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First-in-human study of asciminib monotherapy in adults with relapsed/refractory Philadelphia-positive acute lymphoblastic leukemia

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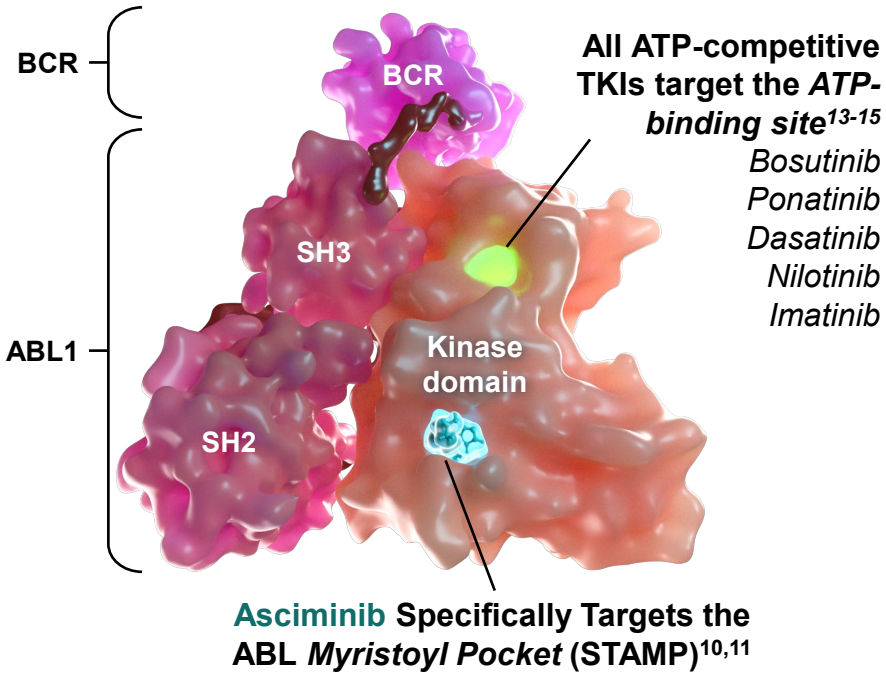
This study is sponsored by Novartis Pharma AG. For more information, please refer to https://clinicaltrials.gov/study/NCT02081378

Oral presentation at: EHA2025 Congress; June 12-15, 2025; Milan, Italy.

The first-in-human study of asciminib monotherapy addresses a critical unmet need in heavily pretreated patients with R/R Ph+ ALL

- Overall survival (OS) in patients with Ph+ ALL has improved with the approval of chemotherapy or blinatumomab in combination with ATP-competitive TKIs and allogeneic stem cell transplantation resulting in 5-year OS rates up to 71%[1-5]
- Approximately 43% of patients experience relapse, most commonly due to BCR::ABL1 KD point mutations (e.g., T315I);[2,6-8] patients with TKI resistance may have limited treatment options and poor outcomes[2,9]
- There is an unmet need for efficacious treatment options with favorable safety and tolerability for patients with R/R Ph+ ALL
- This analysis of asciminib monotherapy in patients with R/R Ph+ ALL was done in a small subgroup within the last cohort of the first-in-human phase 1 study (NCT02081378) conducted from 2014 to 2023[a]

Asciminib: designed to improve efficacy and reduce off-target effects vs current ATP-competitive TKIs[10-12]



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We present primary and secondary endpoint results from patients with R/R Ph+ ALL, the final cohort to report in the phase 1 asciminib monotherapy trial

ATP, adenosine triphosphate; ALL, acute lymphoblastic leukemia; KD, kinase domain; Ph+, Philadelphia chromosome positive; R/R, relapsed/refractory; TKI, tyrosine kinase inhibitor.

[a] The study initiation date (first patient first visit) was April 24, 2014, and the completion date (last patient last visit) was March 14, 2023.

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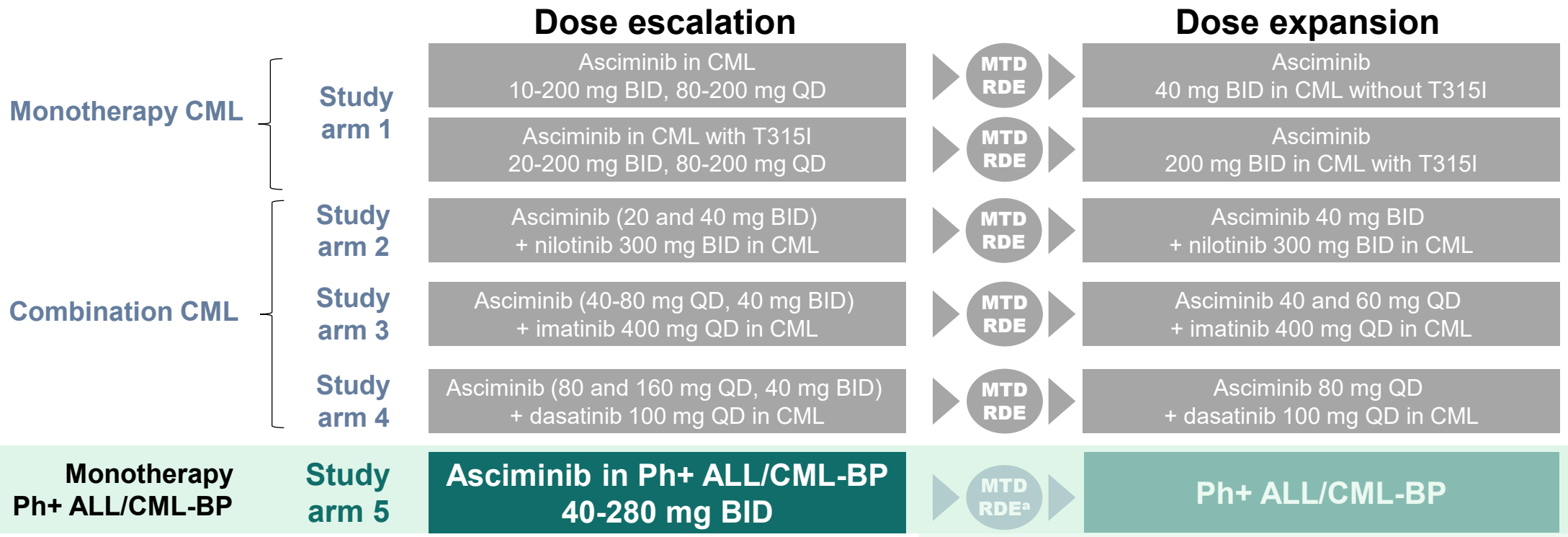
Study arm 5 included patients with R/R Ph+ ALL treated with ≥1 prior TKI, and included patients with relapse posttransplant



Primary objective	•	Determine MTD and/or RDE
Select secondary objective	•	Assess safety and tolerability, and anti-Ph+ ALL activity of asciminib monotherapy

From Hughes TP, et al. *New Engl J Med.* 2019;381(24):2315-2326. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.
AP, accelerated phase; BID, twice daily; BP, blast phase; CML, chronic myeloid leukemia; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; QD, once daily; RDE, recommended dose for expansion.
[a] The MTD was not reached; based on 2 DLTs observed with 280 mg BID, an enrichment cohort at 200 mg BID was opened. No further dose levels were assessed and RDE has not been determined.

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Most patients with Ph+ ALL were heavily pretreated at baseline

Variable	Ph+ ALL (n=28)
Age, median (range), years	60 (31-77)
Age category, n (%)	
18 to <65 years	16 (57.1)
≥65 to <75 years	8 (28.6)
≥75 years	4 (14.3)
Male, n (%)	16 (57.1)
ECOG performance status, n (%)	
0 to 1	25 (89.3)
≥2	3 (10.7)
Prior TKIs, n (%)	
1	3 (10.7)
2	13 (46.4)
≥3	12 (42.9)
Prior ponatinib, n (%)	15 (53.6)
Prior HSCT, n (%)	13 (46.4)
Bone marrow blasts at screening, median (range) %	4 (0-92)
***BCR::ABL1* transcript, n (%)**	
Atypical/*p190*/Unknown[a]	23 (82.1)
p210	5 (17.9)
Mutations at screening, n[b]	
Isolated T315I	5
Isolated Y253H	1
Compound mutations[c]	3

ECOG, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplant.
[a] A total of 15 patients had a *p190* transcript and 8 had unknown transcripts. [b] Twenty patients had mutational analysis at screening, 9 of whom had detectable mutations. [c] Compound mutations were Y253H/T315I, Y253H/F317L, and Q252H/T315I.

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Patient disposition at the end of study

Patients, n (%)	Ph+ ALL (n=28)
Primary reason for end of treatment	
Adverse event	4 (14.3)
Death	2 (7.1)
Physician decision	6 (21.4)
Progressive disease	13 (46.4)
Patient/guardian decision	3 (10.7)

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Progressive disease	13 (46.4)
Patient/guardian decision	3 (10.7)

- Among the 6 patients who discontinued treatment based on physician decision:
  - Two patients enrolled in the asciminib rollover study
  - One patient each discontinued to undergo HSCT, receive alternative therapy, and due to experiencing molecular progression with suspected chloroma, and having refractory disease

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Patient disposition at the end of study

Patients, n (%)	Ph+ ALL (n=28)
Primary reason for end of treatment	
Adverse event	4 (14.3)
Death	2 (7.1)
Physician decision	6 (21.4)
Progressive disease	13 (46.4)
Patient/guardian decision	3 (10.7)

- Among the 3 patients who discontinued treatment based on patient/guardian decision:
  - One patient started treatment with dasatinib and had a protocol deviation
  - One patient transitioned to palliative care
  - One patient with persistent disease changed to alternative therapy

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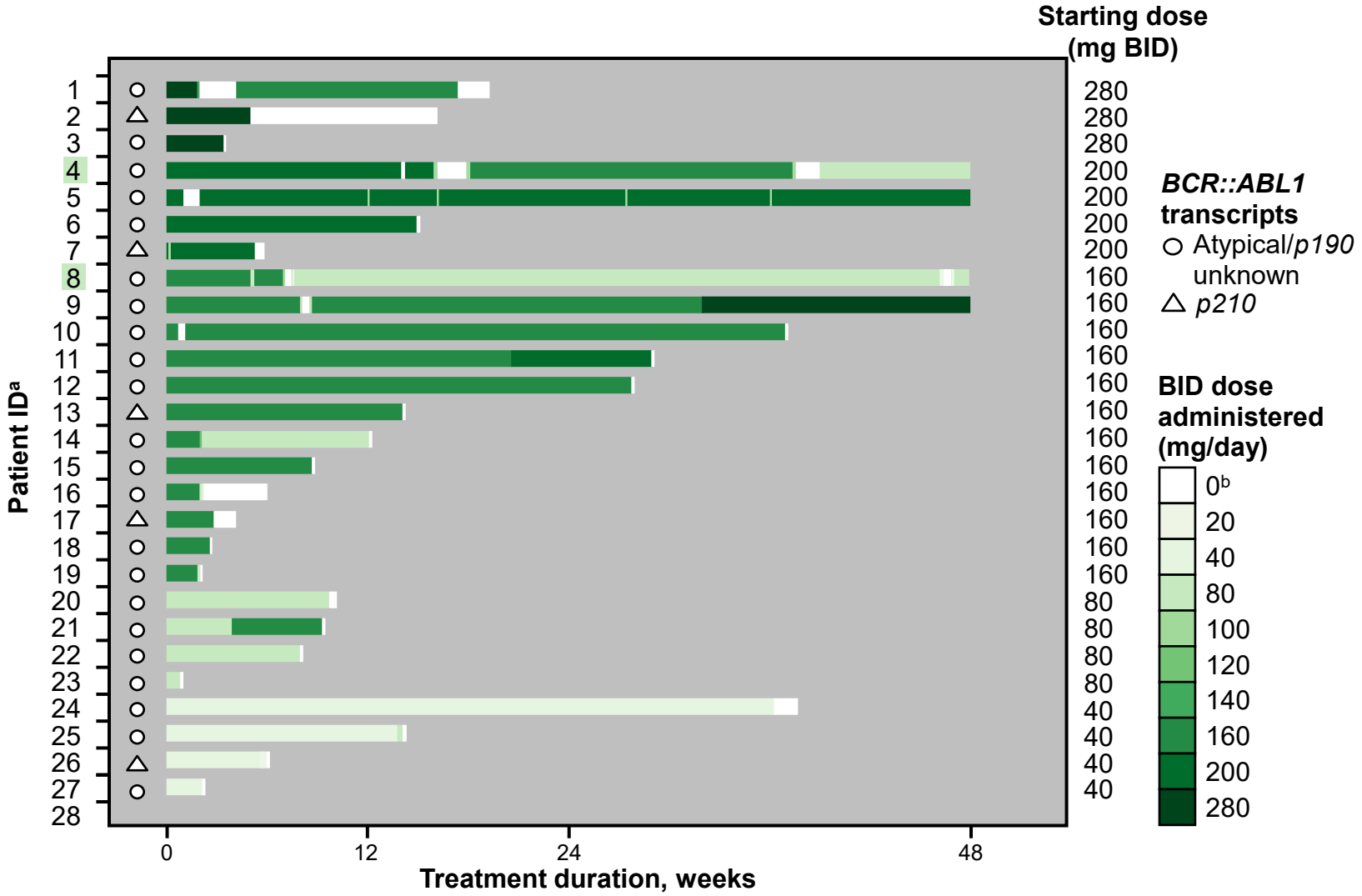
Doses of asciminib up to 280 mg BID were assessed



- A total of 3 patients had DLTs in the first 28 days
  - Asciminib 160 mg BID: 1 patient experienced grade 4 increased lipase and grade 2 pancreatitis
  - Asciminib 280 mg BID: 1 patient had grade 4 increased ALT, grade 4 increased AST, and grade 4 increased GGT, and 1 patient had grade 3 cerebrovascular accident
- RDE was not determined, and a dose expansion cohort was not opened for enrollment

ALT, alanine aminotransferase; AP, accelerated phase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.
[a] Patient 28 received asciminib 160 mg BID for 19 days before discontinuing treatment and is not shown here. Green highlighted patient numbers indicate patients who continued to receive asciminib monotherapy in rollover studies after the end of study. [b] White spaces indicate a dose interruption of ≥1 day.

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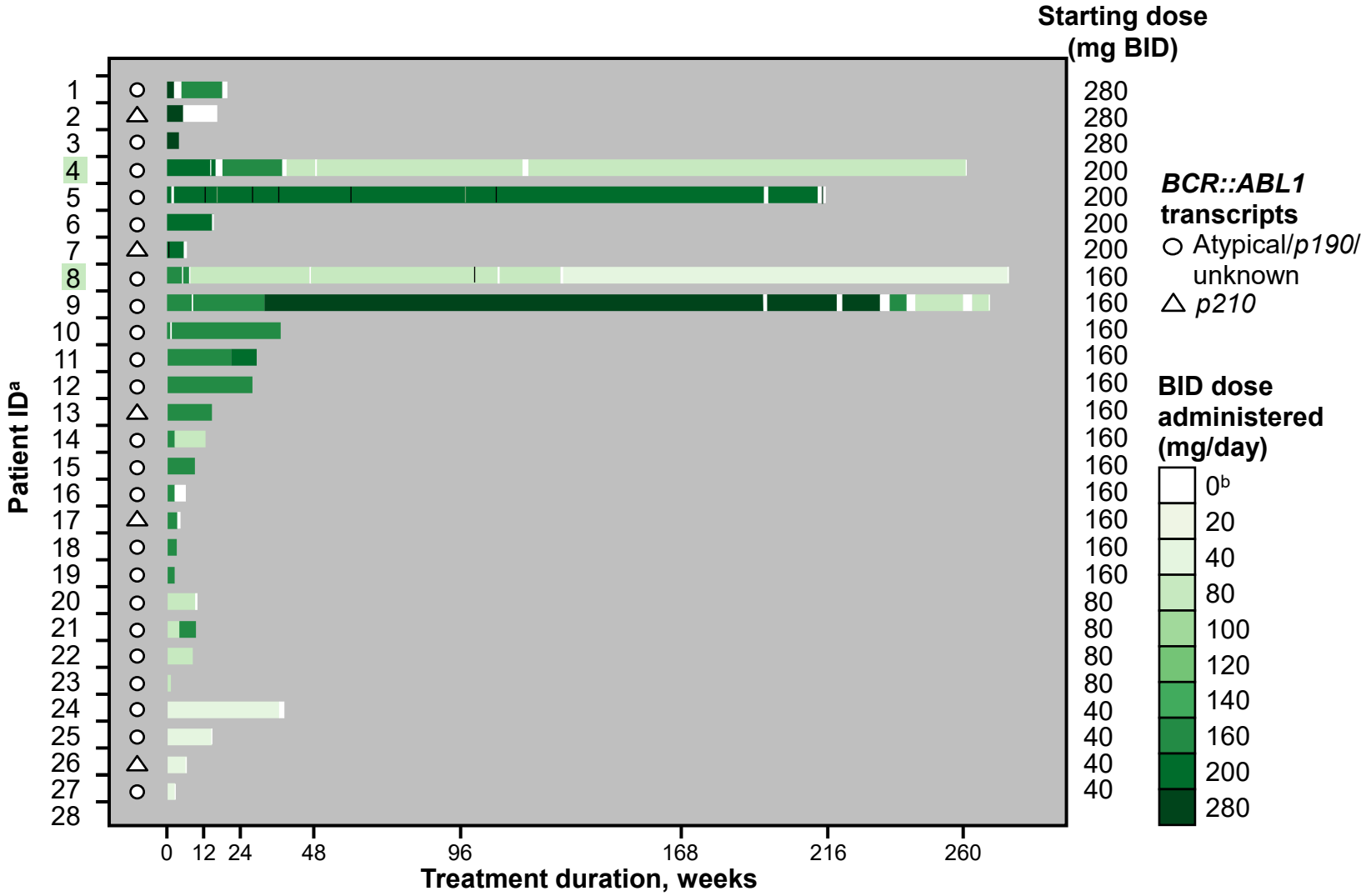
The median duration of exposure for all patients was 9.5 weeks, with a minority of patients having markedly longer exposure



- The median duration of exposure was 9.5 weeks (range: 1-275)
- Of 28 patients, 8 (28.6%) received asciminib for ≥24 weeks and 4 (14.3%) for ≥144 weeks

[a] Patient 28 received asciminib 160 mg BID for 19 days before discontinuing and is not shown here. Green highlighted patient numbers indicate patients who continued to receive asciminib monotherapy in rollover studies after the end of study. [b] White spaces indicate a dose interruption of ≥1 day.

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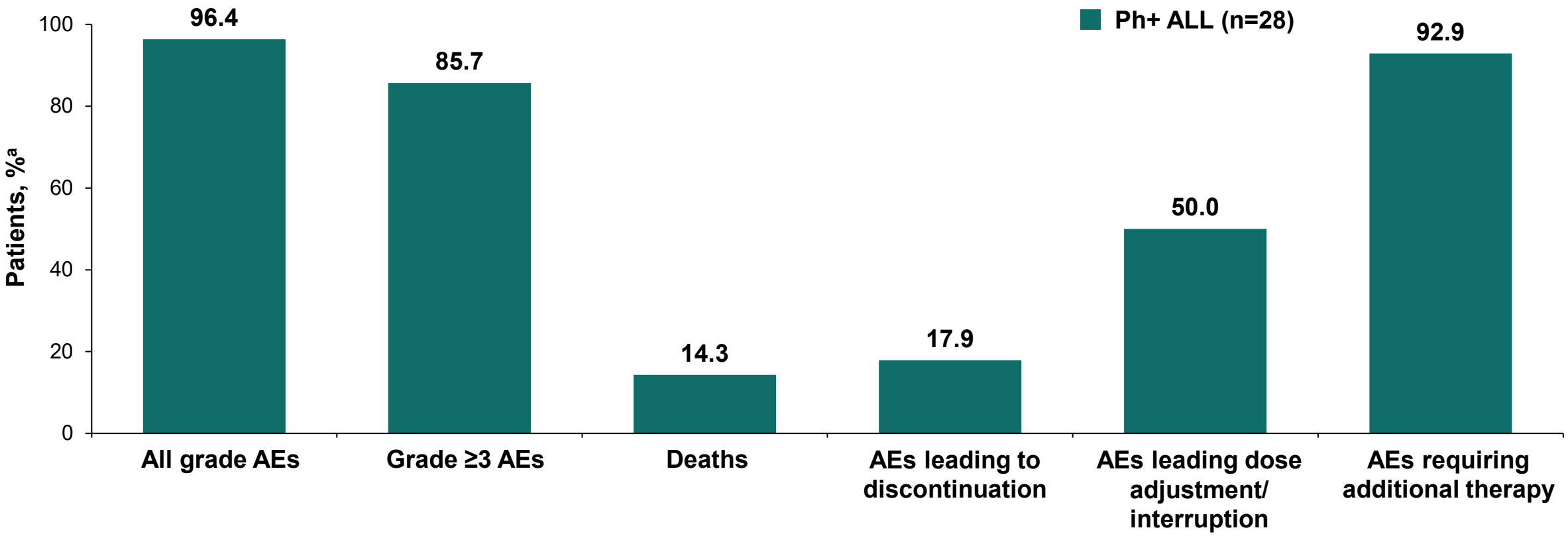
Overview of adverse events



- AEs leading to treatment discontinuation were pancreatitis (n=2), sepsis (n=2),[b] and renal failure (n=1)

[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. [b] One patient who had sepsis died.

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Observed AEs (in ≥20% of all patients) were not dose-dependent

Patients, %[a]	Asciminib 40 mg BID (n=4)		Asciminib 80 mg BID (n=4)		Asciminib 160 mg BID (n=13)		Asciminib 200 mg BID (n=4)		Asciminib 280 mg BID (n=3)		All patients (n=28)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Anemia[b]	50	25	25	25	39	23	100	75	33	33	46	32
Headache	–	–	25	–	46	8	50	–	33	–	36	4
Fatigue	25	25	–	–	23	–	50	–	100	–	32	4
GGT ↑	–	–	–	–	46	23	50	50	33	33	32	21
Neutropenia[c]	50	50	–	–	31	31	50	50	33	33	32	32
Thrombocytopenia[d]	50	50	25	25	31	31	25	25	33	33	32	32
ALT ↑	–	–	–	–	31	23	75	25	33	33	29	18
Lipase ↑	25	25	–	–	23	23	50	25	67	–	29	18
Nausea	25	–	–	–	31	–	50	–	33	–	29	–
ALP increased	25	–	–	–	39	8	25	–	–	–	25	4
Dyspnea	50	–	–	–	15	–	50	–	33	–	25	–
Leukopenia[e]	50	50	–	–	23	23	25	25	33	33	25	25
Pyrexia	25	–	–	–	39	–	–	–	33	–	25	–
Vomiting	–	–	25	–	15	–	75	25	33	–	25	4
AST ↑	–	–	–	–	31	15	25	–	33	33	21	11

↑, increased; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. All values were rounded to the nearest whole number. [b] Includes hemoglobin decreased and anemia. [c] Includes neutrophil count decreased and neutropenia. [d] Includes platelet count decreased and thrombocytopenia. [e] Includes white blood cell count decreased and leukopenia.

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Observed AEs (in ≥20% of all patients) were not dose-dependent

Patients, %[a]	Asciminib 40 mg BID (n=4)		Asciminib 80 mg BID (n=4)		Asciminib 160 mg BID (n=13)		Asciminib 200 mg BID (n=4)		Asciminib 280 mg BID (n=3)		All patients (n=28)	
	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3	All grade	Grade ≥3
Anemia[b]	50	25	25	25	39	23	100	75	33	33	46	32
Headache	–	–	25	–	46	8	50	–	33	–	36	4
Fatigue	25	25	–	–	23	–	50	–	100	–	32	4
GGT ↑	–	–	–	–	46	23	50	50	33	33	32	21
Neutropenia[c]	50	50	–	–	31	31	50	50	33	33	32	32
Thrombocytopenia[d]	50	50	25	25	31	31	25	25	33	33	32	32
ALT ↑	–	–	–	–	31	23	75	25	33	33	29	18
Lipase ↑	25	25	–	–	23	23	50	25	67	–	29	18
Nausea	25	–	–	–	31	–	50	–	33	–	29	–
ALP increased	25	–	–	–	39	8	25	–	–	–	25	4
Dyspnea	50	–	–	–	15	–	50	–	33	–	25	–
Leukopenia[e]	50	50	–	–	23	23	25	25	33	33	25	25
Pyrexia	25	–	–	–	39	–	–	–	33	–	25	–
Vomiting	–	–	25	–	15	–	75	25	33	–	25	4
AST ↑	–	–	–	–	31	15	25	–	33	33	21	11

↑, increased; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.

[a] A patient with multiple severity grades for an AE is only counted under the maximum grade. All values were rounded to the nearest whole number. [b] Includes hemoglobin decreased and anemia. [c] Includes neutrophil count decreased and neutropenia. [d] Includes platelet count decreased and thrombocytopenia. [e] Includes white blood cell count decreased and leukopenia.

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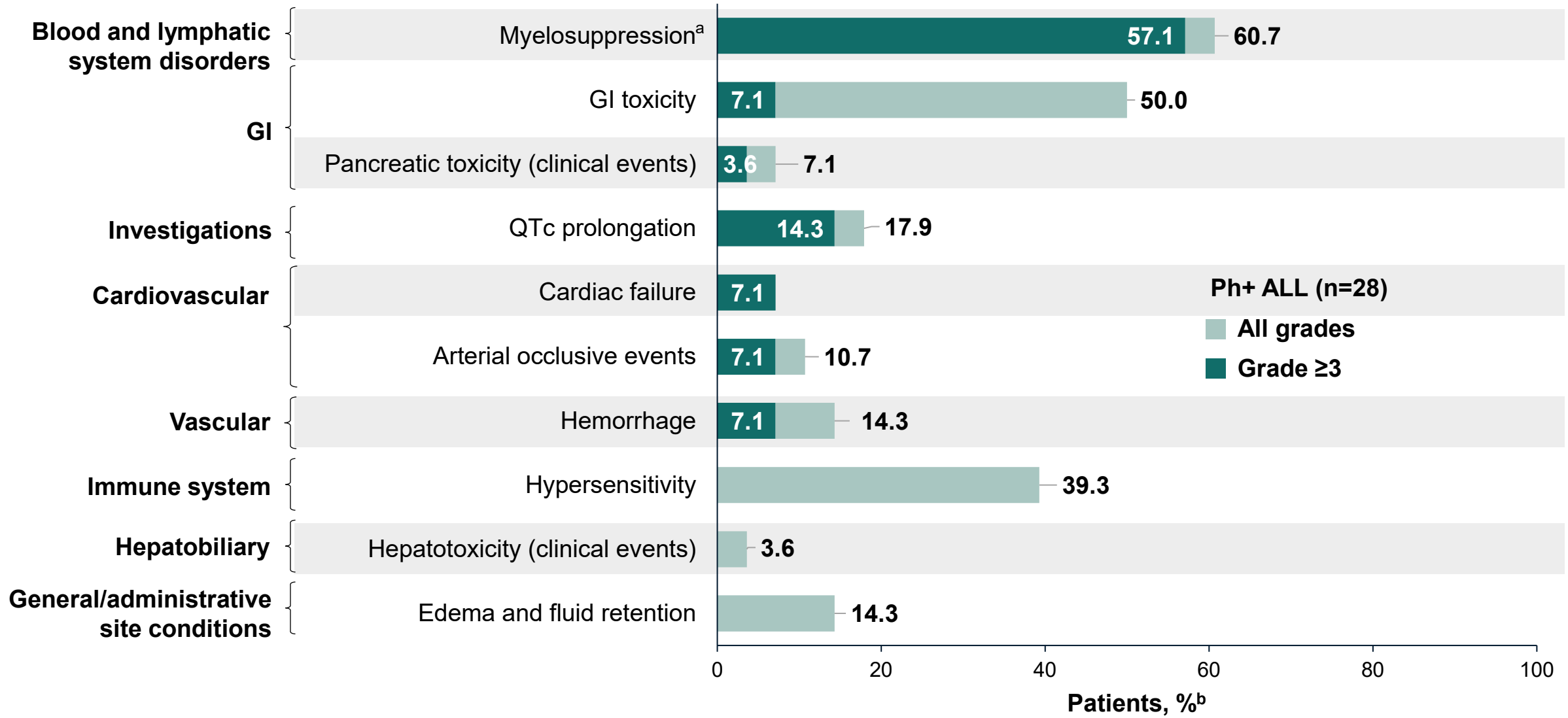
Adverse events of special interest



GI, gastrointestinal.

[a] Includes anemia, leucopenia, thrombocytopenia, and cytopenias affecting more than 1 lineage. [b] A patient with multiple severity grades for an AE is only counted under the maximum grade.

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Four on-treatment deaths were reported[a]

Patient ID	Cause of death	Age, years	Sex	Last dose of asciminib	Key events prior to death
5	Cardiac arrest	75	Male	200 mg BID (day 1499)	Known cardiac history. Patient entered the study in MMR and later achieved MR4. The patient died 7 days after the last dose of asciminib, in week 215
22	Sepsis[b]	47	Male	80 mg BID (day 56)	Developed severe sepsis with hypotension and fever, asciminib was discontinued on study day 56. The patient died 3 days after the last dose of asciminib, in week 9
23	Pneumonia and sepsis	73	Male	80 mg BID (day 6)	Developed pneumonia on day 7 and sepsis on day 9. The patient died 5 days after the last dose of asciminib, in week 2
27	Study indication[b]	65	Male	40 mg BID (day 15)	Asciminib permanently discontinued due to disease progression, thereafter patient received prednisolone and dasatinib. The patient died 25 days after the last dose of asciminib, in week 6

[a] On-treatment deaths were defined as deaths occurring while receiving study medication or within 30 days after last dose of study treatment. [b] Deaths occurred after discontinuation of asciminib.

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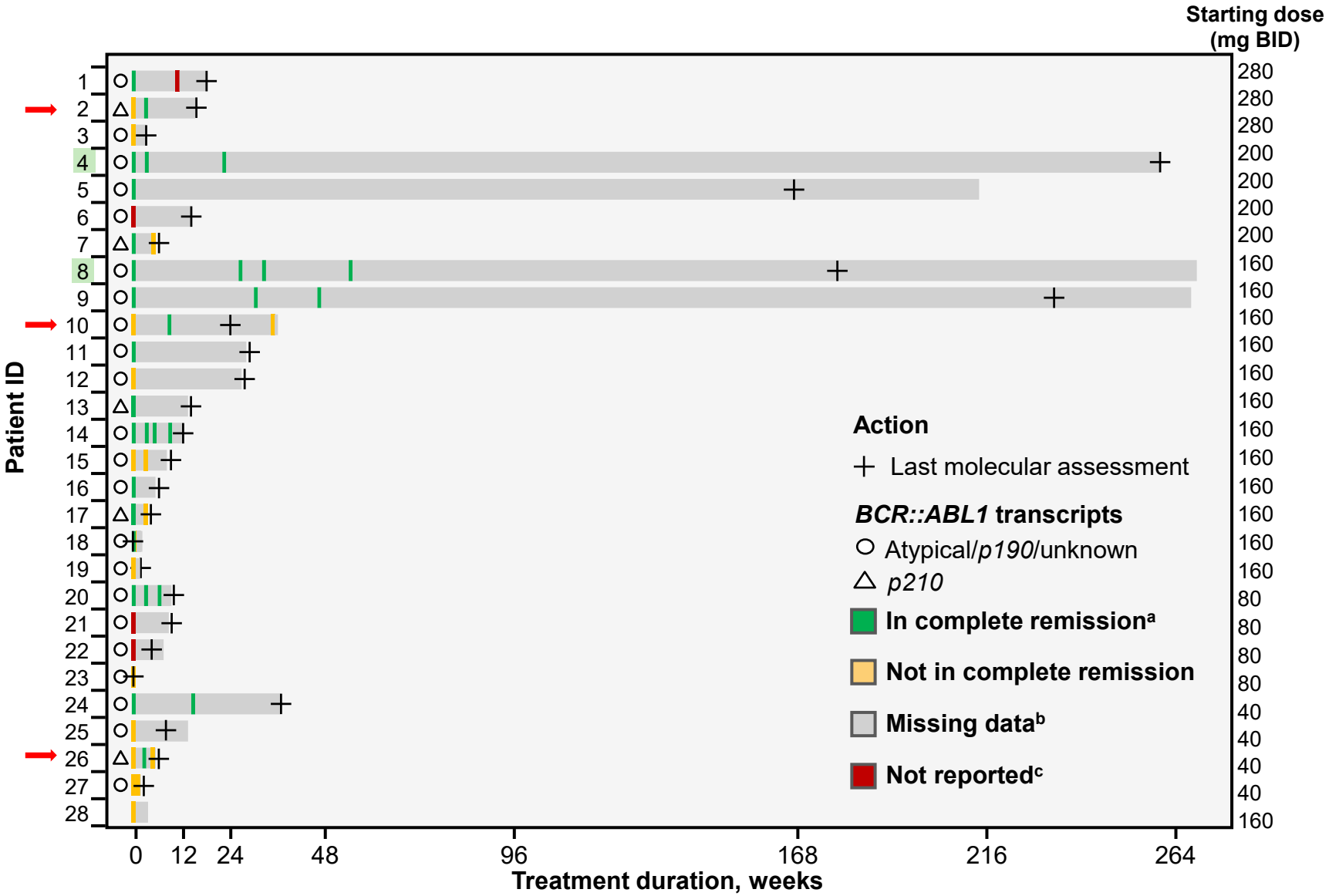
Complete remission (bone marrow blasts <5%) status with asciminib monotherapy and assessments performed



- At screening, 14 patients were in complete remission
  - Between days 1-30, 3 patients maintained complete remission and 2 progressed
- A total of 4 patients with complete remission at screening (and no assessments at days 1-30) had assessments after day 30
  - One patient had progressive disease
  - Three remained in complete remission

[a] Complete remission was defined as bone marrow blasts <5%. Bone marrow blast assessment was not required per the protocol. Red arrows indicate patients who achieved complete remission on therapy. [b] Assessment not done. [c] Assessment done, but the data were not reported due to sample error.

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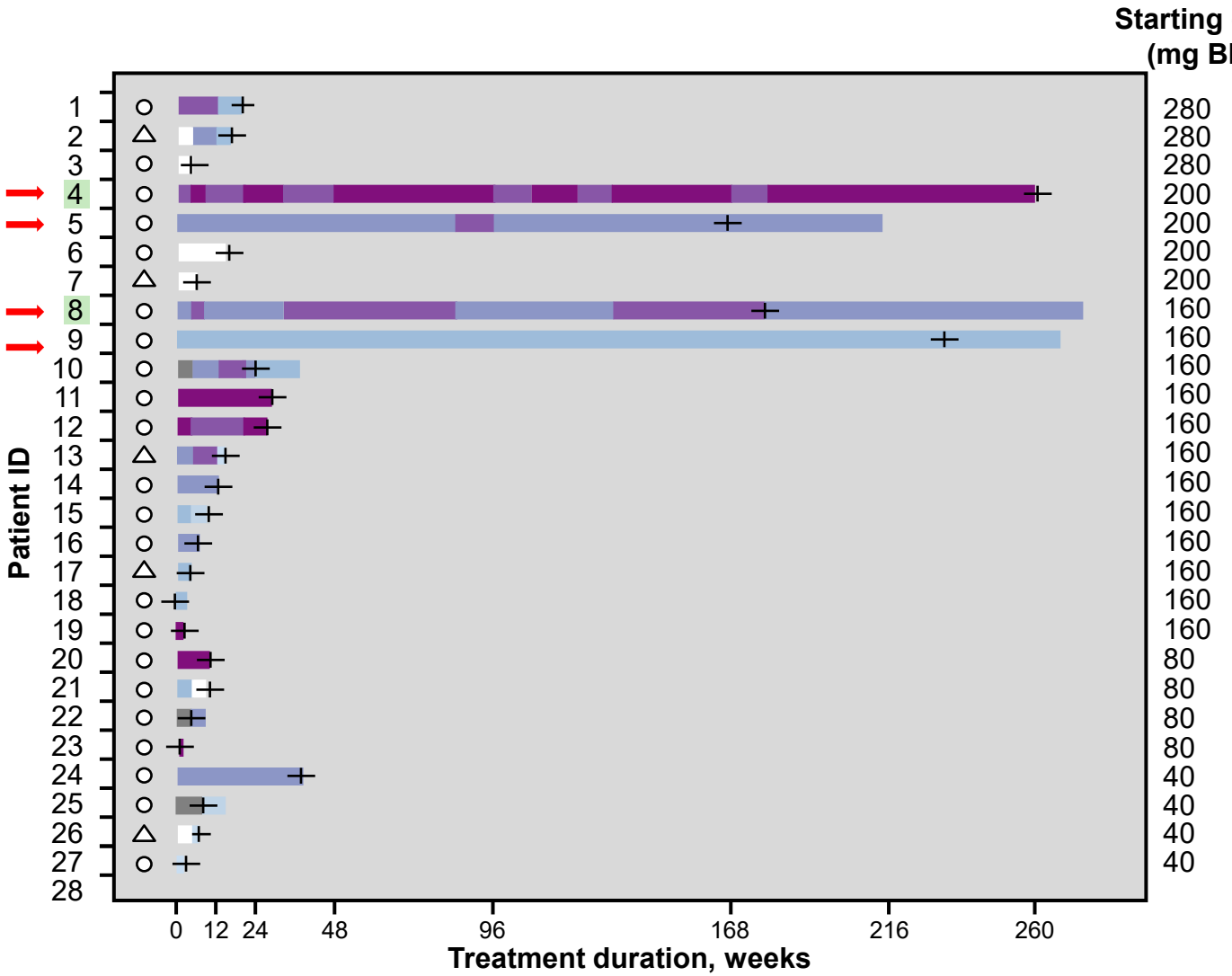
Molecular response assessments by peripheral blood



***BCR::ABL1* transcripts**

○ Atypical/*p190*/unknown

△ *p210*

Action

\+ Last molecular assessment

Molecular response

- No molecular response
- *BCR::ABL1* ≤10%
- *BCR::ABL1* ≤1%
- MMR
- MR4
- MR4.5
- NA

- Four patients in this heavily pretreated population had sustained responses

MMR, major molecular response (*BCR::ABL1* ≤0.1%); MR4, *BCR::ABL1* ≤0.01%; MR4.5, *BCR::ABL1* ≤0.0032%; NA, not applicable.

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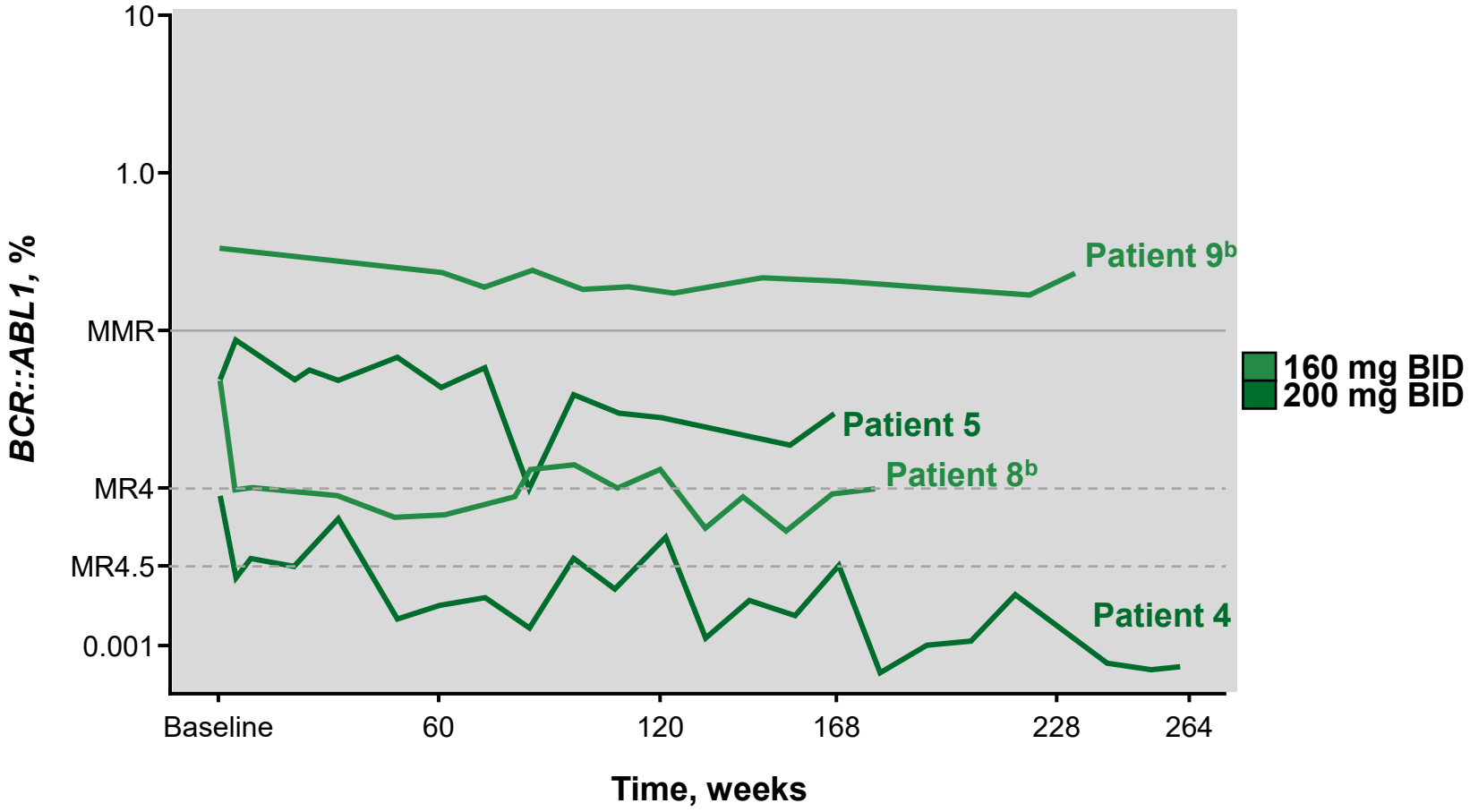
Four patients in this heavily pretreated population had sustained responses

BCR::ABL1 levels over time in patients with sustained responses[a]



SCT, stem cell transplant.

[a] Patients had atypical/*p190*/unknown transcript. No patient with a *p210* transcript achieved a sustained molecular response. [b] Patients had prior allogeneic SCT.

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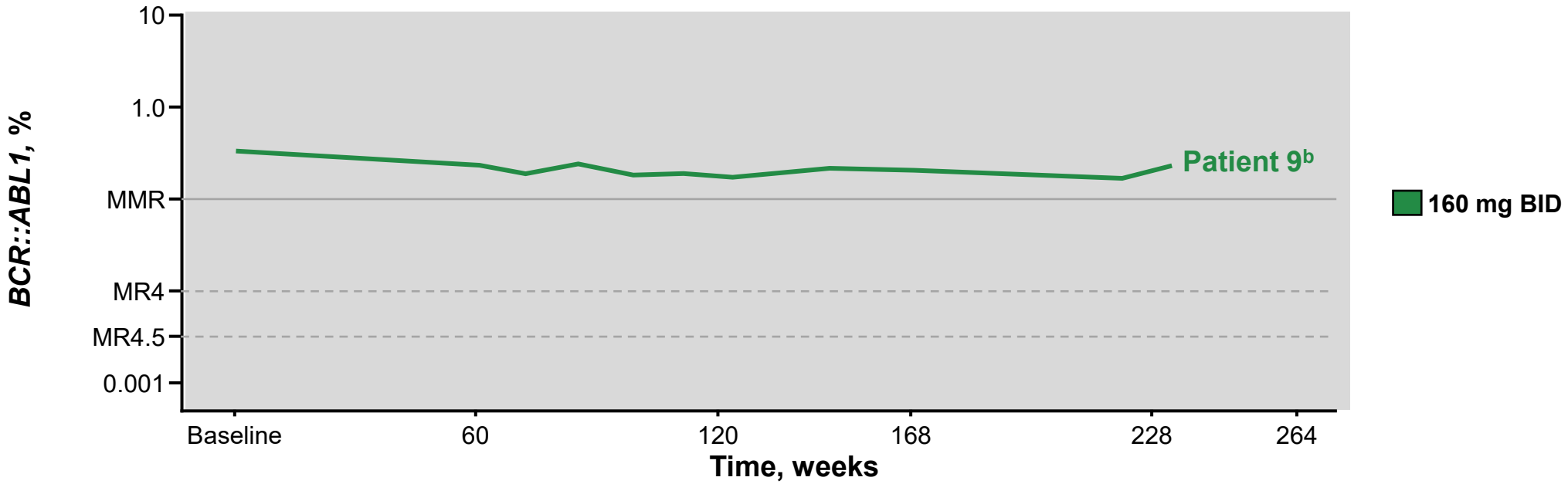
Stable disease in a patient with 3 prior TKIs with prolonged asciminib monotherapy

BCR::ABL1 levels over time in patients with sustained responses[a]



Patient ID	Age	Sex	Starting dose	Prior TKIs	Relevant active medical conditions at screening	Best response on treatment	Duration on treatment	Status
9	70 years	M	160 mg BID	Imatinib, dasatinib, and nilotinib	Hypertension, chronic kidney disease, increased brain natriuretic peptide, peripheral arterial occlusive disease,[c] anemia, prostatomegaly	*BCR::ABL1* ≤1%	268.9 weeks	Died due to cardiac failure 67 days after the last dose (unrelated to disease)

[a] Patient had a *p190* transcript. No patient with a *p210* transcript achieved a sustained molecular response. [b] Patient had prior allogeneic SCT. [c] Led to toe amputation 3 days prior to study treatment.

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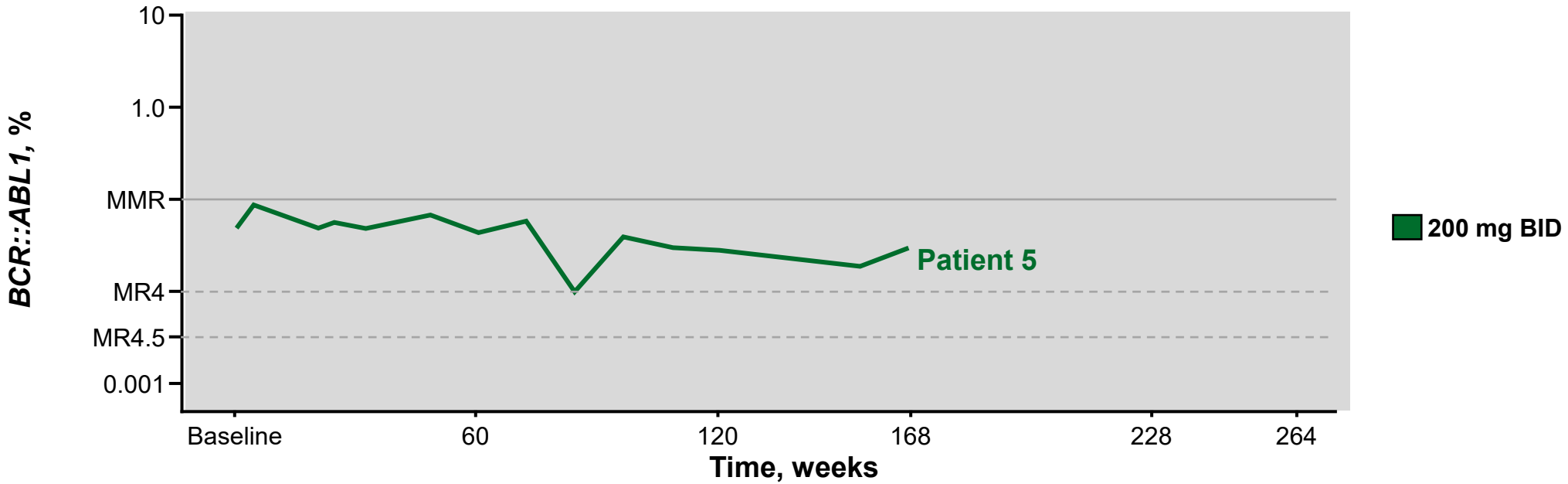
Sustained MMR in a patient with 2 prior TKIs including ponatinib

BCR::ABL1 levels over time in patients with sustained responses[a]

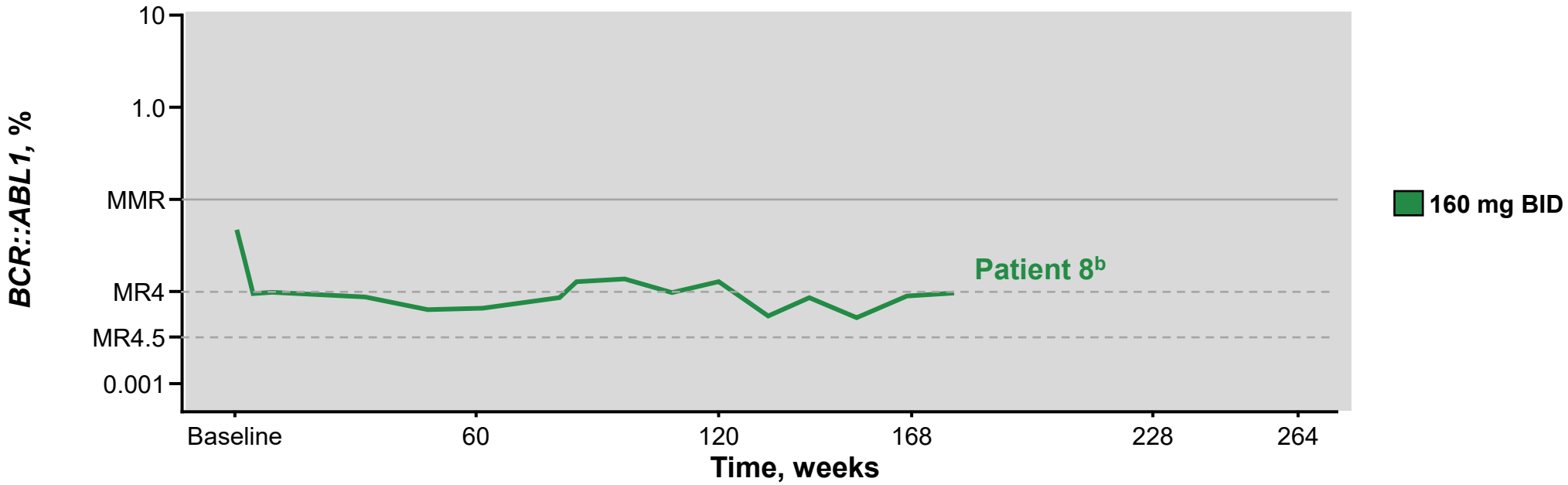


Patient ID	Age	Sex	Starting dose	Prior TKIs	Relevant active medical conditions at screening	Best response on treatment	Duration on treatment	Status
5	75 years	M	200 mg BID	Dasatinib and ponatinib	Coronary artery disease, electrolyte imbalance, cardiac murmur, hypertension, anemia, peripheral edema, sinus bradycardia, atrial fibrillation, hypertriglyceridemia	MR4	215.1 weeks	Died due to cardiac arrest while on treatment[b] (suspected relationship with study treatment)

[a] Patient had a *p190* transcript. No patient with a *p210* transcript achieved a sustained molecular response. [b] On-treatment deaths were defined as deaths occurring while receiving study medication or within 30 days after last dose of study treatment.

Sustained molecular response in a patient with 2 prior TKIs who remains on asciminib monotherapy in rollover trial

BCR::ABL1 levels over time in patients with sustained responses[a]



Patient ID	Age	Sex	Starting dose	Prior TKIs	Relevant active medical conditions at screening	Best response on treatment	Duration on treatment	Status
8	31 years	M	160 mg BID	Imatinib and nilotinib	Hypertension, anemia, thrombocytopenia, popular rash	MR4	275.1 weeks	Ongoing asciminib treatment in rollover study

[a] Patient had a *p190* transcript. No patient with a *p210* transcript achieved a sustained molecular response. [b] Patient had prior allogeneic SCT.

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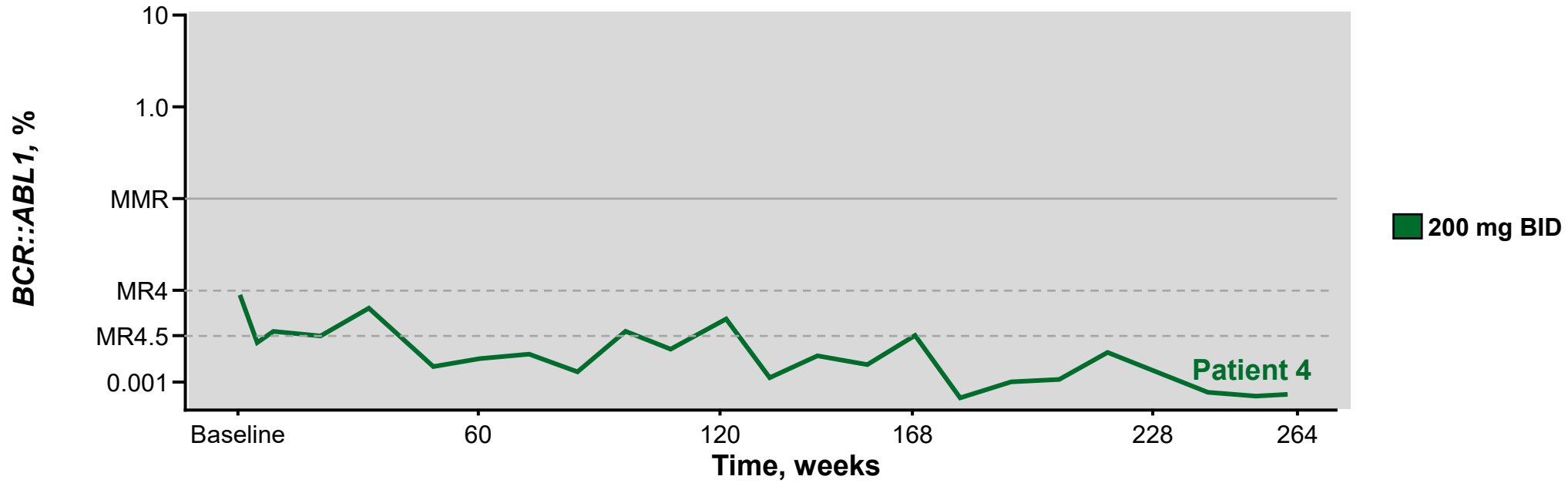
Sustained deep molecular response in a patient with prior nilotinib who remains on asciminib monotherapy in rollover trial

BCR::ABL1 levels over time in patients with sustained responses[a]



Patient ID	Age	Sex	Starting dose	Prior TKIs	Relevant active medical conditions at screening	Best response on treatment	Duration on treatment	Status
4	77 years	F	200 mg BID	Nilotinib	Crohn's disease, intestinal anastomosis, diabetes mellitus, hypertension, cervical intervertebral disc protrusion, thoracic intervertebral disc protrusion, Gilbert's syndrome[b]	*BCR::ABL1* ≤0.001%	261.1 weeks	Ongoing asciminib treatment in rollover study

[a] No patient with a *p210* transcript achieved a sustained molecular response. [b] Only some active medical conditions are listed.

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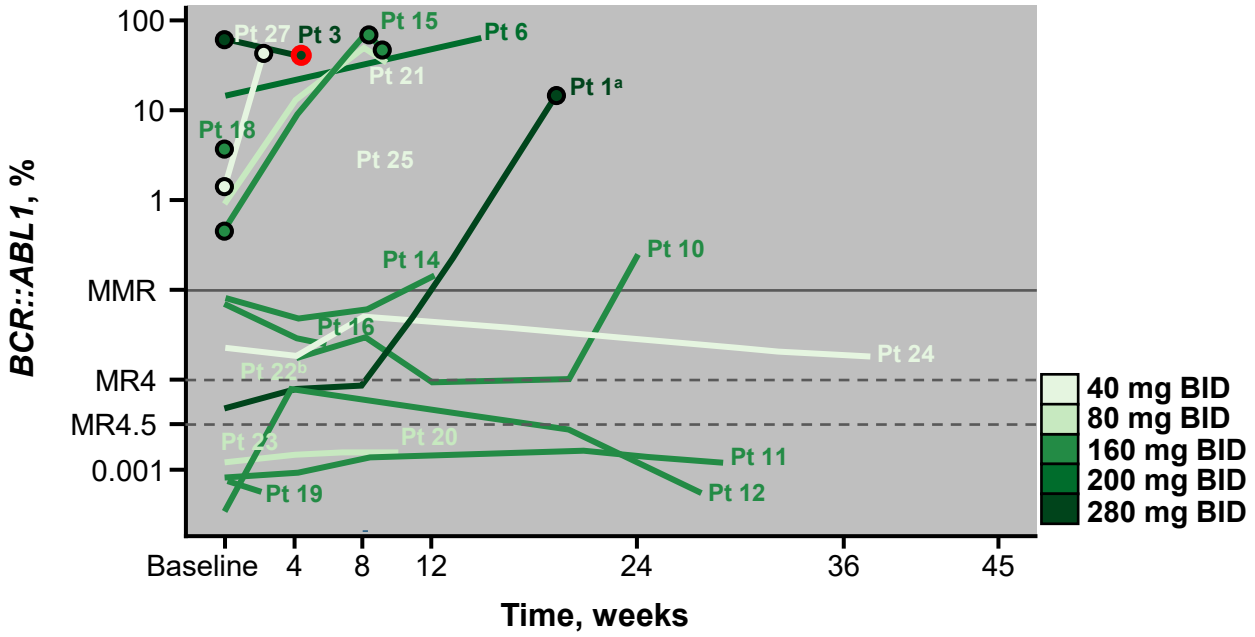
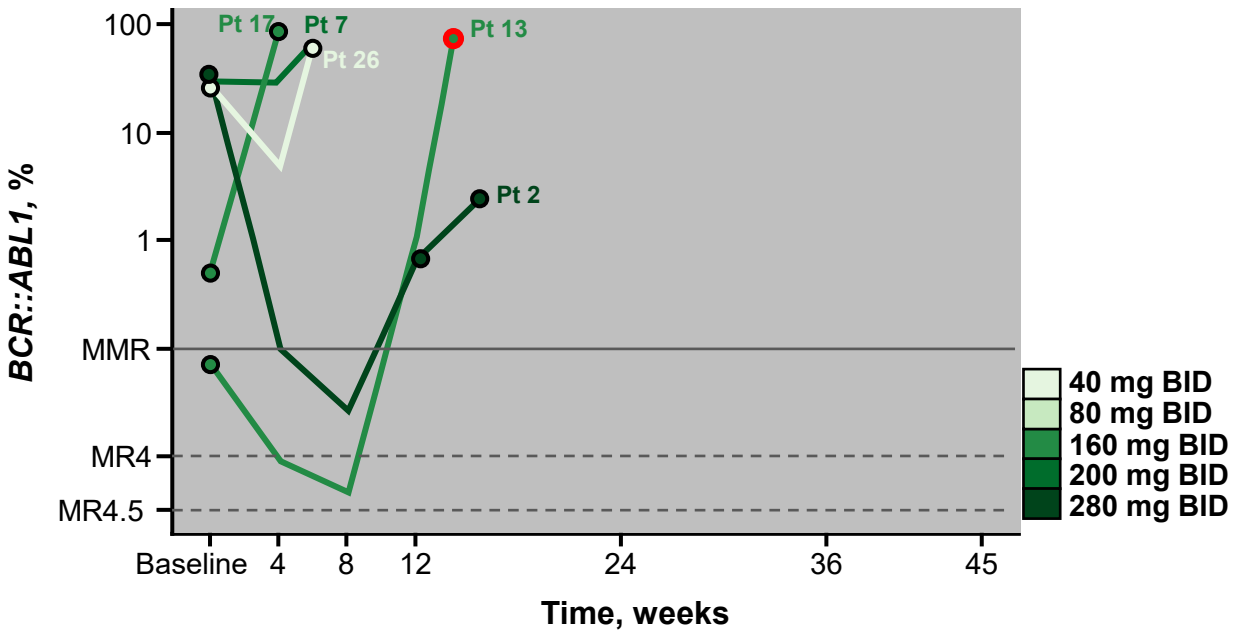
Two patients had treatment-emergent mutations

MMR over time among patients with atypical/*p190*/unknown transcripts



MMR over time among patients with *p210* transcripts



Mutation detected Emergent mutation detected

- Patients 18, 22, and 27 had isolated mutations at screening (T315I, n=3)
- Patients 15 and 3 had compound mutations at screening (Y253H/T315I, n=1; Y253H/F317L, n=1)
- Patient 3 with Y253H/F317L had F486S on study day 32

- Patients 13, 26, and 2 had isolated mutations at screening (T315I, n=2; Y253H, n=1)
- Patient 17 had a compound mutation at screening (Q252H/T315I, n=1)
- Patient 13 with T315I had S501I on study day 100

Pt, patient.

[a] Patient 1 had a compound mutation of T315I/Q252H noted at the end of treatment but did not have baseline mutational assessments performed. Therefore, it is inconclusive whether this compound mutation developed on study. [b] Patient 22 had a T315I mutation at baseline but *BCR::ABL1* levels were not determined.

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Conclusions

- In **heavily pretreated** patients with **R/R Ph+ ALL**—a small subset in the last cohort of the first-in-human phase 1 study that was initiated in 2014—**asciminib monotherapy** showed **antileukemic activity** and was **generally safe** and **well tolerated**
- Most patients discontinued therapy prematurely, primarily due to progressive disease
  - MTD was not reached, RDE was not determined but an enrichment cohort was opened at 200 mg BID, no expansion cohort was initiated
  - This is the first study to show efficacy in the *p190* Ph+ ALL population, the predominant subtype in our dataset
  - Most patients were heavily pretreated, and more than half had previously received ponatinib; 4 remained on therapy for ≥144 weeks and had sustained or deepening molecular responses
    - Over 2.5 years later, 2 patients are continuing asciminib monotherapy in rollover studies
  - All dose levels (40 mg BID to 280 mg BID) were tolerated and safe with no dose-dependent AEs observed
- The current analysis showed **anti-leukemic** activity of **asciminib monotherapy** in patients with **Ph+ ALL**, with a few patients showing long-term disease control
- **Further** exploration of **asciminib in combination therapy regimens for Ph+ ALL** is ongoing[16,17]

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