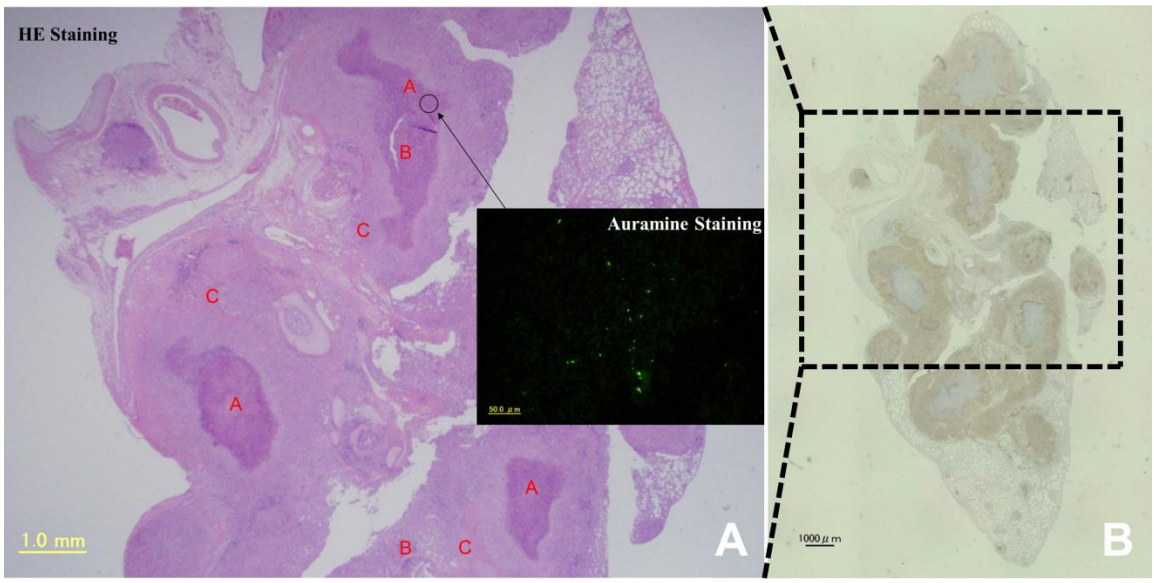
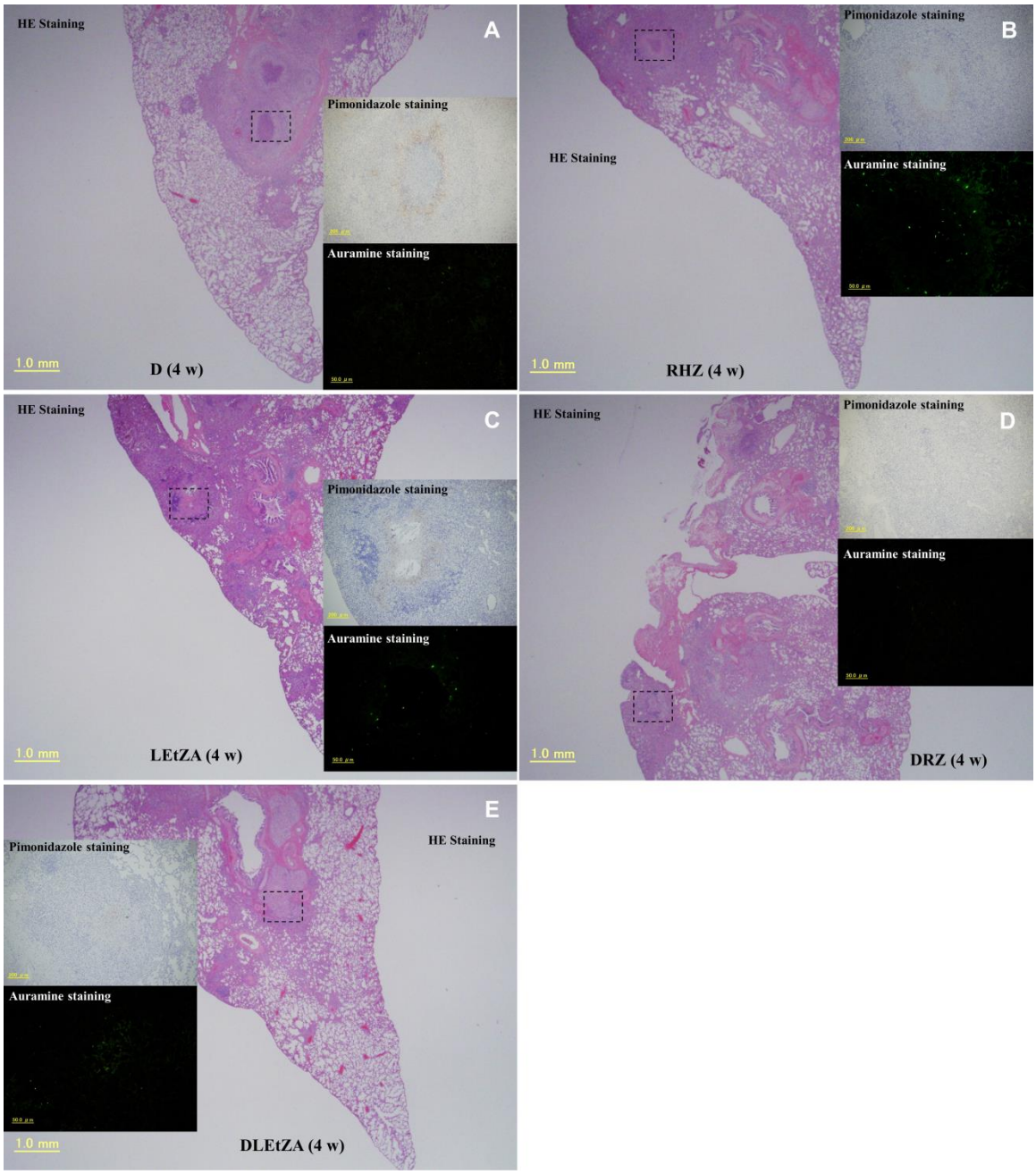


Supplemental data 1. Morphological examination of lungs from a guinea pig infected with MTB.

The morphology of the lung lesions in a lung tissue section from a guinea pig after infection with MTB Kurono strain for 4 weeks. (A) Guinea pig lungs were stained by H&E and auramine staining (the fluorescence image). Area A: A single granuloma showing a central necrotic lesion, Area B: Central calcification was found in a single granuloma, Area C: showing an increased number of epithelioid cells. The position of auramine staining is indicated by a circle with an arrow. TB bacilli are indicated by the green fluorescence. (B) A whole lung section stained by immunohistochemistry for pimonidazole, an agent used to identify hypoxic regions (14). Pimonidazole positive staining (brownish color) can be seen in granulomas in regions surrounding the central necrosis lesions, as necrotic areas themselves cannot be stained due to the lack of live cells. The corresponding area of H&E staining, as shown in Figure 3B, is indicated by the dashed line rectangle.



Supplemental data 2. Comparison of histological changes of lung lesions after treatment.

Representative lung sections after 4 weeks of treatments with (A) D, (B) RHZ, (C) LEtZA, (D) DRZ, and (E) DLEtZA. Animals in each group were sacrificed and lungs were stained by H&E, auramine (to stain TB bacilli, showing as green fluorescence), and pimonidazole (to stain hypoxic lesions as brownish color) staining. The position of

auramine staining is indicated by a rectangle with a dotted line. MTB bacilli were observed in the lungs treated with standard first-line treatment RHZ (B) and MDR-TB regimen LEtZA (C). Importantly, the hypoxic lesions were clearly absent in lungs treated with DRZ (D replaced H in the first-line regimen) (D) or DLEtZA (D with a MDR-TB regimen) (E). (D: DLM, 100 mg/kg; R: RIF, 25mg/kg; H: INH, 25mg/kg; Z: PZA, 150mg/kg; L: LVX, 50mg/kg; Et: ETO, 50 mg/kg; A: AMK, 150 mg/kg)

DLM in guinea pigs	Dose (mg/kg)	Concentration (μg/mL or g)							C_{max} (μg/mL or g)	AUC_t (μg·h/mL or g)	t_{max} (h)	$t_{1/2}$ (h)
		1h	2h	4h	8h	16h	24h	48h				
Plasma	100	0.05 ± 0.02	0.12 ± 0.05	0.20 ± 0.10	0.53 ± 0.14	0.51 ± 0.42	0.08 ± 0.02	0.01 ± 0.01	0.53	9.45	8	6.07
Lung	100	1.17 ± 0.51	2.05 ± 0.84	3.66 ± 2.70	5.86 ± 2.54	10.83 ± 11.68	2.12 ± 0.84	0.28 ± 0.14	10.83	174.25	16	6.48

A

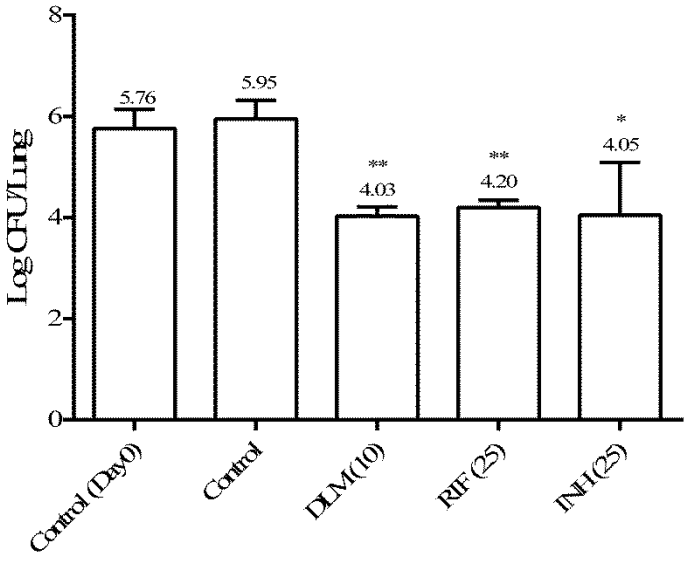
Lung wt (g) of each group (4 wk)	Control	D	RHZ	DRZ	LEtZA	DLEtZA
means	10.38	3.02	3.02	2.49	2.44	2.75
SD	± 2.67	± 0.20	± 0.31	± 0.35	± 0.09	± 0.23

Lung wt (g) of each group (8 wk)	Control*	D	RHZ	DRZ	LEtZA	DLEtZA
means	8.77	3.18	2.46	2.58	2.48	2.49
SD	± 3.95	± 0.22	± 0.06	± 0.19	± 0.20	± 0.30

*: n=2

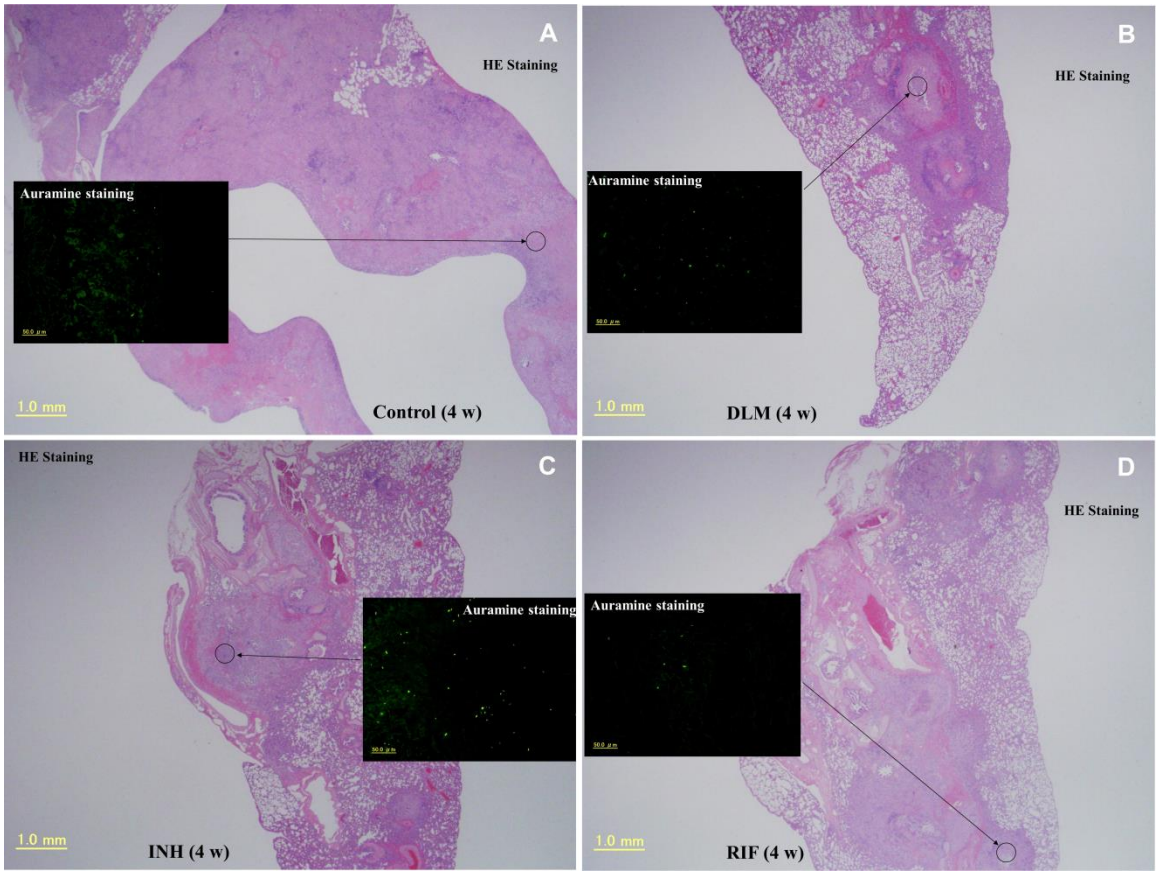
B

Supplemental data 3. Carryover of DLM at 100 mg/kg in guinea pig lungs. (A) Plasma and lung concentrations of DLM after oral administration at a dose of 100 mg/kg in guinea pigs. Based on the mean concentration of DLM in the lungs at 48 h (0.28 μg/g) and the half-life parameter (6.48 h), the concentration of DLM in the lungs after 74 h at a dose of 100 mg/kg was calculated to be about 0.018 μg/g. Each value represents the mean ± SD (n = 3). The pharmacokinetic parameters were calculated using WinNonlin software (version 6.1). (B) The mean lung weights of the animals in each regimen group (D: DLM; R: RIF; H: INH; Z: PZA; L: LVX; Et: ETO; A: AMK). The mean weight of lungs in the treated groups did not exceed 3.18 g. Each value represents the mean ± SD (n = 3, except for Control 8w, as described above). After adding 5 mL of sterile distilled water, the concentration of DLM in lung homogenates at the time of plating was calculated to be about 0.007 μg/mL, which is lower than the MIC of DLM against MTB Kurono (0.012 μg/mL).



Supplemental data 4. Lung CFU of MTB infected guinea pigs treated with DLM, RIF, and INH for 4 weeks.

Guinea pigs were infected with MTB Kurono by an intratracheal inoculation. After 4 weeks post-infection, chemotherapy was initiated and the dosing frequency was 5 days per week by oral gavage. Viable bacterial numbers in whole lungs were counted after the treatment with DLM (10mg/kg), RIF (25mg/kg), or INH (25 mg/kg) for 4 weeks (three animals per group). Each value represented the mean of triplicate samples ± SD of three replicates. **: $P < 0.01$. *: $P < 0.05$ vs. Control.



Supplemental data 5. Histological analysis of lung lesions from guinea pigs treated with DLM, RIF, and INH for 4 weeks.

After 4 weeks of treatments with (A) Control, (B) DLM (10 mg/kg), (C) INH (25 mg/kg), and (D) RIF (25 mg/kg), the animals in each group were sacrificed and lungs were stained by H&E and auramine (to stain TB bacilli) staining. The position of auramine staining is indicated by a circle pointed to by an arrow within a granuloma. Note that DLM at this lowered dose and RIF moderately reduced the number of TB bacilli within a granuloma, while INH had no apparent effect.