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Commentary: Inhibition of Glutaminase Elicits Senolysis in Therapy-Induced Senescent Melanoma Cells

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Melanoma is a serious form of skin cancer derived from melanocytes, which is driven by major oncogenic drivers such as BRAF (~50%, primarily $BRAF^{V600E}$) and NRAS (~20%, $NRAS^{Q61R}$) mutations[1,2]. CDK4/6 inhibitors have been increasingly explored in melanoma, with their ability to drive cells into a durable, metabolically active cell-cycle arrest[3-7]. In $BRAF^{V600E}$ melanoma cells, we demonstrated that prolonged CDK4/6 inhibition induces therapy-induced senescence[8-10], accompanied by GLS1 upregulation, creating a vulnerability to GLS1 inhibitor–mediated senolysis[11]. The central premise of this commentary is that GLS1 inhibition may be most effective not as a broadly applied anti-proliferative strategy, but as a biomarker-guided senolytic approach after senescence and GLS1 dependence have been established. In a broader application, this therapeutic approach could further extend to other cancers via therapy-induced senescence and GLS1 expression.

The clinical activity of CDK4/6 inhibitors has been modest and highly context-dependent. In advanced acral melanoma with CDK4 pathway aberrations, palbociclib monotherapy produced one confirmed partial response and median progression-free survival (PFS) of 2.2 months[12]. In NRAS mutant melanoma, ribociclib plus binimetinib resulted in activity, but achieved a median PFS of only 3.7 months (clinicaltrials.gov-NCT01781572). Greater benefit was found in tumors harboring concurrent cell cycle alterations, such as CDKN2A, CDK4, and CCND1[13]. These findings suggest that while CDK4/6 inhibitors show promise by inducing a therapeutically exploitable senescent state, the use of biomarker-guided combinations can further unlock their clinical utility.

Beyond the identification of a potential drug combination, the paper recognizes that therapy-induced senescence creates targetable vulnerability in melanoma[11]. Cancer cells in a persistent senescent state secrete inflammatory cytokines, leading to carcinogenesis, antitumor immunity resistance, tumor relapse, and metastasis[14-20]. Additionally, senescent melanoma cells accumulate excess acid due to lysosomal proton leaks. GLS1-mediated conversion of glutamine to glutamate generates ammonia, which can buffer intracellular acidification associated with lysosomal proton leakage, protecting senescent cells. Upon inhibiting GLS1, the buffering effect is lost, leading to cell death. This survival mechanism has been demonstrated in senescent cells in aged tissues and in therapy-induced senescent melanoma[11,21]. However, it has not yet been established as a universal feature of therapy-induced senescent solid tumors[22,23]. Extension of this strategy to other cancers will therefore require evidence that

treatment induces durable senescence, GLS1 upregulation or dependence, and ammonia/ammonium-mediated pH buffering. Furthermore, GLS1 upregulation and GLS1 inhibitor–mediated senolysis were also observed in $BRAF^{V600E}$ melanoma models with acquired resistance to vemurafenib, suggesting that this vulnerability can persist despite resistance to BRAF-targeted therapy[11].

Not all melanoma is equally targetable with this senescent-driven strategy. CDK4/6 inhibition can induce a senescent, GLS1-dependent state in BRAF-mutant and NRAS-wild-type melanoma, but fails to do so in NRAS-mutant melanoma due to MAPK and PI3K-mTOR pathway interference[11]. This genotype-specific difference raises concern that broadly enrolling patients with RAS-mutant tumors may dilute therapeutic activity if CDK4/6 inhibition does not first induce a senescent, GLS1-dependent state, as may be relevant to trials (e.g., clinicaltrials.gov-NCT03965845). As such, this subtype may require additional senescence-priming strategies before GLS1-targeted senolysis can be effective. Future clinical translation should consider genetic background and senescence competence, rather than a broad genotype-agnostic use of GLS1 inhibitors.

Examining the clinical performance of GLS1 inhibitors illustrates the need to reframe their therapeutic role in treating melanoma. Proliferating cancer cells utilize glutamine to fuel the TCA cycle for survival[24]. GLS1 inhibitors reduce glutamine-derived glutamate production and downstream anaplerotic metabolism, slowing tumor growth. Telaglenastat (CB-839), a GLS1 inhibitor, used along with nivolumab, has been studied in phase I/II trials and was generally well tolerated (clinicaltrials.gov-NCT02771626). However, no consistent pattern of efficacy was produced across tumor types. In the melanoma cohort previously treated with anti-PD-1/PD-L1 therapy, objective response rate (ORR) was only 5.4% (clinicaltrials.gov-NCT02771626), underscoring the limited clinical activity of first-generation GLS1 inhibition when used as an unselected anti-proliferative or immunometabolic strategy. These results motivate evaluation of a different biological application of GLS1 inhibition: selective elimination of therapy-induced senescent cells after senescence induction and GLS1 dependence have been confirmed. Next-generation GLS1 inhibitors, IACS-6274[25-27], now in phase I trials, are more relevant for these repurposed uses (clinicaltrials.gov-NCT05039801). Clinical experience with CB-839 supports the feasibility of pharmacologic GLS1 inhibition, but also indicates that patient selection and biological context are critical. CB-839 should therefore be viewed as the proof-of-concept compound used in the original study. Next-generation GLS1 inhibitors such as IACS-6274/IPN60090[25], may offer a more practical path for future biomarker-guided translational development. Together, these findings support further development of GLS1 inhibition as a candidate senolytic strategy.

While senescence-targeted strategies are being studied further, immunotherapy remains a backbone of treatment for advanced melanoma, and any proposed sequential senescence-induction and senolytic regimen must therefore be evaluated for its effects on the tumor immune microenvironment. Because the original study used SCID xenografts lacking functional T and B cells, it could not determine whether sequential CDK4/6 and GLS1 inhibition alters CD8+ T-cell infiltration, dendritic-cell activation, antigen presentation, regulatory T-cell abundance, or broader immune suppression. Immunocompetent syngeneic melanoma models are therefore needed to assess both antitumor efficacy and immune consequences. Furthermore, additional testing is needed to determine if reprogramming of the immune microenvironment via senolytic clearance of TIS cells is possible, potentially improving responses to checkpoint blockade. Because senescent cells can produce SASP factors that reshape immune infiltration and inflammation[28], determining whether GLS1-mediated senolysis removes an immune-suppressive senescent population or disrupts beneficial immune activation will be essential before combining this strategy with immune checkpoint blockade. If efficacy, safety, and favorable immune effects are demonstrated, sequential senescence induction and senolysis could eventually be explored in neoadjuvant or adjuvant settings for patients with resectable high-risk melanoma, with the goal of reducing residual disease and subsequent recurrence or metastatic progression.

Overall, these insights position this paper as a conceptual advance, rather than a proposal of a specific treatment combination for melanoma. It demonstrates that the mechanism of disrupting the ammonia-based pH balance via glutaminase inhibition can be leveraged in melanoma therapeutics. More importantly, the paper also identifies a senolytic vulnerability that may be applicable to other senescence-induced tumors. As senescence-targeted strategies continue to evolve, this paper provides a mechanistic foundation for expanding senolytic therapy beyond traditional proliferation-directed approaches, focusing on biomarker-guided combinations with implications that extend beyond melanoma.

References

1. van Not OJ, van den Eertwegh AJM, Haanen JB, et al. Improving survival in advanced melanoma patients: a trend analysis from 2013 to 2021. EClinicalMedicine. 2024; 69: 102485.

2. Michielin O, Atkins MB, Koon HB, et al. Evolving impact of long-term survival results on metastatic melanoma treatment. J Immunother Cancer. 2020; 8: e000948.

3. Kim U, McCormick T, Mangla A, et al. The potential of CDK4/6 inhibitors in advancing the treatment of cutaneous melanoma. Pharmacol Res. 2025; 221: 107955.

4. McHugh D, Gil J. Senescence and aging: Causes, consequences, and therapeutic avenues. J Cell Biol. 2018; 217: 65–77.

5. Kumari R, Jat P. Mechanisms of Cellular Senescence: Cell Cycle Arrest and Senescence Associated Secretory Phenotype. Front Cell Dev Biol. 2021; 9: 645593.

6. Campisi J. Aging, cellular senescence, and cancer. Annu Rev Physiol. 2013; 75: 685–705.

7. Gorgoulis V, Adams PD, Alimonti A, et al. Cellular Senescence: Defining a Path Forward. Cell. 2019; 179: 813–27.

8. Yoshida A, Diehl JA. CDK4/6 inhibitor: from quiescence to senescence. Oncoscience. 2015; 2(11): 896-7.

9. Yoshida A, Lee E, Diehl JA. Induction of Therapeutic Senescence in Vemurafenib-Resistant Melanoma by Extended Inhibition of CDK4/6. Cancer Res. 2016; 76(10): 2990-3002.

10. Yoshida A, Bu Y, Qie S, et al. SLC36A1-mTORC1 signaling drives acquired resistance to CDK4/6 inhibitors. Sci Adv. 2019; 5(9): eaax6352.

11. Kim J, Brunetti B, Kumar A, et al. Inhibition of glutaminase elicits senolysis in therapy-induced senescent melanoma cells. Cell Death Dis. 2024; 15: 902.

12. Mao L, Dai J, Cao Y, et al. Palbociclib in advanced acral melanoma with genetic aberrations in the cyclin-dependent kinase 4 pathway. Eur J Cancer. 2021; 148: 297-306.

13. Schuler M, Zimmer L, Kim KB, et al. Phase Ib/II Trial of Ribociclib in Combination with Binimetinib in Patients with NRAS-mutant Melanoma. Clin Cancer Res. 2022; 28(14): 3002-3010.

14. Ruhland MK, Loza AJ, Capietto A-H, et al. Stromal senescence establishes an immunosuppressive microenvironment that drives tumorigenesis. Nat Commun. 2016; 7: 11762.

15. Mavrogonatou E, Pratsinis H, Kletsas D. The role of senescence in cancer development. Semin Cancer Biol. 2020; 62: 182–91.

16. Guillon J, Petit C, Toutain B, et al. Chemotherapy induced senescence, an adaptive mechanism driving resistance and tumor heterogeneity. Cell cycle (Georget, Tex). 2019; 18: 2385–97.

17. Saleh T, Bloukh S, Carpenter VJ, et al. Therapy Induced Senescence: An "Old" Friend Becomes the Enemy. Cancers. 2020; 12: 822.

18. Krtolica A, Parrinello S, Lockett S, et al. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: A link between cancer and aging. Proc Natl Acad Sci. 2001; 98: 12072–7.

19. Bhowmick NA, Neilson EG, Moses HL. Stromal fibroblasts in cancer initiation and progression. Nature. 2004; 432: 332–7.

20. Schmitt CA, Wang B, Demaria M. Senescence and cancer — role and therapeutic opportunities. Nat Rev Clin Oncol. 2022; 19: 619–36.

21. Johmura Y, Shimada M, Misaki T, et al. Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders. Science. 2021; 371(6526): 265–70.

22. Altman BJ, Stine ZE, Dang CV. From Krebs to clinic: glutamine metabolism to cancer therapy. Nat Rev Cancer. 2016; 16(10): 619–34.

23. Jin J, Byun JK, Choi YK, et al. Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med. 2023; 55(4): 706–15.

24. DeBerardinis RJ, Mancuso A, Daikhin E, et al. Beyond aerobic glycolysis: transformed cells can engage in glutamine metabolism that exceeds the requirement for protein and nucleotide synthesis. Proc Natl Acad Sci U S A. 2007; 104(49): 19345-50.

25. Soth MJ, Le K, Di Francesco ME, et al. Discovery of IPN60090, a Clinical Stage Selective Glutaminase-1 (GLS-1) Inhibitor with Excellent Pharmacokinetic and Physicochemical Properties. J Med Chem. 2020; 63(21): 12957-12977.

26. Vagaggini C, D'Ursi P, Poggialini F, et al. Deciphering the landscape of allosteric glutaminase 1 inhibitors as anticancer agents. Bioorg Chem. 2025; 161: 108523.

27. Yap TA, Dumbrava EE, Ahnert JR, et al. First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients with molecularly selected advanced solid tumors. J Clin Oncol. 2021; 39: 3001.

28. Coppé JP, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008; 6(12): 2853-68.