Dear reviewers,

Thank you for reading our manuscript and reviewing it, which will help us improve it to a better scientific level. We revised our manuscript, and some changes have taken place. So, we have sent the revised manuscript to you with changes marked in red. At the following, the points mentioned by the reviewers will be discussed:

Reviewer #1 comments:

#1 I would suggest to revise the English and check the abbreviations.

Thank you for your comments. In order to avoid any language problems and better polish our revised manuscript, we have submitted our paper to a new language editing company and then upload the certificate. Please see if the revised version met the English presentation standard. Additionally, we have added Abbreviations after Conclusion in the full-text file and checked for all the abbreviations in this review to make sure all of them are under the rules.

#2 I would add more recent literature in the field (studies not older than 5 years).

Thank you for your suggestion. We have browsed all the latest (studies not older than 3 years) articles related to the BET family and gastrointestinal cancers including CRC, GC, pancreatic cancer and liver cancer in the PUBMED. And then we added the references at suitable places and listed all the changes as follow.

1. Joshi S S and Badgwell B D, Current treatment and recent progress in gastric cancer. CA Cancer J Clin, 2021. 71(3): p. 264-279.[PMID:33592120 DOI:10.3322/caac.21657]

2. Dunn C, Hong W, Gibbs P, Ackland S, Sjoquist K, Tebbutt N C, Price T, and Burge M, Personalizing First-Line Systemic Therapy in Metastatic Colorectal Cancer: Is There a Role for Initial Low-Intensity Therapy in 2021 and Beyond? A Perspective From Members of the Australasian Gastrointestinal Trials Group. Clin Colorectal Cancer, 2021.[PMID:34103264 DOI:10.1016/j.clcc.2021.05.001]

3. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall M J, Park J O, Hochhauser D, Arnold D, Oh D Y, Reinacher-Schick A, Tortora G, Algul H, O'Reilly E M, McGuinness D, Cui K Y, Schlienger K, Locker G Y, and Kindler H L, Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med, 2019. 381(4): p. 317-327.[PMID:31157963 DOI:10.1056/NEJMoa1903387]

4. Nussbaum Y I, Manjunath Y, Suvilesh K N, Warren W C, Shyu C R, Kaifi J T, Ciorba M A, and Mitchem J B, Current and Prospective Methods for Assessing Anti-Tumor Immunity in Colorectal Cancer. Int J Mol Sci, 2021. 22(9).[PMID:33946558 DOI:10.3390/ijms22094802]

5. Chen X, Zeh H J, Kang R, Kroemer G, and Tang D, Cell death in pancreatic cancer: from pathogenesis to therapy. Nat Rev Gastroenterol Hepatol, 2021.[PMID:34331036 DOI:10.1038/s41575-021-00486-6]

6. Zhang N, Ng A S, Cai S, Li Q, Yang L, and Kerr D, Novel therapeutic strategies: targeting epithelial-mesenchymal transition in colorectal cancer. Lancet Oncol, 2021. 22(8): p. e358-e368.[PMID:34339656 DOI:10.1016/S1470-2045(21)00343-0]

7. Petretich M, Demont E H, and Grandi P, Domain-selective targeting of BET proteins in cancer and immunological diseases. Curr Opin Chem Biol, 2020. 57: p. 184-193.[PMID:32741705 DOI:10.1016/j.cbpa.2020.02.003]

8. Wang N, Wu R, Tang D, and Kang R, The BET family in immunity and disease. Signal Transduct Target Ther, 2021. 6(1): p. 23.[PMID:33462181 DOI:10.1038/s41392-020-00384-4]

9. Tan M, Brusgaard K, Gerdes A M, Mortensen M B, Detlefsen S, Schaffalitzky de Muckadell O B, and Joergensen M T, Whole genome sequencing identifies rare germline variants enriched in cancer related genes in first degree relatives of familial pancreatic cancer patients. Clin Genet, 2021.[PMID:34313325 DOI:10.1111/cge.14038]

10. Cho J, Chang Y H, Heo Y J, Kim S, Kim N K, Park J O, Kang W K, Lee J, and Kim K M, Four distinct immune microenvironment subtypes in gastric adenocarcinoma with special reference to microsatellite instability. ESMO Open, 2018. 3(3): p. e000326.[PMID:29636988 DOI:10.1136/esmoopen-2018-000326]

11. Gilan O, Rioja I, Knezevic K, Bell M J, Yeung M M, Harker N R, Lam E Y N, Chung C W, Bamborough P, Petretich M, Urh M, Atkinson S J, Bassil A K, Roberts E J, Vassiliadis D, Burr M L, Preston A G S, Wellaway C, Werner T, Gray J R, Michon A M, Gobbetti T, Kumar V, Soden P E, Haynes A, Vappiani J, Tough D F, Taylor S, Dawson S J, Bantscheff M, Lindon M, Drewes G, Demont E H, Daniels D L, Grandi P, Prinjha R K, and Dawson M A, Selective targeting of BD1 and BD2 of the BET proteins in cancer and immunoinflammation. Science, 2020. 368(6489): p. 387-394.[PMID:32193360 DOI:10.1126/science.aaz8455]

12. Faivre E J, McDaniel K F, Albert D H, Mantena S R, Plotnik J P, Wilcox D, Zhang L, Bui M H, Sheppard G S, Wang L, Sehgal V, Lin X, Huang X, Lu X, Uziel T, Hessler P, Lam L T, Bellin R J, Mehta G, Fidanze S, Pratt J K, Liu D, Hasvold L A, Sun C, Panchal S C, Nicolette J J, Fossey S L, Park C H, Longenecker K, Bigelow L, Torrent M, Rosenberg S H, Kati W M, and Shen Y, Selective inhibition of the BD2 bromodomain of BET proteins in prostate cancer. Nature, 2020. 578(7794): p. 306-310.[PMID:31969702 DOI:10.1038/s41586-020-1930-8]

13. Miller A L, Garcia P L, Fehling S C, Gamblin T L, Vance R B, Council L N, Chen D, Yang E S, van Waardenburg R, and Yoon K J, The BET Inhibitor JQ1 Augments the Antitumor Efficacy of Gemcitabine in Preclinical Models of Pancreatic Cancer. Cancers (Basel), 2021. 13(14).[PMID:34298684 DOI:10.3390/cancers13143470]

14. Wang W, Tang Y A, Xiao Q, Lee W C, Cheng B, Niu Z, Oguz G, Feng M, Lee P L, Li B, Yang Z H, Chen Y F, Lan P, Wu X J, and Yu Q, Stromal induction of BRD4 phosphorylation Results in Chromatin Remodeling and BET inhibitor Resistance in Colorectal Cancer. Nat Commun, 2021. 12(1): p. 4441.[PMID:34290255 DOI:10.1038/s41467-021-24687-4]

15. Liu Y, Xue M, Cao D, Qin L, Wang Y, Miao Z, Wang P, Hu X, Shen J, and Xiong B, Multi-omics characterization of WNT pathway reactivation to ameliorate BET inhibitor resistance in liver cancer cells. Genomics, 2021. 113(3): p. 1057-1069.[PMID:33667649 DOI:10.1016/j.ygeno.2021.02.017]

16. Halder T G, Soldi R, and Sharma S, Bromodomain and extraterminal domain protein bromodomain inhibitor based cancer therapeutics. Curr Opin Oncol, 2021.[PMID:34280171 DOI:10.1097/CCO.0000000000000763]

17. Kim Y H, Kim M, Kim J E, Yoo M, Lee H K, Lee C O, Yoo M, Jung K Y, Kim Y, Choi S U, and Park C H, Novel brd4 inhibitors with a unique scaffold exhibit antitumor effects. Oncol Lett, 2021. 21(6): p. 473.[PMID:33907583 DOI:10.3892/ol.2021.12734]

18. Kapoor S, Gustafson T, Zhang M, Chen Y S, Li J, Nguyen N, Perez J E T, Dashwood W M, Rajendran P, and Dashwood R H, Deacetylase Plus Bromodomain Inhibition Downregulates ERCC2 and Suppresses the Growth of Metastatic Colon Cancer Cells. Cancers (Basel), 2021. 13(6).[PMID:33809839 DOI:10.3390/cancers13061438]

19. Liu Y, Xue M, Cao D, Qin L, Wang Y, Miao Z, Wang P, Hu X, Shen J, and Xiong B, Multi-omics characterization of WNT pathway reactivation to ameliorate BET inhibitor resistance in liver cancer cells. Genomics, 2021. 113(3): p. 1057-1069.[PMID:33667649 DOI:10.1016/j.ygeno.2021.02.017]

20. Honselmann K C, Finetti P, Birnbaum D J, Monsalve C S, Wellner U F, Begg S K S, Nakagawa A, Hank T, Li A, Goldsworthy M A, Sharma H, Bertucci F, Birnbaum D, Tai E, Ligorio M, Ting D T, Schilling O, Biniossek M L, Bronsert P, Ferrone C R, Keck T, Mino-Kenudson M, Lillemoe K D, Warshaw A L, Fernandez-Del Castillo C, and Liss A S, Neoplastic-Stromal Cell Cross-talk Regulates Matrisome Expression in Pancreatic Cancer. Mol Cancer Res, 2020. 18(12): p. 1889-1902.[PMID:32873625 DOI:10.1158/1541-7786.MCR-20-0439]

21. Yasukawa Y, Hattori N, Iida N, Takeshima H, Maeda M, Kiyono T, Sekine S, Seto Y, and Ushijima T, SAA1 is upregulated in gastric cancer-associated fibroblasts possibly by its enhancer activation. Carcinogenesis, 2021. 42(2): p. 180-189.[PMID:33284950 DOI:10.1093/carcin/bgaa131]

22. Lei L, Xie X, He L, Chen K, Lv Z, Zhou B, Li Y, Hu W, and Zhou Z, The bromodomain and extra-terminal domain inhibitor JQ1 synergistically sensitizes human colorectal cancer cells to topoisomerase I inhibitors through repression of Mre11-mediated DNA repair pathway. Invest New Drugs, 2021. 39(2): p. 362-376.[PMID:32981006 DOI:10.1007/s10637-020-01014-0]

23. Choi H I, An G Y, Baek M, Yoo E, Chai J C, Lee Y S, Jung K H, and Chai Y G, BET inhibitor suppresses migration of human hepatocellular carcinoma by inhibiting SMARCA4. Sci Rep, 2021. 11(1): p. 11799.[PMID:34083693 DOI:10.1038/s41598-021-91284-2]

24. Kang S K, Bae H J, Kwon W S, Che J, Kim T S, Chung H C, and Rha S Y, Transcriptome analysis of iBET-151, a BET inhibitor alone and in combination with paclitaxel in gastric cancer cells. Genomics Inform, 2020. 18(4): p. e37.[PMID:33412753 DOI:10.5808/GI.2020.18.4.e37]

25. Yin M, Guo Y, Hu R, Cai W L, Li Y, Pei S, Sun H, Peng C, Li J, Ye R, Yang Q, Wang N, Tao Y, Chen X, and Yan Q, Potent BRD4 inhibitor suppresses cancer cell-macrophage interaction. Nat Commun, 2020. 11(1): p. 1833.[PMID:32286255][doi:10.1038/s41467-020-15290-0]

26. Bechter O and Schoffski P, Make your best BET: The emerging role of BET inhibitor treatment in malignant tumors. Pharmacol Ther, 2020. 208: p.107479. [PMID:31931101][doi:10.1016/j.pharmthera.2020.107479]

#3 Future perspectives of BET proteins in this context should be emphasized in the conclusion.

Thank you for your comment. We have mentioned BET inhibitors failed to administrate as single agents by far. Then we interrogated the recent development of BET inhibitors in reducing the toxicity and enhancing drug sensitivity. Selective BET inhibitors, modified clinical stage BET inhibitors or synergistic inhibitions may contribute to solve the situation that BET inhibitors show poor response in GI cancer treatment. With the in-depth understanding of BET proteins' structure and mechanisms, BET inhibitors emerge as the promising agents for the GI cancer treatment.

Revision Conclusion as follow:

BET inhibitors have emerged as a new possible strategy for the treatment of GI cancers in recent years. However, either nondurable cytotoxic effects, such as thrombocytopenia and gastrointestinal disorders[95] or drug resistance makes BET inhibitors fail to be administrated as single agents by far. To achieve better selectivity and reduce unwanted toxicities, BET inhibitors continue to be updated, increasing their potential in cancer treatment.

The first-generation pan-BET inhibitors have been identified to suppress GI cancer in preclinical results, however, the inevitable side effects limit their clinical applications. Hence, drug discovery efforts concentrate on selectively inhibiting BET proteins[96]. Selective BD inhibitors achieved almost equally efficiency in cancer to the pan-BET inhibitors [97] and showed less toxicity [98]. A set of selective BD inhibitors help to understand the role of BD in cancers and further focusing on specific BD perturbations may provide more efficiency and tolerability in GI cancers treatment.

Another approach to acquire selective inhibition is to target each BET family members. Since BRD4 is the predominant BET protein that mediates the development of GI cancers, selective BRD4 inhibition may have a better outlook. New BRD4 degraders ARV-825 and A1874 that have already shown their antitumor efficiency in preclinical results support further clinical development of BET inhibitors in GI cancers.

Other strategy to improve the efficacy and pharmacokinetic property of BET inhibitors is via modulating their structure. After modification, these major clinical stage BET inhibitors acquire better tumor killing capacity with minimal IC50 in multiple solid tumors[99]. The optimistic preclinical result makes it possible to treat GI cancer with single agents.

Additionally, synergistic inhibition provides an optimistic prospect for increasing the

efficacy of BET inhibitors. The preclinical and clinical results verify high potential in combinational therapy. The resistance to BET inhibitors will be overcome if combined with drugs targeting the pathways that cause resistance[48]. Besides, the dosage will be decreased dramatically if combined with drugs rendering GI cancers more sensitive to BET inhibitors.[100] Without a doubt, BET inhibitors emerge as a promising avenue for the GI cancers treatment.

48. Wu T, Wang G, Chen W, Zhu Z, Liu Y, Huang Z, Huang Y, Du P, Yang Y, Liu C Y, and Cui L, Co-inhibition of BET proteins and NF-kappaB as a potential therapy for colorectal cancer through synergistic inhibiting MYC and FOXM1 expressions. Cell Death Dis, 2018. 9(3): p. 315.[PMID:29472532][doi:10.1038/s41419-018-0354-y]

95. Halder T G, Soldi R, and Sharma S, Bromodomain and extraterminal domain protein bromodomain inhibitor based cancer therapeutics. Curr Opin Oncol, 2021.[PMID:34280171][doi:10.1097/CCO.0000000000000763]

96. Petretich M, Demont E H, and Grandi P, Domain-selective targeting of BET proteins in cancer and immunological diseases. Curr Opin Chem Biol, 2020. 57: p. 184-193.[PMID:32741705][doi:10.1016/j.cbpa.2020.02.003]

97. Gilan O, Rioja I, Knezevic K, Bell M J, Yeung M M, Harker N R, Lam E Y N, Chung C W, Bamborough P, Petretich M, Urh M, Atkinson S J, Bassil A K, Roberts E J, Vassiliadis D, Burr M L, Preston A G S, Wellaway C, Werner T, Gray J R, Michon A M, Gobbetti T, Kumar V, Soden P E, Haynes A, Vappiani J, Tough D F, Taylor S, Dawson S J, Bantscheff M, Lindon M, Drewes G, Demont E H, Daniels D L, Grandi P, Prinjha R K, and Dawson M A, Selective targeting of BD1 and BD2 of the BET proteins in cancer and immunoinflammation. Science, 2020. 368(6489): p. 387-394.[PMID:32193360][doi:10.1126/science.aaz8455]

98. Faivre E J, McDaniel K F, Albert D H, Mantena S R, Plotnik J P, Wilcox D, Zhang L, Bui M H, Sheppard G S, Wang L, Sehgal V, Lin X, Huang X, Lu X, Uziel T, Hessler P, Lam L T, Bellin R J, Mehta G, Fidanze S, Pratt J K, Liu D, Hasvold L A, Sun C, Panchal S C, Nicolette J J, Fossey S L, Park C H, Longenecker K, Bigelow L, Torrent M, Rosenberg S H, Kati W M, and Shen Y, Selective inhibition of the BD2 bromodomain of BET proteins in prostate cancer. Nature, 2020. 578(7794): p. 306-310.[PMID:31969702][doi:10.1038/s41586-020-1930-8]

99. Yin M, Guo Y, Hu R, Cai W L, Li Y, Pei S, Sun H, Peng C, Li J, Ye R, Yang Q, Wang N, Tao Y, Chen X, and Yan Q, Potent BRD4 inhibitor suppresses cancer cell-macrophage interaction. Nat Commun, 2020. 11(1): p. 1833.[PMID:32286255][doi:10.1038/s41467-020-15290-0]

100. Bechter O and Schoffski P, Make your best BET: The emerging role of BET inhibitor treatment in malignant tumors. Pharmacol Ther, 2020. 208: p. 107479.[PMID:31931101][doi:10.1016/j.pharmthera.2020.107479]

Finally, thanks again for your comments. Admittedly, your comments help me and my manuscript a lot. We hope our response could satisfy you.

Millions of thanks.

Yours sincerely

Furong Zeng, MD, Department of Dermatology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China. (zengflorachn@hotmail.com)
Telephone: +86 13723890471
Guangtong Deng, MD Department of Dermatology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China. (dengguangtong@outlook.com)