Supplementary

Table S1 Cohort having received ICIs (n=24) divided into patients having received upfront SRS/SRT and initial ICI treatment

Parameters	Upfront RT (N=10)		Upfront ICI (N=14)		P value
	n or median	% or range	n or median	% or range	
Sex					
Female	4	40.0%	4	28.6%	
Male	6	60.0%	10	71.4%	0.67*
Tumor entity					
Adenocarcinoma	9	90.0%	12	85.7%	
Squamous cell carcinoma	1	10.0%	2	14.3%	>0.99*
EGFR	0	0.0%	0	0.0%	
KRAS	4	40.0%	6	42.9%	
ALK	0	0.0%	0	0.0%	
ROS1	0	0.0%	0	0.0%	
MET	1	10.0%	0	0.0%	
PD-L1 positive	7	70.0%	10	71.4%	>0.99*
Initial brain metastases					
Yes	8	80.0%	11	78.6%	
No	2	20.0%	3	21.4%	>0.99*
Systemic control at diagnosis of brain metastases					
Yes	7	70.0%	5	35.7%	
No	3	30.0%	9	64.3%	0.21*
RT of primary tumor at time of study RT					
Yes	1	10.0%	2	14.3%	
No	9	90.0%	12	85.7%	>0.99*
dsGPA					
Median, range	2.8	0.5–3.0	1.8	0.5–3.0	0.06***
0–2	4	40.0%	12	85.7%	
2.5–4	6	60.0%	2	14.3%	0.03*[a]
iBMV score					
<2	2	20.0%	3	21.4%	
≥2	8	80.0%	11	78.6%	>0.99*
BMV score					
<4	9	90.0%	9	64.3%	
4–13	0	0.0%	3	21.4%	
>13	1	10.0%	2	14.3%	0.42**

Table S1 (*continued*)

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Table S1 (*continued*)

Parameters	Upfront RT (N=10)		Upfront ICI (N=14)		P value
	n or median	% or range	n or median	% or range	
Treatment substance					
Pembrolizumab	10	100.0%	12	85.7%	
Nivolumab	0	0.0%	1	7.1%	
Ipilimumab/nivolumab	0	0.0%	1	7.1%	>0.99**
Combined chemo-/immunotherapy	4	40.0%	5	35.7%	>0.99*
Intracranial progression	7	70.0%	8	57.1%	0.68*
Extracranial progression	6	60.0%	10	71.4%	0.67*
Adverse events					
No	5	50.0%	2	14.3%	
Highest CTCAE 1	5	50.0%	8	57.1%	
Highest CTCAE 2	0	0.0%	2	14.3%	
Highest CTCAE 3	0	0.0%	2	14.3%	0.19**
No. of BM/patient					
Median, range	2.5	1.0–7.0	2.0	1.0–8.0	0.70***
Single metastases	4	40.0%	5	35.7%	
2–4 metastases	5	50.0%	6	42.9%	
5–10 metastases	1	10.0%	3	21.4%	0.87**
Total number of brain metastases	27		41		
RT technique					
SRS	26	96.3%	36	87.8%	
SRT	1	3.7%	5	12.2%	0.39*
Gross tumor volume (GTV), median (cm^3), range	3.3	0.1–8.2	2.7	0.4–17.5	0.86***
Planning target volume (PTV), median (cm^3), range	5.0	0.3–10.6	4.7	0.8–26.1	0.70***
Local tumor progression (No. of lesions)	1	3.7%	1	2.4%	>0.99*
Radiation necrosis (No. of lesions)	1	3.7%	3	7.3%	>0.99*
Dosimetrics SRS					
Median V10 (cm^3), range	3.2	0.8–12.9	2.3	0.5–16.9	
Median V12 (cm^3), range	2.3	0.6–9.5	1.6	0.3–11.2	0.75***
Dosimetrics SRT, median V20 (cm^3), range			24.7	24.1–25.3	

The equal distribution was calculated with the following analyses: *, Fisher-Yates test; **, Fisher-Freeman-Halton test; ***, Mann-Whitney test. [a], P values equal to or below the significance level of 0.05. ICIs, immune checkpoint inhibitors; ALK, anaplastic lymphoma kinase; BM, brain metastases; BMV, brain metastases velocity; CTCAE, Common Terminology Criteria of Adverse Events; dsGPA, disease specific graded prognostic assessment; EGFR, epidermal growth factor; iBMV, initial brain metastases velocity; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal-epithelial transition factor; PD-L1, programmed death ligand 1; ROS1, proto-oncogene tyrosine-protein kinase ROS1; RT, radiation therapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; V10, V12, V20: volume which received at least 10, 12 and 20 Gy, respectively.

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Table S2 Cohort having received tyrosine kinase inhibitors (TKIs) divided into patients having received upfront SRS/SRT and initial TKI treatment

Parameters	Upfront RT (n=7)		Upfront TKI (n=3)		P value
	n or median	% or range	n or median	% or range	
Sex					
Female	4	57.1%	3	100.0%	
Male	3	42.9%	0	0.0%	0.48*
Tumor entity					
Adenocarcinoma	7	100.0%	3	100.0%	
Squamous cell carcinoma	0	0.0%	0	0.0%	–
EGFR	6	85.7%	2	66.7%	>0.99*
KRAS	0	0.0%	0	0.0%	
ALK	0	0.0%	0	0.0%	
ROS1	1	14.3%	1	33.3%	
MET	0	0.0%	0	0.0%	
PD-L1 positive	4	42.8%	2	33.3%	
Initial brain metastases					
Yes	5	71.4%	1	33.3%	
No	2	28.6%	2	66.7%	0.50*
Systemic control at diagnosis of brain metastases					
Yes	1	14.3%	1	33.3%	
No	6	85.7%	2	66.7%	>0.99*
RT of primary tumor at time of study RT					
Yes	0	0.0%	0	0.0%	
No	7	100.0%	3	100.0%	–
dsGPA					
Median, range	2.5	0.5–3.0	2.0	0.5–4.0	0.91***
0–2	3	42.9%	2	66.7%	
2.5–4	4	57.1%	1	33.3%	>0.99*
iBMV score					
<2	2	28.6%	1	33.3%	
≥2	5	71.4%	2	66.7%	>0.99*
BMV score					
<4	3	42.9%	3	100.0%	
4–13	2	28.6%	0	0.0%	
>13	2	28.6%	0	0.0%	0.30**

Table S2 (*continued*)

https://dx.doi.org/10.21037/tlcr-24-132

Table S2 (*continued*)

Parameters	Upfront RT (n=7)		Upfront TKI (n=3)		P value
	n or median	% or range	n or median	% or range	
Treatment substance					
Afatinib	2	28.6%	1	33.3%	
Osimertinib	4	57.1%	0	0.0%	
Crizotinib	1	14.3%	1	33.3%	
Gefitinib	0	0.0%	1	33.3%	0.28**
Intracranial progression	5	71.4%	1	33.3%	0.50*
Extracranial progression	5	71.4%	1	33.3%	0.50*
Adverse events					
No	3	42.9%	1	33.3%	
Highest CTCAE 1	3	42.9%	2	66.7%	
Highest CTCAE 2	1	14.3%	0	0.0%	
Highest CTCAE 3	0	0.0%	0	0.0%	>0.99**
No. of BM/patient					
Median, range	2.0	1.0–5.0	5.0	1.0–7.0	0.34***
Single metastases	3	42.9%	1	33.3%	
2–4 metastases	2	28.6%	0	0.0%	
5–10 metastases	2	28.6%	2	66.7%	0.73**
Total number of brain metastases	18		13		
RT technique					
SRS	16	88.9%	11	84.6%	
SRT	2	11.1%	2	15.4%	>0.99*
Gross tumor volume (GTV), median (cm^3), range	3.7	0.3–17.4	3.1	0.8–16.2	0.73***
Planning target volume (PTV), median (cm^3), range	5.2	0.7–21.9	5.0	1.2–22.3	0.73***
Local tumor progression (No. of lesions)	1	14.3%	0	0.0%	>0.99*
Radiation necrosis (No. of lesions)	0	0.0%	1	33.3%	0.30*
Dosimetrics SRS					
Median V10 (cm^3), range	4.9	1.0–13.0	2.9	0.9–11.8	0.45***
Median V12 (cm^3), range	3.3	0.6–9.6	2.1	0.6–8.4	0.48***
Dosimetrics SRT, median V20 (cm^3), range	12.4	6.5–18.2	8.8	4.6–13.0	0.44***

The equal distribution was calculated with the following analyses: *Fisher-Yates test; **Fisher-Freeman-Halton test; ***Mann-Whitney test. ALK, anaplastic lymphoma kinase; BMV, brain metastases velocity; CTCAE, Common Terminology Criteria of Adverse Events; dsGPA, disease specific graded prognostic assessment; EGFR, epidermal growth factor; iBMV, initial brain metastases velocity; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal-epithelial transition factor; PD-L1, programmed death ligand 1; ROS1, proto-oncogene tyrosine-protein kinase ROS1; RT, radiation therapy; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; V10, V12, V20: volume which received at least 10, 12 and 20 Gy, respectively.

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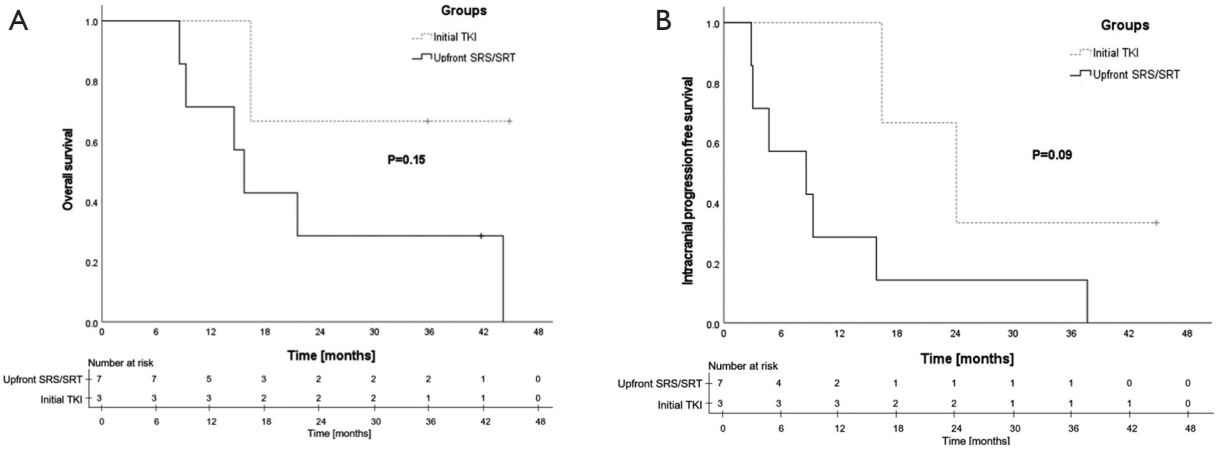

Figure S1 OS (A) and iPFS (B) of initial TKI treatment *vs.* upfront SRS/SRT. SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; TKI, tyrosine kinase inhibitor; OS, overall survival; iPFS, intracranial progression free survival; RT, radiation therapy.

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Table S3 Patients from the main cohort with upfront SRS/SRT (n=17) divided into the patients who received the systemic treatment sequentially (2 weeks or more after RT) and concurrently (within 2 weeks after RT)

Parameters	Sequential (n=7)		Concurrent (n=10)		P value
	n or median	% or range	n or median	% or range	
Sex					
Female	4	57.1%	5	50.0%	
Male	3	42.9%	5	50.0%	>0.99*
Histology					
Adenocarcinoma	7	100.0%	9	90.0%	
Squamous cell carcinoma	0	0.0%	1	10.0%	>0.99*
EGFR	1	14.3%	5	50.0%	0.30*
KRAS	2	14.3%	2	20.0%	
ALK	0	28.6%	0	0.0%	
ROS1	1	14.3%	0	0.0%	
MET	1	14.3%	0	0.0%	
PD-L1 status (positive)	5	71.4%	7	70.0%	>0.99*
Initial brain metastases					
Yes	4	57.1%	9	90.0%	
No	3	42.9%	1	10.0%	0.25*
Systemic control at diagnosis of brain metastases					
Yes	5	71.4%	3	30.0%	
No	2	28.6%	7	70.0%	0.15*
RT of primary tumor at time of study RT					
Yes	0	0.0%	1	10.0%	
No	7	100.0%	9	90.0%	>0.99*
dsGPA					
Median, range	3.0	2.0–3.0	2.0	0.5–3.0	0.15***
0–2	1	14.3%	6	60.0%	
2.5–4	6	85.7%	4	40.0%	0.13*
iBMV score					
<2	1	14.3%	3	30.0%	
≥2	6	85.7%	7	70.0%	0.60*
BMV score					
<4	4	57.1%	8	80.0%	
4–13	2	28.6%	0	0.0%	
>13	1	14.3%	2	20.0%	0.24**

Table S3 (*continued*)

https://dx.doi.org/10.21037/tlcr-24-132

Table S3 (*continued*)

Parameters	Sequential (n=7)		Concurrent (n=10)		P value
	n or median	% or range	n or median	% or range	
Treatment substance					
Pembrolizumab	5	71.4%	5	50.0%	
Afatinib	0	0.0%	2	20.0%	
Osimertinib	1	14.3%	3	30.0%	
Crizotinib	1	14.3%	0	0.0%	0.46**
Combined chemo-/immunotherapy	3	42.9%	3	30.0%	0.64*
Intracranial progression	5	71.4%	7	70.0%	>0.99*
Extracranial progression	5	71.4%	5	50.0%	0.62*
Adverse events					
No	2	28.6%	6	60.0%	
Highest CTCAE 1	5	71.4%	3	30.0%	
Highest CTCAE 2	0	0.0%	1	10.0%	
Highest CTCAE 3	0	0.0%	0	0.0%	0.23**
Number of BM/patient					
Median, range	3.0	1.0–5.0	1.5	1.0–7.0	0.39***
Single metastases	2	28.6%	5	50.0%	
2–4 metastases	4	57.1%	3	30.0%	
5–10 metastases	1	14.3%	2	20.0%	0.81**
Total	19		26		
RT technique					
SRS	19	100.0%	23	88.5%	
SRT	0	0.0%	3	11.5%	0.25*
Gross tumor volume (GTV), median (in cm^3), range	1.0	0.4–6.2	3.8	0.1–17.4	0.21***
Planning target volume (PTV), median (in cm^3), range	2.1	0.9–8.9	5.8	0.3–21.9	0.24***
Local tumor progression (No. of lesions)	1	5.3%	1	3.8%	>0.99*
Radiation necrosis (No. of lesions)	1	5.3%	0	0.0%	0.42*
Dosimetry SRS					
Median V10 (cm^3), range	3.2	0.8–12.9	3.9	0.6–20.5	0.79***
Median V12 (cm^3), range	2.3	0.6–9.5	2.8	0.3–14.7	0.77***
Dosimetry SRT, median V20 (cm^3), range	–	–	6.5	2.5–18.2	–

The equal distribution was calculated with the following analyses: *Fisher-Yates test; **Fisher-Freeman-Halton test; ***Mann-Whitney test. ALK, anaplastic lymphoma kinase; BMV, brain metastases velocity; CTCAE, Common Terminology Criteria of Adverse Events; dsGPA, disease specific graded prognostic assessment; EGFR, epidermal growth factor receptor; iBMV, initial brain metastases velocity; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal-epithelial transition factor; PD-L1, programmed death ligand 1; RT, radiation therapy; V10, V12, V20: volume which received at least 10, 12 and 20 Gy, respectively.

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