Letter to the Editor

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Letter to the Editor: statistics and clinical perception of patients' reported outcomes for palbociclib and abemaciclib: a sliding doors story

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We have read with great and sincere interest the paper by Law *et al.* reporting an indirect comparison of patients' reported outcomes (PRO) in the Paloma-3 and Monarch-2 studies related to cyclin-dependent tyrosine kinase 4/6 (CDK4/6) inhibitors in advanced hormone-positive, HER-2 negative breast carcinoma (HR+/HER-ABC) [1–3]. The authors employed masterfully anchored matching-adjusted indirect comparisons (MAIC) to compare the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ-C30) and its breast cancer specific module (EORTC QLQ-BR23) in two large trials aiming to demonstrate the superiority of the combination of endocrine therapy plus CDK4/6 inhibitors over endocrine therapy plus placebo [1]. The study indicates that palbociclib plus fulvestrant may improve or maintain health related quality of life better than abemaciclib plus fulvestrant (FUL). In addition, the MAIC analysis showed an advantage of palbociclib (PAL) over abemaciclib (ABE) across several functional and symptom subscales, including global QoL, emotional functioning, nausea/vomiting, appetite loss, diarrhea and systemic therapy side effects.

MAIC analyses may be helpful if comparative studies are missing, such as in the case of different CDK4/6 inhibitors. Today many technology assessment agencies accept this methodology thanks to the solidity and rigor of the statistical analysis [4]. Still, the robustness and reliability of results strongly depend on the type of entered data and the clinical context, such as cross-trial differences in patient populations or greater disease severity in one trial versus another, which can lead to incorrect comparisons of treatment outcomes [4]. In addition, the statistics, however well performed, do not necessarily reflect the clinical reality and the treatment efficacy perception of both patients and health professionals.

The Paloma 3 trial included a clinically heterogeneous population of patients. It showed a significantly longer progression-free survival (PFS) with the combination PAL plus FUL therapy than with placebo + FUL, with an absolute difference of 6.6 months in patients with HR+/HER-ABC who had disease progression after previous endocrine therapy or chemotherapy [2,6,7]. The study reported a median of 11.2 months (95% CI: 9.5–12.9) versus 4.6 months (95% CI: 3.5–5.6) with a 0.50 hazard ratio (HR) for disease progression or death (95% CI: 0.40–0.62) in favor of the PAL/FUL arm. Overall survival (OS) showed an absolute improvement of 6.9 months in favor of the PAL plus FUL arm versus the placebo arm being a median OS of 34.8 months (range: 28.8–39.9) versus 28.0 months (range: 23.5–33.8) with a stratified HR for death, 0.81 (95% CI: 0.64–0.99) and a one-sided p = 0.0221. In the endocrine-sensitive subgroup of patients, the HR for death was 0.72 (95% CI: 0.55–0.94),

while the endocrine-resistant group had an HR for death of 1.14 (95% CI: 0.71–1.84), the latter interpreted as definitively negative.

On the other hand, the Monarch-2 trial included only patients with both primary and secondary endocrine-resistant HR+/HER-ABC [3]. PFS was statistically superior for ABE/FUL arm over the placebo, being 16.9 versus 9.3 months, respectively, with an HR of 0.536; (95% CI: 0.445–0.645; $p<0.001$). This difference was present in all subgroups, including patients with visceral disease, primary or secondary endocrine resistance and bone only disease. Also, the time to the second progression was in favor of the ABE/FUL arm. The addition of ABE to FUL resulted in a statistically significant longer OS compared with placebo/FUL (HR: 0.757; 95% CI: 0.606–0.945; $p = 0.01$). The improvement in median OS was 9.4 months, with a median of 46.7 months in the ABE/FUL arm and 37.3 months in the placebo arm.

In the work of Law *et al.*, individual patient data of the Paloma-3 trial were matched with the Monarch-2 study, adjusting for treatment-effect modifiers and anchoring through a common comparator according to the best MAIC analysis [1]. Patients who had prior chemotherapy for HR+/HER-ABC and had ≥2 last lines of endocrine therapy were removed and matched to median aggregated, non individual data of the Monarch-2 study. Therefore, the authors removed the non significant results of PAL (1-sided $p = 0.432$ and 0.440, respectively, of PFS and OS) in patients with prior chemotherapy or endocrine-resistant. The MAIC population included chemotherapy naïve ones and endocrine-sensitive subgroups of patients with the best prognosis. On the contrary Monarch-2 data of abemaciclib in the same settings are statistically significant [3].

Besides the above reported observations, the results elaborated by Law *et al.* present several clinical limitations. First, the authors themselves state that the analysis could not account for differences in the management of adverse events and associated tolerability of the drugs. The differences may be based on adherence, dose modification/titration and discontinuation data that may have impacted the comparison because access to individual patient data was only available for the Paloma-3 trial [1].

Second, the results of the MAIC analysis may also be poorly helpful in clinical practice. The incidence and severity of clinically meaningful diarrhea and other side-effects in patients receiving ABE has dramatically decreased with time from initial trials to more recent ones and real-life reports reflecting a good learning curve for oncologists and skill management of patients and caregivers [7,8]. The clinical results represent a second crucial issue. Law *et al.* did not select patients also for endocrine sensitivity. In the Paloma-3 trial, the OS of patients without sensitivity to previous endocrine therapy failed to show any advantage for PAL/FUL over FUL/placebo with an HR for death of 1.14 (95% CI: 0.71–1.84) [2]. Visual evaluation of curves raises the impression of a somewhat detrimental effect. On the other hand, the results of the Monarch-2 study are strongly positive in favor of the ABE/FUL arm in the overall population and all specific subgroup analyses [3]. These efficacy and tolerability data of ABE and PAL are also confirmed by retrospective, real-life reports [9,10].

The clinical effectiveness of ABE is further strengthened by Monarch-e data in the adjuvant setting in patients with surgically excised breast cancer at high risk of recurrence. However, such evidence for PAL is missing despite two specifically designed studies [11,12]. In addition, diarrhea, nausea and appetite loss scores statistically favored the control arm among metastatic BC patients receiving ABE, whereas they were superimposable in the early setting [11].

In conclusion, PROs are exceedingly important but must be interpreted in light of the clinical results [13]. It is probable that the patient's subjective perception is influenced positively or not by their previous experience and knowledge of their disease. Taking into account the remarkable clinical activity of abemaciclib in all settings, even if there is an excess risk of diarrhea or slightly lower PRO, which treatment would any patient prefer?

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