

Considerations in the Development of Beta-Lactamase Inhibitor Combination Products for MDR Pathogens

Michael N. Dudley, PharmD, FCCP
Rempex Pharmaceuticals, San Diego, CA USA

Beta-lactamase Inhibitor Combinations

- **Key advantage** in restoring efficacy of beta-lactam antimicrobial agents (safety and efficacy)
 - **Successful products** in clinical use for over 3 decades
 - Resulted in **over a decade of additional use** of important agents
- Demonstrates that **overcoming resistance mechanism** can restore activity of highly useful antibiotic class in vitro and in vivo (translation)
 - Not possible with agents with novel mechanism of action
- Important approach for treatment of **MDR pathogens**
 - Enables dual approach for overcoming resistance
 - Can exploit prior knowledge about prior antibiotic to increase certainty
 - Preclinical information on inhibition of beta-lactamase and restoration of beta-lactam activity in preclinical systems has translated to efficacy in the clinic

Configurations of Beta-lactamase Inhibitor (BLI) Products in Clinical Development*

Antibiotic	BLI	Number of Products in Clinical Development
“Approved”	“New”	4
“New”	“Old”	1
“New”	“New”	1
[none]	“New”	(none)

*: From www.clinicaltrials.gov, accessed 12 Oct 2012

- Prior Information on one or both components of the combination product can promote certainty:
 - “Confirmation” of prior information that may be known about a component of the combination (e.g., the beta-lactam)
 - Generation of new information on efficacy and safety of each component of the combination product

Beta-lactamase Inhibitor Combinations are Highly Pathogen-Focused

- Makes use of prior knowledge of key class of drugs (beta-lactams) and all known resistance mechanisms (beta-lactamases, efflux, porin mutations)
- Importance of assessment of contribution of each component of combination product
 - Enables comparison of impact of combination therapy of organisms “resistant” to beta-lactam alone
 - “microbiological deconvolution”: assessment of effects of each component of the combination against patient’s pathogen (“internal control” within a trial- see later)
- Important implications for Tier B and Tier C trial designs

Sections of the Draft Addendum (July 2012) of Special Relevance to BL/BLI Combination Products

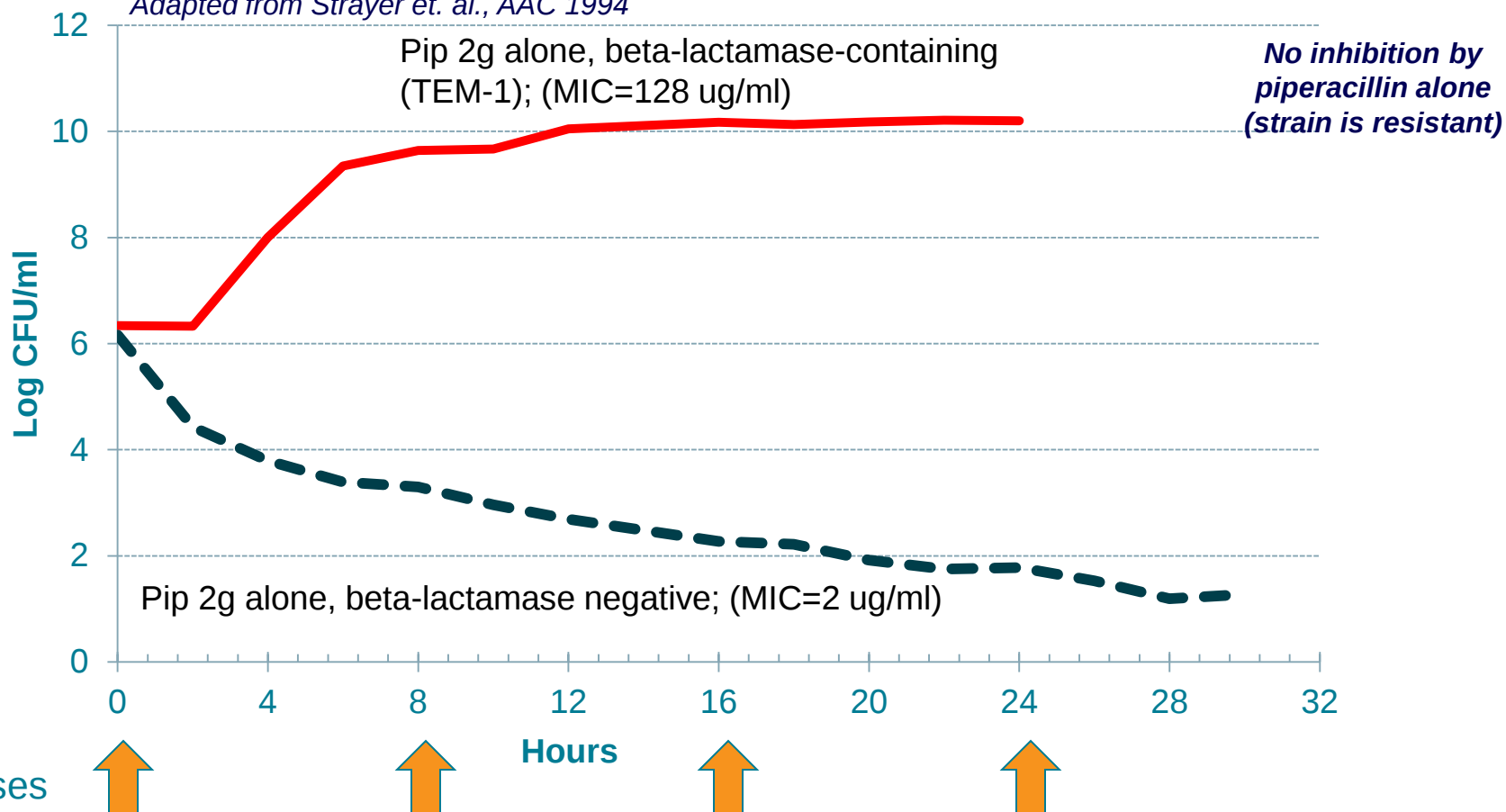
- Section 3.4- “Situations in which only limited clinical data can be generated”
 - 3.4.3: Combinations would take into account *“relevant prior data for the known active substance”*
 - *“Total evidence for safety and efficacy”*
 - Prior information on PK-PD relationships, safety, mechanisms of resistance are helpful
 - *“..relevant prior data”*
 - Should also apply for a BLI
- 3.4.3.ii: PK-PD analyses
 - Need to consider *“...other mechanisms of resistance and effects of multiple mechanisms...”*
- Pathogen specific statements in SMPC
 - SMPC should describe activity that beta-lactam/BLI has activity vs. pathogen, with or without beta-lactamase production

Role of Preclinical Efficacy Data

- Animal or in vitro hollow fiber data can unequivocally demonstrate the effects of exposures of the BLI on bacterial killing by partner beta-lactam
- These data show restoration of activity of partner beta-lactam and should approach that seen in “susceptible strains”
 - Identifies key PK-PD index for both beta-lactam and BLI
 - Preclinical data can be compelling to show that one does not have to exclusively rely on designs and enrollment of patients with “resistant” pathogens into clinical studies

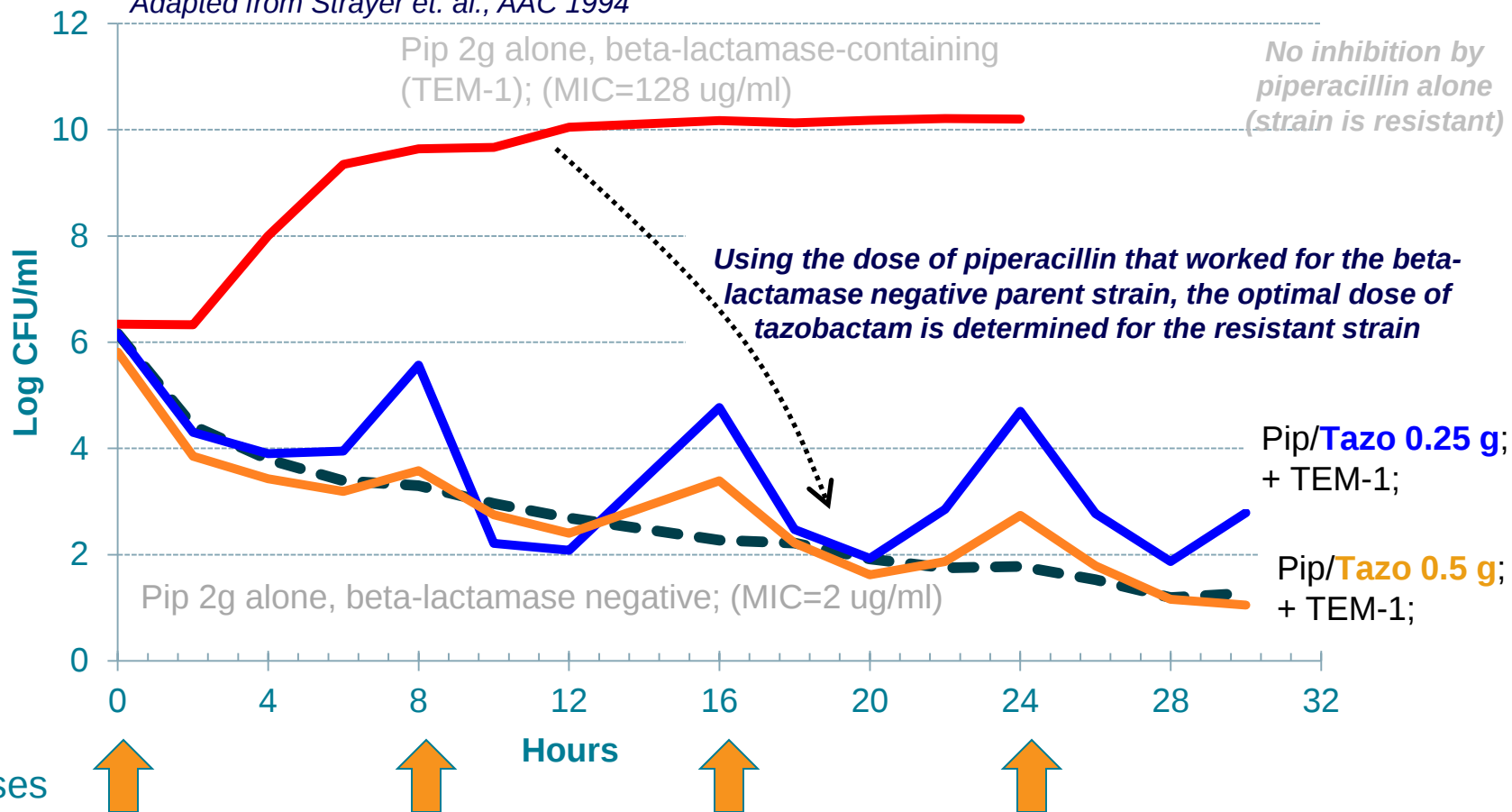
Hollow Fiber PD Models Using Isogenic Strains of *E. coli* with or without Beta-Lactamase Can Readily Identify Doses and Exposures of **Tazobactam (Tazo)** to Restore Sensitivity to Human Exposures of **Piperacillin (Pip)**

Adapted from Strayer et. al., AAC 1994



Hollow Fiber PD Models Using Isogenic Strains of *E. coli* with or without Beta-Lactamase Can Readily Identify Doses and Exposures of **Tazobactam (Tazo)** to Restore Sensitivity to Human Exposures of **Piperacillin (Pip)**

Adapted from Strayer et. al., AAC 1994



Proof of Efficacy and Pharmacometrics

- PK-PD analysis
 - Insures there is “pharmacodynamic” potentiation (not drug-drug interaction that elevated beta-lactam exposures (e.g., PK “boosting”))
 - Translation of preclinical data
- Pharmacometric analysis in patients can help quantify effect of potentiator
 - See efficacy at (low) $T > MIC$ for beta-lactam which is not expected to provide efficacy.
 - For example:
 - Beta-lactam $MIC = 128$ to beta-lactam; $T > MIC < 5\%$ - no efficacy expected
 - MIC with BLI is 2 ug/ml when tested with fixed conc of BLI
 - » One sees efficacy with combination with documented exposures of beta-lactam not expected to be active → pharmacometric POC
- There is a level of “internal control” in the trial by treatment of “susceptible organisms” treated with the combination

Assessment of Proof of Efficacy vs. Resistant Pathogens

Outcome	BL/BLI Rx: Beta-lactam “R”	BL/BLI Rx: Beta-Lactam “S”	Comparison Group
Clin Response	X%	Y%	Z%

- X ~ Y: Indicates BLI is effective
 - Comparisons of levels of efficacy for beta-lactam with or without BLI effect in R pop
 - Need to adjust for differences in patient population that have MDR pathogens
- Combined Data from Beta-lactam R and S: Overall response rate:
 - Comparison with Z as a randomized active comparator (Tier B)
 - Comparison with Z as external or historical control (Tier C)

- Old Beta-Lactam/New BLI
 - Does one need to run beta-lactam alone as a control group to show superiority?
 - NO
 - Can't do superiority trial as it would be unethical to treat patient with BL alone in setting of resistance
 - One can deconvolute data for each patient using MIC testing and PK to determine the contribution of each component of the combination to patient result.
 - Comparisons with historical or “external” data for “old” beta-lactam with combination product vs. susceptible organism—but need to adjust since patients who get MDR pathogens are often different than those with susceptible ones
- New BL/Old BLI or New BL/New BLI
 - Same considerations as above, plus
 - **All information on efficacy informs for the new beta-lactam, regardless of presence or absence of “resistance”**

Clinical Safety

- Consideration of prior knowledge of safety of drug or class
- Old BL/New BLI
 - How does addition of BLI change known safety profile of antibiotic? (e.g., use of prior data cited in Addendum)
- New BL/Old BLI
 - There is likely no known safety profile of the previously marketed BLI administered alone, since it was used as a fixed combination with another agent, and thus its safety profile may be confounded.
- New BL/New BLI
 - All information is new and defines safety profile of combination product

Beta-Lactamase Inhibitor Combination Products: Summary of Key Points

- Beta-lactamase inhibitor combination products are a well-established approach for overcoming resistance, often in MDR strains
- Approach is well-suited for a pathogen-directed approach in drug development
- Importance of “MIC deconvolution” of contribution of each component of combination product for each pathogen in patient studies
 - Patient with “sensitive” organisms can provide “internal control” for effects with inhibitor, providing that there are adjustments for differences in patient populations
- Tier B and Tier C approaches in development can be applied