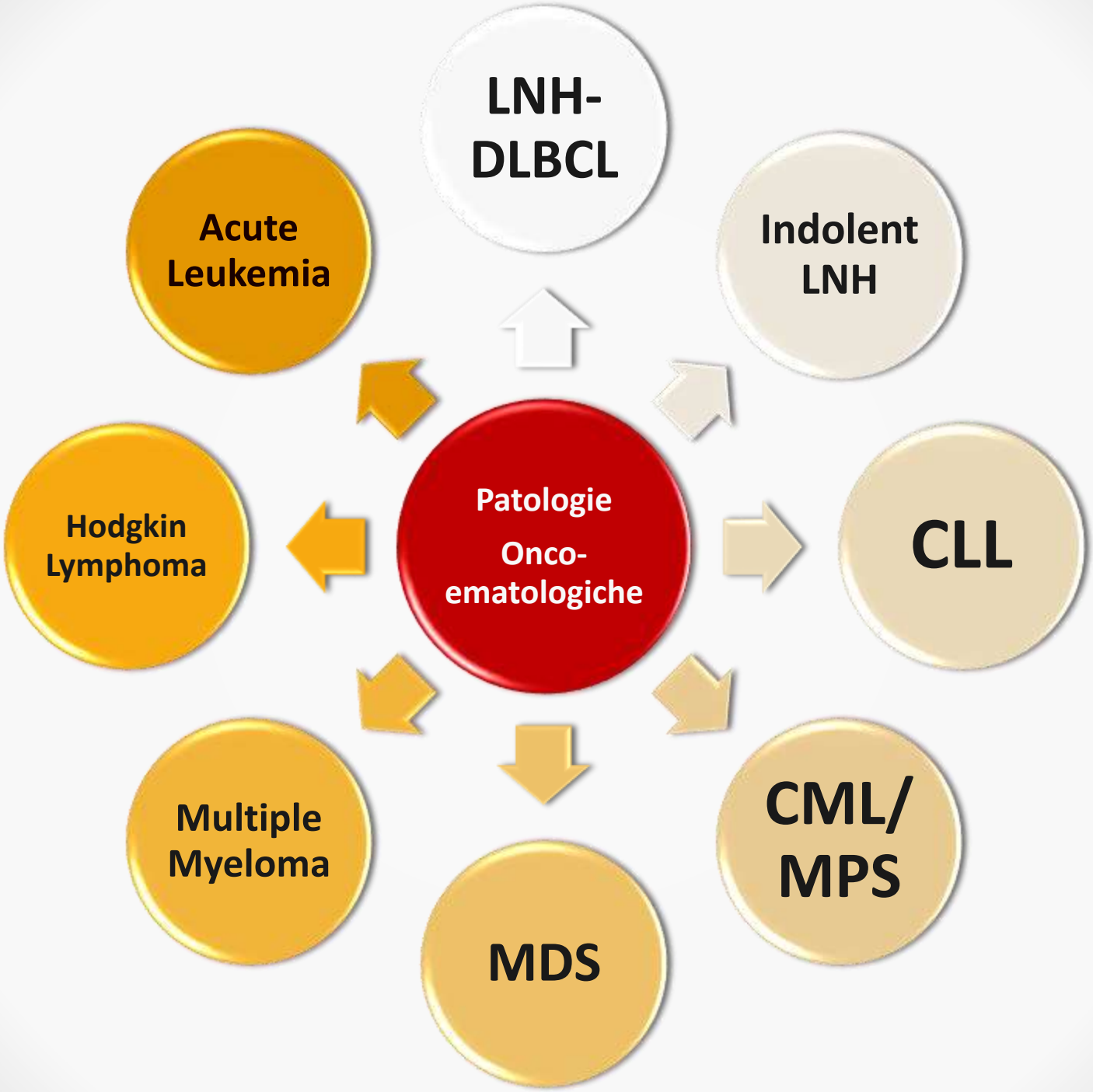
LA SOSTENIBILITÀ FUTURA DEL SERVIZIO SANITARIO: POSSIBILI STRATEGIE E SINERGIE

Firenze, 31 marzo 2017

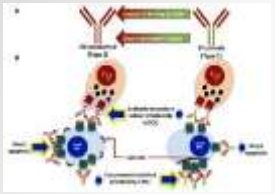
Le innovazioni nel trattamento delle patologie ematologiche

D.ssa Nadia Cecconi

UO Ematologia- Università di Pisa

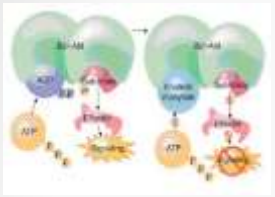

LNH-DLBCL
Indolent LNH
CLL
CML/ MPS
MDS
Multiple Myeloma
Hodgkin Lymphoma
Acute Leukemia
Patologie Onco-ematologiche

Quali le innovazioni



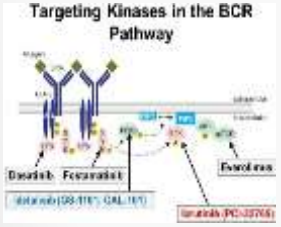
Immunoterapia.

Nuovi **anticorpi monoclonali** che a breve andranno ad impattare non solo sulle future sperimentazioni cliniche ma anche sulla comune pratica clinica ematologica, grazie a meccanismi d'azione innovativi.



farmaci mirati al bersaglio molecolare (inibitori della tirosin-chinasi nella LMC: uno di prima generazione (**imatinib**), tre di seconda generazione (**nilotinib, dasatinib, bosutinib**) e uno di terza generazione (**ponatinib**) **).**

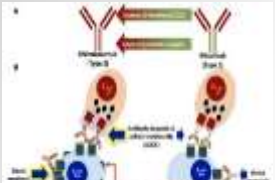
Inibitori del FLT3



inibitori che agiscono sull'attivazione delle **cellule linfoidi**, in particolare quelli di **tipo B**, in grado di bloccare i segnali di uno specifico **recettore**, il **BCR**

Inibitori del proteosoma (bortezomib, carfilzomib, ixazomib)

Immunomodulanti



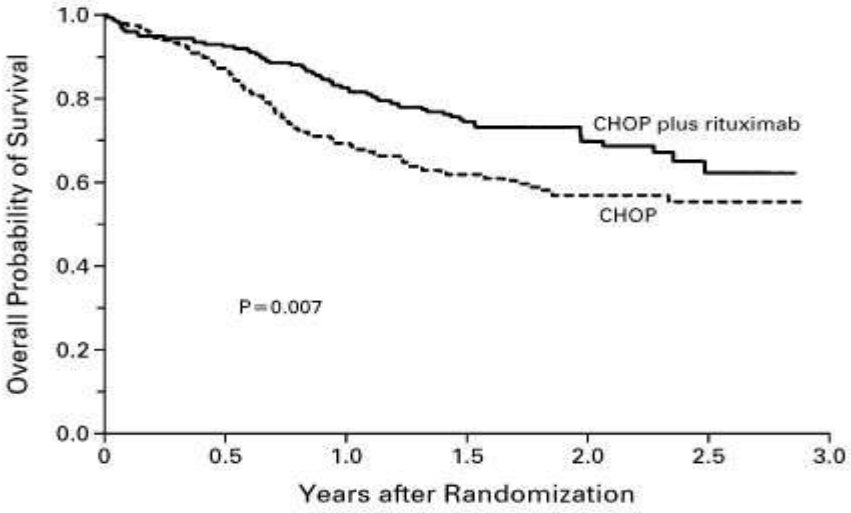
Immunoterapia.

CHOP Chemotherapy plus Rituximab Compared with CHOP Alone in Elderly Patients with Diffuse Large-B-Cell Lymphoma

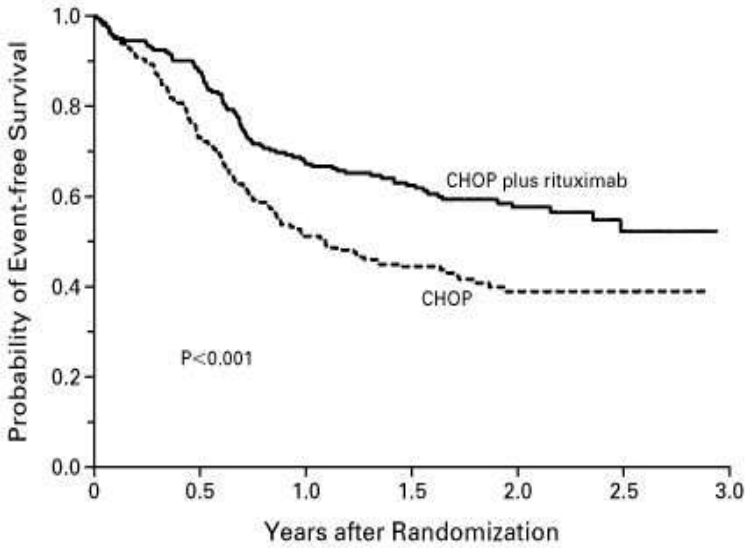
Coiffier B, NEJ Med 2002

TABLE 3. RESPONSE TO TREATMENT WITH CHOP OR CHOP PLUS RITUXIMAB.*

RESPONSE	CHOP PLUS RITUXIMAB (N=202)	CHOP (N=197)
	no. (%)	
Complete response	106 (52)	72 (37)
Unconfirmed complete response	46 (23)	52 (26)
Partial response	15 (7)	11 (6)
Stable disease	2 (1)	1 (1)
Progressive disease	19 (9)	43 (22)
Death without progression	12 (6)	11 (6)
Could not be assessed†	2 (1)	7 (4)



No. at Risk						
CHOP plus rituximab	202	187	167	118	64	21
CHOP	197	171	136	96	58	16



No. at Risk						
CHOP plus rituximab	202	177	137	108	63	19
CHOP	197	144	101	72	42	17

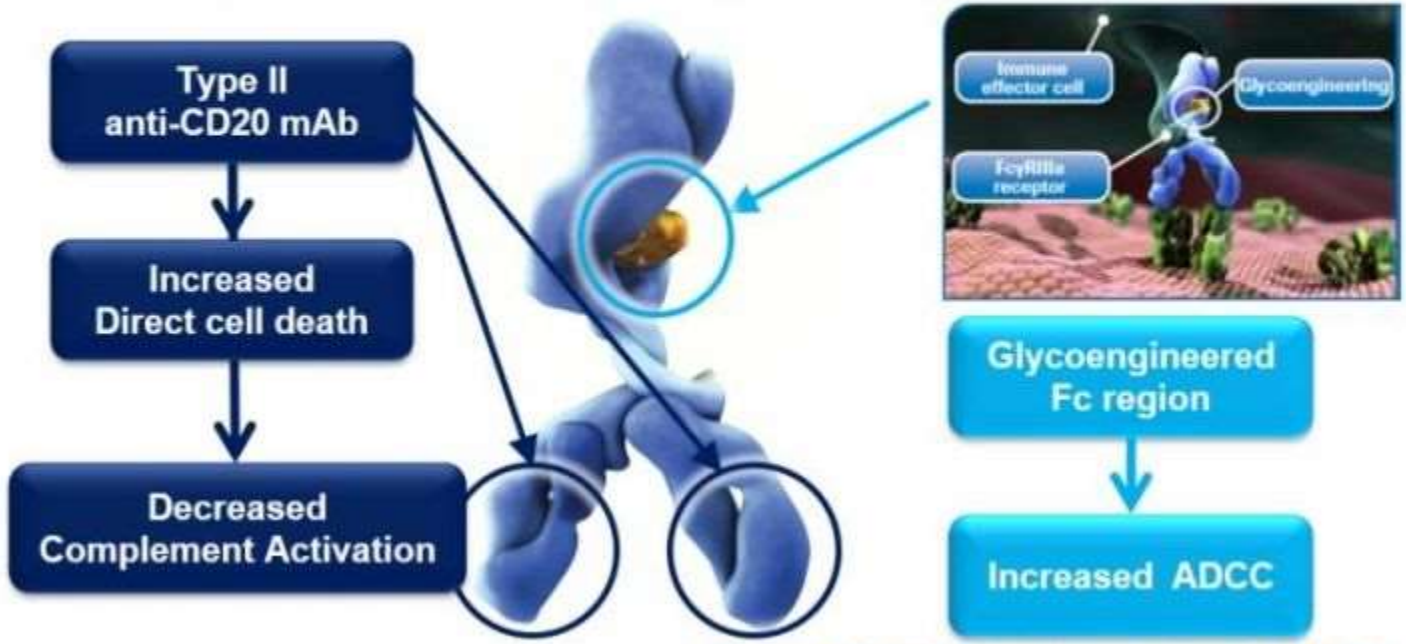
Type I CD20 antibodies	Ty
CD20 accumulation in lipid rafts	no
High CDC	lo
ADCC	
ADCP	
Full CD20 binding capacity	
CD20 downregulation (FcγRIIb-mediated)	
Weak/no homotypic cell aggregation	
Direct cell death	
Rituximab, ocrelizumab, ofatumumab, veltuzum ublituximab	

CDC = Complement-depe
cellular cytotoxicity; ADC

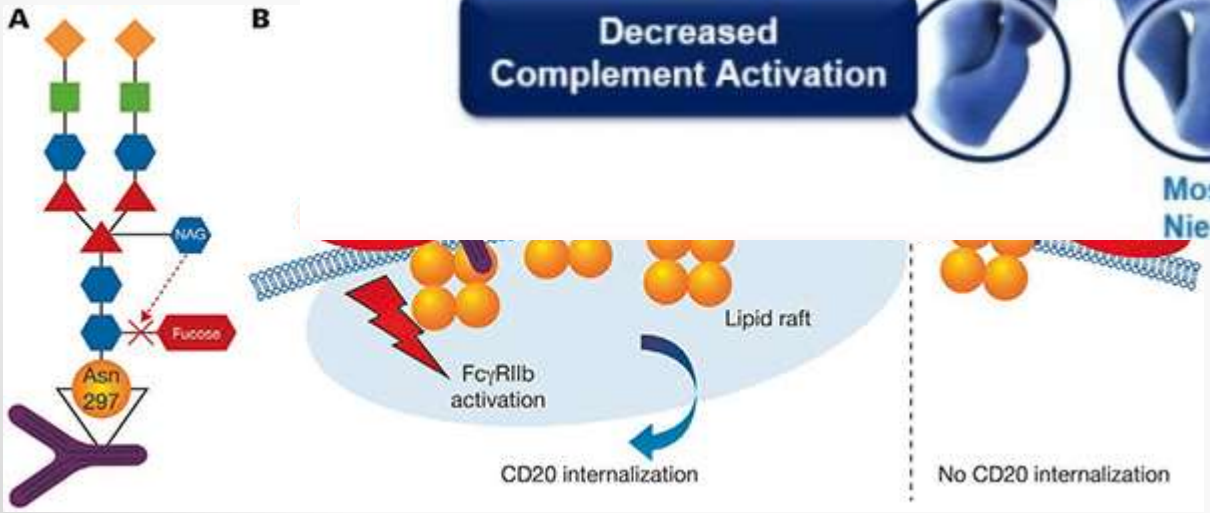
GA101 (Obinutuzumab) – The First Glycoengineered, Type II Anti-CD20 mAb

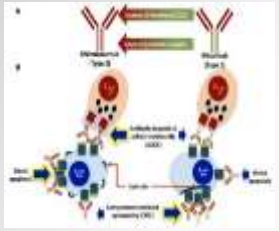
Compared with non-glycoengineered, type I mAbs, GA101 has:

- ✓ increased direct cell death
- ✓ Increased antibody-dependent cellular cytotoxicity (ADCC)
- ✓ decreased complement dependent cytotoxicity (CDC)



Mossner E et al. *Blood.* 2010;115(22):4393-402.
Niederfellner G et al. *Blood.* 2011;118:358–67.





Immunoterapia.

B-Cell Neoplasm

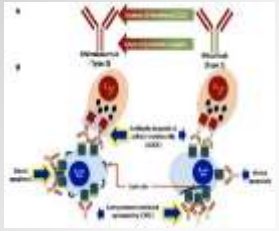
MCL ~7% — Rituximab

FL ~29% — Rituximab, Obinutuzumab

CLL/SLL ~ 12% — Rituximab, Ofatumumab, Obinutuzumab, Alentuzumab

DLBCL ~37% — Rituximab, Obinutuzumab

Other B-cell lymphomas ~ 20% — Rituximab



Immunoterapia.

Hodgkin Lymphoma

Anti-CD30

Brentuximab Vedotin

Check point Inhibitors

Qualche numero utile……..

Linfoma di Hodgkin:

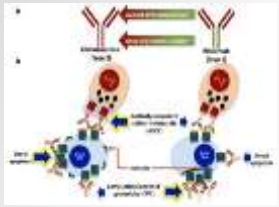
circa 2500 casi/anno in Italia

25-30% non risponde alle cure standard (**circa 625-750**):

il 50% ricorre con successo al trapianto autologo (circa 300-350)

per il restante 50% non esiste un trattamento consolidato

Per 300-350/anno pazienti è fondamentale poter accedere a terapie alternative

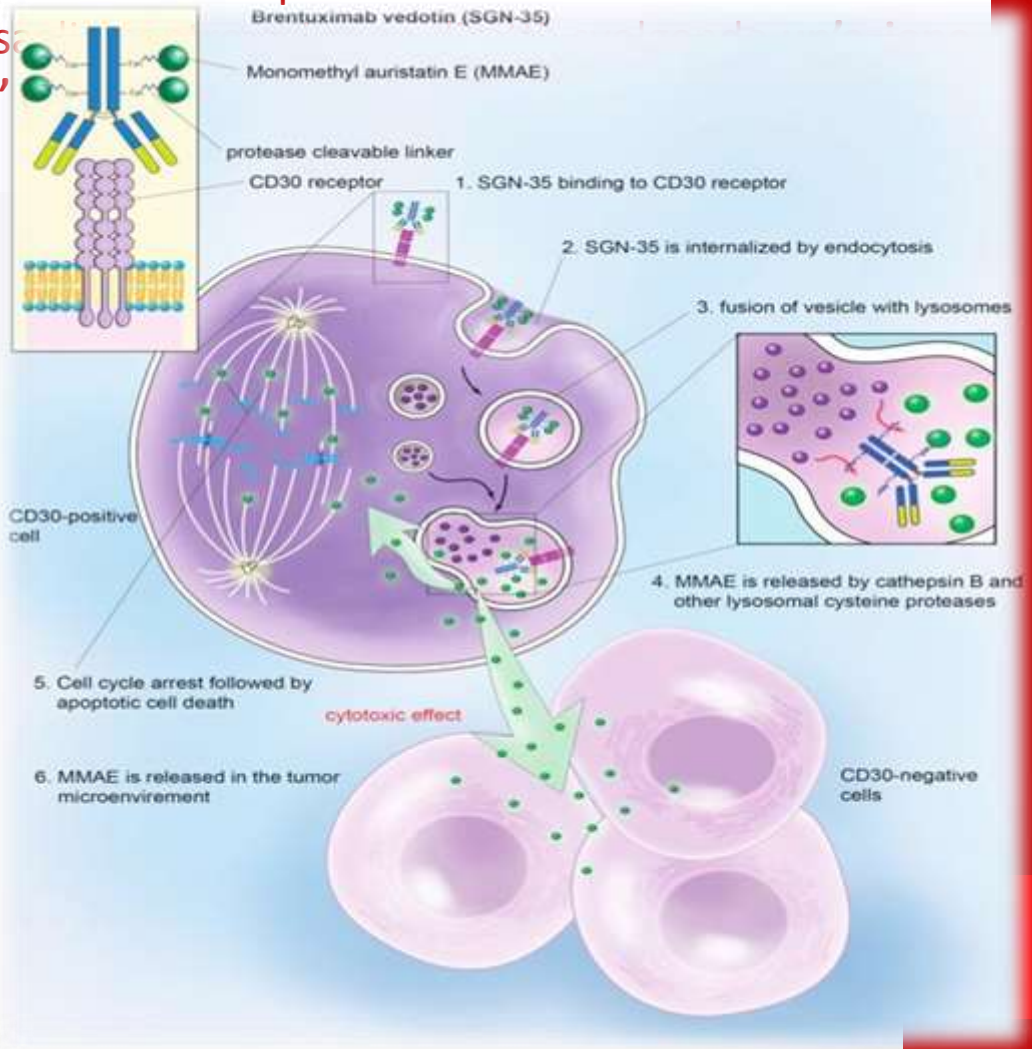


Immunoterapia

HL: Quali le innovazioni

- alcuni anticorpi **monoclonali legano una molecola di chemioterapico** e svolgono dunque la loro azione terapeutica veicolando direttamente il farmaco alle cellule bers
  citotossica "potenziata"

Brentuximab Vedotin
(Adcetris)



INDICAZIONI TERAPEUTICHE

ADCETRIS

CD30+

ADCETRIS è indicato per il trattamento di pazienti adulti affetti da linfoma di Hodgkin (HL) CD30+ recidivante o refrattario:

1. **in seguito a trapianto autologo di cellule staminali (ASCT)**
2. **in seguito ad almeno due precedenti regimi terapeutici quando l'ASCT o la polichemioterapia non è un'opzione terapeutica**

INDICAZIONI TERAPEUTICHE

ADCETRIS

ADCETRIS è indicato per il trattamento di pazienti adulti affetti da linfoma anaplastico a grandi cellule sistemico recidivante o refrattario.

3. trattamento di pazienti adulti affetti da LH CD30+ ad aumentato rischio di recidiva o progressione in seguito a ASCT*

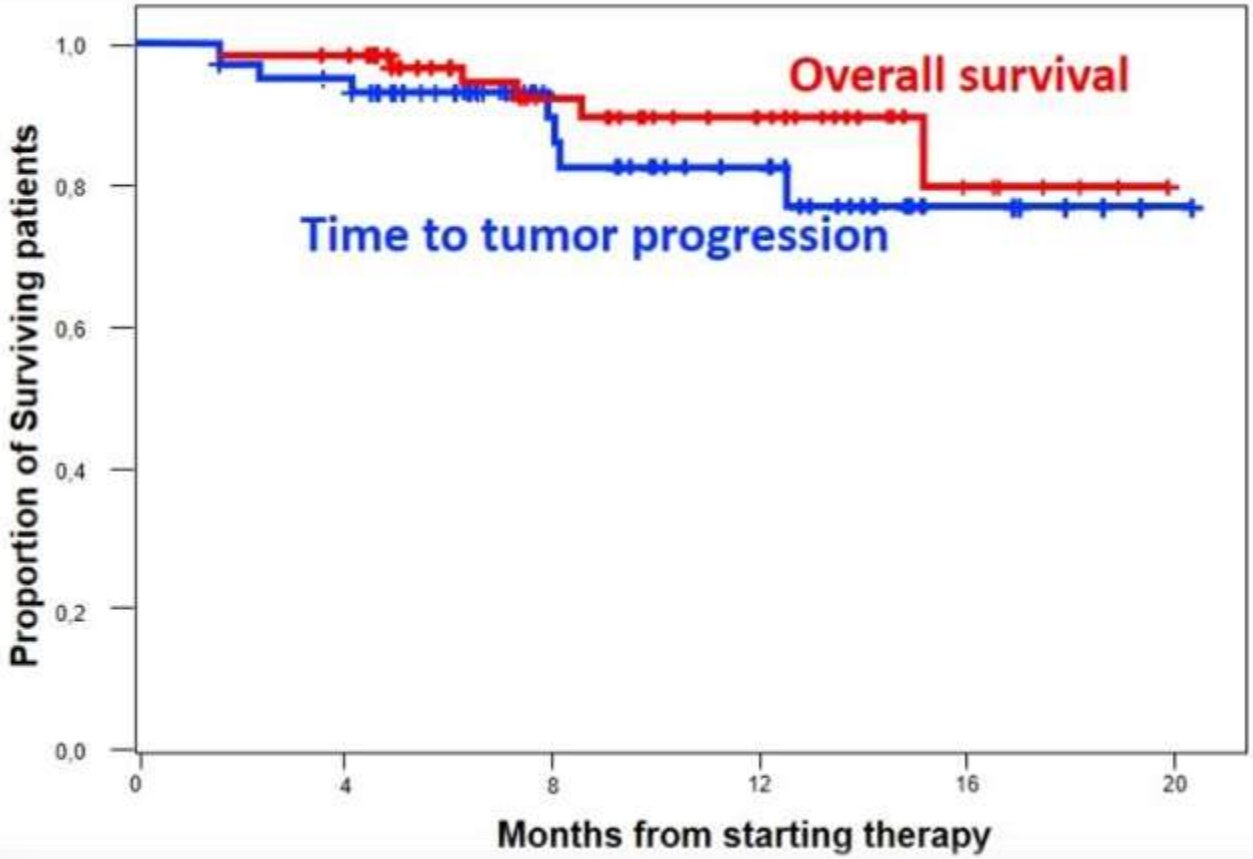
BV + Chemotherapy: BRESHAP

Primary refractory: n= 40 (61%)

Early relapse: n= 16 (24%)

Late relapse: n= 10 (15%)

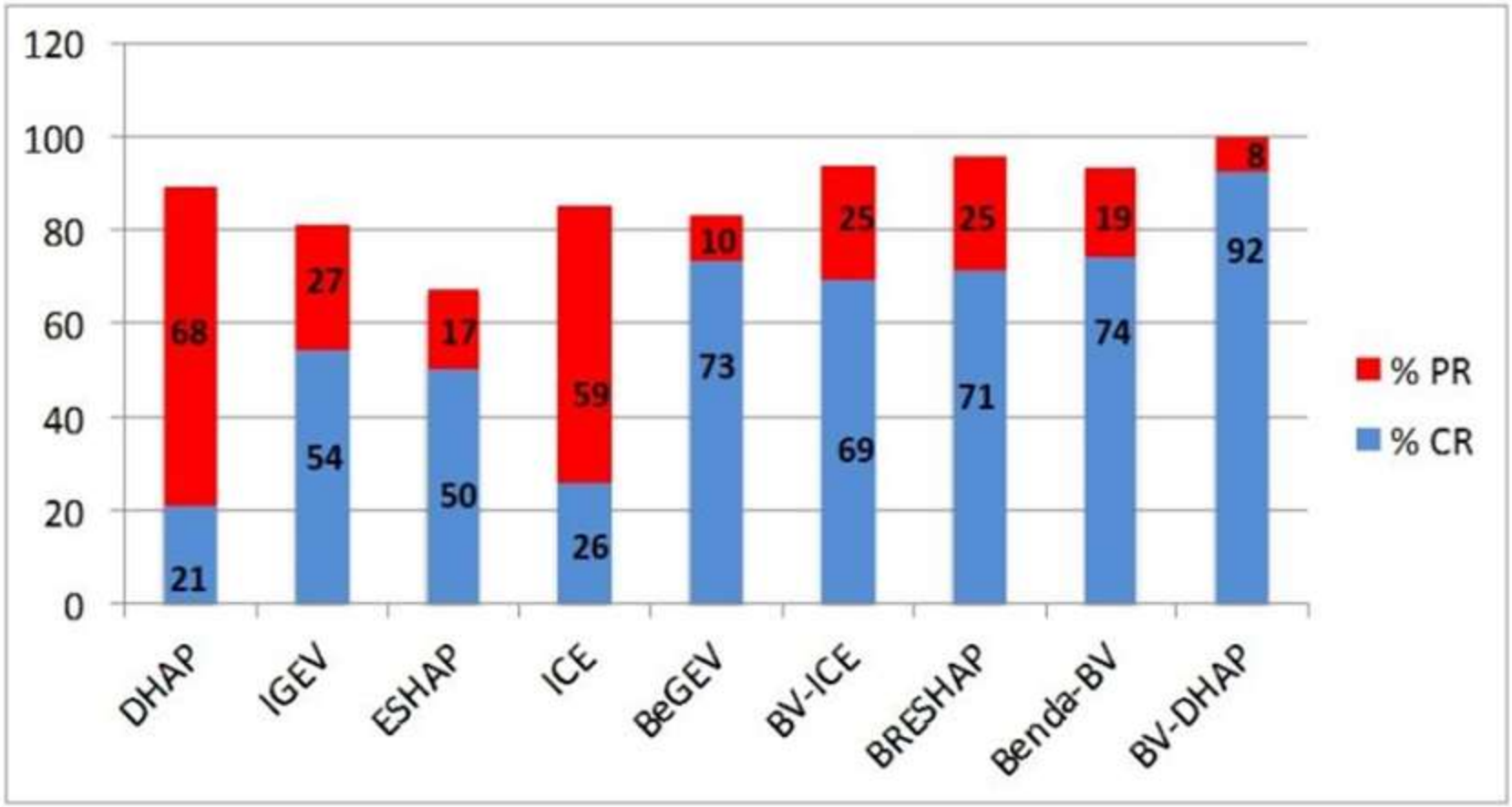
Pre-transplant Response	Evaluable (n=65)	Intent to treat (n=66)
ORR	95%	94%
mCR	71%	70%



from
to +56,
every

ct 1109
-Sanz R et al

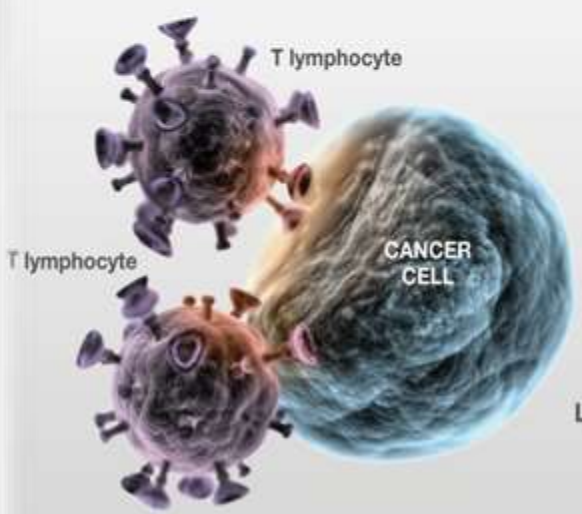
Induction therapy prior to transplant in R/R HL



This is how the new immunotherapy for cancer works

1. Normal work of the immune system

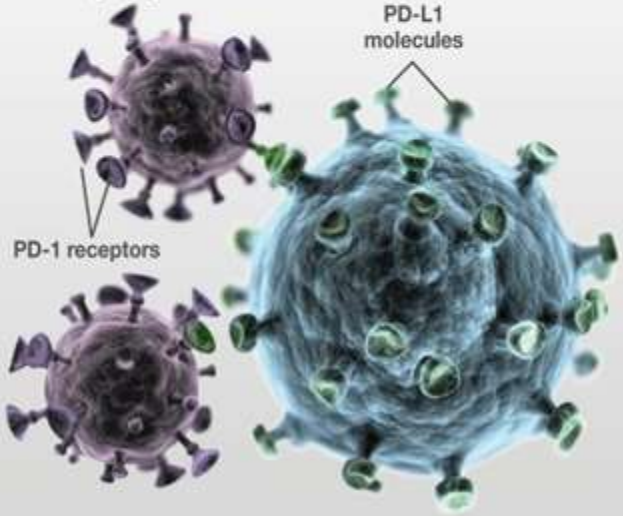
T lymphocytes are the cells of the immune system that identify tumour cells and destroy them.

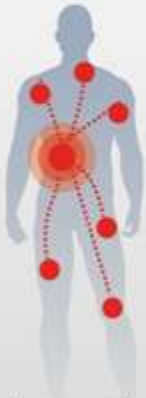


Lymphocytes prevent the tumour from developing.

2. Camouflage of tumour cells

Some tumour cells arm themselves with a shield of molecules called PD-L1. Lymphocytes possess PD-1 receptors which, by bonding to these traps, destroy their capacity to attack.

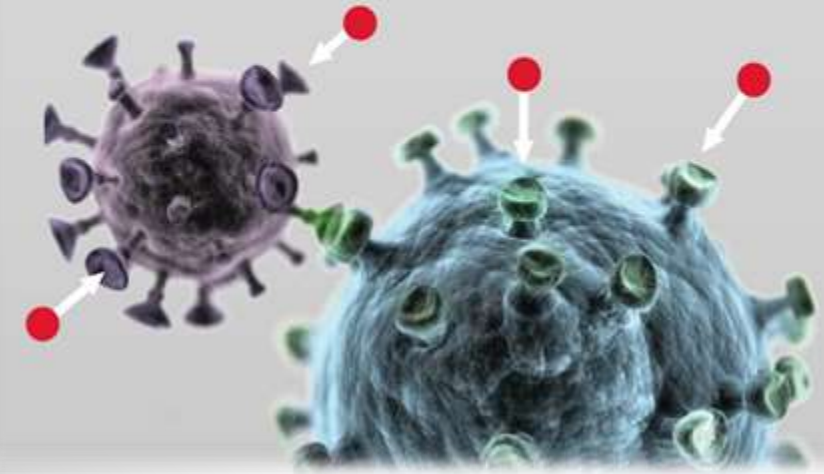




The tumours become invisible to our defences and they spread.

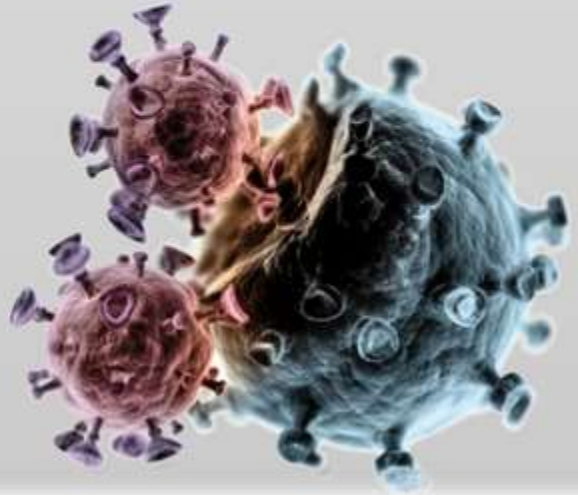
3. Action of the new inhibitor drugs

The new drugs based on antibodies block PD-1 from the cells of the immune system and PD-L1 from tumour cells to prevent their fatal action.



4. Result of immunotherapy

Lymphocytes, once freed from their blindness by the drug, regain their defence potential. They recognise cancer and reduce it.



This treatment, although still in its experimental stage, has had preliminary results on lung, kidney and skin cancers.

- anticorpi monoclonali che agiscono “risvegliando” il sistema immunitario e impedendo alla cellula maligna di creare una tolleranza del sistema immunitario verso la stessa cellula neoplastica. Questi farmaci hanno già dimostrato una elevata efficacia nel **linfoma di Hodgkin**, e sperimentazioni su altri tipi di linfoma sono attualmente in corso.

ABSTRACT 1107
Moskowitz C et al.

Keynote-087- Phase II Study: Pembrolizumab 200 mg q 3w

Pembrolizumab 10 mg/kg : ORR of 65% (Armand P et al, Abstract 1108)

Exposure-respon
2 mg/kg to 10 m

Cohort 1 (n=6
Cohort 2 (n=8
Cohort 3 (n=6

Response	Cohort 1 (n=69) %	Cohort 2 (n=81) %	Cohort 3 (n=60) %	All pts BICR (N = 210) %	Primary refractory (n=73) %	Relapsed (n=146) %
ORR	74	64	70	69	79.5	68
▪ CR	22	25	20	22	23	21
SD	16	12	17	15	5.5	16

Median time to response: 2.8 months (range, 2.1-8.8)

Response duration ≥6 months in 75%

Nivolumab in R/R HL:
Update of Checkmate 205 Trial: phase 2 study

Abstract 1110; Timmerman J et al

Inclusion criteria

Single-arm

Primary endpoint

Response	Cohort A (n=63) %	Cohort B (n=80) %
ORR	68	68
▪ CR	22	8
SD	16	12

Median time to response: 2 months (range, 2-6)

Median PFS not reached in Cohort A, 15 months in Cohort B

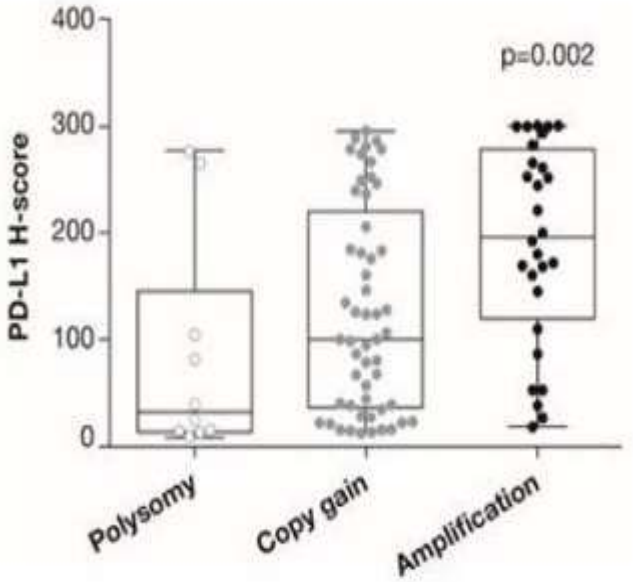
Cohort A: 9-month PFS 68%, 9-month OS 97%

Cohort B: 12-month PFS 54.6%, 12-month OS 95%

PD-L1 expression correlates with response to Nivolumab

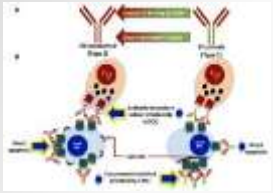
Roemer MC

- 96 pts from CheckMate205 trial
- Tandem analysis of 9p24.1 genetic alteration and PD-L1/Pax5 IHC
- Good correlation between PD-L1 H-score (IHC) and the level of 9p24.1 CNAs
- Extent of 9p24.1 CNAs associated to overall response, no PD in pts with genomic amplification and no CR in pts with only polysomy



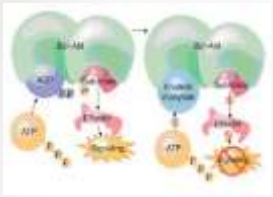
ASH 2016

Quali le innovazioni



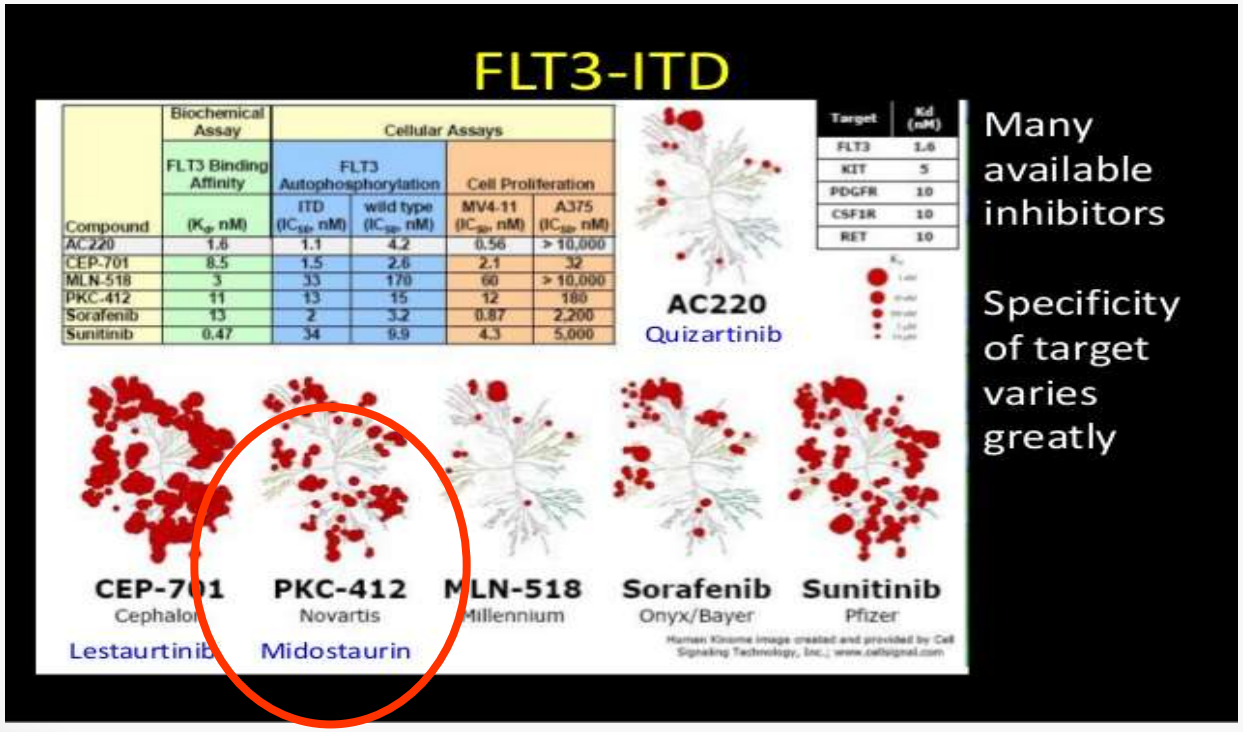
Immunoterapia.

Nuovi **anticorpi monoclonali** che a breve andranno ad impattare non solo sulle future sperimentazioni cliniche ma anche sulla comune pratica clinica ematologica, grazie ai loro meccanismi d'azione innovativi.



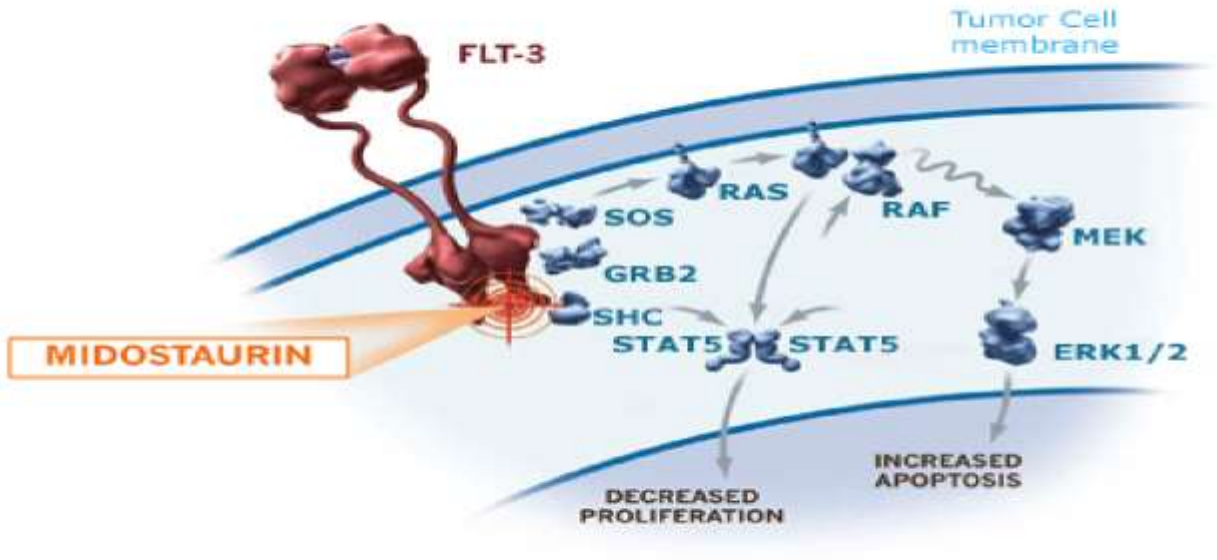
farmaci mirati al bersaglio molecolare (**inibitori della tirosin-chinasi nella LMC:** uno di prima generazione (**imatinib**), tre di seconda generazione (**nilotinib, dasatinib, bosutinib**) e uno di terza generazione (**ponatinib**)).

Inibitori del FLT3

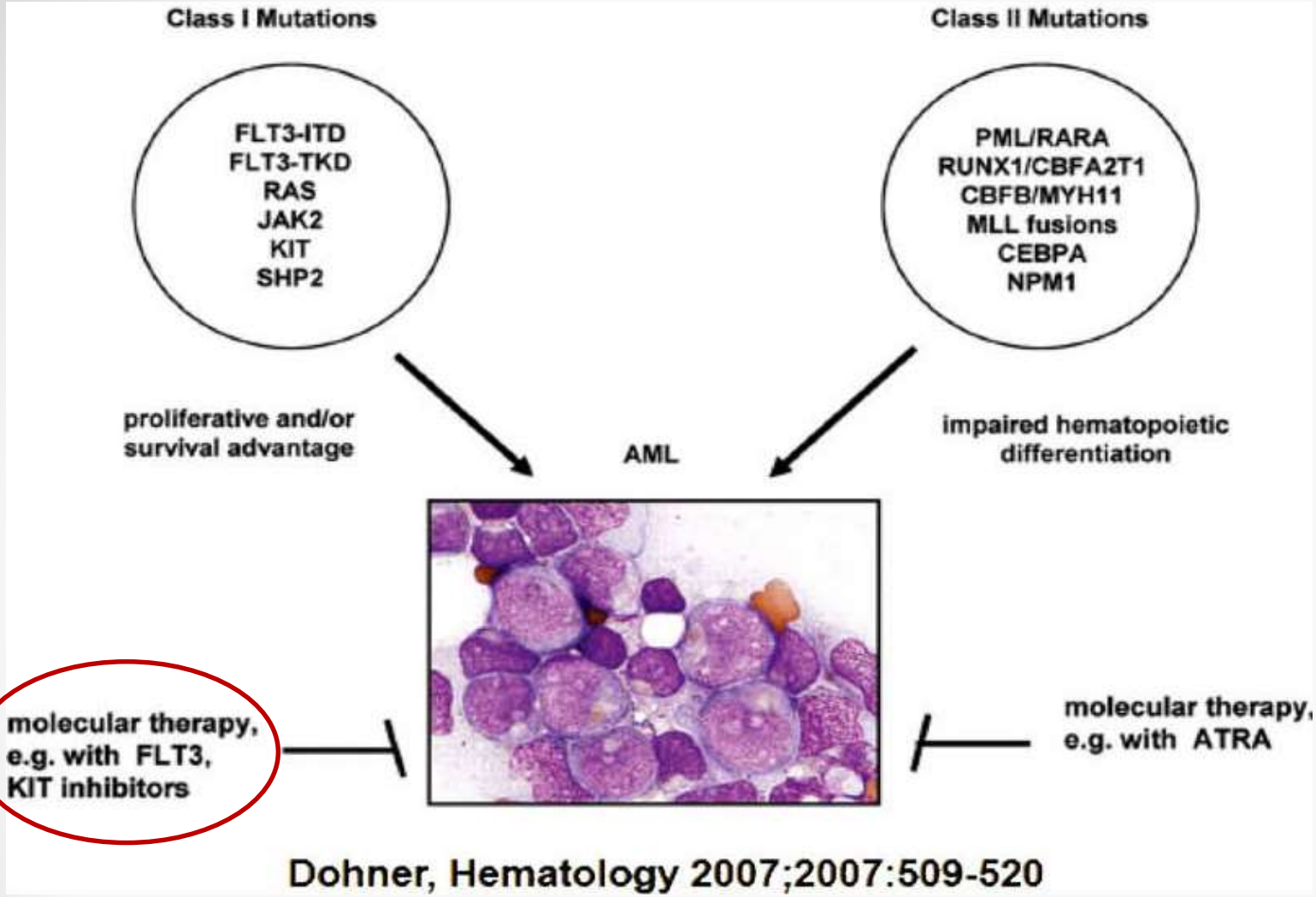


Le novità per la Leucemia Mieloide Acuta. Per questa malattia del sangue si profila la prima importante novità terapeutica dopo oltre 25 anni: **midostaurina ,**designato come "breakthrough therapy" dalla FDA statunitense, utilizzato insieme alla chemioterapia negli studi clinici dimostra un aumento significativo della sopravvivenza.

FLT3 è un recettore della tirosin-chinasi, posto sulla superficie cellulare, che svolge un ruolo nella proliferazione, o nell'aumento del numero di alcune cellule ematiche.



La midostaurina inibisce la mutazione genetica FLT3, presente in circa 1/3 dei pazienti con Leucemia Mieloide Acuta. Usata in combinazione con la chemioterapia, riduce in maniera significativa il rischio di recidiva offrendo una maggiore probabilità di lunga sopravvivenza.
La nuova molecola dovrebbe essere disponibile in Italia dal 2017.

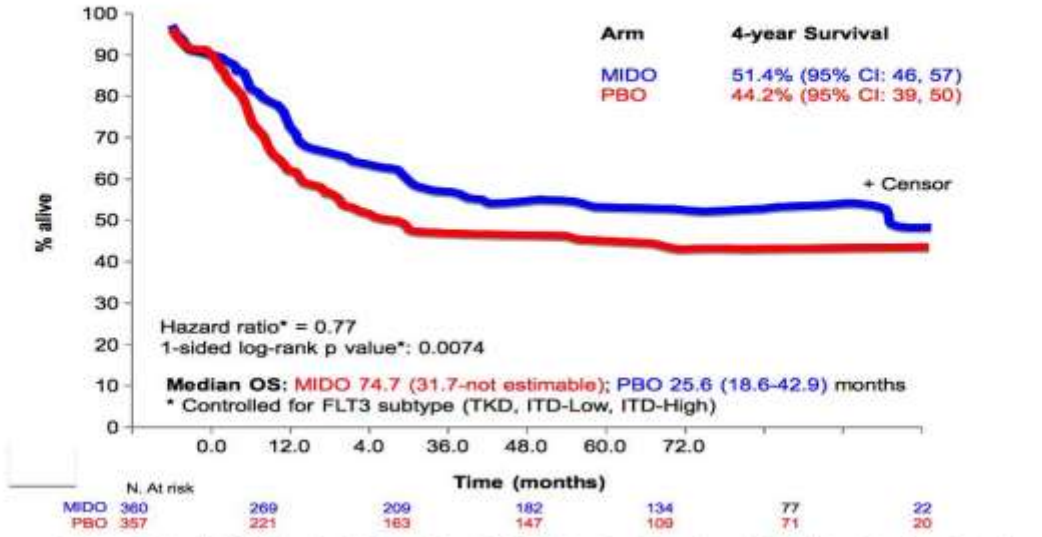


Modelli di cooperazione e mutua esclusività suggeriscono una forte relazione biologica tra disregolazione di specifici geni e distinte categorie di LAM .

Studio clinico di fase III RATIFY (CALGB 10603). 717 paz arruolati

ASH 2015 Highlights dal 57° congresso annuale dell'American Society of Hematology
Orlando (Florida), 5-8 dicembre 2015

Figure 1. Overall Survival With Midostaurin Versus Placebo in AML

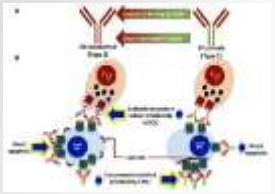


MIDO, midostaurin; PBO, placebo; OS, overall survival; TKD, tyrosine kinase domain; ITD, internal tandem duplication.

Gruppo A	CH standard + Midostaurina	OS 74.7 mesi	EFS 8.0 mesi
Gruppo B	CH standard + Placebo	OS 25.6 mesi	EFS 3.0 mesi

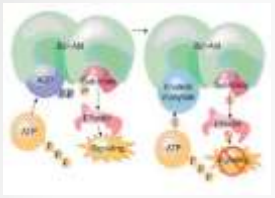
I pazienti sono stati stratificati in base ai seguenti sottotipi di mutazione:
- dominio tirosin-chinasico (TKD),
- frequenza di mutazione allelica alta ITD [duplicazioni interne in tandem] (superiore a 0.7) e
- frequenza di mutazione allelica bassa ITD (0.05-0.7)

Quali le innovazioni



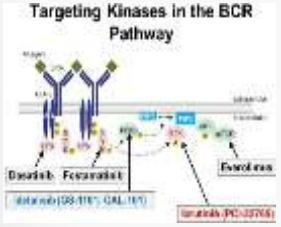
Immunoterapia.

Nuovi **anticorpi monoclonali** che a breve andranno ad impattare non solo sulle future sperimentazioni cliniche ma anche sulla comune pratica clinica ematologica, grazie ai loro meccanismi d'azione innovativi.



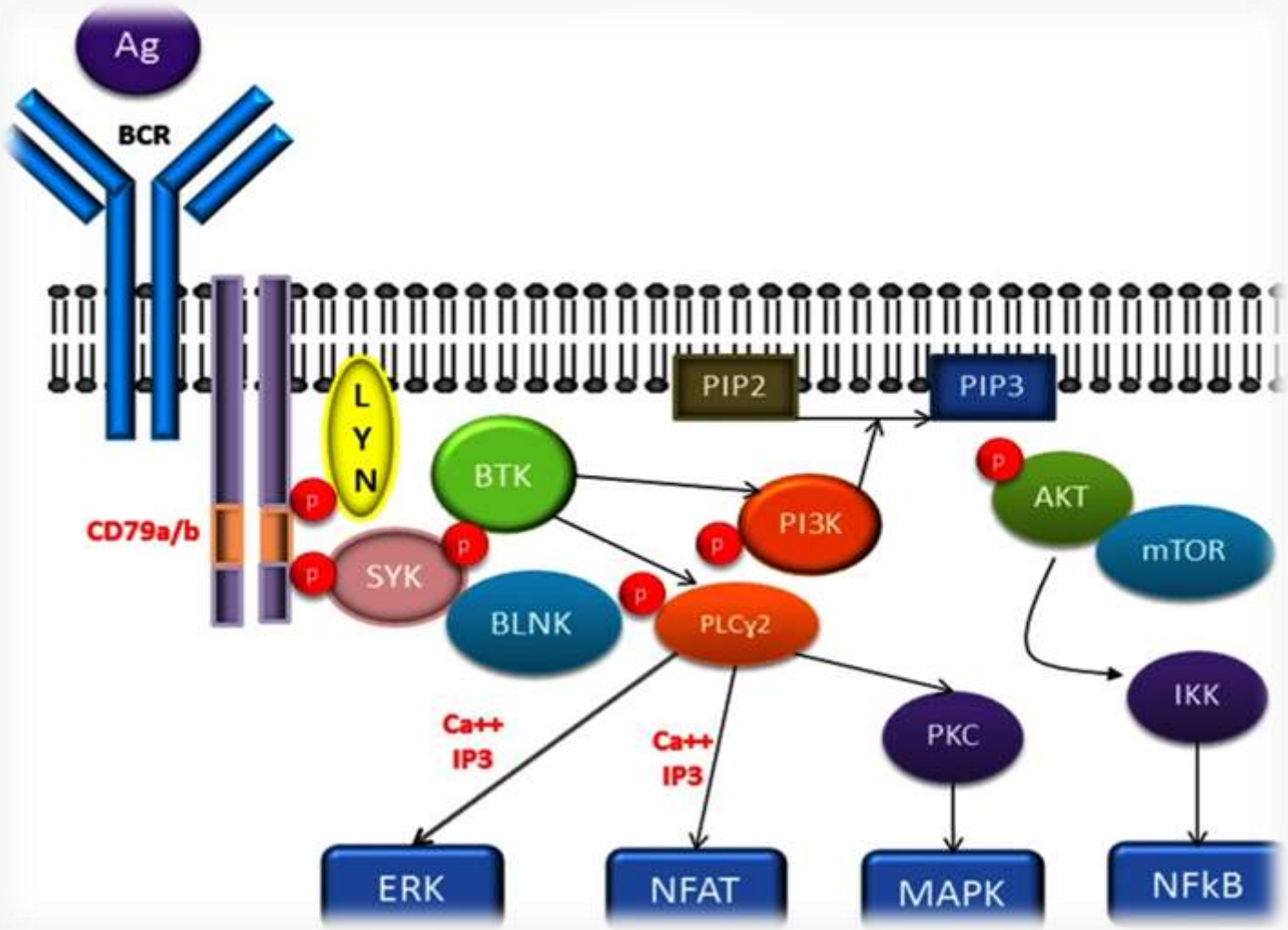
farmaci mirati al bersaglio molecolare (inibitori della tirosin-chinasi nella LMC: uno di prima generazione (**imatinib**), tre di seconda generazione (**nilotinib, dasatinib, bosutinib**) e uno di terza generazione (**ponatinib**) **).**

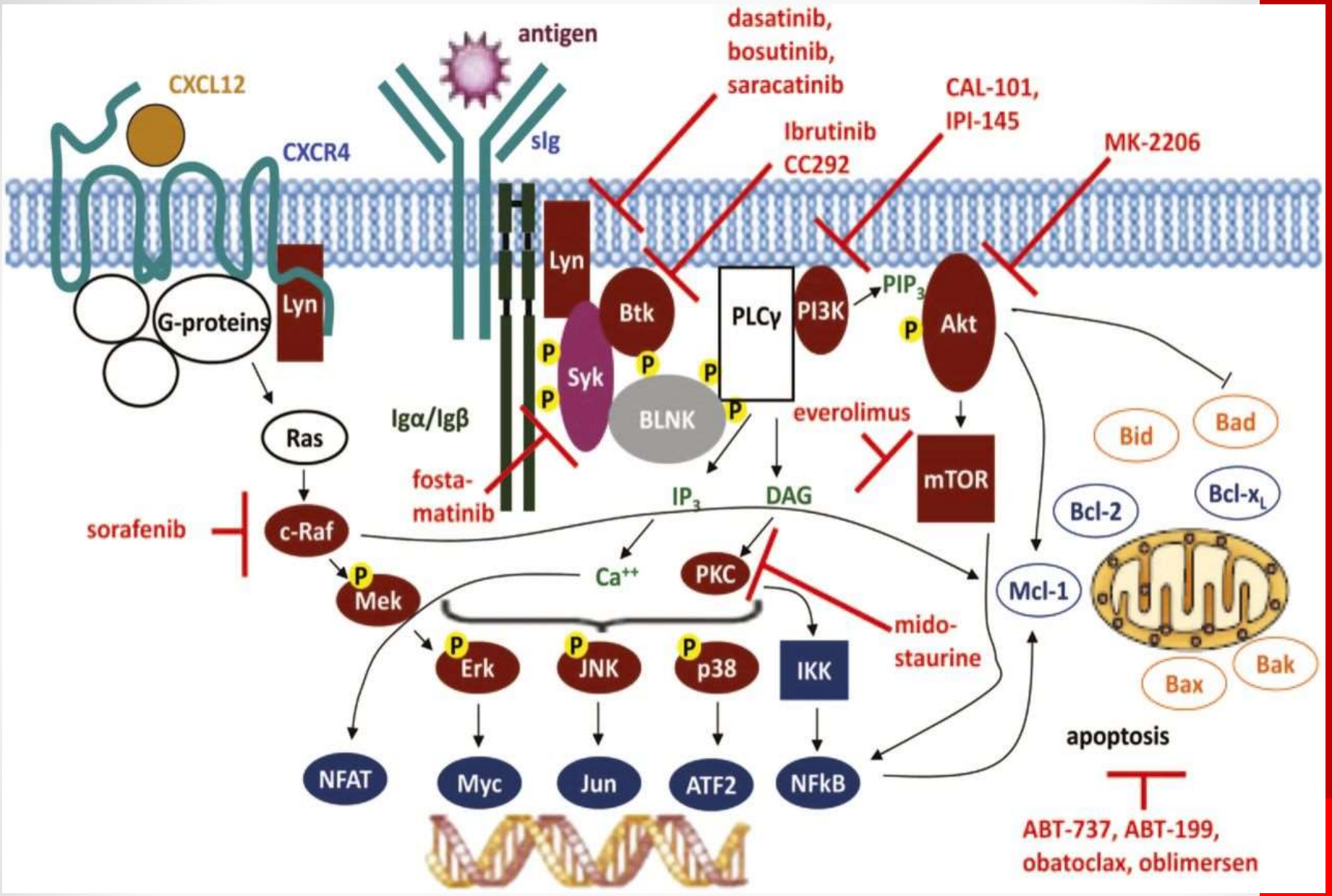
Inibitori del FLT3

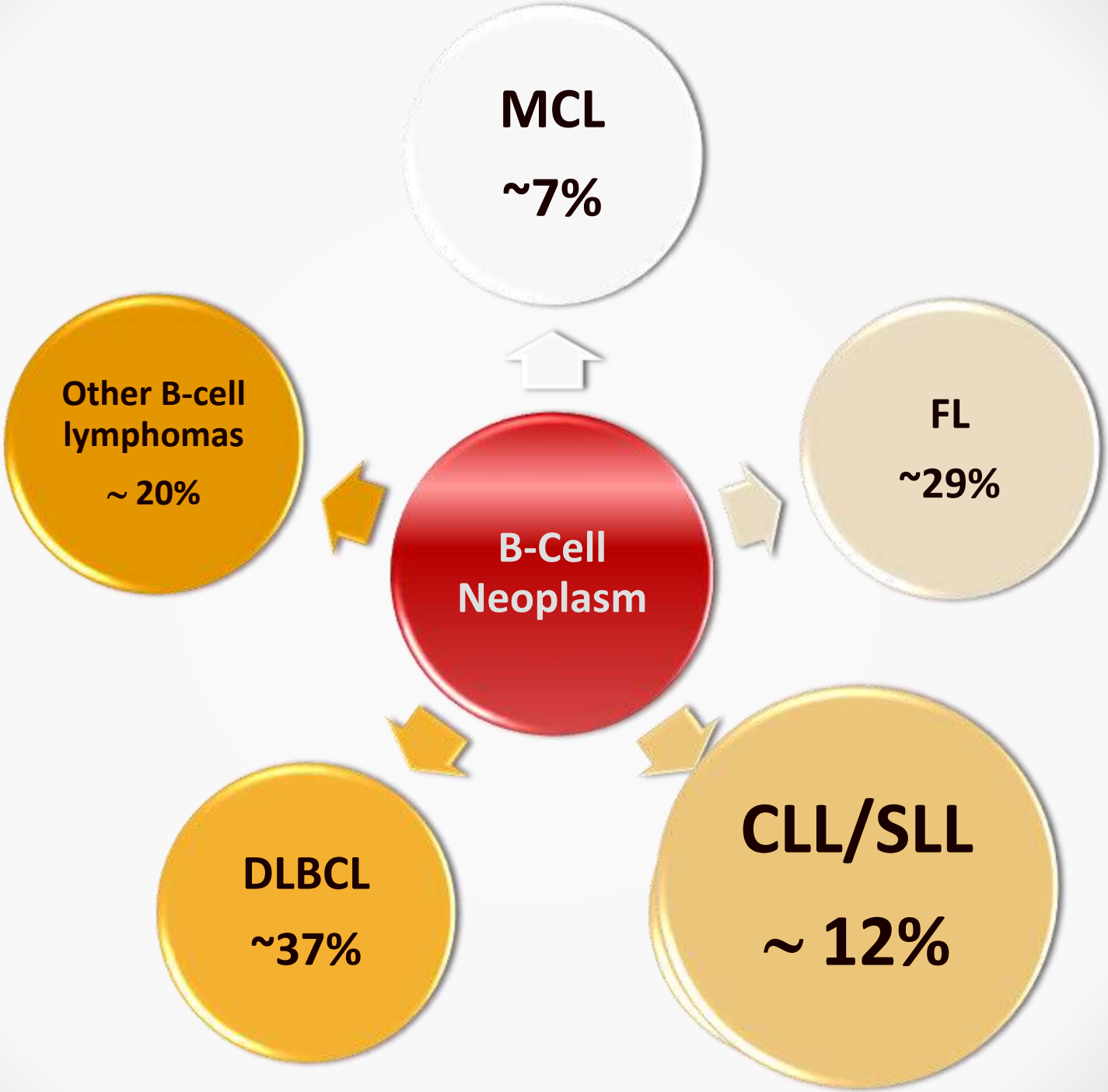


inibitori che agiscono sull'attivazione delle **cellule linfoidi**, in particolare quelli di **tipo B**, in grado di bloccare i segnali di uno specifico **recettore**, il **BCR**

BCR- targeted treatment




antigen
dasatinib,
bosutinib,
saracatinib
CAL-101,
IPI-145
MK-2206
CXCL12
CXCR4
sIg
Ibrutinib
CC292
Lyn
Lyn
G-proteins
Btk
PLCγ
PI3K
PIP3
Akt
P
Syk
BLNK
Igα/Igβ
everolimus
Bid
Bad
Ras
fosta-
matinib
IP3
DAG
mTOR
Bcl-2
Bcl-xL
sorafenib
c-Raf
Ca++
PKC
Mcl-1
Mek
mido-
staurine
Erk
JNK
p38
IKK
Bax
Bak
apoptosis
NFAT
Myc
Jun
ATF2
NFkB
ABT-737, ABT-199,
obatoclax, oblimersen


MCL
~7%
Other B-cell lymphomas
~ 20%
FL
~29%
B-Cell Neoplasm
DLBCL
~37%
CLL/SLL
~ 12%

CLL: obiettivi del trattamento

Assenza/ controllo prolungato dei sintomi

1

Efficacia della terapia

ORR, RC,MDR- → DFS, TTNT

Miglioramento qualità della vita

2

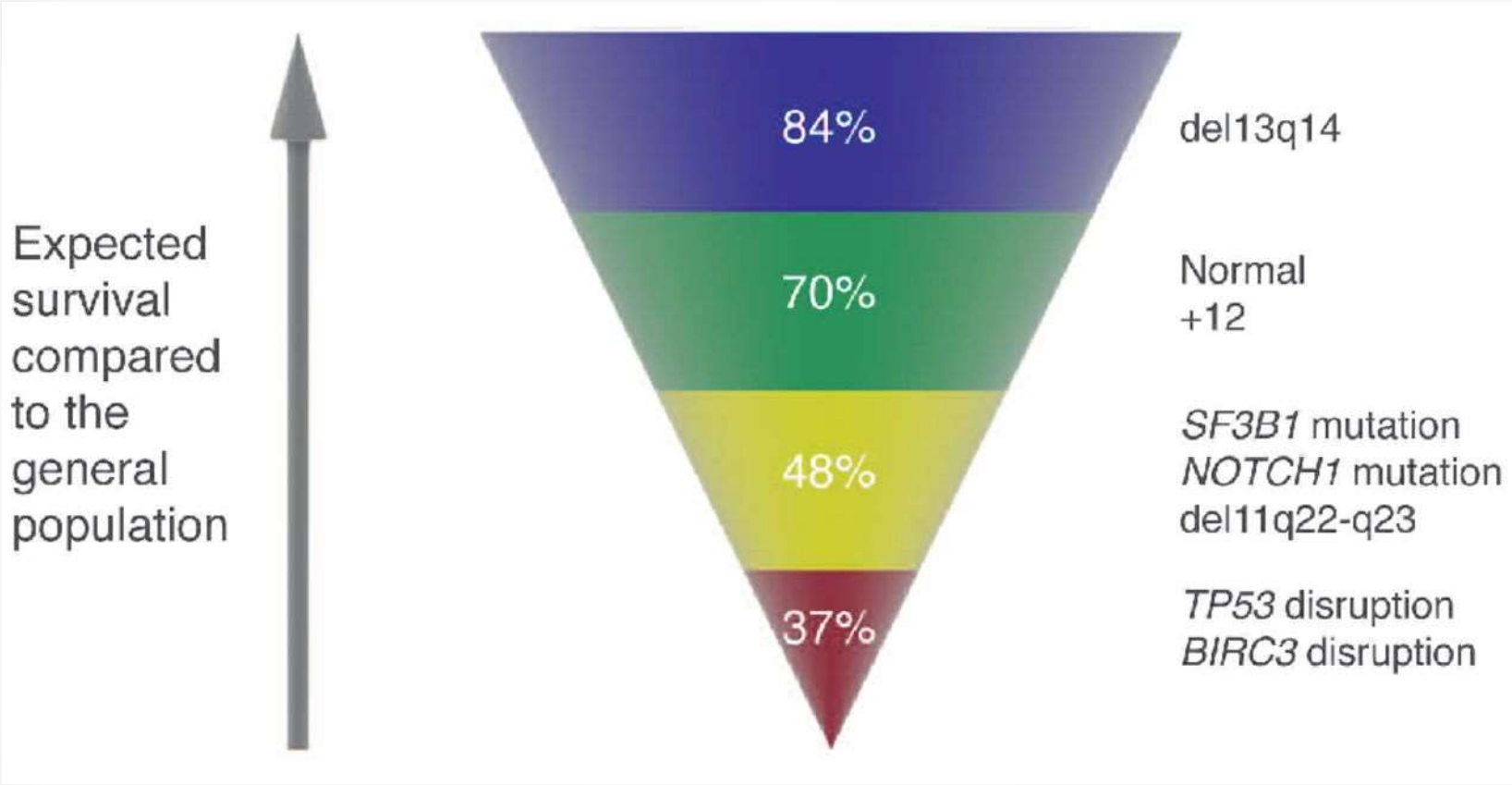
- riduzione/assenza di sintomi
- effetti collaterali minimi/ assenti
- non aggravamento delle co-morbilità

Aumento della sopravvivenza

3

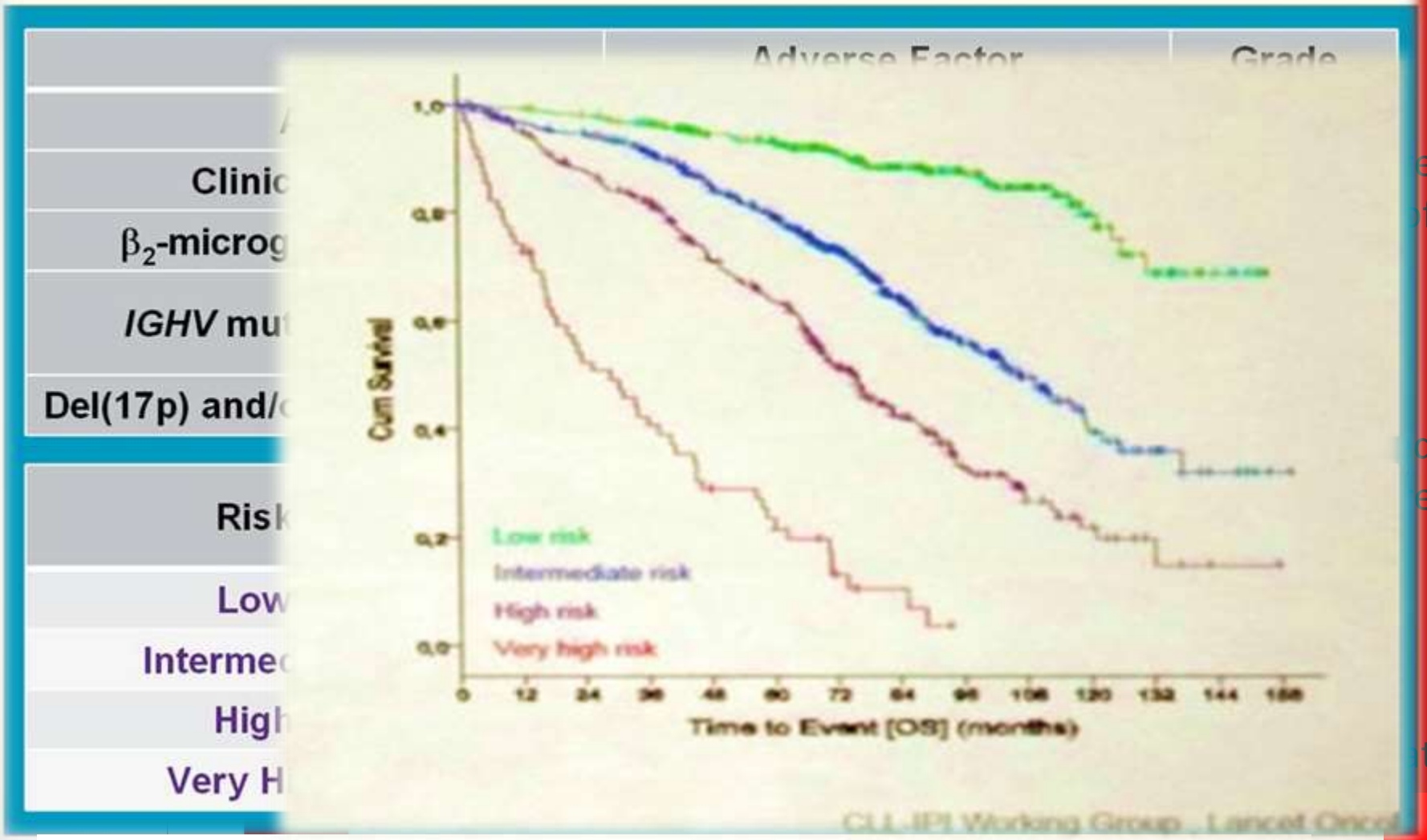
Effetto combinato **1** + **2**

Expected survival of CLL patients stratified according to the integrated mutational and cytogenetic model and compared to the matched general population.



Foà R et al. Haematologica 2013;98:675-685

CLL International Prognostic Index (2016)



3472 pazienti da 5 gruppi di studio in Europa ed in USA

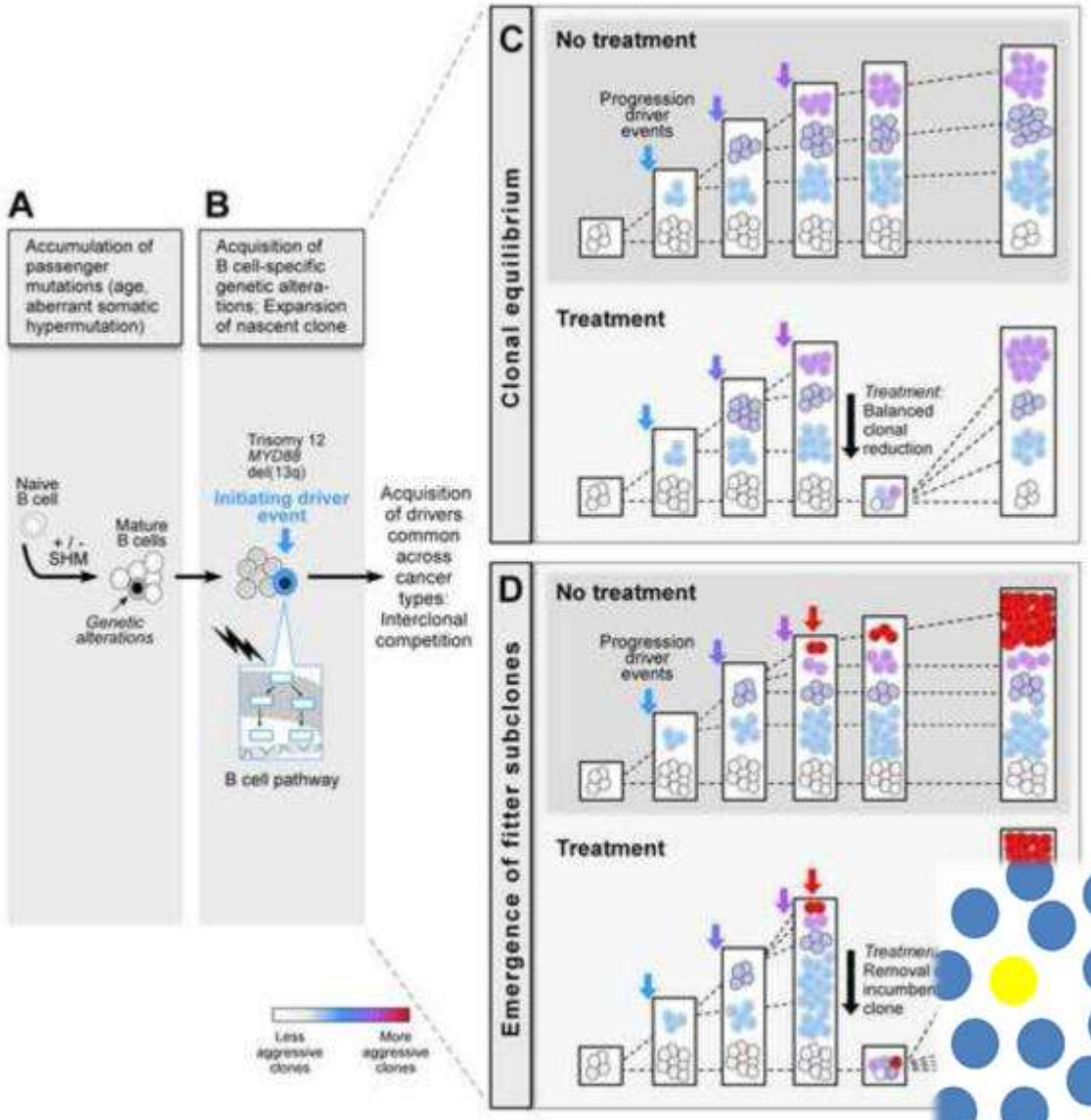
1254 pazienti da una coorte Usa e Scandinava per la validazione

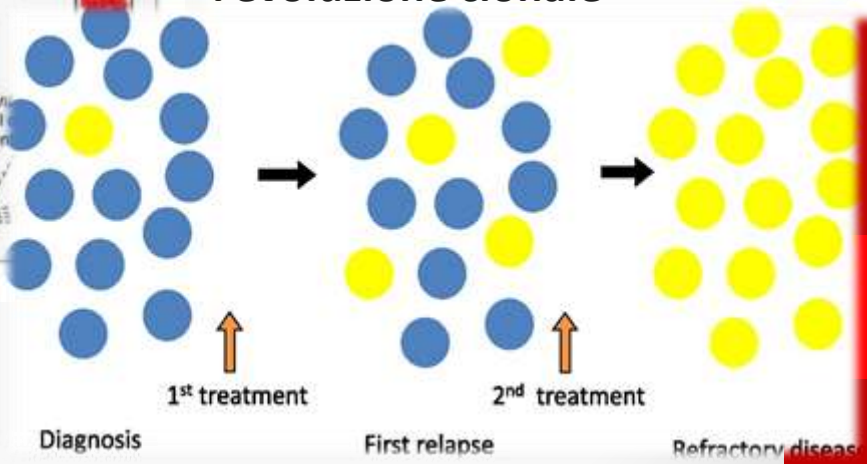
Dighiero G, *et al. N Engl J Med* 1998; 338:1506–1514.

Le recidive sono fondamentalmente legate ad una evoluzione clonale

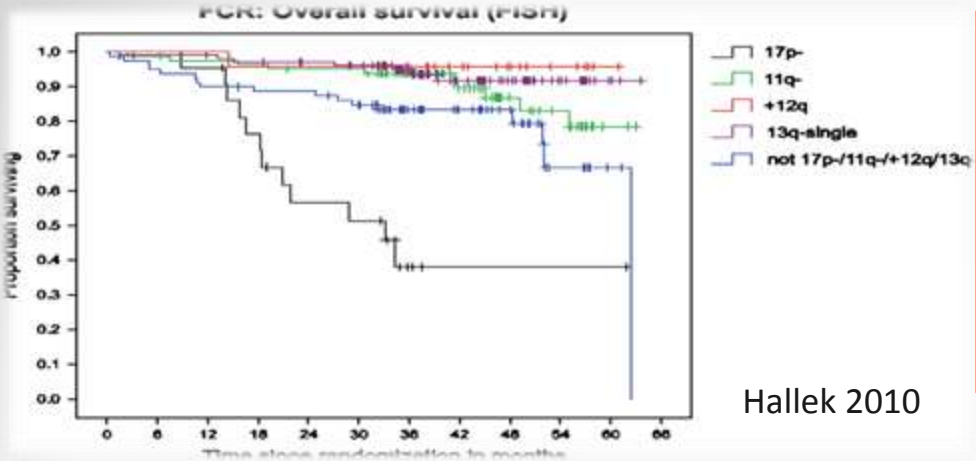
L'evoluzione clonale ed il trattamento mostrano una complessa relazione. Molte CLL non trattate ed una minoranza di quelle trattate mantengono un equilibrio clonale stabile negli anni.

Tuttavia in presenza di un subclone resistente, la terapia può distruggere l'equilibrio interclonale e accelerare l'evoluzione clonale





Landau DA et al, Cell 2013

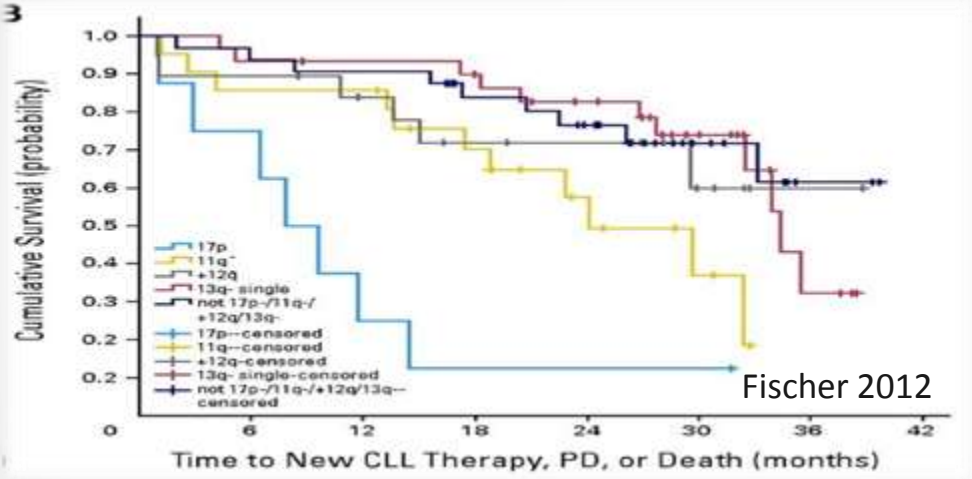


Hallek 2010

FCR TN

OS at 3 years

De17p	**=38%**
Not abnormal	**=83%**

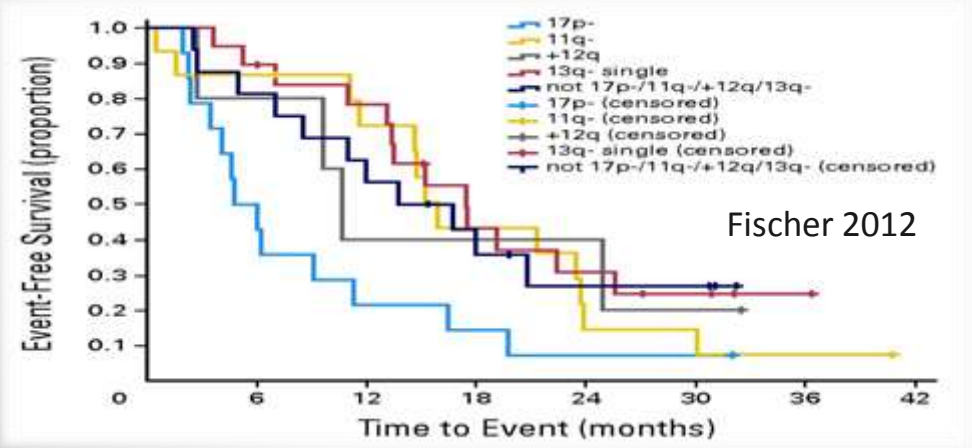


Fischer 2012

BR TN

Median Cumulative Survival

De17p	**=7.8 mo**
Not abnormal	**=not reached**



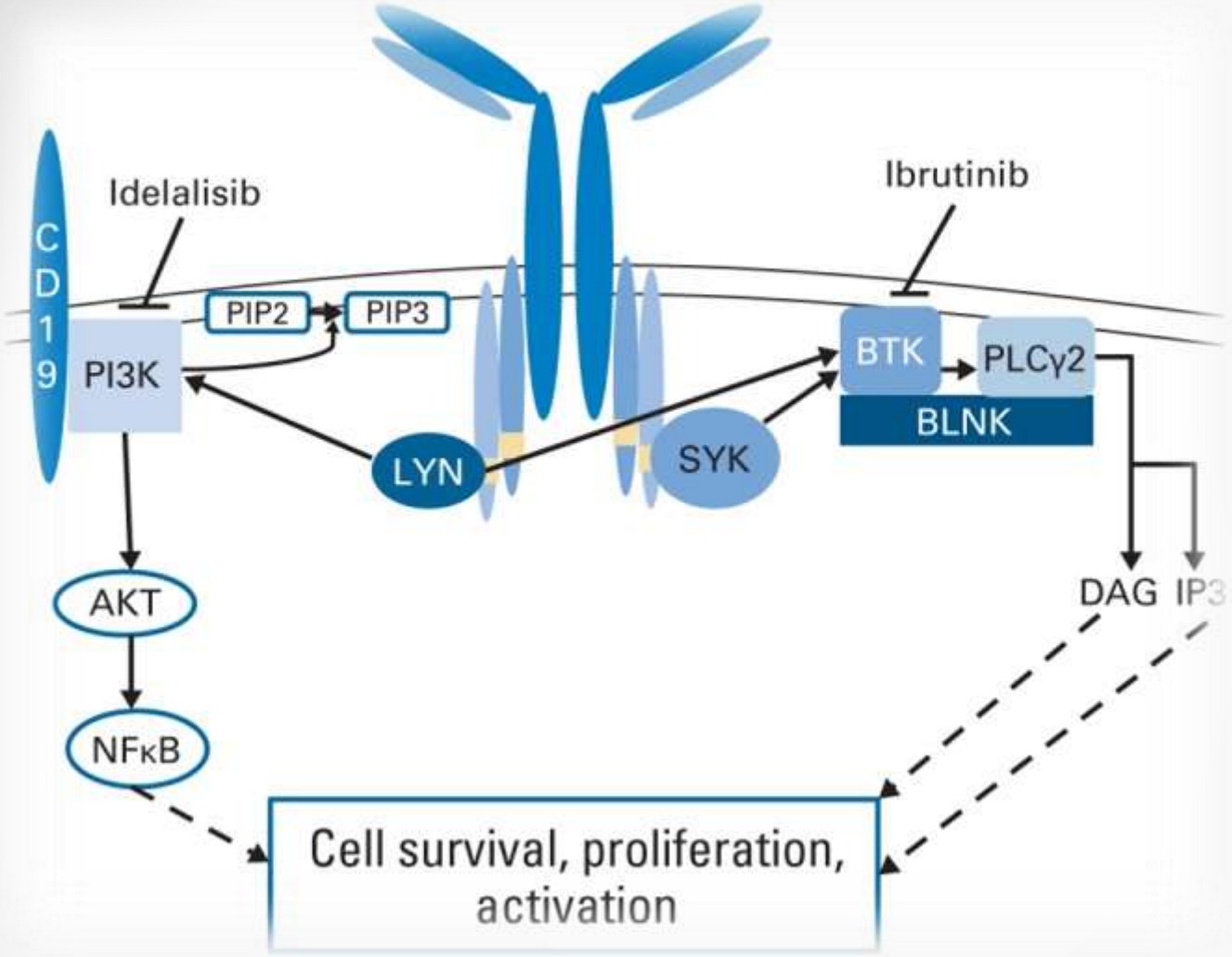
Fischer 2012

BR RR

Median EFS

De17p	**=4.8 mo**
Not abnormal	**=13.8 mo**

del 17p/p53m: negative predictive marker for FCR & BR



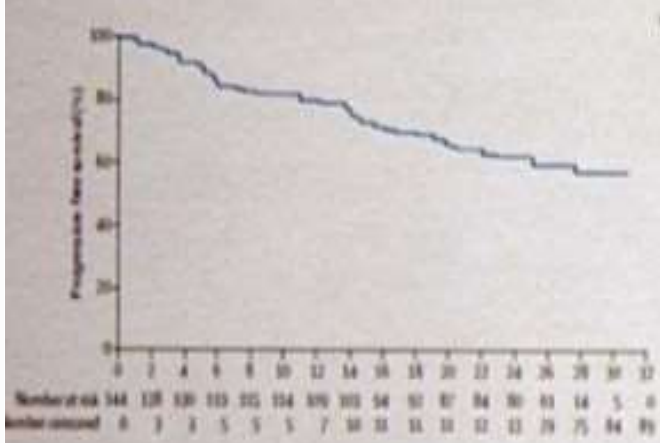
Bird JC et al, J Clin Oncol 2014

New drugs

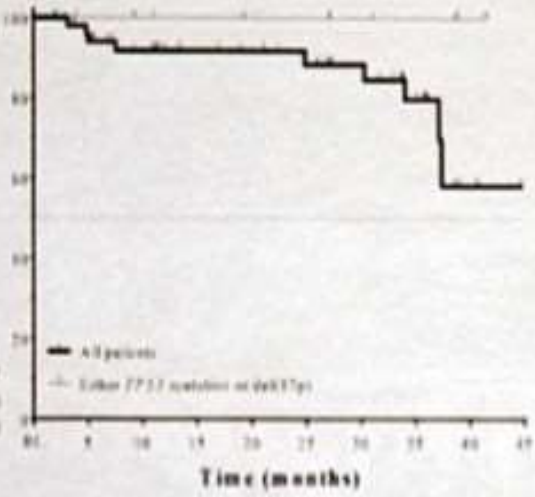
Regimen	PFS	Tocicity (all grades)
Ibrutinib	79,3% 12 months PFS in rel/ref with 17p-	Atrial fibrillation (8%) Bleeding (50%)
Idelalisib+R	19,4 months	GI toxicity (42%) Pneumonitis (6%)
Idelalisib+various combination	28 months median PFS in rel/ref CLL	Grade 3 Diarrhea 51% Pneumonitis 3%

del17p/p53m: *improved outcome with new agents*

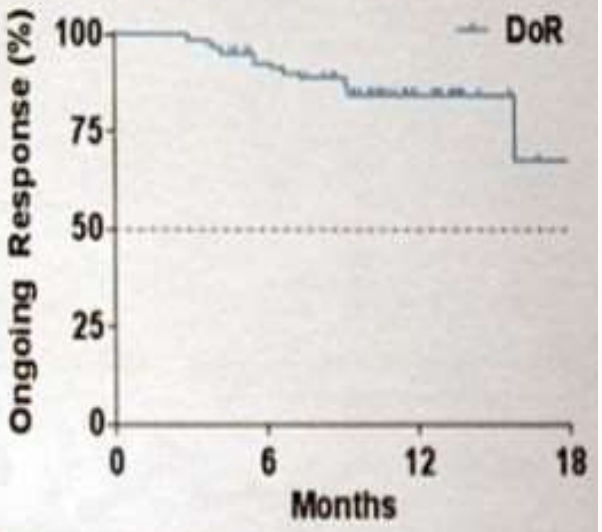
Ibrutinib in R/R with del(17p)



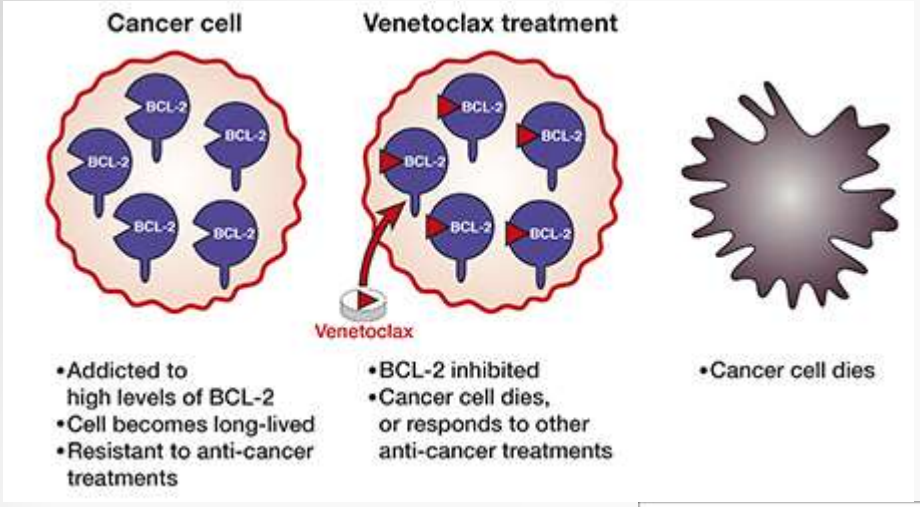
Idelalisib + R in elderly patients



Venetoclax in R/R with del(17p)



O'Brien S et al., Lancet Oncology 201
O'Brien S et al., Blood 201
Stilgenbauer S et al., Lancet Oncology 201



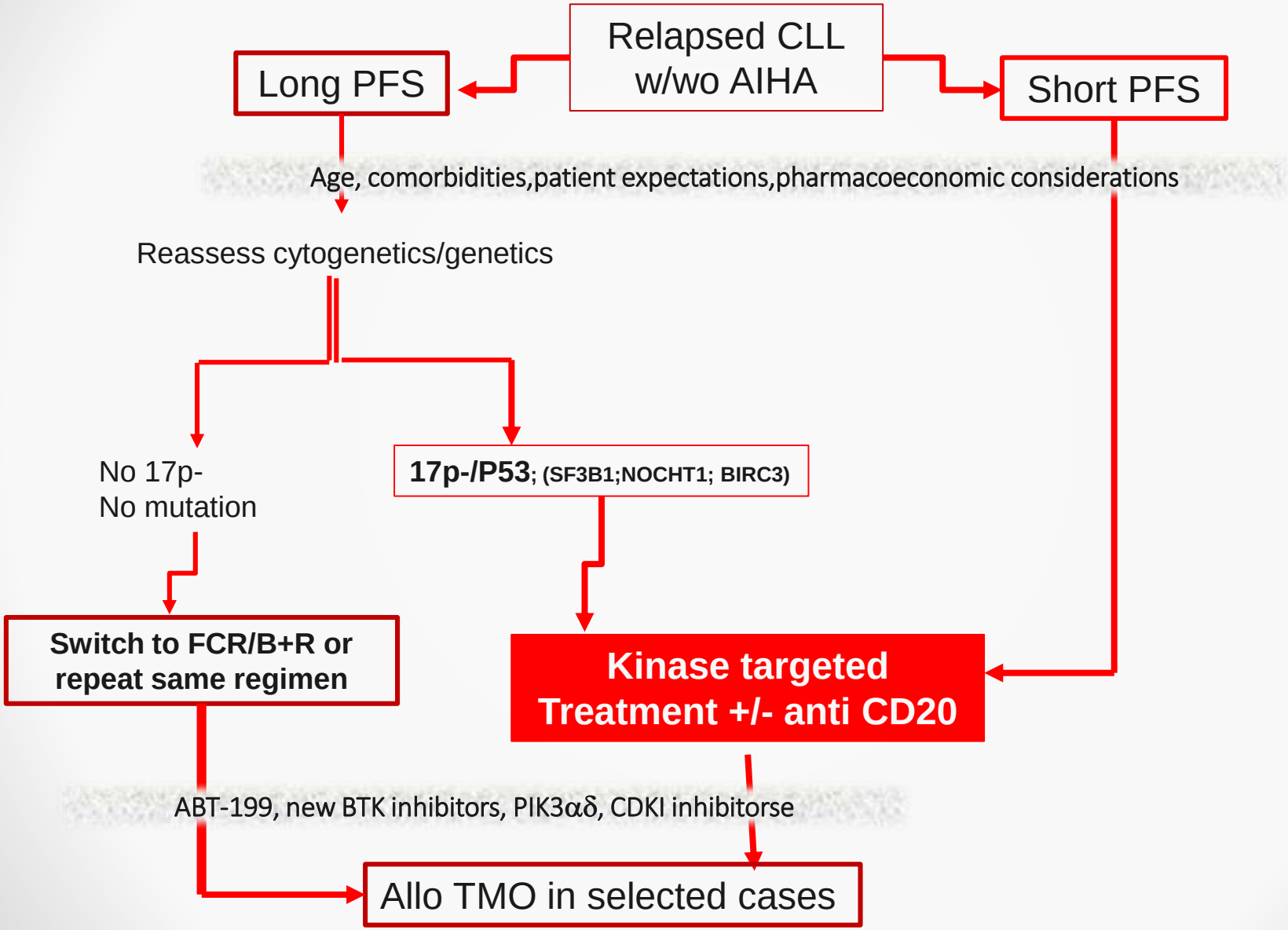
Venetoclax Monotherapy in Ultra-High Risk CLL With del(17p) — *Results*

- Median time on study: 12.1 months (0.03–21.5 range)
- 37 patients discontinued venetoclax
- 22 patients had disease progression (11/107 had Richter's transformation; 11/107 had CLL progression)
- Treatment AEs: Any grade = 96%; grade 3/4 = 76%
  - Most common AEs (any grade): neutropenia (43%), diarrhea (29%), nausea (29%), anemia (27%)

Best Response	Investigator, %	IRC, %
No response	26.2	20.6
Stable disease	22.4	NA
Disease progression	1.9	NA
Incomplete data	1.9	NA
Overall response	73.8	79.4
CR/CRi	15.9	7.5
nPR	3.7	2.8
PR	54.2	69.2

Stilgenbauer S, et al. ASH 2015. Abstract LBA6.

Relapsed CLL

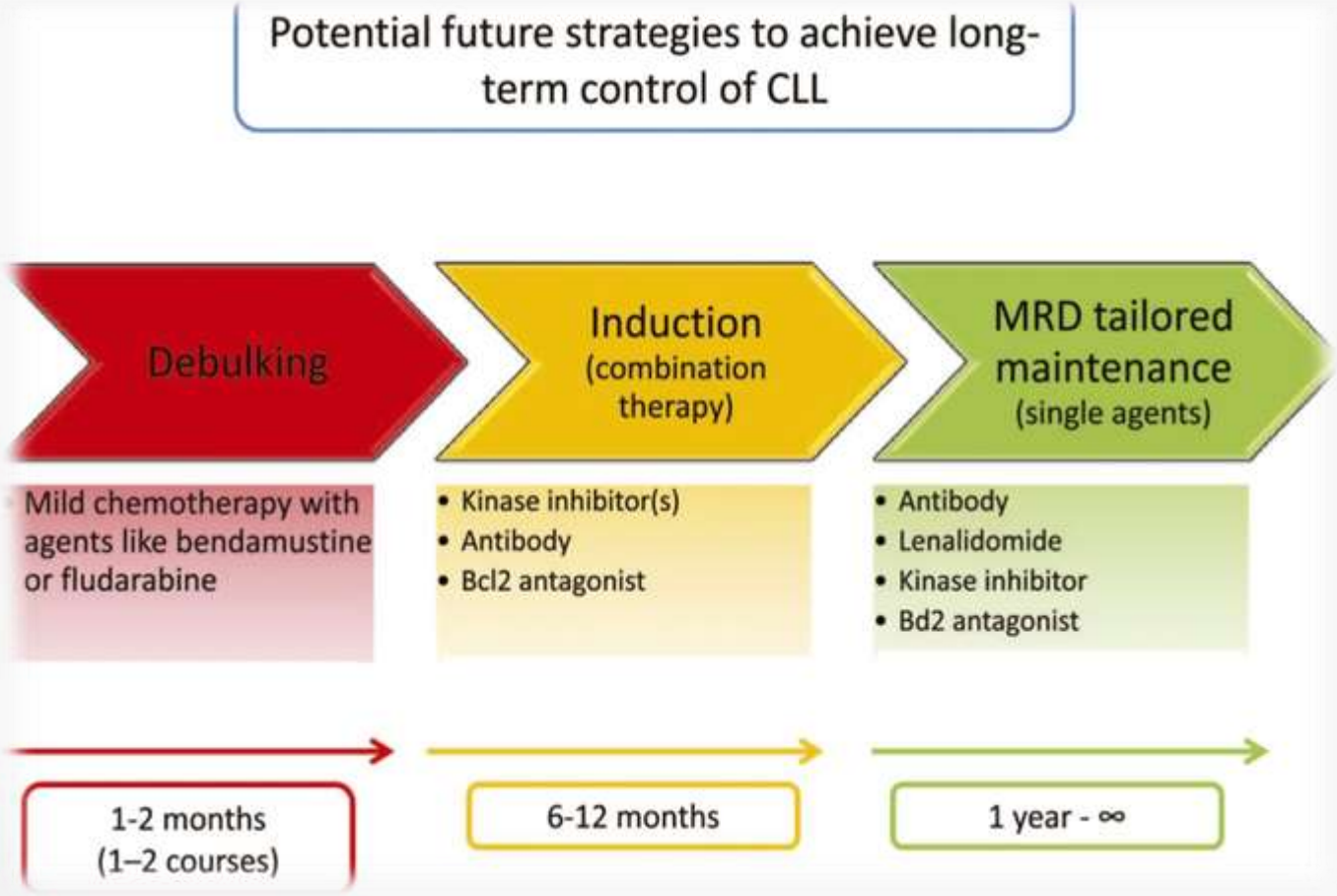


Terapia CLL: *come muoversi oggi?*
I nuovi farmaci

- In 1°-2° linea o linee successive in tutti i casi 17p-/P53m
- In 2° linea anche nei casi non 17p-/P53m se la PFS dopo una 1^ linea con chemio-immunoterapia è di breve durata (tempo non definito :<30 mesi?)
- Nelle linee successive

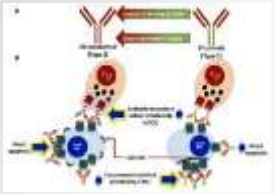
Come ottenere un controllo di una patologia che risulta inguaribile con i trattamenti disponibili?

Future treatment concept with novel agents.



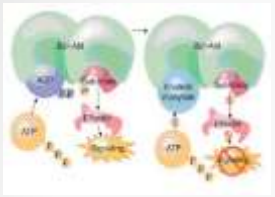
Michael Hallek Blood 2013;122:3723-3734

Quali le innovazioni



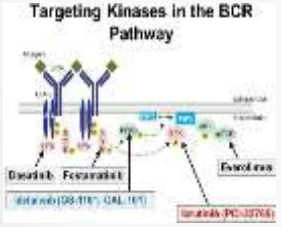
Immunoterapia.

Nuovi **anticorpi monoclonali** che a breve andranno ad impattare non solo sulle future sperimentazioni cliniche ma anche sulla comune pratica clinica ematologica, grazie a meccanismi d'azione innovativi.



farmaci mirati al bersaglio molecolare (inibitori della tirosin-chinasi nella LMC: uno di prima generazione (**imatinib**), tre di seconda generazione (**nilotinib, dasatinib, bosutinib**) e uno di terza generazione (**ponatinib**) **).**

Inibitori del FLT3



inibitori che agiscono sull'attivazione delle **cellule linfoidi**, in particolare quelli di **tipo B**, in grado di bloccare i segnali di uno specifico **recettore**, il **BCR**

Inibitori del proteosoma (bortezomib, carfilzomib, ixazomib)

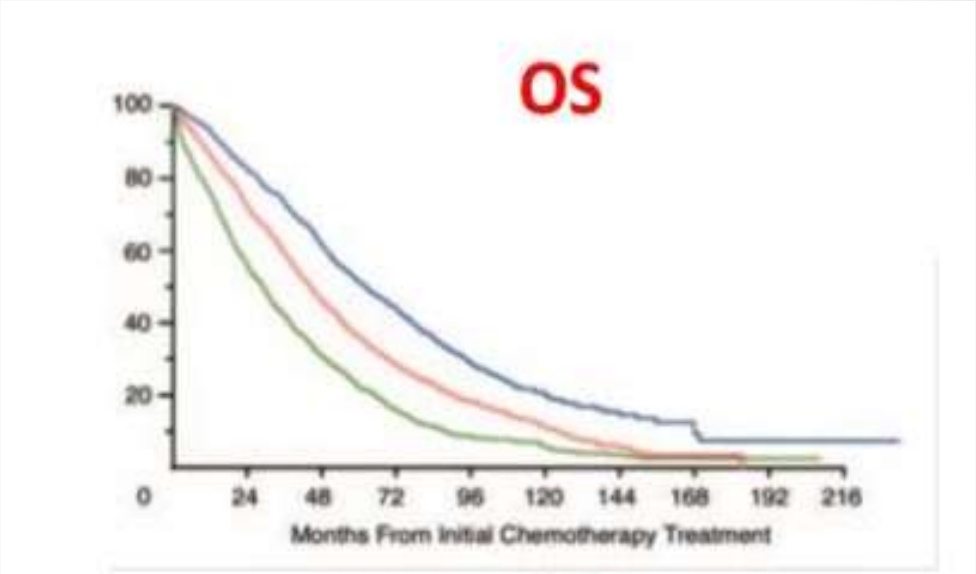
Immunomodulanti

Prognostic scores

ISS[1]

Based on

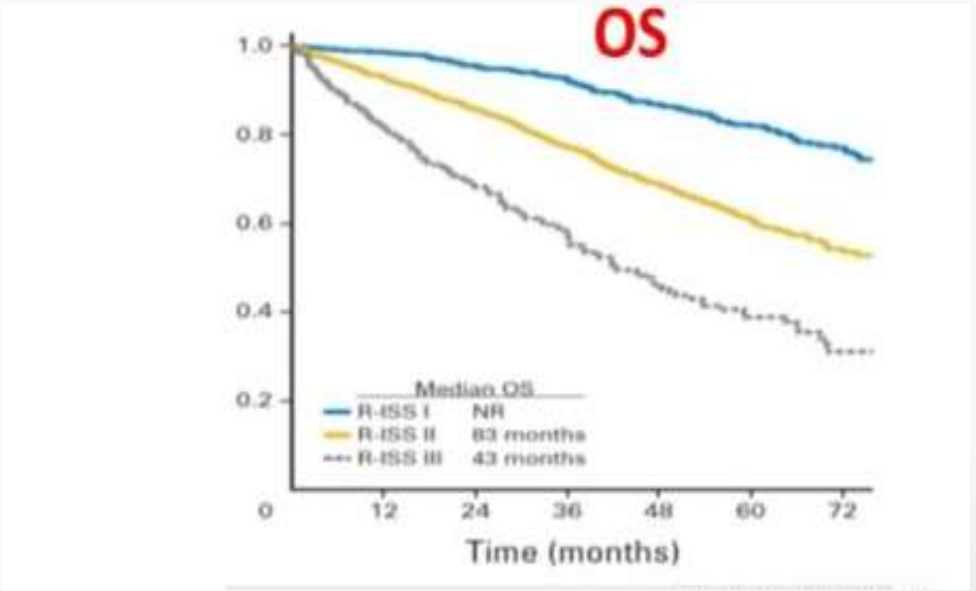
- **β2-microglobylin**
- **Albumin**

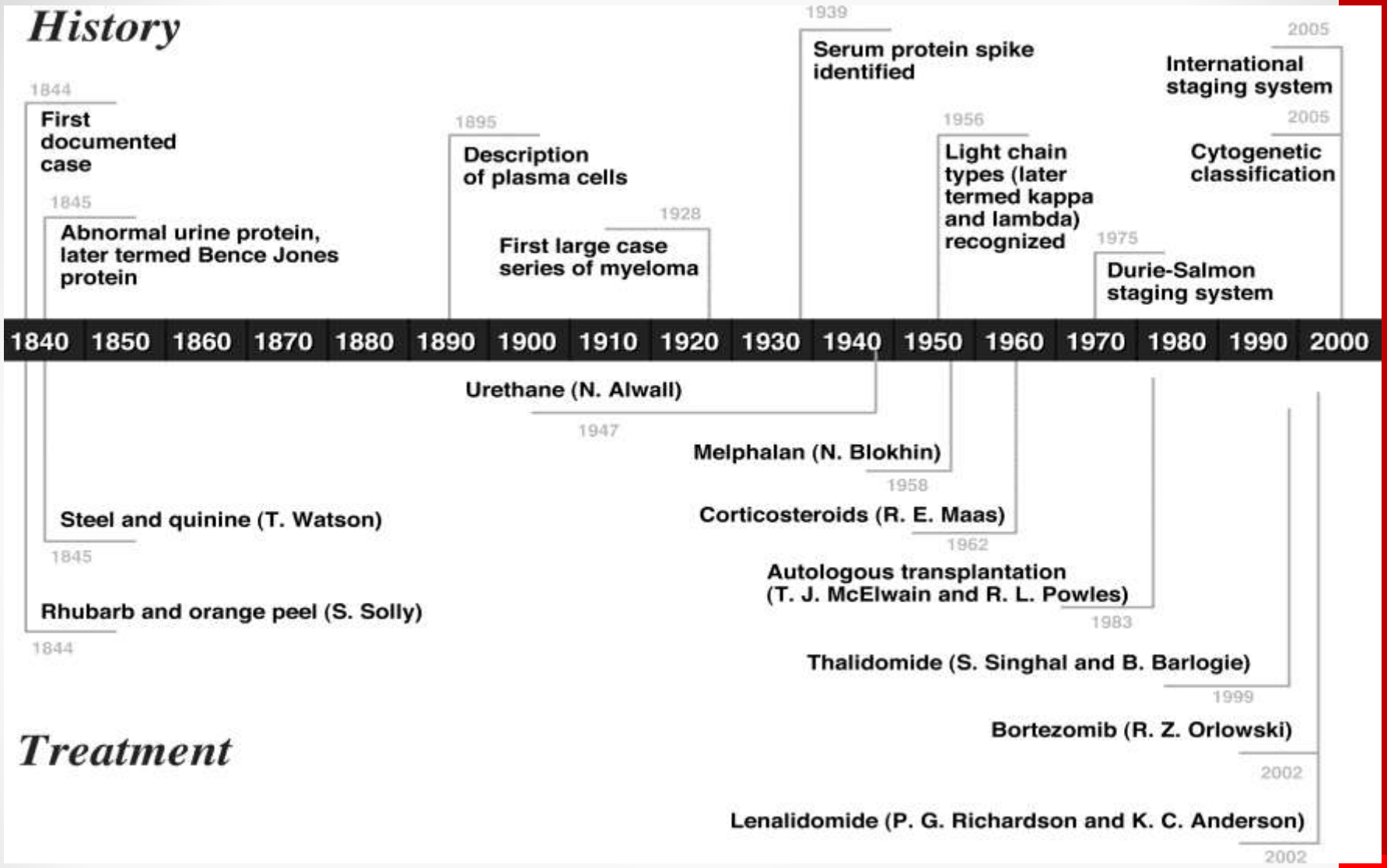


R-ISS[2]

Based on

- **ISS**
- **LDH**
- **FISH** [17p-, t(4;14), t(14;16)]





Robert A. Kyle and S. Vincent Rajkumar, *Blood 2008*

Inibitori del proteosoma (bortezomib, carfilzomib, ixazomib)

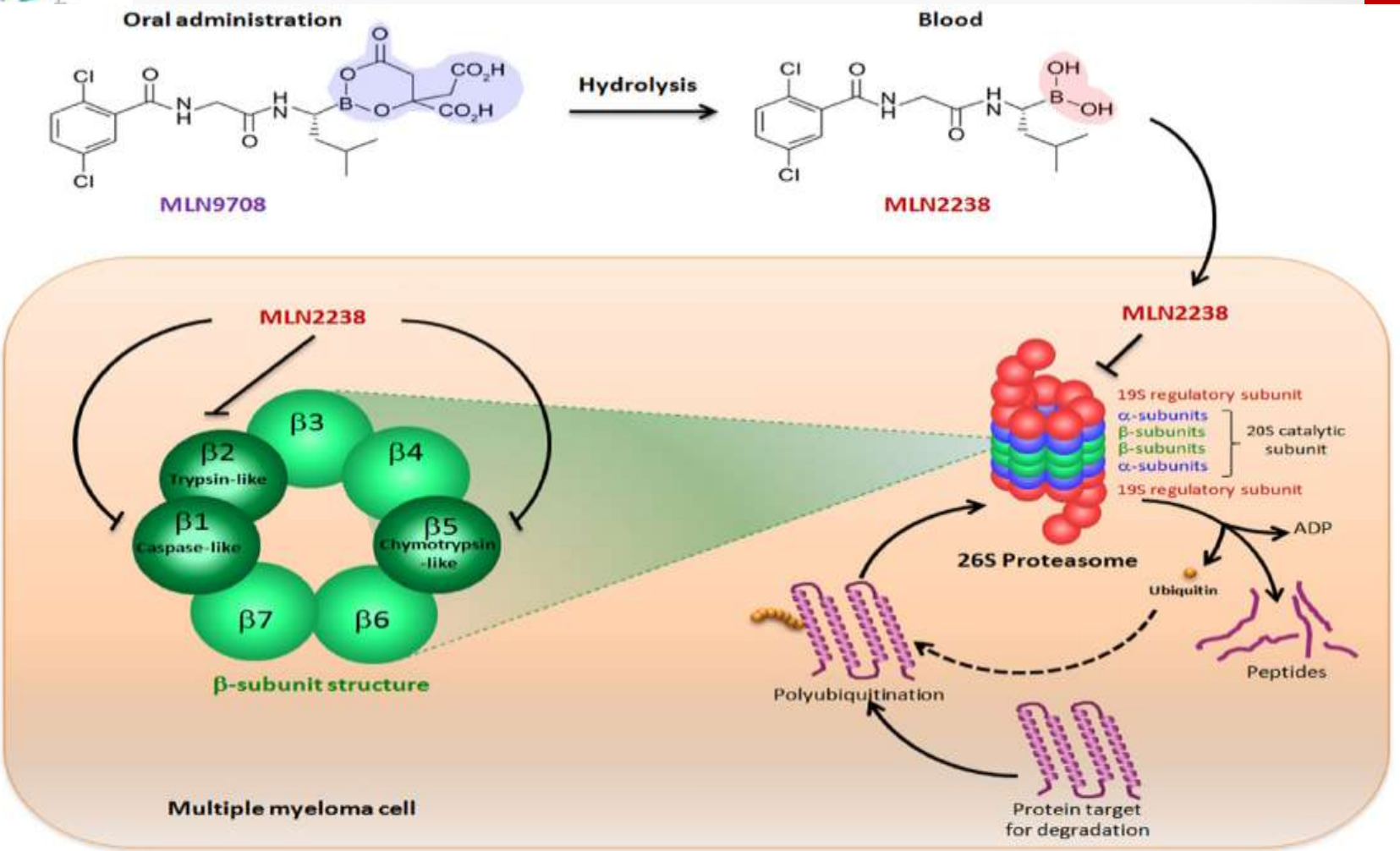
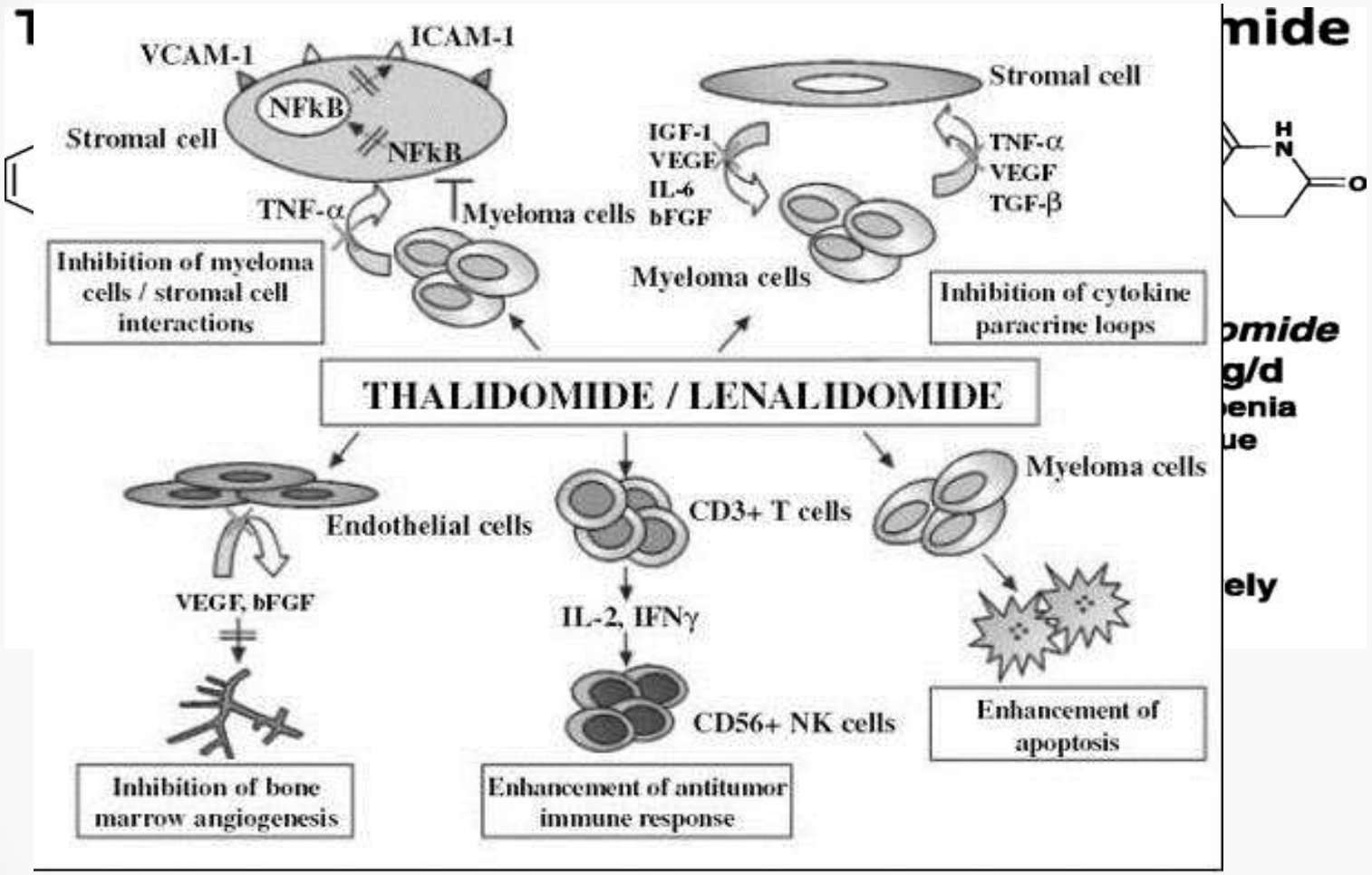
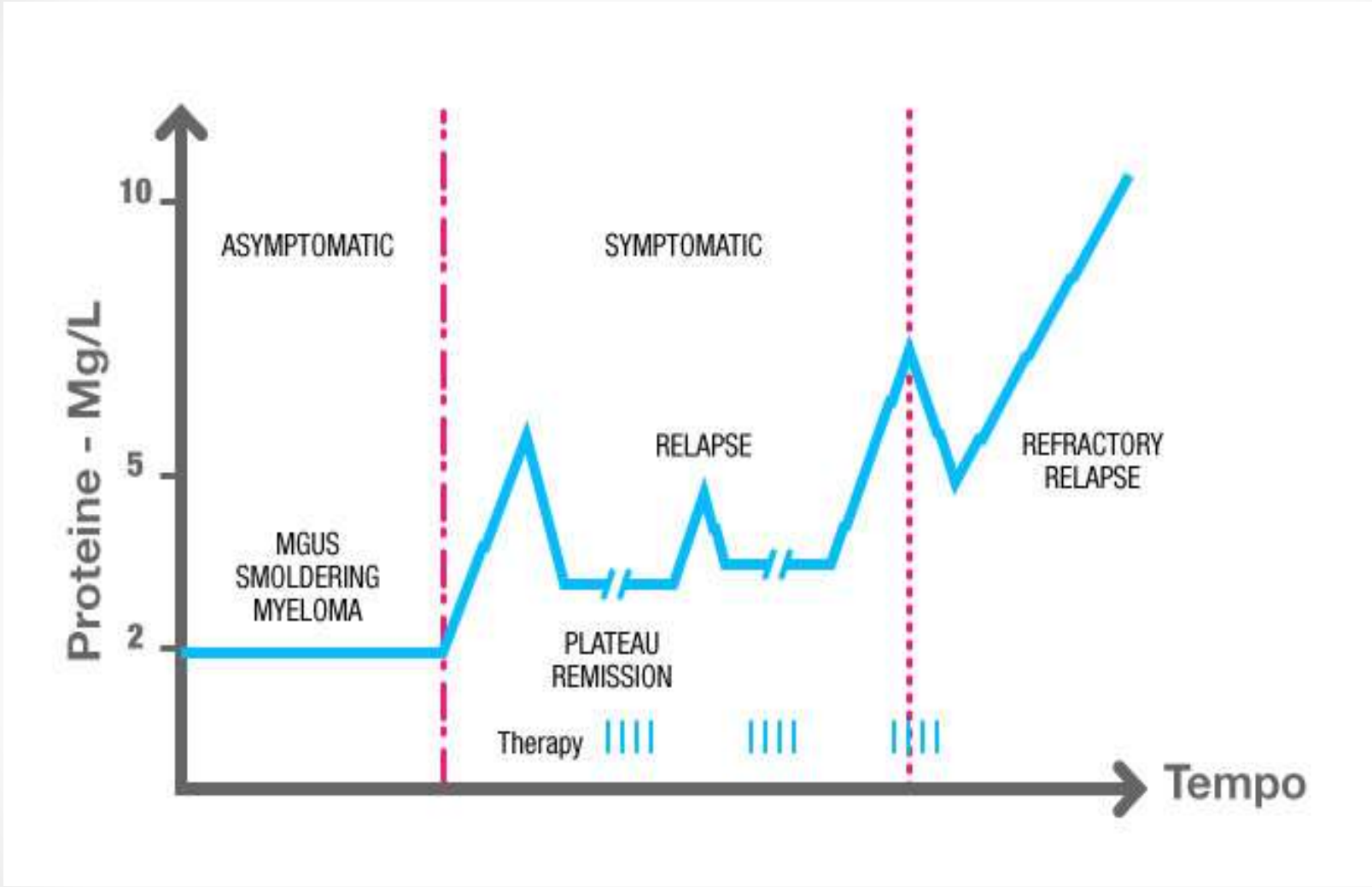


Figure 1 Mechanism of action of ixazomib.
Notes: Ixazomib (MLN9708) administered orally as a capsule is rapidly absorbed and hydrolyzed to the biologically active form (MLN2238) when it comes in contact with aqueous plasma. Ixazomib blocks protein degradation by inhibiting the 20S catalytic subunit of the 26S proteasome. More specifically, at lower concentrations, MLN2238 inhibits the β5 chymotrypsin-like subunit, which cleaves proteins after hydrophobic residues. At high concentrations, MLN2238 inhibits the β1 caspase-like subunit and β2 trypsin-like subunit, which cleave proteins after acidic and basic residues, respectively.

Kortuem KM et al. Blood 2013.7;121(6):893-7.

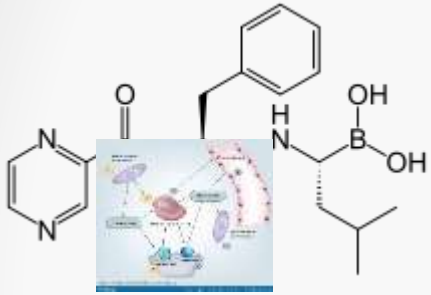
Immunomodulanti (IMIDs)

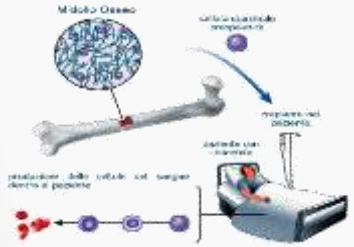



Proteine - Mg/L
10
5
2
ASYMPTOMATIC
SYMPTOMATIC
MGUS
SMOLDERING
MYELOMA
RELAPSE
REFRACTORY
RELAPSE
PLATEAU
REMISSION
Therapy
Tempo

Malattia alla diagnosi nel giovane

Bortezomib-based Induction	Mel 200	Consolidation	Maintenace





Terapia di induzio

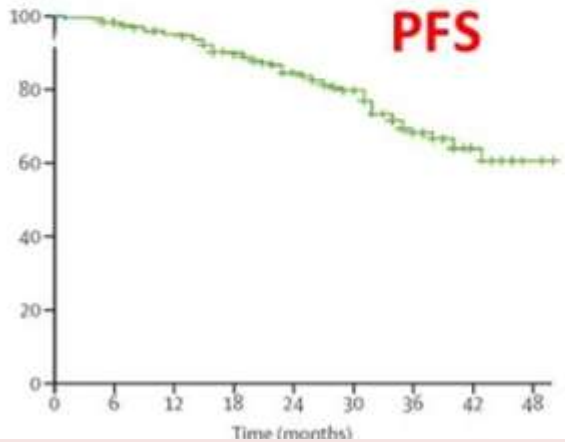
ASCT MEL 200
MEL 100

Consolidamento/mar

ORR: 96%

CR : 58%

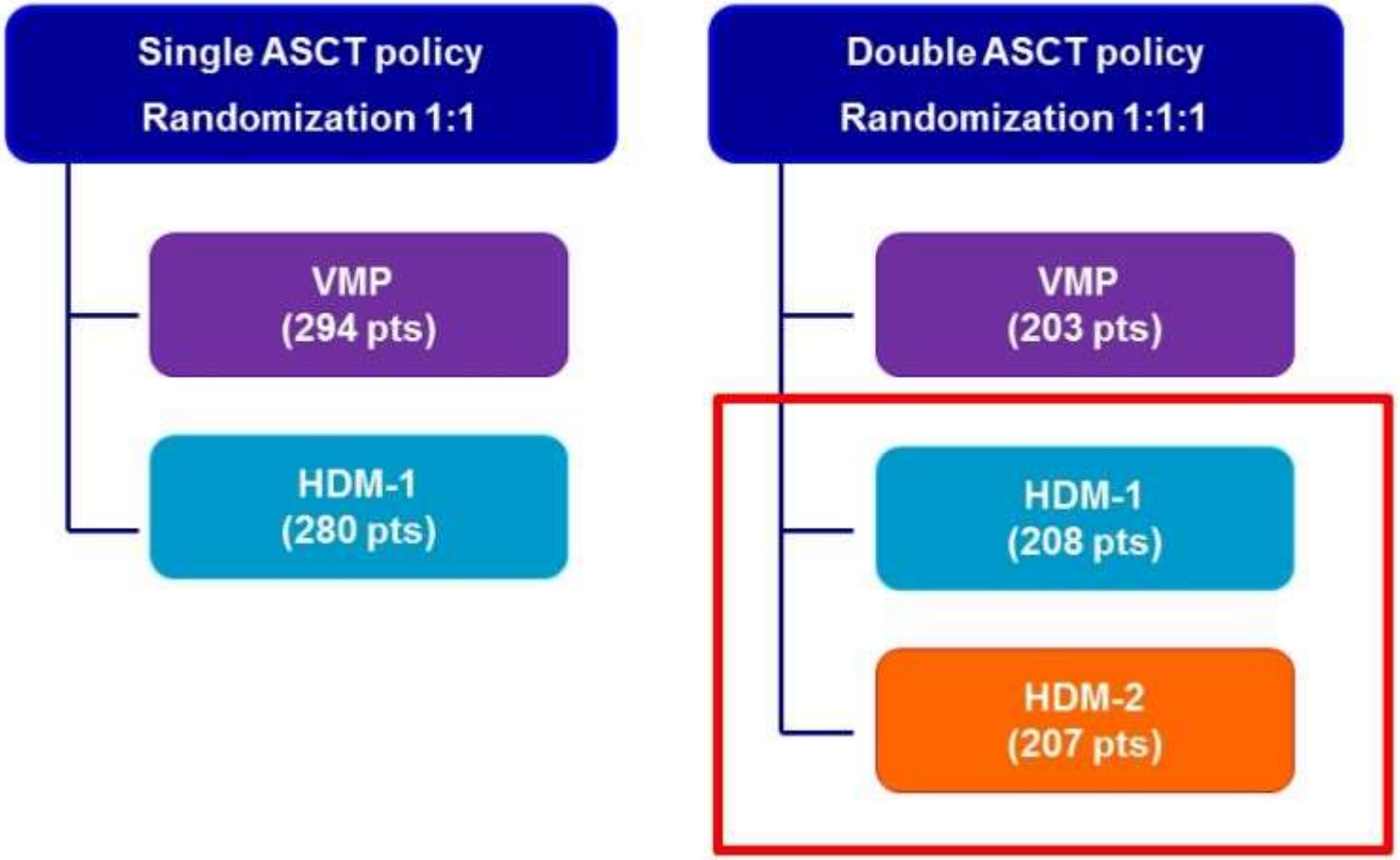
Median PFS: 57 mos



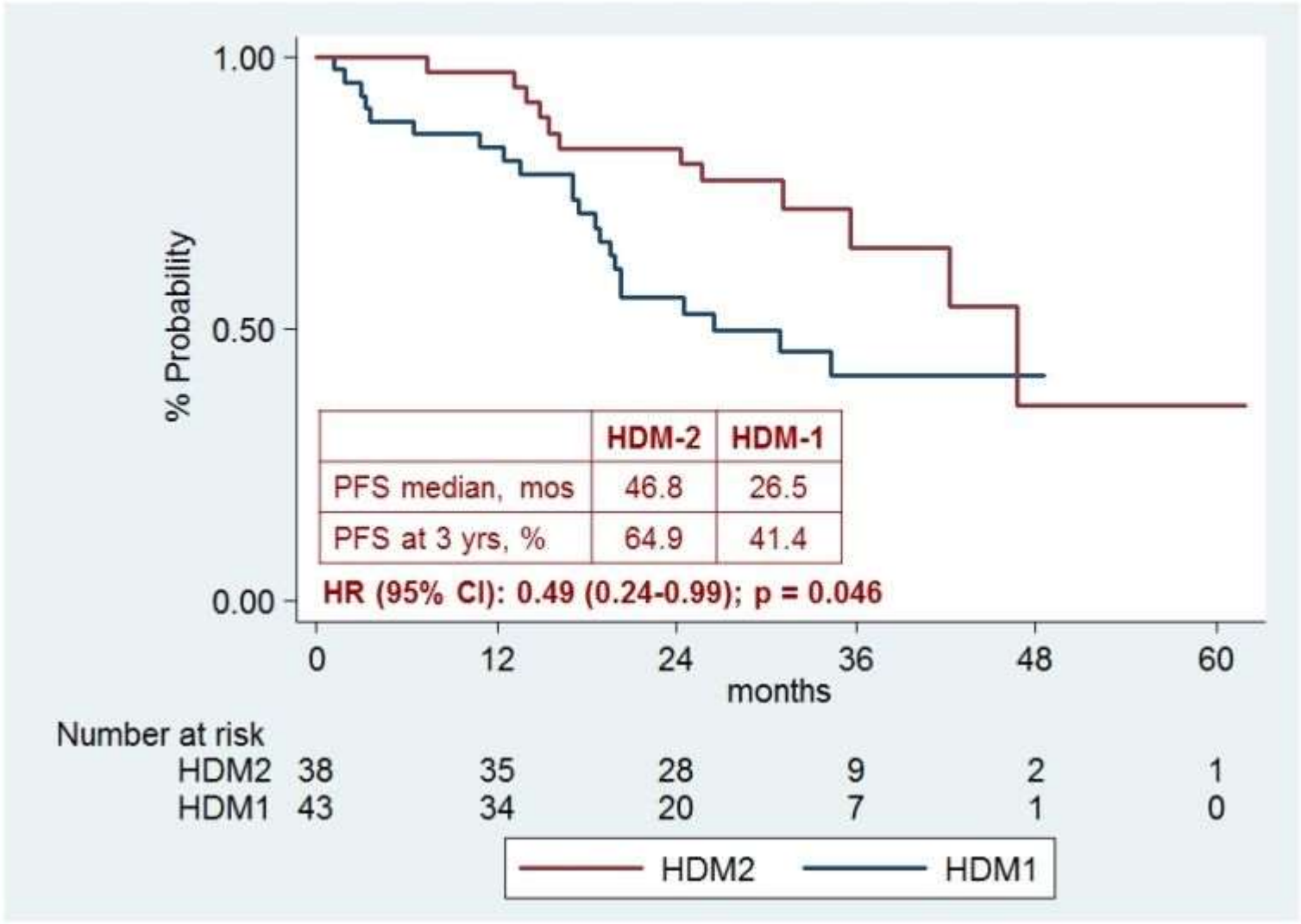
- Cosa abbiamo di nuovo nel programma sequenziale?

Randomization 1

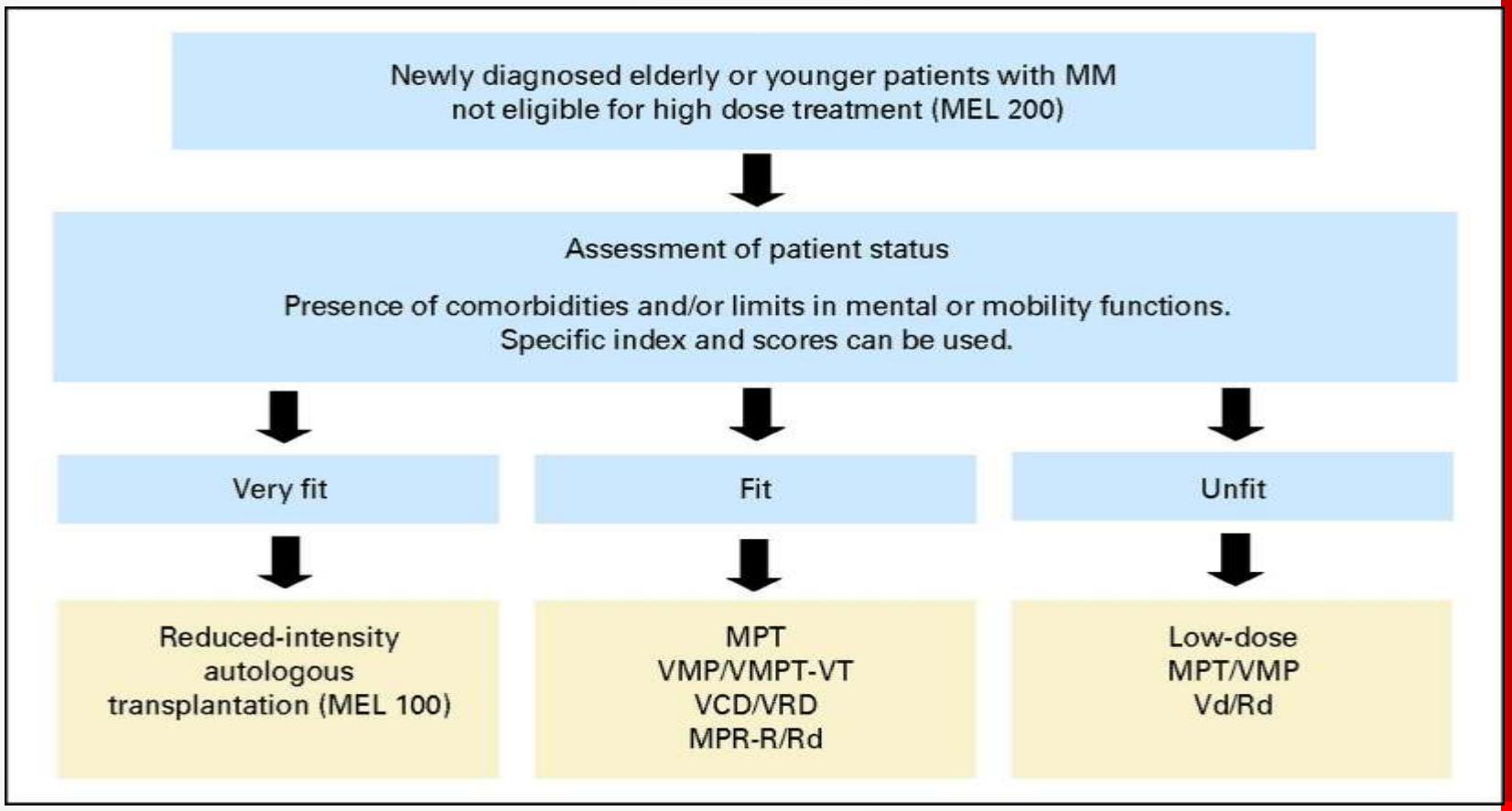
1192 pts were eligible for randomization 1



PFS by high-risk cytogenetics



Treatment algorithm for elderly patients with multiple myeloma (MM).



Antonio Palumbo et al. JCO 2014;32:587-600

New treatment paradigm for patients who

Treatment

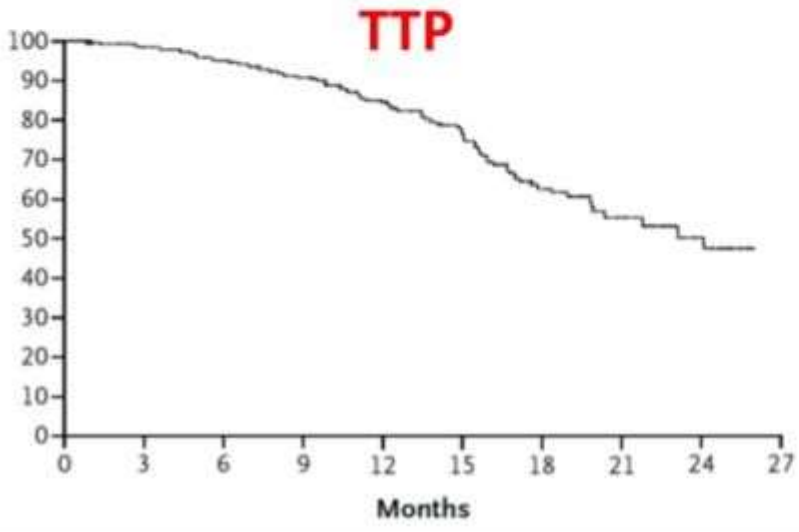
Not transplant-eligible patients

VMP x 9

ORR: 71%

CR + nCR: 33%

Median TTP: 24 mos



San Miguel. NEJM 2008

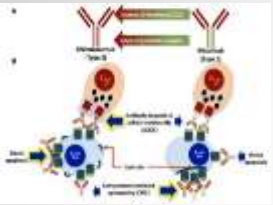
Treatment

Relapsed patients

Rd continuously	ORR: 60% Median PFS: 16 months
VD x 8	ORR: 65% Median PFS: 7 months
BVd x 12	ORR: 71% Median TTP: 16 months
KRd x 18	ORR: 87% Median TTP: 26 months
PomaDex contin.	ORR: 32% Median PFS: 4 months

Stewart K. NEJM 2015 Palumbo A. NEJM 2016 Offidani M. Blood Cancer J 2013 San Miguel J. Lancet 2013

t immunity:
ccines



Immunoterapia nel MM

Multiple Myeloma

Anti- CD38

Daratunumab (Darzalex)

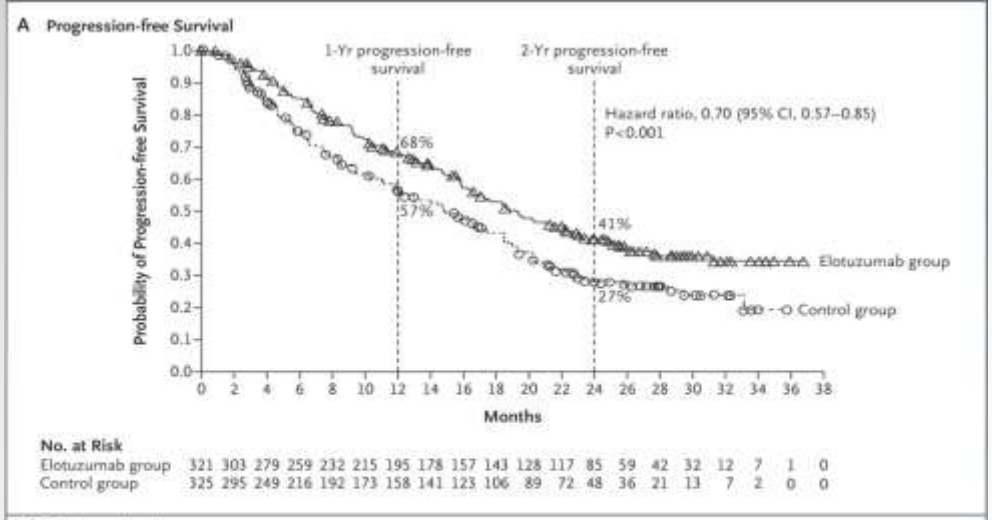
Elotuzumab (Empliciti)

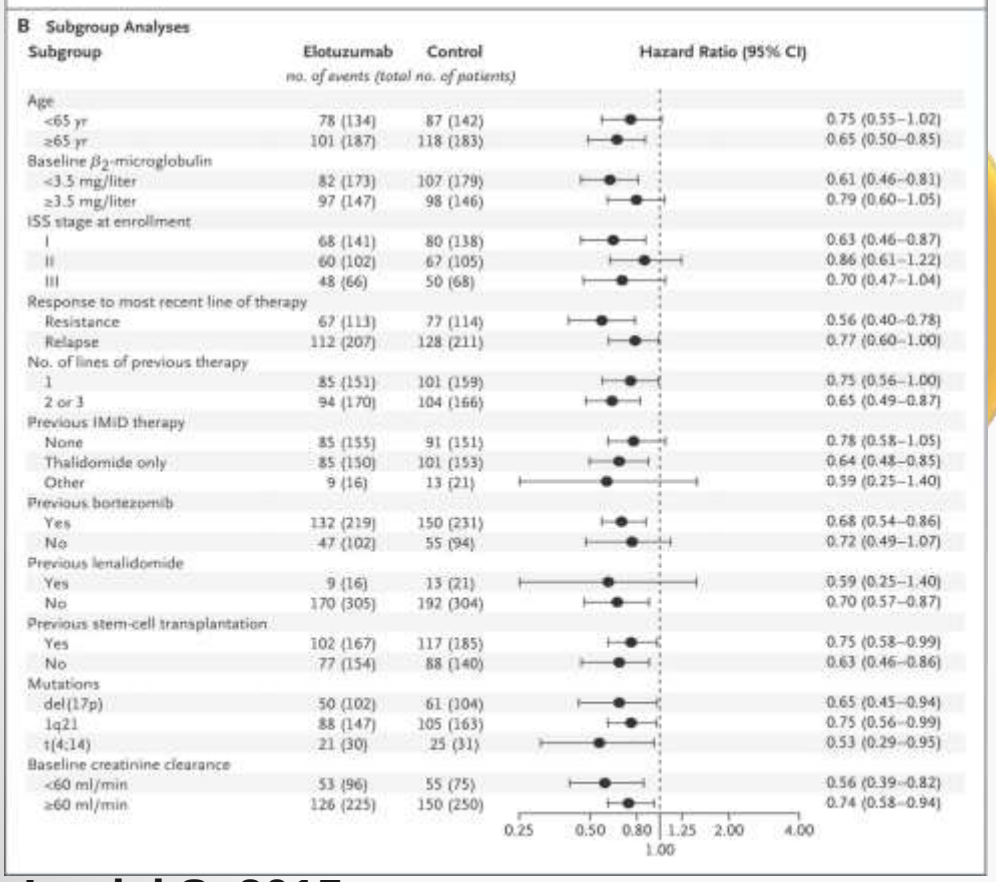
Targetin SLAMF7 o CS1

Direct Effects

ntracellular signaling
nction of growth factor receptors
nction of adhesion molecules

Antigen
MAC
C1q
CDC
Myeloma Cell
Lysis
Cell Death





Elotuzumab (Empliciti)

Multiple Myeloma

- Effetto ADCC
- Inibizione interazione con cellule stromali
- Potenziamento attività NK

Lonial S, 2015

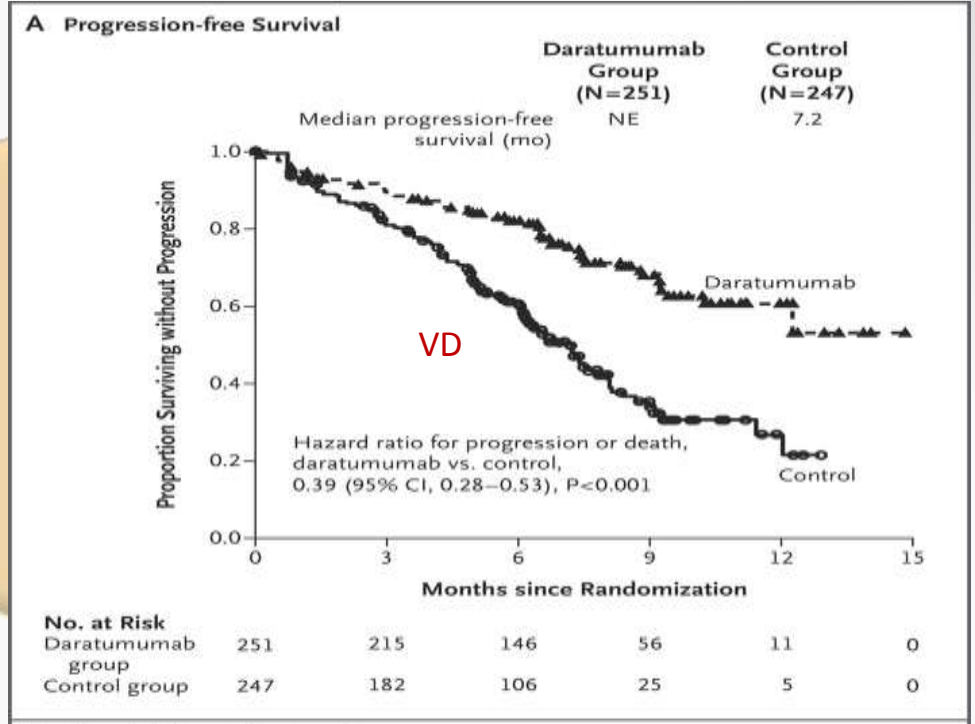
Multiple Myeloma

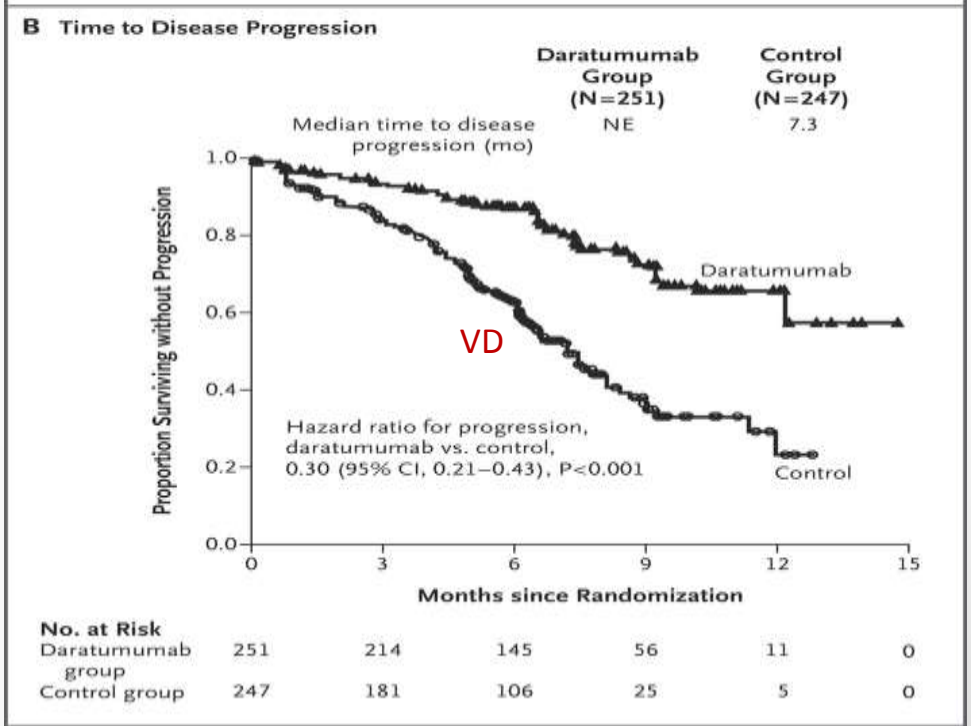
Anti- CD38

Daratunumab

(Darzalex)

Palumbo A, 2016






"Per aspera sic itur ad astra"