혈액암 알아보기
숨은 혈액암 찾기

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부산경남내과학회 부산 코모도호텔 20211202

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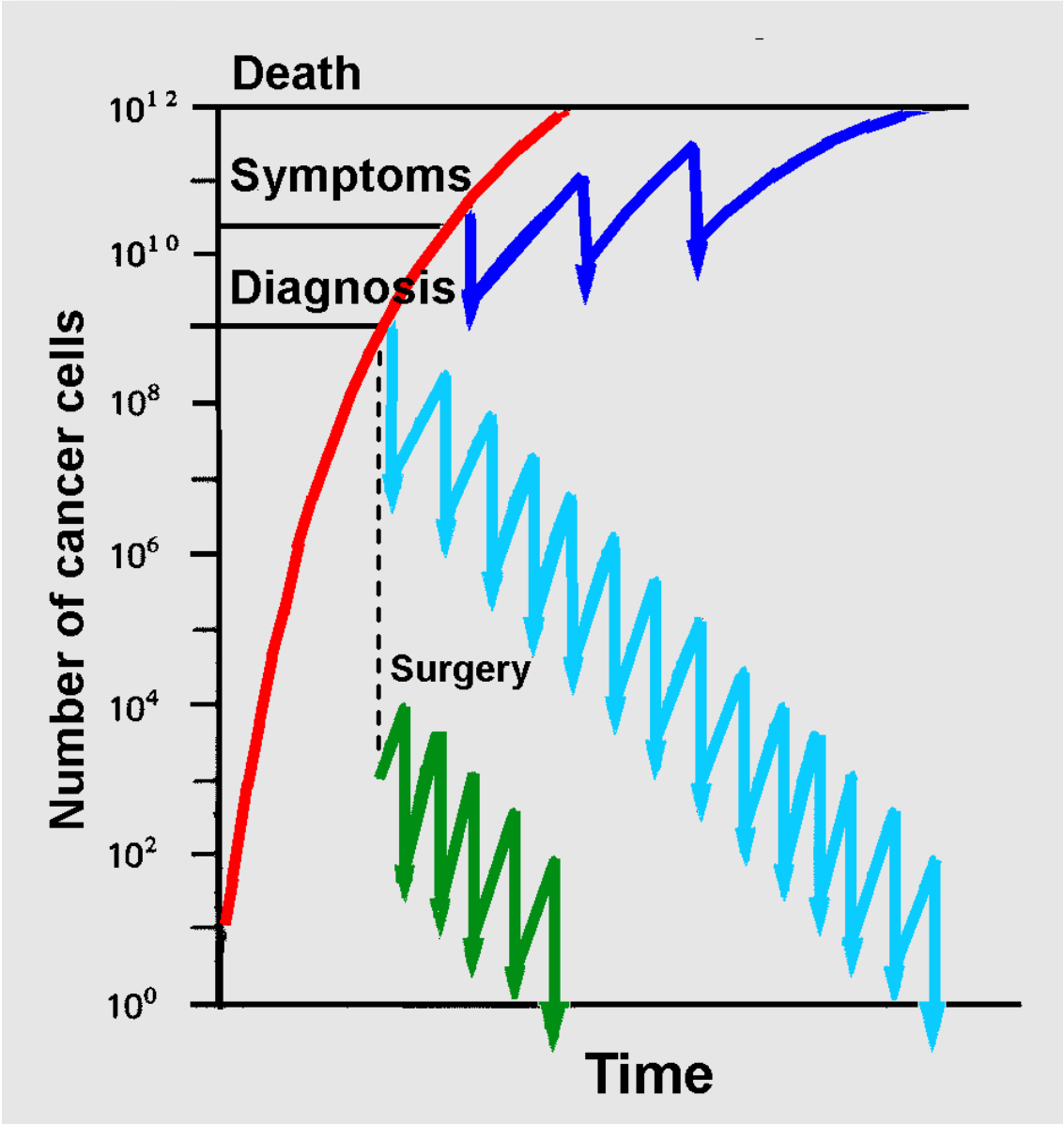
혈액암 알아보기

혈액암의 표적 치료제

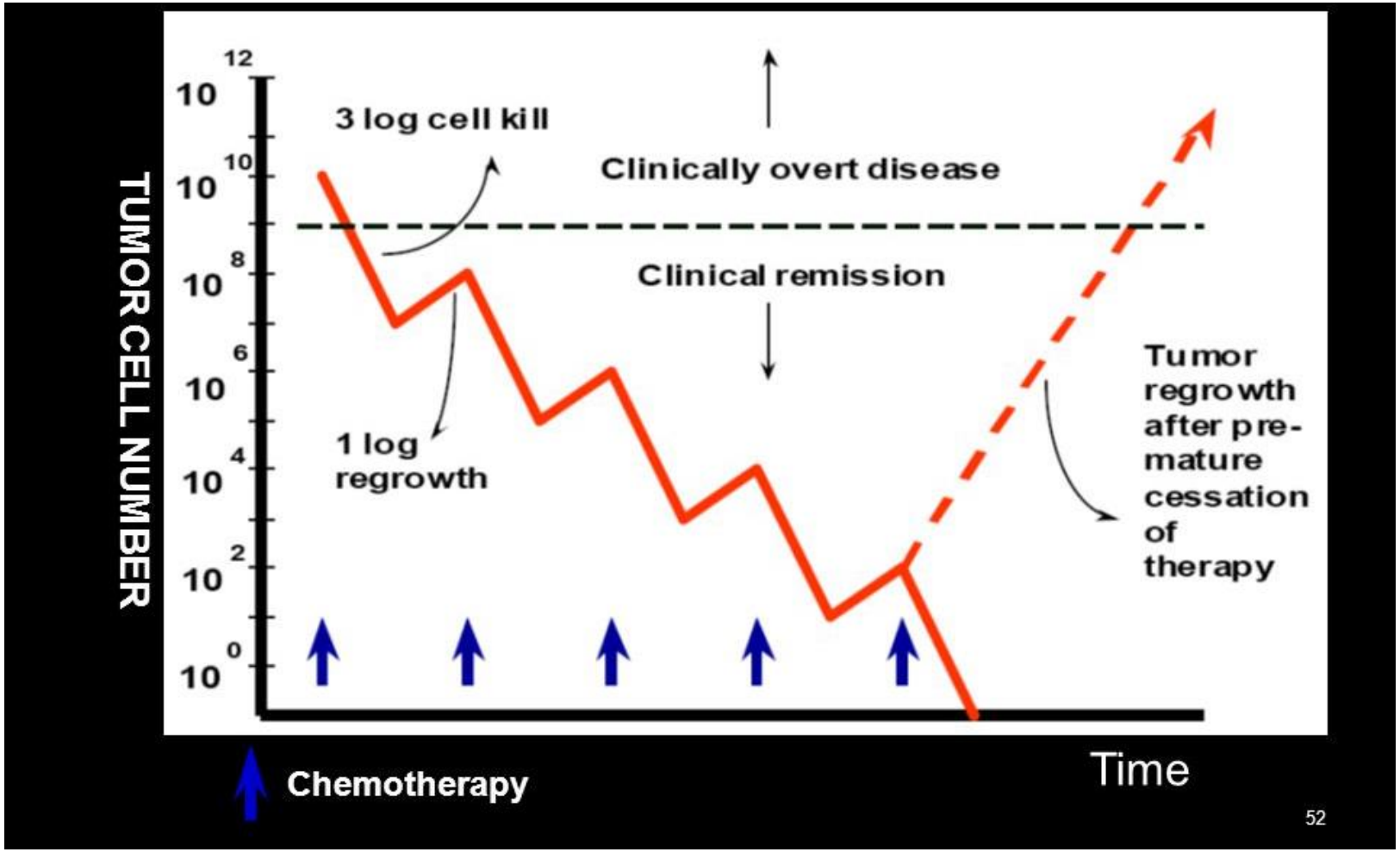
- 림프종
  - 비호지킨 림프종 (B세포 림프종, T세포 림프종)
  - 호지킨 림프종
- 다발 골수종
- 만성 골수성 백혈병 (CML)
- 급성 골수성 백혈병 (AML)

Reference:

항암치료 사이클 개념 (1)


Death
Symptoms
Diagnosis
Surgery
Number of cancer cells
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
Time

항암치료 사이클 개념 (2)


TUMOR CELL NUMBER
10^{12}
10^{10}
10^{8}
10^{6}
10^{4}
10^{2}
10^{0}
3 log cell kill
Clinically overt disease
Clinical remission
1 log regrowth
Tumor regrowth after pre-mature cessation of therapy
Chemotherapy
Time
52

림프종 치료 예(1)

- **54/F**
- **C/C: jaundice**

  -> obstructive jaundice

  -> biopsy: diffuse large B cell lymphoma

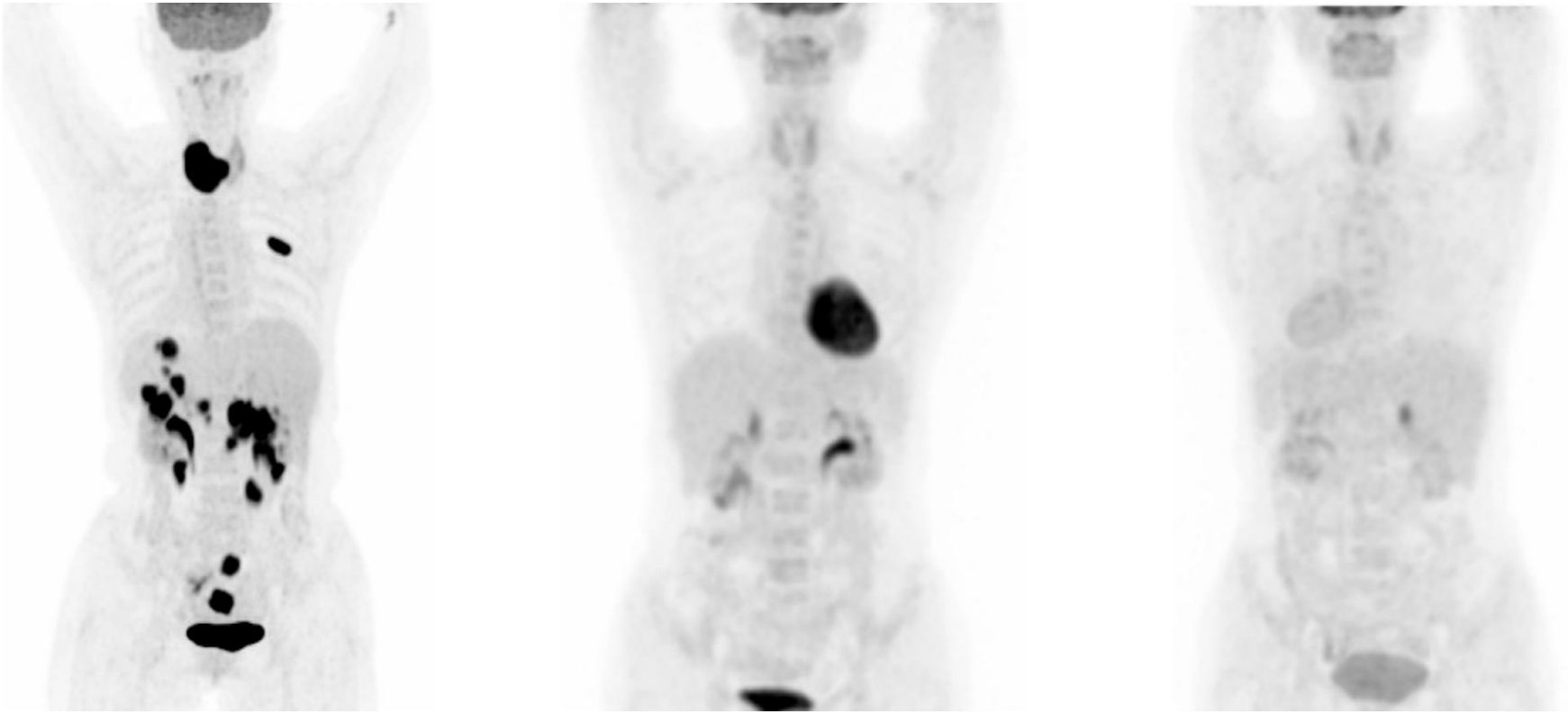
- **Staging work up**
  - **DLBCL 4EA pancreas(Bx.) duodenum(Bx.) stomach, small bowel, thyroid(Bx.) Rt. hemithorax**

- **Therapeutic plan**
  - **R-CHOP C6 followed by upfront ASCT**

Reference:

림프종 항암치료 예(1)

진단시 → R-CHOP C3 → R-CHOP C6

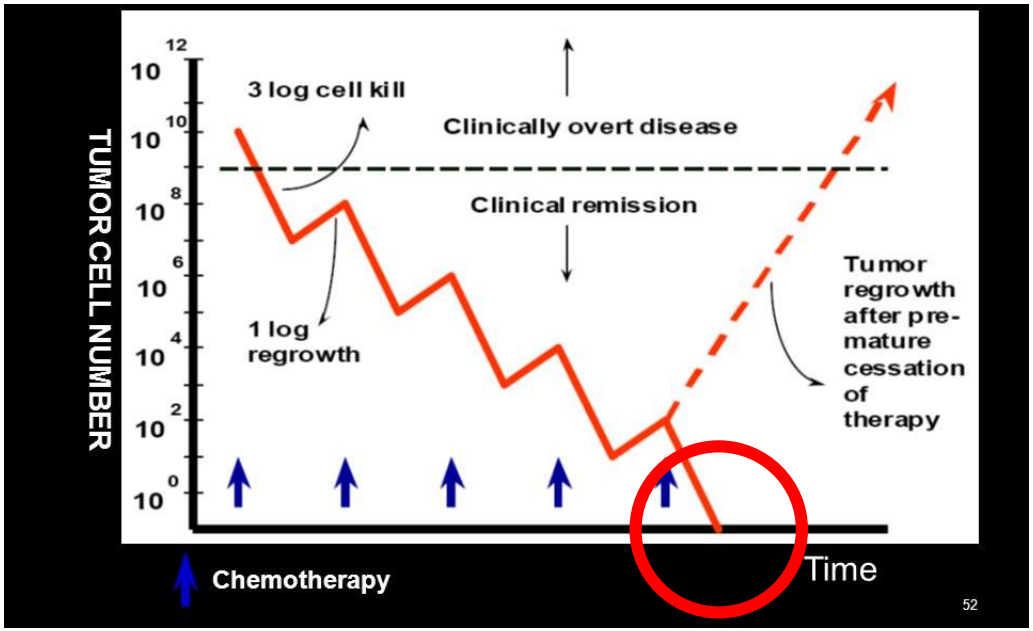


림프종 항암치료 예(1)

진단시 → R-CHOP C3 → R-CHOP C6

↓

고용량항암치료 및
자가조혈모세포이식

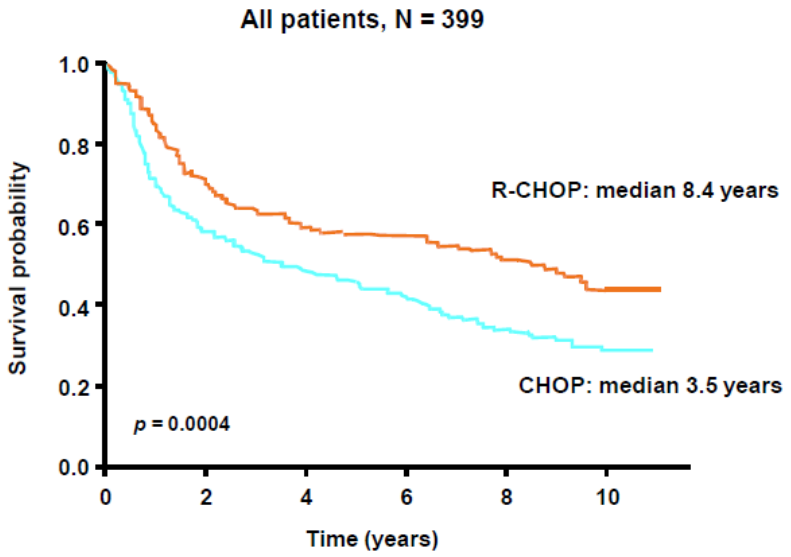


Rituximab in B cell lymphoma

◆ Rituximab

- Survival rates are significantly increased by the addition of rituximab to CHOP or a CHOP-like regimen

Diffuse large B cell lymphoma



Blood. 2010 Sep 23; 116(12): 2040–2045

Follicular lymphoma

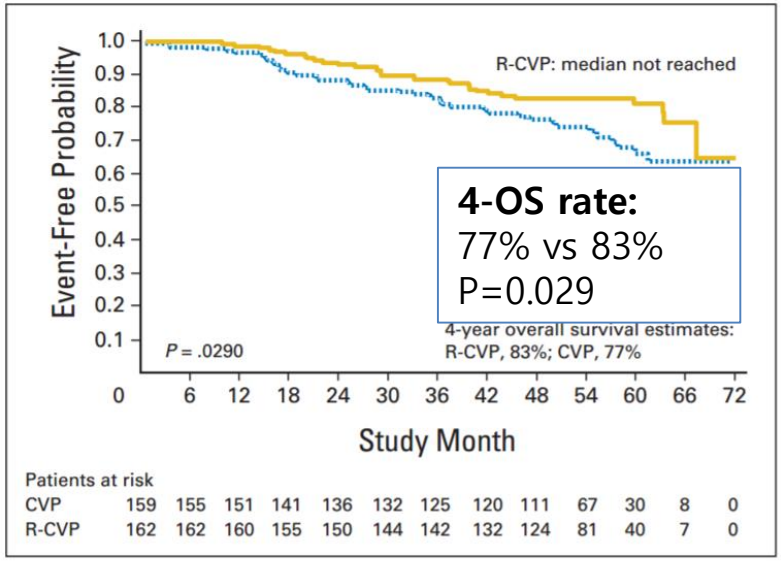
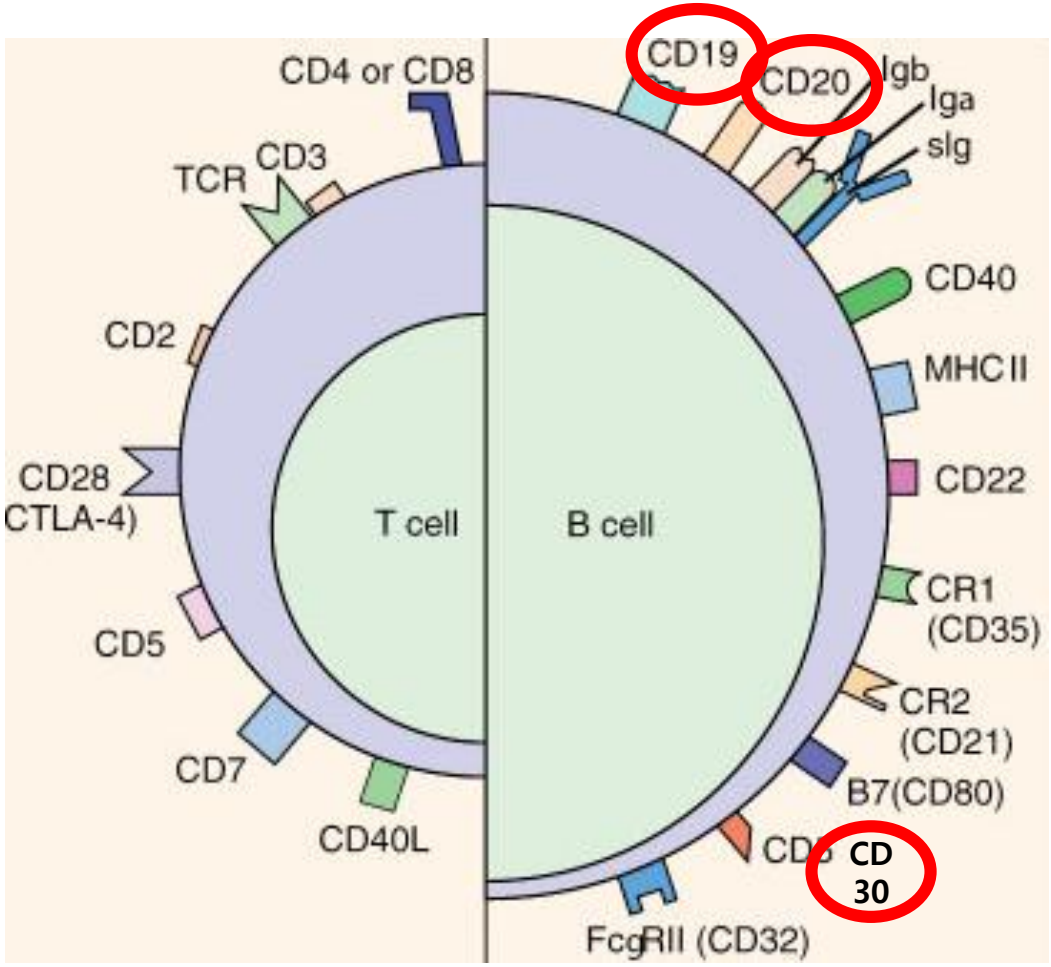


Fig 2. Overall survival in patients assigned to chemotherapy with cyclophosphamide, vincristine, and prednisone (CVP) or with CVP plus rituximab (R-CVP).

J Clin Oncol 26:4579–4586

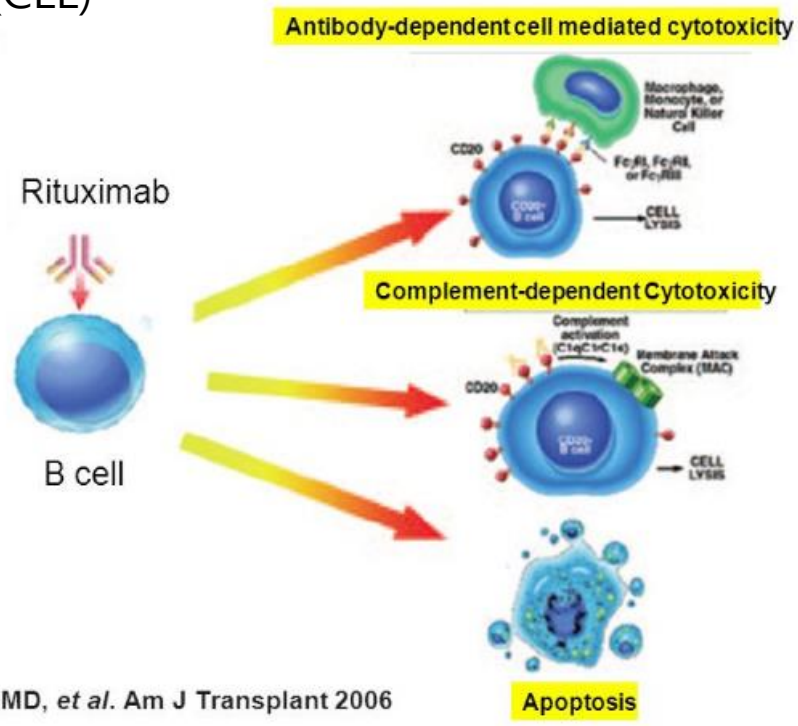
Cell surface markers on lymphoma cells



Rituximab: anti-CD20 monoclonal Ab

◆ Rituximab

- **A chimeric murine/human anti-CD20 monoclonal antibody**
- approved more than 15 years ago
- Rituximab has dramatically improved clinical outcomes in B cell NHL and chronic lymphocytic leukemia (CLL)

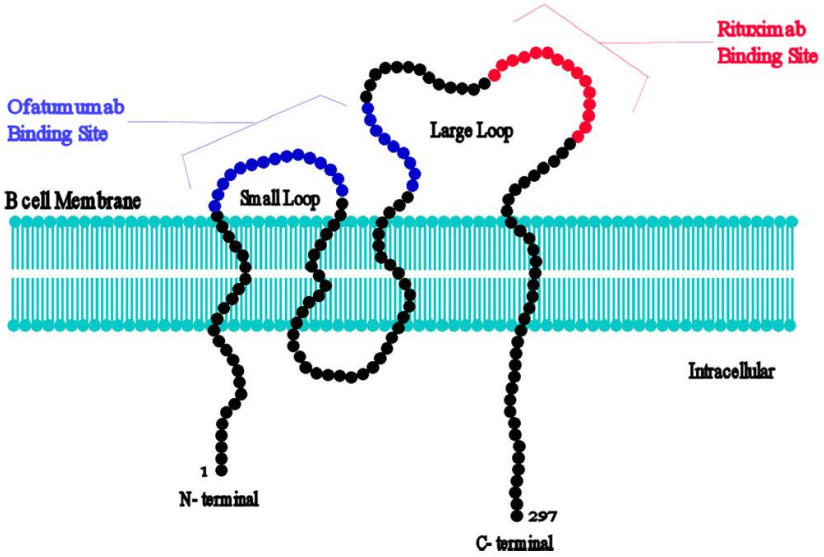


Pescovitz MD, *et al*. Am J Transplant 2006

Other anti-CD20 monoclonal Ab

Biosimilar
셀트리온
삼성바이오

- ❖ **Anti CD20- monoclonal Abs**
- ◆ **Ofatumumab**
- ◆ **Obinutuzumab**



CD 20 molecule

Journal of Hematology & Oncology 2012, 5:64

Route: subcutaneous!! instead of IV

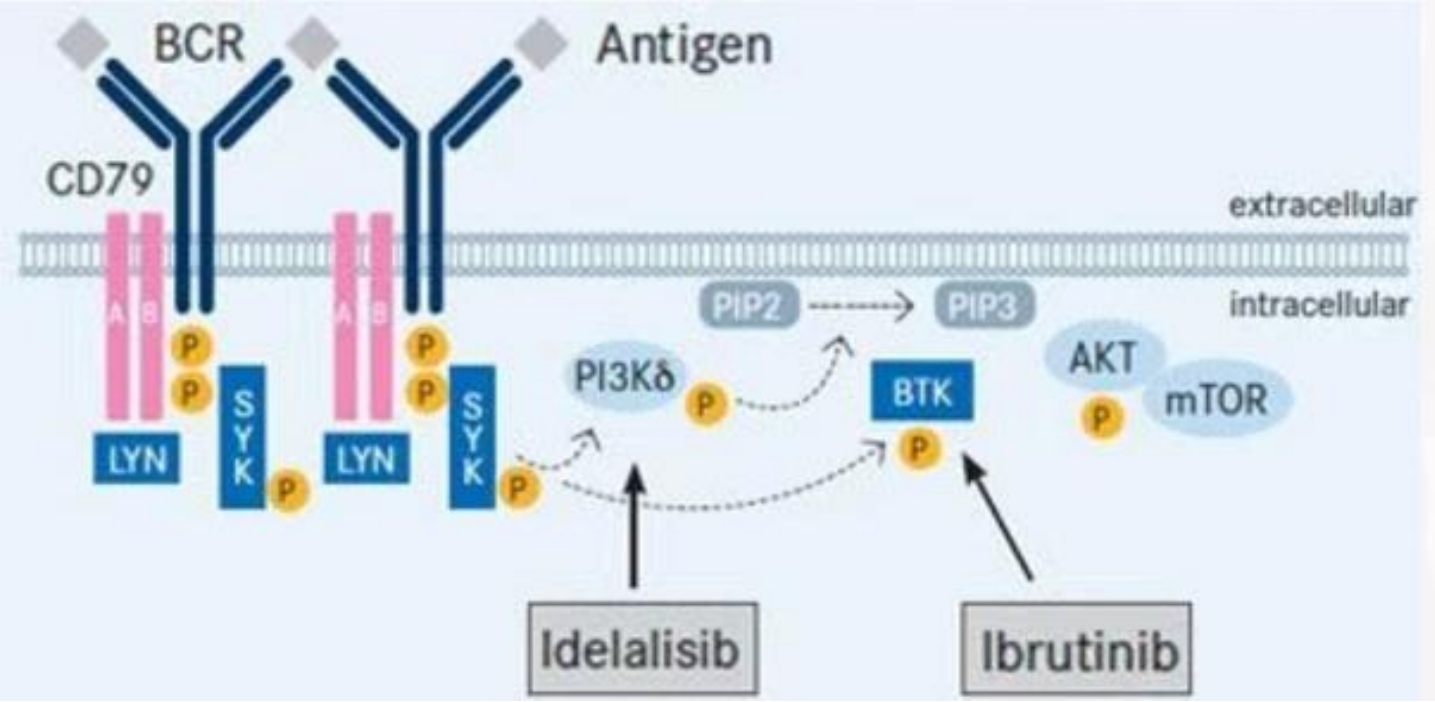
- **Rituximab: IV vs. SC formulation**

Factor	Formulation	
	Subcutaneous	Intravenous
Dosing	Fixed, no dose calculations required	IV bag preparation Dose calculations based on body surface area can be susceptible to error
Pharmacy preparation	Short prep time	Longer prep time, especially for doses >500 mg because multiple vials are required for preparation
Wastage	None	Leftovers in vial cannot be used more than 24 hours after preparation and rely on another patient being booked the same day
Administration	Approximately 5 minutes	90 Minutes
Chair time	Reduced by 64%–91% compared with IV time	—
Health care provider time	Reduced by 7–38 minutes per session compared with IV time	—

Reference: **D. MacDonald et al 2017 Curr Oncol**

Signaling pathway in B cell lymphoma

❖ B cell signaling inhibitor



- The B-cell–receptor signaling pathway plays a key role in the pathogenesis

B cell signaling inhibitors

◆ Ibrutinib

– first-in-class oral Bruton Tyrosine Kinase inhibitor

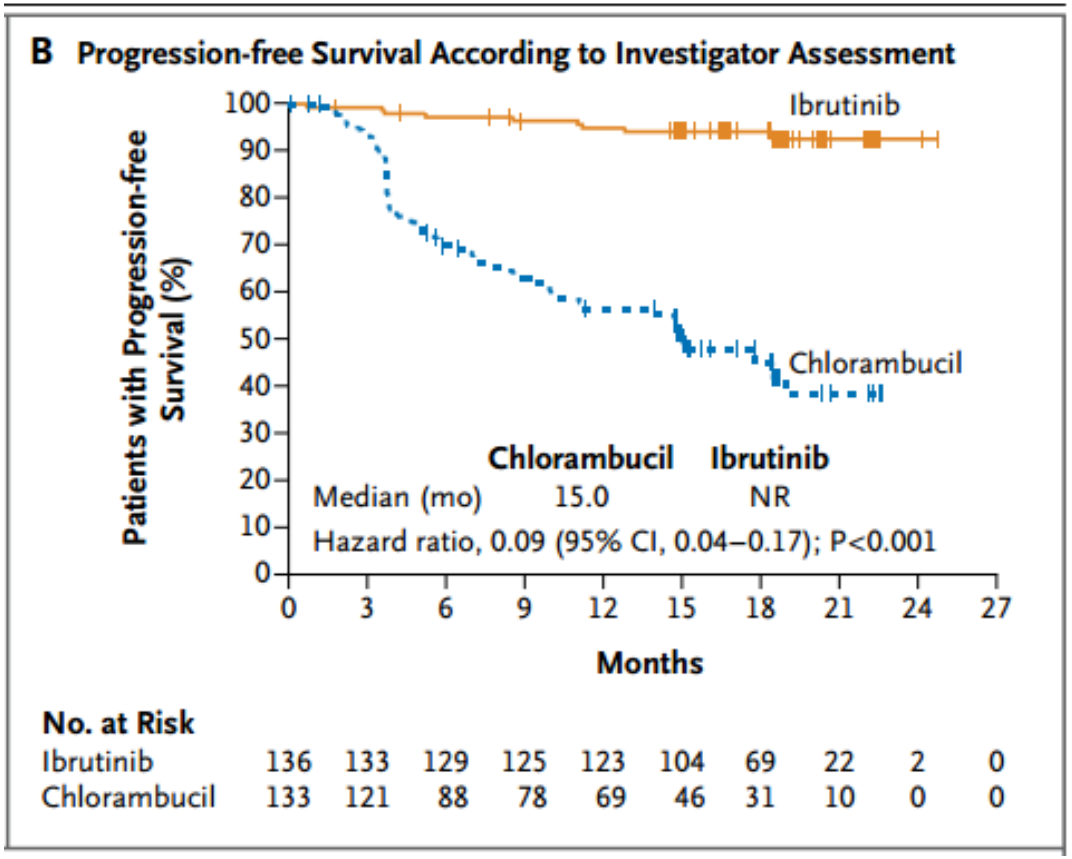
- FDA approved for previously treated CLL (2014), Waldenstrom macroglobulinemia, mantle cell lymphoma (2013)

◆ Idelalisib

- potent, oral, selective small-molecule inhibitor of PI3Kδ
- FDA approved for relapsed CLL (2014), follicular lymphoma and small lymphocytic lymphoma

Ibrutinib: BTK inhibitor

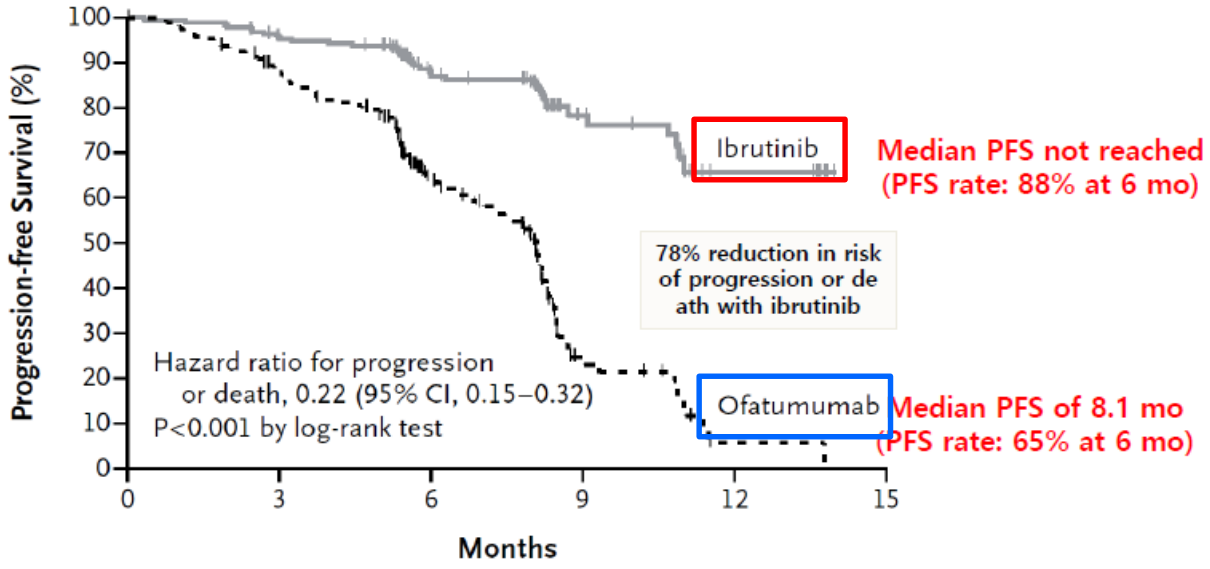
- 269 previously untreated CLL/SLL patients
- Ibrutinib or chlorambucil
- Median PFS;
  not reached vs. 15.0 months



N Engl J Med 2015; 373:2425-243

Ibrutinib: BTK inhibitor

- 391 previously ≥1 treated CLL/SLL patients
- Ibrutinib
  vs. IV ofatumumab
- Median PFS;
  not reached vs. 8.1 months



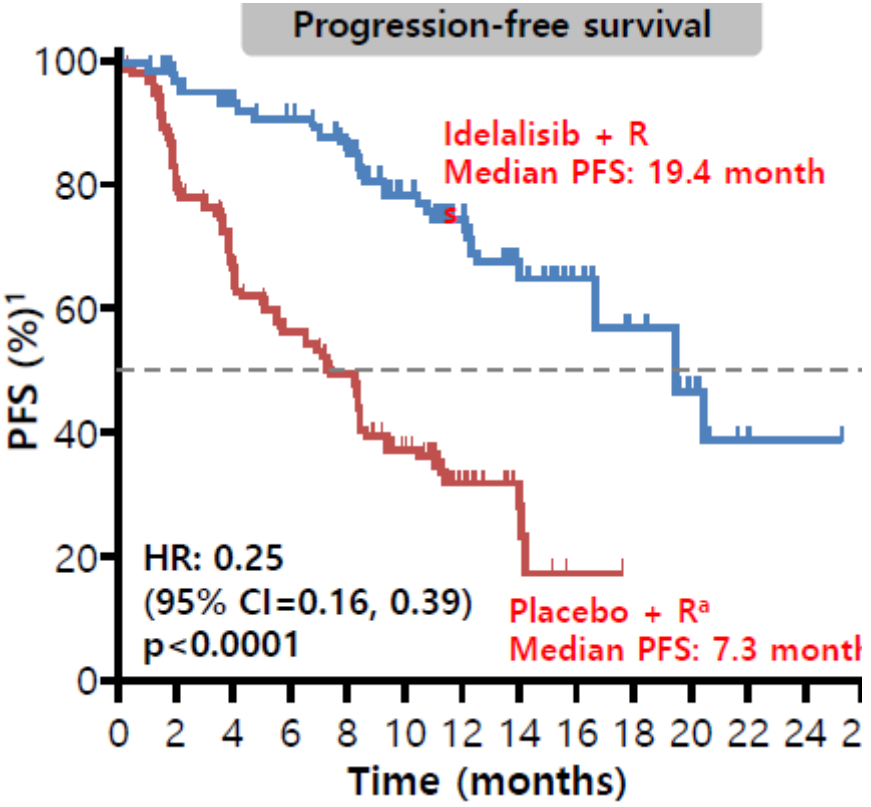
No. at Risk						
Ibrutinib	195	183	116	38	7	
Ofatumumab	196	161	83	15	1	0

- Median follow up 9.4 months
- The effect of ibrutinib on PFS was robust and observed across all subgroups examined

Byrd JC et al. N Engl J Med 2014; 371(3): 213-223

Idelalisib: PI3Kδ inhibitor

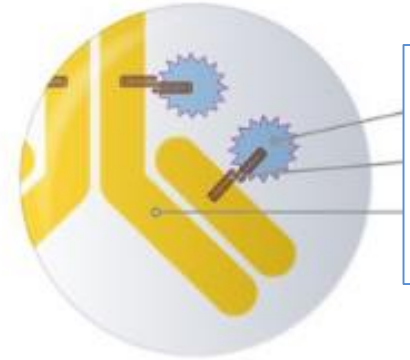
- N=220
- previously treated CLL patients
- **Idelalisib + Rituximab vs. placebo+ rituximab**
- **Response rate: 77% vs. 15%** (P<0.0001)



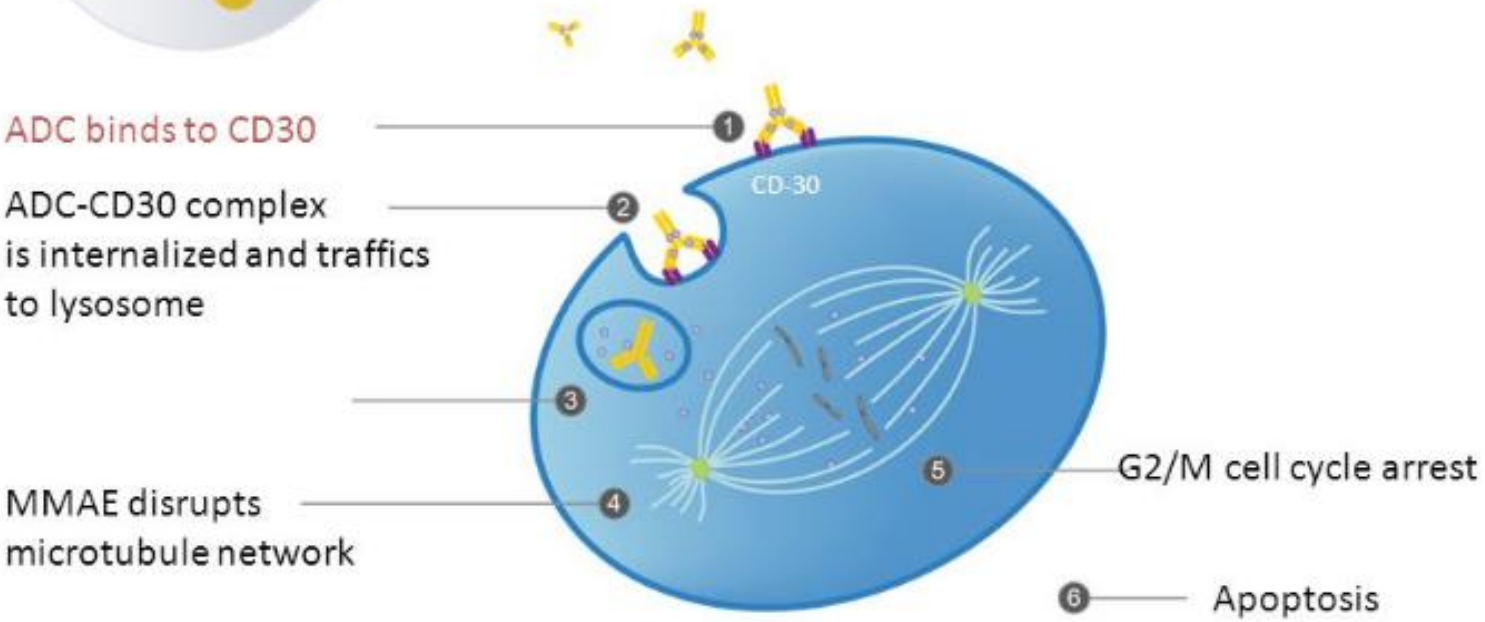
Barrientos JC, et al. ASCO 2015 (Abstract 8563)

Brentuximab:
Anti CD30 monoclonal antibody-drug conjugate

◆ Brentuximab vedotin



Anti CD30 monoclonal antibody-drug conjugate
-Monomethyl auristatin E (MMSE) , potent antitubulin agent



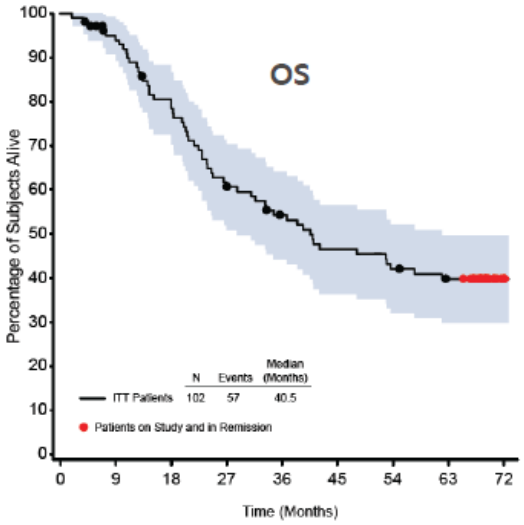
Brentuximab in Hodgkin lymphoma

◆ Brentuximab

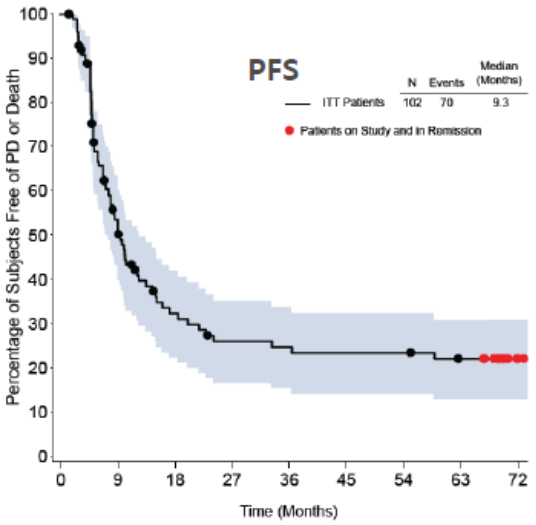
- Anti CD30 monoclonal antibody-drug conjugate

- **Relapsed or refractory CD30+ HL**
- **Prior ASCT**

ORR: 72%
CR rate: 33%



Median OS: 40.5 mos
(95% CI: 28.7, 61.9 [1.8–72.9+])
5-yr OS: 41%
(95% CI: 31%, 51%)



Median PFS: 9.3 mos
(95% CI: 7.1, 12.2)

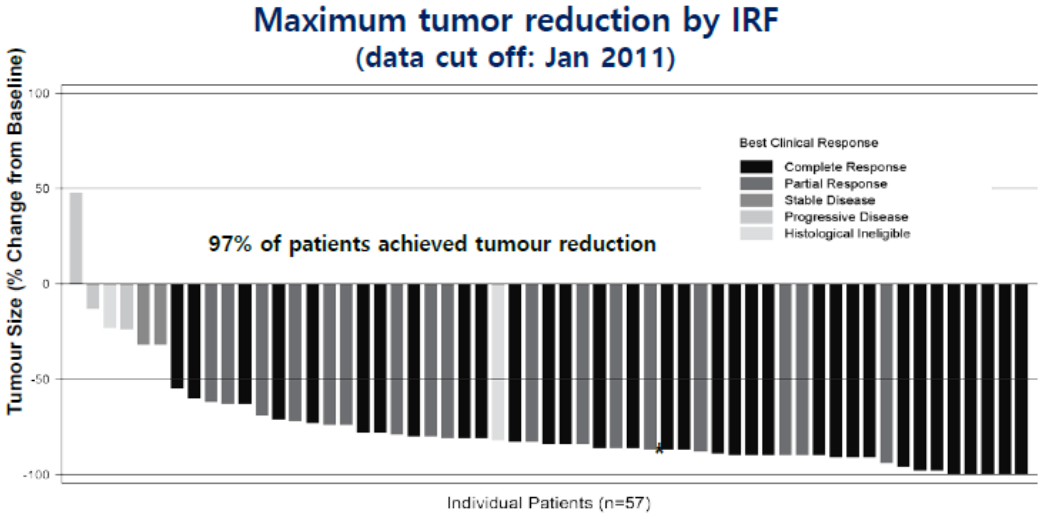
Chen R, et al. ASH 2015, Poster presentation from Abstract #2736
Previous publications: Younes A, et al. J Clin Oncol 2012;30:2183–9; Gopal AK, et al. Blood 2015;125:1236–43

Brentuximab in T cell lymphoma

◆ Brentuximab

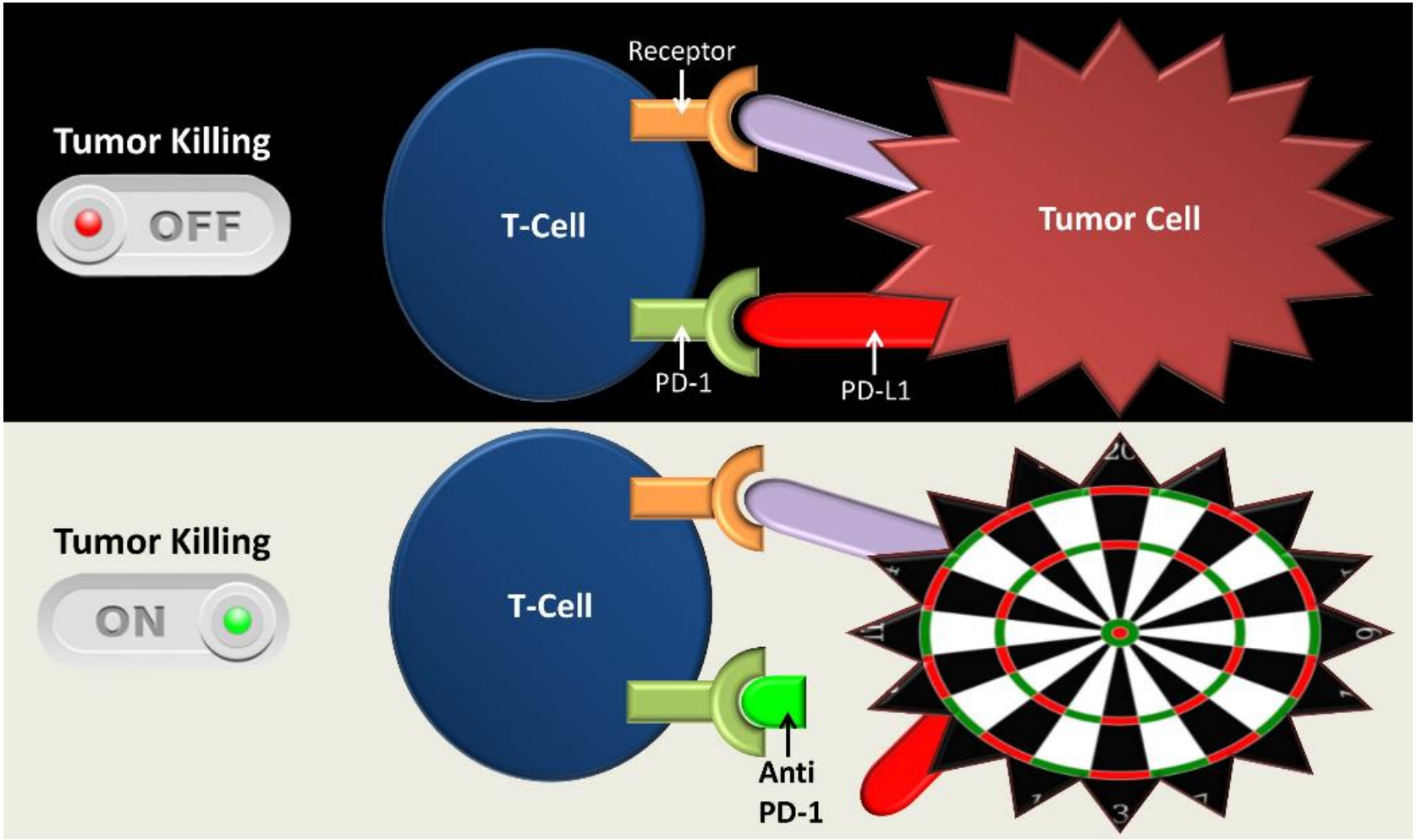
- Anti CD30 monoclonal antibody-drug conjugate

- **Relapsed or refractory anaplastic large cell lymphoma**
- **Brentuximab 1.8mg/kg iv q 3weeks**
- **Response rate: 86%**



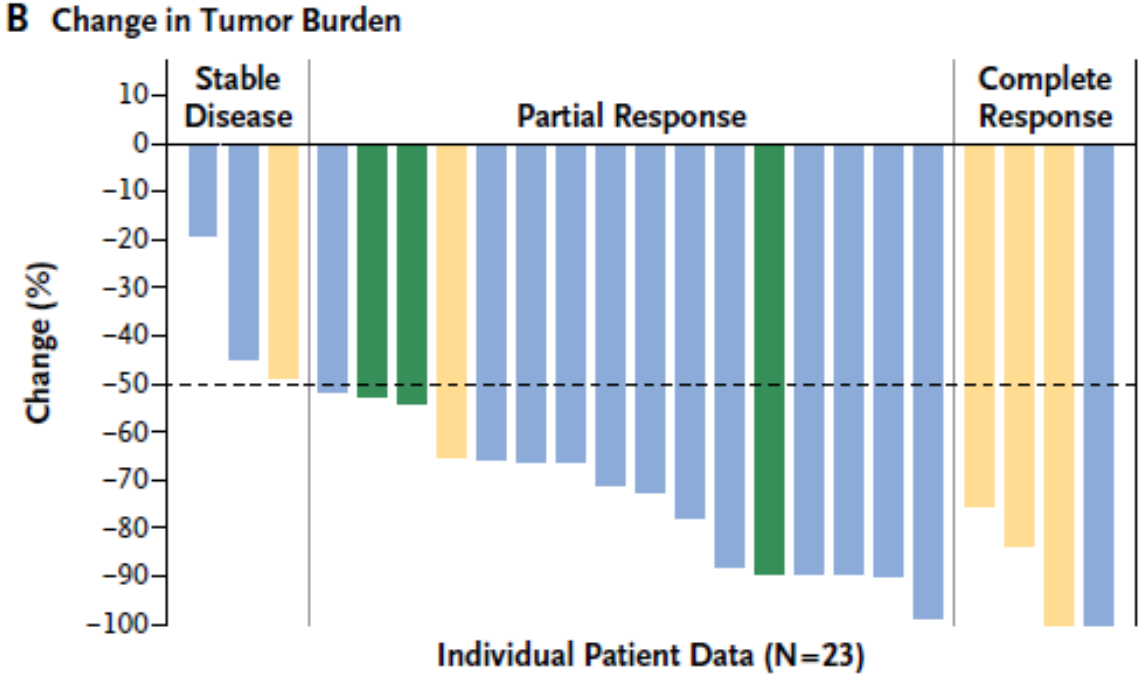
Pro B, et al. J Clin Oncol 2012; 30:2190–6.

PD-1/PD-L1 inhibitors



Nivolumab in Hodgkin lymphoma

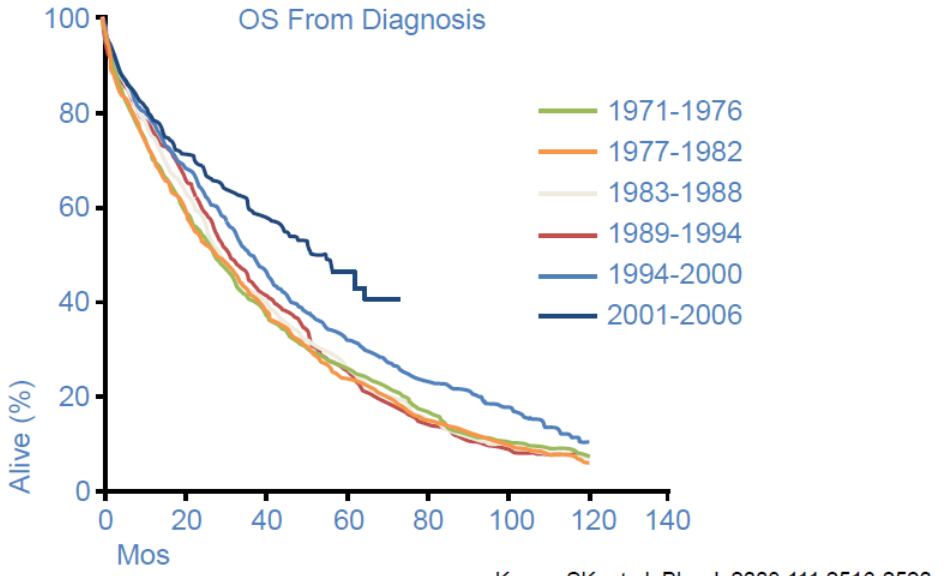
- Fully human immunoglobulin G4 monoclonal antibody
- **Targeting the programmed death-1 (PD-1)** immune checkpoint pathway
- Response rate in R/R hodgkin lymphoma: 87%



New England Journal of Medicine 372 (4):311-319

Multiple myeloma

Effect of Novel Agents on Outcome in Newly Diagnosed Myeloma

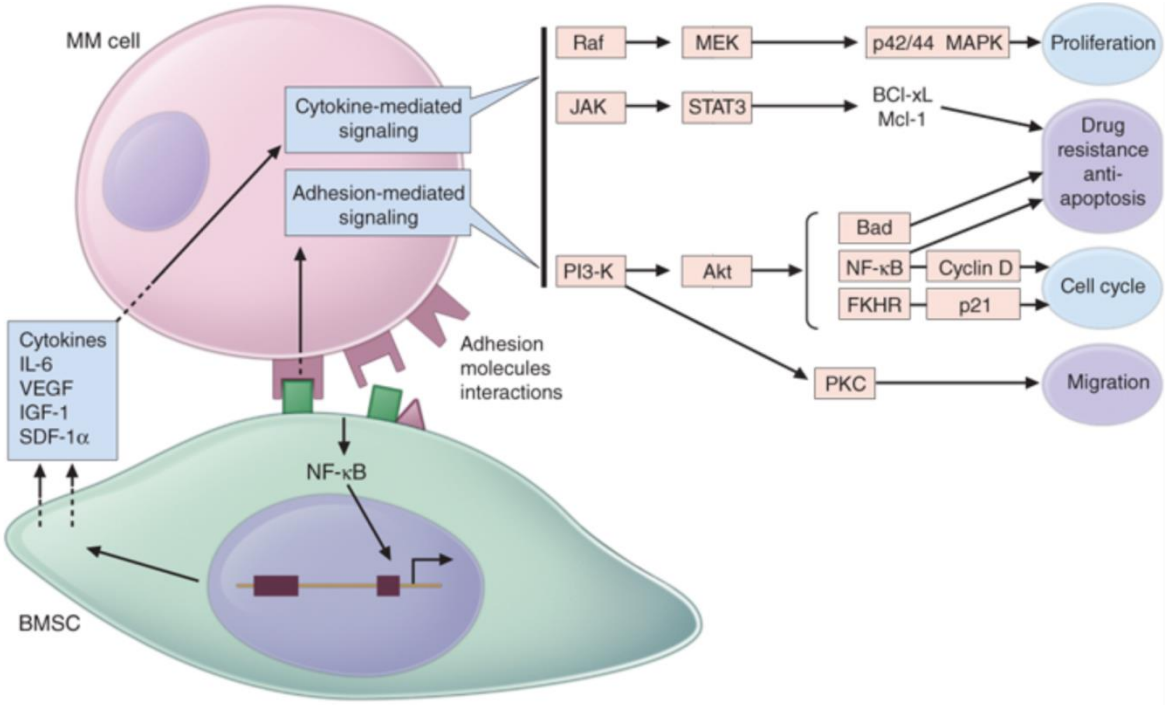


Kumar SK, et al. Blood. 2008;111:2516-2520..

Multiple myeloma cells

Multiple myeloma (MM) cells interact with bone marrow stromal cells (BMSCs) and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signaling as well as cytokine production.

This triggers cytokine-mediated signaling that provides growth, survival, and anti-apoptotic effects as well as development of drug resistance.



Anti-myeloma drugs

◆ Immune modulatory drugs

- co-stimulation of T cells and augmentation of NK and NKT cells

- **Thalidomide**
- **Lenalidomide**
- **Pomalidomide**

◆ Proteasome inhibitors

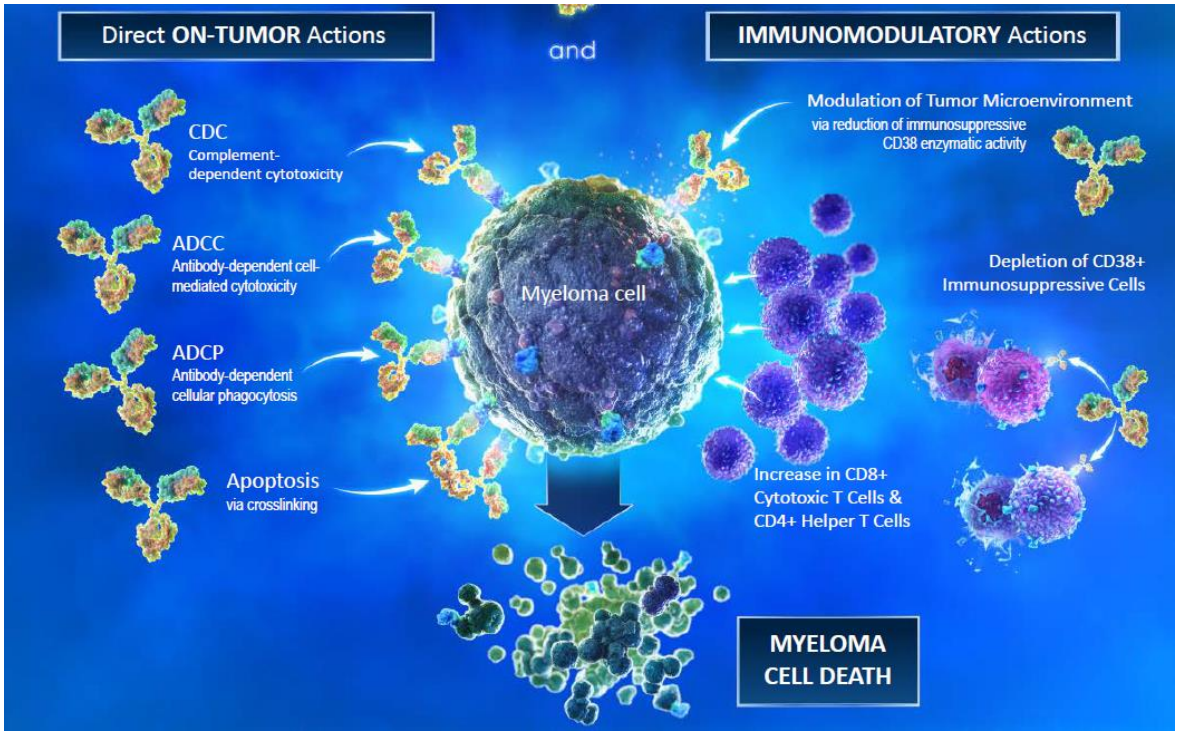
- **proteasome:** regulatory protein degradation → cell homeostasis

- **Bortezomib**
- **Carfilzomib**
- **Ixazomib**

Daratumumab in multiple myeloma

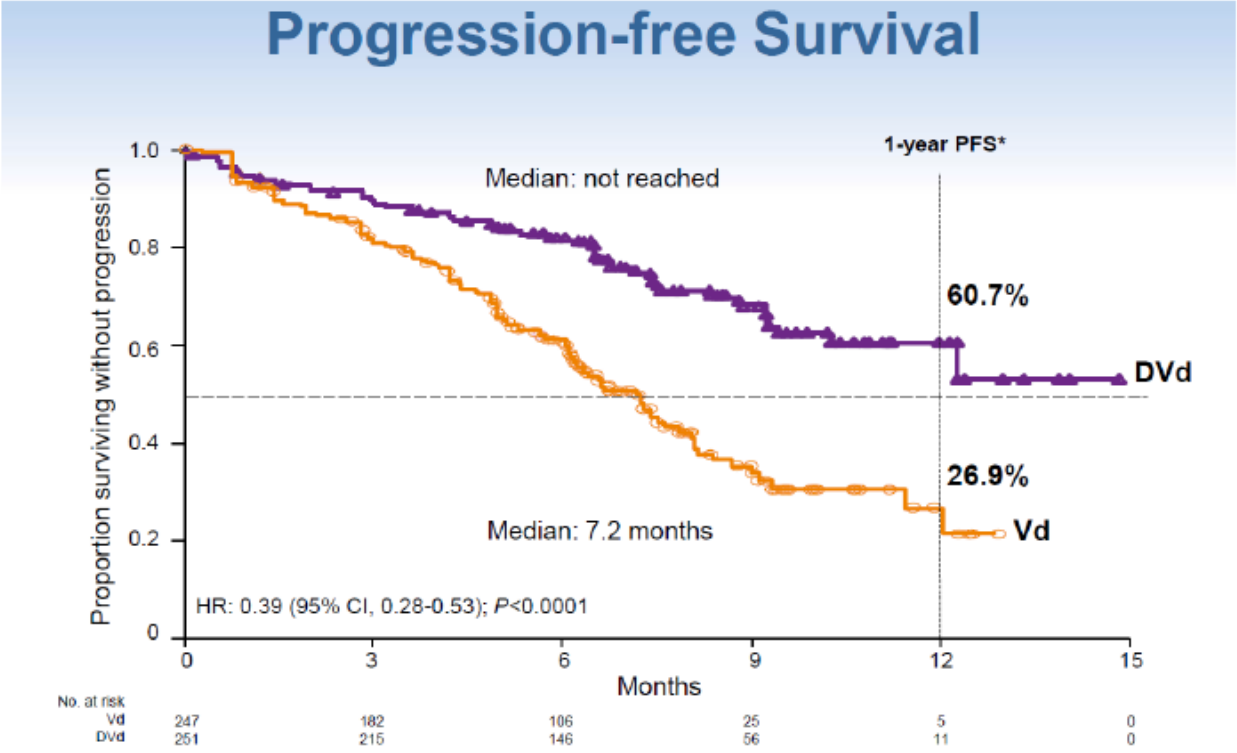
◆ Daratumumab

- Human anti CD38 monoclonal Ab
- CD38 is highly and uniformly expressed on myeloma cells
- CD38 is expressed at relatively low levels on normal lymphoid and myeloid cells



Daratumumab: Anti-CD38 monoclonal Ab

◆ Daratumumab



61% reduction in the risk of disease progression or death for DVd vs Vd

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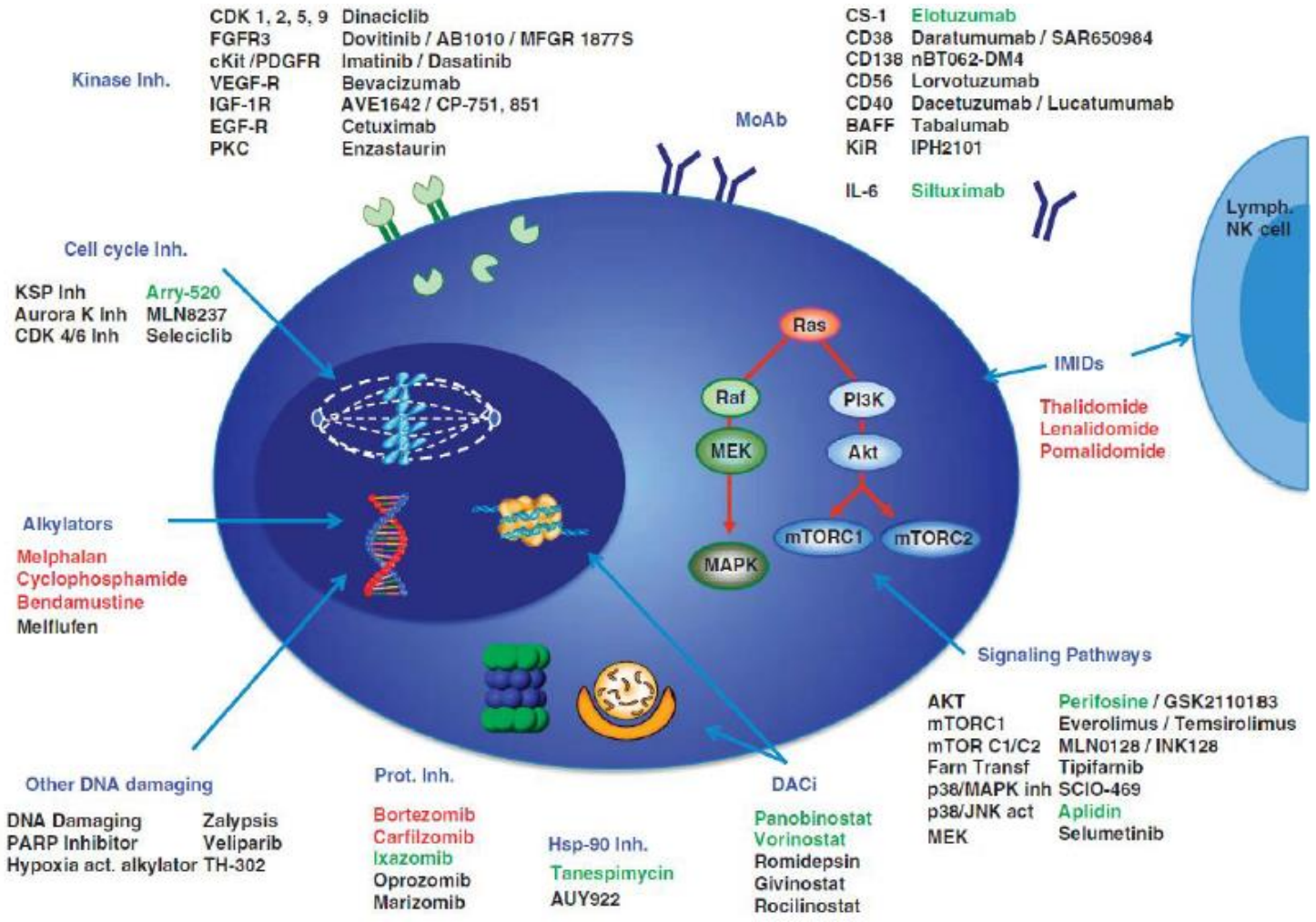
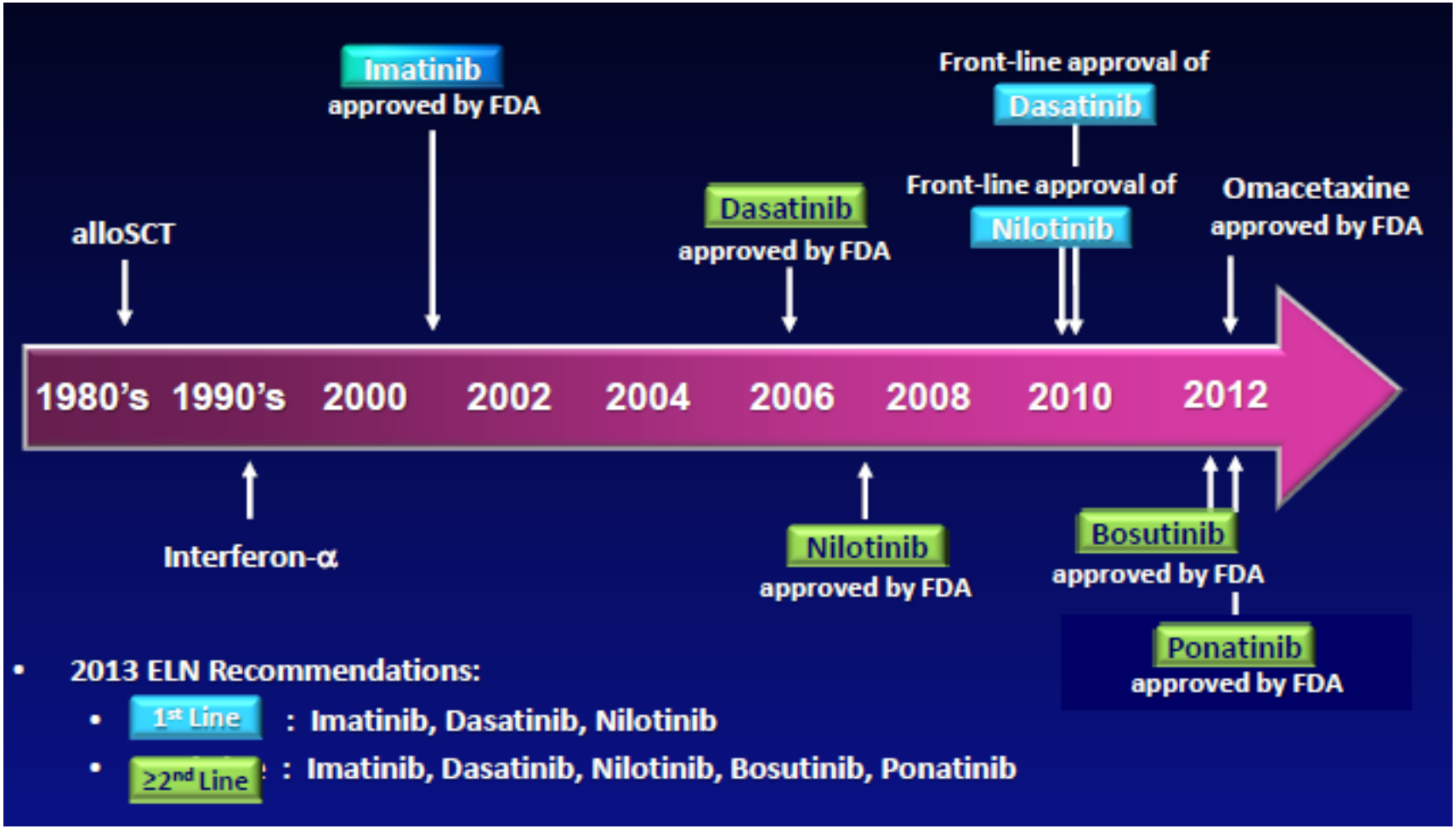
New England Journal of Medicine 375 (8):754-766.

Many targets for multiple myeloma



Ocio et al. Leukemia (2014) 28, 525–542

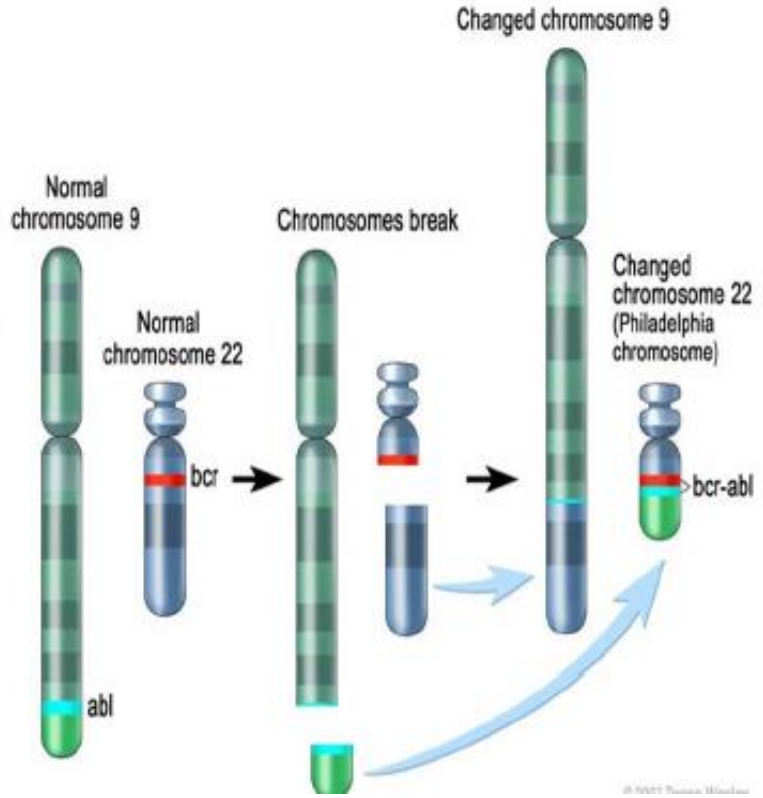
Chronic myeloid leukemia



CML drugs

◆ Imatinib mesylate (Gleevec®)

- a well-known first-generation molecular targeted drug
- **targets the BCR-ABL oncoprotein**
- blocking the binding site for ATP in the Abl kinase
- approved in 2001 in the US



CML drugs

- **Dasatinib, Nilotinib and Radotinib**
  - Second-generation drugs
  - Synthesized to overcome imatinib resistance due to the emergence of mutant clones of bcr-abl.
  - Effective against most mutant clones except T315I mutation

New England journal of medicine 348 (11):994-1004.
New England journal of medicine 362 (24):2260-2270.
New England journal of medicine 362 (24):2251-2259.

Acute myeloid leukemia

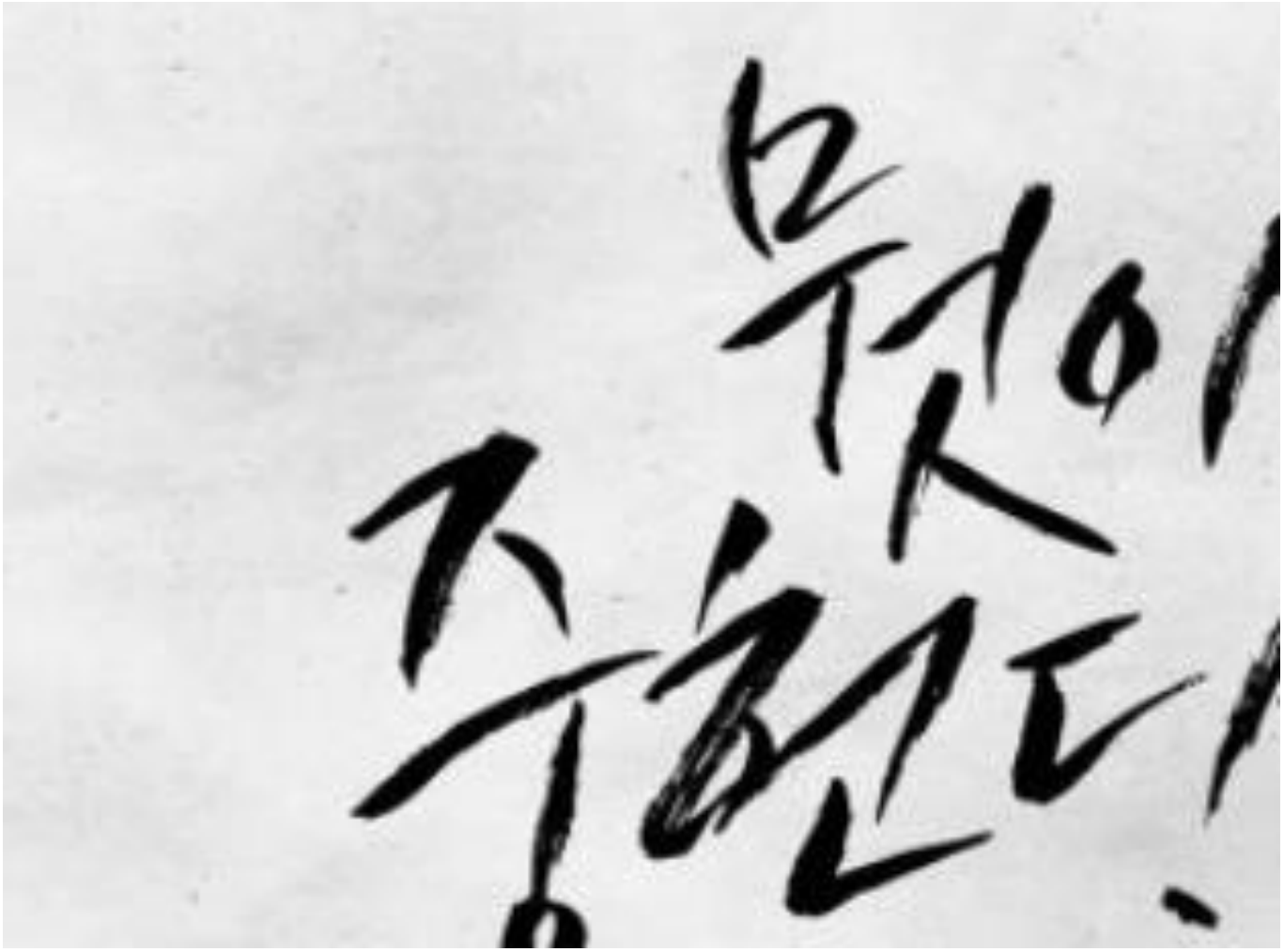
- IDH1/IDH2
- Kinase inhibitors
  - **FLT3inhibitors**
  - KIT inhibitors
  - JAK2 inhibitors
- Targeting the RAS pathway
  - Farnesyltransferase inhibition
  - MET-AKT pathway inhibition
- Chromatin modulators
  - DOT1L inhibition in MLL-rearranged AML
  - EZH2 inhibitors
  - BET inhibitors
  - HDAC inhibitors

New Combination Therapy Approved for Acute Myeloid Leukemia in Adults

MONDAY, MAY 8, 2017

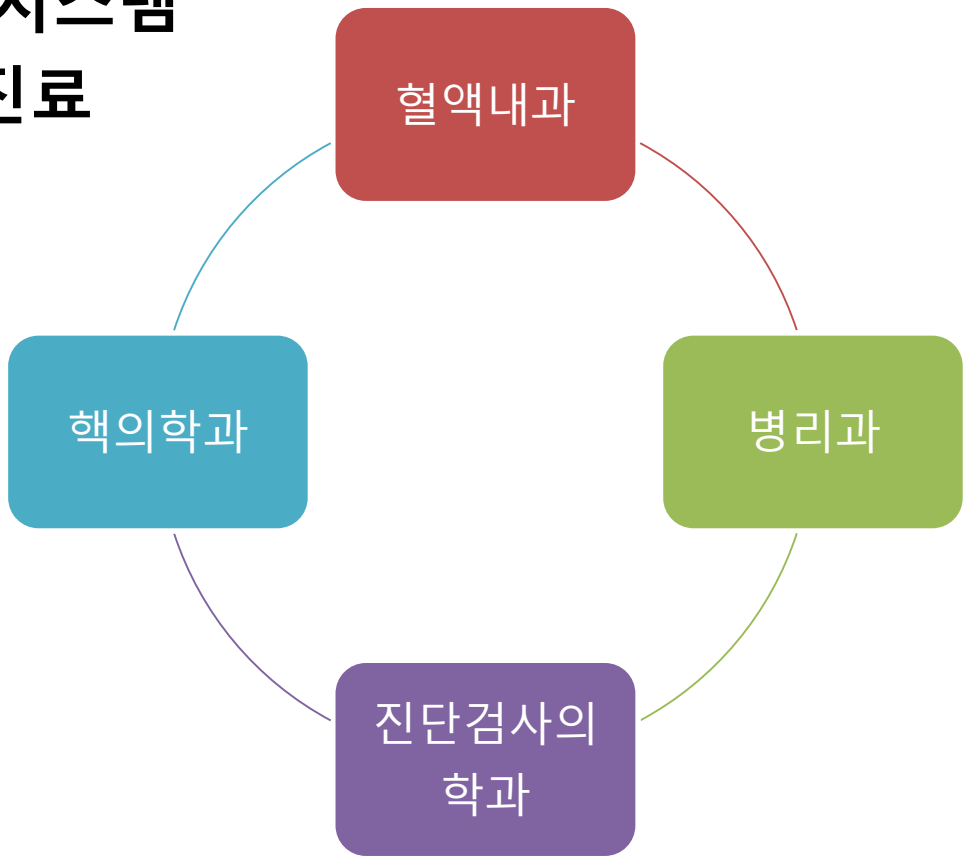
The U.S. Food and Drug Administration (FDA) approved midostaurin in combination with chemotherapy for the treatment of adults with newly diagnosed *FLT3*-mutated acute myeloid leukemia (AML). Midostaurin is the first FDA-approved targeted therapy for AML.

American health & drug benefits 9 (Spec Issue):1-21



혈액암 치료

- **신속한 검사 및 진단**
- **유기적 팀 시스템**
- **외래 통합진료**



Reference:

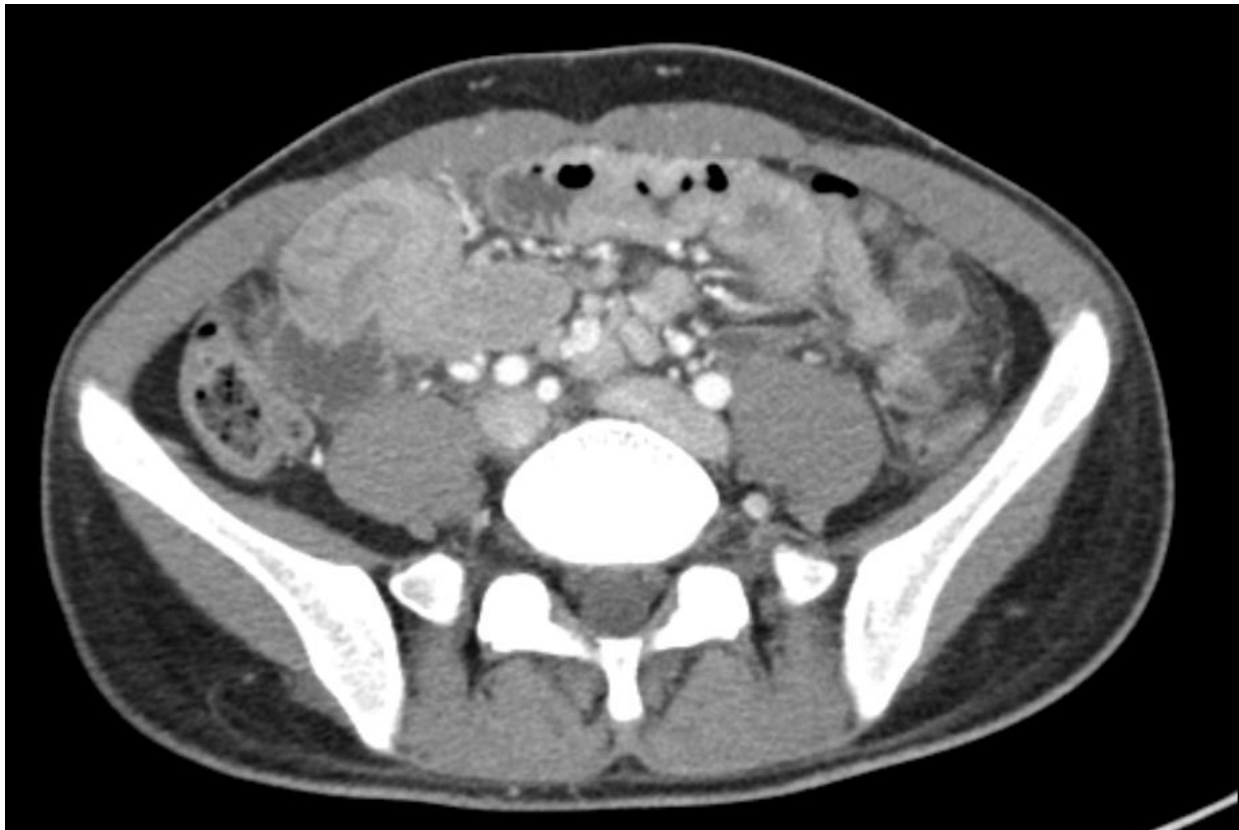
다발골수종 신속진단

- **빈혈 및 요통으로 외래 내원**
- **당일 오후 입원**
  -> 당일 골수검사, 전기영동 검사, 영상검사 진행
- **익일 혈액암 진단 상담후 항암치료 시작!**

Reference:

림프종 신속진단 예

- **19/M**
- **C/C: abdominal pain, vomiting, weight loss (7kg)**
- **APCT: multiple small bowel intususceptions with generalized lymphadenopathy**



림프종 신속진단 예

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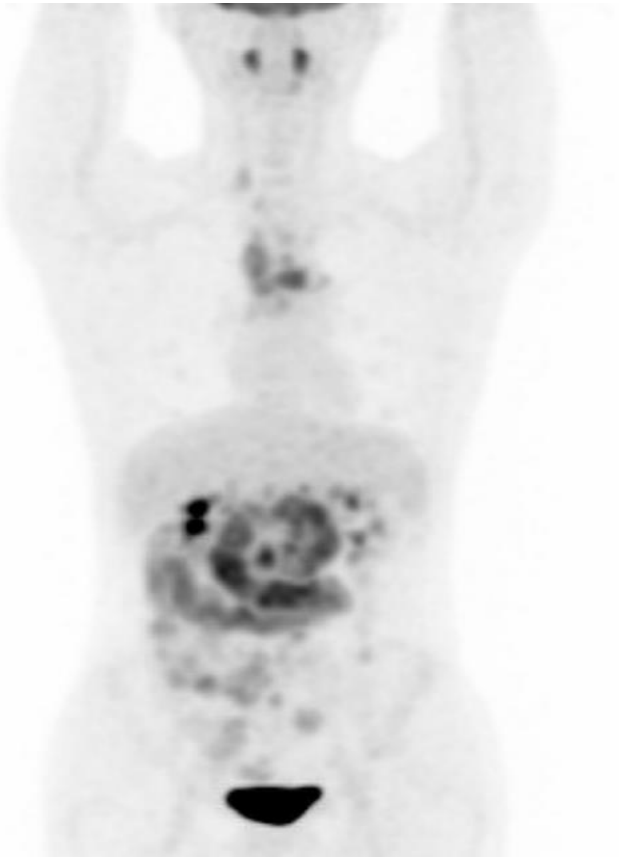
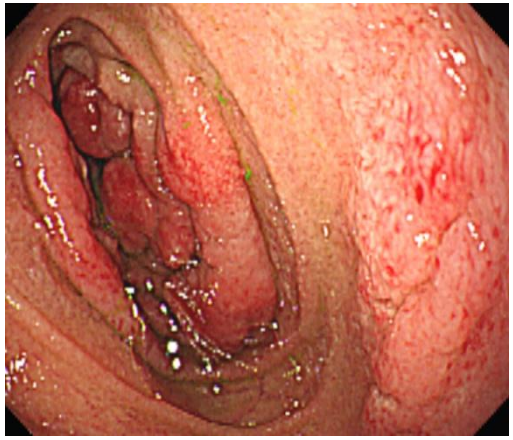
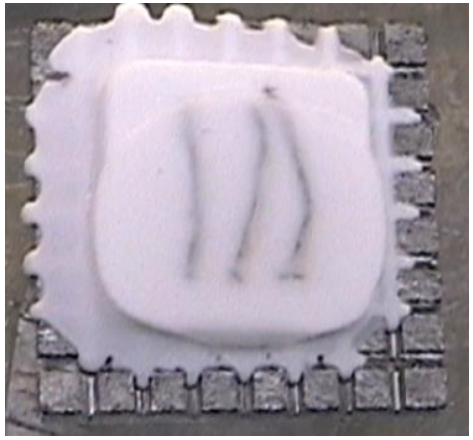


림프종 신속진단 예

- **Gastroscopy**
  - **Duodenal 3rd portion mass**
  - **EGD Biopsy -> frozen section!!**



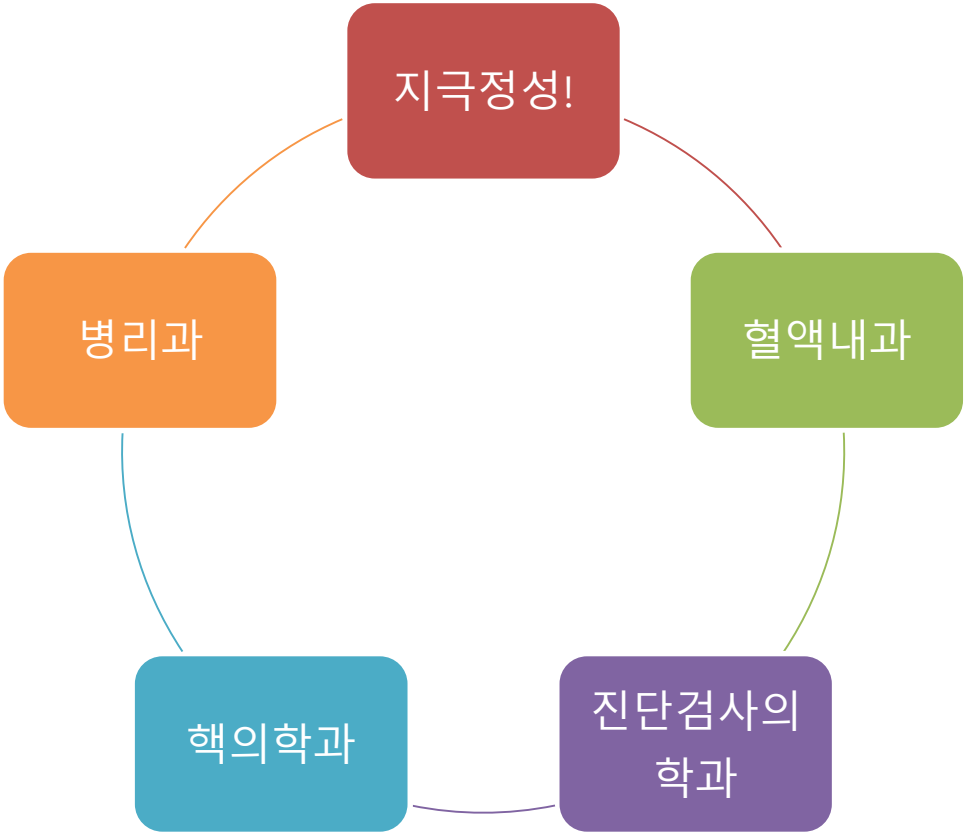


  - **조직검사 당일 림프종 가능성 높음을 진단!!**

Reference:

림프종 신속진단 예

- **당일 Steroid 사용후 증상 호전**
  - **수술적 조치 가능성을 사전 예방!**
  - **증상 조기 호전으로 적절한 항암제 사용 원활**



Summary

- Principle of Chemotherapy cycle
- Target agents in hematologic malignancies
  - Monoclonal antibodies
  - Immune check point inhibitors
  - Signaling pathway inhibitors
- Multidisciplinary & Rapid approach is essential for hematologic malignancies

Reference:

울산대학교병원
ULSAN UNIVERSITY HOSPITAL

숨은 혈액암 찾기

Contents

a. Monoclonal Gammopathy of Undetermined Significance

(MGUS, 의미 불명 단클론 감마병증)

b. Monoclonal B-cell lymphocytosis

(MBL, 단클론성 B 림프구 증식증)

c. Clonal hematopoiesis of indeterminate potential

(CHIP, 클론성 조혈증)

Case 1: M/70 김 O O

C/C 가려움증과 빈혈

S "온몸이 가려워요"
"부항을 자주 했어요"

O 2019.7.9 CBC (6.6-10300-371k) MCV 77.4 MCHC 28.8
TP/abl 7.1/3.8 BUN/Cr 20.3/0.99
Ca 9.3 mg/dl
Iron/TIBC 11/493 Ferritin 10.3 ng/ml
VtB12 284pg/ml Folate 3.6 ng/ml

판독소견:

1) 백혈구: 백혈구수 증가; 미성숙백혈구 보이지 않음
2) 적혈구: 적혈구수 감소; microcytic hypochromic; fragmented RBC(1.0/HPF)
3) 혈소판: 혈소판수 정상; 특이한 형태변이 보이지 않음

추정진단:

1) r/o iron deficiency anemia

추천소견:

1) PBS F/U with reticulocyte

Case 1: M/70 김 O O

Assessment

 # Iron deficiency anemia

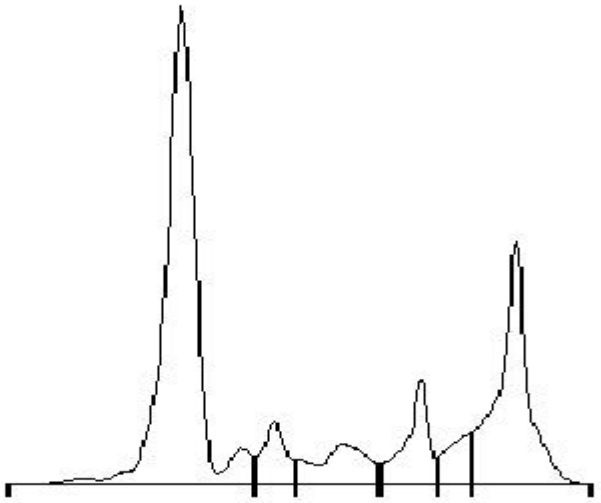
#

#

Plan

1. **feroba 1T bid**
2. **EGD/CFS, tumor marker**
3. **MM screening lab**

Case 1: M/70 김 O O



Fractions	%	g/dl	Ref.%	Ref.g/dl
Albumin	**51.3**	**3.80**	55.8 - 66.1	4.02 - 4.76
Alpha 1	**5.0**	**0.37**	2.9 - 4.9	0.21 - 0.35
Alpha 2	**7.1**	**0.53**	7.1 - 11.8	0.51 - 0.85
Beta 1	**8.2**	**0.61**	4.7 - 7.2	0.34 - 0.52
Beta 2	**4.4**	**0.33**	3.2 - 6.5	0.23 - 0.47
Gamma	**24.0**	**1.78**	11.1 - 18.1	0.80 - 1.35
Total	**100**	**7.42**		6.40 - 8.30

A/G 1.05

[Comments]

Monoclonal peak at gamma-globulin (1.45 g/dL)

C/W Monoclonal gammopathy

Rec> serum IFE, urine EP/IFE

Reference:

Case 1: M/70 김 O O

2019.7.9 CBC (6.6-10300-371k)

2019.8.6 CBC (12.6-9390-254k)

Serum PEP : 1.45g/dL

Serum Kappa 50.33 (3.3-19.4 mg/L)

Serum Lambda 29.45 (5.71-26.3 mg/L)

sFLC ratio:1.71 (<0.26 or >1.65)

2019.8.20 CBC (13.4-8220-272k)

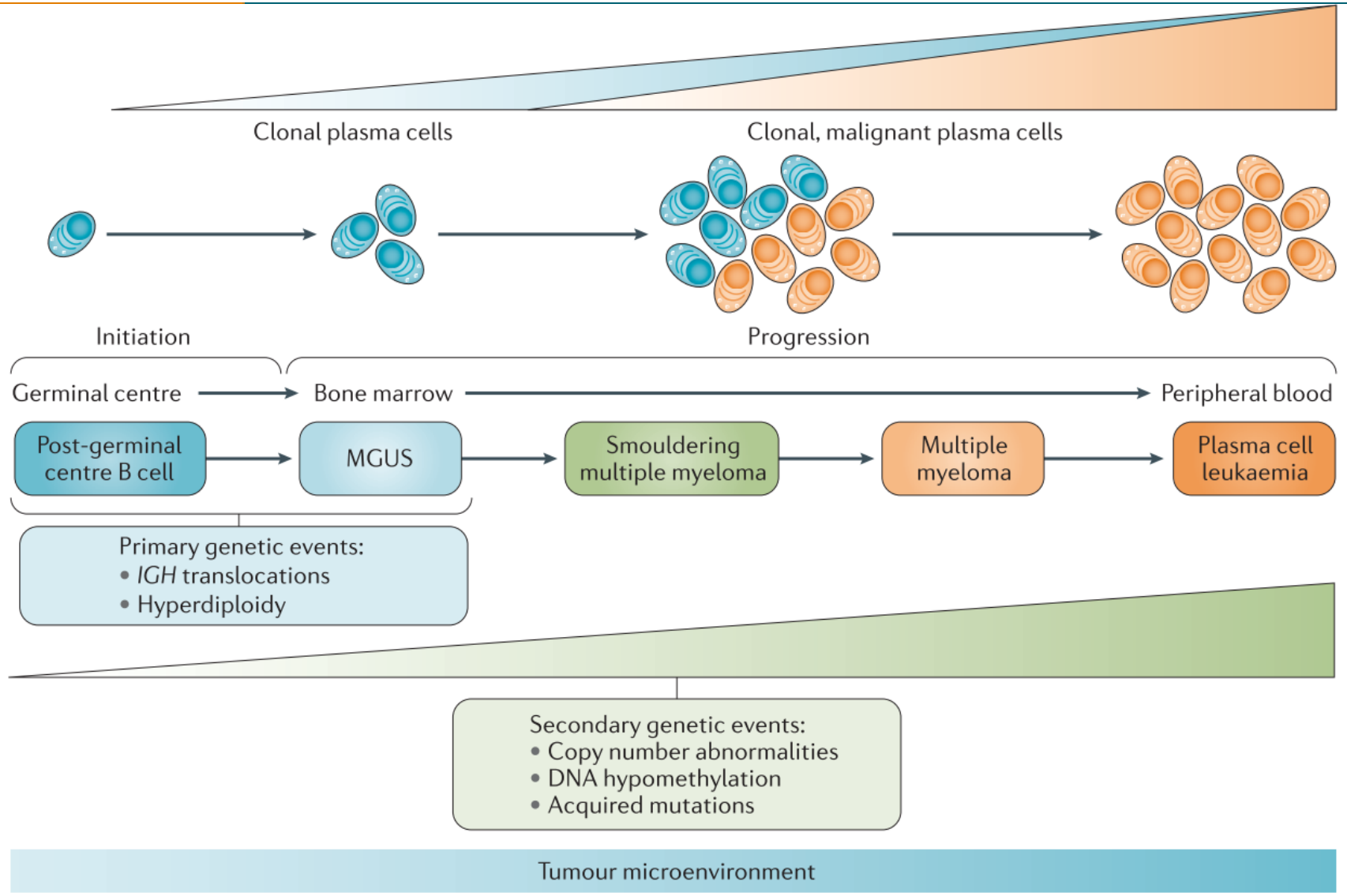
Urine PEP : mixed proteinuria

Serum Immuno fixation E.P: IgG/Kappa

Serum FLC: Kappa/Lambda 28.45/22.93

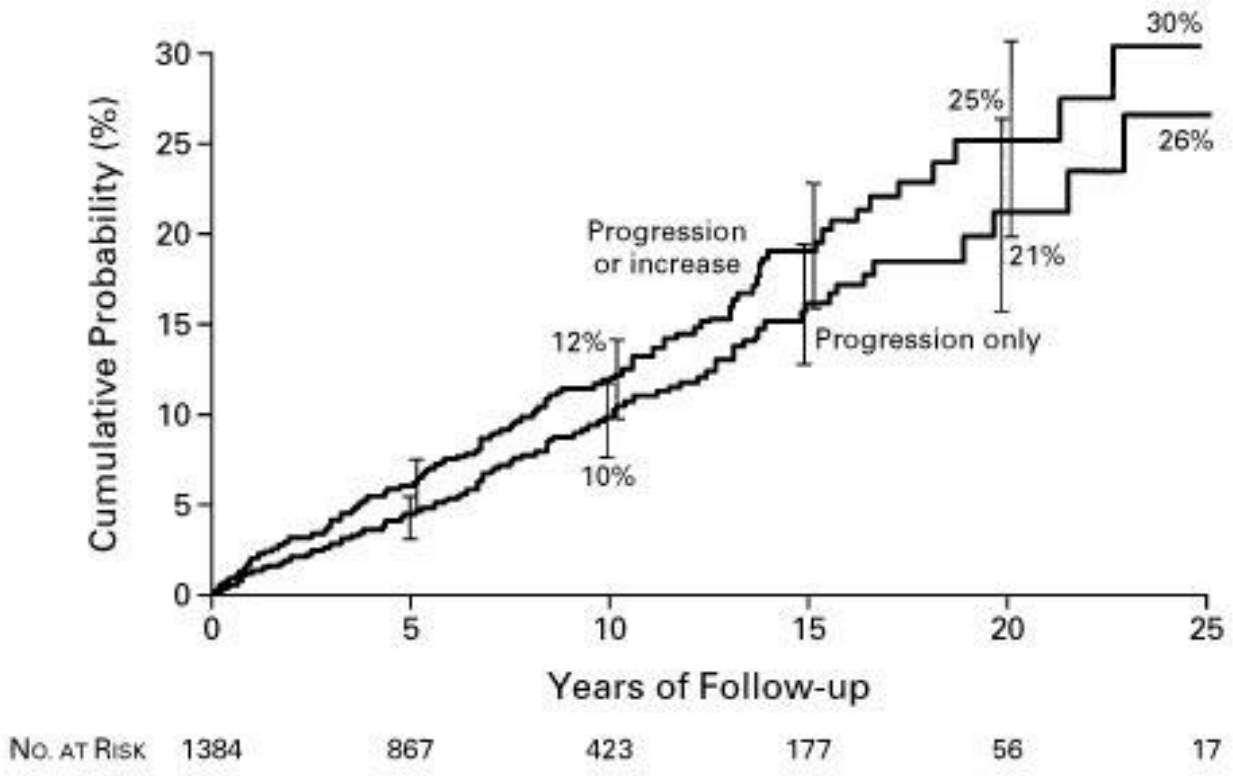
sFLC ratio: 1.24

Development of Multiple Myeloma



Reference: Kumar SK et al. Nat Rev dis Primers : 2017;3:17046

MGUS to Plasma cell disorder



N Engl J Med 2002; 346:564-569

Reference:

Criteria for diagnosis and risk of progression in MGUS

MGUS

Subtype of MGUS	Diagnostic criteria	Risk of progression	Pattern of progression
IgM MGUS	All 3 criteria must be met: • Serum IgM monoclonal protein <3 gm/dL • Bone marrow lymphoplasmacytic infiltration <10%* • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	1% per year	Waldenström macroglobulinemia, AL amyloidosis; rarely IgM multiple myeloma
Non-IgM MGUS	All 3 criteria must be met: • Serum monoclonal protein (non-IgM type) <3 gm/dL • Clonal bone marrow plasma cells <10%* • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	0.5% per year	Multiple myeloma, solitary plasmacytoma, AL amyloidosis
Light-chain MGUS	All criteria must be met: • Abnormal FLC ratio (<0.26 or >1.65) • Increased level of involved light chain (increased κ FLC in patients with FLC ratio >1.65 and increased λ FLC in patients with FLC ratio <0.26) • No immunoglobulin heavy-chain expression on immunofixation • Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells <10%* • Urinary monoclonal protein <500 mg per 24 h	0.3% per year	Light-chain multiple myeloma and AL amyloidosis

Reference: *Blood* (2018) 131 (2): 163–173.

Case 1: M/70 김 O O

Assessment

 # Iron deficiency anemia

 # r/o MGUS

Plan

1. MM w/u (BM study & image)

Case 1: M/70 김 O O

< Clinical Information >

Reson for request : Monoclonal gammopathy, IgG kappa type,MUGS, W/U.

< Differential Count >

Total cell count:100 M:E ratio: 1.02 **Aspirates** Rt. **Biopsy** Rt.

검사코드	결과		검사코드	결과		검사코드	결과	
Myeloblast	0.5	%	Pronormoblast	1.0	%	Blast		%
Promyelocyte	0.5	%	Baso. normoblast	1.0	%	Monoblast		%
Myelocyte	9.0	%	Polychrom. normoblast	13.5	%	Promonocyte		%
Metamyelocyte	4.5	%	Orthochrom. normoblast	25.0	%	Monocyte		%
Band neutrophil	8.0	%	Lymphoblast		%	Plasmablast		%
Polyseg neutrophil	18.5	%	Prolymphocyte		%	Plasma cell	11.0	%
Eosinophil	0.5	%	Lymphocyte	7.0	%	other1		%
Basophil		%	Histocyte		%	Other2		%

BM aspiration and touch print shows normocellular marrow with increased infiltration of neoplastic plasma cells (11.0%). BM biopsy and clot section show normocellular marrow with increased infiltration of neoplsatic plasma cells.
CD138: positive on increased neoplastic plasma cells
kappa: positive on increased neoplastic plasma cells
lambda: negative

Case 1: M/70 김 O O

Assessment

 # Iron deficiency anemia

 # Smoldering Multiple Myeloma

IgG-Kappa, CRAB (-/-/-/-) 2019.11.2

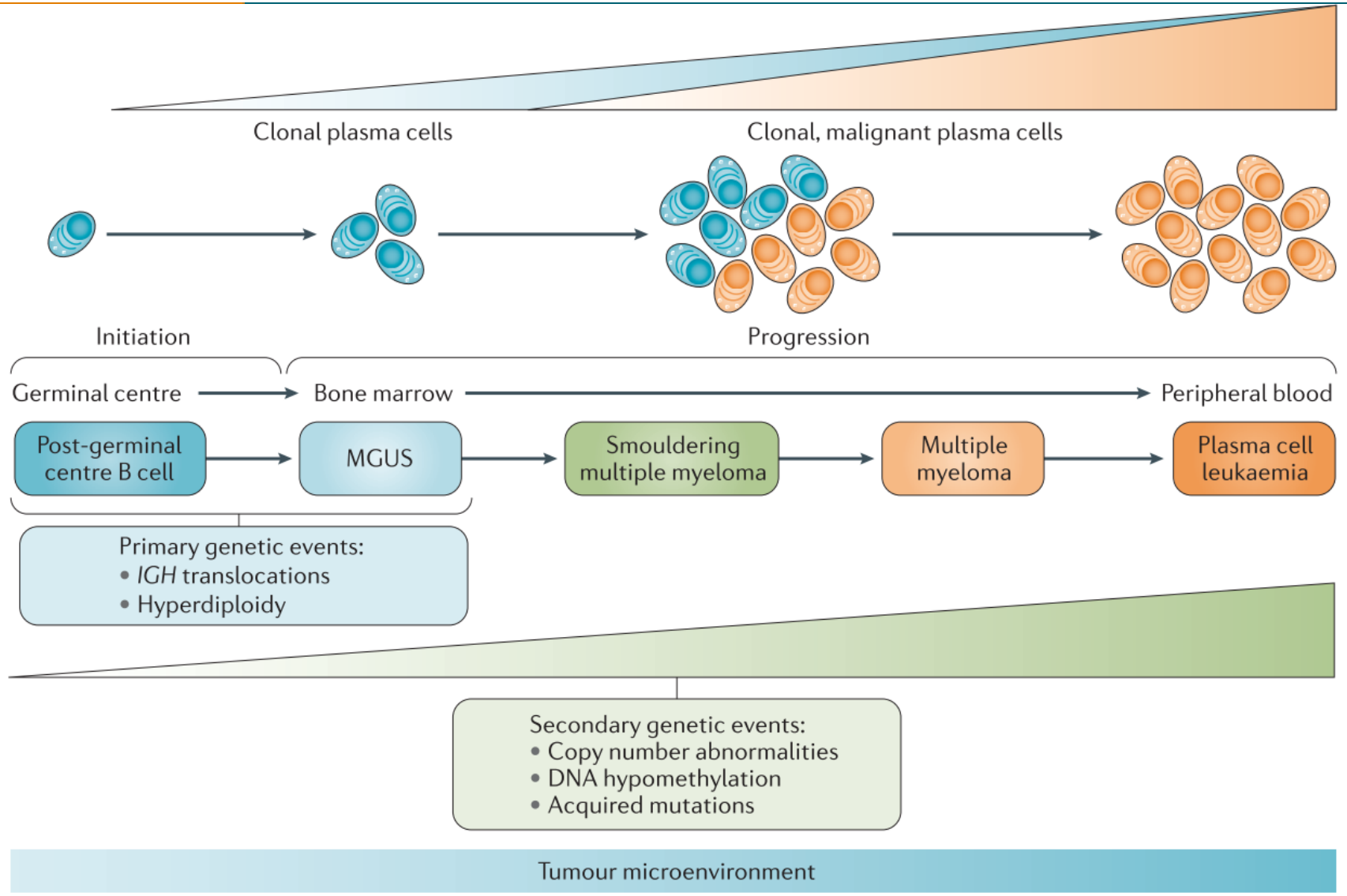
sPEP 1.45

sFLC ratio 1.71

BM PC: 11%

FISH negative

Development of Multiple Myeloma

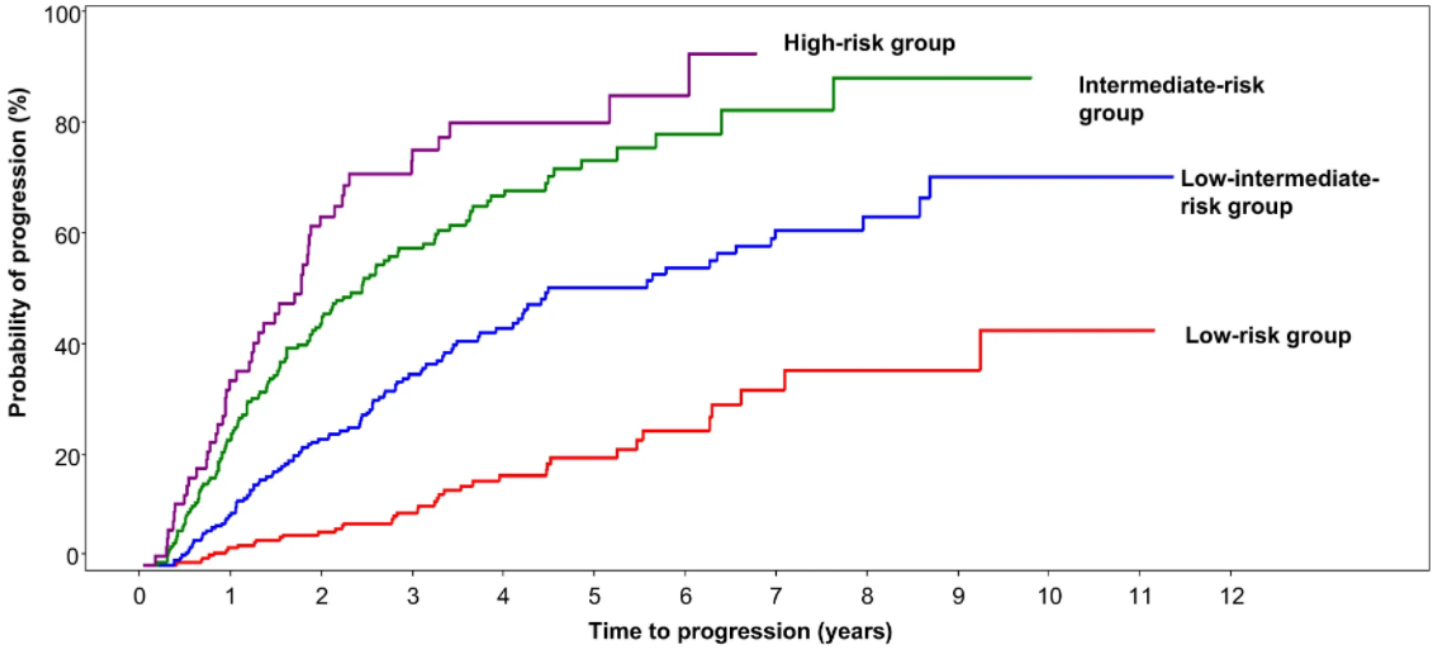


Reference: Kumar SK et al. Nat Rev dis Primers : 2017;3:17046

IMWG risk stratification for SMM

	Level at SMM diagnosis
Serum M-protein	**> 2 g/dL**
Involved to uninvolved serum free light-chain ratio	**> 20**
Bone marrow plasma cells infiltration	**> 20%**
Additional risk factor: presence a chromosomal abnormality	t(4;14) t(14;16) +1q Del13q / monosomy 13

	Score
Low risk	**0**
Low-intermediate risk	**1**
Intermediate risk	**2**
High-risk	**3-4**



Reference:

Case 1: M/70 김 O O

Assessment

 # Iron deficiency anemia

 # Smoldering Multiple Myeloma, Low risk by IMWG
IgG-Kappa, CRAB (-/-/-/-) 2019.11.2
sPEP 1.45
sFLC ratio 1.71
BM PC: 11% FISH negative

Plan

1. risk of progression 6% at 2 years
3Mo evaluation

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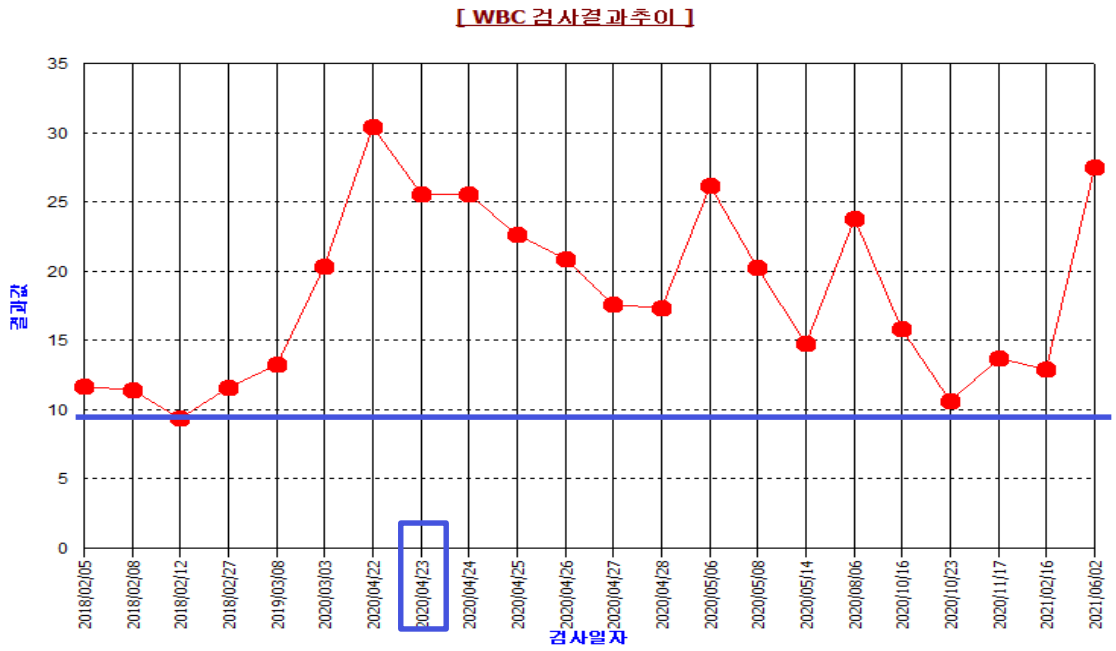
c. Clonal hematopoiesis of indeterminate potential
(CHIP, 클론성 조혈증)

Reference:

Case 2: F/75 이 O O

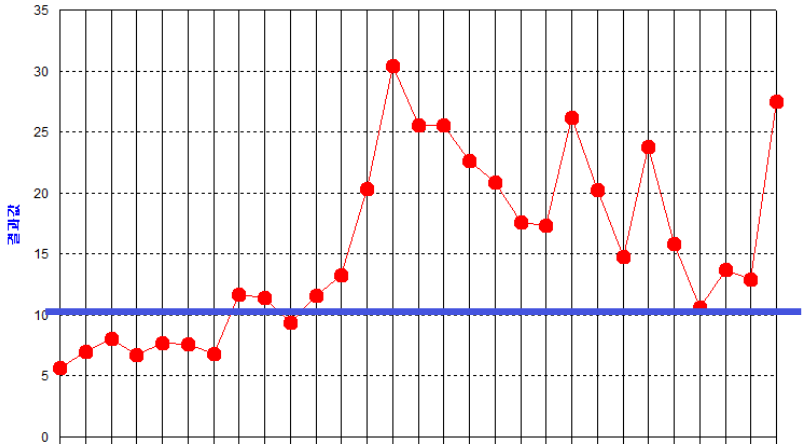
2020.4.23 Heart failure 로 ICD insertion 준비 중 Leukocytosis 로 의뢰

CBC (11.6-25520-140k) lymphocyte 81%



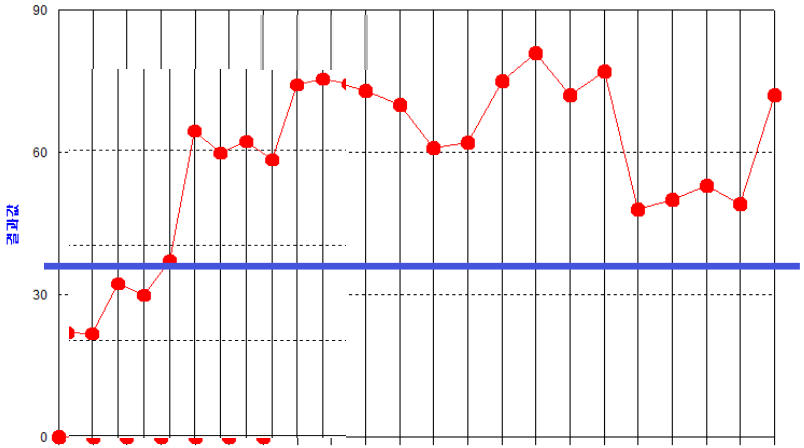
Case 2: F/75 이 O O

Leukocytosis



2011 2016 2018 **2020/03~**

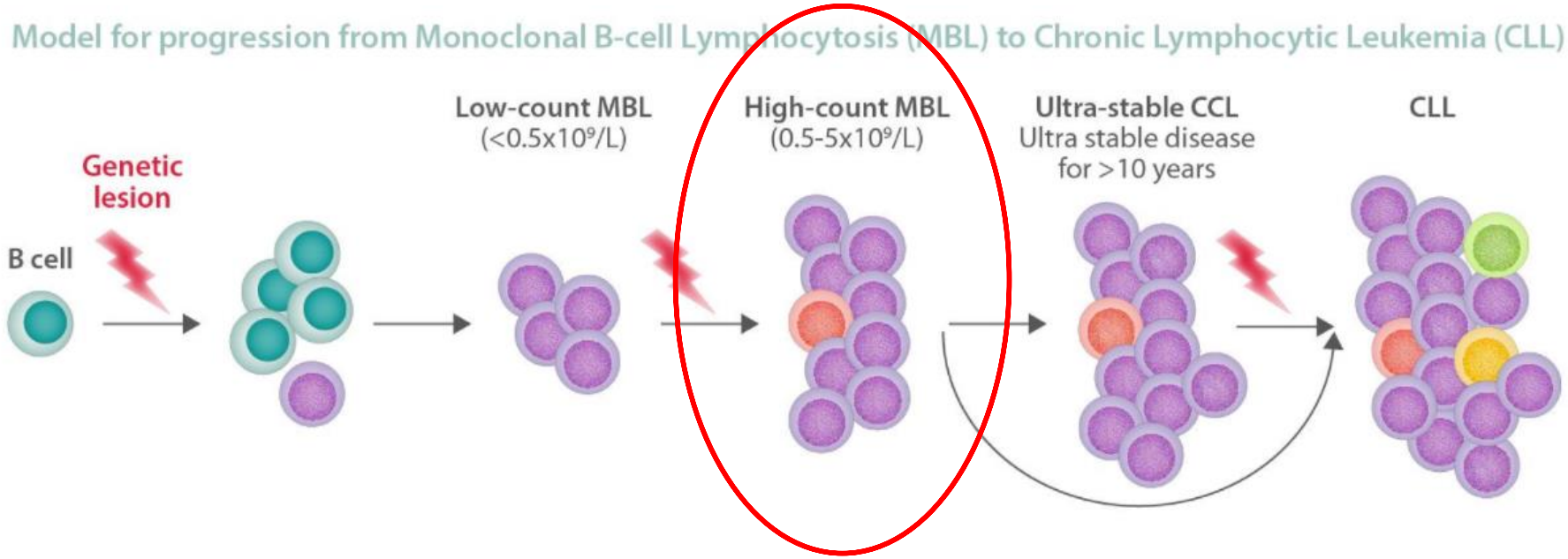
Lymphocytosis



2018 2019 **2020/03~**

Reference:

Monoclonal B-cell lymphocytosis (MBL)



Haematologica. 2018 ;103(5):865-873

Reference:

Monoclonal B-cell lymphocytosis (MBL)

① light-chain restriction (kappa:lambda of <3:1 or <0.3:1), *or*

② monoclonal immunoglobulin heavy-chain gene rearrangement, *or* 25% B cells with low or absent expression of surface immunoglobulins, *or*

③ B-cell population with an aberrant immunophenotype

These findings must be reproducible and stable for at least 3 months.

However, MBL is ruled out by the following criteria:

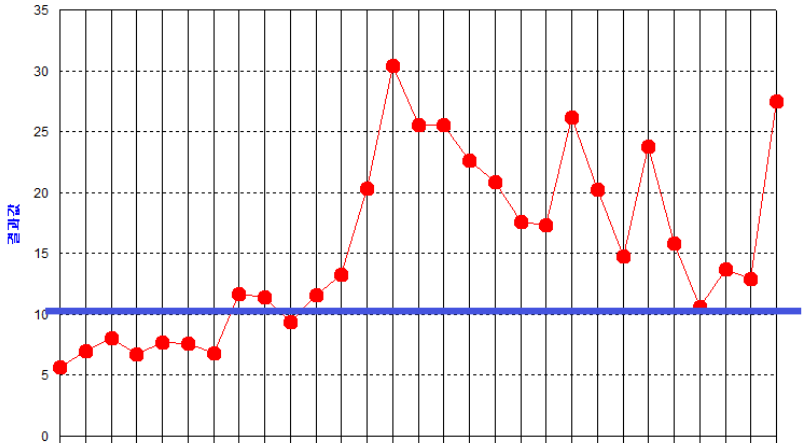
- ✓ lymphadenopathy or organomegaly, *or*
- ✓ associated autoimmune disease (e.g. AIHA) or infectious complications, *or*
- ✓ B lymphocytes >5,000/uL in the peripheral blood, *or*
- ✓ any other feature of manifested lymphoproliferative neoplasm.

Reference:
Marti GE, et al. Br J Haematol 2005;130:325-332.
Rawstron AC, et al. N Engl J Med. 2008;359:2065-2066

Case 2: F/75 이 O O

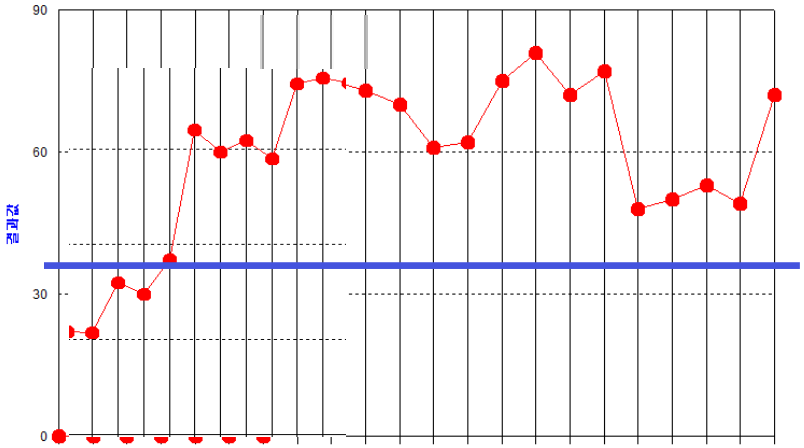
2020.4.23 Heart failure 로 ICD insertion 준비 중
Leukocytosis with lymphocytosis → BM study

Leukocytosis



2011 2016 2018 **2020/03~**

Lymphocytosis



2018 2019 **2020/03~**

Case 2: F/75 이 O O

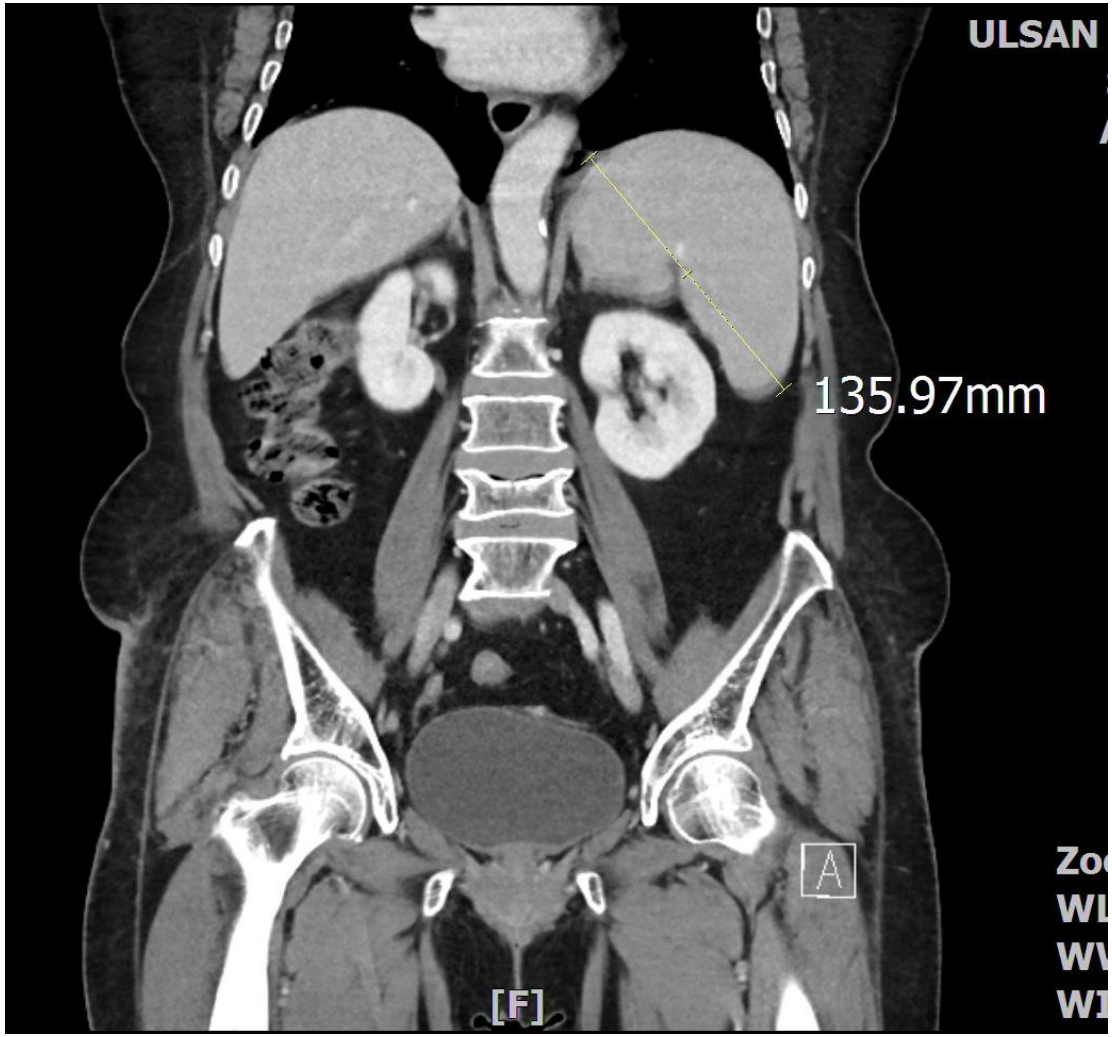
Markers	판정	비율(%)	intensity	비 고
CD45	+	37.6	Intermediate	
HLA DR	+	66.3	Intermediate	
CD3	-	19.8		
CD7	-	19.3		
CD10	-	0.6		
CD19	+	64.3	Intermediate	
CD20	+	61.3	Intermediate	
CD22	+	62.3	Intermediate	
CD23	-	14.2		
FMC7	+	62.4	Intermediate	
TdT	-	6.5		
Kappa	+	75.7	Dim	
Lambda	+	73.2	Intermediate	MPO (-) 9.7
CD4	-	19.1		CD5 (-) 19.8
CD8	-	10.0		CD56 (-) 9.1

PBS show presence of neoplastic lymphoid cells (81.0%) with abundant cytoplasmic projections. BM aspiration and touch print show slightly hypercellular marrow with increased infiltration of neoplastic lymphoid cells (22.5%). Neoplastic lymphoid cells are small to medium sized with small amount of cytoplasm and occasional cytoplasmic projections. BM biopsy and clot section show normocellular marrow with infiltration of neoplastic lymphoid cells in interstitial pattern. CD20: positive on increased neoplastic lymphoid cells.

Immunophenotyping : CD5-CD19+CD20+CD22+kappa dim+lambda intermediate+HLA-DR+FMC7+

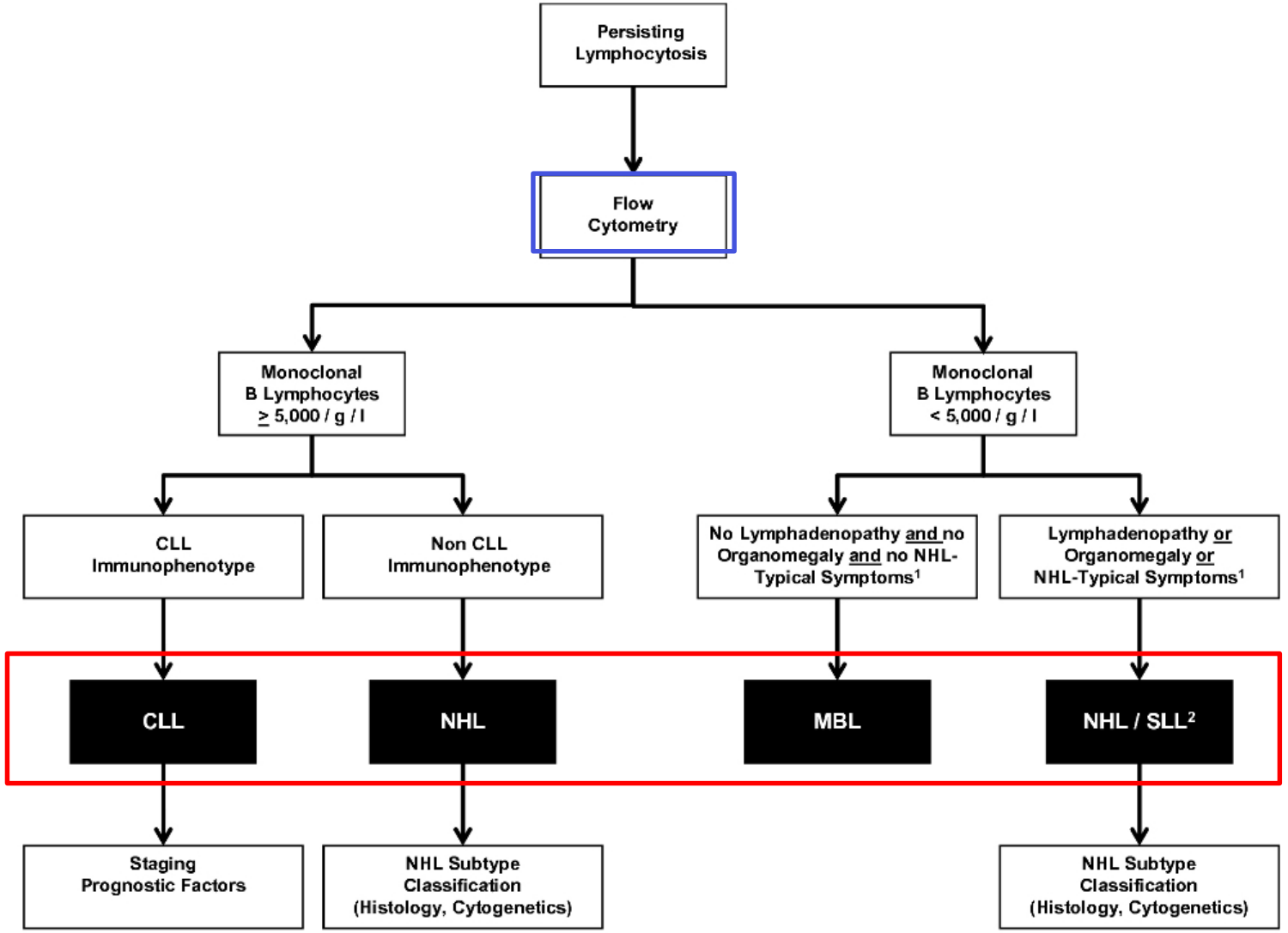
Bone marrow involvement of B-lineage lymphoma, r/o splenic marginal zone B cell lymphoma by morphologic findings.

Case 2: F/75 이 O O



Reference:

Differential Diagnostics of B-Cell Lymphocytosis



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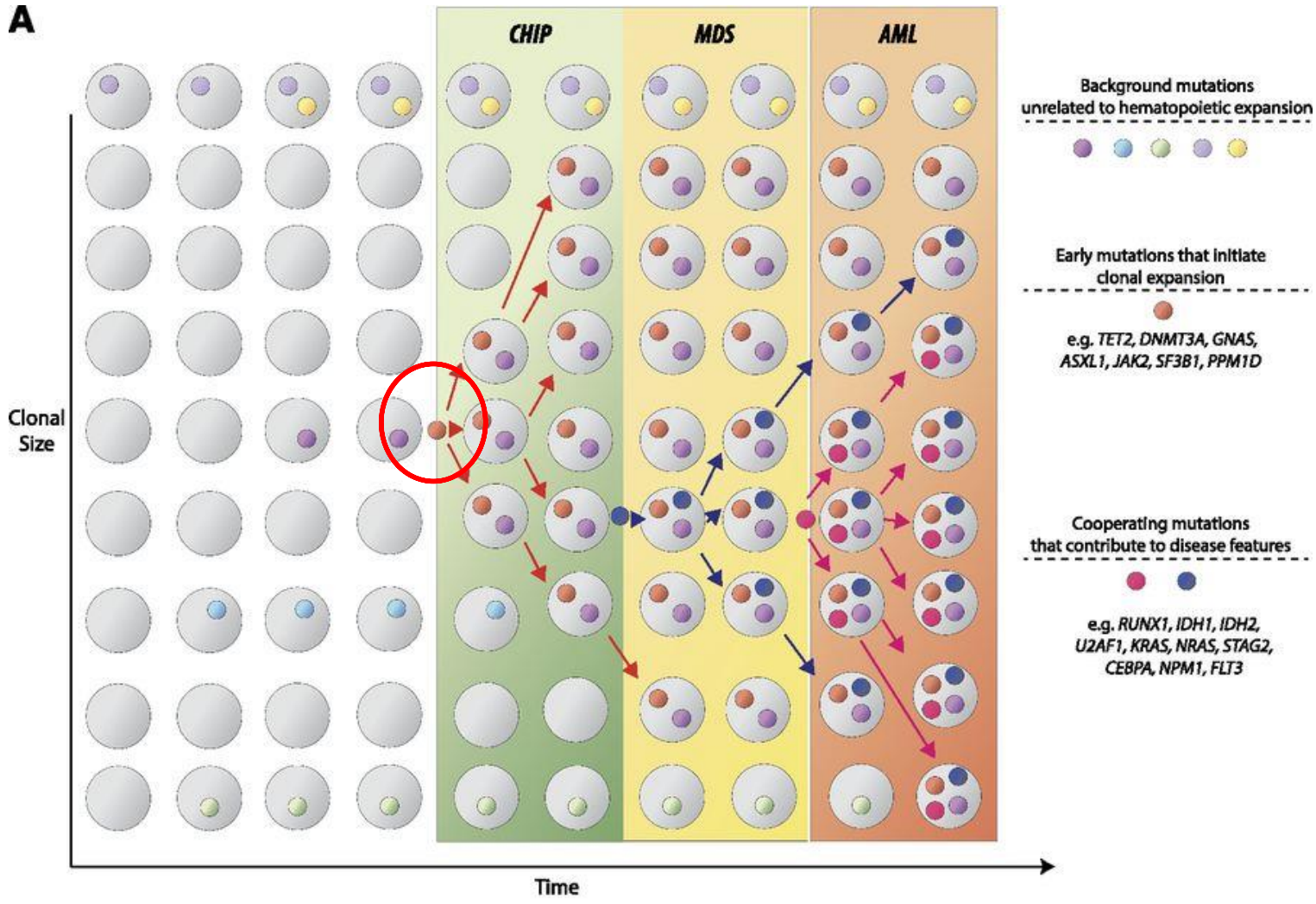
c. Clonal hematopoiesis of indeterminate potential
(CHIP, 클론성 조혈증)

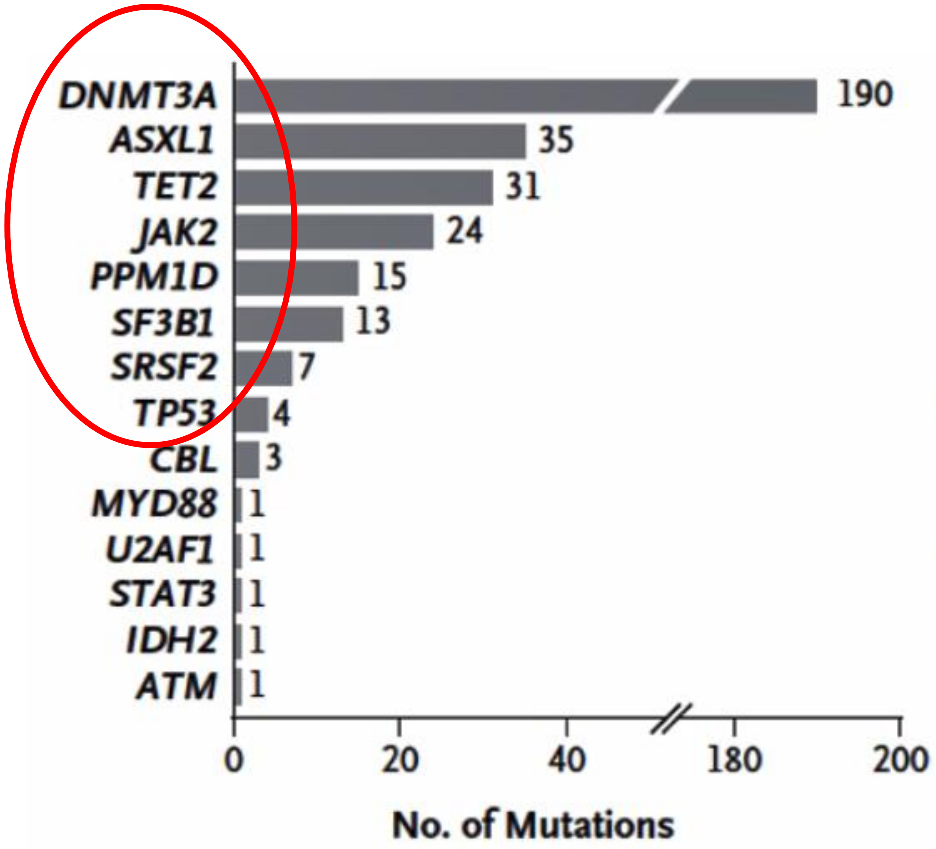
Reference:

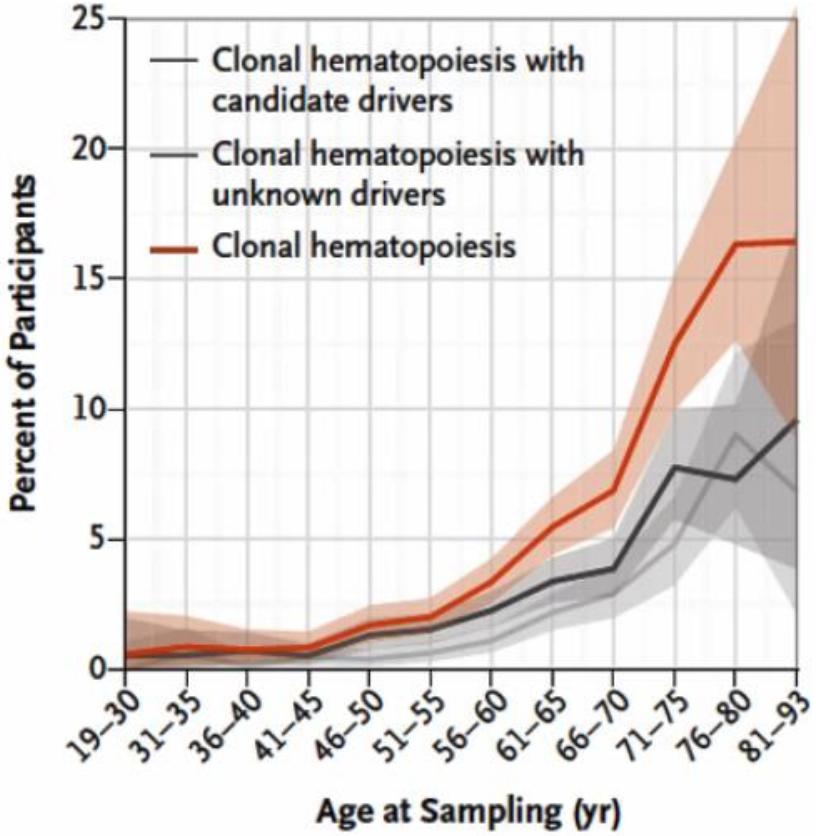
Clonal Hematopoiesis of Indeterminate Potential
as a precursor state for hematological neoplasms



Reference:

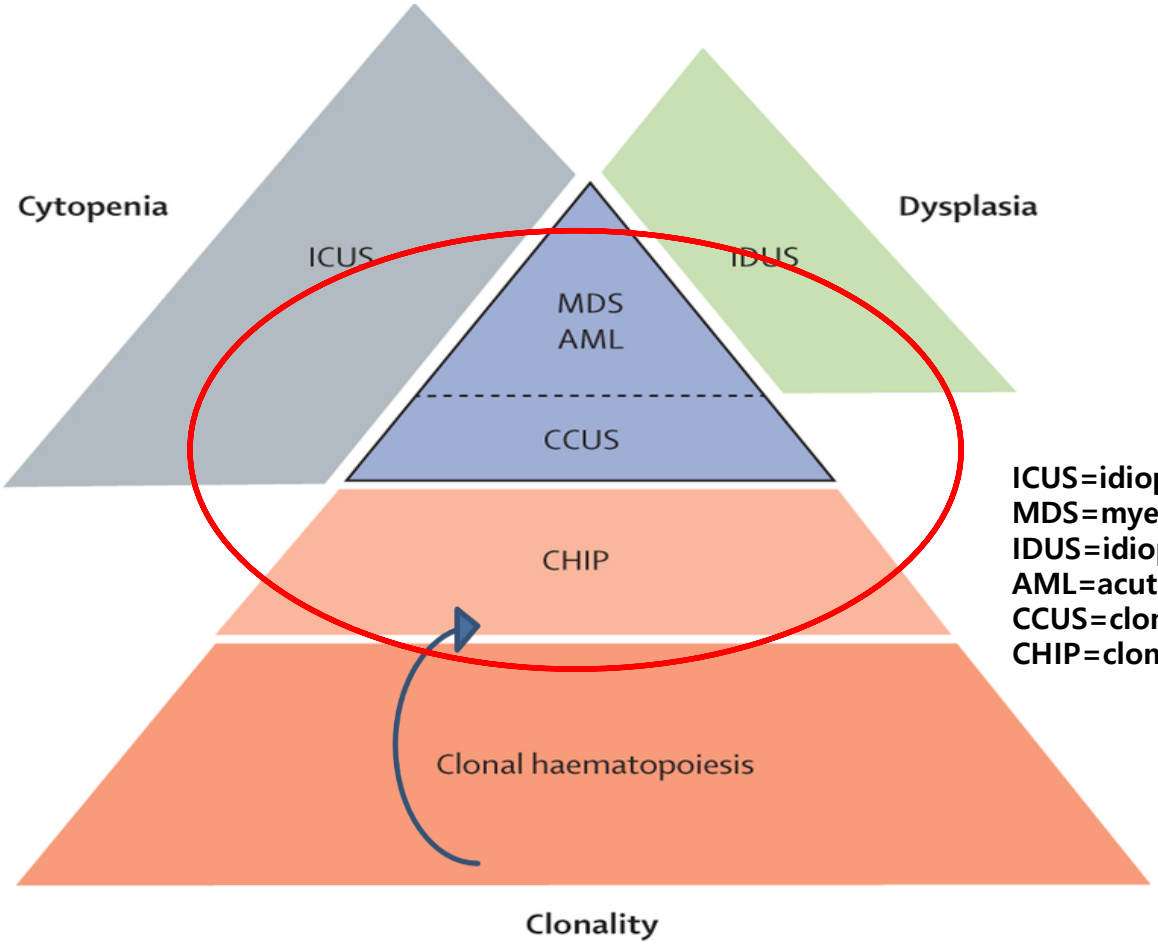
Clonal hematopoiesis





Genovese, et al. NEJM 2014
Xie et al. Nat Med 2014
McKerrell et al. Cell Rep 2015

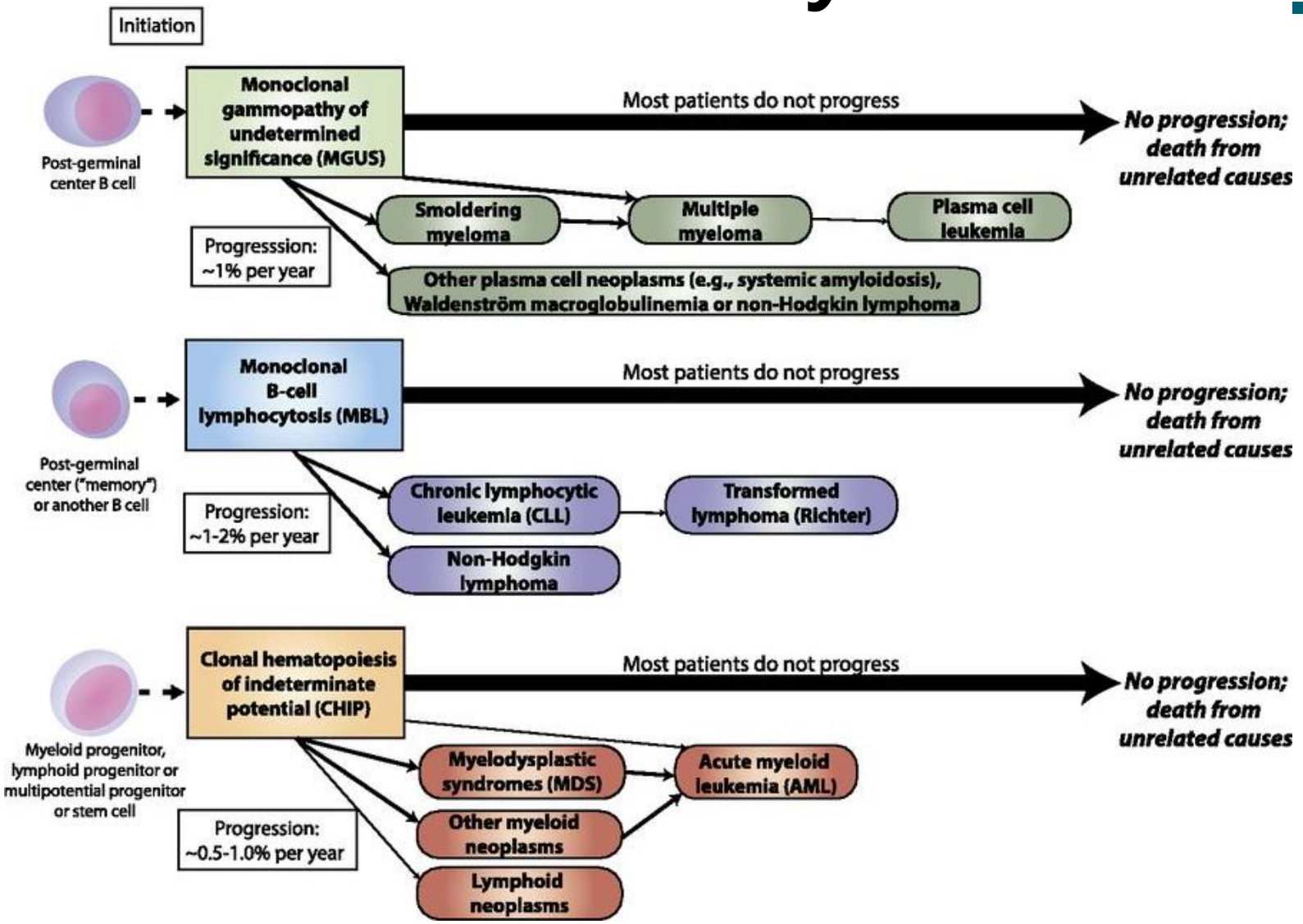
Cytopenia, dysplasia, and clonality



ICUS=idiopathic cytopenia of unknown significance.
MDS=myelodysplastic syndrome
IDUS=idiopathic dysplasia of unknown significance
AML=acute myeloid leukaemia
CCUS=clonal cytopenia of unknown significance
CHIP=clonal haematopoiesis of indeterminate potential.

Reference: Lancet Haematol. 2020; 7(1): e73–e81

Summary



Reference: Blood. 2015 Jul 2; 126(1): 9–16


MERCI
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Grazie
arigato
OBRIGADO
Thank You
GRACIAS
Dziekuje
DANKE
PALDIES
VANDANE
xiexie
Mamnuun