模型引导的早期抗肿瘤临床试验设计

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早期临床试验总体考虑

早期试验总体考虑

剂量相关的发现

1. 最大耐受量/最大推荐剂量 (MTD/MRD)
2. 限制性毒剂量(DLT)
3. II期推荐剂量（RP2D）

PK相关的发现 (含大于10%代谢物)

1. PK特征：参数、线性范围、蓄积
2. PK-EKG：TQT /C-QTc /E-QTc
3. PK外因：如食物与药物的相互作用
4. PK内因：如体重、性别、年龄、基因
5. 物质平衡/10%代谢产物
6. 剂型评价与选择 (常做BE/比较PK)

PD相关的发现 （疗效与安全）

1. 剂量-暴露-反应（疗效/AE）关系
2. 个体间差异：如影响因素，生物制剂免疫原性(ADA)
3. 剂量发现：目标人群的优化治疗剂量（PoC）
4. 生物标志物发现（biomarker）

制定总体研究策略

1. 安全第一 vs MTD发现
2. 前进法 vs 后退法
3. 剂量递增 vs 高效完成
4. 社会责任 vs 伦理获益

实例写法

1. 主要终点
   - 后续试验最大推荐剂量（MRD）
   - PK特征
2. 次要终点
   - 病人的有效性评价
   - 不良反应指标的安全性评价
3. 探索性终点
   - 生物标志物评价
   - 免疫原性评价（ADA抗体）

实例：中国早期试验结果的FDA反馈

中国企业在国内完成I期试验后，拟在FDA申请II期临床试验，FDA要求补充分析（2019）：

1. … via quantitative modeling to evaluate steady state exposures at 100 mg Q3W in the current proposed population.

2. … exposure-response relationships with PD-L1 receptor occupancy

3. … Pool clinical pharmacokinetic, pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated dose-response and exposure-response analyses for dose optimization.

忽视PK/PD设计与建模分析，特别是血样采集困难，是目前国内临床试验最大通病之一

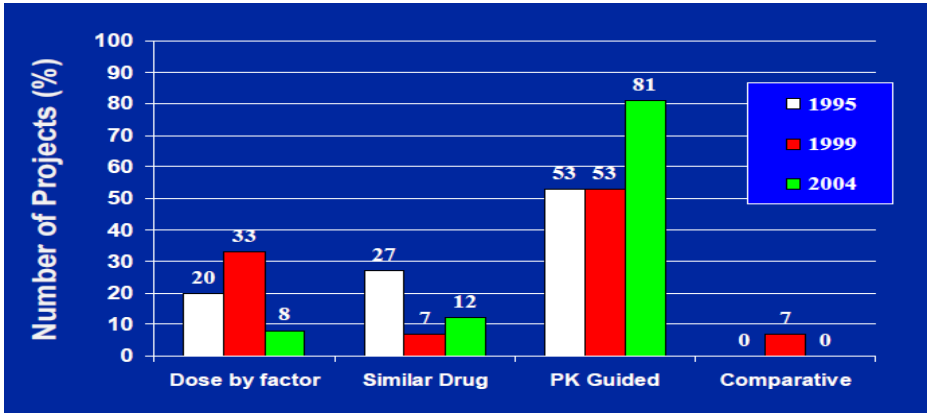
早期试验的新模式

1. **FIH前：转化医学分析报告**
   - 首次人体试验方案设计前完成，提供FIH试验设计所需的全部信息，如起始剂量、最大剂量及预测结果等
   - 研究方法：整合所有临床前药理与毒理、体内与体外数据，通过PK/PD建模与模拟分析
2. **FIH中：方案要点/操作**
   - PK/PD模型引导的剂量递增为最优选择
   - 动态试验设计（adaptive design）成为常态，试验期间数据实时分析、方案实时修正
   - 试验药+安慰剂 = 8+2 远优于 6+2 （ADR 发现率 30% vs 20%）
3. **FIH后：扩展试验**
   - 制定研究策略，如篮式设计
   - 动态试验设计：SAD → MAD，健康人→ 患者，单中心 → 多中心…
   - 专家委员会：学术支撑
   - 风险控制措施：安全保证

起始剂量与递增方案

起始剂量(SD)

1. NOAEL (dose by factor, FDA)
2. MABLE (minimum anticipated biologic effect level, EMA)
3. PK引导法 (the pharmacokinatically guided approach)
4. 类似药法 (the similar drug approach)
5. 比较法 (the comparative approach)



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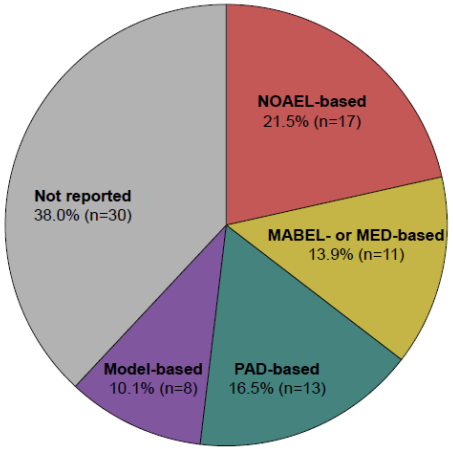


生物制剂

1. NOAEL法

- 第一步：列出毒理实验中NOAEL (mg/kg)
- 第二步： NOAEL转换至人体等同量 (HED)
- 第三步：选择最合适动物的HED
- 第四步：选择安全因子(SF, 通常≥ 10)，求最大推荐起始量 (MRSD) = HED/SF*体重kg
- 第五步：多个动物的MRSD的选择，如接近药理学活性剂量（PAD）

Species	NOAEL (mg/kg/d)	BSA-CF	HED (mg/kg)	MRSD (mg)
rat	50	x 0.162	8.1	49*
dog	2	x 0.541	1.08	6.5*

*Safety Factor = 10

不足之处：

- 使用是剂量，不是暴露
- 基于43个抗肿瘤药和体表面积推导而来
- 没有验证
- 安全因子SF属人为所定

2. MABLE法

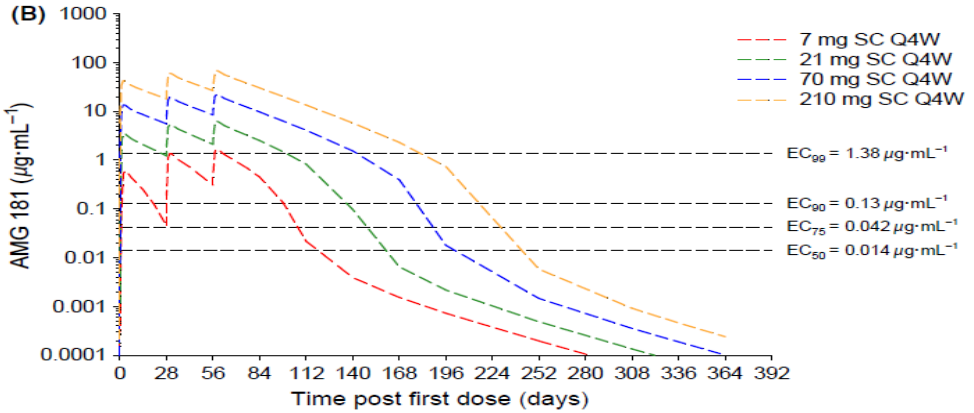
- 通常选用最低预期生物效应（minimal anticipated biological effect level, MABLE）预测MRSD， MABLE剂量包括疗效和安全性反应剂量，如最小药理活性剂量（pharmacologically active dose, PAD）、最小有效量(minimum effective dose, MED)等，故MABLE通常是综合了多项生物效应数据。
- MABLE法的本质与PK/PD建模法相同，即人与动物剂量换算基于的原理：**相同的暴露，相同的效应**
- PK的暴露可选 Cmin，Cmax，Cave，AUC，根据临床前实验确定
- 优势明显，FIH之前应有一个详细的**转化医学报告**
  1. 提供更多信息：如起始剂量（SD）、给药间隔、警示量（NOAEL）、对应于最大治疗量（MD）的最大暴露（maximum exposure）、治疗剂量区间（anticipated therapeutic dose range, ATD)等信息；
  2. 以暴露进行人体外推时，通常无需人为规定的安全校正因子（SF）；
  3. 可以完整地预测出FIH给药方案（剂量，给药间隔，等）
  4. 既考虑毒性，又考虑药效放大反应。

2006年6名健康志愿者在英国注射单抗TGN1412起始剂量1 h 左右出现剧列反应，最终导致1 人全部足趾和部分手指切除。2016 年法国进行BIA10-2474 多次给药健康志愿者人体耐受性试验，1名连续5 次口服50 mg 7 d 后死亡，另外5 人出现脑损伤。EMA推荐用MABLE法

1. EMA. Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (2018.2)
2. Drug Design, Development and Therapy 2016:10 4005–4016

通常步骤：

1. PK：从非临床动物PK外推人体PK参数（如NONMEM法，异数放大法，PBPK），即剂量-暴露关系；
2. PD：临床前药理/毒理剂量建立剂量-效应模型，计算PD参数（Emax, EC50）；
3. PK/PD：基于以上剂量-暴露-效应关系，模拟人体不同给药方案，获得MRSD、NOAEL、MD等



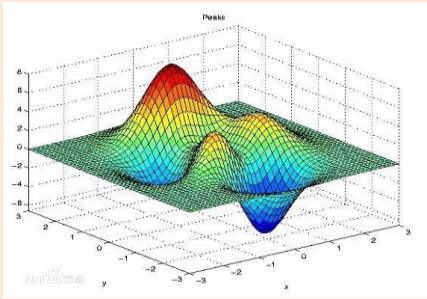
- **特例1**：作用靶点清楚的药物，当缺乏有效数据、无法建立PK/PD模型时，MABLE主要依据体外试验的平衡解离常数（KD）数据进行推算: **RO=[C]/KD+[C]** RO为受体占有率（receptor occupancy）、C为人体血浆中的药物浓度、KD为受体配体平衡解离常数。一般受体抑制剂采用10%-20%的RO来推算确定临床起始剂量，受体激动药应选择RO小于10%
- **特例2**：无PK数据，通过PD模型求出动物ED50(kg)，再换算人体HED，MRSD=HED/SF，多数情况下 SF=10

1. Applications of human pharmacokinetic prediction in first-in-human dose estimation. *AAPS J. 2012;14(2):262–281*
2. On the anticipation of the human dose in first-in-man trials from preclinical and prior clinical information in early drug development. ***Xenobiotica***. 2007;37:1331–1354
3. Prediction of clinical pharmacokinetics of AMG 181, a human anti-a4b7 monoclonal antibody for treating inflammatory bowel diseases. ***Pharma Res Per***, 3(1), 2014, e00098, doi: 10.1002/prp2.98

3. PK引导法

步骤与实例

1. AUC_{animal}: 靶值在犬NOAEL= 17.3 mg.h/L
2. Cl_{man}: 人用预测值 = 16.0 L/h
3. SD = AUC_{animal} × CL_{man} =17.3×16.0 = 277 mg
4. SD × SF = 277 × 1/10 = 28 mg



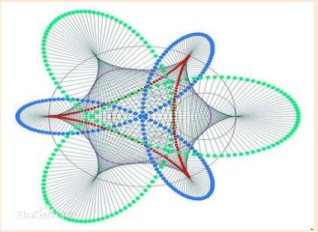
另外PK参数计算，SD = 动物体内稳态血药浓度(C_{SS}) × 预测的人体内V_d

- 使用浓度外推，而不是剂量外推
- AUC靶值：定义了系统暴露的靶值（如AUC）
- CL_{man}由异数放大法或PBPK法获得（定量药理学方法）
- 不足：有AUC靶值(上限)，但与药理学活性剂量（PAD）无关联，无AUC下限。

4. 类似药法

实例与步骤：新药=ND，类似药=OD

1. 犬NOAEL(OD)= 0.1 mg/kg/day
2. 犬NOAEL(ND)= 2.0 mg/kg/day
3. OD安全有人用剂量 = 10 mg
4. 起始剂量 SD = 10 mg × 0.1/2.0 × 1/10 = 20 mg



没有类似药，则无法采用此法

5. 比较法

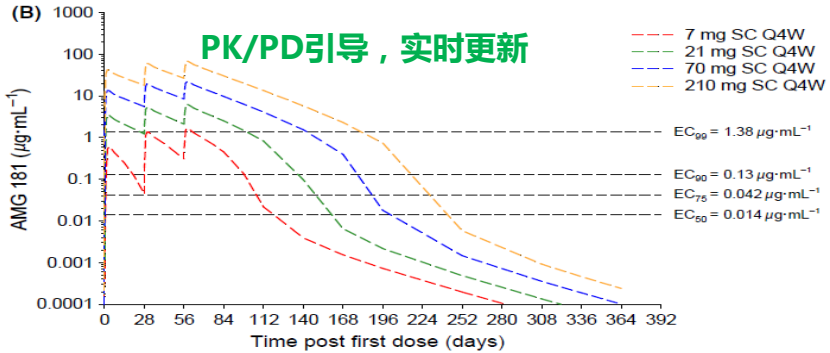
- 使用不同方法，获得不同的SD
- 毒性大的药物，或窄治疗窗药，选择较小值
- 毒性小的药物，或宽治疗窗药，选择较大值

Method	HED	Safety F	SD (mg)
1. FDA Guidance	65	10	6.5
2. Similar Drug	250	10	25
3. PK Guided	277	10	28

剂量递增：PK/PD引导的原理

1. 算术级递增(arithmetic progression) (如1, 2, 3, 4, 5, 6倍X等), X为起始剂量（下同）
2. 几何级递增(geometric progression) (如1, 2, 4, 8, 16, 32倍X等)
3. Fibonacci 法递增 (如1, 2, 3.3, 5, 7倍X等)
4. PK/PD引导法: 根据FIH当前已获得的暴露-反应曲线陡度，实时分析并调整后续试验的剂量递增幅度，属于安全、高效的方法。
   - ✓ 于前期结果综合评估后决定下一剂量，提供更快速和安全完成FIH研究，并减少接受亚治疗剂量的患者数。
   - ✓ 安全指标的PD阈值(threshold)，如QTc, BP, HR, 血糖，肝肾功能
   - ✓ 在每个剂量水平，将PK和PD数据并入交互式更新的PKPD模型

Ref.1 EMA guideline for first-in-human
Ref2. Xenobiotica, 2007; 37: P1343



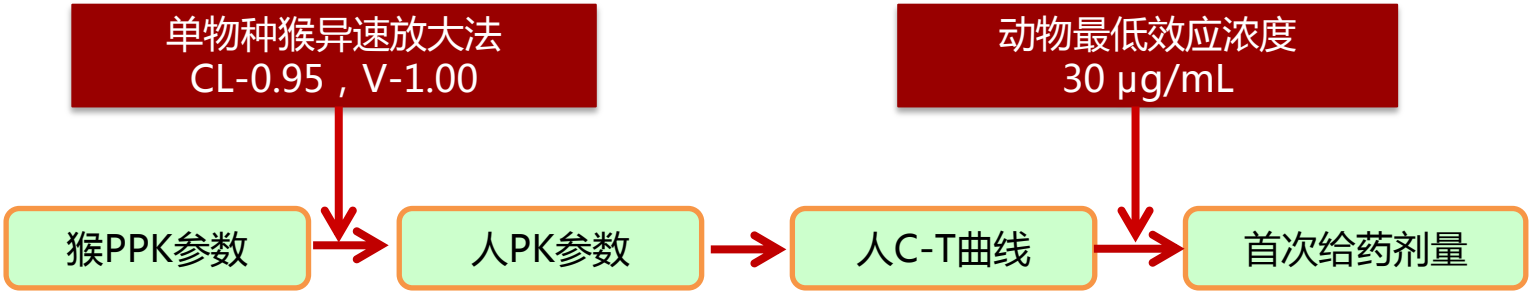
递增比例确定原则：

1. 暴露反应关系的陡度：越陡，递增比例越小
2. 不良反应严重性和可逆性：越严重，递增比例越小
3. 潜在不良事件可监测性：不可监测，递增比例越小
4. 是否为非线性PK：非线性，递增比例越小
5. AUC_{MABLE}/AUC_{NOAEL}：比值越大，递增比例越小
6. 受体激动剂较阻断剂的递增比例小

实例：单抗药的FIH方案设计

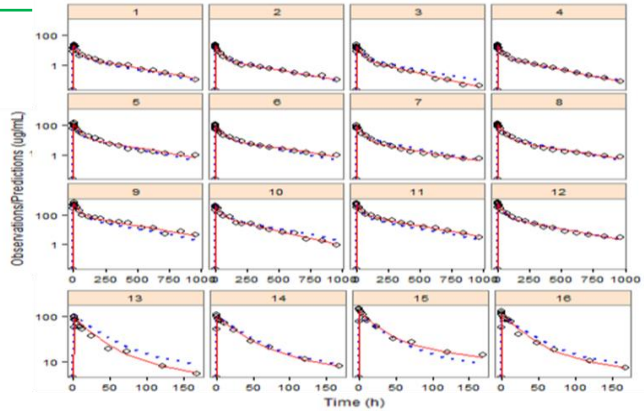
- Hab 1 ：人源化修饰型嵌合IgG1单克隆抗体
- 适应症：抗肿瘤
- 给药方式：静脉滴注

食蟹猴16只，分为4组，每组4只，平均体重2.5kg
- 单次给药3组分别单次静脉给予 1mg/kg、5mg/kg、25mg/kg
- 多次给药1组使用5mg/kg

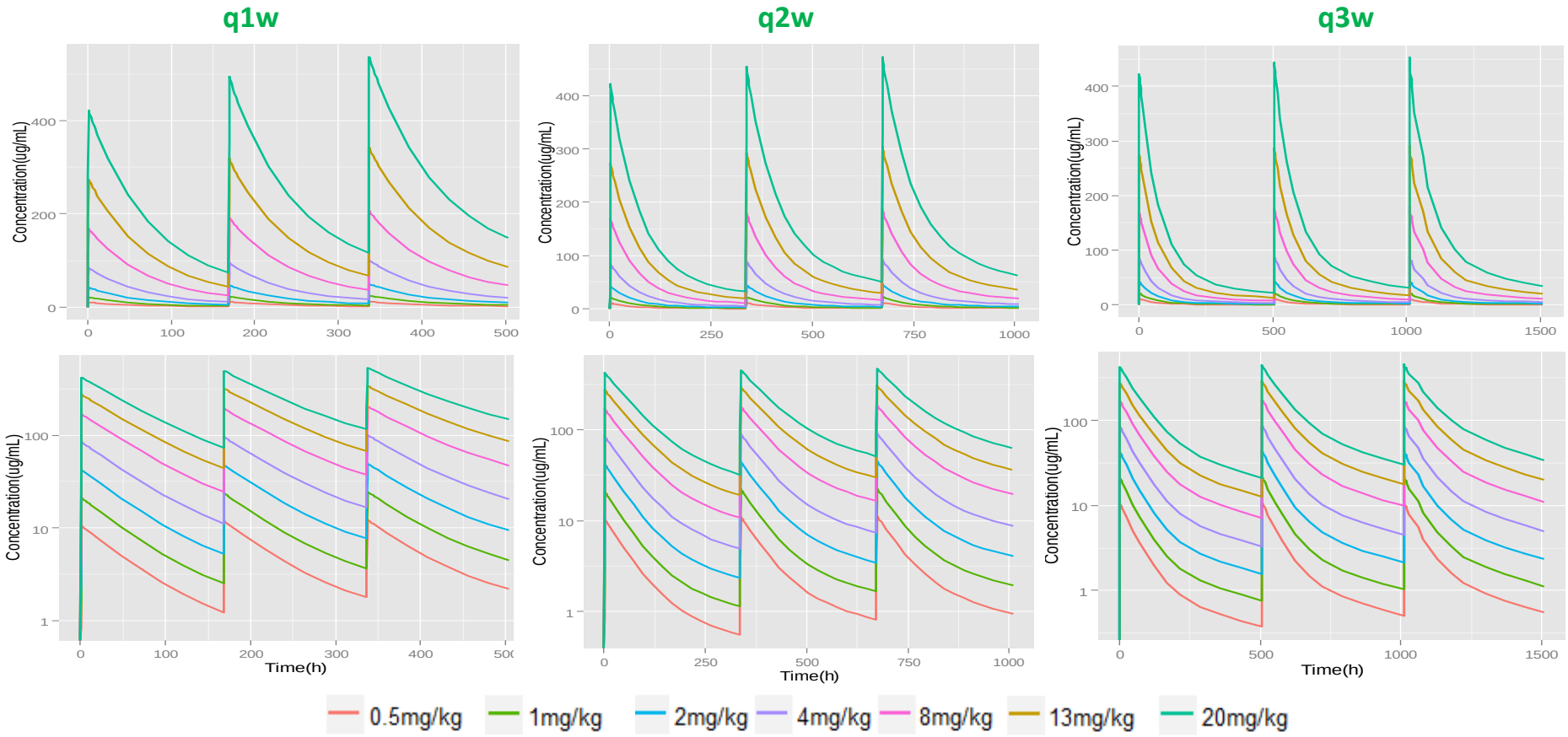


Monkey PK Parameters	Estimates (SE%)	1000 Bootstrap Median(95% CI)
Pharmacokinetic parameter		
V_1，mL/kg	47.4(3.4)	47.4(44.3~50.5)
V_2，mL/kg	73.4(5.9)	73.4(65.7~83.3)
CL_1， mL/h/kg	0.711(5.1)	0.713(0.648~0.799)
CL_2，mL/h/kg	0.573(10.9)	0.58(0.461~0.714)
Interindividual variability		
V_1， %	11.8(33.1)	11.2 (7.00~15.1)
V_2，%	11.4(61.8)	11.0 (0.300~16.8)
CL_1，%	18.9(35.7)	18.2(12.0~26.2)
CL_2，%	25.8(81.8)	22.95(0.300~52.7)
Residual variability		
Proportional error， %	16.1(10.8)	16.0 (14.1~17.6)

Human PK	Human 60kg	Human 70kg
V_1, mL/kg	47.4	47.4
V_2, mL/kg	73.4	73.4
CL_1, mL/h/kg	0.606	0.602
CL_2, mL/h/kg	0.489	0.485



- 动物间的异数放大法预测效果良好
- 从动物PK参数桥接到人的PK参数，其合理性有较大的把握



人体C-T曲线预测：不同给药剂量（0.5 – 20 mg/kg），滴注1h

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剂量	首次给药		3次谷浓度			第3次给药后		
mg/kg	Cmax	AUC 0-inf	C0	C0	C0	Cmax,ss	AUCss	Cav
gtt, q3w	ug/mL	h*ug/mL	ug/mL	ug/mL	ug/mL	ug/mL	h*ug/mL	ug/mL
0.5	10.50	1044	0.38	0.50	0.55	11.00	1039	2.06
1	21.10	2115	0.76	1.03	1.12	22.10	2111	4.19
2	42.10	4330	1.57	2.12	2.32	44.30	4341	8.61
4	84.30	9008	3.30	4.51	4.95	88.80	9111	18.08
8	169.00	19066	7.16	9.92	11.00	179.00	19604	38.90
13	274.00	32767	12.60	17.70	19.80	292.00	34080	67.62
20	422.00	53034	21.10	30.30	34.30	452.00	56115	111.34

- 人体1 mg/kg，Cmax = 21μg/mL< MABEL，q3w
- PK采样时间点：首次给药静脉输注前和结束时，以及在完成静脉输注后0.5h、2h、4h、8h、12h、24h、2d、3d、5d、7d、9d、12d、15d、21d。
- 猴药代动力学实验最高剂量未出现毒性反应
- 猴25mg/kg → Cmax≥441 μg/mL, AUC=31069 h*μg/m
- 人体1 mg/kg AUC、Cmax = 21倍猴安全剂量AUC、Cmax

- ❑ 起始剂量: 1mg/kg
- ❑ 最高剂量: 有效血浓度300 ug/mL, 约为10 mg/kg
- ❑ 给药间隔: q2w or q3w, 静滴1h

动物外推人体PK参数

动物外推人体的假设与原则

研究假设

1. 种属差异可以较正
2. 相同暴露，相同疗效，相同毒性

实施原则

- 血药暴露比剂量重要，重视游离浓度
- PK (AUC, Cave,ss, Cmax) 和 PD (IC50, ED50)连接与模拟分析重要
- 临床前数据应丰富：药动/药效，体内/体外，分子/细胞/整体，有效/安全
- 毒理试验重视敏感动物，有效试验重视不敏感动物
- 风险最小化措施：哨兵法等

Xenobiotica, October–November 2007; 37(10–11): 1331–1354

On the anticipation of the human dose in first-in-man trials from preclinical and prior clinical information in early drug development

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Abstract

The drug development process is divided into phases with decisions required on compound selection and promotion to each subsequent development phase. In preclinical drug development the main objective is to bring the compound into human trials and there is an inability of many preclinical information packages to predict clinical responses. Since clinical responses are functions of the dose, the human dose anticipation should be a key deliverable of any preclinical package of drug candidate. The human dose should be anticipated by integration of information from multiple sources, *in vitro* and *in vivo*, non-human and human, using a variety of methodologies and approaches. Prediction of human safe and active dose relies on the availability of validated animal models for effect. Although there are many exceptions to the rule, the paper defines a four-step approach for the anticipation of human dose for first-in-man trials: 1, characterization of non-human exposure-response relationships; 2, correction for interspecies differences; 3, diagnosing compound absorption, distribution, metabolism and excretion (ADME) properties and prediction of human pharmacokinetics; and 4, prediction of human dose–responses and dose selection for phase I protocols.

Keywords: *Prediction of first dose in man, preclinical, species differences, absorption, bioavailability, clearance, pharmacokinetic–pharmacodynamic (PKPD) integration, design of Phase I clinical trials*

Introduction

The conversion of a novel chemical or biological agent to a medicine proceeds along a path of milestones selected to reduce the risk of failure due to a lack of efficacy or safety.

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RIGHTSLINK

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1. NONMEM法

经典的群体法合并Dedrick Plot /Css-MRT/AS，形成NONMEM法(population approach)

1. 将不同动物血药数据或PK参数模拟的浓度建PK模型
2. 用不同生理学指标(如体重)作为协变量进行PK参数校正
3. 获得校正因子，并外推至人体

动物种属间PK、毒性、生物效应差异越大者，外推至人体的偏差较大，需选择接近人体的动物

协变量生理学指标

- 体重
- 寿命
- Conc/Css, Time/MRT
- 肝体积、重量、表面积
- 肾血流量和GFR
- 药物游离分数
- 血浆蛋白结合率
- …

吸收置于较宽的区间

- Ka
- F%

异数放大(AS法)纳入NONMEM法

假设药物在体内的消除过程为线性消除，以体内清除率CL 在不同种属间与体重(W) 存在某种关系，可用异数指数模型或固定指数模型表达

通过临床前获得的至少3 种不同种属动物的CL值，建立回归方程，得到的常数a，b 的值，依此推算人体总清除率，成为基本模型。

1. 当指数 b =0. 55 ~ 0. 70 时，可采用基本模型
2. 当指数b = 0. 70 ~ 0. 99 时，应将最大生命值(MLP) 代替体重，采用基本模型预测人体PK 参数，或按右式计算
3. 当指数 b > 1. 0 时，将用脑重(BrW) 代替体重，采用基本模型预测人体PK 参数，或按右计算

$$CL = aW^{b}$$

$$CL_{human} = CL_{animal} \times \left(\frac{W_{human}}{W_{animal}}\right)^{0.75}$$

$$CL_{human} = \frac{a\left(MLP \times CL_{animal}\right)^{b}}{8.18 \times 10^{5}}$$

$$CL_{human} = \frac{a\left(BrW \times CL_{animal}\right)^{b}}{1.53}$$

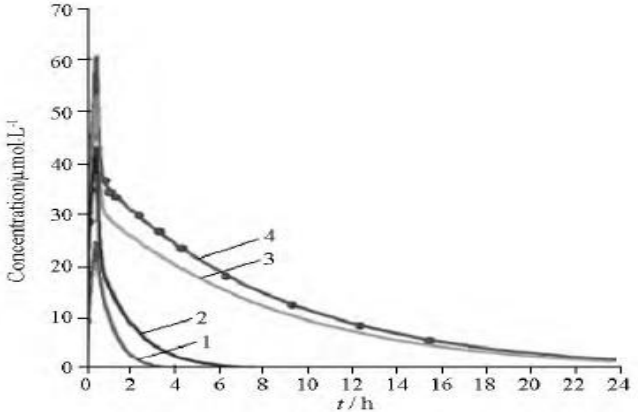
V_d用类似方法获得

2. PBPK法

生理药代动力学模型(PBPK) 可依次加入，逐步优化最终获得的种属间外推至人群PK参数

1. 药物理化特征参数(如脂溶性、组织亲和力等) 、
2. 种属特异生理特征参数(如组织器官重量、组织血流量等) 、
3. 药物游离分数
4. 描述药物生化处置过程的动力学参数，如最大反应速率(Vmax) 、米氏常数(Km) 等
5. 组织特异性代谢酶和转运体基因表达谱

- 其中的药物组织亲和力、脂溶性、酶代谢动力学等体外特征参数可通过体外实验测定
- 软件通常提供人体或常见实验动物的器官体积、表面积等生理参数，也可通过文献获得，组织或器官血流量与药物体内代谢、分布过程密切相关，应当注意的是啮齿类动物常采用大静脉血管，人体则常采用外周静脉血管，在进行药时曲线拟合时应充分考虑，设置不同参数



以咖啡因为例，由小鼠药时曲线简单外推可获得初始的人体PK 特征曲线(线1) ，模型中加入种属特异性生理学数据后，药物的分布相特征得到明显改善(线2) ，在此基础上又增加人体细胞CYP1A2活性和预测的组织药物浓度等药代动力学参数(线3) ，最后增加人和小鼠游离药物分数差异即血浆蛋白结合率等因素后再次拟合，获得与实测值(圆点) 非常接近的最终模型(线4)

3. IVIVC法

当药物主要是肝代谢时，可以用体外肝微粒体或离体肝细胞试验获得肝代谢速度，假设药物代谢酶在肝内为均匀分布，药物在肝的分布取决于肝灌流，不存在扩散屏障，且只有游离药物可以跨膜并占据酶代谢活性位点，当药物浓度远低于K_m时，可以按右式推算肝清除率C_{int}。V_{max}为最大反应速率，K_m为米氏常数，f_u为药物在肝微粒体或肝细胞中的游离分数，中Q_h为肝血流量，求人体肝清除率（CL_h）

$$CL_{int} = \frac{V_{max} / K_m}{f_u}$$

$$CL_h = \frac{Q_h \times f_u \times CL_{int}}{Q_h \times f_u \times CL_{int}}$$

当CYP450 酶和葡萄糖醛酸酶均参与药物代谢时，上式转化为右式。以两者之和计算人体肝总清除率。在此基础上，还可进一步考虑蛋白摄取、药物解离、pH值等因素，进一步优化模型，计算药物在人体肝的清除率

$$CL_{h,cyp} = \frac{Q_h \times f_u \times CL_{int,cyp}}{Q_h + f_u \times (CL_{int,cyp} + CL_{int,glu})}$$

$$CL_{h,glu} = \frac{Q_h \times f_u \times CL_{int,glu}}{Q_h + f_u \times (CL_{int,cyp} + CL_{int,glu})}$$

当药物主要肾排泄为主药物，常使用GFR和肾血流校正的异速放大方法。

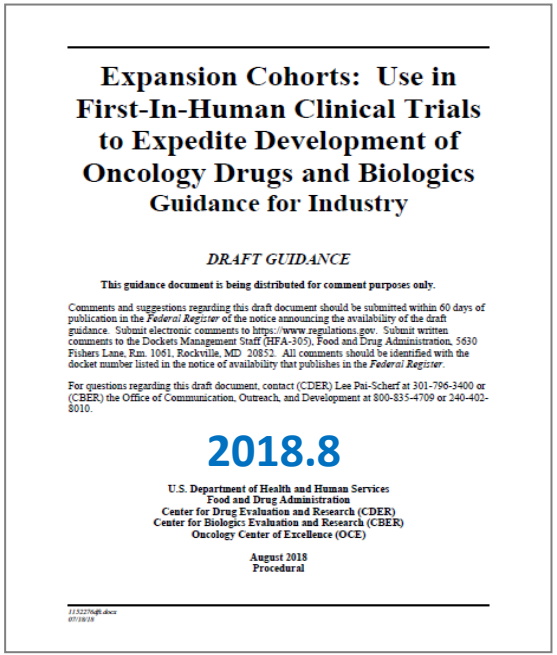
$$CL_R \approx \left[GFR \times f_{u,p} + \frac{CL_{secr} \times f_{u,b} \times Q_R}{CL_{secr} \times f_u + Q_R} \right] \times (1 - f_{reabs})$$

Peng Zou，et al（2012） Applications of Human Pharmacokinetic Prediction in First-in-Human Dose Estimation，The AAPS Journal

首次人体试验FIH

抗肿瘤药拓展队列的FIH

- 新指南将对**first-in-human**的临床试验进行指导，协助开设**多个可拓展的队列**，加速新药临床试验的进程。这些临床试验需要通过**生物标志物**对患者进行选择，并能基于科学方法，告诉我们哪些中期临床终点或替代终点可能与长期临床效果有关，从而更为便捷地找到药物的积极作用。
- 对于那些已经获得**突破性疗法**认定的新药来说，对于临床试验队列的扩增，则能通过筛选1期临床试验阶段发现的生物标志物，扩大招募的范围，以在无缝、连续的临床试验中对新药展开评估。
- 同时进展的多个独立队列，能让我们在单项大型临床试验中获得大量有用的信息，了解新药的安全性、新药在人体内吸收与分布有关的**药动学**、以及新药的抗**肿瘤活性**。只要为这些不同的重要问题设立单独的队列，它们就有望得到评估与解答。“通过**无缝的试验设计**，新药开发会变得更有效率，” Gottlieb博士说道：“**整个试验流程仅需要几百名患者就能完成**。”



Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lee Pai-Scherf at 301-796-3400 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

2018.8

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

August 2018
Procedural

[1] Implementing the 21st Century Cures Act: An Update from FDA and NIH - Oral Statement
[2] FDA官方网站

EMA哨兵法

It is considered appropriate to design the administration of the first dose in any cohort so that a **single subject** receives a single dose of the active IMP (often known as sentinel dosing). Flexibility in this approach is allowed but should be on a risk-proportionate basis with a clear scientific rationale for any proposals not to use this strategy.

When the study design includes the use of placebo it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort.

This approach is expected for all single and multiple dosing cohorts, in order to reduce the risks associated with exposing all subjects in a cohort simultaneously. This sentinel approach may continue or also start to be appropriate at later stages of study design, e.g. on the steep part of the dose response curve, when approaching target saturation levels or the maximum clinical exposure levels defined in the protocol, in case of non-linear PK, or in light of emerging clinical signs or adverse events that do not meet stopping criteria.

EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

20 July 2017
EMEA/CHMP/SWP/28367/07 Rev. 1
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Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products

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Keywords	First-in-human, phase I, early clinical trials, investigational medicinal product, risk mitigation, integrated protocols, multiple ascending dose, dose escalation.

2018.2

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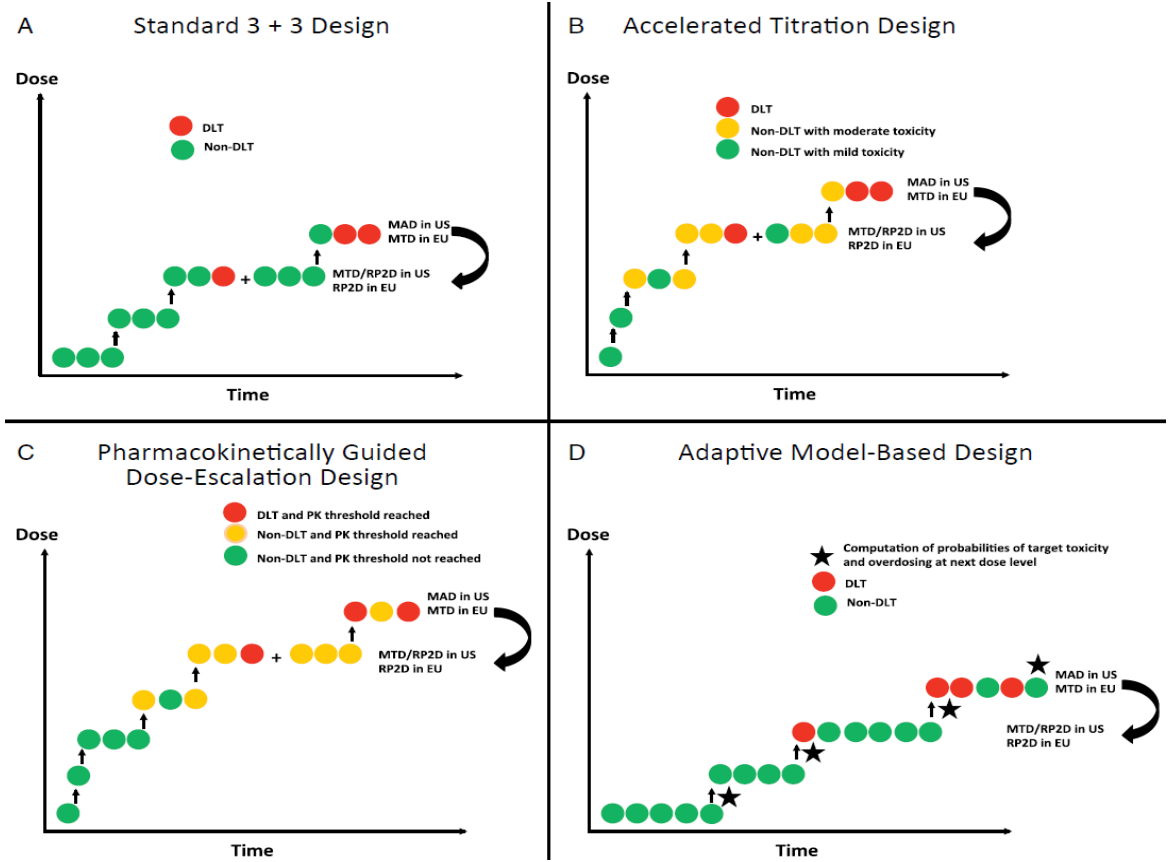
中国CDE：抗肿瘤药物临床试验技术指导原则： “每个剂量组不应同时入组2名或2名以上受试者” ?



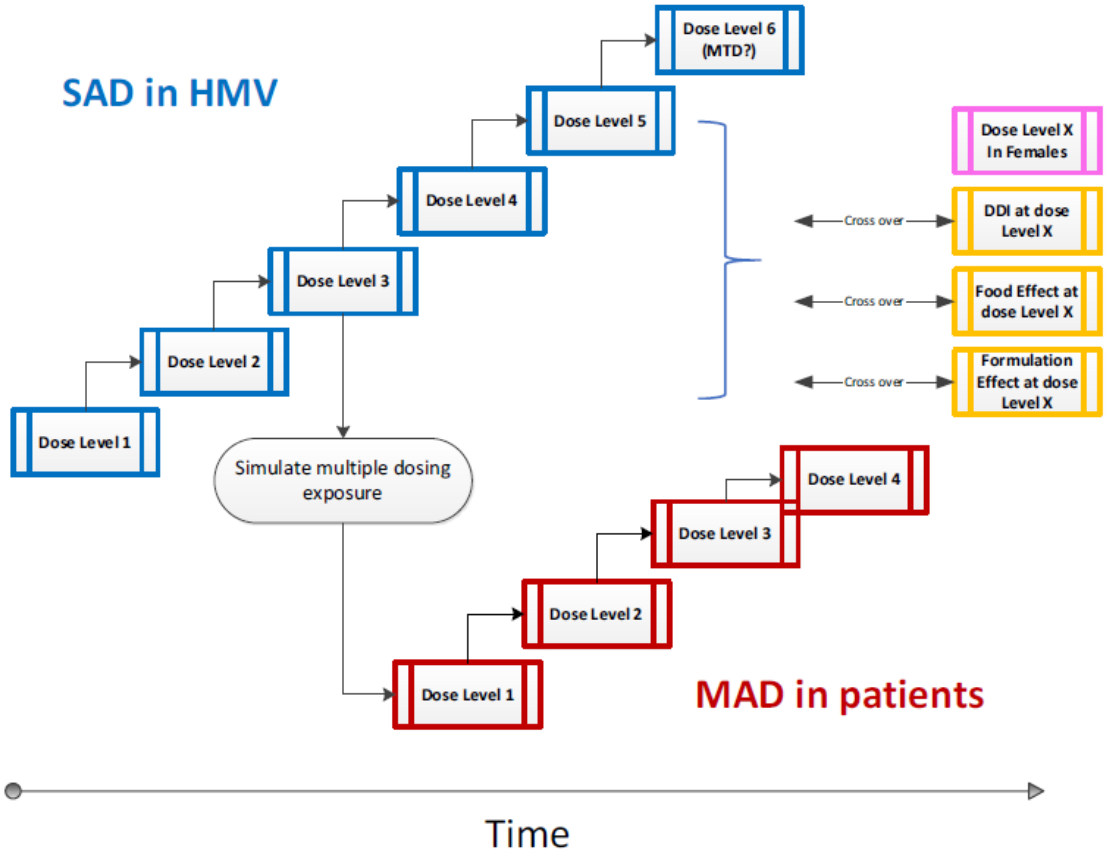
Cancer Control
2014, Vol. 21, No. 3

抗肿瘤细胞毒药
MAD = maximum administered dose
MTD = maximum tolerated dose
RP2D = recommended phase 2 dose

递增设计策略

篮式设计

- SAD/PK
- MAD/PK
- FE（食物影响）
- DDI
- 性别
- 剂型选择

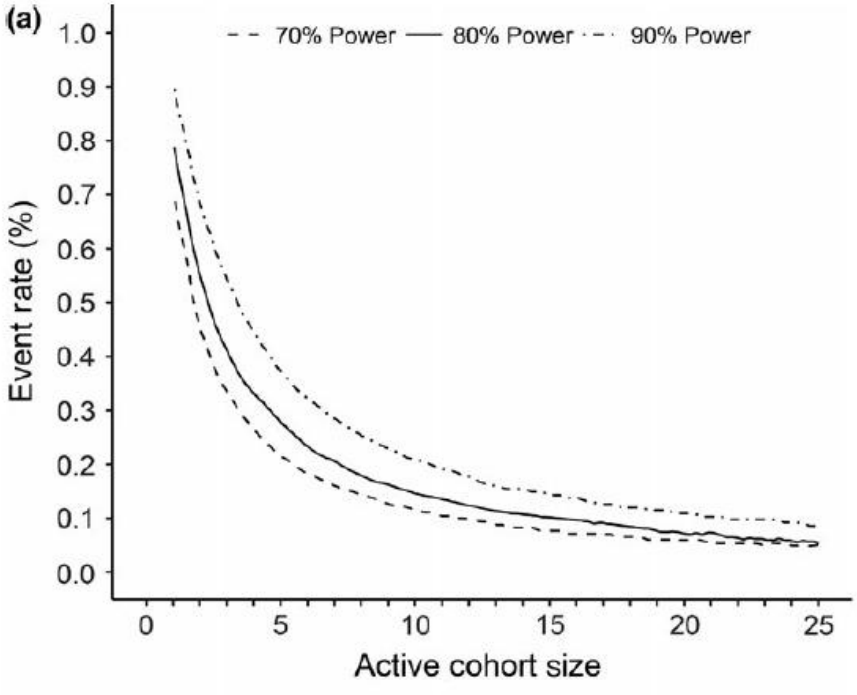


Clin Transl Sci (2019) 12, 6–19;
doi:10.1111/cts.12582

剂量递增试验的样本量

1. 一般进行双盲、安慰剂对照试验，不做估算样本量，总样本量通常大于40
2. 每个队列（剂量组）通常的样本量8-12例
   - T（受试药）6-10 人
   - P（安慰剂）2人
3. 从AE发现率（至少发现1例）的把握度为70%-80%来看
   - 6例大约发现发生率在30%的AE
   - 8例大约发现发生率在20%的AE
   - 10例大约发现发生率在15%的AE
4. 从PK参数（CL,V）精度precision要求（把握度=80%），受试药一般达到 8-12 例

T6+P2曾广泛采用，T8 + P2 是更好的选择



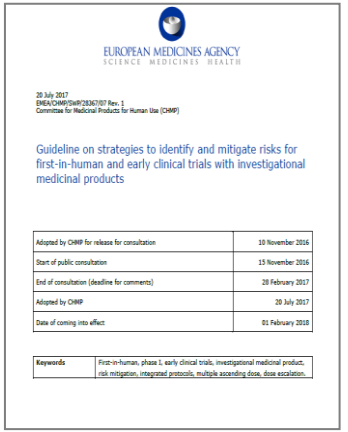
Clin Transl Sci (2019) 12, 6–19; doi:10.1111/cts.12582

递增剂量间隔时间

根据药物安全性和药效特点，灵活确定：

- 间隔1-3天：即完成24-72h的观察
- 间隔5-7个半衰期：主要针对短半衰期药
- 间隔7天：长半衰期药，相互间隔至少7天（Clinical Immunology 2014; 154: 37-46）

EMA: There should be an adequate period of time between the administration of treatment to these first subjects in a cohort and the remaining subjects in the cohort to observe for any reactions and adverse events. The duration of the interval of observation will depend on **the PK and PD** characteristics and the level of uncertainty associated with the product. At the end of the observation period, there should be a clearly defined review of all available data for the sentinel subjects before dosing of further subjects in the cohort, with dose stopping rules in place to prevent further dosing if any rule is met.



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给药剂量-时间-体积-速率-浓度

- 创新药在III期试验之前确定规格，甚至剂型
- 一般原则：基于**安全、有效、可行、依从**，选择给药剂量-时间-体积-速率-浓度

1. 片剂与胶囊：一般固定给药**体积**，不超过6粒/次，尽可能减少用药频率，必要改缓释
2. 皮下/肌肉注射：一般固定给药**体积**
3. 静脉推注：一般固定给药**体积**
4. 静脉滴注
   - ✓ 一般固定**滴注时间**（通常0.5-2h），必要时考虑其他因素
   - ✓ 从有效性角度：半衰期过短的药物，为延长暴露时间，静滴**时间**大于1.5h
   - ✓ 从安全性角度：局部刺激强，**滴速**慢，或**浓度**低

心脏等重要脏器负荷承载低时，**体积**小，**滴速**慢

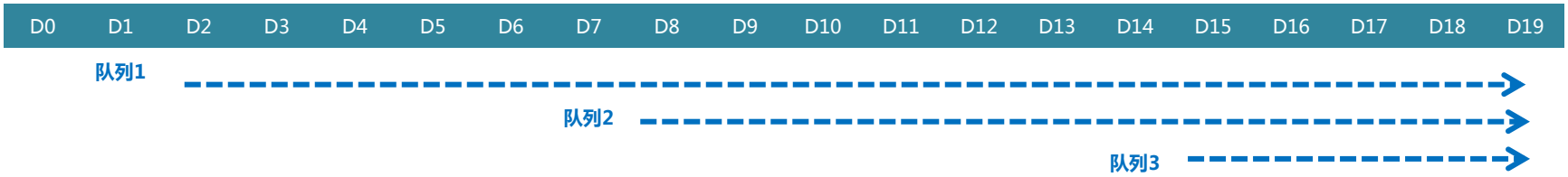
高风险药的设计

一般原则

1. **单次给药**观察
2. **哨兵入组，样本量**不宜太少，队列(cohort) = 6+2
3. **错位给药**，P1= 安慰剂1例，T1 = 受试药1例，T5 =受试药5例
4. **专家委员会**：判断剂量递增中止
5. **中止标准**：2例或以上有临床意义异常者；达到PK阈值
6. **风险控制计划**

Phase 1 dose-escalating study to evaluate the safety, pharmacokinetics, and pharmacodynamics of a recombinant factor Xa. J Throm Haem, 15: 931

关键节点组	时间	受试者队列	观察
准备	0d		基线, PD, PK, ADA
哨兵入组	1d	P1+T1	PD, PK, AE
	2d		PD, PK, AE
全部入组	3d	P1+T5	PD, PK, AE
	4d		PD, PK, AE
	5d		PD, PK, AE
耐受结束	7d		PD, PK, AE
	14d		ADA
	21d		
	28d		ADA
延长观察结束	42d		ADA

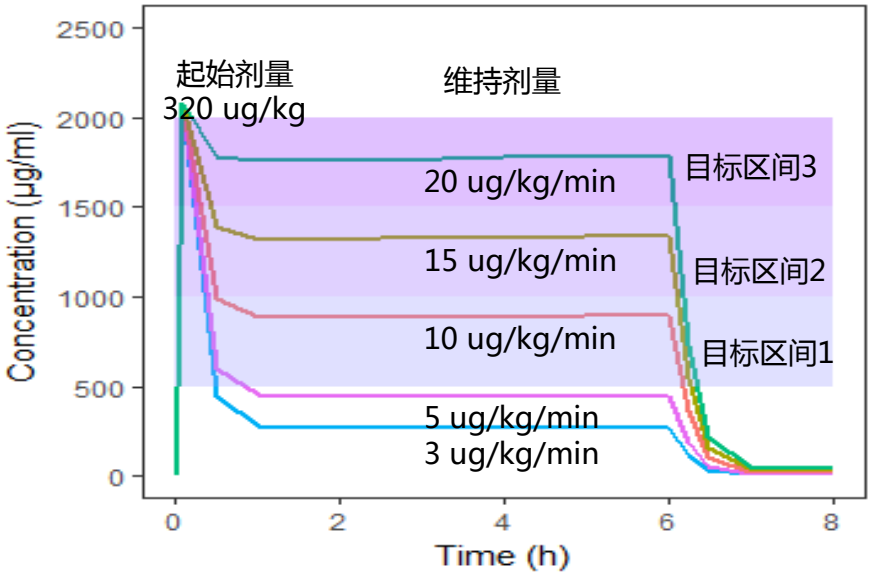


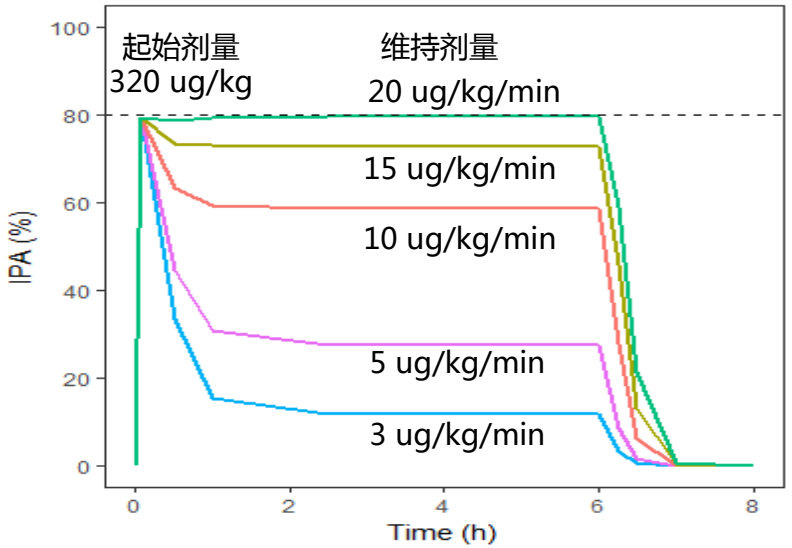
PK/PD引导的试验设计

健康受试者单次推注给药+持续滴注

- 随机、双盲、剂量递增研究
- 给药途径: 静脉推注，5 min推注完成；再开始静脉滴注，6 h完成
- PK数据：药物浓度
- PD数据：血小板聚集抑制率

组别	例数 + 安慰剂	剂量 (推注 + 滴注)
1	1+0	5 μg/kg + 0.1 μg/kg/min
2	2+0	10 μg/kg + 0.2 μg/kg/min
3	3+1	30 μg/kg + 0.3 μg/kg/min
4	6+2	60 μg/kg + 0.6 μg/kg/min
5	6+2	120 μg/kg + 1.2 μg/kg/min
6	6+2	180 μg/kg + 2.0 μg/kg/min
7	3+1	240 μg/kg + 2.5 μg/kg/min
8	3+1	320 μg/kg + 3.0 μg/kg/min





PK/PD模拟浓度-效应关系，提示：如达到80%以上的血小板抑制率，维持剂量需达到20 ug/kg/min

Clinical Immunology (2014) 154, 37–46

available at www.sciencedirect.com

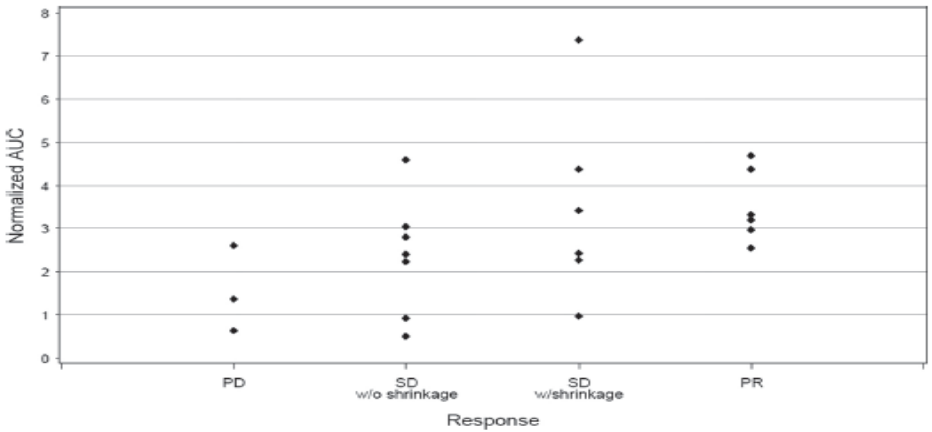
Clinical Immunology

www.elsevier.com/locate/yclim

A phase I study of PRO131921, a novel anti-CD20 monoclonal antibody in patients with relapsed/refractory CD20+ indolent NHL: Correlation between clinical responses and AUC pharmacokinetics

Clinical Immunology http://dx.doi.org/10.1016/j.clim.2014.06.005

- PRO131921 was administered as a single agent to patients with CD20+, relapsed or refractory, indolent non-Hodgkin lymphoma (NHL) who had been treated with a prior rituximab-containing regimen.
- **Correlation between dose-normalized AUC and clinical response (P = .03)**.
- The observation emphasizes the importance of early PK studies to optimize antibody efficacy.



* Note the CRu response (subject 1026) was reclassified as PR for this figure.

博之音&博佳
BioVoice & BioGuider

超长半衰期药物

- 指T1/2过长，达到稳态时间长达数月，使受试者住院观察变成不可行，无实际操作性
- 单次给药没有特别之处
- 多次给药设计
  - 间隔1周给药1次，连续3次，观察7周，无需达到稳态
  - 观察7周的暴露，作为最大耐受浓度

PLOS ONE DOI:10.1371/journal.pone.0134703, 2015

RESEARCH ARTICLE

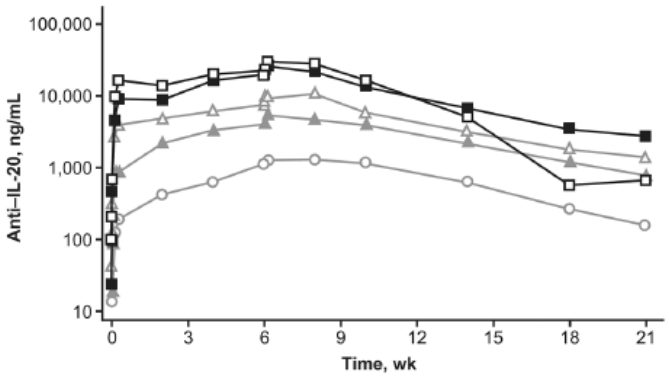
First-In-Human, Phase 1, Randomized, Dose-Escalation Trial with Recombinant Anti–IL-20 Monoclonal Antibody in Patients with Psoriasis

Alice B. Gottlieb[1,2]*, James G. Krueger[3], Mia Sandberg Lundblad[4], Marie Göthberg[4], Brett E. Skolnick[5]

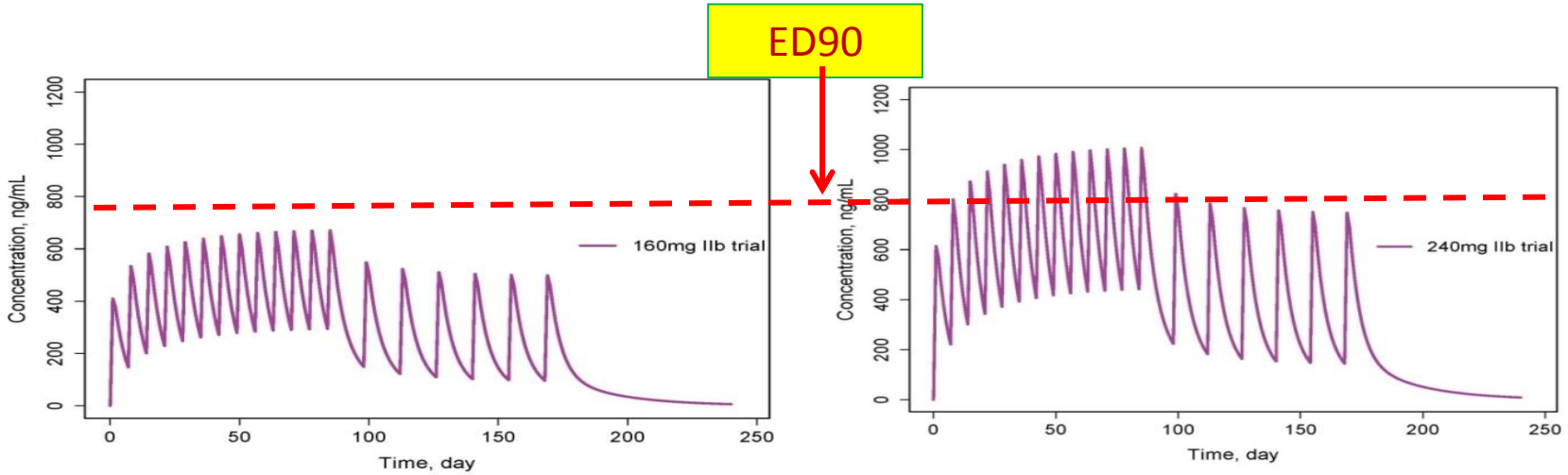
1 Department of Dermatology, Tufts Medical Center, Boston, MA, United States of America, 2 Department of Dermatology, Tufts University School of Medicine, Boston, MA, United States of America, 3 The Rockefeller University, New York, NY, United States of America, 4 Clinical Pharmacology, Novo Nordisk A/S, Søborg, Denmark, 5 Medical-Science, Inflammation, Novo Nordisk Inc., Princeton, NJ, United States of America

Table 4. Summary of Pharmacokinetic Parameters After Dosing With Anti-IL-20.

		Geometric Mean (CV%)					
		C_{max}, μg/mL		AUC, μg·h/mL		$t_{½}$, h	
Anti-IL-20 Dose, mg/kg	Dose Number	n	Value	n	Value	n	Value
Single dose							
0.01	1	3	0.08 (53)	3	82 (40)	3	631 (12)
0.05	1	4	0.41 (27)	3	500 (31)	3	641 (14)
0.2	1	3	1.43 (36)	3	1496 (34)	3	536 (7)
0.6	1	3	3.37 (49)	3	3311 (37)	3	507 (7)
1.5	1	2	8.79 (5)	2	9203 (5)	2	580 (2)
3.0	1	4	24.09 (38)	4	25,143 (30)	4	616 (13)
Multiple doses							
0.05	4	3	1.08 (44)	2	1848 (21)	2	629 (3)
0.2	4	3	3.88 (26)	2	6720 (7)	2	772 (4)
0.5	4	3	9.19 (28)	2	10,900 (39)	2	594 (30)
1.0	4	3	19.96 (32)	3	22,712 (30)	3	767 (16)
2.0	4	3	23.62 (48)	3	20,373 (60)	3	353 (32)



实例：给药间隔评价



每周一次给药持续12 wk，再按每两周一次的给药方案持续12 wk，则后12 wk游离药物的体内浓度处在一个较低的水平，可能会影响药效的发挥

PK/PD与结果表达

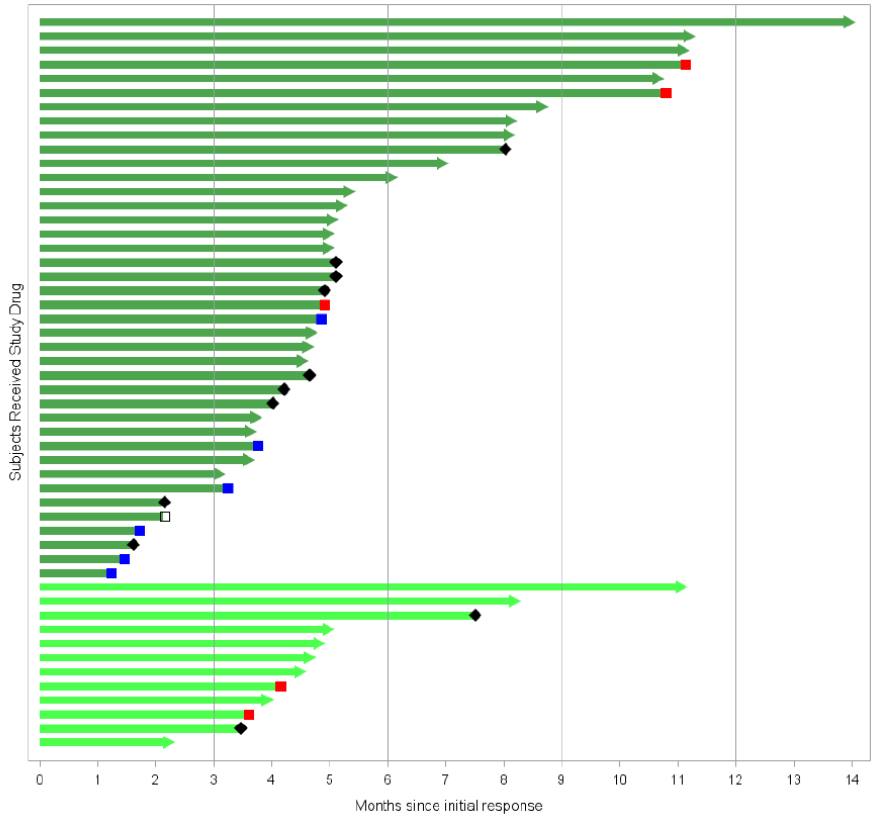
PK参数及系统评价

1. **基本参数：CL, V**
   - 与剂量无关，但一般不用于判断线性PK
   - 生理意义：反映药物消除和分布的参数
   - 模拟用参数
2. **暴露参数：Cmax, AUC, Cmin, Cave**
   - 与PD相关紧密者，用于E/R分析
   - 用于判断PK线性判断
   - Cmin作为PK参数，通常采样重复3次以上
   - 离散度大，比较时用几何均数比值的90%表达，80%-125%作为差别的判断
3. **时间参数：T1/2, Tmax**
   - 经常为非正态数据
   - 比较也可用几何均数比值的90%表达

1. **PK参数的Meta分析**
   - 针对 Cmax，AUC，T1/2
   - 正态性问题的处理
   - 线性范围的判断
   - 有活性的代谢产物
   - 多指标一致性问题
   - 选择随机效应模型
2. **PK参数MBMA**
   - 线性范围判断
   - 较Meta分析更稳健

游泳图 Swimmer Plot

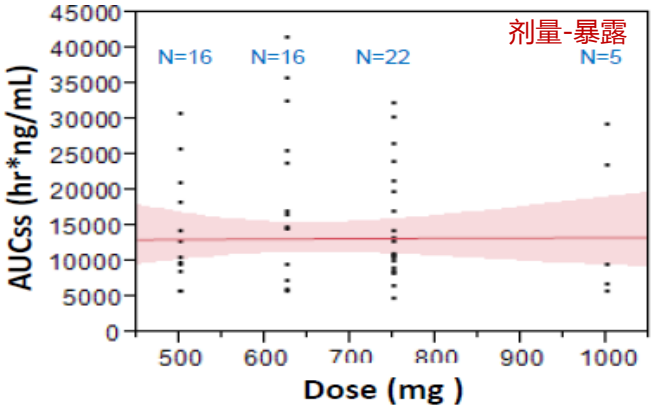
- 剂量递增试验常用
- 试验结果的全貌展示
- 每个柱的长短反映其治疗时间
- 每个柱剑头的颜色和形状表示不同的结果



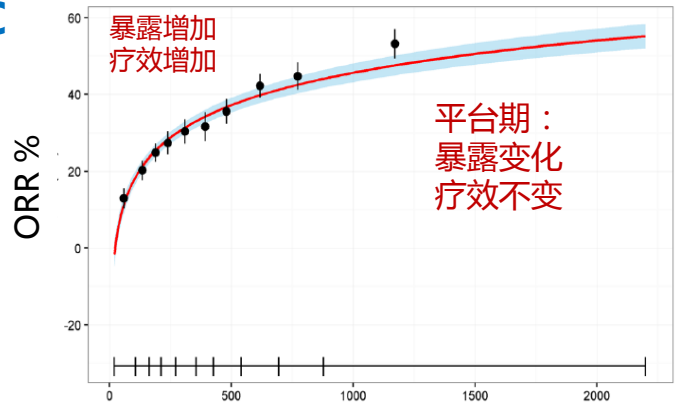
New cancer therapy other than HSCT
Relapse
CR
CRi
HSCT
Adequate assessment no longer available

剂量-暴露-反应关系

A



C



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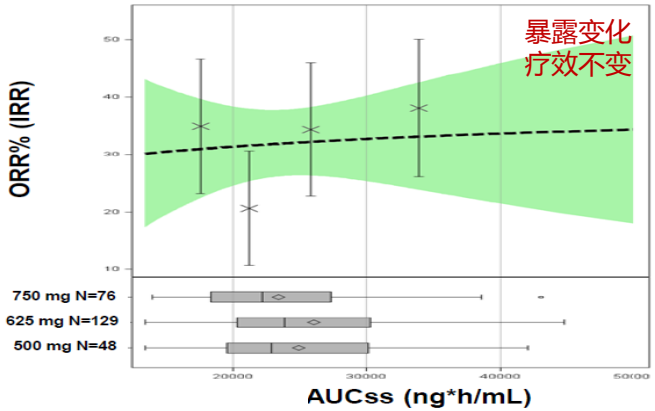

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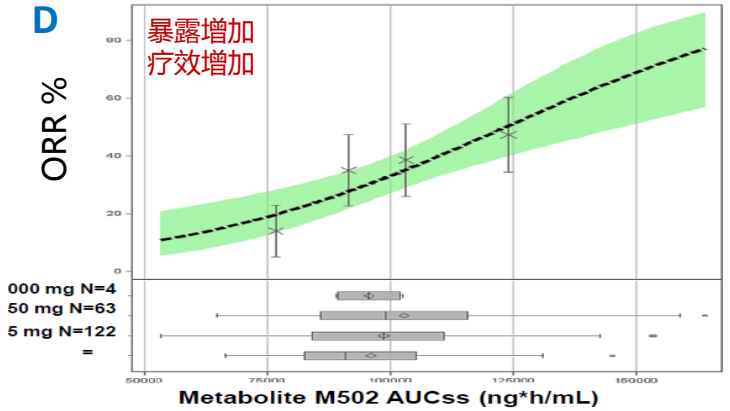


伊潘立酮T1/2与采样时间

PK参数（Mean±SD）		C_{max}(ng/ml)	采样时间/h	$t_{1/2}$(h)	T_{max}（h）	样本量
中国-4mg		2.43±1.48		27.08±5.89	2.00±0.63	12
中国PK试验	3mg	4.48±1.42	120	43.69±16.21	1.42±0.49	12
	1mg	2.52±1.17	120	49.48±8.69	2.0±0.74	12
中国BE试验	1mg 受试制剂	1.41±0.78		61.38±23.90	2.5(1-4)	36
	1mg 参比制剂	1.41±0.81		58.84±12.33	2.0(1-4)	36
欧美	3mg	2.2±0.8	2	5.4±1.3	2.7±0.8	6
	5mg	3.12±1.14	2	7.0±0.8	2.3±0.8	6
FDA审评资料	3mg*	2.79±0.75	72	17.6±6.34	2.5(2-3)	19
	2mg	2.63±1.47		24.44±7.31	3.5(2-5)	8
印度3mg		2.52±0.48		12.23±1.06	2.46±0.39	12

T1/2与采样时间相关，过低浓度造成t1/2延长，且不造成蓄积时，此t1/2无实际意义

PK参数组间分析

Table 6. Statistical Comparison of SerumTigecycline Pharmacokinetic Parameters (n=20)

Parameter (units)	Tigecycline Alone[a] (mean ± SD)	Tigecycline With Digoxin[b] (mean ± SD)	GLS Mean Ratio (%)[c] (90% CI)
$t_{1/2}$ (h)	27.7 ± 7.5	40.4 ± 11.9	146 (131-162)
AUC (ng•h/mL)[d]	2837± 732	2625 ± 524	94 (88-99)
CL (mL/h/kg)	229 ± 56	243 ± 54	107 (101-113)
V_{ss} (L/kg)	6.53 ± 1.30	8.13 ± 2.68	121 (109-134)
MRT (h)	30.0 ± 8.3	34.4 ± 10.8	113 (104-123)
$AUC_{0\text{-}12h}$ (ng•h/mL)	2480 ± 379	2625 ± 524	105 (100-111)

Abbreviations: GLS = geometric least squares; SD = standard deviation; CI = confidence interval; $t_{1/2}$ = terminal phase elimination half-life; AUC = area under the concentration time curve; CL = intravenous clearance; V_{ss} = apparent steady-state volume of distribution, MRT = mean residence time.

a: Tigecycline single intravenous dose (100 mg). Estimates of AUC, V_{ss}, and MRT are based on tigecycline concentrations normalized to a 50-mg dose.

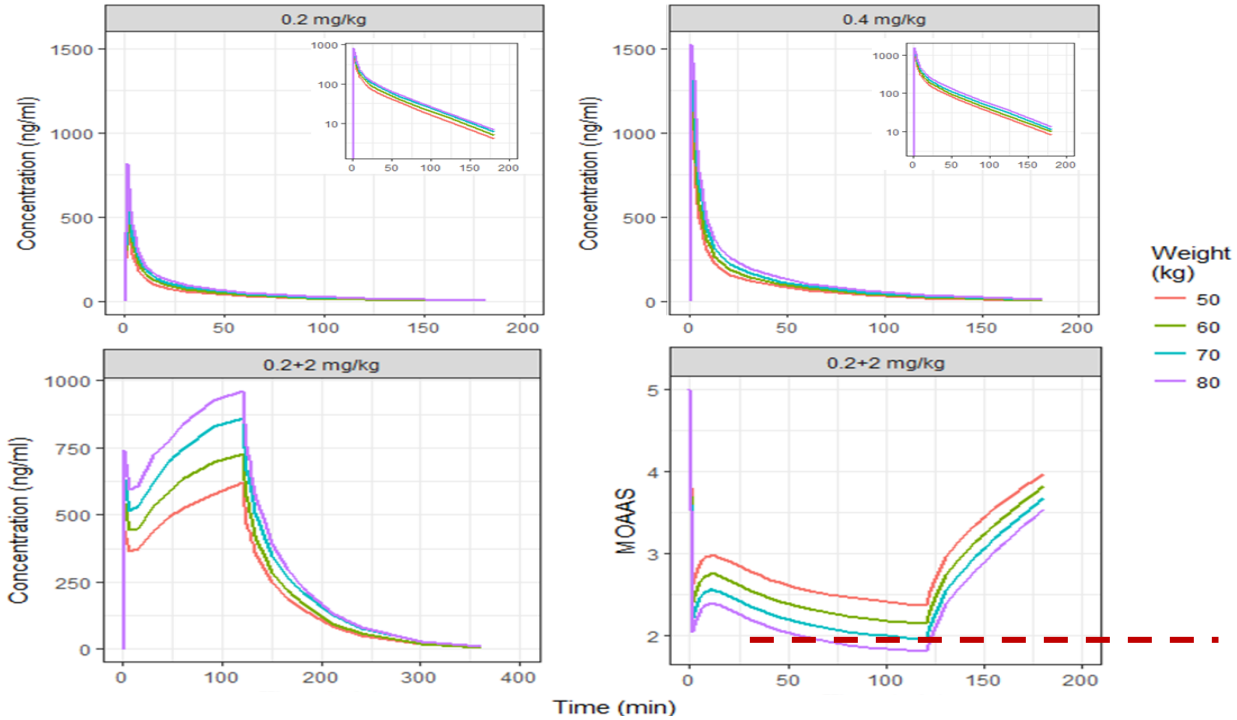
b: Tigecycline multiple intravenous doses (50 mg/12 hours).

c: Ratio of (tigecycline + digoxin)/(tigecycline alone).

d: AUC = dose-normalized $AUC_{0\text{-}\infty}$for tigecycline alone, and AUC = $AUC_{0\text{-}12h}$ for tigecycline with digoxin.

最合适的组间比较方法是几何均数比值的90%CI，注意剂量应相同，否则需要标准化

按体重给药的判断



体重作为协变量纳入群体药动学模型可以判断是否需要按体重给药；与疗效关联的PK/PD分析更佳

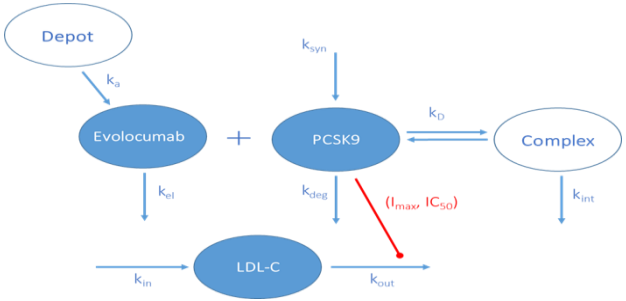
种族差异的表达

DOI:10.1111/bcp.13767

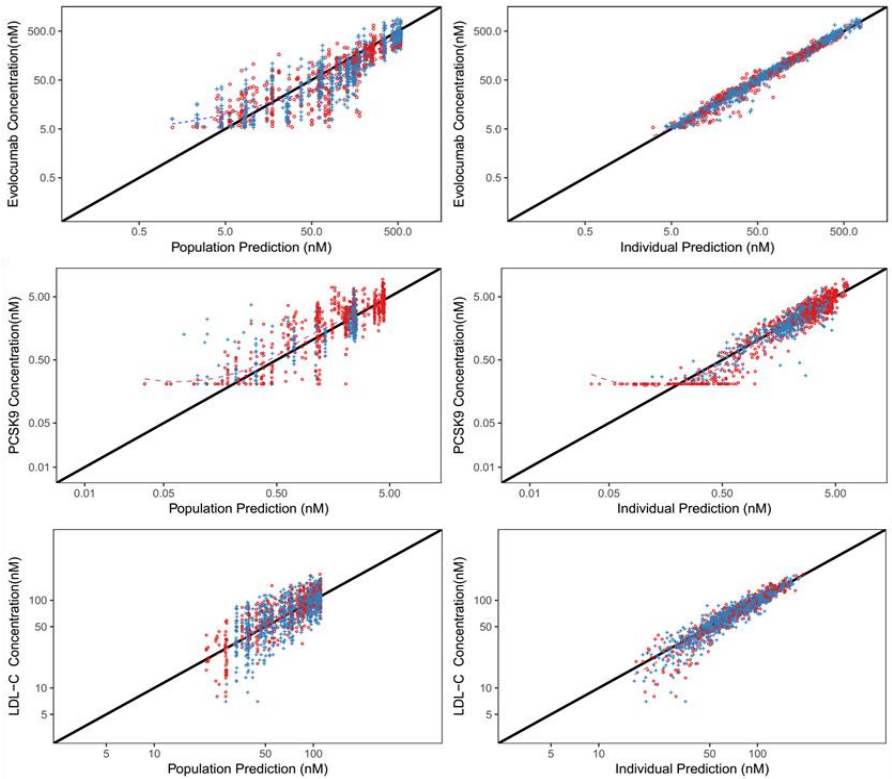
British Journal of Clinical Pharmacology

ORIGINAL ARTICLE

Lack of ethnic differences in the pharmacokinetics and pharmacodynamics of evolocumab between Caucasian and Asian populations



- 群体药动学分析是种族差异的主要分析方法，种族作为协变量呈现
- 最坚实的结果由PK/PD模型提供
- 大分子药物由于代谢途径特殊，一般没有种族差异



C-QTc分析

试验设计

1. 单次给药爬坡多次给药爬坡试验
2. 设计灵活，平行剂量递增、交叉递增
3. 安慰剂对照，以减少偏倚提高把握度
4. 基线：通常不需要采集，对于影响心率的药物需要采集（用药前后HR变化>10bpm）
5. 样本量：通常每组4-8试验药+2-4例安慰剂，>4个剂量
6. 心电图：减少干扰、操作稳定（如，QT测量重复、盲法，建立SOP）
7. 剂量：暴露充分，达到临床最高剂量两倍（2倍Cmax）
8. 不需要阳性药（如莫西沙星），但如果试验药物暴露不充分，则仍需TQT
9. 不推荐合并不同研究进行C-QTc分析，如无法避免，则需讨论不同研究的异质性
10. ECG和血药浓度采样时间匹配，采样点足够（发现效应是否延迟），先ECG再采血

首次人体试验的模型化分析结果可以作为TQT豁免的证据

Journal of Pharmacokinetics and Pharmacodynamics
https://doi.org/10.1007/s10928-017-9558-5

REVIEW PAPER

Scientific white paper on concentration-QTc modeling

Christine Garnett[1] · Peter L. Bonate[2] · Qianyu Dang[4] · Georg Ferber[3] · Dalong Huang[4] · Jiang Liu[5] · Devan Mehrotra[6] · Steve Riley[7] · Philip Sager[8] · Christoffer Tornoe[9] · Yaning Wang[5]

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Abstract
The International Council for Harmonisation revised the E14 guideline through the questions and answers process to allow concentration-QTc (C-QTc) modeling to be used as the primary analysis for assessing the QTc interval prolongation risk of new drugs. A well-designed and conducted QTc assessment based on C-QTc modeling in early phase 1 studies can be an alternative approach to a thorough QT study for some drugs to reliably exclude clinically relevant QTc effects. This white paper provides recommendations on how to plan and conduct a definitive QTc assessment of a drug using C-QTc modeling in early phase clinical pharmacology and thorough QT studies. Topics included are: important study design features in a phase 1 study; modeling objectives and approach; exploratory plots; the pre-specified linear mixed effects model; general principles for model development and evaluation; and expectations for modeling analysis plans and reports. The recommendations are based on current best modeling practices, scientific literature and personal experiences of the authors. These recommendations are expected to evolve as their implementation during drug development provides additional data and with advances in analytical methodology.

Keywords Concentration-QTc model · ICH E14 · Thorough QT (TQT) study · Pharmacokinetics/pharmacodynamics

Abbreviations
AIC Akaike information criteria

C Concentration
CI Confidence intervals
C_{max} Maximum concentration
C-QTc Concentration-QTc
ΔHR Baseline-corrected heart rate
ΔQTc Baseline-corrected QTc interval
ΔΔQTc ΔQTc interval corrected for placebo
ECG Electrocardiogram

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10928-017-9558-5) contains supplementary material, which is available to authorized users.

✉ Christine Garnett
christine.garnett@fda.hhs.gov

试验操作

目的：在考察安全耐受、PK特征的基础上同时观察试验药物是否对影响QT间期延长

设计：盲法、安慰剂对照试验

ECG采集

- 药代采血点同时测量心电图
- 卧位方式采集心电图，于给药前及给药后各个时间点采集，在PK采血点前开始采集，连续采集3次。如果冲突时，以心电图采集优先

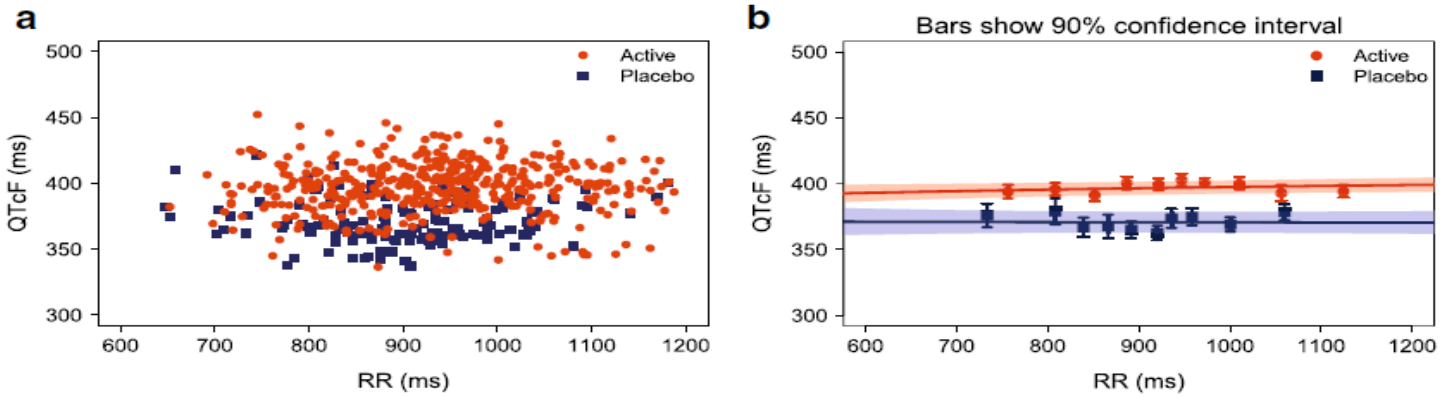
QTc测量

- 中心读ECG，如由固定的2名心电图室医师盲法测量QTc（其中试验药物名称、剂量及给药时间均对测量人员实施盲法），测量前盲法读片50份，以评价其一致性
- 专门的QTc测量机构盲法进行
- 高精度、可靠的仪器

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 97 NUMBER 4 | APRIL 2015

试验评价

- 通常用Fridericia校正：$QTcF=QT/RR^{0.33}$　$RR=60/HR$　(下图为校正后)
- 以人工测量第II导联ECG中的QTc为准



$$\Delta QTc_{ijk+} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 TIME_j + \theta_4 (QTc_{i,j=0} - \overline{QTc_0})$$

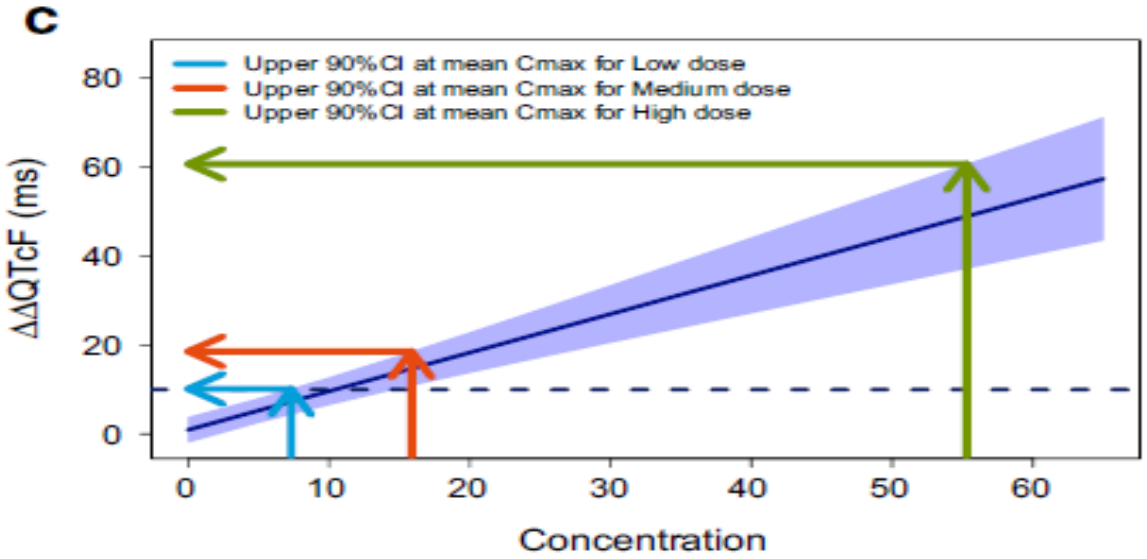
- FDA专家推荐的暴露-反应的线性模型分析能适用于大多数情况
- 也根据数据特征可使用自定义模型

博之智&博佳
BioVoice & BioGuider

阳性判定标准

- 阴性：高剂量C_{max}几何均值所对应的ΔΔQTcF双侧90%CI上限≤10ms
- 阳性：低剂量C_{max}几何均值所对应的ΔΔQTcF双侧90%CI上限>10ms

ΔΔQTcF: 基线和安慰剂效应校正的QTcF值　或者　试验药组ΔQTcF群体典型值与安慰剂组ΔQTcF群体典型值之差



博之音&博佳
BioVoice & BioGuider

E14(2005): 抗肿瘤药QTc分析

2.4 Clinical Development When the ‘Thorough QT/QTc Study’ Cannot be Performed in Healthy Volunteers

There are some drugs that cannot be studied in a ‘thorough QT/QTc study’ in healthy volunteers due to safety or tolerability concerns (e.g., cytotoxic cancer drugs). In such cases, the ‘thorough QT/QTc study’ can often be conducted in patient populations. **When this is not possible, the importance of detecting and modifying this safety risk means that other ways of detecting effects on the QT/QTc interval need to be developed. These might include the collection of ECGs at multiple timepoints under tightly controlled settings that target a broad range of doses early in development.**

肿瘤药物QT评价-FDA审评文件

C-ΔQTc的线性混合效应模型斜率和0无差异，无影响

QT	
Impact of durvalumab exposure on QT interval	In QTc substudy included in Study ATLANTIC, no relationship was identified between durvalumab serum concentration and ΔQTcF based on the concentration-ΔQTcF analysis. Linear mixed-effects modeling of QTcF as a function of durvalumab concentrations estimated a non-significant relationship between durvalumab concentration and change in QTcF. The slope for the relationship of the change in QTcF to durvalumab concentration was -0.00114 msec per µg/mL, with a p-value of 0.902, indicating that the slope is not significantly different from 0 or no effect, and the mean intercept was 2.16 msec (p-value: 0.253; 90% CI -0.956, 5.28 ms). The predicted mean change in QTcF and upper 90% CI at each of the post-therapy visits are below the threshold of clinical concern.

NDA or BLA Number	761069
Link to EDR	\\CDSESUB1\evsprod\BLA761069\
Submission Date	10/13/2016
Submission Type	Priority review
Brand Name	IMFINZI
Generic Name	Durvalumab
Dosage Form and Strength	500 mg/10mL or 120 mg/2.4mL solution in single-dose vial
Route of Administration	Intravenous infusion

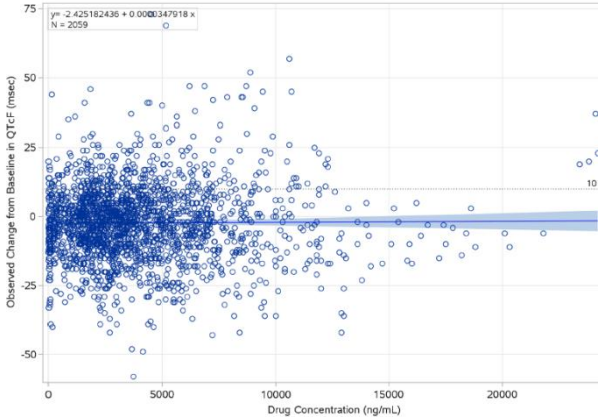
肿瘤药物C-QTc分析-文献

无安慰剂；合并多个研究

模型化分析：linear mixed effect model

$$\Delta QTc = (\theta 1 + \eta 1) + (\theta 2 + \eta 2) \times Conc + \varepsilon,$$

where Conc is the observed idasanutlin plasma concentration, θ1 is the populations mean intercept (representing ΔQTc at a concentration of zero), $\theta 2$ is the populations mean slope (describing the dependency of ΔQTc on concentration), $\eta 1$ and $\eta 2$ are the inter-individual variability (IIV) of $\theta 1$ and $\theta 2$, respectively, and ε is the residual error. $\eta 1$, $\eta 2$, and ε are random variables assumed to be normally distributed with a mean of 0 and a variance of $\omega 12$, $\omega 22$, and $\sigma 2$, respectively [i.e., $\eta 1 \sim N(0, \omega 12)$, $\eta 2 \sim N(0, \omega 22)$, and $\varepsilon \sim N(0, \sigma 2)$]. A model with intercept fixed to 0, removing $(\theta 1 + \eta 1)$ from the model, was also explored.



分类统计分析

阳性标准阳性90CI上限>10ms

Phase 1 summary of plasma concentration–QTc analysis for idasanutlin, an MDM2 antagonist, in patients with advanced solid tumors and AML. Cancer Chemotherapy and Pharmacology (2018) 81:597–607

欢迎合作！

科学合理的设计

规范严谨的流程

准确可信的结论

Thanks!