Cancer Chemother Pharmacol (2017) 79:697–703
DOI 10.1007/s00280-017-3260-6

ORIGINAL ARTICLE

A phase II study of REOLYSIN® (pelareorep) in combination with carboplatin and paclitaxel for patients with advanced malignant melanoma

Devalingam Mahalingam[1,2] · Christos Fountzilas[1] · Jennifer Moseley[1,2] · Nicole Noronha[3] · Hue Tran[3] · Romit Chakrabarty[3] · Giovanni Selvaggi[3] · Matthew Coffey[3] · Brad Thompson[3] · John Sarantopoulos[1,2]

Received: 18 November 2016 / Accepted: 8 February 2017 / Published online: 13 March 2017

Abstract REOLYSIN® (pelareorep) is an investigational new drug, consisting of a live, replication-competent, Reovirus Type 3 Dearing strain in a proprietary formulation. Several preclinical and clinical trials with REOLYSIN® on a wide range of cancer indications have demonstrated antineoplastic activity on cells with activated RAS-signaling pathway. Furthermore, long-term survival benefits were evident in post-treatment patients indicating a potential antitumor immune response triggered by REOLYSIN®. Numerous mono and/or combination therapy studies with the agent showed a consistent safety profile. The current study is a phase II, single-arm, open label trial of REOLYSIN® in combination with carboplatin and paclitaxel for patients with advanced melanoma. Results from the 14 patients enrolled in the study exhibited no grade 4 adverse events or deaths but manageable grade-3 toxicities commonly attributed to REOLYSIN®, including pyrexia, chills, myalgia, pain, fatigue, and nausea. The number of treatment cycles ranged from 2 to 20 with a median of 6 cycles. The study met its treatment and efficacy goal for the first stage with three partial responses (ORR was 21%). No complete responses were noted. The median PFS and OS were 5.2 and 10.9 months, respectively. The 1-year OS was 43% with a disease control rate of 85%. In conclusion, REOLYSIN® combined with carboplatin and paclitaxel is a safe and potentially efficacious therapy for patients with advanced malignant melanoma. Additional combination studies using REOLYSIN® with chemo/immunotherapy drugs may support more favorable outcomes for patients in this indication.

Keywords REOLYSIN® · Reovirus · Oncolytic virus · Melanoma · Pelareorep

Introduction

The incidence of melanoma is rapidly increasing, with almost 76,000 new cases expected in the US in 2016; it is the fifth most commonly diagnosed cancer in males and seventh in females [1]. Until 2011, there were no life-extending systemic therapies for patients diagnosed with metastatic disease, de novo or after treatment for locoregional disease. The median overall survival was less than 1 year, with similar outcomes with dacarbazine monotherapy or polychemotherapy and immunotherapy regimens [2]. The widespread use of BRAF/MEK and immune checkpoint inhibitors has increased the number of the patients living with metastatic melanoma beyond a year to more than 50%, and at least 30% are alive long-term and potentially cured [3].

REOLYSIN® (pelareorep), a Type 3 Dearing reovirus, is a naturally occurring oncolytic virus that can selectively infect and kill cells with an activated RAS pathway [4, 5]. This activation can be the effect of RAS mutations

Electronic supplementary material The online version of this article (doi:10.1007/s00280-017-3260-6) contains supplementary material, which is available to authorized users.

✉ Devalingam Mahalingam
Mahalingam@uthscsa.edu

[1] Division of Hematology/Oncology, Cancer Therapy and Research Center, University of Texas Health Science Center, 7979 Wurzbach Rd, San Antonio, TX 78229, USA

[2] Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center San Antonio, San Antonio, TX, USA

[3] Oncolytics Biotech Inc., 210, 1167 Kensington Cr. NW, Calgary, AB, Canada

or activation of upstream kinases in the mitogen-activated protein kinase pathway (MAPK). Preferential killing of RAS-activated cells is mostly related to the inhibition of autophosphorylation of the double-stranded RNA-activated protein kinase (PKR) in these cells that allows viral replication to take place [5]. Melanoma cells are highly permissive to viral cytopathogenic effect in vitro and in vivo [6]; clinical studies of REOLYSIN® suggested some activity in melanoma as a single agent administered either locally or systemically [7, 8]. REOLYSIN® can also induce adaptive antitumor immunity [9, 10]. The limited clinical efficacy of REOLYSIN® as single agent has been linked to the development of neutralizing antibodies that can potentially decrease viral access to the tumor. Attenuation of antibody responses with cytotoxic or immunosuppressive agents in animal models has been demonstrated to enhance antitumor activity [11–13].

In 2009, we undertook a phase II trial of paclitaxel and carboplatin in combination with REOLYSIN®. Paclitaxel/carboplatin chemotherapy has shown activity in melanoma [14–16], and can attenuate neutralizing antibody responses, thus allowing higher viral penetration in the tumor [17]. Furthermore, REOLYSIN® has synergistic effects with platinum agents and taxanes [18, 19] and has been safely combined with paclitaxel and carboplatin in prior studies [17, 20, 21]. Herein, we report the final results of this phase II trial.

Materials and methods

Study design

REO 020 is a phase II, single-arm, open label study of REOLYSIN® administered in combination with paclitaxel and carboplatin in patients with metastatic melanoma, who experienced disease progression after one or more prior therapies or were deemed ineligible for the standard first-line therapy.

Patients were eligible for participation if they had histologically or cytologically confirmed melanoma, regardless of site of origin, and at least one measureable lesion by cross-sectional imaging or direct visualization of skin lesions. Other inclusion criteria included a performance status of at least 2 in the Eastern Cooperative Group scale (ECOG), a life expectancy of at least 3 months and adequate bone marrow, liver, and renal function [absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, Platelets $\geq 100 \times 10^9$/L without platelet transfusion, hemoglobin ≥9.0 g/dL with or without RBC transfusion, serum creatinine ≤1.5 × upper limit of normal (ULN), bilirubin ≤1.5 × ULN and aspartate transaminase/alanine transaminase (AST/ALT) ≤2.5 × ULN]. Key exclusion criteria included prior therapy with carboplatin and or paclitaxel, the presence of or history of metastatic disease to the brain, significant cardiac disease, including pre-existing arrhythmia, uncontrolled angina pectoris, myocardial infarction within 1 year prior to study entry, or grade 2 or higher compromised left ventricular ejection fraction. Patients on immunosuppressive therapy or with known HIV or active hepatitis B or C infection were also excluded. Any prior surgery or systemic therapy (cytotoxic chemotherapy, immunotherapy or hormonal therapy) should have occurred more than 28 days from study entry.

Study objectives

The primary objective was to assess the antitumor effect of the treatment regimen in the study population in terms of objective response rate, ORR [i.e., partial response (PR) and complete response (CR) to treatment]. Key secondary objectives were to assess progression-free survival (PFS) and overall survival (OS) for the treatment regimen, the disease control [CR + PR + stable disease (SD)] rate and duration, and the safety and tolerability of the treatment regimen in the study population.

Patients were assessed for response with the response evaluation criteria for solid tumors (RECIST) version 1.1. Evaluation of tumor status was conducted at baseline, at the end of week 6 on study and then every 6 weeks on study until disease progression, study termination, initiation of subsequent anticancer therapy, death, loss to follow-up, or withdrawal of consent.

Study treatment

Patients were treated on day 1 of each cycle with paclitaxel as a 3 h intravenous infusion at a dose of 200 mg/m^2, followed by carboplatin as a 30 min intravenous infusion at a dose of AUC 6 mg/mL/min calculated by the Calvert's formula, and then followed by REOLYSIN® administered as a 1 h intravenous infusion at a dose of 3×10^{10} $TCID_{50}$. On days 2 through 5, REOLYSIN® was administered alone using the same dose on day 1. Patients received standard premedication for paclitaxel treatment (corticosteroid, H1 and H2 antagonist) to prevent hypersensitivity reactions. The treatment cycles were repeated every 21 days for up to 8 cycles. If the patient derived benefit from therapy, treatment with paclitaxel/carboplatin and REOLYSIN® could continue for more than 8 cycles. Patients could continue REOLYSIN® alone at the same schedule indefinitely under this protocol, provided they have not experienced either progressive disease or unacceptable drug-related toxicity that does not respond to either supportive care or dose reduction.

Patients experiencing severe toxicity had their REOLYSIN®, paclitaxel and carboplatin treatments withheld until toxicity resolved to baseline or grade 1. Severe toxicity included in any cycle ANC $<0.5\times10^9$/L lasting for >7 days, ANC $<0.1\times10^9$/L lasting for >3 days, or ANC $<0.5\times10^9$/L with fever (>100.5 °F or >38.1 °C), platelet count $<25\times10^9$/L, grade ≥ 2 cardiotoxicity, persistent grade 2 neurotoxicity or any other drug-related non-hematological grade 3/4 toxicity, except grade 3 flu-like symptoms, diarrhea, nausea and vomiting which may require dose reduction if persistent and not clinically manageable. Upon resolution, REOLYSIN®, paclitaxel and carboplatin therapy could recommence at a lower dose level as presented in Supplement Table 1. Minor flu-like illness, diarrhea, nausea, or vomiting was managed with the standard supportive care.

Statistical analysis and sample size calculation

The phase II trial used a Simon two-stage design. The null hypothesis was that the ORR is less than or equal to 0.10. The alternative hypothesis was that the ORR is greater than or equal to 0.25. With a type I error of 0.05 and 80% power, the estimated sample size was 24.66 and the probability of early termination for futility of 0.736. Therefore, with an initial accrual of 18 patients in the first stage, the trial would be terminated if 2 or fewer obtain an objective response. If the trial proceeds to the second stage, a total of 43 patients will be studied. For both stages combined, if the total number responding is less than or equal to 7, the therapy would be deemed inactive. For the secondary endpoints, the 6-month PFS and OS were estimated using the Kaplan–Meier method.

Results

Fourteen patients were enrolled in one center (CTRC at University of Texas Health Science Center San Antonio) between November 16th, 2009 and September 24th, 2012. The last patient completed the study in February 2014. The patient disposition is shown in Fig. 1. All patients discontinued the study therapy secondary to disease progression. Even though the study met the efficacy requirement for activation of the second stage (more than two patients attained an objective response to therapy), a decision was made to terminate the study given the advances in immunotherapy and molecularly targeted therapy for the treatment of melanoma.

The baseline characteristics are shown in Table 1. Fifty-seven percent were female, 86% Caucasian/Non-Hispanic. The median number of metastatic sites was 3 (range 2–6), and the most common metastatic site was the lung. Patients had received a median of two prior systemic therapies, with progressive disease as the best response to the most recent therapy in 62.5% of the eight patients who had received systemic therapy for metastatic disease prior to study enrollment. The most common prior systemic treatments were INF-α and dacarbazine.

Table 1 Demographics of patients enrolled in the study

Parameter	$N=14$
Age (years)	
Median	56
Range	23–78
Age group (years)	
<70	12 (86)
>70	2 (14)
Gender (*n*/%)	
Male	6 (43)
Female	8 (57)
Ethnicity/race (*n*/%)	
Caucasian/Non-Hispanic	12 (86)
African-American	0
Asian	0
Hispanic	2 (14)
Other	0
PS (*n*/%)	
0	7 (50)
1	7 (50)
Sites of metastasis median/range	
Median	3
Range	2–6
Location of metastasis (*n*/%)	
Skin	4 (28)
Lymph nodes	6 (43)
Lung	13 (93)
Liver	7 (50)
Bone	4 (28)
Other	
Radiotherapy (*n*/%)	5 (36)
Prior systemic therapy (*n*/%)	9 (64)
Number of prior systemic therapies	
Median	2
Range	0–4
Best response to most recent systemic therapy for metastatic disease (*n*/%)[a]	
CR/PR	1 (12.5)
SD	2 (25)
PD	5 (62.5)

CR complete response, *PD* progressive disease, *PR* partial response, *PS* performance status/Eastern Cooperative Oncology Group, *SD* stable disease

[a]8 patients had received therapy for metastatic disease prior to trial enrollment

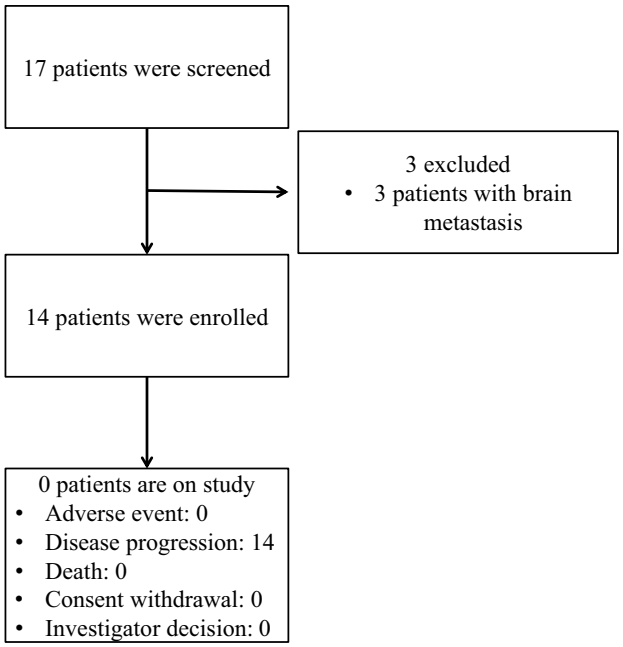

Fig. 1 Patient disposition for the study

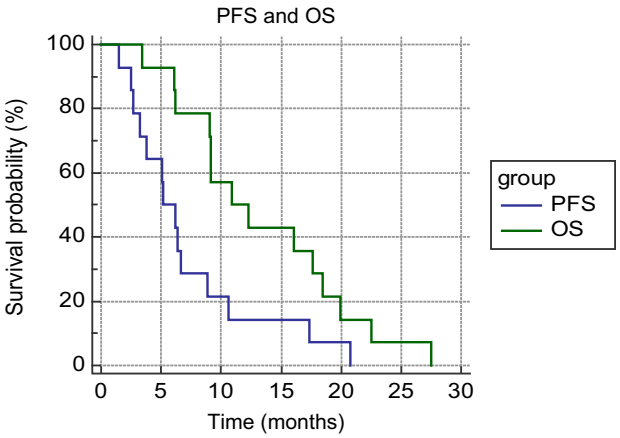

Fig. 2 Graph with OS (median 10.9 months) and PFS (median 5.2 months) probabilities

Treatment and efficacy

The median number of treatment cycles was 6 (range 2–20); two patients went on to receive more than 8 cycles of combination therapy, one patient continued on REOLYSIN® maintenance after cycle 8. Only one patient required a dose reduction of the paclitaxel and carboplatin for low neutrophil count. There was no reduction in the REOLYSIN® dose, but patients missed a median of one dose (range 0–6). Thirty-four cycles out of a total of 106 cycles delivered were delayed (32%); the range per patient was 0 to 15. Nineteen cycles (56%) were delayed for low neutrophil count (mostly grade 2–68%).

The study met its efficacy goal for the first stage with three partial responses (ORR was 21%, Table 2). No complete responses were noted. The disease control rate was 85%. The median PFS and OS were 5.2 and 10.9 months, respectively (Fig. 2). The 1-year OS rate was 43%.

Safety

The adverse event profile was consistent with the prior experience of REOLYSIN® in combination with cytotoxic chemotherapy (Table 3) and was manageable with supportive care. REOLYSIN® did not appear to worsen any of the known chemotherapy-related adverse events. The most common toxicity (86% of the patients) was pyrexia and was mostly attributed to REOLYSIN®. There was one patient with grade 3 febrile neutropenia. Other potential serious adverse events included implanted device infection in two patients, staphylococcal infection in one patient, and spinal compression in one patient (all grade 3); however these were not related to REOLYSIN® or chemotherapy administration. There were no grade 4 adverse effects or death on study.

Table 2 Overall response rate by RECIST 1.1 ($N = 14$)

Response by RECIST	*n* (%)
Complete response	0 (0)
Partial response	3 (21)
Stable disease	9 (64)
Progressive disease	2 (15)

Discussion

Effective treatments for metastatic melanoma were rare before the advent of molecularly targeted agents and immunotherapy in 2011, with dacarbazine providing modest palliation and no real improvement in survival. The paclitaxel/carboplatin combination for the treatment of metastatic melanoma has been investigated in at least three small trials using different doses and schedules, with overall response rates ranging between 19 and 26%, clinical benefit rate of 45–67% and overall survival of 8–9 months [14–16].

REOLYSIN®, a Type 3 Dearing oncolytic reovirus, has in vitro and in vivo activity against melanoma, with a favorable adverse event profile that allows combination with other agents. Building on the antineoplastic activity of the paclitaxel/carboplatin combination, REOLYSIN® monotherapy, and evidence of synergy between chemotherapeutics and oncolytic viruses, in 2009, we designed a two-stage, phase II trial examining the efficacy of paclitaxel/carboplatin & REOLYSIN® combination strategy. Even though the results of the first stage did allow us to

Table 3 Toxicity profile (>10% frequency) of chemo and REOLYSIN® in the study

Toxicity	All ($N=14$), n %	Grade 3–4 ($N=14$), n %	Chemotherapy-related ($N=14$), n %	REOLYSIN®-related ($N=14$), n %
Pyrexia	12 (86)	0	1 (7)	11 (77)
Nausea	10 (71)	1 (7)	4 (27)	3 (21)
Anorexia	10 (75)	0	3 (21)	1 (7)
Alopecia	9 (64)	0	8 (57)	0
Neutropenia	9 (64)	7 (50)	7 (50)	1 (7)
Vomiting	9 (64)	0	5 (36)	2 (14)
Hypokalemia	9 (64)	0	2 (14)	2 (14)
Chills	8 (57)	0	1 (7)	7 (50)
Diarrhea	8 (57)	0	1 (7)	2 (14)
Myalgia	7 (50)	0	2 (14)	7 (50)
Hypomagnesemia	7 (50)	0	3 (21)	2 (14)
Headache	7 (50)	0	0	0
Constipation	6 (43)	0	5 (36)	1 (7)
Fatigue	6 (43)	0	6 (43)	4 (27)
Pain in extremity	6 (43)	2	0	0
Pain	5 (36)	0	1 (7)	5 (36)
Upper respiratory infection	5 (36)	0	0	1 (7)
Neuropathy	5 (36)	0	5 (36)	0
Paresthesia	5 (36)	0	4 (27)	1 (7)
Anemia	5 (36)	1 (7)	3 (21)	0
Thrombocytopenia	5 (36)	3 (21)	4 (27)	0
Arthralgia	4 (27)	0	1 (7)	1 (7)
Back pain	4 (27)	0	2 (14)	1 (7)
Dizziness	4 (27)	0	1 (7)	0
Dysgeusia	4 (27)	0	4 (27)	1 (7)
Cough	4 (27)	0	0	0
Hypotension	4 (29)	0	0	0
Device infection	3 (21)	2 (14)	0	0
Maculopapular rash	3 (21)	0	2 (14)	2 (14)
Flushing	3 (21)	0	1 (7)	0
Dyspepsia	3 (21)	0	0	0
Abdominal distention	2 (14)	0	0	0
Flu-like illness	2 (14)	0	0	2 (14)
Cellulitis	2 (14)	0	0	0
Increased creatinine	2 (14)	0	0	0
Weight decreased	2 (14)	0	0	0
Hyperglycemia	2 (14)	0	0	0
Peripheral sensory neuropathy	2 (14)	0	2 (14)	0
Dysuria	2 (14)	0	0	0
Dyspnea on exertion	2 (14)	0	0	1 (7)
Pulmonary embolism	2 (14)	0	0	0
Pruritus	2 (14)	0	2 (14)	0
Deep vein thrombosis	2 (14)	0	0	0

proceed with the second stage, the success of novel targeted therapies and immunotherapy in melanoma triggered the termination of the study. Our results confirm the safety of the combination and suggest improved efficacy as clinical benefit rate, PFS, and OS appear improved compared with historical controls (5.2 vs. 3 and 10.9 vs. 9 months, respectively) [14, 16].

Recently, IMLYGIC™ (T-VEC/Talimogene Laherparepvec), a genetically engineered Herpes Simplex Virus administered intratumorly, became the first oncolytic virus approved for use in the United States for patients with locally advanced or non-resectable melanoma. Its approval was based on a phase III study revealing improved efficacy compared to subcutaneous granulocyte–macrophage colony stimulating factor (GM-CSF) [22]. The combination of T-VEC with immune checkpoint inhibitors in melanoma has shown promising results in early phase I/II trials, with response rates ranging between 48 and 56%, time to response 4–5.6 months and PFS of 10.6 months; grade 3/4 treatment-related adverse events occurred in a third of the patients [23–25].

REOLYSIN® can induce an adaptive antitumor immunity [9, 10] and has shown in vitro and in vivo synergy with immune checkpoint inhibitors as well as BRAF and MEK inhibitors [26, 27]. Given the impressive early results of T-VEC with immunotherapy, as well as preclinical data, combination strategies of REOLYSIN® with immune checkpoint inhibitors deserve further study in the treatment of patients with metastatic melanoma, possibly combined with low doses of chemotherapy to increase viral penetration in the tumor. In summary, REOLYSIN® combined with paclitaxel and carboplatin is a safe and potentially efficacious therapy for patients with metastatic or unresectable melanoma.

Conclusion

The phase II, single-arm, open label study of REOLYSIN® in combination with carboplatin and paclitaxel was found safe for patients with advanced malignant melanoma. The study met its efficacy goal for the first stage with three partial responses (ORR was 21%) and the disease control rate was 85%. The median PFS and OS were 5.2 and 10.9 months, respectively, with a 1-year OS rate of 43%. Additional combination studies using REOLYSIN® with chemo/immunotherapy drugs may support more favorable outcomes for patients in this indication.

Acknowledgements Devalingam Mahalingam (first author) and the sponsor (Oncolytics Biotech Inc.) designed the study. The sponsor also covered all study-related expenses and provided REOLYSIN® free of charge. Christos Fountzilas is a recipient of a Cancer Research Training Award from the Cancer Prevention and Research Institute of Texas (RP140105).

Compliance with ethical standards

Funding This study was funded by Oncolytics Inc (study sponsor).

Conflict of interest Devalingam Mahalingam declares that he has no conflict of interest. Christos Fountzilas declares that he has no conflict of interest. Jennifer Moseley declares that she has no conflict of interest. John Sarantopoulos declares that he has no conflict of interest. Nicole Noronha, Hue Tran, Romit Chakrabarty, Matt Coffey, and Brad Thompson are employed by Oncolytics Biotech Inc., with stock options and/or stock. Giovanni Selvaggi was employed with Oncolytics Biotech Inc. during a portion of this study and manuscript preparation.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. CA Cancer J Clin 66(1):7–30. doi:10.3322/caac.21332
2. Eigentler TK, Caroli UM, Radny P, Garbe C (2003) Palliative therapy of disseminated malignant melanoma: a systematic review of 41 randomised clinical trials. Lancet Oncol 4(12):748–759
3. Ugurel S, Röhmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, Larkin J, Long GV, Lorigan P, McArthur GA, Ribas A, Robert C, Schadendorf D, Garbe C (2016) Survival of patients with advanced metastatic melanoma: the impact of novel therapies. Eur J Cancer 53:125–134. doi:10.1016/j.ejca.2015.09.013
4. Coffey MC, Strong JE, Forsyth PA, Lee PW (1998) Reovirus therapy of tumors with activated Ras pathway. Science 282(5392):1332–1334
5. Strong JE, Coffey MC, Tang D, Sabinin P, Lee PW (1998) The molecular basis of viral oncolysis: usurpation of the Ras signaling pathway by reovirus. Embo J 17 (12):3351–3362
6. Errington F, White CL, Twigger KR, Rose A, Scott K, Steele L, Ilett LJ, Prestwich R, Pandha HS, Coffey M, Selby P, Vile R, Harrington KJ, Melcher AA (2008) Inflammatory tumour cell killing by oncolytic reovirus for the treatment of melanoma. Gene Ther 15(18):1257–1270
7. Morris DG, Feng X, DiFrancesco LM, Fonseca K, Forsyth PA, Paterson AH, Coffey MC, Thompson B (2013) REO-001: a phase I trial of percutaneous intralesional administration of reovirus type 3 dearing (Reolysin®) in patients with advanced solid tumors. Invest New Drugs 31(3):696–706. doi:10.1007/s10637-012-9865-z
8. Galanis E, Markovic SN, Suman VJ, Nuovo GJ, Vile RG, Kottke TJ, Nevala WK, Thompson MA, Lewis JE, Rumilla KM, Roulstone V, Harrington K, Linette GP, Maples WJ, Coffey M, Zwiebel J, Kendra K (2012) Phase II trial of intravenous administration of reolysin[reg] (reovirus serotype-3-dearing strain) in patients with metastatic melanoma. Mol Ther 20(10):1998–2003
9. Prestwich RJ, Errington F, Ilett EJ, Morgan RSM, Scott KJ, Kottke T, Thompson J, Morrison EE, Harrington KJ, Pandha HS, Selby PJ, Vile RG, Melcher AA (2008) Tumor infection by oncolytic reovirus primes adaptive antitumor immunity. Am Assoc Cancer Res 14(22):7358–7366. doi:10.1158/1078-0432.ccr-08-0831
10. Prestwich RJ, Ilett EJ, Errington F, Diaz RM, Steele LP, Kottke T, Thompson J, Galivo F, Harrington KJ, Pandha HS, Selby PJ, Vile RG, Melcher AA (2009) Immune-mediated antitumor

activity of reovirus is required for therapy and is independent of direct viral oncolysis and replication. Am Assoc Cancer Res 15(13):4374–4381. doi:10.1158/1078-0432.ccr-09-0334

11. White CL, Twigger KR, Vidal L, De Bono JS, Coffey M, Heinemann L, Morgan R, Merrick A, Errington F, Vile RG, Melcher AA, Pandha HS, Harrington KJ (2008) Characterization of the adaptive and innate immune response to intravenous oncolytic reovirus (Dearing type 3) during a phase I clinical trial. Gene Ther 15(12):911–920. http://www.nature.com/gt/journal/v15/n12/suppinfo/gt200821s1.html
12. Qiao J, Wang H, Kottke T, White C, Twigger K, Diaz RM, Thompson J, Selby P, de Bono J, Melcher A, Pandha H, Coffey M, Vile R, Harrington K (2008) Cyclophosphamide facilitates antitumor efficacy against subcutaneous tumors following intravenous delivery of reovirus. Am Assoc Cancer Res 14(1):259–269. doi:10.1158/1078-0432.ccr-07-1510
13. Hirasawa K, Nishikawa SG, Norman KL, Coffey MC, Thompson BG, Yoon C-S, Waisman DM, Lee PWK (2003) Systemic reovirus therapy of metastatic cancer in immune-competent mice. Cancer Res 63(2):348–353
14. Rao RD, Holtan SG, Ingle JN, Croghan GA, Kottschade LA, Creagan ET, Kaur JS, Pitot HC, Markovic SN (2006) Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 106(2):375–382. doi:10.1002/cncr.21611
15. Zimpfer-Rechner C, Hofmann U, Figl R, Becker JC, Trefzer U, Keller I, Hauschild A, Schadendorf D (2003) Randomized phase II study of weekly paclitaxel versus paclitaxel and carboplatin as second-line therapy in disseminated melanoma: a multicentre trial of the Dermatologic Co-operative Oncology Group (DeCOG). Melanoma Res 13(5):531–536. doi:10.1097/01.cmr.0000056274.56735.c6
16. Hodi FS, Soiffer RJ, Clark J, Finkelstein DM, Haluska FG (2002) Phase II study of paclitaxel and carboplatin for malignant melanoma. Am J Clin Oncol 25(3):283–286
17. Karapanagiotou EM, Roulstone V, Twigger K, Ball M, Tanay M, Nutting C, Newbold K, Gore ME, Larkin J, Syrigos KN, Coffey M, Thompson B, Mettinger K, Vile RG, Pandha HS, Hall GD, Melcher AA, Chester J, Harrington KJ (2012) Phase I/II trial of carboplatin and paclitaxel chemotherapy in combination with intravenous oncolytic reovirus in patients with advanced malignancies. Am Assoc Cancer Res 18(7):2080–2089. doi:10.1158/1078-0432.ccr-11-2181
18. Pandha HS, Heinemann L, Simpson GR, Melcher A, Prestwich R, Errington F, Coffey M, Harrington KJ, Morgan R (2009) Synergistic effects of oncolytic reovirus and cisplatin chemotherapy in murine malignant melanoma. Am Assoc Cancer Res 15(19):6158–6166. doi:10.1158/1078-0432.ccr-09-0796
19. Sei S, Mussio JK, Yang Q-e, Nagashima K, Parchment RE, Coffey MC, Shoemaker RH, Tomaszewski JE (2009) Synergistic antitumor activity of oncolytic reovirus and chemotherapeutic agents in non-small cell lung cancer cells. Mol Cancer 8:47–47. doi:10.1186/1476-4598-8-47
20. Mita AC, Argiris A, Coffey M, Gill G, Mita M (2013) Abstract C70: A phase 2 study of intravenous administration of REOLYSIN® (reovirus type 3 dearing) in combination with paclitaxel (P) and carboplatin (C) in patients with squamous cell carcinoma of the lung. Am Assoc Cancer Res 12(11 Supplement):C70-C70. doi:10.1158/1535-7163.targ-13-c70
21. Villalona-Calero MA, Lam E, Otterson GA, Zhao WQ, Timmons M, Subramaniam D, Hade EM, Gill GM, Coffey M, Selvaggi G, Bertino E, Chao B, Knopp MV (2016) Oncolytic reovirus in combination with chemotherapy in metastatic or recurrent non-small cell lung cancer patients with KRAS-activated tumors. Cancer 122(6):875–883. doi:10.1002/cncr.29856
22. Andtbacka RHI, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, Delman KA, Spitler LE, Puzanov I, Agarwala SS, Milhem M, Cranmer L, Curti B, Lewis K, Ross M, Guthrie T, Linette GP, Daniels GA, Harrington K, Middleton MR, Miller WH, Zager JS, Ye YN, Yao B, Li A, Doleman S, VanderWalde A, Gansert J, Coffin RS (2015) Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 33(25):2780–2798. doi:10.1200/jco.2014.58.3377
23. Puzanov I, Milhem MM, Andtbacka RHI, Minor DR, Hamid O, Li A, Chastain M, Gorski K, Anderson A, Vanderwalde AM, Chou J, Kaufman H (2014) Primary analysis of a phase 1b multicenter trial to evaluate safety and efficacy of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. ASCO Meeting Abstr 32(15_suppl):9029
24. Puzanov I, Milhem MM, Andtbacka RHI, Minor DR, Hamid O, Li A, Chou J, Kaufman H (2015) Survival, safety, and response patterns in a phase 1b multicenter trial of talimogene laherparepvec (T-VEC) and ipilimumab (ipi) in previously untreated, unresected stage IIIB-IV melanoma. ASCO Meeting Abstr 33(15_suppl):9063
25. Long GV, Dummer R, Ribas A, Puzanov I, VanderWalde A, Andtbacka RHI, Michielin O, Olszanski AJ, Malvehy J, Cebon JS, Fernandez E, Kirkwood JM, Gajewski T, Gause CK, Chen L, Gorski K, Anderson A, Kaufman DR, Chou J, Hodi FS (2016) Efficacy analysis of MASTERKEY-265 phase 1b study of talimogene laherparepvec (T-VEC) and pembrolizumab (pembro) for unresectable stage IIIB-IV melanoma. ASCO Meeting Abstr 34 (15_suppl):9568
26. Roulstone V, Pedersen M, Kyula J, Mansfield D, Khan AA, McEntee G, Wilkinson M, Karapanagiotou E, Coffey M, Marais R, Jebar A, Errington-Mais F, Melcher A, Vile R, Pandha H, McLaughlin M, Harrington KJ (2015) BRAF- and MEK-targeted small molecule inhibitors exert enhanced antimelanoma effects in combination with oncolytic reovirus through ER stress. Mol Ther 23(5):931–942. doi:10.1038/mt.2015.15
27. Rajani K, Parrish C, Kottke T, Thompson J, Zaidi S, Ilett L, Shim KG, Diaz R-M, Pandha H, Harrington K, Coffey M, Melcher A, Vile R (2016) combination therapy with reovirus and anti-PD-1 blockade controls tumor growth through innate and adaptive immune responses. Mol Ther 24(1):166–174. doi:10.1038/mt.2015.156