Research To Practice

Optimal Management of Adverse Events Associated with BTK and Bcl-2 Inhibitors

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Ibrutinib's toxicity profile is now well-established

Safety Analysis of Four Randomized Controlled Studies of Ibrutinib in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma or Mantle Cell Lymphoma

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Supplemental Figure 2 Prevalence of Most Common (≥ 3%) Grade 3/4 Adverse Events With Ibrutinib Over Time

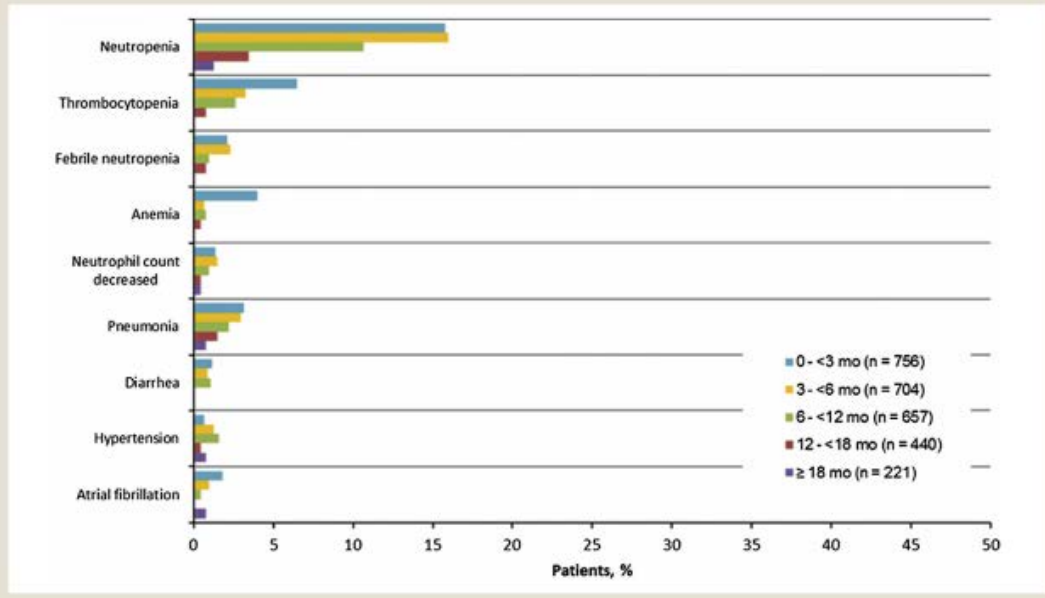


Table 7 Bleeding Events: Cumulative and Exposure-adjusted Incidence Rates

Event	Ibr (n = 756)		Comp (n = 749)		Δ, %[a]	Δ, EAIR[a]
	%	EAIR	%	EAIR		
Any bleeding event[b]	38	0.486	17	0.2628	21.3	0.2232
Grade 3/4 bleeding event	3	0.0252	2	0.0276	0.8	−0.0024
Major hemorrhage	4	0.0348	3	0.0348	1.3	0
Grade 3/4 major hemorrhage	3	0.0252	2	0.0276	0.8	−0.0024

Abbreviations: Comp = comparator; EAIR = exposure-adjusted incidence rate per patient-years; Ibr = ibrutinib.
[a]Negative numbers indicate higher rates with comparator.
[b]Based on the number of patients with any bleeding event by preferred term.

Courtesy of Matthew S Davids, MD, MMSc

O'Brien et al., *Clin Lymphoma Myeloma Leuk*. 2018 Oct;18(10):648-657.e15

Recent US cooperative group studies suggest Gr 3/4 ibrutinib toxicities may be less in younger patients

Adverse event	IR Arm Alliance n=181	IR Arm E1912 N=352
Median Age Age range	71 yrs 65 – 86	57 yrs 31 - 70
Infection	19%	5%
Atrial fibrillation	6%	3%
Bleeding	4%	1%
Hypertension	34%	7%
Deaths during active treatment +30 days	**7%**	**1%**

Courtesy of Matthew S Davids, MD, MMSc

Adapted from Shanafelt et al., ASH, 2018

Toxicity is the most common reason for ibrutinib discontinuation

Table 3. Most common reasons for KI discontinuation in patients who have discontinued ibrutinib or idelalisib

	Ibrutinib % (n)	Idelalisib % (n)
Toxicity	51 (73)	52 (18)
CLL progression	28 (40)	31 (11)
RT	8 (11)	6 (2)
Cellular therapies (chimeric antigen receptor T cells or allogeneic stem cell transplantation)	2 (3)	0 (0)
Unrelated death/Other	11 (16)	11 (4)

KI = kinase inhibitor

Courtesy of Matthew S Davids, MD, MMSc

Mato, *et al*, Blood, 2016

CLL12: CLL patients commonly have symptoms and complications

	Ibrutinib n=158
Any grade AEs (%)	150 (94.9)
AEs ≥ grade 3 (%)	80 (50.6)
AEs leading to interruption (%)	77 (41.6)
Arrhythmias	18
Bleeding	8
Diarrhea	4
Neoplasia	4
Infection	3
Myocardial infarction	1
other	39
Fatal AEs* (%)	4 (2.5)
Treatment-related	0

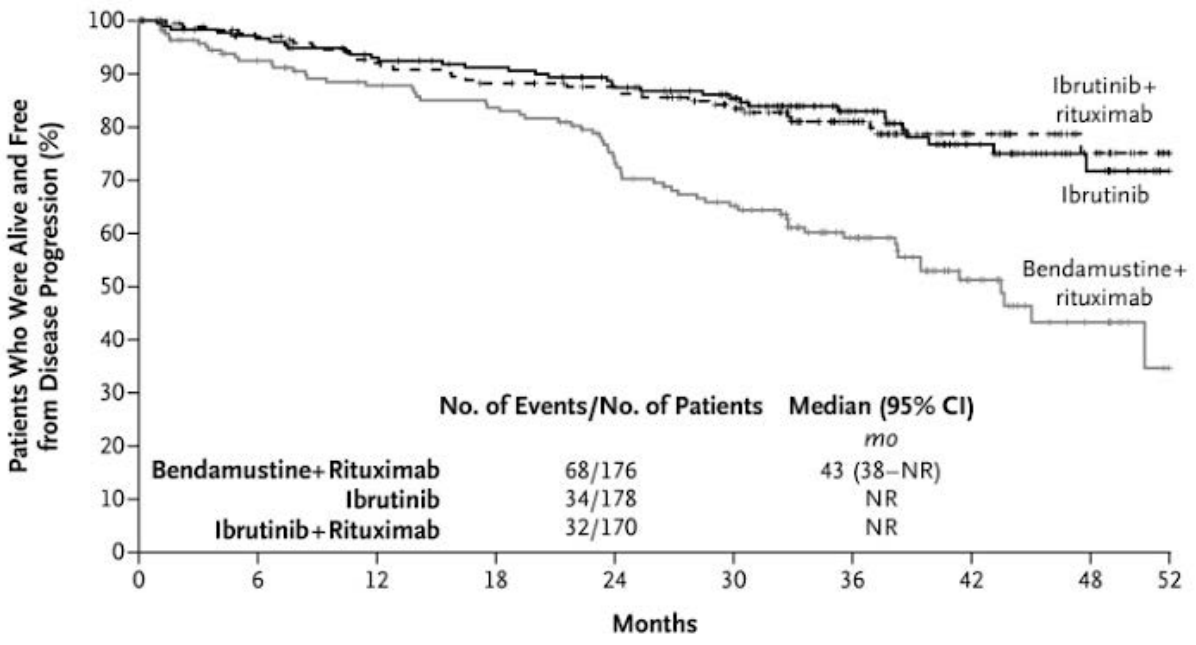
* Death of unknown cause (n=4), infection (n=2), second cancer (n=2), cardiac failure (n=1)

Courtesy of Matthew S Davids, MD, MMSc

Langerbeins et al., *iwCLL*, 2019

Rituximab does not add benefit or significant toxicity to ibrutinib

BTK inhibitors



No. at Risk

Bendamustine+rituximab	176	140	129	122	103	88	57	26	11	0
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib+rituximab	170	159	145	138	132	115	74	40	20	0

Woyach et al., *NEJM*, 2018

Courtesy of Matthew S Davids, MD, MMSc

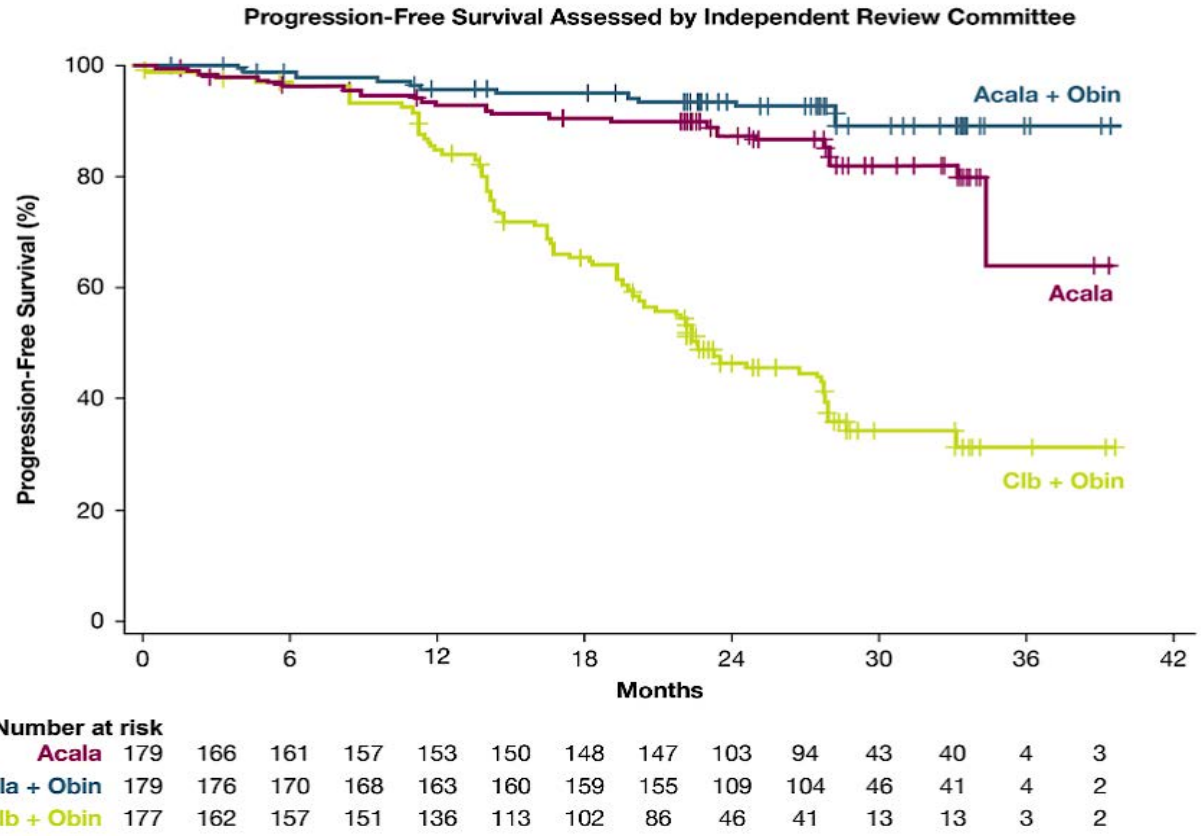
Table 2. Summary of Grade 3, 4, or 5 Adverse Events.*

Adverse Event	Bendamustine+ Rituximab (N=176)	Ibrutinib (N=180)	Ibrutinib+ Rituximab (N=181)	P Value†
	number of patients (percent)			
Hematologic				
Any				<0.001
Grade 3	62 (35)	59 (33)	49 (27)	
Grade 4	45 (26)	15 (8)	21 (12)	
Anemia				0.09
Grade 3	22 (12)	20 (11)	11 (6)	
Grade 4	0	1 (1)	0	
Decreased neutrophil count				<0.001
Grade 3	39 (22)	15 (8)	20 (11)	
Grade 4	32 (18)	12 (7)	19 (10)	
Decreased platelet count				0.008
Grade 3	16 (9)	9 (5)	8 (4)	
Grade 4	10 (6)	3 (2)	1 (1)	
Nonhematologic				
Any				0.04
Grade 3	76 (43)	97 (54)	100 (55)	
Grade 4	20 (11)	12 (7)	12 (7)	
Grade 5	15 (9)	24 (13)	22 (12)	
Bleeding‡				0.46
Grade 3	0	2 (1)	3 (2)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	0	0	1 (1)	
Infection§				0.62
Grade 3	17 (10)	29 (16)	28 (15)	
Grade 4	6 (3)	6 (3)	7 (4)	
Grade 5	3 (2)	2 (1)	2 (1)	
Febrile neutropenia				<0.001
Grade 3	13 (7)	3 (2)	1 (1)	
Atrial fibrillation				0.05
Grade 3	5 (3)	15 (8)	10 (6)	
Grade 4	0	2 (1)	0	
Hypertension				<0.001
Grade 3	24 (14)	53 (29)	60 (33)	
Grade 4	1 (1)	0	1 (1)	
Secondary cancer				0.17
Grade 3	6 (3)	5 (3)	13 (7)	
Grade 4	0	1 (1)	1 (1)	
Grade 5	1 (1)	4 (2)	1 (1)	
Unexplained or unwitnessed death				0.24
Grade 5	2 (1)	7 (4)	4 (2)	

* Shown are adverse events that occurred during treatment or follow-up, excluding events that occurred after crossover. The adverse-event analysis included all patients who began the assigned treatment.
† All P values are for comparisons across all three treatment groups and are two-sided. P values were calculated with the use of Fisher's exact test.
‡ Bleeding events included epistaxis (in three patients), epistaxis and oral hemorrhage (in one patient), and intracranial hemorrhage (in four patients, including one with a grade 5 event).
§ Details regarding infections are provided in Table 3.

Obinutuzumab *may* add benefit and toxicity to acalabrutinib

BTK inhibitors



	Acalabrutinib–obinutuzumab (n=178)			Acalabrutinib monotherapy (n=179)			Obinutuzumab–chlorambucil (n=169)		
	Any grade	Grade 1–2	Grade ≥3	Any grade	Grade 1–2	Grade ≥3	Any grade	Grade 1–2	Grade ≥3
Summary of adverse events									
Any	171 (96·1%)	46 (25·8%)	125 (70·2%)	170 (95·0%)	81 (45·3%)	89 (49·7%)	167 (98·8%)	49 (29·0%)	118 (69·8%)
Serious	69 (38·8%)	11 (6·2%)	58 (32·6%)	57 (31·8%)	4 (2·2%)	53 (29·6%)	37 (21·9%)	4 (2·4%)	33 (19·5%)
Led to drug discontinuation (any grade)	20 (11·2%)	..	..	16 (8·9%)	..	..	25 (14·1%)	..	..
Most common adverse events									
Headache	71 (39·9%)	69 (38·8%)	2 (1·1%)	66 (36·9%)	64 (35·8%)	2 (1·1%)	20 (11·8%)	20 (11·8%)	0
Diarrhoea	69 (38·8%)	61 (34·3%)	8 (4·5%)	62 (34·6%)	61 (34·1%)	1 (0·6%)	36 (21·3%)	33 (19·5%)	3 (1·8%)
Neutropenia	56 (31·5%)	3 (1·7%)	53 (29·8%)	19 (10·6%)	2 (1·1%)	17 (9·5%)	76 (45·0%)	6 (3·6%)	70 (41·4%)
Fatigue	50 (28·1%)	47 (26·4%)	3 (1·7%)	33 (18·4%)	31 (17·3%)	2 (1·1%)	29 (17·2%)	28 (16·6%)	1 (0·6%)
Contusion	42 (23·6%)	42 (23·6%)	0	27 (15·1%)	27 (15·1%)	0	7 (4·1%)	7 (4·1%)	0
Arthralgia	39 (21·9%)	37 (20·8%)	2 (1·1%)	28 (15·6%)	27 (15·1%)	1 (0·6%)	8 (4·7%)	6 (3·6%)	2 (1·2%)
Cough	39 (21·9%)	39 (21·9%)	0	33 (18·4%)	32 (17·9%)	1 (0·6%)	15 (8·9%)	15 (8·9%)	0
Upper respiratory tract infection	38 (21·3%)	34 (19·1%)	4 (2·2%)	33 (18·4%)	33 (18·4%)	0	14 (8·3%)	13 (7·7%)	1 (0·6%)
Nausea	36 (20·2%)	36 (20·2%)	0	40 (22·3%)	40 (22·3%)	0	53 (31·4%)	53 (31·4%)	0
Dizziness	32 (18·0%)	32 (18·0%)	0	21 (11·7%)	21 (11·7%)	0	10 (5·9%)	10 (5·9%)	0
Back pain	25 (14·0%)	24 (13·5%)	1 (0·6%)	25 (14·0%)	23 (12·8%)	2 (1·1%)	14 (8·3%)	13 (7·7%)	1 (0·6%)
Constipation	25 (14·0%)	25 (14·0%)	0	20 (11·2%)	20 (11·2%)	0	17 (10·1%)	16 (9·5%)	1 (0·6%)
Infusion-related reaction	24 (13·5%)	20 (11·2%)	4 (2·2%)	0	0	0	67 (39·6%)	58 (34·3%)	9 (5·3%)
Vomiting	24 (13·5%)	23 (12·9%)	1 (0·6%)	22 (12·3%)	21 (11·7%)	1 (0·6%)	19 (11·2%)	18 (10·7%)	1 (0·6%)
Pyrexia	23 (12·9%)	23 (12·9%)	0	12 (6·7%)	11 (6·1%)	1 (0·6%)	35 (20·7%)	34 (20·1%)	1 (0·6%)
Thrombocytopenia	23 (12·9%)	8 (4·5%)	15 (8·4%)	13 (7·3%)	8 (4·5%)	5 (2·8%)	24 (14·2%)	4 (2·4%)	20 (11·8%)
Oedema peripheral	22 (12·4%)	21 (11·8%)	1 (0·6%)	16 (8·9%)	15 (8·4%)	1 (0·6%)	12 (7·1%)	12 (7·1%)	0
Pain in extremity	22 (12·4%)	21 (11·8%)	1 (0·6%)	11 (6·1%)	11 (6·1%)	0	7 (4·1%)	7 (4·1%)	0
Urinary tract infection	22 (12·4%)	21 (11·8%)	1 (0·6%)	22 (12·3%)	19 (10·6%)	3 (1·7%)	8 (4·7%)	8 (4·7%)	0
Anaemia	21 (11·8%)	11 (6·2%)	10 (5·6%)	25 (14·0%)	13 (7·3%)	12 (6·7%)	20 (11·8%)	8 (4·7%)	12 (7·1%)
Rash	21 (11·8%)	20 (11·2%)	1 (0·6%)	25 (14·0%)	24 (13·4%)	1 (0·6%)	8 (4·7%)	8 (4·7%)	0
Chills	20 (11·2%)	20 (11·2%)	0	8 (4·5%)	8 (4·5%)	0	14 (8·3%)	13 (7·7%)	1 (0·6%)
Nasopharyngitis	20 (11·2%)	19 (10·7%)	1 (0·6%)	17 (9·5%)	17 (9·5%)	0	7 (4·1%)	7 (4·1%)	0
Pneumonia	19 (10·7%)	9 (5·1%)	10 (5·6%)	13 (7·3%)	9 (5·0%)	4 (2·2%)	5 (3·0%)	2 (1·2%)	3 (1·8%)
Decreased appetite	18 (10·1%)	18 (10·1%)	0	10 (5·6%)	10 (5·6%)	0	13 (7·7%)	12 (7·1%)	1 (0·6%)
Dyspnoea	15 (8·4%)	15 (8·4%)	0	12 (6·7%)	9 (5·0%)	3 (1·7%)	17 (10·1%)	14 (8·3%)	3 (1·8%)

Data are n (%).

Table 2: Adverse events occurring in at least 10% of patients in any treatment group

Courtesy of Matthew S Davids, MD, MMSc

Sharman et al. *Lancet.* 2020

We recently reported that pneumocystis jiroveci pneumonia (PJP) incidence on BTKi was low, even in patients not on prophylaxis

- Overall prevalence of PJP in patients NOT on prophylaxis: **3.4%** (3/87)
- Prevalence of PJP in patients ON prophylaxis: 0% (0/125)
- Incidence rate in patients not on prophylaxis: 1.9 per 100 person-years
- Number needed to treat to prevent 1 case of PJP: 42 patients

Courtesy of Matthew S Davids, MD, MMSc

Ryan, *et al*, *iwCLL*, 2019

Invasive fungal infections (IFIs) were also uncommon but were seen in ibrutinib combination regimens

- 3 additional cases of proven or probable IFIs
  - 1 case of histoplasmosis on ibrutinib + FCR trial (n=57)
  - 2 cases of aspergillosis on ibrutinib + umbralisib trial (n=14)

- Prevalence of aspergillosis or histoplasmosis in entire cohort: 1.4% (3/212)
- Prevalence in single-agent BTK-inhibitor therapy patients: 0% (0/141)
- Prevalence in ibrutinib combination therapy-treated patients: 4.2% (3/71)

Courtesy of Matthew S Davids, MD, MMSc

Ryan, *et al*, iwCLL, 2019

Acalabrutinib: a safer BTKi?

Compared to ibrutinib:

- ***Overlapping toxicities*: mild diarrhea, mild bleeding, infections**
- ***New toxicities*: headache, weight gain**
- ***Less commonly seen with acalabrutinib*: afib, major hemorrhage, significant skin toxicity, pneumonitis**
- **No ventricular arrhythmias reported**

Adverse Event	All Grades	Grades 1–2	Grades 3–4
Number of patients (%)			
Headache	26 (43)	26 (43)	0
Diarrhea	24 (39)	23 (38)	1 (2)
Increased weight	16 (26)	15 (25)	1 (2)
Pyrexia	14 (23)	12 (20)	2 (3)
Upper respiratory tract infection	14 (23)	14 (23)	0
Fatigue	13 (21)	11 (18)	2 (3)
Peripheral edema	13 (21)	13 (21)	0
Hypertension	12 (20)	8 (13)	4 (7)
Nausea	12 (20)	12 (20)	0
Contusion	11 (18)	11 (18)	0
Arthralgia	10 (16)	9 (15)	1 (2)
Petechiae	10 (16)	10 (16)	0
Decreased weight	10 (16)	10 (16)	0

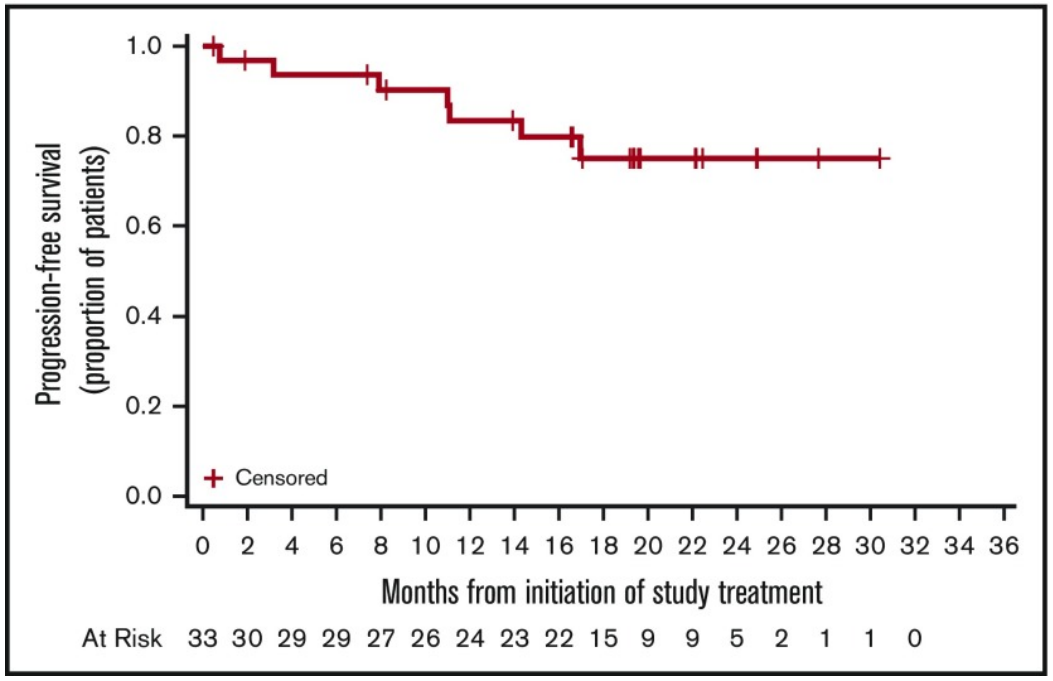
Courtesy of Matthew S Davids, MD, MMSc

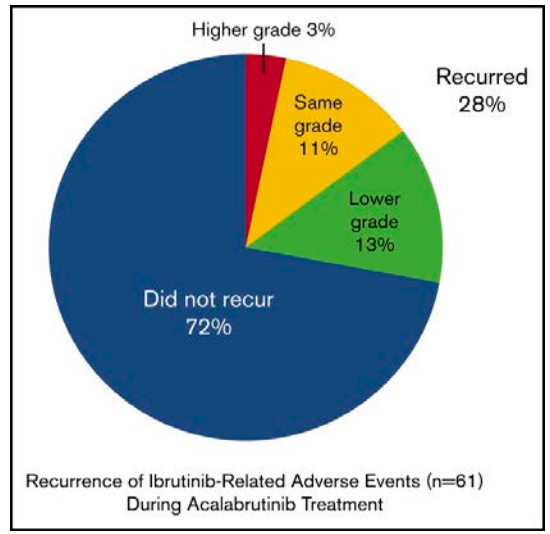
Byrd JC, et al. *N Engl J Med*. 2016; Wang M, et al. *Lancet*. 2017; FDA Prescribing Information.

Acalabrutinib in Ibrutinib-Intolerant Patients

Subset analysis of patients with ibrutinib intolerance enrolled in phase 1/2 ACE-CL-001 (n = 33)

- Median duration of prior ibrutinib, 11.6 months
- ~70% of patients remained on acalabrutinib after a median of 19 months
  - 3 patients had discontinued acalabrutinib due to AEs; 4 patients discontinued due to progressive disease





- Median duration of response was not reached
- Median PFS was not reached
- 1-year PFS was 83.4% (95% CI, 64.5%-92.7%)

Courtesy of Matthew S Davids, MD, MMSc

Awan FT, et al. *Blood.* 2019

Summary of Significant AEs Occurring in Patients Treated With Ibrutinib or Acalabrutinib

BTK inhibitors

BTK Clinical Trial	Arthralgia (%)	Atrial Fibrillation (%)	Hematologic[a] (%)	Bleeding/ Hemorrhage (%)	Hypertension (%)	Infection (%)
RESONATE						
Ibrutinib (n=195)	17	3	17-23	44[b]	NR	NR
RESONATE-2						
Ibrutinib (n=136)		6	–	4	14	–
iLLUMINATE						
Ibrutinib/obin (n=113)	22	12	17-44	NR	17	14[e]
A041202						
Ibrutinib (n=180)	NR	17	41[c]	2[c]	29[c]	20[c]
Ibrutinib/rituximab (n=181)	NR	14	39[c]	4[c]	34[c]	20[c]
ECOG-E1912						
Ibrutinib/rituximab (n=352)	4.8	7.4	34.7[c]	NR	18.8[c]	9.4[c]
ASCEND						
Acalabrutinib (n=155)	NR	5.2	28[d]	26	NR	NR
ELEVATE-TN						
Acalabrutinib (n=179)	15.6	4.0	9.5[c]	15.1	NR	18.4[e]
Acalabrutinib/obin (n=179)	21.9	3.4	29.8[c]	23.6	NR	21.3[e]

NR, not reported.
[a] Includes anemia, neutropenia, thrombocytopenia.
[b] Any grade, most commonly petechiae including ecchymoses.
[c] Grade 3 or higher.
[d] Anemia and neutropenia, grade 3 or higher.
[e] Upper respiratory tract.

Courtesy of Matthew S Davids, MD, MMSc

ASPEN Trial (Waldenström Macroglobulinemia): BTKi Class Adverse Events of Interest

AE Categories, %	All Grades		Grade ≥ 3	
	Zanubrutinib (n = 101)	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Ibrutinib (n = 98)
Atrial fibrillation/flutter*	3.0	18.4	0.0	7.1
Diarrhea (PT)	21.8	32.7	3.0	2.0
Hemorrhage	50.5	60.2	5.9	9.2
▪ Major hemorrhage‡	5.9	10.2	5.9	9.2
Hypertension	12.9	20.4	7.9	15.3
Neutropenia*†	31.7	15.3	22.8	8.2
Infection	69.3	71.4	18.8	23.5
Second malignancy	12.9	12.2	3.0	1.0
Discontinuation rate	4.0	9.0		

*Descriptive 2-sided $P < .05$.

†PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.

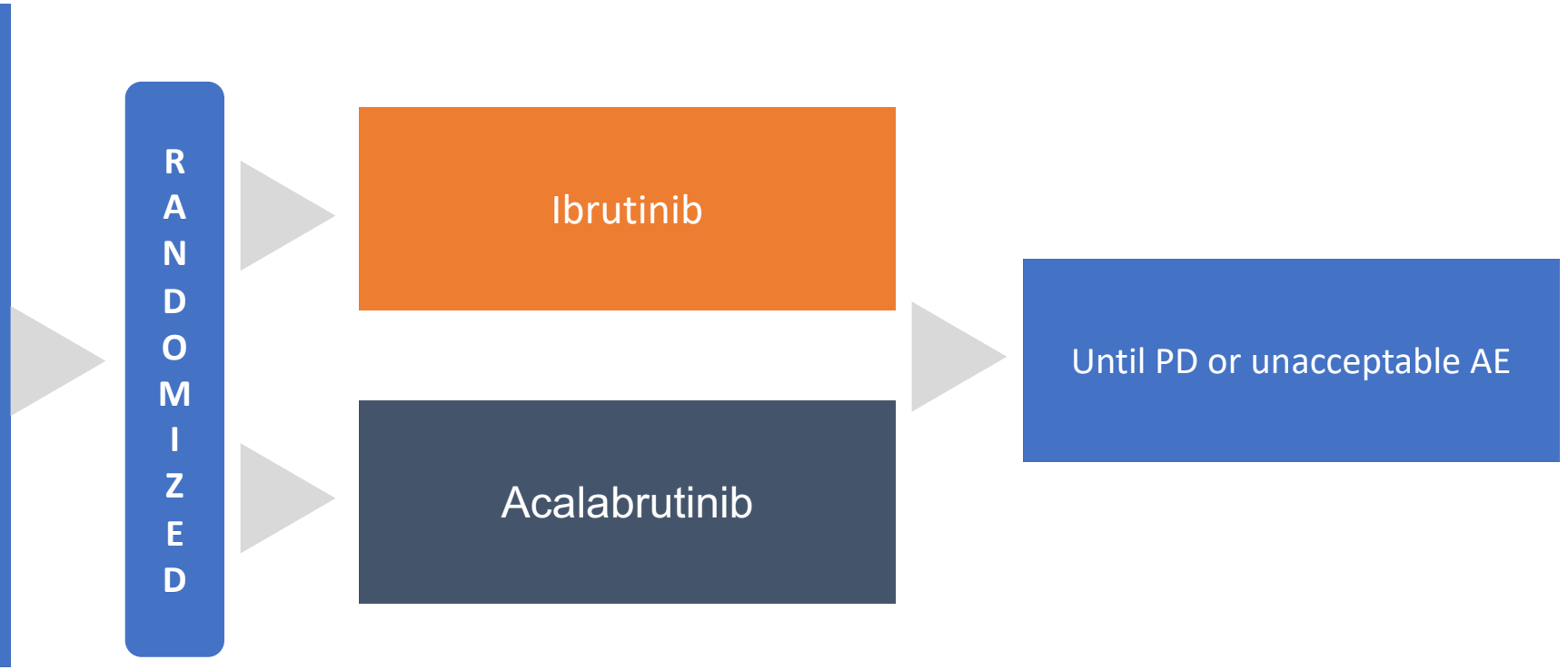
‡Major hemorrhage defined as grade ≥ 3 hemorrhage or any grade CNS hemorrhage.

Courtesy of Matthew S Davids, MD, MMSc

Tam et al., *Blood*, 2020

ELEVATE-R/R Trial: Ibrutinib vs Acalabrutinib in Patients With High-Risk R/R CLL

- Ongoing phase 3, randomized, multicenter, open-label, noninferiority trial
- Patients with del(17p) or del(11q) CLL with active disease (N=533)
- ≥1 previous line of treatment
- ECOG 0-2



Status:
Active, fully accrued

Primary endpoint: PFS

Secondary endpoints: OS, incidence of treatment-emergent AEs, atrial fibrillation, Richter's transformation

Courtesy of Matthew S Davids, MD, MMSc

MAIC: Acalabrutinib ± G Demonstrated Lower Rates of Several Clinically Important AEs vs Ibrutinib ± G in TN CLL

AEs With Statistically Significant Differences After Matching

Acalabrutinib vs Ibrutinib

AE rate, %	Acala ESS=79	Ibr n=136	Rate difference % (95% CI)	*P*-value
Grade 3/4 AEs				
Infections	12.4	24.0	−11.6 (−21.9,−1.0)	<0.05
Atrial fibrillation	0	4.0	−4.0 (−7.3 ,0.0)	<0.05
Grade 1-4 AEs				
Peripheral edema	7.5	21.0	−13.5 (−21.7,−5.0)	<0.001
Pyrexia	6.2	20.0	−13.8 (−21.6,−6.0)	<0.001
Hypertension	6.4	18.0	−11.6 (−19.9,−3.0)	<0.01
Major hemorrhage	1.8	7.0	−5.2 (−10.2,0.0)	<0.05

Acalabrutinib + G vs Ibrutinib + G

AE rate, %	Acala + G ESS=97	Ibr + G n=113	Rate difference % (95% CI)	*P*−value
Grade 3/4 AEs				
Peripheral edema	0.6	12.0	−11.4 (−17.5,−5.3)	<0.001
Febrile neutropenia	0.5	5.0	−4.5 (−8.6,−0.4)	<0.05
Grade 1-4 AEs				
Headache	32.1	8.0	+24.1 (+14.6,+33.6)	<0.001
Thrombocytopenia	20.7	36.0	−15.3 (−26.8,−3.9)	<0.01
Atrial fibrillation	3.4	12.0	−8.6 (−15.6,−1.7)	<0.05

G = Obinutuzumab

Courtesy of Matthew S Davids, MD, MMSc

Davids et al., EHA, 2020 (Abstract EP724)

Phase I FIH: venetoclax was generally well tolerated, although specific toxicities were noted

Adverse events, serious adverse events and toxicity in the 116 study patients

Adverse event*	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	**115** (99)	**96** (83)
Diarrhea	**60** (52)	**2** (2)
Upper respiratory tract infection	**56** (48)	**1** (1)
Nausea	**55** (47)	**2** (2)
Neutropenia	**52** (45)	**48** (41)
Fatigue	**46** (40)	**4** (3)
Cough	**35** (30)	**0**
Pyrexia	**30** (26)	**1** (1)
Anaemia	**29** (25)	**14** (12)
Headache	**28** (24)	**1** (1)
Constipation	**24** (21)	**1** (1)
Thrombocytopenia	**21** (18)	**14** (12)
Arthralgia	**21** (18)	**1** (1)
Vomiting	**21** (18)	**2** (2)
Peripheral edema	**18** (16)	**0**
Pyrexia	**17** (15)	**10** (9)

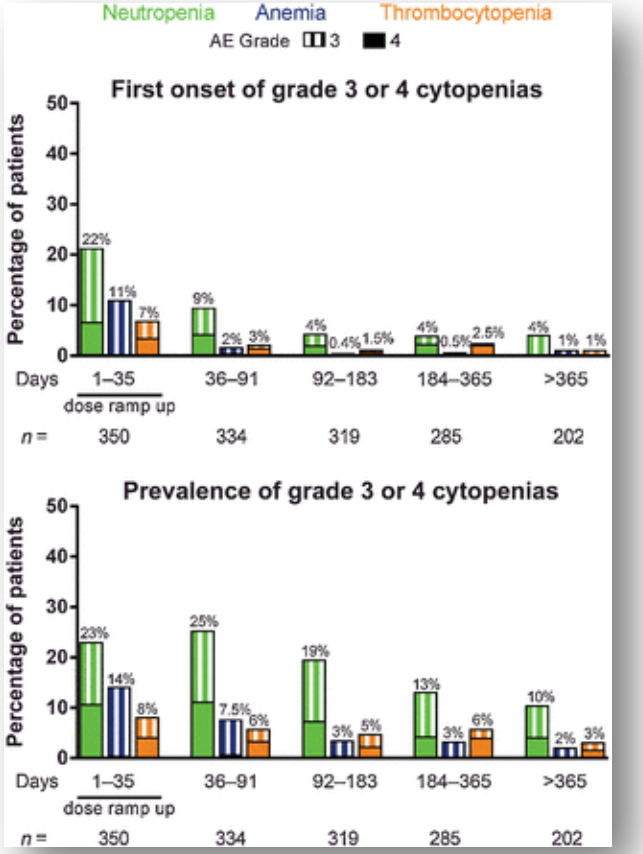
Serious adverse event†	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	**52** (45)	
Febrile neutropenia	**7** (6)	
Pneumonia	**5** (4)	
Upper respiratory tract infection	**4** (3)	
Immune thrombocytopenia	**3** (3)	
Tumor lysis syndrome	**3** (3)	
Diarrhoea	**2** (2)	
Fluid overload	**2** (2)	
Hyperglycemia	**2** (2)	
Prostate cancer	**2** (2)	
Pyrexia	**2** (2)	

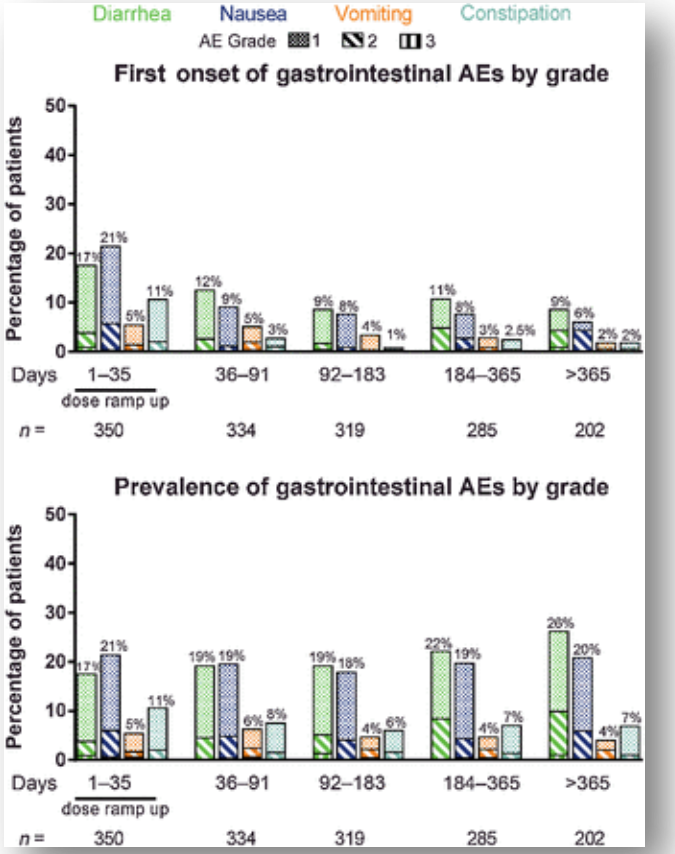
Toxicity	Any Grade (%)	Grade 3 or 4 (%)
Neutropenia	**45**	**41**
GI	**52**	**2**
TLS	**3**	**3**

*Listed are adverse events that were reported in at least 15% patients. Preexisting grade 1/2 abnormalities not reported, unless grade increased during the study.
†Listed are serious adverse events that were reported in at least two patients. Excluded are serious adverse events that were related to disease progression in two patients.
GI, gastrointestinal; **TLS**, tumor lysis syndrome
Roberts AW, et al. *N Engl J Med* 2016;374:311–322.

Courtesy of Matthew S Davids, MD, MMSc

Venetoclax risks include neutropenia, GI toxicities, and TLS



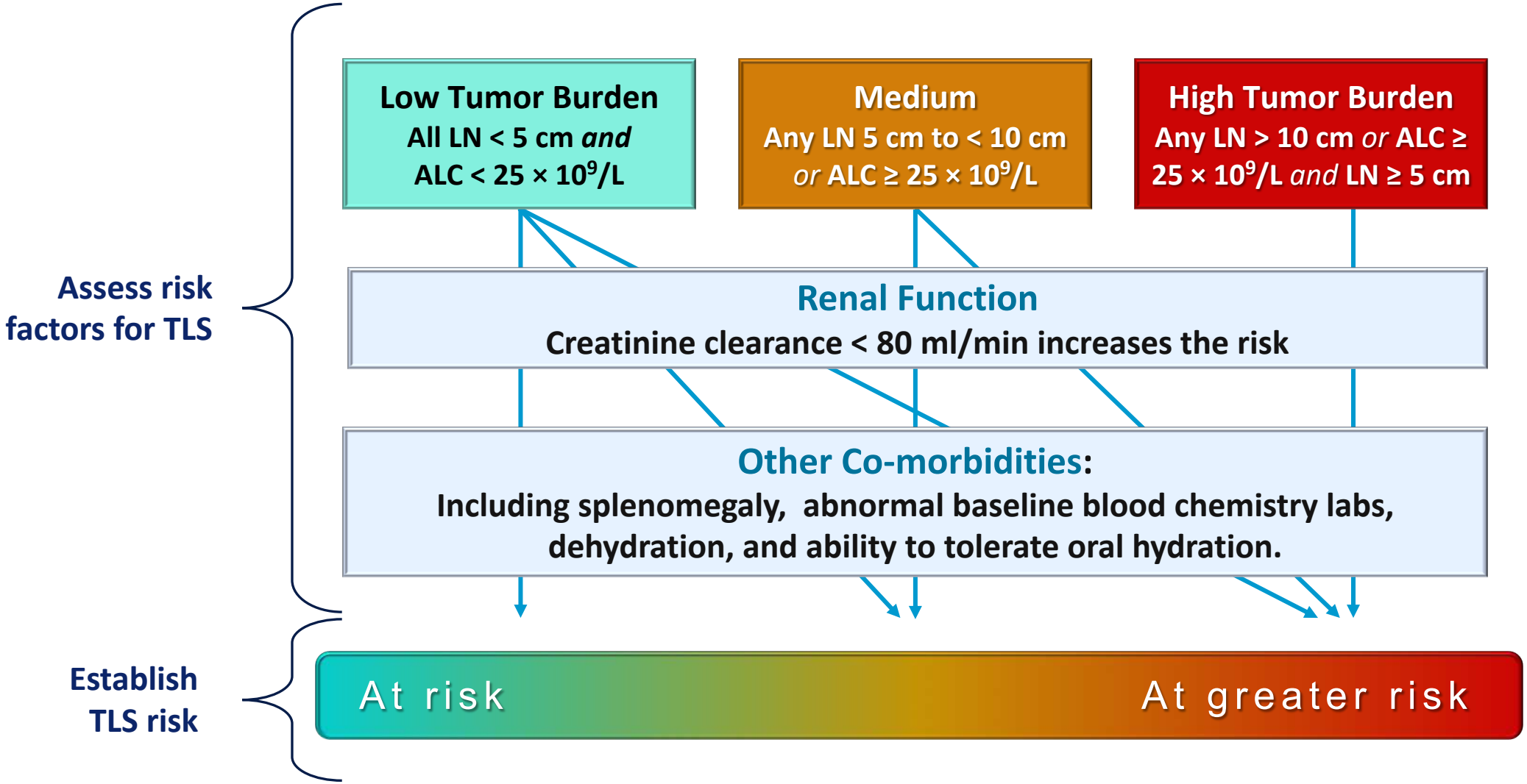


- **2/166 (1.4%) treated with current dosing had lab TLS, but none had clinical TLS**
- **TLS in phase 3 trials:**
  - **MURANO (ven + rituximab) 3.1% (1 clinical, 5 lab)**
  - **CLL14 (ven + obinutuzumab) 3 patients all before starting venetoclax**

Courtesy of Matthew S Davids, MD, MMSc

Davids MS et al., *Clin Cancer Res*, 2018

TLS risk with venetoclax is a continuum based on multiple factors

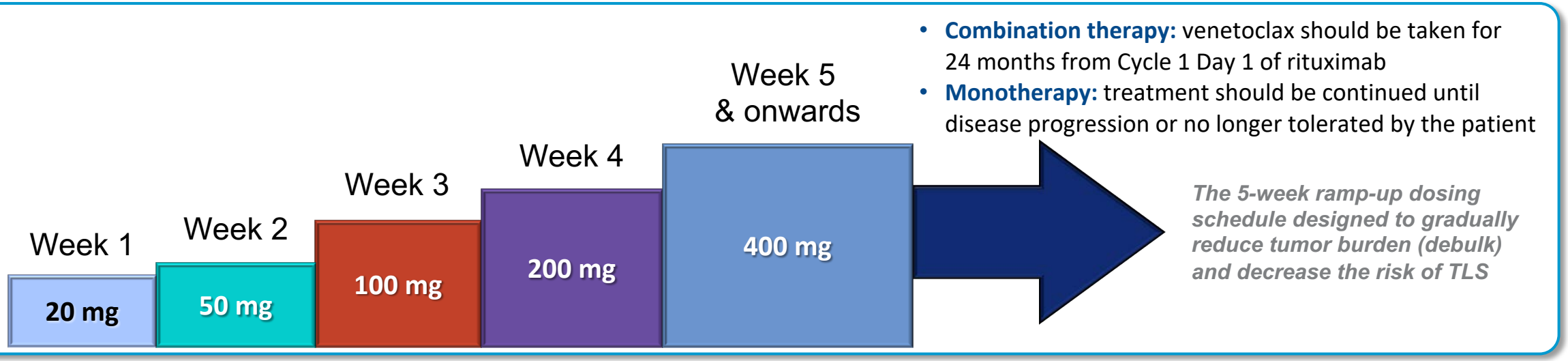


ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumor lysis syndrome

1. Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol* 2016;17:768–778.

Courtesy of Matthew S Davids, MD, MMSc

Venetoclax dose initiation



- **Combination therapy:** venetoclax should be taken for 24 months from Cycle 1 Day 1 of rituximab
- **Monotherapy:** treatment should be continued until disease progression or no longer tolerated by the patient

The 5-week ramp-up dosing schedule designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS

The 5-week dose-titration schedule is designed to gradually reduce tumour burden and decrease the risk of TLS

Combination therapy: recommended dose of venetoclax in combination with rituximab is 400 mg once daily; rituximab should be administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days.

Monotherapy: the recommended dose of venetoclax is 400 mg once daily.

Venetoclax SmPC: https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019).

Courtesy of Matthew S Davids, MD, MMSc

Venetoclax: TLS prophylaxis and monitoring

[a] **HYDRATION**	**Oral** (1.5 – 2 L); start 2 days prior to treatment start. **IV** if needed due to higher TLS risk
ANTI-HYPER-URICAEMIC AGENTS	Patients with high uric acid or TLS risk should be administered with anti-hyperuricaemic agents **2 to 3 days prior** to treatment start
[b,c] **LABORATORY MONITORING**	• **Pre-dose, 6–8, 24 hours** (at 1st dose of 20 mg and 50 mg, and for patients who continue to be at risk • Pre-dose at subsequent ramp-up doses Evaluate blood chemistries and review in real time
HOSPITALIZATION	Based on physician assessment, some patients consider hospitalisation on first dose of venetoclax for more intensive prophylaxis and monitoring during the first 24 hours.

[a]Administer intravenous hydration for any patient who cannot tolerate oral hydration; [b]Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time; [c]For patients at risk of TLS, monitor blood chemistries at 6–8 hours and at 24 hours at each subsequent ramp-up dose. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose of venetoclax, and at each dose increase. **LN,** lymph node; **ALC**, absolute lymphocyte count; **TLS**, tumour lysis syndrome; **VEN**, venetoclax

1. Venetoclax SPC https://www.medicines.org.uk/emc/product/2267/smpc (accessed October 2019); 2. Stilgenbauer S, et al. *Lancet Oncol.* 2016; 17:768–778

Courtesy of Matthew S Davids, MD, MMSc

General considerations for toxicity management with novel agents

- **In the setting of active infection it is generally best to hold drug at least until seeing signs of clinical improvement**
- **For most toxicities requiring drug hold, it is preferable to either rechallenge with full dose or to start back at dose reduction but then get back to full dose**
- **In general I am more hesitant to hold drug soon after starting a novel agent or in a patient who is progressing on a novel agent**
- **I am less concerned about stopping drug in patients who have been on novel agents for at least a few months and are in a good clinical response**

Courtesy of Matthew S Davids, MD, MMSc

General considerations (continued)

- **Novel agents are infrequently the main cause of cytopenias (exception: venetoclax and neutropenia)**
- **It is generally safe to give growth factor support concomitantly with novel agents**
- **Patients who have to permanently discontinue a novel agent due to toxicity do not necessarily need to immediately start on a new therapy**

Courtesy of Matthew S Davids, MD, MMSc

Case 1

A 73 y/o man with HTN and diet-controlled DM has del(11q), unmutated IGHV, TP53 wildtype, Rai stage 4 CLL and needs initial treatment. He starts on ibrutinib, and about 10 weeks into his course he has marked reduction in lymphadenopathy and improvement in cytopenias, but on routine check is found to be in afib with a rate in the low 100s. Ibrutinib is held, and anticoagulation is started.

How do you proceed at this point?

Courtesy of Matthew S Davids, MD, MMSc

Case 2

A fit 67 y/o woman with del(17p) CLL relapsed 2 years after FCR now develops recurrent bulky internal lymphadenopathy and splenomegaly of 22 cm. She is started on venetoclax + rituximab, and on week 2 of rituximab her ANC has trended down from a baseline of 1,600 to 950. She is afebrile and tolerating therapy well.

How do you proceed?

Courtesy of Matthew S Davids, MD, MMSc