Modulo 007_RES - LOCANDINA

Revisione n. 3
Data di emissione : 1 settembre 2017
Approvato ed emesso in originale

S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

Evento Formativo Residenziale

L'IMPORTANZA
DELL'ADERENZA TERAPEUTICA
NELLE TERAPIE ONCOEMATOLOGICHE
PER VIA ORALE

DATE

Ediz.1: 20 dicembre 2017

Patrizia Pregno

S.C. Ematologia

Città della Salute e della Scienza di Torino

Le terapie orali in oncoematologia: opportunità e sfide

Ematologia

Premesse

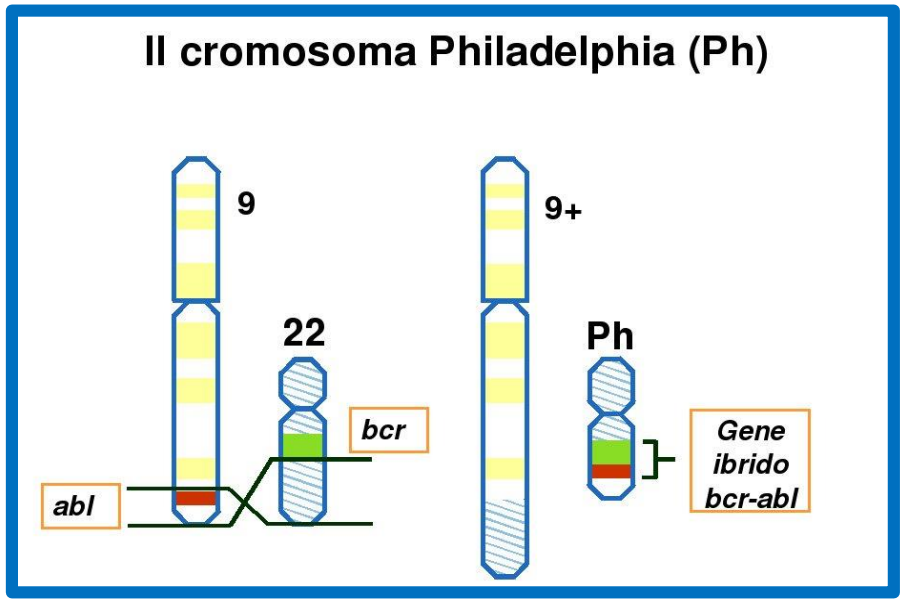
La terapia oncologica orale consente di eliminare i limiti ed i rischi legati alle perfusioni (CVC).

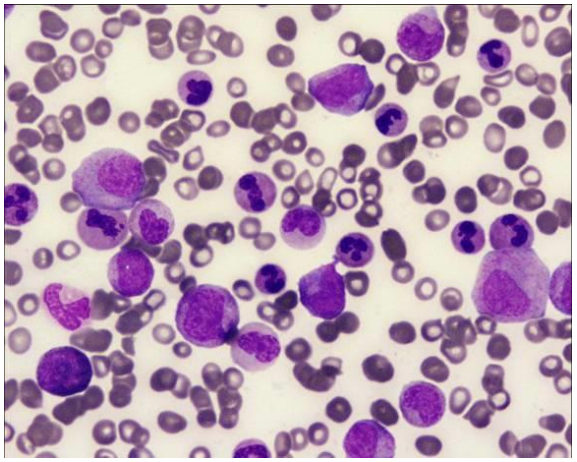
Consente spesso una terapia di precisione che colpisce bersagli specifici.

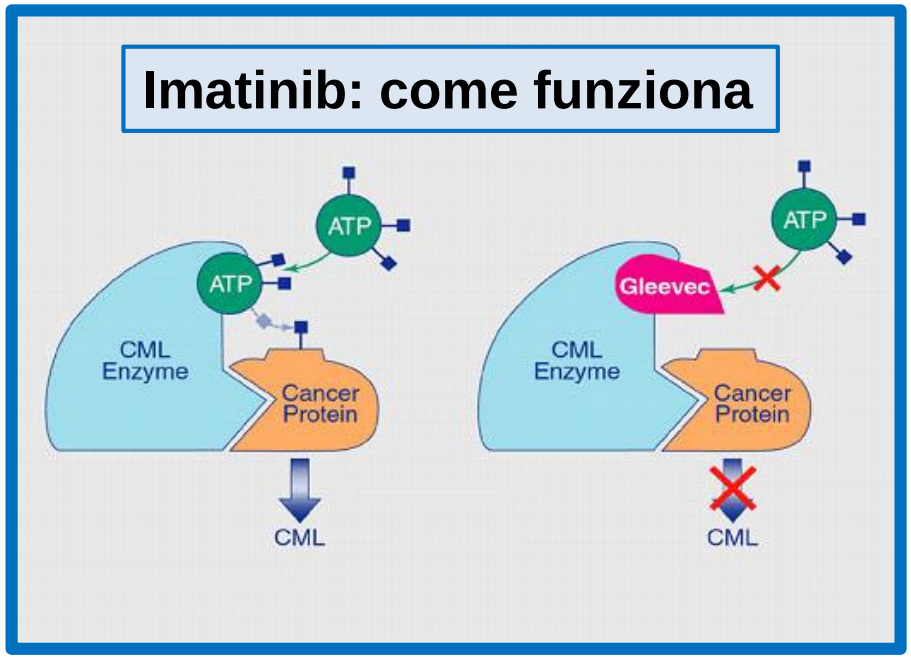
Pone il paziente al centro del percorso di cura in quanto diretto responsabile dell'assunzione corretta del farmaco.

Consente un adattamento alle attività quotidiane e preserva il comfort del paziente.

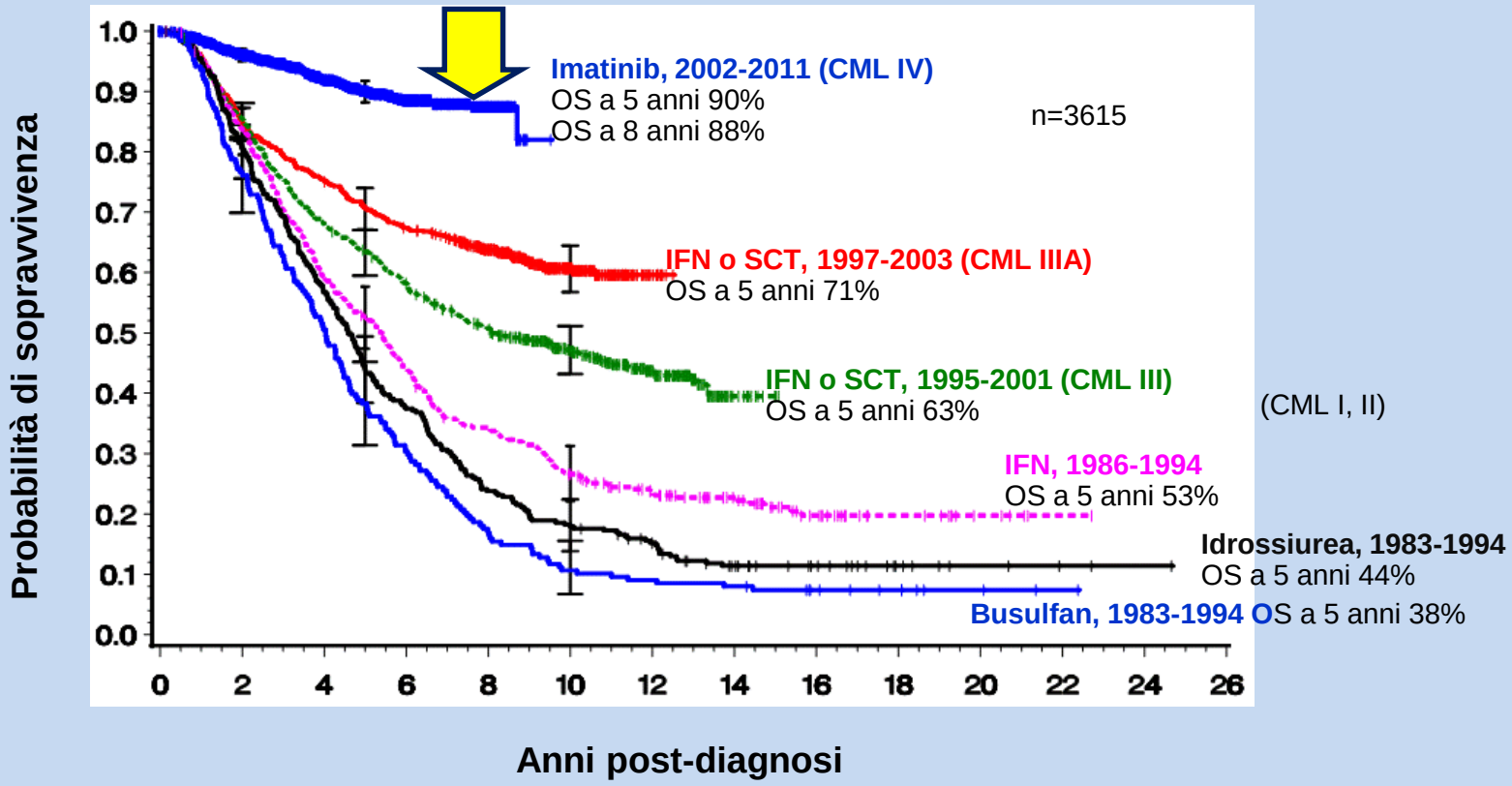
LA LEUCEMIA MIELOIDE CRONICA





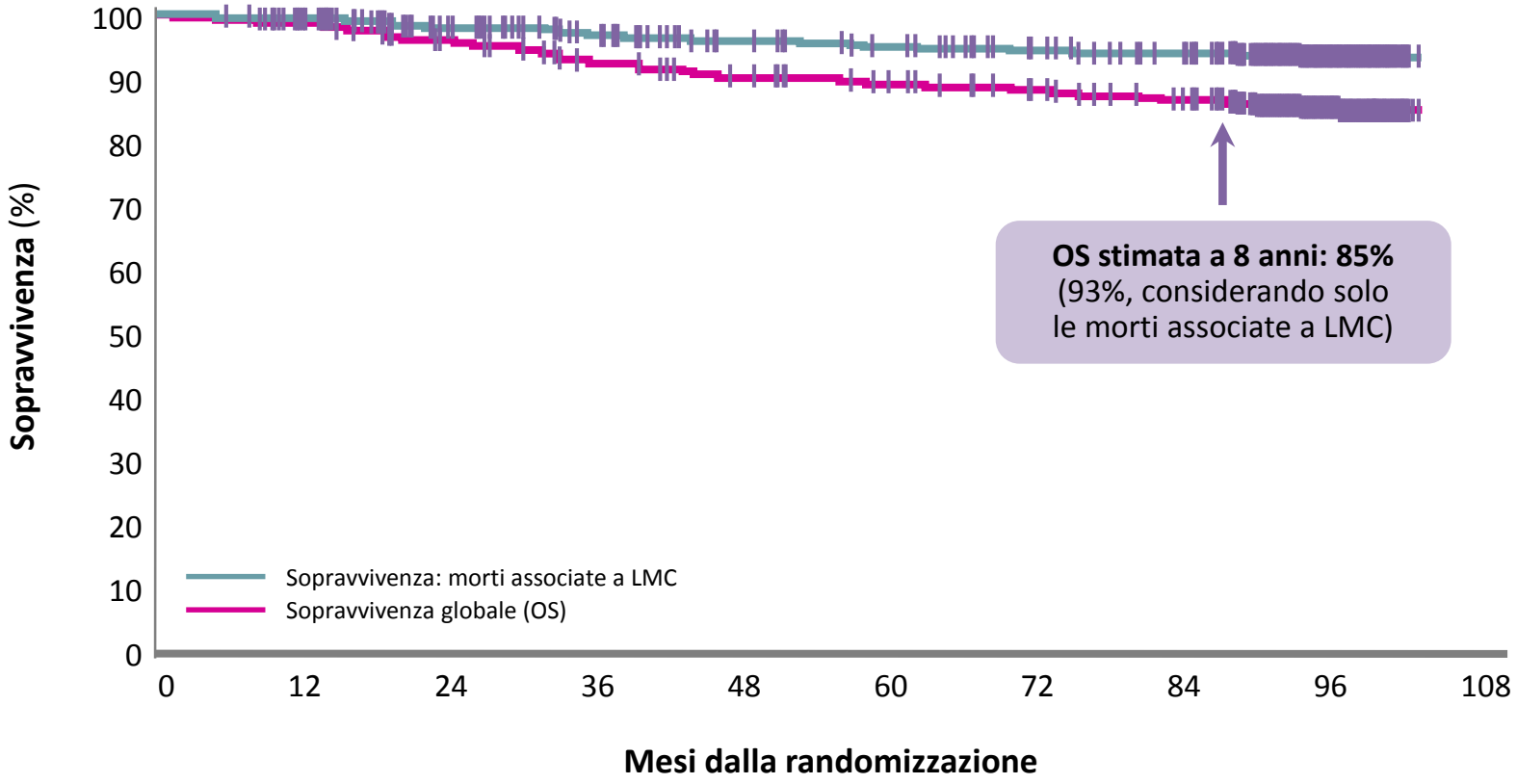


Miglioramento della sopravvivenza nella LMC in base alla terapia 1983-2011



German CML Study Group

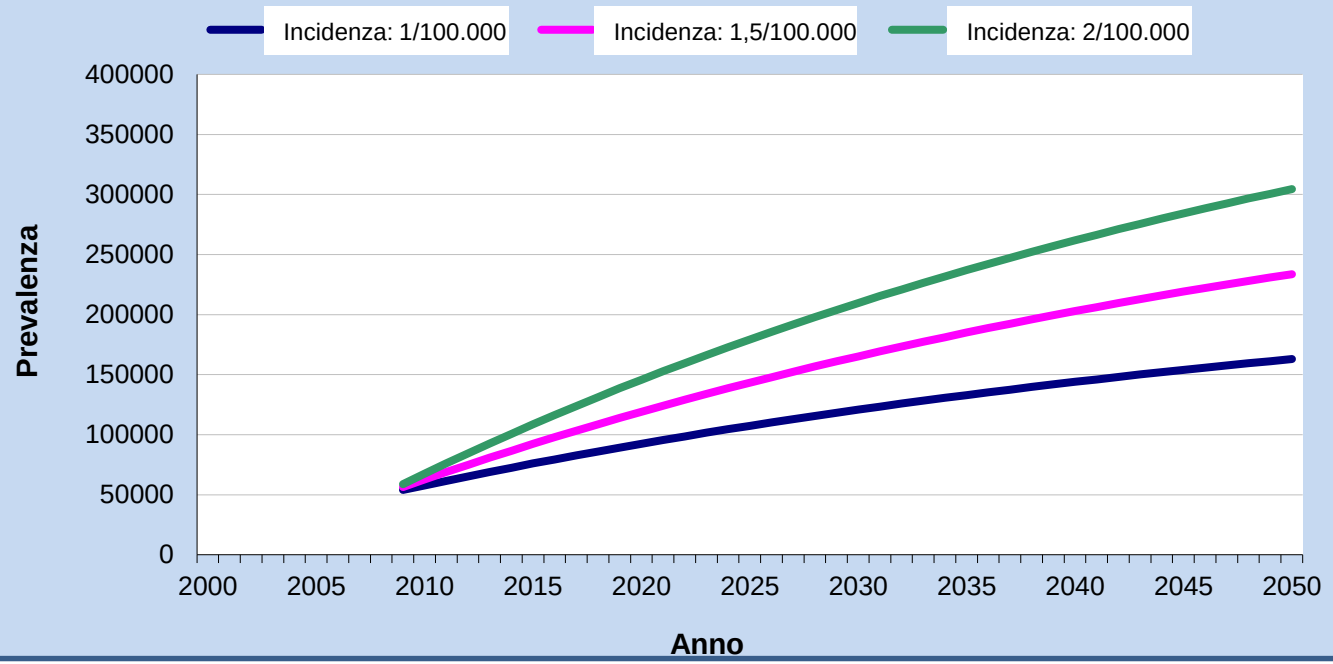
IRIS - Aggiornamento a 8 anni Sopravvivenza globale (ITT) – Braccio imatinib



Deininger M, et al. Blood. 2009;114(22):462. Abs # 1126.

Prevalenza

- **50.000 pz con LMC nel 2009 in Europa… Quale futuro?**



Ipotesi:

Tasso di mortalità annuale su una popolazione di 500.000.000 pazienti pari al 2%, incidenza costante

Per gentile concessione del Dr. J. Hasford, IBE, Munich

EUROPEAN LEUKEMIA NET 2013: TREATMENT RECOMMENDATIONS

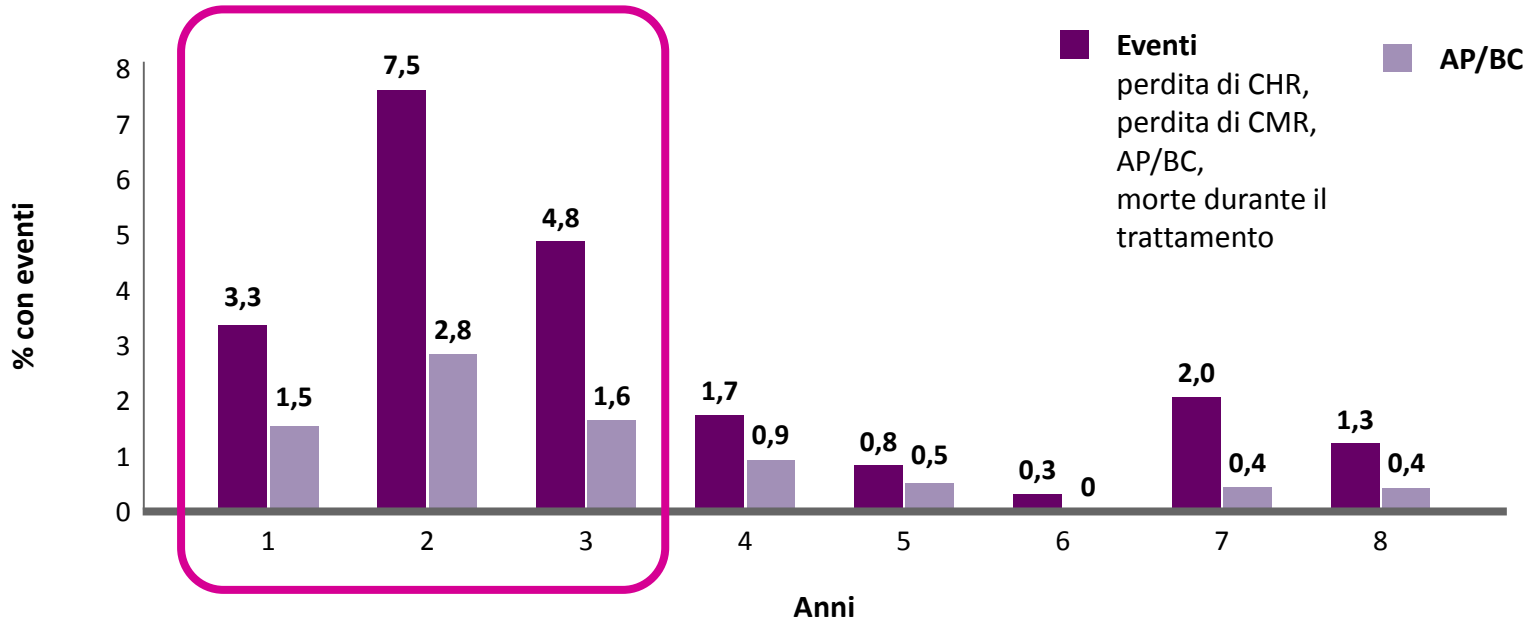
Table 7. Chronic phase treatment recommendations for first, second, and subsequent lines of treatment

First line
Imatinib or nilotinib or dasatinib
HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
Second line, intolerance to the first TKI
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)
Second line, failure of imatinib first line
Dasatinib or nilotinib or bosutinib or ponatinib
HLA type patients and siblings
Second line, failure of nilotinib first line
Dasatinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Second line, failure of dasatinib first line
Nilotinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Third line, failure of and/or intolerance to 2 TKIs
Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T315I mutation
Ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT

Baccarani M, et al. Blood. 2013;122(6):872-884

IRIS Aggiornamento a 8 anni
Risultati: tasso di eventi annuo, braccio imatinib

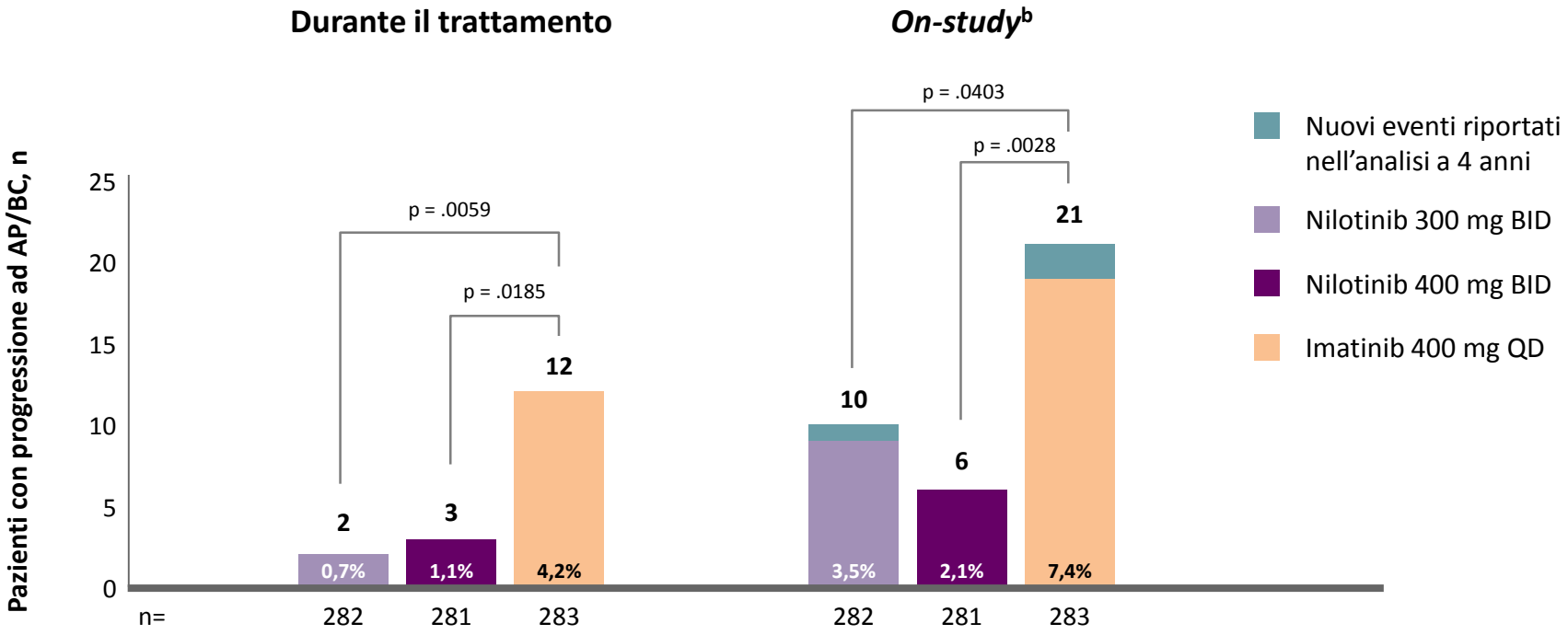
- EFS stimata con KM a 8 anni = 81% (3 eventi*)
- Tasso stimato con KM senza AP/BC a 8 anni = 92%



* Gli eventi totali (n=3) hanno compreso 1 progressione e 2 morti (non correlate a LMC).

Deininger M, et al. Blood. 2009;114(22):462. Abs # 1126.

Nilotinib in I linea: Progressione ad AP/BC[a]

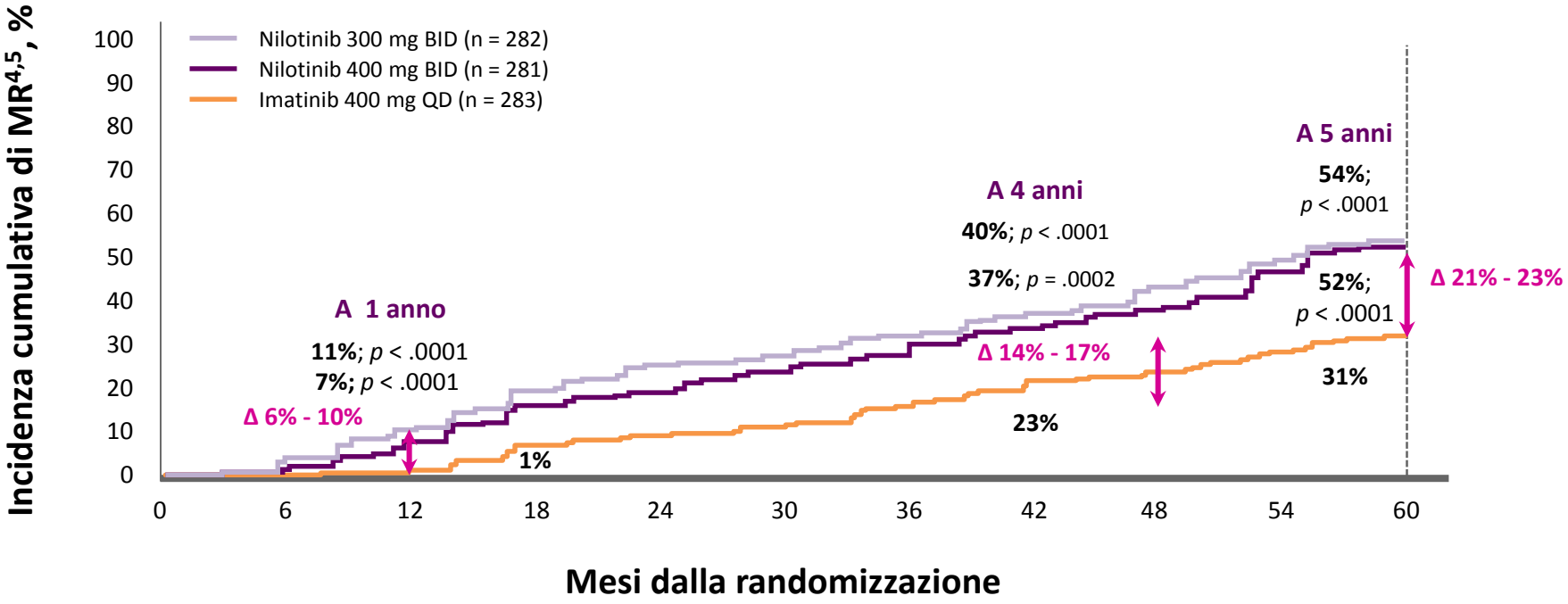


– Sono stati riportati 3 nuovi casi di progressione ad AP/BC nell'analisi a 4 anni (valutazione *on-study*), tutti dopo l'interruzione del trattamento

AP/BC, fase accelerata/crisi blastica
[a] Definita come progressione ad AP/BC o morte dovuta a LCM avanzata
[b] Durante il trattamento o durante il follow-up dopo l'interruzione del trattamento

Data cutoff: 30 settembre 2013

Incidenza cumulativa di MR^{4,5}



Nessun paziente che ha raggiunto la MR^{4,5} è andato incontro a progressione ad AP/BC

MR^{4,5}, risposta molecolare ≥ 4,5-logs (BCR-ABL^{IS} ≤ 0,0032%)

For distribution in response to an unsolicited request for medical information pending local NP4 approval.
Data cutoff: 30 settembre 2013

LMC: cos'è cambiato....

1994

- La fase cronica dura solo 4-5 anni
- Avrà stanchezza, febbre, dolori osteoarticolari
- Solo un trapianto potrà guarirla

2004

- Abbiamo una medicina mirata
- Dobbiamo raggiungere una CCyR
- La possiamo curare bene, ma non guarire
- La terapia sarà «per sempre»

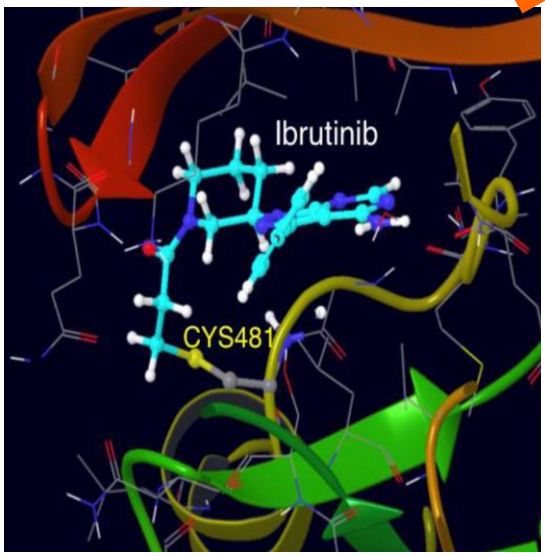
2017

- Possiamo scegliere tra diversi farmaci molto efficaci
- Potrà raggiungere una risposta molecolare profonda
- La sua aspettativa di vita sarà quella di una persona della sua stessa età
- Potrà avere dei figli
- In alcuni casi è possibile sospendere la terapia

Courtesy of Monica Bocchia

La terapia orale nei linfomi

Targeting B-Cell Receptor Signaling Through Inhibition of Bruton Tyrosine Kinase (BTK)

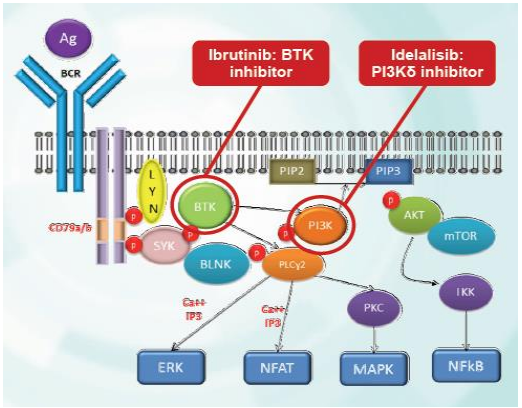


Daily oral dosing produces 24-hour BTK inhibiton

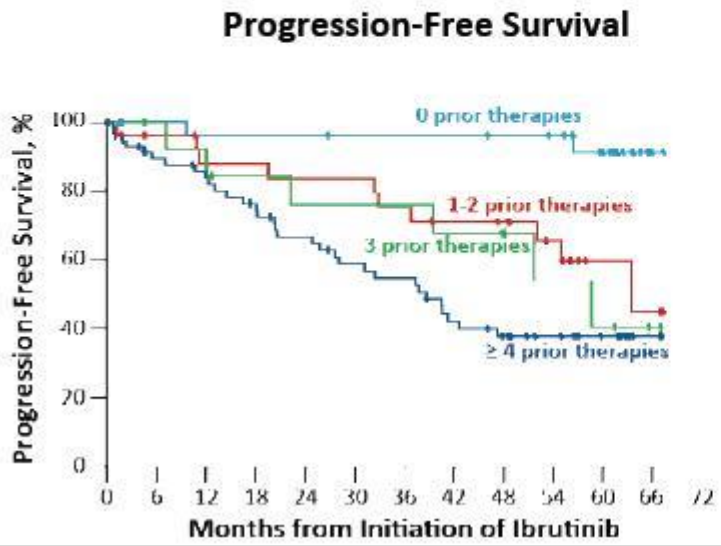
It blocks NF-κB

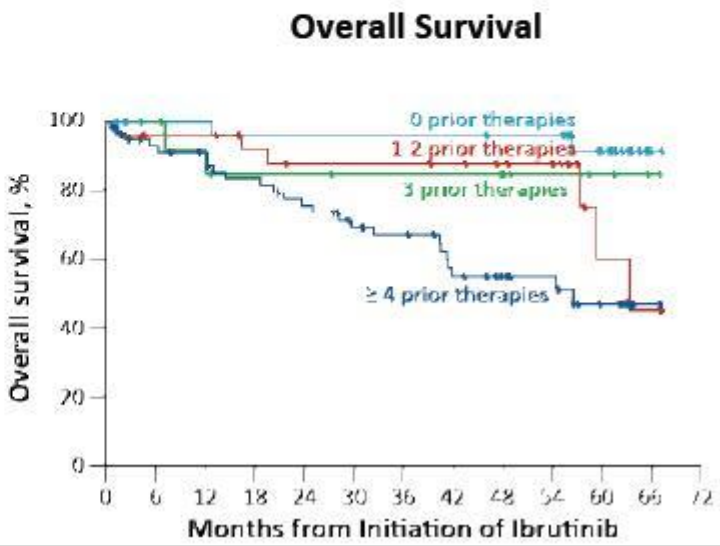
inhibition of proliferation
adhesion disruption
apoptosis

The BTKi IBRUTINIB is the new standard of care in untreated del17p or p53 mutated B-LLC or relapsed/refractory B-LLC and MCL and in Waldenstrom Macroglobulinemia.



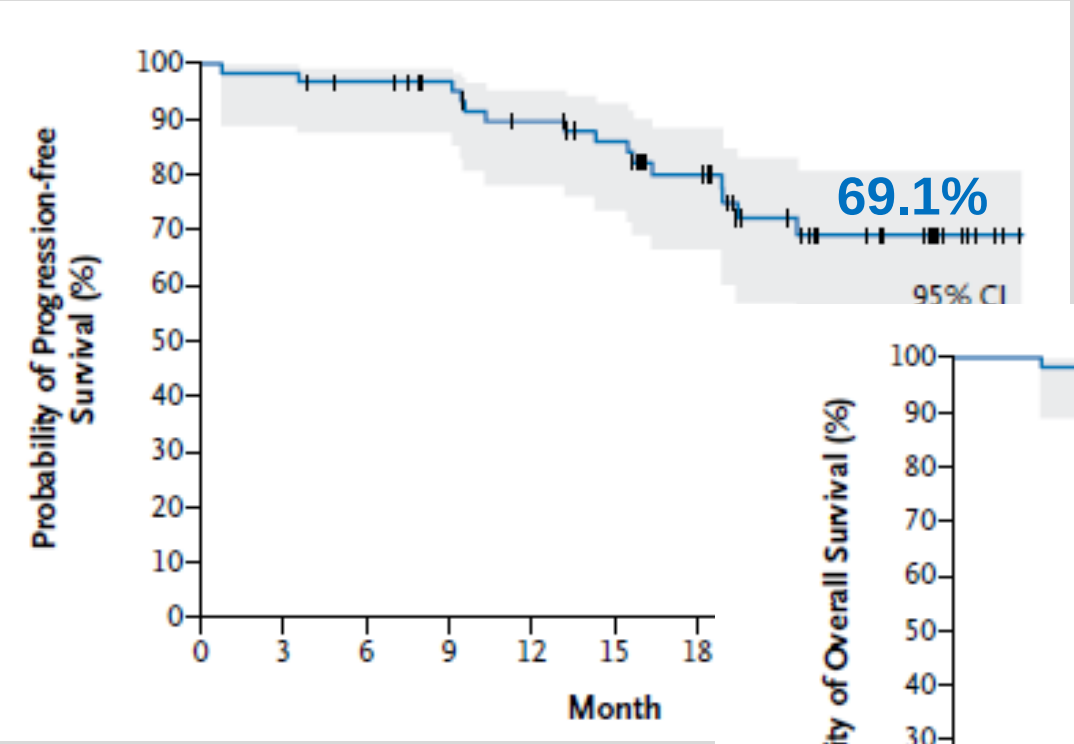
Ibrutinib Survival by Number of Lines of Prior Therapies

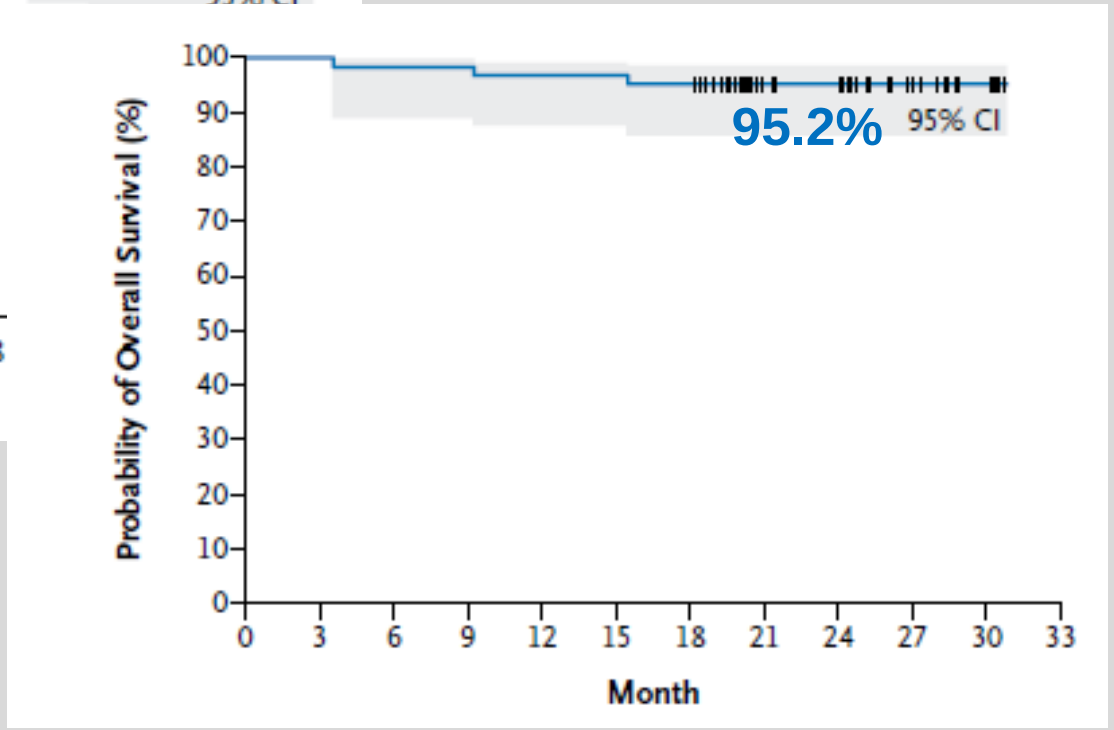




Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Overall, 2-yrs PFS and OS were 69.1% and 95.2%, respectively



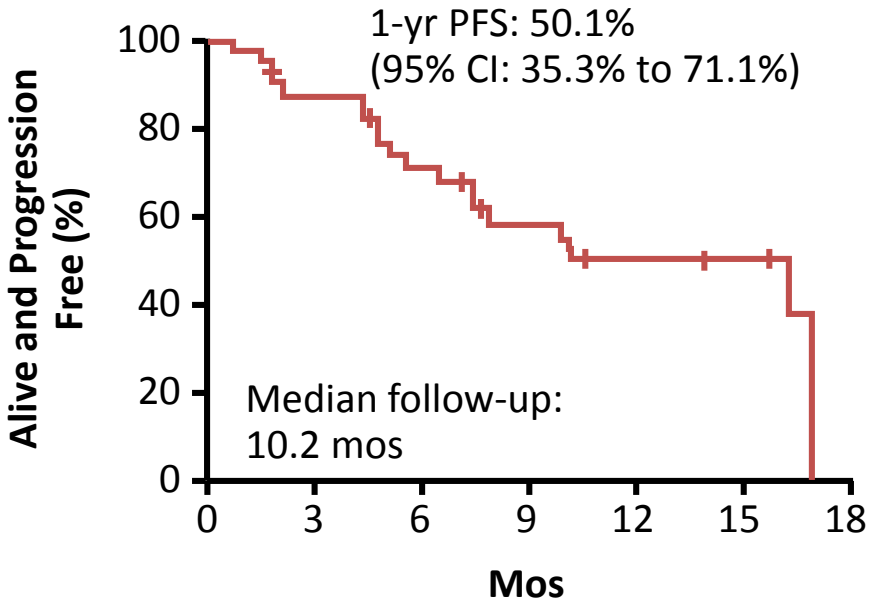


Treon SP et al; N Engl J Med 2015

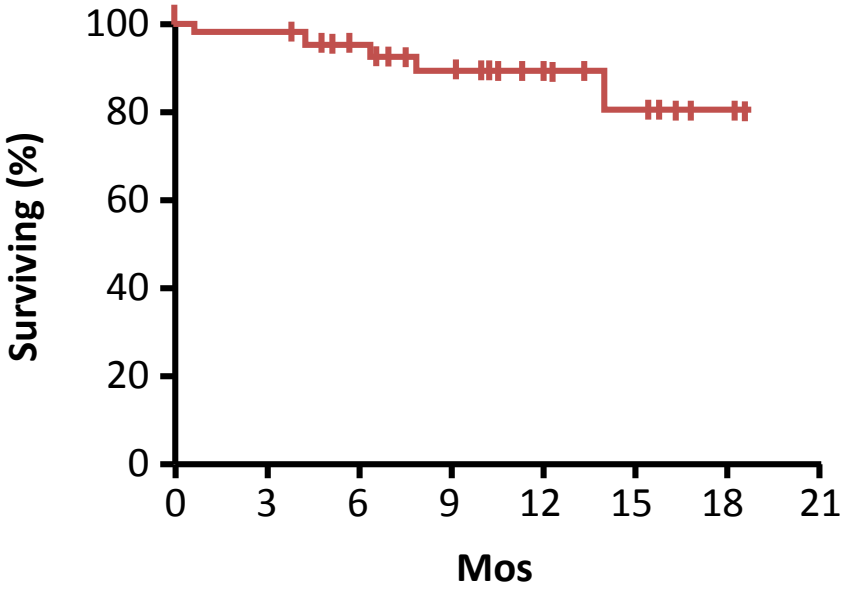
Phase II Consortium: Ibrutinib Monotherapy in R/R FL

- Single-agent ibrutinib associated with antitumor responses in relapsed/refractory FL
  - ORR: 28%
  - ORR in rituximab-sensitive disease: 42%
  - ORR in rituximab-insensitive disease: 6%

PFS

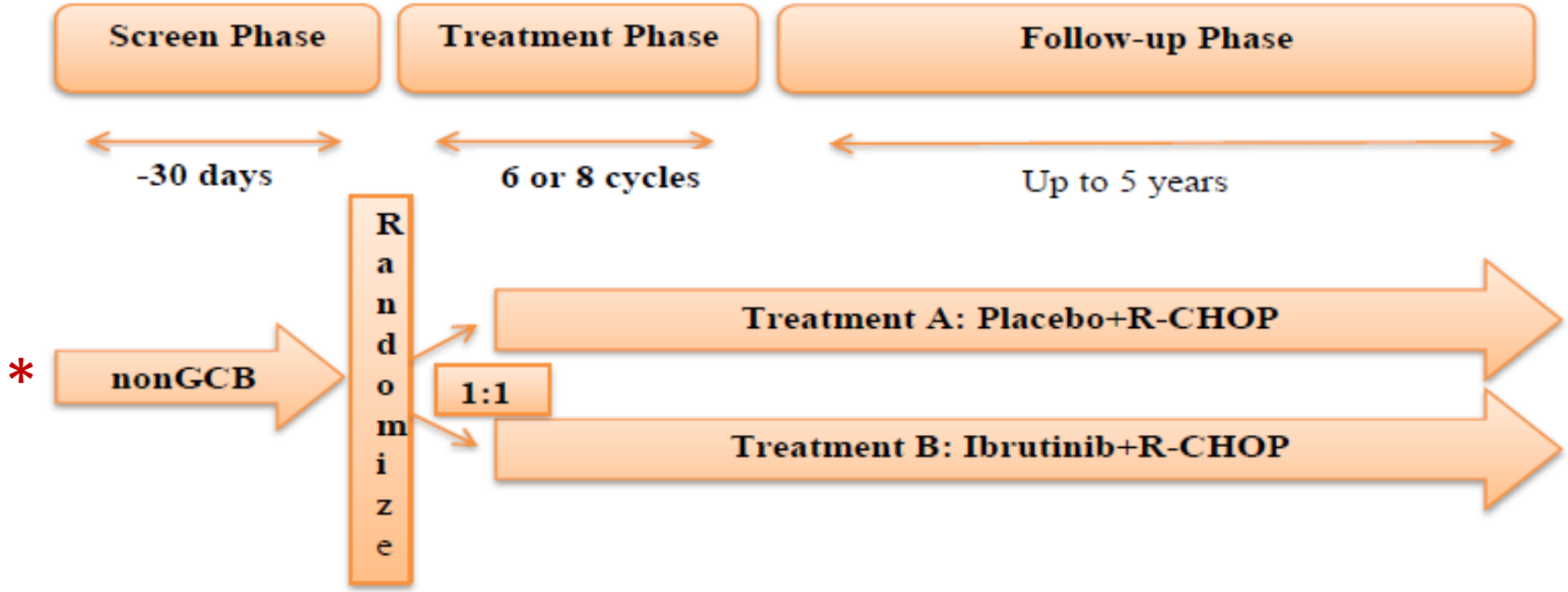


OS



Bartlett et al. ASH 2014

R-CHOP + iBtk for untreated DLBCL, non GCB



Population:
Subjects with DLBCL who in non-GCB sub-population determined by central IHC

Stratification factors:

- R-IPI score low risk (1) vs. intermediate risk (2-3) vs. high risk (4-5)
- Region (United States/Western Europe vs. Rest of World)
- Number of treatment cycles (6 vs. 8 cycles)

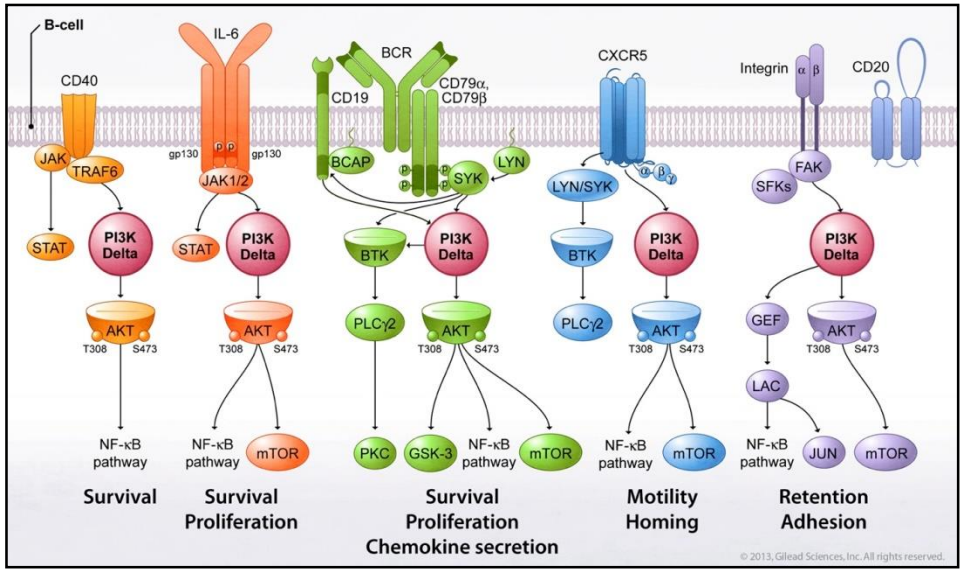
PHOENIX
PCI-32765DBL3001

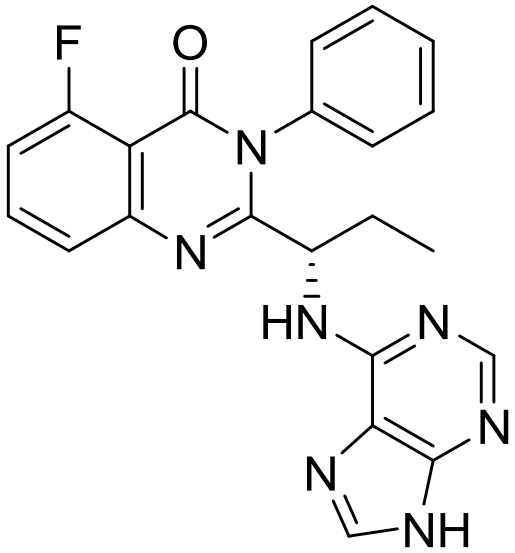
***IHC based on Hans' algorithm.**

Janssen
PHARMACEUTICAL COMPANIES of Johnson & Johnson

PI3Kδ inhibition impacts multiple critical pathways in indolent lymphomas

Idelalisib oral, selective PI3Kδ inhibitor





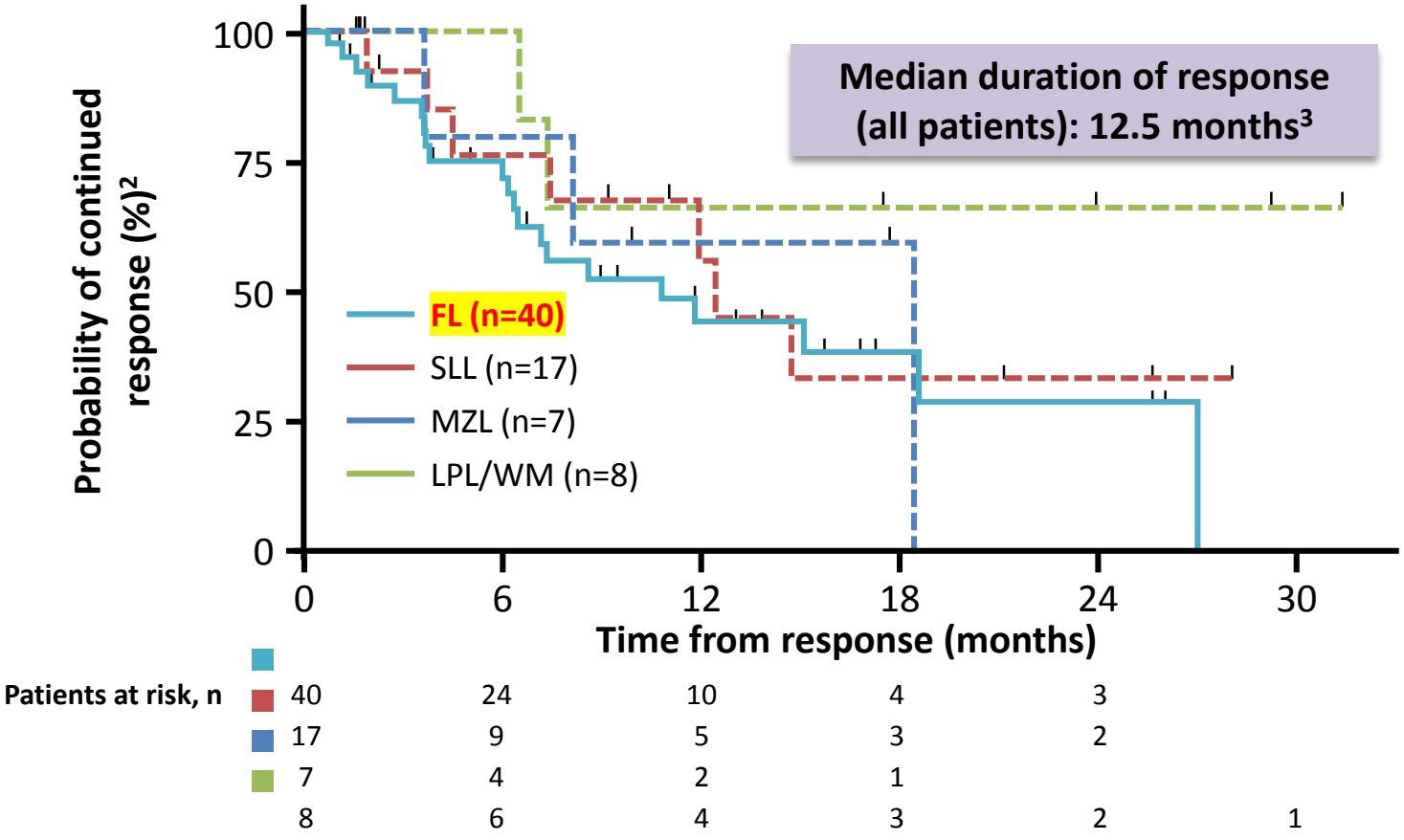
Direct and indirect attack on malignant B cells to:
Reduce proliferation

- **Induce apoptosis**
- **Inhibit homing and retention of B cells in the protective microenvironments (lymph nodes and bone marrow)**

Study 101-09: single-group, open-label Phase II study of Zyledig 150 mg BID in heavily pretreated iNHL pts

Duration of response

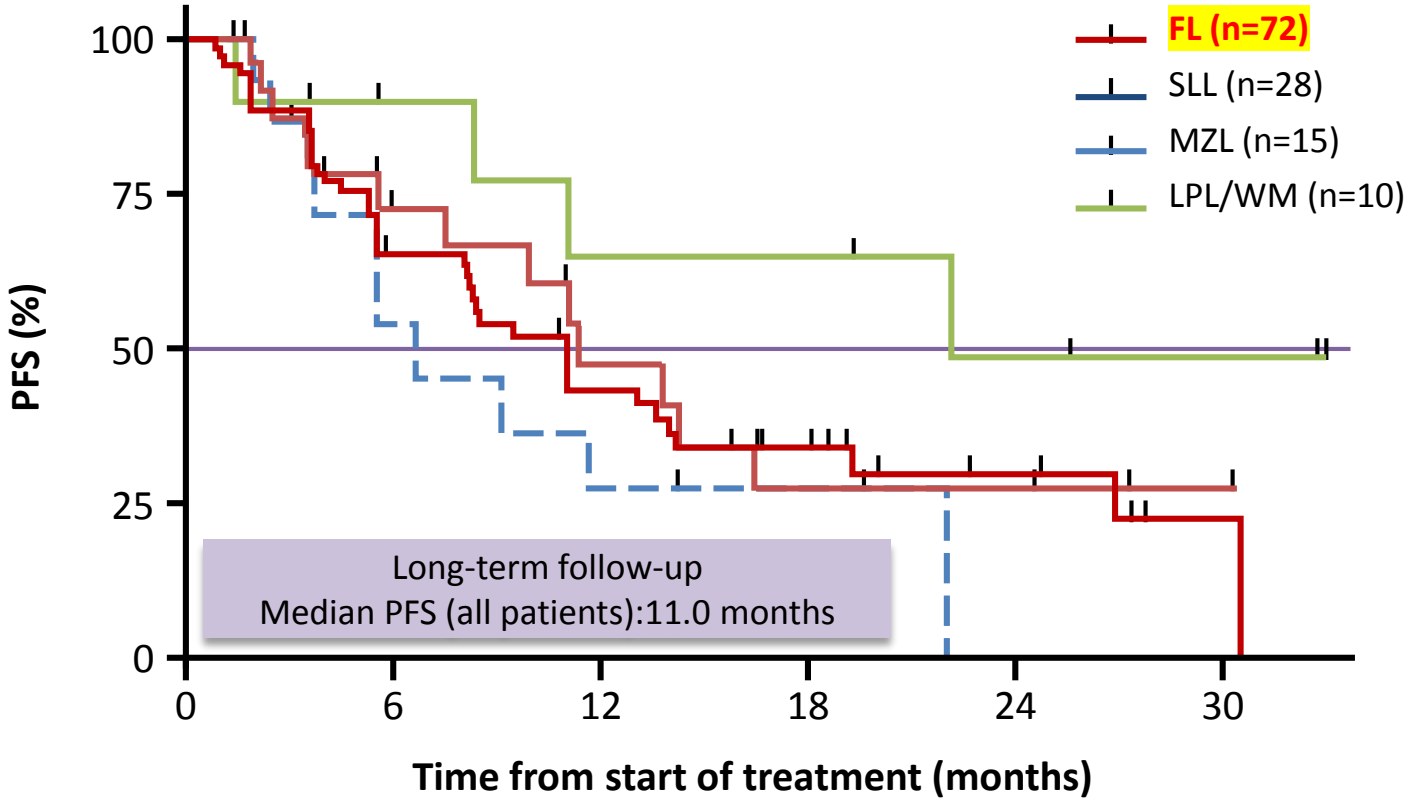
Median time to response (all patients): 1.9 months[1]



Includes patients who achieved complete/partial response (or minor response for LPL/WM) according to independent review committee assessments

Gopal et al ASH 2014

Progression-free survival



Patients at risk, n						
FL (n=72)	72	35	18	11	5	1
SLL (n=28)	28	12	7	4	4	1
MZL (n=15)	15	6	3	2	–	–
LPL/WM (n=10)	10	7	5	5	3	2

Includes patients who achieved a complete response or partial response
(or minor response for LPL/WM) according to independent review committee assessments

Zydelig® (idelalisib) licensed indications

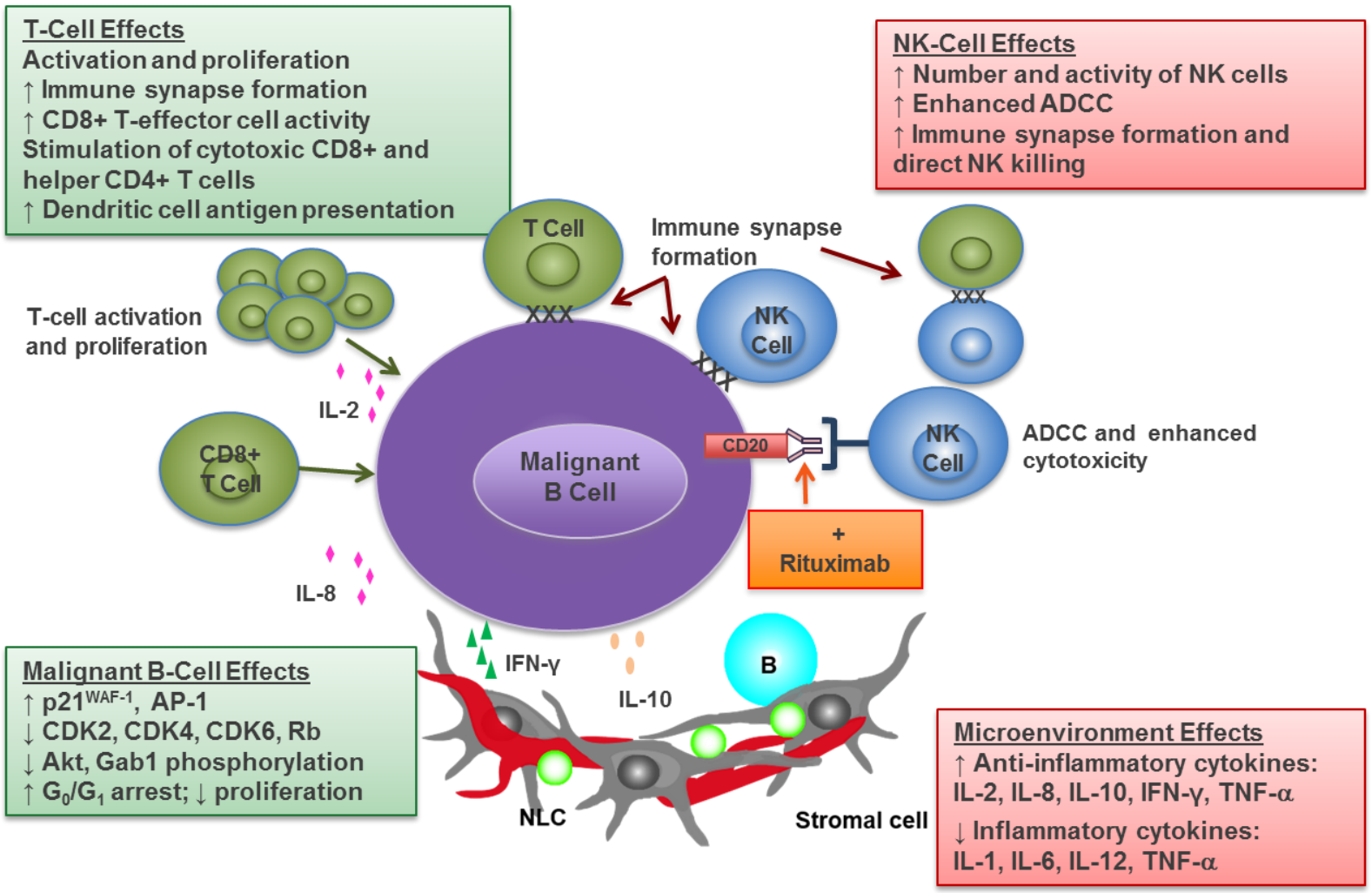
FL	Indicated as monotherapy for the treatment of adult patients with FL that is refractory to two prior lines of treatment
CLL	Indicated in combination with rituximab for the treatment of adult patients with CLL • who have received at least one prior therapy, or • as first-line treatment in the presence of 17p deletion or *TP53* mutation in patients unsuitable for chemo-immunotherapy

Recommended dose of Zydelig is 150 mg, one tablet, twice daily

CLL: chronic lymphocytic leukaemia
FL: follicular lymphoma

Zydelig SmPC (Oct 2014; available at www.ema.europa.eu).

Mechanisms of action of lenalidomide in lymphoma cells and nodal microenvironment



Gribben JG, et al. J Clin Oncol. 2015;33:2803-11.

LENALIDOMIDE

PHASE II RANDOMIZED MULTICENTER STUDY OF L VS. LR IN RECURRENT FL (CALGB 50401- ALLIANCE)

Recurrent FL (N = 91)

- Age > 18 yrs
- ECOG 0.2
- FL gr 1-3°
- Previous rituximab
- TTP from last R > 6 months

RANDOMIZE

1:1

- **Rituximab** ✗ — *Arm closed due to poor accrual*
- **Lenalidomide (n = 45)**
- **Lenalidomide + Rituximab (n = 46)**

→ **≤12 cycles or until PD, toxicity, or study withdrawal**

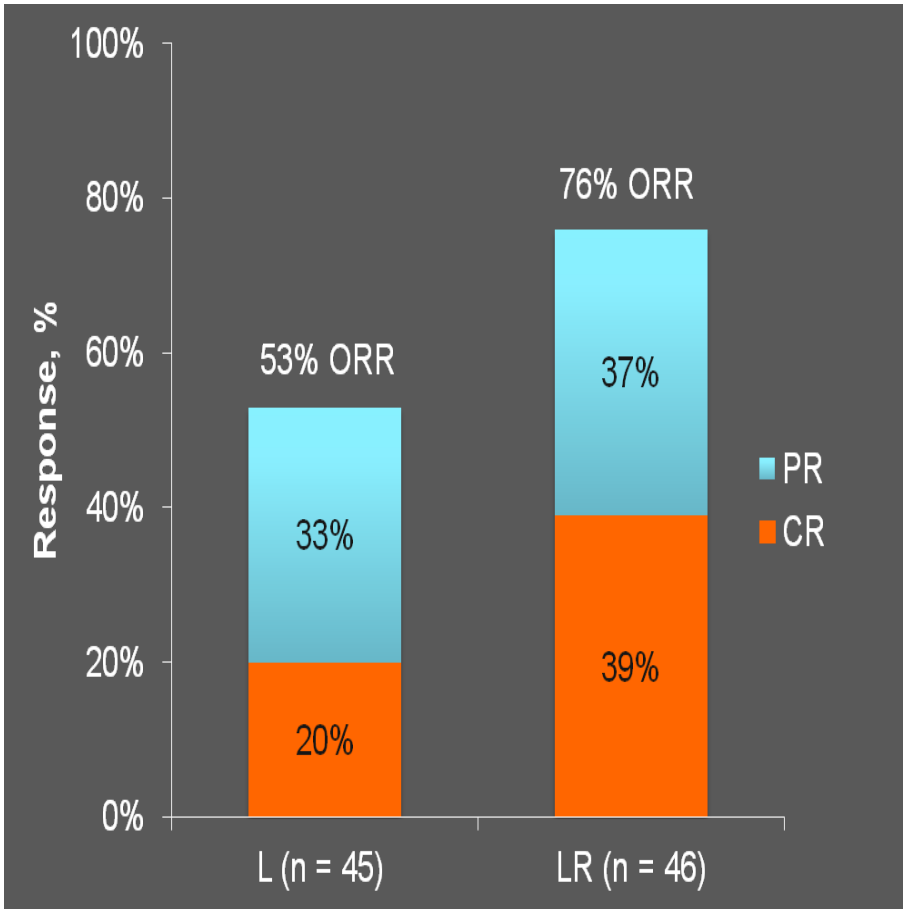
Lenalidomide: 15 mg/d PO cycle 1, 20 mg/d cycles 2-12; d1-21/28 (25 mg/d if tolerated)*

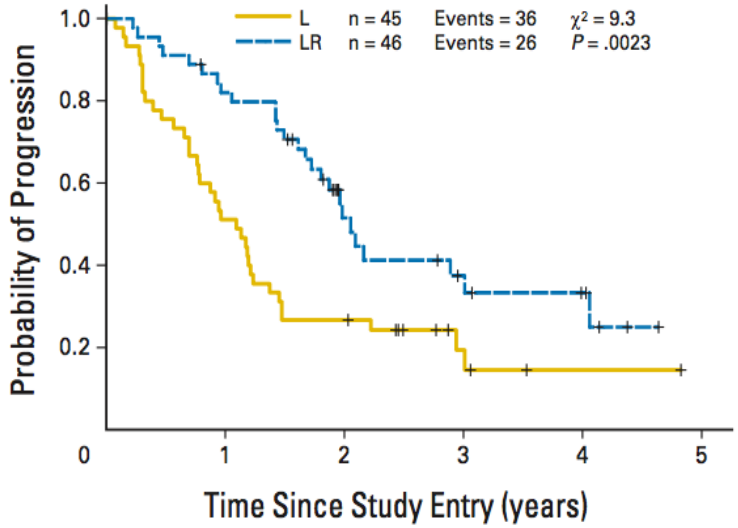
Rituximab: 375 mg/m^2 IV d8, 15, 22, 29 of cycle 1

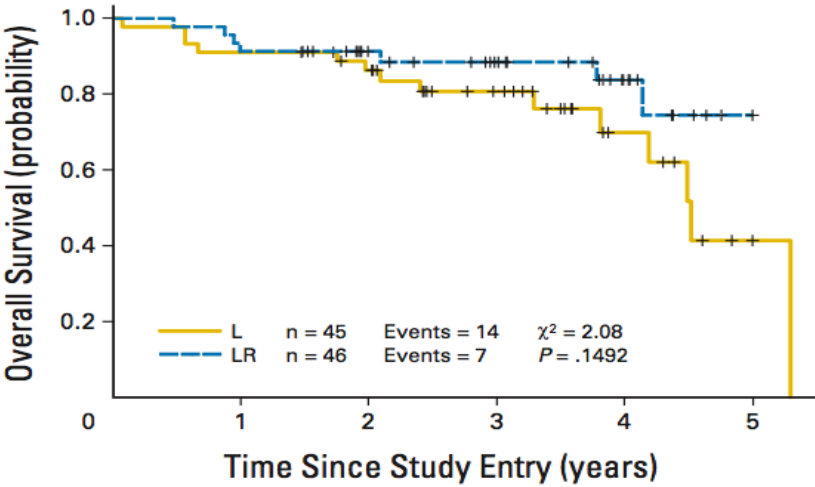
Primary endpoints: ORR and CR†
Secondary endpoints: TTP, OS, and safety

Leonard et al. JCO 2015

R2 in relapsed fl







- ORR was significantly improved for LR vs. L (*P*=0.029)

Leonard et al. JCO 2015

Leonard et al. *J Clin Oncol.* 2015; doi: 10.1200/JCO.2014.59.9258. Epub ahead of print.

RENOIR trial FIL

PCR analysis for Bcl-2 rearrangement on PB/BM

REALPSED/REFRACTORY FOLLICULAR LYMPHOMA NEED TO THERAPY

R-Bendamustine x 4 once a month

Rituximab 375 mg/m^2 day 0 or 1 (day 8 on cycle 1)

Bendamustine 90 mg/m^2 iv days 1-2

Restaging and PCR analysis for Bcl-2 rearrangement on PB/ BM

CR/PR

NR

OFF

Random

R2

Rituximab 375 mg/m2 day 1 q 90 days (8 cycles)

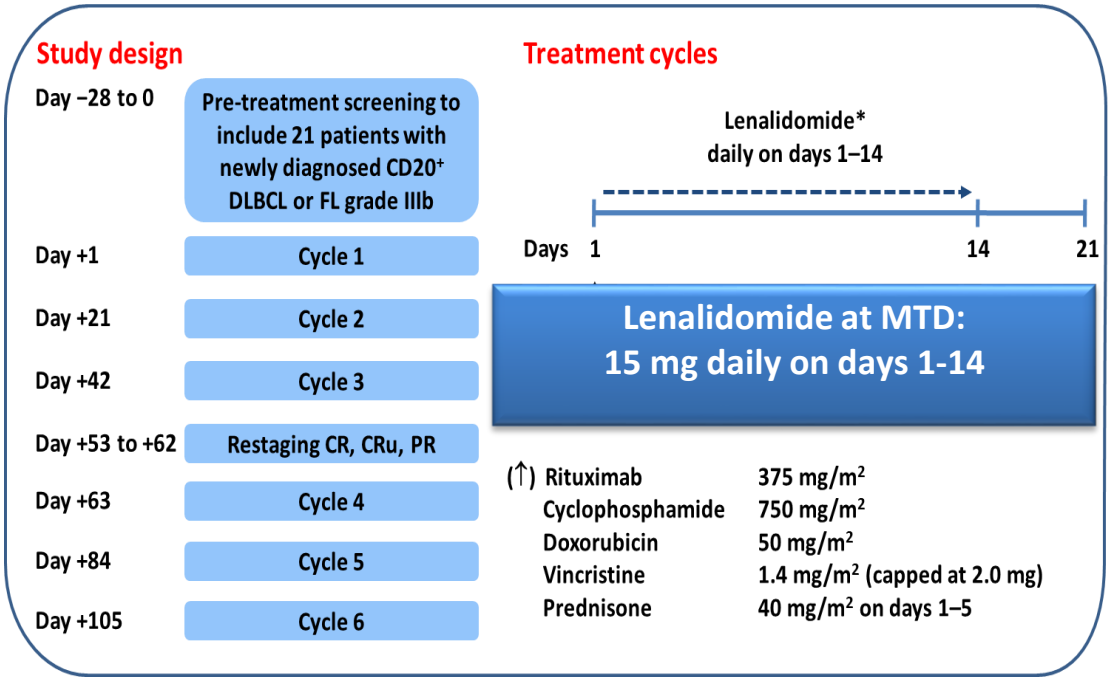
Lenalidomide (10 mg dd 1-21 q 28) (24 cycles)

R alone

Rituximab 375 mg/m2 day 1 q 90 days (8 cycles)

Clinical and molecular follow-up months 12, 18, 24 and 30 (end of study)

Lenalidomide + R-CHOP in elderly patients with untreated DLBCL, REAL07 phase I-II trial



CNS prophylaxis according to Italian Society of Hematology guidelines
Pegfilgrastim or G-CSF as neutropenia prophylaxis
Low Molecular Weigh Heparin as DVT prophylaxis

Lenalidomide provided free by Celgene

	Enrolled patients (n=49)
Age (years)	69 (64–71)
Sex	
Men	29 (59%)
Women	20 (41%)
Eastern Cooperative Oncology Group performance status	
0–1	42 (86%)
2	7 (14%)
Ann Arbor stage	
II	6 (12%)
III	8 (16%)
IV	35 (71%)
International Prognostic Index risk	
Low-intermediate risk	19 (39%)
High-intermediate or high risk	30 (61%)
Lymphoma type	
Diffuse large B-cell lymphoma	45 (92%)
Follicular lymphoma grade 3b	4 (8%)
Bone marrow involvement	17 (35%)
B symptoms	21 (43%)
Increased lactate dehydrogenase concentration*	22 (45%)
Increased β_2 microglobulin*	34 (69%)

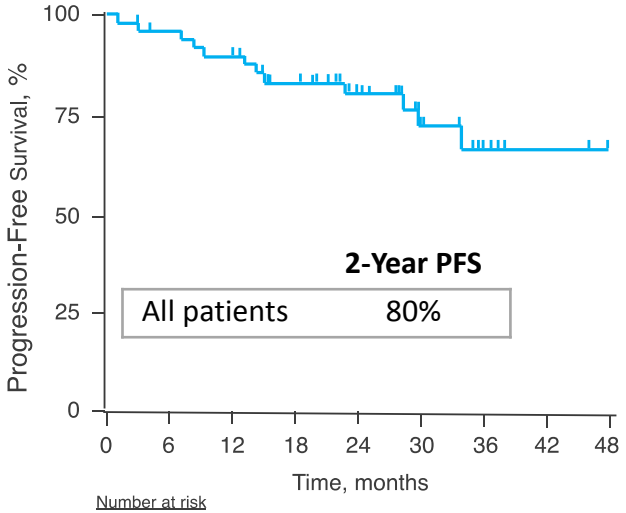
Data are median (IQR) or n (%). *Higher than the upper limit of normal.

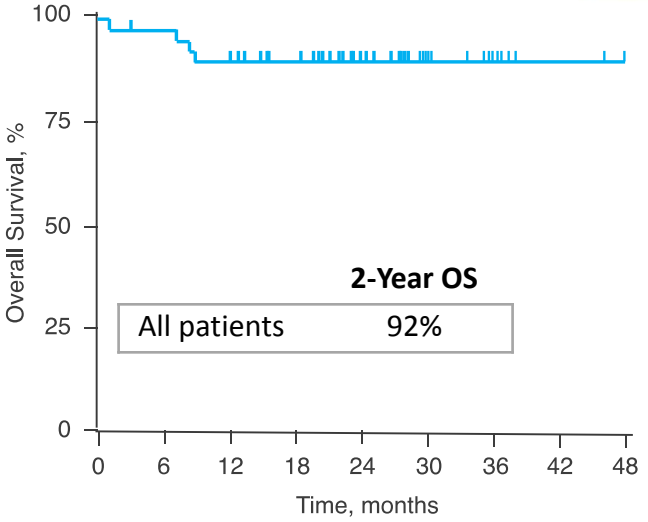
Table 1: **Baseline clinical characteristics**

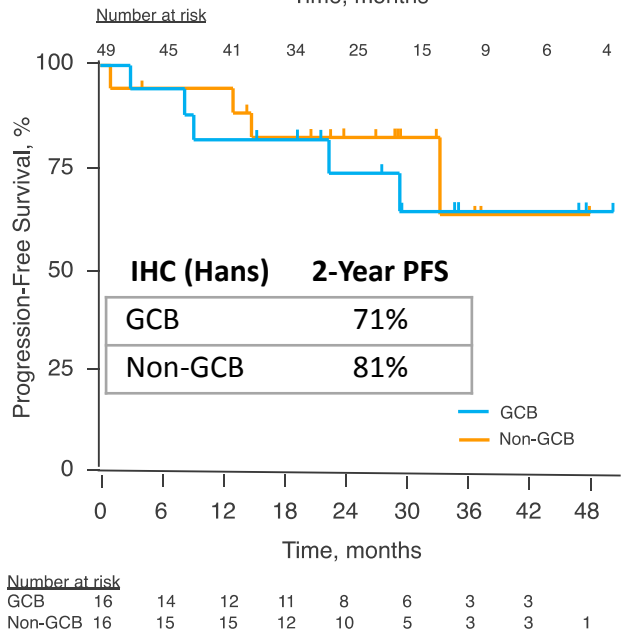
Chiappella A et al, Haematologica 2013; Vitolo U et al, Lancet Oncol 2014

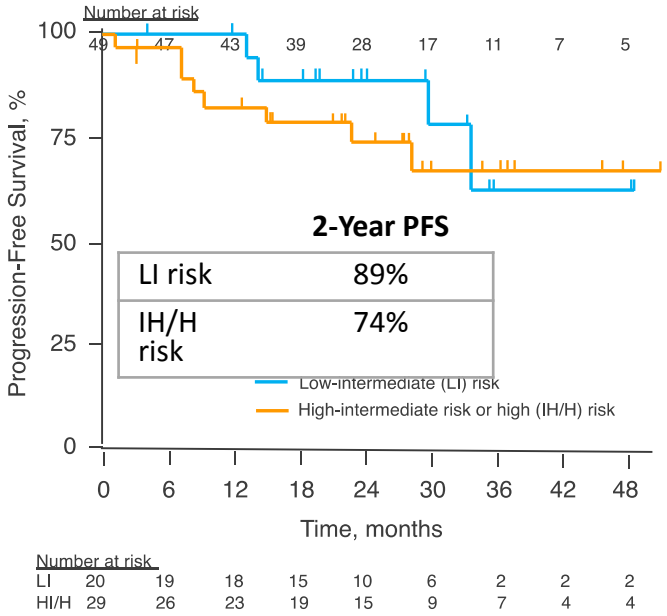
REAL07 Phase II R2-CHOP21 in Elderly Untreated DLBCL: PFS and OS; PFS by COO and PFS by IPI

Median follow-up of 28 months







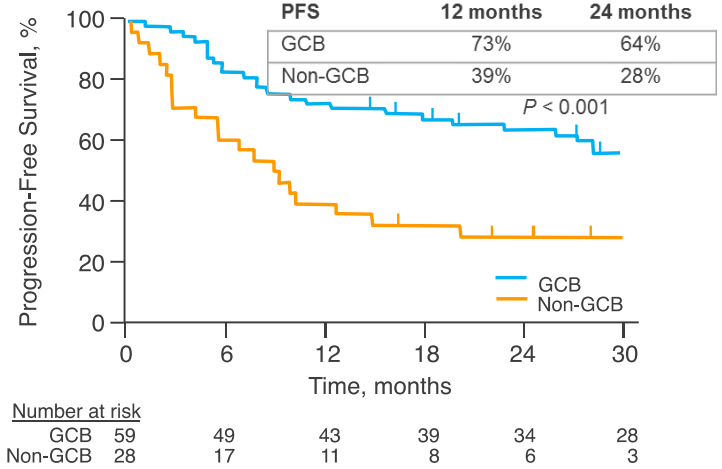


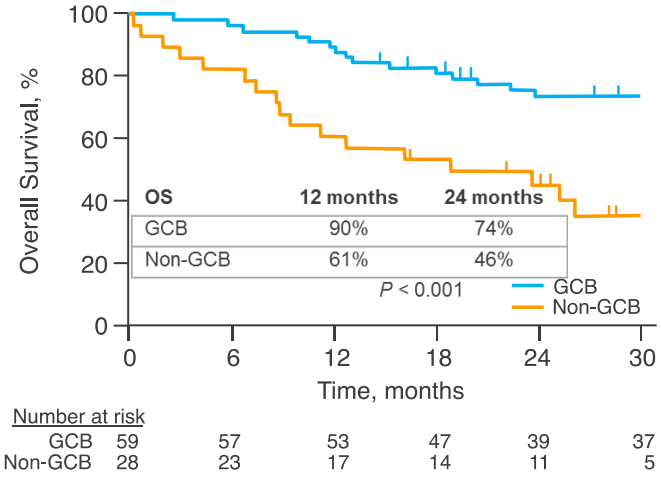
Vitolo U et al, Lancet Oncol 2014

Phase II R2-CHOP21 in Untreated DLBCL and comparison with historical R-CHOP21 group

MAYO CLINIC

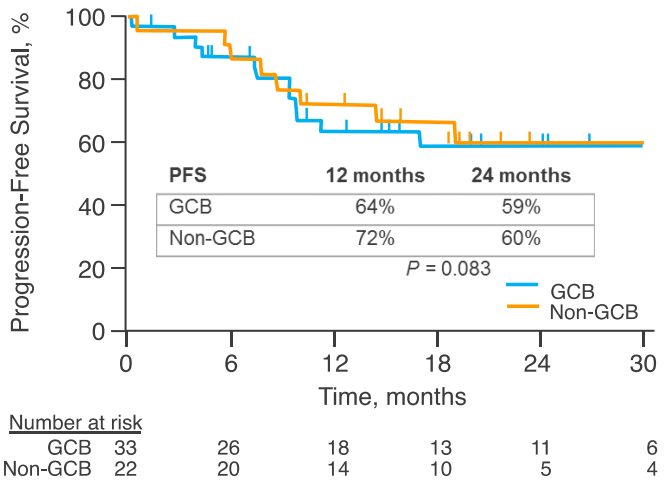
Historical R-CHOP

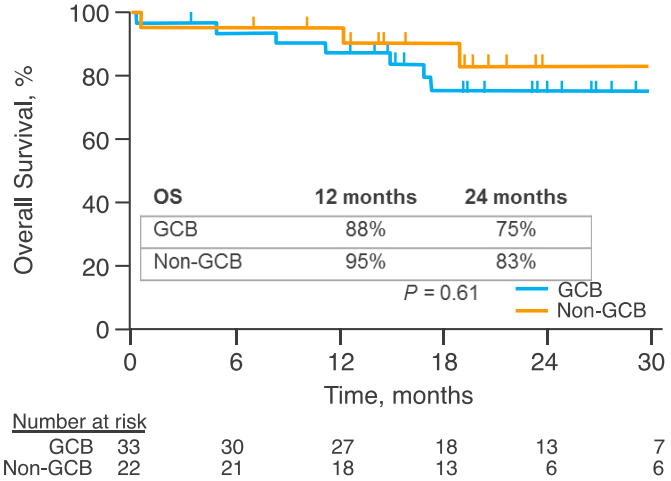




IHC (Hans)

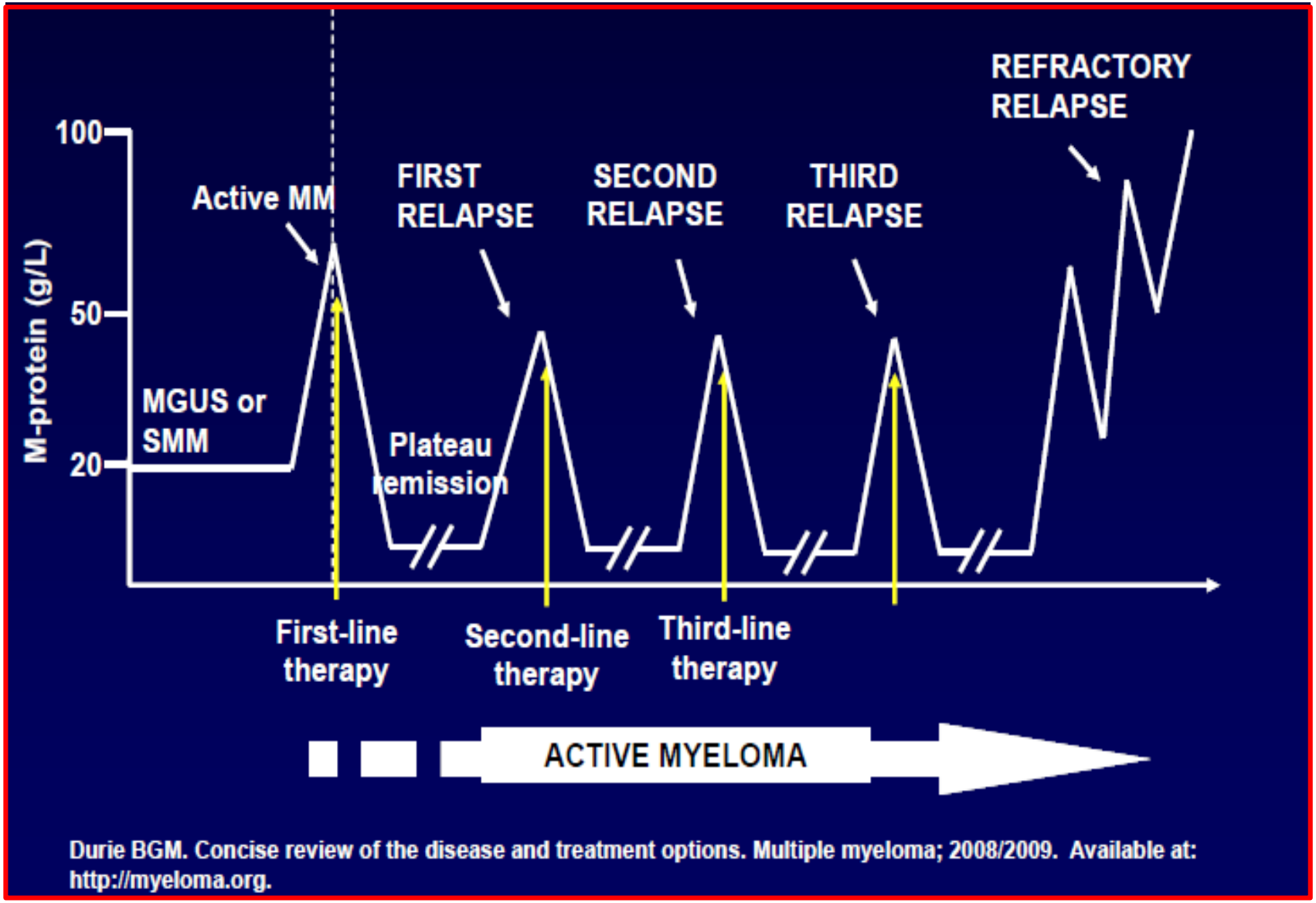
R²-CHOP





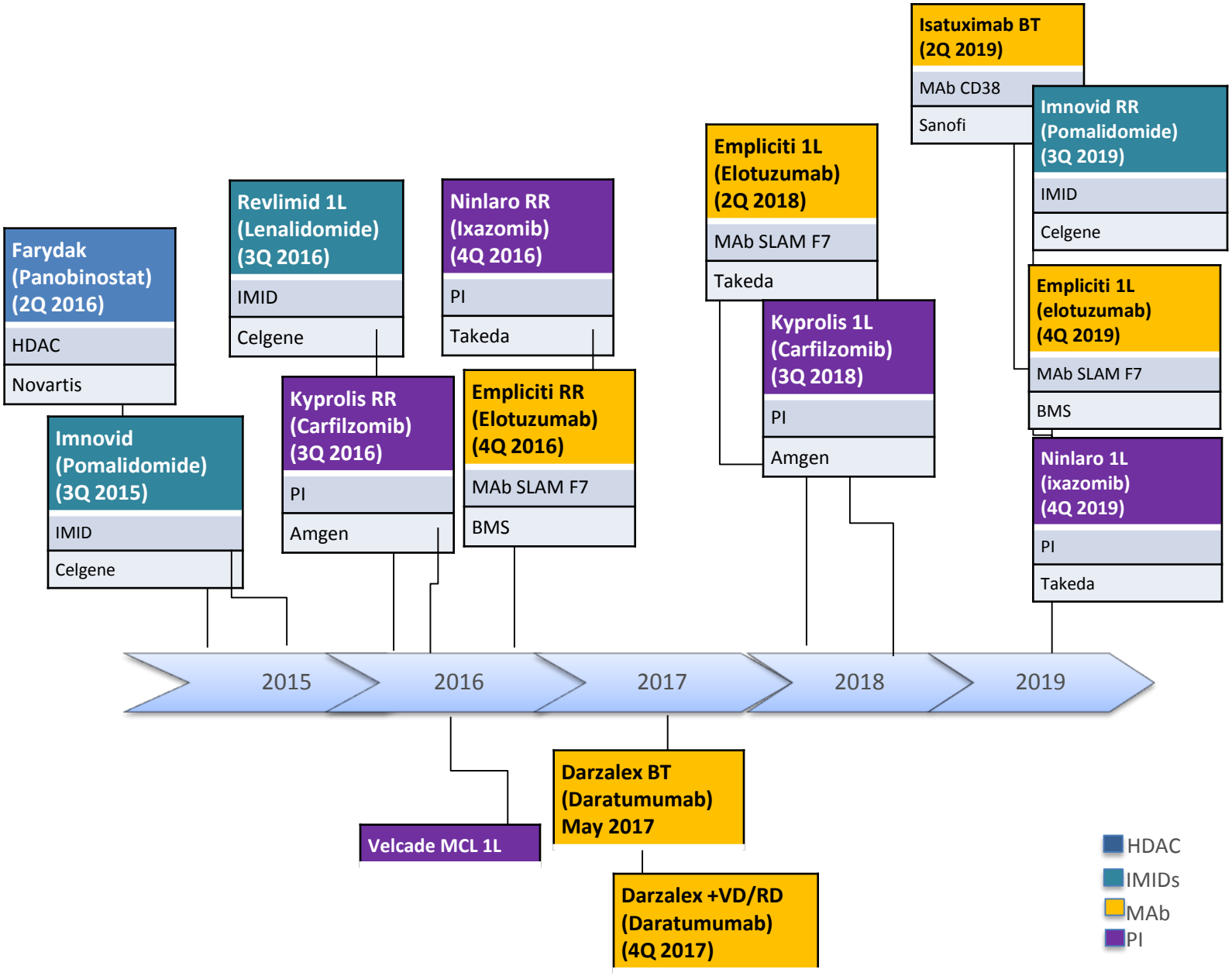
Nowakowski et al, J Clin Oncol 2015

MYELOMA



Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009. Available at: http://myeloma.org.

Mieloma Multiplo scenario 2015-2019



Terapia di 1 linea del paziente anziano (NO ASCT)

VMP

è indicato per il trattamento di pazienti adulti con mieloma multiplo precedentemente non trattato non eleggibili a chemioterapia ad alte dosi con trapianto di cellule staminali ematopoietiche.

MPT

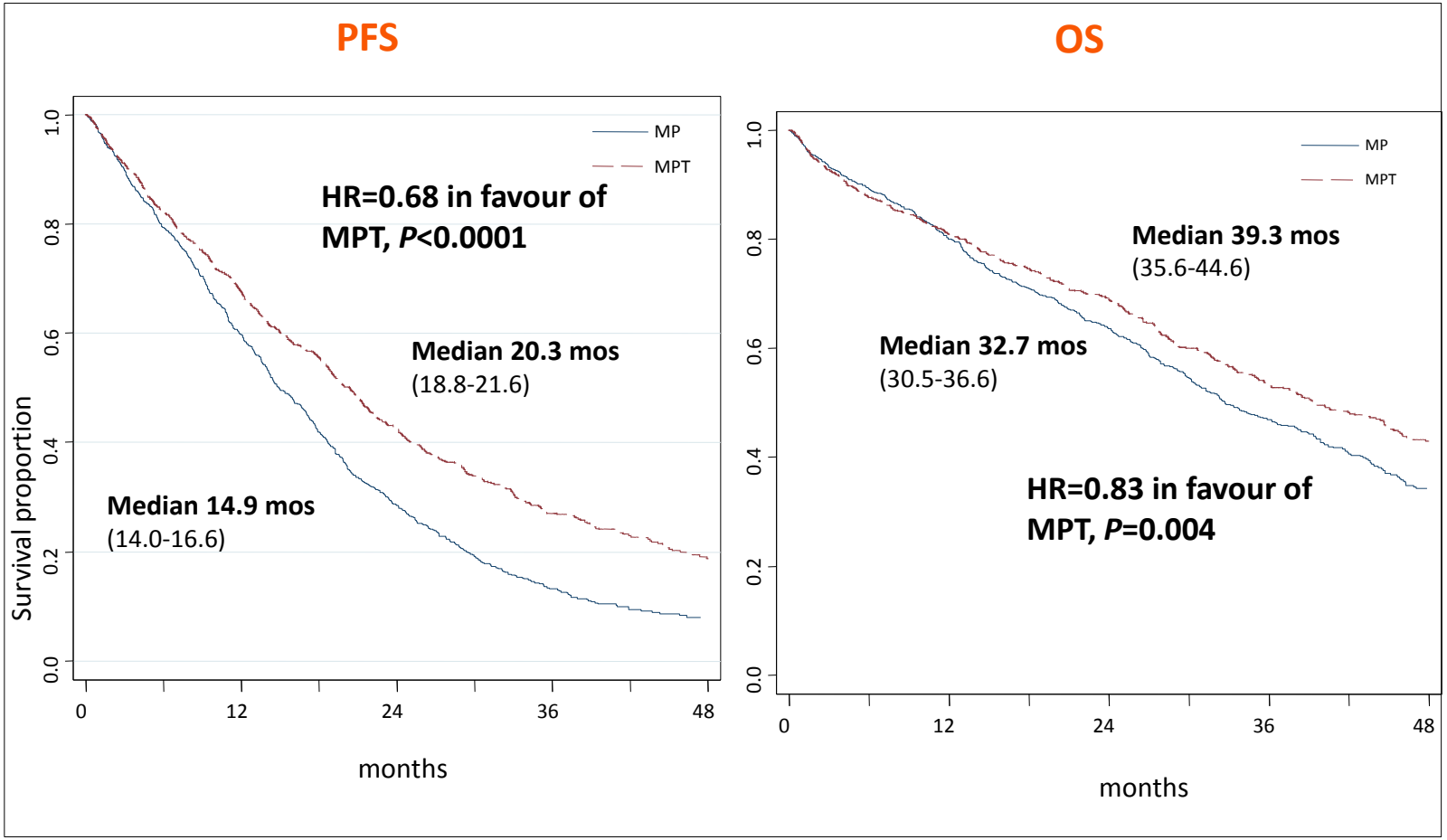
è indicato per il trattamento di prima linea di pazienti con mieloma multiplo non trattato di età ≥ 65 anni o non idonei a chemioterapia a dosi elevate.

Rd

indicato per il trattamento di pazienti adulti con mieloma multiplo non precedentemente trattato che non sono eleggibili al trapianto

MPT vs MP
Meta-analysis of Phase 3 studies

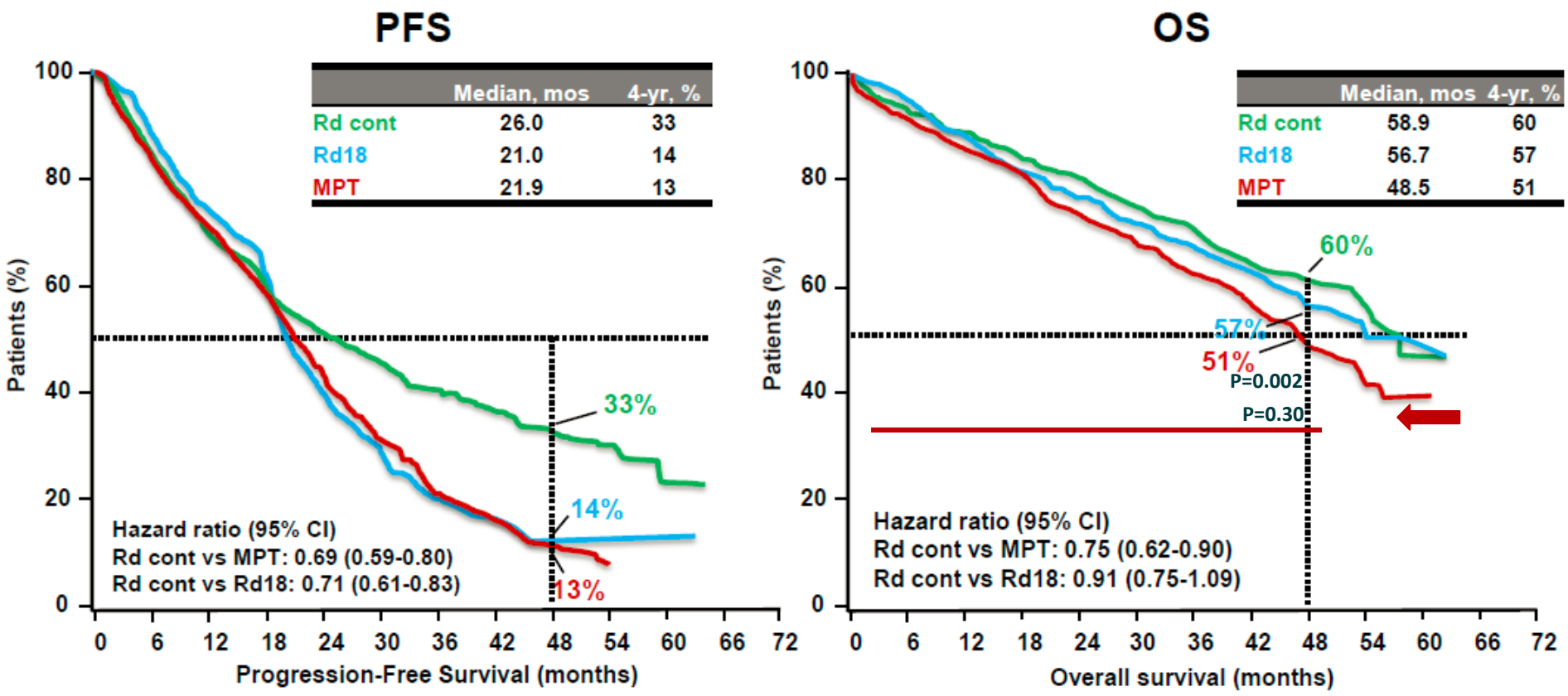
- Individual-patient data (n=1685) from 6 randomized trials



Thalidomide added to MP improves OS and PFS

Fayers et al. Blood 2011;118(5):1239-1247

Rd in NDMM patients – FIRST trial



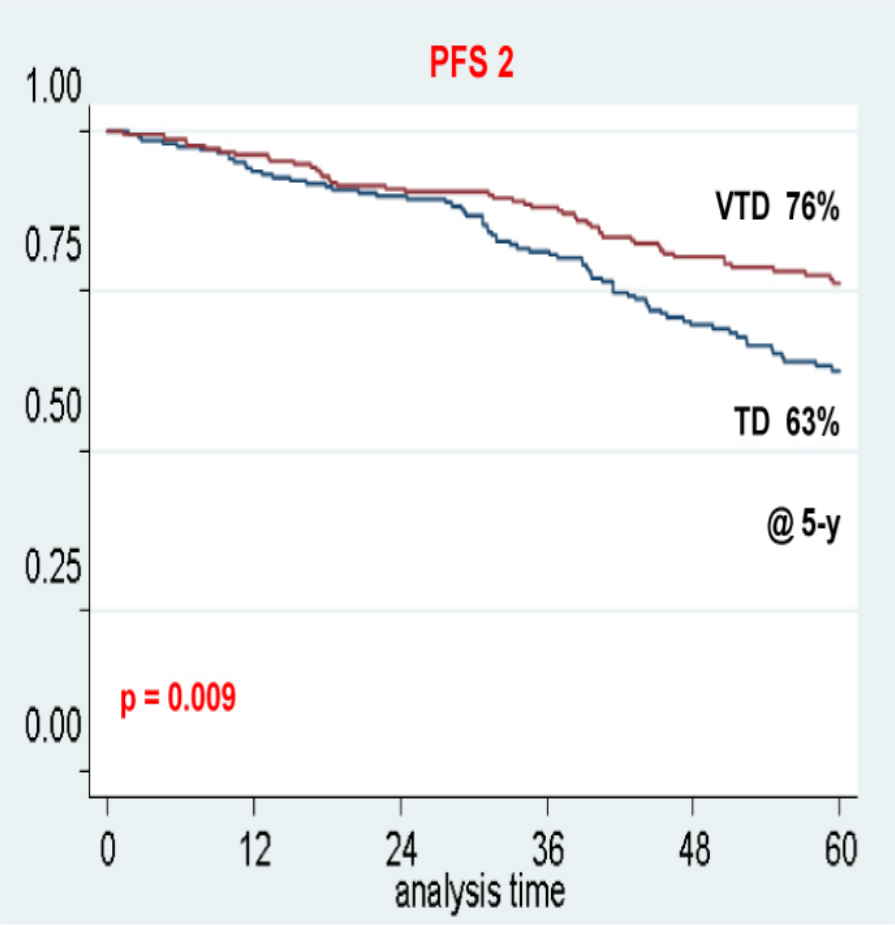
Facon T, et al. *J Clin Oncol.* 2015;33(suppl): Abstract 8524.

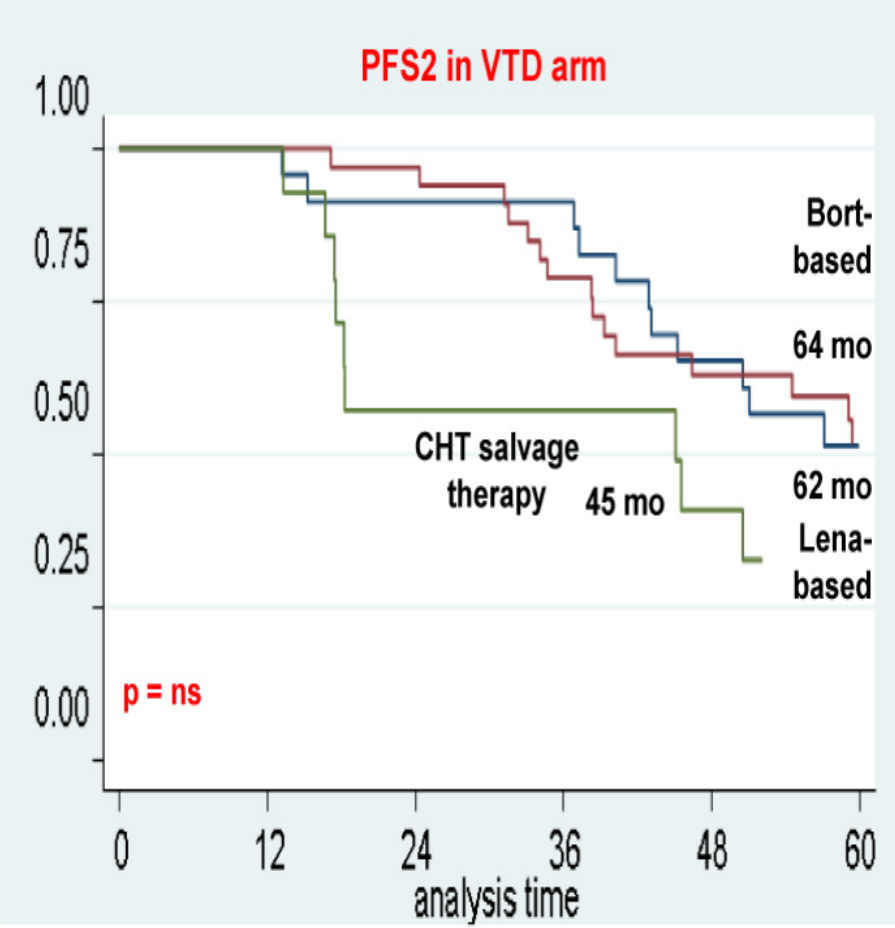
NDMM patients eligible to ASCT

VTD

PFS2 significantly longer, with no difference regardless of the use of bortezomib or an IMiD as part of second-line therapy

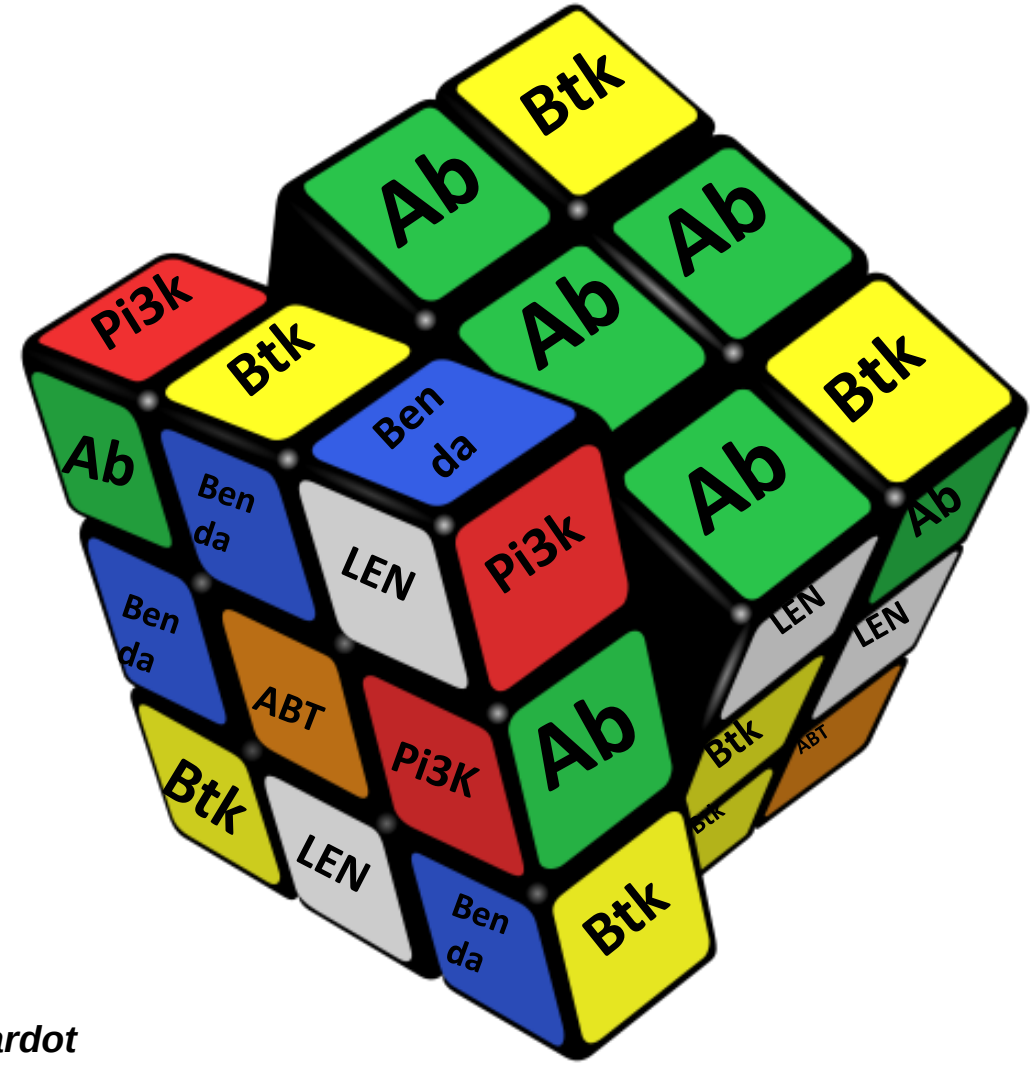
Extended follow up of 65 months





Pantani et al. EHA 2014. Poster 362

The era of combinations



Conclusioni

- Le terapie oncologiche orali, da sole o in associazione ad altri trattamenti endovenosi, stanno occupando aree sempre più importanti in Ematologia, grazie agli studi e a nuove tecnologie farmaceutiche.

- Numerosi studi clinici hanno infatti dimostrato che il trattamento con i farmaci orali permette di ottenere tassi di sopravvivenza e tempi di progressione della malattia equivalenti ed in alcuni casi superiori a quelli della terapia in somministrazione endovena, riducendo, in alcuni casi, anche gli effetti collaterali.

- La somministrazione orale permette ai pazienti di essere parte attiva nel processo di cura senza modificare troppo le loro abitudini quotidiane .

GRAZIE PER L’ATTENZIONE