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Blood 142 (2023) 1642–1643

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

622.LYMPHOMAS: TRANSLATIONAL-NON-GENETIC

Macrophages Play a Key Role in Controlling Tumor Growth and Response to Immunotherapy in Primary Central Nervous System Lymphoma

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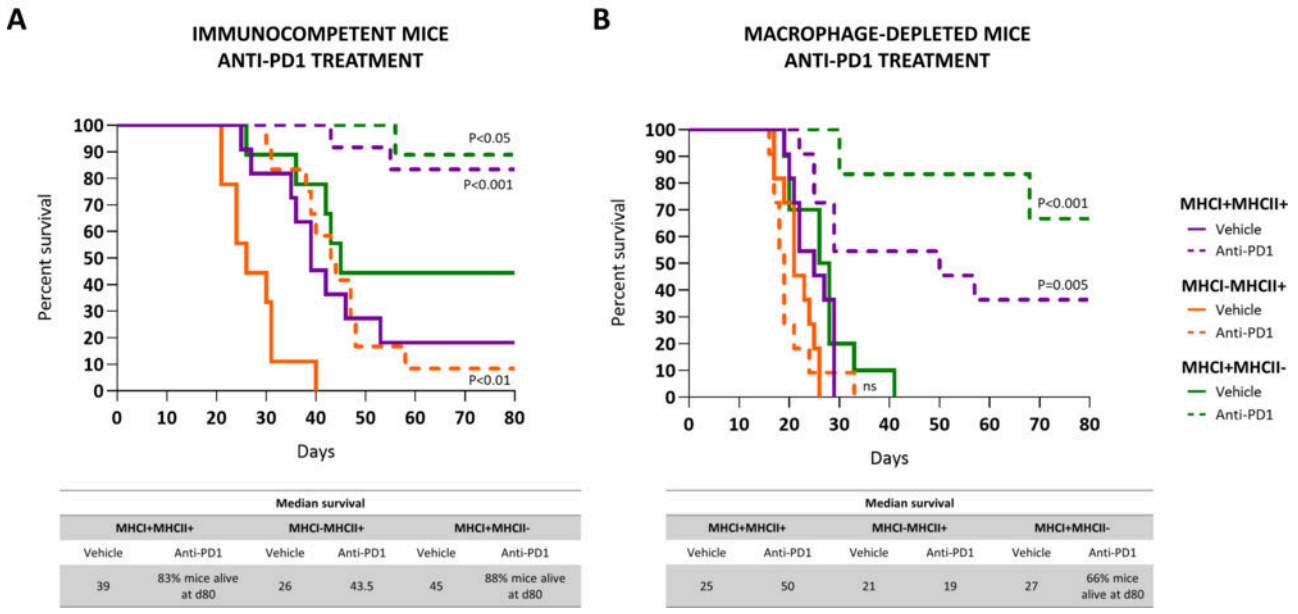
Introduction Primary Central Nervous System Lymphoma (PCNSL) represents 5% of extranodal lymphomas. Current treatments include high-dose chemotherapy in combination with an anti-CD20 antibody, and whole-brain radiation, both of which are limited by their toxicity. Although some advances have been achieved during the last few years, the prognosis of patients with CNS lymphoma is substantially worse than those with other type of lymphomas, with 5-year survival rates around 30%.
The highly aggressive nature of CNS lymphomas is in part due to the fact that the brain is an immunoprivileged organ; it presents very low levels of immunosurveillance, which contributes to inefficient immune responses against malignant cells. Of note, up to 70% of patients diagnosed with PCNSL also exhibit genetic alterations to avoid recognition by the immune system, like loss of MHC-I, that prevent presentation of tumor antigens, and amplifications in PD-L1, which increase the negative stimuli in cytotoxic T cells.
The PD-1/PD-L1 interaction has mainly been considered to be a checkpoint that regulates T cells. However, it has recently been found that tumor-associated macrophages can also express PD-1 and become activated to attack tumor cells when it is blocked. Moreover, macrophages have also been found to be inhibited by MHC-I expression on cancer cells. Thus, cancer cells that downregulate MHC-I to avoid T cell surveillance are particularly vulnerable to macrophages phagocytosis, especially when other macrophage immune checkpoints are blocked, such as CD47.
Against this background, we aimed to decipher the differential role of macrophages and T cells in the tumor growth and response to immunotherapy in primary CNS lymphoma.
Methods Luciferase-expressing A20 murine B-cell lymphoma cells were genetically modified to knock-out MHCI or MHCII by CRISPR-Cas9 and injected into the brain of immunocompetent (IC) or macrophage-depleted (MD) mice. Once tumours were stablished, mice were treated intravenously with seven injections, twice a week, of anti-PD1, anti-CD47 or the combination of both. We monitored mice for survival and tumoral growth. Additionally, brains were collected from mice treated with three injections for analysis of macrophages, B cells and T cells using flow cytometry and IHC.
Results In IC mice, all anti-PD1 treated mice showed significant differences in tumoral growth and survival compared to vehicle; however, MHCI- tumors had the lowest overall survival (Figure 1A). With anti-CD47 therapy, only MHCI- PCNSL mice had a significantly increased survival compared to vehicle. Combination was effective in all groups, but no drug synergy was seen. In MD mice, all tumors were more aggressive than in IC mice. With anti-PD1, MHCI+ PCNSL mice achieved a complete tumor regression and survived longer in comparison to vehicle. On the contrary, MHCI- PCNSL mice didn't respond to anti-PD1 therapy (Figure 1B). Of notice, MHCI+ PCNSL in both MD and IC models had a higher infiltration of active T cells when treated with anti-PD1. In MHCI- PCNSL, infiltrated T cells had less expression of activation markers in both models and macrophages were polarized to an M2 phenotype in IC mice.
Conclusions Our study revealed a remarkable response to anti-PD1 therapy in MHCI+ CNS lymphoma tumors, regardless of the presence of macrophages in the tumor microenvironment. This indicates that T cells would be primarily responsible for the observed tumour regression. However, targeting CD47 in MHCI+ PCNSL was found to be insufficient in restoring macrophage phagocytosis. Despite observing positive effects of anti-PD1 and anti-CD47 drugs in our MHCI- immunocompetent mouse model, MHCI downregulation still induces a very aggressive, lethal disease. This suggests that these tumors can only be controlled by macrophages, as supported by the lack of treatment response in a MD microenvironment.
Our findings highlight the critical role of macrophages in controlling the growth of lymphoma cells in the brain and their significance in the immunotherapy response for CNS lymphomas, particularly when MHCI expression is deficient. Blocking

PD1 exhibits superior efficacy when macrophages are present, indicating T cells are not the only player in this tumoral scenario. As a result, our study suggests that a promising approach for treating primary CNS lymphomas would involve targeting both T cells and macrophages.

Disclosures Bosch: *Roche:* Honoraria; *BeiGene:* Consultancy; *Lilly:* Consultancy; *Mundipharma:* Consultancy, Honoraria; *Gilead:* Consultancy, Honoraria; *Janssen:* Consultancy, Honoraria; *AbbVie:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Takeda:* Consultancy, Honoraria; *AstraZeneca:* Consultancy, Honoraria; *Karyospharm:* Other; *Celgene:* Consultancy, Honoraria; *Roche:* Consultancy, Honoraria.

Figure 1



Median survival

MHCI+MHCII+		MHCI-MHCII+		MHCI+MHCII-	
Vehicle	Anti-PD1	Vehicle	Anti-PD1	Vehicle	Anti-PD1
39	83% mice alive at d80	26	43.5	45	88% mice alive at d80

Median survival

MHCI+MHCII+		MHCI-MHCII+		MHCI+MHCII-	
Vehicle	Anti-PD1	Vehicle	Anti-PD1	Vehicle	Anti-PD1
25	50	21	19	27	66% mice alive at d80

Figure 1

https://doi.org/10.1182/blood-2023-180719