Severe acute cutaneous-only graft-*versus*-host disease after late relapse of chronic myeloid leukemia and ultraviolet B phototherapy

Allogeneic hematopoietic cell transplantation (allo-HCT) is a curative therapy for leukemias, but has significant morbidity including transplantation-related mortality. Acute graft-*versus*-host disease (GvHD) is a common life-threatening complication after allo-HCT; it occurs when donor T cells recognize recipient antigens as foreign and initiate an immune response against recipient epithelial cells expressing the antigen (primarily in the skin, gut, and/or liver).[1,2] Immunosuppression reduces the risk of acute GvHD, but increases that of serious infections and reduces graft-*versus*-leukemia activity. Prior to the development of *BCR::ABL1* tyrosine kinase inhibitors (TKI), allo-HCT was the only curative therapy for individuals with chronic myeloid leukemia (CML), due largely to a powerful graft-*versus*-leukemia effect.[3-5] Allo-HCT is now used sparingly in CML because of the superior efficacy and safety of *BCR::ABL1* TKI, although it remains the only curative option in patients intolerant to TKI or those with advanced disease.[3,4] Herein, we present a case of severe acute cutaneous GvHD after late relapse of CML with mixed chimerism and ultraviolet B-light (UVB) phototherapy for suspected lichen planus.

A 45-year-old woman was diagnosed with chronic phase CML in 2003 and, over the subsequent 7 years, was treated with all available *BCR::ABL1* TKI, to which she was intolerant. She underwent allo-HCT in May 2010 due to her poor quality of life on TKI therapy. With myeloablative conditioning (total body irradiation, thiotepa, fludarabine, antithymocyte globulin) she was given a CD34-selected (T-cell depleted) peripheral blood graft from a 36-year-old male 7/10 matched unrelated donor (HLA-B, -C, and -DQ mismatched) due to a poor donor search. She was not given GvHD prophylaxis. The post-transplant course was complicated by cytomegalovirus duodenitis and possible stage 1 cutaneous acute GvHD (papular, erythematous facial and upper chest rash) which resolved after a short course of prednisone 20 mg. A bone marrow biopsy taken on day 100 and examined by fluorescence *in situ* hybridization (FISH) showed full donor chimerism and no *BCR::ABL1*. The patient was started on maintenance treatment with dasatinib in December 2010 because of polymerase chain reaction (PCR)-determined *BCR::ABL1* positivity in the bone marrow (0.014%). By 2018 she was in complete molecular remission off dasatinib without acute or chronic GvHD, prompting discharge from the oncology clinic. A routine complete blood count in 2019 remained normal.

In May 2023 she presented to primary care with a history of several days of a pruritic erythematous rash on her trunk and thighs. Topical triamcinolone was prescribed, but the rash spread, leading to dermatologic evaluation on June 14, 2023. Skin biopsies of the erythematous scaling plaques and papules were felt to represent lichen planus. She was treated with oral prednisone for 2 weeks with mild improvement; followed by minocycline, doxycycline, and metronidazole without benefit. By July 13, 2023, the rash covered 80% of her body surface and was severely pruritic. A complete blood count demonstrated significant leukocytosis (white blood count 49x10^9/L), severe thrombocythemia (platelet count 1,323x10^9/L), and anemia (hemoglobin 11.5 g/dL). The differential demonstrated an absolute increase in neutrophils (31.6x10^9/L), basophils (2.4x10^9/L), and monocytes (1.5x10^9/L), with no increase in blasts. Narrowband UVB phototherapy three times weekly was initiated and she was referred back to the oncology clinic.

She re-established oncology care on July 20, 2023, when a bone marrow biopsy was performed and hydroxyurea 2 g/day was started. The marrow was hypercellular with marked myeloid and megakaryocytic hyperplasia, without any increase in blasts, consistent with relapsed chronic phase CML. FISH showed a *BCR::ABL1* rearrangement in 96% of nuclei and short tandem repeat studies identified <5% donor cells. The acquisition of a new complex karyotype on metaphase cytogenetics and mutations in myeloid neoplasm driver genes, including A*SXL1* (E1015Rfs*; variant allele frequency 32%), *RAD21* (P355L; 29%), and *SMC1A* (Q994R; 45%), were consistent with clonal evolution. Skin biopsy on July 20, 2023 showed a prominent lichenoid type, dermo-epidermal lympho-histiocytic infiltrate with scattered dyskeratotic keratinocytes within the epidermis, and dermo-epidermal junction clefting (Figure 2A) as well as 47% donor cells by FISH (Figure 2B). Given clinical concern about cutaneous GvHD, peripheral blood chimerism studies were performed and showed mixed chimerism with short tandem repeat CD15 <5% donor and CD3 >95% donor (Figure 2C).

The patient was seen in the clinic on July 26, 2023 and blood tests showed improving leukocytosis (17x10^9/L) on hydroxyurea. Treatment with asciminib 40 mg twice daily was started, given an unknown *BCR::ABL1* tyrosine kinase domain mutation status (ultimately negative) and prior intolerance of ATP-pocket binding TKI. The same day she also received a sixth course of UVB phototherapy, which she had previously tolerated and was helping with the rash (Figure 1A, B). Despite being on a stable UVB dose, after this treatment she developed severe burning, which her der-

matologist found surprising. She reported new skin peeling and severe pain on July 28, 2023 and was prescribed prednisone 40 mg and opioids. Her pain worsened progressively over the next 3 days and was so severe she was unable to make it to the clinic on July 31, 2023, prompting direct admission by emergency service transportation.

She had a long 3-month hospital course. The findings of a repeat skin biopsy on admission were similar to those 11 days earlier, except for a relatively sparse dermo-epidermal chronic inflammatory infiltrate. Both biopsies were consistent with grade 3 acute GvHD; there was no evidence of acute GvHD in sites other than the skin. Her acute cutaneous

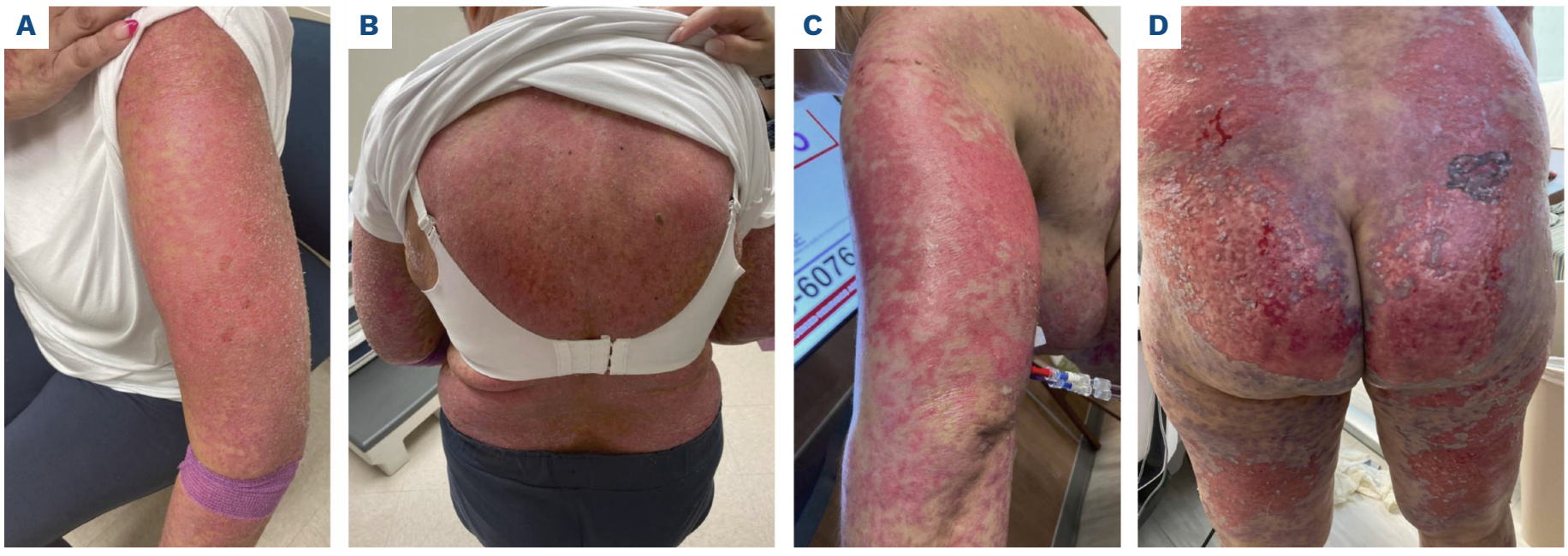
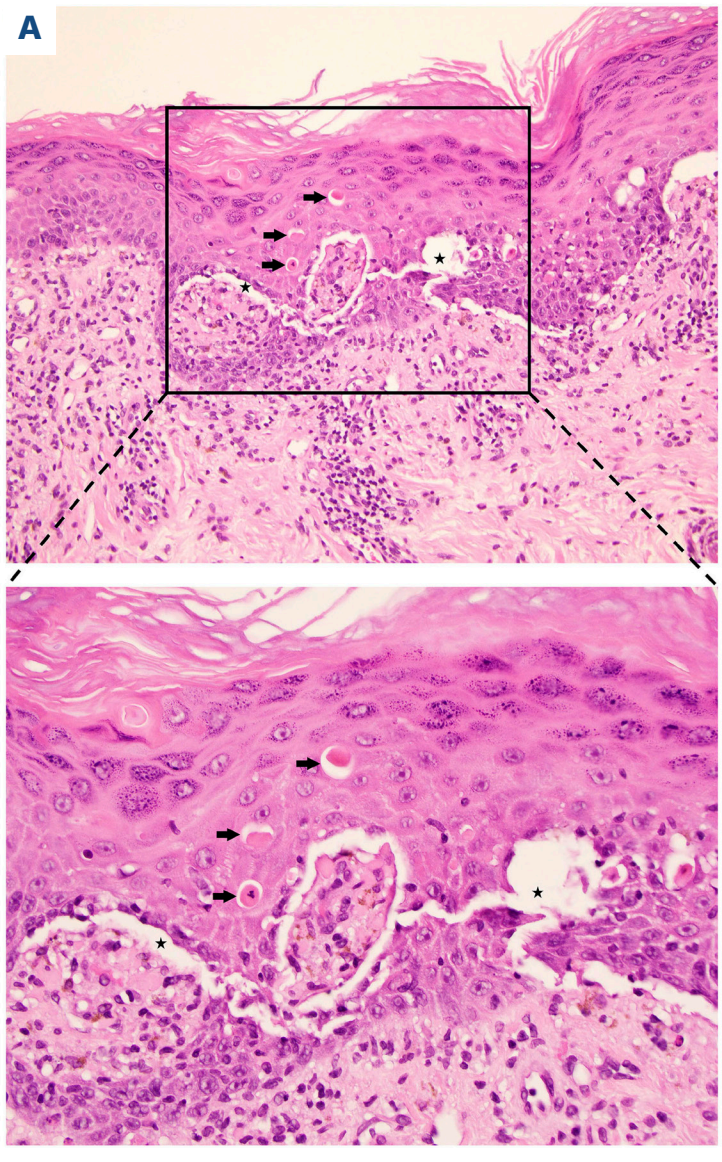


Figure 1. Representative images of the diffuse erythematous rash initially diagnosed as lichen planus, but later identified as acute cutaneous graft-*versus*-host disease. (A, B) Rash on July 26, 2023, before the onset of severe rash-associated pain. (C, D) Rash on August 4, 2023, following the onset of severe rash-associated pain.



C

Sample	Immune Cell Type	% Donor Chimerism
Bone marrow	Pan	<5%
	CD15+ (myeloid)	<5%
	CD3+ (T cells)	>95%
Peripheral blood	CD15+ (myeloid)	<5%
	CD3+ (T cells)	>95%
Skin	Pan	47

Figure 2. Skin biopsy and chimerism analysis identified acute cutaneous graft-*versus*-host disease in a patient with late relapse of chronic myeloid leukemia with mixed chimerism after allogeneic hematopoietic cell transplant. (A) Right forearm skin biopsy hematoxylin and eosin-stained images at 200X (top) and 400X (bottom) magnification. The biopsy shows a lichenoid-type lympho-histiocytic infiltrate with features of grade 3 acute graft-*versus*-host disease including epidermal dyskeratotic keratinocytes (arrows), and dermo-epidermal interface clefting (star). (B) Fluorescence *in situ* hybridization CEPXY image of a right forearm skin biopsy demonstrating 53% recipient (XX) and 47% donor (XY) cells. (C) Table presenting the donor chimerism percentage (%) stratified by sample and immune cell type at the time of the diagnosis of late graft failure/chronic myeloid leukemia relapse. The third column of the table is color-coded using a blue-yellow-orange gradient scale.

GvHD slowly resolved over several months with treatment including prednisone 2 mg/kg daily (with tapering), ruxolitinib 10 mg twice daily (with tapering), and intravenous immunoglobulin. During her admission, she remained on treatment with asciminib, with the dose reduced to 40 mg daily when ponatinib 15 mg daily was added in October 2023 because of persistent *BCR::ABL1* PCR positivity >10% and mixed chimerism. Subsequent PCR showed significant improvement (0.36%) on dual therapy by December 2023.

This case highlights fundamental immunological principles governing immune tolerance after allo-HCT. The CML relapse likely occurred months to years before the onset of the rash in May 2023, indicating that the patient lived for an extended time with a chimeric immune system functioning in harmony. This was possible due to the unique nature of her allo-HCT including a CD34-selected graft and the fact that it was performed at an age (32 years) at which there was some residual thymic function. Consequently, her donor T cells underwent proper thymic and extrathymic selection, thereby inducing tolerance to recipient self-antigens. This helps to explain why she did not have acute or chronic GvHD at the time of discharge from the oncology clinic, despite use of an only 7/10 matched unrelated donor with no GvHD prophylaxis. Her relapsed CML exhibited clonal evolution after allo-HCT with acquisition of a complex karyotype and pathogenic mutation in *ASXL1*, likely contributing to her relapse while off TKI therapy.[6,7] The persistence of CD3 chimerism at relapse points to immune escape also being a potential relapse mechanism in this case; it can occur due to loss of heterozygosity at HLA class I, which is primarily seen in transplants using poorly matched donors (as in this case).[8]

While the May 2023 rash was initially diagnosed as lichen planus, retrospectively it was clearly felt to be due to late onset acute GvHD with atypical features (prominent lichenoid type dermo-epidermal lympho-histiocytic infiltrate). The trigger of the initial donor T-cell activation and subsequent GvHD remains unclear, but the lack of gastrointestinal or hepatic involvement points to skin-specific antigens being the alloreactive T-cell target. While chimerism studies showed >95% recipient *BCR::ABL1* mutant myeloid cells in the bone marrow, >95% donor T cells were retained in the peripheral blood, providing an explanation for the GvHD occurrence despite minimal bone marrow donor chimerism. The growing dominance of *BCR::ABL1* mutant cells in the myeloid compartment might have played a role in GvHD initiation, as *BCR::ABL1* has been shown to drive the expression of multiple antigens that induce HLA-restricted T-cell responses.[9]

The sudden worsening of rash-related symptoms following UVB phototherapy and the largely unchanged skin biopsy results after UVB point towards acute GvHD being the primary driver of the symptoms. While UVB phototherapy is efficacious for numerous inflammatory skin conditions due to its diverse immunosuppressive effects on the tissue, toxic doses of UVB phototherapy can induce excessive apoptosis of keratinocytes and dermal immune cells.[10] It is plausible that this tissue injury and the subsequent inflammatory response resulted in activation of antigen-presenting cells, including both recipient and donor (e.g. long-lived tissue macrophages)-derived antigen-presenting cells, leading to alloreactive donor T-cell activation, thereby driving the progression of GvHD specifically in the skin directly affected by UVB (Figure 3). Moreover, cutaneous GvHD is known to involve sun-exposed areas initially and multiple cases linking UVB exposure to development of cutaneous GvHD after allo-HCT have been reported.[11,12] Since the patient had previously tolerated the UVB dose that led to burning, the introduction of hydroxyurea and asciminib may also have contributed to the skin toxicity observed. Both medications are recognized to induce photosensitivity and could have amplified the impact of exposure to UVB. Additionally, their use may have contributed to the death of *BCR::ABL1* mutant cells within the skin, thereby promoting activation of antigen-presenting cells.

The patient in this report consented to treatment and the publishing of her case in a journal, in compliance with institutional policy and national ethical standards.

To the best of our knowledge, this is the first case report

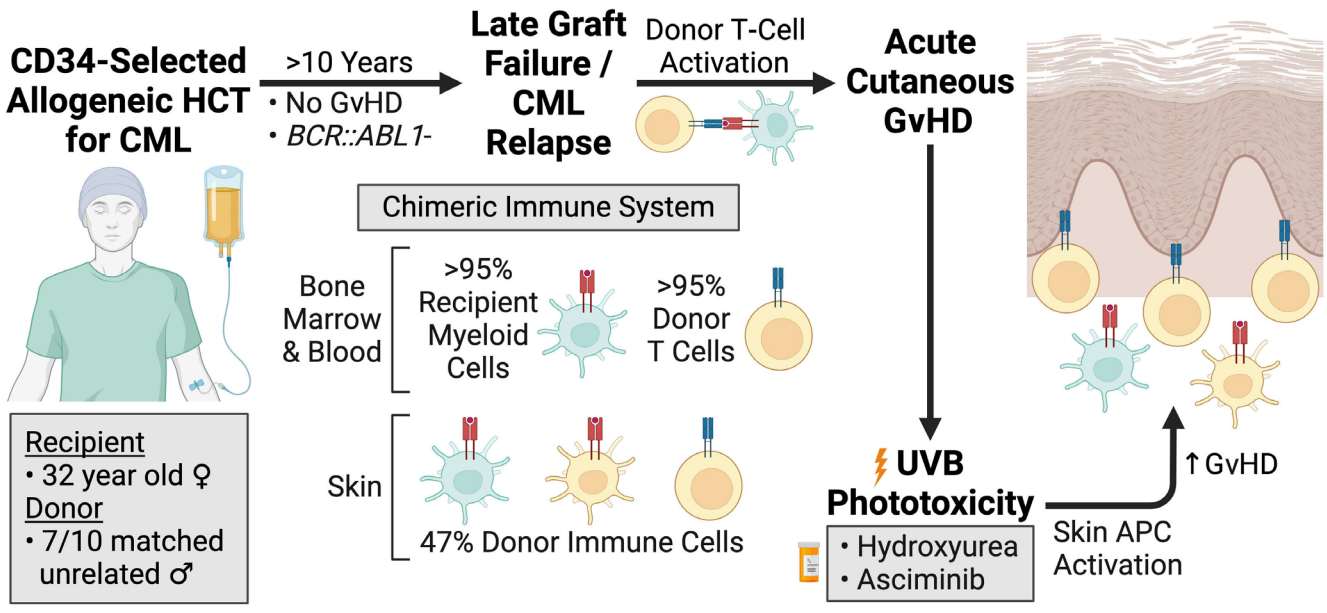


Figure 3. Schema of the proposed immunological mechanisms underlying the events of this case report. HCT: hematopoietic cell transplant; CML: chronic myeloid leukemia; GvHD: graft-*versus*-host disease; UVB: ultraviolet B; APC: antigen-presenting cell. Created in BioRender.

of late CML relapse after allo-HCT complicated by acute cutaneous GvHD. Our case highlights that combination therapy with asciminib and ponatinib can be tolerable and highly effective in heavily pretreated individuals with adverse genetic features, consistent with findings in pre-clinical studies.[13,14] It also emphasizes the need for caution if considering the use of UBV phototherapy after allo-HCT, particularly in combination with medications that can cause photosensitivity (e.g., asciminib); this may become increasingly relevant with the uptick in TKI maintenance therapy after allo-HCT.

Authors

J. Scott Beeler,[1] Rahul Peravali,[2] Kristan M. Augustin,[3] Amy C.M. Musiek,[4] Kiran Vij,[1,5] Dilan A. Patel[1] and John F. DiPersio[1]

[1]Division of Oncology, Department of Medicine, Washington University School of Medicine; [2]Division of Gastroenterology, Department of Medicine, Washington University School of Medicine; [3]Department of Pharmacy, Barnes-Jewish Hospital; [4]Division of Dermatology, Department of Medicine, Washington University School of Medicine and [5]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, MO, USA

Correspondence:
J.F. DIPERSIO - jdipersi@wustl.edu

https://doi.org/10.3324/haematol.2024.286369

Received: July 31, 2024.
Accepted: October 9, 2024.
Early view: October 17, 2024.

Disclosures

No conflicts of interest to disclose.

Contributions

JSB, RP, KMA, ACMM, DAP, and JFD took part in clinical treatment and assessment of the patient. KV analyzed skin biopsies. JSB, DAP, and JFD wrote the manuscript. All authors critically assessed and approved the final manuscript.

Acknowledgments

The authors gratefully acknowledge the patient described in this case report. The authors thank Angela Spray and Ilana Rosman for their expertise and assistance in interpreting the dermatological findings and skin biopsies.

Funding

This work was supported in part by the National Cancer Institute (NCI) of the National Institutes of Health (NIH) under grant number R35 CA210084 to JFD.

Data-sharing statement

The original data and protocols pertaining to this case are available from the corresponding author upon reasonable request.

References

1. Ferrara JLM, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet. 2009;373(9674):1550-1561.
2. Zeiser R, Blazar BR. Acute graft-versus-host disease - biologic process, prevention, and therapy. N Engl J Med. 2017;377(22):2167-2179.
3. Niederwieser C, Kröger N. Transplantation in CML in the TKI era: who, when, and how? Hematology Am Soc Hematol Educ Program. 2022;2022(1):114-122.
4. Craddock CF. We do still transplant CML, don't we? Hematology Am Soc Hematol Educ Program. 2018;2018(1):177-184.
5. Dazzi F, Szydlo RM, Cross NC, et al. Durability of responses following donor lymphocyte infusions for patients who relapse after allogeneic stem cell transplantation for chronic myeloid leukemia. Blood. 2000;96(8):2712-2716.
6. Bidikian A, Kantarjian H, Jabbour E, et al. Prognostic impact of ASXL1 mutations in chronic phase chronic myeloid leukemia. Blood Cancer J. 2022;12(10):144.
7. Schönfeld L, Rinke J, Hinze A, et al. ASXL1 mutations predict inferior molecular response to nilotinib treatment in chronic myeloid leukemia. Leukemia. 2022;36(9):2242-2249.
8. Vago L, Perna SK, Zanussi M, et al. Loss of mismatched HLA in leukemia after stem-cell transplantation. N Engl J Med. 2009;361(5):478-488.
9. Scheich F, Duyster J, Peschel C, Bernhard H. The immunogenicity of Bcr-Abl expressing dendritic cells is dependent on the Bcr-Abl kinase activity and dominated by Bcr-Abl regulated antigens. Blood. 2007;110(7):2556-2560.
10. Raj D, Brash DE, Grossman D. Keratinocyte apoptosis in epidermal development and disease. J Invest Dermatol. 2006;126(2):243-257.
11. Hardy JM, Marguery M-C, Huynh A, et al. Photo-induced graft-versus-host disease. Photodermatol Photoimmunol Photomed. 2016;32(5-6):291-295.
12. Vassallo C, Brazzelli V, Zecca M, Locatelli F, Alessandrino PE, Borroni G. Isomorphic cutaneous graft-versus-host disease reaction after ultraviolet exposure: clinical, histological and direct immunofluorescence studies of four allo-transplanted patients. J Eur Acad Dermatol Venereol. 2009;23(8):913-918.
13. Gleixner KV, Filik Y, Berger D, et al. Asciminib and ponatinib exert synergistic anti-neoplastic effects on CML cells expressing BCR-ABL1 T315I-compound mutations. Am J Cancer Res. 2021;11(9):4470-4484.
14. Eide CA, Zabriskie MS, Savage Stevens SL, et al. Combining the allosteric inhibitor asciminib with ponatinib suppresses emergence of and restores efficacy against highly resistant BCR-ABL1 mutants. Cancer Cell. 2019;36(4):431-443.