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Short Communication

Rare transformation from lung adenocarcinoma to sarcomatoid carcinoma mediates resistance to inhibitors targeting different driver oncogenes

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ABSTRACT

Background: Phenotypic transition is a common resistance mechanism of targeted therapy. While transformations from lung adenocarcinoma (LUAD) to small-cell lung cancer or squamous-cell carcinoma have been extensively studied, the conversion into sarcomatoid carcinoma (SC) is rarely reported.

Methods: Genetic and histological examinations were systematically performed on tumor re-biopsy samples obtained from patients with advanced EGFR-mutant LUAD who progressed on EGFR-tyrosine kinase inhibitors (TKIs). EGFR wild-type patients were also identified who underwent the rare transformation from adenocarcinoma to SC following the ineffectiveness of inhibitors that target distinct driver oncogenes. Furthermore, we also retrospectively collected 42 cases diagnosed with primary pulmonary SC as a comparison cohort to comprehensively characterize the biological events and clinical outcomes of transformed SC.

Results: The sarcomatoid transformation mediated drug resistance in 2.5 % and 4.8 % of patients after failure on the first/second, and third-generation EGFR-TKIs. Transformation of sarcomatoid carcinoma is characterized by a higher frequency of *TP53, RB1*, and *MET* genetic alterations compared to cases lacking histological transformation; the PI3K signaling pathway was also significantly activated. Fifteen individuals were identified with a rare transition from adenocarcinoma to SC, consisting of seven cases with *EGFR*-activating mutations and eight cases without *EGFR* mutations. All sarcomatoid-transformed samples not only retained their original driver mutations but also shared specific genetic alterations with primary LUAD. Moreover, transformed sarcomatoid carcinomas mimic the primary SC in terms of immunochemical and molecular features.

Conclusions: The transformation from lung adenocarcinoma to SC is a resistance mechanism wildly applied to inhibitors targeting different driver oncogenes. Immunotherapy plus chemotherapy shows potential to benefit patients with sarcomatoid transformation and warrants further study in larger cohorts.

1. Introduction

The treatment approach for non-small cell lung cancer (NSCLC) has been significantly transformed by targeted therapy directed at oncogenic driver abnormalities, specifically somatic mutations in the genes that encode the epidermal growth factor receptor (EGFR).[1,2] Notwithstanding the remarkable clinical responses, drug resistance inevitably emerges in a clinical setting.[3] EGFR secondary mutation, activating bypass signaling pathway, and the histologic transformation collectively constitute the primary resistance mechanism leading to treatment failure.[3-5] Of note, the diagnosis of phenotype change is hampered by the invasive and unconventional use of tumor tissue repeat biopsy following the failure of EGFR-tyrosine kinase inhibitors (TKIs) treatment. Extensive research has been dedicated to examining the histologic transition of EGFR mutant adenocarcinoma to small-cell lung cancer (SCLC) or squamous cell carcinoma (SCC).[6,7] In contrast, its transformation into sarcomatoid carcinoma (SC) continues to be a subject that requires additional investigation. In addition, despite the minimal clinical data, morphologic changes have also been reported in non-EGFR-mutated adenocarcinoma.[8,9] This suggests that phenotypic switch may constitute a universally applicable resistance mechanism in targeted therapy.

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Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of NSCLC with a prevalence of ~0.4 %.[10] SC is characterized by a high degree of malignancy, rapid progression, and poor prognosis.[10] In patients diagnosed with primary SC, an effective treatment modality is an unmet and urgent need due to the rapid recurrence following surgical resection and the low responsiveness to chemotherapy.[11,12] Significantly, the sarcomatoid transformation of epithelial neoplasms signifies the epithelial-mesenchymal transition (EMT) within the neoplastic cell; this is a well-established intrinsic resistance mechanism in EGFR-mutant NSCLC.[4] The majority of information on EMT-mediated drug resistance was derived from cell line studies.[4,13,14] Sarcomatoid transformation confirmed by pathological examination in clinical practice is occasionally reported due to the infrequent use of repeat biopsies.

In the current study, we performed in-depth genetic and histological analyses of tumor repeat biopsies from patients with advanced EGFR mutant lung adenocarcinoma (LUAD) who had progressed on first/second and third-generation EGFR-TKIs treatment. This systematic exploration into resistance mechanisms enables a deeper understanding of the frequency of sarcomatous transformation and the high-risk genetic factors associated with histological transformation. Furthermore, we shed new light on the transformed SC among patients with different driver oncogenes and compared their biological characteristics with the primary SC.

2. Materials and methods

2.1. Enrolled patients

The study cohort comprised all consecutive EGFR-mutant lung cancer patients who developed resistance to EGFR-TKIs (including the first, second, and third generations) and underwent a standard post-resistance biopsy of their tumor tissue. These patients were registered in the Sun Yat-sen University Cancer Center (SYSUCC) personalized lung cancer database between June 2019 and June 2023. The present study examined resistance mechanisms directed by phenotypic and genotypic alterations. Therefore, cases in which resistance mechanisms were identified solely through liquid biopsy and pleural aspiration were ruled out.

In light of the infrequent occurrence of histological transformation in non-EGFR mutant NSCLC, additional screening was conducted on consecutive stages IIIB/C or IV NSCLC patients with other oncogenic genetic alterations who underwent SC transformation after progression on targeted therapy. Pairwise examinations of samples before and after transformation were performed to determine which immunohistochemical and genetic alterations were associated with histologic evolution. We also retrospectively analyzed a cohort of patients diagnosed with primary pulmonary SC who underwent next-generation sequencing (NGS) testing at baseline as a comparison group, to characterize the biological events of transformed SC in a comprehensive manner.

2.2. Data collection and outcomes of interest

In EGFR-activating mutant NSCLC following the failure of first/second or third-generation EGFR-TKIs, the outcomes of interest comprised the frequency of sarcomatoid transformation, and the high-risk genetic factors associated with histological transformation. In addition, this study underscored variations in pathological, immunohistochemical, and genetic characteristics across patients prior to and subsequent to transformation. Furthermore, a comparison was also made between the transformed and primary SC in terms of their molecular and immunohistochemical properties.

Patients' baseline clinicopathologic characteristics (including age, gender, smoking status, and clinical TNM stage) and treatment histories were retrospectively collected from digital medical records. The outcomes of interest included best overall response (BOR) and progression-free survival (PFS). Two senior oncologists independently assessed the radiographic tumor response following the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) guideline. Computed tomography (CT) scans are typically performed on patients within the initial month following anti-cancer treatment. Subsequently, imaging is routinely scheduled every 8–12 weeks to assess disease progression. PFS is the time interval from initiating treatment to the first documented disease progression or death from any cause, whichever occurred first.

2.3. Genetic and immunohistochemical analyses

NGS testing was performed by SYSUCC Personalized Diagnostics Panel, in which a hybrid captured-based NGS assay (Gene Plus-Beijing, China) covered the genomic sequences of 1021 cancer-related genes. Genomic alterations assessed in the SYSUCC Personalized Diagnostics Panel included single nucleotide variants (SNVs), short insertion and deletion (Indel), copy number variation (CNV), and rearrangement. Targeted capture sequencing required a minimal mean adequate depth of coverage of 300 × in tissue samples. The sequencing coverage and detailed description are summarized in Supplementary Table 1. MET copy number was evaluated via fluorescence in situ hybridization (FISH).

Histopathologic markers, including programmed cell death protein-ligand 1(PD-L1), cytokeratin (CK), cytokeratin 7 (CK7), thyroid transcription factor 1 (TTF-1), NapsinA, Vimentin, and neuroendocrine markers (e.g. CD56, CgA, and Syn), were independently evaluated by two pathologists.

2.4. Statistical analysis

All statistical analyses were performed in the R-4.3.1 software, with all tests being two-sided and $P < 0.05$ being statistically significant. Phylogenetic trees were constructed according to all detected alterations, including SNVs, small Indels, and CNVs.[15] Shared genetic alterations between primary adenocarcinoma and transformed sarcomatoid carcinoma were located in the tree trunk, and specific alterations were in the tree branch. The length of the trunk and branch does not represent the number of variations. All phylogenetic trees were drawn manually with GraphPad 8.0 software.

3. Results

3.1. Genotypic and phenotypic mechanisms of EGFR-TKIs resistance

After progressing on first/second generation and third generation EGFR-TKIs, 80 and 115 patients with advanced EGFR mutant LUAD underwent standard tumor re-biopsy, respectively. The detailed baseline clinic-pathological characteristics are summarized in Supplementary Tables 2 and 3. For patients receiving first/second generation EGFR-TKIs, EGFR p.T790 M mutation (43.8 %) and the development of MET (11.2 %), PIK3CA (10.0 %), CDK4/6(6.3 %) and CCND1/CCNE1 (6.3 %) genetic alterations composed the majority of acquired resistance mechanisms at the genotypic level (Fig. 1A). Meanwhile, a histological transformation from LUAD to SCC (6.3 %), SCLC (3.8 %), or SC (2.5 %) was observed in 10 of 80 cases (12.5 %). Of note, genotypic and phenotypic alterations may coexist within a single instance of the resistant tumor.

Similarly, for patients after failure of the third-generation EGFR-TKIs, we identified the well-established molecular mechanisms of acquired resistance: EGFR-dependent resistance mechanism including EGFR p.C797X (12.2 %) and EGFR p.L718Q (2.7 %); and EGFR-independent mechanism including MET amplification (14.8 %), PIK3CA mutation (14.8 %) and ERBB2 amplification (11.3 %) (Fig. 1B). A greater incidence of histological conversions (~20.0 % of cases) was observed in patients on third-generation EGFR-TKIs compared to patients progressing on first/second-generation EGFR-TKIs. These conversions included transformed SCLC (11.3 %), SCC (5.2 %), and SC (4.3 %). The overlap of the genotypic and phenotypic changes could also be observed in certain patients resistant to the third-generation EGFR-TKIs.

Fig. 1. Genotypic and phenotypic mechanisms of EGFR-TKIs resistance. (A, B) The frequency of observed drug resistance mechanisms. The pie chart depicts the prevalence of observed mechanisms of resistance to first/second-generation EGFR TKIs in 80 patients (A) and third-generation EGFR-TKIs in 115 patients (B) with NSCLC re-biopsied at the time when resistance was acquired. (C) Genomic landscape of re-biopsy tumor samples after failure on previous EGFR-TKIs and comparison in the heterogeneity of genetic features between patients with and without histological transformation. (D) Comparison in the mutation rate of frequent genetic alterations among patients with different histological transformation status. Amp, amplification; CN, copy number; Del, deletion; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; TKI, tyrosine kinase inhibitor.

3.2. Genomic profiles of EGFR mutant patients with and without post-transformation

We compared the distinctive genomic characteristics of patients who underwent histological transformation to those who did not, using re-biopsy tumor samples obtained after EGFR-TKIs failed (Fig. 1C). *TP53, MET, PIK3CA, LRP1B, RBM10*, and *RB1* were the most frequent genomic abnormalities in the resistant setting. Notably, patients who underwent sarcomatoid transformation exhibited a greater frequency of *TP53* and *RB1* mutations than those who did not undergo histological transformation, mirroring the pattern observed in SCLC transformation (Fig. 1D). Furthermore, a considerable number of *MET* genetic alterations were observed in both patients undergoing SCC transformation and sarcomatoid transformation. PI3K signaling pathways involving mutations in *PIK3CA, PTEN*, and *MTOR* were also significantly activated in transformed sarcomatoid carcinomas, along with an abundance of *FAT2, CDKN2A*, and *IKZF1* genetic alterations.

3.3. Clinicopathologic features of lung adenocarcinoma with sarcomatoid transformation

Besides the seven patients mentioned above with EGFR activating mutation who underwent sarcomatoid transformation, the other eight patients harboring non-EGFR oncogenic-addicted mutations diagnosed with transformed SC were also identified. Among the enrolled 15 patients [median age, 56 years (IQR, 45–66)], 8 (53.3 %) patients were males, and five patients (33.3 %) had a smoking history. All patients were diagnosed with stage IV or recurrent, and extra-thoracic metastases were recorded in 11 out of 15 (73.3 %) patients. After sarcomatoid transformation, tumor size ranged from 22 to 81 mm in maximum diameter, with a mean diameter of 45 mm. The interval from the initial diagnosis of lung adenocarcinoma to pathologically confirmed sarcomatoid transformation ranged from 3.3 to 47.9 months, with a median interval of 14.7 months. The detailed clinicopathologic features of patients who developed sarcomatoid transformation were summarized in Table 1.

There were 13 patients with actionable targeted genetic alteration who underwent sarcomatoid transformations after progressing on targeted therapy. Three patients who exhibited *EML4-ALK* fusion were prescribed ALK-TKIs, with two patients receiving Ensartinib and one patient receiving Crizotinib. Three patients who had EGFR exon 19 deletion (19del) were treated with Aumolertinib, an EGFR-TKI of the third generation (two cases received it as a first-line treatment and one as a second-line treatment following progression on Gefitinib). Three patients with EGFR L858R mutation received EGFR-TKIs (including two cases with Osimertinib and one with Gefitinib). In addition, one patient with rare *EGFR-RAD51* fusion received Afatinib; one patient with *de novo MET* amplification received Crizotinib; one patient with *KIF5B-RET* fusion was

Table 1
Clinical information of advanced lung adenocarcinoma cases with sarcomatoid transformation upon inhibitor treatments targeting different driver oncogenes.

Case	Sex	Age, years	Smoking history	Site	Size, mm	TNM stage	Extra-thoracic metastasis	Oncogenic driver	First-line therapy	Interval time, months
1	Male	66	No	Right	43	IV	Bone; Liver; Kidney; Adrenal gland	MET amplification	Crizotinib	31.17
2	Female	43	No	Right	38	IV	Bone	EGFR-RAD51 fusion	Afatinib	19.9
3	Female	53	No	Left	60	IV	Brain; Bone	EGFR L858R	Gefitinib	6.67
4	Male	54	Yes	Left	31	IV	Brain	EML4-ALK fusion	Crizotinib/Ceritinib	35.53
5	Male	58	Yes	Left	81	IV	Bone; Adrenal gland	KIF5B-RET fusion	Pralsetinib	5.4
6	Male	64	Yes	Left	34	IV	Bone	CD74-ROS1 fusion	Crizotinib	13.03
7	Female	72	No	Right	67	IV	No	EGFR L858R	Osimertinib	10.83
8	Female	44	No	Right	42	IV	No	EML4-ALK fusion	Ensartinib	5.97
9	Female	44	No	Left	52	IV	No	EML4-ALK fusion	Ensartinib	46
10	Male	49	Yes	Right	45	IV	Brain; Adrenal gland	EGFR L858R; *De novo* EGFR T790M	Osimertinib	16.33
11	Male	58	No	Right	46	IV	Brain; Bone	NF1	Chemotherapy	47.87
12	Male	68	Yes	Left	UK	IV	Bone	KRAS G12C	Anlotinib	3.27
13	Female	66	No	Left	69	IV	Bone; Liver; Kidney	EGFR 19del	Aumolertinib	4.3
14	Male	59	No	Right	22	IV	Liver; Brian	EGFR 19del	Aumolertinib	3.3
15	Female	59	No	Right	45	IV	No	EGFR 19del	Gefitinib; Aumolertinib	25.87

Abbreviations: TNM, tumor node metastasis; UK, unknown.

administered with Pralsetinib; and one patient with *CD74-ROS1* fusion took Crizotinib as first-line treatment. Besides the actionable targeted therapy, chemotherapy and multi-target therapies also could contribute to the sarcomatoid transformation. One patient with *TP53* missense mutation and *NF1* frame-shift mutation received chemotherapy but suffered from progression eventually, and re-biopsy revealed phenotypic changes from LUAD to SC. Also, one case harboring KRAS G12C mutation took Anlotinib as salvage therapy but experienced a histologic switch.

We also systemically reviewed the previously published reports and summarized 19 cases that developed phenotypic transformation from adenocarcinoma to SC and two cases with sarcomatous transformation (Supplementary Table 4). Integrating previously reported data and our cases, we found that sarcomatoid transformation frequently occurred in patients with *EGFR* 19del and *EGFR* L858R, followed by *EML4-ALK* and *ROS1* rearrangements.

3.4. Underlying immunohistochemical and genomic changes in the histologic evolution from LUAD to SC

Before the sarcomatoid transformation, immunohistochemistry showed that all cases were strongly positive for CK and CK7. In contrast, after transformation, all cases were strongly positive for Vimentin and negative for TTF-1 and NapsinA, revealing a linear evolutionary model from epithelial to mesenchymal phenotype (Supplementary Fig. 1A). Through NGS testing on paired pre-transformation and post-transformation tumor samples, we investigated the shared and private alterations of primary adenocarcinoma and transformed SC to track the genetic changes reflecting phenotypic change. A heatmap was depicted showing each patient's shared and private variations, and the corresponding phylogenetic tree was constructed (Fig. 2A). All sarcomatoid-transformed samples not only retained their original driver mutations but also shared specific genetic alterations with primary LUAD. The NGS results of the primary and recurrent lesion suggest a linear evolutionary pattern from primary LUAD to SC and further the relapsed SC in these patients.

In addition, 42 primary SC with available NGS results were enrolled as a comparison cohort. Most cases arise in male patients (85.7 %), particularly smokers (73.8 %), with a median tumor size of 55.0 mm. Similar clinical characteristics were found between patients with sarcomatoid transformation and primary SC (Supplementary Table 5). In terms of immunohistochemical characteristics, sarcomatoid tumors transformed from adenocarcinoma resembled primary SC (Supplementary Fig. 2). Next, we compare the genomic landscape of lung cancer with transformed SC and primary SC to comprehensively uncover the underlying genetic changes that shape the histologic transformation (Fig. 2B). Nine of 15 patients underwent NGS testing after sarcomatoid transformation. The genomic characteristics of patients undergoing sarcomatoid transformation were remarkably similar to those with primary SC. Of note, unlike primary PSC, the *EGFR* mutation rate in sarcomatoid tumors transformed from adenocarcinoma was high because they retained their founder *EGFR* mutations after histologic evolution. In contrast, the *KRAS* mutation rate was higher in the primary PSC due to the limited use of targeted therapy against *KRAS*. Among all cases with SC phenotype, *TP53* (68.6 %) was the most common genetic alteration, followed by *LRP1B* mutation (19.6 %) and *RB1* mutation (17.6 %). Notably, the PI3K signaling pathway involving *NF1* (17.6 %), *PIK3CA* (15.7 %), and *NF2* (9.8 %) genetic alteration were found to be significantly activated. Besides, a notable prevalence of *MET* exon 14 skipping or amplification (11.8 %) was observed in these patients, which underscores the likelihood that tumors with sarcomatoid transformation mimic primary SC through acquiring genetic mutation. In addition, one patient in our cohort developed increased *MET* gene copy numbers after progression on EGFR-TKIs treatment (Supplementary Fig. 3). Integrating previously reported data, we found that MET activation is a common phenomenon in the case of sarcomatoid transformation (Supplementary Table 6).

However, the tumor mutation burden in tumors with sarcomatoid was relatively lower than in those with SC, which could be attributable to the tumor transforming from adenocarcinoma to SC (Fig. 2C). Nevertheless, no significant difference was observed in patients with actionable driver mutations irrespective of primary or transformed SC. Tumor samples from eight of 15 patients with sarcomatoid transformation and 13 of 42 patients with primary PSC were stained and assessed for PD-L1 expression level. Tumors with sarcomatoid transformation displayed relatively high PD-L1 expression levels compatible with PSC (Fig. 2D).

3.5. Clinical benefit of immunotherapy plus chemotherapy in patients with SC after failure of targeted therapy

Considering that the proportion of positive *EGFR/ALK* mutations in primary and transformed SC may be not well balanced, we chose patients with actionable driver mutations for further analysis to avoid potential bias. However, due to the limited sample size of patients

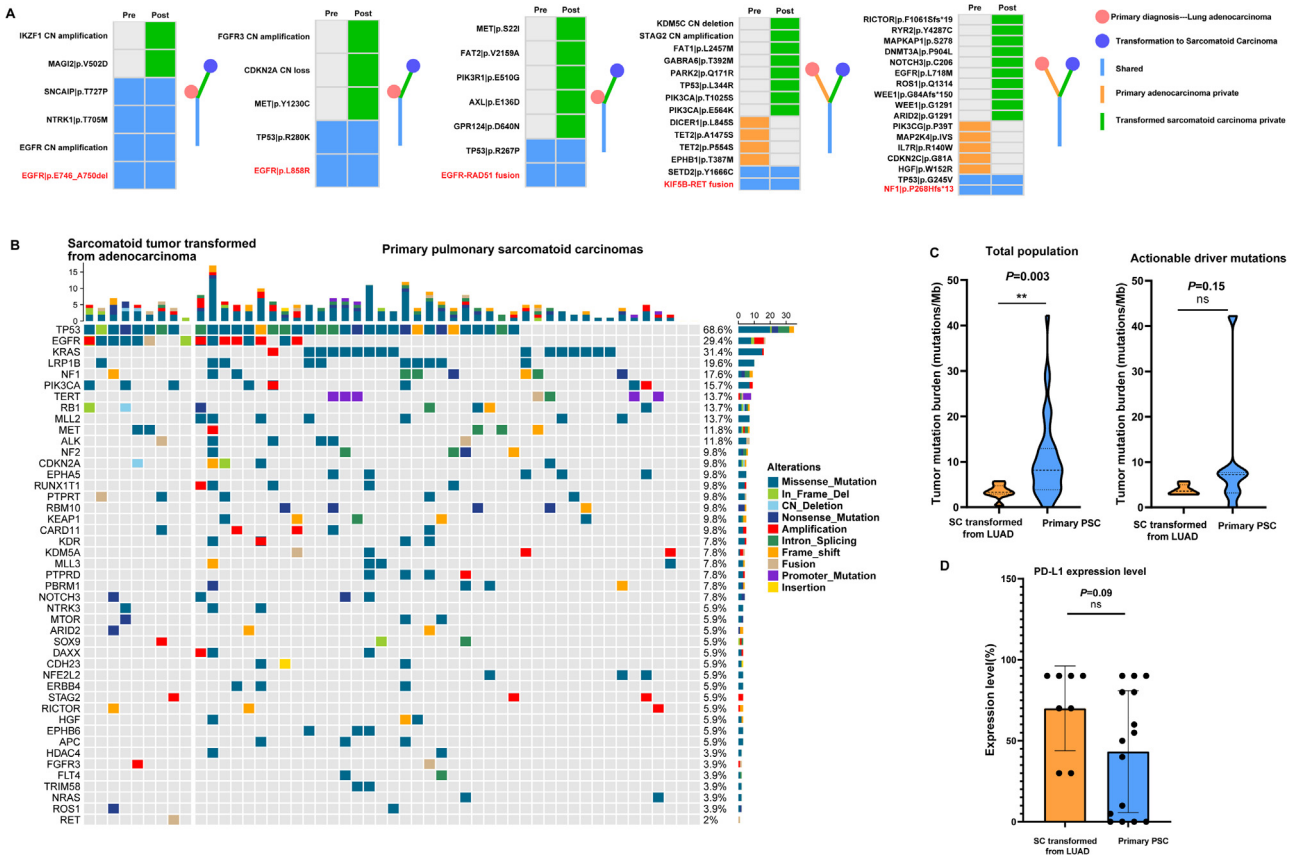

Fig. 2. Underlying genomic changes in the histologic evolution from lung adenocarcinoma to sarcomatoid carcinoma. (A) The shared and private alterations of primary adenocarcinoma and transformed sarcomatoid carcinoma in five patients with NGS testing of paired pre- and post-transformation tumor samples. A heatmap was constructed to show shared and private variations for each patient and the corresponding phylogenetic trees. Driver variations are marked by dark red. (B) Comparison in the genomic landscape between lung cancer with sarcomatoid transformation and primary sarcomatoid carcinoma. (C) Comparison of the tumor mutation burden of patients with sarcomatoid transformation and primary sarcomatoid carcinoma. Left, total population; Right, patients with actionable driver mutations. (D) Comparison of the PD-L1 expression level of patients with sarcomatoid transformation and primary sarcomatoid carcinoma. CN, copy number; LUAD, lung adenocarcinoma; ns, not significant; SC, sarcomatoid carcinoma; PD-L1, programmed cell death protein-ligand 1; PSC, pulmonary sarcomatoid carcinoma.

with complete follow-up data after progression on targeted therapy, we could not perform statistical analysis. For patients with advanced PSC, three patients achieved partial response to the immunotherapy plus chemotherapy treatment after failure of matched targeted therapy (Fig. 3A). Meanwhile, a trend favoring improved chemoimmunotherapy treatment outcomes as opposed to chemotherapy was found in the five *EGFR* mutant patients with complete efficacy data after experiencing sarcomatoid transformation. Also, we present one patient with rare *EGFR* fusion who initially responded to Afatinib but acquired resistance because of sarcomatoid transformation. In the second-line treatment, this patient received immunotherapy plus chemotherapy lasting 29 months until the last follow-up (Fig. 3B).

4. Discussion

The conversion of LUAD to SC is exceedingly uncommon; nevertheless, it signifies a universal mechanism by which targeted therapies are thwarted.[6,8] The present study performed comprehensive genetic and histological analyses of tumor biopsies from patients with EGFR-TKIs resistant LUAD harboring *EGFR* mutations. Sarcomatoid transformation was found to confer drug resistance in 2.5 % and 4.8 % of patients, following the failure of first/second and third-generation EGFR-TKIs, respectively. Furthermore, our study highlighted that sarcomatoid transformation could mediate resistance to inhibitors targeting different driver oncogenes, including *EGFR* and non-*EGFR* alteration (e.g., *ALK/ROS1/RET* fusion and *MET* amplification). Besides, sarcomatoid-transformed samples not only retained the original oncogenic drivers and displayed shared specific alterations with primary LUAD but also exhibited immunohistochemical and genomic characteristics that resembled those of PSC. Immunotherapy plus chemotherapy may provide benefits for patients who have undergone a phenotypic transition from adenocarcinoma to SC.

In general, resistance mechanisms mediated by the complex EMT process have been systematically and extensively investigated in cancer cell line studies.[13,14] Nevertheless, EMT has not yet been well validated on histologic examination in the clinical setting. To bridge this knowledge gap, the present study first reported the frequency of sarcomatoid transformation that resulted in the failure of EGFR-TKI treatment. Indeed, the histological transformation from LUAD into SC is extremely rare in patients following the failure of first/second-generation EGFR-TKIs. In contrast, its frequency increased with third-generation EGFR-TKI treatment. It is hypothesized that the increased selective pressure resulting from the enhanced inhibitory activity along with the extended treatment duration of third-generation EGFR-TKIs versus first/second-generation EGFR-TKIs could partly explain this disparity. Several possible mechanisms of histologic transformation after treatment have been revealed, encompassing pluripotent cancer stem cell differentiation, intratumor heterogeneity, and additional acquired mutations of certain genes.[16] As outlined in the previous reports, the TP53 and RB1 inactivation increases the risk of SCLC transformation.[17-19] In comparison to non-histological transformation, *TP53* and *RB1* genetic modifications are frequently observed in sarcomatoid transformation, which resembles SCLC transformation. Moreover, PI3K signal pathways involving

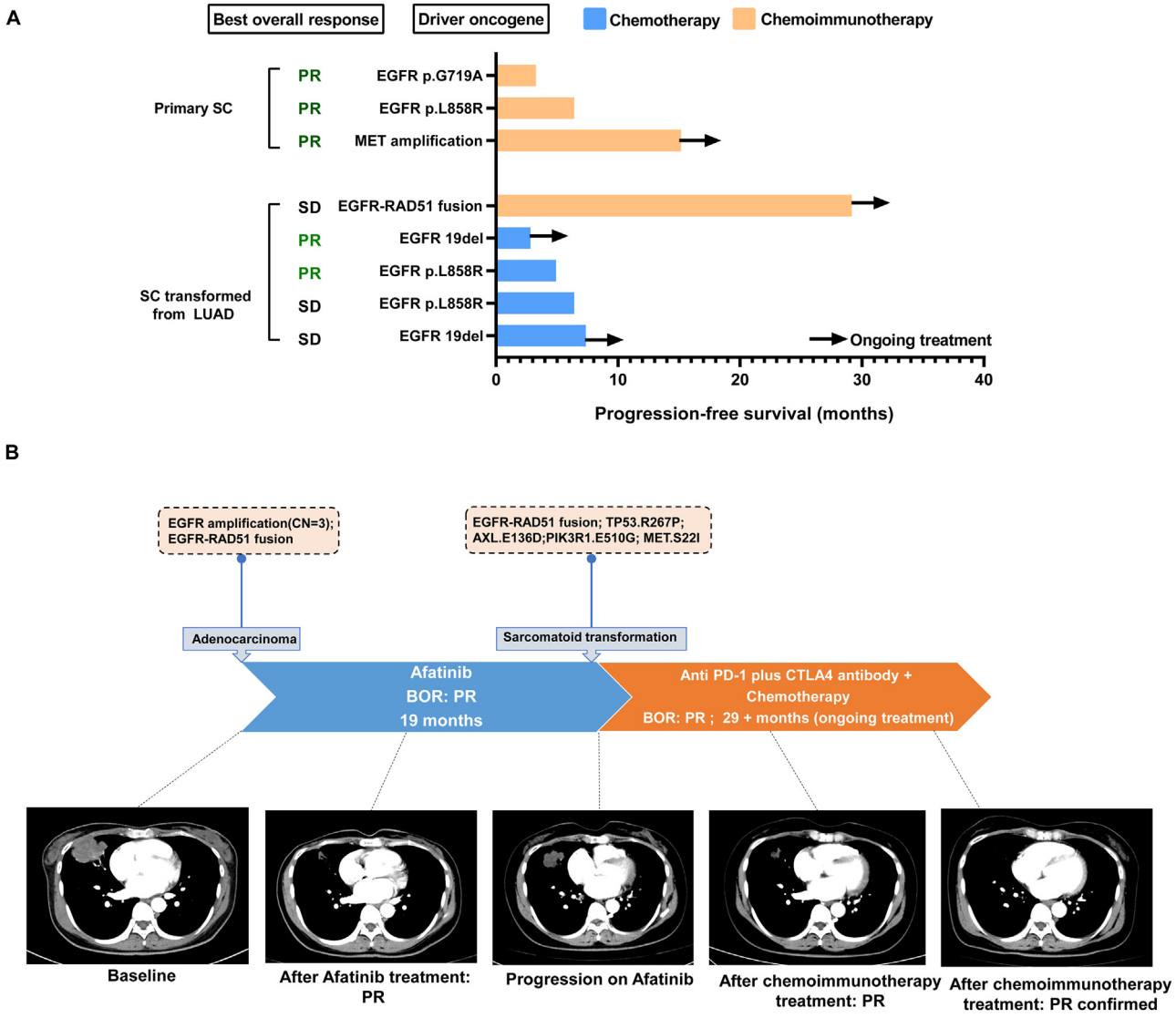

Fig. 3. Clinical benefit of immunotherapy plus chemotherapy in patients with sarcomatoid carcinoma after failure of targeted therapy. (A) Swimmer plot showed the treatment outcome of chemotherapy or immunotherapy after progression on targeted therapy for patients with primary sarcomatoid carcinoma (upper) or with sarcomatoid carcinoma transformed from lung adenocarcinoma (lower). (B) Case presentation: lung adenocarcinoma with sarcomatoid transformation upon EGFR-TKIs treatment targeting rare EGFR fusion. CN, copy number; LUAD, lung adenocarcinoma; PR, partial response; SC, sarcomatoid carcinoma; SD, stable disease.

PIK3CA, *PTEN*, and *MTOR* mutation were highly activated in transformed SC. It deserves to be mentioned that PI3K-activating pathways could trigger the initiation of the EMT process and play a central role in cancer cell lines.[20,21] However, the underlying genetic abnormality that drives lung adeno-to-sarcomatoid transition and identifying therapeutic strategies to overcome or prevent it requires more clinical confirmation and exploration.

Transformed SC mimic the PSC with similar biological events. However, the rare occurrence of PSC has substantially limited the definition of its genetic and molecular basis, thus hampering the elaboration of PSC-oriented clinical trials and the development of PSC-tailored treatment strategies.[22,23] Of note, surgical operation is currently considered a primary approach to treat PSC, despite the rapid recurrence. Yet, patients with sarcomatoid transformation often have lost the opportunity for surgery due to the advanced course of the disease. Encouragingly, rich immune infiltrates and high levels of PD-L1 define SC as a type of "hot" tumor.[24] Compared to traditional platinum-based chemotherapy, immunotherapy strikingly prolongs PFS and improves tumor response for patients with SC.[25,26] The present study also provides evidence that immunotherapy plus chemotherapy showed its potential to benefit patients with primary SC after the failure of matched targeted therapy or transformed SC original from LUAD. With the wide application of NGS testing, a higher frequency of *MET* exon 14 splicing site mutations (4.9 %to 31.8 %) has been reported in SC, and Savoltinib targeting *MET* mutation has shown potent treatment efficacy.[27,28] *MET* amplification plays a vital role in sarcomatoid transformation, thereby offering promising avenue for optimizing treatment strategies.

The retrospective nature and single-center study are obstacles. However, the present study represented the largest cohort of patients from adenocarcinoma into SC and compared the pathological and molecular features of primary SC with sarcomatoid transformation. Large-scale investigations are still warranted, especially the analysis of molecular characteristics and PD-L1 expression level in paired pre- and post-transformation samples and the exploration of more effective therapeutic strategies.

5. Conclusions

The findings of this study represent a breakthrough in the comprehension and management of targeted therapy resistance mediated

by sarcomatoid transformation. Although transformation into sarcomatoid is rare (<5 % in *EGFR* mutant LUAD), it confers a common resistance mechanism to inhibitors targeting different driver oncogenes. SC-transformed samples retain their founder mutations and are associated with a high frequency of *TP53, RB1*, and *MET* mutation as well as PI3K activating signal pathways. Transformed SC mimic the PSC with comparable immunochemical and molecular features. Chemoimmunotherapy showed the potential to benefit patients with SC yet warrants further confirmation and investigation on the transformed group, especially in patients with classical *EGFR* exon 19 deletion or L858R mutation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical statement

This study was conducted in compliance with the principles of the Declaration of Helsinki Declaration (as revised in 2013) and approved by Sun Yat-sen University Cancer Center IRB (approval number: B2023–468–01).

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Consent for publication

The patients whose medical images are presented in this manuscript provided consent for publication of their medical images for the manuscript. Only de-identified data and images are used in this review.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Author contributions

W.F. supported the conceptualization. L.P. and W.Z. curated the data. L.P. and W.Z conducted the formal analysis. W.F acquired the funding. L.P. and Y.H. performed the investigation and methodology. L.Z. and W.F. supported the resources. W.F administrated, supervised and validated the project. All of the authors visualized and wrote the original draft and revised and edited the revision. The work reported in the paper has been performed by the authors unless specified in the text.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jncc.2024.12.005.

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