

**Supplementary Table S1.** Renal function category shift (ITT population)

<b>Baseline renal function category (CL<sub>CR</sub>)</b>	<b>Postbaseline renal function category</b>	<b>C/T (N<sup>a</sup>=361), n/N1 (%)</b>	<b>MEM (N<sup>a</sup>=359), n/N1 (%)</b>
Normal renal function (≥80 mL/min)	Normal	221/227 (97.4)	229/235 (97.4)
	Mild	4/227 (1.8)	4/235 (1.7)
	Moderate	0/227	0/235
	Severe	2/227 (0.9)	2/235 (0.9)
	ESRD	0/227	0/235
Mild RI (>50 to <80 mL/min)	Normal	17/82 (20.7)	20/77 (26.0)
	Mild	62/82 (75.6)	52/77 (67.5)
	Moderate	2/82 (2.4)	4/77 (5.2)
	Severe	1/82 (1.2)	1/77 (1.3)
	ESRD	0/82	0/77
Moderate RI (≥30 to ≤50 mL/min)	Normal	2/35 (5.7)	2/26 (7.7)

	Mild	10/35 (28.6)	9/26 (34.6)
	Moderate	20/35 (57.1)	12/26 (46.2)
	Severe	3/35 (8.6)	3/26 (11.5)
	ESRD	0/35	0/26
Severe RI ( $\geq 15$ to $< 30$ mL/min)	Normal	0/17	0/21
	Mild	3/17 (17.6)	2/21 (9.5)
	Moderate	4/17 (23.5)	4/21 (19.0)
	Severe	10/17 (58.8)	15/21 (71.4)
	ESRD	0/17	0/21

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CL<sub>CR</sub>, creatinine clearance; C/T, ceftolozane/tazobactam; ESRD, end-stage renal disease; ITT, intention-to-treat; MEM, meropenem; RI, renal impairment.

<sup>a</sup>N=Number of patients randomized to receive treatment. Six patients were not treated; of those, four patients were missing baseline CL<sub>CR</sub>, one patient had normal baseline renal function, and one patient had ESRD at baseline.

**Supplementary Table S2.** Clinical response at TOC visit by baseline CL<sub>CR</sub> group (ITT population)

	Normal renal function (CL <sub>CR</sub> ≥80 mL/min)		Mild RI (CL <sub>CR</sub> >50 to <80 mL/min)		Moderate RI (CL <sub>CR</sub> ≥30 to ≤50 mL/min)		Severe RI (CL <sub>CR</sub> ≥15 to <30 mL/min)	
	C/T	MEM	C/T	MEM	C/T	MEM	C/T	MEM
	(n=227)	(n=236)	(n=82)	(n=77)	(n=35)	(n=26)	(n=17)	(n=21)
Cure	132 (58.1)	138 (58.5)	45 (54.9)	35 (45.5)	13 (37.1)	11 (42.3)	7 (41.2)	10 (47.6)
Failure	95 (41.9)	98 (41.5)	37 (45.1)	42 (54.5)	22 (62.9)	15 (57.7)	10 (58.8)	11 (52.4)
Observed failure	15 (6.6)	14 (5.9)	3 (3.7)	6 (7.8)	1 (2.9)	3 (11.5)	—	—
Failure carried forward from EOT	51 (22.5)	43 (18.2)	17 (20.7)	19 (24.7)	12 (34.3)	7 (26.9)	6 (35.3)	5 (23.8)
Observed indeterminate	14 (6.2)	18 (7.6)	6 (7.3)	8 (10.4)	6 (17.1)	4 (15.4)	1 (5.9)	2 (9.5)
Died from cause other than VNP	9 (4.0)	7 (3.0)	6 (7.3)	4 (5.2)	3 (8.6)	3 (11.5)	1 (5.9)	2 (9.5)
Other	5 (2.2)	11 (4.7)	0	4 (5.2)	3 (8.6)	1 (3.8)	—	—

Imputed								
indeterminate	15 (6.6)	23 (9.7)	11 (13.4)	9 (11.7)	3 (8.6)	1 (3.8)	3 (17.6)	4 (19.0)
Died from cause								
other than VNP	11 (4.8)	13 (5.5)	8 (9.8)	7 (9.1)	2 (5.7)	1 (3.8)	3 (17.6)	4 (19.0)
Other	4 (1.8)	10 (4.2)	3 (3.7)	2 (2.6)	1 (2.9)	0	—	—

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CL<sub>CR</sub>, creatinine clearance; C/T, ceftolozane/tazobactam; EOT, end of treatment; ITT, intention-to-treat; MEM, meropenem; RI, renal impairment; TOC, test of cure; VNP, ventilated nosocomial pneumonia.

**Supplementary Table S3.** Summary of AEs<sup>a</sup> by renal function group (safety population)

AE category, <i>n</i> (%)	Normal renal function							
	function (CL <sub>CR</sub> ≥80 mL/min)		Mild RI (CL <sub>CR</sub> >50 to <80 mL/min)		Moderate RI (CL <sub>CR</sub> ≥30 to ≤50 mL/min)		Severe RI (CL <sub>CR</sub> ≥15 to <30 mL/min)	
	C/T	MEM	C/T	MEM	C/T	MEM	C/T	MEM
	( <i>n</i> =227)	( <i>n</i> =235)	( <i>n</i> =82)	( <i>n</i> =77)	( <i>n</i> =35)	( <i>n</i> =26)	( <i>n</i> =17)	( <i>n</i> =21)
<b>Blood and lymphatic system disorders</b>	<b>31 (13.7)</b>	<b>46 (19.6)</b>	<b>11 (13.4)</b>	<b>8 (10.4)</b>	<b>6 (17.1)</b>	<b>9 (34.6)</b>	<b>4 (23.5)</b>	<b>6 (28.6)</b>
Anemia	15 (6.6)	23 (9.8)	10 (12.2)	6 (7.8)	5 (14.3)	3 (11.5)	2 (11.8)	6 (28.6)
Anemia of chronic disease	3 (1.3)	1 (0.4)	0	0	0	1 (3.8)	2 (11.8)	0
Leukocytosis	2 (0.9)	0	0	0	0	1 (3.8)	1 (5.9)	0
Thrombocytopenia	1 (0.4)	11 (4.7)	0	2 (2.6)	1 (2.9)	3 (11.5)	0	1 (4.8)
<b>Cardiac disorders</b>	<b>33 (14.5)</b>	<b>36 (15.3)</b>	<b>15 (18.3)</b>	<b>22 (28.6)</b>	<b>9 (25.7)</b>	<b>8 (30.8)</b>	<b>3 (17.6)</b>	<b>6 (28.6)</b>
Atrial fibrillation	4 (1.8)	7 (3.0)	3 (3.7)	6 (7.8)	1 (2.9)	2 (7.7)	1 (5.9)	1 (4.8)
Bradycardia	4 (1.8)	2 (0.9)	0	3 (3.9)	0	1 (3.8)	1 (5.9)	1 (4.8)
Cardiac failure	4 (1.8)	1 (0.4)	2 (2.4)	1 (1.3)	1 (2.9)	1 (3.8)	1 (5.9)	0

Cardiac failure acute	4 (1.8)	6 (2.6)	2 (2.4)	1 (1.3)	2 (5.7)	1 (3.8)	1 (5.9)	0
<b>Gastrointestinal disorders</b>	<b>55 (24.2)</b>	<b>55 (23.4)</b>	<b>19 (23.2)</b>	<b>15 (19.5)</b>	<b>9 (25.7)</b>	<b>9 (34.6)</b>	<b>5 (29.4)</b>	<b>10 (47.6)</b>
Diarrhea	14 (6.2)	19 (8.1)	6 (7.3)	1 (1.3)	1 (2.9)	1 (3.8)	2 (11.8)	4 (19.0)
Gastritis erosive	4 (1.8)	1 (0.4)	0	1 (1.3)	2 (5.7)	0	0	1 (4.8)
Gastrointestinal hemorrhage	5 (2.2)	1 (0.4)	1 (1.2)	1 (1.3)	1 (2.9)	3 (11.5)	0	1 (4.8)
Gastrointestinal hypomobility	0	2 (0.9)	0	2 (2.6)	0	0	1 (5.9)	0
Hemorrhagic erosive gastritis	0	0	0	0	0	0	1 (5.9)	0
Impaired gastric emptying	1 (0.4)	3 (1.3)	2 (2.4)	0	0	0	1 (5.9)	0
Intestinal ischemia	0	0	0	0	0	0	1 (5.9)	0
Peptic ulcer	0	0	0	0	0	1 (3.8)	0	2 (9.5)
Vomiting	6 (2.6)	5 (2.1)	2 (2.4)	1 (1.3)	2 (5.7)	1 (3.8)	2 (11.8)	3 (14.3)
<b>General disorders and administration</b>	<b>27 (11.9)</b>	<b>28 (11.9)</b>	<b>15 (18.3)</b>	<b>10 (13.0)</b>	<b>5 (14.3)</b>	<b>5 (19.2)</b>	<b>2 (11.8)</b>	<b>8 (38.1)</b>
<b>site conditions</b>								
Death	2 (0.9)	1 (0.4)	1 (1.2)	1 (1.3)	0	0	0	2 (9.5)
Generalized edema	0	5 (2.1)	3 (3.7)	0	0	2 (7.7)	0	1 (4.8)
Multi-organ failure	6 (2.6)	1 (0.4)	5 (6.1)	5 (6.5)	2 (5.7)	1 (3.8)	1 (5.9)	3 (14.3)

Pain	0	1 (0.4)	0	0	0	0	1 (5.9)	1 (4.8)
Pyrexia	7 (3.1)	7 (3.0)	2 (2.4)	0	3 (8.6)	0	0	1 (4.8)
<b>Hepatobiliary disorders</b>	<b>6 (2.6)</b>	<b>13 (5.5)</b>	<b>2 (2.4)</b>	<b>5 (6.5)</b>	<b>3 (8.6)</b>	<b>0</b>	<b>0</b>	<b>2 (9.5)</b>
<b>Infections and infestations</b>	<b>75 (33.0)</b>	<b>86 (36.6)</b>	<b>25 (30.5)</b>	<b>25 (32.5)</b>	<b>19 (54.3)</b>	<b>10 (38.5)</b>	<b>5 (29.4)</b>	<b>9 (42.9)</b>
Clostridium difficile colitis	6 (2.6)	0	0	0	1 (2.9)	1 (3.8)	1 (5.9)	0
Conjunctivitis	1 (0.4)	2 (0.9)	0	4 (5.2)	0	0	0	0
Pneumonia, bacterial	0	0	0	1 (1.3)	2 (5.7)	0	0	0
Sepsis	3 (1.3)	2 (0.9)	1 (1.2)	1 (1.3)	5 (14.3)	1 (3.8)	1 (5.9)	0
Septic shock	3 (1.3)	9 (3.8)	7 (8.5)	3 (3.9)	2 (5.7)	2 (7.7)	1 (5.9)	3 (14.3)
Systemic candida	0	3 (1.3)	1 (1.2)	0	0	0	1 (5.9)	0
Tinea cruris	0	0	0	0	0	0	1 (5.9)	0
Urinary tract infection	15 (6.6)	12 (5.1)	4 (4.9)	10 (13.0)	4 (11.4)	1 (3.8)	1 (5.9)	2 (9.5)
Urinary tract infection fungal	5 (2.2)	2 (0.9)	0	1 (1.3)	0	0	1 (5.9)	1 (4.8)
Urosepsis	0	0	0	0	0	0	1 (5.9)	0
<b>Injury, poisoning, and procedural complications</b>	<b>18 (7.9)</b>	<b>16 (6.8)</b>	<b>4 (4.9)</b>	<b>3 (3.9)</b>	<b>4 (11.4)</b>	<b>2 (7.7)</b>	<b>0</b>	<b>2 (9.5)</b>

Post procedural hemorrhage	1 (0.4)	2 (0.9)	1 (1.2)	1 (1.3)	2 (5.7)	0	0	1 (4.8)
<b>Investigations</b>	<b>47 (20.7)</b>	<b>35 (14.9)</b>	<b>18 (22.0)</b>	<b>8 (10.4)</b>	<b>4 (11.4)</b>	<b>7 (26.9)</b>	<b>3 (17.6)</b>	<b>2 (9.5)</b>
Alanine aminotransferase increased	16 (7.0)	10 (4.3)	4 (4.9)	2 (2.6)	1 (2.9)	1 (3.8)	0	1 (4.8)
Aspartate aminotransferase increased	14 (6.2)	10 (4.3)	4 (4.9)	2 (2.6)	1 (2.9)	1 (3.8)	0	1 (4.8)
Blood creatinine increased	2 (0.9)	1 (0.4)	2 (2.4)	0	0	2 (7.7)	0	0
Blood urea increased	1 (0.4)	0	2 (2.4)	0	0	2 (7.7)	0	0
C-reactive protein increased	1 (0.4)	0	0	0	1 (2.9)	0	1 (5.9)	0
Hepatic enzyme increased	4 (1.8)	4 (1.7)	4 (4.9)	2 (2.6)	1 (2.9)	1 (3.8)	1 (5.9)	0
<b>Metabolism and nutrition disorders</b>	<b>22 (9.7)</b>	<b>36 (15.3)</b>	<b>17 (20.7)</b>	<b>11 (14.3)</b>	<b>5 (14.3)</b>	<b>4 (15.4)</b>	<b>3 (17.6)</b>	<b>8 (38.1)</b>
Diabetic ketoacidosis	1 (0.4)	0	0	0	0	0	1 (5.9)	0
Hyperkalemia	1 (0.4)	2 (0.9)	3 (3.7)	0	0	0	0	3 (14.3)
Hypernatremia	3 (1.3)	4 (1.7)	2 (2.4)	0	1 (2.9)	2 (7.7)	0	4 (19.0)
Hypoalbuminemia	3 (1.3)	1 (0.4)	2 (2.4)	2 (2.6)	1 (2.9)	1 (3.8)	1 (5.9)	1 (4.8)
Hypoglycemia	1 (0.4)	2 (0.9)	2 (2.4)	4 (5.2)	1 (2.9)	1 (3.8)	0	2 (9.5)



Hypokalemia	4 (1.8)	12 (5.1)	7 (8.5)	2 (2.6)	1 (2.9)	0	0	2 (9.5)
Metabolic acidosis	3 (1.3)	0	1 (1.2)	0	0	0	1 (5.9)	0
<b>Musculoskeletal and connective tissue disorders</b>	<b>5 (2.2)</b>	<b>5 (2.1)</b>	<b>1 (1.2)</b>	<b>0</b>	<b>0</b>	<b>2 (7.7)</b>	<b>0</b>	<b>0</b>
<b>Nervous system disorders</b>	<b>42 (18.5)</b>	<b>39 (16.6)</b>	<b>16 (19.5)</b>	<b>13 (16.9)</b>	<b>6 (17.1)</b>	<b>1 (3.8)</b>	<b>2 (11.8)</b>	<b>3 (14.3)</b>
Brain midline shift	2 (0.9)	0	1 (1.2)	0	0	0	1 (5.9)	1 (4.8)
Brain edema	6 (2.6)	9 (3.8)	1 (1.2)	2 (2.6)	1 (2.9)	0	1 (5.9)	0
<b>Psychiatric disorders</b>	<b>12 (5.3)</b>	<b>24 (10.2)</b>	<b>5 (6.1)</b>	<b>2 (2.6)</b>	<b>5 (14.3)</b>	<b>1 (3.8)</b>	<b>0</b>	<b>4 (19.0)</b>
Agitation	1 (0.4)	5 (2.1)	3 (3.7)	2 (2.6)	1 (2.9)	0	0	4 (19.0)
Confusional state	0	7 (3.0)	1 (1.2)	0	2 (5.7)	0	0	0
<b>Renal and urinary disorders</b>	<b>23 (10.1)</b>	<b>24 (10.2)</b>	<b>15 (18.3)</b>	<b>7 (9.1)</b>	<b>8 (22.9)</b>	<b>7 (26.9)</b>	<b>3 (17.6)</b>	<b>2 (9.5)</b>
Hematuria	1 (0.4)	2 (0.9)	0	2 (2.6)	0	2 (7.7)	0	1 (4.8)
Renal cyst	0	1 (0.4)	0	0	2 (5.7)	0	0	0
Renal failure	4 (1.8)	2 (0.9)	1 (1.2)	0	1 (2.9)	0	1 (5.9)	0
Renal failure acute	6 (2.6)	8 (3.4)	6 (7.3)	2 (2.6)	3 (8.6)	2 (7.7)	2 (11.8)	1 (4.8)

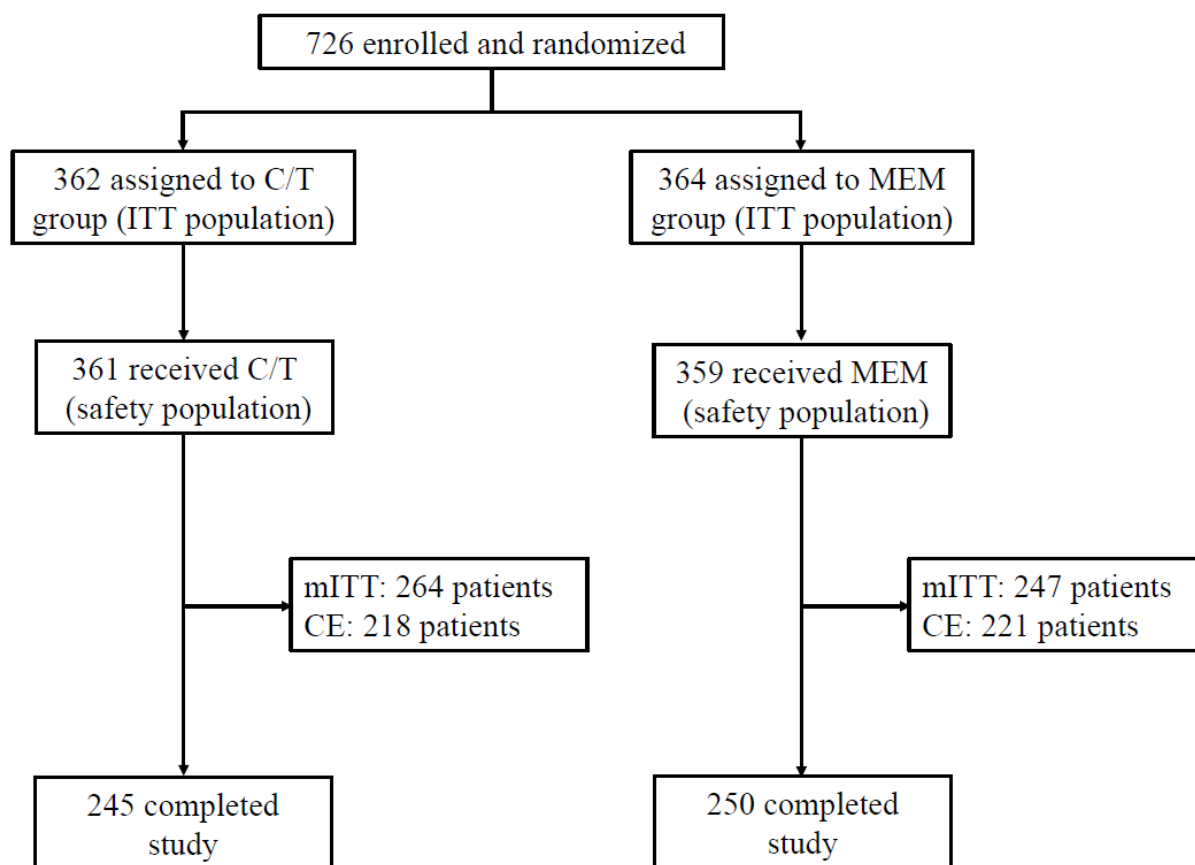
<b>Respiratory, thoracic, and mediastinal disorders</b>	<b>45 (19.8)</b>	<b>53 (22.6)</b>	<b>20 (24.4)</b>	<b>12 (15.6)</b>	<b>8 (22.9)</b>	<b>11 (42.3)</b>	<b>3 (17.6)</b>	<b>7 (33.3)</b>
Acute pulmonary edema	1 (0.4)	0	0	0	0	2 (7.7)	0	0
Acute respiratory failure	0	3 (1.3)	2 (2.4)	0	0	2 (7.7)	0	0
Aspiration	1 (0.4)	3 (1.3)	0	1 (1.3)	2 (5.7)	0	0	0
Atelectasis	2 (0.9)	4 (1.7)	1 (1.2)	1 (1.3)	2 (5.7)	0	0	0
Bronchospasm	1 (0.4)	4 (1.7)	0	0	0	3 (11.5)	0	0
Chronic respiratory failure	0	0	0	0	0	0	1 (5.9)	0
Hydrothorax	7 (3.1)	11 (4.7)	7 (8.5)	8 (10.4)	2 (5.7)	1 (3.8)	0	0
Pleural effusion	5 (2.2)	3 (1.3)	2 (2.4)	2 (2.6)	1 (2.9)	2 (7.7)	0	3 (14.3)
Pulmonary congestion	0	0	0	0	0	0	1 (5.9)	0
Pulmonary embolism	5 (2.2)	3 (1.3)	1 (1.2)	2 (2.6)	0	0	1 (5.9)	0
Tachypnea	0	3 (1.3)	1 (1.2)	0	0	0	0	2 (9.5)
<b>Skin and subcutaneous tissue disorders</b>	<b>33 (14.5)</b>	<b>36 (15.3)</b>	<b>16 (19.5)</b>	<b>11 (14.3)</b>	<b>1 (2.9)</b>	<b>1 (3.8)</b>	<b>4 (23.5)</b>	<b>2 (9.5)</b>
Decubitus ulcer	13 (5.7)	10 (4.3)	7 (8.5)	7 (9.1)	1 (2.9)	0	4 (23.5)	0

<b>Vascular disorders</b>	<b>23 (10.1)</b>	<b>25 (10.6)</b>	<b>5 (6.1)</b>	<b>13 (16.9)</b>	<b>4 (11.4)</b>	<b>4 (15.4)</b>	<b>3 (17.6)</b>	<b>4 (19.0)</b>
Deep vein thrombosis	1 (0.4)	5 (2.1)	0	3 (3.9)	0	0	1 (5.9)	0
Hematoma	1 (0.4)	1 (0.4)	0	0	0	0	1 (5.9)	0
Hypotension	11 (4.8)	8 (3.4)	0	6 (7.8)	4 (11.4)	2 (7.7)	0	2 (9.5)
Phlebitis	1 (0.4)	0	1 (1.2)	0	0	0	1 (5.9)	0
Varicose vein	0	0	0	0	0	0	1 (5.9)	0

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AE, adverse event; CL<sub>CR</sub>, creatinine clearance; C/T, ceftolozane/tazobactam; MEM, meropenem; RI, renal impairment.

<sup>a</sup>Most common AEs were defined as an incidence rate of  $\geq 5\%$  in at least one renal function group/treatment arm.



**Supplementary Fig. S1.** Patient disposition. The ITT population included all randomized patients, regardless of whether they received study drug. The mITT population, which was a subset of the ITT population, received any amount of study drug and had at least one bacterial respiratory pathogen isolated from the baseline lower respiratory tract culture that was susceptible to at least one study drug. The CE population, which was a subset of the ITT population, received study drug, adhered to the study protocol through the TOC visit, and had an evaluable clinical outcome (cure or failure) at the TOC visit. CE, clinically evaluable; C/T, ceftolozane/tazobactam; ITT, intention-to-treat; MEM, meropenem; mITT, microbiological intention-to-treat; TOC, test of cure.