Recognizing Toxicities of Oral Oncolytics in the Management of Hematologic Malignancies

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Objectives & Disclosure

Assess the safety of oral oncolytic therapies based on recently published data

Propose a strategy to manage a patient experiencing an adverse effect while receiving an oral oncolytic agent

Disclosure

- *I have no conflicts of interest to disclose*
- *All materials and content presented do not infringe or violate any copyright, trademark, patent or intellectual property rights of any person or entity, nor do they promote or endorse any product, service, or device which may or is at the time of the program not approved by any governing agency*

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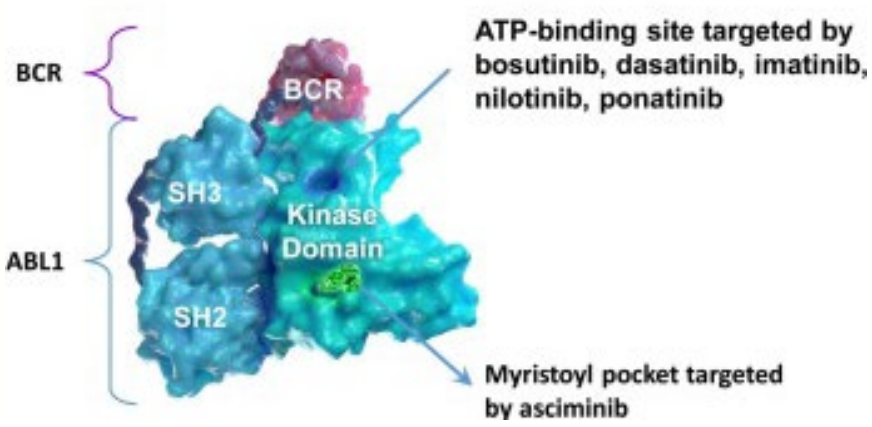
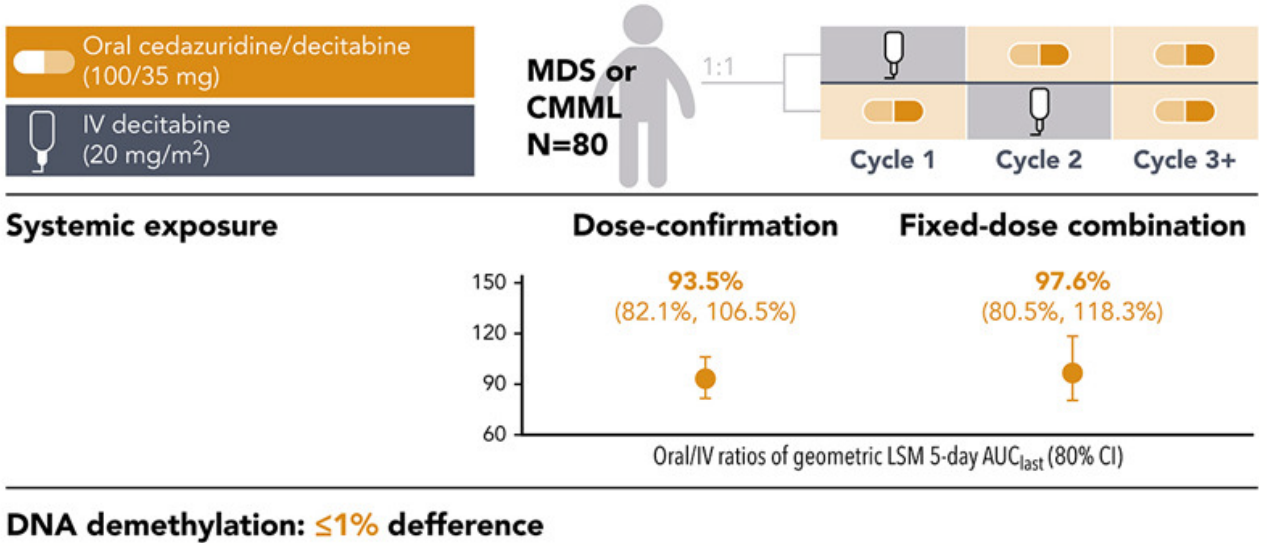
New(ish) Drug Approvals

Asciminib (Scemblix) – 10/29/21

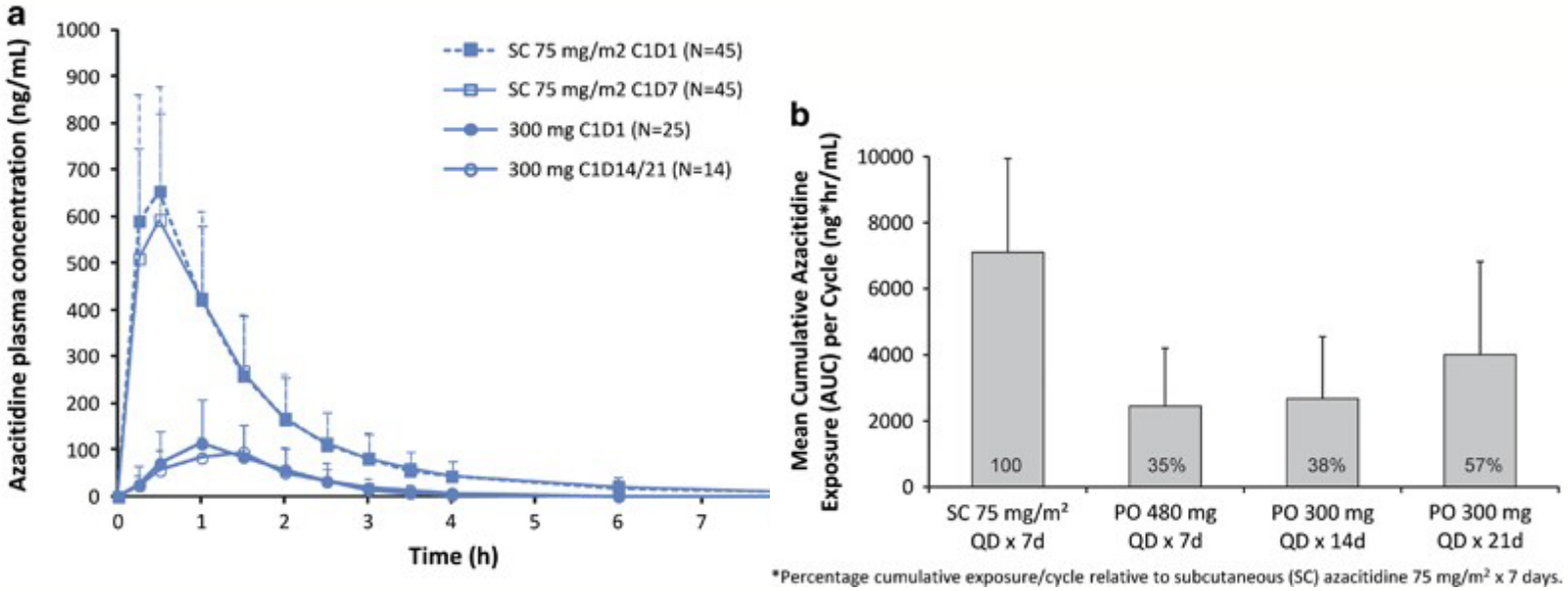


Leukemia Res. 2020;98:106458
Blood. 2020;136:674-683.
Leukemia. 2016;30:889-896

Decitabine/cedazuridine (Inqovi) – 9/1/20



Azacitidine (Onureg) – 7/7/20



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Oral Azacitidine

PO vs Placebo

Event	Oral AZA (N=236)		Placebo (N=233)	
	Any Grade	*Grade 3 or 4*	*Any Grade*	*Grade 3 or 4*
Any adverse event	98%	72%	97%	63%
Nausea	65%	3%	24%	<1%
Vomiting	60%	3%	10%	0%
Diarrhea	50%	5%	21%	1%
Neutropenia	44%	41%	26%	24%
Constipation	39%	1%	24%	0%
Thrombocytopenia	33%	22%	27%	21%
Fatigue	30%	3%	19%	1%
Anemia	20%	14%	18%	13%

PO/Placebo Study vs. Inj/Placebo Study

Outcome		QUAZAR AML-001		HOVON97	
		Oral AZA	Placebo	Inj AZA	Obs
Serious Adverse Event	Rate/pt-yr	0.34	0.32 ←	0.36	0.11 ←
	Rate ratio (95% CI)	1.06 (0.63-1.90)		3.12 (2.71-3.62)	
	Relative risk (95% CI)	0.35 (0.18 – 0.68)			
Hospitalization	Rate/pt-yr	0.42	0.71 ←	0.20	0.14 ←
	Rate ratio (95% CI)	0.59 (0.39-0.89)		1.43 (1.23-1.65)	
	Relative risk (95% CI)	0.41 (0.24-0.71)			

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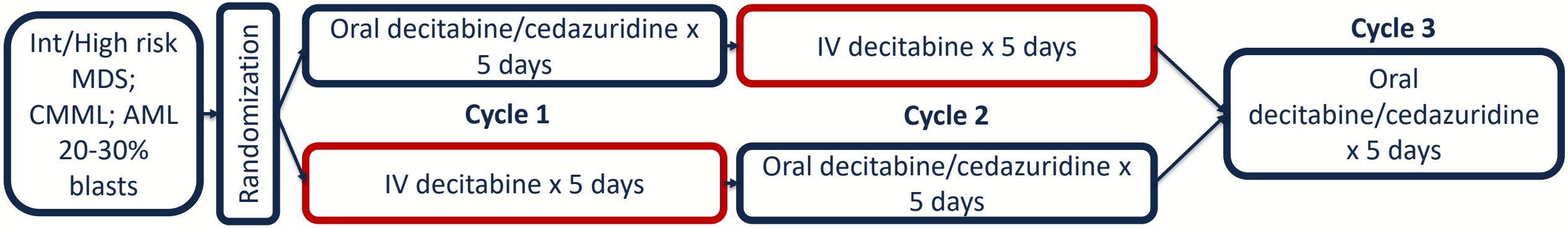
N Engl J Med. 2020;383:2526-2537.
Blood. 2021;138:3015-3017

Oral Decitabine/Cedazuridine



Treatment Emergent Adverse Events

	All Grades	Grade 3 or higher
Neutropenia	51%	49%
Thrombocytopenia	53%	47%
Anemia	41%	35%
Leukopenia	25%	22%
Febrile Neutropenia	14%	13%
Fatigue	24%	2%
Diarrhea	17%	2%
Nausea	25%	0

Safety profile consistent with that of IV decitabine

No new safety concerns with longer follow up

Savona MR, McCloskey JK, Griffiths EA, et al. Prolonged survival observed in 133 MDS patients treated with oral decitabine/cedazuridine. Presented at: 16th International Congress on Myelodysplastic Syndromes; September 23-26; virtual poster. Abstract P48. https://bit.ly/3ENe1cV

Asciminib

Most Frequent AE from Asciminib Monotherapy

Event	All Grades	Grade 3 or 4
Total	100%	60%
Fatigue	29%	1%
Headache	28%	<1%
Lipase increased	27%	10%
Arthralgia	24%	1%
Nausea	24%	<1%
Diarrhea	23%	0
Rash	23%	0
Thrombocytopenia	22%	9%
Vomiting	21%	3%
Hypertension	19%	9%

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N Engl J Med. 2019;138:2315-26
Blood. 2021;138:2031-2041

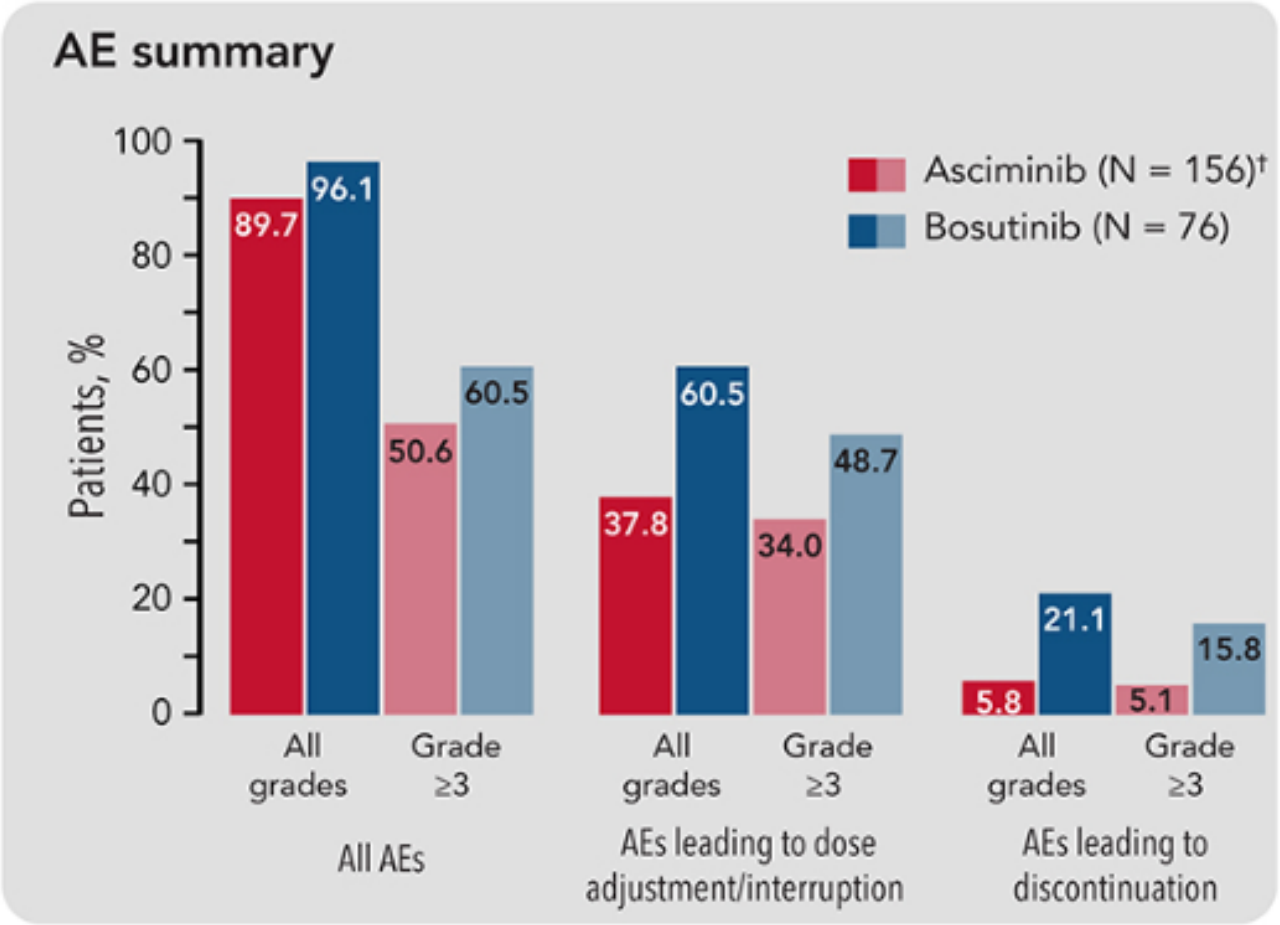
Asciminib vs Bosutinib in CML after 2 or More Prior TKIs

- Adults with CML-CP, previously treated with ≥ 2 TKI
- Failure or intolerance of the most recent TKI

R 2:1

Asciminib 40 mg twice daily

Bosutinib 500 mg once daily



Venetoclax's Ever Expanding Use

NCCN Drugs and Biologics Compendium Recommended Uses

Cancer Diagnosis	Regimen
CLL/SLL	Venetoclax Venetoclax + obinutuzumab Venetoclax + rituximab
AML	Venetoclax + azacitidine, decitabine, or low-dose cytarabine Venetoclax + reinduction therapy
T-ALL	Venetoclax + decitabine Venetoclax + HyperCVAD or mini-HyperCVAD Venetoclax + nelarabine
Mantle Cell Lymphoma	Venetoclax Venetoclax + rituximab ± lenalidomide Venetoclax + ibrutinib
Waldenstrom Macroglobulinemia	Venetoclax
Systemic Light Chain Amyloidosis	Venetoclax ± dexamethasone (relapsed/refractory disease)
Multiple Myeloma	Venetoclax

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https://www.nccn.org/compendia-templates/compendia/nccn-compendia

Venetoclax: New Safety Data in AML from ASH 2021

AML Real World Evidence (ARC) Initiative
Newly diagnosed; N=133 (N=102 in US, N=31 in Israel)
VEN + AZA (80%), VEN + DEC (18%), VEN + LDAC (2%)
9.7% D/C due to intolerance
30% with dose interruptions: Febrile neutropenia (33%), Neutropenia (38%)
Ramp-up: 74% (67% of US patient initiated in inpatient setting)
Antifungal use during 1st cycle: 66% 42% with interaction remained on reduced dose (100 mg)

VEN: venetoclax, AZA: azacitidine, DEC: decitabine, LDAC: low dose cytarabine, R/R: relapsed/refractory, ND: newly diagnosed, AE: adverse effect

Outpatient 1st Cycle in AML
N=59 (43 R/R, 16 ND), Single center retrospective study
VEN + AZA (59%), VEN + DEC (37%)
Median Age: 70, 15% with ECOG > 1
68% received cycle 1 in outpatient (OP) setting
Ramp-up: 2 cases of TLS, 5 AE
During 1st course: Inpatient (IP) AE rate: 84% OP AE rate: 50%
Most common AE: Hematologic (31%), Infection (55%)
Bacterial infections: OP 25%, IP 63% (p=0.009) Sepsis: 13% OP, 68% IP (p<-0.001)
Therapy suspension: OP 25%, OP 53% (p=0.04)
Average number of days hospitalized: 6 OP, 40 IP (p<0.001)

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Blood. 2021;138:1271-1273
Blood. 2021;138: 2340-2341

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Venetoclax: New Safety Data in CLL from ASH 2021 - Monotherapy

Tumor Lysis Syndrome
N=69, Median age: 71, Median 2 prior lines of therapy
TLS risk: Low 30%, Medium 54%, High 16%
4 laboratory TLS events 3 medium risk, 1 high risk 2 at 20 mg ramp-up, 1 at 50 mg ramp-up, 1 at 200mg ramp-up
No renal dysfunction, rasburicase use, or dialysis needed
All patient continued on VEN
Antiuricemic therapy used in 97% Median duration: 29 days
64% completed ramp-up outpatient (2 high risk for TLS) Of 23 patients with high/medium TLS risk and CrCL <80, only 12 hospitalized

Blood. 2021;138: 3744-3745

Venetoclax: New Safety Data in Octogenarians from ASH 2021

AML
N=21, VEN-HMA, Median age: 82, ECOG >1: 43%
24% died during cycle 1 from sepsis
All patients required VEN dose/schedule reduction Median final VEN dose: 200 mg x 14 days
Average final cycle length: 35 days
Anemia 67%, thrombocytopenia 81%, neutropenia 86%
Febrile neutropenia: 81%
No infectious deaths after cycle 1

CLL
N=77, Median age: 86, Median ECOG: 1 Median prior therapies: 2 VEN alone 42%, with rituximab (58%)
TLS risk: Moderate 57%, High 8%
50% hospitalized at each ramp-up (4% treated outpatient)
14% TLS (2 discontinuations – 1 dialysis, 1 death)
25% with infectious complications
Grade 3 AE: hematologic 42%, GI 22%
82% reached 400 mg daily dose
33% required dose reduction
40% DC therapy (21% due to intolerance)

VEN: venetoclax, HMA: hypomethylating agent, AE: adverse effect, DC: discontinued

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Blood. 2021;138:1259-1260
Blood. 2021;138: 3747-3748

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Venetoclax: New safety data with Oral Combinations from ASH 2021

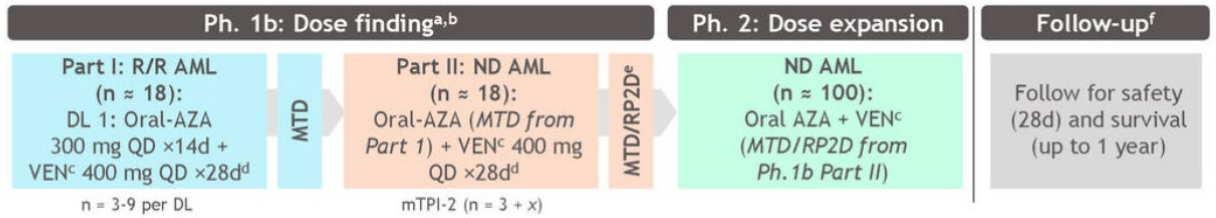
Ibrutinib/Venetoclax - CLL
IBR 420 mg/d + VEN ramp-up to 400 mg/d after 8 weeks
N=22
5 patients interrupted due to toxicity
3 reduced IRB (2 rash, 1 atrial fibrillation) 5 reduced VEN (1 fatigue, 2 neutropenia, 2 diarrhea)
7 patients experienced 11 serious AE (3 sepsis, 3 pneumonia, 2 atrial fibrillation, 1 diarrhea, 1 dehydration, 1 pulmonary embolism)
No TLS

Zanubrutinib/Venetoclax - CLL
ZAN 160 mg 2x/d + VEN ramp-up to 400 mg/d after 3 mo)
N=35 to date
AE: 83%, serious AE: 11.4%
Most frequent grade ≥ 3: neutropenia, diarrhea
No TLS (24% high risk, 63% medium risk)

Decitabine-cedazuridine/Venetoclax - MDS or CMML
Pretreatment WBC <10
N=7 to date
No dose limiting toxicities or TLS
Appears safe

Oral Azacitidine/Venetoclax
Trial underway

Figure. OMNIVERSE trial design



Blood. 2021;138:3754-3756
Blood. 2021;138:245-247
Blood. 2021;138:2314-2316
Blood. 2021;138:67-70

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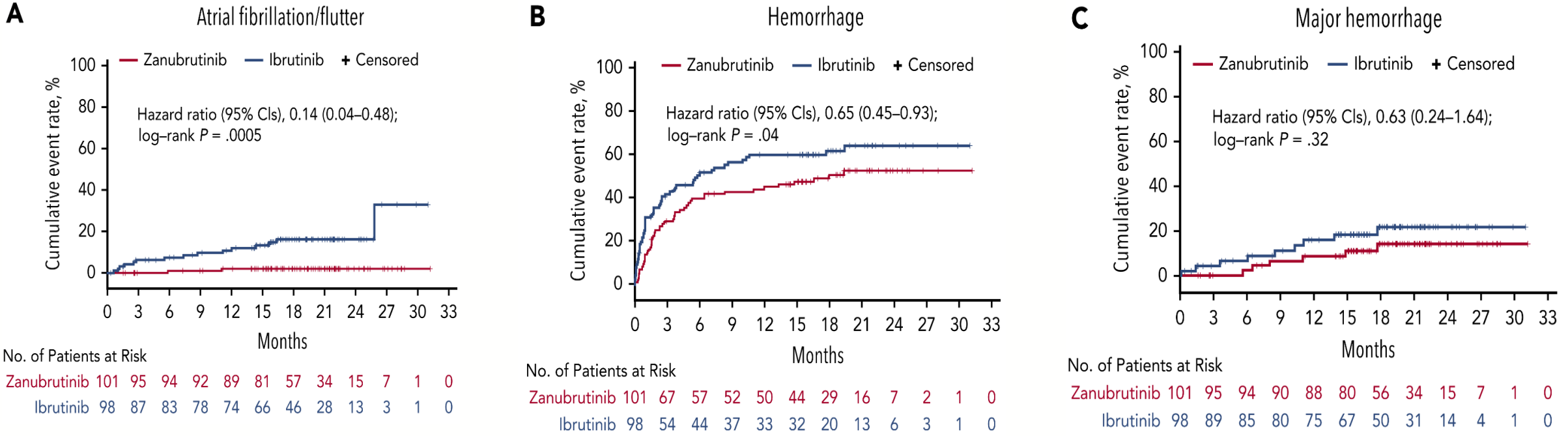
BTK inhibitors – Comparing the Available Agents

Drug	AF Risk		Bleeding Risk	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Acalabrutinib	9%	4.5%	4%	3%
Ibrutinib	15.6%	3.4%	8%	4%
Zanubrutinib	2%	0.8%	11%	3.4%

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study



NCCN Guidelines. CLL/SLL Version 1.2022

Blood 2020;136:2038-2050

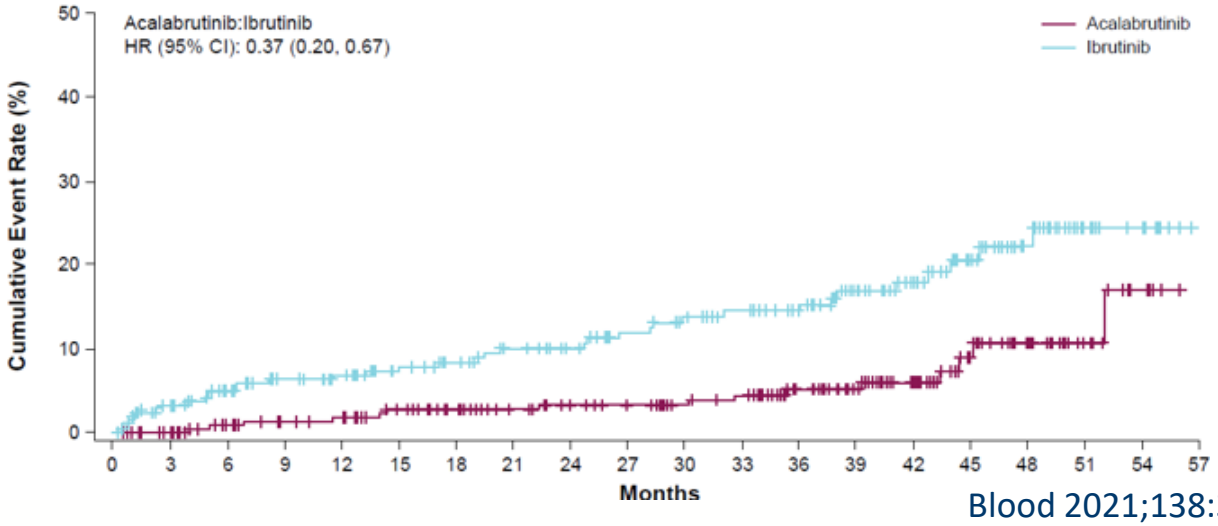
Update on CV Adverse Effects: Acalabrutinib vs. Ibrutinib

Events of Clinical Interest in patients receiving Acala (n=266) or Ibr (n=263)

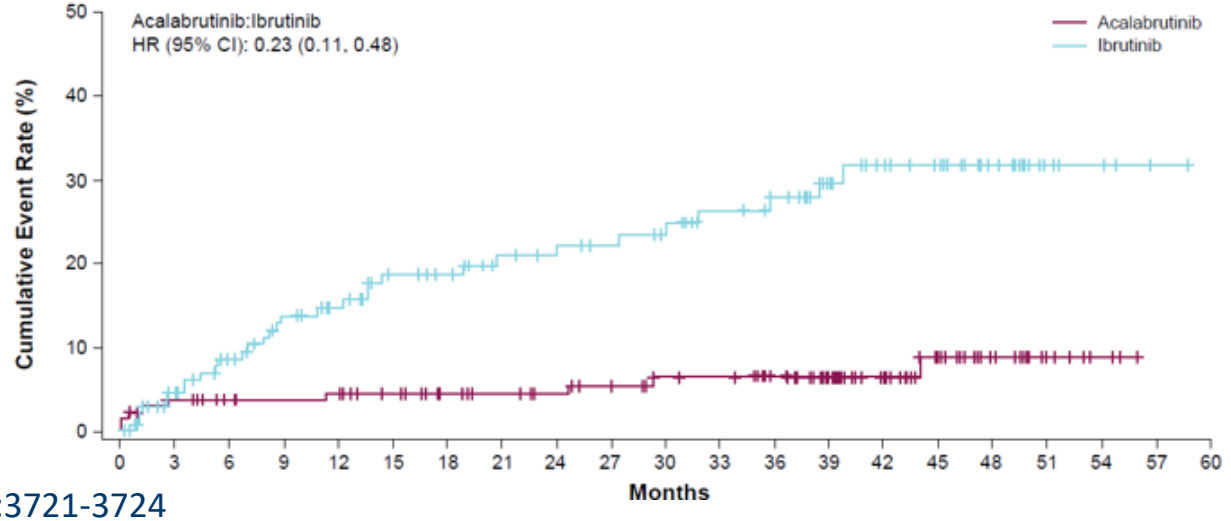
	Incidence, n (%)		Exposure-Adjusted Incidence[a]		Exposure-Adjusted Time with Event[b]	
	Acala	Ibr	Acala	Ibr	Acala	Ibr
Cardiac Events	24%	30%	1.2	1.9	7.1	13.0
Atrial fibrillation	9%	16%*	0.4	0.7	1.3	3.8
Hypertension	9%	23%*	0.4	1.2	4.1	15.0
Bleeding events	38%	51%*	2.4	3.8	13.7	24.6
Bleeding events	5%	5%	0.2	0.2	0.1	0.3

*p<0.05
a: events per 100 person-months
b: months with event per 100 person-months

Cumulative incidence of AF in pts without a prior history



Cumulative incidence of HTN in pts without a prior history

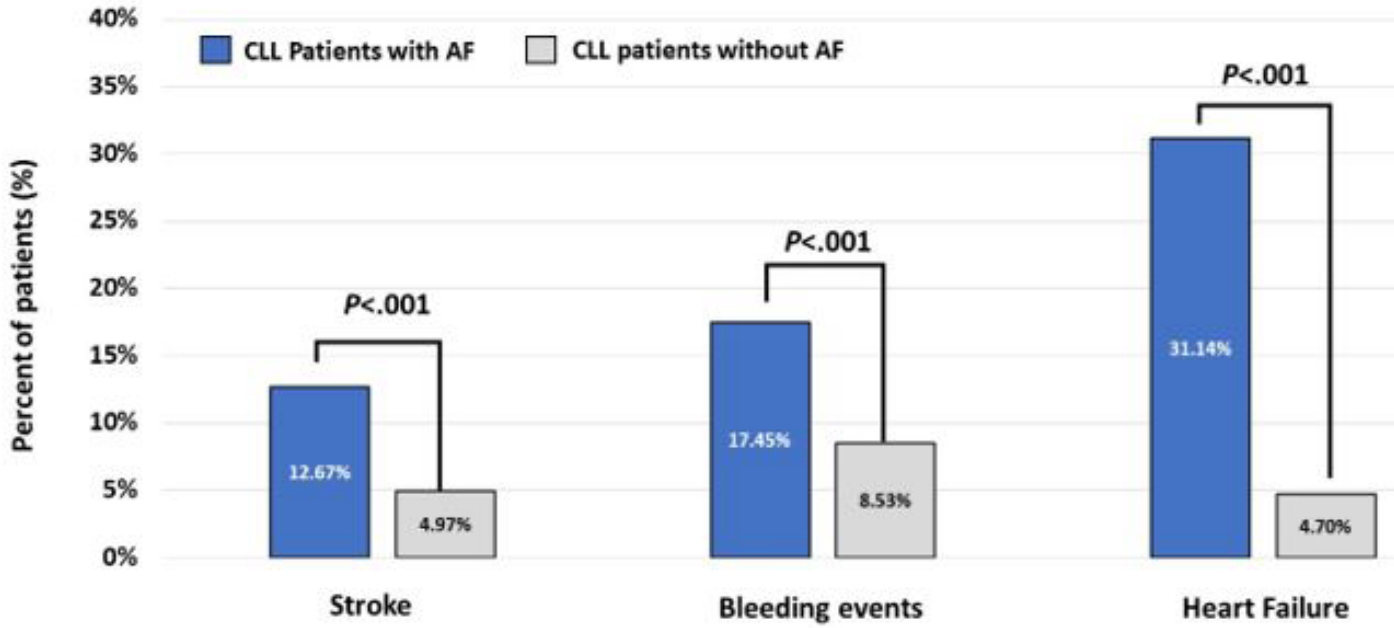


Blood 2021;138:3721-3724

Consequences of BTKi induced AF

- 23,756 newly diagnosed CLL patients in IBM MarketScan Research Database from 1/2009 – 7/2020
- 11% AF within 1 yr of CLL diagnosis
- Median age (AF vs no AF): **82** vs 67 yrs
- Male (AF vs no AF): 65% vs 57%
- Those with AF 2x as likely to be hospitalized and had 44% higher total costs

Figure 1. Cardiovascular outcomes between CLL patients with and without AF



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Blood 2021;138:4077-4078

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Management of Ibrutinib AF

- Estimate stroke risk (CHA_2DS_2-VASc)
  - Score: 0-1→ No anticoagulation, continue ibrutinib
  - Score ≥ 2 → Anticoagulation necessary; hold ibrutinib and reinitiate once AF controlled or D/C ibrutinib

- Consider alternate BTK inhibitor
  - Patients with AF or hypertension that is not medical controllable
  - Zanubrutinib may be an option due to AF risk lower risk

Anticoagulant Use in Ibrutinib-Related Atrial Fibrillation

Antithrombotic therapy	Initial dosing recommendations*	Maintenance dose
Apixaban	2.5 mg twice daily	5 mg twice daily
Rivaroxaban	15 mg daily, with food	20 mg daily with food
Dabigratran	Avoid, potential for drug interaction	
Warfarin	Avoid, increased risk for bleeding	
LMWH	Lack of long-term safety/efficacy data	
Aspirin	May be considered in patients unable to use DOACs	

*Consider for 1st 7-10 days if HAS-BLED >3

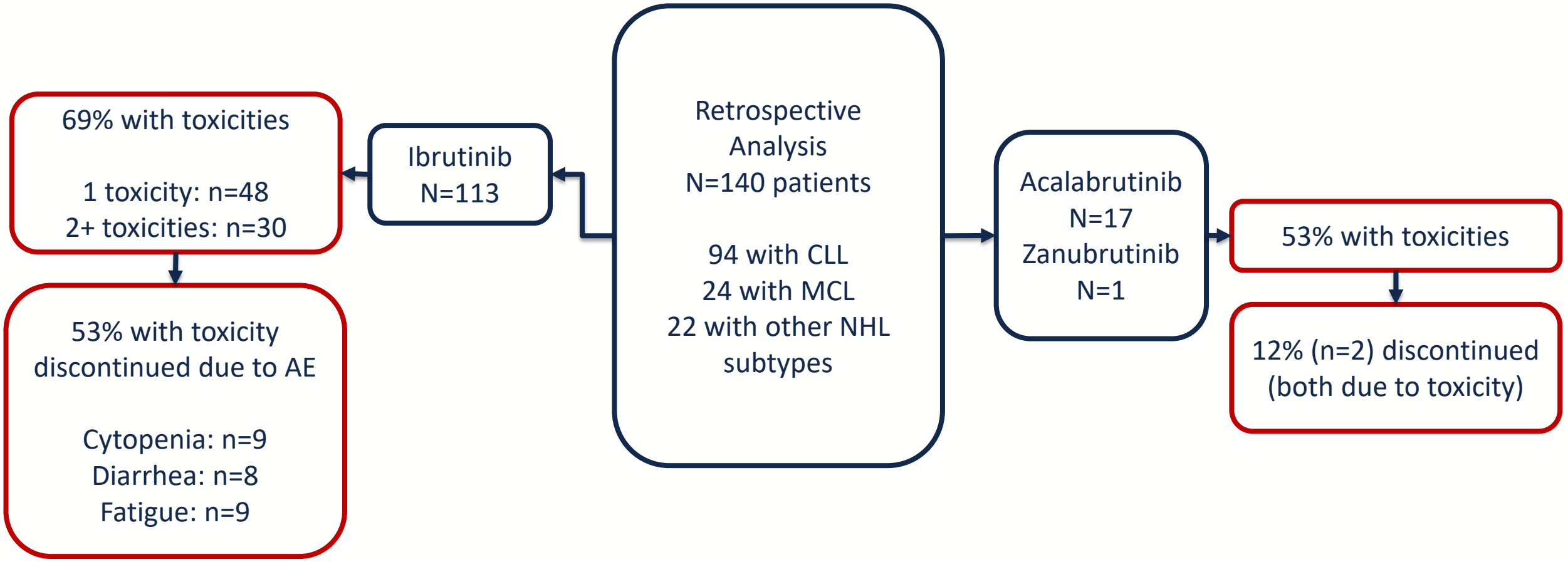
Bleeding Risk: Single center retrospective Canadian study

N=170 receiving ibrutinib for CLL

Characteristic	N=170
Anticoagulant	19%
Warfarin	4%
DOAC	15%
Antiplatelet	18%
Dual Antiplatelet	2%
Single Antiplatelet	16%
Bleeding Outcomes	
Documented Bleeding	25%
Major bleed	10%
Minor Bleed	15%

Blood. 2019;133:1298-1307
Hematology 2020. ASH Education Program, pgs 336-345
JHOP. 2019;9:47-50.
Hematol Oncol. 2018;36:624-32.
NCCN Gudelines. CLL/SLL Version 2.2022
Blood. 2021; 138:4682

BTKi Toxicity Impact on Therapy



- >1/3 stopping therapy prematurely due to toxicity
- Proactive identification and management of toxicity could prolong therapy

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Blood 2021;138:4685

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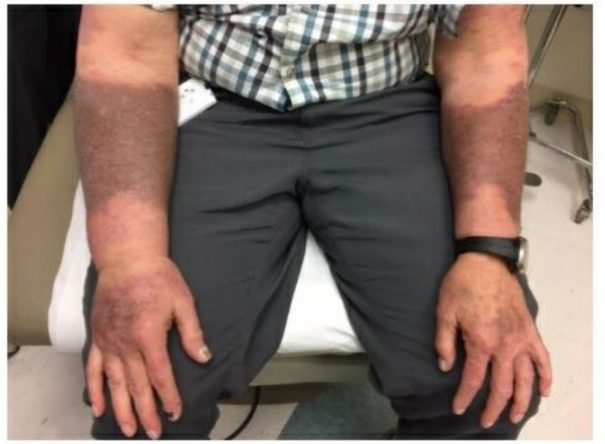
Cutaneous Effects of BTKi: Hemorrhagic Dermatologic Toxicities

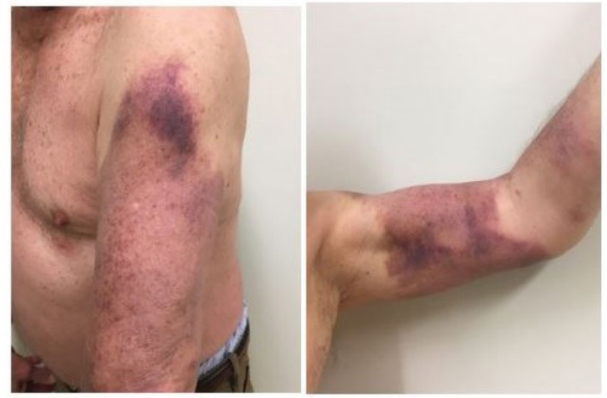
- Single center retrospective review
- N=7 (3 acalabrutinib, 4 ibrutinib)
- Average onset: 63 days acalabrutinib, 642 days ibrutinib

Age	Sex	Dx	Skin Toxicity	BTKi	Time to Toxicity (days)	Subsequent Therapy
72	M	MCL	Hematoma, ecchymoses	Ibr	246	Acala
73	F	WM	Hematoma	Ibr	904	Acala
78	M	CLL	Hematoma	Ibr	1216	Ibr (continued)
70	M	MCL	Petechial rash	Ibr	203	Venetoclax
70	F	CLL	Hematoma	Acala	14	Ibr
74	M	MCL	Ecchymoses	Acala	28	Acala (continued)
78	M	CLL	Ecchymoses, hematoma	Acala	146	Observation

Acala: Acalabrutinib; CLL: Chronic lymphocytic leukemia; Dx: Diagnosis; Ibr: Ibrutinib; MCL: Mantle cell lymphoma; WM: Waldenstrom Macroglobulinemia



Patient 1



Patient 7

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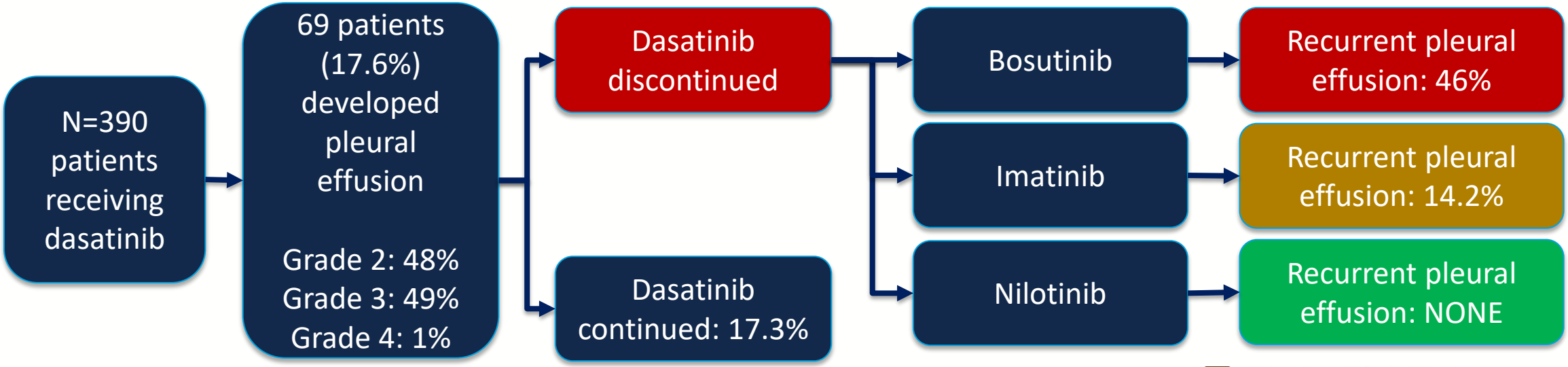
Blood 2021;138:4528

Subsequent Therapy after Dasatinib Pleural Effusion

- Pleural effusion risk
  - 6-9% per year (DASISION)
  - 5-15% per year (CA180-034)
- Results in discontinuation in 6-7%
- Switching to bosutinib: 30% risk of recurrent pleural effusion

- Retrospective chart review of patients on dasatinib 1992 – 2020 at Moffitt Cancer Center



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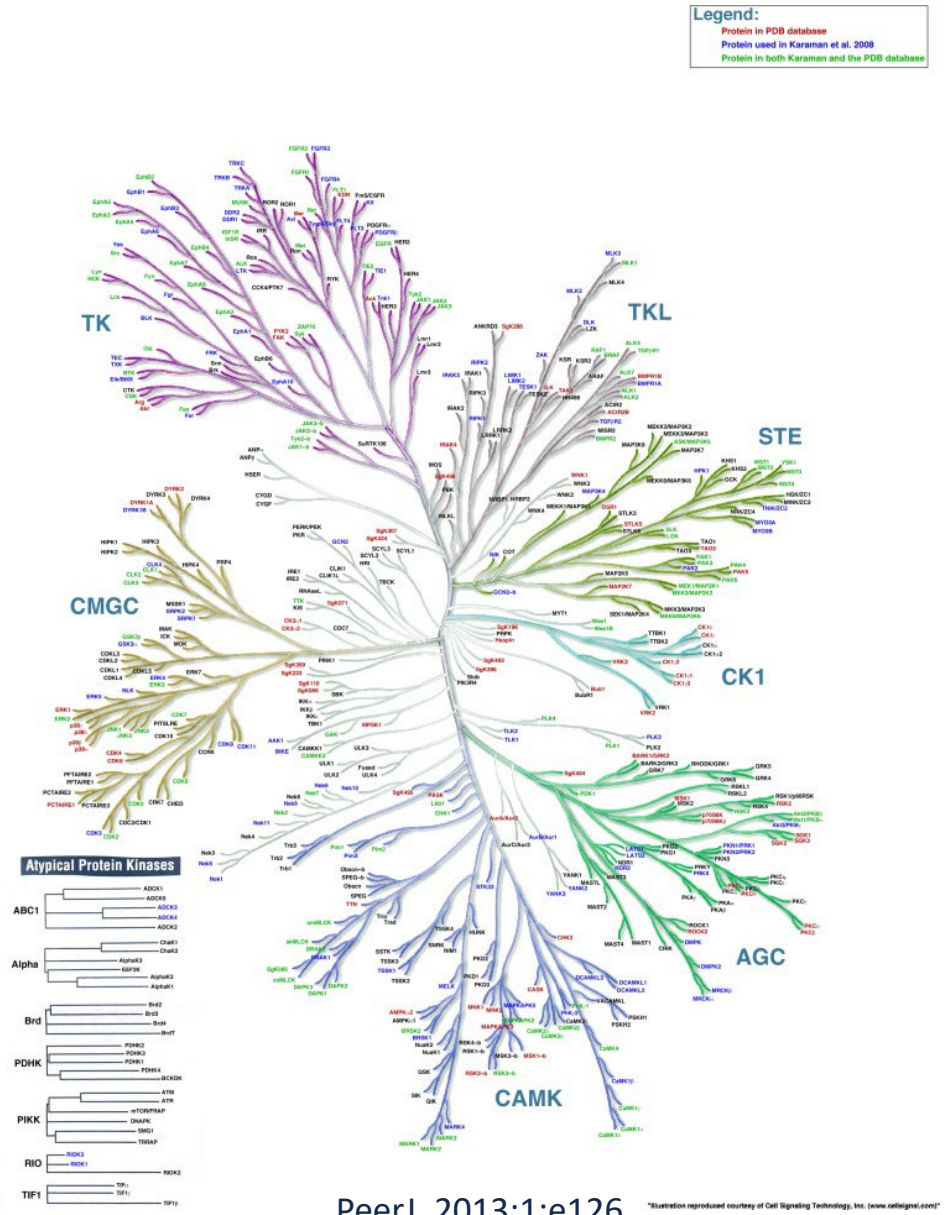
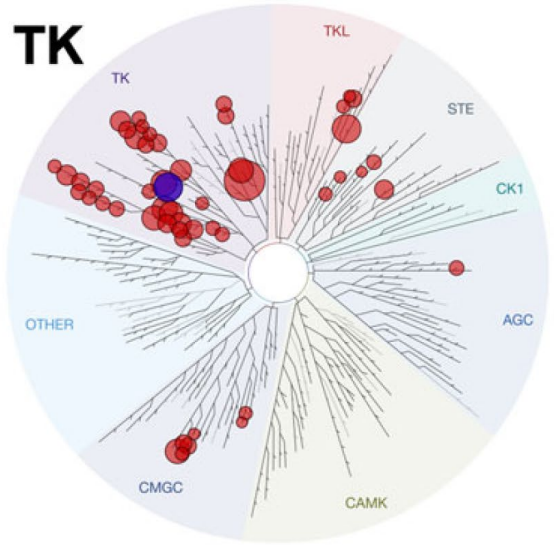
Blood 2021;138:1484-1485

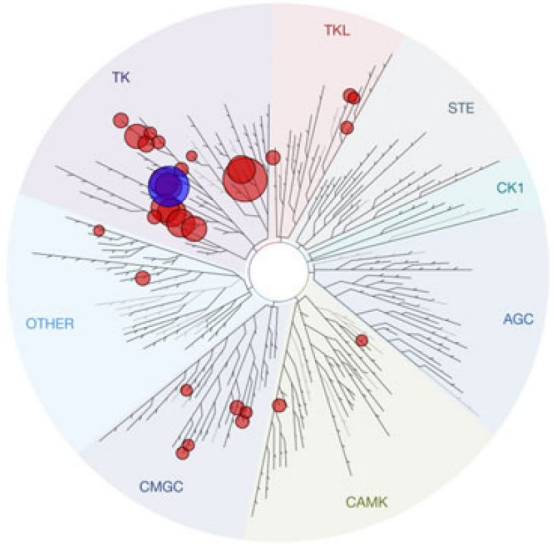
Human Kinome



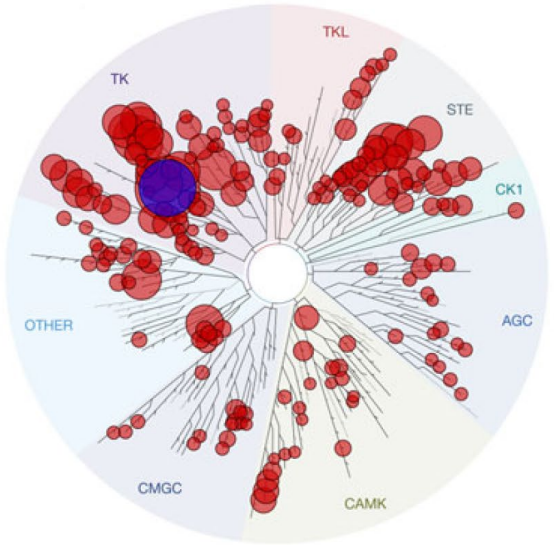
PeerJ. 2013;1:e126.



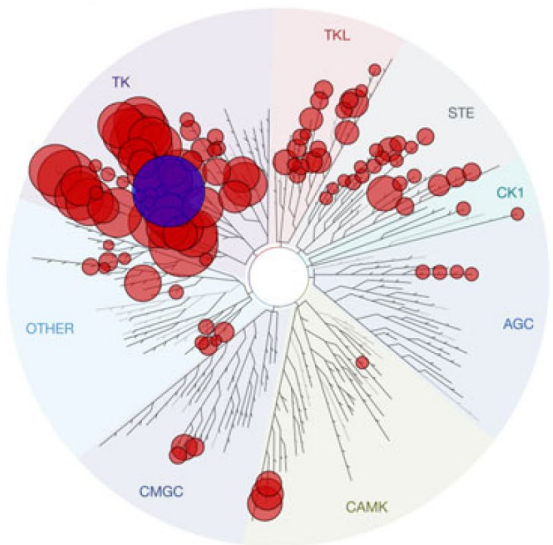
Nilotinib



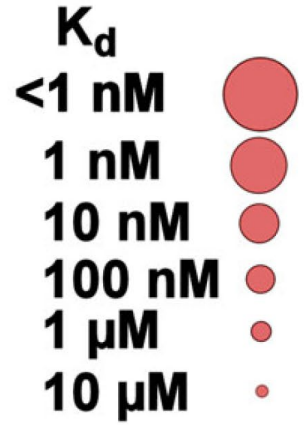
Imatinib



Bosutinib



Dasatinib



Cardiovasc Toxicol. 2017 Jul;17(3):297-306.

Nilotinib Cardiovascular Effects – Real-Life Use

- ENESTnd trial
  - 5 year follow up: 7.5% cardiovascular event (CVE) rate
  - 10 year follow up: 20% CVE rate
  - Risk factors: Framingham general CV risk score and total dose exposure

- Canadian Registry study
  - 94 patients receiving 1st line nilotinib for CML

Patient Demographics and Clinical Characteristics

Demographics	
Age, median	58
Male	47%
Female	46%
Baseline Comorbidities	
CHF	0
HTN	23%
Hyperchlosterolemia	21%
Atrial Fibrillation	2%
CAD/MI	6%
PE/DVT	1%
PVD	2%
Ischemic Stroke	2%
Smoking History	25%

Clinical and Molecular Outcomes

Cardiovascular Complications, n, 95% CI	7 (3.4-13.7)
MI, n	6
Ischemic stroke, n	1
PVD, n	0
Characteristics of Patients with Cardiovascular Events	
Prior Comorbidities	N=6
HTN	50%
Diabetes	50%
Elevated Cholesterol	33%
MI	17%

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Blood 2021;138:4602

Cardiovascular Outcomes – Increased Focus on Atherosclerosis

Nilotinib doubles LDL cholesterol

Dasatinib and ponatinib: endothelial damage

Management

- European LeukemiaNet 2020 recommendations: caution against use of nilotinib and ponatinib if concomitant/prior vascular disease
- Cardiac risk assessment and management of risk factors
- ACE inhibitor or ARBs have demonstrated a lower frequency of arterial occlusive events
- Imatinib may have less of an impact (may be protective)

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Curr Opin Cardiol. 2022;37:372-379

Conclusions

- Oral decitabine/cedazuridine and azacitidine have comparable (or better) safety profile to parenteral formulations
- No new concerning safety signals with asciminib

- Venetoclax use continues to expand
  - TLS manageable – some can initiate therapy in outpatient setting
  - Octogenerians able to tolerate therapy – likely require dose reduction
  - New combinations tolerable

- Atrial fibrillation risk likely highest with ibrutinib
  - May result in increased health care utilization
- Appropriate management of BTKi adverse effects necessary to optimize therapy

- Imatinib/nilotinib may be a subsequent option after dasatinib pleural effusion
- Real-world CV effects of BCR/Abl TKI likely similar to phase 3 trials

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Recognizing Toxicities of Oral Oncolytics in the Management of Hematologic Malignancies

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