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In Reply

We really appreciate the commentary and careful reading from Dr. Pusceddu and colleagues of our manuscript about the role of palbociclib in patients with low-grade pancreatic neuroendocrine tumors (pNETs) [1]. Unfortunately, we could not show any significant activity at least in terms of relevant tumor shrinkage in the 21 patients with pNETs with grade G1/2 treated in the study [2].

We agree that patients with G3 or neuroendocrine carcinomas (NECs) may potentially have a more activated cell cycle signaling with a direct involvement of *RB1* and *TP53* genes. However, the cyclin-dependent kinase 4/6 (CDK4/6)–cyclin D pathway is not the only regulator of the cell cycle machinery [3]. If palbociclib could have a role in high proliferative tumors, it would have demonstrated activity in urothelial carcinomas [4], or in molecularly selected squamous cell lung cancer [5] and glioblastoma [6] with RB1-positive tumors. Unfortunately, responses on these different highly proliferative tumors were always lower than 10%. It seems that cell cycle–related factors other than CDK4/6 such as CDK2/cyclin E complex; the Cip/Kip family, including p21, p27, and p57; or Forkhead box protein M1 may also have a role, and further research is needed in this sense [7, 8].

In nonreported data, we observed that 4 out of 17 patients molecularly characterized in our study were *RB1* wild type. We found no correlation between this finding and responses, or progression-free interval or even Ki67 proliferation index.

Current approvals of CDK4/6 inhibitors are consistently based on combinations with mammalian target of rapamycin (mTOR) inhibitors or hormone treatments in other tumors. Regarding the use of cyclin inhibitors in combination with mTOR inhibitors, we agree that this proposal may be a promising strategy for patients with NETs. We are expecting shortly the results of a phase II trial of the combination of ribociclib and everolimus in patients with well-differentiated NETs (NCT03070301) [9]. Other drug combinations, such as somatostatin analogs, can also be explored in patients with metastatic NETs who have not been previously treated. A potential combination strategy of chemotherapy plus a CDK4/6 inhibitor could be potentially active in NECs, but overlapping toxicity, mainly high-grade neutropenia, is foreseen.

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Disclosures

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