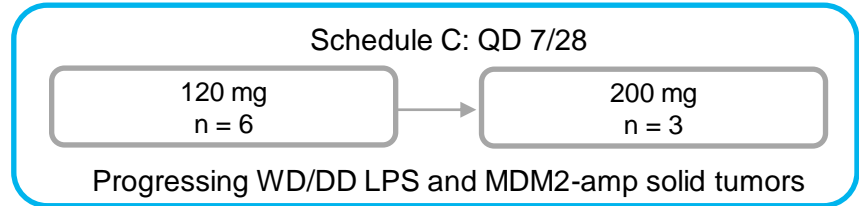
Key exclusion criteria

- **KNOWN** - *TP53* mutation, insertion, or deletion

Dose Escalation



Intermittent Schedule



Baseline Patient Characteristics

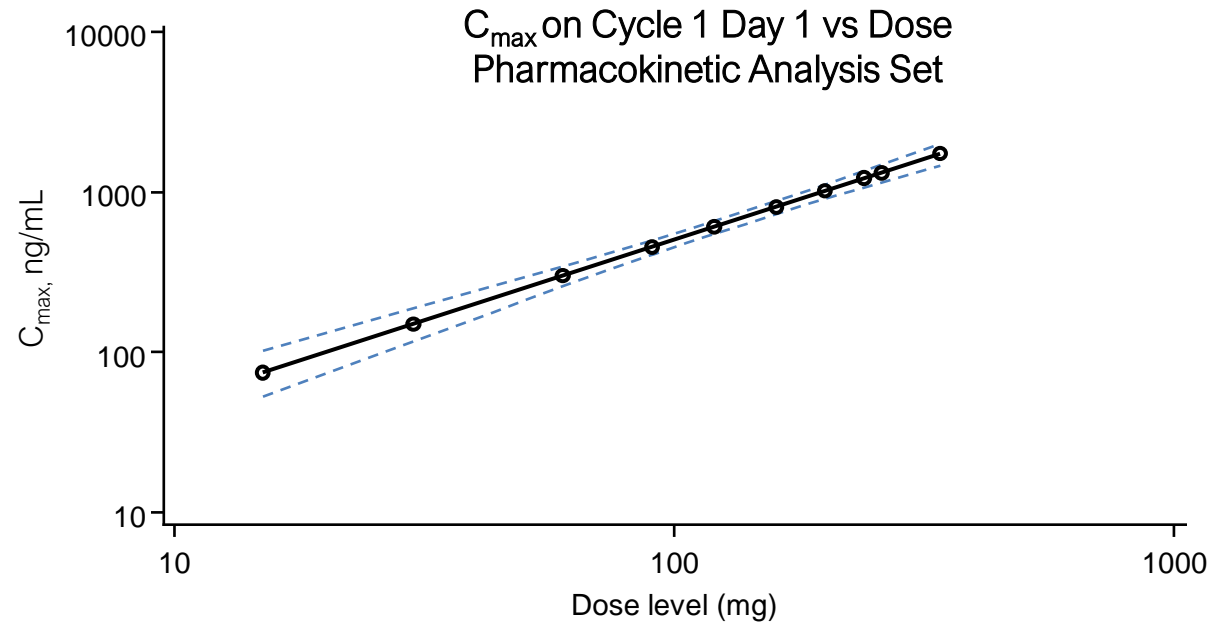


Baseline Characteristics		All Cohorts (N = 107)	Patients with LPS (n = 53)
Age, median (range), y		61 (25-88)	62.0 (37-88)
Gender, n (%)	Male	54 (50.5)	29 (54.7)
Cancer type, n (%)	WD/DD LPS (MDM2 amp)	53 (49.5)	NA
	Osteosarcoma (MDM2 amp)	3 (2.8)	
	Intimal sarcoma (MDM2 amp)	2 (1.8)	
	Synovial sarcoma (MDM2 amp)	2 (1.8)	
	Leiomyosarcoma	1 (0.9)	
	Other	44 (41.1)	
Cancer stage at entry, n (%)	0-II	13 (12.1)	8 (15.1)
	III-IV	92 (85.9)	44 (83.0)
ECOG PS, n (%)	0	43 (40.2)	23 (43.4)
	1	64 (59.8)	30 (56.6)
No. of prior cancer therapies, n (%)	0	17 (15.9)	17 (32.1)
	1	10 (9.3)	7 (13.2)
	2	14 (13.1)	8 (15.1)
	≥3	66 (61.7)	21 (39.6)
TP53 mutation status, n (%) ^a	Wild type	83 (77.6)	40 (75.5)
	Inactivating mutation	1 (0.9)	1 (1.9)
	Indeterminate/unknown	23 (21.5)	12 (22.6)

Half of the patients had WD/DD LPS

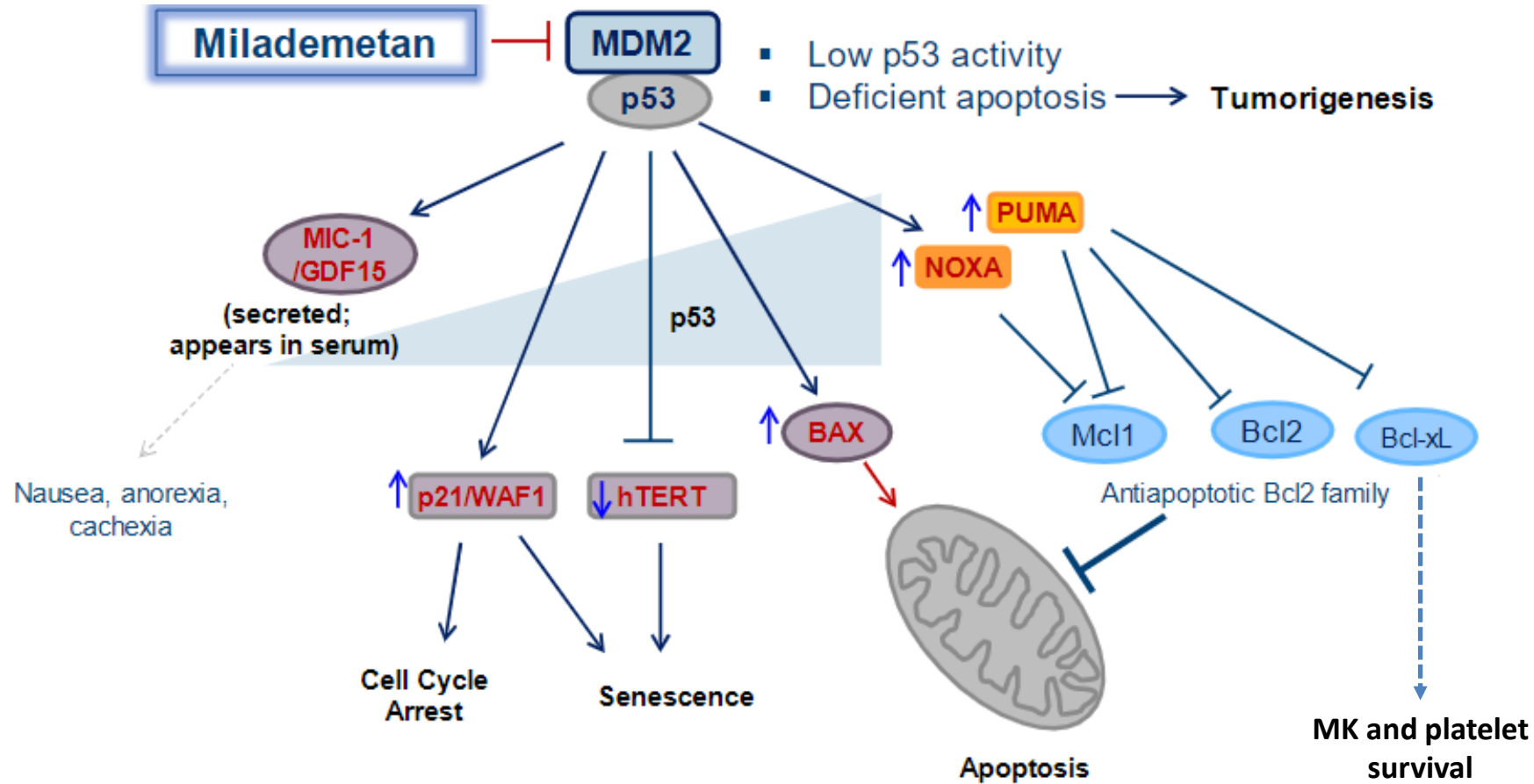
The majority of patients received ≥2 prior therapies

Milademetan Dosing Shows Linear PK



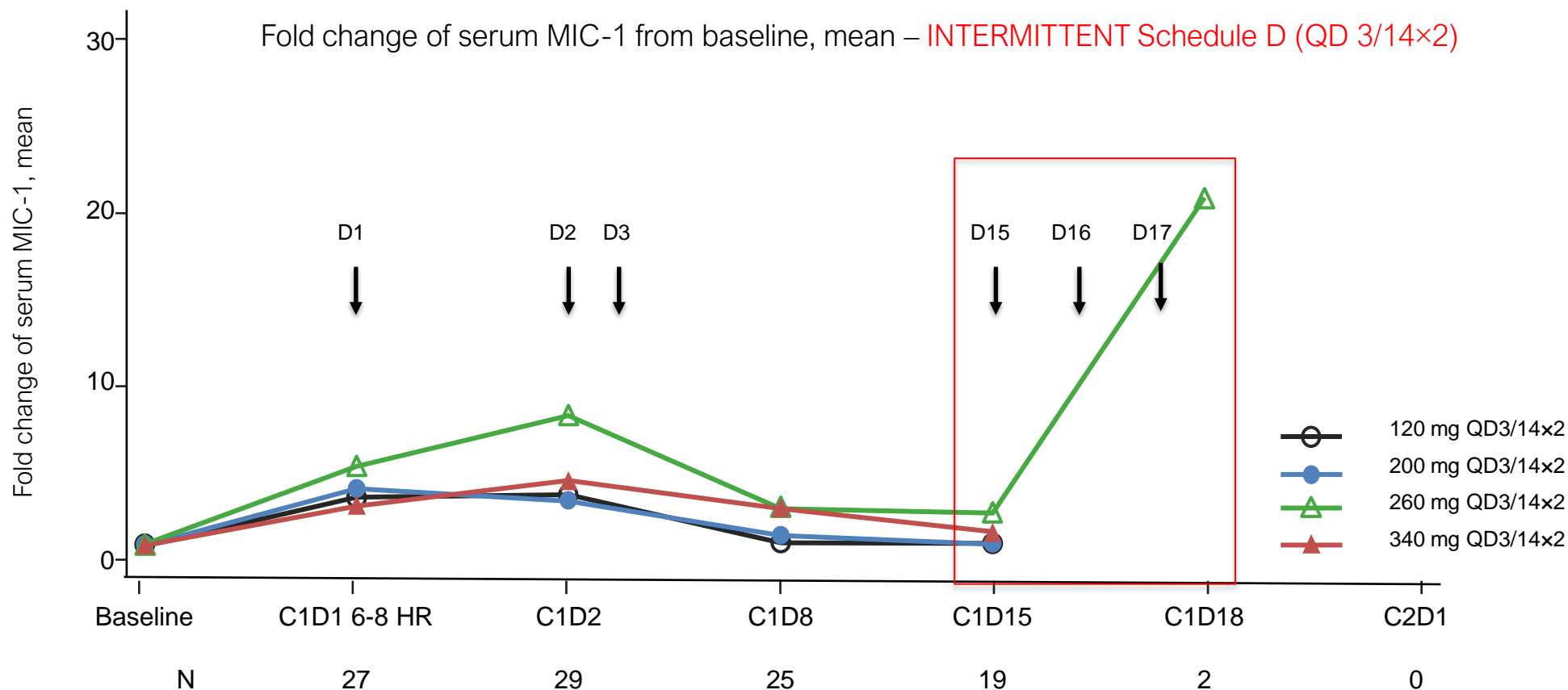
- Plasma C_{max} (and AUC) of milademetan increased in a dose-dependent manner following single doses from 15 mg to 340 mg¹
- Median T_{max} was approximately 3 hours

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

Pharmacodynamics: Increase in Serum MIC-1 Signals p53 Reactivation



Intermittent Dosing of Milademetan Markedly Improves Toxicity Profile

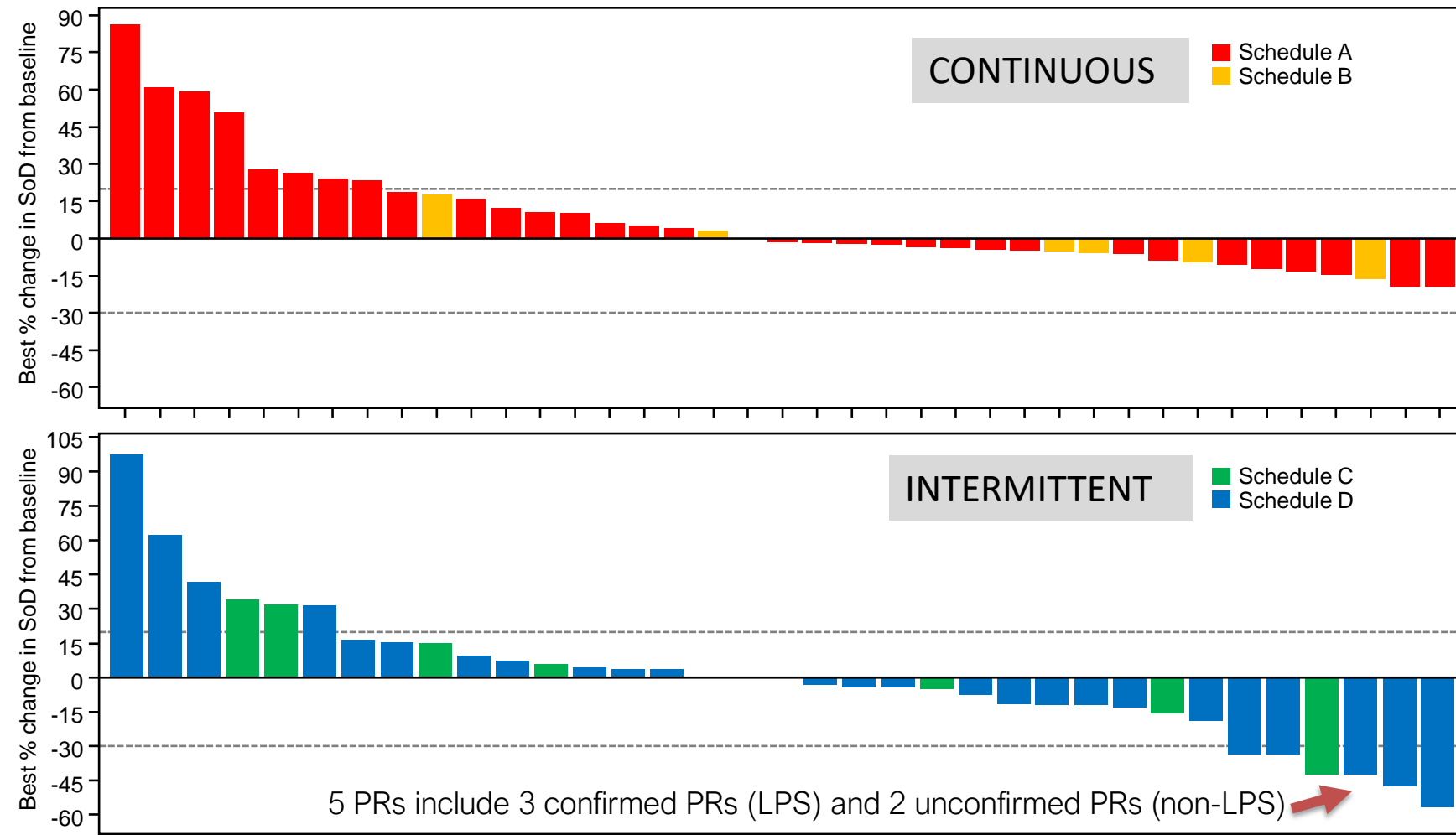


Select Drug-Related TEAEs of Interest

System Organ Class, Preferred Term, n (%)	Schedule A, B, and C CONTINUOUS (n = 78)		Schedule D INTERMITTENT (n = 29)		Schedule D INTERMITTENT (260mg) (n=20)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All drug-related TEAEs	74 (94.9)	43 (55.1)	25 (86.2)	5 (17.2)	18 (90.0)	4 (20.0)
Blood and lymphatic system						
Thrombocytopenia	52 (66.7)	27 (34.6)	13 (44.8)	4 (13.8)	9 (45.0)	3 (15.0)
Anemia	33 (42.3)	14 (17.9)	5 (17.2)	0	4 (20.0)	0
Neutropenia	10 (12.8)	8 (10.3)	1 (3.4)	1 (3.4)	1 (5.0)	1 (5.0)
Gastrointestinal						
Nausea	57 (73.1)	2 (2.6)	20 (69.0)	0	16 (80.0)	0
Vomiting	22 (28.2)	2 (2.6)	13 (44.8)	1 (3.4)	10 (50.0)	1 (5.0)
Diarrhea	26 (33.3)	0	9 (31.0)	0	5 (25.0)	0
General disorders						
Fatigue	36 (46.2)	3 (3.8)	12 (41.4)	0	8 (40.0)	0

- Milademetan 260 mg QD 3/14 has been chosen as the dose to develop further

Milademetan Was Effective in Patients With All Solid Tumors



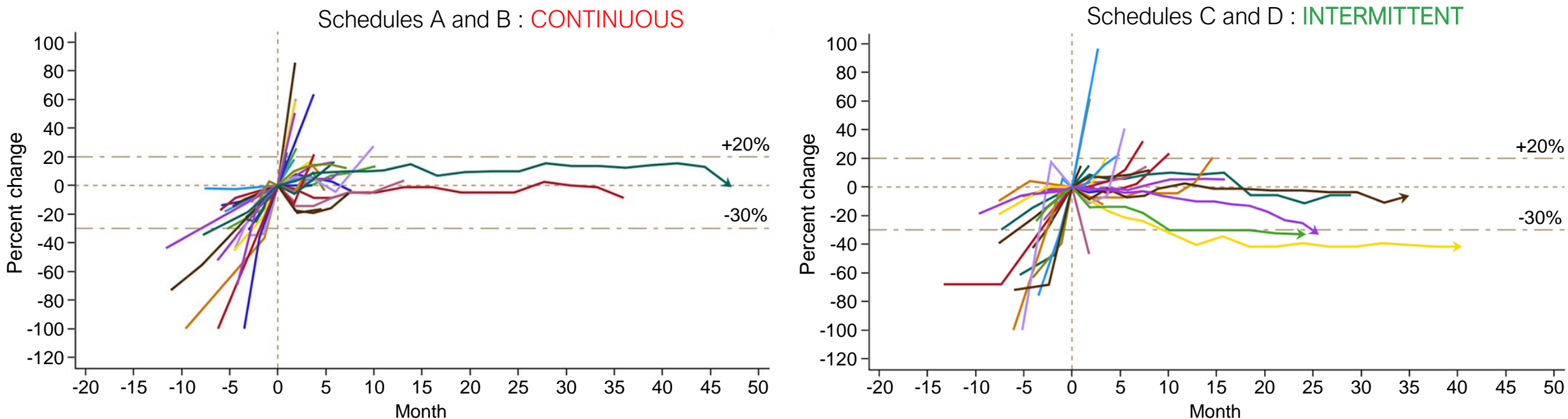
Response (All Patients)		N = 107
Best Overall Response, n (%)		
CR		0
PR		5 (4.7)
SD		56 (52.3)
PD		29 (27.1)
Not evaluable		17 (15.9)
ORR (CR+PR), n (%)		5 (4.7)
95% CI		1.5-10.6
DCR (CR+PR+SD), n (%)		49 (45.8)
95% CI		36.1-55.7

DCR LPS vs non-LPS, % (95% CI)	
WD/DD LPS (n = 53)	58.5% (44.1, 71.9)
Non-LPS (n = 34)	32.4% (17.4, 50.5)

Milademetan Alters Tumor Growth Kinetics in Progressing WD/DD Liposarcoma

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

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



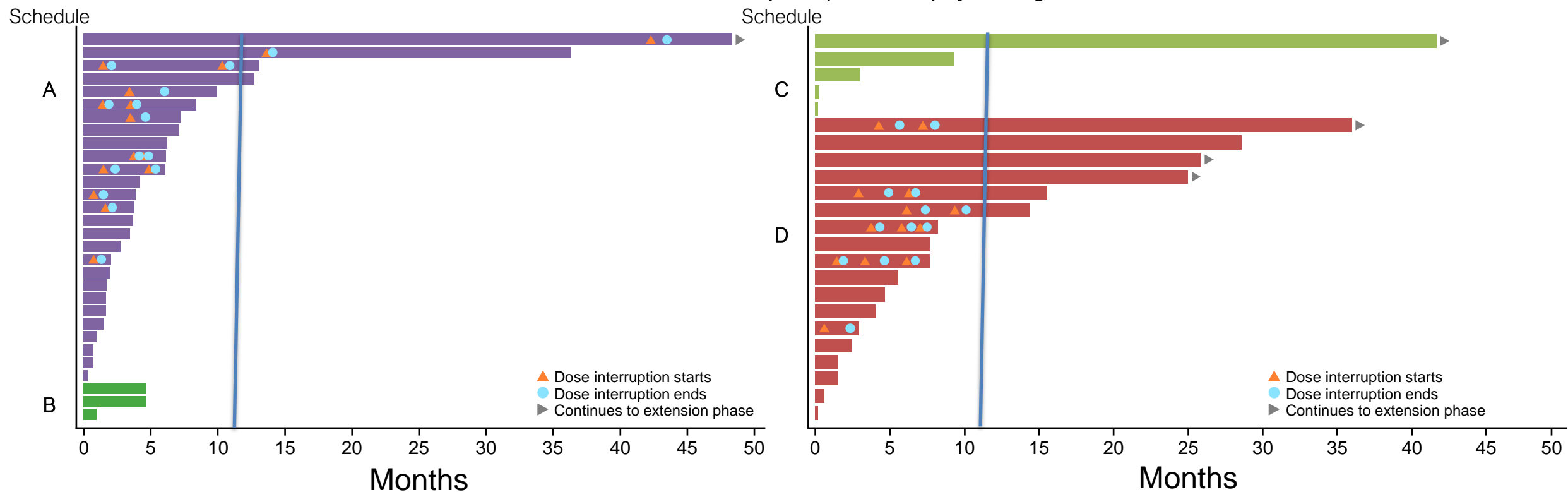
- Median (95% CI) duration of stable disease was 59.9 (15.1 to NR) weeks

Patients With Liposarcoma Achieved Long Duration of Therapy



- Patients were able to interrupt milademetan dose and continue therapy

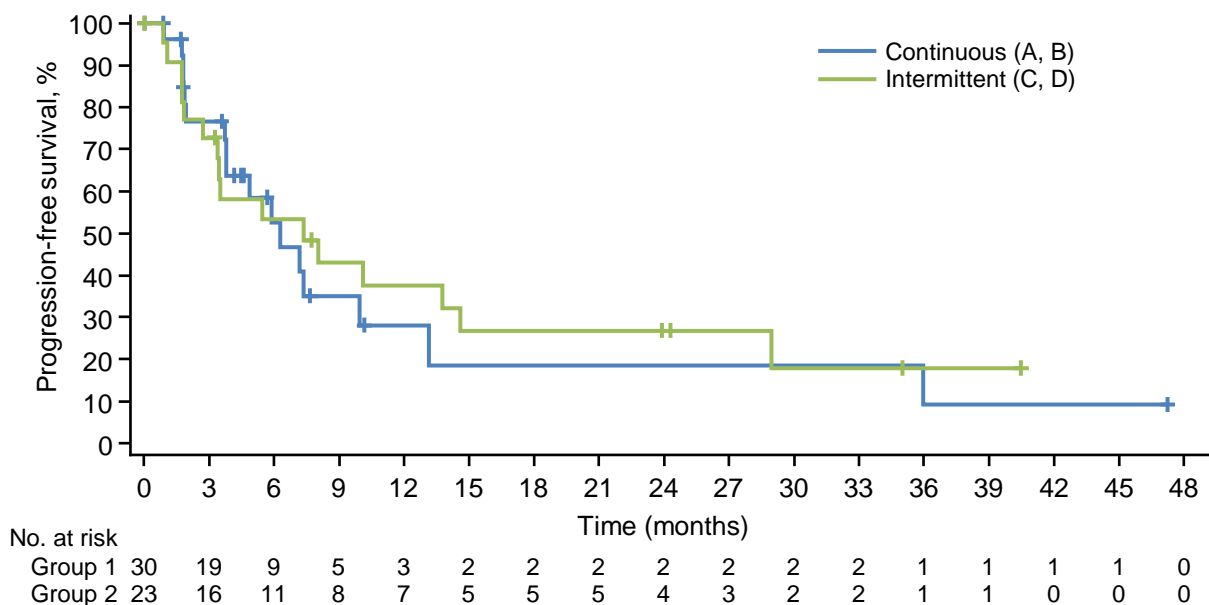
Treatment Duration and Dose Interruption (≥ 2 Weeks) by Dosing Schedule



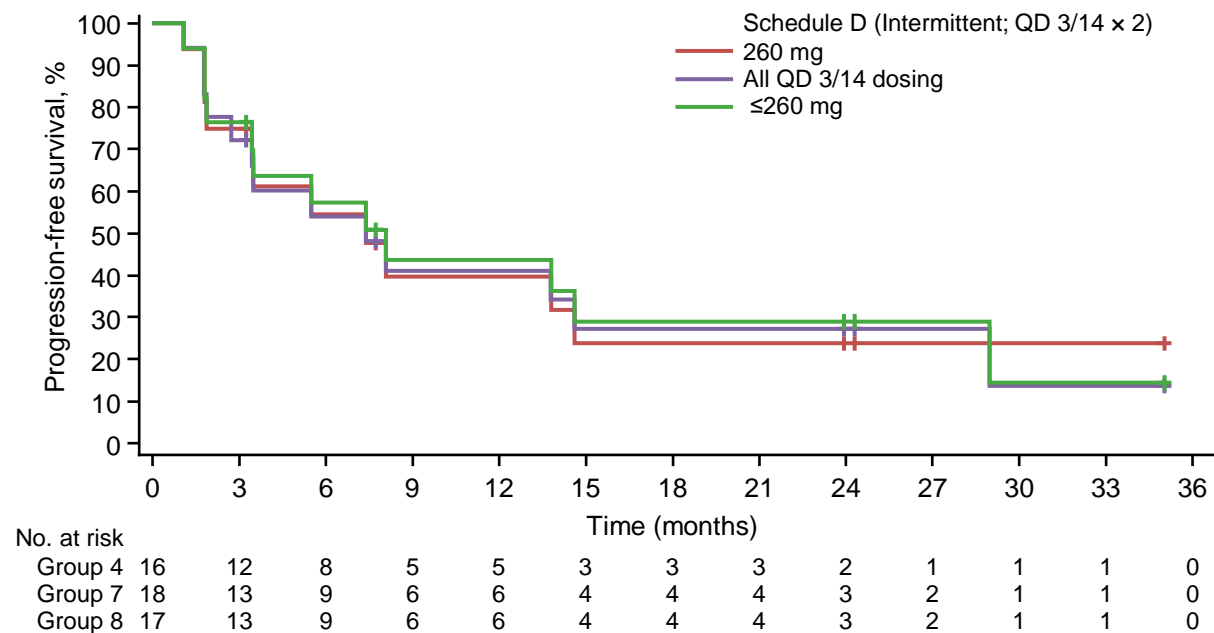
- 5 patients ongoing >2 years

Intermittent Dosing Maintains Efficacy in Patients With LPS

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



	Continuous (A/B)	Intermittent (C/D)
Median PFS, mo (95% CI)	6.3 (3.8, 10.0)	7.4 (2.7, 14.6)



	Schedule D 260 mg	Schedule D including 340 mg	Schedule D ≤ 260 mg
Median PFS, mo (95% CI)	7.4 (1.8, 14.6)	7.4 (2.7, 28.9)	8.0 (1.8, 28.9)

- 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 *MDM2* gene amplification, indicating potential for agnostic clinical trial using biomarker selection



- We thank the patients and their families, as well as the study investigators and staff
- This study was funded by Daiichi Sankyo