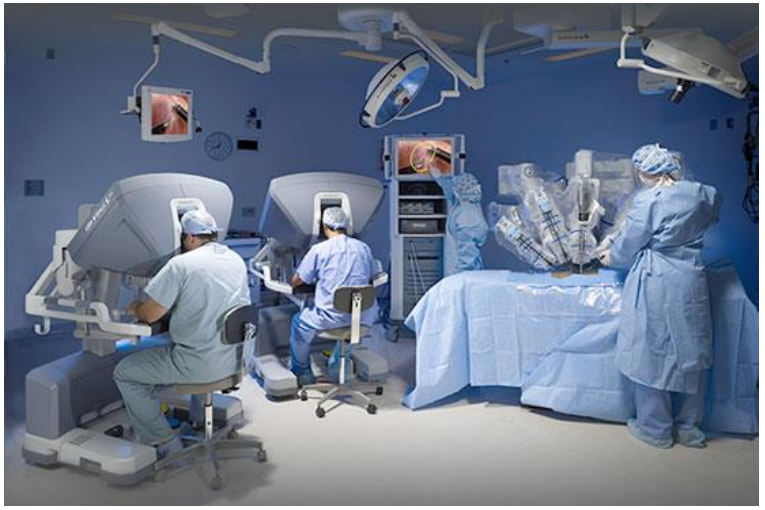
癌症免疫療法治療新進展

臺北榮總 腫瘤醫學部 腫瘤免疫治療中心主任
顏厥全 醫師

癌症治療方式

手術

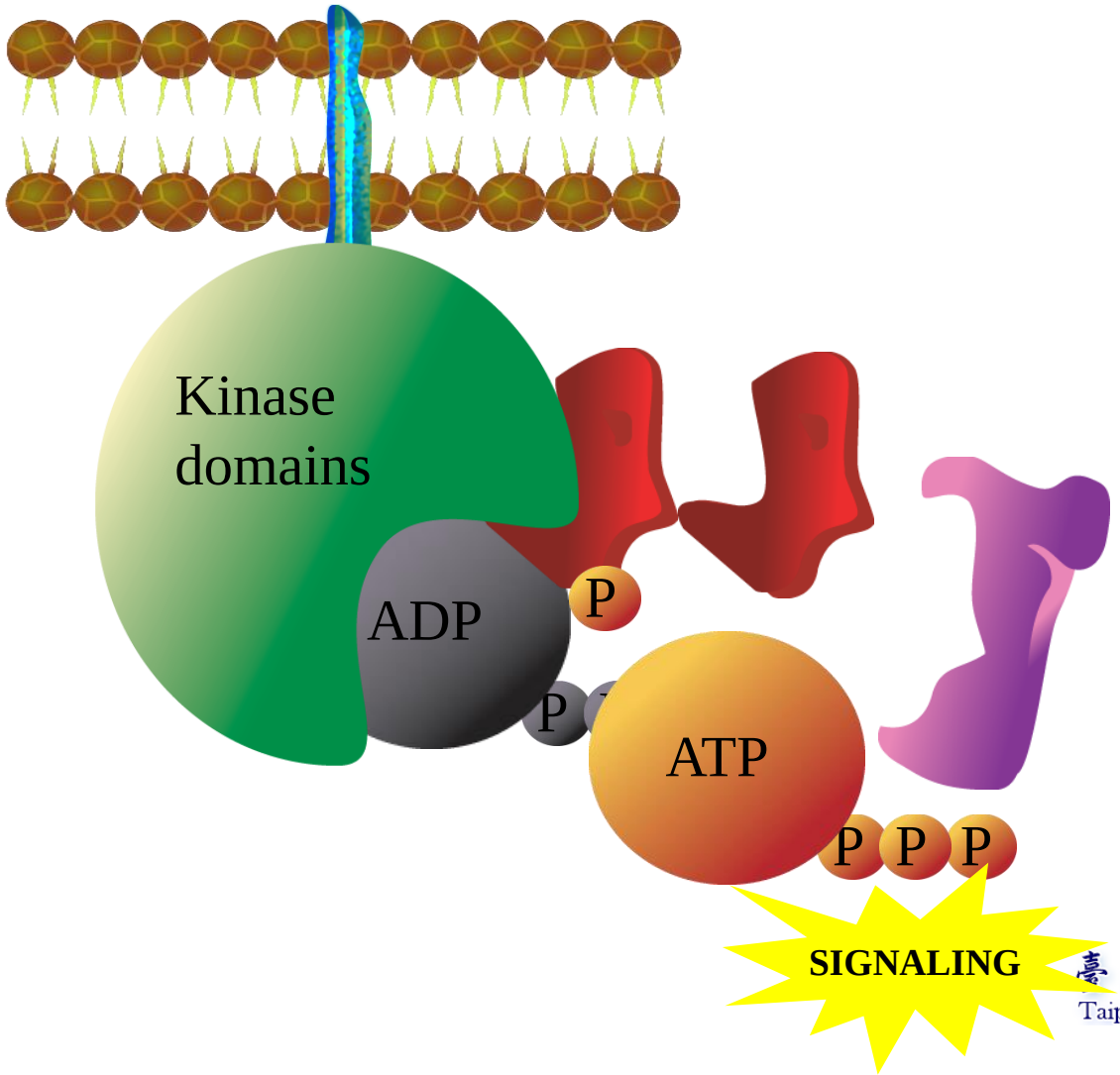


放射治療

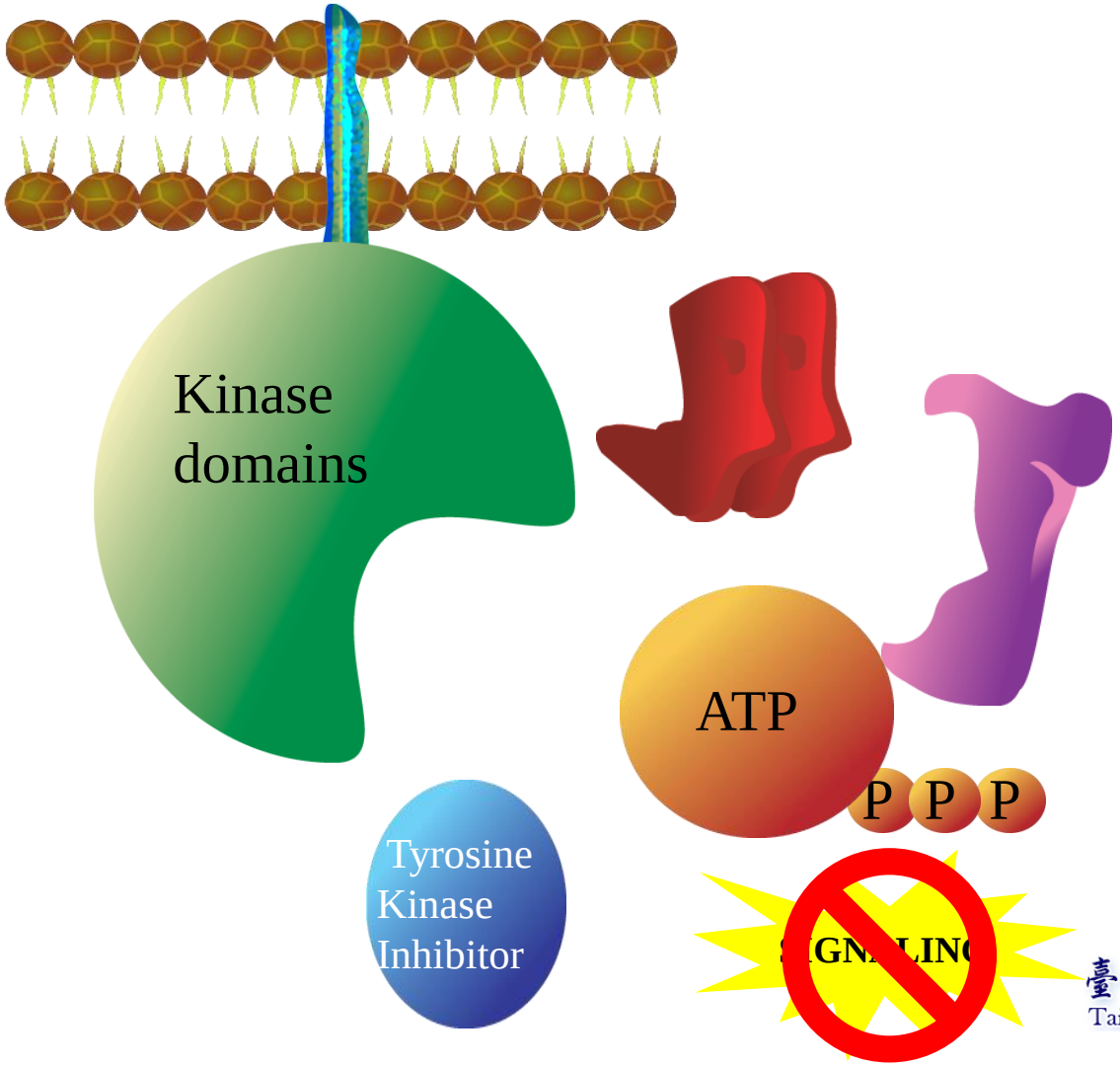
化學治療

Taxanes	Vinca Alkaloids
Paclitaxel	Vincristine
Docetaxel	Vinblastine

標靶治療: 正常訊號傳遞



標靶治療: 抑制訊號傳遞


Kinase
domains
ATP
P P P
Tyrosine
Kinase
Inhibitor
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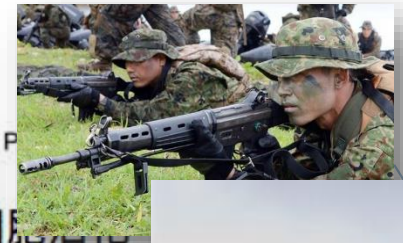
Taipei Veterans General Hospital

免疫系統和癌症:免疫循環








抗原釋出

殺死癌細胞

Chen DS & Mellm

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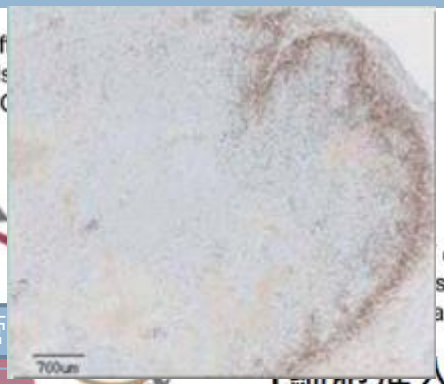
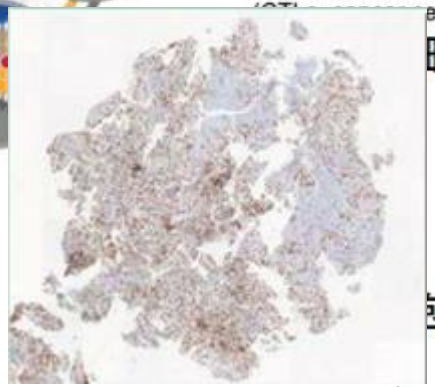
Taipei Veterans General Hospital

免疫循環: 癌症的免疫缺損

免疫沙漠



免疫阻礙



免疫火熱

Chen DS & Mellman I., Immunity. 2013;39:1-10
Hegde PS, et al., Clin Cancer Res. 2016;22(8):1865-74

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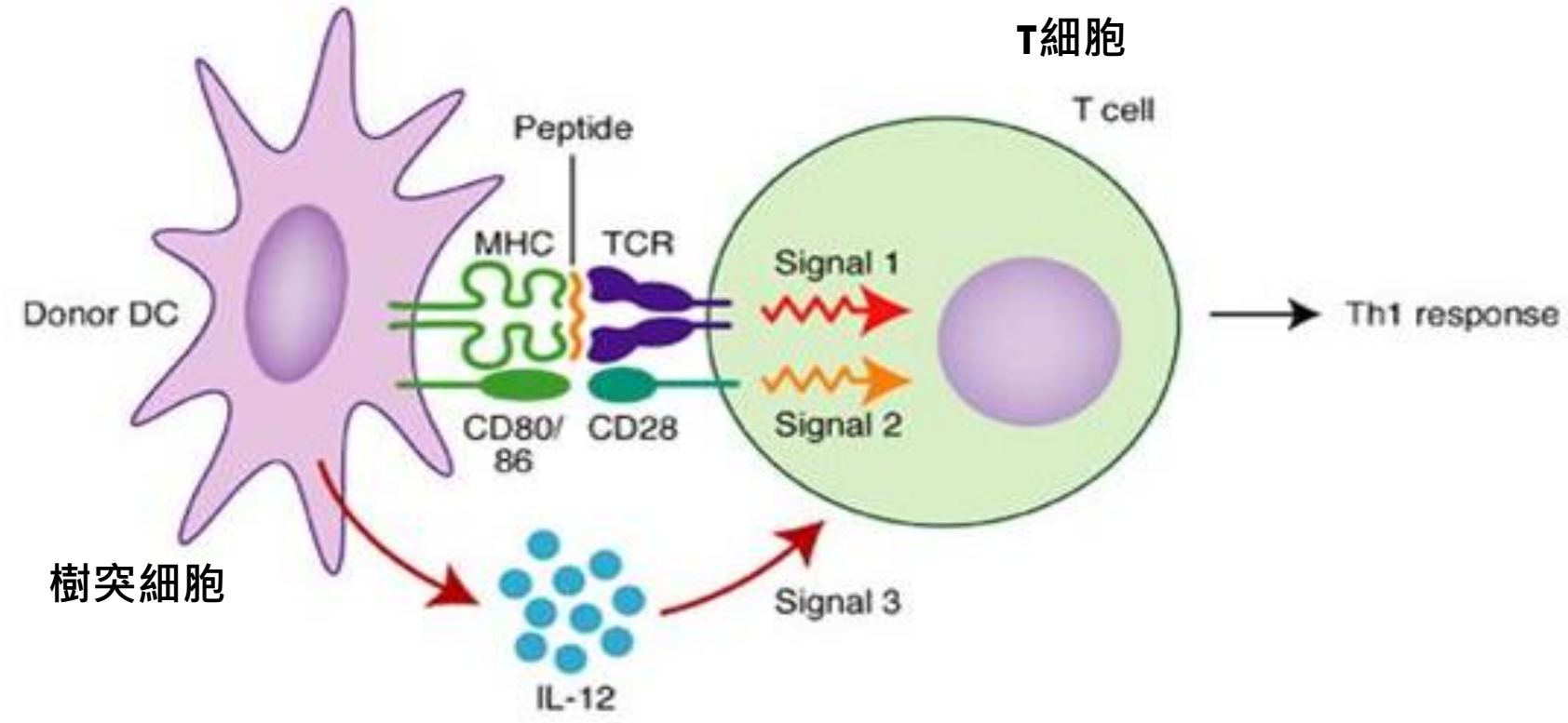
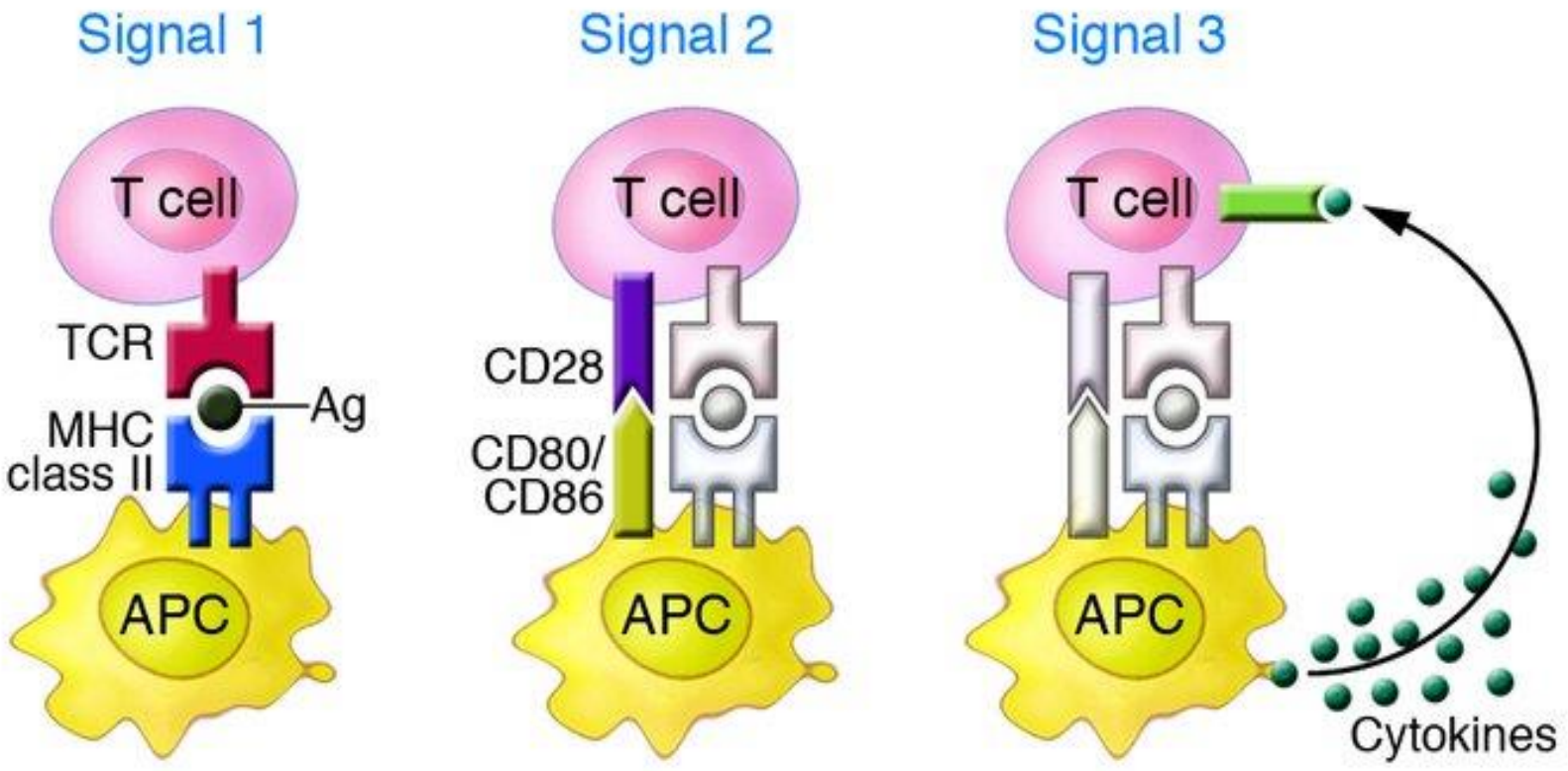
免疫系統辨識癌細胞



TCR: T細胞受體
MHC:主要組織相容性複合體

Coates PT, et al., Expert Rev Mol Med. 2002;4(3):1-21.

Antigen presenting cell (APC) and T cell



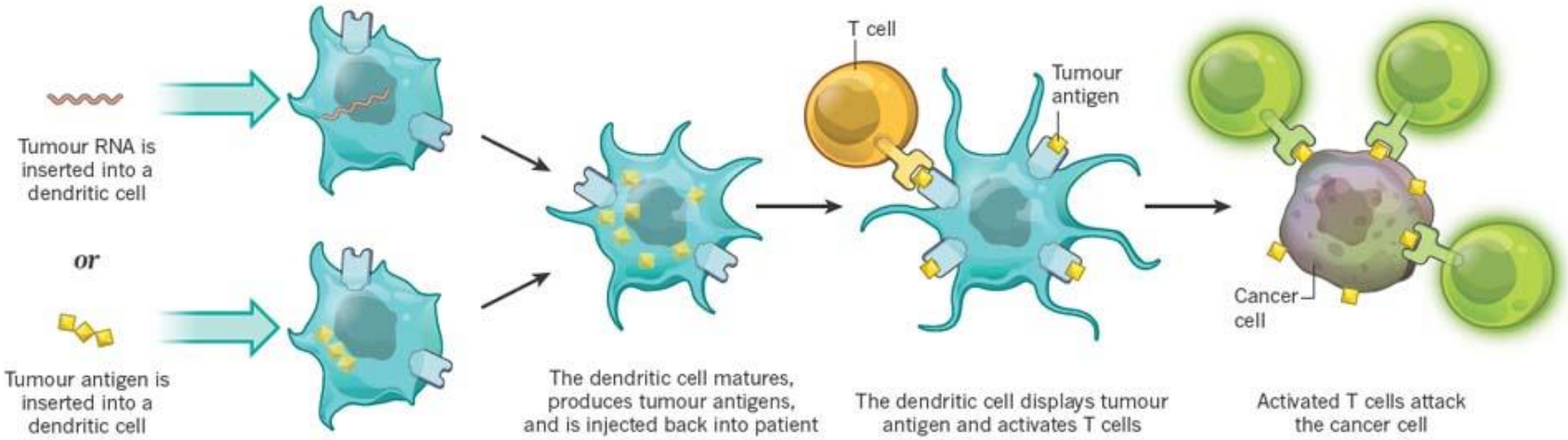
Antigen recognition

Immune checkpoints

Cytokine stimulation

Gutcher I & Becher B, J Clin Invest. 2007;117(5):1119-27..

癌症疫苗/細胞治療



腫瘤抗原蛋白或RNA
注射到/刺激樹突細胞

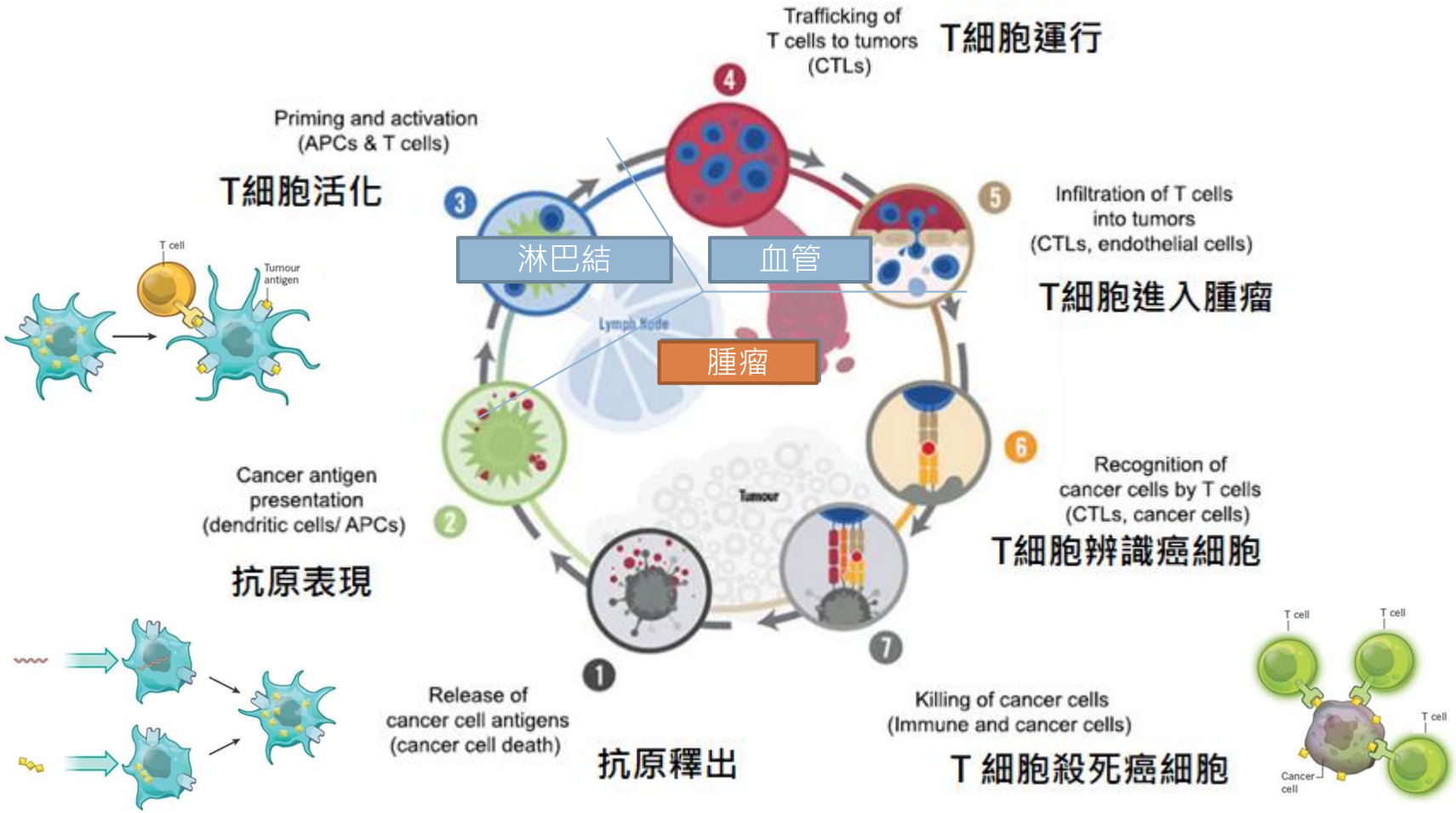
樹突細胞
表現腫瘤抗原

樹突細胞
活化T細胞

T細胞殺死癌細胞

http://www.breastcarenetwork.com/news/breast-cancer-vaccines-back-to-the-future

免疫循環:癌症疫苗/細胞治療的困境

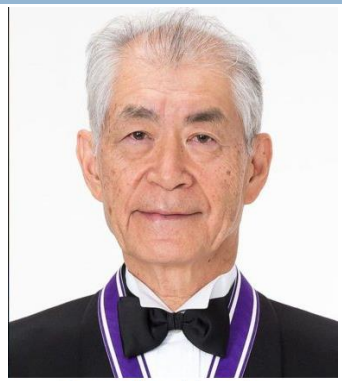


Chen DS & Mellman I., Immunity. 2013;39:1-10

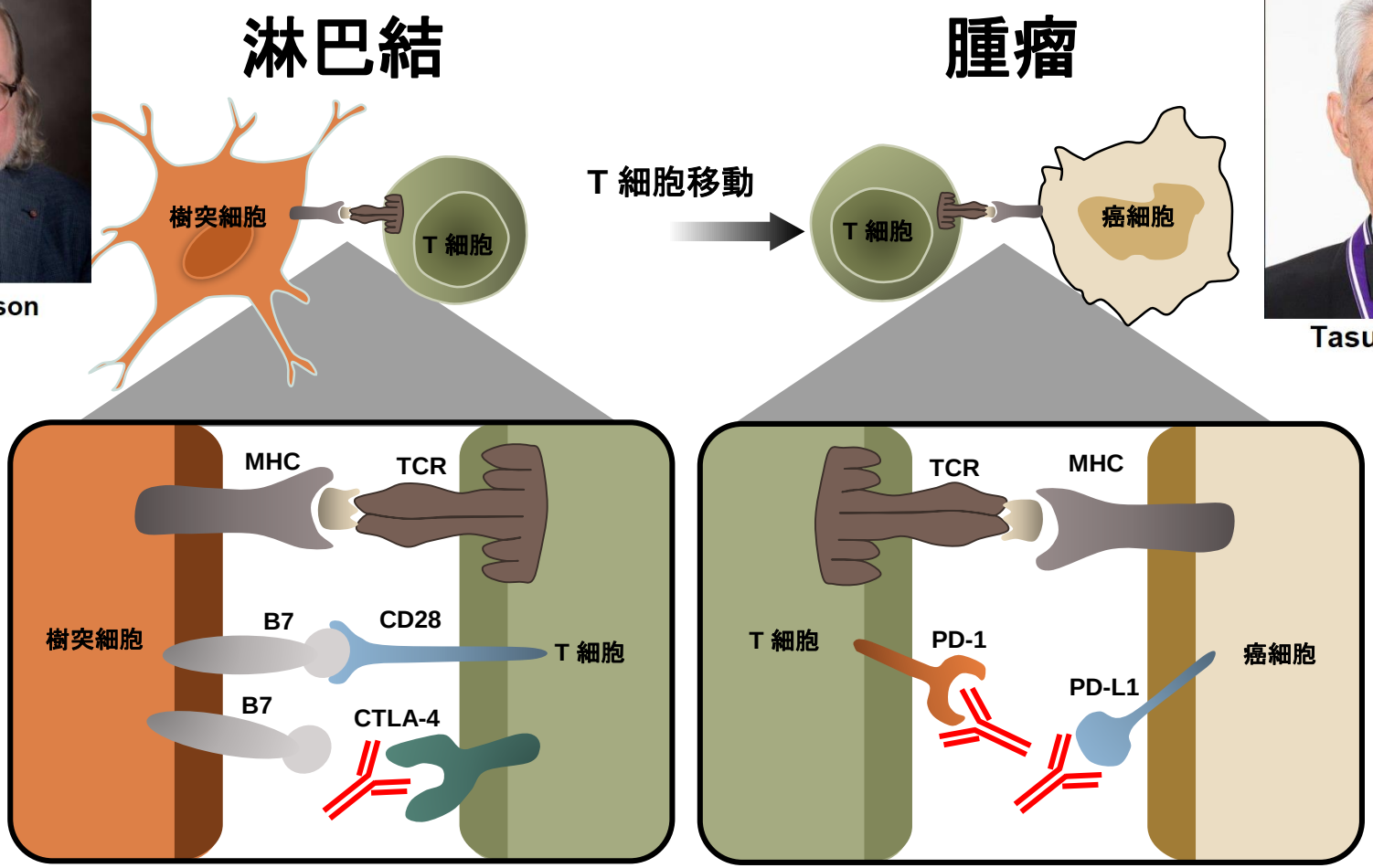
http://www.breastcarenetwork.com/news/breast-cancer-vaccines-back-to-the-future

CTLA-4 及 PD-1/L1免疫檢查點抑制劑

James P. Allison



Tasuku Honjo



CTLA-4: 細胞毒T淋巴细胞相關抗原4

PD-1: 程序性死亡受体1

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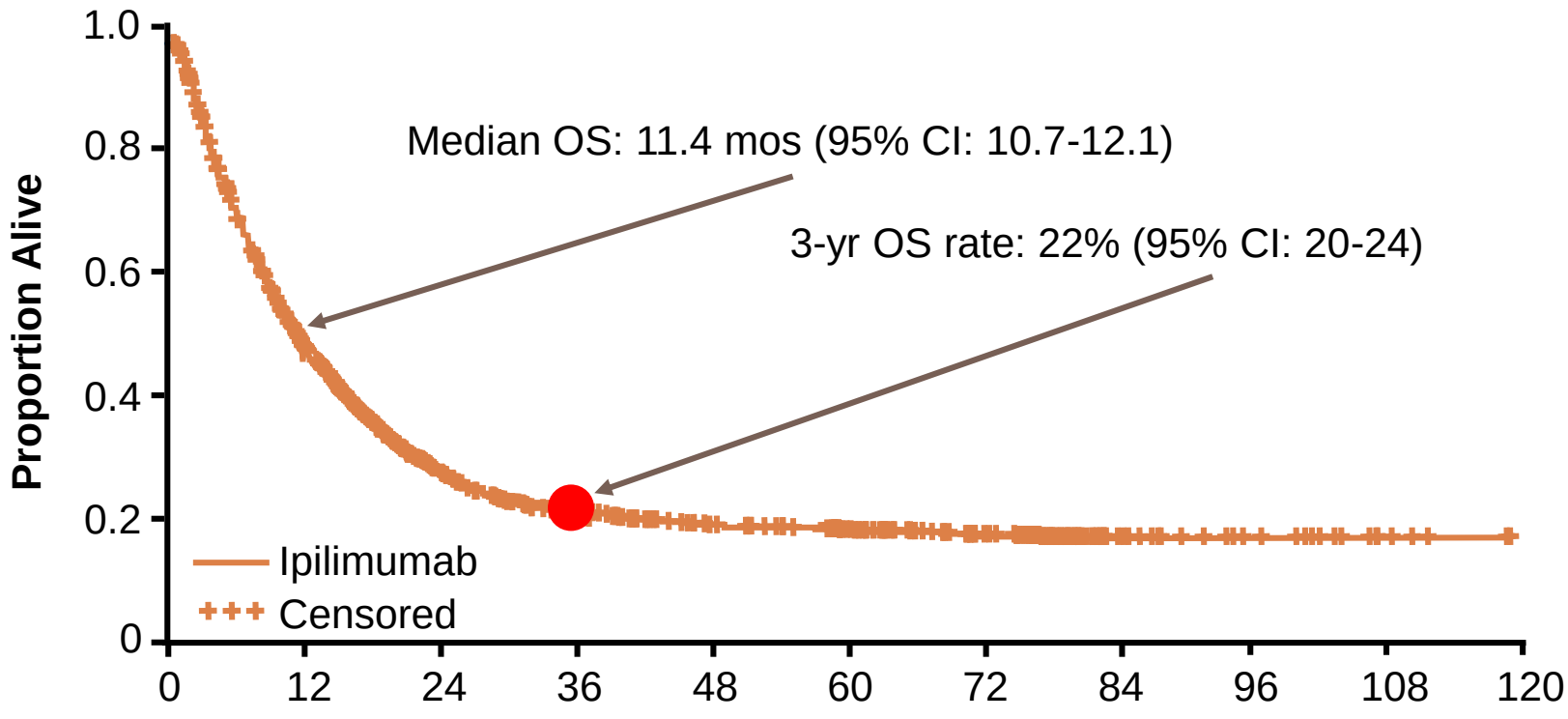
Ribas A. N Engl J Med. 2012;366:2517-2519.

免疫檢查點抑制劑

- CTLA4抑制劑
  - Ipilimumab (Yervoy®, BMS)
  - Tremelimumab
- PD-1抑制劑
  - Pembrolizumab (Keytruda®, MSD)
  - Nivolumab(OPDIVO®, ONO)
- PD-L1抑制劑
  - Atezolizumab (Tecentriq®, Roche)
  - Durvalumab (Imfinzi®, AstraZeneca)
  - Avelumab

CTLA-4 免疫檢查點抑制劑Ipilimumab在黑色素細胞瘤的療效 (OS: 總生存期)



Pts at Risk, n

Ipilimumab	1861	839	370	254	192	170	120	26	15	5	0

Hodi S, et al. 2013 European Cancer Congress. Abstract LBA 24. Schadendorf D, et al. J Clin Oncol. 2015;[Epub ahead of print].

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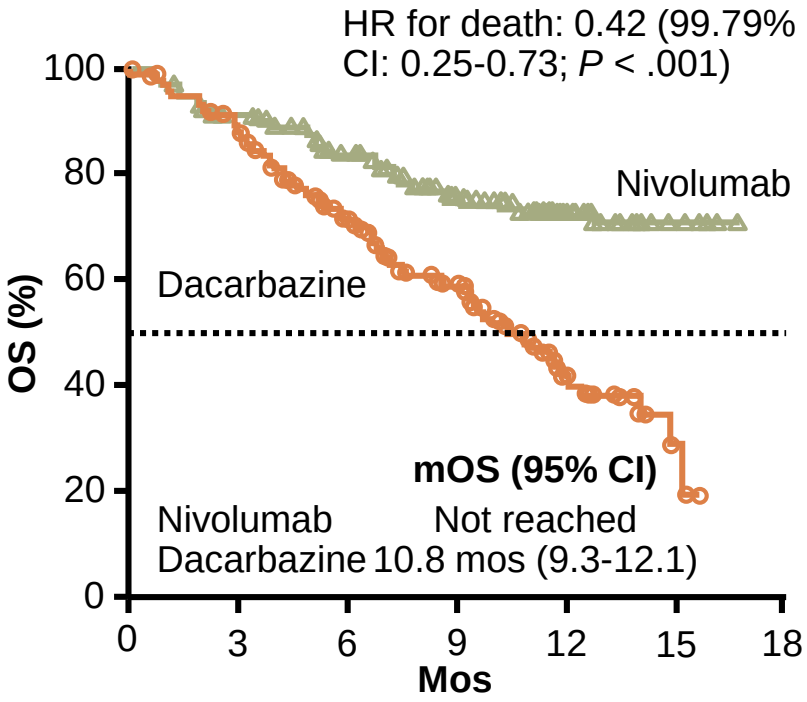
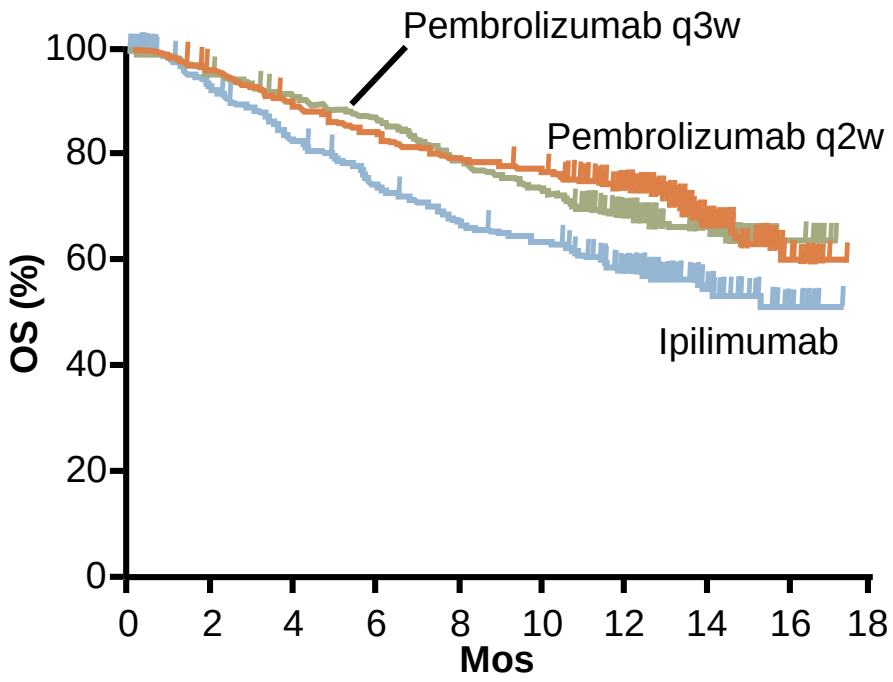
PD-L1 inhibitor in melanoma

Nivolumab vs DTIC in *BRAF*-negative, previously untreated melanoma[1]



Pembrolizumab vs Ipilimumab in Advanced Melanoma[2]



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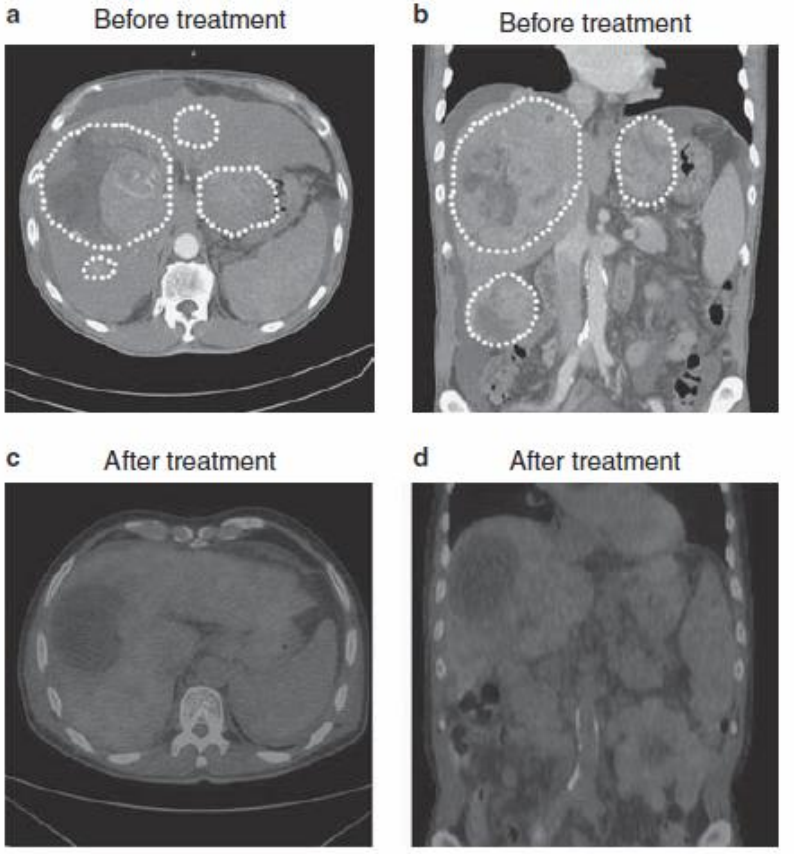
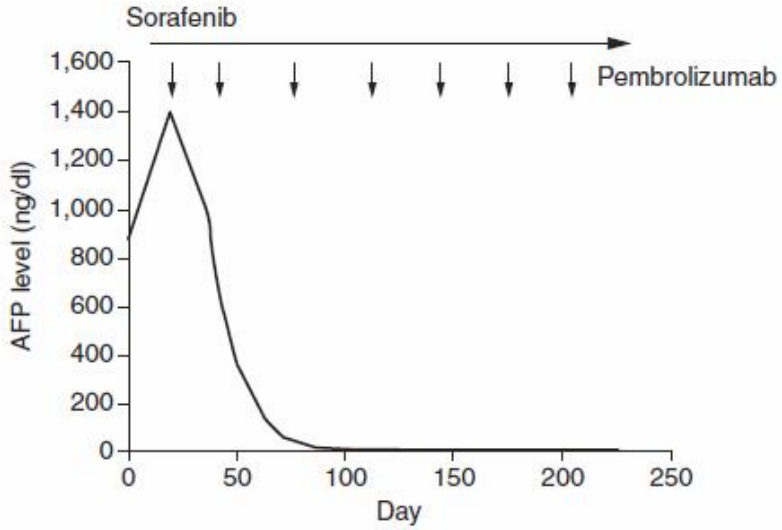
1. Robert C, et al. N Engl J Med. 2015;372:320-330. 2. Robert C, et al. N Engl J Med. 2015;372(26):2521-32.

美前總統卡特抗癌成功！掃描顯示癌細胞消失

Complete Response to the Combination of Pembrolizumab and Sorafenib





Chen SC, et al., Am J Gastroenterol. 2017;112(4):659-660

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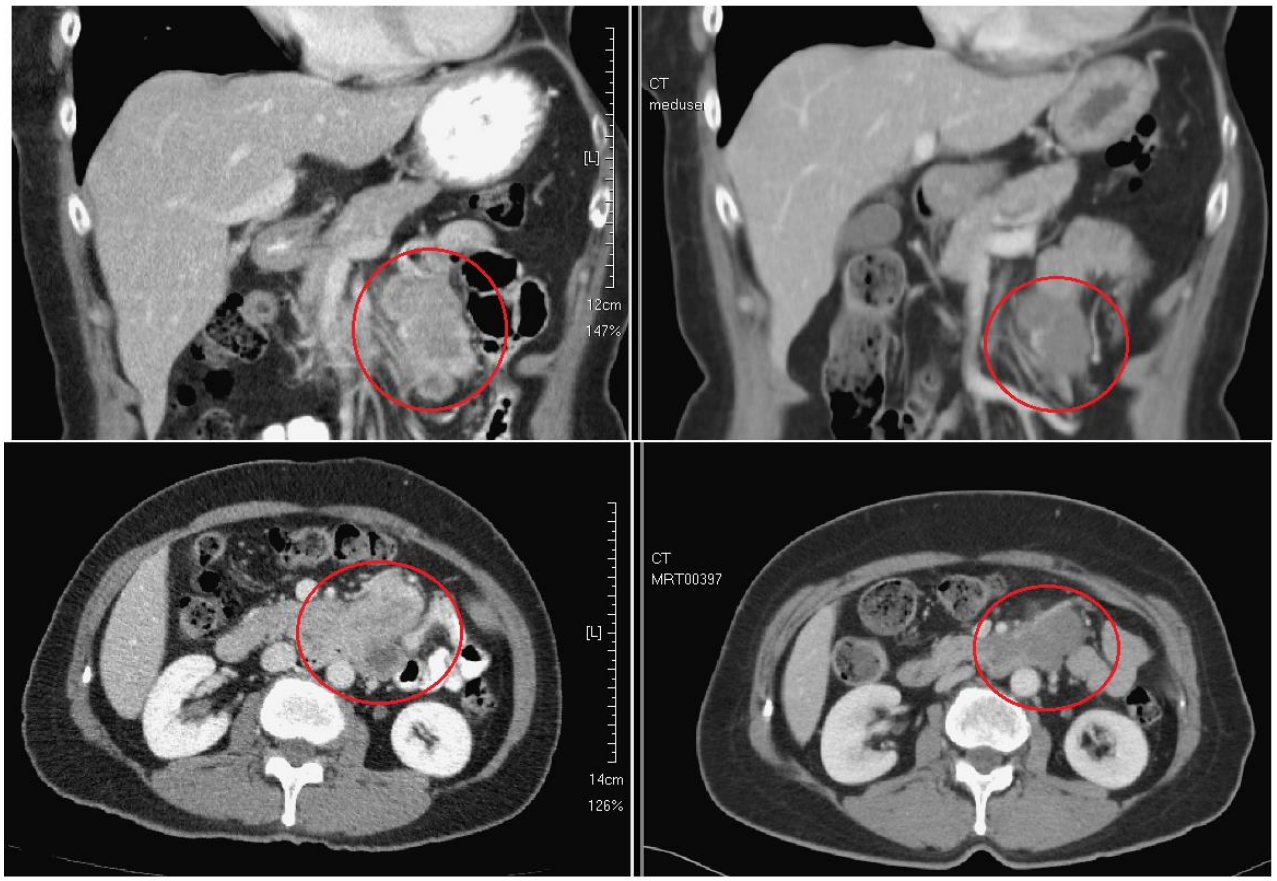
Secondary 2nd undifferentiated pleomorphic sarcoma of chest with intra-abdominal metastasis

治療前

治療後



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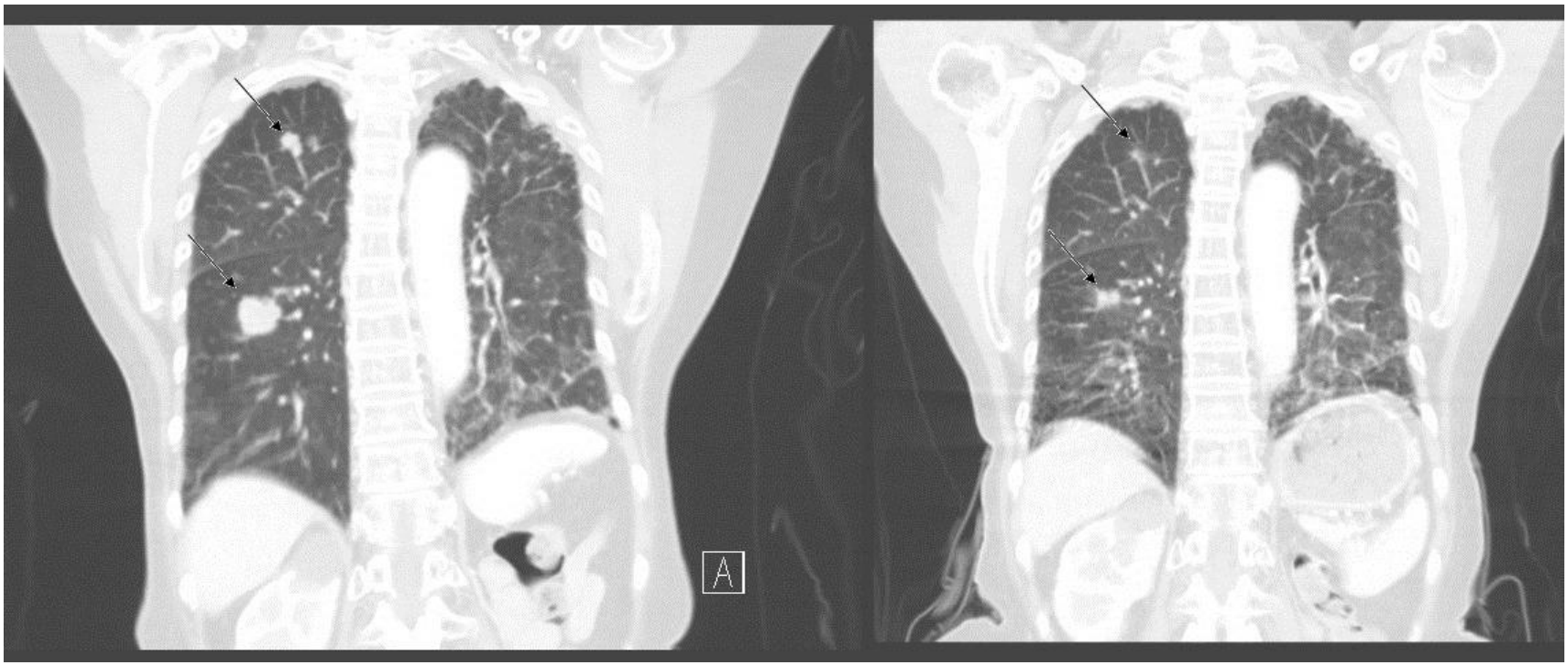
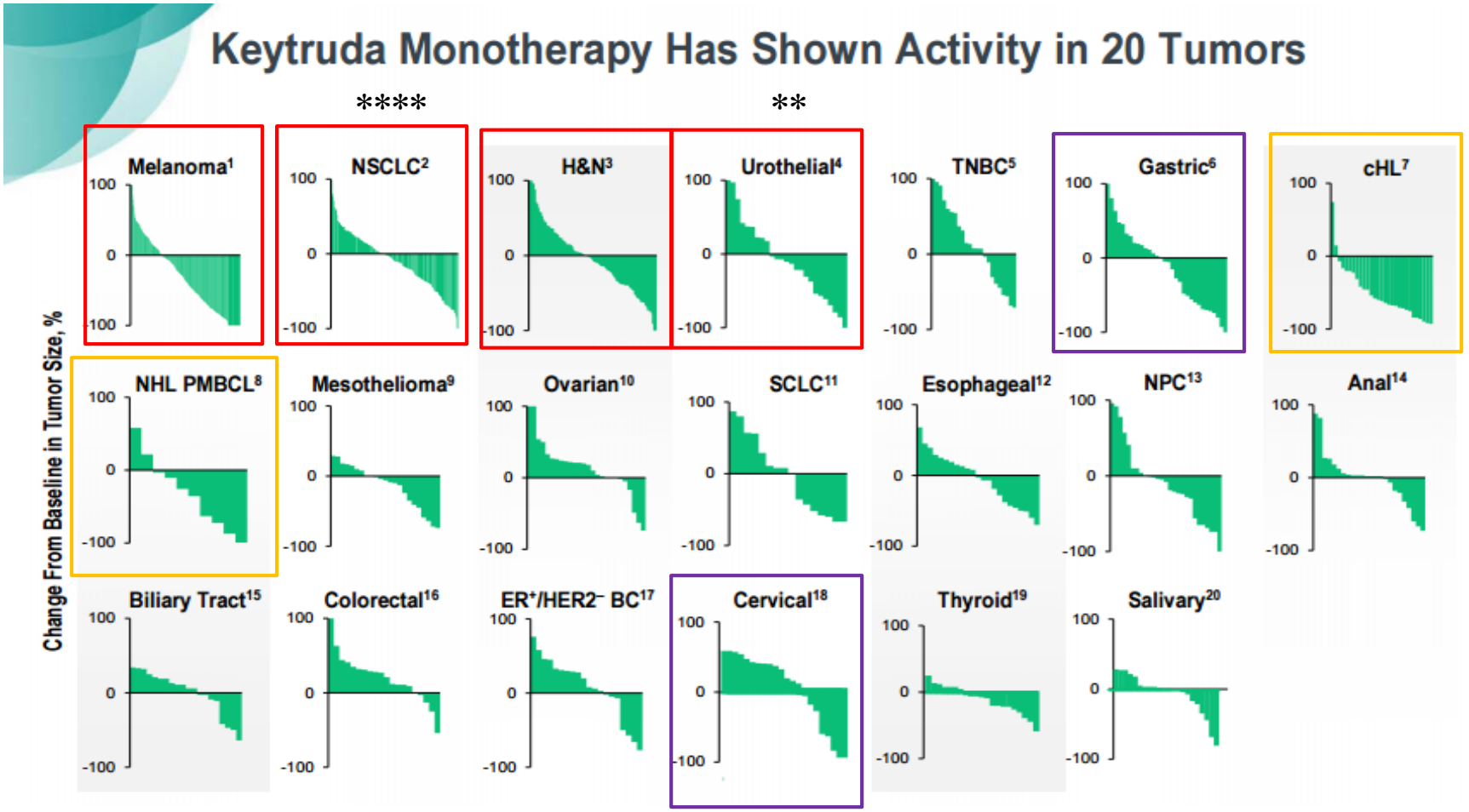
Urothelial carcinoma with lung metastasis (91 Y/O)



Pembrolizumab (Keytruda) efficacy



HCC; MSI-H

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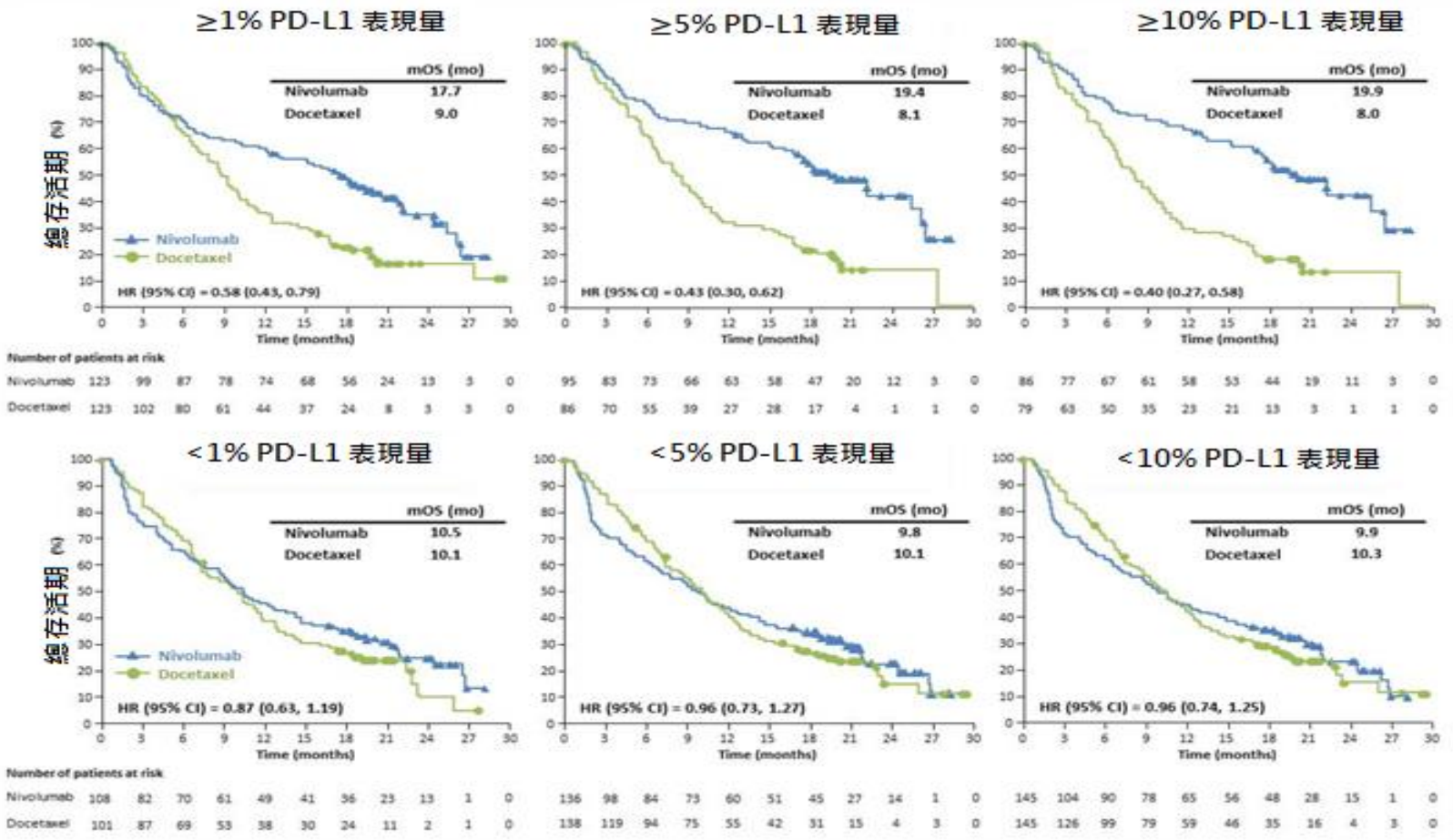
CheckMate 057:Nivolumab 比較 Docetaxel 在非小細胞肺癌的二線化療的療效



Borghaei H, et al., N Engl J Med 2015;373:1627-39.

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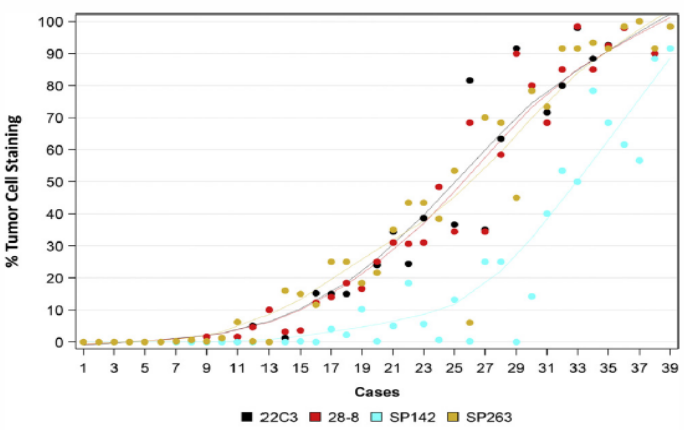
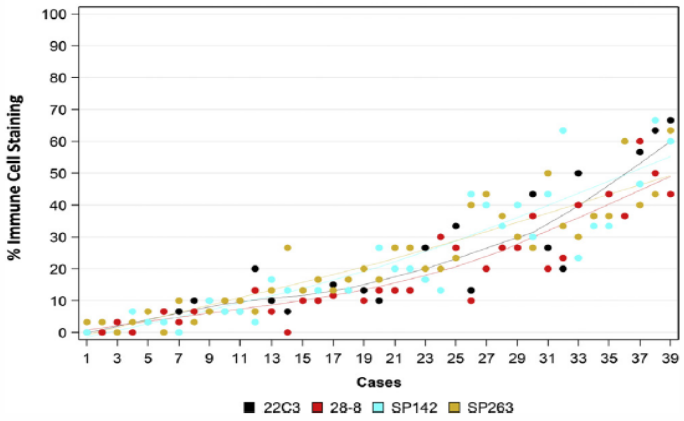
Five-Assay Comparison

Assay Antibody PD-L1 Clone	Staining Platform	Immunotherapy Drug	Clinical Cut-off(s) for PD-L1 Expression	FDA Designation
28-8	Dako Link 48	Nivolumab (Bristol-Myers Squibb)	≥ 1%, ≥ 5%	Complementary device
22C3	Dako Link 48	Pembrolizumab (Merck)	≥ 1%, ≥ 50%	Companion device
SP142	Ventana Benchmark or Ultra	Atezolizumab (Genentech/Roche)	Tumor cells ≥ 1%, ≥ 5%, ≥ 50% Immune cells ≥ 1%, ≥ 5%, ≥ 10% by area	Complementary device
SP263	Ventana Benchmark or Ultra	Durvalumab (AstraZeneca/ MedImmune)	≥ 25%	No designation
73-10	Dako Link 48	Avelumab (Pfizer/Merck Serono)	≥ 1%, ≥ 50%, ≥ 80%,	In development

PD-L1 在腫瘤表現量的一致性

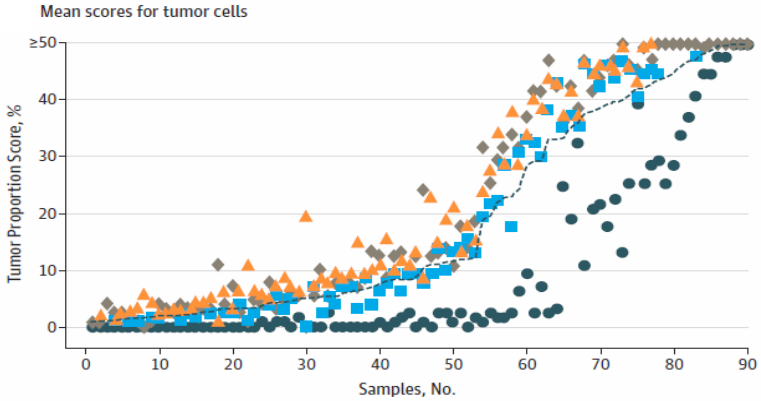
Blueprint

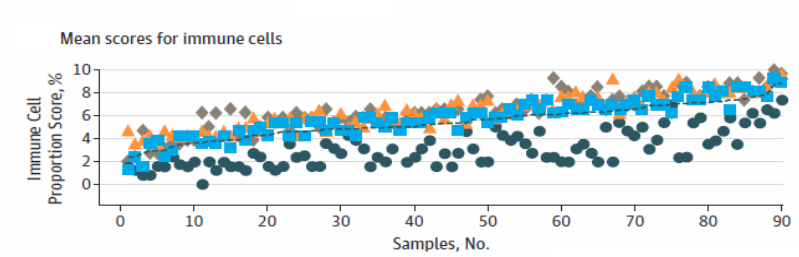


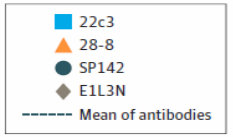


39 病人, 3病理醫師

NCCN/BMS







90病人, 13病理醫師

Rimm DL, et al., JAMA Oncol. 2017;3(8):1051-1058
Hirsch FR, et al., J Thorac Oncol. 2017 ;12(2):208-222

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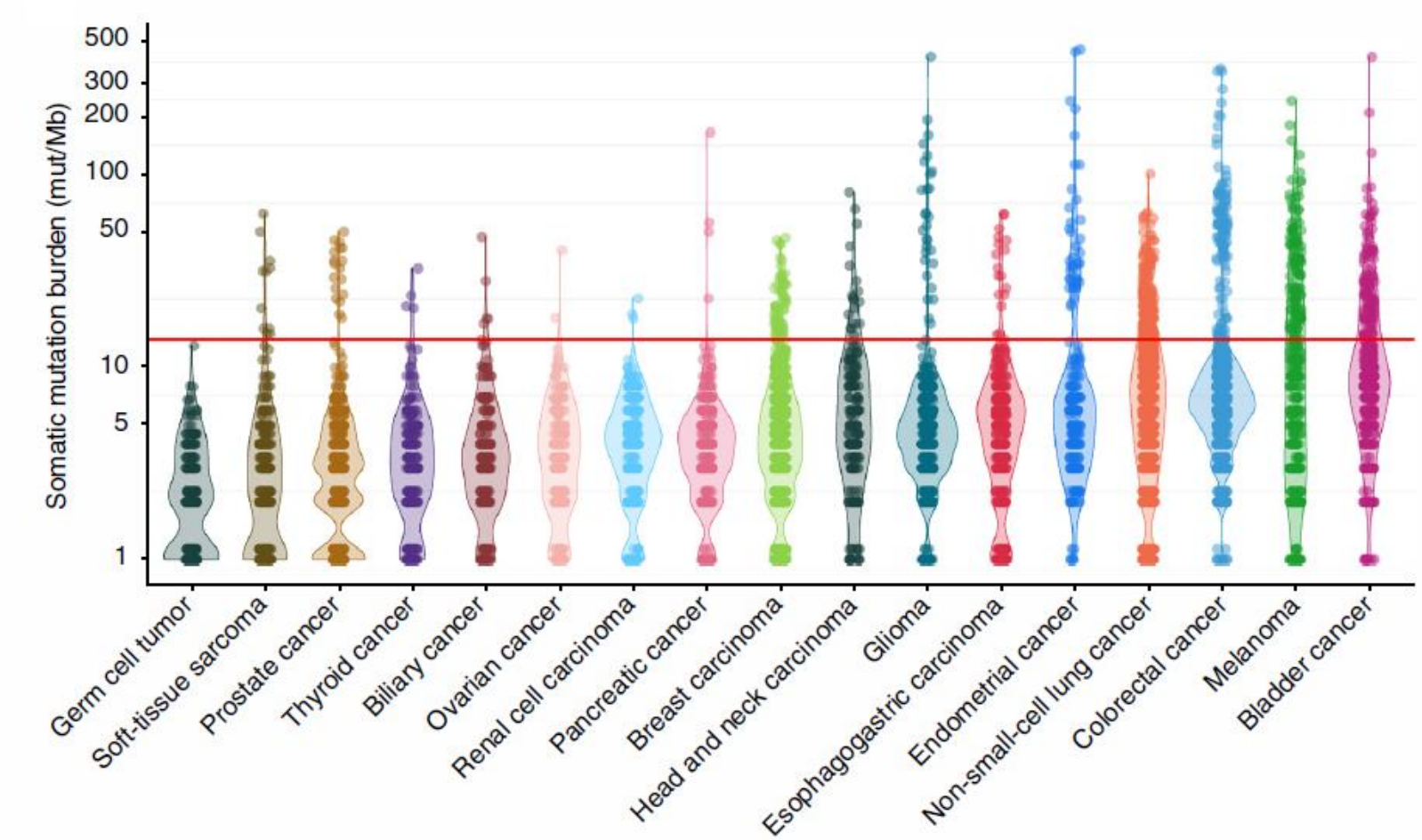
不同腫瘤的基因突變量不同



Zehir A, et al., Nat Med. 2017;23(6):703-713

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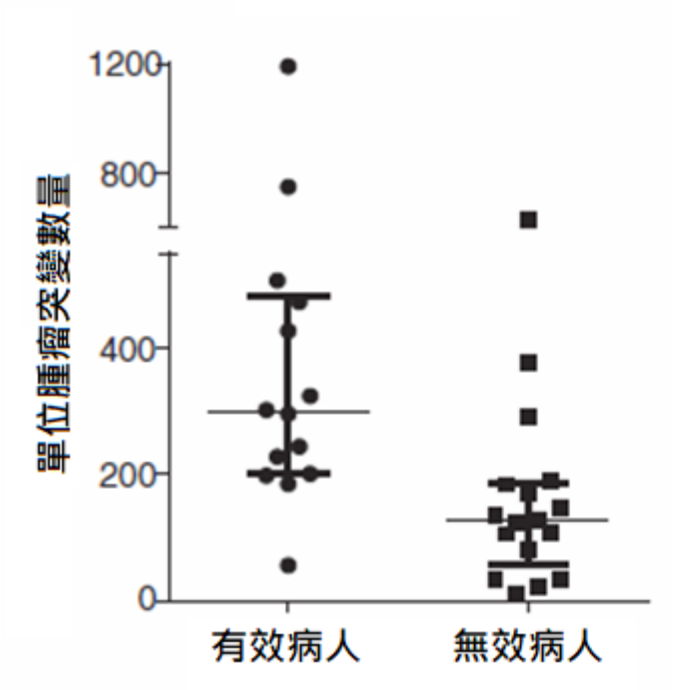
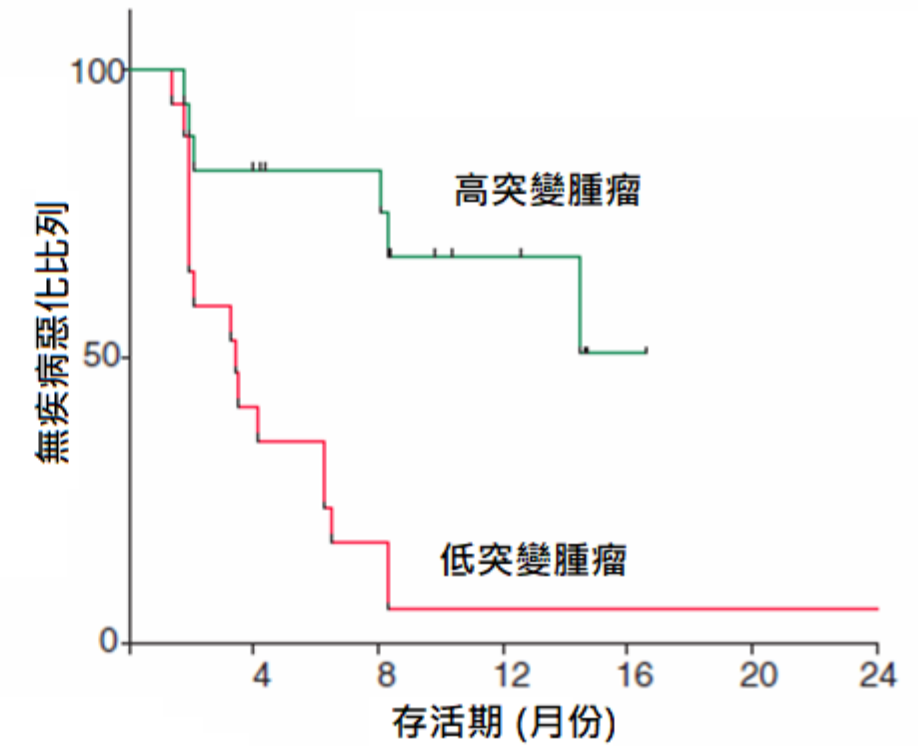
基因突變量愈高 免疫療法效果愈好





Rizvi NA, et al. Science. 2015 Apr 3;348(6230):124-8.

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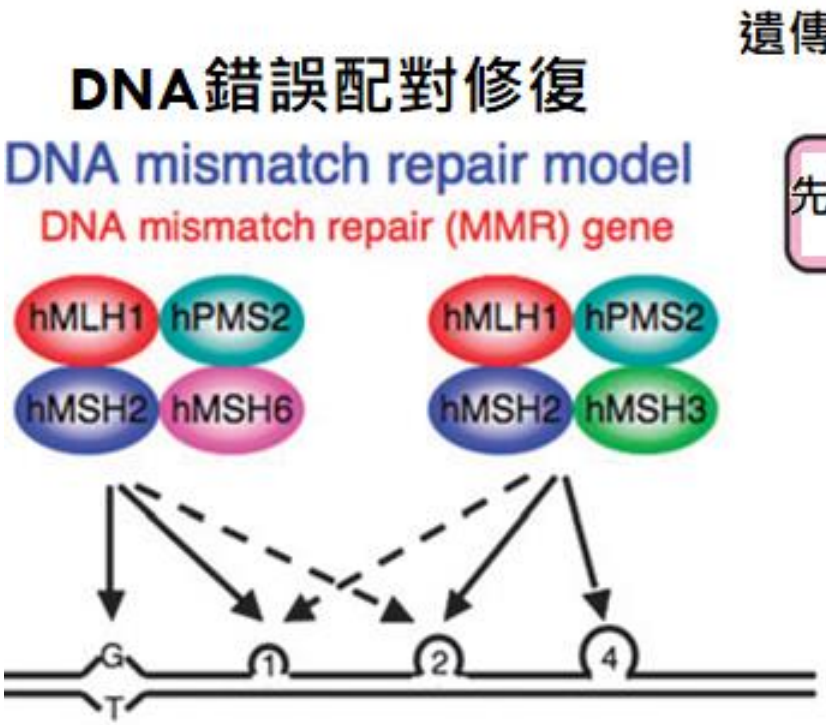
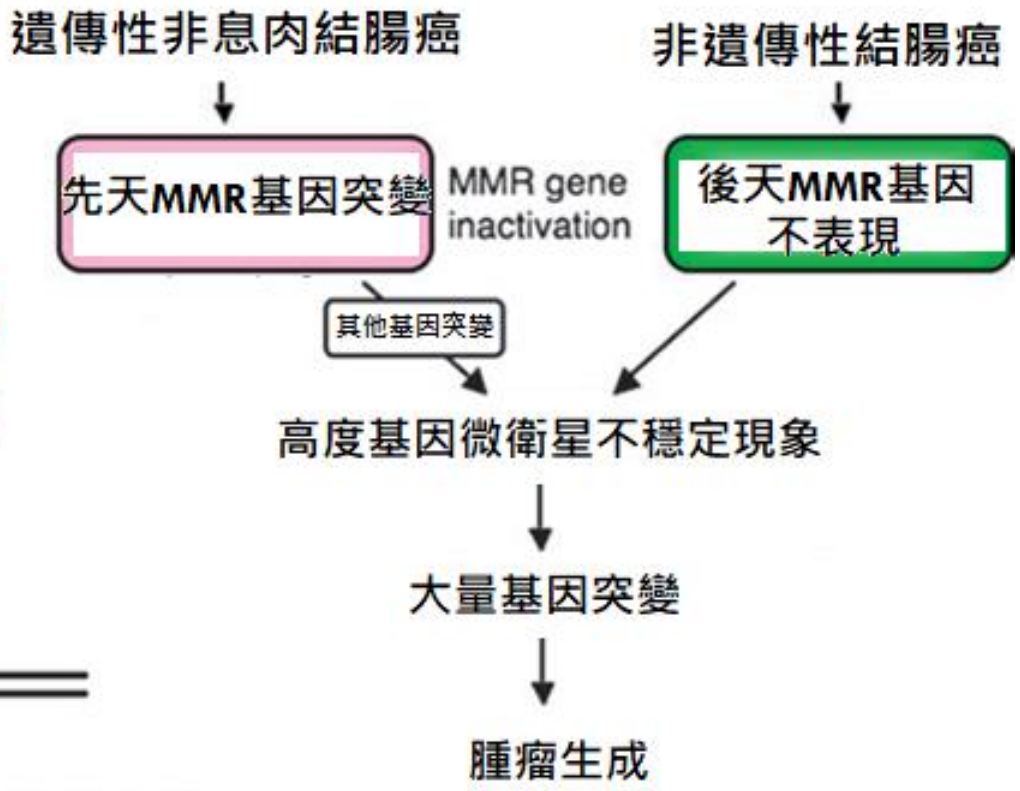
基因微衛星不穩定現象 (Microsatellite Instability; MSI)





Imai K, et al. Carcinogenesis 2008;29: 673-680

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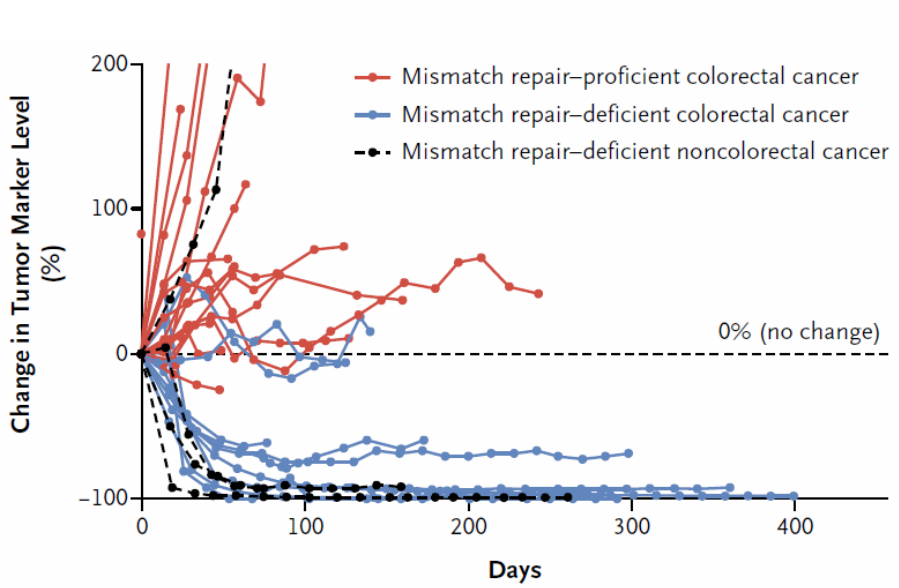
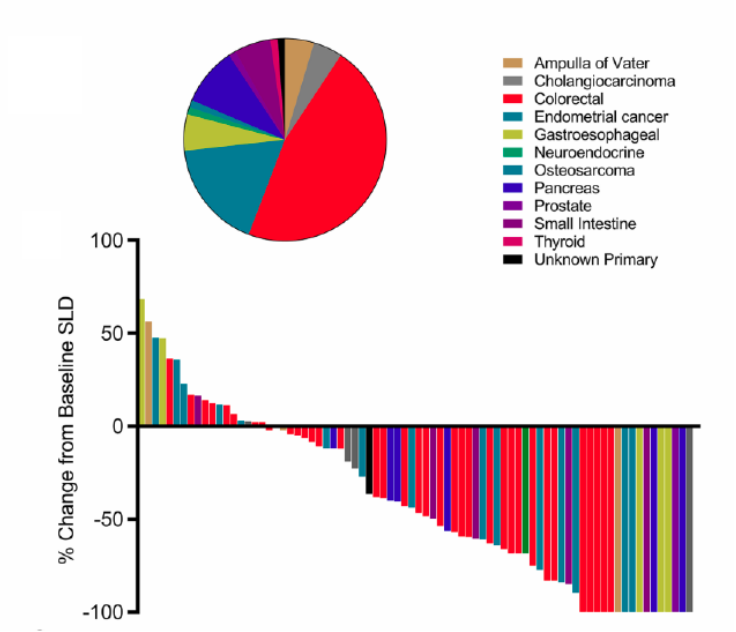
Mutation signatures and benefit from immunotherapy

Mismatch repair deficient cancers respond to immune checkpoint blockade





Le DT, et al., N Engl J Med 2015;372:2509-20.
Le DT, et al., Science. 2017;357(6349):409-413

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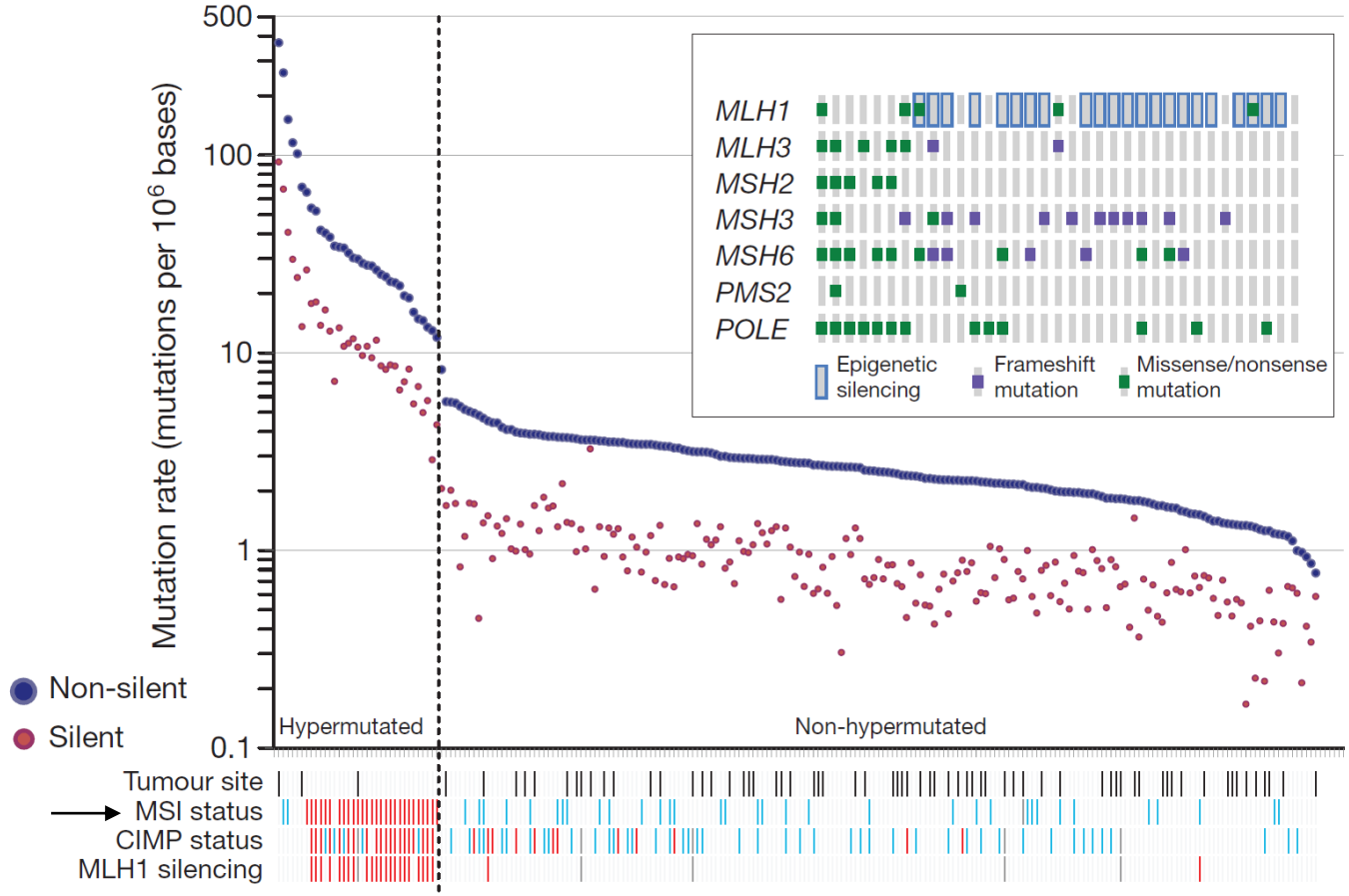
具基因微衛星不穩定現象的大腸癌基因突變機會高

N=224



The Cancer Genome Atlas Network, Nature. 2012;487(7407):330-7

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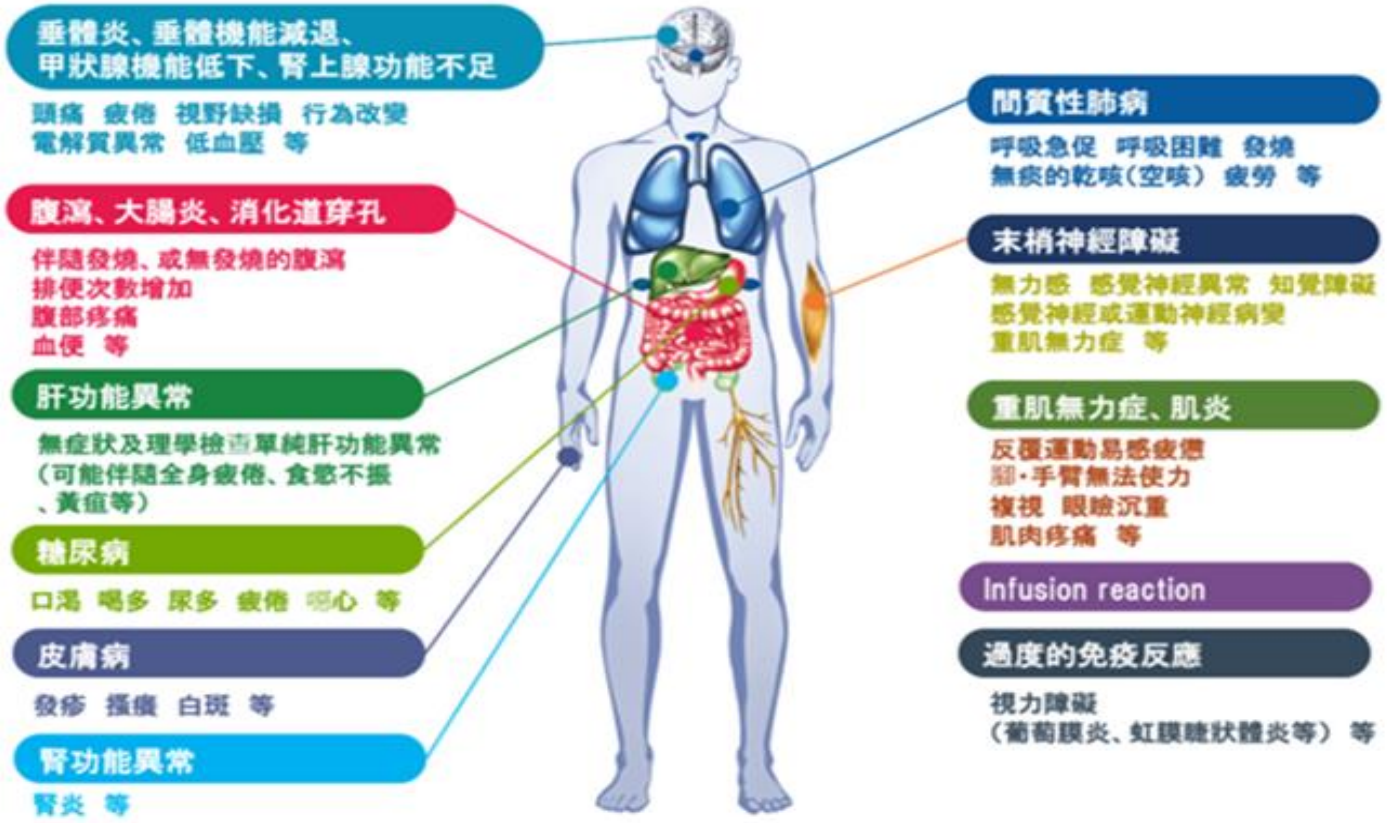
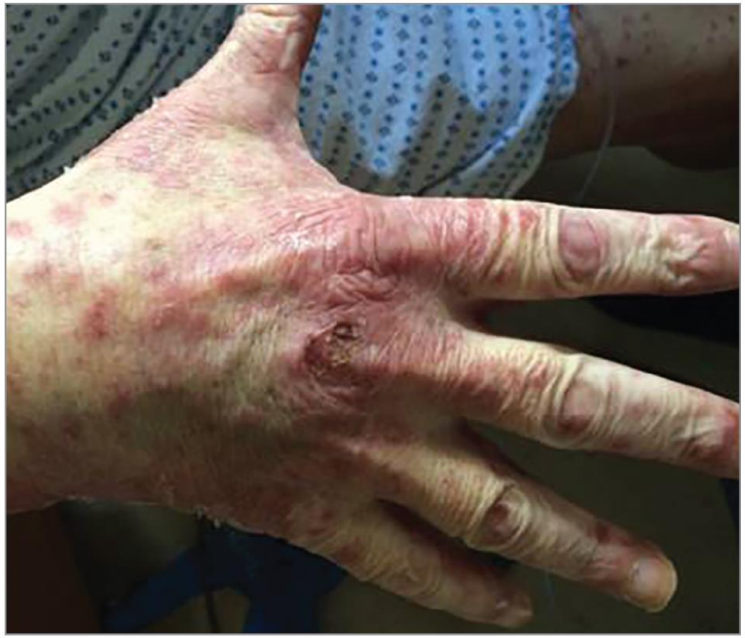
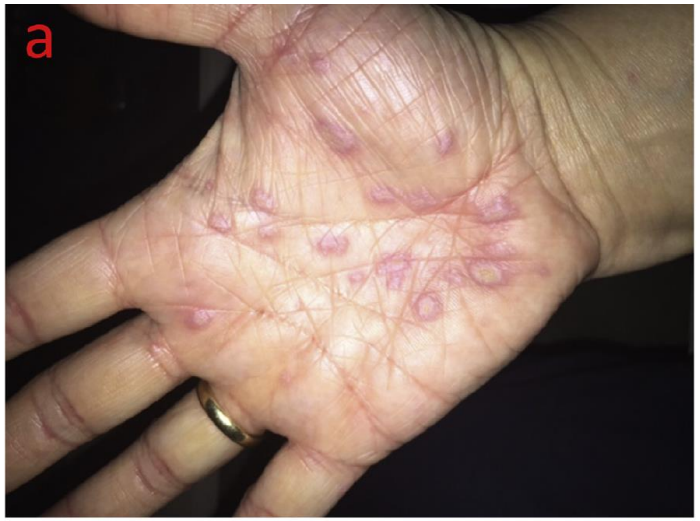
免疫治療副作用

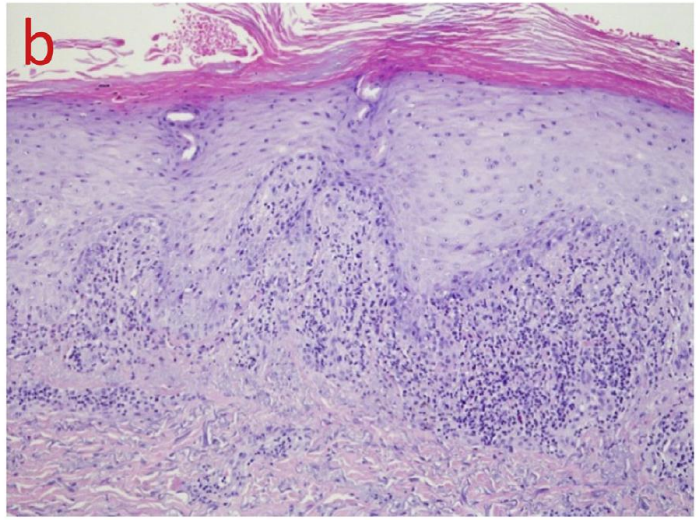


1..Amos SM, et al. Blood. 2011;118:499-509 2. Phan GQ, et al. PNAS. 2003;100:8372-8377 3. Rosenberg SA, White DE. Immunother Emphasis Tumor Immunol. 1996;19:81-84
4. Chianese-Bullock KA, et al. J Immunother. 2005;28:412-419 5. Chow LQ. Am Soc Clin Oncol Educ Book. 2013:280-285 6. Soni N, et al. Cancer Immunol Immunother. 1996;43:59-62
7. Ronnblom LE, et al. Ann Intern Med. 1991;115:178-183 8. Fraenkel PG, et al. J Immunother. 2002;25:373-378 9. Lamers CH, et al. J Clin Oncol. 2006;24:e20-e22
10. Roskrow MA, et al. Leuk Res. 1999;23:549-557 11. Parkhurst MR, et al. Mol Ther. 2011;19:620-626 12. Pellkofer H, et al. Brain. 2004;127:1822-1830 13. Smalley RV, et al. Blood. 1991;78:3133-3141;
14. Dudley ME, et al. J Clin Oncol. 2008;26:5233-5239 15. Yeh S, et al. Ophthalmology. 2009;116:981-989 16. Robinson MR, et al. J Immunother. 2004;27:478-479 17. Morgan RA, et al. Mol Ther. 2010;18:843-851
18. Kochenderfer JN, et al. Blood. 2010;116:4099-4102 19. Lin TS, et al. J Clin Oncol. 2010;28:4500-4506

皮膚毒性



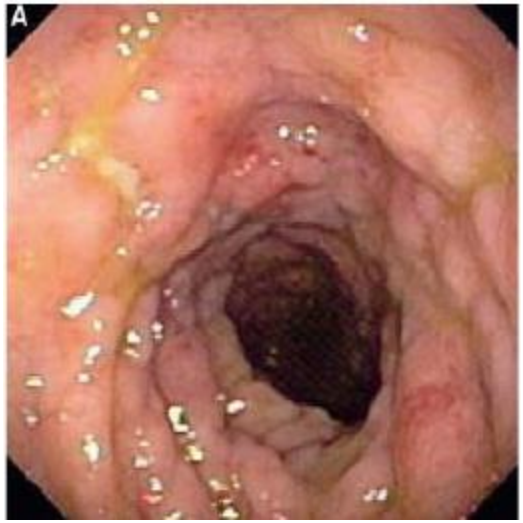




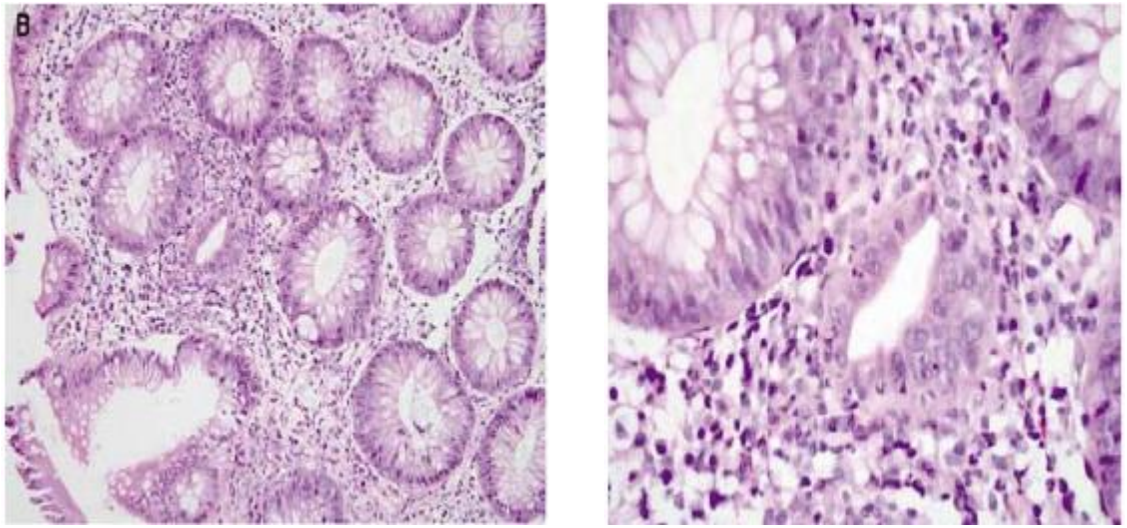
Hofmann L, et al., Eur J Cancer. 2016 Jun;60:190-209

大腸毒性

Immune-related colitis in a patient with metastatic melanoma



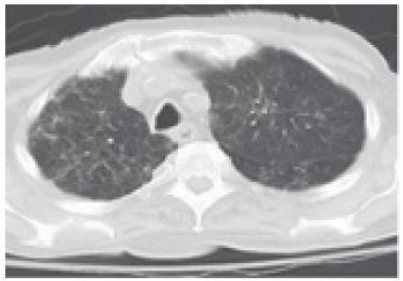
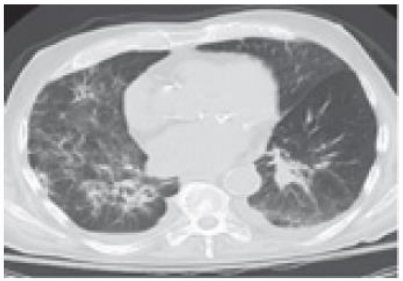
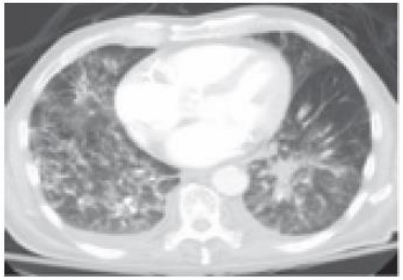
Colonoscopic view of bowel edema and ulceration in the descending colon



Histopathologic analyses show focal active colitis (left) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right)

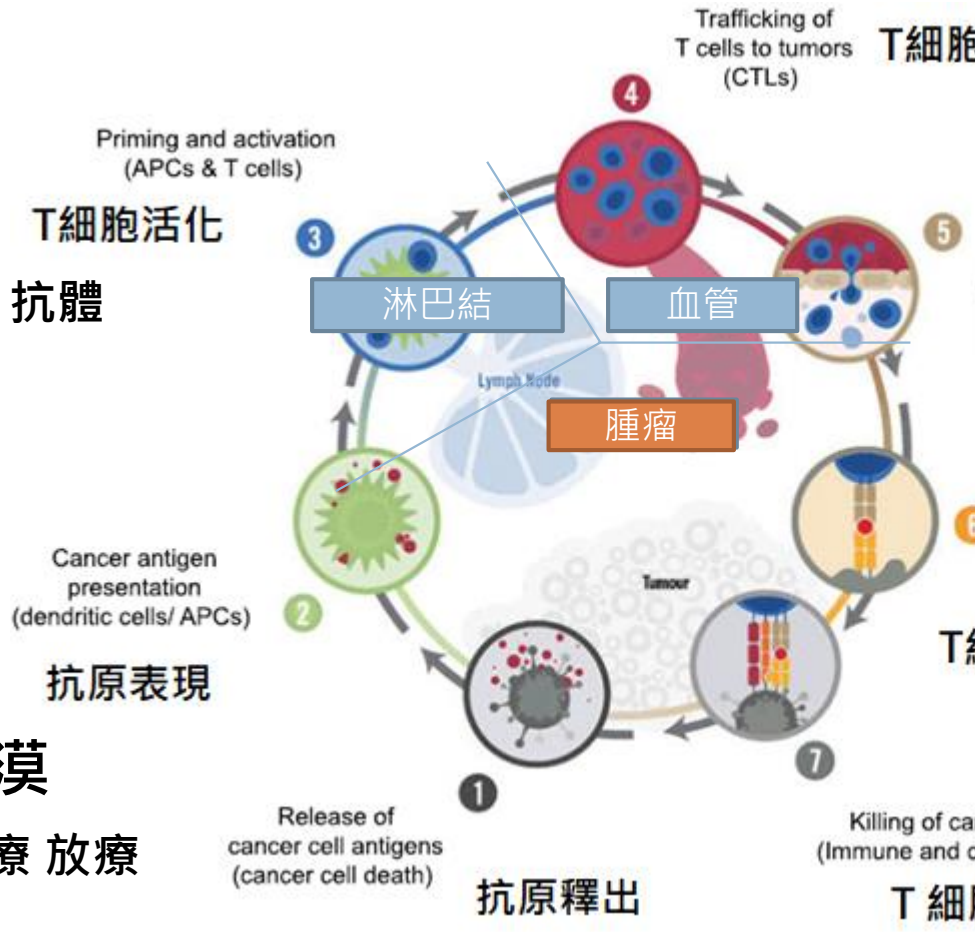
Maker AV et al. Ann Surg Oncol 2005;12:1005-1016

肺毒性

Severity	Mild	Moderate	Severe
CT Image			
Description	Confined to one lobe of the lung or Confined to < 25% of lung parenchyma	Involves more than one lobe of the lung or Involves 25%-50% of lung parenchyma	Involves all lobes of the lung or Involves > 50% of lung parenchyma

Naidoo J, et al. J Clin Oncol. 2016;34 (Epub)

免疫循環: 組合治療的策略



免疫阻礙

抗 血管新生藥物

抗 CTLA-4 抗體

免疫沙漠

化療 放療

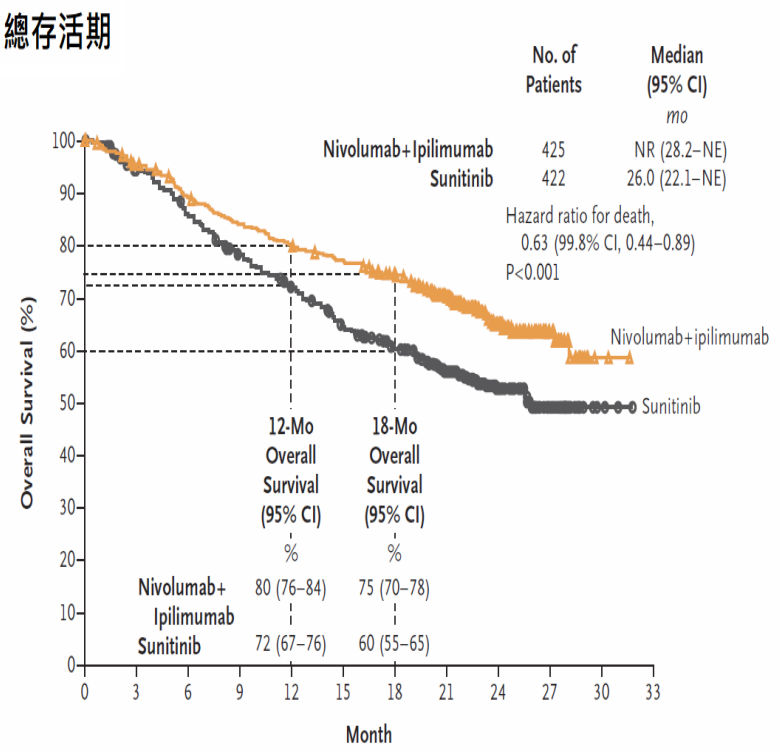
免疫火熱

抗PD-1/PD-L1 抗體

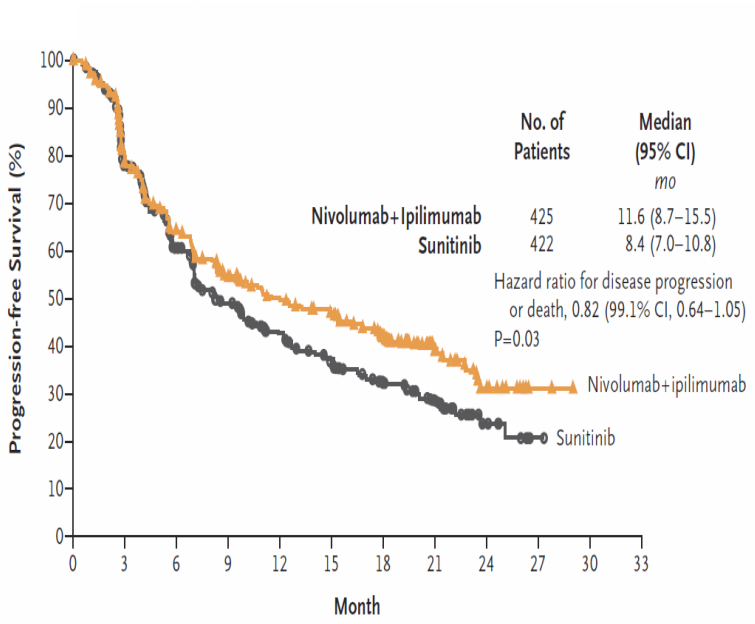
Chen DS & Mellman I., Immunity. 2013;39:1-10
Hegde PS, et al., Clin Cancer Res. 2016;22(8):1865-74

免疫加免疫在腎癌成效

總存活期



無疾病惡化存活期



Motzer RJ, et al., N Engl J Med. 2018;378(14):1277-1290

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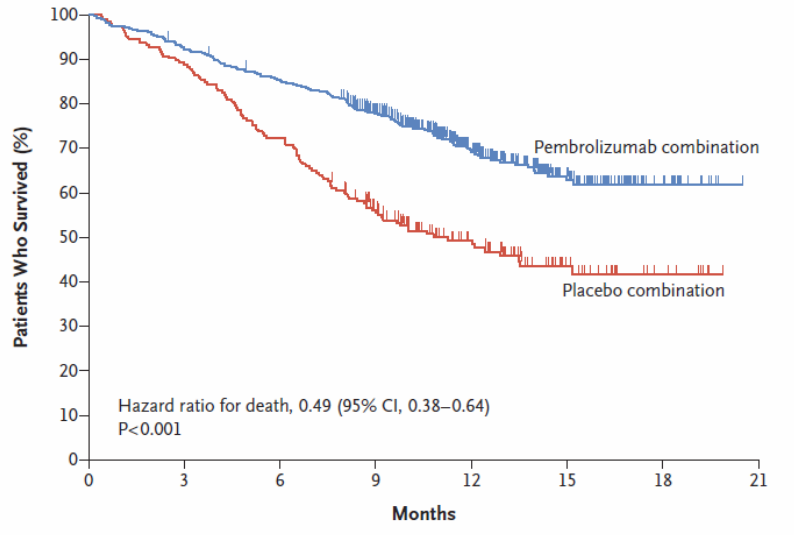
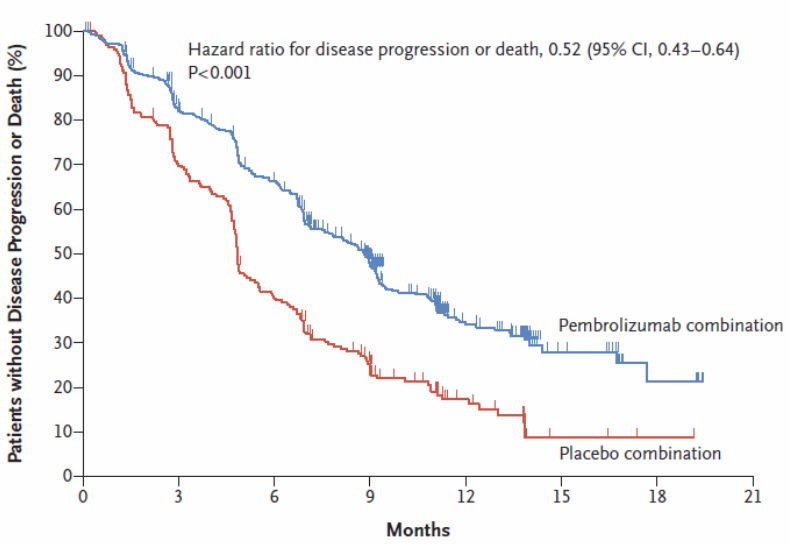
免疫加化療在肺癌成效

總存活期



無疾病惡化存活期



Gandhi L, et al., N Engl J Med. 2018 Apr 16. [Epub ahead of print]

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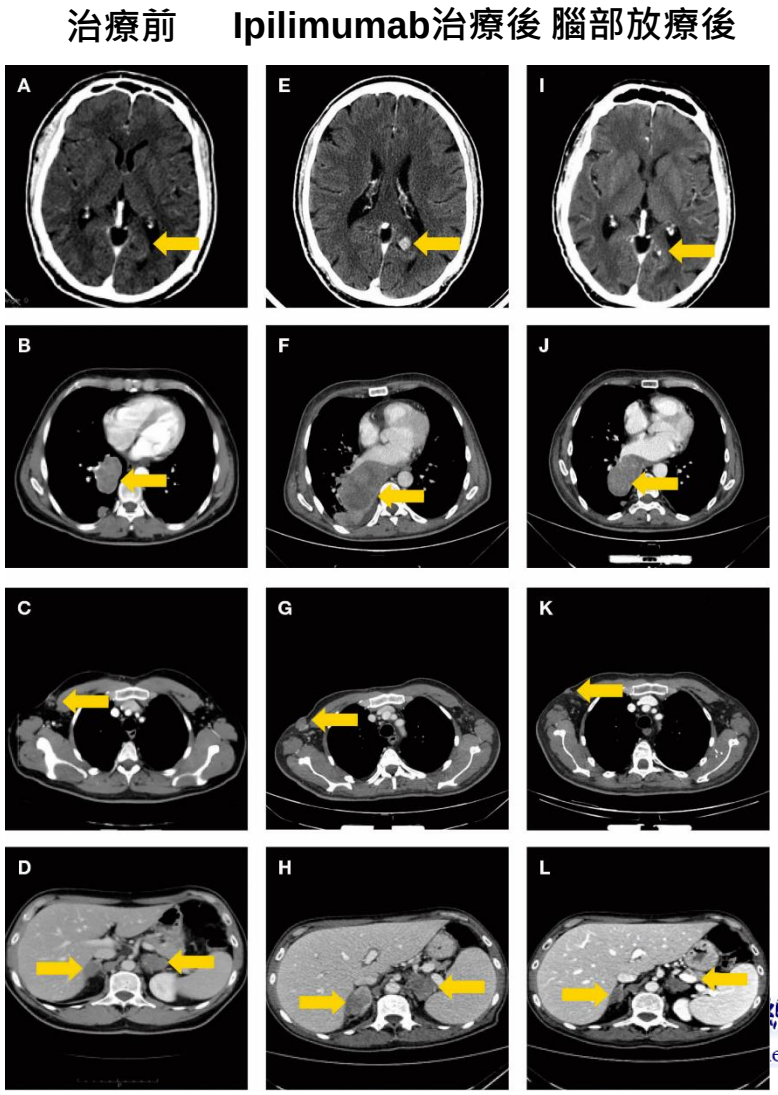
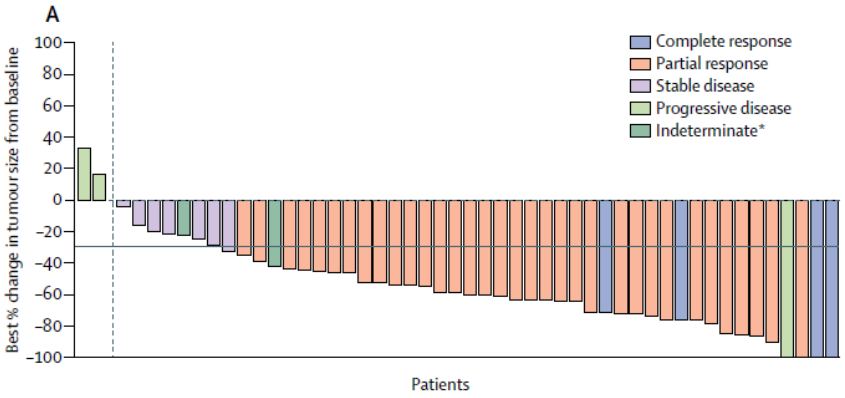
放射遠位效應

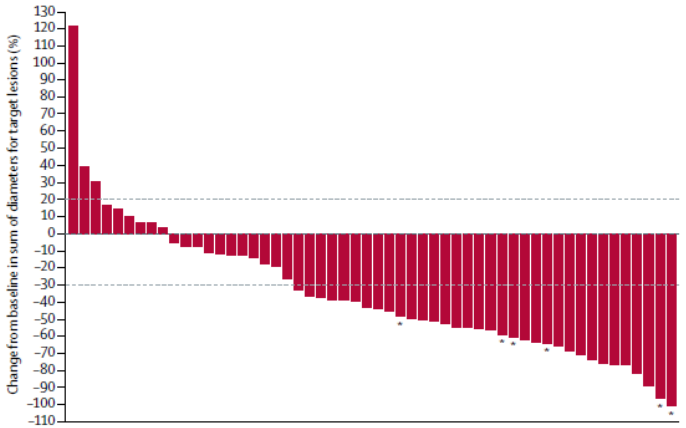
- 54歲男性
- 接受四週期 ipilimumab 治療, 腫瘤無明顯改善
- 之後接受全腦照射
- 全身腫瘤開始改善



Grimaldi AM, et al. Oncoimmunology 2014;3:e28780

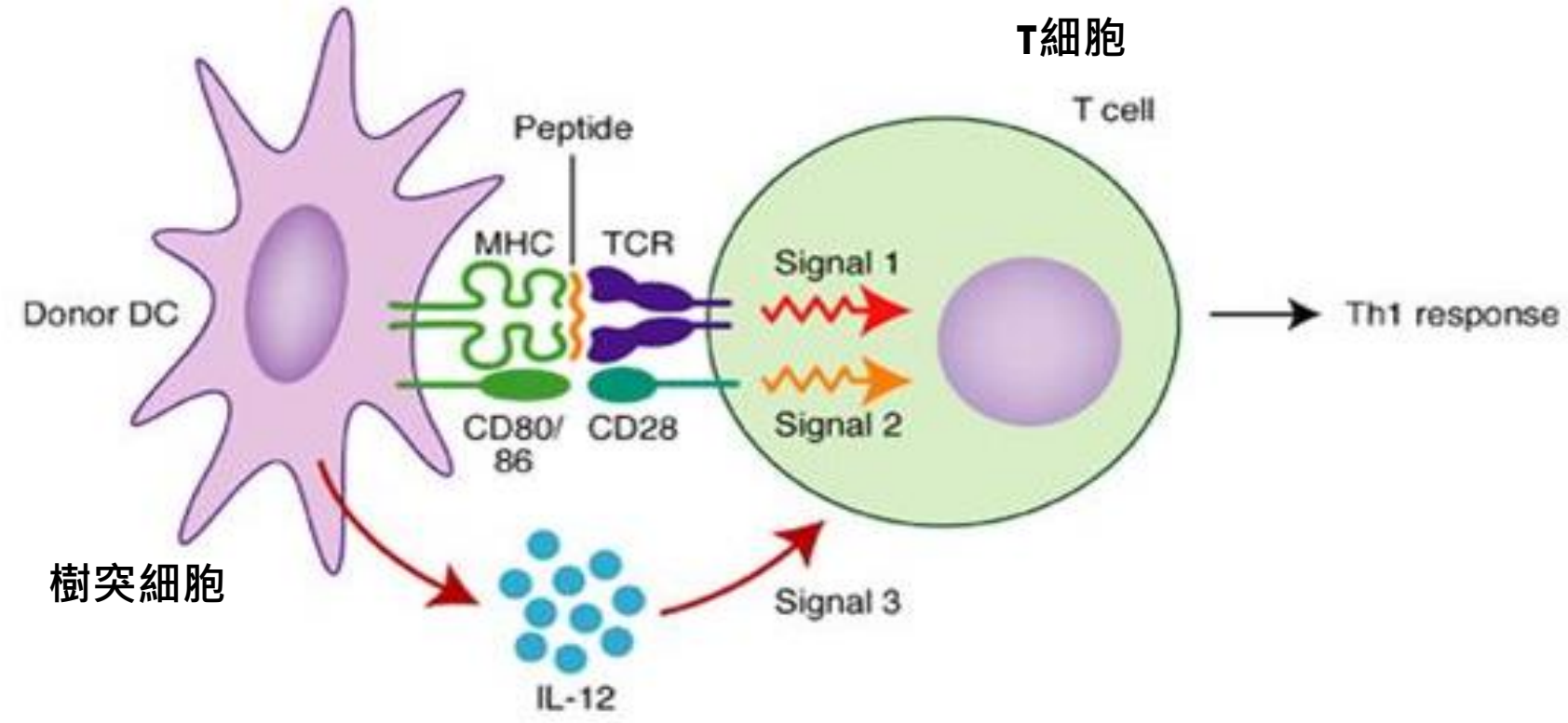
免疫加血管再生抑制劑在腎癌成效





Choueiri TK, et al. Lancet Oncol. 2018;19(4):451-460.
Atkins MB, et al. Lancet Oncol. 2018;19(3):405-415

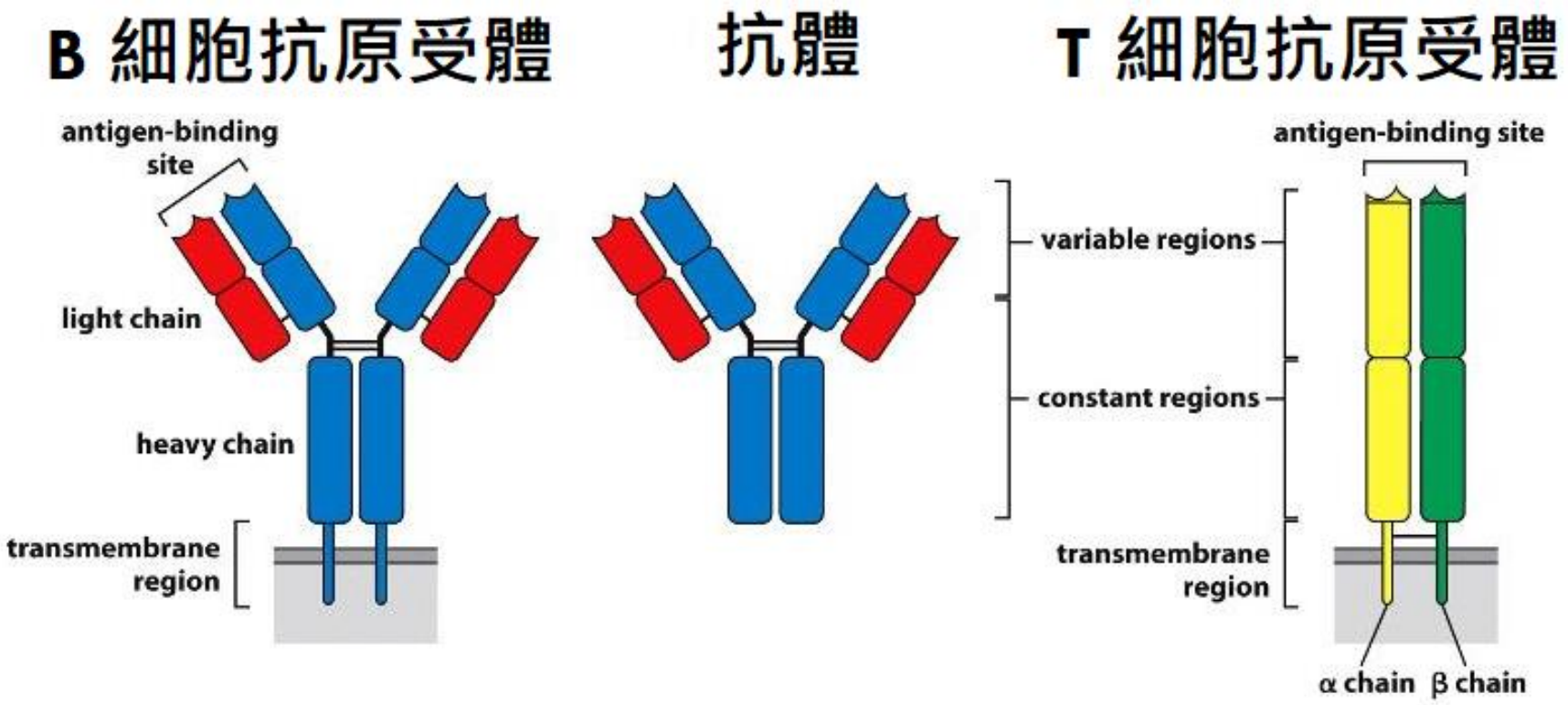
免疫系統辨識癌細胞



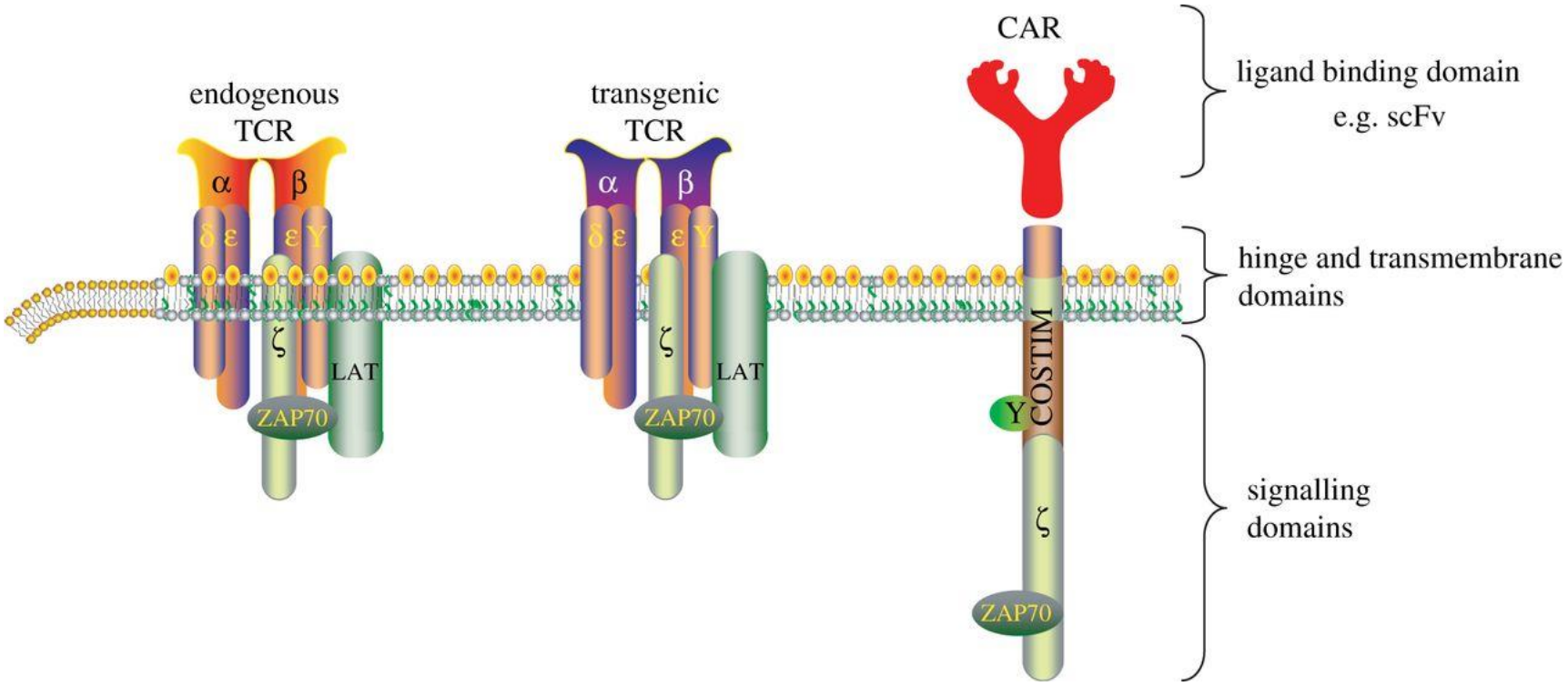
TCR: T細胞受體
MHC:主要組織相容性複合體

Coates PT, et al., Expert Rev Mol Med. 2002;4(3):1-21.

抗體, B 細胞抗原受體, T 細胞抗原受體



基因改造T 細胞抗原受體 (TCRs) 和嵌合抗原受體 (Chimeric antigen receptors: CAR)



June CH & Levine BL., Philos Trans R Soc Lond B Biol Sci. 2015;370(1680):20140374

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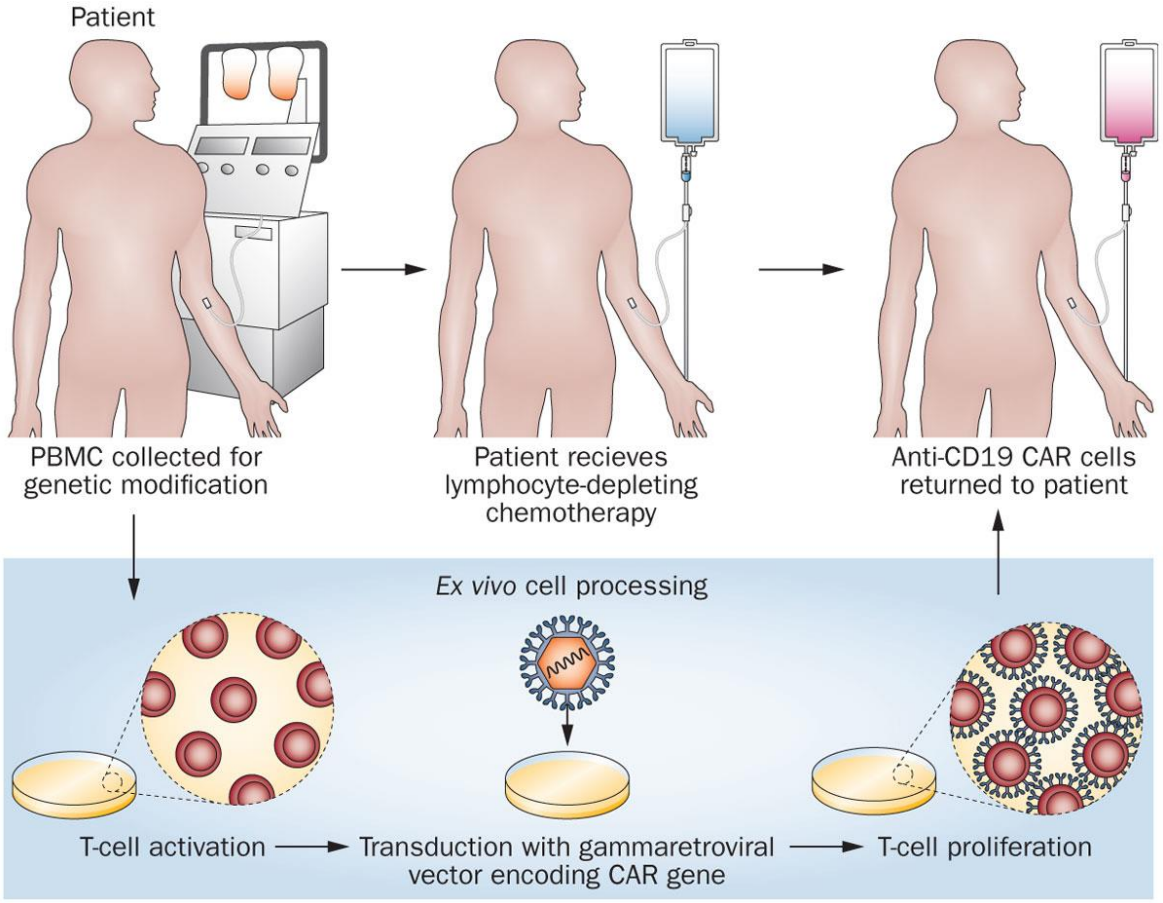
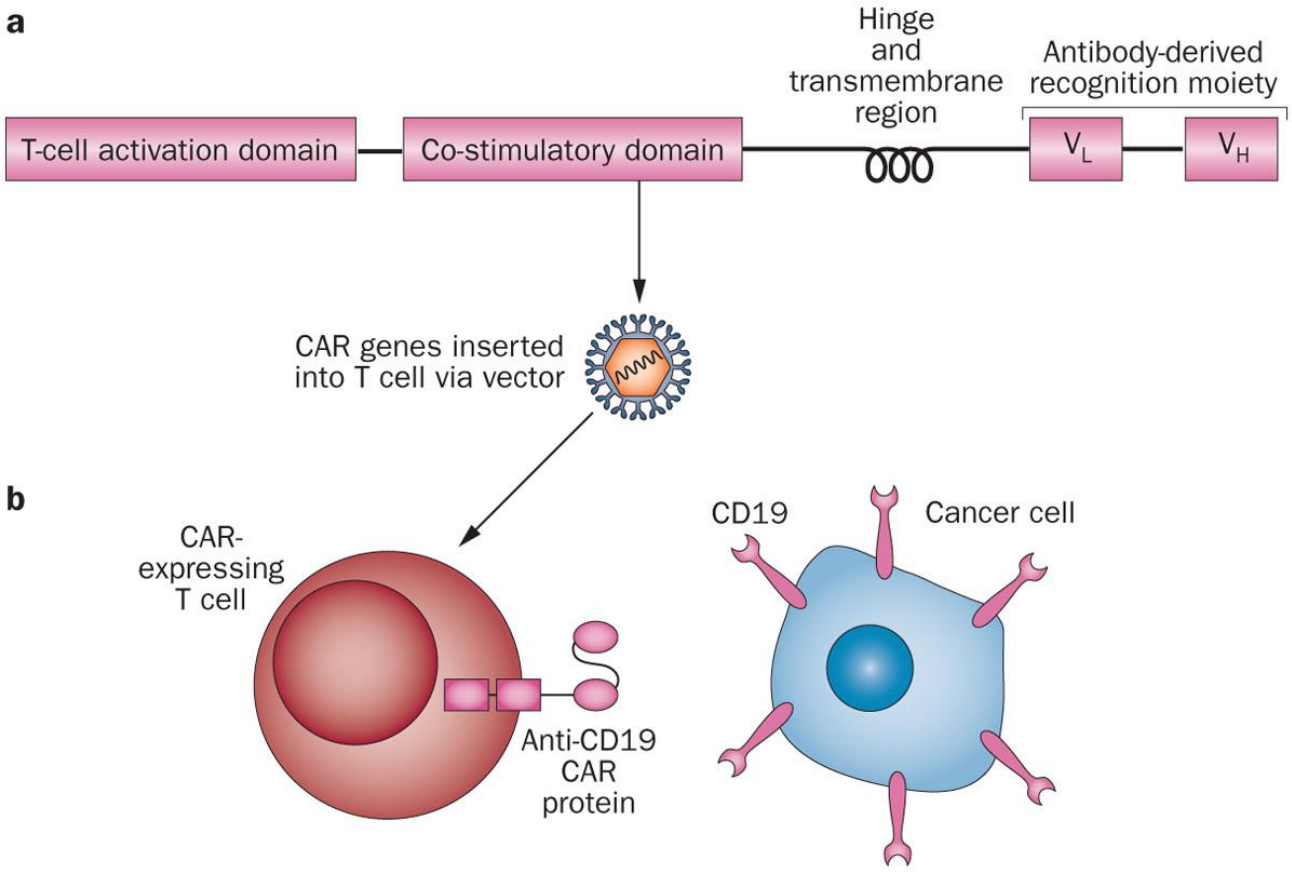
基因改造T細胞



Kochenderfer JN, Rosenberg SA, Nat Rev Clin Oncol. 2013;10(5):267-76

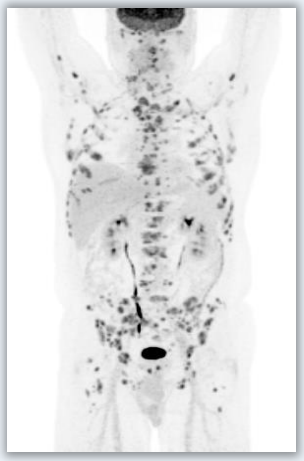
嵌合抗原受體T細胞對抗表現CD19抗原 (Anti-CD19 CART) 的B細胞白血病或淋巴瘤

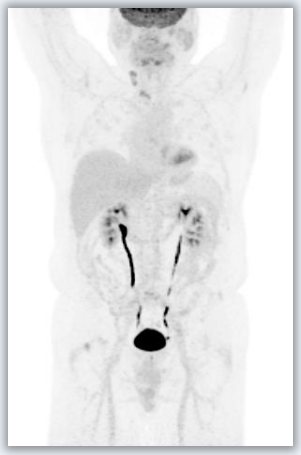


Kochenderfer JN, Rosenberg SA, Nat Rev Clin Oncol. 2013;10(5):267-76

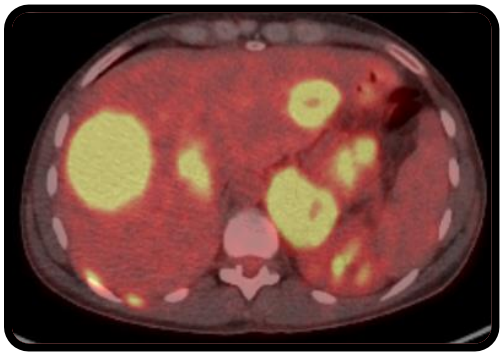
Anti-CD19 CART 對B細胞淋巴瘤的療效

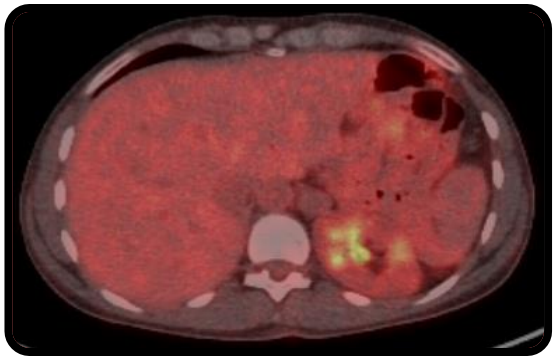
Before Treatment **Post Treatment**





A patient with recurrent DLBCL post-SCT treated with anti-CD19 CAR T cells





Ongoing Complete Response 15+ months in a patient with chemo-refractory PMBCL

Kochenderfer JN, et al., J Clin Oncol. 2015;33(6):540-9

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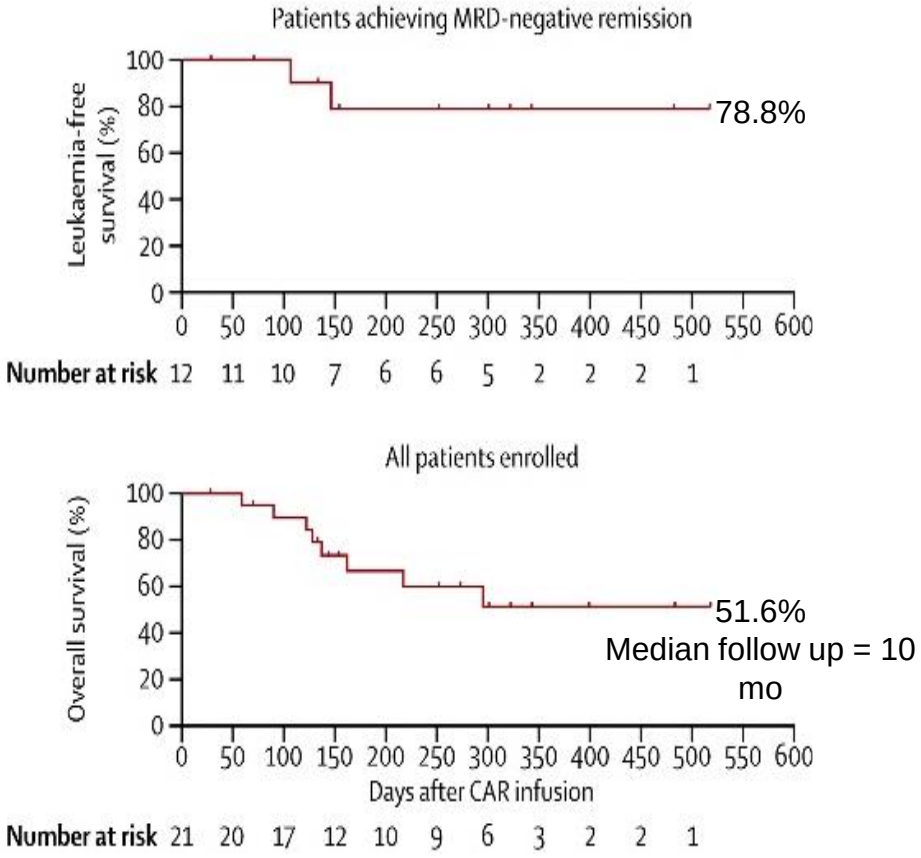
Anti-CD19 CART 對急性B細胞白血病的療效

Intention-to-Treat Analysis	ALL (N=20)
Complete Response	14 (70%)
MRD negative Complete Response	12 (60%)
Allogeneic Transplant	10 (50%)
Relapse Post Allogeneic Transplant	0 (0%)



Lee DW, et al., Lancet. 2015;385:517-528

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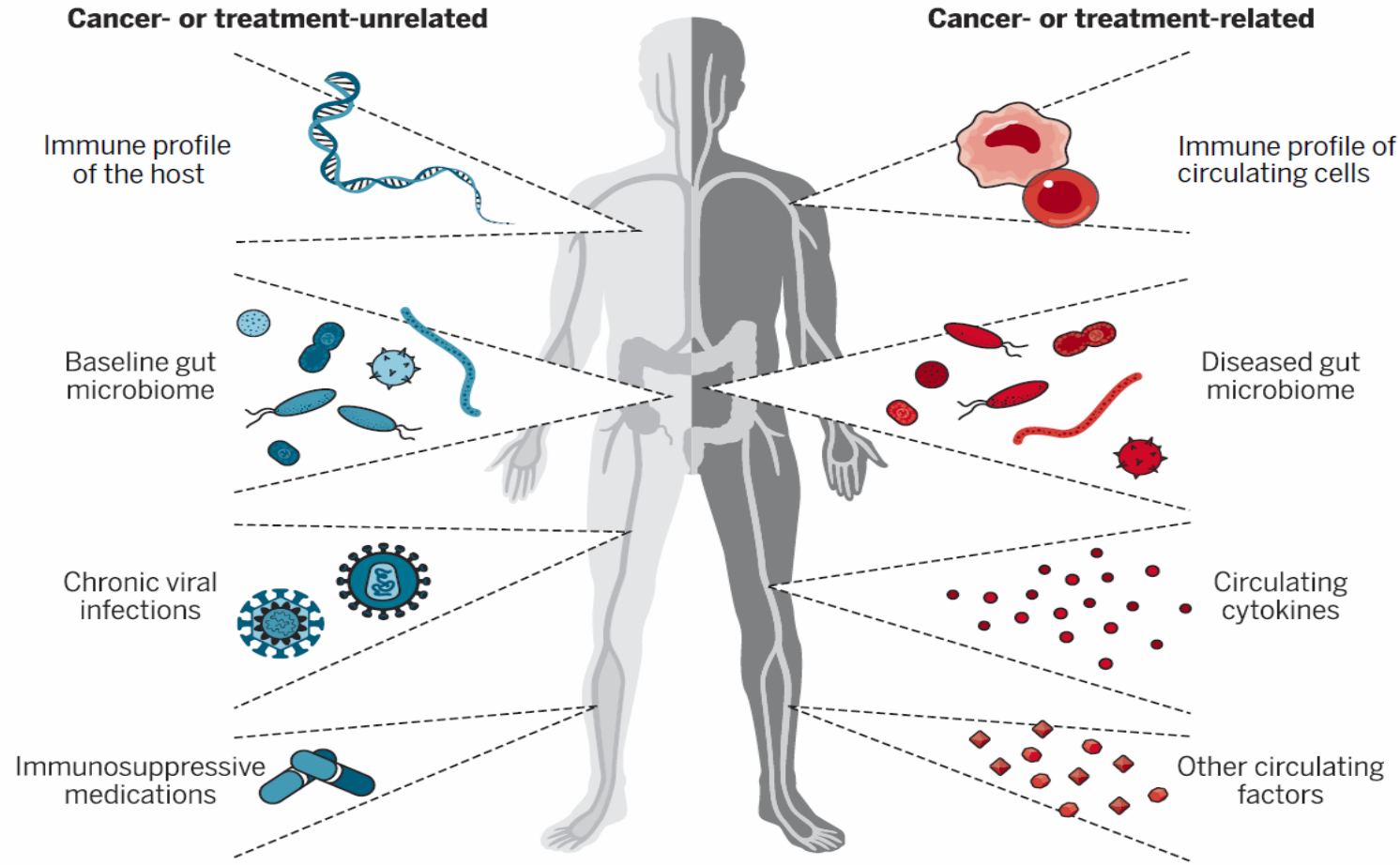
世界首例！諾華 CAR-T 療法獲 FDA 核准 開啟癌症治療新時代

- 美國 FDA 於美國時間 8 月 30 日宣布批准諾華製藥 (Novartis) 的 CAR-T 治療藥物 Kymriah (tisagenlecleucel) 上市，價格為美金 475,000元，預計將帶來創造數十億美元的營收，為近年來基因修改技術應用於癌症免疫療法 (immunotherapy) 的重大突破，也對多年投身於該領域研究的科學家們帶來令人振奮的好消息.

基因療法造成病患死亡 Cellectis股價一天蒸發掉逾4億美元

- Cellectis 公司在 9 月 4 日宣布 CAR-T 治療療法 被 FDA 喊停。主因為 78 歲的男性病人罹患了罕見的惡性淋巴瘤，急性漿細胞樣樹突狀細胞瘤 (BPDCN)。該病人使用過後，結果在治療的 8 天後，出現致命反應而死亡。該聲明發布後， Cellectis 股價在 9 月 5 日這天暴跌了 32%，市值一天蒸發超過 4 億美元。
- 和諾華公司的CAR-T基因療法相比，Cellectis公司的通用性CAR-T療法並非從病人體內提取自身T細胞、並對此進行基因編輯使其具有攻擊癌細胞的能力，而是通過改造其他捐獻者的T細胞，再輸到病人體內。

Systemic hallmarks of successful anticancer immunotherapy



Galluzzi L, et al., Sci Transl Med. 2018;10(459). pii: eaat7807

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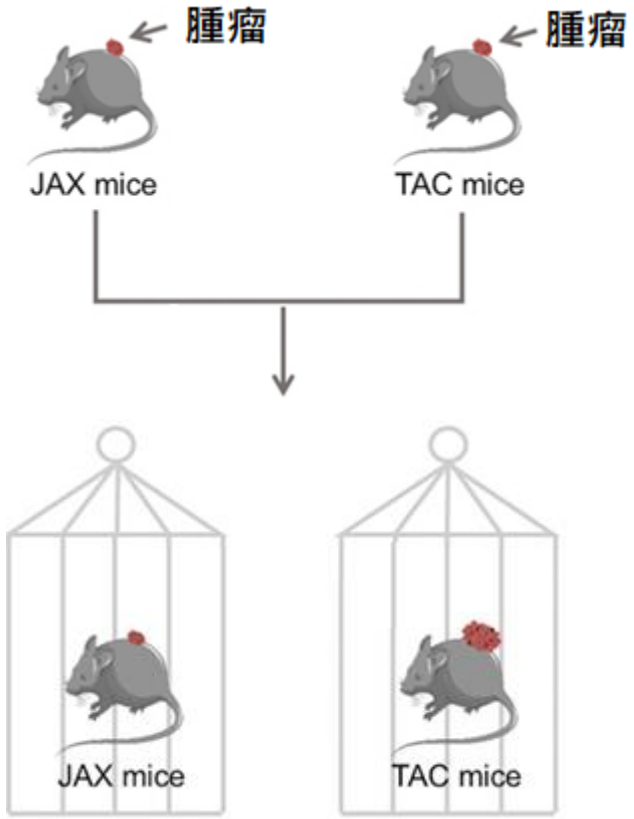
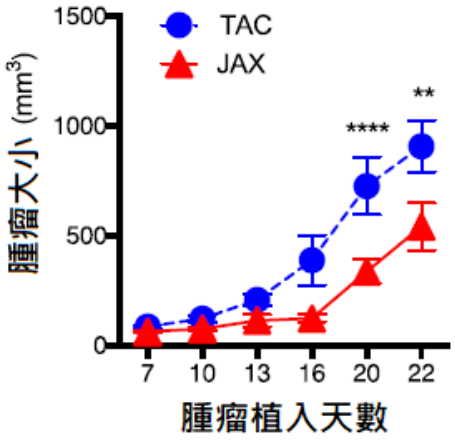
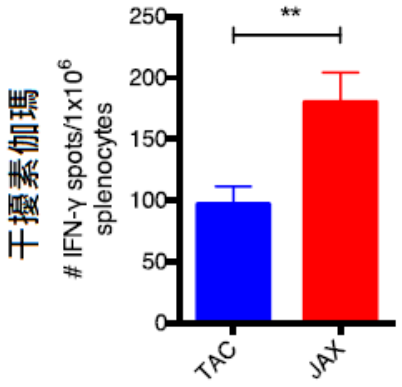
不同環境養殖的老鼠因免疫力不同 導致腫瘤生長速度不同







Sivan A, et al., Science. 2015;350(6264):1084-9
Wang Y., Front Immunol. 2018;9:374

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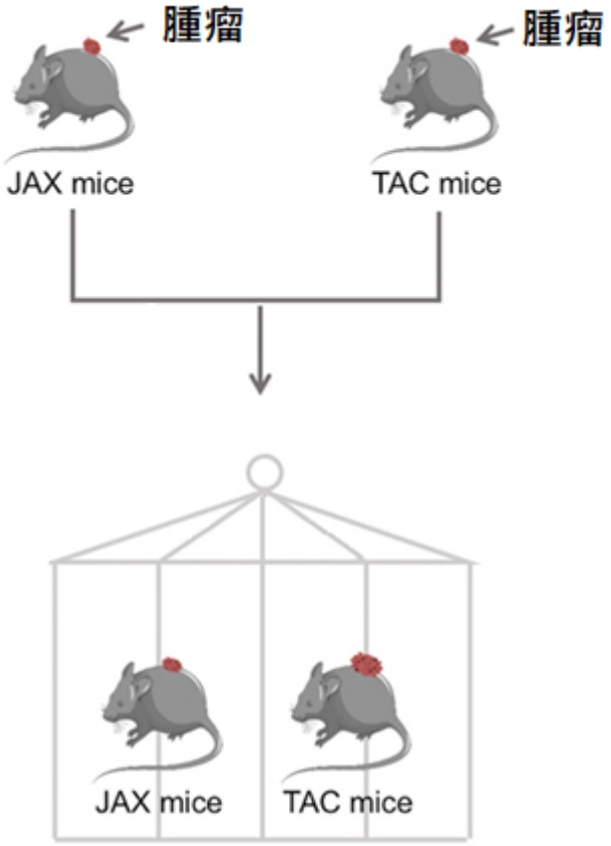
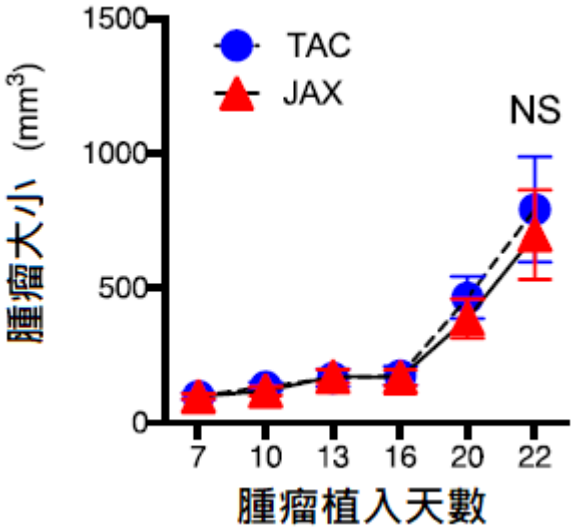
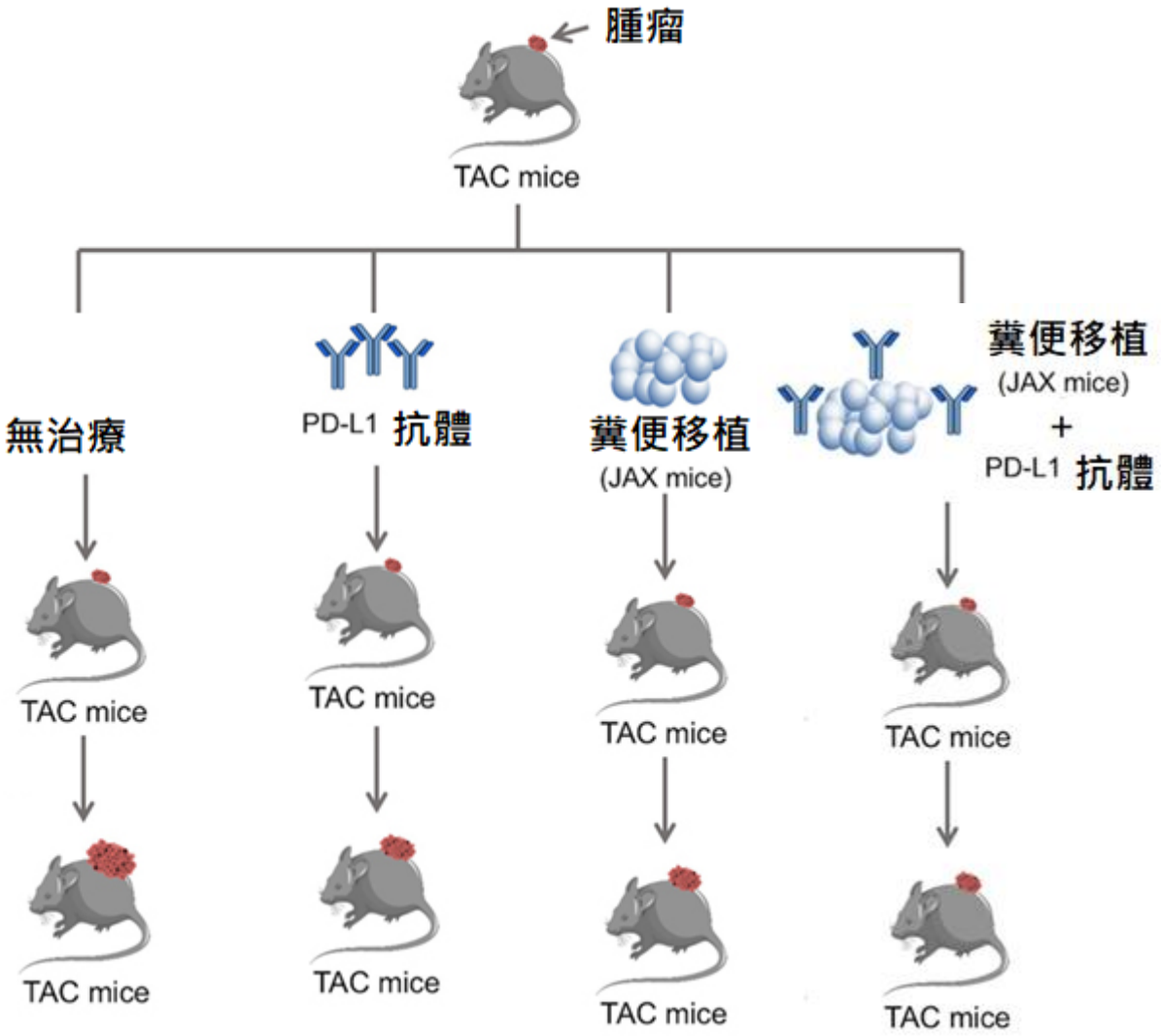
不同環境養殖的老鼠因免疫力不同 導致腫瘤生長速度不同





Sivan A, et al., Science. 2015;350(6264):1084-9
Wang Y., Front Immunol. 2018;9:374

糞便移植增加免疫治療效果



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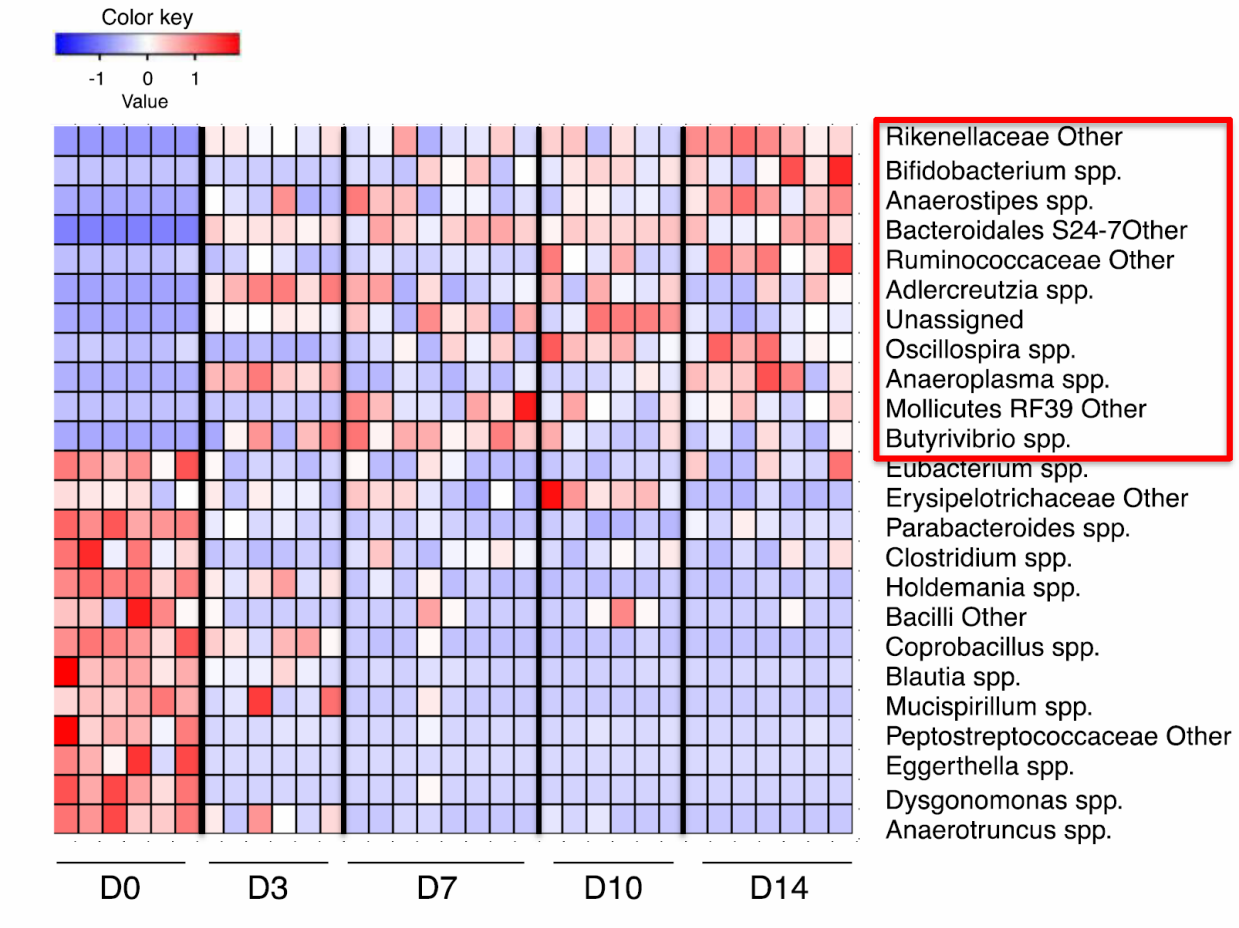
Sivan A, et al., Science. 2015;350(6264):1084-9; Wang Y., Front Immunol. 2018;9:374

Bifidobacterium (比菲德氏菌)為可能相關菌種



Sivan A, et al., Science. 2015;350(6264):1084-9

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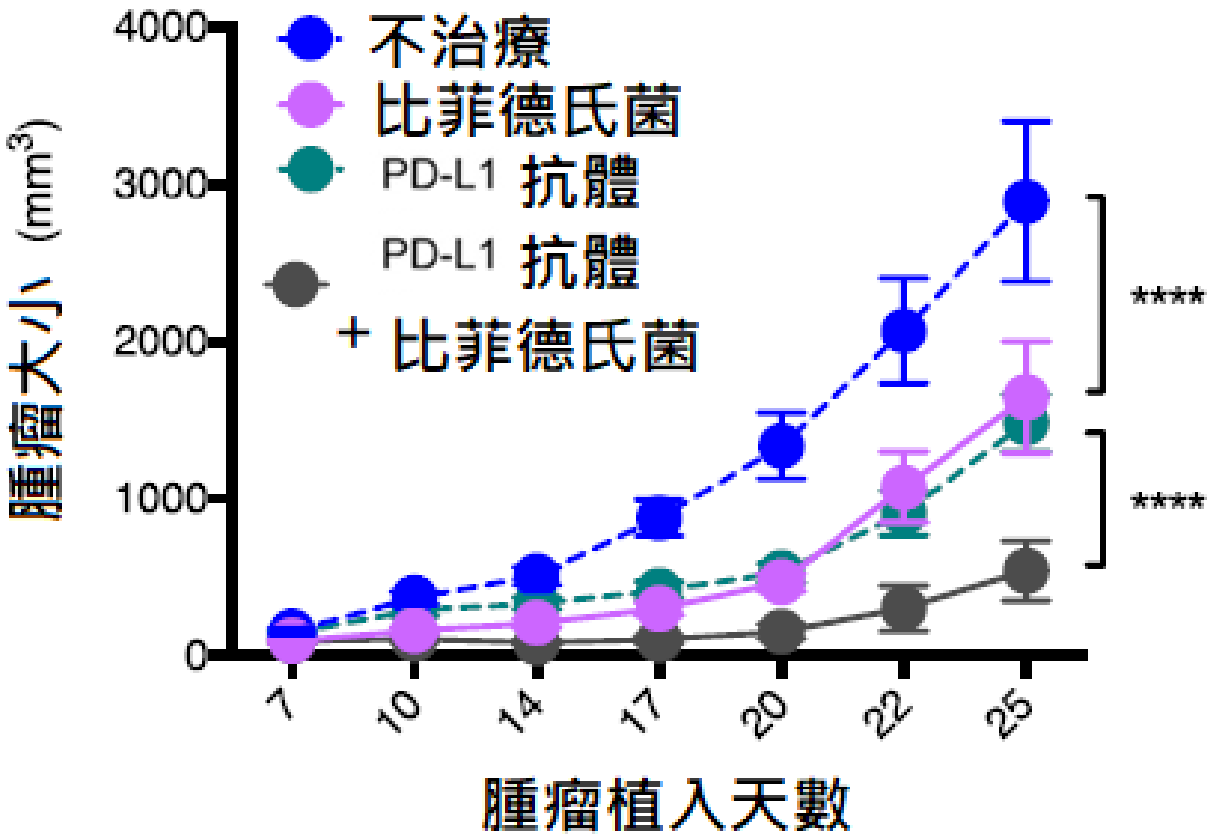
比菲德氏菌增加免疫治療效果



Sivan A, et al., Science. 2015;350(6264):1084-9

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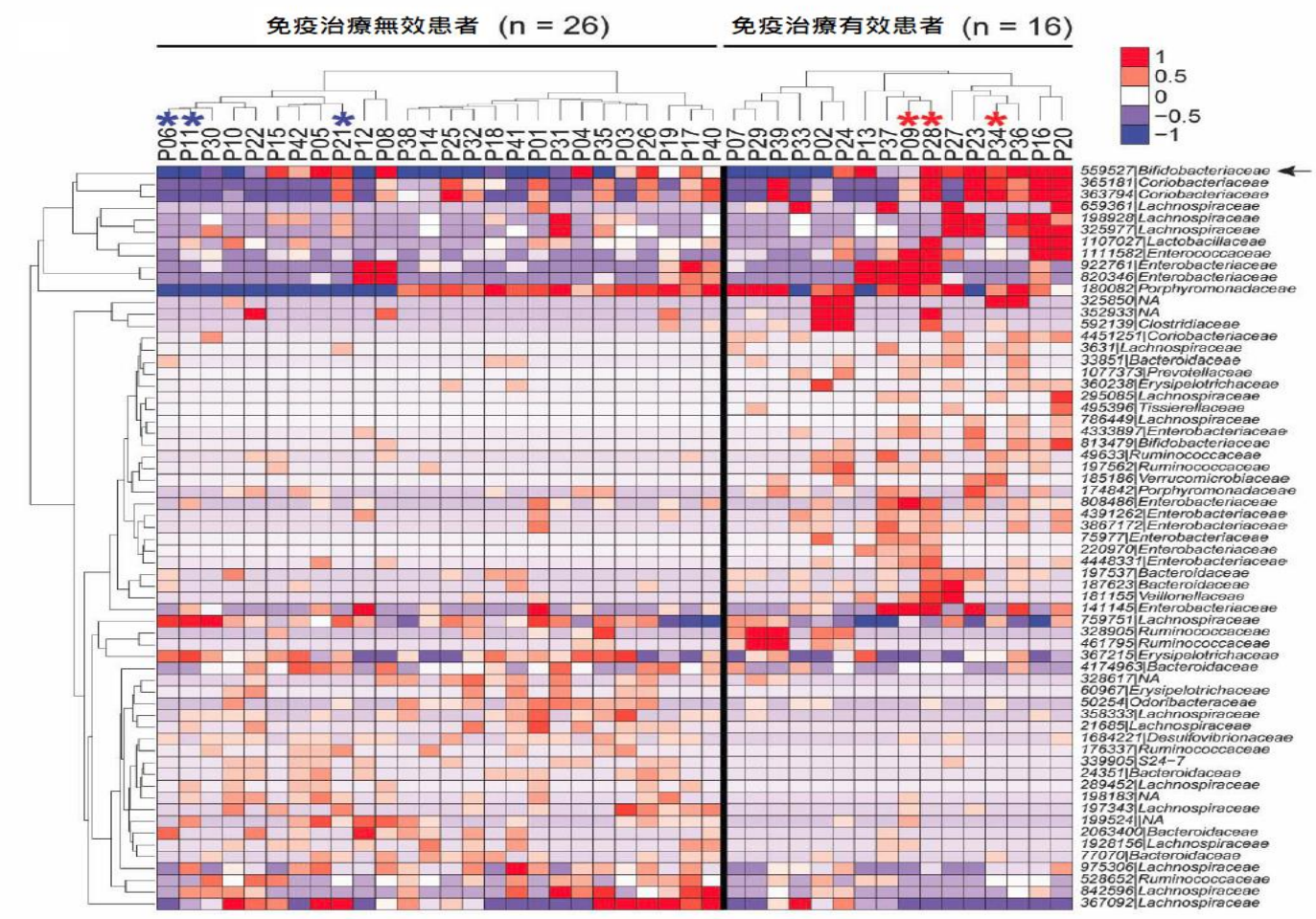
比菲德氏菌在免疫療法有效患者也是主要菌種



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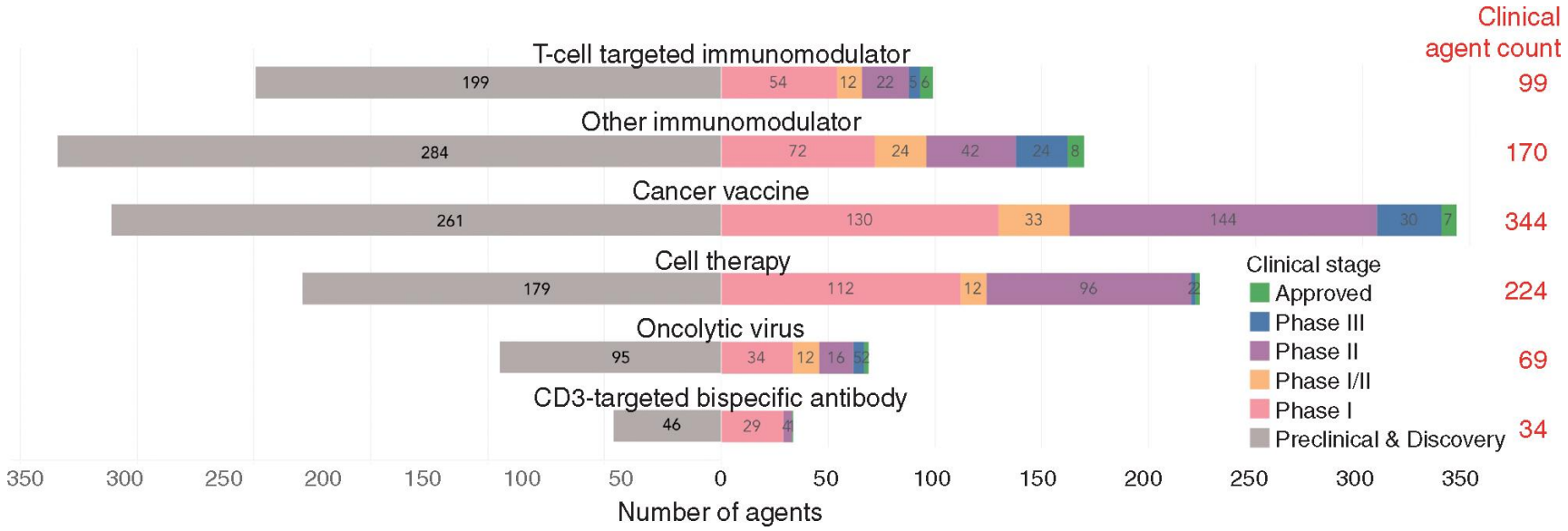
Matson V, et al., Science. 2018 ;359(6371):104-108

2004個發展中癌症免疫藥物 (940臨床發展階段; 1064臨床前期發展階段)



Tang J, et al. Ann Oncol. 2018;29(1):84-91.

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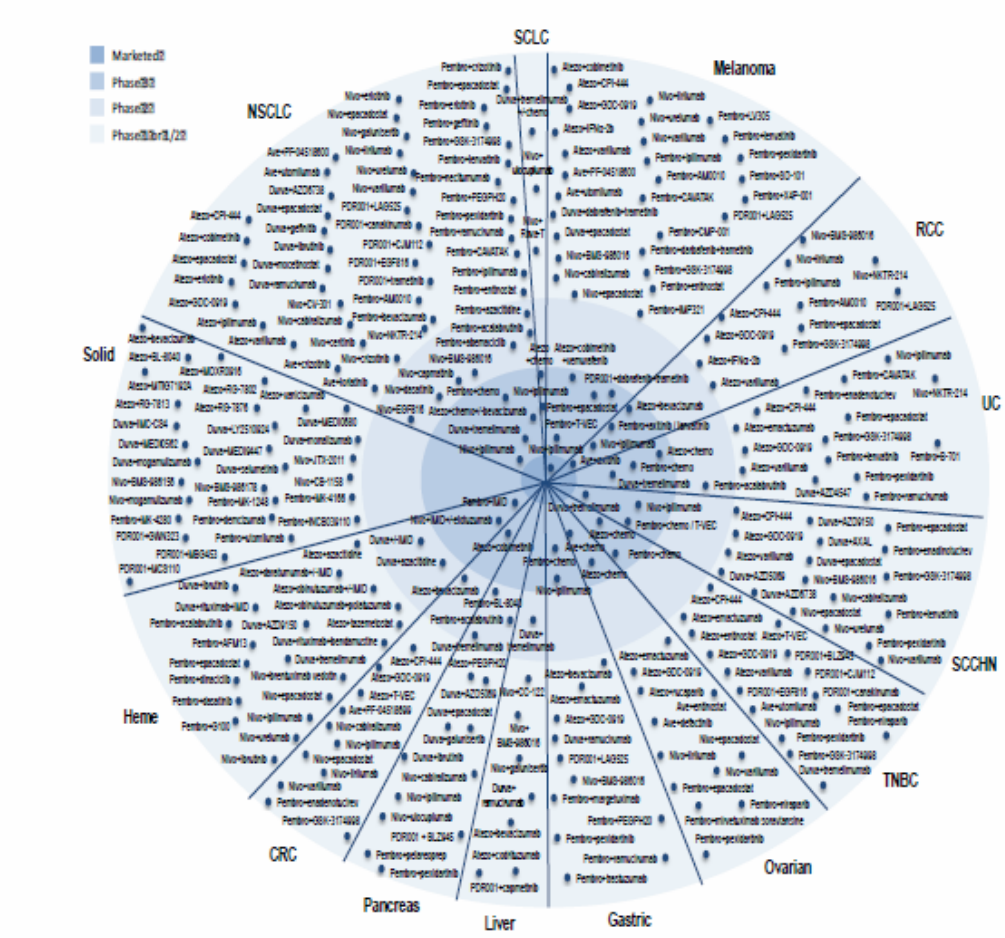
超過1500個臨床試驗 收納約30000個病人



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總結

- 免疫療法：癌症治療新希望
- 日新月異，進步神速
- 如何選擇病人?
- 如何預防/治療毒性?
- 環境與免疫/免疫治療的關係
- 臨床試驗的困境：嚴謹度
- 價格居高不下 (個人財力毒性)
- 健保給付限制多
- 細胞治療?