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Menin and BCL2 inhibitors– shaken and stirred

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Running title: Menin and BCL2 inhibitor combination

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Targeted therapy is rapidly evolving in the treatment of acute myeloid leukemia (AML). The introduction of the BCL2 inhibitor venetoclax has transformed the therapeutic landscape of this disease, and additional novel agents are poised to further reshape the future. Among these, menin inhibitors have emerged as promising therapies for patients with *KMT2A* rearranged (*KMT2Ar*) or *NPM1* mutated (*NPM1*^{mut}) AML, and potentially other molecular subtypes. Nonetheless, we are still in the early stages of determining the optimal drug combinations with menin inhibitors for each different AML subtype, or with either targeted therapies versus conventional chemotherapies.

In this work by Ciaurro et al[1], the authors evaluated the *in vitro* and *in vivo* synergy between the menin inhibitor DS-1594b and venetoclax across multiple AML subtypes. Treatment with single-agent DS-1594b induced differentiation and some degree of apoptosis in *KMT2Ar* and *NPM1*^{mut} AML cell lines. Notably, combining DS-1594b with venetoclax produced a clear synergistic effect, enhancing the antileukemic activity in both cell lines and primary patient samples. In addition, using an *NPM1*^{mut} PDX model, they demonstrate that the combination of DS-1594b and venetoclax induced differentiation of the leukemic cells and improved efficacy. Interestingly, transcriptomic analysis revealed that DS-1549b was the primary driver of gene expression changes, leading to downregulation of key apoptosis regulators, such as BCL2 and MCL1, therefore providing a novel mechanistic rationale for the observed synergy between menin inhibiton and venetoclax (Figure 1).

Menin inhibitors have been recently approved as single agents for relapsed or refractory leukemias with either *NPM1*^{mut} *or KMT2Ar* [2-4]. However, the duration of response with monotherapy in the relapsed or refractory setting has been limited, highlighting the need for combination therapies. Several clinical trials are currently evaluating multiple combination strategies with menin inhibitors, either in the frontline or relapsed and refractory settings[5]. Importantly, unlike many targeted therapies, menin inhibitors directly inhibit the transcriptional program of leukemic cells, inducing not only cell differentiation, but also modulate additional critical leukemia pathways, potentially creating new therapeutic vulnerabilities. As previously reported—and further demonstrated by the authors in this manuscript—menin inhibition downregulates antiapoptotic proteins such as BCL2 and MCL1, thereby enhancing the activity of venetoclax[6]. This provides a strong rationale for evaluating menin inhibitor–venetoclax combinations clinically, with the potential to further augment the therapeutic benefits of menin inhibition. However, can menin inhibition restore BCL2 inhibitor sensitivity after progression on venetoclax regardless of the AML genotype? Early signals suggest it might, but definitive studies are lacking [7,8].

Nonetheless, there is still progress to be made in this field. As the authors observed, not all cell lines responded similarly to DS-1594b or venetoclax, either as monotherapies or in combination, highlighting the inherent heterogeneity that exists even among leukemias with similar genotypes. Furthermore, because menin inhibitors differ in their molecular structure, and likely their pharmacokinetic profile, selectivity, or drug binding affinity, this synergistic interaction may vary across agents in the clinic. An important consideration is that while many of these antileukemic combinations show promise and feasibility in vitro and in vivo, translating them from bench to bedside remains challenging. Menin inhibitors could affect proliferation of hematopoietic progenitors under stress hematopoiesis, leading to cytopenias as an on-target, off-tumor effect[9]. Venetoclax, likewise, is associated with delayed count recovery when used in

combination with chemotherapy. In this context, combining menin inhibitors with venetoclax is under clinical investigation, but dose optimization is complex, as clinicians must balance efficacy with the risk of excessive myelosuppression or other toxicities. In addition, differentiation syndrome is a well-recognized and potentially life-threatening adverse effect of menin inhibitors, reflecting their ability to restore leukemic cell differentiation. Despite encouraging preclinical activity, many investigational compounds or combinations do not progress past early clinical testing due to limited therapeutic windows or unforeseen toxicities. Therefore, early identification of pharmacodynamic biomarkers of efficacy, or even adverse events such as differentiation syndrome, may enable more efficient development of related agents and enhance their likelihood of successful clinical translation.

In summary, menin inhibitors represent a transformative advancement in AML therapy. By directly targeting the leukemic transcriptional program, they may create new vulnerabilities that can enhance the antileukemic efficacy of other agents. The authors in this manuscript clearly demonstrate such synergy using in vitro and in vivo models combining the menin inhibitor DS-1594b with venetoclax. These findings may stimulate future investigations of next-generation menin inhibitors or similar therapies and rational combination approaches, thereby informing the development of effective therapeutic strategies that can be translated into robust and impactful clinical trials for patients with AML.

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Figure 1. Combining DS-1594 and Venetoclax in AML.