American Society of Hematology Annual Meeting 2015 Orlando, FL

Non-Core Competitor and Disease-related Data Deck
Medical Affairs
December 5-8, 2015

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Gilead does not encourage the use of medicines outside of their recommended indication per SmPC and healthcare professionals are encouraged to refer to the SmPC.

Idelalisib is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions via www.lareb.nl or Gilead Sciences Netherlands BV Tel: 020-718-3650 Fax: 020-718-3651 e-mail: Benelux.safety@gilead.com

Abbreviations

CLL, Chronic Lymphocytic Leukemia
SCT, Stem Cell Transplant
CR, Complete Response
PR, Partial Response
DoR, Duration of Response
PFS, Progression Free Survival
EFS, Event Free Survival
OS, Overall survival
MRD, Minimal Residual Disease
mo, month
ALC, Absolute Lymphocyte Count
PD, Progressive Disease
CIRS, Cumulative Illness Rating Scale
CrCl, Creatinine Clearance
TLS, Tumor Lysis Syndrome
MCL, Mantle Cell Lymphoma
HTN, Hypertension
SVT, supraventricular Tachycardia
HF, Heart Failure
CAD, Coronary Artery Disease
CV, Cardiovascular
AF: Atrial fibrillation
PAF, paroxysmal atrial fibrillation
CVA, Cerebrovascular Accident
HR, Heart Rate
NOAC, Novel Oral Anticoagulant
CRi, Complete Response, incomplete bone marrow recovery
nPR, Nodular Partial Response
PB, Peripheral Blood
IRC, Independent Review Committee
TEAE, Treatment-Emergent Adverse Events
FLIPI, Follicular Lymphoma International Prognostic Index
WM, Waldenström Macroglobulinemia
IPSSWM, International Prognostic Score System for WM
RPSFT, Rank-Preserving Structural Failure Time
HR, Hazard Ratio
ITT, Intent-to-Treat

BL, Baseline
G-CSF, Granulocyte-Colony Stimulating Factor
AIHA, Autoimmune Hemolytic Anemia
AE, Adverse Event
HSCT, Hematopoietic stem cell transplantation
PD, Progressive Disease
RT, Richter's Transformation
CI, Confidence Interval
AC/AP, Aticoagulant/Antiplatelet
NSAIDS, Non-Steroidal Anti-Inflammatory Drugs
SSRI, Selective Serotonin Reuptake Inhibitor
DC'd, Discontinued
n, number
Δ, Change
IQR, interquartile range
MF, Myelofibrosis
BAT, Best Available Therapy
ERIC, European Research Initiative on CLL
iwCLL, International workgroup on CLL
IGHV, Immunoglobulin heavy chain variable region genes
ET, Essential Thrombocythemia
PV, Polycythemia Vera;
RUX, Ruxolitinib
BID, twice daily
tx, treatment
SVR: Spleen Volume Reduction
ECOG PS, Eastern Cooperative Oncology Group Performance Score
JAK, Janus Kinase
WBC, White Blood Cell
Hgb, Hemoglobin
RBC- TD: Red Blood Cell Transfusion Dependent
TSS, Total Symptom Score
PRO, Patient Reported Outcome
HRQoL, Health Related Quality of Life
DIPSS, Dynamic International Prognostic Scoring System
AML, Acute Myeloid Leukemia
GI, Gastrointestinal
NMSC, Nonmelanoma skin cancer
UTI, Urinary Tract Infection

Favorable Outcomes in CLL Pts with Alternate Kinase Inhibitors Following Ibrutinib or Idelalisib Discontinuation

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Presented at 2015 ASH Annual Meeting; December 5–8, 2015; Orlando, FL, USA.
Oral #719

Study Design & Patient Characteristics

- 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 use standard criteria to define responses 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

Baseline Characteristics	Result (range)	Total (N)
Median age at diagnosis, years	60 (33-89)	178
Median # prior therapies	3.0 (0-11) 8% untreated (n=14)	178
Del17p present (FISH)	34%	155
Del11q present (FISH)	33%	152
p53 mutation present	27%	95
Complex karyotype ≥3	29%	128
ZAP 70 positive CLL	67%	60
IGHV unmutated	69%	49

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Ibrutinib/ Idelalisib Dosing

	Ibrutinib	Idelalisib
Median time from CLL dx to KI start, months	84	81
Median time on KI (range), months	5 (0.25 - 41)	5.5 (5 - 38)
Median starting dose (range)	420 mg daily (140-560 mg) 86% FDA approved dose	150 mg BID (100-150 mg) 69% FDA approved dose
Proportion requiring dose modification	18% (out of n=141)	35% (out of n=34)
Proportion requiring dose interruption	43% (out of n=96)	64% (out of n=33)
KI administered as monotherapy, %	85	20 (mostly paired with anti-CD20)

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Response and Discontinuation to First KI

Best Reported Response to First KI*

Per Investigator	Ibrutinib-based	Idelalisib-based (mostly paired with anti-CD20)
Number with reported response assessment	124/143	34/35
ORR (CR + PR / PR-L)	58%	76%
SD	22%	12%
PD	20%	12%

*Reported responses lower than those reported in clinical trials likely reflects subgroup selected for KI failure

Most common Reasons for KI Discontinuation

	Ibrutinib (%)	Idelalisib (%)
Toxicity	51	52
CLL progression	28	31
Richter's transformation	8	6
SCT/ CAR-T	2	0
Unrelated death or other	11	11

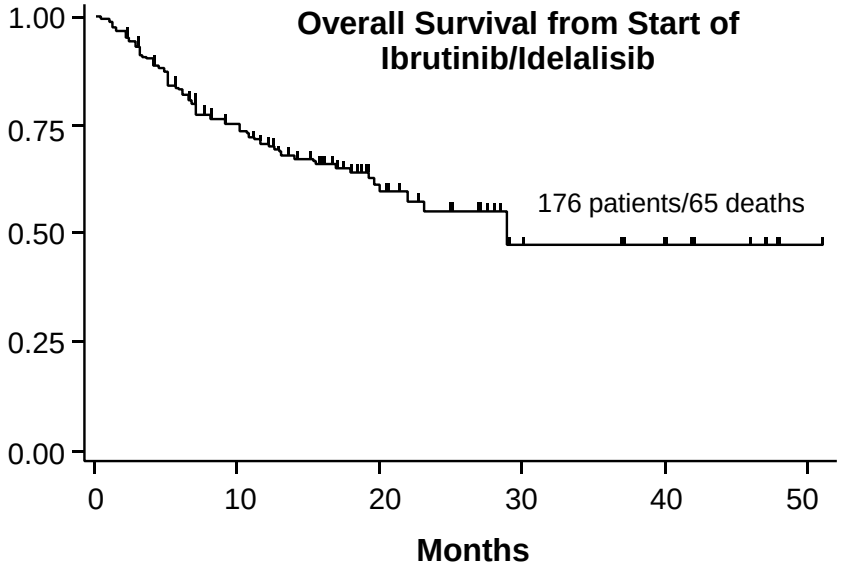
5 Most Common Toxicities as a Reason for Discontinuation

"Kinase Inhibitor Intolerant" patients

Ibrutinib (n=66)	Idelalisib (n=18)
Atrial fibrillation 20%	Pneumonitis 33%
Infection 12 %	Colitis 28%
Hematologic 9%	Rash 17%
Bleeding 9%	Transaminitis 11%
Pneumonitis 8%	Infection 6%

Long-Term Endpoints

- Median PFS from start of first KI (IDL, Ibr) was 10.5 months
- First KI choice did not significantly affect PFS by ibrutinib vs idelalisib (Cox model; HR: 1.2, CI: 0.8-1.8)
  - Median PFS RT = 6 months
  - Median PFS CLL progression = 8 months
  - Median PFS KI intolerance = 10 months
- Median overall survival (OS) from start of Ibrutinib / Idelalisib was 29 months, and initial KI choice did not impact OS
  - HR: 0.8, CI: 0.4-1.5



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Treatment Patterns Following Discontinuation & Reason

Treatment Patterns Following Discontinuation

Treatment Pattern	N (%)
Total Number	-
Idelalisib-based	25 (21.9)
Ibrutinib-based	19 (16.7)
BCL2-i (CT)	16 (14.0)
Other	10 (8.7)
Fludarabine / Bendamustine CIT	9 (7.9)
Anthracycline-based	9 (7.9)
Cellular-based	8 (7.0)
Rituximab	7 (6.1)
Obinutuzumab	5 (4.4)
Syk-i (CT)	2 (1.8)
Ofatumumab	2 (1.8)
IMID-based	2 (1.8)

Treatment Patterns by Discontinuation Reason

	CLL Progression	KI Intolerance	Richter's Transformation
Total Number	37	60	12
Idelalisib-based	9	14	1
Ibrutinib-based	7	12	0
BCL2-i (CT)	10	6	0
Other	3	4	3
CIT	3	6	0
Anthracycline-based	2	1	6
Cellular-based	3	0	2
CD20 Mo Abs	0	13	0
Syk-i (CT)	0	2	0
IMID-based	0	2	0

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%

- Alternate KI choice did not impact PFS from start of alternate kinase inhibitor (combined), where the median PFS was 11.9 months
- Individuals switching KIs because of CLL PD had a median PFS of 7 months where individuals switching because of KI intolerance have not yet met median PFS after 20 months

Author Discussion and 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
- A clinical trial targeting the "KI intolerant" patient population will be undertaken to validate these findings prospectively