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Fawzi Abu Rous
Henry Ford Health, faburo1@hfhs.org

Radhika Gutta
Henry Ford Health, rgutta1@hfhs.org

Pin Li
Henry Ford Health, pli3@hfhs.org

Balazs Halmos

Shirish M. Gadgeel
Henry Ford Health, sgadgee1@hfhs.org

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SHORT COMMUNICATION

Pembrolizumab in Combination with Chemotherapy in Patients with ERBB2-Mutated Non-Small Cell Lung Cancer

Fawzi Abu Rous[1] · Radhika Gutta[2] · Pin Li[3] · Balazs Halmos[4] · Shirish Gadgeel[1]

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Abstract

Background Human epidermal growth factor receptor 2 (ERBB2) mutation is a known oncogenic driver mutation in a small proportion of non-small cell lung cancers (NSCLCs). Many targeted therapies are being developed and investigated for the treatment of ERBB2-mutated NSCLC, however none of these agents have yet been approved as a front-line treatment. Thus, platinum-based chemotherapy with or without immunotherapy remains the preferred first-line therapy for ERBB2-mutated NSCLC.

Objective We aimed to study the activity of chemotherapy in combination with pembrolizumab as first-line treatment in patients with stage IV ERBB2-mutated NSCLC.

Patients and Methods We retrospectively identified five patients with ERBB2-mutated NSCLC treated with carboplatin, pemetrexed and pembrolizumab as first-line therapy between 2018 and 2020. Overall survival (OS), progression-free survival (PFS), and time to next therapy (TTNT) were summarized by Kaplan–Meier methodology using R 4.0.5 with median time to event. Response rates defined by partial response (PR) or PR + stable disease (SD) and 95% Clopper–Pearson confidence interval (CI) were calculated.

Results The median age of these five patients was 60 years and all five patients' tumors had ERBB2 mutations—4 had exon 20 mutation and 1 had exon 23 mutation. With a median follow-up of 32 months, the median OS was 24 months, the median PFS was 9 months, and the median TTNT was 9 months. The response rate was 0.6 for PR (Clopper–Pearson exact 95% CI 0.147–0.947) and 0.8 for PR and SD (Clopper–Pearson exact 95% CI 0.284–0.995). No unexpected toxicities were observed.

Conclusion In a small number of patients, chemotherapy and pembrolizumab as first-line therapy in ERBB2-mutated NSCLC patients demonstrated activity similar to previous reports with this regimen. Future clinical trials are needed to determine the role of chemotherapy and immunotherapy for this patient population in the context of emerging targeted agents.

Key Points

Chemotherapy and immunotherapy remain the preferred first-line therapy for patients with non-small cell lung cancer (NSCLC) lacking any actionable mutation.

There are no approved targeted therapies in the first-line setting for ERBB2-mutated NSCLC, and there is paucity of data regarding the efficacy of pembrolizumab and chemotherapy in this patient population.

Our study showed that the activity of first-line chemotherapy and pembrolizumab in patients with ERBB2-mutated NSCLC was similar to previous reports with this regimen.

✉ Shirish Gadgeel
sgadgee1@hfhs.org

1 Division of Hematology and Oncology, Department of Internal Medicine, Henry Ford Cancer Institute, Henry Ford Health System, Detroit, MI, USA

2 Department of Internal Medicine, Henry Ford Health System, Detroit, MI, USA

3 Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, USA

4 Department of Medical Oncology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

1 Introduction

Lung cancer is the most common cancer worldwide and is one of the leading causes of cancer-related deaths [1]. Management of advanced stage IV non-small cell lung cancer (NSCLC) depends largely on several tumor characteristics such as histologic subtype, molecular alterations and programmed death-ligand 1 (PD-L1) status. Targeted therapies have been approved in the front-line setting for stage IV NSCLCs that have driver (i.e. targetable) genetic alterations such as EGFR mutation and ALK translocation [2]. Other genetic alterations in NSCLC, such as human epidermal growth factor receptor 2 (ERBB2) sequence variants, have been identified and constitute promising targets for the development of directed therapies [3].

ERBB2 is a member of the ErbB receptor tyrosine kinase family, which also includes EGFR, HER3, and HER4. It is encoded by the ERBB2 gene on the long arm of chromosome 17 (17q12). Alterations of ERBB2 can occur in three ways: amplification, overexpression, and mutation [4]. The predominant ERBB2 alteration in NSCLC is mutations in the ERBB2 gene, specifically in exon 20 [3].

Many targeted therapies are currently being developed or have been evaluated for ERBB2-positive NSCLC, including antibody drug conjugates (ADCs) such as ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan, and small-molecule tyrosine kinase inhibitors (TKIs) such as lapatinib and afatinib, which are dual EGFR/ERBB2 inhibitors, and dacomitinib, neratinib, poziotinib, and pyrotinib, which are irreversible pan-ErbB receptor inhibitors [3].

Over the last few years, the preferred front-line therapy in advanced NSCLC patients without targetable alteration is the combination of chemotherapy and immunotherapy. There is paucity of data regarding the activity of chemotherapy and immunotherapy in ERBB2-mutated NSCLC patients, therefore we conducted a retrospective review of ERBB2-mutated NSCLC patients treated with a combination of chemotherapy and pembrolizumab as front-line therapy.

2 Methods

We retrospectively identified five patients who had ERBB2-mutated NSCLC by reviewing the charts of patients with stage IV NSCLC treated at two cancer centers between 2018 and 2020. All patients in this series were treated with a combination of carboplatin, pemetrexed, and pembrolizumab as front-line therapy. All patients were evaluated and treated between 2018 and 2020 at two cancer centers in the US. ERBB2 mutations were detected using next-generation sequencing (NGS) assays of the tumor tissue obtained at diagnosis (in-house assay in four patients and a commercial NGS assay in one patient). Overall survival (OS) was defined as the length of time from the start of first-line treatment to the date of death or the date of last contact; progression-free survival (PFS) was defined as the length of time from the start of first-line treatment to the date of progression (PD) or death as defined by the treating physician; and time to next therapy (TTNT) was defined as the length of time between the start of first-line treatment to the start of second-line treatment or death. Response rate (RR) was defined as the rate of partial response (PR) and/or stable disease (SD) achieved after two to three cycles of chemotherapy and pembrolizumab; response was rated per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Patients had imaging studies at least every 12 weeks, with shorter intervals during the initial four to six cycles. OS, PFS, and TTNT were summarized by Kaplan–Meier methodology using R 4.0.5 with median time to event. RRs summarized by PR or PR + SD and 95% Clopper–Pearson confidence interval (CI) were calculated.

3 Results

The median age of the five patients was 60 years. Three patients never smoked cigarettes and two patients had a smoking history (20 and 25 pack-years). PD-L1 tumor proportion score (TPS) was 5% in two patients and < 1% in three patients. Four patients had bone metastases and three patients had brain metastases at diagnosis. All five patients' tumors had ERBB2 mutations—4 had exon 20 mutation and 1 had exon 23 mutation (Table 1).

The median number of chemotherapy and immunotherapy cycles received (including maintenance pemetrexed and pembrolizumab) was 14 cycles (range 2–20), the median number of pembrolizumab cycles was 14 (range 2–26), and the median number of maintenance chemotherapy cycles (with pembrolizumab) was 10 (range 3–15).

With a median follow-up of 32 months, the median OS was 24 months, 1-year survival probability was 0.750 (95% CI 0.426–1), and 2-year survival probability was 0.375 (95% CI 0.084–1) (Fig. 1). The median PFS was 9 months, 1-year progression probability was 0.40 (95% CI 0.137–1), and 2-year progression probability was 0.2 (95% CI 0.035–1) (Fig. 2). The median TTNT was 9 months and the 1-year TTNT probability after first-line therapy was 0.40 (95% CI 0.137–1) (Fig. 3). PR was achieved in three of five patients with an RR of 0.6 (Clopper–Pearson exact 95% CI 0.147–0.947), and four of five patients achieved PR

Table 1 Patient characteristics

Characteristic	
Median age, years	60
Sex	
Male	2
Female	3
Smoking	
Never smokers	3
Limited smoking	2
ECOG performance status	
0	2
1	3
PD-L1 TPS	
5%	2
< 1%	3
Metastases at diagnosis	
Bone	4
Brain	3
ERBB2 mutation	
Exon 20	4
Exon 23	1

ECOG Eastern Cooperative Oncology Group, *PD-L1* programmed death-ligand 1, *TPS* tumor proportion score

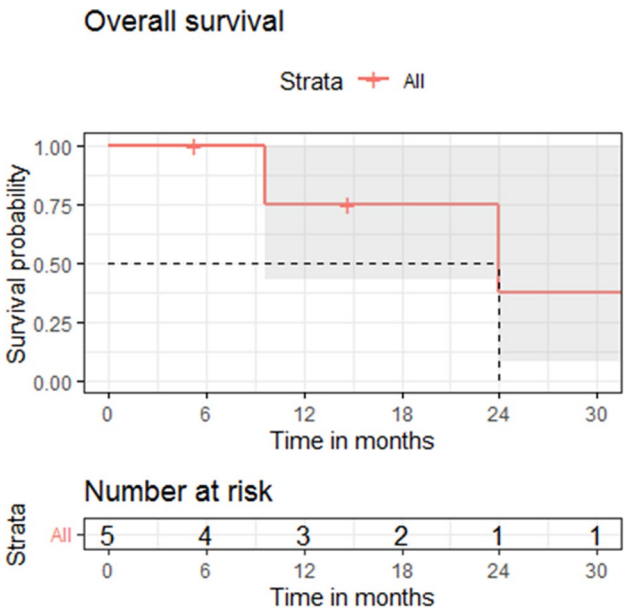

Fig. 1 Overall survival for patients with ERBB2-mutated non-small cell lung cancer treated with chemotherapy and immunotherapy

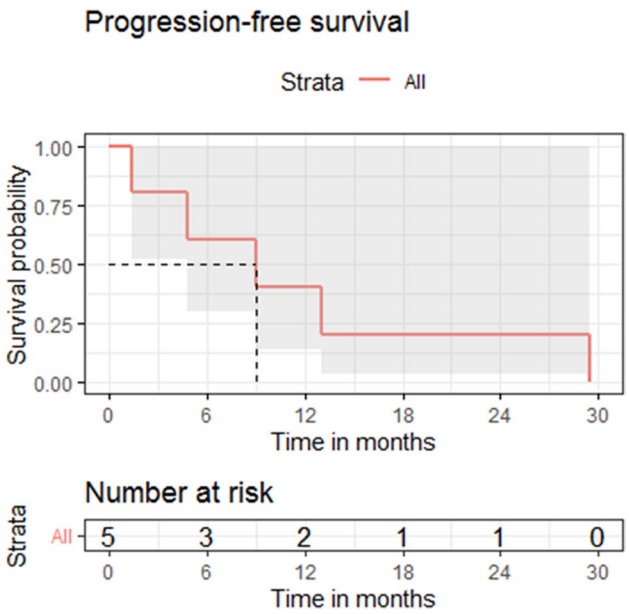

Fig. 2 Progression-free survival for patients with ERBB2-mutated non-small cell lung cancer treated with chemotherapy and immunotherapy

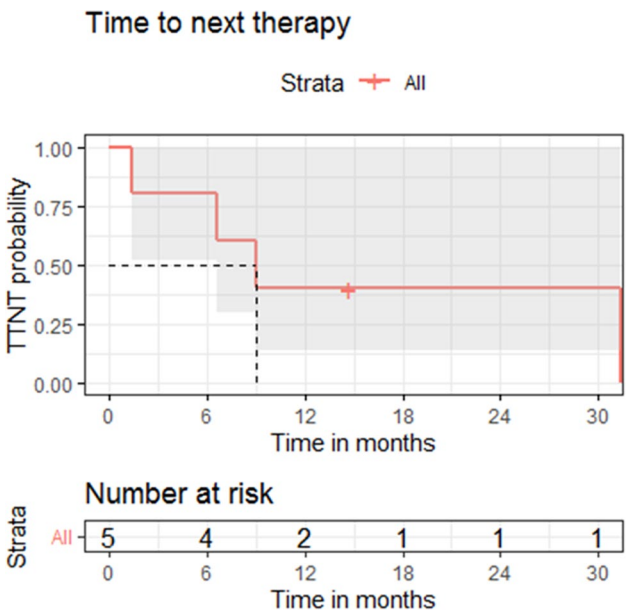

Fig. 3 TTNT for patients with ERBB2-mutated non-small cell lung cancer treated with chemotherapy and immunotherapy. *TTNT* time to next therapy

and SD with an RR of 0.8 (Clopper–Pearson exact 95% CI 0.284–0.995).

Treatment-related adverse events were collected retrospectively from patients' charts. The most common adverse events of the studied regimen were nausea and vomiting, fatigue (100%), watery eyes (60%), and cytopenia (40%). All adverse events were grade 1–2. Regarding immunotherapy-related adverse events, one patient had hypothyroidism that was managed with thyroid hormone replacement and another

patient had fever following pembrolizumab infusion that was managed with corticosteroids after treatment. Other adverse events that were possibly related to immunotherapy were diarrhea and arthritis in two patients, however they were grade 1 and did not require any treatment.

Of the three patients who progressed on chemotherapy and pembrolizumab, two were treated with docetaxel and ramucirumab as subsequent therapy and one patient was started on an investigational ERBB2-directed agent. Two patients received fam-trastuzumab deruxtecan as third-line therapy and one patient received ado-trastuzumab emtansine. Only one patient received an ERBB2-directed TKI (poziotinib).

4 Discussion

Very limited data are available on the efficacy of the combination of chemotherapy and immunotherapy in patients with ERBB2-mutated NSCLC. We report the results of five patients with ERBB2-mutated NSCLC treated with carboplatin/pemetrexed and pembrolizumab as first-line therapy. The median OS in these patients was 24 months, PFS was 9 months, and TTNT was 9 months.

We assessed TTNT, in addition to PFS, as this was a retrospective review of patients managed by different physicians with different disease assessment schedules. This endpoint has been considered as a measure of efficacy by other investigators.

Approximately 2–4% of patients with NSCLC carry ERBB2 sequence variants, which are most commonly found in women, individuals of Asian ethnicity, those with no history of smoking, and in adenocarcinomas [5]. ERBB2-positive NSCLC has the tendency to metastasize to the lungs and bones [5]. The most common ERBB2 variants are insertions or duplications of the amino acids tyrosine, valine, methionine, and alanine (YVMA) at codon 776 (YVMA 776–779 ins) in exon 20, accounting for 80–90% of all ERBB2 variations [6]. With greater use of NGS to detect all the relevant genetic alterations in NSCLCs, there is an expectation that ERBB2 mutations in NSCLC will be detected more frequently [6]. While ERBB2 sequence variations are thought to not occur with other driver genetic alterations, such as in ALK and EGFR, the European EUHER2 cohort has reported concomitant alterations in EGFR, ALK, and ROS1 in five patients [7].

The effect of ERBB2 variant status on the response to chemotherapy is controversial. Wang et al. [8] showed inferior outcomes in patients with ERBB2 allelic alterations who received first-line treatment with pemetrexed, and platinum chemotherapy, compared with patients with ALK and ROS1 rearrangements or EGFR sequence variations. On the contrary, Li et al. [9] reported better outcomes in patients with ERBB2 alterations who received pemetrexed and platinum chemotherapy. Mazières et al. identified 101 patients with ERBB2-positive NSCLC who had an overall RR (ORR) of 43.5% and a median PFS of 6 months with conventional first-line chemotherapy [7].

Targeted therapies are being extensively studied in ERBB2-mutated NSCLC, with some showing promising results. Trastuzumab-emtansine (T-DM1), an ADC targeted against ERBB2, showed a PFS of 5 months in a phase II basket trial [10]. Its efficacy was confirmed in a subsequent phase II trial reporting an ORR of 44% in the same patient population [11]. Fam-trastuzumab deruxtecan-nxki (T-Dxd), another ADC against ERBB2, was granted a breakthrough designation by the US FDA based on the results of the Destiny-Lung01 trial. The study reported an ORR of 55%, median PFS of 8.2 months, and median OS of 17.8 months in ERBB2-mutated NSCLC patients previously treated with platinum chemotherapy [12]. Small-molecule TKIs were also effective in the treatment of ERBB2-mutated NSCLC and have shown an ORR ranging from 3.8% to approximately 40%. Gastrointestinal adverse effects can be the major dose-limiting toxicities with these TKIs [13].

Evidence of the impact of ERBB2 alterations on the response to immune checkpoint inhibitors (ICIs) as a single agent or in combination with chemotherapy is limited. Mazieres et al. reported 29 patients with ERBB2-positive NSCLC who had received single-agent ICIs. The PFS for these patients was 2.5 months and was positively associated with smoking status, whereas the OS was 20.3 months and did not correlate with smoking status or PD-L1 level [14]. Guisier et al. reported on 23 patients with activating ERBB2 sequence variations who received ICIs after progressing on first-line treatment. The median PFS was 2.2 months (range 1.7–15.2) and the median OS was 20.4 months (range 9.3–not reached) [15]. Patil et al. reported a significantly prolonged PFS in patients with ERBB2 allelic variations (10 within exon 20 and 1 within exon 19) and patients with atypical EGFR mutations who received ICIs with platinum doublet chemotherapy relative to those who received ICIs as monotherapy (7 vs. 2 months; $p < 0.001$; hazard ratio 0.06, 95% CI 0.01–0.53) [5].

In our study, five patients with ERBB2 sequence variations (exon 20 in four patients and exon 23 in one patient) were treated with carboplatin, pemetrexed and pembrolizumab as first-line therapy. The median TTNT of 9 months, median PFS of 9 months, and median OS of 24 months are consistent with the results reported with this therapy in non-squamous NSCLC patients in the Keynote 189 trial [16]. The three patients who required the next line of therapy went on to receive HER2-directed therapy. PR was achieved in three of five patients after two to three cycles of chemotherapy and pembrolizumab, and SD was achieved in one patient. No unexpected adverse events were observed in these

patients. It is not clear if the addition of pembrolizumab to chemotherapy provides superior outcomes in all molecularly defined subsets of NSCLC. Previous retrospective reviews suggest that in ERBB2-mutated NSCLC patients, front-line chemotherapy demonstrates a median PFS of 6 months [7, 8]. Further studies will need to be conducted to assess if the addition of pembrolizumab to platinum-based chemotherapy provides superior outcomes in ERBB2-mutated NSCLC.

The are several limitations to our study. First, this was a retrospective analysis and included a small number of patients. In addition, TTNT is not a commonly utilized efficacy criterion. Finally, adverse events may not be recorded as diligently as in clinical trial patients. Very limited data are available regarding the efficacy of chemotherapy and immunotherapy as front-line therapy in ERBB2-mutated NSCLC patients; therefore, despite the limitations of a retrospective analysis, the results in these five patients provides information regarding the outcomes of ERBB2-mutated NSCLC treated with chemotherapy and immunotherapy as first-line therapy.

5 Conclusion

NSCLCs harboring sequence variations in ERBB2 constitute a specific entity of lung cancer with driver mutations. The role of chemotherapy and immunotherapy as first-line therapy for this specific subset of NSCLC patients remains to be defined. Due to the lack of targeted therapy options in the front-line setting, chemotherapy with pembrolizumab should be considered for first-line therapy in stage IV ERBB2-altered NSCLC. However, it remains to be determined whether the addition of pembrolizumab to platinum-based chemotherapy provides any additional benefit in this patient population. Our results warrant further study of chemotherapy and immunotherapy as first-line therapy in ERBB2-mutated NSCLC patients.

Declarations

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Conflict of interest Shirish Gadgeel is a member of the consulting/advisory board for Merck, Pfizer, Genentech/Roche, Astra-Zeneca, Takeda, Bristol Myers-Squibb, Dava Oncology, Blueprint, Mirati, Daichii-Sanyko, and Novartis; is a member of the independent data monitoring committee (IDMC) for Astra-Zeneca; and has received research support from Merck. Balazs Halmos has received research funding from Boehringer Ingelheim, Astra-Zeneca, Merck, BMS, Advaxis, Amgen, AbbVie, Daiichi, Pfizer, GSK, Beigene, and Janssen, and has received consulting fees from Astra Zeneca, Boehringer Ingelheim, Veracyte, Janssen, Takeda, Merck, BMS, Genentech, Pfizer, Eli-Lilly. Fawzi Abu Rous, Radhika Gutta, and Pin Li declare they have no conflicts of interest that might be relevant to the contents of this manuscript.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions SG and BH: Study design and manuscript review. FA and RG: Data collection and manuscript writing. PL: Statistical analysis.

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