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## (12) United States Patent

#### Zitvogel et al.

#### (54) COMBINATION OF ONCOLYTIC VIRUS WITH IMMUNE CHECKPOINT MODULATORS

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#### (56) **References Cited**

#### U.S. PATENT DOCUMENTS

5,225,539	А	7/1993	Winter
5,457,035	Α	10/1995	Baum et al.
5,530,101	Α	6/1996	Queen et al.
5,773,578	Α	6/1998	Hercend et al.
6,180,370	B1	1/2001	Queen et al.
6,984,720	B1	1/2006	Korman et al.
7,109,003	B2	9/2006	Hanson et al.
7,291,331	B1	11/2007	Croft et al.
7,410,644	B2	8/2008	Schlom et al.
7,622,444	B2	11/2009	Weinberg
8,017,114	B2	9/2011	Korman et al.
8,143,379	B2	3/2012	Hanson et al.
8,491,895	B2	7/2013	Hanson et al.
2014/0140959	A1*	5/2014	Szalay A61K 49/006
			424/93.2
2016/0271239	A1 $*$	9/2016	Foy A61K 39/0011
2017/0106065	A1*	4/2017	Foy A61K 39/0011
2017/0157188	A1*	6/2017	Silvestre A61K 35/768
2017/0266270	A1*	9/2017	Foy A61K 39/0011
2018/0028626	A1*	2/2018	Slos A61K 39/0011
2018/0078591	A1 $*$	3/2018	Deng A61K 35/768

#### FOREIGN PATENT DOCUMENTS

IT	1 907 000	B1 4/2008
WO	WO 97/20574	6/1997
WO	WO 03/045197	6/2003
WO	WO 03/082919	10/2003
WO	WO 03/106498	12/2003
WO	WO 2004/004771	1/2004
WO	WO 2004/056875	7/2004
WO	WO 2006/121168	11/2006
	(	Continued)

#### OTHER PUBLICATIONS

Rojas et al (Clin Cancer Res. Dec. 15, 2015; 21(24): 5543-5551).\* (Continued)

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#### (57) ABSTRACT

The present invention provides a combination comprising at least an oncolytic virus and one or more immune checkpoint modulator(s) for use for the treatment of a proliferative disease such as cancer. It also relates to a kit comprising an oncolytic virus and one or more immune checkpoint modulator(s) in separate containers. It also concerns a pharmaceutical composition comprising effective amount of an oncolytic virus and one or more immune checkpoint modulator(s).

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#### (56) References Cited

#### FOREIGN PATENT DOCUMENTS

WO WO 2007	/123737 11/2007
WO WO 2008	/113078 9/2008
WO WO 2008	/156712 12/2008
WO WO 2009	/014708 1/2009
WO WO 2009	/065546 5/2009
WO WO 2009	/065547 5/2009
WO WO 2009	/114335 9/2009
WO WO 2010	/014784 2/2010
WO WO 2012	/110360 8/2012
WO WO 2013	/043569 3/2013
WO WO 2014	/022138 2/2014
WO WO 2014	/047350 3/2014

#### OTHER PUBLICATIONS

Zamarin et al. (Molecular Therapy—Oncolytics (2014) 1, 14004; published online Dec. 10, 2014).\*

Dias et al. (2010) Clin. Canc. Res., vol. 16(9), 2540-2549.\*

Fend et al. (Cancer Res; 77(15) Aug. 1, 2017: 4146-4257).\*

Remy-Ziller (Human Vaccines & Immunotherapeutics 2018, vol. 14, No. 1, 140-145).\*

Buijs et al. (Hum Vaccin Innnnunother. 2015;11(7):1573-84).\*

Berenbaum Clin. Exp. Immunol. 28:1-18 (1977).

Berenbaum Pharmacol. Rev. 41:93-141 (1989)).\*

Tallarida "Drug Synergism and Dose Effect Analysis" Ed. Chapman & Hall (2000), pp. 1-71.).\*

Merrick et al. (Curr Opin Investig Drugs. Dec. 2009;10(12):1372-82).\*

Beaud Biochemie 77:774-779 (1995)).\*

Agata et al., Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes, 8(5) International Immunology 765-772 (1996).

Andtbacka et al., OPTiM: A randomized phase III trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocytemacrophage colony-stimulating factor (GM-CSF) for the treatment (tx) of unresected stage IIIB/C and IV melanoma, 31 J. Clin Oncol 1-2 (2013).

Bedke et al., *Targeted therapy in renal cell carcinoma: moving from molecular agents to specific immunotherapy*, 32 World J. Urol. 31-38 (2014).

Bennett et al., Program Death-1 Engagement Upon TCR Activation Has Distinct Effects on Costimulation and Cytokine-Driven Proliferation: Attenuation of ICOS, IL-4, and IL-21, But Not CD28, IL-7, and IL-15 Responses, 170 J. Immunol 711-718 (2003).

Blank et al., *Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy*, 54 Cancer Immunol Immunother 307-314 (2005).

Blank et al., *The perspective of immunotherapy: new molecules and new mechanisms of action in immune modulation*, 26(2) Current Opin. Oncol. 204-214 (2014).

Boviatsis et al., Antitumor activity and reporter gene transfer into rat brain neoplasms inoculated with herpes simplex virus vectors defective in thymidine kinase or ribonucleotide reductase, 1(5) Gene Therapy 323-331 (Sep. 1994).

Breitbach et al., Targeted and Armed Oncolytic Poxvirus for Cancer: the Lead Example of JX-594, 13 Current Pharmaceutical Biotechnology 1768-1772 (2012).

Brunet et al., A new member of the immunoglobulin superfamily— CTLA-4, 328 Nature 267-270 (Jul. 16, 1987).

Champiat et al., *Incorporating Immune-Checkpoint Inhibitors into Systemic Therapy of NSCLC*, 9(2) Journal of Thoracic Oncology 144-153 (Feb. 2014).

Carter et al., *PD-1:PD-L inhibitory pathway affects both CD4*<sup>+</sup> and *CD8*<sup>+</sup> *T cells and is overcome by IL-2*, 32 Eur. J. Immunol 634-643 (2002).

Chambers et al., Comparison of genetically engineered herpes simplex viruses for the treatment of brain tumors in a scid mouse Chernajovsky et al., *Fighting cancer with oncolytic viruses*, 332 BMJ 170-172 (Jan. 21, 2006).

Cohen et al., ONYX-015 Onyx Pharmaceuticals, 2(12) Current Opinion in Investigational Drugs 1770-1775 (2001).

Dariavach et al., Human Ig superfamily CTLA-4 gene: chromosomal localization and identity of protein sequence between murine and human CTLA-4 cytoplasmic domains, 18 Eur. J. Immunol. 1901-1905 (1988).

Dong et al., *B7-H1 pathway and its role in the evasion of tumor immunity*, 81 J. Mol Med 281-287 (2003).

Dong et al., *Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion*, 8(8) Nature Medicine 793-800 (Aug. 2002).

Engeland et al., *Measles Virus Mediated Immune Checkpoint Blockade Enhances Cancer Immunovirotherapy*, 22(Supplement 1) Molecular Therapy (May 2014) (abstract only).

Foloppe et al., Targeted delivery of a suicide gene to human colorectal tumors by a conditionally replicating vaccinia virus, 15 Gene Therapy 1361-1371 (2008).

Freeman et al., Engagement of the PD-1 Immunoinhibitory Receptor by a Novel B7 Family Member Leads to Negative Regulation of Lymphocyte Activation, 192(7) J. Exp. Med. 1027-1034 (Oct. 2, 2000).

Freeman et al., *Phase I/II Trial of Intravenous NDV-HUJ Oncolytic Virus in Recurrent Glioblastoma Multiforme*, 13(1) Molecular Therapy 221-228 (January 2006).

Gammon et al., Vaccinia Virus-Encoded Ribonucleotide Reductase Subunits are Differentially Required for Replication and Pathogenesis, 6(7) PLoS Pathogens 1-20 (Jul. 2010).

Geevarghese et al., *Phase I/II Study of Oncolytic Herpes Simplex Virus NV1020 in Patients with Extensively Pretreated Refractory Colorectal Cancer Metastatic to the Liver*, 21 Human Gene Therapy 1119-1128 (Sep. 2010).

Guse et al., Oncolytic vaccinia virus for the treatment of cancer, 11(3) Expert Opin. Biol. Ther. 595-608 (2011).

Hermiston, T., *A demand for next-generation oncolytic adenovirus*, 8(4) Current Opinion in Molecular Therapeutics 322-330 (Aug. 2006).

Kaufmann et al., Chemovirotherapy of Malignant Melanoma with a Targeted and Armed Oncoytic Measles Virus, 133 Journal of Investigative Dermatology 1034-1042 (2013).

Khuri et al., A controlled trial of intratumoral ONYX-015, a selectively-replicating adenovirus, in combination with cisplatin and 5-fluorouracil in patients with recurrent head and neck cancer, 6(8) Nature Medicine 879-885 (Aug. 2000).

Kirn et al., *Replication-selective virotherapy for cancer: Biological principles, risk management and future directions*, 7(7) Nature Medicine 781-787 (Jul. 2001).

Kirn et al., Targeted and armed oncolytic poxviruses: a novel multi-mechanistic therapeutic class for cancer, 9 Nature 64-71 (Jan. 2009).

Leach et al., Enhancement of Antitumor Immunity by CTLA-4 Blockade, 271 Science 1734-1736 (Mar. 22, 1996).

Lorence et al., *Phase 1 Clinical Experience Using Intravenous Administration of PV701, an Oncolytic Newcastle Disease Virus*, 7 Current Cancer Drug Targets 157-167 (2007).

Martuza et al., Experimental Therapy of Human Glioma by Means of a Genetically Engineered Virus Mutant, 252 Science 854-856 (Oct. 3, 1990).

McDonald et al., A measles virus vaccine strain derivative as a novel oncolytic agent against breast cancer, 99 Breast Cancer Research and Treatment 177-184 (2006).

Mineta et al, Treatment of Malignant Gliomas Using Ganciclovirhypersensitive, Ribonucleotide Reductase-deficient Herpes Simplex Viral Mutant, 54 Cancer Research 3963-3966 (Aug. 1, 1994).

Okazaki et al., *New regulatory co-receptors: inducible co-stimulator and PD-1*, 14 Current Opinion in Immunology 779-782 (2002).

Phuangsab et al., Newcastle disease virus therapy of human tumor

#### (56) **References Cited**

#### OTHER PUBLICATIONS

Presta et al., Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders, 57 Cancer Research 4593-4599 (Oct. 15, 1997). Pyles et al., Evidence that the Herpes Simplex Virus Type 1 Uracil DNA Glycosylase is Required for Efficient Viral Replication and Latency in the Murine Nervous System, 68(8) Journal of Virology

4963-4972 (Aug. 1994). Qureshi et al., *Trans-endocytosis of CD80 and CD86: a molecular basis for the cell extrinsic function of CTLA-4*, 332(6029) Science 600-603 (2011).

Rudin et al., Phase I Clinical Study of Seneca Valley Virus (SVV-001), a Replication-Competent Picornavirus, in Advanced Solid Tumors with Neuroendocrine Features, 17(4) Clin Cancer Res 888-895 (Feb. 15, 2011).

Senzer et al., Phase II Clinical Trial of a Granulocyte-Macrophage Colony-Stimulating Factor-Encoding, Second-Generation Oncolytic Herpesvirus in Patients With Unresectable Metastatic Melanoma, 27(34) Journal of Clinical Oncology 5763-5771 (Dec. 1, 2009).

Stojdl et al., *Exploiting tumor-specific defects in the interferon pathway with a previously unknown oncolytic virus*, 6(7) Nature Medicine 821-825 (Jul. 2000).

Stojdl et al., VSV strains with defects in their ability to shutdown innate immunity are potent systemic anti-cancer agents, 4 Cancer Cell 263-275 (2003).

Thorne, Immunotherapeutic potential of oncolytic vaccinia virus, 4(Article 155) Frontiers in Oncology 1-5 (Jun. 2014).

Thorne et al., *Rational strain selection and engineering creates a broad-spectrum, systemically effective oncolytic poxvirus, JX-963*, 117(11) The Journal of Clinical Investigation 3350-3358 (Nov. 2007).

Topalian et al., *Targeting the PD-1/B7-H1(PD-L1) pathway to activate anti-tumor immunity*, 24(2) Curr. Opin. Immunol. 207-212 (Apr. 2012).

Wong et al., Oncolytic Viruses for Cancer Therapy: Overcoming the Obstacles, 2 Viruses 78-106 (2010).

Xia, et al., *Phase III randomized clinical trial on intratumoral injection of E1B gene-deleted adenovirus (H101) combined with cispliatin-based chemotherapy in treating squamous cell cancer of head and neck or esophagus*, 23(12) Ai Zheng 1666-1670 (Dec. 2004) (abstract only).

Zhang et al., Eradication of Solid Human Breast Tumors in Nude Mice with an Intravenously Injected Light-Emitting Oncolytic Vaccinia Virus, 67(20) Cancer Research 10038-10046 (Oct. 15, 2007). International Search Report dated Sep. 21, 2015, and Written Opinion in corresponding PCT Application No. PCT/EP2015/ 066353.

Gomella et al., *Phase I study of intravesical vaccinia virus as a vector for gene therapy of bladder cancer*, 166(4) Journal of Urology 1291-1295 (Oct. 2001) (abstract only).

Study of Pembrolizunab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-028/KEYNOTE-28), (First Posted Feb. 4, 2014) (https://clinicaltrials.gov/ct2/show/NCT02054806?term=MK-3475&rank=43) (Jul. 24, 2019).

A Phase 1/2 Study Exploring the Safety, Tolerability, and Efficacy of Pembrolizumab (MK-3475) in Combination with Epacadostat (INCB024360) in Subjects With Selected Cancers (INCB 24360-202 / MK-3475-037 / KEYNOTE-037/ ECHO-202) (First Posted Jul. 1, 2014) (https://clinicaltrials.gov/ct2/show/NCT02178722?term=MK-3475&rank=29) (Jul. 24, 2019).

CT-011 and p53 Genetic Vaccine for Advanced Solid Tumors, (First Posted Jul. 1, 2011) (https://clinicaltrials.gov/ct2/show/NCT01386502? term=CT-011&cond=cancer&rank=4) (Jul. 24, 2019).

Anti PD1 Antibody in Diffuse Intrinsic Pontine Glioma, (First Posted Sep. 30, 2013) (https://clinicaltrials.gov/ct2/show/NCT01952769? term=%28anti-PD1%29+or+%28anti-PD-1%29&cond=glioma&rank= 1) (Jul. 24, 2019).

Safety Study of Recombinant Vaccinia Virus to Treat Refractory

SARC028: A Phase II Study of the Anti-PD1 Antibody Pembrolizumab (MK-3475) in Patients with Advanced Sarcomas, (First Posted Nov. 25, 2014) (https://clinicaltrials.gov/ct2/show/NCT02301039?term= anti-PD1+or+anti-PD-1&cond=bone+cancer&ranks=3) (Jul. 24, 2019). Camacho et al., A multi-targeted approach to treating bone metas-

tases, 33 Cancer Metastasis Rev. 545-553 (Online Jan. 4, 2014). Chan et al., Oncolytic Poxviruses, 1(1) Ann Rev Virol., 119-141 (2014).

Berghoff et al., *PD1 (CD279) and PD-L1 (CD274, B7H1) expression in primary central nervous system lymphomas (PCNSL)*, 33(1) Clinical Neuropathology, 42-49 (online Dec. 20, 2013).

Finnefrock et al., PD-1 Blockade in Rhesus Macaques: Impact on Chronic Infection and Prophylactic Vaccination, 182 J. Immunol 980-987 (2009).

Gholami et al., Novel therapy for anaplastic thyroid carcinoma cells using an oncolytic vaccinia virus carrying the human sodium iodide symporter, 150(6) Surgery, 1040-1047 (2011).

He et al., Effective Oncolytic Vaccinia Therapy for Human Sarcomas, 175(2) J Surg Res. e53-e60 (2012).

Hui et al., Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein-Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients, 73(6) Cancer Res. 1676-1688 (2013).

Lin et al., Oncolytic Vaccinia Virotherapy of Anaplastic Thyroid Cancer in Vivo, 93(111) J Clin Endocrinol Metab. 4403-4407 (2008).

Liu et al., Oncolytic Vaccinia Virotherapy for Endometrial Cancer, 132(3) Gynecol Oncol. 722-729 (Mar. 2014).

Lun et al., Double-deleted vaccinia virus in virotherapy for refractory and metastatic pediatric solid tumors, 7 Molecular Oncology, 944-954 (2013).

Qui et al., *Programmed death-1 (PD-1) polymorphisms in Chinese patients with esophageal cancer*, 47 Clinical Biochemistry 612-617 (Online Jan. 2, 2014).

Pardoll, *The blockade of immune checkpoints in cancer immunotherapy*, 12(4) Nat Rev Cancer 252-264 (May 4, 2016).

Shen et al., *Programmed Cell Death Ligand 1 Expression in Osteosarcoma*, 2(7) Cancer Immunol Res. 690-698 (Online Apr. 21, 2014).

Sliwkowski et al., Antibody Therapeutics in Cancer, 341 Science 1192-1198 (Sep. 13, 2013).

Topalian et al., Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer, 366(26) N. Engl. J. Med. 2443-2454 (Jun. 28, 2012).

Zitvogel, *Targeting PD-1/PD-L1 interactions for cancer immunotherapy*, 1(8) Oncolmmunology 1223-1225 (Nov. 2012).

OPDIVO® Prescribing Information, Reference ID:4421379, Initial U.S. Approval 2014, Revised Mar. 2019.

Opdivo Approval History https://www.drugs.com/history/opdivo. html (Jul. 26, 2019).

Study of Pembrolizumab (MK-3475) in Previously-Treated Participants With Advanced Carcinoma of the Esophagus or Esophagogastric Junction (MK-3475-180/KEYNOTE-180)(First Posted Sep. 24, 2015) (https://www.clinicaltrials.gov/ct2/show/NCT02559687 (Jul. 26, 2019). Pembrolizumab With Locally Delivered Radiation Therapy for the Treatment of Metastatic Esophageal Cancers (First Posted Dec. 30, 2015) (https://www.clinicaltriais.gov/ct2/show/NCT02642809) (Jul. 26, 2019).

Study of Pembrolizumab (MK-3475) in Platinum Pre-treated Recurrent/ Metastatic Nasopharyngeal Cancer (MK-3475-122/KEYNOTE-122) (First Posted Nov. 23, 2015) (https://clinicaltrials.gov/ct2/show/ NCT02611960) (Jul. 26, 2019).

Nivolumab Alone or in Combination With Ipilimumab in Treating Patients With Advanced Uterine Leiomyosarcoma (First Posted Apr. 28, 2015) (https://clinicaltrials.gov/ct2/show/NCT02428192) (Jul. 26, 2019).

Nivolumab in Treating Patients With Persistent, Recurrent, or Metastatic Cervical Cancer (First Posted Oct. 6, 2014) (https:// clinicaltrials.gov/ct2/show/NCT02257528) (Jul. 26, 2019).

Nivolumab and Ipilimumab in Treating Patients With HIV Associated Relapsed or Refractory Classical Hodgkin Lymphoma or Solid Tumors That are Metastatic or Cannot Be Removed by Surgery

Find authenticated court documents without watermarks at docketalarm.com.

#### (56) **References Cited**

#### OTHER PUBLICATIONS

Study of Pembrolizumab (MK-3475) in Participants With Advanced Solid Tumors (MK-3475-158/KEYNOTE-158) (First Posted Dec. 11, 2015) (https://clinicaltrials.gov/ct2/show/NCT02628067) (Jul. 26, 2019).

Phase 1/11 Study of PDR001 in Patients With Advanced Malignancies (First Posted Mar. 31, 2015) (https://clinicaltrials.gov/ct2/show/ NCTO2404441) (Jul. 26, 2019).

Pembrolizumab in Treating Younger Patients With Recurrent Progressive, or Refractory High-Grade Gliomas, Diffuse Intrinsic Pontine Gliomas, Hypermutated Brain Tumors, Ependymoma or Medulloblastoma (First Posted Feb. 10, 2015) (https://www. clinicaltrials.gov/ct2/show/NCT02359565) (Jul. 26, 2019).

Atkins et al., Phase 2, multicenter, safety and efficacy study of pidilizumab in patients with metastatic melanoma, 32(15 Supplemental) Oncology (May 20, 2014).

Garon et al., Safety and clinical activity of MK-3475 in previously treated patients (pts) with non-small cell lung cancer (NSCLC), 30(15 Supplemental) Journal of Clinical Oncology (May 20, 2012). Kaufman et al., Poxvirus-based vaccine therapy for patients with advance pancreatic cancer, 5(60) Journal of Translational Medicine 1-10 (2007).

Kefford et al., *Clinical efficacy and correlation with tumor PD-L1 expression in patients (pts) with melanoma*, 30(15 Supplemental) Journal of Clinical Oncology (May 20, 2014).

Lu et al., Combined PD-1 blockade and GITR triggering induce a potent antitumor immunity in murine cancer models and synergizes

DOCKE

with chemotherapeutic drugs, 12(36) Journal of Translational Medicine 1-11 (2014).

Nomi et al., Clinical Significance and Therapeutic Potential of the Programmed Death-1 Ligand/Programmed Death-1 Pathway in Human Pancreatic Cancer, 13(7) Clin. Cancer. Res. (Apr. 1, 2007). Shchelkunov et al., Vaccinia Virus Molecular Biology, Orthopoxviruses Pathogenic for Humans 37-44 (2005).

Patnaik et al., *Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors*, 30(15 Supplemental) Journal of Clinical Oncology (May 20, 2012).

Part A1: Information Required Under Article 11 (Schedule 2) of the 2002 Regulations, BN Immunotherapeutics, Inc. (Sep. 13, 2012).

Rizvi et al., Safety and clinical activity of MK-3475 as initial therapy in patients with advanced non-small cell lunch cancer (NSCLC), 30(15 Supplemental) Journal of Clinical Oncology (May 20, 2012).

Seiwert et al., A phase Ib study of MK-3475 in patients with human papillomavirus (HPV)-associated and non-HPV-associated head and neck (H/N) cancer, 30(15 Supplemental) Journal of Clinical Oncology (May 20, 2012).

Verbrugge et al., Radiotherapy Increases the Permissiveness of Established Mammary Tumors to Rejection by Immunomodulatory Antibodies, 72(13) Cancer Res 3163-3174 (Jul. 1, 2012).

Westin et al., Safety and Activity of PD1 Blockade by Pidilizumab in Combination with Rituximab in Patients with Relapsed Follicular Lymphoma: a Single Group, Open-label, Phase 2 Trial, 15(1) Lancet Oncol. 69-77 (Jan. 2014).

\* cited by examiner



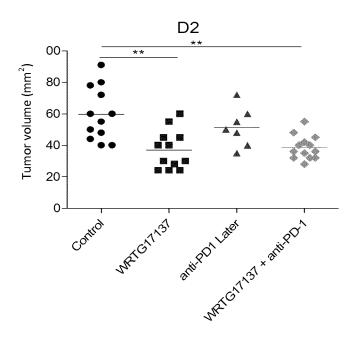
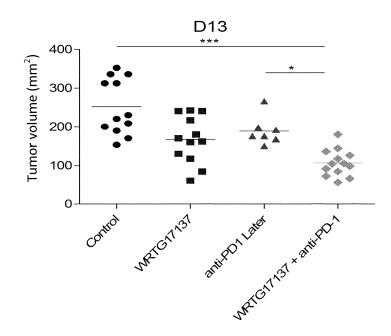


Figure 1B



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