correspondence

Reply to L. Marandino et al

We thank Marandino et al[1] and agree that cognitive function is important and complex in men with metastatic, hormone-sensitive prostate cancer. Cognitive decline increases with age, as does the incidence of metastatic prostate cancer, and has been associated with a diagnosis of cancer, androgen deprivation therapy, early generation antiandrogens, novel androgen signaling inhibitors, and chemotherapy.[2] ENZAMET provides unique information about self-ratings of cognitive function and other aspects of health-related quality of life (HRQoL) in men receiving these treatments for metastatic, hormone-sensitive prostate cancer.[3]

Marandino et al[1] suggest that analyses of deterioration-free survival should handle deaths and clinical progressions as competing risks rather than events. Deterioration-free survival is a composite end point that reflects net benefit on the basis of freedom from clinical progression (with possible associated physical and psychological symptoms), death, or a 10-point deterioration in specified, individual aspects of self-rated HRQoL. The rationale for combining these events is that this accurately reflects the problem faced by those affected and making decisions about treatment and corresponds with published guidelines.[4,5] We agree that combining events related to the tolerability of treatment and the efficacy of treatment can obscure effects in opposite directions. We, therefore, presented both the composite end point (Fig 3) and separate cumulative incidence functions for first deterioration in each aspect of HRQoL and for clinical progression (Data Supplement, Supplementary Figure 6).[3] This comprehensive approach provides the data that clinicians need to better support patients making decisions about treatment.

For example, Figure 2A of our report[3] shows that 10-point or greater deteriorations in self-rated cognitive function within 3 months were more frequent among participants assigned enzalutamide than control (39% *v* 30%; difference 9%; 95% CI, 3 to 15). We also reported these frequencies within subgroups (Fig 2B) in which testosterone suppression was used without docetaxel or enzalutamide (27%) or in combination with docetaxel alone (34%), with enzalutamide alone (35%), or with both enzalutamide and docetaxel (44%). We have no data on the frequency of self-reported deteriorations in cognitive function among men recently diagnosed with metastatic prostate cancer in the absence of testosterone suppression.

Self-ratings of cognitive function are important, but they are more strongly associated with self-ratings of fatigue, anxiety, depression, and overall quality of life, than with objective measures of cognitive impairment.[6-8] We considered the objective assessment of cognitive function with formal neurocognitive testing, but judged it impractical for an international, phase 3 trial. We also agree that cognitive function after cancer progression is of interest and may be affected by previous and subsequent treatments, but we judged that the additional information provided by HRQoL assessment beyond progression would not warrant the added burden for participants.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Marandino L, Raggi D, Necchi A, et al: Impact of novel hormonal therapy on cognitive function: Essential to measure, difficult to present. J Clin Oncol 40:2174-2175, 2022
2. Lange M, Joly F, Vardy J, et al: Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. Ann Oncol 30:1925-1940, 2019
3. Stockler MR, Martin AJ, Davis ID, et al: Health-related quality of life in metastatic, hormone-sensitive prostate cancer: ENZAMET (ANZUP 1304), an international, randomized phase III trial led by ANZUP. J Clin Oncol 40:837-846, 2022
4. Anota A, Hamidou Z, Paget-Bailly S, et al: Time to health-related quality of life score deterioration as a modality of longitudinal analysis for health-related quality of life studies in oncology: Do we need RECIST for quality of life to achieve standardization? Qual Life Res 24: 5-18, 2015
5. Bonnetain F, Bonsing B, Conroy T, et al: Guidelines for time-to-event end-point definitions in trials for pancreatic cancer. Results of the

DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials). Eur J Cancer 50:2983-2993, 2014

6. Bray VJ, Dhillon HM, Vardy JL: Systematic review of self-reported cognitive function in cancer patients following chemotherapy treatment. J Cancer Surviv 12:537-559, 2018
7. Hutchinson AD, Hosking JR, Kichenadasse G, et al: Objective and subjective cognitive impairment following chemotherapy for cancer: A systematic review. Cancer Treat Rev 38:926-934, 2012
8. Boscher C, Joly F, Clarisse B, et al: Perceived cognitive impairment in breast cancer survivors and its relationships with psychological factors. Cancers (Basel) 12:3000, 2020

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