

康健雜誌

CHF
康健趨勢論壇
Commercial Health Forum

蛻
變

2019 康健癌症論壇

新人生

癌症終生管理

免疫藥物在 肺癌治療之角色

王金洲

高雄長庚紀念醫院肺癌團隊召集人



免疫藥物在肺癌治療之角色

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高雄長庚紀念醫院 胸腔內科

2019-04-27



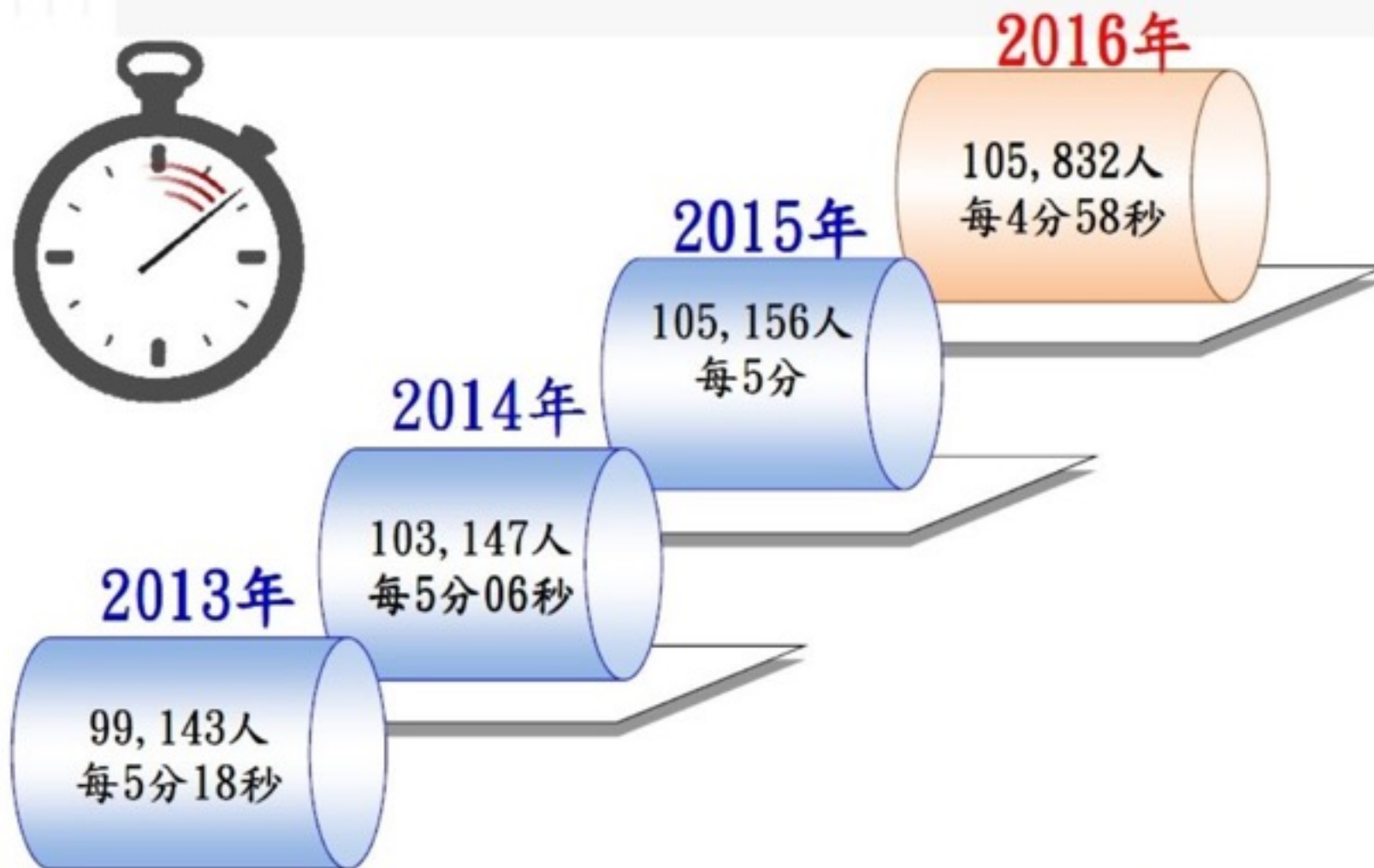
大綱

- 肺癌流行病學與治療現況
- 癌症免疫治療
 - 人體的免疫系統
 - 癌症免疫循環
 - 免疫檢查點抑制劑
 - 免疫治療相關副作用
- 目前台灣健保給付

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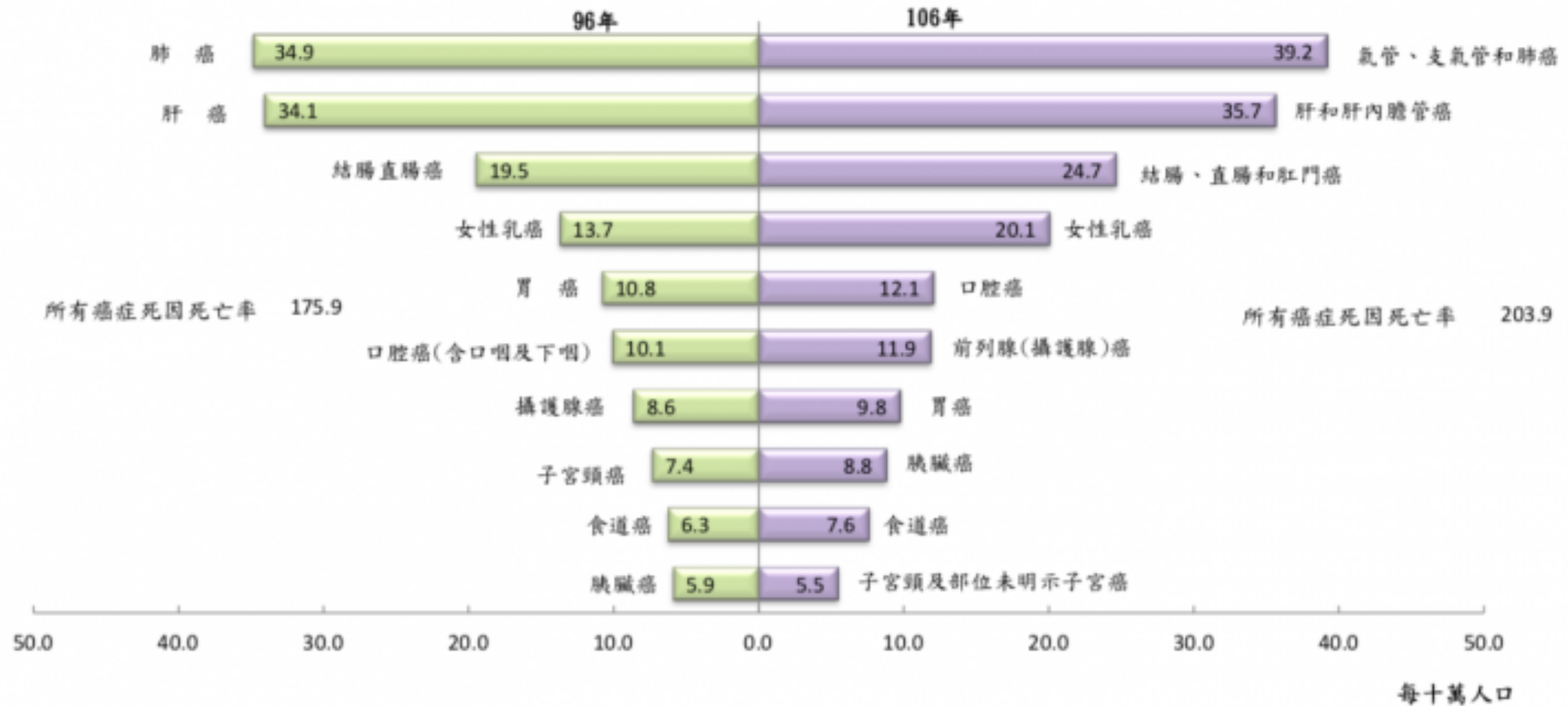
癌症時鐘再加快2秒



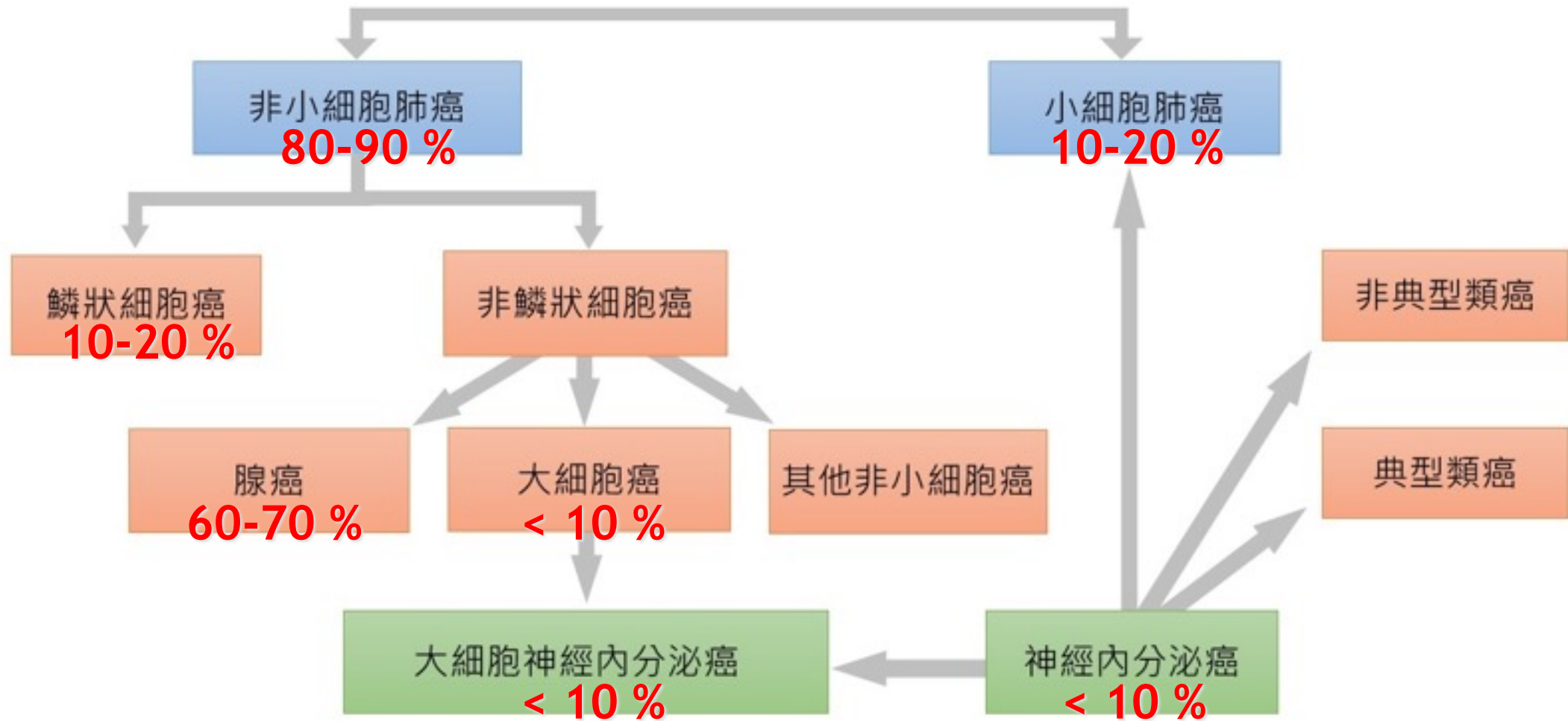


註: 1. 台灣癌症登記資料庫 (不含原位癌)
2. 此張發生率係指年齡標準化率, 以2000年世界標準人口計算 (單位: 每10萬人)
3. 圖片來源: Flaticon (www.flaticon.com)

十大癌症死因死亡率



肺癌的分類



2018年 高雄長庚 肺癌個案

	I	II	IIIA	IIIB	IIIC	IV	總和
腺細胞肺癌 (肺腺癌)	139	20	22	23	10	317	531 (75.1%)
鱗狀細胞肺癌	5	5	6	8	6	50	80 (11.3%)
其他	3	1	2	2	0	22	30 (4.2%)
總和	149 (21.1%)	28 (4.0%)	32 (4.5%)	36 (5.1%)	23 9 (3.3%)	439 (62.1%)	707

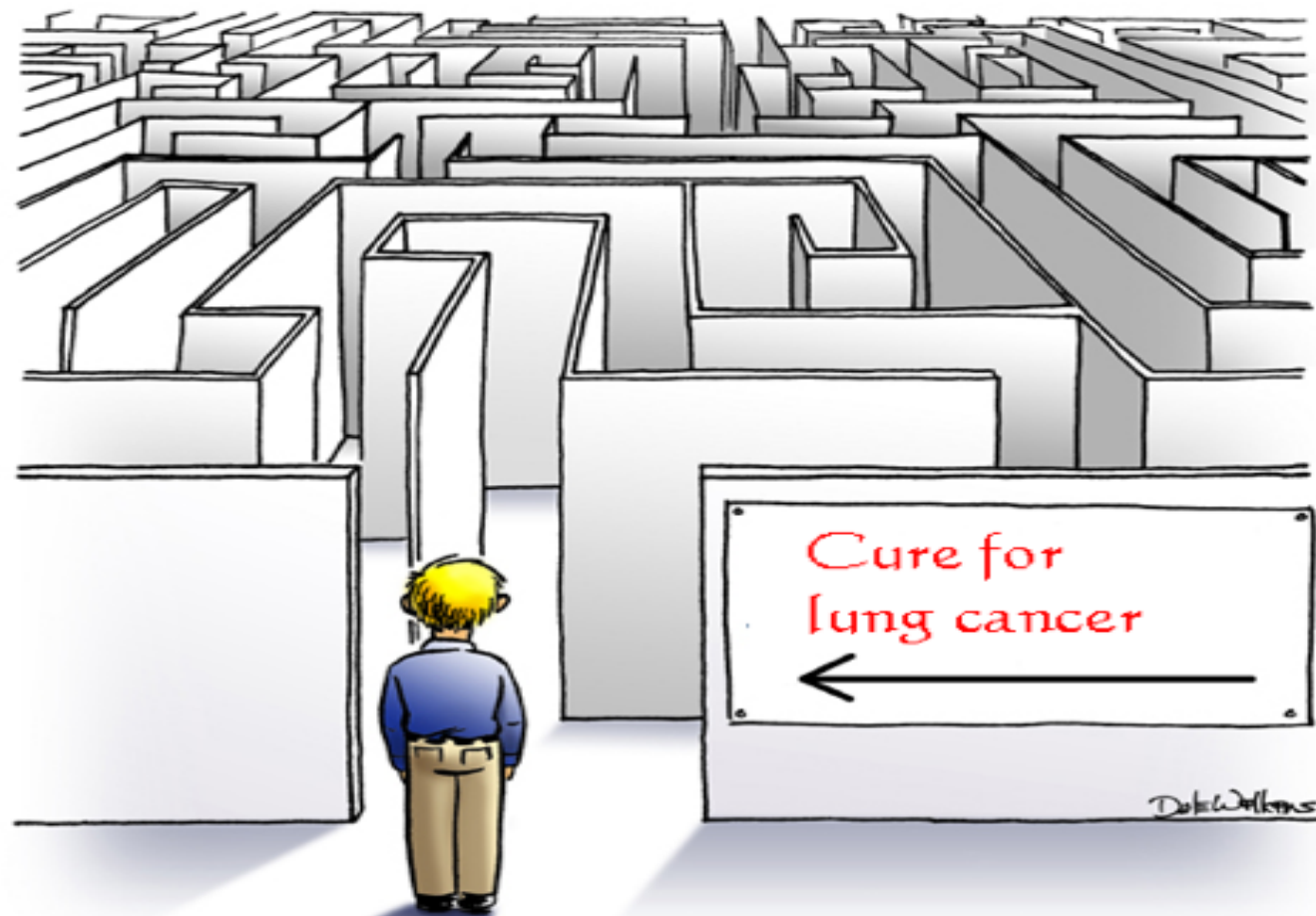
細胞型態的改變
分期比例的改變

Before 2016

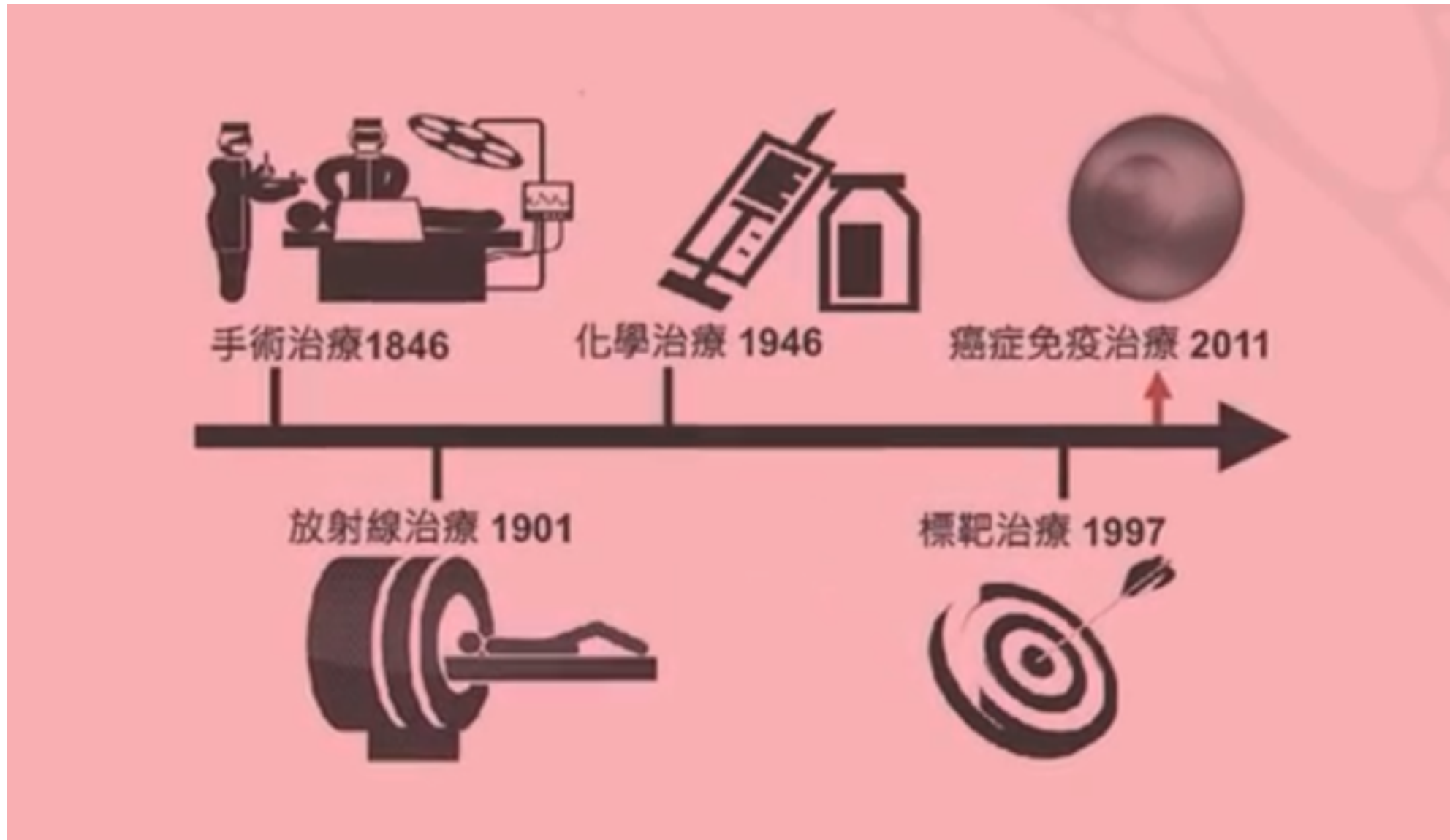
~10%



~72%

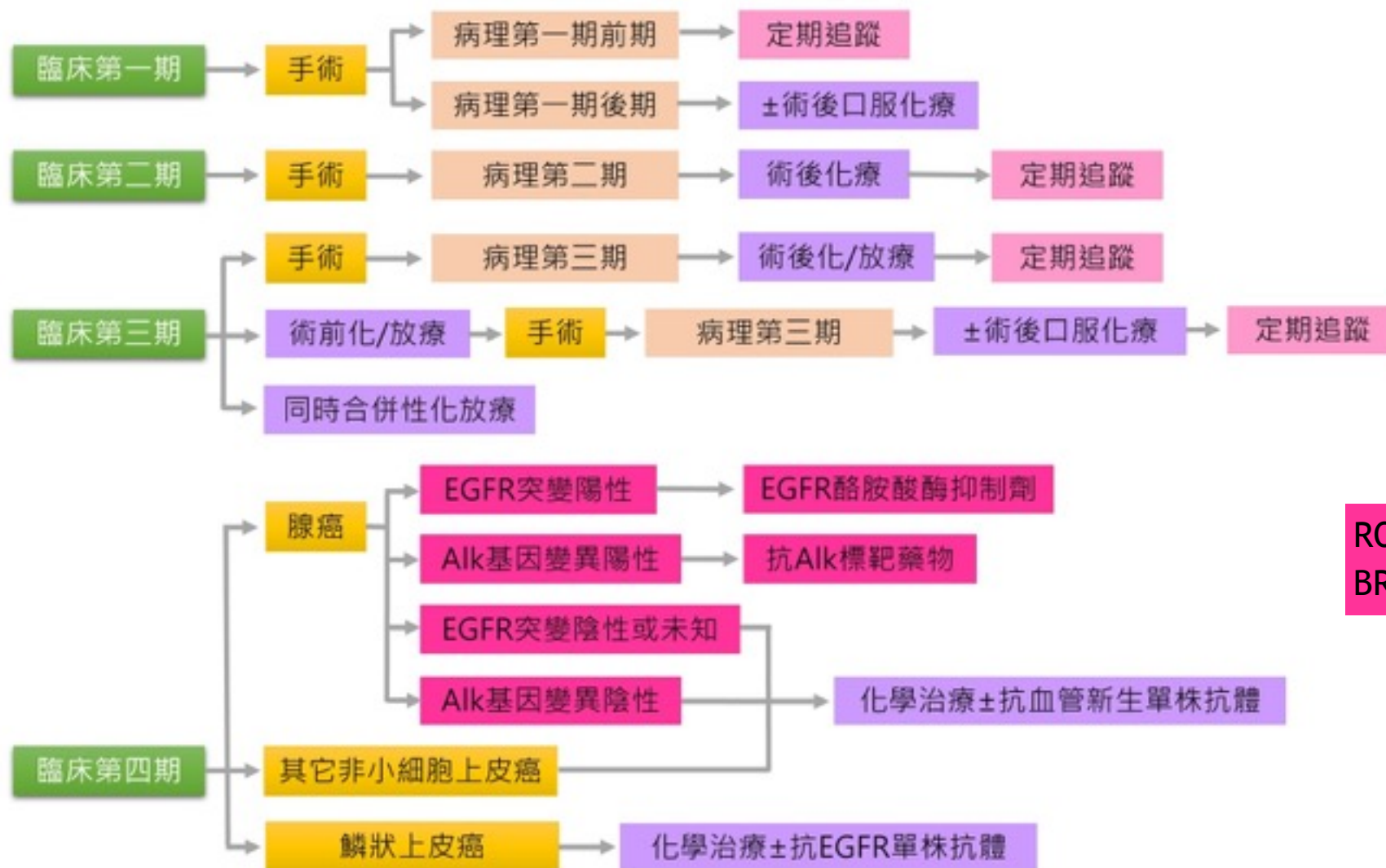


90年代之前
晚期肺癌治療像謎宮





非小細胞肺癌 治療指引流程圖



ROS 1 基因變異 標靶藥物
BRAF基因變異 標靶藥物

免疫藥物

美國國家癌症資訊網癌症診療指引

CLINICAL PRESENTATION

Advanced or metastatic Disease

- Establish histologic subtype^a with adequate tissue for molecular testing (consider rebiopsy^{gg} if appropriate)
- Smoking cessation counseling
- Integrate palliative care^c (See [NCCN Guidelines for Palliative Care](#))

HISTOLOGIC SUBTYPE^a

- Adenocarcinoma
- Large cell
- NSCLC not otherwise specified (NOS)

Squamous cell carcinoma

TESTING^{hh}

- Molecular testing
 - EGFR mutation testing (category 1)
 - ALK testing (category 1)
 - ROS1 testing
 - BRAF testing
 - Testing should be conducted as part of broad molecular profiling^{ii,jj}
- PD-L1 testing (category 1)

- Molecular testing
 - Consider EGFR mutation and ALK testing^{kk} in never smokers or small biopsy specimens, or mixed histology^{ll}
 - Consider ROS1 and BRAF testing in small biopsy specimens or mixed histology
 - Testing should be conducted as part of broad molecular profiling^{ii,jj}
- PD-L1 testing (category 1)

TESTING RESULTS^{hh}

- Sensitizing EGFR mutation positive (see [NSCL-18](#))
- ALK positive (see [NSCL-21](#))
- ROS1 positive (see [NSCL-24](#))
- BRAF V600E positive (see [NSCL-25](#))

- PD-L1 ≥50% and EGFR, ALK negative or unknown (see [NSCL-27](#))

- EGFR, ALK, ROS1, BRAF negative or unknown, PD-L1 <50% or unknown (see [NSCL-28](#))

- Sensitizing EGFR mutation positive (see [NSCL-18](#))
- ALK positive (see [NSCL-21](#))
- ROS1 positive (see [NSCL-24](#))
- BRAF V600E positive (see [NSCL-25](#))

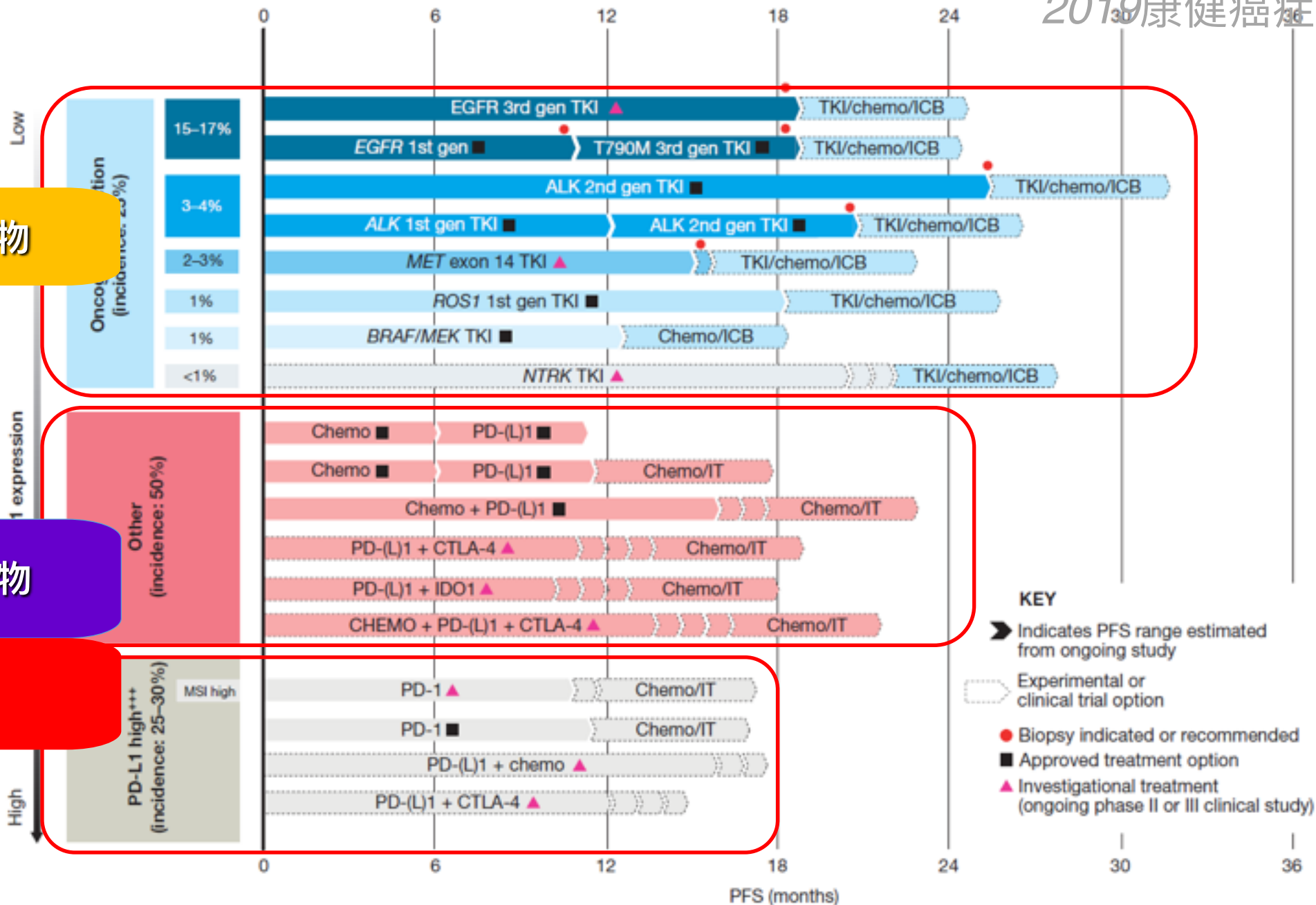
- PD-L1 ≥50% and EGFR, ALK negative or unknown (see [NSCL-27](#))

- EGFR, ALK, ROS1, BRAF, negative or unknown, PD-L1 <50% or unknown (see [NSCL-29](#))

標靶藥物

免疫藥物

化療

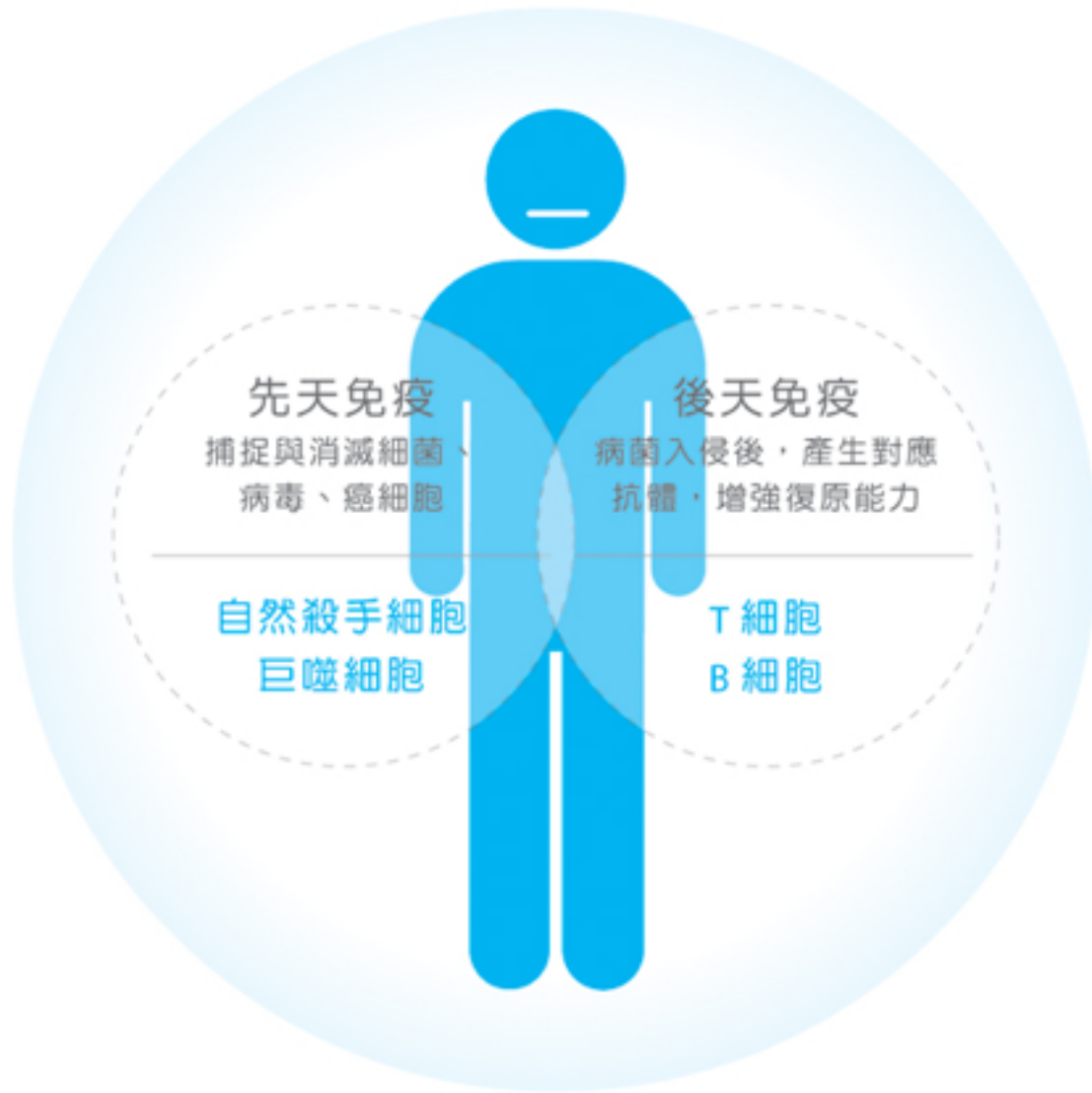


大綱

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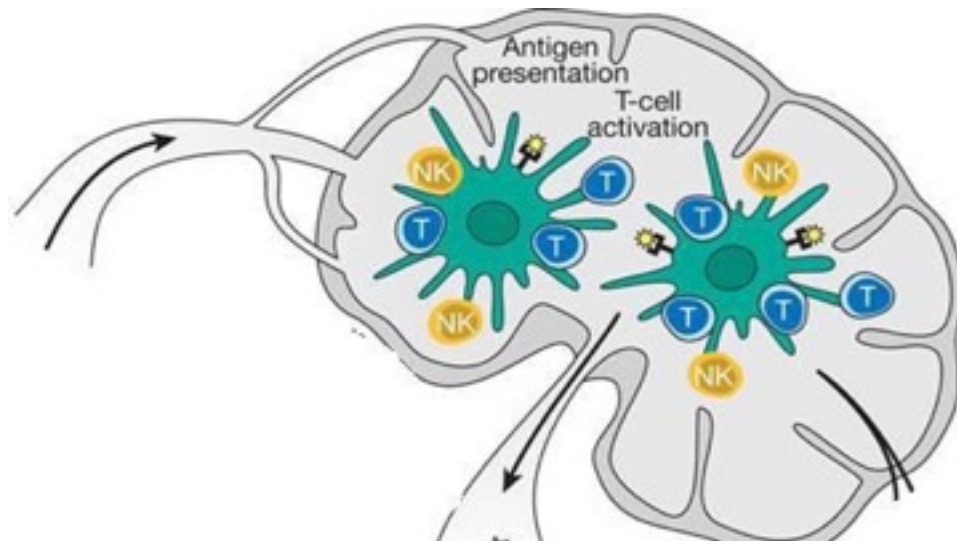
人體的免疫系統

1. 殺死入侵的細菌、病毒
2. 殺死癌細胞



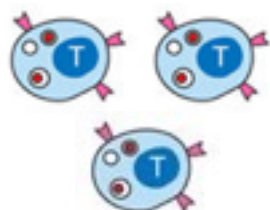
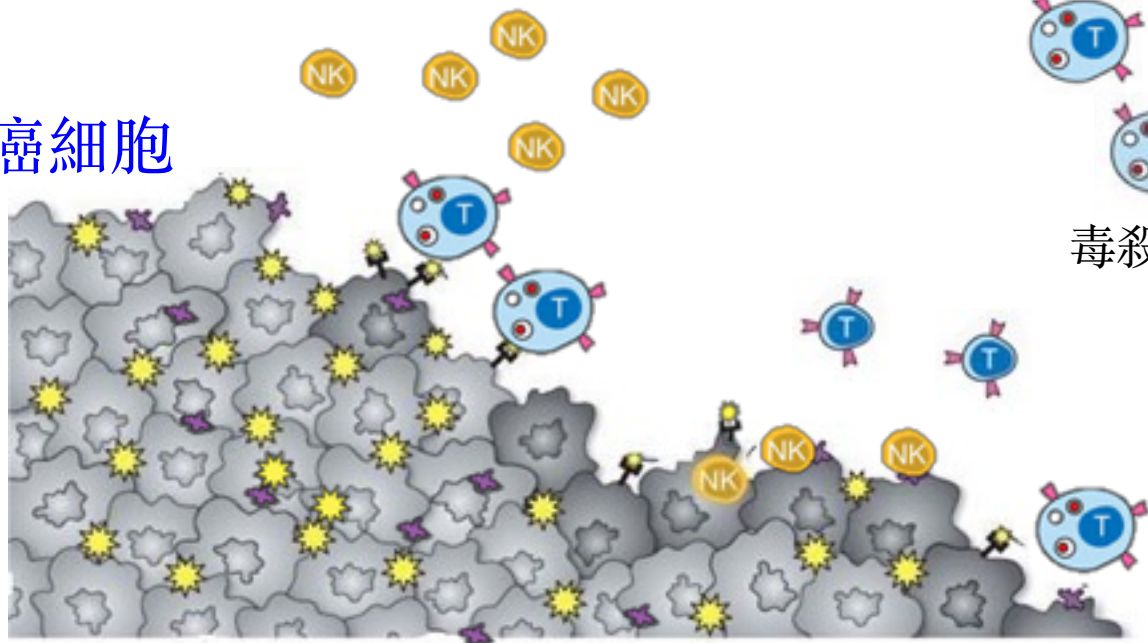
DC樹突細胞
(T細胞的教練)

- ☀️ 腫瘤特異抗原
- 👤 MHC+腫瘤特異抗原
- 👤 原
- 👤 PD-L1

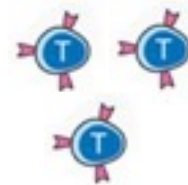


淋巴結等
免疫器官

癌細胞



毒殺T細胞



T細胞



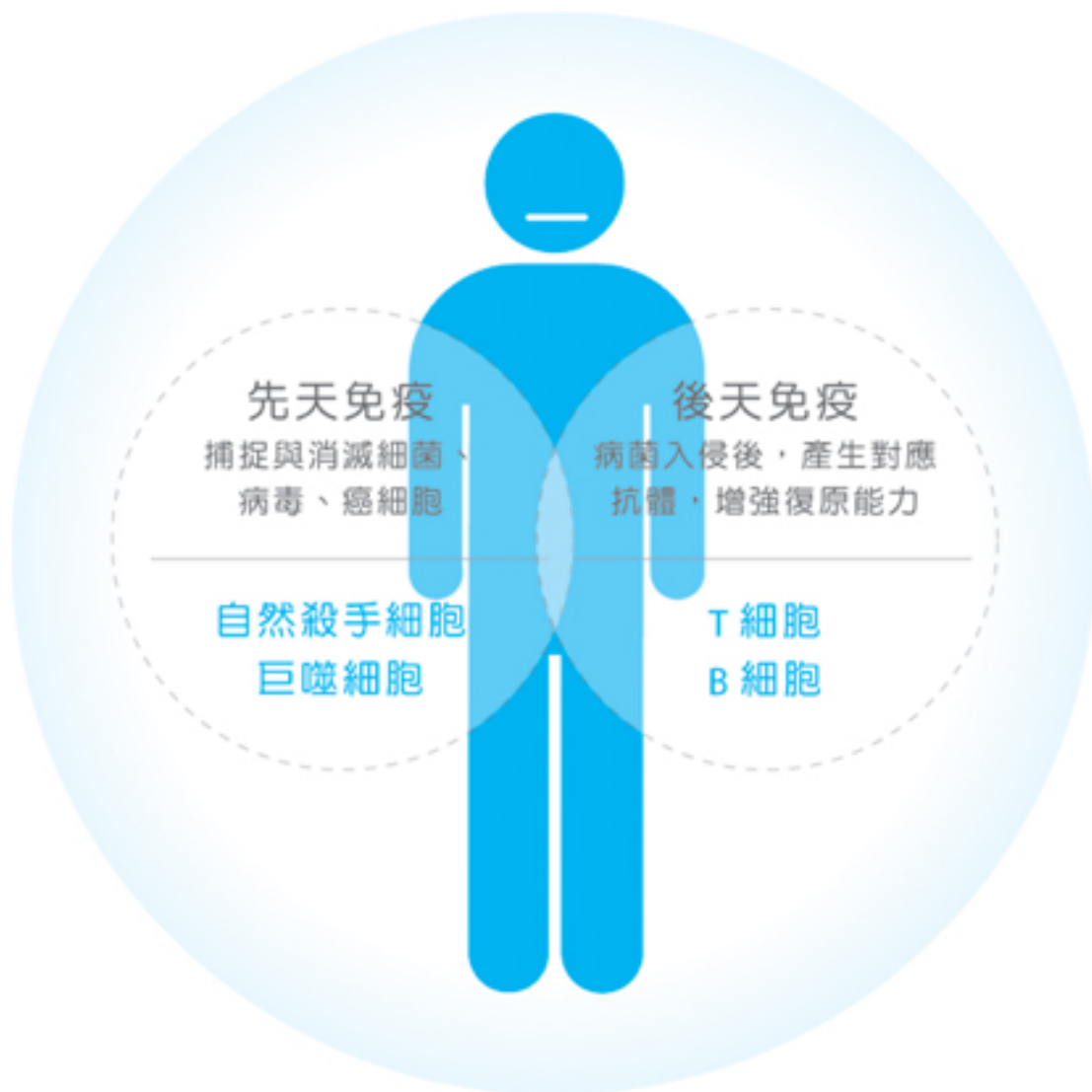
NK自然殺手細胞



B細胞

- T細胞攻擊時，須藉助MHC幫忙才認得癌細胞
- 癌細胞通常減少MHC表達，逃避T細胞追殺
- 癌細胞可能表達PD-L1，阻止T細胞追殺

免疫療法 分類



- 單株抗體
- 免疫檢查點抑制劑
- 細胞治療
- 癌症疫苗

免疫療法 分類



- 單株抗體
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- 癌症疫苗

Carter Says He Is Cancer-Free After Taking Keytruda

Dec 11, 2015 Tim Povtak



Former U.S. President Jimmy Carter is crediting his recent rebound from melanoma cancer to the [immunotherapy drug Keytruda](#), the subject of a phase II clinical trial involving [malignant pleural mesothelioma](#).

Keytruda, known generically as pembrolizumab, is manufactured by Merck.

Carter, 91, made his pronouncement earlier this week at the Maranatha Baptist Church in Plains, Georgia, where he teaches Sunday school.



2018年諾貝爾生醫獎得主

2018 Nobel Prize In Physiology or Medicine



◀ **艾利森**

James P. Allison

**得獎
原因**

分別發現 T 細胞表面的兩種受體 CTLA-4 及 PD-1，為癌症治療帶來全新的策略。

本庶佑

Tasuku Honjo ▶

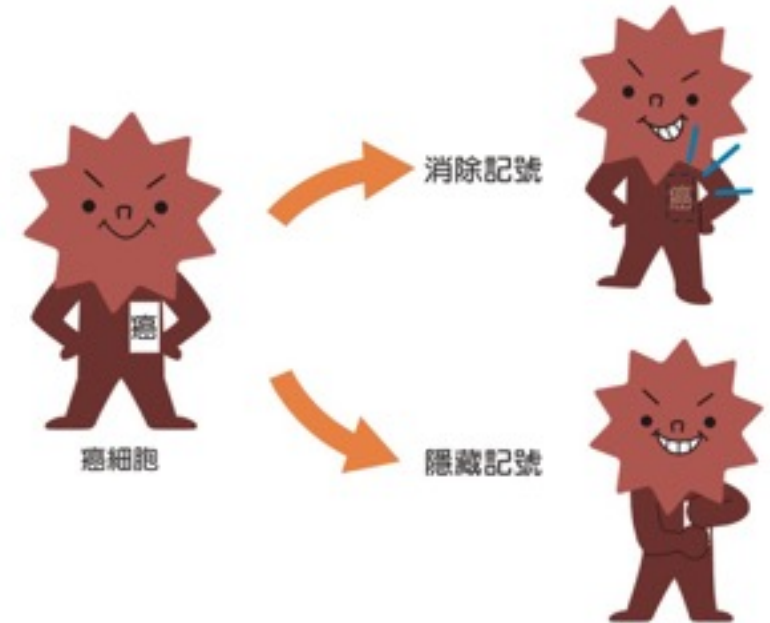


癌細胞利用各種方法避開免疫細胞的攻擊

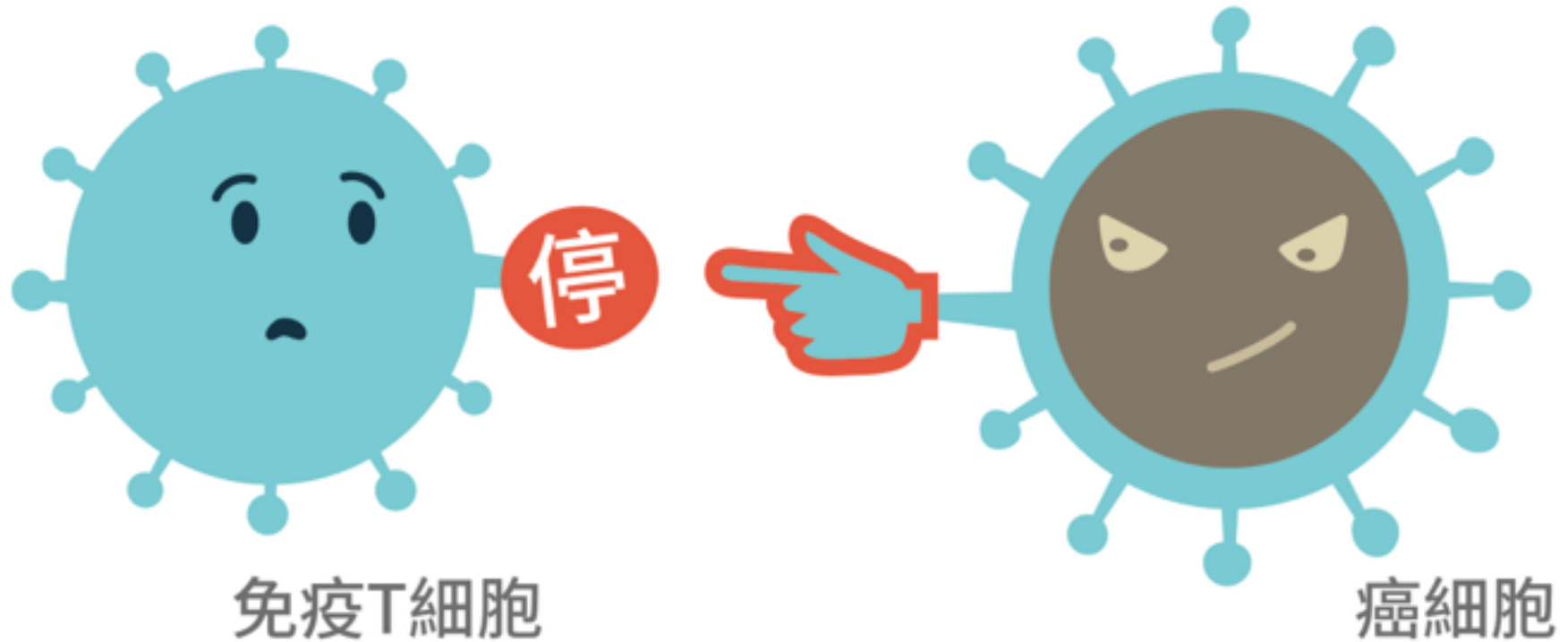
癌細胞逃離免疫細胞攻擊的方法有很多種。

➤ 癌細胞表面有記號，免疫細胞藉由發現記號並將它視為異物發動攻擊。因此，癌細胞會將記號消除，或是隱藏記號，以逃避免疫細胞的攻擊。

➤ 癌細胞還會產生一種物質，讓免疫細胞無法完全發揮功效等，癌細胞可透過改變周遭環境來延續自己的生命。



1. 癌細胞開啟T細胞的剎車按鈕， 取消免疫攻擊



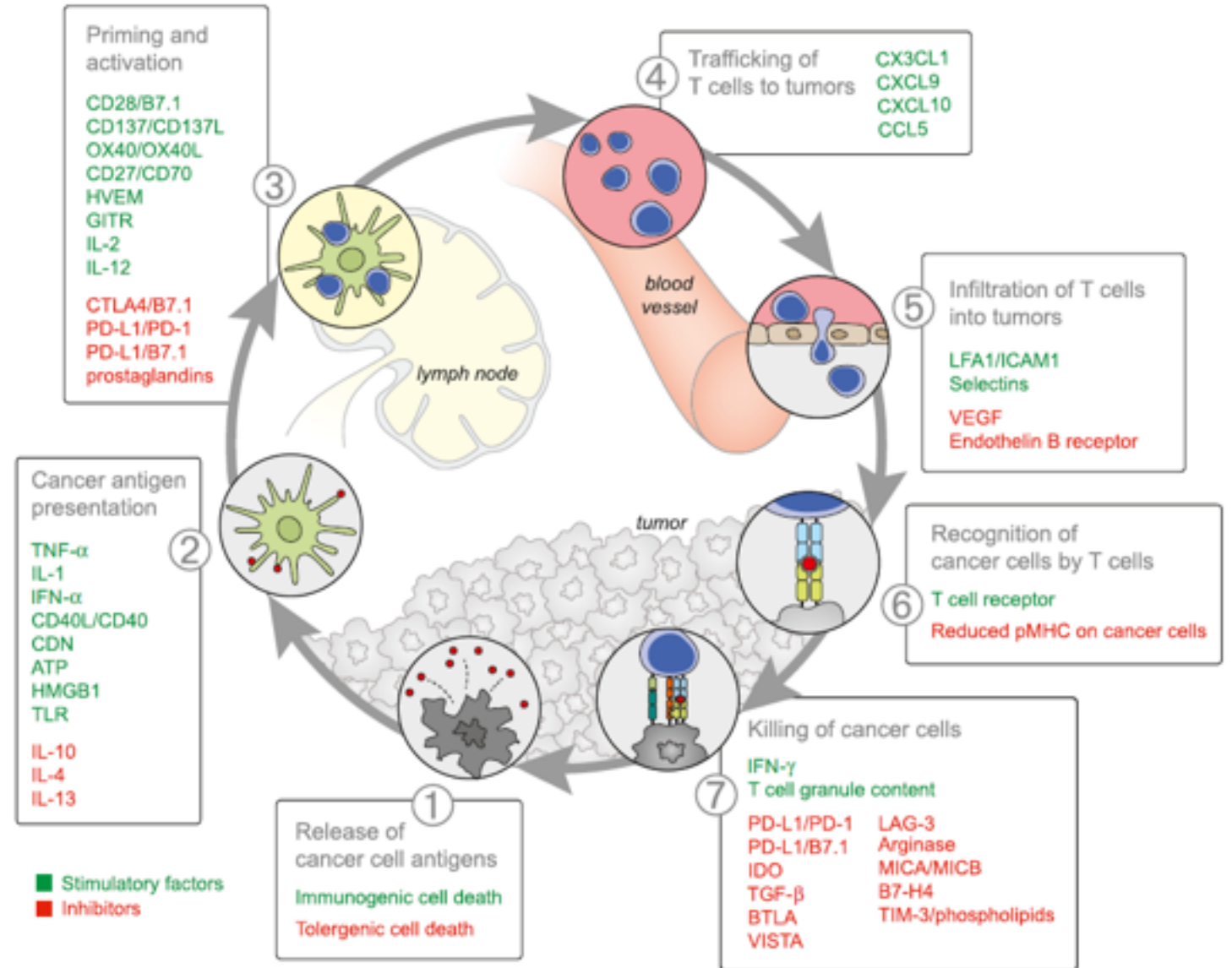
2. 免疫檢查點抑制劑擋掉剎車按鈕， “放開免疫細胞的剎車”



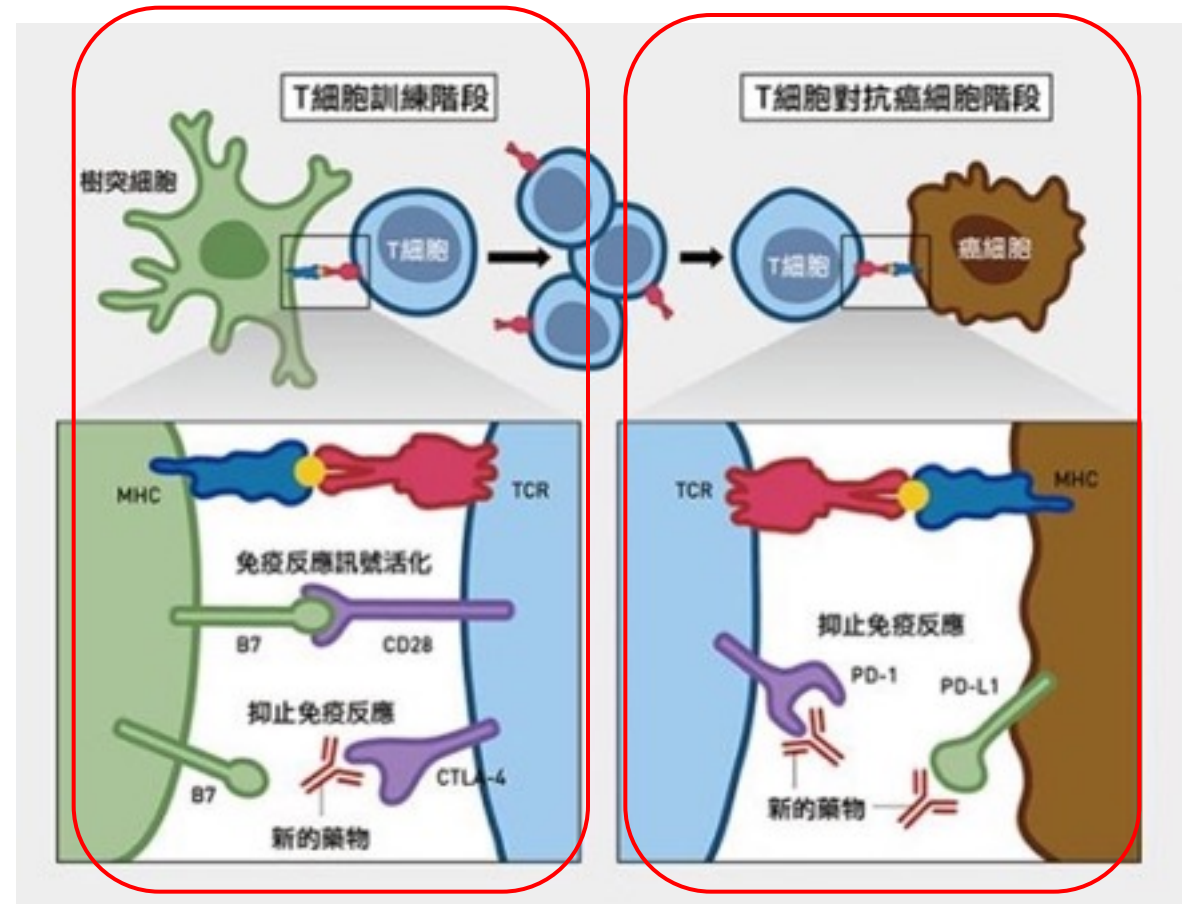
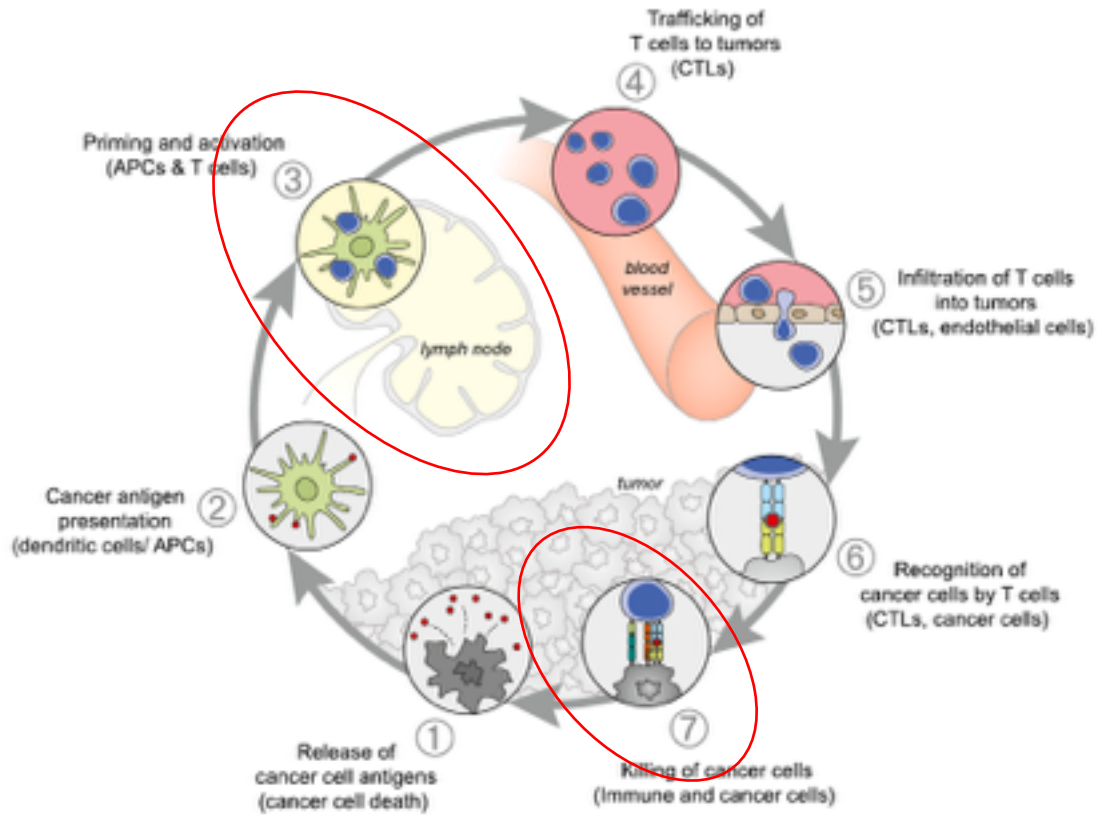
3. 免疫T細胞被重新活化，開始攻擊 癌細胞



癌症免疫循環



癌症免疫循環：免疫檢查點抑制劑

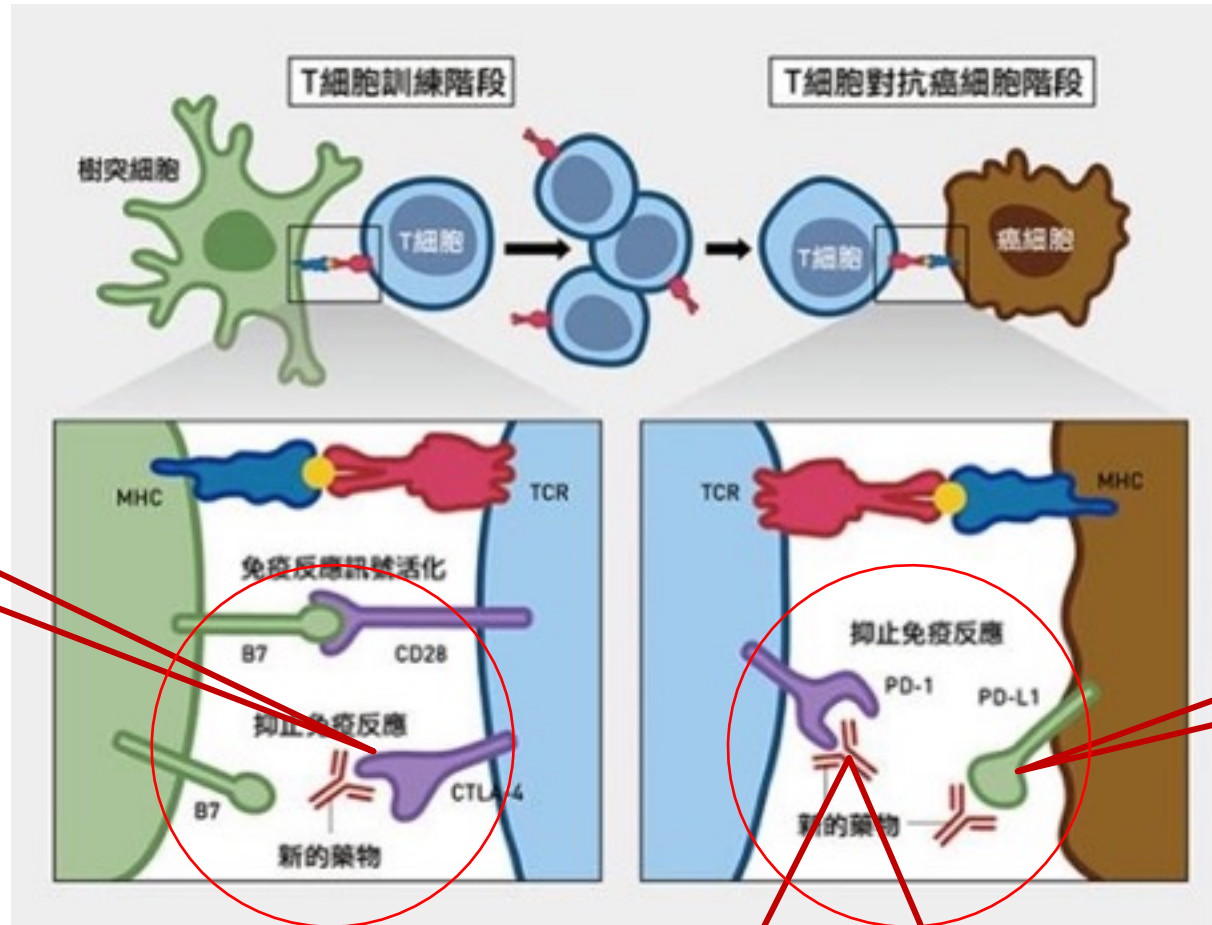


CTLA-4: cytotoxic T-lymphocyte-associated protein 4

PD-1 & PD-L1: Programmed cell death protein 1

免疫檢查點抑制劑

CTLA-4 versus PD-1 & PD-L1



Ipilimumab (Yervoy)
Tremelimumab

癌自禦 Atezolizumab (Tecentriq)
抑癌寧 Durvalumab (Imfinzi)
MSB0010718C (Avelumab)
BMS-936559

保疾伏 Nivolumab (Opdivo)
吉舒達 Pembrolizumab (Keytruda)

免疫檢查點抑制劑：二線之後

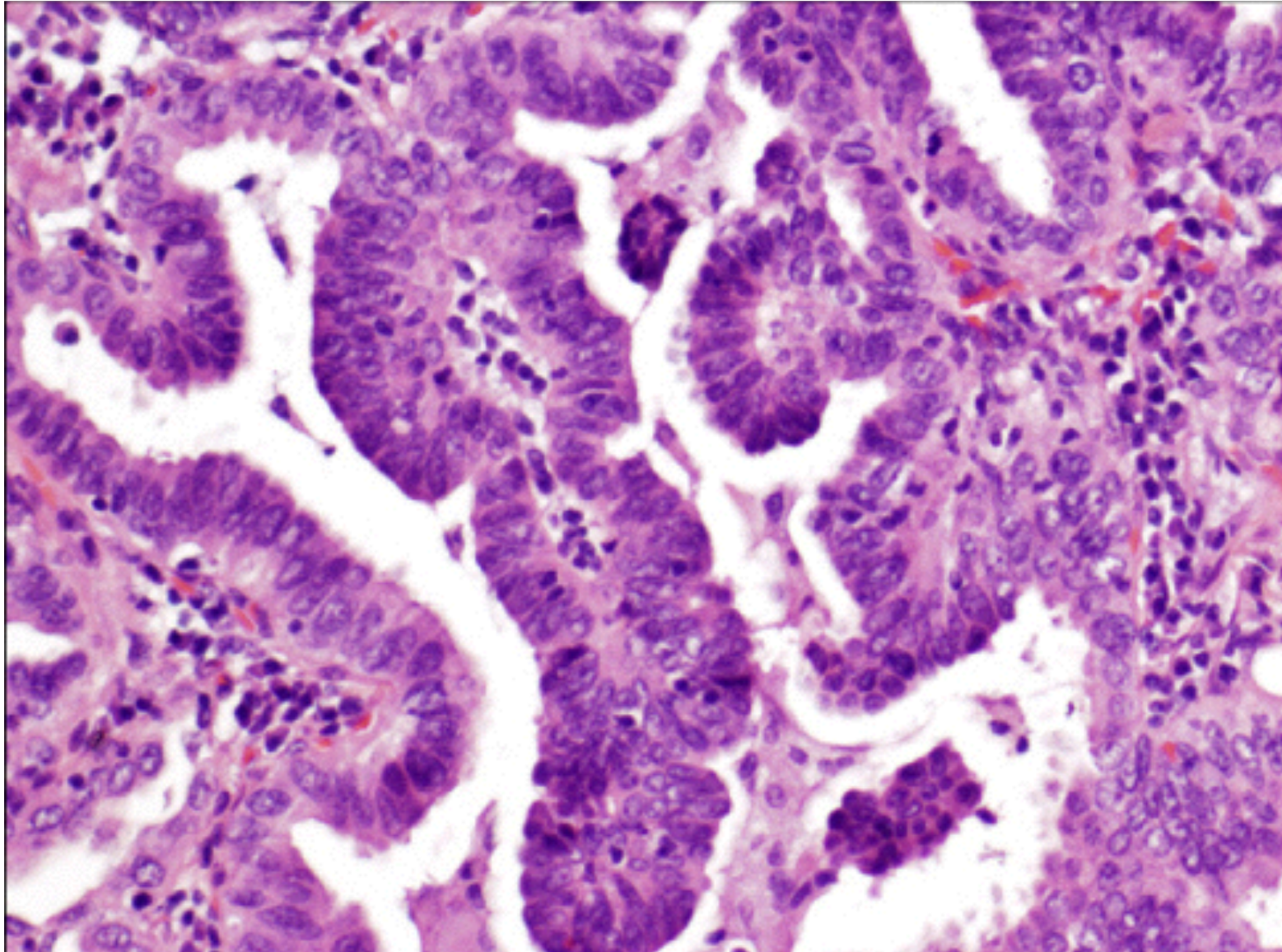
	<u>CheckMate 017</u> ¹	<u>CheckMate 057</u> ²	KEYNOTE-010 ³	OAK ⁴
Study arms	Nivolumab vs docetaxel	Nivolumab vs docetaxel	<u>Pembrolizumab 2 or 10mg/kg</u> vs docetaxel	Atezolizumab vs docetaxel
Phase of study	III	III	II/III	III
PD-L1 selected	No	No	Yes (TPS* $\geq 1\%$)	No
Study size, n	272 (135 vs 137)	582 (292 vs 290)	1033 (344 vs 346 vs 343)	850 (425 vs 425)
Histology, %				
Non-squamous	0	100	70	74
Squamous	100	0	21	26
Other/unknown	-	-	8	-
Line of therapy, %				
2L	100	88	69	75
3L	0	11	20	25
>3L	0	<1	9	0
Other/unknown	0	0	<1	0

非鱗狀細胞癌：一線

單用

KN024

KN042



合併化療

KN189

IMpower1
50

IMpower1
32

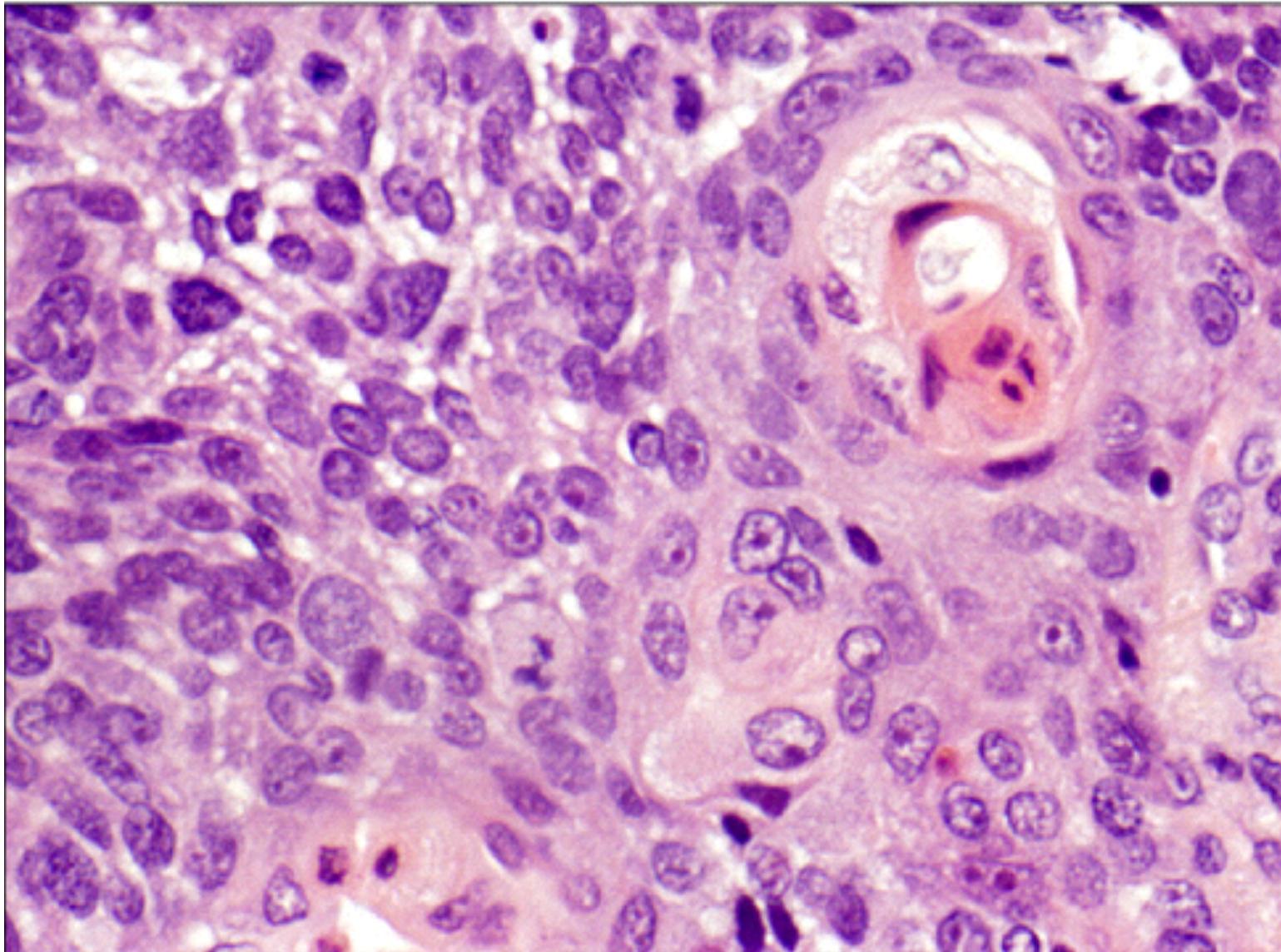
CM227

鱗狀細胞癌：一線

單用

KN024

KN042



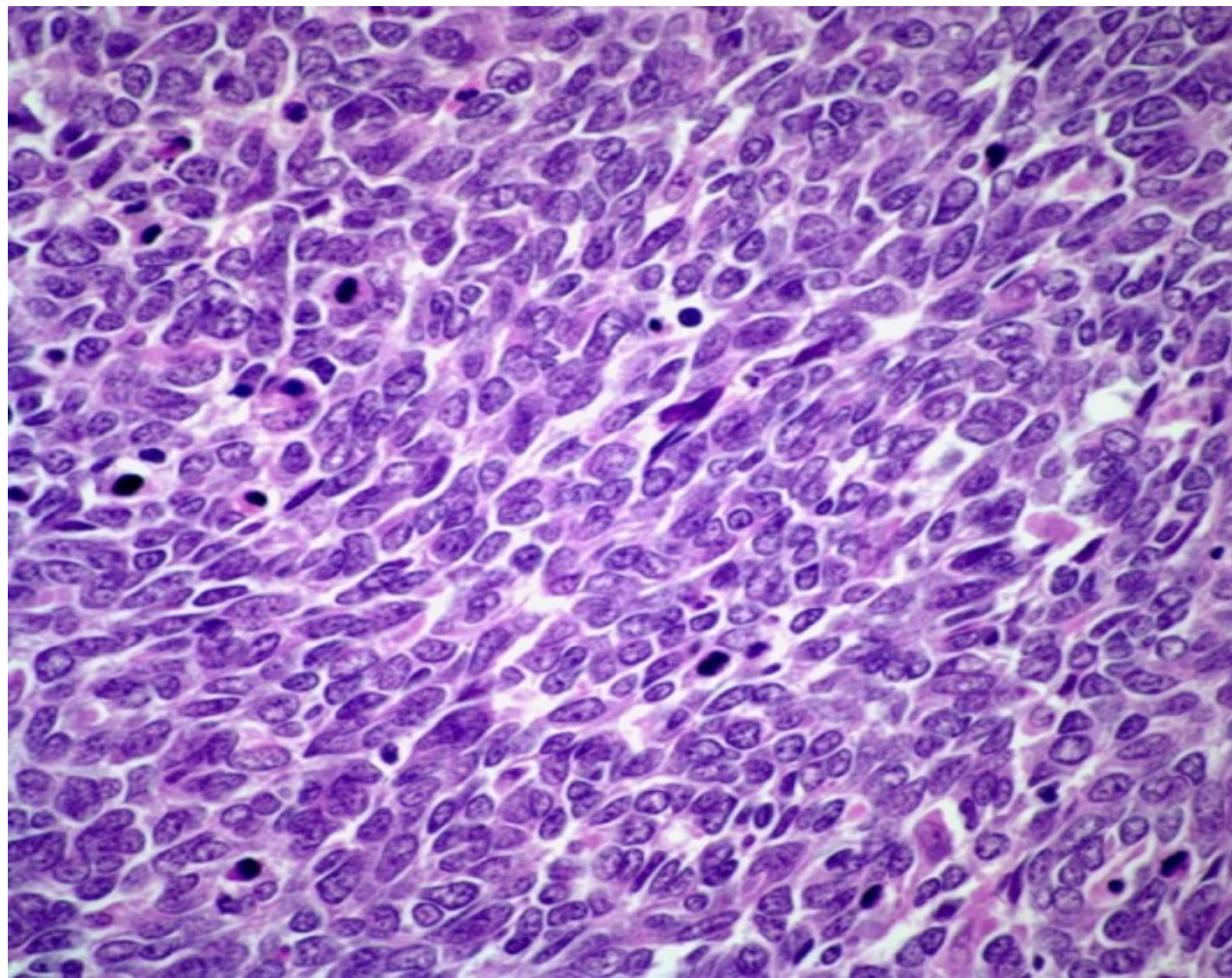
合併化療

KN407

IMpower1
31

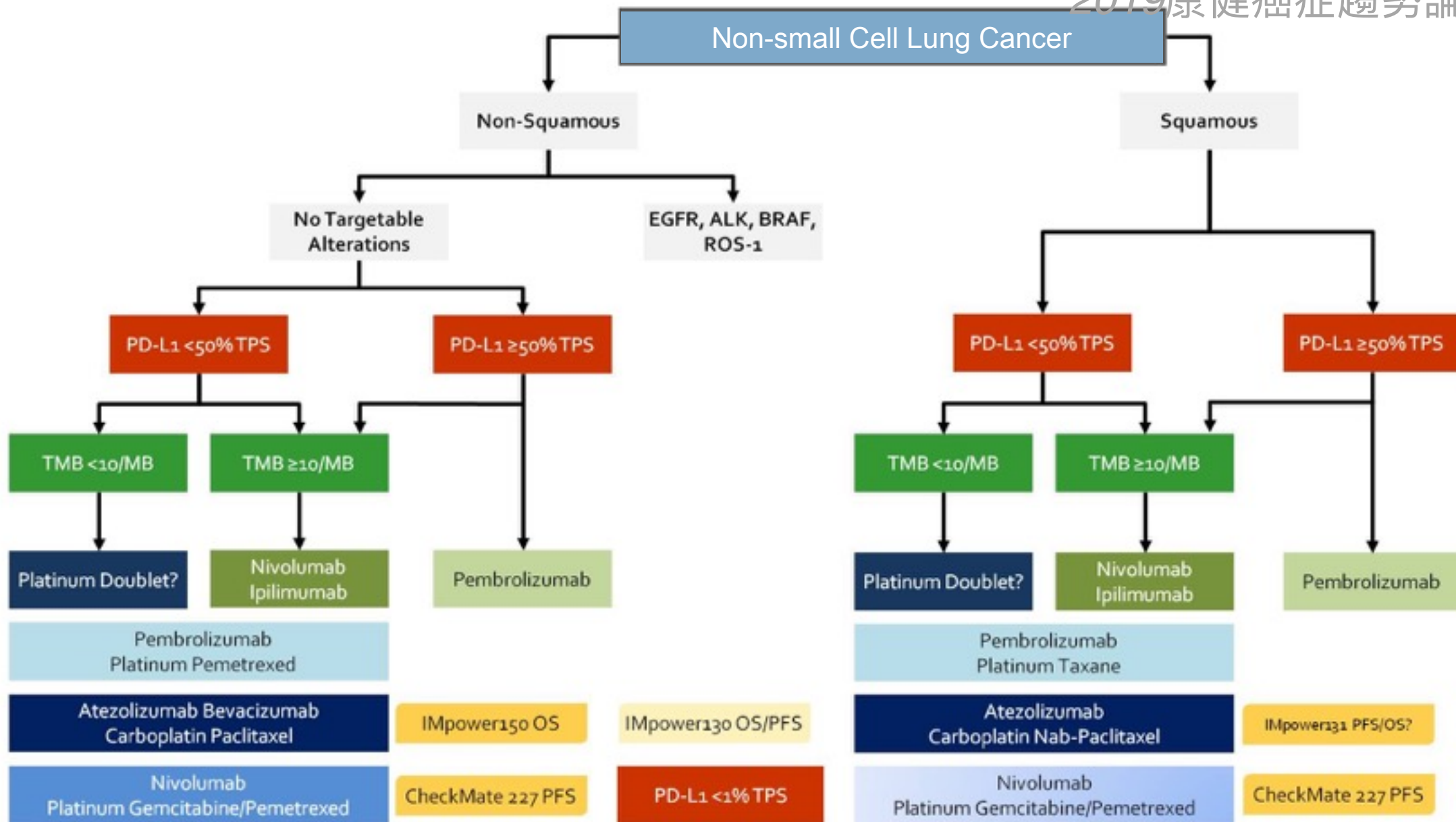
CM227

小細胞肺癌：一線

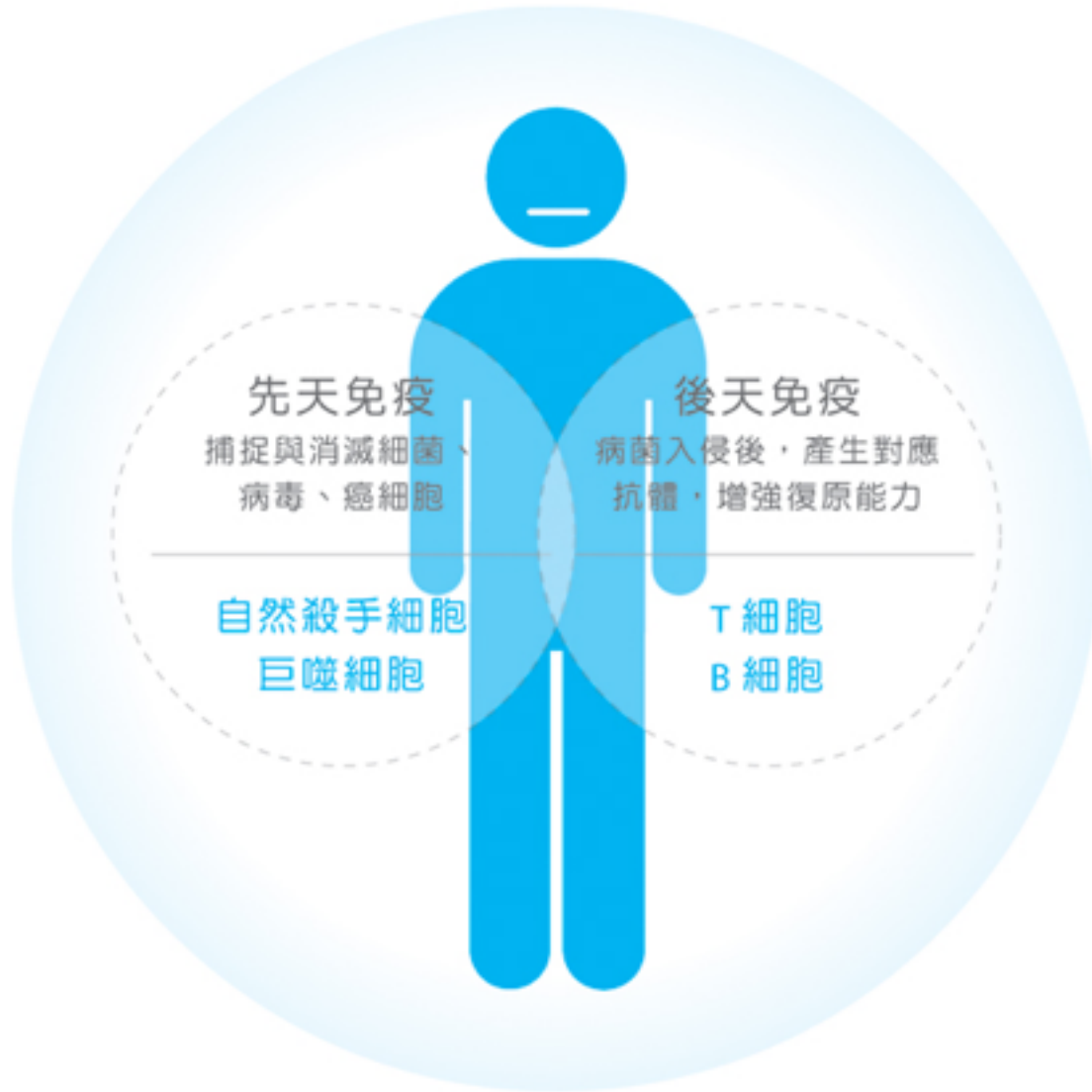


合併化療

IMpower1
33



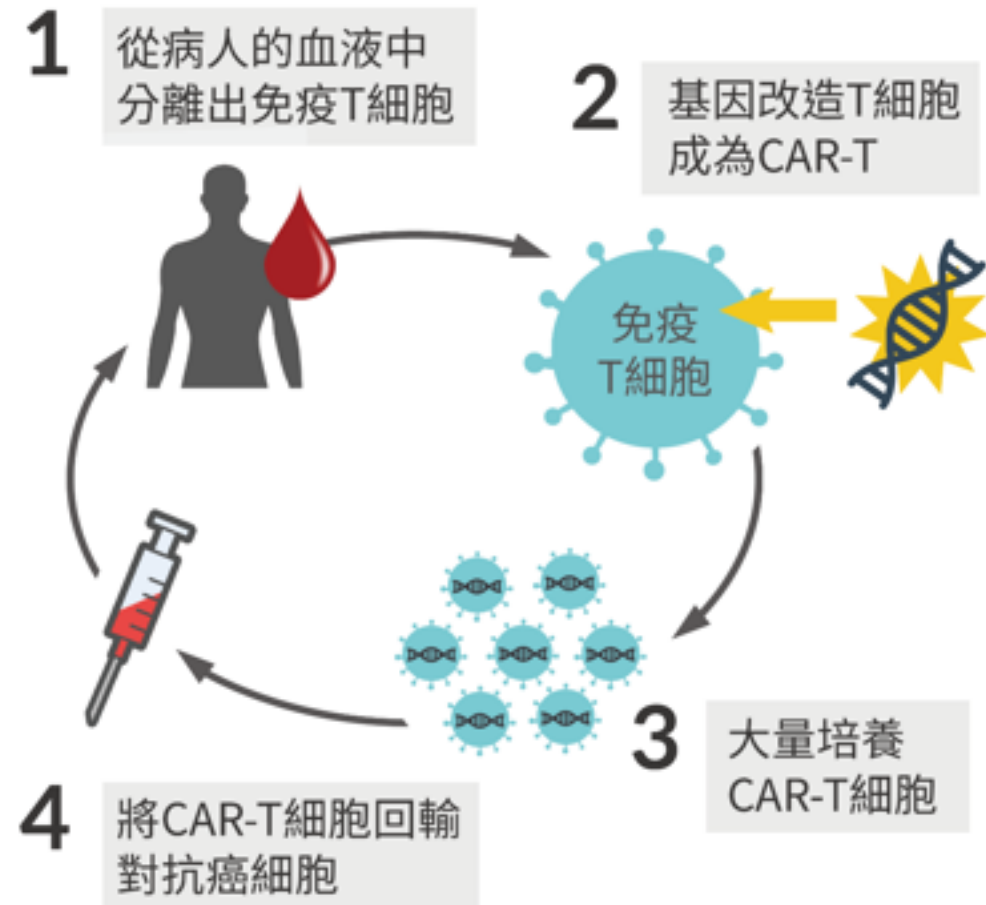
免疫療法 分類



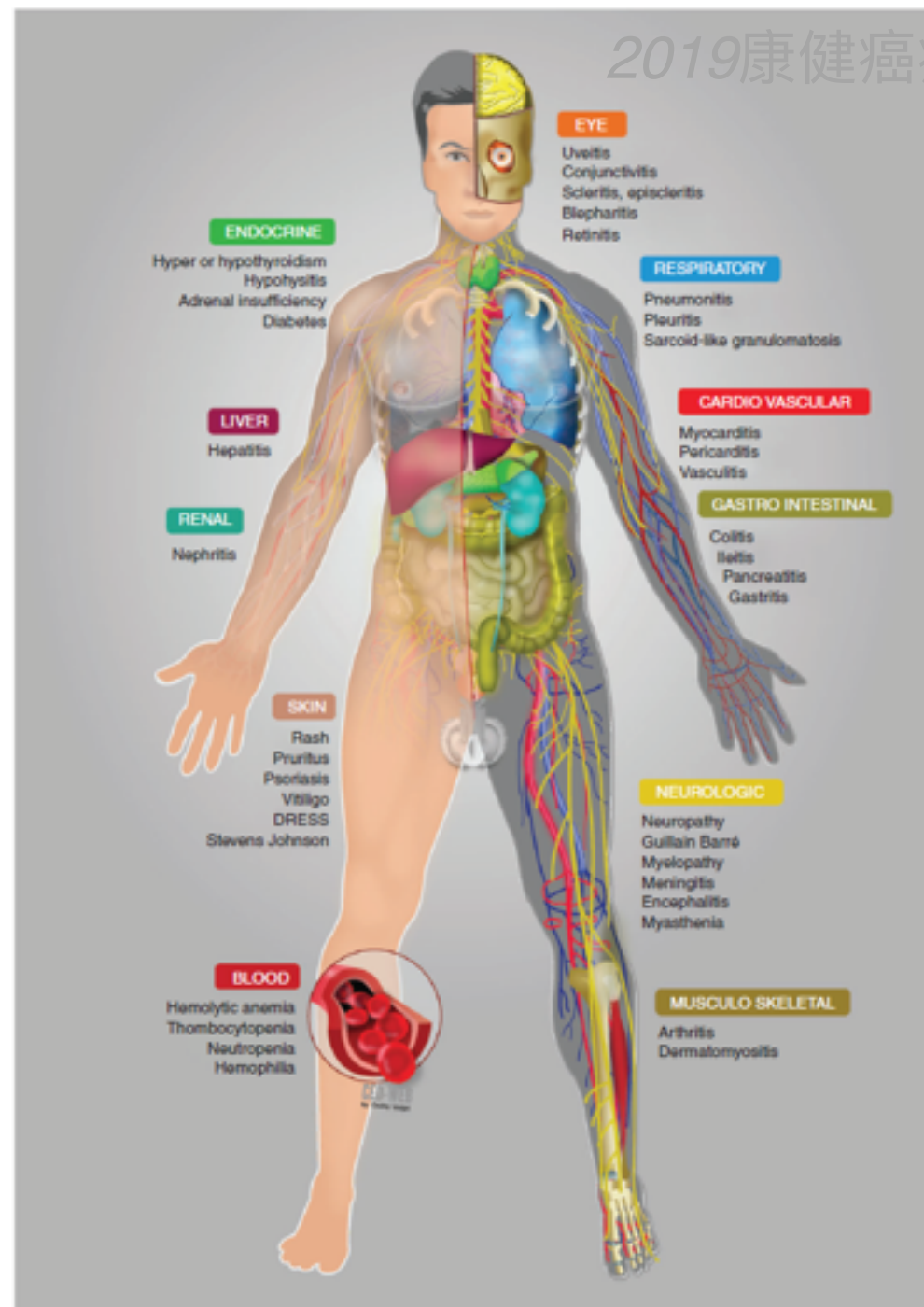
- 單株抗體
- 免疫檢查點抑制劑
- 細胞治療
- 癌症疫苗

CAR-T 細胞治療

- 血液分離出免疫T細胞
 - T細胞進行基因改造
 - 出現對癌症細胞抗原的接收器
 - 專一性的增強其辨識癌症細胞的能力
- 改造後的細胞即為CAR-T細胞
- 大量培養後的CAR-T細胞回輸體內，對癌症細胞進行攻擊

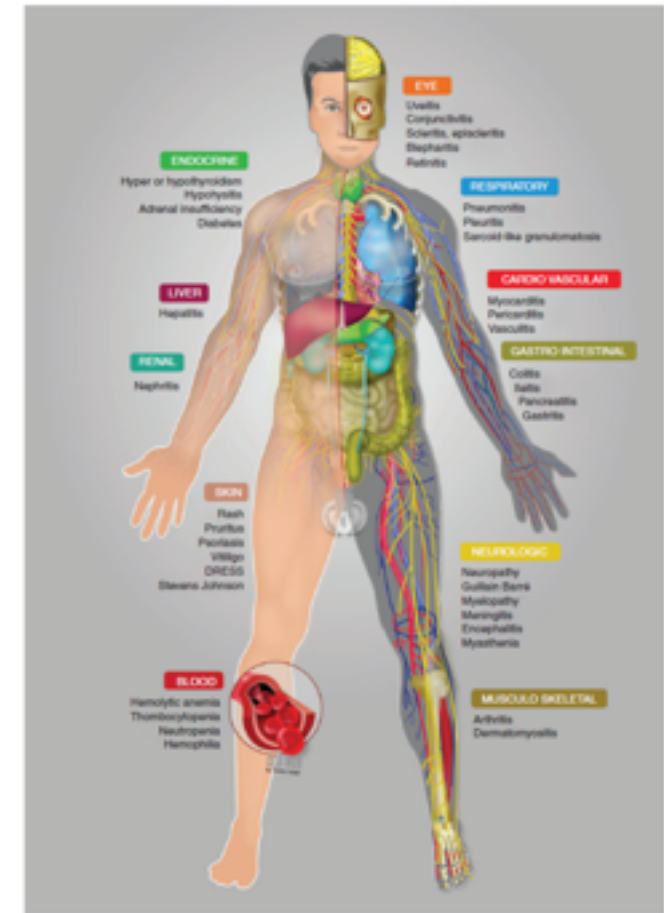


免疫治療相關副作用



免疫治療相關副作用

- 大部分很輕微，但有些可以很嚴重
- 衛教，早期發現，儘早治療
- 多專科團隊協助



大綱

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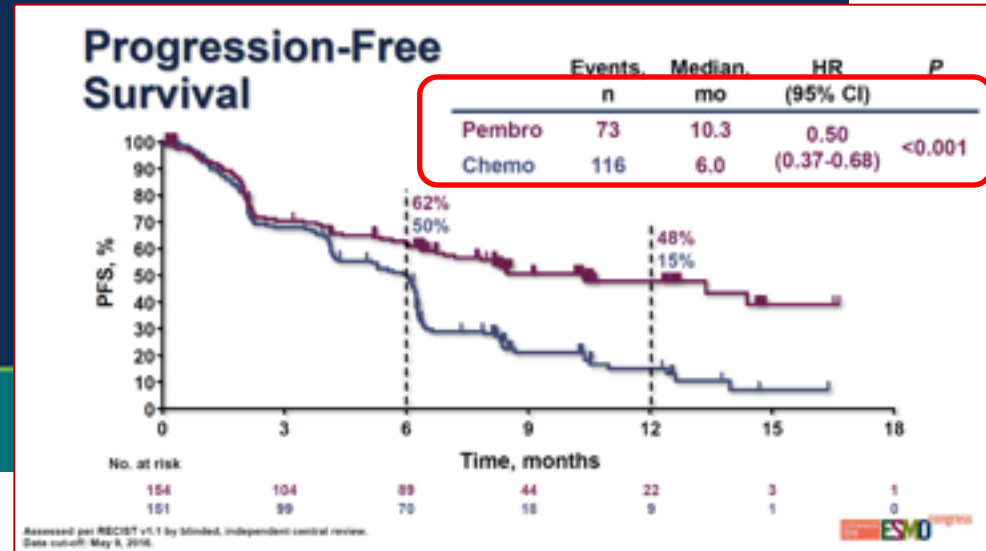
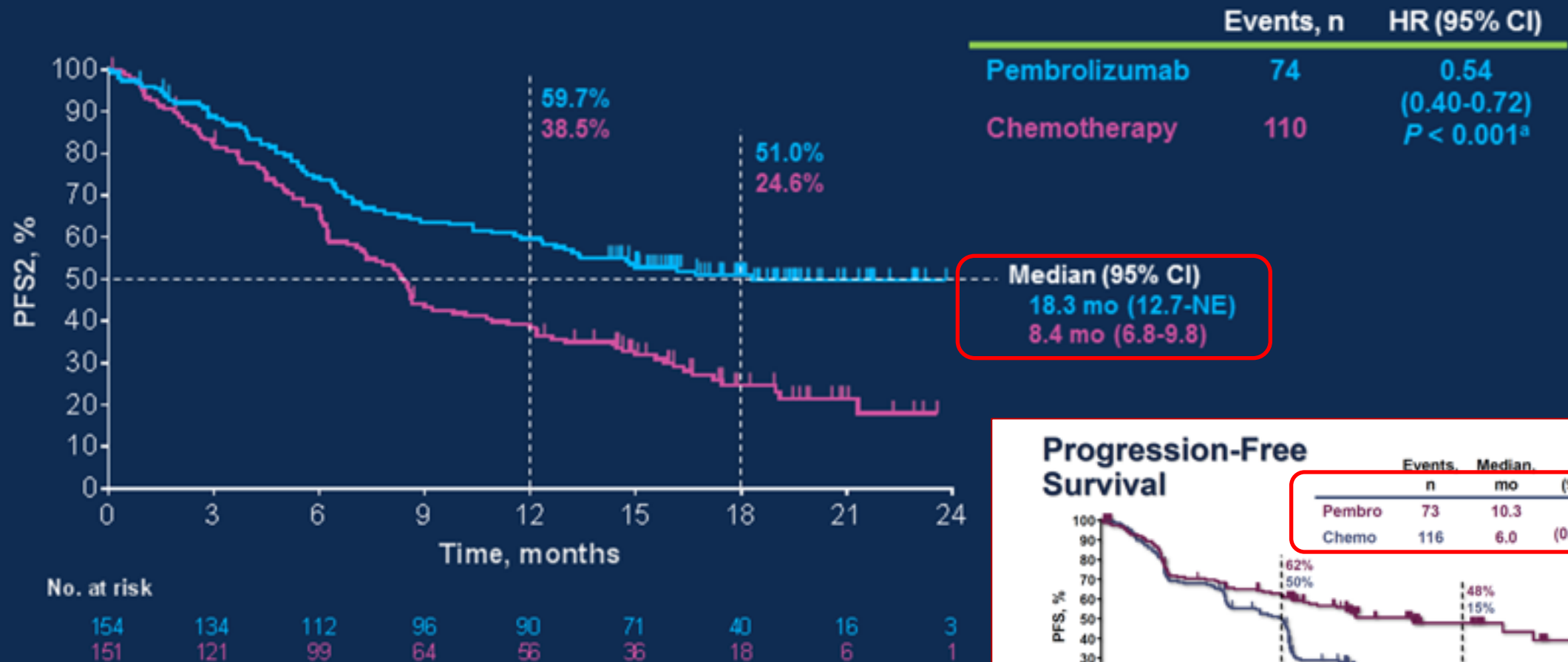
目前台灣健保給付

給付範圍	pembrolizumab (Dako 22C3)	nivolumab (Dako 28-8)	atezolizumab (Ventana SP142)
黑色素瘤	不需檢附報告	不需檢附報告	尚未給付
非小細胞肺癌第一線用藥	TPS \geq 50%	尚未給付	尚未給付
非小細胞肺癌第二線用藥	TPS \geq 50%	TC \geq 50%	TC \geq 50% 或 IC \geq 10%
非小細胞肺癌第三線用藥	TPS \geq 50%	TC \geq 50%	TC \geq 50% 或 IC \geq 10%

*Thanks for your
attention!!*
ccwang5202@yahoo.com.tw



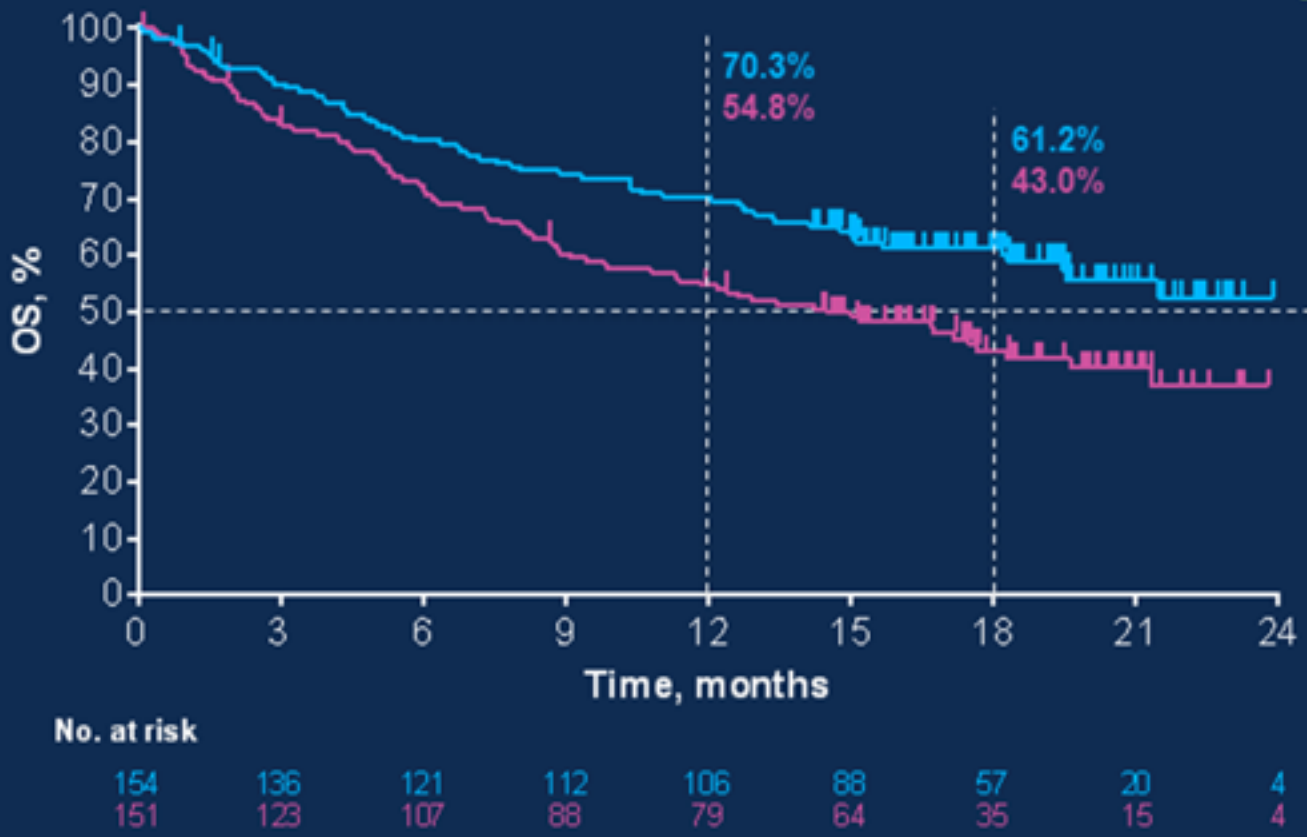
Kaplan-Meier Estimate of PFS2



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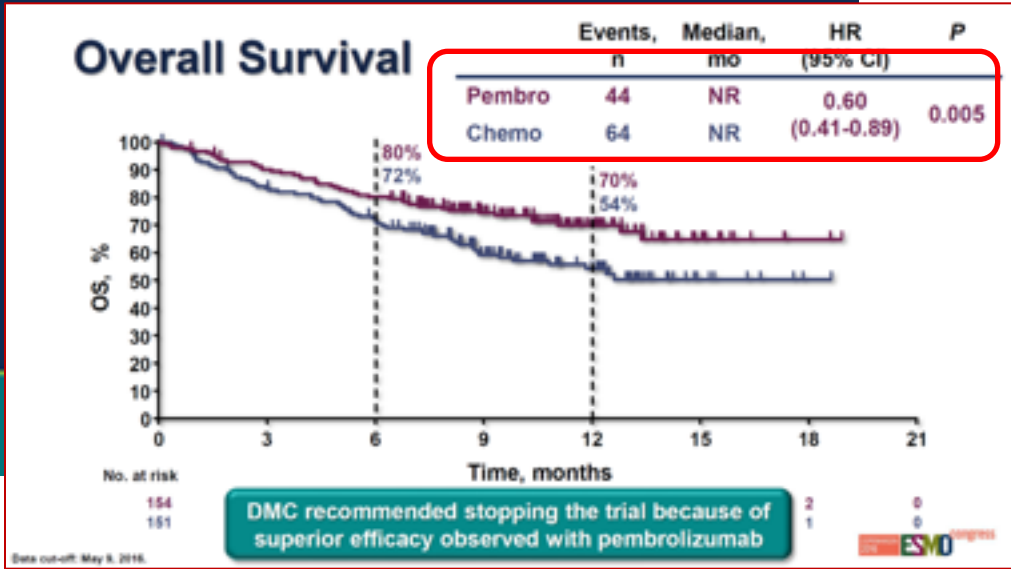
Kaplan-Meier Estimate of OS: Updated Analysis



	Events, n	HR (95% CI)
Pembrolizumab	63	0.63 (0.46-0.88)
Chemotherapy	84	$P = 0.003^a$

Median (95% CI)
 NR (19.4 mo-NE)
 14.5 mo (9.8-19.6)

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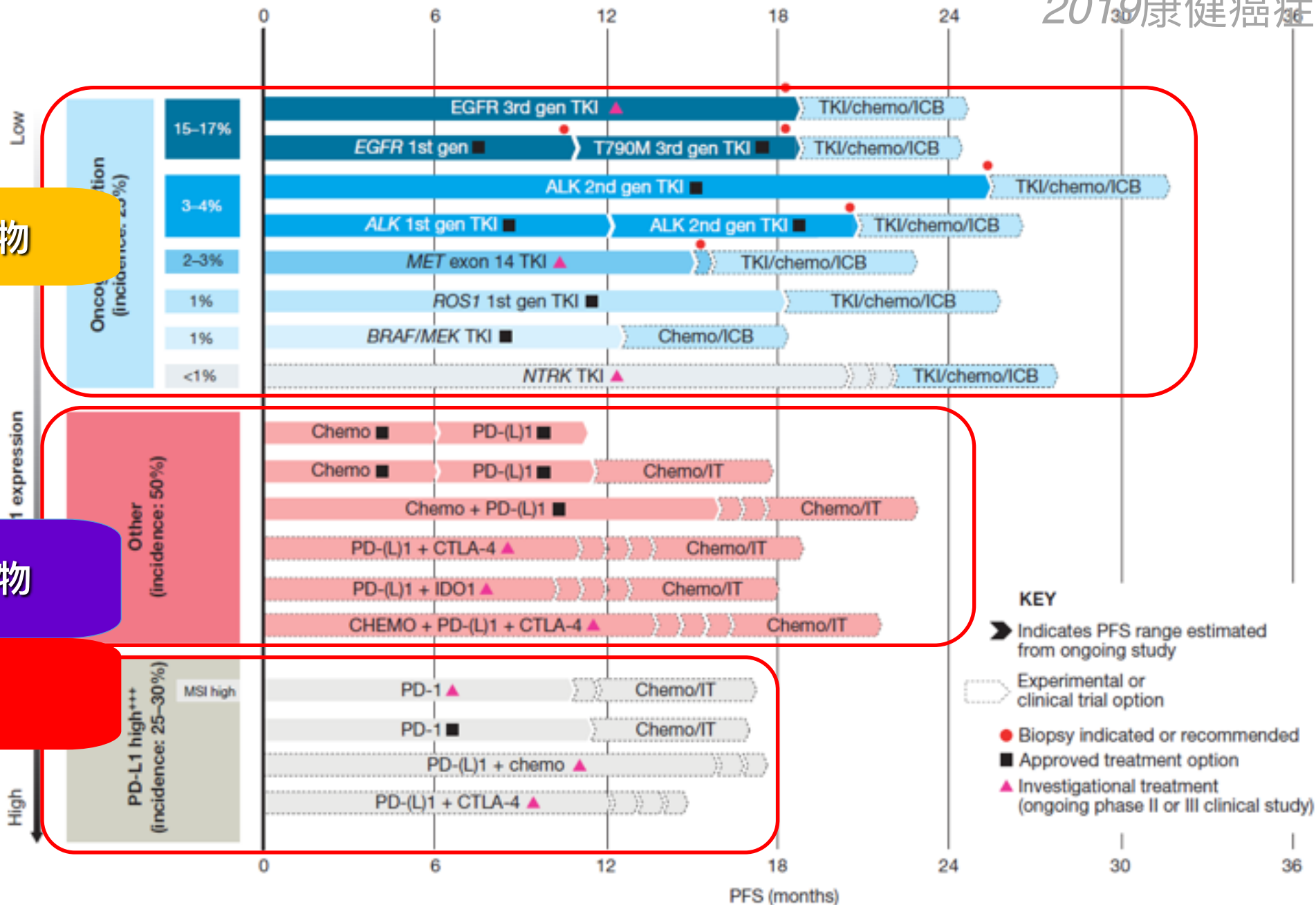
	KN189 (Phase III)	IMPower 132 (Phase III)	IMPower 150 (Phase III)
Patients	N=616, (2:1) 1L line NSQ	N=578 1L line NSQ	N=1202 1L line EGFR/ALK mut NSQ
Biomarker/ Subgroup	PD-L1 all comer	PD-L1 all comer	PD-L1 all comer Teff-High EGFR/ALK Liver metastasis
Efficacy	<ul style="list-style-type: none"> • <u>ORR = 47.6% vs. 18.9%</u> • <u>mPFS = 8.8 mo vs. 4.9 mo (HR=0.52)</u> 12-mo PFS = 34.1% vs. 17.3% <ul style="list-style-type: none"> • <u>mOS = NR vs. 11.3 mo (HR=0.49)</u> 12-mo OS = 69.2% vs. 49.4%	<ul style="list-style-type: none"> • <u>ORR = 47% vs. 32%</u> • <u>mPFS = 7.6 mo vs. 5.2 mo (HR=0.60)</u> 12-mo PFS = 33.7 vs. 17.0% <ul style="list-style-type: none"> • <u>mOS = 18.1 mo vs. 13.6 mo (HR=0.81)</u> 12-mo OS = 59.6% vs. 55.4%	<ul style="list-style-type: none"> • <u>[ITT-WT] ORR = 56% vs. 41%</u> • <u>[ITT-WT] mPFS = 8.3 mo vs. 6.8 mo (HR=0.59)</u> 12-mo PFS = 66% vs. 56% <ul style="list-style-type: none"> • <u>[ITT-WT] OS = 19.2 mo vs. 14.7 mo (HR=0.78)</u> 12-mo OS = 67% vs. 61%
Safety	All cause AE: 99.8% vs. 99% Grade 3-5 AEs: 67.2% vs. 65.8% Discontinuous: 13.8% vs. 7.9%	All cause AE: 98% vs. 97% Grade 3-5 AEs: 62% vs. 54% Discontinuous: 24% vs. 18%	Treatment-related AE: 94% vs. 96% Grade 3-5 AEs: 60% vs. 51% Discontinuous: 34% vs. 25%

	KN407 (Phase III)	IMPower 131 (Phase III)
Patients	N=559 1L line (+chemo) SQ	N=683 (armB+armC) 1L line (+chemo) SQ
Biomarker/ Subgroup	PD-L1 all comer (≥50%, 1-49%, <1%)	PD-L1 all comer (TC3/IC3, TC1/2 or IC1/2, TC0/IC0)
Efficacy	<ul style="list-style-type: none"> • <u>ORR = 57.9% vs. 38.4%</u> • <u>mPFS = 6.4 mo vs. 4.8 mo (HR=0.56)</u> 12-mo PFS = 30% vs. 15% • <u>mOS = 15.9 vs. 11.3 mo (HR=0.64)</u> 12-mo OS = 65% vs. 50% 	<ul style="list-style-type: none"> • <u>ORR = 49% vs. 41%</u> • <u>mPFS = 6.3 mo vs. 5.6 mo (HR=0.71)</u> 12-mo PFS = 24.7% vs. 12.0% • <u>mOS = 14.0 vs. 13.9 mo (HR=0.96)</u> 12-mo OS = 55.6% vs. 56.9%
Safety	<p>All cause AE: 98.2% vs. 97.9%</p> <p>Grade 3-5 AEs: 69.8% vs. 68.2%</p> <p>Discontinuous: 13.3% vs. 6.4%</p>	<p>All cause AE: 99% vs. 97%</p> <p>Grade 3-5 AEs: 82% vs. 70%</p> <p>Discontinuous: 29% vs. 17%</p>

標靶藥物

免疫藥物

化療



康健

For a better life

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