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# Reply

**Sanjib Chaudhary**[1], **Imayavaramban Lakshmanan**[1], **Apar Kishor Ganti**[2], **Muzafar A. Macha**[3], **Surinder K. Batra**[1]

[1]Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE, USA.

[2]Veterans Affairs Nebraska Western Iowa Health Care System, Omaha, NE; Department of Hematology and Oncology, University of Nebraska Medical Center, Omaha, NE, USA.

[3]Watson-Crick Center for Molecular Medicine, Islamic University of Science and Technology, Awantipora, Jammu and Kashmir, India

We want to thank Liang (2021) for his comments on using afatinib and palbociclib as a combination treatment for head and neck cancer. The author has raised the question regarding the effectiveness of combining afatinib with palbociclib to treat HNSCC [1]. To date, various studies have shown the preclinical and clinical activity of afatinib alone or in combination with other chemotherapeutic agents or radiation therapy [2–6]. A recent clinical trial (NCT01345682) by Haddad et al. (2019) with afatinib as a second-line therapy has shown improvement in the progression-free survival of HNSCC patients with recurrent/metastatic disease [7]. Note that such clinical advantage was demonstrated on patients that have progressed from platinum-based therapy with little-to-no other effective treatment options [7]. Our previous study with afatinib as a radiosensitizer have indicated a reduction in the tumor growth and cancer stem cell population in HNSCC [6].

As indicated in our manuscript [1], xenografts that were nonresponsive to the treatments demonstrated a dramatic increase in the cyclin D1, CDK4/6, and activated form of EGFR, suggesting the existence of a by-passing mechanism for tumor cell survival. Additionally, treatment with palbociclib alone too can lead to the activation of EGFR signaling in HNSCC cells suggesting the need to target EGFR and CDK4/6 signaling to prevent tumor cells from using alternative pathways for its survival and growth. The effectiveness of this combination can be observed in the synergy score estimate with both the drugs (afatinib and palbociclib) that have shown an additive effect in HNSCC cells which signifies the clinical importance of the combination.

mTOR/Ribosomal protein S6 signaling is associated with cellular metabolism, cell size, and protein synthesis. Phosphorylated S6 may also predict therapy response in cancer [8, 9]. Similarly, there was an increased pS6 expression in HNSCC tumors and cell lines (two to three-fold) during treatment with palbociclib as a monotherapy which can be

Conflict of interest

SKB is one of the co-founders of Sanguine Diagnostics and Therapeutics, Inc. AKG has received consulting fees from AstraZeneca, Jazz Pharmaceuticals, G1 Therapeutics, Blueprint Medicines, Genentech, Flagship Biosciences, Mirati Therapeutics and research support form Takeda. AKG also serves on a DSMC for YMAbs. Other authors declare no potential conflicts of interest.

abrogated when treated in combination with afatinib [1]. Although treatment with afatinib or palbociclib as a monotherapy showed a decrease in tumor volume and tumor weight as evident in Ki67 expression, the use of alternative bypassing survival mechanism by the cancer cells cannot be eliminated [1]. Under such condition, combination therapy with afatinib with palbociclib present a better therapeutic option to restrict the tumor cells from using alterative survival mechanisms in HNSCC.

## References

[1]. Chaudhary S, Pothuraju R, Rachagani S, Siddiqui JA, Atri P, Mallya K, Nasser MW, Sayed Z, Lyden ER, Smith L, Gupta SD, Ralhan R, Lakshmanan I, Jones DT, Ganti AK, Macha MA, Batra SK, Dual blockade of EGFR and CDK4/6 delays head and neck squamous cell carcinoma progression by inducing metabolic rewiring, Cancer Letters, 510 (2021) 79–92. [PubMed: 33878394]

[2]. Hasegawa H, Yasuda H, Hamamoto J, Masuzawa K, Tani T, Nukaga S, Hirano T, Kobayashi K, Manabe T, Terai H, Ikemura S, Kawada I, Naoki K, Soejima K, Efficacy of afatinib or osimertinib plus cetuximab combination therapy for non-small-cell lung cancer with EGFR exon 20 insertion mutations, Lung Cancer, 127 (2019) 146–152. [PubMed: 30642543]

[3]. Vengoji R, Macha MA, Nimmakayala RK, Rachagani S, Siddiqui JA, Mallya K, Gorantla S, Jain M, Ponnusamy MP, Batra SK, Shonka N, Afatinib and Temozolomide combination inhibits tumorigenesis by targeting EGFRvIII-cMet signaling in glioblastoma cells, J Exp Clin Cancer Res, 38 (2019) 266. [PubMed: 31215502]

[4]. Margalit DN, Haddad RI, Tishler RB, Chau NG, Schoenfeld JD, Bakst RL, Misiukiewicz KJ, Gupta V, Posner M, Hanna GJ, Mahmood U, Rawal B, Catalano PJ, Rath L, Bacay A, McHugh P, Rabinowits G, A Phase 1 Study of Afatinib in Combination with Postoperative Radiation Therapy with and Without Weekly Docetaxel in Intermediate- and High-Risk Patients with Resected Squamous Cell Carcinoma of the Head and Neck, Int J Radiat Oncol Biol Phys, 105 (2019) 132–139. [PubMed: 31082494]

[5]. Specenier P, Vermorken J, Afatinib in squamous cell carcinoma of the head and neck, Expert Opin Pharmacother, 17 (2016) 1295–1301. [PubMed: 27160335]

[6]. Macha MA, Rachagani S, Qazi AK, Jahan R, Gupta S, Patel A, Seshacharyulu P, Lin C, Li S, Wang S, Verma V, Kishida S, Kishida M, Nakamura N, Kibe T, Lydiatt WM, Smith RB, Ganti AK, Jones DT, Batra SK, Jain M, Afatinib radiosensitizes head and neck squamous cell carcinoma cells by targeting cancer stem cells, Oncotarget, 8 (2017) 20961–20973. [PubMed: 28423495]

[7]. Haddad R, Guigay J, Keilholz U, Clement PM, Fayette J, de Souza Viana L, Rolland F, Cupissol D, Geoffrois L, Kornek G, Licitra L, Melichar B, Ribaldo Nicolau U, Rauch D, Zanetta-Devauges S, Cohen EEW, Machiels JP, Tahara M, Vermorken J, Geng Y, Zografos E, Gauler T, Afatinib as second-line treatment in patients with recurrent/metastatic squamous cell carcinoma of the head and neck: Subgroup analyses of treatment adherence, safety and mode of afatinib administration in the LUX-Head and Neck 1 trial, Oral Oncol, 97 (2019) 82–91. [PubMed: 31450171]

[8]. Iwenofu OH, Lackman RD, Staddon AP, Goodwin DG, Haupt HM, Brooks JS, Phospho-S6 ribosomal protein: a potential new predictive sarcoma marker for targeted mTOR therapy, Modern pathology, 21 (2008) 231–237. [PubMed: 18157089]

[9]. Hirashita Y, Tsukamoto Y, Kudo Y, Kakisako D, Kurogi S, Hijiya N, Nakada C, Uchida T, Hirashita T, Hiratsuka T, Akagi T, Ueda Y, Shiroshita H, Etoh T, Mizukami K, Honda K, Okimoto T, Kodama M, Inomata M, Moriyama M, Murakami K, Early response in phosphorylation of ribosomal protein S6 is associated with sensitivity to trametinib in colorectal cancer cells, Lab Invest, 101 (2021) 1036–1047. [PubMed: 33911189]