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LETTER TO THE EDITOR

Pre-radiotherapy identification of individual genomic profile to avoid, by resort to customized radiosensitizers, the risk of radioresistance development in patients with localized prostate cancer: author reply

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(The Editors do not hold themselves responsible for opinions expressed by correspondents)

To the Editor,

We appreciate the kind remarks and comments from Dr Alberti¹ on our review entitled “An arranged marriage for precision medicine: hypoxia and genomic assays in localized prostate cancer radiotherapy”.² We did not use the review as a vehicle or compendium to list all possible biomarkers of prostate cancer (PCa) aggression or potential markers of radiotherapy (RT) response. Instead, the thrust of this review was that the three-dimensional cancer microenvironment can affect the inherent genetic abnormalities and signalling pathways in cancer cells that drive local radioresistance (*i.e.* increase local failure following RT) and/or systemic metastases.

We would like to highlight four points that reflect upon some of the comments brought up by Dr Alberti.

First, treatment failure after RT is commonly defined in PCa by the Phoenix criteria in which a rising prostate-specific antigen (PSA) attains a value of 2.0 ng ml⁻¹ beyond the post-therapy PSA nadir.³ A major shortcoming of this operational definition is the inability of a PSA rise to differentiate between persistent local disease *vs* pre-existing occult metastatic disease if it is a rapid rise after therapy unless post-RT prostatic biopsies are also carried out to determine local control. In pre-clinical research, many times, there is overlap in abnormal signalling pathways that lead to radioresistant tumour clones and those that drive progression to metastases. Indeed, some of the mentioned markers by Dr Alberti conferring “radioresistance” have also been linked to the acquisition of aggressive invasive and metastatic phenotypes (*e.g.* Wnt/ β -catenin, Hedgehog and notch pathways).^{4–6}

However, it is important to point out that to date, RT dose-escalation trials have not improved PCa-specific survival nor overall survival. Improving survival requires the additional eradication of occult or secondary waves of metastases: this is one rationale to add androgen deprivation therapy (ADT) to RT in intermediate- and high-risk PCa. Understanding this distinction is important, as it could lead erroneously to concurrent RT-drug radiosensitization trials at the expense of RT-drug systemic adjuvant treatments that could increase survival. It is our bias that PCa RT research must also determine molecular-based therapies that are designed to treat occult or secondary metastases due to failure.

Second, the combined potential for tumour microenvironment and tumour genomics to better define prognosis or predict therapy response should not be underestimated. Hypoxia has been consistently shown to confer an adverse prognosis in localized PCa, as it can lead to decreased local control; but, it also heralds the development of rapid failure following RT or surgery owing to occult metastases.^{7,8} In recent work from our group (Lalonde et al, personal communication), we have demonstrated synergistic prognostic capability by using both tumour hypoxia and genomic instability to predict aggressive patient subgroups that may optimally benefit from treatment intensification using RT plus a bespoke systemic therapy.

Additionally, most, if not all, the intrinsic resistance pathways mentioned by Dr Alberti, are also modified when cells are placed under hypoxia, suggesting that intratumoural signalling may be heterogeneous from one area of the tumour to another despite similar genomes. For example, hypoxia can modify the signalling secondary to DNA

damage responses and DNA repair,^{9,10} the PI3K-Akt-mTOR pathway signalling,¹¹ the MAPK pathway,¹² increase tumour clonogens (initiating cells) within a hypoxic “niche”^{13–16} and CXCR4 pathways.^{17,18} Interestingly, the drug BEZ235 (a dual PI3K/mTOR inhibitor; mentioned in Dr Alberti’s letter), does not overcome hypoxia-associated radioresistance (e.g. at the same sensitizer and radiation dose, hypoxic cells remain more resistant).¹⁹ We also need to be cautious when extrapolating targets from genetic findings based on metastatic castrate-resistant PCa,²⁰ as it represents a different disease state following ADT and/or chemotherapy selection, and mutations in targetable pathways in localized disease are rare.²¹ Complex and interactive crosstalk between inherent tumour genomics and the microenvironment must therefore be understood to improve the success of molecular targeting approaches in the upcoming Phase II–III trials.

Third, we agree that in defining a “molecular therapeutic ratio” further research into the potential genetics of normal tissue radiotoxicity is required, and this has been also recently reviewed.²² Regarding germline polymorphisms (SNPs) conferring increased disease risk, aggressive characteristics or radioresistance, we agree that this should be actively pursued using

large pooled and multigenic analyses given conflicting data on the role of SNPs in defining PCa RT side effects.²³

Fourth, potential markers of RT response have been recently summarized.²⁴ However, predictive markers rather than solely prognostic markers will be optimal for changing treatment for the individual patient with PCa. A sobering truth is that, despite much research, the only validated predictive (e.g. treatment-dependent) genetic marker in genitourinary oncology for clinical RT tumour response is MRE11 protein expression in muscle-invasive bladder cancer.^{25,26} Potentially, nibrin (NBN) gains in localized PCa (Berlin et al, personal communication) may also selectively predict radioresistance in PCa, but further validation is required. Such markers will also have to overcome the problem of intraprostatic biologic heterogeneity²⁷ in which a marker must be robust enough to “call” a patient’s treatment course based on pre-treatment biopsies.

Joint, multi-institutional studies with large clinical databases and pre-treatment, biobanked material will absolutely be required to rule in, or rule out, specific targets to better define the “precision” and improve survival in precision PCa medicine.

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