Title
Adjuvant checkpoint inhibitor trials: Is disease-free survival an appropriate endpoint?

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Adjuvant checkpoint inhibitor trials: Is disease-free survival an appropriate endpoint?

Immune checkpoint inhibitors (ICI) have revolutionized cancer care for many patients. Just under half of all patients with metastatic solid tumors have an FDA-approved indication for treatment with an ICI [1]. More recently, trials supporting the use of these agents as adjuvant therapy have been published for melanoma, renal cell carcinoma, urothelial carcinoma, esophageal cancer and non-small cell lung cancer (Table 1). In 7/9 cases, trials were positive and all of these led to US Food and Drug Administration approval. These trials all utilized disease-free survival (DFS) or recurrence-free survival (RFS), a time-to-event composite endpoint of recurrence, new primary and death, as the primary endpoint, but there are reasons to be concerned that this endpoint may not be patient-centered. In other words, it is not certain that gains in DFS or RFS will ensure improvements in duration or quality of life for this class of agents. In this commentary, we outline these concerns.

First, it is important to acknowledge that the majority of agents with activity in the metastatic setting, even those used widely in clinical practice, have failed when investigated in the same tumor in the adjuvant setting. Among agents approved for the treatment of metastatic breast, lung and colorectal cancer, only 36% (25/69) were successfully approved or recommended for use in the adjuvant setting [2].

Second, outside of limited settings, DFS or RFS is not a well-validated surrogate of overall survival (OS). Appropriate validation requires meta-analysis of trial level data confirming strong correlation between a surrogate end-point (e.g. DFS or RFS) and the corresponding patient-centered endpoint (e.g. OS). DFS has been found to be a valid surrogate for OS in NSCLC and colon cancer, but this association applies only to cytotoxic drugs [3]. This has not been shown in other cancer types with positive ICI adjuvant studies nor has it been shown with NSCLC or colon cancer with ICIs.

ICI's offer different biological properties that may alter the surrogacy between DFS and OS. Cytotoxic drugs in most solid tumors are incapable of curing metastatic disease, yet these same agents, when administered early, in the adjuvant setting, may eradicate microscopic disease and increase curative fractions. In contrast, ICIs are capable of durable remission in a fraction of patients with a variety of malignancies in the metastatic setting, and thus, it is not necessarily the case that moving the drug to the adjuvant setting results in a difference in kind (i.e. increase curable fraction vs. delay tumor growth). In the same way screening for a cancer makes less sense when outcomes become excellent even with advanced presentation (testicular cancer – USPSTF grade D), adjuvant use of drugs becomes less theoretically appealing if those same drugs can result in similar durability of disease control if administered later.

Third, earlier use of immunotherapy may have implications if a patient's cancer recurs. Consider the case of kidney cancer, ICI treatment in the metastatic setting is given as combination therapy (e.g. ICI + tyrosine kinase inhibitor) with suggestion of synergism in the combinations [4,5]. The earlier exposure to ICI monotherapy may lead to resistance and make a patient less sensitive to front-line combinations. Given this consideration, one may hypothesize adjuvant ICIs could even lead to a paradoxically worse OS, underscoring the importance of measuring OS as the primary endpoint.

Fourth, while ICIs are considered less toxic than chemotherapy, they are not benign. Immune related adverse events may occur in just under half of treated patients, including grade 3 or higher events, which can be a source of significant morbidity, in 8–42% and deaths in up to 2% (Table 1). Further, as many as 52% of patients treated with ipilimumab and 21% of patients treated with an anti-programmed cell death discontinued therapy early due to toxicity.

Fifth, there have been divergent results with different adjuvant ICI studies in the same tumor type that raises questions about clinical efficacy. In urothelial carcinoma, while the Checkmate-274 study of adjuvant nivolumab was positive for DFS (HR 0.70 95% CI 0.55–0.90) [6], the IMvigor-010 study of adjuvant atezolizumab was negative (HR 0.89 95% CI 0.74–1.08) [7]. Similarly, in renal cell carcinoma, the Keynote-564 study of adjuvant pembrolizumab yielded a positive outcome (HR 0.68 95% CI 0.53–0.87), but the Prosper RCC trial (neoadjuvant and adjuvant nivolumab) was stopped early for futility and both IMmotion-010 (adjuvant atezolizumab) and Checkmate-914 (adjuvant nivolumab and ipilimumab) have failed. While it is possible that differences in trial design, population or activity of checkpoint inhibitor may explain the divergent results, an alternate explanation is the positive trials may be positive due to chance in the setting of multiplicity. Multiplicity has long been a known threat to causal inference from observational studies but has recently been suggested as a threat with randomized clinical trials (especially with anti-PD-(L)1 checkpoint inhibitors) given multiple similar trials in the same disease [8].

Finally, adjuvant therapy inherently means that many people will be treated who cannot benefit from therapy. In all of these studies, the fraction of patients randomized to an inactive control arm who did not recur ranged from 30% to 70%. These people were cured of their disease from surgery alone. If similar patients are now treated with ICIs, they will endure additional cost, toxicity and therapeutic time burden without any clinical benefit. In fact, in a recent cost analysis quantifying the cost and benefit of adjuvant ICIs, it was estimated that the median cost of adjuvant ICI was $158,000 per patient and the cost per event averted was $1,610,000 [9].

In this commentary, we have shown the importance of using a patient-centered primary endpoint (i.e. OS) in adjuvant ICI trials given the history of failures in adjuvant therapy, the lack of DFS as a validated endpoint for OS, the possibility of compromising sensitivity to future combination therapies, and the unnecessary exposure of toxicity to patients without clear benefit. In light of these concerns, we feel strongly that OS is the appropriate endpoint for ICI adjuvant clinical trials and

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Table 1
Published clinical trials investigating adjuvant immune checkpoint inhibitors in oncology.

Trial	Cancer Type	Study Arms	HR for DFS (95% CI)	Approximate fraction cured in inactive control arm, %^	% Grade ≥ 3 treatment-related AE	% Grade 5 AEs	% Discontinue due to AE
Checkmate 274	Urothelial	Nivolumab vs Placebo	0.70 (0.55–0.90)	40	18	1 (3/351)*	13 *
IMvigor 010+	Urothelial	Atezolizumab vs Observation	0.89 (0.74–1.08)	40	15	2 (7/390)	16
Keynote 564	Renal Cell	Pembrolizumab vs Placebo	0.68 (0.53–0.87)	70	19	< 1 (2/488)	21
IMmotion 010+	Renal Cell	Atezolizumab vs Placebo	0.93 (0.75–1.15)	60	14	< 1 (1/390); considered unrelated to treatment	12
EORTC 1325-MG/Keynote 054	Melanoma	Pembrolizumab vs Placebo	0.60 (0.49–0.73)	50	Not reported	Not reported	Not reported
EORTC 18071	Melanoma	Ipilimumab vs Placebo	0.75 (0.64–0.90)	40	42	1 (6/471)	52
Checkmate 238	Melanoma	Nivolumab vs Ipilimumab	0.65 (0.51–0.83)	NA#	14% on nivolumab and 46% on ipilimumab	0 on nivolumab and < 1% (2/453) on ipilimumab	10% on nivolumab and 43% on ipilimumab
IMpower 010	NSCLC	Atezolizumab vs Best Supportive Care	0.81 (0.67–0.99)	40	8	2 (8/495)	18
Checkmate 577	Esophageal	Nivolumab vs Placebo	0.69 (0.56–0.86)	30	13	< 1 (1/532)*	13

^ Rounded to nearest 10.
# Active control arm
* Only treatment-related adverse events reported
+ Negative study that did not lead to FDA drug approval

would recommend regulators not approve ICI drugs for adjuvant therapy until OS benefit has been demonstrated or DFS is appropriately validated as a surrogate endpoint. In the setting where these drugs are approved without demonstrated OS benefit, we would advocated for price reductions to appropriately reflect the uncertainty of benefit of this therapy. ICIs are a mainstay of treatment in a variety of cancers, but how should they best be used warrants careful consideration.

Declaration of Competing Interests

Ali Raza Khaki reports research collaborations with Tempus Labs and Natera. Mark Lythgoe does not report any financial conflicts of interest. Vinay Prasad reports research funding from Arnold Ventures; royalties from Johns Hopkins Press, Medscape and MedPage; consulting fees from UnitedHealthcare; speaking fees from Evicore and New Century Health; and Plenary Session Podcast has Patreon backers.

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