肝癌免疫治疗的假性进展探索

免疫检查点抑制剂加速获批多种适应症

Nivolumab makes headwinds into HCC 2015

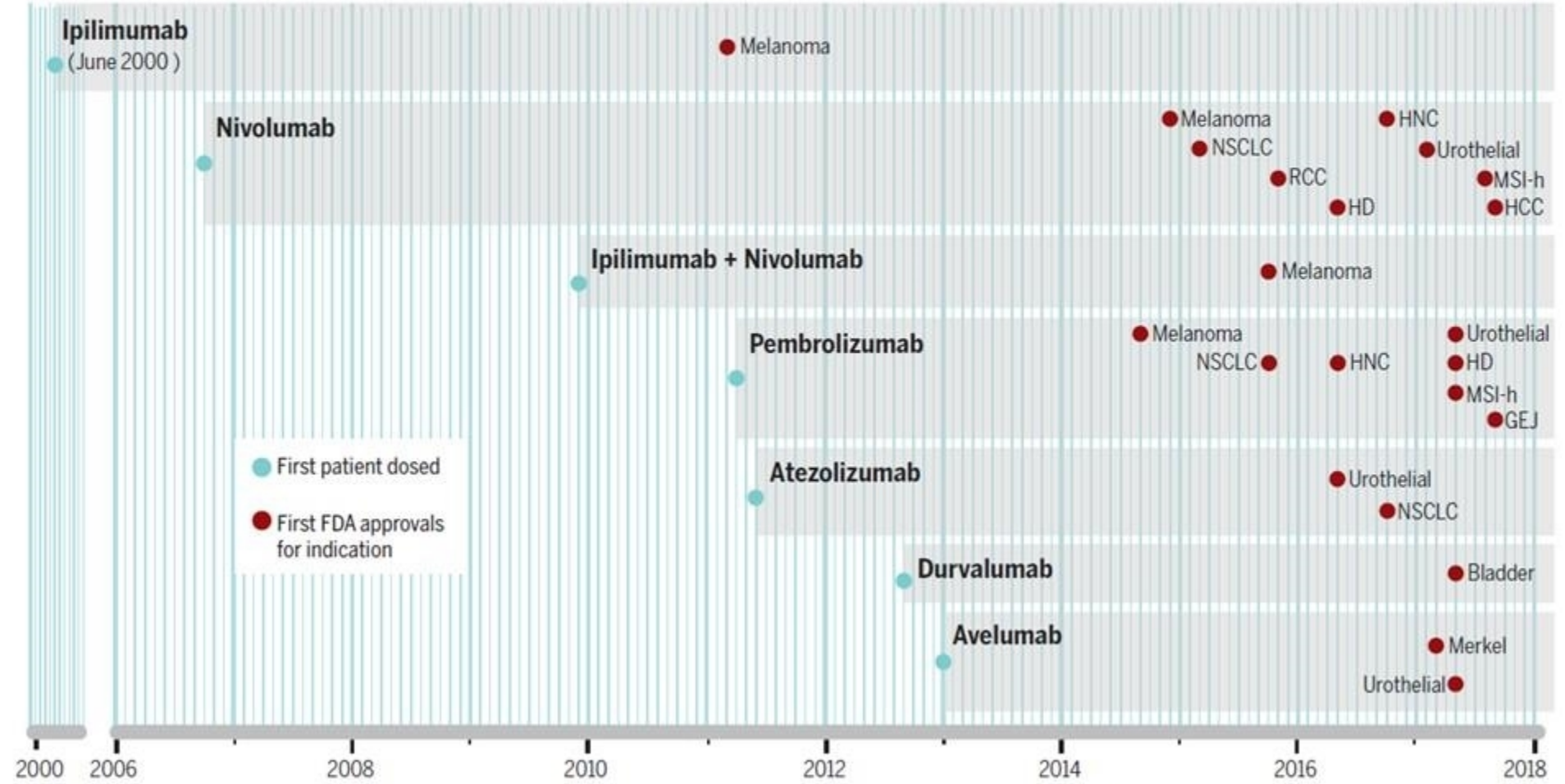
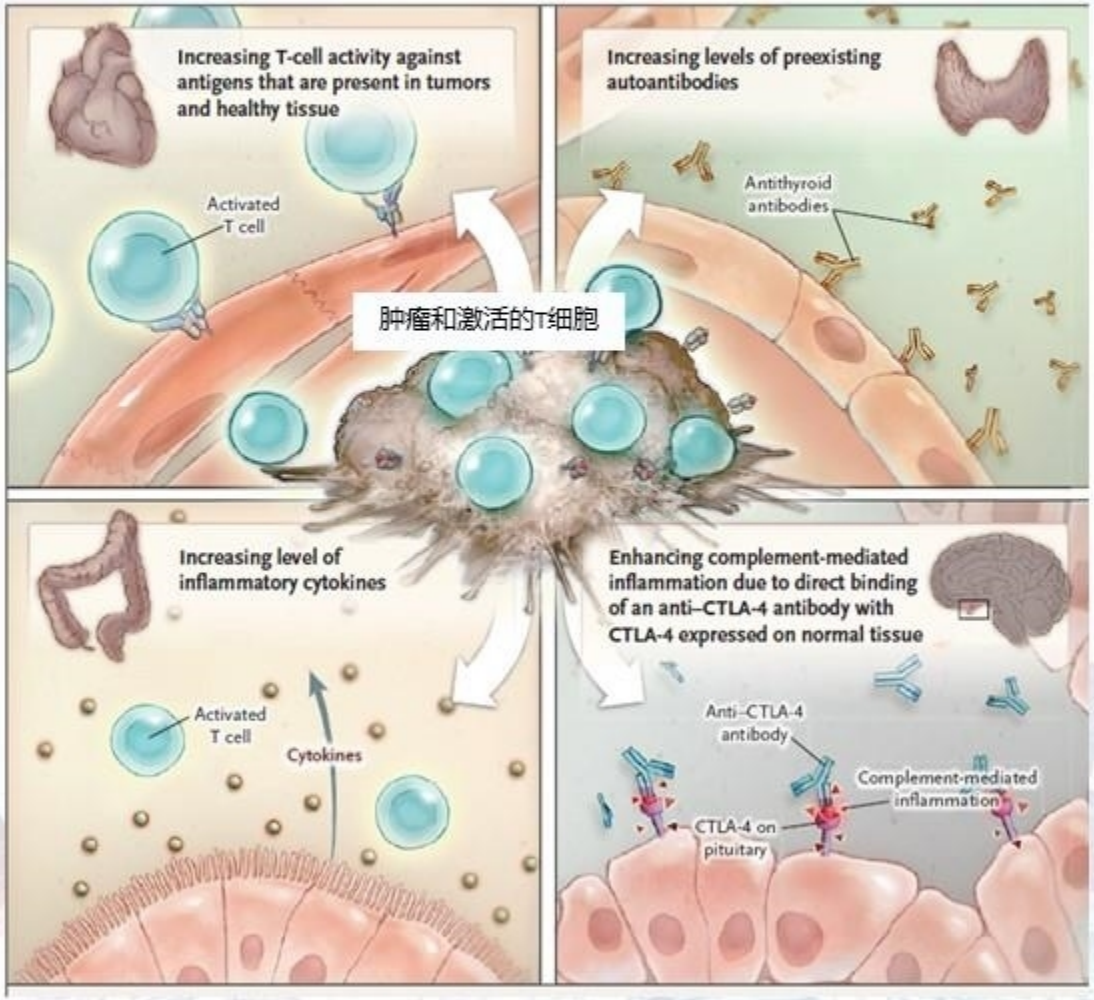


Fig. 2. Timing of clinical development of anti–CTLA-4, anti–PD-1, and anti–PD-L1 antibodies, from first administration to humans to FDA approval.

- Ribas et al., Science 359, 1350–1355 (2018)

免疫治疗的特点

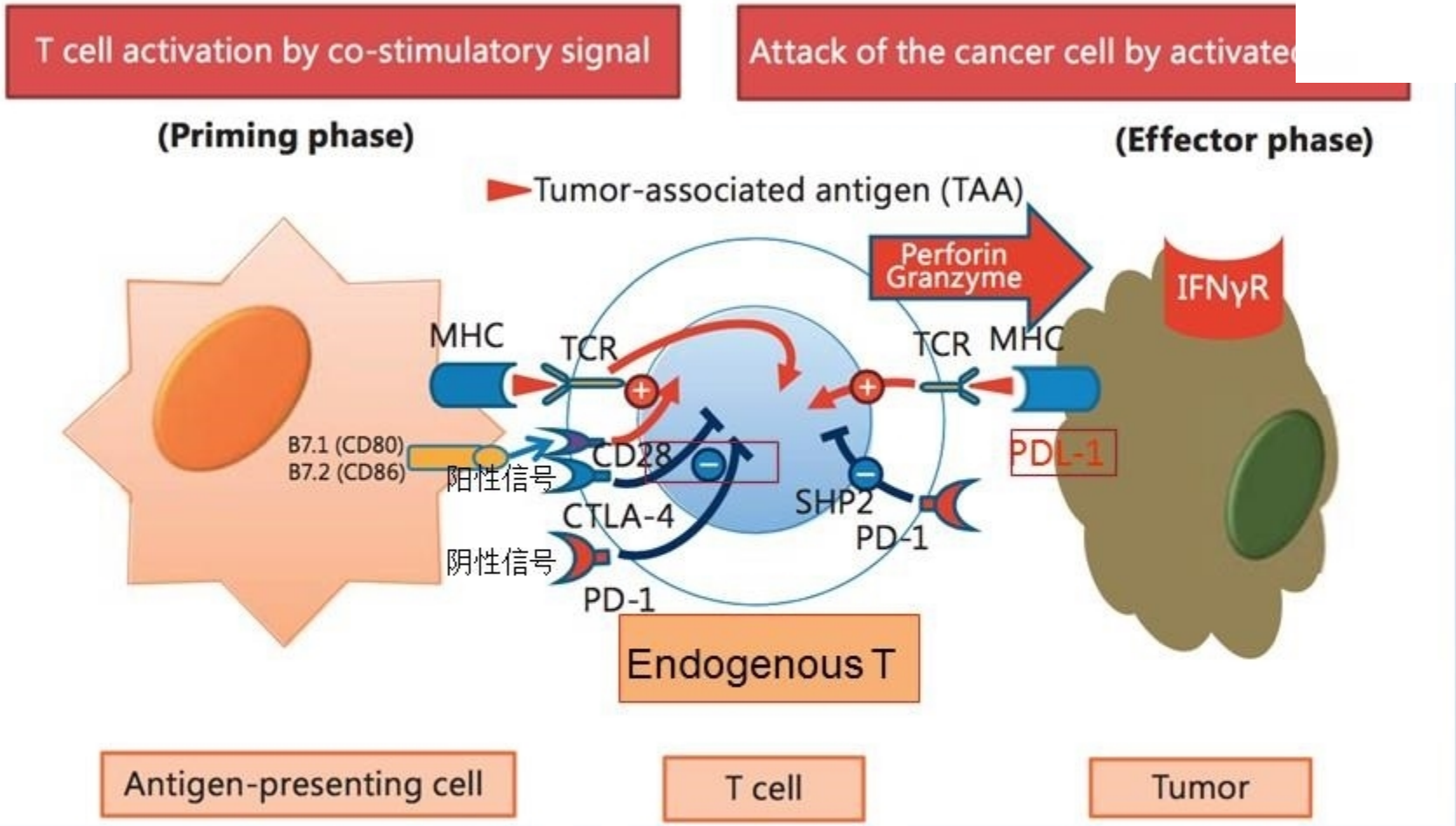
- T细胞激活，攻击肿瘤细胞的同时可能会攻击正常细胞



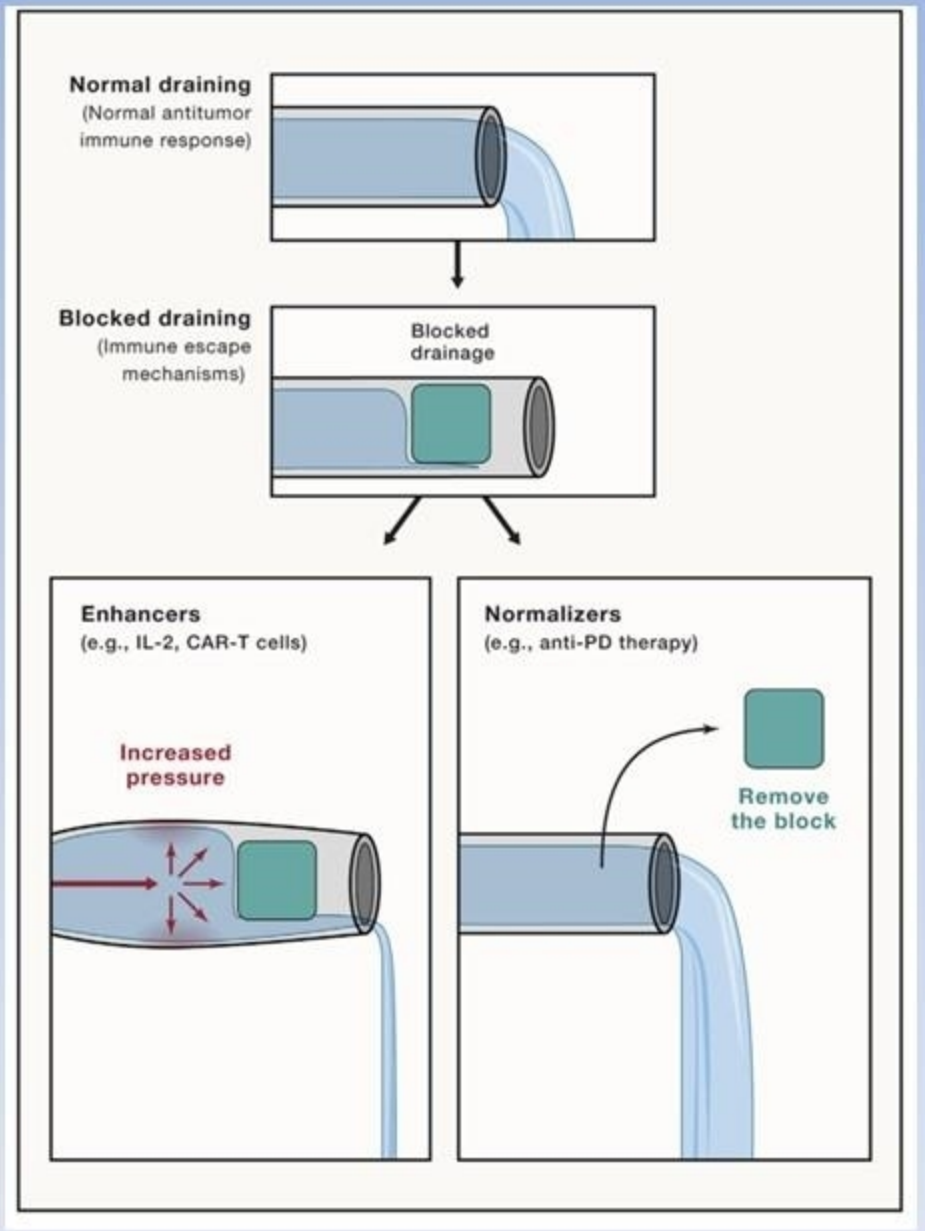
- 提高已经存在的自身免疫抗体水平
- 提高炎性细胞因子水平
- CTLA-4抗体和正常细胞上的CTLA-4受体结合，从而增强补体介导的炎症

- N ENGL J MED 378;2

免疫检查节点抑制剂治疗机制



Cancer attack by activated T cells. Presentation of tumor-associated antigen by MHC expressed by the antigen-presenting cell leads to the release of an activating signal in combination with a co-stimulatory signal via the B7-CD28 pathway, resulting in activation of T cells in the lymph node. Subsequently, activated T cells attack the tumor by releasing perforin or granzymes.



免疫正常及免疫增强的方法

Using proper flow and drainage of a pipeline as a comparison for the antitumor immune response. The flow of the pipeline can be insufficient when a blockade impairs flow, as the antitumor immune response can be insufficient when there is an immune impairment. The immune enhancement approach is illustrated as an increase in flow or pressure to return to proper function/flow with the risk of breaking the pipe (adverse effects). In contrast, the immune normalization approach would be to identify and try to unblock this specific blockage and restore the flow.

Miguel F. Sanmamed[1] and Lieping Chen Cell *175*, October 4, 2018

CheckMate-040nivolumab用于进展期肝癌的1/2期多队列研究

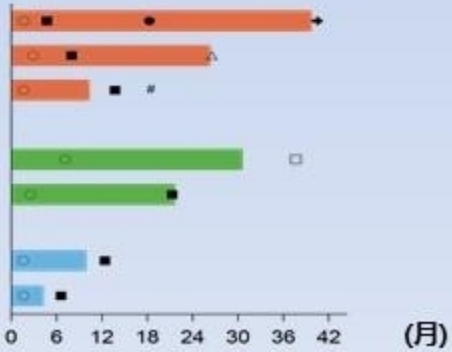
- 大部分患者的客观缓解发生在治疗后3个月内
- 未接受过索拉非尼治疗的患者中位持续缓解时间（mDOR）达到17个月
- 接受过索拉非尼治疗mDOR为19个月（递增组）和16.6个月（扩展组）

未接受索拉非尼治疗

中位TTR(范围)，月	2.7(1.3-5.5)
中位DOR(范围)，月	17.15(4.2-17.1+)

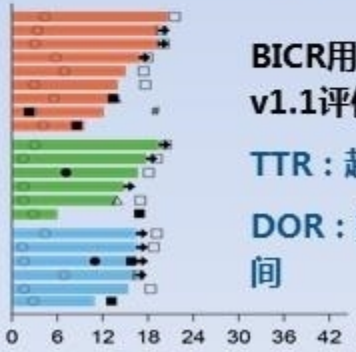
既往接受索拉非尼治疗 ESC

中位TTR(范围)，月	1.4(1.3-6.9)
中位DOR(范围)，月	19.35(2.8-38.2+)



既往接受索拉非尼治疗 EXP

中位TTR(范围)，月	2.8(1.2-7.0)
中位DOR(范围)，月	16.59(3.2-16.8+)



BICR用RECIST v1.1评估肿瘤缓解

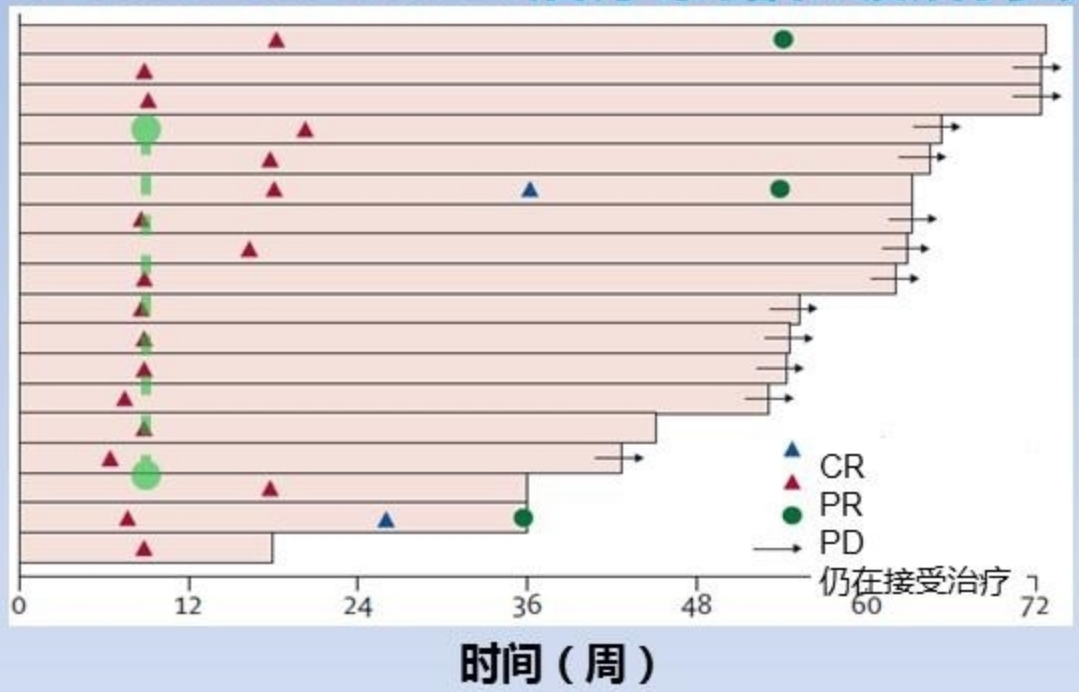
TTR：起效时间

DOR：持续缓解时间

●CR ○PR □末次给药 ■ 停止治疗 →持续缓解 △删失 #死亡

KEYNOTE-224：Pembrolizumab中位至缓解时间~2个月，DOR大于9个月

Pembrolizumab治疗暴露和缓解持续

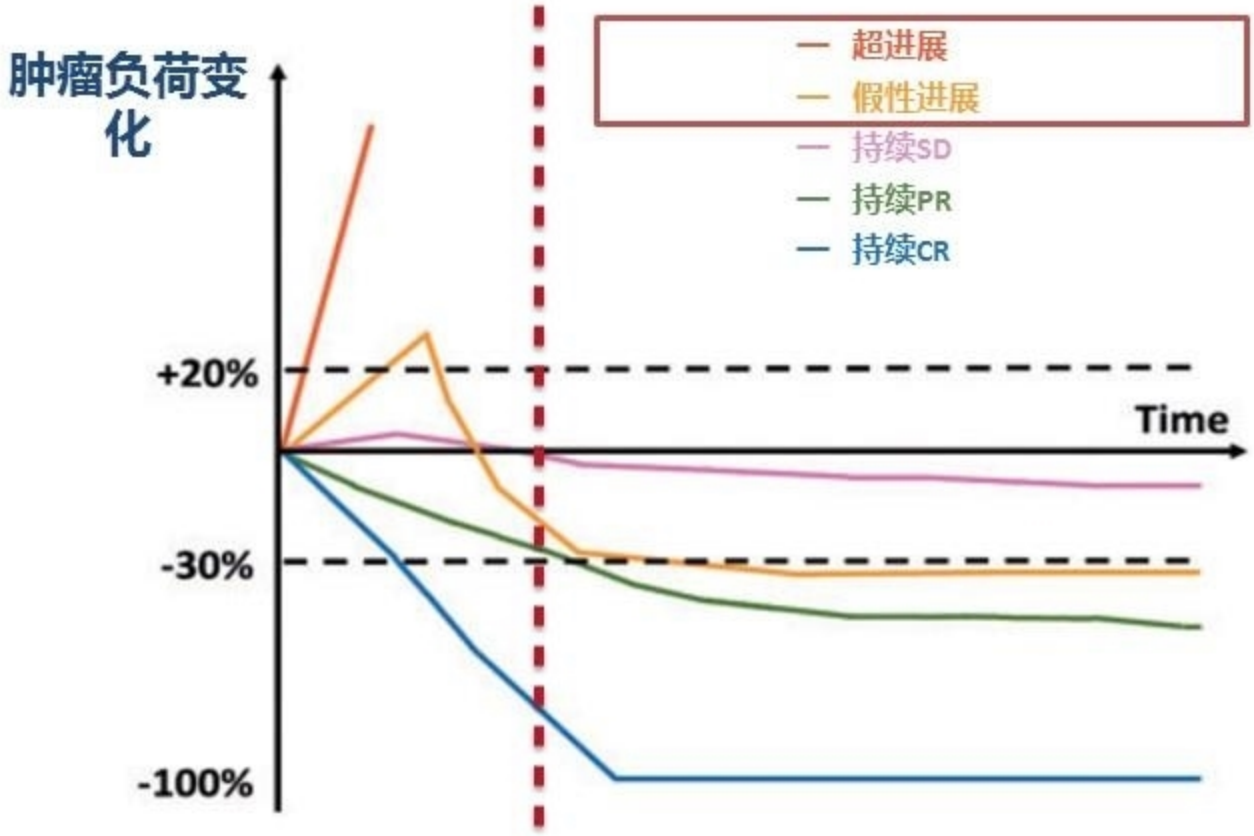


*截止至2018年2月13日，17位（16%）患者仍在用药

- 18例患者（17%）获得缓解†
- 中位至缓解时间，月（范围）=2.1（2.1-4.1）
- 缓解持续时间≥9个月‡=77%
- 中位缓解持续时间，月（范围）§未达到（3.1 – 14.6+）

†最佳总体缓解仅为经证实的CR或PR；‡采用Kaplan-Meier方法处理删失数据；§“+”表示患者在最后一次疾病评价时未出现疾病进展。数据截止日期为2018年2月13日。

免疫治疗中应答和进展的类型

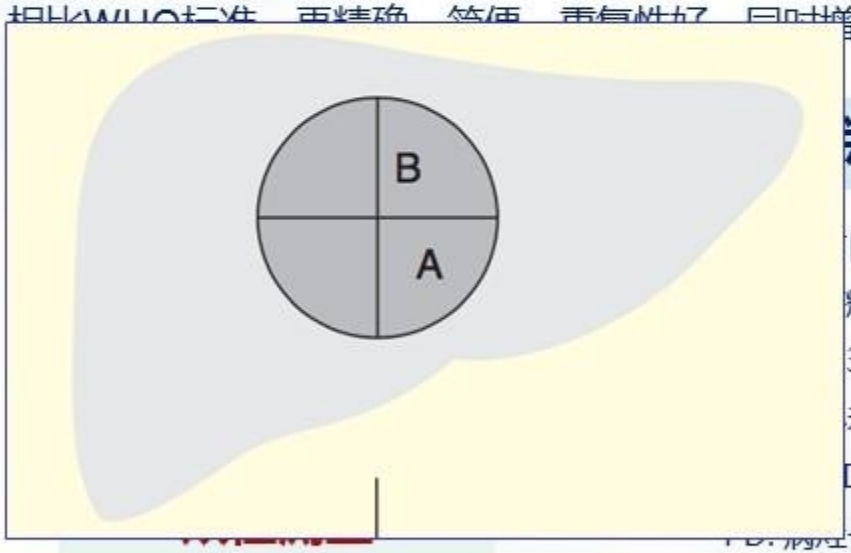


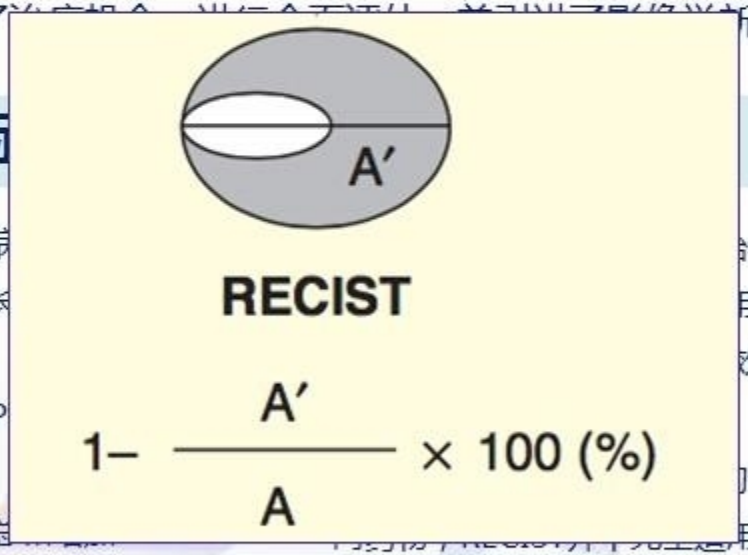
- Annals of Oncology 0: 1–12, 2019

RECIST标准
以肿瘤大小的变化作为判断疗效的标准

RECIST标准是以WHO疗效评估标准为基础进行修改和补充形成的新的实体瘤疗效评估标准，2000年发表在JNCI杂志上：

- 保留WHO标准中的CR、PR、SD、PD概念
- 相比WHO标准，更精确、简便、重复性好，同时增加了[illegible]概念





- ≥20%或出现新病灶

孙燕,等.临床肿瘤内科手册(第5版).人民卫生出版社.2007:149-156.
Therasse P,et al.J Natl Cancer Inst.2000;92(3):205-16.

肝癌主要疗效评估标准的演变

basis of WHO

1. Annals of Oncology 21: 1944–1951, 2010

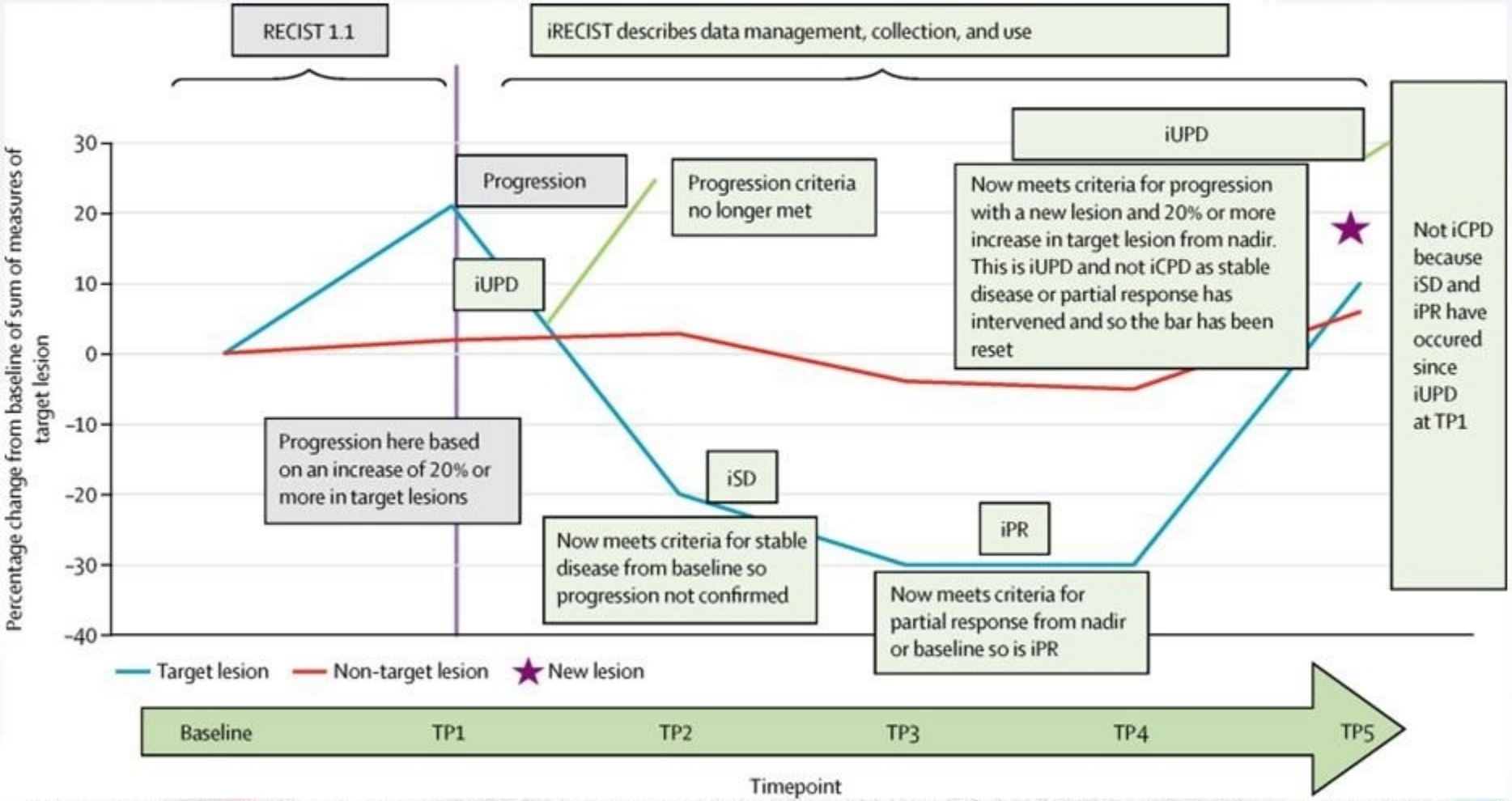
韩国宏,等.临床肝胆病杂志.2016;32(1):62-7.

RECIST 1.0和1.1标准比较
仍然以肿瘤大小的变化作为评估标准

	RECIST 1.0标准	RECIST 1.1标准
测量病灶的数目	每个器官最多5个，总数不超过10个	每个器官最多2个靶病灶，总数不超过5个
淋巴结	未指定	靶病灶短径>15mm，良性病灶<10mm
病灶缓解定义	CR 淋巴未指定 PD 长径的总和增大〉20%；出现新病灶	CR 淋巴结短径必须<10mm PD 长径的总和增大〉20%；出现新病灶；绝对值增加〉5mm
非靶病灶缓解定义	明显的进展=PD	明显的进展代表总体疾病状态，并不指单一病灶

http://www.recist.com

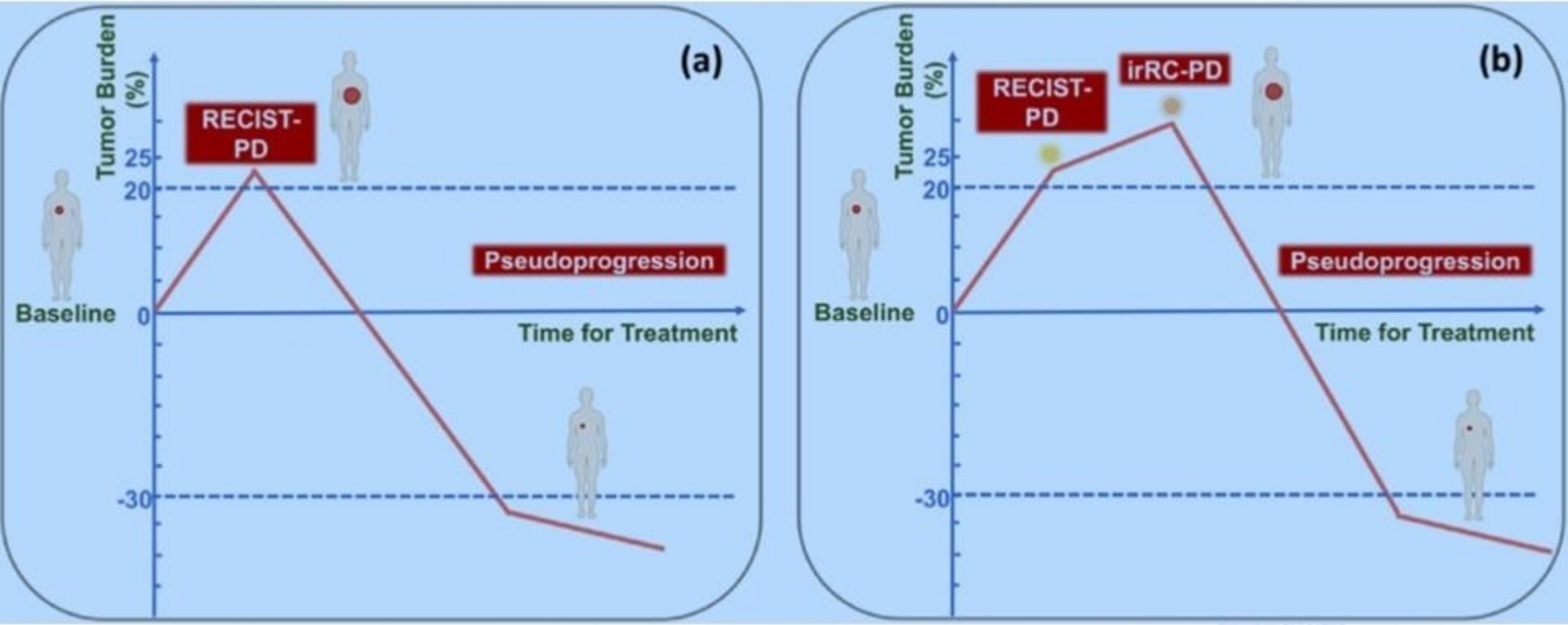
免疫治疗的疗效评估：iRECIST



"immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirm

Lancet Oncol. 2017 Mar;18(3):e143-e152.

4 weeks



The timeframe of pseudoprogression and subsequent response may have a wider range. (a) Tumor r

Immune-related response criteria (irRC)

International Immunopharmacology 58 (2018) 125–135