Osimertinib with or without SRS for Brain Metastases from EGFRm NSCLC: Pooled Analysis of Two RCTs

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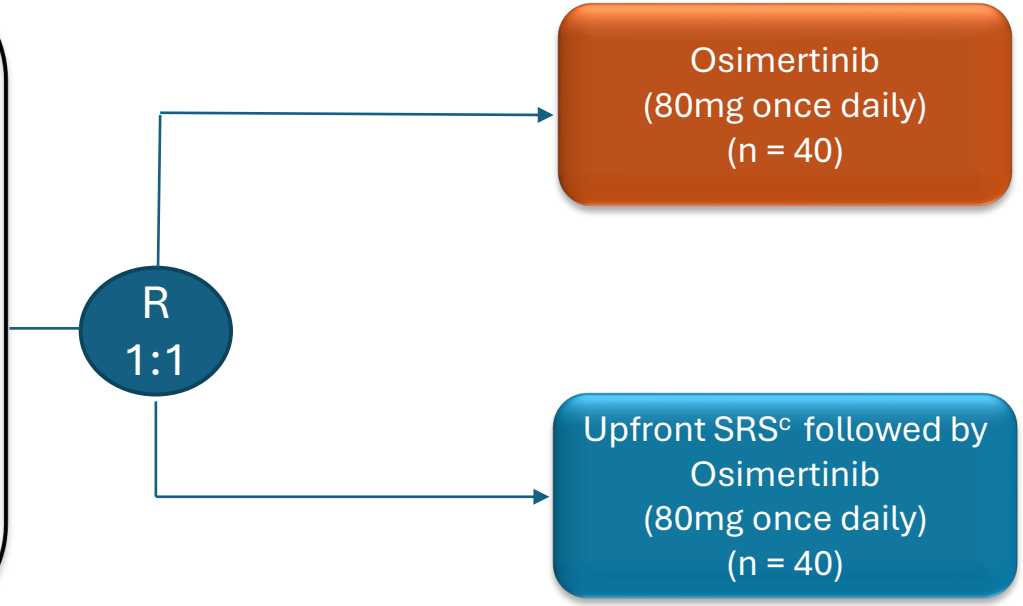
Clinicaltrials.gov Identifier
LUOSCINS: NCT03769103
OUTRUN (TROG 17.02): NCT03497767

OUTRUN (TROG 17.02): Randomized, Phase 2 Trial

<u>Key Eligibility Criteria</u>

1. EGFR mutant NSCLC[a]
2. De Novo BM or **BM developed after 1st or 2nd generation EGFR TKI[b]**
3. **Not mandatory to have at least one measurable BM[d]**
4. Asymptomatic or Minimally symptomatic
5. ≤ 10 lesions. Max diameter ≤ 30mm
6. Lesions in brainstem **NOT** allowed



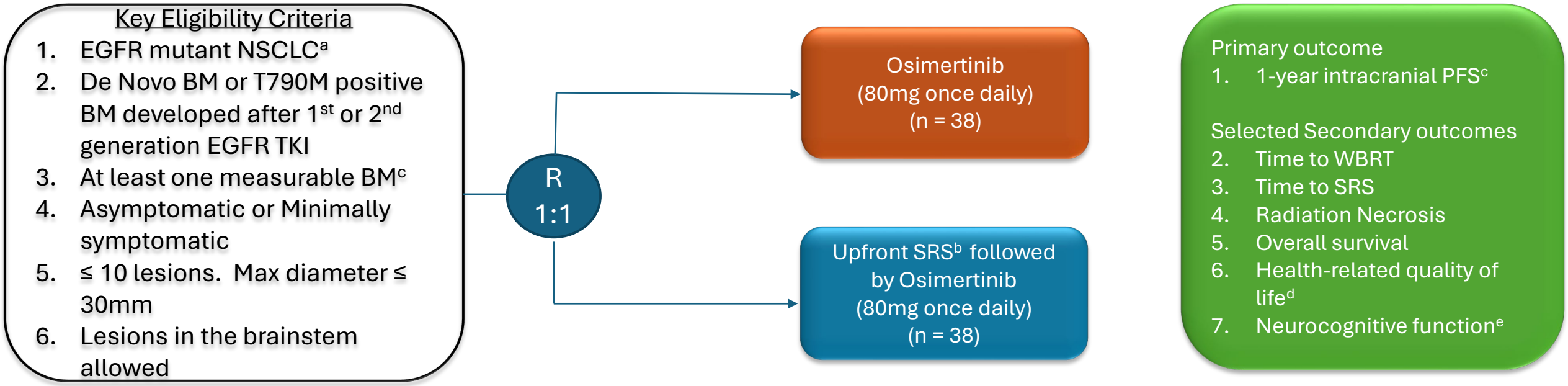
Primary outcome
1. 1-year intracranial PFS[d]

Selected Secondary outcomes
2. Time to subsequent BM-directed local therapies
3. Radiation Necrosis
4. Overall survival
5. Health-related quality of life[e]

Sample size: 80 participants, based on the likely number of participants expected to be recruited over 2 years.
Assuming 1-year intracranial PFS of 80% for SRS + Osimertinib and 65% for Osimertinib, we expect 8 events for SRS + Osimertinib and 14 events for Osimertinib. The expected 90% confidence interval for the HR is 0.48 to 2.07 if there is no difference between the two arms.

[a]EGFR mutation: exon 19 del; L858R (exon 21); G719x (exon 18); L861Q (exon 21); S768I (exon 20) and T790M (exon 20)
[b]T790M positive, T790M negative with no or stable extracranial disease
[c]SRS: 15Gy-20Gy in 1 fraction; 24Gy in 3 fractions
[d]Measured using RANO-BM criteria
[e]Measured using EORTC QLQ C30 and BN20

LUOSICNS: Randomized, Phase 2 Trial



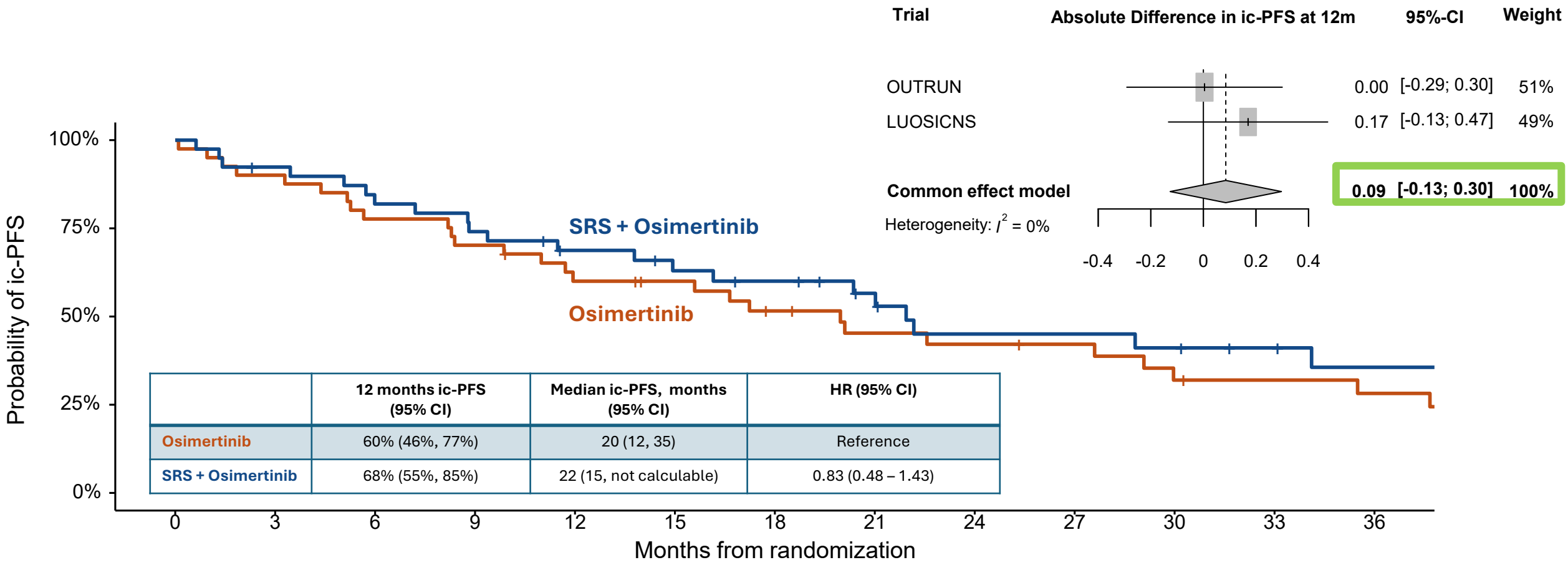
Sample size: 76 participants are needed, assuming 1-year intracranial PFS of 77% for SRS + Osimertinib and 60% for Osimertinib, with a Power of 0.75 and two-sided alpha of 0.10.

[a]EGFR mutation: exon 19 del; L858R (exon 21); T790M (exon 20)
[b]SRS: 15Gy-20Gy in 1 fraction; 21Gy – 27Gy in 3 fractions; 30Gy – 40Gy in 5 fractions
[c]Measured using RANO-BM criteria
[d]Measured using EORTC QLQ C30 and BN20
[e]Measured using Montreal Cognitive Assessment

Baseline characteristics

Characteristic	Osimertinib (N = 40)	SRS + Osimertinib (N = 39)
Median Age (IQR)	66 (57 – 73)	69 (62 – 75)
Female	24 (60%)	29 (74%)
Asian	29 (73%)	26 (70%)
History of never smoking	28 (70%)	29 (74%)
Exon 19 deletion	19 (48%)	19 (49%)
Exon 21 mutation	21 (53%)	20 (51%)
De novo BM	35 (88%)	35 (90%)
Number of BM		
One	7 (18%)	11 (28%)
Two to four	20 (50%)	13 (33%)
Five to ten	13 (33%)	15 (38%)
Median (IQR)	3 (2 – 5)	4 (1 – 6)
At least one BM ≥ 10mm	25 (63%)	28 (72%)
Median size of largest BM (mm) (IQR)	12 (10 – 15)	14 (10 – 16)

Primary outcome: Intracranial PFS



	12 months ic-PFS (95% CI)	Median ic-PFS, months (95% CI)	HR (95% CI)
Osimertinib	60% (46%, 77%)	20 (12, 35)	Reference
SRS + Osimertinib	68% (55%, 85%)	22 (15, not calculable)	0.83 (0.48 – 1.43)

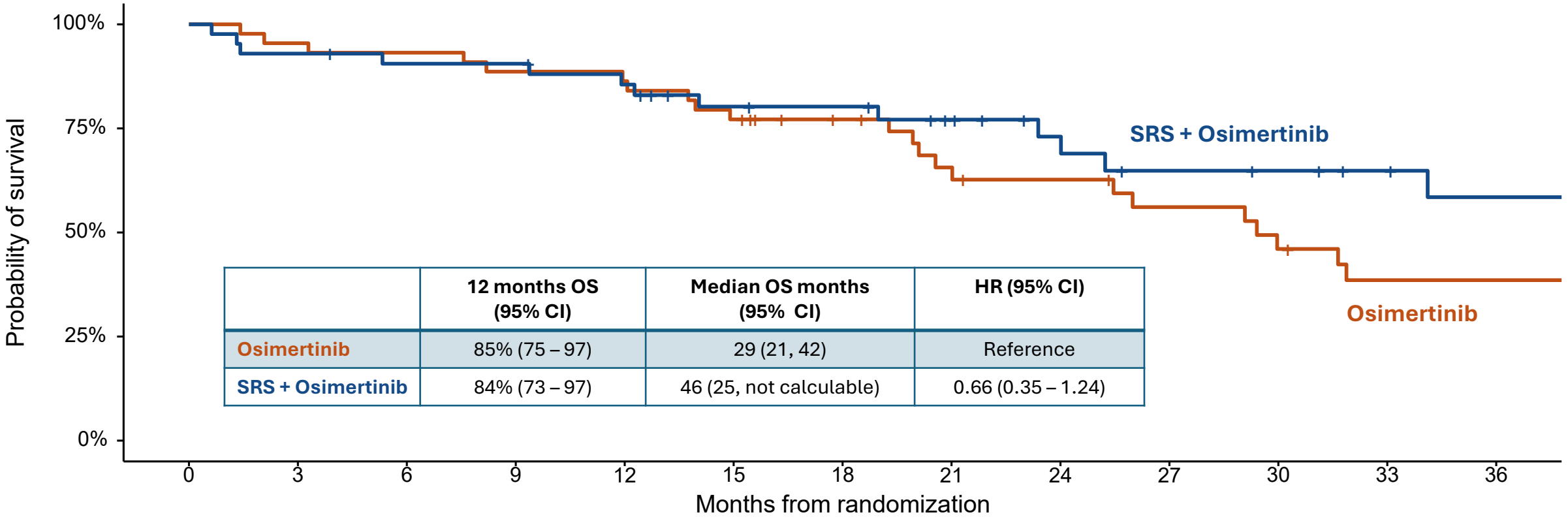
Number at risk

40	36	31	28	23	21	17	14	13	12	9	8	7
39	35	31	28	24	21	19	15	11	11	10	8	6

Patterns of First Intracranial Progression and Subsequent Management

Pattern of first intracranial progression	**Osimertinib (N = 40)**	**SRS + Osimertinib (N = 39)**
Local progression only	5 (13%)	5 (13%)
Distant only	13 (33%)	7 (18%)
Local and distant progression	3 (8%)	5 (13%)
Subsequent treatment		
SRS	12 (30%)	6 (15%)
SRS rate at 12 m	18%	5%
Whole brain RT	2 (5%)	0 (0%)

Overall survival

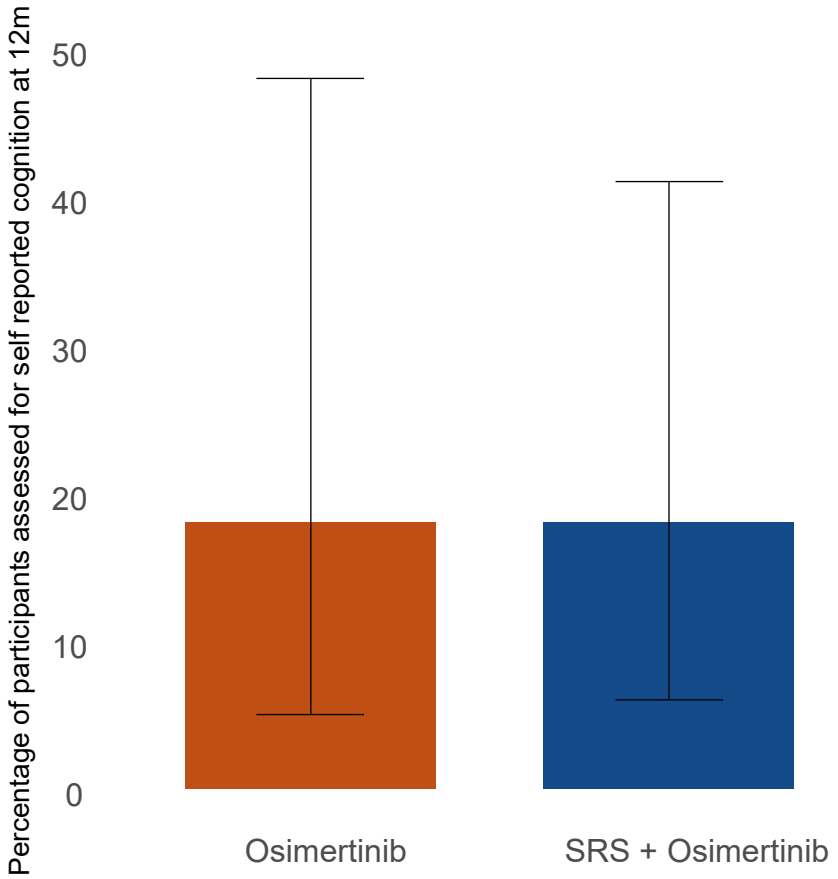


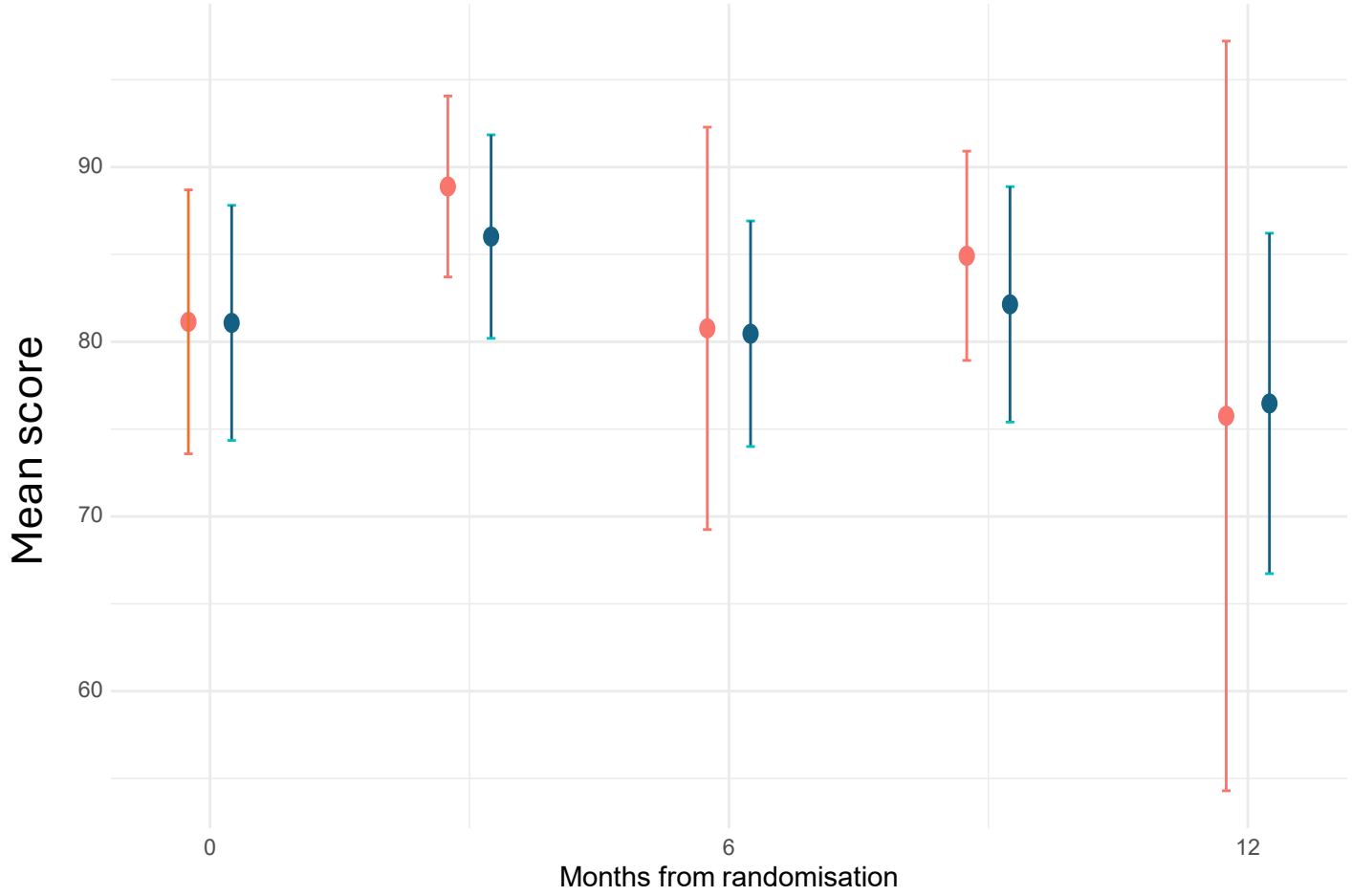
	12 months OS (95% CI)	Median OS months (95% CI)	HR (95% CI)
Osimertinib	85% (75 – 97)	29 (21, 42)	Reference
SRS + Osimertinib	84% (73 – 97)	46 (25, not calculable)	0.66 (0.35 – 1.24)

Number at risk

Osimertinib	40	38	37	35	34	30	25	20	18	15	12	9	9
SRS + Osimertinib	39	36	34	34	31	26	24	20	16	13	12	10	8

Deterioration in self reported cognition at 12 months

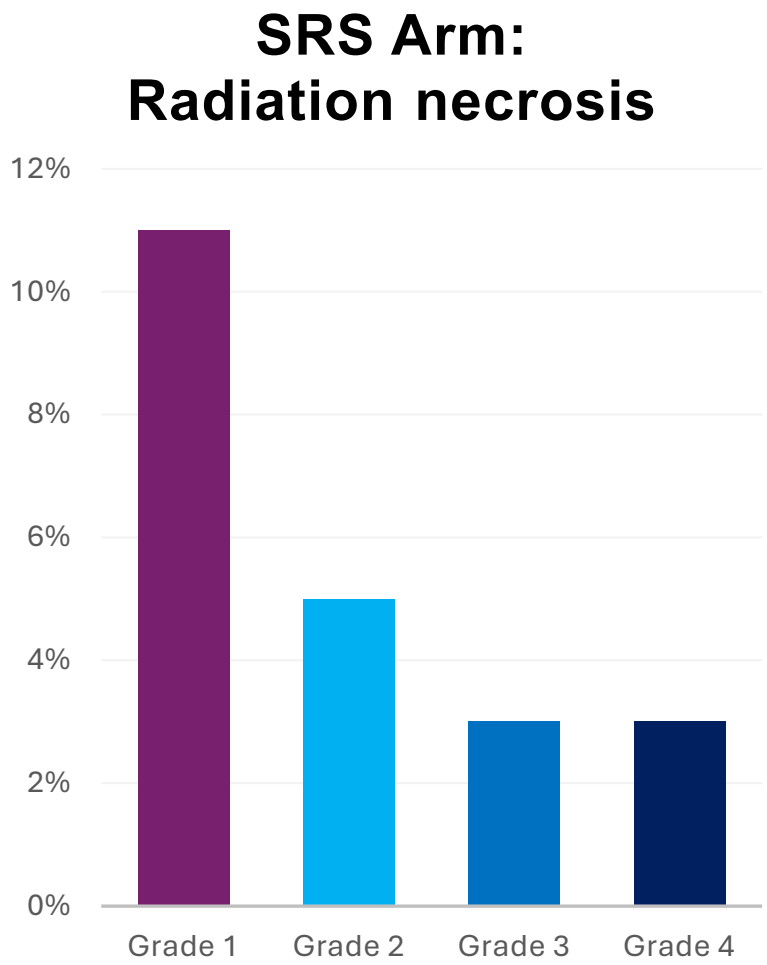




QLQ-C30 Self reported cognitive functioning

Adverse events of special interest

AESI Grade >=3	Osimertinib (N = 40)	SRS + Osimertinib (N = 39)
Dizziness	1 (2%)	-
Seizures	2 (5%)	-
Intracranial hemorrhage	-	1 (2%)
Cerebral edema	-	1 (2%)
Radiation necrosis	-	2 (6%)



Conclusions

There was **insufficient evidence** to demonstrate a difference between upfront versus no upfront SRS:

- Intracranial progression-free survival at 12 months
- Overall survival
- Self-reported cognition at 12 months
- Use of subsequent SRS at 12 months

The incidence of radiation necrosis was low

The results of our pooled randomized control studies should be interpreted within the context of the sample size of the individual trials and the evolving first line EGFRm systemic treatment paradigms

Can **upfront SRS improve ic-PFS** for EGFRm NSCLC with newly diagnosed **measurable BM with the sum of longest diameters ≥ 15mm** treated with Osimertinib +/- chemotherapy?

Key Eligibility Criteria

1. EGFR mutated NSCLC
2. **De Novo BM**
3. Asymptomatic or Minimally symptomatic
4. ECOG PS 0-2
5. **Sum of longest diameters of measurable BM ≥ 15mm**
6. Max diameter **≤ 40mm**
7. Lesions in the brainstem allowed

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1:1

Osimertinib
+/- chemotherapy
(n = 105)

Upfront SRS followed by Osimertinib
+/- chemotherapy
(n = 105)

Primary outcome

1. Intracranial PFS

Selected Secondary outcomes

2. Cognitive deterioration
3. Patterns of intracranial progression
4. Radiation necrosis
5. Time to next BM-directed local therapies
6. Overall survival
7. Health-related quality of life

Sample size: 210 participants,
assuming 80% Power, 2-sided alpha of 5%, HR of 0.60, and 60% of participants in the Osimertinib +/- chemo will experience an event.
This will be an event-driven study.
The study will reach completion at a total of 126 events.