Stereotactic radiosurgery combined with anti-PD1 for the management of melanoma brain metastases: A retrospective study of safety and efficacy

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Highlights

- Real-world cohort of patients with a standardized strategy of treatment
- Stereotactic radiosurgery and anti-PD1 can be safely combined and proves an effective strategy
- This combination is effective for the treatment of melanoma brain metastases
- Outcomes are favorable with a 2 -years brain PFS rate of 50 %
- Data do not suggest an increased risk of adverse radiation events

ABSTRACT (251 words)

Background

Brain metastases can be effectively treated with stereotactic radiosurgery (SRS). Immune checkpoint inhibitors are now pivotal in metastatic melanoma care but some concerns have emerged regarding the safety of their combination with radiation therapy.

Methods

We present a retrospective analysis of a cohort of patients treated by anti-PD1 and SRS as a sole modality of radiation therapy (no whole brain radiation therapy (WBRT) at any time) in a single institution. We included patients on anti-PD1 at the time of SRS or patients who started anti-PD1within a max period of 3 months following SRS and were treated at least one year before the analysis. Clinical and serial imaging data were reviewed to determine the efficacy and the rate of adverse radiation events (ARE) of the combination.

Results

A total 50 patients were included. SRS targeted 1, 2 to 3, and > 3 brain metastases (BMs) in 17, 16 and 17 patients, respectively. Two patients died before the first evaluation. Nine patients presented with an increase in peri-tumoral edema, 3 with intracranial hemorrhage and one patient with both edema and hemorrhage. Median follow-up was 38.89 months (IQR 24.43; 45.28). Median OS from SRS was 16.62 months with 1, 2, and 3-years rates of 60%, 40% and 35% respectively. Median brain-PFS was 13.2 months with 1, 2, and 3-years rates of 62.1%, 49.7% and 49.7% respectively.

Conclusions

This real-world cohort of patients treated with a homogeneous strategy combining upfront stereotactic radiosurgery and anti-PD1 show remarkable survival rates and does not reveal unexpected toxicity.

BACKGROUND

New systemic treatments have dramatically improved the course of metastatic melanoma (MM); however patients with brain metastases (BMs) still have a very poor prognosis [1]. As these patients were generally excluded from clinical trials, data regarding check-point inhibitors efficacy in the treatment of BMs remains limited[2-10]. Both ipilimumab and anti-PD1 have shown efficiency as single agent in phase 2 studies with response rates of 10-24 % for ipilimumab[11], 20-22 % for anti-PD1[12-14], and 46-57% for ipilimumab-nivolumab[14,15].

Stereotactic radiosurgery (SRS) has been increasingly used for the treatment of MM-BMs due to excellent local control rates, minimal invasiveness and possibility of repeated treatment in case of new BMs[16-18]. Preclinical and clinical data suggest a potential synergy with radiation therapy[19,20].

The combination of radiation therapy and check-point inhibitors is currently being tested prospectively (NCT03340129, NCT02978404, NCT02858869). A common concern is a possible increase of adverse radiation effects (ARE). This risk has been assessed differently in many series, most of them including different radiation modalities such as SRS and/or WBRT. In a recently-published meta-analysis focusing on the combination of SRS and immunotherapies the overall incidence of radionecrosis was 5.3% and all studies reporting radionecrosis involved the use of ipilimumab[21].

Our institutional strategy for the management of BMs is exclusively based on stereotactic radiosurgery (SRS) to all eligible patients, and excludes WBRT. We retrospectively assessed the efficacy and radiotoxicity of this stereotyped strategy in the setting of monotherapy by anti-PD1.

METHODS

Retrospective analysis of all consecutive patients with MM-BMs treated in our institution between Nov, 2013 and Dec, 2017. Inclusion criteria: 1: patients who received anti-PD1 concomitantly with SRS, i.e. ongoing at the time of SRS; or patients who started anti-PD1 no later than 3 months (m) after SRS; 2: patients who were treated at least one year before the analysis and 3: patients who maintained anti-PD1 treatment at least 3 m after SRS.

SRS eligibility was discussed in the specific tumor board.

All BMs below 2.5 cm in max diameter were considered eligible for SRS. BM of bigger volume (volume > 10 cc) were referred to microsurgery unless very deeply located and regarded as inoperable. Patients with a single, large and symptomatic BM who underwent microsurgical resection were excluded. There was no change in practice over the period of the study.

All patients were treated with the Gamma-knife Perfexion (Elekta, Stockholm, Sweden) in the same unit within 4 weeks of the diagnosis of BMs.

All BMs were treated in a single framed-based session with a highly selective and conformal dose planning based on the appearance of the lesion on the contrast-enhanced 3D T1-weighted stereotactic MRI scan. The selection of dosimetric parameters was made according to volume, location, and proximity of organs at risk. The marginal prescription dose ranged from 22 Gy to 26 Gy at the 50% isodose. This regimen of dose was deliberately high in order to optimize control rates but in line with published series[16,22] and took into consideration the fact that no patient had been submitted to any form of prior radiation therapy. SRS was repeated in case of new brain metastases on MRI follow-up scans according to an "on-demand "strategy. Whenever ongoing, anti-PD1s were not stopped for SRS. No patient received whole brain radiotherapy at any time.

All patients received monotherapy by anti-PD1 because the ipilimumab-nivolumab combination is not reimbursed in France.

Endpoints and Statistical analysis

Toxicity

The medical records were reviewed to assess neurological symptoms. Brain MRI-scans and full body CT-scans were performed every 3 months. A volumetric assessment of each BM was done with Leksell Gamma Plan version 10.1.1 software (LGP, Elekta, Stockholm, Sweden). The contouring was performed with the dedicated tool of LGP. The appearance or increase of preexisting edema as well as the occurrence of any hemorrhagic event within treatment volume were reported. The FU MRIs scans (3D post-contrast T1-weighted, Flair and T2-weighted axial acquisitions) were systematically imported and fused with the stereotactic images of treatment day with LGP software in order to allow reliable volumetric comparisons of each treated BM. All follow-up MRI scans were analyzed by a

neuroradiologist and a neurosurgeon with expertise in SRS (RC) in order to determine whether the observed alterations within the treatment volume were suggestive of an ARE ("radionecrosis"), suggestive of a bleeding, or a progression (uncontrolled BMs defined as an increase in volume by more than 20%). The following criteria were used for the definition of ARE: a lesion showing a central area of low-signal with irregular, ill-defined, peripheral enhancement associated with a moderate increase in volume (up to 15%) and conspicuous augmentation of peritumoral edema on post-contrast T1-weighted acquisitions[23, 24]. An initial shrinkage and subsequent volumetric increase as well as a T1-T2 mismatch[25] were considered in favor of an ARE. Indeed it is still to date very difficult to demonstrate with certainty without pathological documentation that postoperative MRI alterations correspond clearly to an adverse radiation effect. As no irrefutable criterion exists, we considered any suspicious MRI alterations suggestive of an ARE unless proven otherwise.

Survival

Median follow up was calculated with a reverse Kaplan-Meier method [26]. Overall survival (OS) was calculated from the time of SRS (OS_{SRS}). Brain-PFS was defined as the time between SRS and evidence of local or distant progression in the brain (Brain-PFS_{SRS}). When patients underwent several SRS sessions in the setting of anti-PD1 treatment, survival rates were calculated from the date of the first SRS session. OS and brain-PFS curves were estimated by the Kaplan–Meier method and compared with the use of the log-rank test.

Univariate and multivariate Cox proportional hazard regression models were performed on prognostic factors associated with OS_{SRS} and brain-PFS_{SRS}. The following variables were included in the model: age, gender, ECOG PS, BRAF mutation status, , total volume of BMs treated, number of extra-cranial metastatic sites, presence of neurological symptoms, use of corticosteroids at the time of SRS, type of systemic treatment received before anti-PD1 and timing of SRS and anti-PD1 administration. Variables with a $p<.05$ in univariate analysis or clinically relevant were kept in the multivariate model. Statistical analysis was performed using PASW Statistics version 17.02 (IBM SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as means ±SD or as median with range (min, max), and categorical variables as count and percentages. Means values were compared by student t-test, and percentages by Chi-Square test (or Fisher's exact test, as appropriate). The results are reported as two-sided p values with 95 % confidence intervals (CI). All the tests were two-sided. The

statistical significance was defined as $p<.05$. All statistical analyses were performed by AL from the department of public health and biostatistics.

RESULTS

Patients'characteristics

Among 125 patients treated by SRS at BM diagnosis over the study period, 50 fulfilled the inclusion criteria (concomitant SRS and anti-PD1 treatment) (Fig 1). Detailed characteristics of the population are given in Table 1.

Overall, 188 BMs were treated during 50 SRS sessions in 50 patients. A solitary BM was targeted in 17 patients (34%), and multiple BMs in 33 patients (66%). The median number of BM treated per patient was 3 (min 1-max 21). The median aggregate metastases volume treated per patient was 366 mm^3 (min 15- max 21.570). Twenty-seven patients received Nivolumab and 23 patients received Pembrolizumab. Nine patients had neurological symptoms and 8 patients were under corticosteroids at the time of SRS. Twenty-six patients (52%) started anti-PD1 within 3 months after SRS (median time 0.79 m (min 0.10-max 3 m) and 24 patients (48%) were already under anti-PD1 at the time of SRS (median duration of anti-PD1 treatment at the time of SRS 3.28 m (min 0.2-max 22).

Median clinical follow-up time after SRS was 38.89 months (IQR 24.43; 45.28). The neuroimaging evaluation was performed in 48 patients (2 patients died of highly disseminated disease before the first planned follow-up brain imaging).

Outcome of the whole cohort

Time to brain progression, survival from SRS, treatment exposure (SRS, duration of anti-PD1 treatment) and onset of suspected AREs are summarized in Fig 2

Toxicity

Eighteen patients (36%) presented neurological symptoms during the follow-up period: intracranial hypertension (n=5), headache (n=1), diplopia (n=1), proprioceptive ataxia (n=2), hemiparesis (n=6), hemiplegia (n=1), mental confusion (n=1) and sensory deficit (n=1). These

events were related to SRS-treated BMs in 8 of the 18 patients (others were attributed to the appearance of new BMs or lepto-meningeal involvement).

Three patients required surgical resection of a BM later during their follow-up for SRS failure (n=1) or new symptomatic large BM (n=2).

In the 181 BMs treated by SRS, for which cerebral imaging was available, 11 (6.1%) cases of increased peritumoral edema (3 with a mass-effect) and 4 hemorrhages (2.2%) occurred in 13 patients. There were no significant differences as a function of the timing of SRS and anti-PD1 administration. Out of these 15 events, 9 events, given their neuro-imaging characteristics, were regarded as potential ARE by both neuroradiologists and SRS experts, being symptomatic in 6 patients (Fig 3 and Table S1 in supplemental data). In one patient, pathological documentation enabled to rule out an adverse radiation effect (pathological evidence of BM recurrence without foci of radionecrosis). Three of the 181 treated BMs recurred in 3 patients. Among these 3 patients only one developed new BMs in addition to the local recurrence (Table S2 in supplemental data). Twenty-three patients (46 %) developed new BMS and 10 (20%) underwent a new SRS session for new BMs.

Survival

At the time of the data analysis (Jan 2019), 18 patients were still alive. Six patients had stopped anti-PD1 for a complete response and 10 patients were still treated with anti-PD1. Nine patients among the 50 received another systemic treatment after anti-PD1 including ipilimumab (n=1), dacarbazine (n=1), imatinib (n=1), vemurafenib (n=1), dabrafenib-trametinib (n=3) and vemurafenib-cobimetinib followed by ipilimumab (n=2).

The median OS_{SRS} was 16.62 m (95% CI 7.33-34.4 m) and 1-year, 2 year and 3-year OS_{SRS} rates were 60%, 40 % and 35% respectively (Fig 4). The median brain-PFS_{SRS} was 13.25 m (95% CI 0-44.77 m) and 1-year, 2 year and 3-year brain-PFS_{SRS} rates were 52.1, 49.7% and 49.7% respectively (Fig 5).

Baseline characteristics associated with a worse prognosis in univariate analysis were ECOG >1, total volume of BMS treated, number of extra cranial metastatic site, and previous treatment with a BRAF +/-MEK inhibitor for OS_{SRS} (Table 2), and ECOG> 1 and total volume of BMS treated for brain-$PFS_{SRS,}$ respectively .

In multivariate analysis, gender, ECOG, number of extra cranial metastatic site and total volume of BMS treated remained significantly associated with OS_{SRS} while ECOG, total volume of BMS treated and previous treatment with ipilimumab remained significantly associated with brain PFS_{SRS} (Tables 2 and 3). A high proportion of patients who died early (within 6 months of SRS) had numerous BMs (10/15 with ≥4 BMs), high tumor cumulated volume (13/15 with volume >1000 mm3), tumor located in the brainstem or posterior fossa (cerebellar) (11/15), leptomeningeal disease (LMD) 14/15), poor performance status (6/15 with ECOG >1) and resistance to a BRAF/MEK inhibitor (12/15).

DISCUSSION

This retrospective series of 50 real-world MM patients is meaningful since all patients were treated with the same strategy combining a homogeneous radiation procedure (upfront SRS without WBRT) and anti-PD1 monotherapy. Furthermore, the follow-up duration (median follow-up of 38.89 months) allows to address the question of ARES that are often delayed by 8-9 months. To our knowledge, in the current literature, there is no equivalent cohort of patients with the same characteristics (Table S3 in supplemental data highlights the main differences between series).

The combination of upfront SRS and anti-PD1 enables to achieve high survival rates, and brain-PFS, around 40% and 50% respectively at 2 years with 6 patients (12%) achieving a durable complete response allowing anti-PD1 discontinuation.

The local control rate in this cohort confirmed the high local efficacy of SRS, even in patients with a high number of BMs ($1/3^{d}$ of patients with ≥4 BMs). The brain-PFS (49.7% at 2 years) suggests that anti-PD1 exerts some protective adjuvant effect on the development of new BMs, although this strategy is not completely protective as 46 % of the patients developed new BMS.

It is always difficult to compare different trials and especially retrospective and prospective ones. The interpretation must be very cautious but, due to the systematic and standardized practice in our tumor board, our results can be discussed in the context of prospective trials results (Table S4 in supplemental data). Keeping in mind there is an 80% intracranial progression rate at 6-months with anti-PD1 monotherapy alone reported in the ABC study[14], the combination with SRS seems to yield much superior results in our analysis. The combined

ipilimumab-nivolumab regimen is currently regarded as the most efficient systemic treatment for melanoma BMs[15], despite high toxicity. In the largest phase 2 study published Checkmate 204 (94 patients), the intracranial progression rate was 33% with 6-m intra-cranial PFS and OS rates of 64.2 % and 92.3 % respectively, and a 12-m OS rate of 81.5.
The 60% 12-m OS rate obtained by combining systematic SRS with anti-PD1 proves quite comparable with the estimated 81.5% 12-m OS rate with the ipilimumab-nivolumab combination reported in the Checkmate 204 study, since our series included patients with more advanced disease and poorer prognosis. Indeed, solitary BM patients represent 52% of the trial population in the CheckMate 204 study[15], versus 29.8% in our study. This results strongly support the rationale for a prospective comparison between the 2 strategies and a trial combining upfront SRS combination of ipilimumab-nivolumab, which is now ongoing (NCT03340129).

Despite biological data suggesting that radiotherapy may improve the response to check point inhibitors by increasing the immune infiltration of BMs[19,27], there is only limited information about the efficacy of combined radiation and immune checkpoint inhibitors. These studies are usually small and highly heterogeneous regarding the systemic treatment, doses (single and multiple fraction) and type of radiation (SRS and WBRT) [2,-10,28].

A meta-analysis of 17 studies) [21] using SRS (Gamma-Knife, Cyberknife or Linac) and checkpoint inhibitors between 2013 and 2018 pooled together studies with different types of cancers (not only melanomas), heterogeneous regimen of immunotherapy (mostly ipilimumab) and limited follow-up (median 9 months). Our series is thus hardly comparable with these disparate studies. However the high local control rate, the rather long survival and the low rate of radionecrosis in this meta-analysis are in line with our results.

Increased rates of radionecrosis have been reported in 3 small series of patients treated with SRS and ipilimumab[29-31] but this was not confirmed in larger cohorts[32-35]. Conversely the few reports on the combination of SRS and anti-PD1 do not suggest a high rate of ARE[2-10,36]. Despite a low number of available data, the overall summary estimate for radionecrosis was 5.3% in the largest meta-analysis[21]. Our own series with a rather high number of patients and sufficient follow-up permits to address the question of radiotoxicity. Our data do not provide evidence that combining anti-PD1 therapy and SRS does increase radiotoxicity. The neurological symptoms observed during the follow-up period were related to SRS-treated

BMs in only 7 patients. Despite the high number of patients with multiple BMs (66%), the 2.2 % bleeding rate, the 6 % rate of edema, and the 4.4% of ARE are within the expected figures of adverse events in a SRS-treated population. Indeed, there is a natural propensity of MM-BMs for bleeding[37,38] and it is not infrequent to observe ARE following radiosurgery for BM, particularly when large volume metastasis are treated[17,18]. One limitation of our study is that our 38.89 month median follow-up might not be long enough to rule out very late radiotoxicity. One must be aware that any strategy increasing survival of patients with BMs will naturally increase the rate of late AREs, since these events could not be captured before because of premature deaths by melanoma evolution.

Within the frame of this study OS and brain-PFS did not differ in patients already treated with anti-PD1 at the time of SRS and who started anti-PD1 just after SRS. Both can be considered as concurrent radio-immunotherapy in line with some series[39-42] and meta-analysis data[21] suggesting that concurrent anti-PD1 and SRS achieves the best results. Looking for predictive markers of response, we found that the poor prognostic factors of BMs play a role in our cohort as expected (ECOG, number of extra cerebral metastatic site and total BM's volume). It is noteworthy that having receive ipilimumab prior to SRS and antiPD1 seems to have a significant protective on brain PFS, although the low number of patients does not allow to draw reliable conclusions. We found no association between corticosteroids and survival.

A significant proportion (roughly 1/3[d]) of patients in our cohort died within 6 months of SRS. This may lead to discuss whether there is an actual indication of SRS +/- immunotherapy in patients cumulating poor prognosis factors such as very high cumulative volume (especially in the posterior fossa and brainstem) or associated LMD. Decision has to be made case by case in tumor boards since even these patients can have an immediate benefit from SRS without toxicity issue.

Although this study is retrospective, the systematic and standardized practice in our tumor board whose policy is to treat all BMs < 10cc, including multiple ones, with SRS at first BM diagnosis and anti-PD1 reduces the selection bias of this study, knowing however that large volume BMs are by definition not candidates for SRS. The best argument is that patients with severe disease were not excluded as 33% of patients had ≥4 BMs and 50% of patients had received prior targeted therapy with BRAF-MEK inhibitors.

Declaration of interest : none.

CONCLUSION

SRS combined with anti-PD1 achieves favorable outcomes without evidence of increased radiotoxicity in brain metastatic melanoma patients. Whether this benefit is due to the combination of local control and a systemic response or to an actual biological synergy between the 2 strategies is an open question. Given the excellent short term results recently obtained in BMs with the ipilimumab-nivolumab regimen[11], a strategy combining SRS and this bi-therapy is now ongoing (NCT03340129).

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Figure legends

Fig 1: Retrospective selection of a cohort of patients homogeneously treated by SRS and anti-PD1 within 3 months, among consecutive patients with melanoma brain metastases

Fig 2: Time to brain progression, survival from SRS, treatment exposure (SRS, duration of anti-PD1 treatment) and onset of suspected AREs in the 50 patients

Fig 3: Assessment of toxicity among the 188 BMs treated by SRS

Fig 4: OS from SRS

Fig 5: Brain-PFS from SRS

526 **Table 1: Patients' characteristics at SRS (n=50)**

527

Patients' characteristics	**Number (%)**
Age (year)	
Median (min-max)	66 (36.5-88)
Sex	
Male	30 (60)
Female	20 (40)
Performance status (ECOG-PS)	
0	15 (30)
1	27 (54)
2	8 (16)
BRAF mutation status	
Mutant	29 (58)
Wild type	21 (42)
Number of BMs treated	
1	17 (34)
2-3	16 (32)
≥4	17 (34)
Total volume of BMs treated	
<1 cm^3	19 (38)
1-3 cm^3	12 (24)
>3 cm^3	19 (38)
Number of extra-cranial metastatic site	
0	7 (14)
1	11 (22)
2	10 (20)
≥3	22 (44)
Neurological symptoms at the time of SRS	
Yes	9 (18)
No	41 (82)
Corticosteroids at the time of SRS	
Yes	8 (16)

No	42 (84)
LDH	
≤ ULN	15 (30)
>ULN (250 UI)	8 (16)
Missing	27 (54)
Systemic treatment before anti-PD1	
None	18 (36)
BRAF+/-MEK inhibitors only	20 (40)
Ipilimumab only	6 (12)
BRAF+/-MEK inhibitors and ipilimumab	5 (10)
Chemotherapy only	1 (2)
Timing of index SRS and anti-PD1 administration	
SRS before anti-PD1 (max 3 months)	26 (52)
SRS under anti-PD1	24 (48)

528

Table 2: Impact of patient and disease's characteristics at the time of SRS on the overall survival from SRS (OS_{SRS}): univariate and multivariate analyses (n=50)

		Univariate		Multivariate	
Variable	**Number (%)**	**HR 95% IC**	**P**	**HR 95% IC**	**P**
Age (years)					
< 65	23 (46)	1			
≥ 65	27 (54)	0.64 (0.32-1.30)	0.220		
Sex					
Male	30 (60)	1		1	
Female	20 (40)	0.80 (0.39-1.65)	0.544	**0.25 (0.10-0.63)**	**0.03**
Performance status (ECOG)					
0	15 (50)	1		1	
1	27 (54)	2.18 (0.86-5.56)	0.102	1.18 (0.40-3.52)	0.765
2	8 (16)	**9.17 (3.01-27.92)**	**<.001**	**20.99 (4.59-95.93)**	**<.001**
BRAF mutation					
Mutant	29 (58)	1			
Wild-type	21 (42)	0.63 (0.30-1.32)	0.219		
Number of EC metastatic sites					
0	7 (14)	0.72 (0.24-2.16)	0.560	0.28 (0.06-1.28)	0.101

1	11 (22)	**0.22 (0.07-0.77)**	**0.017**	0.38 (0.10-1.55)	0.178
2	10 (20)	0.86 (0.36-2.08)	0.737	**0.26 (0.07-0.93)**	**0.039**
≥3	22 (44)	1		1	
Total volume of BMs treated (cm^3)					
<1 cm^3	19 (38)	1			
1-3 cm^3	12 (24)	**5.07 (1.93-13.3)**	**0.001**	**8.52 (2.10-34.54)**	**0.003**
>3 cm^3	19 (38)	**3.18 (1.26-8.02)**	**0.014**	**6.72 (1.64-27.5)**	**0.008**
Neurological symptoms at the time of SRS					
No	41 (82)	1			
Yes	9 (18)	1.74 (0.75-4.06)	0.201		
Corticosteroids at the time of SRS					
No	42 (84)	1		1	
Yes	8 (16)	1.04 (0.4-2.72)	0.932	0.35 (0.09-1.42)	0.141
Systemic treatment before anti-PD1					
None	18 (36)	1		1	
BRAF+/- MEK inhibitor only	20 (40)	**3.03 (1.30-7.05)**	**0.010**	1.85 (0.61-5.57)	0.274
Ipilimumab only	6 (12)	1.05 (0.28-3.98)	0.940	0.48 (0.11-2.06)	0.325
BRAF+/- MEK inhibitor and Ipilimumab	5 (10)	1.23 (0.32-4.65)	0.762	1.43 (0.26-7.78)	0.681
Chemotherapy only	1 (2)	NR	0.979	NR	0.983
Timing of index SRS and anti-PD1 administration					

SRS before anti-PD1 (max 3 months)	26 (52)	1		
SRS under anti-PD1	24 (48)	0.77 (0.38-1.57)	0.472	

EC: extra cerebral BM: brain metastases

532

533 **Table 3: Impact of patient and disease's characteristics at the time of SRS on the brain progression free survival from SRS (Brain-**
534 **PFS_{SRS}): univariate and multivariate analyses (analysis performed on 48 patients since 2 patients died before the first cerebral imaging)**
535

		Univariate		Multivariate	
Variable	**Number (%)**	**HR 95%IC**	**P**	**HR 95%IC**	**P**
Age (years)					
< 65	23 (47.9)	1			
≥ 65	25 (52.1)	1.11 (0.49-2.48)	0.806		
Sex					
Male	28 (58.3)	1		1	
Female	20 (41.7)	1.10 (0.49-2.48)	0.817	0.65 (0.25-1.70)	0.385
Performance status (ECOG)					
0	13 (27.1)	1		1	
1	27 (56.2)	2.23 (0.73-6.80)	0.158	1.38 (0.32-6.07)	0.666
2	8 (16.7)	**6.15 (1.71-22.14)**	**0.006**	**14.43 (2.42-86.10)**	**0.003**
BRAF mutation					
Mutant	28 (58.3)	1			
Wild-type	20 (41.7)	0.607 (0.26-1.42)	0.250		
Total volume of BMs treated					
<1 cm^3	19 (39.6)	1		1	

1-3 cm^3	10 (20.8)	**4.62 (1.58-13.5)**	**0.005**	**8.84 (1.58-49.44)**	**0.013**
>3 cm^3	19 (39.6)	**2.54 (0.92-7.03)**	**0.074**	3.33 (0.81-13.64)	0.095
Number of EC metastatic sites					
0	7 (14.6)	0.87 (0.24-3.15)	0.825	0.40 (0.08-2.10)	0.278
1	11 (22.9)	0.53 (0.16-1.68)	0.278	0.98 (0.26-3.65)	0.972
2	10 (20.8)	1.37 (0.52-3.61)	0.523	0.71 (0.20-2.49)	0.589
≥3	20 (41.7)	1		1	
Neurological symptoms at the time of SRS					
No	39 (81.2)	1			
Yes	9 (18.8)	1.56 (0.62-3.95)	0.343		
Corticosteroids at the time of SRS					
No	40 (83.3)	1		1	
Yes	8 (16.7)	0.91 (0.31-2.66)	0.857	0.35 (0.10-1.55)	0.166
Systemic treatment before anti-PD1					
None	18 (37.5)	1		1	
BRAF+/- MEK inhibitor only	19 (39.6)	2.10 (0.87-5.08)	0.101	0.67 (0.18-2.46)	0.541
Ipilimumab only	5 (10.4)	0.33 (0.04-2.64)	0.296	**0.08 (0.01-0.79)**	**0.031**
BRAF+/- MEK inhibitor and Ipilimumab	5 (10.4)	0.75 (0.16-3.56)	0.716	0.90 (0.16-5.18)	0.903
Chemotherapy only	1 (2.1)	NR	0.982	NR	0.986
Timing of index SRS and anti-PD1 administration					

SRS before anti-PD1 (max 3 months)	26 (54.2)	1		
SRS under anti-PD1	22 (45.8)	0.75 (0.33-1.70)	0.489	

EC: extra cerebral BM: brain metastases

536

Figure legends

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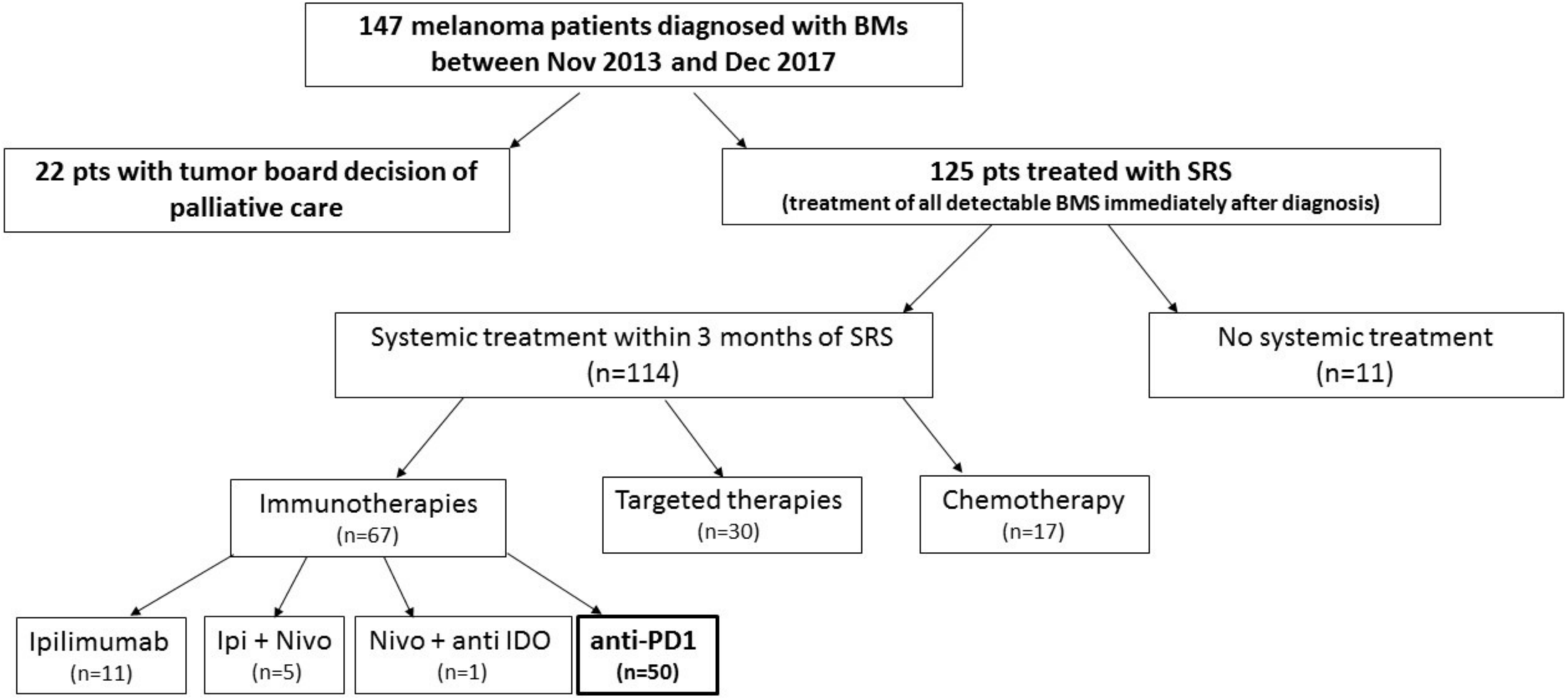
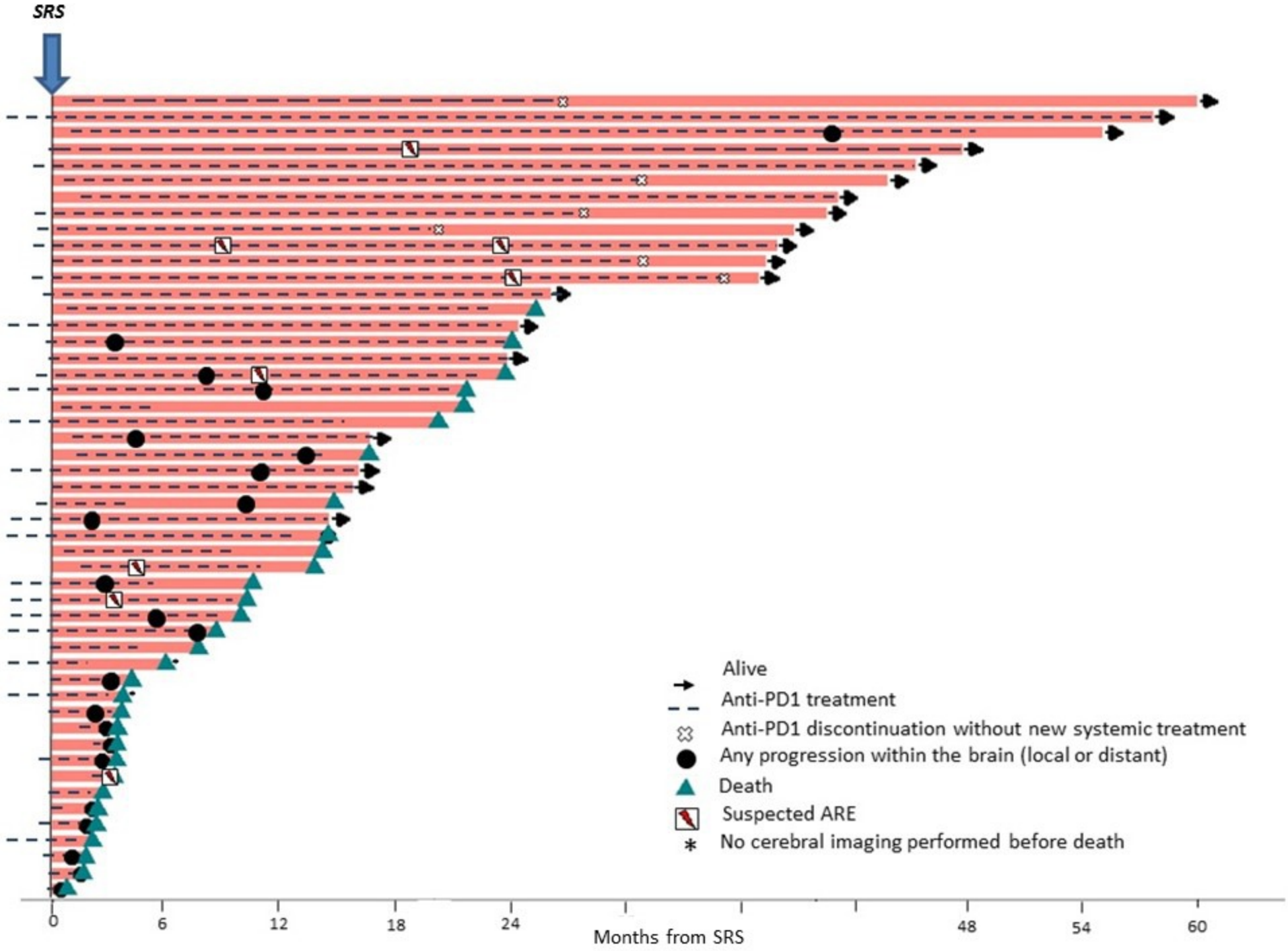
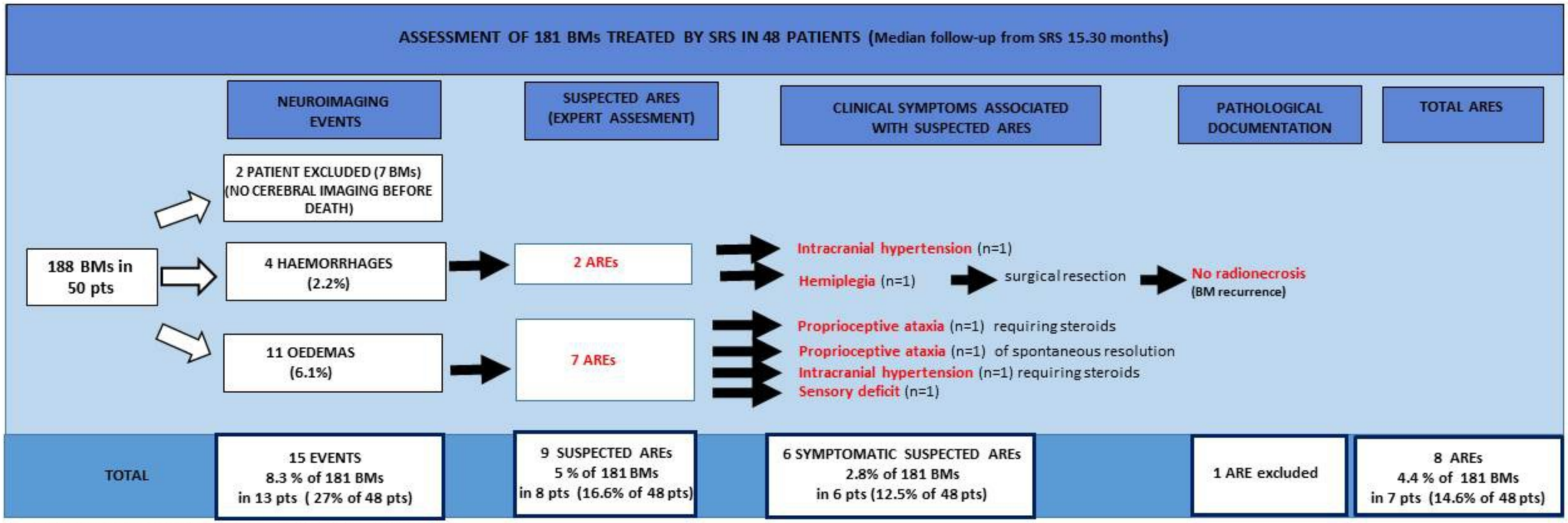
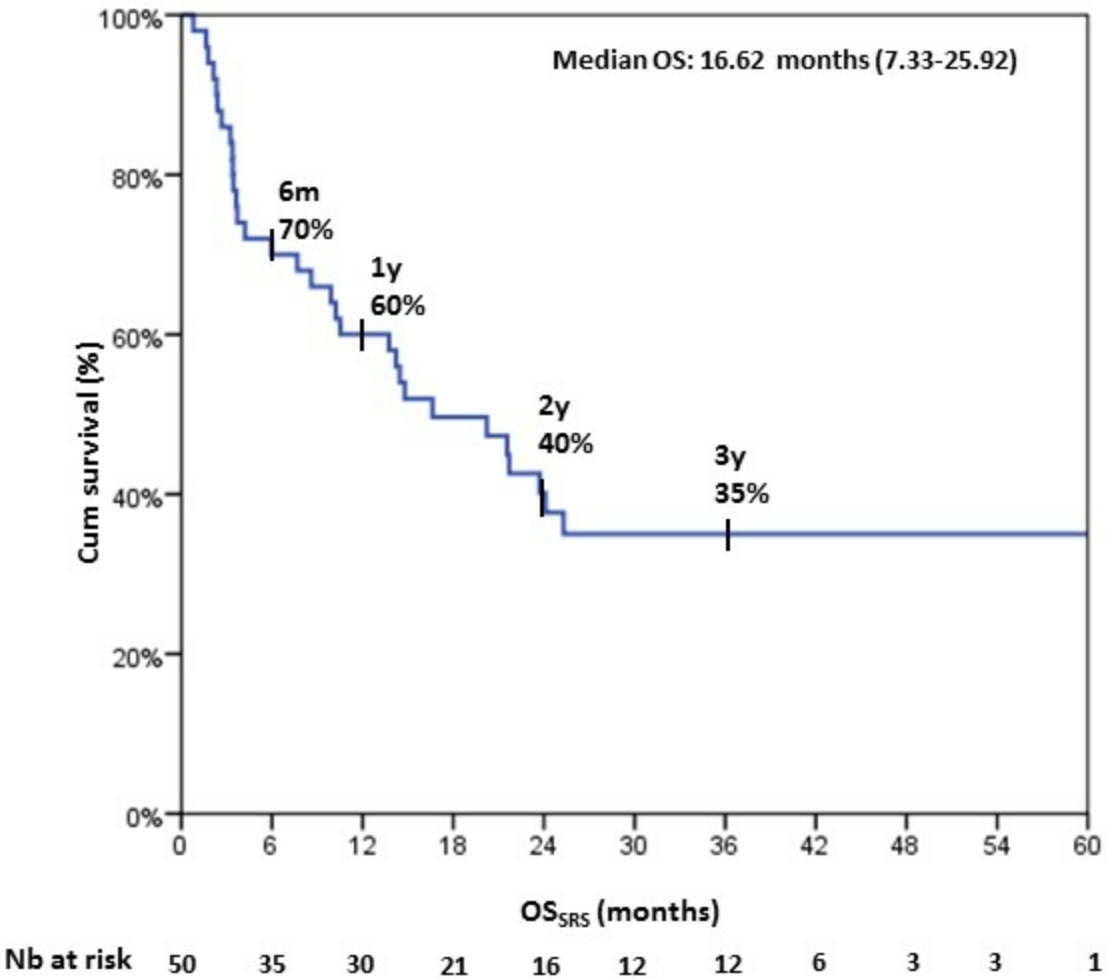
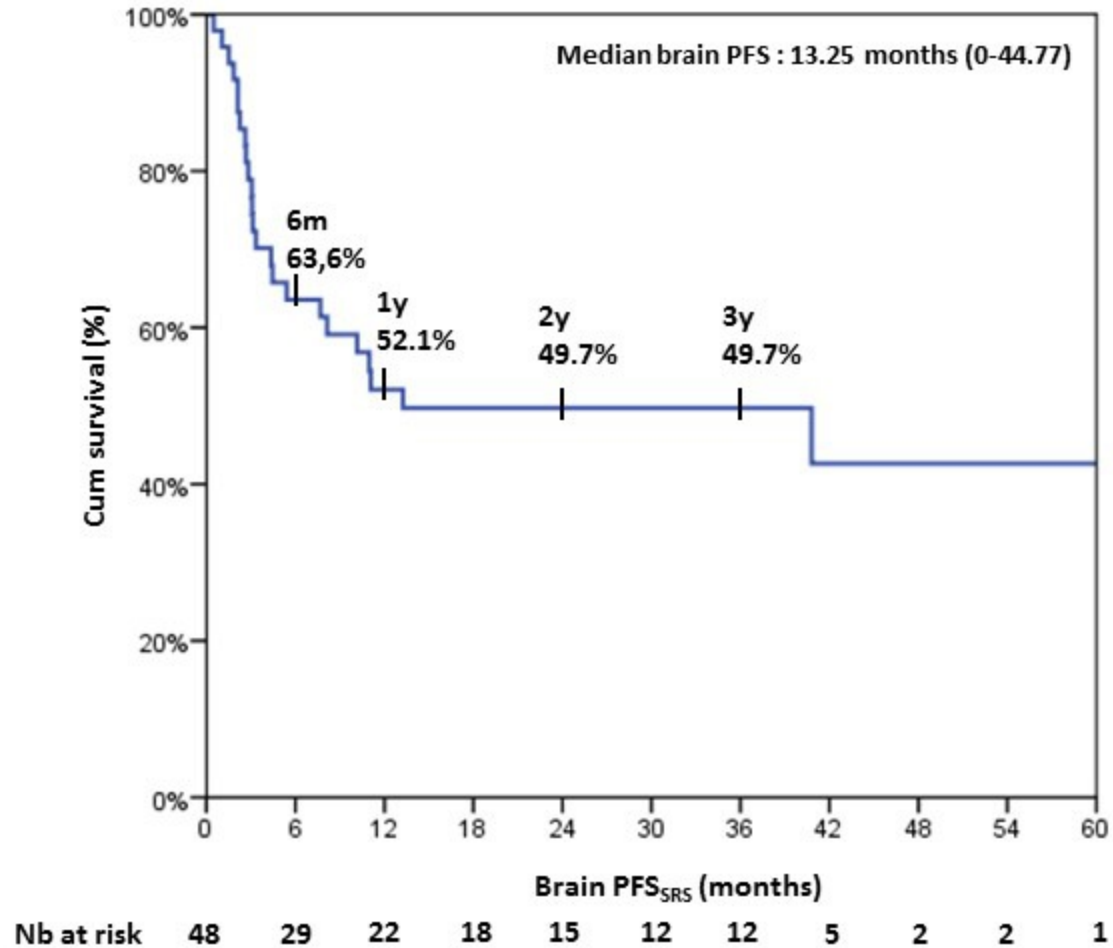

147 melanoma patients diagnosed with BMs between Nov 2013 and Dec 2017
22 pts with tumor board decision of palliative care
125 pts treated with SRS
(treatment of all detectable BMS immediately after diagnosis)
Systemic treatment within 3 months of SRS (n=114)
No systemic treatment (n=11)
Immunotherapies (n=67)
Targeted therapies (n=30)
Chemotherapy (n=17)
Ipilimumab (n=11)
Ipi + Nivo (n=5)
Nivo + anti IDO (n=1)
anti-PD1 (n=50)


SRS
Alive
Anti-PD1 treatment
Anti-PD1 discontinuation without new systemic treatment
Any progression within the brain (local or distant)
Death
Suspected ARE
No cerebral imaging performed before death
0
6
12
18
24
48
54
60
Months from SRS



* SRS PERFORMED UNDER anti-PD1 OR NO MORE THAN 3 MONTHS BEFORE ANTI-PD1 INTRODUCTION


Median OS: 16.62 months (7.33-25.92)
6m
70%
1y
60%
2y
40%
3y
35%
100%
80%
60%
40%
20%
0%
Cum survival (%)
0
6
12
18
24
30
36
42
48
54
60
OS_SRS (months)
Nb at risk
50
35
30
21
16
12
12
6
3
3
1


Median brain PFS : 13.25 months (0-44.77)
6m
63,6%
1y
52.1%
2y
49.7%
3y
49.7%
Cum survival (%)
100%
80%
60%
40%
20%
0%
0
6
12
18
24
30
36
42
48
54
60
Brain PFS$_{SRS}$ (months)
Nb at risk 48 29 22 18 15 12 12 5 2 2 1