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Title:

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

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2

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10

11 Part of this work was presented in poster form at the American Society of Clinical Oncology
12 congress, Chicago, USA, June 2-6, 2017

13

14 **Highlights**

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

21

22

23 **ABSTRACT (251 words)**

24

25 **Background**

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

29

30 **Methods**

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

37

38 **Results**

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

46

47 **Conclusions**

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

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55

56 **BACKGROUND**

57

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

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

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

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

79

80 **METHODS**

81

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

87

88 SRS eligibility was discussed in the specific tumor board.

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

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

96

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

107

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

110

111 **Endpoints and Statistical analysis**

112

113 ***Toxicity***

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

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

135

136 **Survival**

137

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

144

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

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

159

160 **RESULTS**

161

162 **Patients' characteristics**

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

166

167 Overall, 188 BMs were treated during 50 SRS sessions in 50 patients. A solitary BM was
168 targeted in 17 patients (34%), and multiple BMs in 33 patients (66%). The median number of
169 BM treated per patient was 3 (min 1-max 21). The median aggregate metastases volume
170 treated per patient was 366 mm³ (min 15- max 21.570). Twenty-seven patients received
171 Nivolumab and 23 patients received Pembrolizumab. Nine patients had neurological
172 symptoms and 8 patients were under corticosteroids at the time of SRS. Twenty-six patients
173 (52%) started anti-PD1 within 3 months after SRS (median time 0.79 m (min 0.10-max 3 m)
174 and 24 patients (48%) were already under anti-PD1 at the time of SRS (median duration of
175 anti-PD1 treatment at the time of SRS 3.28 m (min 0.2-max 22).

176

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

180

181 ***Outcome of the whole cohort***

182

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

185

186 ***Toxicity***

187

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

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

193

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

196

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

208

209 ***Survival***

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

215

216 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}
217 rates were 60%, 40 % and 35% respectively (Fig 4). The median brain-PFS_{SRS} was 13.25 m
218 (95% CI 0-44.77 m) and 1-year, 2 year and 3-year brain-PFS_{SRS} rates were 52.1, 49.7% and
219 49.7% respectively (Fig 5).

220

221 Baseline characteristics associated with a worse prognosis in univariate analysis were ECOG
222 >1, total volume of BMS treated, number of extra cranial metastatic site, and previous
223 treatment with a BRAF +/-MEK inhibitor for OS_{SRS} (Table 2), and ECOG> 1 and total
224 volume of BMS treated for brain-PFS_{SRS}, respectively .

225

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

234

235 **DISCUSSION**

236

237 This retrospective series of 50 real-world MM patients is meaningful since all patients were
238 treated with the same strategy combining a homogeneous radiation procedure (upfront SRS
239 without WBRT) and anti-PD1 monotherapy. Furthermore, the follow-up duration (median
240 follow-up of 38.89 months) allows to address the question of ARES that are often delayed by
241 8-9 months. To our knowledge, in the current literature, there is no equivalent cohort of
242 patients with the same characteristics (Table S3 in supplemental data highlights the main
243 differences between series).

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

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

252

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

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

271

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

277

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

284

285 Increased rates of radionecrosis have been reported in 3 small series of patients treated with
286 SRS and ipilimumab^[29-31] but this was not confirmed in larger cohorts^[32-35]. Conversely the
287 few reports on the combination of SRS and anti-PD1 do not suggest a high rate of ARE^[2-10,36].
288 Despite a low number of available data, the overall summary estimate for radionecrosis was
289 5.3% in the largest meta-analysis^[21]. Our own series with a rather high number of patients and
290 sufficient follow-up permits to address the question of radiotoxicity. Our data do not provide
291 evidence that combining anti-PD1 therapy and SRS does increase radiotoxicity. The
292 neurological symptoms observed during the follow-up period were related to SRS-treated

293 BMs in only 7 patients. Despite the high number of patients with multiple BMs (66%), the 2.2
294 % bleeding rate, the 6 % rate of edema, and the 4.4% of ARE are within the expected figures
295 of adverse events in a SRS-treated population. Indeed, there is a natural propensity of MM-
296 BMs for bleeding^[37,38] and it is not infrequent to observe ARE following radiosurgery for
297 BM, particularly when large volume metastasis are treated^[17,18]. One limitation of our study is
298 that our 38.89 month median follow-up might not be long enough to rule out very late
299 radiotoxicity. One must be aware that any strategy increasing survival of patients with BMs
300 will naturally increase the rate of late AREs, since these events could not be captured before
301 because of premature deaths by melanoma evolution.

302
303 Within the frame of this study OS and brain-PFS did not differ in patients already treated with
304 anti-PD1 at the time of SRS and who started anti-PD1 just after SRS. Both can be considered
305 as concurrent radio-immunotherapy in line with some series^[39-42] and meta-analysis data^[21]
306 suggesting that concurrent anti-PD1 and SRS achieves the best results. Looking for predictive
307 markers of response, we found that the poor prognostic factors of BMs play a role in our
308 cohort as expected (ECOG, number of extra cerebral metastatic site and total BM's volume).
309 It is noteworthy that having receive ipilimumab prior to SRS and antiPD1 seems to have a
310 significant protective on brain PFS, although the low number of patients does not allow to
311 draw reliable conclusions. We found no association between corticosteroids and survival.

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

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

324

325 **Declaration of interest :** none.

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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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512

513

514 **Figure legends**

515

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

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

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

521 **Fig 4:** OS from SRS

522 **Fig 5:** Brain-PFS from SRS

523

524

525

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)

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

531

Variable	Number (%)	Univariate		Multivariate	
		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 (cm³)					
<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

Variable	Number (%)	Univariate		Multivariate	
		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

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”

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

Fig 4: OS from SRS

Fig 5: Brain-PFS from SRS

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)

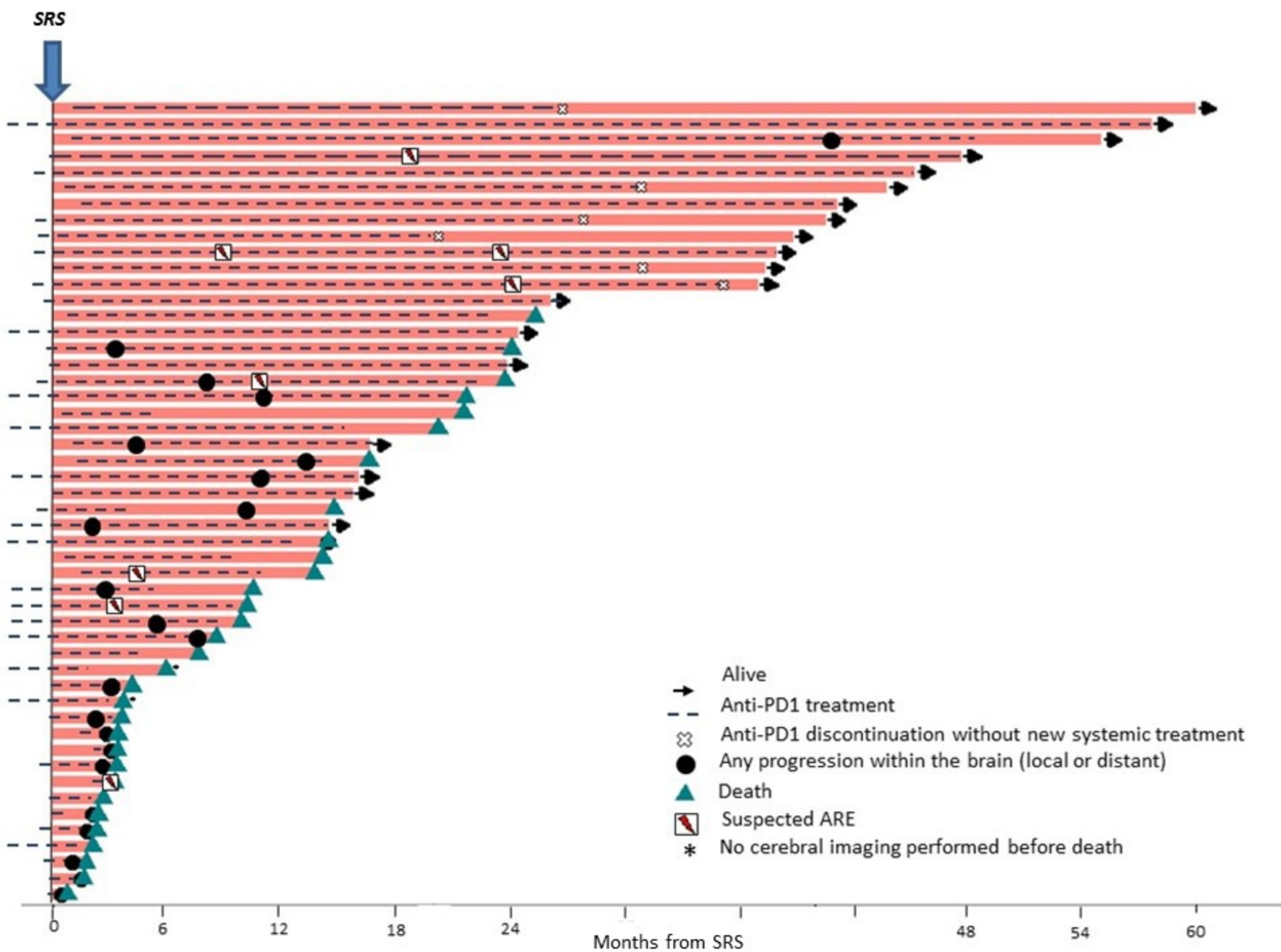
Chemotherapy
(n=17)

Ipilimumab
(n=11)

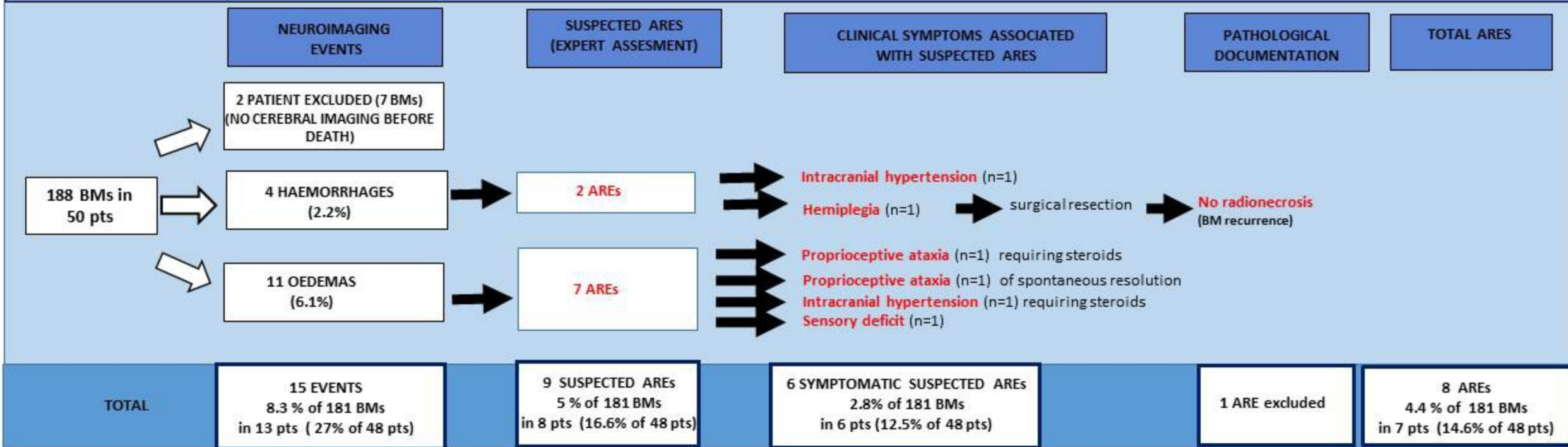
Ipi + Nivo
(n=5)

Nivo + anti IDO
(n=1)

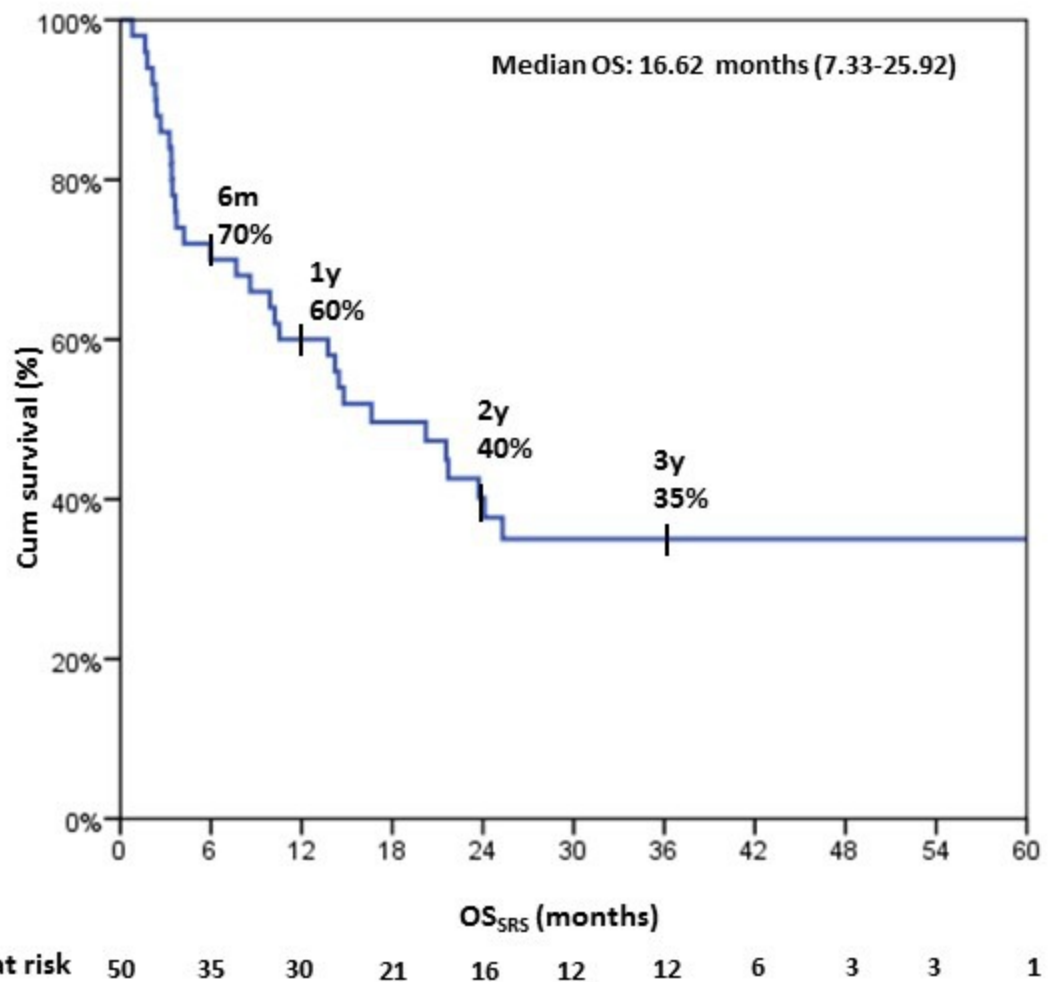
**anti-PD1
(n=50)**



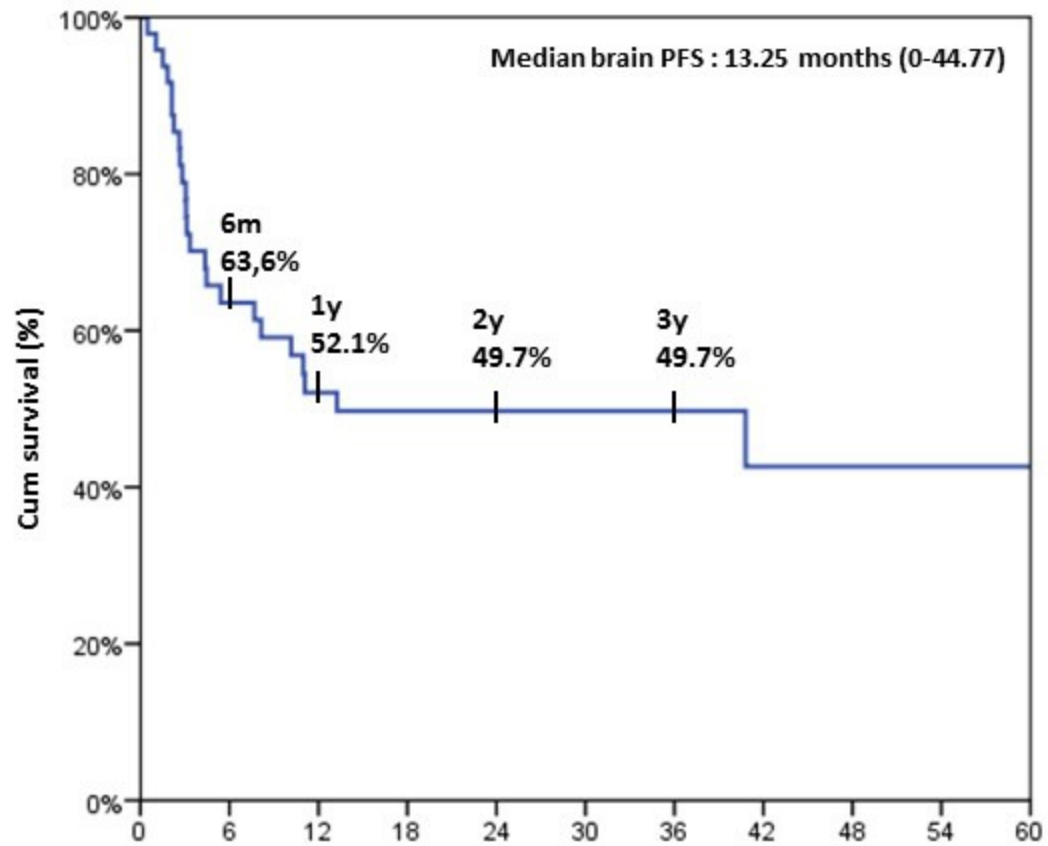
ASSESSMENT OF 181 BMs TREATED BY SRS IN 48 PATIENTS (Median follow-up from SRS 15.30 months)



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



Median brain PFS : 13.25 months (0-44.77)



Brain PFS_{SRS} (months)

Nb at risk 48 29 22 18 15 12 12 5 2 2 1