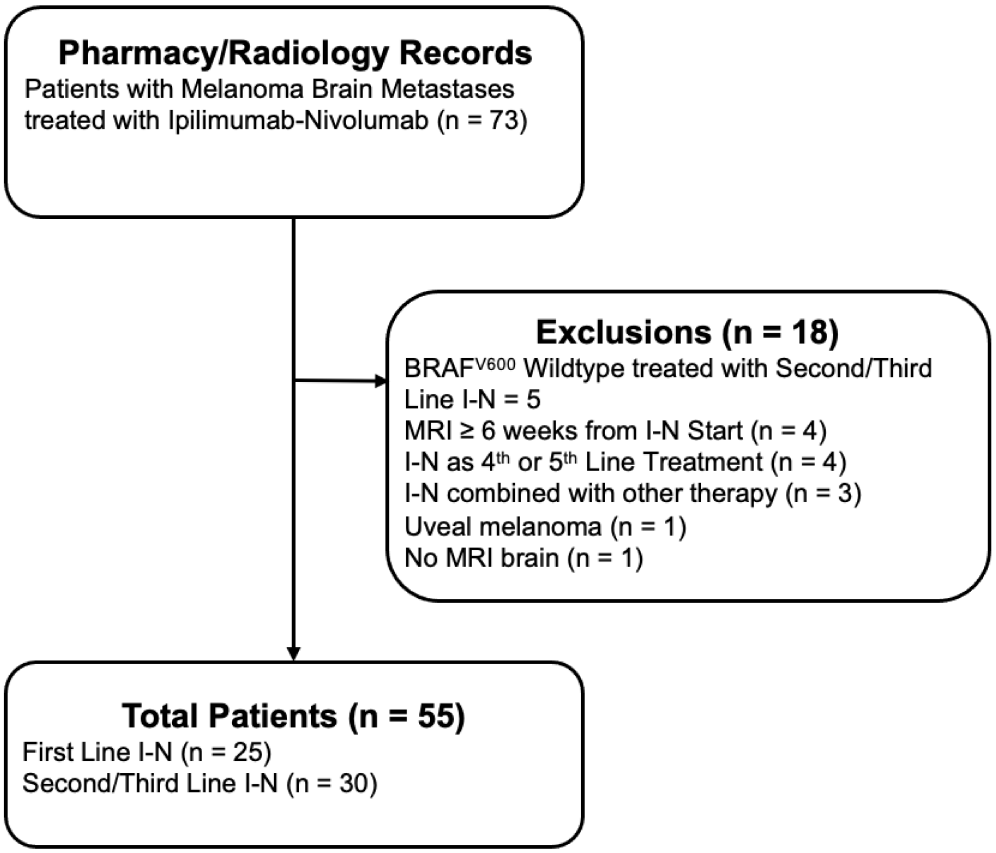
Supplementary Appendix A

Figure S1: CONSORT diagram of patients with melanoma brain metastases treated with ipilimumab-nivolumab (I-N)



Patients were identified by review of radiology imaging and Peter MacCallum Cancer Centre pharmacy dispensing records from March 1, 2015 to June 30, 2018. All patients underwent thin slice, gadolinium enhanced MRI brain imaging.

I-N: ipilimumab-nivolumab

Supplementary Appendix A

Table S1: Treatment sequence of patients with BRAF^{V600} mutant melanoma brain metastases receiving second/third line ipilimumab-nivolumab (I-N)

	First Line		Second Line			Third Line
	BRAF-MEKi	Anti-PD1	BRAF-MEKi	Anti-PD1	I-N	I-N
BRAF Mutant – no. (%) Total = 30	28 (93.3)	2 (6.7)	4* (13.3)	3 (10.0)	23 (76.7)	7 (23.3)

* Four patients received second line BRAF-MEKi. Of this subgroup 2 patients received prior anti-PD1 monotherapy and the other 2 were switched to vemurafenib-cobimetinib due to intolerance of first line dabrafenib-trametinib.

All 30 patients with BRAF V600 mutations received BRAF-MEKi (dabrafenib-trametinib) prior to ipilimumab-nivolumab (I-N). Twenty three patients received second line I-N and seven received third line I-N.

Supplementary Appendix A

Table S2: Baseline characteristics of BRAF V600 mutant patients who received second/third line ipilimumab-nivolumab (I-N)

	Denovo MBMs (n=17)	Acquired MBMs (n=13)	Total (n=30)	p value
Age				
Median	52	61	53	0.147 M-W *U* = 75.5
Range	34-69	29-75	29-73	
Sex – no. (%)				
Male	12 (70.6)	9 (69.2)	21 (70.0)	0.687
ECOG – no. (%)				
0	7 (41.2)	10 (76.9)	17 (56.7)	0.071
1	10 (58.8)	3 (23.1)	13 (43.3)	
Primary Melanoma – no. (%)				
Cutaneous	9 (52.9)	11 (84.6)	20 (66.7)	0.119
Unknown	8 (47.1)	2 (15.4)	10 (33.3)	
Stage at Commencement of Systemic Therapy – no. (%)				
III	0 (0.0)	2 (15.4)	2 (6.7)	
IV M1A	0 (0.0)	1 (7.7)	1 (3.3)	
IV M1B	0 (0.0)	1 (7.7)	1 (3.3)	
IV M1C	0 (0.0)	9 (69.2)	9 (30.0)	
IV M1D	17 (100.0)	0 (0.0)	17 (56.7)	
LDH at Commencement of Systemic Therapy – no. (%)				
Normal	4 (23.5)	2 (15.4)	6 (20.0)	0.999
High (< 2X ULN)	12 (70.6)	5 (38.5)	17 (56.7)	
High (> 2X ULN)	0 (0.0)	0 (0.0)	0 (0.0)	
Missing	1 (5.9)	5 (38.5)	6 (20.0)	
BRAF V600 Mutation – no. (%)				
BRAF V600E	13 (76.5)	9 (69.2)	22 (73.3)	0.698
BRAF V600K	4 (23.5)	4 (30.8)	8 (26.7)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	
Time to Intracranial Progression on First line Systemic Therapy				
Median (Months)	6.8	15.4	-	0.017, M-W *U* = 46.5
Range (Months)	1.2 – 13.3	1.7 – 21.3	-	
Duration of BRAF-MEKi Therapy				
Median (Months)	7.5	21.6	-	0.008, M-W *U* = 48.0
Range (Months)	1.6-25.1	2.0-42.5	-	

MBMs: melanoma brain metastases

Supplementary Appendix A

Table S3 Local therapy prior to ipilimumab-nivolumab (I-N)

Local Therapy – no. (%)	First Line I-N (n=25)	Second & Third Line I-N (n=30)	Total (n=55)
No Local Prior Therapy	**8 (32.0)**	**12 (40.0)**	**20 (36.4)**
Surgery Only	**3 (12.0)**	**3 (10.0)**	**6 (10.9)**
Radiation Only	**5 (25.0)**	**6 (20.0)**	**11 (20.0)**
SRS	3 (12.0)	3 (10.0)	7 (10.9)
WBRT	1 (4.0)	3 (10.0)	4 (7.3)
Extracranial Site	2 (8.0)	0 (0.0)	2 (3.6)
Surgery and Radiation	**8 (32.0)**	**11 (36.7)**	**19 (34.5)**
SRS to Cavity Only	2 (8.0)	1 (3.3)	3 (5.5)
SRS to Cavity & Other MBM	2 (8.0)	1 (3.3)	3 (5.5)
SRS to Non Excised Lesion	2 (8.0)	3 (10.0)	5 (9.1)
WBRT	2 (8.0)	5 (16.7)	7 (12.7)
SRS and WBRT	0 (0.0)	1 (3.3)	1 (1.8)

I-N denotes: Ipilimumab-nivolumab, SRS: Stereotactic radiosurgery, WBRT: Whole brain radiotherapy

Supplementary Appendix A

Table S4: Pattern of BRAF melanoma brain metastasis progression with second/third line ipilimumab-nivolumab

	De Novo MBMs (n=17)	Acquired MBMs (n=13)	Total (n=30)
Patients with MRI Brain Confirming Progression – no. (%)	14 (82.4)	12 (92.3)	26 (86.7)
Symptomatic Progression – no. (%)	9 (64.3)	9 (69.2)	18 (60.0)
New CNS Lesion ± Pre-existing MBM Progression – no. (%)	7 (41.2)	3 (23.1)	10 (33.3)
Pre-Existing MBM Progression Only – no. (%)	7 (41.2)	7 (53.8)	14 (46.7)
Extracranial Progression – no. (%)	0 (0.0)	1 (7.7)	1 (3.3)

MBMs: melanoma brain metastases

Supplementary Appendix A

Table S5: Therapy following progression of second/third line ipilimumab-nivolumab

Post Progression Therapy	Total (n=30)
Systemic Therapy	
BRAF-MEKi	6 (20.0)
PD-1 Monotherapy	3 (10.0)
Immunotherapy + Targeted Therapy	2 (6.7)
Chemotherapy	1 (3.3)
None	17 (56.7)
Unknown	1 (3.3)
Radiation	
Whole Brain Radiotherapy	12 (40.0)
Stereotactic Radiosurgery	8 (26.7)
Surgery	10 (33.3)

Post progression therapy after second/third line ipilimumab-nivolumab for $BRAF^{V600}$ melanoma brain metastases.

Supplementary Appendix A

Table S6: Local and systemic therapy following progression of second/third line ipilimumab-nivolumab in survivors ≥ 2 years

Post Progression Therapy	Total (n=7)
Systemic Therapy	
BRAF-MEKi	3 (42.9)
PD-1 Monotherapy	2 (14.3)
Immunotherapy + Targeted Therapy	1 (14.3)
None	1 (28.6)
Radiation	
Whole Brain Radiotherapy	1 (14.3)
Stereotactic Radiosurgery	5* (71.4)
Surgery	2 (28.6)

Post progression therapy after second/third line ipilimumab-nivolumab for $BRAF^{V600}$ melanoma brain metastases in patients with overall survival of 2 years or more. *1 patient received stereotactic radiosurgery to a solitary extracranial site