慢性淋巴性白血病
(Chronic Lymphocytic Leukemia, CLL)

從CLL的治療突破
看精準醫療的成功與盲點
~以BTKi為例~

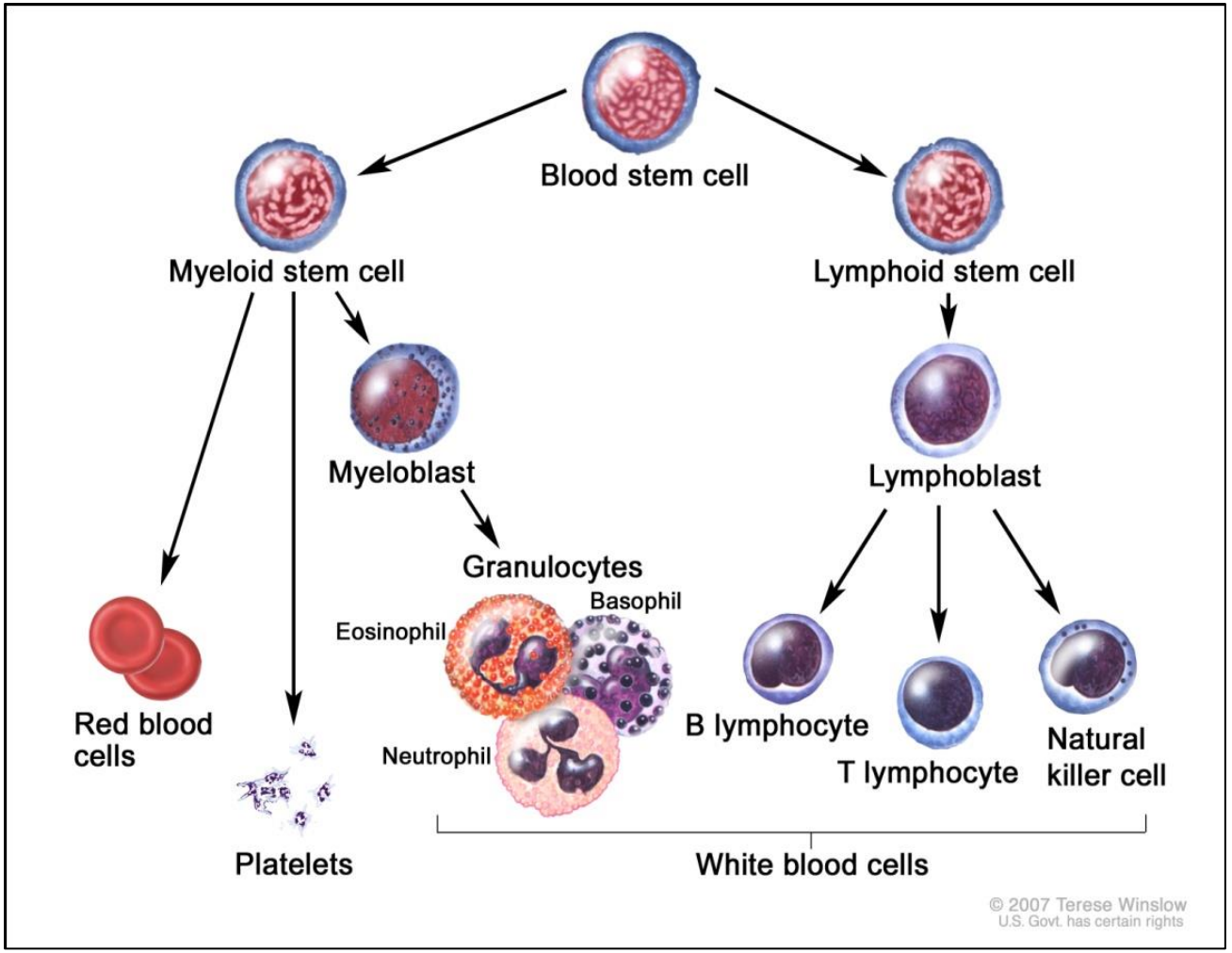
臺大醫院 內科部 吳尚儒

淋巴細胞

淋巴腫瘤

低惡性度
淋巴腫瘤

CLL！

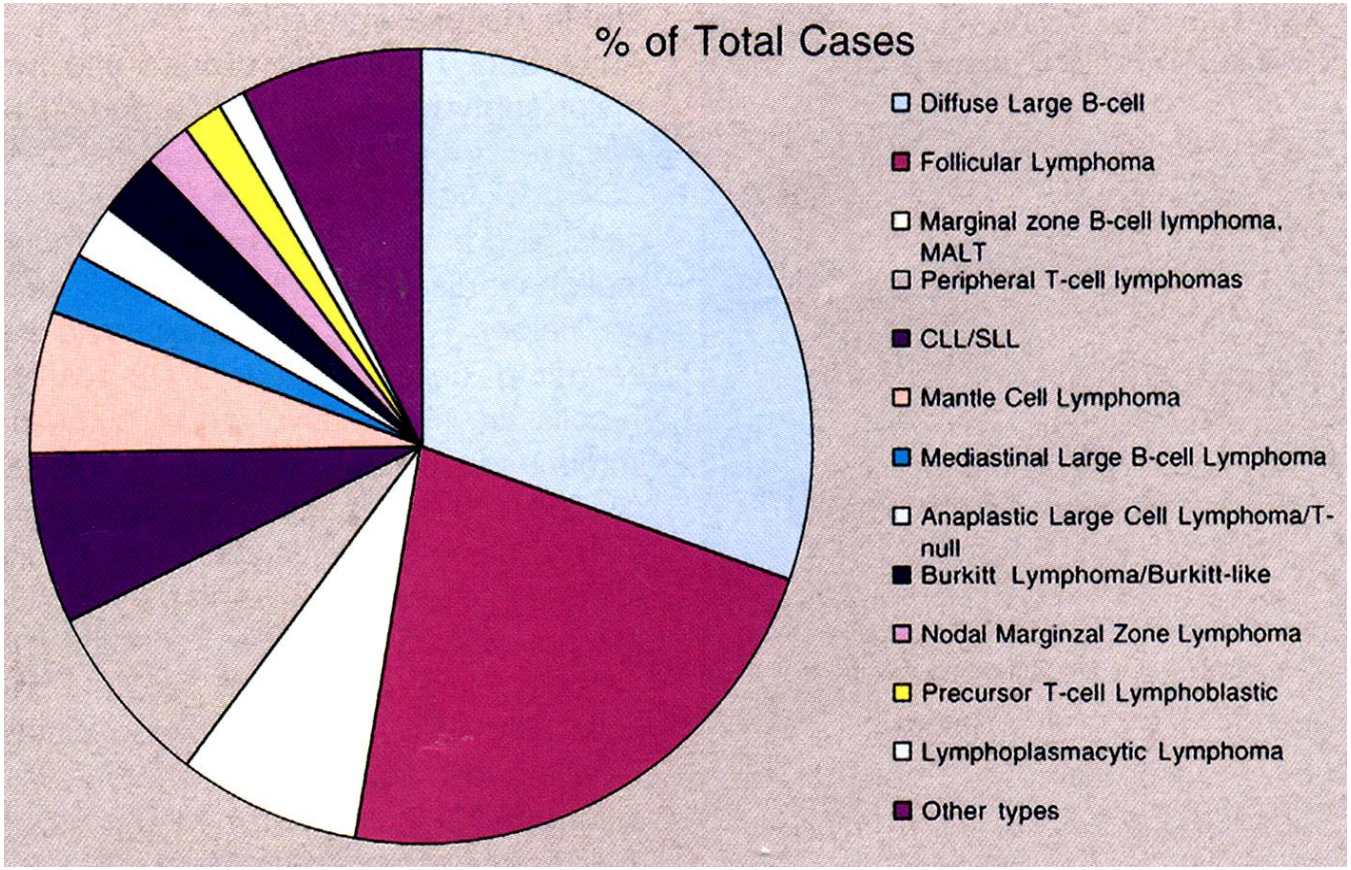


淋巴細胞

淋巴腫瘤

低惡性度
淋巴腫瘤

CLL！

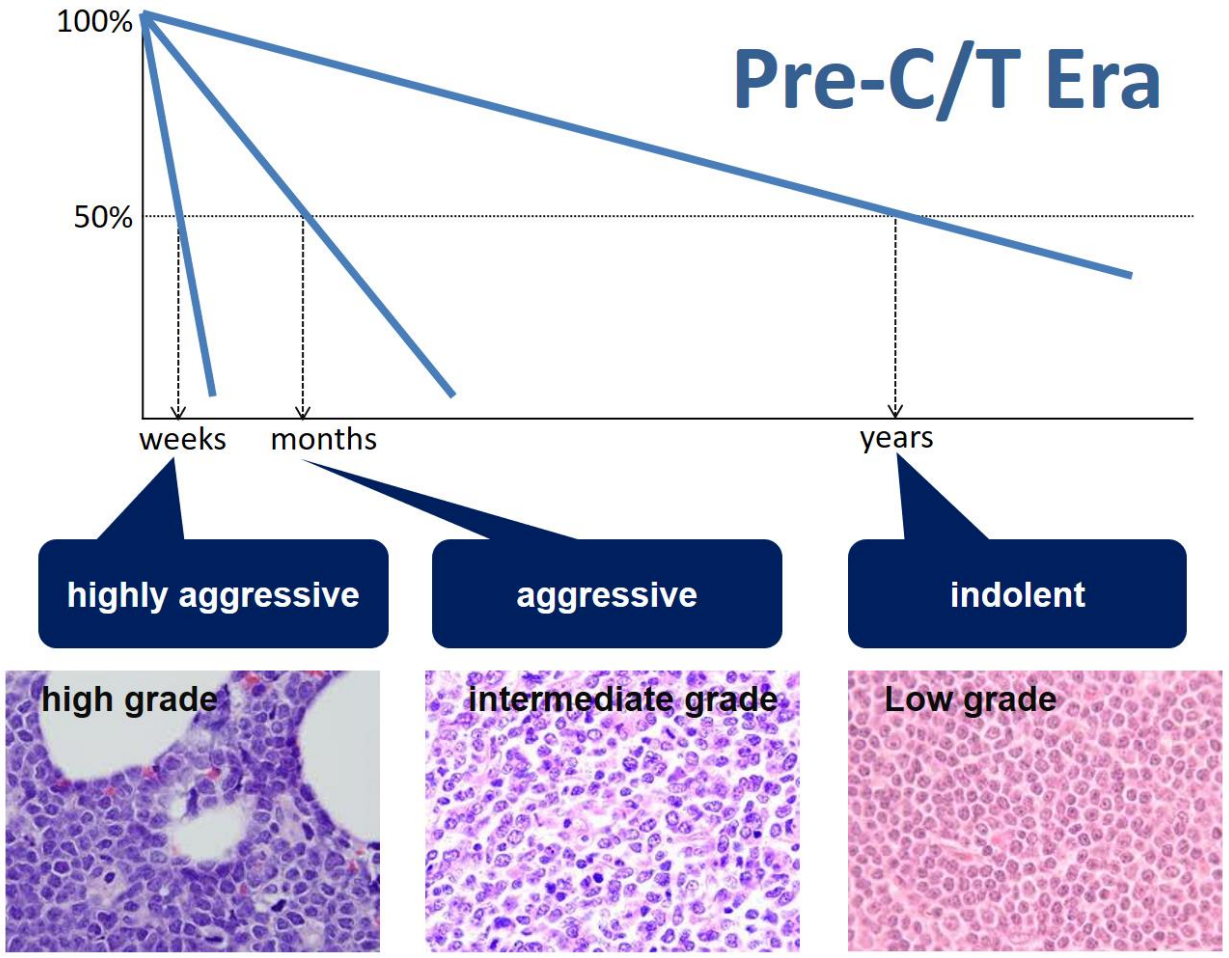


淋巴細胞

淋巴腫瘤

低惡性度
淋巴腫瘤

CLL !

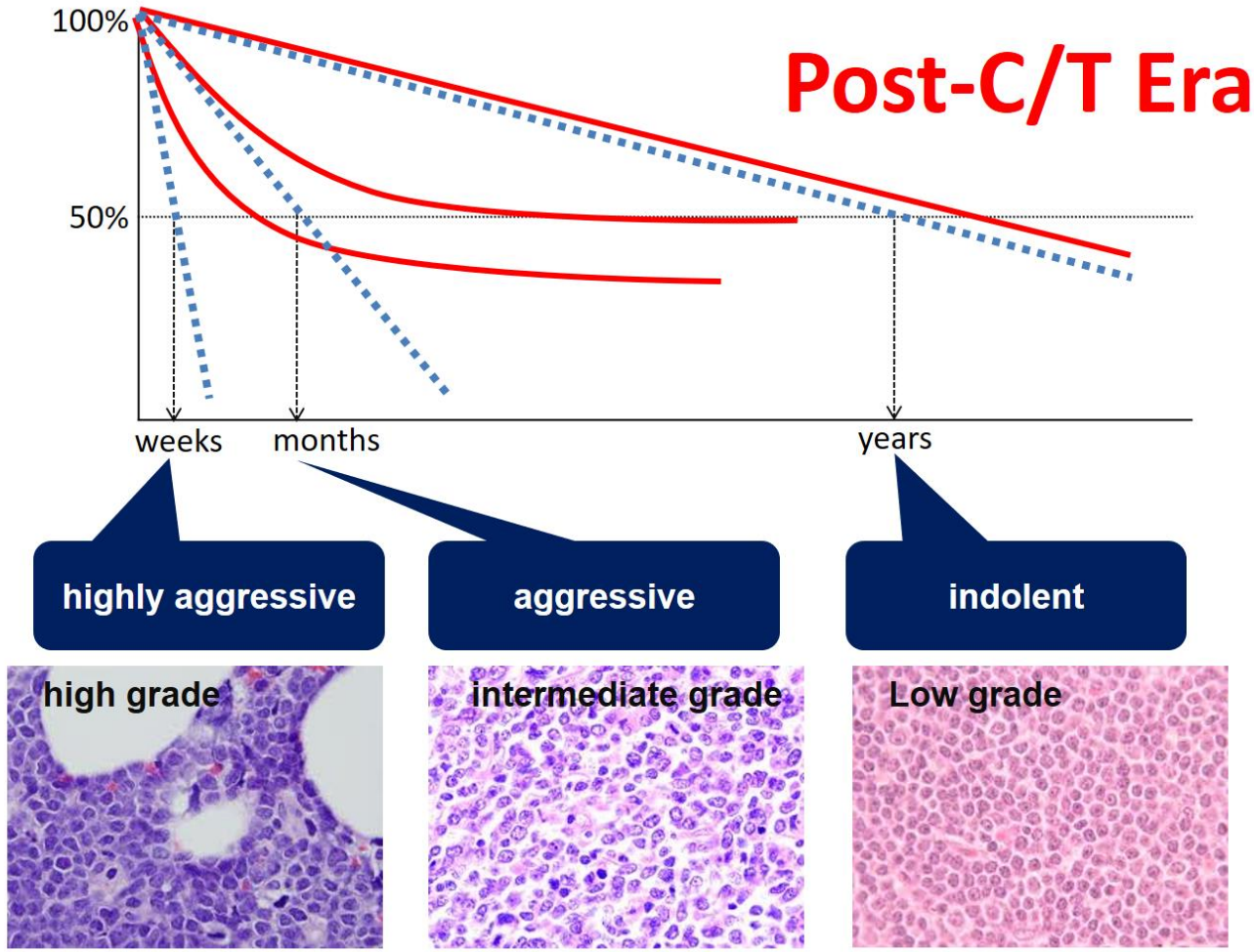


淋巴細胞

淋巴腫瘤

低惡性度
淋巴腫瘤

CLL !



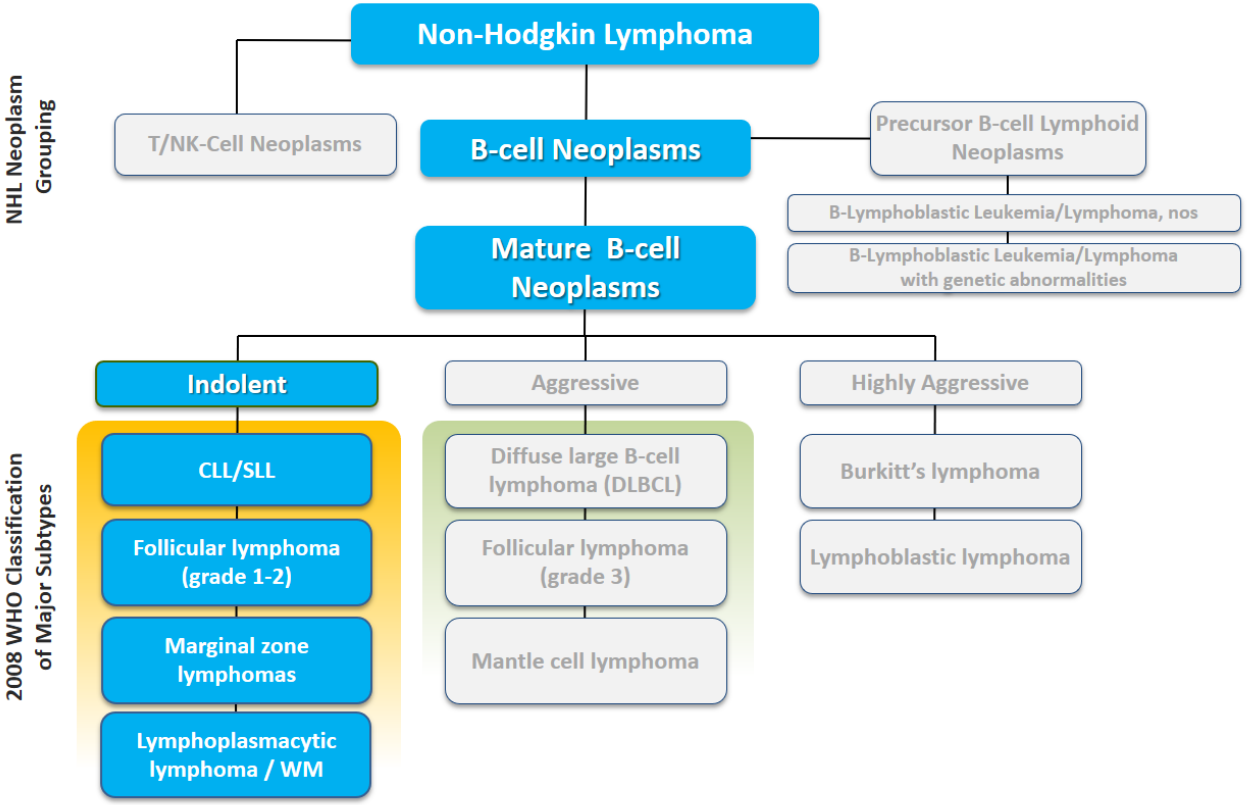
淋巴細胞

淋巴腫瘤

低惡性度
淋巴腫瘤

CLL !

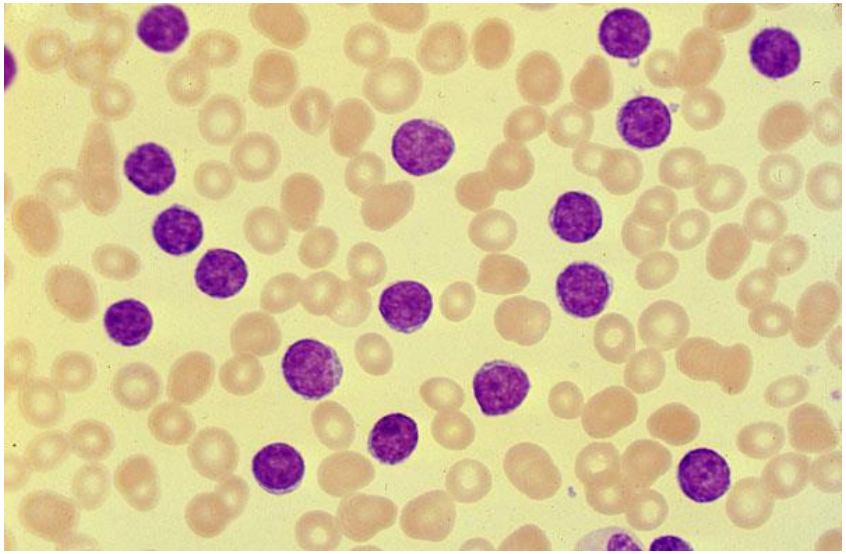
Simplified WHO Classification: Indolent B-Cell Neoplasms



CLL/SLL: chronic lymphocytic leukemia/small lymphocytic leukemia; WM: Waldenström macroglobulinemia
Adapted from Swerdlow S, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008.

Chronic lymphocytic leukemia
慢性淋巴性白血病

- 低惡性度淋巴腫瘤，病程緩慢
- 平均診斷年齡>65歲
- 年發生率：2-6/10萬人
- 表現:
  - 大部分人無症狀
  - 貧血 血小板降低
  - 淋巴結
  - 自體免疫
- 無法治癒 ，保守的化療策略:
  - 改善血球數
  - 縮小淋巴結
  - 無法改善存活期/自然病程?



BLOG

Category:

- Any -

Archives by Month:

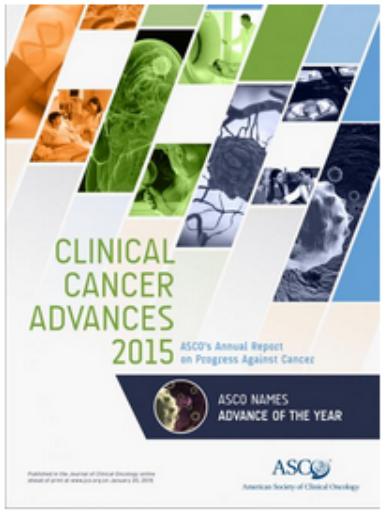
All Entries

Tags:

clinical trials communication coping decision making emotions expert information healthy living podcast side effects

Cancer Advance of the Year: Transformation of CLL Treatment

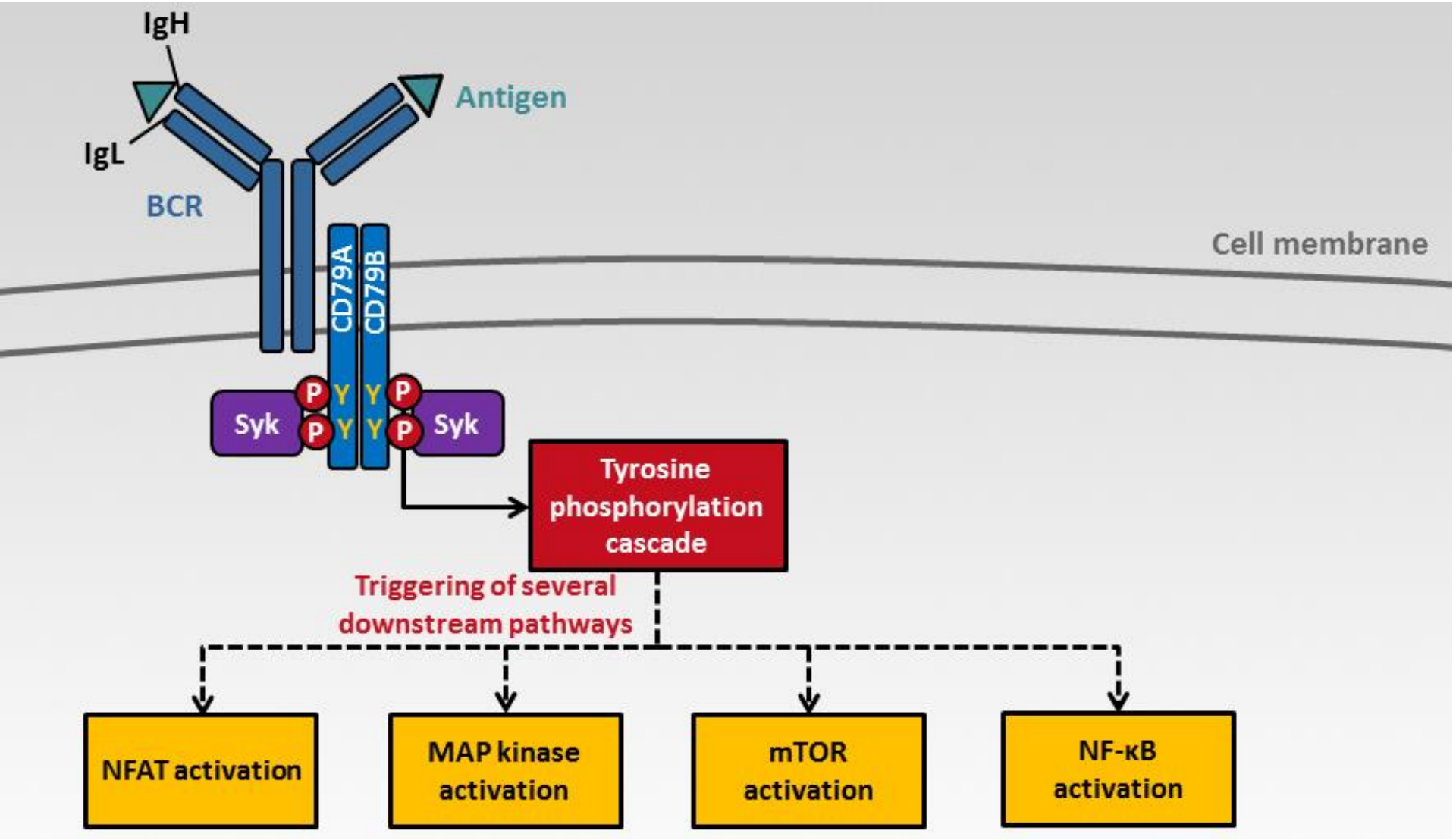
January 20, 2015 · Amber Bauer, ASCO staff



Clinical research has brought about tremendous progress in cancer care, resulting in longer survival and better quality of life for the more than half a million Americans diagnosed with cancer each year. During the last decade, more than 60 new cancer drugs have been approved by the U.S. Food and Drug Administration (FDA). Entire new classes of drugs have been developed, each targeting a specific molecule, gene, or protein required for tumor survival, growth, or spread.

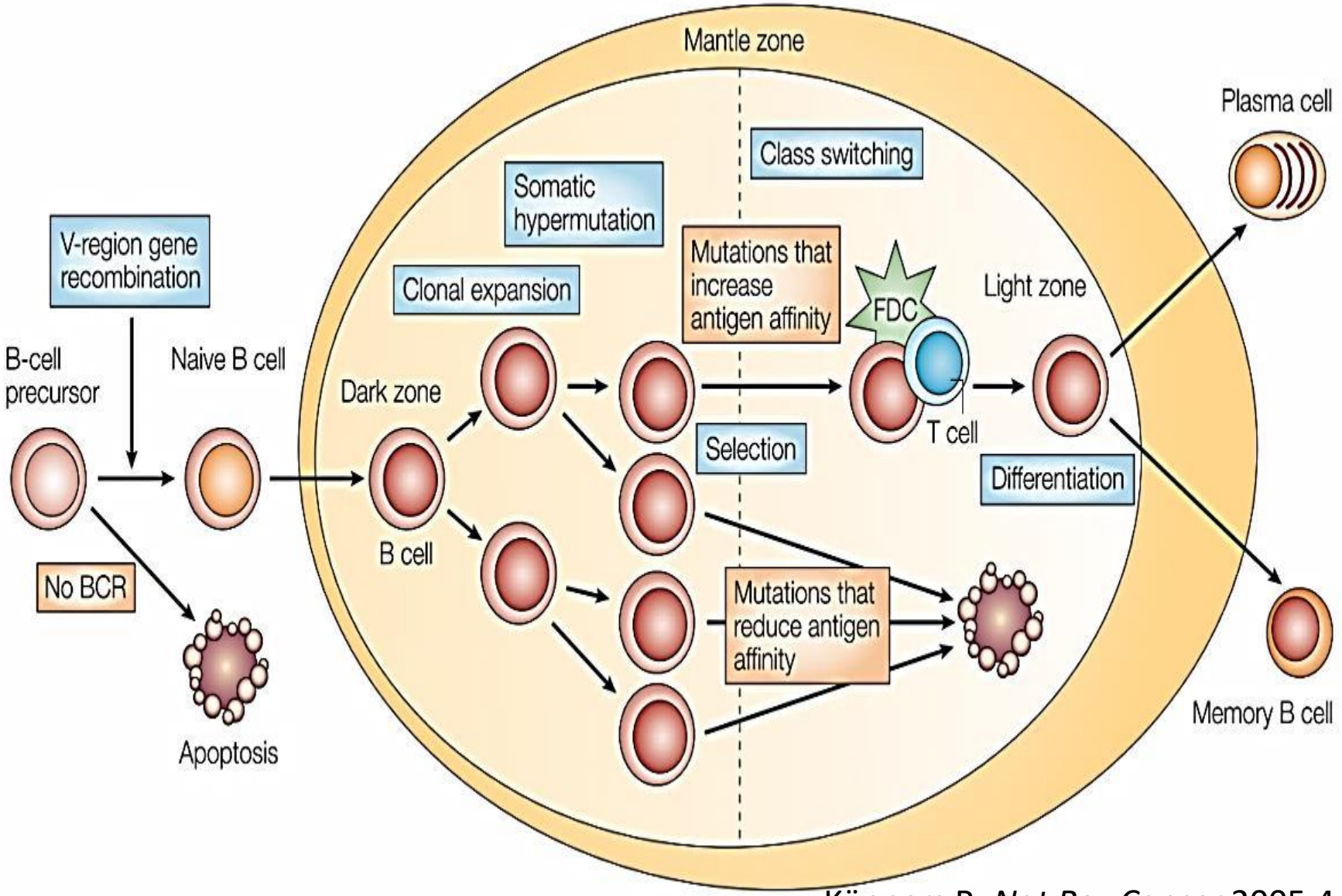
In the last year alone, four new therapies were approved for patients with chronic lymphocytic leukemia (CLL). These treatments are more effective and cause far fewer side effects than the treatment options that were previously available. For this reason, ASCO has named the transformation of CLL treatment the cancer Advance of the Year in its *Clinical Cancer Advances 2015* report.

B-Cell Receptor (BCR) Signaling
B細胞受體下游訊息傳遞路徑



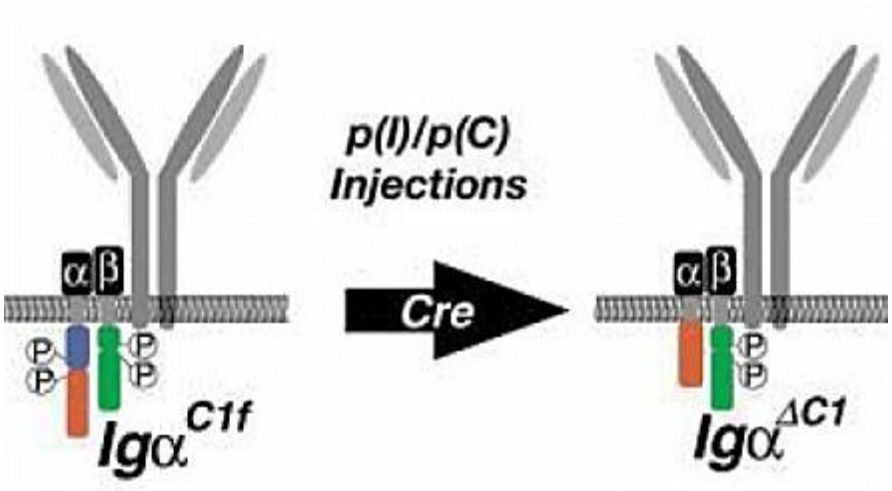
Staudt et al. *N Engl J Med* 2010;362:1417

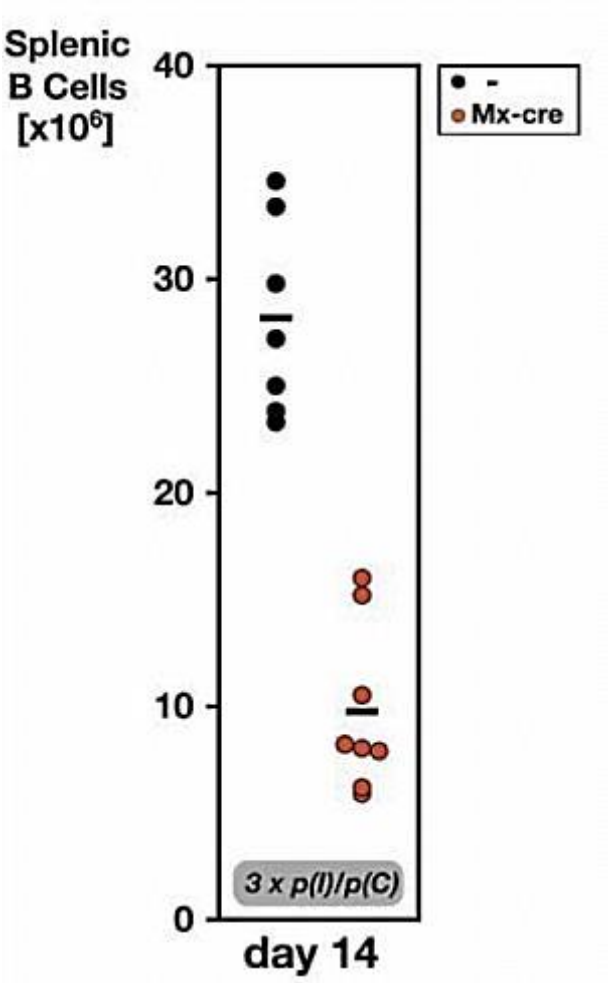
B細胞受體與B細胞成熟



Küppers R, *Nat Rev Cancer* 2005;4:251

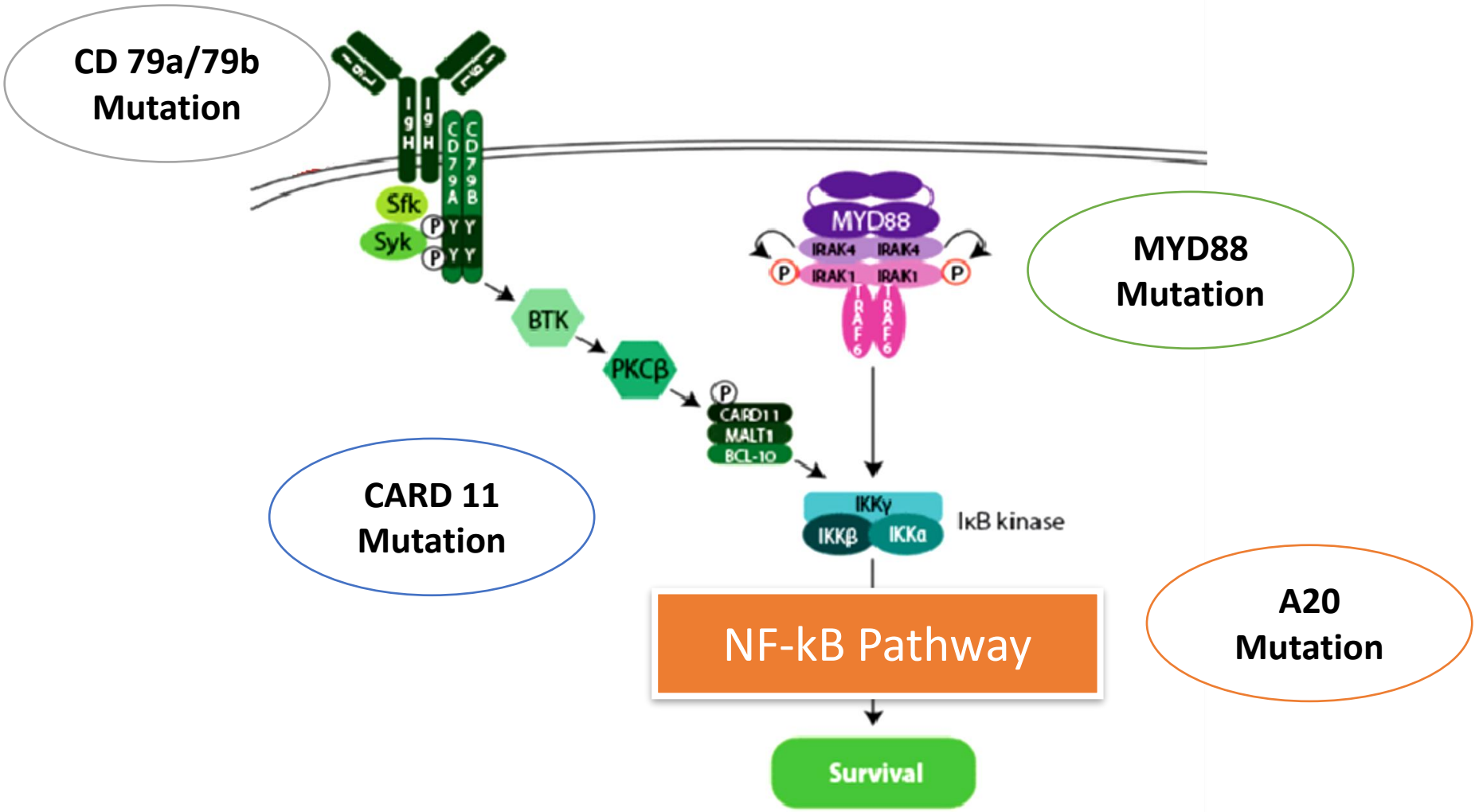
B細胞受體與B細胞成熟





K.P. Lam et al. *Cell*, 2004;117:787

ABC-DLBCL中之B細胞受體訊息路徑突變



Dunleavy K et al. *Oncology*, 2014: 4:326

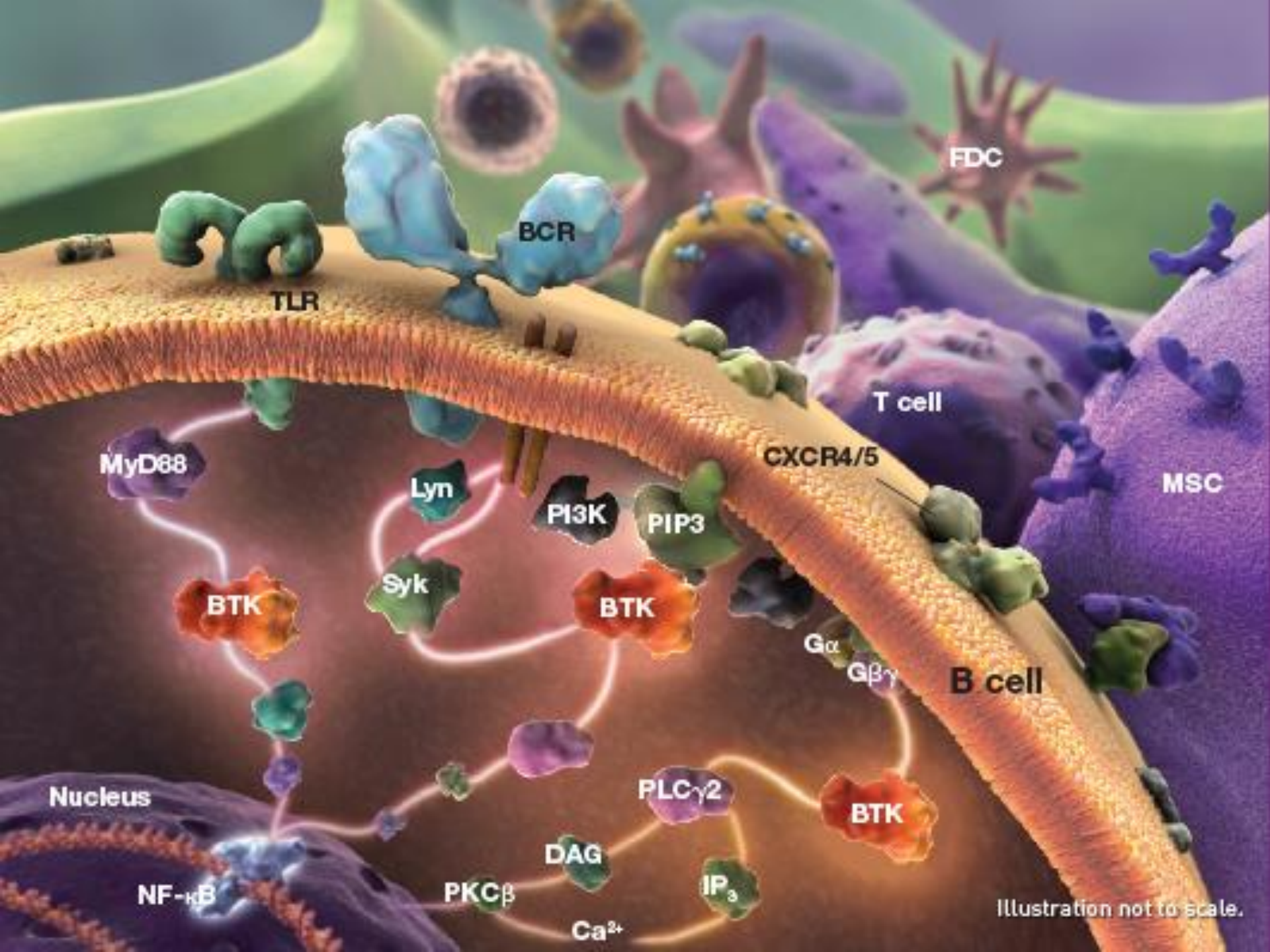
TKIs治療癌症之成功典範

Lung Ca.

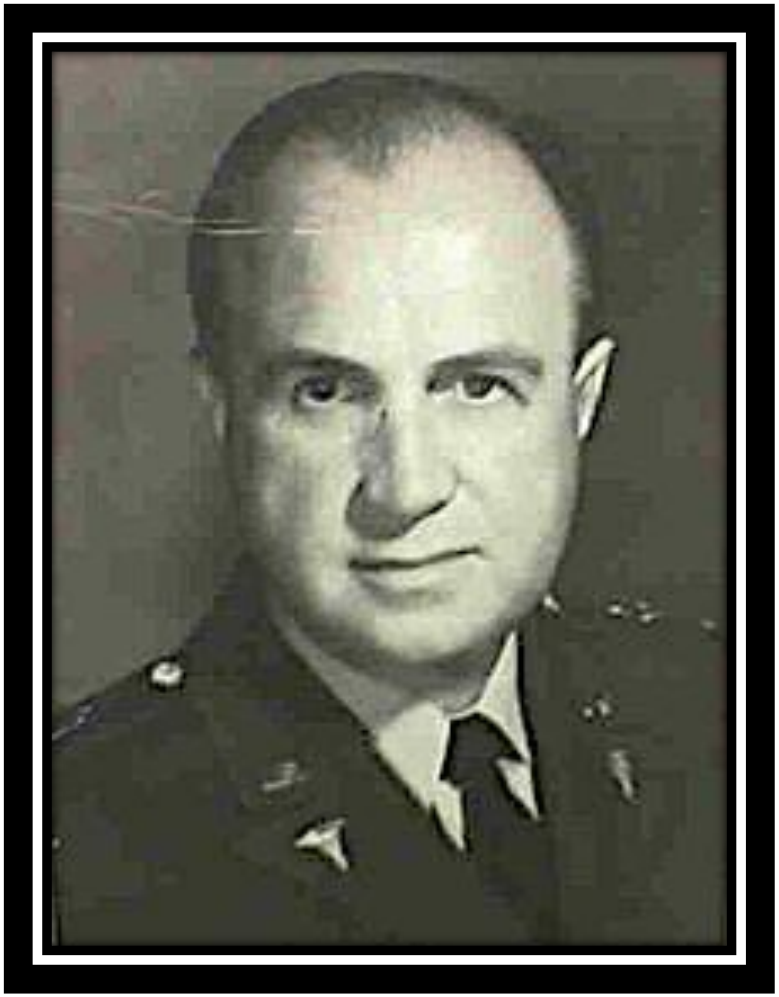
- Driver mutations: EGFR, ALK
- TKI: EGFRi, ALKi
- Resistance: mutations of or bypassing the target

CML

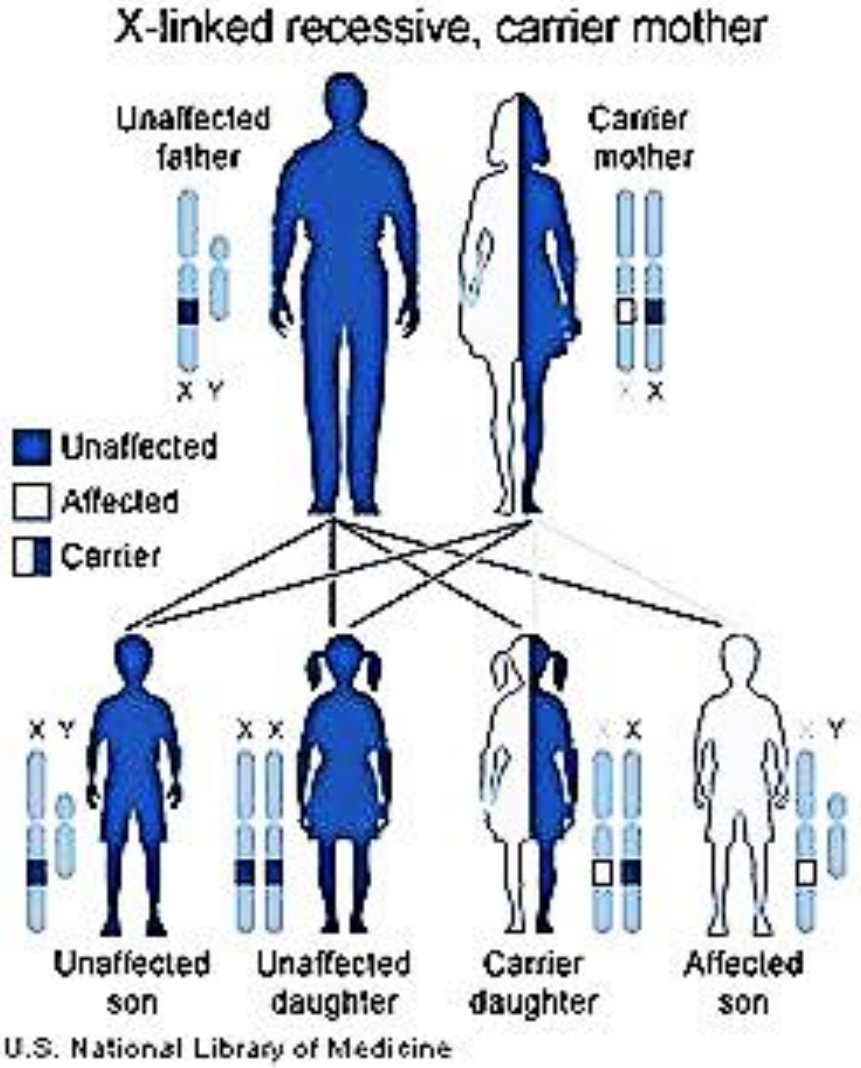
- Driver mutation: BCR-ABL
- TKI: ABLi
- Resistance: mutations of or bypassing the target


FDC
BCR
TLR
T cell
MyD88
Lyn
PI3K
PIP3
CXCR4/5
MSC
Syk
BTK
BTK
Gα
Gβγ
B cell
Nucleus
PLCγ2
BTK
DAG
NF-κB
PKCβ
IP3
Ca2+
Illustration not to scale.

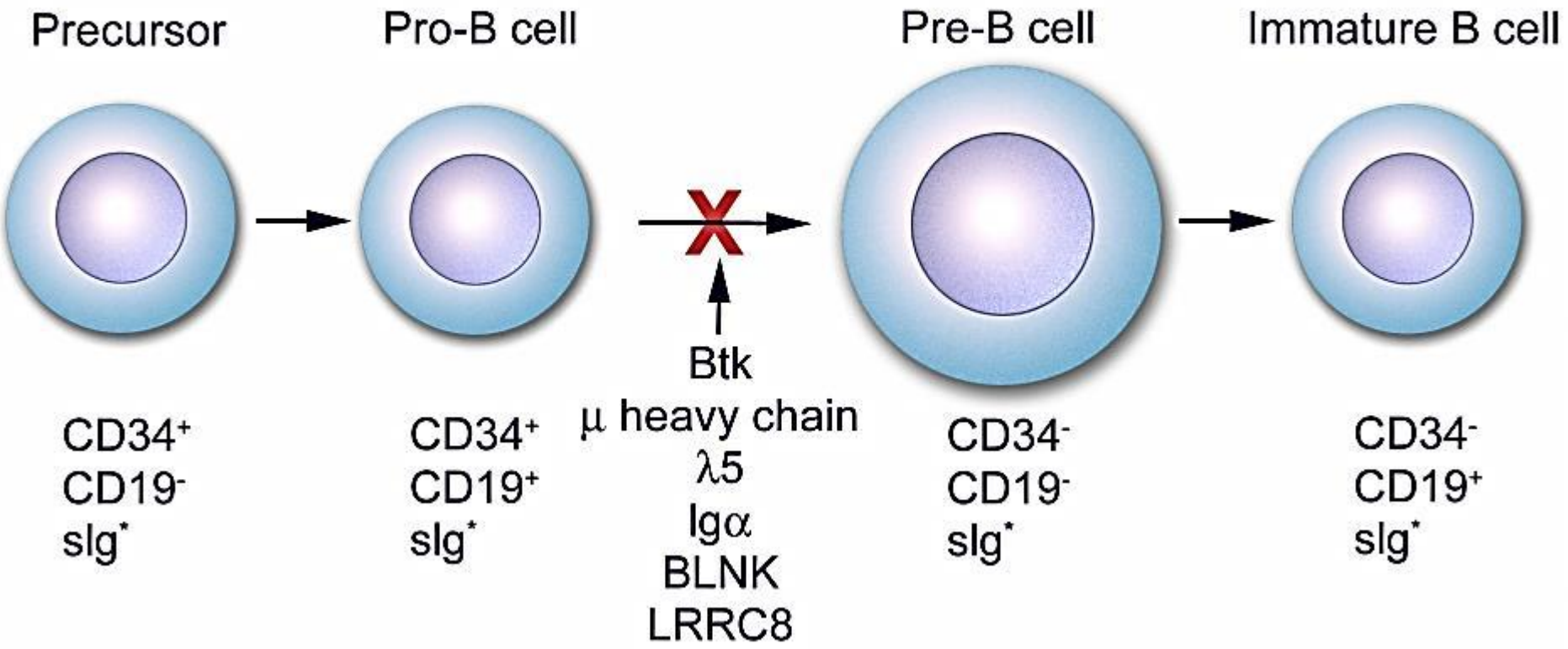
BTK: Bruton Tyrosine Kinase



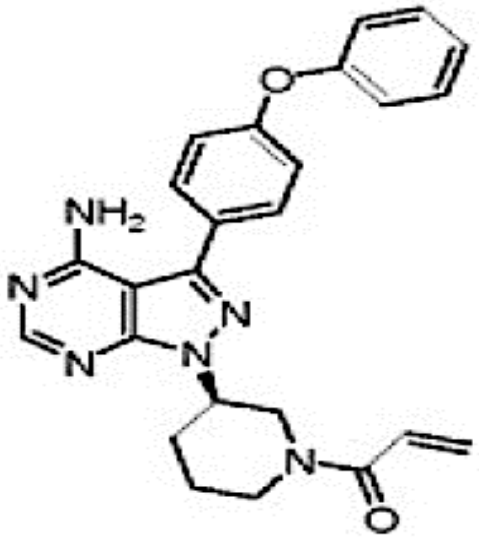
Ogden Bruton



BTK缺失讓B細胞無法正常成熟



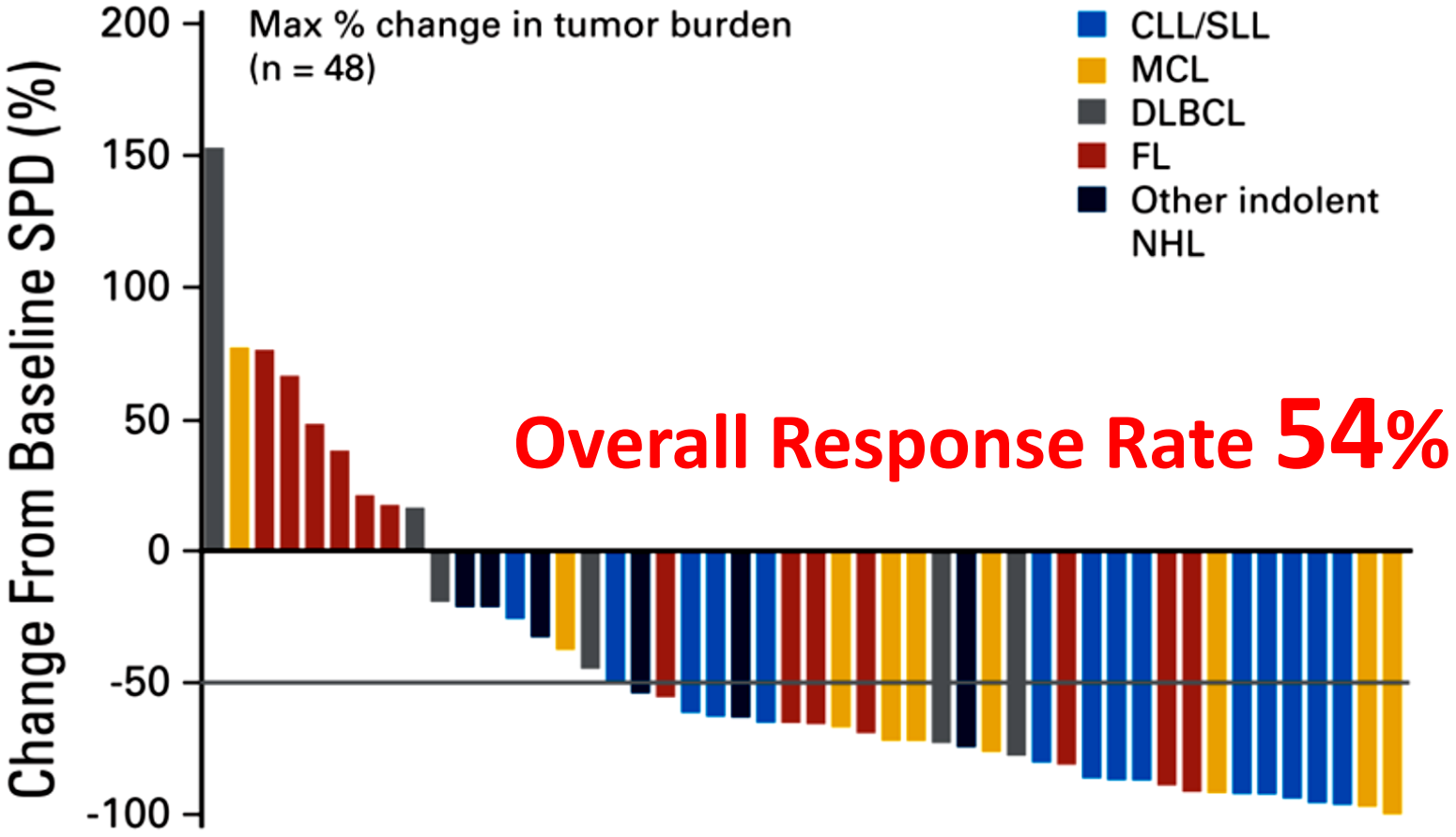
Ibrutinib (Ibruvica,億科)



潘峥婴, **Dr. Zhengying Pan**

驚豔的第一期臨床試驗結果

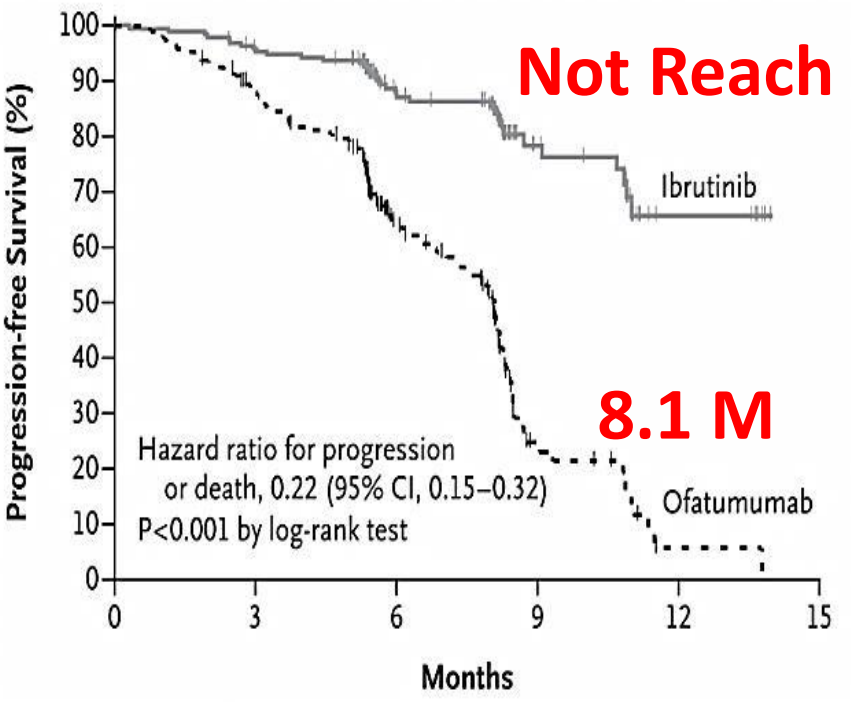
病患族群: 復發/難治B細胞淋巴瘤或白血病

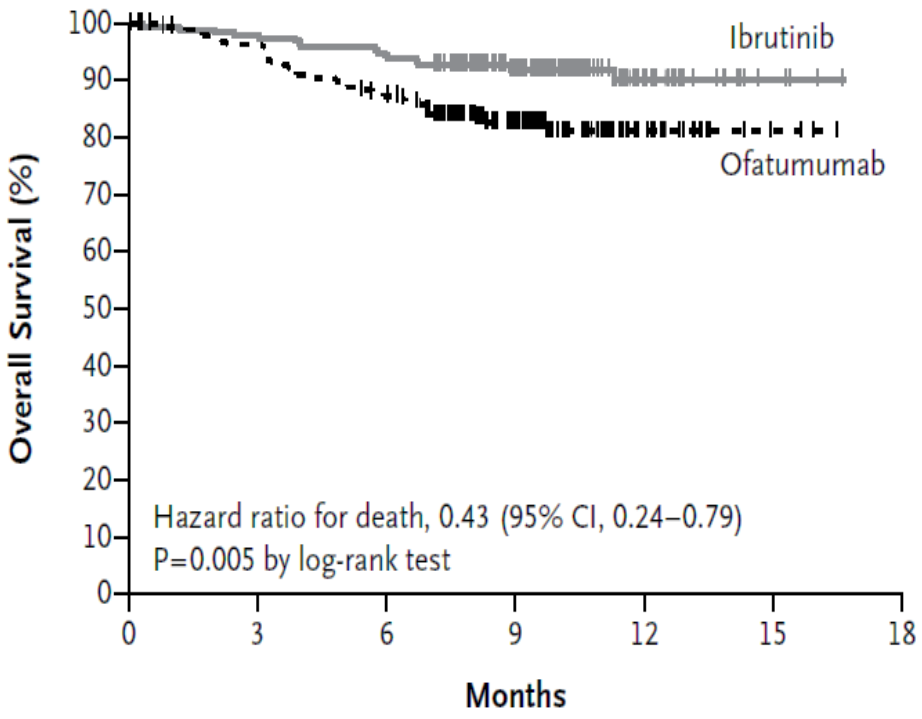


Fowler et al. *J Clin Oncol,* 2012; 31:88

於CLL後線治療之第三期試驗:達標

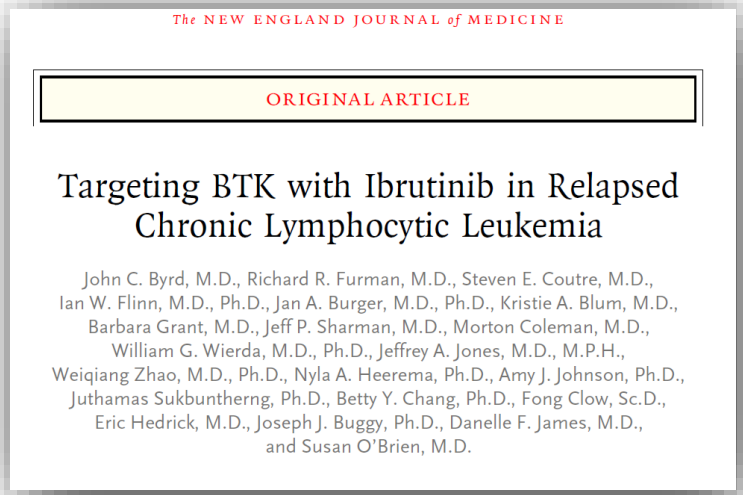
對照組: Ofatumumab
N=391





J.C. Byrd et al. *N Engl J Med* 2014;371:213

後線治療



The NEW ENGLAND JOURNAL of MEDICINE

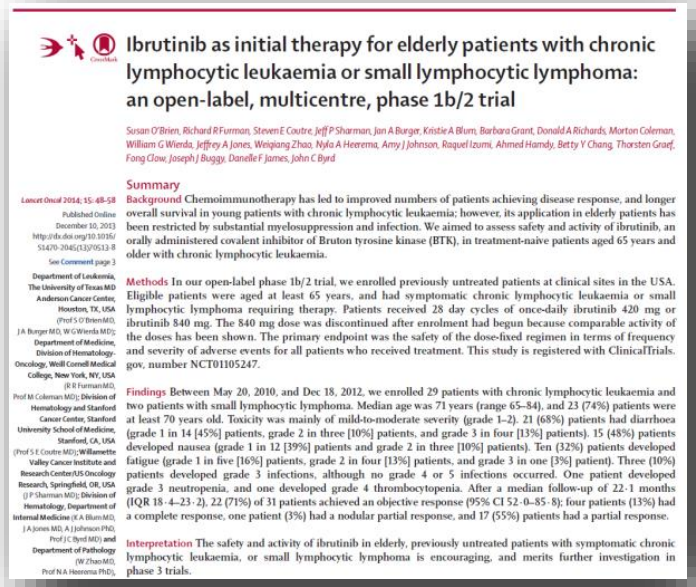
ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

Byrd J, et al. *New Engl J Med*. 2013; 369 (1): 32-42.

老年病患第一線治療



Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: an open-label, multicentre, phase 1b/2 trial

Summary

Background Chemoimmunotherapy has led to improved numbers of patients achieving disease response, and longer overall survival in young patients with chronic lymphocytic leukaemia; however, its application in elderly patients has been restricted by substantial myelosuppression and infection. We aimed to assess safety and activity of ibrutinib, an orally administered covalent inhibitor of Bruton tyrosine kinase (BTK), in treatment-naive patients aged 65 years and older with chronic lymphocytic leukaemia.

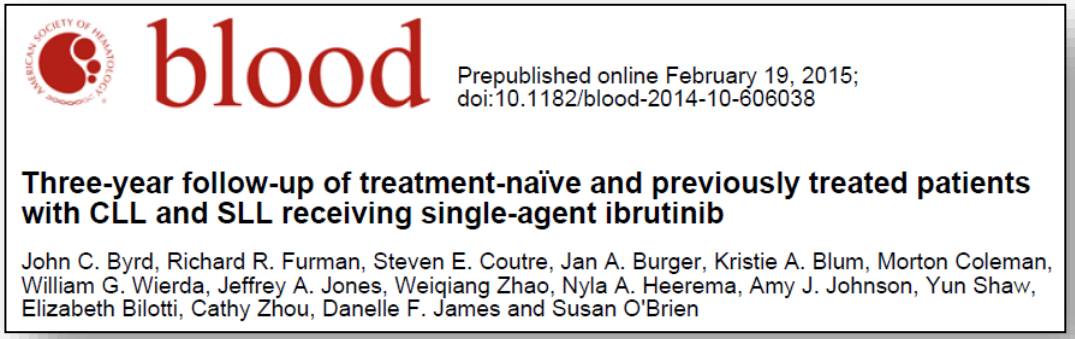
Methods In our open-label phase 1b/2 trial, we enrolled previously untreated patients at clinical sites in the USA. Eligible patients were aged at least 65 years, and had symptomatic chronic lymphocytic leukaemia or small lymphocytic lymphoma requiring therapy. Patients received 28 day cycles of once-daily ibrutinib 420 mg or ibrutinib 840 mg. The 840 mg dose was discontinued after enrolment had begun because comparable activity of the doses has been shown. The primary endpoint was the safety of the dose-fixed regimen in terms of frequency and severity of adverse events for all patients who received treatment. This study is registered with ClinicalTrials.gov, number NCT01105247.

Findings Between May 20, 2010, and Dec 18, 2012, we enrolled 29 patients with chronic lymphocytic leukaemia and two patients with small lymphocytic lymphoma. Median age was 71 years (range 65–84), and 23 (74%) patients were at least 70 years old. Toxicity was mainly of mild-to-moderate severity (grade 1–2). 21 (68%) patients had diarrhoea (grade 1 in 14 [45%] patients, grade 2 in three [10%] patients, and grade 3 in four [13%] patients). 15 (48%) patients developed nausea (grade 1 in 12 [39%] patients and grade 2 in three [10%] patients). Ten (32%) patients developed fatigue (grade 1 in five [16%] patients, grade 2 in four [13%] patients, and grade 3 in one [3%] patient). Three (10%) patients developed grade 3 infections, although no grade 4 or 5 infections occurred. One patient developed grade 3 neutropenia, and one developed grade 4 thrombocytopenia. After a median follow-up of 22·1 months (IQR 18·4–23·2), 22 (71%) of 31 patients achieved an objective response (95% CI 52·0–85·8); four patients (13%) had a complete response, one patient (3%) had a nodular partial response, and 17 (55%) patients had a partial response.

Interpretation The safety and activity of ibrutinib in elderly, previously untreated patients with symptomatic chronic lymphocytic leukaemia, or small lymphocytic lymphoma is encouraging, and merits further investigation in phase 3 trials.

O'Brien S. et al. *Lancet Oncol.* 2014; 15(1): 48-58.

長期療效追蹤



blood

Prepublished online February 19, 2015;
doi:10.1182/blood-2014-10-606038

Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib

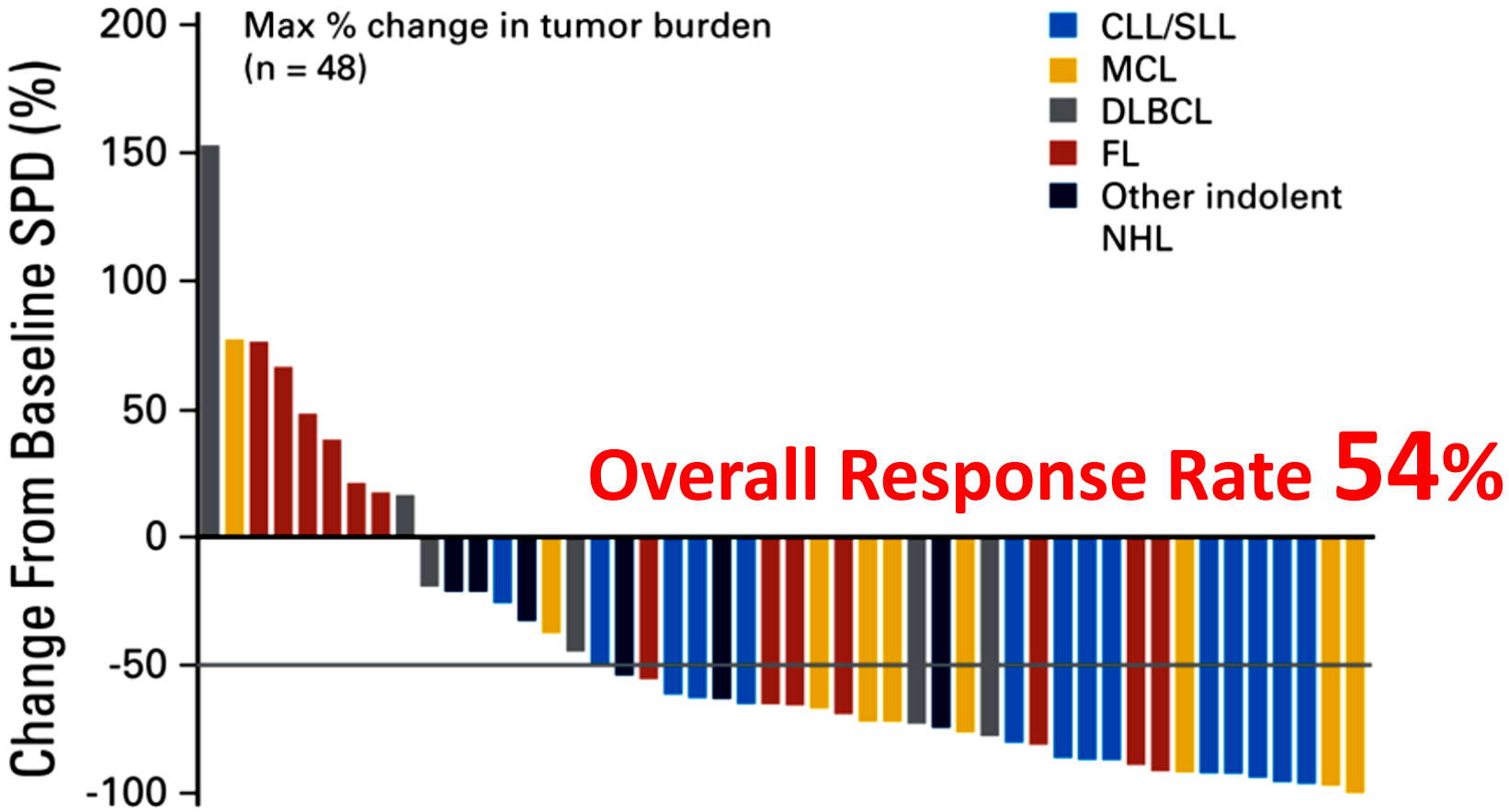
John C. Byrd, Richard R. Furman, Steven E. Coutre, Jan A. Burger, Kristie A. Blum, Morton Coleman, William G. Wierda, Jeffrey A. Jones, Weiqiang Zhao, Nyla A. Heerema, Amy J. Johnson, Yun Shaw, Elizabeth Bilotti, Cathy Zhou, Danelle F. James and Susan O'Brien

Byrd JC, et al.Blood. Epub Ahead of Print 24Feb 2015

Ibrutinib美國官方之核准進程

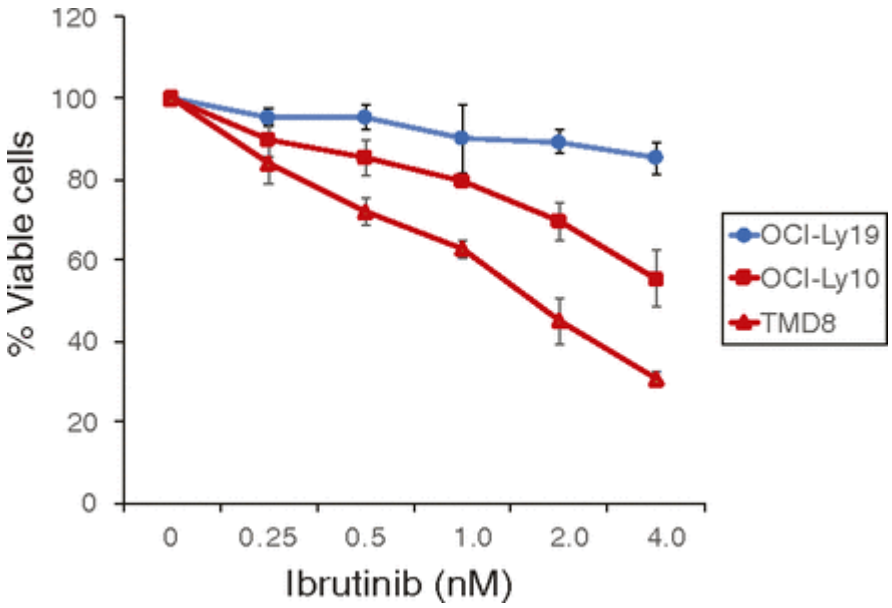
Date	FDA approval
Mar., 2016	**1st line CLL**
Jan., 2015	**WM/LPL**
Jul., 2014	**17p- CLL**
Feb., 2014	**Salvage CLL**
Nov., 2013	**MCL**

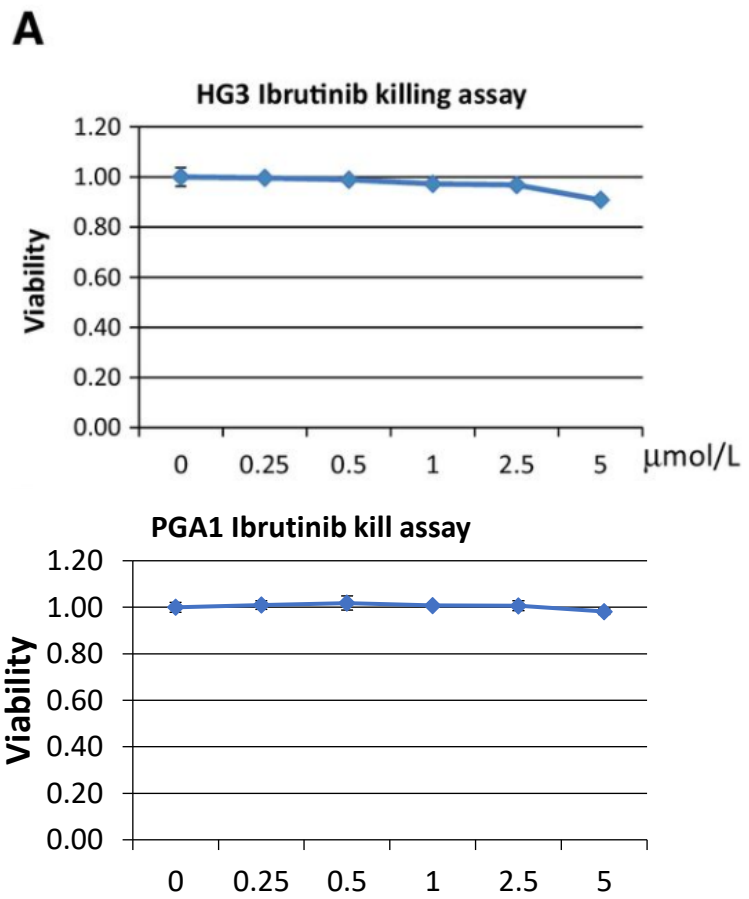
但…慢性淋巴性白血病???



Fowler et al. *J Clin Oncol,* 2012; 31:88

體外毒殺效果 – ABC-DLBCL > CLL

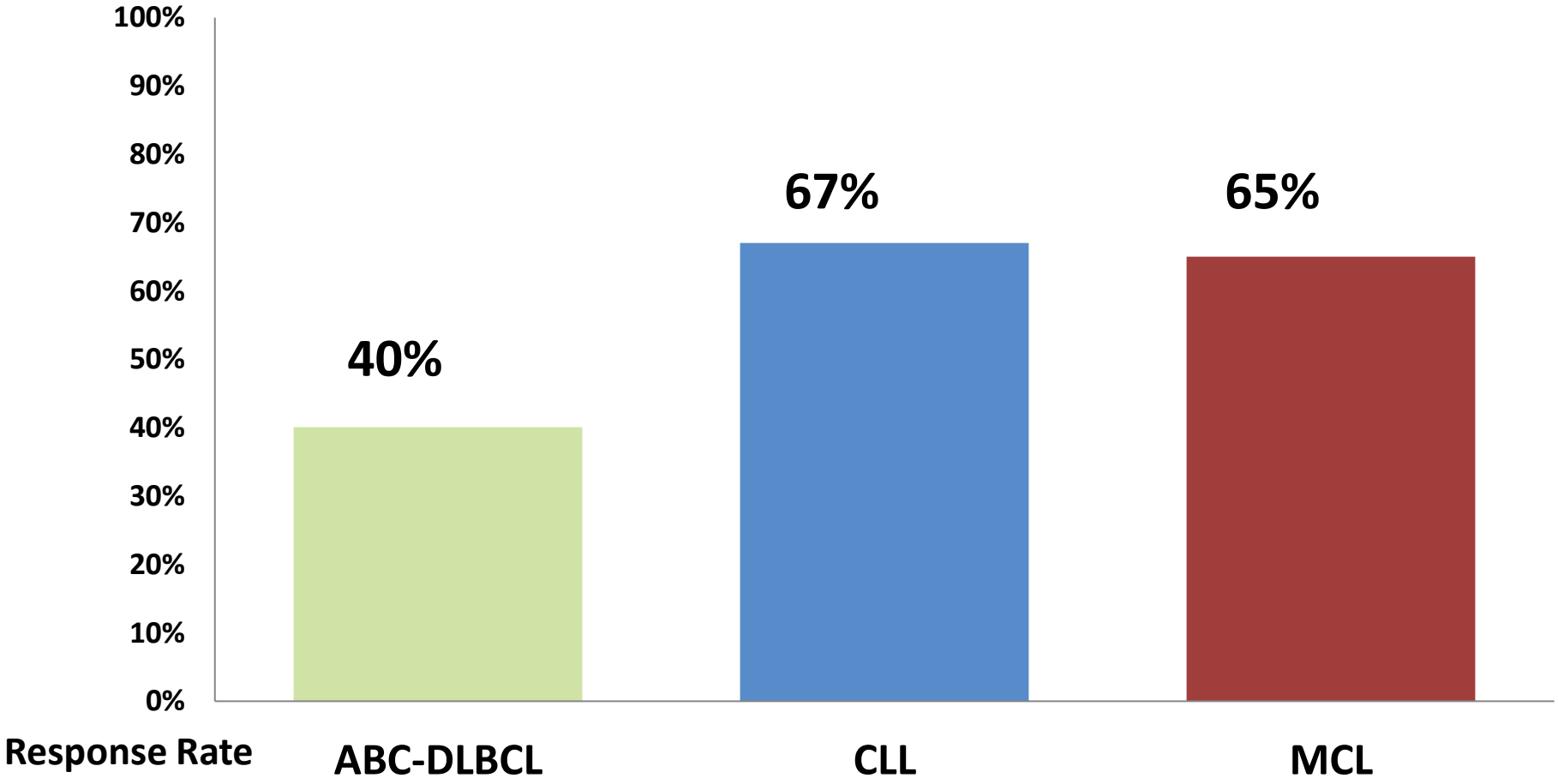




PNAS 2016, 113(46): E7260–E7267

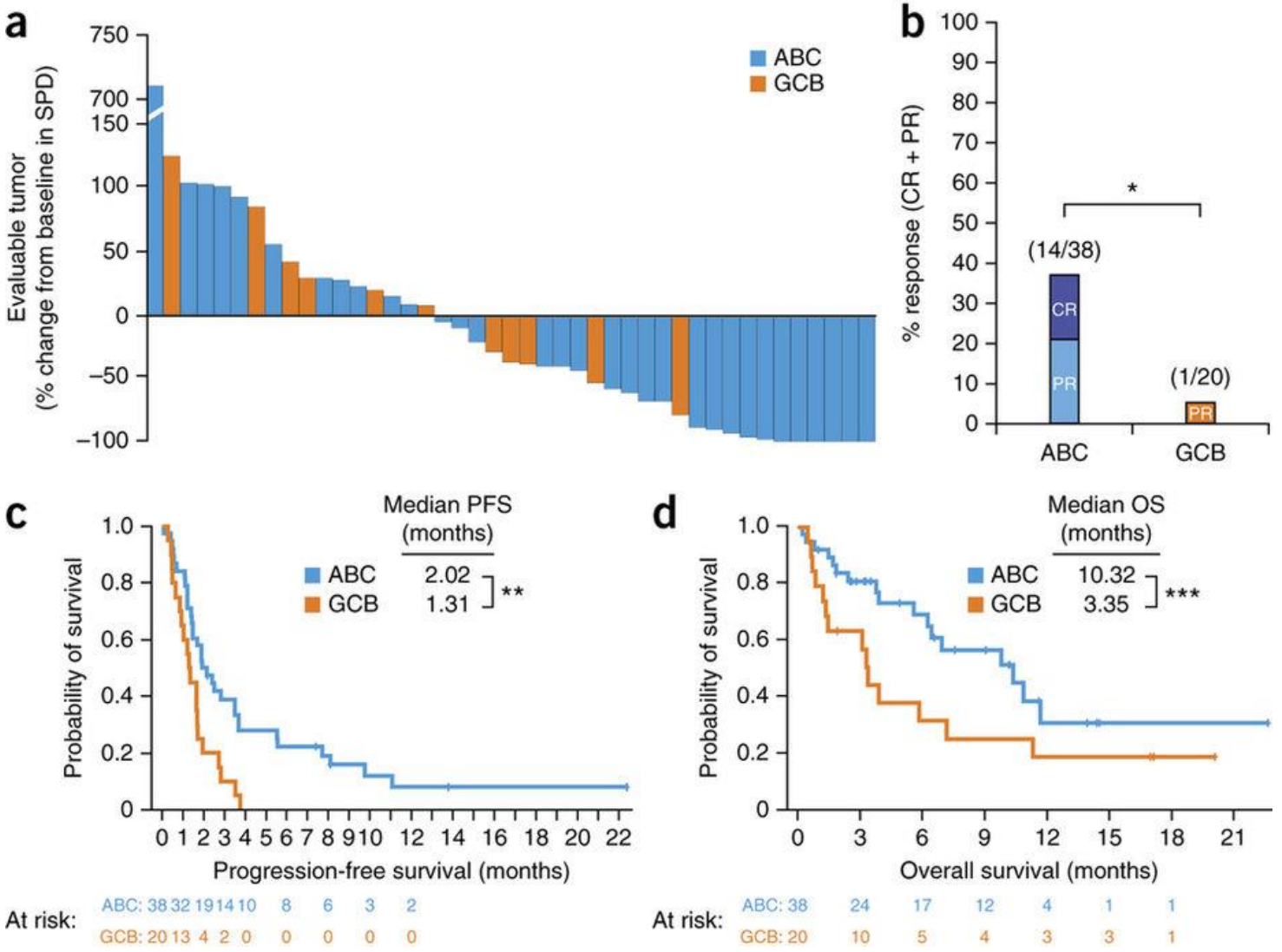
Clin Cancer Res; 23(4); 1049–59

真實世界~~~“無突變者”效果勝

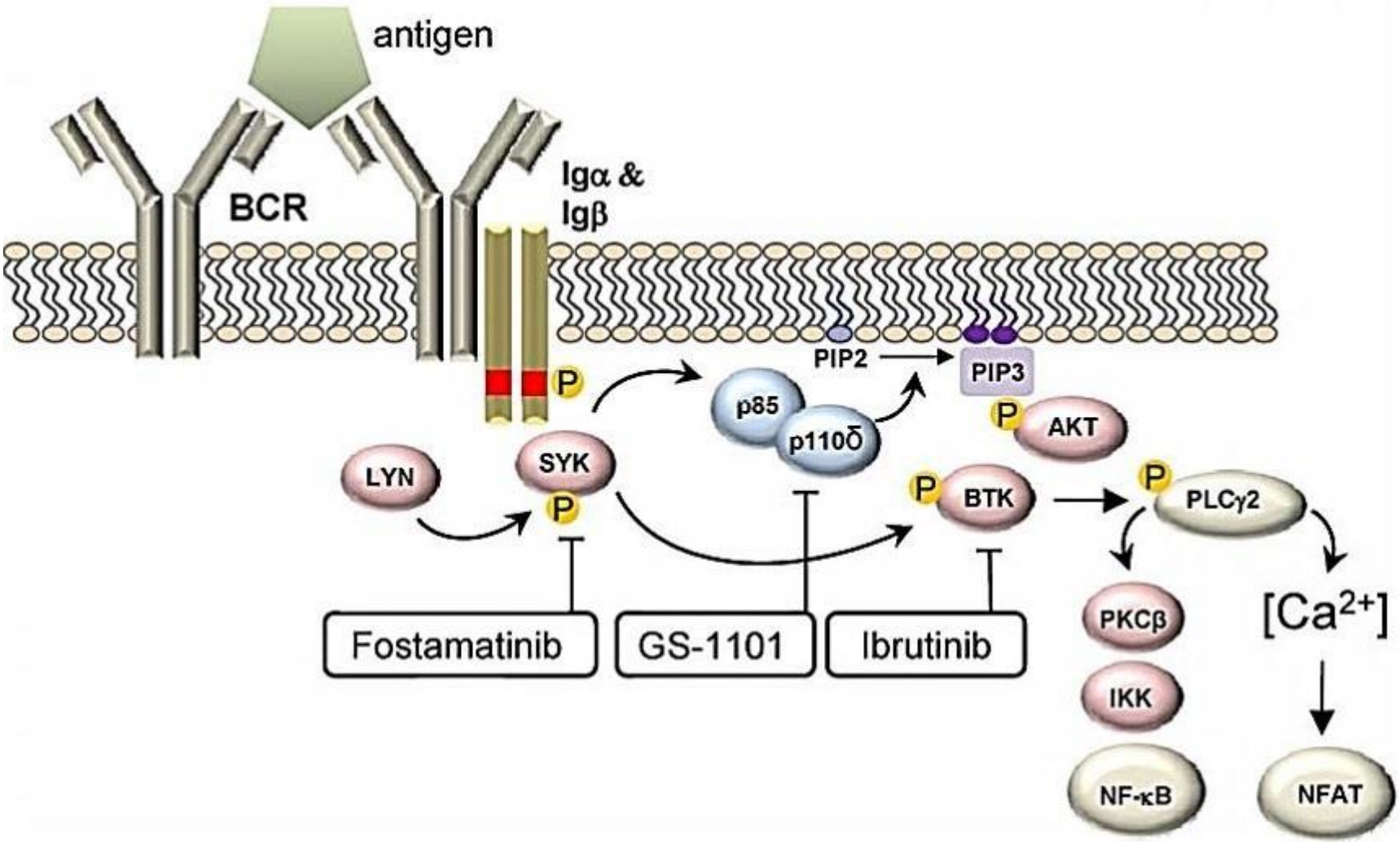


Wyndham H. W, et al. ASH Abstracts, 2012, Abstract 686
Susan O. et al. ASH Abstracts, 2011, Abstract 983
Michael W., et al. ASH Abstracts 2012, Abstract 904

真實世界~~~“無突變者”效果勝



•*Nature Medicine* **21**, 922–926 (2015)

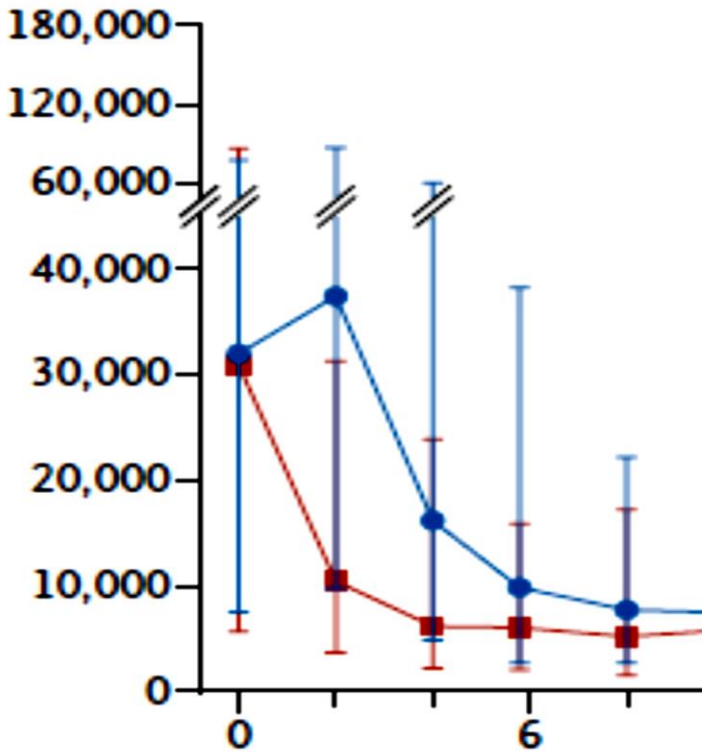


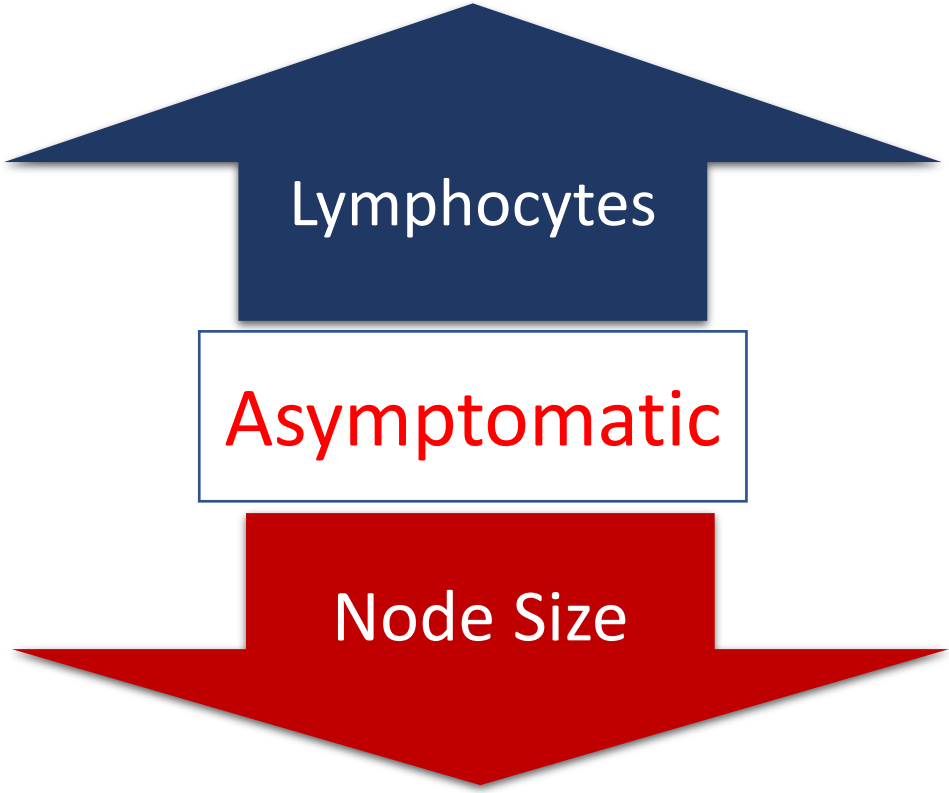
有效，WHY？

Adrian W. et al. *Hematology Am Soc Hematol Educ Program*. 2012;88

毒殺 VS 驅逐？

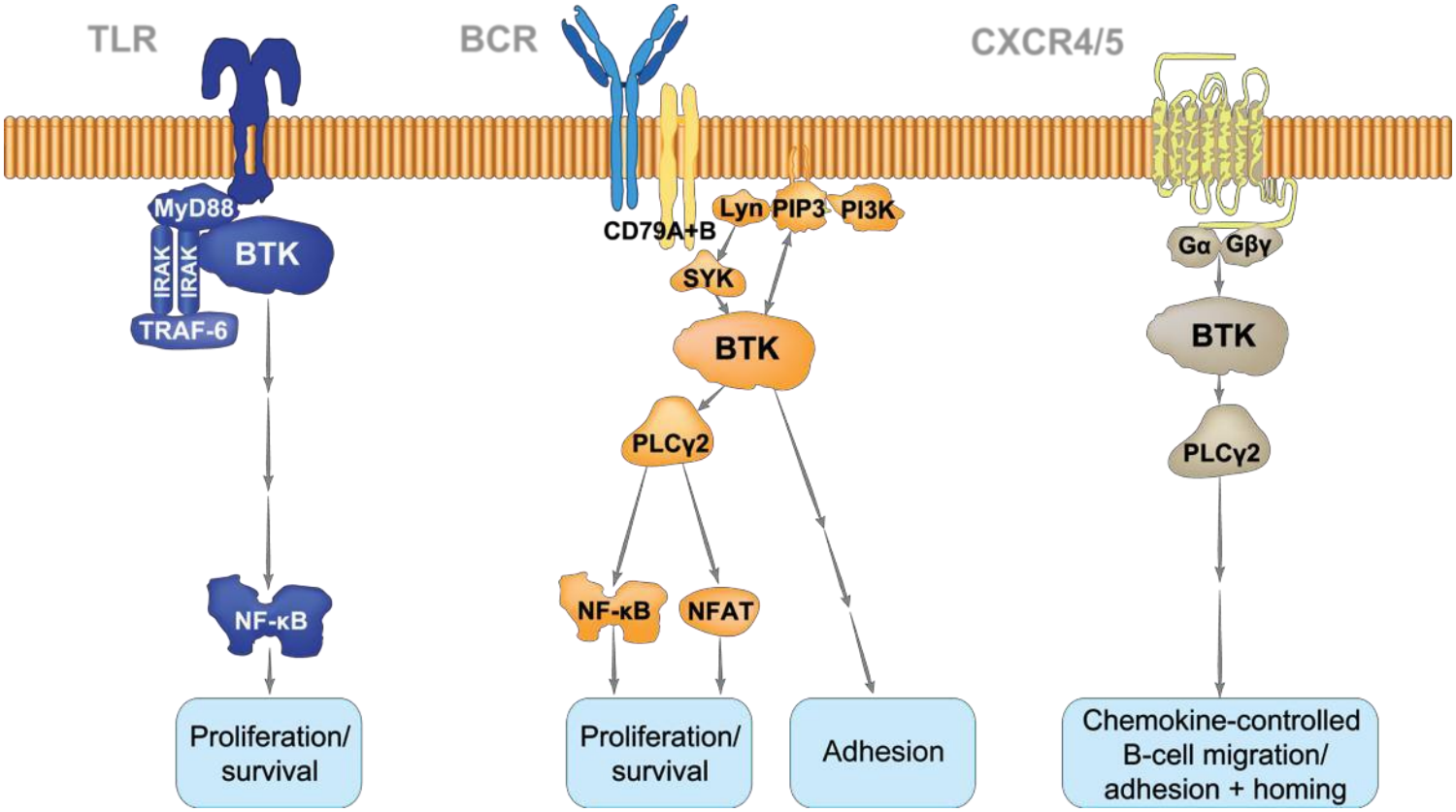
Absolute lymphocyte count (per mm³)





Richard R. Furman et al. *N Engl J Med,* 2014;370:997

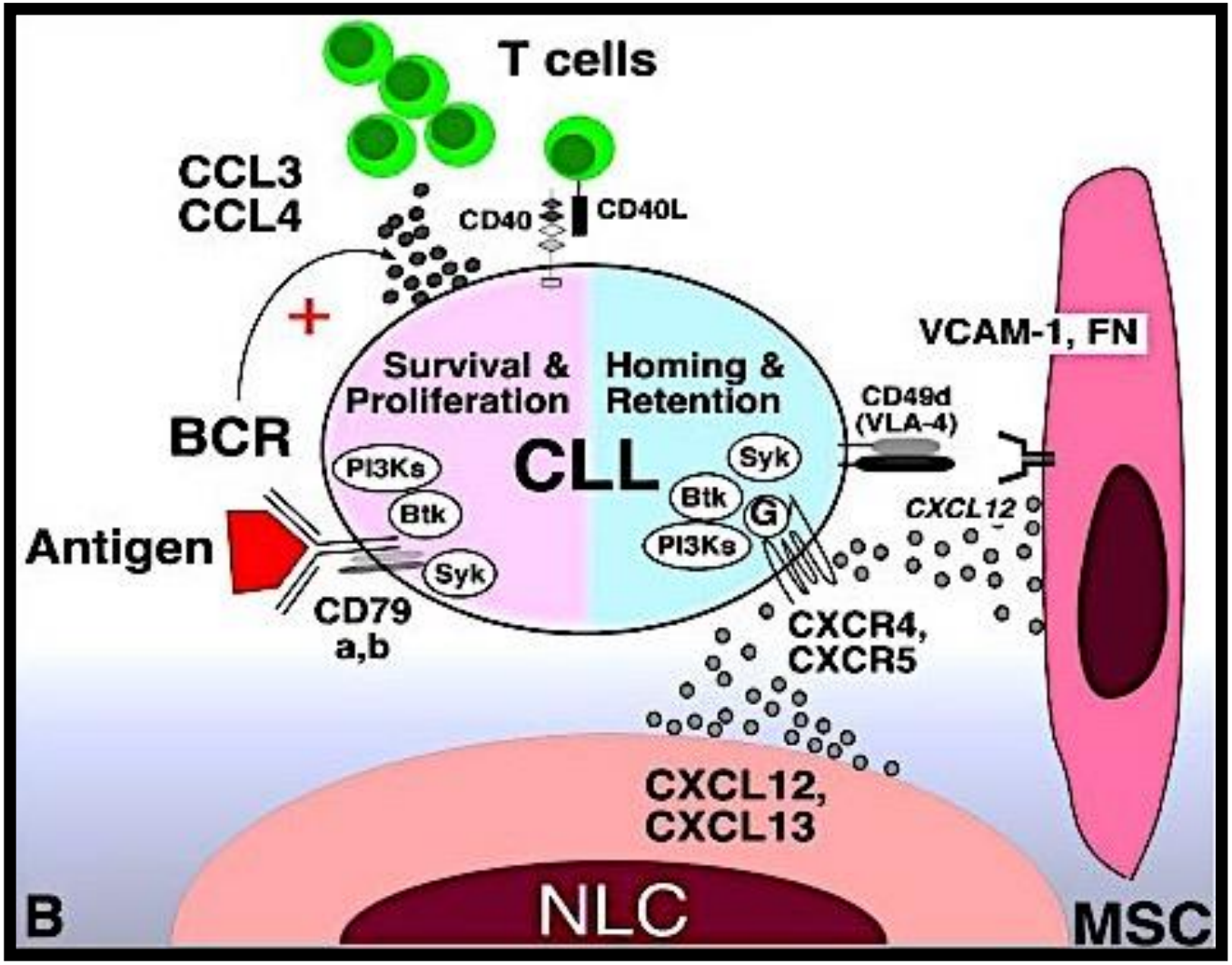
BTK與B細胞的各種浪漫



- BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion[1-5]
- Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro

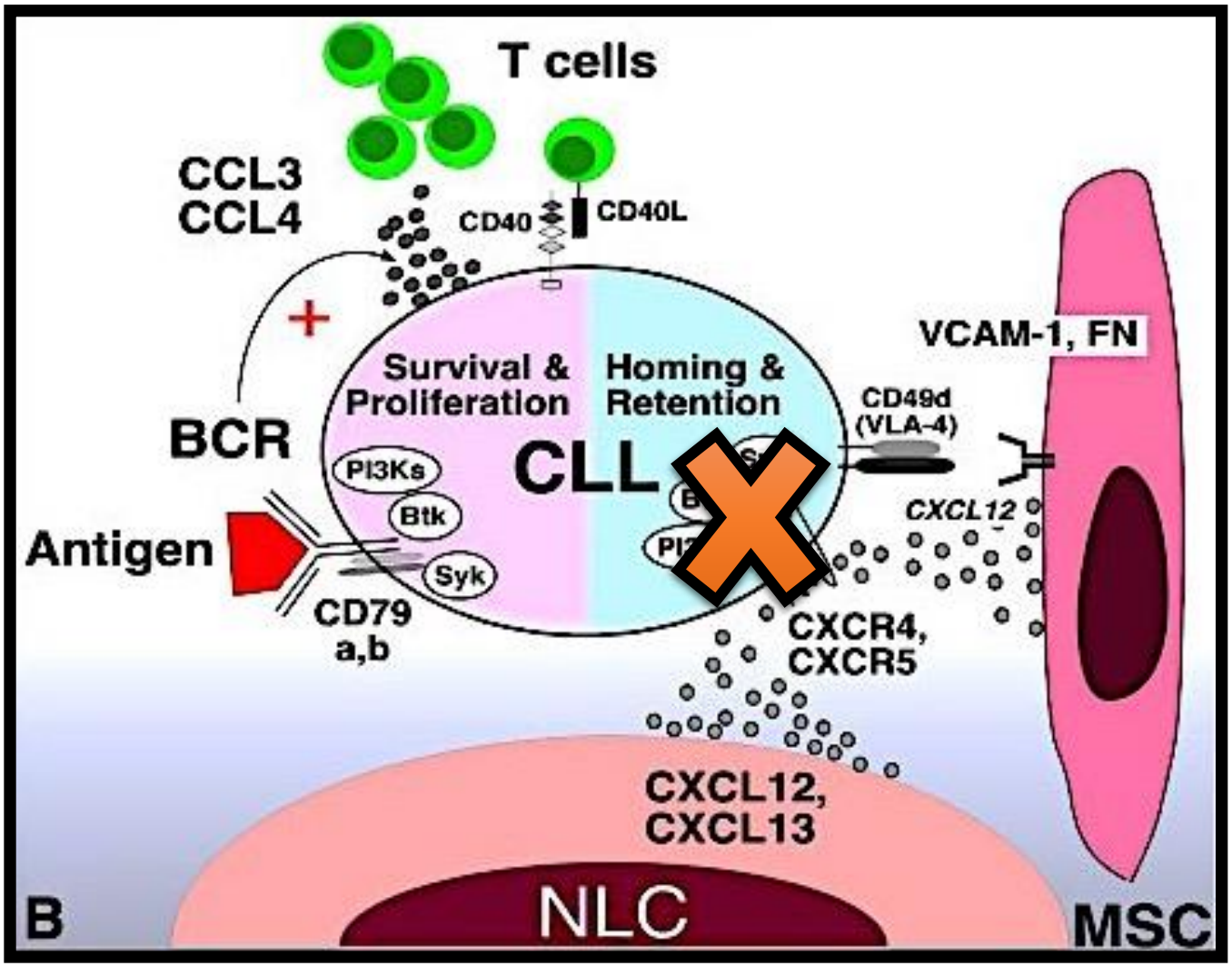
1. Niiro H, Clark EA. *Nat Rev Immunol*. 2002;2:945-956. **2.** Brunner C, Muller B, Wirth T. *Histol Histopathol*. 2005;20:945-955. **3.** de Gorter DJ, Beuling EA, Kersseboom R, et al. *Immunity*. 2007;26:93-104. **4.** Buggy JJ, Elias L. *Int Rev Immunol*. 2012;31:119-132. **5.** Spaargaren M, Beuling EA, Rurup ML, et al. *J Exp Med*. 2003;198:1539-1550

BTK與B細胞的各種浪漫



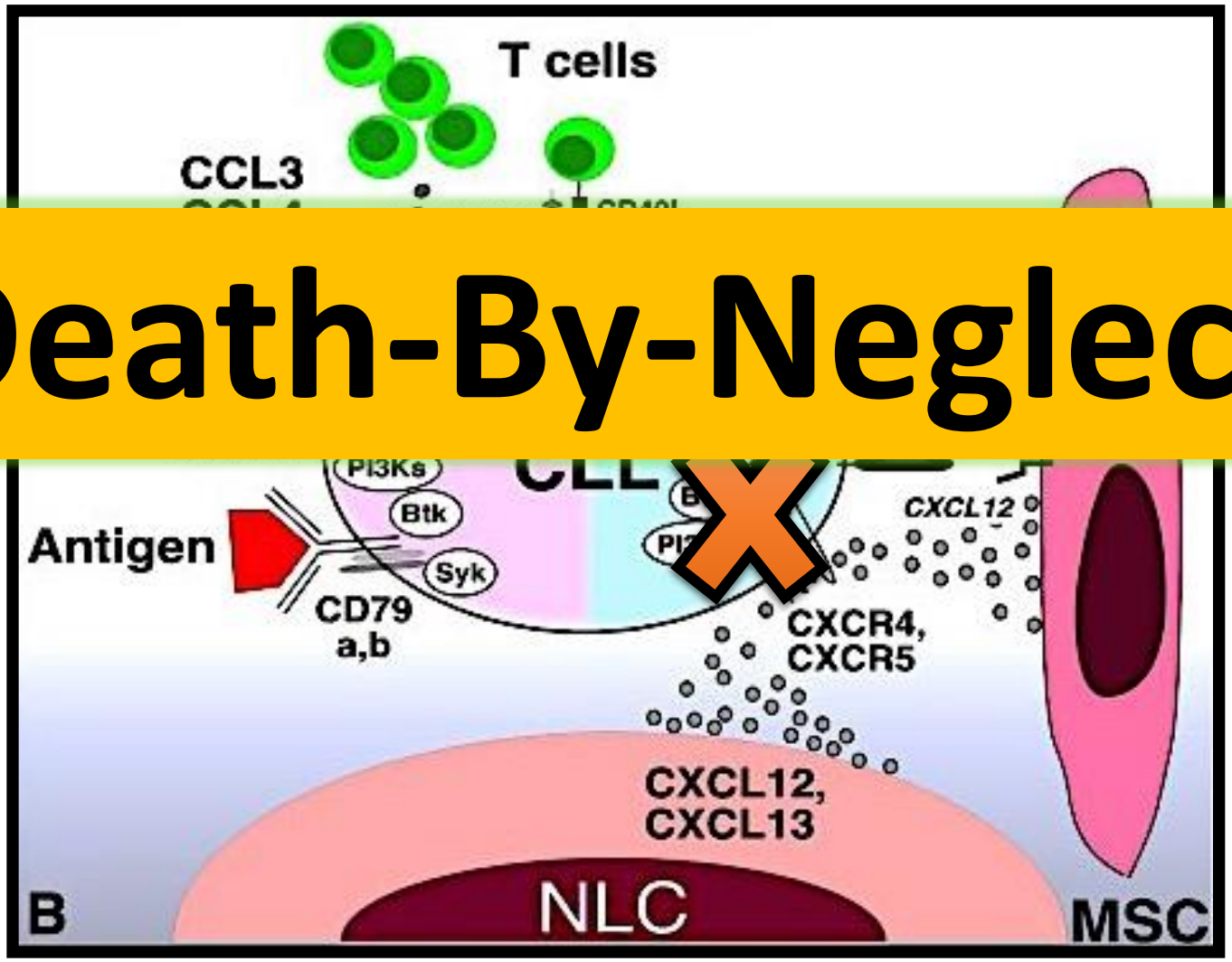
J. Burger et al. , *Curr Opin Oncol* 2012 ;24:643

BTK與B細胞的各種浪漫



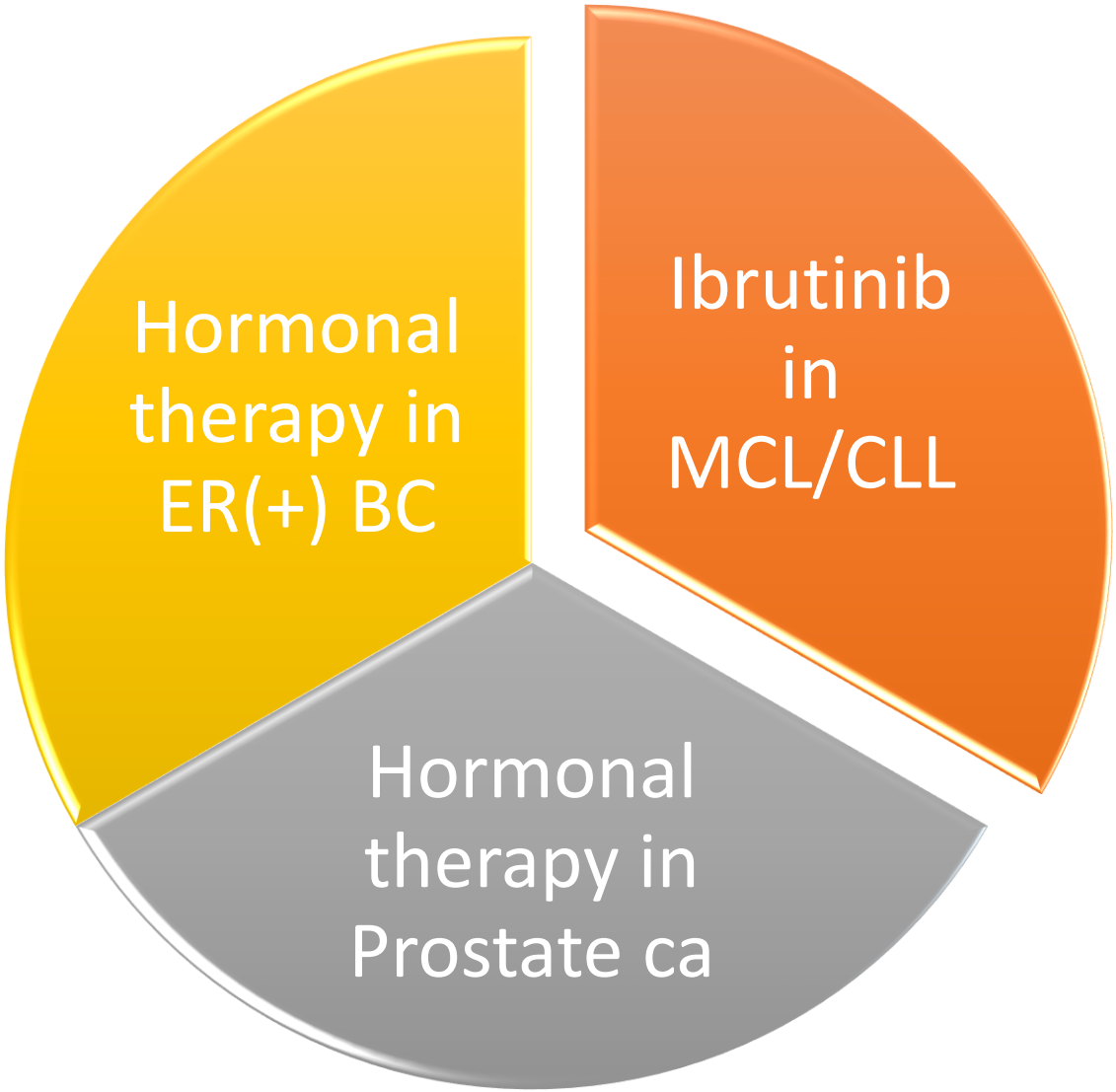
J. Burger et al. , *Curr Opin Oncol* 2012 ;24:643

Microenvironment



J. Burger et al. , *Curr Opin Oncol* 2012 ;24:643

遠目: 最早的標靶治療...


Hormonal therapy in ER(+) BC
Ibrutinib in MCL/CLL
Hormonal therapy in Prostate ca

NCCN：Preferred CLL治療建議
（V2, 2021）

第一線 with Del(17p)	第一線 without Del(17p)	後線 with Del(17p)	後線 without Del(17p)
• Ibrutinib	• Ibrutinib	• Ibrutinib	• Ibrutinib
• Acalabrutinib ± G	• Acalabrutinib ± G	• Venetoclax ± R	• Venetoclax ± R
• Venetoclax + G	• Venetoclax + G	• Acalabrutinib	• Acalabrutinib
	• FCR*	• Duvelisib	• Duvelisib
		• Idelalisib+R	• Idelalisib + R

AND…

- Gene mutations
  - Mutation-unrelated “functional dependence”?
  - Microenvironment-oriented therapies?
- Toxicities
  - it seems fine to have no B, but for others?
- Precision medicine
  - something there beyond mutations.