ARGONAUT-V: Susceptibility of multidrug-resistant (MDR) *Pseudomonas aeruginosa* to Cefepime-Taniborbactam

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INTRODUCTION

Figure 1: CDC Threat Assessment for Multidrug-resistant *Pseudomonas aeruginosa*. (1)

***Pseudomonas aeruginosa* and β-lactamases**

- *P. aeruginosa* is a Gram-negative pathogen responsible for many serious infections.
- Multidrug resistance, both intrinsic and acquired, presents major clinical challenges and is classified by the CDC as a "serious threat" (1)

Cefepime and Taniborbactam

- Taniborbactam (formerly VNRX-5133; Fig 1) is a bicyclic boronate β-lactamase inhibitor (BLI) uniquely possessing activity toward all four Ambler classes of β-lactamases, both serine and metallo, with the exception of select class B IMP β-lactamases (2).
- Cefepime is a commonly used anti-Pseudomonal cephalosporin antibiotic.
- The β-lactam-BLI (BL-BLI) combination cefepime-taniborbactam (FTB; Fig 1) is currently in phase 3 clinical trials.

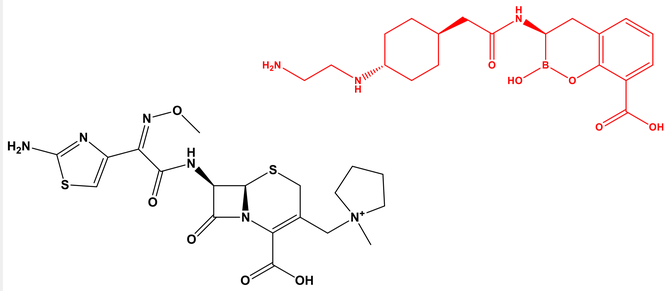

Figure 2: Structures of cefepime (β-lactam antibiotic; black) and taniborbactam (β-lactamase inhibitor; red).

Materials and Methods

Bacterial Strains

A selection of 197 *P. aeruginosa* strains collected as part of the Platforms for Rapid Identification of MDR-Gram-negative bacteria and Evaluation of Resistance Studies IV (PRIMERS-IV) study (3) were tested. Approximately half of the strains were determined to be carbapenem and/or expanded spectrum cephalosporin resistant by origin clinical laboratories. ATCC control strains were also included for quality control purposes. Carbapenem resistance was associated with porin changes, efflux pumps, and the presence of acquired carbapenemases (KPC and VIM). A sampling of twenty of the strains were whole genome sequenced.

Minimum Inhibitory Concentrations (MICs)

MICs were determined using the ThermoFisher Sensititre system with custom assay panels and were read visually. This methodology is based on the CLSI M7 Reference Microdilution Susceptibility Method. Breakpoints were interpreted using the CLSI M100 standard, except for FTB as no breakpoints have been established and the cefepime breakpoint was instead provisionally applied.

RESULTS

MICs Reveal High Levels of FTB Activity and Potentiation of FEP by TAN

MIC (μg/ml)	AMK	ATM	C/T	CAZ	CZA	FEP	FTB	IPM	MEM	MVB	TZP	TOB
0.03	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	4 (2%)	0 (0%)	0 (0%)
0.06	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (3.6%)	12 (6.1%)	0 (0%)	0 (0%)
0.12	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	24 (12.2%)	40 (20.3%)	0 (0%)	2 (1%)
0.25	0 (0%)	0 (0%)	10 (5.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	39 (19.8%)	29 (14.7%)	0 (0%)	13 (6.6%)
0.5	2 (1%)	0 (0%)	90 (45.7%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)	7 (3.6%)	19 (9.6%)	7 (3.6%)	0 (0%)	109 (55.3%)
1	7 (3.6%)	0 (0%)	32 (16.2%)	12 (6.1%)	24 (12.2%)	9 (4.6%)	38 (19.3%)	31 (15.7%)	12 (6.1%)	13 (6.6%)	0 (0%)	28 (14.2%)
2	49 (24.9%)	7 (3.6%)	7 (3.6%)	55 (27.9%)	82 (41.6%)	64 (32.5%)	55 (27.9%)	50 (25.4%)	8 (4.1%)	7 (3.6%)	16 (8.1%)	2 (1%)
4	77 (39.1%)	55 (27.9%)	14 (7.1%)	34 (17.3%)	26 (13.2%)	34 (17.3%)	36 (18.3%)	10 (5.1%)	7 (3.6%)	8 (4.1%)	49 (24.9%)	1 (0.5%)
8	28 (14.2%)	44 (22.3%)	9 (4.6%)	19 (9.6%)	25 (12.7%)	25 (12.7%)	33 (16.8%)	98 (49.7%)	80 (40.6%)	77 (39.1%)	39 (19.8%)	1 (0.5%)
16	9 (4.6%)	17 (8.6%)	35 (17.8%)	12 (6.1%)	40 (20.3%)	10 (5.1%)	34 (17.3%)				8 (4.1%)	41 (20.8%)
32	4 (2%)	74 (37.6%)		65 (33%)		55 (27.9%)					15 (7.6%)	
64	21 (10.7%)										10 (5.1%)	
> 64											60 (30.5%)	

Table 1: MIC distribution for 197 *P. aeruginosa* strains. AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; TOB, tobramycin.

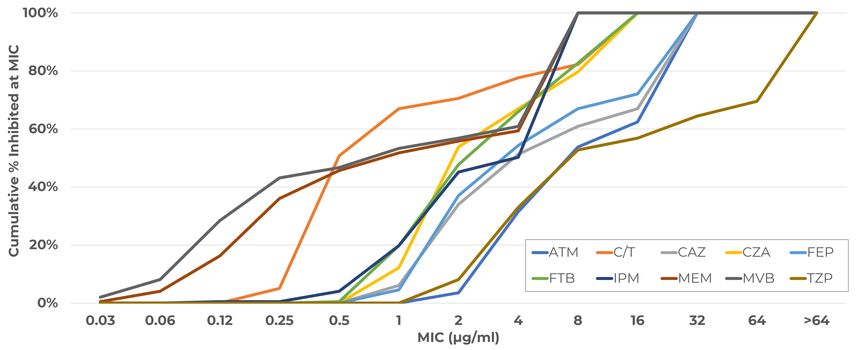

Figure 3: Cumulative % of *P. aeruginosa* isolates (n=197) inhibited at MIC. AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; TOB, tobramycin.

FTB Achieves the Highest Coverage Among BL/BLI Combinations Tested

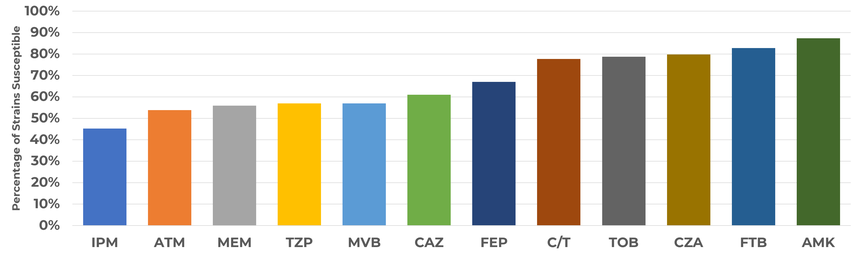

Figure 4: Percent of *P. aeruginosa* strains susceptible, (n = 197). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; TOB, tobramycin.

	AMK	ATM	C/T	CAZ	CZA	FEP	FTB	IPM	MEM	MVB	TZP	TOB
MIC_{50}	4	8	0.5	4	2	4	4	4	1	1	8	0.5
MIC_{90}	>32	>16	>8	>16	>8	>16	>8	>4	>4	>4	>64	>8
% S	87.3	53.8	77.7	60.9	79.7	67	82.7	45.2	55.8	56.9	56.9	78.7

Table 2: MIC_{50} and MIC_{90} values for *P. aeruginosa*, (n = 197). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; TOB, tobramycin.

FTB Maintains High Activity Against Carbapenem-non-susceptible Strains

	Strains at MIC (Percent at MIC)											
MIC (μg/ml)	AMK	ATM	C/T	CAZ	CZA	FEP	FTB	IPM	MEM	MVB	TZP	TOB
0.03	0 (0%)	(0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
0.06	0 (0%)	0 (0%)	0 (0%)	(0%)	0 (0%)	(0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)
0.12	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)	2 (1.9%)	0 (0%)	0 (0%)
0.25	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)	5 (4.6%)	0 (0%)	4 (3.7%)
0.5	0 (0%)	0 (0%)	24 (22.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (3.7%)	1 (0.9%)	0 (0%)	41 (38%)
1	4 (3.7%)	0 (0%)	20 (18.5%)	2 (1.9%)	8 (7.4%)	0 (0%)	8 (7.4%)	0 (0%)	6 (5.6%)	8 (7.4%)	0 (0%)	18 (16.7%)
2	11 (10.2%)	2 (1.9%)	7 (6.5%)	11 (10.2%)	20 (18.5%)	13 (12%)	14 (13%)	0 (0%)	7 (6.5%)	6 (5.6%)	1 (0.9%)	2 (1.9%)
4	40 (37%)	10 (9.3%)	13 (12%)	8 (7.4%)	16 (14.8%)	10 (9.3%)	22 (20.4%)	10 (9.3%)	7 (6.5%)	8 (7.4%)	12 (11.1%)	1 (0.9%)
8	19 (17.6%)	15 (13.9%)	9 (8.3%)	12 (11.1%)	24 (22.2%)	21 (19.4%)	30 (27.8%)	98 (90.7%)	80 (74.1%)	77 (71.3%)	8 (7.4%)	1 (0.9%)
16	9 (8.3%)	10 (9.3%)	35 (32.4%)	11 (10.2%)	40 (37%)	9 (8.3%)	34 (31.5%)				4 (3.7%)	41 (38%)
32	4 (3.7%)	71 (65.7%)		64 (59.3%)		55 (50.9%)					14 (13%)	0 (0%)
64	21 (19.4%)										9 (8.3%)	
>64											60 (55.6%)	

Table 3: MIC distribution for carbapenem-non-susceptible *P. aeruginosa,* (n = 108). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; TOB, tobramycin.

	AMK	ATM	C/T	CAZ	CZA	FEP	FTB	IPM	MEM	MVB	TZP	TOB
MIC_{50}	4	>16	4	>16	8	>16	8	>4	>4	>4	>64	1
MIC_{90}	>32	>16	>8	>16	>8	>16	>8	>4	>4	>4	>64	>8
% S	9	15	13	12	24	40.7	68.5	0	7	N/A	4	1

Table 4: MIC_{50} and MIC_{90} values for carbapenem-non-susceptible *P. aeruginosa*, (n = 108). AMK, amikacin; ATM, aztreonam; C/T, ceftolozane-tazobactam; CAZ, ceftazidime; CZA, ceftazidime/avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; IPM, imipenem; MEM, meropenem; MVB, meropenem/vaborbactam; TZP, piperacillin/tazobactam; TOB, tobramycin.

CONCLUSIONS

- Compared to MVB, CZA, and C/T, FTB demonstrated the greatest activity against the 197 *P. aeruginosa* strains tested
- FTB maintains greater activity against carbapenem-non-susceptible strains compared to MVB, CZA, and C/T
- Pending completion of clinical development, FTB may be a promising therapeutic option for MDR *P. aeruginosa* infections.

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