

# 大腸直腸癌 之化學治療、標靶治療

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Q: 您認為在2013年，轉移性大腸直腸癌病人的平均存活時間是？



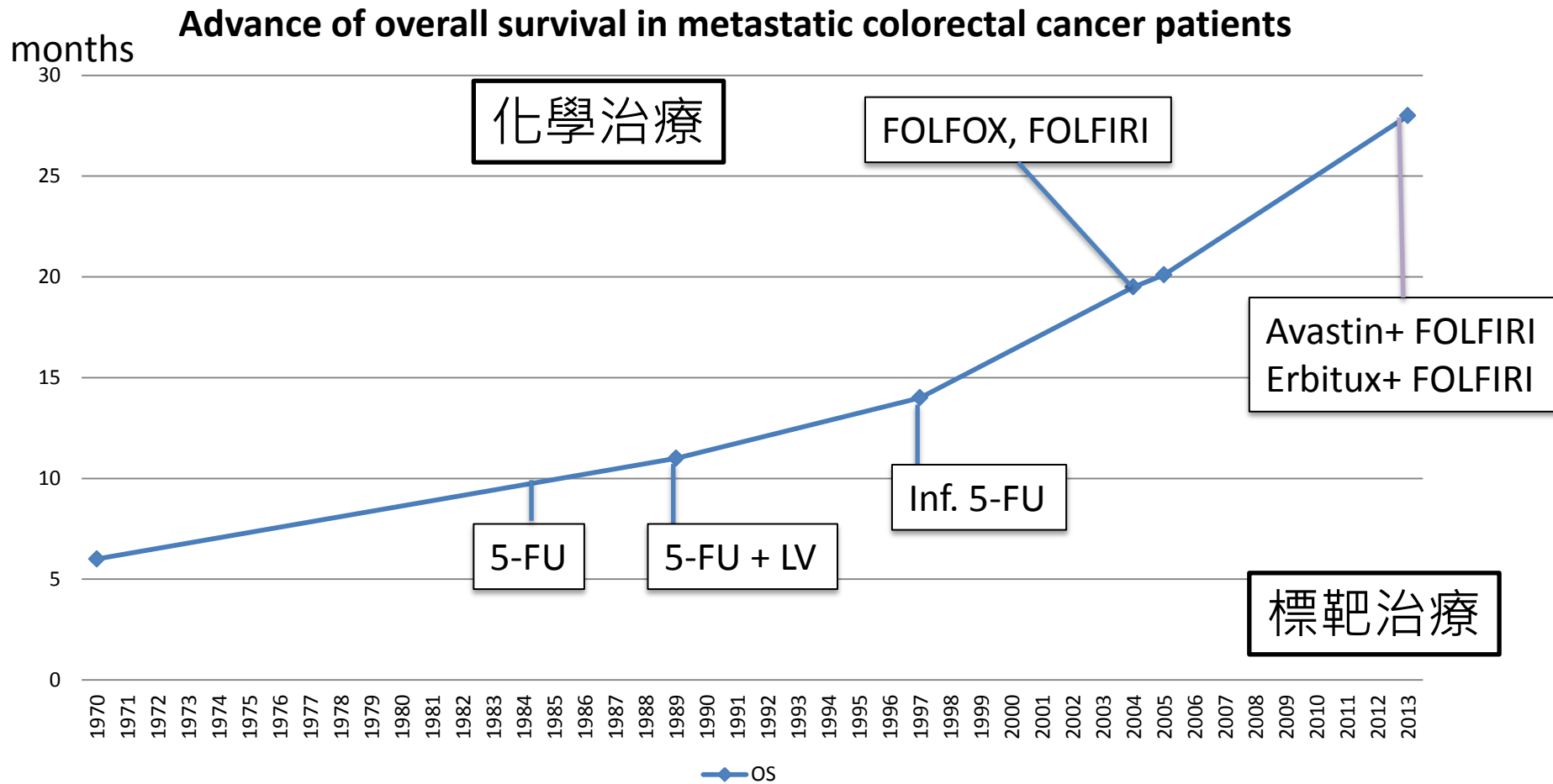
A.3 個月

B.6 個月

C.12 個月

D.24 個月

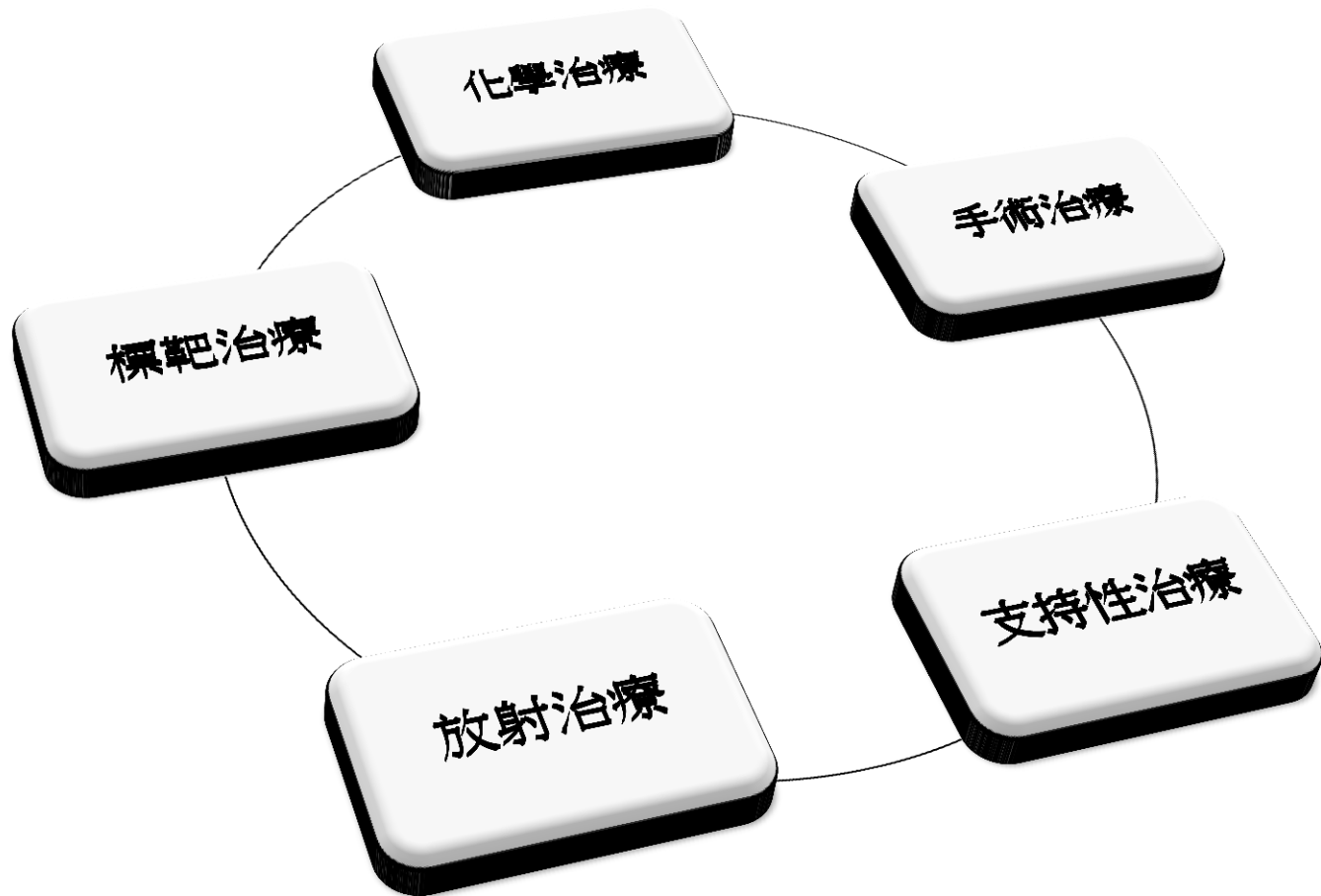
# 存活時間大幅延長!



# 大綱

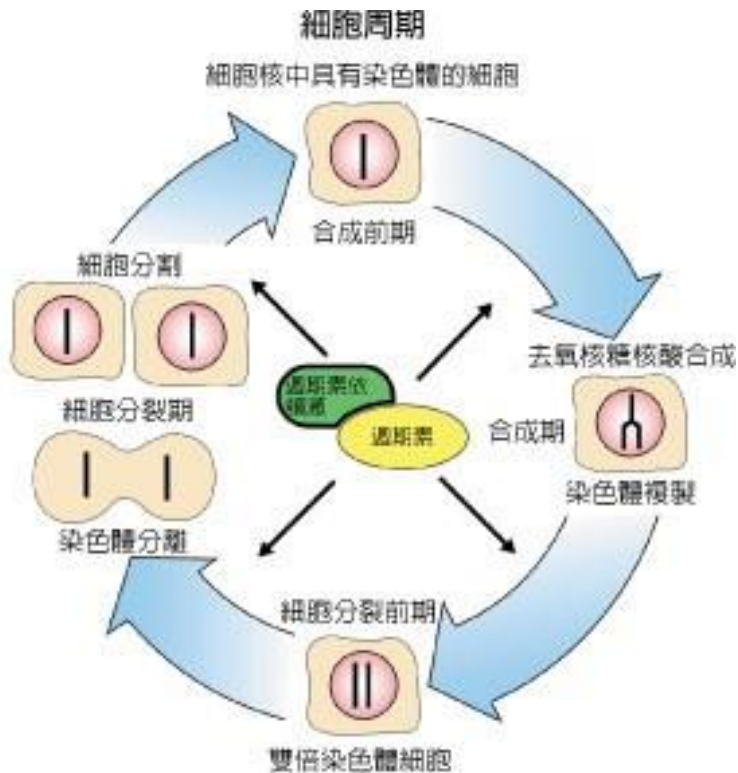
- 大腸直腸癌之化學治療
- 大腸直腸癌之標靶治療
- 大腸直腸癌個人化治療
- 總結

# 大腸直腸癌之治療選擇

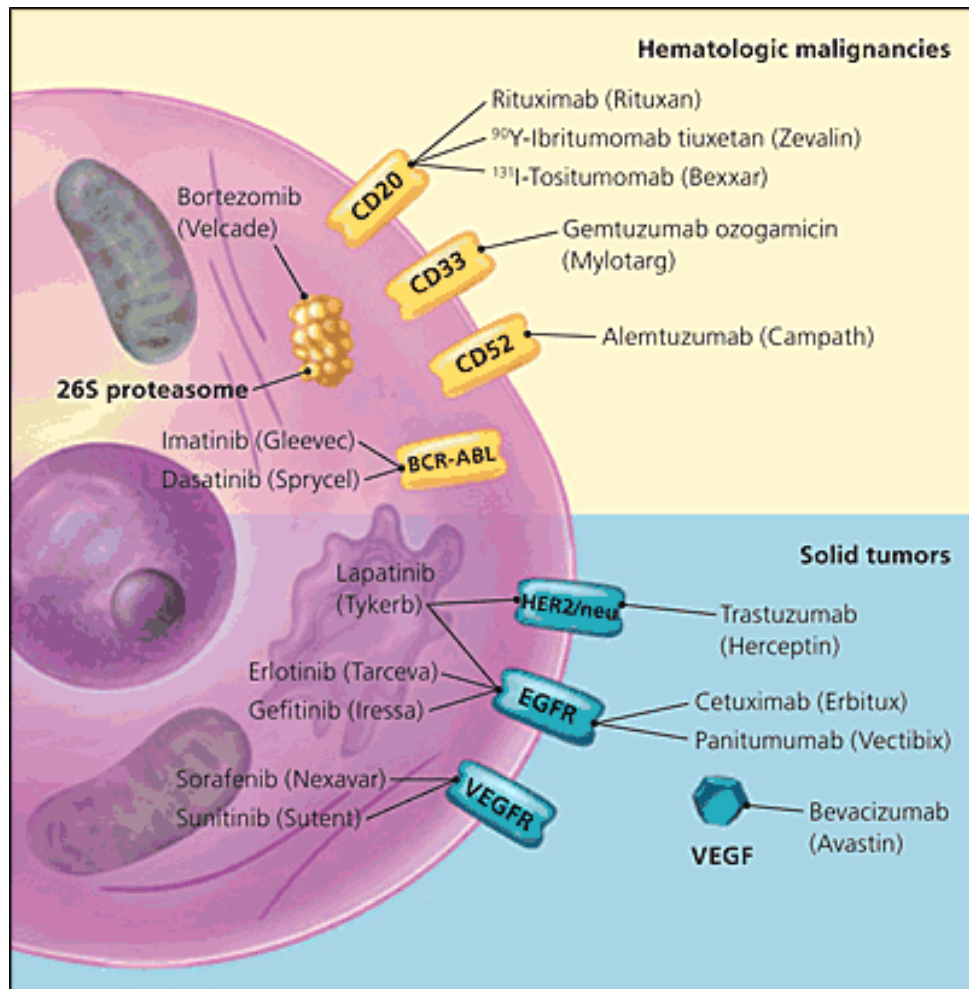


# 何謂化學治療(Chemotherapy)?

- 使用一種或多種具細胞毒性的藥物來治療惡性腫瘤



# 何謂標靶治療(Targeted Therapy)?



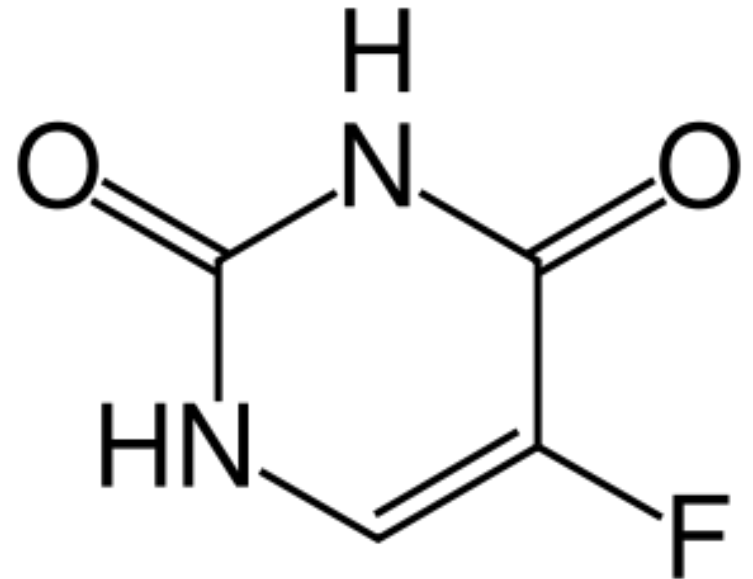
# 大腸直腸癌之化學治療

- 注射化學治療藥品
  - Fluorouracil (5-FU) (有利癌)
  - FOLFIRI
  - FOLFOX
- 口服化學治療藥品
  - Capcitabine (Xeloda®) (截瘤達)
  - UFUR® (友復)

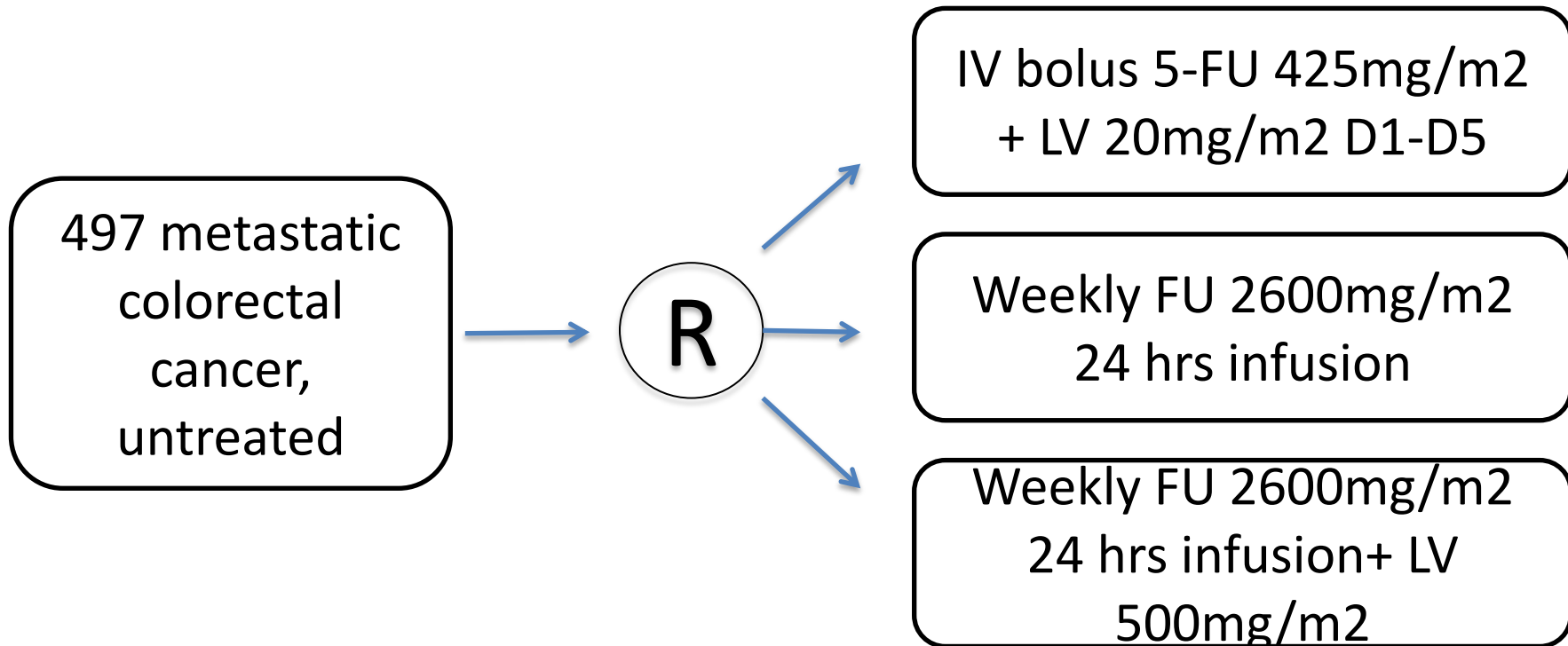


# Fluorouracil (5-FU)(有利癌)

- 合成於西元1957
- 1980s年找到好伙伴:  
folinic acid  
(leucovorin)
- 口服: UFUR (友復)
- 常見副作用:
  - 骨髓抑制
  - 口腔發炎
  - 腹瀉



# Infusion is Better than Bolus



# Infusion is Better than Bolus

	FU bolus + LV	FU24h inf.	FU24h inf. + LV
Progression-free survival (months)	4	4.1	5.6
Overall survival (months)	11.1	13	13.7
Gr3-4 Leukopenia (%)	6.7	4	1.7
Gr3-4 Stomatitis (%)	11	3	5
Gr3-4 Diarrhea (%)	9	6	22

PFS: progression free survival

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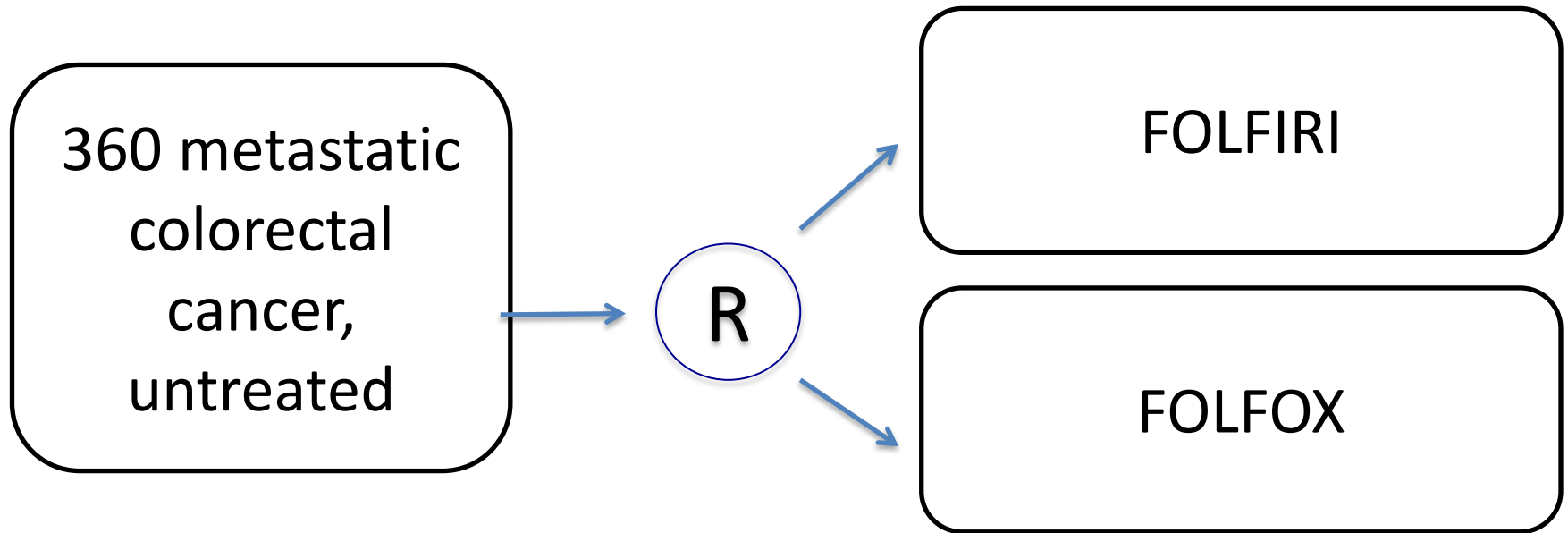
# FOLFIRI

- FOLFIRI= Folinic acid + 5-FU + Irinotecan
- 5-FU: 2400~3000mg/m<sup>2</sup> 46 hours infusion +/- 400mg/m<sup>2</sup> bolus
- Irinotecan (campto®) (抗癌妥)
- Bi-weekly

# FOLFOX

- FOLFOX = Folinic acid + 5-FU + Oxaliplatin
- 5-FU: 2400~3000mg/m<sup>2</sup> 46 hours infusion +/- 400mg/m<sup>2</sup> bolus
- Oxaliplatin (oxalip®) (歐力普)
- Bi-weekly

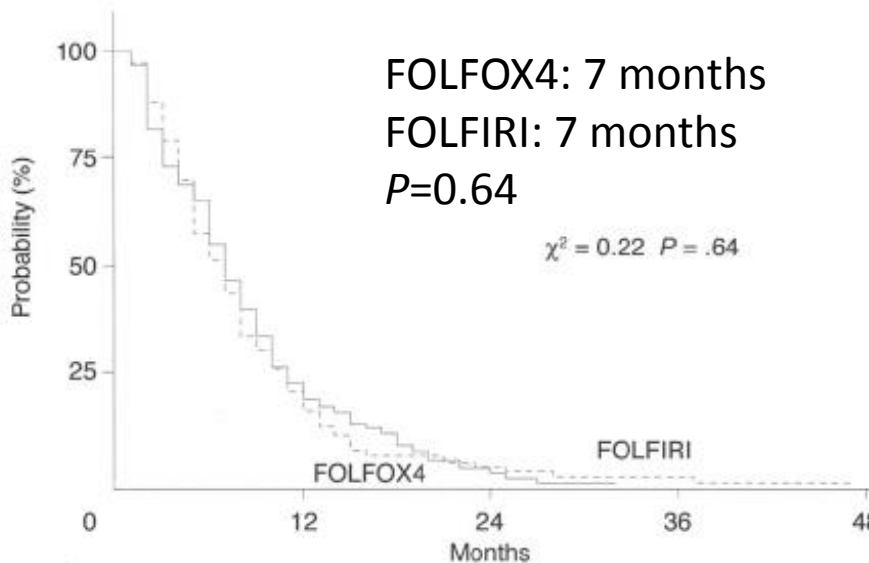
# FOLFOX vs. FOLFIRI



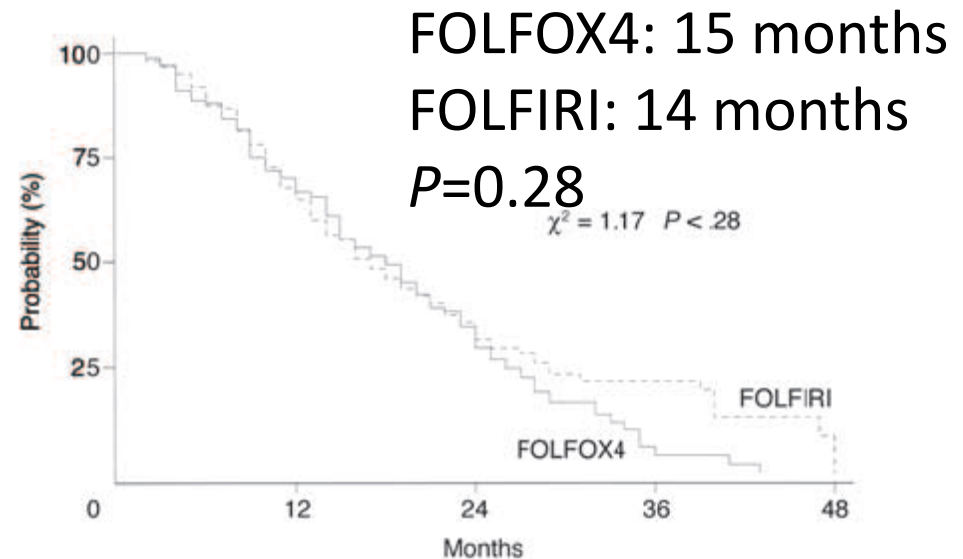
FOLFIRI: irinotecan 180mg/m<sup>2</sup> + /- leucovorin 100mg/m<sup>2</sup> inf. 2 hours on D1 →  
5-FU 400mg/m<sup>2</sup> IV → 5-FU 600mg/m<sup>2</sup> inf. 22 hours on D1-D2  
FOLFOX: oxaliplatin 85mg/m<sup>2</sup> + /- leucovorin 100mg/m<sup>2</sup> inf. 2 hours on D1 →  
5-FU 400mg/m<sup>2</sup> IV → 5-FU 600mg/m<sup>2</sup> inf. 22 hours on D1-D2

# FOLFOX, FOLFIRI 抗癌效果相當

## Time to progression



## Overall survival





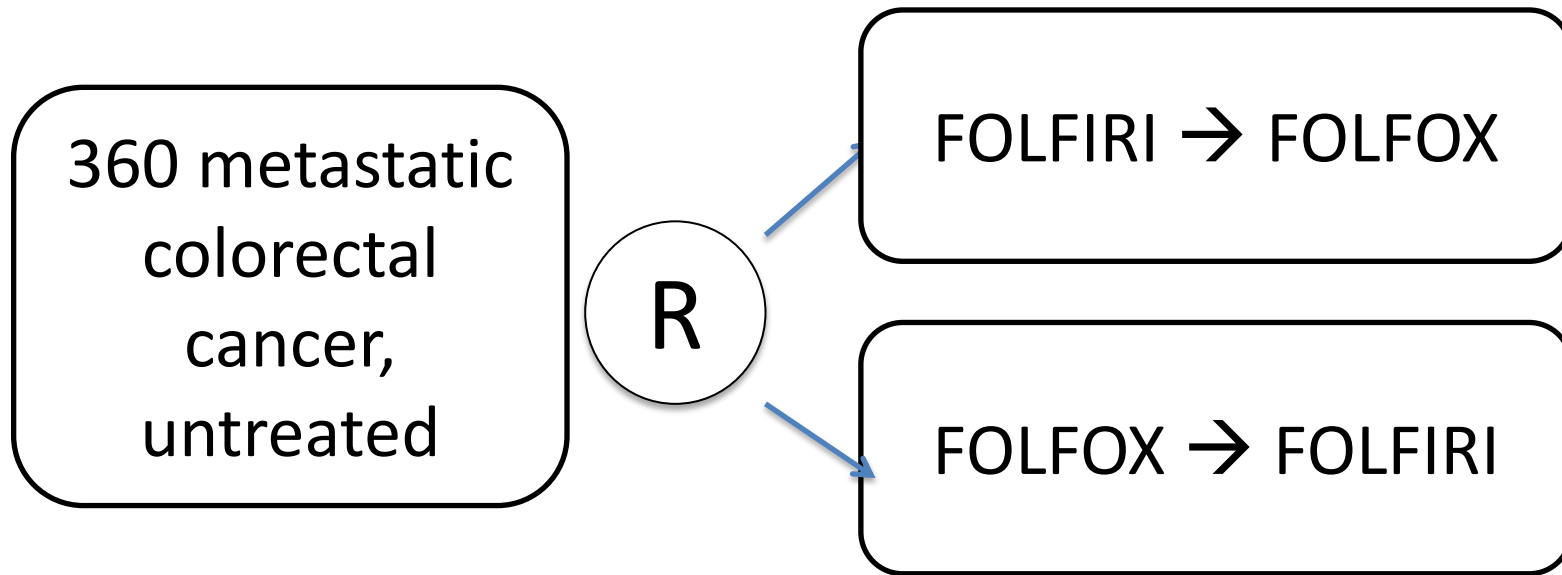
# FOLFOX, FOLFIRI副作用不同

Toxicity	FOLFIRI				FOLFOX4			
	Grade 1 to 2		Grade 3 to 4		Grade 1 to 2		Grade 3 to 4	
	No.	%	No.	%	No.	%	No.	%
Anemia	67	38	1	1	60	33	3	2
Leukopenia	65	37	5	3	70	38	5	3
Neutropenia	63	35	17	10	58	32	18	10
Thrombocytopenia	26	15	1	1	76	42	3	3
Nausea/vomiting	120	67	8	4	102	56	5	3
<u>Diarrhea</u>	95	53	<u>18</u>	<u>10</u>	74	41	<u>9</u>	<u>5</u>
Mucositis	61	34	2	1	52	29	2	1
Loss of hair	75	42	—	—	35	19	—	—
<u>Cholinergic syndrome</u>	<u>18</u>	<u>10</u>	—	—	—	—	—	—
<u>Neurologic*</u>	9	5	<u>—</u>	<u>—</u>	74	41	<u>8</u>	<u>4</u>
Fever	26	15	2	1	37	20	—	—
Asthenia	28	16	—	—	24	13	—	—
Cardiac	2	1	1	1	3	2	2	1
Skin	6	3	—	—	7	4	—	—
Hypersensitivity	—	—	—	—	4	2	2	1

Abbreviations: FOLFIRI, irinotecan, fluorouracil, and leucovorin; FOLFOX4, oxaliplatin, leucovorin, and bolus plus infusional fluorouracil.

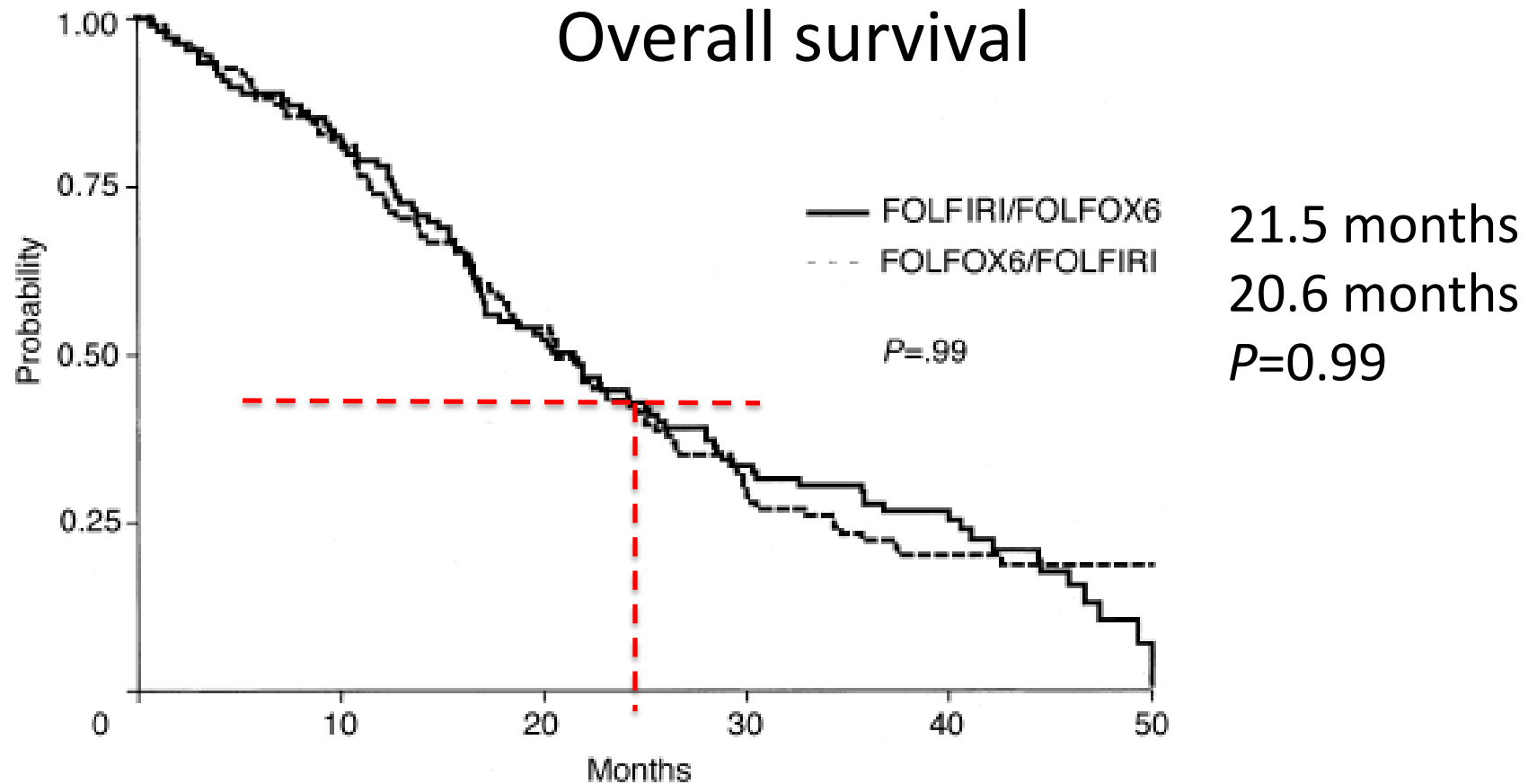
\*Peripheral neuropathy was graded according to the specific grading system of Levi et al.<sup>22</sup>

# FOLFOX or FOLFIRI, 誰先誰後?



FOLFIRI: irinotecan 180mg/m<sup>2</sup> + /- leucovorin 200mg/m<sup>2</sup> inf. 2 hours on D1 → 5-FU 400mg/m<sup>2</sup> IV → 5-FU 2400mg/m<sup>2</sup> 46 hours inf. On D1  
FOLFOX: oxaliplatin 85mg/m<sup>2</sup> + /-leucovorin 200mg/m<sup>2</sup> inf. 2 hours on D1 → 5-FU 400mg/m<sup>2</sup> IV → 5-FU 2400mg/m<sup>2</sup> 46 hours inf. On D1

# FOLFOX or FOLFIRI, 誰先誰後?



# 口服化學治療

- Capcitabine (Xeloda®) (截瘤達)
  - 作用機轉類似5-FU
  - 增加對抗腫瘤專一性
  - 可取代5-FU與其他注射化療併用:  
XELOX, XELIRI...
  - 常見副作用: 手足症候群、腹瀉

# 截瘤達引起之手足症候群



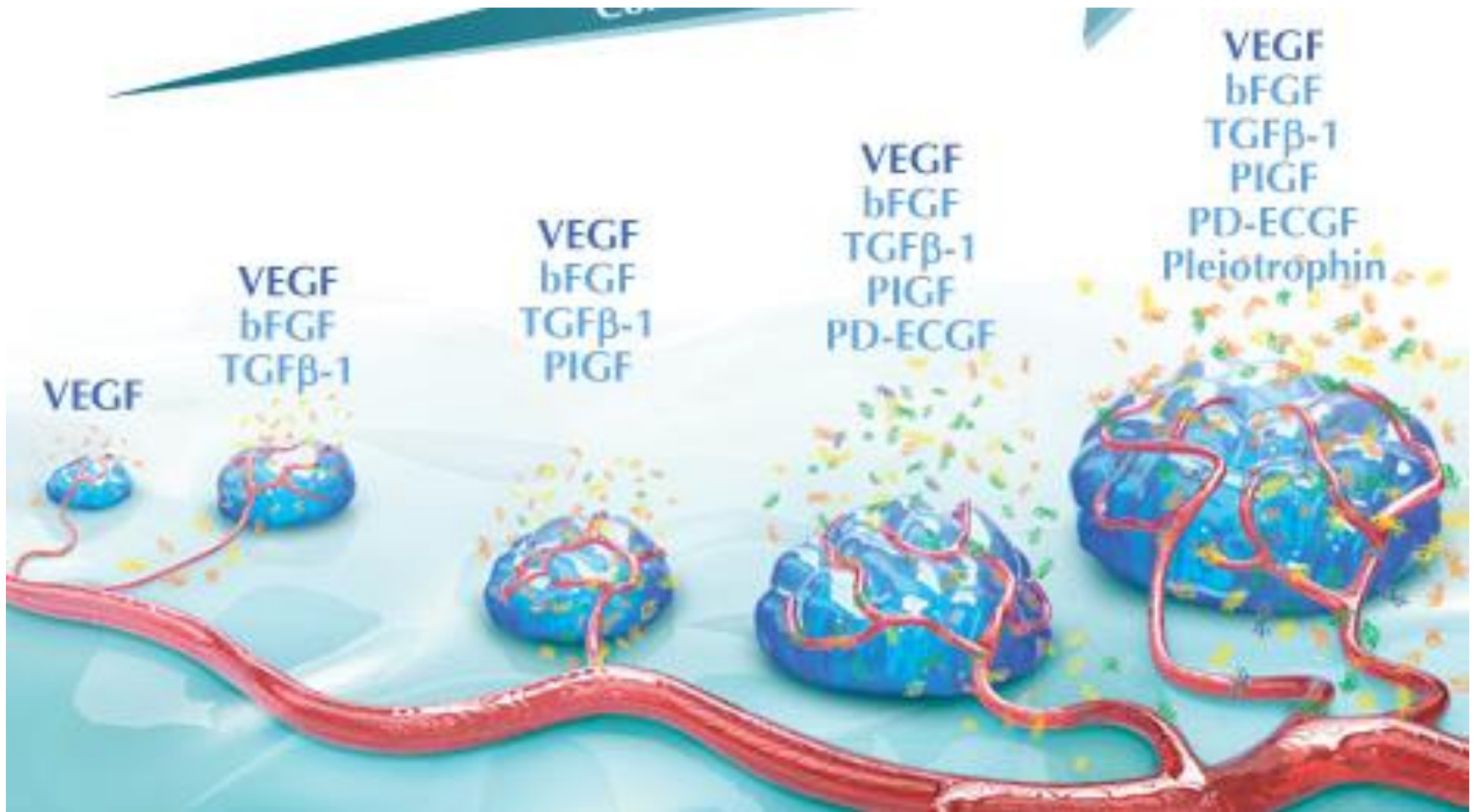
# 化學治療的使用目的

- Palliative: 症狀緩解，延長存活時間
  - 第四期病人
  - FOLFOX, FOLFIRI, Capcitabine, UFUR, fluorouracil...
- Adjuvant: 治癒更多病人
  - 第二、三期病人
  - FOLFOX

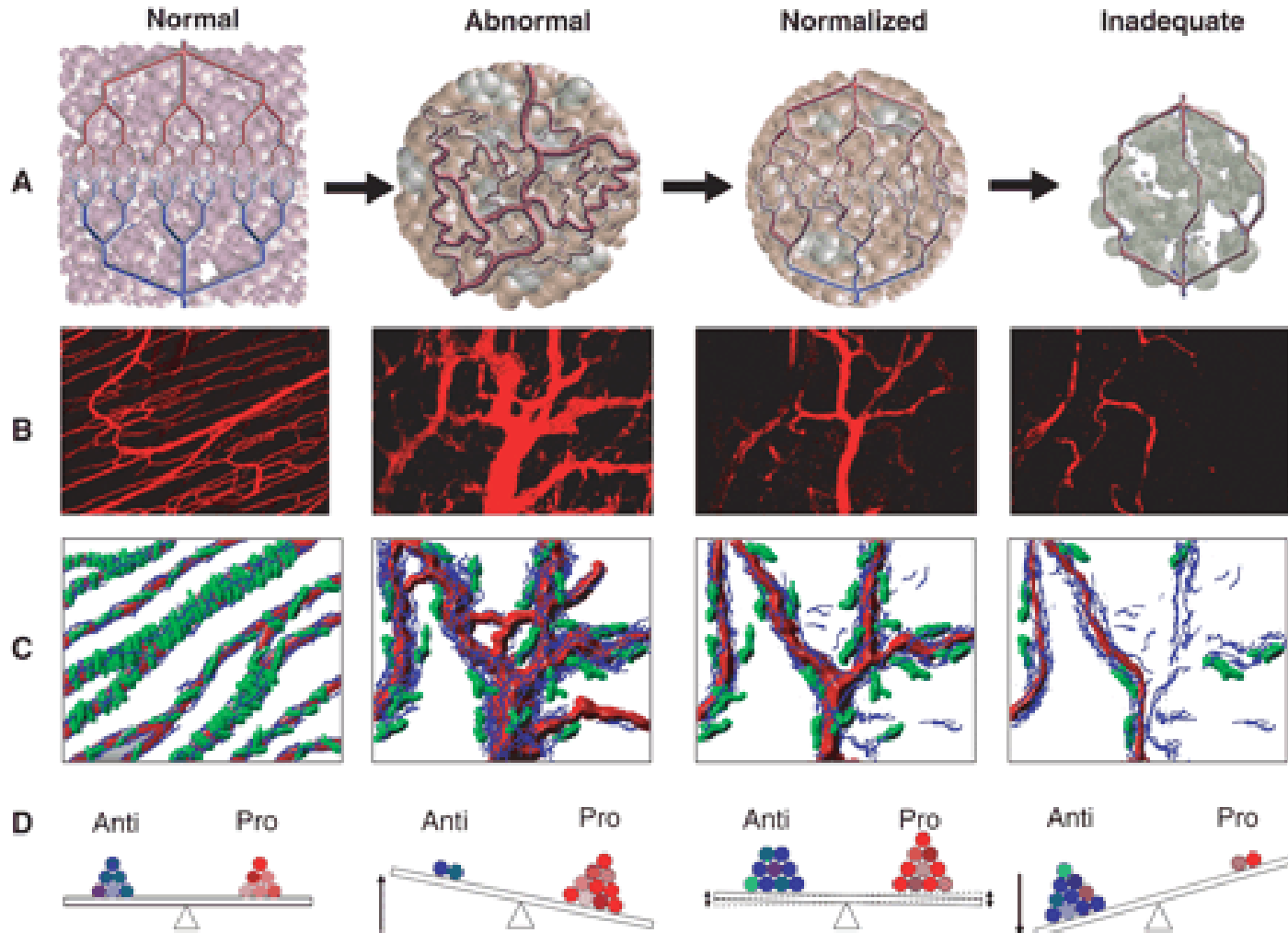
## 大腸直腸癌之標靶治療

- 血管新生抑制劑
- EGFR 單株抗體

# 抑制血管新生→使腫瘤缺血(營養)



# 抑制血管新生 → 增加藥物傳遞





# 血管新生抑制劑

- Bevacizumab (avastin®)(癌思停): 健保有條件給付
- Regorafenib (stivarga®): 需專案申請
- Ziv-aflibercept (zaltrap®): 未進入台灣

# Bevacizumab (avastin®)(癌思停)

- VEGF antibody
- 合併FOLFIRI (健保給付)、FOLFOX、Fluorouracil、Capcitabine 會增加其療效
- 副作用：
  - 高血壓、蛋白尿、血管栓塞、增加出血機率、腸穿孔

# EGFR 單株抗體

- Cetuximab (erbitux®)(爾必得舒): 健保有條件給付
- Panitumumab (vectibix®): 未進入台灣

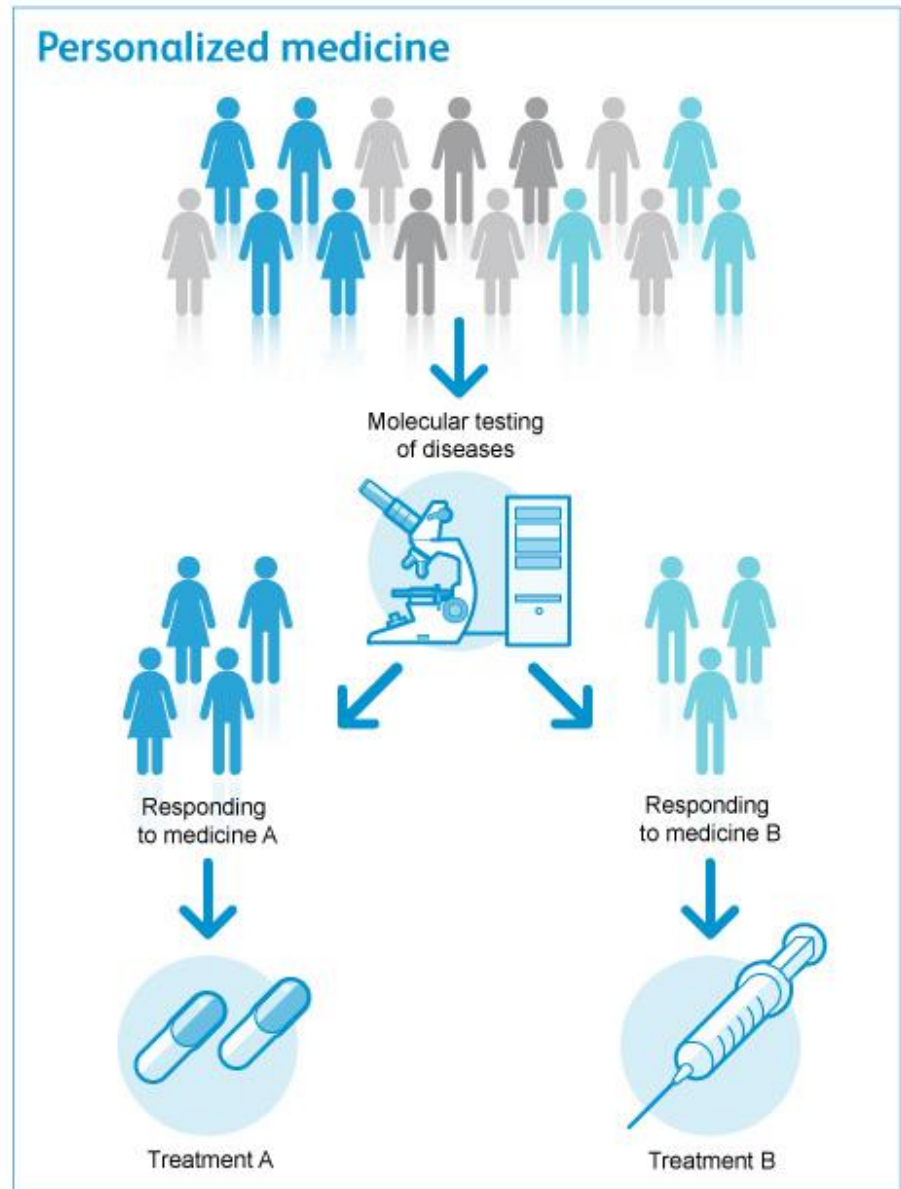
# Cetuximab (erbitux®) (爾必得舒)

- EGFR monoclonal antibody
- 單獨使用或合併FOLFIRI, 5-FU使用可延長大腸直腸癌病人存活期
- 副作用:
  - 痲瘡般皮疹
  - 腹瀉
  - 噁心、嘔吐
  - 發燒

# 痤瘡般皮疹

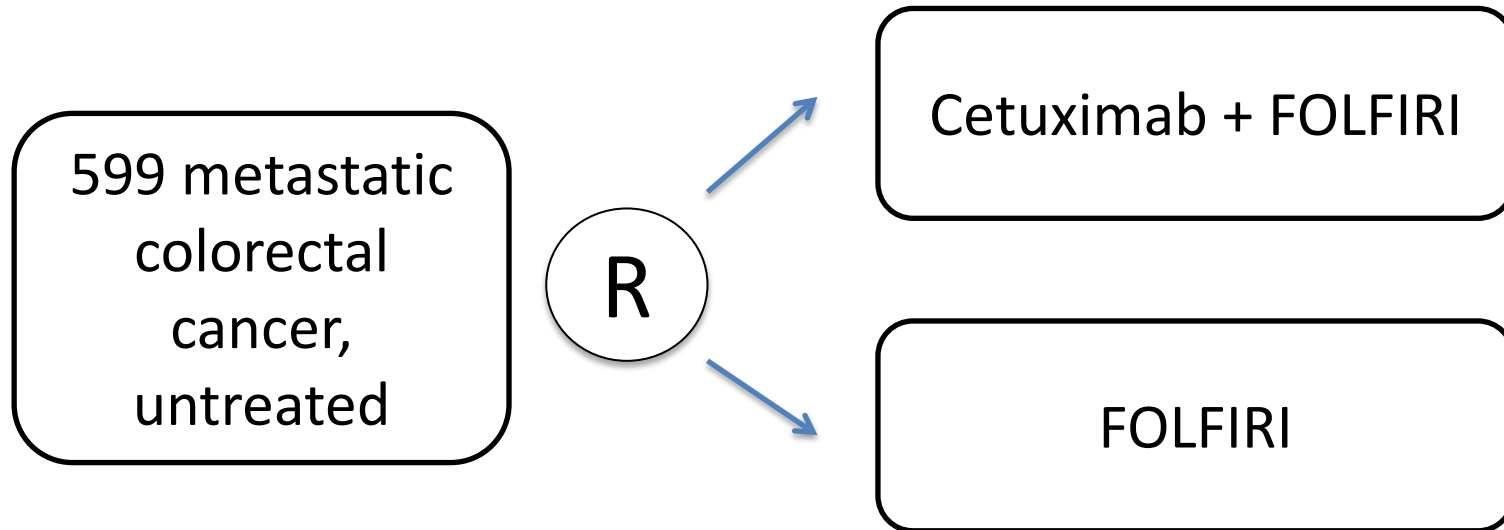


# 個人化治療 (Personalized Therapy)



New molecular and diagnostic technologies can be used to match select groups of patients with treatments that may give them the best results

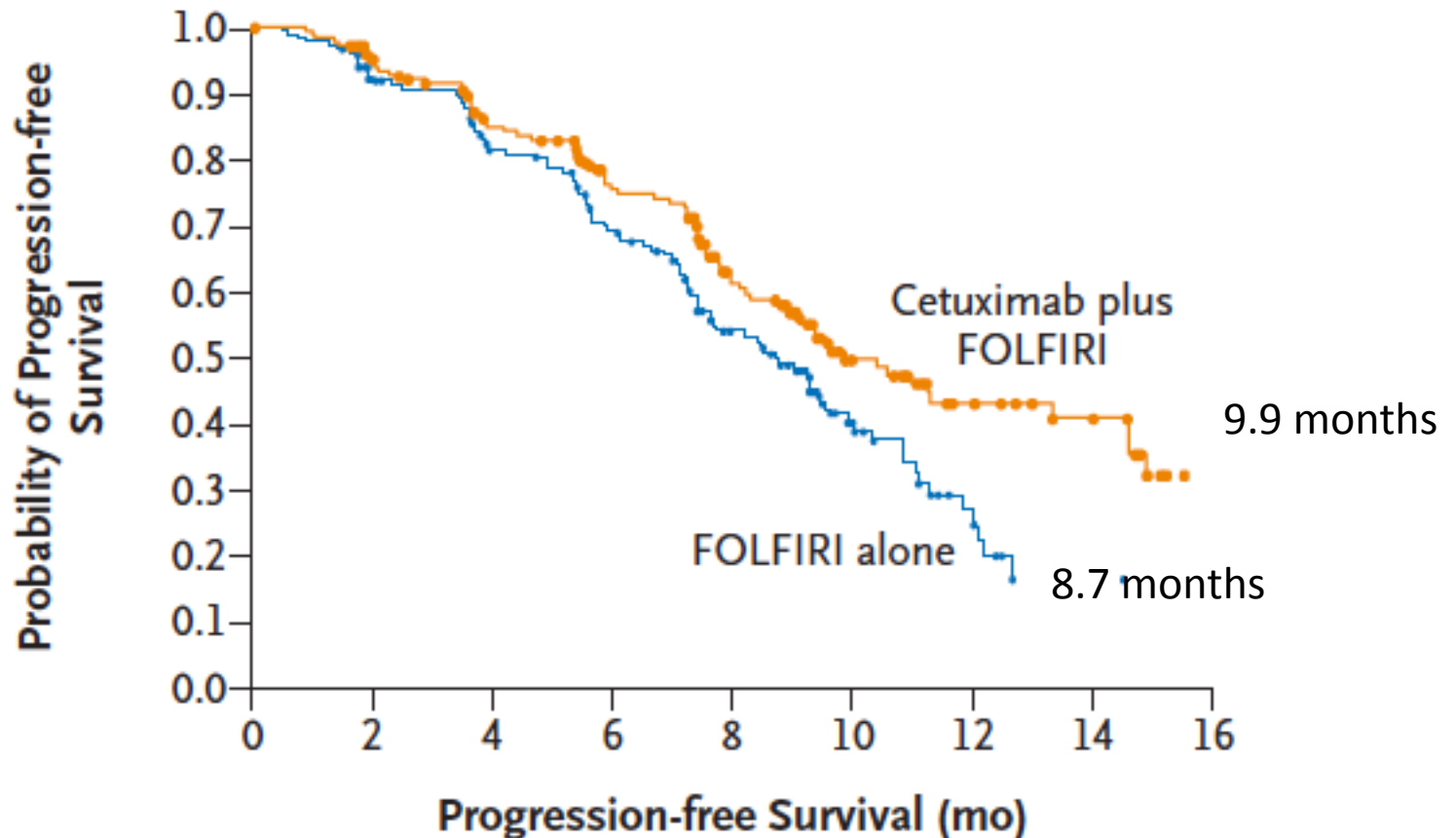
# CRYSTAL Study



FOLFIRI: irinotecan 180mg/m<sup>2</sup> + /- leucovorin 200mg/m<sup>2</sup> inf. 2 hours on D1 →  
5-FU 400mg/m<sup>2</sup> IV → 5-FU 2400mg/m<sup>2</sup> 46 hours inf. On D1  
Cetuximab: 400mg/m<sup>2</sup> loading on D1, then 250mg/m<sup>2</sup> weekly

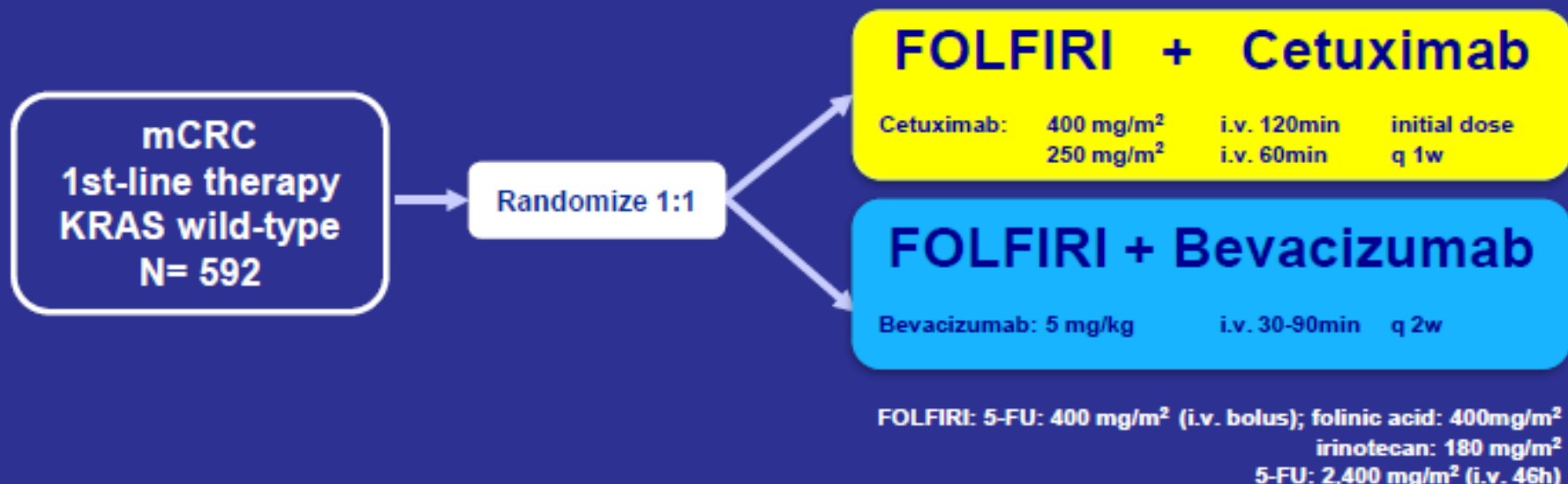
# KRAS – Predictive Biomarker

Wild-Type-KRAS Population



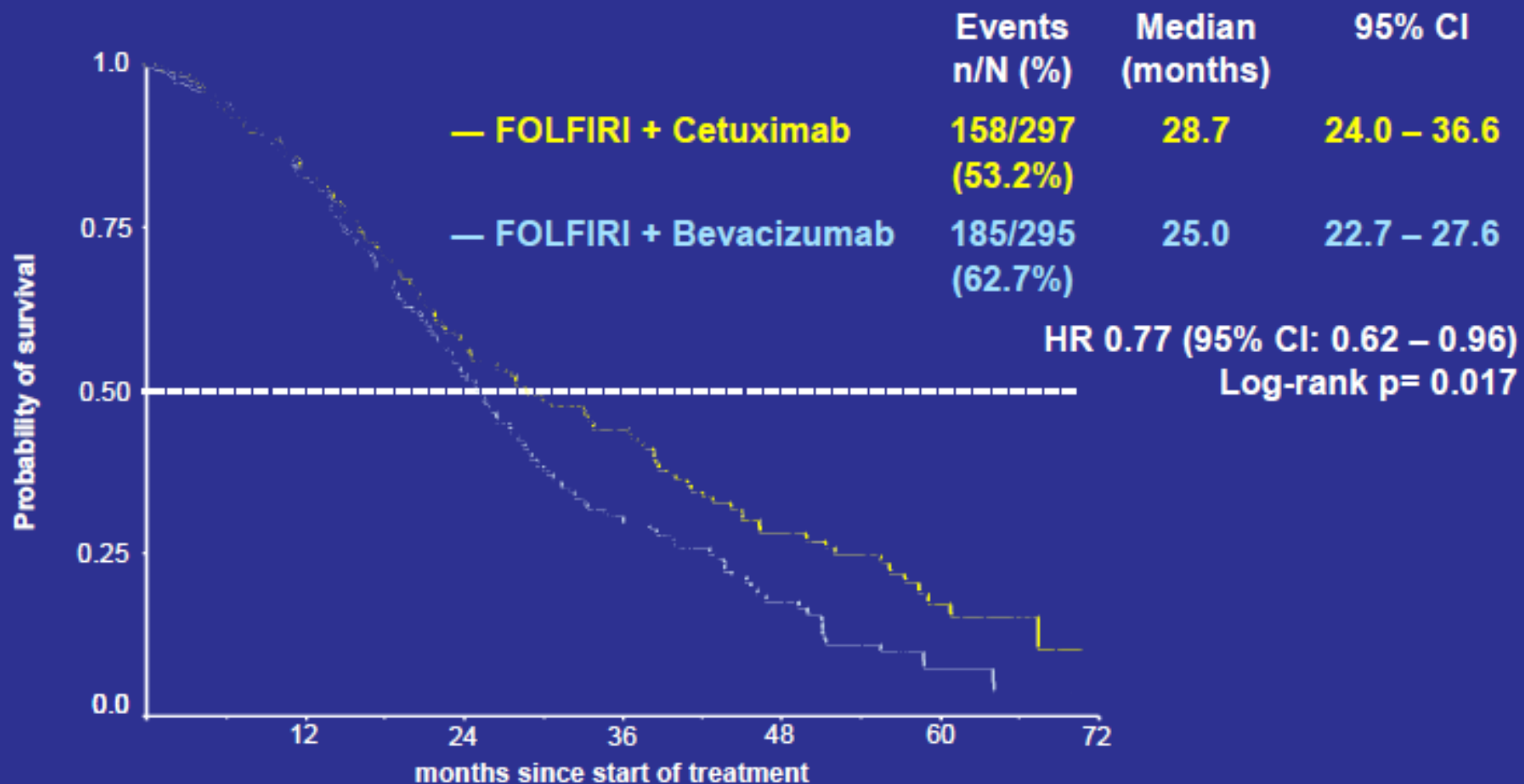


# Phase III study design



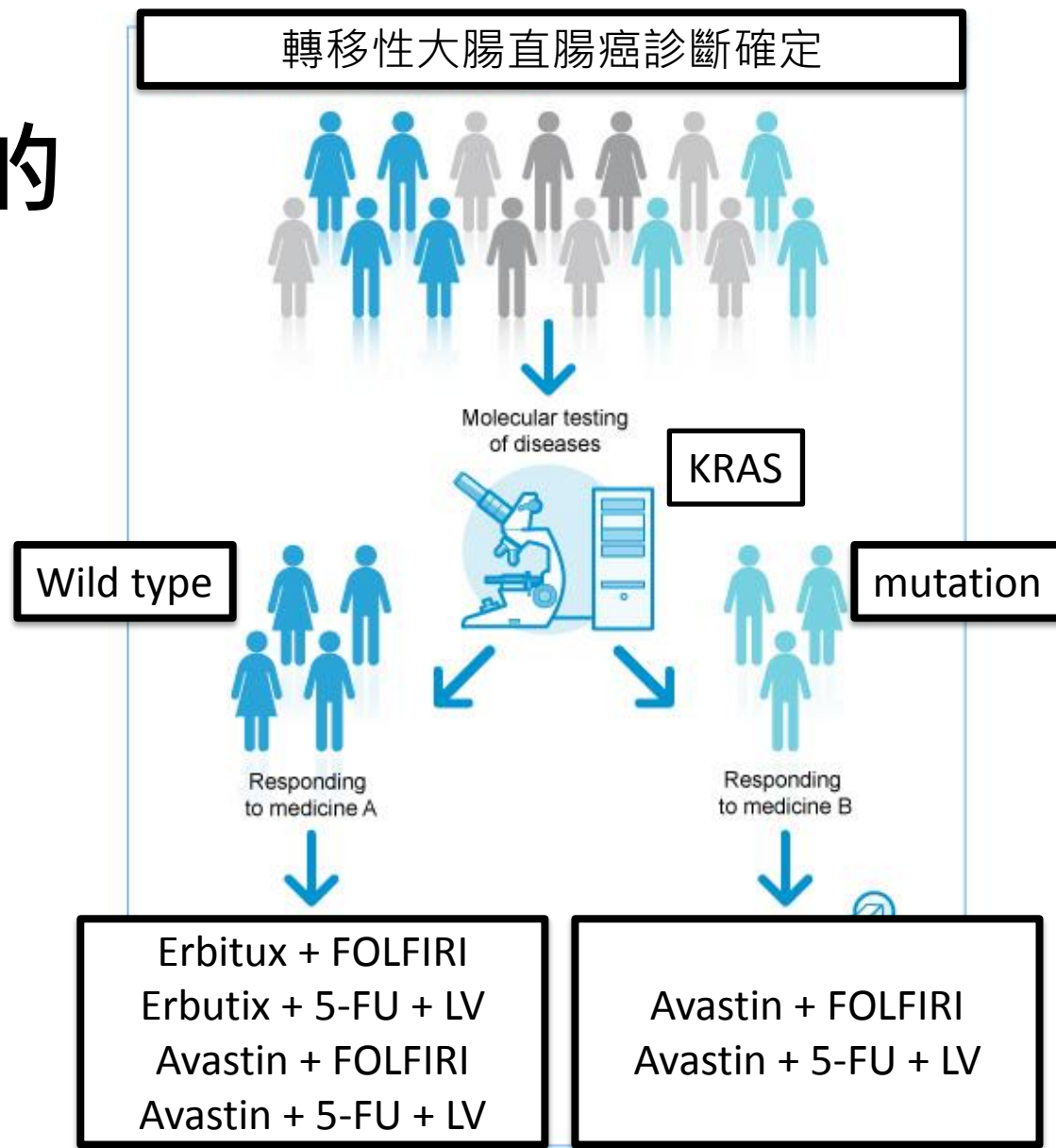
- **Key inclusion criteria**
  - Patients ≥18 years with histologically confirmed diagnosis of mCRC
  - ECOG PS 0-2
  - prior adjuvant chemotherapy allowed if completed >6 month before inclusion
- **Amendment in October 2008** to include only KRAS wildtype patients
- 150 active centers in Germany and Austria

# Overall survival



numbers	297	218	111	60	29	9
at risk	295	214	111	47	18	2

# 大腸直腸癌的 個人化治療 (Personalized Therapy in Colorectal Cancer)



New molecular and diagnostic technologies can be used to match select groups of patients with treatments that may give them the best results

# 總結

- 大腸直腸癌之化學、標靶治療種類很多，治療效果近年來有顯著進步
- 分子檢驗醫學的進步，使大腸直腸癌也開始進入個人化醫療的治療理想