NEW EVIDENCE

# Outcomes of patients with CLL after discontinuing idelalisib

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# Background

- CLL is the most common leukemia among adults, with an estimated 14,620 new cases in the U.S. in 2015[1]
- Idelalisib is a first-in-class oral PI3Kδ inhibitor approved for use, in combination with rituximab, in patients with R/R CLL[2,3]
- The objective of this study was to describe the characteristics of patients who discontinued treatment after idelalisib therapy, as well as the causes of discontinuation and outcomes

1. American Cancer Society. Cancer Facts & Figures 2015.
2. Zydelig® (idelalisib) tablets prescribing information. Gilead Sciences, Inc., Foster City, CA. Revised July 2014.
3. Zydelig summary of product characteristics. Gilead Sciences International Ltd, Cambridge, United Kingdom. September 2014.

CLL = chronic lymphocytic leukemia; PI3Kδ = phosphatidylinositol 3-kinase delta; R/R = relapsed/refractory

# Study Design

- The analysis included 37 patients with R/R CLL who participated in five idelalisib combination therapy trials at the North Shore-LIJ Cancer Institute*
- Patients were enrolled from 2011–2014, and data were locked on November 24, 2015
- Patients were evaluated for time to therapy discontinuation and reasons for discontinuation

| Start date | Protocol | Identification number | Regimen | Number of patients randomized to idelalisib/total enrolled | Number of patients who discontinued idelalisib |
|---|---|---|---|---|---|
| March 31, 2011/ March 8, 2012 | CAL 101-07/ CAL 101-99 | NCT01088048 NCT01090414 | Multiple† | 21/21 | 19 |
| May 21, 2012 | GS-US-312-0115 | NCT01569295 | Bendamustine rituximab + idelalisib | 4/6 | 2 |
| March 29, 2012 | GS-US-312-0116 | NCT01539512 | Rituximab + idelalisib | 4/11 | 2 |
| March 29, 2012 | GS-US-312-0117 | NCT01539291 | Idelalisib | 8/8‡ | 6 |
| | | | TOTAL | 37/46 | 29 |

* Data cutoff: November 24, 2015.
† Regimens include bendamustine, rituximab + idelalisib; bendamustine + idelalisib; ofatumumab + idelalisib; fludarabine + idelalisib; rituximab, chlorambucil + idelalisib; and chlorambucil + idelalisib.
‡ Two patients randomized to idelalisib on the GS-US-312-0116 study were rolled over to the GS-US-312-0117 study.

CLL = chronic lymphocytic leukemia; R/R = relapsed/refractory

# Characteristics of Patients who Discontinued Idelalisib

- Most patients had been heavily pretreated prior to idelalisib therapy, and 55% had a high-risk prognostic marker, including del(11q) or del(17p)

| Characterisitc | N = 29 |
|---|---|
| **Median age, years (range)** | 70 (59–84) |
| **Median white blood cell count (range), K/μL** | 48.3 (0.7–305.5) |
| **Rai stage III/IV, %** | 45 |
| **CD38 >30%, %** | 52 |
| **ZAP-70 positive by immunohistochemistry, %** | 59 |
| **β2 M ≥4 mg/L, %** | 79 |
| **IGHV unmutated, %** | 69 |
| **Fluorescence in situ hybridization category, %** | |
| **Del(17p)** | 24 |
| **Del(11q)** | 31 |
| **Del(13q)** | 55 |
| **Complex karyotype, %** | 55 |
| **≥3 prior therapies, %** | 62 |
| **Median number of prior therapies (range)** | 3 (1–11) |
| **Median time from diagnosis to idelalisib, months (range)** | 115 (27–275) |

β2 M = beta-2 microglobulin; CD38 = cluster of differentiation 38; del(11q) = deletion of 11q; del(13q) = deletion of 13q; del(17p) = deletion of 17p; IGHV = immunoglobulin heavy chain variant; ZAP-70 = zeta-chain-associated protein kinase 70

# Outcomes After Idelalisib Discontinuation (n = 29)

| Patient | Duration of idelalisib, months | Cause of discontinuation | Outcome after idelalisib treatment | Survival after idelalisib treatment, months | Survival status |
|---|---|---|---|---|---|
| Progressed but did not transform (n = 8) | | | | | |
| 1 | 19.9 | PD | Ofatumumab, ibrutinib | 8.6 | Deceased |
| 2 | 25.0 | PD | Deceased | 2.9 | Deceased |
| 3 | 0.4 | PD | Deceased | 0.0 | Deceased |
| 4 | 28.5 | PD | Ibrutinib | 8.3 | Deceased |
| 5 | 5.7 | PD | Deceased | 0.6 | Deceased |
| 6 | 28.0 | PD | Ibrutinib, venetoclax | 16.5 | Alive |
| 7 | 12.5 | PD | Deceased | 0.0 | Deceased |
| 8 | 18.2 | PD | Radiation, multiple regimens | 10.1 | Deceased |
| Transformed (n = 1) | | | | | |
| 1 | 5.0 | Richter transformation | Ofatumumab-CHOP | 1.4 | Deceased |

CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; PD = progressive disease

# Outcomes After Idelalisib Discontinuation (n = 29), *cont'd*

| Patient | Duration of idelalisib, months | Cause of discontinuation | Outcome after idelalisib treatment | Survival after idelalisib treatment, months | Survival status |
|---|---|---|---|---|---|
| Discontinued because of colitis (n = 9) | | | | | |
| 1 | 7.7 | Colitis | Deceased* | 37.1 | Alive* |
| 2 | 19.1 | Colitis | No further treatment | 10.5 | Alive |
| 3 | 15.1 | Colitis | No further treatment | 18.9 | Alive |
| 4 | 19.2 | Colitis | Bendamustine + rituximab | 4.5 | Deceased |
| 5 | 8.5 | Colitis | Richter transformation 484 days after stopping idelalisib; treated with spine radiation, ibrutinib | 20.3 | Deceased |
| 6 | 12.2 | Colitis | Ibrutinib | 32.1 | Alive |
| 7 | 18.7 | Colitis | No further treatment | 36.9 | Alive |
| 8 | 17.6 | Colitis | Deceased | 0.7 | Deceased |
| 9 | 1.7 | Colitis | Multiple regimens | 39.6 | Alive |
| Discontinued because of pneumonitis (n = 4) | | | | | |
| 1 | 4.5 | Pneumonitis | Obinutuzumab, ibrutinib | 35.6 | Alive |
| 2 | 16.3 | Pneumonitis | Radiation, ibrutinib | 25.6 | Alive |
| 3 | 8.1 | Pneumonitis | Ibrutinib | 19.4 | Alive |
| 4 | 4.7 | Pneumonitis | Deceased | 4.0 | Deceased |

* As displayed in the ASH 2015 poster presentation.

# Outcomes After Idelalisib Discontinuation (n = 29), *cont'd*

| Patient | Duration of idelalisib, months | Cause of discontinuation | Outcome after idelalisib treatment | Survival after idelalisib treatment, months | Survival status |
|---|---|---|---|---|---|
| Discontinued because of transaminitis (n = 1) | | | | | |
| 1 | 2.1 | Transaminitis | Ofatumumab, ibrutinib | 50.1 | Alive |
| Discontinued because of other reasons (n = 6) | | | | | |
| 1 | 35.4 | COPD | Deceased | 8.9 | Deceased |
| 2 | 9.0 | AIHA, sepsis | Deceased | 0.5 | Deceased |
| 3 | 5.7 | Aplastic anemia | Deceased | 1.0 | Deceased |
| 4 | 23.4 | PML | Deceased | 0.4 | Deceased |
| 5 | 10.0 | Too many CTs | Ibrutinib | 11.6 | Deceased |
| 6 | 5.9 | Too many CTs | Obinutuzumab, ibrutinib | 35.6 | Alive |

AIHA = autoimmune hemolytic anemia; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; COPD = chronic obstructive pulmonary disease; CT = computed tomography; PML = progressive multifocal leukoencephalopathy

# Reasons for and Outcomes After Idelalisib Discontinuation

- Twenty-one patients with R/R CLL participated in the phase Ib trial of idelalisib as combination therapy
  - The trial was designed to last 48 weeks, and patients were allowed to continue on an extension trial with idelalisib if it still derived benefit
  - Patients were on therapy for a median of 335 days; 42% (n = 11/21) continued in the extension trial
  - Of the patients on the extension trial, the median time on drug was 412 days
  - For the two patients that remained in the study at the time of this presentation, the median time on therapy was 1,006 days without evidence of toxicities

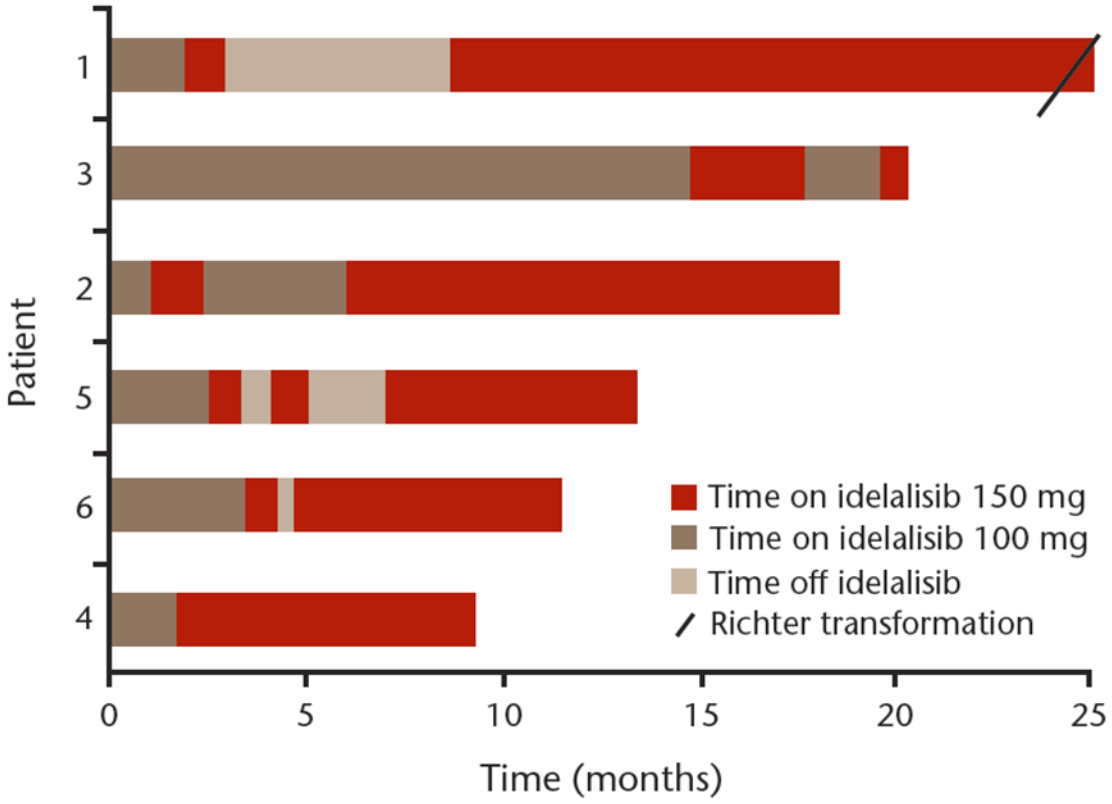
CLL = chronic lymphocytic leukemia; R/R = relapsed/refractory

# Reasons for and Outcomes After Idelalisib Discontinuation *(cont'd)*

- Of the 17 patients who participated in placebo-controlled phase III studies, 11 received rituximab with or without idelalisib (Study 116) and six received BR with or without idelalisib (Study 115)
  - Study 116 was unblinded; 35% of patients (n = 4/11) received idelalisib plus rituximab upfront
    - Two of the four patients (50%) continued on the extension study (GS-0117); one patient was still in the study at day 1,279
    - A total of 86% (n = 6/7) of the remaining patients who were randomized to the placebo crossed over to idelalisib in the extension study at the time of confirmed progression
  - Study 115 was unblinded during the trial; six patients were enrolled, four of whom had received idelalisib plus BR upfront
    - Two of the four patients (50%) are still continuing in the study

BR = bendamustine plus rituximab

# Outcomes of Idelalisib Rechallenge in Six Patients with Colitis




- None of the patients with severe diarrhea/colitis were able to maintain lower doses of idelalisib for a prolonged period without recurrent colitis or the development of pneumonitis
- Immunohistochemistry results showed that all samples tested positive for CD4 and negative for CD8, natural killer cells, and macrophages

CD = cluster of differentiation

# Overall Survival

- Since the start of these trials, 49% of patients have died; the overall survival after discontinuation varies widely (0–1,503 days, with a median of 303 days)
    - Most patients with R/R CLL who discontinued idelalisib early were difficult to treat and had poor outcomes
- The rate of Richter transformation was extremely low in this study (2.7%)

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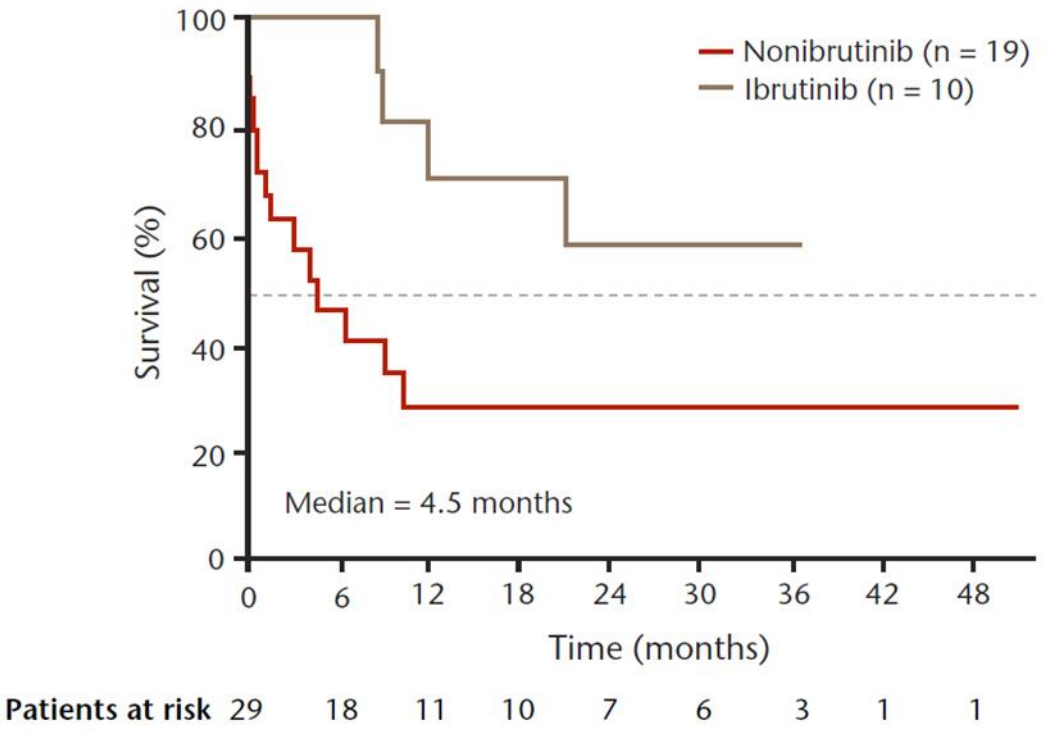
# Survival of Patients With and Without Ibrutinib Salvage Therapy




- Over the course of the trials, ibrutinib was approved and used as salvage therapy in 10 patients with confirmed progression
  - Except for one patient, all patients successfully achieved a prolonged response with ibrutinib
  - This suggests salvage therapy with a targeted agent may be a reasonable therapeutic approach for patients after idelalisib failure

# Summary and Conclusion

- This single-institution experience with idelalisib identified baseline factors associated with therapy discontinuation
    - Grade 3/4 diarrhea/colitis and progression of disease were the main reasons for discontinuation from therapy
- The data suggest that ibrutinib may be a reasonable choice in patients after idelalisib failure