Outcomes by Resistance Phenotype and Genotype among Baseline Pathogen in Patients with Complicated Urinary Tract Infection (cUTI) in the Phase 3 CERTAIN-1 Study

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Background

- Widespread antibiotic use has resulted in the global dissemination of public health threat pathogens including extended spectrum β-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and multidrug-resistant (MDR) *P. aeruginosa* (WHO 2017; CDC 2021).
- CRE and CRPA producing metallo-β-lactamases (e.g., NDM, VIM) are emerging (Castanheira 2022; Tenover 2022; Estabrook 2023), with few treatment options.
- Taniborbactam is an investigational β-lactamase inhibitor that restores cefepime activity against cefepime-, carbapenem-, and multidrug-resistant Enterobacterales and *P. aeruginosa* producing serine- and metallo-β-lactamases (Hamrick 2020; Liu 2020; Karlowsky 2022).
- In the Phase 3 CERTAIN-1 study (ClinicalTrials.gov identifier NCT03840148), cUTI patients were randomized 2:1 to cefepime-taniborbactam 2.5g q8h (2-h infusion) or meropenem 1g q8h (30-min infusion). Cefepime-taniborbactam was superior to meropenem for the primary composite endpoint at Test of Cure (TOC) in the microITT population (treatment difference, 12.6%; 95% CI: 3.1%, 22.2%; P=0.0088) (McGovern 2022).
- We assessed clinical and microbiological outcomes in patient subsets defined by baseline pathogen resistance phenotypes and genotypes in the CERTAIN-1 study.

Methods

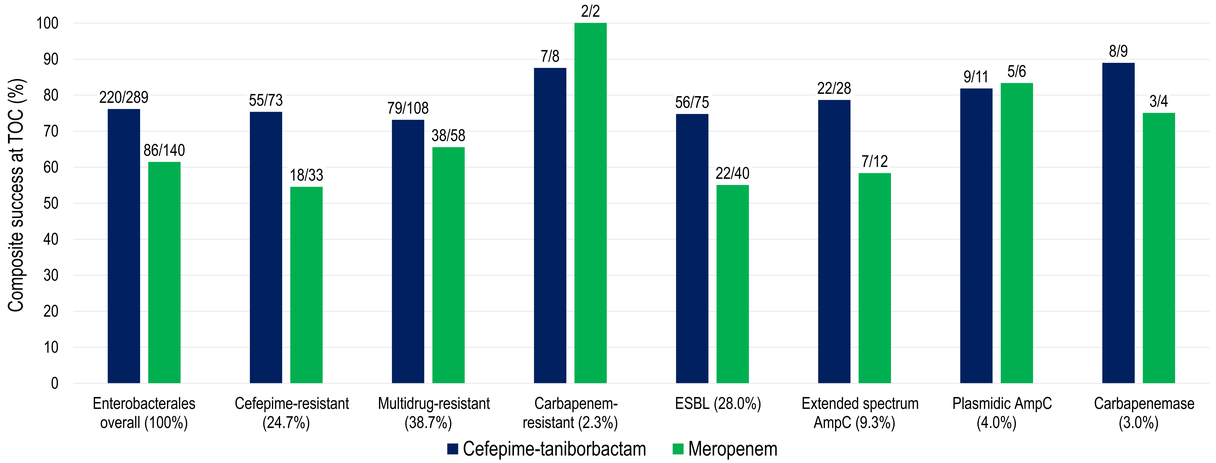
- MICs were determined by reference broth microdilution (CLSI M07 Ed. 11; ISO 20776-1:2019) at the central microbiology laboratory (LabCorp; Indianapolis, USA and Shanghai, China). Resistance phenotypes included cefepime-, multidrug-, and carbapenem resistance (CLSI M100 Ed. 29).
- Enterobacterales isolates with aztreonam, ceftazidime, imipenem, and/or meropenem MICs of ≥2 µg/mL, and *P. aeruginosa* isolates with ceftazidime MICs of ≥16 µg/mL and/or imipenem and/or meropenem MIC values of ≥2 µg/mL were tested for the presence of genes encoding β-lactamases (ESBLs, extended-spectrum/intrinsic AmpC, plasmidic AmpC, carbapenemases) by whole genome sequencing and in silico analysis.
- Composite (microbiologic and clinical), microbiologic, and clinical responses at TOC (Day 19 to 23) were assessed in the extended microbiologic intent-to-treat (extended microITT) population which consisted of patients with Enterobacterales and/or *P. aeruginosa* at ≥10^5 CFU/mL in urine at study entry against which at least 1 study drug had activity (cefepime-taniborbactam MIC ≤16 µg/mL [provisional Susceptible breakpoint]; meropenem MIC ≤2 µg/mL [Enterobacterales] or ≤4 µg/mL [*P. aeruginosa*]). Microbiologic success required reduction of all gram-negative pathogen(s) found at baseline to <10^3 CFU/mL. Clinical success required symptomatic resolution or return to premorbid baseline of all core signs and symptoms, with no use of additional antibacterial agents for cUTI.
- Clonal relatedness of post-baseline pathogens to baseline pathogens of the same species was assessed by multilocus sequence typing and pulsed field electrophoresis. For this analysis, patients with a uropathogen at ≥10^3 CFU/mL at TOC that was clonally unrelated to the baseline pathogen of the same species were assessed with a microbiologic response of eradication.
- For patients with two baseline pathogens of different species (two gram-negative or one gram-negative and one gram-positive), an overall per-patient microbiologic response of success at TOC required microbiologic eradication of each pathogen.

Table. Outcomes[1] at Test of Cure by resistance phenotype and genotype in patients with Enterobacterales or *P. aeruginosa* at baseline (extended microITT population)

Organism group Phenotypic[2] or genotypic[3] resistance subset (% of total)	Composite Success n/N (%)[6]		Microbiologic Success n/N (%)[6]		Clinical Success n/N (%)[6]	
	Cefepime-taniborbactam	Meropenem	Cefepime-taniborbactam	Meropenem	Cefepime-taniborbactam	Meropenem
Enterobacterales overall (100%)	220/289 (76.1)	86/140 (61.4)	242/289 (83.7)	97/140 (69.3)	249/289 (86.2)	113/140 (80.7)
Cefepime-resistant (24.7%)	55/73 (75.3)	18/33 (54.5)	58/73 (79.5)	20/33 (60.6)	61/73 (83.6)	27/33 (81.8)
Multidrug-resistant[4] (38.7%)	79/108 (73.1)	38/58 (65.5)	82/108 (75.9)	43/58 (74.1)	95/108 (88.0)	48/58 (82.8)
Carbapenem-resistant (2.3%)	7/8 (87.5)	2/2 (100)	7/8 (87.5)	2/2 (100)	8/8 (100)	2/2 (100)
ESBL[5] (28.0%)	56/75 (74.7)	22/40 (55.0)	59/75 (78.7)	25/40 (62.5)	63/75 (84.0)	31/40 (77.5)
Extended spectrum AmpC (9.3%)	22/28 (78.6)	7/12 (58.3)	24/28 (85.7)	9/12 (75.0)	24/28 (85.7)	9/12 (75.0)
Plasmidic AmpC (4.0%)	9/11 (81.8)	5/6 (83.3)	9/11 (81.8)	5/6 (83.3)	11/11 (100)	6/6 (100)
Carbapenemase (3.0%)	8/9 (88.9)	3/4 (75.0)	8/9 (88.9)	3/4 (75.0)	9/9 (100)	3/4 (75.0)
P. aeruginosa overall (100%)	8/16 (50.0)	4/7 (57.1)	8/16 (50.0)	5/7 (71.4)	13/16 (81.3)	6/7 (85.7)
Cefepime-resistant (26.1%)	2/5 (40.0)	1/1 (100)	2/5 (40.0)	1/1 (100)	3/5 (60.0)	1/1 (100)
Multidrug-resistant[4] (30.4%)	2/5 (40.0)	1/2 (50.0)	2/5 (40.0)	1/2 (50.0)	3/5 (60.0)	2/2 (100)
Carbapenem-resistant (21.7%)	1/3 (33.3)	2/2 (100)	1/3 (33.3)	2/2 (100)	2/3 (66.7)	2/2 (100)
Carbapenemase (4.3%)	1/1 (100)	0	1/1 (100)	0	1/1 (100)	0

[1]For this analysis, patients with a uropathogen at ≥10^3 CFU/mL at TOC that was clonally unrelated to the baseline pathogen of the same species were assessed with a microbiologic response of eradication.
[2]Phenotypes were assessed by reference broth microdilution (CLSI M07 11th ed. [2018]; CLSI M100 29th ed. [2019]).
[3]β-lactamase genotypes among baseline isolates with MIC ≥2 µg/mL for aztreonam, ceftazidime, imipenem, and/or meropenem were determined by whole genome sequencing and in silico screening of β-lactamase genes.
[4]Resistance to ≥1 agent in ≥3 classes of antibacterial agents.
[5]Extended-spectrum β-lactamase genotype.
[6]Patients were randomized 2:1 to cefepime 2.5 g q8h (2-h infusion) or meropenem 1 g q8h (30-min infusion).

Figure. Composite success at Test of Cure in patients with Enterobacterales at baseline, overall and by phenotypic and genotypic resistance subset (extended microITT population)



Values in parentheses represent % of patients within each subset defined by baseline pathogen resistance phenotype or genotype

Results

- Among Enterobacterales from patients in the extended microITT population, 24.7%, 38.7%, and 2.3% of isolates were cefepime resistant, MDR, and/or carbapenem resistant, respectively, whereas 28.0%, 9.3%, 4.0%, and 3.0% were genotypically confirmed to carry genes for ESBLs, extended spectrum AmpC, plasmidic AmpC, and carbapenemases, respectively (Table).
- For patients in the cefepime-taniborbactam treatment group with Enterobacterales at baseline, composite success rates at TOC in cefepime-resistant, MDR, ESBL, extended-spectrum AmpC, and plasmidic AmpC subsets ranged from 73.1% to 81.8% and were therefore similar to the composite success rate for Enterobacterales overall (76.1%) (Table, Figure).
- Notably, cefepime-taniborbactam achieved composite success in 7/8 patients with CRE and in 8/9 patients with Enterobacterales carrying a carbapenemase gene (5 OXA-48-group; 2 KPC-3; 2 NDM-1).
- Meropenem composite success rates in cefepime-resistant, MDR, ESBL, and extended-spectrum AmpC subsets of Enterobacterales were similar to that for Enterobacterales overall and numerically lower than the corresponding cefepime-taniborbactam composite success rates in these resistant subsets
- In the extended microITT population, cefepime-taniborbactam achieved composite and microbiologic success at TOC in 8/16 patients and clinical success in 13/16 patients with *P. aeruginosa* overall (Table). Within each treatment group, success rates at TOC in patients with resistant isolates of *P. aeruginosa* were similar to those overall; however, modest numbers of patients limited further interpretation.
- One patient in the cefepime-taniborbactam group had at baseline isolate of *P. aeruginosa* carrying a gene for VIM-2 metallo-β-lactamase and achieved composite success at TOC.

Conclusions

- Cefepime-taniborbactam demonstrated efficacy in adult cUTI patients with cefepime-, multidrug-, and carbapenem-resistant pathogens and with pathogens carrying ESBL, AmpC, and carbapenemase genes.
- Within each treatment group, rates of success at Test of Cure in each phenotypic and genotypic resistance subset were similar to those overall.
- These results are consistent with the ability of taniborbactam to restore cefepime activity against cefepime-, multidrug-, and carbapenem-resistant gram-negative pathogens producing serine- and metallo-β-lactamases in nonclinical studies.

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