Ruolo del trapianto allogenico nella leucemia linfatica cronica nell'era dei nuovi farmaci

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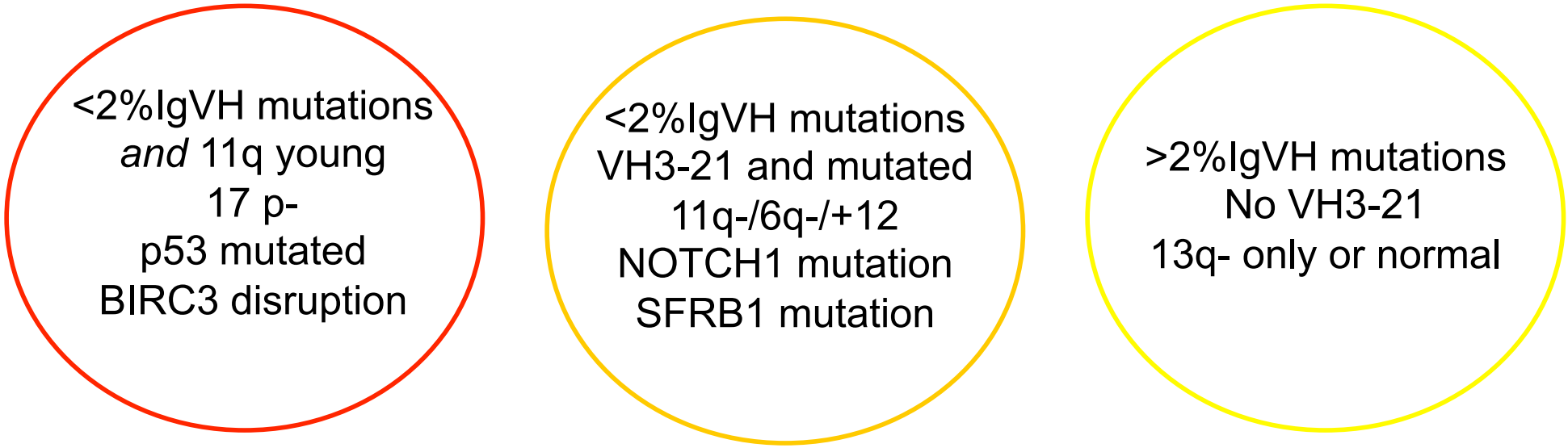
Controversie nel trapianto di cellule staminali emopoietiche

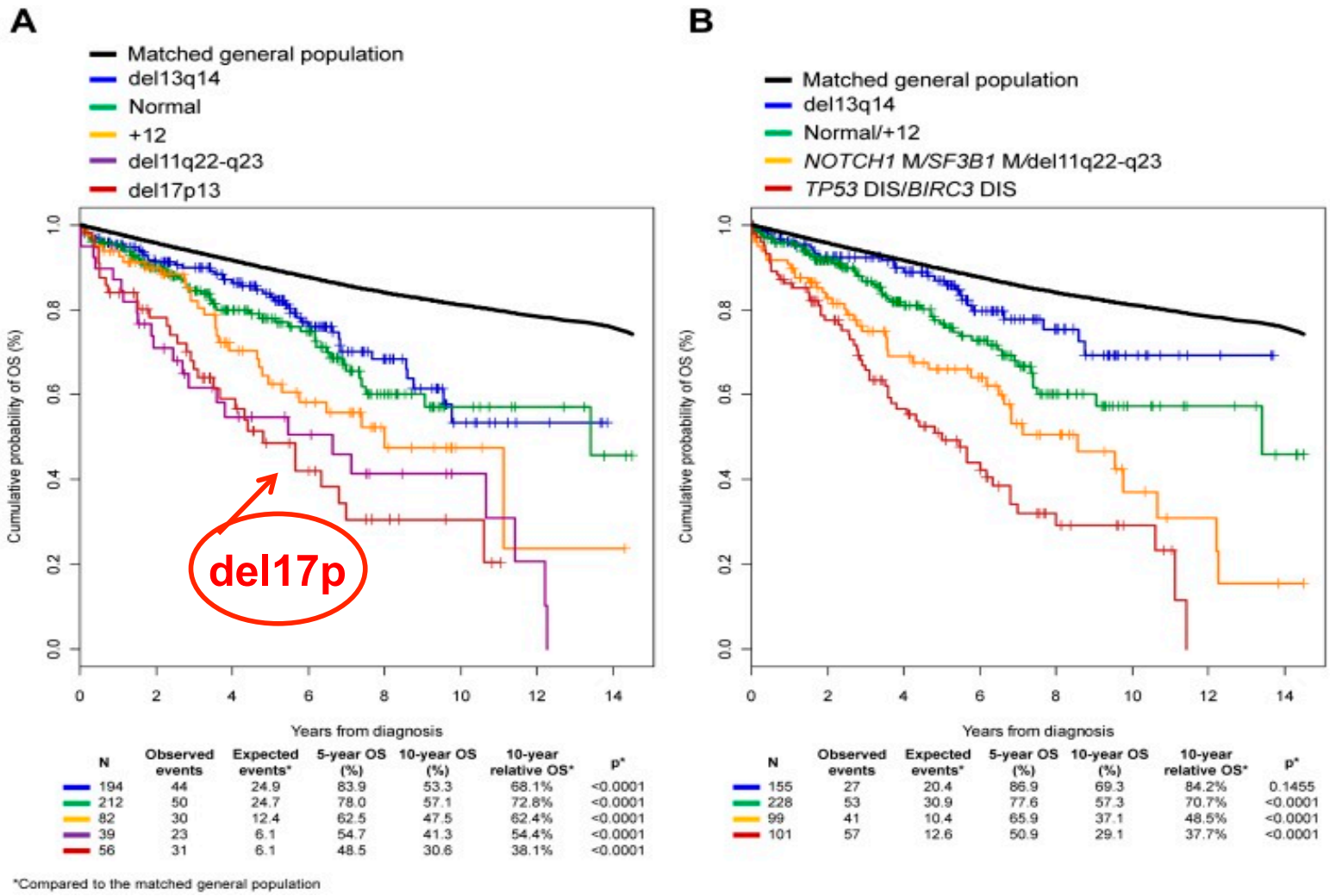
ISTITUTO NAZIONALE PER LO STUDIO E LA CURA DEI TUMORI

Outcome of CLL patients

Median age at diagnosis 72 years
≤ 20% of patients are younger than 60 years

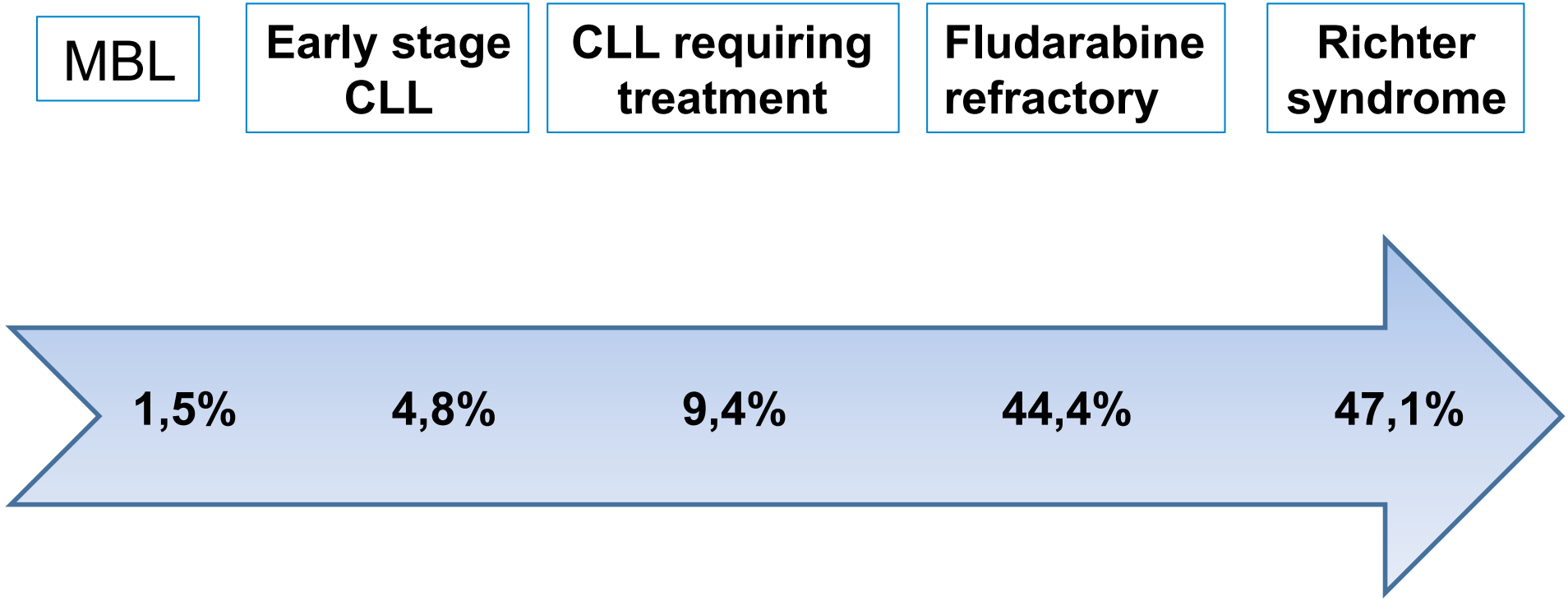


Integrating mutation and cytogenetics for CLL survival prognostication



Rossi et al, Blood 2013

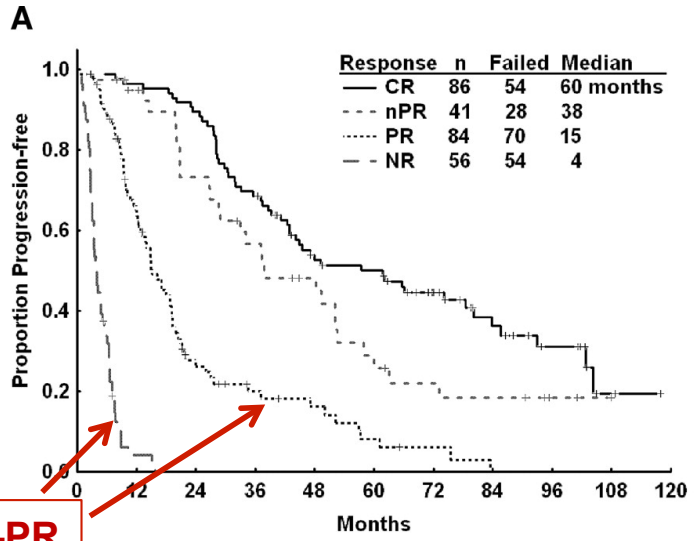
TP53 abnormalities in CLL increase with disease progression

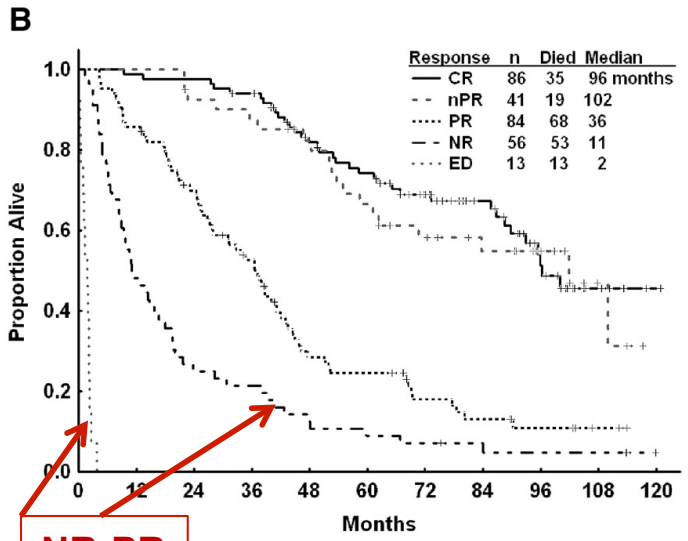


Rossi D, Blood 2014

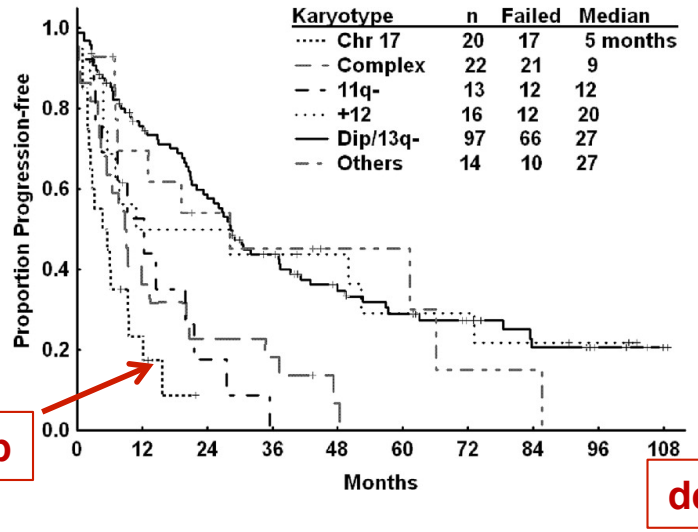
Results of FCR in refractory and del17p relapsed CLL

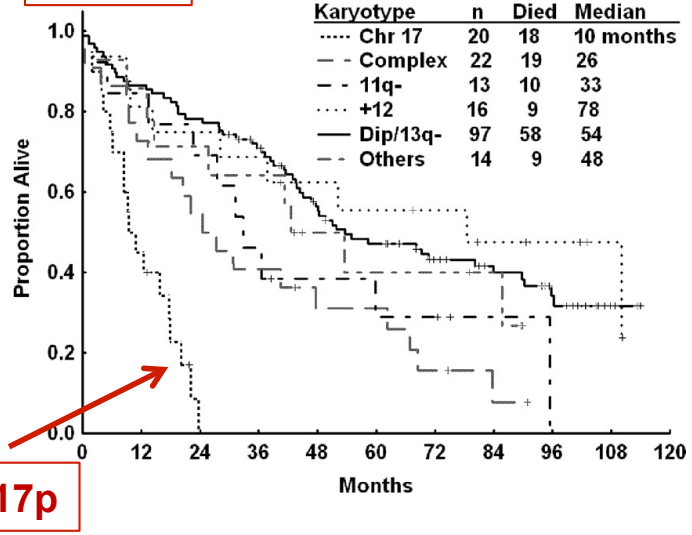
PFS and OS by response to FCR in R/R CLL





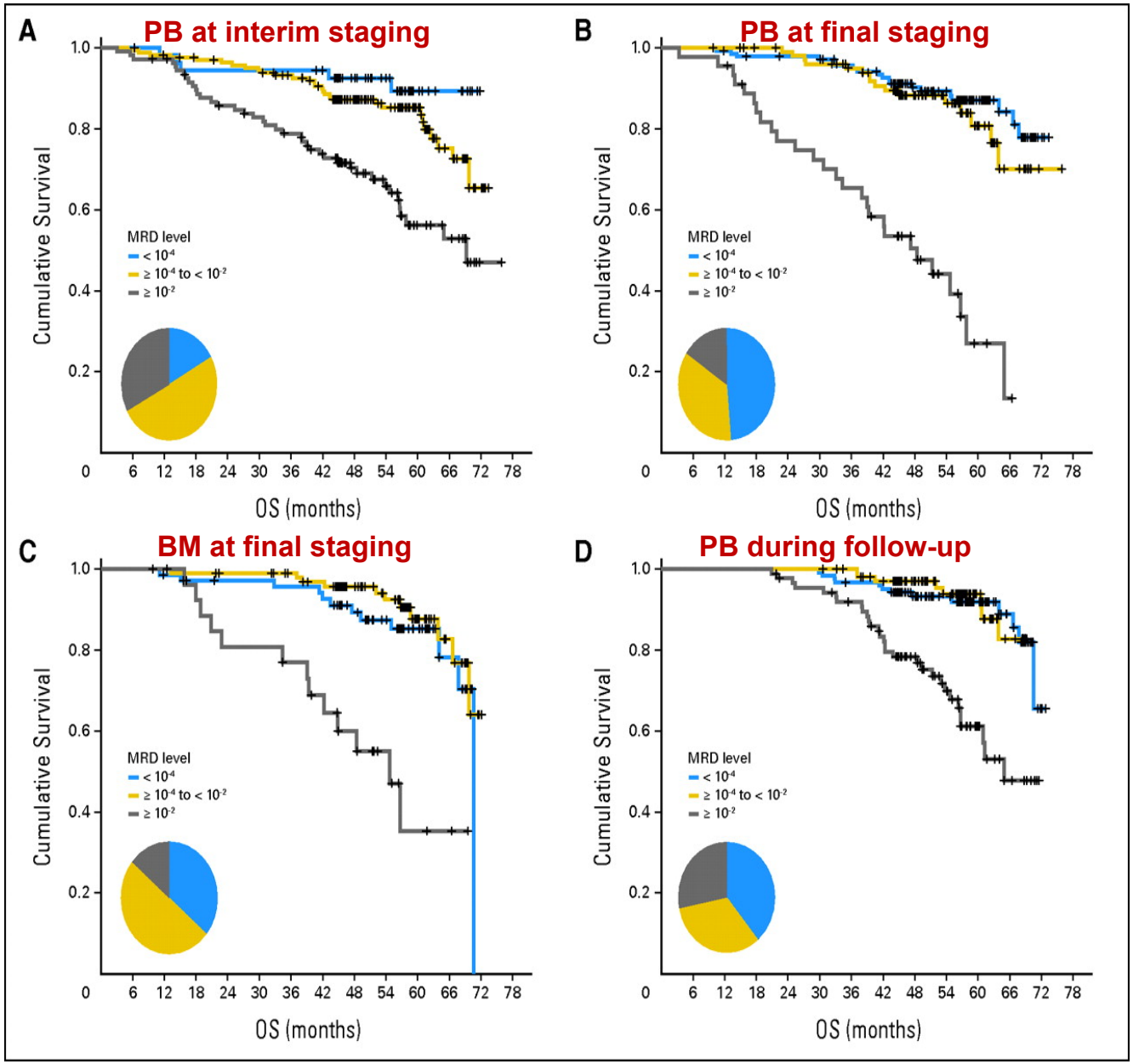
PFS and OS by karyotype In R/R CLL





Badoux X C et al. Blood 2011

Minimal Residual Disease Quantification Is an Independent Predictor of Progression-Free and Overall Survival in Chronic Lymphocytic Leukemia: A Multivariate Analysis From the Randomized GCLLSG CLL8 Trial: OS curves based on MRD results



Higher MRD results at all time points were associated with significantly shorter OS

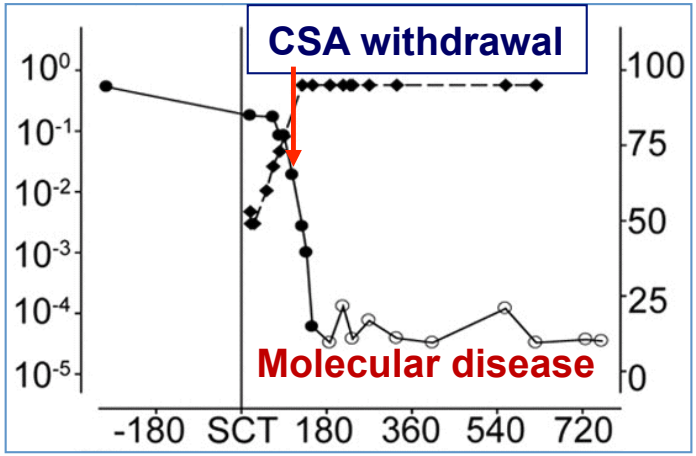
MRD remained predictive of OS and PFS in multivariate analysis

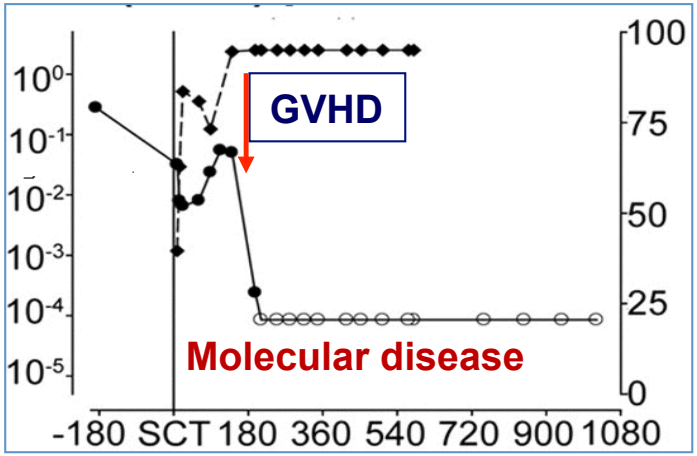
Böttcher S et al. JCO 2012

HOW CAN WE ACHIEVE LONG-TERM DISEASE CONTROL IN RELAPSED AND HIGH RISK DISEASE?
RATIONALE OF ALLOGENEIC STEM CELL TRANSPLANTATION

- Allogeneic stem cells are free of tumor contamination

- "Graft-versus-Leukemia" effect demonstrated by:
  - Clinical and molecular responses after immune suppression withdrawal or the onset of GVHD





  - Response after donor limphocyte infusions

RESPONSE TO DLI	ORR	GVHD
Khouri IF, *Exp Hematol 2004*	86%	70%
Delgado J, *Blood 2006*	27%	44%

Indications for allogeneic stem cell transplantation in chronic lymphocytic leukemia: the EBMT transplant consensus

P Dreger[1], P Corradini[2], E Kimby[3], M Michallet[4], D Milligan[5], J Schetelig[6], W Wiktor-Jedrzejczak[7], D Niederwieser[8], M Hallek[9] and E Montserrat[10], on behalf of the Chronic Leukemia Working Party of the EBMT

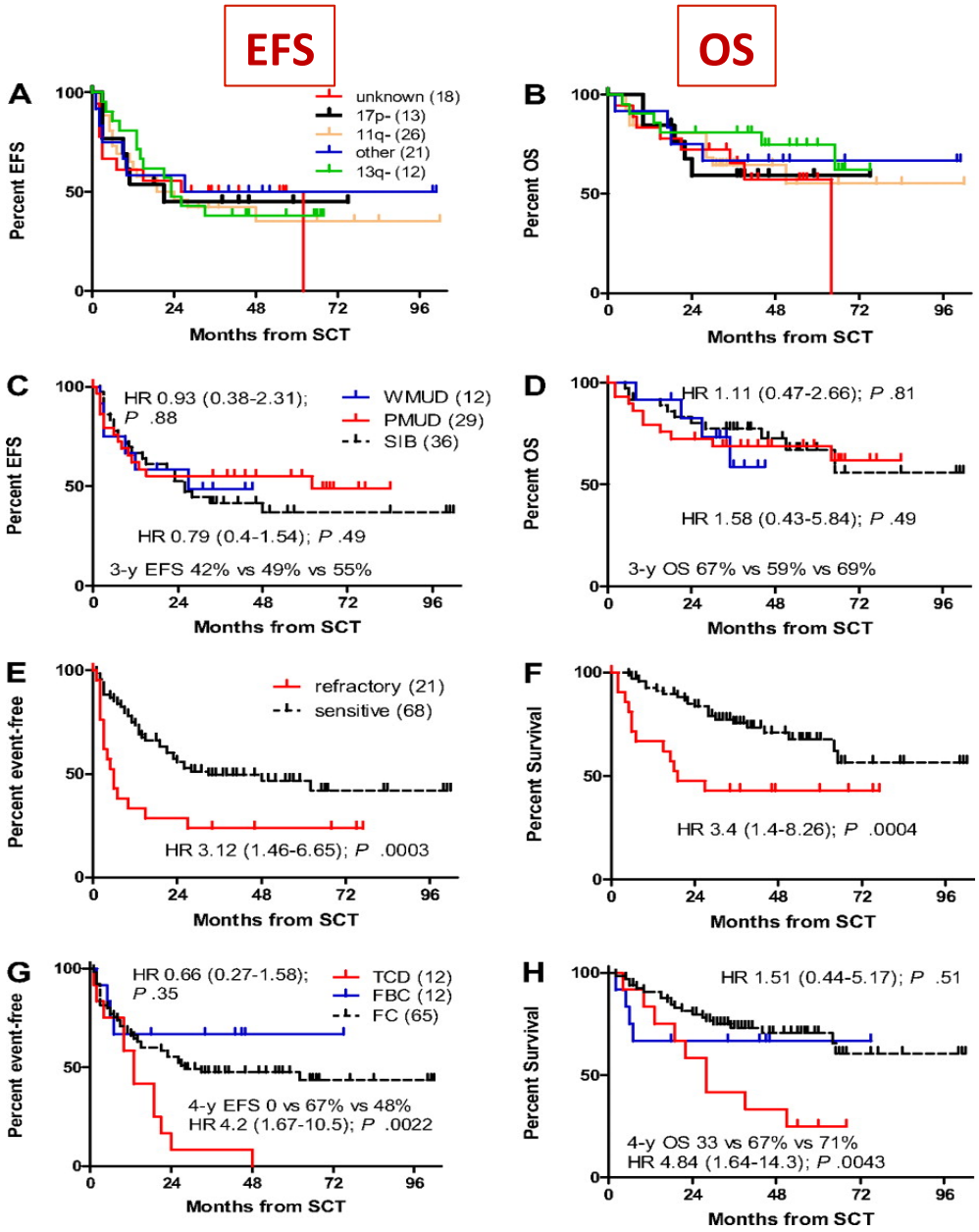
Key elements of the consensus are
(1) allo-SCT is a procedure with evidence-based efficacy in poor-risk CLL

(2) although definition of 'poor-risk CLL' requires further investigation, allo-SCT is a reasonable treatment option for younger patients with
(i) non-response or early relapse (within 12 months) after purine analogues
(ii) relapse within 24 months after having achieved a response with purine-analogue-based combination therapy or autologous transplantation
(iii) patients with p53 abnormalities requiring treatment

(3) optimum transplant strategies may vary according to distinct clinical situations and should be defined in prospective trials.

Dreger P et al, Leukemia 2007

German CLL Study Group CLL3X trial: Impact of pre-transplant variables on survival



EFS and OS based on:

A-B: FISH karyotype: ns

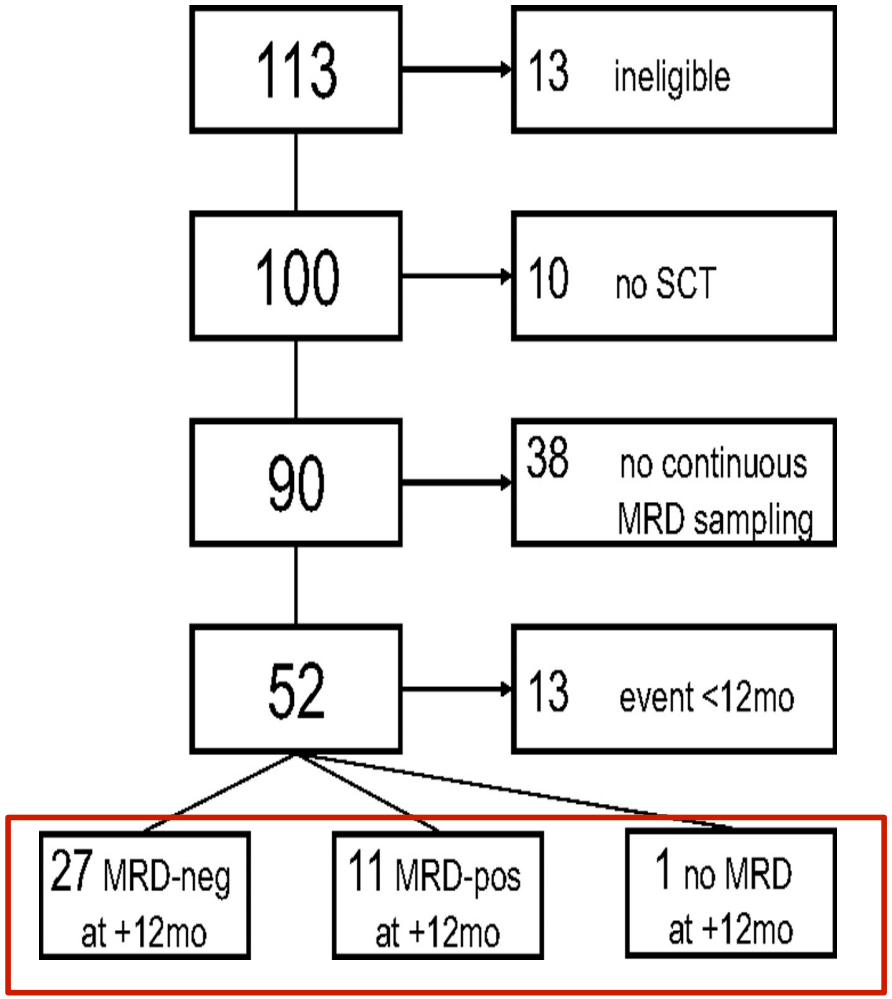
C-D: donor match: ns

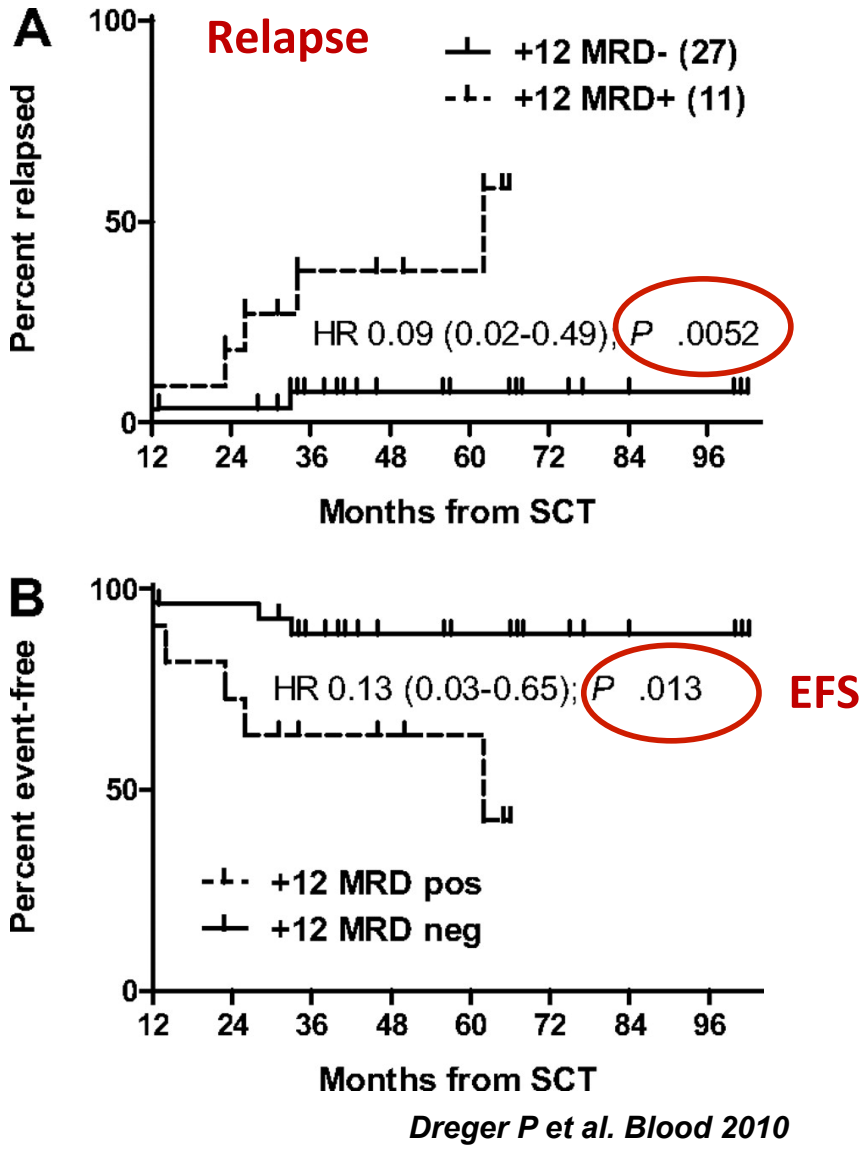
E-F: refractory disease at alloSCT negative impact of refractory disease

G-H: conditioning regimen: negative impact of alemtuzumab

Dreger P et al. Blood 2010

Allogeneic stem cell transplantation provides durable disease control in poor-risk CLL: long-term clinical and MRD results of the German CLL Study Group CLL3X trial

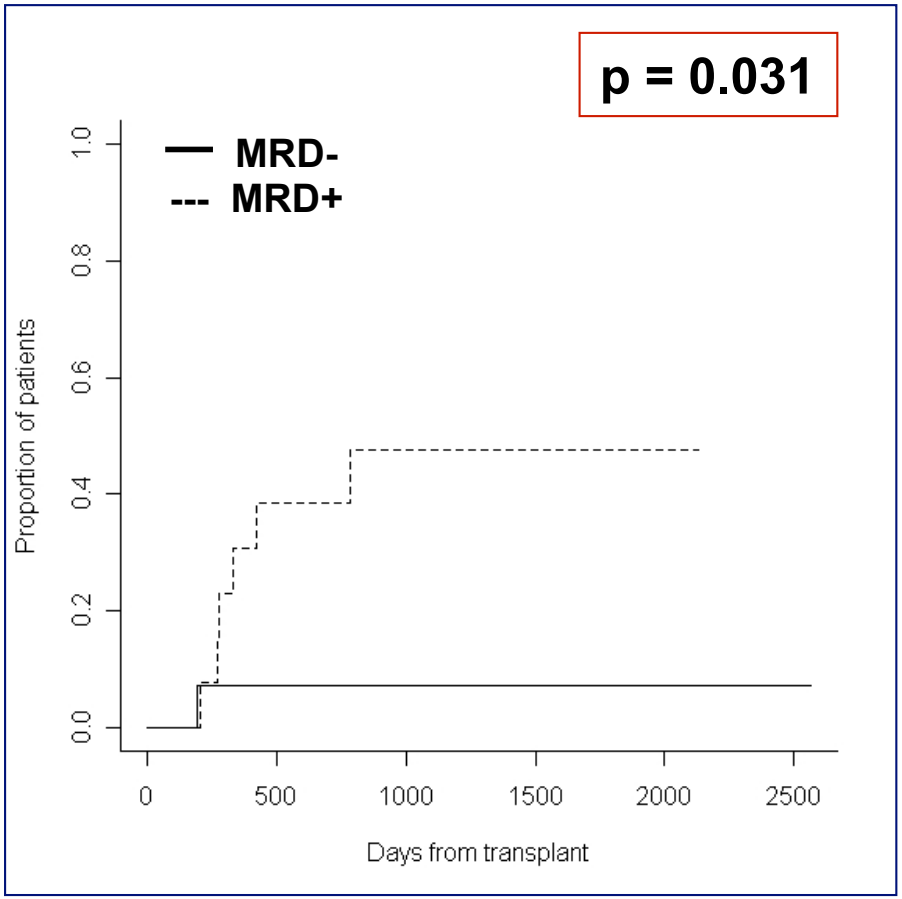




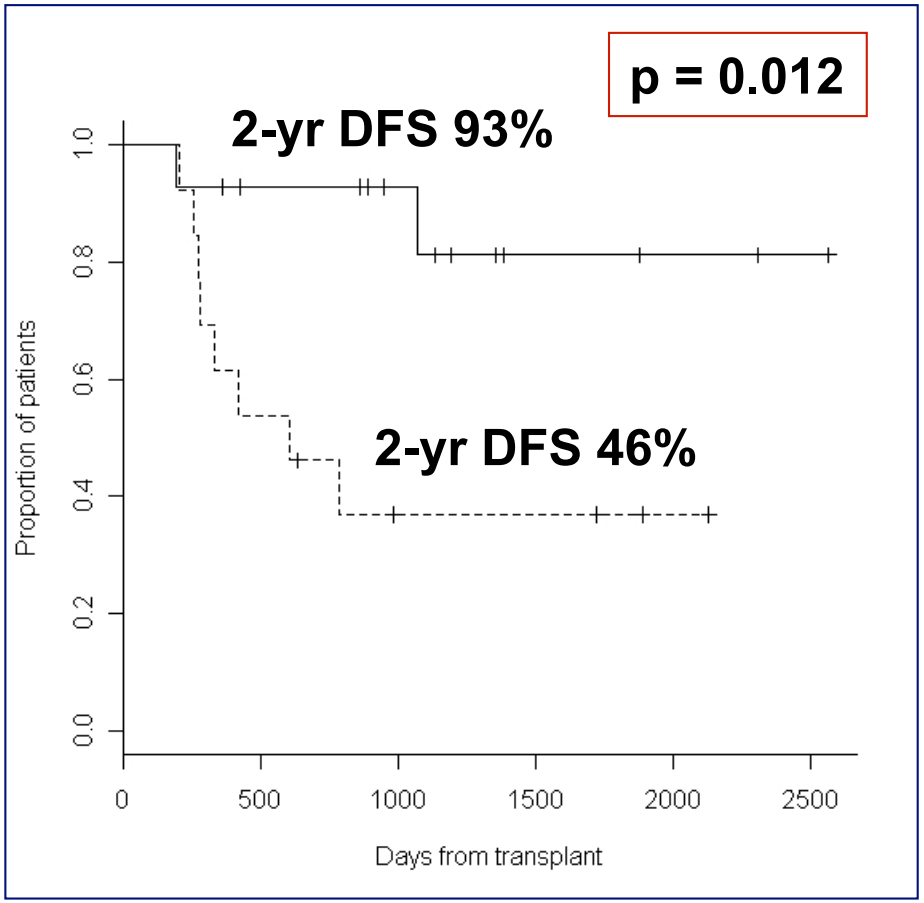
Dreger P et al. Blood 2010

Clinical impact of MRD status after RIC alloSCT in CLL: GITMO study

Cumulative incidence of relapse based on PCR status at 6 mos



DFS based on PCR status at 6 mos



Farina L et al, Haematol 2009

RIC alloSCT in CLL: long-term results

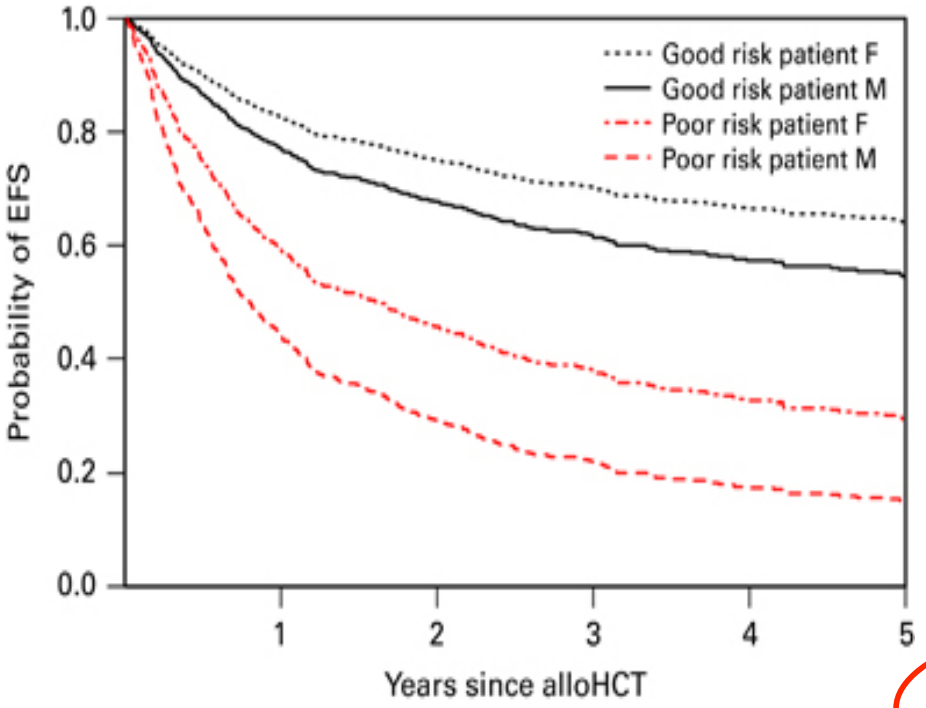
	GCLLSG	MDACC	FHCRC	DFCI	French
n	100*	86	82	76	40
Follow-up	10 years	5 years	5 years	5 years	3 years
OS	51%	51%	48%	63%	55%
Relapse	57%	na	37%	40%	22%
Early death	<3%	3%	<10%	< 3%	na
NRM	26%	17% (1 year)	23%	16%	27%
Extensive chronic GVHD	55%	56%	50%	48%	42%

Dreger, ASH 2016; Khouri, Cancer 2011; Sorror, JCO 2008; Brown, Leukemia 2013; Michallet, Exp Hematol 2013

Challenges associated with alloSCT for patients with CLL

- **Lack of agents to induce effective debulking of CLL prior to SCT**
- **Immunosuppression and GVHD**
  - Morbidity and mortality
- **Majority of patients aged over 70 years:**
  - Concomitant comorbidities
  - Poor related donor availability
  - Access limitations

Factors affecting outcome after alloSCT in CLL



Abbreviations:
EFS – Event-free survival
F – Female
M – Male

-Disease status
-Donor Match
-Donor sex
had a major impact on NRM and long term PFS

<u>High risk patient:</u>
Male aged > 55 years, KPS < 80, SD/PD at alloSCT and with a female donor

2-yr NRM 11%→42%
5-yr EFS 55%→15%

Schetelig et al, BMT 2017
Van Gelder et al, ASH 2016

New drugs have changed alloSCT indications

- **Availability of target agents as an alternative to intensive therapy**
  - effective in high risk patients
  - well tolerated with low side effect profiles
- **Durable disease control (5-years results)**
- **Further development potential**
  - Sequencing BCR-inhibitors
  - Sequencing BCR inhibitors and bcl-2 inhbitors
  - Combinations with monoclonal antibody and chemotherapy

NEW TARGET THERAPIES IN CLL

	Mechanism of action	Phase	N	DAILY DOSE	ORR (CR)	PFS	
IBRUTINIB *(NEJM 2013)*	BTK inhibitor	II	85	420 MG	71%	26-m: 75%	**Approved in del17p/TP53mut and R/R CLL**
IDELALISIB *(NEJM 2014)*	PI3Kδ inhibitor	III	110	150 MG BID	81%	12-m: 66%	**Approved R/R CLL** ***No more approved del17/ TP53MUT first line**
VENETOCLAX *(NEJM 2016)*	Bcl-2 inhibitor	I	116	400 MG (ramp-up in doses)	79% **(20%)**	15-m: 69%	**Approved in R/R after BCR inhibitor or not eligible to BCRi**

***No difference in outcome for del17p or refractory patients**
****Low complete response rate**

PCYC-1102/1103:
Five-year experience of ibrutinb in naive and R/R CLL

- Phase 2 study of ibrutinib monotherapy 420 mg or 840 mg daily in naive ≥ 65 years (n=31) or R/R (n=101)

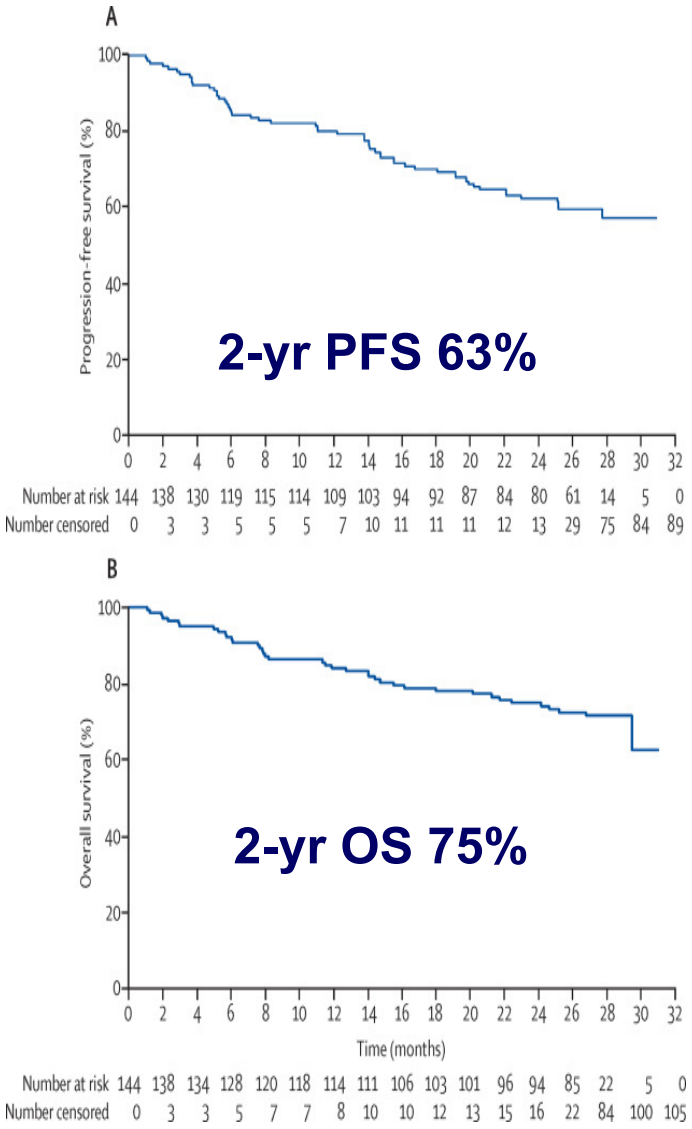
	TN	R/R
Median follow-up	62 (1-67)	49 (1-67)
Best reponse**	ORR 87%, CR 29%	**ORR 89%, CR 10%**
Median time on study, months	62, 1-67	49, 1-67
Patients remaining on ibrutinib	65%	**30%**
Median DOR	NR	56,8 (0-65)
Primary reason of discontinuation PD AE *** Investigator decision	 3% 19% 0%	 33% 21% 11%

** **Median PFS 26 m in del17 vs NR**
Median PFS 39 m for pts with 3 previous lines vs 63 m with 1-2 previous regimens

***AE decrease over time

O'Brien S et al, ASH 2016

Ibrutinib monotherapy in R/R del17p/TP53mut CLL patients: results from RESONATE17



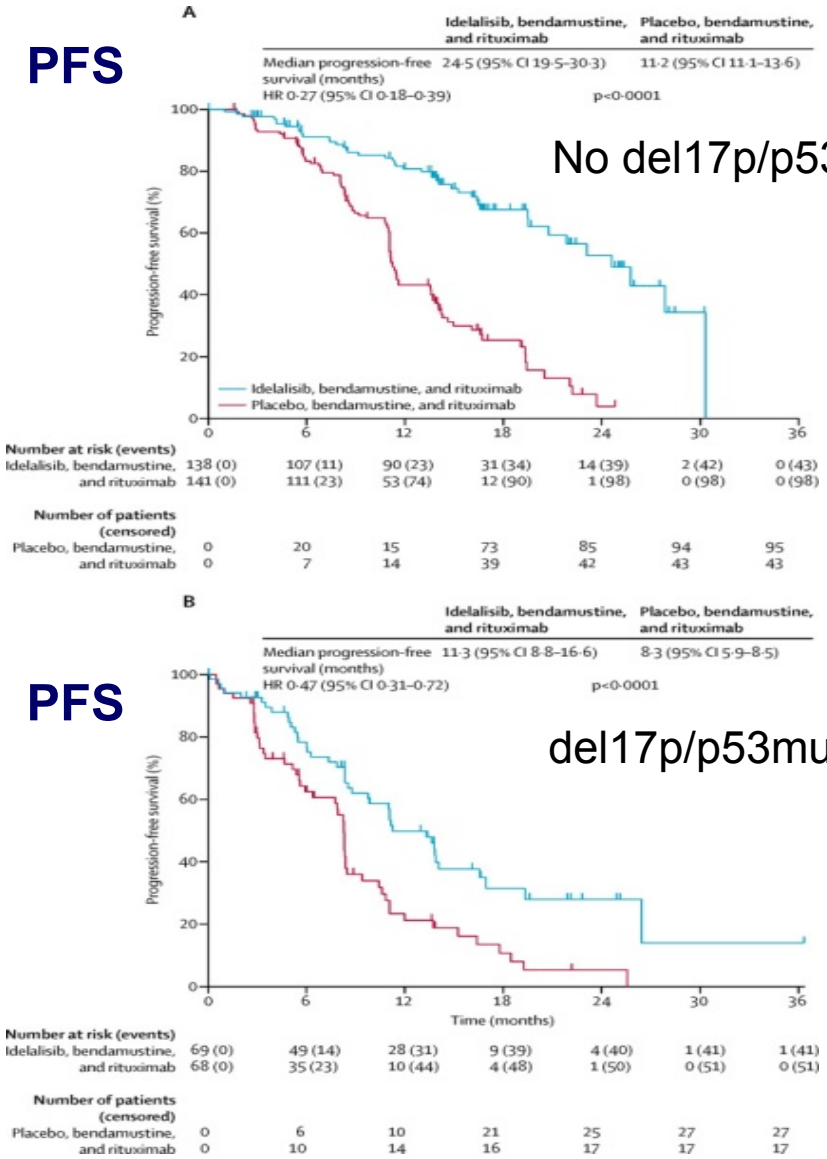
n=144	
Median age ≥70 years	64 (57-72) 69 (48%)
Rai stage III-IV	63%
Bulky ≥ 5	49%
VDJ UNM	67%
% cell with del17p	66%
P53 mut	92%
Median n° previous th	2 (1-3)

Median follow-up, months	27,6 (6-27,7)
Best reponse**	ORR 83%, CR 8%
Median DOR	Not reached
PD/ Richter	39 (27%) / 17 (12%)
Treatment discontinuation	50% (34 PD, 24 AE)

O'Brien S et al, Lancet Oncol 2016

Idelalisib or placebo in combination with bendamustine and rituximab in patients with R/R CLL: interim results from a phase 3, randomised, double-blind trial

PFS



No del17p/p53mut

PFS

del17p/p53mut

	I-RB n=207	Placebo + R-benda n=209
Median age, years	62 (56-69)	64 (56-70)
Del17p/p53mut	33%	33%
Median n° prior therapies	2 (1-4)	2 (1-4)
Previous BR/FCR	18%/68%	11%/66%
ORR	**70%**	**45%**
Median PFS in del17p, months	**11.3**	**8.3**
Median PFS in no del17p, months	**24.5**	**11.2**

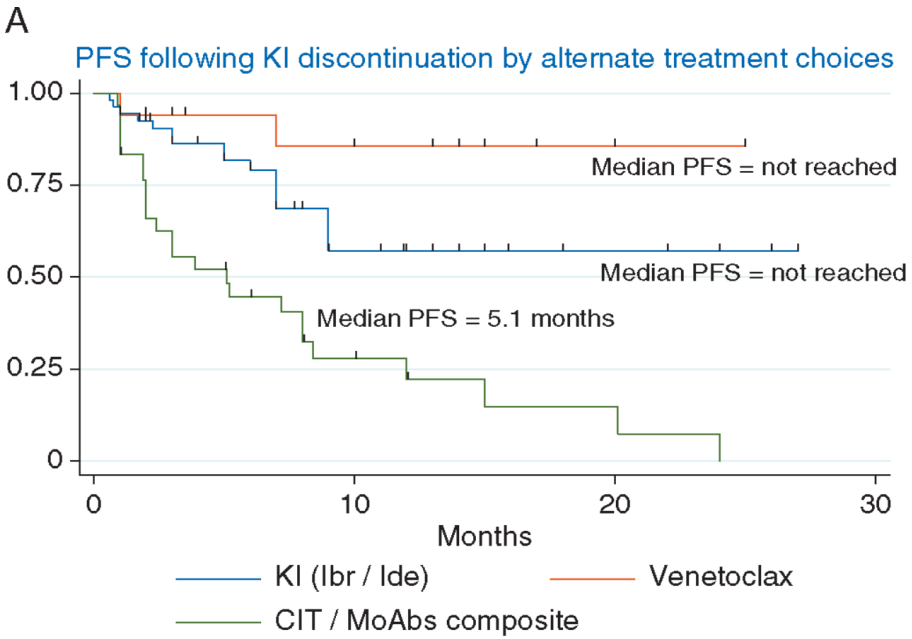
Zelenetz A et al, Lancet Oncol 2017

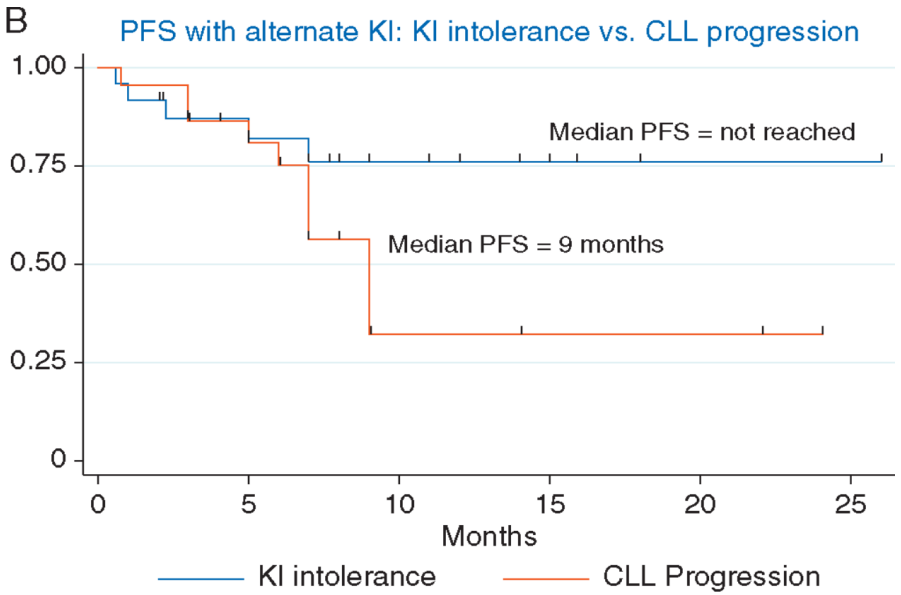
Idelalisib or placebo in combination with bendamustine and rituximab in patients with R/R CLL:
interim results from a phase 3, randomised, double-blind trial

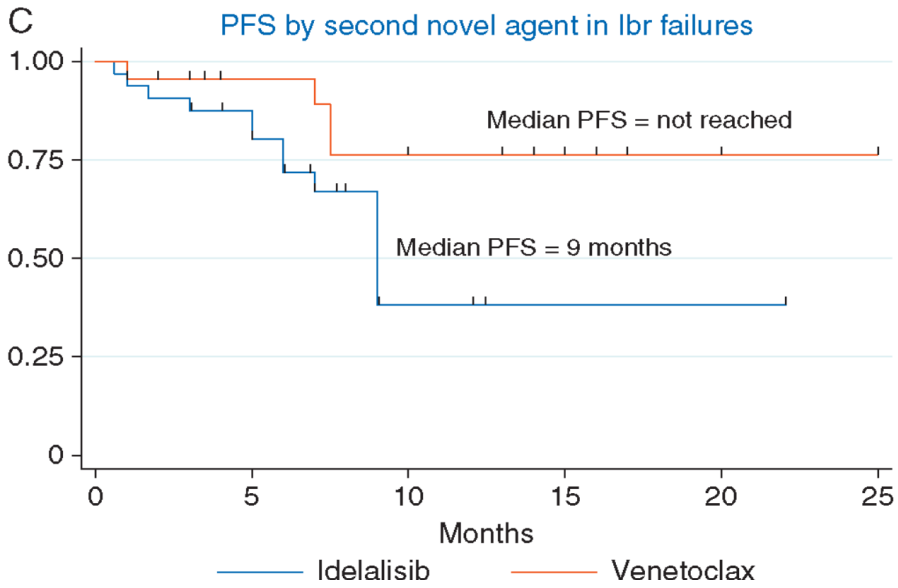
	I-RB n=207	Placebo + R-benda n=209
Duration of exposure	14,8 (5,9-18,9)	11,1 (5,8-15,3)
AE as reason for discontinuation	27%	13%
<u>AE leading to</u> Study drug dose reduction Tretament discontinuation Death	 13% 28% 11%	 6% 14% 7%
PJP infection	2%	0
CMV reactivation	6%	1%

Zelenetz A et al, Lancet Oncol 2017

Optimal Sequencing of Ibrutinib, Idelalisib, and Venetoclax in CLL: Results from a Large Multi-Center Study of 683 US-Patients

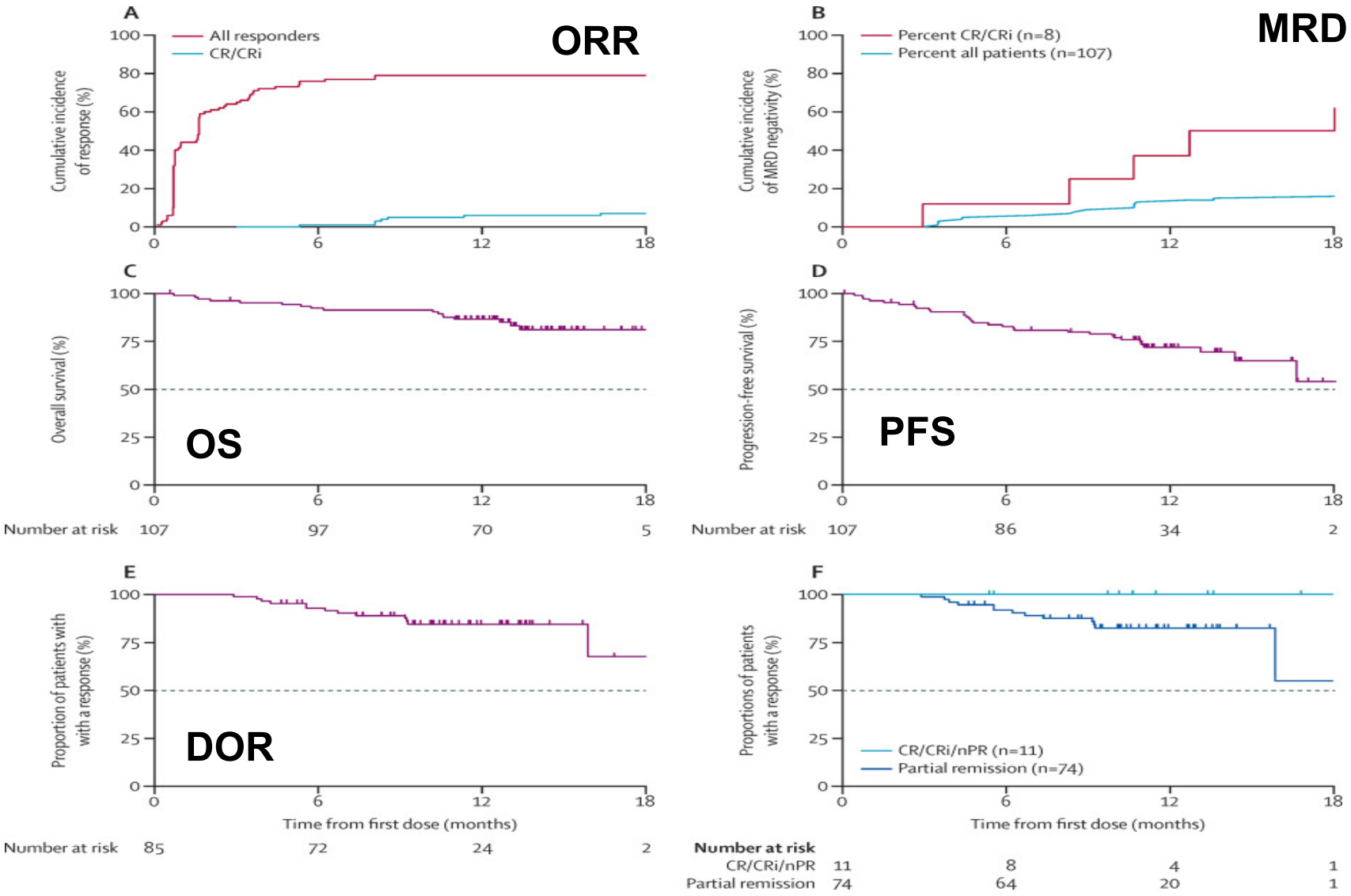






Mato et al, Annal Oncol 2017

Venetoclax in R/R del17p CLL: a multicenter phase II study

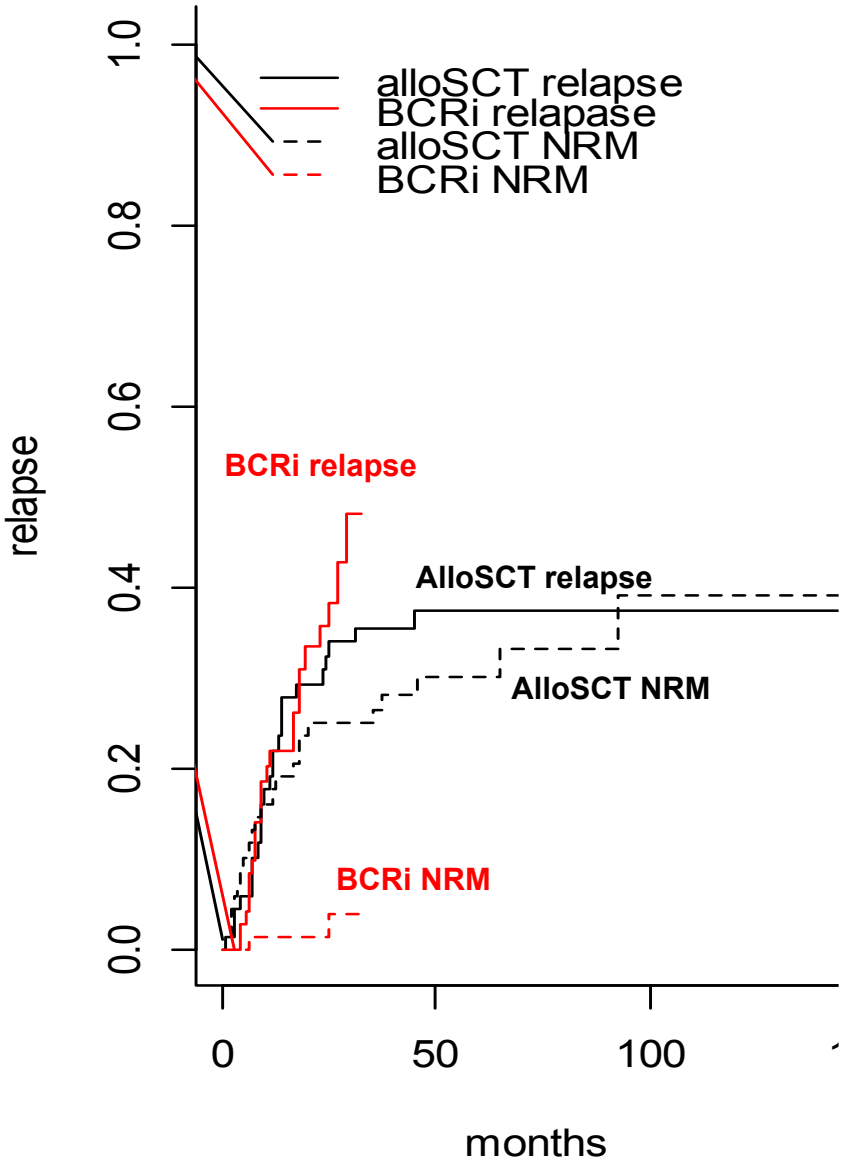


Stilgenbauer S et al, Lancet Oncol 2016

New drugs: the other side of the coin

- RELAPSE
- TOXICITY
- RESISTANCE

Comparative analysis of outcome after alloSCT or BCRi in R/R del17p CLL



	AlloSCT N=68	BCRi N=76	p
2-yr CI Relapse	32%	36%	0.53
Time to progression/ relapse, days	330 (30-1358)	280 (121-865)	0.89
Time to next therapy, days	377 (101-1468)	368 (90-888)	0.58

Farina L et al, ASH 2016

WHAT WILL BE THE ROLE OF NEW DRUGS in the alloSCT SETTING?

New target therapies should:

-bridge young high-risk patients to allotransplant (better if CR)

-act synergistically with the 'GVL effect' after alloSCT to maintain and induce clinical and molecular remission

-be feasible in the post-transplant phase to treat relapse

Ibrutinib for bridging to alloSCT: the EBMT data

N=63 (CLL: 43, MCL: 17)	
Median age, years	56 (38-72)
Del17p/p53mut	37%
Median number of lines prior to ibrutinib	2 (1-9)
Median time on ibrutinib, days	187 (11-671)
Interval between ibrutinib and alloSCT 15-120 days 4-14 days 0-1 days	 39% 42% 14%
Chemosensitive at alloSCT	81%

Dreger P , EBMT 2017

Ibrutinib for bridging to alloSCT: the EBMT data

N=63 (CLL: 43, MCL: 17)	
Median time to neutrophils >0.5, days	17 (6-68)
Median time to PLT > 20000, days	14 (5-46)
aGVHD (grade III-IV)	37% (7%)
cGVHD (extensive)	41% (24%)
1-yr NRM	9%
1-yr relapse (in ibrutinib sensitive)	36% (28%)
1-yr PFS (in ibrutinib sensitive)	58% (63%)
1-yr OS (in ibrutinib sensitive)	63% (80%)

Dreger P , EBMT 2017

No influence of ibrutinib exposure, TP53 status, conditioning

Salvage use of ibrutinib after alloSCT: the EBMT data

N=60 (CLL: 55, MCL: 5)	
Median age, years	55 (38-66)
Del17p/p53mut	31%
Median number of lines prior to ibrutinib	3 (1-10)
Chemosensitive at alloSCT	75%
RIC regimen	68%
Sibling donor	35%

Michallet M , EBMT 2017

Salvage use of ibrutinib after alloSCT: the EBMT data

N=60 (CLL: 55, MCL: 5)	
Median time from alloSCT to ibrutinib , months	21 (0.5-81)
Median time on ibrutinib at last follow-up, days	407 (14-937)
ORR /CR	**70%/ 33%**
Ibrutinib discontinuation	23%
2-yr PFS	51%
2-yr OS	72%

Michallet M , EBMT 2017

- **Ibrutinib** was able to induce
  - **full T-cell donor chimerism**
  - **donor B-cell reconstitution**
  - **MRD negativity**
  - **resolution of oral and skin GVHD**

Ryan S, Blood 2016

Multicenter Open-Label Phase 2 Study of Ibrutinib in Chronic Graft Versus Host Disease (cGVHD) after Failure of Corticosteroids

Patient population: received ≤3 prior regimens for cGVHD and had either >25% body surface area erythematous rash or NIH mouth score >4
Recommended dose 420 mg daily

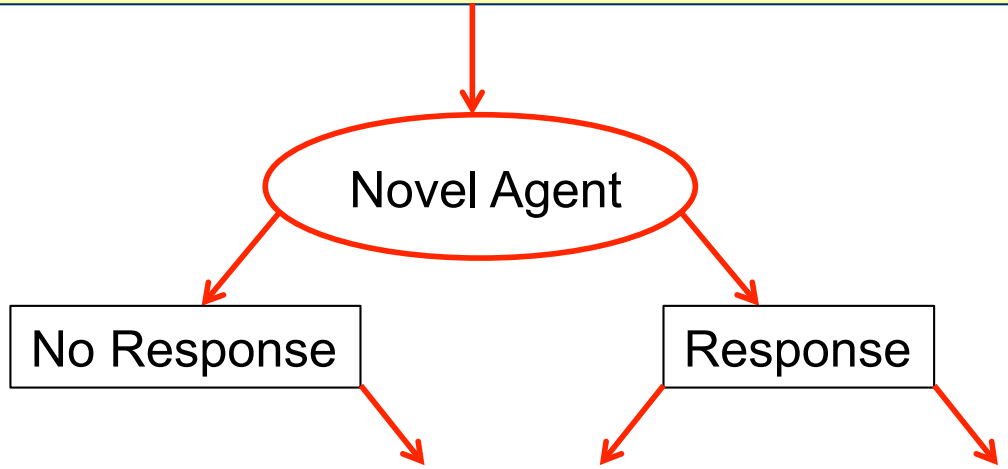
N= 42, median duration of cGVHD before study entry was 13.7 mo (range, 1.1-63.2). Median number of prior regimens was 2 (range, 1-3).

At a median follow-up of 13.9 mo,
ORR 67%, CR 21%
Overall, 21 responders (75%) had corticosteroid doses <0.15 mg/kg/die.
56% response in ≥2 organs
42% response in ≥3 organs

5 pts discontinued therapy for progressive cGVHD and 14 for AEs including fatigue (n=3) and pneumonia (n=2).
Twelve pts (29%) continued ibrutinib; their treatment duration ranges from 5.6-24.9 mo.

Miklos et al, ASH 2016

New indications for alloSCT in CLL



Consider alloSCT
after alternative novel agent

Factor favoring options
(if no clinical trial comparing
HSCT with novel agent is available)

alloSCT

High disease risk
-High risk cytogenetics
(17p-, TP53mut, 11q-)
Low transplant risk
-younger age
-no comorbidity
-well matched donor

Continue novel agent

Low disease risk
-No high risk cytogenetics

Higher transplant risk
-Older age
-significant comorbidity
-mismatched donor

Dreger, Blood 2014

Patient's desires/expectations

Clinical Practice Recommendations for Use of Allogeneic Hematopoietic Cell Transplantation in Chronic Lymphocytic Leukemia on Behalf of the Guidelines Committee of the American Society for Blood and Marrow Transplantation

Standard risk: absence of del17p and/or TP53 mut, absence of complex Karyotype and absence of del11

The panel **recommends** offering allogeneic HCT when there is lack of response or evidence of disease progression after BCR inhibitors

High risk: del17p and/or TP53 mut and/or complex Karyotype

The panel **recommends** allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line (not BCR inhibitors), but show an objective response to BCR inhibitors or to a clinical trial

The panel **recommends** allogeneic HCT for patients who relapse after front-line therapy, demonstrate refractory disease after second-line therapy including BCR inhibitors (not BCL-2 inhibitors), but show an objective response to BCL-2 inhibitors, namely venetoclax, or to a clinical trial

The panel **recommends** allogeneic HCT when there is lack of response or there is progression after BCL-2 inhibitors, namely venetoclax

Early relapse and refractory to FCR is no more an indication for immediate alloSCT

Kharfan-Dabaja MA et al, BBMT 2016

CONCLUSIONS and OPEN QUESTIONS

- AlloSCT in CLL will probably decrease over time, but so far it is still worthy in young relapsed del17p patients at low risk of NRM and after therapy with new drugs

- Novel agents should be integrated in the transplant program (when? how? how long?)

- The clinical course of CLL patients will probably change in the future making ‘new’ candidates for alloSCT