editor/peer-reviewers (for the risk of carry-on effects either positive or negative of the two companion papers).

The TRINOVA-1 solution stays in the middle as in the primary publication, Monk and co-workers already described the most important QoL results, but specified that detailed data would have been reported in a separate publication [1]. This strategy may in principle reduce the interest of scientific editors and reviewers in the QoL paper; therefore the risk of not publishing, publishing with delay or publishing in low impact journals increases. As a consequence, for ever or at least for a long time, the QoL data will be published with low reporting quality [6]. This introduces a bias unfavouring the value of PRO in clinical trials.

In conclusion, we propose that a reflection should be done by the editorial scientific community regarding which is the best system to allow complete and qualitative reporting of clinical trials, including all the outcomes that are important for an exhaustive comprehension of the value of the new drug.

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disclosure

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references

1. Monk BJ, Poveda A, Vergote I et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014; 15: 799–808.
2. Ledermann J, Harter P, Gourley C et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med 2012; 366: 1382–1392.
3. Ledermann J, Harter P, Gourley C et al. Health-related quality of life (HRQoL) during olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer (PSR SOC) and a BRCA mutation (BRCAm). Ann Oncol 2014: 25 (suppl 4): iv305–iv326.
4. du Bois A, Luck HJ, Meier W et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003; 95: 1320–1329.
5. Pignata S, Scambia G, Katsaros D et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014; 15: 396–405.
6. Efficace F, Fayers P, Pusic A et al. Quality of patient-reported outcome reporting across cancer randomized controlled trials according to the CONSORT patient-reported outcome extension: a pooled analysis of 557 trials. Cancer 2015; 121: 3335–3342.

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Diagnostic Gleason score and castration-resistant prostate cancer

The COU-AA-302 and PREVAIL trials of abiraterone–prednisone and enzalutamide, respectively, confirmed the efficacy of potent androgen receptor (AR) targeting when compared with placebo in asymptomatic chemotherapy-naive men with metastatic castration-resistant prostate cancer (mCRPC) [1, 2]. The COU-AA-301 and AFFIRM trials confirmed efficacy in symptomatic men who had previously received docetaxel [3, 4]. There are currently no direct prospective comparisons of either AR targeting agent with other effective treatments for mCRPC, notably taxane chemotherapy or radium-223. The St Gallen Advanced Prostate Cancer Consensus Guidelines Conference in March 2015 [5] reached a consensus that it was appropriate to extrapolate the results of the COU-AA-302 and PREVAIL trials to certain symptomatic chemotherapy-naive men with mCRPC, including patients with visceral metastases, recognising that symptoms do not inform on which treatment is most likely to be beneficial. However, the absence of prospectively qualified predictive biomarkers meant that there was no consensus on recommending strategies for selecting between taxanes or AR targeting treatments for patients who had not previously received either treatment.

A number of clinic–pathological features are readily available to physicians treating mCRPC and several studies have now evaluated their association with outcome. In a recent issue of *Annals of Oncology*, Fizazi et al. [6] assessed the predictive value of Gleason score (<8 or ≥8) in the two abiraterone regulatory phase III trials, COU-AA-301 [3] and COU-AA-30 [2]. This is an important study as Gleason score has been muted as a biomarker in mCRPC. Historically, Gleason score has been used as a standardised risk assessment for biochemical recurrence, development of metastases and overall survival (OS) in men with localised non-castrate prostate cancer. A small study of 381 patients reported that a high initial Gleason score (8–10) at the time of diagnosis is an independent risk factor for poor response to abiraterone [7]. Fizazi et al. demonstrated that while Gleason score of the original diagnostic sample may have weak prognostic value in mCRPC (HR = 1.20; 95% CI 1.03–1.39, $P = 0.0221$ pre-chemotherapy and HR = 1.17; 95% CI 1.01–1.37, $P = 0.04$ post-chemotherapy), the benefits from abiraterone compared with that from prednisone for OS and response were favourable, irrespective of Gleason score. By leveraging these two large trials, this analysis provides probably the strongest data to date of the clinical value of baseline Gleason score in mCRPC. A post hoc analysis of 482 patients from the TAX327 study demonstrated a survival benefit and greater PSA declines with docetaxel in preference to mitoxantrone for cancers with an initial Gleason score of ≥7, but the benefit was not significant for cancers with a Gleason score of <7 (about a third of the total number were Gleason score 7–10) [8]. The relevance of the TAX327 analysis on Gleason score <7 cancers is uncertain given the smaller number of cancers (and events) in this group and does not allow comparison with the Fizazi cohort, given the different

cutoffs and comparator arm treatment. Overall, Gleason score may provide weak prognostic information. Other features may, however, be superior. These include a higher neutrophil-to-lymphocyte ratio that associates with worse outcomes in patients treated with abiraterone or chemotherapy [9–11]. Moreover, prognostic models could prove more informative than single factors. Recently, Chi et al. [12] developed and tested a prognostic index model in 762 post-chemotherapy patients treated with abiraterone and demonstrated that 6 out of 15 baseline clinic–pathological factors were the strongest independent predictors of OS. These factors included lactate dehydrogenase (LDH), ECOG PS, liver metastases, albumin, alkaline phosphatase and time from the start of initial androgen-deprivation therapy to start of abiraterone. On the basis of the number of baseline risk factors, patients were categorised into three risk groups (good, intermediate and poor), and different OS rates and 2-year survival probabilities were identified. In keeping with the Fizazi study, Gleason score was not sufficiently prognostic to be included in this model.

Given these data, focus should probably shift to response surrogates and molecular biomarkers. A circulating tumour cell (CTC) count ≥5/7.5 ml blood (using CellSearch™) was prognostic in patients treated in the COU-AA-301 study but arguably more importantly, changes in CTC count and LDH levels after 12-week treatment were strongly predictive of OS [13]. These data may be less relevant to earlier stage mCRPC where fewer CTCs are detected with currently available technologies. A pre-planned analysis of archival tumour samples on a subgroup of patients treated in the COU-AA-302 suggested that patients with a hormone-driven TMPRSS2-ERG gene fusion secondary to deletion and associated duplication of gene fusion sequences (2 + Edel) could derive the greatest improvement in radiological progression-free survival and time to PSA progression [14]. However, the benefit in this group was not statistically significant compared with that in other *ERG* classes. Larger datasets would be required to qualify this biomarker given the prevalence (~15%) and the moderate difference in outcome.

Given both abiraterone and enzalutamide directly target AR signalling, aberrations involving the AR have been studied as causes of resistance and potentially biomarkers for identifying resistant patients. Aberrations appear to emerge following the potent selective pressures of initial androgen-deprivation therapies and molecular characterisation has therefore focused on real-time studies using liquid biopsies. AR splice variants lacking the ligand-binding domain that putatively lead to resistance to androgen synthesis inhibitors and AR antagonists (currently most notably AR-V7) can be detected in CTCs from patients with advanced mCRPC and associate with resistance to abiraterone or enzalutamide [15]. In contrast, AR-V7-positive patients appear to have a better outcome with chemotherapy in preference to abiraterone or enzalutamide [16], suggesting that this test could be used for treatment selection. Similarly, patients with *AR* gene copy number gain or functionally relevant point mutations (namely T878A or L702H) detected in plasma DNA analyses have a lower chance of responding to abiraterone or enzalutamide [17]. Before their implementation into clinical practice, these data to date reported in small, single-arm cohorts require prospective qualification in randomised trials where a treatment decision is made based on an analytically robust assay.

Overall on the basis of the current evidence, Gleason score has no role in treatment selection in mCRPC. Biomarker-driven multi-institutional studies to describe the landscape of alterations in multidrug-resistant CRPC are informing on the drivers of resistance and identifying molecular subgroups that can be targeted therapeutically with novel approaches [18]. Such translational efforts could lead to personalised treatment strategies for mCRPC.

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references

1. Beer TM, Armstrong AJ, Rathkopf DE et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371: 424–433.
2. Ryan CJ, Smith MR, Fizazi K et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015; 16: 152–160.
3. de Bono JS, Logothetis CJ, Molina A et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011; 364: 1995–2005.
4. Scher HI, Fizazi K, Saad F et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012; 367: 1187–1197.
5. Gillessen S, Omlin A, Attard G et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol 2015; 26: 1589–1604.
6. Fizazi K, Flaig TW, Stöckle M et al. Does Gleason score at initial diagnosis predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer? An analysis of abiraterone acetate phase III trials. Ann Oncol 2016; 27: 699–705.
7. Azria D, Massard C, Tosi D et al. An ambispective observational study in the safety and efficacy of abiraterone acetate in the French temporary authorizations for use (ATU): Predictive parameters of response. ASCO Meeting Abstr 2012; 30: 149.
8. van Soest RJ, de Morree ES, Shen L et al. Initial biopsy Gleason score as a predictive marker for survival benefit in patients with castration-resistant prostate

cancer treated with docetaxel: data from the TAX327 study. Eur Urol 2014; 66: 330–336.

9. Leibowitz-Amit R, Templeton AJ, Omlin A et al. Clinical variables associated with PSA response to abiraterone acetate in patients with metastatic castration-resistant prostate cancer. Ann Oncol 2014; 25: 657–662.
10. Lorente D, Mateo J, Templeton AJ et al. Baseline neutrophil–lymphocyte ratio (NLR) is associated with survival and response to treatment with second-line chemotherapy for advanced prostate cancer independent of baseline steroid use. Ann Oncol 2015; 26: 750–755.
11. van Soest RJ, Templeton AJ, Vera-Badillo FE et al. Neutrophil-to-lymphocyte ratio as a prognostic biomarker for men with metastatic castration-resistant prostate cancer receiving first-line chemotherapy: data from two randomized phase III trials. Ann Oncol 2015; 26: 743–749.
12. Chi KN, Kheoh T, Ryan CJ et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. Ann Oncol 2016; 27: 454–460.
13. Scher HI, Heller G, Molina A et al. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. J Clin Oncol 2015; 33: 1348–1355.
14. Attard G, de Bono JS, Logothetis CJ et al. Improvements in radiographic progression-free survival stratified by erg gene status in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. Clin Cancer Res 2015; 21: 1621–1627.
15. Antonarakis ES, Nakazawa M, Luo J. Resistance to androgen-pathway drugs in prostate cancer. N Engl J Med 2014; 371: 2234.
16. Antonarakis ES, Lu C, Luber B et al. Androgen receptor splice variant 7 and efficacy of taxane chemotherapy in patients with metastatic castration-resistant prostate cancer. JAMA Oncol 2015; 1: 582–591.
17. Romanel A, Tandefelt DG, Conteduca V et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med 2015; 7: 312re10.
18. Robinson D, Van Allen EM, Wu YM et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015; 161: 1215–1228.