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Author's Response: The unified definition of relapse-free survival should be used for evaluating survival benefit in oesophageal adenocarcinoma

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We appreciate the commentary of Dr Li regarding our study on the application of the DNA Damage Immune Response (DDIR) assay to predict benefit from neo-adjuvant chemotherapy in oesophageal adenocarcinoma.[1,2] We do not agree that there is a single, unified definition of relapse-free survival (RFS) and, indeed, the variation in definitions is a well described problem in clinical trials. A key difference is the inclusion of deaths in the absence of evidence of tumour re-growth as recurrences, rather than censored events. The Food and Drug Administration (FDA) have commented that the 'application of the definition of relapse or disease-free survival can be complicated, particularly when deaths are noted without prior tumour progression documentation.'[3] They remark that these events can be scored either as disease recurrences or as censored events and note that including deaths from all causes as recurrences can overestimate RFS, especially in patients who die after a long period without observation.

In light of the criticism by Dr Li we have re-analysed our RFS data, considering deaths without evidence of recurrence as events. A total of 15 patients died without proven disease relapse. Using this definition of RFS, DDIR positivity continued to be associated with an improved RFS in univariate analysis (HR 0.65, 95% CI 0.47-0.97; p= 0.033) (Table 1) compared to the previous analysis (HR 0.58, 95%CI 0.38-0.90; p= 0.015), in which deaths without recurrence were not included. A similar trend was found in multivariate analysis (HR 0.60, 95% CI 0.38-0.95; p= 0.031, compared to HR 0.61, 95%CI 0.38-0.98; p= 0.042), adjusting for clinico-pathological factors as previously described.

In addition to RFS, it is also important to consider overall survival (OS), for which RFS is a surrogate endpoint. The FDA have commented that OS is the often the preferred endpoint where trial design permits, noting its precision, relative ease of

measurement and elimination of bias.[3] In the DDIR cohort, DDIR positivity was correlated with improved OS following multivariate analysis (HR 0.52, 95% CI 0.31 – 0.88 ; p = 0.015), in line with the RFS analysis.

We agree that there is a pressing need for standardisation of definitions of survival endpoints and events across clinical trials, particularly with the increased prominence of RFS as a primary endpoint.[4] Implementation of the endpoints proposed by Punt et al. and the Standardized Definitions for Efficacy End Points (STEEP) criteria by Hudis et al. to all solid tumour trials will lead to greater comparability among clinical studies.[5][6]

Table1: Univariate and multivariate analysis of DDIR status and Relapse-free survival (including deaths from all causes) in OAC.

MULTIVARIATE MODEL, c-index = 0.616				
		HR	**95% CI**	**p-value**
DDIR	Negative	1		
	Positive	0.60	0.38-0.95	0.031
Clinical T Stage	1, 2	1		
	3, 4	0.97	0.53-1.77	0.909
Clinical N Stage	0	1		
	1, 2 ,3	1.47	0.94-2.32	0.093
Differentiation	Poor	1		
	Well, moderate	0.60	0.41-0.90	0.012
UNIVARIATE MODEL				
		HR	95% CI	p-value
DDIR	Negative	1		
	Positive	0.65	0.44-0.97	0.033

1 Li W. Unified definition of relapse-free survival should be used for evaluating survival benefit in oesophageal adenocarcinoma. *Gut* 2020;:gutjnl-2020-321482. doi:10.1136/gutjnl-2020-321482

2 Turkington RC, Knight LA, Blayney JK, *et al.* Immune activation by DNA damage predicts response to chemotherapy and survival in oesophageal

adenocarcinoma. *Gut* 2019;:gutjnl-2018-317624. doi:10.1136/gutjnl-2018-317624

3 U.S. Food and Drug Administration. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry. *US Food Drug Adm* Published Online First: 2019.http://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics

4 Booth CM, Eisenhauer EA. Progression-free survival: Meaningful or simply measurable? *J Clin Oncol* 2012;**30**:1030–3. doi:10.1200/JCO.2011.38.7571

5 Punt CJA, Buyse M, Köhne CH, *et al.* Endpoints in adjuvant treatment trials: A systematic review of the literature in colon cancer and proposed definitions for future trials. *J Natl Cancer Inst* 2007;**99**:998–1003. doi:10.1093/jnci/djm024

6 Hudis C a, Barlow WE, Costantino JP, *et al.* Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007;**25**:2127–32. doi:10.1200/JCO.2006.10.3523