diagnosed with mCRPC or mCSPC has not received at least one life-prolonging therapy in addition to ADT, that should now be considered suboptimal care. Importantly, the LATITUDE trial further highlights the importance of early introduction of life-prolonging drugs in addition to ADT in patients with lethal prostate cancer. Patients' survival and quality of life depend on these concepts.

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1 James ND, Spears MR, Clarke NW, et al. Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). *Eur Urol* 2015; **67:** 1028–38.
2 Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2019; published online April 12. http://dx.doi.org/10.1016/S1470-2045(19)30082-8.
3 Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017; **377:** 352–60.
4 Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; **368:** 138–48.
5 Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014; **371:** 424–33.
6 James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med* 2017; **377:** 338–51.
7 James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016; **387:** 1163–77.
8 Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015; **373:** 737–46.
9 Sydes MR, Spears MR, Mason MD, et al. Adding abiraterone or docetaxel to long-term hormone therapy for prostate cancer: directly randomised data from the STAMPEDE multi-arm, multi-stage platform protocol. *Ann Oncol* 2018; **29:** 1235–48.

Conclusions from quality of life studies in patients with resected high-risk melanoma: one part of the full story

In *The Lancet Oncology*, Dirk Schadendorf and colleagues[1] report the health-related quality-of-life outcomes from the COMBI-AD trial using the European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L) instrument. In the COMBI-AD trial, patients with resected stage III melanoma, with *BRAF*^{V600E} or *BRAF*^{V600K} mutations, were randomly assigned to receive adjuvant dabrafenib and trametinib or matching placebos. The authors report no difference in health-related quality of life during the 12 months of treatment, and conclude that the risk–benefit profile of this adjuvant therapy is therefore favourable. There is an implication that the high proportion of patients with pyrexia (273 [63%] of 435 patients) and fatigue (204 [47%]), as well as the 114 [26%] patients who discontinued trial therapy because of adverse events,[2] are not factors associated with the outcome. For an individual patient, the conclusions from this trial are just one part of the full story.

There are two additional adjuvant therapy trials, in a similar patient population, that report no difference in health-related quality of life despite a high incidence of severe adverse events, including deaths.[3,4] These trials investigated the role of adjuvant immunotherapy. One assessed adjuvant ipilimumab compared with placebo[3] and the other compared ipilimumab with nivolumab.[4] These three adjuvant therapy trials are likely to affect the future treatment of this patient group. As adjuvant trials, they all assessed patients who were disease-free, but who had been exposed to potentially morbid adverse reactions that could also affect quality of life. It is important to consider that there seems to be no difference when comparing health-related quality-of-life outcomes in these randomised trials, and how this message can be conveyed to patients.

Limitations in health-related quality-of-life assessments can include several factors. The EQ-5D questionnaire, which is validated to assess patients with cancer,[5] does not have symptom specificity that might be relevant to the assessments in COMBI-AD, with respect to fatigue and pyrexia. The European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire–30 (EORTC QLQ-30) instrument was used in the other two adjuvant therapy trials, but has not been specifically validated to assess immunotherapy and does not address endocrinopathies or dermatological immune-related adverse events, both of which are very relevant to those trials.[3,4,6]

All of the trials previously described were done with a protocol of timed assessments, including health-related


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quality of life. The EQ-5D-3L assessment questions health status at the time of completion of the instrument and the EORTC QLQ-30 questions health status during the previous week. If the event does not occur at that time of assessment, it will not be recorded. An example in the COMBI-AD study is the common severe event of pyrexia. In patients who had pyrexia, 209 (72%) of 292 patients had two or more episodes, with the pyrexia lasting a median of 3 days (range 2–7).[2] The timing of the completion of the questionnaire will have affected the ability to capture these adverse events, such that the patients who stopped receiving therapy because of adverse effects might have recovered to equivalence with the less toxic group. The frequency of discontinuation and reversibility of adverse events is likely to be a reason for the apparent lack of effect on the average health-related quality-of-life score when the whole cohort is analysed.[1] The high frequency of discontinuation in the two adjuvant immunotherapy trials could have affected reporting of health-related quality of life.[4,6] These adjuvant trials were powered to assess survival and recurrence endpoints, not health-related quality of life. As designed, there would need to be several severe adverse events with long-term consequences before one would see a substantial effect on the comparison of health-related quality of life between groups, particularly in the two placebo-controlled trials.

Clinicians might have affected the health-related quality-of-life assessment because of early recognition and management of adverse events, including withdrawal of therapy, which could affect results, dependent on the timing of completion of the questionnaire. Patients' assessments might be influenced by being motivated and feeling optimistic about agreeing to participate in the trial. Patients might also perceive drug-induced toxicity as being indicative of potential benefit, or could believe they are receiving active treatment; as such, a true assessment of the effect of drug toxicity on quality of life is not recorded.[7]

In the COMBI-AD trial, for an individual who does not have known metastatic melanoma, the overall conclusion—that treatment with dabrafenib plus trametinib has the same health-related quality-of-life outcome as placebo—does not tell the full story. However, the patient can be reassured that if they have an adverse event or have ceased therapy that they are likely to return to a satisfactory functioning level. In COMBI-AD, the absence of a detrimental effect on longer term health-related quality of life, if the disease does not recur, is also reassuring. For immunotherapy trials, patients can be offered similar counselling related to recovery after adverse events and at the end of the treatment, although in these trials, the longer term impact on health-related quality of life is awaited.

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1 Schadendorf D, Hauschild A, Santinami M, et al. Patient-reported outcomes in patients with resected, high-risk melanoma with *BRAF*^{V600E} or *BRAF*^{V600K} mutations treated with adjuvant dabrafenib plus trametinib (COMBI-AD): a randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2019; published online March 27. http://dx.doi.org/10.1016/S1470-2045(18)30940-9.
2 Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF mutated melanoma. *N Engl J Med* 2017; **377**: 1813–23.
3 Coens C, Suciu S, Chiarion-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. *Lancet Oncol* 2017; **18**: 393–403.
4 Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. *N Engl J Med* 2017; **377**: 1824–35.
5 Howell D, Molloy S, Wilkinson K, et al. Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. *Ann Oncol* 2015; **26:** 1846–58.
6 Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. *N Engl J Med* 2016; **375**: 1845–55.
7 Cornish D, Holterhues C, van de Poll-Franse LV et al. A systematic review of health-related quality of life in cutaneous melanoma. *Ann Oncol* 2009; **20** (suppl 6)**:** 51–58.

Inhibition of PD-1 and VEGF in microsatellite-stable endometrial cancer

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A 2018 study[1] showed that the incidence of endometrial cancer increased over the past 25 years in several countries, especially those undergoing rapid socioeconomic transitions. Although early-stage endometrial cancer is treatable with surgery and adjuvant therapy, long-term outcomes for patients with advanced disease are