

Supplementary Online Content

Table S1. Search Strategy for the Pubmed Database

Table S2. Information of Excluded 42 Trials Due to Unavailable SAEs Data

Table S1. Search Strategy for the Pubmed Database

#1	"ipilimumab"[MeSH Terms] OR "ipilimumab"[All Fields]
#2	("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields])
#3	#1 and #2

Table S2. Information of Excluded 42 Trials Due to Unavailable SAEs Data

Study name	Phase	Tumor Type	Drug	Dose (mg/kg)	No. of Patients
Phan, 2003 ^[1]	NA	melanoma	IPI+gp100	3	14
Maker, 2005 ^[2]	I/II	melanoma	IPI+IL-2	mutiple	36
Sanderson, 2005 ^[3]	I	melanoma	IPI+peptide vaccine	mutiple	19
O'Mahony,2007 ^[4]	II	advanced malignancies	IPI	mutiple	11
Ansell, 2009 ^[5]	I	lymphoma	IPI	mutiple	18
Bashey, 2009 ^[6]	I	malignancy	IPI	mutiple	29
Carthon, 2010 ^[7]	NA	UC	IPI+surgery	mutiple	12
Hodi, 2010 ^[8]	III	melanoma	IPI	3	131
			IPI+ gp100	3	380
Royal, 2010 ^[9]	II	pancreatic cancer	IPI	3	27
Sarnaik, 2011 ^[10]	II	melanoma	IPI	3	25
			IPI	10	50
Giacomo, 2012 ^[11]	II	melanoma	IPI+fotemustine	10	86
Madan, 2012 ^[12]	I	prostate cancer	IPI+vaccine	mutiple	30
Margolin, 2012 ^[13]	II	melanoma	IPI	10	51
Eertwegh, 2012 ^[14]	I	prostate cancer	IPI+GVAX	mutiple	12
				3	16
Weber, 2013 ^[15]	I	melanoma	IPI	10	20
			IPI+dacarbazine	10	19
			IPI+paclitaxel+carboplatin	10	20
Hodi, 2014 ^[16]	I	melanoma	IPI+bevacizumab	10	22
			IPI+bevacizumab	3	24
Hodi, 2014 ^[17]	II	melanoma	IPI	10	120
			IPI+sargramostim	10	118
Kwon, 2014 ^[18]	III	prostate cancer	IPI+radiotherapy	10	399
Zimmer, 2015 ^[19]	II	melanoma	IPI	3	103
Zimmer, 2015 ^[20]	II	melanoma	IPI	3	53
Antonia, 2016 ^[21]	I/II	SCLC	IPI+Nivolumab	1	54
			IPI+Nivolumab	3	61
Brohl, 2016 ^[22]	I	melanoma	IPI+alfa-2b	mutiple	31
Arriola, 2016 ^[23]	II	SCLC	IPI+carboplatin+etoposide	10	39
Bjoern, 2016 ^[24]	I	melanoma	IPI+IDO	3	10
Davids, 2016 ^[25]	I	hematologic cancer	IPI	mutiple	28
Hiniker, 2016 ^[26]	I	melanoma	IPI+radiotherapy	3	22

Table S2. Information of Excluded 42 Trials Due to Unavailable SAEs Data (continued)

Study name	Phase	Tumor Type	Drug	Dose (mg/kg)	No. of Patients
Hodi, 2016 [27]	II	melanoma	IPI	3	46
			IPI+nivolumab	3	94
Ray, 2016 [28]	I	melanoma	IPI+IL-2	multiple	12
Weber, 2016 [29]	II	melanoma	nivolumab followed by IPI	3	68
			IPI followed by nivolumab	3	70
Wilgenhof, 2016 [30]	II	melanoma	IPI+TriMixDC-MEL	10	39
Jamal, 2017 [31]	II	melanoma	IPI+carboplatin/paclitaxel	3	30
Khouri, 2017 [32]	II	lymphoid malignancies	IPI plus Lenalidomide	3	17
Lheureux, 2017 [33]	I/II	cervical cancer	IPI	multiple	42
Long, 2017 [34]	I	melanoma	IPI+pembrolizumab	1	153
Patel, 2017 [35]	II	melanoma	IPI+temozolomide	10	64
Reilley, 2017 [36]	I	advanced malignancies	IPI+Imatinib	multiple	35
Sakamuri, 2017 [37]	I	advanced cancer	IPI+lenalidomide	multiple	36
Tang, 2017 [38]	I	advanced cancer	IPI+radiotherapy	3	35
Williams, 2017 [39]	I	melanoma	IPI+radiotherapy	multiple	16
Wolchok, 2017 [40]	III	melanoma	IPI	3	311
			IPI+nivolumab	3	313
Yi, 2017 [41]	II	NSCLC	chemotherapy+IPI+surgery	10	24
Yang, 2017 [42]	II	NSCLC	chemotherapy+IPI+surgery	10	13

Abbreviation: IPI, ipilimumab; NA, not available; IL-2, interleukin-2; UC, urothelial carcinoma of the bladder; NSCLC, non-small-cell lung cancer; SCLC, small cell lung cancer; GVAX, The granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells vaccine; IDO, Indoleamine 2,3-dioxygenase; TriMixDC-MEL, Autologous Monocyte-Derived mRNA Electroporated Dendritic Cells.

References

1. Phan GQ, Yang JC, Sherry RM, Hwu P, Topalian SL, Schwartzentruber DJ, et al. Cancer regression and autoimmunity induced by cytotoxic T lymphocyte-associated antigen 4 blockade in patients with metastatic melanoma. Proc Natl Acad Sci U S A. 2003; 100: 8372-7.
2. Maker AV, Phan GQ, Attia P, Yang JC, Sherry RM, Topalian SL, et al. Tumor regression and autoimmunity in patients treated with cytotoxic T lymphocyte-associated antigen 4 blockade and interleukin 2: a phase I/II study. Ann Surg Oncol. 2005; 12: 1005-16.
3. Sanderson K, Scotland R, Lee P, Liu D, Groshen S, Snively J, et al. Autoimmunity in a phase I trial of a fully human anti-cytotoxic T-lymphocyte antigen-4 monoclonal antibody with multiple melanoma peptides and Montanide ISA 51 for patients with resected stages III and IV melanoma. J Clin Oncol. 2005; 23: 741-50.
4. O'Mahony D, Morris JC, Quinn C, Gao W, Wilson WH, Gause B, et al. A pilot study of CTLA-4 blockade after cancer vaccine failure in patients with advanced malignancy. Clin Cancer Res. 2007; 13: 958-64.

5. Ansell SM, Hurvitz SA, Koenig PA, LaPlant BR, Kabat BF, Fernando D, et al. Phase I study of ipilimumab, an anti-CTLA-4 monoclonal antibody, in patients with relapsed and refractory B-cell non-Hodgkin lymphoma. *Clin Cancer Res.* 2009; 15: 6446-53.
6. Bashey A, Medina B, Corringham S, Pasek M, Carrier E, Vrooman L, et al. CTLA4 blockade with ipilimumab to treat relapse of malignancy after allogeneic hematopoietic cell transplantation. *Blood.* 2009; 113: 1581-8.
7. Carthon BC, Wolchok JD, Yuan J, Kamat A, Ng Tang DS, Sun J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. *Clin Cancer Res.* 2010; 16: 2861-71.
8. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. *N Engl J Med.* 2010; 363: 711-23.
9. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother.* 2010; 33: 828-33.
10. Sarnaik AA, Yu B, Yu D, Morelli D, Hall M, Bogle D, et al. Extended dose ipilimumab with a peptide vaccine: immune correlates associated with clinical benefit in patients with resected high-risk stage IIIc/IV melanoma. *Clin Cancer Res.* 2011; 17: 896-906.
11. Di Giacomo AM, Ascierto PA, Pilla L, Santinami M, Ferrucci PF, Giannarelli D, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. *Lancet Oncol.* 2012; 13: 879-86.
12. Madan RA, Mohebtash M, Arlen PM, Vergati M, Rauckhorst M, Steinberg SM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol.* 2012; 13: 501-8.
13. Margolin K, Ernsthoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol.* 2012; 13: 459-65.
14. van den Eertwegh AJ, Versluis J, van den Berg HP, Santegoets SJ, van Moorselaar RJ, van der Sluis TM, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol.* 2012; 13: 509-17.
15. Weber J, Hamid O, Amin A, O'Day S, Masson E, Goldberg SM, et al. Randomized phase I pharmacokinetic study of ipilimumab with or without one of two different chemotherapy regimens in patients with untreated advanced melanoma. *Cancer Immun.* 2013; 13: 7.
16. Hodi FS, Lawrence D, Lezcano C, Wu X, Zhou J, Sasada T, et al. Bevacizumab plus ipilimumab in patients with metastatic melanoma. *Cancer Immunol Res.* 2014; 2: 632-42.
17. Hodi FS, Lee S, McDermott DF, Rao UN, Butterfield LH, Tarhini AA, et al. Ipilimumab plus sargramostim vs ipilimumab alone for treatment of metastatic melanoma: a randomized clinical trial. *JAMA.* 2014; 312: 1744-53.
18. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *The Lancet Oncology.* 2014; 15: 700-12.
19. Zimmer L, Eigentler TK, Kiecker F, Simon J, Utikal J, Mohr P, et al. Open-label, multicenter, single-arm phase II DeCOG-study of ipilimumab in pretreated patients with different subtypes of

- metastatic melanoma. *J Transl Med.* 2015; 13: 351.
20. Zimmer L, Vaubel J, Mohr P, Hauschild A, Utikal J, Simon J, et al. Phase II DeCOG-study of ipilimumab in pretreated and treatment-naive patients with metastatic uveal melanoma. *PLoS One.* 2015; 10: e0118564.
 21. Antonia SJ, Lopez-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* 2016; 17: 883-95.
 22. Brohl AS, Khushalani NI, Eroglu Z, Markowitz J, Thapa R, Chen YA, et al. A phase IB study of ipilimumab with peginterferon alfa-2b in patients with unresectable melanoma. *J Immunother Cancer.* 2016; 4: 85.
 23. Arriola E, Wheater M, Galea I, Cross N, Maishman T, Hamid D, et al. Outcome and Biomarker Analysis from a Multicenter Phase 2 Study of Ipilimumab in Combination with Carboplatin and Etoposide as First-Line Therapy for Extensive-Stage SCLC. *J Thorac Oncol.* 2016; 11: 1511-21.
 24. Bjoern J, Iversen TZ, Nitschke NJ, Andersen MH, Svane IM. Safety, immune and clinical responses in metastatic melanoma patients vaccinated with a long peptide derived from indoleamine 2,3-dioxygenase in combination with ipilimumab. *Cytotherapy.* 2016; 18: 1043-55.
 25. Davids MS, Kim HT, Bachireddy P, Costello C, Liguori R, Savell A, et al. Ipilimumab for Patients with Relapse after Allogeneic Transplantation. *N Engl J Med.* 2016; 375: 143-53.
 26. Hiniker SM, Reddy SA, Maecker HT, Subrahmanyam PB, Rosenberg-Hasson Y, Swetter SM, et al. A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. *Int J Radiat Oncol Biol Phys.* 2016; 96: 578-88.
 27. Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. *The Lancet Oncology.* 2016; 17: 1558-68.
 28. Ray A, Williams MA, Meek SM, Bowen RC, Grossmann KF, Andtbacka RH, et al. A phase I study of intratumoral ipilimumab and interleukin-2 in patients with advanced melanoma. *Oncotarget.* 2016; 7: 64390-9.
 29. Weber JS, Gibney G, Sullivan RJ, Sosman JA, Slingluff CL, Lawrence DP, et al. Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. *Lancet Oncol.* 2016; 17: 943-55.
 30. Wilgenhof S, Corthals J, Heirman C, Van BN, Lucas S, Kvistborg P, et al. Phase II Study of Autologous Monocyte-Derived mRNA Electroporated Dendritic Cells (TriMixDC-MEL) Plus Ipilimumab in Patients With Pretreated Advanced Melanoma. *J Clin Oncol.* 2016; 34: 1330-8.
 31. Jamal R, Lapointe R, Cocolakis E, Thebault P, Kazemi S, Friedmann JE, et al. Peripheral and local predictive immune signatures identified in a phase II trial of ipilimumab with carboplatin/paclitaxel in unresectable stage III or stage IV melanoma. *J Immunother Cancer.* 2017; 5: 83.
 32. Khouri IF, Fernandez Curbelo I, Turturro F, Jabbour EJ, Milton DR, Bassett RL, Jr., et al. Ipilimumab plus Lenalidomide after Allogeneic and Autologous Stem Cell Transplantation for Patients with Lymphoid Malignancies. *Clin Cancer Res.* 2018; 24: 1011-8.
 33. Lheureux S, Butler MO, Clarke B, Cristea MC, Martin LP, Tonkin K, et al. Association of Ipilimumab With Safety and Antitumor Activity in Women With Metastatic or Recurrent Human Papillomavirus-Related Cervical Carcinoma. *JAMA Oncol.* 2018; 4: e173776.

34. Long GV, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. *Lancet Oncol.* 2017; 18: 1202-10.
35. Patel SP, Kim DW, Bassett RL, Cain S, Washington E, Hwu WJ, et al. A phase II study of ipilimumab plus temozolamide in patients with metastatic melanoma. *Cancer Immunol Immunother.* 2017; 66: 1359-66.
36. Reilley MJ, Bailey A, Subbiah V, Janku F, Naing A, Falchook G, et al. Phase I clinical trial of combination imatinib and ipilimumab in patients with advanced malignancies. *J Immunother Cancer.* 2017; 5: 35.
37. Sakamuri D, Glitza IC, Betancourt Cuellar SL, Subbiah V, Fu S, Tsimberidou AM, et al. Phase 1 dose-escalation study of anti CTLA-4 antibody ipilimumab and lenalidomide in patients with advanced cancers. *Mol Cancer Ther.* 2017; 17: 671-6.
38. Tang C, Welsh JW, de Groot P, Massarelli E, Chang JY, Hess KR, et al. Ipilimumab with Stereotactic Ablative Radiation Therapy: Phase I Results and Immunologic Correlates from Peripheral T Cells. *Clin Cancer Res.* 2017; 23: 1388-96.
39. Williams NL, Wuthrick EJ, Kim H, Palmer JD, Garg S, Eldredge-Hindy H, et al. Phase 1 Study of Ipilimumab Combined With Whole Brain Radiation Therapy or Radiosurgery for Melanoma Patients With Brain Metastases. *Int J Radiat Oncol Biol Phys.* 2017; 99: 22-30.
40. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *N Engl J Med.* 2017; 377: 1345-56.
41. Yi JS, Ready N, Healy P, Dumbauld C, Osborne R, Berry M, et al. Immune Activation in Early-Stage Non-Small Cell Lung Cancer Patients Receiving Neoadjuvant Chemotherapy Plus Ipilimumab. *Clin Cancer Res.* 2017; 23: 7474-82.
42. Yang CJ, McSherry F, Mayne NR, Wang X, Berry MF, Tong B, et al. Surgical Outcomes After Neoadjuvant Chemotherapy and Ipilimumab for Non-Small-Cell Lung Cancer. *Ann Thorac Surg.* 2017; 105: 924-9.