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Anticipating and overcoming resistance in blastic plasmacytoid dendritic cell neoplasm: new insights from pivekimab sunirine

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Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare and clinically aggressive hematologic malignancy for which durable remission remains challenging to achieve.[1] Treatment options are limited and have historically relied on chemotherapy regimens adopted from acute leukemias.[1] The discovery that BPDCN uniformly overexpresses interleukin-3 receptor-α (CD123) has provided a strong biological rationale for targeted therapy, leading to the development of CD123-directed approaches including tagraxofusp, CAR-T cells, and bispecific antibodies.[2,3]

Building on this CD123-targeting therapeutic paradigm, pivekimab sunirine (PVEK)—a first-in-class CD123-targeting antibody-drug conjugate (ADC)—has recently demonstrated promising activity in the pivotal CADENZA trial.[4]

PVEK comprises a high-affinity anti-CD123 antibody linked to an indolinobenzodiazepine pseudodimer payload that induces DNA alkylation and cytotoxicity.[4] Unlike ligand-toxin fusion strategies such as the FDA-approved tagraxofusp, PVEK relies on antibody-mediated internalization and intracellular payload release, aligning it mechanistically with next-generation ADC platforms (Figure 1A).[4] As an ADC, however, PVEK remains subject to the broader biological principles that govern this drug class.[5,6] Resistance to ADCs may arise through several non-mutually exclusive mechanisms, including antigen loss or downregulation, impaired receptor internalization, altered intracellular trafficking, and upregulation of drug efflux transporters—all of which reduce intracellular payload exposure and diminish therapeutic efficacy.[5,6] In BPDCN, where relapse remains the pivotal event that ultimately limits survival,[1] understanding how such resistance

mechanisms might emerge after PVEK treatment is critical to ensuring durable responses.

In this context, the work by Poussard and colleagues, in the current issue of *Haematologica*, provides important mechanistic insight by analyzing PVEK resistance in BPDCN preclinical models and mapping the potential emergence of protective niches capable of sustaining disease persistence after PVEK treatment.[7] Beyond confirming the potent *in vitro* activity of PVEK in the GEN2.2 BPDCN cell line—consistent with prior preclinical observations[8]—the authors establish a GEN2.2 cell line-derived xenograft model that enables spatial assessment of treatment response *in vivo*. Their data indicate that although overall tumor burden is markedly reduced, residual malignant cells may persist within specific anatomical compartments, including spleen, bone marrow, and the central nervous system, suggesting that specific tissue environments may function as protective niches supporting disease persistence (Figure 1B).

Protective niches within the tumor microenvironment are increasingly recognized as critical mediators of therapy resistance, allowing residual malignant cells to survive despite effective systemic treatment.[9] Such protective niches may be identified at the organ level, as in classical sanctuary sites, or at the tissue level, where non-uniform drug distribution and microenvironmental heterogeneity create localized pharmacologic protection.

In BPDCN, multiple anatomic compartments may serve as reservoirs of residual malignant cells. While bone marrow and skin represent common disease sites,[1] the central nervous system (CNS) has emerged as a particularly concerning sanctuary site. CNS involvement occurs in approximately 30% of BPDCN patients at relapse, and microRNA profiling studies have revealed that BPDCN cells possess neural traits that may facilitate their interaction with the nervous system.[10] The blood-brain barrier represents a formidable obstacle to drug penetration, potentially allowing BPDCN cells to escape therapeutic pressure and maintain clonal persistence. The spatial mapping provided by Poussard et al. confirms persistent CNS infiltration following PVEK exposure, underscoring the clinical relevance of this sanctuary site.[7]

Beyond anticipating the potential spatial distribution of BPDCN cells under PVEK therapeutic pressure, Poussard and colleagues develop a resistant GEN2.2 cell model to gain deeper understanding of ADC resistance at the molecular level. Through transcriptomic profiling of the resistant cell model, the authors identify two potential mediators of resistance: reduced surface CD123 protein expression and upregulation of P-glycoprotein (P-gp/ABCB1) (Figure 1B).[7]

Reduced CD123 expression is consistent with adaptive antigen modulation described in other targeted strategies.[5,6] Antigen recognition represents the initial step in the functional mechanism of ADCs, as antibody-antigen binding is required for receptor-mediated internalization and subsequent payload delivery. Prolonged exposure to ADCs can lead to decreased antigen expression and fewer available drug-binding sites, as previously demonstrated with HER2-targeted therapies in breast cancer.[5,6] Poussard et al. observe that CD123 downregulation in BPDCN cells occurs at the protein but not mRNA level, suggesting post-translational mechanisms that warrant further investigation.[7]

The second resistance mechanism identified involves upregulation of ABC transporters, known to reduce the effectiveness of structurally diverse chemotherapeutic agents.[5,6] P-gp/ABCB1 upregulation was confirmed at transcript and protein levels,[7] consistent with a potential drug efflux mechanism, though functional validation remains to be demonstrated. P-gp/ABCB1, a member of the ABC transporter family, significantly increases the efflux of anticancer drugs from tumor cells. Its overexpression limits intracellular payload exposure, as previously documented in ADC resistance.[5,6]

The possible coexistence of these two mechanisms of resistance raises important questions regarding their temporal relationship and whether combinatorial approaches addressing both antigen modulation and drug efflux pathways might delay or prevent resistance emergence. Moreover, the identification of CNS sanctuaries by Poussard et al. reinforces the importance of integrating systematic CNS surveillance and risk-adapted intrathecal prophylaxis into combination treatment strategies, as recommended by expert consensus.[1]

However, while the study by Poussard et al. makes important contributions, some limitations merit consideration. The reliance on a single cell line and xenograft system cannot fully recapitulate the genetic heterogeneity and microenvironmental complexity of human BPDCN. Furthermore, experimentally induced resistance may not precisely mirror clinical resistance dynamics. These findings warrant further validation in additional preclinical models and clinical settings.

Despite these limitations, the study offers novel insights into resistance mechanisms that may emerge after PVEK treatment and informs the development of anticipatory therapeutic strategies. In response to the need for more effective therapies that not only induce but also sustain remission, multiple active clinical trials are currently evaluating combinatorial regimens in BPDCN, including tagraxofusp/azacitidine/venetoclax and tagraxofusp/hyper-CVAD/venetoclax (NCT03113643, NCT04216524).[11] These combination approaches aim to address multiple resistance pathways and enhance cytotoxicity through complementary molecular targets.[11]

The study by Poussard et al. reveals critical mechanisms by which PVEK resistance may emerge in BPDCN.[7] By identifying both anatomical sanctuaries and molecular mechanisms of adaptation before they manifest clinically, the study provides a roadmap for proactive therapeutic design. As PVEK continues its clinical development, integrating spatial biology, antigen monitoring, and resistance surveillance may prove critical to transforming promising response rates into durable disease control. In a malignancy where relapse remains the defining clinical obstacle, anticipating resistance may be as important as achieving initial remission.

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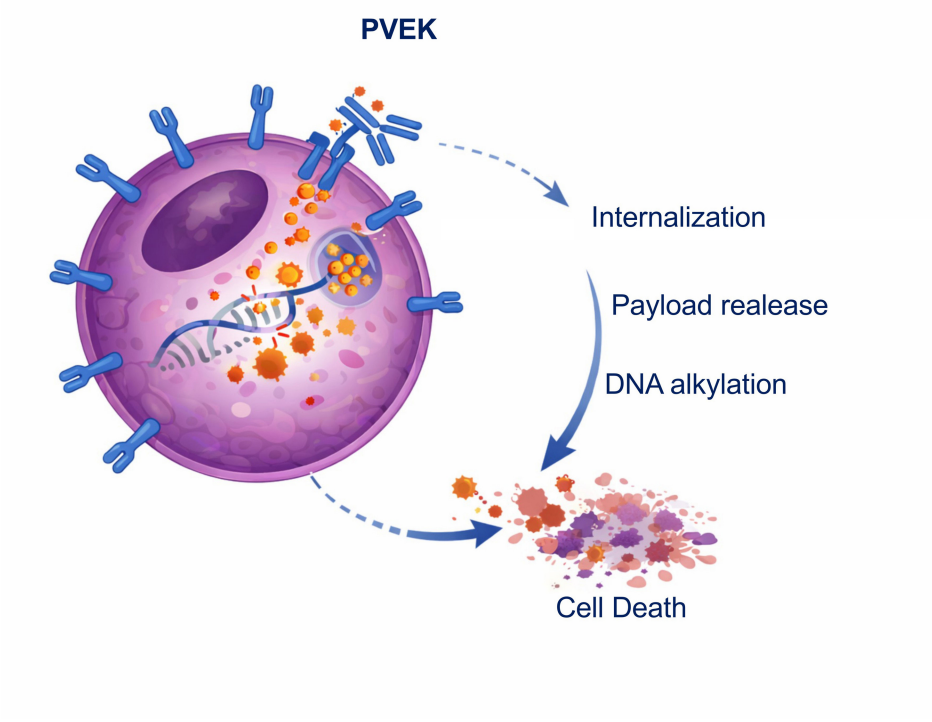
FIGURE 1. **PVEK mechanism of action and resistance in BPDCN.** (A) PVEK antibody-drug conjugate delivers cytotoxic payload via CD123-mediated internalization, leading to DNA alkylation and cell death. (B) Resistance mechanisms include spatial sanctuaries (bone marrow, spleen, brain), ABCB1 upregulation and CD123 antigen loss.

A

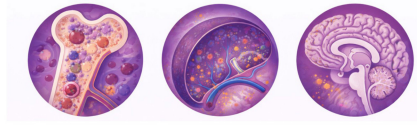
PVEK ACTION



B

PVEK RESISTANCE

PROTECTIVE NICHES



ANTIBODY-DRUG CONJUGATE RESISTANCE