When is crossover desirable in cancer drug trials and when is it problematic?

The use of crossover, as a design feature of randomized trials, is common, with reports indicating that up to 22% of all randomized controlled trials utilize this feature [1]. In cancer medicine, crossover typically refers to uni-directional crossover at the time of progression. Uni-directional: meaning that patients assigned to placebo are offered access to the investigation agent, but not *vice versa* (bi-directional). Crossover in cancer trials is typically specified by the protocol and occurs before any action taken by the monitoring committee. A positive trial may allow patients to crossover to the active drug after un-blinding, but this use of crossover is a prerequisite to ethical trial design and not the subject of this essay. Instead, we focus on situations where, at the outset and without knowing the trial results, crossover is or is not permitted.

Although common, crossover is a confusing and controversial subject. The purported benefits to crossover are that it may make a trial more desirable to participants, aiding in recruitment, or, in certain situations, crossover is considered ethically desirable or necessary. However, elsewhere in the Journal, Chen and Prasad find that crossover trials do not accrue more patients per month [2]. The limitation to crossover is that it can confound end points that are measured after the crossover event, such as the second progression-free survival (PFS2) interval or overall survival (OS). For this reason, crossover has been the topic of several commentaries with varying opinions [3–5].

Here, we offer a framework to think about crossover using contemporary clinical trial examples. In cancer medicine, crossover may or may not be desirable, depending on the circumstance, and may or may not occur, depending on the trial. In reality, there are errors of both kinds: crossover should have happened but did not, or should not have happened but did. Using Table 1, we wish to clarify these situations.

Crossover is desirable in settings where a drug has already proven benefit in a subsequent line of therapy and an attempt is being made to advance it to an earlier line. Such was the case in the KEYNOTE-024 trial, where patients with non-small-cell lung cancer (NSCLC) and high expression of PD-L1 received either pembrolizumab or a platinum-based chemotherapy in the front line [6]. Before this study, PD-1 antibody therapy had shown improved overall survival over docetaxel in second line NSCLC, and had become standard of care. Thus, in KEYNOTE-24, participants were allowed to crossover to pembrolizumab, if they had disease progression. KEYNOTE asks the clinical relevant question: is there a survival advantage to administering PD-1 antibody therapy for these patients upfront versus giving the same drug as second line, as is current practice? The trial answered this question with a positive conclusion.

Conversely, other studies have not provided the experimental drug in a later line, despite the fact that such agents represent global best practice or standard of care. In the LATITUDE trial [7], patients with castrate sensitive prostate cancer received androgen-deprivation therapy with or without abiraterone acetate. The treatment led to an improvement in overall survival. However, trial participants did not receive abiraterone for progressive prostate cancer, as was standard of care in the USA and other nations. In response to LATITUDE, De Bono et al. write, 'the majority of men in the control groups in the STAMPEDE and LATITUDE trials died without exposure to abiraterone or enzalutamide. Thus, the drugs used in these control groups were inconsistent with current prevailing standards of care. This has implications for the conclusions of the trials. . .' [8].

Finally, at other times, crossover is desirable, but it is unclear whether and to what extent it occurred. In a global trial of PD-1 antibody consolidation for patients with stage III NSCLC, a PFS benefit was shown, while overall survival remains immature [9]. However, it is not reported how often patients in the control arm had access to PD-1 antibody therapy if their cancer recurred as metastatic disease. Knowledge of this fact is important, just as in KEYNOTE-024, where the clinically relevant question is whether consolidation is superior to receipt of the drug as current standard of care for metastatic disease.

Crossover is problematic in trials that seek to establish the basic efficacy of a therapy (see Table 1). In a randomized trial of sipuleucel-T or placebo for metastatic prostate cancer [10], patients who progressed were allowed a frozen version of the vaccine, though efficacy of this therapy was not established. This meant there were more patients in the control arm than the active therapy arm who did not receive docetaxel or received it after a delay. Docetaxel had already shown a survival benefit in this cancer. Response rate and PFS, end points not affected by crossover, were not improved by the therapy, while survival was. In this case, allowing crossover (72% for patients in the control arm of this study) resulted in ambiguity whether prolonged survival was because the treatment was truly effective or because of a delay in alternative and effective therapy for those in the control arm. This was noted in an Agency for Healthcare Research & Quality (AHRQ) report on sipuleucel-T [11].

Alternatively, in the CLEOPATRA trial [12], patients with HER2-positive metastatic breast cancer received trastuzumab and docetaxel with or without pertuzumab. Crossover was not permitted until overall survival was resulted, permitting for a clear measurement of therapeutic effect.

Much of the difficulty in interpreting crossover studies arises from the fact that crossover can be desirable or undesirable, depending on the situation. Modern trials have had errors of both kinds: omission of crossover when it is needed, or inclusion when it is undesirable. Also, in some trials, the presence of or rate of crossover is not provided. Understanding these situations is

Table 1. An explanation of how crossover can occur or not occur, be desirable or problematic, or any combination of these two

	Crossover occurred	Crossover did not occur	Uncertainty as to whether crossover occurred
Crossover is desirable: Situations in which the experimental drug has ALREADY proven benefit in a later line of therapy or is standard of care in the latter line	KEYNOTE-024 trial [6] tested whether platinum doublet or PD-1 antibody was superior in the front line of NSCLC. As PD-1 antibody therapy had already been approved in the second line, the trial is essentially testing whether upfront administration is superior to current standard of care (as second line). In fact, crossover was permitted and 43.7% of control arm crossed over to pembrolizumab.	In the LATITUDE trial [7], 1199 patients with castrate sensitive metastatic prostate cancer were randomized to receive androgen-deprivation therapy, with or without abiraterone. Before this trial, standard of care was to administer abiraterone to these patients in a later line of therapy. As such, Prasad and Berger wrote 'we cannot be sure that the survival advantage of early treatment would still exist if control patients had fair access to this drug' [13].	The PACIFIC trial [9] tested whether, for patients with stage III lung cancer, 12 months of Durvalumab improved PFS and OS. For patients whose disease recurs however, the trial does not specify whether and to what degree they receive PD-1 therapy. Given the trial was conducted at many global sites, one concern is control arm patients may not receive these drugs as they would in the USA. This would not affect the PFS estimate, but may affect OS.
	DESIRABLE SITUATION	**UNDESIRABLE SITUATION**	**UNDESIRABLE SITUATION**
Crossover is problematic: Situations in which the fundamental efficacy of the experimental agent has not been established in any prior study	In the randomized trial leading to regulatory approval of sipuleucel-T [9], 225 patients were randomized to the vaccine or placebo. Patients who progressed were allowed to receive a similar drug as sipuleucel-T (a frozen salvage product). Disease progression and PFS were not improved, yet overall survival was. This led to the suggestion in an AHRQ report that sipuleucel-T exhibited efficacy not by improving outcomes but rather because crossover harmed the control group by delaying alternate effective therapy. In this case, fewer patients received docetaxel in the control arm and, on average, after a delay.	In the CLEOPATRA study [11], patients with HER2-positive metastatic breast cancer were randomly assigned to receive trastuzumab and docetaxel, with or without the addition of pertuzumab. Crossover was not permitted before analysis of overall survival.	Occasionally, published trials do not clearly specify if crossover did or did not occur [14].
	UNDESIRABLE SITUATION	**DESIRABLE SITUATION**	**UNDESIRABLE SITUATION**

invaluable for interpreting cancer clinical trials, and using crossover appropriately ensures clinical trials answer questions that impact clinical decisions.

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Molecular risk stratification to direct therapy in endometrial cancer: ready for the clinic?

The Cancer Genome Atlas (TGCA) studies have defined the molecular genetic landscape of endometrial cancer and highlighted the molecular genetic diversity of both endometrioid and non-endometroid cancers [1]. The TCGA established four distinct endometrial cancer subclasses based on the extent of mutational load and somatic copy number alterations. The first molecular subclass of ultramutated cancers is characterised by mutations in the exonuclease domain of DNA polymerase epsilon (*POLE*), which has evoked substantial interest and specific research, as these cancers have an exceptionally good prognosis with very few recurrences despite mostly being high grade [2]. The second subclass is characterised by mismatch-repair deficiency (MMRD), mostly as a consequence of *MLH1* promoter hypermethylation but also including cancers that arise in the context of germline mutations in one of the MMR-genes (Lynch syndrome). The third subclass is characterised by high copy number alterations and *TP53* mutations and contains typically serous cancers but also grade 3 endometrioid cancers. The remaining subgroup, referred to as 'copy number low' group by TGCA, is molecularly heterogeneous with Wnt- and PI3/AKt-alterations, and includes most prototypical low grade endometrioid endometrial cancers [1]. As these four subclasses have distinct biological properties with specific clinical implications, the development of clinically available, reproducible and affordable tumour tests to identify these subclasses and confirm their prognostic significance have been priorities in subsequent research. Several international collaborative groups have shown that they could successfully determine the four TGCA subclasses on formalin-fixed, paraffin-embedded tissues with cheaper, reproducible, more rapid and clinically available techniques, and have confirmed their prognostic significance [3, 4]. Recent studies have shown that the additional value of an integrated molecular classification is particularly strong in patients that would currently be regarded as intermediate risk, while data on low- and high-risk endometrial cancer are still limited [5].

In the current issue of *Annals of Oncology*, Kommoss et al. report on the final validation step in the development process of a molecular classifier for endometrial cancer [6]. Their so-called Proactive Molecular Risk Classifier for Endometrial cancer (ProMisE) has been shown to identify the four TCGA subclasses and to be applicable on both diagnostic and definitive specimens in previous studies [7, 8]. In their current study, an unselected retrospective German cohort of endometrial cancers has been used for independent validation, and the authors conclude that the classifier is now fully validated and ready for clinical evaluation.

Strengths of their study are the comprehensive analysis and validation process according to the Institute of Medicine Guidelines, the confirmation of the concordance in diagnostic and surgical specimens, and the evaluation of the ProMisE classifier with other clinical and pathological variables. However, the validation study is still relatively small, as among the 452 evaluable cases, 62% had grade 1 and only 21% grade 3 tumours; 61% had very early disease stage (IA), and only 6% and 13% had stage II and III disease, respectively. This may be one of the reasons why the molecular classifier was significantly associated with progression-free survival, but not with overall survival. Just over 50% of their cohort were copy number low tumours (called p53wt by Kommoss), for which no additional prognostic information is obtained with the molecular classifier. Another important limitation is the lack of central pathology review [9]. The question remains how representative this low-risk validation group is for the women with high-risk endometrial cancers who would benefit most of the prognostic information and potential predictive role for molecular driven adjuvant therapies. Finally, a small subset of EC (1.8% in the study by Kommoss, 3%–4% in other studies) [3, 10] remains unclassifiable due to multiple mutations (e.g. *POLE* and *TP53* mutation). This warrants further investigation, as the proposed ProMisE decision tree that dictates the order in which tumours are assigned to a specific type seems not to be based on specific data.

Is this the final step and should molecular classification of endometrial cancer now be considered standard to inform and determine patient management? Due to the retrospective nature of the studies, the molecular classifiers can be used to refine prognosis in women with intermediate-risk endometrial cancer, but data for those with high-risk, non-endometrioid (e.g. clear cell) cancers or with advanced stage of disease are still limited [10]. An additional concern is which prognostic parameters other than the four molecular subclasses should be taken into account in clinical patient management [3, 11]. This is particularly relevant for the 50% of cases that ProMisE could not classify as they were 'p53 wildtype'. Overexpression of L1 cell adhesion molecule (L1CAM) and mutations in exon3 of *CTNNB1* have been shown in multiple studies to have significant impact on the risk of recurrence and endometrial cancer-related death [12–14]. L1CAM