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## Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer.

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## CORRESPONDENCE



## Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

**TO THE EDITOR:** In the PALOMA3 study, Turner et al. (July 16 issue)<sup>1</sup> report that the addition of palbociclib to fulvestrant improved progression-free survival as compared with fulvestrant alone in patients with advanced breast cancer, with similar discontinuation rates because of adverse effects (2.6% and 1.7%, respectively). However, molecularly targeted therapies have moderate toxic effects that may become unacceptable over the long term and result in a deterioration in the quality of life, as shown in a previous report.<sup>2,3</sup> The PALOMA1 study, a previous phase 2 trial of palbociclib with a median follow-up of approximately 30 months, showed that the combination of palbociclib and letrozole, as compared with letrozole alone, was associated with higher rates of discontinuation (11% vs. 2%) and dose interruption (33% vs. 4%) because of adverse effects.<sup>4</sup> Furthermore, the rate of pulmonary embolism in the PALOMA1 study was higher than that in the PALOMA3 study (4% vs. 0.9%). Thus, because the authors report the results of a predetermined interim analysis with a median observation period of only 5.6 months, it is possible that further follow-up may reveal long-term toxic effects that disturb the regular

administration of the combination therapy or hamper the use of subsequent therapies.

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Dr. Saji reports receiving lecture fees from Pfizer. No other potential conflict of interest relevant to this letter was reported.

1. Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor–positive advanced breast cancer. *N Engl J Med* 2015;373:209-19.
  2. Soria JC. Phase 1 trials of molecular targeted therapies: are we evaluating toxicities properly? *Eur J Cancer* 2011;47:1443-5.
  3. Ratain MJ. Targeted therapies: redefining the primary objective of phase I oncology trials. *Nat Rev Clin Oncol* 2014;11:503-4.
  4. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25-35.
- DOI: 10.1056/NEJMc1510345

**THE AUTHORS REPLY:** In the PALOMA3 study, on the advice of the independent data and safety monitoring committee, we reported substantial efficacy for palbociclib in combination with fulvestrant at the time of the interim analysis. The median of 5.6 months of follow-up at the interim analysis was too short a period to assess possible long-term adverse effects associated with palbociclib. Ozaki and colleagues note that molecularly targeted therapies may have long-term low-grade toxic effects and suggest that such adverse events can lead to a reduced quality of life. In contrast, in PALOMA3, patients' quality of life was maintained among those receiving palbociclib–fulvestrant as compared with substantial deterioration among those receiving fulvestrant alone.

Follow-up continues in the PALOMA3 study,

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and we will be updating efficacy and safety data. The first updated data, which were collected in March 2015 with a median follow-up of 8.9 months, showed that the rate of pulmonary embolism remained low (0.9%) among patients treated with palbociclib. Moreover, the discontinuation rate because of adverse effects among patients receiving palbociclib remained at 4.0%, as compared with a rate of 1.7% for those receiving fulvestrant alone. These findings support the long-term safety of palbociclib that was reported in the smaller PALOMA1 study.<sup>1</sup>

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Since publication of their article, the authors report no further potential conflict of interest.

1. Slamon D, Crown J, Lang I, et al. Long-term safety profile of palbociclib (P) in combination with letrozole (L) as first-line treatment for postmenopausal patients with ER+ and HER2- advanced breast cancer (ABC) (PALOMA-1/TRIO-18). *J Clin Oncol* 2015;33: abstract.

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## Somatic Mutations and Clonal Hematopoiesis in Aplastic Anemia

**TO THE EDITOR:** In their study involving 439 patients with aplastic anemia, Yoshizato and colleagues (July 2 issue)<sup>1</sup> bring us closer to understanding clonal hematopoiesis in patients with this disease. However, a key conceptual aspect of the study is that the investigators prescreened patients for somatic mutations in genes that are mutated in myeloid cancers using targeted sequencing, followed by whole-exome sequencing, mainly in patients with mutations in the targeted genes. Furthermore, the study population included those with the post-aplastic anemia myelodysplastic syndrome (MDS), which further biased the identified pattern of clonal hematopoiesis toward MDS-associated mutations. Using an unbiased approach of comparative whole-exome sequencing of bone marrow and skin DNA, we recently found somatic mutations in 73% of 22 patients with aplastic anemia who were not prescreened with targeted sequencing.<sup>2</sup> None of the patients who were included in our study had evidence of myelodysplasia. Somatic mutations were significantly enriched in pathways of immunity, whereas only 9% of the patients carried mutations associated with MDS. Further studies using unbiased approaches with long-term follow-up will help to capture the full spectrum and biologic significance of clonal hematopoiesis in aplastic anemia.

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No potential conflict of interest relevant to this letter was reported.

1. Yoshizato T, Dumitriu B, Hosokawa K, et al. Somatic mutations and clonal hematopoiesis in aplastic anemia. *N Engl J Med* 2015;373:35-47.

2. Babushok DV, Perdignes N, Perin JC, et al. Emergence of clonal hematopoiesis in the majority of patients with acquired aplastic anemia. *Cancer Genet* 2015;208:115-28.

DOI: 101056/NEJMc1509703

**TO THE EDITOR:** Yoshizato et al. report that somatically mutated clones are detectable in 47% of patients with aplastic anemia. The single most frequently mutated gene was *DNMT3A* (in 8.4% of patients), which, along with *ASXL1*, was associated with a poorer response to immunosuppressive therapies than were mutations in *PIGA* or *BCOR/BCORL1* and with worse overall survival. However, we notice that *DNMT3A* mutations were almost twice as frequent among Japanese patients as among U.S. patients. In the Japanese patients, whole blood was compared with buccal-smear DNA; in the U.S. patients, granulocytes were compared with CD3+ T cells. Since *DNMT3A*-mutated clones are frequently detectable in both myeloid and lymphoid cells of healthy older persons,<sup>1</sup> the significance of their occurrence in patients with aplastic anemia, as well as the discor-