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REVIEW

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Clinical optimization of bexmarilimab as a myeloid checkpoint therapy

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ABSTRACT

Checkpoint blockade has revolutionized cancer therapy, yet durable responses are limited by myeloid-driven immunosuppression. Bexmarilimab, a first-in-class monoclonal antibody targeting the scavenger receptor Clever-1 (Stabilin-1), represents a novel strategy to recondition tumor-associated macrophages and malignant myeloid cells. This review summarizes the biological rationale for Clever-1 targeting, appraises clinical and translational evidence, and outlines strategies to enhance therapeutic efficacy through patient selection, rational drug combinations, biomarker-driven patient stratification, and timing of intervention. We also highlight future opportunities for integrating bexmarilimab with next-generation immunotherapies and precision medicine approaches.

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Cancer; Clever-1; tumor-associated macrophages; myeloid checkpoint blockade; immunotherapy; AML; MDS

1. Introduction - expanding the checkpoint paradigm beyond T cells

Immune checkpoint inhibitors have transformed cancer treatment, yet durable benefit is limited to a subset of patients. While PD-1/PD-L1 or CTLA-4 blockade reinvigorates exhausted T cells, many tumors remain refractory due to persistent immunosuppressive myeloid populations [1]. Tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells constitute a dominant immunoregulatory force within the tumor microenvironment (TME), blunting antigen presentation, suppressing CD8+ T-cell cytotoxicity, and promoting regulatory T-cell differentiation [2,3]. Targeting this myeloid axis has emerged as a promising therapeutic strategy [4,5].

In this context, the term myeloid checkpoint has been introduced to describe inhibitory receptors and regulatory pathways within macrophages, monocytes, and dendritic cells that restrain antitumor immunity. Similar to T-cell checkpoints, these pathways, including SIRPα/CD47 [6], LILRBs [7], TIM-3 [8], VISTA [9], TREM2 [10], and MARCO [11], maintain myeloid cells in a suppressive or tolerogenic state, limiting phagocytosis, antigen presentation, and support for effector T-cell responses. As a result, myeloid checkpoint blockade represents a complementary immunotherapeutic approach aimed at releasing the suppressive constraints imposed by the innate immune compartment.

While the clinical translation of macrophage-reprogramming therapies is still evolving, the field has reached an important point of maturity with both opportunities and challenges ahead. A key priority is the development of predictive biomarkers that can identify patients most likely to benefit, either from single-agent activity or from specific rational combinations, thereby avoiding unnecessary escalation to complex multi-agent regimens. At the same time, systematic comparison of mechanistically related agents at earlier stages of development will be essential to distinguish the most promising strategies and streamline progress. Although durable single-agent responses remain uncommon, these refinements in patient selection and trial design have the potential to unlock the full therapeutic impact of macrophage-targeted approaches and accelerate their integration into clinical practice [12].

Bexmarilimab is a first-in-class humanized monoclonal antibody against Clever-1 (also known as Stabilin-1), a multifunctional scavenger receptor expressed on immunosuppressive macrophages and sinusoidal endothelial cells [13]. Within the TME, Clever-1–positive macrophages orchestrate an anti-inflammatory state that facilitates immune escape. Blocking Clever-1 impairs lipid uptake, disrupts endosomal trafficking, enhances antigen processing and presentation, upregulates MHC class II and co-stimulatory molecules, and drives macrophages toward a pro-inflammatory phenotype characterized by TNF-α and IL-12 secretion [14–18]. Among these functions, the primary mechanistic driver of therapeutic activity is the inhibition of lipid scavenging and the rerouting of endosomal cargo, which together initiate a metabolic shift that enables downstream activation of antigen processing and proinflammatory macrophage programming. These effects recondition the TME from an immunologically "cold" to a "hot" state, restoring the potential for robust T-cell responses (Figure 1).

In line with this biology, single-agent bexmarilimab has demonstrated expected activity in macrophage reprogramming, however, only modest clinical efficacy in heavily pretreated metastatic patients. The key opportunity, therefore, is to build on these macrophage-driven changes as a foundation for other treatments: Clever-1 blockade could prime the tumor microenvironment for checkpoint inhibition, chemotherapy, or radiotherapy, thereby broadening the therapeutic reach of established agents through macrophage reprogramming

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Article highlights

- Clever-1 blockade with bexmarilimab induces systemic and intratumoral macrophage reprogramming, driving proinflammatory activation, enhanced antigen processing, and adaptive immune engagement.
- Integrative TCGA analysis reveals context-dependent *STAB1* expression and prognostic impact, identifying tumor and immune subtypes most likely to benefit from Clever-1 inhibition.
- Clinical and translational findings demonstrate optimal immune activation at 1–3 mg/kg, with pharmacodynamic effects exceeding drug exposure and supporting intermittent dosing strategies.
- Bexmarilimab establishes a foundation for rational combinations, priming tumors for checkpoint inhibitors, chemotherapy, or radiotherapy, and expanding therapeutic potential across solid and hematologic malignancies.

(Table 1). Given its favorable safety profile and manageable toxicity, bexmarilimab may also be well suited for earlier treatment lines, where the immune microenvironment is less compromised by prior therapy and suppressive TAM niches have not yet become established. These considerations provide a strong rationale for ongoing translational studies and clinical trials to define optimal combinations, timing, and indications for Clever-1 blockade. An additional consideration is treatment sequencing: in some settings, a short lead-in period of Clever-1 blockade may best prepare the immune landscape for subsequent therapy, while in others, simultaneous administration may maximize synergy.

2. Pre-clinical, translational and clinical evidence for Clever-1 targeting in cancer

Preclinical studies have identified macrophages as the principal compartment through which Clever-1 promotes tumor progression. In cell-specific knockout models and bone marrow chimeras, deletion of Clever-1 in macrophages, significantly impaired the growth of diverse tumors [15,23,24]. Therapeutic blockade of Clever-1 in these models reprogrammed TAMs toward a proinflammatory phenotype, characterized by enhanced cytokine production, increased antigen presentation, and subsequent activation of cytotoxic CD8+ T cells [15]. Consistent findings were observed in human systems, where Clever-1 silencing or antibody-mediated targeting in monocytes induced proinflammatory gene expression, elevated TNF-α secretion, and dampened Th2 responses, underscoring Clever-1 as a central immunosuppressive regulator [18]. These insights have provided the rationale for developing macrophage-directed therapies and position Clever-1 as a tractable myeloid checkpoint [25]. Building on this foundation, comprehensive preclinical characterization of bexmarilimab has demonstrated high-affinity binding to Clever-1 on monocytes, blockade of its natural ligand acetylated LDL, and induction of TNF-α secretion from human monocytes, while showing minimal Fc receptor or complement activation and a favorable safety profile in non-human primates [20].

The first-in-human phase I/II MATINS trial evaluated bexmarilimab monotherapy across ten refractory solid tumor types and confirmed both safety and preliminary efficacy, with disease control observed in subsets of patients suffering from such as melanoma, gastric, hepatocellular, biliary tract, and ER-positive breast cancers [17]. This study provided the first clinical proof of concept for TAM reprogramming, as spatial and transcriptional analyses in responding tumors revealed increased interferon and T-cell receptor signaling. In parallel, immune monitoring demonstrated that systemic Clever-1 blockade reprogrammed circulating monocytes and triggered lymphocyte activation, accompanied by downregulation of checkpoint molecules including PD-1 and CTLA-4 [16]. Collectively, these findings

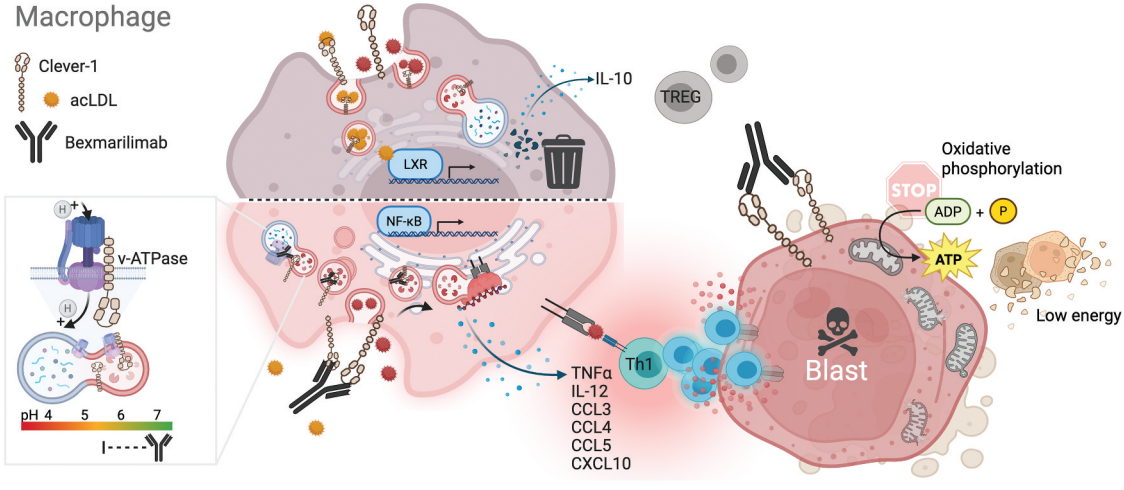

Figure 1. Mechanism of action of bexmarilimab in macrophages and leukemic blasts. Clever-1 is a multifunctional scavenger receptor expressed on macrophages and malignant blasts. In the immunosuppressive state (top), Clever-1 mediates uptake of acetylated (ac)LDL and other ligands, leading to altered lysosomal trafficking, LXR activation, NF-κB suppression, IL-10 production, and expansion of regulatory T cells (Tregs). This maintains an anti-inflammatory macrophage phenotype that supports cancer progression and therapeutic resistance. Bexmarilimab, a humanized anti – Clever-1 antibody, blocks acLDL binding and disrupts endosomal acidification, resulting in dendritic cell (DC)-like kinetics of antigen processing and presentation. This reprograms macrophages toward a proinflammatory, antigen-presenting state, characterized by increased secretion of IL-1β, TNF-α, IL-12, CCL3, CCL4, CCL5 and CXCL10, enhanced Th1 polarization, and improved activation of CD8+ T cells and NK cells. In parallel, Clever-1 inhibition impairs the metabolic fitness of leukemic blasts by disrupting ATP homeostasis, contributing to reduced leukemic survival. Collectively, these effects recondition the tumor microenvironment and enhance antitumor immunity. Figure created with Biorender.

Table 1. Bexmarilimab responses in human (single agent).

Observation [ref]	Blood [16,17]	Tumor [17]	PDEC [19]	*Ex vivo* [16,18,20–22]	*In vitro* [16,*]
Proinflammatory conversion of monocytes and macrophages					
TNFα secretion	★		★	★	
IL1β production	★		★		
CD163 downregulation	★				
CD206 downregulation	★			★	
Increase in HLA-DR				★	☆
Increase in NFκB activation	★				★
Decreased M2/M1 ratio		★			
Inhibition of LXR/PPARγ signaling	★				
Suppression of mitochondrial respiration		★			★
Modulation of macrophage endocytosis and antigen processing					
Lysosomal de-acidification				★	★
Antigen presentation				★	
Activation of the adaptive immune system					
CD3 and TCR signalling		★			
Immune checkpoint downregulation	★			★	
CXCR3 and CD25 upregulation	★			★	
Enhanced IFN signalling	★	★	★	★	★
Enhanced LPS response (type I IFNs)				★	
Inhibition of sClever-1 production	★				☆
Immune cell recruitment					
Increased T cell numbers	★	★		★	
Increased B cell numbers	★	★			
Increased macrophage numbers		★			
Secretion of CXCR3 ligands	★	★	★	★	
Secretion of CCL3, −4 and −5			★	★	

Adapted from Rannikko JH, 2026: Clever-1 inhibition in human cancer: Consequences and control of macrophage activation by bexmarilimab. [Doctoral dissertation, University of Turku].
PDEC, patient-derived explant culture; *ex vivo*, primary cells isolated from patients or healthy donors; *in vitro*, immortalized cell lines (mainly KG-1 and THP-1).
*Unpublished observations.
★observed; ☆, tested but not observed.

establish Clever-1 as a modulator of both myeloid and lymphoid immunity, supporting its development as a broad immunotherapeutic strategy. Subsequent analyses indicate that these effects are most pronounced in interferon-poor tumor microenvironments, where Clever-1 blockade shifts TAMs toward a proinflammatory, antigen-presenting phenotype and thereby can overcome baseline immunosuppression [21]. Together, these results identify Clever-1 inhibition as a rational approach for tumors resistant to PD-1/PD-L1 blockade.

Building on these insights, biomarker research has focused on refining patient stratification for Clever-1 blockade. Clinical data and patient-derived explant models demonstrate that the response-associated gene signature following bexmarilimab treatment indicates enhanced efficacy in interferon-poor TMEs [19]. In addition, a soluble form of Clever-1 (sClever-1) has been discovered at elevated levels in the plasma of cancer patients. Produced through protease-mediated cleavage and released in microvesicles, sClever-1 binds activated T cells via IGF2R, disrupts T-cell receptor signaling, limits Th1 responses, and promotes TGF-β secretion [26]. Elevated sClever-1 has been linked to resistance to PD-1 blockade, while treatment with bexmarilimab reduces circulating levels, directly connecting target engagement with alleviation of systemic immune suppression. These findings position sClever-1 not only as an active mediator of immune evasion but also as a pharmacodynamic biomarker with potential utility for patient selection and therapy monitoring.

In contrast to solid tumors, where Clever-1 is predominantly expressed by stromal macrophages and endothelial cells, recent evidence demonstrates that in hematological malignancies Clever-1 is broadly expressed by malignant myeloid cells, including leukemic blasts and monocyte-like populations, with high levels observed in acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) [22]. This observation expands the relevance of Clever-1 beyond the tumor microenvironment and provides a strong rationale for therapeutic targeting in myeloid neoplasms (Figure 1). In *ex vivo* studies, Clever-1 inhibition enhances HLA-DR expression and improves responsiveness of AML blasts to standard-of-care therapies such as azacitidine and venetoclax [22]. In the dose-escalation part of the BEXMAB trial, combining bexmarilimab with azacitidine in patients with higher-risk MDS and relapsed/refractory AML is feasible and shows encouraging clinical activity, especially in MDS [27]. Pharmacodynamic analyses further indicate increased HLA-DR expression on monocytes in many cases, consistent with target engagement and myeloid activation. Furthermore, early translational observations suggest a potential third mechanism, whereby Clever-1 blockade supports bone marrow recovery following chemotherapy, indicating therapeutic opportunities that extend beyond immunomodulation [28].

Taken together, these studies establish Clever-1 as a multifunctional checkpoint regulating macrophage polarization, systemic immunity, tumor metabolism, and bone marrow homeostasis. Bexmarilimab therefore emerges as a versatile therapeutic platform, with applications across solid and hematologic malignancies, and with clear opportunities for biomarker-guided treatment stratification and rational combination strategies.

3. Positioning Clever-1 blockade across cancer types

3.1. Solid tumors

The scientific rationale for including ten different tumor types in the MATINS trial was derived from a combination of

preclinical efficacy in mouse models, immunohistochemical evidence of Clever-1 expression in patient samples, and analyses of Clever-1 mRNA (*STAB1*) abundance and prognostic value in The Cancer Genome Atlas (TCGA). Notably, patients with higher baseline levels of intratumoral Clever-1+ macrophages responded significantly better to bexmarilimab treatment [17], suggesting that assessment of Clever-1 expression could guide patient stratification and help prioritize tumor types most likely to benefit from Clever-1 blockade.

Analysis of the TCGA and GDC (Genomic Data Commons) datasets shows that *STAB1* is broadly expressed across multiple tumor types, with the highest levels observed (median $\log_2$-transformed TPM) in mesothelioma (5.59, range 3.91–8.23), sarcoma (5.46, range 1.77–9.83), glioma (4.90, range 1.38–9.38), neuroblastoma (4.74, range 1.53–7.51, and renal cell carcinoma (RCC) (4.55, range 0.75–8.25) (Figure 2(A)). High *STAB1* expression was significantly associated with poor prognosis in glioma and RCC, but not in sarcoma (Figure 2(B)). Because Clever-1 is also expressed by tumor-associated endothelial cells, these may contribute both to the measured transcript levels and to the observed prognostic associations in bulk RNA-seq data. Consistent with this, Clever-1 expression shows compartment-specific prognostic patterns across cancers: in breast, head and neck, and colorectal tumors, endothelial or lymphatic Clever-1 correlates with metastatic dissemination and poor survival [31,32], whereas in gastric, colorectal and urothelial bladder cancers, high densities of Clever-1+ TAMs predict reduced survival and immune/chemotherapy resistance [32–36]. Together, these data suggest that the prognostic impact of Clever-1 depends on its cellular source and function within the tumor microenvironment. It is important to note, however, that TCGA primarily comprises samples from untreated primary tumors, which may not accurately reflect Clever-1 expression patterns in metastatic or heavily pretreated disease. This limitation was evident in the MATINS trial, where a substantial proportion of metastatic biopsies contained very few Clever-1+ TAMs, suggesting that advanced tumors, particularly after multiple prior therapies, may progressively lose the myeloid compartments required for effective bexmarilimab activity. Such discrepancies highlight the need for disease-stage – specific profiling when evaluating Clever-1 as a therapeutic target.

Analysis of pathway enrichment associated with high *STAB1* expression revealed shared biological programs across most tumor types consistent with an "inflamed but immunosuppressive" microenvironment, where interferon activity coexists with strong myeloid-driven suppression. However, these similarities did not align well with the prognostic significance of high *STAB1* expression and poor overall survival (Figure 2(C)). For example, the inflammatory response pathway was shared between 20 cancer types that had high *STAB1* expression but only in six did this have prognostic significance in relation to *STAB1* expression. This discrepancy suggests that the clinical impact of Clever-1 may depend not only on the presence of specific pathways but also on how these pathways integrate with tumor-intrinsic features (e.g., mutational landscape, metabolic dependencies) and tissue-specific immune contextures. Thus, prognostic relevance of Clever-1 appears context-dependent, underscoring the need for tumor-type – specific biomarker strategies. Interestingly, breast cancers displayed a distinct pattern, with high *STAB1* showing negative associations with metabolic pathways such as oxidative phosphorylation, MYC targets, and DNA repair. *Ex vivo* assessment of bexmarilimab responsiveness in breast tumors, however, indicate that MYC- and OXPHOS-high tumors are more sensitive to treatment [19]. This raises the possibility that when Clever-1 is highly expressed, these metabolic programs are downregulated and not required to sustain tumor growth. Such heterogeneity underscores the importance of tailoring Clever-1 blockade strategies to tumor context, with the potential to unlock suppressed immunity in inflamed tumors while targeting metabolic dependencies in more immunologically silent settings.

Based on the above-mentioned observations, a logical strategy for positioning Clever-1 blockade in solid tumors is also to consider the immune subtype of the tumor rather than its tissue of origin. Analysis of *STAB1* expression across the six pan-cancer immunological subtypes defined by Thorsson et al. [37] in TCGA revealed that high expression is associated with inferior overall survival specifically in inflammatory, lymphocyte-depleted, and TGF-β–dominant contexts [19]. Consistent with these observations, recent clinical findings indicate that bexmarilimab activity is most pronounced in interferon-poor TMEs, where TAM reprogramming can shift the balance toward antigen presentation and effector T-cell activation [21]. This alignment between transcriptomic data and clinical outcomes suggests that Clever-1 targeting may be most effective when guided by immune landscape rather than histology, offering the potential to extend its use across tumors that share similar immunological features (Figure 3).

However, immune phenotypes are rarely static; they can evolve with disease progression and under selective pressure from prior therapies, complicating the reliable application of such biomarkers in clinical practice. Adding to this complexity, landmark multi-region sequencing studies have shown that tumors are not only genetically heterogeneous [38] but also display striking spatial variability in their immune infiltrates, with some regions enriched for exhausted or tissue-resident T cells while others remain immunologically inert [39]. These findings highlight that both genomic and immune features are unevenly distributed within tumors, making it difficult to extrapolate from single biopsies.

Altogether, a tumor sensitive to bexmarilimab seems to need sufficient Clever-1+ macrophages, non-IFN-dampened TAMs, ability to elicit T-cell responses (antigens, T-cell entry, absence of overly suppressive pathways) and a TME that still can be modulated by the induction of immune responses. Since, tumors differ based on these factors at the same time, finding correlations with a single factor can be confounded by the differences in others. Thus, studying bexmarilimab sensitivity in tumors could have more power, when looking at the combinations of multiple factors. e.g., the effect of cancer type or immunological context in patients with sufficient number of macrophages and Clever-1 expression.

3.2. Hematological malignancies

Multiple independent studies and translational data demonstrate that Clever-1 is expressed at both the mRNA and protein

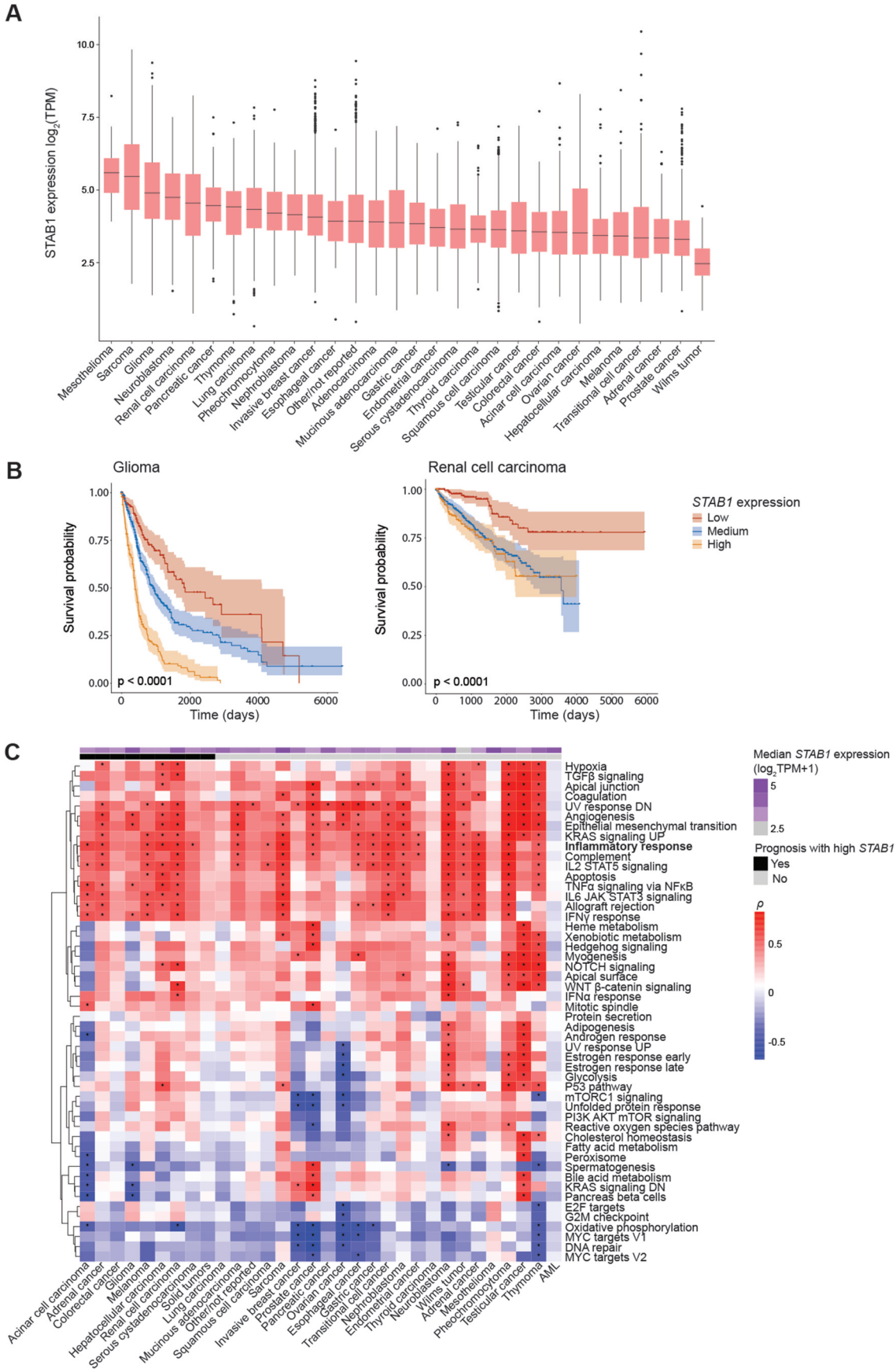

Figure 2. *STAB1* expression patterns and pathway associations across cancer types. A, Boxplot showing $\log_2$-transformed transcription per million (TPM) values of *STAB1* expression. Line represents the median, hinges correspond to the first and third quartiles and the whiskers extend to 1.5 times the interquartile range from the hinges. Outliers outside of the whiskers are plotted as dots. B, Kaplan – Meier survival analysis of glioma and renal cell carcinoma patients stratified by *STAB1* expression, demonstrating that high *STAB1* levels are associated with significantly poorer overall survival ($p < 0.0001$). Overall survival was modelled with the survival

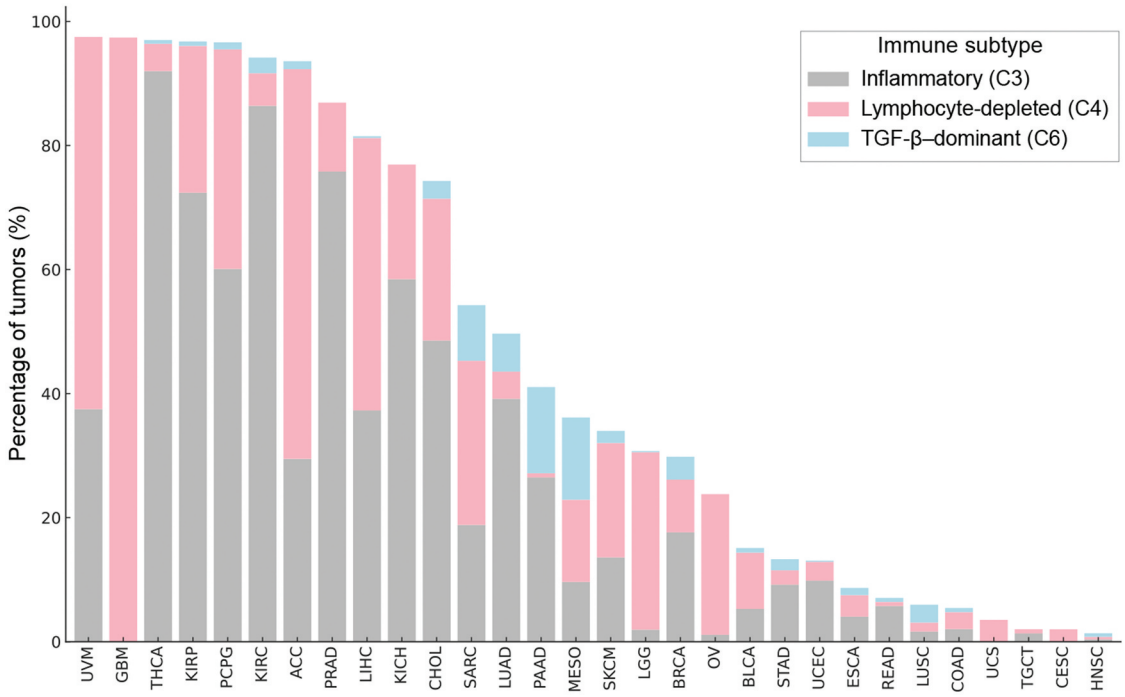

Figure 3. Prevalence of immune subtypes in which high *STAB1* expression confers inferior prognosis across TCGA cancers. Stacked bar plot showing the relative proportions of C3 (Inflammatory, gray; 26.3%), C4 (Lymphocyte-depleted, light pink; 12.7%), and C6 (TGF-β-dominant, light blue; 2.0%) tumors across 33 TCGA cancer types. Cancer types are ordered from left to right by the total proportion of C3 + C4 + C6 subtypes within each tumor type. Percentages are calculated relative to all tumors within a given cancer type. Data obtained from Thorsson et al., 2018 [37] and plotted to show immune subtypes where high *STAB1* expression associates with poor prognosis. TCGA abbreviations: UVM (uveal melanoma), GBM (glioblastoma multiforme), THCA (thyroid carcinoma), KIRP (kidney renal papillary cell carcinoma), PCPG (pheochromocytoma and paraganglioma), KIRC (kidney renal clear cell carcinoma), ACC (adrenocortical carcinoma), PRAD (prostate adenocarcinoma), LIHC (liver hepatocellular carcinoma), KICH (kidney chromophobe), CHOL (cholangiocarcinoma), SARC (sarcoma), LUAD (lung adenocarcinoma), PAAD (pancreatic adenocarcinoma), MESO (mesothelioma), SKCM (skin cutaneous melanoma), LGG (brain lower grade glioma), BRCA (breast invasive carcinoma), OV (ovarian serous cystadenocarcinoma), BLCA (bladder urothelial carcinoma), STAD (stomach adenocarcinoma), UCEC (uterine corpus endometrial carcinoma), ESCA (esophageal carcinoma), READ (rectum adenocarcinoma), LUSC (lung squamous cell carcinoma), COAD (colon adenocarcinoma), UCS (uterine carcinosarcoma), TGCT (testicular germ cell tumors), CESC (cervical squamous cell carcinoma and endocervical adenocarcinoma), HNSC (head and neck squamous cell carcinoma).

level in AML cell lines and patient samples, with particularly high expression reported in myelomonocytic (FAB M4/M5) subtypes [22]. Across patient datasets, high *STAB1* levels consistently correlate with inferior clinical outcomes, underscoring its role not only in shaping an immunosuppressive microenvironment but also as a tumor-intrinsic survival factor [40]. While no recurrent genetic lesion uniformly defines a Clever-1–high phenotype, blasts carrying FLT3 or NPM1 mutations tend to display higher levels of expression [22]. Current evidence suggests that patient selection for Clever-1–directed therapies in hematologic malignancies may be best guided by expression profiling rather than mutational status. However, recent clinical findings from the BEXMAB trial indicate that neither baseline Clever-1 expression nor blast count correlate with response [27]. Instead, patients with higher baseline T-cell numbers appeared to derive the greatest benefit, highlighting the importance of the immune context in shaping therapeutic outcomes.

4. Rational combinations to optimize efficacy

Although MATINS and the dose-escalation phase of BEXMAB confirm on-target immune activation by bexmarilimab, single-agent clinical efficacy in heavily pre-treated patients has been limited, with most benefits seen as disease stabilization in selected cases. This pattern is consistent with other macrophage-directed strategies: CSF1R inhibitors and CD47/SIRPα-blocking agents demonstrate clear pharmacodynamic effects on TAMs and phagocytosis, yet have achieved limited monotherapy responses in solid tumors, with more promising activity emerging in combination with immunotherapy or chemotherapy [41–44]. Together, these data suggest that macrophage checkpoint therapies, including bexmarilimab, are unlikely to function as stand-alone salvage treatments in extensively pre-treated disease, but rather as microenvironment-modifying partners that can enhance the efficacy of other modalities, particularly when deployed earlier and in biomarker-selected populations.

R package and Kaplan-Meier curves were plotted with the survminer R package. Samples with *STAB1* expression in the lowest and highest quartile were stratified into the low and high expression groups, respectively. Samples with expression values within the interquartile range were labelled as medium expressing. C, Heatmap of Spearman correlations between *STAB1* expression and Hallmark pathways across cancer types ordered based on prognostic significance (yes – no). Hallmark pathway scores were calculated using the ssGSEA method from GSVA package [29]. Spearman correlation between the ssGSEA scores and *STAB1* expression was calculated using base R. Heatmap of the correlation coefficients in different cancers was created with the pheatmap package [30]. Asterisks indicate correlations with $\rho > 0.5$ and $p < 0.001$.

High tumor burden, prior lymphocyte-depleting therapies, and insufficient tumor antigen availability are likely contributors to the limited activity of bexmarilimab monotherapy. Preclinical mouse studies have shown that CD8+ T cells are essential for Clever-1 blockade – induced antitumor responses [15], highlighting the importance of an intact adaptive immune compartment. These observations suggest several strategies to improve efficacy, including moving bexmarilimab into earlier treatment lines, combining it with checkpoint inhibitors to reverse T-cell exhaustion, or integrating it with chemotherapy or radiotherapy to increase antigen release. In particular, the ability of bexmarilimab to induce interferon responses within the tumor microenvironment provides a strong rationale for its combination with immune checkpoint inhibitors. Supporting this, Clever-1 blockade has been shown to synergize with anti – PD-1 therapy in mouse tumor models, overcoming resistance in otherwise refractory settings [15]. Mechanistically, high infiltration of Clever-1+ TAMs has been associated with poor responses or adaptive resistance to PD-1 blockade. By reprogramming these macrophages toward a proinflammatory phenotype, Clever-1 inhibition enhances CD8+ T-cell cytotoxicity and proliferation, thereby restoring antitumor immunity [36]. Co-targeting Clever-1 and PD-1 therefore engages complementary mechanisms that together may yield superior therapeutic efficacy.

Several cytotoxic agents, including paclitaxel and doxorubicin, induce immunogenic cell death (ICD), a process that enhances antitumor immunity by exposing danger signals such as calreticulin and releasing ATP and HMGB1 from dying tumor cells [45]. These damage-associated molecular patterns recruit and activate antigen-presenting cells, thereby expanding the pool of tumor antigens available for processing. In the context of Clever-1 blockade, bexmarilimab enables macrophages not only to phagocytose this increased antigen load but also to adopt a proinflammatory, antigen-presenting phenotype. The combination therefore offers a synergistic strategy in which chemotherapy increases the quantity and immunogenicity of tumor antigens, while bexmarilimab improves their presentation and promotes T-cell priming.

In high-grade serous ovarian cancer, chemotherapy has been shown to upregulate Clever-1 expression on macrophages, creating an even stronger rationale for combining cytotoxic agents with Clever-1 blockade. Indeed, pairing carboplatin and paclitaxel with Clever-1 targeting enhances antitumor immunity by increasing antigen release and simultaneously reprogramming macrophages toward a proinflammatory, antigen-presenting state. The therapeutic effect can be further amplified when modulators of regulatory T cells are added to this backbone, suggesting that the triplet combination is more effective than chemotherapy plus Clever-1 blockade alone *in vivo* [46]. This is likely because the addition of Treg modulation relieves a second major axis of immunosuppression, thereby allowing the full benefit of antigen release and macrophage repolarization to translate into sustained T-cell – mediated tumor clearance.

Similarly, radiation therapy induces ICD and activates the cGAS – STING pathway, stimulating type I interferon production and enhancing antigen presentation [47]. Macrophages engulf irradiated tumor debris and can be polarized toward an inflammatory phenotype, particularly at moderate doses (~8–12 Gy), which favor proinflammatory reprogramming. In contrast, very high doses are more likely to increase fibrosis and TGF-β release, driving macrophages toward an immunosuppressive state. Combining bexmarilimab with radiation therapy may be especially impactful in oligometastatic settings, where local radiation at immunogenic doses can maximize abscopal responses. Notably, immune outcomes also vary by treatment schedule: conventional fractionated radiotherapy often induces more gradual immunomodulation, whereas hypofractionated or stereotactic regimens deliver higher single doses that can more effectively stimulate innate sensing pathways but also risk enhanced TGF-β–driven suppression, making dose and fractionation critical variables in combination strategies [48].

Beyond immune modulation, Clever-1 targeting may also exploit metabolic dependencies of leukemic stem and resistant cell populations. Leukemic stem cells (LSCs) display a distinct metabolic program characterized by reliance on oxidative phosphorylation (OXPHOS) for energy production and survival, reflecting their limited glycolytic capacity and need to maintain low levels of reactive oxygen species [49]. In contrast, therapy-resistant AML subclones frequently adapt by engaging fatty acid oxidation (FAO) as an auxiliary fuel source, thereby sustaining mitochondrial metabolism and promoting persistence under therapeutic pressure [50]. These insights highlight OXPHOS and FAO as critical metabolic vulnerabilities that could be exploited through rational combination strategies, particularly when paired with chemotherapies that further disrupt leukemic cell fitness. Given Clever-1's role in lysosomal trafficking and lipid metabolism, its inhibition could disrupt these programs and sensitize leukemic cells to agents that further intensify metabolic stress. Rational combinations include pairing bexmarilimab with venetoclax, which suppresses OXPHOS by impairing mitochondrial integrity, or with FAO inhibitors such as etomoxir, an irreversible blocker of CPT1 that prevents mitochondrial fatty acid import. These strategies may weaken leukemic persistence while simultaneously reprogramming the immune microenvironment.

Altogether, while many combination strategies are mechanistically justified but not yet experimentally validated, several pairings with bexmarilimab already have supportive evidence. Preclinically, synergy between Clever-1 blockade and anti – PD-1 therapy has been demonstrated across multiple tumor models, including lung, breast, and colorectal cancer [15], where the combination enhances T-cell activation and overcomes resistance. In ovarian cancer mouse models, combining bexmarilimab with carboplatin and paclitaxel improves antitumor immunity [46], and in ex vivo human gastric cancer explants, dual Clever-1 and PD-1 inhibition augments interferon-driven responses [36]. Clinically, the most advanced validation comes from hematologic malignancies: in the BEXMAB trial, bexmarilimab combined with the hypomethylating agent azacitidine shows clear immunologic activity and encouraging efficacy in higher-risk MDS [27]. These findings highlight that while the mechanistic rationale for several other combinations

is strong, only a subset has been experimentally verified, underscoring the importance of continued translational and clinical investigation to define the most effective therapeutic partners for Clever-1 blockade.

5. Dose, timing and treatment setting

Clinical experience indicates that bexmarilimab achieves optimal immune activation at doses of 1–3 mg/kg, following a bell-shaped response curve in which higher exposures do not enhance efficacy [17]. In the MATINS trial, adaptive immune activation was observed around seven days after the first dose despite the antibody's relatively short plasma half-life, showing that pharmacodynamic effects extend well beyond pharmacokinetics [16]. These findings suggest that sustained target engagement is not required in solid tumors, where transient Clever-1 inhibition may be sufficient to induce interferon responses and reprogram macrophages. In hematologic malignancies, however, higher or more sustained dosing may be needed, given the dual targeting of malignant blasts and the monocyte – macrophage compartment. For combinations, a short priming period of Clever-1 blockade, such as one week prior to PD-1/PD-L1 therapy, may enhance efficacy by boosting interferon signaling and antigen presentation before T-cell reinvigoration. With chemotherapy, bexmarilimab may be most effective when given concurrently or shortly after cytotoxic treatment, coinciding with maximal antigen release and macrophage phagocytosis. Intermittent dosing aligned with chemotherapy cycles (e.g., day 1 of each cycle) could therefore provide sufficient priming of the tumor microenvironment, while future studies should clarify whether a lead-in dose adds further benefit. In resistant settings, Clever-1 inhibition has also re-sensitized patients to standard therapies such as azacitidine [27], underscoring its promise in refractory disease when used in combination. Collectively, these PK/PD insights support the use of intermittent or pulsed dosing strategies to sustain immune activation while balancing efficacy with long-term safety.

6. Synergy with next-generation immunotherapies

A promising avenue involves pairing bexmarilimab with novel immunotherapies that extend beyond conventional PD-1/PD-L1 or CTLA-4 inhibitors. One such approach is dual myeloid checkpoint inhibition, combining Clever-1 blockade with agents targeting alternative macrophage pathways such as LILRBs, VISTA, TIM-3, and TREM2. This strategy could dismantle compensatory suppressive networks that may arise when a single pathway is inhibited. Similarly, combining bexmarilimab with anti-CD47/SIRPα antibodies may simultaneously lift the "don't eat me" signal and enhance antigen processing, amplifying phagocytosis and subsequent T-cell priming. A recent pre-clinical study, however, showed that dual TIM-3/VISTA blockade alone is insufficient to control tumor growth, as resistant tumors remain dominated by immunosuppressive TAMs. Only when combined with paclitaxel did TIM-3/VISTA inhibition reprogram these macrophages into a proinflammatory, tumoricidal state, achieving effective tumor control through macrophage-driven, T-cell – independent mechanisms [51].

Beyond myeloid-specific interventions, Clever-1 blockade may augment innate immune agonists such as STING or TLR ligands. These agents activate type I interferon signaling and dendritic cell maturation, processes that bexmarilimab potentiates by increasing antigen availability and presentation. Finally, the integration of bexmarilimab with cellular immunotherapies, including CAR-T, CAR-NK, or bispecific T-cell engagers, could address the challenge of T-cell exclusion in macrophage-rich tumors by converting immune-desert environments into ones supportive of adoptive cell expansion and activity.

In hematological malignancies, Clever-1 expression on leukemic blasts creates an opportunity for dual targeting of malignant cells and their immunosuppressive niches. Precision approaches may involve correlating Clever-1 expression with metabolic dependencies such as OXPHOS or BCL-2 addiction, thereby identifying patients who would benefit most from bexmarilimab combined with hypomethylating agents or venetoclax, respectively. Similarly, cytokine-driven signatures, such as IL-10–rich environments, may serve as functional biomarkers for Clever-1 dependence and therapeutic susceptibility.

7. Conclusions

Clever-1 blockade has emerged as a versatile immunotherapeutic strategy capable of reprogramming immunosuppressive macrophages, enhancing antigen presentation, and reshaping both solid and hematologic tumor microenvironments. Clinical and translational findings with bexmarilimab demonstrate clear on-target biological activity, including induction of interferon signaling, T-cell activation, and myeloid reconditioning, yet also highlight the limitations of monotherapy in heavily pretreated disease. By integrating preclinical models, patient-derived explants, and large-scale transcriptomic analyses, our review outlines how tumor context, immune landscape, metabolic dependencies, and Clever-1 expression patterns together shape therapeutic responsiveness. These insights support a shift toward biomarker-guided deployment of bexmarilimab, particularly in interferon-poor settings and earlier lines of therapy. They also provide a mechanistic basis for rational combinations, most notably with checkpoint inhibitors, cytotoxic therapies, metabolic agents, and emerging innate immune agonists, that could unlock the full therapeutic potential of myeloid checkpoint modulation. As such, Clever-1 inhibition stands poised to complement and enhance multiple existing treatment modalities, offering a promising avenue for broadening the reach of immunotherapy across diverse malignancies.

8. Future perspectives

The clinical development of bexmarilimab exemplifies the maturation of immuno-oncology beyond T-cell – directed checkpoints, highlighting the centrality of myeloid reprogramming in overcoming resistance. While current evidence demonstrates safety, target engagement, and immune

activation, critical questions remain regarding durability of response, mechanisms of resistance, and the identification of patient populations most likely to benefit. Addressing these challenges will require coordinated efforts that integrate translational science with innovative clinical trial design. One key priority is to establish predictive biomarkers that can reliably identify Clever-1–dependent tumors and guide therapy selection. Advances in single-cell and spatial profiling are likely to be instrumental in refining such strategies, enabling real-time assessment of TAM states and their interactions with T cells. In parallel, unraveling the mechanisms of resistance, such as compensatory activation of alternative myeloid checkpoints, persistence of TGF-β–driven macrophage polarization, or metabolic rewiring of malignant cells, will inform rational combination strategies.

Bexmarilimab's favorable safety profile and immunomodulatory potency suggest that its greatest impact may emerge in earlier treatment lines, before the TME becomes irreversibly immunosuppressive. Integration into first-line regimens for both solid and hematological malignancies could prevent establishment of suppressive niches and maximize the window for immune reconstitution. Looking ahead, Clever-1 blockade offers the potential to transform immunotherapy from a primarily T-cell – centric paradigm to a dual-axis model that simultaneously targets adaptive and innate immune dysfunction. If validated through biomarker-driven, combination-based clinical development, bexmarilimab may establish macrophage reprogramming as a cornerstone of next-generation cancer immunotherapy.

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Author contributions

The study was conceptualized by MK and MH. MK prepared the first draft of the manuscript, and JM conducted the TCGA data analysis. All authors contributed to the writing, revision, and approval of the final manuscript.

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