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Dissociated response and treatment outcome with immune checkpoint blockade in advanced cancer

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Immune-related dissociated response (DR) has been recently recognized and have become a subject of ongoing interest. The purpose of the present study was to evaluate the frequency, treatment outcome, and predictors of DR in cancer patients with immune checkpoint inhibitors. We retrospectively collected clinicopathological data from a cohort of patients with cancer who received PD-1/PD-L1 inhibitor-based monotherapy or combination therapy at a single institution (developing cohort). An independent cohort of advanced non-small cell lung cancer (NSCLC) patients treated with immunotherapy at two institutions was used as the validating cohort. Progression-free survival (PFS) and overall survival (OS) were used as outcome measures. The pantumor cohort included 177 patients. DR were observed in 12 (6.8%) patients. The median PFS and OS were significantly longer in patients with atypical response versus nonresponse but shorter versus true response. Patients with DR had a longer median PFS and OS than those with true progressive disease (PD). Local treatment seemed to have a positive influence on DR patient outcomes, with a median OS of 32.3 months versus 21.9 months for no local treatment. No clinical characteristics remained significant predictors for DR. In the NSCLC cohort, DR was observed in 10 (12.5%) patients. Inferior PFS and OS were validated in patients with real PD when compared with patients with DR. Patients who experience DR exhibit a relatively favorable prognosis. Some patients with DR may benefit from the continuation of ICI administration and local treatment to the growing lesions and achieve a longer survival.

Keywords Atypical response, Pseudoprogression, Dissociated response, Programmed cell death protein-1, Immune checkpoint inhibitor, Advanced cancer

Treatment with immune checkpoint inhibitors (ICIs), including cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibitors, has achieved extraordinary response rates and revolutionized the systematic management of various malignancies at the early or advanced stage. Unlike conventional cytotoxic agents and targeted therapies that act directly to impair or destroy cancer cells, ICIs selectively restore and normalize the body's antitumor immune responses by disrupting the immunoinhibitory signals mediated by the PD-1/PD-L1 and CTLA-4 axes[1]. Furthermore, the response patterns of tumors with ICIs may differ from those with conventional cytotoxic agents and targeted therapies owing to their characteristic mechanisms of action[2].

A majority of patients with ICIs present with typical responses per conventional response evaluation criteria in solid tumors (RECIST) 1.1, including a complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Patterns of atypical response (AR) or heterogeneous response to ICIs have been identified in a subgroup of patients, including delayed response (DeR), pseudoprogressive disease (PsPD), hyperprogressive disease (HPD), and dissociated response (DR). DeR is observed following initial SD and subsequent therapeutic responses[3]. PsPD is observed as tumor shrinkage after temporary tumor growth. HPD

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is an aggressive pattern of cancer progression and causes tumor progression at an accelerated and unexpected rate[4]. DR, namely, mixed response, refers to a phenomenon of a heterogeneous response in which responding and nonresponding lesions or new lesions coexist within the same patient simultaneously. DR in patients with immunotherapy is uncommon and rarely reported. It has been recently recognized and is a subject of ongoing interest[5]. The rate of DR reported in different studies encompasses a wide range of 3.3–47.8% based on diverse clinical definitions of DR and cancer types. Although the mechanism of DR remains unclear, tumor heterogeneity within individual patients and tissue penetration by drugs in organs may be associated with inconsistent responses to ICI treatment[6]. DR is also associated with the treatment efficacy of ICIs and a relatively favorable prognosis, but its types, radiological evaluation criteria, treatment outcome, prediction, and subsequent clinical management have not been fully understood and elucidated in different cancer types. The purpose of this study was to comprehensively evaluate the frequency, treatment outcome, management, and predictors of DR in advanced solid cancers receiving ICI therapy.

Methods

Patient cohort

We retrospectively reviewed a cohort of patients with advanced solid cancers who presented to The First Affiliated Hospital of Shandong First Medical University and were treated with ICIs from December 2019 to April 2022 (development cohort). An independent cohort of advanced non-small cell lung cancer (NSCLC) patients treated with immunotherapy at two institutions from June 2019 to January 2022 was used as the validation cohort. The inclusion criteria were as follows: age older than 18 years; histologically or cytologically confirmed locally advanced or metastatic solid cancer according to the American Joint Committee on Cancer (AJCC) staging system, 8th version; receiving at least two cycles of PD-1/PD-L1 inhibitor (nivolumab, pembrolizumab, camrelizumab, sintilimab, tislelizumab, durvalumab, or atezolizumab) monotherapy or a combination with chemotherapy as a first-, second- or later line of treatment for at least one tumor evaluation by imaging; and having an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2. Patients without any measurable lesions using CT or MRI within 28 days prior to the initiation of immunotherapy, whose response to therapy was not evaluated after the initiation of immunotherapy, and having a history of immunotherapy with ICIs were excluded.

Clinical annotation

Data were gathered through the electronic medical record. The clinical characteristics of the patients included age, sex, ECOG PS, smoking status, body mass index (BMI), histology, complete blood count before and after immunotherapy initiation, and tumor node metastasis (TNM) stage at the start of treatment. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil counts by the lymphocyte counts, as measured in peripheral blood. The derived NLR (dNLR) was defined as the absolute neutrophil count/white cell count – absolute neutrophil count. Progression-free survival (PFS) was defined as the date of immunotherapy initiation to the date of disease progression or death from any cause, whichever occurred first. Patients who were alive without disease progression were censored on the date of their last disease assessment. Overall survival (OS) was defined as the time from immunotherapy initiation to death from any cause. Patients who were still alive were censored at the date of last contact. This study was approved by the independent research ethics committee of The First Affiliated Hospital of Shandong First Medical University (NO: YXLL-KY-2022–059) and conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects and/or their legal guardian(s).

Enzyme-linked immunosorbent assay (ELISA)

Baseline serum samples were isolated from patients and diluted for further analysis. Cytokines in human serum samples, including interleukin (IL)-2, IL-4, IL-6, IL-10, interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α), were determined by ELISA using a Human Cytokine Standard Assays panel (ET Healthcare, Inc., Shanghai, China) and the Bio-Plex 200 system (Bio-Rad, Hercules, CA, USA) according to a previously reported procedure[6].

Evaluation of efficacy

Objective response by radiographic findings was assessed as CR, PR, SD, or PD according to RECIST 1.1. The objective response rate (ORR) was defined as the proportion of patients with a CR or PR to immunotherapy. The disease control rate (DCR) was defined as the percentage of patients who achieved CR, PR, and SD after immunotherapy. Durable clinical benefit (DCB) was defined as CR, PR or stable disease (SD) that lasted longer than 6 months. In patients who showed PR, SD, or PD according to RECIST, we evaluated all measurable lesions in each organ to identify PsPD and DR. PsPD is defined as unconfirmed disease progression and is observed as tumor shrinkage after temporary tumor growth. DR refers to a disease where some lesions shrink but some grow or new lesions emerge. PR not classified as DR was defined as true PR, SD not classified as DR was defined as true SD, and PD not classified as DR was defined as true PD. Here, atypical responses included PsPD and DR. True response refers to CR and PR, and nonresponse refers to true SD and true PD.

Statistical analysis

Categorical variables, such as patient demographics, disease characteristics, and medical history, were reported as frequencies and percentages. Quantitative variables are presented as medians and ranges. For categorical variables, we used Fisher's exact test to compare patient characteristics among different groups. For continuous variables, independent sample *t* tests or Mann–Whitney *U* tests were used to compare patient groups. Univariable and multivariable logistic regression on prespecified outcomes of DR and PsPD were performed. Predictor

variables that did not satisfy a linearity assumption in logistic regression were binarized according to medians and treated as categorical variables. PFS and OS were compared using the Kaplan–Meier method and the log-rank test. The hazard ratio was calculated using Cox proportional hazards regression models. All significant factors identified in the univariate analysis were entered in the multivariate analysis. Statistical analyses were performed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA), and SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) was used for all statistical tests. All statistical tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Patient characteristics and treatment outcome

In the pantumor cohort including 200 advanced cancer patients with immunotherapy, 23 patients were excluded because they did not have measurable lesions or were not evaluated after the initiation of immunotherapy. Finally, a total of 177 patients were included in the development cohort. The most common malignancies were NSCLC (30%), gastric carcinoma (22%), small cell lung cancer (SCLC; 9%), and hepatocellular carcinoma (HCC; 8.5%). The median follow-up was 9.5 months (range 1.3 to 27.6) from initiation of ICI therapy. The median age was 63.0 years (range 18 to 81), and 65.5% were male. Thirty-two patients received ICI monotherapy. Patients received a median of two previous lines of systematic therapy for their advanced disease. At the end of follow-up, 99 patients had relapsed, and 94 patients had died. For the entire population, the ORR was 17.0%, the DCR was 83.1%, and the median OS and PFS were 16.4 months (95% CI: 15.3–18.1) and 8.1 months (95% CI: 9.8–12.7), respectively (Fig. 1a). The DCB was 52.7% in the entire population. The patients' baseline characteristics are summarized in Table 1. The validation cohort included 80 advanced NSCLC patients treated with immunotherapy at two institutions. The NSCLC patients' baseline characteristics are summarized in Table 2.

Atypical and dissociated response

We first analyzed the atypical response rate and frequencies of DR according to RECIST response and cancer types. In the development cohort with 177 cancer patients, 19 (10.7%) exhibited AR while receiving ICI therapy. PsPD and DR were observed in 7 (4.0%) and 12 (6.8%) patients, respectively (Fig. 1b). DR occurred in patients with PR, SD, or PD at the first radiographical evaluation, with percentages of 13.8% (4/29), 5.9% (7/117), and 3.3% (1/30), respectively (Fig. 1c). Four patients with DR were NSCLC, and others were SCLC ($n = 2$), gastric cancer ($n = 1$), ovarian cancer ($n = 2$), pancreatic cancer ($n = 2$), and HCC ($n = 1$) (Fig. 1d). Progressive lesions in DR patients occurred in the liver ($n = 3$), lymph nodes ($n = 3$), lungs ($n = 2$), bone ($n = 2$), brain ($n = 1$), and adrenal glands ($n = 1$). In patients with DR, progressed lesions can be target lesions, nontarget lesions, or newly appeared lesions. Here, 75% of DR cases occurred due to the appearance of new lesions, and 25% of DR cases

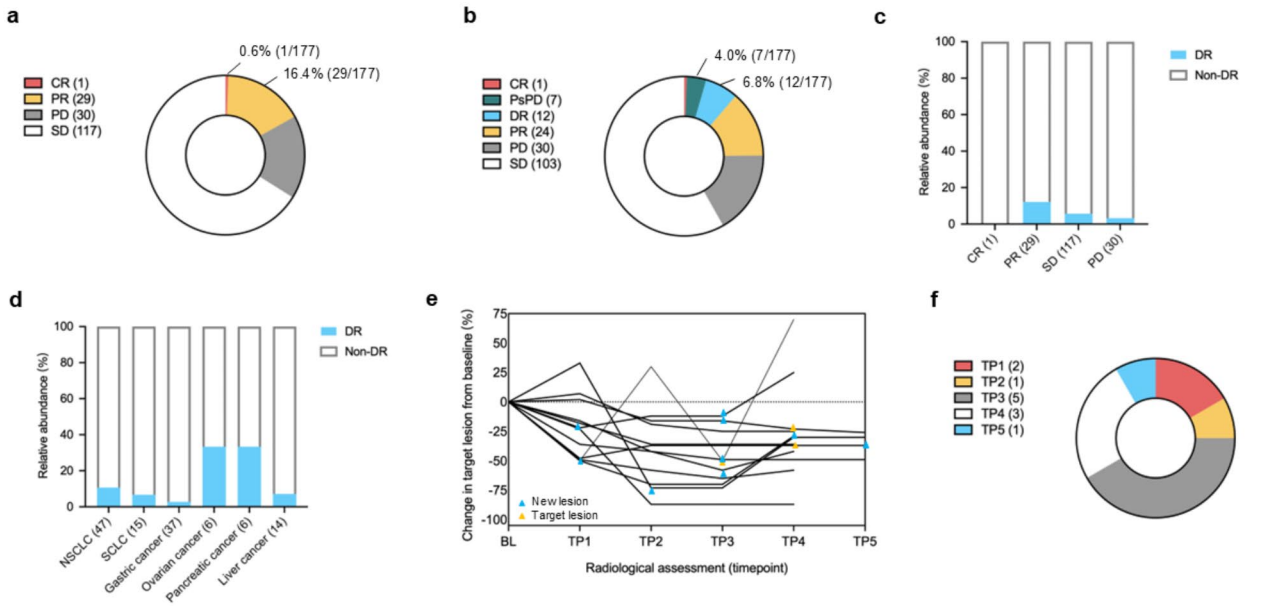

Fig. 1. Objective response rate, atypical response rate, frequencies of DR according to RECIST response and cancer types in the development cohort. (**a**) Objective response rate in all patients at the first radiographical assessment. (**b**) Atypical response rate, including PsPD and DR rates, in all patients. (**c**) Frequencies of DR according to RECIST response (PR, SD, and PD). (**d**) Frequencies of DR according to cancer types. (**e**) Percent change from baseline in target lesions in patients with DR. (**f**) Frequencies of DR according to the timepoint of radiological assessment. *PsPD* pseudoprogressive disease, *DR* dissociated response, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *BL* baseline, *TP* timepoint.

Baseline characteristics, *n* (%)		All patients (*n* = 177)	DR (*n* = 12)	PsPD (*n* = 7)	CR/PR (*n* = 25)	SD (*n* = 103)	PD (*n* = 30)
Sex	Male	116 (65.5)	10 (83.3)	3 (42.9)	23 (92.0)	72 (69.9)	8 (26.7)
	Female	61 (34.5)	2 (16.7)	4 (57.1)	2 (8.0)	31 (30.1)	22 (73.3)
Age, years	< 60	75 (42.4)	4 (30.0)	2 (28.6)	8 (32.0)	50 (48.5)	11 (36.7)
	≥ 60	102 (57.6)	8 (60.0)	5 (71.4)	17 (68.0)	53 (52.5)	19 (63.3)
Smoking status	Never	92 (52.0)	6 (50.0)	5 (71.4)	10 (40.0)	55 (53.4)	16 (53.3)
	Previous/current	85 (48.0)	6 (50.0)	2 (28.6)	15 (60.0)	48 (46.6)	14 (46.7)
ECOG PS	0–1	144 (81.4)	10 (83.3)	5(71.4)	22 (88.0)	81 (78.6)	26 86.7)
	≥ 2	33 (18.6)	2 (16.7)	2 (28.6)	3 (12.0)	22 (21.4)	4 (13.3)
BMI, kg/m^2	< 18.6	18 (10.2)	2 (16.7)	3 (42.9)	2 (8.0)	9 (8.7)	2 (6.7)
	≥ 18.6	159 (89.8)	10 (83.3)	4 (57.1)	23 (92.0)	94 (91.3)	28 (93.3)
Tumor type	NSCLC	53 (30.0)	4 (33.3)	1 (14.3)	12 (48.0)	36 (35.0)	0 (0)
	SCLC	16 (9.0)	2 (16.7)	0 (0)	0 (0)	9 (8.6)	5 (16.7)
	GC	39 (22.0)	1 (8.3)	2 (28.6)	7 (28.0)	22 (21.4)	7 (23.3)
	HCC	15 (8.5)	1 (8.3)	1 (14.3)	0 (0)	8 (7.8)	5 (16.7)
	Others	54 (30.5)	4 (33.3)	3 (42.9)	6 (24.0)	28 (27.2)	13 (43.3)
Treatment line	First-line	79 (44.6)	6 (50.0)	3 (42.9)	14 (56)	44 (42.7)	12 (40.0)
	Second line or Later	98 (55.4)	6 (50.0)	4 (57.1)	11 (44.0)	59 (57.3)	18 (60.0)
ICI treatment	PD-1 inhibitor	159 (89.8)	11 (91.7)	7 (100)	21 (84.0)	94 (91.3)	26 (86.7)
	PD-L1 inhibitor	18 (10.2)	1 (8.3)	0 (0)	4 (16.0)	9 (8.7)	4 (13.3)
Treatment strategy	Monotherapy	32 (18.1)	0 (0)	3 (42.9)	4 (16.0.0)	20 (19.4)	5 (16.7)
	Combination therapy	145 (81.9)	12 (100)	4 (57.1)	21 (84.0)	83 (80.6)	25 (83.3)
PD-L1 expression	Not available	56 (31.6)	8 (66.7)	1 (14.3)	14 (56.0)	23 (22.3)	10 (33.3)
	< 1%	83 (46.9)	1 (8.3)	3 (42.9)	6 (24.0)	58 (56.3)	15 (50.0)
	1–49%	27 (15.3)	2 (16.7)	2 (28.6)	2 (8.0)	16 (15.5)	5 (16.7)
	≥ 50%	11 (6.2)	1 (8.3)	1 (14.3)	3 (12.0)	6 (5.8)	0 (0)
NLR	< 5	147 (83.1)	10 (83.3)	5 (71.4)	25 (100)	84 (81.6)	23 (76.7)
	≥ 5	30 (16.9)	2 (16.7)	2 (28.6)	0 (0)	19 (18.4)	7 (23.3)
Radiotherapy	No	131 (74.0)	7 (58.3)	6 (85.7)	18 (72.0)	76 (73.8)	24 (80.0)
	Yes	46 (26.0)	5 (41.7)	1 (14.3)	7 (28.0)	27 (26.2)	6 (20.0)

Table 1. Patient characteristics in the pan-tumor cohort. *DR* dissociated response, *PsPD* pseudoprogressive disease, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ECOG PS* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *GC* gastric cancer, *HCC* hepatocellular carcinoma, *ICI* immune checkpoint inhibitor, *PD-1* programmed cell death protein-1, *PD-L1* programmed cell death ligand-1, *NLR* neutrophil-to-lymphocyte ratio.

occurred due to the progression of target lesions (Fig. 1e). DR occurred at different timepoints of radiological assessment after ICI therapy. Two DR patients were identified at TP1, 1 at TP2, 5 at TP3, 3 at TP4, and 1 at TP5 (Fig. 1f). Baseline clinicopathological characteristics were generally balanced between the DR and real PD groups in terms of age, smoking status, ECOG PS, BMI, treatment line, ICI, baseline NLR, and history of radiotherapy. There was no significant difference regarding PD-L1 expression between the two groups. Male ($p = 0.003$) and NSCLC ($p = 0.006$) patients were more common among patients with DR (Supplementary Table S1). In the validation cohort with 80 advanced NSCLC patients, 10 (12.5%) exhibited DR while receiving ICI therapy.

Prognosis of patients with DR

We next asked whether AR or DR affected the prognosis of immunotherapy in advanced cancer. The patients with AR had a decreased PFS (10.9 versus 35.4 months; $p < 0.0001$) and OS (24.1 versus NR months; $p < 0.0001$) than those with true response. However, AR patients had a prolonged PFS (10.9 versus 5.6 months; $p < 0.0001$) and OS (24.1 versus 13.2 months; $p < 0.0001$) compared with those with nonresponse(Fig. 2a,b). Furthermore, patients showing DR had an increased PFS and OS than those showing concordant progressive disease (median PFS: 11.3 versus 1.6 months; $p < 0.0001$; median OS: 23.9 versus 5.6 months; $p = 0.0001$) but not patients with real SD (median PFS: 11.3 versus 8.5 months; $p = 0.401$; median OS: 23.9 versus 16.8 months; $p = 0.325$) (Fig. 2c,d). In a multivariate analysis using the Cox proportional hazards regression model, adjusting for various clinical factors, including sex, age, smoking status, ECOG PS, BMI, tumor type, treatment line, ICI treatment, treatment strategy, PD-L1 status, and radiotherapy, only DR remained an independent indicator for predicting PFS (adjusted HR: 0.019; 95% CI: 0.003–0.116; $p < 0.0001$) (Supplementary Table S2). The presence of DR (adjusted HR: 0.091; 95% CI: 0.031–0.269; $p < 0.0001$), second-line or later treatment (adjusted HR: 0.347; 95%

Baseline characteristics, *n* (%)		All patients (*n* = 80)	DR (*n* = 10)	CR/PR (*n* = 19)	SD (*n* = 27)	PD (*n* = 24)
Sex	Male	54 (67.5)	8 (80.0)	17 (89.5)	17 (63.0)	12(50)
	Female	26 (32.5)	2 (20.0)	2 (10.5)	10 (37.0)	12 (50)
Age, years	< 60	23 (28.8)	5 (50.0)	4 (21.1)	8 (29.6)	6 (25)
	≥ 60	57 (71.2)	5 (50.0)	15 (78.9)	19 (70.4)	18 (75)
Smoking status	Never	29 (36.3)	4 (40.0)	3 (15.8)	9 (33.3)	13 (54.2)
	Previous/current	51 (63.7)	6 (60.0)	16 (74.2)	18 (66.7)	11 (45.8)
ECOG PS	0–1	78 (97.5)	10 (100.0)	18 (94.7)	27 (100)	23 (95.8)
	≥ 2	2 (2.5)	0 (0)	1 (5.3)	0 (0)	1 (4.2)
BMI, kg/m^2	< 18.6	6 (7.5)	0 (0)	1 (5.3)	2 (7.4)	3 (12.5)
	≥ 18.6	72 (92.5)	10 (100.0)	18 (94.7)	25 (92.6)	21 (87.5)
Tumor type	AC	45 (56.2)	6 (60.0)	8 (42.1)	15 (55.6)	16 (66.7)
	SCC	28 (35.0)	3 (30.0)	9 (47.4)	10 (37.0)	6 (25)
	Others	7 (8.8)	1 (10.0)	2 (10.6)	2 (7.4)	2 (8.3)
Treatment line	First-line	20 (25.0)	1 (10.0)	5 (26.3)	11 (40.7)	3 (12.5)
	Second line or Later	60 (75.0)	9 (90.0)	14 (73.7)	16 (59.3)	21 (87.5)
ICI treatment	PD-1 inhibitor	69 (86.3)	8 (80.0)	17 (89.5)	21 (77.8)	23 (95.8)
	PD-L1 inhibitor	11 (13.7)	2 (20.0)	2 (10.5)	6 (22.2)	1 (4.2)
Treatment strategy	Monotherapy	41 (51.3)	7 (70.0)	9 (47.4)	14 (51.9)	11 (45.8)
	Combination therapy	39 (48.7)	3 (30.0)	10 (52.6)	13 (48.1)	13 (54.2)
PD-L1 expression	Not available	19 (23.8)	3 (30.0)	9 (47.4)	6 (22.2)	6 (25.0)
	< 1%	20 (25.0)	3 (30.0)	4 (21.1)	7 (25.9)	6 (25.0)
	1–49%	31 (38.8)	3 (30.0)	4 (21.1)	13 (48.1)	11 (45.8)
	≥ 50%	10 (12.5)	1 (10.0)	2 (10.5)	1 (3.7)	1 (4.2)
NLR	< 5	60 (75.0)	7 (70.0)	15 (78.9)	22 (81.5)	16 (66.7)
	≥ 5	20 (25.0)	3 (30.0)	4 (21.1)	5 (18.5)	8 (33.3)
Radiotherapy	No	67 (83.8)	5 (50.0)	16 (84.2)	22 (81.5)	24 (100.0)
	Yes	13 (16.2)	5 (50.0)	3 (15.7)	5 (18.5)	0 (0)

Table 2. Patient characteristics in the NSCLC cohort. *DR* dissociated response, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ECOG PS* Eastern Cooperative Oncology Group performance status, *BMI* body mass index, *NSCLC* non-small cell lung cancer, *AC* adenocarcinoma, *SCC* squamous cell carcinoma, *ICI* immune checkpoint inhibitor, *PD-1* programmed cell death protein-1, *PD-L1* programmed cell death ligand-1, *NLR* neutrophil-to-lymphocyte ratio.

CI: 0.162–0.742; $p = 0.006$), and a baseline NLR < 5 (adjusted HR: 0.206; 95% CI: 0.077–0.557; $p = 0.002$) had an independent effect on OS (Supplementary Table S3).

Independent validation of DR patient prognosis in the NSCLC cohort

We subsequently validated whether DR affected the prognosis of patients with DR in an independent cohort consisting of advanced NSCLC treated with ICIs (validation cohort). DR was identified in NSCLC patients with PR, SD, or PD at the first radiographical evaluation, with percentages of 13.0% (3/23), 18.2% (6/33), and 4.2% (1/24), respectively. Patients with DR had a comparable PFS (6.7 versus 7.8 months; $p = 0.087$) and OS (14.9 versus 14.1 months; $p = 0.317$) to those with SD but had a reduced PFS (6.7 versus 23.0 months; $p < 0.0001$) and OS (14.9 versus NR months; $p < 0.0001$) than those with CR/PR. However, inferior PFS (3.1 versus 6.7 months; $p = 0.008$) and OS (3.2 versus 14.9 months; $p = 0.042$) were validated in patients with real PD when compared with patients with DR (Fig. 3a,b).

Subsequent treatment for patients with DR

We next analyzed whether local treatment or continuous immunotherapy influenced the prognosis of patients with DR or true PD. In our cohort, all DR but not true PD patients were administered with continuous ICI therapy following the identification of progressed lesions. Four patients in the DR group and 6 in the real PD group received local treatments after the appearance of a progressed target or new lesions, including local radiotherapy (2 DR and 4 PD patients) and image-guided thermal ablation (2 DR and 2 PD patients). Local treatment seemed to have a positive influence on the outcome of patients with DR, with a median OS of 32.3 months for local treatment compared with 21.9 months for no local treatment ($p = 0.074$) (Fig. 2e). However, there was a similar median OS for true PD patients with local treatment compared with those without local treatment (4.8 versus 6.1 months; $p = 0.752$) (Fig. 2f). Even one patient remained PR, and 2 patients remained SD at the first radiographical evaluation after local treatment for patients with DR. Furthermore, real PD patients treated beyond progression did not present a significantly longer OS than those not treated beyond progression.

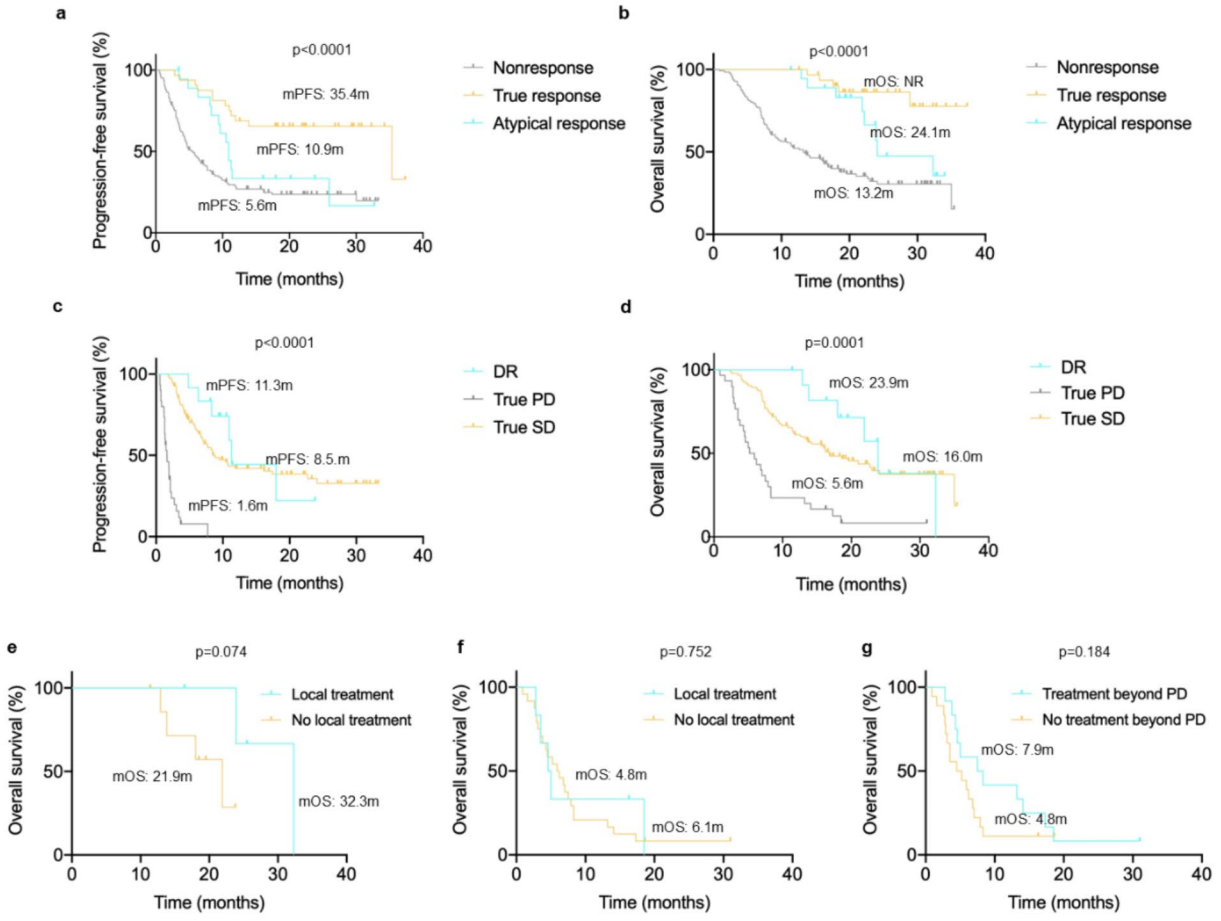

Fig. 2. Kaplan–Meier survival curves in patients with different treatment responses in the development cohort. (**a**, **b**), PFS and OS for patients with nonresponse, atypical response, and true response. (**c**, **d**), PFS and OS for patients with DR, true SD, and true PD. (**e–g**) OS in patients with DR or true PD according to local treatment or in patients with real PD according to treatment beyond progression .

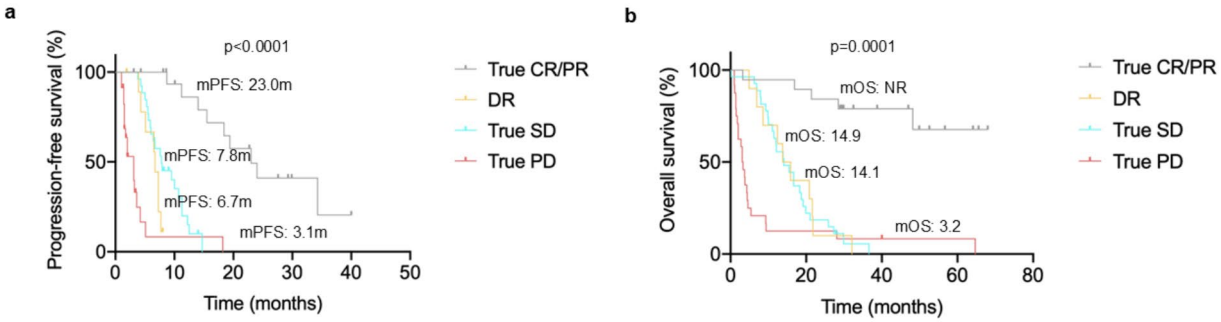

Fig. 3. Kaplan–Meier survival curves in patients with different treatment responses in the validation cohort. (**a**, **b**) PFS and OS for patients with DR, CR/PR, true SD, and true PD.

The median OS was 7.9 months for patients treated beyond progression versus 4.8 months for patients not treated beyond progression ($p=0.184$) (Fig. 2g).

Predictors of DR

We also evaluated demographic and clinical characteristics as predictive variables for DR. Unfortunately, univariable logistic regression analysis showed that no clinical characteristics remained significant predictors of DR (Supplementary Table S4) or PsPD (Supplementary Table S5). Patients with DR failed to have a different pretreatment and posttreatment absolute lymphocyte count, lymphocyte percentage, NLR, dNLR, and lactate dehydrogenase (LDH) levels compared with those with CR/PR, SD, or PD (Fig. 4a,c,d). The levels of circulating cytokines, including IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α, were not significantly different among these groups with diverse responses (Fig. 4b) (Supplementary Fig. S1). However, patients with PsPD ($p=0.002$) or CR/PR ($p=0.032$) had a higher posttreatment lymphocyte count than those with real PD (Fig. 4d). Posttreatment lymphocyte percentages were also higher in these patients with PsPD ($p=0.007$) or CR/PR ($p=0.0002$) than in patients with real PD. Patients with CR/PR also had a lower posttreatment NLR than those with real PD ($p=0.016$) (Fig. 4d).

Discussion

DR is characterized by some lesions shrinking and others growing and can be observed with ICI monotherapy or combination therapy[6]. In this study, DR was uncommon and identified in 6.8% of advanced or metastatic solid tumors and 12.5% of advanced NSCLC through evaluation of all lesions according to RECIST 1.1. DR was associated with intermediate survival outcomes, and the survival of DR patients was significantly longer than that observed in true PD patients in the cohort of patients with pantumor and NSCLC treated with ICIs.

The precise incidence of DR is unknown. The reported incidence of DR varies between 3.3 and 47.8%, depending on the definition of DR, different histological subtypes, treatment strategies, and specific radiological evaluation methods[7]. The rate of DR in our pantumor cohort was lower than that reported in previous NSCLC (17.7%) and melanoma (22%) cohorts[8,9], but was similar to that reported in a previous NSCLC study (8%) and a solid tumor study (3.3%)[10,11]. In particular, the definition of DR has a significant impact on the incidence of DR. The rate of DR occurrence could be overestimated because of the incorporation of true stable target lesions but not true progressive and responsive lesions for DR evaluation[12,13].In this study, we used the definition of DR by Bernard-Tessier et al., where DR was defined as a concomitant relative decrease greater than 30% in some tumor lesions and a relative increase greater than 20% in others (significant increase ≥ 5 mm in the sum of measures) or appearance of new lesions or deterioration of unmeasurable lesions[11]. Thus, DR can occur in patients with PR, SD, or PD at the first assessment by RECIST 1.1, with percentages of 13.8%, 5.9%, and 3.3%, respectively. Furthermore, specific immune-related radiological criteria such as immune RECIST (iRECIST) and immunotherapy-modified PERCIST (imPERCIST) that are used to capture PsPD should be considered to analyze DR[14,15]. According to the iRECIST criteria, the overall response for an individual patient with DR

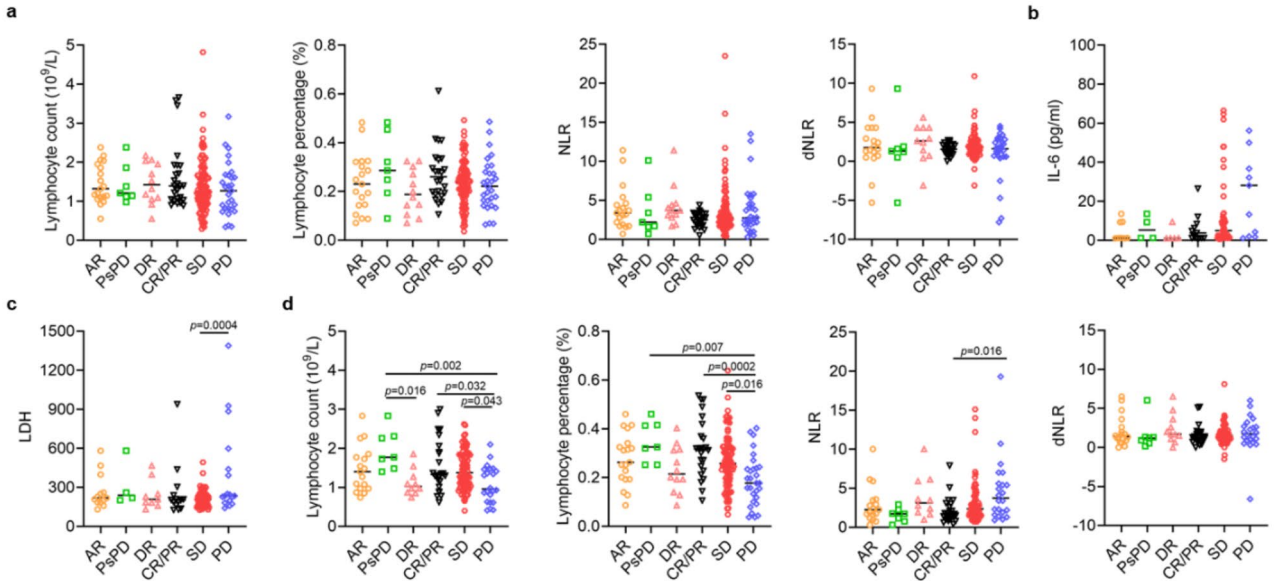

Fig. 4. Pretreatment and posttreatment circulating biomarkers in patients with AR, PsPD, DR, CR/PR, SD, and PD. (**a**) Pretreatment absolute lymphocyte count, lymphocyte percentage, NLR, and dNLR. (**b**) Pretreatment IL-6 levels. (**c**) Pretreatment LDH levels. (**d**) Posttreatment absolute lymphocyte count, lymphocyte percentage, NLR, and dNLR. *AR* atypical response, *PsPD* pseudoprogressive disease, *DR* dissociated response, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NLR* neutrophil-to-lymphocyte ratio, *dNLR* derived neutrophil-to-lymphocyte ratio, *LDH* lactate dehydrogenase, *IL-6* interleukin 6.

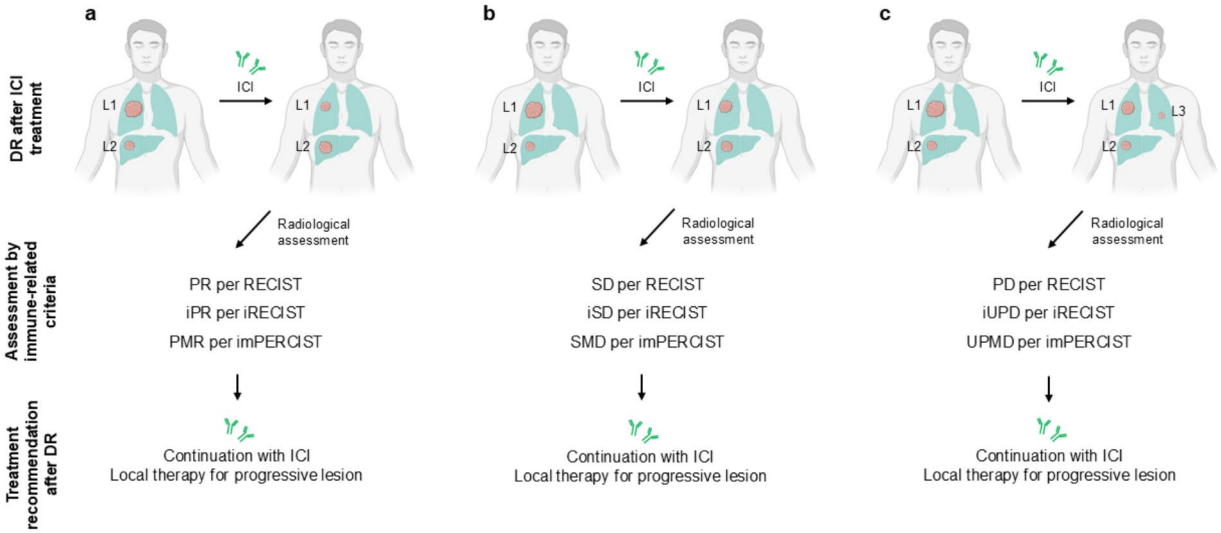

Fig. 5. Response assessment per immune-related criteria and subsequent treatment recommendations for DR patients. Although CR/PR and PD can be identified for different target lesions, the overall response for a patient could be PR, SD, or PD, which is dependent on the extent of the change for responding and nonresponding lesions. The criteria should be recommended to define DR per iRECIST and imPERCIST. (**a**) The overall evaluation is PR, iPR, or PMR, and the patient has both CR/PR (at least a 30% decrease in some lesions) and progressive lesions (at least a 20% increase in other lesions) simultaneously. (**b**) The overall evaluation is SD, iSD, or SMD, and the patient has both CR/PR (at least a 30% decrease in some lesions) and progressive lesions (at least a 20% increase in other lesions) simultaneously. (**c**) The overall evaluation is PD, iUPD, or UPMD, and the patient has CR/PR/SD lesions but with the appearance of one or more new lesions or apparent deterioration of nontarget lesions. Given that DR patients have a relatively favorable survival outcome compared with real progressive patients, these patients may benefit from continued ICI administration and local therapy for lesions with progression. *L1 and L2* target lesion, *L3* new lesion or nontarget lesion, *PR* partial response, *iPR* immune partial remission, *PMR* partial metabolic response, *SD* stable disease, *iSD* immune stable disease, *SMD* stable metabolic disease, *PD* progressive disease, *iUPD* immune unconfirmed progressive disease, *UPMD* unconfirmed progressive metabolic disease, *RECIST* Response Evaluation Criteria in Solid Tumors, *iRECIST* immuno-RECIST, *imPERCIST* immunotherapy-modified PERCIST, *ICI* immune checkpoint inhibitor.

could be iPR, iSD, or iUPD (Fig. 5). According to the imPERCIST criteria, the overall response for an individual patient with DR could be PMR, SMD, or UPMD. Overall, the kinetics and heterogeneity of the response to ICIs are insufficiently captured by RECIST 1.1. The DR patient cohort was enriched for RECIST SD and PD, and these responses were dynamic and could evolve over time after immunotherapy. In fact, our study showed that only 2 DR patients (16.7%) were identified at TP1 after immunotherapy. Therefore, in contrast to PsPD, a DR pattern can be captured at the later time points of disease development, rather than on the first follow-up assessment only.

In contrast to patients with PR/CR, patients with DR had more unfavorable survival outcomes when receiving immunotherapy in the pantumor and NSCLC cohorts. The survival of patients with DR was comparable to that reported for patients with concordant SD. However, patients with DR had prolonged survival and increased clinical benefit compared with those who developed true disease progression. In a retrospective study of advanced nivolumab monotherapy-treated NSCLC, patients with DR had significantly longer OS than those with concordant PD (46.9 versus 8.2 months, $p = 0.038$). The median OS was significantly longer in patients showing DR versus true PD in NSCLC patients who received anti-PD-1/PD-L1 inhibitors as second- or later-line treatments (14.0 versus 6.6 months, $p = 0.022$)[16].Thus, the clinical survival benefit of immunotherapy may be underestimated when patients have a DR but not true SD or PD by conventional radiological evaluation using RECIST 1.1.

In our study, all DR but not true PD patients were administered continuous ICI therapy following the identification of progressed lesions. Four (33%) patients in the DR group and 6 (21.4%) in the real PD group received local treatments after the appearance of progressed target lesions or new lesions. Local radiotherapy and image-guided thermal ablation were conducted in these patients. Local treatment seemed to have a positive influence on the survival outcome of patients with DR (median OS: 32.3 versus 21.9 months for patients with or without local treatment, respectively, $p = 0.074$). In a study of lung cancer treated with ICIs, the continuing ICI treatment post-DR cohort still had a significantly longer median post-DR OS than the discontinuing ICI treatment post-DR cohort (10.6 versus 4.3 months, $p = 0.016$)[17]. DR patients who continued treatment also had significantly longer OS than DR patients who did not continue PD-1 inhibitors combined with RT or PD-1 inhibitor monotherapy (15.7 versus 8.2 months, $p = 0.035$)[18]. Consistent with our findings, patients with DR who

received local therapies (radiotherapy, surgical resection, or arterial injection chemotherapy for liver metastasis) tended to have longer OS than the others who did not receive local therapies[19]. Recent retrospective studies showed that early surgical resection brought the potential benefit and remained the only definitive method to render patients free of disease, particularly for those whose adrenal glands were viewed as a potential sanctuary site of metastases in advanced colorectal cancer, melanoma, and renal cancer[20–24]. In another proof-of-concept study of advanced HCC patients who had stable or mixed responses to anti-PD-1 therapy, additional ablation increased the objective response rate and prolonged OS with tolerated toxicity[25]. Local consolidative therapies, including radiotherapy and microwave ablation, may produce durable abscopal effects associated with local therapy-induced systemic immune responses[26–29]. Because a majority of progressive lesions in DR patients manifest as oligometastases in target or new lesions, patients with DR should benefit from local treatment. In our study, real PD patients treated beyond progression did not have a significantly longer OS compared with those not treated beyond progression, which is different from a previous report where real progressive patients can survival benefit from ICI treatment beyond progression[11]. Thus, DR may be considered a useful clinical marker to make a clinical decision regarding whether one patient should continue or discontinue immunotherapy when he or she has progressive lesions by RECIST 1.1. In general, DR cannot be simply considered true PD and does not represent real secondary resistance to ICIs. If a patient is initially assessed as having DR, oncologists must perform the next assessment in the subsequent 4–8 weeks and continue on immunotherapy or/and consider local therapy for progressive lesions. Immediate discontinuing immunotherapy or direct switching to the next line of systematic treatment may not be a priority of treatment (Fig. 5).

The identification of potential predictive biomarkers, including clinical factors and laboratory findings for atypical responses either before or during treatment, remains an enormous unmet need in cancer immunotherapy[30]. In this study, no clinical characteristics were identified as predictors of DR. Patients with DR failed to have a different pretreatment and posttreatment absolute lymphocyte count, lymphocyte percentage, and NLR compared with patients with CR/PR, SD, and PD. Circulating cytokine levels by ELISA and LDH levels were comparable among patients with DR, CR/PR, SD, and PD. In fact, the circulating tumor DNA (ctDNA) profile and the pre- and posttreatment NLRs are helpful for accurately distinguishing between PsPD and true PD in NSCLC and metastatic melanoma with ICIs[31–33]. Even the level of plasma KRAS-mutated ctDNA by digital droplet PCR may act as an additional factor to discriminate PsPD from true PD for KRAS-mutated adenocarcinoma[34]. In a multicenter analysis of advanced HCC patients receiving atezolizumab plus bevacizumab, patients with CR/PR had lower NLR values at the start of the second course than those with SD/PD[35].In metastatic NSCLC with a PD-L1 TPS $\geq$ 50%, the baseline dNLR can differentiate treatment responders from nonresponders to first-line pembrolizumab, with an optimal dNLR cutoff of 2.6. Low dNLR was also associated with increased tumor T-cell infiltration and favorable outcomes[36]. The present study showed that patients with PsPD had a higher posttreatment lymphocyte count than those with real PD, and patients with CR/PR also had a higher posttreatment lymphocyte count and lower posttreatment NLR than those with real PD, which is in accordance with previous findings. On day 7 after initiation of treatment with PD-1/PD-L1 inhibitors in advanced NSCLC, the frequency of circulating $CD4^+CD25^+CD127^{lo}FoxP3^+$ Treg cells was significantly decreased compared with baseline in patients who experienced PsPD[37]. In 112 patients with metastatic melanoma treated with immune checkpoint inhibition, noninvasive PET/CT-based radiomics, especially in combination with the blood parameters LDH/S100, are promising biomarkers for the early differentiation of PsPD[38]. Unfortunately, some serological biomarkers and tumor tissues showing mixed responses were not available in this study and prevented further analysis of their predictive value for DR or other AR.

DR may only represent a mixed radiological or heterogeneous response to ICIs for individual lesions or organs but not an overall result of response within the same patient. Baseline serological or host-based biomarkers or their dynamics may fail to be used for the early differentiation of DR, which is different for the differentiation of PsPD and CR/PR, where a systematic immune response occurs instead of a simultaneous local immune response and immunosuppression in discordant sites. Although the mechanism of DR remained undetermined, intertumoral heterogeneity in metastatic organs showing a mixed response to immunotherapy altered the characteristics of TILs of discordant lesions even in the same patient, leading to a significant difference in survival outcomes[11]. Recent studies have shown that organ-specific features of the suppressive tumor microenvironment (TME) or heterogeneous TME of various organs potentially affect tumor growth and responses to immunotherapy. The response rate was dependent on the site of target lesions[39–41]. ICI monotherapy showed limited efficacy in patients with liver and bone metastasis but not lung and lymph node metastasis[12,40–43]. In patients with advanced HCC who received first-line lenvatinib plus anti-PD-1 antibodies, the ORR for patients with macrovascular tumor thrombi (54.5%) was higher than those with intrahepatic tumors (32.8%), extrahepatic lung metastases (37.5%), or lymph node metastases (33.3%)[44]. A clinical cohort study including NSCLC patients with liver metastases receiving immunotherapy indicated that one-third of patients showed DR, and 88.2% of DR presented with increasing liver lesions but decreasing pulmonary lesions[41]. Metastatic liver and pulmonary lesions had a similar genomic landscape, while the live lesions displayed a different TME from pulmonary lesions, with lower levels of immune activation and infiltration of natural killer and $CD8^+$ T cells[41,43]. Overall, the appearance of DR indicates a site-specific or organ-specific immune-related TME and an inconsistent response to immunotherapy within the same patient, providing a potential mechanism for different survival outcomes.

Our study had some limitations. First, this was a retrospective multicohort study of different cancer types. Second, heterogeneity of the population existed because we included solid and NSCLC patients receiving first-line, second-line, and later-line therapy, which may lead to bias. Third, some circulating biomarkers, including ctDNA, Tregs, and image-based radiomics, were not available. Finally, primary and metastatic lesions and tumors growing in specific organs and sites with distinct tumor microenvironments could influence the extent of responses to immunotherapy and lead to different therapeutic responses, including DR. Genetic alterations and the specific microenvironment of DR lesions should be prospectively investigated. However, adequate tumor

tissues showing a mixed response are not always available due to some difficulties of performing rebiopsy for physicians, including small metastatic DR lesions, nontarget DR lesions, and bleeding risk. Sometimes patients can refuse to receive a rebiopsy after immunotherapy. In a recent study including five patients with DR, only two patients consented to biopsies of the growing lesions, including cell block analysis of the pleural effusion and kidney biopsy[17]. These conditions prevented further analysis of the molecular and cellular mechanisms of DR in patients with anti-PD-1/PD-L1 inhibitors.

In conclusion, our real-world study indicates that DR, a type of mixed or heterogeneous radiological response, is uncommon in patients with advanced solid tumors and NSCLC treated with anti-PD-1/PD-L1 antibodies. The frequency of DR could be overestimated because of the incorporation of stable target lesions into DR evaluation. Conventional RECIST 1.1 does not adequately capture the dynamics and heterogeneity of DR, which may underestimate the survival benefit in patients with DR. iRECIST and imPERCIST may be considered to analyze DR. DR does not always mean acquired resistance to immunotherapy, and DR patients have a relatively favorable survival outcome compared with real PD patients. The clinical characteristics and relative frequencies reported here may help clinicians discern DR and decide the continuation of immunotherapy with or without local therapy to achieve a longer overall survival. However, obtaining tissue samples from lesions showing mixed responses for further expression and molecular analysis remains a challenge. Specific clinical treatment options, including continuous immunotherapy, additional local therapy, and intratumoral or tumor tissue-targeted immunotherapies, should be developed in specific tumor tissues for individual progressive lesions in patients with DR.

Data availability

The authors confirm that the supporting the findings of this study are available within the article and its supplementary materials.

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Author contributions

Y.P.G., Y.C., Y.H.G., X.J.L., X.Y.H., Y.C.C., and H.X., collected patient information clinical data. Y.K.Z. and B.C.W. performed experiments. B.C.W. and X.Y. critically reviewed the analysis. Y.P.G., Y.C., and Y.H.G. wrote this manuscript and prepared the figures. Y.P.G., X.Y., and J.W. conceived and wrote this manuscript and X.Y. and J.W. were the corresponding author. All the authors have read and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study was approved by the independent research ethics committee of The First Affiliated Hospital of Shandong First Medical University (NO: YXLL-KY-2022–059) and conformed to the principles of the Declaration of Helsinki.

Additional information

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