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Meropenem-Vaborbactam (VABOMERE) vs. Best Available Therapy for Carbapenem-Resistant Enterobacteriaceae Infections in TANGO II: Primary Outcomes by Site of Infection

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Abstract

Introduction
Meropenem-vaborbactam (M-V) is a beta-lactamase inhibitor combination active against *Klebsiella pneumoniae* carbapenemase (KPC)-producing CRE. Few clinical trials of new agents have been conducted in patients with CRE.

Methods
TANGO II is a randomized, Phase 3, open-label trial in patients with infections due to known or suspected CRE, including complicated urinary tract infection (cUTI), acute pyelonephritis (AP), HABP/VABP, bacteremia, or complicated intra-abdominal infection (cIAI). Eligible patients were randomized 2:1 to monotherapy with M-V or Best Available Therapy (BAT) for 7-14 days. BAT could include (alone or in combination): a carbapenem, aminoglycoside, polymyxin B, colistin, tigecycline or ceftazidime-avibactam (monotherapy only). Enrollment was stratified by infection type and geographic region. Endpoints differed by infection: overall success (clinical cure + microbial eradication) in cUTI/AP, 28-day all-cause mortality in HABP/VABP + bacteremia, and clinical cure in cIAI. It was not powered for inferential statistical testing; results are presented descriptively.

Results
72 patients were enrolled: 43 (59.7%) had baseline CRE and comprised the microbiologic CRE modified intent-to-treat population (mCRE-MITT, primary population). In mCRE-MITT, 20 had bacteremia, 15 had cUTI/AP, 5 had HABP/VABP, and 3 had cIAI.

Efficacy by Infection Type	M-V (N=28) n/N' (%)	BAT (N=15) n/N' (%)
Bacteremia + HABP/VABP All-Cause Mortality, Day 28	4/16 (25.0%)	4/9 (44.4%)
cUTI/AP Overall Success at End of Treatment (EOT) Overall Success at Test of Cure (TOC, EOT + 7 d)	8/11 (72.7%) 3/7 (42.9%)*	2/4 (50%) 2/4 (50%)
cIAI Clinical Cure at TOC	1/1 (100%)	0/2 (0)

AEs occurred in 84.4% of M-V patients vs. 92% on BAT. M-V was associated with fewer drug-related AEs (24.4% vs. 44%), severe AEs (13.3% vs. 28%), and serious AEs (33.3% vs. 44%) vs. BAT.

Conclusions
In this first prospective comparative trial of a beta-lactam/beta-lactamase inhibitor combination as monotherapy of CRE infections, M-V showed consistent improvement over BAT in efficacy endpoints across infections, and improved safety/tolerability. M-V appears to be an improved treatment option for CRE infections.

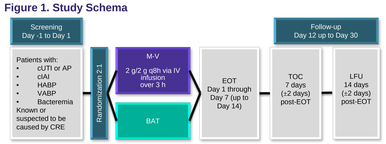
Background

- Increasing carbapenem resistance among Enterobacteriaceae pathogens has been recognized by the CDC and WHO as an urgent antimicrobial resistance threat.[1,2]
- In the US, the production of *Klebsiella pneumoniae* carbapenemase (KPC) enzyme is the major mechanism of carbapenemase-mediated resistance in carbapenem-resistant Enterobacteriaceae (CRE).[3]
- Despite the recent approval of an antimicrobial agent that has activity against target CRE pathogens, few clinical trials have been conducted in patients with infections due to confirmed CRE pathogens.
- Meropenem-vaborbactam (M-V; VABOMERE) is a novel beta-lactam/beta-lactamase inhibitor combination with potent activity against KPC-producing CRE.
- TANGO II is a Phase 3, multi-center, randomized, open-label comparative trial designed to evaluate efficacy and safety of M-V vs. best available therapy (BAT). It is the only clinical trial of a novel agent given as monotherapy compared against BAT in patients with serious CRE infections.
- Randomization into the comparator phase of TANGO II was stopped on July 21, 2017, in accordance with recommendations of the independent Data Safety Monitoring Board, which concluded that a risk-benefit analysis of available data no longer supported randomization of patients to BAT.
- Here we report primary outcomes by site of infection in patients with confirmed CRE infection.

Methods

- Phase 3, multi-center, randomized, open-label study of adults with infections due to known or suspected CRE, including complicated urinary tract infection (cUTI), acute pyelonephritis (AP), hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), bacteremia, or complicated intra-abdominal infection (cIAI).
- Eligible patients were randomized 2:1 to monotherapy with M-V (2g/2g every 8h via 3-h infusion) or BAT for 7-14 days (**Figure 1**).
  - BAT included mono/combination therapy with polymyxins, carbapenems, aminoglycosides, tigecycline; or ceftazidime-avibactam alone.
- Enrollment was stratified by infection type and geographic region.
- Key inclusion criteria: known or suspected (evidence of CRE in culture or molecular testing within past 90 d) CRE pathogen, requirement of ≥7 days IV therapy, confirmed cUTI/AP, HABP/VABP, bacteremia, or cIAI.
- Key exclusion criteria: Receipt of >24 hours of potentially effective antimicrobials (unless clinical failure), immediate life-threatening disease, known infection due to NDM, VIM, IMI or OXA-encoded beta-lactamase.
- Efforts to reduce bias included onsite blinded investigator, blinded adjudication committee, and source control adjudication committee (for cIAI).

Figure 1. Study Schema



EOT, end of treatment; TOC, test of cure; LFU, last follow-up.

- Study endpoints differed by infection type based on prevailing FDA guideline recommended endpoints:
  - 28-day all-cause mortality in the combined HABP/VABP and bacteremia infections.
  - Overall success (composite endpoint of clinical cure and microbial eradication) in cUTI/AP at End of Treatment (EOT) and Test of Cure (TOC).
    - Clinical cure was defined as a complete resolution of signs/symptoms such that no further antimicrobial therapy was required.
    - Clinical cure was assessed by both an unblinded (PI) and a blinded investigator (BI) at two time points: EOT and TOC. In cases where their assessments differed, clinical cure was adjudicated by the blinded adjudication committee.
  - Clinical cure in cIAI at TOC
    - For cIAI, proper source control in all patients was assessed and adjudicated by committee.
- Safety endpoints were assessed in those who received ≥1 dose of study drug.
- Results are presented descriptively. The study was not powered for inferential statistical testing.

Results

- Of the 72 enrolled patients, 43 (59.7%) had a baseline CRE and comprised the microbiologic CRE modified intent-to-treat population (mCRE-MITT, primary population). Baseline characteristics for the mCRE-MITT population are shown in **Table 1**.
- In mCRE-MITT, 20 had bacteremia, 15 had cUTI/AP, 5 had HABP/VABP, and 3 had cIAI.
  - Of the 15 patients with cUTI/AP, 7 were cUTI and 8 were AP.
    - 5 of the 7 cUTI patients had an indwelling urinary catheter at baseline.
  - Of the 5 patients with HABP/VABP, 1 was HABP and 4 were VABP.
  - Of the 3 patients with cIAI, one was due to a perforated viscus, one was in the setting of cholangitis/cholecystitis, and one was in the setting of intra-abdominal abscess.

Table 1. Baseline Demographic and Clinical Characteristics (mCRE-MITT)

	M-V N=28	BAT N=15	Total N=43
Age, mean (standard deviation), y	63.9 (14.0)	60.2 (13.0)	62.6 (13.6)
Age cohort, n (%)			
<65 y	14 (50.0)	9 (60.0)	23 (53.5)
≥65 y	14 (50.0)	6 (40.0)	20 (46.5)
≥75 y	6 (21.4)	3 (20.0)	9 (20.9)
Female gender, n (%)	15 (53.6)	5 (33.3)	20 (46.5)
White race, n (%)	24 (85.7)	12 (80.0)	36 (83.7)
Region, n (%)			
North America	6 (21.4)	7 (46.7)	13 (30.2)
Europe	17 (60.7)	8 (53.3)	25 (58.1)
Rest of World (Israel, Colombia, Brazil, Argentina)	5 (17.9)	0 (0)	5 (11.6)
Body mass index, mean (SD)	28.4 (9.4)	25.8 (7.6)	27.5 (8.8)
Infection type, n (%)			
Bacteremia	12 (42.9)	8 (53.3)	20 (46.5)
cUTI/AP	11 (39.3)	4 (26.7)	15 (34.9)
HABP/VABP	4 (14.3)	1 (6.7)	5 (11.6)
cIAI	1 (3.6)	2 (13.3)	3 (7.0)
Baseline pathogen[a], n (%)			
Klebsiella pneumoniae	25 (89.3)	12 (80.0)	37 (86.0)
Escherichia coli	2 (7.1)	1 (6.7)	3 (7.0)
Enterobacter cloacae complex	1 (3.6)	2 (13.3)	3 (7.0)
Proteus mirabilis	0 (0)	2 (13.3)	2 (4.7)
Serratia marcescens	1 (3.6)	1 (6.7)	2 (4.7)
Enrolled as known CRE, n (%)	20 (71.4)	14 (93.3)	34 (79.1)
Enrolled as suspected CRE, n (%)	8 (28.6)	1 (6.7)	9 (20.9)
Creatinine clearance, mL/m, n (%)			
>50	22 (78.6)	9 (60.0)	31 (72.1)
30–49	3 (10.7)	2 (13.3)	5 (11.6)
20–29	1 (3.6)	2 (13.3)	3 (7.0)
<20	1 (3.6)	0 (0)	1 (2.3)
Missing	1 (3.6)	2 (13.3)	3 (7.0)
Charlson Comorbidity Index, n (%)			
≤2	4 (14.3)	1 (6.7)	5 (11.6)
3–4	3 (10.7)	2 (13.3)	5 (11.6)
5	10 (35.7)	1 (6.7)	11 (25.6)
>6	11 (39.3)	11 (73.3)	22 (51.2)
Diabetes mellitus, n (%)	9 (32.1)	7 (46.7)	16 (37.2)
Systemic inflammatory response syndrome, n (%)	12 (42.9)	6 (40.0)	18 (41.9)
Intensive care unit admission	5 (17.8)	2 (13.3)	7 (16.3)
Immunocompromised[b], n (%)	10 (35.7)	8 (53.3)	18 (41.9)
Prior treatment failure[c], n (%)	9 (32.1)	0 (0)	9 (20.9)

[a] Baseline pathogens listed occurred in 2 or more patients.
[b] Leukemia or lymphoma (not in remission), prior solid organ/stem cell transplantation, ongoing neutropenia, or active receipt of immunosuppressive medications (including high-dose systemic steroids for ≥2 weeks).
[c] Clinical evidence of prior antimicrobial failure as ascertained by the study investigator at screening and randomization.

- BAT antibiotic regimens by infection type (mCRE-MITT) are shown in **Table 2**.
- There was no consensus BAT regimen. BAT ranged from 1 to >4 drug combinations, which included ceftazidime/avibactam, polymyxins, carbapenems, aminoglycosides, and tigecycline.
- For all infection types, the primary pathogen was *Klebsiella pneumonia*. The most common molecular mechanism of carbapenem resistance was production of KPC carbapenemase (90%).
- Meropenem MIC50s and 90s were similar across both arms. For cUTI and bacteremia, the meropenem MIC50 was 64 µg/mL. For HABP/VABP and cIAI, the MIC50s were 16 and >16 µg/mL, respectively.

Table 2. BAT Antibiotic Regimens by Infection Type (mCRE-MITT)

BAT Regimen	cUTI/AP N=4 n (%)	HABP/VABP N=1 n (%)	Bacteremia N=8 n (%)	cIAI N=2 n (%)	Total N=15* n (%)
Monotherapy	2 (50)	0 (0)	2 (25)	0 (0)	4 (26.7)
Aminoglycoside	1 (25)	0 (0)	0 (0)	0 (0)	1 (6.7)
Carbapenem	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (6.7)
Ceftazidime-Avibactam	0 (0.0)	0 (0)	1 (12.5)	0 (0)	1 (6.7)
Polymyxin/Colistin	1 (25)	0 (0)	0 (0)	0 (0)	1 (6.7)
Dual Therapy	2 (50)	1 (100)	3 (37.5)	1 (50)	7 (46.7)
Carbapenem + Aminoglycoside	1 (25)	0 (0)	0 (0)	0 (0)	1 (6.7)
Carbapenem + Polymyxin/Colistin	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (6.7)
Carbapenem + Tigecycline	0 (0)	0 (0)	1 (12.5)	1 (50)	2 (13.3)
Polymyxin/Colistin + Aminoglycoside	1 (25)	1 (100)	1 (12.5)	0 (0)	3 (20)
Triple Therapy	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (6.7)
Carbapenem + Polymyxin/Colistin + Tigecycline	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (6.7)
4 Drugs or More	0 (0)	0 (0)	2 (25)	0 (0)	2 (13.3)
Carbapenem + Polymyxin/Colistin + Aminoglycoside + Tigecycline	0 (0)	0 (0)	2 (25)	0 (0)	2 (13.3)

*One patient received ceftazidime-avibactam (which was only permitted per protocol as monotherapy) in combination with other antimicrobial agents and is therefore not represented.

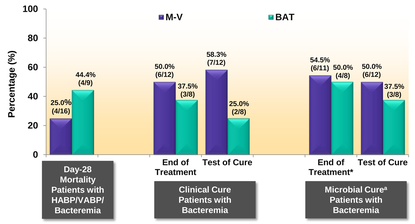
- Efficacy among patients with confirmed CRE infections by infection type is summarized in **Table 3** and **Figures 2 and 3**.
- Exploratory risk-benefit analyses were conducted to determine the risk-benefit profile of M-V vs. BAT. Results showed a significant decrease in poor outcomes in patients treated with M-V compared to BAT (mCRE-MITT), as shown in **Table 4**.
  - For the composite endpoint of mortality-nephrotoxicity (defined as either a ≥1.0 mg/dL increase in creatinine or renal AEs of failure, acute failure or impairment), M-V was associated with a reduction in mortality-nephrotoxicity compared to BAT (25.0% vs. 40.0%; 95%CI -44.5% to 14.5%, *P*=.32 and 21.4% vs. 60.0%; 95% CI -67.7% to -9.5%, *P*<.01, respectively).
  - For the composite endpoint of failure-nephrotoxicity (same definitions), M-V was associated with a superior risk-benefit profile compared to BAT (32.1% vs. 80.0%; 95%CI -74.5% to -21.2%, *P*<.001 both definitions).
- Adverse events (AEs) and safety endpoints (safety population/MITT) are shown in **Poster#1862, Kaye K et al, IDWeek 2017**.

Table 3. Efficacy Endpoints by Infection Type Among Patients with Confirmed CRE Infections (mCRE-MITT)

	M-V n/N' (%)	BAT n/N' (%)	Absolute Difference (M-V – BAT)	Relative Difference [(M-V – BAT)/BAT]
Patients with HABP/VABP and bacteremia, combined				
Day-28 all-cause mortality	4/16 (25.0)	4/9 (44.4)	−19.4%	−43.7%
Patients with cUTI/AP				
Overall success rate[a] at EOT	8/11(72.7)	2/4 (50.0)	22.7%	45.4%
Overall success rate[a] at TOC (EOT +7d)[b]	3/7 (42.9)	2/4 (50.0)	−7.1%	−14.0%
Patients with cIAI				
Clinical cure at TOC	1/1 (100)	0/2 (0)	100%	–

[a] Overall success rate was a composite of clinical cure and microbial eradication.
[b] 4 Patients in the M-V group were indeterminate/not assessed at TOC.

Figure 2. Efficacy Endpoints in Patients with HABP/VABP or Bacteremia, by Timepoint (mCRE-MITT)



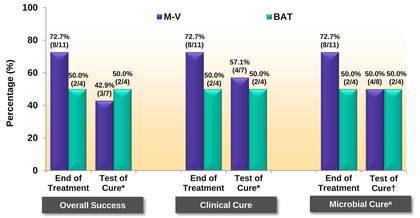
[a] Composite of either microbial eradication or presumed eradication at respective visit.
* One subject in the M-V arm was indeterminate/not assessed at TOC.

Table 4. Exploratory Risk-Benefit Analysis: Patients with Poor Outcomes of Confirmed CRE Infections (mCRE-MITT)

Outcome	M-V (N=28) n (%)	BAT (N=15) n (%)	Absolute Difference (M-V – BAT) (95% CI)	*P* value	Relative Difference [(M-V – BAT)/BAT]
Day-28 All-Cause Mortality or Nephrotoxicity[a]	7 (25.0)	6 (40.0)	-15.0 (-44.5 to 14.5)	.32	-37.5
Clinical Failure or Nephrotoxicity[b]	9 (32.1)	12 (80.0)	-47.9 (-74.5 to -21.2)	<.001	-59.9
Day-28 All-Cause Mortality or Renal AEs[c]	6 (21.4)	9 (60.0)	-38.6 (-67.7 to -9.5)	<.01	-64.3
Clinical Failure or Renal AEs[d]	9 (32.1)	12 (80.0)	-47.9 (-74.5 to -21.2)	<.001	-59.9

[a]Composite outcome of either Day-28 all-cause mortality or a post-baseline increase in serum creatinine ≥1.0 mg/dL.
[b]Composite outcome of either clinical failure at test of cure or a post-baseline increase in serum creatinine ≥1.0 mg/dL.
[c]Composite outcome of either Day-28 all-cause mortality or adverse event of renal failure, renal failure acute or renal impairment.
[d]Composite outcome of either clinical failure at test of cure or adverse event of renal failure, renal failure acute or renal impairment.

Figure 3. Efficacy Endpoints in Patients with cUTI/AP, by Timepoint (mCRE-MITT)



[a] Composite of either microbial eradication or presumed eradication at respective visit.
* 4 Patients in the M-V arm were indeterminate/not assessed at TOC.
† 3 Patients in the M-V arm were indeterminate /not assessed at TOC.

Conclusions

Monotherapy with M-V in CRE infections, including immunocompromised, renally impaired, and prior antibiotic failure patients, resulted in the following:

- M-V showed improvement over BAT in efficacy endpoints in all infection types studied, including HABP/VABP, BSI, cUTI, and cIAI.
- M-V demonstrated a lower rate of renal-related adverse events and increases in serum creatinine compared to BAT (**Poster #1879**).
- M-V was associated with reduction in poor outcomes compared to BAT including failure-nephrotoxicity and mortality-nephrotoxicity on exploratory risk-benefit analyses across all infection types combined.
- M-V is a potent new option for treatment of KPC-driven carbapenem resistance.
- Based on the totality of these results, the independent Data Safety Monitoring Board recommended discontinuing randomization to BAT.

Disclosures

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