**Title:** A Pilot Study of Ceftolozane-Tazobactam in Conjunction with Rapid Molecular Diagnosis for Directed Treatment of *Pseudomonas aeruginosa* Bacteremia and Pneumonia in Patients with Hematological Malignancies and Hematopoietic Stem Cell Transplantation

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## Précis

*Background*

- The primary empirical treatment of patients with hematological malignancies is being eroded by the emergence of multi-drug resistance. There is a limit to the armamentarium of agents that is validated for use in profoundly neutropenic or highly immunocompromised patients with hematological malignancies and HSCT.
- Ceftolozane/tazobactam is an important advance in the treatment of infections caused by *Pseudomonas aeruginosa*
- Based upon our in vitro and in vivo data as well as the current challenges of emergence of primary resistance, we propose instead that ceftolozane/tazobactam be used in patients with hematological malignancies in HSCT as frontline initial therapy for life-threating *Pseudomonas aeruginosa* infections

*Objectives*

- To define the efficacy of ceftolozane/tazobactam in treatment of life-threatening pneumonias and bacteremia caused by *Pseudomonas aeruginosa* in patients with hematological malignancies and stem cell transplantation (HSCT) in the setting of rapid molecular diagnosis.
- To document the *in vitro* activity and prevention of emergence of ceftolozane/tazobactam resistance during treatment of *Pseudomonas aeruginosa* bacteremia and pneumonia in this population.

*Eligibility*

- Presence of hematologic malignancy or HSCT.
- Identification of *Pseudomonas aeruginosa* by rapid molecular diagnostic assay from a blood culture or from a respiratory sample in the setting of radiologically documented pneumonia and clinical symptoms compatible with pneumonia.

*Design*

- This is a prospective, single arm, open label study of ceftolozane/tazobactam (IV 3g q8h (or equivalent adjustment for renal dysfunction) x 10-14 days) for the primary treatment of culture-confirmed *Pseudomonas aeruginosa* bacteremia and/or pneumonia in patients with hematological malignancies and hematopoietic stem cell transplantation with contemporaneous case control matching. In patients with persistent or refractory bacteremia or pneumonia, duration of therapy may be extended to a total of 21 days.

# 1 Introduction

## 1.1 Study Objectives

### 1.1.1 Primary Objectives

- To define the efficacy of ceftolozane/tazobactam in treatment of life-threatening pneumonias and bacteremia caused by *Pseudomonas aeruginosa* in patients with hematological malignancies and stem cell transplantation (HSCT) in the setting of rapid molecular diagnosis.

### 1.1.2 Secondary Objective

- To document the *in vitro* activity and prevention of emergence of ceftolozane/tazobactam resistance during treatment of *Pseudomonas aeruginosa* bacteremia and pneumonia in this population.

## 1.2 Background and Rationale

### 1.2.1 Loss of effective antimicrobial agents

The primary empirical treatment of patients with hematological malignancies is being eroded by the emergence of multi-drug resistance [1]. There is a limit to the armamentarium of agents that is validated for use in profoundly neutropenic or highly immunocompromised patients with hematological malignancies and HSCT [2]. These include ceftazidime, cefepime, piperacillin/tazobactam, imipenem, and meropenem.

### 1.2.2 Rationale for primary use of C/T for treatment of *Pseudomonas* infections in hematological malignancies coupled with rapid molecular diagnosis

Ceftolozane/tazobactam is an important advance in the treatment of infectious caused by *Pseudomonas aeruginosa* [3-5]. Positioning ceftolozane/tazobactam as the primary treatment for *Pseudomonas aeruginosa* bacteremia and pneumonia in this immunocompromised patient population with hematological malignancies and HSCT could have a profound effect in improving outcome from these life-threatening infections. Once *Pseudomonas* bacteremia or pneumonia would be documented in this population, rather than continuing conventional agents for which there is a high likelihood for emergence of resistance and failure, ceftolozane/tazobactam instead could be used as primary therapy. Using ceftolozane/tazobactam for these documented *Pseudomonas* infections could establish a paradigm shift for this new antimicrobial agent targeted specifically to *Pseudomonas* infection in our most vulnerable patient population.

The current use of ceftolozane/tazobactam in patients with hematological malignancies and HSCT is relegated to salvage therapy after all other avenues have been exhausted.

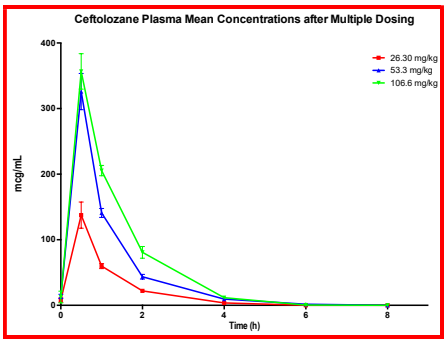
Based upon our *in vitro* and *in vivo* data as well as the current challenges of emergence of primary resistance, we propose instead that ceftolozane/tazobactam be used in patients with hematological malignancies in HSCT as frontline initial therapy for life-threating *Pseudomonas aeruginosa* infections. Given the devastating consequences of progressive *Pseudomonas* bacteremia and pneumonia in this population, allowing for emergence of resistance creates the risk of increased mortality and morbidity. Using ceftolozane/tazobactam as initial therapy for *Pseudomonas* bacteremia and pneumonia in this highly vulnerable population would also be consistent with high standards of antimicrobial stewardship by conserving the use of carbapenems.

The use of ceftolozane/tazobactam for primary treatment of life-threating *Pseudomonas aeruginosa* bacteremia and pneumonia in patients with hematological malignancies and HSCT would be a transformative advance in the management of these highly vulnerable patients.

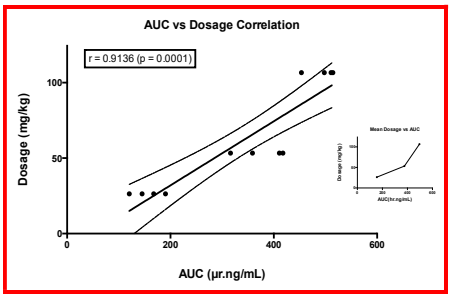
### 1.2.3 Preclinical data in support of C/T for treatment of multidrug resistant *Pseudomonas aeruginosa* infections

We recently conducted a study of ceftolozane/tazobactam in humanized doses that simulate 3 grams every 8 hours in the persistently neutropenic rabbit model *Pseudomonas aeruginosa* pneumonia [6]. The model closely simulates the clinical, microbiological, histological and radiological manifestations of *Pseudomonas* pneumonia in profoundly immunocompromised patients with the hematological malignances. This model is distinctive from that of traditional murine models in that (1) treatment of 12 to 14 days is achieved, (2) untreated controls have the duration of survival of approximately 7 days, (3) the emergence of resistance can be detected over the course of time, and (4) profound persistent neutropenia is achieved to the level of that seen in patient with hematological malignances. The data from this animal model system in collaboration with Merck colleagues demonstrated that ceftolozane/tazobactam when administered in a humanized dose simulating 3 grams every 8 hours allows for potent eradication of *Pseudomonas aeruginosa* of wild type, efflux pump expression, *AmpC* hyper-expression, and porin loss.

Plasma exposure over the dosage range of TZC from 26 mg/kg//13 mg/kg to 53 mg/kg//26 mg/kg reflected the plasma pharmacokinetic parameters observed in humans. The exposure of 375.83 ± 23.84 hr·µg/mL achieved by 53 mg/kg//26 mg/kg is comparable to that of the adult human dose of 2 g ceftolozane. Treatment with TZC resulted in $\geq 10^5$ reduction in residual bacterial pulmonary burden caused by all 4 strains ($p \leq 0.01$). This antibacterial activity coincided with reduction of lung weight ($p < 0.05$), which is a marker of organism-mediated pulmonary injury. CTZ was less active in ACHE-infected rabbits, while TZP had less activity in EPE, ACHE, and OPRDPL strains. Survival was prolonged in TZC and CTZ treatment groups in comparison to that of TZP and UC ($p < 0.001$).



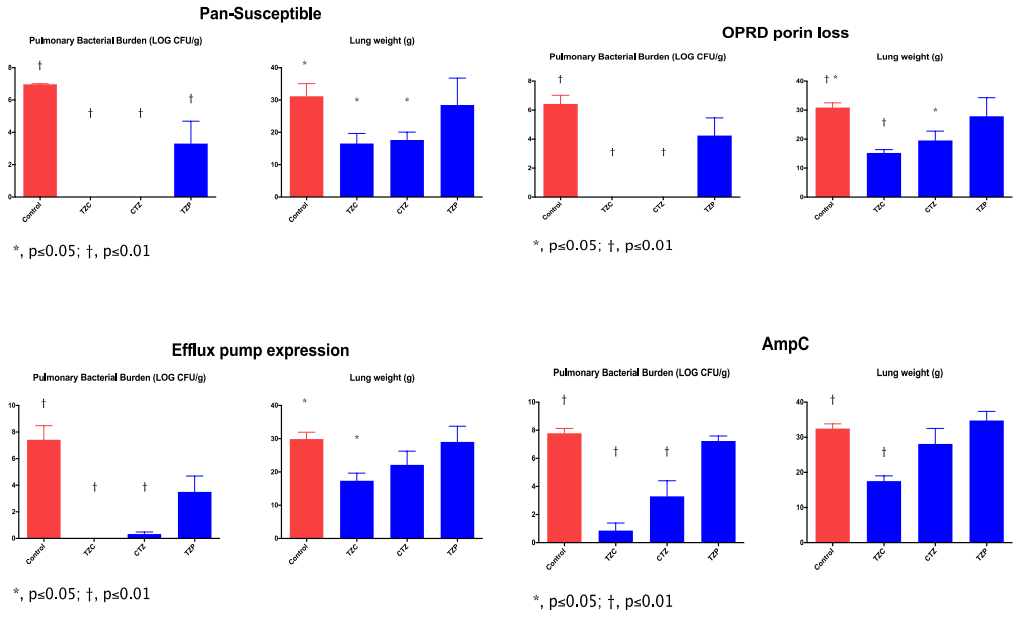

Plasma pharmacokinetics of ceftolozane on day 6 after intravenous administration of ceftolozane/tazobactam at 40, 80, and 160 mg/kg Q8h to healthy New Zealand white rabbits.



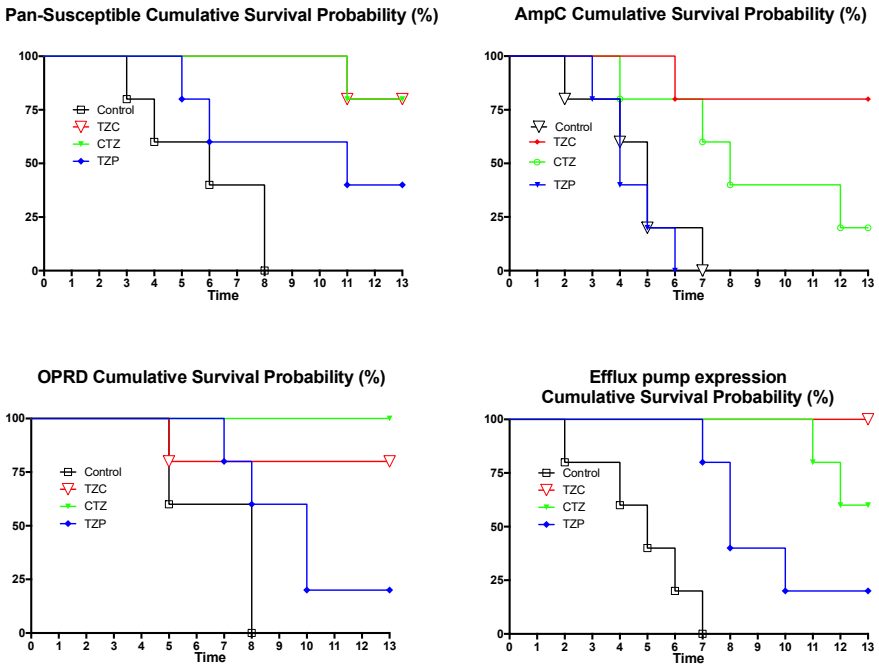

Dose proportionality of ceftolozane administered as ceftolozane/tazobactam across dosages of 26.6 and 53.3 mg/kg IV.

Plasma pharmacokinetic parameters of ceftolozane/tazobactam on day 6 after intravenous administration of ceftolozane/tazobactam Q8h to healthy NZW rabbits

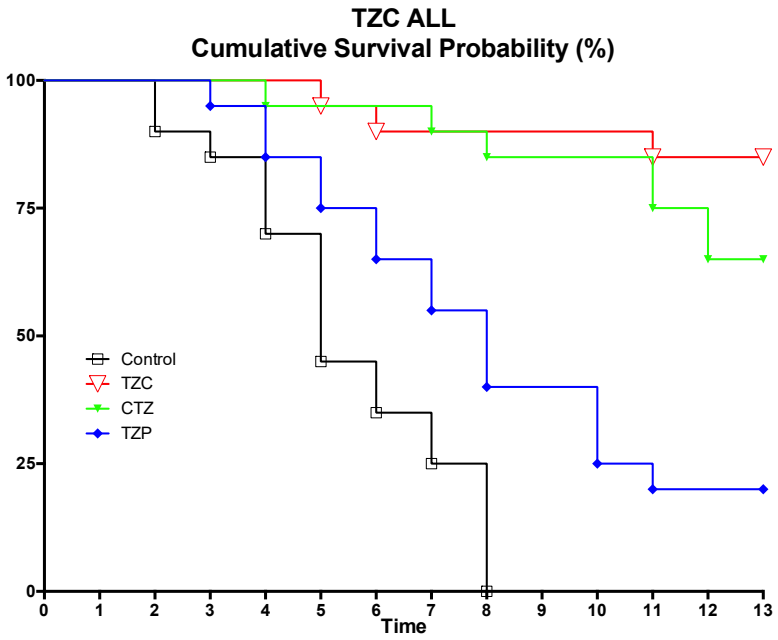
| **Ceftolozane Dosage (mg/kg)** | **$AUC_{(0-8)}$** | **$C_{max}$** | **CL** | **$V_d$** |
|---|---|---|---|---|
| | **(hr·µg/mL)** | **(µg/mL)** | **(mL/hr/kg)** | **(mL/kg)** |
| 26 | 155.87 ± 15.02 | 137.56 ± 20.02 | 162.23± 17.22 | 173.64 ± 17.53 |
| 53 | 375.83 ± 23.84 | 325.96 ± 27.62 | 142.13 ± 9.01 | 161.18 ± 6.29 |
| 106 | 494.06 ± 14.00 | 356.74 ± 27.04 | 212.29 ± 5.51 | 216.58 ± 10.47 |
| **Tazobactam Dose (mg/kg)** | **$AUC_{(0-8)}$** | **$C_{max}$** | **CL** | **$V_d$** |
| | **(hr·µg/mL)** | **(µg/mL)** | **(mL/hr/kg)** | **(mL/kg)** |
| 13 | 15.50 ± 4.73 | 20.77 ± 8.16 | 1199.18 ± 487.82 | 248.35 ± 65.07 |
| 26 | 30.09± 4.82 | 47.84 ± 9.28 | 929.57 ± 127.33 | 154.14 ± 16.65 |
| 53 | 25.18 ± 6.81 | 33.67 ± 9.62 | 2613.92 ± 747.69 | 638.25 ± 167.30 |




Pulmonary bacterial burden and lung weights (markers of organism-mediated pulmonary injury) in rabbits with experimental *Pseudomonas aeruginosa* pneumonia treated with ceftolozane tazobactam (TZC), ceftazidime (CTZ), and piperacillin/tazobactam (TZP) according to mechanism of resistance. The normal lung weight for rabbits used in this study is approximately 15 g.




Survival in rabbits with experimental *Pseudomonas aeruginosa* pneumonia treated with ceftolozane tazobactam (TZC), ceftazidime (CTZ), and piperacillin/tazobactam (TZP) according to mechanism of resistance.




Summary survival of rabbits with experimental *Pseudomonas aeruginosa* pneumonia treated with ceftolozane tazobactam (TZC), ceftazidime (CTZ), and piperacillin/tazobactam (TZP) summarized for all isolates.

### 1.2.4 Clinical Implications of current preclinical studies of C/T in treatment of experimental *Pseudomonas aeruginosa* pneumonia

Ceftolozane/tazobactam administered in humanized dosages achieved comparable plasma exposures in rabbits to permit detailed studies of experimental *Pseudomonas aeruginosa* pneumonia. Ceftolozane/tazobactam was highly active in treatment of experimental *Pseudomonas aeruginosa* pneumonia in persistently neutropenic rabbits, including infections caused by strains with the most common resistance mechanisms.

The results of these preclinical studies clearly demonstrated potent activity of ceftolozane/tazobactam in treatment of experimental pneumonia caused by *Pseudomonas aeruginosa* expressing major resistant mechanisms. That the results were achieved with a humanized adult dose of 3g IV Q8h in persistently neutropenic animals over the course of 12 days provides a solid foundation from which to develop a prospective clinical trial of *Pseudomonas aeruginosa* pneumonia and bacteremia in persistently neutropenic patients with hematological malignancies and HSCT recipients.

The use of rapid molecular diagnostics in detection of *Pseudomonas aeruginosa* blood stream infection and/or pneumonia in this profoundly immunocompromised host population would then be transformative in improving survival.

These findings were predictive of the recently completed phase 3 clinical trial (https://clinicaltrials.gov/ct2/show/NCT02070757), "A Prospective, Randomized, Double-Blind,

Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam Compared With Meropenem in Adult Patients With Ventilated Nosocomial Pneumonia ((MK-7625A-008) (ASPECT-NP)," which demonstrated activity in treatment of this serious infection. In patients with positive lower respiratory tract cultures (70%), at baseline causative gram-negative pathogens were predominately Enterobacteriaceae (74%) and *P aeruginosa* (25%). Ceftolozane/tazobactam was found to be non-inferior to meropenem for the primary endpoint (28-day all-cause mortality (10% non-inferiority margin)) and the secondary endpoint (clinical response at test-of-cure (7-14 days after end-of-therapy; 12.5% non-inferiority margin) in the intent-to-treat population). Mortality was higher in meropenem-treated patients with vHABP.

These data have now led to the recently FDA-approved indication for the 3 gram Q8h dose of ceftolozane/tazobactam as a regimen for the treatment of ventilator-associated pneumonia.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 Eligibility Criteria

Patients are eligible for enrollment into this clinical trial if they fulfill the inclusion criteria and they or their medical proxy sign informed consent.

### 2.1.1 Inclusion Criteria

1. Presence of hematologic malignancy or HSCT.
2. Identification of *Pseudomonas aeruginosa* by rapid molecular diagnostic assay from a blood culture or from a respiratory sample in the setting of radiologically documented pneumonia and clinical symptoms compatible with pneumonia.
3. Age: ≥18 years

### 2.1.2 Exclusion Criteria

1. Prior non-study anti-pseudomonal therapy for >72 hours
2. Anaphylactic hypersensitivity or allergic reaction to cephalosporins
3. History of a strain of *Pseudomonas aeruginosa* with MIC > 4 μg/ml to ceftolozane/tazobactam
4. Polymicrobial aerobic Gram-negative infection as determined by ID research team
5. Hemodialysis, continuous renal replacement therapy, or creatinine clearance <15 ml/min
6. Patients with expected mortality within 48 hours of screening

Patients who complete this study and who subsequently experience a separate, recurrent *Pseudomonas aeruginosa* infection (as confirmed by the Principal Investigator) may be consented and enrolled in this study again if all eligibility criteria are met.

**2.1.3 Control group**: Inclusion criteria includes 1-3, and exclusion criteria includes 2-5 as above. Historical control patients will be alive >48 hours from initiation of anti-pseudomonal therapy for *Pseudomonas* bacteremia and/or pneumonia.

## 2.2 Eligibility Evaluation

### 2.2.1 General

2.2.1.1 The following elements will be evaluated to confirm study eligibility and provide baseline measurements, when appropriate:

- medical history
- physical and laboratory examination findings
- immune status
- hypersensitivities
- current medications

2.2.1.2 These measurements may be obtained from the primary treatment team evaluations or from the assessment of the research team.

## 2.3 Patient Registration

2.3.1 All patients are registered on study once consent has been obtained. Historical controls will have a waiver for informed consent.

# 3 Study Implementation

## 3.1 Study Design

### 3.1.1 Overall Trial Design

This is a prospective, open label study of ceftolozane/tazobactam (IV 3g q8h (or equivalent adjustment for renal dysfunction) x 10 – 14 days with matched historical controls; up to 21 days will be permitted for persistent or refractory bacteremia or pneumonia) for the primary treatment of culture-confirmed *Pseudomonas aeruginosa* bacteremia and/or pneumonia in patients with hematological malignancies and hematopoietic stem cell transplantation with contemporaneous case control matching. Ten patients will be enrolled to receive ceftolozane/tazobactam in the first year.

If further review demonstrates feasibility, 10 more patients will be enrolled to receive ceftolozane/tazobactam the in the second year.

Patients enrolled into the study will be matched 1:3, enrolled:control. For each prospectively enrolled subject, there will be 3 retrospective subjects from this patient population identified from patients managed at NYPH over the past five years with culture-confirmed *Pseudomonas aeruginosa* bacteremia and/or pneumonia. The retrospective controls will be reviewed and data collected via chart review only from July 28, 2015 to December 31, 2022, with the same data elements obtained for enrolled and control subjects.

Case matching will be performed on the following variables:

1. bacteremia vs no bacteremia
2. neutropenic vs non-neutropenic

The standard of care will be the best available anti-pseudomonal beta-lactam (cefepime, ceftazidime, piperacillin/tazobactam, or meropenem) +/- aminoglycoside or fluoroquinolone.

### 3.1.2 Study Flowchart

| Activity | Screening | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Days 11-28 | End of Study[a] | 30-day Assessment | 60-day Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit window | D -1 to D1 | ± 1 day | ± 1 day | ± 1 day | ± 1 day | ± 1 day | ± 1 day | ± 1 day | ± 1 day | ± 1 day | ± 2 days | ± 2 days | N/A | ± 7 days | ± 7 days |
| Informed consent | **X** | | | | | | | | | | | | | | |
| Inclusion/Exclusion | **X** | | | | | | | | | | | | | | |
| Medical History, Demographics | **X** | | | | | | | | | | | | | | |
| Rapid molecular diagnostic testing (for eligibility) | **X** | | | | | | | | | | | | | | |
| Prospective: Limited physical exam, including fever, RR, HR, BP (highest); resolution of sepsis; and presence of cutaneous lesions (rash, black lesions, petechiae, ecthyma, bullae blisters)<br><br>Retrospective: Review of historic physical exam to identify fever, RR, HR, BP (highest); resolution of sepsis; and presence of cutaneous lesions (rash, black lesions, petechiae, ecthyma, bullae blisters) | **X** | **X** | | | | **X* any day here** | | | | | **X** | | | | |
| Sp02 (lowest) and oxygen requirements (highest) | **X** | **X** | | **X** | | **5 AND 7** | | | | | **X** | | | | |
| Diagnostic imaging (ex. CT scans, chest x-rays) if obtained as standard of care (SOC) only (pulmonary infiltrates/opacities, pulmonary nodules, pleural effusions, groundglass opacities, lympthadenopathy, lung abcess, cavitary lesion) | **X** | To be recorded in EDC if collected/completed as SOC | | | | | | | | | | | | | |
| BAL if obtained as standard of care (SOC) only (Gram stain and culture, cell count, protein, glucose) | **X** | To be recorded in EDC if collected/completed as SOC | | | | | | | | | | | | | |
| Repeat blood culture, if enrolled with bacteremia | | **X**[b] | To be recorded in EDC if collected/completed as SOC | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sub-culturing of any SOC microbiologic isolates, for molecular genetic testing and whole genome sequencing | Completed on any SOC microbiologic isolates obtained | | | | | | | | | | | | | | |
| Administration of ceftolozane-tazobactam 3g IV Q8h | | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X**[c] | | | |
| Global Response Assessment | | **X**[d] | | | | | | | | | | | | **X** | **X** |
| Karnofsky Performance Status | | **X** | | | | | | | | | **X**[e] | | | | **X** |
| Survival Assessment[f] | | | | | | | | | | | | | | **X** | **X** |
| Hospitalization Status Assessment | | Recorded throughout | | | | | | | | | | | | **X** | **X** |
| Concomitant antimicrobials for treatment of infection under study, chemotherapy (yes/no), prednisone (yes/no)* at screening and through study | **X** | Recorded throughout | | | | | | | | | | | | **X** | **X** |
| Serious Adverse Events Assessment (CTCAE Grade 4 and 5 only) | **X** | **X** | | | | | | | | | | | | **X** | **X** |
| Adverse Events of Interest Assessment (renal failure, allergic reaction, leukopenia, elevated liver function values, *Clostridium difficile* infection) that meet CTCAE Grade 3 and above | Recorded throughout | | | | | | | | | | | | | | |

**Table 1. Schedule of Assessments**

[a] Patients will be monitored per protocol for up to 8 weeks while inpatient. End of study will be 8 weeks or discharge, whichever is first. Patients will additionally be monitored for up to 6 months specifically for rehospitalizations for *Pseudomonas* bacteremia/pneumonia, ceftolozane-tazobactam resistance, and to collect associated treatment and outcomes.

[b] Blood culture must be positive prior to initiation of ceftolozane-tazobactam if patient enrolled with bacteremia.

[c] Study drug will be extended at these time points, unless daily blood cultures are negative for two sequential days.

[d] Global Response Assessment to be completed once, at the end of treatment.

[e] Completed at Day 10, or at hospital discharge if treatment duration not completed.

[f] To be assessed by chart review, or phone visit, as appropriate.

### 3.1.3 Pre-screening

Screening for candidate patients would be conducted through several mechanisms.

1. All blood cultures and BAL fluid obtained from patients will be screened with rapid molecular diagnostic systems using two platforms, as appropriate:
    a. BioFire Film Array Blood Culture Identification Panel (BCID) (https://www.biofiredx.com/products/the-filmarray-panels/filmarraybcid/)
    b. BioFire Film Array Pneumonia Panel (https://www.biofiredx.com/products/the-filmarray-panels/filmarray-pneumonia/)
2. Clinical Microbiology logs from blood cultures and from bronchoalveolar lavage cultures.
3. Paging system from clinical microbiology laboratory in real time to team members "Dr. Satlin, Dr. Plate"
4. Twice daily discussions with clinical microbiology, and primary care team for in patients and intensive care unit patients.
5. Daily discussions with the Weill Cornell Medicine, NYPH transplantation-oncology infectious diseases team

### 3.1.4 Screening

1-Patients who are identified as being eligible for study will be presented with informed consent explaining potential benefits and risks associated with the clinical trial.

2-A history and physical examination will be conducted as well as review of relevant laboratories following signed and consent.

3-Prior to administration of study drug, repeat blood cultures will be performed.

### 3.1.5 Enrollment/Day 1

1-Written and informed consent, ceftolozane/tazobactam (3gIV q8h or renal equivalent) will be administered urgently from the NYPH pharmacy.

## 3.4 On Study Evaluation

### 3.4.1 General

1. During the course of study, patients will be followed in the intensive care unit or the hematology oncology, HSCT floors under meticulous observation of the Transplantation Oncology Infectious Diseases staff.
2. Protocol defined follow-up visits will be conducted thrice weekly.
3. Blood cultures, diagnostic imaging, a CT scan, vital signs, and resolution of any cutaneous lesions (ecthyma gangrenous) will be monitored and obtained as standards of care.
4. All clinical microbiological isolates including baseline and available follow-up isolates of *Pseudomonas aeruginosa* will be sub-cultured and preserved on agar slants for further assessment of antimicrobial susceptibility. Isolates will be further characterized for susceptibility to ceftolozane/tazobactam, as well as other advanced antimicrobial agents by reference broth microdilution methods.

5. Molecular genetic screening will also be performed for the presence of KPC, NDM, VIM, IMP and OXA-48 genes. Whole genome sequencing will be conducted on all baseline isolates and any isolates recovered at end of therapy.

### 3.4.2. Outcome Parameters

1. Primary outcome variable: Clinical success at day 30 from collection of the index culture (Shields et al. Lancet Inf Dis 2025), defined as meeting all of the following criteria:

   a) Survival
   b) Resolution or near resolution of baseline clinical manifestations, including fever, hypoxia, and signs or symptoms of sepsis
   c) Absence of recurrent infection due to *P. aeruginosa* or persistent infection despite >7 days of anti-pseudomonal therapy

2. Secondary outcome variables:

   a) survival at 30 and 60 days (from time of initiation of anti-pseudomonal therapy), assessed by chart review or phone visit, as appropriate
   b) time to resolution of bacteremia, obtained from blood cultures
   c) length of stay, obtained from Hospitalization Status Assessment
   d) emergence of resistant isolates
   e) time to appropriate therapy, obtained from assessing concomitant medications
   f) resolution of baseline clinical manifestations, obtained from physical exam assessments
   g) modifications to initial antimicrobial therapy, obtained from assessing concomitant medications
   h) the emergence of other bacteria during the course of therapy, obtained from blood cultures
   i) number of days on ventilator, as measured by the Ordinal Scale, Assessment of Clinical Status
   j) ICU length of stay, obtained from Hospitalization Status Assessment

### 3.4.3. Study Duration

The study will last one year, during which time, we anticipate enrollment of 10 patients with *Pseudomonas aeruginosa* infection. If the study enters a second phase, then another 10 patients will be enrolled in the following year.

Patients will be followed throughout their hospitalization for a minimum of three scheduled visits per week during treatment with ceftolozane/tazobactam.

## 3.5 Concurrent Therapies

### 3.5.1 Combination therapy

Combination antimicrobial therapy is permitted on this protocol for treatment of Gram-positive bacterial infections, anaerobic infections with metronidazole, invasive fungal infections, and viral infections.

### 3.6 Off Study Criteria

#### 3.6.1 Criteria for removal from protocol

- Persistent elevation of hepatic transaminases >10x ULN for > 72 hours.
- Discretion of the primary physician.
- Patient desires to discontinue study.
- Patient expires.
- MIC of C/T is found to be > 4 μg/mL for the infecting pathogen.

#### 3.6.2 End of treatment

Patients will be monitored per protocol for up to 8 weeks while inpatient. End of study will be 8 weeks or discharge, whichever is first. Patients will additionally be monitored for up to 6 months specifically for rehospitalizations for *Pseudomonas* bacteremia/pneumonia, ceftolozane-tazobactam resistance, and to collect associated treatment and outcomes.

## 4 SUPPORTIVE CARE

Supportive care will be provided through the patient's primary treatment protocol.

## 5 DATA COLLECTION AND EVALUATION

### 5.1 Data Collection

The principal investigators will be responsible for the collection, maintenance, and quality control of the study data. C/T treated patient data will be prospectively collected and recorded by individual AIs responsible for study data. Toxicity and response data will be entered into the database at least once every 2 weeks.

#### 5.1.1 Data Elements

5.1.1.1 H&P data: signs and symptoms of toxicity

5.1.1.2 Karnofsky Performance Status **(Appendix B)**

5.1.1.3 Laboratory microbiological data

5.1.1.4 Results of scans and radiographs

### 5.2 Response criteria

The primary endpoint of clinical success at day 30 includes

a) Survival and
b) Resolution of baseline clinical manifestations, including fever, hypoxia, and signs or symptoms of sepsis
c) Absence of recurrent infection due to *P. aeruginosa* or persistent infection despite >7 days of anti-pseudomonal therapy

The secondary outcome variables:

a) survival at 30 and 60 days (from time of initiation of anti-pseudomonal therapy)
b) time to resolution of bacteremia
c) length of stay
d) emergence of resistant isolates
e) time to appropriate therapy
f) resolution of baseline clinical manifestations
g) modifications to initial antimicrobial therapy
h) the emergence of other bacteria during the course of therapy

## 5.3 Toxicity Criteria

This study will utilize the Cancer Therapy Evaluation Program Common Toxicity Criteria Adverse Event Reporting (CTCAE) Version 5.0 for classification of the SAE by type and grade. A copy of the CTCAE version 5.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 5.0

## 5.4 Statistical Considerations

### 5.4.1 Subject Accrual

Subjects of both genders, from all racial and ethnic groups are eligible for this trial if they meet the criteria outlined in Section 2.1.

### 5.4.2 Statistics and Feasibility

As this clinical trial is a pilot study, sample size determination is based on feasibility of enrollment of 10 eligible patients within a one year period.

The retrospective analysis will consist of a 5-year review of patients with hematological malignancy and/or HSCT with *Pseudomonas aeruginosa* bacteremia and/or pneumonia. While the control arm may have limitations in its retrospective nature, the objective character of the different variables studied will assure an informative analysis.

An analysis of outcome variables will be performed in comparison to controls matched for underlying hematological malignancy or HSCT. Further statistical analysis will include descriptive statistics of mean □standard error of the mean and 95% confidence intervals for the differences in response. Differences in continuous variable will be analyzed by Wilcoxon rank-sum test. Differences in categorical variables will be assessed by Chi-square or Fisher's exact test. Kaplan Meier analysis will be used to plot survival and Mantel-Haenszel chi square will be utilized for analysis of differences in survival. All P values are two-tailed and a threshold of 0.05 is designated statistically significant.

In univariate analysis, categorical variables were compared by either Chi-squared or Fisher's exact tests and continuous variables were compared by the Wilcoxon rank-sum test. For determining factors independently associated with outcome, we will use multivariate logistic regression. All variables with a P value ≤0.1 in univariate analysis are initially entered into the multivariate model. Backward selection is then applied until only variables with P values ≤0.1 remain in the final model. For determining factors independently associated with survival, a Cox proportional hazards model is applied. Prism 8 will be used for data analysis (/www.graphpad.com/scientific-software/prism/).

If the analysis for the outcome is favorable for the first 10 patients enrolled into the study, then consideration will be given to revising the protocol to include an additional 10 patients.

A review of the demographics of *Pseudomonas aeruginosa* infections in patients with hematological malignancies and HSCT at our institution anticipates that we could enroll 20 to 30 patients with life-threatening *Pseudomonas aeruginosa* bacteremia and/or pneumonia in a two-year period.

#### 5.4.3 Accrual Ceiling

Target enrollment is 10 evaluable patients with a total of 20 patients who may be enrolled.

## 6 DATA REPORTING

### 6.1 Safety Reporting

#### 6.1.1 Adverse Events

As ceftolozane/tazobactam has been approved by FDA, its safety profile is well characterized. We will therefore not collect adverse events.

Serious adverse events (SAEs) other than hospital readmission will be monitored and reported to the IRB. As patients undergoing chemotherapy and hematopoietic stem cell transplantation are commonly readmitted to hospital reporting these events would be unlikely to be meaningful.

Adverse Events of Interest that meet CTCAE Grade 3 and above will also be assessed, and include the following: renal failure, allergic reaction, leukopenia, elevated liver function values, *Clostridium difficile* infection.

**Serious Adverse Event Reporting Requirements.**

The principal investigator of the coordinating center will report to the IRB

- All deaths

- All serious adverse events (SAEs) that are **not** listed in the consent form, but are possibly, probably, or definitely related to the research.

An SAE is defined as an untoward medical occurrence that:

- Resulted in death
- Was life-threatening
- Required or prolonged hospitalization
- Caused persistent or significant disability/incapacity
- Resulted in congenital anomalies or birth defects
- Required intervention to prevent permanent impairment or death

Reports must be received by the IRB within 7 days of notification of the event.

### 6.2 Withdrawal from Study

In the event that a patient withdraws from the study, the reason will be recorded in the CRF. Withdrawal occurs when an enrolled patients ceases to participate in the study, prior to completion of the protocol. The investigator will record the cause for study withdrawal and would arrange for appropriate follow-up if required.

### 6.3 Record Keeping

The PI will maintain a copy of all signed informed consent documents as well as the Study Samples Log sheets documenting the receipt and distribution of samples. The PI will maintain all relevant data in locked files. Coded data within the RedCap database will be securely maintained and password protected, to which only study investigators will have access.

### 6.4 Data Sharing

The de-identified, coded data from this study and study results will be shared with the sponsor.

## 7. REFERENCES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## Appendix A
## Karnofsky Performance Status

| | | |
|---|---|---|
| Able to carry on normal activity and to work; no special care needed. | 100 | Normal no complaints; no evidence of disease. |
| | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| | 80 | Normal activity with effort; some signs or symptoms of disease. |
| Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed. | 70 | Cares for self; unable to carry on normal activity or to do active work. |
| | 60 | Requires occasional assistance, but is able to care for most of his personal needs. |
| | 50 | Requires considerable assistance and frequent medical care. |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly. | 40 | Disabled; requires special care and assistance. |
| | 30 | Severely disabled; hospital admission is indicated although death not imminent. |
| | 20 | Very sick; hospital admission necessary; active supportive treatment necessary. |
| | 10 | Moribund; fatal processes progressing rapidly. |
| | 0 | Dead |