LLC ed LNH

Ibrutinib e Idelalisib: l'esperienza real world della REP

P. R. Scalzulli

Ematologia – San Giovanni Rotondo

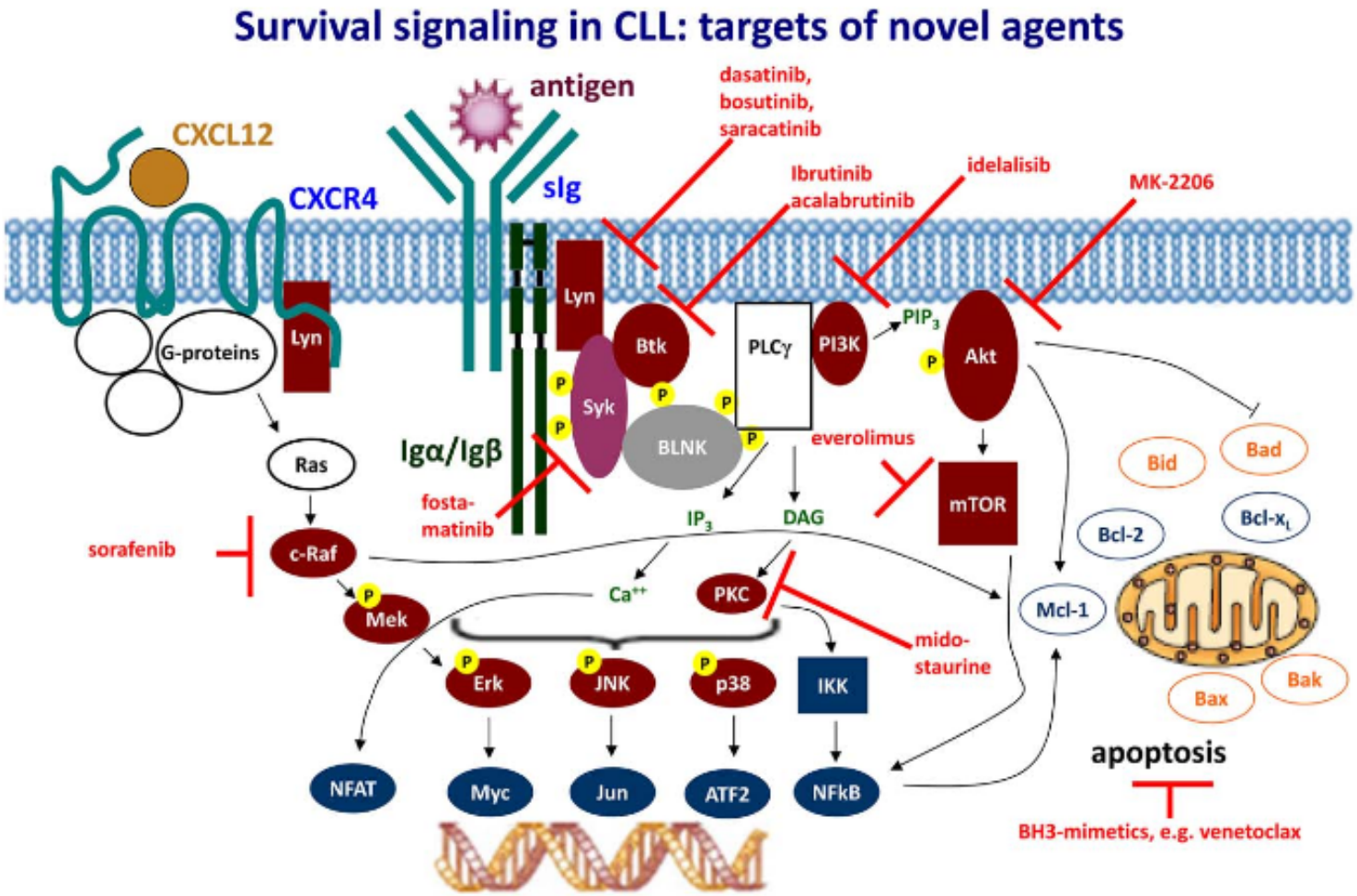


FIGURE 2 Targeting of specific signaling pathways as a therapeutic strategy for CLL. Red symbols and letters indicate new therapeutics as discussed in the text. Some of these compounds have reached mature clinical testing or approval by the regulatory bodies and are therefore not broadly covered in the manuscript. Figure created by Dr Gunter Krause, Cologne; used with permission of the author.

Received: 14 June 2017 | Accepted: 15 June 2017
DOI: 10.1002/ajh.24826

WILEY AJH

Chronic lymphocytic leukemia: 2017 update on diagnosis, risk stratification, and treatment

Michael Hallek

TABLE 1 Different CLL-IPI categories

CLL-IPI category	OS at 5 years (%)	Potential clinical consequence
Low risk	93.2	Do not treat
Intermediate risk	79.3	Do not treat except if the disease is really symptomatic
High risk	63.3	Treatment indicated except if the disease is asymptomatic
Very high risk	23.3	If you need to treat, do not use chemotherapy but rather novel agents or treatment in clinical trials.

CLL first line treatment

Stage	Fitness	del(17p) p53mut	Therapy
Binet A-B, Rai 0-II, inactive	Irrelevant	Irrelevant	None
Active disease or Binet C or Rai III-IV	Go go	No	FCR (BR above 65 years?)
		Yes	Ibrutinib, Idelalisib+Rituximab (Allogeneic SCT)
	Slow go	No	Chlorambucil + Obinutuzumab (GA-101) or + Rituximab or + Ofatumumab or Ibrutinib
		Yes	Ibrutinib, Alemtuzumab, HD Rituximab or Ofatumumab

CLL second line treatment

Response to 1L Therapy	Fitness	Therapy
Refractory or progress within 3 years	Go go	Change therapy to one of the following options: Ibrutinib, Idelalisib + R, FA, FCR (after BR), Venetoclax, A-Dex, Lenalidomide (+ R), BR (after FCR). Discuss consolidation with allogeneic SCT.
	Slow go	Change therapy to one of the following options: Ibrutinib, Idelalisib + R, Venetoclax, A, FCR-lite, BR, Lenalidomide (+R), Ofatumumab, HD R
Progress after 3 years	All	Repeat first-line therapy

FIGURE 3 (a and b) Treatment algorithm for CLL patients in first- and second-line indications. A, alemtuzumab; R, rituximab; O, ofatumumab; F, fludarabine; C, cyclophosphamide; CLB, chlorambucil; HD, high dose

blood

Special Report

iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL

Michael Hallek,[1,2] Bruce D. Cheson,[3] Daniel Catovsky,[4] Federico Caligaris-Cappio,[5] Guillermo Dighiero,[6] Hartmut Döhner,[7] Peter Hillmen,[8] Michael Keating,[9] Emili Montserrat,[10] Nicholas Chiorazzi,[11] Stephan Stilgenbauer,[7] Kanti R. Rai,[11] John C. Byrd,[12] Barbara Eichhorst,[1] Susan O'Brien,[13] Tadeusz Robak,[14] John F. Seymour,[15] and Thomas J. Kipps[16]

Table 1. Baseline evaluation of patients with CLL

Diagnostic test	General practice	Clinical trial
Tests to establish the diagnosis		
CBC and differential count	Always	Always
Immunophenotyping of peripheral blood lymphocytes	Always	Always
Assessment before treatment		
History and physical, performance status	Always	Always
CBC and differential count	Always	Always
Marrow aspirate and biopsy	When clinically indicated (unclear cytopenia)	Desirable
Serum chemistry, serum immunoglobulin, and direct antiglobulin test	Always	Always
Chest radiograph	Always	Always
Infectious disease status	Always	Always
Additional tests before treatment		
Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always	Always
Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI*	Desirable
TP53 mutation	Always	Always
IGHV mutational status	Always	Always
Serum β_2-microglobulin	Desirable	Always
CT scan of chest, abdomen, and pelvis	NGI	Desirable
MRI, PET scans	NGI	NGI
Abdominal ultrasound†	Possible	NGI

General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

CBC, complete blood count; MRI, magnetic resonance imaging; NGI, not generally indicated; PET, positron emission tomography.

*Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful before therapy, if established methodology is available.

†Used in some countries to monitor lymphadenopathy and organomegaly.

Table 2. Recommendations regarding indications for treatment in CLL

	General practice	Clinical trial
Treat with Rai stage 0	NGI*	RQ
Treat with Binet stage A	NGI*	RQ
Treat with Binet stage B or Rai stage I or II	Possible*	Possible*
Treat with Binet stage C or Rai stage III or IV†	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treat without active/progressive disease	No	RQ

General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial. Early therapy of CLL is generally not recommended outside of clinical trials; however, we recognize the need to conduct clinical trials testing the early use of novel agents.

RQ, research question.

*Treatment is indicated, if the disease is active as defined in section 4.

†Anemia and/or thrombocytopenia from CLL-unrelated causes should be excluded.

CLL, FL, MCL: “NEW DRUGS”

IBRUTINIB

IDELALISIB

OBINUTUZUMAB (anti CD20)

VENETOCLAX

Ibrutinib: CLL, FL, MCL

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 159° - Numero 207

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Giovedì, 6 settembre 2018 — SI PUBBLICA TUTTI I GIORNI NON FESTIVI

Art. 1.

Classificazione ai fini della rimborsabilità

Le nuove indicazioni terapeutiche del medicinale IMBRUVICA:

«"Imbruvica" in monoterapia è indicato per il trattamento di pazienti adulti con leucemia linfocitica cronica (CLL) precedentemente non trattata», sono rimborsate

Burger et al EHA 2017

Resta ferma l'attribuzione dell'innovatività per l'indicazione:

«Linfoma mantellare (MCL) recidivato o refrattario

CLL nei pazienti che hanno ricevuto almeno una precedente terapia, o in prima linea in presenza della delezione

del 17p o della mutazione TP53 per i quali una chemio-immunoterapia non è appropriata

IMacroglobulinemia di Waldenström (WM) nei pazienti che hanno ricevuto almeno una precedente terapia, o in prima linea per i pazienti per i quali una chemio-immunoterapia non è appropriata», da cui consegue:

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia

John C. Byrd, M.D., Richard R. Furman, M.D., Steven E. Coutre, M.D., Ian W. Flinn, M.D., Ph.D., Jan A. Burger, M.D., Ph.D., Kristie A. Blum, M.D., Barbara Grant, M.D., Jeff P. Sharman, M.D., Morton Coleman, M.D., William G. Wierda, M.D., Ph.D., Jeffrey A. Jones, M.D., M.P.H., Weiqiang Zhao, M.D., Ph.D., Nyla A. Heerema, Ph.D., Amy J. Johnson, Ph.D., Juthamas Sukbuntherng, Ph.D., Betty Y. Chang, Ph.D., Fong Clow, Sc.D., Eric Hedrick, M.D., Joseph J. Buggy, Ph.D., Danelle F. James, M.D., and Susan O'Brien, M.D.

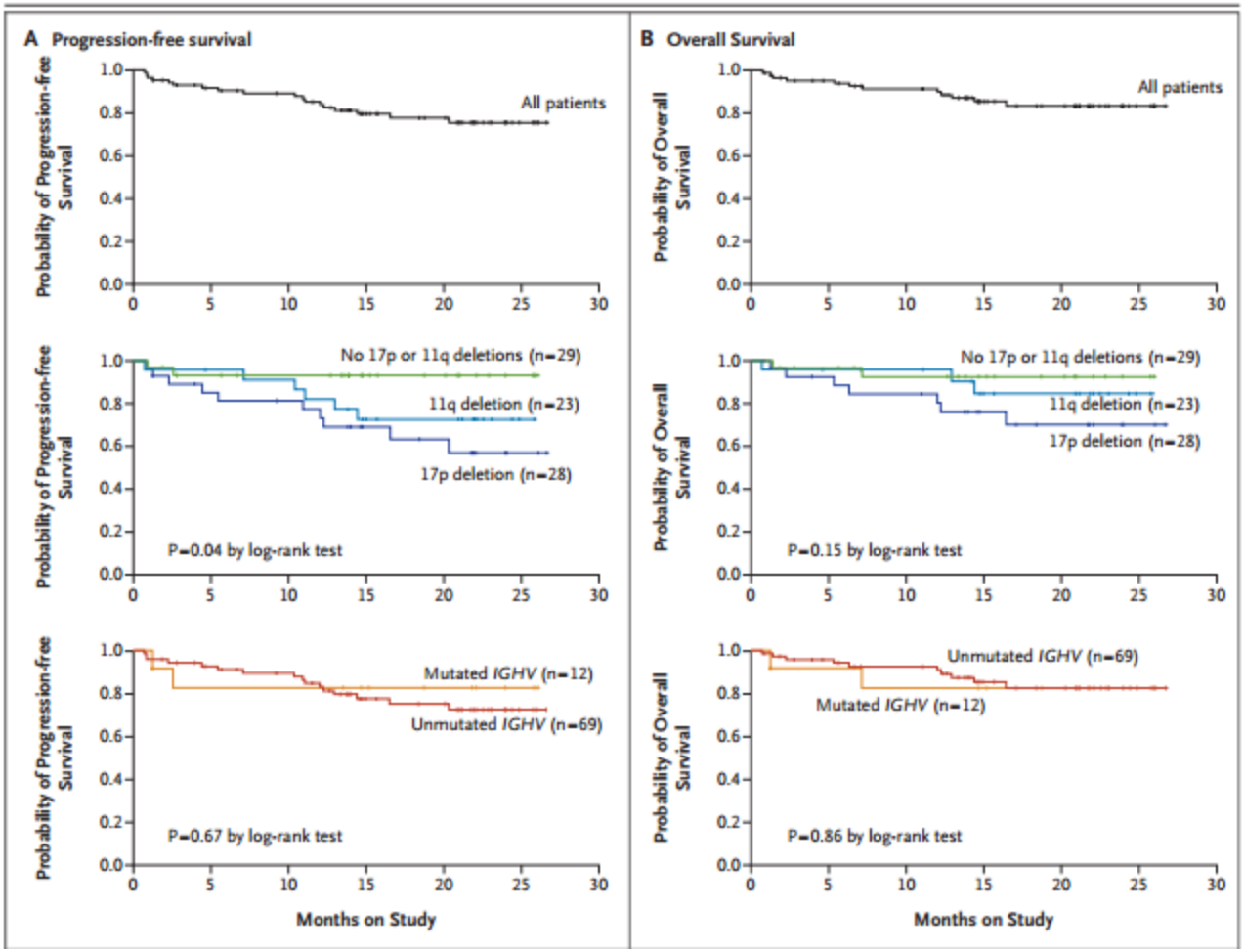


Figure 3. Kaplan–Meier Curves for Progression-free Survival and Overall Survival.

Panels A and B show the probability of progression-free survival and overall survival, respectively, for all 85 patients (top graphs) and according to status with respect to the 17p13.1 and 11q22.3 deletions (middle graphs) and *IGHV* mutation status (bottom graphs). Tick marks indicate censored data.

Table 2. Adverse Events.*

Adverse Event	Grade 1–2	Grade 3–4	Total†
	number of patients (percent)		
Diarrhea	40 (47)	2 (2)	42 (49)
Upper respiratory tract infection	28 (33)	0	28 (33)
Fatigue	24 (28)	3 (4)	27 (32)
Cough	26 (31)	0	26 (31)
Arthralgia	23 (27)	0	23 (27)
Rash	23 (27)	0	23 (27)
Pyrexia	19 (22)	4 (5)	23 (27)
Edema, peripheral	18 (21)	0	18 (21)
Muscle spasms	16 (19)	1 (1)	17 (20)
Constipation	14 (16)	1 (1)	15 (18)
Dizziness	14 (16)	1 (1)	15 (18)
Headache	14 (16)	1 (1)	15 (18)
Hypertension	11 (13)	4 (5)	15 (18)
Nausea	14 (16)	1 (1)	15 (18)
Sinusitis	11 (13)	4 (5)	15 (18)
Contusion	14 (16)	0	14 (16)
Vomiting	13 (15)	1 (1)	14 (16)
Neutropenia‡	0	13 (15)	13 (15)
Oropharyngeal pain	13 (15)	0	13 (15)

blood

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience

Susan O'Brien,[1,2] Richard R. Furman,[3] Steven Coutre,[4] Ian W. Flinn,[5] Jan A. Burger,[1] Kristie Blum,[6] Jeff Sharman,[7] William Wierda,[1] Jeffrey Jones,[6] Weiqiang Zhao,[6] Nyla A. Heerema,[6] Amy J. Johnson,[6] Ying Luan,[8] Danelle F. James,[8] Alvina D. Chu,[8] and John C. Byrd[6]

KEY POINTS

- **Our 5-year experience shows sustained single-agent efficacy of ibrutinib in CLL patients, with complete response rates increasing over time.**
- **Long-term ibrutinib was well tolerated with no new safety signals; rates of grade ≥3 cytopenias decreased with continued therapy.**

We previously reported durable responses and manageable safety of ibrutinib from a 3-year follow-up of treatment-naïve (TN) older patients (≥65 years of age) and relapsed/refractory (R/R) patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). We now report on long-term efficacy and safety with median follow-up of 5 years in this patient population with TN (N = 31) and R/R (N = 101) CLL/SLL. With the current 5-year follow-up, ibrutinib continues to yield a high overall response rate of 89%, with complete response rates increasing over time to 29% in TN patients and 10% in R/R patients. The median progression-free survival (PFS) was not reached in TN patients. The 5-year PFS rate was 92% in TN patients and 44% in R/R patients. Median PFS in R/R patients was 51 months; in those with del(11q), del(17p), and unmutated *IGHV*, it was 51, 26, and 43 months, respectively, demonstrating long-term efficacy of ibrutinib in some high-risk subgroups. Survival outcomes were less robust for R/R patients with del(17p) and those who received more prior therapies. The onset of grade ≥3 cytopenias, such as neutropenia and thrombocytopenia, decreased over time. Treatment–limiting adverse events were more frequent during the first year compared with subsequent periods. These results demonstrate sustained efficacy and acceptable tolerability of ibrutinib over an extended time, providing the longest experience for Bruton tyrosine kinase inhibitor treatment in patients with CLL/SLL. These trials were registered at www.clinicaltrials.gov as #NCT01105247 and #NCT01109069. (*Blood*. 2018;131(17):1910-1919)

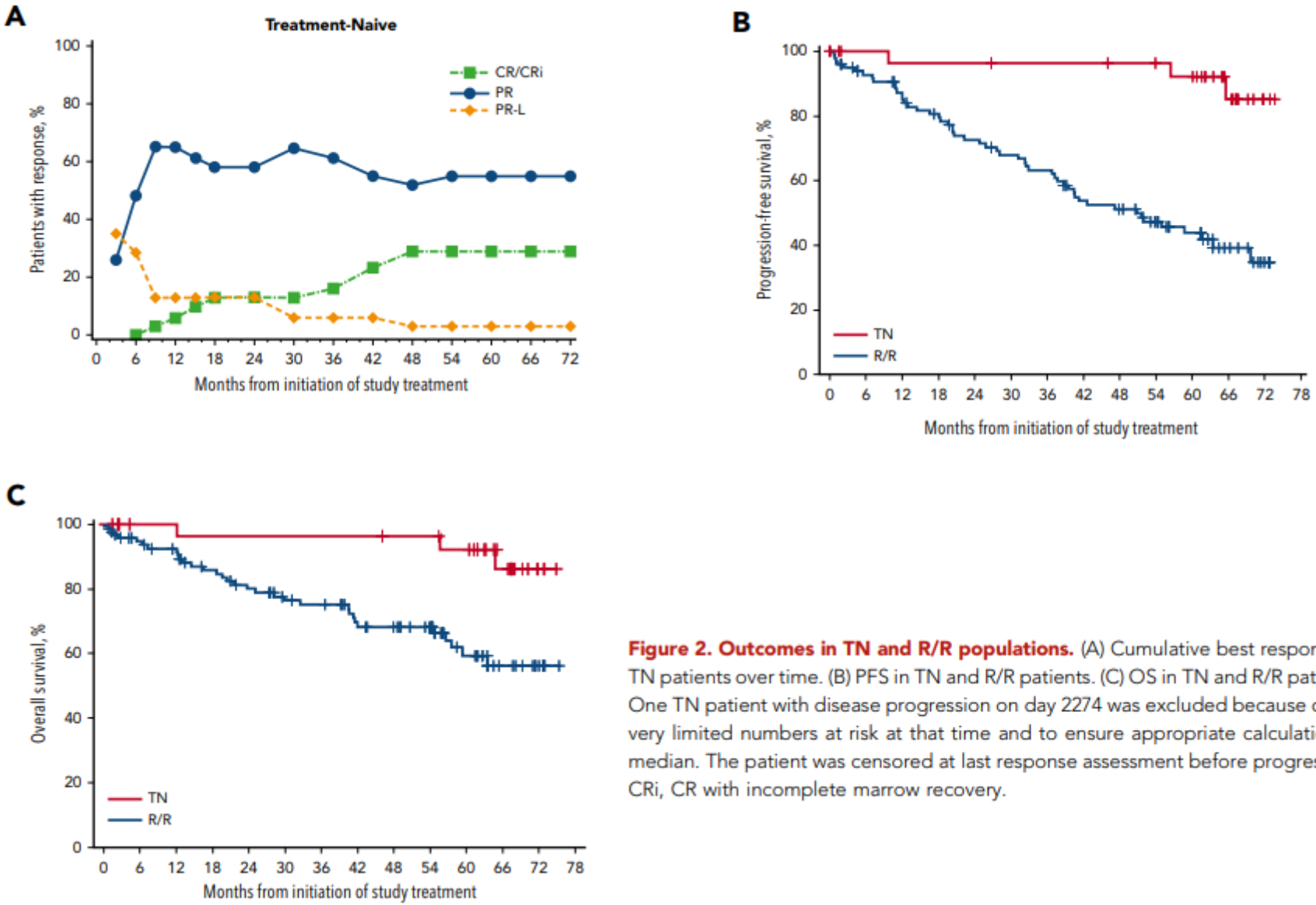


Figure 2. Outcomes in TN and R/R populations. (A) Cumulative best response in TN patients over time. (B) PFS in TN and R/R patients. (C) OS in TN and R/R patients. One TN patient with disease progression on day 2274 was excluded because of the very limited numbers at risk at that time and to ensure appropriate calculation of median. The patient was censored at last response assessment before progression. CRi, CR with incomplete marrow recovery.

ORIGINAL ARTICLE

N ENGL J MED 373;25 NEJM.ORG DECEMBER 17, 2015

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

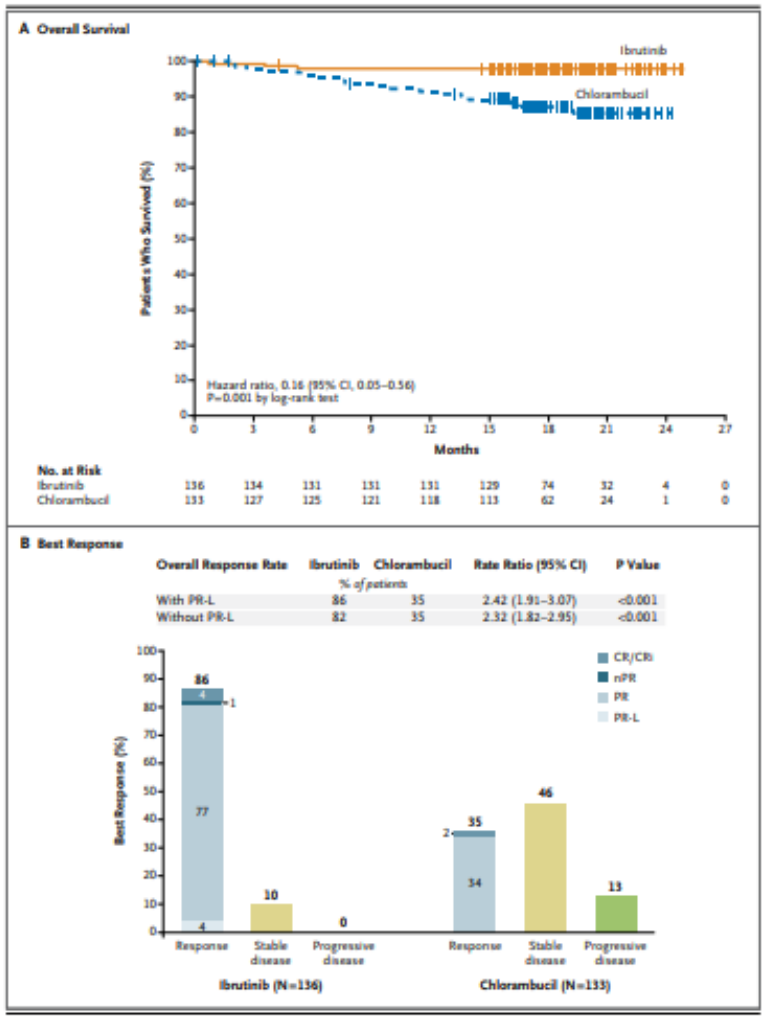


Table 2. Adverse Events and Duration of Treatment.

Variable	Ibrutinib (N=135)	Chlorambucil (N=132)
Duration of treatment — mo		
Median	17.4	7.1
Range	0.7–24.7	0.5–11.7
Most common adverse event of any grade — no. of patients (%)*		
Diarrhea	57 (42)	22 (17)
Fatigue	41 (30)	50 (38)
Cough	30 (22)	20 (15)
Nausea	30 (22)	52 (39)
Peripheral edema	25 (19)	12 (9)
Dry eye	23 (17)	6 (5)
Arthralgia	22 (16)	9 (7)
Neutropenia	21 (16)	30 (23)
Vomiting	18 (13)	27 (20)
Adverse event of grade ≥3 — no. of patients (%)†		
Neutropenia	14 (10)	24 (18)
Anemia	8 (6)	11 (8)
Hypertension	6 (4)	0
Pneumonia	5 (4)	2 (2)
Diarrhea	5 (4)	0
Maculopapular rash	4 (3)	2 (2)
Decreased platelet count	4 (3)	1 (1)
Abdominal pain	4 (3)	1 (1)
Hyponatremia	4 (3)	0
Thrombocytopenia	3 (2)	8 (6)
Febrile neutropenia	3 (2)	3 (2)
Upper respiratory tract infection	3 (2)	2 (2)
Pleural effusion	3 (2)	1 (1)
Cellulitis	3 (2)	0
Fatigue	1 (1)	7 (5)
Syncope	1 (1)	3 (2)
Hemolytic anemia	0	3 (2)
Serious adverse event — no. of patients (%)†		
Pneumonia	5 (4)	2 (2)
Basal-cell carcinoma	5 (4)	0
Hyponatremia	3 (2)	0
Pyrexia	1 (1)	5 (4)

* The events listed are adverse events of any grade that occurred in at least 15% of patients in either treatment group and for which the frequency differed between treatment groups by at least 5%.

† The events listed are adverse events of grade 3 or higher or serious adverse events that occurred in at least 2% of the patients in either treatment group. One death due to toxic hepatitis in the chlorambucil group was considered by the investigator to be possibly related to the study treatment; no other deaths were considered by the investigator to be related to the study treatment.

Rete Ematologica Pugliese

Ibrutinib, single agent BTK inhibitor, for treatment-naive (TN) and relapsed/refractory (R/R) Chronic Lymphocytic Leukemia:

a real-life experience from

Rete Ematologica Pugliese

P.R.Scalzulli

Ematologia San Giovanni Rotondo

131 CLL/SLL patients

8 Hematologic Centers of REP

	no. patients
Bari Oncologico	28
Bari Policlinico	19
Barletta	6
Brindisi	14
Lecce	11
San Giovani Rotondo	34
Taranto	13
Tricase	6

Methods: In 131 CLL/SLL patients (including previously treated and untreated with del17) from eight different hematologic centers of REP (Rete Ematologica Pugliese) Ibrutinib 420 mg once daily was administrated until disease progression or unacceptable toxicity. PFS, OS and Overall response rate (ORR) were calculated.

131 CLL/SLL patients

9 (6,9%) (TN) Ibrutinib as first line therapy

122 (93,1%) (R/R) prior therapies before Ibrutinib

39,7% BR
19,3% FCR
42% other treatments

90% (1-2) lines of therapy
8% (3-4) lines of therapy
2% (>5) lines of therapy

Tabel 1a 131 patients

	%
Gender	
Male	63
Female	37
Age (yrs) at dx	
median (range)	65 (28-84)
Time (months) dx-ibrutinib	
median (range)	4 (0-16)
Stage BINET/RAI	
BINET	
A	17
B	21
C	37
RAI	
0	1
1	7
2	7
3	8
4	2
ECOG Performance Status	
0	56
1	40
2	4
FISH*	
del17p	42
del11q	4
del13q	16
trisomy 12	7
NEG	31
IGVH	
mutated	37
unmutated	63

**not mutually exclusive mutations*

131 CLL/SLL patients

Median Time on study
17 months (range, 1-45)

Median Time on study 17 months (range, 1-45)

ORR 80% 131 pts (CR 10%)

* ORR TN 86%

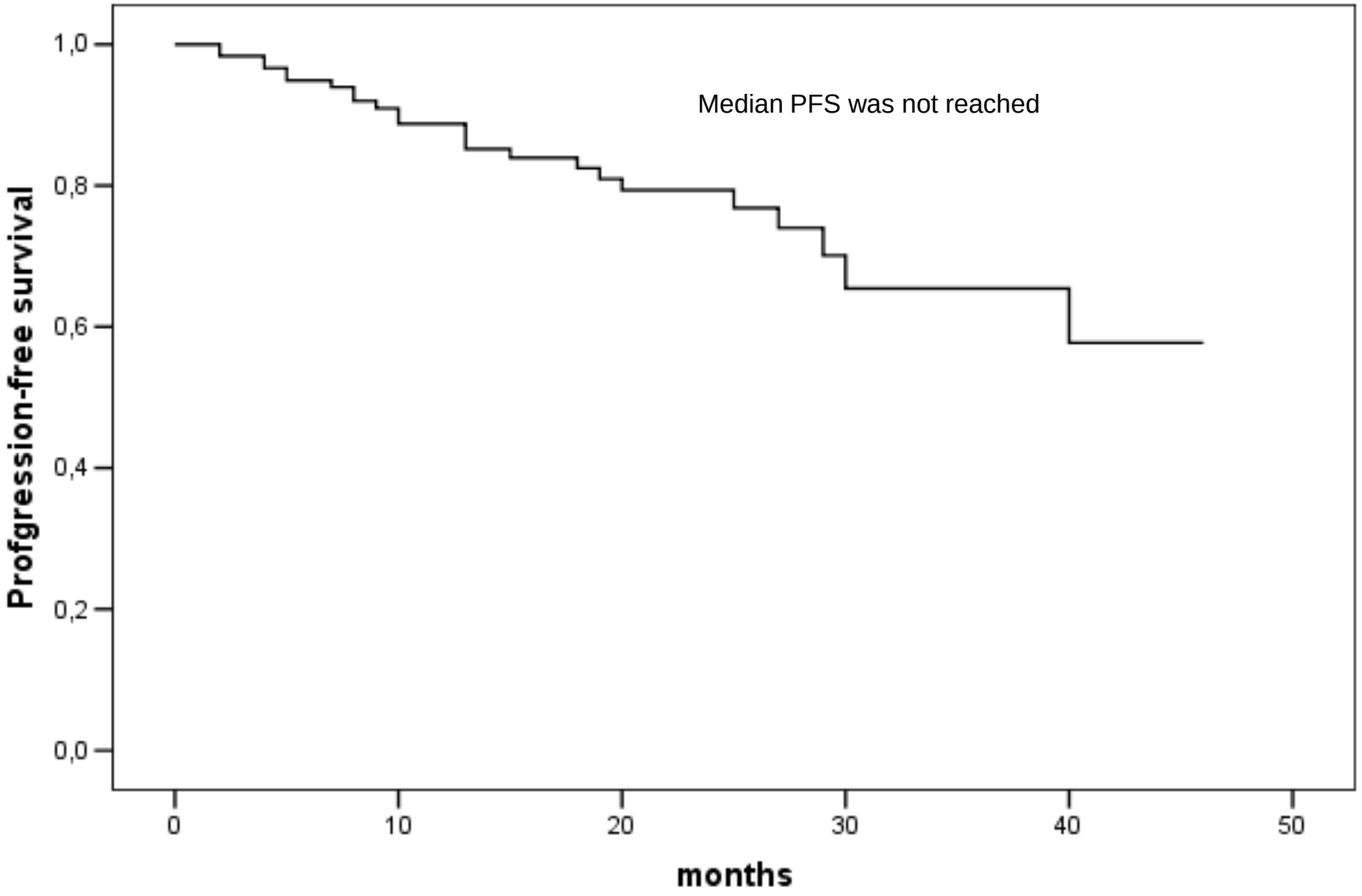
ORR R/R 77%

ORR R/R with del17p 61%

*We exclude from our further analysis 9 TN patients because of the small sample size and the lack of events

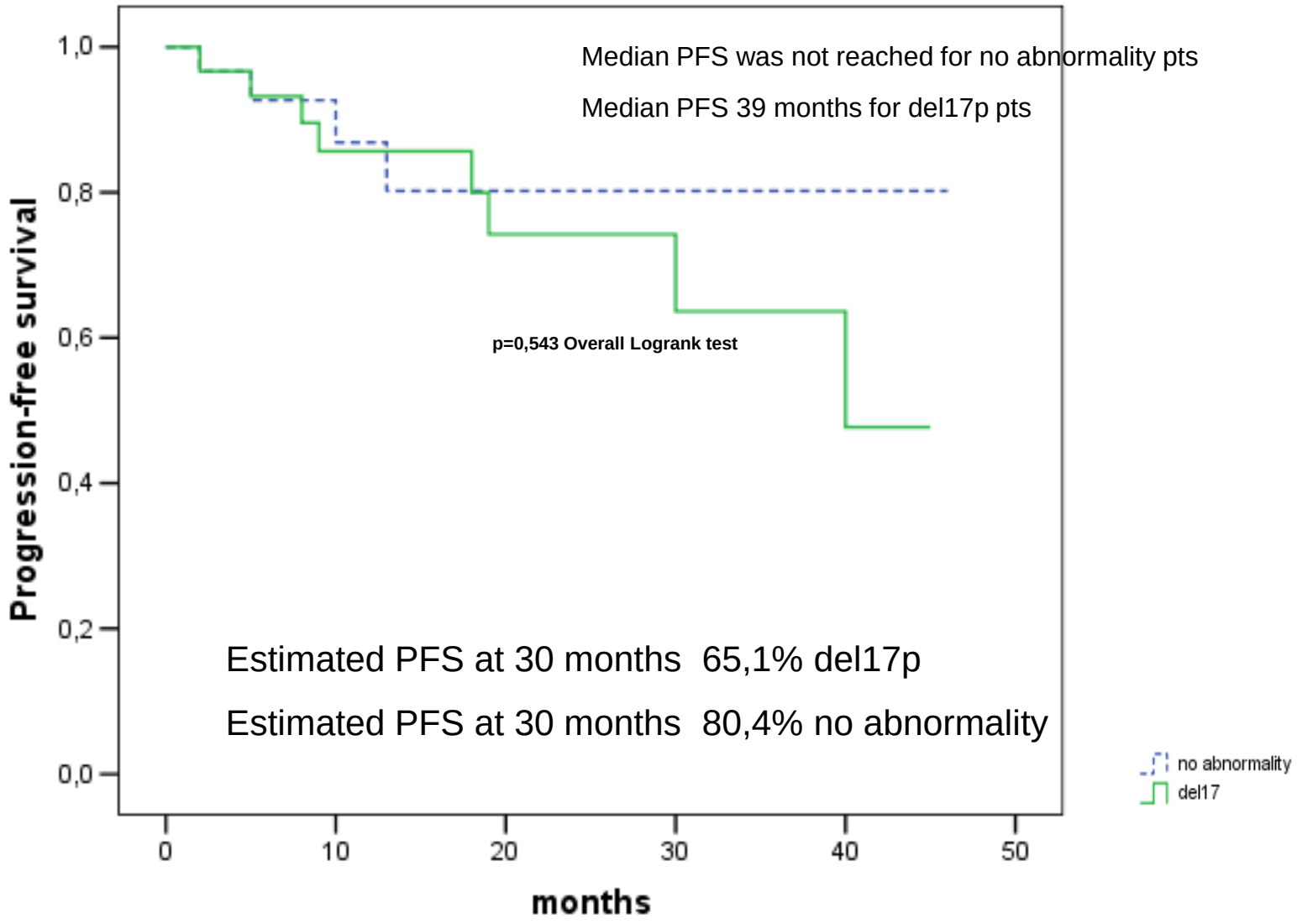
PFS

Figure 1 PFS for R/R patients



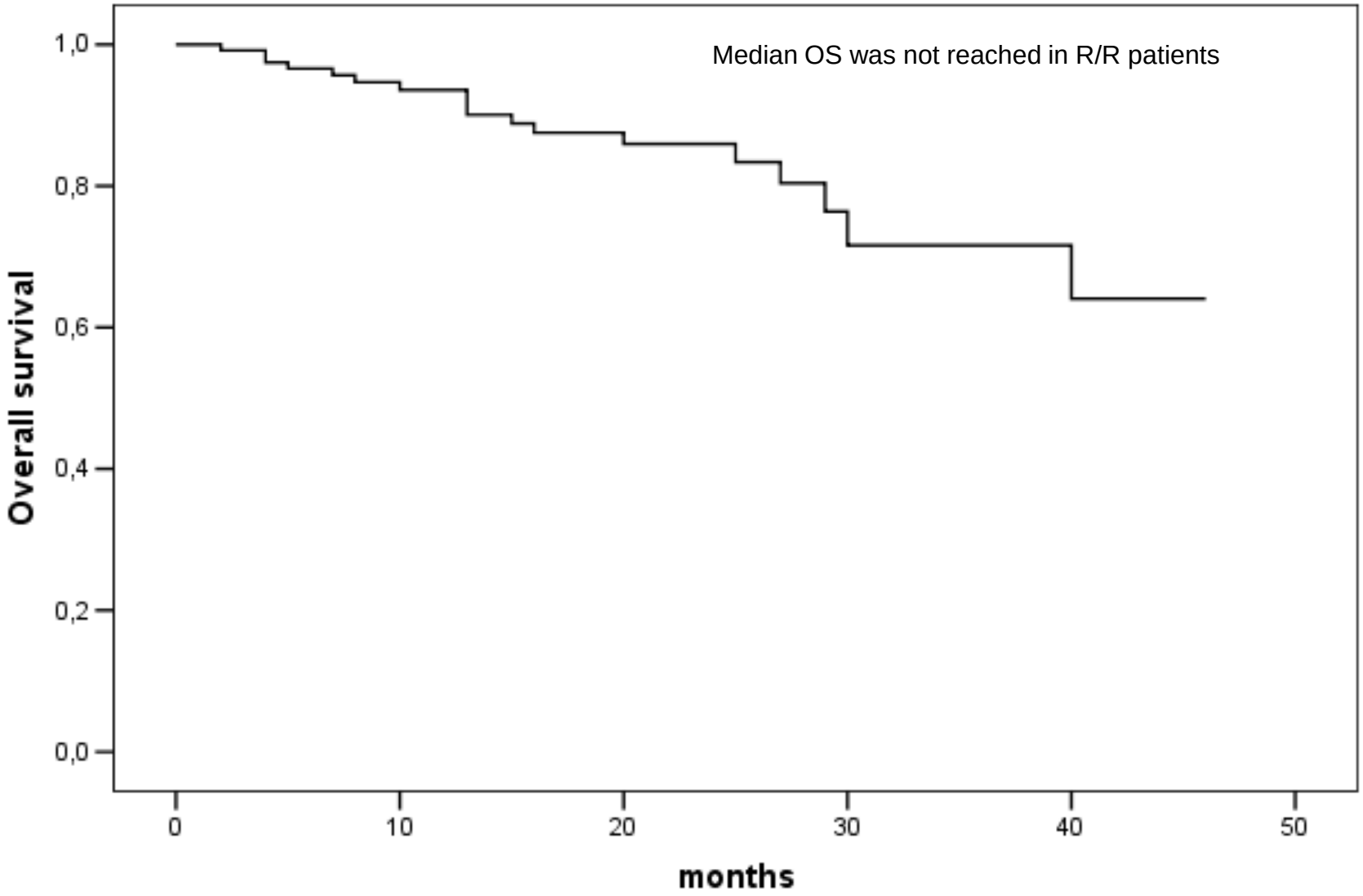
PFS

Figure 2 PFS for R/R patients with del17p or no abnormality



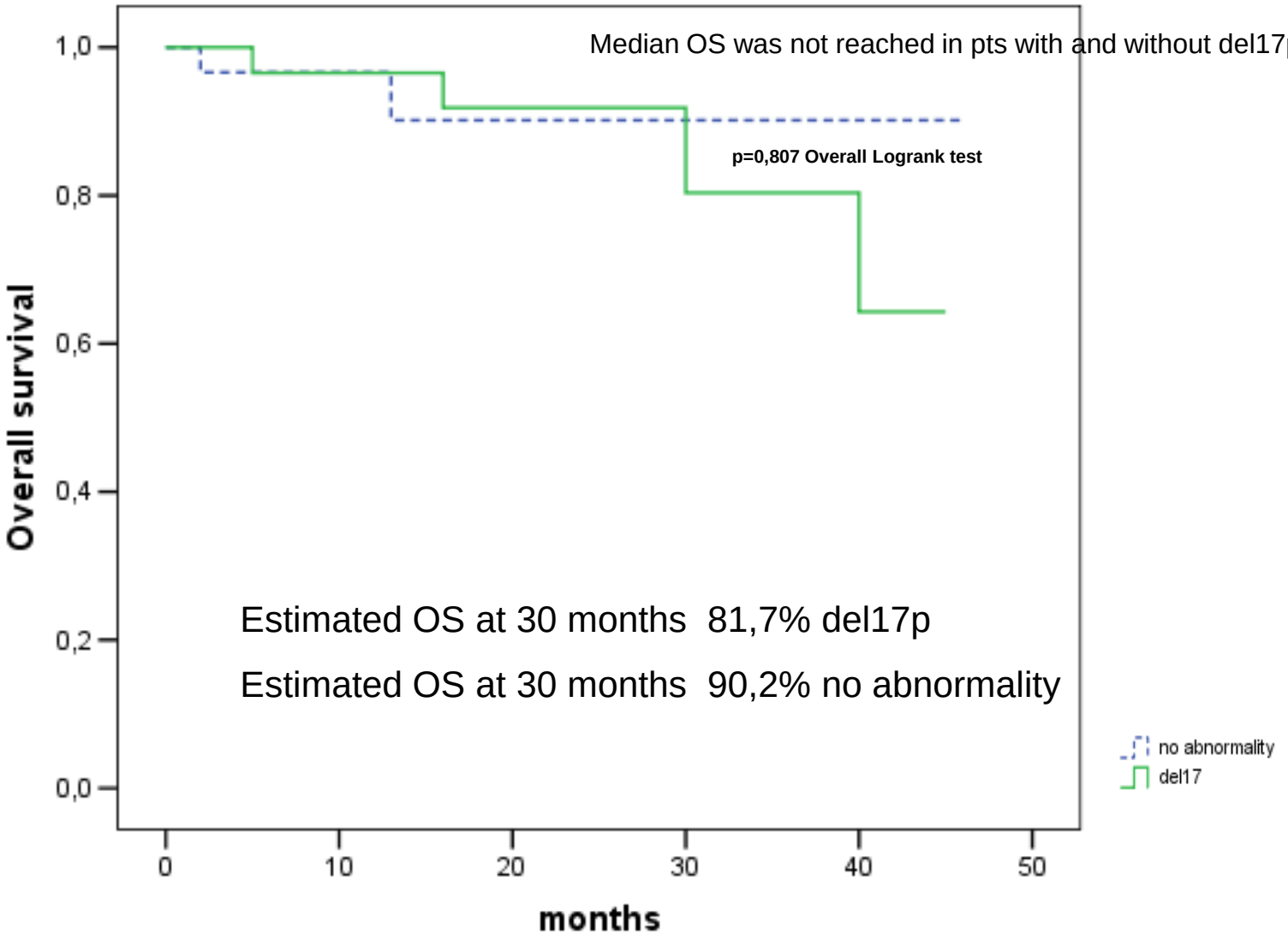
OS

Figure 3 OS for R/R patients



OS

Figure 4 OS for R/R patients with del17p or no abnormality



ADVERSE EVENTS (AEs)

AEs	61 pts (47%)
AEs grade ≥ 3	22 pts (36%)

AEs grade ≥ 3

Neutropenia 16%

Hypertensione 12%

Atrial Fibrillation 3%

Anemia 3%

Diarrhea 2%

Conclusions

PFS Not differences statistically significative (p=0.543) between pts with and without del17p

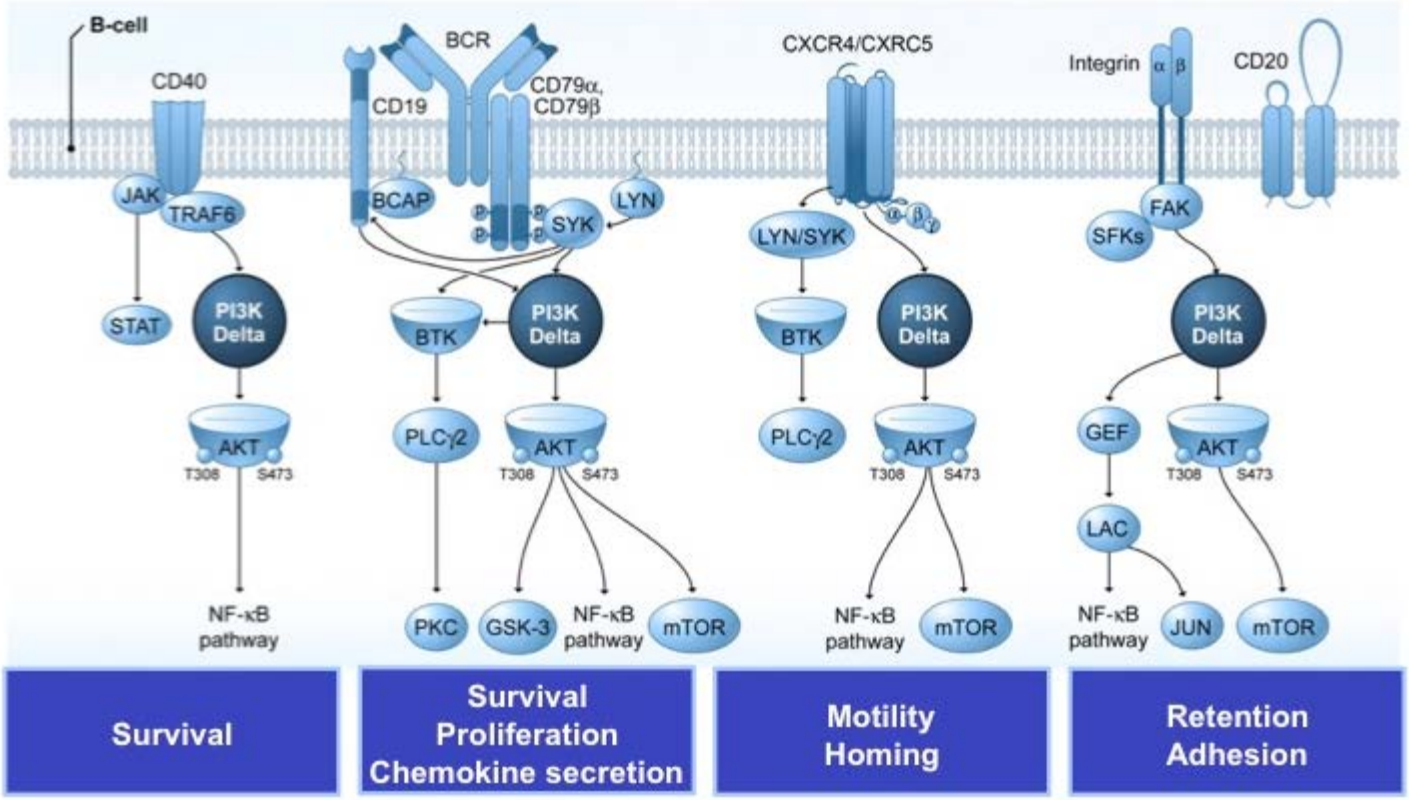
Median time on study 17 months (range, 1-45)

Estimated PFS at 30 months lower in del17p pts than in no abnormality pts (65,1 % vs 80,4%)

Adverse Events ≥ 3 in a low percentage

80% pts remain on Ibrutinib treatment on study

PI3Kδ inhibition impacts multiple critical pathways in B-cell malignancies



BCAP: B-cell adaptor for PI3K; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; GEF: guanine nucleotide exchange factor; mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol-3-kinase; PKC: protein kinase C; SFK: Src family kinase; SYK: spleen tyrosine kinase

Coutre S, *et al. Leuk Lymphoma* 2015; ePub ahead of print.

Idelalisib: CLL, FL

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 156° - Numero 1

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA — Roma - Venerdì, 2 gennaio 2015 — SI PUBBLICA TUTTI I GIORNI NON FESTIVI

DIREZIONE E REDAZIONE PRESSO IL MINISTERO DELLA GIUSTIZIA - UFFICIO PUBBLICAZIONE LEGGI E DECRETI - VIA ARENULA, 70 - 00186 ROMA
AMMINISTRAZIONE PRESSO L'ISTITUTO POLIGRAFICO E ZECCA DELLO STATO - VIA SALARIA, 1027 - 00138 ROMA - CENTRALINO 06-85081 - LIBRERIA DELLO STATO
PIAZZA G. VERDI, 1 - 00198 ROMA

Indicazioni terapeutiche

Zydelig è indicato in associazione con rituximab per il trattamento di pazienti adulti affetti da leucemia linfatica cronica (LLC):

- che hanno ricevuto almeno una terapia precedente, o
- come trattamento di prima linea in presenza di una delezione 17p o una mutazione *TP53* in pazienti non idonei alla chemioimmunoterapia.

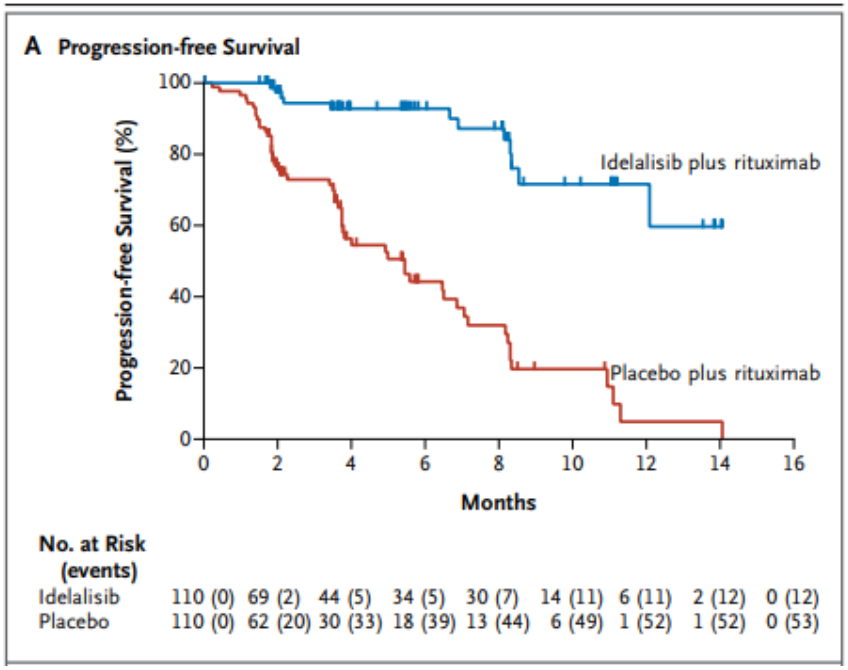
Zydelig è indicato in monoterapia per il trattamento di pazienti adulti affetti da linfoma follicolare (*follicular lymphoma*, FL) refrattario a due precedenti linee di trattamento.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 13, 2014 VOL. 370 NO. 11

Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia

Richard R. Furman, M.D., Jeff P. Sharman, M.D., Steven E. Coutre, M.D., Bruce D. Cheson, M.D., John M. Pagel, M.D., Ph.D., Peter Hillmen, M.B., Ch.B., Ph.D., Jacqueline C. Barrientos, M.D., Andrew D. Zelenetz, M.D., Ph.D., Thomas J. Kipps, M.D., Ph.D., Ian Flinn, M.D., Ph.D., Paolo Ghia, M.D., Ph.D., Herbert Eradat, M.D., Thomas Ervin, M.D., Nicole Lamanna, M.D., Bertrand Coiffier, M.D., Ph.D., Andrew R. Pettitt, Ph.D., F.R.C.Path., Shuo Ma, M.D., Ph.D., Stephan Stilgenbauer, M.D., Paula Cramer, M.D., Maria Aiello, M.A., Dave M. Johnson, B.S., Langdon L. Miller, M.D., Daniel Li, Ph.D., Thomas M. Jahn, M.D., Ph.D., Roger D. Dansey, M.D., Michael Hallek, M.D., and Susan M. O'Brien, M.D.



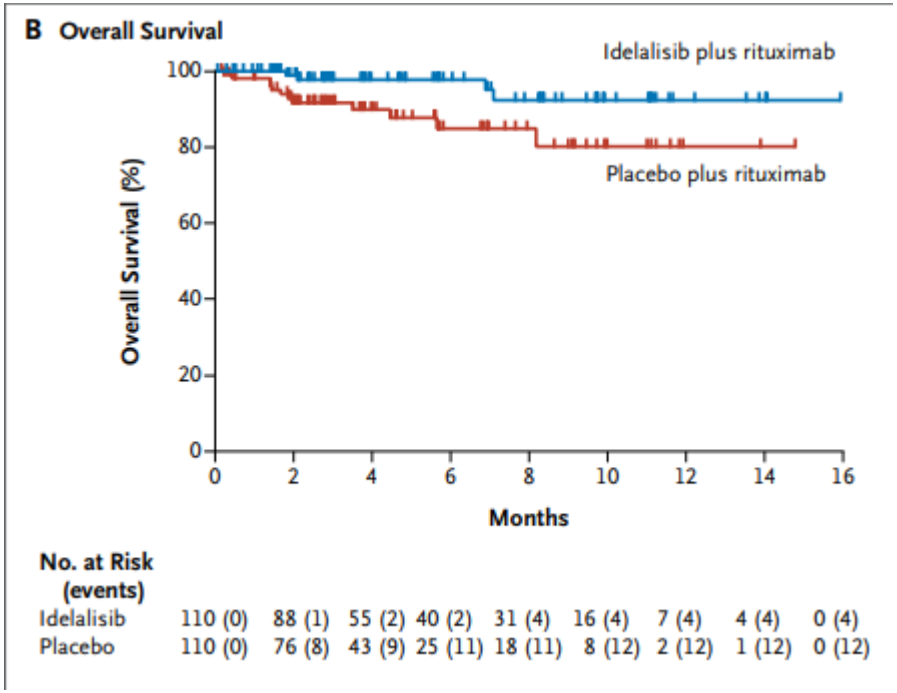


Figure 1. Progression-free and Overall Survival.

At the time the study was stopped, the median duration of progression-free survival among 110 patients receiving idelalisib and rituximab had not yet been reached; among the 110 patients receiving placebo and rituximab, the median duration of progression-free survival was 5.5 months (hazard ratio for progression or death in the idelalisib group, 0.15; 95% confidence interval [CI], 0.08 to 0.28; P<0.001) (Panel A). The median duration of overall survival in the two study groups had also not been reached; the overall survival rate was 92% in the idelalisib group versus 80% in the placebo group at 12 months (hazard ratio for death, 0.28; 95% CI, 0.09 to 0.86; P=0.02) (Panel B).

Subgroup	Idelalisib plus Rituximab	Placebo plus Rituximab	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
Overall	110	110	0.15 (0.08–0.28)
IGHV			
Mutated	19	17	0.25 (0.07–0.95)
Unmutated	91	93	0.13 (0.06–0.27)
17p Deletion or *TP53* mutation			
Either	46	50	0.12 (0.05–0.32)
Neither	64	60	0.17 (0.07–0.43)
17p Deletion			
Yes	26	31	0.14 (0.04–0.47)
No	84	79	0.14 (0.07–0.31)
Sex			
Male	76	68	0.10 (0.04–0.24)
Female	34	42	0.30 (0.11–0.78)
Age			
<65 yr	21	27	0.24 (0.07–0.77)
≥65 yr	89	83	0.11 (0.05–0.26)

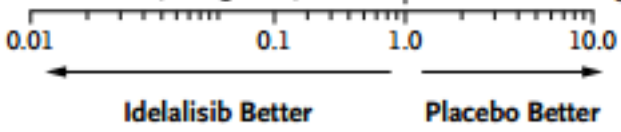


Figure 2. Forest Plot of Progression-free Survival in Prespecified Subgroups.

Hazard ratios of less than 1.00 for disease progression or death indicate better results in the idelalisib group.

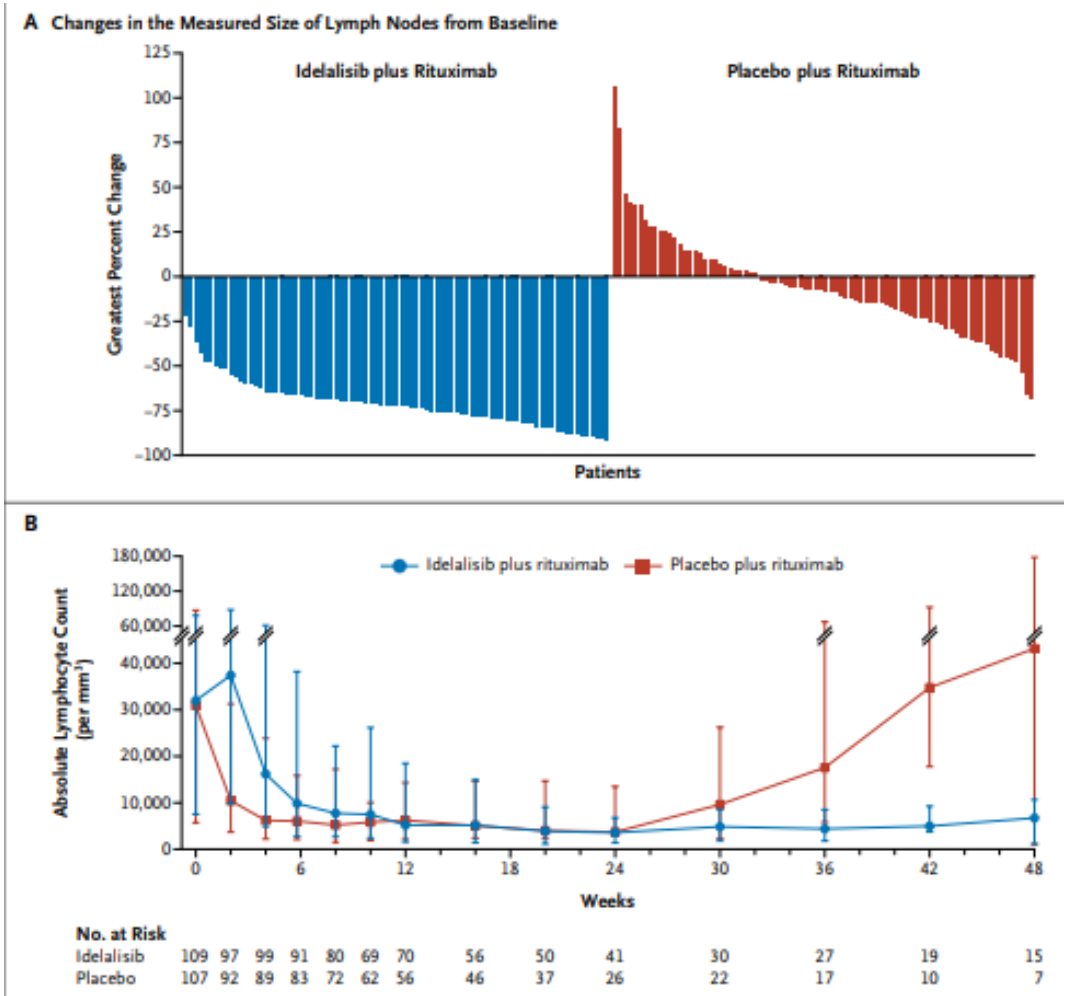


Figure 3. Changes in Lymph Nodes and Lymphocytes.

Shown are the greatest percentage changes in the sum of the products of the perpendicular diameters of measured lymph nodes for each study patient (Panel A) and the median absolute lymphocyte counts over a period of 48 weeks (Panel B). The I bars represent interquartile ranges.

Table 2. Adverse Events, Serious Adverse Events, and Key Laboratory Abnormalities.*

Event	Idelalisib plus Rituximab (N=110)		Placebo plus Rituximab (N=107)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number (percent)			
Adverse event during treatment	100 (91)	62 (56)	101 (94)	51 (48)
Pyrexia	32 (29)	3 (3)	17 (16)	1 (1)
Fatigue	26 (24)	3 (3)	29 (27)	2 (2)
Nausea	26 (24)	0	23 (21)	0
Chills	24 (22)	2 (2)	17 (16)	0
Diarrhea	21 (19)	4 (4)	15 (14)	0
Infusion-related reaction	17 (15)	0	30 (28)	4 (4)
Cough	16 (15)	0	27 (25)	2 (2)
Constipation	13 (12)	0	12 (11)	0
Decreased appetite	13 (12)	0	9 (8)	1 (1)
Vomiting	13 (12)	0	8 (7)	0
Dyspnea	12 (11)	2 (2)	20 (19)	3 (3)
Night sweats	11 (10)	0	8 (7)	0
Rash	11 (10)	2 (2)	6 (6)	0
Serious adverse event	44 (40)	NA	37 (35)	NA
Pneumonia	7 (6)	NA	9 (8)	NA
Pyrexia	7 (6)	NA	3 (3)	NA
Febrile neutropenia	5 (5)	NA	6 (6)	NA
Sepsis	4 (4)	NA	3 (3)	NA
Pneumonitis	4 (4)	NA	1 (1)	NA
Diarrhea	3 (3)	NA	1 (1)	NA
Neutropenia	3 (3)	NA	1 (1)	NA
Pneumocystis jirovecii pneumonia	3 (3)	NA	1 (1)	NA
Neutropenic sepsis	3 (3)	NA	0	NA
Dyspnea	1 (1)	NA	4 (4)	NA
Cellulitis	1 (1)	NA	3 (3)	NA
Laboratory abnormality				
ALT or AST elevation	38 (35)	6 (5)	20 (19)	1 (1)
Anemia	28 (25)	6 (5)	32 (30)	15 (14)
Neutropenia	60 (55)	37 (34)	52 (49)	24 (22)
Thrombocytopenia	19 (17)	11 (10)	28 (26)	17 (16)

* Listed are all adverse events that were reported in at least 10% of patients and all serious adverse events that were reported in at least three patients in at least one of the study groups. Patients with more than one occurrence of the same type of adverse event or serious adverse event are listed only once. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and NA not applicable (because serious adverse events are reported as severe regardless of the severity grading).

PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma

Ajay K. Gopal, M.D., Brad S. Kahl, M.D., Sven de Vos, M.D., Ph.D., Nina D. Wagner-Johnston, M.D., Stephen J. Schuster, M.D., Wojciech J. Jurczak, M.D., Ph.D., Ian W. Flinn, M.D., Ph.D., Christopher R. Flowers, M.D., Peter Martin, M.D., Andreas Viardot, M.D., Kristie A. Blum, M.D., Andre H. Goy, M.D., Andrew J. Davies, M.R.C.P., Ph.D., Pier Luigi Zinzani, M.D., Ph.D., Martin Dreyling, M.D., Dave Johnson, B.S., Langdon L. Miller, M.D., Leanne Holes, M.B.A., Daniel Li, Ph.D., Roger D. Dansey, M.D., Wayne R. Godfrey, M.D., and Gilles A. Salles, M.D., Ph.D.

N ENGL J MED NEJM.ORG

The New England Journal of Medicine

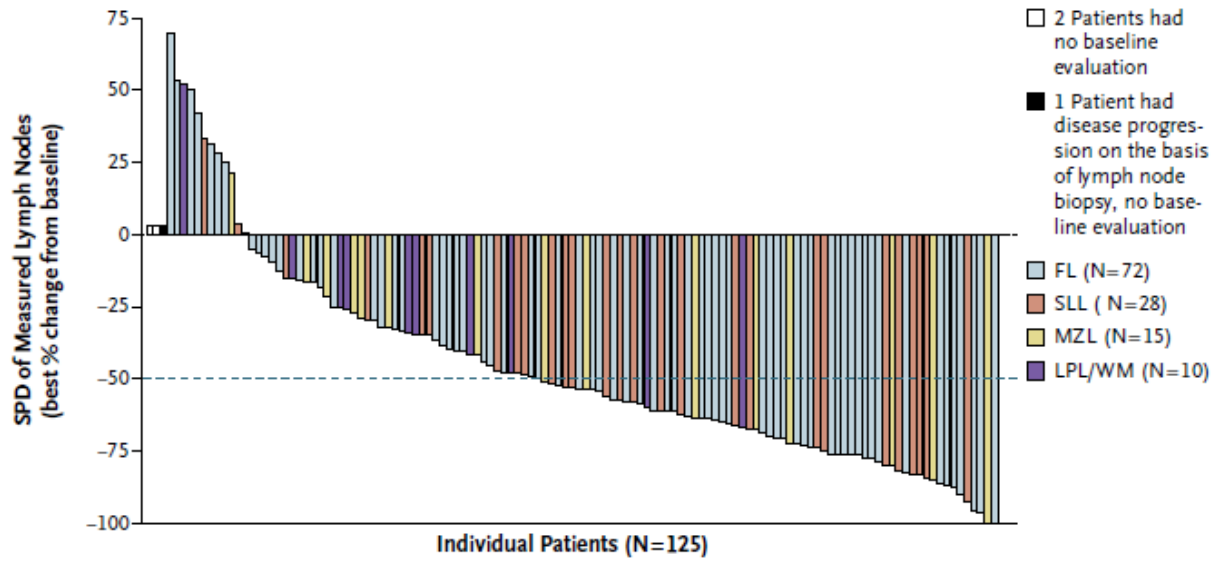


Figure 1. Best Overall Response.

The best response with respect to tumor size during idelalisib treatment, according to assessment by an independent review committee, is shown for the 125 patients in the study. Among the 122 patients with measurable lesions both at baseline and after baseline, 110 patients (90%) had improvements in lymphadenopathy, as assessed by changes in the sums of the products of the perpendicular dimensions (SPD) of index lesions. The dashed line shows the percentage change that represents the criterion for lymphadenopathy response, according to Cheson et al.[25] FL denotes follicular lymphoma, LPL/WM lymphoplasmacytic lymphoma with or without Waldenström's macroglobulinemia, MZL marginal-zone lymphoma, and SLL small lymphocytic lymphoma.

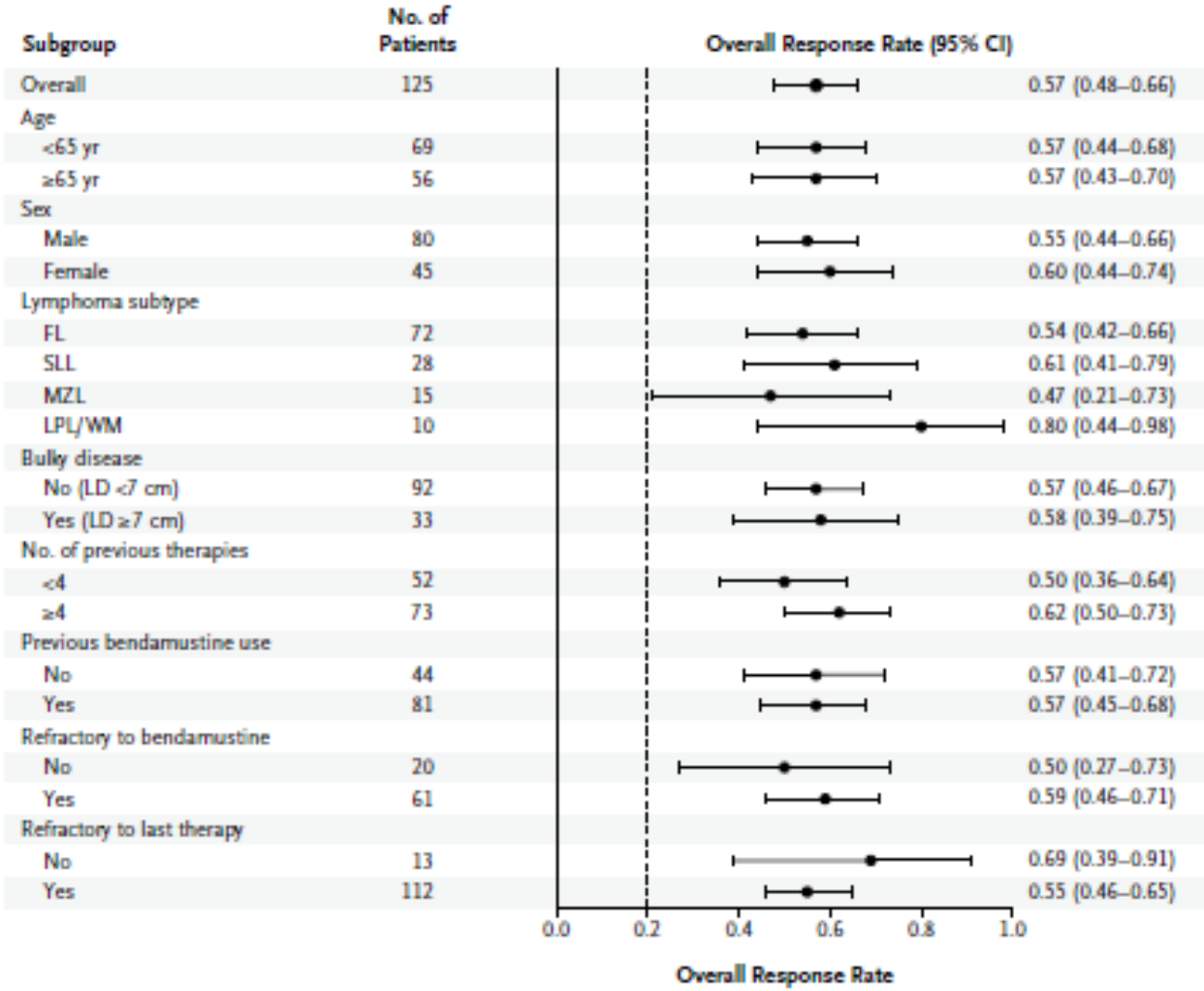


Figure 2. Forest Plot of Overall Response Rate.

A forest plot is shown of the overall response rate, in the total cohort and according to subgroups, among patients with refractory indolent non-Hodgkin's lymphoma. The response rate was assessed by an independent review committee. The dashed line shows the null hypothesis response rate of 20%. LD denotes longest diameter.

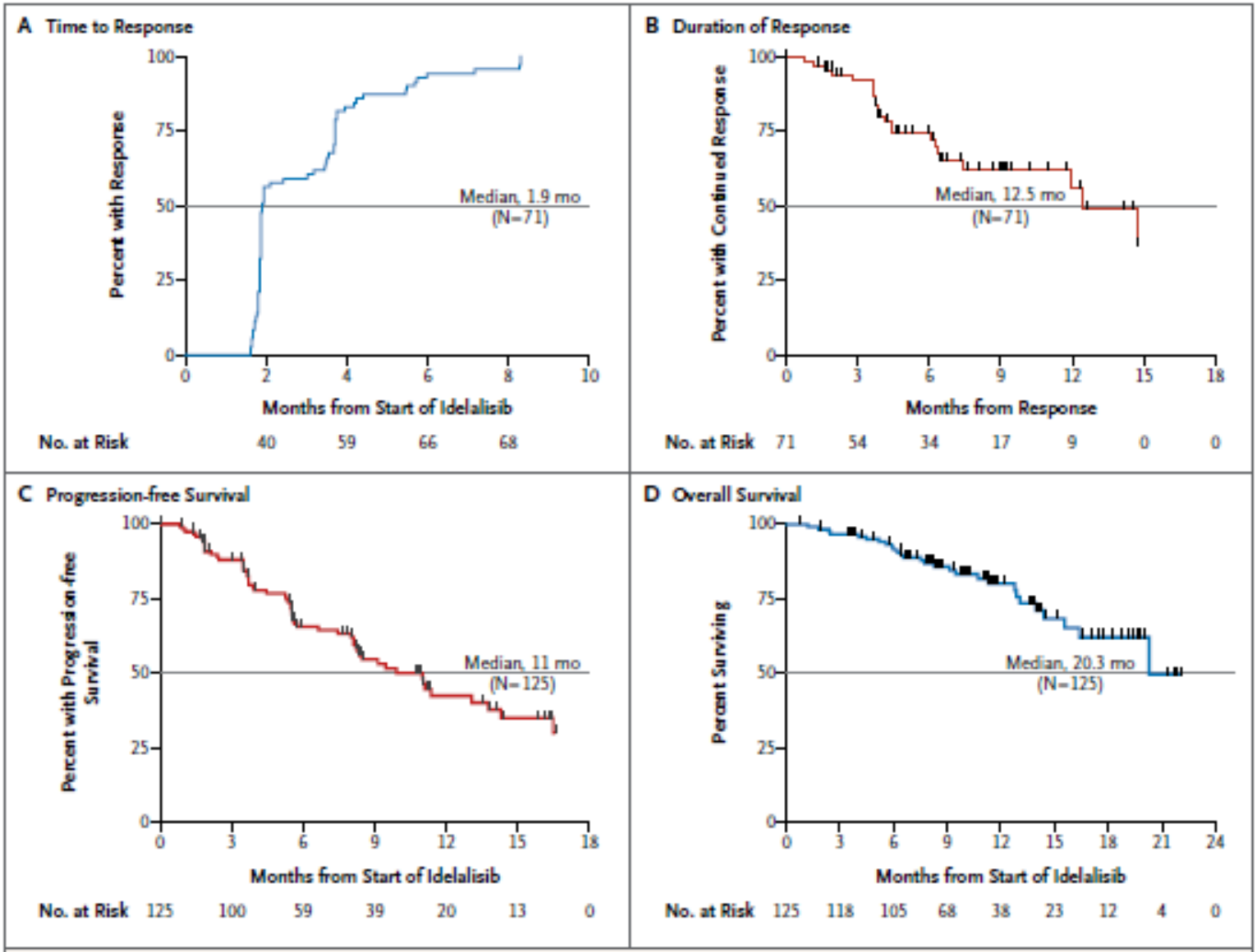


Figure 3. Kaplan–Meier Curves for Secondary End Points.

Kaplan–Meier curves are shown for the secondary end points of the time to response (Panel A), the duration of response (Panel B), progression-free survival (Panel C), and overall survival (Panel D) among patients with refractory indolent non-Hodgkin's lymphoma who were treated with idelalisib (intention-to-treat population). The end points were assessed by an independent review committee.

Table 2. Adverse Events during Treatment.*

Event or Abnormality	Grade	
	Any	≥3
	no. (%)	
Adverse event	103 (82)	68 (54)
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0
Pyrexia	35 (28)	2 (2)
Decreased appetite	22 (18)	1 (1)
Dyspnea	22 (18)	4 (3)
Abdominal pain	20 (16)	3 (2)
Vomiting	19 (15)	3 (2)
Upper respiratory tract infection	18 (14)	0
Weight decreased	17 (14)	0
Rash	16 (13)	2 (2)
Asthenia	14 (11)	3 (2)
Night sweats	14 (11)	0
Pneumonia	14 (11)	9 (7)
Peripheral edema	13 (10)	3 (2)
Headache	13 (10)	1 (1)
Hematopoietic laboratory abnormality		
Decreased neutrophils	70 (56)	34 (27)
Decreased hemoglobin	35 (28)	2 (2)
Decreased platelets	32 (26)	8 (6)
Chemical laboratory abnormality		
Increased ALT	59 (47)	16 (13)
Increased AST	44 (35)	10 (8)
Increased alkaline phosphatase	28 (22)	0
Increased bilirubin	13 (10)	0

* Included are adverse events and selected laboratory abnormalities that occurred during treatment in 10% or more of the 125 patients in the study, regardless of whether the event was related to the study drug. Adverse events that occurred during treatment are classified according to the preferred term in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.1. Patients who had multiple events within the same preferred-term category were counted once in that category. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.

Rete Ematologica Pugliese

IDELALISIB NEL LINFOMA FOLLICOLARE R/R. L'ESPERIENZA DELLA RETE EMATOLOGICA PUGLIESE

Giuseppe Tarantini

U.O.C. di Ematologia con Trapianto

Barletta

Rete Ematologica Pugliese

	N (%)
TRICASE	3 (10)
BRINDISI	1 (3)
LECCE	5 (16)
SGR	10 (32)
BARI POLICLINICO	4 (13)
TARANTO	4 (13)
BARI ONCOLOG.	3 (10)
BARLETTA	1 (3)

Between November 2015 and March 2018: 31 patients enrolled

Caratteristiche popolazione FL

Characteristic	N=31
Age, median (range), yr*	**70 (51-87)**
Male n (%)	9 (29)
ECOG, n (%) 0 1 2 3	 12 (39) 14(45) 5(16) 0
FL Grade, n (%) 1 2 **3a**	 5 (16) 16 (52) **10 (32)**
High-risk FLIPI2 score, n (%) **Low** Intermediate High	 1(4) 12(46) 13(50)
Ann Arbor Stage III-IV, n (%) **Stage III or IV** Elevated LDH Bulky disease	46 (70) **30(97)** 8(27) 7(23)
Prior regimens, median (range)	2 (1-7)

Idelalisib Efficacy and Safety in FL

Baseline Characteristics and Patient Disposition

Characteristics	Patients (n=72)
Median (range) age, y	62 (33-84)
FL grade, n (%)	
1	21 (29.2)
2	39 (54.2)
3A	12 (16.7)
Disease burden, n (%)	
Stage III or IV	60 (83.3)
Elevated LDH*	21 (29.2)
Bulky disease†	16 (22.2)
High FLIPI risk score, n (%)	39 (54.2)
ECOG performance score	
2	6 (8.3)
1	35 (48.6)
0	31 (43.1)
Baseline cytopenia‡	
Neutropenia	9 (12.5)
Anemia	8 (11.1)
Thrombocytopenia	5 (6.9)

*LDH increase defined as levels ≥234 U/L.
†Bulky disease defined as ≥1 node with ≥1 dimension of ≥7 cm.
‡Neutropenia was defined as ANC <1500 cells/mm3, anemia as Hgb <10 g/dL, and thrombocytopenia as a platelet count <75,000 cells/mm^3.
§All patients were double-refractory to rituximab and an alkylating agent.
**Cause of death: heart failure, cardiac arrest, splenic infarct/acute abdomen, drug-induced pneumonitis, and unknown (n=1 each).

Characteristics	n=72
Median (range) time since diagnosis, y	4.7 (0.8-18.4)
Median (range) # of previous treatments	4 (2-12)
Prior therapy, n (%)	
Bendamustine	50 (69.4)
Anthracycline	51 (72.2)
Purine analog	17 (23.6)
Autologous stem-cell transportation	12 (16.7)
Prior therapy to which disease was refractory§	
Bendamustine	32/50 (64.0)
Bendamustine and rituximab	23/36 (72.2)
R-CHOP	23/35 (65.7)
R-CVP	15/20 (75.0)
Refractory to ≥ 2 regimens	57 (79.2)
Refractory to most recent regimen	62 (86.1)

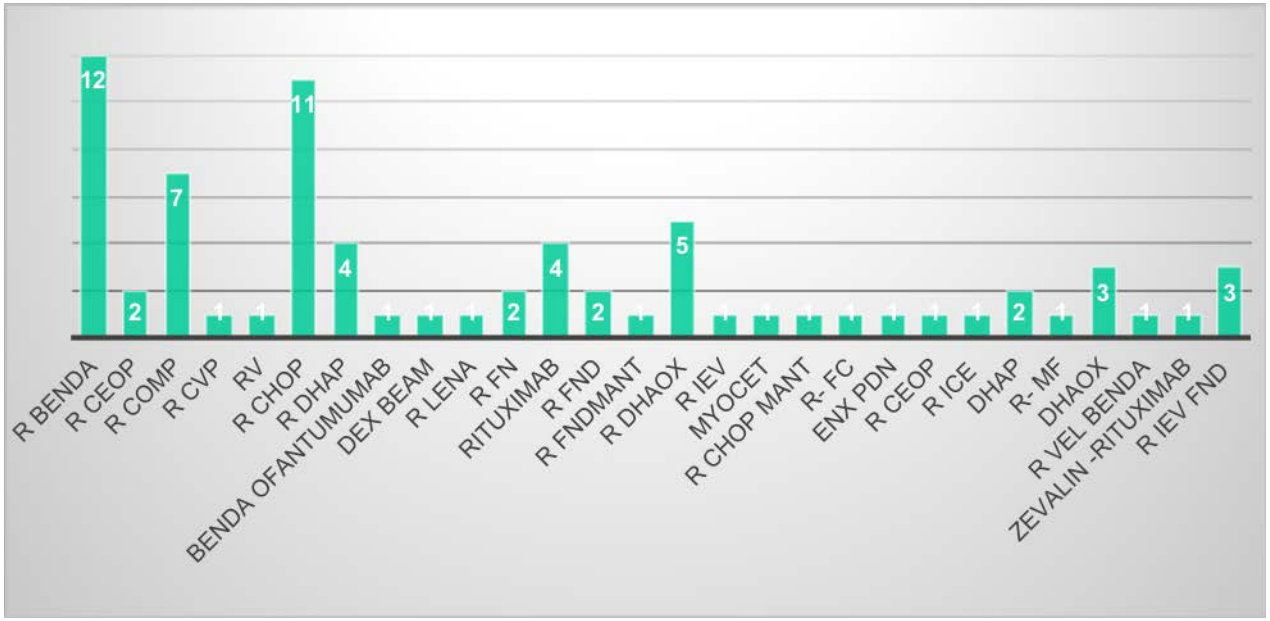
Disposition	n=72
Ongoing, n (%)	7 (9.7)
Discontinued, n (%)	
PD	38 (52.8)
AE	15 (20.8)
Investigator request	4 (5.6)
Death**	5 (6.9)
Withdrew consent	3 (4.2)

Salles, ASCO, 2015, 8529

Results of a multicentre UK-wide compassionate use programme evaluating the efficacy of idelalisib monotherapy in relapsed, refractory follicular lymphoma

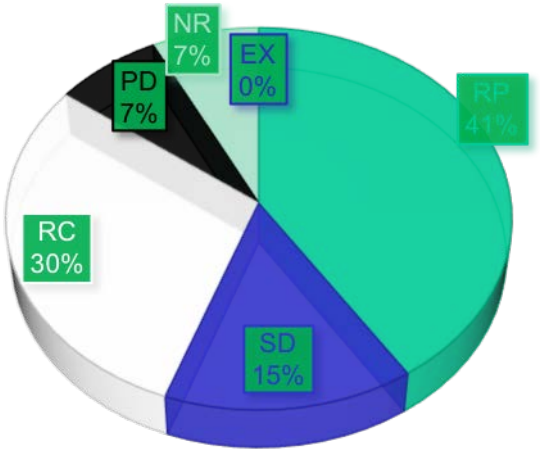
Characteristic	Phase II trial (Gopal *et al*, 2014) (n = 72)	Retrospective cohort (present study) (n = 79)
Median age (range), years	62 (33–84)	64 (29–86)
>60 years	Not available	51/79 (65%)
Gender		
Male	39 (54%)	40 (51%)
Female	33 (46%)	39 (49%)
ECOG performance score		
0–1	66 (92%)	59 (75%)
2–4	6 (8%)	20 (25%)
Median NHL duration (range), years	4·7 (0·8–18·4)	4·5 (0·4–24·6)
Baseline tumour assessment		
Refractory	62 (86%)	41 (54%)
Relapsed	10 (14%)	35 (46%)
		3 unclassifiable
Histology – DLBCL at any time point		
Yes	0 (0%)	7 (9%)
No	72 (100%)	72 (91%)
Ann Arbor staging		
1–2	12 (17%)	12 (15%)
3–4	60 (83%)	67 (85%)
FLIPI score		
0–2	33 (46%)	19 (25%)
3–5	39 (54%)	59 (75%)
		1 unclassifiable
Response to most recent chemotherapy		
CR/CRu	Not available	19
PR		29
SD		16
PD		13
		2 unavailable

TERAPIE PRE IDELALASIB

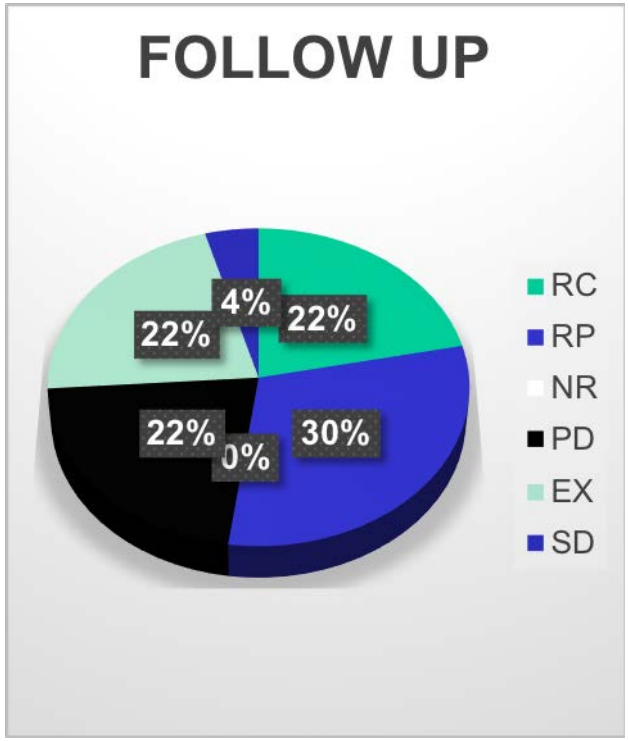


RISPOSTA ULTIMA TERAPIA PRIMA DI IDELALISIB

Response (n=)	n (%)
RP	11
SD	4
RC	8
PD	2
NR	2
EX	0



RISPOSTA POST IDELALISIB



RC	5
RP	7
NR	0
PD	5
EX	5
SD	1

Idelalisib – 3a FL: treatment response

Idealisib Response	
N(%)	
CR	1 (10)
PR	4 (40)
PD+NR	2 (20)
NV	2 (20)

PRINCIPALI EVENTI AVVERSI

Adverse event		n (%)
Hematological toxicity	**Grade, n (%)**	
	Any	**>= 3**
Anemia	2(7)	1(3)
Thrombocitopenia	3(10)	2(7)
Neutropenia	2(7)	1(3)

Idelalisib Treatment Is Associated With Improved Cytopenias in Patients With Relapsed/Refractory iNHL and CLL

Susan M O'Brien,[1] Andrew J Davies,[2] Ian W Flinn,[3] Ajay K Gopal,[4] Thomas J Kipps,[5] Gilles A Salles,[6] Terry Newcomb,[7] Christopher C Waldapfel,[7] Zhihai Zhang,[7] Stephan Stilgenbauer[8]

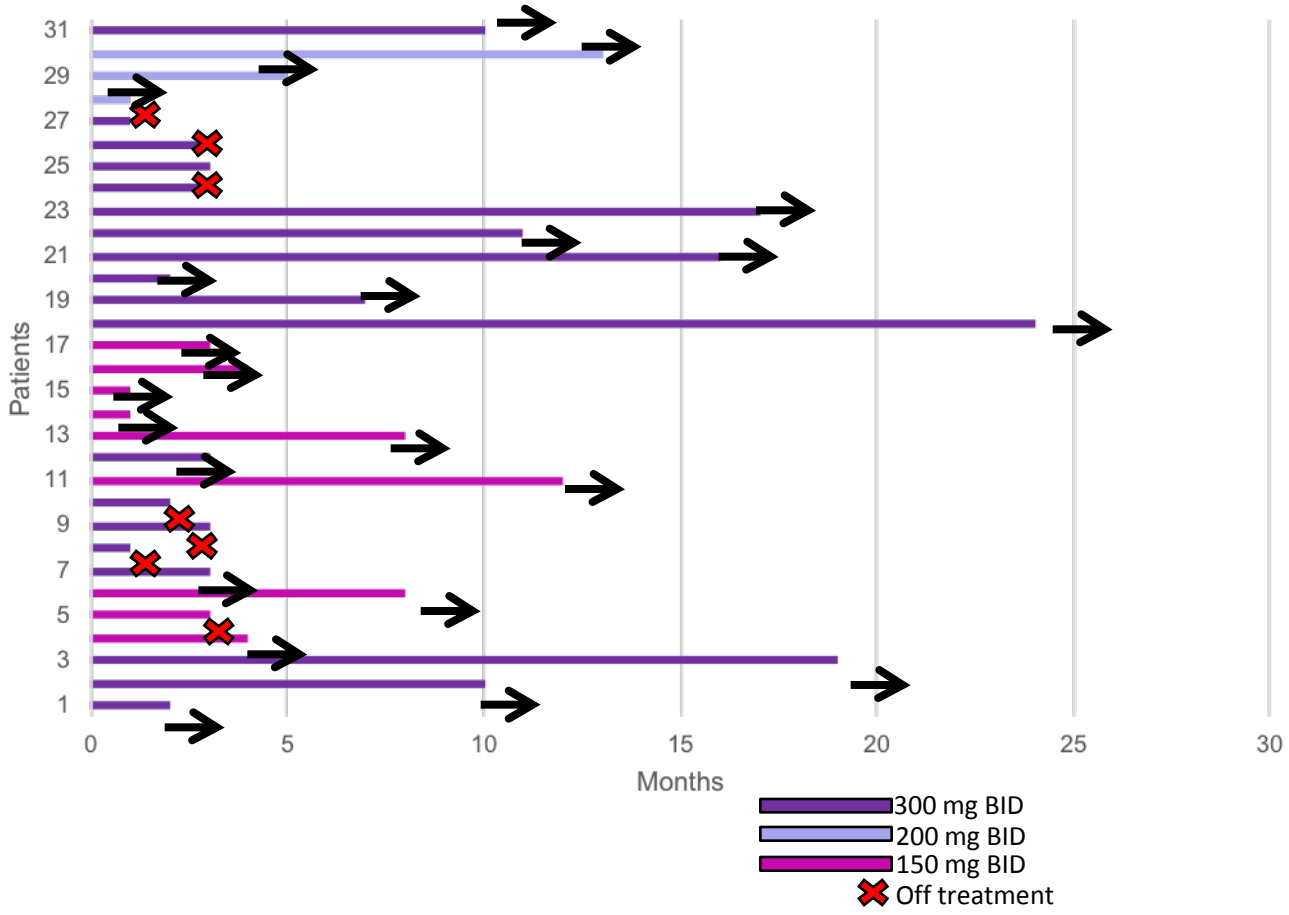
[1]University of California, Irvine/Chao Family Comprehensive Cancer Center, Orange, CA, USA; [2]Cancer Sciences Unit, University of Southampton, Salisbury, UK; [3]Hematologic Malignancies Research Program, Sarah Cannon Research Institute, Nashville, TN, USA; [4]Division of Medical Oncology, University of Washington School of Medicine, Seattle, WA, USA; [5]Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA; [6]Hospices Civils de Lyon, University Claude Bernard, Pierre-Benite, France; [7]Gilead Sciences, Inc., Foster City, CA, USA; [8]University of Ulm, Ulm, Germany

Presented at 2015 ASH Annual Meeting; December 5–8, 2015; Orlando, FL, USA. Poster #1747

PRINCIPALI EVENTI AVVERSI

	Grade, n (%)	
	Any	**>=3**
Increased AST/ALT	4(13)	2(7)
Diarrhea	2(7)	1(3)
Rash	1(3)	0
Oral Mucositis	1(3)	1(3)
Oral Candidiasis	2(7)	1(3)

Individual Patient Results



Treatment Disposition at time data cutoff , n%

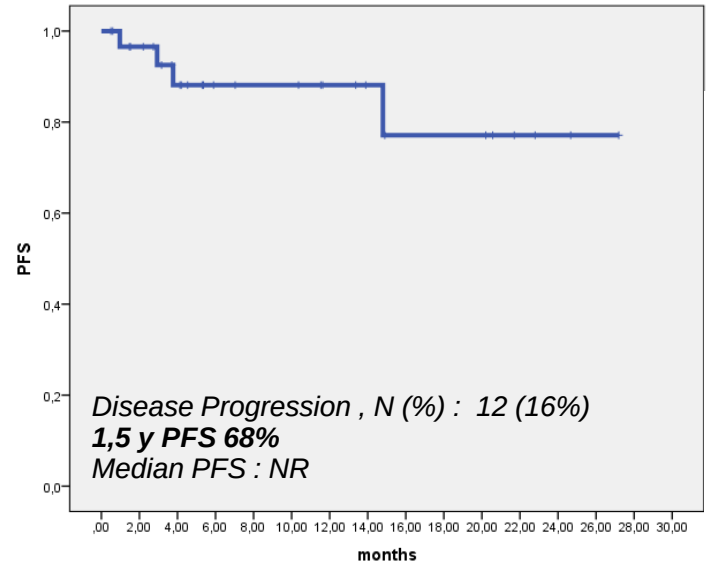
	N (%)	Cause of Discontinued
Ongoing	24 (77)	
Idealisib Discontinued	7 (23)	2 TOXICITY 5 Progressive Disease(Death)

	N (%)
Idealisib Reduction dose	4 (13)

Reasons for Discontinuation of First KI

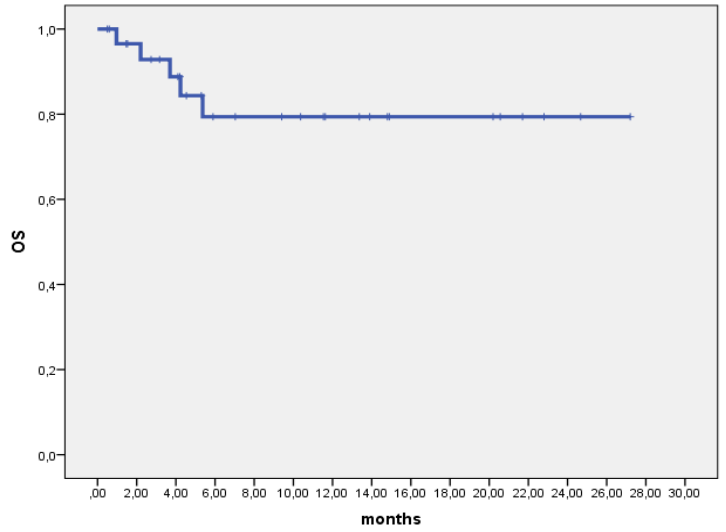
Common Toxicities Leading to discontinuation

Discontinuation	IDELA n=31
Total discontinuations, n	7
Discontinuation rate, %	(23)
Toxicity Transaminitis	2(6)
Progression	5 (16)
Richter's transformation	0
Secondary malignancy	0
Other	0



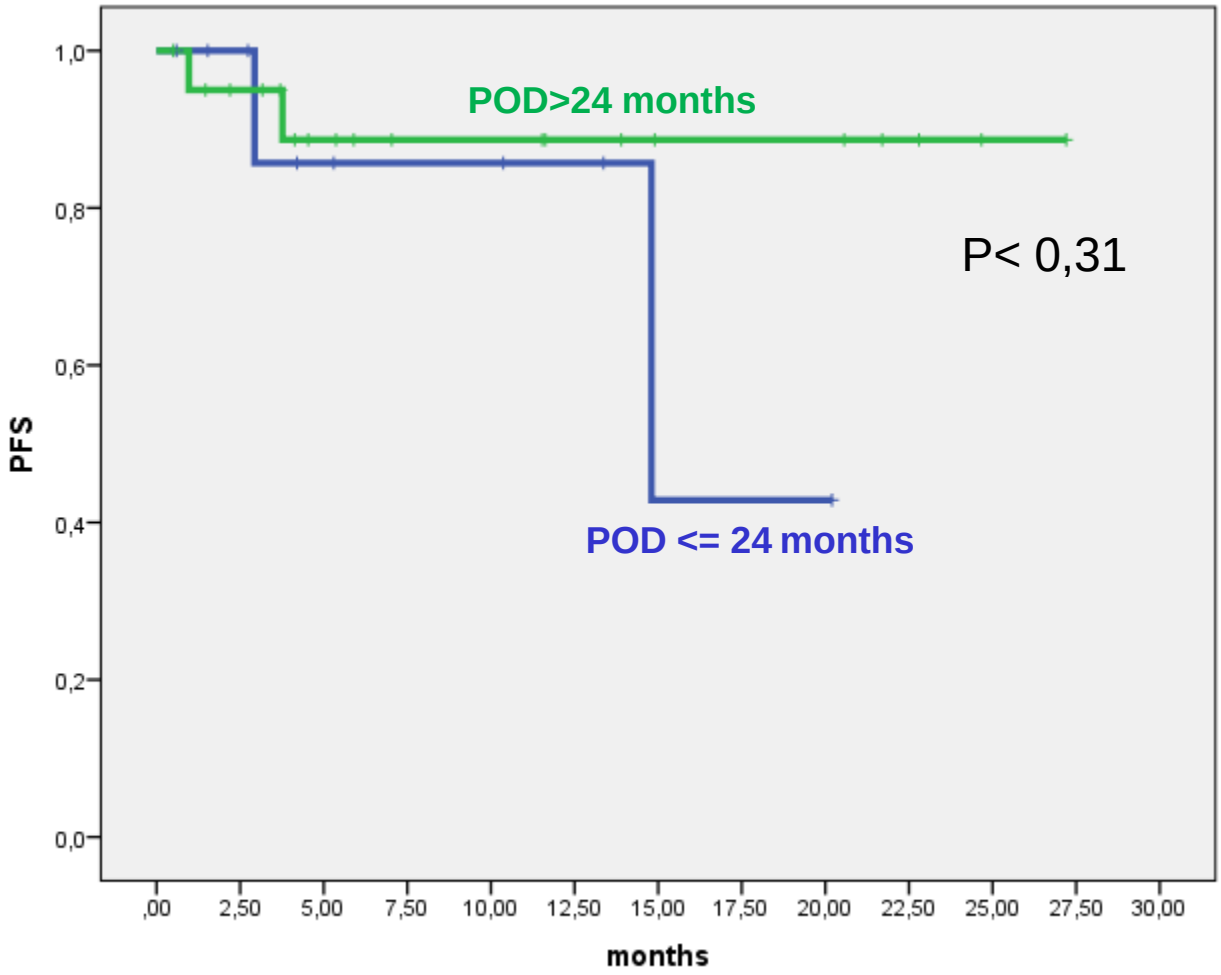
Disease Progression , N (%) : 12 (16%)
1,5 y PFS 68%
Median PFS : NR

Median Follow-up: 5,9 months (0,5-27)



Disease Progression , N (%) : 5 (16%)
1,5 y OS 80%
Median PFS : NR

Median Follow-up: 5,3 months (0,5-27)



POD <=24 months	Disease Progression , N (%) : 2 (20%); Median PFS 14,8 months (IC95%: 1-31)
POD > 24 months	Disease Progression , N (%) : 2 (9%); Median PFS : NR

Conclusioni

- Età mediana dei pz. pugliesi più alta che negli studi in letteratura
- Maggiore percentuale di gradi III A (anche rispetto ai real life)
- Minor numero di linee di terapia precedenti
- Minore tossicità
- Maggiore efficacia
- POD 24

SGR: MCL R/R trattati con Ibrutinib N=11 pazienti

M 4 (36%) F 7 (64%)

Mediana di trattamento 5 mesi (range,1-49)

Pazienti ancora in trattamento n=6 (55%)

1 paziente in trattamento, Ibr dopo recidiva di ASCT (+ 2 anni).
1 paziente ha effettuato Ibr per 1 anno «bridge to Allo TMO». PET- al momento dell'Allo TMO.

SGR: LLC R/R Idelalisib+R
N=9 pts

M 6 (67%) F 3 (33%)

Mediana di trattamento 7 mesi (range,1-23)

Pts in trattamento n=5 (56%)

Eventi avversi che hanno determinato la sospensione/discontinuazione del trattamento: 1 Polmonite, 3 Colite (dopo 7-9 mesi di trattamento), 1 Transaminite.