

Supplementary Materials: The Current Status of Immune Checkpoint Inhibitors in Neuro-Oncology: A Systematic Review

Cyrillo G. Brahm, Myra E. van Linde, Roelien H. Enting, Maaïke Schuur, René H.J. Otten, Martijn W. Heymans, Henk M.W. Verheul and Annemiek M.E. Walenkamp

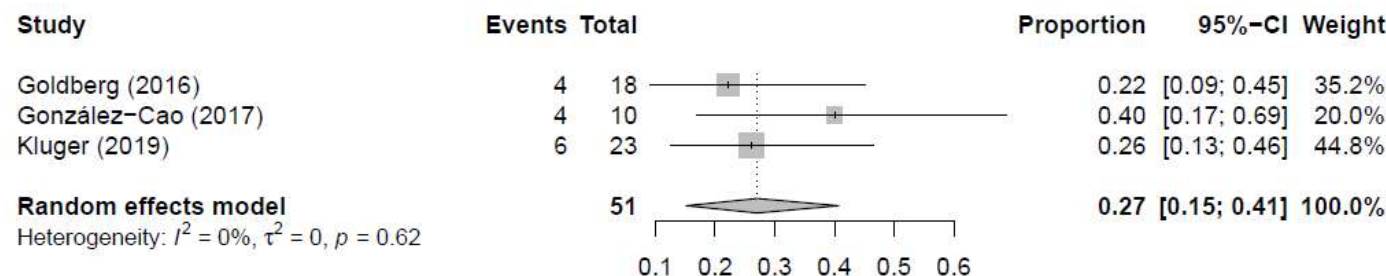


Figure S1. Pooled analysis for intracranial ORR of pembrolizumab in patients with melanoma brain metastases.

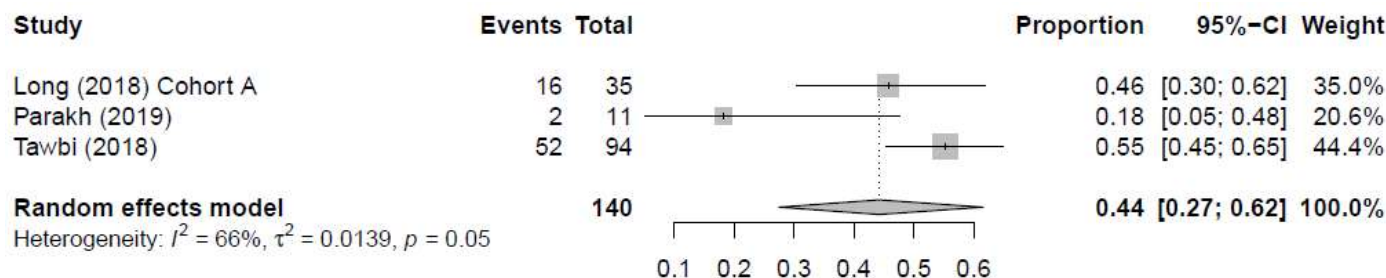


Figure S2. Pooled analysis for intracranial ORR of nivolumab combined with ipilimumab in patients with melanoma brain metastases.

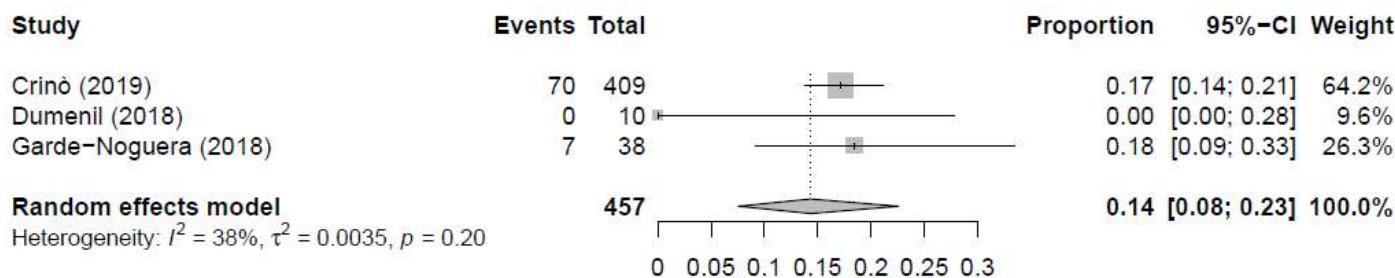


Figure S3. Pooled analysis for ORR of nivolumab in patients with NSCLC brain metastases.

Table S1. Full overview of the complete search strategies.**Search strategy in PubMed (2019 November 11th)**

#	Query	Results
#15	#13 OR #14	3120
#14	#8 AND #12	1542
#13	#1 AND #12	1704
#12	#9 OR #10 OR #11	327442
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	Pembrolizumab*[tiab] OR keytruda[tiab] OR lambrolizumab*[tiab] OR "mk 3475"[tiab] OR mk3475[tiab] OR Ipilimumab*[tiab] OR "bms 734016"[tiab] OR bms734016[tiab] OR "mdx 010"[tiab] OR "mdx 101"[tiab] OR mdx010[tiab] OR mdx101[tiab] OR strentarga[tiab] OR yervoy[tiab] OR Durvalumab*[tiab] OR imfinzi[tiab] OR 'medi 4736'[tiab] OR medi4736[tiab]	
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#8	#6 AND #7	59524
#7	"Neoplasm Metastasis"[Mesh] OR metasta*[tiab] OR advanced[tiab] OR "secondary" [Subheading] OR secondary[tiab]	1533583
#6	#2 OR #5	474860
#5	#3 AND #4	474860
#4	"Brain"[Mesh] OR "Brain Diseases"[Mesh] OR brain*[tiab] OR supratentori*[tiab] OR periventricul*[tiab] OR cerebr*[tiab] OR cerebe*[tiab] OR cranial*[tiab] OR white matter[tiab] OR basal gangli*[tiab] OR thalam*[tiab] OR nucleus caudat*[tiab]	2586863
#3	"Neoplasms"[Mesh] OR cancer[sb] OR adenoma*[tw] OR anticarcinogen*[tw] OR blastoma*[tw] OR cancer*[tw] OR carcinogen*[tw] OR carcinom*[tw] OR carcinosarcoma*[tw] OR chordoma*[tw] OR germinoma*[tw] OR gonadoblastoma*[tw] OR hepatoblastoma*[tw] OR hodgkin disease[tw] OR hodgkin's disease[tw] OR hodgkins disease[tw] OR leukemia*[tw] OR lymphangioma*[tw] OR lymphangiomyoma*[tw] OR lymphangiosarcoma*[tw] OR lymphom*[tw] OR malignan*[tw] OR melanom*[tw] OR meningioma*[tw] OR mesenchymoma*[tw] OR mesonephroma*[tw] OR metasta*[tw] OR neoplas*[tw] OR neuroma*[tw] OR nscl[tw] OR oncogen*[tw] OR oncolog*[tw] OR paraneoplastic[tw] OR plasmacytoma*[tw] OR precancerous[tw] OR sarcoma*[tw] OR teratocarcinoma*[tw] OR teratoma*[tw] OR tumor*[tw] OR tumour*[tw]	6201757
#2	"Brain Neoplasms"[Mesh]	147383
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Search strategy in Embase.com (2019 November 11th)

#	Query	Results
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#14	#8 AND #12	5675
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#8	#6 AND #7	102801
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Search strategy in the Cochrane Library via Wiley (2019 November 11th)

#	Query	Results
#13	#11 or #12	505
#12	#6 and #10	330
#11	#1 and #10	200
#10	#7 or #8 or #9	19928
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	or "protein b7 h1":ti,ab,kw or "protein b7h1":ti,ab,kw or "protein pd1":ti,ab,kw or "protein pd 1":ti,ab,kw or "protein pdcd1":ti,ab,kw or "protein pdcd1lg1":ti,ab,kw or "protein programmed cell death 1":ti,ab,kw or "protein programmed death 1":ti,ab,kw	
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#7	immunotherap*:ti,ab,kw or immunization*:ti,ab,kw or immunisation*:ti,ab,kw	17221
#6	#4 and #5	4713
#5	metasta*:ab,ti,kw or advanced:ab,ti,kw or secondary:ti,ab,kw	286976
#4	#2 and #3	10449
#3	brain*:ti,ab,kw or supratentori*:ti,ab,kw or periventricul*:ti,ab,kw or cerebr*:ti,ab,kw or cranial*:ti,ab,kw or "white matter":ti,ab,kw or ((basal gangli*):ti,ab,kw) or thalam*:ti,ab,kw or ((nucleus caudat*):ti,ab,kw)	89456
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#1	glioblastoma*:ti,ab,kw or "grade iv astrocytoma*":ti,ab,kw or gbm*:ti,ab,kw	2113

Table S2. Studies with immune checkpoint inhibitors in patients with brain metastases that only reported overall survival data.

Author	Study Design	Tumor Type	Agent	No. of Patients	OS Months
Ahmad (2015) [1]	EAP (Retrospective)	Melanoma	IPI	35	3.5 (95% CI 2.5–4.9)
Alexander (2014) [2]	Retrospective	Melanoma	IPI	44	9.3 (95% CI 4.9–12.4)
Ascierto (2017) Cohort A [3]	III	Melanoma	IPI	65	7.0 (95% CI 4.0–12.8)
Ascierto (2017) Cohort B	III	Melanoma	IPI	62	5.7 (95% CI 4.2–7.0)
Dagogo-Jack (2017) [4]	Retrospective	Melanoma	PEMBRO	36	20.4 (95% CI 15.0–N.R.)
Forschner (2017) [5]	Real-world	Melanoma	N.A.	10	7.0 (95% CI 0.0–17.9)
Jinga (2018) [6]	EAP	Melanoma	IPI	16	3.9 (95% CI 0.0–9.2)
Larkin (2018) [7]	III	Melanoma	NIVO	55	8.7 (95% CI 6.3–13.7)
Liu (2019) [8]	Retrospective	Melanoma	PEMBRO	96	18.4 (95% CI 10.8–25.1)
Mangana (2017) [9]	Retrospective	Melanoma	IPI or anti-PD-1	14	10.9

Milsch (2018) [10]	Retrospective	Melanoma	IPI, NIVO or PEMBRO	177	10.5 (95% CI 8.6–12.4)
Schvartsman (2019) [11]	Retrospective	Melanoma	NIVO or PEMBRO	75	32.2 (95% CI 22.9–N.R.)
Vosoughi (2018) [12]	Retrospective	Melanoma	anti-CTLA-4	39	19.2 (95% CI 1.2–65.0)
Vosoughi (2018)	Retrospective	Melanoma	anti-PD-1	28	37.9 (95% CI 5.3–65.0)
Juergens (2018) [13]	Retrospective	NSCLC	NIVO	62	9.0 (95% CI 5.5–13.3)

EAP Expanded access program; ICI Immune checkpoint inhibitor; IPI Ipilimumab; N.A. Not available; NIVO Nivolumab; N.R. Not reached; PEMBRO Pembrolizumab.

Table S3. Primary outcomes of clinical studies with immune checkpoint inhibitors and radiotherapy in patients with brain metastases.

Author	Study Design	Tumor Type	Agent	Type of Radiation Therapy	No. of Patients	Local BM Control % at 12 months	Distant BM Control % at 12 months	PFS Months	OS Months
Acharya (2017) [14]	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS within 3 months	18	85.0	60.0	N.A.	N.A.
Ahmed (2016) anti-PD-1 [15]	Retrospective	Melanoma	NIVO PEMBRO	SRS within 3 months	21	83.0	38.0	3.4	8.9
Ahmed (2016) anti-CTL-4	Retrospective	Melanoma	IPI	SRS within 3 months	25	83.0	21.0	3.4	8.9
An (2017) Cohort A1 [16]	Retrospective	Melanoma	IPI	SRS within 5.5 months	51	51.0	N.A.	8.4†	13.4
An (2017) Cohort A2	Retrospective	Melanoma	IPI	SRS after 5.5 months	20	25.0	N.A.	3.6†	11.5
An (2017) Cohort B1	Retrospective	Melanoma	IPI	SRS within 5.5 months	15	46.2	N.A.	6.3†	13.4
An (2017) Cohort B2	Retrospective	Melanoma	IPI	SRS after 5.5 months	13	20.6	N.A.	3.5†	11.5
Choong (2017) anti-PD-1 [17]	Retrospective	Melanoma	Anti-PD-1	SRS	11	48.0	N.A.	12.7† (95% CI 5.5–N.A.)	20.4 (95% CI 8.8–N.A.)
Choong (2017) anti-CTLA-4	Retrospective	Melanoma	Anti-CTLA-4	SRS	28	48.0	N.A.	7.5† (95% CI 4.0–15.6)	7.5 (95% CI 4.4–15.6)
Cohen-Inbar (2017) Cohort A [18]	Retrospective	Melanoma	IPI	SRS prior to /concurrent with ICI	32	54.0	26.0	7.2†	13.8
Cohen-Inbar (2017) Cohort B	Retrospective	Melanoma	IPI	SRS after ICI	14	17.0	17.0	5.0†	6.4
Diao (2018) Cohort A [19]	Retrospective	Melanoma	IPI	Concurrent SRS within 1 month	23	58.0	23.0	N.A.	11.8

Diao (2018) Cohort B	Retrospective	Melanoma	IPI	Non-concurrent SRS after 1 month	28	70.0	45.0	N.A.	18.7
Gerber (2015) [20]	Retrospective	Melanoma	IPI	WBRT	13	N.A.	N.A.	N.A.	4.0
Kaidar-Person (2017) [21]	Retrospective	Melanoma	IPI PEMBRO NIVO	SRS or HFRT	29	52.0	35.0	3.5†	15.0 (95% CI 10.0–15.8)
Mathew (2013) [22]	Retrospective	Melanoma	IPI	SRS	25	N.A.	N.A.	N.A.	N.A.
Minniti (2019) Cohort A [23]	Retrospective	Melanoma	IPI	SRS concurrent with ICI	45	70.0	N.A.	6.0†	14.7
Minniti (2019) Cohort B	Retrospective	Melanoma	NIVO	SRS concurrent with ICI	35	85.0	N.A.	10.0†	22.0
Murphy (2019) [24]	Retrospective	Melanoma	IPI PEMBRO NIVO	SRS	26	95.4	N.A.	N.A.	26.1
Nardin (2018) [25]	Retrospective	Melanoma	PEMBRO	SRS	25	N.A.	36.0	4.0† (95% CI 2.2–5.8)	11.0 (95% CI 5.3–16.7)
Olson (2016) [26]	Retrospective	Melanoma	IPI	SRS	27	44.0	26.0	3.3 (95% CI–2.8–N.R.)	10.4 (94% CI 6.5–23.4)
Patel (2017) [27]	Retrospective	Melanoma	IPI	SRS	54	71.4	12.7	N.A.	N.A.
Robin (2018) [28]	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS	38	N.A.	N.A.	3.4	N.R.
Silk (2013) Cohort A [29]	Retrospective	Melanoma	IPI	SRS or WBRT prior to ICI	21	N.A.	N.A.	2.7† (95% CI 1.5–6.0)	18.4
Silk (2013) Cohort B	Retrospective	Melanoma	IPI	SRS or WBRT after ICI	12	N.A.	N.A.	2.7† (95% CI 1.5–6.0)	8.1
Williams (2017) Cohort A [30]	I	Melanoma	IPI	WBRT concurrent with ICI	5	N.A.	N.A.	2.5† (95% CI 0.3–18.0)	8.0
Williams (2017) Cohort B	I	Melanoma	IPI	SRS concurrent with ICI	11	N.A.	N.A.	2.5† (95% CI 1.0–37.0)	N.R.
Yusuf (2017) [31]	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS concurrent with ICI	18	N.A.	N.A.	N.A.	7.4
Chen (2018) Cohort A [32]	Retrospective	Melanoma NSCLC RCC	Anti-PD-1 and/or	Concurrent SRS-SRT	28	88.0	N.A.	11.5†	24.7

			Anti-CTLA-4						
Chen (2018) Cohort B	Retrospective	Melanoma NSCLC RCC	Anti-PD-1 and/or Anti-CTLA-4	Non- concurrent SRS-SRT	51	79.0	N.A.	5.1†	14.5
Lanier (2019) [33]	Retrospective	Melanoma NSCLC	Anti-PD-1 and/or Anti-CTLA-4	SRS	101	91.0	46.0	N.A.	15.9 (95% CI 13.3–24.8)
Schapira (2018) Cohort A [34]	Retrospective	NSCLC	Anti-PD-1	SRS prior to ICI	24	72.3	34.2	N.A.	N.A.
Schapira (2018) Cohort B	Retrospective	NSCLC	Anti-PD-1	SRS concurrent with ICI	8	100.0	61.5	N.A.	N.A.
Schapira (2018) Cohort C	Retrospective	NSCLC	Anti-PD-1	SRS after ICI	5	100.0	0.0	N.A.	N.A.
Shepard (2019) Cohort A [35]	Retrospective	NSCLC	NIVO or PEMBRO	SRS within 5 months	17	100.0	47.5	N.A.	N.R.
Shepard (2019) Cohort B	Retrospective	NSCLC	NIVO or PEMBRO	Non- concurrent SRS	34	85.2	66.5	5.5†	15.9
Koenig (2019) Cohort A [36]	Retrospective	N.A.	Anti-PD-1 and/or Anti-CTLA-4	SRS within 5 months	70	95.9	33.8	N.A.	11.3
Koenig (2019) Cohort B	Retrospective	N.A.	Anti-PD-1 and/or Anti-CTLA-4	Non- concurrent SRS	27	97.1	28.0	N.A.	5.9

* Intracranial ORR; †Intracranial PFS. *EAP* Expanded access program; *ICI* Immune checkpoint inhibitor; *IPI* Ipilimumab; *N.A.* Not available; *NIVO* Nivolumab; *N.R.* Not reached; *PEMBRO* Pembrolizumab

Table S4. Clinical studies with immune checkpoint inhibitors and radiotherapy in patients with brain metastases that only reported overall survival data.

Author	Study design	Tumor type	Agent	Type of radiation therapy	No. of patients	OS Months
Amaral (2019)[37]	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS	36	25.0 (95% CI 14.6–35.4)
Anderson (2017) Cohort A [38]	Retrospective	Melanoma	PEMBRO	SRS, HFRT or WBRT within 4 months	21	N.A.
Anderson (2017) Cohort B	Retrospective	Melanoma	IPI	SRS, HFRT or WBRT within 4 months	20	N.A.

Gabani (2018) Cohort A [39]	Retrospective	Melanoma	IPI	SRS	89	17.0 (95% CI 10.7–23.2)
Gabani (2018) Cohort B	Retrospective	Melanoma	IPI	WBRT	103	8.5 (95% CI 6.5–10.5)
Galli (2019) Cohort A [40]	Retrospective	Melanoma	IPI	SRS or WBRT within 6 months	23	5.0
Galli (2019) Cohort A	Retrospective	Melanoma	NIVO or PEMBRO	SRS or WBRT within 6 months	13	18.0
Kiess (2015) Cohort A [41]	Retrospective	Melanoma	IPI	SRS prior to ICI	19	12.4 [range 2.0–89.0]
Kiess (2015) Cohort B	Retrospective	Melanoma	IPI	SRS concurrent with ICI	15	12.4 [range 2.0–89.0]
Kiess (2015) Cohort C	Retrospective	Melanoma	IPI	SRS after ICI	12	12.4 [range 2.0–89.0]
Knisely (2012) Cohort A [42]	Retrospective	Melanoma	IPI	SRS prior to ICI	16	21.3 (95% CI 15.7–N.R.)
Knisely (2012) Cohort B	Retrospective	Melanoma	IPI	SRS after ICI	11	19.8 (95% CI 1.5–N.R.)
Rahman (2018) Cohort A [43]	Retrospective	Melanoma	IPI PEMBRO NIVO	Concurrent SRS within 1 month	35	13.9
Rahman (2018) Cohort B	Retrospective	Melanoma	IPI PEMBRO NIVO	Non-concurrent SRS	39	13.9
Rauschenberg (2019) Cohort A [44]	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS	87	21.0 (95% CI 12.9–29.1)
Rauschenberg (2019) Cohort A1	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS prior to ICI	26	17.6 (95% CI 10.3–25.0)
Rauschenberg (2019) Cohort A2	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS concurrent with ICI	49	N.R.
Rauschenberg (2019) Cohort A3	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS after ICI	12	21.9 (95% CI 10.4–33.4)
Rauschenberg (2019) Cohort B	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	WBRT	51	7.1 (95% CI 5.1–9.1)
Rauschenberg (2019) Cohort B1	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	WBRT prior to ICI	21	8.9 (95% CI 6.0–11.8)
Rauschenberg (2019) Cohort B2	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	WBRT concurrent with ICI	22	6.7 (95% CI 3.3–10.1)
Rauschenberg (2019) Cohort B3	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	WBRT after ICI	8	2.4 (95% CI 0.0–9.4)
Schmidberger (2018) Cohort A [45]	Retrospective	Melanoma	IPI	SRS or WBRT prior to ICI	21	11.0
Schmidberger (2018) Cohort B	Retrospective	Melanoma	IPI	SRS or WBRT after ICI	20	3.0
Stokes (2017)	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	SRS	185	10.8 (95% CI 9.1–12.5)
Tazi (2015) Cohort A [46]	Retrospective	Melanoma	IPI	SRS	10	16.5 (95% CI 10.4–N.A.)
Tétu (2019) [47]	Retrospective	Melanoma	Anti-PD-1 and/or Anti-CTLA-4	Concurrent SRS	64	16.8
Trommer-Nestler (2018) [48]	Retrospective	Melanoma	Anti-PD-1	Concurrent SRS	13	N.A.
Ahmed (2017) [49]	Retrospective	NSCLC	NIVO DUR	SRS	17	5.6

Singh (2019) [50]	Retrospective	NSCLC	PEMBRO NIVO ATEZO	SRS	39	10.0 (95% CI 8.3–13.2)
Kotecha (2019) [51]	Retrospective	N.A.	Anti-PD-1 and/or Anti-CTLA-4	Concurrent and non-concurrent SRS	150	30.0 (95% CI 24.0–38.0)
Shen (2016) [52]	Retrospective	N.A.	Anti-PD-1 and/or Anti-CTLA-4	Concurrent SRS	20	5.5 (95% CI 1.8–9.2)

EAP Expanded access program; *ICI* Immune checkpoint inhibitor; *IPI* Ipilimumab; *N.A.* Not available; *NIVO* Nivolumab; *N.R.* Not reached; *PEMBRO* Pembrolizumab.

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