Published in final edited form as:

Clin Cancer Res. 2017 July 01; 23(13): 3475. doi:10.1158/1078-0432.CCR-17-0479.

Letter to the Editor Response to CCR-16-0362R:

Authors' reply

Brenda F. Kurland, Hannah M. Linden, and David A. Mankoff

We thank Drs. Groheux and Benard for their interest in and insight into our work, and for sharing their concerns. We agree that quantitative assessment of ^{18}F -fluorodeoxyglucose (FDG) and ^{18}F -fluoroestradiol (FES) PET together may help guide breast cancer treatment for patients with ER-expressing tumors. Our study with a progression-free survival (PFS) endpoint and updated static ^{18}F -fluoroestradiol (FES) positron emission tomography (PET) measures did not precisely replicate earlier studies for which FES standardized uptake value (SUV) predicted response (1,2). However, the optimal cutpoint for FES avidity was quite similar to that in prior studies, and – as emphasized by Drs. Groheux and Benard – a role for FDG PET in predicting clinical benefit on endocrine monotherapy is expected in the context of prior studies.

We interpret our results as indicating that low pre-therapy FDG uptake identifies indolent, less aggressive cancers that have favorable PFS regardless of treatment. In other words, FDG uptake acted as a prognostic marker in the study cohort. For the subgroup of patients with high FDG uptake, with unfavorable PFS without effective therapy, higher FES uptake was associated with better outcome on endocrine therapy. Thus, our results supported the therapy-specific predictive capability of FES uptake.

We note in the work cited by Drs. Groheux and Benard (3), 2/84 patients with lesion FDG $\text{SUV}_{\text{max}} < 1.8$ or 2.0 were excluded from the primary analysis of response to breast cancer neoadjuvant therapy. In our cohort, 24/84 patients had an average FDG $\text{SUL}_{\text{max}3}$ (geometric mean of lean body mass-adjusted SUV_{max} for up to 3 lesions with highest FDG uptake) 2.2, which corresponded to an FDG SUV_{max} (same geometric mean but using SUV_{max} normalized to body weight) of about 3.0. Our modest FDG SUV cutoff is also much lower than the SUV_{max} cutpoint of 10.0 used in the neoadjuvant study and likely reflects a difference in the type of patients and tumors referred for metastatic endocrine therapy as opposed to primary cytotoxic chemotherapy.

We agree completely with Drs. Groheux and Benard that the combination of FDG and FES PET is of considerable interest in guiding treatment selection for ER-expressing breast cancer. This premise is supported by our study, where the combination of measures predicted outcome after endocrine therapy better than either measure alone. Biomarker selection and application should consider the context of the patient population and available treatments. The breast cancer community has been a pacesetter, using ER status and Oncotype Dx recurrence score as biomarkers that are used to help decide whether or not patients are likely to benefit from the use of adjuvant chemotherapy. With careful development, including a multicenter prospective observational study (EAI142, NCT02398773), the combination of FDG and FES PET may of considerable benefit for

directing the use of directing primary endocrine therapy, as well as modern combinations of endocrine therapy with molecularly targeted agents such as cell cycle and mTOR inhibitors (4,5). Patients with metastatic ER-expressing breast cancer may live many years with high quality of life and functional status, so it important to optimize the selection and sequence of anticancer therapy.

References

1. Linden HM, Stekhova SA, Link JM, et al. Quantitative fluoroestradiol positron emission tomography imaging predicts response to endocrine treatment in breast cancer. *J Clin Oncol*. 2006; 24:2793–2799. [PubMed: 16682724]
2. Dehdashti F, Mortimer JE, Trinkaus K, et al. PET-based estradiol challenge as a predictive biomarker of response to endocrine therapy in women with estrogen-receptor-positive breast cancer. *Breast Cancer Res Treat*. 2009; 113:509–517. [PubMed: 18327670]
3. Groheux D, Sanna A, Majdoub M, et al. Baseline Tumor 18F-FDG Uptake and Modifications After 2 Cycles of Neoadjuvant Chemotherapy Are Prognostic of Outcome in ER+/HER2- Breast Cancer. *J Nucl Med*. 2015; 56:824–831. [PubMed: 25883123]
4. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med*. 2012; 366:520–529. [PubMed: 22149876]
5. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol*. 2016; 17:425–439. [PubMed: 26947331]