Online Supplementary File 1: Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:
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1 Talimogen* laherparepvec.mp. (28)
2 t vec.mp. (24)
3 OncoVEX*.mp. (15)
4 Imlygic.mp. (2)
5 JS1 34*.tw. (5)
6 or/1-5 (51)
7 Oncolytic Virotherapy/ or Oncolytic Viruses/ or cancer vaccines/tu (7016)
8 (cancer adj2 (vaccine* or virus* or virotherap* or viral therap*)).tw. (5206)
9 exp neoplasms/ or cancer.tw. (3097511)
10 or/7-9 (3097684)
11 simplexvirus/ or herpesvirus 1, human/ or Herpes Simplex/ (32955)
12 (hsv1 or hsv or herpesvirus or Herpes).tw. (72684)
13 11 or 12 (77360)
14 10 and 13 (12929)
15 ((oncolyt* or cancer or tumor or tumour) adj3 (hsv1 or hsv or hsv or herpesvirus or Herpes)).tw. (846)
16 (oncolyt* adj3 (virotherap* or virus* or viral therap*)).tw. (2183)
17 or/14-16 (14671)
18 exp animal experimentation/ or exp models, animal/ or animals/ or mammals/ or vertebrates/ or exp fishes/ or exp amphibia/ or exp reptiles/ or exp birds/ or exp hyraxes/ or exp marsupialia/ or exp monotremata/ or exp scandentia/ or exp chiroptera/ or exp carnivora/ or exp cetacea/ or exp Xenarthra/ or exp elephants/ or exp insectivora/ or exp lagomorpha/ or exp rodentia/ or exp sirenia/ or exp Perissodactyla/ or primates/ or exp strepsirhini/ or haplorhini/ or exp tarsii/ or exp platyrrhini/ or catarrhini/ or exp cercopithecidae/ or gorilla gorilla/ or pan paniscus/ or pan troglodytes/ or exp pongo/ or exp hylobatidae/ or hominidae/ (5893175)
19 (animal$1 or chordata or vertebrate* or fish$2 or amphibian* or amphibium* or reptile$1 or bird$1 or mammal* or dog or dogs or canine$1 or cat or cats or hyrax* or marsupial* or monotrem* or scandentia or bat or bats or carnivor* or cetacea or edentata* or elephant* or insect or insects or insectivore or lagomorph* or rodent$2 or mouse or mice or murine or murinae or muridae or rat or rats or pig or pigs or piglet$1 or swine or rabbit$1 or sheep$1 or goat$1 or horse$1 or equus or cow or cows or cattle or calf or calves or bovine or sirenia or ungulate$1 or primate$1 or prosimian* or haplorhini* or tarsiiform* or simian*or platyrrhini or catarrhini or cercopithecidae or ape or apes or hylobatidae or hominid* or chimpanzee* or gorilla* or orangutan* or monkey or monkeys or ape or apes).tw. (4149175)
20 (preclinic$ or pre clinic$).tw. (72274)
21 or/18-20 (6474971)
22 17 and 21 (6511)
23 6 or 22 (6545)

Online Supplementary File 2. Preclinical Study Characteristics

Author, Year	Year Study Conducted	Country	Study Design	Species	Strain	Model	Type of Cancer	Baseline Tumor Size	Gender	Mean Age	Mean Weight	Co-Interventions	Duration of Follow Up
Cooke, 2015	---	USA	Interventional; Non-Controlled	Mouse	Balb/c	A20 Murine Lymphoma	Lymphoma	150 mm^3	Female	---	---	N/A	---
Piasecki, 2015	---	---	Controlled Comparison	Mouse	C57Bl/6	Syngeneic MC-38 Colon Carcinoma	Colon Cancer	---	---	---	---	Anti-PD-1	---
Piasecki, 2013	---	---	Controlled Comparison	Mouse	---	A20 Syngeneic Contralateral Model	Lymphoma	---	---	---	---	N/A	10 days
Liu, 2003	2002	UK	Controlled Comparison	Mouse	Balb/c	Syngeneic A20 Lymphoma	Lymphoma	0.5 cm diameter	---	---	---	Immunization wild type HSV1	35 days

---: not reported
N/A: not applicable
Cooke, 2016 did not provide any relevant information

Online Supplementary File 3. Preclinical Intervention and Comparator Characteristics

Author, Year	Experiment	Group	N	Dose 1	Frequency Dose 1	Duration Dose 1	Dose 2	Frequency Dose 2	Duration Dose 2	Dose 3	Frequency Dose 3	Duration Dose 3
Cooke, 2015	1	Cohort 1: TVEC	10	$3x10^4$ PFU	---	---	N/A	N/A	N/A	N/A	N/A	N/A
		Cohort 2:	10	---	---	---	N/A	N/A	N/A	N/A	N/A	N/A
		Cohort 3: TVEC	10	$3x10^6$ PFU	Every 3 days	1 week	N/A	N/A	N/A	N/A	N/A	N/A
		Cohort 4:	10	---	---	---	N/A	N/A	N/A	N/A	N/A	N/A
Piasecki, 2015	1	Int: OncoVEXmuGM-CSF + Anti-PD1	---	T-VEC: ---	Every 3 days	3 doses	Anti-PD-1: ---	Twice per wk	---	N/A	N/A	N/A
		Int: OncoVEXmuGM-CSF	---	T-VEC: ---	---	---	---	---	---	---	---	---
		Con: Anti-PD-1	---	Anti-PD-1: ---	---	---	---	---	---	---	---	---
Piasecki, 2013	1	Int: T-VEC	---	$5x10^6$ PFU	single	single	N/A	N/A	N/A	N/A	N/A	N/A
		Con: Vehicle	---	---	single	single	N/A	N/A	N/A	N/A	N/A	N/A
Liu, 2003	1	Int: JS1/34.5-/47-/mGM-CSF	10	10^6 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
			10	10^7 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
			10	10^8 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
		Int: JS1/34.5-/47-	10	10^6 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
			10	10^7 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
			10	10^8 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
		Con: vehicle	10	50µl	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
	2	Int: JS1/34.5-/47-/mGM-CSF	10	10^8 PFU/ml (50µl)	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A
		Con: Vehicle	10	50µl	Every other day	3 doses – 5 days	N/A	N/A	N/A	N/A	N/A	N/A

All doses of T-VEC were given by injection intratumorally
---: not reported
Int: intervention; Con: control; wk: week; PFU: plaque forming units
Cooke, 2016 did not provide any relevant information

Online Supplementary File 4. Clinical Study Characteristics

Author, Year	Country	Year Study Conducted	Study Type	Type of Cancer	Primary Outcomes	Secondary Outcomes
Andtbacka, 2015	USA, UK, Canada and South Africa	2009-2014	Interventional; Randomized (OPTiM Trial)	Melanoma	Efficacy: DRR	Efficacy: ORR OS Best Overall Response Onset and duration of response Time to treatment failure
Long 2015	USA, Australia, Switzerland, Spain	2014-2022	Interventional: Non-randomized, No control	Melanoma	Safety: Dose Limiting Toxicities	Efficacy: DRR OS Progression Free Survival Safety: AEs
Puzanov, 2015	USA	2013-2014	Interventional: Non-Randomized	Melanoma	Safety: Dose Limiting Toxicities	Efficacy: ORR Safety: Grade ≥3 AEs
Chang, 2012	USA	2006-2008	Interventional: Non-randomized, No control	Pancreatic Cancer	Efficacy: Detection of T-VEC in blood and urine Presence of Anti-HSV1 Antibodies Safety: AEs	Efficacy: ORR Change in sum of longest tumor diameter Change in pain intensity
Harrington, 2010	UK	2005-2010	Interventional: Non-randomized, No control	Squamous Cell Carcinoma of the head and neck	Safety: AEs	Efficacy: Antitumor Activity OS* Complete Response* Partial Response* Progression Free Survival*
Senzer 2009	USA	2005-2008	Interventional; (non-controlled, non randomized)	Melanoma	Efficacy: ORR	Efficacy: OS Safety: AEs
Hu, 2006	USA, UK	---	Interventional: Non-randomized, No control	Breast, Colorectal, Melanoma, Head and Neck	Efficacy: Biodistribution Safety: AEs	Efficacy: GM-CSF expression HSV antigen associated necrosis Viral Replication Local Reactions

---: Not Reported
*: not reported a priori
AEs - adverse events; CHN– cutaneous head and neck; DRR – durable response rate; ECOG – Eastern Cooperative Oncology Group; ORR- objective response rate; OS – overall survival

Online Supplementary File 5. Clinical Patient Characteristics

Author, Year	Group	Patients (N)	Median Age (range)	Sex (n; F)	Metastasis Stage (n; Stage IVM1b/c)	Line of Therapy (n; first line)	HSV Serostatus (n; Seropositive, n; unknown)
Andtbacka, 2015	T-VEC	295	63 (22-94)	122	131	138	175, 23
Long, 2015	T-VEC + Pembrolizumab	21	58	13	11	---	---
Puzanov, 2015	T-VEC + Ipilimumab	18	---	---	---	18	---
Chang, 2012	T-VEC	17	54	6	---	---	---
Harrington, 2010	T-VEC and Chemo radiotherapy	17	58 (41-74)	2	3	---	---
Senzer, 2009	T-VEC	50	62 (34-88)	28	24	0	36, 1
Hu, 2006	T-VEC	30	55 (30-80)	23	---	0	19

--- : Not Reported

Online Supplementary File 6. Clinical Intervention and Comparator Characteristics

Author, Year	Arm	Dose 1	Time of Dose 1	Frequency of Dose 1	Dose 2	Time of Dose 2	Frequency of Dose 2	Dose 3	Time of Dose 3	Frequency of Dose 3	Intervention Window	Follow Up Duration
Andtbacka, 2015	T-VEC	10^6 PFU/ml (≤4ml)	Week 1	single	10^8 PFU/ml (≤4ml)	Week 4	Q2W	N/A	N/A	N/A	Median: 23 wks (0.1-79 wks)	Median: 44 mo (32-58 mo)
	GM-CSF	125 µg/m^2	Week 1	Once daily 14/28 day cycles	N/A	N/A	N/A	N/A	N/A	N/A	Median: 10 wks (0.6 to 72 wks)	---
Long, 2015	T-VEC + Pemb.	TVEC: 10^6 PFU/ml	Day 1	single	T-VEC: 10^8 PFU/ml	Day 22	Q2W	Pemb: 200 mg	Day 36	Q2W	Median TVEC: 13 wks Median Pemb: 10 wks	---
Puzanov, 2015	T-VEC + Ipilimumab	TVEC: 10^6 PFU/ml (≤4ml)	Week 1	single	TVEC: 10^8 PFU/ml (≤4ml)	Week 4	Q2W	Ipilimumab: 3mg/kg	Week 6	Q3W	TVEC: until DLT Ipi: 12 wks	17 mo minimum
Chang, 2012	Cohort 1	10^4 PFU/ml	Week 1*	single	10^5 PFU/ml	Week 4*	Q3W*	N/A	N/A	N/A	up to 15 wks	---
	Cohort 2	10^5 PFU/ml	Week 1	single	10^6 PFU/ml	Week 4	Q3W	N/A	N/A	N/A	up to 15 wks	---
	Cohort 3	10^6 PFU/ml	Week 1	single	10^7 PFU/ml	Week 4	Q3W	N/A	N/A	N/A	up to 15 wks	---
Harrington, 2010	Cohort 1	T-VEC: 10^6 PFU/ml	Day 1	Q3W	Cisplatin: 100mg/m^2	Day 1	Q3W	N/A	N/A	N/A	Up to 9 weeks	Median: 29mo (19-40mo)
	Cohort 2	T-VEC: 10^6 PFU/ml	Day 1	single	T-VEC: 10^7 PFU/ml	Day 22	Q3W	Cisplatin: 100mg/m^2	Day 1	Q3W	Up to 9 weeks	Median: 29mo (19-40mo)
	Cohort 3	T-VEC: 10^6 PFU/ml	Day 1	single	T-VEC: 10^8 PFU/ml	Day 22	Q3W	Cisplatin: 100mg/m^2	Day 1	Q3W	Up to 9 weeks	Median: 29mo (19-40mo)
	Cohort 4	T-VEC: 10^6 PFU/ml	Day 1	single	T-VEC: 10^8 PFU/ml	Day 22	Q3W	Cisplatin: 100mg/m^2	Day 1	Q3W	Up to 9 weeks	Median: 29mo (19-40mo)
Senzer, 2009	T-VEC	10^6 PFU/ml (≤4ml)	Week 1	Single	10^8 PFU/ml (≤4ml)	Week 4	Q2W	N/A	N/A	N/A	Max: 48 wks Median: 11 wks	Median: 18 mo (11-36 mo)
Hu, 2006	Single Dose Group 1	10^6 PFU/ml	---	single	N/A	N/A	N/A	N/A	N/A	N/A	Single dose	6 wks
	Single Dose Group 2	10^7 PFU/ml	---	single	N/A	N/A	N/A	N/A	N/A	N/A	Single dose	6 wks
	Single Dose Group 3	10^8 PFU/ml	---	single	N/A	N/A	N/A	N/A	N/A	N/A	Single dose	6 wks
	Multi-dose Group 1	10^6 PFU/ml	---	single	10^7 PFU/ml	---	Q1-3W	N/A	N/A	N/A	3-9 wks*	6 wks post final injection
	Multi-dose Group 2	10^6 PFU/ml	---	single	10^8 PFU/ml	---	Q1-3W	N/A	N/A	N/A	3-9 wks*	6 wks post final injection

Author, Year	Arm	Dose 1	Time of Dose 1	Frequency of Dose 1	Dose 2	Time of Dose 2	Frequency of Dose 2	Dose 3	Time of Dose 3	Frequency of Dose 3	Intervention Window	Follow Up Duration
	Multi-dose Group 3	10^6 PFU/ml	---	Q1-3W	N/A	N/A	N/A	N/A	N/A	N/A	3-9 wks*	6wks post final injection

DLT: Dose Limiting Toxicity; Pemb: Pembrolizumab; Q2W: every two weeks Q3W: every three weeks; Q1-3W: every 1-3 weeks; Q6W every 6 weeks
--- : not reported
T-VEC was given by intra-tumoral injection in all studies

Online Supplementary File 7. Preclinical Efficacy Data

Author, Year	Experiment	Group	N – Animals Studied	N – Lesions Studied	Baseline Mean Tumor Measure (Standard Error of Mean)	Final Mean Tumor Measure (Standard Error of Mean)	CR - Injected	CR - Contralateral	Duration of Follow Up
Cooke, 2015	1	INT: TVEC $3x10^4$ PFU	10	---	---	---	---	---	---
		INT: TVEC $3x10^6$ PFU	10	10	~150mm^3	---	10/10	5/10	**---**
		---	10	---	---	---	---	---	---
		---	10	---	---	---	---	---	---
Piasecki, 2015	1	INT: OncoVexmuGM-CSF	---	---	---	---	---	---	---
		INT: OncoVexmuGM-CSF + Anti-PD-1	---	20	---	---	8/10	2/10	---
		CON: Anti Pd-1	---	---	---	---	---	---	---
Piasecki, 2013	1	INT: T-VEC	---	---	---	---	70-100%	50-60%	10 days
		CON: Vehicle	---	---	---	---	---	---	---
Liu, 2003	1	INT: JS1/34.5-/47-/mGM-CSF; injected	10	N/A	5.2mm (0.34)	0.004mm (0.31)	N/A	N/A	22 days
		INT: JS1/34.5-/47-/mGM-CSF; uninjected	10 (same as injected)	N/A	5.7mm (0.29)	1.1 mm (0.73)	N/A	N/A	22 days
		INT: JS1/34.5-/47-; injected	10	N/A	5.4mm (0.37)	1.4 mm (1.36)	N/A	N/A	22 days
		INT: JS1/34.5-/47-; uninjected	10 (same as injected)	N/A	6.2mm (0.29)	5.4mm (2.01)	N/A	N/A	22 days
		CON: Vehicle; injected	10	N/A	5.4mm (0.40)	11.9mm (2.69)	N/A	N/A	22 days
		CON: Vehicle; uninjected	10 (same as injected)	N/A	5.6mm (0.46)	13.2mm (2.76)	N/A	N/A	22 days
	2	INT: JS1/34.5-/47-/mGM-CSF	10	N/A	5.5mm (0.34)	2.2mm (1.6)	N/A	N/A	21 days
		CON: Vehicle	10	N/A	5.6mm (0.23)	13.8mm (1.2)	N/A	N/A	21 days

--- : not reported
INT: intervention
CON: control
Liu 2003 data from experiment 1 taken from 10^8 dose
Cooke, 2016 did not provide any relevant information