Letters to the editor

Noninferiority for Short-HER or short-chemotherapy?

Dear Editor,

The Short-HER trial investigators reported that the noninferiority of 9 weeks trastuzumab administration compared with standard 1 year administration has failed to be shown [1]. Five-year disease-free survival (DFS) was 88% in the 1 year and 85% in the 9 weeks arm. The hazard ratio was 1.13 [90% confidence interval (CI) 0.89–1.42], with the upper limit of the CI crossing the noninferiority margin. In this study, chemotherapy in arm A (trastuzumab 1 year) consisted of Adriamycin-Cyclophosphamide or Epirubicin-Cyclophosphamide administered every 3 weeks for four courses followed by paclitaxel 175 mg/m^2 or docetaxel 100 mg/m^2 every 3 weeks for four courses whereas chemotherapy in arm B (trastuzumab 9 weeks) consisted of docetaxel 100 mg/m^2 every 3 weeks for three courses followed by 5 Fluorouracil-Epirubicin-Cyclophosphamide administered every 3 weeks for three courses. We suggest that differences in the chemotherapy backbone (i.e. higher anthracycline and taxane doses in arm A) might have confounded the results favoring the 1-year trastuzumab arm. Indeed, the recently reported SOLD trial [2] which also compared 9-weeks and 1 year adjuvant trastuzumab therapy showed that a significant interaction (P=0.007) was found between docetaxel dosing and DFS; the 1678 patients who received docetaxel 80 mg/m^2 had inferior and the 480 who received 100 mg/m^2 had similar DFS to patients in the 1-year group treated with the same docetaxel dosing. An earlier randomized phase II study with identical chemotherapy backbones in two arms also [3] demonstrated that conventional 1 year trastuzumab therapy was not superior to abbreviated 12 weeks therapy. Two previous large phase III trials compared trastuzumab 6 months versus 1 year in the adjuvant setting. In the UK PERSEPHONE trial, noninferiority of the 6 months regimen was demonstrated [4] whereas in the French PHARE trial, noninferiority could not be shown [5]. Details of the anthracycline and taxane dosing were not reported in either study but dose differences (if any) may account for the contradictory results. We propose that chemotherapy dose and schedule should also be considered as a confounder and appropriate adjustments should be made when interpreting the results of adjuvant trastuzumab duration trials.

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Activity of EGFR antibody in non-V600 *BRAF* mutant metastatic colorectal cancer

V600E *BRAF* mutation occurs in 8%–10% of metastatic colorectal cancer (mCRC) and is associated with resistance to epidermal growth factor receptor (EGFR) inhibitors and a poor prognosis [1, 2]. In contrast, non-V600 *BRAF* mutations occur in ∼2% of mCRC, and correlate with a significantly better survival [3]. It is unknown whether non-V600 *BRAF* mutations also induce resistance to EGFR inhibitors. We report a case of non-V600 *BRAF* mutant mCRC responding remarkably to single-agent panitumumab.

A 51-year-old woman was diagnosed with mCRC with a *BRAF* G469V mutation. Her disease progressed after several lines of therapy including 5-fluorouracil, oxaliplatin, irinotecan, and TAS-102. Considering a non-V600 *BRAF* mutation may not confer resistance to EGFR inhibitors, we started her on single-agent