
## Leucemia Linfatica Cronica (LLC)

# L'approccio terapeutico

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# DISCLOSURE

Nome: **Maria Rosaria**
Cognome: **Villa**

Impiego nell'industria farmaceutica negli ultimi 5 anni: **NO**

Interssi finanziari nel capitale di un'industria farmaceutica: **NO**

Altri rapporti con l'industria farmaceutica: **NO**


## Session III

### Novel Targeted Therapies

*Chairmen: P. Ghia, E. Montserrat*

| | | |
|---|---|---|
| 2.00 pm | Ibrutinib | *J.A. Burger* |
| 2.15 pm | General discussion | |
| 2.30 pm | Idelalisib | *S. O'Brien* |
| 2.45 pm | General discussion | |
| 3.00 pm | Venetoclax | *P. Hillmen* |
| 3.15 pm | General discussion | |
| 3.30-4.30 pm | Round Table | *J.A. Burger, P. Hillmen, S. O'Brien* |

## Session IV

### Newer Agents

*Chairmen: J.R. Brown, P.L. Zinzani*

| | | |
|---|---|---|
| 8.30 am | Next-generation BTK inhibitors: | |
| | - Acalabrutinib | *J.R. Brown* |
| | - BGB-3111 | *C. Tam* |
| 9.00 am | General discussion | |
| 9.15 am | Other PI3K inhibitors: | |
| | - Duvelisib | *S. O'Brien* |
| | - TGR-1202 | *A.R. Mato* |
| | - Pilaralisib | *J.R. Brown* |
| 10.00 am | General discussion | |

## AGENDA

- Treatment decisions
- Patients with del 17p/TP53 mutations
- Complex Karyotype/NOTCH1
- IGHV mutational status
- Outcomes in 1 line and R/R

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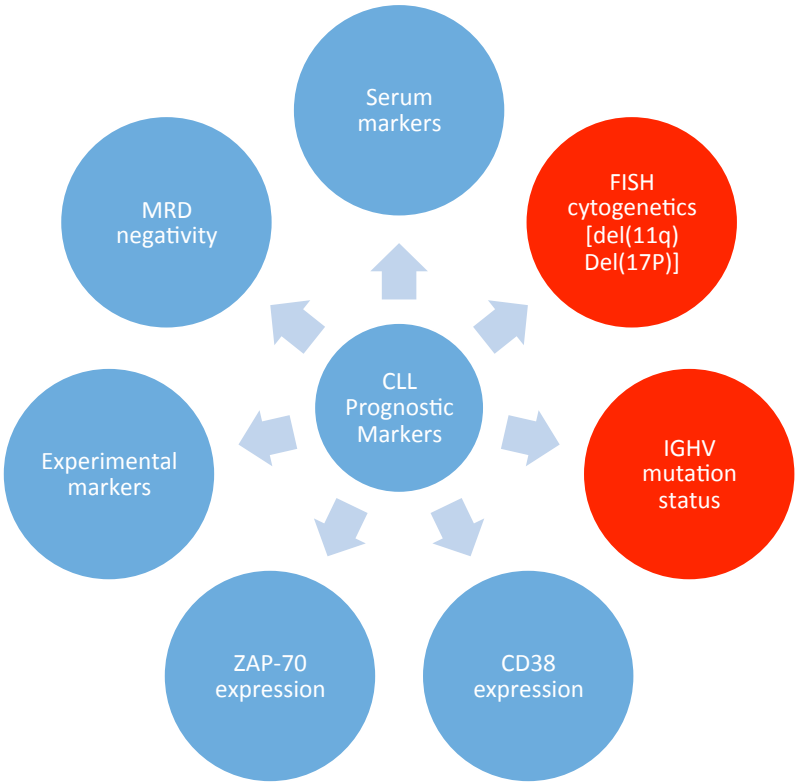
# Treatment decisions

- **A large number of biological, genetic and molecular markers of prognosis in CLL have been identified[1]**
  - Of these, IGHV mutation status and del(11q) are among the most well-studied[1]
- **Recent evidence indicates that testing for IGHV mutation status and del(11q) should be performed as standard for all patients with newly-diagnosed CLL patients[1]**
  - As these are consistent and robust prognostic markers, independent of clinical stage, which provides complementary information on PFS and OS[1]
- **ESMO guidelines recommend analysis for the detection of del(11q) and of IGHV mutation status as 'desirable' before the start of therapy[2,3]**

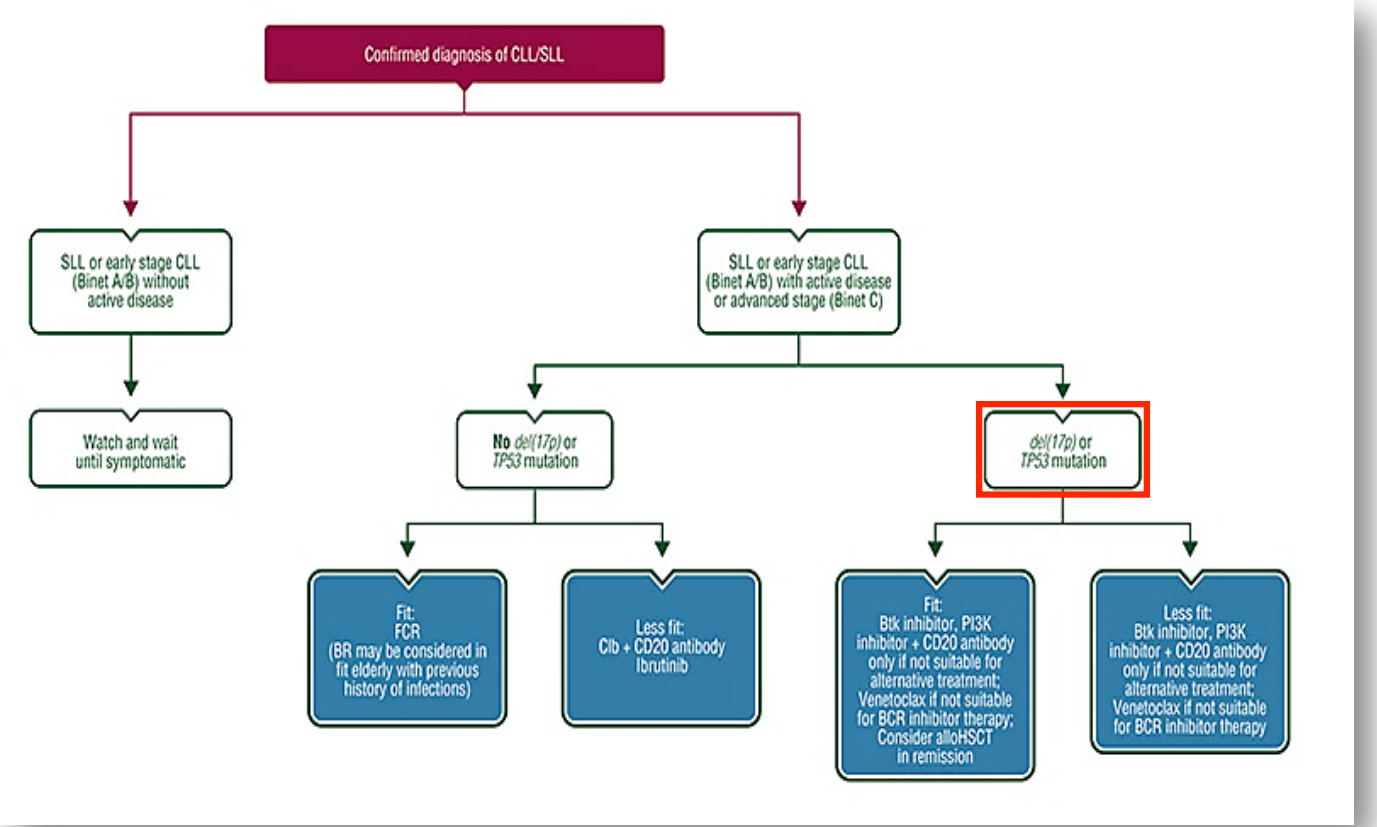




1. Parikh S, et al. Semin Oncol 2016; 43(2): 233-40.
2. Strati P, et al. Blood 2015; 126(4): 454-462.
3. Eichhorst B, et al. Ann Oncol 2015; 26(Suppl 5): v78-v84.

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Welcome to the **EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY**, the leading European professional organisation for medical oncology.




## Frontline CLL

- **ESMO guidelines recommend analysis for the detection of del(11q) and of IGHV mutation status as 'desirable' before the start of therapy**
- **Only patients with del(17p) and/or TP53 mutation are highlighted as needing specific regimens**

**Published: 27 June 2017.** Authors: ESMO Guidelines Committee

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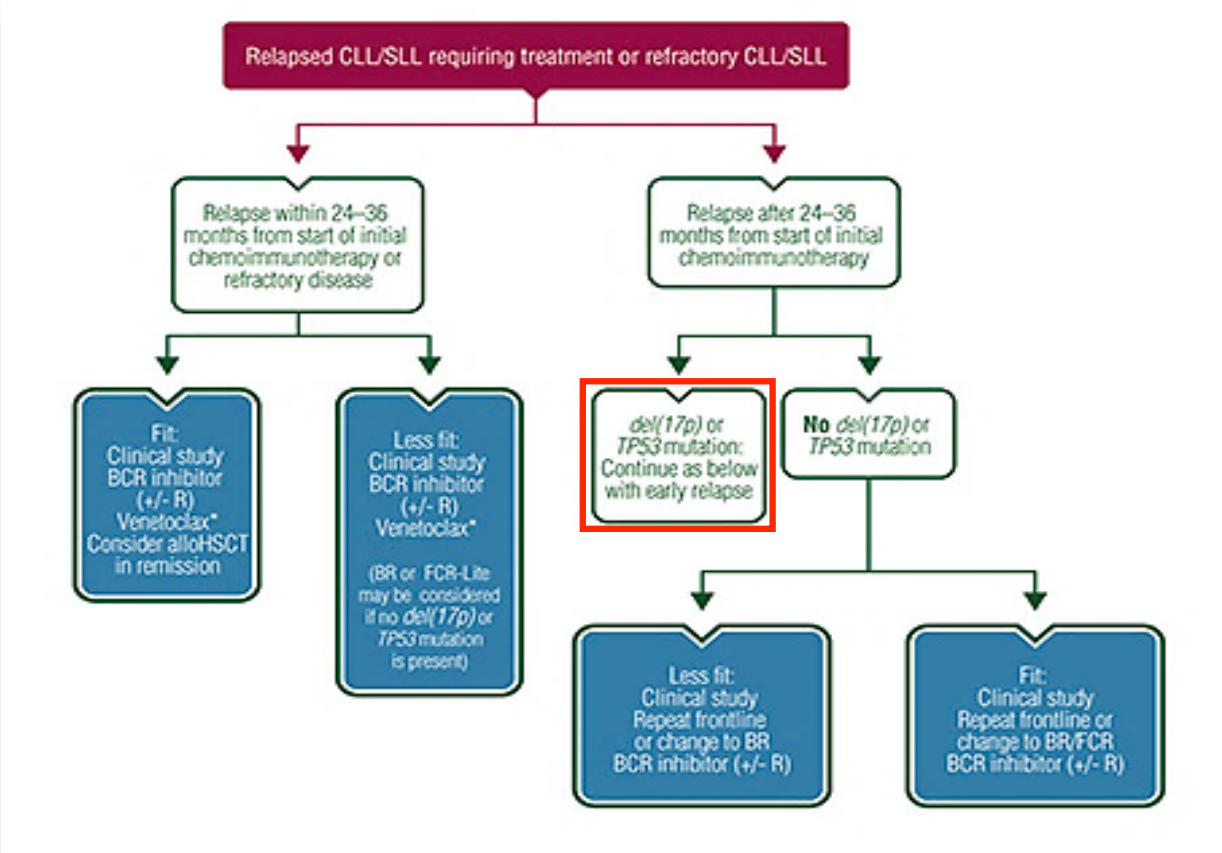


## Relapsed CLL

- **Current ESMO treatment guidelines do <u>not</u> recommend treatments according to IGHV or del(11q) mutational status**
- **Only patients with del(17p) and/or TP53 mutation are highlighted as needing specific regimens**

**Published: 27 June 2017.** Authors: ESMO Guidelines Committee

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- Complex Karyotype
- IGHV mutational status
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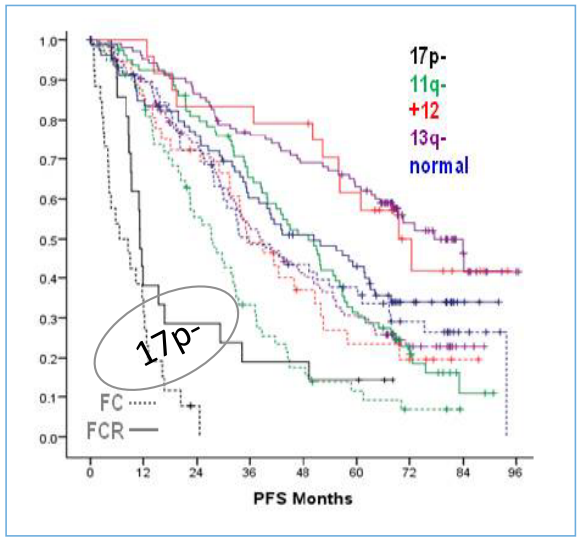
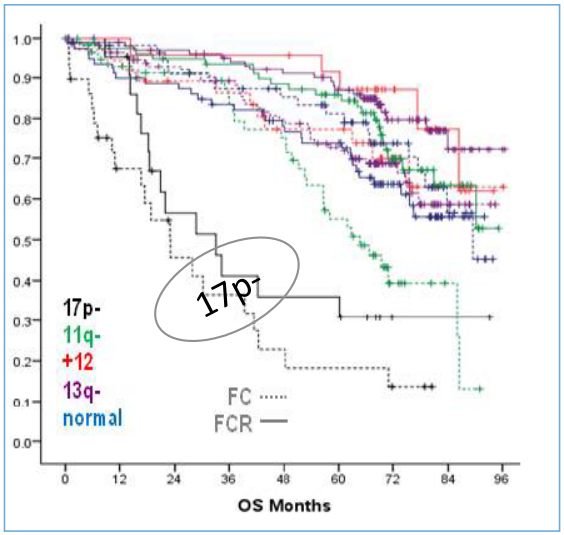
# Background: Updated results from CLL8 trial (FC vs FCR): By FISH

## Progression Free Survival




## Overall Survival

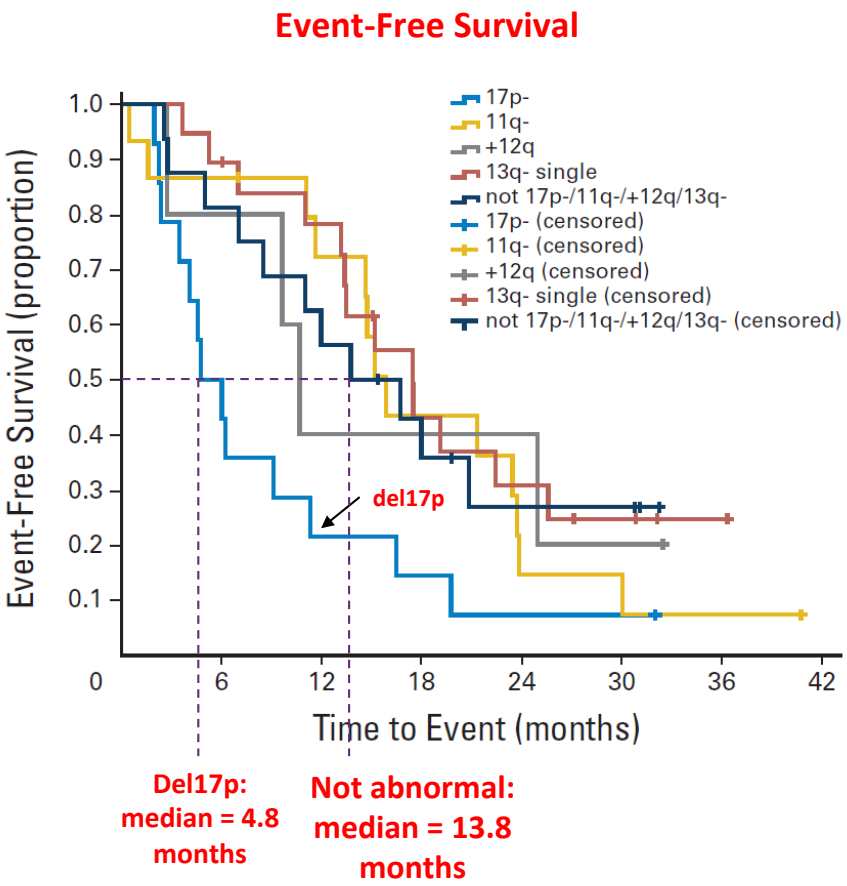



**Del17p: patients treated with FC /FCR PFS less than 12 months![3]**

Patients with ***TP53*** **aberrations** respond less well to treatment than do those without this high-risk genetic lesion, resulting in **early relapse** and **inferior survival**[1,2]

1. Hallek M, et al. *Lancet*. 2010;376:1164-1174. 2. Strati P, et al. *Haematologica*. 2014;99:1350-1355. *3. Stilgenbauer et al., Blood 2014*

# BR is Less Effective in Relapsed or Refractory CLL With Del17p



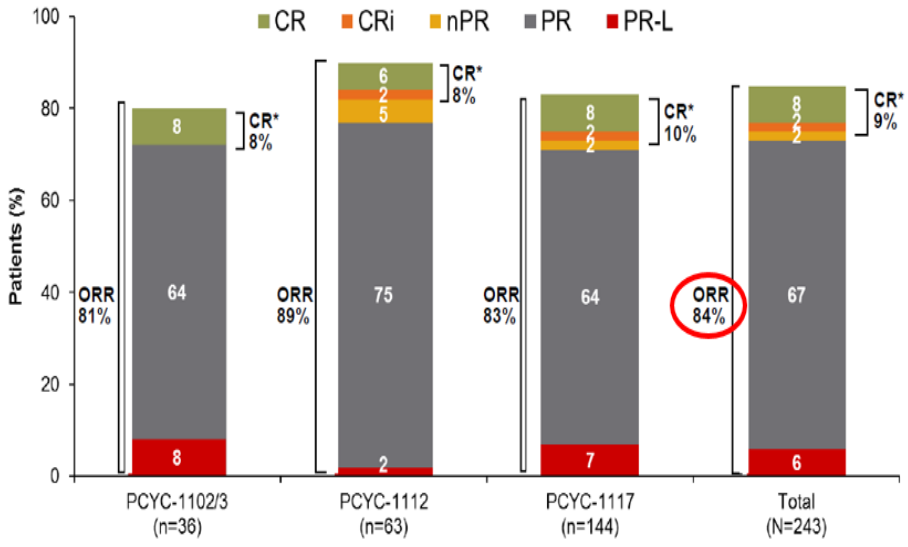

Multicenter, phase 2 study
78 patients

| Cytogenetics by FISH | Overall Response Rate |
|---|---|
| Not abnormal | 62.5% |
| Del17p | 7.1%* |
| Del11q | 92.3% |
| 12q trisomy | 100.0% |
| Del13q | 75.0% |

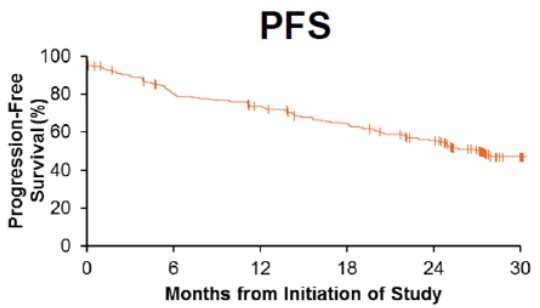
**P* = 0.006 vs not abnormal.

Fischer K et al. J Clin Oncol. 2011;29:3559-3566

# CLL R/R patients with del17p patients treated with ibrutinib

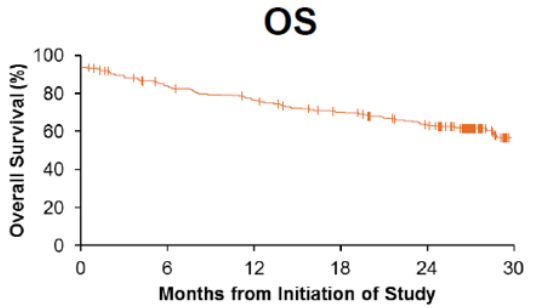



| | PCYC-1102/3 (n=36) | PCYC-1112 (n=63) | PCYC-1117 (n=144) | Total (N=243) |
|---|---|---|---|---|
| Median time on study, mo (range) | 42 (0.9-61) | 31 (0.3-37) | 28 (0.5-31) | 28 (0.3-61) |




| 12-mo PFS, % (95% CI) | 24-mo PFS, % (95% CI) | 30-mo PFS, % (95% CI) |
|---|---|---|
| 80% (74, 84) | 63% (57, 69) | 55% (48, 62) |

Median PFS not reached




| 12-mo OS, % (95% CI) | 24-mo OS, % (95% CI) | 30-mo OS, % (95% CI) |
|---|---|---|
| 85% (80, 89) | 75% (68, 80) | 67% (59, 74) |

Median OS not reached

Of patients with CR/CRi (n=23), 81% maintained response at 30 months

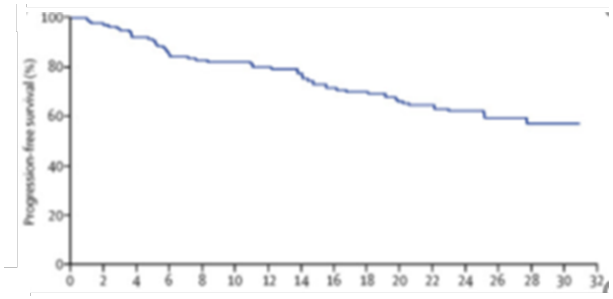
With a median (range) study duration of 28 (0.3-61+) months, median PFS and OS were not reached

Jones et al., EHA 2016

# New agents in R/R patients with del 17p/*TP*53 mutations

## IBRUTINIB

**Ibrutinib in R/R patients with del17p/TP53 mutation (the RESONATE-17™ Study)**

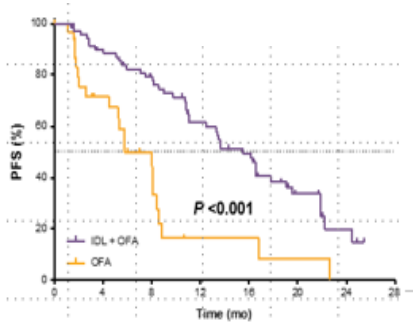



**PFS @ 2 yrs= 63%**

O'Brien et al., Lancet Oncol. 2016

## IDELALISIB

**Idelalisib+Ofatumumab vs Ofatumumab in R/R patients with del17p/TP53 mutation**

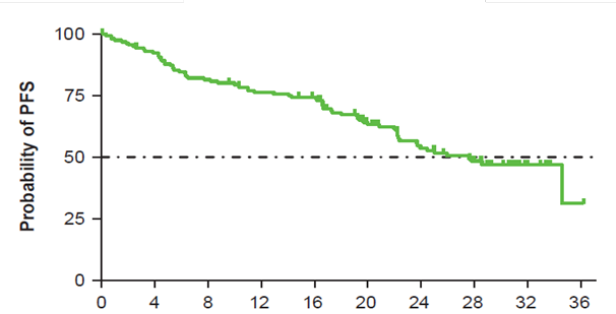



**Med. PFS= 15.5 months**

Jones et al. Lancet Hematology 2017

## VENETOCLAX

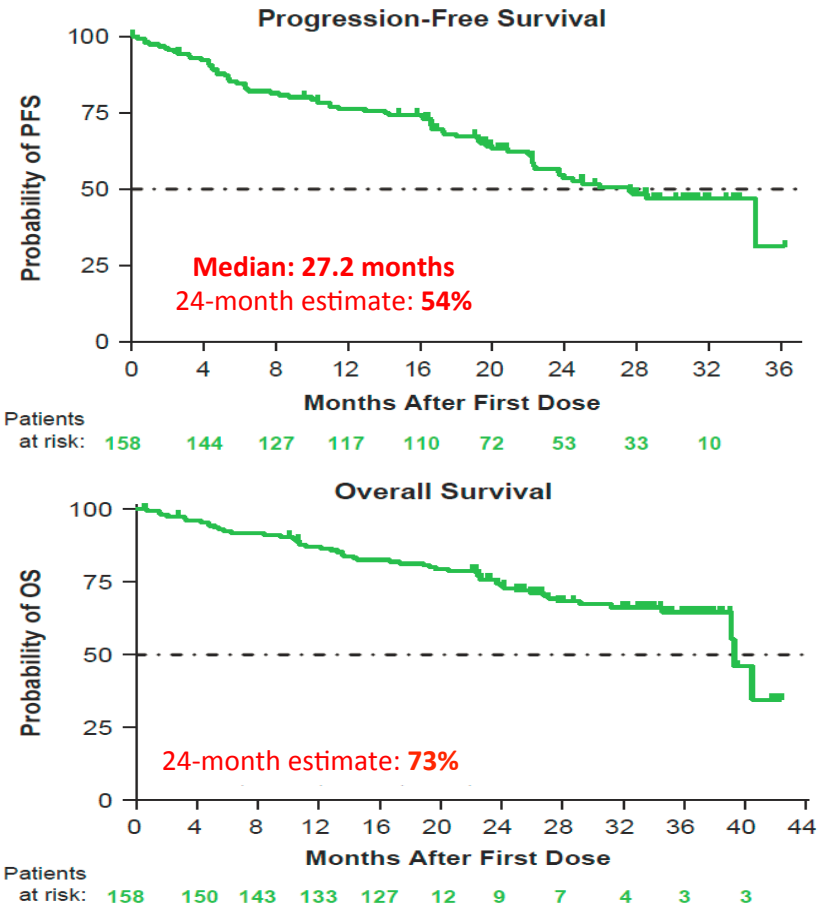
**Venetoclax in R/R patients with del 17p CLL**




**Med. PFS= 27.2 months**

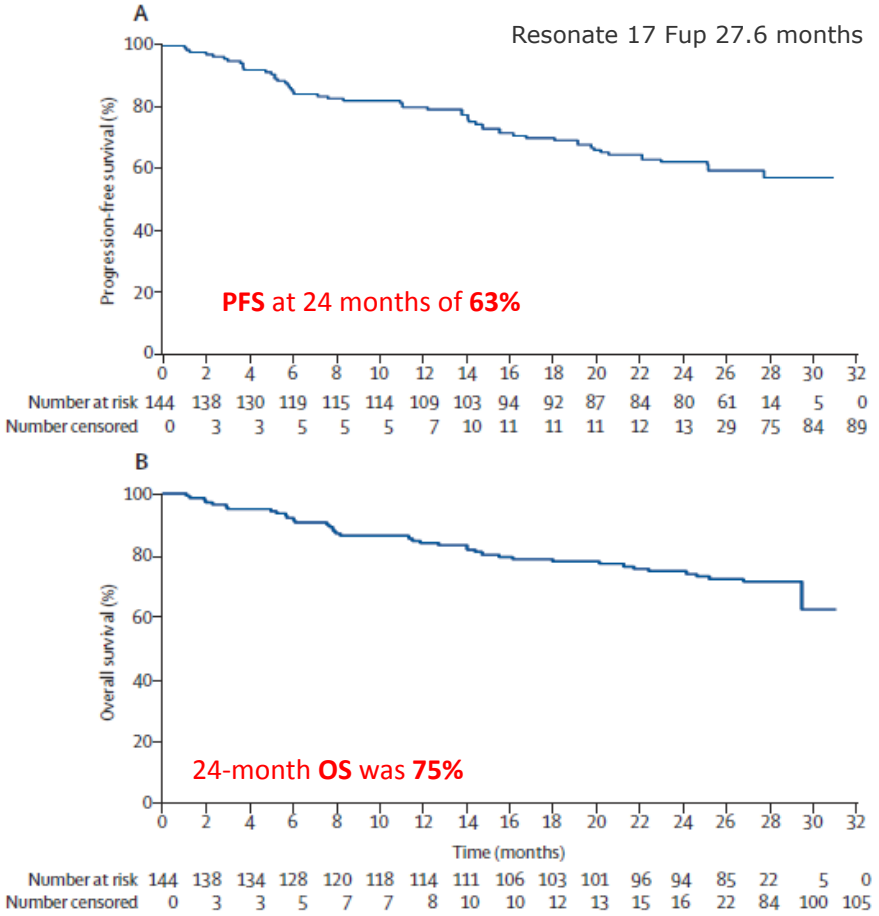
Stilgenbauer et al., iwCLL 2017, abstract 420

# Venetoclax in R/R CLL with 17p deletion: PFS and OS




Stilgenbauer et al., Presented at EHA 2017 (abstract S771, oral presentation)

# Ibrutinib in R/R CLL with 17p deletion: PFS and OS




*Susan O'Brien et al. Published online September 13, 2016*
*http://dx.doi.org/10.1016/S1470-2045(16)30212-1*

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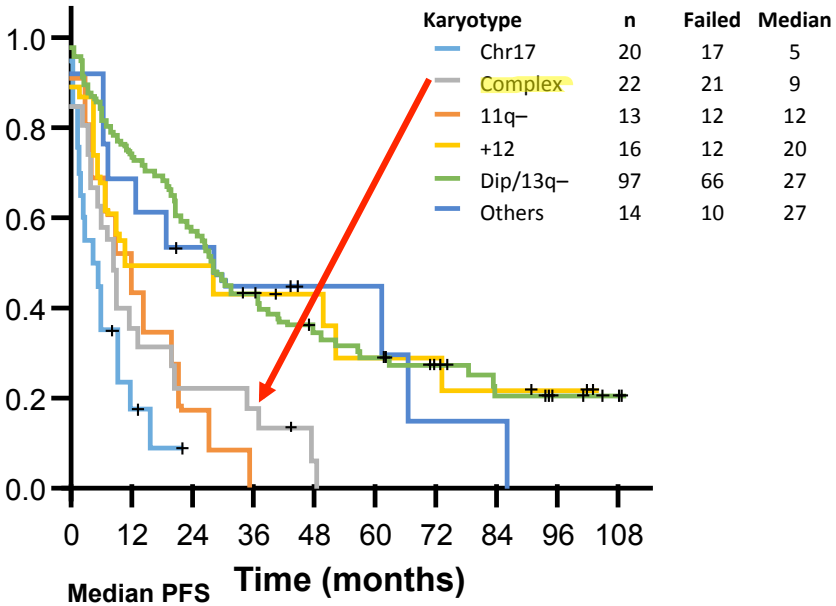
# FCR: Complex Karyotype

## sensitivity without Chr17 abnormalities - benefits patients with ≤3 prior treatments

Phase II, single-arm trial in patients with relapsed/refractory CLL (N=284)

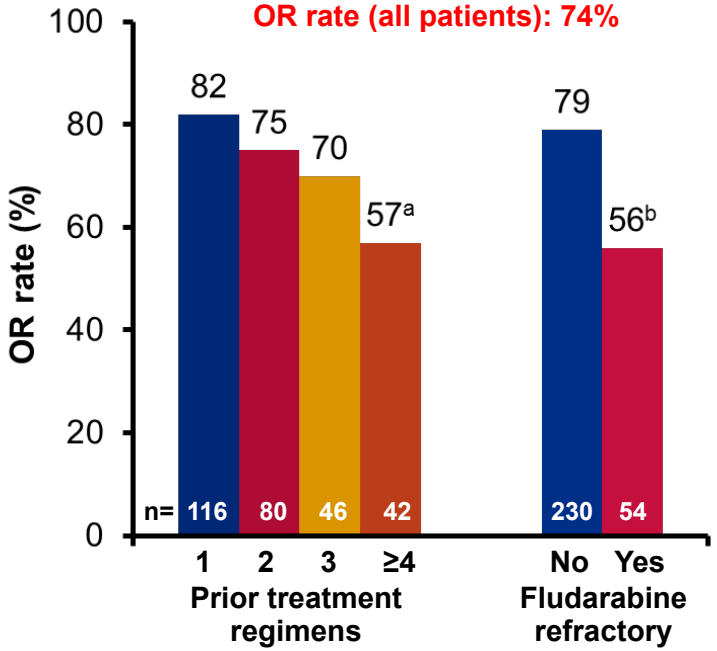
**PFS (subgroup analysis)**




**Median PFS**
All patients: 20.9 months
Chr17 abnormalities: 5 months
HR 4.6 (95% CI: 2.5, 8.2) p<0.001

Badoux XC, *et al. Blood* 2011; 117:3016–3024.

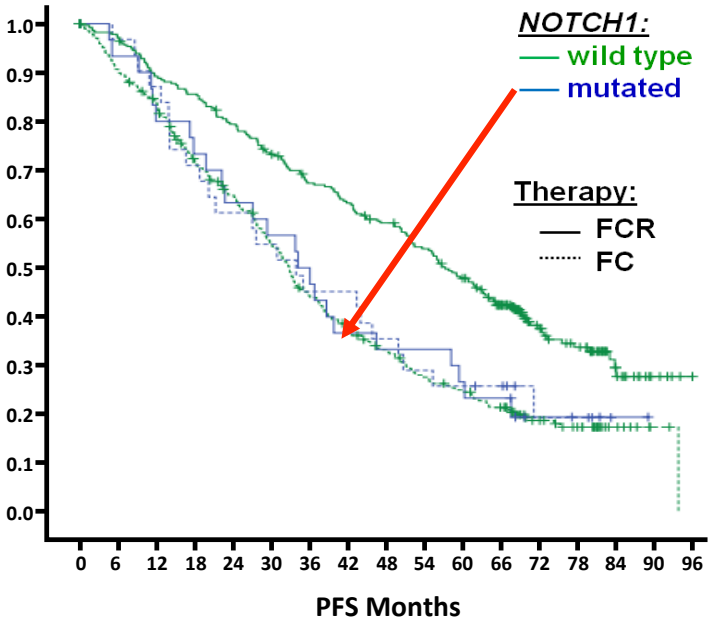
**OR rate (all patients): 74%**




[a]p<0.05 vs. ≤3 prior therapies
[b]p<0.001 vs. not F refractory
C: cyclophosphamide; Chr17: chromosome 17; CI: confidence interval; CLL: chronic lymphocytic leukaemia; F: fludarabine; OR: overall response; PFS: progression-free survival; R: rituximab

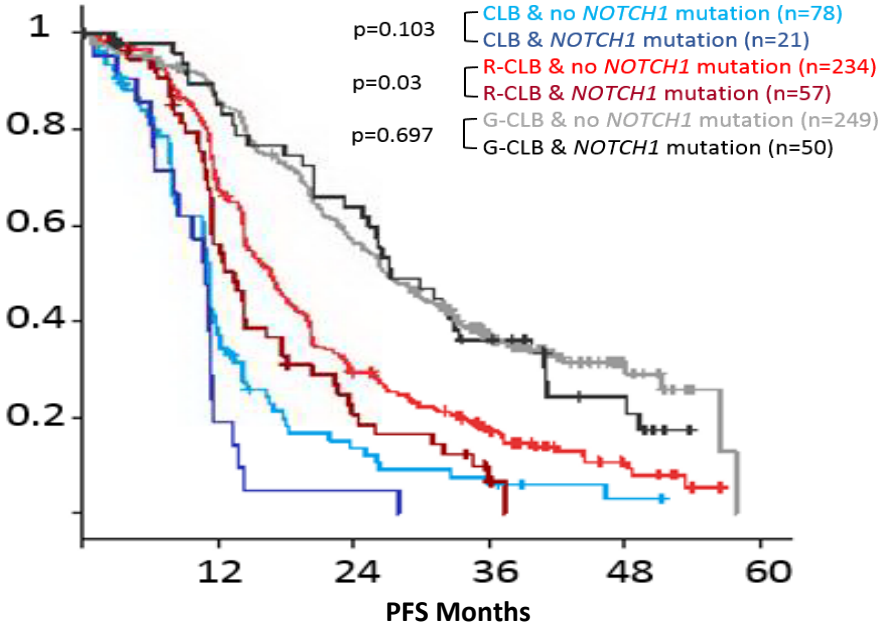
# FCR: NOTCH1 mutations

## GCLLSG CLL8




Stilgenbauer S et al. Blood 2013

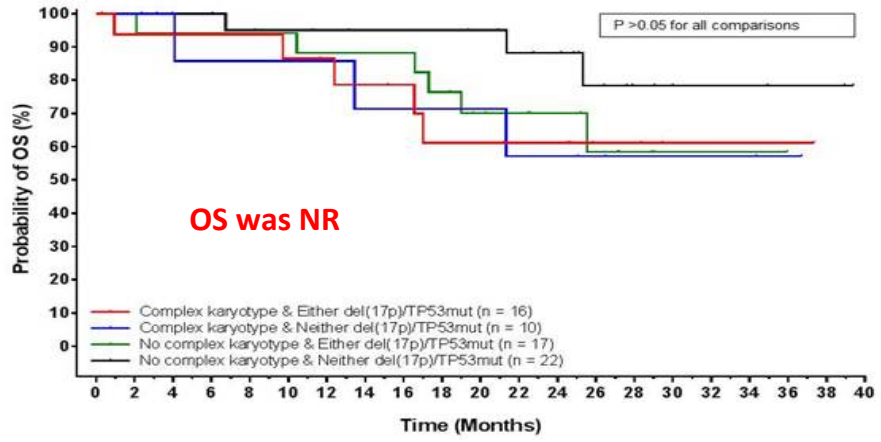
## GCLLSG CLL11

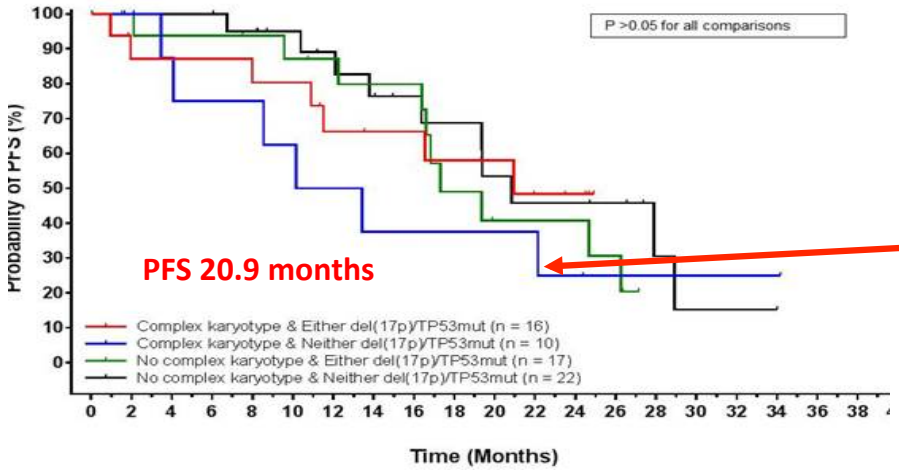



Estenfelder S et al. Blood 2016 128:3227

Rossi D., iwCLL 2017 (invited oral presentation)

# Idelalisib in pts with Complex Karyotype status



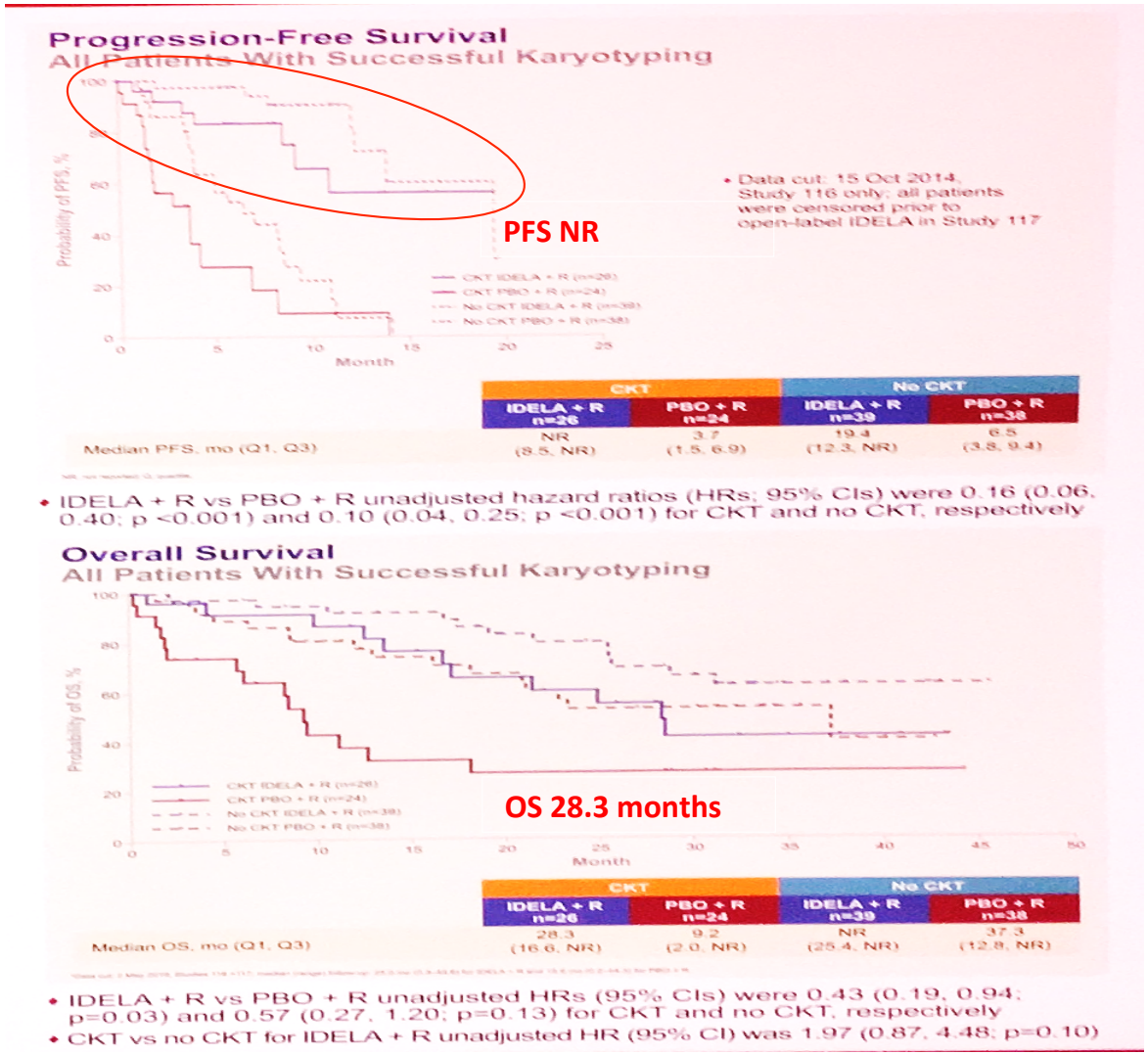




The med **OS was NR** vs NR in CKT vs non-CKT, HR = 1.78 (95%CI 0.69-4.64; p = 0.23).

The presence or absence of del(17p)/TP53mut and CKT status did not significantly affect PFS or OS in pts randomized to IDELA

the median **PFS was 20.9 months** in CKT vs **19.4 in non-CKT**, HR = 1.18 (p = 0.63);

Karl-Anton Kreuzer et al. ASH 2016 Poster

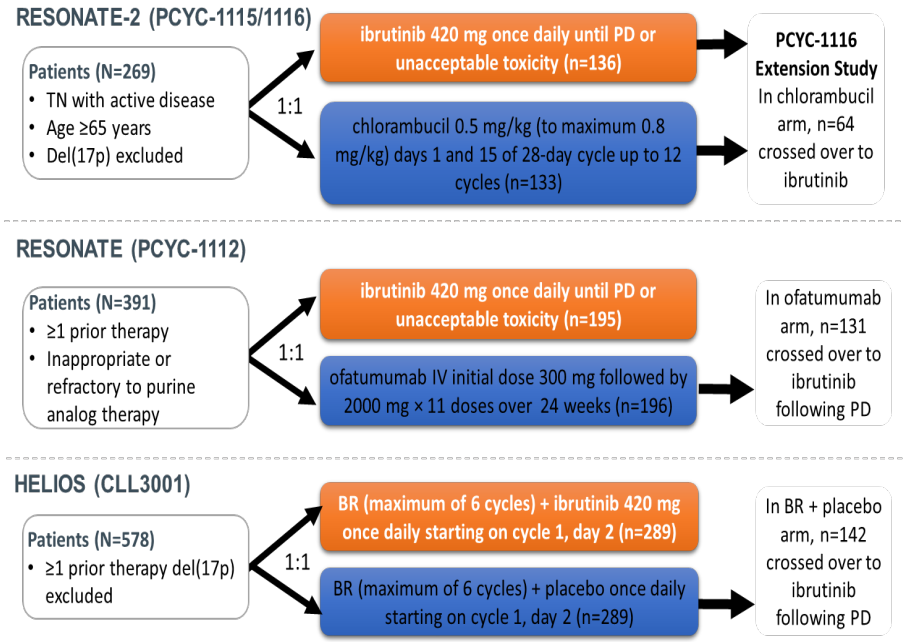



# Patients with Complex Karyotype (CK) treated with Idela+R

- Retrospective exploratory analysis of Study 1116 (Idelal+R vs R)
- Update on the OS data at ASH 2016
- Now with median FU 25 months
- Continues to show no significant adverse effect of CK in Idela-treated patients (HR 1.97, p=0.10), with the caveat of limited sample size

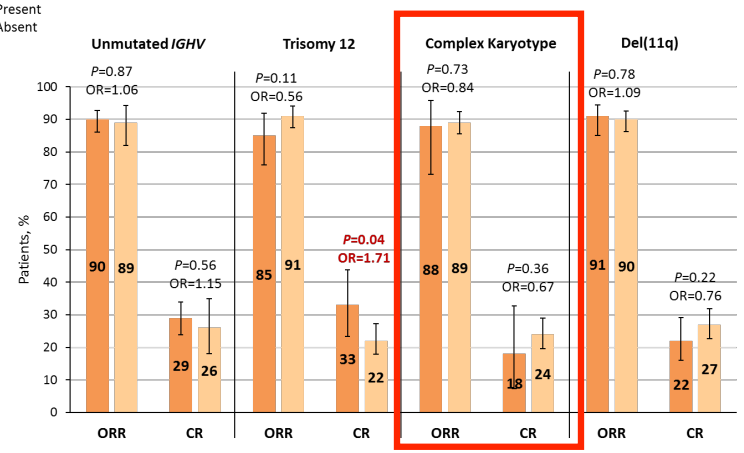
Kreuzer et al. iwCLL 2017, poster 410

# Ibrutinib in Complex Karyotype

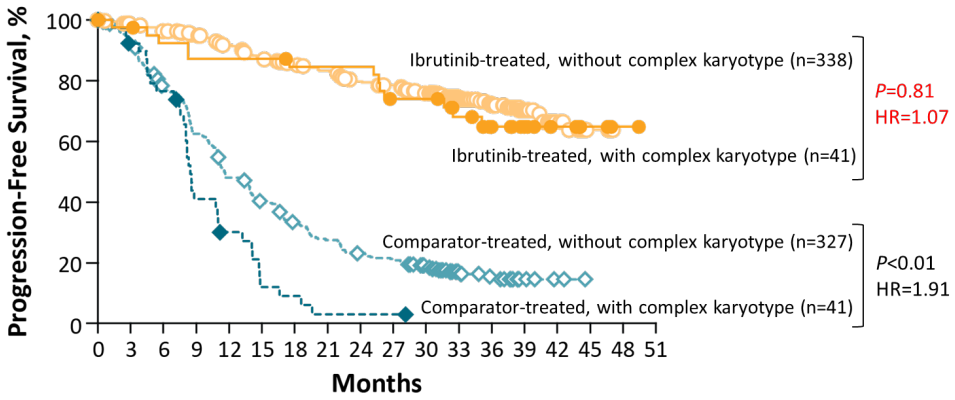



Genomic Risk Factors are not Associated With Inferior Response Rates in Ibrutinib-Treated Patients

Median follow-up 36.4 months (95% CI 35.8-37.1)




**PFS With vs without CK**




- In ibrutinib-treated patients, PFS at 36 months:
  - 65% with presence of complex karyotype vs 72% with absence of complex karyotype

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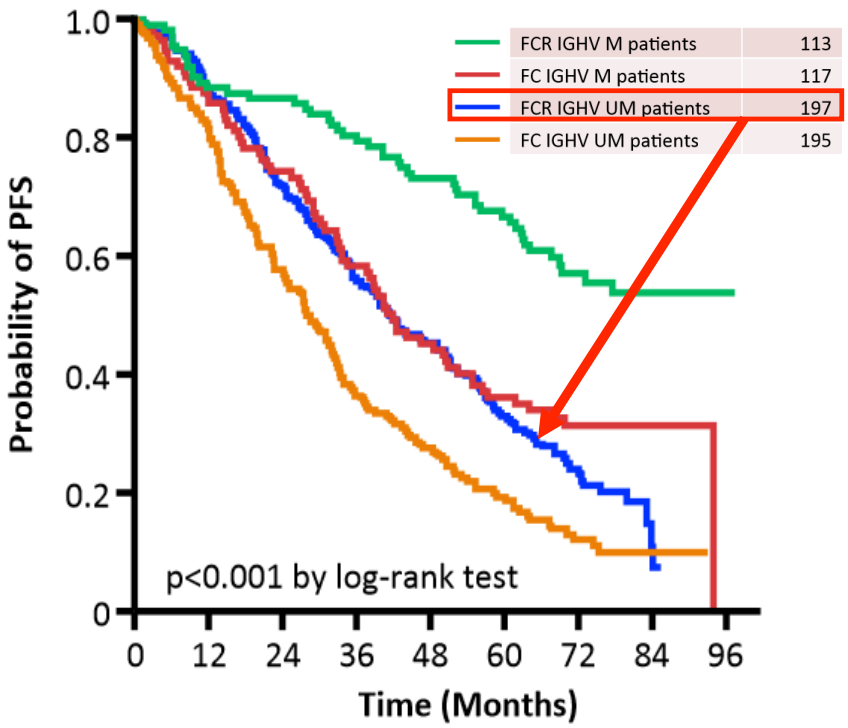
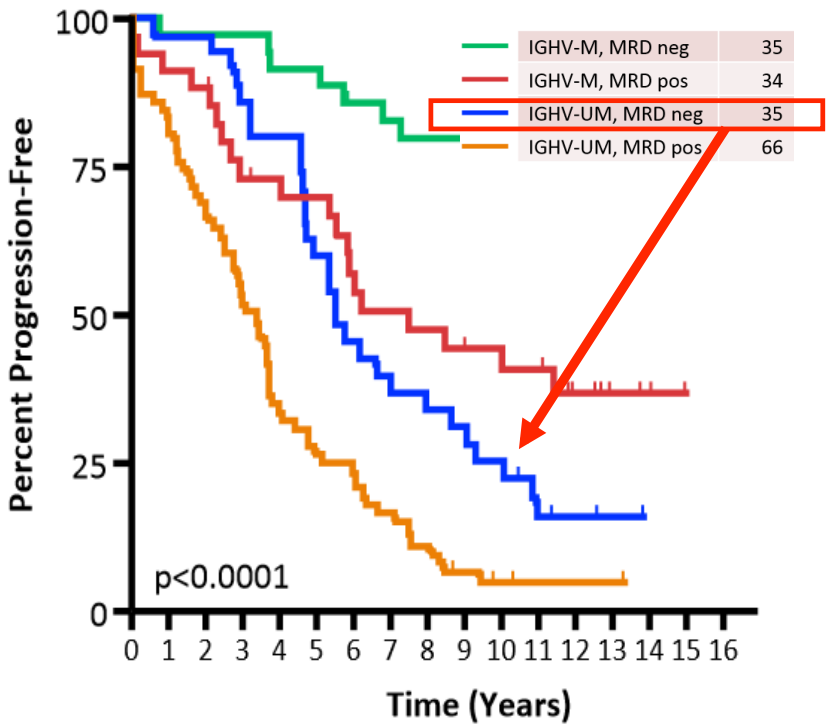
# PFS by IGHV after front-line FCR: FCR300 and CLL8 trials




**IGVH mutated**
**54% Prog-free @ 13 yrs**
curve plateaued beyond 10.4 yrs

Thomson et al., Blood 2015

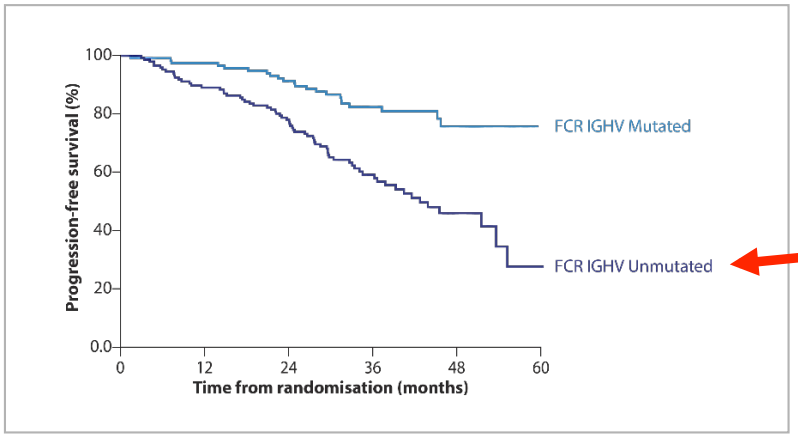



**IGVH mutated**
**>50% Prog-free @ 6yrs**

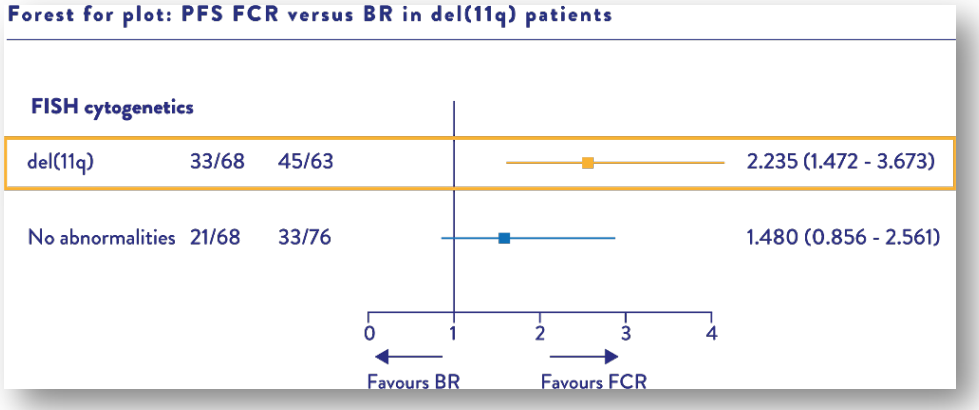
Fisher et al., Blood 2015

Frontline CLL

# FCR PFS by unmutated IGHV or del(11q) : CLL 10




| FCR CLL10 | IGHV-unmutated N=152 | IGHV-mutated N=123 |
|---|---|---|
| **Median PFS** | **42.7 months** | **Not reached** |
| Median OS | Not reported | Not reported |

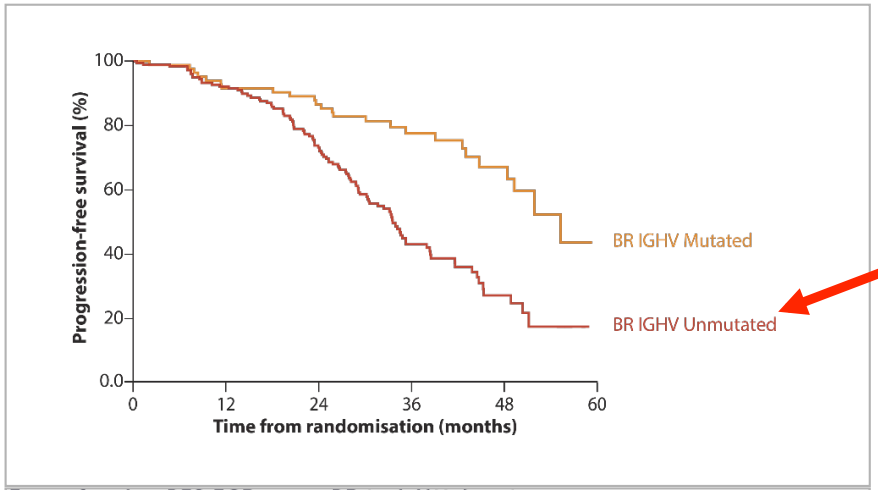



| FCR CLL10 | Del(11q) present N=68 | All patients N=282 |
|---|---|---|
| Median PFS | 37.8 months | 55.2 months |
| Median OS | Not reported | Not reported |

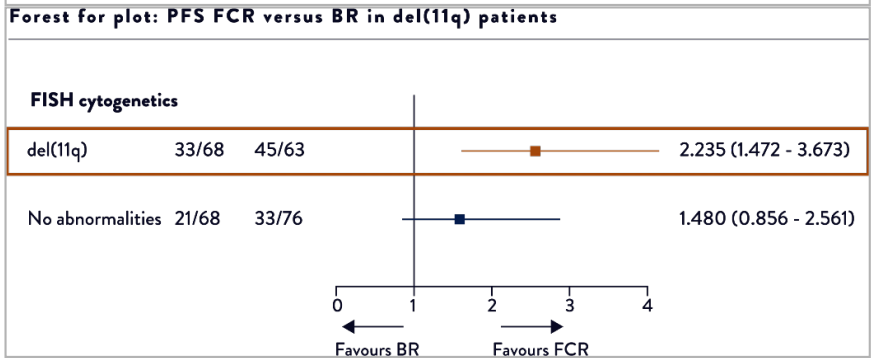
Eichhorst B, et al. Lancet Oncol 2016; 17(7): 928-42.

# CLL 10: BR PFS by unmutated IGHV or del(11q)

Frontline CLL




| BR CLL10 | IGHV-unmutated N=183 | IGHV-mutated N=87 |
|---|---|---|
| **Median PFS** | **33.6 months** | **55.4 months** |
| Median OS | Not reported | Not reported |

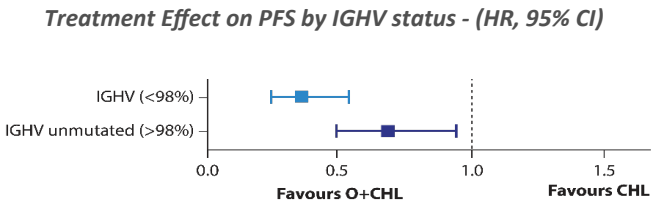



| BR CLL10 | Del(11q) present N=63 | All patients N=279 |
|---|---|---|
| Median PFS | 25.3 months | 41.7 months |
| Median OS | Not reported | Not reported |

Eichhorst B, et al. Lancet Oncol 2016; 17(7): 928-42.

# CLL 11: Chl + Ofatumumab efficacy by IGHV mutational status

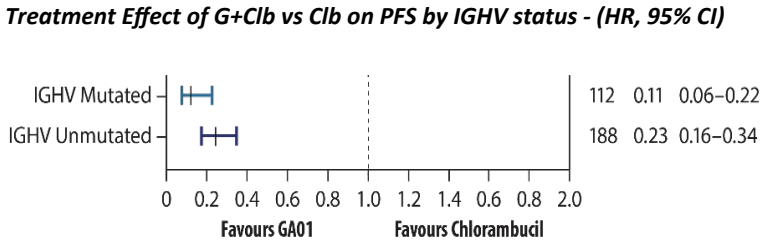
Frontline CLL




| O+Clb vs Clb<br>Complement-1 | IGHV-unmutated<br>N= 114 vs 113 | IGHV-mutated<br>N= 87 vs 90 |
|---|---|---|
| **Reduction in risk of PD or death with O+Clb vs Clb** | HR for PFS is improved with O+Clb vs Clb regardless of IGHV status<br>But there is a trend suggesting outcomes are reduced in patients with unmutated IGHV vs mutated IGHV<br>*(Forrest Plot on right)* | |

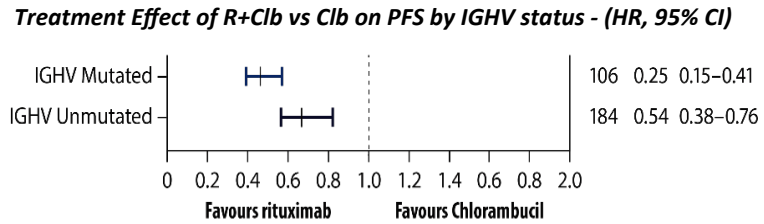
Hillmen P, et al. Lancet 2015; 385: 1873-83.

# CLL 11: Chl + Obinutuzumab PFS is decreased by unmutated IGHV




| G+Clb vs Clb<br>CLL11 | IGHV-unmutated<br>N= 129 vs 58 | IGHV-mutated<br>N= 76 vs 36 |
|---|---|---|
| PFS, HR (95% CI) | **0.23** (0.16-0.34) | 0.11 (0.06-0.22) |
| **Reduction in risk of PD or death with G+Clb vs Clb** | **77%** | **89%** |

# CLL: Chl + Rituximab PFS is decreased by unmutated IGHV

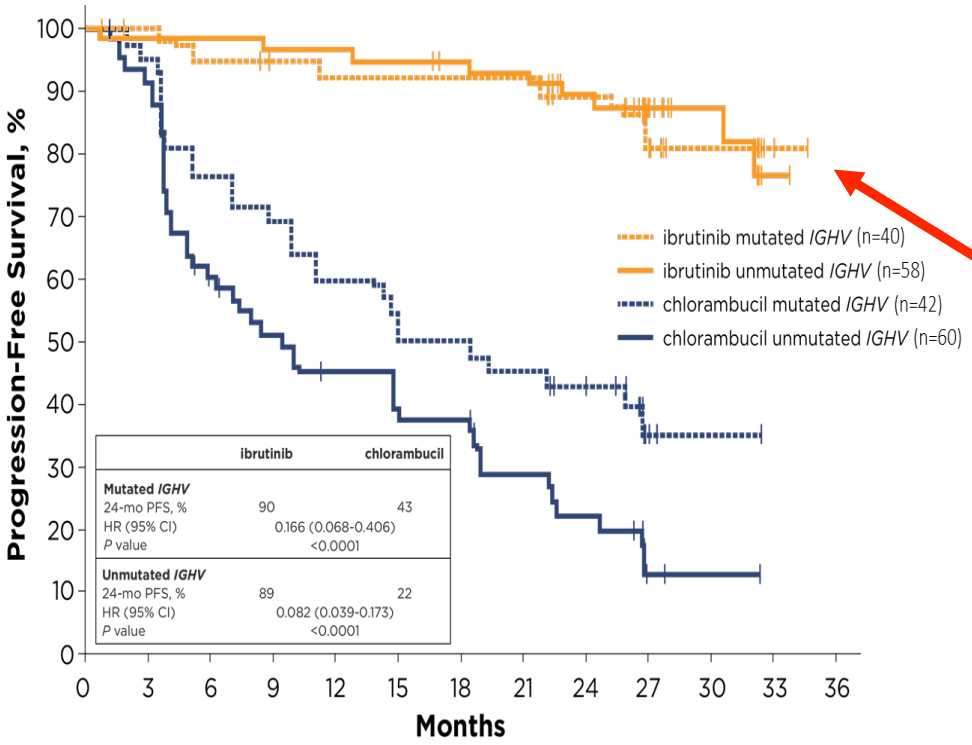



Goede V, et al. N Engl J Med 2014; 370(12): 1101-10.

| R+Clb vs Clb<br>CLL11 | IGHV-unmutated<br>N= 126 vs 58 | IGHV-mutated<br>N= 70 vs 37 |
|---|---|---|
| PFS, HR (95% CI) | 0.54 (0.38-0.76) | 0.25 (0.15-0.41) |
| **Reduction in risk of PD or death with R+Clb vs Clb** | **46%** | **75%** |

Frontline CLL

# Ibrutinib PFS benefit is maintained in presence of unmutated IGHV




| Ibrutinib vs Clb<br>RESONATE-2 | IGHV-unmutated<br>N=58 vs 60 | IGHV-mutated<br>N=40 vs 42 |
|---|---|---|
| PFS, HR (95% CI) | **0.082** (0.039-0.173)<br>P<0.0001 | **0.166** (0.068-0.406)<br>P<0.0001 |
| **Reduction in risk of PD or death with Ibrutinib vs Clb** | **92%** | **83%** |

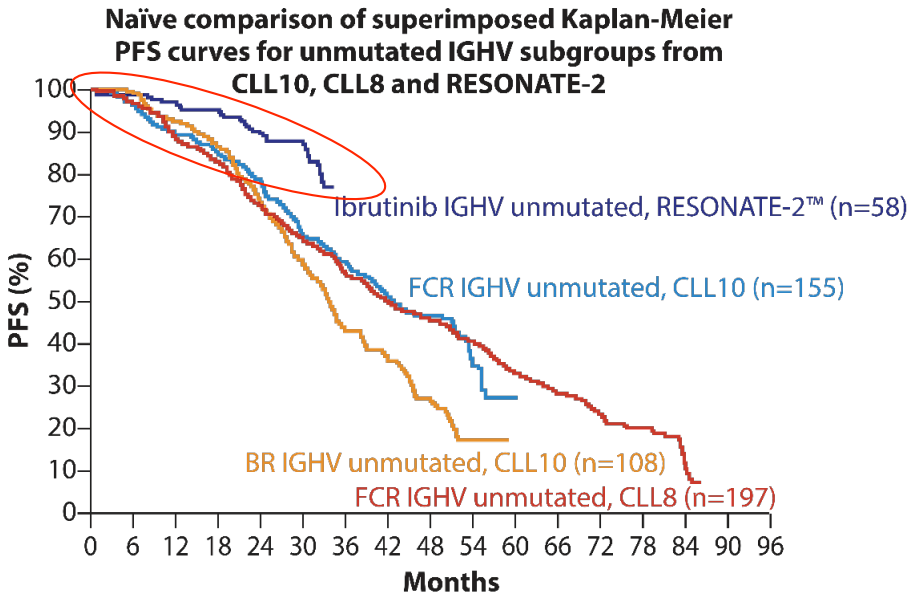
Barr P et al. Oral presentation at ASH 2016

# Ibrutinib PFS benefit vs FCR and BR in presence of unmutated IGHV

**Frontline CLL**

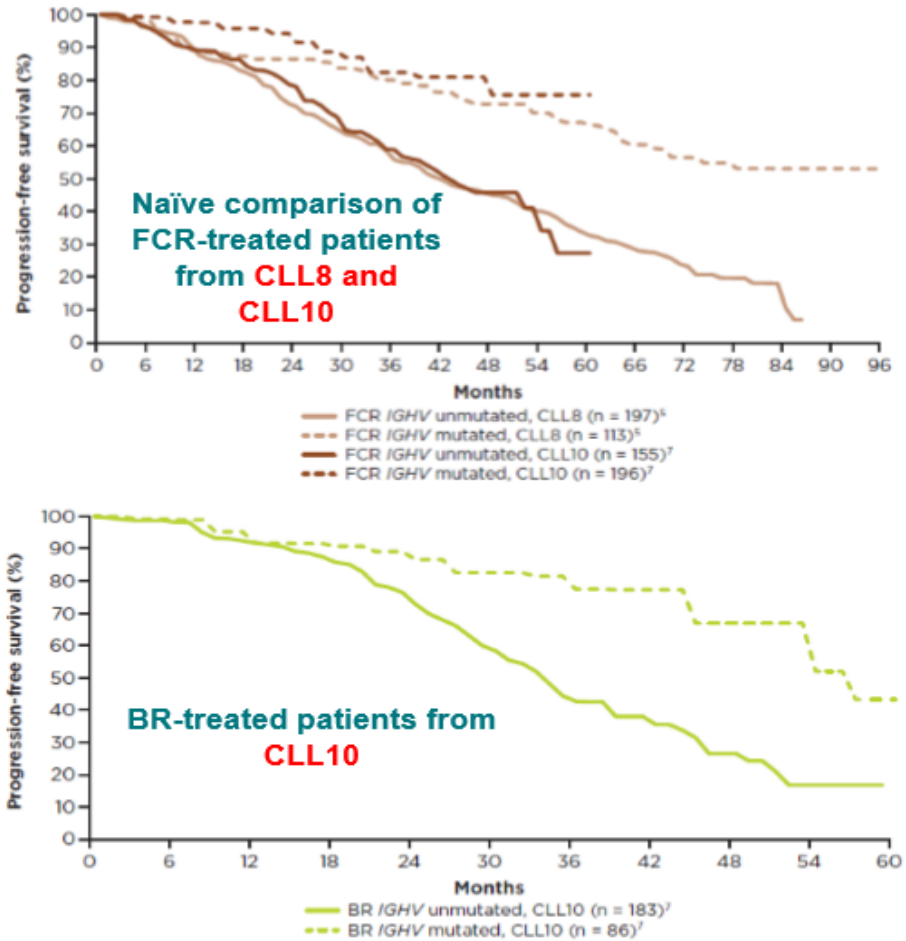
| Ibrutinib vs BR and FCR | IGHV-unmutated | IGHV-mutated |
|---|---|---|
| **30-month PFS rates:** | | |
| **CLL8**<br>**FCR** (N= 197) | **64%** | **84%** |
| **CLL10**<br>**FCR** (N= 155)<br>**BR** (N= 190) | **65%**<br>**59%** | **87%**<br>**83%** |
| **RESONATE-2**<br>**Ibrutinib** (N= 58) | **87%** | **81%** |

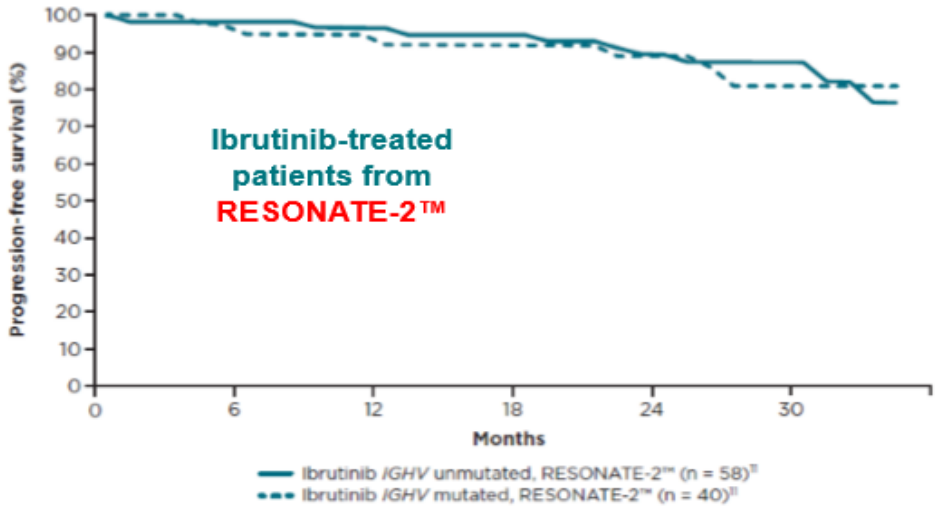
*N in the above table denotes the number of patients with unmutated IGHV*




Ghia P et al. Poster 188 presented at XVII iwCLL 2017.

# Progression-free survival by IGHV: front-line CIT and ibrutinib



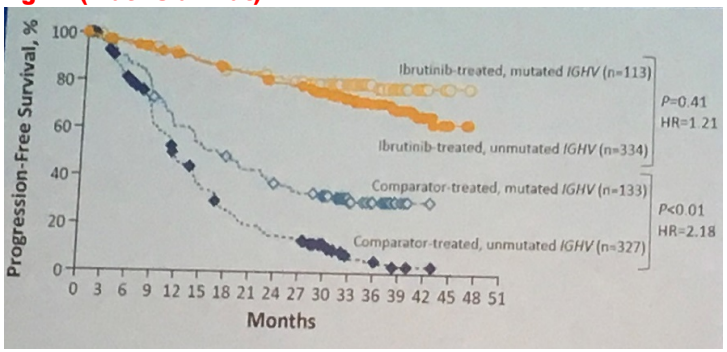

Ghia et al., iwCLL 2017; abstract 128 (poster presentation)

# 100 - Outcome of ibrutinib-treated patients with CLL/SLL with high-risk prognostic factors in an integrated analysis of 3 randomized phase 3 studies

Genomic abnormalities del 17p and del11q, as well as unmut IgHV, are prognostic factors for poor outcomes to chemoimmunotherapy for pts with CLL/SLL

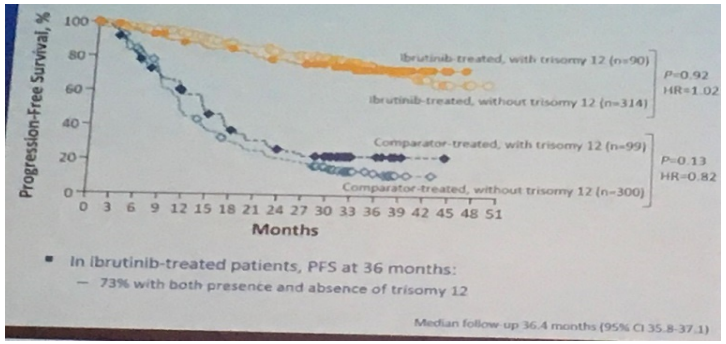
This is a pooled analysis on 3 phase III studies (RESONATE2, RESONATE, HELIOS) to assess outcomes based on genomic abnormalities (FU: 36,4 months)

**IgHV (mut vs unmut)**



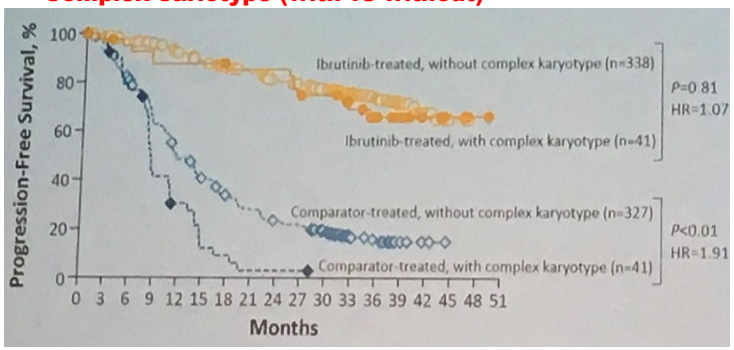

PFS@36m: 70% unmut vs 77% mut

**Trisomy 12 (with vs without)**



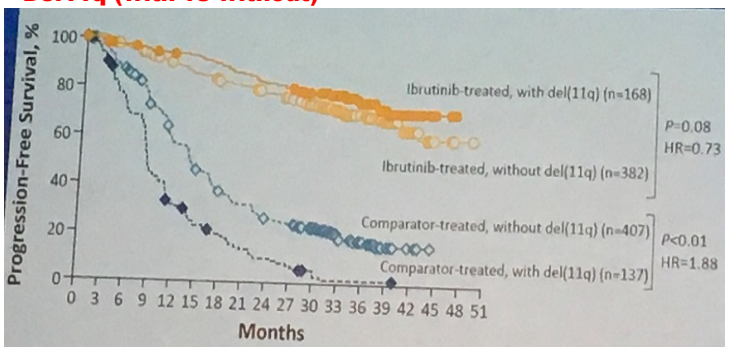

PFS@36m: 73% in both groups

**Complex cariotype (with vs without)**




PFS@36m: 65% with CK vs 72% without CK

**Del11q (with vs without)**




PFS@36m: 74% with del11q vs 68% no del11q

Kipps et al. ICML 2017; Abstract 100 (Oral presentation)

## AGENDA

- Treatment decisions
- Patients with del 17p/TP53 mutations
- Complex Karyotype/NOTCH1
- IGHV mutational status
- Outcomes in 1 line and R/R

# 1L CLL

| | FCR | | | BR | | | | Chl-Obi | IBRUTINIB | |
|---|---|---|---|---|---|---|---|---|---|---|
| All Patients | FCR N=408 | FCR N=404 | FCR N=282 | BR N=279 | BR (elderly) N=70 | BR (elderly) (n=279) | BR (elderly) N=121 | CHL-OBI (elderly) N=330 | Ibrutinib (elderly) N=136 | Ibrutinib (elderly) N=31 |
| Age, median (range) | 61 (36-81) | Not reported | 62.1 (55-67) | 61 (54-69) | 72 (65-87) | 70.0 (43-86) | 75 (approx) | 74 (39-88) | 73 (65-89) | 71 (65-84) |
| PFS, median | **56.8 mo** | **54.8 mo** | **57.6 mo** | **42.3 mo** | **35 mo** | **40.0 mo** | **40 mo** | **26.7 mo** | **NR 89% at 2 Yr** | **NR 92% at 5 Yr** |
| OS, median | NR 78.7% at 5Yr | Not reached | NR 80.9% at 5Y | NR 80.1% at 5Y | 55 mo 89.6% at 2Yr | NR 94.3% at 2Yr | 44mo | Not reached | NR 95% at 2Yr | NR 92% at 5 Yr |
| Median Fu | **5.9 yrs** | **70 mo** | **58.2 mo** | **58.2 mo** | **N rep.** | **24m** | **24 mo** | **18.8 mo** | **28.6 mo** | **62 mo** |
| Reference | CLL8 Fischer et al 2016 | Rossi 2015 Retrospective | CLL10 Eichhorst, et al. ASH 2016. Abstract 4382 | CLL10 Eichhorst, et al. ASH 2016. Abstract 4382 | Laurenti 2015 Leuk Res Retrospectiv "Real Life" | Gentile M et al. Eur J Cancer 2016 "Real Life" | MABLE Michallet iwCLL2015 #178 | CLL 11 Goede V, et al. N Engl J Med. 2014; | RESONATE-2 Barr et al. ASH 2016 | PCYC-1102 Susan M. O'Brien et al. ASH 2016 ORAL |

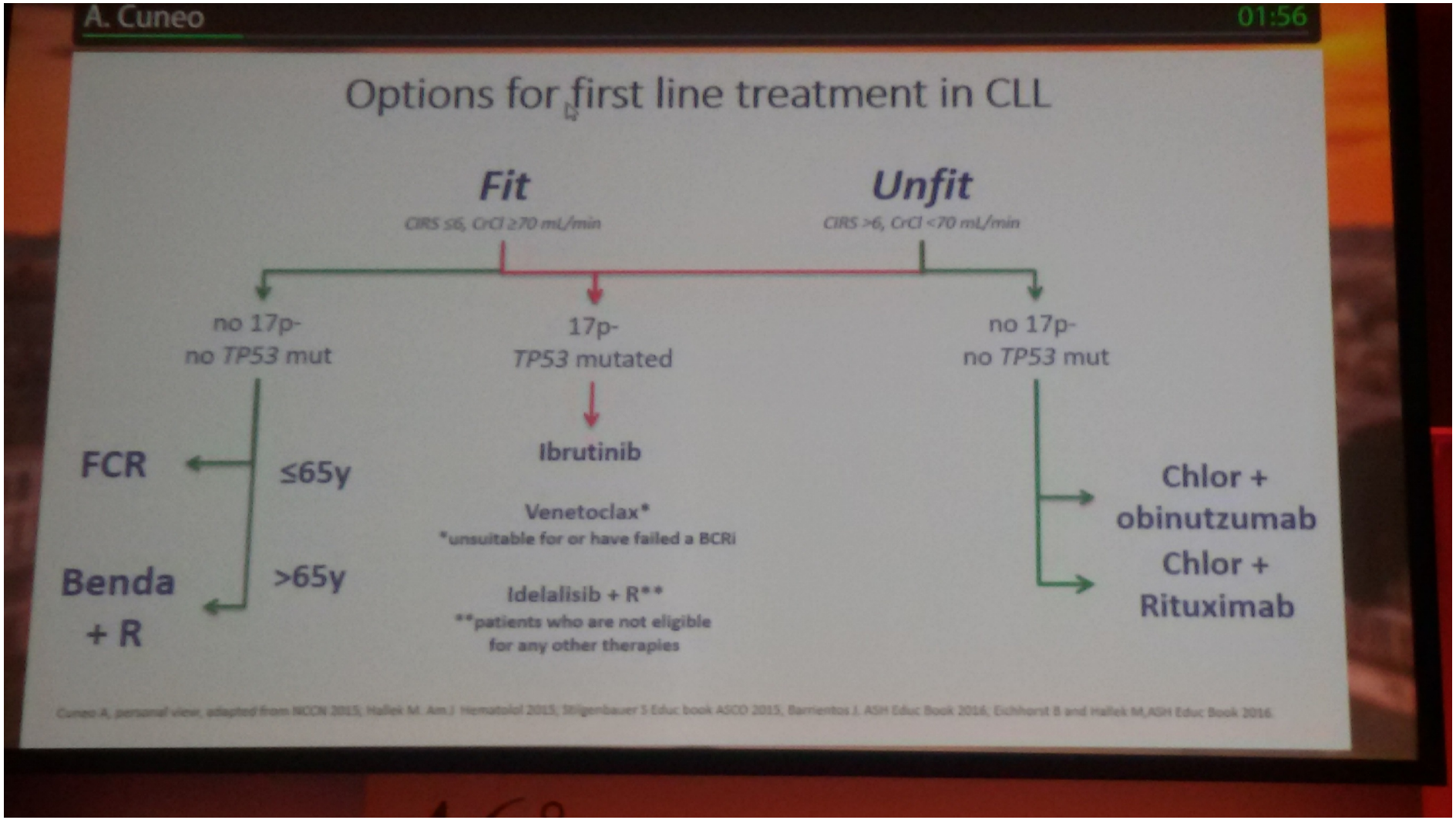
**Need longer follow up to draw any conclusions from naïve comparisons against FCR or BR in 1L CLL cohorts**

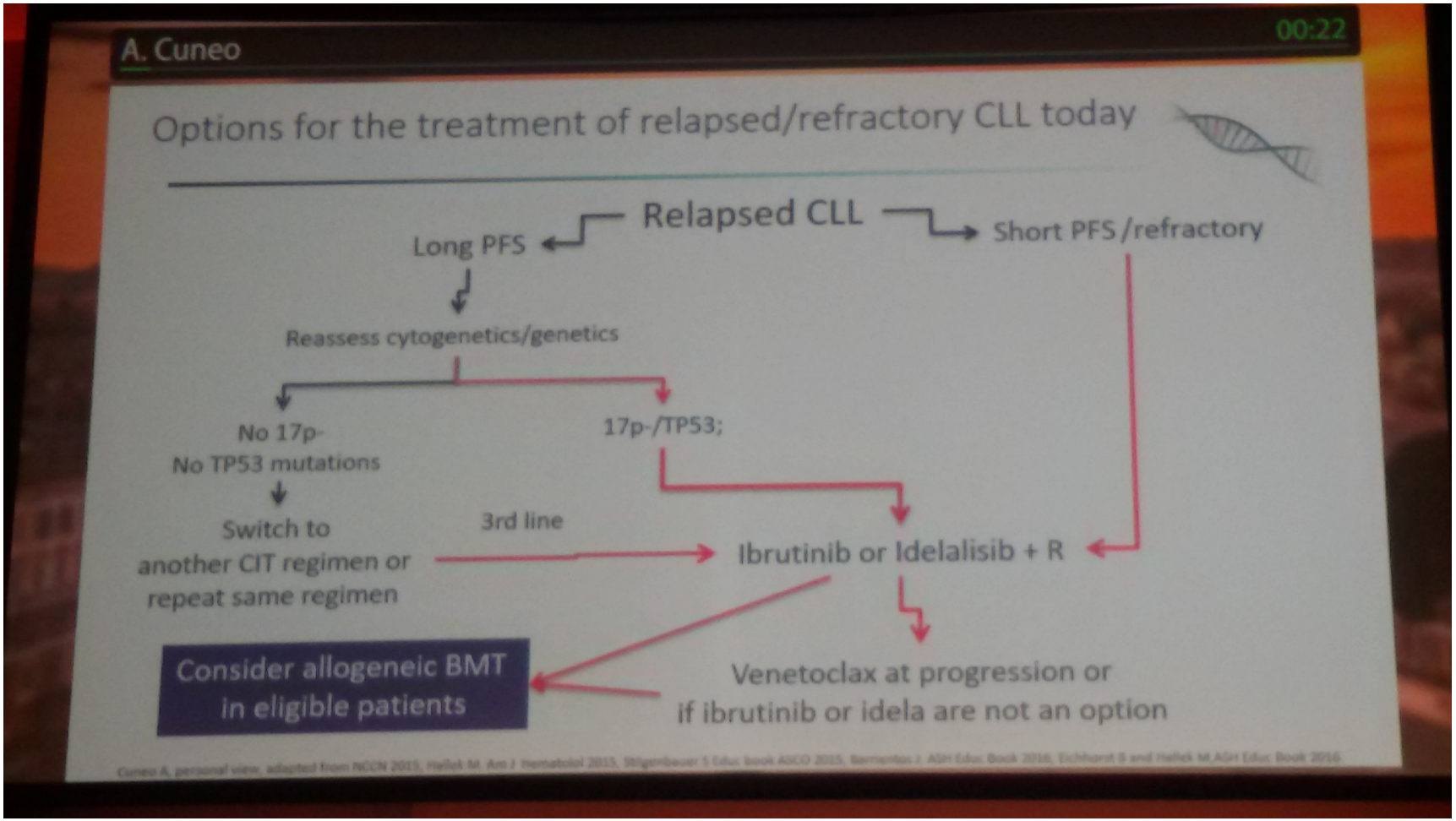
Caution: Naive Comparison

# R/R CLL

| | IBRUTINIB | | BR | | | FCR | | Ide | Ven |
|---|---|---|---|---|---|---|---|---|---|
| **Comparators** | **ibrutinib R/R** PCYC-1102 O'Brien ASH 2016 | **ibrutinib R/R** RESONATE J. Byrd ASCO 2017 | **BR** Fisher et al. JCO 2011 | **$BR_{HELIOS}$ (n=289)** Fraser iwCLL 2017 | **BR** A.Cuneo et al. ASH 2017 | **FCR** Badoux Blood 2011 | **FCR** Robak JCO 2010 REACH | **IDELA+R** Sharman ASH 2014 | **Venetoclax** Roberts 2016 |
| Median PFS, months | 52 | **NR** 3-year PFS rate was 59% | 15.2 | 14.3 | 25 | 20.9 | 30.6 | 19.4 | 66% at 15 mo |
| Median OS, months | NR 57% at 60 mp | **NR** 3-year OS rate was 74% | 33.9 | NR | NR 92.7% at 12 mo | 46 | NR | NR | NR |
| ORR, % | 86% | 91% | 59% | 66.1% | 82.3% | 74% | 69.9% | 81% 1 interim analysis | 77% |
| mFUp | 5-year (60 month) | 4-year (44 month) | 24 | 34.8 | 37.1 | 43 | 25 | 13 | 16.7 |


Susan M. O'Brien et al. ASH 2016 ORAL
John C. Byrd et al. ASCO 2017 Poster 272 - RESONATE 4 Year Follow-Up PCYC
Fisher et al. JCO 2011
Fraser et al., iwCLL 2017, abstract 400 (poster presentation)
Badoux C. et al. Blood March 17, 2011
Roback et al. JCO 2010
Sharman et al. ASH 2014; Abstract 330 (Oral Presentation)
Andrew W. Roberts et al. ASH 2016 POSTER
Roberts A.W. et al. – NEJM 2016
A.Cuneo et al. Abstract 642 - ASH 2017


A. Cuneo
01:56
Options for first line treatment in CLL
Fit
CIRS ≤6, CrCl ≥70 mL/min
Unfit
CIRS >6, CrCl <70 mL/min
no 17p-
no TP53 mut
17p-
TP53 mutated
no 17p-
no TP53 mut
FCR
≤65y
Benda
+ R
>65y
Ibrutinib
Venetoclax*
*unsuitable for or have failed a BCRi
Idelalisib + R**
**patients who are not eligible
for any other therapies
Chlor +
obinutzumab
Chlor +
Rituximab
Cuneo A, personal view, adapted from NCCN 2015; Hallek M. Am J Hematolol 2015; Stilgenbauer S Educ book ASCO 2015; Barrientos J. ASH Educ Book 2016; Eichhorst B and Hallek M,ASH Educ Book 2016


A. Cuneo
00:22
Options for the treatment of relapsed/refractory CLL today
Relapsed CLL
Long PFS
Short PFS /refractory
Reassess cytogenetics/genetics
No 17p-
No TP53 mutations
17p-/TP53;
Switch to
another CIT regimen or
repeat same regimen
3rd line
Ibrutinib or Idelalisib + R
Consider allogeneic BMT
in eligible patients
Venetoclax at progression or
if ibrutinib or idela are not an option

# DISCUSSION

- Cytogenetic:
  When? Who? Where? Why?
- IGHV mutational status
  When? Who? Where? Why?
- Therapeutic Algorithm
- New drugs
  alone or combination?


Nuovi scenari
in Ematologia
RESPONSABILI SCIENTIFICI
Fabrizio Pane
Claudio Cerchione
Giro Svanera
Maria Rosaria Villa
NAPOLI
1 dicembre 2017
PALAZZO ESEDRA

# *Grazie…*

*…*