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► **To cite this version:**

Clémentine Sarkozy, Benoit Tessoulin, David Chiron. Unraveling MCL biology to understand resistance and identify vulnerabilities. *Blood*, In press, 10.1182/blood.2023022351 . hal-04547407

HAL Id: hal-04547407

<https://hal.science/hal-04547407>

Submitted on 16 Apr 2024

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Unraveling MCL biology to understand resistance and identify vulnerabilities

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Running Title, MCL Ecosystem targeting: worth the bet

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Disclosure: Authors declare no competing financial interests.

Abstract word count: 227

Article word count: 4397

Number of Figure: 2

Reference count: 153

Abstract

Mantle cell lymphoma (MCL) is a rare (5-7%), aggressive B-cell non-Hodgkin's lymphoma with well-defined hallmarks (e.g. Cyclin D1, SOX11), and whose expansion is highly dependent on the tumor microenvironment (TME). Parallel drastic progresses in the understanding of the lymphomagenesis and improved treatments led to paradigm shift in this B-cell malignancy with now prolonged disease-free survival after intensive chemotherapy and anti-CD20 based maintenance. However, this toxic strategy is not applicable in frail or elderly patients and a small but significant part of the cases will present a refractory disease representing unmet medical needs. Importantly, the field has recently seen the rapid emergence of targeted and immune-based strategies with effective combinations relying on biological rationales to overcome malignant plasticity and intratumor heterogeneity. In this review, we expose how unraveling the biology of MCL allows to better understand the therapeutic resistances and to identify neo-vulnerabilities of tumors, which are essential to offer efficient novel strategies for high-risk patients. We first highlight the tumor intrinsic resistance mechanisms, and associated Achilles heels within various pathways such as NFkB, mitochondrial apoptosis, DNA repair or epigenetic regulators. We then place the tumor in its complex ecosystem to decipher the dialog with the multiple TME components and show how the resulting protumoral signals could be disrupted with innovative therapeutics strategies. Finally, we discuss how these progresses could be integrated in a personalized approach in MCL.

Background

Mantle cell lymphoma (MCL) is an aggressive subtype of B-cell non-Hodgkin's lymphoma (NHL). The most common MCL subtype is derived from IgM+ CD5+ mature B-cells with well-characterized hallmarks such as Cyclin-D1 and SOX11 overexpression¹. In recent years, median survival has increased dramatically, in particular thanks to improved first line strategies based on anti-CD20, high-dose cytarabine, and stem cell transplantation².

Efforts to characterize the molecular profile of MCL and the interactions that occur in its ecosystem have greatly enhanced our understanding of the disease^{3,4}. Among the major advances, targeting constitutive BCR signaling with BTK inhibitors and dysregulated mitochondrial apoptosis with BCL2 inhibitors have shown promise as single agents or in combination with chemotherapy⁵⁻⁷. These agents' combination efficacy has paved the way for chemo-free trials to improve patients' quality of life while maintaining high clinical efficacy in the first line^{8,9} and RR setting¹⁰. In the real-life setting, very few data for such chemo-free options have been reported, with mitigated results for Rituximab-Ibrutinib combination¹¹.

Despite this progress, drug resistance remains a significant challenge¹² as current targeted treatments have reduced long-term efficacy due to malignant cell plasticity and intratumor heterogeneity¹³⁻¹⁵. Given the rapid expansion of new therapeutic options (targeted, cellular, and immune therapies), identifying biomarkers of response, escape mechanisms, as well as the potential neo-vulnerabilities of the resistant tumors, is essential for shifting strategies for patients.

Here, we review our current knowledge of MCL biology, focusing on recent findings at a tumor and ecosystem levels. We highlight how these insights could explain the tumor resistance to current therapies, and how they may participate in the rationale of future mechanism-based therapeutic strategies.

Part-1 Uncovering MCL intrinsic anomalies and associated vulnerability

The mutational profile and (epi)genomic alterations of MCL are now well-defined^{16–19}. MCLs are characterized by a low mutational load (~1 mutation per megabase) associated with a complex genomic landscape defined by many copy-number alterations (CNAs) and structural variants. At diagnosis, apart from *ATM* (>40%) and *TP53* (>25%), most mutations are found at low frequencies (<15%) and include variants in *NSD2*, *KMT2A/C/D*, *S1PR1*, *CARD11*, *SMARCA4*, *SP140* or *NOTCH1/2*, resulting in a significant inter-patient heterogeneity. The most frequent CNAs include deletion of *ATM*, *CDKN2A/B*, *BIRC3*, *RB1* and *TP53*, and the amplification of *PIK3CA*²⁰ and *CCND1*¹⁷. Interestingly, among these hits, cross-sectional analyses across NHLs have highlighted MCL-specific anomalies, such as *ATM*, *RB1*, *NSD2*, *CDKN2A/B*, *NOTCH1/2* and *UBR5*²¹.

In this first part, we will focus on the frequent intrinsic abnormalities described in MCL regarding their role in tumor progression and resistance, and how some of them result in selective druggable vulnerabilities (Figure 1).

1- Targeting the hallmarks of MCL: Cyclin-D and SOX11

The translocation t(11;14)(q13;q32), which juxtaposes the *CCND1* gene with an enhancer of the immunoglobulin heavy chain gene, leads to aberrant Cyclin-D1 expression²². Interestingly, the few Cyclin-D1-negative cases described carried an alternative rearrangement of Cyclin-D2/D3, highlighting that cell-cycle dysregulation is the hallmark of MCL²³. Aberrant Cyclin-D, associated with high levels of its molecular partner CDK4, not CDK6, leads to uncontrolled G1-S cell-cycle transition through phosphorylation and the inactivation of the Rb checkpoint. Furthermore, the *CDKN2A* locus (9p21), which encodes the CDK4 inhibitor p16^{INKA4}, is frequently deleted (25-33%), a feature associated with poor prognosis after chemotherapy²⁴. The role of cell proliferation assessment on prognosis is currently used in the routine, with Ki67 staining in IHC²⁵, leading to potential risk stratification strategy in clinical trials.

Overall, targeting the Cyclin-D1/CDK4 holoenzyme represents a rational approach to controlling cell-cycle in MCL. Accordingly, clinical trials using palbociclib, the first-in-class

selective CDK4/6 inhibitor, confirmed effective G1 arrest, associated with a durable response and an acceptable safety profile²⁶. Nevertheless, only a few trials have been subsequently developed in MCL. Of these, a phase 2 combination with BTK inhibitors is underway (*NCT03478514*)^{27,28}. The main mechanism of resistance to CDK4/6 inhibitors is the deletion of the *RB1* locus (13q14)(30% of patients at diagnosis)²⁹. Among alternative targets outside the CDK4/Rb axis, selective inhibition of CTPS1, a catalyzer of a rate-limiting step in CTP synthesis, selectively hinders the proliferation of lymphoid malignancies cells outside the hematopoietic system depending on CTPS2³⁰. Pre-clinical studies have demonstrated cell-cycle arrest, including in Rb- MCL³¹, and the first-in-class CTPS1 inhibitor entered clinical development in 2022 (*NCT05463263*).

In addition to Cyclin-D1, most cases of MCL are characterized by aberrant expression of the SOX11 transcription factor³². Of note, the minor subgroup (10-15%) of clinically indolent "leukemic non-nodal MCL", is negative for SOX11¹⁸. SOX11 expression likely derives from epigenetic changes, such as enhancer demethylation¹⁹ and Cyclin-D1 sequestration of HDAC1/2 from the SOX11 locus³³. SOX11 is implicated in impaired terminal B-cell differentiation through PAX5 inhibition³⁴, it enhances antigen-independent BCR signaling in the SOX11 transgenic mouse model³⁵, and impacts the MCL ecosystem^{36,37} (detailed in the Part-2). First in class small SOX11 inhibitors are in development³⁸. Paradoxically, it has recently been described that SOX11 inhibits SAMHD1, making MCL cells more vulnerable to cytarabine and highlighting the need to design rational combinations with SOX11 inhibitors³⁹.

2- Multiple hits for several NFkB pathways in MCL

Classical NFkB1 and alternative NFkB2 pathways are both activated in MCL, particularly in protective lymph node niches^{40,41}. Among the various stimuli that engage NFkB, NFkB1 activity depends on active BCR signaling in MCL, while NFkB2 is triggered by the activation of CD40 and BAFFR^{13,42}.

MCL cells also frequently present anomalies which lead to constitutive activation of NFκB2, as loss of function mutations of *BIRC3* and *TRAF2* (15%)⁴³ or BIRC2/3 locus deletion (11q22, 26%)⁴⁴, leading to constitutive activation of the NFκB-inducing NIK kinase (*MAP3K14*), itself mutated, but at low frequency⁴³. These anomalies make MCL cells independent of the BCR/NFκB1 pathway, and resistant to BTK inhibitors (BTK-i), but dependent on the NIK/NFκB2 pathway⁴³. This neo-vulnerability has highlighted selective NIK inhibitors but further studies are needed to assess the safety of NIK targeting *in vivo*⁴⁵.

Within the classical BCR/NFκB1 pathway, on-target BTK mutations are rare, but ultimately lead to resistance to both covalent²⁸ and non-covalent⁴⁶ BTK-i. Innovative strategies, such as BTK-degraders, have been designed to circumvent this resistance⁴⁷ and phase-I studies are underway (*NCT04830137*). The CARD11-BCL10-MALT1 (CBM) complex is essential for transducing BCR-dependent NFκB1 signaling, and *CARD11* gain-of-function mutation (8% in MCL)^{17,48} leads to constitutive activity and consequent BTK-i resistance^{13,49}. MCL cells are also dependent on MALT1⁵⁰, and the *in-vitro* efficacy of MALT1 protease inhibitors is independent of the mutational status of *BTK* or *CARD11*^{13,51}. Furthermore, MALT1 activity controls the protein stability of MYC⁵⁰, which is a high risk factor in MCL⁵². Basic research⁵³ and ongoing phase-1 (*NCT03900598*) will soon provide further information on the efficacy of this strategy in MCL.

3- BCL2 overexpression, apoptosis priming and vulnerability to BH3-mimetics

In contrast to the NFκB pathway, MCL cells exhibit only a few genetic abnormalities within the BCL2 family. These include amplification of the *BCL2* locus (18q21, 20%)⁵⁴ and loss of the miR-15a/miR-16 locus (13q14, 50%), which normally negatively regulate BCL2 at a post-transcriptional level⁵⁵. Overexpression of BCL2 leads to drug resistance by neutralizing pro-apoptotic proteins (BH3-only), preventing the activation of BAK and BAX and, ultimately, the induction of apoptosis. The resulting BCL2/pro-apoptotic complexes make cells "primed for death" and vulnerable to BH3-mimetics (*i.e.* venetoclax), which release pro-apoptotic proteins from BCL2 and trigger cell death^{48,56}. In line with this, venetoclax achieved a high ORR (50-

75%) in relapsed/refractory patients, but only a moderate CR rate (20%) and short duration of response has been reported^{57,58}, underlining the need for combinations.

Loss of BCL2 amplicon has been associated with venetoclax resistance in MCL⁵⁹ and, contrarily to CLL⁶⁰, mutations are uncommon. Alternatively, intrinsic abnormalities and extrinsic signals leading to high levels of BCLXL^{14,40}, BCL2A1¹³ and MCL1^{40,61}, are associated with venetoclax resistance. This has led to the use of BH3-mimetics which target BCLXL or MCL1 in combination with venetoclax, resulting in high efficacy in MCL *in vitro* and animal models⁶², but excessive toxicity in humans⁶³. Targeting the pathways that regulate these anti-apoptotic proteins has also been evaluated. BCR inhibitors, such as BTK-i or MALT1-i, result in the downregulation of *BCL2A1*¹³, while second-generation anti-CD20 antibodies (Obinutuzumab) counteract microenvironment-dependent BCLXL induction⁴⁰, both leading to synergy with venetoclax, confirmed in several phase-I/II trials^{8,14}. Regarding MCL1, several strategies aiming at targeting its transcription or translation have shown promising pre-clinical efficacy^{59,64,65}. Innovative strategies for minimizing toxicity, such as tumor-targeting nanoparticles or protein degraders, are being evaluated⁶⁶.

Longitudinal analysis of patients on venetoclax monotherapy highlights clonal selection of MCL cells mutated for selective hits⁵⁷, especially *TP53*, known to be essential for maintaining a durable response to BH3-mimetics through BAX regulation⁶⁷.

4- The unmovable blockade on p53 road

MCL is no exception in the lymphoma field regarding *TP53* dysregulation⁶⁸, both at diagnosis and in the R/R setting¹⁷. *TP53* mutation occurs in 10-48% of newly diagnosed cases (depending on studies and techniques), without identified vulnerability. For young patients, *TP53* deletion negatively impacted outcome along with *CDKN2A* deletion²⁴. Whether *CDKN2A* loss is detrimental remains debatable, as most patients harboring *CDKN2A* abnormalities also demonstrate other abnormalities in *TP53*, *ATM*, *MYC*, or *RB1*⁶⁹. Furthermore, *TP53* mutation is independently associated with impaired survival in young⁷⁰, elderly⁷¹ and general

populations⁷². An effort should be made to encompass the high heterogeneity of hits that may alter p53 functioning⁷³.

BTK-i may create a new path for these patients, nevertheless, Rule *et al* reported that no patient with *TP53* mutation reached CR with Ibrutinib alone in the R/R setting⁷⁴. Combinations of targeted and chemo-therapy may not be the answer to p53 abnormality, as neither bendamustine combined with lenalidomide⁷⁵ or ibrutinib⁵ showed improved efficacy. Conversely, ibrutinib associated with venetoclax or lenalidomide yielded significant CR rates (respectively, 45-60%; and 64%)^{8,9,76}. The Acalabrutinib-Lenalidomide and Rituximab combination has also been investigated with, in first line, ORR, 100%, and CRR, 92% but a safety profile associated with 42% of grade 3-4 rash⁷⁷. Notably, the BOVEN combination (Zanubrutinib, Obinutuzumab and Venetoclax) demonstrated sustained CRR of 88% in patients with *TP53* mutations in the first line setting⁷⁸. Finally, while encouraging response rates for *TP53*^{Abn} patients were initially reported with anti-CD19 CAR-T cells in the Zuma-2 trial, real-world evidence from US experiences reported reduced PFS for patients with *TP53* aberration⁷⁹. While being a main hit at diagnosis (~50% of cases), *ATM* and *TP53* status are mutually exclusive^{3,80}. Hence, *ATM* specific prognosis impact independently of *TP53* cannot be easily assessed⁸¹.

Targeting DNA-damage repair's (DDR) may be of interest for exploiting synthetic lethality⁸² in MCL, as many actors are abnormal at diagnosis (*ATM*, *TP53*, *CHK1*, *p14^{ARF}*). Menezes *et al* demonstrated that DDR defective cells exhibited particular sensitivity to ATR-i⁸³, similarly to CLL⁸⁴. These results were confirmed in a limited set of MCL cell lines and whether the effect of ATR-i relied on DDR-deficiency is yet to be confirmed⁸⁵. *CHK1* and *Wee1* inhibitors were used to bypass cell-cycle checkpoints and maintain heavy DNA-damage. *In vitro* and *in vivo* efficacy were noted, without clear evidence of strong synthetic lethality, but without translation into the clinical space^{85,86}. Clinical trials with the ATR-i Elimusertib are currently being set up (*NCT03188965*). Finally, several *in-vitro* reports of PARP-i have shown moderate effects⁸⁷, with

no clinical activity with Olaparib alone (N=4 MCL patients) or PARP-i and Rituximab and Bendamustine⁸⁸.

5 – Above genetics: a landscape to harness

If many epigenetic actors are mutated in MCL patients¹⁷ (*KMT2D*, 14-30%; *NSD2*, 6-18%; *SMARCA4*, 7-12%; *SP140*, 13%; *KMT2C* 5%), the epigenetic landscape relates to the cell history before/during malignant transformation including its Germinal Center experience^{18,19}, with underexplored therapeutic opportunities.

EZH2-i (e.g. Tazemetostat) are under investigation, and have demonstrated *in vitro* activity, especially in BTK-i resistant isogenic cells⁸⁹. Bromodomain-containing protein 4 (BRD4) regulates several cycle-involved genes (*MYC*, *CDK4/6*, *CCND1*). Bromodomain and Extra-terminal motif (BET)-i have been tested alone, or in combination (HDAC-i, CDK4/6-i, anti-BCL2), producing synergy, and overcoming some resistance to BTK-i^{90,91}. Recent findings of BET-i associated with inhibitors of CK2 (coded by *CSNK2* under the regulation of BRD4), demonstrated improved apoptosis and proliferation arrest in MCL cells⁹². PROTACs' targeting of BRD4 may overcome the toxicity profile that has hampered the clinical development of these treatments⁹³.

Histone deacetylase's (HDACs) targeting by pan HDAC-i has a narrow therapeutic index. Vorinostat (HDAC-i) demonstrated *in vitro* activity alone and in combination with palbociclib (CDK4-i) or bortezomib, without clinical response^{94,95}. Abexinostat showed a higher ORR (27.3%)⁹⁶ and is being studied in combination with Ibrutinib (*NCT03939182*). Vorinostat combined with Cladribine and Rituximab yielded impressive responses (80%CR, n=39) in untreated MCL patients with a median PFS of 84 months⁹⁷. NSD2 methyltransferase may also be of interest in MCL, as it is associated with oncogenic reprogramming⁹⁸.

PRMT5 is a type-II arginine methyltransferase, upregulated in R/R MCL patients⁹⁹ that demethylates histones and other proteins, triggering homologous recombination mechanisms and modulating expression of p53, MYC and CCND1. PRMT5-i demonstrated *in vitro* activity alone¹⁰⁰ and in combination with venetoclax¹⁰¹ as well as synergy with PARP-i and ATR-i in

BTK-i resistant MCL⁹⁹. PRMT5-i should be used in combinations, as a compensatory modulation of pathways may counterbalance the compounds' effects¹⁰².

Considering the overall epigenetic marker that sets during lymphomagenesis, which differentiates conventional SOX11+ from indolent SOX11- MCL¹⁹, leveraging methylome may prove to be of interest. DNMT1 was found to be upregulated in MCL¹⁰³ however very limited literature exists on this subject for inhibitors (decitabine, azacytidine). Mitochondrial oxidative phosphorylation (OXPHOS) is presumed to be governed by DNMT3A, and EGR1, and is a major player in the resistance to Ibrutinib. Decitabine may revert this resistance-associated phenotype when used with IM156, a mitochondrial-complex-I inhibitor^{104–106}.

Part-2: Place the tumor in its environment and rethink MCL as a tumor ecosystem.

The heterogeneity of MCL behavior probably doesn't just rely on the variability of acquired cellular abnormalities, but also on a more complex ecosystem, where the TME provides the fertile soil for proliferation and drug resistance^{40,41}. This complex interaction also results in vulnerabilities that provide options for drug combinations. In this second part, we will describe the main TME components, their interactions with the tumor cells, and the resulting therapeutic options (Figure 2).

1- BCR signaling induced by various interactions within the ecosystem.

BCR-dependency, which leads to NFkB1 activation and consequently BTK-i sensitivity, relies on multiple mechanisms related to intrinsic abnormalities (see Part-1), and also interactions with the TME. Indeed, thanks to a cyclin-D2-driven murine model, B1a cell with a restricted self-reactive BCR repertoire and elevated BCR signaling has been hypothesized as the cell of origin of MCL. Hence, continuous self-antigen-driven triggering of B1a cells may aid in their long-term self-renewal. These cells have been seen to be sensitive to BTK and MALT1 inhibition¹⁰⁷, and MALT1-dependence has been confirmed in human MCL cells^{13,50}. Interestingly, a self-antigen, LRPAP1, has been recently identified¹⁰⁸. LRPAP1 auto-antibodies

were detected in 13% patients with MCL, when treated in European MCL Network Younger and Elderly trials, and their presence was associated with prolonged, failure-free survival and overall survival, adjusted on MIPI score¹⁰⁹.

The distinction observed between circulating and LN-resident MCL cells, supports the interaction with the TME which leads to BCR and NFkB activation⁴¹. Accordingly, selective inhibition of BTK within BCR and CXCR4 inhibitor disrupts this interaction, leading to peripheral lymphocytosis¹¹⁰. The specific phenotype of these circulating cells shows markers for the disconnection from TME components: reduction of CXCR4 expression (involved in the homing to lymphoid tissues), in plasma chemokines (CCL22, CCL4, and CXCL13) and of BCLXL (and consequent venetoclax sensitivity)^{48,111}.

2- Stromal cell adhesion-mediated drug resistance and vulnerability

The stromal cells in MCL have a key role in triggering BCR, PI3K, JAK or NFkB activation, through chemokine receptors and adhesion molecules critical to the trafficking and homing of the tumor cells. Adhesion to stromal cells is partly attributed to the high level of expression of functional CXCR4, CXCR5 chemokine receptors, and VLA-4 adhesion molecules on the surface of MCL¹¹². BCR activation by stroma is multifactorial, *via* a variety of molecules, including BAFF, antigen receptors and integrin^{113,114}.

Targeting BCR signaling using BTK-i attenuated MCL adhesion to stroma, partly by blocking stromal-induced integrin-beta1 (β 1) expression. One mechanism of both acquired and *de novo* resistance to BTK-i has been demonstrated to be associated with increased expression of β 1 and MCL/stromal cell adhesion, due to a reciprocal activation loop of PI3K-AKT-mTOR, and β 1/ILK signaling¹¹⁵. AKT or PI3K inhibitors could overcome this compensatory mechanism, with a reduction in β 1 expression and stroma cell adhesion, providing a rationale for the combination.

The identification of BAFF and its receptor in the dialog with stromal cells make this factor a central actor in the MCL ecosystem, and a potential target, as BAFF-R knockdown leads to MCL cell death. In CLL, anti-BAFF-R antibody enhanced ADCC, blocked BAFF-mediated

survival, and enhanced the *in vivo* activity of BTK-i in a murine model, leading to the development of a phase-I trial¹¹⁶. Different humanized BAFF-R antibodies were optimized for ADCC and showed anti-tumor activity in animal models, and hope for clinical development in MCL^{117,118}.

This stromal-lymphoma cell interaction has other vulnerabilities that can be targeted, such as FAK (*PTK2*, upregulated by SOX11) involved in cell adhesion-mediated resistance through ERK1/2 and PI3K/AKT downstream activation³⁷. FAK-i have been shown to block cell invasion and induce apoptosis *via* a disruption in the NFκB pathway in co-culture models using bone marrow stromal cells and MCL cell lines. Moreover, synergy was found between BTK and FAK inhibitors, that could bypass BTKi primary resistance¹¹⁹. FAK-i also showed efficiency in reversing bortezomib resistance³⁷, as well as CXCR4 inhibitors that impaired SOX11+ cell engraftment in the bone marrow of MCL xenograft models. Finally, stroma-mediated venetoclax resistance was observed through upregulation of MCL1, which could be counteracted by CK2 inhibition, identified thanks to kinome-centered CRISPR-Cas9 sensitizer screening.⁶⁴

3- T-cells in MCL: from pro-tumoral signals to promising therapeutic tools

Deconvolution of "bulk" transcriptomic datasets has recently identified four MCL TME subtypes, from immune-cell enriched "hot" to a depleted "cold" ecosystem¹²⁰. T-cell infiltration plays a key role in this diversity, and while a depleted immune ecosystem is associated with BTK-i resistance, CD8+ T-cell infiltration is associated with tumor aggressiveness, and higher CD4 levels with more indolent disease^{120,121}. Globally, LN-infiltrating T-cells display an exhausted phenotype, characterized by the high expression of the PD1 and TIGIT immune checkpoints, and MCL cells express the TIGIT ligands CD155 and CD122 as well as PDL1^{122,123}. Furthermore, a recent study reported SOX11-dependent overexpression of CD70 by MCL cells associated with increased CD27+ T-reg infiltration, elevated proliferation, and an aggressive clinical course³⁶. Therefore, while most MCL cells express moderate levels of MHC

class-I/II, mainly loaded with Ig neoantigens¹²⁴, T-cells are ineffective against tumor cells, their effector functions and cytokine production capacity having been suppressed.

Worse than just being silenced, T-cells that infiltrate MCL could also provide pro-tumoral signals, notably through the expression of CD40 ligand (*CD40LG*). Based on integrated transcriptomic and functional testing, several studies have shown that *ex vivo* CD40 triggering leads to the activation of cellular (proliferation, survival) and molecular (NFkB, apoptosis regulation) signatures, characteristics of LN-resident MCL cells^{40,41,125}. This is associated with a profound modulation of the BCL2 family, leading to a loss of mitochondrial priming and increased drug resistance^{40,126}.

These findings underscore the need to target the T and MCL cells interactions. In contrast to solid tumors and Hodgkin's lymphomas¹²⁷, checkpoint inhibition strategies (i.e. anti-PD1/PD-L1) in MCL has not shown a significant clinical response (Nivolumab). Combinations with ibrutinib (*NCT03153202*) or lenalidomide (*NCT03015896*) are under investigation. Innovative immunotherapies, such as ROR1-CD3 or CD20-CD3 bispecific antibodies and chimeric antigen receptor T-cells (CAR T-cells) directed against CD19, both aiming at restoring effective T-cell-mediated cytotoxicity^{128–130} have shown encouraging clinical efficacy in MCL. However, the outcomes of patients are heterogeneous, and further studies will be needed to understand what the determinants of response are in the tumor (e.g. *TP53*)⁷⁹, and also within the immune ecosystem. For example, high TIGIT expression has recently been associated with relapse in MCL patients treated with CART-cell therapies¹³¹.

4- Innovative strategies for disrupting the pro-tumoral dialogue between MCL and macrophages

In addition to T-cells, myeloid cells are also a key compartment of the ecosystem that can be corrupted by the tumor and participate in the disease's resistance and progression^{132,133}. Although there are few *in situ* infiltrating CD68+CD163+ macrophages (<0.1%), their presence has been associated with aggressiveness and poor prognosis in MCL¹³⁴, confirming the need to better understand the molecular interactions between those cells. Of note, soluble CD163,

measured in the serum of MCL at diagnosis, also predicts the outcome of patients. The correlation with a poor prognosis was independent of tumor status (MIPI, Ki67, TP53), providing a novel, TME-dependent predictive marker, easily assessed in non-invasive samples¹³⁵.

In line with these observations, macrophages support MCL cell survival, proliferation and resistance^{42,125,136,137}. While MCL cells polarize monocytes into selective pro-tumor macrophages through their aberrant secretome (i.e. CSF1, IL10, CCL3 and IL32), macrophages support MCL survival through BAFF secretion^{42,136,137}. Notably, most of these soluble factors are controlled by NFkB pathways, and while NFkB2/NIK- targeting impairs IL32 production and BAFF protumoral support, IL10 and CSF1 are controlled by the BCR/NFkB1 axis^{42,136}. Accordingly, MCL patients who respond to BTK-i therapy show an early reduction of CSF1/IL10, as well as a reduction in the pro-tumor marker CD163 in circulating monocytes. As this was not observed in refractory patients, this suggests that BTK-i's efficacy is, at least partly, due to its ability to disrupt the pro-tumoral dialogues within the MCL's protective niches¹³⁶. To counteract BTK-i resistance and take advantage of the tumor's dependence on its microenvironment, strategies targeting macrophages through CSF1R-i have been proposed¹³⁶. Alternative strategies include the inhibition of "don't-eat-me" signals, carried by the CD47/SIRP α and CD24/Siglec-10 axis, to restore anti-tumor phagocytosis. Interestingly, expression of CD24, not CD47, is associated with a poor prognosis in MCL¹³⁸.

5- Novel immune-based therapeutic strategies

B cell surface antigens can be efficiently targeted in MCL. Several agents are already available or in late development phase such as monoclonal or bispecific antibodies targeting CD20, ADC targeting CD79a or cellular therapies targeting CD19. Indeed, anti-CD19 CAR-T are currently approved (Zuma-2 trial), with a CRR of 68%, and a median duration of response of 28 months. Importantly, previous bendamustine usage was associated with attenuated T cell functionality¹³⁹, and real-life studies showed that high-risk features (ki67, TP53, MIPI, CK) were still associated with a shorter PFS⁷⁹. In the first line setting, CD20 remains a target of choice,

as shown by the impressive results of the LYMA-101 trial and superiority of Obinutuzumab versus Rituximab in a matched comparison with patients included in LYMA trial¹⁴⁰, justifying the presence of an anti-CD20 in various combinations in the RR setting. It is to note that while most of BTK-i based regimens rely on oral monotherapy, several combinations with anti-CD20 therapies have been and are currently under investigation (reviewed by Jain et al.)¹²⁹. The preliminary results of bispecific antibodies in the RR setting are also very promising as Glofitamab (α CD3-CD20) offers a CRR of 73%, with an acceptable safety profile when CRS are mitigated with Obinutuzumab¹⁴¹. Polatuzumab-vedotin (anti-CD79a ADC) combined with Mosunetuzumab (α CD3-CD20) demonstrated impressive results with 70% of CRR¹⁴². Finally, novel targets such as the receptor tyrosine kinase ROR-1 are also under investigation¹⁴³, with a very good safety profile, offering hope for combination in the near future. Longer follow-ups are needed for these trials, especially regarding toxicities occurrence, in order to improve sequence organization among different strategies.

Perspectives: Integration of intrinsic and extrinsic features: towards MCL ecotypes?

We have so far detailed the ecosystem and multiple pathways supporting MCL growth, showing that MCL heterogeneity is both driven by the distinct tumor cell of origin, the cellular pathways activated, and the TME interactions within the complex ecosystems. Landmark discoveries in the field of DLBCL have strengthened the concept of “ecosystem”. Indeed, intrinsic abnormalities have consequences on the tumor and TME interactions, leading to specific vulnerabilities such as *CARD11* or *MYD88* aberrations, promoting macrophages that mediate lymphoma cell senescence, as well as evasion of cytotoxic T-cell immunity, which is targetable with PDL1 inhibitors¹⁴⁴. Similarly, *EZH2* mutations have been shown to induce aberrant repression of the genes required for productive immune synapses, using T-cell and immune infiltrate in murine models of lymphoma. It was further shown that EZH2-i upregulate the expression of *CCL17* and T-cell recruitment¹⁴⁵. These findings pave the way for the development of complementary therapeutic approaches which combine immunotherapy, including CART-cells, with epigenetic reprogramming^{146–148}.

To be usable at the patients' level, for personalized approaches, the different levels of biological heterogeneity must be routinely available as a theranostic classification. The field of DLBCL was the first to go beyond genomic classification¹⁴⁹ and use single-cell data to develop unsupervised classification based on different cell-state co-occurrence patterns, derived from 13 major cell types, and leading to 9 distinct "ecotypes" with varying cell-state associations¹⁵⁰. This study resolves the DLBCL TME and tumor B-cell interactions at systems-level resolution, extending therapeutic targeting opportunities beyond cell-of-origin and genotypic classes.

Echoing the shift in DLBCL classification systems, the field of MCL is also evolving. A first molecular assay MCL35, developed by the LLMPP consortium¹⁵¹ and applicable for FFPE biopsies, was aimed at a risk-adapted strategy, to stratify MCL patients based on a proliferation signature associated with overall survival. Later, integrating genomic (WES in 148 patients) and transcriptomic profiling (RNA-seq in 48 patients) of MCL biopsies at diagnosis, Yi et al developed a classification based on different clusters with coordinate genetic signature that have unique gene expression patterns and distinct outcome³. Briefly, the tumors in the C1 group presented active BCR signaling, those in C2 were enriched with *ATM*^{Abn} and upregulation of NFkB and DNA repair pathways, C3 tumors were characterized by mutations in *SP140*, *NOTCH1*, *NSD2*, downregulation of BCR signaling and MYC targets, and in C4, associated with the worse outcome, they harbored *TP53*^{Abn}, del(13q), and del(9p), active MYC pathway and hyperproliferation signatures. Concerning TME, Jain et al showed that patients with immune-depleted TME were more likely to be BTK-i refractory, and that this TME feature was associated with *TP53*, *NOTCH1*, *NSD2*, *SMARCA4* mutations¹²⁰. If the field of DLBCL starts to apply such classifications for clinical trial stratification and a personalized approach¹⁵², the intersection of genomic and TME-based classification in MCL will require further exploration.

All in all, recent progress in the biology of MCL, including its TME, has led to a better understanding of drug resistance related to the complex interactions within the ecosystem. Biological rationale for combination strategies for overcoming resistance are becoming clearer,

and clinical trials tend to show better results when applied early on in the evolution of the disease¹⁵³. The field is now eagerly awaiting the results from various early-phase clinical trials which are assessing the safety and efficacy of inhibitors that act to disrupt the ecosystem, to then develop novel combinations, based on future classifications.

Figure 1

Mantle cell lymphoma intrinsic deregulations and resulting targetable vulnerabilities

Summary of the main signaling pathways dysregulated as a consequence of MCL intrinsic anomalies. They include hallmarks of MCL such as uncontrolled cell cycle driven by Cyclin-D1-CDK4 and SOX11 aberrant expression. In addition, MCL cells are often characterized by classical (BCR/NFkB1) and alternative (NIK/NFkB2) abnormal activities, mitochondrial apoptosis inhibition through BCL2 family unbalance, several hits in DNA repair processes (i.e. p53, ATM) and epigenetic protumoral deregulations. A number of dependencies result from these deregulations, and constitute potentially targetable Achilles' heels. GOF, gain of function; LOF, loss of function; BAFFR, B-cell activating factor receptor; BCR, B-cell receptor; β 1, Intregin-beta1; IC: Immune checkpoints, * see Figure 2

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Figure 2

Mantle cell lymphoma ecosystems: interplays and targets

A) Dialogs between the various tumor microenvironment (TME) components and the tumor cells are bidirectional with on the one side a supportive and pro-tumoral TME (represented in yellow) and on the other side a tumor cell that will re-educate the anti-tumor TME function (inhibitory TME, represented in red)). Within the non-hematopoietic cells, the stromal or endothelial cells, and its associated extra-cellular matrix protein, play key roles by activating the NFkB, PI3K/AKT, BCR but also FAK/ERK pathways, resulting in cell adhesion, tumor growth and proliferation. Within the hematopoietic niche, both macrophages and T cells have supportive function: the first one thanks to BAFF secretion, and a “don’t eat me signal”, and the second one thanks to the CD27-CD70 or CD40-CD40L axis.

B) Potential targets to disrupt the dialog in the MCL ecosystem. This complex interplay presents some vulnerabilities with potential targets both on the TME components and tumor cells. In red are represented the drugs that aim at disrupting the crosstalk and in green those that will take the advantage of the immune components to target the tumor cell. The communication axes between stromal cells and extra-cellular matrix and the tumor cells can be targeted with BAFF receptor antibodies, or kinase inhibitors such as FAK-inhibitors, PI3K or AKT inhibitors, or MALT-inhibitors that can bypass BTK-i resistance. Immune therapies such as anti CD70 antibodies, or anti CD47 (aiming to inhibit the don’t eat me signal of CD47-SIRPa interaction) represent novel therapeutic options able to recapitulate the anti-tumor immune functions with high potential for combinations. Novel immunotherapies such as bispecific antibodies will attempt to recruit functional T cells in the tumor. Combination with target agents aiming at fostering the T cell fitness, such as epigenetic modifier, or recruiting NK/T cells to increase the immune-synapse, such as IMiD, offer some promising options. *Created with BioRender.com*

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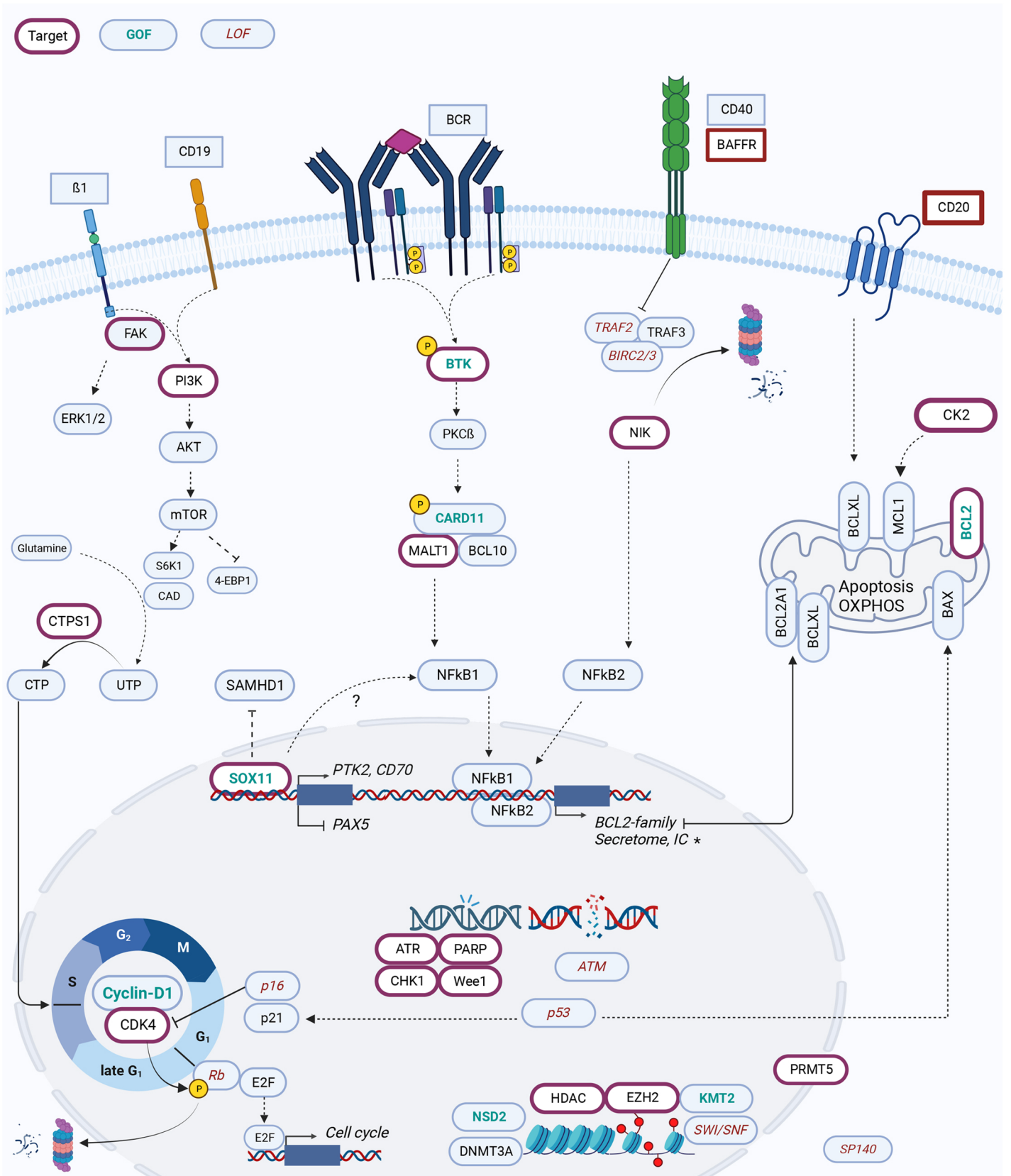
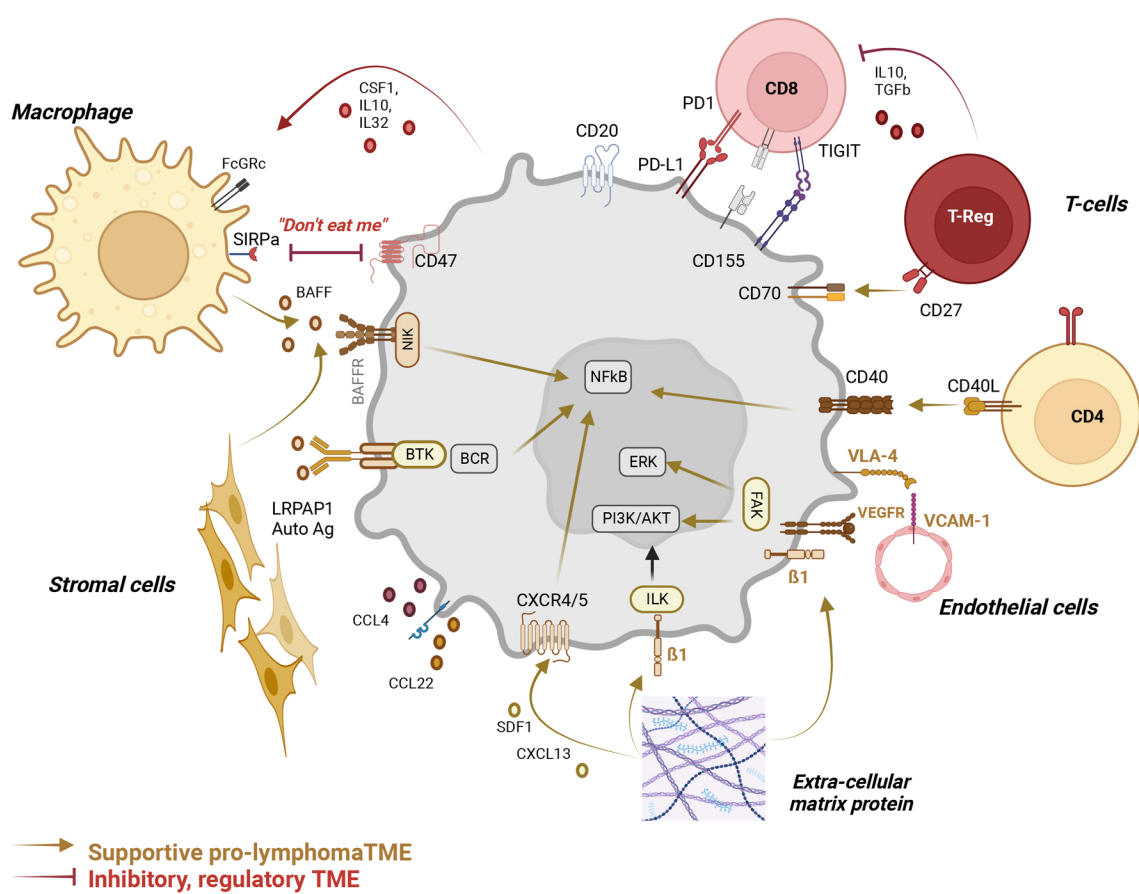


FIGURE 1

A



B

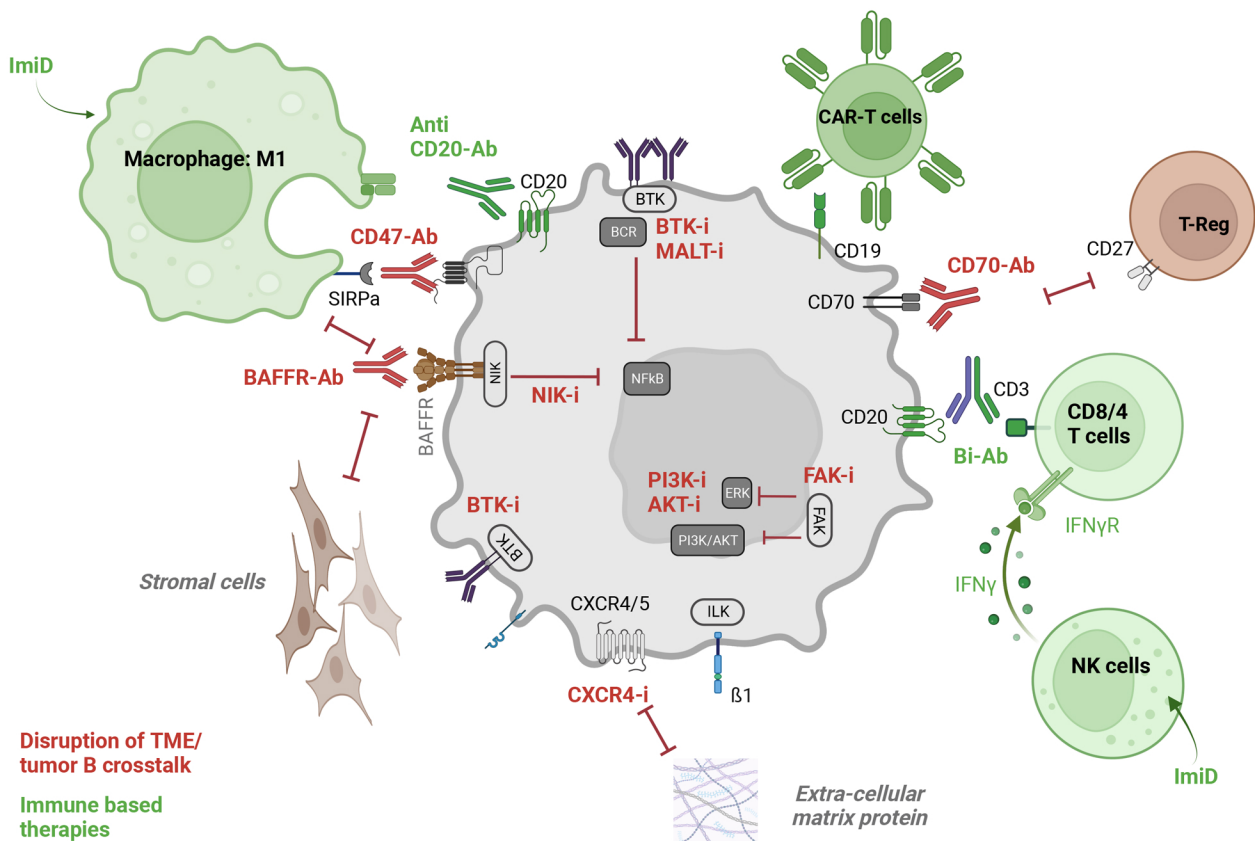


FIGURE 2