Management of brain metastases from multiple cancer types

Yu Yang Soon

ASTRO Practice Guidelines

Asymptomatic BM eligible for CNS active systemic therapy

"Multidisciplinary and patient-centered decision making is **conditionally** recommended to determine whether local therapy may be safely deferred"

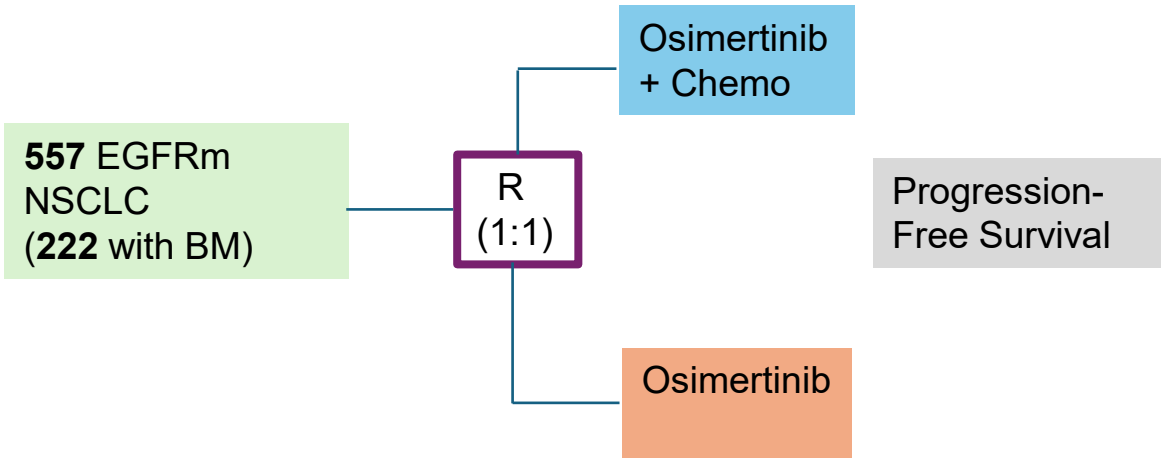
Gondi PRO 2022

Cancer Types	CNS active systemic therapies	Quality of Evidence	Strength of Recommendation
EGFR mutated NSCLC	Osimertinib	LOW	WEAK
ALK re-arranged NSCLC	Alectinib, brigatinib, ceritinib		
PDL1 positive NSCLC	Pembrolizumab + Platinum + Pemetrexed		
HER2 positive breast cancer, progressed on trastuzumab, pertuzumab and TDM1	Tucatinib + Trastuzumab + Capecitabine		
Melanoma (regardless of BRAF)	Ipilimumab + Nivolumab		
Melanoma (BRAF-V600E mutation)	Dabrafenib + Trametinib		

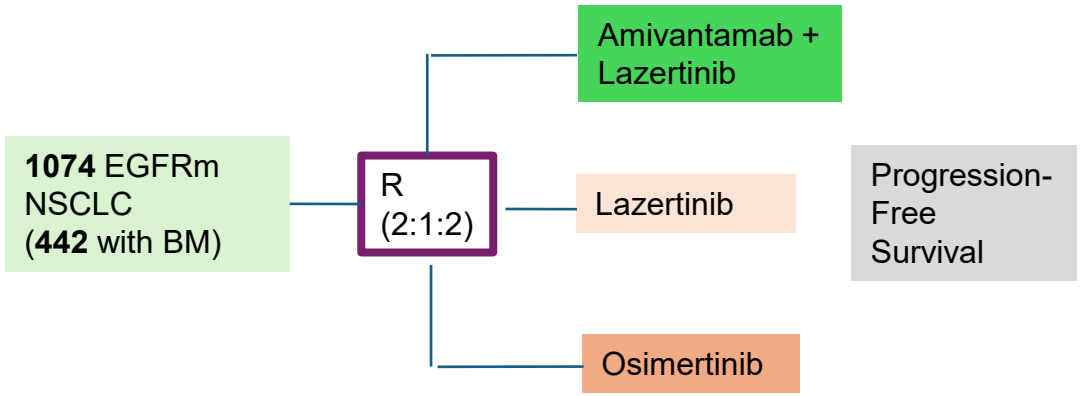
Vogelbaum JCO 2021

New CNS active systemic therapies in EGFR mutated NSCLC

FLAURA 2



MARIPOSA



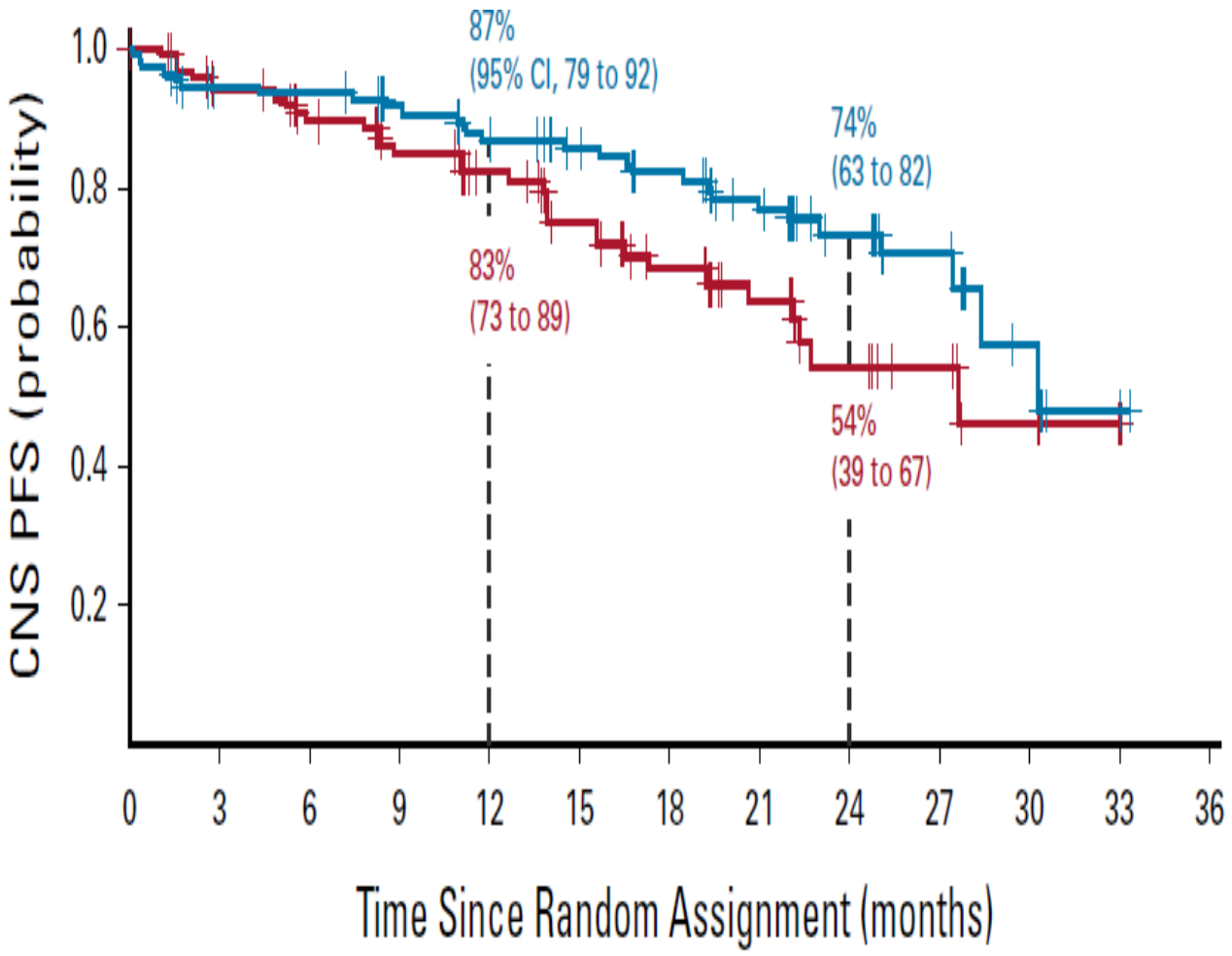
Hazard Ratios (95% CI) for Progression-Free Survival		
Population	FLAURA 2	MARIPOSA
Overall	0.62 (0.49 – 0.79)	0.70 (0.58 – 0.85)
Brain Metastases	**0.47 (0.33 – 0.66)**	0.69 (0.53 – 0.92)
No Brain Metastases	0.75 (0.55 – 1.03)	0.69 (0.53 – 0.89)

Planchard NEJM 2023, Cho NEJM 2024

Osimertinib + Chemotherapy improved CNS-PFS

Baseline Characteristic	Osimertinb + Chemo (N = 118)	Osimertinib (N = 104)
Prior brain RT	**16 (14)**	**18 (17)**
Prior brain surgery	1 (1)	7 (7)
No. with LMD	13 (11)	5 (5)
CNS lesions		
1 lesion	**53 (45)**	**45 (43)**
2-3 lesions	31 (26)	32 (31)
4-10 lesions	33 (28)	26 (25)
> 10 lesions	1 (1)	1 (1)

HR: 0.58 (0.33 – 1.01)

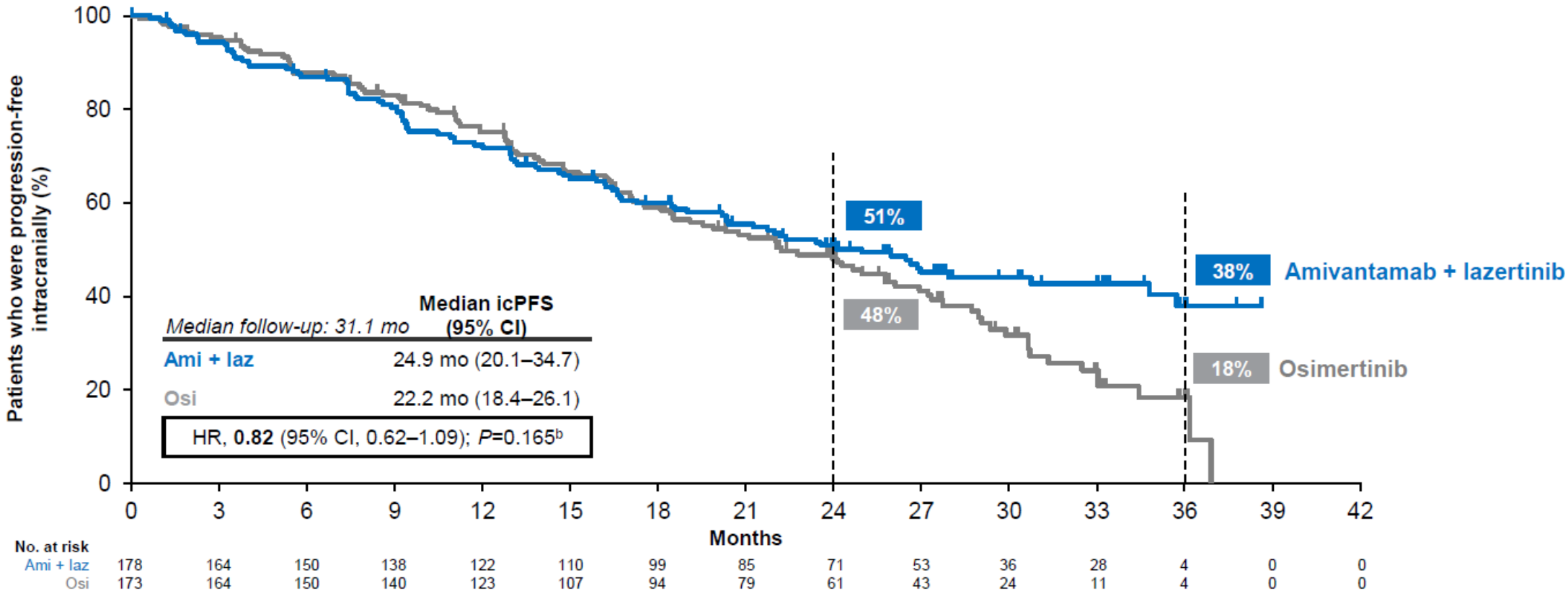


Janne JCO 2024

Intracranial PFS[a]

MARIPOSA required serial brain imaging for all patients, which provides robust evaluation of CNS outcomes

Amivantamab + lazertinib showed a favorable trend in icPFS with sustained and durable CNS control at 3 years

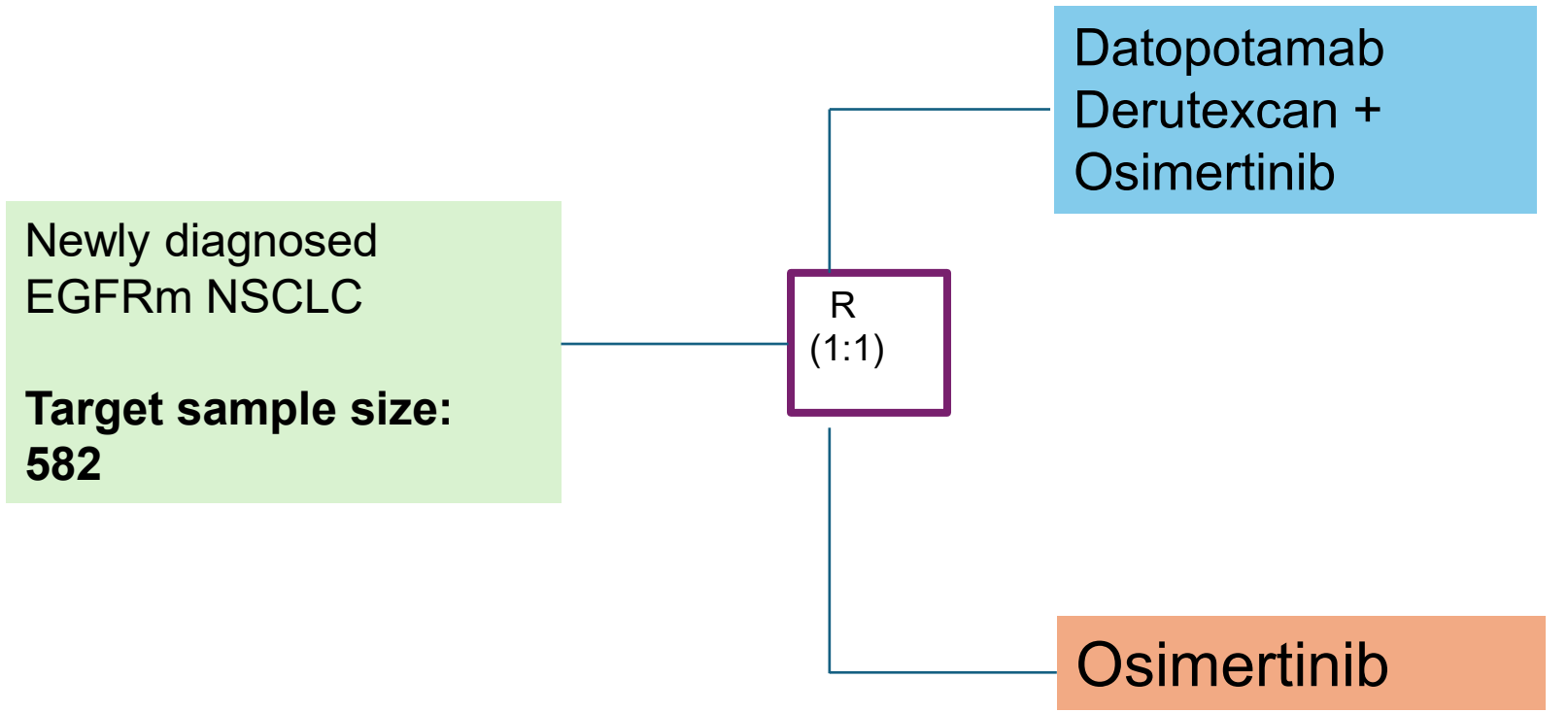


3-year landmark icPFS was double for amivantamab + lazertinib vs osimertinib (38% vs 18%)

[a]Intracranial PFS was defined as time from randomization until the date of intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1 among patients with a history of brain metastases. Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months, then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. [b]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R) and race (Asian or Non-Asian). Hazard ratio was calculated from a stratified proportional hazards model.

Potential new standard CNS active systemic therapies

TROPION-Lung 14 (NCT 06350097)

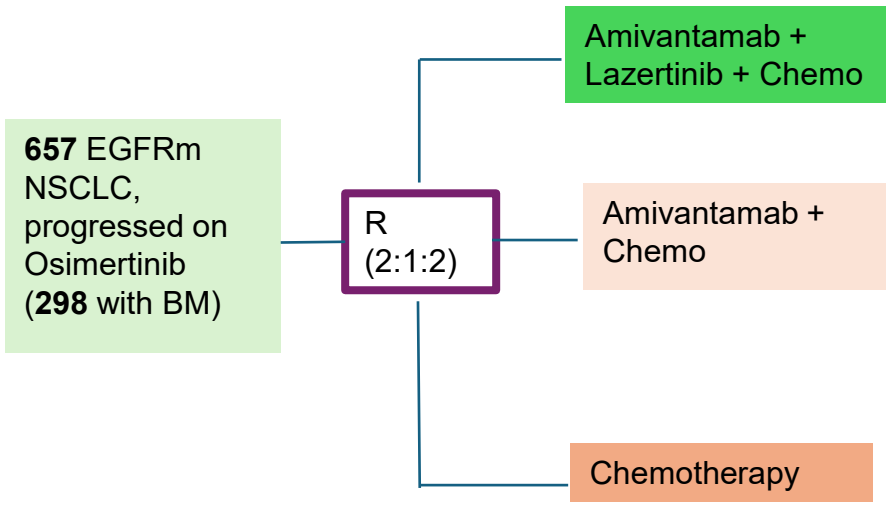


Primary endpoint
PFS

Selected secondary endpoints
OS
CNS PFS
ORR
DoR

Rapidly evolving CNS active systemic therapies in EGFR mutated NSCLC post Osimertinib

MARIPOSA-2



Primary endpoint
Progression-Free Survival

Selected secondary endpoints
Overall survival
Intracranial (IC) PFS
Adverse events

Characteristic	Ami + Laz + Chemo (N = 263)	Ami + Chemo (N = 131)	Chemo (N = 263)
History of BM	120 (46)	58 (44)	120 (46)
Prior BM RT	61 of 120 (51)	24 of 58 (41)	56 of 120 (47)

Group	HR for PFS (95% CI)	HR for IC PFS (95% CI)
Amivantamab + Lazertinib + Chemotherapy	0.44 (0.35 – 0.56)	**0.58 (0.44 -0.78)**
Amivantamab + Chemotherapy	0.48 (0.35 – 0.56)	**0.55 (0.38 – 0.79)**
Chemotherapy	Reference	Reference

Passaro Ann Onc 2023

Potential new standard CNS active systemic therapies

HERTHENA 2 – Lung01

Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

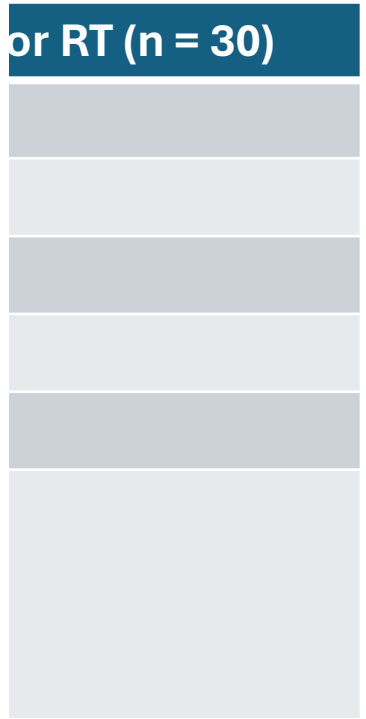
277 EGFRm NSCLC, progressed on EGFR TKI and Chemo (**115** with BM)

Save

September 17, 2024 6:00 am ET

Daiichi Sankyo and Merck's patritumab deruxtecan demonstrates a statistically significant progression-free survival improvement in this EGFR-mutated non-small cell lung cancer population with high unmet need following prior EGFR TKI treatment

Discussions with global regulatory authorities to be initiated



Yu JCO 2023

TUXEDO-III (NCT05865990)
HER3-DXd

Multicenter, open-label, single arm, three-cohort, non-comparative, Simon's two-stage design

BM or LMD can be asymptomatic untreated or progressing after local treatment

≥ 1 Measurable brain lesion (≥ 10mm on MRI) or LMD with CSF positive cytology and/or MRI

≥ 1 line of systemic treatment for MBC and aNSCLC

- MBC with active BM
  10 pts stage I / 10 pts / stage II
- aNSCLC with active BM
  10 pts stage I / 10 pts stage II
- Advanced solid tumours with LMD
  10 pts stage I / 10 pts stage II

Primary endpoint
MBC and aNSCLC: ORR (RANO-BM)

LMD: 3 month OS rate

Selected secondary endpoints
Clinical Benefit Rate
Duration of response
Best percentage of change in tumor burden
Safety
Quality of life (EORTC QLQ c30, BN 20 and BR 45)

Futility: 0/10 pts achieve primary endpoint

Success: ≥ 3/ 20 pts achieve primary endpoint

Alpha = 10%, Power = 88%

ATEZO-BRAIN

40 Nonsquamous NSCLC with at least one untreated BM (≥ 10mm)

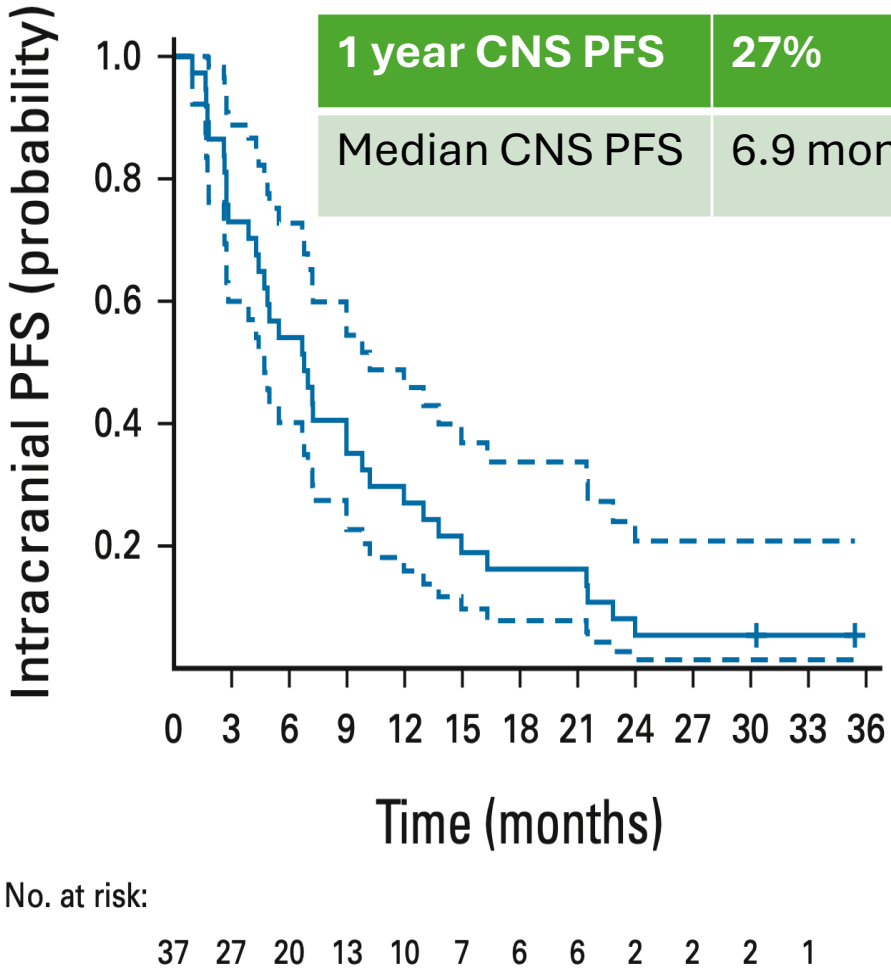
Carbo + Pem + Atezo followed by Pem + Atezo

CNS PFS (RANO-BM)

Characteristic	N = 40
Synchronous BM diagnosis	37 (93%)
Median no. of BM (range)	5 (1- 20)
PDL1 ≥ 50%	10 (25%)
PDL1 ≥ 1 - 49%	10 (25%)
PDL1 = 0%	18 (45%)

Outcome	N = 40
CNS CR	5 (13%)
CNS PR	12 (30%)
Subsequent brain RT	24 (60%)
Median Time to Brain RT	10.9 months

1 year CNS PFS	27%
Median CNS PFS	6.9 months



Nadal JCO 2023

NCI Workshop's Recommended Priorities

1. Identify those who are at high risk for BM
2. Identify those who are at high risk for functional and cognitive impairment from treatment
3. Align preclinical and clinical research opportunities
4. Optimize the framework for the design and conduct of brain metastases specific trials

Kim Lancet Oncol 2023

1. Identify those who are at high risk for BM

ARTIFICIAL INTELLIGENCE

original reports

Prediction of Brain Metastases Development in Patients With Lung Cancer by Explainable Artificial Intelligence From Electronic Health Records

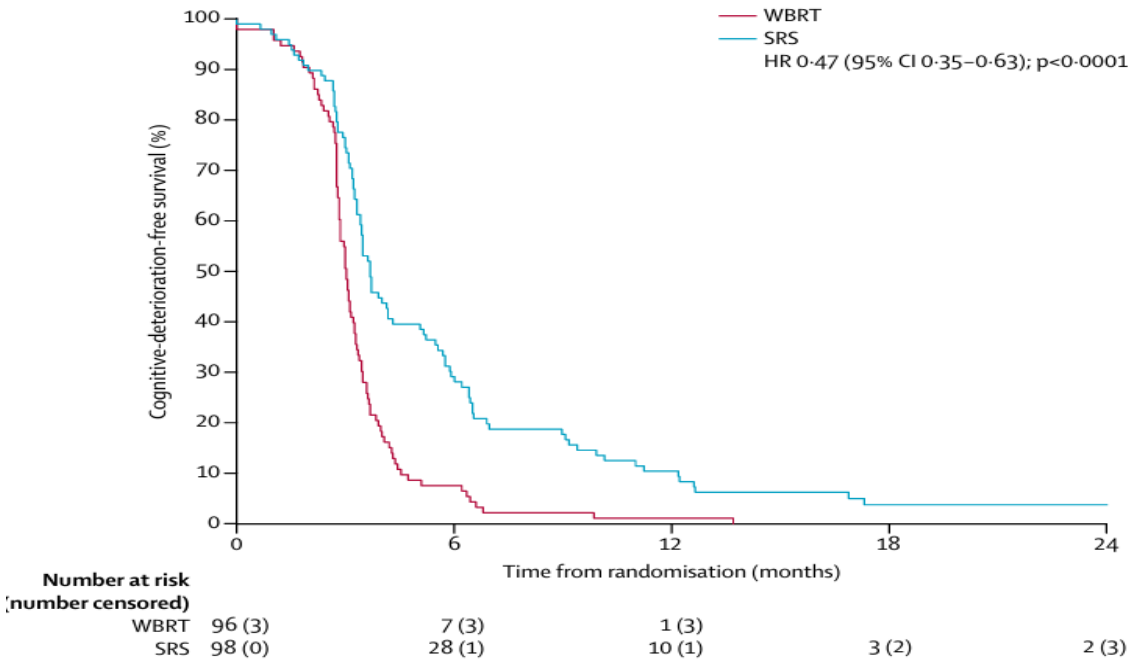
Zhao Li, MS[1]; Rongbin Li, BS[1]; Yujia Zhou, MS[1]; Laila Rasmy, PhD[1]; Degui Zhi, PhD[1]; Ping Zhu, MD, PhD[2,3]; Antonio Dono, MD[2]; Xiaoqian Jiang, PhD[1]; Hua Xu, PhD[1]; Yoshua Esquenazi, MD[2]; and W. Jim Zheng, PhD[1]

Dataset: 37710 without BM and 4782 with BM	
Model	AUC
RETAIN (recurrent neural network)	**0.825**
Logistic regression	0.751

Li JCO CCI 2023

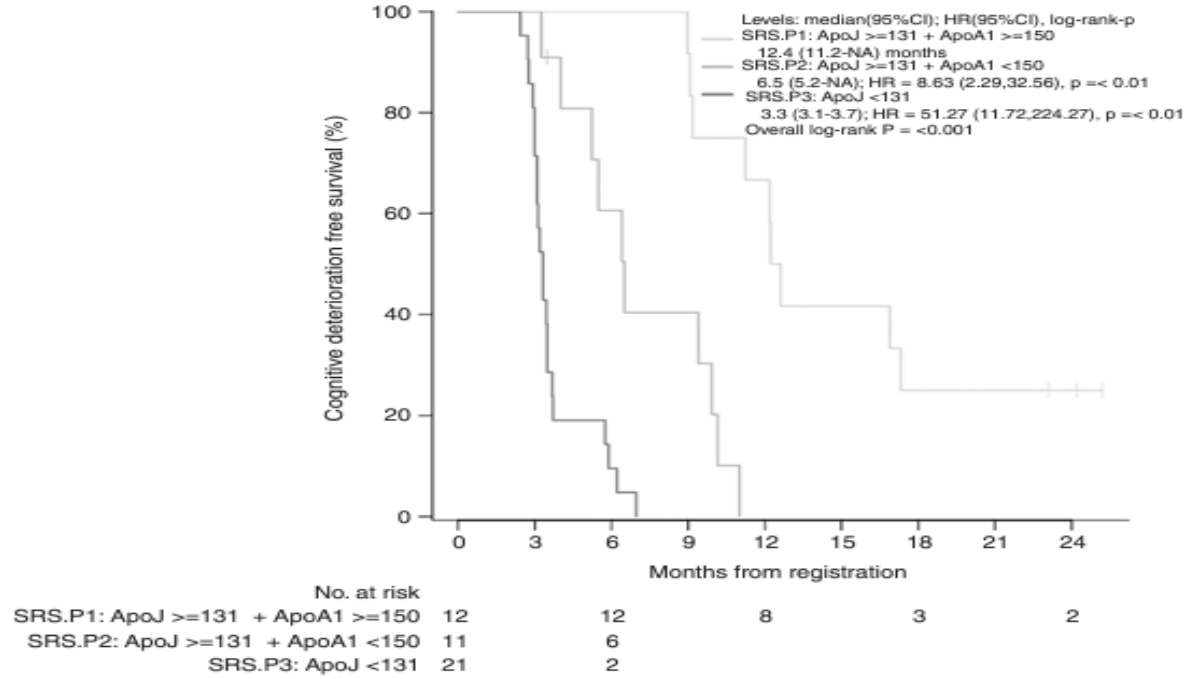
2. Identify those who are at high risk for functional and cognitive impairment from treatment

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial



Neuro-Oncology
25(6), 1123–1131, 2022 | https://doi.org/10.1093/neuonc/noac262 | Advance Access date 6 December 2022

Association of circulating markers with cognitive decline after radiation therapy for brain metastasis



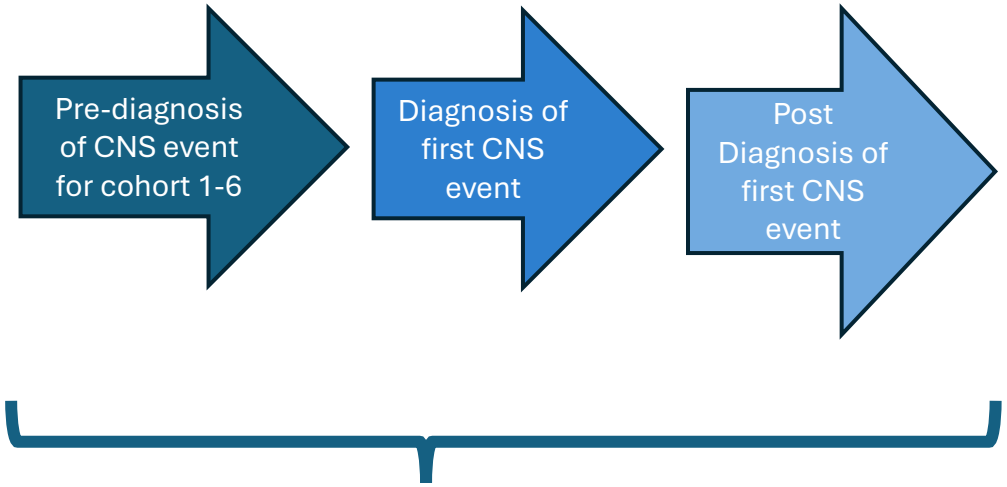
Brown Lancet Oncol 2017
Huntoon NO 2022

3. Align preclinical and clinical research opportunities

BrainStorm (NCT 04109131)

Seven Cohorts of metastatic disease without CNS metastases
(N = 600)

1. Triple-negative Breast Ca
2. HER2 positive Breast Ca
3. Non-small cell lung Ca
4. Small cell lung Ca
5. Melanoma
6. Other solid tumors
7. Radiologically or cytologically confirmed LMD



Mandatory CSF sampling at the first CNS event
Regular MRI brain surveillance for the entire study

Outcomes

1. Time to first CNS event
2. Time to second CNS after first treatment and subsequent CNS events
3. Time to whole brain RT
4. Overall survival

4. Optimize the framework for the design and conduct of brain metastases specific trials

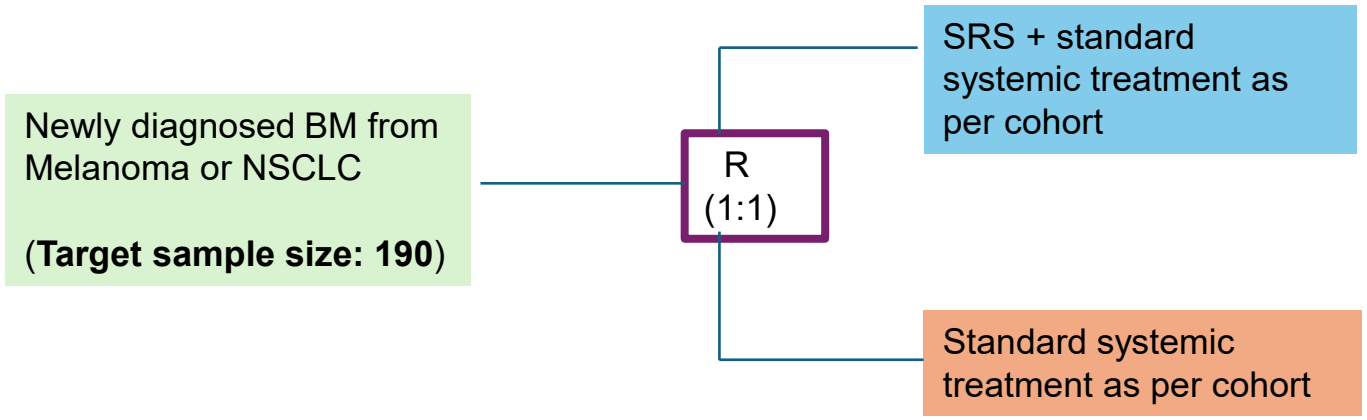
Need for a standardized approach for neurocognitive outcomes

Trial	Primary outcome	Definition	Instrument	Outcome measure
NCCTG N107C / CEC.3	Cognitive-deterioration-free survival	Time from randomization to a drop of greater than 1SD from baseline in at least one of the six cognitive tests	HVLT-R COWAT TMT-A TMT-B HVLT-R Delayed Recall HVLT-R Recognition	Hazard ratio
PREMER	Decline in Delayed free recall score at 3 months	Odds of patients with a decrease in recall scores of 3 scaled points (1 SD) or more from baseline	Free and Cued Selective Reminding Test	Odds ratio
Netherlands Cancer Institute	Decline in HVLT-R Total Recall at 4 months	Proportion of patients with a decrease in 5 points or more from baseline	HVLT-R Total Recall	Absolute difference in proportions

Brown Lancet Oncol 2017
Rodriguez de Dios JCO 2021
Belderbos JTO 2021

4. Optimize the framework for the design and conduct of brain metastases specific trials

ETOP 19-21 (NCT 05522660)



Primary endpoint
CNS PFS, locally assessed as per RANO

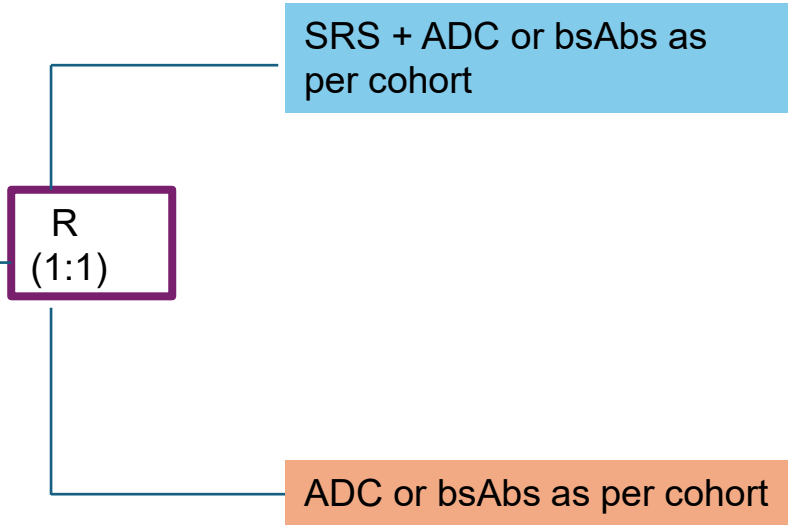
Selected secondary endpoints
CNS PFS per cohort, locally assessed as per RANO
Patterns of CNS progression
Overall survival, overall and as per cohort
Incidence of radiation necrosis
Neurocognitive function
Health-related quality of life

Cohort	Disease	Standard systemic treatment
1a	Melanoma	Ipilimumab + Nivolumab
1b	Melanoma	Anti-PD-1/L1 monotherapy
2a	NSCLC	Targeted therapy
2b	NSCLC	Anti-PD-1/L1 therapy ± Chemo

4. Optimize the framework for the design and conduct of brain metastases specific trials

Upcoming RCT: EORTC (BTG-BCG-LCG) ACROSS

Active BM (newly diagnosed or progressive)
Measurable disease (RANO-BM)
ECOG ≤ 2
Indication for SRS of BM
No active treatment
Maximum prior 2 lines of systemic treatment for breast cohorts and 1 line of chemotherapy for lung cohorts.
Progression on EGFR TKI for EGFRm NSCLC



Primary endpoint
Time to next CNS intervention

Selected secondary endpoints
Overall survival
Progression-free survival
Radiation necrosis
Neurocognitive function
Health-related quality of life

Stratification factors
Systemic disease status (ECD present vs absent)

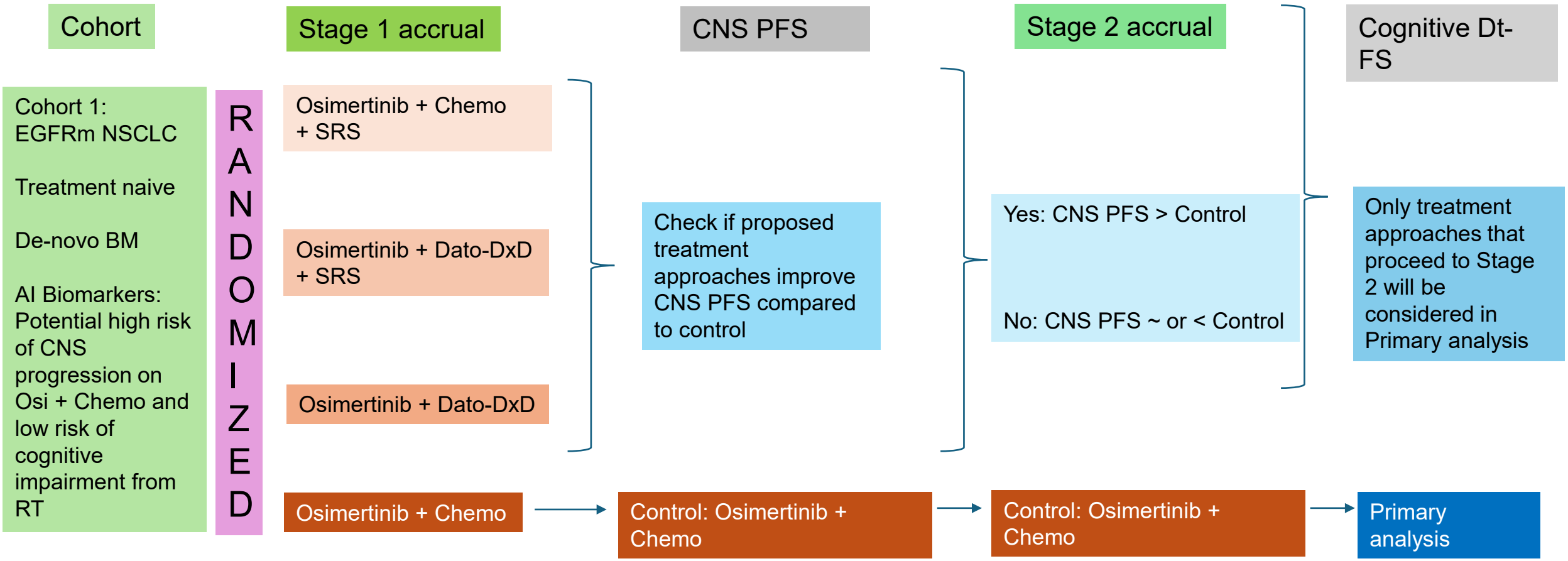
No. of prior systemic therapies for metastatic disease (1 vs 2)

Previous surgical resection or radiation therapy for BM (yes vs no)

Cohort	Disease
1a	HER2 +ve Br Ca
1b	Triple negative Br Ca
2a	HER2 +ve NSCLC
2b	EGFRm NSCLC
2c	NSCLC without targetable molecular aberrations

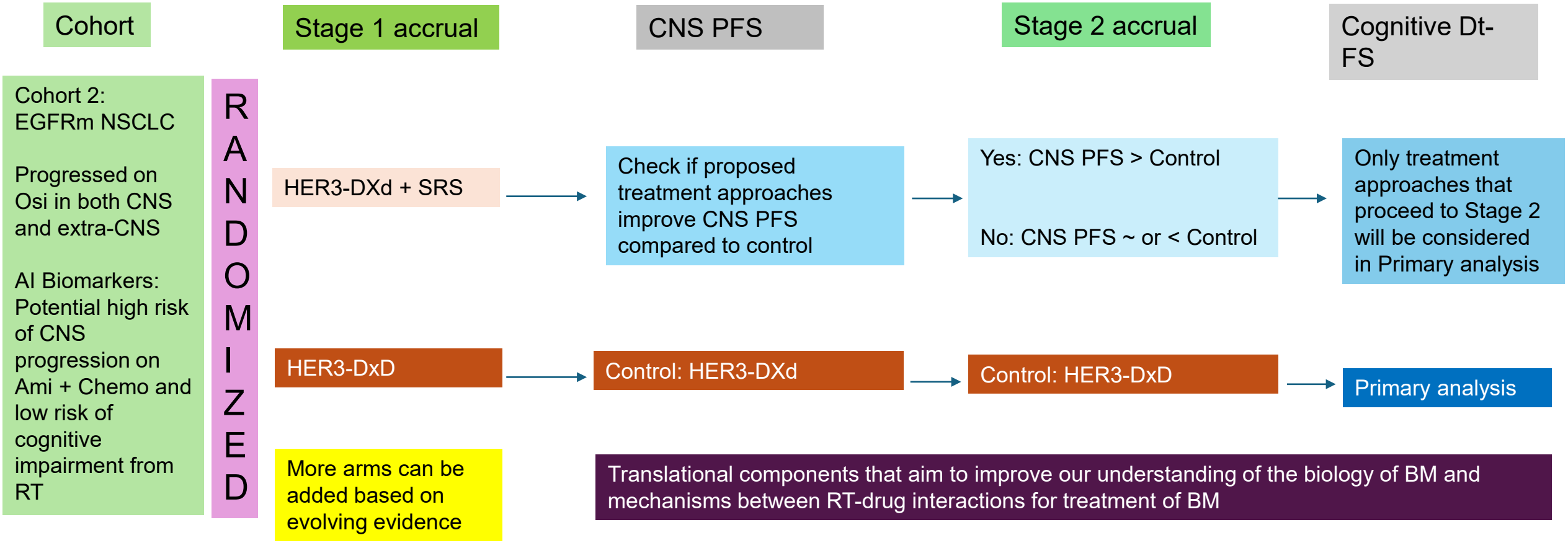
4. Optimize the framework for the design and conduct of brain metastases specific trials

A Hypothetical Future BM Trial



4. Optimize the framework for the design and conduct of brain metastases specific trials

A Hypothetical Future BM Trial



Take Home Messages

Rapid development of CNS active systemic therapies

The next generation of trials for brain metastases will likely

Aim to determine the effects of

AI-based approaches in personalizing brain metastasis-directed treatments on

An Array of standardized disease-related and patient-reported outcomes by

Adopting biomarker-based designs with master protocols and translational components