FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

# Sequencing therapy for the relapsed/refractory CLL

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# Evaluate the need for treatment

- Is it time to re-treat?

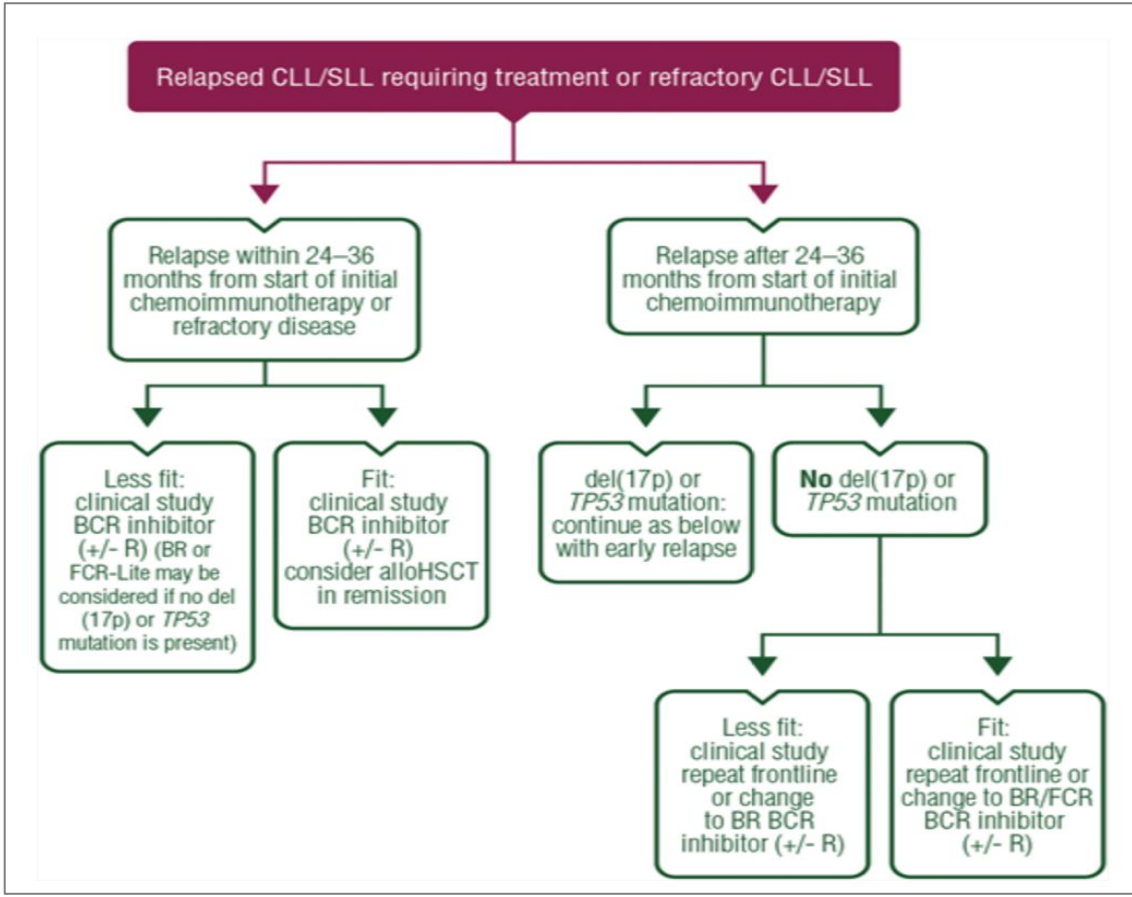
- IWCLL guidelines:
  - Second- and subsequent-line treatment decisions should generally follow the same indications as those used for first-line treatment.
  - For patient who did not achieve good response it is reasonable to initiate second-line treatment without waiting for formal disease progression to be manifest.
  - The rate of disease progression after some newer therapies can be rapid; it can be acceptable to initiate subsequent therapy before formal progression

*Hallek M, Blood, 2018*

# Strategies in relapsed CLL : ESMO guidelines 2017

- Relapse post chemo
- 2 parameters are considered:
  - Presence of TP53 alteration
  - Early versus late relapse
- Basically: BCR inhibitors possible in every situation
- Late relapse TP53 wild type :
  - Chemo still discussed

*Eichhorst, Ann Oncol 2017*



# Targeted therapies in R/R trials

**Ibrutinib**

- Trials
  - RESONATE (Ibru vs ofa)
  - HELIOS (BR vs IBR)
- *Real life data*

**Idelalisib (+ R)**

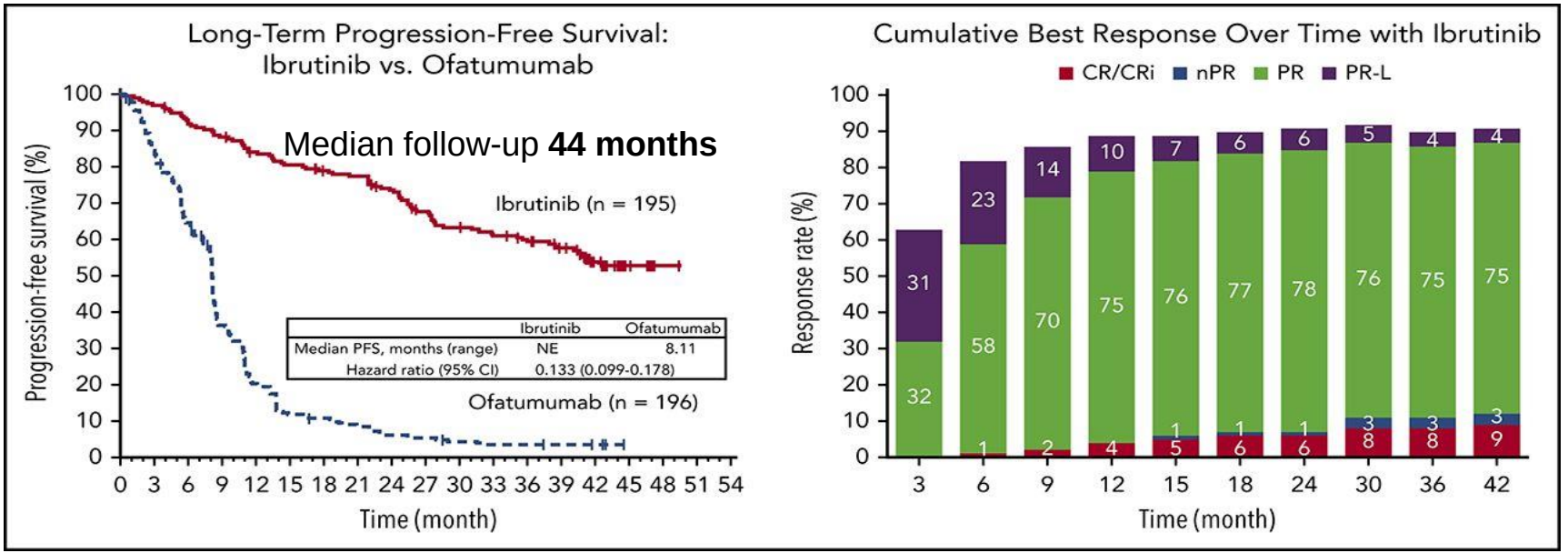
- Trials
  - Phase 3 (R-Idela vs rituximab)
- *Real life data*

**Venetoclax**

- V+R after CIT
  - MURANO trial
- V after BCRi failure
  - M1432 trial
- *Real life data*

Results outside of trials are good but never as good as in clinical trials

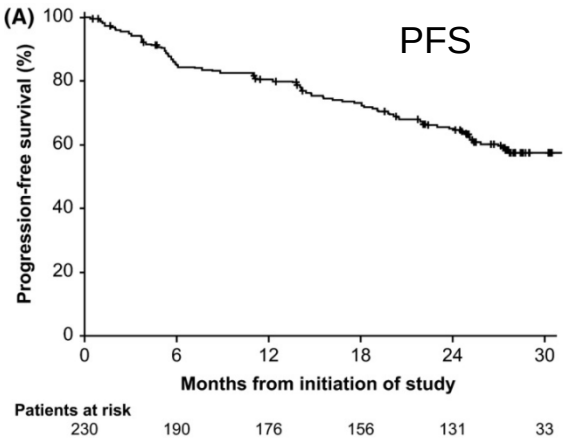
# Ibrutinib in relapsed CLL | RESONATE trial

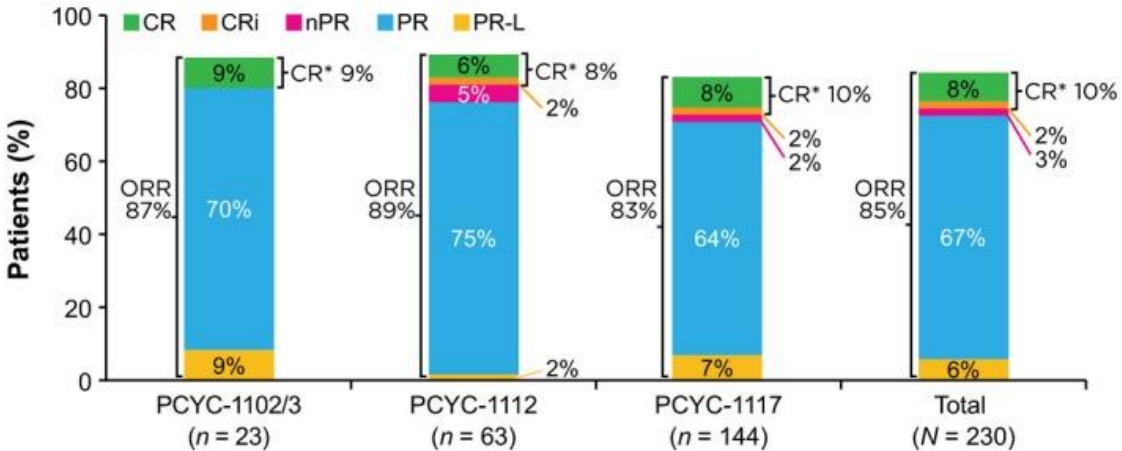



- ORR 91% in the ibrutinib arm
- Inferior PFS if prior therapies ≥ 2
- 56% of pts still on ibrutinib at 44 months

*Byrd, Blood 2019*

# Ibrutinib for relapsed 17p



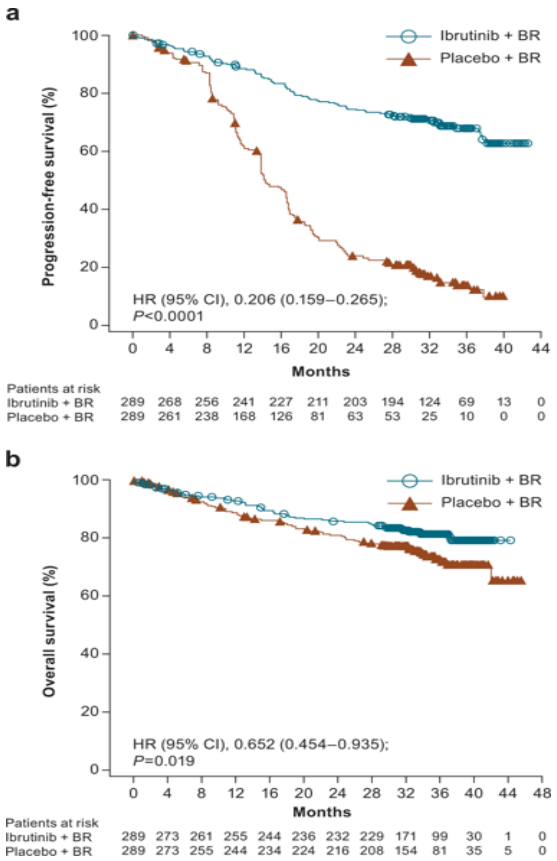




Outcomes in 230 patients with relapsed/refractory del(17p) CLL/SLL from three ibrutinib studies.

- Median follow-up of 28 months
- Overall response rate was 85%
- Estimated 30-month PFS was 57%

*J Jones Br J Haematol.2018*

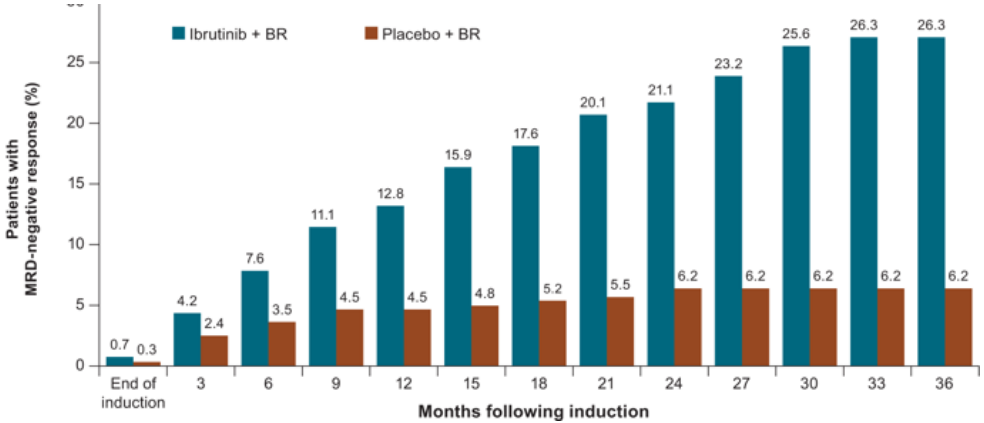
# Ibrutinib + chemo? I-BR vs BR / HELIOS trial




**I-BR** (vs BR) in R/R CLL without 17p del

Median follow-up **34.8 months**

- Median PFS NR vs 14.8 months
- 36-month PFS 68 % vs 13.9 %
- MRD(-) 26.3 % vs 6.2 %




No direct comparison with ibrutinib alone
Not indicated for TP53 alterations

*Fraser, Leukemia 2019*

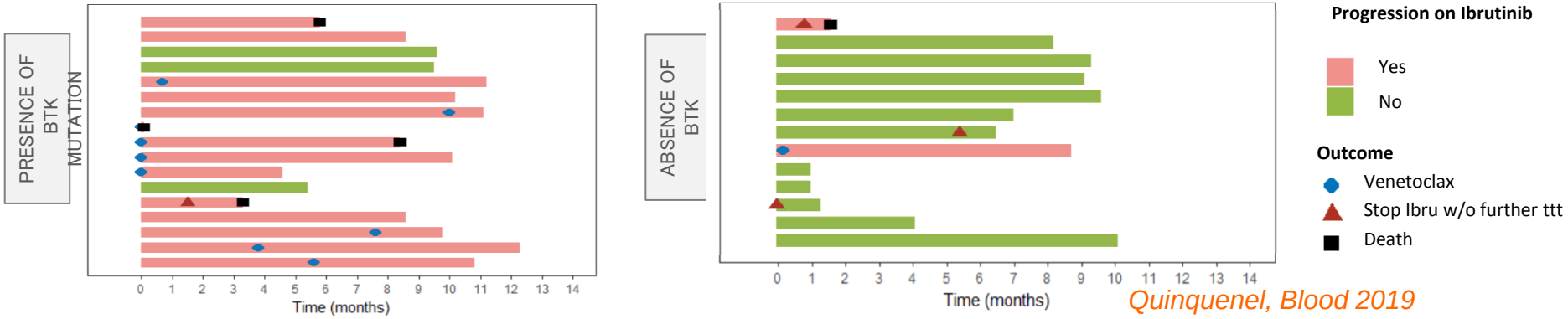
# Safe Ibrutinib use

- In theory, ibrutinib may be indicated for control of CLL in all relapsed settings after immunochemotherapy
- But rather than CLL characteristics, decision to use ibrutinib is driven by the risk of adverse events and drug interactions
- Ibrutinib treatment decision should include
  - Cardiovascular risk assessment
  - Extensive analysis of co-medications
    - CYP3A4 inducers and inhibitors, anticoagulants, antiplatelet therapy+++
  - Understanding and willingness to follow long term therapy
- It is important to raise awareness of treating physician and patient on adverse events and comedications

# Resistance to Ibrutinib

- Ibrutinib is used as a prolonged monotherapy until progression

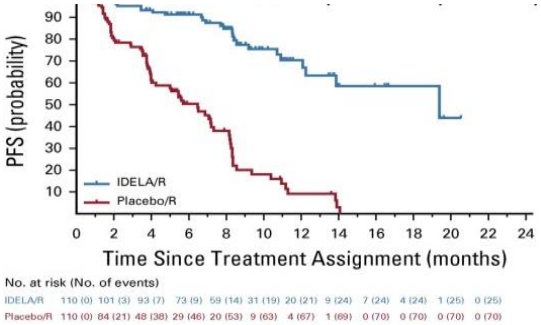
- Resistance mutations occur, notably after 3 years
  - mostly located at C481S Btk
  - PLC$\gamma$2 mutations may also occur
  - In a recent snapshot study of patients on ibrutinib for 3 years we observed that
    - Half of the patients were in very good response,
    - Among the other half, 17/30 had a Btk mutations, and 14/17 progressed within 9 months, whereas only 2 /13 progressed in the absence of mutations



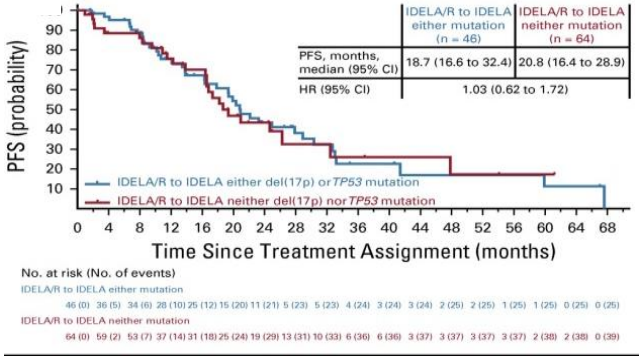

*Quinquenel, Blood 2019*

# Idela + R: relapse after chemoimmunotherapy

Short term PFS compared with Placebo+R




**PFS**



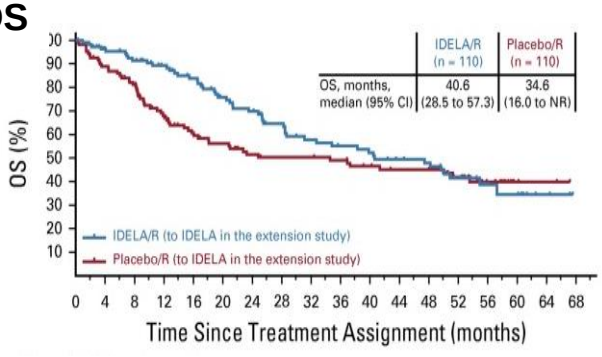

Long term PFS Idela+R with and without TP53 alteration

## Results of the pivotal phase 3 trial Idela + R versus placebo + R alone

Elderly patients
Several lines, comorbidities
Presence of del(17p) or TP53 mutations did not negatively affect clinical outcome

Mediane OS 40,6 vs 34,6 months
Cross over allowed

**OS**




*Sharman JP, JCO 2019;*

# Venetoclax in R/R CLL: VR vs BR (MURANO trial)

**R/R CLL (n = 389)**
- ≥ 18 years old
- 1-3 previous lines

R 1:1

C1D1

VEN 5 weeks *ramp-up*

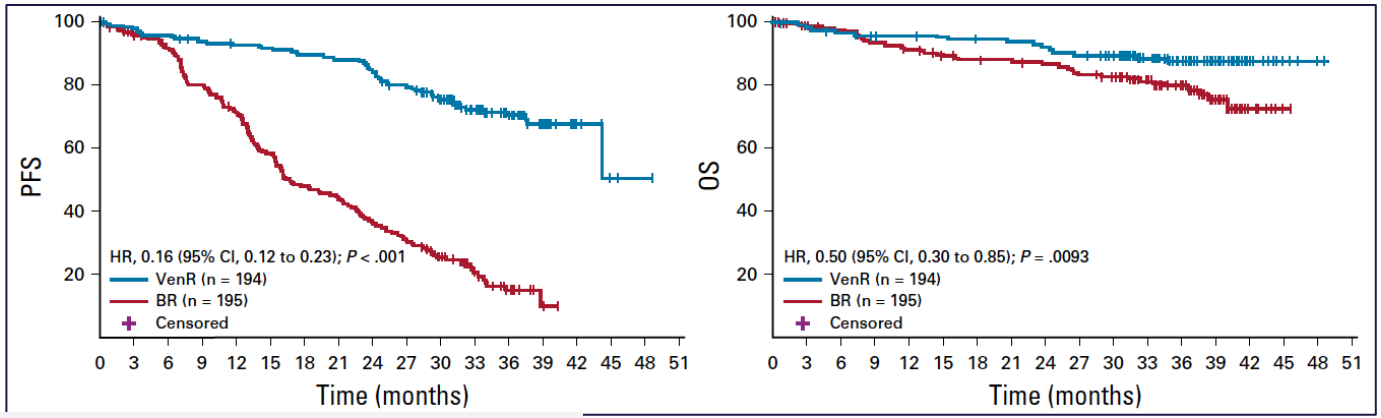
**Venetoclax 400 mg/d**

**+ Rituximab 6 cycles**

**Bendamustine**
70 mg/m² D1 et D2 cycles 1-6
+ **Rituximab 6 cycles**

Until progression or toxicity max 2 years

Fixed duration therapy




| Treatment | 3-y PFS, % ( 95 CI %) |
|---|---|
| **V + R** (n = 194) | 71.4 (64.8-78.1) |
| **BR** (n = 195) | 15.2 (9.1-21.4) |

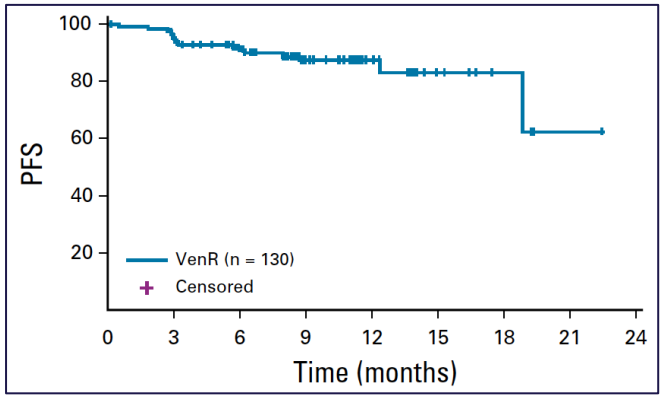
| Treatment | 3-y OS, % ( 95 CI %) |
|---|---|
| **V + R** (n = 194) | 87.9 (83.1-92.7) |
| **BR** (n = 195) | 79.5 (73.3-85.6) |

Median follow-up 36 months

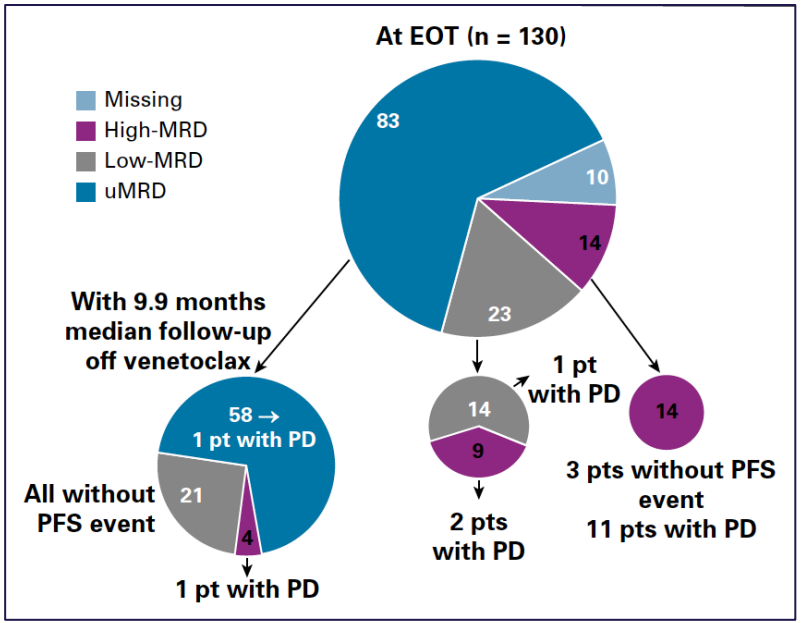
*Kater A, JCO 2019*

# VR vs BR (MURANO) | MRD and PFS

PFS from venetoclax discontinuation




- Median follow-up 9.9 months post treatment
- 1y-PFS 87% (95% CI 81.1-93.8)
- Predictive factors for relapse
  - TP53 abnormalities
  - Absence of 11q deletion
  - MRD (blood) at M24




| | VenR arm: HR (95% CI) |
|---|---|
| uMRD *v* L-MRD | 0.48 (0.24 to 0.98) |
| uMRD *v* H-MRD | 0.15 (0.06 to 0.40) |

Correlation between MRD and PFS

*Kater A, JCO 2019*

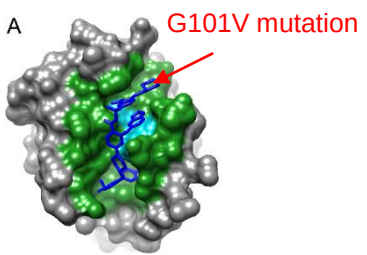
# Venetoclax and BCL2 mutations

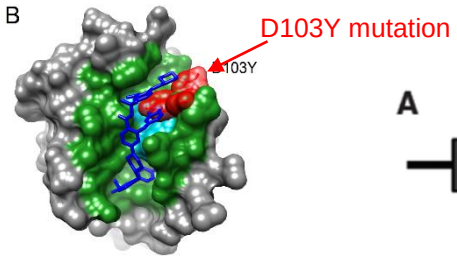
- 15 pts progressing on venetoclax
- Targeted sequencing (33 genes)
  - before venetoclax
  - at relapse
- BCL2 mutations
  - 7/15 pts
  - reduces the affinity of venetoclax to BCL2

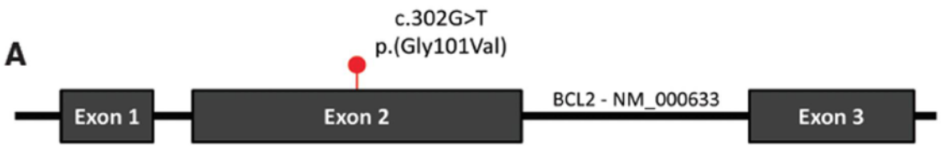
*Blombery, Cancer Discovery 2019*

- 3 of 4 patients with >3 years on drug and refractory disease are mutated in BCL2
- Another mutation D103Y identified
- Preceding the G101V in one patient
- The 2 mutations were present in 2 different subclones

*Tausch, Hematologica 2019*



# First relapse after chemotherapy: I or V+R?

- *Provided we have access to both therapies*
- Some similar arguments
  - Clinical trials results
  - Oral therapy
  - Efficient in unfavorable risk groups

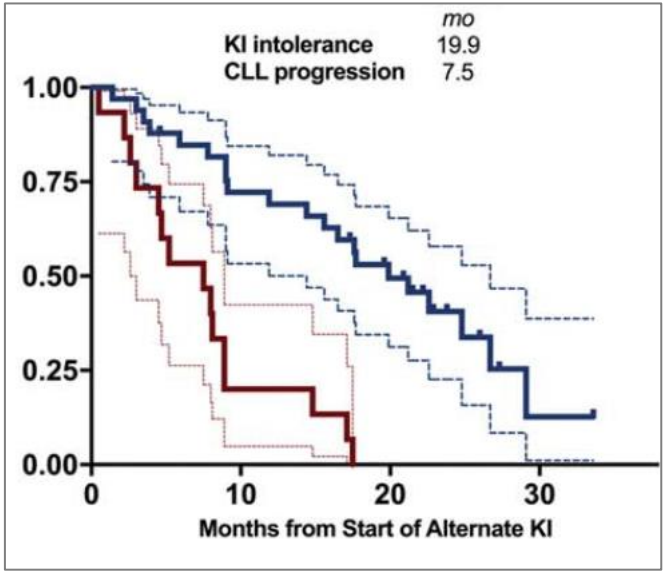
- Ibrutinib
  - Caution with comorbidities/comed
  - Various adverse events
  - Prolonged therapy
  - Long term data available
  - Developpement of resistances

- Venetoclax + R
  - Ramp up and hospitalization
  - Neutropenias
  - Fixed duration therapy
  - No long term data available,
  - Developpement of resistances

- Decision often made on comorbidities and physician/patient preferences

# First relapse after Ibrutinib

- Is there a place for Idela + R?
  - For patients intolerant  or ineligible to Ibrutinib remains an option
    - Ex: Patients with autoimmune thrombocytopenias?
  - In Ibrutinib failure, not recommended
    - Retrospective studies show very poor results
    - Presence of PLC$\gamma$2 mutation lead to Idela resistance as well
- Other BTK inhibitors?
  - Similar toxicities
  - Non covalent BCRi may be effective in case of Btk mutations



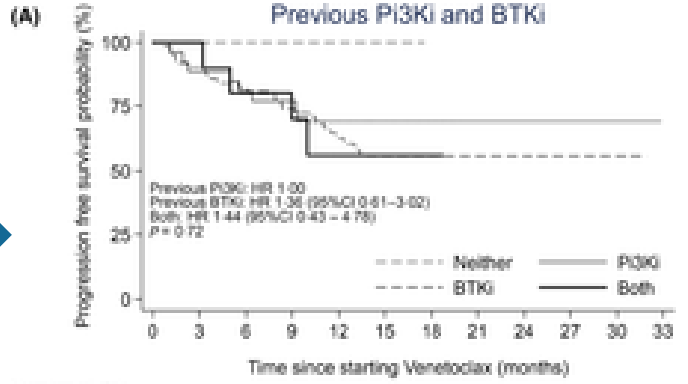

*Quinquenel, Am J Hematol, 2019*
*Godet, Am J Hematol 2018*

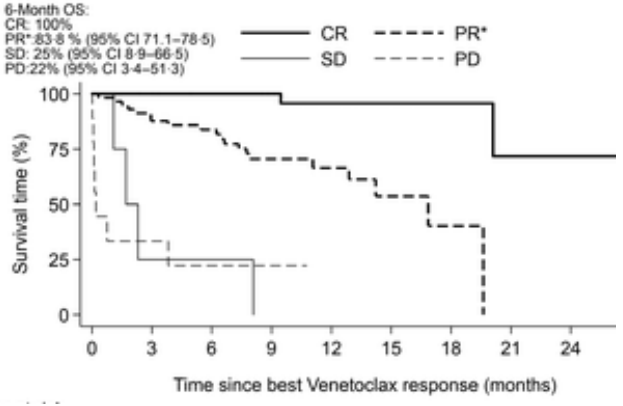
# What is the best sequence of chemofree?

- Patients will relapse after either I or V+R.

- Then what is the best sequence?
  - There are data of Venetoclax use after Ibrutinib
    - Same response according to the BCRi used
    - If patient reach CR with venetoclax  very good
  - Very little data of Ibrutinib after Venetoclax failure
  - Considering mechansims of resistance
    - Btk mutations do not impair response to other therapies
    - But Ibrutinib does not prevent clonal evolution
    - Venetoclax induced resistance mutations target either Bcl-2 mutations or some important pathways that could be more difficult to circumvent

British cohort in a non trial setting

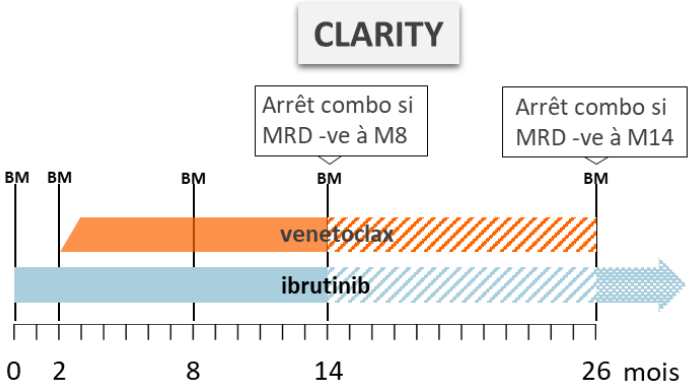


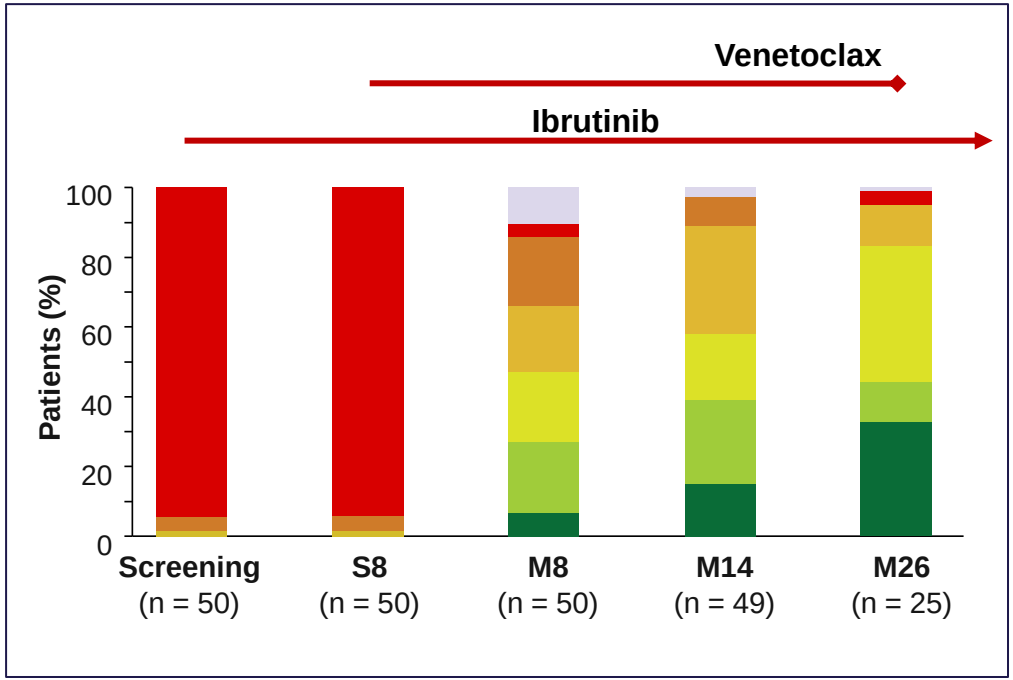

*TA Eyre, BJH 2019*

# Future options – combination of V and I (CLARITY trial) ?

Combining Venetoclax and Ibrutinib in a fixed therapy duration and/or MRD driven Is certainly a very promising option




Primary endpoint : MRD4 (BM) at M12 I + V




*Hilmen, ASH 2018*

# Sequencing therapy in relapsed CLL: conclusions