TG Therapeutics

Investor & Analyst Event June 2018

Michael S. Weiss

Executive Chairman & CEO

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

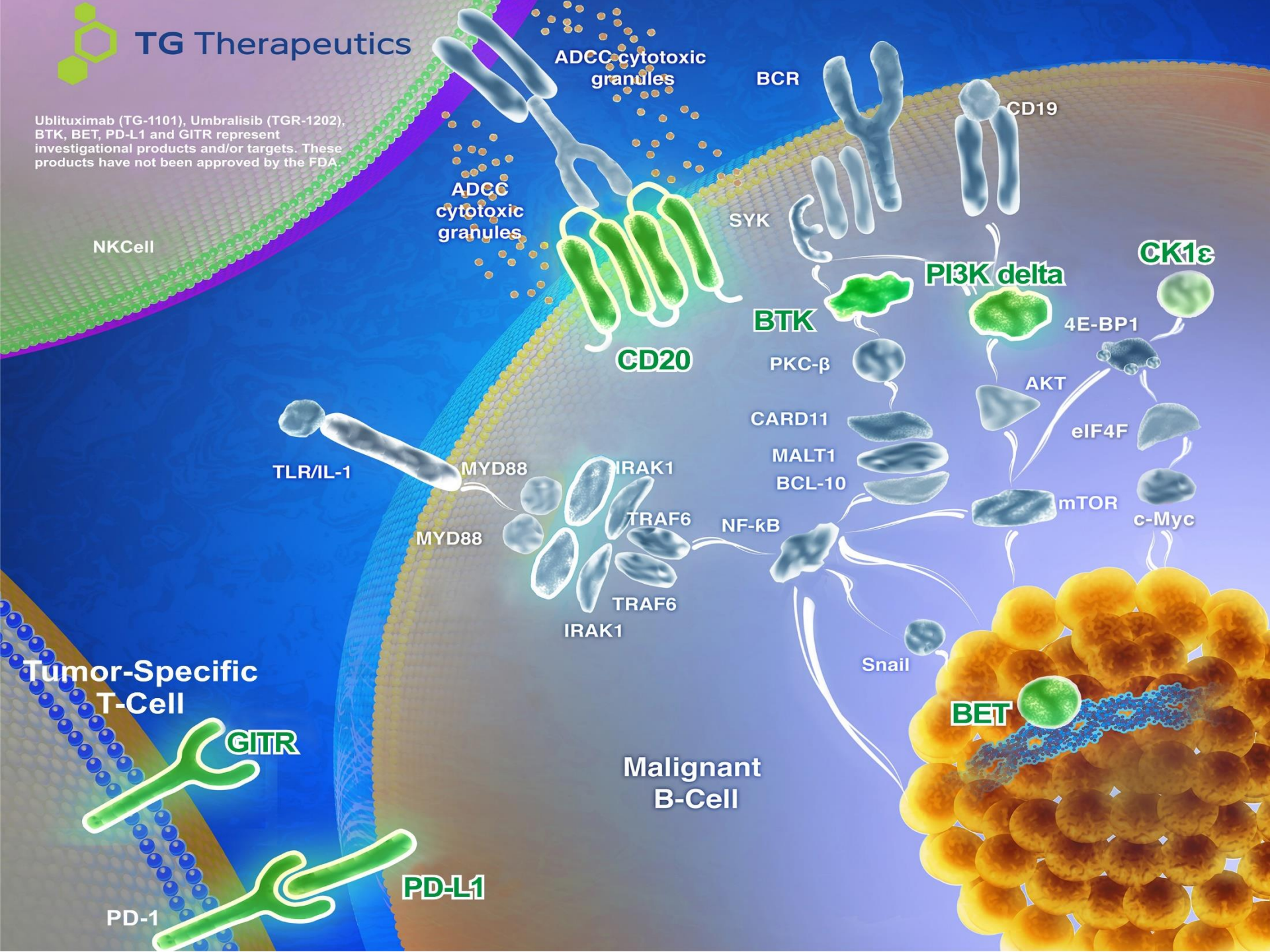
UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

Forward Looking Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. These statements are often, but not always, made through the use of words or phrases such as "anticipates", "expects", "plans", "believes", "intends", and similar words or phrases. Such statements involve risks and uncertainties that could cause TG Therapeutics' actual results to differ materially from the anticipated results and expectations expressed in these forward-looking statements. These statements are only predictions based on current information and expectations and involve a number of risks and uncertainties. Actual events or results may differ materially from those projected in any of such statements due to various factors, including the risks and uncertainties inherent in clinical trials, drug development, and commercialization. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement and TG Therapeutics undertakes no obligation to update these statements, except as required by law.

AGENDA

Topic	Presenter
Welcome / Introductions	Michael S. Weiss, CEO TG Therapeutics
KI Intolerant Review	Anthony Mato, MD
Emerging Challenges in CLL: Drug Drug Interactions	Alexey Danilov, MD, PhD
Questions & Answer Session	
Closing Remarks	Michael S. Weiss


TG Therapeutics
Ublituximab (TG-1101), Umbralisib (TGR-1202), BTK, BET, PD-L1 and GITR represent investigational products and/or targets. These products have not been approved by the FDA.
ADCC cytotoxic granules
ADCC cytotoxic granules
NKCell
BCR
CD19
SYK
PI3K delta
CK1ε
BTK
4E-BP1
CD20
PKC-β
AKT
CARD11
eIF4F
MALT1
BCL-10
TLR/IL-1
MYD88
IRAK1
mTOR
c-Myc
TRAF6
NF-kB
MYD88
TRAF6
IRAK1
Snail
Tumor-Specific T-Cell
BET
GITR
Malignant B-Cell
PD-L1
PD-1

TG Therapeutics, Inc.

- Biopharmaceutical company focused on B-cell cancers (CLL and NHL) & autoimmune-related diseases (MS, RA, Lupus)
- **Headquarters:** New York, NY
- **NASDAQ:** TGTX

- Developing portfolio of B-cell targeted agents

- **Ublituximab (TG-1101) – Novel Glycoengineered, Anti-CD20 monoclonal antibody**
  - Enhanced ADCC profile for increased potency, similar to Gazyva® (GA101)
  - Robust activity demonstrated in CLL and NHL
  - **GENUINE Phase 3 Registration Trial in CLL positive results announced!**
  - **ULTIMATE I & II Phase 3 Trials Ongoing in Multiple Sclerosis under SPA**

- **Umbralisib (TGR-1202) – Novel PI3Kδ inhibitor**
  - Highly active and well tolerated as monotherapy and in combination treatment
  - Demonstrated best-in-class attributes
  - **UNITY- CLL Phase 3 trial under FDA-Special Protocol Assessment (SPA)**
    - **Full Enrollment reached- October 2017**

TG Therapeutics Update

- **UNITY-CLL**
  - On target for ORR data this summer

- **GENUINE**
  - Filing decision pending outcome of UNITY-CLL and KOL outreach
  - Our goal is to put our best filing package in first (if possible)
    - Including, filing accelerated approval based on the UNITY-CLL ORR data and/or GENUINE ORR data or neither.

- **UNITY-NHL**
  - DLBCL- on track to complete target enrollment of U2+B by end of June
  - FL/SLL- on track to complete target enrollment in Umbralisib monotherapy arm by mid-2018 and commence U2 single arm
  - MZL- on track to complete Umbra monotherapy in 3Q

TG Therapeutics Update

- **MS Program**
  - Phase 2 final data expected before YE
  - **ULTIMATE I & II Phase 3 Program Update!**
    - Complete enrollment now targeted by YE 2018 (prior guidance by end of 1Q19)

- **Pipeline Update**
  - **Anti PD-L1 monoclonal antibody:**
    - Phase 1 dose escalation complete
    - Commencement of heme focused cohort by YE 2018
  - **TG-1701- BTK inhibitor**
    - Phase 1 currently enrolling in China
    - TG sponsored Phase 1/2 trial to open in 3Q18

- **Corporate Update**
  - Appointment of Adam Waldman as Chief Commercial Officer
    - Most recently, Adam led Marketing for the US Hematology-Oncology franchise at Celgene Corporation, where he spent the prior 13 years of his career

ASCO & EHA Upcoming Presentations

ASCO:

- Poster: A Phase 2 Study to assess the safety and efficacy of umbralisib (TGR-1202) in patients with chronic lymphocytic leukemia (CLL) who are intolerant to prior BTK or PI3K delta inhibitor therapy (Abstract #: S808)
  - Date & Time: Monday June 4, 2018; 8:00 – 11:30 CT

EHA:

- Oral: A Phase 2 Study to assess the safety and efficacy of umbralisib (TGR-1202) in patients with chronic lymphocytic leukemia (CLL) who are intolerant to prior BTK or PI3K delta inhibitor therapy (Abstract #: S808)
  - Date & Time: Saturday June 16, 2018; 12:30 – 12:45 CEST

- Oral: Resurrecting response to ruxolitinib: a phase I study testing the combination of ruxolitinib and the PI3Kdelta inhibitor umbralisib in ruxolitinib-experienced myelofibrosis (Abstract #: S133)
  - Date & Time: Friday June 15, 2018, 12:30 – 12:45 CEST

- Poster: Long term integrated safety analysis of umbralisib (TGR-1202), a PI3K delta/CK1-epsilon inhibitor with a differentiated safety profile in patients with relapsed/refractory lymphoid malignancies (Abstract #: PF444)
  - Date & Time: Friday June 15, 2018; 17:30 – 19:00 CEST

- Poster: TG-1701 a novel, orally available, and covalently-bound BTK inhibitor (Abstract #: PF638)
  - Date & Time: Friday June 15, 2018; 17:30 – 19:00 CEST

TG Therapeutics

Anthony Mato, MD

Director, CLL Program

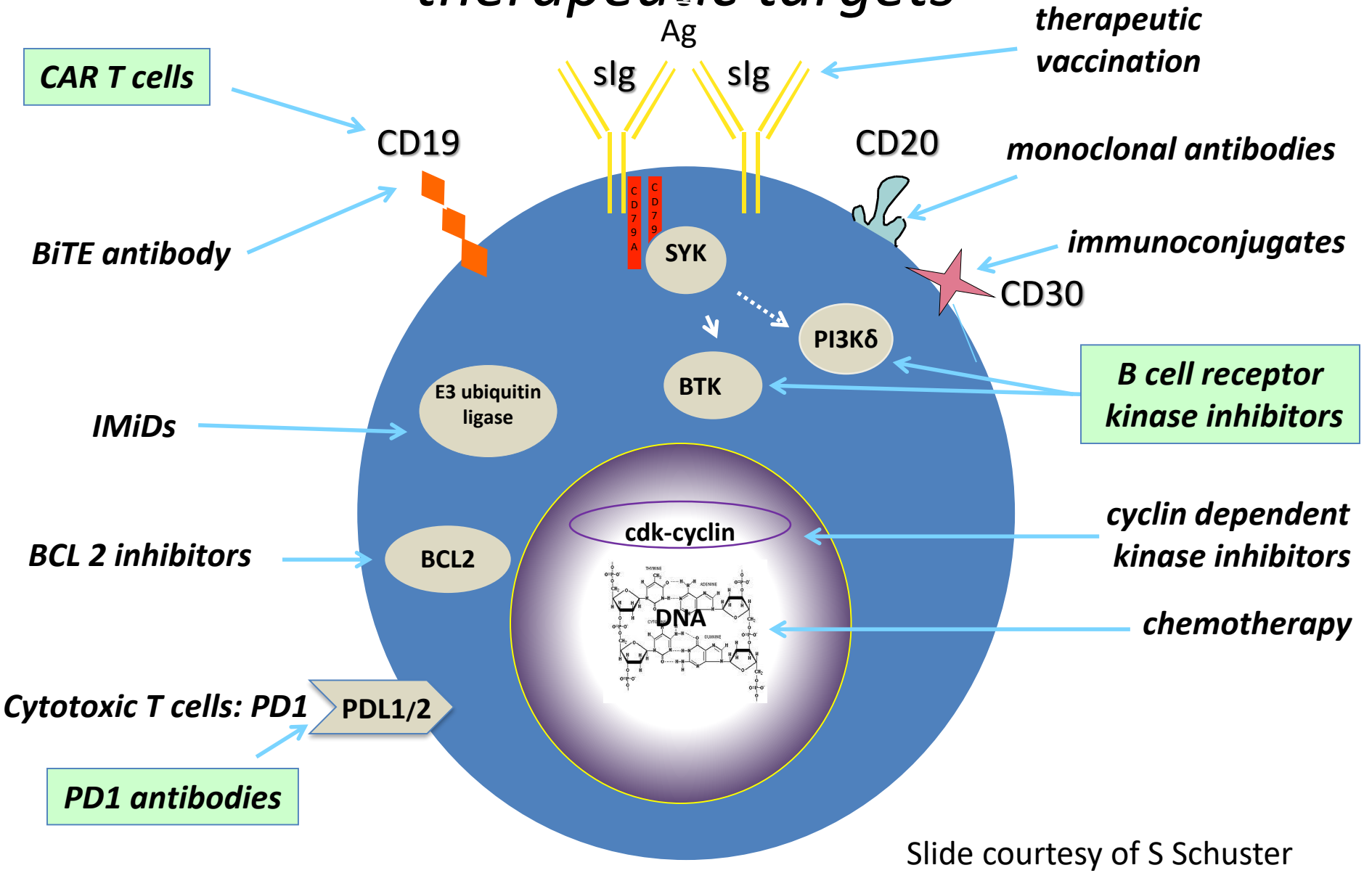
Memorial Sloan Kettering Cancer Center

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

B cell lymphomas and CLL: expanding!

therapeutic targets



Slide courtesy of S Schuster

CLL in 2018

- Utilization of prognostic factors to **personalize therapies**
- **Paradigm shift** from CIT → KI in the front-line setting
- Widespread **adaptation of KI therapies** (ibrutinib / idelalisib) in relapse / refractory settings
- **KI as a backbone** (vs. KI + CIT backbone)
- **KI associated toxicities** (intolerance = emerging issue)
- **CLL progression** following KI (Ibrutinib resistance mechanisms and monitoring)
- Study of **next generation KI** (better activity? less toxicity?)
- Incorporation of **BCL2-i** in CLL management (time limited approaches)
- **Incorporation of MRD** into CIT / BCL2-i treatment strategies
- **Diminished role of SCT** (even in high risk patients) and emerging role for CAR T cells
- As options expand, recognition that **sequencing of CIT / novel agents** is important area of research but prospective data lacking.

Sequencing Strategy in 2018

Goal: For each patient, select a sequence of therapies that maximizes efficacy and minimizes toxicities while prolonging survival and quality of life.

Expectation: Because of genetic heterogeneity, prior therapies and comorbidities, this approach will have to be **highly patient specific** with some common underlying themes.

57 year old with relapsed-refractory CLL

- **CLL** Diagnosis 2011 (age 51)
  - Symptomatic splenomegaly
  - Symptomatic, bulky LAD
  - Rapid LDT (< 6 months)
  - **Del 11q (+)**
  - **Unmutated IGHV**
  - **NGS not performed**
- PMH
  - Type I diabetes on insulin pump
- SH/FH: Brother with CLL. No potential available donors through NMDP.

- **Treatment history**
- 2011**: FCR** (6 cycles)
- **Response = CR / MRD + BM (FCM)**
- **Unexpectedly** → 2012 (< 12 months): Overt symptomatic relapse with rapid LDT / LAD and B symptoms
- Repeat genetic assessment: **del11q (+)** / **del17p (+)**
- 2013: R-Bendamustine (4 cycles) (complicated by TLS)
- **Response = SD**

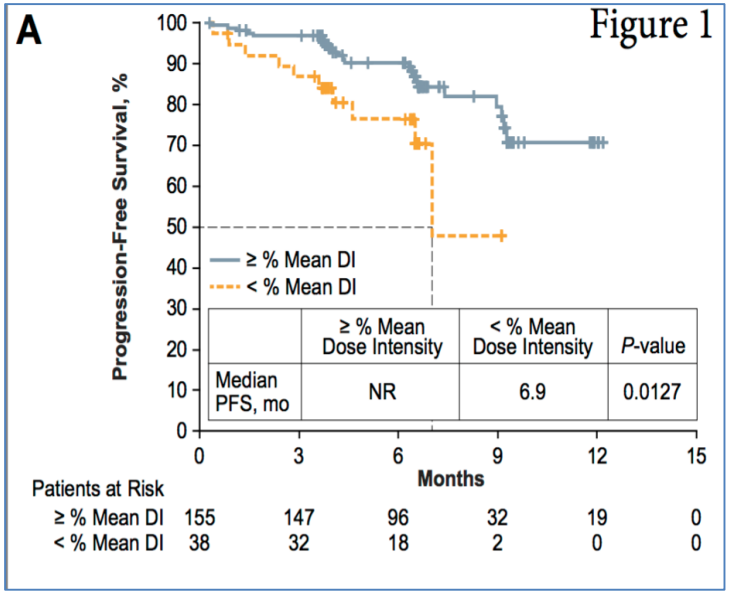
CIT candidacy: 2018

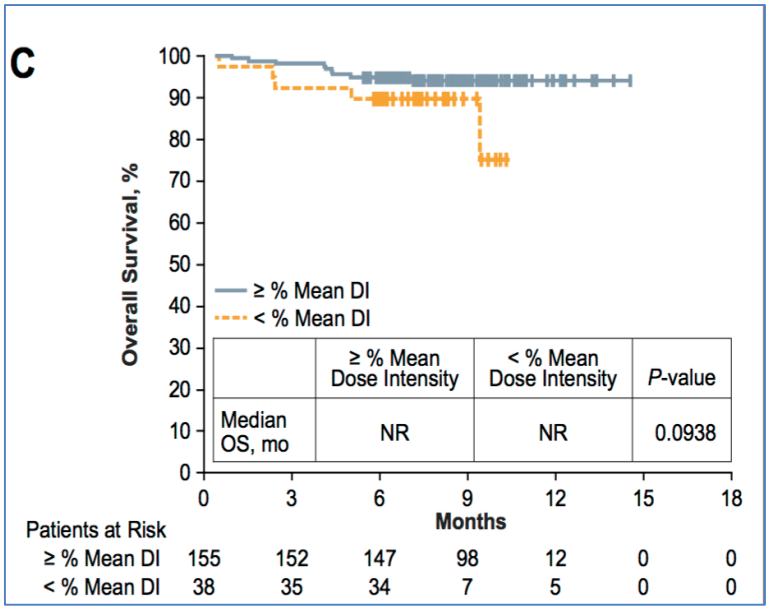
1. CIT (FCR) **may cure select patients** with CLL in the front line setting and should be considered…
2. Testing with **FISH, NGS and IGHV is mandated** when considering CIT as front line therapy.
3. For younger fit (age < 65) patients, **FCR is preferred** to BR (CLL 10) although BR is effective in IGHV mutated CLL (age > 65).
4. FCR candidates should be **IGHV mutated and not harbor del17p or TP53 mutations** (NGS).
5. **MRD** (validated) should be tested after 3 cycles and therapy limited if mutated IGHV / MRD negative in BM.
6. **Responding MRD positive patients** should receive 6 cycles of FCR and MRD reassessed following treatment.

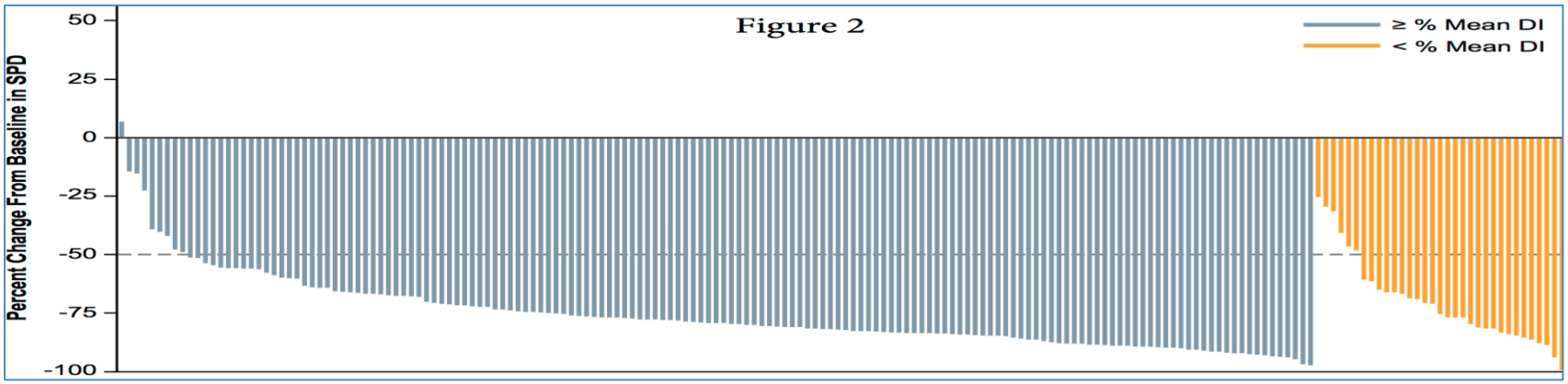
Back to the case…

- CT imaging: Progression of axillary / intrathoracic adenopathy. Stable, bulky abdominal / pelvic lymphadenopathy. Splenomegaly (23 cm).
- 1/2014: Ibrutinib initiated 420 mg daily.
  - 4/2014: Stomatitis with neutropenia: Ibrutinib held and restarted at 280 mg **(reduced-dose strategy to minimize toxicity)**

Impact of Ibrutinib Dose Adherence on Therapeutic Efficacy in Patients with Previously Treated CLL/SLL





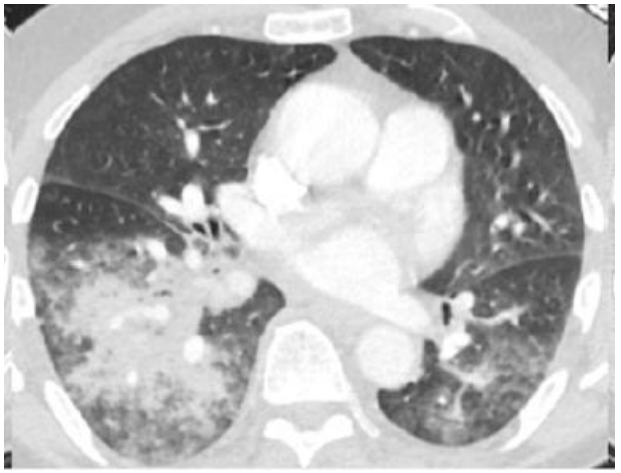


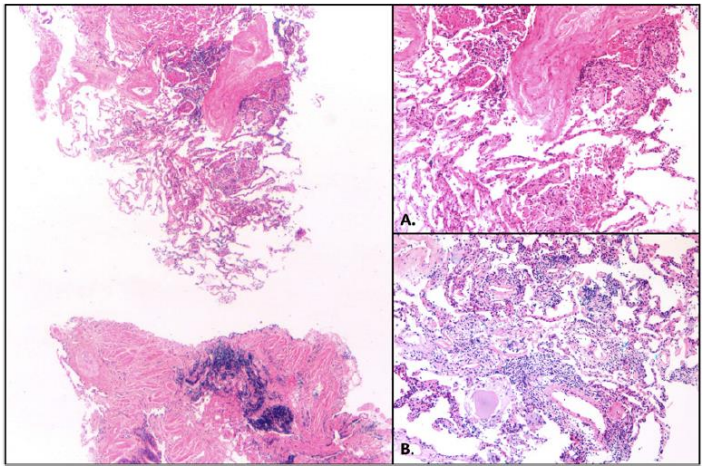
Barr *et al*, Blood 2017

blood

Diagnostic evaluation of dyspnea

- Hospitalized for dyspnea / hypoxia.
- High-resolution chest CT scan revealed diffuse ground glass opacities with small nodular opacities.
- Transbronchial biopsies and cytology revealed **acute inflammation without evidence of malignancy or infection**.
- Ibrutinib was discontinued and prednisone initiated at 60 mg daily for **drug induced pneumonitis**
- Symptoms promptly resolved and ibrutinib was held
- A follow-up CT scan confirmed radiographic improvement.



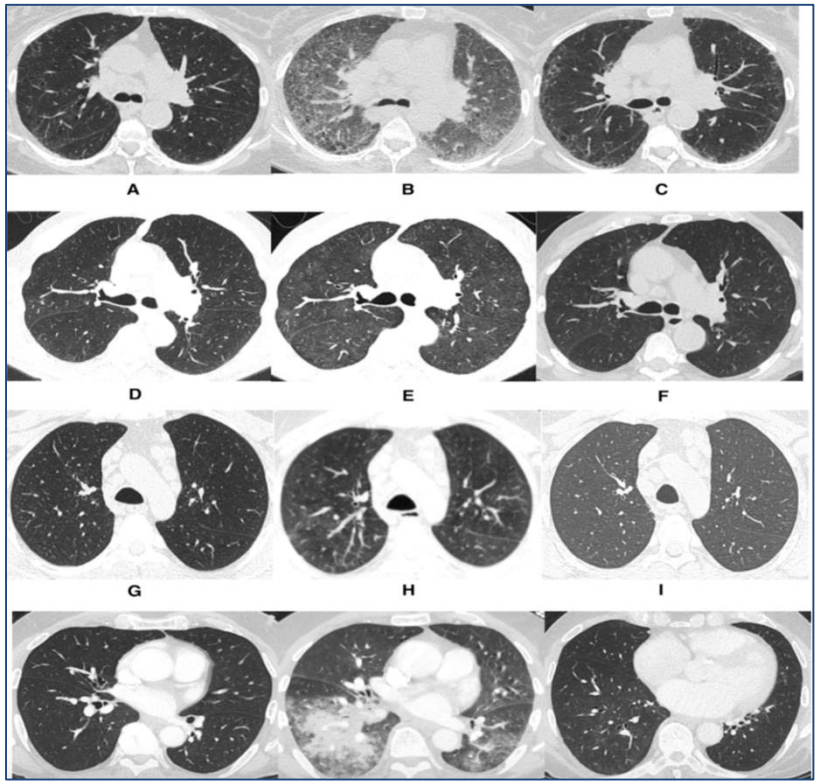


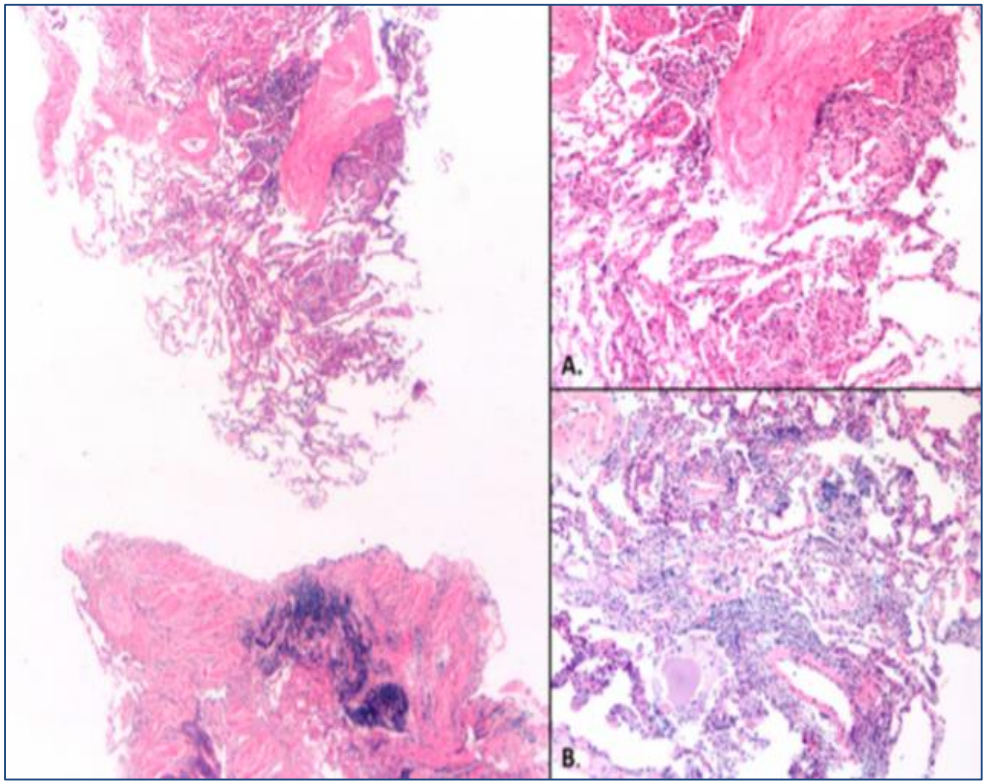
To the editor:

Ibrutinib-induced pneumonitis in patients with chronic lymphocytic leukemia

Anthony R. Mato,[1] Prioty Islam,[1] Catherine Daniel,[1] Lauren Strelec,[1] Adam H. Kaye,[1] Sarah Brooks,[1] Alex Ganetsky,[1] Sunita Nasta,[1] David L. Porter,[1] Jakub Svoboda,[1] Chadi Nabhan,[2] and Stephen J. Schuster[1]

[1]Center for Chronic Lymphocytic Leukemia, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA; and [2]The University of Chicago Medicine, Chicago, IL





Mato *et al*, Blood 2016

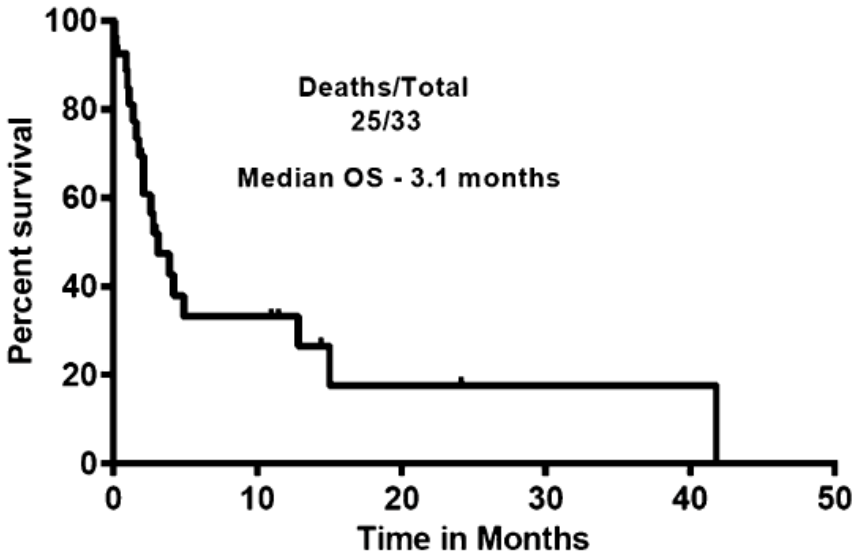
Ibrutinib discontinued…

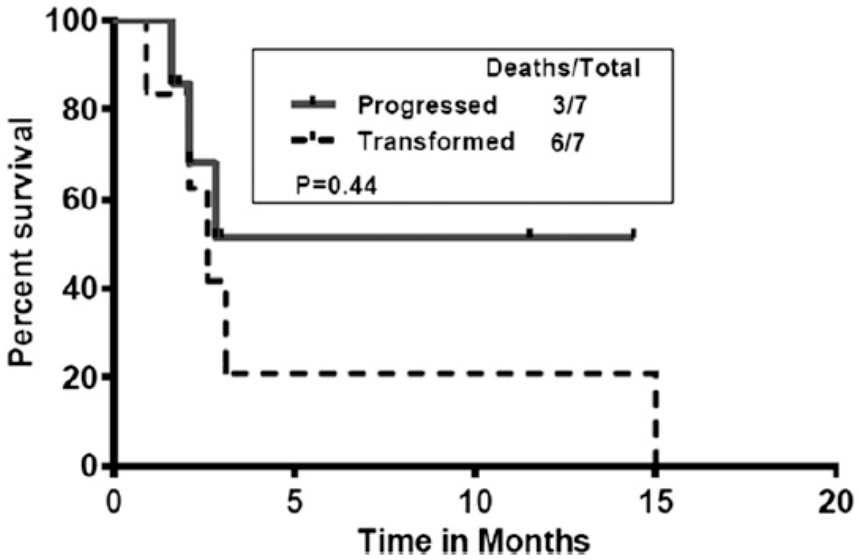
What data exist for patient outcomes and treatment options after ibrutinib discontinuation?

CLINICAL TRIALS AND OBSERVATIONS

Outcomes of patients with chronic lymphocytic leukemia after discontinuing ibrutinib

Preetesh Jain,[1,2] Michael Keating,[1] William Wierda,[1] Zeev Estrov,[1] Alessandra Ferrajoli,[1] Nitin Jain,[1] Binsah George,[1] Danelle James,[3] Hagop Kantarjian,[1] Jan Burger,[1] and Susan O'Brien[1]





Median OS for RT = 3.1 months

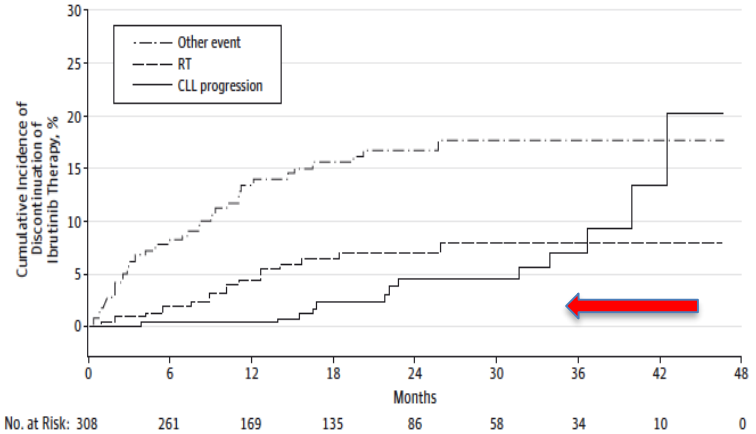
Jain *et al*, Blood 2015

Original Investigation

Etiology of Ibrutinib Therapy Discontinuation and Outcomes in Patients With Chronic Lymphocytic Leukemia

Kami J. Maddocks, MD; Amy S. Ruppert, MAS; Gerard Lozanski, MD; Nyla A. Heerema, PhD; Weiqiang Zhao, MD; Lynne Abruzzo, MD; Arletta Lozanski, MS; Melanie Davis, PhD; Amber Gordon, MS; Lisa L. Smith, MT; Rose Mantel, BS; Jeffrey A. Jones, MD; Joseph M. Flynn, DO; Samantha M. Jaglowski, MD; Leslie A. Andritsos, MD; Farrukh Awan, MBBS; Kristie A. Blum, MD; Michael R. Grever, MD; Amy J. Johnson, MD; John C. Byrd, MD; Jennifer A. Woyach, MD

Figure. Cumulative Incidence of Discontinuation of Ibrutinib Therapy



Cumulative Incidence Estimates, % (95% CI)

	At 12 mo	At 18 mo
CLL progression	0.3 (0-1.0)	2.4 (0.3-4.6)
RT	4.5 (2.0-7.0)	6.5 (3.3-9.6)
Other event	13.5 (9.5-17.6)	15.6 (11.1-20.0)

Table 2. Multivariable Models for Cumulative Incidence of 2 Failure Types: Disease Progression and Toxicity, Adjusted for Monotherapy

	Event			
	Progression		Toxicity	
Variable	HR (95% CI)[a]	*P* Value	HR (95% CI)[a]	*P* Value
Age, 10-y increase	NA	NA	1.87 (1.33-2.64)	<.001
No. of prior treatments, 1 unit increase	NA	NA	1.09 (1.00-1.19)	.054
BCL6 abnormality, yes vs no	2.70 (1.25-5.85)	.01	NA	NA
Complex karyotype, yes vs no	4.47 (1.50-13.34)	.007	NA	NA

Median OS for RT = 3.5 months

Maddocks *et al*, Jama Onc 2015

Key Unanswered Questions

1. Are experiences in clinical practice similar to clinical trials?
2. Can we refine major reasons for discontinuation?
3. What therapies are prescribed following kinase inhibitor discontinuation?
4. Are toxicity profiles distinct between agents such that “class switching” can maintain adequate response?
5. Are resistance mechanisms clinically unique, such that BCR signal transduction inhibition is a treatment consideration in CLL progression?

Methods

- **Study design:** Multicenter, retrospective cohort study
- **Patient population:** CLL patients, discontinued Ibrutinib or Idelalisib
- **Primary objective:** Describe response pattern / outcomes following KI discontinuation (1) CLL progression (2) KI toxicity (3) RT
- **Outcomes:** Investigators used standard criteria to define responses[6,7] and outcomes (PFS, OS)
- **Statistical analysis plan:**
  - Survival analyses were performed using Kaplan-Meier estimates
  - All other analyses were descriptive in nature
- **Regulatory:** Each institution received IRB approval
- **Funding source:** Unfunded study / All investigators volunteered their time

Hallek *et al*, Blood: 2008;111:5446-5456, **Cheson** et al; JCO: 30(23):2820-2822.

Toxicity was the most common reason for kinase inhibitor 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

Toxicity profiles were not overlapping

Supplemental Table 1. Most common toxicities as a reason for kinase inhibitor (KI) discontinuation.

Ibrutinib (N=73)	Idelalisib (N=18)
Atrial fibrillation 20%	Pneumonitis 33%
Infection 12%	Colitis 28%
Hematologic 9%	Rash 17%
Bleeding 9%	Transaminitis 11%
Pneumonitis 8%	Infection 6%

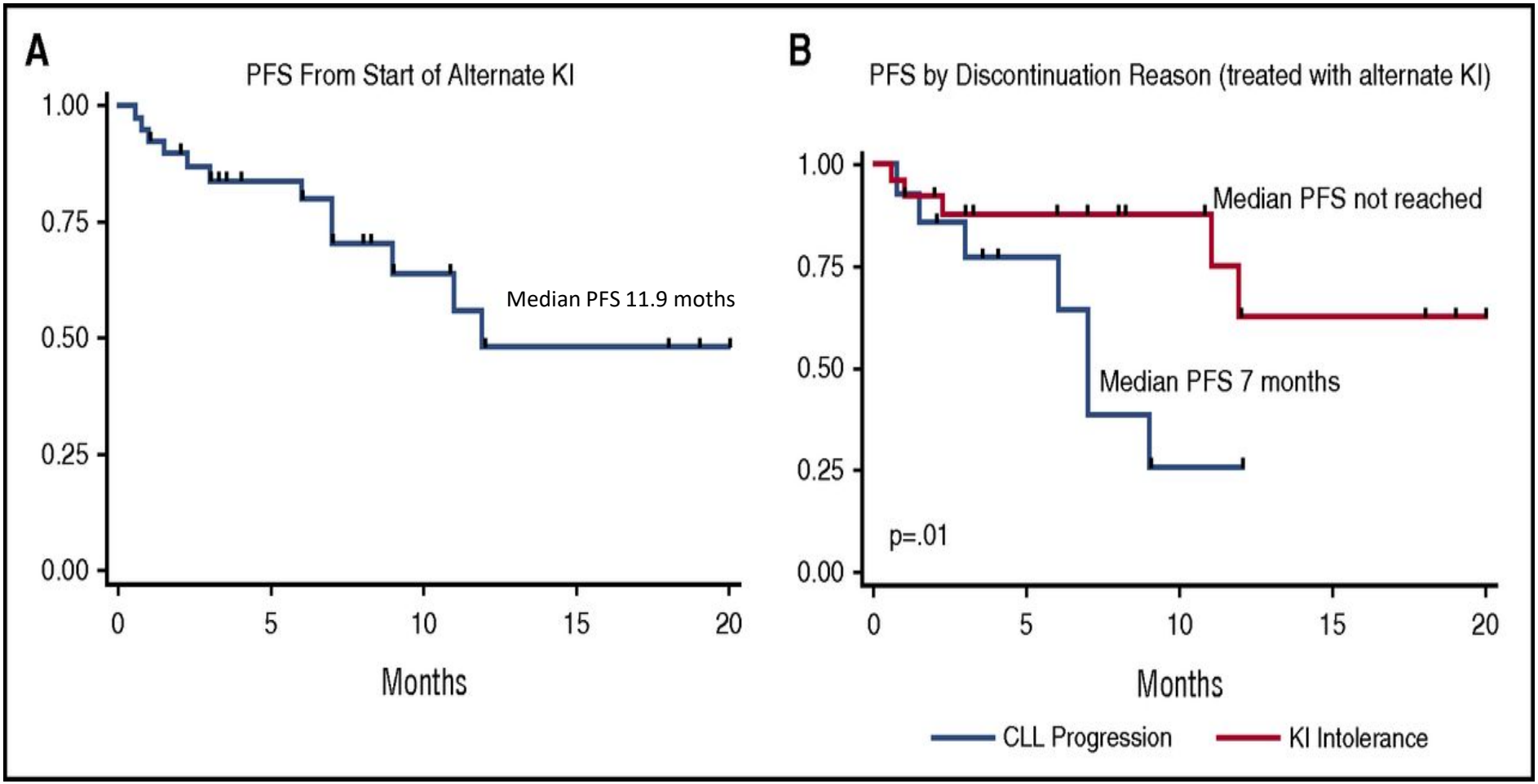
Mato *et al*, Blood 2016

Responses following KI Discontinuation

	Alternate KI	BCL2-i (CT)	CITs	CD20 Tx
Number	38	13	12	11
ORR	50%	76%	25%	36%
CR	0%	7%	17%	9%
PR	50%	69%	8%	27%
SD	30%	16%	33%	45%
PD	20%	8%	42%	19%

No direct comparisons performed

KI-intolerant patients can be successfully treated with alternate KI



Mato *et al*, Blood 2016

Conclusions

- Largest experience of practice patterns and outcomes following KI discontinuation in CLL
- Majority of patients discontinued KI therapy due to toxicity or CLL progression (≈80%), not Richter's transformation
- Alternate KI therapy following KI discontinuation can be efficacious
- Patients who discontinue KI due to toxicity can achieve a durable response with alternate KI
- Patients who discontinue KI due to CLL progression achieve a less durable response with alternate KI

Toxicities and Outcomes of Ibrutinib-Treated Patients in the United States: Large Retrospective Analysis of 621 Real World Patients

Anthony R. Mato, Nicole Lamanna, Chaitra S. Ujjani, Danielle M. Brander, Brian T. Hill, Christina Howlett, Alan P Skarbnik, Bruce Cheson, Clive S Zent, Jeffrey J Pu, Pavel Kiselev, Spencer Henick Bachow, Allison M Winter, Allan-Louie Cruz, David F. Claxton, Catherine Daniel, Krista Isaack, Kaitlin H Kennard, Colleen Timlin, Melissa Yacur, Molly Fanning, Lauren E. Strelec, Daniel J. Landsburg, Sunita Dwivedy Nasta, Stephen J. Schuster, David L Porter, Chadi Nabhan and Paul Barr

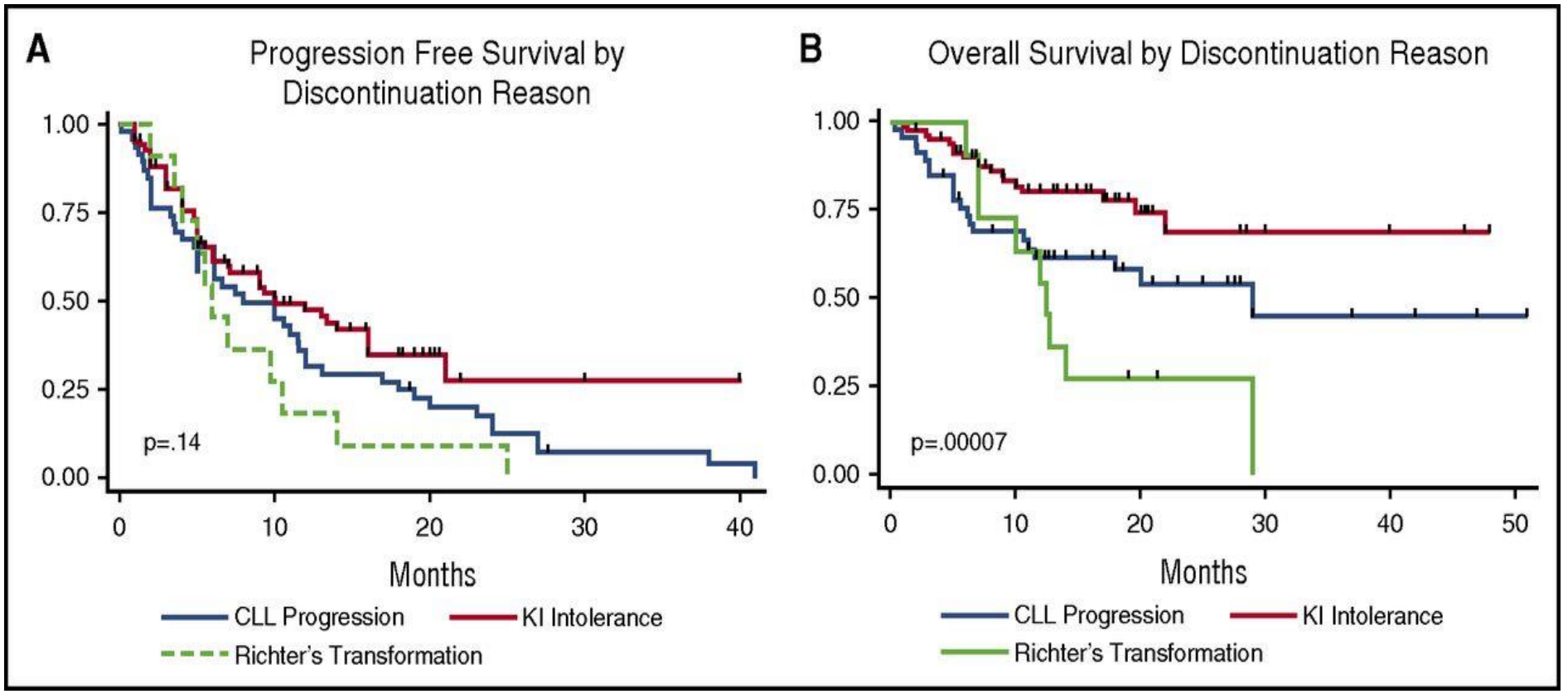
Baseline characteristics		
	Ibrutinib in front line	**Ibrutinib in relapse**
Total Number	80	536
Med age dx (range)	62 (37-88), n=78	60 (22-95), n=532
Med prior tx (range)	0 (0-0), n=80	2 (1-10), n=536
del17p (+)	37%, n=76	26%, n=368
del11q (+)	19%, n=75	35%, n=367
p53 mut (+)	12%, n=42	13%, n =142
Complex karyotype (+) (≥ 3)	40%, n=60	34%, n=214
Med time dx to Ibr (range)	26 months (1-232)	78 months (1-660)
Med Ibr starting dose	420 mg	420 mg
Ibr administered as monotherapy	68%, n=80	89%, n=536
Ibr hold required	30%, n=79	37%, n=310
Ibr dose adjusted	15%, n=79	20%, n=309
Median follow up	17 months	

Reason for ibrutinib Discontinuation	Ibrutinib in front line		Ibrutinib in relapse	
	Commercial Use (%) n=10	Clinical Trial (%) n=9	Commercial Use (%) n=200	Clinical Trial (%) n=31
Toxicity	**50.0**	**77.7**	**52.5**	**38.7**
CLL progression	10.0	22.2	19.0	35.5
Other/unrelated death	10.0	0.0	12.0	12.9
Physician or patient preference	20.0	0.0	6.0	9.7
RT DLBCL	0.0	0.0	4.5	0.0
Stem cell transplantation/ CAR T-cell	0.0	0.0	3.5	3.2
Financial concerns	0.0	0.0	1.0	0.0
Secondary malignancy	10	0.0	1.0	0.0
RT Hodgkin lymphoma	0.0	0.0	0.5	0.0

Median times to ibrutinib discontinuation stratified by toxicity	
Bleeding	8 months
Diarrhea	7.5 months
Atrial fibrillation	7 months
Infection	6 months
Arthralgia	5 months
Pneumonitis	4.5 months
Rash	3.5 months

Mato *et al*, Blood – ASH 2016

Outcomes differ when stratified by reason for discontinuation



Mato *et al*, Blood 2016

Case continued….

- Painful, symptomatic LAD and B-symptoms (requiring PCA)
- ABT 199 (venetoclax) initiated (clinical trial for KI failures)
- Dose escalated 20 mg → 400 mg over 5 weeks
- No evidence of TLS noted
- Improvement in disease related symptoms at 50 mg
- **Week 8 response assessment = PR**
- Month 6: New right inguinal LAD
- Incisional LN biopsy → CLL without evidence of large cell transformation
- Month 9: EOS for disease progression, ABT 199 discontinued

Case continued…
Further therapy is warranted

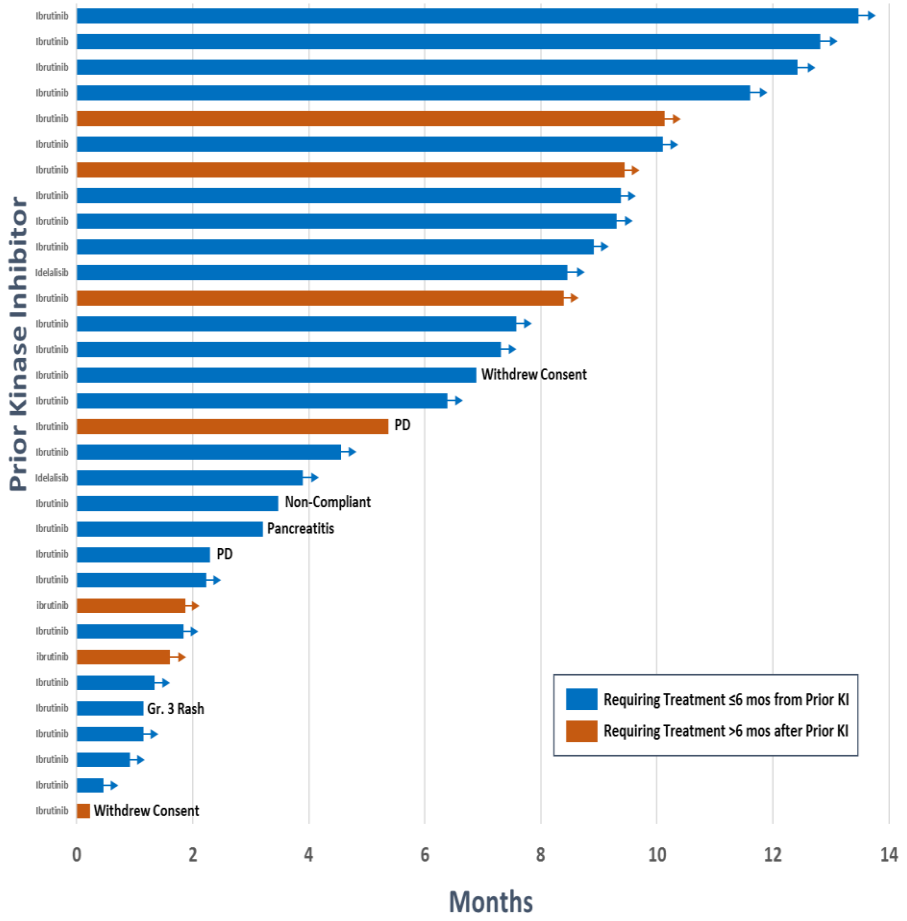
- **Now undergoing screening for TGR-1202-201 in the setting of ibrutinib intolerance…**

ASH 2017: KI Intolerant Results

All Grade AE's >15% or Grade 3/4 > 5% (N = 33)

Adverse Event	All Grades		Grade 3/4	
	N	%	N	%
Nausea	16	48%	-	-
Diarrhea	14	42%	2	6%
Thrombocytopenia	8	24%	2	6%
Insomnia	8	24%	-	-
Neutropenia	7	21%	6	18%
Fatigue	7	21%	-	-
Peripheral Edema	7	21%	-	-
Cough	6	18%	-	-
Dizziness	6	18%	-	-
Febrile neutropenia	3	9%	3	9%
Hypophosphatemia	2	6%	2	6%

Swimmer Plot



Mean time on study = 6 mos (range 1 – 13 mos)

Mato et al, ASH 2017

UPDATED DATA WILL BE PRESENTED TOMORROW AT ASCO AND AT EHA!

KI Intolerance Study: A Phase 2 Study to Assess the Safety and Efficacy of Umbralisib (TGR-1202) In Patients with Chronic Lymphocytic Leukemia (CLL) Who Are Intolerant to Prior BTK or PI3Kδ Inhibitor Therapy

Anthony R. Mato, MD* 1, Stephen J. Schuster, MD2, Nicole Lamanna, MD3, Ian W. Flinn, MD, PhD4, Jacqueline Barrientos, MD5, Suman Kambhampati, MD6, Bruce D. Cheson, MD7, Paul M. Barr, MD8, John M. Pagel, MD, PhD9, James A. Reeves, MD10, Frederick Lansigan, MD11, Jeffrey J. Pu, MD, PhD12, Alan Skarbnik, MD13, Gustavo Fonseca, MD14, Colleen Dorsey, RN, BSN1, Elizabeth T. Chatburn, BS2, Hanna Weissbrot, BS3, Jacob Svoboda, MD2, Eline T. Luning Prak, MD, PhD15, Patricia Tsao, MD, PhD15, Andrea Sitlinger, MD16, Chaitra S. Ujjani, MD7, Dana Paskalis17, Peter Sportelli, BS17, Hari P. Miskin, MS17, Michael S. Weiss17, Danielle M. Brander, MD16

1CLL Program, Leukemia Service, Memorial Sloan Kettering Cancer Center, New York, NY, 2University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA, 3New York-Presbyterian Columbia University Medical Ctr, New York, NY, 4 Tennessee Oncology/Sarah Cannon Research Institute, Nashville TN, 5Northwell Health/CLL Research and Treatment Program, New Hyde Park, NY, 6Sarah Cannon Research Institute at Research Medical Center, Kansas City, KS, 7 Georgetown University Hospital Lombardi Comprehensive Cancer Center, Washington, DC, 8Wilmot Cancer Institute, University of Rochester, Rochester, NY, 9Swedish Cancer Institute, Seattle, WA, 10Florida Cancer Specialists South/Sarah Cannon Research Institute, Fort Myers, FL, 11Dartmouth-Hitchcock Medical Center, Lebanon, NH, 12Penn State Health, Hershey, PA, 13John Theurer Cancer Center, Hackensack, NJ, 14Florida Cancer Specialists North/Sarah Cannon Research Institute, St. Petersburg, FL, 15Clinical Immunology Laboratory at the Hospital of the University of Pennsylvania, Philadelphia, PA, 16Duke University Medical Center, Durham, NC, 17TG Therapeutics, Inc., New York, NY, United States

TG Therapeutics

Alexey V. Danilov, MD, PhD
Associate Professor of Medicine
Knight Cancer Institute
Oregon Health & Science U

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

CLL Clinical Case

- 53 year old man
- Diagnosed with CLL in 2010.
- Comorbidities:
  - Diabetes mellitus, on insulin
  - Hypertension

- Followed every 6-12 months by watch-and-wait
- FISH – trisomy 12

CLL Clinical Case

- 2012 – White cell count 40,000.
- Worsening shortness of breath and night sweats. Lost about 10 lbs of weight over 3-4 months
- Developed progressive lymphadenopathy
- Anemia
- Started Bendamustine-Rituximab, completed 6 cycles with good response

CLL Clinical Case

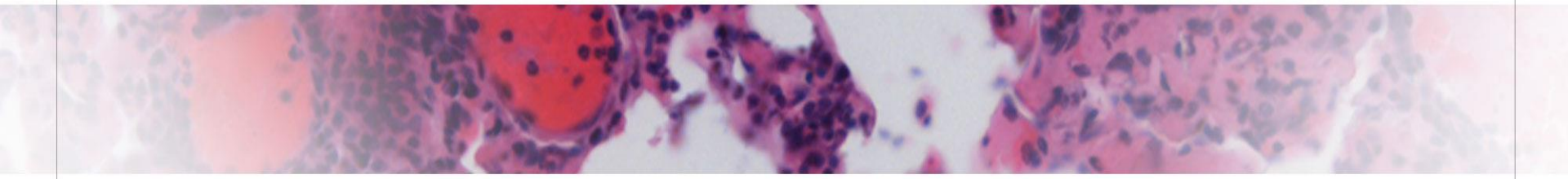
- 2015 (age 58) – White cell count 60,000.
- Symptoms come back
- Recurrent lymphadenopathy and anemia
- Started ibrutinib
- After 2 weeks on ibrutinib, developed Atrial Fibrillation
- Admitted to the hospital, developed severe lung infection, required 2 weeks of hospital stay, including Intensive Care Unit

Long-term follow-up of ibrutinib therapy on clinical trials

Disposition	TN (n=31)	R/R (n=101)
Median time on study, months (range)	62 (1–67)	49 (1–67)
Patients remaining on ibrutinib therapy, n (%)	**20 (65%)**	**30 (30%)**
Primary reason for discontinuation, n (%)		
Progressive disease	1 (3%)	33 (33%)
Adverse event	6 (19%)	21 (21%)
Consent withdrawal	3 (10%)	5 (5%)
Investigator decision	0	11 (11%)
Lost to follow-up	1 (3%)	1 (1%)

O'Brien, Furman et al, ASH 2016

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

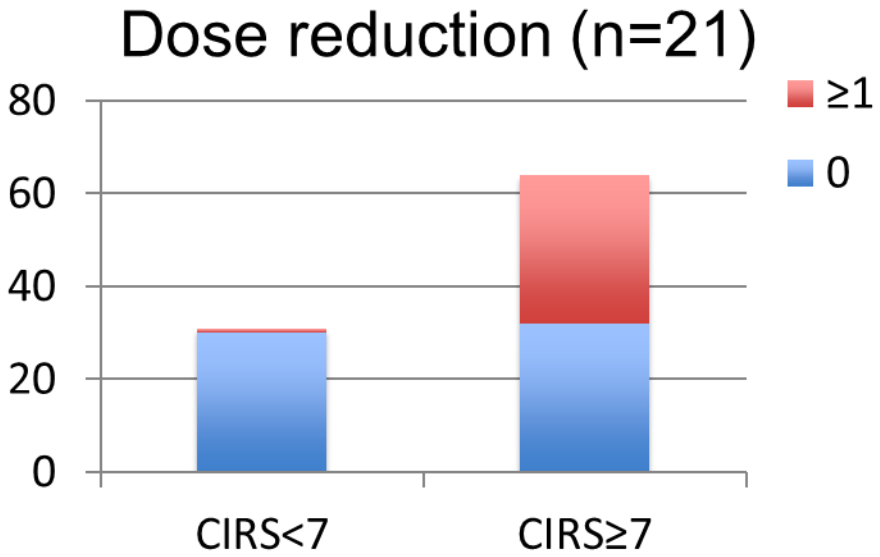


Medical comorbidities assessed by CIRS negatively impact survival in the era of targeted therapies in CLL: a multicenter retrospective analysis

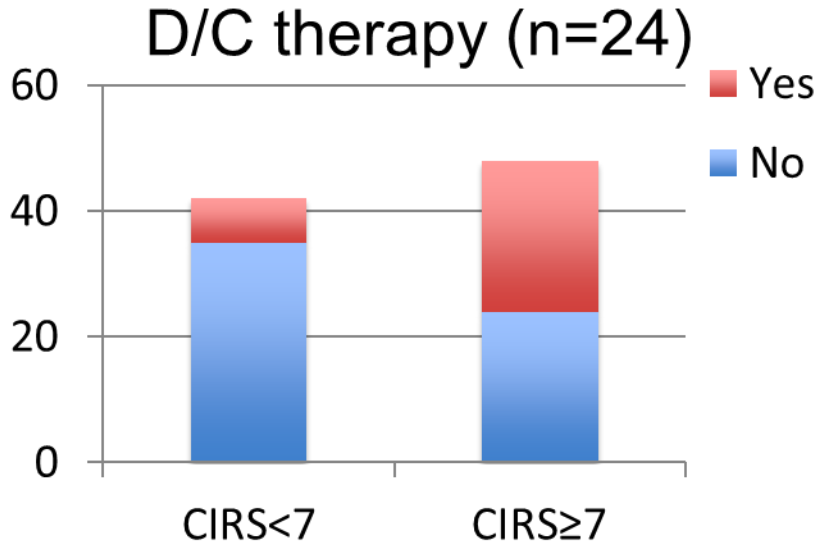
Max J. Gordon MD[1], Stephen M. Amrock MD SM[1], Xavier Rivera[3], Spencer James MD MPH[2], Sudhir Manda MD FACP[2], Stephen E. Spurgeon MD[1], Daniel Persky [3],Alexey V. Danilov MD PhD[1]

[1]Oregon Health & Science University, Portland, OR [2]Geisel School of Medicine at Dartmouth, Hanover, NH
[3]University of Arizona, Tucson, AZ

Tolerance of ibrutinib

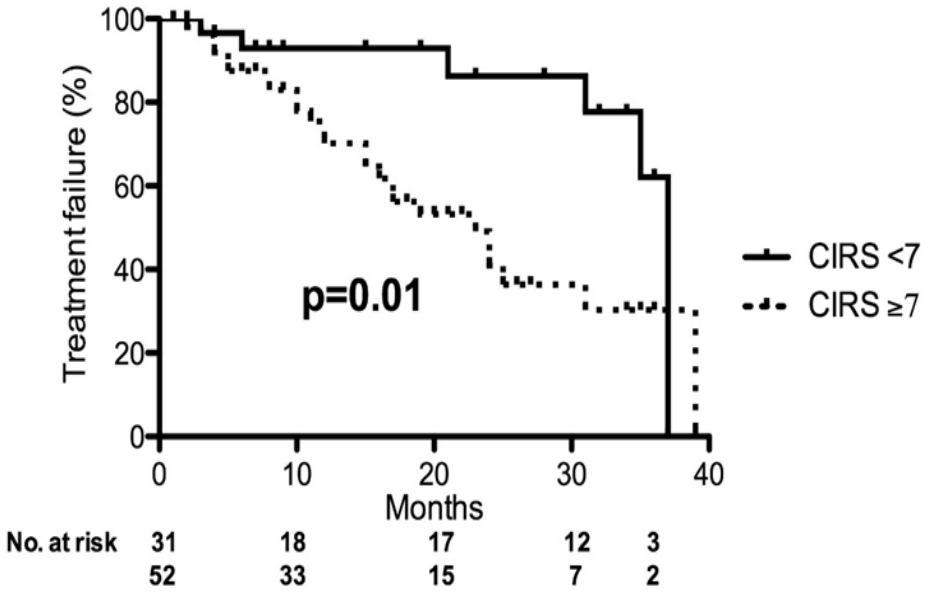


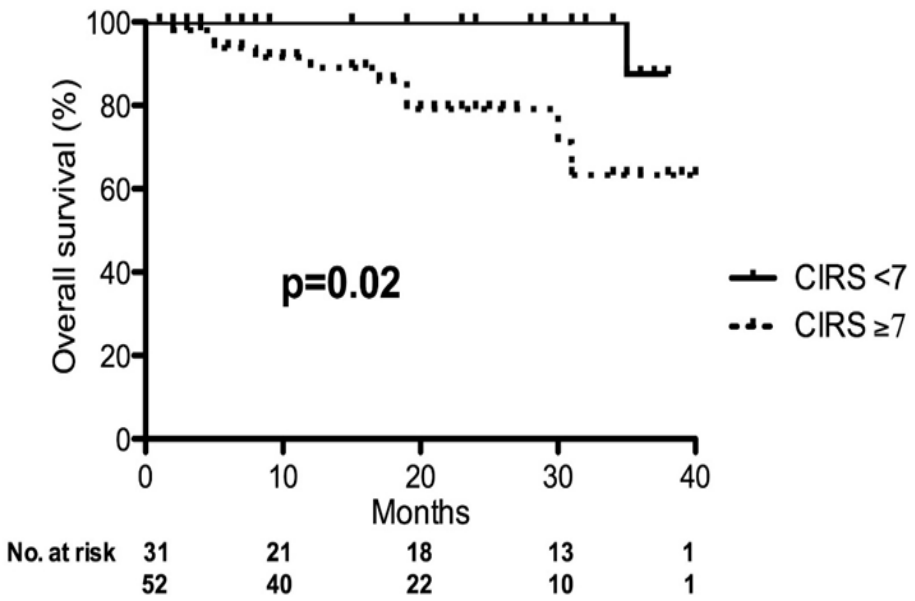
	Relative risk	P=
CIRS ≥7	11.9	<0.001
CIRS 3-4	4.6	0.01



	Relative risk	P=
CIRS ≥7	2.5	0.02
CIRS 3-4	3.8	0.005

Outcomes with ibrutinib





- Median 37 vs 23 months
- OS at 24 months 100 vs 79%

CLL Clinical Case

- Not a good candidate for chemotherapy (diabetes on insulin, warfarin for a fib, hypertension, poor activity level)
- CLL slowly progressive
- Options:
  - Rechallenge with ibrutinib
  - Idelalisib
  - Rituximab or obinutuzumab single agent
- Patient followed off therapy

CLL Clinical Case

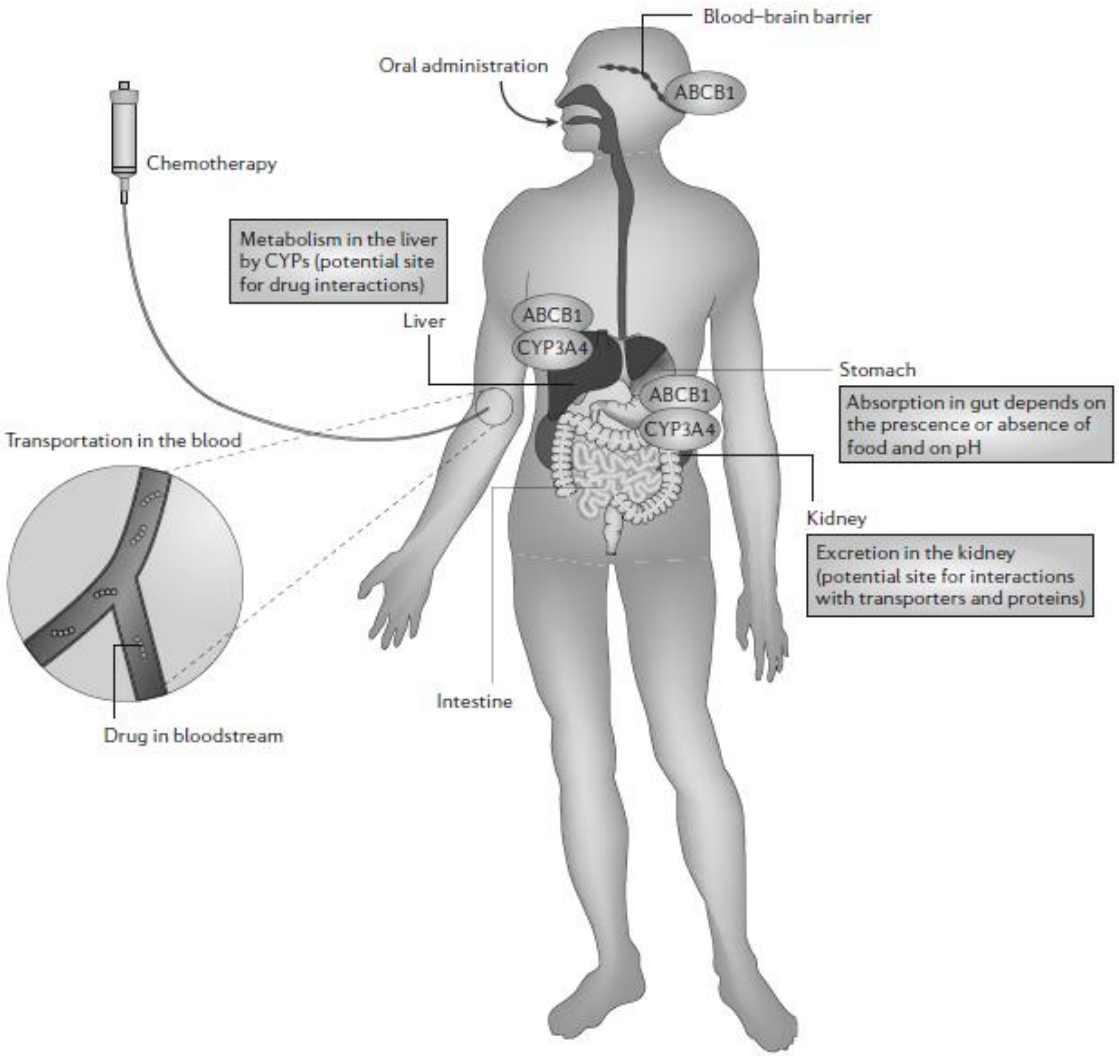
- 2016 – developed worsening shortness of breath
- Lung work-up: aspergillus _and_ PJP pneumonia
- Started on Voriconazole and Bactrim for treatment of both
- CLL is progressive. FISH trisomy 12, Notch1 mutation
- Therapeutic options?

- Idelalisib?
- Ibrutinib?
- Venetoclax?

Drug-drug interactions (DDI) – is this a problem?

- Among U.S. pts >65 yo, 40% take ≥5 medications; 20% take ≥10 meds; 50% take supplements
- Among patients >70 yo, 75% took drugs which had known DDIs with chemotherapy, of them 20-30% were ‘major’
- DDI’s are estimated to account for 20-30% of all AE’s

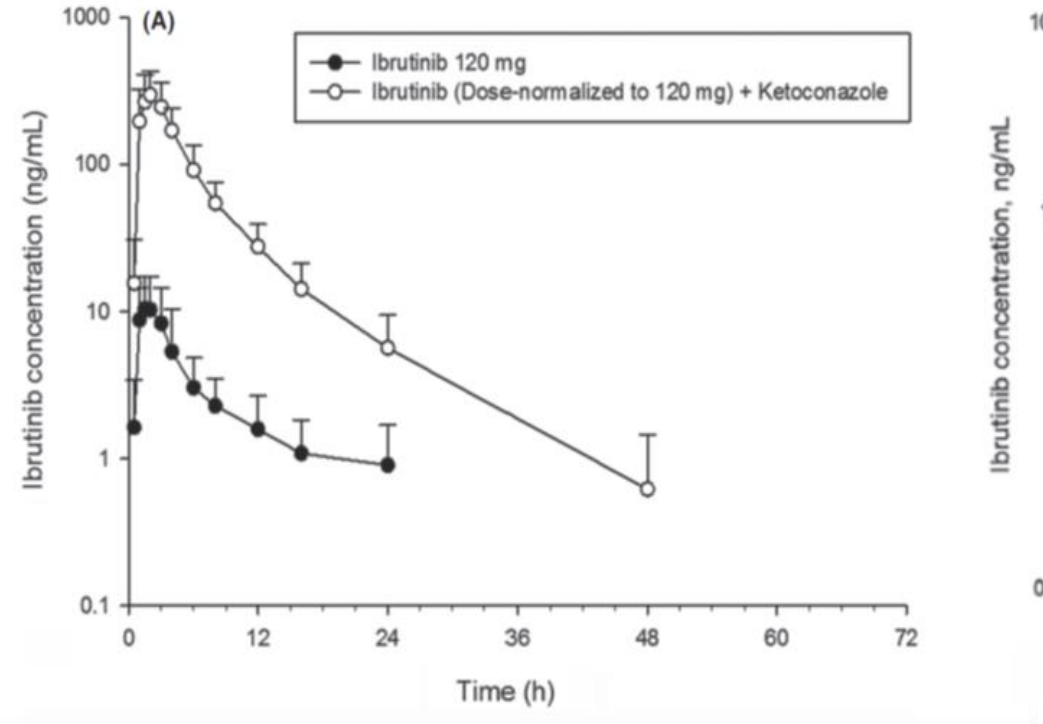
Sites of DDI: CYP3A4 and p-glycoprotein

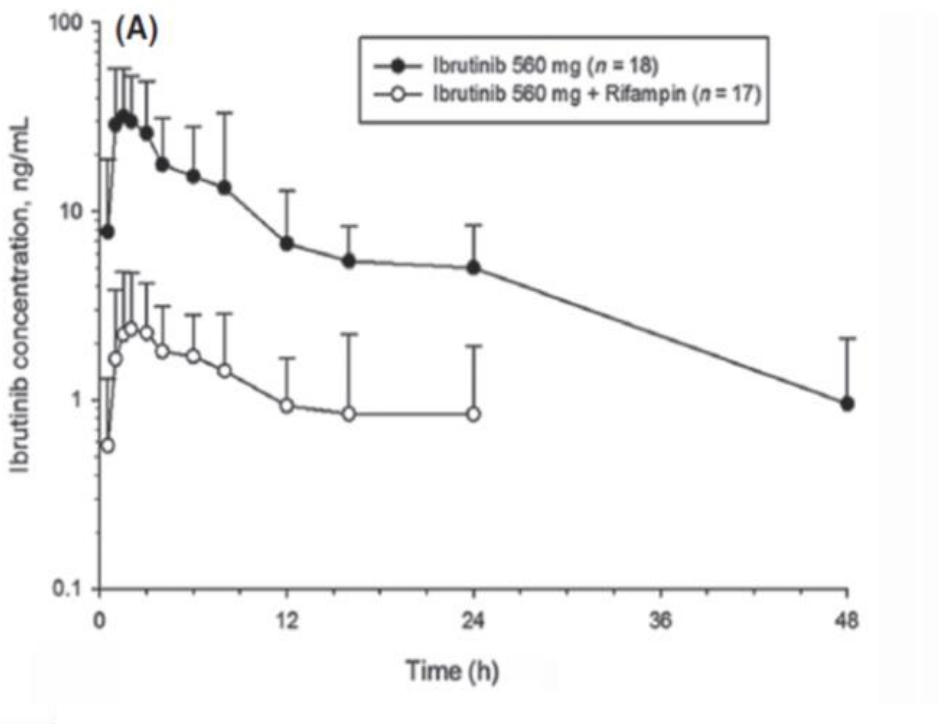


KNIGHT CANCER INSTITUTE
Oregon Health & Science University

Scripture & Figg, 2006

Ibrutinib is a CYP3A4 substrate





Black dots – ibrutinib alone
White dots – ibrutinib PLUS

De Jong et al, 2015

CYP3A4 Inhibitors and Inducers

	Strong	Moderate
CYP3A Inhibitors	boceprevir clarithromycin conivaptan indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil nefazodone nelfinavir posaconazole saquinavir telaprevir telithromycin Voriconazole	amprenavir aprepitant atazanavir ciprofloxacin darunavir/ritonavir diltiazem grapefruit juice erythromycin fluconazole fosamprenavir Imatinib tamozifen verapamil
CYP3A inducers	avasimibe carbamazepine phenobarbital phenytoin rifampin St. John's wort	bosentan efavirenz etravirine modafinil nafcillin

Ibrutinib & Bleeding

Trial	Comparison	Median f/u, months	Any bleeding	Grade 1-2	Grade 3-4 (major)	Platelets, g3-4
Chanan-Khan, Lancet 2016	BR-ibr vs BR	17	31% vs 15%	28% vs 9%	4% vs 2%	15% vs 15%
Burger, NEJM 2015 (RES-2)	Ibr vs. chl	18.4			4% vs 2%	2% vs 6%
Byrd, NEJM 2014 (RES)	Ibr vs ofa	9.4	44% vs. 12%	27% vs. 10%	1% vs. 2%	6% vs. 4%

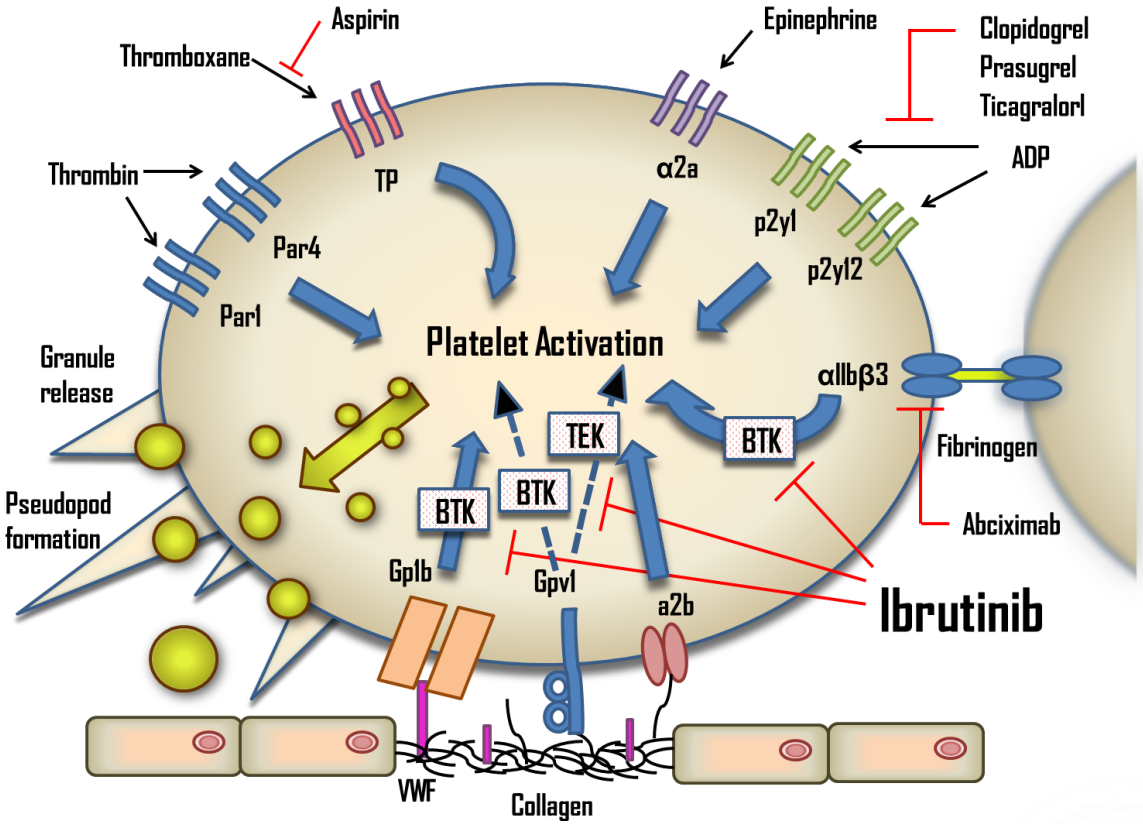
Shatzel, Danilov et al, 2017

Mechanisms of ibrutinib-mediated platelet dysfunction

- Collagen-mediated (adhesion/activation)
- vWF-GPIb interactions (primary haemostasis adhesion)
- Fibrinogen to integrin αIIbβ3 outside-in signaling
- Clec-2 (aggregation)

↓ ↓ ↓

INHIBITED



Ibrutinib: concurrent use of antiplatelet agents or anticoagulants -> increased rates of bleeding: 60-70% any grade, 8% grade 3-4

KNIGHT CANCER INSTITUTE
Oregon Health & Science University

Shatzel, Danilov et al, 2017

	N (total=71)	%
Concurrent Anti-platelet	*50*	*70%*
Aspirin	33	46%
NSAIDs	14	20%
Other	29	41%
Concurrent Anti-coagulant	*12*	*17%*
Apixaban	6	8%
Warfarin	3	4%
Other	3	4%
Interacting Medication (CYP3A4)	7	*10%*
Diltiazem	3	4%
Verapamil	1	1%
Other	4	6%
Bleeding Events		
All	40	56%
Grade 1, e.g. bruising	20	28%
Grade 2, e.g. epistaxis	7	10%
Grade 3, e.g. GIB	8	11%
Grade 4, e.g. ICH	4	6%
Grade 5	1	1%
Major Bleeding Events (Grade 3 or more)		
Total	13	18%
Antiplatelet + anticoagulant	7	54%
Antiplatelet alone	4	30%
Anticoagulant alone	1	8%
Interacting Medication alone	1	8%
None of the above	0	0

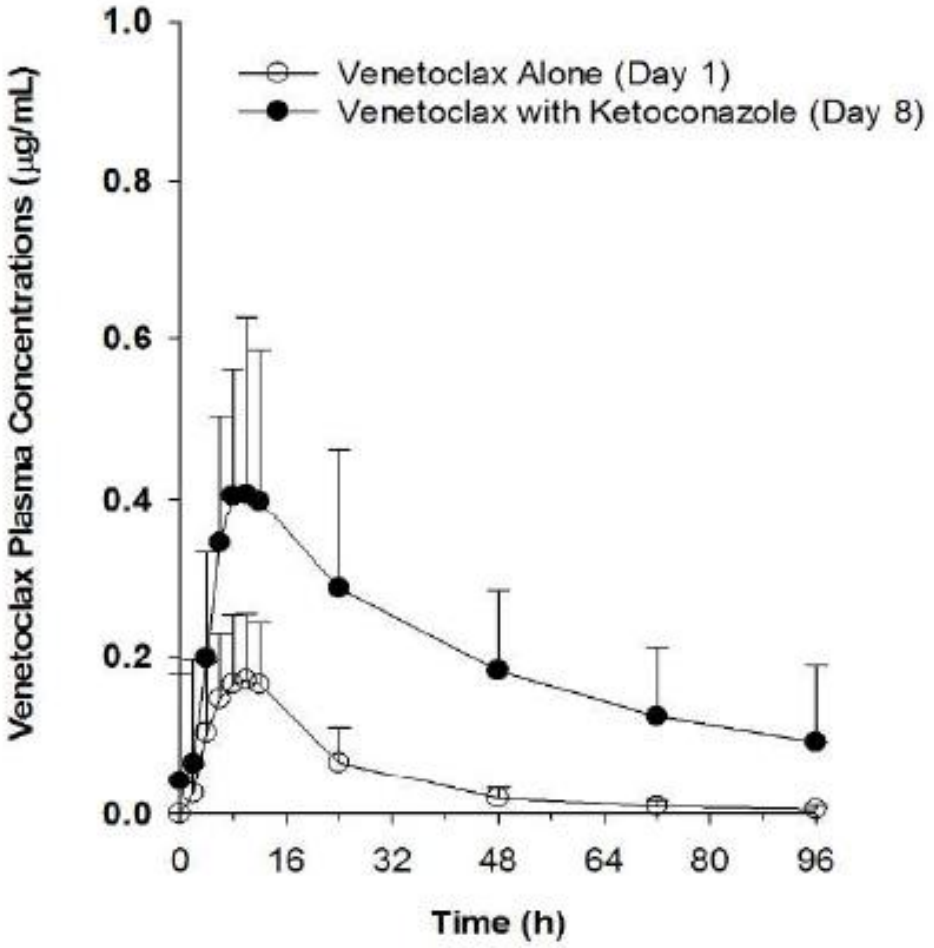
GIB: gastrointestinal bleed; ICH: intra-cranial hemorrhage

DDIs account for major bleeding events on ibrutinib

- All major bleeding events on anticoagulants/antiplatelet agents/interacting drugs
- 7/9 pts on anti-coag/plt therapy had a major bleed
- 3 major episodes in patients post-surgical procedures (ibrutinib not held)

Kunk et al, ASH 2016, UVa

Venetoclax – BH3-mimetic



KNIGHT CANCER INSTITUTE
Oregon Health & Science University

Agarwal, Danilov et al, 2016

Other agents

- Acalabrutinib (ACP-196) - CYP3A4 substrate
- Umbralisib (TGR-1202) - _not_ metabolized by CYP3A4

CLL Clinical Case

- 2016 – patient started on U2 regimen (UNITY)
- Lung continues to heal, no reactivation of PCP or aspergillus
- Patient manifests response

Umbralisib, a novel PI3K inhibitor, in CLL

Alexey V. Danilov, MD, PhD
Associate Professor of Medicine
Knight Cancer Institute
Oregon Health & Science U

KNIGHT CANCER INSTITUTE
Oregon Health & Science University

TG Therapeutics

Questions & Answer Session

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS

TG Therapeutics

Concluding Remarks

Michael S. Weiss
Executive Chairman & CEO

UNITY CLL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PHASE 3 TRIAL IN CLL

UNITY NHL
TG THERAPEUTICS
GLYCOENGINEERED UBLITUXIMAB + PI3K DELTA TGR-1202
PREVIOUSLY TREATED NHL PATIENTS