2nd Postgraduate CLL Conference

Management of side-effects during targeted therapy

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Disclosures for Matthew S. Davids, MD, MMSc

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Outline

- BTK inhibitors
- PI3K inhibitors
- Venetoclax
- General considerations

CLL12: CLL patients commonly have symptoms and complications

BTK inhibitors

	Ibrutinib n=158	Placebo n=155
Any grade AEs (%)	150 (94.9)	148 (95.5)
AEs ≥ grade 3 (%)	80 (50.6)	67 (43.2)
AEs leading to interruption (%)	77 (41.6)	38 (21.3)
Arrhythmias	18	0
Bleeding	8	1
Diarrhea	4	3
Neoplasia	4	3
Infection	3	4
Myocardial infarction	1	3
other	39	24
Fatal AEs* (%)	4 (2.5)	5 (3.2)
Treatment-related	0	0

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

Langerbeins et al., *iwCLL*, 2019

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%**

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)

Mato, *et al*, Blood, 2016

PJP and IFIs have been reported on ibrutinib

- Study of 96 CLL patients treated with single-agent ibrutinib reported 5 cases of PJP - cumulative incidence of 5.6% at 2 years[1]
- Multi-institutional survey of IFI cases in ibrutinib-treated patients: 35 cases amongst patient populations from 22 centers in 8 countries. 26 patients (74%) had CLL[2]
  - Mortality rate: 69%
- Guidelines for use of antimicrobial prophylaxis in CLL patients being treated with BTK-inhibitors do not exist

[1]Ahn et al., *Blood.* 2016
[2]Ruchlemer et al., *Mycoses.* 2019

BTK inhibitors

We found that 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
- Until further data available, suggest individualizing prophylaxis depending on patient characteristics

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

Invasive fungal infections 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)

Ryan, *et al*, iwCLL, 2019

Ibrutinib: Side Effect Management

- **High bleeding risk including lack of data with plts < 30K**
  - **Hold for procedures**
    - General guideline: Cataracts (1/1), Colonoscopy (3/3), Cholecystectomy (7/7)
    - May need to modulate based on depth of response, duration on ibrutinib, CLL prognostic markers
    - Consider platelet transfusion for emergent surgery
- **Cardiac disease**
  - Difficult to control hypertension
  - Atrial fibrillation
- **Active infection, esp. fungal**
  - Usually hold drug to control infection
- **Active autoimmunity can show early flare before achieving longer term control**

Ibrutinib: What to Watch Out For

- Anticoagulants (avoid if possible esp. warfarin, if necessary use DOACs)
- Avoid dual antiplatelet therapy
- Strong CYP3A inhibitors: generally avoid, but can use higher dose posaconazole if reduce dose to 70 mg daily
- Moderate CYP3A inhibitors or voriconazole: reduce dose to 140 mg daily

BTK inhibitors

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

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

PI3K-delta inhibitors have a characteristic toxicity profile with immune-mediated AEs

Grade ≥ 3 AE, n (%)	Idelalisib + Rituximab*[1] (n = 110)	Duvelisib[2] (n = 160)
Neutropenia	31 (28)	48 (30)
Anemia	10 (9)	20 (13)
Pneumonia	17 (16)	22 (14)
Diarrhea	18 (16)	23 (15)
Colitis	9 (8)	19 (14)
Pyrexia	4 (4)	4 (3)
Rash	3 (3)	3 (2)
Fatigue	5 (4)	2 (1)
Nausea	3 (3)	0
Upper respiratory tract infection	3 (3)	0

*Primary + extension studies.

1. Sharman. JCO. 2019;37:1391. 2. Flinn. Blood. 2018;132:2446.

Additional toxicities of note with idelalisib

- **<u>Neutropenia and sepsis:</u>**
  (primary cause of infectious deaths on halted upfront trials)
  - Less common without BR
  - Monitor and use growth factor

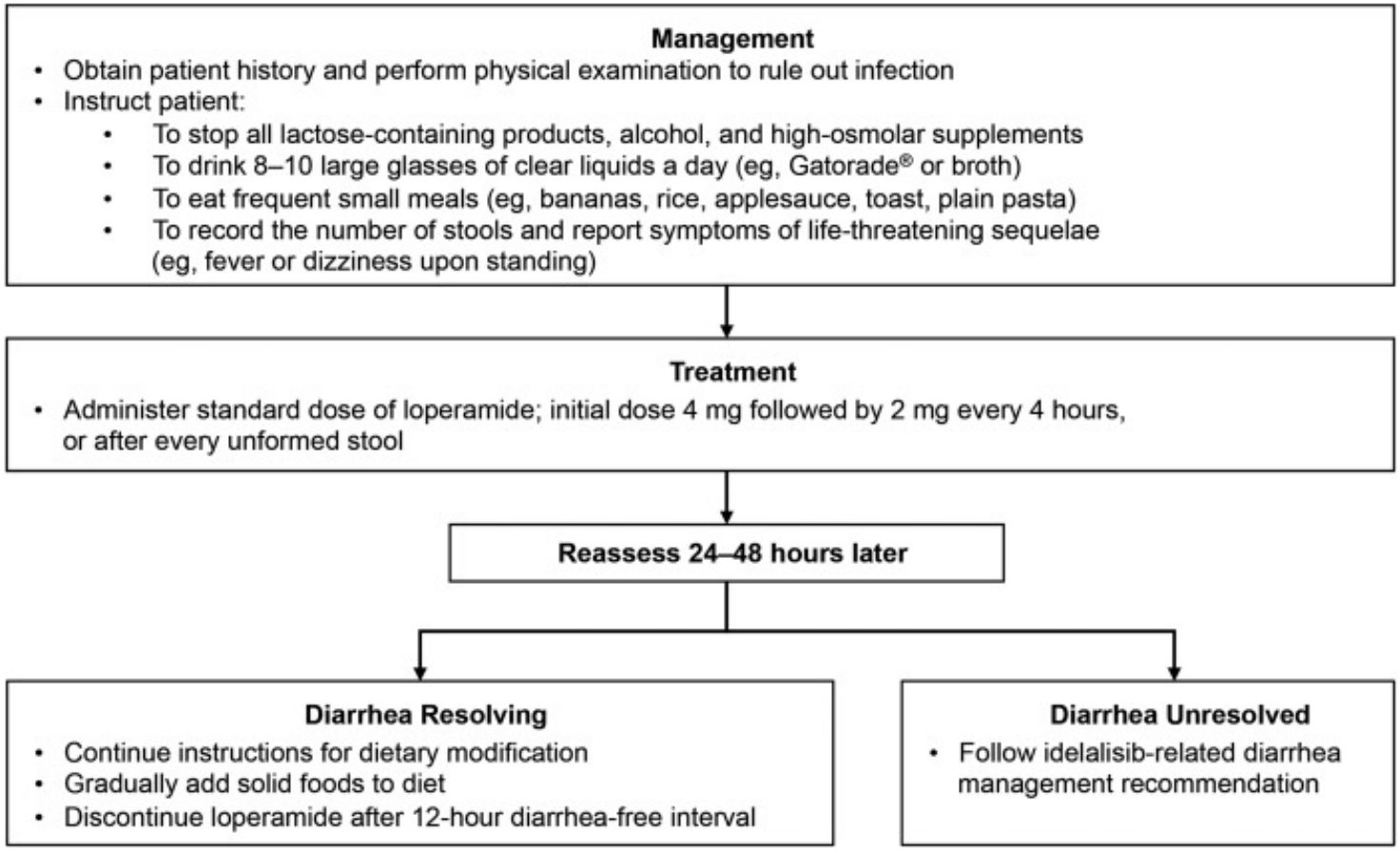
- **<u>Opportunistic infections</u>:** PJP, CMV
  - PJP prophylaxis for all
  - CMV monitoring, low threshold to institute treatment

With idelalisib, Gr 3–4 immune tox has been more common in less pretreated patients

	Phase I[3]	Overall Relapsed[2]	Initial Therapy[1]	Upfront idela + ofa
Median Prior Therapies	5	≥1 (2-3)	0	0
Diarrhoea/Colitis	5.6%	14%	42%	13%
Transaminitis	2%	14%	23%	52%
Pneumonitis	5.6%	3%	6%	13%
Rash	0	5%	13%	13%

1. O'Brien SM *et al.* Poster 1994 presented at ASH 2014; 2. Coutré SE *et al.* Oral presentation at EHA 2015: S433.OI:10.3109/10428194.; 3. Brown JR *et al. Blood* 2014;123:3390–7.

PI3Ki: Management of Gr 1/2 Diarrhea



Coutre et al., *Leuk Lymph*, 2015

PI3Ki: Management of Gr 3/4 Diarrhea

Initial Management

- Perform evaluation and work-up to rule out infection
- Discontinue idelalisib
- Continue diet instruction
- IV fluid supplementation or oral hydration as warranted in case of signs of dehydration or grade ≥3 diarrhea or colitis

↓

Infectious Etiology Is Excluded

- Budesonide* or oral steroids (prednisone)†: if patient can tolerate medications PO

OR

- IV steroids: if patient is being treated with IV fluid therapy or cannot tolerate medications PO

↓

Patient Can Tolerate Medication PO

- Switch from IV steroid to budesonide or oral steroids

↓

Diarrhea Resolved to Grade ≤1

- Continue instructions for dietary modification
- Gradually add solid foods to diet
- Consider taper off budesonide and oral steroid
- Reinstitute idelalisib at lower dose per clinical judgment and consider concomitant use of budesonide

Coutre et al., *Leuk Lymph*, 2015

PI3Ki: What To Watch Out For

- Avoid using in patients with active:
  - Hepatic disease
  - Inflammatory bowel disease
  - Active autoimmunity
  - Active infection

- Strong inhibitor of CYP3A4 itself, avoid combining with CYP3A4 substrates

- Side effect profile can be more challenging but is likely better in older patients with multiple prior therapies (particularly chemoimmunotherapy)

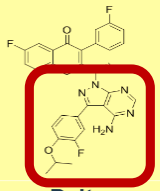
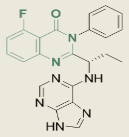
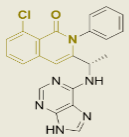
- Patients not developing autoimmune tox have very few side effects

PI3Ki: Prevent / Manage Tox?

- PJP / VZV prophylaxis
- Myeloid growth factors to avoid neutropenia
- IVIG if infections
- Low threshold to initiate budesonide with diarrhea – may be able to continue drug. If have to stop drug, re-initiate at dose reduction
- Aggressive management of rash, with topicals, derm consult if at all unusual
- Hold drug immediately with any febrile pulmonary syndrome. If no infection identified, start steroids

PI3K inhibitors

Umbralisib (TGR-1202) is a next generation PI3Kδ inhibitor with a favorable safety profile

TGR-1202	Idelalisib (GS-1101)	Duvelisib (IPI-145)
		
Delta	Delta	Delta/Gamma
QD	BID	BID

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
Umbralisib	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]Duvelisib	>640	>34	>11	1

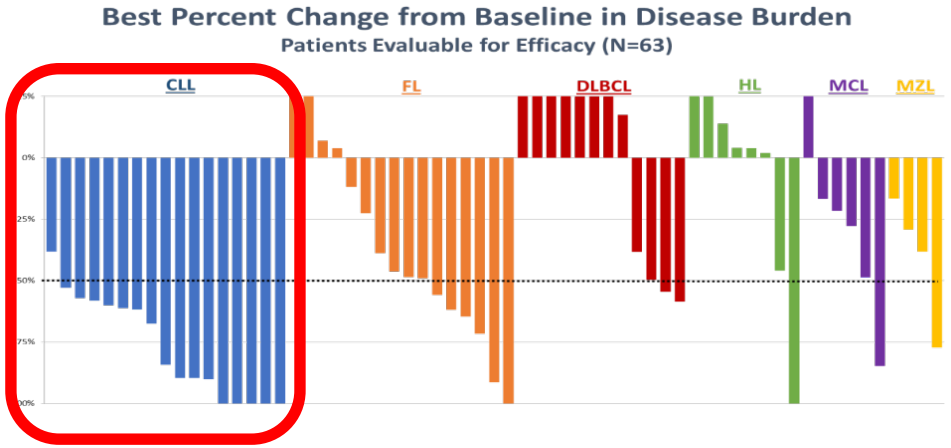
Safety

In 347 patients treated with umbralisib (TGR-1202) alone or with anti-CD20:

- **Grade 3/4 AST/ALT in 2.3% (8.6% all grades)**
- **Diarrhea in 44%, mainly grade 1, with 4% Grade 3**
- **10% of patients off study due to an AE**

Davids et al, EHA, 2018

Efficacy



O'Connor et al, ASH 2015

[1]Flinn et al. 2009, [2]Porter et al. 2012

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

Venetoclax

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

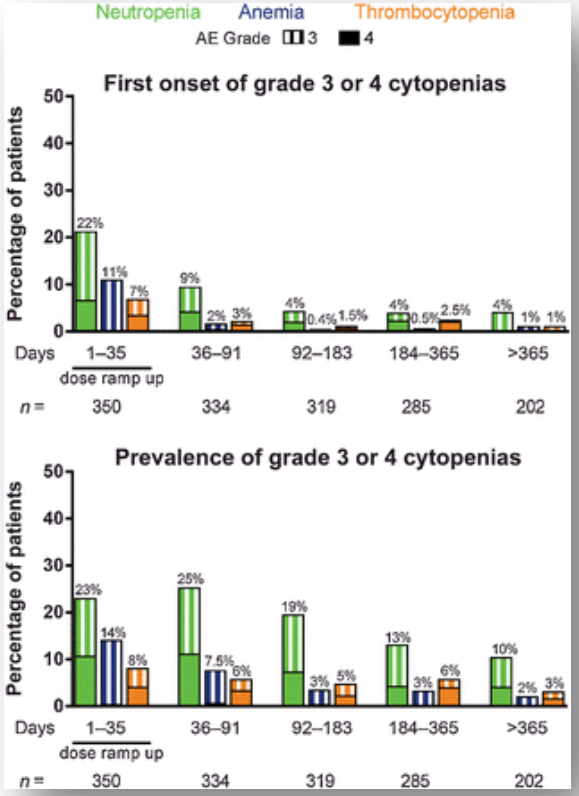
Adverse event*	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	115 (99)	96 (83)
Diarrhoea	60 (52)	2 (2)
Upper respiratory tract infection	56 (48)	1 (1)
Nausea	55 (47)	2 (2)
Neutropenia	52 (45)	48 (41)
Fatigue	46 (40)	4 (3)
Cough	35 (30)	0
Pyrexia	30 (26)	1 (1)
Anaemia	29 (25)	14 (12)
Headache	28 (24)	1 (1)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

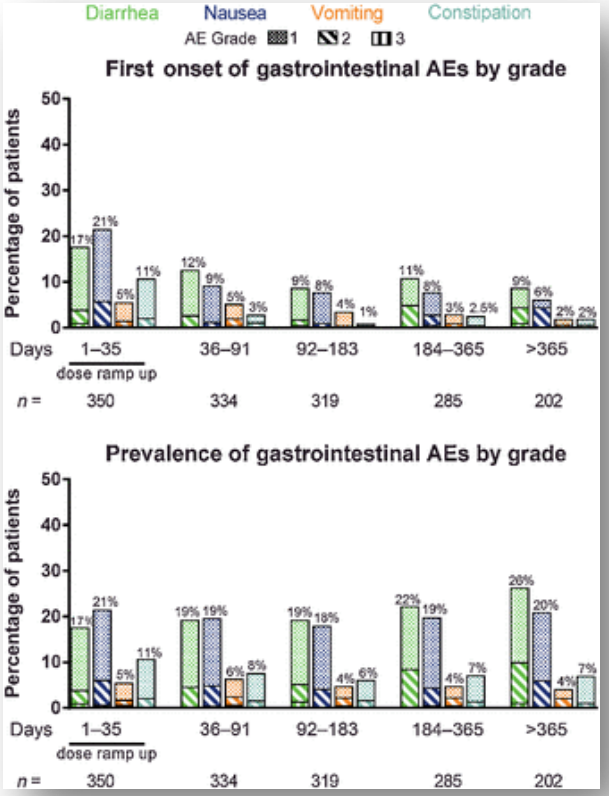
Serious adverse event†	Any Grade [n (%)]	Grade 3 or 4 [n (%)]
Any	52 (45)	
Febrile neutropenia	7 (6)	
Pneumonia	5 (4)	
Upper respiratory tract infection	4 (3)	
Immune thrombocytopenia	3 (3)	
Tumour lysis syndrome	3 (3)	
Diarrhoea	2 (2)	
Fluid overload	2 (2)	
Hyperglycaemia	2 (2)	
Prostate cancer	2 (2)	
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**, tumour lysis syndrome
Roberts AW, et al. *N Engl J Med* 2016;374:311–322.

Venetoclax risks include neutropenia, GI toxicities, and TLS

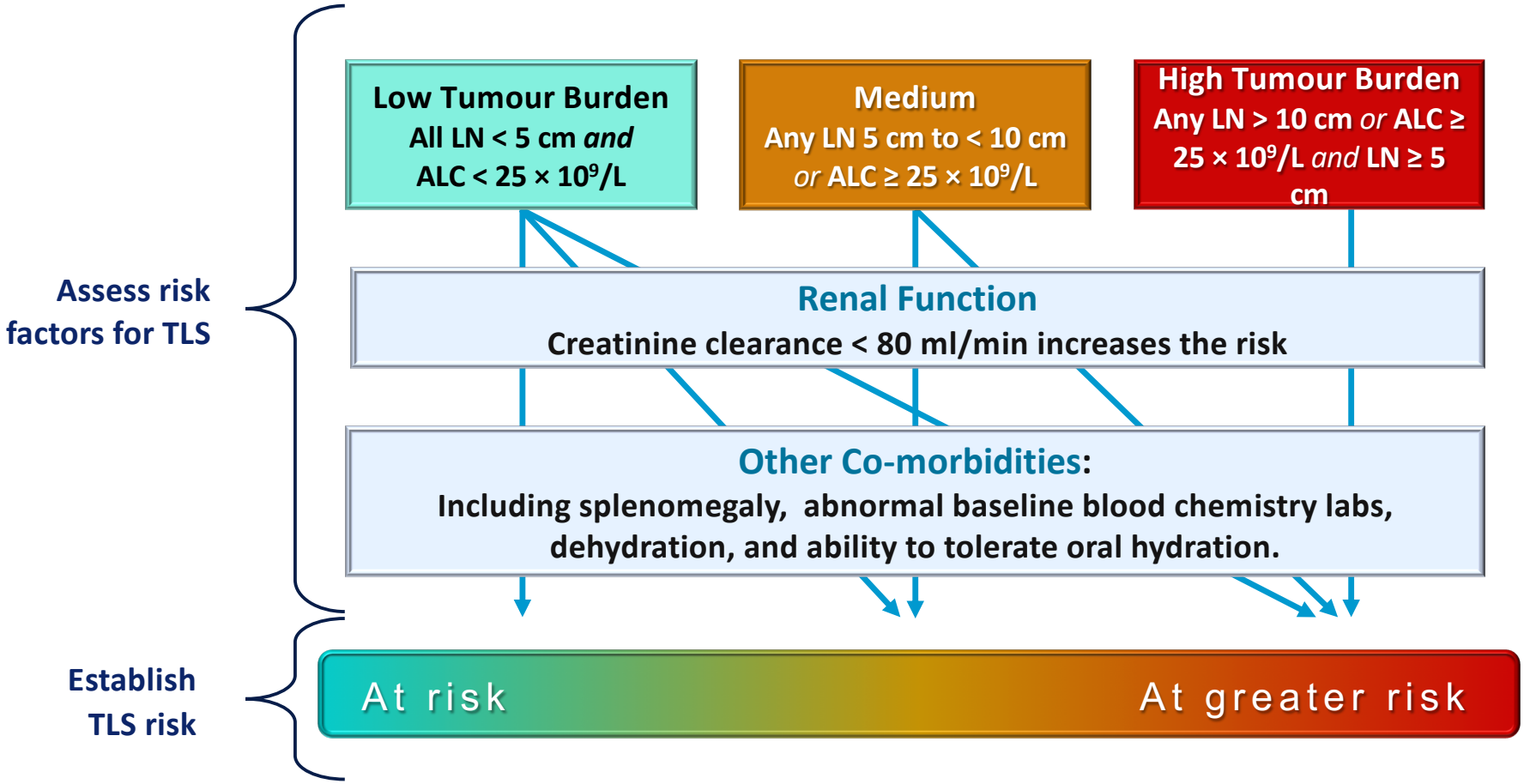




- **2/166 (1.4%) of patients treated with current dosing algorithm had biochemical laboratory changes in TLS parameters, but none had clinical TLS**

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

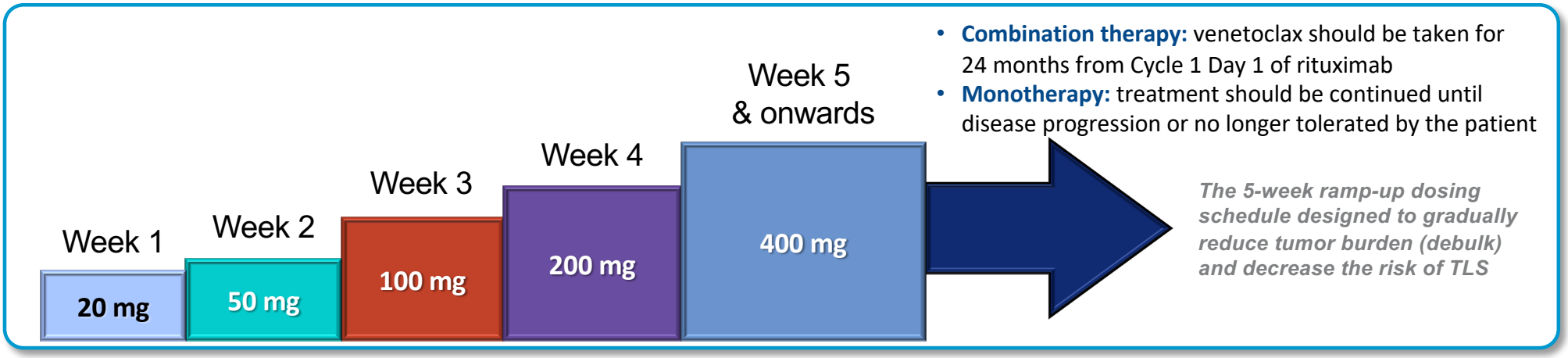
TLS risk with venetoclax is a continuum based on multiple factors



ALC, absolute lymphocyte count; **CrCl**, creatinine clearance; **LN**, lymph node; **TLS**, tumour 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.

Venetoclax dose initiation



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).

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-URICEMIC AGENTS	Patients with high uric acid or TLS risk should be administered with anti-hyperuricaemics 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 be at risk • Pre-dose at subsequent ramp-up doses Evaluate blood chemistries and review in real time
HOSPITALISATION	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

Tips for venetoclax toxicity management

- For neutropenia (e.g. ANC <1,000), it is helpful to give growth factor support (pegfilgrastim when available) and continue venetoclax
  - Individualized frequency based on patient response
- For diarrhea, infectious etiologies should be ruled out and then anti-diarrhoeals can be used while continuing venetoclax
- Dose interruption and dose reduction can be used for persistent toxicities despite the above measures
- Does **not** need to be held perioperatively

ANC, absolute neutrophil count

Davids MS. *Blood* 2017;130:1081–1088

Food considerations on venetoclax

Drug-Food Interactions

Effect of Low- and High-Fat Meals on the Pharmacokinetics of Venetoclax, a Selective First-in-Class BCL-2 Inhibitor

The Journal of Clinical Pharmacology
2016, 56(11) 1355–1361

DOI: 10.1002/jcph.741

Ahmed Hamed Salem, PhD[1,2], Suresh K. Agarwal, PhD[1], Martin Dunbar, DrPH[1], Silpa Nuthalapati, PhD[1], David Chien, MD[3], Kevin J. Freise, PhD[1], and Shekman L. Wong, PhD[1]

- Median T_{max} delayed by 2 hours when administered with food
- C_{max} and AUC increased 3.4X after low-fat breakfast, with additional 50% increase after high-fat breakfast with similar half-life of 16–19 hours
- Venetoclax should be administered with food, no specific fat content needed

AUC, area under the curve; **C_{max}**, maximum serum concentration; **T_{max}**, time to reach C_{max}

Salem AH, et al. *J Clin Pharm* 2016;56:1355–1361.

Additional considerations for venetoclax

- **Metabolized by CYP3A – therefore:**
  - Strong CYP3A inducers should be avoided so as not to compromise efficacy
  - Strong CYP3A inhibitors require 75% dose reduction, moderate 50% reduction
  - Grapefruit, Seville oranges (marmalade), and star fruit should be avoided
- **May increase the toxicity of warfarin and P-glycoprotein substrates with narrow therapeutic index**
- **Dosing in renal insufficiency: minimal urinary excretion so dose adjustment not required, but risk of TLS increases**
- **Dosing in hepatic insufficiency:**
  - no dose adjustment for mild or moderate hepatic impairment
  - dose reduction of at least 50% throughout treatment for severe hepatic impairment (monitor for signs of toxicity)

Summary of side effects seen with novel agents for CLL

	Ibrutinib			Idelalisib				Venetoclax		
Reference	2	18	19	20	21	9	8	15	22	16
Study	RES	RES17	RES2	Furman	Jones	O'Brien	Lampson	Roberts	Stilgenbauer	Seymour
N	195	145	135	110	173	64	24	116	107	49
Prior treatment	RR	RR	TN	RR	RR	TN	TN	RR	RR	RR
Median age	67	64	73	71	68	71	67	66	67	75
Median follow-up (mo)	9	28	18	4*	16	22*	15	21	12	28
Comments	—	17p	—	+R	+Ofa	+R	+Ofa	—	17p	+R
Heme AE (% any grade/% grade 3-4)										
Neutropenia	22 /16	NR/22	16/10	55/34	35/35	53/28	46/29	45/41	43/40	66/53
Anemia	23/5	26/10	19/6	25/5	23/14	23/3	8/4	25/12	27/18	24/14
Thrombocytopenia	17/6	NR/11	<15/2	17/10	14/11	14/2	8/0	21/12	19/15	27/17
Non-heme AE (% any grade/% grade 3-4)										
Hemorrhage	44/1	16/9	15/4	NR	NR/2	NR/3	NR	NR	NR	NR/4
Atrial fibrillation	5/3	NR/7	6/2	7/NR	NR/2	NR	NR	NR	NR/2	6/NR
Hypertension	10/-	27/13	14/4	NR	13/5	NR	8/4	NR	6/4	8/NR
Infections	23/4	14/5	17/4	NR	NR	NR	13/13	46/1	72/19	82/16
Pneumonia	10/7	25/13	15/4	6/NR	20/14	28/19	13/13	NR/4	9/5	16/6
Pneumonitis	NR	NR	NR	NR/0	6/5	19/3	13/8	NR 4	NR	NR
Diarrhea or colitis	48/4	41/3	42/4	19/4	54/19	64/42	46/ 21	52/2	29/0	57/2
Abnormal AST/ALT	NR	NR/<1	NR	35/5	47/ 12	67/23	79/54	NR	1/1	7/3
Tumor lysis syndrome	NR	NR/<1	NR	NR	NR/<1	NR	NR	4/3	5/5	10/4

Ahn and Davids, *ASH Education Book*, 2017

General considerations

- 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

General considerations

- **Novel agents are infrequently the 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**


Grazie mille!