MD Anderson IND Sponsor Cover Sheet

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Protocol Title	AN INVESTIGATOR INITIATED, PHASE II SINGLE-CENTER, RANDOMIZED, OPEN-LABEL, PROSPECTIVE, COMPARATIVE STUDY TO DETERMINE THE EFFICACY, SAFETY, AND TOLERABILITY OF CEFTOLOZANE-TAZOBACTAM PLUS VANCOMYCIN, LINEZOLID VERSUS STANDARD OF CARE PLUS VANCOMYCIN, LINEZOLID AS EMPIRIC THERAPY IN FEBRILE NEUTROPENIC ADULTS WITH CANCER
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AN INVESTIGATOR INITIATED, PHASE II SINGLE-CENTER, RANDOMIZED, OPEN-LABEL, PROSPECTIVE, COMPARATIVE STUDY TO DETERMINE THE EFFICACY, SAFETY, AND TOLERABILITY OF CEFTOLOZANE-TAZOBACTAM PLUS VANCOMYCIN, LINEZOLID VERSUS STANDARD OF CARE PLUS VANCOMYCIN, LINEZOLID AS EMPIRIC THERAPY IN FEBRILE NEUTROPENIC ADULTS WITH CANCER

Ceftolozane-Tazobactam

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1.0 TABLE 2–1. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Assessment or Procedure	*Baseline*[a]	*Treatment*		*Follow-up*	
		Study Days 1 to ≤ 14[b]	*EOIV*[c]	*TOC*[d]	*LFU*[e]
Informed consent[f]	X				
Inclusion/exclusion criteria	X				
Medical and surgical history[g]	X				
Height and weight[h]	X				
Chest radiography[i]	X		If clinically indicated		
Physical examination	X	X[j]	X	X	X[k]
Vital signs[l]	X	X	X	X	X[k]
Prior/concomitant medications[m]	X	X	X	X	X
AEs and SAEs	X	X	X	X	X
Clinical outcome			X	X	***X***
Laboratory tests[n]	X	If clinically indicated[o]	X[p]		
Absolute neutrophil count	X	X[q]	X	X	
Urine or Serum pregnancy test[r]	X				
CrCl calculation[s]	X	X[j]	if clinically indicated		
Blood sample and urine culture/urine analysis (when clinically needed)[t]	X	X	X[u]	if clinically indicated	
Other samples for culture from possible suspected infected site if clinically indicated	if clinically indicated				
Randomization	X				
Study drug administration		X[v]	X		

a Perform baseline assessments within 24 hours beforefirst dose of IV study drug.

b Study Day 1 is the first day of inpatient IV study drug administration; subsequent study days are consecutive calendar days. Baseline and Study day 1 assessment could be combined if they occur on the same calendar day.. On
Study Days 1 to ≤ 14, study drug administration applies to all patients, and assessments are to be performed for patients on inpatient IV study drug only. Treatment duration is 5 to 14 days with a minimum of 3 days (ie, 72 hours and a minimum of 9 doses for *Ceftolozane-Tazobactam* and SOC therapies, except piperacillin/tazobactam, which is a minimum of 12 doses) of inpatient IV study drug.

c Perform EOIV assessments in person within 72 hours after administration of the last dose of inpatient IV study drug. A patient may be eligible to switch to oral or IV therapy after at least 72 hours of IV gram negative antimicrobial coverage (Section 9.4.1.4).

d Perform TOC assessments in person between Study Days 21 and 28.

e Perform LFU assessments between Study Days 35 and 42. LFU assessments may be conducted via telephone for any patient who has not experienced clinical failure since TOC, did not have ongoing study drug related AEs or SAEs at TOC, or did not develop any study drug related AEs or SAEs since TOC. If symptoms consistent with clinical failure or new study drug related AEs or SAEs are noted, or at the discretion of the Investigator, the patient should be immediately scheduled for an in-person visit. Also, telephone visit is acceptable for patients who cannot present for a clinic visit.

f Obtain written informed consent before initiating any study assessment or procedure.

g Obtain a complete medical and surgical history, including all active conditions and all conditions diagnosed within the previous 3 months.

h If height or weight is not obtainable (eg, patient is immobilized), use the last known or stated height and weight.

i CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms.

j Every 3 days after first dose, while the patient is hospitalized and receiving inpatient IV study drug, whereby the week begins on the day of enrollment. The patient could receive unscheduled assessment, if deemed necessary at the discretion of the investigator. The investigator can rely on the physical exam performed by a professionally trained physician or health professional licensed to perform physical examinations.

k Do not perform if LFU is conducted via telephone.

l Blood pressure (systolic and diastolic) and pulse rate, respiratory rate, oxygen saturation (if applicable), and highest daily temperature.

m Record medications, including antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the-counter medications (eg, vitamins, herbal medications), and parenteral nutrition taken or received within 30 days of first dose of ***inpatient*** IV study drug through LFU.

n Refer to Section 9.5.2.5 for a detailed list of laboratory tests. Results from unscheduled laboratory tests will not be collected, unless associated with an SAE or AE leading to discontinuation of IV study drug. Any abnormal laboratory test possibly attributable to IV study drugs will be repeated at appropriate intervals until it returns to normal.

o Perform on Study Day 7 if still on IV study drug.

p At EOIV, perform laboratory tests if laboratory tests for EOIV is obtained ≥ 24 hours prior to the last dose (if applicable).

q Record absolute neutrophil count a minimum of 3 times per week while on study therapy (IV or oral). For patients who switch to oral ***or IV*** therapy, at the discretion of the Investigator, record absolute neutrophil count as clinically indicated between EOIV and TOC.

r Women of childbearing potential only (including those who are fewer than 2 years postmenopausal); ensure test is negative before randomization within 72 hours.

s The estimated CrCl should be calculated with the Cockcroft-Gault formula using the actual weight. If weight is not obtainable (eg, patient is immobilized), use the last known or stated weight.

t Obtain 2 sets of blood samples from an existing CVC, if present, and from a peripheral vein site, preferably before antibiotics are administered. If no CVC is present, collect 1-2 blood cultures from separate venipuncture sites, preferably. Obtain blood samples for culture every other day until temperature is ≤ 101°F (38.3°C) and cultures are negative.

u If baseline cultures were positive, repeat blood cultures at EOIV to determine microbiological response.

v Administer per Section 9.4.1.

AE = adverse event; CrCl = creatinine clearance; CT = computed tomography; CVC = central venous catheter; CXR = chest radiography; EOIV = End of ***Inpatient*** Intravenous Therapy; IV = intravenous; LFU = Late Follow-up; SAE = serious adverse event; TOC = Test-of-Cure.

2.0 LIST OF IN-TEXT TABLES

3.0 LIST OF IN-TEXT FIGURES

4.0 LIST OF ABBREVIATIONS

%*f*T > CT	percent of time that free drug concentrations are above a threshold concentration over a dose interval
%*f*T > MIC	percent of time that free drug concentrations are above the minimum inhibitory concentration over a dose interval
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AmpC	Ambler Class C
AST	aspartate aminotransferase
CE	clinically evaluable
CFR	Code of Federal Regulations
cIAI	complicated intra-abdominal infection
CrCl	creatinine clearance
CT	computed tomography
cUTI	complicated urinary tract infection
CXR	chest x-ray
eCRF	electronic case report form
EDC	electronic data capture
EOIV	End of ***Inpatient*** Intravenous Therapy
ESBL	extended-spectrum β-lactamase

FDA	US Food and Drug Administration
FR	Federal Register
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous, intravenously
LAR	legally authorized representative
LFU	Late Follow-up
MDR	multidrug resistant
ME	microbiologically evaluable
MedDRA	*Medical Dictionary for Regulatory Activities*
MITT	modified intent-to-treat
mMITT	microbiological modified intent-to-treat
MTZ	metronidazole
PCS	potentially clinically significant
PHL	potential Hy's Law
PID	patient identification
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
q8h	every 8 hours
q6h	every 6 hours
RSM	Regional Site Manager

SAE	serious adverse event
SOC	standard of care
TEAE	treatment-emergent adverse event
TOC	Test-of-Cure
ULN	upper limit of normal

5.0 ETHICAL CONSIDERATIONS

5.1 Institutional Review Board

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Merck, Inc. along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRB in conformance with the CFR, Title 21, Part 56.

5.2 Ethical Conduct Of The Study

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and Good Clinical Practice (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the CFR.

5.3 Patient Information And Informed Consent

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA authorization (in compliance with 21 CFR, Parts 50 and 312) before participating in any study-related procedures.

Each patient (or his or her legally authorized representative) will read, assent to an understanding of, and sign an instrument of ICF after having had an opportunity to discuss it with the study staff before signing; each patient will be made aware that he or she may withdraw from the study at any time.

The informed consent statement contains all the elements of informed consent listed in Appendix I of this protocol. Signed copies of the ICF will be given to the patient, and both documents will be placed in the Investigator’s study files.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at 1 study center in the United States (MD Anderson Cancer Center, Houston, Texas).

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator must meet his or her obligations to the patients, ethics committee, Sponsor, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of their capabilities and performance consistent with the study investigational plan. The Investigator will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

7.1 Background and Study Rationale

The steady rise of antibiotic-resistant bacteria is an imminent and urgent threat to individual patients and public health. Yet the treatment of infection is an area where there have been few major advances in recent years and the number of new antibiotics in this area of research has dropped off steadily. Despite the current hopeful efforts of the antibiotics stewardship programs, new resistances continue to emerge. There consequently remains an unmet medical need for new antibiotics, particularly those directed against multidrug-resistant (MDR) Gram-negative bacteria in hospitals. Already, some nonfermenters of the genera *Acinetobacter* and *Pseudomonas* are resistant to all well-tolerated antibiotics, and many *Enterobacteriaceae* are resistant to all except carbapenems.

In a world of increasing resistance, standard empirical monotherapy for patients with cancer and febrile neutropenia with piperacillin-tazobactam, cefepime, or carbapenems would be 'inappropriate' against an increasing proportion of Gram-negative pathogens. Infections in onco-hematologic patients produced by extended-spectrum β-lactamase (ESBL), or Ambler Class C (AmpC)-β-lactamase-producing *Enterobacteriaceae*, MDR *Pseudomonas aeruginosa*, *Acinetobacter spp*., or *Stenotrophomonas spp*. are significantly more likely to be treated using an inadequate initial empirical antibiotic therapy. As a consequence, failure to cover Gram-negative pathogens, particularly ESBL producers and MDR *P. aeruginosa,* significantly and independently impairs outcomes in onco-hematology patients, increasing mortality and prolonging hospitalization (Giamarellou, 2010; Gudiol et al, 2011; Ortega et al, 2009; Trecarichi et al, 2009; Tumbarello et al, 2006).

Infections caused by ESBL-producing Enterobacteriaceae (ESBL-ENT), particularly *Escherichia coli* and *Klebsiella pneumoniae*, are on the increase. Resistance among ESBL producers extends not only to β-lactams (BL) including penicillin and third-generation cephalosporins but also to aminoglycosides and fluoroquinolones. Carbapenems remain the preferred treatment for severe infections caused by ESBL producers. New antibiotics, such as BL/β-lactamase inhibitor (BLI) combinations, may be useful carbapenem-sparing options against ESBL-ENT. Furthermore, there is a paucity of novel classes of antimicrobials to target resistant Gram-negatives.

7.2 Clinical Overview

Ceftolozane/tazobactam consists of a novel cephalosporin and an established β-lactamase inhibitor that is being developed to address antimicrobial resistance in serious infections caused by gram-negative pathogens. Ceftolozane/tazobactam is approved in the United States as Zerbaxa™ (ceftolozane and tazobactam) for the treatment of complicated intra-abdominal infections (administered with metronidazole) (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis, in adults (1-3). Additionally, ceftolozane/tazobactam is being developed for the treatment of ventilated nosocomial pneumonia in adults. In vitro activity of ceftolozane/tazobactam has been confirmed against a wide range of pathogens, including MDR/XDR drug-resistant *Pseudomonas aeruginosa* and ESBL-producing Enterobacteriaceae (4-7).

7.2.1 Summary Of Efficacy In Completed Clinical Studies

Ceftolozane/tazobactam was studied in a large Phase 3 clinical programme [Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam (ASPECT)] in patients with cIAI or cUTI. In ASPECT-cIAI, ceftolozane/tazobactam plus metronidazole was non-inferior to meropenem, and in ASPECT-cUTI, ceftolozane/tazobactam demonstrated efficacy superior to that of high-dose levofloxacin.

In ASPECT-cIAI, for the primary endpoint, clinical cure rates were 83.0% (323/389) with ceftolozane/tazobactam plus metronidazole and 87.3% (364/417) with meropenem in the MITT population at the TOC visit, which occurred at a median of 27 days (interquartile range, 26–28 days) after the TOC visit. The weighted difference in clinical cure rates (ceftolozane/tazobactam plus metronidazole minus meropenem) was −4.2% with a 2-sided 95% CI of −8.91% to .54%, thus meeting the statistical criteria for noninferiority. Statistical noninferiority was also demonstrated for the ME population, where clinical cure rates were 94.2% and 94.7% (weighted difference, −1.0; 95% CI, −4.52 to 2.59) at the TOC visit.

Clinical cure rates in the ITT population at TOC were 83.6% for ceftolozane/tazobactam plus metronidazole and 86.2% for meropenem (difference, −2.6; 95% CI, −7.08 to 1.87), similar to those observed in the MITT population. In the CE population, cure rates were 94.1% and 94.0%, respectively (difference, 0.1; 95% CI, −3.30 to 3.55). At the end of therapy, clinical cure rates in the MITT population were higher in both treatment groups: 89.2% for ceftolozane/tazobactam plus metronidazole and 92.3% for meropenem (difference, −3.1; 95% CI, −7.23 to .89).

In the Trial with cUTI for the mMITT population, there were 212 patients (26.5%) with at least one baseline uropathogen that was resistant to levofloxacin. The majority of uropathogens in this subgroup were Enterobacteriaceae (n=186) that were susceptible to ceftolozane/tazobactam [MIC ≤2 mg/L, 88.7% (165/186)]. Among patients with levofloxacin-resistant pathogens, ceftolozane/tazobactam demonstrated significantly higher composite cure rates than levofloxacin in both the mMITT [60.0% (60/100) versus 39.3% (44/112); 95% CI for the treatment difference, 7.2%-33.2%] and ME [64.0% (57/89) versus 43.4% (43/99); 95% CI for the treatment difference, 6.3%-33.7%] populations, respectively. In conclusion, seven day treatment with ceftolozane/tazobactam was more effective than high-dose levofloxacin treatment in patients with cUTI caused by levofloxacin-resistant bacteria, and it may be an alternative treatment in settings of increased fluoroquinolone resistance.

7.2.2 Activity against Pseudomonas Aeruginosa

Multidrug-resistant *P. aeruginosa* often requires complex antimicrobial regimens and, when treated inadequately, infections caused by this pathogen are associated with particularly poor outcomes including postoperative complications, longer hospital stays, and increased mortality [8-10]. In vitro studies have shown that ceftolozane/tazobactam is the most potent antipseudomonal agent, maintaining activity against many multidrug-resistant strains [4]. Ceftolozane/tazobactam demonstrated efficacy against *P. aeruginosa*, even though experience with multidrug-resistant *P. aeruginosa* was limited.

These results suggest that ceftolozane/tazobactam is a potential alternative to the currently recommended antimicrobials for the treatment of cIAIs and cUTIs, especially when resistant Enterobacteriaceae or *P. aeruginosa* are suspected, such as in healthcare-associated infections.

7.3 Summary of Safety

The incidence of AEs that developed during the phase 3 treatment of cIAI trial was similar between the ceftolozane/tazobactam plus metronidazole group and the meropenem group (44.0% and 42.7%, respectively), and most events were mild to moderate in severity. The most common laboratory AEs were increased alanine aminotransferase and aspartate aminotransferase, which occurred in 2.5% and 1.6% of all patients, respectively. Drug-related AEs leading to discontinuation were few,

occurring in 3 patients (0.6%) in the ceftolozane/tazobactam plus metronidazole group and 4 patients (0.8%) in the meropenem group. Serious AEs occurred in 39 of 482 (8.1%) and 36 of 497 (7.2%) patients in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively. Drug-related serious AEs occurred in 1 patient in each treatment group (both *Clostridium difficile* infection).

There were 11 deaths (2.3%) in the ceftolozane/tazobactam plus metronidazole group and 8 deaths (1.6%) in the meropenem group; no death was considered by the investigators to be related to study treatment.

In conclusion, these results suggest that ceftolozane/tazobactam plus metronidazole is a potential alternative to the currently recommended antimicrobials for the treatment of cIAIs, especially when resistant Enterobacteriaceae or *P. aeruginosa* are suspected, such as in healthcare-associated infections.

8.0 STUDY OBJECTIVES

Primary:

- To evaluate the efficacy of ceftolozane/tazobactam plus vancomycin, daptomycin or linezolid vs standard of care (SOC) plus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to favorable clinical response at ***End of Inpatient Intravenous Therapy (***EOIV***)*** in the Modified Intent-to-Treat (MITT) Analysis Set

- To evaluate the safety and tolerability of ceftolozane/tazobactam plus vancomycin, daptomycin, or linezolid compared with SOC plus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer

Secondary:

- To evaluate the efficacy of ceftolozane/tazobactam plus vancomycin, daptomycin or linezolid compared with SOC plus vancomycin< daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to the following:

  - Favorable clinical response at EOIV in the mMITT and Clinically Evaluable (CE) analysis sets

  - Favorable clinical response at TOC (ie, 21 to 28 days after start of IV therapy) ***and LFU (ie, 35 to 42 days after start of IV therapy)*** in the MITT Analysis Set

  - Favorable clinical response and by baseline Gram-negative pathogen at EOIV**,** TOC***, and LFU*** in the mMITT and CE analysis sets

  - Favorable microbiological response by patient and by baseline Gram-negative pathogen at EOIV**,** TOC***, and LFU*** in the mMITT and ME analysis sets

  - Infection-related mortality rate at TOC ***and LFU*** in the MITT and mMITT analysis sets

  - 30-day all-cause mortality rate in the MITT and mMITT analysis sets

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Description

This clinical study will be a single-center, randomized, open-label, parallel-group study comparing ceftolozane/tazobactam plus vancomycin, daptomycin or linezolid with SOC plus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer. The total duration of study therapy will be 5 to 14 days; a minimum of 3 days (ie, 72 hours of IV antimicrobial gram negative coverage is required; duration of treatment is discussed in Section 9.4.1.5. ***IV study drug is defined as the IV treatment for Gram-negative coverage (or SOC) that the patient is receiving for the neutropenic febrile episode.*** A switch to open-label oral ***or IV*** therapy may be allowed after at least 72 hours IV gram negative antimicrobial coverage per Section 9.4.1. Doses given before signing informed consent will be counted.
Gram positive antimicrobial coverage (ie vancomycin, linezolid or daptomycin) is optional and can be given if clinically indicated at the discretion of the primary team or emergency center physician. Gram positive antimicrobial coverage can also be switched at any time during the study.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

To be eligible to participate in the study, a patient must meet the following criteria:

1. Has provided written informed consent, and has the willingness and ability to comply with all study procedures

2. Male or female, ≥ 18 years old

3. Patients with neutropenic fever who have existing malignancy or have undergone hematopoietic stem cell transplantation. Neutropenic fever is defined as the presence of neutropenia defined by: 1) Absolute neutrophil count (ANC) < 500 cells/mm^3 or has an ANC that is expected to decrease to < 500 cells/mm^3 within 48 hours of trial entry and fever defined as: 2) Single oral temperature measurement of ≥ 101°F (38.3°C) or a temperature of ≥ 100.4°F (38.0°C) sustained over a 1-hour period

4. Requires hospitalization for IV empiric antibiotic therapy

5. If female:

- Not breastfeeding

- Agrees to not attempt to become pregnant during the study

Is surgically sterile or at least 2-years postmenopausal, or if of childbearing potential, has negative screening serum or urine pregnancy test within 72 hours

- If of childbearing potential (including being < 2 years postmenopausal), is willing to practice sexual abstinence or use an effective dual form of contraception with her partner (eg, 2 barrier methods, barrier method plus hormonal method) during treatment and up 28 days post treatment.

9.3.2 Exclusion Criteria

Patients who meet any of the following criteria will not be eligible to participate in the study**:**

1. History of any hypersensitivity or allergic reaction to any cephalosporin antibiotic or tazobactam,
2. Fever suspected to be caused by a noninfectious cause (eg, fever related to drug or blood product administration)
3. Confirmed fungal infection (eg, *Pneumocystis jirovecii* etiology in patients with pneumonia) that justifies adding additional empiric antimicrobial therapy (eg, antifungals)
4. Confirmed viral infection that justifies adding additional empiric antiviral therapy (eg, ganciclovir, foscarnet)
5. Evidence of significant hepatic impairment (any of the following):

- Known acute viral hepatitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level > 5 times the upper limit of normal (× ULN). Patients with values > 3 × ULN and < 5 × ULN are eligible if the value is acute and directly related to the infectious process being treated.
- Total bilirubin > 3 × ULN unless isolated hyperbilirubinemia is directly related to the acute infection or due to known Gilbert disease
- Manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy

6. Known to be human immunodeficiency virus positive
7. Severely impaired renal function, defined as creatinine clearance (CrCl) ≤ 30 mL/min estimated by the Cockcroft-Gault formula (Section 9.5.3.1)
8. Expected requirement for hemodialysis while on study therapy
9. Received > 24 hours of IV antibacterial therapy (with study drugs) within 72 hours of the initiation of ***inpatient*** IV study drug for treatment of suspected infection. Antibiotic prophylaxis and oral antibiotics is allowed. Prophylactic use of antiviral or antifungal medication is permitted.
10. Requirement for any non-study potentially effective concomitant systemic antibacterial therapy
11. Past or current history of epilepsy or seizure disorder; **exception:** well-documented febrile seizure of childhood

12. Evidence of immediately life-threatening disease, progressively fatal disease, or life expectancy of 3 months or less (eg, moribund or with shock unresponsive to fluid replacement)

13. Unable or unwilling to adhere to the study-specified procedures and restrictions

14. Any condition that would make the patient, in the opinion of the Investigator, unsuitable for the study (eg, would place a patient at risk or compromise the quality of the data

15. Participation in any other ongoing ceftolozane/tazobactam trial.

9.3.3 Removal of Patients from Therapy or Study Assessment

Patients should be encouraged to complete all study assessments. However, a patient may be discontinued from ***inpatient*** IV study drug ***or*** oral ***or IV*** therapy or may withdraw consent to participate in this study at any time without penalty or loss of benefits to which the patient is otherwise entitled.

A premature discontinuation from the study will occur when a patient who signed the ICF, regardless of circumstances, ceases participation in the study, before the completion of all study assessments (ie, before completing all protocol-stipulated activities). In addition, patients can be prematurely discontinued from the study after careful consideration for one of the reasons listed in Section 9.3.3.4.

Follow-up of patients prematurely discontinued from *inpatient* IV study drug or oral or IV therapy or withdrawn from the study will be conducted as described below.

9.3.3.1 Premature Discontinuation from Inpatient IV Study Drug Due To Safety

Reasons: Possible reasons for premature discontinuation from study drug administration *due to safety* include, but are not limited to:

Occurrence of a related, possibly or probably related AE that, in the opinion of the Investigator, warrants the patient's permanent discontinuation from IV study drug

Known pregnancy or breastfeeding during the study therapy administration period.

The patient meets criteria for drug-induced liver injury per Appendix V, at the discretion of the Investigator

Investigator determines that it is in the best interest of the patient to discontinue study drug, due to reasons other than an adverse event (AE)

Assessments and Procedures: A patient who is prematurely discontinued from ***inpatient*** IV study drug (ie, before the anticipated full course of study therapy required for effective treatment of febrile neutropenia) *for safety reasons* should have EOIV assessments conducted and undergo safety assessments at TOC and LFU.

Clinical Outcome Assessment: See Table 9.7.5.3–1

9.3.3.2 Premature Discontinuation from Inpatient IV Study Drug

Due To Insufficient Therapeutic Effect

Reasons: Possible reasons for discontinuation from study drug *due to insufficient therapeutic effect* include, but are not limited to:

Clinical worsening: A patient who shows signs of clinical worsening may be prematurely discontinued from ***inpatient*** IV study drug at any time. If the Investigator deems the benefit-to-risk ratio of ***inpatient*** IV study drug continuance acceptable, administration of at least 48 hours is encouraged before discontinuation.

Lack of clinical progress: For a patient who is stable, yet does not show signs of improvement, the Investigator is encouraged to continue ***inpatient*** IV study drug for at least 72 hours before such a patient is considered a clinical failure and is prematurely discontinued from IV study drug

Assessments and Procedures: A patient who is prematurely discontinued from ***inpatient*** IV study drug *due to insufficient therapeutic effect* should have EOIV assessments conducted and undergo safety assessments at TOC and LFU. If a patient is discontinued from ***inpatient*** IV study drug *due to insufficient therapeutic effect* and is switched to an alternative IV antibiotic, that therapy should be recorded.

Clinical Outcome Assessment: See Table 9.7.5.3–1.

9.3.3.3 Premature Discontinuation from Oral or IV Therapy

A patient who is prematurely discontinued from oral ***or IV*** therapy for any reason will not have protocol assessments conducted until TOC (ie, there is no scheduled visit between EOIV and TOC). At an unscheduled visit or at TOC, whichever occurs first, record the date of and reason for discontinuation. See Table 9.7.5.3–1 for clinical outcome definitions at TOC.

9.3.3.4 Withdrawal from Study

Reasons: Possible reasons for withdrawal from study depend on the timing of the withdrawal, and include, but are not limited to:

Before administration of first dose of study therapy:

Screen failure (failure to meet inclusion/exclusion criteria)

Withdrawal of consent

AE

Protocol violation

Lost to follow-up

Study terminated by Sponsor

Site terminated by Sponsor

Investigator determines that it is in the best interest of the patient to withdraw from the study protocol, due to reasons other than an AE

Other

During treatment period:

Withdrawal of consent

Lost to follow-up

Study terminated by Sponsor

Site terminated by Sponsor

Investigator determines that it is in the best interest of the patient to withdraw from the study protocol, due to reasons other than an AE

Other

During follow-up period (ie, no longer receiving study therapy):

Withdrawal of consent

Lost to follow-up

Study terminated by Sponsor

Site terminated by Sponsor

Investigator determines that it is in the best interest of the patient to withdraw from the study protocol, due to reasons other than an AE

Other

An AE should not be a reason for withdrawal from study after study drug has been administered. The patient may be discontinued from study drug due to an AE, in which case they should be encouraged to stay in the study for follow-up safety assessments.

Note: If death was due to an AE, then the AE is the reason for discontinuing study drug and death is the reason for withdrawal from study. If the death is due to lack of efficacy, then lack of efficacy is the reason for discontinuing study drug, and death is the reason for withdrawal from study.

Assessments and Procedures: Patients may withdraw from the study, or be withdrawn at the request of the Investigator or Sponsor. A patient who is withdrawn completely from the study during ***inpatient*** IV study drug ***or*** oral ***or I***V therapy should be encouraged to undergo, if possible, EOIV (if on ***inpatient*** IV study drug) or TOC (if on oral ***or IV*** therapy) assessments on the day of withdrawal. Patients withdrawn from the study need not undergo subsequent TOC efficacy assessments (if on ***inpatient*** IV study drug) or LFU (if on oral ***or IV*** therapy) assessments.

Clinical Outcome Assessment: A patient withdrawn from the study who is not assessed as a clinical failure should be assessed as indeterminate at all subsequent outcome evaluation time points (Table 9.7.5.3–1).

9.3.4 Patient Replacement Procedures

Randomized patients who are withdrawn will not be replaced.

9.4.1 TREATMENTS

Treatments Administered

9.4.1 Treatment Group

As shown in Table 9.4.1.3-1, patients randomized to the *Ceftolozane-Tazobactam* treatment group will receive:

IV Ceftolozane/tazobactam ***(minimum of 9 doses)***

Gram positive antimicrobial coverage (ie vancomycin, linezolid or daptomycin) is optional and can be given if clinically indicated at the discretion of the primary team or emergency center physician. Gram positive antimicrobial coverage can also be switched at any time during the study.
Daptomycin could be given if there is no evidence of pneumonia.

Patient may continue on the study drug up to 14 days if clinically indicated by the assessment of the treating physician

Patients may receive other additional therapy as discussed in Section 9.4.1.3. Patients may be eligible to switch to ***outpatient IV or*** oral therapy, as discussed in
Section 9.4.1.4.

9.4.1.3 Standard of Care Treatment Group

As shown Table 9.4.1.3–1, patients randomized to the SOC treatment group will receive:

One of the following IV therapies:

Cefepime (minimum of 9 doses)

Meropenem (minimum of 9 doses)

Piperacillin/tazobactam (minimum of 12 doses)

Doses given before signing informed consent will be counted if antibiotics remain the same (dose and frequency) after signing informed consent.

Gram positive coverage is optional as clinically indicated with IV vancomycin, daptomycin or linezolid (oral linezolid is allowed ***).*** Daptomycin could be given if there is no evidence of pneumonia.

Patients may receive other additional therapy as discussed in Section 9.4.1.3. Patients may be eligible to switch to ***outpatient IV or*** oral therapy, as discussed in
Section 9.4.1.4.

9.4.1.3 Other Additional Antibacterial Therapy

Patients in either treatment group may receive other additional therapy as needed (Table 9.4.1.3–1) at the discretion of the primary physician or Investigator, per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II; or Appendix III for patients with documented or suspected pneumonia), as follows:

Double Gram-negative coverage should be considered with complicated tissue-based infections, neutropenic enterocolitis, pneumonia, and perirectal infections; if indicated, add Tobramycin, Amikacin Ciprofloxacin, Minocycline, Tigecycline, Doxycycline, or Bactrim.
Table 9.4.1.3–1

Additional antibacterial therapy may be added at any time during the study for management of complications or if antibacterial resistance is suspected or proven

A Switch to a Once-Daily Gram- Negative IV Agent for The Purposes Of Outpatient Or Home IV Treatment Is Allowed After 72 Hours As Described In Table 9.4.1.3–1

Empirical Treatment Of C. Difficile With Oral Vancomycin Or Metronidazole (IV or oral) May Be Added at any time For Patients With Symptoms Of Abdominal Cramping And Diarrhea Until Diagnostic Results Are Available Or If C. Difficile Infection Is Strongly Suspected Clinically.

Table 9.4.1.3–1. Investigational Products

Investigational Product	***Dosage[a] and Route***	***Form and Strength***	***Supplier***
Treatment Group:			
Ceftolozane-Tazobactam	1.0 g CEF and 0 .5 g of Tazo IV over 1 hour q8h	***Investigational***	FRI
PLUS one of the following adjunctive Gram-positive therapies:			
Vancomycin[b]	15 mg/kg (rounded to nearest 250-mg dose) IV q12h (+/– 30 min)	***Commercial Supply as per FDA approved package insert***	MDA
Linezolid[b]	600 mg IV (or oral) q12h	***Commercial Supply as per FDA approved package insert***	MDA
Standard of Care (Comparator) Treatment Group:			
ONE of the following:			
Cefepime	2 g IV q8h	***Commercial Supply as per FDA approved package insert***	MDA
Meropenem	1 g IV q8h	***Commercial Supply as per FDA approved package insert***	MDA
Piperacillin/tazo bactam	4.5 g IV q6h	***Commercial Supply as per FDA approved package insert***	MDA
PLUS one of the following adjunctive Gram-positive therapies:			
Vancomycin[b]	15 mg/kg (rounded to nearest 250-mg dose) IV q12h	***Commercial Supply as per FDA approved package insert***	MDA
Linezolid[b]	600 mg IV (or oral) q12h	***Commercial Supply as per FDA approved package insert***	MDA
Optional for Either Treatment Group (IV Gram-Negative Therapy Switch After at Least 72 Hours of IV Gram-Negative antimicrobial coverage)			
Ceftriaxone	***2 g IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Ertapenem	***1 g IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Optional for Either Treatment Group (IV Gram-Positive Adjunctive Therapy Switch at any time for Patients With Suspected Line Infections and/or Bacteremia)			
Daptomycin[b]	***6-8 mg/kg IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***

Table 9.4.1.3–1. Investigational Products

Investigational Product	***Dosage[a] and Route***	***Form and Strength***	***Supplier***
Optional for Either Treatment Group (Adjunctive Double Gram-Negative Therapy):			
Tobramycin[c]	7 mg/kg IV q24h	***Commercial Supply as per FDA approved package insert***	MDA
Optional for Either Treatment Group (Adjunctive Double Gram-Negative Therapy):			
Amikacin[c]	***15 - 20 mg/kg IV q24h***	***Commercial Supply as per FDA approved package insert***	***MDA***
Ciprofloxacin[c]	400 mg IV q8h	***Commercial Supply as per FDA approved package insert***	MDA
Minocyclin	100mg q12h	***Commercial Supply as per FDA approved package insert***	MDA
Tigecycline	100 mg/day (day 1- day 2 on) 50 mg q12h	***Commercial Supply as per FDA approved package insert***	MDA
Doxycycline	100 mg q12h	***Commercial Supply as per FDA approved package insert***	MDA
Bactrim	5-20mg/kg/day	***Commercial Supply as per FDA approved package insert***	MDA

a Dosages shown for patients with normal renal/hepatic function. Appropriate dosage modifications for renal function will be made per Section 9.4.5.1-1

b Per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines (Appendix III).

c As needed for double Gram-negative coverage per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II).

Ceftolozane-Tazobactam; IV = intravenous; MDA = MD Anderson; q6h = every 6 hours; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours.

All antibiotic doses and infusion time will be administered according to standard doses and time of administration defaulted in EPIC system.

Subsequent antibiotic doses may be administered according to MDACC policy (Standard 28Medication Administration Time Policy (UTMDACC Institutional Policy # CLN1091) timed on the next whole hour. If unable to administer a dose at scheduled time, give the next dose ASAP (according to MDACC institutional policy # 1091, Standard medication administration Exception list attachment). Once the delay has been resolved, re-time future doses to coincide with the most recent administration time.

9.4.1.4 Optional Oral or IV Therapy Switch

9.4.1.4.1 Criteria for Switching to Oral or IV Therapy

A switch to oral *or IV* therapy may be allowed after at least 72 hours of IV gram negative antimicrobial coverage if all of the following criteria are met:

Oral therapy or IV therapy (for outpatient or home administration) is clinically indicated

Patient received at least 72 hours of IV gram negative antimicrobial coverage.

EOIV clinical signs and symptoms have been assessed

Patient has the ability to maintain oral intake

Patient is clinically stable

Patient is afebrile

Improvement in clinical signs and symptoms of infection from baseline

Patient has negative blood culture (taken within past 24 hours) (for patients with positive blood cultures at baseline)

For Patients Who Are Randomized To SOC, Doses Given Before Signing The Informed Consent Will Be Counted If Antibiotics Remain The Same (Dose And Frequency) After Signing The Informed Consent.

9.4.4.4.2 Oral and IV Switch Therapy Options

After completion of at least 72 hours of IV gram negative antimicrobial coverage, the patient may be switched to an appropriate combination of oral and/or IV therapy such as:

Linezolid (oral)

Ampicillin

Amoxicillin

Amoxicillin/clavulanate (oral)

Minocycline (oral)

Ciprofloxacin (oral)

Levofloxacin (oral)

Cefpodoxime (Oral)

Trimethoprim/sulfamethoxazole (oral)

Ceftriaxone (IV)

Ertapenem (IV)

Daptomycin (IV)

Vancomycin (IV)

The specific combination chosen is at the discretion of the Investigator *in accordance with local SOC* and should provide coverage for isolated pathogens and appropriate empirical therapy in the absence of microbiological data.
Consult the package inserts, labels, and local dosing guidelines regarding storage, administration, maximum doses, contraindications (eg, drug-drug interactions), warnings, precautions, and adverse drug reactions reported with the use of oral *or IV* therapies.

9.4.1.5 Duration of Treatment

The total duration of study therapy will be 5 to 14 days; a minimum of 3 days (ie, 72 hours) of IV gram negative antimicrobial coverage is required. After at least 3 days (ie, 72 hours [of IV gram negative antimicrobial coverage, the Investigator will assess if inpatient IV study drug should be continued or a switch to oral or IV therapy is warranted (Section 9.4.1.4). After at least 120 hours (ie, 5 days, typically on or after Study Day 5) of antibiotic therapy (IV plus oral), the Investigator will assess if inpatient IV study drug or oral or IV switch therapy should be continued or if all therapy should be discontinued.

Duration of therapy is at the discretion of the Investigator, considering clinical response, presence of clinically and /or microbiologically documented infections, and signs of bone marrow recovery.

An assessment of clinical outcome will be made at the end of all study therapy as defined in **Section 9.7.5.3.**

9.4.2 Identity of Investigational Products

Investigational product Ceftolozane-Tazobactam contains both Ceftolozane and Tazobactam, which will be administered together in a single infusion bag. A single vial filled with the sterile crystalline form of Ceftolozane (1 g) and the sterile crystalline form of Tazobactam (0.5 g) for IV administration. The crystalline powders are reconstituted using Sterile Water for Injection, resulting in a concentrate solution. An amount of this solution, corresponding to the dose to be administered, is withdrawn from the vial and transferred into an infusion bag containing 100 mL saline.

With the exception of ceftolozane/tazobactam all other study drugs (IV or oral) will be commercially labeled. All inpatient IV study drug and oral and IV therapies should be kept in a secure place under appropriate storage conditions, as specified on the drug labeling and package insert.

Upon completion of the study or termination of the site, all used and unused study drugs that were supplied by the sponsor will be destroyed according to the standard operating procedures of MD Anderson.

9.4.3 Method of Assigning Patients to Treatment Groups

After patient enrollment, randomization will be conducted by the clinical coordinator on an institutional Clinical Trial Conduct (CTC) website, developed by the Department of Biostatistics. At the end of the study, 50% patients will be divided equally at the end of the study between both arms. If the patient is started on one of the three agents, we will continue the same agent if he is assigned to SOC arm. The choice of the antibiotic will be kept at the discretion of the primary team. Patients in SOC arm will be analyzed as one treatment group in the intent to treat analysis and other analysis.

At the time of signing the ICF and consenting to participate in this study. The first patient to sign the ICF at the study center will be assigned the first accession number, and each subsequent patient will be assigned the next sequential number. This patient identification number will be used to

identify the patient at all phases of the study.

9.4.4 Selection of Dosages in the Study

The dosages of each investigational product are shown in Table 9.4.1.3–1 and, if applicable, in the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, in the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines
(Appendix III).

The dose of ceftolozane-tazobactam that was selected for this study was based on phase I pharmacokinetic and safety studies in healthy adults and the probability of target attainment (30%$T_{>MIC}$) against pathogens with an MIC of up to 8 µg/ml (≥90%). It is the FDA-approved dose for the treatment of cIAI and cUTI.

Clinical efficacy data from the Phase 3 cIAI and cUTI studies demonstrated that administered at a dose of 1.5 g (1 g Ceftolozane and 0.5 g of Tazobactam) IV q8h is effective for the treatment of cIAI and cUTI caused by common gram-negative pathogens and is a beneficial adjunct to the current armamentarium of parenteral antimicrobial therapy for serious and severe infections.

The dosages of the other investigational products are considered SOC and are used in current treatment of febrile neutropenic patients at MD Anderson, as shown in the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, in the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines (Appendix III).

9.4.5 Selection and Timing of Dose for Each Patient

Investigational products will be administered per Table 9.4.1.3–1 and, if applicable, per the MD Anderson Neutropenic Fever Inpatient Adult Treatment Guidelines (Appendix II) or, for patients with documented or suspected pneumonia, in the MD Anderson Pneumonia in Adult Patients with Cancer Treatment Guidelines (Appendix III).

9.4.5.1 Dose Adjustments for Ceftolozane/Tazobactam

In the case of renal impairment, at any time, the dose of ceftolozane/tazobactam (including the initial dose) may be adjusted by the pharmacist or designee per the dosage regimen in Table 9.4.5.1–1. At any time, the dose of ceftolozane/tazobactam may be readjusted to the appropriate dosage when renal function improves. If a patient's estimated CrCl (as calculated using the Cockcroft-Gault formula [Section 9.5.3.1]) decreases to ≤ 30 mL/min during the treatment period, the Study Physician should be contacted immediately to discuss if continuation of study drug therapy is appropriate and to discuss additional dose adjustments for CrCl ≤ 30 mL/min.

Table 9.4.5.1–1. Dosage Adjustments for Renal Impairment

Recommended dosages of Ceftolozane- Tazobactam by renal function

Estimated CL Cr (ml/min)	**Dose**

>50	1.5 g IV every 8 hours
30-50	750 mg IV every 8 hours
15-29	375 mg IV every 8 hours
ESRD on HD	750 mg IV loading dose, followed by 150 mg every 8 hours: administer at earliest time possible after completion of dialysis

9.4.5.2 Dose Adjustments - Other Investigational Products

For all other investigational products, appropriate dosage modifications for renal function will be made per the respective package insert or institutional guidelines.

9.4.6 Blinding

This study will be conducted as an open-label investigation; no blinding of assigned treatment will occur.

9.4.7 Unblinding

Not applicable.

9.4.8 Prior and Concomitant Therapy

All prior (taken or received within 30 days before the first dose of IV study drug) and concomitant (taken during the study) medications, including but not limited to, antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the-counter medications (eg, vitamins, herbal medications), and parenteral nutrition, will be documented on the appropriate screens of the eCRF (concomitant meds will be captured in subjects medical record in Epic).

Concomitant use of the following is not permitted: 1) potentially effective systemic antibacterial therapy; 2) any drug known to exhibit a contraindicated drug-drug interaction with any of the study therapies or a labeled contraindication to use of any study therapies.

All other concomitant medications and nutrients necessary for the health and well-being of the patient are permitted.

9.4.9 Monitoring Treatment Compliance

Treatment compliance will be closely monitored by recording the date, time, and whether or not each dose of ***inpatient*** IV study drug ***or IV switch therapy*** was infused and, if applicable, whether or not each intended dose of oral ***switch*** therapy was taken.

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Primary and Secondary Efficacy Assessments

Primary Efficacy Assessment

The ***Investigator's*** assessment of clinical response will be used to determine the primary efficacy assessment. The Investigator should consider the entirety of the patient's clinical course and current status, including an evaluation of infection signs and symptoms (eg, fever, neutropenia), radiological findings (if applicable), and physical examination in order to classify the patient's clinical response at EOIV according to the definitions listed in Table 9.7.5.3–1. The investigator could rely on physical exam performed by a professionally trained physician or health professional licensed to perform physical examinations.

Secondary Efficacy Assessments

Clinical Assessments
The ***Investigator's*** assessment of clinical response at EOIV***,*** TOC***, and LFU*** will be used to determine the secondary clinical efficacy endpoints according to the definitions listed in Table 9.7.5.3–1.

Microbiological Assessments
A patient's microbiological response at EOIV***,*** TOC***, and LFU*** will be determined programmatically based on individual outcomes for each baseline pathogen according to the definitions listed in Table 9.7.5.4–1.

9.5.1.2 Microbiological Assessments

Blood Samples for Culture

Blood samples for culture will be obtained at the following time points, preferably before the next scheduled dose of study antibiotics is administered:

Baseline

Study Days 1 to ≤ 14: every other day until temperature is ≤ 101°F (38.3°C) and blood cultures are negative

EOIV: if baseline cultures were positive (to determine microbiological response)

TOC and LFU: as clinically indicated per the discretion of the Investigator (eg, if clinical worsening and/or persistence of fever ***or other signs or symptoms consistent with clinical failure***)

Blood cultures should be repeated upon knowledge of a positive result from any visit until sterilization is confirmed.

When blood cultures are required, 2 sets of blood samples should be obtained from an existing central venous catheter, if present, and from a peripheral vein site. If no central venous catheter is present, collect 2 blood cultures from separate venipuncture sites.

Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility to all drugs used.

Microbiological samples will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

Other Samples for Culture

Culture specimens from other sites of suspected infection should be obtained as clinically indicated.

Culture, organism identification, and susceptibility testing will be conducted at the local laboratory. All pathogens will be tested for susceptibility to all drugs used.

Microbiological samples will be collected, processed, and stored in accordance with local procedures (refer to Microbiology Manual).

9.5.1.3 Clinical Outcome of The Infection

Per the Schedule of Assessments and Procedures (Table 2–1), the Investigator or sub-investigator is to assess the Clinical Outcome at EOIV, TOC and LFU.

9.5.2 Safety Assessments

Throughout the clinical trial, each patient will be observed for adverse reactions. All patients will be monitored for the development of study-related adverse events through the entire study period including the thirty (30) days following the last dose of study drug. Any serious, unexpected adverse event(s) will be reported to the sponsor and IRB per policy, and reported to the FDA accordingly. Patients who have received at least one dose of the study drug will be included in the safety analysis. Patients who withdraw consent prior to receiving any dose of study drug, will not be included in the analysis and will be replaced by an evaluable patient. Evaluation done by the primary team and the attending physician following the patient are acceptable.

9.5.2.1 Adverse Events

Recording of Adverse Events.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse event for this protocol will be documented into the medical record and entered into RedCap according to the Recommended Adverse Event Guidelines for Phase II Protocols (please refer to chart on page 37). The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Version 4.03 of the Common Toxicity Criteria for adverse events will be used to assess AEs and SAE (please refer to **Section 9.5.2.1**)

Study subjects should be instructed to report all adverse events to the Investigator. In addition, the Investigator should

seek to elicit any clinical or objective reactions by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded on the case report form. All clearly related signs, symptoms and abnormal diagnostic procedures should be grouped together and recorded as a single diagnosis. The component parts of the diagnosis may be listed for verification. For each adverse, the Investigator is to assess the severity of the reaction, and to determine the relationship to study drug. In addition, the duration will be noted, and whether intermittent or continuous **also** documentation of the outcomes and what was done with study drug is needed.

Please note medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

Any worsening of the infection under study because of lack of therapeutic effect of any study drug is captured as an efficacy analysis variable and is not to be considered an AE, unless the event is an SAE resulting in death (Section 9.5.2.3).

Pregnancies should not be automatically assessed as AEs.

The Investigator is responsible for completing an efficacy/safety summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 10 evaluable patients per arm, complete in-patient intravenous therapy, and every 10 evaluable patients per arm, thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

9.5.2.2 Causality Assessment

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. Assessments done by the primary team following the patient are acceptable.

Is there a reasonable possibility the investigational product caused the event?

Yes: There Is Evidence To Suggest A Causal Relationship Between The Investigational Product And The Ae; Ie:

- There is a reasonable temporal relationship between the investigational product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There Is No Evidence To Suggest A Causal Relationship Between The Investigational Product And The Ae, Ie:

- There is no reasonable temporal relationship between the investigational product and the event, or
- The patient did not take the investigational product, or

- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or

- The event is commonly occurring in the (study) population independent of investigational product exposure

9.5.2.3 Serious Adverse Events (SAE) Reporting

9.5.2.3. Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution

of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

Any worsening of the infection under study because of lack of therapeutic effect of any study drug is captured as an efficacy analysis variable and is not to be considered an SAE, unless the event results in death.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

9.5.2.5 Clinical Laboratory Determinations

Blood sample and urine culture/urine analysis (when clinically needed) will be collected according to the Schedule of Assessments and Procedures (Table 2-1).

Women of childbearing potential (including those who are fewer than 2 years postmenopausal) will be required to have a serum or urine pregnancy test at baseline (within 72 hours). The test must be

negative before randomization. If the serum test results cannot be obtained before randomization, a urine pregnancy test may be used for enrollment.

The following clinical laboratory levels will be measured (those marked with an asterisk [*] are required for eligibility):

Hematology: Basophils (absolute count and %), eosinophils (absolute count and %), erythrocyte count, hematocrit, hemoglobin, leukocytes (absolute count and differential), lymphocytes (absolute count and %), monocytes (absolute count and %), neutrophils (absolute count* and %), immature neutrophils (bands; %), platelet count, red blood cell indices (mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration)

Chemistry: Albumin, ALT*, bilirubin (total), blood urea nitrogen, calcium, creatinine*, electrolytes (ie, bicarbonate, chloride, potassium, sodium), glucose

Urinalysis if clinically indicated: Appearance (color, clarity), bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen, and urine microscopy (ie, red blood cells, white blood cells, casts, crystals, bacteria, yeast cells, parasites)

Other: pregnancy test*
The MD Anderson local laboratory will be used to evaluate all urine and blood samples. Results from unscheduled laboratory tests will not be collected, unless associated with an SAE or AE leading to discontinuation of IV study drug. EXCEPTION: At the discretion of the Investigator, unscheduled ANC values will be recorded as clinically indicated while on oral ***or IV Switch therapy*** (ie, between EOIV and TOC).

Any abnormal laboratory test possibly attributable to ***inpatient*** IV study ***drug*** will be repeated at appropriate intervals until stabilization.

9.5.2.6 Vital Signs, Body Weight, and Height

Vital signs will be recorded at every visit; the parameters are:

Blood pressure: systolic and diastolic

Pulse rate

Respiratory rate

Oxygen saturation: patients with respiratory signs or symptoms

Temperature: record highest daily temperature

Body weight and height will be measured at baseline. If height or weight is not obtainable (eg, patient is immobilized), the last known or stated height and weight may be used.

9.5.2.7 Chest Radiography

A chest x-ray (CXR) (posteroanterior and lateral) or chest computed tomography (CT) scan will be obtained at baseline for patients with respiratory signs or symptoms. If the patient's condition does not allow for a standard posteroanterior and lateral examination, a portable anteroposterior CXR is

acceptable. Chest radiography will be obtained postbaseline, ie, at EOIV, TOC, or LFU if clinically indicated.

9.5.2.8 Physical Examination

A complete physical examination will be conducted by a professionally trained physician or health professional licensed to perform physical examinations.

9.5.3 Schedule of Assessments

The schedule of study assessments and procedures is tabulated by visit in Table 2–1. The descriptions of the procedures to be performed at each visit are provided below.

9.5.3.1 Baseline

Baseline procedures must be completed within 24 hours before the start of the first dose of ***inpatient*** IV study drug. Any protocol-required eligibility laboratory evaluations already done as part of the patient's regular medical care within 24 hours before the start of the ***inpatient*** IV study drug infusion on Study Day 1 do not have to be repeated to determine patient eligibility.

At baseline, informed consent will be obtained, a review of inclusion/exclusion criteria will be conducted to determine the patient's eligibility for enrollment, and study procedures will be reviewed with the patient and/or caregiver, and the legally authorized representative (if different from the caregiver). After signing the ICF, the patient will be assigned a unique PID number (or accession number) (see Section 9.4.3). If, after review of the inclusion/exclusion criteria, it is determined that the patient is eligible to enter the study, the patient will be randomized according to the randomization procedures in Section 9.4.3.

At baseline, the following procedures will be performed:

Obtain written informed consent per Section 5.3

Verify that inclusion criteria are met and none of the exclusion criterion apply

Obtain medical and surgical history including all active conditions and all conditions diagnosed within the previous 3 months

Obtain height and weight (if height or weight is not obtainable [eg, patient is immobilized], use the last known or stated height and weight)

Perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms (per Section 9.5.2.11)

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record prior medications, including antimicrobials (ie, antibacterials, antivirals, antifungals, antiparasitics), over-the-counter medications (eg, vitamins, herbal medications), and parenteral nutrition taken or received within 30 days of first dose of ***inpatient*** IV study drug.

Evaluate and record infection signs and symptoms per Section 9.5.1.3

Laboratory assessments:
Collect blood and urine samples for clinical laboratory determinations per Section 9.5.2.5.

Record ANC

Collect blood sample for pregnancy test (females of childbearing potential only, including those who are fewer than 2 years postmenopausal); ensure test is negative before randomization. If the serum test results cannot be obtained before randomization within 72 hours, a urine pregnancy test may be used for enrollment

Estimate CrCl using the following Cockcroft-Gault formula (use actual body weight and conventional units; if weight is not obtainable [eg, patient is immobilized], use the last known or stated weight):

Males: CrCl= (140 – age in years) X weight in kg / 72 X serum creatinine (mg/dL)

Female: CrCl= 0.85 X (140-age in years) X weight in kg / 72 X serum creatinine (mg/dL)

Microbiological assessments:

Collect blood sample for culture per Section 9.5.1.2 (See pages 33-34).

If clinically indicated, collect other samples for culture per Section 9.5.1.2

Randomize patient after verifying that the patient meets all study inclusion criteria and no exclusion criteria

9.5.3.2 Study Days 1 To ≤ 14

Study Day 1 is the calendar day that ***inpatient*** IV study drug is first administered. Baseline and Study day 1 assessment could be combined if they occur on the same calendar day.

On Study Days 1 to ≤ 14, administer study therapy to all patients and conduct the following assessments and procedures daily *while the patient is hospitalized and receiving IV study drug*, unless otherwise specified:

Perform complete physical examination twice a week after first dose of inpatient IV study drug, at least every 3 days, ***whereby the week begins on the day of enrollment. The physical examination will be conducted by a professionally trained physician or health professional licensed to perform physical examinations. Patients may have unscheduled visit sooner than the scheduled date if deemed necessary by the investigator.***

Record vital signs (blood pressure and pulse rate a, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and record infection signs and symptoms per Section 9.5.1.3

Laboratory assessments:

Collect blood and urine samples for clinical laboratory determinations (Section 9.5.2.5) if clinically indicated

On Study Day 7 +/- 24 hours, if still on IV study drug, collect blood and urine samples for clinical laboratory determinations (Section 9.5.2.5).

Record ANC a minimum of 3 times per week while on study therapy (IV or oral)

Record estimated CrCl ***every 3 days after first dose of inpatient IV study drug beginning on Study Day 1***

Microbiological assessments:

Obtain blood samples (per Section 9.5.1.2) for culture every other day until temperature is ≤ 101°F (38.3°C) and cultures are negative

If clinically indicated, collect other samples for culture per Section 9.5.1.2.

Administer study therapies per Section 9.4.1 and Table 9.4.1.3–1

9.5.3.3 End of Inpatient Intravenous Therapy

Conduct EOIV assessments within 72 hours after administration of the last dose of ***inpatient*** IV study drug.

Administer the last dose of ***inpatient*** IV study drug, and conduct the following assessments and procedures in all patients, unless otherwise specified:

If clinically indicated, perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and record infection signs and symptoms per Section 9.5.1.3

Assess clinical outcome per Section 9.7.5.3

Laboratory assessments:

Collect blood and urine samples for clinical laboratory determinations
(Section 9.5.2.5) if laboratory tests for EOIV is performd ≥ 24 hours prior to EOIV (if applicable)

Record ANC

If clinically indicated, record estimated CrCl

For patients on oral ***or IV*** therapy: At the discretion of the Investigator, record ANC as clinically indicated (ie, during an unscheduled visit between EOIV and TOC)

Microbiological assessments:

If baseline blood cultures were positive, repeat blood cultures (per Section 9.5.1.2)

If clinically indicated, collect other samples for culture (per Section 9.5.1.2)

9.5.3.4 Test-Of-Cure (Toc)

Conduct TOC assessments in person at any time between Study Days 21 and 28 (ie, 21 to 28 days after the start of ***inpatient*** IV study drug).

For patients who were switched to oral ***or IV*** therapy: Assess if oral ***or IV*** therapy was completed and if not, record date of and reason for discontinuation

If clinically indicated, perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate and record infection signs and symptoms per Section 9.5.1.3

Assess clinical outcome per Section 9.7.5.3

Laboratory assessments:

Record ANC

Microbiological assessments:

If clinically indicated, collect blood sample for culture (per Section 9.5.1.2)

If clinically indicated, collect other samples for culture (per Section 9.5.1.2)

9.5.3.5 Late Follow-Up

Conduct LFU assessments any time between Study Days 35 and 42 (ie, 35 to 42 days after the start of ***inpatient*** IV study drug). The LFU may be conducted by telephone for any patient who has not experienced clinical ***failure since TOC***, did not have ongoing study drug related AEs or SAEs at TOC, or did not develop study drug related AEs or SAEs since TOC. If symptoms ***consistent with clinical failure*** or new study drug related AEs or SAEs are noted, or at the discretion of the Investigator, the patient should be immediately scheduled for an in-person visit. Also, telephone visit is acceptable for patients who cannot present for a clinic visit.

If LFU is conducted by telephone:

Record new concomitant medications

Review and record AEs and SAEs

Record Infection Symptoms, Including Recurring Or Worsening Symptoms Indicative Of Clinical Failure

Note: If symptoms consistent with clinical failure or new AEs or SAEs are noted during the telephone interview, or at the discretion of the investigator, the subject should be immediately scheduled for an in-person visit

Assess clinical outcome per Section 9.7.5.3

If LFU is conducted in person:

If clinically indicated, perform CXR (eg, portable anteroposterior film) or chest CT for patients with respiratory signs or symptoms

Perform complete physical examination

Record vital signs (blood pressure and pulse rate, respiratory rate, oxygen saturation [if applicable], highest daily temperature)

Record new concomitant medications

Review and record AEs and SAEs

Evaluate And Record Infection Signs And Symptoms Per Section 9.5.1.3

Assess clinical outcome per Section 9.7.5.3

Microbiological assessment: ***In patients experiencing clinical failure after TOC or if*** clinically indicated, collect samples for culture per Section 9.5.1.2.2

Any clinical findings obtained during the final examination or at premature discontinuation for any reason, including clinically significant laboratory abnormalities, will be followed until the condition returns to prestudy status, has resolved or stabilized, or can be explained as being unrelated to the investigational product. A follow-up visit, if one should be necessary, will take place within 30 days of investigational product termination.

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Recording, Documentation and Monitoring

The Investigator and the study site staff will be responsible for data entry of patient data into REDCap. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

9.6.2 Data Recording And Documentation

Data collection will involve the use of REDCap to which only authorized personnel will have access. Patient's data are to be entered into the system by the Investigator or designee using their assigned user account. After data entry into the system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol.

After all data have been reviewed and all issues have been resolved, the database will be locked.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents, etc) will be retained at the site, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for., its authorized representatives, and the FDA or other health authorities.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

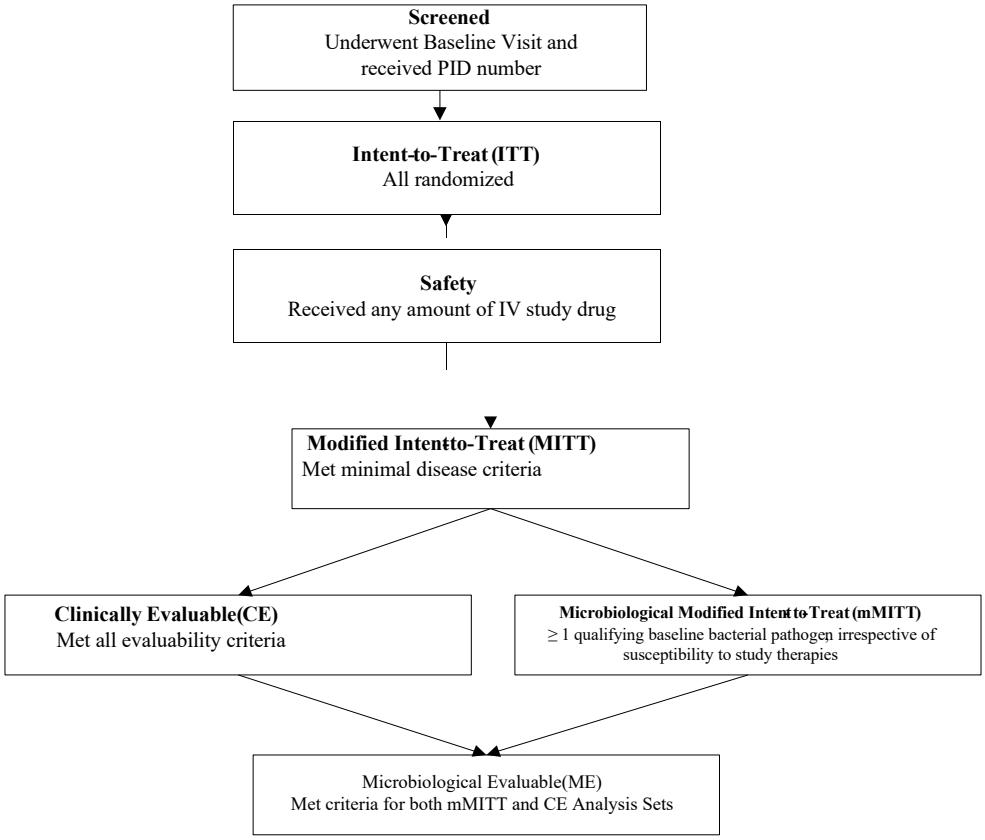
Descriptive statistics (number, mean, SD, median, minimum, and maximum) will be provided for continuous variables, and frequency distributions (counts and percentages) will be shown for categorical variables. All summaries will be presented by treatment group. Summaries will be provided for all randomized patients that received any amount of ***inpatient*** IV study drug (MITT Analysis Set) and for the subgroup of patients with a pathogen identified (mMITT Analysis Set). Listings of individual patients' data will also be produced.

A comprehensive statistical analysis plan will be prepared and finalized before database lock and analysis of the data.

9.7.1 Analysis Sets

Analysis sets are described below and displayed in Figure 9.7.1–1.

Figure 9.7.1–1. Analysis Sets for Study



9.7.1.1 Screened Analysis Set

The Screened Analysis Set will consist of all patients who undergo the Baseline Visit and receive a PID number.

9.7.1.2 Intent-To-Treat Analysis Set

The Intent-to-Treat Analysis Set will consist of all patients in the Screened Analysis Set who are randomized to a treatment group in the study.

9.7.1.3 Safety Analysis Set

The Safety Analysis Set will be a subset of the ITT Analysis Set and will include all randomized patients who receive any amount of ***inpatient*** IV study drug. Patients will be analyzed according to the treatment actually received.

9.7.1.4 Modified Intent-To-Treat Analysis Set

The MITT Analysis Set will be a subset of the ITT Analysis Set and will include all randomized patients who received any amount of ***inpatient*** IV study drug and meet minimal disease criteria (Inclusion Criterion 3). Patients will be analyzed according to randomized treatment group, regardless of treatment received.

9.7.1.5 Microbiological Modified Intent-To-Treat Analysis Set

The mMITT Analysis Set will be a subset of the MITT Analysis Set and will include those patients for whom at least 1 qualifying bacterial pathogen was isolated from an appropriate microbiological specimen at baseline, irrespective of susceptibility to study therapies.

9.7.1.6 Clinically Evaluable Analysis Set

The CE Analysis Set will be a subset of the ***MITT*** Analysis Set and will include patients who meet the following specific conditions for evaluability:

Received at least 80% of the intended doses of ***inpatient*** IV study drug

Received at least 48 hours of ***inpatient*** IV study drug to be considered an evaluable clinical failure, unless deemed a clinical failure based on a treatment-limiting AE

> Received at least 72 hours of IV gram negative antimicrobial coverage to be considered an evaluable clinical cure

Did not receive any amount of ***inpatient*** IV study drug from the treatment arm to which the patient was not randomly assigned

Had clinical outcome assessment at TOC (other than indeterminate) or was assessed as a clinical failure at EOIV (or at any time up to TOC)

Did not receive > 24 hours of any potentially effective, systemic antibacterial therapy within 72 hours before randomization for treatment of suspected infection. Any amount of prophylactic (in the absence of an infection) antimicrobial (eg, antibacterial, antifungal, antiviral) therapy administered prior to starting study therapy is allowed.

9.7.1.7 Microbiologically Evaluable Analysis Set

The ME Analysis Set will include patients who meet the criteria for both the CE and mMITT analysis sets.

9.7.2 Patient Disposition

Patient disposition (enrollment, discontinuations from ***inpatient*** IV study drug, oral ***or IV*** therapy, and the study) by treatment group will be provided based on the ITT Analysis Set. The number of patients with a TOC and/or LFU visit will be summarized. Reasons for exclusion from study analysis sets will be summarized for the ITT Analysis Set.

The number of patients in the Safety and ITT analysis sets will be summarized by treatment group.

Screen failures (ie, patients screened but not randomized) and the associated reasons for failure will be tabulated overall.

The number and percentage of patients who complete the treatment period and of patients who prematurely discontinue during the same period will be presented for each treatment group and pooled across treatment groups for the ITT Analysis Set. The reasons for premature discontinuation from the treatment period as recorded on the termination pages of the eCRF will be summarized (number and percentage) by treatment group for all randomized patients.

9.7.3 Demographics And Other Baseline Characteristics

Demographics (eg, age, race, gender, body mass index), medical and surgical history, description of the infection, markers of disease severity and co-morbidities (eg, presence of bacteremia, renal impairment), type of malignancy, baseline assessment of the clinical signs and symptoms, and microbiological assessment of the primary infection site will be summarized by treatment group in the MITT Analysis Set.

Prior medication is defined as any medication taken before the date of the first dose of investigational product. Concomitant medication is defined as any medication started on or after the date of the first dose of investigational product. Any prior medications stopped more than 3 days before the date of the first dose of investigational product and any concomitant medications started after the date of the last dose of investigational product will not be presented in the summary tables, but will be included in the patient data listings. Medications that are ongoing at the time of first dose of ***inpatient*** IV study drug will be counted both as prior and concomitant.

Both prior and concomitant medication use will be summarized by the number and proportion of patients in each treatment group receiving each medication within each therapeutic class for the Safety Analysis Set. Multiple administrations of the same medication to a patient will be counted only once for the given patient.
Medication-related summaries will be presented separately by “systemic antimicrobial medications” and “other medications not in this class” subgroups.

9.7.4 Extent of Exposure and Treatment Compliance

9.7.4.1 Extent of Exposure

Exposure to ***inpatient*** IV study drug***,*** oral ***and IV switch*** therapy will be summarized by treatment

group for the Safety Analysis Set. Calendar days of exposure of ***inpatient*** IV only, oral ***or IV switch*** only, and overall (***inpatient*** IV plus oral ***or IV switch***) will be calculated as the number of calendar days on ***inpatient*** IV study drug/oral ***or IV switch*** therapy (***ie the difference between*** the last dose of specified ***inpatient*** IV study drug/oral ***or IV switch*** therapy ***and*** the first dose of specified ***inpatient*** IV study drug/oral ***or IV switch*** therapy ***date and time converted to days*** + 1 day). For each type of exposure both descriptive statistics (number of patients, mean, SD, median, minimum, and maximum) and a frequency tabulation of days of specified study drug treatment by classes < 3 days, 3-5 days, 6-8 days, 9-***14*** days, and > ***14*** days and oral therapy by classes < 3, 3, 4, 5 and > 5 days will be presented.

The number and percentage of patients who switch to oral ***or IV*** therapy will be presented. Among this subset of patients, the number and percentage of patients receiving each specific protocol-approved oral ***or IV*** therapy will be summarized. Descriptive statistics will be provided for either the study day of switch to oral or ***IV*** therapy, as well
as calendar days of oral ***or IV*** therapy (calculated as the date of last dose of the oral ***or IV*** Therapy – date of the first dose of the oral ***or IV*** therapy + 1 day).

9.7.4.2 Measurement Of Treatment Compliance

Each patient's compliance with study therapy (***inpatient*** IV or oral ***or IV switch***) will be calculated based on the number of doses of study drug the patient would have been expected to receive based on the number of treatment days, the specific dosing regimen indicated for the given treatment, and the start and stop date and times of the first and last dose of each specific study therapy. Treatment compliance is defined as the number of doses actually received divided by the number of doses expected (× 100) over the time period of first dosing date and time to last dosing date and time.

Three types of study therapy compliance will be calculated: IV study therapy compliance, all study therapies (both IV and oral) compliance, and, in the subgroup of patients who switch to oral ***or IV*** therapy, oral ***or IV*** therapy compliance. For each compliance measure, descriptive statistics (number of patients, mean, SD, minimum, median, and maximum value) and the number and percentage of patients whose compliance is < 80% versus ≥ 80% will be presented by treatment group for the Safety and MITT analysis sets.

9.7.5 Efficacy Analyses

Efficacy analyses will be based on the MITT and mMITT analysis sets. Baseline for efficacy is defined as the last measurement collected just before the first dose of inpatient IV study drug. The primary objective of the study is show that efficacy of Ceftolozane-Tazobactam plus vancomycin, daptomycin or linezolid is non-inferior to standard of care (SOC) plus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to favorable clinical response. Non-inferiority test will be performed with the margin of 10%, that is, if the favorable clinical response of Ceftolozane-Tazobactam is not 10% worse than the SOC, it is deemed non-inferior to the SOC. The one-sided chi-square test will be used for this non-inferiority test at the significance level of 0.05.

For each efficacy parameter listed below, the 2-sided 95% confidence intervals for the percentage of patients with favorable response will be obtained using the Clopper-Pearson method for each treatment group (Clopper and Pearson, 1934).

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the proportion of patients in the MITT Analysis Set with favorable clinical response at EOIV ***in accordance with Section 9.7.5.3***

9.7.5.2 Secondary Efficacy Parameters

The proportion of patients in the mMITT and CE analysis sets with favorable clinical response at EOIV

The proportion of patients in the MITT Analysis Set with favorable clinical response at TOC ***and LFU***

The proportion of patients in the mMITT and CE analysis sets with favorable clinical response by baseline Gram-negative pathogen at EOIV***,*** TOC***, and LFU***

The proportion of patients in the mMITT and ME analysis sets with a favorable microbiological response by baseline Gram-negative pathogen at EOIV***,*** TOC***, and LFU***. A favorable microbiological response is defined as eradication or presumed eradication of the infecting pathogen among patients with microbiologically document infections

The proportion of patients in the MITT and mMITT analysis sets with infection-related mortality at TOC ***and LFU***

The proportion of patients in the MITT and mMITT analysis sets with 30-day all-cause mortality

9.7.5.3 Clinical Outcome Definitions

The definitions of Investigator-determined clinical outcome, by time point, are shown in Table 9.7.5.3–1.

Table 9.7.5.3–1. Clinical Outcome Definitions

Applicable Time Point	***Outcome***	***Definition***
EOIV	Favorable clinical response	Resolution of all acute signs and symptoms of the primary infection or improvement to such an extent that no ***additional*** antibacterial therapy is required (***ie,*** except for protocol-allowed adjunctive therapies and/or oral ***or IV*** switch) ***and such that no more than 14 days of total antibacterial therapy is required***
TOC[a]	Clinical cure[b]	***Sustained resolution*** of all acute signs and symptoms of the primary infection or ***continued*** improvement to such an extent that no further IV antibacterial therapy is required for the original episode. ***Another episode of neutropenic fever during the follow-up period will not be considered as a failure unless the patient present for a relapse of the same documented infection that was present at baseline.***
LFU[a]	***Clinical cure[b]***	***Sustained resolution of all acute signs and symptoms (or of symptoms only if LFU visit is conducted by telephone) of the primary infection or continued improvement to such an extent that no further IV antibacterial therapy is required. Another episode of neutropenic fever during the follow-up period will not be considered as a failure unless the patient present for a relapse of the same documented infection that was present at baseline.***
EOIV[a] TOC[a] ***LFU[a]***	Clinical failure	Patients who meet **any** of the following: • Has persistent fever (ie, a single oral temperature measurement of≥> 38.3°C [101°F] or a temperature of ≥ 38.0°C [100.4°F] sustained over a 1-hour period) 96 hours after the initiation of study drug. (NOTE: if the febrile neutropenia is documented to be caused by an invasive fungal or viral infection at any time during the study, the patient should be considered to have an indeterminate outcome for all clinical outcome assessments) • Has documented breakthrough gram negative bacteremia (ie, recurrence of bacteremia that resolved or occurrence while on study drug of new bacteremia with gram negative pathogen not present at baseline) • Has a documented gram negative pathogen that is resistant to any study therapy received and requires alternative nonstudy antimicrobial therapy • Discontinuation of study therapy(ies) due to insufficient therapeutic effect including persistence, incomplete clinical resolution, or worsening in signs and symptoms of primary documented infection with gram negative organism that requires alternative nonstudy antimicrobial therapy (Investigator is encouraged to continue study therapy[ies] for at least 72 hours before such a patient is considered a clinical failure and is prematurely discontinued from study therapy[ies].) • Developed shock, acute respiratory distress syndrome, disseminated intravascular coagulation, or multiorgan failure related to the primary infection • Discontinuation of study drug therapy(ies) due to an AE and requirement for alternative nonstudy antimicrobial therapy for the primary infection

Table 9.7.5.3–1. Clinical Outcome Definitions

Applicable Time Point	***Outcome***	***Definition***
		• Died as a result of the primary infection • ***Patients who require more than 1 switch in therapy after discontinuing their original randomized IV treatment will be assessed as a clinical failure at TOC and LFU***
EOIV[a] TOC[a] ***LFU[a]***	Indeterminate	• Patients who developed a documented invasive fungal infection or a documented viral infection at any time during the study (Note: the documented fungal or viral infection must be the cause of the study qualifying episode of febrile neutropenia) • Patient has an infection with documented gram positive organisms • Study data are not available for evaluation of efficacy for **any** reason, including: o Death in which febrile neutropenia is clearly noncontributory o Lost to follow-up o Extenuating circumstances precluding classification as a clinical cure or clinical failure • Subjects withdrawn from the study not assessed as a clinical failure should be assessed as indeterminate at all subsequent outcome evaluation time points as noted in Section 9.3.3.3

a A clinical failure at EOIV will be carried forward to TOC. ***A clinical failure at TOC will be carried forward to LFU.*** TOC evaluations include events between EOIV and TOC ***(including events through the end of oral or IV switch therapy, if applicable). LFU evaluations include events between TOC and LFU.*** No scheduled assessment is performed at end of oral ***or IV switch*** therapy**.**

b Favorable outcome at TOC ***or LFU***.

AE = adverse event; EOIV = End of ***Inpatient*** Intravenous Therapy; ***LFU = Late Follow-up;*** TOC = Test-of-Cure.

9.7.5.4 Microbiological Response Definitions

The timing and definitions of per-pathogen microbiological response are shown in Table 9.7.5.4–1. Per-patient microbiological response will be determined programmatically based on individual outcomes for each baseline pathogen. For a patient to have a favorable microbiological response, the outcome for each baseline pathogen must be favorable (eradicated or presumed eradicated). If the outcome for any pathogen is unfavorable (persistence or presumed persistence), the patient will be considered to have an unfavorable microbiological response.

Table 9.7.5.4–1. Microbiological Response Definitions

Applicable Time Point	***Microbiological Response***	***Definition***
EOIV TOC ***LFU***	Eradication[a]	Source specimen demonstrates absence of the original baseline pathogen
EOIV TOC ***LFU***	Presumed eradication[a]	Source specimen was not available to culture and the patient was assessed as a clinical cure
EOIV TOC ***LFU***	Persistence	Source specimen demonstrates continued presence of the original baseline pathogen
EOIV TOC ***LFU***	Presumed persistence	Source specimen was not available to culture and the patient was assessed as a clinical failure
EOIV TOC ***LFU***	Indeterminate	Source specimen was not available to culture and the patient's clinical response was assessed as indeterminate

a Favorable outcome.

EOIV = End of ***Inpatient*** Intravenous Therapy; ***LFU = Late Follow-up;*** TOC = Test-of-Cure.

9.7.5.5 Emergent Infections

Organisms or pathogens first appearing after baseline (emergent infections) are defined in Table 9.7.5.5–1 ***and will be summarized separately***.

Table 9.7.5.5–1. Emergent Infections

Infection Category	***Definition***
Colonization	Isolation of a new organism(s) different than any isolated at baseline from the site of infection in a patient who is assessed as a clinical cure
Superinfection	Isolation of a new pathogen(s) different than any isolated at baseline from the site of infection during treatment with study drug therapy, which is associated with emergence or worsening of signs and symptoms of infection
New infection	Isolation of a new pathogen(s) different than any isolated at baseline from the site of infection after completion of all study drug therapy, which is associated with emergence or worsening of signs and symptoms of infection

9.7.6 Safety Analyses

Incidences of TEAEs, SAEs, deaths, and discontinuations due to AEs in the Safety Analysis Set

Changes in clinical laboratory parameters and vital sign parameters in the Safety Analysis Set at each study visit that assessments are performed

Safety summaries will be presented using the Safety Analysis Set, according to the treatment actually received. For each safety parameter, the last assessment made before the first dose of ***inpatient*** IV study drug will be used as the baseline for all analyses.

The incidence of TEAEs, SAEs, deaths, and discontinuations due to AEs will be summarized by treatment group, system organ class and preferred term according to the *Medical Dictionary for Regulatory Activities*, relationship to study therapy, and severity.

Descriptive statistics of observed results and the change from baseline will be presented for clinical laboratory results and vital signs. The incidence of potentially clinically significant (PCS) laboratory results will be summarized. A list of all TEAEs/SAEs that resulted in deaths will also be generated.

9.7.6.1 Adverse Events

An AE (classified by preferred term) that occurs during the treatment period will be considered a TEAE if it was not present before the date of the first dose of investigational product or was present before the date of the first dose of investigational product and increased in severity during the treatment period. If more than 1 AE is reported before the date of the first dose of investigational product and coded to the same preferred term, the AE with the greatest severity will be used as the benchmark for comparison with the AEs occurring during the treatment period that were also coded to that preferred term. An AE that occurs more than 30 days after the date of the last dose of investigational product
will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by system organ class and preferred term; by system organ class, preferred term, and severity; and by system organ class, preferred term, and causal relationship to the investigational product. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by causal relationship to the investigational product.

The distribution of TEAEs by severity and causal relationship to the investigational product will be summarized by treatment group.

The incidence of common (eg, ≥ 2% of patients in any treatment group) TEAEs, on-therapy SAEs, and AEs leading to premature discontinuation of the investigational product will be summarized by preferred term and treatment group and will be sorted by decreasing frequency for the test treatment. In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. An SAE will be defined as an on-therapy SAE if it occurred on or after the date of the first dose of double-blind investigational product and within 30 days of the date of the last dose of investigational product.

Listings will be presented for patients with SAEs, patients with AEs leading to discontinuation, and patients who die (if any).

9.7.6.2 Clinical Laboratory Parameters

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented by treatment group for each clinical laboratory parameter.

The number and percentage of patients with PCS post baseline clinical laboratory values will be tabulated by treatment group. The criteria for PCS laboratory values will be detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 post baseline assessment. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS post baseline value. A supportive listing of patients with PCS post baseline values will be provided, including the PID number, and baseline and post baseline values. A listing of all AEs that occur in patients who have PCS laboratory values will also be provided.

9.7.6.3 Vital Signs

Descriptive statistics for vital signs (ie, systolic and diastolic blood pressure, pulse rate, respiratory rate, oxygen saturation [if applicable], temperature) and changes from baseline values at each visit and at end of study will be presented by treatment group.

Vital sign values will be PCS if they meet both the observed-value criteria and the change from baseline–value criteria detailed in the statistical analysis plan. The percentages will be calculated relative to the number of patients with baseline values and at least one postbaseline assessment. The numerator will be the total number of patients with available baseline values and at least one PCS postbaseline value. A supportive listing of patients with PCS postbaseline values will be provided, including the PID number, and baseline and postbaseline values. A listing of all AEs that occur in patients who have PCS vital sign values will also be provided.

9.7.6.4 Chest Radiography

Readings of the baseline chest radiographs including the presence of pleural effusion, whether the pleural effusion was unilateral or bilateral, and whether the pulmonary infiltrate was uni- or multi-lobar and/or cavitated will be summarized by treatment group for the MITT Analysis Set.

9.7.6.5 Stopping Rule

Toxicity will be monitored for each arm independently. Toxicities used for this monitoring consist of severe drug related adverse events leading to the discontinuation of the study drug. For this trial,

the upper limit of the toxicity rate is 20%. The trial will be discontinued if the observed data indicates that there is a 90% chance that the true toxicity rate is higher than 20% in any treatment arm. Statistically, this means that if the posterior probability of toxicity greater than 0.2 is greater than 0.9 (ie, Pr (toxicity > 0.2|data) > 0.9), the trial will be discontinued for toxicity. Toxicity will be monitored when the accrual is approximately 10, 20, 30, and 40. Accrual will be temporarily suspended for analysis after each of the following interim accrual goals. The parameters of the beta prior Beta (a, b) were chosen based on the following two considerations: (1) we wanted the prior to be vague and equivalent to an effective size of
0.5 patient such that the estimates are essentially determined by the data. This requirement is equivalent to a+b=0.5; (2) the prior mean of the toxicity rate is 20%, which is equivalent to a/(a+b)=0.2. Solving these two equations, we obtained a=0.1 and b=0.4, that is, the beta prior Beta (0.1, 0.4). Assuming the prior beta distribution Beta (0.1, 0.4) for the toxicity, the above stopping rule translates into the following stopping boundary: the study will be terminated if the observed toxicity is >= 4/10, 7/20, 10/30, 12/40 (# of patients experienced toxicities/# of patients treated). The table below shows the operating characteristics of the stopping rule based on 1,000 simulated trials (Thall et al, 1995).

Operating characteristics of the proposed stopping rule

True toxicity probability	0.1	0.2	0.3	0.4
Stopping Probability	1.4%	20.0%	65.9%	94.9%
Average number of patients treated	49.5	44.0	29.5	17.7

9.7.7 Health Economics and Outcomes Research Analyses

Not applicable.

9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

The primary objective of the study is show that efficacy of Ceftolozane-Tazobactam plus vancomycin, daptomycin or linezolid is non-inferior to standard of care (SOC) plus vancomycin, daptomycin or linezolid as empiric therapy in febrile neutropenic adults with cancer with respect to favorable clinical response. Based on historical data, the estimate of favorable clinical response for the SOC is approximately 65%. We expect that the favorable clinical response of Ceftolozane-Tazobactam plus vancomycin, daptomycin or linezolid is 80%. Given the non-inferiority margin of 10% (i.e., if the favorable clinical response of Ceftolozane-Tazobactam is >55%, it is deemed non-inferior to the SOC), the sample size of 50 patients per arm will have 80% power to establish the non-inferiority. This power calculation is performed using nQuery Advisor with null response rate of 0.55, alternative response rate of 0.8, one-sided chi-squared test at significance level of 0.05.

9.7.10 Computer Methods

Statistical analyses will be performed using SAS version 9.3.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS

A *protocol deviation* is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, and scheduling of visits not in accordance with specifications.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients.

The IRB must be notified according to the criteria and time period dictated by the IRB associated with this study.

10.0 STUDY SPONSORSHIP

MD Anderson Cancer Center IND office (Study Sponsor); Merck, Inc. (Supporting Company)

10.1 STUDY TERMINATION

Merck, Inc.. reserves the right to terminate the study in its entirety before study completion.

10.2 REPORTING AND PUBLICATION

An integrated clinical and statistical report will be prepared at the completion of the study. Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and Merck Institute, Inc., and will follow ***the current Applicable*** SOP on publications

11.0 INVESTIGATOR OBLIGATIONS

11.1 DOCUMENTATION

The Investigator must maintain the following during the study:

A copy of the original IRB approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB, as stated in Section 5.1

A copy of the IRB-approved ICF

11.2 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Sub-Investigators listed on Form FDA 1572. The investigational products must be stored in a secured place and must be locked. The MDA standard operating procedures for drug accountability will be followed. All unused investigational products will be destroyed according to the standard operating procedures at MD Anderson. It is the Investigator's responsibility to ensure that patients return their investigational product.

11.3 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs. The Investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct. The Investigator must maintain and retain accurate documentation that supports the information entered for source document verification and possible regulatory inspection.

11.4 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including case report forms, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results and electrocardiogram reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) must be retained by the Investigator according to institutional policies.

The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party.

11.5 PATIENT CONFIDENTIALITY

All patient records will only be identified by initials and accession number.

12.0 APPENDICES

APPENDIX I. ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's legally authorized representative. This consent must include the following items:

- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation

- A description of any reasonably foreseeable risks or discomforts to the patient

- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; Merck, Inc.; the IRB; or an authorized contract research organization may inspect the records

- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained

- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB may be required)

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable

- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent

- Any additional costs to the patient that may result from participation in the research

- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation

- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient

- The approximate number of patients involved in the study

- A statement of consent (eg, "I agree to participate . . .")

- A place for the patient's signature and date of signing

- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

- A copy of the signed consent form must be given to the patient.

APPENDIX II. MD ANDERSON NEUTROPENIC FEVER INPATIENT ADULT TREATMENT GUIDELINES

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Neutropenic Fever Inpatient Adult Treatment

ANC less than 1,000/mm^3 or temperature gr
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Patient presents with fever or develops fever at MDACC -Consider Sepsis[1]

- Complete Physical Exam
- Start IV fluids
- Heme Survey with ANC, BUN, creatinine, Sodium, Potassium, Chloride, CO2
- Urinalysis
- Lactic Acid
- Urine culture and sensitivity, Blood Cultures (with a set collected from each lumen simultaneously if CVC present, and 1 peripheral. If no CVC present, 2 blood cultures from peripheral site) and other cultures as clinically indicated.
- Chest x-ray if clinically indicated (signs/symptoms of respiratory involvement) or other tests as clinically indicated.

Hemodynamically stable? **(Does patient meet SIRS criteria[1])** See Appendix A for signs of organ dysfunction

Yes

- See Adult Sepsis Management Algorithm and use Sepsis Order Set
- If pneumonia is suspected, see algorithm for Pneumonia in Adult Patients (18 years and older) with Cancer
- See Early Intervention for Suspected Adult Sepsis Algorithm and Early Intervention Sepsis Order Set.
- See Pages 2 - 4 to determine appropriate antibiotic regimen and use Inpatient Neutropenic Fever Order Set.

No

- Please call MERIT (Medical Emergency Rapid Intervention Team)
- See Adult Sepsis Management Algorithm and use Sepsis Order Set.
- Consider adding ICU Addendum Severe Sepsis or Septic Shock Order Set.

[1] **SIRS Criteria (Systemic Inflammatory Response Syndrome)**
Patient exhibits two or more of the following :

- Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F)
- Heart Rate greater than 90 beats/minute
- Respiratory rate greater than or equal to 20 breaths/minute or $PaCO_2$ less than or equal to 32 mmHg
- WBC greater than or equal to 12,000/mm^3 or less than or equal to 4,000/mm^3
- Suspected or proven infection

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Pa

Criteria for Selecting Antibiotics (antibiotics should be given within 2 hrs)
SIRS patients refer to sepsis treatment algorithm.
When selecting antibiotic regimen, take into account the following:
-Recent culture and sensitivity results
-History of positive VRE, MRSA, Multi-Drug Resistant organisms (i.e. Pseudomonas aeruginosa and Stenotrophomonas maltophilia)
-CVC in place
-Antibiotic history and prophylaxis
-Source of infection if identified
-Antibiotic allergies (see page 4 for beta lactam allergy)
-Organ dysfunction

[1] Consider Meropenem if patient has:
- allergy to alternative agents or
- failed treatment with cefepime or piperacillin/tazobactam or
- infection with ESBL (extended spectrum beta-lactamase) organism
- infection with organism only susceptible to carbapenem

[2] Double gram negative coverage should be considered with complicated tissue based infections, neutropenic enterocolitis, pneumonia and perirectal infections. If quinolone prophylaxis, add vancomycin to the regimen.

FINDINGS		ANTIMICROBIAL THERAPY RECOMMENDATIONS
Neutropenic Fever	A	**Choose one:** • Piperacillin and Tazobactam 4.5 grams IVPB every 6 hours **or** • Cefepime 2 grams IVPB every 8 hours **or** • Meropenem[1] 1 grams IVPB every 8 hours **If indicated, for double gram negative coverage[2], add one of the following:** • Tobramycin 7 mg/kg IVPB daily **or** • Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis **Beta-lactam allergy:** see Page 4 for antibiotic options
Suspected Line Infection and/or Bacteremia	B	**Choose one:** • Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or** • Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia) **Plus one of the following:** • Piperacillin and Tazobactam 4.5 grams IVPB every 6 hours **or** • Cefepime 2 grams IVPB every 8 hours **or** • Meropenem[1] 1 gram IVPB every 8 hours **If indicated, for double gram negative coverage[2], add one of the following:** • Tobramycin 7 mg/kg IVPB daily **or** • Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis **Beta-lactam allergy:** see Page 4 for antibiotic options
MRSA Colonization/ Skin and Soft Tissue Infection/ Mucositis greater than or equal to Grade 2	C	**Choose one:** • Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or** • Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia) **or** • Linezolid 600 mg IVPB every 12 hours **Plus one of the following:** • Piperacillin and Tazobactam 4.5 grams IVPB every 6 hours **or** • Cefepime 2 grams IVPB every 8 hours **or** • Meropenem[1] 1 gram IVPB every 8 hours **If indicated, for double gram negative coverage[2], add one of the following:** • Tobramycin 7 mg/kg IVPB daily **or** • Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis **Beta-lactam allergy:** see Page 4 for antibiotic options

NOTES:
- Doses indicated are for patients with normal renal/hepatic function.
- Antibiotics for gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

See Page 5 for Day 5 Re-assessment

See Pages 3 and 4 for additional findings and antibiotic options

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Continued from previous page – see Page 2 for "Antibiotic Selection Criteria"

ANTIMICROBIAL THERAPY RECOMMENDATIONS

FINDINGS

Stenotrophomonas maltophilia

Consider adding one of the following antibiotics to one of the regimens from Box A, B, or C on Page 2 or 3 of this algorithm:
- Sulfamethoxazole and Trimethoprim (TMP) 3.75 mg TMP/kg IVPB or oral every 6 hours **or**
- If sulfa allergy, Tigecycline 100 mg IVPB times 1 dose then 50 mg IVPB every 12 hours

Multi-Drug Resistant Organisms

- Consider Infectious Disease Consult
- Consider adding the following antibiotic to one of the regimens from Box A, B, or C on Page 2 or 3 of this algorithm:
  Colistin 2.5 mg/kg every 12 hours

VRE Colonization or Infected Patients

Consider using one of the following antibiotics, in place of vancomycin, with one of the regimens from Box A, B, or C on Page 2 of this algorithm:
- Linezolid 600 mg IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

See Page 5 for Day 5 Re-assessment

NOTES:
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- Antibiotics for gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

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FINDINGS

ANTIMICROBIAL THERAPY RECOMMENDATIONS

Serious beta-lactam allergy

Neutropenic Fever[1]

Choose:
- Aztreonam 2 grams IVPB every 8 hours

Plus one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Plus one of the following:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Linezolid 600 mg IVPB every 12 hours

Suspected Line Infection and/or Bacteremia[1]

Choose:
- Aztreonam 2 grams IVPB every 8 hours

Plus one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Plus one of the following
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

MRSA Colonization/ Skin and Soft Tissue Infection[1]

Choose:
- Aztreonam 2 grams IVPB every 8 hours

Plus one of the following:
- Tobramycin 7 mg/kg IVPB daily **or**
- Ciprofloxacin 400 mg IVPB every 8 hours if no quinolone prophylaxis

Plus one of the following:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Linezolid 600 mg IVPB every 12 hours **or**
- Daptomycin 6-8 mg/kg IVPB every 24 hours (if no evidence of pneumonia)

Mucositis[1] greater than or equal to Grade 2

Choose:
- Aztreonam 2 grams IVPB every 8 hours **and** Clindamycin 900 mg IVPB every 8 hours **and** Tobramycin 7 mg/kg IVPB daily

Plus one of the following:
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IVPB every 12 hours **or**
- Linezolid 600 mg IVPB every 12 hours

See Page 4 for Day 5 Re-assessment

[1]NOTES:
- Doses indicated are for patients with normal renal/hepatic function.
- Double gram negative coverage recommended due to reduced aztreonam susceptibility to gram negative pathogens according to local antibiograms
- Antibiotics for gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

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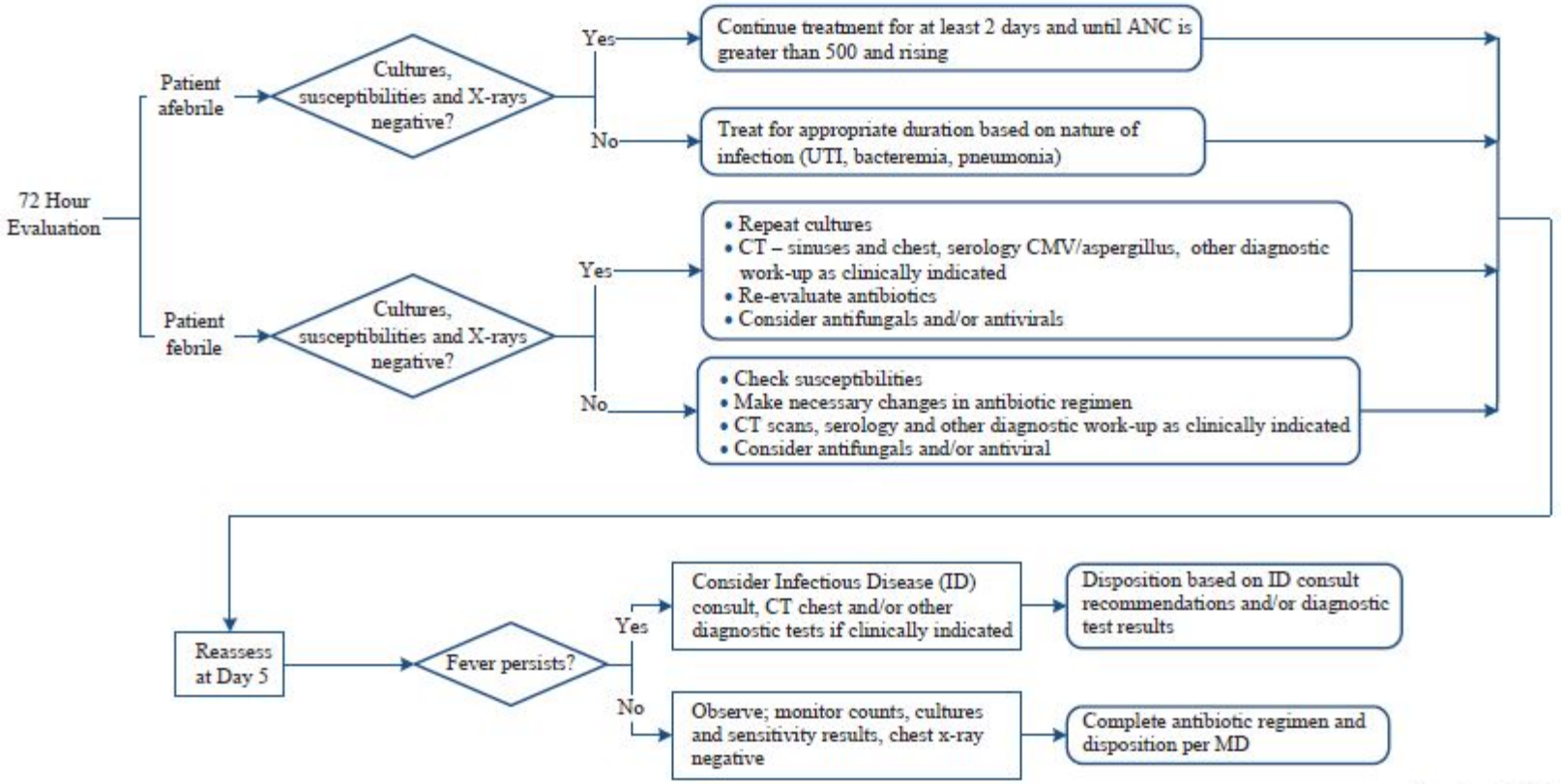

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APPENDIX A: Suspicion of Organ Dysfunction

- Decreased perfusion (capillary refill greater than 3 seconds, skin mottling, cold extremities, lactate greater than 2 mmol/L)
- Circulatory (SBP less than 90 mmHg, MAP less than 65 mmHg, decrease in SBP greater than 40 mmHg)
- Respiratory (PaO_2/FiO_2 less than 300; PaO_2 less than 70 mmHg; SaO_2 less than 90%)
- Hepatic (jaundice; total bilirubin greater than 4 mg/dL; increased LFT's; increased PT)
- Renal (creatinine greater than 0.3 mg/dL; urine output less than 0.5 mL/kg/hour for at least 2 hours)
- Central nervous system (altered consciousness, confusion, psychosis)
- Coagulopathy (INR greater than 1.5 or aPTT greater than 60 seconds); thrombocytopenia (platelets less than 100,000/mm^3)
- Splanchnic circulation (absent bowel sounds)

MAP = Mean Arterial Pressure
LFT = Liver Function Test

APPENDIX B: Criteria for ICU Admission

Major Criteria - one required for admission to ICU:
- Need for mechanical ventilation
- Septic shock with the need of vasopressor(s) (See Institutional Sepsis Algorithm)

Minor Criteria - at least 3 required for admission to ICU:
- Noninvasive ventilation
- PaO_2/FiO_2 ratio less than 250
- Respiratory rate greater than 30 breaths per minute
- SBP less than 90 mmHg
- Oxygen supplementation greater than 50%
- Hypotension requring aggressive fluid resuscitation
- Acute renal failure
- Multilobar pulmonary infiltrates
- Confusion
- BUN greater than 20 mg/dL
- WBC less than 4,000/mm^3
- Thrombocytopenia less than 100,000/mm^3
- Hypothermia (less than 36°C)

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Neutropenic Fever Inpatient Adult Treatment

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson's specific patient population; MD Anderson's services and structure; and MD Anderson's clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. Based on general principles, local microbiology and susceptibility/resistance patterns should be taken into consideration when selecting antibiotics.

DEVELOPMENT CREDITS

This practice consensus algorithm is based on majority expert opinion of the Neutropenic Fever Work Group at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following core group members:

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APPENDIX III. MD ANDERSON PNEUMONIA IN ADULT PATIENTS WITH CANCER TREATMENT GUIDELINES

Pneumonia in Adult Patients (18 years and older) with Cancer

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PATIENT PRESENTATION

Patient presents with:
- Cough, with or without sputum production
- Temperature greater than 38°C
- Dyspnea
- Pulmonary infiltrates
- Unexplained crackles, dullness or egophony on physical examination
- Hypoxemia

- Focused History and Exam (include vaccination and smoking history[1])
- Vital signs
- Oxygen Saturation
- CBC
- Sputum Culture
- Nasal wash (if indicated during high risk season)
- Chest x-ray (PA and Lateral)
- Isolation precautions as indicated
- Blood Cultures[2]: at least 2 sets of blood cultures are recommended, with a set collected simultaneously from each lumen of an existing CVC, if present, and from a peripheral vein site. Two blood culture sets from separate venipunctures should be sent if no central catheter present.

History, exam or chest x-ray compatible with pneumonia?

Yes
- Verify blood and sputum cultures obtained
- Complete history with information on vaccinations and smoking history[1]

No
- Work up for other diagnosis and disposition as clinically indicated

Is patient high risk* requiring hospitaliza-tion?

Yes

Is patient hemodynamically unstable[3] and/or with signs and symptoms of respiratory distress?

Yes
- If in clinic, call Emergency Center (EC) and send patient to EC

No
- Initiate Adult Pneumonia Admission Orders and admit to hospital

See Page 2

No
- Low risk community acquired pneumonia, treat as outpatient
- Give first dose of antibiotic as soon as possible [4]
- If in Emergency Center, give first dose(s) of each indicated antibiotic while in EC [5]
- Discharge patient if discharge criteria met (see Appendix C) and if able to take oral medications/fluids and patient able to take care of self
- Refer to General Internal Medicine or Primary Care Physician to be seen in 3 working days to receive vaccines
- Refer to Tobacco Treatment Program, if indicated

RECOMMENDED

*__High risk patient__:
- Health Care Associated Pneumonia (HCAP), Hospital Acquired Pneumonia (HAP) or Multidrug-Resistant Pathogen (MDRP) suspected (Appendix A) and/or
- Neutropenic (ANC less than 1 K/microliter) or
- Stem cell transplant or
- Radiation therapy to chest within 4 weeks of pneumonia or
- Community Acquired Pneumonia (Appendix A) with PSI higher than 2 (Appendix B)

[1] Information to request from all patients:
- Has the patient received Pneumococcal vaccine in the last 5 years? (If Stem Cell Transplantation and Cellular Therapy, per physician recommendation.)
- Has the patient received Influenza Virus vaccine during season (October – March)?
- Is the patient a smoker?

[2] Collect blood cultures prior to antibiotic administration.

[3] Hemodynamically unstable is defined as new onset of hypoxemia, oxygen saturation less than 90 % or hypotension (blood pressure less than 90 mmHg); patient in respiratory distress. Respiratory Distress may include the following: acute onset of dyspnea, tachypnea, hypoxemia, increased accessory muscle use with breathing, and/or intercoastal and sternal retractions.

[4] The goal is to give the antibiotics as soon as possible, preferably within 2 hours of evaluation and diagnosis.

[5] Antibiotics with gram negative coverage should be given first and may be infused via y-site with other antibiotics if compatible.

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Pneumonia in Adult Patients (18 years and older) with Cancer

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Patient Admission to Hospital

Patient hemodynamically unstable[1] and/or in respiratory distress[1] and sent to EC for further evaluation and admission to hospital

Patient meets one or more of the criteria for ICU admission*?

Yes

- Blood cultures, if not previously obtained
- Lactic Acid
- Give first dose of antibiotic[2] in EC (See Pages 3 - 5 for medications)
- Admit to ICU
- Activate ICU orders
- Consider consults with Pulmonology and Infectious Diseases (ID) Specialists[3]

No

Patient hemodynamically stable and not in respiratory distress[1] and admission to hospital initiated

- Blood cultures, if not previously obtained
- Give first dose of antibiotic[2] in Clinic (See Pages 3 - 5 for medications)
- Activate Pneumonia Admission Orders
- Admit to regular floor
- Activate appropriate vaccination orders, if indicated
- Early consult with Pulmonology and/or ID Specialists[3], if indicated
- Tobacco Treatment Program Consult, if indicated

- Once patient is stable and ready to be discharged from hospital: see Appendix C for discharge criteria
- Once discharge criteria met, administer vaccines as clinically indicated
- Refer to Tobacco Treatment Program if indicated
- Reconcile vaccinations in patient's medical records

***ICU Admission Criteria**

Major Criteria - one required for admission to ICU:

- Need for mechanical ventilation
- Septic shock with the need of vasopressor(s) (See Institutional Sepsis Algorithm)

Minor Criteria - at least 3 required for admission to ICU:

- Noninvasive ventilation
- PaO_2/FiO_2 ratio less than 250
- Respiratory rate greater than 30 breaths per minute
- Systolic blood pressure less than 90 mmHg
- Oxygen supplementation greater than 50%
- Hypotension requiring aggressive fluid resuscitation
- Acute renal failure
- Multilobar pulmonary infiltrates
- Confusion
- BUN greater than 20 mg/dL
- WBC less than 4 K/microliter
- Platelets less than 100 K/microliter
- Hypothermia (less than 36°C)

[1] Hemodynamically unstable: new onset of hypoxemia, oxygen saturation less than 90% or hypotension (blood pressure less than 90 mmHg); patient in respiratory distress. Respiratory Distress may include the following: Acute onset of dyspnea, tachypnea, hypoxemia, increased accessory muscle use with breathing, and/or intercostal and sternal retractions.

[2] The goal is to give the antibiotics as soon as possible, preferably within 2 hours of arrival to the EC or admission to inpatient unit. If septic or admitted to ICU, the goal is to give the antibiotic within one hour of arrival.

[3] ID Specialist consultation should be considered but not limited in the following clinical scenarios:

- Suspicion for viral pneumonia (interstitial pneumonia in the setting of seasonal activity of community respiratory viruses)
- Pneumocystis (carinii) jiroveci (interstitial pneumonia in the setting of steroid tapering)
- Early re-admission or recent bacteremia
- Multiple antibiotic allergies
- Known colonization by multi-drug resistant pathogen

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Pneumonia in Adult Patients (18 years and older) with Cancer

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SUSPECTED PNEUMONIA

HAP, HCAP[1] or MDRP[1] →

Initiate institutional pneumonia order and give first dose of the 3 antibiotic regimen (dosing is based on normal renal function):

One of the following:
- Cefepime 2 grams IV every 8 hours **or**
- Piperacillin/tazobactam 4.5 grams IV every 6 hours **or**
- Meropenem[2] 1 gram IV every 8 hours **or**
- If PCN allergic, aztreonam 2 grams IV every 8 hours

Plus one of the following:
- If no quinolone prophylaxis:
  - --Ciprofloxacin 400 mg IV every 8 hours **or**
  - --Levofloxacin 750 mg IV every 24 hours **or**
- Amikacin 20 mg/kg **or** tobramycin 7-10 mg/kg IV every 24 hours
  - --For patients receiving amikacin or tobramycin, obtain drug levels 4 and 10 hours after start of dose for individualized pharmacokinetics

Plus one of the following:
- Linezolid 600 mg IV every 12 hours **or**
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IV every 12 hours

CAP[1] →

If planned admission to general floor, **one** of the following options:
- Ceftriaxone 2 grams IV every 24 hours AND azithromycin 500 mg IV every 24 hours **or**
- Ceftriaxone 2 grams IV every 24 hours AND doxycycline 100 mg IV every 12 hours (if intolerant of macrolides) **or**
- Ampicillin/sulbactam 3 grams IV every 8 hours AND azithromycin 500 mg IV every 24 hours **or**
- Ampicillin/sulbactam 3 grams IV every 8 hours AND doxycycline 100 mg IV every 12 hours (if intolerant of macrolides) **or**
- Levofloxacin 750 mg IV every 24 hours **or**
- Moxifloxacin 400 mg IV every 24 hours

If planned admission to the ICU or stepdown, **one** of the following options:
- Ceftriaxone 2 grams IV every 24 hours AND azithromycin 500 mg IV every 24 hours **or**
- Ceftriaxone 2 grams IV every 24 hours AND levofloxacin 750 mg IV every 24 hours **or**
- Ceftriaxone 2 grams IV every 24 hours AND moxifloxacin 400 mg IV every 24 hours **or**

AND
- Vancomycin 15 mg/kg (round to nearest 250 mg dose) IV every 12 hours **or**
- Linezolid 600 mg IV every 12 hours

→ Once patient is stable and discharge criteria met (see Appendix C), disposition as clinically indicated

[1] See Appendix A for description of each pneumonia
CAP – Community Acquired Pneumonia
HAP – Hospital Acquired Pneumonia
HCAP – Healthcare Associated Pneumonia
MDRP – Multidrug Resistant Pathogens

[2] Consider Meropenem if patient has: allergy to alternative agents; failed treatment with cefepime or piperacillin/tazobactam; infection with extended spectrum beta-lactamase (ESBL) organism; infection with organism only susceptible to carbapenem

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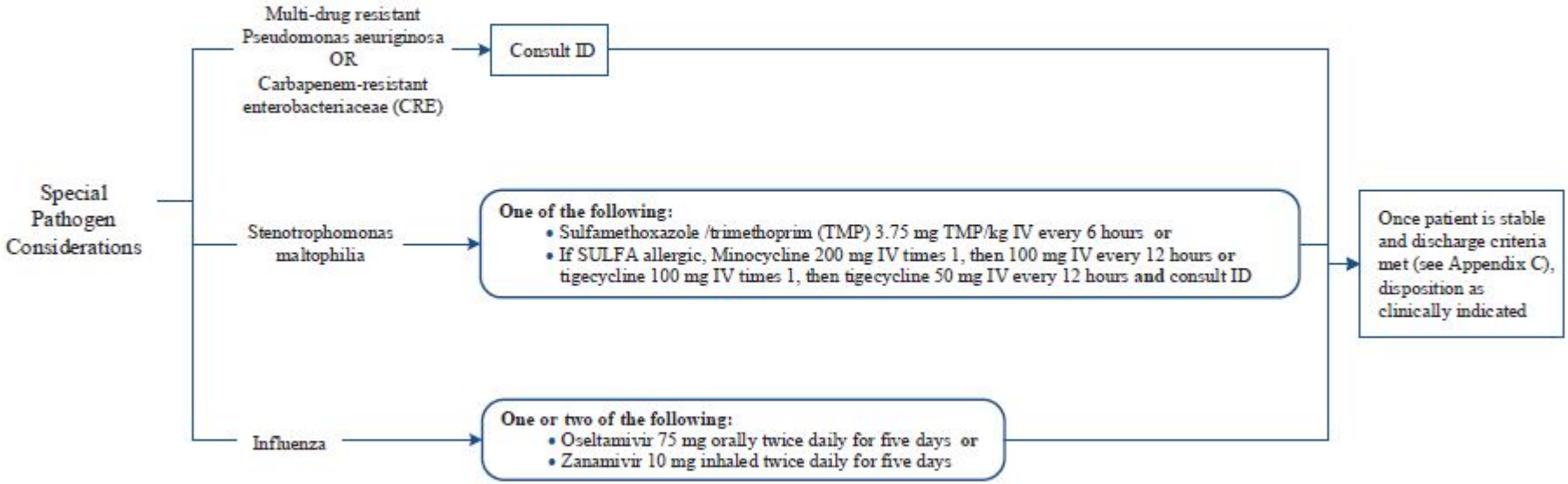
NOTE: antibiotic dosing based on normal renal function



Special Pathogen Considerations continued on next page

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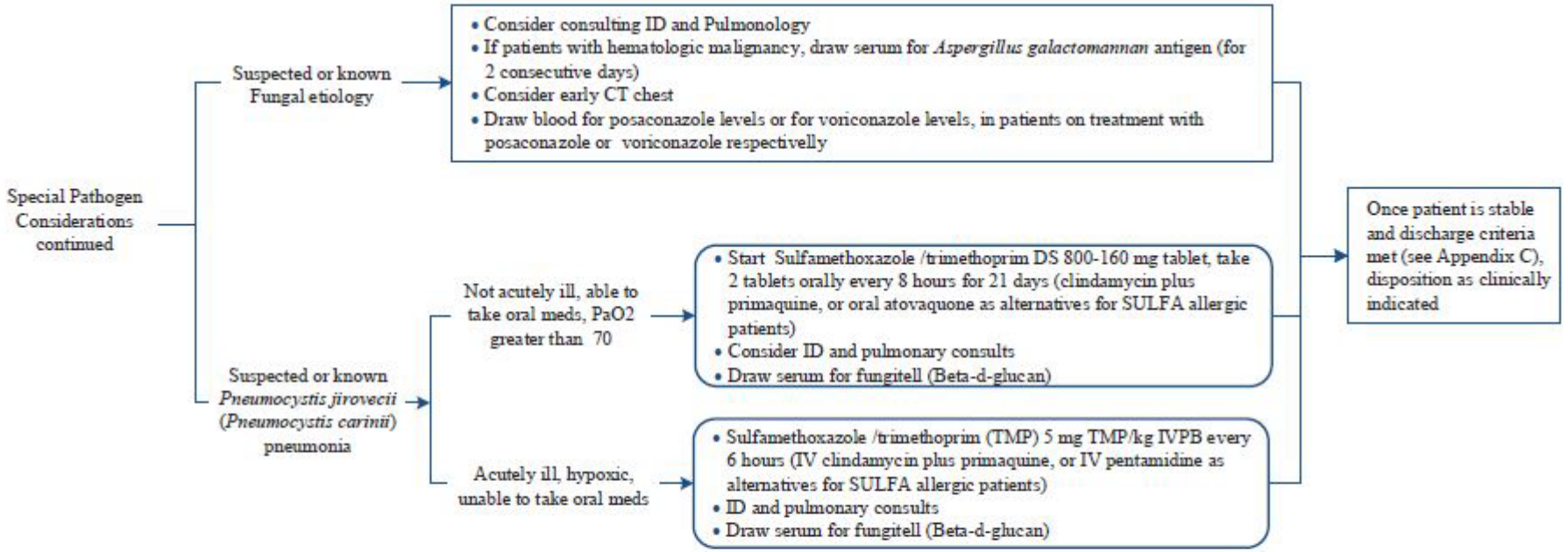
NOTE: Antibiotic dosing based on normal renal function



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APPENDIX A: Suspicion of Health Care-Associated Pneumonia (HCAP), Hospital-Acquired Pneumonia (HAP), Community Acquired Pneumonia (CAP), and Multi-Drug-Resistant Pathogen (MDRP) Risk Factors

Health Care Associated Pneumonia (HCAP) Risk Factors:

- **Undergoing or recent chemotherapy/radiation therapy or any cancer therapy**
- Hospitalization for 2 or more days within 90 days
- Residence in a nursing home or extended care facility
- Home infusion therapy (including antibiotics)
- Chronic Dialysis within the last 30 days
- Home wound care
- Family member with MDRP

Hospital Acquired Pneumonia (HAP):

- Pneumonia that occurs 48 hours or more after admission, which was not present at the time of admission.

Community Acquired Pneumonia (CAP):

- Patient with pneumonia that does not fit criteria for HCAP, HAP or Ventilation Associated Pneumonia (VAP) without MDRP risk factors. At MD Anderson Cancer Center, this could be a patient in surveillance, an employee with no patient contact or a visitor.

Multi-Drug-Resistant Pathogen (MDRP) Risk Factors:

- **Immunosuppressive disease or therapy**
- Antibiotics within 90 days
- Current hospitalization of 5 days or more
- High frequency of antibiotic resistance in the community or specific hospital unit
- Presence of risk factors for HCAP

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Pneumonia in Adult Patients (18 years and older) with Cancer

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APPENDIX B: Pneumonia Severity Index (PSI)[1,2]

To obtain a total point score for a given patient add the patient's age in years (age minus 10 for women) plus the points for each applicable characteristic.

CHARACTERISTIC	POINTS ASSIGNED
• Nursing home resident	+10
• Coexisting illnesses[3]	
◦ Neoplastic disease	+30
◦ Liver disease	+20
◦ Congestive heart failure	+10
◦ Cerebrovascular disease	+10
◦ Renal disease	+10

CHARACTERISTIC	POINTS ASSIGNED
• Laboratory and radiographic findings	
◦ Arterial pH less than 7.35	+30
◦ BUN greater than or equal to 30 mg/dL (11 mmol/liter)	+20
◦ Sodium less than 130 mmol/liter	+20
◦ Glucose greater than or equal to 250 mg/dL (14 mmol/liter)	+10
◦ Hematocrit less than 30%	+10
◦ Partial pressure of arterial oxygen less than 60 mmHg	+10
◦ Pleural effusion	+10

CHARACTERISTIC	POINTS ASSIGNED
• Physical-examination findings	
◦ Altered mental status[4]	+20
◦ Respiratory rate greater than or equal to 30 minutes	+20
◦ Systolic blood pressure less than 90 mmHg	+20
◦ Temperature less than 35°C or greater than or equal to 40°C	+15
◦ Pulse greater than or equal to 125 beats per minute	+10

PSI Risk Score Interpretation	
I	Absence of all predictors: • Less than age 50 and • No neoplastic disease, congestive heart failure, cerebrovascular disease, renal disease, liver disease, and • No abnormalities on physical exam including: altered mental status, pulse greater than or equal to 125/minute, respiratory rate greater than or equal to 30/minute, systolic blood pressure less than 90 mmHg, temperature less than 35°C or greater than or equal to 40°C
II	Less than or equal to score of 70
III	71 – 90
IV	91 – 130
V	Greater than 130

[1] The use of this score is to facilitate site of care decisions for those patients that are classified as CAP, and have not been validated (requires prospective validation) for the HAP, HCAP or immunocompromised population that are the majority of patients seen at MDACC. This guideline is not meant to replace clinical judgment.

[2] The Pneumonia Severity Index may be found on the MDACC Intranet under Clinic Portal – Clinical Calculators.

[3] Coexisting illnesses definitions:
- Neoplastic disease - any cancer except basal- or squamous-cell cancer of the skin that was active at the time of presentation or diag-nosed within one year of presentation.
- Liver disease - a clinical or histologic diagnosis of cirrhosis or another form of chronic liver disease,such as chronic active hepatitis.
- Congestive heart failure - a systolic or diastolic ventricular dysfunction documented by history, physical examination, and chest x-ray, echocardiogram, multiple gated acquisition scan, or left ventriculogram.
- Cerebrovascular disease – a clinical diagnosis of stroke or transient ischemic attack or stroke documented by MRI or CT.
- Renal disease - a history of chronic renal disease or abnormal BUN and creatinine concentrations documented in the medical record.

[4] Altered mental status is defined as disorientation with respect to person, place, or time that is not known to be chronic stupor or coma.

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APPENDIX C:
Discharge Criteria

- Temperature less than 37.8°C
- Pulse less than 100 beats per minute
- Systolic BP greater than 90 mmHg
- Blood oxygenation greater than 90%
- Able to maintain oral intake

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SUGGESTED READINGS

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Pneumonia in Adult Patients (18 years and older) with Cancer and on Therapy

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DEVELOPMENT CREDITS

This practice consensus algorithm is based on majority expert opinion of the Pneumonia core development team at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following clinicians.

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[Ŧ] Core Development Team

APPENDIX IV. POTENTIAL DRUG-INDUCED LIVER INJURY/HY'S LAW IDENTIFICATION

The Investigator is responsible for determining whether a patient meets the following potential Hy's law (PHL) criteria at any point after initiation of study therapy (IV or oral). For a PHL case to meet Hy's Law, the increases from baseline in AST or ALT and
total bilirubin values, in the Investigator's clinical judgment, should be temporally related to one another and to the administration of study drug, without an alternative explanation.

PHL

AST or ALT ≥ 3 × ULN; total bilirubin ≥ 2 × ULN and ALP < 2 × ULN

If there are increases from baseline in AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN:

- The Investigator must follow the instructions in this appendix
- The investigative site must complete the appropriate screen(s) of the eCRF with the local laboratory test results

FOLLOW-UP AND REPORTING

If the Investigator determines that the patient has not met PHL criteria (has not had increases from baseline in AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN and ALP < 2 × ULN, at any point after initiation of study drug), the Investigator is to perform follow-up on subsequent laboratory results as required for patient care and per protocol Section 9.5.2.9.2.

If the Investigator determines that the patient has met PHL criteria (has had AST or ALT ≥ 3 × ULN and total bilirubin ≥ 2 × ULN, and ALP < 2 × ULN, elevated from baseline at any point after initiation of study drug):

- The Investigator should review the criteria for premature discontinuation of study drug due to elevated liver chemistry values, per protocol Section 9.3.3
- Any PHL case should be handled as an SAE associated with the use of the drug and reported as an SAE per protocol Section 9.5.2.5 (ie, even before all other possible causes of liver injury have been excluded). It should be promptly reported before doing a full workup on the patient to rule out other etiologies

- The Investigator will investigate the etiology of the event and establish if another explanation/alternative cause other than drug-induced liver injury caused by the study drug is possible. The Sponsor may be contacted to discuss the work-up.

- The investigative site must complete the appropriate screens of the eCRF

  If there is an alternative explanation or the liver chemistry values increased from baseline arenot temporally related to one another and to the initiation of study drug, the Investigator should update the PHL SAE to reflect the attributed underlying illness and reassign an appropriate causality assessment, per protocol Sections 9.5.2.5 and 9.5.2.2, respectively.

  If there is no alternative explanation and the liver chemistry values increased from baseline are temporally related to one another and to the initiation of study drug, the Investigator should update the PHL SAE to a Hy's Law case (reported term 'Hy's Law') and reassign a causality assessment of "related."

  If, despite the Investigator's attempts to conduct follow-up and the guidance provided in this appendix, there is an unavoidable delay of > 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for a Hy's case, then it is assumed that there is no alternative explanation until such time as an informed decision can be made.

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13.0 LITERATURE CITED

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