The impact of xeruborbactam on *in vitro* activity of cefiderocol against a challenge panel of *Acinetobacter baumannii* enriched in isolates with increased cefiderocol MICs

New Therapies for Bad Bugs

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Disclosure:

- Yoshinori Yamano, Takafumi Hara, Naoki Ishibashi, Dai Miyagawa and Motoyasu Onishi are an Employee of Shionogi & Co., Ltd. that is cefiderocol development company
- Olga Lomovskaya is an Employee of Qpex Biopharma that is developing xeruborbactam
- Shionogi & Co., Ltd. and Qpex Biopharma Inc. are group company

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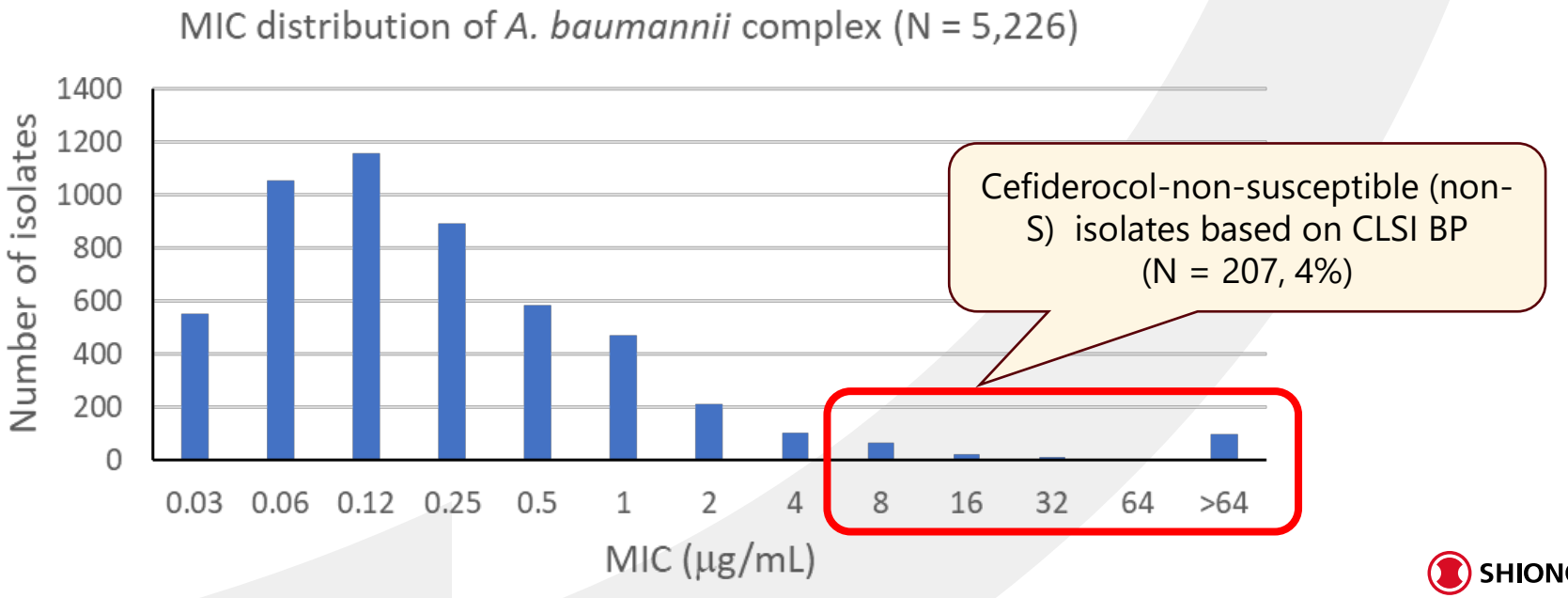
Objective

- Cefiderocol is a siderophore-conjugated cephalosporin antibiotic which is highly active against *A. baumannii* although the cefiderocol-resistant strains appeared at low frequency in surveillance studies
  - The combination of multiple factors such as NDM carbapenemase production, PER/VEB ESBL production and iron transporter PiuA deficiency seemed to cause high resistance to cefiderocol
- In this study, the effect of the combination use of xeruborbactam, a β-lactamase inhibitor with broad spectrum for Class A-D serine and metallo enzymes, on the activity of cefiderocol against cefiderocol-resistant isolates was observed



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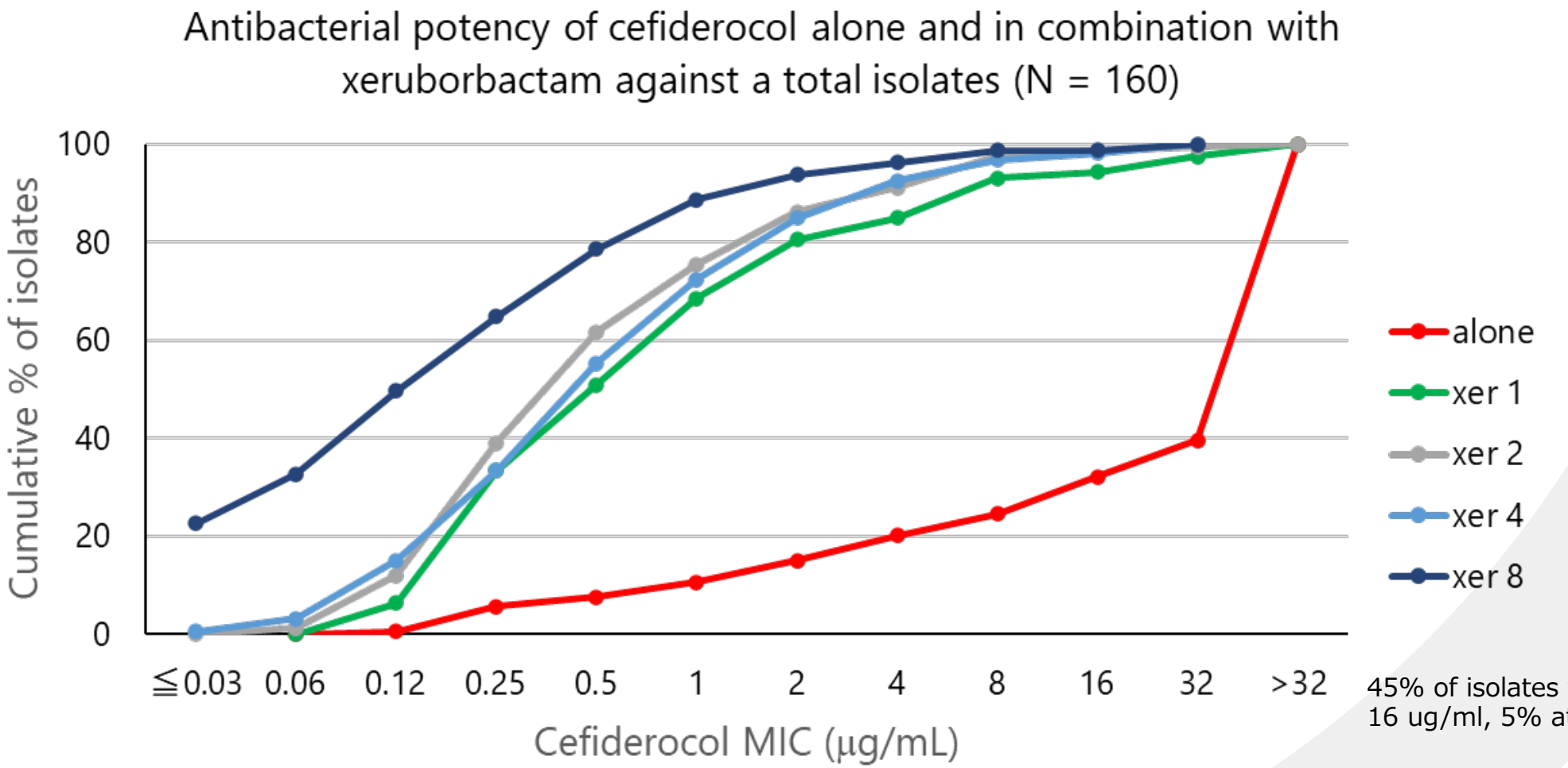
Materials and methods for susceptibility testing

- MIC was determined by broth microdilution method as recommended by CLSI
  - Iron-depleted CAMHB was used for cefideocol in combination with xeruborbactam (1, 2, 4 and 8 μg/mL)
- Test isolates
  - ➢ 160 *A. baumannii* isolates including 128 isolates with cefiderocol MIC >4 μg/mL (non-susceptible by CLSI BP)
    - ✓ Including 61 PER/VEB and 22 NDM producers
    - ✓ Highly resistant to comparators

< $MIC_{50/90}$ (μg/mL) and %S (based on CLSI breakpoint) against *A. baumannii* challenge panel isolates >

Antimicrobials (S breakpoint by CLSI)	Total (N = 160)	PER/VEB (N=59)	NDM (N = 22)
Cefiderocol (4)	>32 / >32 (20.1%)	>32 / >32 (1.6%)	>32 / >32 (9.1%)
Meropenem (2)	64 / >64 (11.9%)	32 / >64 (24.6%)	>64 / >64 (0%)
Imipenem/ Relebactam (NA)	32 / >64 (NA)	32 / 64 (NA)	>64 / >64 (NA)
Sulbactam/ Durlobactam (4/4)	2 / 64 (78.8%)	2 / 4 (100%)	>64 / >64 (4.5%)
Ampicillin/ Sulbactam (8/4)	>64/32 / >64/32 (0.6%)	64/32 / >64/32 (0%)	>64/32 / >64/32 (0%)
Colistin (2, non-R)	1 / 4 (88.8%)	1 / 2 (93.4%)	2 / 2 (95.5%)
Tigecycline (4)	4 / 8 (89.4%)	2 / 4 (93.4%)	2 / 4 (100%)

Effect of xeruborbactam on the potency of cefiderocol against a panel of *A. baumannii* test isolates (N = 160)



45% of isolates were inhibited by XER alone at 16 ug/ml, 5% at 8 ug/ml and none at 4 ug/ml

Xeruborbactam significantly increased the potency of cefiderocol against *A. baumannii* at 1 μg/mL

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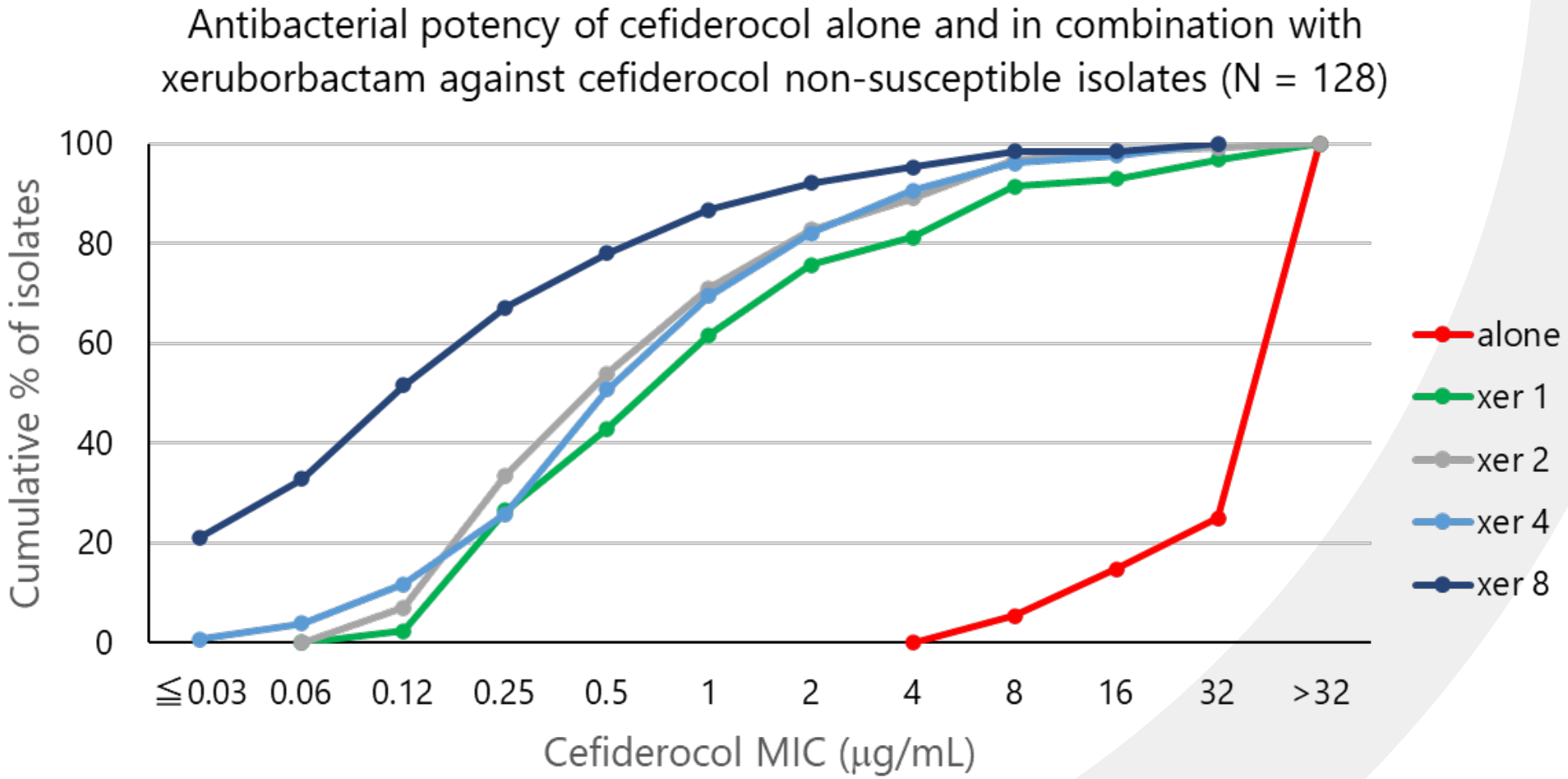
Effect of xeruborbactam on the potency of cefiderocol against **cefiderocol non-susceptible *A. baumannii*** test isolates (MIC >4 μg/mL)



Against the subset of cefiderocol non-susceptible isolates, xeruborbactam significantly increased the potency of cefiderocol

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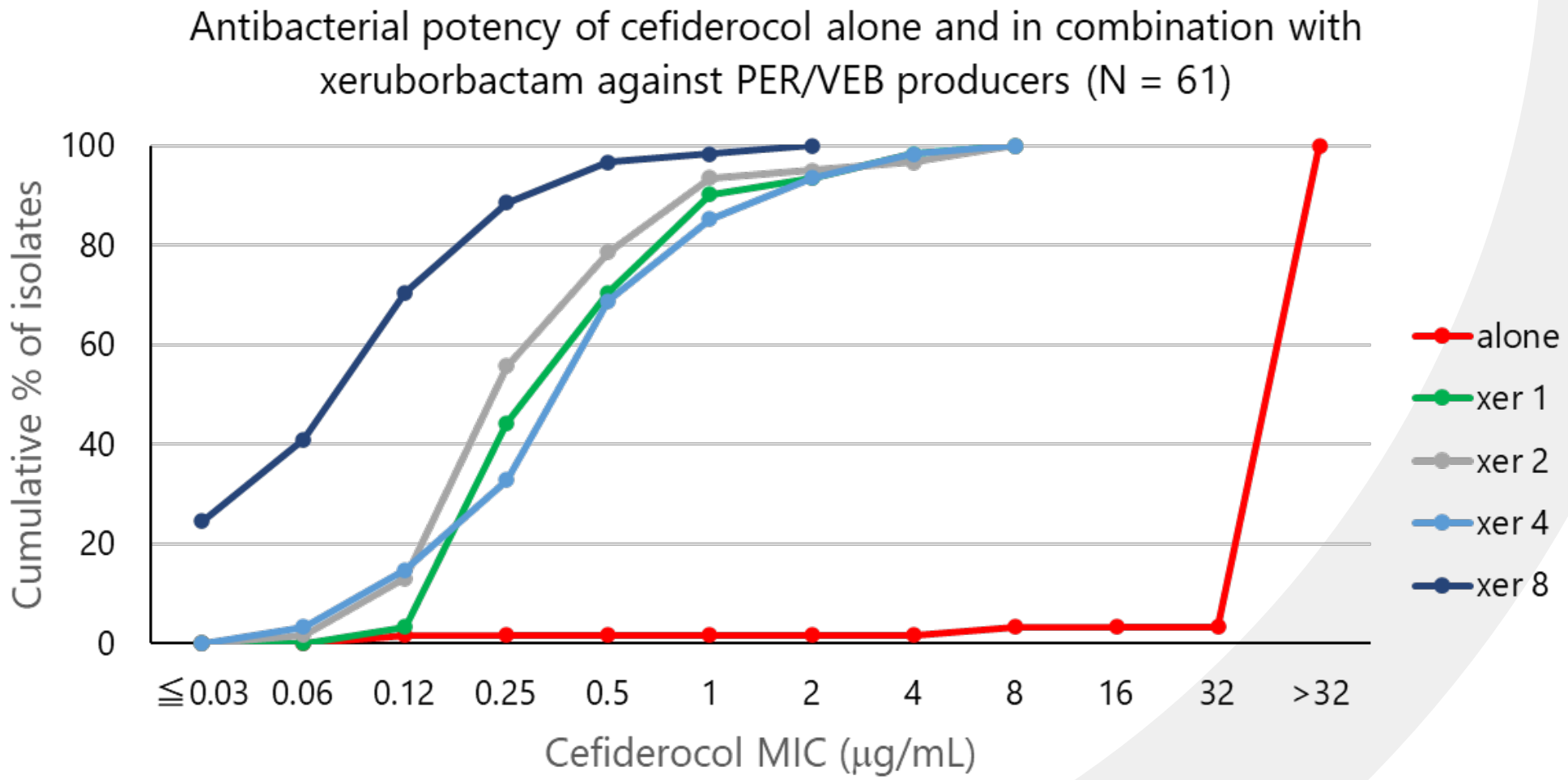
Effect of xeruborbactam on the potency of cefiderocol against **PER/VEB producing *A. baumannii*** test isolates



Against the subset of PER/VEB producing isolates, xeruborbactam significantly increased the potency of cefiderocol

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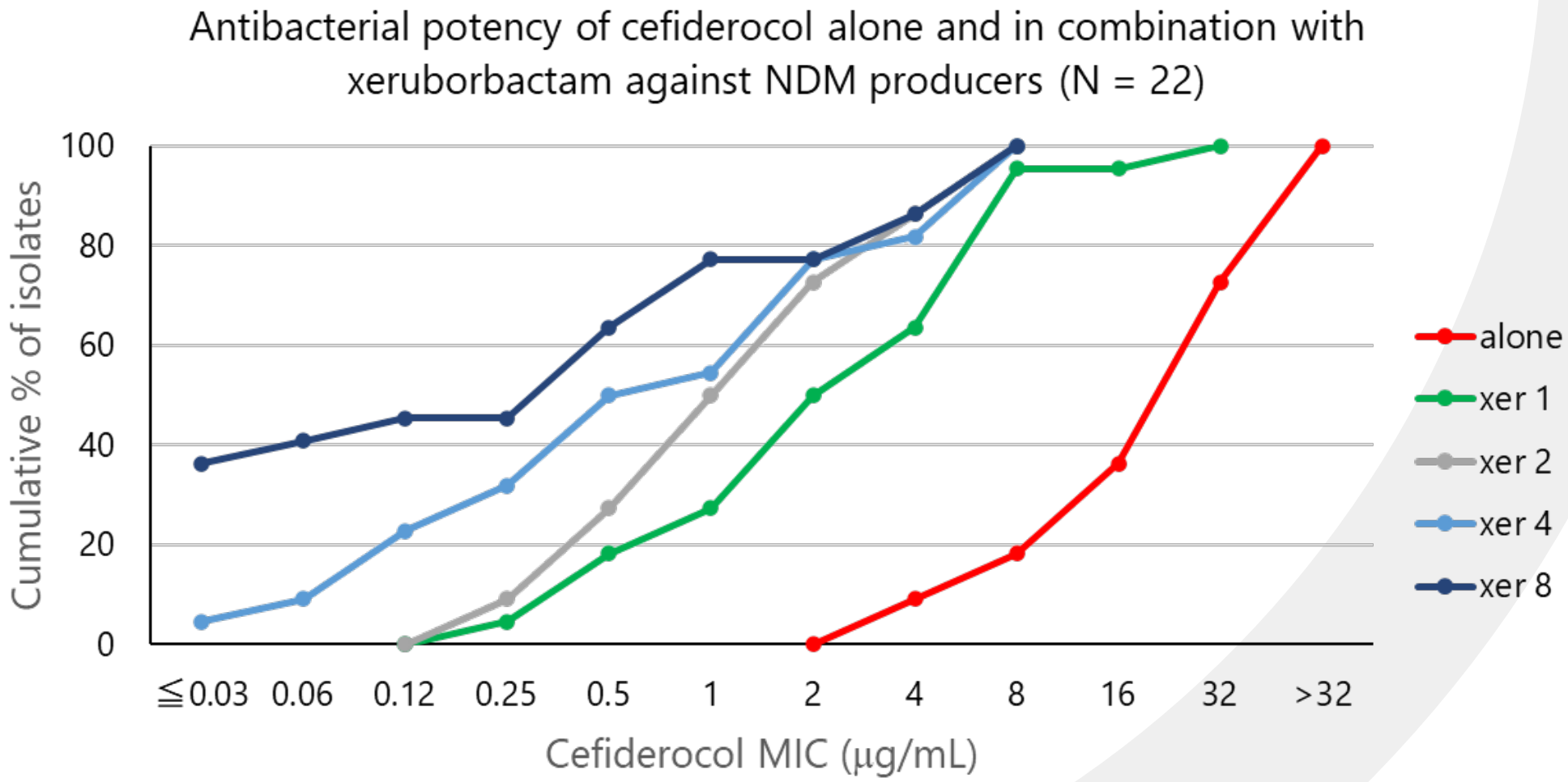
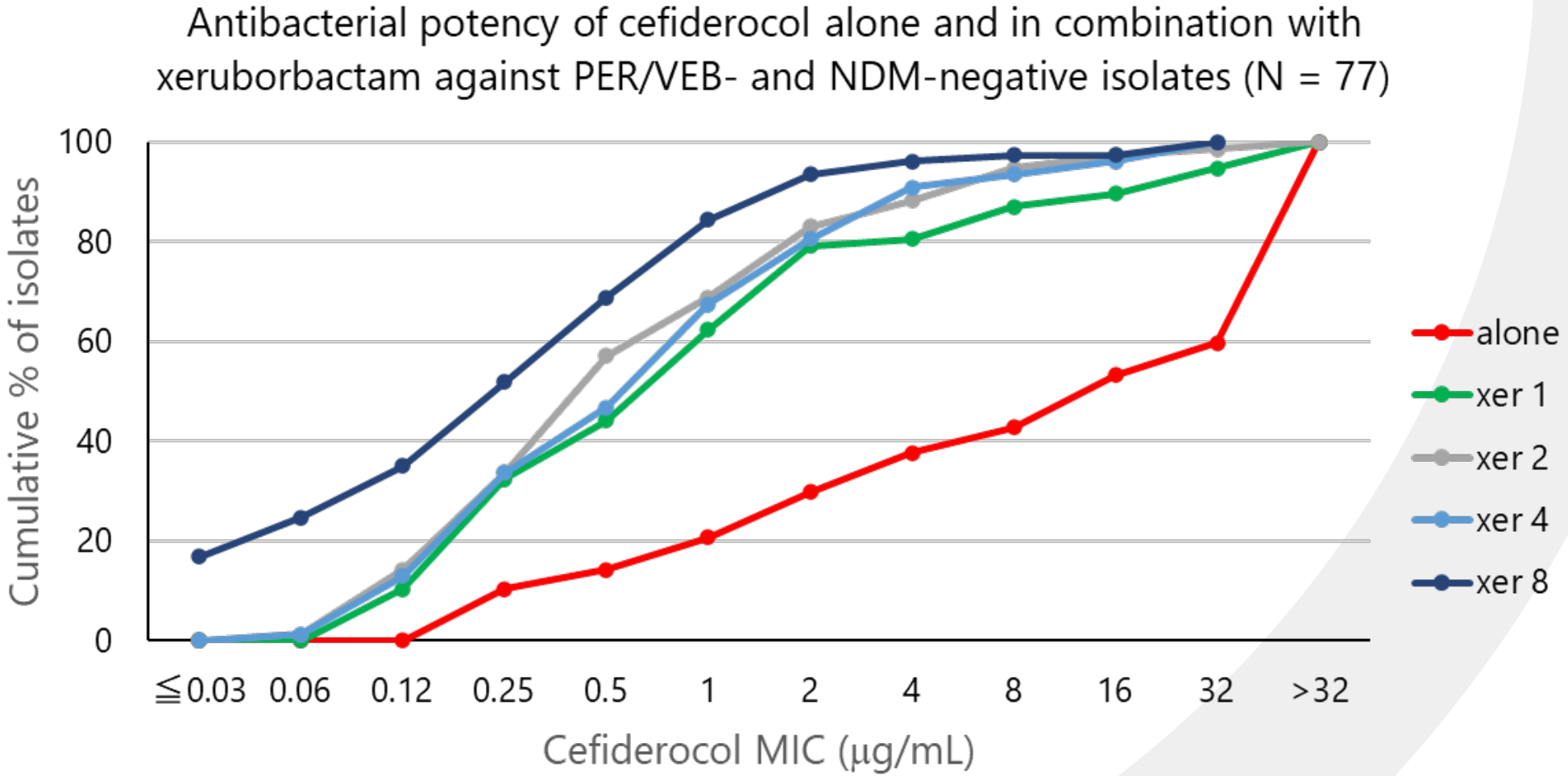
Effect of xeruborbactam on the potency of cefiderocol against **NDM producing *A. baumannii*** test isolates



Against the subset of NDM producing isolates, xeruborbactam enhanced the potency of cefiderocol in a concentration-dependent manner. At 1 μg/mL of xeruborbactam, 8-fold increase in cefiderocol potency was observed.

Effect of xeruborbactam on the potency of cefiderocol against **PER/VEB- and NDM-negative *A. baumannii*** test isolates



Against the subset of PER/VEB- or NDM-negative isolates, xeruborbactam significantly increased the potency of cefiderocol at 1 μg/mL although a few isolates still showed high MIC (>4 μg/mL).

Increased potency of cefiderocol in combination with xeruborbactam

	MIC_{50}/MIC_{90} (mg/mL) against				
	Total (N = 160)	Cefiderocol non-S (N = 128)	PER/VEB producers (N = 61)	NDM producers (N = 22)	PER/VEB or NDM negative isolates (N = 77)
Cefiderocol alone	>32 / >32	>32 / >32	>32 / >32	32 / >32	16 / >32
Cefiderocol with xeruborbactam (1 μg/mL)	0.5 / 8	1 / 8	0.5 / 1	2 / 8	1 / 32
Cefiderocol with xeruborbactam (2 μg/mL)	0.5 / 4	0.5 / 8	0.25 / 1	1 / 8	0.5 / 8
Cefiderocol with xeruborbactam (4 μg/mL)	0.5 / 4	0.5 / 4	0.5 / 2	0.5 / 8	1 / 4
Cefiderocol with xeruborbactam (8 μg/mL)	0.25 / 2	0.12 / 2	0.12 / 0.5	0.5 / 8	0.25 / 2

- Xeruborbactam enhanced the potency of cefiderocol in a concentration-dependent manner.
- Enhancement of cefiderocol potency was observed irrespective of molecular profiles in combination with xeruborbactam at 4 μg/mL, which showed no intrinsic antibacterial activity.

Conclusion

- Xeruborbactam is able to restore cefiderocol activity against cefiderocol non-susceptible *A. baumannii* isolates, including isolates carrying PER, VEB and/or NDM beta-lactamases at concentrations ranging from 1 to 8 µg/ml.

- Xeruborbactam potency to reduce cefiderocol MIC was dependent of a particular molecular profile of cefiderocol non-susceptible isolates: larger amount of xeruborbactan was required for the same MIC shift for NDM-producing isolates than for PER/VEB-producing strains reflecting xeruborbactam biochemical activity.

- 4 µg/ml of xeruborbactam was required to achieve the maximal potentiating effect not related to the intrinsic activity of xeruborbactam.

- The results of this study would be used for cefiderocol/xeruborbactam susceptibility test development and further investigation of this combination is warranted