Clinical Outcomes with Meropenem-Vaborbactam (M-V) by Extended-Spectrum β-Lactamase (ESBL) Production in TANGO 1, a Phase 3 Randomized Trial vs Piperacillin-Tazobactam (P-T)

The Medicines Company
3013 Science Park Rd.
San Diego, CA 92121 USA
8 Sylvan Way
Parsippany, NJ 07054 USA

Keith S. Kaye[1], Thomas M. File[2], Andrew Shorr[3], Jeff Loutit[4], Michael Dudley[4], Olga Lomovskaya[4], Marcus Zervos[5]

[1]University of Michigan Health System, Ann Arbor, MI, USA; [2]Summa Health System, Akron, OH, USA; [3]Washington Hospital Center, Washington, DC, USA; [4]The Medicines Company, San Diego, CA, USA; [5]Henry Ford Health System, Detroit, MI, USA

Revised Abstract

Background: M-V is a new beta-lactam/beta-lactamase inhibitor combination developed to treat gram-negative infections. This analysis compared outcomes with M-V and P-T in patients enrolled in a Phase 3 trial of complicated urinary tract infection (cUTI) according to beta-lactamase production.

Methods: TANGO 1 was a randomized Phase 3 study of the efficacy, safety, and tolerability of meropenem-vaborbactam compared with piperacillin-tazobactam in the treatment of adults with cUTI or acute pyelonephritis (AP). Subjects with cUTI or AP were randomized 1:1 to receive M-V (2 g/2 g via 3-hr infusion) or P-T (4 g/0.5 g via 30-min infusion) every 8 hours. Patients with a ≥1 baseline pathogen at ≥10^5 CFU/ml were included in the microbiologic modified intent-to-treat (m-MITT) population (popn). Beta-lactamase production in baseline isolates was determined following whole genome sequencing and screening for beta-lactamase genes and expression assays for chAmpC. Overall success (clinical cure and microbial eradication) rates at the End of IV Therapy (EOIVT) and the Test of Cure (TOC) visits were assessed for pathogens with a frequency of ≥15 subjects with the pathogen at baseline.

Results: 550 patients were enrolled; 374 (68%) were included in the m-MITT popn. 31.3% of isolates in the M-V group and 28% in the P-T group were shown to produce various class A extended spectrum beta-lactamases (ESBLs), class A carbapenemases (KPC), class B metallo-beta-lactamases, plasmidic AmpC, and class D beta-lactamases. Increased expression of chromosomal AmpC was also detected in several isolates. For patients with baseline pathogens producing these beta-lactamases, overall success was similar at EOIVT between the 2 treatment groups (see table). At TOC, the rate of overall success was higher in subjects in the M-V group compared with the P-T group in ESBL-producing isolates.

Pathogen	Beta-lactamase Status	Overall Success by Baseline Pathogen and Beta-lactamase Status at EOIVT	
		M-V (N=192)	P-T (N=182)
Escherichia coli	+	27/27 (100.0)	25/27 (92.6)
	-	92/94 (97.9)	82/87 (94.3)
Klebsiella pneumoniae	+	20/21 (95.2)	15/15 (100.0)
	-	8/8 (100.0)	10/11 (90.9)
Enterobacter cloacae species complex	+	7/7 (100.0)	3/3 (100.0)
	-	2/2 (100.0)	1/1 (100.0)
Proteus mirabilis	+	4/4 (100.0)	2/2 (100.0)
	-	2/2 (100.0)	10/10 (100.0)
Pseudomonas aeruginosa	+	2/2 (100.0)	6/8 (75.0)
	-	2/2 (100.0)	2/2 (100.0)

Conclusions: In this post hoc analysis, overall success rates were slightly higher with M-V compared with P-T across assessment time points, irrespective of beta-lactamase status.

Background

Meropenem-vaborbactam (M-V) is a new beta-lactam/beta-lactamase inhibitor combination developed to treat serious gram-negative infections due to multidrug-resistant organisms, such as complicated urinary tract infection (cUTI) or acute pyelonephritis (AP). This analysis compared outcomes in patients with cUTI or AP enrolled in a Phase 3 trial of M-V versus piperacillin-tazobactam (P-T), according to beta-lactamase production at baseline.

Methods

TANGO I was a Phase 3, multicenter, double-blind, double-dummy, randomized, parallel-group study of the efficacy, safety, and tolerability of M-V compared with P-T in the treatment of adult patients with cUTI, including AP. The study design is outlined in **Figure 1**.

- Eligible patients with cUTI or AP were randomized 1:1 to receive M-V (2 g/2 g via 3-hr infusion) or P-T (4 g/0.5 g via 30-min infusion) every 8 hours.
- Total duration of therapy was 10 days and included treatment with either M-V or P-T, as well as step-down therapy to oral levofloxacin in patients meeting pre-specified criteria.

Patients who received at least one dose of study drug were included in the modified intent-to-treat population (MITT).

- Patients who met criteria for the MITT population and who had a ≥1 baseline pathogen at ≥10^5 CFU/mL were included in the microbiologic modified intent-to-treat population (m-MITT).

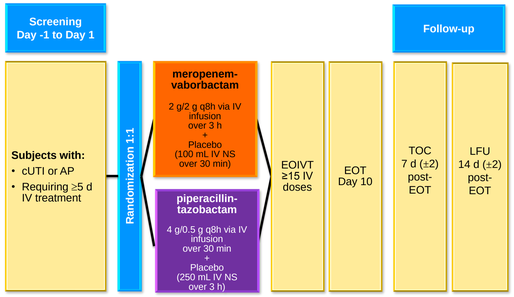
Molecular testing was performed on a subset of bacterial isolates by the central laboratory.

- For Enterobacteriaceae, determination of beta-lactamase production was performed for baseline isolates that had ESBL phenotype according to CLSI guidelines[1] and those that were non-susceptible to meropenem.
- For *Pseudomonas aeruginosa* or *Acinetobacter baumannii*, beta-lactamases were determined for baseline isolates that had ceftazidime MIC ≥16 µg/ml or meropenem MIC ≥8 µg/ml.
- Beta-lactamases were identified based on whole genome sequencing followed by the screen for beta-lactamase genes.
- Beta-lactamase producers were defined based on positive assays for class A ESBL, class D, pAmpC, or carbapenemase, or based on overexpression or moderate expression of chAmpC.
- This analysis assessed overall success rates at the end of IV therapy (EOIVT) and test of cure (TOC) visits by baseline pathogen and beta-lactamase status.
- Only pathogens with a frequency of ≥15 patients were included in the analysis.

The primary efficacy endpoint per FDA criteria was overall success in the m-MITT population at the EOIVT visit.

- Overall success was defined as a composite outcome including both clinical outcome and microbiologic outcome.
- Overall success at the TOC visit was a key secondary efficacy endpoint.

Figure 1. Study Schema



EOIVT, end of IV treatment; EOT, end of treatment; TOC, test of cure; LFU, last follow-up.
Note: For subjects with cUTI, isolation of pathogens was obtained after any indwelling urinary catheter or instrumentation was removed or replaced (if removal is not clinically acceptable).

Results

550 patients were enrolled in the study, with 545 receiving at least 1 dose of study drug (either M-V or P-T) constituting the MITT population.

- 37 (68%) patients had ≥1 pathogen at ≥10^5 CFU/mL at baseline and were included in the m-MITT population.
- Beta-lactamase status for common baseline gram-negative pathogens are listed in **Table 1**.

Distribution of beta-lactamases in Enterobacteriaceae and *P. aeruginosa* across the 2 treatment groups is summarized in **Table 2**.

- CTX-M-15 was the most common type of beta-lactamase amongst the ESBL-producing strains of Enterobacteriaceae (45/52 isolates of *Escherichia coli*, 30/35 isolates of *Klebsiella pneumoniae*, and 6/9 isolates of *Enterobacter cloacae* or *E. cloacae* spp. complex). Other CTX-M-type beta-lactamases included CTX-M-1 (1 isolate), CTX-M-3 (5), CTX-M-14 (2), CTX-M-27 (3), CTX-M-55 (3).
  - Another frequently encountered beta-lactamase with a broad spectrum of activity was class D OXA-1/OXA-30.
  - A total of 24 isolates of *E. cloacae* or *E. cloacae* spp. complex (10), *K. pneumoniae* (5), *E. coli* (5), *Citrobacter freundii* or *C. freundii* spp. complex (2), *P. mirabilis* (2) expressed plasmid-encoded AmpC enzymes.
  - Small numbers of baseline pathogens overexpressed chromosomally encoded beta-lactamase enzymes. In particular, chAmpC was overexpressed in 6 isolates of *E. cloacae* or *E. cloacae* spp. complex and in one isolate of *C. freundii* spp. complex.
- In *P. aeruginosa*, the most frequent beta-lactamases were class C PDC (pyruvate dehydrogenase complex) enzymes with 10 out 15 isolates producing the following enzymes: PDC-1 (2), PDC-3 (1), PDC-8 (2), PDC-12 (1), and PDC-16-(1).
  - Four isolates produced CTX-M beta-lactamases, CTX-M-3 (3) and CTX-M-15 (1).
  - One isolate produced class B carbapenemase (IMP-1).

In the m-MITT population, 28.9% of subjects were infected with organisms possessing beta-lactamase genes (104/359). This ratio was similar across study groups, with 29.3% of isolates in the M-V group (54/184) and 28.6% of isolates in the P-T group (50/175) being beta-lactamase producers.

- For patients with a beta-lactamase–producing isolate at baseline, overall success was similar at EOIVT between the 2 treatment groups and between ESBL and non-ESBL (**Figure 2**).
- At TOC, overall success was higher in patients in the M-V group compared with the P-T group in beta-lactamase–producing isolates (**Figure 2**).
- These results were similar to those seen in the MITT population.
- Overall success rates at EOIVT and TOC timepoints by baseline pathogen and beta-lactamase status are shown in **Table 3**.

Figure 2. Overall Success Rates at EOIVT and TOC in Beta-lactamase– Producing Isolates (m-MITT Population)

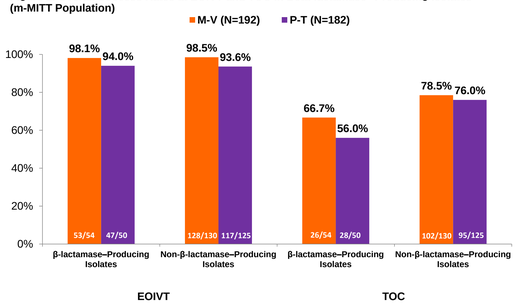


Table 1. Baseline Pathogen by Beta-lactamase Status (m-MITT Population)

Pathogen (no. of subjects) β-lactamase Presence	M-V (N=192) n/N' (%)	P-T (N=182) n/N' (%)
Escherichia coli		
All Beta-lactamases	27/125 (21.6)	27/117 (23.1)
Carbapenemases	0/125 (0.0)	0/117 (0.0)
Klebsiella pneumoniae		
All Beta-lactamases	21/30 (70.0)	15/28 (53.6)
Carbapenemases	1/30 (3.3)	1/28 (3.6)
Proteus mirabilis		
All Beta-lactamases	4/6 (66.7)	2/12 (16.7)
Carbapenemases	1/6 (16.7)	1/12 (8.3)
***Enterobacter cloacae* species complex**		
All Beta-lactamases	7/10 (70.0)	3/5 (60.0)
Carbapenemases	0/10 (0.0)	0/5 (0.0)
Pseudomonas aeruginosa		
All Beta-lactamases	2/5 (40.0)	8/10 (80.0)
Carbapenemases	1/5 (20.0)	0/10 (0.0)

Percentage is calculated using N' as the denominator, where N' is the number of subjects who had the specific baseline pathogen.

Table 2. ESBL, Class D, and Class C Beta-lactamase Production Among Baseline Pathogens of *Enterobacteriaceae* (m-MITT Population)

Pathogen β-lactamase	Class	M-V (N=192) n	P-T (N=182) n
Enterobacteriaceae			
CTX-M-15	A	43	38
CTX-M-15 (1, 3, 14, 27, 55)	A	10	4
SHV-12	A	1	2
KPC-2	A	1	1
OXA-1/OXA-30	D	26	31
VIM-1	B	1	1
ACT-like (14, 20, 23, 25)	C	7	3
SMY-like (2, 4, 46, 99)	C	8	5
DHA-1	C	1	0
chAmpC overexpressed	C	4	2
Pseudomonas aeruginosa			
CTX-M-3	A	0	3
CTX-M-15	A	1	1
PDC (1, 3, 8, 12, 16, 31)	C	2	8
chAmpC overexpressed	C	0	1
IMP-1	B	1	0

Table 3. Overall Success Rates by Baseline Pathogen and Beta-lactamase Status at EOIVT and TOC (m-MITT Population)

Pathogen	β-lactamase Status	Overall Success at EOIVT: M-V (N=192) n/N' (%)	Overall Success at EOIVT: P-T (N=182) n/N' (%)	Overall Success at TOC: M-V (N=192) n/N' (%)	Overall Success at TOC: P-T (N=182) n/N' (%)
Escherichia coli	+	27/27 (100.0)	25/27 (92.6)	19/27 (70.4)	16/27 (59.3)
	-	92/94 (97.9)	82/87 (94.3)	77/94 (81.9)	66/87 (75.9)
Klebsiella pneumoniae	+	20/21 (95.2)	15/15 (100.0)	12/21 (57.1)	6/15 (40.0)
	-	8/8 (100.0)	10/11 (90.0)	5/8 (62.5)	7/11 (63.6)
***Enterobacter cloacae* species complex**	+	7/7 (100.0)	3/3 (100.0)	5/7 (71.4)	3/3 (100.0)
	-	2/2 (100.0)	1/1 (100.0)	2/2 (100.0)	0/1 (0.0)
Proteus mirabilis	+	4/4 (100.0)	2/2 (100.0)	3/4 (75.0)	2/2 (100.0)
	-	2/2 (100.0)	10/10 (100.0)	0/2 (0.0)	7/10 (70.0)
Pseudomonas aeruginosa	+	2/2 (100.0)	6/8 (75.0)	2/2 (100.0)	3/8 (37.5)
	-	2/2 (100.0)	2/2 (100.0)	2/2 (100.0)	1/2 (50.0)

Conclusions

In this post hoc analysis, overall success rates were slightly higher with M-V compared with P-T across EOIVT and TOC timepoints, irrespective of beta-lactamase status.

- Approximately 30% of subjects in the m-MITT population were infected with organisms possessing ESBL genes at baseline.
- At EOIVT, outcomes were similar between the M-V and P-T groups, as well as between beta-lactamase–producing organisms and non-beta-lactamase–producing organisms.
- At TOC, outcomes in both study groups were lower in the pooled subjects with beta-lactamase–producing organisms compared with subjects without beta-lactamase–producing organisms.
- Outcomes were numerically higher in the M-V group compared with the P-T group regardless of the presence of beta-lactamase–producing organisms.

Disclosures

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References

1. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing*, 26th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

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