2nd Postgraduate CLL Conference

How Should We Sequence These Novel Agents?

Matthew S. Davids, MD, MMSc
Assistant Professor of Medicine | Harvard Medical School
Associate Director, CLL Center |Dana-Farber Cancer Institute
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Disclosures for Matthew S. Davids, MD, MMSc

- **Consultancy/Advisory Boards:** AbbVie, Genentech, Pharmacyclics, Janssen, Astra-Zeneca, Acerta, MEI Pharma, Verastem, Gilead, Syros, Sunesis, Adaptive Biotechnologies, TG Therapeutics

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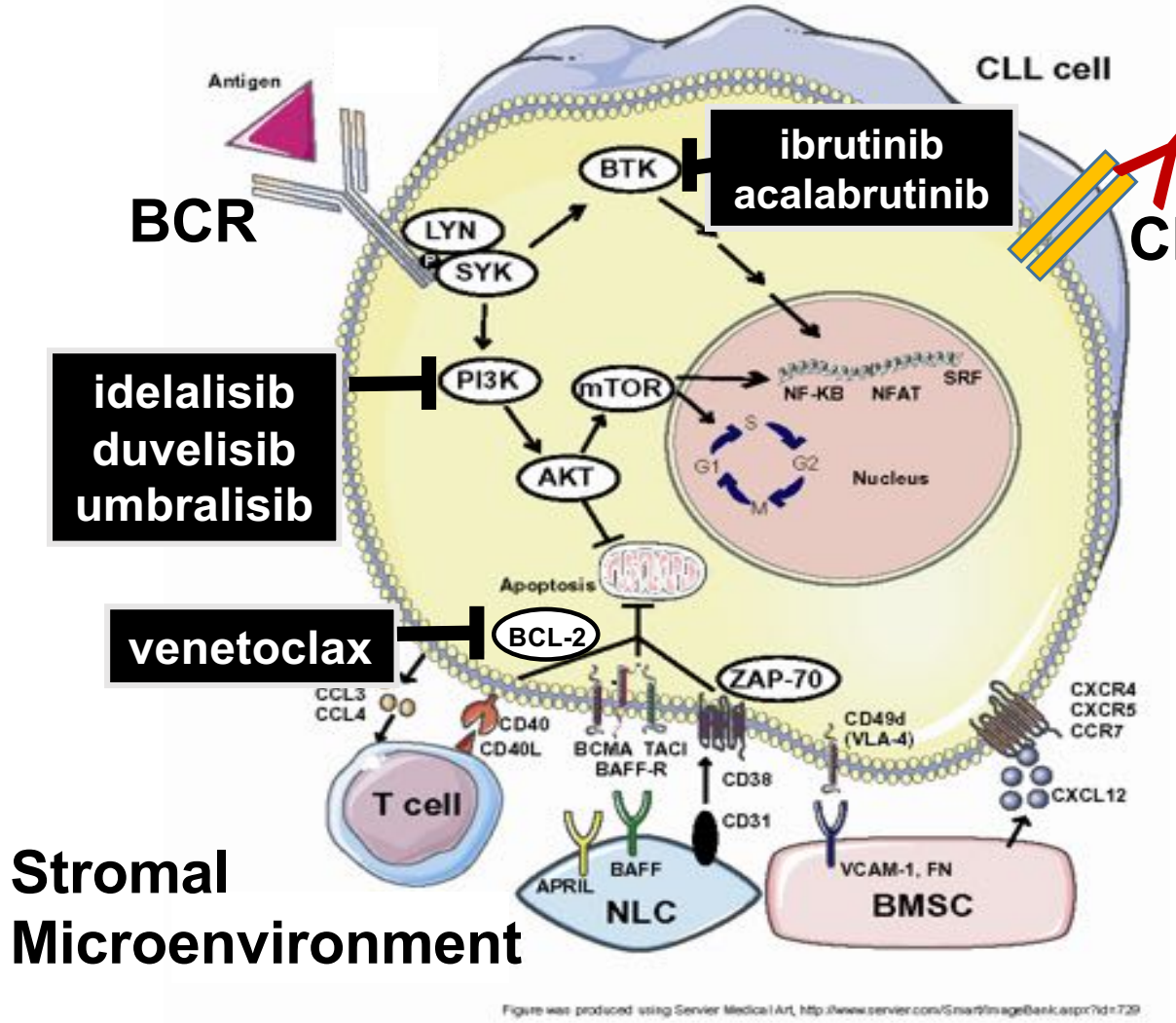
Novel agents in CLL are mechanistically diverse



Adapted from Davids and Brown, *Leuk Lymph*, 2012

What should our goals of care be for CLL patients?

Control?

Cure?

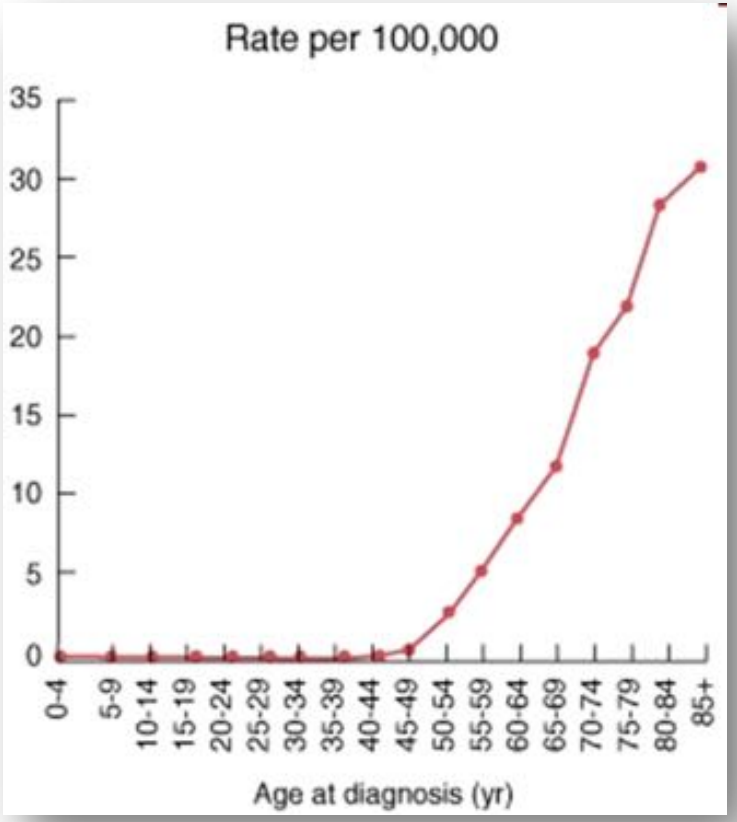
Two treatment strategies are emerging

Sequential
novel agent monotherapy

Metronomic
novel agent combinations

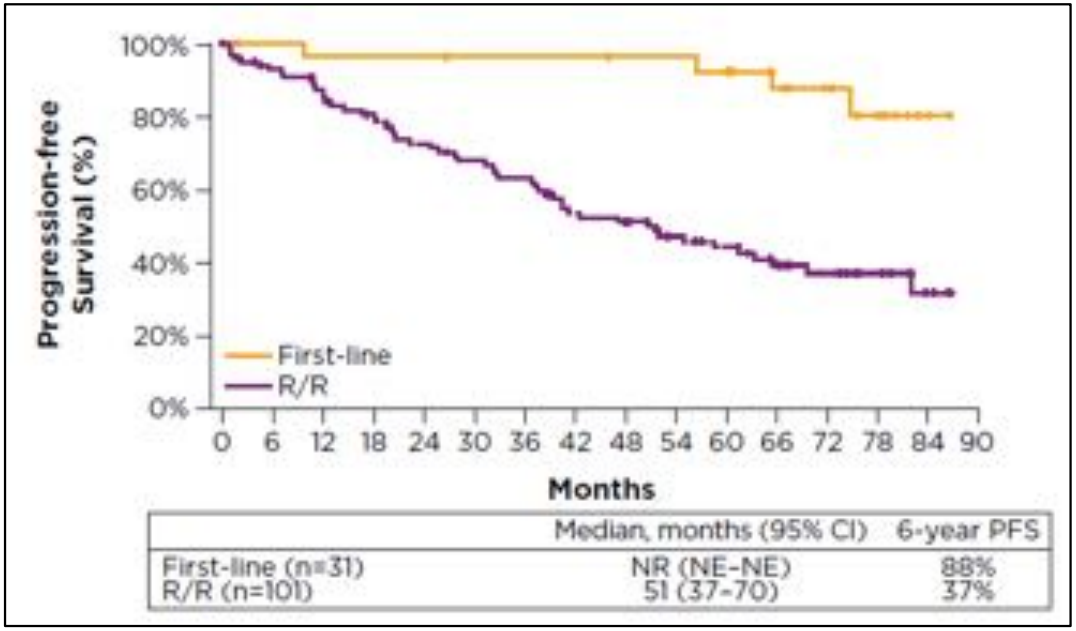
CLL is a primarily a disease of the elderly

- **Median age at diagnosis:** ~72 years
- **Median age at first treatment:** ~77 years



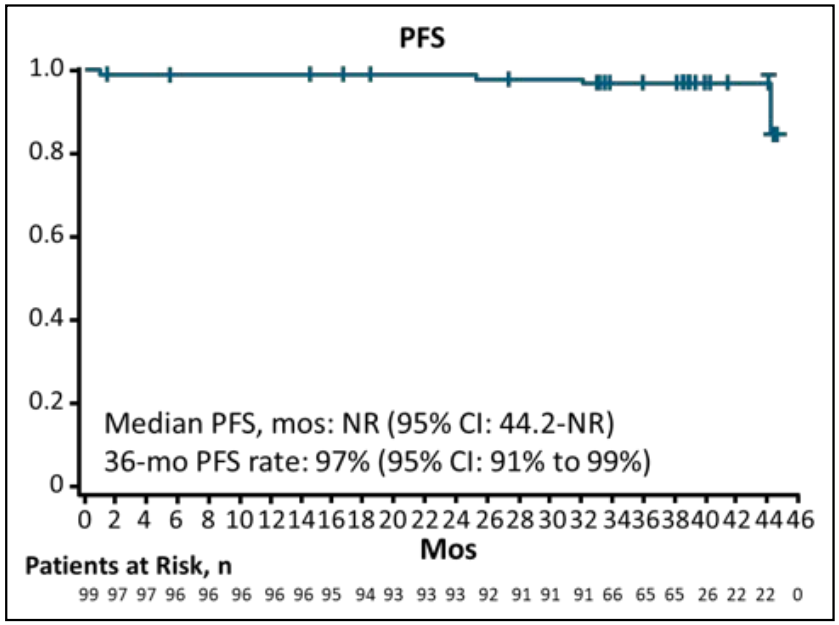
Long term data confirm durable response to 1L BTKi

Ibrutinib 6 year PFS: 88%



	Median, months (95% CI)	6-year PFS
First-line (n=31)	NR (NE-NE)	88%
R/R (n=101)	51 (37-70)	37%

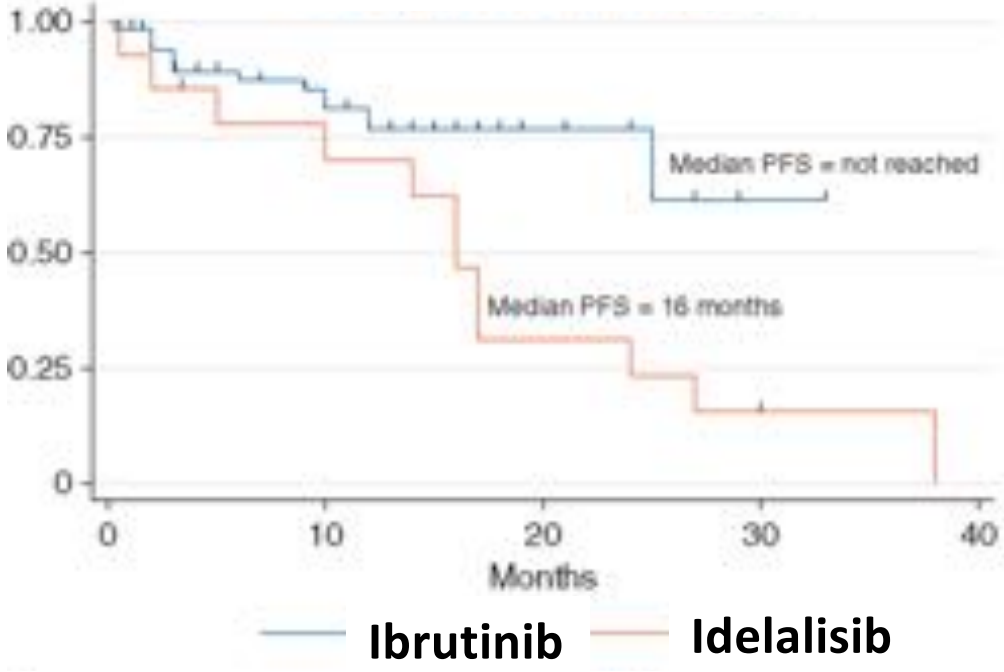
Acalabrutinib 3 year PFS: 97%



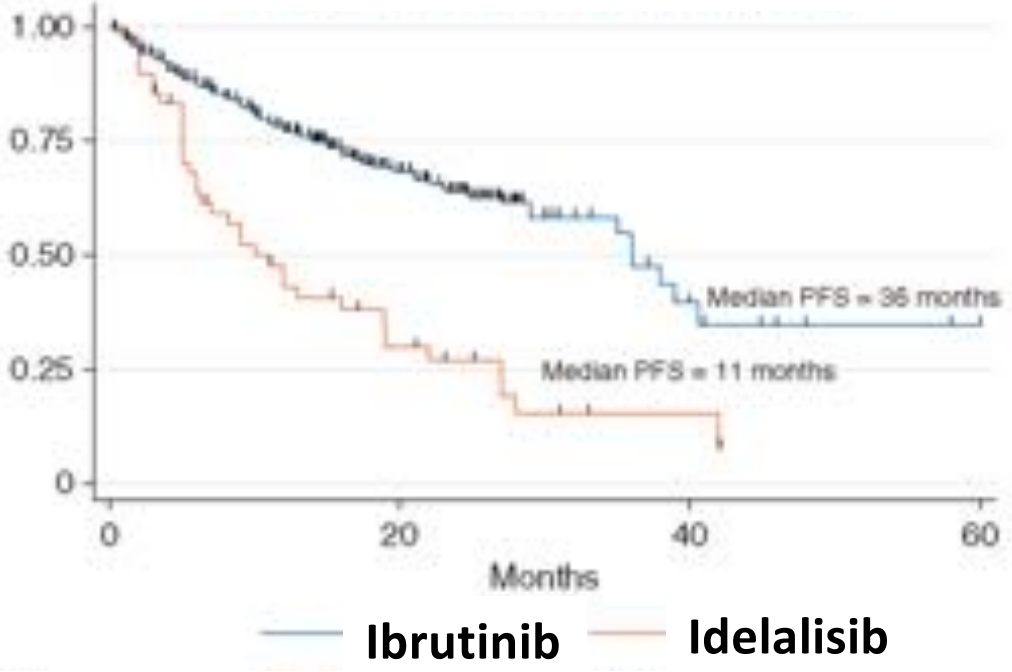
Byrd et al., ASH, 2018

A retrospective study in 683 pts found that pts treated with ibrutinib as first kinase inhibitor (KI) had superior PFS

PFS by first KI: Front-line



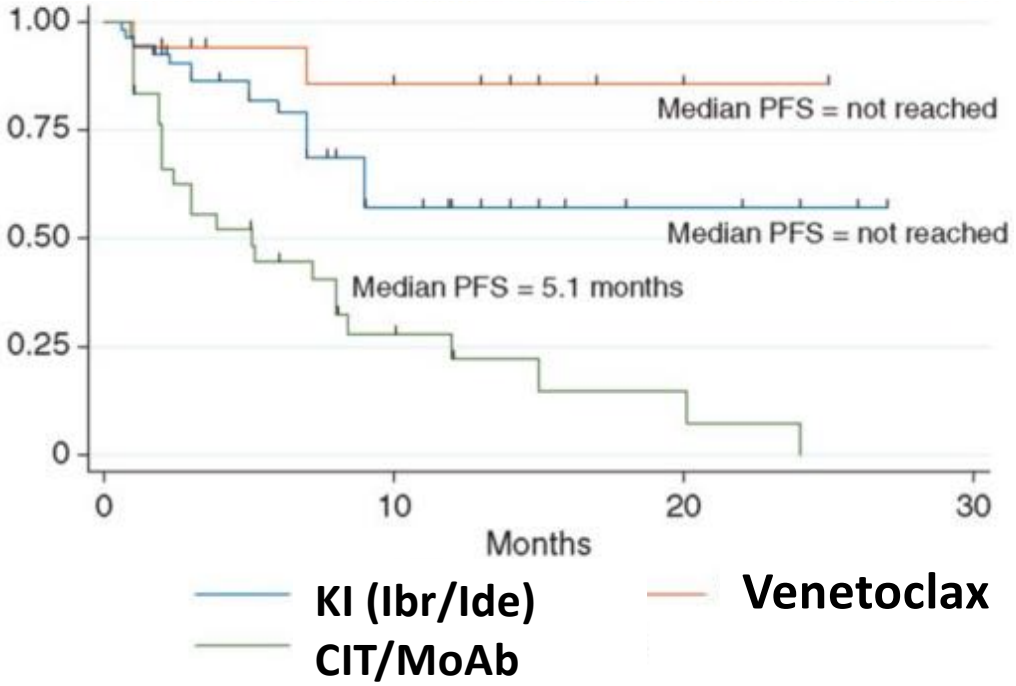
PFS by first KI: R/R after CIT



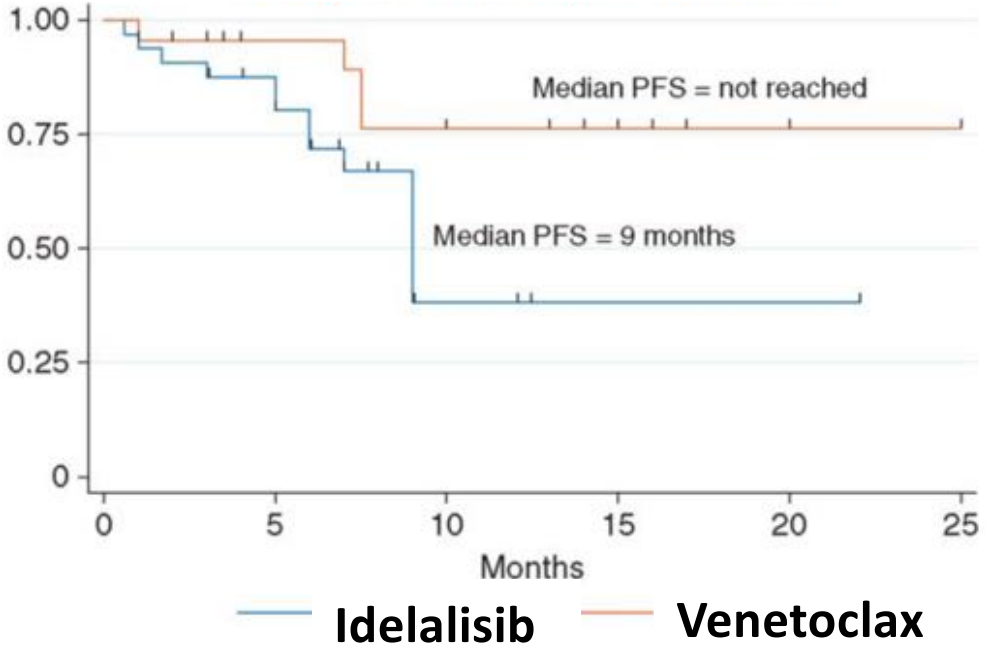
Mato et al., *Annals of Oncology*, 2017

In patients progressing on first KI, PFS was better on venetoclax than another KI or CIT/MoAb

PFS after KI discontinuation

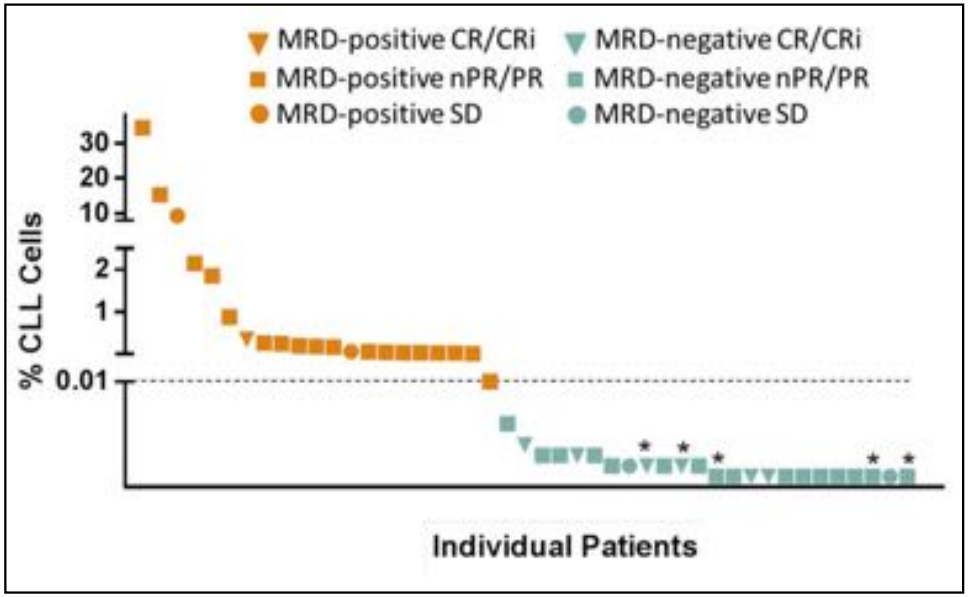


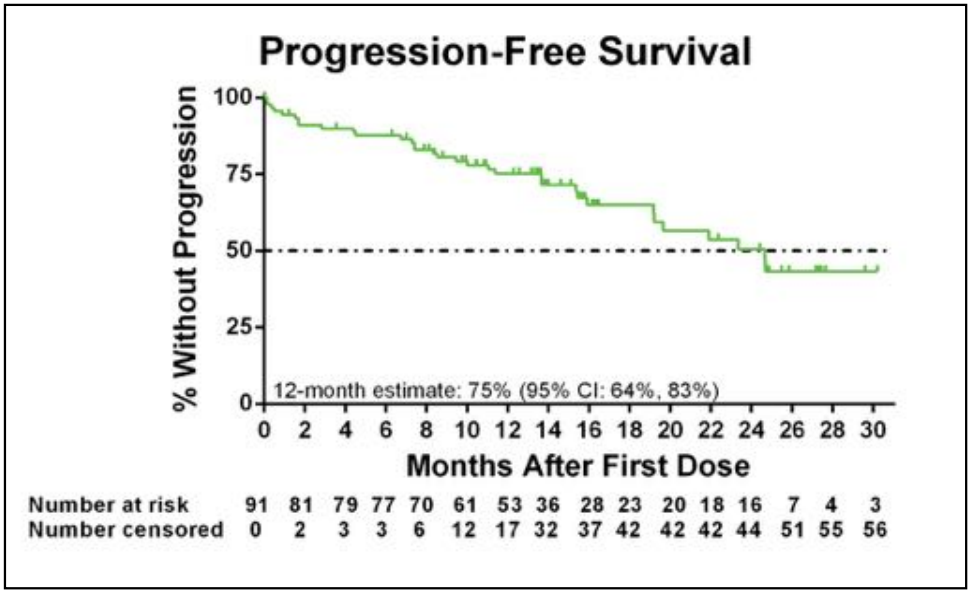
PFS by second novel agent in Ibr failures



Mato et al., *Annals of Oncology*, 2017

M14-032, the first prospective study of any treatment for pts progressing on a KI, found that venetoclax is active post ibrutinib



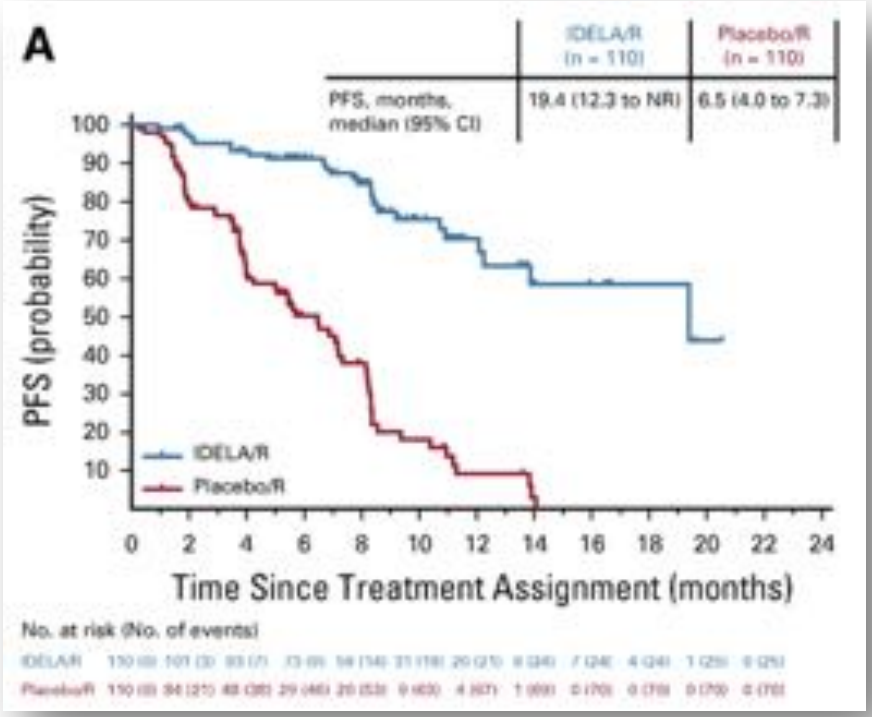


- 91 pts progressed after ibrutinib, treated with venetoclax
- Median 4 prior therapies (range 1-15), del(17p) in 44%
- Overall response rate: 65%, CR/CRi rate: 9%
- Peripheral Blood MRD rate at 24 weeks (n=57): 42%
- Median follow-up: 14 mo.

Jones et al., *Lancet Oncol*., 2018

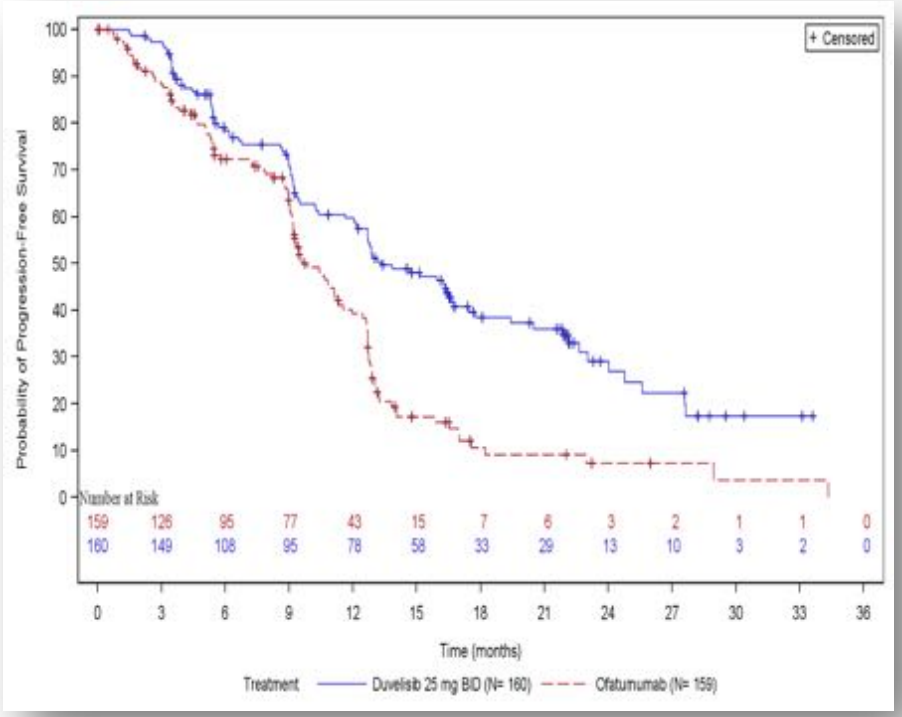
Approved PI3Ki are efficacious, with manageable toxicity in R/R CLL

Idelalisib + Rituximab



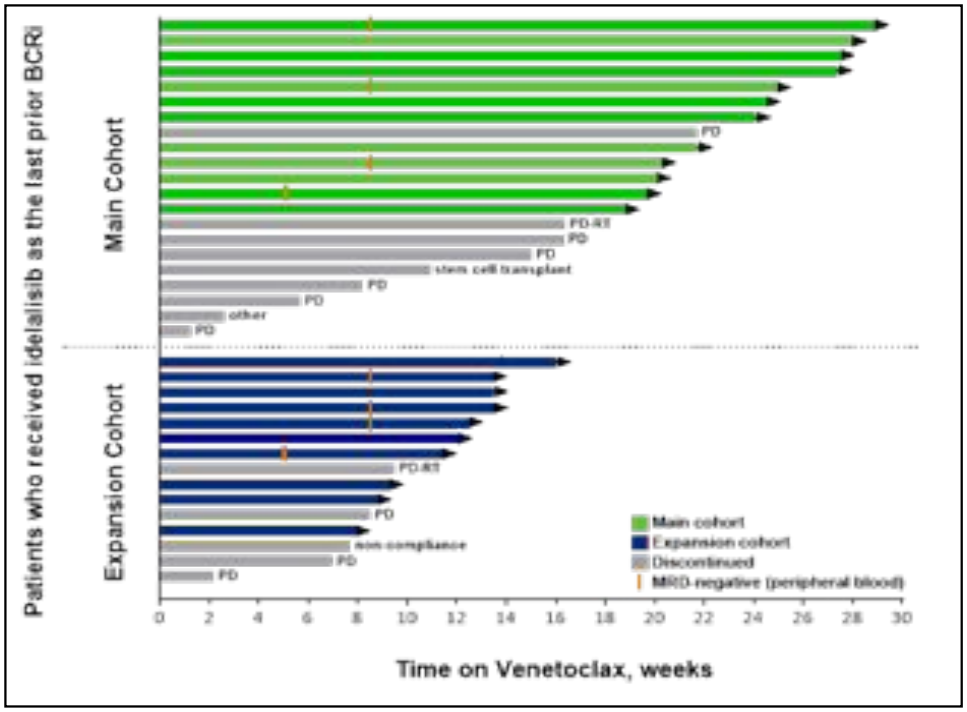
Sharman et al., J Clin Oncol, 2019

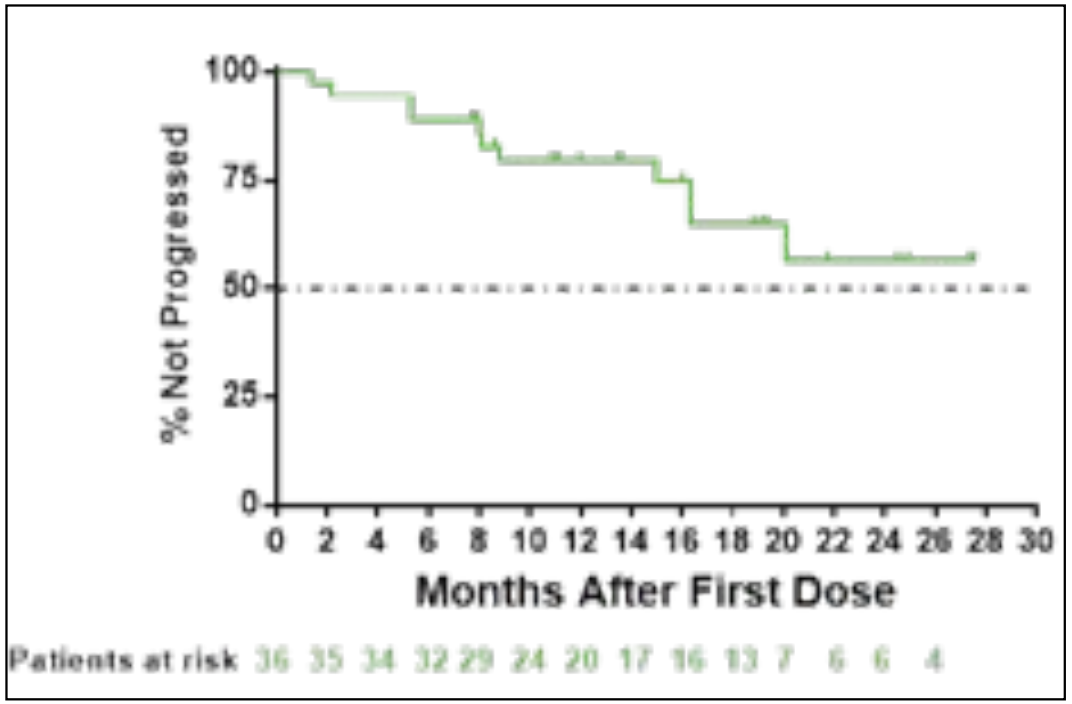
Duvelisib



Flinn et al., *Blood*, 2018

M14-032: venetoclax is also active for pts progressing on idelalisib





- 36 pts progressed after idelalisib were treated with venetoclax
- Median 3 prior therapies (range 1-11)
- Del(17p) in 22%, unmutated *IGHV* in 88%

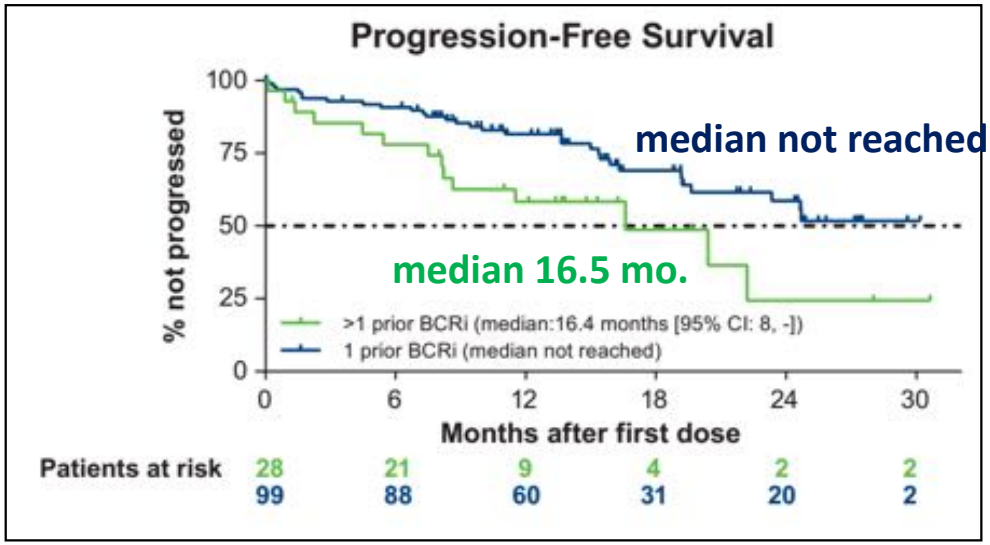
- Overall response rate: 67%
- Median follow-up: 14 mo.

Coutre et al, *Blood*, 2018

Venetoclax is also active for patients progressing on >1 BCRi, though response rates and PFS are poorer

- 28 pts who progressed after >1 prior BCRi were treated with venetoclax
- Median 6.5 prior therapies (range 2-15)
- Del(17p) in 36%, unmutated *IGHV* in 70%

n (%)	>1 prior BCRi n=28	1 prior BCRi n=99
ORR	12 (43)	74 (75)
CR/CRi	1 (4)	10 (11)
nPR	0	3 (3)
PR	11 (39)	61 (61)
SD	11 (39)	17 (17)



Wierda, et al., *Br J Haematol*, 2018

Considerations in choosing a first NA for R/R disease

- Ibrutinib currently being used most commonly as first NA therapy for relapse after CIT

- If significant cardiac or bleeding risks, consider:
  - Venetoclax (+/- rituximab); potential for CR with MRD-neg.; need to monitor for TLS, neutropenia)

  - Idelalisib (+/- rituximab) or duvelisib: consider for pts with renal dysfunction; need to monitor for immune-mediated AEs)

Considerations in choosing a second NA for R/R disease

- Prospective data are limited
- If ibrutinib has been used as the first NA:
  - Venetoclax (+/- rituximab)
  - Idelalisib (+/- rituximab) or duvelisib
- If ibrutinib has not been used as the first NA:
  - Ibrutinib or venetoclax (+/- rituximab)

Possible timeline for a typical CLL patient treated with sequential monotherapies

77 y/o man with del(13q), m*IGHV* CLL

BTKi
~8 yrs

BCL-2i
~3 yrs

PI3Ki
~2 yrs

Duration of CLL therapy: 13 years (now 90 years old)

Actuarial life expectancy for 77 y/o man: 10 years

Future novel agent options will further expand options for sequential therapy

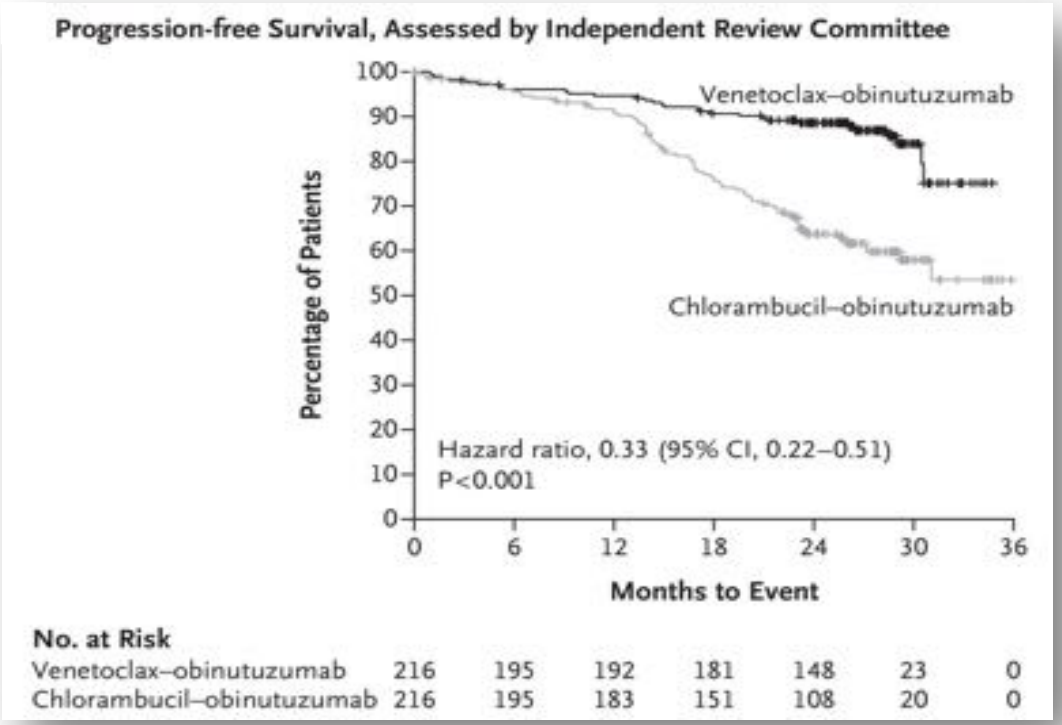
Two treatment strategies are emerging

Sequential
novel agent monotherapy

Metronomic
novel agent combinations

Durability data for frontline Ven/Obin are promising

CLL 14 Study



Fischer et al., *NEJM*, 2019

A key question is the feasibility of venetoclax retreatment

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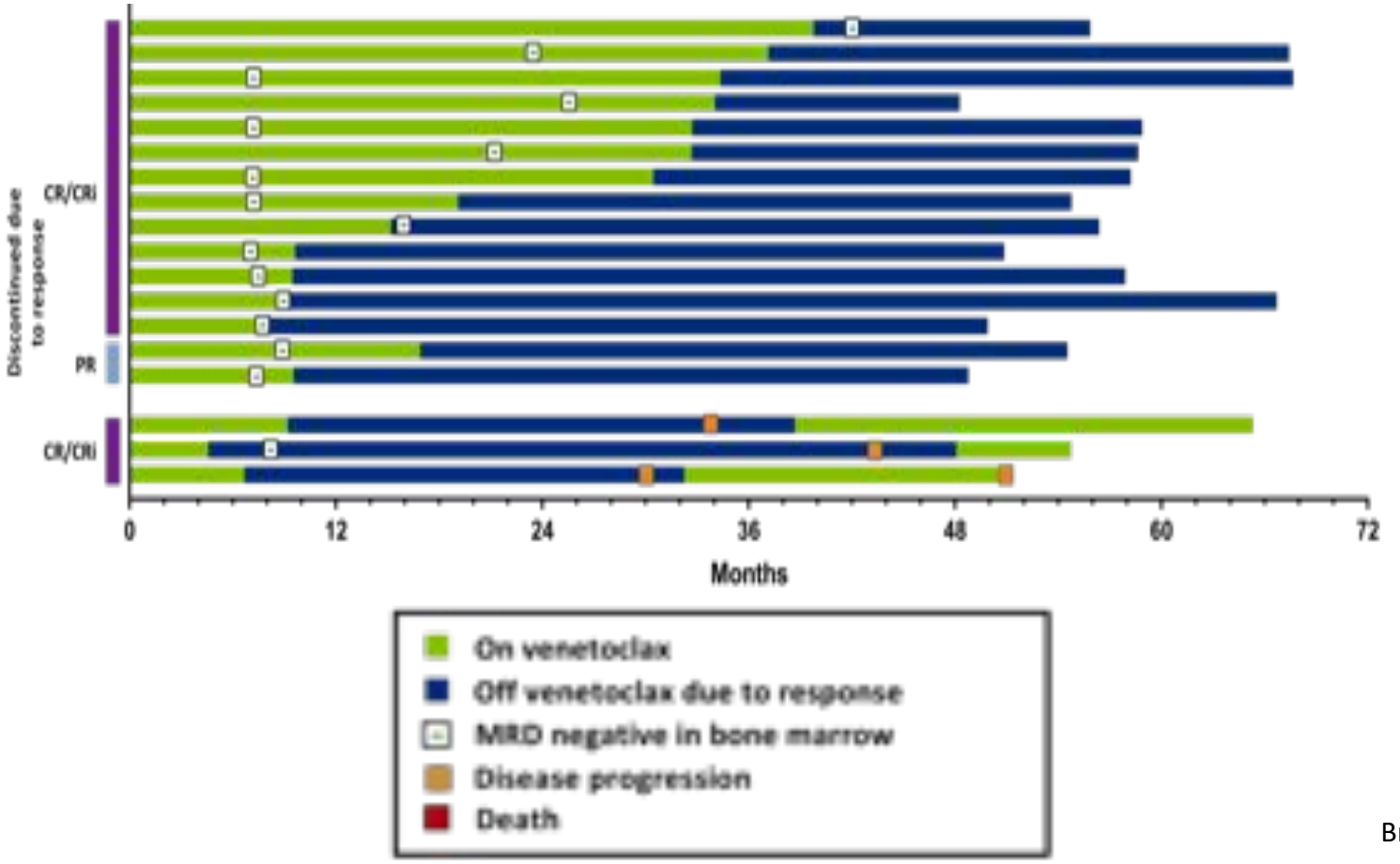
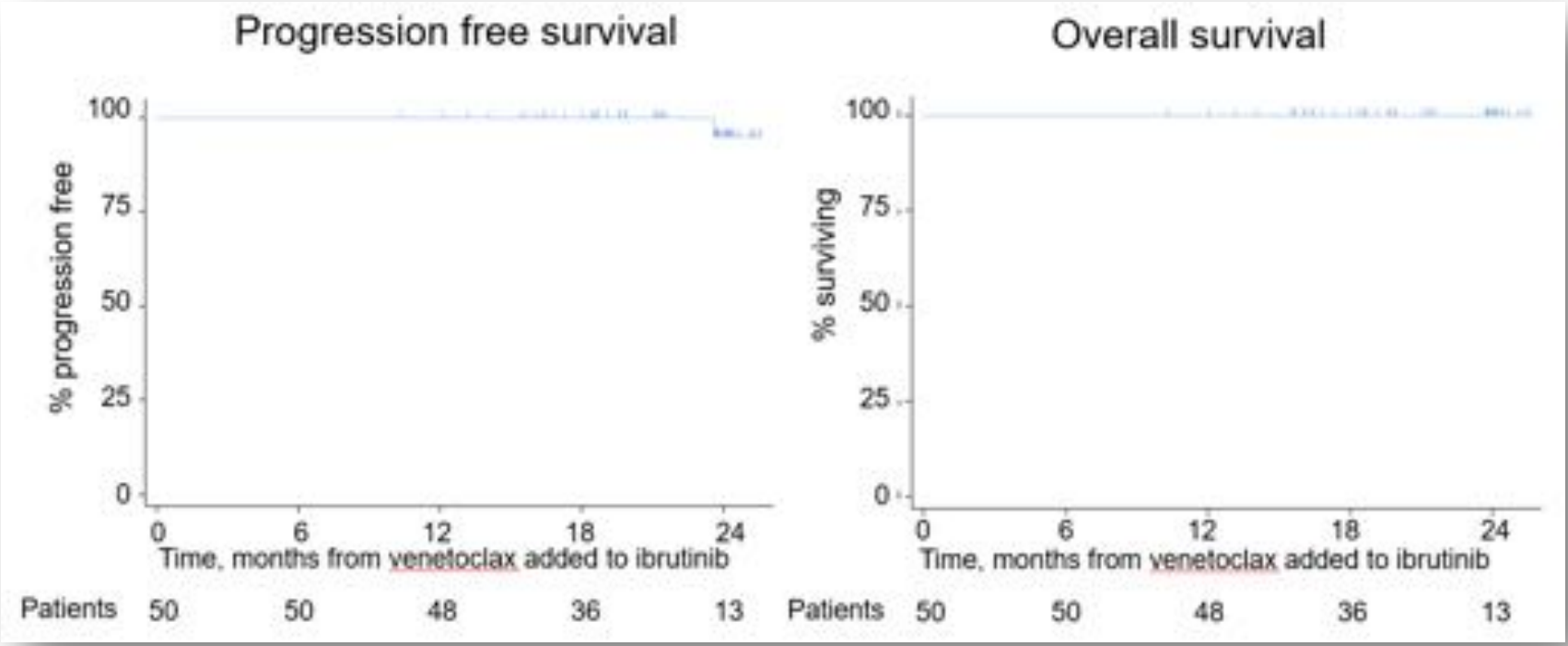


Brander et al., *ASH*, 2018

Other promising novel agent combinations are on the horizon

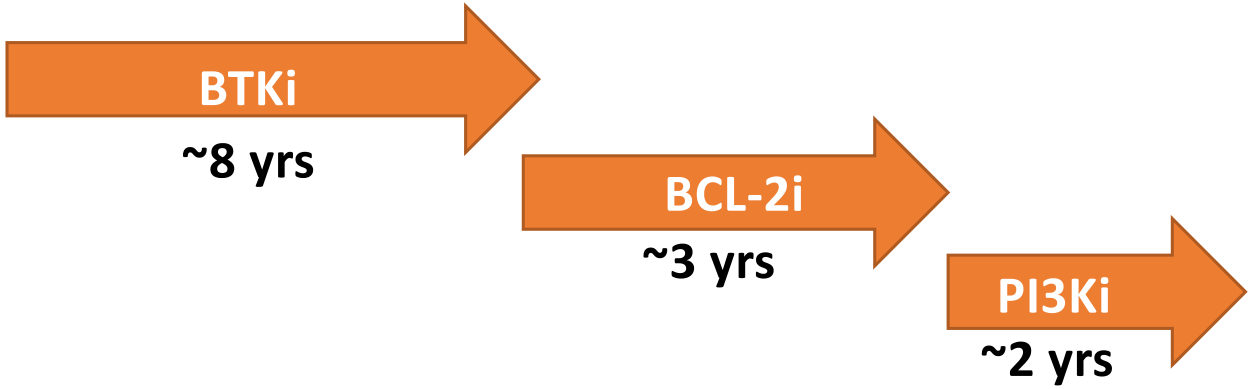
Ibrutinib + Venetoclax (CLARITY)



Hillmen et al., ASH, 2018

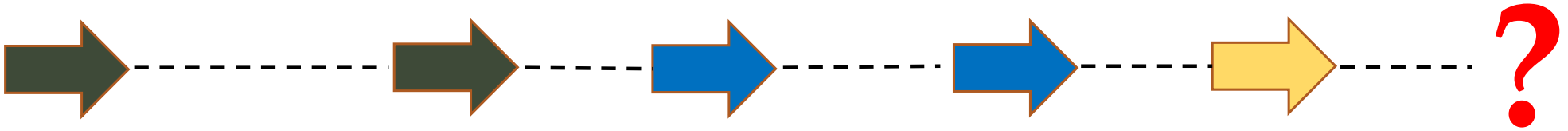
Possible timeline for a CLL patient treated with metronomic combination therapy

Sequential



60 y/o man with del(11q), u*IGHV* CLL

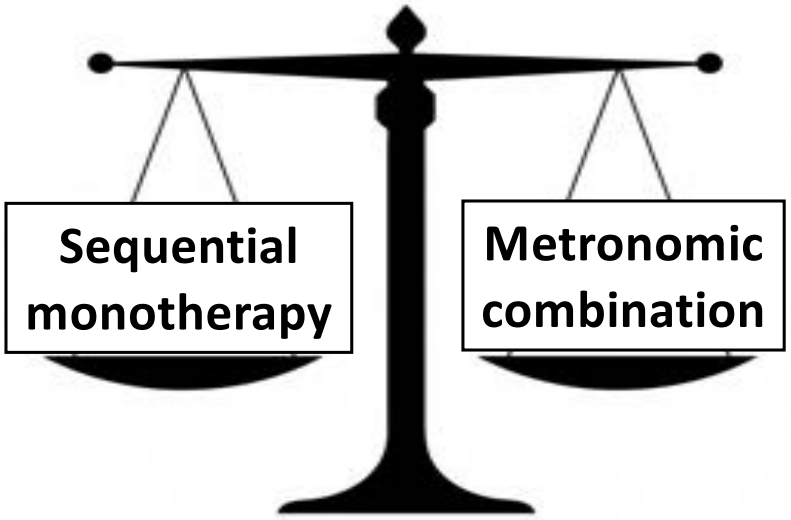
Metronomic Combination



Intermittent novel agent (NA) combo therapy

NA + CD20, NA + NA, NA + NA + CD20

Sequential Monotherapy vs. Metronomic Combination Approaches: Factors to Consider



- Longterm efficacy data already available
- Simplicity (for patients and physicians)
- Fewer, more predictable toxicities on therapy
- More predictable resistance patterns that are potentially targetable

- Less concern for longterm adherence
- Theoretical lower risk of resistance mutations arising
- Cost-saving if each course is durable
- Curative potential for a subset (?)


Grazie mille!