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In Defence of Context: Surrogates, Sequencing, and Real-world Evidence in Genitourinary Oncology

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Recent discussions in the literature have underscored the limitations of the design of current phase 3 oncology trials, particularly the excessive dependence on weak surrogate endpoints and the prevalence of underpowered studies that are based on overly optimistic assumptions [1]. While we concur with the general premise that oncology trials must prioritise meaningful patient outcomes, we would like to offer a complementary perspective regarding genitourinary (GU) cancers, which is a domain in which exceptions to these rules have often resulted in genuine therapeutic progress.

Although we acknowledge the concern that trials with weak control arms or minimal survival gains may overestimate the apparent benefit of new treatments, it is worth noting that several major advances in GU oncology have nevertheless emerged from studies that used historically "imperfect" comparators. Examples include the use of placebo or outdated targeted therapy as control arms in trials in prostate cancer and renal cell carcinoma. Yet these studies have consistently led to the approval of treatments that dramatically changed clinical practice and extended patients' lives in real-world settings. This suggests that—at least for some tumour types—methodological imperfection does not necessarily undermine clinical relevance. A second point concerns the role of progression-free survival (PFS) as a primary endpoint. PFS is often a weak surrogate for overall survival (OS) or quality of life (QoL) in many cancers [2,3]. Moreover, its definition may vary across studies, and reliance on biochemical markers such as PSA decline without parallel improvement in clinical outcomes may not be justified. However, in GU malignancies—particularly in advanced or metastatic renal cell carcinoma and prostate cancer—OS often exceeds 36 mo because of the availability of multiple subsequent treatment options. While PFS has traditionally been used as a practical and timely endpoint in this context, we acknowledge that it is meaningful only when accompanied by evidence of clinical benefit (eg, symptom control, delay of skeletal events) and when reasonably consistent with longer-term outcomes. Its value as a surrogate for meaningful clinical benefit therefore remains debated, particularly when not clearly associated with improvements in QoL or survival. Table 1 provides a synthesis of our perspective on the comparative strengths and limitations of OS and PFS in GU oncology. A related endpoint, metastasis-free survival (MFS), has increasingly been adopted in trials in localised high-risk prostate cancer. However, its validity is not absolute, as it may be strongly influenced by the intensity and frequency of imaging across study arms. In particular, differential surveillance in control groups may artificially shorten the time to detection of metastasis, which introduces ascertainment bias. While MFS can provide clinically relevant information—particularly in settings which a delay in metastatic progression is associated with symptom prevention—it should be interpreted with caution and always in the context of trial design and imaging protocols.

The rapid evolution of treatment strategies in GU oncology also makes it highly unlikely that randomised head-to-head trials comparing the various novel first-line combinations will ever be conducted, as such studies are often commercially unfeasible and logistically complex. As a result, reliance on PFS alone may no longer suffice to guide clinical decision-making in such a dynamic landscape. Fig. 1 provides a schematic comparison of the relative strengths and limitations of OS and PFS in GU oncology that reflects our perspective.

However, we also recognise that many randomised controlled trials (RCTs) in GU oncology have historically relied

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Table 1 – Comparison of overall survival and progression-free survival as endpoints in genitourinary oncology

Characteristic	Overall survival	Progression-free survival
Correlation with quality of life	High, but influenced by postprotocol treatments	Variable, but reflects disease control
Applicability in genitourinary oncology	Limited because of long survival trajectories	High: relevant in the short to medium term
Time required for maturation	Very long (often >36 mo)	Shorter (6–18 mo)
Sensitivity to subsequent treatments	High: outcomes may be confounded	Low: less influenced by later therapy lines
Risk of results becoming outdated	High	Low
Decision-making value in clinical practice	Lower value in trials with long follow-up	High: aligned with real-world clinical timelines

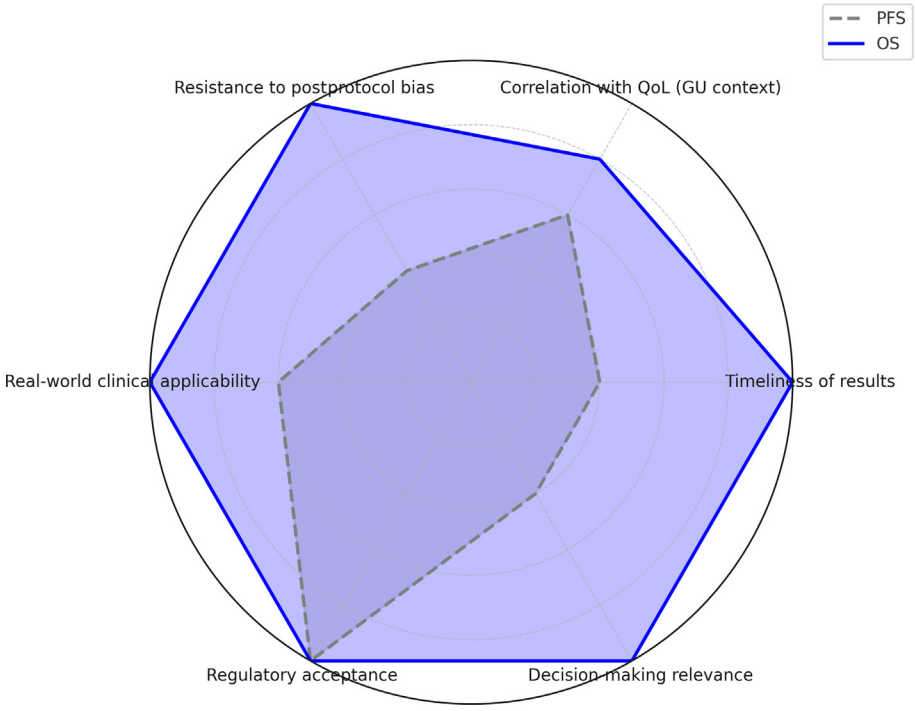

Fig. 1 – Comparative strengths of progression-free survival (PFS) and overall survival (OS) as clinical trial endpoints in genitourinary (GU) oncology. QoL = quality of life.

on control arms that can be considered undertreatment according to current standards . This design choice may have exaggerated treatment effects and limits the generalisability of some trial conclusions. Furthermore, no adequately powered randomised studies have been conducted to systematically evaluate sequencing strategies, even though sequencing is a crucial determinant of long-term outcomes in real-world practice. In this context, real-world data are essential to bridge the gap left by traditional RCTs.

In this light, real-world studies such as the multicentre ARON project (https://aronwg.com) are crucial for providing data that reflect everyday clinical practice and patient diversity. Unlike RCTs, which involve selected patients in ideal settings, real-world evidence includes broader populations, such as the elderly and individuals with comorbidities. These studies complement RCTs, especially when direct comparisons between new treatments are not feasible.

Real-world evidence also offers insights into treatment sequences, toxicity, adherence, and resource use, which are areas that are often overlooked in RCTs. In fast-changing fields such as GU oncology, studies like ARON help in guiding clinical decisions by balancing efficacy, tolerability, and real-world applicability, and ultimately in supporting more practical, patient-centred care.

Postprotocol therapies in GU oncology often vary widely as well and can dilute OS differences, making PFS a more robust and timely signal of therapeutic impact. At the same time, the growing availability of effective postprotocol options reinforces the need to confirm an eventual impact on OS, which remains the most reliable endpoint for capturing the ultimate patient benefit. The challenge, however, lies in the fact that subsequent therapies can obscure the direct contribution of the experimental treatment to survival, making OS more difficult to interpret in isolation. Therefore, while OS continues to represent the gold standard, complementary endpoints such as PFS and QoL—interpreted within the appropriate context—retain a role in shaping therapeutic decision-making in GU oncology. Most importantly, waiting for mature OS data in this setting can delay results so substantially that they are no longer aligned with the contemporary treatment landscape. In fast-moving therapeutic areas, this creates the paradox of conducting trials that are already outdated by the time they are pub-

lished. Therefore, in the GU setting, PFS—despite its limitations—may still offer a contextually relevant signal of treatment activity, particularly when interpreted alongside other clinical endpoints. Importantly, economic sustainability must also be considered. In an era of rising health care costs, reliance on surrogate endpoints without clear correlation to long-term survival or QoL risks not only clinical uncertainty but also inefficient use of resources. Therefore, while intermediate endpoints such as PFS and MFS may provide timely signals in GU oncology, their adoption should always be balanced against both patient-centred outcomes and broader cost-effectiveness implications.

We fully agree with the call for stronger methodological standards and more patient-centred endpoints. However, we caution against one-size-fits-all application of these principles. The history of GU oncology shows that progress has sometimes emerged from methodologically "flawed" trials. Therefore, we advocate for contextual flexibility: rigor should remain the goal, but not at the cost of denying real-world benefits in clinically heterogeneous fields.

Finally, innovation in cancer care requires both methodological excellence and clinical sensitivity, particularly in fields such as GU oncology in which disease behaviour, therapeutic sequencing, and trial logistics all pose unique challenges.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Teuwen LA, Pond GR, Gyawali B. Success in oncology phase 3 trials: a small P value or patient value. J Natl Cancer Inst 2025;117:1761–3. https://doi.org/10.1093/jnci/djaf183.

[2] Mittal A, Kim MS, Dunn S, et al. Frequently asked questions on surrogate endpoints in oncology—opportunities, pitfalls, and the way forward. eClinicalMedicine 2024;76:102824.

[3] Gyawali B, Booth CM. Defining clinically important overall survival thresholds: lessons from quality of life. Nat Rev Clin Oncol 2022;19:613–4.