Caso Clinico 2: LLC

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MILANO

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HILTON MILAN

Disclosures of Lucia Farina

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen							x
AbbVie							x
AstraZeneca							x

CLINICAL CASE

- Male, born 1952
- Moderate IRC due to polycystic kidney
- June 2000: diagnosis of CLL, unknown IGH and FISH status

- **April-September 2006 (54 years old):** FC x 6 cycles → CR
- Treatment criteria not known

CLINICAL CASE

- **September 2012 (6 years after FC):** lymphocyte doubling time < 6 months and progressive adenopathies
- Patient is 60 years old, ECOG 0, CIRS 2 (HbsAg pos and IRC)
- At this time FISH was positive for del13q (negative for del11q, del17p, and try12) and IGH rearrangement was mutated (VH3-23 ID 97%)

- Treatment options in 2012:

repeating chemoimmunotherapy (FCR vs BR)?

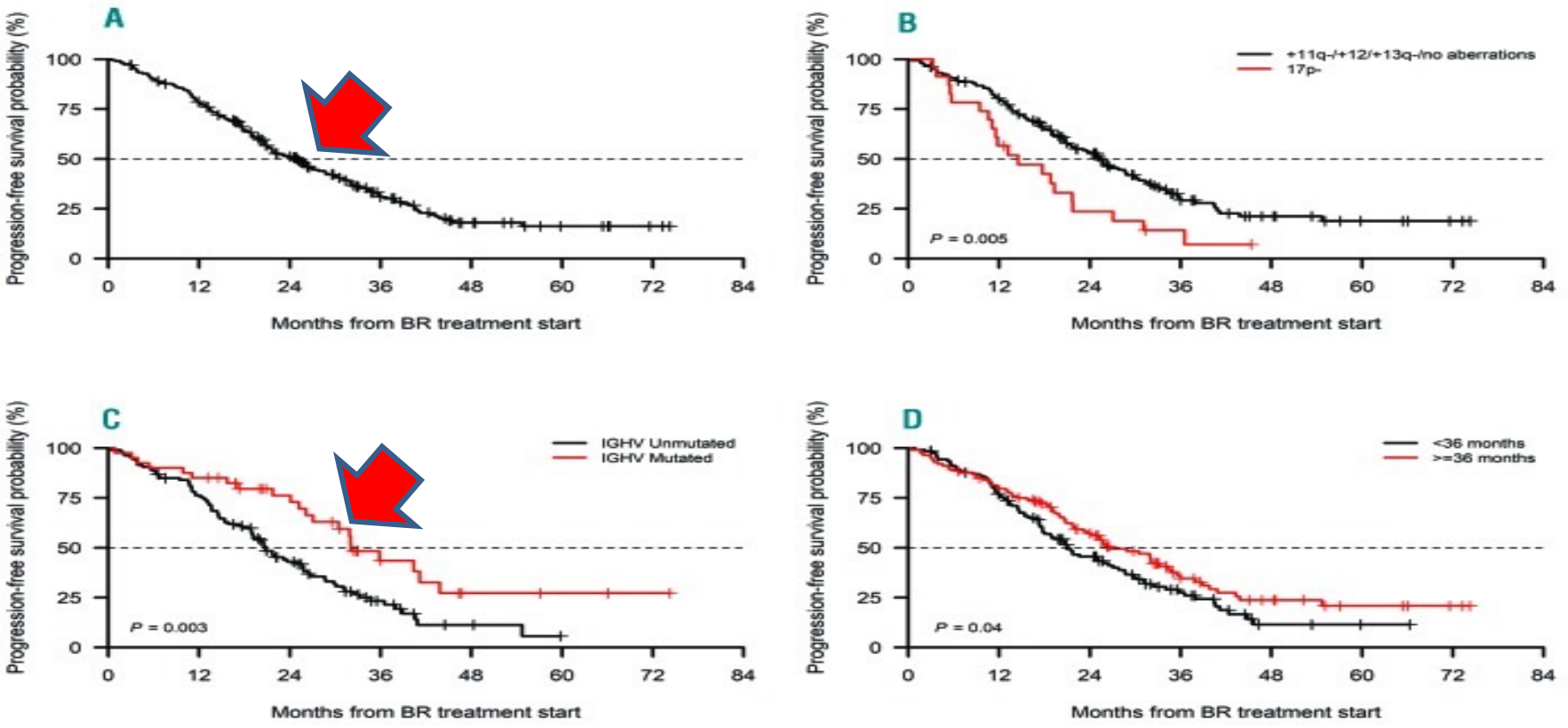
CLINICAL CASE

- **November 2012 to April 2013:** BR x 6 cycles (with tenofovir prophylaxis)

CR MRD pos by flow cytometry on PB

PFS after R-benda as second-line therapy

PFS



Cuneo et al, Heamtol 2018

CLINICAL CASE

- **November 2015 (2 years-6 months after BR):**

lymphocyte doubling time < 6 months, anemia and thrombocytopenia

- Patient is 63 years old, ECOG 0, CIRS 2 (HbsAg pos and IRC)
- At this time FISH was negative for 17p deletion (TP53 mutation not performed)
- CT scan showed lymph nodes max 40 mm and progressively increasing and spleen was 13 cm by bipolar diameter

- Treatment options at that time:
  ibrutinib vs idelalisib-rituximab?

CLINICAL CASE

- **December 2015:** the patient started idelalisib-rituximab

CLL best response → PR

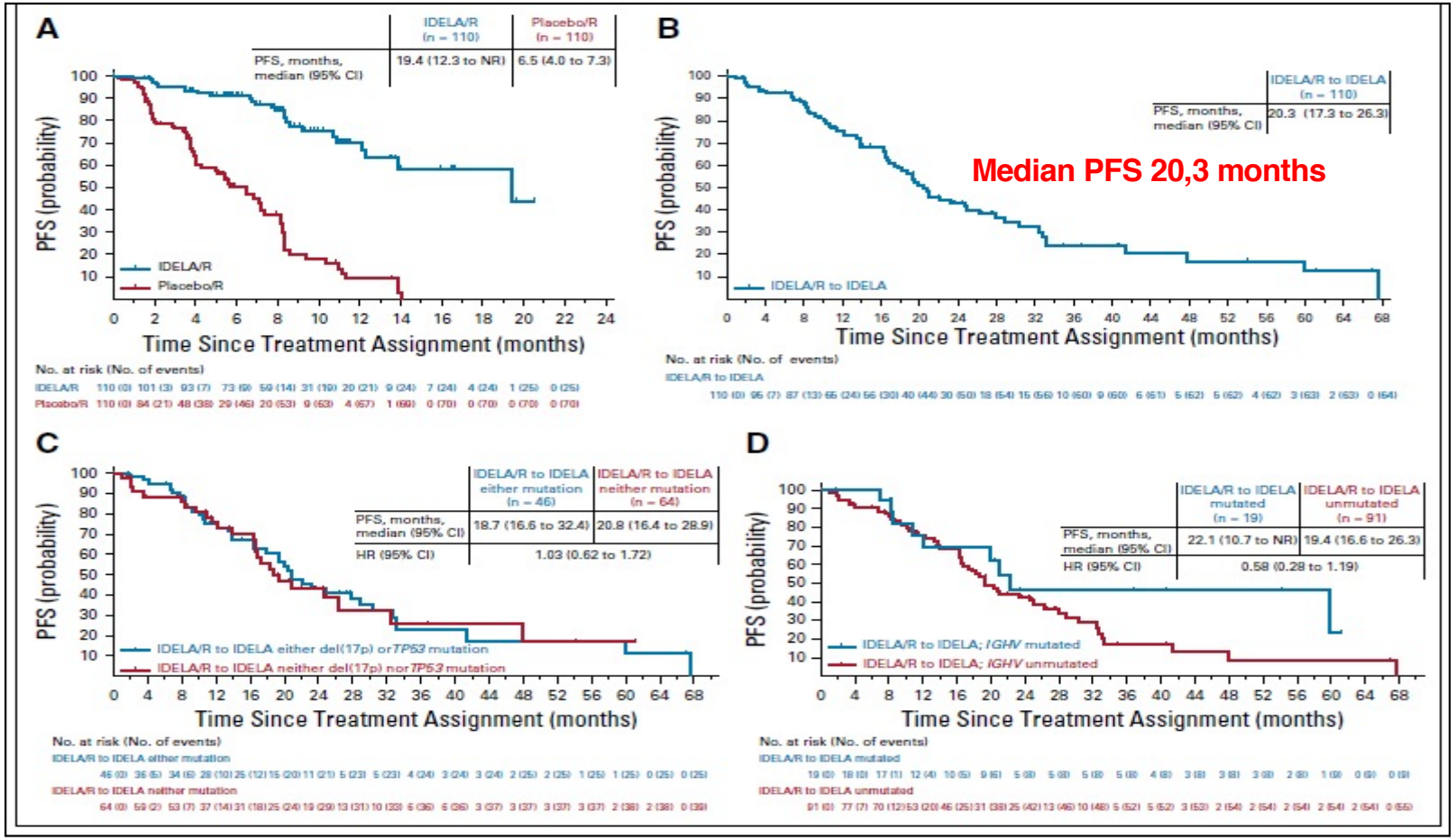
Clincal course was complicated
by recurrent CMV reactivation (February 2017)
and grade 2-3 diarrhea (October 2017) treated with budesonide

CLINICAL CASE

Hospital admission in November 2019 because of grade 3 diarrhea:
histologic diagnosis con CMV colitis complicated by acute renal failure and bacterial pneumonia → **idelalisib definitely stopped 4 years after therapy start**

- Diarrhea and CMV reactivation persisted from November 2019 to March 2020
- Valgancyclovir was definetively stopped in May 2020
- Clincal course was complicated by ureteral calculosis with hydrouretheronephrosis

Idelalisib-rituximab: final results of a phase III study



Sharman JP et al JCO 2019

Idelalisib-rituximab: final results of a phase III study

TABLE 2. Summary of Adverse Events

	No. (%) of Patients		
	Primary Study		Primary + Extension Studies
Adverse Event	**IDELA/R (n = 110)***	**Placebo/R (n = 108)***	**IDELA/R-to-IDELA (n = 110)†**
Summary			
Any	108 (98.2)	106 (98.1)	108 (98.2)
Grade ≥ 3	81 (73.6)	58 (53.7)	100 (90.9)
Any study drug related	61 (55.5)	26 (24.1)	75 (68.2)
Study drug related grade ≥ 3	36 (32.7)	8 (7.4)	52 (47.3)
Serious	65 (59.1)	43 (39.8)	89 (80.9)
Led to death	4 (3.6)	11 (10.2)	13 (11.8)‡
Infection or infestation			
Grade ≥ 3 in ≥ 5%§	36 (32.7)	25 (23.1)	59 (53.6)
Lower respiratory tract infection	16 (14.5)	12 (11.1)	26 (23.6)
Sepsis, bacteremia, viremia, and fungemia	11 (10.0)	5 (4.6)	19 (17.3)
Bacterial infection	3 (2.7)	3 (2.8)	8 (7.3)
Upper respiratory tract infection	1 (0.9)	2 (1.9)	6 (5.5)

Sharman JP et al JCO 2019

CLINICAL CASE

- **June 2020 (7 months after idelalisib stop):** progressive adenopathy, anemia, thrombocytopenia and splenomegaly
- Patient is 68 years old, ECOG 0, CIRS 3 (HbsAg pos, IRC, calculosis, IPB)
- FISH positive for del13q, negative for del17p, del11q, try 12;
- PT53 not-mutated

- Treatment options at this time:

ibrutinib vs venetoclax based therapy?

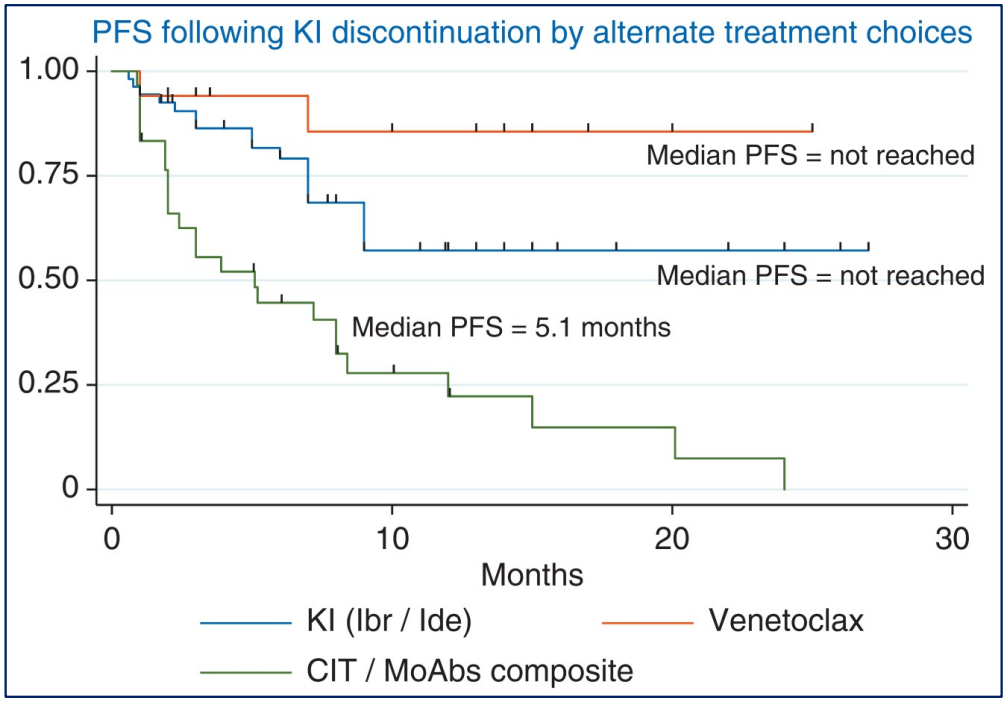
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

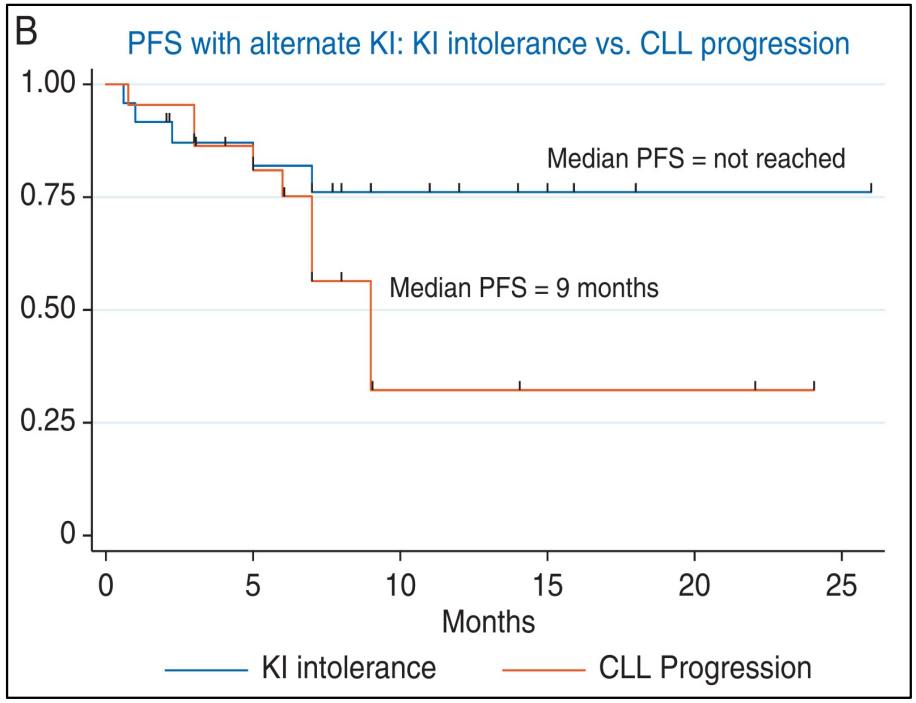
Annals of Oncology 28: 1050–1056, 2017
doi:10.1093/annonc/mdx031
Published online 25 January 2017

ORIGINAL ARTICLE

Optimal sequencing of ibrutinib, idelalisib, and venetoclax in chronic lymphocytic leukemia: results from a multicenter study of 683 patients

A. R. Mato[1*], B. T. Hill[2], N. Lamanna[3], P. M. Barr[4], C. S. Ujjani[5], D. M. Brander[6], C. Howlett[7,8],





CLINICAL CASE

- **June 2020 (7 months after idelalisib stop): ibrutinib 420 mg daily was started** (after cardiac evaluation)
- July 2020: hemolytic anemia treated with steroids and Rituximab

•November 2020: therapy was temporary stopped due to grade 3 diarrhea (blood CMV-negative) combined with grade 2 nausea and arthralgia

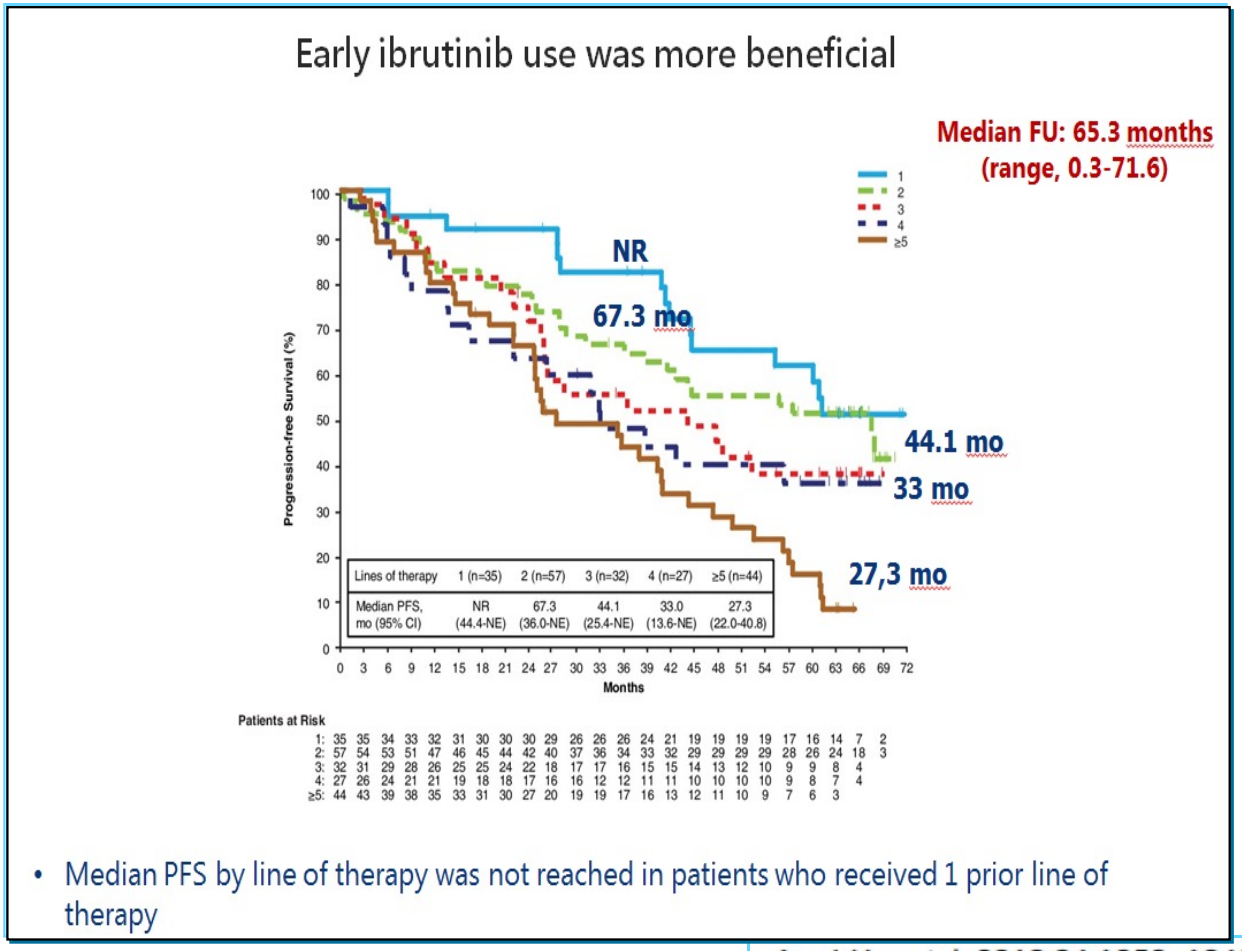
•February 2021: therapy was temporary stopped due to COVID-negative pneumonia **and then restarted at 280 mg daily** (also due to the low compliance of the patient)

Final analysis of RESONATE: up to six year of follow-up in R/R CLL treated with ibrutinib

Median PFS decreased with the increase of the number previous lines of therapies:

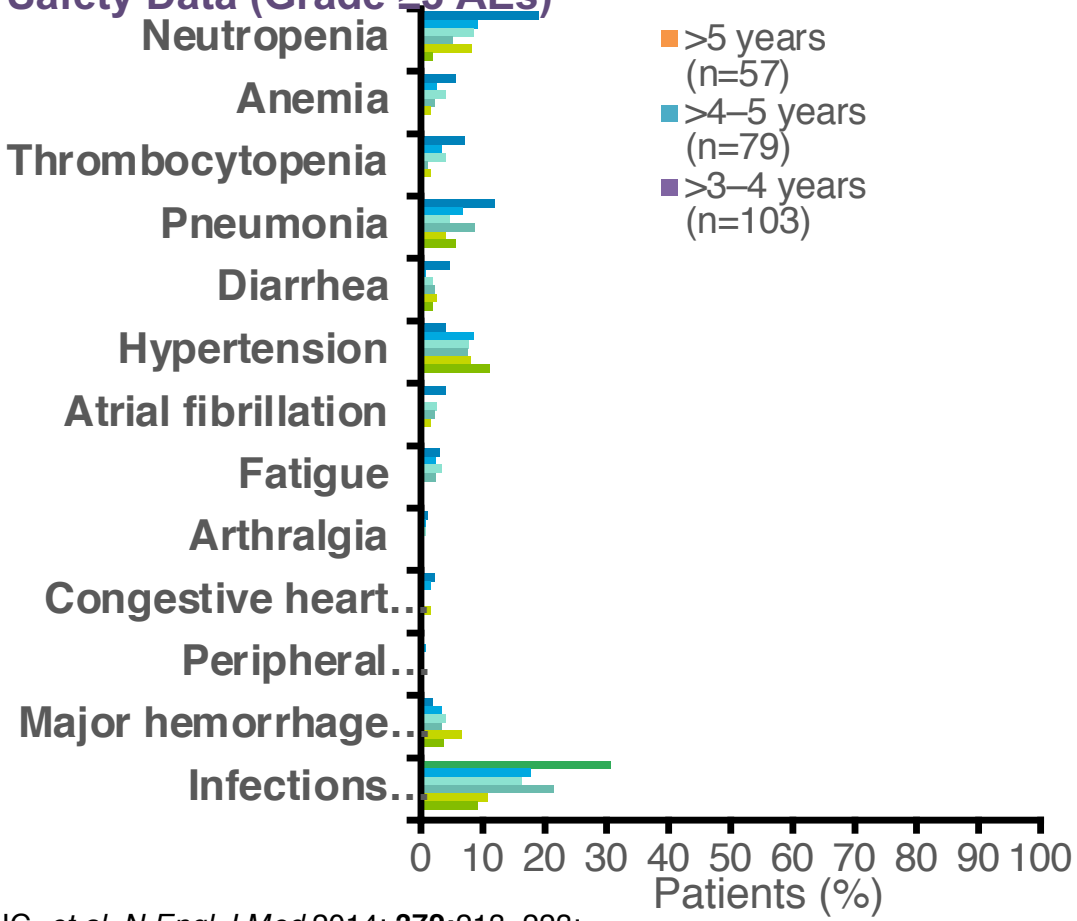
-NOT reached after 1 line
-67 m after 2 lines
-44 m after 3 lines
-33 m after 4 lines

PFS may be reduced by NOT continuous therapy



Am J Hematol. 2019;94:1353–1363.

Safety Data (Grade ≥3 AEs)



RESONATE:
65 months follow-up

1. Byrd JC, *et al. N Engl J Med* 2014; **372:**213–223;
2. Munir T, *et al. Am J Hematol* 2019; 2019; **94:**1353–1363;
3. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120 (including supplement).

CLINICAL CASE

- Best reponse with ibrutinib → PR after 22 months

- At the last follow-up patient is fine but lymphocytes are increasing after 22 months → increase ibrutinib to 420 mg daily

- Treatment options at this time:
  Venetoclax monotherapy?

CLINICAL CASE
Conclusions

- CLL patients have many treatment options compared to the past

- Therapy sequencing may be crucial for the best management of the patient

- New inhibitors are not devoid of side effects and patient compliance may be an issue for continuous therapy in the long-term