Le nuove terapie hanno modificato l'indicazione al trapianto nelle LLC ?

Udine, 22 gennaio 2016

Francesco Zaja

1. Indicazioni e risultati del trapianto allogenico RIC nella LLC
2. Risultati relativi all'uso degli inibitori di BCR nella LLC
3. Discussione sui risultati e possibili nuove strategie

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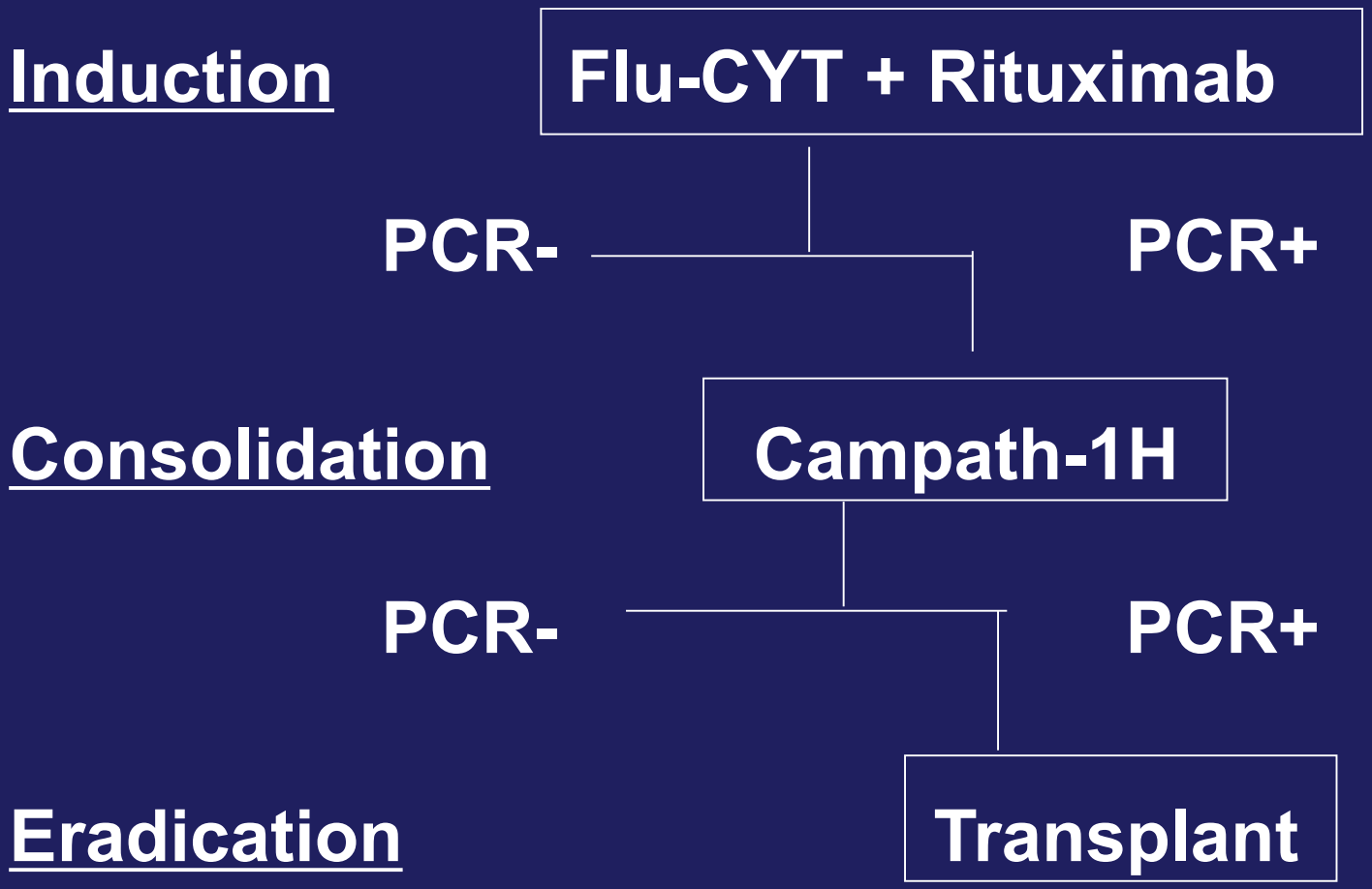
Curative strategy for CLL

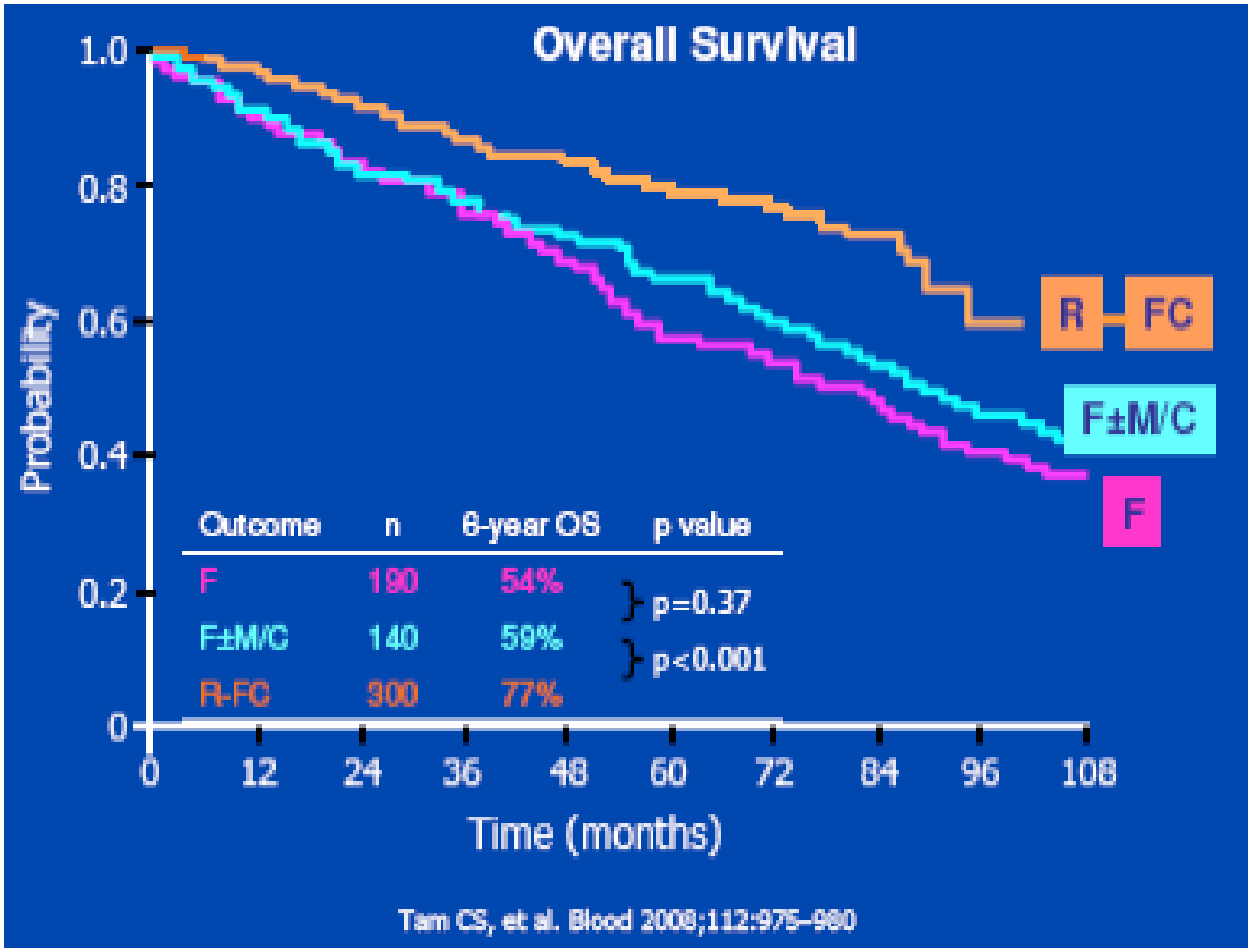


M. Keating

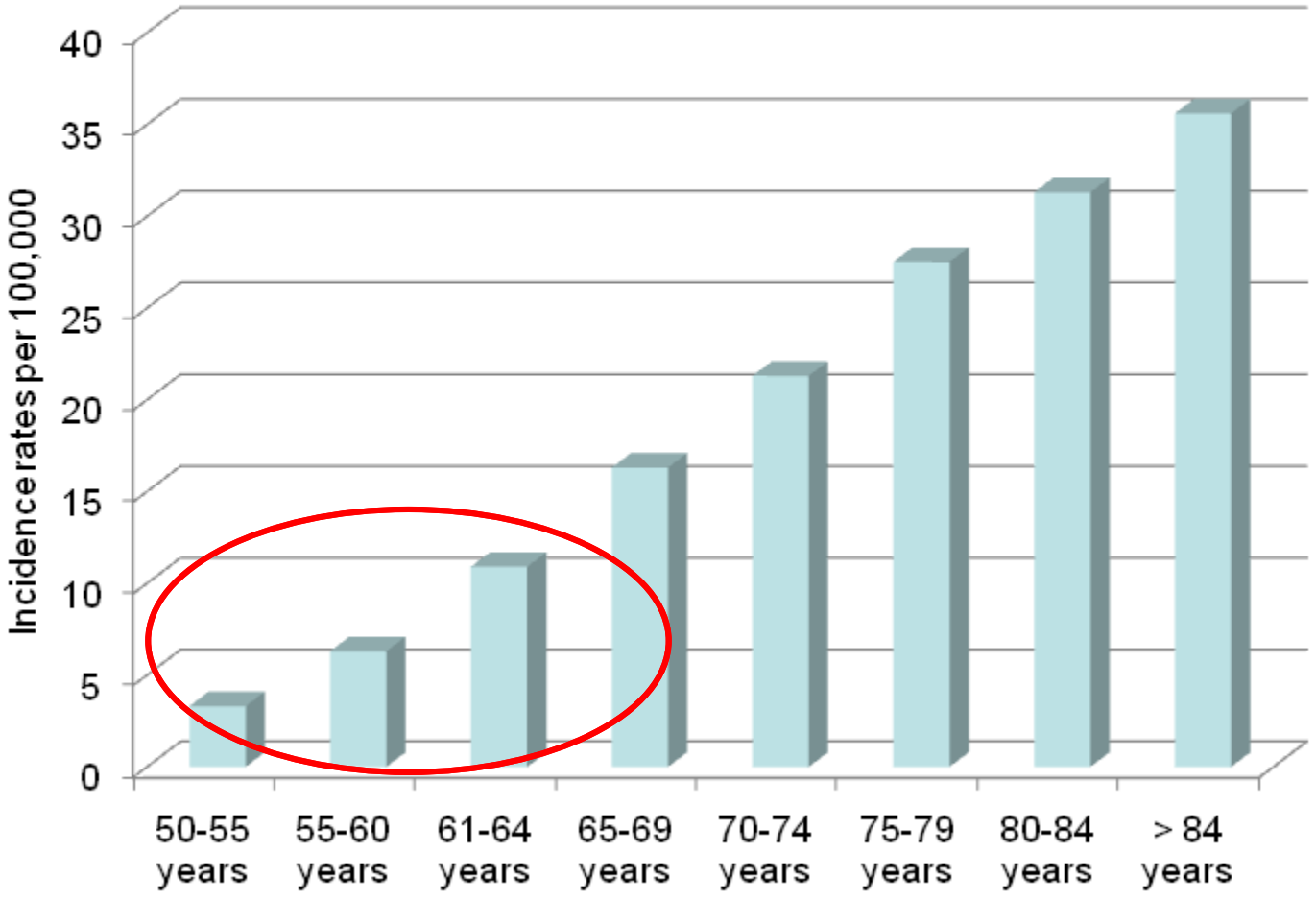
CLL: strategie terapeuti

impatto sulla sopravvivenza

MD Anderson, historical comparison FC vs FC+R



SEER 2011: Incidence of CLL



SEER Cancer Statistics Review 1975-2008

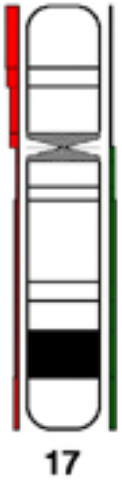
EBMT guidelines for SCT in CLL

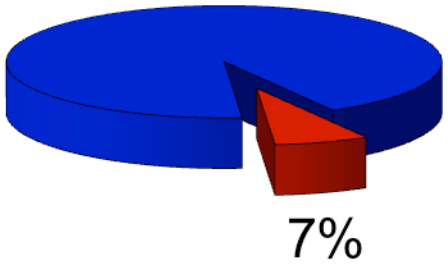
Allo-SCT in poor-risk CLL including:

- **Fludarabine resistence – non response or early relapse (<12 months) after purine analogue-based tx**
- **Relapse <24 months after purine analogue combinations or auto-SCT (+ high risk genetics)**
- **p53 mutation with treatment indication**

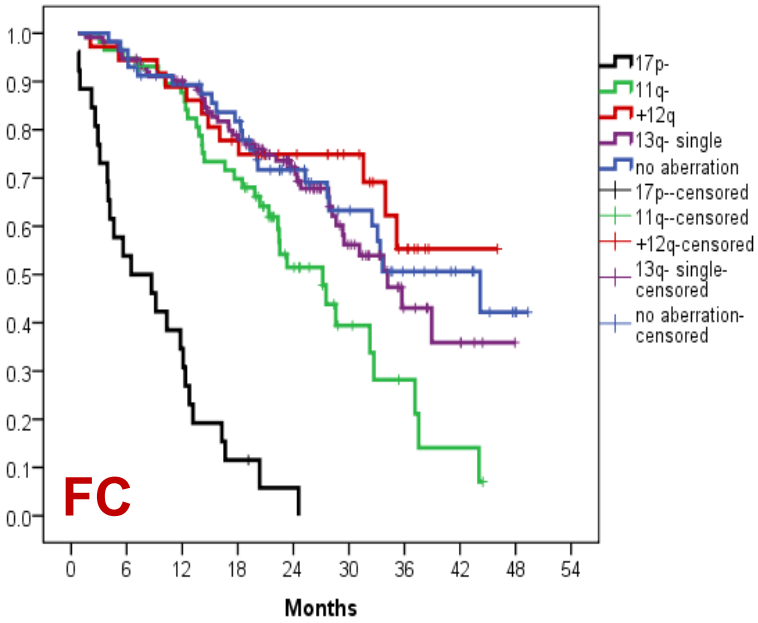
Dreger, Corradini, Kimby et al. Leukemia ’07 (EBMT consensus panel)

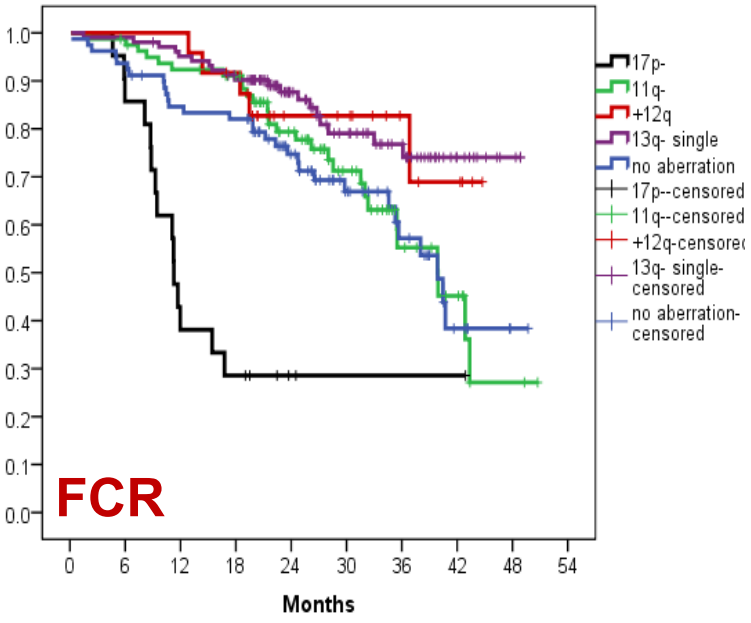
FCR is active against all cytogenetic subgroups with the exception of del17p13 (*TP53* disruption)





Aberration	Incidence (%)	3-years OS
17p del	8	38%
11q del	24	94%
+12	12	96%
Normal	22	83%
13q del	57	95%

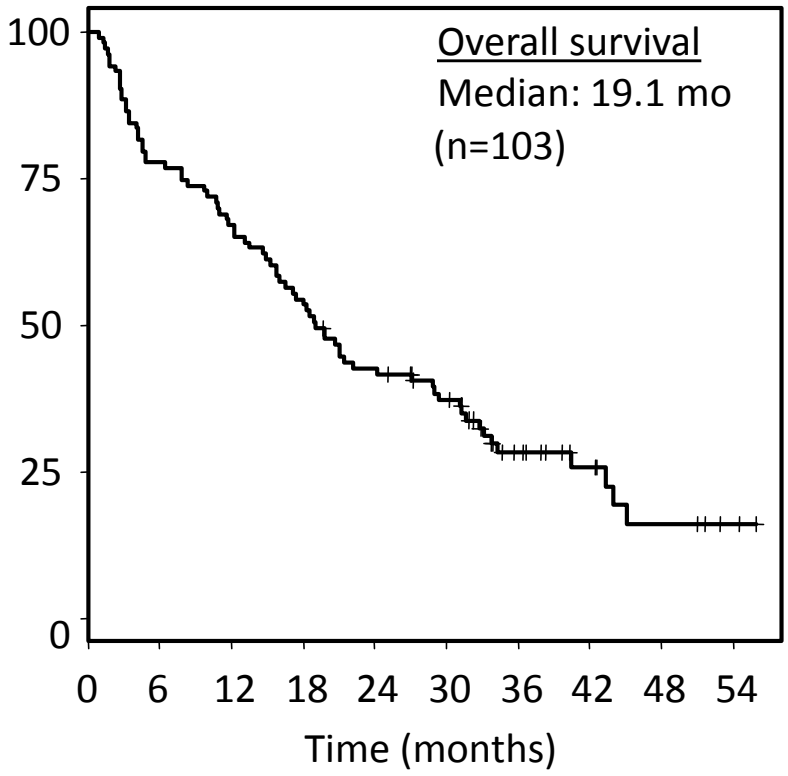




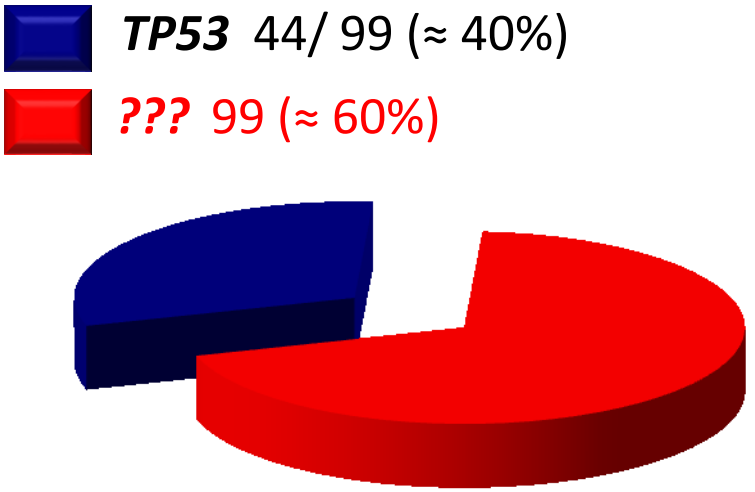
Hallek et al, Lancet 2011

TP53 disruption does not fully account for fludarabine-refractoriness in CLL

CLL2H trial (GCLLSG)= Alemtuzumab s.c.



Courtesy of T. Zenz



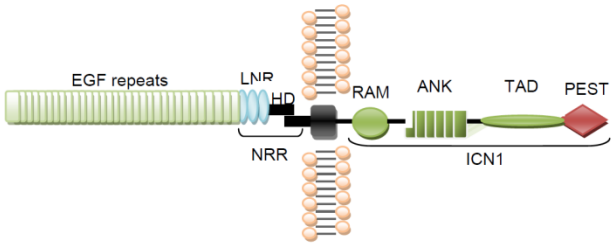
Zenz T, et al, Blood 2009
Stilgenbauer S, et al. J Clin Oncol 2009

Need to search for other genetic determinants

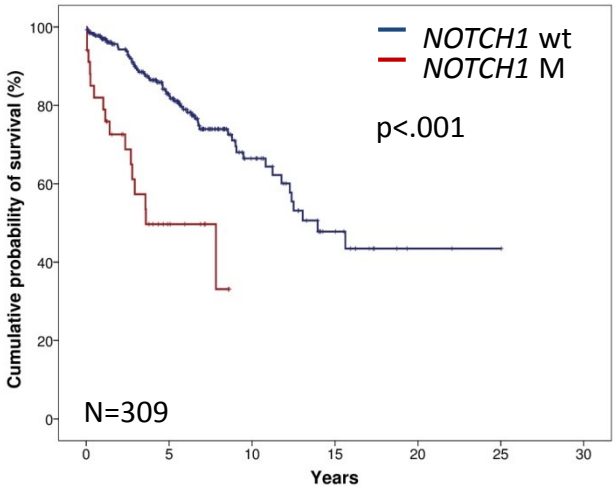
of fludarabine-refractoriness in CLL

Novel recurrent genentic lesions individually showing impact on CLL survival

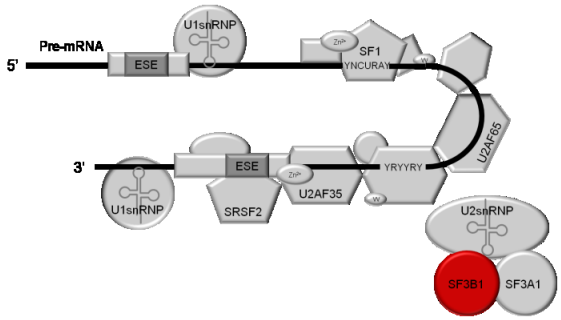
NOTCH1



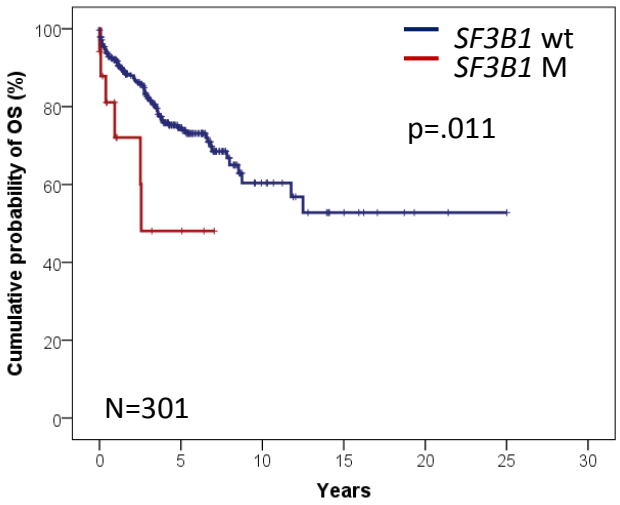
8-11%



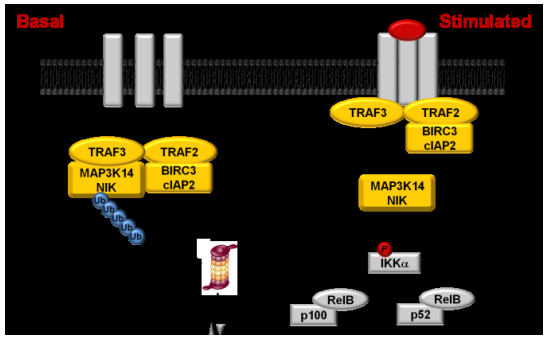
SF3B1



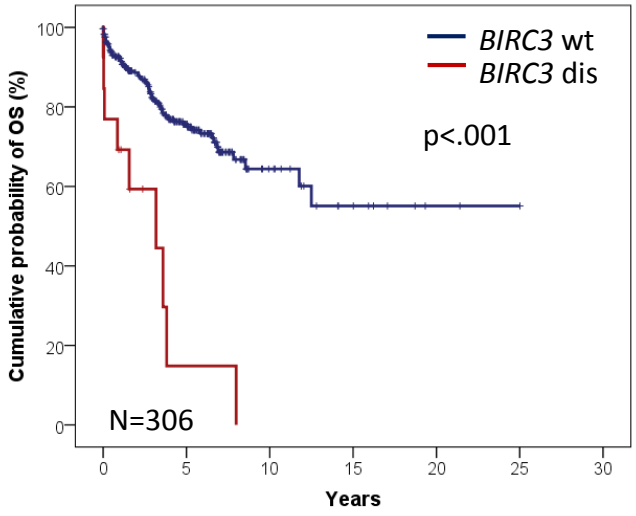
5-7%



BIRC3



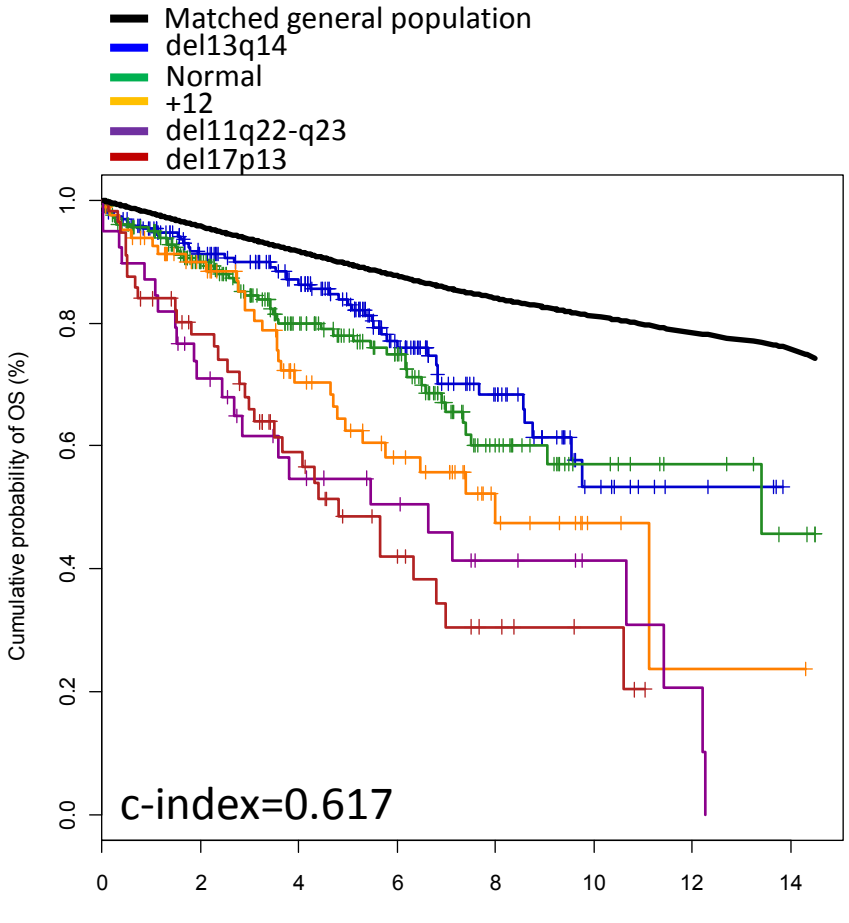
4%



Fabbri, J Exp Med 2011; Puente, Nature 2011; Rossi, Blood 2011; Quesada, Nat Genet 2011; Wang, N Engl J Med 2011; Rossi, Blood 2012

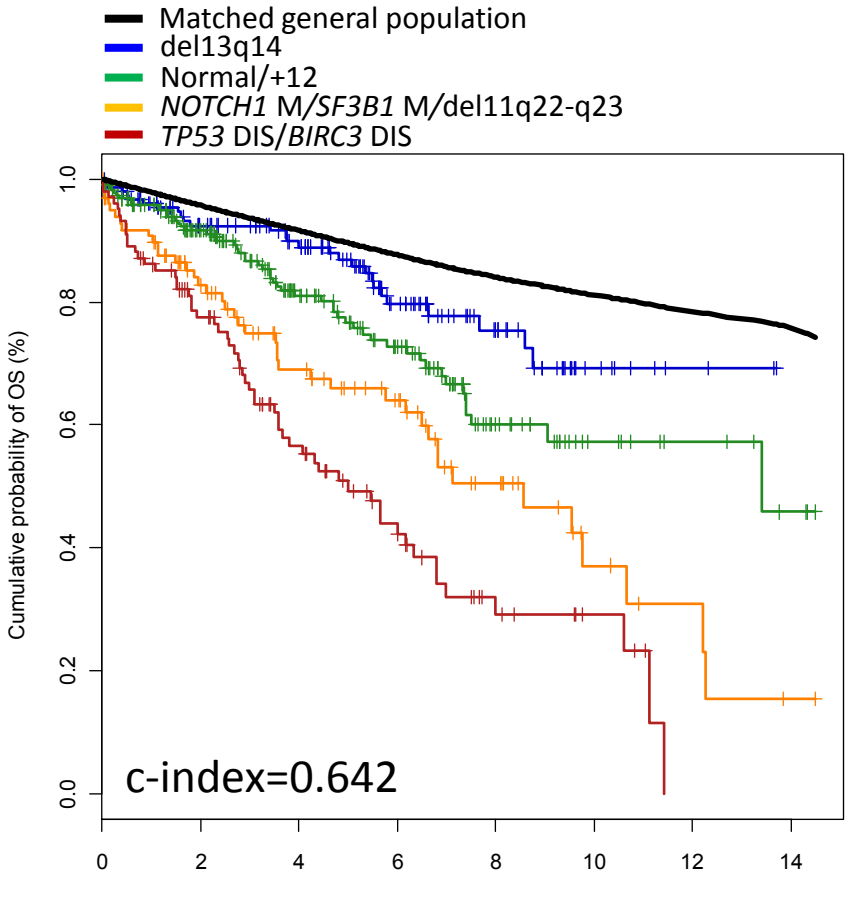
Inclusion of mutations in addition to FISH abnormalities significantly improves the accuracy of CLL prognostication

FISH model



N	Observed events	Expected events*	5-year OS (%)	10-year OS (%)	10-year relative OS*	p*
194	44	24.9	83.9	53.3	68.1%	<0.0001
212	50	24.7	78.0	57.1	72.8%	<0.0001
82	30	12.4	62.5	47.5	62.4%	<0.0001
39	23	6.1	54.7	41.3	54.4%	<0.0001
56	31	6.1	48.5	30.6	38.1%	<0.0001

Mutational and cytogenetic model



N	Observed events	Expected events*	5-year OS (%)	10-year OS (%)	10-year relative OS*	p*
155	27	20.4	86.9	69.3	84.2%	0.1455
228	53	30.9	77.6	57.3	70.7%	<0.0001
99	41	10.4	65.9	37.1	48.5%	<0.0001
101	57	12.6	50.9	29.1	37.7%	<0.0001

Conclusioni (1)

- Circa il 20% dei pazienti con CLL è eleggibile per terapie intensive
- Disponiamo di indicatori clinici (refrattarietà a schemi contenenti Fludarabina) e biologici in grado di meglio selezionare i pazienti ad alto rischio

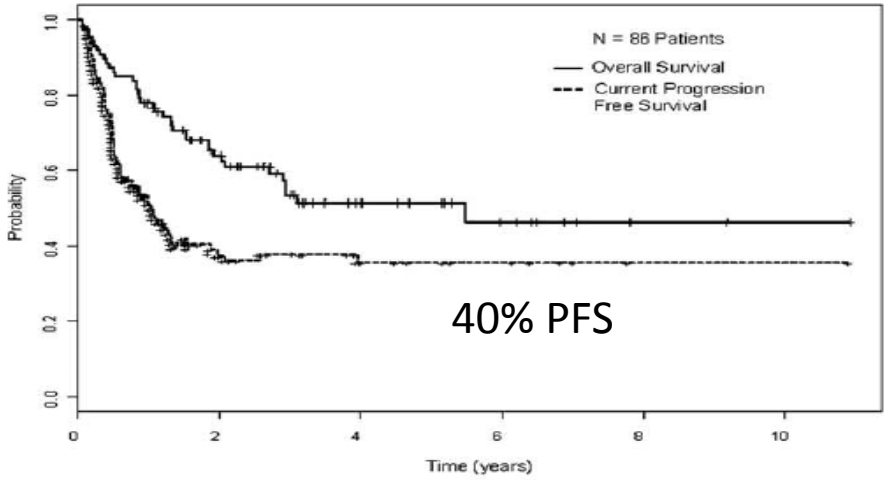
RIC conditioning

- Feasible in larger proportion of patients
- GVL effect
- TRM 11-34%
- Long-term OS: 48%-72%
- Late relapse uncommon compared with auto-SCT
- Extensive chronic GVHD 10% (in vivo T cell-depletion) to 59% (unmanipulated grafts)

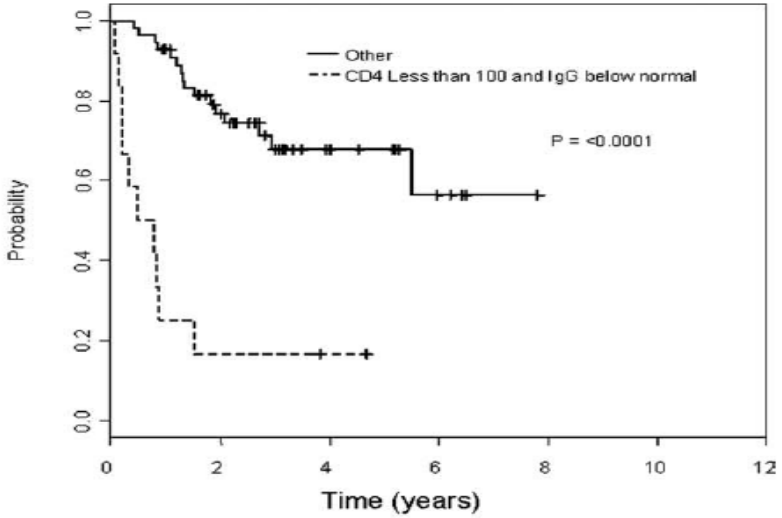
MD Anderson experience

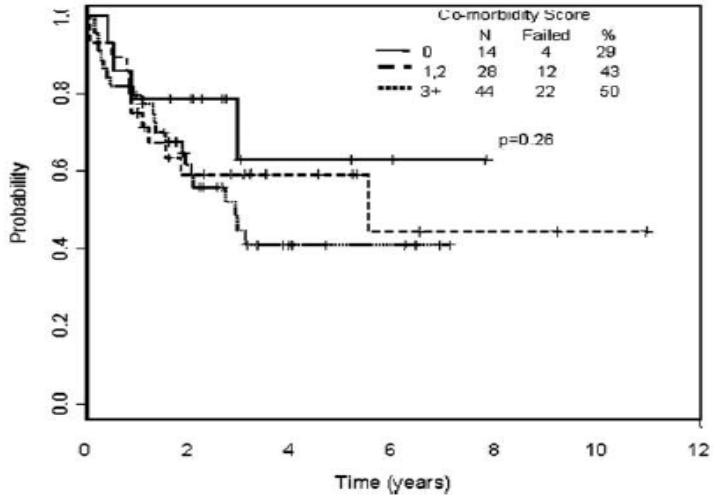
- **86 patients**
- median age **58 years** (30-70)
- Hct-CI ≥3: 44 patients (51%)
- Richter: 19 patients (22%)
- P53+: 15/65 (23%)
- Fluda refractory: 71 patients (83%)
- RIC conditioning with Fluda, CTX, RTX
- Unrelated donors: 43 patients (50%)

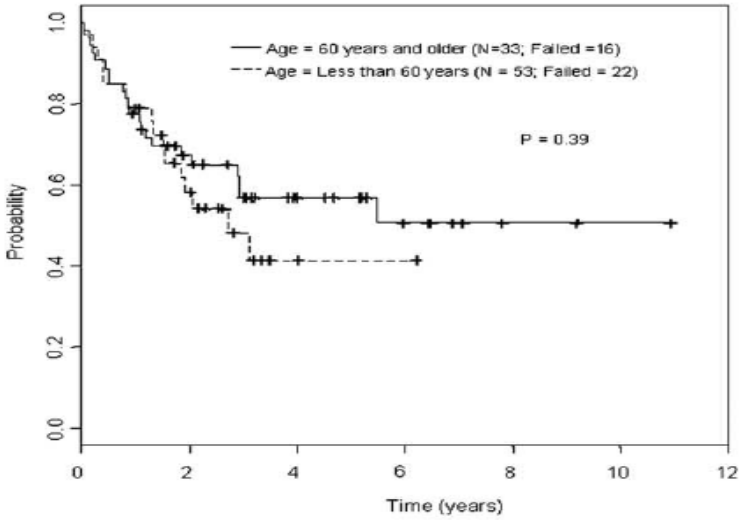
Khouri et al, Cancer 2011



40% PFS



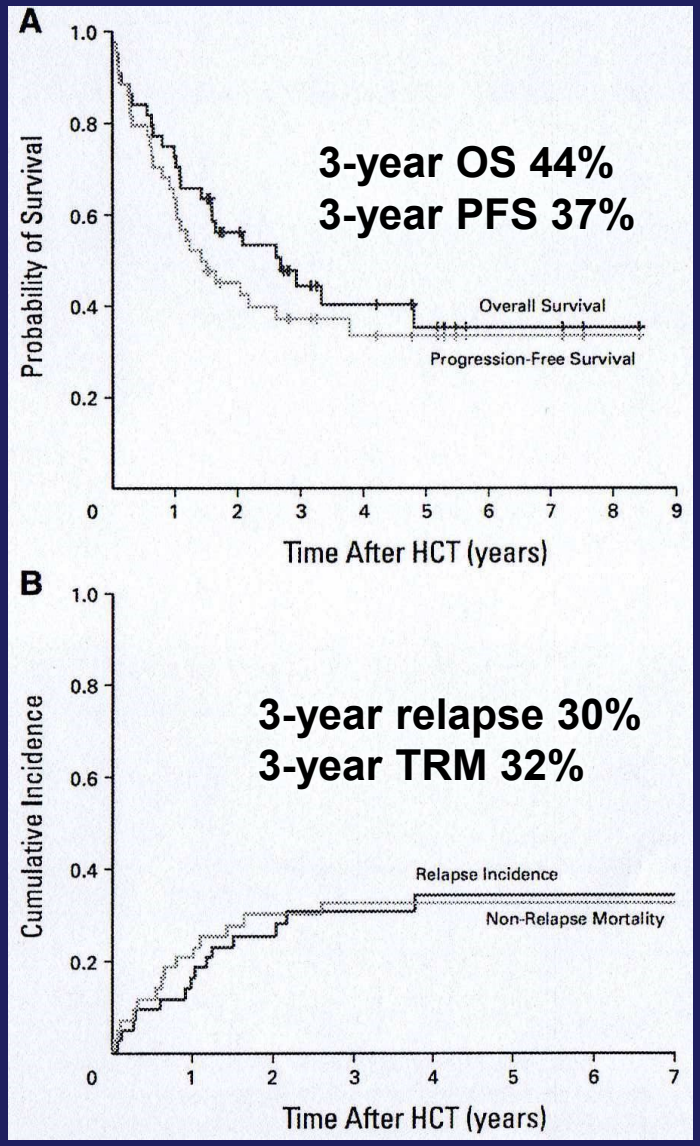


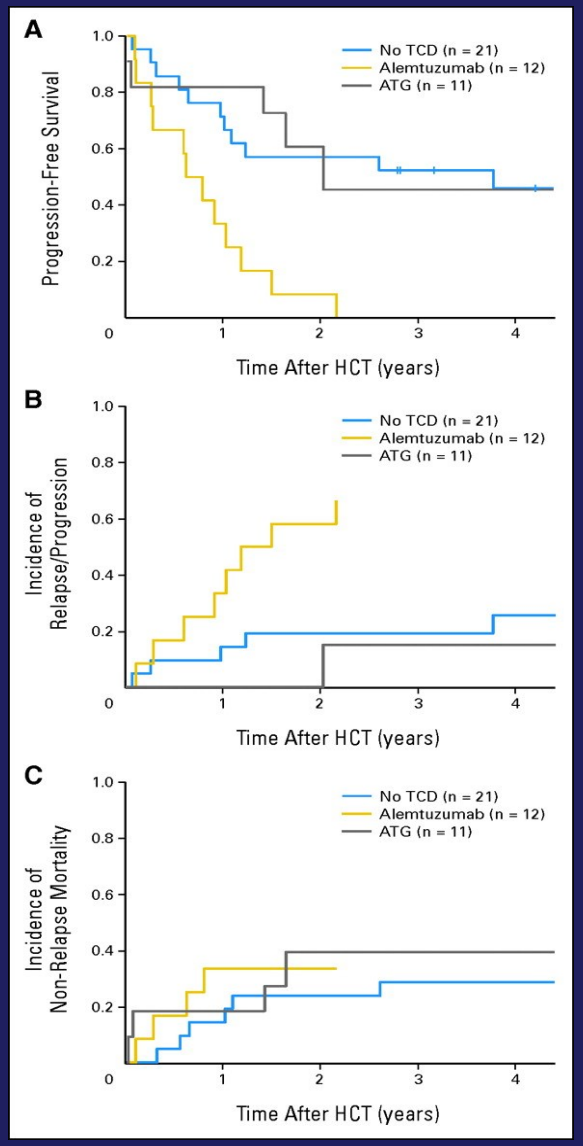


- No impatto CI, età, del 17, Richter
- Impatto ipogammaglobulinemia e linfopenia (aumentano TRM)

Khouri et al, Cancer 2011

RIC allo-SCT in 17p- CLL: EBMT





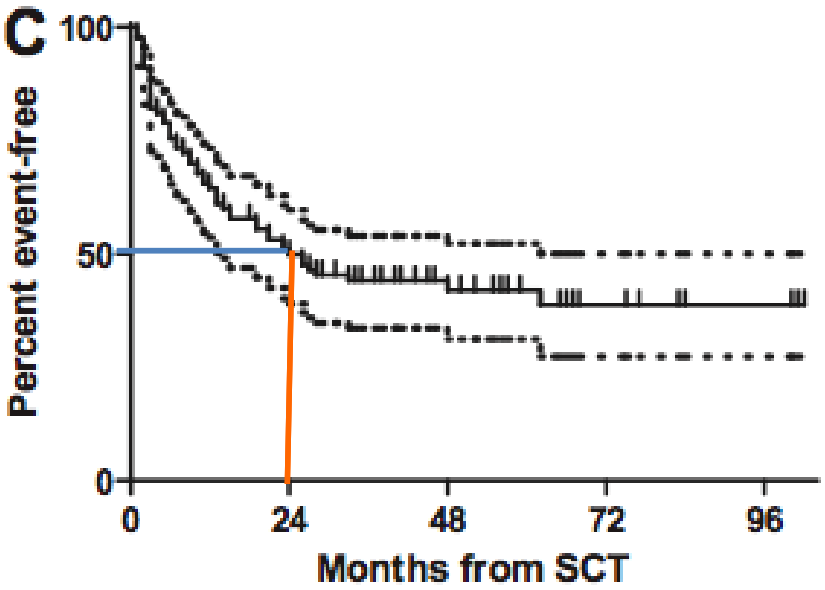
Schetelig et al JCO 2008

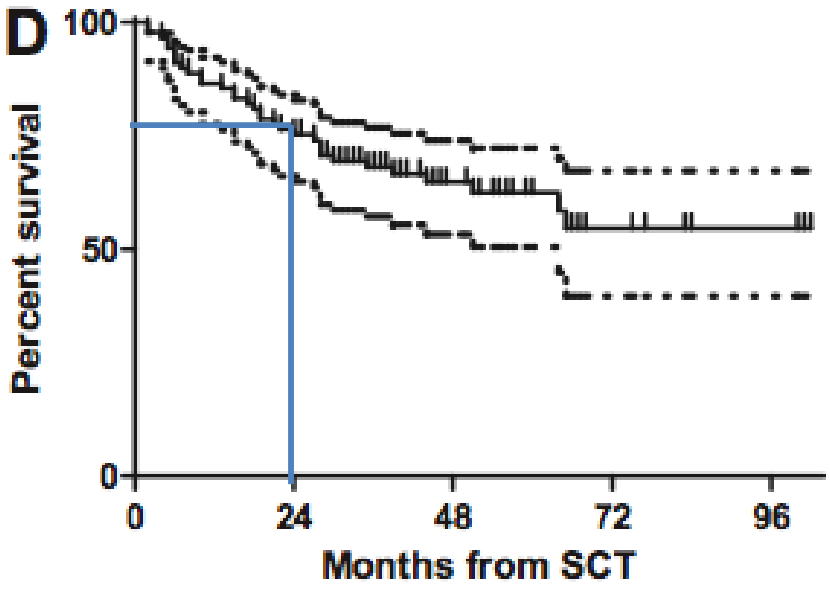
The German experience

- phase 2 prospective CLL3X trial
- **100 patients eligible according EBMT criteria**
- Median age: **53 years**
- 90 patients underwent RIC allo-SCT
- Conditioning: Fluda + CTX or Fluda + CTX + 2 Gy TBI + alentuzumab
- Unrelated donors: 54/90 (60%)
- Median follow up: 46 months

Dreger et al, Blood 2010

The German experience





2 y-EFS 50%

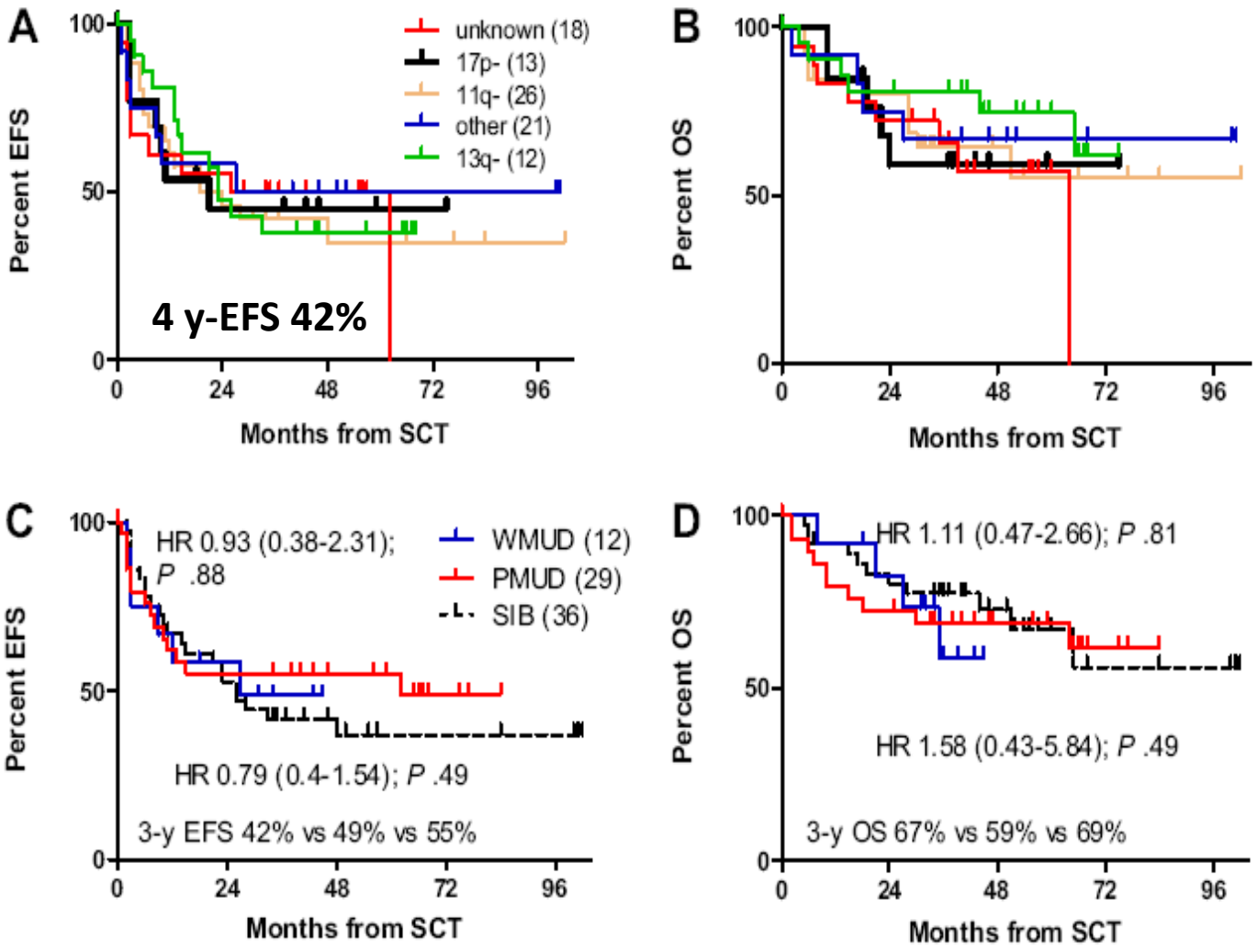
4 y-EFS 42%

2 y-OS 80%

4 y-OS 65%

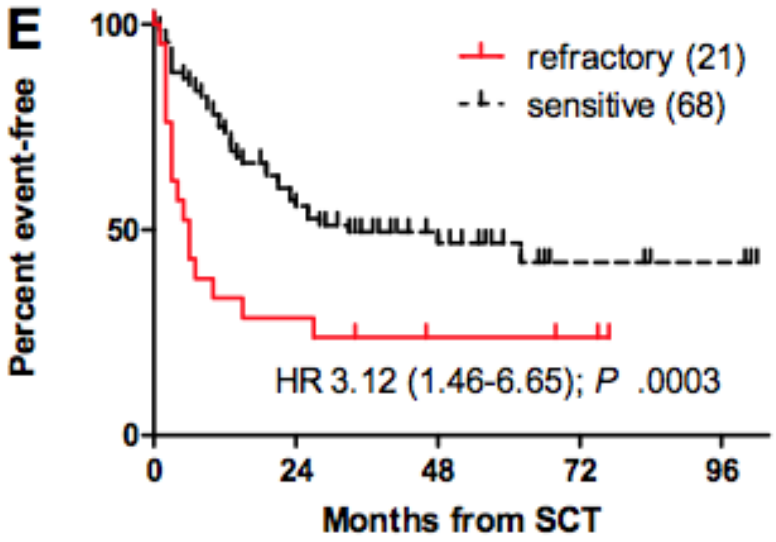
Dreger et al, Blood 2010

No significative impact of karyotype and donor on OS and PFS



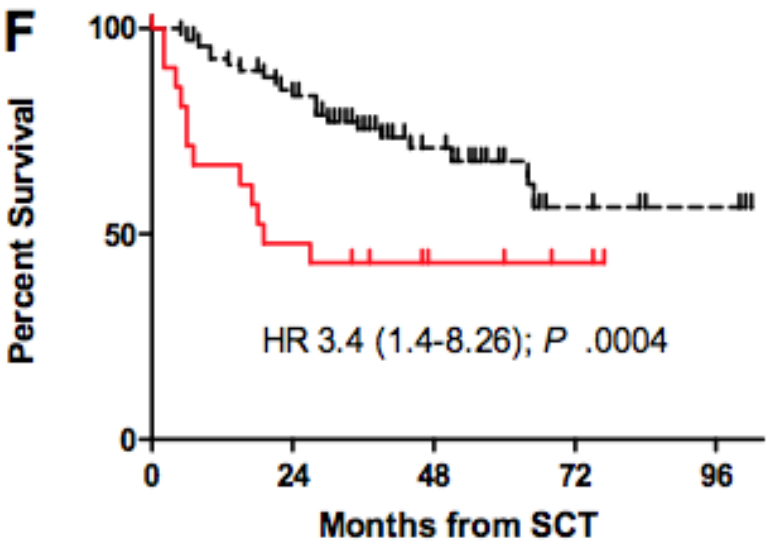
Dreger et al, Blood 2010

Significative impact of pre-transplant response status on OS and PFS



2 y-EFS 60%

4 y-EFS 50%



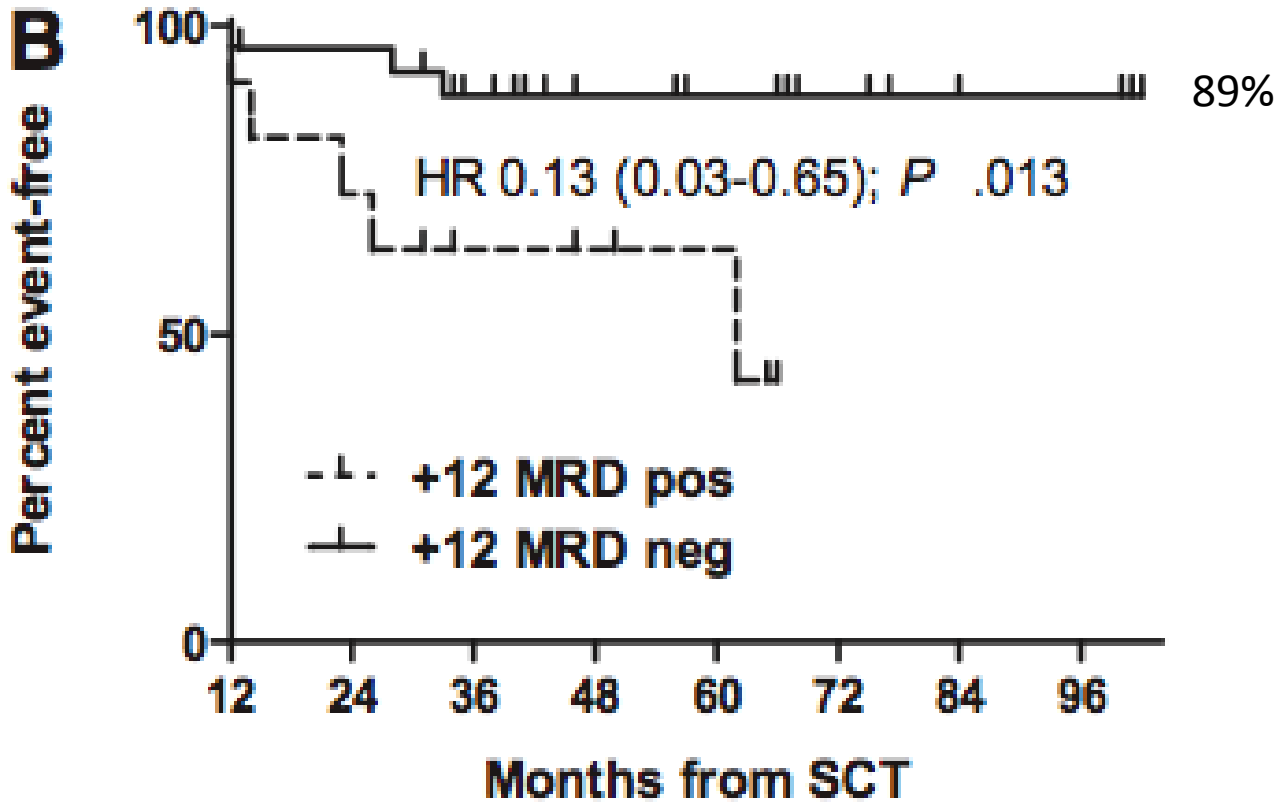
2 y-OS 85%

4 y-OS 70%

Dreger et al, Blood 2010

Significative impact of MRD on PFS

MRD analysis: 52 patients



Dreger et al, Blood 2010

Conclusioni (2)

- Consenso su CLL alto rischio
- Allo-SCT RIC è > efficace in pazienti con malattia chemosensibile
- **PFS 40% con plateau**
- **OS 40-60% con plateau**
- Importanza del timing allo-SCT timing
- Non impatto cariotipo sfavorevole
- Risultati simili allo SCT related e unrelated donors
- PFS e OS migliori nei pazienti in cui si raggiunge MRD -

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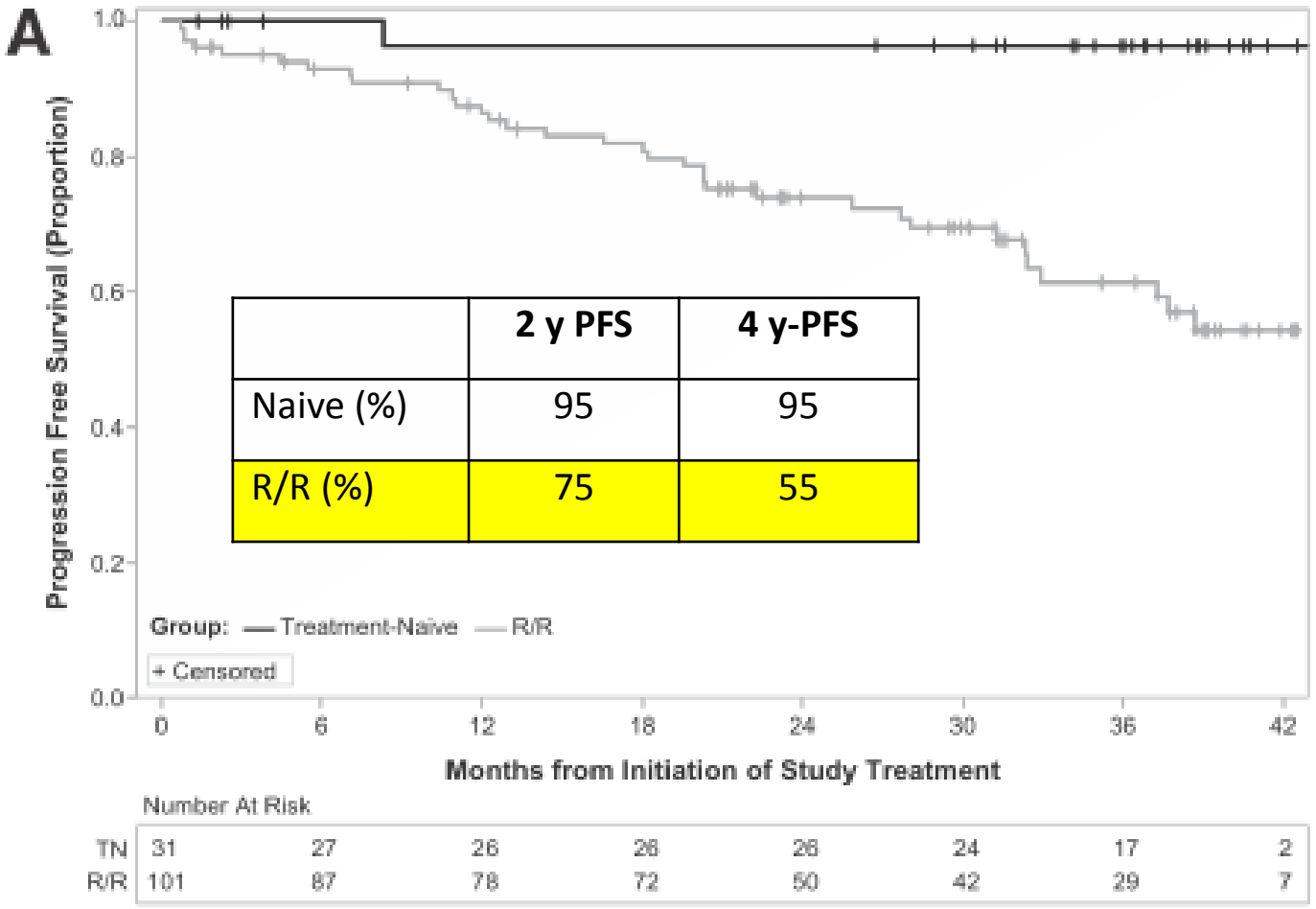
Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib

Patients	132
Median age	68
≥ 70 years	57 (43%)
Teatment naive ≥ 65 years	31
Median n. previous treatments	4
17p/p53	36 (27%)

Byrd et al Blood 2015

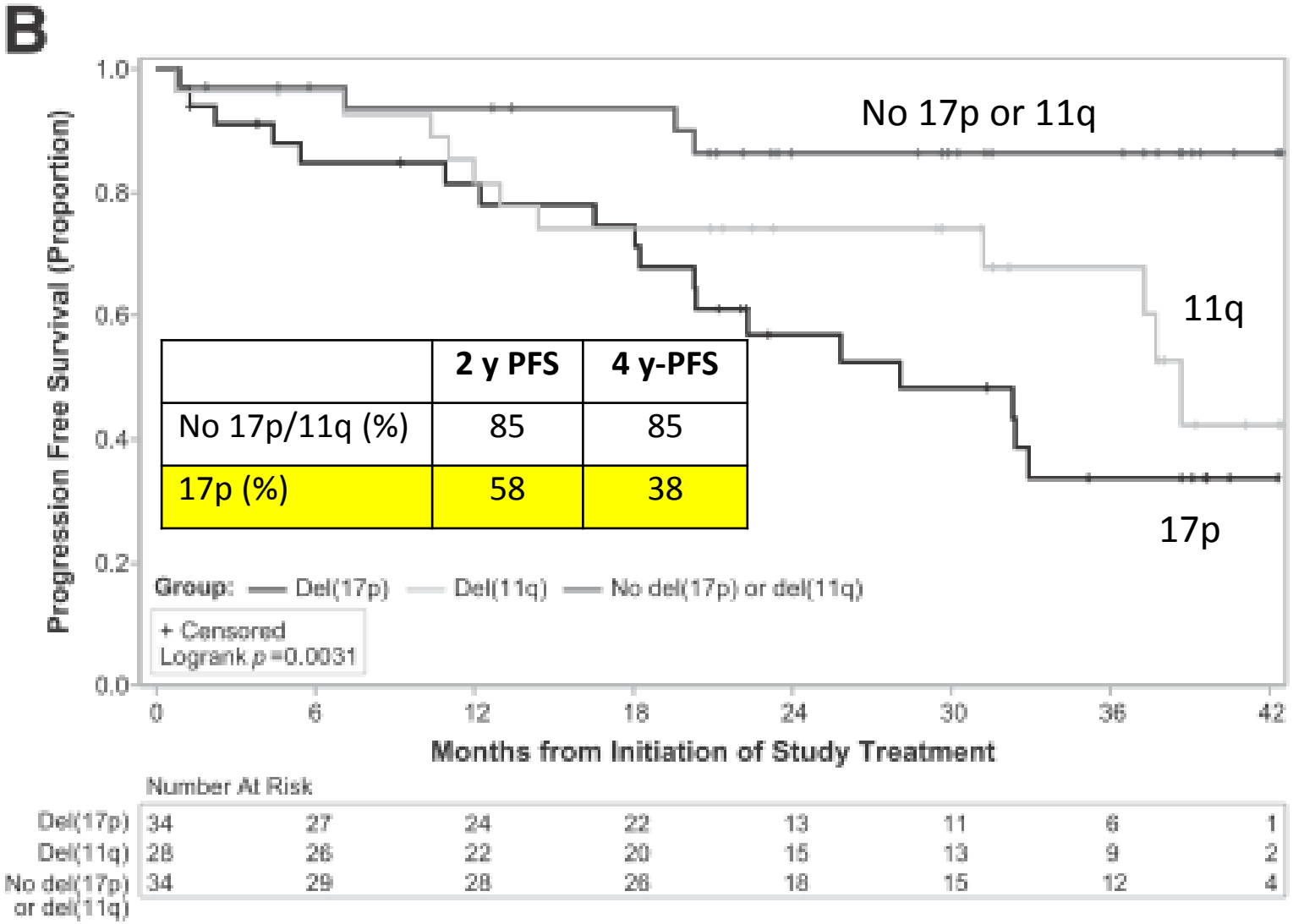
Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib



	2 y PFS	4 y-PFS
Naive (%)	95	95
R/R (%)	75	55

Byrd et al Blood 2015

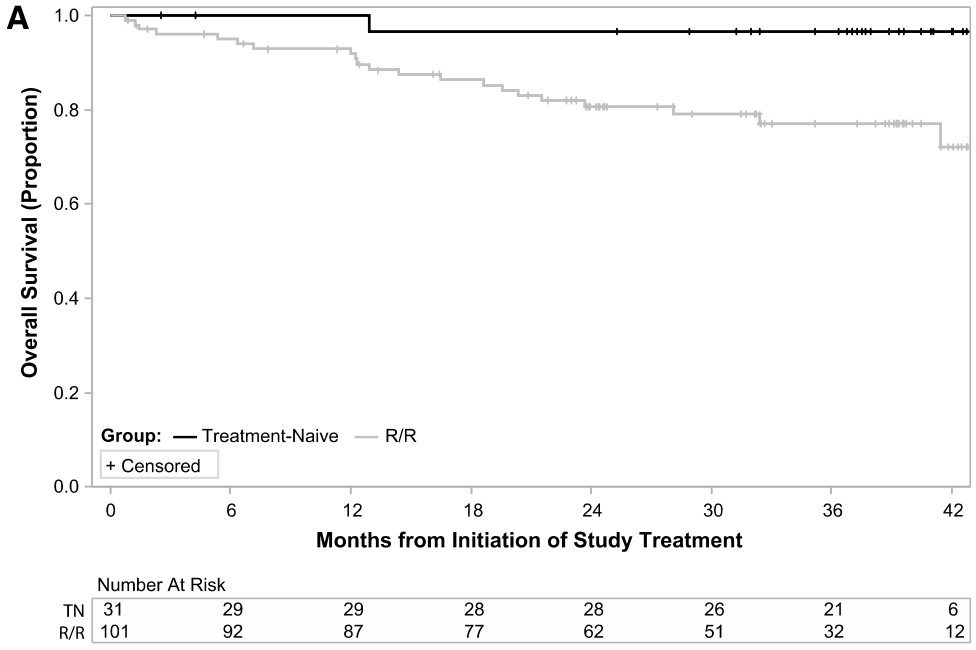
Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib

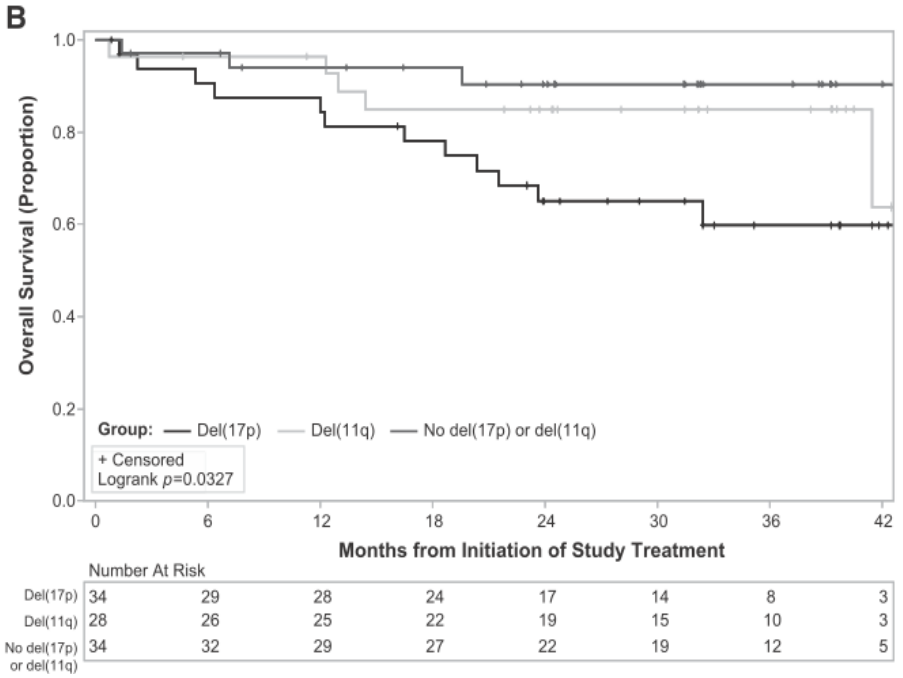


	2 y PFS	4 y-PFS
No 17p/11q (%)	85	85
17p (%)	58	38

Byrd et al Blood 2015

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





	2 y OS	4 y-OS
Naive (%)	95	95
R/R (%)	80	70

	2 y OS	4 y-OS
No 17p/11q (%)	90	90
17p (%)	65	60

Byrd et al Blood 2015

Conclusioni

- Alta efficacia anche in pazienti pretrattati con numerose linee di terapia e con fattori biologici di rischio
- **PFS a 2 e 4 anni: 75% e 55%, senza plateau**
- **OS a 2 e 4 anni: 80% e 70%**
- Impatto di 17p su PFS (58% e 38% a 2 e 4 anni) e OS (65% e 60% a 2 e 4 anni)
- No MRD

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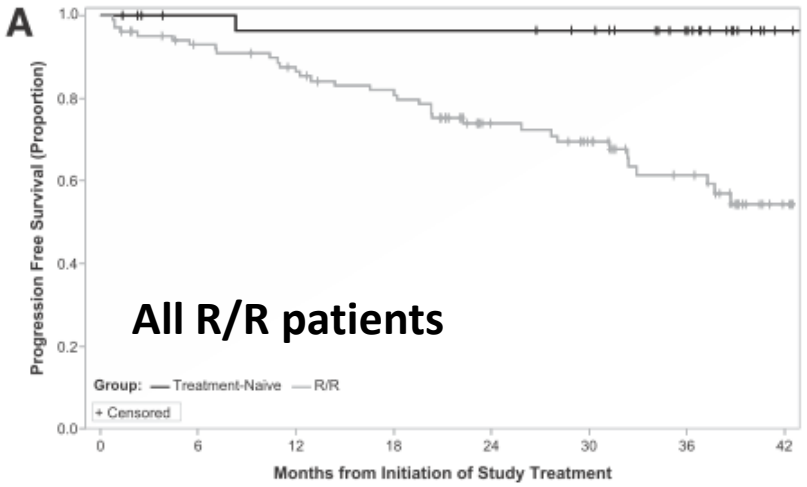
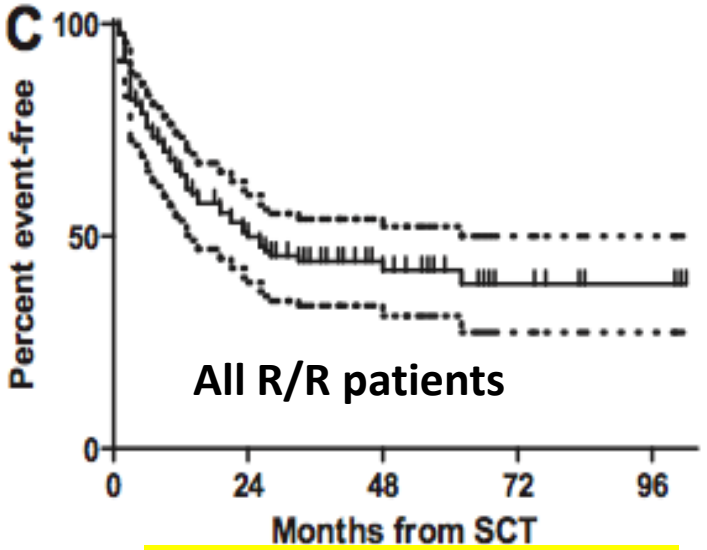
Ibrutinib

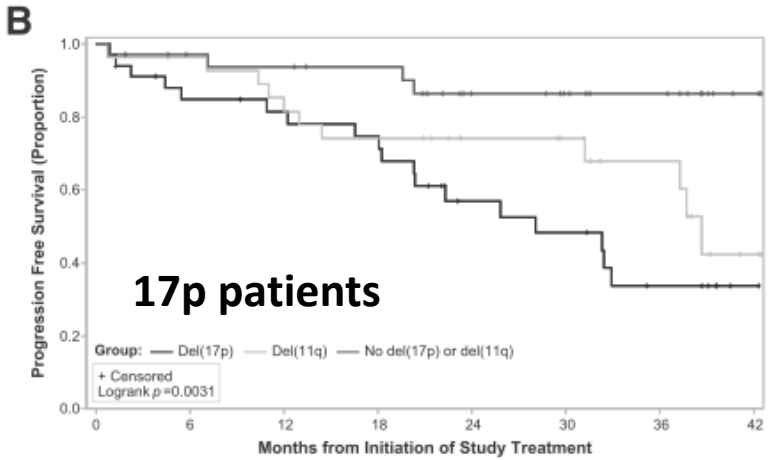


2 and 4 y-PFS: 75% and 55%

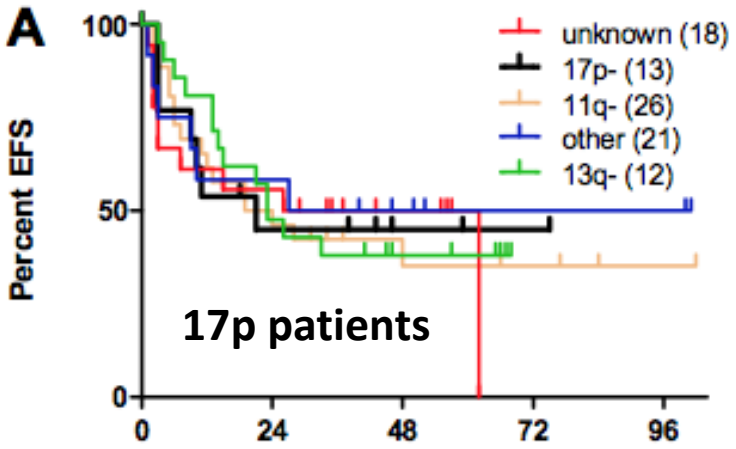
RIC allogeneic SCT



2 and 4 y-PFS: 50% and 42%



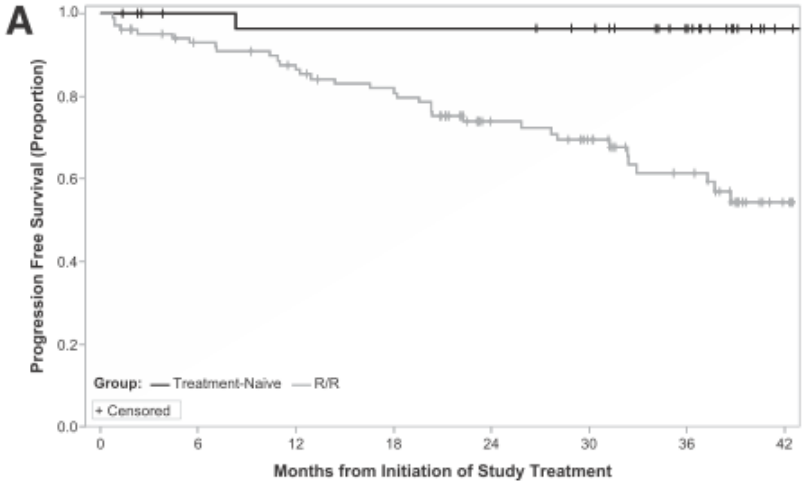
2 and 4 y-PFS: 58% and 38%



4 y-PFS: 42%

Byrd 2015, Khouri, 2011, Dreger 2010

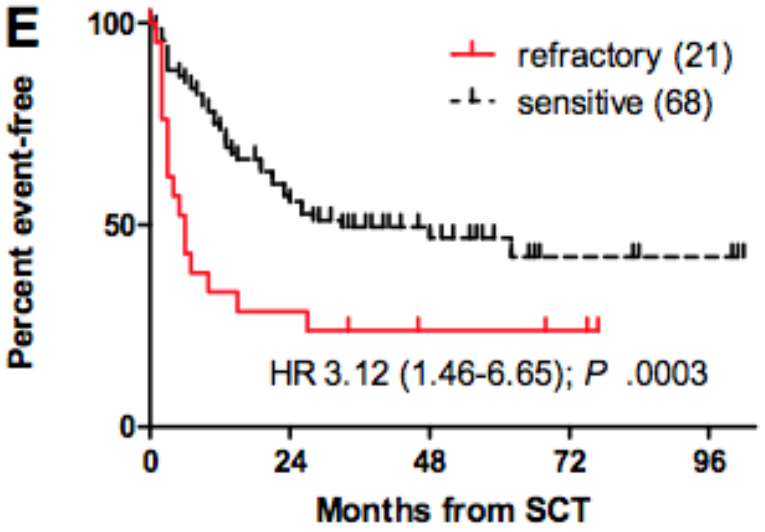
Ibrutinib



All R/R patients

- **2 y-PFS= 75%**
- **4 y-PFS= 55%**

RIC allogeneic SCT



Chemosensitive patients

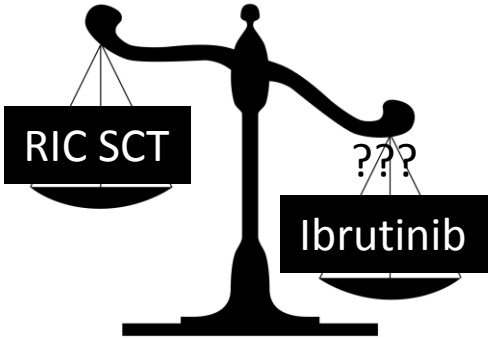
- **2 y-PFS= 60%**
- **4 y-PFS= 50%**

Byrd 2015, Khouri, 2011, Dreger 2010

RIC SCT or Ibrutinib in CLL ?

NB: no controlled prospective studies, indirect comparison, different characteristics of the patients and different follow up

RIC SCT	Ibrutinib
• Longer follow up • **MRD-** • **Plateau as far as PFS and OS** • **No impact of 17p** • Better outcome in chemosensitive and in MRD	• High ORR but no MRD • Lower toxicity • **Better 2 and 4 years PFS and OS** • No plateau • What will happen with longer FU ? • Impact of 17p



Possible future scenario

Therapy	Goal of therapy
1. New agents until progression	QoL, disease stabilization
2. New agents ➔ SCT	MRD
3. New agents ➔ SCT ➔ New agents	MRD

SCT  **New agents**

Need for prospective controlled studies

Backup

Inhibition of BTK and ITK with Ibrutinib Is Effective in the Prevention of Chronic Graft-versus-Host Disease in Mice

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Abstract

Bruton's Tyrosine Kinase (BTK) and IL-2 Inducible T-cell Kinase (ITK) are enzymes responsible for the phosphorylation and activation of downstream effectors in the B-cell receptor (BCR) signaling and T cell receptor (TCR) signaling pathways, respectively. Ibrutinib is an FDA-approved potent inhibitor of both BTK and ITK that impairs B-cell and T-cell function. CD4 T cells and B cells are essential for the induction of chronic graft-versus-host disease (cGVHD). We evaluated these targets by testing the ability of Ibrutinib to prevent or ameliorate cGVHD, which is one of the major complications for patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). We found that Ibrutinib significantly alleviated cGVHD across four different mouse models, accompanied by increased long-term survival and reduced clinical score. The clinical improvements in Ibrutinib-treated recipients were associated with decreased serum-autoantibodies, costimulatory molecule activation, B-cell proliferation, and glomerulonephritis compared to vehicle controls. Ibrutinib was also able to alleviate the clinical manifestations in acute GVHD (aGVHD), where the recipients were given grafts with or without B cells, suggesting that an inhibitory effect of Ibrutinib on T cells contributes to a reduction in both aGVHD and cGVHD pathogenesis. An effective prophylactic regimen is still lacking to both reduce the incidence and severity of human cGVHD following allo-HSCT. Our study shows that Ibrutinib is an effective prophylaxis against several mouse models of cGVHD with minimal toxicity and could be a promising strategy to combat human cGVHD clinically.

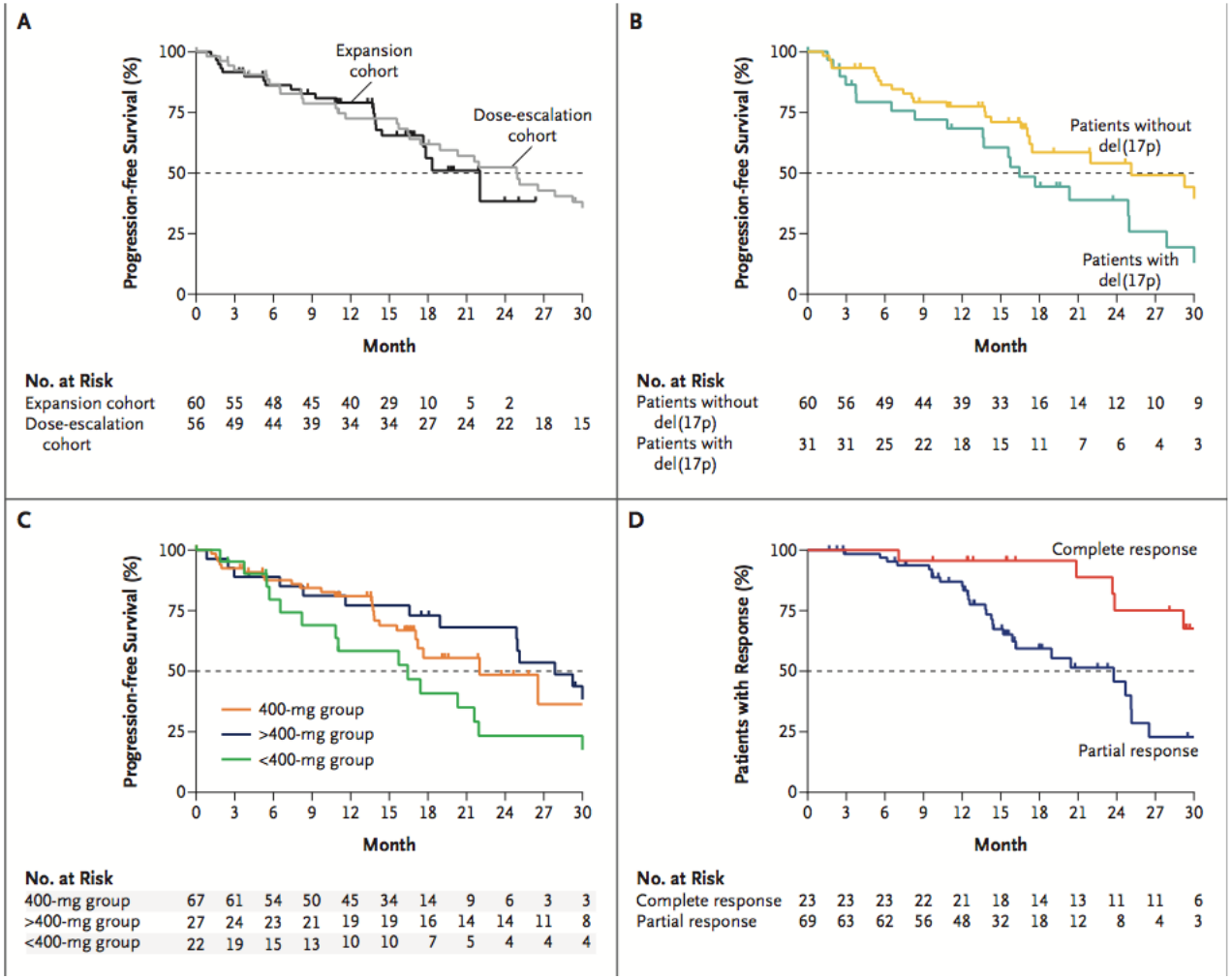
Indirect comparison between RIC SCT and Ibrutinib in CLL

	RIC allogeneic SCT			Ibrutinib
	Khouri 2011 All patients	Dreger 2010 All patients	Dreger 2010 CHT sensitive	Byrd 2015 All patients
Patients	86	90	68	101
Median age	58	53	53	64
2 y-PFS (%)	40	50	60	75
4 y-PFS (%)	38	42	50	55
2 y-OS (%)	62	80	85	80
4 y-OS (%)	52	65	70	70

Indirect comparison between RIC SCT and Ibrutinib in 17pCLL

	RIC allogeneic SCT	Ibrutinib
	Shetelig 2008 17p- CLL	**Byrd 2015 17p-**
Patients	44	34
2 y-PFS (%)	43	58
4 y-PFS (%)	35	38
2 y-OS (%)	55	65
4 y-OS (%)	42	60

Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia



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