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LETTER TO EDITOR

Joint association of patients' sex and PD-L1 expression with overall survival benefits and tumor-immune microenvironment in immune checkpoint inhibitors for cancers

Dear Editor,

Currently, the association of patients' sex with survival benefit of immune checkpoint inhibitor (ICI) is being actively investigated, but inconsistent results have been produced. A meta-analysis[1] reported that male patients had significantly lager overall survival (OS) benefits from ICI versus control treatment than did female patients. However, an updated meta-analysis[2] found no significant difference in OS between sexes. This conflict indicated that the sex-related effects on ICI efficacy involved complex and unknown elements of tumor microenvironment.

The phase III KEYNOTE-024 trial[3] enrolled cancer patients with PD-L1 expression on at least 50% tumor cells and found a strikingly improved OS benefit with ICI compared with chemotherapy in male but only a minimal improvement in female. However, neither male nor female had significant OS benefit from ICI over chemotherapy in some trials recruiting cancer patients with a lower PD-L1 expression threshold (≥1%).[4,5] Therefore, we hypothesize that PD-L1 expression has essential impact on the clinical usefulness of sex. This study, based on a post hoc analysis of prospective individual patient data from five clinical trials including OAK, POPLAR, IMvigor210, KEYNOTE-001, and CheckMate-012, and a meta-analysis of nine randomized controlled trials (RCTs), is the first to clarify the sex-related difference in ICI efficacy by using PD-L1 expression (Figure 1A). We further evaluated the landscape of tumor immune microenvironment to explore potential factors underpinning this difference. Full methods were described in the Supporting Information Methods. Characteristics and references of included trials and patients were described in the Supporting Information Result 1 and Tables S1 and S2.

The individual-patient level analysis of OAK, POPLAR, and IMvigor210 trials showed that for patients receiving ICI, there was no significant difference in OS between male and female (HR 0.85, 95% CI 0.72-1.02; $P = .073$; Figure S2A). However, stratified by PD-L1 expression of 1%, OS for patients with PD-L1 expression <1% was significantly longer for female compared with male (HR 0.58, 95% CI 0.42-0.80; $P < .001$), but OS for patients with PD-L1 expression≥1% did not significantly differed between the sexes (HR 1.01, 95% CI 0.79-1.29; $P = .910$) (Figure 1B,C and Table S3).

Results were consistent stratified by PD-L1 expression of 50%. Overall survival was significantly longer for female than for male at PD-L1 threshold of <50% (HR 0.76, 95% CI 0.61-0.95; $P = .013$), but OS did not significantly differ between the sexes at PD-L1 threshold of 1–49% (HR 0.76, 95% CI 0.52-1.13; $P = .173$) or ≥50% (HR 0.64, 95% CI 0.31-1.33; $P = .231$) (Figure S2B-D and Table S3). When examining chemotherapy, sex was not associated with OS regardless of PD-L1 expression (see details in Supporting Information Results 2, Figure 1D-E, and Figure S3).

The individual-patient level analysis of POPLAR and OAK trials found that ICI improved OS compared with chemotherapy in both female (HR 0.67, 95% CI 0.53-0.84; $P < .001$) and male (HR 0.74, 95% CI 0.62-0.88; $P < .001$) (Figure S4A,B). However, among patients with PD-L1 expression <1%, the benefit from ICI versus chemotherapy was significantly different in female (HR 0.57, 95% CI 0.38-0.85; $P = .006$; Figure 2A), but there was no significant difference between the two treatments in male (HR 0.93, 95% CI 0.68-1.26; $P = .621$; Figure 2B).

Conversely, among patients with PD-L1 expression ≥1%, there was no significant difference between the two treatments in female (HR 0.69, 95% CI 0.47-1.01; $P = .057$; Figure 2C), whereas the benefit from ICI over chemotherapy was significantly different in male (HR 0.71, 95% CI 0.54-0.95; $P = .022$; Figure 2D). Further, we improved the

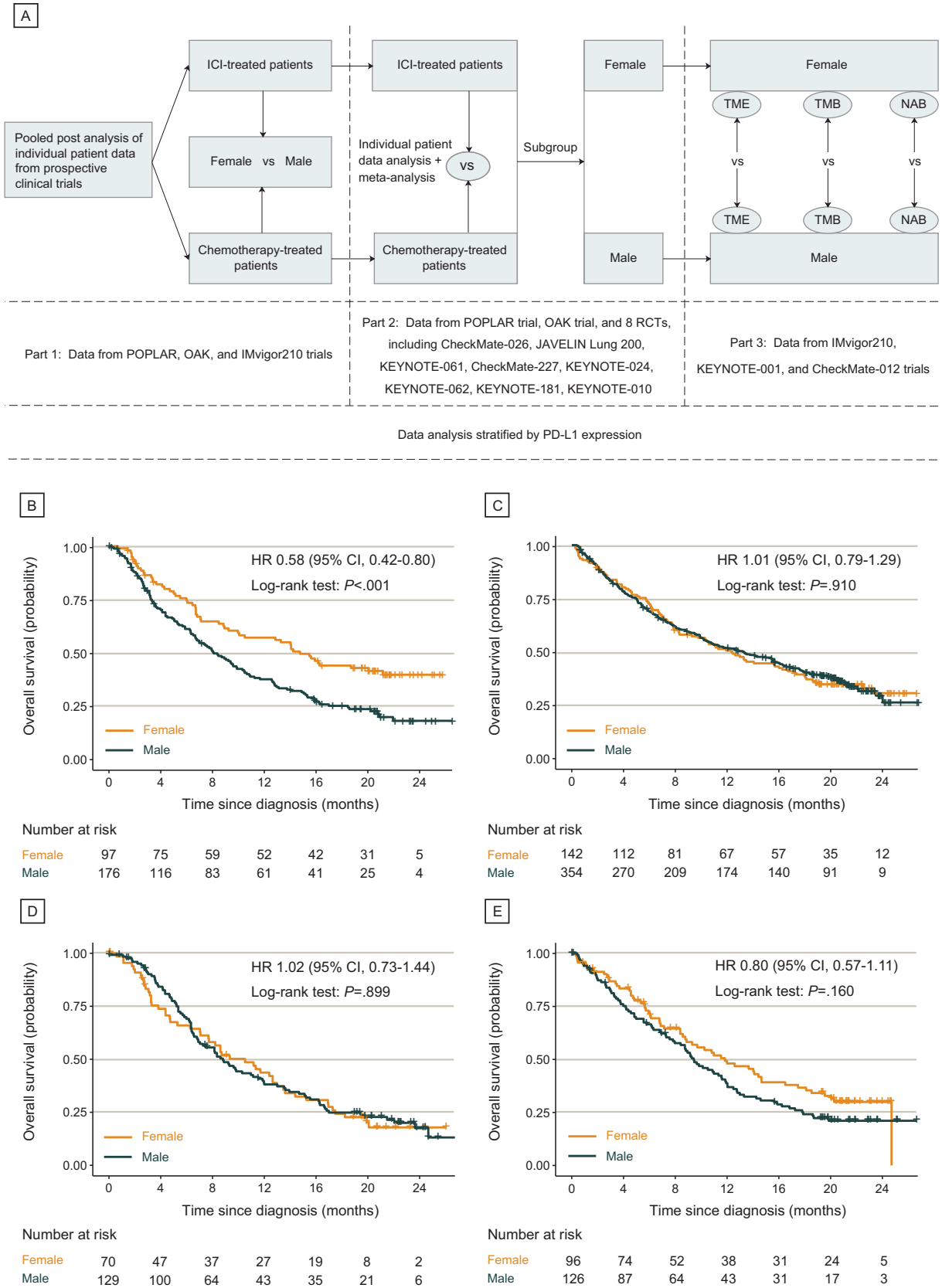

FIGURE 1 Individual patient-level analysis of overall survival in male versus female. A, Overview of study design. B and C, ICI-treated patients with PD-L1 expression <1% and ≥1%, respectively. D and E, Chemotherapy-treated patients with PD-L1 expression <1% and ≥1%, respectively. ICI, immune checkpoint inhibitor; HR, hazard ratio; CI, confidence interval; PD-L1, programmed-death ligand 1; TME, tumor microenvironment; TMB, tumor mutation burden; NAB, neoantigen burden

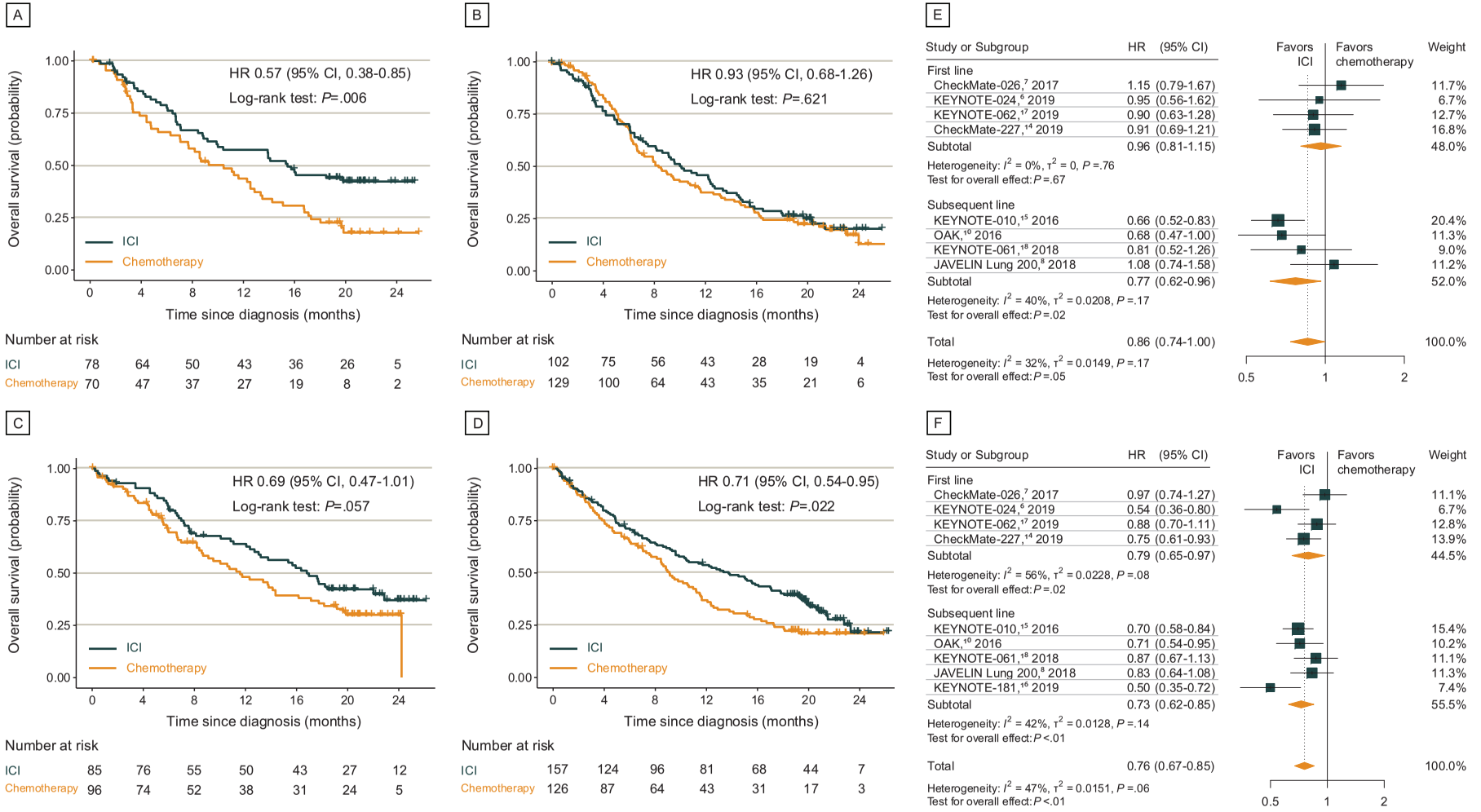

FIGURE 2 Overall survival with immune checkpoint inhibitor versus chemotherapy. A-D, Individual-patient level analysis of female patients with PD-L1 expression <1%, male patients with PD-L1 expression <1%, female patients with PD-L1 expression ≥1%, and male patients with PD-L1 expression ≥1%, respectively. We further improved the evidence for patients with PD-L1 expression ≥1% by pooling the individual patient-level results with the meta-analysis in female (E) and male (F) patients grouped by treatment line. HR, hazard ratio; CI, confidence interval; PD-L1, programmed-death ligand 1

evidence for patients with PD-L1 expression ≥1% by pooling the individual patient-level result with the meta-analysis result of eight other trials, which showed that although female patients showed significant OS benefit from ICI over chemotherapy (eight RCTs, 1602 patients; HR 0.86, 95% CI 0.74-1.00; $P = .05$), this benefit only remained significant in subsequent line (four RCTs, 850 patients; HR 0.77, 95% CI 0.62-0.96; $P = .02$), without significant benefits for patients in first-line setting (four RCTs, 752 patients; HR 0.96, 95% CI 0.81-1.15; $P = .67$) or in subgroups by regimen and ICI class (Figure 2E, Figures S5 and S6 and Table S4). Male patients with PD-L1 expression ≥1% could derive significant OS benefit from ICI over chemotherapy (nine RCTs, 3166 patients; HR 0.76, 95% CI 0.67-0.85; $P < .01$; Figure 2F). This benefit remained significant in both first line (four RCTs, 1393 patients; HR 0.79, 95% CI 0.65-0.97; $P = .02$) and subsequent line (five RCTs, 1723 patients; HR 0.73, 95% CI 0.62-0.85; $P < .01$), and in other tested subgroups (Figure 2F, Figures S7 and S8 and Table S4). There were no significant differences in effects on OS between subgroups. Similar findings were observed stratified by PD-L1 expression of 50% (see details in Supporting Information Results 3 and Figures S9 and S10). Finally, central memory T cells (Tcm), rather than tumor mutation burden (TMB) and neoantigen burden (NAB), was found to potentially correlated with the OS differences between the sexes (see details in Supporting Information Results 4; Figures S11-S24 and Tables S5-S7).

To our knowledge, this is the first study to reveal that PD-L1 expression has decisive effect on sex-associated differences in ICI efficacy. Previous meta-analyses included patients across varieties of PD-L1 thresholds, which might explain their inconsistency.[1,2] Previous research indicated that sex differences in mutational landscape might explain ICI efficacy differentially associated with sex,[6] but neither TMB nor NAB was significantly differed between male and female at any PD-L1 expression thresholds in our study. Instead, Tcm probably has potential impact on sex differences in ICI efficacy. However, with only bladder cancer patients from IMvigor210 trial having RNA sequencing data, we were unable to evaluate the role of Tcm in other cancer types. Additionally, multi-omics have been shown to mutually predict ICI efficacy[7,8]; therefore, future studies are warranted to comprehensively investigate sex difference in immune landscape using multi-omics across different cancer types.

This study found the survival benefits of ICI in male and female were greatly influenced by PD-L1 expression, especially in NSCLC. At PD-L1 expression <1%, ICI should be recommended for female but not for male, and Tcm might be essential to drive this recommendation. We suggest that sex and PD-L1 expression should be jointly taken into account in the clinical decision making for ICI in cancer.

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AUTHORS' CONTRIBUTIONS

Li, Chen, Zhang, Zhong, Ou, Hu, Yu, and Yao jointly designed the study and drafted of the manuscript. Hu, Yu, and Yao provided supervision. Li and Yao obtained funding. All authors contributed to the data collection, data analysis and interpretation, manuscript revision, and approval of the final version.

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request (yaoherui@mail.sysu.edu.cn).

ETHICAL APPROVAL

The study protocol was approved by the ethics committee of the Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The requirement for informed consent of study participants was waived because the human data were obtained from publicly available datasets.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

Anlin Li[1,2,*]
Yongjian Chen[1,3,*]
Wenda Zhang[1,2,*]
Haitao Zhong[1,4,*]

Qiyun Ou[1,*]
Yang Gu[1]
Junqing Xia[4]
Dagui Lin[5]
Tuping Fu[5]
Ruixin Liu[2]
Hai Hu[1]
Yunfang Yu[1]
Herui Yao[1]

[1] *Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Medical Oncology, Phase I Clinical Trial Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China*
[2] *Guangdong Key Laboratory for Research and Development of Natural Drugs, Guangdong Medical University, Zhanjiang, China*
[3] *Department of Medical Oncology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*
[4] *The First Clinical Medical College, Southern Medical University, Guangzhou, China*
[5] *Sun Yat-sen University Cancer Center, Guangzhou, China*

Correspondence
Herui Yao and Yunfang Yu, Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Department of Medical Oncology, Phase I Clinical Trial Centre, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, No. 107 Yanjiang West Road, Guangzhou 510120, China.
Email: yaoherui@mail.sysu.edu.cn; yuyf9@mail.sysu.edu.cn

*These authors contributed equally to this work as co-first authors.

ORCID
Herui Yao https://orcid.org/0000-0001-5520-6469

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.