Envonalkib、Iruplinalkib和Crizotinib在治疗间变性淋巴瘤激酶阳性晚期非小细胞肺癌——基于中国角度的经济学评价

Economic evaluation of envonalkib, iruplinalkib, and crizotinib in the treatment of anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer in China

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背景 background

- Participants: Advanced or metastatic NSCLC patients ALK-positive in whom no systemic treatment with ALK inhibitors has been received
- Data sources: *Two phase III* randomized, double-blind, multi-center *clinical trials* –See Fig.1
  - Compared envonalkib to crizotinib (NCT04009317)
  - Compared iruplinalkib to crizotinib (NCT03635749)
- Cost sources:
  - *Enavonalkib* (assuming that the price of envonalkib is the average of iruplinalkib, crizotinib, and alectinib)
  - *Iruplinalkib, crizotinib, and alectinib* (www.yaozh.com)
- Decision-analytical model and model inputs:
  - Model: Partitioned survival model (*PSM*)
  - Model cycle: *3 weeks*
  - Model time horizon: Lifetime range (*15 years*)
  - Main model output indicators: Cost, quality-adjusted life year (*QALY*), and incremental cost-effectiveness ratio (*ICER*)
- Analysis strategy:
  - Processing of survival data: R was used to reconstruct, fit and extend the original data. (*assuming* that the *OS distribution of envonalkib* = the best-fit distribution for *crizotinib in the OS curve*)

$$Y_{intervention} = Y_{comparator} \times HR$$

  - Scenario analysis:
  - 1.Assuming that the OS curve of *envonalkib* = the OS curve of *iruplinalkib*
  - 2.The utility value of the base analysis changed

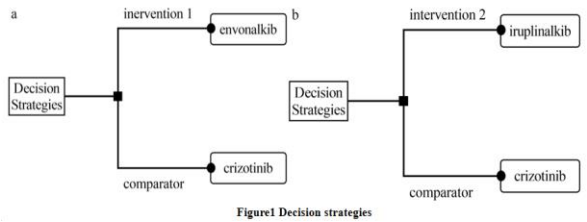

Figure1 Decision strategies

方法 Methods

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Envonalkib, a novel anaplastic lymphoma kinase (ALK) inhibitor, demonstrated promising anti-tumor activity and safety in advanced ALK-positive non-small cell lung cancer (NSCLC) in the first-in-human phase III study. Iruplinalkib is a second-generation ALK tyrosine kinase inhibitor (TKI) with efficacy in patients with ALK-positive advanced NSCLC. Crizotinib is currently the recommended treatment drug according to the guidelines.

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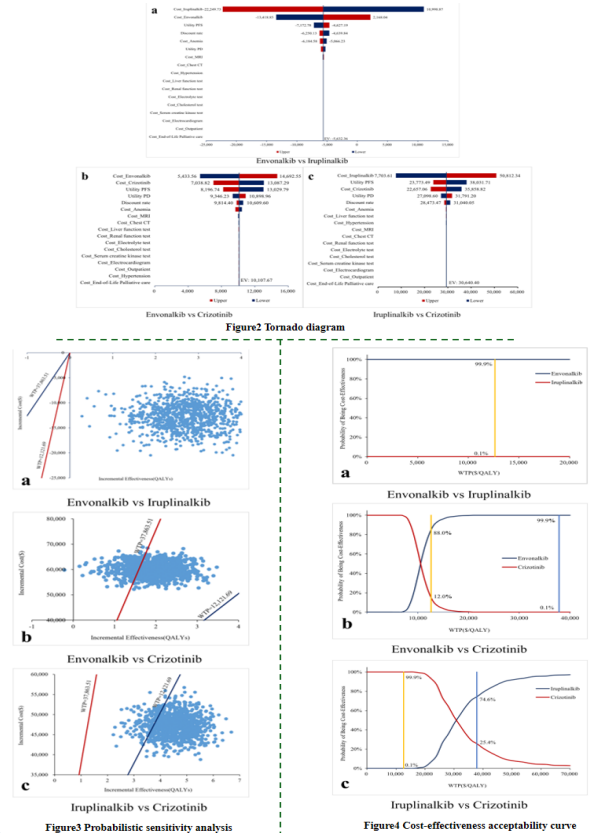

结果 Results

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Based on two phase III randomized, double-blind, multi-center clinical trials. A three-health state PSM was developed to simulate the progression of disease, with a model cycle of 3 weeks and a lifetime range; the main output indicators of the model were total cost QALY, and ICER; the cost and health output were discounted using 5.0% discount rate. Using 1~3 times China's per capita gross domestic product (GDP) in 2023 as the WTP threshold, the cost-utility analysis method was used for analysis.

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- The costs of envonalkib iruplinalkib, and crizotinib were *$178,999.54, $189,331.94, and $147,882.76* and the outcomes were *6.02, 4.18, and 2.93 QALY*, respectively.–See Tab.1
- The cost of iruplinalkib and the cost of envonalkib were the most consequential factors affecting the economy.–See Tab.3
- The results of the scenario analysis illustrated that the envonalkib was still the most cost-effective solution.–See Tab.2

Group	Cost	Incremental cost	Effectiveness/ QALY	ICER
Envonalkib (vs iruplinalkib)	167,036.7	-22,295.2	0.16	-138,536.6
Envonalkib (vs crizotinib)		19,153.9	1.42	13,524.2

Table1 The results of base–case analysis

Group	Total QALYs	Incre QALYs	ICER
Envonalkib (vs iruplinalkib)	6.56 (5.61)	0.95	-10,874.34
Envonalkib (vs crizotinib)	6.56 (5.27)	1.29	24,135.23
Iruplinalkib (vs crizotinib)	5.82 (5.27)	0.55	74,692.93

Table2 Results of changed utility value

结论 Conclusions

The costs of envonalkib iruplinalkib, and crizotinib were $178,999.54, $189,331.94, and $147,882.76 and the outcomes were 6.02, 4.18, and 2.93 QALY, respectively. Envonalkib and iruplinalkib were dominant compared with crizotinib, and the ICER of envonalkib compared with iruplinalkib was -5,625.41, which was much greater than WTP; therefore, envonalkib was the most cost-effective option.

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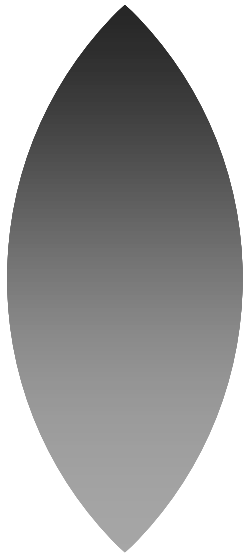
- Envonalkib and iruplinalkib were dominant compared with crizotinib, and the ICER of envonalkib compared with iruplinalkib was -5,625.41, which was much greater than WTP.
- Envonalkib was the most economical drug compared with iruplinalkib and crizotinib at the set price ($1,161.78), and iruplinalkib was cost-saving and utility-increasing compared to crizotinib.
- The ICER appeared to be modest with the WTP threshold for a high disease severity in ALK-positive NSCLC population.

Envonalkib is the most economical compared with iruplinalkib and crizotinib at the set price ($1,161.78), and iruplinalkib is cost-saving and utility-increasing compared to crizotinib, which can help the healthcare system in making optimal policies and help clinicians in the medication of patients.



数据

Data

成本数据来源

Cost data source

1 药品成本：www.drugs.com，药智网

Drug cost: www.drugs.com, www.yaozhi.com

2 监测成本：文献

Monitoring cost: literature

3 不良反应成本：文献

AE cost: literature

生存数据来源

Survival data source

1 两篇III期临床试验

Two phase three clinical trails

*TQ-B3139-III-01 (NCT04009317), Envonalkib **vs** Crizotinib;*

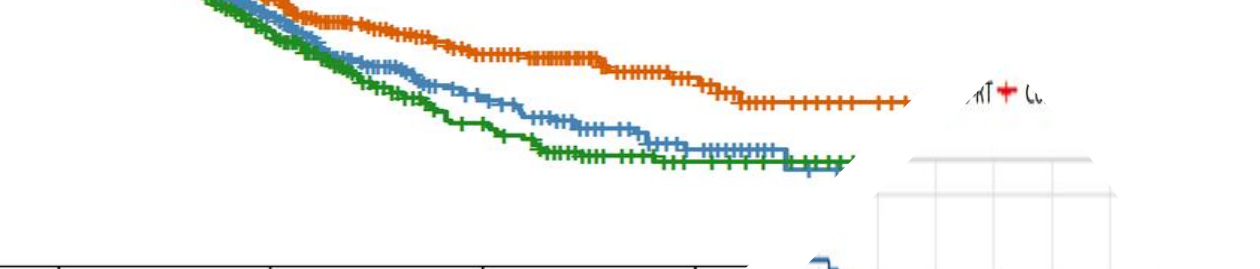
2 *INSPIRE (NCT03635749), Iruplinalkib **vs** Crizotinib*

效用数据来源

Value data source

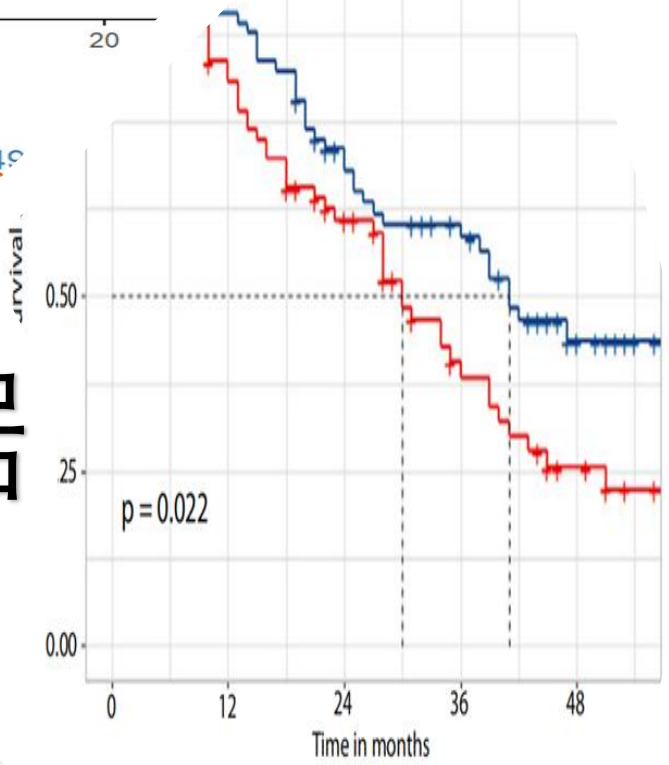
无进展生存期，疾病进展，死亡：效用值测量文献

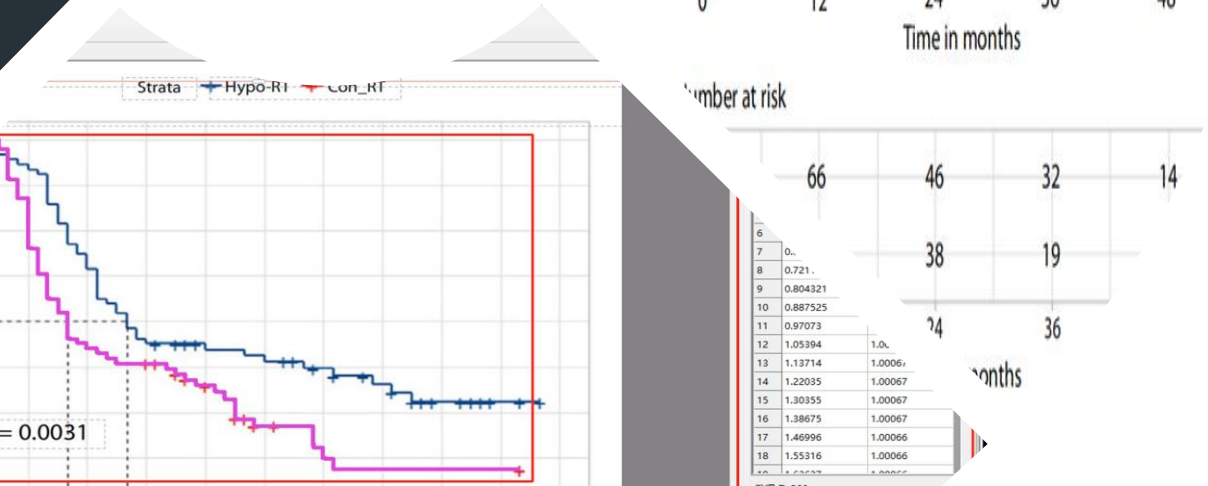
PFS, PD, Death: Utility value measurement literature



生存数据

Survival data





一、选取临床试验（Select clinical trials）

- **P（Population）研究对象：**

  间变淋巴瘤激酶阳性的晚期非小细胞肺癌（*ALK-positive NSCLC*）

- **I（Intervention）干预措施：**

  1 依奉阿克（*Envonalkib*）；2 伊鲁阿克（*Iruplinalkib*）

- **C（Comparison）比较组：**

  克唑替尼（*Crizotinib*）：临床试验对照组+指南推荐

- **O（Outcome）结局：**

  OS（*Overall Survival*）总生存期

  PFS（*Progression-Free Survival*）总生存期

  PD（*Progression Disease*）疾病进展　　PD = OS-PFS

- **S（Study design）研究类型：**

  基于III期临床试验的药物经济学评价（*Cost-effectiveness evaluation based on Phase III clinical trials*）

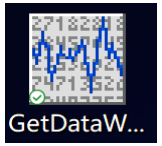
生存数据

Survival data

二、生存数据处理（ Survival Data Processing ）

- **软件（*Software*）：**

  Getdata



- **第 1 步（*First step*）：**

  将临床试验中的OS图/PFS图另存为JPG/JPEG图（*Save the OS/PFS graphs from the clinical trial as JPG/JPEG images*）

- **第 2 步（*Second step*）：**

  在GetData中放入OS/PFS图片,并设置X轴，Y轴的最低值和最高值（ *In GetData, insert the OS/PFS graphs and set the minimum and maximum values for the X-axis and Y-axis*）

- **第 3 步（*Third step*）：**

  背景部分颜色更改为选取曲线颜色，然后挨个点进行选取，注：拐点必取（*In the background, change the color to the color of the selected curve, and then select each point individually, noting that inflection points must be included*）

- **第 4 步（*Third step*）：**

  取完点之后→文件，另存为Excel数据（ *After selecting the points, go to File, and save as Excel data* ）

三、生存数据再处理（1）（ Reprocessing of Survival Data）

- 软件（*Software*）：

  Excel

- 第 1 步（*First step*）：

  整理生存数据（*Organize survival data*）

OS曲线生存时间的顺序（K）	OS曲线生存时间（Tk）	生存时间对应的生存率（S）
1	0	1
2	0.091491946	0.999999567
3	0.166348993	0.999999213
4	0.24120604	0.999998859
5	0.316063086	0.999998505
6	0.390920133	0.999998151
7	0.46577718	0.999997797
8	0.540634227	0.999997443
9	0.615491274	0.999997089

- 第 2 步（*Second step*）：

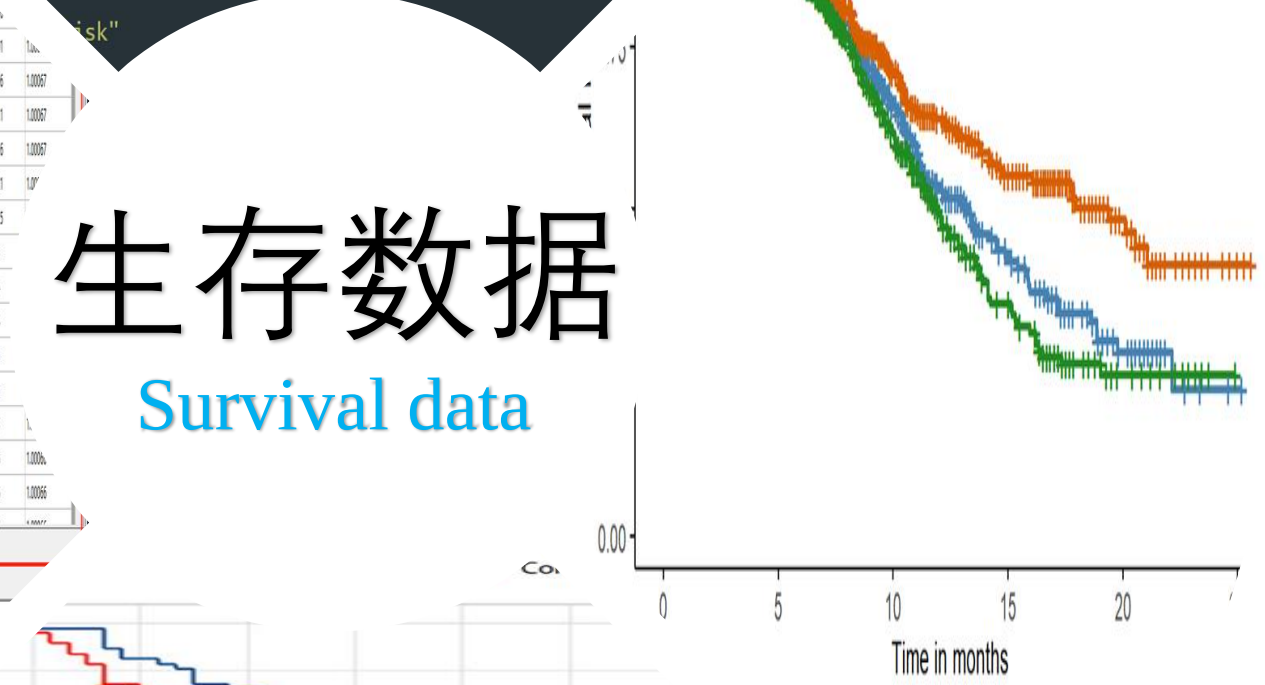
  处理残缺值

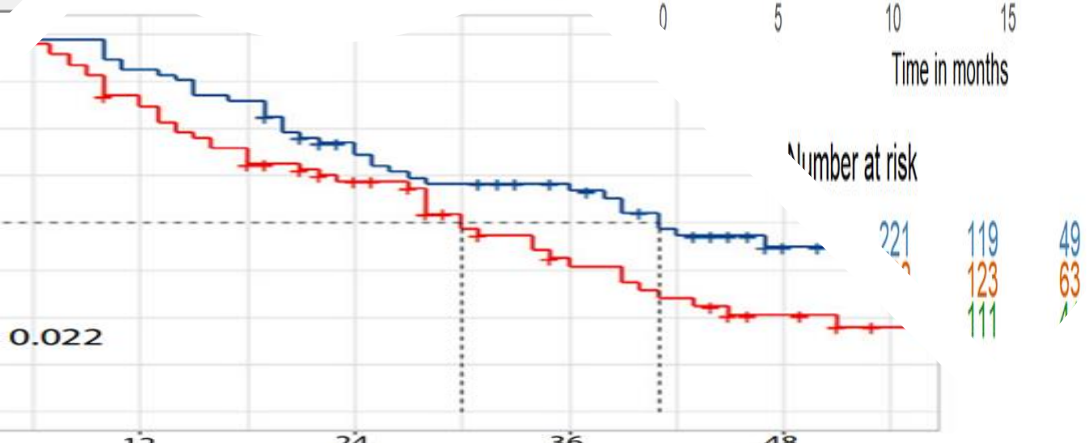
  （*Handle missing values*）

i	Trisk	Lower	Upper	Nrisk
1	0	1	204	73
2	12	205	455	66
3	24	456	653	46
4	36	654	879	32
5	48	880	974	14

生存数据

Survival data





三、生存数据再处理（2）（Reprocessing of Survival Data）

- 软件（*Software*）：

  R Studio

- 第 1 步（*First step*）：

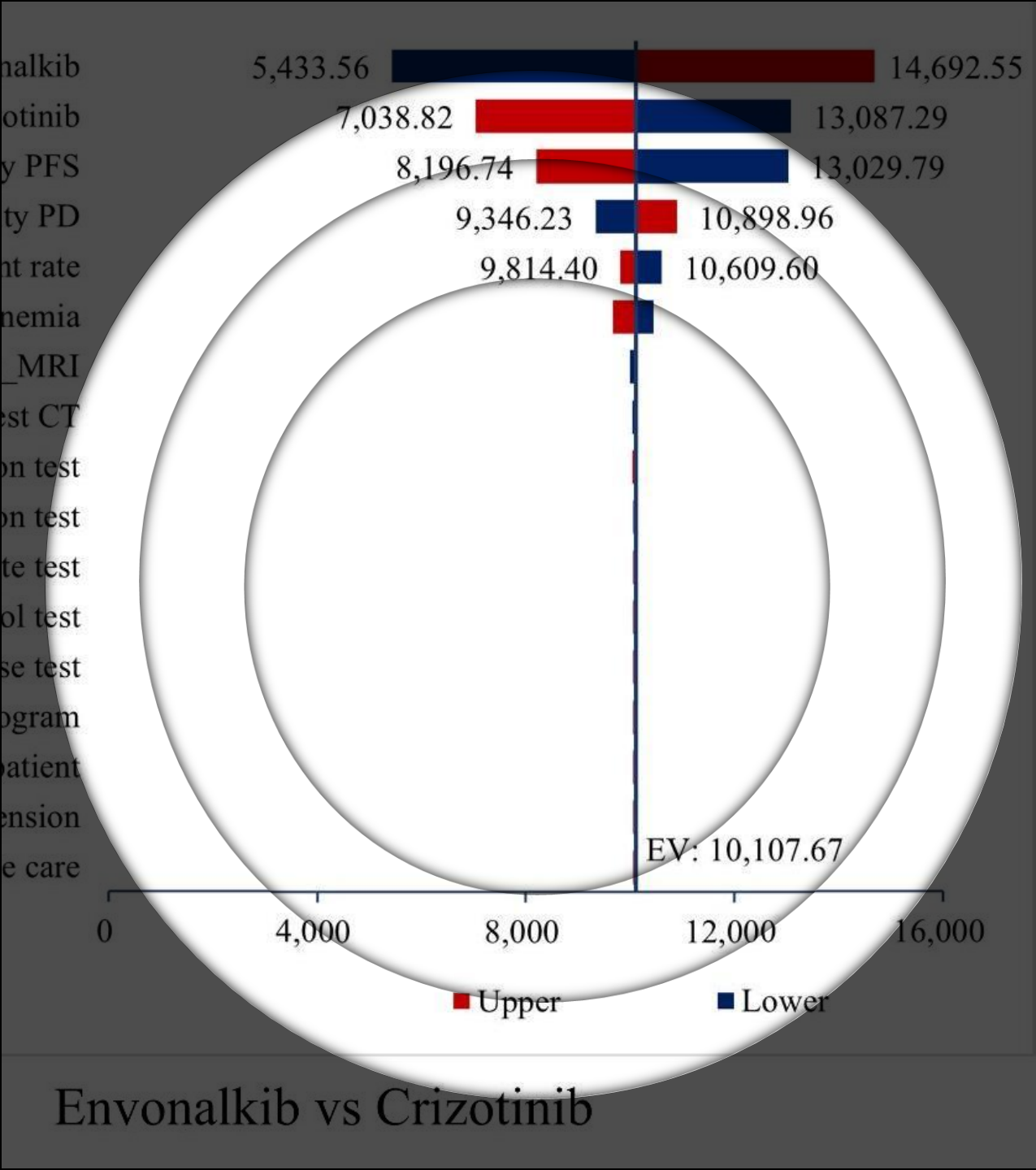
  拟合数据（*Fit data*）

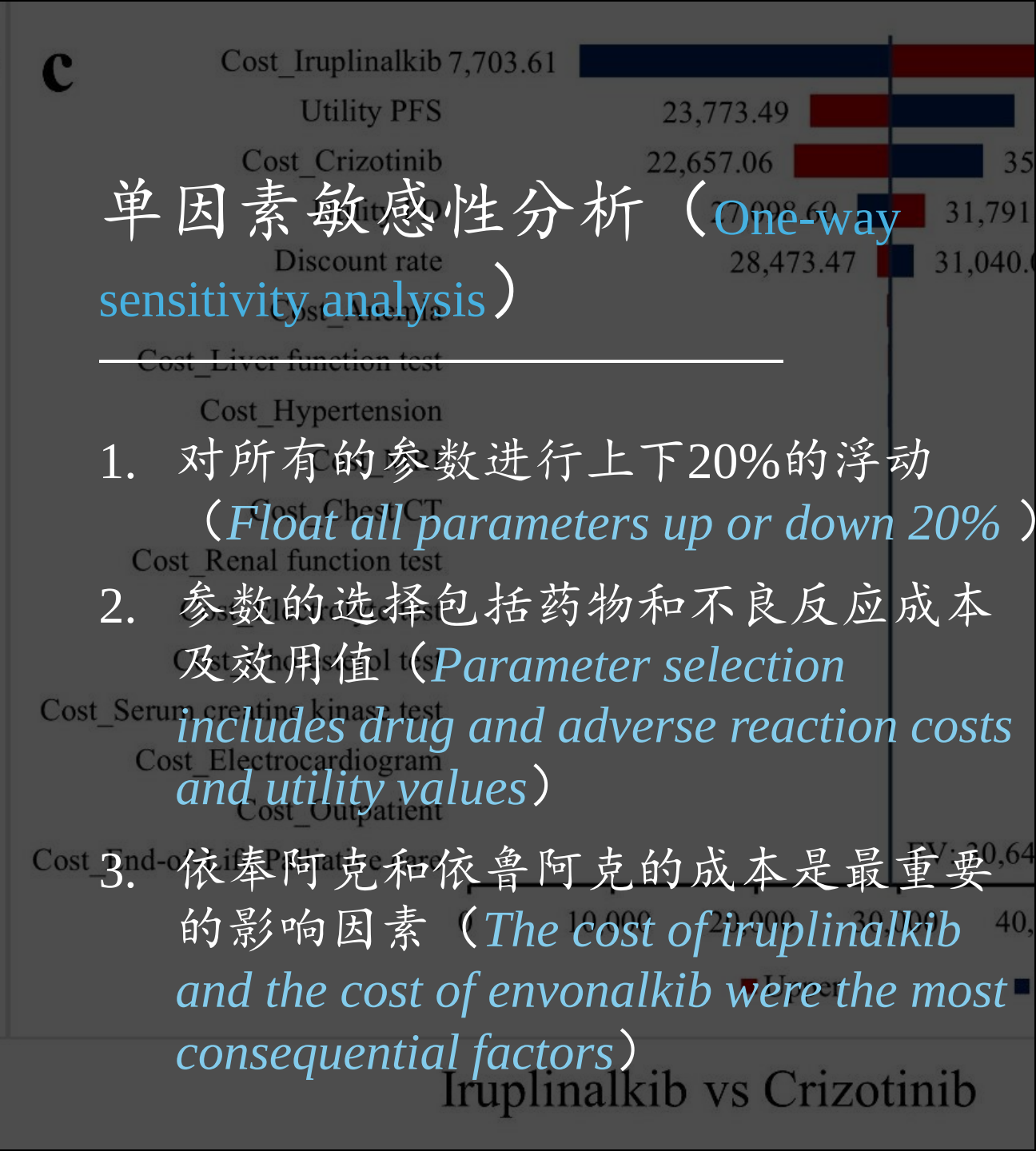
```
ggsurvplot(
  fit,
  data = data,
  pval = TRUE,
  risk.table = TRUE,
  palette = c("#D95F02", "steelblue"),
  legend.title = "Treatment",
  legend.labs = c("Con-RT", "Hypo-RT"),
  risk.table.height = 0.2,
  xlab = "Time in months",
  ylab = "Overall survival rate",
  risk.table.col = "strata",
  tables.theme = theme_cleantable(),
  ggtheme = theme_classic() +
    theme(plot.title = element_text(size = 12), # 调整其他标题大小示例
          legend.title = element_text(size = 10), # 调整图例标题大小示例
          axis.title = element_text(size = 10), # 调整坐标轴标题大小示例
          # 调整风险表标题大小
          strip.text.x = element_text(size = 8)),
  pval.coord = c(55, 1),
  pval.text = TRUE,
  pval.size = 4,
  fontsize = 4,
  risk.table.title = "Number at risk"
)
```

- 第 2步（*Second step*）：

  重构数据（*reconstruct data*）

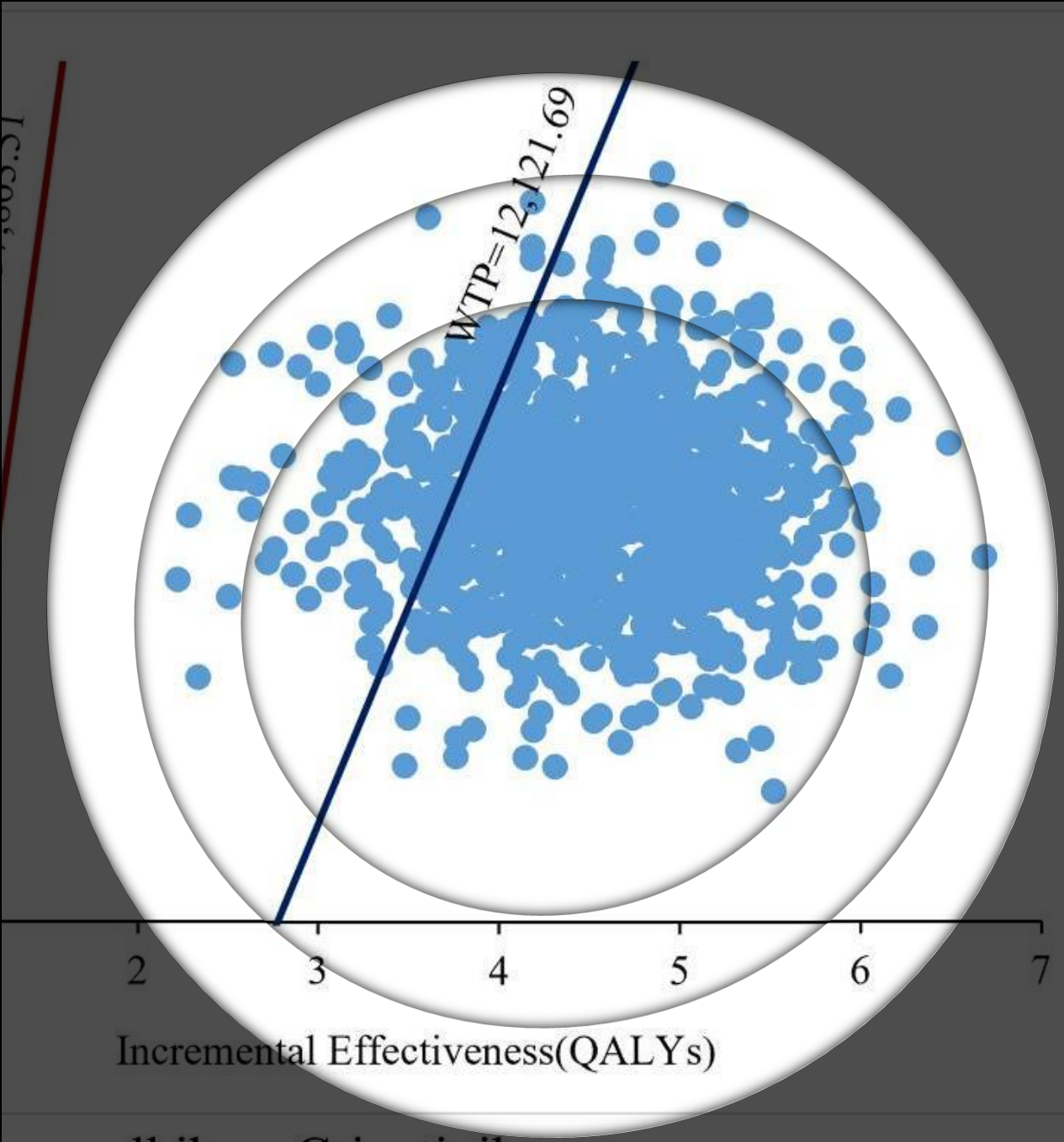
```
mods1<-c("exponential","gamma","gengamma", "gompertz","weibull","weibullPH","loglogistic","lognormal")
mods2<-c("exp","weibull","lnorm","llogis")
formula<-Surv(time,event)~1
#regora
regora_mle=fit.models(formula=formula,data=regora, distr=mods1,method="mle")
place_mle=fit.models(formula=formula,data=place, distr=mods1,method="mle")
print(place_mle,mod=8)
place_mle$model.fitting
make.surv(place_mle,t=seq(0,258,by=0.7),mod = 8,nsim = 1)
tt <- make.surv(place_mle,t=seq(0,258,by=0.7),mod = 8,nsim = 1)
as.data.frame(tt$S)
```





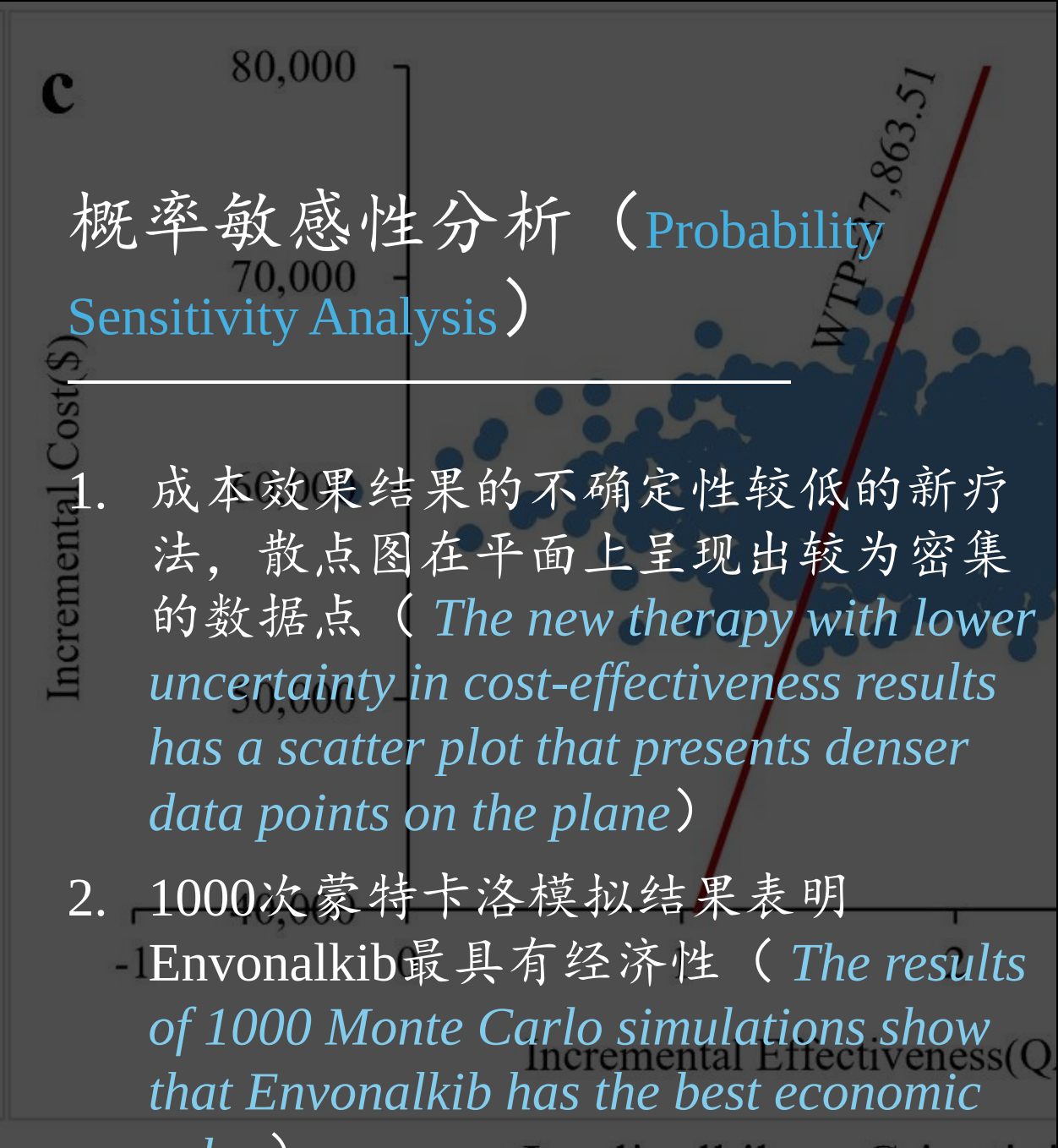
单因素敏感性分析（One-way sensitivity analysis）

1. 对所有的参数进行上下20%的浮动（*Float all parameters up or down 20%*）
2. 参数的选择包括药物和不良反应成本及效用值（*Parameter selection includes drug and adverse reaction costs and utility values*）
3. 依奉阿克和依鲁阿克的成本是最重要的影响因素（*The cost of iruplinalkib and the cost of envonalkib were the most consequential factors*）



nvonalkib vs Crizotinib

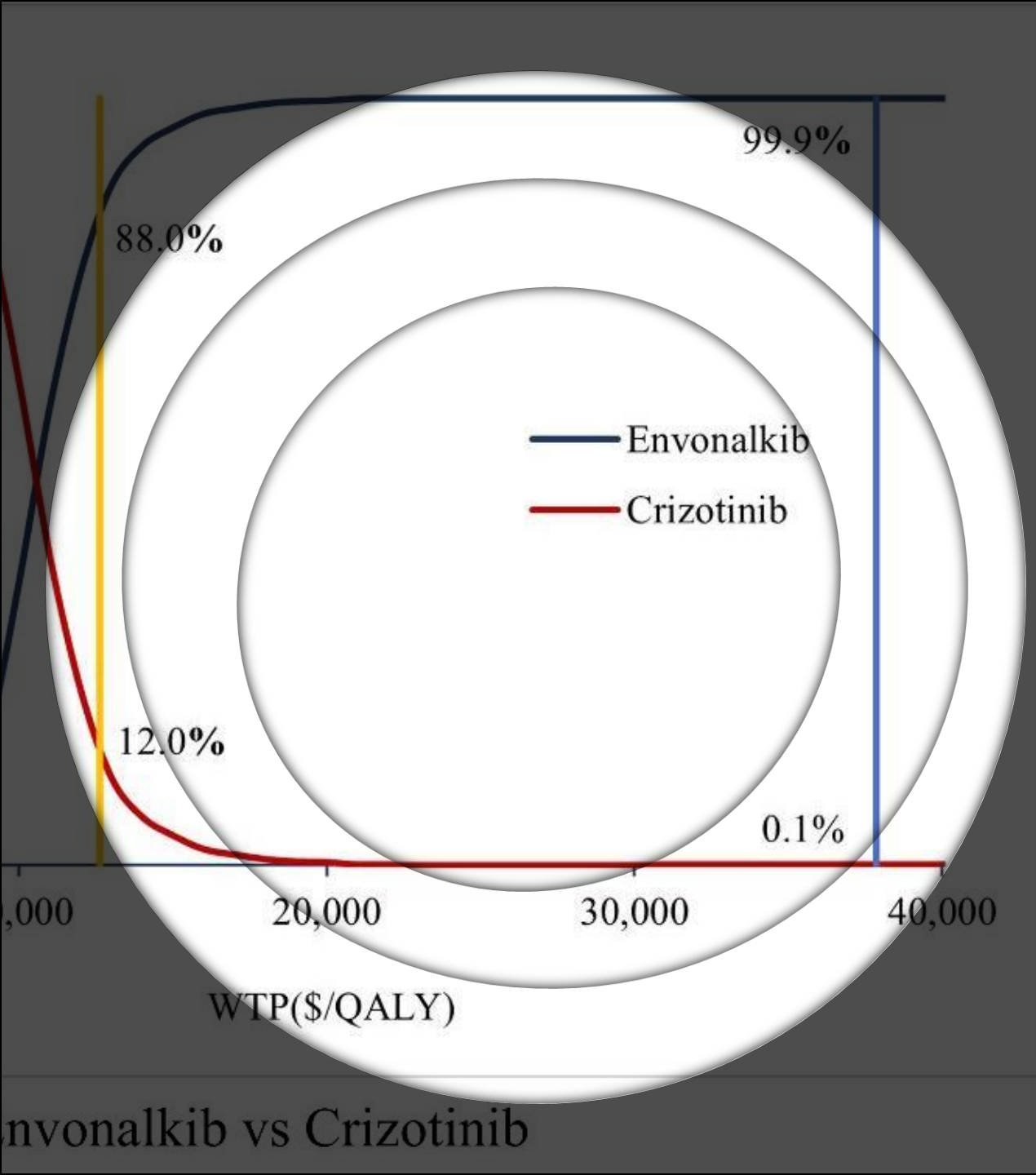
c



Iruplinalkib vs Crizotini

概率敏感性分析（Probability Sensitivity Analysis）

1. 成本效果结果的不确定性较低的新疗法，散点图在平面上呈现出较为密集的数据点（*The new therapy with lower uncertainty in cost-effectiveness results has a scatter plot that presents denser data points on the plane*）
2. 1000次蒙特卡洛模拟结果表明Envonalkib最具有经济性（*The results of 1000 Monte Carlo simulations show that Envonalkib has the best economic value*）



nvonalkib vs Crizotinib

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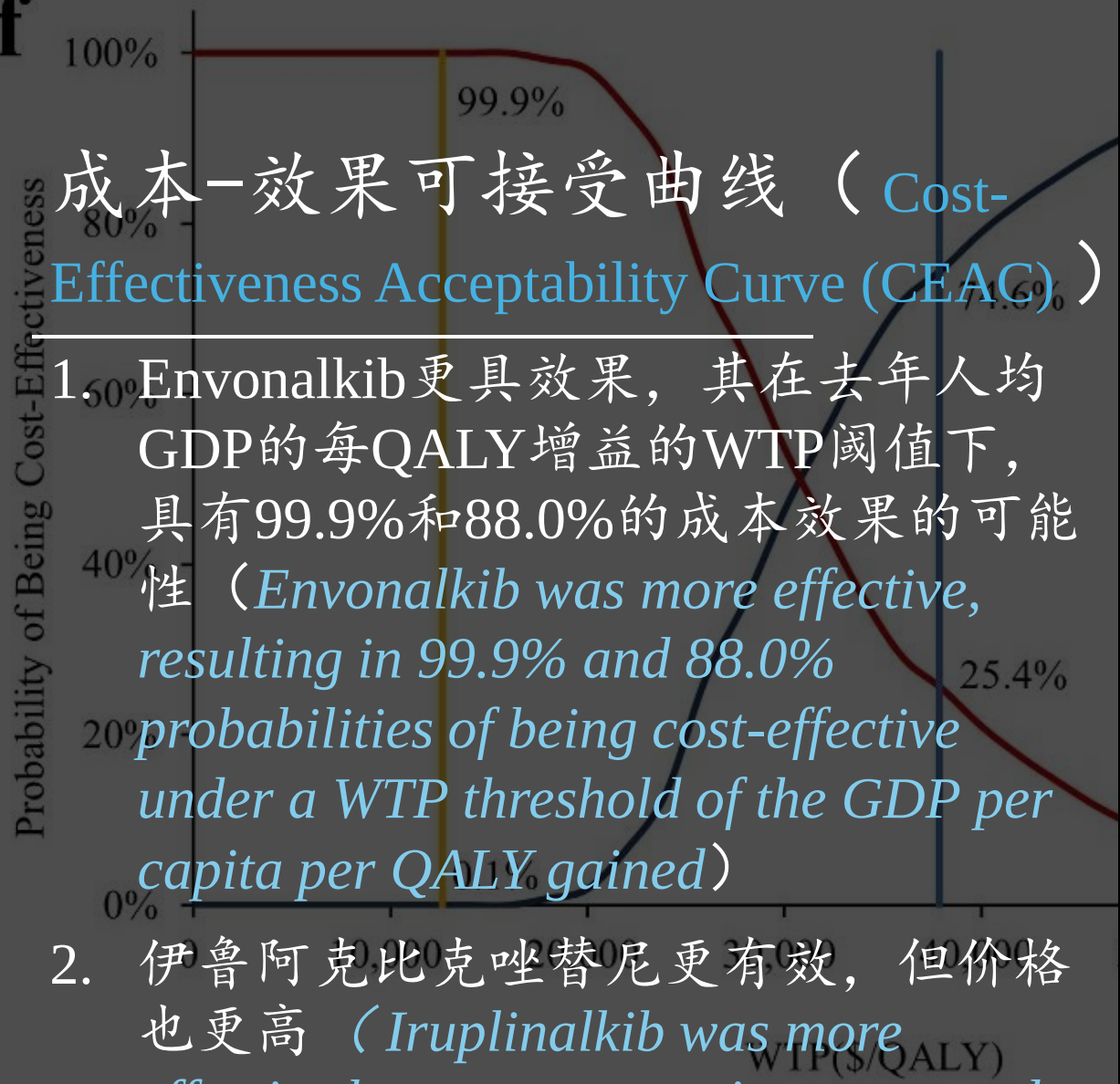

Iruplinalkib vs Crizot

成本-效果可接受曲线（Cost-Effectiveness Acceptability Curve (CEAC)）

1. Envonalkib更具效果，其在去年人均GDP的每QALY增益的WTP阈值下，具有99.9%和88.0%的成本效果的可能性（*Envonalkib was more effective, resulting in 99.9% and 88.0% probabilities of being cost-effective under a WTP threshold of the GDP per capita per QALY gained*）
2. 伊鲁阿克比克唑替尼更有效，但价格也更高（*Iruplinalkib was more effective but more expensive compared with crizotinib*）


THANKS

感谢各位老师和同学们的宝贵时间聆听汇报
（*Thank you, all teachers and students for your valuable time and encouragement*）

期待未来有更多的交流与合作
（*Looking forward to more communication and cooperation in the future*）