PK/PD Based Selection of Drugs for Combination Therapy : AUC Shift

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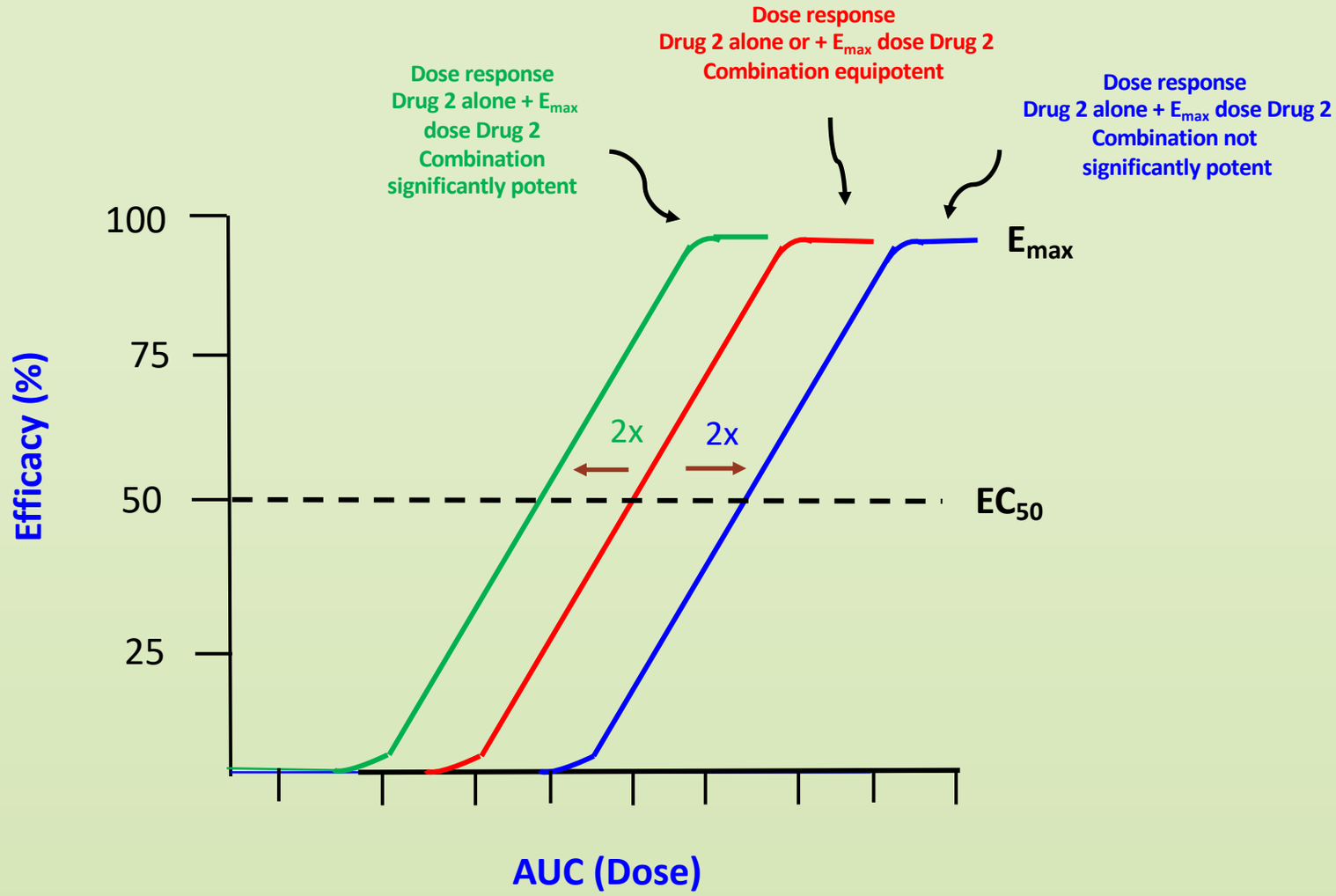
Combining two drugs for therapy should be based on efficacy (E_{max}), potency (EC_{50}) and toxicity of the combination compared to the efficacy and potency of the individual drugs. In the AUC based approach the changes in AUC linked to E_{max} and EC_{50} can be used to assess combination PD



Experimental design parameters for assessing Pharmacodynamic benefit of combination

Dose Response	Efficacy (% response)	Potency (AUC)
Drug 1	$E_{max,D1}$	$EC_{50,D1}$
Drug 2	$E_{max,D2}$	$EC_{50,D2}$
Drug 2 + Drug 1*	$E_{max,D2}$#	$EC_{50,D2}$#

*At E_{max} dose (AUC) of Drug 1

Determined at constant E_{max} AUC of Drug 1

Assumption: *No drug-drug interaction between Drug 1 and Drug 2. If DDI present then drugs should not be combined or should be assessed for risk benefit*

Potential Outcome	Inference based on Efficacy & Potency	Decision based on adverse effects of combination
$EC_{50,D2}^{\#} \leq 2*EC_{50,D2}$	If E_{max} same, combination potent. If E_{max} decreases, combination not effective	If absent – Set combination with altered E_{max} dose of drug 2 If seen- titrate drug 2 with $E_{75\%}$ or $E_{50\%}$ dose of drug 1
$EC_{50,D2}^{\#} \sim EC_{50,D2}$	If E_{max} remains same, combination equipotent	If absent- combination still good to reduce resistance development
$EC_{50,D2}^{\#} \geq 2*EC_{50,D2}$	If E_{max} remains the same, combination not beneficial	Combination not effective