remain dormant in its microenvironment, and the effect of trastuzumab in maintaining that dormancy. In summary, our report case cautions against discontinuing trastuzumab in patients with DCR.

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## Risks and benefits from CDK inhibitors for advanced HR+ Her 2− breast cancer

Targeting the estrogen-receptor signalling pathway represented for many decades the standard of care for both locally and advanced hormone receptor positive (HR+) breast cancer. Deregulation of cyclin-D/cyclin-dependent kinase 4/6/retinoblastoma gene product pathway is implicated in resistance to endocrine therapy (ET). Three randomized trials showed that adding the CDK inhibitors (CDKi) palbociclib/ribociclib to letrozole significantly improved progression-free survival (PFS) than letrozole in upfront treatment of postmenopausal women with advanced HR+/Her2− breast cancer [1–3]. Moreover, combining palbociclib plus fulvestrant meaningfully prolonged PFS compared with fulvestrant in women with any menopausal status and advanced HR+/Her 2− breast cancer who had progressed to prior ET [4].

Recently, the MONARCH-2 trial showed that abemaciclib plus fulvestrant significantly improved PFS compared with fulvestrant in this setting for women with any menopausal status who had progressed to prior ET [5]. Hence, we carried out a meta-analysis to assess the benefit and the risk of abemaciclib/palbociclib plus fulvestrant and the pooled impact of all CDKi plus ET in advanced HR+/Her2− breast cancer. PFS and G3–G4 adverse events (AEs) data were extracted from five randomized trials. Random-effect models were used for pooling data to account for heterogeneity in these studies. Analysis was carried out using Cochrane RevMan version 5.2 software. A total of 1190 patients (793 abemaciclib/palbociclib–fulvestrant and 397 fulvestrant) were included. Patients treated with abemaciclib/palbociclib–fulvestrant achieved a meaningful improvement in PFS (HR 0.51, 95% CI 0.43–0.60), although significant difference in G3–G4 AEs (Table 1). Despite methodological limitation concerning the indirect comparison of results achieved adding CDKi to letrozole or fulvestrant in first- and second-line treatment, CDKi plus fulvestrant might provide similar or even slightly better PFS (HR 0.51 versus 0.56) than CDKi plus letrozole although a higher odds of G3–G4 AEs (OR 6.81 versus 4.23).

Pooling together results of the five trials, CDKi plus ET provide better outcome than ET (PFS, HR 0.53, 95% CI 0.47–0.60) in advanced HR+/Her2− breast cancer despite higher toxicities (OR 5.48, 95% CI 3.00–10.02). These results reinforce data on CDKi plus ET efficacy in advanced HR+/Her2− breast cancer and according to data of FALCON trial constitute the rationale to design new studies evaluating the efficacy of CDKi plus fulvestrant or letrozole in first-line setting.

Although an individual patient data meta-analysis should be carried out, our results highlights that adding CDKi to ET improves clinical outcomes than ET, regardless the number of prior treatment received, menopausal status and represents an alternative option to current standard treatment. The PFS benefit is consistent across the five trials, is clinically relevant and even in the absence of mature data, the pooled HR 0.53 is likely to translate in a significant improvement in overall survival.

Emerging data provide a new potential standard treatment of advanced HR+/Her2− breast cancer, although benefits should be balanced with longer treatment duration, toxicities and costs. Head-to-head trials are warranted to compare the efficacy of CDKi plus ET or chemotherapy especially for those women with high tumour burden and visceral metastases to improve patients' selection and maximize the benefit from the two strategies.

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**Table 1. Comparison between hazard ratios (HRs) for progression-free survival (PFS) and odds ratios (ORs) for G3–G4 adverse events (AEs) from five randomized controlled clinical trials of abemaciclib/palbociclib plus fulvestrant compared with fulvestrant, palbociclib/ribociclib plus letrozole compared with letrozole and all CDK inhibitors (CDKi) plus endocrine therapy (ET) compared with ET in patients with advanced HR+/Her2− breast cancer**

| Treatment under investigation | Abe/Palbo +Ful versus Ful | Ribo/Palbo + Letro versus Letro | CDKi + ET versus ET |
|---|---|---|---|
| Trials included for the pooled analysis | PALOMA-3 [4], MONARCH 2 [5] | PALOMA-1 [1], PALOMA-2 [2], MONALEESA [3] | PALOMA-1 [1], PALOMA-2 [2], MONALEESA [3], PALOMA-3 [4], MONARCH 2 [5] |
| Number of patients | 1190 (793 versus 397) | 1499 (862 versus 637) | 2689 (1655 versus 1034) |
| Pooled HR for PFS | HR 0.51 95% CI (0.43–0.60) | HR 0.56 95% CI (0.48–0.66) | HR 0.53 95% CI (0.47–0.60) |
| Heterogeneity test for PFS | $\tau 2$=0.0; $\chi 2$=1.12; df = 1 ($P$=0.29); $I^2$=10%; $Z$=7.63 ($P$<0.00001) | $\tau^2$=0.00; $\chi 2$=0.45; df = 2 ($P$=0.80); $I^2$=0%; $Z$=7.05 ($P$<0.00001) | $\tau 2$=0.00; $\chi 2$=2.24; df = 4 ($P$=0.69); $I^2$=0%; $Z$=10.68 ($P$<0.00001) |
| Pooled OR for G3–G4 AEs | OR = 6.81 95% CI (3.68–12.58) | OR = 4.23 95% CI (1.30–13.74) | OR = 5.48 95% CI (3.00–10.02) |
| Heterogeneity test for G3–G4 AEs | $\tau 2$=0.15; $\chi^2$=4.73; df = 1 ($P$=0.03); $I^2$=79%; $Z$=6.12 ($P$<0.00001). | $\tau^2$=1.02; $\chi^2$=40.70; df = 2 ($P$<0.00001).; $I^2$=95%; $Z$=2.40 ($P$=0.02). | $\tau^2$=0.42; $\chi^2$=40.51; df = 4 ($P$<0.00001); $I^2$=90%; $Z$=5.53($P$<0.00001). |

Pooled HRs and ORs were computed using random-effects model.
Abe, abemaciclib; CI, confidence interval; df, degree of freedom; ET, endocrine therapy; Ful, fulvestrant; Palbo, palbociclib; Ribo, ribociclib.

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## Absence of evidence is not evidence of absence: the case of non-inferiority

With interest we read the recent article by Kwakman et al. [1] reporting on S-1 and capecitabine in Western patients with metastatic colorectal cancer.

In the abstract, the authors conclude that treatment with S-1 in this population has an efficacy comparable to that of capecitabine. This is only correct when using 'comparable' in the sense of 'capable of comparison', but not in the sense of 'similar' or 'like'. In the discussion, the authors claim that S-1 is 'not compromising efficacy'. These claims are simply not supported by the data—as the authors point out later this trial was 'not sufficiently powered for clinical efficacy end points'.

We would like to commemorate the classic paper by Altman and Bland [2] where it is pointed out that authors often wrongly conclude that a study has shown that there is no difference, whereas usually all that has been shown is an absence of evidence of a difference and that these are quite different statements.

Similar response rates and overlapping curves seem prone for this kind of misinterpretation as such conclusions could be heard