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Immune checkpoint inhibitors combined with chemotherapy and targeted therapy yield high remission rates in advanced cancer diseases

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ABSTRACT

Treating advanced refractory malignancies remains a major challenge. In some cancers, the combination of immune checkpoint inhibitors (ICI) and chemotherapy has been shown to be superior to chemotherapy alone. We chose to add targeted therapy (TT) to this combination to treat these diseases as the three approaches have convergent efficacy but divergent toxicity. Between 04/2016 and 10/2018, 19 consecutive patients with advanced malignancies were treated with the above combination based on diagnosis, prior therapy, and eligibility for TT. The median patient age was 62 years (range 27-82), and 15 were female. The median Eastern Cooperative Oncology Group performance status was 2 (range 0-4). Tumor types included lung, pancreas, lymphoma, melanoma, cholangiocarcinoma, ureter, cervix, and glioblastoma multiforme. Of the 14 patients who underwent prior therapy, 7 received ICI and 3 received TT. The ICIs used were pembrolizumab, nivolumab, and atezolizumab. Chemotherapy was given in 28-day cycles. Platinum-based combinations were used in 13 patients and taxanes in 10. Four patients were not eligible for TT. Complete responses were achieved in 11 patients (57%) for a median 6+ months (range 1+-15+), and partial responses in 7 (37%) for a median 4 months (1-7). One patient had stable disease. Responses were observed even in patients with intracranial metastases, extensive prior therapy, bulky disease, poor performance, and prior ICI. No unexpected side effects were observed. This personalized combination of ICI, chemotherapy, and TT yielded impressive results in advanced refractory cancer diseases. Further evaluation in properly designed clinical trials is recommended.

KEYWORDS: targeted therapy, advanced malignancies, immunotherapy, combination therapy.

INTRODUCTION

Over the last eight years, the emergence of immune checkpoint inhibitors (ICIs) has significantly changed the landscape of cancer treatment [1]. ICIs are now effective against a wide variety of neoplasms, including melanoma, Hodgkin's lymphoma, and kidney, urothelial, lung, and liver cancers [1]. Their toxicity has been shown to be substantially less severe than that of chemotherapy, particularly with regard to hair loss, nausea, vomiting, and marrow suppression; however, some adverse effects have been described, including diarrhea, skin rash, and occasional pulmonary infiltrates [2]. Also, therapies targeted towards specific molecules in cancer cells are well tolerated and have a different toxicity profile than that of chemotherapeutic agents [3].

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In lung cancer, the combination of chemotherapy with ICIs is more effective than chemotherapy alone [4]. Further, the combination of two ICI agents may be superior to monotherapy [5], and a recent study showed that this combination was more effective in the treatment of brain metastases in melanoma [6]. Additionally, combining ICI therapy with anti-BRAF therapy in melanoma appears to confer an advantage [7, 8].

We are reporting our experience treating 19 patients with diverse diagnoses of cancer and advanced disease using personalized combinations of ICIs, chemotherapy, and targeted therapy (TT).

METHODS

Between April 2016 and October 2018, 30 patients with advanced malignancies were seen. Of these 19 consecutive patients were enrolled for the triple modality treatment using personalized combinations of ICI, chemotherapy, and TT. Four of them ended up not receiving TT. Inclusion criteria were advanced malignancy with limited (= or < 30%) response potential to conventional treatment options, if available. The treatment approach was explained to patients along with other alternative options. Patient consent was obtained. No particular exclusion criteria outlined. However, no major organ dysfunction was noted in this group. Brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status 3/4, and bulky disease (> or = 10 cm) were not excluded. The median patient age was 62 years (range, 27-82). Fifteen patients were female. The median ECOG performance status [9] was 2 (range, 0-4). Seven patients had received prior ICI therapy with variable responses: one patient had a complete response (CR), two had partial responses (PR), one had a mixed response, and three had progressive disease. Five patients had not received prior systemic chemotherapy, while the remaining 14 patients had received a median of two prior therapies (range, 1-11). Three patients had received prior TT. Six patients had bulky disease. Genetic testing was performed depending on the availability of pathology specimens. Nine patients underwent Next-Generation Sequencing, six had individual gene testing, and four had no available specimens for genetic testing. Patient demographics are shown in Table 1; detailed patient profiles are provided in Supplemental Data.

Patients received personalized treatment. Drugs, doses, and schedules were tailored to each patient based on diagnosis, prior treatment, and tumor mutation status. All patients were treated in our facility and were seen on an almost-daily basis. Patients were closely monitored for response to treatment and tolerance. Treatments are summarized in Table 2. Detailed information regarding treatment dosing and timing is provided in Supplemental Data.

All patients were treated with ICI therapy; 6 patients received pembrolizumab (2 in conjunction with ipilimumab), 10 received nivolumab, and 3 received atezolizumab. These agents were given in the standard dose schedules described in Supplemental Data. Chemotherapy was given in 28-day cycles for all patients. Seventeen patients received multi-agent chemotherapy, and two received single agents. Thirteen patients received platinum-based combinations and 10 received taxanes. Drugs were delivered on different days during days 1-21, with the last 7 days of the cycle as rest for bone marrow recovery. Hemogram monitoring was performed at least three times per week on Mondays, Wednesdays, and Fridays. Filgrastim support was used as needed to allow completion of the planned cycle. Intermittent oral levofloxacin antibiotic prophylaxis was given for the duration of severe neutropenia. Antibiotic administration for specific infection episodes (e.g., urinary tract infection, respiratory infections, abscesses, Clostridium difficile colitis) was common. Other support measures included granisteron (antiemetic) on the day of and the day following chemotherapy. Patients also received daily low-dose dexamethasone (0.5-1 mg) in conjunction with H2 antagonists or proton-pump inhibitors.

In regard to TT, four patients received erlotinib, three received cetuximab, two received bevacizumab, three received combined dabrafenib/trametinib (one of whom also received sorafenib), one received crizotinib, one received alectanib, and one received everolimus. The remaining four patients were ineligible for TT.

Patient response to treatment was evaluated by serial positron emission tomography/computed tomography (PET/CT) PERCIST 1.0 criteria. The first evaluation was performed following the first treatment cycle. Evaluations were then repeated every 1-2 cycles until the maximum response was

Table 1. Summary of patient demographics and prior treatments.

Patient	Age	Sex	Diagnosis	PDL-1	Disease extent	ECOG status	Prior treatments	Prior ICI
1	74	F	Lung adenocarcinoma	+	LUL, mediastinal and cervical lymph nodes	1	0	0
2	61	F	Lung adenocarcinoma	-	Lung, thorax, subcutaneous nodule, abdomen	4	4	1
3	56	F	Lung adenocarcinoma	-	Lung	0	3	1
4	66	M	Lung squamous cell carcinoma	-	Mediastinum, bone	2	2	1
5	73	F	Lung adenocarcinoma	+	Lung, mediastinal and supraclavicular lymph nodes	2	2	0
6	59	F	Lung adenocarcinoma	+	LUL, left pleural effusion, lung nodules, bone, liver, brain	1	0	0
7	67	F	Lung adenocarcinoma	+	Left pleural effusion, liver, brain, mediastinum	2	2	2
8	46	F	Lung squamous cell carcinoma	+	Bone, liver, brain, skin, pancreas	3	3	2
9	65	F	Pancreatic adenocarcinoma	U	Pancreas, retroperitoneal, pretracheal	2	5	0
10	62	F	Pancreatic adenocarcinoma	-	Liver, pancreas	0	2	0
11	78	F	Pancreatic adenocarcinoma	U	Pancreas	3	0	0
12	68	M	Large B cell lymphoma	U	Liver, bone, bilateral pleural effusion, peritoneum	3	6	0
13	27	M	Hodgkin's lymphoma	U	Mediastinum, bone, lymph nodes	3	11	1
14	66	F	Melanoma	-	Soft tissue, bone, lymph nodes, skin	4	1	1
15	29	F	Melanoma	+	Liver, lymph nodes, soft tissue	1	1	0
16	59	F	Cholangio-carcinoma	-	Liver, abdomen, lymph nodes	1	0	0
17	82	M	Right ureteral carcinoma	-	Pelvic lymph nodes	1	0	0
18	48	F	Cervical adenocarcinoma	-	Abdomen	1	1	0
19	45	F	Glioblastoma Multiforme	U	Brain	0	1	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; LUL, left upper lobe; U = Unknown/not done.

achieved. Thereafter, evaluation was repeated after every 2-3 cycles. Brain magnetic resonance imaging was performed at a similar frequency when indicated. Echocardiograms were performed every 4-6 months. The decision to utilize PERCIST 1.0 criteria for establishing a measure of treatment response was made because this patient population presented a myriad of anatomical

Table 2. Summary of patient diagnoses and treatments[a].

Patient	Diagnosis	Chemotherapy	ICI	Targeted therapy
1	Lung adenocarcinoma	Gemcitabine, Carboplatin, Vinoralbine	Pembrolizumab	Crizotinib
2	Lung adenocarcinoma	Gemcitabine, Carboplatin, Pemetrexed	Atezolizumab	Bevacizumab
3	Lung adenocarcinoma	Nab-paclitaxel	Nivolumab	Cetuximab
4	Lung squamous cell carcinoma	Nab-paclitaxel, Cisplatin	Pembrolizumab	··
5	Lung adenocarcinoma	Nab-paclitaxel, Irinotecan	Nivolumab	Cetuximab
6	Lung adenocarcinoma	Gemcitabine, Carboplatin, Vinoralbine	Pembrolizumab	··
7	Lung adenocarcinoma	Pemetrexed, Cisplatin, Vinoralbine	Atezolizumab	Alectinib
8	Lung squamous cell carcinoma	Nab-paclitaxel, Etoposide	Pembrolizumab	Cetuximab
9	Pancreatic adenocarcinoma	Nab-paclitaxel	Nivolumab	Erlotinib
10	Pancreatic adenocarcinoma	Nab-paclitaxel, Gemcitabine	Nivolumab	Erlotinib
11	Pancreatic adenocarcinoma	Nab-paclitaxel, Gemcitabine	Nivolumab	Erlotinib
12	Large B cell lymphoma	Gemcitabine, Oxaliplatin	Nivolumab	··
13	Hodgkin's lymphoma	Cyclophosphamide, Oxaliplatin	Nivolumab	Everolimus
14	Melanoma	Docetaxel, Cisplatin, Temozolomide	Pembrolizumab, Ipilimumab	Dabrafenib, Trametinib
15	Melanoma	Docetaxel, Cisplatin, Temozolomide	Pembrolizumab, Ipilimumab	Dabrafenib, Trametinib
16	Cholangiocarcinoma	Gemcitabine, Cisplatin	Nivolumab	Sorafenib, Dabrafenib, Trametinib
17	Right ureteral carcinoma	Gemcitabine, Cisplatin, Vinoralbine	Atezolizumab	··
18	Cervical adenocarcinoma	Gemcitabine, Cisplatin, Paclitaxel, Vinoralbine	Nivolumab	Erlotinib
19	Glioblastoma Multiforme	Irinotecan, Cisplatin, Temozolomide	Nivolumab	Bevacizumab

[a]Detailed descriptions of dosages and timing of administration of drugs can be found in the Supplement.
Abbreviations: ICI, immune checkpoint inhibitor.

findings, often complicated by extensive prior medical, surgical, and radiation treatment. The presence of a complete or partial metabolic response with or without a significant anatomical response was utilized to manage these patients and make clinical treatment decisions. PERCIST 1.0 most accurately predicted clinical response, stable disease, or progression in this heterogeneous cohort according to our radiologist.

RESULTS

11 patients achieved a CR (complete disappearance of hypermetabolic activity) for a median of 6+ months (range, 1+ to 15+) and 7 achieved a PR (a decrease of more than 50% in metabolic activity) for a median of 4 months (range, 1+ to 7). One patient had stable disease (7 months). A summary of patient treatment responses is provided in Table 3, and representative imaging studies are shown in

Table 3. Patients, diagnoses, and responses to treatment.

Patient Number	Diagnosis	PET response	Duration of response (Months)[a]
1	Lung adenocarcinoma	CR	7+
2	Lung adenocarcinoma	PR	4
3	Lung adenocarcinoma	PR	6
4	Lung squamous cell carcinoma	SD	7
5	Lung adenocarcinoma	CR	3
6	Lung adenocarcinoma	PR	5
7	Lung adenocarcinoma	CR	15+
8	Lung squamous cell carcinoma	CR	1+
9	Pancreatic adenocarcinoma	CR	9+
10	Pancreatic adenocarcinoma	PR	1+
11	Pancreatic adenocarcinoma	PR	2+
12	Large B cell lymphoma	CR	12
13	Hodgkin's lymphoma	CR	7+
14	Melanoma	PR	7
15	Melanoma	PR	3+
16	Cholangiocarcinoma	CR	6+
17	Right ureteral carcinoma	CR	3
18	Cervical adenocarcinoma	CR	4+
19	Glioblastoma Multiforme	CR	3+

[a]Responses with durations ending in "+" are ongoing as of last evaluation.
Abbreviations: CR, complete response; PET, positron emission tomography; PR, partial response; SD, stable disease.

Figure 1. In some patients who achieved a CR, an FDG-negative residual mass could still be observed, but this mass remained stable or regressed over time. Radiologic tumor regression was usually observed after the first cycle.

While 4 patients in this consecutive patient enrollment did not end up receiving TT, the only patient with stable disease did not receive TT. Moreover, all responses in these 4 patients were not ongoing, while responses in the 11 of the 15 patients who received TT, were ongoing. However, such pattern of response in this limited patient population will not permit us to draw conclusions in regard to the difference in response between those who received TT and those who did not.

Disease relapsed in four patients following delay of treatment (in three, due to the patient's decision to delay treatment for reasons other than toxicity, and in one, for grade 3 fatigue). Death occurred in two, but was unrelated to the underlying malignancy. All six patients with bulky disease responded, with four achieving a CR. All three patients with intracranial metastases from lung cancer responded in the brain. Two of these had a CR and one a PR. All of the six patients with poor performance status (ECOG 3-4) responded (two CRs and four PRs).

Overall, treatment was well tolerated. There was no treatment-related death and no patient stopped therapy because of toxicity. Adverse events are described in Table 4, with the level of toxicity listed being the highest observed during treatment. Hematological events were related to the extent of prior chemotherapy and the treatment duration. Grade 3/4 events accounted for 12.7% and were primarily hematologic. Two patients developed pulmonary infiltrates that were non-progressive, but the relationship of these infiltrates to treatment was unclear. One patient demonstrated ICI-associated

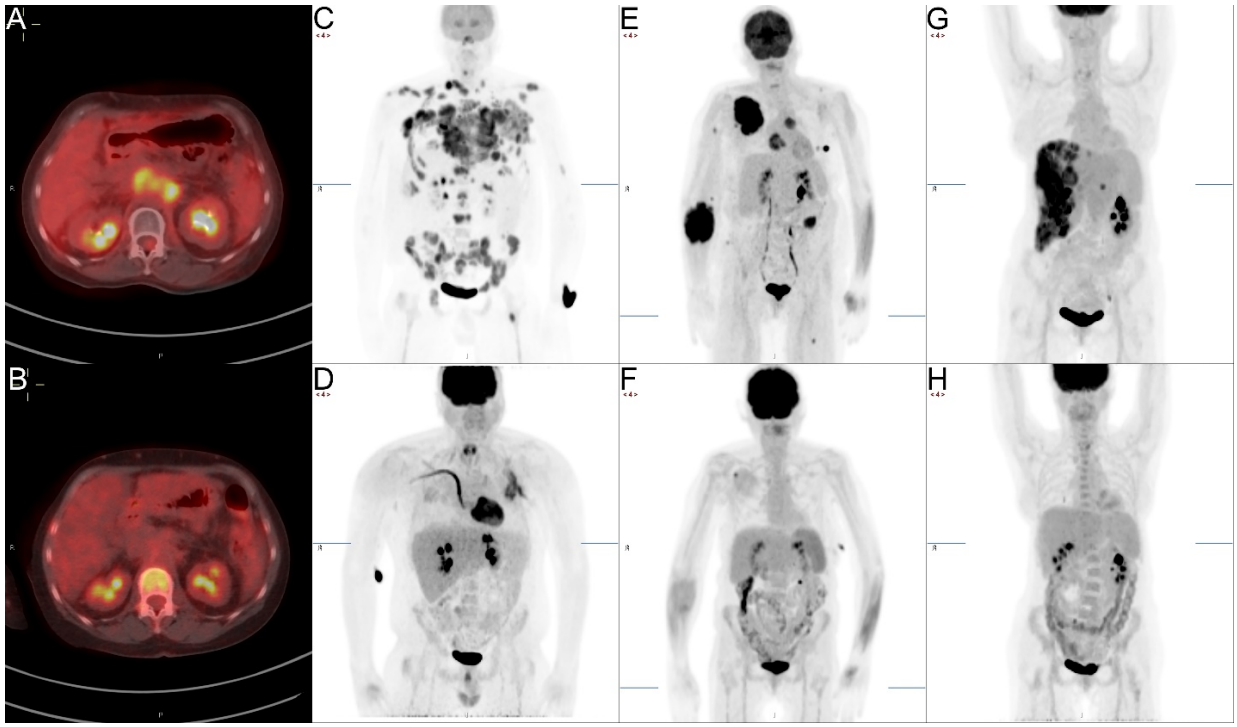

Figure 1. Representative tumor responses to treatment. Representative tumor images pre- (top) and post-treatment (bottom) showing **A-B** a complete response (CR) of pancreatic adenocarcinoma (Patient 9), **C-D** a CR of Hodgkin's lymphoma (Patient 13), **E-F** a partial response of melanoma (Patient 14), and **G-H** a CR of cholangiocarcinoma (Patient 16).

Table 4. Detailed list of adverse events.

Adverse event	Grade[a]					Total[b]
	0	**1**	**2**	**3**	**4**	
Alopecia	11	3	3	2	-	19
Anemia	3	3	6	6	0	18
Diarrhea	12	5	0	2	0	19
Elevated SGOT/SGPT	11	6	1	0	0	18
Fatigue	9	8	1	1	0	19
Infection	8	6	3	1	1	19
Neutropenia	4	2	4	2	4	16
Nausea/vomiting	11	7	1	0	0	19
Peripheral Neuropathy	14	3	1	0	0	18
Skin	12	6	1	0	0	19
Thrombocytopenia	6	0	5	4	3	18
Total:	101	47	21	18	8	204

[a]Toxicity is graded according to World Health Organization (WHO) criteria [14].
[b]Numbers represent the number of patients experiencing the adverse event.
Abbreviations: SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase.

colitis and hypothyroidism, and another exhibited bradycardia related to anti-ALK agents. No patient had elevated serum creatinine levels.

DISCUSSION

In this case series, 19 patients with advanced cancer were treated with personalized treatments that combined ICIs, chemotherapy, and, in 15 patients TT. Despite the inclusion of diverse cancer diagnoses and refractory advanced diseases, this patient population demonstrated an unexpectedly high response rate of 94.7% (18/19). These results emphasize the need for carefully designed clinical trials to further explore the efficacy and feasibility of such treatment regimens. Also, these treatment combinations were well tolerated, as we did not observe any significant toxicity.

Patients were treated consecutively as they presented to Salem Oncology Center. All patients had advanced disease. In 14, the disease was already shown to be refractory to standard treatment. Unlike many standard clinical trials, poor performance status and metastases to the brain were not considered contraindications to treatment. Four patients were considered terminal and ineligible for additional treatment by major cancer centers; three of them achieved a CR. Notably, the patients had diverse diagnoses, and responses were not confined to one disease. Of the 11 patients who achieved a CR, 5 had cancer types known to be poorly responsive to treatment, including cholangiocarcinoma, ureteral cancer, refractory pancreatic cancer, refractory cervical cancer, and glioblastoma multiforme.

Imaging studies were performed at a single center and were evaluated by the same team of radiologists, but one experienced radiologist, Dr. Stenoien, carefully reviewed all the images of every patient. Of the 18 patients who responded, 11 achieved a CR and 7 had a PR. However, 5 of the 7 patients who achieved a PR had over 90% reduction in disease.

Immunotherapy is effective against disease that has metastasized to the brain in melanoma patients [5, 6]. Also, in our study, three patients with lung cancer metastatic to the brain achieved remission in the brain (2 CRs and 1 PR).

Antibiotic therapy alters the microbiome and is associated with poorer outcomes following ICI therapy [10, 11]. This was not the case in our study. Outcomes were impressive despite prophylactic antibiotic therapy being used in all patients. A similar concern is the use of corticosteroids with these inhibitors [12, 13]. Although the data from previous studies are inconsistent, the use of dexamethasone did not appear to adversely impact response in our study.

Prior ICI therapy was not associated with a low response rate, as six of the seven patients who received prior ICI therapy responded. Consequently, we believe that prior ICI therapy should not preclude treatment with our combination.

CONCLUSION

This case series analyzed the outcomes of a small number of patients treated at a single center. We do not claim that this approach is practice changing. However, despite the heterogeneity of diagnosis and particular agents given under the umbrella of personalized ICI, chemotherapy, and TT combination, we observed an impressive tumor response in advanced refractory malignancies. These results provide strong justification for further evaluation of this treatment approach in carefully designed clinical trials to determine its precise role in cancer treatment.

STATEMENT OF ETHICS

Ethics approval was not required.

CONSENT FOR PUBLICATION

Consent for publication was not required.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this published article and its supplementary information file.

FUNDING SOURCES

No funding was received for this research.

AUTHORS' CONTRIBUTIONS

PAS conceptualized the study and developed the treatment protocols. PAS, KJ, TW, and MV collected data. RS assisted with imaging. PAS and KJ analyzed the data and drafted the manuscript.

ABBREVIATIONS

Immune checkpoint inhibitors (ICI); targeted therapy (TT); Eastern Cooperative Oncology Group (ECOG); complete response (CR); partial responses (PR); positron emission tomography/computed tomography (PET/CT); fluorodeoxyglucose (FDG); left upper lobe (LUL); stable disease (SD); serum glutamic-oxaloacetic transaminase (SGOT); serum glutamic pyruvic transaminase (SGPT).

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

SUPPLEMENTAL DATA

Individual patient profiles

Patient 1

A 74-year-old nonsmoking Caucasian female presented with cough. Computed tomography (CT) and positron emission tomography (PET) revealed a 4.2 × 2.4 cm right upper lobe cavitary, speculated mass surrounding the right mainstem bronchus. Large hilar and mediastinal lymphadenopathy were observed along with bilateral supraclavicular lymphadenopathy. Needle biopsy of the right upper lobe primary mass revealed adenocarcinoma, and needle biopsy of the right supraclavicular lymph node confirmed poorly differentiated metastatic adenocarcinoma (PDL-1+ and C-MET+).

In 03/2017, we started systemic therapy of gemcitabine 750 mg/m^2 IV day 1, 500 mg/m^2 IV days 8 and 15, carboplatin 200 mg IV days 7 and 19, and vinorelbine 20 mg/m^2 days 5 and 12 in a 28-day chemotherapy cycle, as well as pembrolizumab 200 mg IV every 3 weeks. Regressing disease was documented after cycle #1. In 01/2018, complete remission (CR) was reached. Carboplatin was replaced by nab-paclitaxel 60 mg/m^2 IV days 1, 8, and 19 after development of acute hypersensitivity to carboplatin. Crizotinib 250 mg p.o. b.i.d. [15] was initiated but was discontinued secondary to bradycardia. The patient remains in CR as of 08/2018.

Patient 2

A 61-year-old Caucasian female who was a heavy smoker presented in 07/2012 with a right upper lung mass. The final staging was $T_3N_1M_0$ bronchogenic adenocarcinoma (K-RAS+, EGFR-, and ALK-). The patient received 2 cycles of cisplatin/pemetrexed followed by radiotherapy with partial response. Surgical resection was achieved in 11/2012. Shortly after surgery, multiple brain metastases were detected and whole-brain radiation was completed in 12/2012. By 01/2013, there were eight residual intracranial lesions. The patient was started on vinorelbine, gemcitabine, and paclitaxel. In 03/2013, an MRI documented regressing intracranial lesions which cleared by 05/2013. By 10/2014, right hilar relapse was noted after 6 months off chemotherapy. Chemotherapy was restarted with carboplatin, vinorelbine, and paclitaxel with later addition of radiation in 11/2014. In 11/2017, the third extracranial relapse was noted with bilateral pulmonary nodules and left axillary lymphadenopathy, for which she was started on ipilimumab, nivolumab, vinorelbine, and erlotinib with disease progression by 01/2018.

Accordingly, we changed treatment to pemetrexed 250 mg/m^2 days 1 and 2, carboplatin 400 mg day 20, and gemcitabine 500 mg/m^2 days 14 and 21 in a 28-day chemotherapy cycle, as well as atezolizumab 1200 mg IV every 3 weeks and bevacizumab 10 mg/kg IV every 2 weeks. Major partial response (≥75% regression) was observed after cycle #1, which was maintained through 04/2018. The patient decided to receive further treatment at a significantly lower dose and closer to home. The patient expired in 08/2018 due to pulmonary embolism.

Patient 3

A 56-year-old Caucasian female smoker presented with metastatic bronchogenic well- to moderately differentiated adenocarcinoma of the right parahilar region with extensive mediastinal nodal disease and bilateral pulmonary nodules. The diagnosis was established in 11/2011. The patient achieved CR in 12/2013 after treatment with cisplatin, pemetrexed, and bevacizumab, and that combination was administered with increasing intervals between courses as maintenance. In 03/2017, relapsed disease was documented when the patient presented with new pulmonary nodules and mediastinal lymphadenopathy. Evaluation after chemotherapy rechallenge with gemcitabine, oxaliplatin, and vinorelbine revealed progressive

disease (PDL-1-, EGFR-, and ALK-). Nivolumab 240 mg IV every 2 weeks was started in 05/2017. CR was documented by PET/CT in 07/2017.

However, disease recrudescence was noted by PET/CT in 11/2017 and we added to the ongoing nivolumab treatment nab-paclitaxel 65 mg/m^2 IV days 1, 9, and 16 in a 28-day chemotherapy cycle and cetuximab at a 400 mg/m^2 IV induction dose followed by weekly 250 mg/m^2 doses. PET/CT revealed response in 01/2018 and partial remission in 03/2018, which was maintained until 09/2018.

Patient 4

A 65-year-old Caucasian male smoker had incidental chest x-ray and CT chest findings of a right 2.5 cm hilar mass with mediastinal and paratracheal lymphadenopathy. PET scan revealed a hypermetabolic right suprahilar mass without nodal uptake. Bronchoscopic biopsy revealed well- to moderately differentiated squamous cell cancer. The final staging was $T_4N_0M_0$. Concurrent weekly paclitaxel/carboplatin radiochemotherapy was completed in 05/2016. As of 08/2016, chest CT and PET/CT evaluation indicated early progression of post-treatment residual disease. The patient was started on vinorelbine, gemcitabine, and pembrolizumab with additional radiation to the tumor site.

After 2 cycles, PET/CT evaluation was suggestive of disease progression, and in 11/2016 we switched treatment to nab-paclitaxel 100 mg/m^2 IV days 1, 8, and 15 and cisplatin 10 mg/m^2 IV days 13, 14, and 18 in a 28-day chemotherapy cycle, as well as pembrolizumab 200 mg IV every 3 weeks, for a total of 9 cycles with stable disease. In 08/2017, PET/CT revealed disease progression. Subsequently, the patient developed cavitary pneumonia that resulted in fatal hemoptysis in 03/2018.

Patient 5

A 73-year-old Caucasian female smoker presented with cold-like symptoms. Radiologic evaluation in 01/2015 revealed a right middle lobe lung primary tumor with extensive mediastinal as well as bilateral supraclavicular and infraclavicular nodal disease with extensive bilateral pulmonary nodules. The histology indicated poorly differentiated adenocarcinoma. Systemic chemotherapy with vinorelbine, pemetrexed, and cisplatin was initiated in 01/2015. By 01/2016, CR by PET was achieved.

As of 03/2017, new mediastinal nodal disease (PDL-1+) was noted. We started the patient on nab-paclitaxel 100 mg/m^2 IV days 1, 8, and 15 and irinotecan 50 mg/m^2 days 2, 9, and 16 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks, starting on 04/2017. As of 06/2017, PET/CT revealed mixed response, with very good partial response of the signal lesions but with the development of two new hypermetabolic lesions. Accordingly, cetuximab was added at a 400 mg/m^2 IV induction dose then 250 mg/m^2 IV weekly. PET showed CR on 08/2017. However, subsequent treatment was interrupted and delayed due to the development of severe fatigue related to treatment. In 01/2018, PET/CT showed recurrent hypermetabolic omental lesion.

Patient 6

A 59-year-old nonsmoking Latino female presented with one-year history of cough. Radiologic evaluation revealed 3.9 × 3.2 cm left parahilar mass with large pleural effusion, a lesion in the right inferior liver, osteolytic lesion of the C7 vertebral body, and six enhancing intracranial brain metastases without significant vasogenic edema. Left lung mass biopsy showed well- to moderately differentiated adenocarcinoma. Left pleural fluid cytology was suspicious for malignant cells.

In 02/2017, we started the patient on vinorelbine 20 mg/m^2 IV days 1 and 14, carboplatin 300 mg IV day 4, and gemcitabine 750 mg/m^2 IV days 10 and 18 in a 28-day chemotherapy cycle, as well as pembrolizumab 200 mg IV every 3 weeks. After cycle #1, radiologic evaluation showed a decrease in size of the lung primary disease, disappearance of liver metastasis, recalcification of the C7 lytic lesion, and minor improvement of the brain metastases. After cycle #2, further radiologic evaluation showed partial response of intracranial and extracranial disease. The last evaluation in 09/2017 continued to show partial response. The patient was lost to follow up beyond that date but remains alive as of 08/2018.

Patient 7

A 67-year-old Caucasian female nonsmoker presented with 2-month history of cough. Chest CT revealed a left lower lobe mass, hilar lymphadenopathy, and pleural effusion, with positive cytology for adenocarcinoma. Further

workup revealed multiple enhancing brain metastases and a left hepatic metastasis. Treatment was started on 04/2016 with paclitaxel, carboplatin, and nivolumab, resulting in extracranial and intracranial partial response in 10/2016. As of 01/2017, there was the suggestion of hepatic disease reactivation and subsequently treatment was switched to gemcitabine, carboplatin, and pembrolizumab. However, after 2 cycles, PET/CT showed increased metabolic activity in the left lower lobe and left hepatic metastasis.

Subsequently, we switched treatment in 03/2017 to vinorelbine 20 mg/m^2 IV days 1 and 12; cisplatin 15 mg/m^2 IV days 5, 6, 8, and 9; and pemetrexed 500 mg/m^2 IV day 9 in a 28-day chemotherapy cycle, as well as atezolizumab 1200 mg IV every 3 weeks and alectinib 600 mg p.o. b.i.d. (ALK+). In 05/2017, PET showed CR of extracranial disease, and CR of intracranial disease was documented in 08/2017. As of 09/2018, the patient remains in CR.

Patient 8

A 46-year-old Caucasian female smoker with the diagnosis of poorly differentiated squamous cell lung cancer presented with a right lung primary tumor and right hilar adenopathy. Carboplatin/ paclitaxel radiochemotherapy was started in 12/2017 and the third chemotherapy cycle was completed in early 02/2018. By mid-02/2018, persistent fever and bone pain heralded metastatic disease. She was started on nivolumab but experienced continued eruption of metastatic skin lesions. Evaluation revealed ECOG performance status 3 and skin metastases, with radiologic workup showing metastases to the bone, pancreas, gallbladder, and omentum as well as 7–9 intracranial metastatic lesions. The patient was started on gemcitabine, vinorelbine, cisplatin, irinotecan, avelumab, and olaparib. After 3 28-day cycles, evaluation revealed responding intracranial metastases with mixed response of the extracranial disease.

As of 06/2018, we changed her treatment to nab-paclitaxel 75 mg/m^2 days 1, 8, and 15 and etoposide 30 mg/m^2 days 3, 4, and 5 in a 28-day chemotherapy cycle, as well as pembrolizumab 200 mg IV every 3 weeks and cetuximab at an initial dose of 400 mg/m^2 IV followed by 250 mg/m^2 IV weekly. Partial regression was noted by 07/2018 with two small residual intracranial lesions. In 11/2018, CR of intracranial disease was noted. PET CR of extracranial disease was reached in 01/2019.

Patient 9

A 65-year-old Latino female was diagnosed with unresectable pancreatic adenocarcinoma in 11/2015. Prior therapy included 7 cycles of FOLFIRINOX with stable disease, followed by capecitabine radiochemotherapy. Upon disease progression, she received 10 cycles of gemcitabine.

Our pretreatment evaluation showed hypermetabolic extensive bulky regional disease, bulky retroperitoneal lymphadenopathy, and pretracheal lymphadenopathy by PET/CT. In 08/2017, we started nab-paclitaxel 100 mg/m^2 day 1 and 75 mg/m^2 days 9 and 16 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and erlotinib 75 mg p.o. daily. The elevated CA19.9 seen at our pretreatment evaluation (333 U/mL; normal <35 U/mL) normalized after cycle #3. In 09/2017, PET/CT evaluation revealed major partial response, and PET revealed CR with decreasing residual FDG-negative masses after cycle #5. The patient remained in remission as of 08/2018.

Patient 10

A 62-year-old Caucasian female presented with one week of abdominal discomfort. Radiological evaluation revealed pancreatic body mass with superior mesenteric artery and splenic artery involvement. CA19.9 was elevated at 74 U/mL and fine-needle aspiration confirmed the diagnosis of pancreatic adenocarcinoma in 11/2017. She underwent 6 cycles of neoadjuvant FOLFIRINOX followed by capecitabine radiochemotherapy with objective response. In 05/2018, she underwent extended distal pancreatectomy. The resected specimen revealed only 1–2-mm microscopic foci of poorly differentiated ductal adenocarcinoma with clear surgical margins and without tumor involvement in 0/10 lymph nodes. However, postoperative CT reevaluation in 06/2018 revealed a 1-cm left hepatic lesion. Fine-needle aspiration revealed adenocarcinoma. Further evaluation with PET/CT identified a 1-cm left hepatic hypermetabolic nodule in addition to two hypermetabolic lesions, one in the right lateral

gastrohepatic space and another at the medial aspect of the uncinate process. A third density was noted at the ventral aspect of the pancreatic head. CA19.9 was elevated at 67 U/mL.

We started systemic therapy in 6/2018 with nab-paclitaxel 75 mg/m^2 IV day 1, 60 mg/m^2 day 9, and 50 mg/m^2 day 16 and gemcitabine 750 mg IV day 2, 400 mg/m^2 day 17, and 300 mg/m^2 day 28 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and erlotinib 100 mg p.o. daily. After 2 cycles, PET/CT reevaluation showed partial response with decreased metabolic activity of the left hepatic lobe lesion and resolution of the hypermetabolic pancreatic lesions, denoting partial remission that has been maintained as of cycle #4.

Patient 11

A 78-year-old Caucasian female presented with obstructive jaundice in 06/2018 with the finding of a 3-cm pancreatic mass in the uncinate process with local invasion into the third part of the duodenum, causing obstructive symptoms and weight loss. Endoscopic ultrasound-guided biopsy of the pancreatic mass showed moderately differentiated adenocarcinoma. The patient underwent endoscopic biliary and duodenal stenting.

Our pretreatment evaluation showed mild progression of the pancreatic mass. CA19.9 was elevated at 780 U/mL. In 10/2018, we started the patient on gemcitabine 750 mg/m^2 IV days 1 and 8; 500 mg/m^2 IV day 18; and nab-paclitaxel 50 mg/m^2 IV days 2, 9, and 19 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and erlotinib 100 mg/day p.o. PET/CT after cycle #1 showed partial response and CA19.9 dropped to 130 U/mL. Continued tumor regression and a decline of CA19.9 to 52 U/mL was noted after cycle #2.

Patient 12

A 68-year-old Latino male with history of adalimumab therapy for ankylosing spondylitis was diagnosed with diffuse large B-cell lymphoma in 01/2014 and achieved a CR after 6 cycles of R-CHOP. The disease relapsed on maintenance rituximab in 09/2015. He received multiple treatment programs, including 2 cycles each of obinutuzumab-DHAP, MINE, and ESHAP, and one cycle 6-MP [16].

Our pretreatment evaluation revealed evident bilateral pleural effusion, ascites, peritoneal lymphomatosis, liver and bone involvement in addition to diffuse lymphadenopathy. Treatment was initiated in 08/2016 with gemcitabine 500 mg/m^2 IV days 18 and 19 and oxaliplatin 50 mg/m^2 IV days 2, 12, and 21 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks. PET/CT established disease regression in 09/2016 and CR in 01/2017. He expired 1 year later from respiratory failure without evidence of relapsed lymphoma.

Patient 13

A 27-year-old Caucasian male was diagnosed with stage IV B classical Hodgkin's lymphoma in 07/2013 and achieved partial response on ABVD followed by ICE, GND, and DHAP [17]. He achieved CR following BEAM/autologous transplant and brentuximab maintenance. Upon relapse in 11/2014, successive therapies including radiotherapy, brentuximab rechallenge, and gemcitabine/vinorelbine resulted in no response. In 11/2015, pembrolizumab therapy resulted in partial response until 10/2016. Subsequently, he enrolled in two trials with investigational agents until 05/2017 followed by palliative radiation to the mediastinal disease with continued disease progression.

Our pretreatment evaluation in 09/2017 revealed severe B symptoms including night sweats, weight loss, low grade fever, and pancytopenia. Extensive and necrotic mediastinal disease, hypermetabolic sub- and supradiaphragmatic lymph nodes, and extensive blastic bone involvement were noted on PET/CT. Treatment was initiated in 09/2017 with oxaliplatin 50 mg/m^2 IV day 1 and 25 mg/m^2 days 8 and 15 and cyclophosphamide 300 mg/m^2 IV days 4 and 8 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and everolimus [18] 5 mg p.o. daily. PET/CT showed major disease regression in 10/2017 and PET showed CR after cycle #5. CR status continued as of the last evaluation in 09/2018.

Patient 14

A 66-year-old Caucasian female had a history of melanoma of the back that was resected in 2006 without evidence of nodal involvement. Her first relapse in the right axilla was treated in 11/2010

with local excision followed by extensive right axillary recurrence treated with axillary dissection in 11/2016. The patient had a short course of nivolumab.

Our pretreatment evaluation in 04/2017 revealed that the patient had a bulky painful right infraclavicular soft tissue mass and proximal right forearm bone metastases with a bulky soft tissue component. These bulky masses were hypermetabolic, and mediastinal lymphadenopathy, large atrial metastasis, and omental mass were also noted as well as multiple areas of scattered subcutaneous and intramuscular nodules. ECOG performance status was 3-4 with elevated lactic dehydrogenase (LDH) of 4215 U/L (normal range 309-622 U/L). Treatment was started with docetaxel 25 mg/m^2 IV days 8 and 15; cisplatin 20 mg/m^2 IV days 2, 3, 4, and 8; and temozolomide 150 mg/m^2 IV days 1, 2, 3, 4, and 5 in a 28-day chemotherapy cycle, as well as pembrolizumab 200 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 3 weeks. By cycle 2, the result of BRAF V600E mutation was reported and dabrafenib 150 mg b.i.d. and trametinib 2 mg were started on alternating days. PET/CT after cycle #2 showed evidence of partial response. After cycle 8, PET/CT showed continued regression with only 1 cm residual FDG uptake in the right infraclavicular area with resolution of other metastatic sites including the right atrial metastasis.

Patient 15

A 29-year-old Caucasian female with melanoma of the left cheek was diagnosed in 04/2015. Initial treatment with adequate local excision and neck dissection up to level I revealed three out of five positive lymph nodes followed by postoperative radiation therapy to the left neck (level II–IV). In 07/2015, liver biopsy confirmed metastatic disease where PET/CT showed a solitary hypermetabolic hepatic lesion. The tumor was positive for BRAF mutation V600E, and in 08/2015 dabrafenib and trametinib were started with subsequent achievement of CR by PET. The patient chose to stop therapy in 04/2017.

In 04/2018, recurrent disease was demonstrated. Our PET/CT evaluation revealed extensive hypermetabolic disease in the liver with limited nodal uptake in the left supraclavicular area and mediastinum in addition to a right paraspinous soft tissue nodule. LDH was elevated at 3002 U/L (normal range 309-622 U/L). Subsequently, the patient was started on docetaxel 20 mg/m^2 IV days 1, 8, and 15; cisplatin 15 mg/m^2 IV days 3, 4, 5, and 7; and temozolomide 130 mg/m^2 IV days 3, 4, 5, 6, and 7 in a 28-day chemotherapy cycle, as well as pembrolizumab 200 mg IV every 3 weeks, ipilimumab 1 mg/kg IV every 3 weeks, dabrafenib 150 mg b.i.d., and trametinib 2 mg daily. Radiologic reevaluation after cycle #1 showed early disease regression. Reevaluation following cycle #2 showed disappearance of extrahepatic metastases and partial response in the liver. Partial response was maintained as of 09/2018 with continued disease regression.

Patient 16

A 59-year-old Caucasian female presented with right upper quadrant pain with extensive hepatomegaly. PET/CT revealed extensive hypermetabolic lesions with a dominant right hepatic mass in addition to hypermetabolic lymph nodes within the gastrohepatic ligament and porta hepatis. A hypermetabolic focus in the left lateral pelvis was also seen. Bilirubin was within normal range (0.8 mg/dL), with mild elevation of aspartate transaminase at 115 U/L (normal range 8-83 U/L) and alanine transaminase at 57 U/L (normal range 7-56 U/L). Hepatitis C antibody was reactive, and alpha-fetoprotein was elevated at 4535 ng/mL (normal <9.0 ng/mL). Liver biopsy showed moderately differentiated cholangiocarcinoma. Subsequent next generation sequencing revealed BRAF mutation.

We initiated treatment in 11/2017 in the form of gemcitabine 500 mg/m^2 IV days 1, 13, and 21 and cisplatin 10 mg/m^2 IV days 2, 3, and 4 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and sorafenib [19] 400 mg p.o. b.i.d. Anti-BRAF therapy with dabrafenib and trametinib was added starting at cycle #2. Within 2 weeks of starting treatment, alpha-fetoprotein dropped to 2882.5 mg/mL. A PET scan after cycle #4 showed complete metabolic remission. Alpha-fetoprotein normalized after cycle #7. The patient experienced cytopenia that mandated delay and dose reduction of chemotherapy. Continued remission was noted at the last evaluation in 08/2018.

Patient 17

An 82-year-old Caucasian male who was diagnosed with superficial urinary bladder urothelial cancer 6 years previously and was in remission presented with hematuria. Cystoscopic evaluation revealed a distal right ureteric mass 5 cm proximal to the ureterovesical junction. PET/CT revealed pelvic and periaortic lymphadenopathy.

In 02/2017, we started the patient on gemcitabine 500 mg/m^2 days 1 and 15, cisplatin 10 mg/m^2 days 5 and 7, and vinorelbine 20 mg/m^2 days 11 and 18 in a 28-day chemotherapy cycle, as well as atezolizumab 1200 mg IV every 3 weeks. Radiologic evaluation after cycle #4 showed complete regression. Subsequent therapy was delayed as per patient's choice with recurrent disease noted 3 months later.

Patient 18

A 48-year-old Caucasian female with history of hypertrophic cardiomyopathy and borderline ovarian tumor underwent conization of the cervix in 02/2013 for adenocarcinoma with subsequent salpingo-oophorectomy and hysterectomy in 05/2013. In 03/2017, she underwent debulking surgery for recurrent intraabdominal disease on the assumption that the patient had recurrent ovarian cancer, followed by 6 cycles of paclitaxel/ carboplatin, completed in 10/2017. Follow-up CT evaluation in 03/2018 showed recurrent intraabdominal disease. Upon pathology review of debulking surgery, the nature of recurrent tumor was confirmed as cervical adenocarcinoma. PET/CT showed seven hypermetabolic intraabdominal lesions with mild ascites. CA125 was elevated at 1388 U/mL (normal <38 U/mL).

We initiated treatment in 04/2018 with paclitaxel 75 mg/m^2 IV days 1, 8, and 15; cisplatin 15 mg/m^2 IV days 2, 3, and 5; gemcitabine 750 mg/m^2 IV day 6; 400 mg/m^2 day 22; and vinorelbine 20 mg/m^2 IV day 7 in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and erlotinib100 mg daily [20]. After cycle #1, CR was documented by PET, and CA125 dropped to 541 U/mL. CA125 normalized in 10/2018 and the patient has remained in CR.

Patient 19

A 45-year-old Caucasian female presented with a right frontoparietal 6.6 × 5.5 cm mass in 09/2017 as part of the workup for persistent nausea. Craniotomy with gross tumor resection was achieved in 10/2017. Pathology revealed glioblastoma World Health Organization (WHO) grade IV. The patient received temozolomide radiochemotherapy for a total of 60 Gy in 30 fractions, completed in 01/2018. However, post-radiation brain MRI revealed a new 18 × 7 mm enhancing lesion near the resection margin in 02/2018, which slightly increased by 04/2018 while the patient was on temozolomide maintenance.

In 05/2018, we started the patient on irinotecan 75 mg/m^2 IV days 1 and 8; cisplatinum 15 mg/m^2 IV days 2, 3, and 4; and temozolomide 150 mg/m^2/day 5× per day orally in a 28-day chemotherapy cycle, as well as nivolumab 240 mg IV every 2 weeks and bevacizumab 10 mg/kg IV every 2 weeks. After cycle #1, brain MRI showed decreasing enhancement. As of 08/2018, brain MRI showed no residual enhancing mass that would suggest residual viable neoplasm.

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