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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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MDM2 Overexpression Can Inactivate p53

- p53 is the most commonly mutated protein across cancer[1]
- Missense/inactivating mutations in *TP53* are most common
- Several additional mechanisms of WT p53 inactivation exist – one such mechanism is MDM2 overexpression[1]

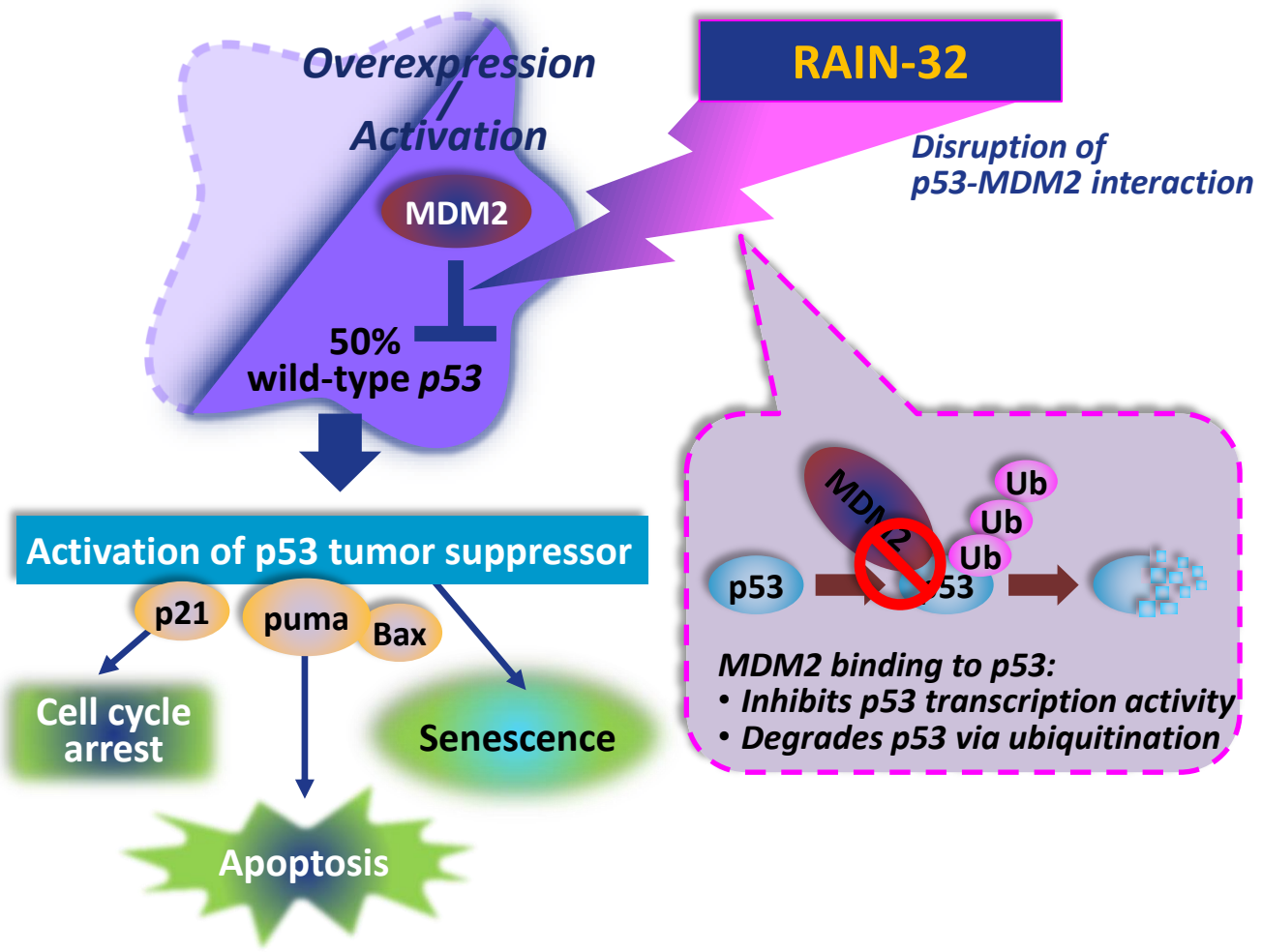
MDM2, murine double minute 2

1. Hientz, K, et al. *Oncotarget.* 2017;8(5):8921-8946.

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



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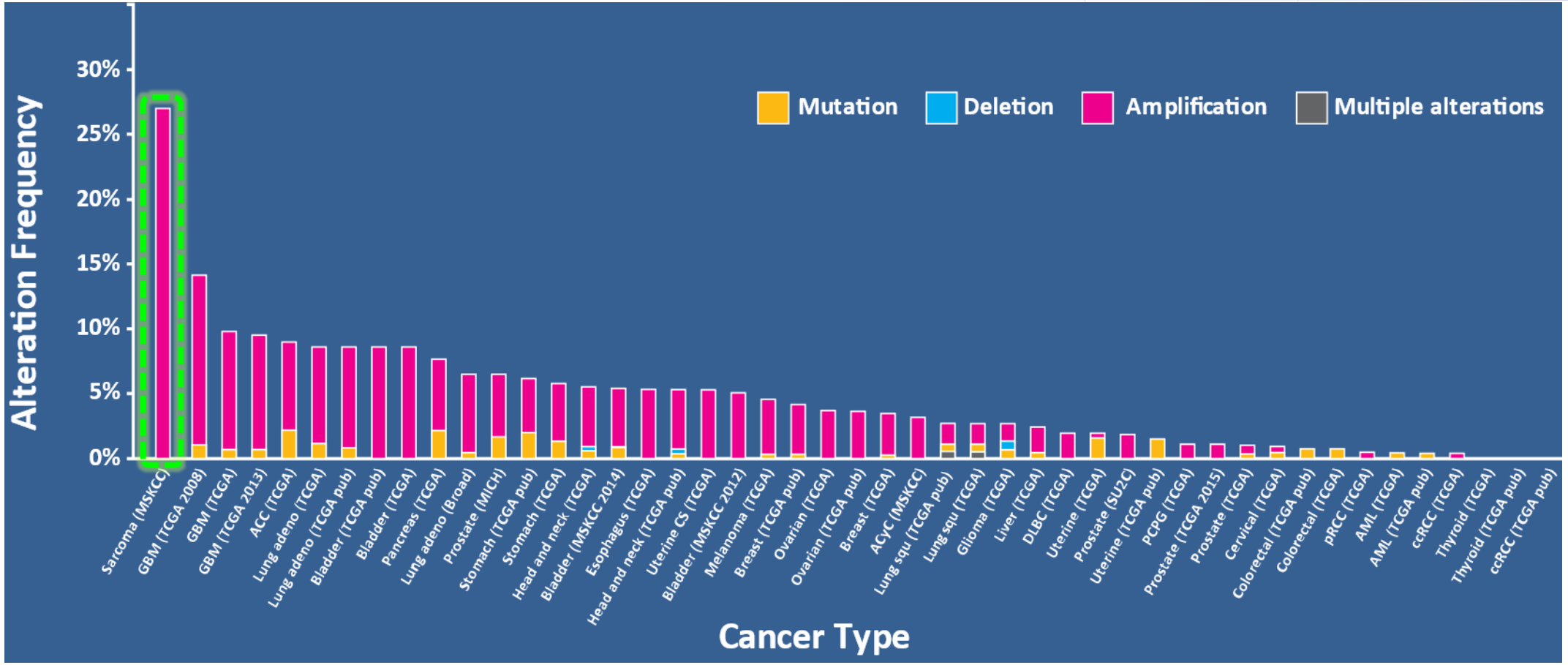
MDM2 Amplification ~ 17% Across All Cancers



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

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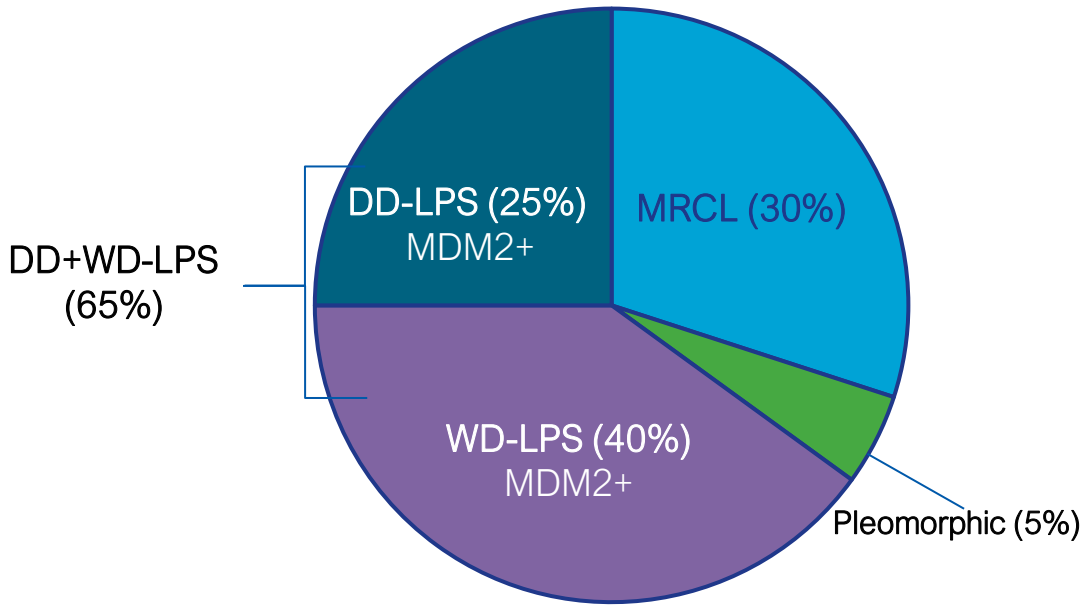
Wasylishen and Lozano, 2016. *Cold Spring Harb Perspect Med.* 2015;6:a026211, © Cold Spring Harbor Laboratory Press.

MDM2 Gene Amp: A Hallmark of WD/DD LPS

- Liposarcoma (LPS) accounts for approximately 15 - 20% of adult soft tissue sarcomas[1-4]
- Well-differentiated/dedifferentiated LPS (WD/DD) LPS is characterized by *MDM2* gene amplification in up to 100% of cases[1]
- 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 Frequency[7-11]



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.

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Trial Design – First in Human

Primary endpoints:

Safety, MTD, PK, PD

Secondary endpoints:

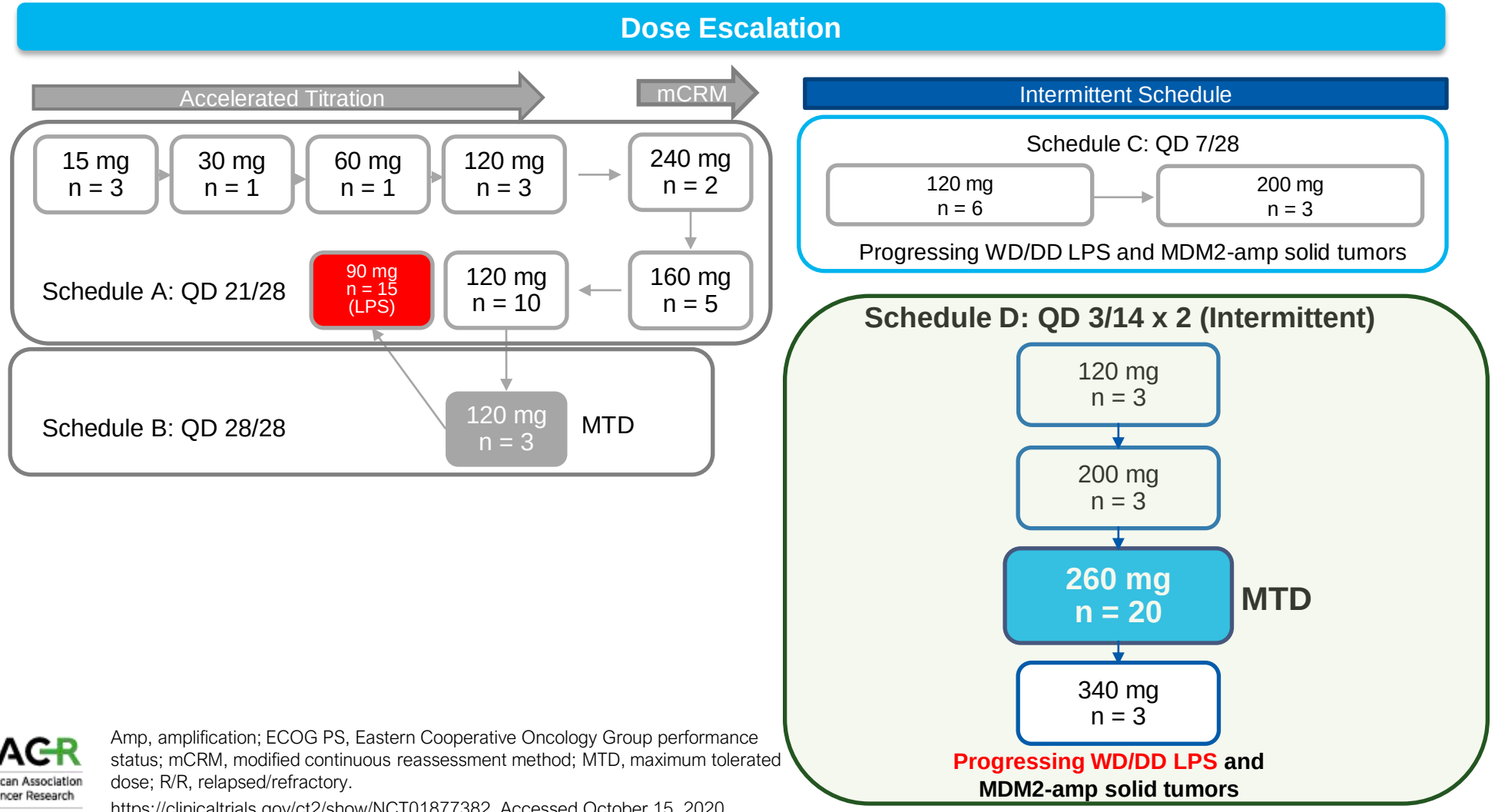
Tumor response

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



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

https://clinicaltrials.gov/ct2/show/NCT01877382. Accessed October 15, 2020.

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Baseline Patient Characteristics

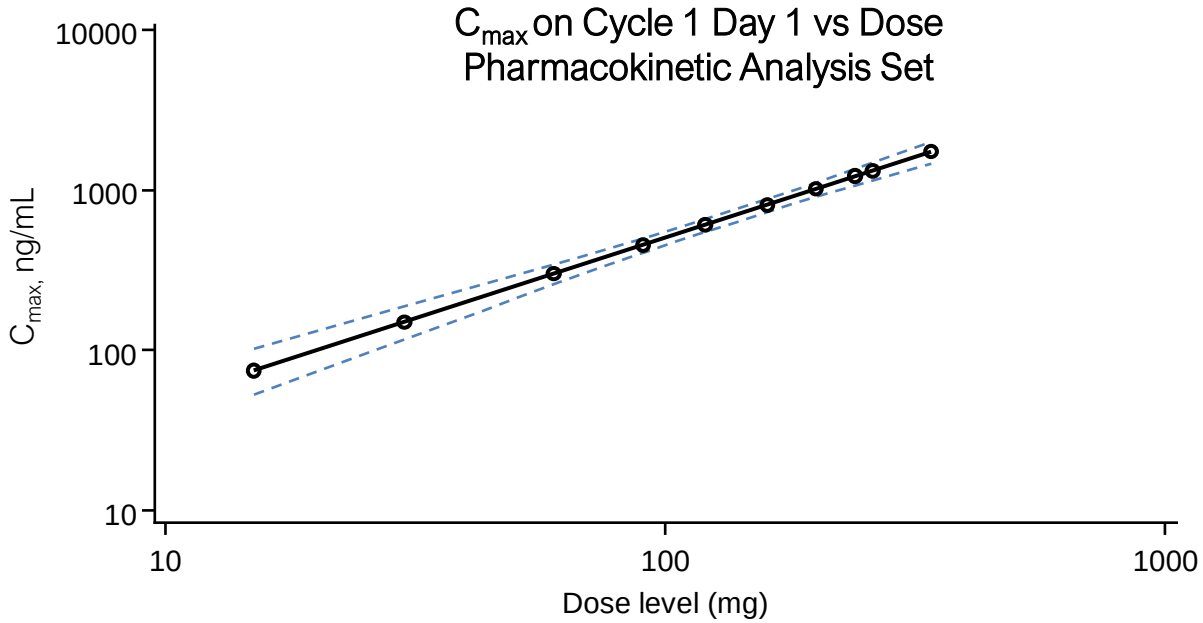
Baseline Characteristics		All Cohorts (N = 107)	Patients with LPS (n = 53)
Age, median (range), y		61 (25-88)	62.0 (37-88)
Gender, n (%)	Male	54 (50.5)	29 (54.7)
Cancer type, n (%)	WD/DD LPS (MDM2 amp) Osteosarcoma (MDM2 amp) Intimal sarcoma (MDM2 amp) Synovial sarcoma (MDM2 amp) Leiomyosarcoma Other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

Half of the patients had WD/DD LPS

The majority of patients received ≥2 prior therapies

NA, not applicable
[a]Reported by local laboratory.
Percentages may not sum to 100 due to rounding.

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 mg[1]
- Median T_{max} was approximately 3 hours

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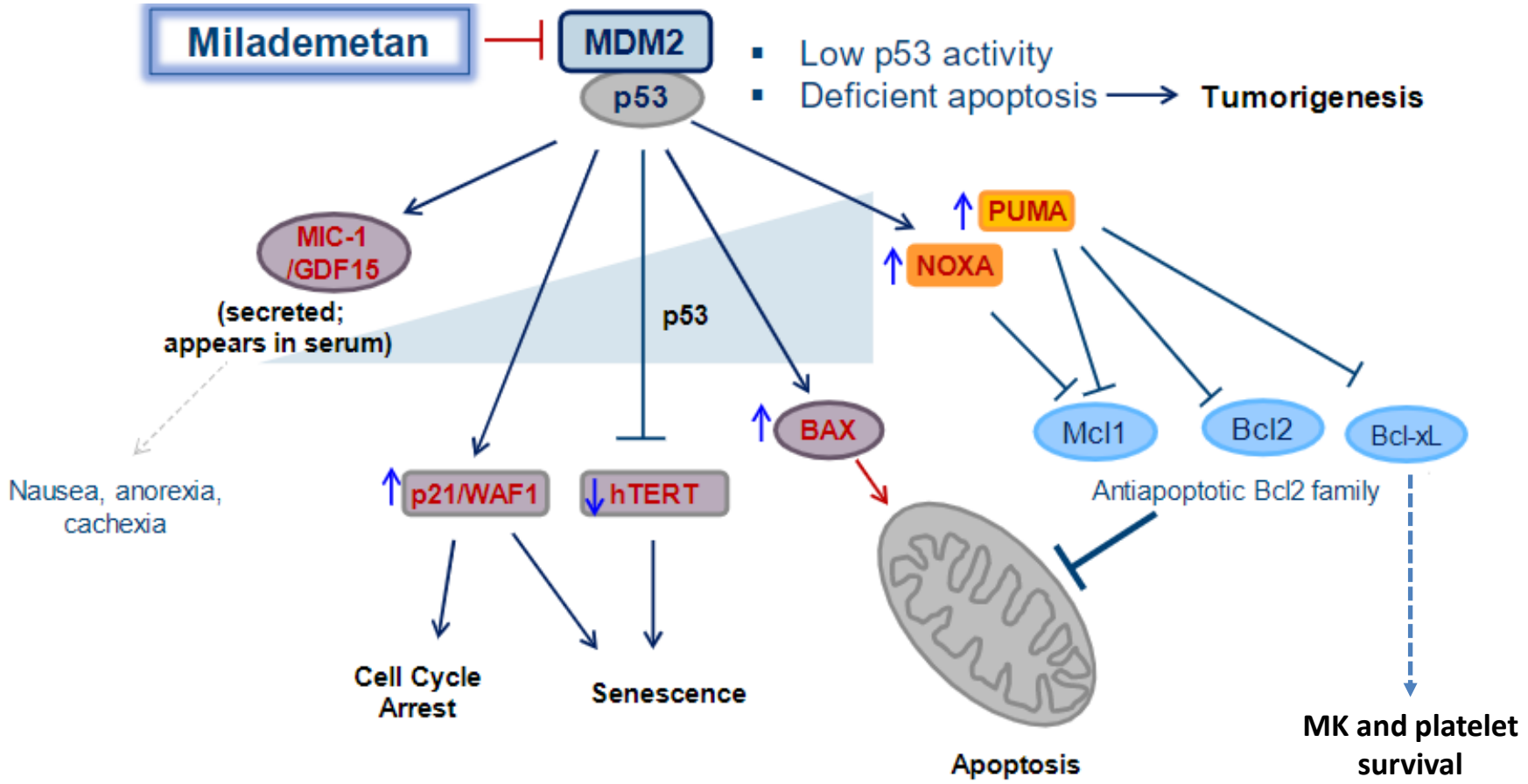
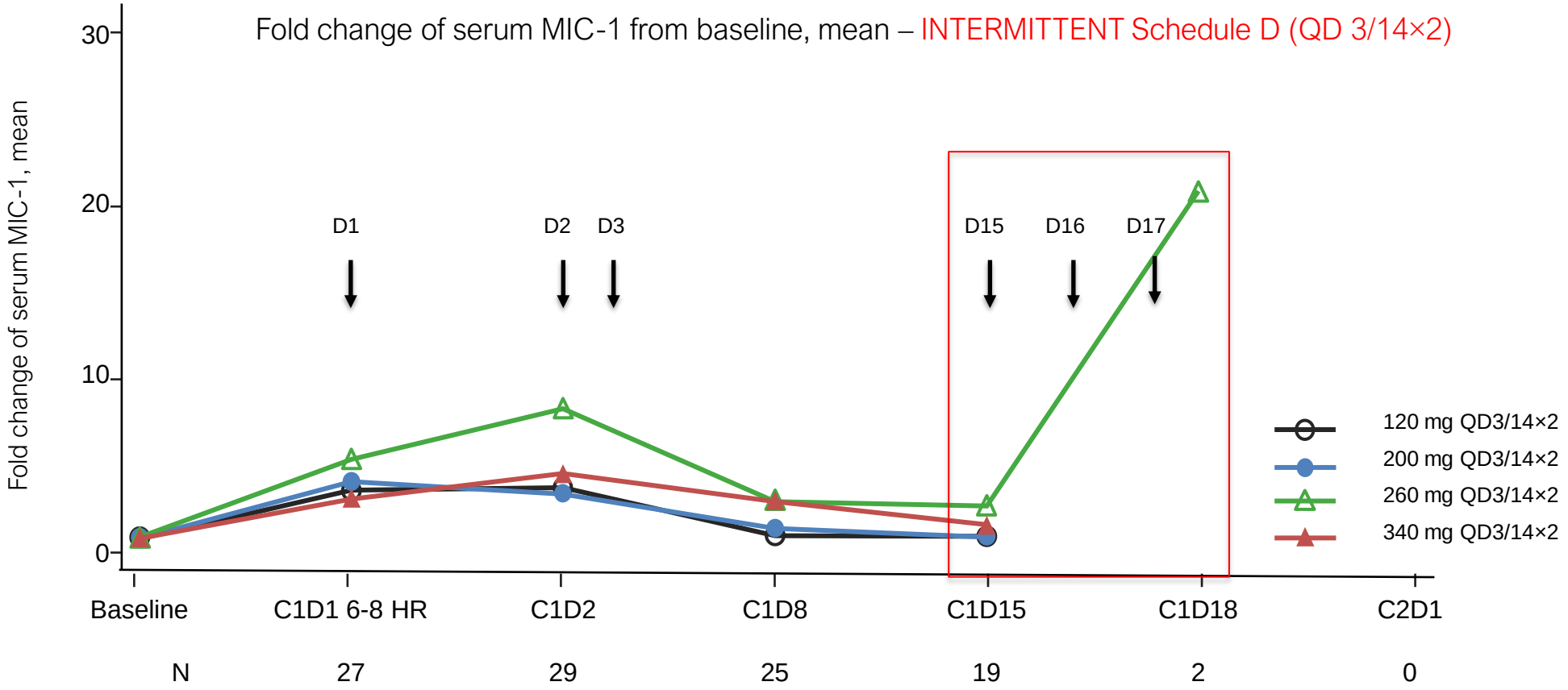
Activation of p53: Upregulation of MIC-1



- Mirademetan 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

Khoo et al. *Nature Rev.* 2014;13:217-236. Hata et al. *Cancer Discov.* 2015;5(5):475-487. Kanaya et al. *Clin Cancer Res.* 2000;6,1239-1247.
Chen et al. *Mol Cell.* 2005;17:393-403. Jeay et al. *Cancer Res*. 2018;78:6257-6267.
MIC-1 = macrophage inhibitory cytokine 1; PD = pharmacodynamic.

Pharmacodynamics: Increase in Serum MIC-1 Signals p53 Reactivation



AUC, area under the concentration–time curve; C, cycle; C_{max}, maximal concentration; D, day; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily; T_{max}, time to peak concentration.

1. Gounder M, et al. CTOS 2018 Annual Meeting; November 14-17, 2018; Rome, Italy. Paper 019.

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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

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TEAE, treatment-emergent adverse event.

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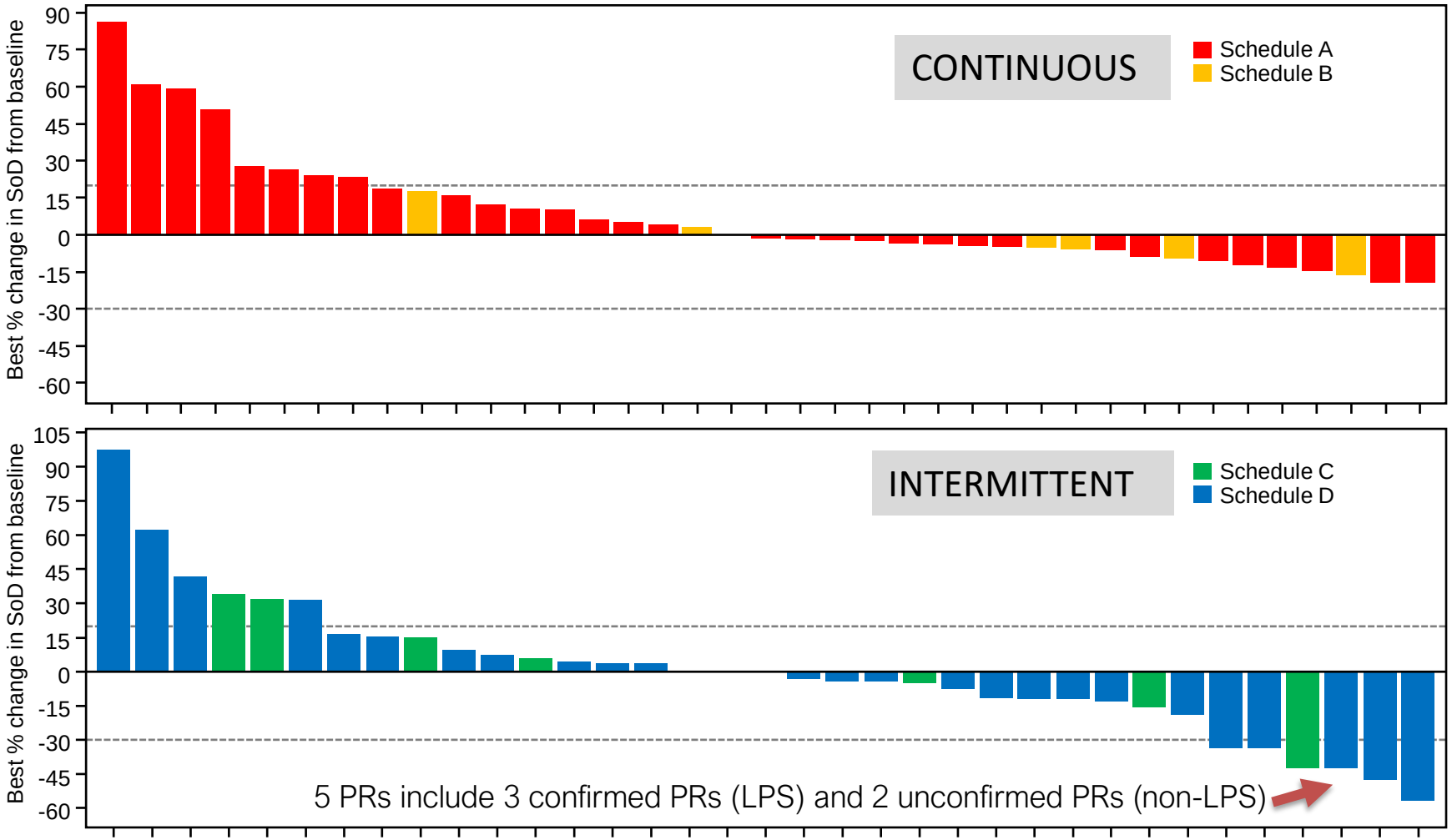
Mlademetan Was Effective in Patients With All Solid Tumors



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)

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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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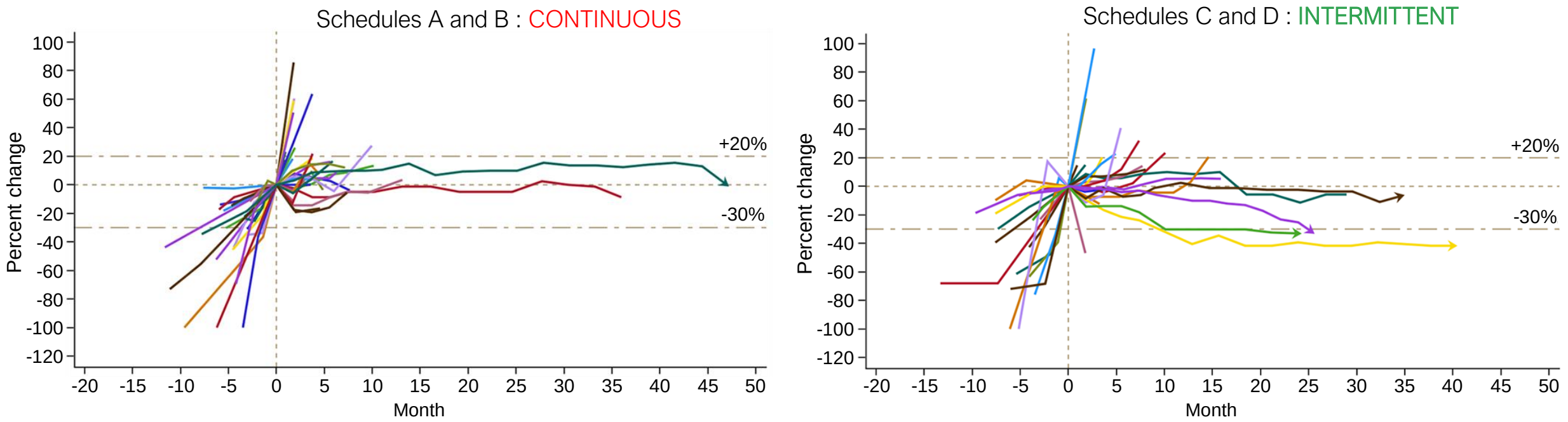
Miladematan Alters Tumor Growth Kinetics in Progressing WD/DD Liposarcoma

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

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



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

NR, not reported.

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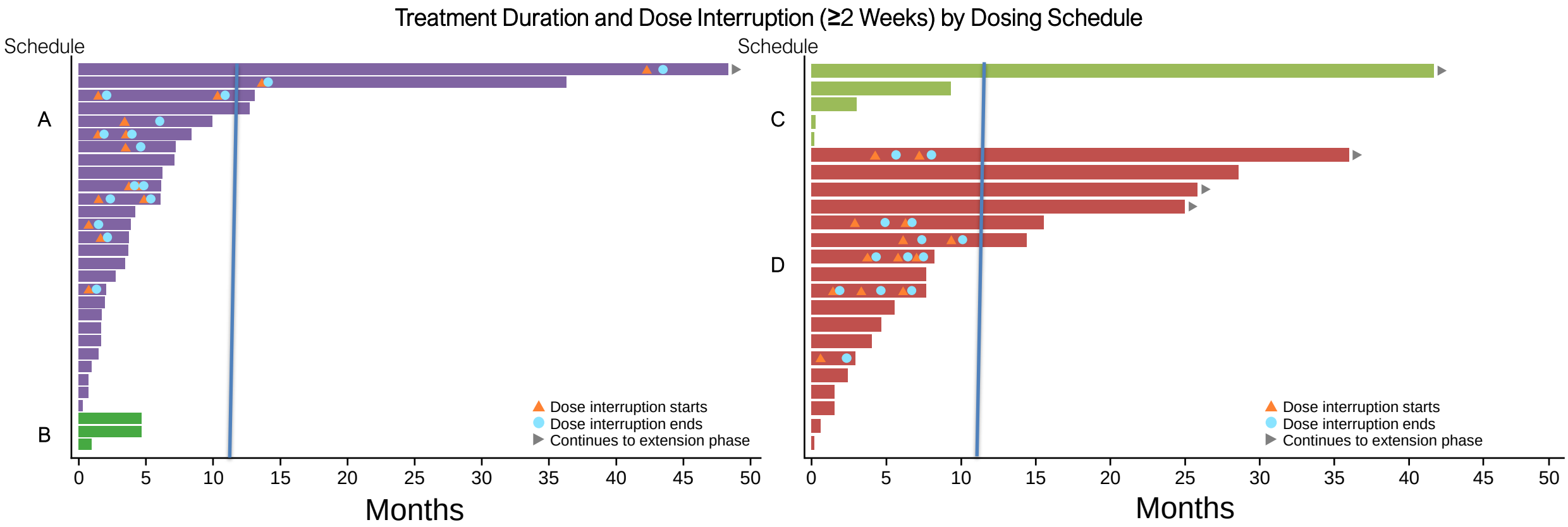
Patients With Liposarcoma Achieved Long Duration of Therapy

- Patients were able to interrupt miladametan dose and continue therapy



- 5 patients ongoing >2 years

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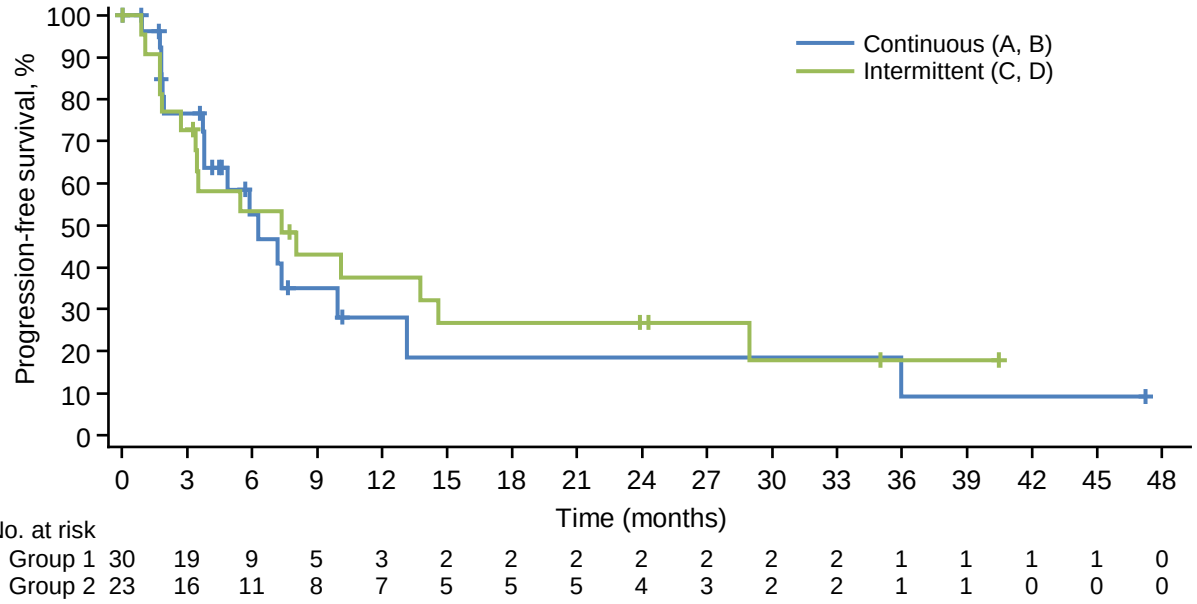
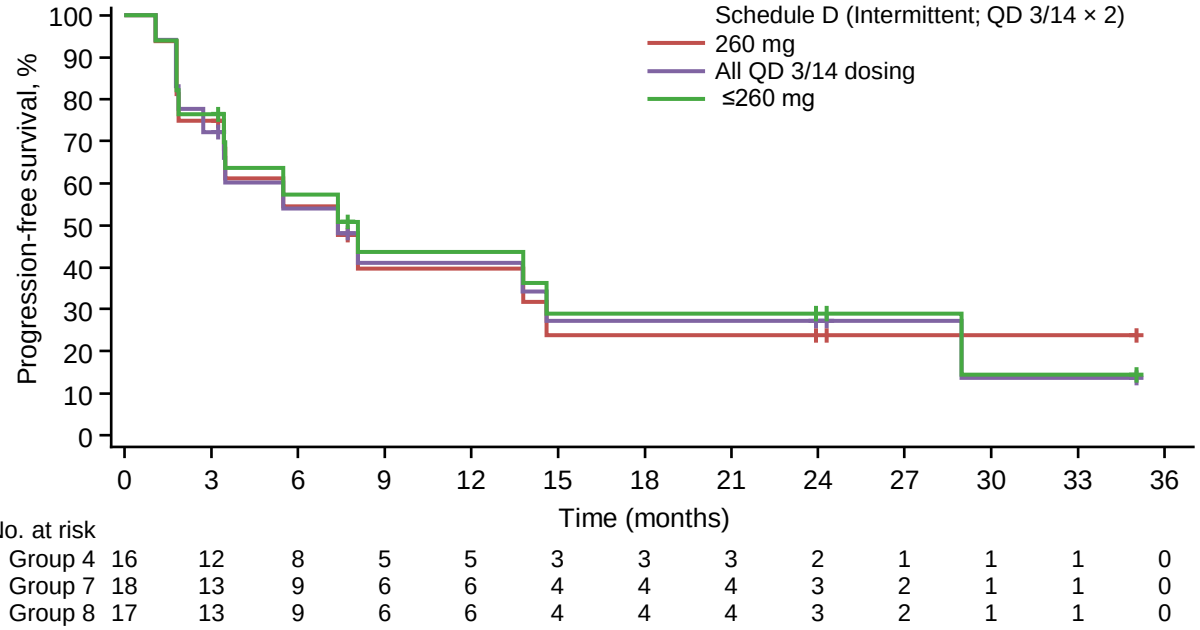
Intermittent Dosing Maintains Efficacy in Patients With LPS

- 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)

PFS, progression-free survival.

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

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Acknowledgments

- We thank the patients and their families, as well as the study investigators and staff
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