HOT NEWS

# NELLE SINDROMI LINFOPROLIFERATIVE:
## la storia continua

## CASI CLINICI
## La leucemia linfatica cronica

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ROMA

19 Settembre 2023
UNAHOTELS Decò

# Disclosures of Name Surname

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| BEIGENE | | | | | | x | |
| ASTRAZENECA | | | | | | x | |
| JANSSEN | | | | | x | | |
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| | | | | | | | |

♂ 70 yrs

**COMORBIDITIES:**

- Hypertension
- Hypercholesterolaemia
- Gastric ulcer in treatment with PPI

**APRIL 2023** →

| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 11 g/dl | **105 500/mmc** | 1800/mmc | **92 030/mmc** | **62 000/mmc** |

**Flow cytometry**: CD5, CD19, dim CD20, dim CD22, CD23, bright CD43, dim CD45, dim to negative CD79b, dim CD81, CD200, and dim monoclonal surface immunoglobulin.

**APRIL 2023**

- **ABDOMEN ULTRASOUND:** spleen bp dm 21 cm
- **LYMPH NODES ULTRASOUND:** paracaval-, periaortic- and bilateral peri-iliac lymph node dm max 6 cm

Stage Binet C - Rai IV

**TREATMENT REQUIRED**

**Table 1. Staging systems for CLL**

| Stage | | Definition |
|---|---|---|
| **Binet system** | | |
| Binet A | | Hb ≥100 g/l (6.21 mmol/l), platelets ≥100 × $10^9$/l <3 involved lymphoid sites[a] |
| Binet B | | Hb ≥100 g/l (6.21 mmol/l), platelets ≥100 × $10^9$/l ≥3 involved lymphoid sites[a] |
| Binet C | | Hb <100 g/l (6.21 mmol/l), platelets <100 × $10^9$/l |
| **Rai system** | | |
| Low-risk | Rai 0 | Lymphocytosis >5 × $10^9$/l |
| Intermediate-risk | Rai I | Lymphocytosis and lymphadenopathy |
| | Rai II | Lymphocytosis and hepatomegaly and/or splenomegaly with/without lymphadenopathy |
| High-risk | Rai III | Lymphocytosis and Hb <110 g/l (6.83 mmol/l) with/without lymphadenopathy/organomegaly |
| | Rai IV | Lymphocytosis and platelets <100 × $10^9$/l with/without lymphadenopathy/organomegaly |

Hallek M, Al-Sawaf O.. Am J Hematol. 2021 Dec 1;96(12):1679-1705.

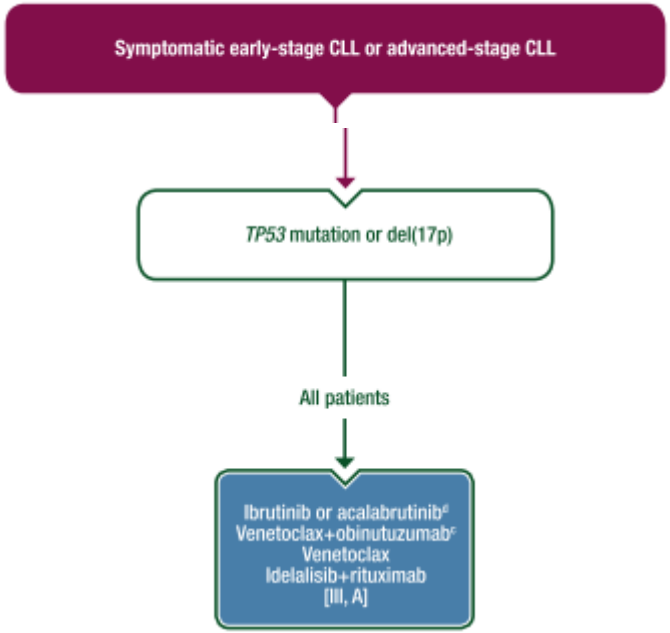
**APRIL 2023**

## BIOLOGICAL PROGNOSTIC FACTORS

- **IGVH STATUS**: unmutated
- **FISH:** del 17p
- **TP53:** mutated

→ **RISK CATEGORY UNFAVORABLE**

# GUIDELINES




**SUGGESTED TREATMENT REGIMENS[a,b,c,d]**
**CLL/SLL with del(17p)/*TP53* mutation**
**(alphabetical by category)**
**Chemoimmunotherapy is not recommended since del(17p)/*TP53* mutation is associated with low response rates.**

**FIRST-LINE THERAPY[e]**

| Preferred regimens | Other recommended regimens |
|---|---|
| • Acalabrutinib[f] ± obinutuzumab | • Alemtuzumab[r] ± rituximab |
| • Ibrutinib[f] | • HDMP + rituximab |
| • Venetoclax[f,g] + obinutuzumab | • Obinutuzumab |
| • Zanubrutinib[f] | |

**SECOND-LINE AND SUBSEQUENT THERAPY[e]**

| Preferred regimens | Other recommended regimens |
|---|---|
| • Acalabrutinib[f,n] (category 1) | • Alemtuzumab[r] ± rituximab |
| • Ibrutinib[f] (category 1) | • Duvelisib[f] |
| • Venetoclax[f,g] + rituximab (category 1) | • HDMP + rituximab |
| • Venetoclax[f,g] | • Idelalisib[f] ± rituximab[o] |
| • Zanubrutinib[f,n] | • Lenalidomide[p] ± rituximab |
| | • Ofatumumab[q,s] |

B. Eichhorst, Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, 2020

NCCN Guidelines® Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022

**MAY 2023**

# START IBRUTINIB

**w1**

| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 11.7 g/dl | 190.500/mmc | 1.600/mmc | 104.030/mmc | 70.000/mmc |

**w3**

| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 11.8 g/dl | 255.000/mmc | 6.500/mmc | 239.000/mmc | 79.000/mmc |

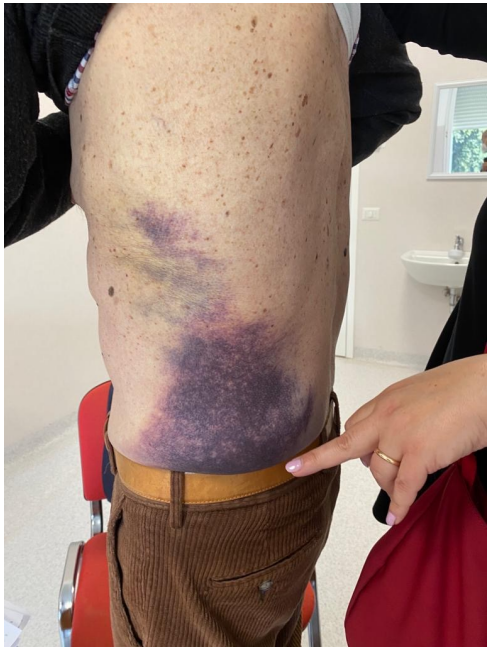
**w5**

| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 12.1 g/dl | 200.000/mmc | 7.200/mmc | 184.000/mmc | 88.000/mmc |

**JUNE 2023**

**w8**

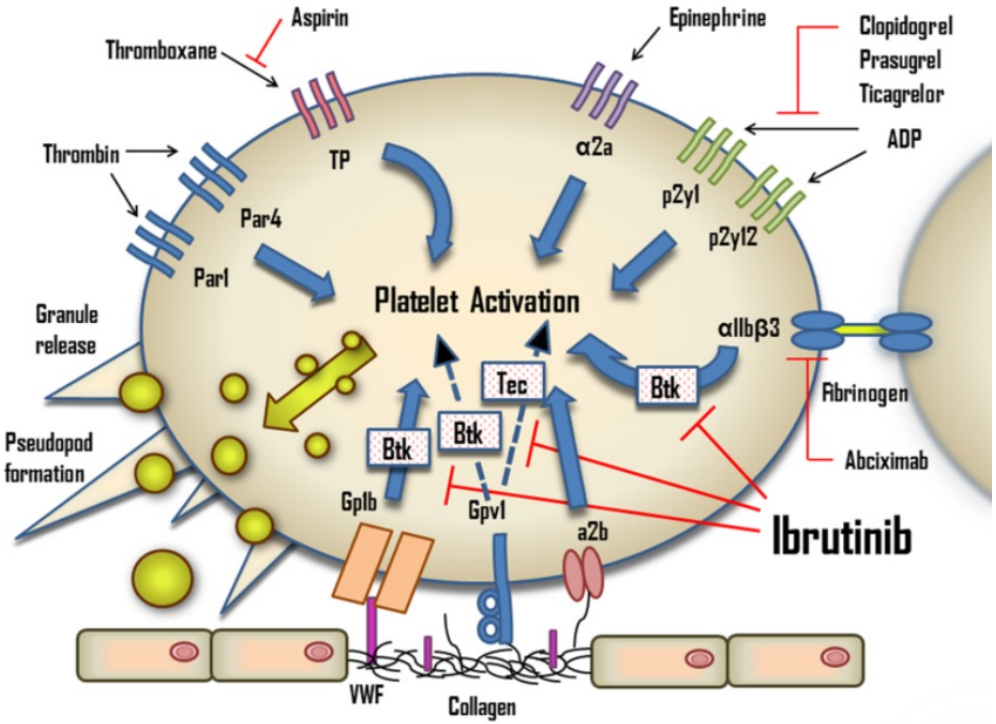
| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 7.8 g/dl | 151.000/mmc | 8.000/mmc | 137.000/mmc | 89.000/mmc |



**OCCURRENCE OF SPONTANEOUS SKIN HEMATOMA IN THE HIP REGION**
**GRADE 3**

**TEMPORARY IBRUTINIB WITHDRAWAL (15 DAYS)**
**SUPPORTIVE CARE - TRANSFUSION**

# PATHOPHYSIOLOGY OF IBRUTINIB-ASSOCIATED BLEEDING

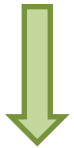



Shatzel JJ, et al. J Thromb Haemost. 2017

**JULY 2023**

**w10**

**RESOLUTION OF SKIN HAEMATOMA**



**RE-START IBRUTINIB AT DOSE OF 280 MG**

## AUGUST 2023

### w13

| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 7.9 g/dl | 90.000/mmc | 4.000/mmc | 68.000/mmc | 92.000/mmc |

**2° EPISODE OF SPONTANEOUS SKIN HEMATOMA IN THE HIP REGION**
**GRADE 3**

- **DEFINITIVE IBRUTINIB WITHDRAWAL**
- **SUPPORTIVE CARE - TRANSFUSION**

# DATA FROM CLINICAL TRIALS

- The **majority** of reported bleeding events are low grade (Grade I-II).
- The most common bleeding phenotypes are **subcutaneous or mucosal bleeding**, including contusions, epistaxis, petechial bleeding, hematuria or ecchymosis.
- **Major hemorrhage** (Grade III-IV) has been reported with rates varying **from 4% to 8%** in trials that followed patients for over a year with fatal hemorrhage occurring in less than 1% of patients (0.6–0.7%).
- Subdural hematoma is the most commonly reported form of central nervous system bleeding, though hemorrhagic conversion of ischemic stroke, subarachnoid hemorrhage after a fall and vitreous hemorrhage have also been reported.

| Trial | Phase | Comparison | Median follow up | Any bleeding (%) | Grade 1–2 hemorrhage (%) | Major hemorrhage Grade III-IV (%) | Fatal hemorrhage (%) |
|---|---|---|---|---|---|---|---|
| Chanan-Kahn, Lancet 2016 | Phase III | Ibrutinib R-Benda (n=287) Vs. R-Benda (N=287), CLL | 17 mo | 31% vs 15% | 28% vs 9% | 4% vs. 2% | 0.6% vs 0 |
| Burger, NEJM 2015 | Phase III | Ibrutinb (N=136 )Vs. Chlorambacil (N=133), CLL | 18.4 mo | Not Reported | Not Reported | 4% vs. 2% | 0 vs 0 |
| Byrd, NEJM 2014 | Phase III | Ibrutinib (N=195) Vs. Ofatumumab (N= 196), CLL | 9.4 mo | 44% vs 12% | 27% vs 10% | 1% vs 2% | 0 vs 0 |
| Dreyling, Lancet 2016 | Phase III | Ibrutinib (N=139) Vs. temsirolimus (N= 141), MCL | 20 mo | Not Reported | Not Reported | 10%vs 6% | 0 vs 0 |
| Byrd, Blood 2015 | Phase II | Ibrutinib (N=132) CLL | 36 mo | 61% | 53% | 8% | 0.7%(1) |
| Wang, Blood 2015 | Phase II | Ibrutinib (N= 111 ) MCL | 26.7 mo | 50% | 44% | 6% | 0 |

Shatzel JJ, et al. J Thromb Haemost. 2017

# WHAT TO DO NEXT?

- WATCH AND WAIT
- EARLY DISEASE EVALUATION

- HIGH BURDEN OF DISEASE
- UNFAVORABLE FISH

**SEPTEMBER 2023**

# RE-EVALUATION

| Hb | WBC | Ne | Ly | PLT |
|---|---|---|---|---|
| 10.2 g/dl | **111.000/mmc** | 5.000/mmc | **75.000/mmc** | **82.000/mmc** |

- **ABDOMEN ULTRASOUND:** spleen bp dm 18 cm
- **LYMPH NODES ULTRASOUND:** paracaval-, periaortic- and bilateral peri-iliac lymph node dm max 5,5 cm

**SUGGESTED TREATMENT REGIMENS[a,b,c,d]**
**CLL/SLL with del(17p)/*TP53* mutation**
**(alphabetical by category)**
**CIT is not recommended since del(17p)/*TP53* mutation is associated with low response rates.**

| FIRST-LINE THERAPY[e] | |
|---|---|
| **Preferred regimens** | **Other recommended regimens** |
| • Acalabrutinib[f,*] ± obinutuzumab<br>• Venetoclax[f,g] + obinutuzumab<br>• Zanubrutinib[f,*] | • Alemtuzumab[t] ± rituximab<br>• HDMP + rituximab<br>• Ibrutinib[f,h,*]<br>• Obinutuzumab<br>• Ibrutinib[*] + venetoclax[f,g] (category 2B) |

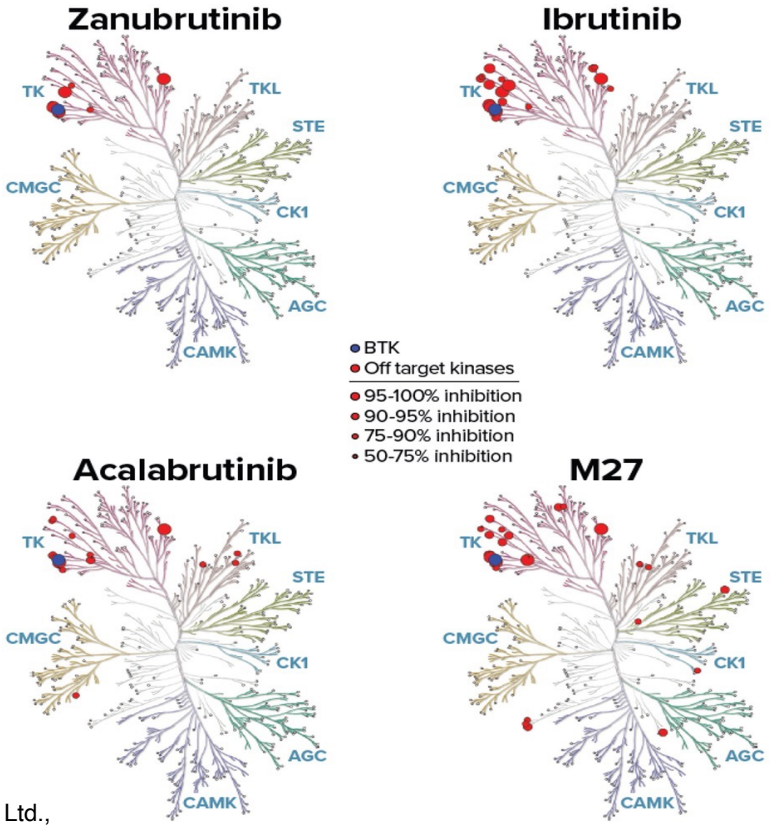
**Zanubrutinib is approved by FDA since January 2023 and it is available for compassionate use in Italy**

NCCN Guidelines® Insights: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 3.2022

# BGB-3111-215 – UPDATED ANALYSIS

**Zanubrutinib** showed better selectivity than Ibrutinib and Acalabrutinib and its metabolite M27

**Zanubrutinib** has a favourable tolerability profile in patients previously intolerant to ibrutinib and/or acalabrutinib




Reprinted from Shadman M, et al. Lancet Haematol. 2023;10(1):e35-e45. Copyright © 2022 Elsevier Ltd.,
1. Burger JA. Cancer J. 2019;25(6):386-393. 2. Stephens DM, Byrd JC. Blood. 2019;133(12):1298-1307. 3. Guo Y, et al. J Med Chem. 2019;62(17):7923-7940. 4. Shadman M, et al. Lancet Haematol. 2023;10(1):e35-e45. 5. Shadman M, et al. Blood. 2021;138(suppl 1):1410-1413..
Shadman M et al. Poster presented at EHA 2023; abstract number: P683

# Trial Design

## BGB-3111-215

**PHASE 2**

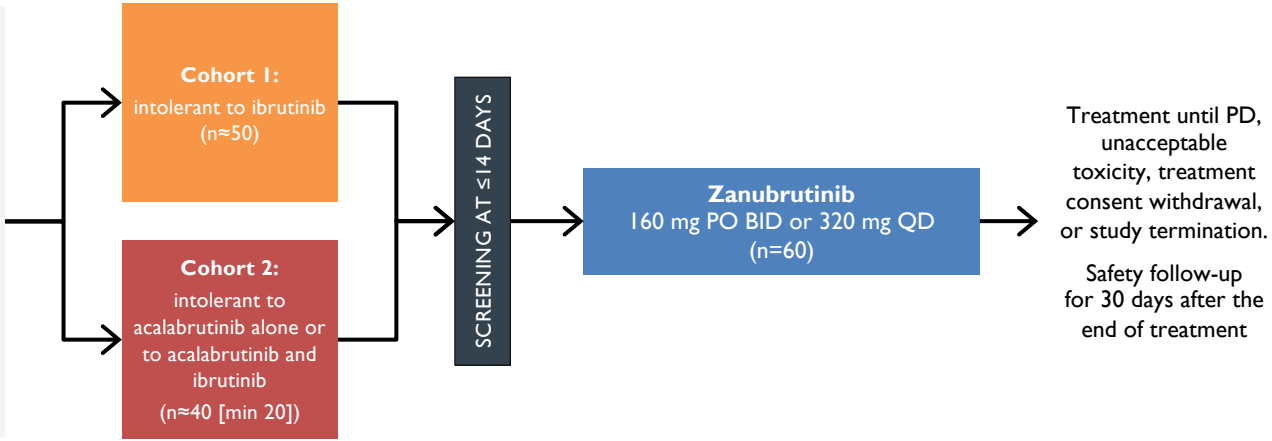
**Study Identifier:** BGB-3111-215, NCT04116437

**Primary Endpoint:** Investigator-assessed recurrence and change in severity of ibrutinib or acalabrutinib intolerance events*
**Key Secondary Endpoints:** ORR, DoR, PFS and HRQoL

### KEY ELIGIBILITY CRITERIA

- Previously treated CLL/SLL, WM, MCL or MZL patient intolerant of ibrutinib and/or acalabrutinib†
- ≥18 years old
- Indication for treatment per iwCLL prior to ibrutinib
- Ibrutinib- and/or acalabrutinib intolerant in opinion of investigator‡
- Ibrutinib- and/or acalabrutinib-related toxicities resolved to Gr ≤1 or baseline
- ECOG PS ≤2
- ANC ≥1000/mm$^3$ and platelet count ≥50,000/mm$^3$
- No documented PD during ibrutinib and/or acalabrutinib treatment§
- No clinically significant cardiovascular disease

### TREATMENT

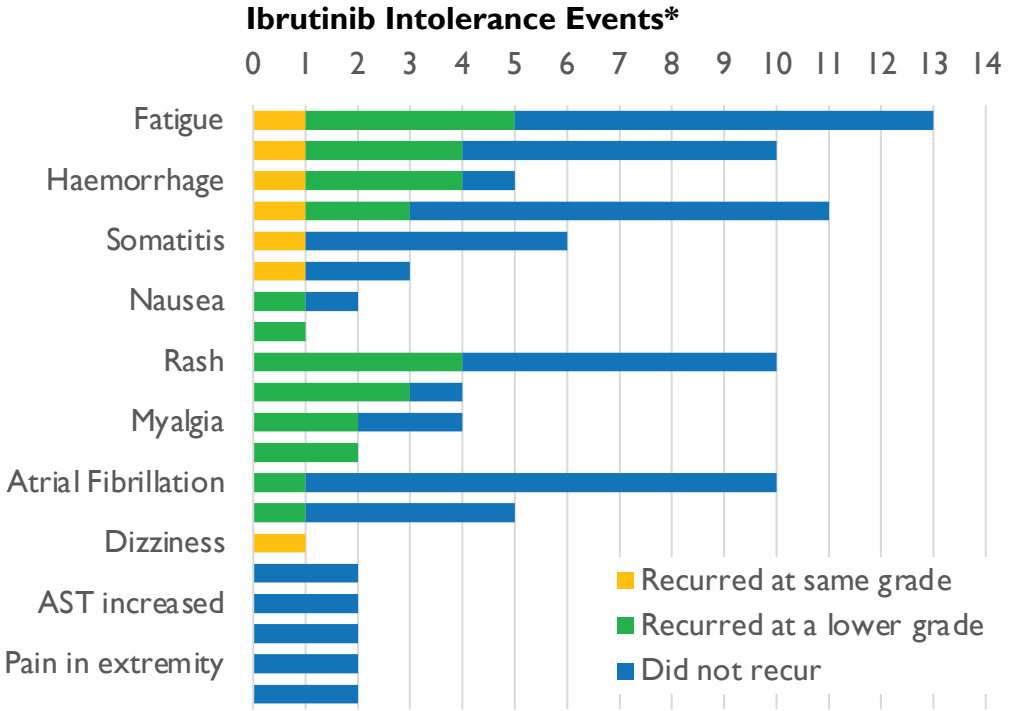



*TEAEs of interest: arthralgia, atrial fibrillation, diarrhea, fatigue, hemorrhage, hypertension, muscle spasms, myalgia, rash. †There is a ≥7-day washout period for any anticancer therapy and a ≥4-week washout period for immunotherapy, taken alone or as part of a chemoimmunotherapy regimen. ‡Intolerance is defined as an unacceptable toxicity where, in the opinion of the investigator, treatment should be discontinued in spite of optimal supportive care as a result of: Grade ≥2 non-hematologic toxicities for >7 days; Grade ≥3 non-hematologic toxicity of any duration; Grade 3 neutropenia with infection or fever; or Grade 4 hematologic toxicity that persists until ibrutinib therapy is discontinued due to toxicity NOT until progression. §A disease flare meeting PD criteria while the patient is off ibrutinib and/or acalabrutinib treatment is not considered to be true PD
ANC=absolute neutrophil count, BID=twice daily, BTKi=Bruton tyrosine kinase inhibitor, CLL=chronic lymphocytic leukemia, DoR=duration of response, ECOG PS=Eastern Cooperative Oncology Group performance status, Gr=grade, HRQoL=health-related quality of life, iwCLL=International Workshop on CLL, MCL=mantle cell lymphoma, MZL=marginal zone lymphoma, ORR=overall response rate, PD=progressive disease, PFS=progression-free survival, PO=per oral, QD=once daily, SLL=small lymphocytic lymphoma, TEAE=treatment-emergent adverse event, WM=Waldenström's macroglobulinemia.

1. Shadman M et al. Lancet Haematology. 2023. 10(1):e35-e45This study is registered at ClinicalTrials.gov (NCT04116437).

# Recurrence and Change in Severity of Ibrutinib Intolerance Events During Treatment with Zanubrutinib

## BGB-3111-215




- Most (37 [60%]) ibrutinib treated patients (in either cohort) did not have a recurrence of their ibrutinib intolerance event
  - 70% of intolerance events (81/115) did not recur
  - 30% intolerance events (34/115) recurred
    - None recurred at a higher severity
    - Most (27 [79%]) events recurred at a lower severity
    - Most (12 [92%]) grade 3 events recurred at a lower severity and no grade 4 events recurred
- Median time to first recurrence of an ibrutinib intolerance event was 61 days (IQR 21–106)
- 6 patients who experienced an ibrutinib intolerance event discontinued zanubrutinib
  - No recurrent ibrutinib intolerance event resulted in treatment discontinuation

Shadman M et al. Lancet Haematology. 2023. 10(1):e35-e45

# Investigator-Assessed Responses in Patients with >90 days follow-up

## BGB-3111-215

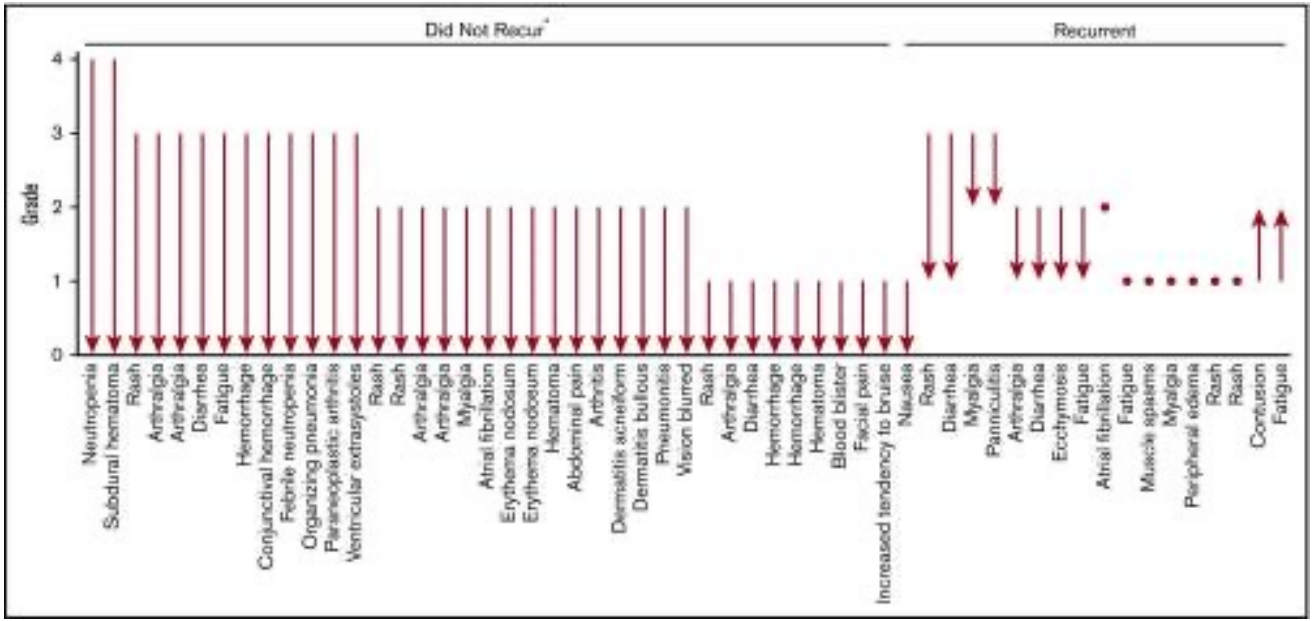
- Among 64 efficacy-evaluable patients:
  - 60 (93.8%;95% CI 84.8–98.3) had disease control
  - 41 (64.1%; 51.1–75.7) had an overall response
- Median time to first response (better than SD) was 3.0 months (IQR 2.8–5.7)
- Median DoR was not reached
  - 12-month event-free duration of response rate was 95.0% (95% CI 69.5–99.3)
- Median PFS was not reached
  - 18-month PFS was 83.8% (95% CI 62.6–93.6)

| | Cohort 1 Ibrutinib intolerance (n=57) | Cohort 2 Acalabrutinib or acalabrutinib & ibrutinib intolerance (n=7) | Total (n=64) |
|---|---|---|---|
| DCR (SD or better) | 54 (94.7% [85.4–98.9]) | 6 (85.7% [42.1–99.6]) | 60 (93.8% [84.8–98.3]) |
| ORR (better than SD) | 36 (63.2% [49.3–75.6]) | 5 (71.4% [29.0–96.3]) | 41 (64.1% [51.1–75.7]) |
| BOR rate | | | |
| PR-L or better* | 36 (63%) | 5 (71%) | 41 (64%) |
| SD | 18 (32%) | 1 (14%) | 19 (30%) |
| PD | 1 (2%) | 1 (14%) | 2 (3%) |
| Not done | 2 (4%)† | 0 | 2 (3%) |
| Months to BOR‡ | 5.5 (2.8–8.3) | 7.9 (5.9–8.4) | 5.6 (2.8–8.3) |
| Months to first overall response | 2.9 (2.7–5.6) | 3.0 (2.9–7.9) | 3.0 (2.6–11.1) |

Shadman M et al. Lancet Haematology. 2023. 10(1):e35-e45

# Acalabrutinib monotherapy in patients with chronic lymphocytic leukemia who are intolerant to ibrutinib

blood advances




Of the 10 bleeding events that occurred during ibrutinib treatment and resulted in intolerance, 2 (contusion and ecchymosis) recurred during acalabrutinib treatment.

Awan FT et al. Blood Adv 2019

# Richiesta autorizzazione uso compassionevole per Zaunbrutinb