#P0285

MEROPENEM-VABORBACTAM VERSUS BEST AVAILABLE THERAPY FOR CARBAPENEM-RESISTANT ENTEROBACTERIACEAE INFECTIONS IN TANGO II: OUTCOMES IN PATIENTS WITH CANCER

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ABSTRACT

Background: Patients with cancer, particularly those with hematological malignancies, are at high risk for mortality due to infections caused by carbapenem-resistant Enterobacteriaceae (CRE). Meropenem-vaborbactam (M-V) is a novel cyclic boronic acid beta-lactamase inhibitor combination developed for treatment of serious gram-negative infections, including CRE. This analysis reports outcomes among oncology patients in TANGO II, a randomised, open-label comparative trial with best available therapy (BAT) in patients with complicated urinary tract infection (cUTI), acute pyelonephritis (AP), hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP), bacteremia, and complicated intra-abdominal infection (cIAI), due to known or suspected CRE.

Methods: Eligible patients were randomised 2:1 to M-V (2g/2g every 8h) or BAT for 7 to 14 days. BAT included any of the following, alone or in combination: carbapenems, aminoglycosides, polymyxin B, colistin, tigecycline, or ceftazidime-avibactam (monotherapy only). Clinical cure was defined as complete resolution of symptoms such that no further antimicrobial therapy was required. Microbiologic cure was defined as a composite of microbial eradication or presumed eradication at respective visit. Outcomes were assessed at end of treatment (EOT) and test of cure (TOC) visits.

Results: 72 patients were randomised. 50 (69.4%) had a baseline pathogen. 22 (30.5%) had a prior diagnosis of malignancy (14 active diagnoses, 8 inactive-past diagnoses). 15 of these patients presented with a CRE pathogen (mCRE-MITT) and with infection types of: bacteremia (53.3%), cUTI/AP (20%), HABP/VABP (13.3%), and cIAI (13.3%). In this group, 10 (66.7%) patients were also immunocompromised. Clinical cure, microbiologic cure, and Day 28 mortality among the oncology patients in the mCRE-MITT population are shown. M-V was associated with fewer drug-related adverse events (16.7% vs. 33.3%), any serious adverse event (25.0% vs. 77.8%), and renal adverse events (8.3% vs. 22.2%) than BAT.

Outcomes in Oncology, mCRE-MITT	M-V (N = 8) n (%)	BAT (N = 7) n (%)	All (N = 15) n (%)	Difference (95% CI)[1]
Clinical cure at EOT	7 (87.5)	1 (14.3)	8 (53.3)	+73.2 (21.0, 96.4)
Clinical cure at TOC (EOT+ 7 days)	6 (75.0)	0 (0)	6 (40.0)	+75.0 (27.1, 96.8)
Microbiologic cure at TOC (EOT+7 days)[2]	5 (62.5)	0 (0)	5 (33.3)	+62.5 (14.3, 91.5)
All-cause mortality Day 28	1 (12.5)	4 (57.1)	5 (33.3)	-44.6 (-82.2, 10.2)

EOT, end of treatment; TOC, test of cure.
[1] Exact test.
[2] Microbiologic cure is a composite of microbiologic eradication and presumed eradication at TOC.

Conclusion: In patients with a prior diagnosis of malignancy who presented with confirmed CRE infections, treatment with M-V was associated with higher clinical and microbiologic cure rates and a lower mortality rate than BAT (mCRE-MITT population). M-V is a promising treatment option for CRE in this population.

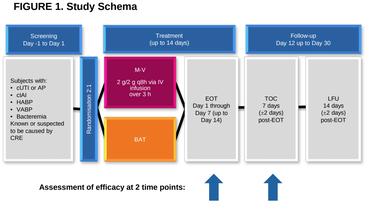
INTRODUCTION

- Patients with underlying malignancies, particularly hematologic malignancies, are at increased risk for carbapenem-resistant Enterobacteriaceae (CRE) infections due to factors such as: underlying immunosuppression, impaired mucocutaneous barrier mechanisms (e.g., due to mucositis), prolonged hospital stay, and empiric and/or prophylactic use of broad-spectrum antimicrobial agents.[1]
- Among patients with solid tumors or hematologic malignancy and CRE infections, mortality rates are extremely high – up to 60%.[2]
- The current best available therapy involves treatment with one or more of a limited pool of antimicrobial agents that have been associated with high levels of toxicity, potential for interaction with immunosuppressive and chemotherapeutic agents, or emergence of resistance.[3-5]
- Meropenem-vaborbactam (M-V) is a novel beta-lactam/beta-lactamase inhibitor combination developed for the treatment of serious gram-negative infections, including CRE.[6,7]
- TANGO II is a Phase 3, multi-center, open-label comparative trial of the efficacy and safety of M-V versus best available therapy (BAT) in the treatment of serious infections caused by known or suspected CRE pathogens.
- Unlike most Phase 3 studies of new antimicrobials, TANGO II included patients with underlying and active malignancy, including immunocompromised patients, patients with hematological malignancies, and hematopoietic stem cell transplant recipients.[8-11]

METHODS

- Phase 3, multi-center, randomised, 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 randomised 2:1 to monotherapy with M-V or BAT for 7-14 days (**FIGURE 1**).
  - BAT included (alone or in combination): a carbapenem, aminoglycoside, polymyxin B, colistin, tigecycline, or (monotherapy only) ceftazidime-avibactam.

FIGURE 1. Study Schema



cUTI, complicated urinary tract infection; AP, acute pyelonephritis; HABP/VABP, hospital-acquired/ventilator-associated bacterial pneumonia; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant Enterobacteriaceae; EOT, end of therapy; TOC, test of cure; LFU, last follow up.

- 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 days) CRE pathogen, requirement of ≥7 days IV antimicrobial therapy, confirmed cUTI/AP, HABP/VABP, bacteremia, or cIAI.
- Key exclusion criteria: receipt of more than 24 hours of potentially effective antimicrobials (unless documented clinical failure), immediate life-threatening disease, known infection due to NDM, VIM, IMP or OXA-encoded beta-lactamase.
- Efforts to reduce bias included blinded investigator (BI), blinded adjudication committee (BAC), and a source control adjudication committee (for cIAI).
- Clinical cure was defined as a complete resolution of signs/symptoms such that no further antimicrobial therapy was required and was assessed by the BI and primary investigator (PI) at two time points: end of therapy (EOT) and test of cure (TOC). In cases where the assessment by the BI and PI differed, clinical cure was adjudicated by the BAC.
- Patients with underlying malignancy included all those with the key terms "cancer" or "malignancy" reported in the medical history in TANGO II. A manual review of all patients and the qualifying key terms was then performed to ensure validity, in which one patient with a key term of "malignant melanoma removal" was removed from the population. Malignancy was determined by the PI to be either ongoing or not ongoing.
- Immunocompromised status was defined as underlying active leukemia, lymphoma, prior transplant or splenectomy on medical history; any active receipt of immunosuppressive drugs including selective immuno-suppressants, calcineurin inhibitors, or high-dose systemic steroids (equivalent to ≥20 mg/day of prednisone for ≥2 weeks); or neutropenia (ANC <1000 cells/mm^3) at any point during the study period.
- Difference estimates and 95% confidence intervals (CI) were obtained by Fisher's Exact test of equality.

RESULTS

- 72 patients with known or suspected CRE were enrolled.
  - 50/72 (69.4%) were subsequently confirmed to have a qualifying (CFU criteria, corresponding sterile source) baseline gram-negative pathogen (micro-MITT population).
  - 22/72 (30.5%) had an underlying malignancy; 13 of these were immunocompromised.
  - 70/72 (97.2%) received study drug (MITT population).
    - 43/70 (61.4%) had a qualifying CRE pathogen (mCRE-MITT population).
      - 15 had an underlying malignancy, of which 10 of these were immunocompromised.
      - The most common infection type was bacteremia (8/15 patients, 53.3%) followed by cUTI/AP (3/15 patients, 20.0%) (**TABLE 1**).

TABLE 1. Baseline Characteristics of Patients with Cancer (mCRE-MITT population)

	M-V (n=8) n (%)	BAT (n=7) n (%)
Underlying malignancy[1]		
Leukemia/lymphoma[1]	4 (50.0)	2 (28.6)
Any solid tumor[1]	4 (50.0)	5 (71.4)
Metastatic solid tumor[1]	2 (25.0)	2 (28.6)
Non-metastatic solid tumor[1]	2 (25.0)	3 (42.9)
Immunocompromised	6 (75.0)	4 (57.1)
Infection type		
cUTI/AP	2 (25.0)	1 (14.3)
cIAI	0 (0)	2 (28.6)
HABP/VABP	2 (25.0)	0 (0)
Bacteremia	4 (50.0)	4 (57.1)

[1] Patients may have more than one malignancy reported.

- A significantly higher clinical cure rate at EOT and TOC was observed in patients with cancer who were treated with M-V compared to those treated with BAT (mCRE-MITT population). The difference in clinical cure rate at EOT was 73.2% (95% CI: 21.0% to 96.4%) and at TOC was 75.5% (95% CI: 27.1% to 96.8%) for patients treated with M-V.
- A significantly higher microbiologic cure rate at TOC (62.5%, 95% CI: 14.3% to 91.5%) was observed in patients with cancer treated with M-V (mCRE-MITT population).
- M-V treatment was associated with a significant decrease in Day 28 mortality (absolute risk reduction 44.6%, 95% CI: -82.2% to 10.2%) (**TABLE 2**).

TABLE 2. Efficacy Outcomes Among Patients With Cancer (mCRE-MITT population)

Outcomes in Oncology, mCRE-MITT	M-V (n=8) n (%)	BAT (n=7) n (%)	All (n=15) n (%)	Difference (95% CI)[1]
Clinical cure at EOT	7 (87.5)	1 (14.3)	8 (53.3)	+73.2 (21.0, 96.4)
Clinical cure at TOC (EOT+ 7 days)	6 (75.0)	0 (0)	6 (40.0)	+75.0 (27.1, 96.8)
Microbiologic cure at TOC (EOT+7 days)[2]	5 (62.5)	0 (0)	5 (33.3)	+62.5 (14.3, 91.5)
Day 28 mortality	1 (12.5)	4 (57.1)	5 (33.3)	-44.6 (-82.2, 10.2)

[1] According to Fisher's Exact test. ; [2] Microbiologic cure is a composite of clinical cure and microbiologic eradication.

- Among patients with cancer, M-V was associated with fewer drug-related adverse events (16.7% vs. 33.3%), serious adverse events (25.0% vs. 77.8%), and renal adverse events (8.3% vs. 22.2%) than BAT (**TABLE 3**).

TABLE 3. Adverse Events and Safety Endpoints Among Patients With Cancer (Safety population)

Adverse Events in Oncology, Safety population	M-V (n=12) n (%)	BAT (n=9) n (%)	Total (n=21) n (%)
Treatment-emergent adverse events (TEAEs)			
Any	9 (75.0)	9 (100.0)	18 (85.7)
Drug-related	2 (16.7)	3 (33.3)	5 (23.8)
Serious adverse events			
Any	3 (25.0)	7 (77.8)	10 (47.6)
Drug-related	0 (0)	0 (0)	0 (0)
Study drug discontinuation due to TEAEs	1 (8.3)	2 (22.2)	3 (14.3)
Study discontinuation due to TEAEs	1 (8.3)	4 (44.4)	5 (23.8)
Renal-related safety endpoints	1 (8.3)	2 (22.2)	3 (14.3)
Hematuria	1 (8.3)	0 (0)	1 (4.8)
Renal failure	0 (0)	1 (11.1)	1 (4.8)
Renal failure acute	1 (8.3)	1 (11.1)	2 (9.5)

CONCLUSIONS

- Patients with underlying malignancies (solid tumor and leukemia/lymphoma) are at increased risk for infection and mortality due to CRE pathogens.
- Approximately one-third of patients in TANGO II with a qualifying baseline CRE pathogen (mCRE-MITT population) had a prior or ongoing malignancy.
- Treatment of patients with cancer, including those immunocompromised, with meropenem-vaborbactam was associated with a significantly higher clinical and microbiologic cure rate compared to treatment with best available therapy.
- Treatment of patients with cancer, including those immunocompromised, with meropenem-vaborbactam was associated with a 44.6% absolute risk reduction in Day 28 mortality (95% CI: -82.2% to 10.2%).
- Treatment with meropenem-vaborbactam was associated with decreased adverse events, including serious adverse events and renal-related adverse events, than BAT among patients with cancer.
- Meropenem-vaborbactam is a promising new treatment option for CRE infections in this vulnerable patient population.

DISCLOSURES

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