EUROPEAN UROLOGY ONCOLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

EUO Collaborative Review – Prostate Cancer

Consensus Statement on Circulating Biomarkers for Advanced Prostate Cancer

Semini Sumanasuriya[a,b,†], *Aurelius Omlin*[c,†], *Andrew Armstrong*[d], *Gerhardt Attard*[a,b], *Kim N. Chi*[e], *Charlotte L. Bevan*[f], *Aki Shibakawa*[f], *Maarten J. IJzerman*[g], *Bram De Laere*[h], *Martijn Lolkema*[i], *David Lorente*[j], *Jun Luo*[k], *Niven Mehra*[l], *David Olmos*[m], *Howard Scher*[n], *Howard Soule*[o], *Nikolas H. Stoecklein*[p], *Leon W.M.M. Terstappen*[g], *David Waugh*[q], *Johann S. de Bono*[a,b,*]

[a] *Institute of Cancer Research, Sutton, UK;* [b] *The Royal Marsden Hospital NHS Trust, London, UK;* [c] *Cantonal Hospital St. Gallen, St. Gallen, Switzerland;* [d] *Duke Cancer Institute, Duke University, Durham, NC, USA;* [e] *BC Cancer Agency, Vancouver, BC, Canada;* [f] *Imperial College London, London, UK;* [g] *University of Twente, Twente, The Netherlands;* [h] *Centre for Oncological Research, University of Antwerp, Antwerp, Belgium;* [i] *Erasmus MC Cancer Institute, Rotterdam, The Netherlands;* [j] *Servicio Oncologia Medica Hospital Universitario La Fe, Valencia, Spain;* [k] *James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [l] *Radboud University Nijmegen Medical Center, Nijmegen, The Netherlands;* [m] *Spanish National Cancer Research Centre, Madrid, Spain;* [n] *Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [o] *Prostate Cancer Foundation, Santa Monica, CA, USA;* [p] *University Hospital and Medical Faculty of the Heinrich-Heine University Düsseldorf, Düsseldorf, Germany;* [q] *Queen's University Belfast, Belfast, UK*

Article info

Article history:
Accepted February 20, 2018

Associate Editor:
Paul Nguyen

Keywords:
Advanced prostate cancer
Circulating biomarkers
Circulating tumour cells
Cell-free DNA
Consensus
Androgen receptor splice variants

Abstract

Context: In advanced prostate cancer (PC), there is increasing investigation of circulating biomarkers, including quantitation and characterization of circulating tumour cells and cell-free nucleic acids, for therapeutic monitoring and as prognostic and predictive biomarkers. However, there is a lack of consensus and standardisation regarding analyses, reporting, and integration of results into specific clinical contexts. A consensus meeting on circulating biomarkers was held to address these topics.
Objective: To present a report of the consensus statement on circulating biomarkers in advanced PC.
Evidence acquisition: Four important areas of controversy in the field of circulating biomarkers in PC management were identified: known clinical utility of circulating biomarkers; unmet clinical needs for circulating biomarkers in PC care; most pressing blood-based molecular assays required; and essential steps for developing circulating biomarker assays. A panel of 18 international PC experts in the field of circulating biomarkers developed the programme and consensus questions. The panel voted publicly but anonymously on 50 predefined questions developed following a modified Delphi process.
Evidence synthesis: Voting was based solely on panellist opinions of the predefined topics and therefore not on a standard literature review or meta-analysis. The outcomes of the voting had varying degrees of support, as reflected in the wording of this article and in the detailed voting results provided in the Supplementary material.
Conclusions: The expert voting results presented can guide the future development of circulating biomarkers for PC care. Notably, the consensus meeting highlighted the importance of reproducibility and variability studies, among other significant areas in need of trials specifically designed to address them.
Patient summary: A panel of international experts met to discuss and vote on the use of different blood-based prostate cancer tests, and how they can be used to guide treatment and disease monitoring to deliver more precise and better patient care.

† These authors contributed equally to this work and are joint first authors.
* Corresponding author. Institute of Cancer Research, Royal Marsden NHS Foundation Trust, Sycamore House, Downs Road, Sutton SM2 5PT, UK. Tel.: +44 208 7224029; Fax: +44 208 6427979.
E-mail address: johann.de-bono@icr.ac.uk (J.S. de Bono).

https://doi.org/10.1016/j.euo.2018.02.009

Please cite this article in press as: Sumanasuriya S, et al. Consensus Statement on Circulating Biomarkers for Advanced Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.02.009

1. Introduction

The urgent need for circulating biomarkers for the care of advanced prostate cancer (PC) patients is well described, but there is a lack of consensus regarding how these should be discovered and developed, with little transformative prospective trial data. Investigations focusing on the utility of blood-based assays including plasma cell-free nucleic acids (eg, cell free DNA [cfDNA]) and circulating tumour cells [CTCs] have generated major interest and could transform patient care. A consensus meeting was held to address these issues and produce a statement on circulating biomarkers in advanced PC, defined as metastatic disease or disease that recurred after local treatment. The panel comprised 18 physicians and scientists from nine countries selected on the basis of their academic track record and involvement in clinical or translational research in the field of advanced PC, with expertise in the clinical qualification of biomarkers. None of the invited experts declined the invitation to participate. Before this meeting, the panel identified four areas of controversy for discussion:

1. Current utility of circulating biomarkers.
2. Unmet clinical needs for circulating biomarkers in PC care.
3. Most pressing blood-based molecular assays required.
4. Essential steps for development of circulating biomarker assays.

2. Evidence acquisition

A modified Delphi process was used for consensus development, following procedures described by Gillessen et al. [1]. The meeting comprised state-of-the-art lectures, presentations, and debates by panellists before voting. Following this, 50 questions that were previously agreed on were presented with options for answers in multiple-choice format. Panellists voted anonymously, with results displayed to all attendees immediately. For all questions, responses were based on idealised assumptions that all diagnostic procedures (including expertise in interpretation and application) mentioned were readily available. Importantly, in an effort to address questions from an evidence-based and clinical utility perspective, panellists were specifically instructed not to consider cost, reimbursement, and access in their deliberations, although clearly these are critical factors in decision-making.

We acknowledge that the results reflect the opinions of a small chosen panel of experts on predefined topics, and therefore are not based on a standard literature review or meta-analysis. The results presented are intended to serve only as a guide to clinicians, researchers, and industry partners. The option "unqualified to answer" (short form: "unqualified") should have been chosen if a panellist lacked experience for a specific question, and the "abstain" option if a panellist felt unable to vote for any reason. Detailed voting records for all questions are provided in the Supplementary material. The denominator was based on the number of panel members voting on the particular question, excluding those who voted "unqualified" or "abstain". Consensus was declared if $\geq$75% of the panellists chose the same option and did not abstain or vote "unqualified" [2]. Throughout, the percentage of voting panellists giving a particular response is reported, followed by absolute numbers. All panellists contributed to designing the questions, editing the manuscript, and approving this final document. Importantly, this process was uniquely able to highlight areas of disagreement and identify priorities for future clinical research for which additional data acquisition is warranted.

3. Evidence synthesis

3.1. Current utility of circulating biomarkers

3.1.1. CTC assays

Multiple assays have been described for CTC evaluation; the CellSearch system is the only one with regulatory clearance for monitoring PC and has not been improved since its introduction in 2008. CTC number is robustly associated with poor outcome, with declining counts indicating response to therapy [3,4]. Accurate assessment of the actual number of CTCs is especially important when assessing therapy response, and prospective trials evaluating CTC enumeration as response and surrogate biomarkers of response in PC are ongoing. To eliminate inter- and intra-operator bias, the open source ACCEPT software has been developed, allowing automatic CTC enumeration [5].

For CTC testing/enumeration with any assay, 33% (6/18) of the experts voted that testing was ready for use in daily routine clinical practice, 61% (11/18) that current data support testing in prospective trials, and 6% (1/18) that clinical studies are required before prospective clinical validation trials.

For CellSearch CTC counting specifically, 67% (12/18) of the experts voted that testing was ready for use in daily routine clinical practice, 22% (4/18) that current data support testing in prospective trials, and 11% (2/18) that clinical studies are required prior to prospective, clinical validation trials.

Overall, most of the experts endorsed the utility of CTC counts via CellSearch in clinical practice and trials (given the available data and US Food and Drug Administration [FDA] clearance); however, consensus was not reached regarding routine clinical use.

3.1.2. Alternative CTC detection

The successful development of the CellSearch system prompted the study of alternative CTC detection platforms, with >50 companies currently involved in developing and marketing CTC-based liquid biopsy tools [6]. The use of validated CTC detection methods that minimise false positives and allow molecular analyses is mandated. Limitations in CTC detection have been acknowledged; with several patients having undetectable CTCs despite progressive disease, difficulties in capturing these rare events in those that do, and possible subsequent size-selection bias.

Please cite this article in press as: Sumanasuriya S, et al. Consensus Statement on Circulating Biomarkers for Advanced Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.02.009