Title

Phase Ib study of talimogene laherparepvec in combination with atezolizumab in patients with triple negative breast cancer and colorectal cancer with liver metastases

Journal

ESMO Open, 8(2)

ISSN

2059-7029

Authors

Hecht, JR
Raman, SS
Chan, A
et al.

Publication Date

2023-04-01

DOI

10.1016/j.esmoop.2023.100884

Peer reviewed

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL RESEARCH

Phase Ib study of talimogene laherparepvec in combination with atezolizumab in patients with triple negative breast cancer and colorectal cancer with liver metastases

J. R. Hecht[1*], S. S. Raman[2], A. Chan[3], K. Kalinsky[4], J.-F. Baurain[5], M. M. Jimenez[6], M. M. Garcia[7], M. D. Berger[8], U. M. Lauer[9,10], A. Khattak[11], A. Carrato[12,13], Y. Zhang[14], K. Liu[15], E. Cha[16], A. Keegan[15], S. Bhatta[15], C. P. Strassburg[17] & A. Roohullah[18]

[1]Division of Hematology/Oncology, David Geffen School of Medicine at UCLA, Santa Monica; [2]Department of Radiology, David Geffen School of Medicine at UCLA, Santa Monica, USA; [3]Breast Cancer Research Centre – WA & Curtin University, Perth Breast Cancer Institute Hollywood Consulting Centre, Nedlands, Australia; [4]Emory Winship Cancer Institute, Atlanta, USA; [5]Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; [6]Hospital General Universitario Gregorio Marañon, Universidad Complutense, CIBERONC, Madrid; [7]Department of Medical Oncology, Hospital del Mar, CIOCC Barcelona, CIBERONC, Barcelona, Spain; [8]Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; [9]Department of Medical Oncology and Pneumology, Virotherapy Center Tübingen, University Hospital Tübingen, Tübingen; [10]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), partner site Tübingen, Tübingen, Germany; [11]Fiona Stanley Hospital & Edith Cowan University, Perth, Australia; [12]Medical Oncology Department, Ramon y Cajal University Hospital, Alcala University, IRYCIS, CIBERONC, Madrid, Spain; [13]Pancreatic Cancer Europe Chairman, Brussels, Belgium; [14]Virginia Oncology Associates, Norfolk; [15]Amgen Inc., Thousand Oaks; [16]Genentech, South San Francisco, USA; [17]Department of Medicine I, University Hospital Bonn, Medical Clinic and Polyclinic I, Bonn, Germany; [18]Liverpool Hospital, Liverpool, Australia

Available online 28 February 2023

Background: Talimogene laherparepvec (T-VEC), a first-in-class oncolytic viral immunotherapy, enhances tumor-specific immune activation. T-VEC combined with atezolizumab, which blocks inhibitor T-cell checkpoints, could provide greater benefit than either agent alone. Safety/efficacy of the combination was explored in patients with triple negative breast cancer (TNBC) or colorectal cancer (CRC) with liver metastases.

Methods: In this phase Ib, multicenter, open-label, parallel cohort study of adults with TNBC or CRC with liver metastases, T-VEC (10^6 then 10^8 PFU/ml; $\leq$4 ml) was administered into hepatic lesions via image-guided injection every 21 ($\pm$3) days. Atezolizumab 1200 mg was given on day 1 and every 21 ($\pm$3) days thereafter. Treatment continued until patients experienced dose-limiting toxicity (DLT), had complete response, progressive disease, needed alternative anticancer treatment, or withdrew due to an adverse event (AE). The primary endpoint was DLT incidence, and secondary endpoints included efficacy and AEs.

Results: Between 19 March 2018 and 6 November 2020, 11 patients with TNBC were enrolled (safety analysis set: $n = 10$); between 19 March 2018 and 16 October 2019, 25 patients with CRC were enrolled (safety analysis set: $n = 24$). For the 5 patients in the TNBC DLT analysis set, no patient had DLT; for the 18 patients in the CRC DLT analysis set, 3 (17%) had DLT, all serious AEs. AEs were reported by 9 (90%) TNBC and 23 (96%) CRC patients, the majority with grade $\geq$3 [TNBC, 7 (70%); CRC, 13 (54%)], and 1 was fatal [CRC, 1 (4%)]. Evidence of efficacy was limited. Overall response rate was 10% (95% confidence interval 0.3-44.5) for TNBC; one (10%) patient had a partial response. For CRC, no patients had a response; 14 (58%) were unassessable.

Conclusions: The safety profile reflected known risks with T-VEC including risks of intrahepatic injection; no unexpected safety findings from addition of atezolizumab to T-VEC were observed. Limited evidence of antitumor activity was observed.

Key words: breast neoplasms, drug therapy combination, gastrointestinal neoplasms, virotherapy, viral immunotherapy

INTRODUCTION

Talimogene laherparepvec (T-VEC) is a first-in-class oncolytic viral immunotherapy based on a modified herpes simplex virus (HSV) type-1, designed to produce granulocyte-macrophage colony-stimulating factor (GM-CSF) in the tumor to enhance antigen release, presentation, and anti-tumor immune responses.[1,2] T-VEC likely augments

*Correspondence to: Prof. Joel Randolph Hecht, David Geffen School of Medicine at UCLA, 2020 Santa Monica Blvd., #600, Santa Monica, CA 90404, USA. Tel: +1-310-829-5471

E-mail: jrhecht@mednet.ucla.edu (J. R. Hecht).

dendritic cell-mediated tumor antigen presentation through local expression of GM-CSF and local antigen release by tumor cell lysis.[1] T-VEC is approved by the US Food and Drug Administration for the local treatment of unresectable, cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.[3] T-VEC is also approved by the European Medicines Agency for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (stage IIIB, IIIC and IVM1a) with no bone, brain, lung, or other visceral disease.[4]

Atezolizumab inhibits programmed death-ligand 1 (PD-L1), blocking the interaction of PD-L1 with the programmed cell death protein 1 (PD-1) and B7.1 receptors to release the inhibition of the antitumor response.[5] Atezolizumab initially earned US accelerated approval in combination with nab-paclitaxel for the first-line therapy of triple negative breast cancer (TNBC) expressing PD-L1.[5,6] The approval was on the basis of the phase III IMpassion130 trial, which showed a 2.5-month improvement in the median progression-free survival (PFS) and a 9.5-month improvement in median overall survival (OS) over nab-paclitaxel alone in the PD-L1-positive subgroup [median PFS, 7.5 months versus 5.0 months, hazard ratio (HR) 0.62; 95% confidence interval (CI) 0.49-0.78, median OS: 25.0 months versus 15.5 months, HR 0.62, 95% CI 0.45-0.86].[7] Another phase III study, IMpassion131, pairing atezolizumab with paclitaxel instead of nab-paclitaxel, however, failed to show improvement in PFS, and the accelerated approval with nab-paclitaxel was subsequently withdrawn.[8,9] Single-agent atezolizumab activity was observed in the first-in-human phase I study with the PD-L1-positive ($\geq$1% tumor-infiltrating immune cells) subgroup demonstrating an objective response rate (ORR) of 12% ($n = 91$, 95% CI 6%-21%), but not in the PD-L1-negative subgroup demonstrating an ORR of 0% ($n = 21$, 95% CI 0%-17%).[10]

In colorectal cancer (CRC), the use of PD-1 pathway inhibitors is limited to the subset with high microsatellite instability and/or deficient DNA mismatch repair genes.[11,12] Several studies have failed to demonstrate improved clinical outcome with the addition of atezolizumab to other standards of care in the setting of microsatellite stability (MSS) disease.[13] More recently, polymerase epsilon (*POLE)* mutations have been identified as predictive of sensitivity to checkpoint blockade in patients with CRC.[14]

The combination of an agent that increases tumor-specific immune activation (T-VEC) with one that blocks inhibitory T-cell checkpoints (atezolizumab) could potentially produce greater antitumor activity than either agent alone in both TNBC and CRC. Results from melanoma combining PD-1 inhibitors and T-VEC have been mixed; a response rate of 62% was observed in a phase Ib study of pembrolizumab and T-VEC;[15] however, PFS or OS improvement was not observed in the randomized, double-blinded phase III portion comparing the combination of T-VEC plus pembrolizumab with placebo and pembrolizumab.[16] Given the high rates of liver metastases in patients with TNBC or CRC, and the limited efficacy with PD-1 pathway inhibitor monotherapy,[17-19] this study sought to evaluate safety and explore efficacy of the combination of intrahepatic T-VEC injection in combination with atezolizumab in patients with TNBC with liver metastases and patients with CRC with unresectable liver metastases.

PATIENTS AND METHODS

Study design and treatment

This was a phase Ib, multicenter, open-label, parallel cohort study (NCT03256344). Cohort 1 included patients with TNBC with liver metastases, and cohort 2 included patients with CRC and unresectable liver metastases.

T-VEC was delivered in the hepatic lesions via image-guided injection. T-VEC was initially administered at a concentration of 10^6 PFU/ml intralesionally followed by subsequent doses at 10^8 PFU/ml up to 4.0 ml per treatment session every 21 ($\pm$3) days. The volume of T-VEC delivered depended on the longest diameter of the tumor and/or the necrotic core. Atezolizumab was administered at 1200 mg intravenously on day 1 and every 21 ($\pm$3) days thereafter. For each patient, the dose-limiting toxicities (DLTs) evaluation period was the period between the initial dose of T-VEC in combination with atezolizumab and 3 weeks after the first 10^8 PFU/ml dose of T-VEC and atezolizumab, or the start of cycle 3, whichever occurred first.

Patients continued treatment unless they experienced a DLT (during the DLT evaluation period as described), had a complete response (CR), had a need for an alternative anticancer therapy due to cancer progression, or had an adverse event (AE) that necessitated discontinuation of the investigational treatments. In addition, for T-VEC, patients discontinued if they had no injectable lesions, if progressive disease (PD) was confirmed per modified immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors (irRC-RECIST), or if they experienced rapid clinical deterioration. For atezolizumab, patients discontinued upon symptomatic disease progression.

Patients

Eligible patients were aged $\geq$18 years with diagnosis of TNBC or CRC with liver metastases and had disease progression during or after one or more prior standard-of-care systemic anticancer therapies for metastatic disease or progressed during or within 6 months of receiving adjuvant therapy. Prior therapy with T-VEC, other oncolytic virus therapy, immune checkpoint inhibitor, or other immunostimulatory agent was not permitted. Patients had measurable liver lesions suitable for injection (i.e. less than one-third of liver involvement; no macroscopic intravascular invasion into the main portal vein, hepatic vein or vena cava; and no current or previous liver metastatic-directed therapy), Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate organ function with a normal coagulation profile, and life expectancy $\geq$5 months. Patients provided written informed consent; study procedures received institutional approval

(Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.100884).

Endpoints

Incidence of DLTs by cohort was used to assess the primary endpoint. Assessments for secondary endpoints included ORR [incidence rate of CR or partial response (PR) based on modified irRC-RECIST criteria], best overall response (at least 28 days after first documentation was required for CR or PR), duration of response (DOR), lesion-level responses in injected and uninjected tumor lesions, disease control rate [DCR; proportion of patients with a best overall response in CR, PR, or stable disease (SD)], durable response rate (DRR; rate of patients with an objective response with a DOR of at least 6 months), PFS (time from first dose to first confirmed disease progression per modified irRC-RECIST criteria, or death), OS (time from the first dose to death from any cause), and the incidence of AEs and clinically relevant laboratory abnormalities by cohort. Exploratory endpoints included an analysis of PD-L1 expression by staining with the SP263 antibody in tumor biopsies.

Statistical analysis

The findings reported herein are based on the primary analysis for TNBC (data cut-off, 6 November 2020) and CRC (data cut-off, 16 October 2019). These two cohorts were enrolled and analyzed separately. The DLT analysis set was defined as all DLT-evaluable patients who received two or more cycles of treatment and two or more doses of T-VEC and atezolizumab or who had a DLT during the DLT evaluation period. The safety analysis set was defined as enrolled patients who received one or more doses of T-VEC or atezolizumab. The incidence of treatment-emergent AEs, defined as all AEs between the first dose and 30 days after the last dose, was summarized; AEs were coded per the Medical Dictionary for Regulatory Activities version 17.0 or later, and severity was graded per the Common Terminology Criteria for Adverse Events, version 4. Clinically significant laboratory changes and clinically significant changes in vital signs were summarized using descriptive statistics. For the efficacy endpoints, ORR, DRR, and DCR were summarized with associated 95% CIs. CIs were calculated per Wilson's score method with continuity correction. The Kaplan—Meier method was used to estimate DOR, PFS, and OS.

RESULTS

Patient characteristics, disposition, and treatment

Between 19 March 2018 and 6 November 2020, 11 patients with TNBC were enrolled at nine centers in Australia, Europe, and the United States (Figure 1A). Enrollment in this cohort was stopped early due to low accrual. Ten patients received at least one dose of any investigational agent and were included in the safety analysis set. Twenty-five patients with CRC were enrolled between 19 March 2018 and 16 October 2019, at 12 centers in Australia, Europe, and the United States (Figure 1B). Twenty-four patients were included in the safety analysis set. Baseline characteristics for patients in the safety dataset are listed in Table 1.

Extent of exposure

In patients with TNBC, the median (range) follow-up time was 3.8 (1.2-28.6) months. Patients with TNBC had a median (range) of 3.0 (1-6) injections over 6.3 (0.1-15.1) weeks for T-VEC and 3.0 (1-7) infusions over 6.3 (0.1-18) weeks for atezolizumab. For T-VEC, the median (range) volume was 4.0 (1.0-4.0) ml at first injection (10^6 PFU/ml) and 3.1 (0.9-4.0) ml after the first injection (10^8 PFU/ml), and the median (range) cumulative volume administered was 8.2 (4.0-20.0) ml. Six patients (60%) had a dose of T-VEC changed or withheld during the study, with a median (range) of 1.0 (1.0-2.0) doses changed or withheld per patient. Reasons for doses changed or withheld included AE (three patients) and 'other' (three patients).

In patients with CRC, the median (range) follow-up time was 3.2 (0.7-11.6) months. Patients with CRC received a median (range) of 2.0 (1-5) injections over 3.3 (0.1-14.3) weeks for T-VEC and 2 (1-5) infusions over 3.2 (0.1-14.3) weeks for atezolizumab. The median (range) volume of T-VEC administered was 2.0 (1.0-4.0) ml at first injection (10^6 PFU/ml) and 2.0 (1.0-4.0) ml after the first injection (10^8 PFU/ml), and the median (range) cumulative volume administered was 5.0 (2.0-18.0) ml. Twenty patients (83%) with CRC had a dose of T-VEC changed or withheld during the study, with a median (range) of 1.0 (1.0-3.0) dose changed or withheld per patient. Reasons for doses changed or withheld included AEs (8 patients), atezolizumab being withheld (3 patients), dose administration error (1 patient), and 'other' (12 patients; primarily due to disease progression).

Dose-limiting toxicities

Of the 10 TNBC patients, 5 patients were included in the DLT analysis set; no patient had a DLT during the DLT evaluation period. Of the 24 CRC patients, 18 patients were included in the DLT analysis set. Three patients (17%) had a DLT; all were serious AEs [SAEs; grade 3 electrocardiogram (ECG) QT prolongation, grade 4 respiratory failure; grade 4 decreased platelet count]. The events of ECG QT prolongation and decreased platelet count were reported as recovered/resolved. In contrast, the respiratory failure was not resolved, and the patient died as a result of pleural effusion and pneumonia, which were confirmed by imaging. The differential diagnosis included pneumonia with signs of infection and tumor progression with lung involvement; fulminant pneumonitis could not be excluded.

Adverse events

Nine patients (90%) with TNBC had at least one treatment-emergent AE (Table 2). The most frequently reported AEs ($\geq$25% of patients) were pyrexia (70%), chills (40%), fatigue (40%), arthralgia (30%), diarrhea (30%), headache (30%),

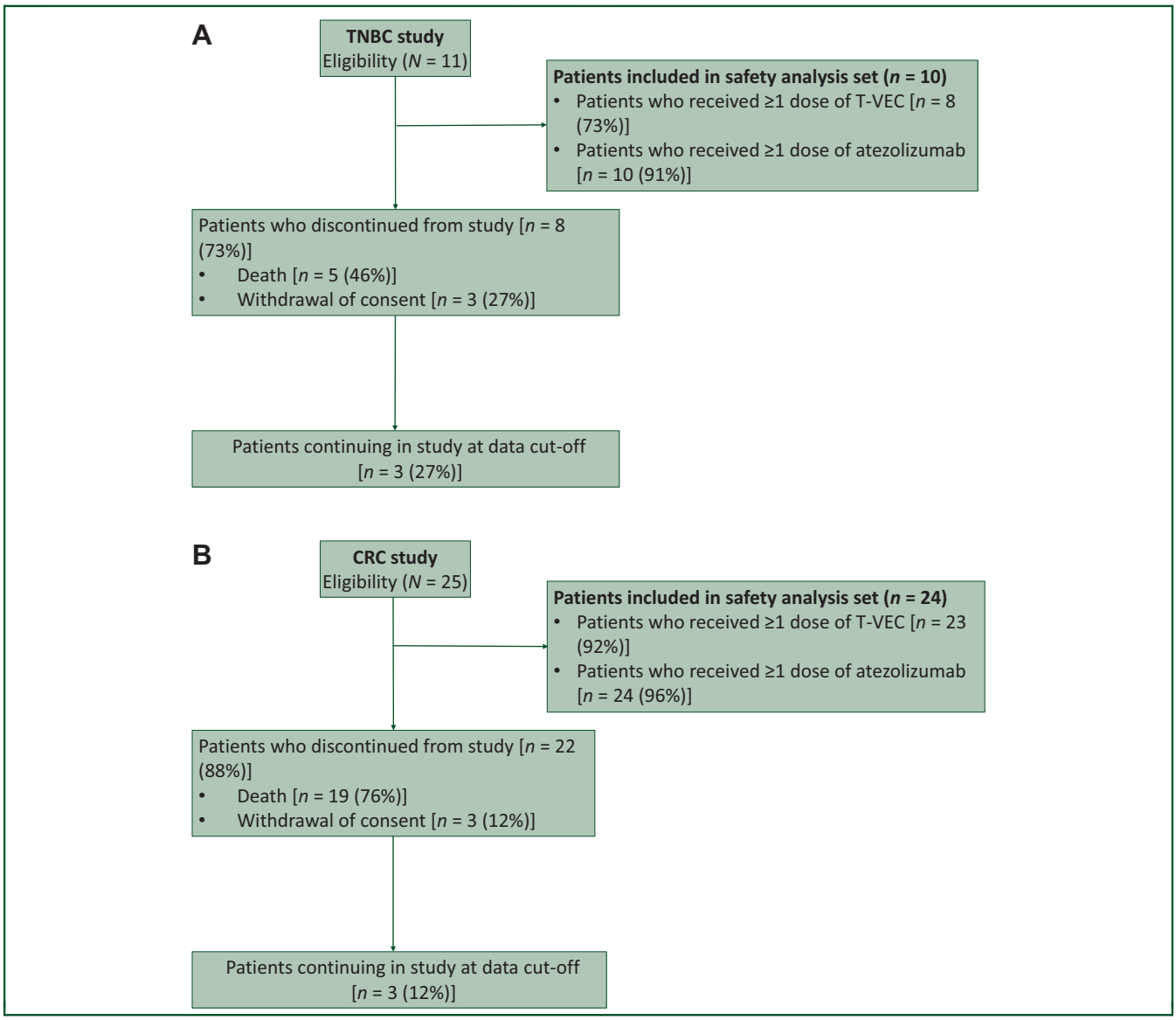

Figure 1. CONSORT diagram (A) TNBC and (B) CRC.
CRC, colorectal cancer; T-VEC, talimogene laherparepvec; TNBC, triple negative breast cancer.

and nausea (30%). Seven patients (70%) had grade ≥3 AEs, such as abdominal infection, cytokine release syndrome, and fatigue (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2023.100884). The only reported grade 4 event was lymphocyte count decrease, and no events were fatal. Four patients (40%) in the TNBC cohort experienced treatment-emergent SAEs; these were abdominal infection, cytokine release syndrome, hepatic hematoma, hypersensitivity, and orthostatic hypotension (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.100884). None of these SAEs were reported by more than one patient. No AE led to the discontinuation of T-VEC or atezolizumab. Eight patients (80%) had AEs considered related to any investigational product; seven patients (70%) had AEs considered related to T-VEC, including grade 3 events of fatigue, cytokine release syndrome, and presyncope. One patient in the TNBC cohort experienced an SAE of hepatic hematoma (grade 3) following both liver biopsy and T-VEC injection carried out on cycle 1, week 1. This was attributed by the investigator to intrahepatic biopsy/injection and resolved with supportive care, but subsequently the patient developed an abdominal infection (grade 3) and was discontinued from the study due to disease progression.

Twenty-three patients (96%) with CRC had at least one treatment-emergent AE (Table 2); the most frequent AEs were pyrexia (67%) and vomiting (33%). Thirteen patients (54%) had grade ≥3 AEs, such as fatigue, decreased platelet count, and anemia. Only decreased platelet count occurred in one or more patients ($n = 2$). Four events were grade 4 (constipation, hyponatremia, respiratory failure, and decreased platelet count), and one event was fatal (pulmonary sepsis). Eleven patients (46%) in the CRC cohort had treatment-emergent SAEs; the only SAE that was reported by more than one patient was pyrexia (13%). One patient in the CRC cohort experienced an SAE of intra-abdominal fluid collection (grade 3) following liver biopsy and three T-VEC injections which, per the investigator, was possibly related

Table 1. Baseline demographics and clinical characteristics[a]

	TNBC (n = 10)	CRC (n = 24)
Age, median (range), years	53.0 (32-63)	62.5 (40-80)
Sex, *n* (%)		
Men	0	13 (54)
Women	10 (100)	11 (46)
Prior lines of therapy in the metastatic setting, *n* (%)		
None	1 (10)	1 (4)[a]
1	5 (50)	3 (13)
2 or more	4 (40)	20 (83)
ECOG performance status, *n* (%)		
0	7 (70)	11 (46)
1	3 (30)	13 (54)
LDH, *n* (%)		
≤ULN	5 (50)	4 (17)
>ULN	5 (50)	19 (79)
Unknown	0	1 (4)
HSV serostatus, *n* (%)		
Positive	8 (80)	17 (71)
Negative	2 (20)	5 (21)
Unknown	0	2 (8)
MSI phenotype for CRC[b]		
MSI high (≥2 loci positive)	—	0
MSI low (1 locus positive)	—	1 (4)
MSS (all loci negative)	—	14 (58)
Not tested	—	8 (33)
Unknown/missing	—	1 (4)

CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; HSV, herpes simplex virus; LDH, lactate dehydrogenase; MSI, microsatellite instability; MSS, microsatellite stability; TNBC, triple negative breast cancer; ULN, upper limit of normal.
[a]Patient entered study due to early failure on adjuvant therapy.
[b]Percentages do not add to 100 due to rounding.

to T-VEC, atezolizumab, and intrahepatic procedure. The patient underwent interventional radiology-guided drainage of the fluid. Two patients had AEs that led to the discontinuation of T-VEC and atezolizumab. Twenty patients (83%) with CRC had AEs considered related to any investigational product. Nineteen patients (79%) had AEs related to T-VEC; most frequently pyrexia (n = 14, 58%). Two patients (8%) had grade ≥3 events resulting in discontinuation of treatment (grade 3 ECG QT prolongation and grade 3 myocarditis). Five patients (21%) with CRC had AEs that were related to any investigational product, and six patients (25%) had SAEs related to any investigational product. One patient had a fatal AE of pulmonary sepsis, that followed a previous diagnosis of respiratory failure (unresolved grade 4 event), which was related to any investigational product. No pathogen was found in the microbiology analysis of tracheal secretion and blood. Secondary diagnosis included tumor progression, and the diagnosis of pneumonitis could not be excluded.

Efficacy

For the TNBC cohort, the ORR per modified irRC-RECIST was 10% (95% CI 0.3%-44.5%); one patient (10%) had a PR (Table 3). One patient (10%) had SD, and three patients (30%) had PD. Three patients (30%) were not assessable. In the remaining two patients (20%), tumor response assessments were not carried out as no scans were undertaken. A PR was observed for one injected hepatic lesion and one uninjected non-hepatic lesion; the response duration was 3 months. The DCR was 20% (95% CI 2.5%-55.6%); the median DOR was not estimable. The patient with a PR was HSV-1-negative at baseline, and tumor biopsy was PD-L1-negative at baseline according to the SP-263 assay.

Table 2. Patient incidence of adverse events

	TNBC (n = 10)	CRC (n = 24)
Any AE, *n* (%)	9 (90)	23 (96)
Grade ≥3 AEs	7 (70)	13 (54)
Serious	4 (40)	11 (46)
Fatal	0	1 (4)
Leading to discontinuation of T-VEC	0	2 (8)
Leading to discontinuation of atezolizumab	0	2 (8)
Related to T-VEC	7 (70)	19 (79)
Grade ≥3 AEs	2 (20)	2 (8)
Serious	1 (10)	4 (17)
Fatal	0	0
Related to any investigational product	8 (80)	20 (83)
Grade ≥3 AEs	5 (50)	5 (21)
Serious	2 (20)	6 (25)
Fatal	0	1 (4)

AE, adverse event; CRC, colorectal cancer; T-VEC, talimogene laherparepvec; TNBC, triple negative breast cancer.

For patients with CRC, the ORR was 0%; 1 patient (4%) had SD; 4 patients (17%) had PD; 14 patients (58%) were unassessable (Table 3). No patient had a lesion-level response in an injected lesion; one patient had a lesion-level PR in an uninjected lesion. The ORR for patients in the uninjected lesion analysis set was 5% (95% CI 0.1%-22.8%). The DCR was 4% (95% CI 0.1%-21.1%).

Progression-free event analysis. In regard to the 10 treated patients with TNBC, for the 5 patients (50%) who had disease progression or died during the study, the median PFS per modified irRC-RECIST was 5.4 months (95% CI 1.0-8.6 months; Figure 2A). In 24 treated patients with CRC, for the 20 patients (83%) who had disease progression or died

Table 3. Efficacy

	TNBC (n = 10)	CRC (n = 24)
Response assessment per modified irRC-RECIST, *n* (%)		
CR	0	0
PR	1 (10)	0
SD	1 (10)	1 (4)
PD	3 (30)	4 (17)
Unevaluable	3 (30)	14 (58)
Not done	2 (20)	5 (21)
Objective response rate (CR/PR), *n* (%) [95% CI]	1 (10) [0.3-44.5]	0 [0-14.2]
Disease control rate (CR/PR/SD), *n* (%) [95% CI]	2 (20) [2.5-55.6]	1 (4) [0.1-21.1]
Durable response rate, *n* (%) [95% CI]	0 [0-30.8]	0 [0-14.2]

CR, complete response; CRC, colorectal cancer; irRC-RECIST, immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple negative breast cancer.

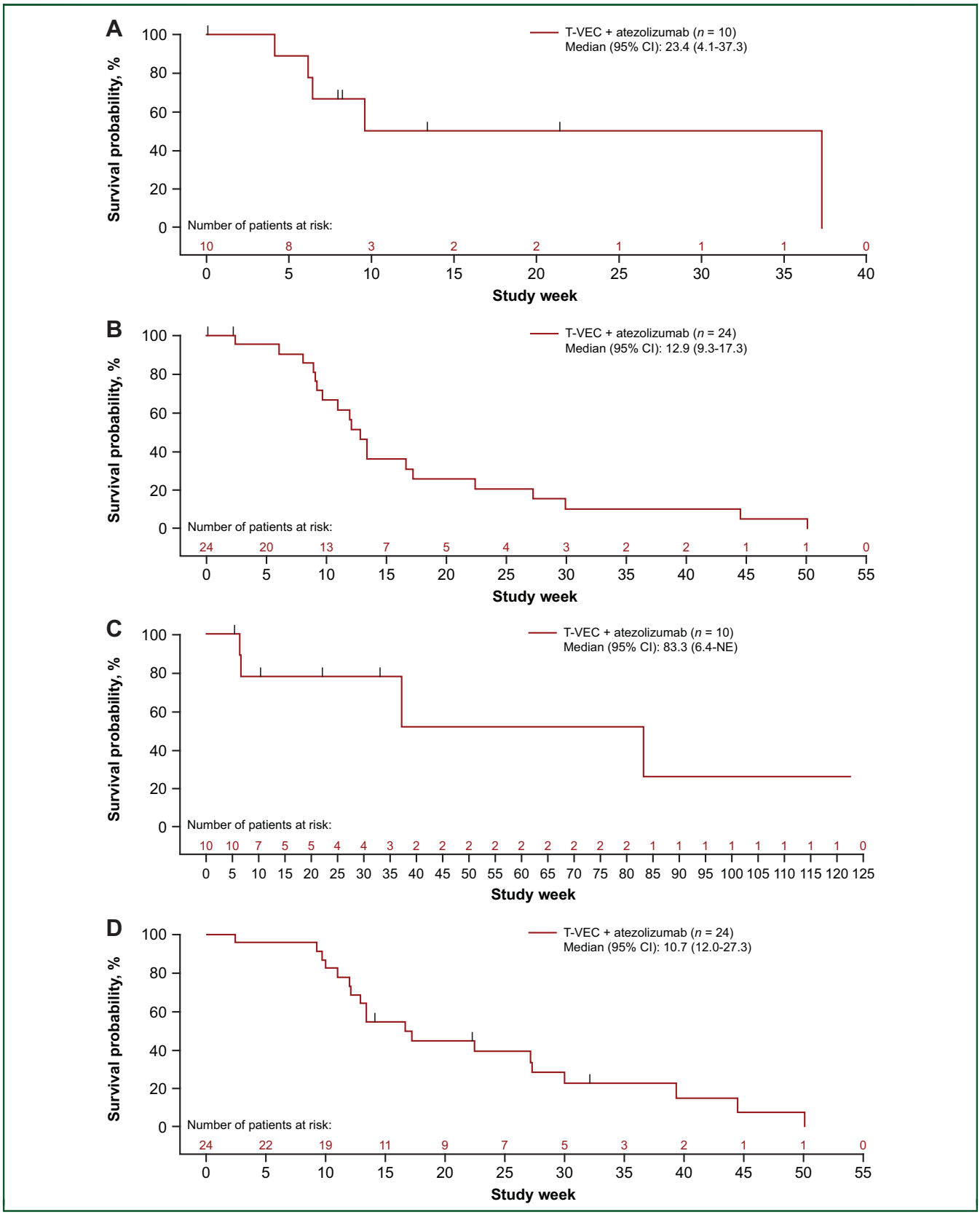

Figure 2. Kaplan–Meier plot for PFS[a] in (A) TNBC and (B) CRC, and OS[b] in (C) TNBC and (D) CRC for all patients who have received ≥1 dose of T-VEC or atezolizumab.

CI, confidence interval; CRC, colorectal cancer; irRC-RECIST, immune-related response criteria simulating Response Evaluation Criteria in Solid Tumors; NE, non-estimable; OS, overall survival; PFS, progression-free survival; TNBC, triple negative breast cancer; T-VEC, talimogene laherparepvec.

[a]PFS per modified irRC-RECIST is the interval from the first dose to the earlier of patient overall response of progressive disease or death from any cause; PFS is censored at the later of their last assessable tumor assessment or date of first dose.

[b]OS is the interval from the first dose to death from any cause; OS is censored at the date the patient was last known to be alive.

during the study, the median PFS was 3 months (95% CI 2.1-4.0 months; Figure 2B).

Overall survival. In patients with TNBC, the median OS was 19.2 months (95% CI 1.5 to not estimable; Figure 2C). The Kaplan—Meier OS estimate at 12 months was 52% (95% CI 8.4%-84.0%); at 27 months it was 26% (95% CI 1.1%-67.0%). In patients with CRC, median OS was 3.8 months (95% CI 2.8-6.3 months; Figure 2D). The Kaplan—Meier OS estimate at 3 months was 64% (95% CI 40.6%-80.1%).

DISCUSSION

This open-label study examined the safety and preliminary efficacy of T-VEC plus atezolizumab in patients with TNBC or CRC and metastases in the liver, a common site of metastasis in these cancers, and one associated with poor prognosis.[20,21] No DLTs were observed in the TNBC cohort, and three DLTs were observed in the CRC cohort. Grade $\geq$3 events occurred in more than half of the patients with TNBC or CRC. In patients with TNBC, there was one grade 4 event, and no events resulted in the discontinuation of treatment. In patients with CRC, there were four grade 4 events, two grade $\geq$3 events resulted in discontinuation of treatment and resolved, and one event of pulmonary sepsis was fatal. This study had three related SAEs (intra-abdominal fluid collection, hepatic hematoma, and abdominal infection), highlighting the risk of transcutaneous liver procedures and the route of administration. Although limited antitumor activity was observed in both cohorts, the PR in a TNBC patient with a tumor that was PD-L1-negative at baseline and the uninjected lesion-level PR in the CRC patient (PD-L1 unavailable) are suggestive of possible limited T-VEC activity.

Other oncolytic viral immunotherapies have been tested in patients with breast cancer[22] and CRC.[23] In a phase II study in patients with metastatic breast cancer, the combination of the oncolytic reovirus pelareorep and paclitaxel led to improved OS compared with paclitaxel alone; however, there was no significant difference in PFS between the treatment groups, and baseline characteristics for the treatment arms were reported to be imbalanced in favor of pelareorep.[24] Pelareorep may be associated with a late-onset adaptive immune response based on high levels of peripheral T-cell clonality, stimulating further research into the combination of pelareorep with checkpoint blockade therapy.[25]

Results from preclinical models and studies using patient-derived cells suggest that liver metastases siphon activated CD8+ T cells from systemic circulation and within the liver, leading to acquired immunotherapy resistance.[21] Liver-directed radiotherapy has been shown to eliminate immunosuppressive hepatic macrophages, increase hepatic T-cell survival, and reduce hepatic siphoning of T cells through a mechanism involving reactivation of the tumor immune microenvironment.[21] This study focused on patients with liver metastases, a group with poor prognosis, and our results suggest that additional approaches are needed to overcome immunotherapy resistance. With T-VEC, a preferred approach could be injecting nodal lesions; another study, currently in progress, examining the combination of pembrolizumab and T-VEC, may indicate if greater clinical activity is dependent on distribution of metastatic/injectable disease.[26] An additional study (NCT02366195) examining CD8+ cell density and biomarkers in T-VEC-injected and uninjected metastases is also ongoing and should provide important data on the tumoral environment of uninjected metastases and provide information on potential combination therapies.[27,28]

Limitations of this study include the small number of patients and the early cessation in the TNBC cohort enrollment due to slow accrual. One potential factor for the slowed enrollment in the latter group was the approval of atezolizumab in combination with paclitaxel protein-bound for PD-L1-positive disease[5] and the study exclusion criterion of prior checkpoint inhibitor therapy. Overall challenges to enrollment are likely related to the study design and the complexity in place to ensure patient safety and to balance the risk of bleeding or decompensation in liver function with the benefits of the injection. For example, patients were required to have less than one-third of the liver involved with metastases and, reflecting the treatment restrictions that apply to administration of atezolizumab in TNBC [i.e. patients could not receive antibody-based therapy or immunotherapy for at least 4 weeks before enrollment, atezolizumab was withheld if baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increase to $>3\times$ the upper limit of normal],[5] patients had to have AST and ALT $<2.5\times$ the upper limit of normal for study enrollment. Injectable lesions were anatomically defined as $\geq$1 cm from the left main, right main, or common biliary ducts or $\geq$1 cm from the hepatic capsule. Allowing injection of lymph node or subcutaneous lesions as was done in the melanoma studies in addition to liver lesions may improve the ability to evaluate the efficacy of T-VEC and possibly improve the immunologic effects of the treatment.[29]

Conclusions

This phase Ib study demonstrated that the safety profile for intralesional T-VEC and atezolizumab aligns with the expected safety profile, including the risks of intrahepatic injection, with very limited evidence of antitumor activity in patients with liver metastases associated with TNBC or CRC.

ACKNOWLEDGEMENTS

Thank you to Sara A. Hurvitz of UCLA for feedback on study design. Writing support was funded by Amgen Inc. and provided by Miranda Tradewell, PhD (ICON plc, Blue Bell, PA) and Christopher Nosala, PhD (Amgen Inc.).

FUNDING

This work was supported by Amgen Inc.

DISCLOSURE

JRH reports advisory board for Amgen, ARMO/Lilly, Gritstone, AstraZeneca, Roche, Bristol-Myers Squibb (BMS), Merck, Acrotech, Ipsen, Astellas, Corcept, Istari, Exelixis, ImmVirX, Notch, Mirati, and Lutris; stockholder of Actym and Rafael; institutional grant from Astellas, Merck, Amgen, Forty Seven/Gilead, AbbVie, Armo/Lilly, Tesaro/GlaxoSmithKline (GSK), Immunomedics, GSK, and Gilead. SSR is a consultant for Bayer, Merck, Johnson and Johnson, and AngioDynamics. KK reports grants/contracts to his institution from Incyte, Novartis, Genentech, Eli-Lilly, Pfizer, Calithera, Immunomedics, Acetylon, Seattle Genetics, Amgen, Zentalis, and CytomX Therapeutics; consulting fees/consultant honorarium from Daiichi Sankyo, Eli-Lilly, Pfizer, Novartis, Eisai, AstraZeneca, Immunomedics, Merck, Seattle Genetics, Cyclacel, OncoSec, and 4D Pharma; speakers bureau: Eli-Lilly; support for attending meetings and/or travel from Eli-Lilly, AstraZeneca, Pfizer; participation on advisory board (steering committee): Immunomedics, AstraZeneca, Ambrx, Genentech; and stock options/employment: Grail (spouse), Array BioPharma (spouse), and Pfizer (spouse); JFB reports no competing interests; payment to his institution for consulting, advisory role or lecture for BMS, Merck Sharp & Dohme (MSD), Novartis, Sanofi, Regeneron, Merck, Pfizer, Pierre-Fabre, Sun Pharma, AstraZeneca, and Immunocore; MMJ reports advisory board for AstraZeneca, Daiichi Sankyo, Lilly, and Roche/Genentech; invited speaker for AstraZeneca, Lilly, Novartis, Pfizer, and Roche/Genentech; institutional grant from Novartis, Puma, and Roche. MMG reports consulting, advisory role, travel expenses, research funding from Roche, Seattle Genetics, Pfizer, Pierre-Fabre; UML reports no competing interests; payment to his institution for consulting, advisory role or lecture from Boehringer Ingelheim, Themis/MSD, and Novartis; AC reports funding from advisory boards from MSD, Roche, Merck, Pfizer, Bayer, Servier, Celgene, and Amgen; KL is an employee of and owns stock in Amgen Inc.; EC is an employee of and owns stock in Roche-Genentech; AK is an employee of and owns stock in Amgen Inc.; SB is an employee of and owns stock in Amgen Inc.; CPS reports speaker honoraria from Falk Pharma, Eisai, Astellas, Chiesi, and MSD; support for seminars from Gilead, BMS, AbbVie, MSD, Norgine, Tillots Pharma, Eisai, Janssen, and Falk Foundation; advisory board for Fa. Schwabe, AstraZeneca, Eisai, and Astellas. All other authors have declared no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol and amendments were reviewed by an independent ethics committee or institutional review board for each site. The study was conducted in compliance with the Declaration of Helsinki and applicable regulatory requirements. Written informed consent was obtained from all patients.

CONSENT FOR PUBLICATION

Not required.

DATA SHARING

Qualified researchers may request deidentified data from Amgen clinical studies. Complete details are available at the following: http://www.amgen.com/datasharing.

REFERENCES

1. Kohlhapp FJ, Kaufman HL. Molecular pathways: mechanism of action for talimogene laherparepvec, a new oncolytic virus immunotherapy. *Clin Cancer Res*. 2016;22(5):1048-1054.
2. Liu BL, Robinson M, Han ZQ, et al. ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties. *Gene Ther*. 2003;10(4):292-303.
3. *IMLYGIC® (talimogene laherparepvec). Full Prescribing Information*. Thousand Oaks, CA: Amgen Inc; 2023. Available at imlygic_pi.ashx (amgen.com). Accessed February 22, 2023.
4. IMLYGICTM. *Summary of Product Characteristics*. London, UK: European Medicines Agency; 2020. Available at https://www.ema.europa.eu/en/documents/product-information/imlygic-epar-product-information_en.pdf. Accessed February 22, 2023.
5. TECENTRIQ (Atezolizumab). Full Prescribing Information. South San Francisco, CA: Genentech Inc.; 2022. Available at tecentriq_prescribing.pdf (gene.com). Accessed February 22, 2023.
6. European Medicines Evaluation Agency. Tecentriq: summary of product characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf. Accessed February 16, 2023.
7. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108-2121.
8. Roche. Roche provides update on Tecentriq US indication for PD-L1-positive, metastatic triple-negative breast cancer. Available at https://www.roche.com/media/releases/med-cor-2021-08-27.htm. Accessed September 14, 2021.
9. Miles D, Gligorov J, André F, et al. Primary results from IMpassion131, a double-blind, placebo-controlled, randomised phase III trial of first-line paclitaxel with or without atezolizumab for unresectable locally advanced/metastatic triple-negative breast cancer. *Ann Oncol*. 2021;32(8):994-1004.
10. Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. *JAMA Oncol*. 2019;5(1):74-82.
11. OPDIVO (Nivolumab). *Full Prescribing Information*. Princeton, NJ: Bristol-Myers Squibb Company; 2022. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/125554s112lbl.pdf. Accessed February 17, 2023.
12. KEYTRUDA (Pembrolizumab). *Full Prescribing Information*. Whitehouse Station, NJ: Merck & Co., Inc.; 2023. Available at https://www.keytrudahcp.com/prescribing-information/. Accessed February 16, 2023.
13. Golshani G, Zhang Y. Advances in immunotherapy for colorectal cancer: a review. *Therap Adv Gastroenterol*. 2020;13:1756284820917527.
14. Rousseau B, Bieche I, Pasmant E, et al. PD-1 blockade in solid tumors with defects in polymerase epsilon. *Cancer Discov*. 2022;12(6):1435-1448.
15. Ribas A, Dummer R, Puzanov I, et al. Oncolytic virotherapy promotes intratumoral T cell infiltration and improves anti-PD-1 immunotherapy. *Cell*. 2017;170(6):1109-1119.e10.
16. Ribas A, Chesney J, Long GV, et al. MASTERKEY-265: A phase III, randomized, placebo (Pbo)-controlled study of talimogene laherparepvec (T) plus pembrolizumab (P) for unresectable stage III-IVM1c melanoma (MEL). *Ann Oncol*. 2021;32(suppl 5):S868-S869.
17. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med*. 2010;363(20):1938-1948.

18. Manfredi S, Lepage C, Hatem C, et al. Epidemiology and management of liver metastases from colorectal cancer. *Ann Surg*. 2006;244(2):254-259.
19. Lin NU, Claus E, Sohl J, Razzak AR, Arnaout A, Winer EP. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: high incidence of central nervous system metastases. *Cancer.* 2008;113(10):2638-2645.
20. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. *Arch Pathol Lab Med*. 2008;132(6):931-939.
21. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. *Nat Med*. 2021;27(1):152-164.
22. Kwan A, Winder N, Muthana M. Oncolytic virotherapy treatment of breast cancer: barriers and recent advances. *Viruses*. 2021;13(6):1128.
23. Chaurasiya S, Warner S. Viroimmunotherapy for colorectal cancer: clinical studies. *Biomedicines*. 2017;5(1):11.
24. Bernstein V, Ellard SL, Dent SF, et al. A randomized phase II study of weekly paclitaxel with or without pelareorep in patients with metastatic breast cancer: final analysis of Canadian Cancer Trials Group IND. 213. *Breast Cancer Res Treat*. 2018;167(2):485-493.
25. Miller K, Zhao F, Clark A, Wilkinson G, Laeufle R, Wolff A. Abstract OT-13-02: Bracelet-1 (pre0113): a study to assess overall response rate by inducing an inflammatory phenotype in metastatic breast cancer with the oncolytic reovirus pelareorep in combination with anti-PD-L1 avelumab and paclitaxel. *Cancer Res*. 2021;81(suppl 4):OT-13-02.
26. Hecht JR, Prat A, Pless M, et al. A phase 1b/2, multicenter, open-label trial to evaluate the safety of talimogene laherparepvec (T-VEC) injected into primary and metastatic liver tumors alone and in combination with pembrolizumab (pembro) (MASTERKEY-318). *J Clin Oncol*. 2018;36(suppl):abstr TPS3105.
27. Ferrucci PF, Pala L, Conforti F, Cocorocchio E. Talimogene laherparepvec (T-VEC): an intralesional cancer immunotherapy for advanced melanoma. *Cancers (Basel)*. 2021;13(6):1383.
28. ClinicalTrials.gov. Single-arm trial to evaluate the role of the immune response to talimogene laherparepvec in unresected melanoma (TVEC-325) (NCT02366195). Available at https://clinicaltrials.gov/ct2/show/NCT02366195?term=02366195&draw=2&rank=1. Accessed February 16, 2023.
29. Melero I, Castanon E, Alvarez M, Champiat S, Marabelle A. Intratumoural administration and tumour tissue targeting of cancer immunotherapies. *Nat Rev Clin Oncol*. 2021;18(9):558-576.