SCANDINAVIAN JOURNAL OF UROLOGY
2021, VOL. 55, NO. 5, 419
https://doi.org/10.1080/21681805.2021.1934107

Taylor & Francis
Taylor & Francis Group

NEWS AND VIEWS

Personalized medicine for bladder cancer

Fredrik Liedberg[a,b]

[a]Institution of Translational Medicine, Lund University, Malmö, Sweden; [b]Department of Urology, Skåne University Hospital, Malmö, Sweden

The authors behind the BISCAY trial are to be congratulated for performing a tremendous effort to scientifically explore adaptive biomarker-directed treatment in patients with advanced urothelial cancer having received one previous platinum-containing regimen in a phase Ib setting [1]. With the primary endpoint to establish safety of four combinations with durvulumab targeting FGFR- (AZD4547), PARP- (Olaparib), and TORC1/2 (vistusertib)-inhibition to treatment with single regimens with durvulumab or FGFR3-inhibition were explored. At a glance, the trial does not support any of the combinations with targeted agents and durvulumab. Grade 3 and 4 therapy-related adverse events increased from 10% with durvulumab only, to proportions ranging between 24%–48% for the combinations. A therapeutic response was identified in 9%–36% of patients in the six trial arms, with the intriguing finding that the lowest proportion response occurred in patients receiving olaparib + durvulumab without any biomarker selection and the highest among those receiving the same combination but with either ATM-, BRCA1/2- or HRR-alterations, today known to occur only in 10% of bladder cancer patients [2].

Views

The complex statistical considerations needed to take into account when testing predictive markers necessitate very large studies when applying marker-based study designs [3]. Considering that bladder cancer is one of the molecularly most heterogeneous tumours [4], a phase Ib trial aiming for 20 patients in each study arm is associated with a significant risk to overlook treatment effect signals. Furthermore, instead of applying randomization after molecular tumour characterization, upfront randomization in which all patients receive the comparator treatment (in this case durvulumab), and those randomized to molecular characterization and additional predictive marker directed treatment, would ensure immediate practice-changing study outcomes.

The alternative approach of applying next-generation sequencing (NGS) in all patients subjected to treatment randomization in ordinary phase III trials, and retrospectively when the trial is completed assess outcomes based on molecular characteristics is becoming more attractive with decreasing costs for these analyses. Such a strategy would convert negative studies, such as the adjuvant IMvigor 010 trial which is the largest randomized study investigating adjuvant checkpoint-inhibition after radical cystectomy in bladder cancer patients [5], to explorative eldorados defining predictive markers and finding the approximately one out of five bladder cancer patients responding on checkpoint inhibition, even at long-term. Furthermore, to assess bladder cancer molecular subtypes in real time using NGS (ISRCTN15459149) applied in phase III trials (ISRCTN87250222) enables search for second generation biomarkers within the context of molecular subtypes.

References

[1] Powles T, Carrol D, Chowdhury S, et al. An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer. Nat Med. 2021; 27(5):793–801.

[2] Börcsök J, Diossy M, Sztupinszki S, et al. Detection of molecular signatures of homologous recombination deficiency in bladder cancer. Clin Cancer Res. 2021. doi: 10.1158/1078-0432.CCR-20-5037

[3] Sargent D, Conley B, Allegra C, et al. Clinical trial designs for predictive marker validation in cancer treatment trials. J Clin Oncol. 2005;23(9):2020–2027.

[4] Hoadley K, Yau C, Hinoue T, et al. Cell-of-origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer. Cell. 2018;173(2):291–304.

[5] Bellmunt J, Hussain M, Gschwend J, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(4):525–537.

CONTACT Fredrik Liedberg fredrik.liedberg@med.lu.se Department of Urology,Skåne University Hospital, Jan Waldenströms gata 7, Malmö, SE-205 02, Sweden; Department of Translational Medicine, Lund University, Malmö, Sweden