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Are Cyclin-Dependent Kinase 4/6 Inhibitors Without Future in Neuroendocrine Tumors?

Dysregulation of the cyclin D -cyclin dependent kinase (CDK)4/6 -retinoblastoma (RB)1 pathway frequently occurs in cancer, and CDK4/6 inhibitors have demonstrated significant clinical activity in several malignancies.

We read with great interest the PALBONET study published by Grande et al., which observed lack of activity of the CDK4/6 inhibitor palbociclib as a single agent in molecularly unselected patients with grade (G) 1/2 advanced pancreatic neuroendocrine tumors (pNETs) [1].

The trial failed to achieve the primary endpoint (objective response rate [ORR] ≥5%) owing to the absence of objective responses in enrolled patients (ORR 0%), with a 55% rate of disease stabilizations that may be related to the natural indolent course of disease rather than to treatment activity.

Despite these disappointing data, we believe that it may be too early to consider CDK4/6 inhibitors with no future in neuroendocrine neoplasms (NENs).

First, NENs are extremely heterogeneous tumors, so careful patient selection is crucial.

In our opinion, cell-cycle inhibition strategy may display more activity in NENs with higher proliferation index (i.e., NET G3 with Ki67 ≥20% and/or poorly differentiated neuroendocrine carcinoma [NEC]) rather than the low-proliferating G1–2 NET forms. Moreover, patient selection based on molecular features is also warranted.

RB1 loss is the most widely recognized biomarker of resistance to CDK4/6 inhibitors. Loss of RB1 protein expression and molecular alterations of *TP53* are the most important biomolecular criteria for discriminating poorly differentiated gastroenteropancreatic NECs from well-differentiated NETs with Ki67 ≥20% (*TP53* mutated/RB1 loss NEC G3 vs *TP53* wild-type/RB1 expression NET G3) [2, 3]. Furthermore, among lung large cell neuroendocrine carcinomas (LCNECs), two mutually exclusive genomic subtypes have been identified: the first, which is similar to small cell lung cancer (SCLC), shows concurrent mutation of *TP53* and *RB1*, whereas the other subtype, more similar to non-small cell lung cancer, is predominantly *RB1* wild-type, harboring concurrent biallelic *TP53* and *STK11/KEAP1* alterations [4–6]. About 10% of SCLC has intact *RB1* [7].

Second, the most significant successes of CDK4/6 inhibition in the clinical setting have occurred when these drugs were administered in combination with endocrine therapy, rather than as single agents [8]. The induction of Akt or mammalian target of rapamycin complex (mTORC) activity as a response to CDK4/6 inhibition has been extensively described. Specifically, CDK4/6 inhibition has been associated with an RB-dependent activation of Akt, that is mediated by mTORC2 [9]. Because the Akt/mTOR pathway plays a relevant role in NEN tumorigenesis and progression, the composite suppression of CDK4/6 activity and the Akt/mTOR axis (e.g., through combination with everolimus and/or somatostatin analogues) may represent a key mechanism of durable cell cycle exit and a particularly promising combination therapy in NENs.

In our opinion, clinical trials evaluating combinations with CDK4/6 inhibitors in *RB1* wild-type NENs should be developed. Criteria for patient eligibility should encompass clinical, pathological, and biomolecular features, selecting patients with well-differentiated tumors with Ki67 ≥20% (such as NET G3), atypical lung carcinoid, and LCNEC and excluding patients harboring genetic features of resistance like acquired *RB1* mutations, cyclin E amplification, *CDK6* amplification, or suppression of CDK2 inhibitors [8].

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