CHRONIC LYMPHOCYTIC LEUKEMIA
New Treatment Options

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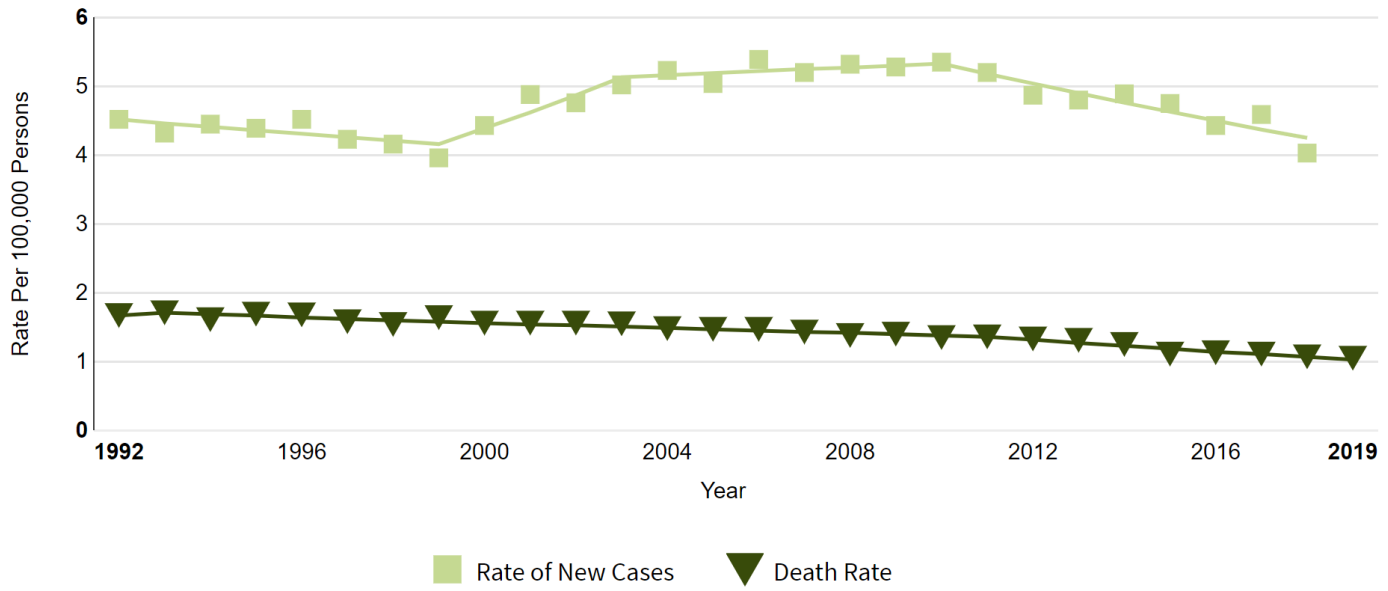
Chronic Lymphocytic Leukemia *Statistics*

Estimated New Cases in 2021	21,250
% of All New Cancer Cases	1.1%

Estimated Deaths in 2021	4,320
% of All Cancer Deaths	0.7%

5-Year Relative Survival
87.2%
2011–2017

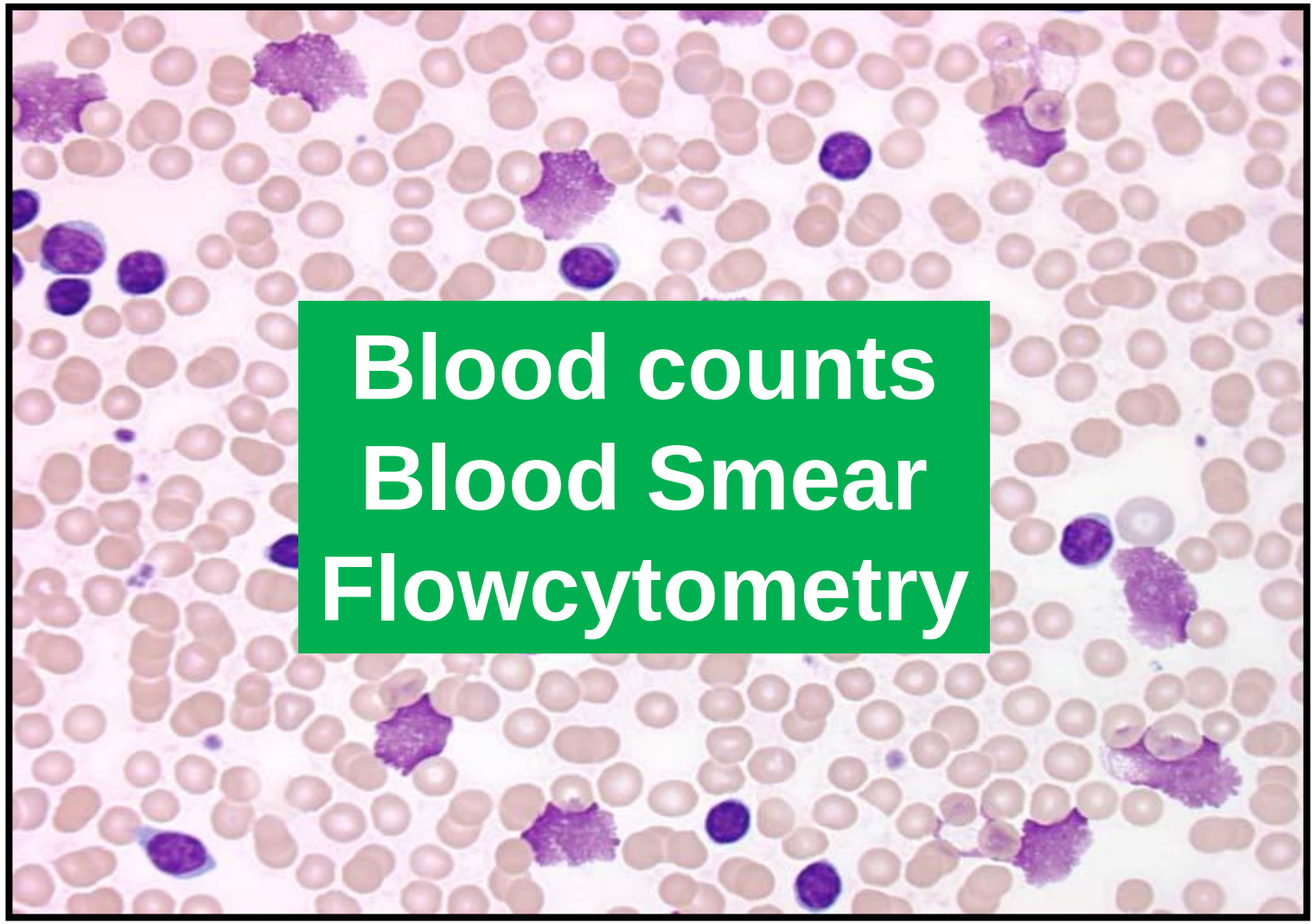


SEER Cancer Statistics: Cancer Stat Facts: Leukemia — Chronic Lymphocytic Leukemia (CLL).

Chronic Lymphocytic Leukemia

How is CLL diagnosed?

Blood Smear in CLL



Chronic Lymphocytic Leukemia

What is my prognosis?

Chronic Lymphocytic Leukemia
Prognostic Factors

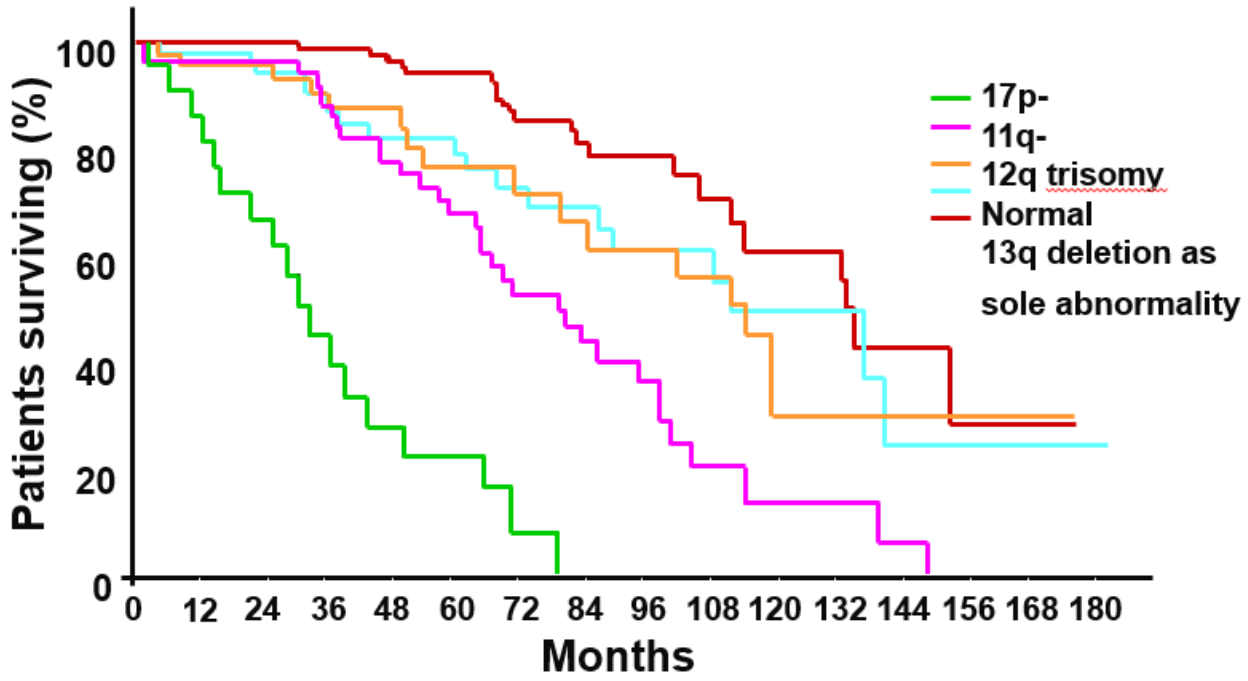
Prognostic Feature	Associated With Poor Prognosis
CD38 expression	sion (30%)
Zap-70 expressio	ssion (20%)
IGHV mutation st	CLL
Serum β2 macrog	mg/L)
FISH cytogenetics	(11q)
Gene mutations	*SF3B1*, or *ATM*

Chromosome Study
FISH
PCR
Mutation Analysis
NGS

Rai KR, Jain P. *Am J Hematol*. 2016;91:330-340.

CLL: Prognostic Value of FISH

- Deletions on the long arm of chromosome 13 is most commonly observed (55% of all cases)
  - Isolated del(13q14) is associated with a benign disease course
- *17p* deletion and/or *TP53* mutation is an adverse prognostic feature, predicting for inferior responses and survival in CLL
  - Lower responses to chemoimmunotherapy
- Important to obtain at diagnosis and should be repeated before subsequent therapies as additional genetic abnormalities may be acquired



Dohner et al, *N Engl J Med.* 2000;343:1910.

Chronic Lymphocytic Leukemia

What are the indications for starting treatment?

NCI-WG Indications to Treat

- Constitutional symptoms referable to CLL
- Progressive marrow failure
- Auto[illegible]nsive to cort[illegible]
- Massive or progressive splenomegaly
- Massive or progressive lymphadenopathy
- Progressive lymphocytosis

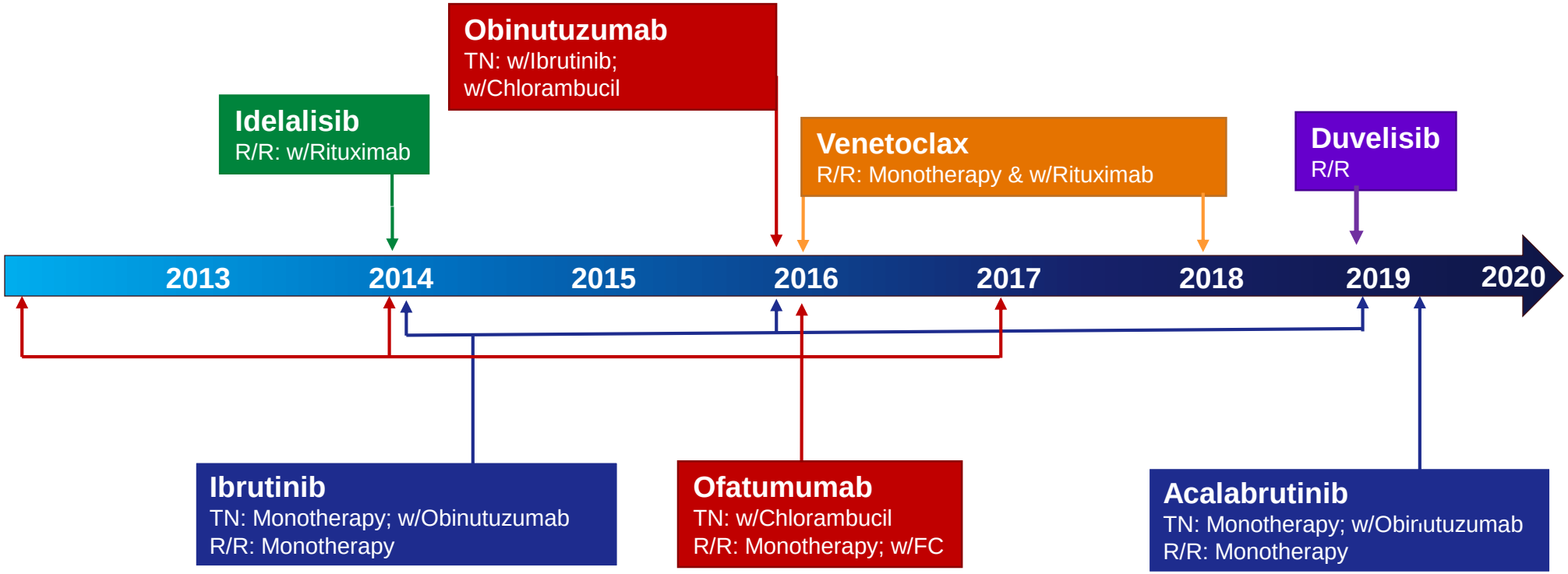
Observation is appropriate in the absence of indication for therapy

Cheson BD et al. *Blood*. 1996;87:4990-4997.

First-Line Treatment

- Chemotherapy
- Monoclonal Antibodies
- Combinations:
  - FCR, BR
- Ibrutinib (Imbruvica)
- Acalabrutinib (Calquence)
- Venetoclax (Venclexta)
- Clinical Trials

Timeline of New Agents for CLL



Not yet approved for CLL

CAR T-cells

TN, treatment naïve; R/R, relapsed/refractory; FC, fludarabine and cyclophosphamide (FC)

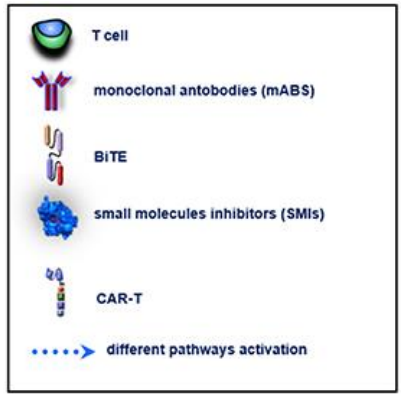
Targeted Treatment Options for CLL

Obinutuzumab
Ofatumumab
Rituximab
Ublituximab

Copanlisib
Duvelisib
Idelalisib
Umbralisib

Acalabrutinib
ARQ 531
Ibrutinib
LOXO-305
Tirabrutinib
Vecabrutinib
Zanubrutinib

Venetoclax



Agents listed in bold are FDA approved

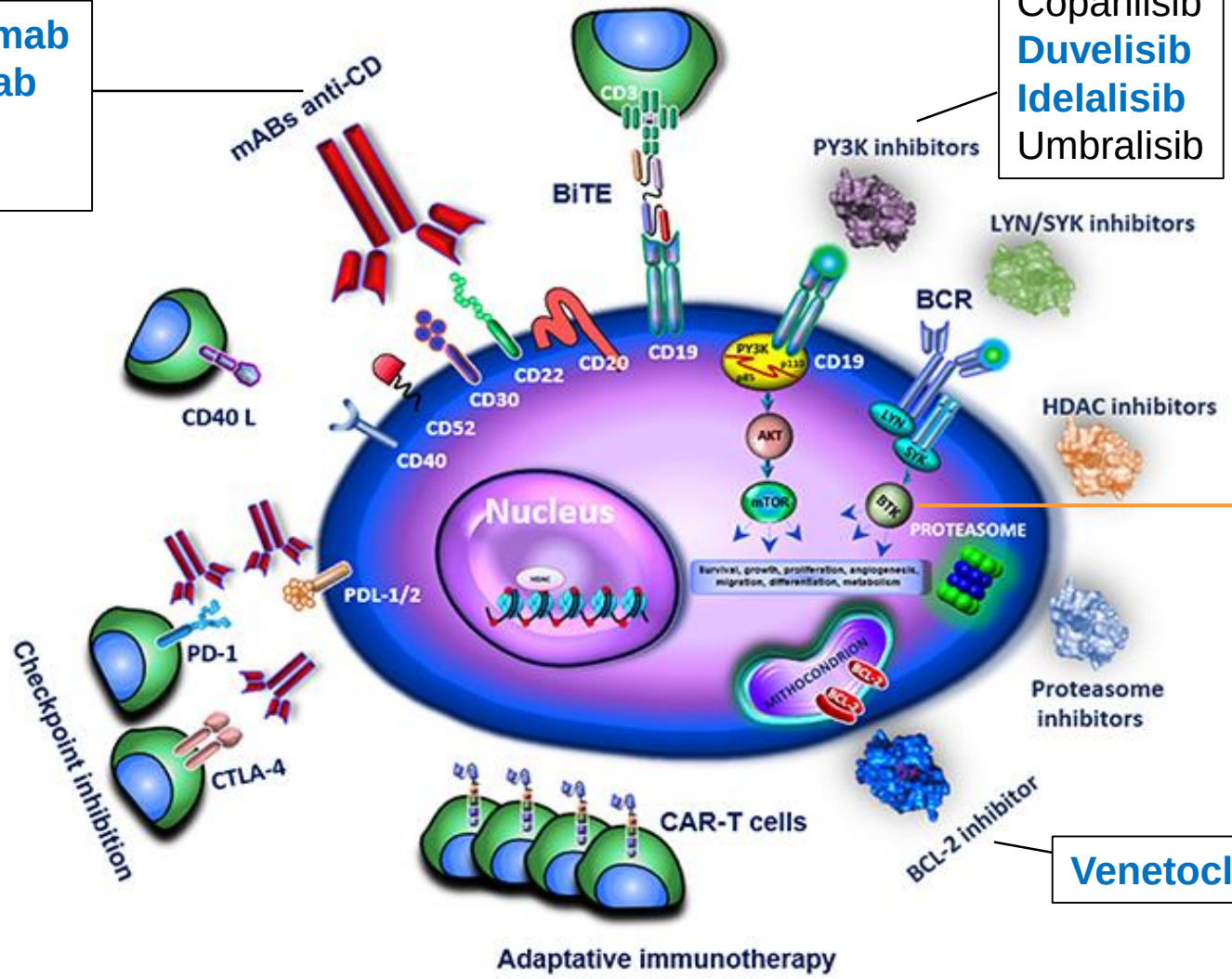
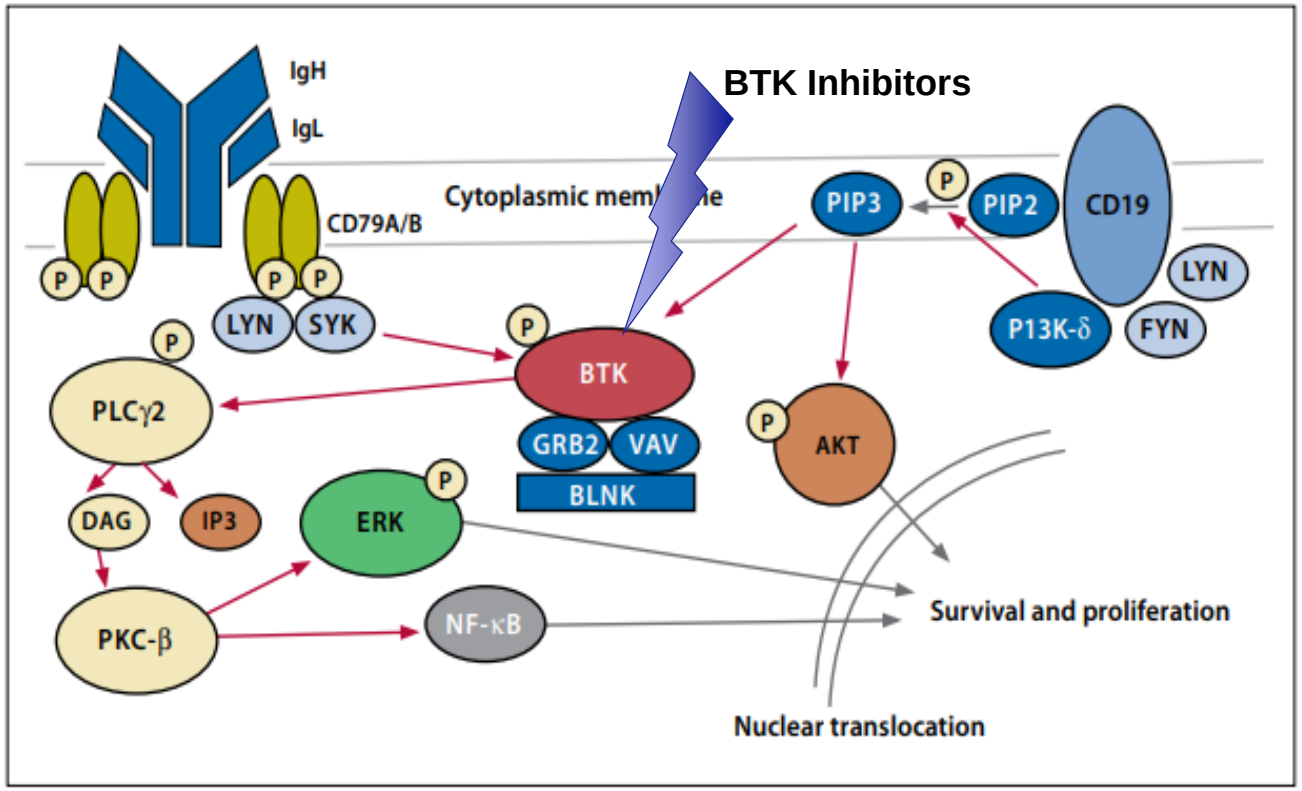


Figure adapted from Crisci, et al. *Front. Oncol*. 2019. doi.org/10.3389/fonc.2019.00443

BTK Inhibitors
Mechanism of Action



- Selective tyrosine kinase inhibitors (TKIs)
- Acalabrutinib, Ibrutinib, Zanubrutinib: Forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity
- Vecabrutinib, LOXO-305, ARQ 531: Noncovalent binding to BTK
- Blocks B-cell receptor signaling and survival, proliferation, and migration of cancerous B cells

Figure from Bond DA et al. *Clin Advances Hematol Oncol* 2019

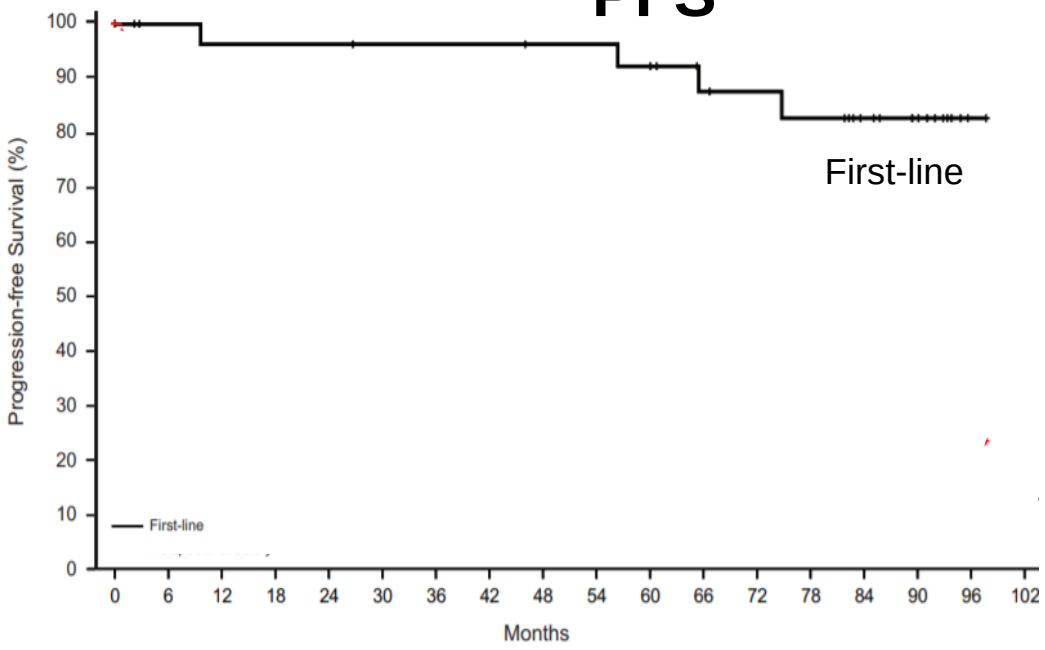
Summary of FDA-Approved BTK Inhibitors

	Ibrutinib	Acalabrutinib	Zanubrutinib
FDA-approved indications	• **CLL (monotherapy or w/ obinutuzumab or rituximab)** • R/R MCL • WM • MZL (after ≥ 1anti-CD20-based therapy) • cGVHD	• **CLL/SLL (monotherapy or with obinutuzumab)** • R/R MCL (monotherapy)	• R/R MCL
Method of administration	• CLL/SLL, WM, and cGVHD: 420 mg taken orally once daily • MCL and MZL: 560 mg taken orally once daily	100 mg every 12 hours orally	Once daily (320 mg) or twice daily (160 mg) orally
Key toxicities	• Bleeding, atrial fibrillation, diarrhea, fatigue, and increased risk for infection	• Headaches, diarrhea, fatigue, infection, anemia	• Diarrhea, infection, fatigue, anemia

Owen, et al. *Curr Oncol.* 2019; 26(2): e233–e240. doi: 10.3747/co.26.4345

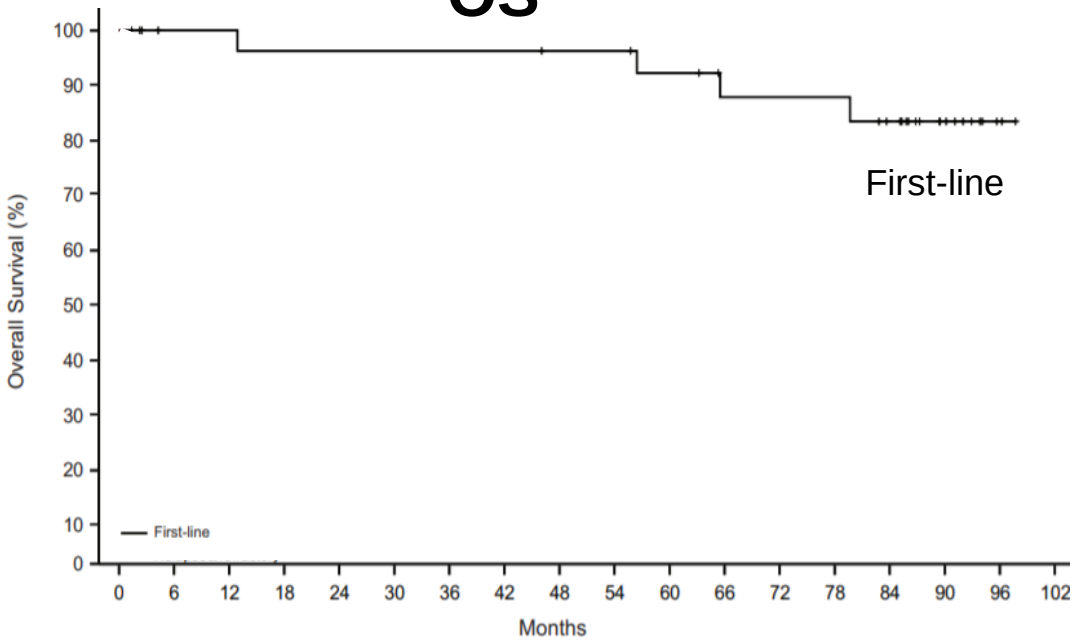
8-Year Follow-up of Ibrutinib Monotherapy: High Rates of OS, ORR and Long-term Tolerability in CLL

PFS



	Median, mos (95%CI)	7-year PFS
First-line (n=31)	NR (NE-NE)	83%

OS



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First-line (n=31)	NR (NE-NE)	84%

Byrd, et al. *Clin Cancer Res*. 2020 Mar 24; clincanres.2856.2019. doi: 10.1158/1078-0432.CCR-19-2856.

Phase 3 RESONATE-2: 5-Year Update

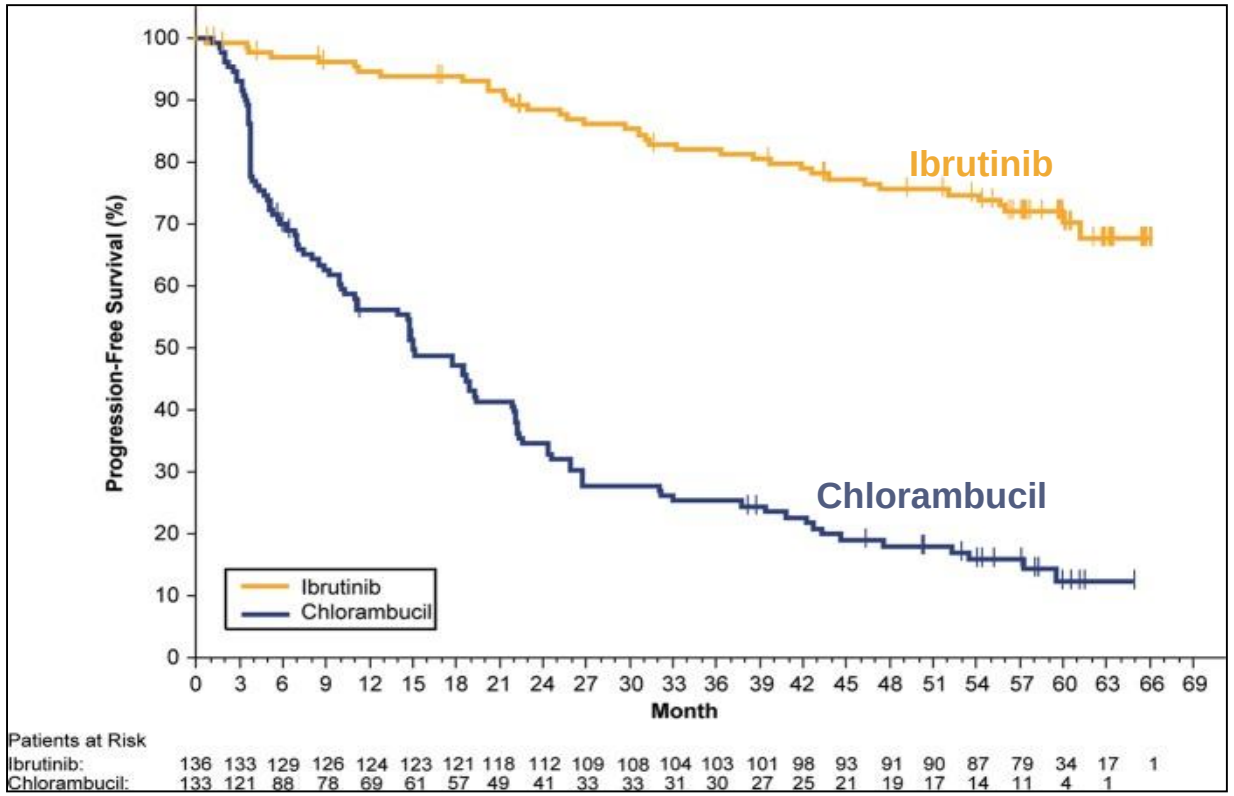
Ibrutinib Provides Durable Response as Initial Therapy in Frail Pts

Efficacy

- Ibrutinib benefit was also consistent in patients with high prognostic risk (*TP53* mutation, 11q deletion, and/or unmutated *IGHV*)

Safety

- Discontinuation due to AEs decreased over time, with 58% of ibrutinib pts continuing daily treatment



	Median PFS, mo	HR (95% CI)
Ibrutinib	NE	0.146 (0.098-0.218)
Chlorambucil	15.0	

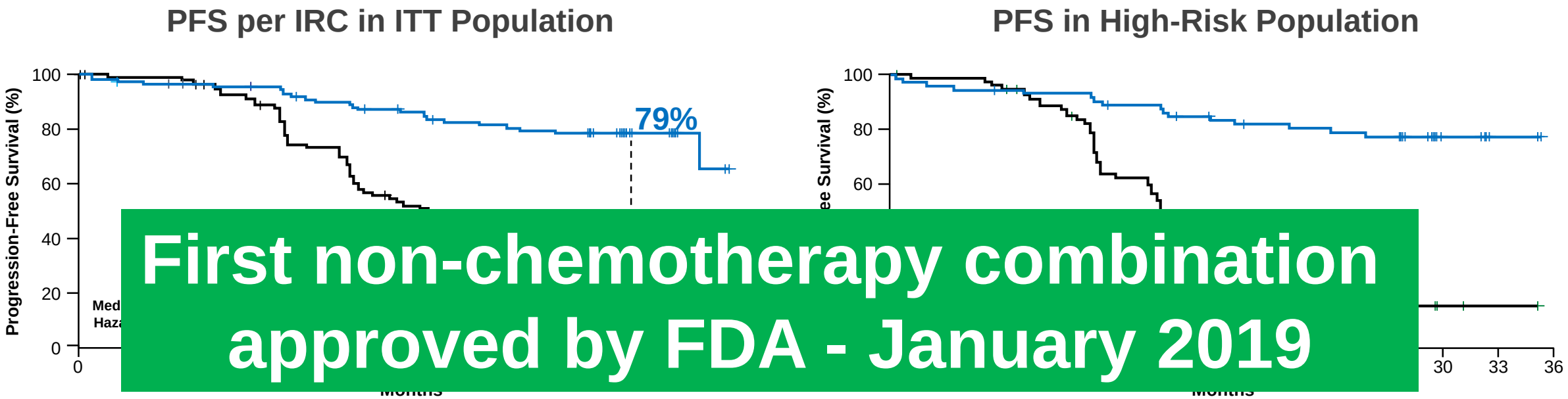
Burger JA, et al. *Leukemia.* 2020;34(3):787-798. doi: 10.1038/s41375-019-0602-x.

Chronic Lymphocytic Leukemia

Three major studies in 2019

that have influenced the first-line therapy of CLL

Obinutuzumab + Ibrutinib or Chlorambucil in Treatment-Naive CLL/SLL *(Phase 3 iLLUMINATE)*



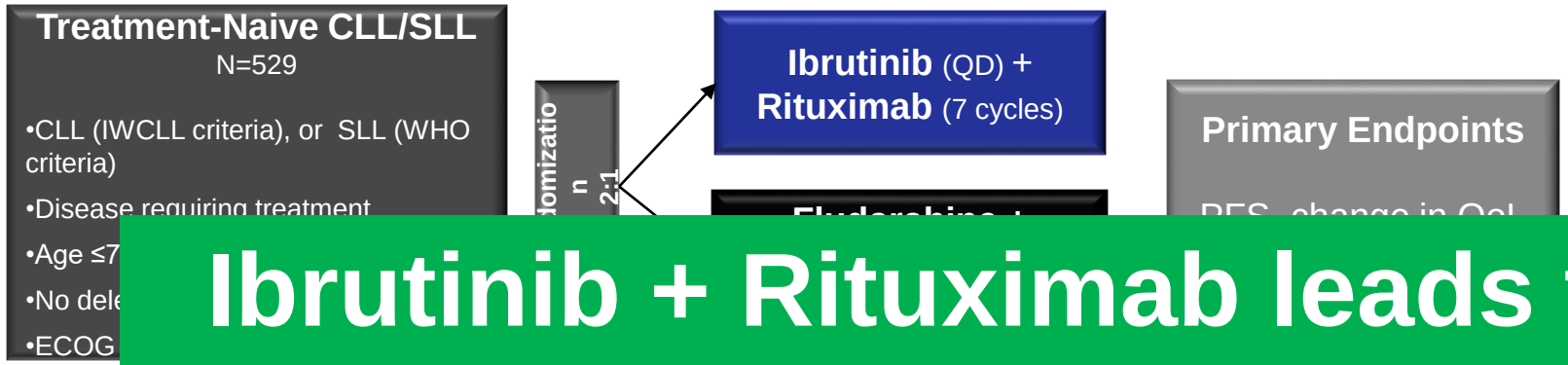
First non-chemotherapy combination approved by FDA - January 2019

	Obinutuzumab + Ibrutinib	Obinutuzumab + Chlorambucil
ORR per IRC (per investigator)	88% (91%)	73% (81%)
CR/CRi per IRC (per investigator)	19% (41%)	8% (16%)
Patients with undetectable MRD	35%	25%
OS rate at 30 months	86%	85%

High-risk population (del(17p)/*TP53* mutation, del(11q), and/or unmutated *IGHV*.

Moreno C et al. ASH 2018. Abstract 691.

IR vs FCR in Pts with Treatment-Naive CLL/SLL *(Phase 3 ECOG-ACRIN E1912)*

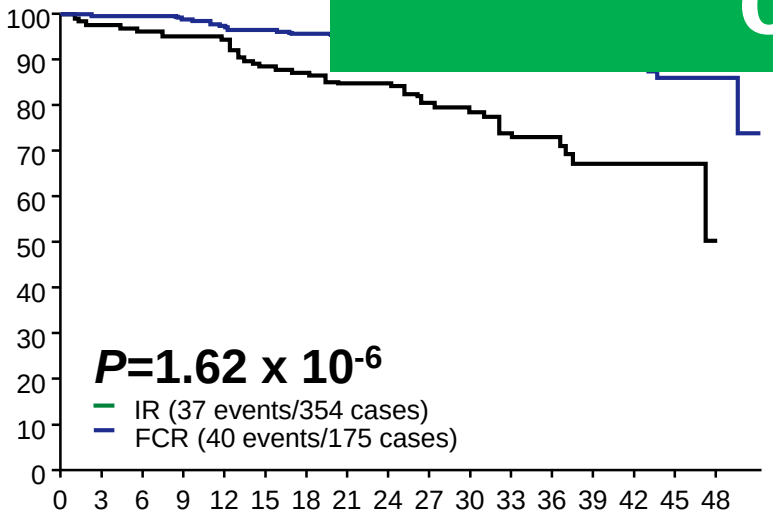


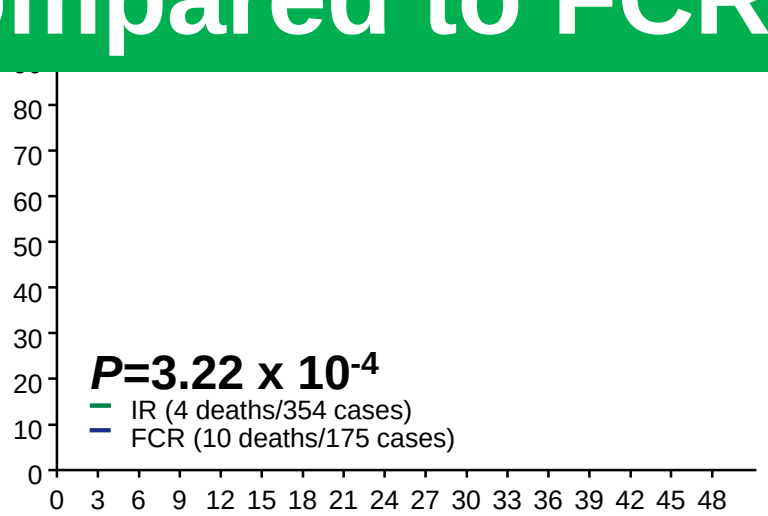
1st Interim Analysis

Ibrutinib + Rituximab leads to better disease control & survival compared to FCR

PFS (All

HR=0.352; 95%



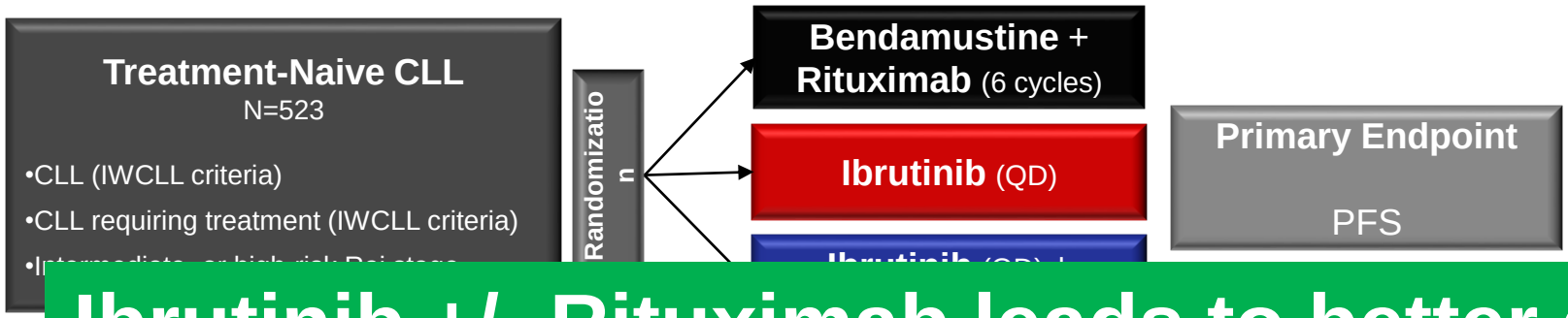


-up 33.4 months

- PFS: IR was superior to FCR independent of age, sex, PS, stage or del11q23 presence/absence
- IR was superior to FCR for *IGHV* unmutated, but not mutated patients

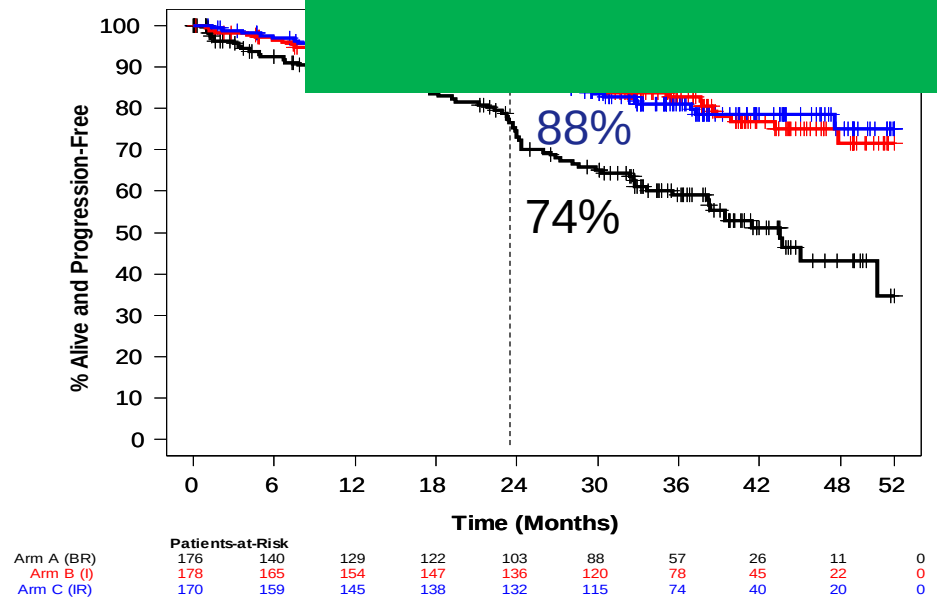
Shanafelt TD et al. ASH 2018. Abstract LBA-4.

BR vs IR vs Ibrutinib Alone in Older Patients with Treatment-Naive CLL *(Phase 3 ALLIANCE A041202)*



1st Interim Analysis

Ibrutinib +/- Rituximab leads to better disease control compared to Bendamustine + Rituximab



IR	170	88% (95% CI: 81, 92%)
I	178	87% (95% CI: 81, 92%)
BR	176	74% (95% CI: 66, 80%)

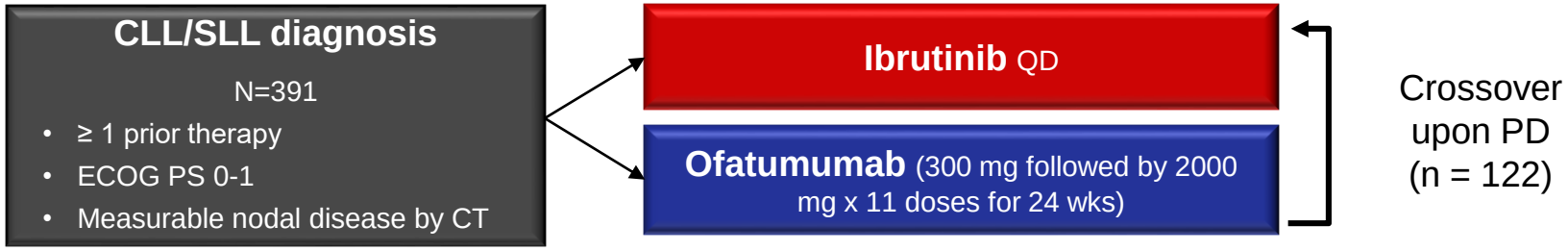
- No significant OS differences among arms
- Median OS not reached for any arm
- 2-year OS estimates
  - Arm 1 (BR) 95%
  - Arm 2 (I) 90%
  - Arm 3 (IR) 94%

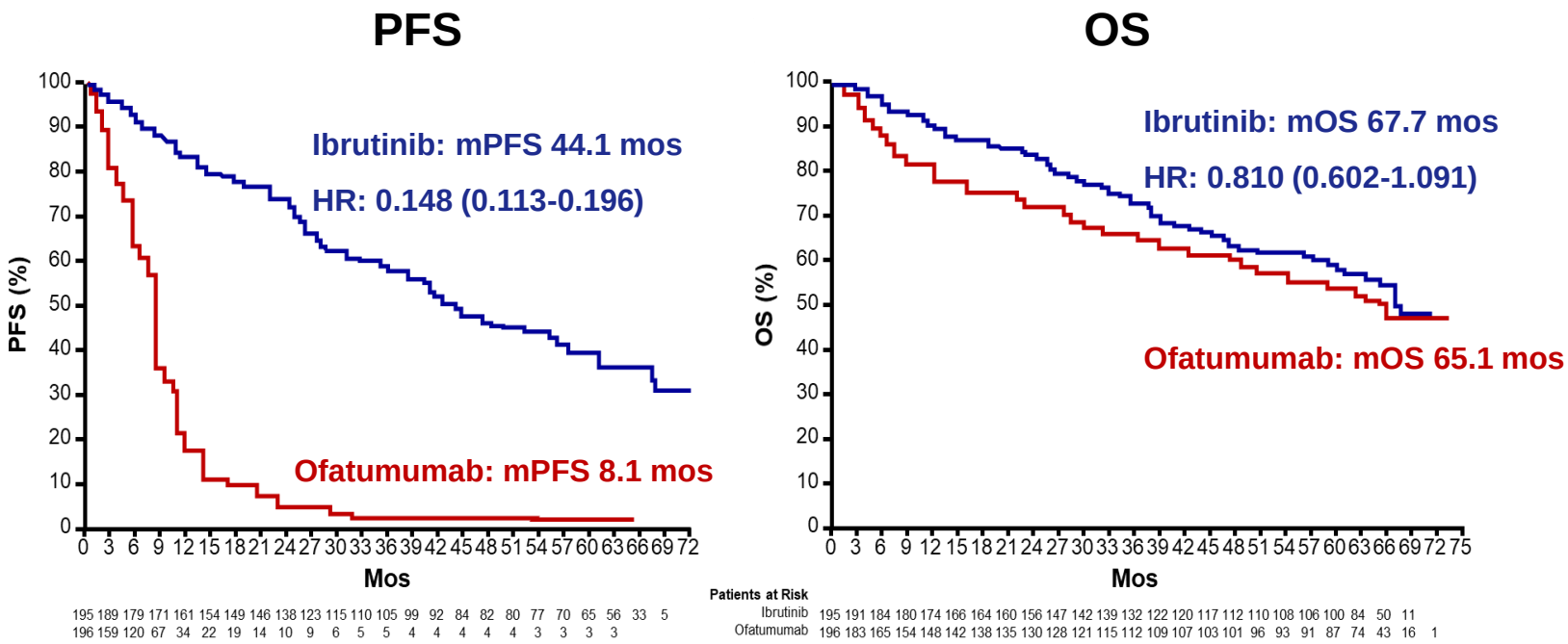
Woyach J, et al. *N Engl J Med.* 2018;379:2517-2528. doi: 10.1056/NEJMoa1812836

Treatment for Relapsed CLL

- Chemotherapy
- Monoclonal Antibodies
  - Ofatumumab (Arzerra)
  - Alemtuzumab (Campath)
- Ibrutinib (Imbruvica)
- Acalabrutinib (Calquence)
- Venetoclax (Venclexta)
- Clinical Trials
- Stem Cell Transplantation

Ibrutinib is Superior to Ofatumumab in R/R CLL *(Phase 3 RESONATE Final Results)*





- Median follow-up 65.3 months
- Long-term treatment with ibrutinib is tolerable and continues to show sustained PFS and OS regardless of high-risk cytogenetics

Munir, et al. *Am J Hematol*. 2019;94(12):1353-1363. doi: 10.1002/ajh.25638.

Acalabrutinib Monotherapy Significantly Improves PFS in R/R CLL *(Phase 3 ASCEND)*

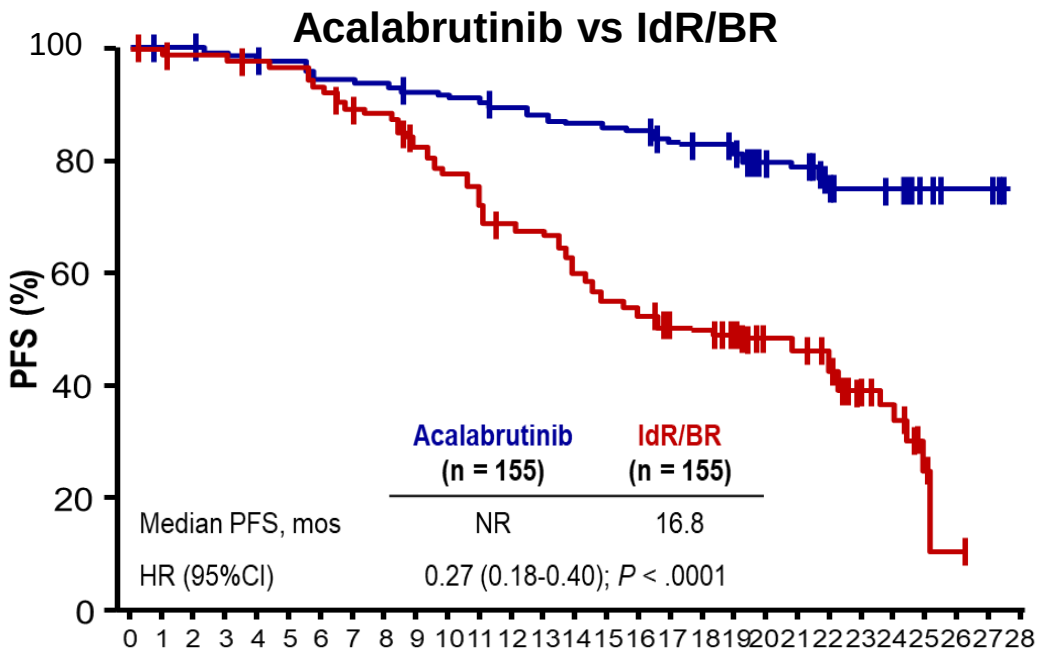
Adult patients with R/R CLL
N = 310

- ≥ 1 prior systemic therapies (no prior exposure to a BCL-2 inhibitor or BCR-signaling inhibitor)
- ECOG PS 0-2
- **Stratified by** Del(17p), ECOG PS 0-1 vs 2, 1-3 vs ≥ 4 prior tx

Randomization

- **Idelalisib + Rituximab or Bendamustine + Rituximab**
- **Acalabrutinib**

Primary endpoint: IRC-assessed PFS



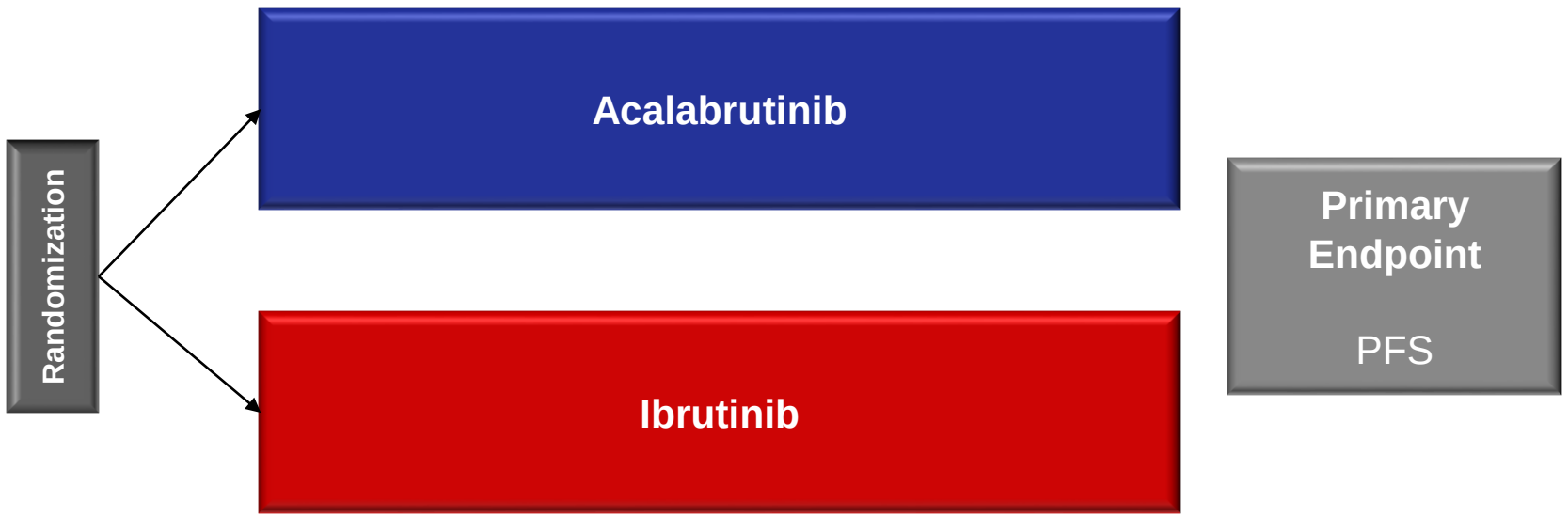
- Median follow-up of 16.1 months
- Estimated 12-month PFS was 88% (95% CI, 81% to 92%) for acalabrutinib vs 68% (95% CI, 59% to 75%) for investigator's choice

Ghia. EHA 2019. Abstr LB2606. NCT02970318. Ghia, et al. *J Clin Oncol*. 2020 May 27;JCO1903355. doi: 10.1200/JCO.19.03355.

Acalabrutinib vs Ibrutinib in R/R High-risk CLL *(Phase 3 ELEVATE-CLL R/R)*

R/R High-risk CLL
N=533

- ≥ 1 prior therapies for CLL
- ECOG of 0-2
- Active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment
- Must have ≥ 1 of the following high-risk prognostic factors:
  - Presence of 17p del by central laboratory
  - Presence of 11q del by central laboratory
- No prior exposure to ibrutinib or to a BCR inhibitor or a BCL-2 inhibitor



Study NCT02477696. ClinicalTrials.gov website. Accessed August 24, 2019.

Zanubrutinib (BGB-3111) vs Ibrutinib in R/R CLL *(Phase III ALPINE)*

N = 400

- R/R to ≥ 1 prior therapies for CLL
- Active disease meeting ≥1 of the IWCLL 2008 criteria for requiring treatment
- No prior BTX tx
- Stratified by age (< 65 vs ≥ 65 years), refractory status (yes vs no), geographic region, and del(17p)/*TP53* mutation status (present vs absent)

Zanubrutinib

Ibrutinib

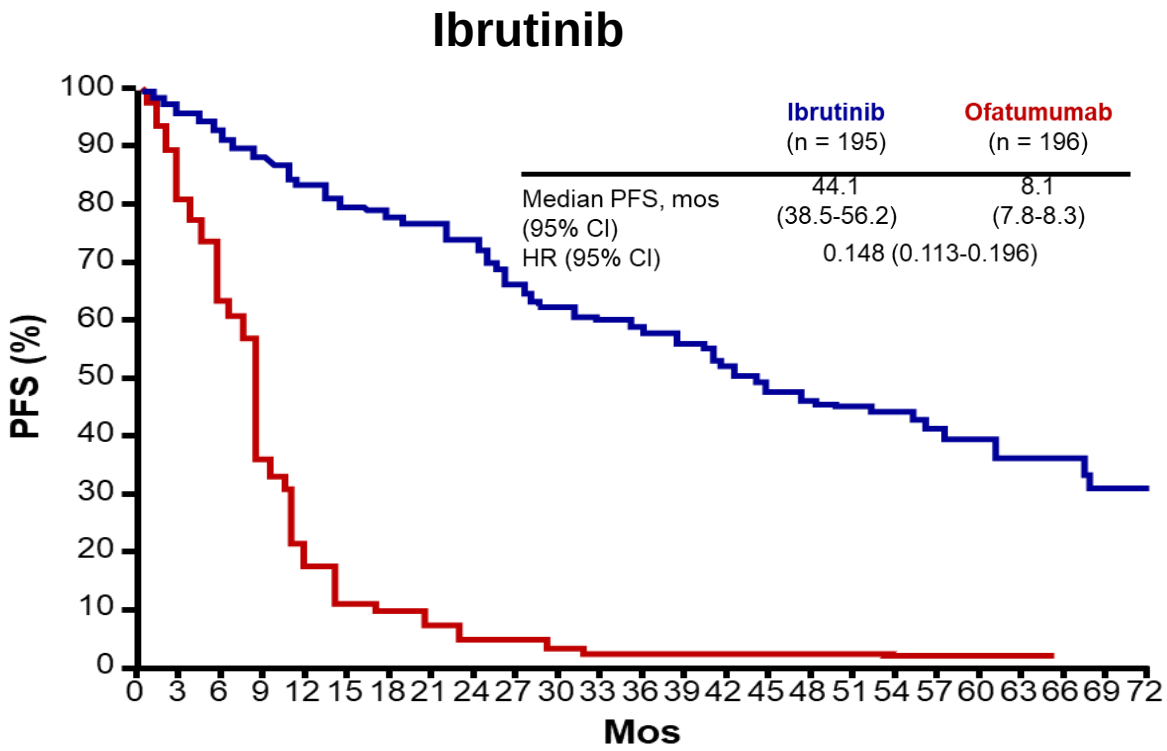
Primary Endpoint

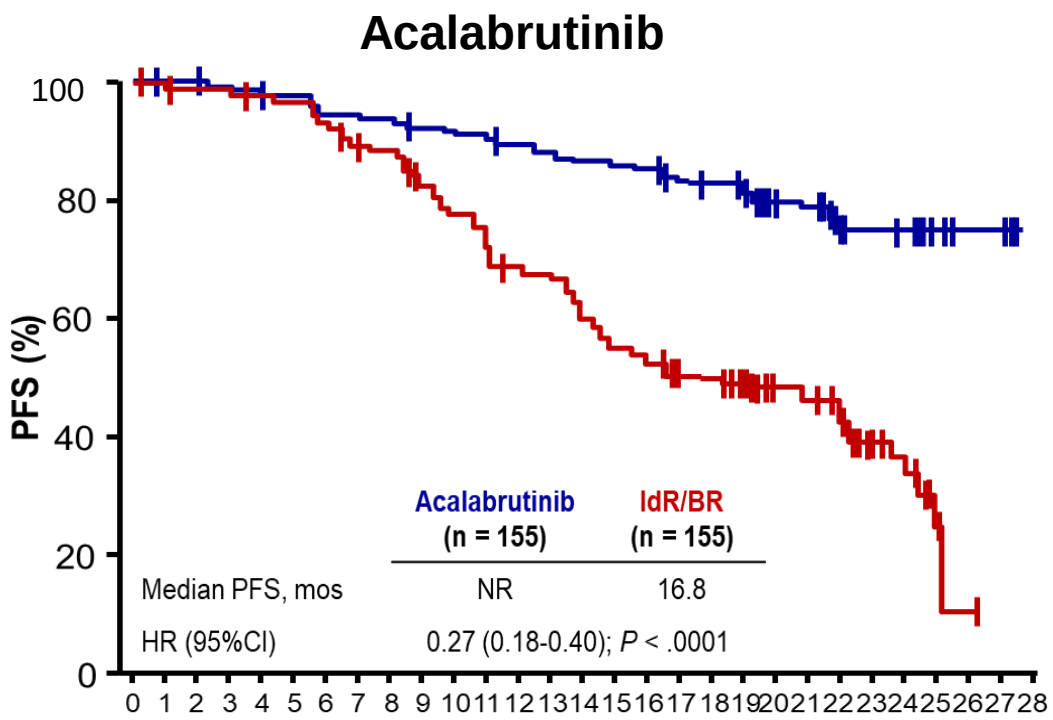
ORR

1. Hillmen P, et al. ASCO 2019. Abstract TPS7581. 2. ClinicalTrials.govNCT03734016.

Summary of BTK Inhibitors for R/R CLL

- Ibrutinib and Acalabrutinib monotherapies are FDA approved therapies for R/R CLL





Munir, et al. *Am J Hematol*. 2019;94(12):1353-1363. doi: 10.1002/ajh.25638. Ghia, et al. *J Clin Oncol*. 2020 May 27;JCO1903355. doi: 10.1200/JCO.19.03355.

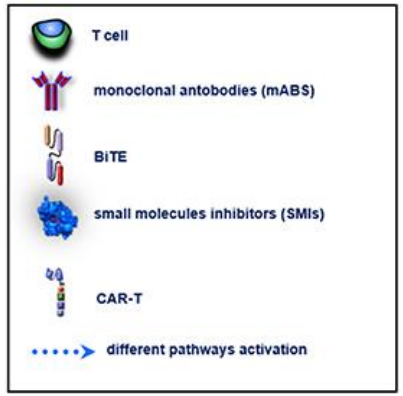
Targeted Treatment Options for CLL

Obinutuzumab
Ofatumumab
Rituximab
Ublituximab

Copanlisib
Duvelisib
Idelalisib
Umbralisib

Acalabrutinib
ARQ 531
Ibrutinib
LOXO-305
Tirabrutinib
Vecabrutinib
Zanubrutinib

Venetoclax



Agents listed in bold are FDA approved

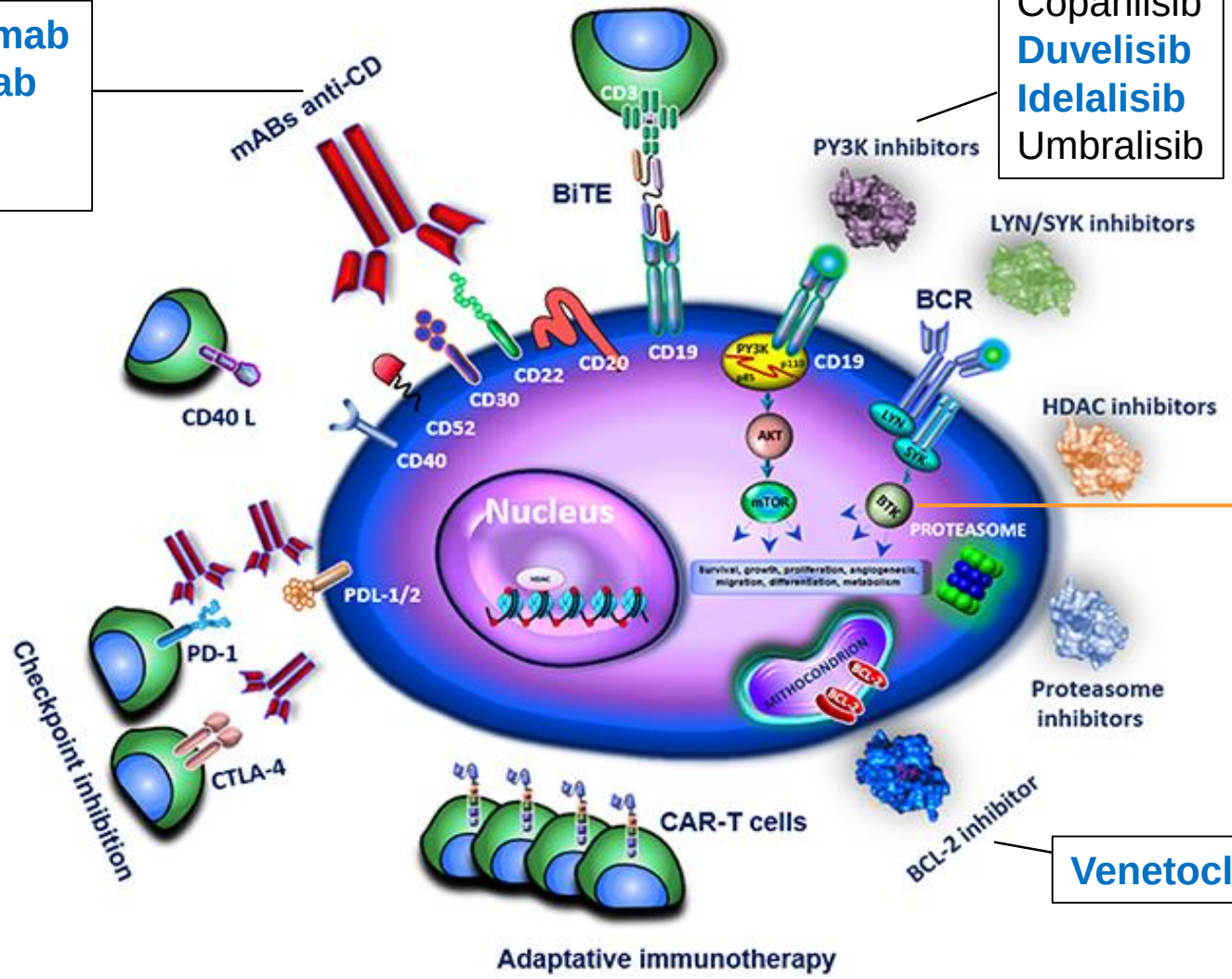


Figure adapted from Crisci, et al. *Front. Oncol*. 2019. doi.org/10.3389/fonc.2019.00443

Venetoclax in CLL: Response

Variable	N	CR, %	ORR, %
All patients	116	20	79
Del(17p)	31	16	71
No del(17p)	60	18	80

Roberts AW, et al. *N Engl J Med.* 2016;374:311-322.

Venetoclax+Rituximab is an Effective Treatment Option for R/R CLL *(Phase 3 MURANO)*

Adult patients with R/R CLL
(N = 389)
- CLL (IWCLL diagnostic criteria)
- Previously tx w/1-3 lines of th
standard chemotherapy-conta

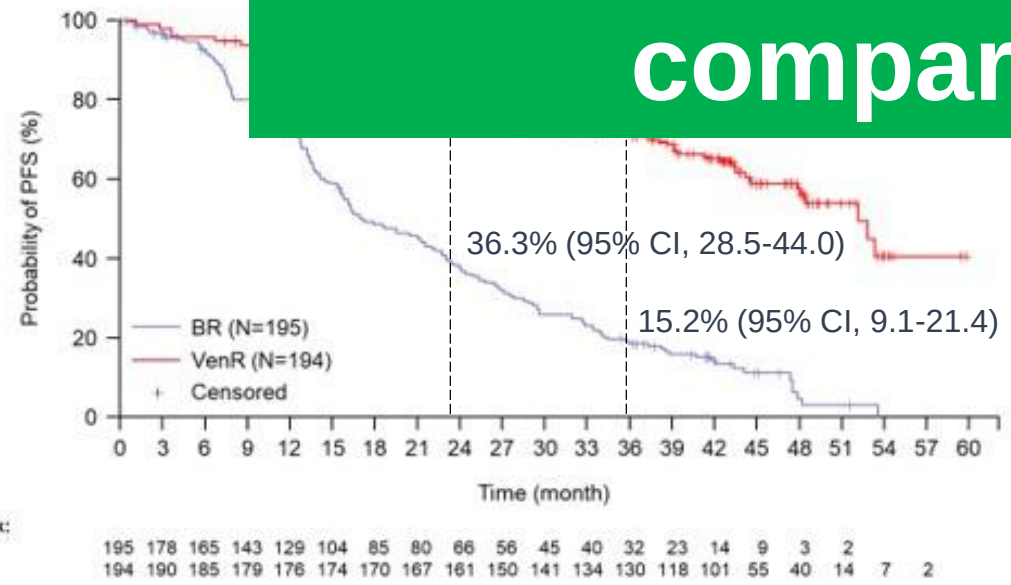
Venetoclax (5-week ramp-up + 6 cycles)
Rituximab (6 cycles)

Venetoclax
max 2 years from D1C1

Primary Endpoints

PFS, PD rate

Venetoclax + Rituxan leads to better disease control compared to BR



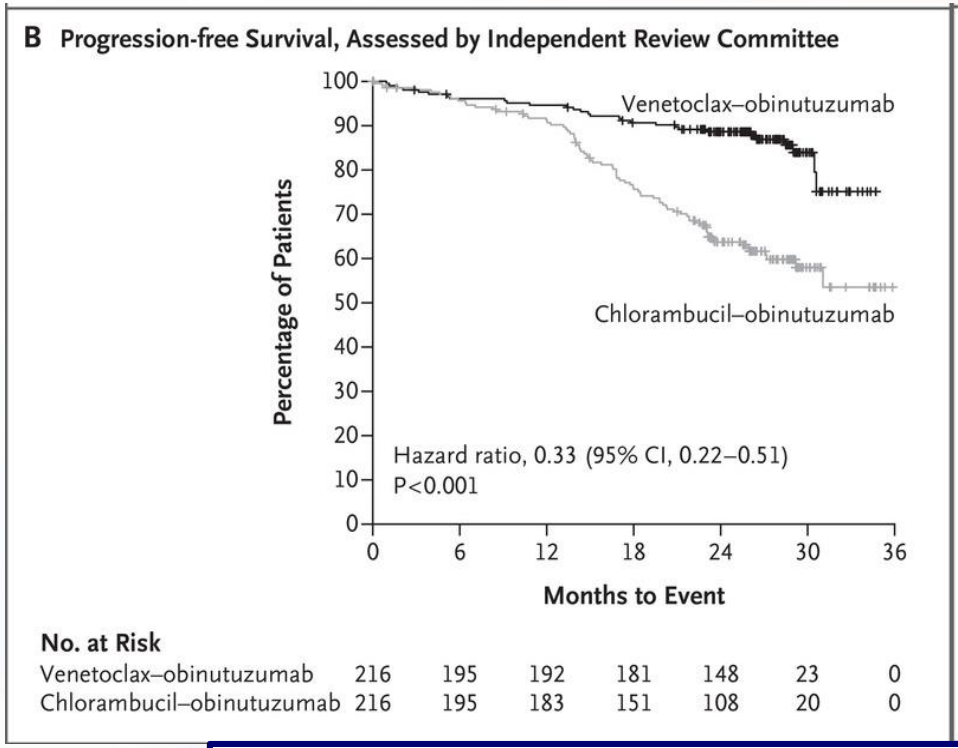
			HR (95% CI)	*P* Value
			0.17 (0.12-0.23)	< .0001
1-yr PFS, %	92.7	72.5	--	--
2-yr PFS, %	84.9	36.3	--	--
4-yr PFS, %	57.3	4.6	--	--

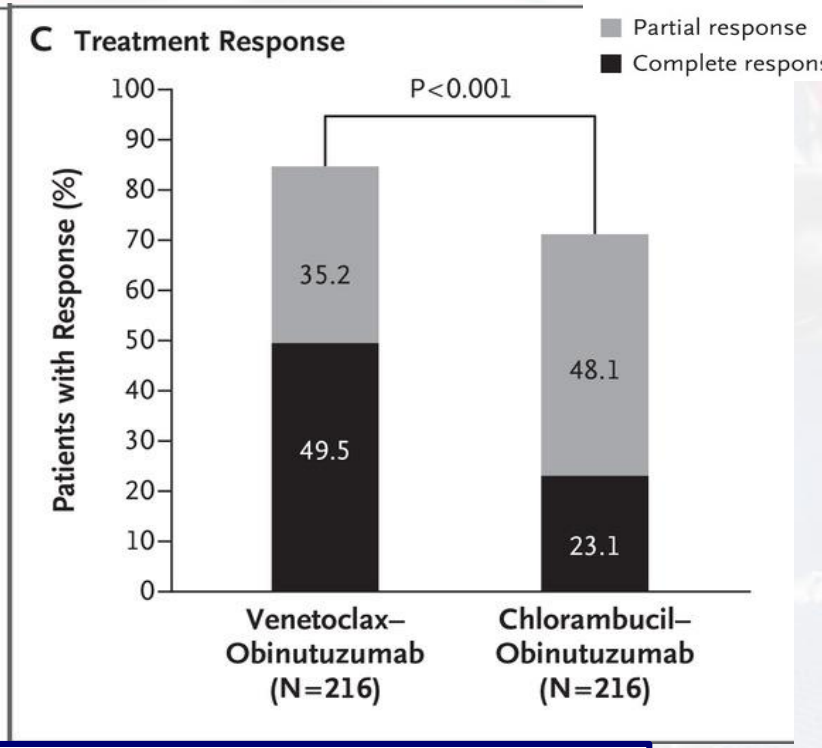
V + R consistently favored across subgroups including del(17p) status, *TP53* status, baseline *IGHV* status, & number of prior treatments

Seymour, et al *Blood.* 2019;134 (Supplement_1): 355. doi.org/10.1182/blood-2019-1239305.

Venetoclax+Obinutuzumab vs Chlorambucil+Obinutuzumab in Treatment-naïve Patients with CLL and Comorbidities *(Phase III CLL14)*

- Venetoclax/obinutuzumab produced significantly longer PFS than chlorambucil/obinutuzumab (HR 0.35, *P* < .001)
  - 2-yr PFS rate: 88% vs 64%
- PFS benefits observed regardless of *IGHV* or *TP53* status
- Venetoclax/obinutuzumab induced rapid and durable MRD negativity
- The safety profile of venetoclax/obinutuzumab was manageable
  - No significant difference in grade 3/4 neutropenia, infections, or all-cause mortality





On May 15, 2019, the FDA approved Venetoclax + Obinutuzumab for adult patients with CLL or SLL

Fischer, et al. *N Engl J Med.* 2019; 380:2225-2236.

Take Home Points: CLL 2020

- Significant improvements in the management of CLL in the past decade
- Importance of personalized therapy based on patient & disease characteristics
- Non-chemotherapy options for first-line & subsequent therapies
- Encourage participation in Clinical Trials