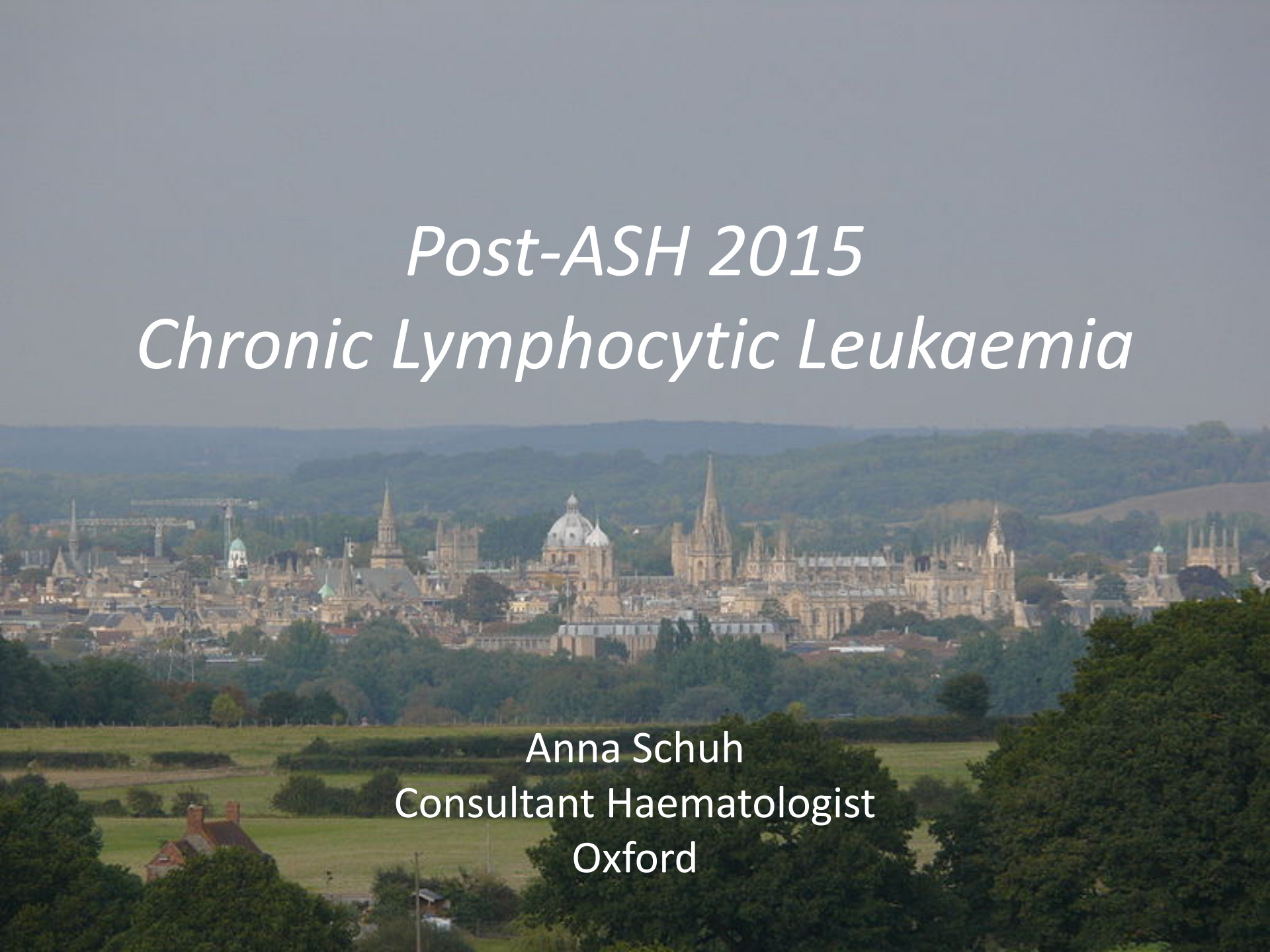
Post-ASH 2015
Chronic Lymphocytic Leukaemia



Anna Schuh
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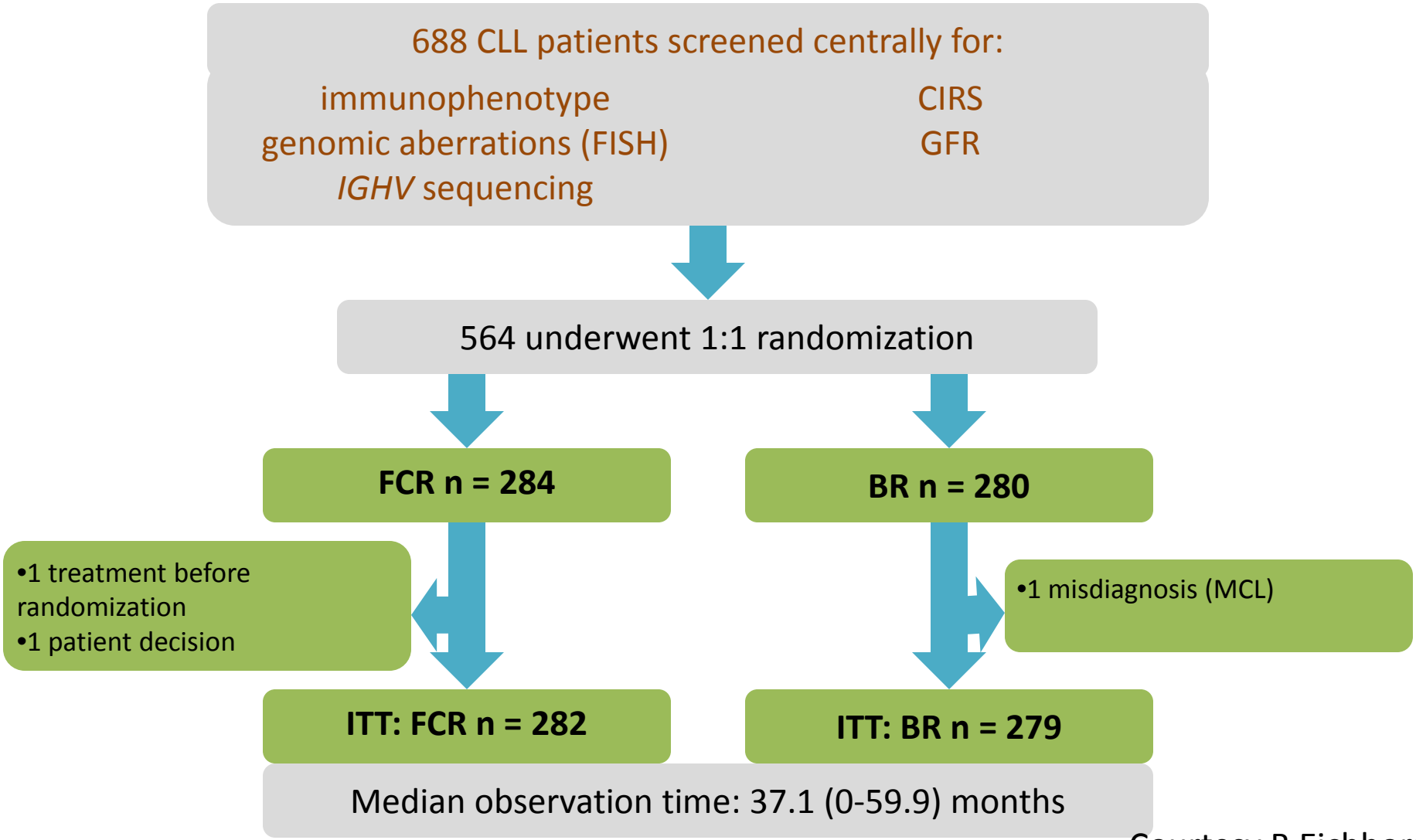
Oxford

NEWS IN FRONT-LINE

CLL10 Study: FCR VS BR in Front-line

DEUTSCHE STUDIENGRUPPE

Consort Diagram



Courtesy B Eichhorst

CLL10 Study: FCR VS BR in Front-Line

DEUTSCHE STUDIENGRUPPE

Patients´ characteristics: prognostic factors

Baseline prognostic factors	FCR n=282	BR n=279	p value
Binet stage A	22.3%	22.2%	
Binet stage B	37.3%	38.4%	0.846
Binet stage C	40.4%	39.4%	
IGHV Unmutated	55.3%	67.8%	0.003
11q deletion	24.1%	22.6%	0.691
Trisomy 12	12.4%	12.2%	1.000
13q deletion	55.0%	52.7%	0.612
s- TK (U/L) > 10.0	72.8%	72.6%	1.000
s- β2m (mg/l) > 3.5	30.9%	38.1%	0.086

Courtesy B Eichhorst

CLL10 Study: FCR VS BR in FrontLine

DEUTSCHE STUDIENGRUPPE

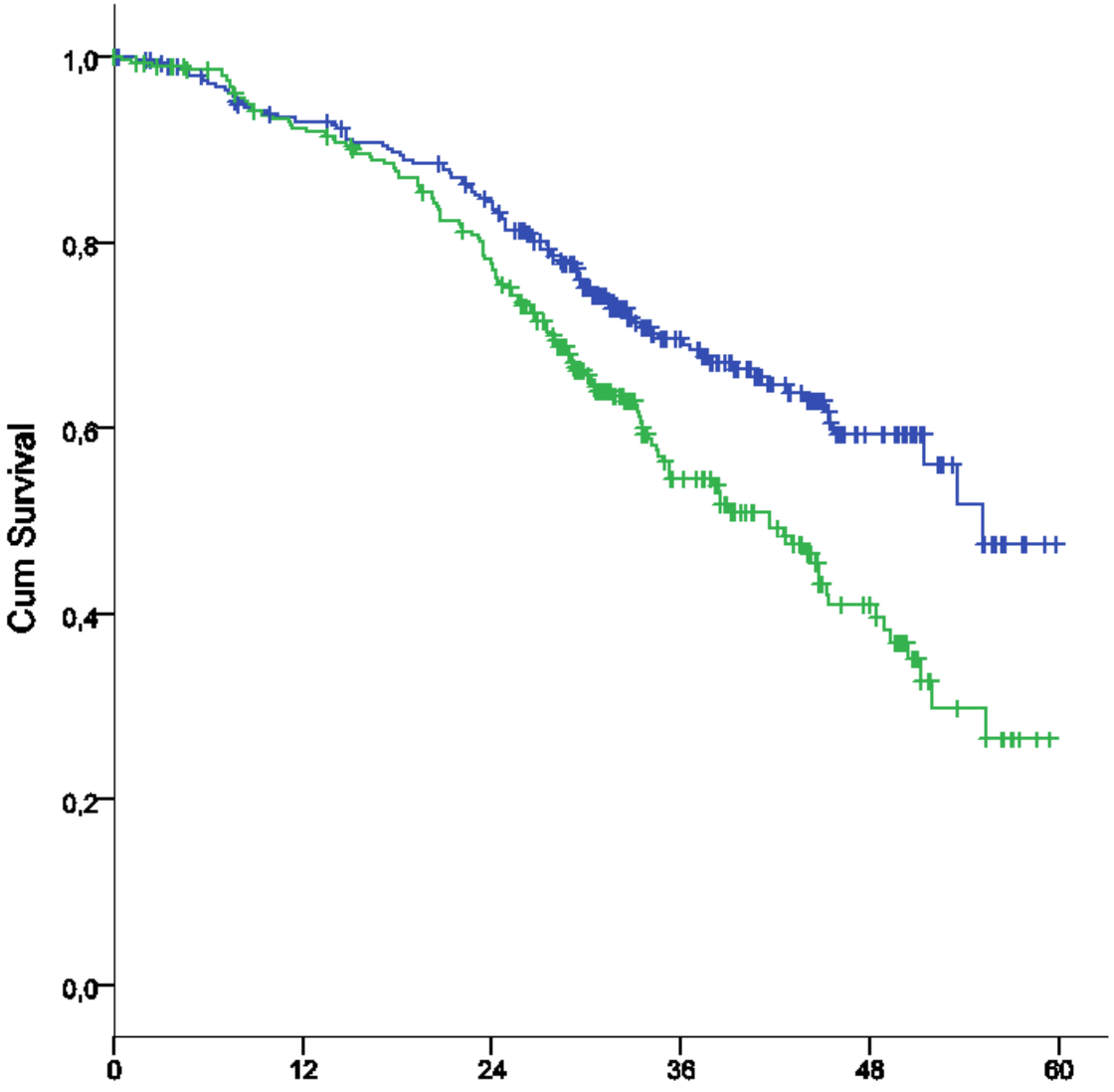
ITT Best Response according to IWCLL

Response	FCR (%) n=282	BR (%) n=279	p value
CR (CR + CRi)	**39.7**	**30.8**	**0.034**
CR	35.1	30.4	
CRi	4.6	0.4	
PR	55.7	64.9	
ORR	**95.4**	**95.7**	**1.0**
SD/PD	2.2	2.2	
Missing response	2.5	2.1	

Courtesy B Eichhorst

CLL10 Study: FCR VS BR in Front-Line

ITT Progression-free survival = Primary endpoint



Median PFS

FCR 55.2 months

BR 41.7 months

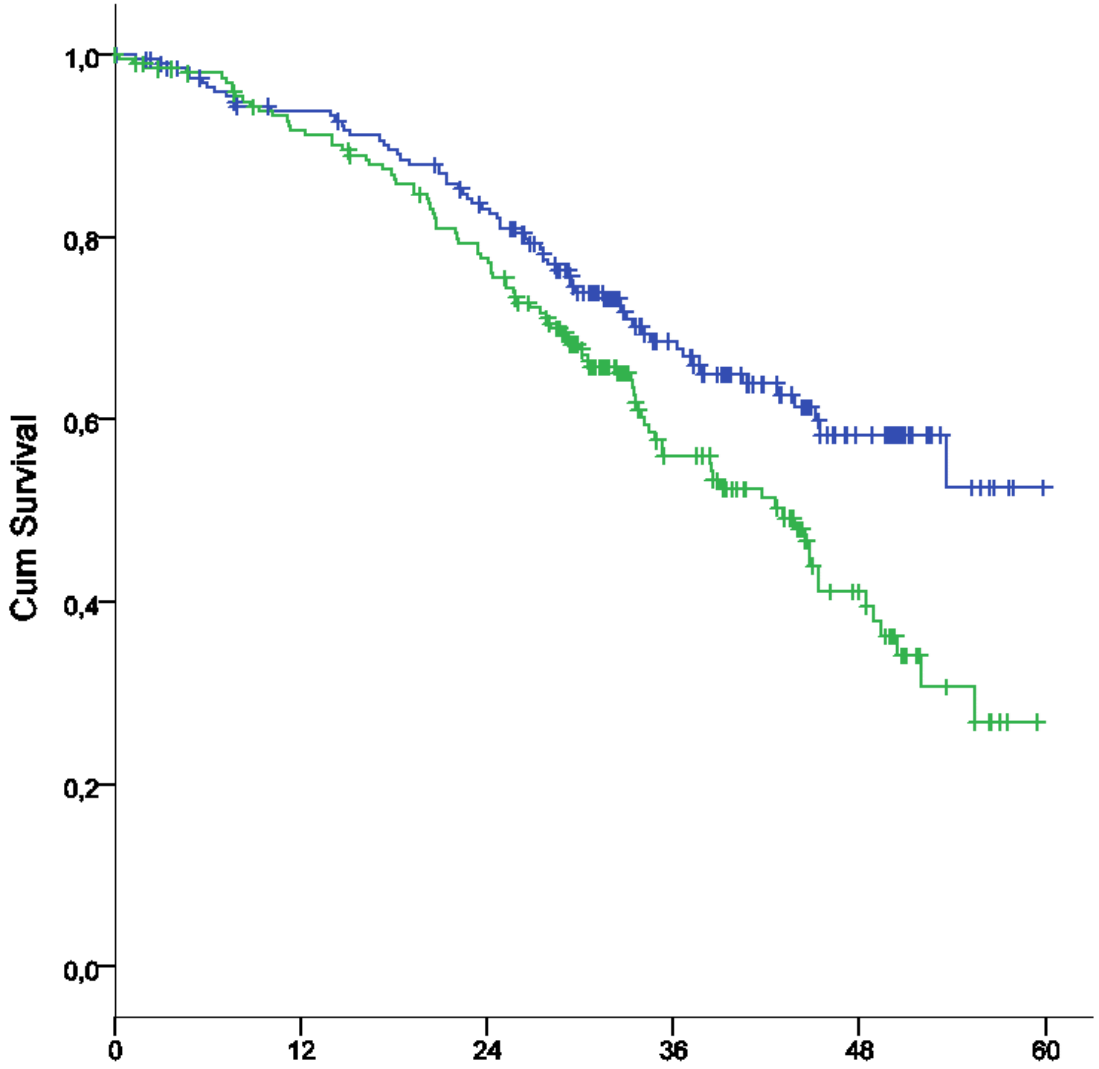
***P* < 0.001**
HR = 1.626 =
> 1.388

Courtesy B Eichhorst

CLL10 Study: FCR VS BR in Front-Line

DEUTSCHE STUDIENGRUPPE

PFS in IGHV matched population (n=398: FCR= 201; BR =197)



Median PFS

FCR NR

BR 43.1 months

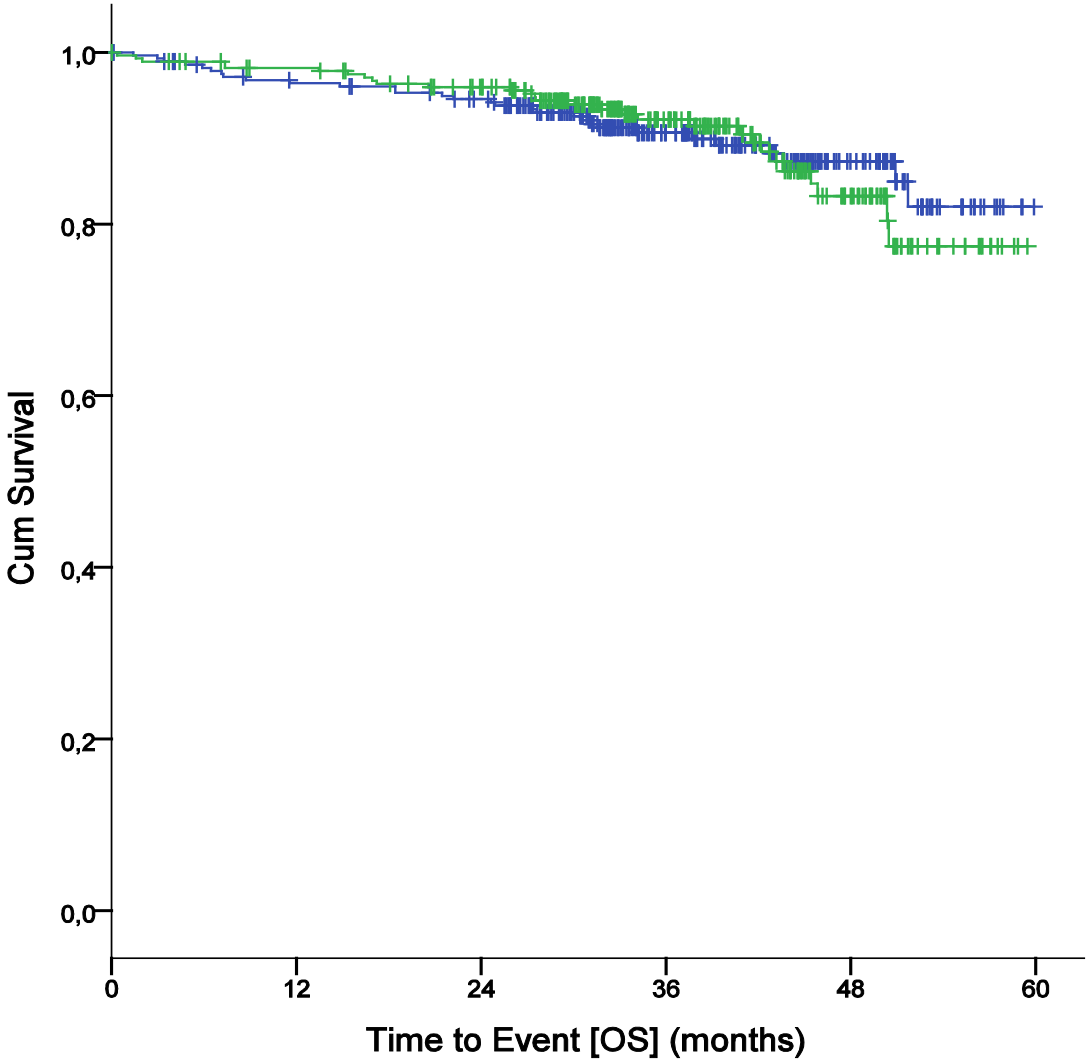
***P* = 0.005**
HR = 1.565 =
> 1.388

Courtesy B Eichhorst

CLL10 Study: FCR VS BR in Front-line

DEUTSCHE STUDIENGRUPPE

Overall survival



OS at 36 months:

FCR 90.6%

BR 92.2%

***P* = 0.897**

Courtesy B Eichhorst

CLL10 Study: FCR VS BR in Front-line

DEUTSCHE STUDIENGRUPPE

Infections CTC 3-4 in detail

Adverse event	FCR (% of pt)	BR (% of pt)	p value
All Infections	**39.1**	**26.8**	**<0.001**
Infections during therapy only	22.6	17.3	0.1
Infections during first 5 months after therapy	11.8	3.6	<0.001
All infections in patients ≤ 65years	35.2	27.5	0.1
All infections in patients > 65years	47.7	20.6	<0.001

Courtesy B Eichhorst

CLL10 Study: FCR VS BR in Front-line

DEUTSCHE STUDIENGRUPPE

Conclusion

Final analysis shows inferiority of BR versus FCR with regard to PFS and CRR.

BR is associated with lower rates of neutropenia and severe infections in elderly patients.

FCR is remains standard therapy in fit patients.

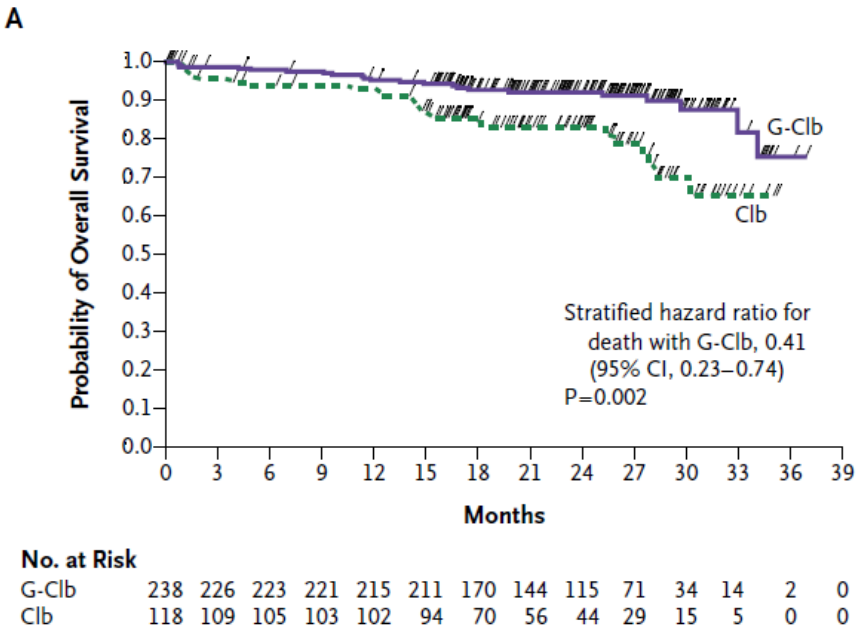
BR may be considered in fit, but elderly patients as alternative.

Courtesy B Eichhorst

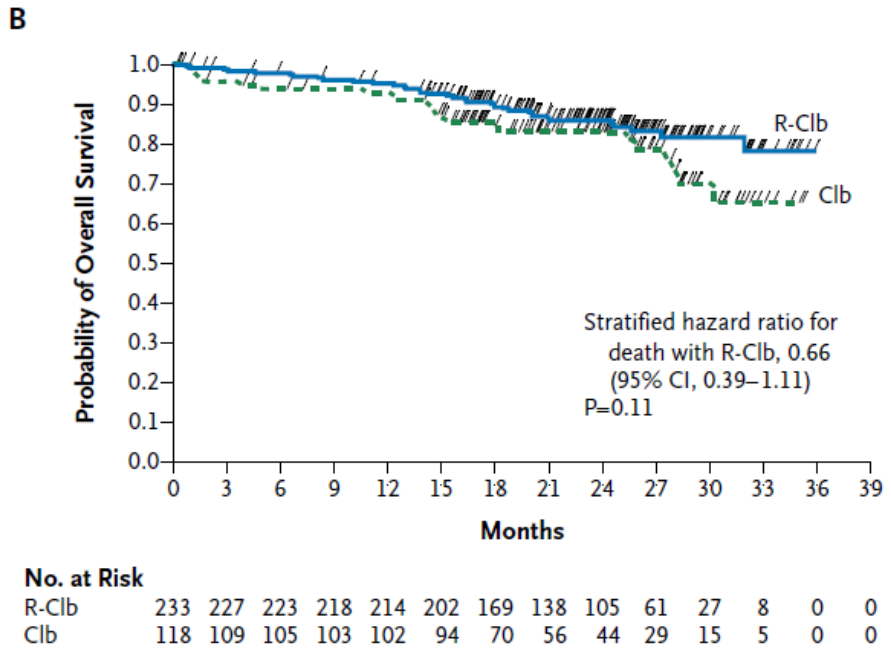
ANTIBODY NEWS

NICE UPDATE: GCCLSG CLL 11

OS: Obinutuzumab + chlorambucil v chlorambucil; P=0.002



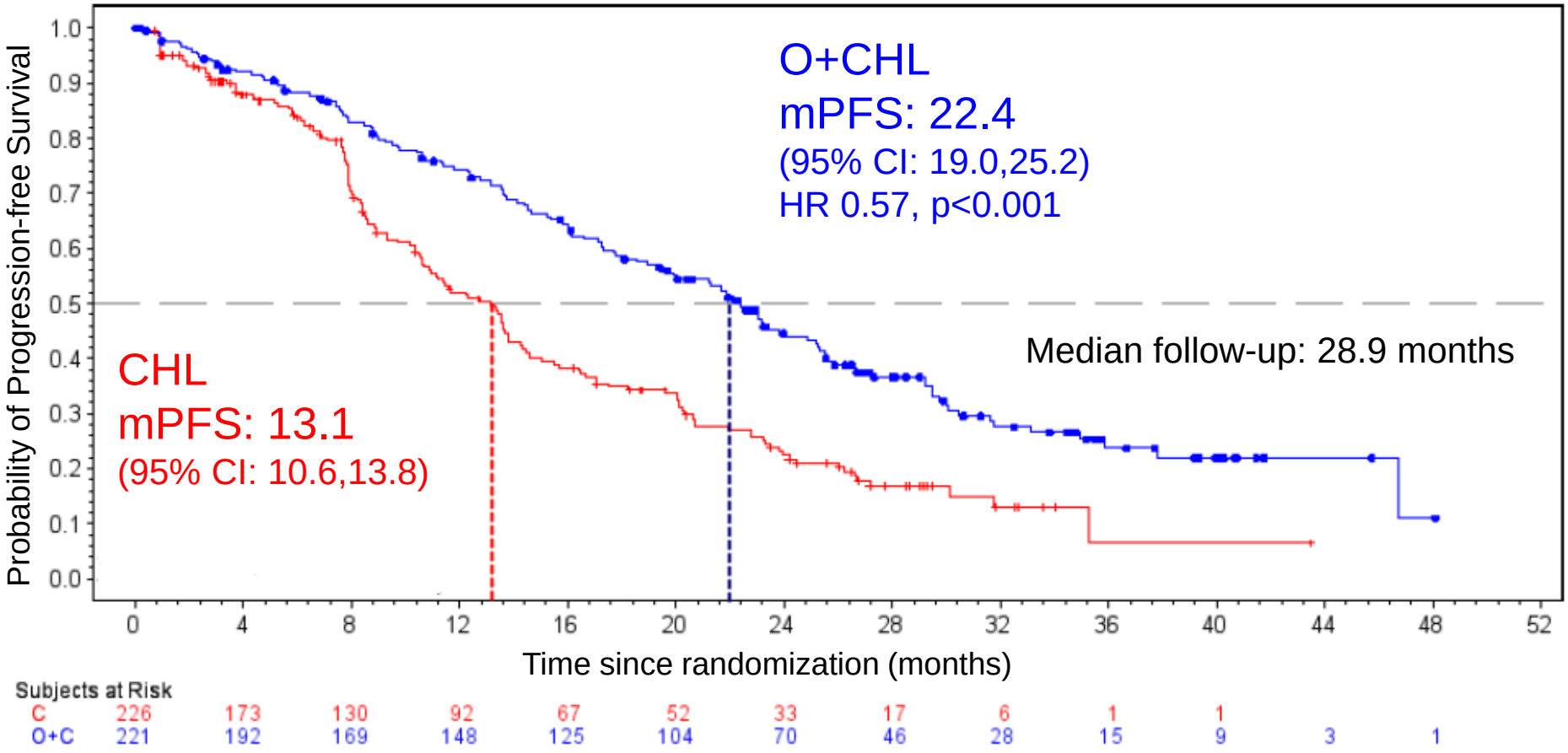
OS: Rituximab + chlorambucil v chlorambucil; P=0.11



Goede et al. N Engl J Med 2014

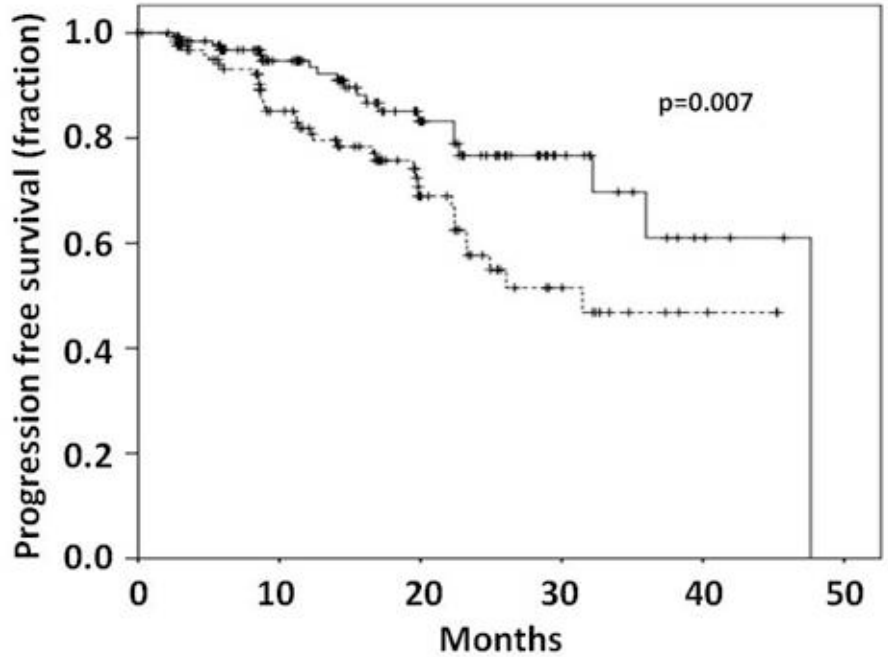
Dose of antibody
Use of steroids
Different mode of action

NICE UPDATE: COMPLEMENT 1



20 Rituximab Maintenance after Chemoimmunotherapy Induction in 1st and 2nd Line Improves Progression Free Survival: Planned Interim Analysis of the International Randomized AGMT-CLL8/a Mabtenance Trial

- 263 Patients were recruited after informed consent at the end of any Rituximab-containing induction treatment in 1st or 2nd line that achieved at least a PR
- 80.6% were enrolled after 1st induction treatment.
- Induction regimen: FCR: 73.5%, BR: 20.2%, CR/Cri : 58%, PR: 41.8%, 57% MRD
- SAE causes were well balanced between arms, but infectious SAEs - 32 in the rituximab and 22 in the observation arm, 3 deaths were attributed to infections (1 in the rituximab arm and 2 in the observation arm) - and secondary malignancies (8 in the rituximab arm vs. 1 in the observation arm). Four of the neoplasms in the rituximab arm were localized non-melanoma skin cancers and the 2 deaths from melanomas occurred one in each arm.

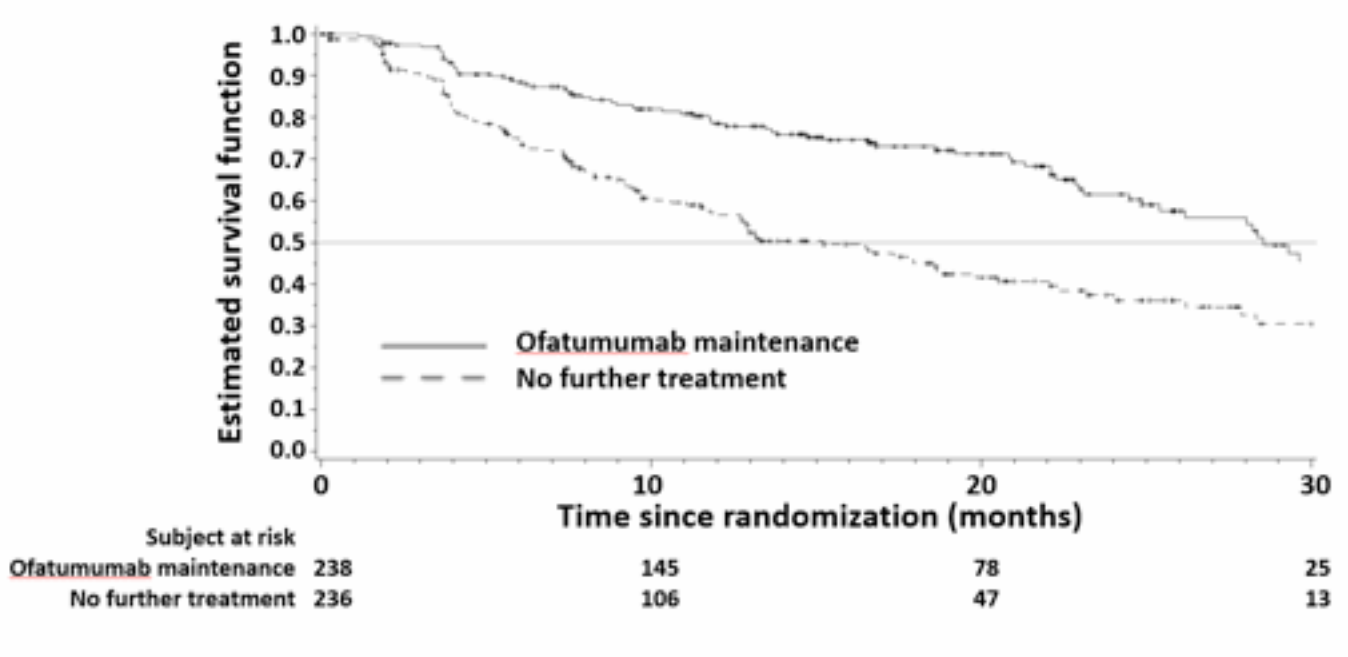


Median observation time: 17.3 months

21 Ofatumumab (OFA) Maintenance Prolongs PFS in Relapsed CLL: Prolong Study Interim Analysis Results

474 Pts in CR or PR after 2nd or 3rd line treatment for CLL were randomized 1:1 to receive OFA (300 mg followed 1 week later by 1000 mg every 8 weeks for up to 2 years) or observation.

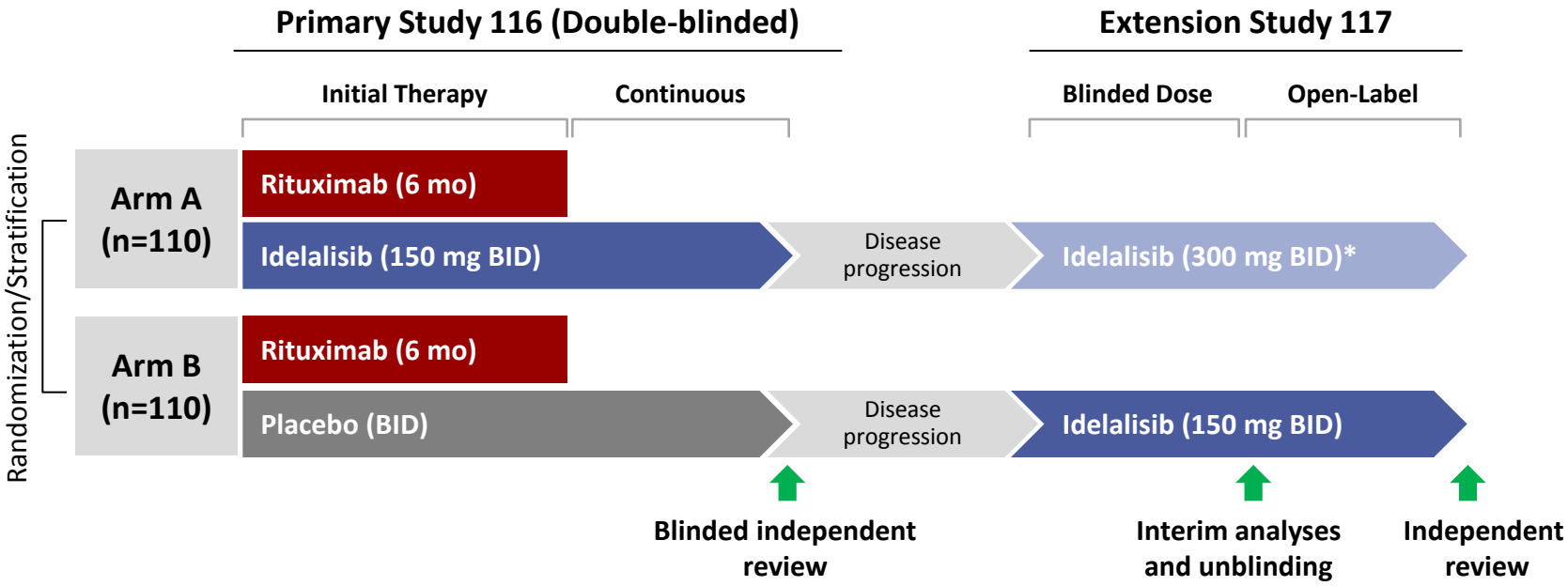
Grade 3-4 infections were 18% OFA vs. 13% obs. The most common (>5% of all pts) grade 3-4 AEs that occurred were neutropenia (22% OFA vs. 9% obs) and pneumonia (7% OFA vs. 4% obs). Death rate was similar in both arms (14%). AEs that lead to permanent discontinuation of treatment occurred in 8% OFA pts.



median follow-up was 25 months

KINASES

330 Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors (ASH 2014)

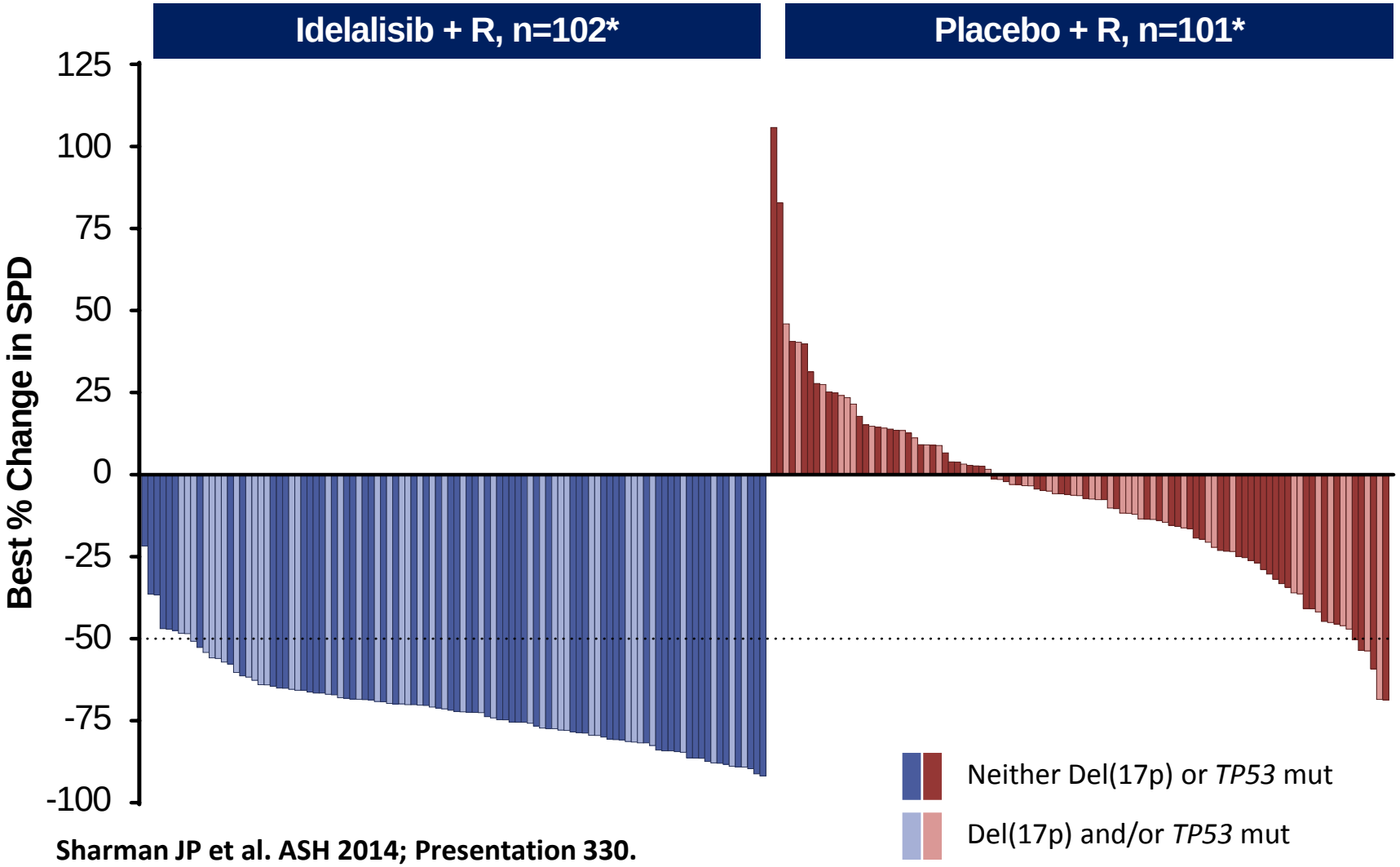


- DMC recommended early study stop after first Interim Analysis (IA)[1]
- Second IA[2] conducted at end of blinded-phase according to amendment; per amended protocol, patients without progression on
  - Arm A continued idelalisib 150 mg BID
  - Arm B received idelalisib 150 mg BID

Sharman JP et al. ASH 2014; Presentation 330.

*4 patients received 300 mg BID idelalisib. 1. Furman R, et al. N Engl J Med 2014;370:997-1007; 2. Coutre S, et al. ASCO 2013, oral presentation.

Lymph Node Response, 2nd Interim Analysis

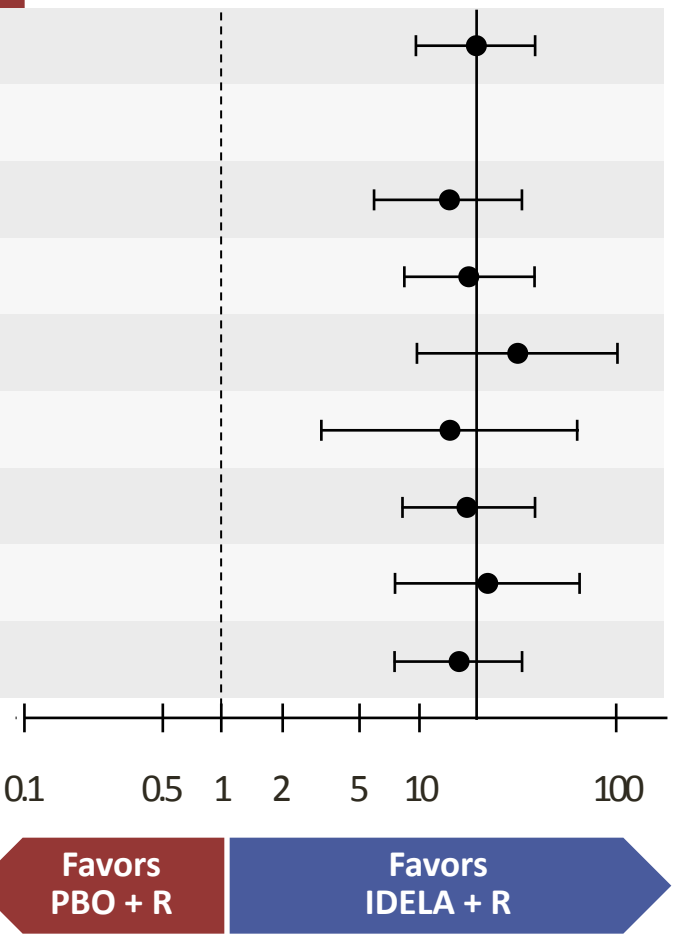


Sharman JP et al. ASH 2014; Presentation 330.

*Evaluable patients.

Overall Response Rates, 2nd Interim Analysis

	IDELA + R % (n)*	Placebo + R % (n)*
All patients	77 (106)	15 (107)
Subgroup		
Rai Stage III/IV	70 (67)	13 (70)
Unmutated *IGHV*	77 (87)	16 (90)
Del(17p)/*TP53* mutation	82 (44)	13 (47)
Del(11q)	68 (25)	17 (23)
ZAP70+	76 (94)	17 (91)
CD38+	78 (59)	16 (49)
ß2-microglobulin: >4 mg/L	77 (90)	16 (80)

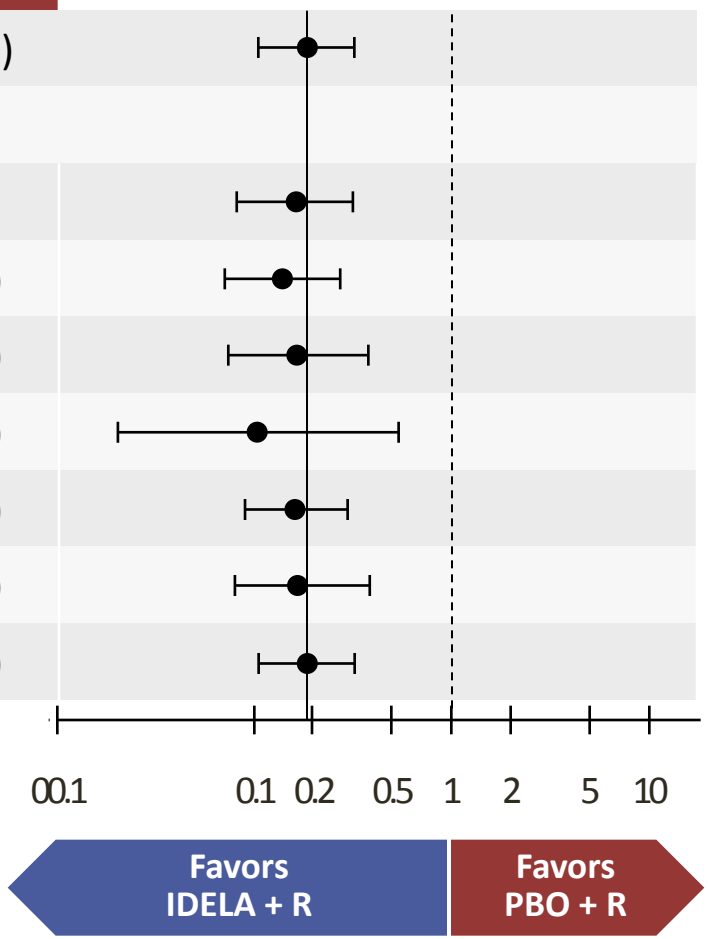


Sharman JP et al. ASH 2014; Presentation 330.

*Evaluable patients (with at least one follow-up assessment) at time of analysis.

Progression-Free Survival, 2nd Interim Analysis

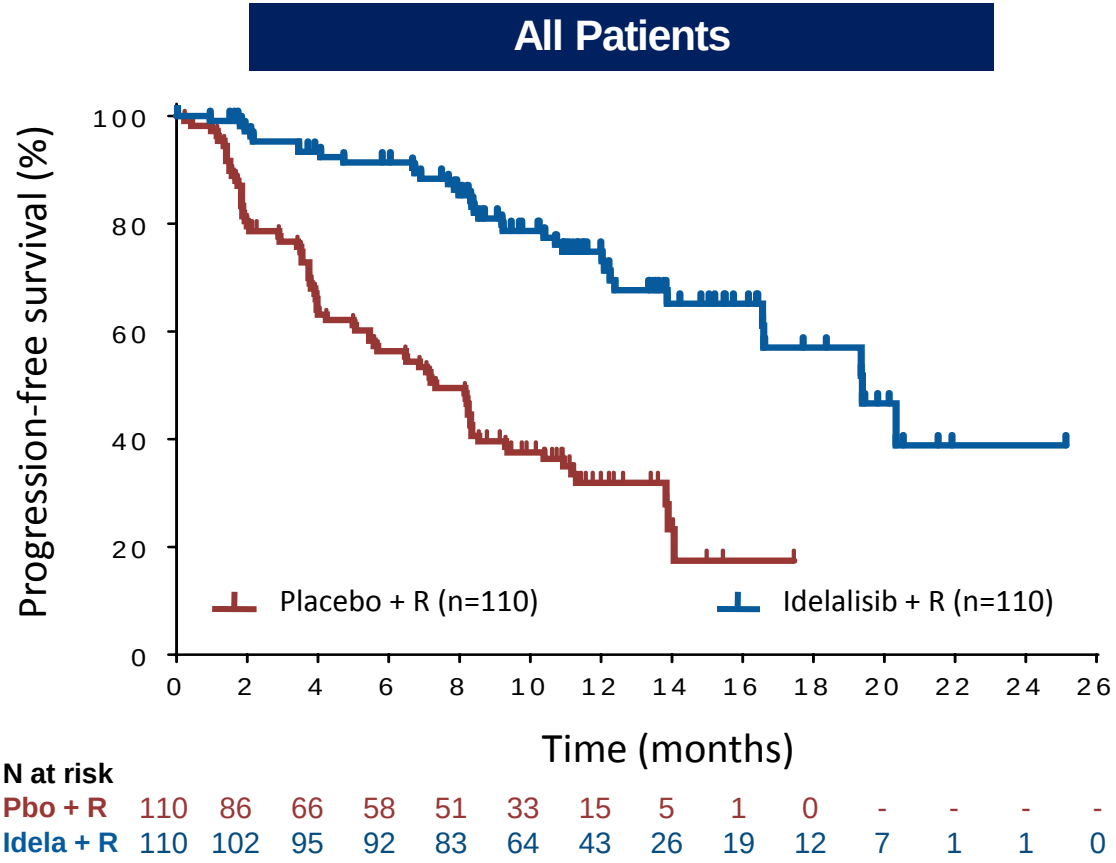
	IDELA + R PFS (n)	Placebo + R PFS (n)
All patients	NR (110)	5.5 (110)
Subgroup		
Rai Stage III/IV	NR (70)	13 (72)
Unmutated *IGHV*	NR (91)	5.5 (93)
Del(17p)/*TP53* mutation	NR (46)	4.0 (49)
Del(11q)	10.7 (25)	6.9 (23)
ZAP70+	NR (98)	5.5 (93)
CD38+	NR (62)	6.9 (51)
ß2-microglobulin: >4 mg/L	NR (94)	5.0 (83)



Sharman JP et al. ASH 2014; Presentation 330.

PFS, Including Extension Study*

Idelalisib + R vs Placebo + R



	Median PFS (95% CI)	HR (95% CI)	p-value
Pbo + R	7.3 mo (5.5, 8.5)	0.25 (0.16, 0.39)	<0.0001
Idela + R	19.4 mo (16.6, NR)		

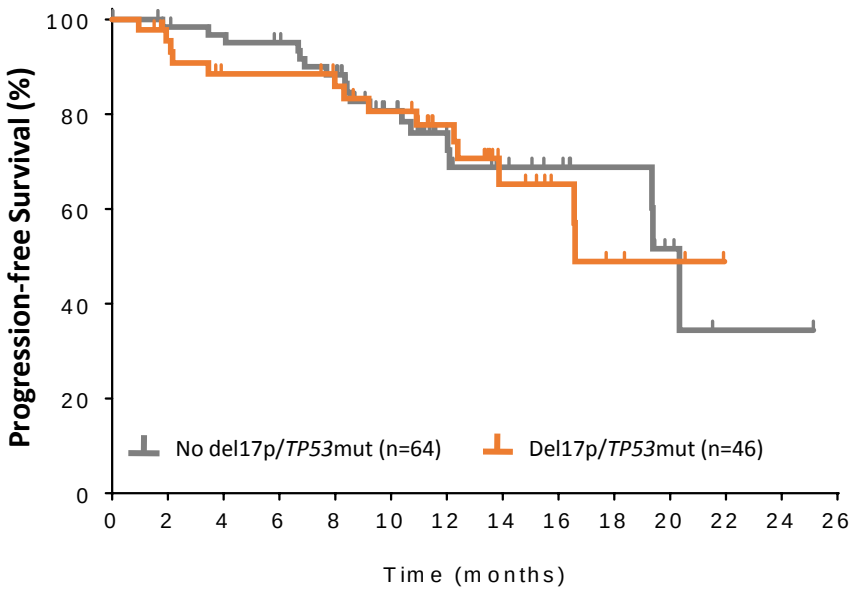
Sharman JP et al. ASH 2014; Presentation 330.

*Placebo + R includes patients who received open-label idelalisib after unblinding without prior progression (n=42).

PFS Subgroup Analysis

Idelalisib + R (n=110)

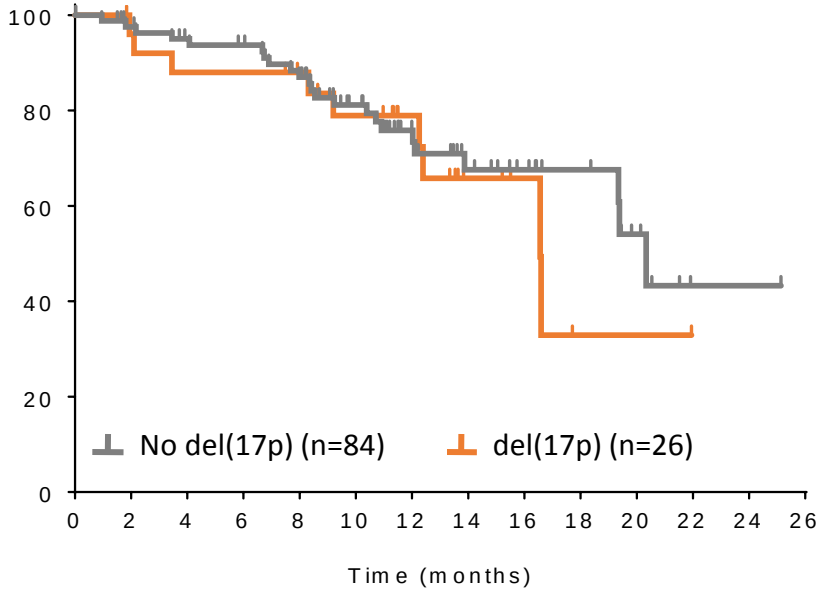
Del17p/TP53mut: Present vs Not Present



N at Risk														
No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0	0	0

	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, NR)	0.94
Del	16.6 mo (13.9, NR)	

Del17: Present vs Not Present



	84	78	73	71	65	49	31	20	15	11	6	1	1	1
	26	23	22	22	20	17	12	6	4	1	1	0	0	-

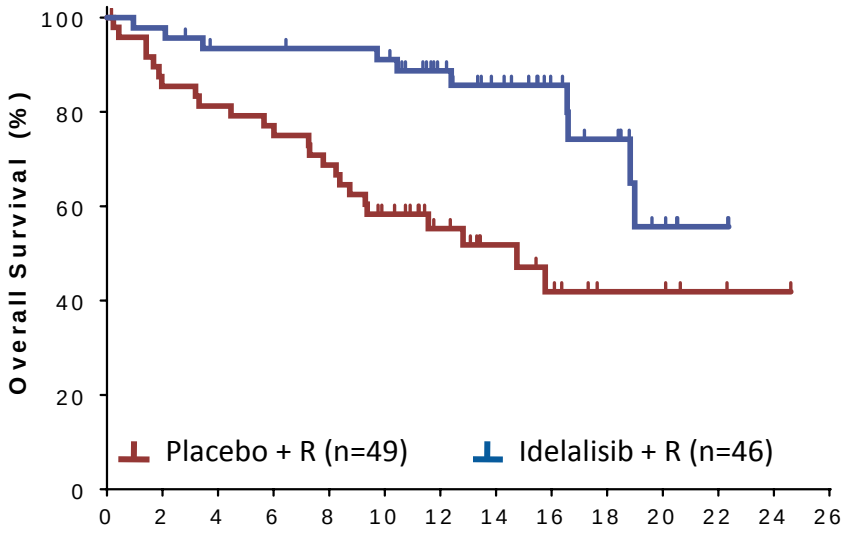
	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, NR)	0.55
Del	16.6 mo (12.3, NR)	

Sharman JP et al. ASH 2014; Presentation 330.

Overall Survival, Including Extension Study*

Idelalisib + R vs Placebo + R → Idealisib

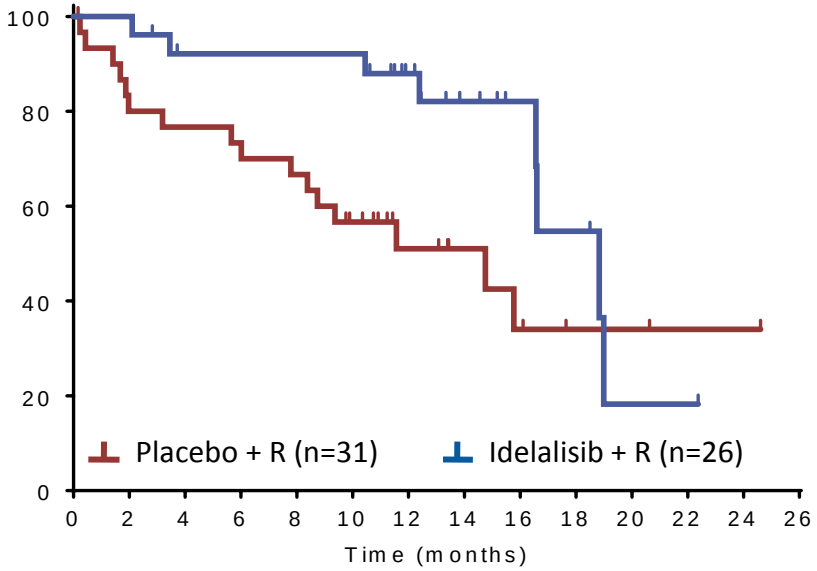
Del17p/TP53 Mutation (Either)



N at risk														
Pbo + R	49	41	39	37	33	25	17	11	8	4	4	2	1	0
Idela + R	46	45	41	41	40	39	30	23	16	12	5	2	0	0

	Median OS (95% CI)	HR (95% CI)	p-value
PBO + R	14.8 mo (8.4, NR)	0.31 (0.15, 0.65)	0.0011
IDELA + R	NR (18.8, NR)		

Del17p Positive



	31	24	23	22	20	15	9	6	4	2	2	1	1	0
	26	26	22	22	22	22	16	10	6	4	1	1	0	-

Median OS (95% CI)	HR (95% CI)	p-value
14.8 mo (7.8, NR)	NA	0.04
18.8 (16.6, NR)		

Sharman JP et al. ASH 2014; Presentation 330.

*As randomized, including crossover study.

Adverse Events* in ≥15% of Patients

Idelalisib + R vs Placebo + R → Idealisib

	Idelalisib + R		Placebo + R → Idelalisib†	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
Any AE	98	80	100	78
Pyrexia	44	6	32	3
Diarrhea/Colitis	42	16	44	13
Fatigue	36	5	43	5
Cough	34	2	44	2
Nausea	31	2	36	1
Chills	26	2	22	–
Infusion reaction	20	–	32	4
Constipation	19	–	21	1
Decreased appetite	19	2	17	3
Pneumonia	18	13	31	20
Dyspnea	17	6	25	5
Rash	17	3	12	1
Vomiting	17	–	21	1
Upper respiratory infection	15	1	24	2
Edema, peripheral	15	–	19	3
Night sweats	14	2	20	–
Asthenia	12	–	19	6
Abdominal pain	10	2	19	2

Sharman JP et al. ASH 2014; Presentation 330.

*By preferred term; †Includes Extension Study.

Select Lab Abnormalities

Idelalisib + R vs Placebo + R → Idealisib

	Idelalisib + R		Placebo + R → Idelalisib	
	Any Grade, %	Grade ≥3, %	Any Grade, %	Grade ≥3, %
ALT/AST elevation	49	6	53	6
Neutropenia	66	41	68	43
Anemia	33	8	50	24
Thrombocytopenia	29	14	40	20

Sharman JP et al. ASH 2014; Presentation 330.

RESONATE: ASCO update
Additional adverse events of interest

Atrial fibrillation[1]

- Any-grade: 10 ibrutinib-treated patients versus 1 ofatumumab-treated patient
- Grade 3 or higher: 3% in the ibrutinib group versus 0% in the ofatumumab group
- Atrial fibrillation led to discontinuation of ibrutinib in only 1 patient
- No evidence of arrhythmias has been observed among patients receiving ibrutinib in clinical studies [2,3]

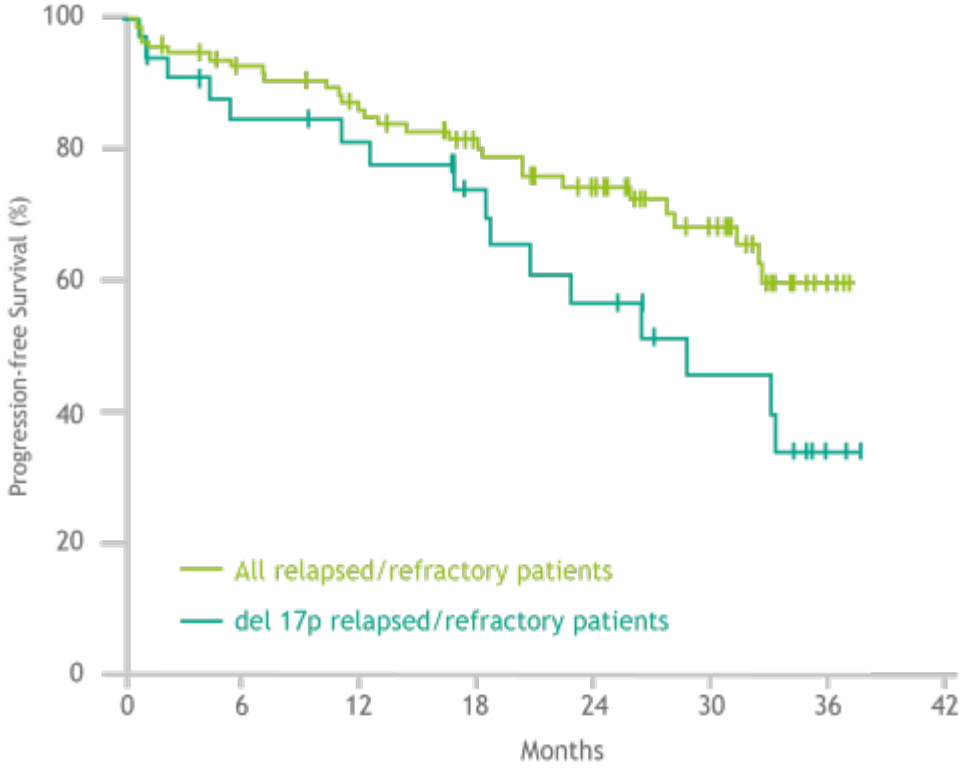
Bleeding events[1]

- Any grade bleeding events (most common petechiae, including ecchymoses) were more frequent with ibrutinib versus ofatumumab (44% vs 12%)
- A haemorrhagic event of grade 3 or higher or resulting in transfusion of red cells or in hospitalization, was reported in only 2 ibrutinib-treated patients (1%) versus 3 ofatumumab-treated patients (2%)

1. Byrd JC, et al. N Engl J Med, 2014;371:213-23. 2. Byrd JC, et al. N Engl J Med. 2013;369:32-42.
3. Advani RH, et al. J Clin Oncol. 2013;31:88-94.

Long-term follow up
Progression-free survival

Progression-free survival with IMBRUVICA® [1]



Graph adapted from O'Brien SM, et al. 2014.

* Long-term, follow-up study (PCYC-1102/1103) in CLL/SLL patients. [1]

Single-agent IMBRUVICA® therapy provided durable remissions in relapsed or refractory CLL.[1]

68.4% of patients were estimated to be progression free at 30 months[1]

•Median PFS not yet reached

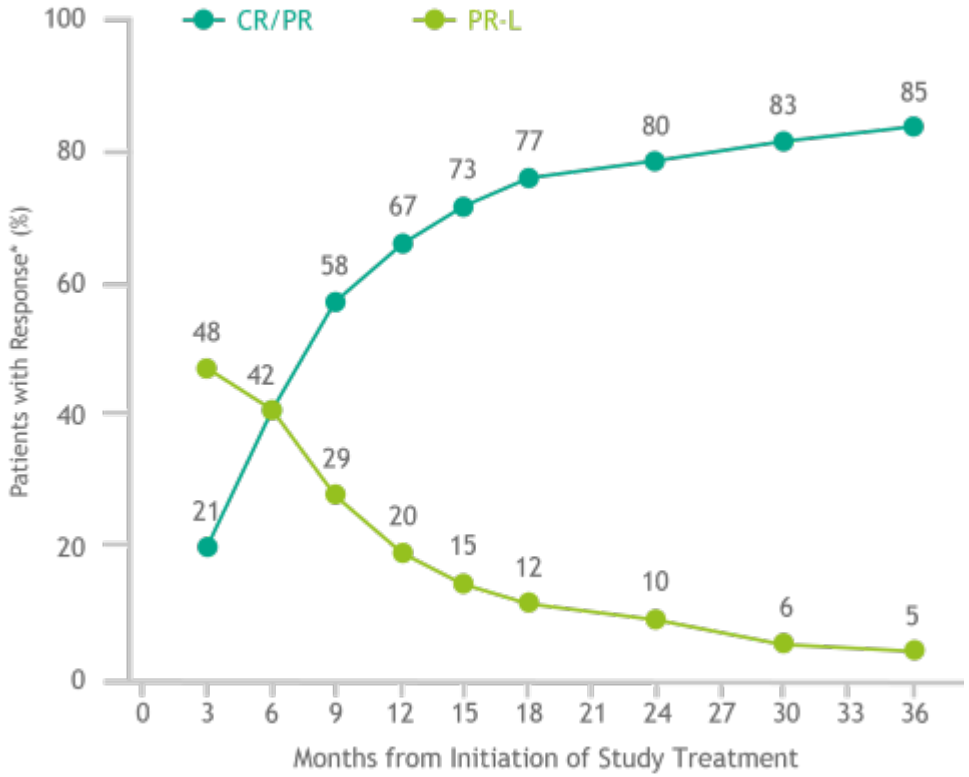
45.9% PFS at 30 months in relapsed/refractory patients with del 17p.[1]

•Median PFS 28.1 months

1. O'Brien SM, et al. J Clin Oncol 2014;32:5s (suppl; abstr 7014) and oral presentation.

Long-term follow up
Response rate

Response rates over 3 years with IMBRUVICA®[1]



Graph adapted from O'Brien SM, et al. 2014.

CR=complete response PR=partial response PR-L=partial response with lymphocytosis
* These results also include data from 31 treatment-naïve CLL/SLL patients (N=132); however, IMBRUVICA is not approved for treatment of treatment-naïve patients, except for those with a 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy [1]

1. O'Brien SM, et al. J Clin Oncol 2014;32:5s (suppl; abstr 7014) and oral presentation.

Best response to single-agent IMBRUVICA® therapy improves over time.[1]

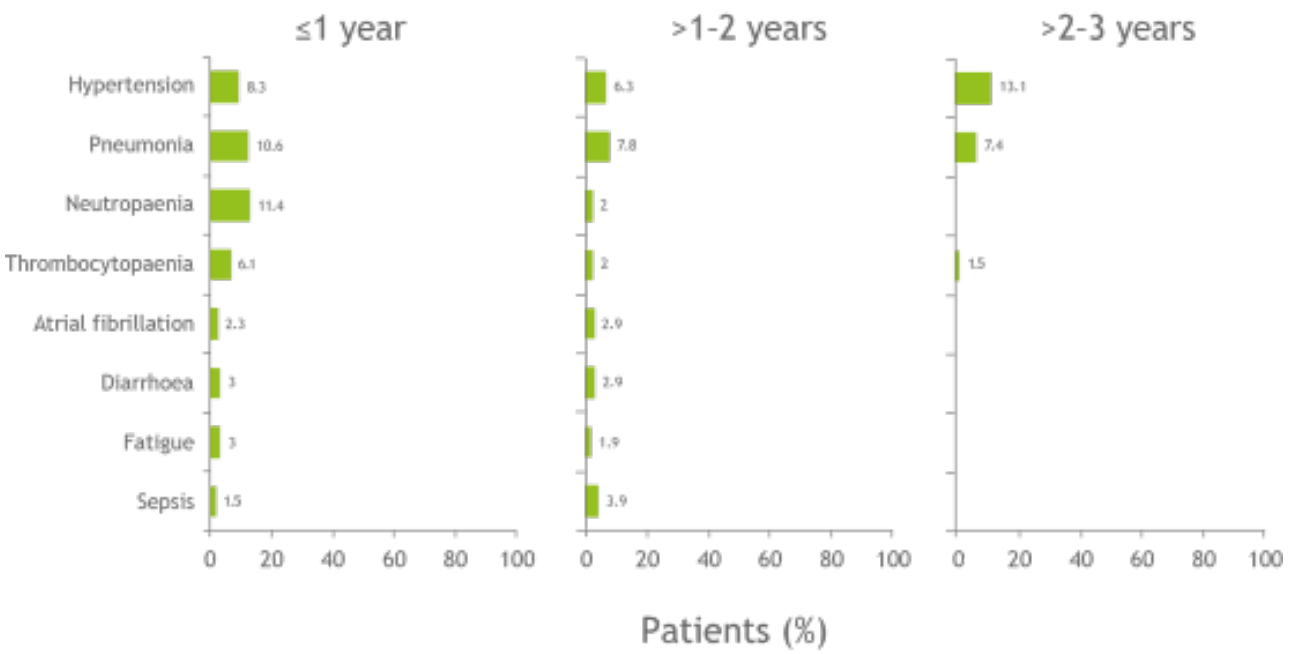
- Median time to first response: 1.9 months (range, 1.4-23.2)
- Median time to best response: 7.3 months (range, 1.7-31.8)
- 92% of patients who achieved a partial response with lymphocytosis converted to better response

Median duration of response not yet reached at 3 years.[1]

- 58% of relapsed/refractory patients remained on single-agent IMBRUVICA® therapy at 3 years[1]

Long-term follow up
Adverse event profile

Grade ≥3 adverse events by time-to-onset [1*†]



Graph adapted from O'Brien SM, et al. 2014.

Long-term treatment with IMBRUVICA® was generally well tolerated, allowing for extended dosing.[1,2]

- 58% of relapsed/refractory patients remained on treatment with single-agent IMBRUVICA® therapy in this long-term study[1]
- No new safety signals were observed in long-term follow-up[1]

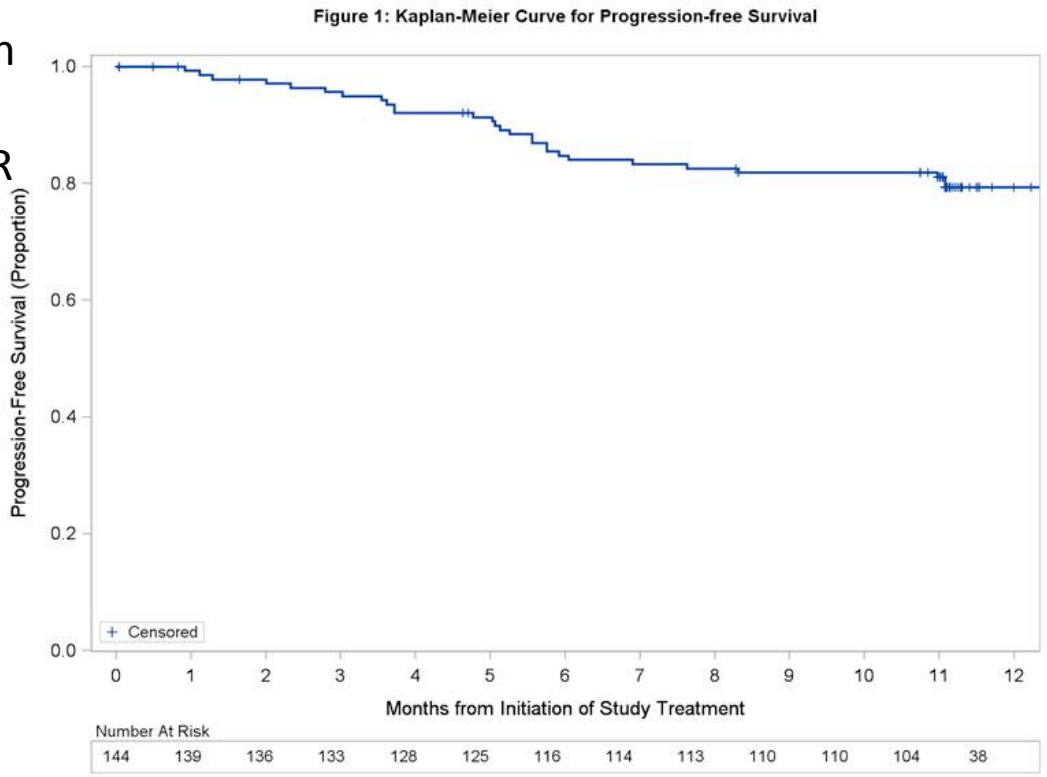
* Long-term, follow-up study (PCYC-1102/1103) in CLL/SLL patients. These results also include data from 31 treatment-naïve CLL/SLL patients (N=132); however, IMBRUVICA is not approved for the treatment of treatment-naïve patients, except for those with a 17p deletion or TP53 mutation who are unsuitable for chemo-immunotherapy. [1]

† Listed adverse events include those that occurred in ≥5% of patients in all-treated population; denominator for each term and time period can vary based on those at risk.

1. O'Brien SM, et al. J ClinOncol 2014;32:5s (suppl; abstr 7014) and oral presentation. **2.** Burger JA & Buggy JJ. Leuk Lymphoma 2013;54(11):2385–2391.

327 Efficacy and Safety of Ibrutinib in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Leukemia with 17p Deletion: Results from the Phase II RESONATE™-17 Trial

144 R/R del17p patients
Investigator-assessed ORR: 82.6% including 17.4% partial response with lymphocytosis (PR-L).
CR/CRi: 3 patients. IRC-assessed ORR is pending.
PD: 13.9% (20 patients), of these: 11 patients had Richter's, 7 of the cases occurring within the first 24 weeks of treatment. **Prolymphocytic leukemia** was reported in 1 patient.
AEs/SAEs: diarrhea, AF, Major hemorrhage was reported in 7 patients (4.9%, all Grade 2 or 3)
Study treatment was discontinued in 16 patients (11.1%) due to AEs with 8 eventually having fatal events (pneumonia, sepsis, myocardial or renal infarction, health deterioration).



ASH 2014

3328 The Bruton's Tyrosine Kinase (BTK) Inhibitor ONO-4059: Promising Single Agent Activity and Well Tolerated in Patients with High Risk Chronic Lymphocytic Leukaemia (CLL)

Phase 1, selective oral BTK, once daily, 20-600mg for 3 years max

25 patients
To date, 19 of 25 patients remain on treatment with a median duration of treatment of 363 days [27-659]. ONO-4059 was found to be well tolerated with few adverse reactions over a long duration.

Best overall response rate according to IWCLL criteria (including modified PR with lymphocytosis) was 84% [based on CT-scan and P/E for 21/25 evaluable patients with 17 PR, 4 PR with lymphocytosis (for 21 responding patients, median reduction of lymph nodes was 83% [51-100]), 1 SD and 2 PD], with 89% response rate on 17p deleted.

CDF INDICATIONS

Idelalisib + rituximab inclusion criteria from Furman et al NEJM 2014

- CLL that had progressed within 24 months after their last treatment
- Previous treatment must have included either a CD20 antibody–based regimen or at least two previous cytotoxic regimens.
- Not able to receive cytotoxic agents for one or more of the following reasons:
- severe neutropenia or thrombocytopenia caused by cumulative myelotoxicity from previous therapies,
- an estimated creatinine clearance of less than 60 ml per minute,
- a score on the Cumulative Illness Rating Scale (CIRS) of more than 6 for coexisting illnesses not related to CLL.
- 17p deletion or mutation (added by CDF)

Ibrutinib inclusion criteria from Byrd et al NEJM 2014

•Must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analog–based therapy, defined by at least one of the following criteria:

- Failure to respond (stable disease or disease progression on treatment), or a progression-free interval of less than 3 years from treatment with a purine analog–based therapy and anti-CD20–containing chemoimmunotherapy regimen after at least two cycles.
- Age ≥70 years, or age ≥65 and the presence of comorbidities (Cumulative Illness Rating Scale [CIRS] ≥6 or creatinine clearance <70 ml/min) that might place the patient at an unacceptable risk for treatment-related toxicity with purine analog–based therapy, provided they have received one or more prior treatment including at least two cycles of an alkylating agent–based (or purine analog–based) anti-CD20 antibody–containing chemoimmunotherapy regimen. CIRS score can be determined using a web-based tool.
- History of purine analog–associated autoimmune anemia or autoimmune thrombocytopenia.
- Fluorescent hybridization showing del17p in ≥20% of cells (either at diagnosis or at any time before study entry) either alone or in combination with other cytogenetic abnormalities, provided the patient has received at least one prior therapy.

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