GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

APPROACH TO PATIENTS WITH NON-ONCOGENE ADDICTED NSCLC & BRAIN METASTASES

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ESMO preceptorship on lung cancer, nov 17-18, Lisbon

DECLARATION OF INTERESTS

Interest	Company/organisation
Grants/research support	Roche, Boehringer Ingelheim, AstraZeneca, Takeda, Merck, Pfizer, Novartis (institution), Gilead under negotiation
Honoraria or consultation fees	Advisory boards (all institution): Amgen, Boehringer Ingelheim, Lilly, Novartis, Pfizer, Takeda, Merck, Janssen, MSD, Anheart
Participation in a company sponsored bureau	Not applicable
Stock shareholder	Not applicable
Spouse/partner	Not applicable
Other support/potential conflict of interest	Speaker educationals/webinars: AstraZeneca, Bayer, Lilly, MSD, high5oncology, Takeda, Janssen, GSK, Sanofi, Pfizer (Inst), Medtalks, Benecke, VJOncology, Medimix (self) Member guideline committees: Dutch guidelines on NSCLC, brain metastases and leptomeningeal metastases (self), ESMO guidelines on metastatic NSCLC and SCLC (non-financial) Local PI pharma studies (Inst): MSD, AstraZeneca, GSK, Novartis, Merck, Roche, Takeda, Blueprint, Mirati, Abbvie, Gilead, MSD Other (non-financial): secretary NVALT studies foundation, subchair EORTC metastatic NSCLC systemic therapy, vice-chair scientific committee Dutch Thoracic Group

OVERVIEW

History of NSCLC brain metastases (BM)

Things to consider before you start treatment

Local treatment options

Systemic treatment options

Future directions & take home messages

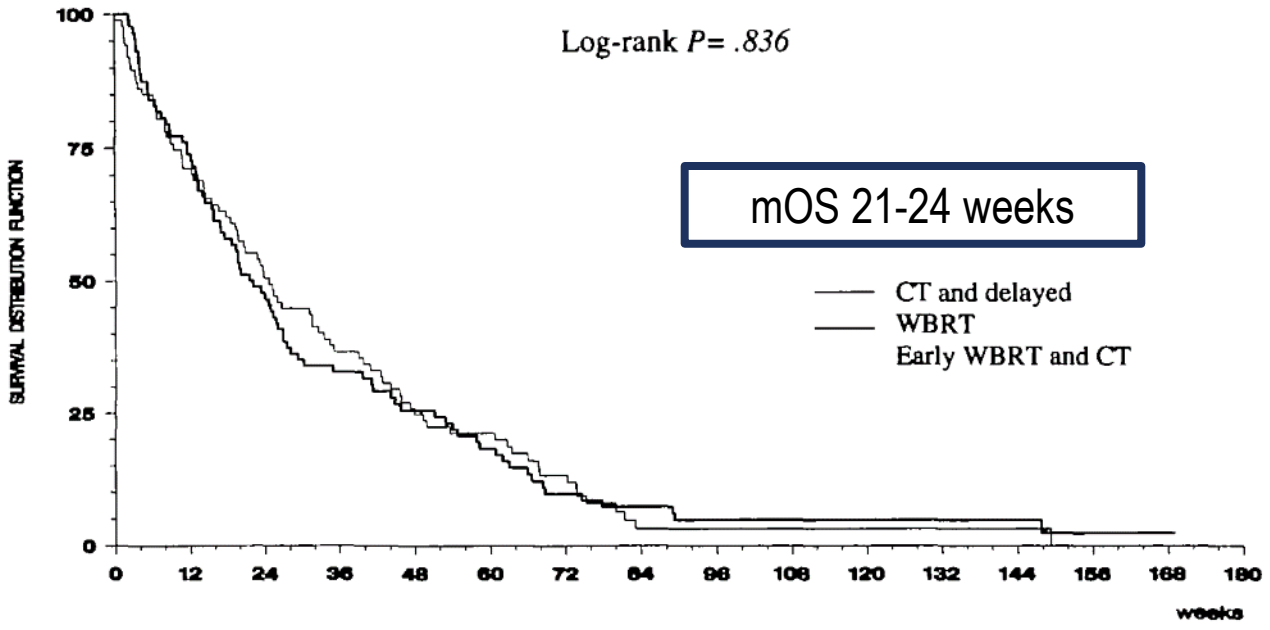
LUNG CANCER BRAIN METS: HISTORICALLY POOR SURVIVAL

N=1888 newly diagnosed BM treated with RTx,1985-2007

Prognostic factor	Ds-GPA Scoring Criteria		
	0	0.5	1
Age (years)	>60	50-60	<50
KPS	<70	70-80	90-100
ECM	+	n/a	-
No. of BM	>3	2-3	1

Total score	NSCLC / SCLC, median OS (months)
0-1.0	3.0 / 2.8
1.5-2.5	6.5 / 5.3
3.0	11.3 / 9.6
3.5-4.0	14.8 / 17.1

Phase III RCT upfront vs delayed WBRT
N= 276 NSCLC, 1995-97



mOS 21-24 weeks

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Sperduto IJROBP 2010; Robinet Ann Oncol 2001

ESMO

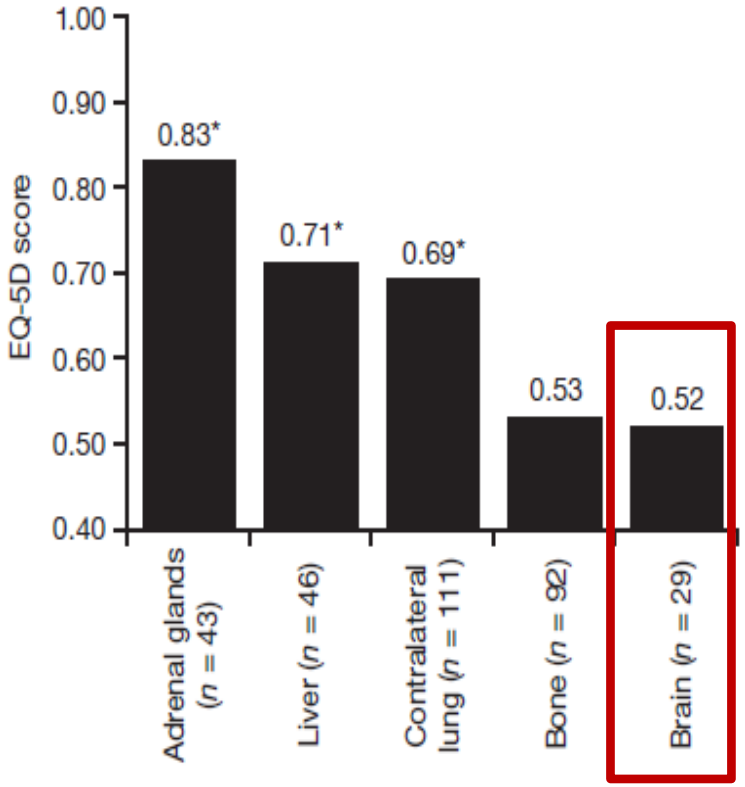
BRAIN METASTASES INCIDENCE IN NSCLC: INCREASING & ASSOCIATED WITH LOW QUALITY OF LIFE

More screening & more MRI

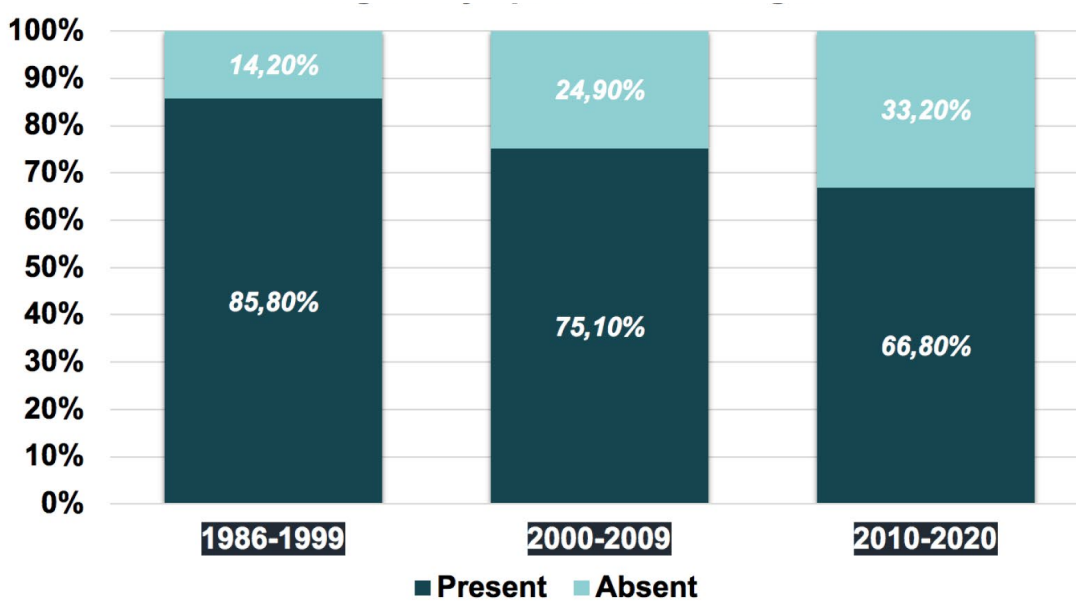
Longer survival -> more time to develop brain metastases (BM)

Prognosis dependent on age, KPS, nr of mets, extracranial disease, oncogenic drivers, possibility systemic therapy

Lower QoL in patients with BM (+ increased healthcare costs)



Also % of patients with asympt BM increasing



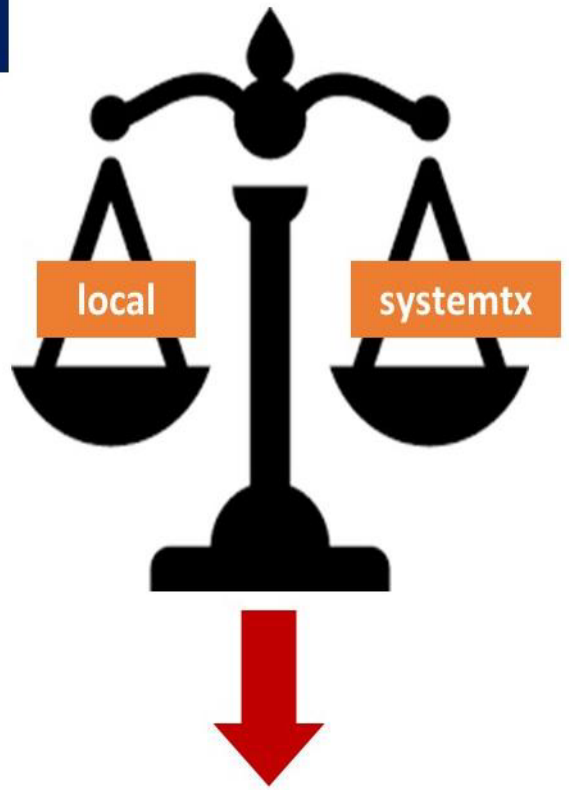
Cohort 6000 patients with BM, 50% lung

Hendriks Ann Oncol 2023; Levy, Hendriks EJC 2018; Steindl ESMO 2020; Peters CRT 2021; sperduto JAMA oncol 2019

TREATMENT GOALS & THINGS TO CONSIDER

Do we need upfront local therapy?

Symptomatic BM?
Risk of (late) toxicity
Need to control extracranial disease

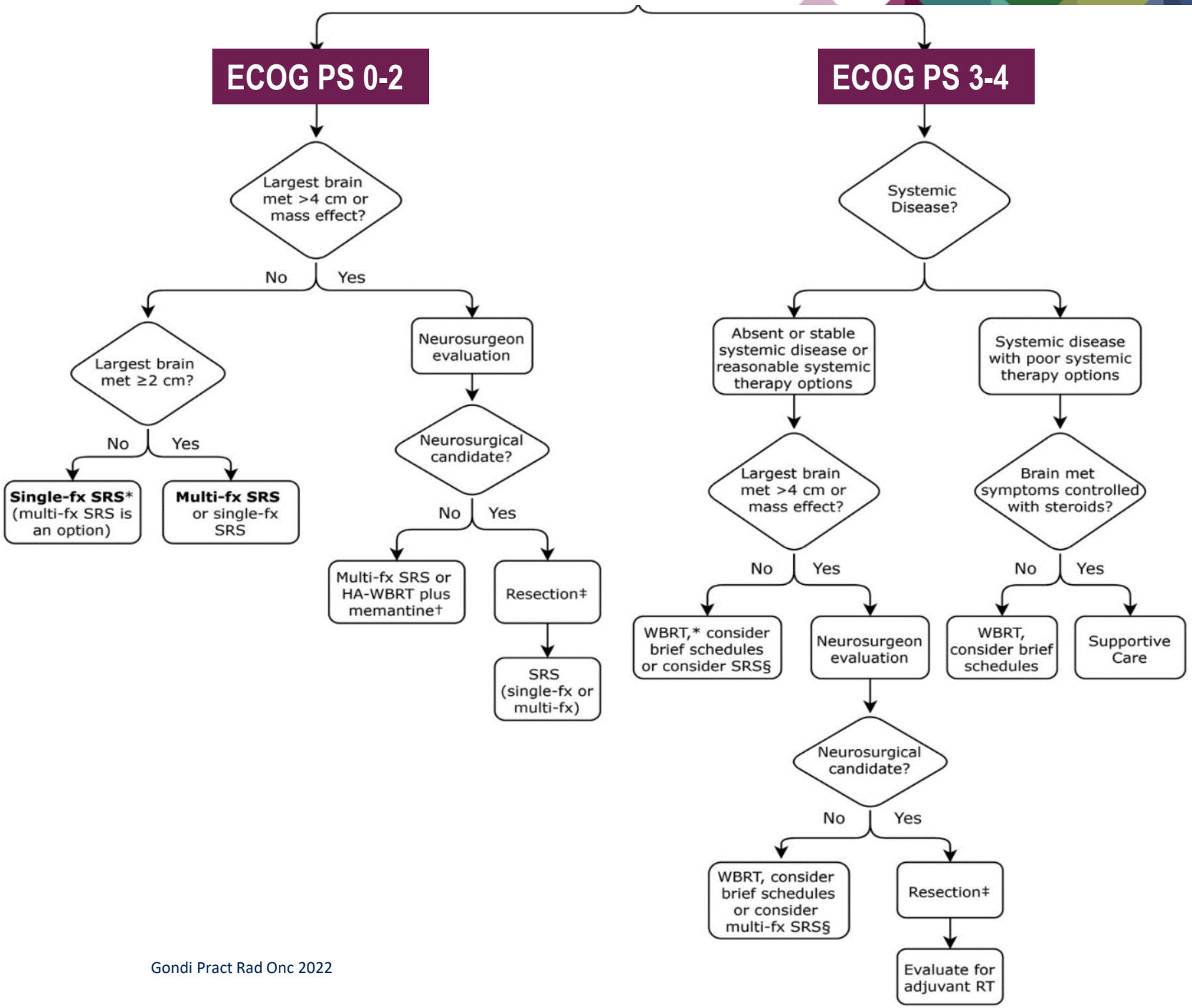


What can we expect from syst tx?

(Intracranial) response rates
Onset of response
Risk pseudoprogression
Risk tox with delayed Rtx

Maintain / improve QoL & improve survival
MULTIDISCIPLINARY TEAM DECISION

LOCAL THERAPY OPTIONS LIMITED BRAIN METS ASTRO GUIDELINE



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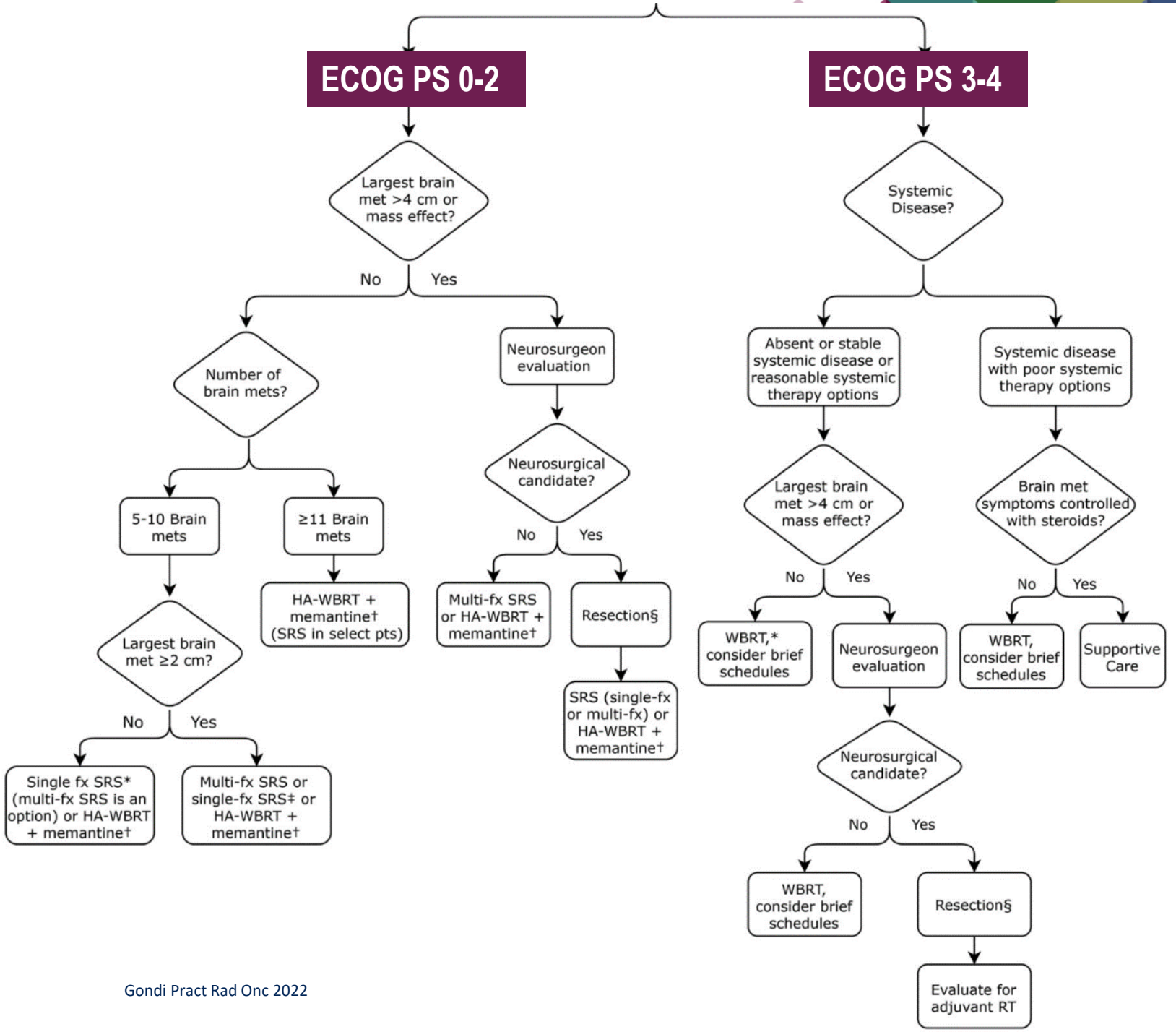
Gondi Pract Rad Onc 2022

LOCAL THERAPY OPTION
EXTENSIVE BRAIN METS
ASTRO GUIDELINE



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SURGERY

Advantages of surgical management

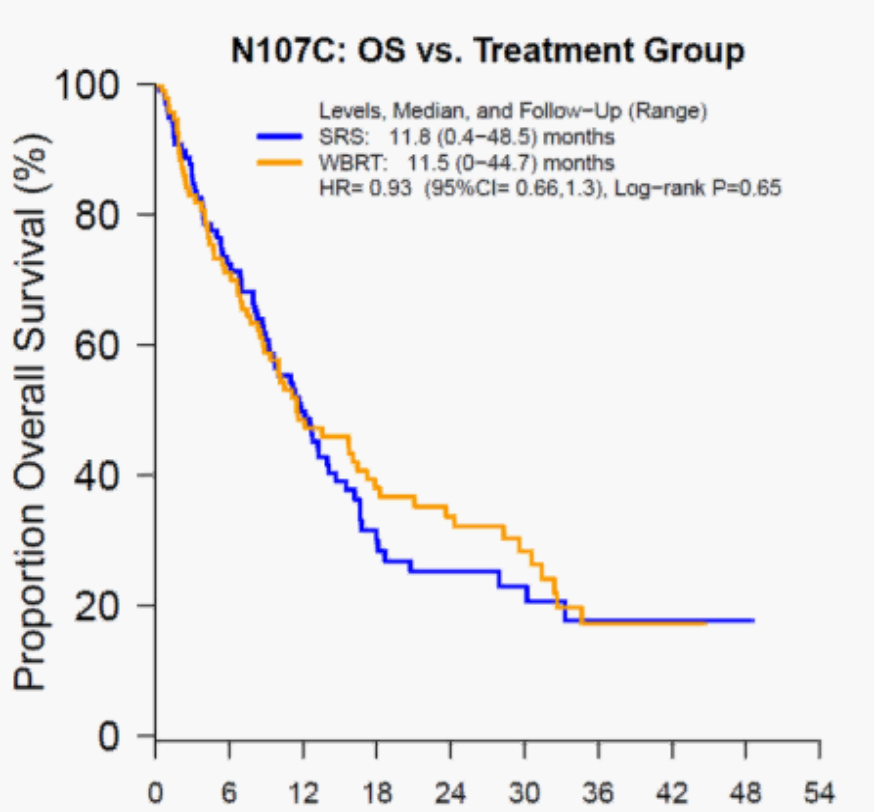
- Fastest option for return of neurological function
- Best option for control of seizures
- Allows access to brain metastasis tissue
- Surgery as a bridge to immunotherapy

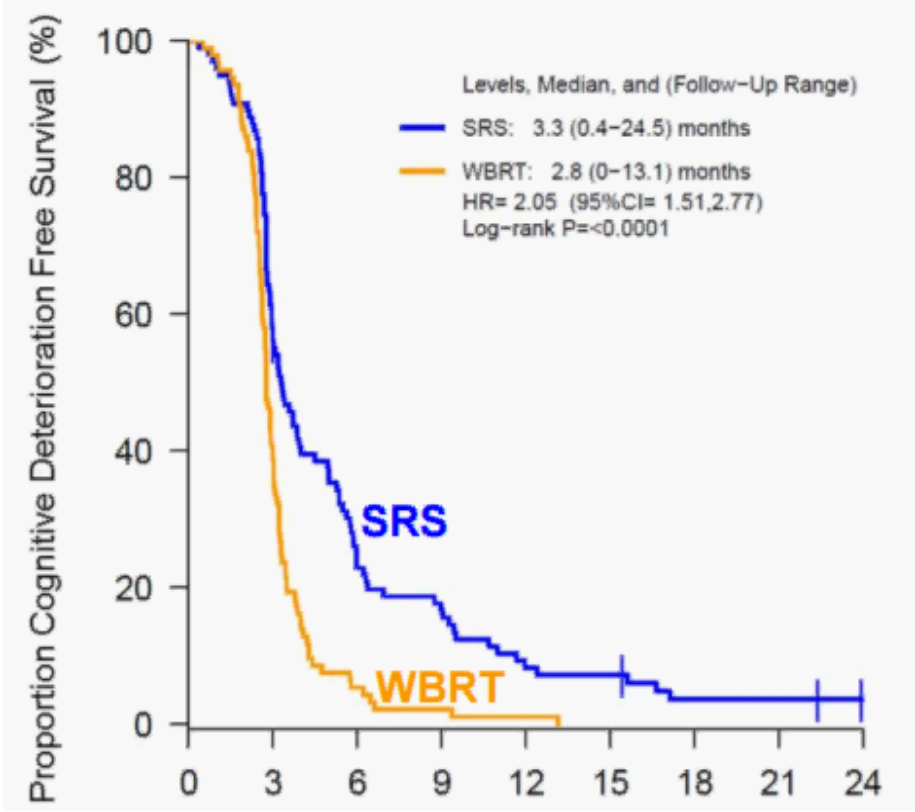
Disadvantages of surgery

- Risks from craniotomy and anesthesia
- 7-28% reported rates of downstream leptomeningeal disease (LMD)

POSTOPERATIVE RADIOTHERAPY: WBRT OR SRS?

With limited intracranial mets, postop single-fraction SRS offers similar OS but improved cognitive outcomes vs. conventional WBRT





Brown Lancet Oncol 2017

SRT ALSO POSSIBLE FOR MULTIPLE BRAIN METS

Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

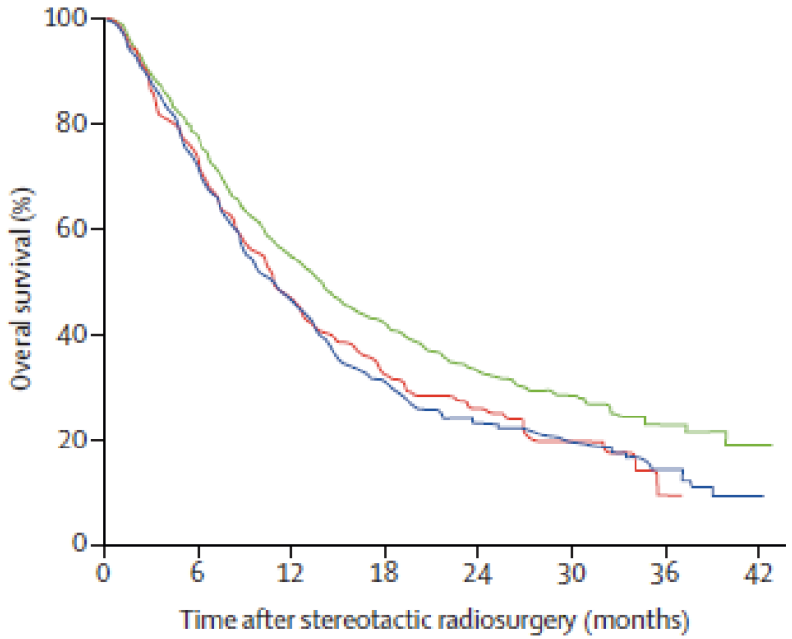
Masaaki Yamamoto, Toru Serizawa*, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo, Yasuhiro Kikuchi, Toru Shibasaki, Tomoaki Goto, Masami Takanashi, Yoshimasa Mori, Kintomo Takakura, Naokatsu Saeki, Etsuo Kunieda, Hidefumi Aoyama, Suketaka Momoshima, Kazuhiro Tsuchiya*

Summary

Background We aimed to examine whether stereotactic radiosurgery without whole-brain radiotherapy (WBRT) as the initial treatment for patients with five to ten brain metastases is non-inferior to that for patients with two to four brain metastases in terms of overall survival.

Lancet Oncol 2014
Published Online
March 10, 2014
http://dx.doi.org/10.1016/

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



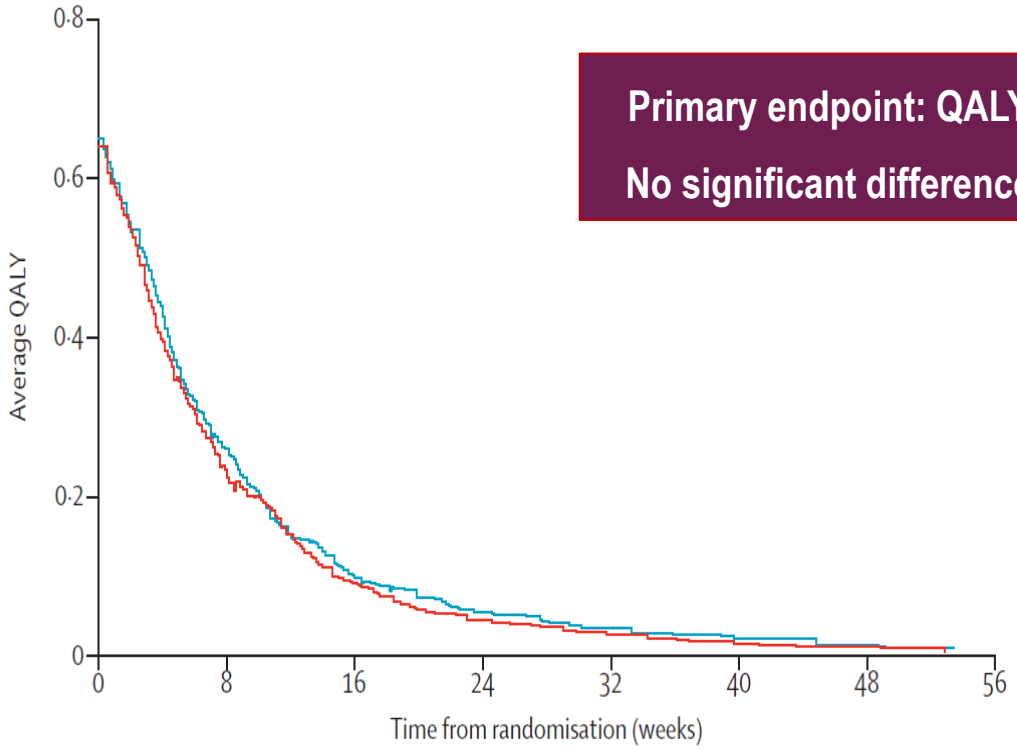
Number at risk

1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

WHY ARE WE RELUCTANT TO PROPOSE WBRT?

Risk of cognitive ↓ after WBRT
Are these values clinically relevant?

Phase III QUARTZ: non-inferiority, NSCLC with BM not eligible for surgery/SRT, WBRT + optimal supportive care (OSC) vs OSC N = 538, KPS < 70: 38%

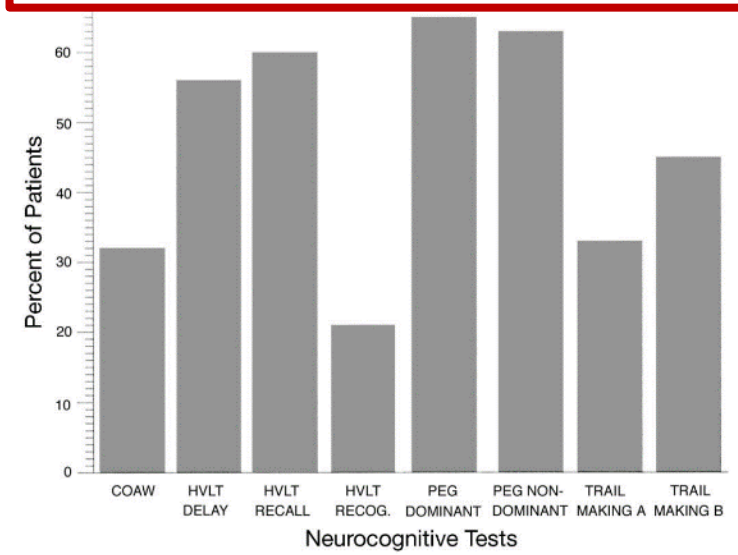


Primary endpoint: QALY

No significant difference

Week 24
- HVLT-R Total Recall
- HVLT-R Delayed Recall
- HVLT-R Delayed Recognition
- TMT-A
- TMT-B
- COWA
- CTB Composite

Be aware: several patients already have baseline impairment before WBRT



Mulvenna Lancet 2016; Brown Neuro-Oncol 2013; Mehta JCO 2003

STRATEGIES FOR SAFER WBRT

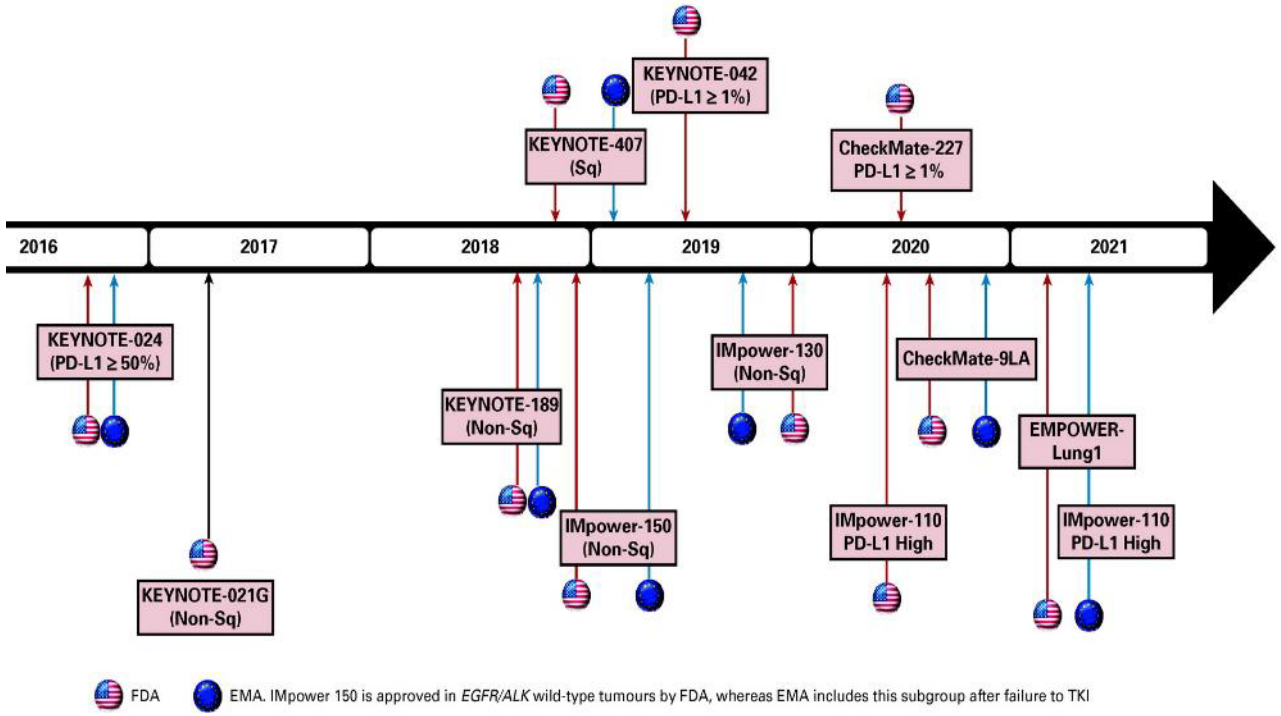
Strategy	Trial	Phase	N	Treatment	Outcome
Memantine added to WBRT	NCT00566852 RTOG 0614	III, Double blind, placebo controlled	508 70% NSCLC	WBRT vs **memantine + WBRT**	Primary endpoint: HVLT Delayed Recall decline Median decline 0 (WBRT + mem) vs -0.90 (WBRT), P=0.059 **Neurocognitive deterioration: 22% relative reduction**
HA during WBRT	NCT01227954 RTOG 0933	II, Single arm	100 56% NSCLC	**HA-WBRT**	Primary endpoint: HVLT-R Delayed Recall decline **7% decline for HA-WBRT** vs. Historical control 30% decline
HA during WBRT	NCT02393131 Taiwanese trial	Randomized II, blind	70 94% NSCLC	WBRT vs **HA-WBRT**	Primary endpoint: HVLT-R Delayed Recall change **8.8% improvement (HA-WBRT) vs.** 3.8% decline (WBRT)
HA added to memantine during WBRT	NCT02360215 NRG CC001	III	518 60% NSCLC	WBRT+mem vs. **HA-WBRT+memantine**	Primary endpoint: Neurocognitive deterioration **26% relative reduction** QoL: Less neurologic symptom burden and interference at 6+12 months and fewer cognitive symptoms over time

Gondi JCO 2014; Brown Neuro Oncol 2013; Brown JCO 2020; Gondi IJROBP In Press

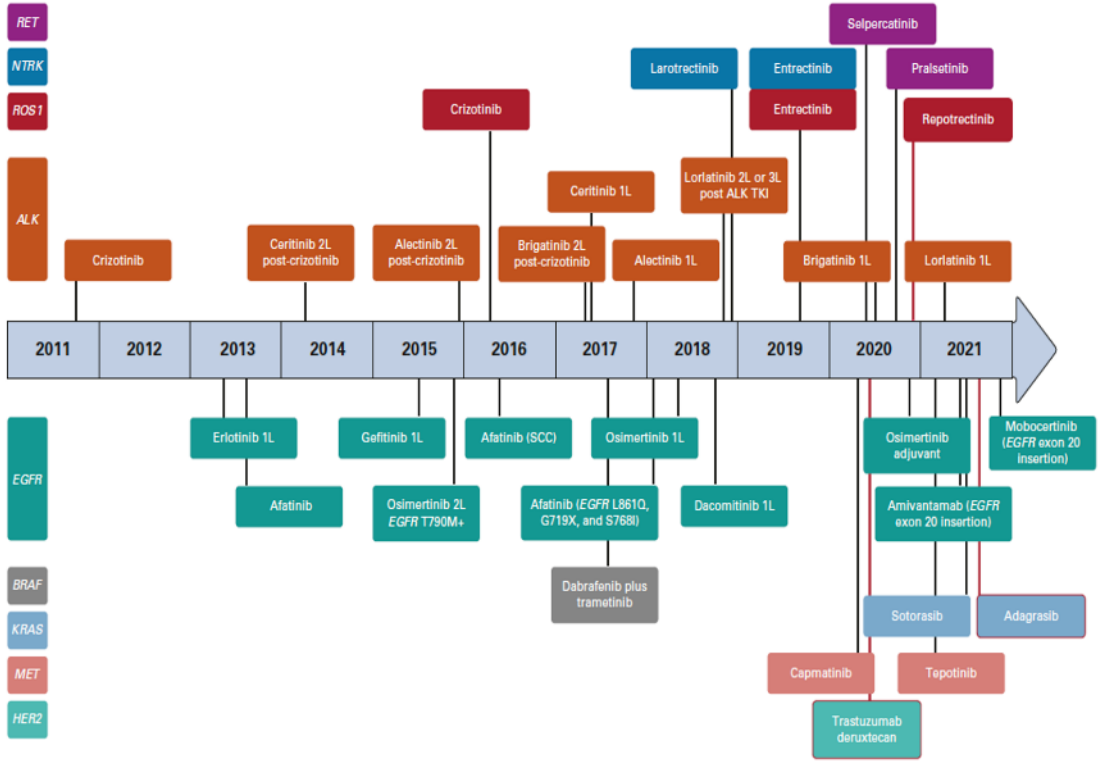
WE HAVE MADE A HUGE PROGRESS IN SYSTEMIC THERAPIES FOR NSCLC

Long-term survival reality for subset of patients

Patients w/o targetable oncogenic driver: ICI mono or chemo-ICI-(ICI) SoC 1st line

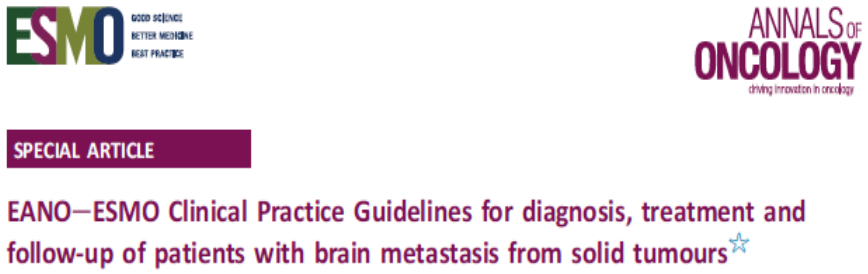


Patients with targetable oncogenic driver: Targeted therapy SoC 1st line (or beyond)



Reck JCO 2022 – Tan JCO 2022

CURRENTLY RECOMMENDED TREATMENT OPTIONS FOR PATIENTS WITH BRAIN METS



Asympt or oligosympt NSCLC BM

Oncogenic driver:

- **CNS penetrating TKI [ESMO: III, B]**

No actionable oncogenic driver

- **PD-L1 ≥ 50%: upfront ICI alone**
- **PD-L1 < 50%: ChT-ICI [ESMO: III, B]**

SCLC

- **Chemo-ICI can be used**

Evidently symptomatic = local treatment
SRS for 1-4 mets or low volume 5-10 mets

Asympt NSCLC BM

EGFR/ALK:

- **CNS penetrating TKI [LoE: low, SoR weak]**

Other drivers: No recommendation

If no driver:

- **Pembro-ChT option [LoE: low, SoR weak]**

SCLC:

- **Not specified**

Symptomatic = local treatment
Do not defer local treatment unless specific recommendation
SRS for 1-4 mets, SCLC always WBRT

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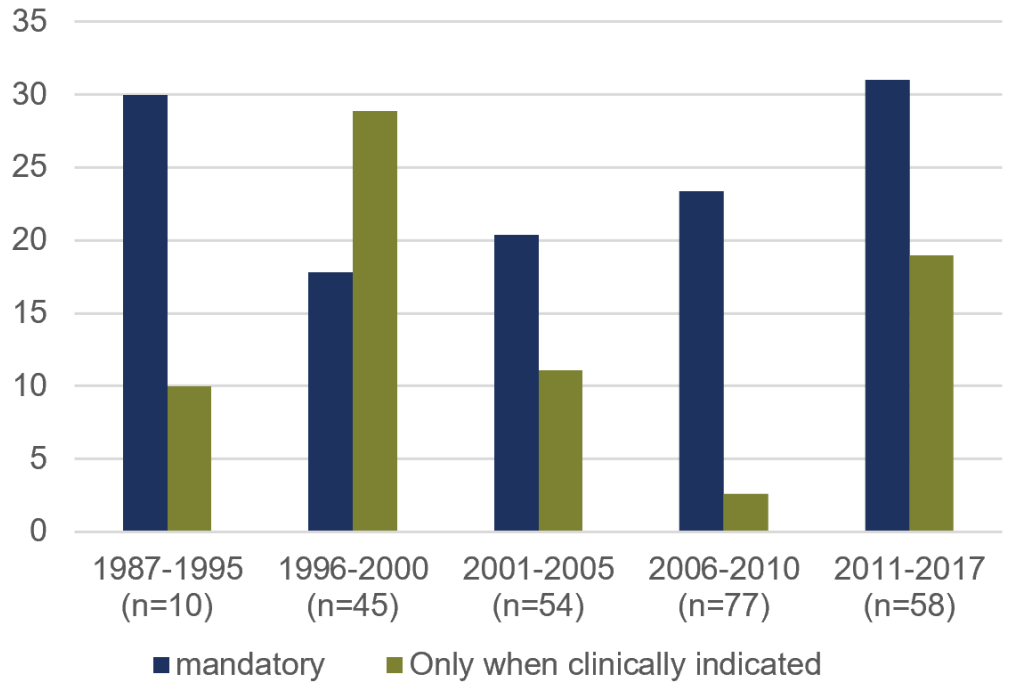
Vogelbaum JCO 2021; Le Rhun Ann Oncol 2021

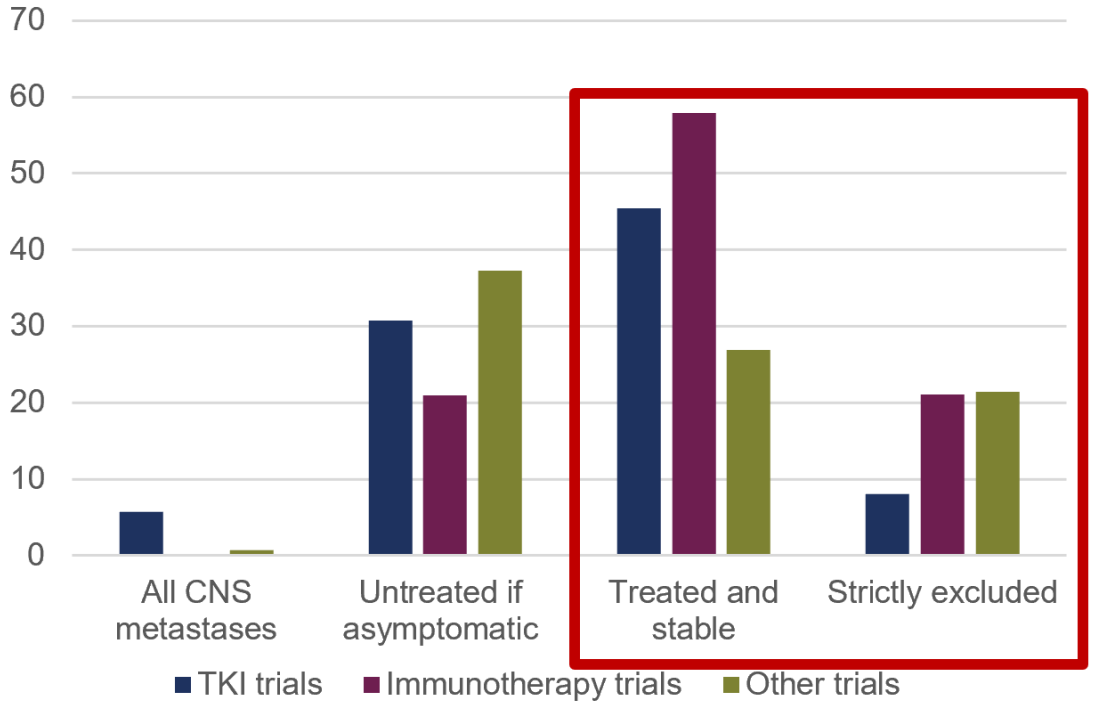
EVIDENCE BEHIND TREATMENT RECOMMENDATIONS

Systematic review on NSCLC BM in phase II/III TKI or phase III ICI trials (2000-2020)

Baseline screening for CNS mets over time



CNS eligibility criteria per type of drug

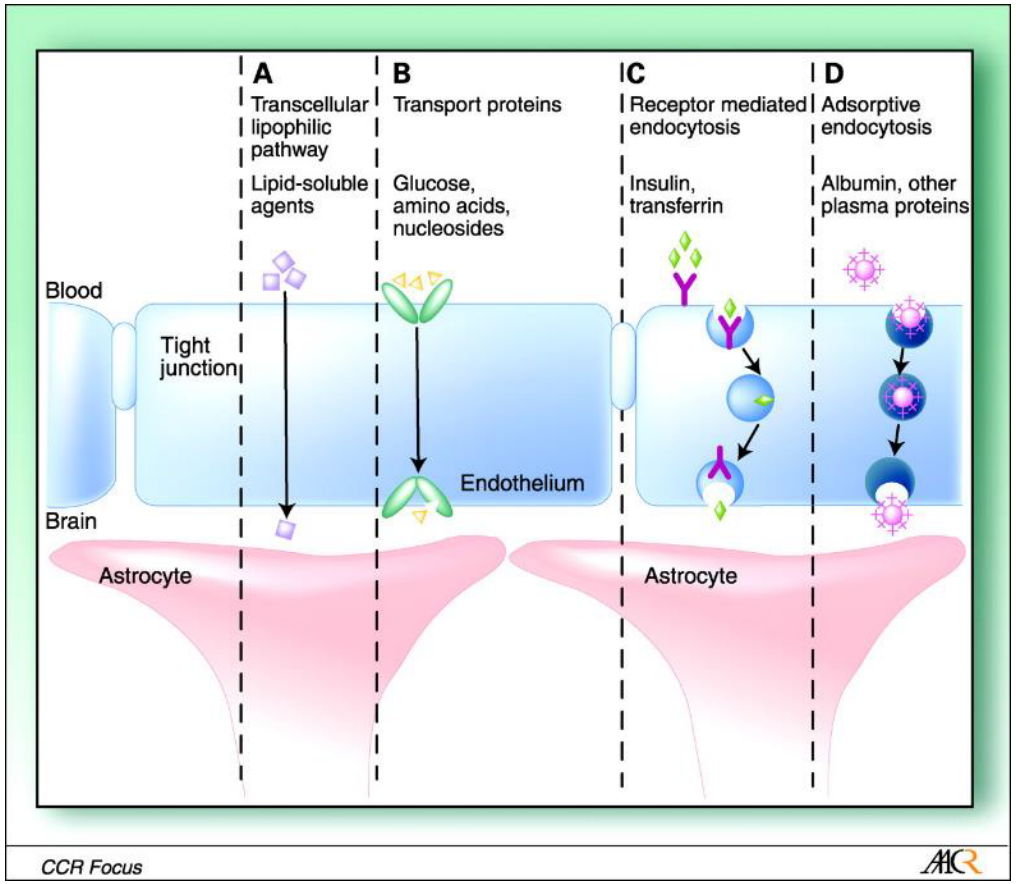


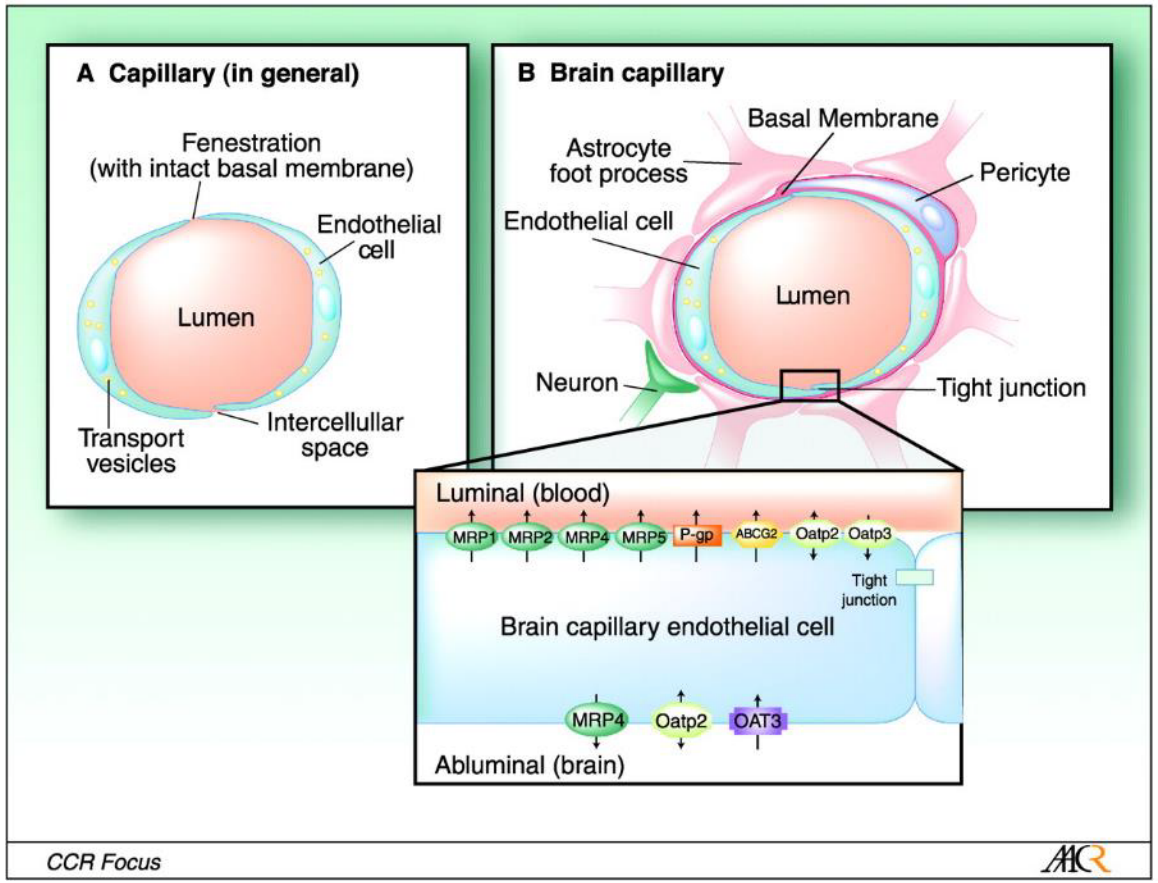
Only 4% prespecified CNS related endpoint

Schoenmaekers & Hendriks CROH 2021

THE BLOOD BRAIN BARRIER

Limiting step for chemo and immunotherapy?





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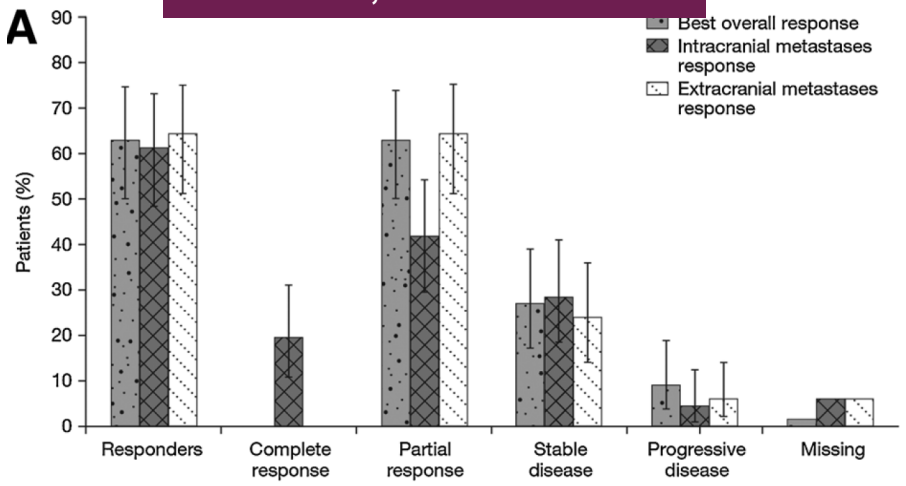
Deeken CCR 2007

CHEMOTHERAPY DATA

Author (Ref.)	*N*	Tumor type	Prior treatment	Treatment	Brain RR (%)	MST (months)
Cortes et al. [19]	26	NSCLC	No	Cisplatin/paclitaxel/vinorelbine or gemcitabine	38	5
Fujita et al. [21]	30	NSCLC	No	Cisplatin/ifosfamide/irinotecan	50	12.7
Cotto et al. [23]	31	NSCLC	No	Cisplatin/fotemustine	23	4
Minotti et al. [20]	23	NSCLC	No	Cisplatin/teniposide	35	5
Bernardo et al. [24]	22	NSCLC	No	Carboplatin/vinorelbine/gemcitabine	45	7
Franciosi et al. [22]	43	NSCLC	No	Cisplatin/etoposide	37	8
Robinet et al. [25]	76	NSCLC	No	Cisplatin/vinorelbine	27	NA
Barlesi et al. [26]	43	NSCLC	No	Cisplatin/pemetrexed	41.9	7.4
Bailon et al. [27]	26	NSCLC	No	Carboplatin/pemetrexed	30	9.1

ORR 61%, mOS 16 months

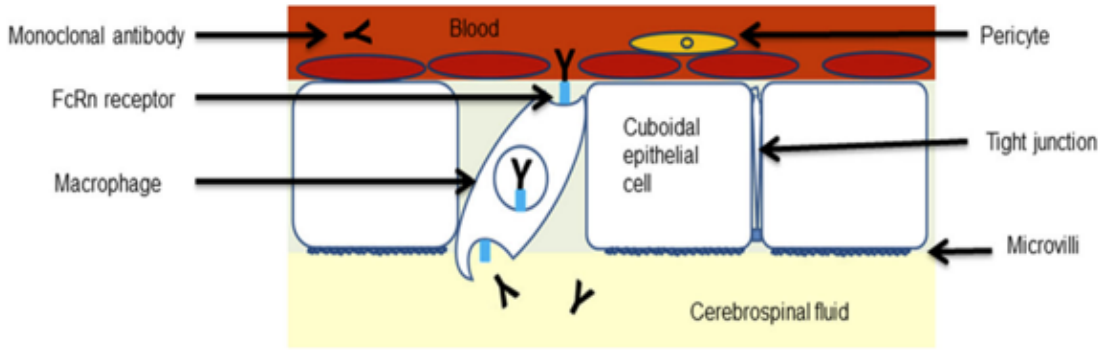


N=67 non-sq, asympt untreated BM, 1st line carbo/paclitaxel/beva

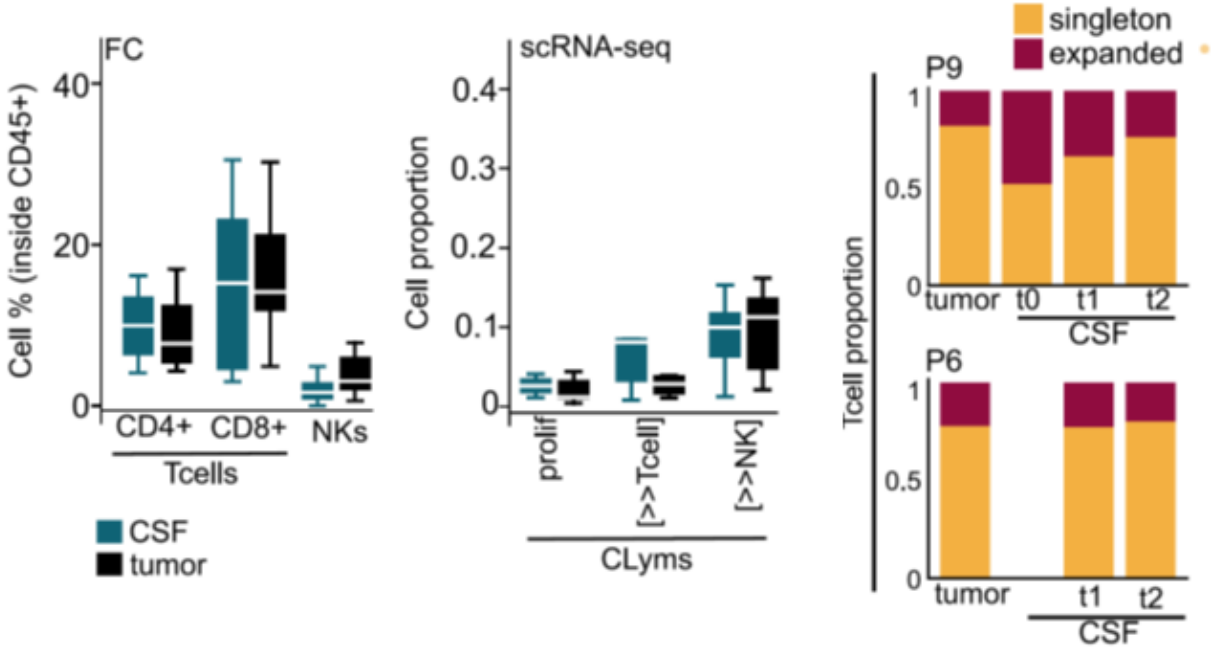
Zimmermann CTR 2014; Besse CTR 2015

IMMUNOTHERAPY AND IMMUNE CELLS CAN CROSS THE BLOOD-BRAIN-BARRIER

ICI can cross BBB CSF serum ratio 0.88-1.9%

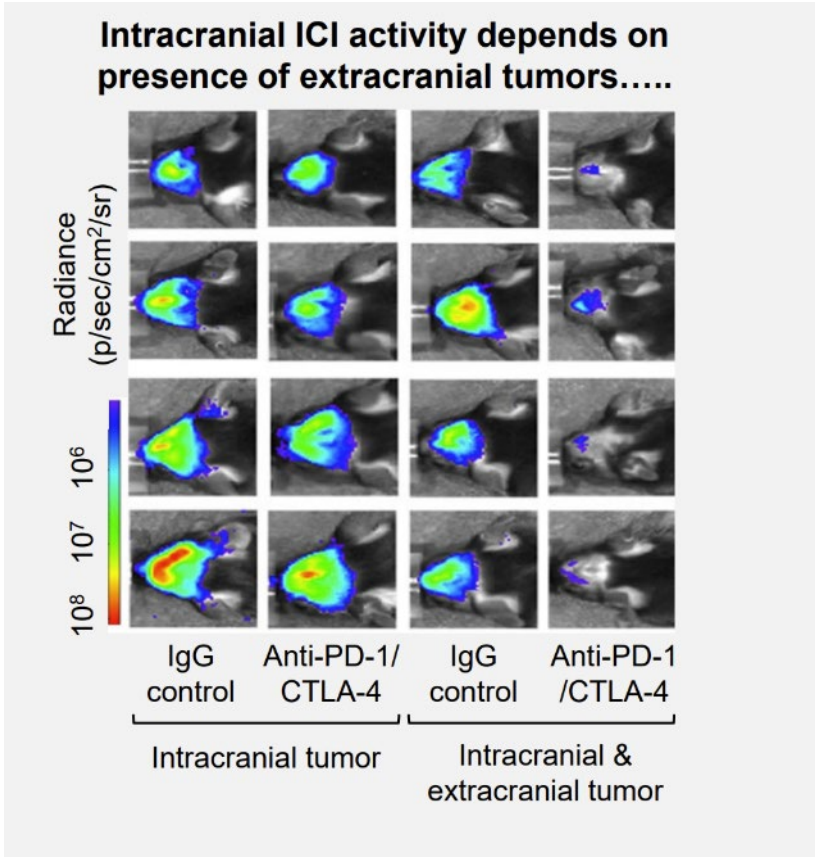


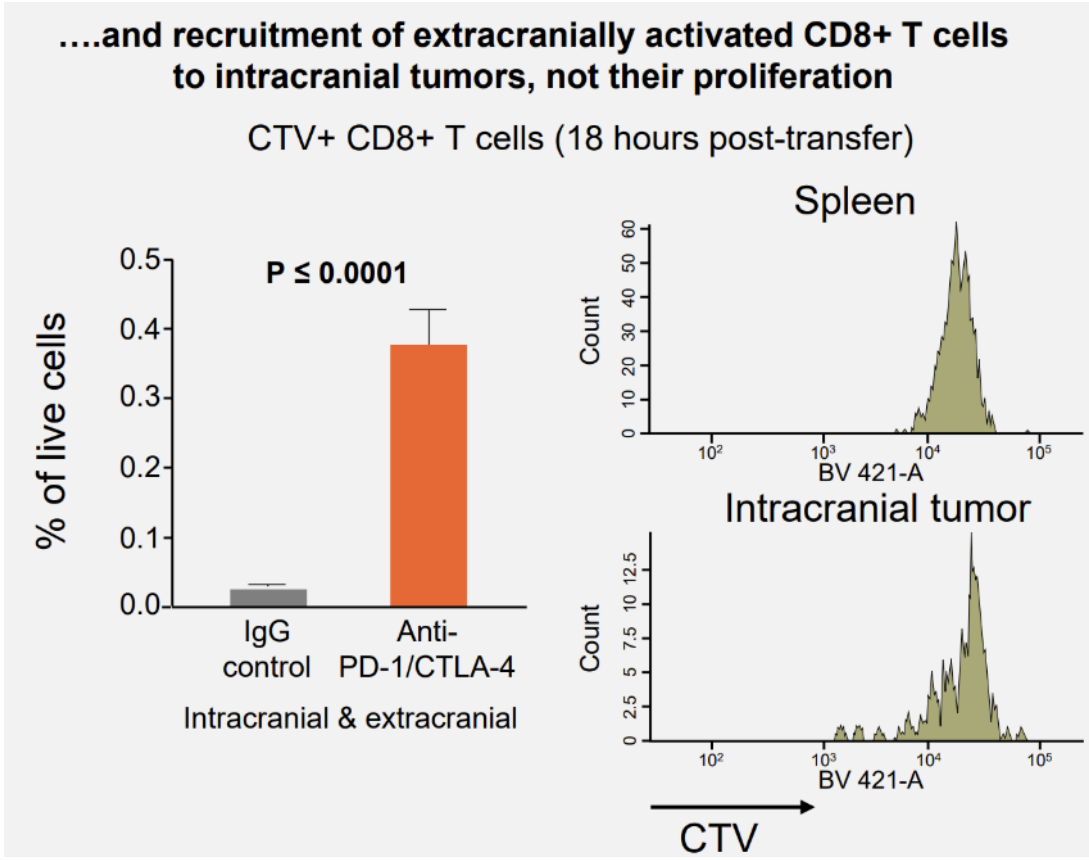
Immune cells present in CSF and brain mets



Reviewed in van Bussel BMC Cancer 2019; Rubio-Perez Nature Comm 2021; Pluim J Pharm Biomed Anal 2018

ICI INTRACRANIAL ACTIVITY IS MEDIATED BY PERIPHERAL T CELL ACTIVATION & EXPANSION

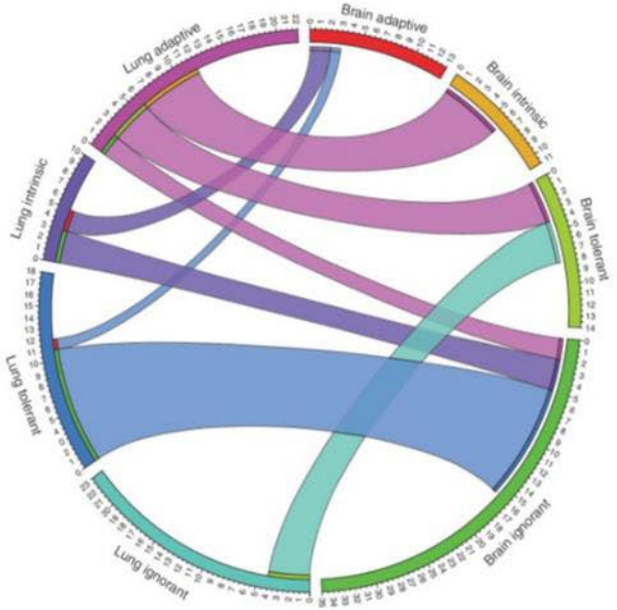




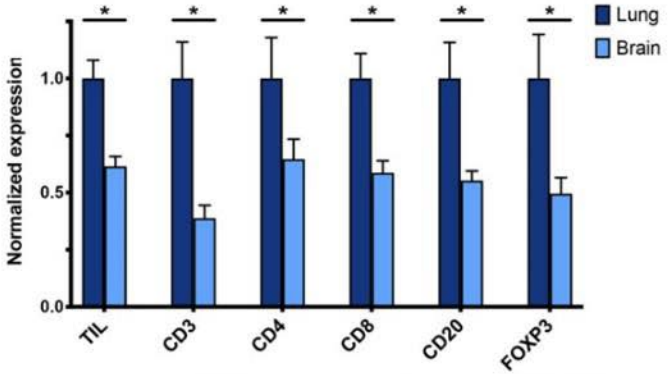
Taggart PNAS 2018

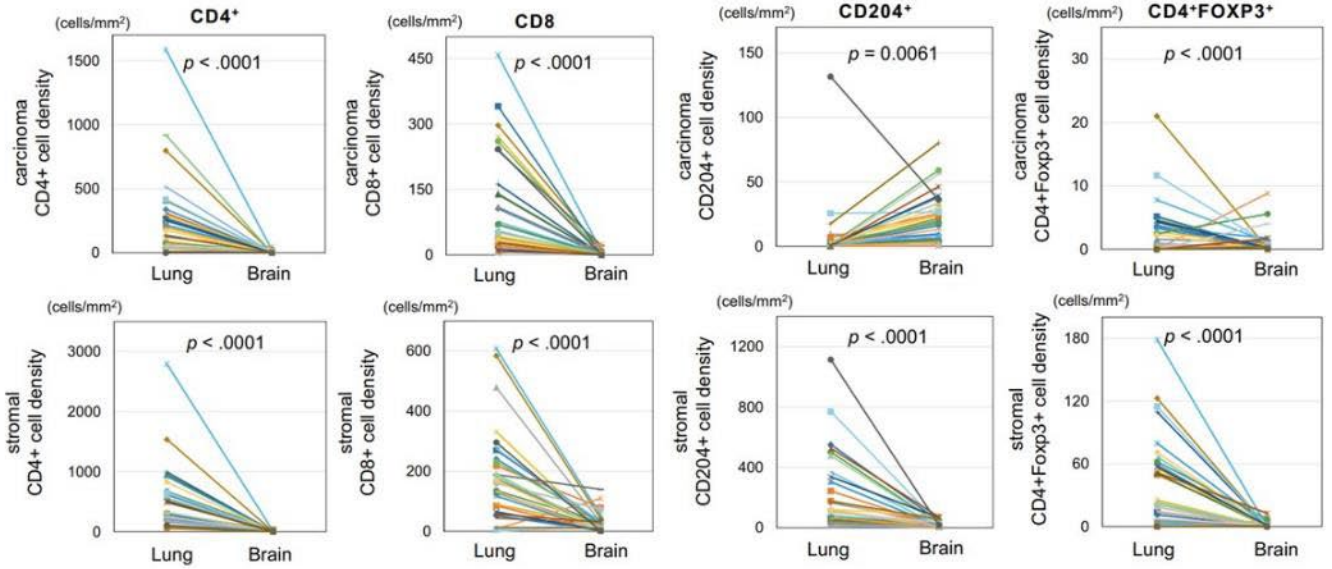
NSCLC BRAIN METS IMMUNE ENVIRONMENT

BM vs primary: ↓ T-cell clonality & ↑ immune ignorant



BM vs primary: ↑ immunosuppressive





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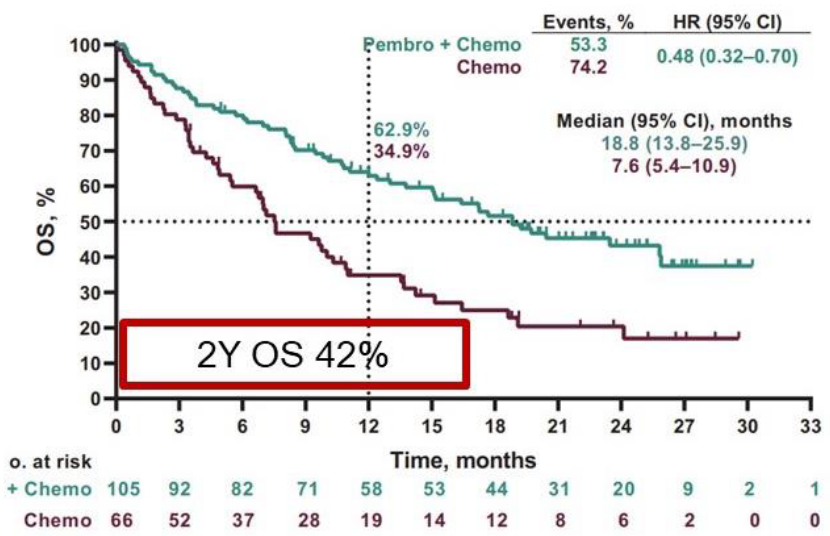
Mansfield Sci Rep 2018 Ikarashi JTO CCR 2021; Lu JITC 2021

CHEMO-ICI-(ICI) & ICI-ICI DATA – MAINLY TREATED BRAIN METS

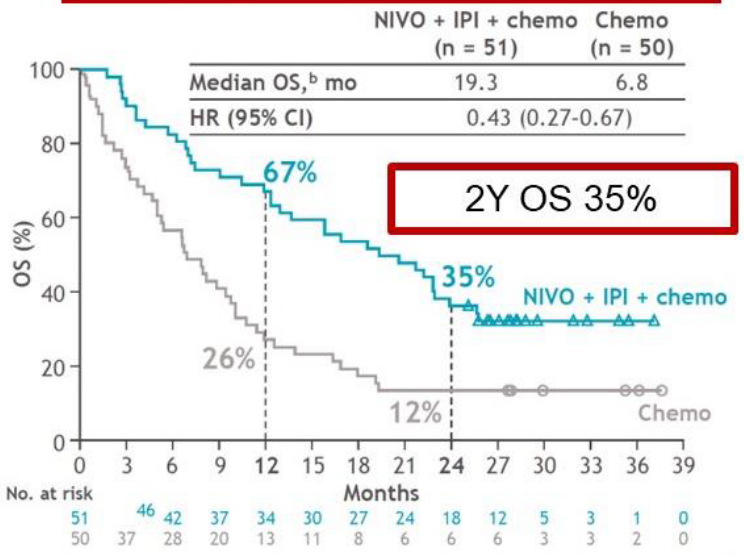
TREATED & UNTREATED BM

KEYNOTE 021-189-407 pooled Chemo-ICI vs chemo



TREATED BM

CheckMate 9LA Chemo-ICI-ICI vs chemo

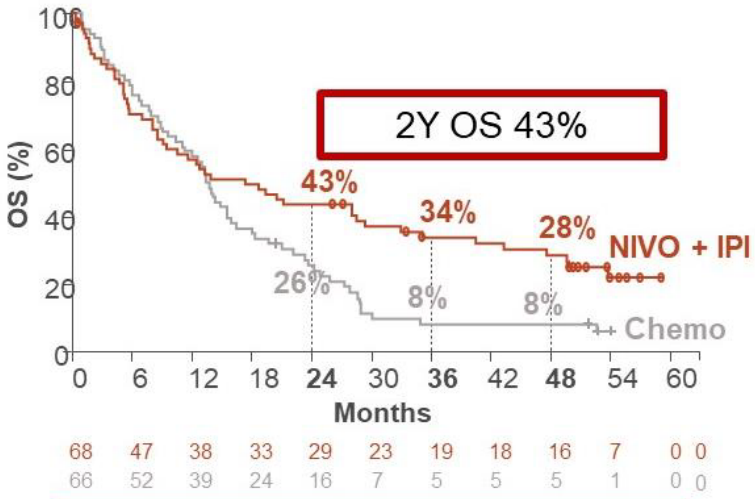


IcPFS 13.5 vs 4.6 months (HR 0.36)

New BM 16% vs 30%

Time to new BM 9.0 vs 4.6 months

CheckMate 227 ICI-ICI vs chemo



icPFS 8.6 vs 8.7 months (HR 0.80)

New BM 4% vs 20%

Time to new BM 4.0 vs 7.1 months

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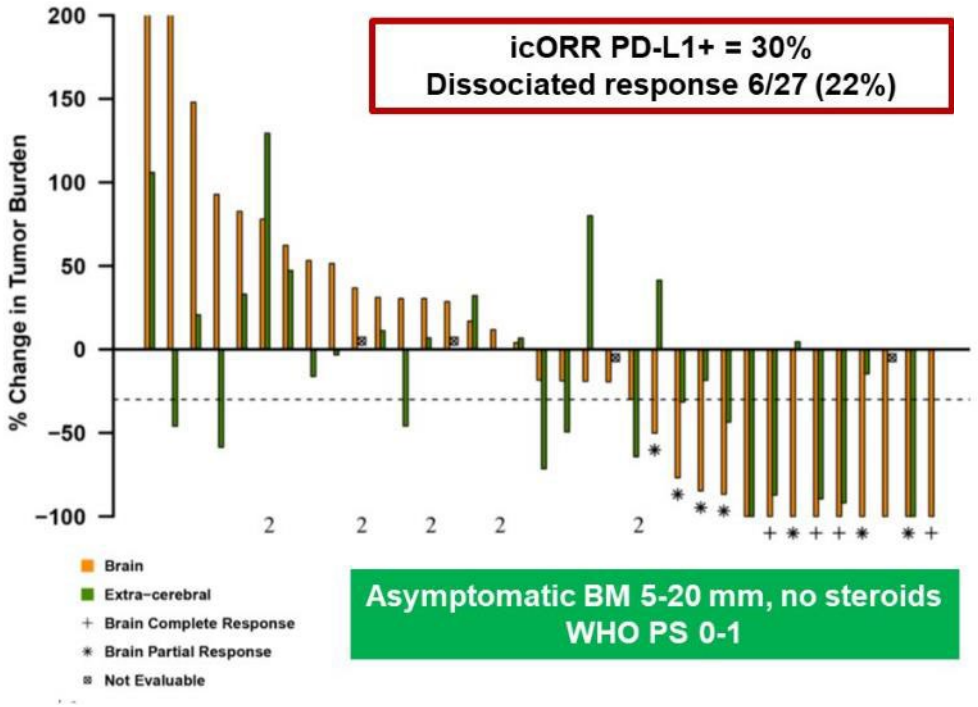
Powell JTO 2021; Carbone WCLC 2021; Reck ESMO IO 2021

IMMUNOTHERAPY TRIAL DATA FOR UNTREATED BRAIN METS

Monotx pembro N = 42 (37 PD-L1+)



icORR PD-L1+ = 30%
Dissociated response 6/27 (22%)

Asymptomatic BM 5-20 mm, no steroids
WHO PS 0-1

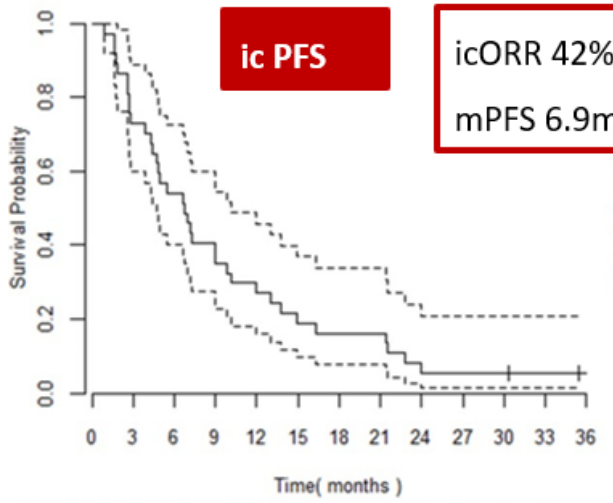
Atezo-chemo N=40, 55% baseline steroids

Key Elegibility Criteria:
Stage IV non-squamous NSCLC
Untreated brain metastases
Treatment naïve
EGFR/ALK negative, any PD-L1
ECOG PS 0-1
Anticonvulsivants and dexamethasone ≤ 4 mg qd allowed
Measurable systemic and brain lesion/s

Carboplatin (5 AUCs) + Pemetrexed 500mg/m² + Atezolizumab 1200mg Q3W for 4-6 cycles → **Pemetrexed 500mg/m2 + Atezolizumab 1200mg Q3W until tumor progression (*), unacceptable toxicity or 2 years**

Tumor evaluation by body CT scan and brain MRI Q6W until the 12th week and thereafter Q9W until PD

(*) If exclusive CNS PD, patients could continue on study after brain RT



ic PFS

icORR 42%

mPFS 6.9m (4.7-11.9)

2y OS rate 28%

OS ↑ if PD-L1+/no steroids

Nadal ASC

Goldberg Lancet Oncol 2020; Nadal JCO2023; Hou JTO 2023

HOW TO IMPROVE? – FUTURE DIRECTIONS

ONGOING PHASE II/III TRIALS FOR NSCLC & UNTREATED ASYMPT BM

Evaluating systemic treatment strategies

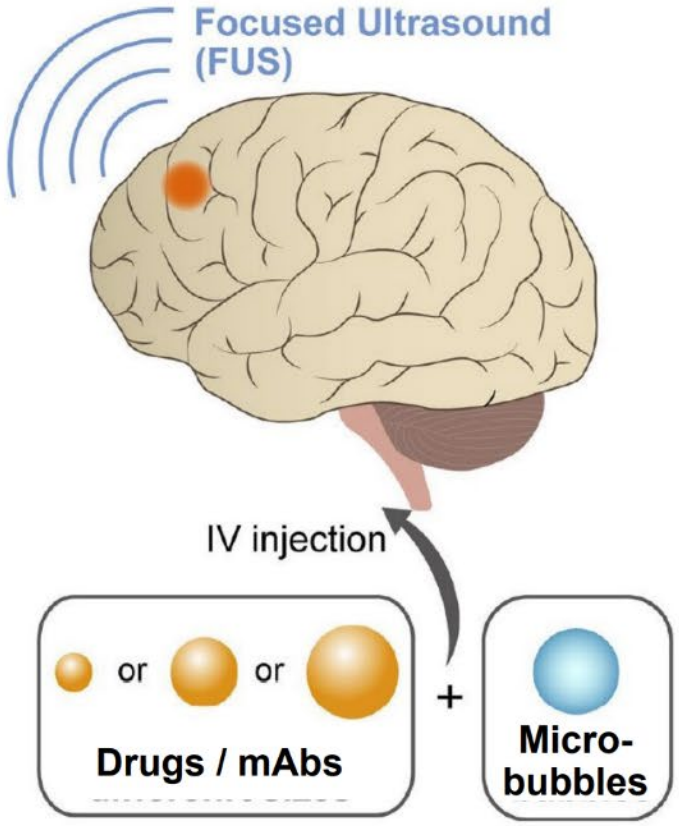
Approach	Region	Study	Enrollment[b]	Treatment(s)	Primary EP	(Other) CNS EPs
ICI	USA	NCT05840770	34	Cemiplimab (NSCLC PD-L1 ≥50%)	**iCBR** (RANO-BM)	**CNS-TTP** (RANO-BM), **TT-WBRT/SRS, TT-Brain met mortality**
ICI + chemo	USA	NCT05746481	35	Atezolizumab + tiragolumab + carboplatin + pemetrexed	**Rate of CNS salvage RT**	**iORR** (RANO-BM)
	Spain	NCT05012254 (NIVIPI-Brain) cohort A	71[b]	Nivolumab + ipilimumab + platinum-based chemo → nivolumab + ipilimumab	**iCBR** (RANO-BM)	**iORR, iPFS** (RANO-BM)
	USA	NCT04964960	45	Pembrolizumab + chemo	**iCBR**	**Cognitive functioning** (FACT-Cog)
ICI + VEGFi	USA	NCT02681549	53	Pembrolizumab + bevacizumab	**iORR** (mRECIST)	**iPFS** (mRECIST), **Steroid use for cerebral edema**
	China	NCT05807893 (SUPER BRAIN)	30	Serplulimab + beva + chemo → serplulimab + beva + pemetrexed	**iPFS**	**iORR**

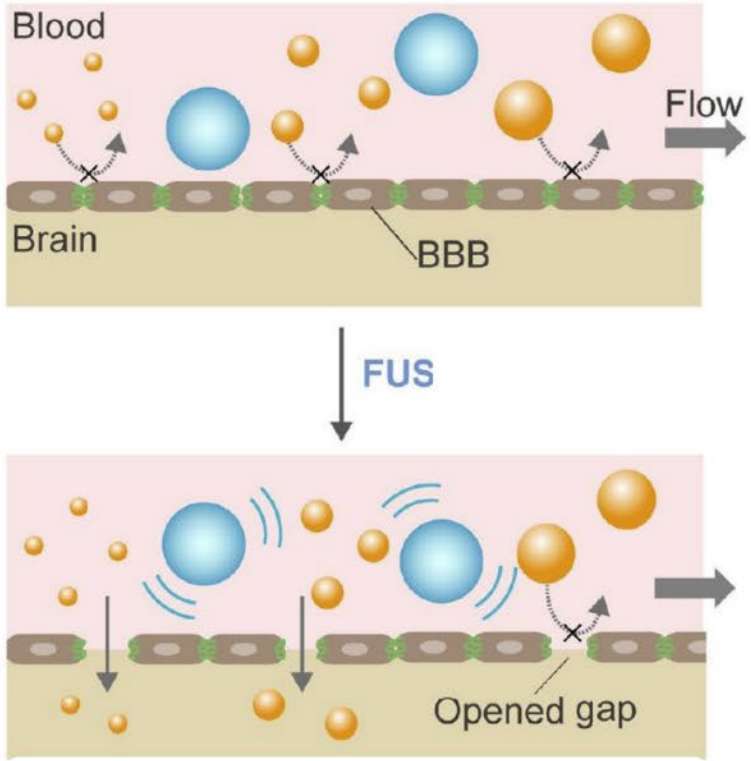
ONGOING PHASE II/III TRIALS FOR NSCLC & UNTREATED ASYMPT BM

Combining systemic therapy & local therapy

Approach	Region	Study	Enrollment[b]	Treatment(s)	Primary EP	(Other) CNS EPs
ICI + RT	Canada	NCT02978404 NSCLC cohort	26	Nivolumab + SRS	**iPFS** (RECIST 1.1)	**iCBR,** (RECIST 1.1), **Neurocognitive function** (HVLT-R, TMT, COWA)
	Europe	NCT05522660 (USZ-STRIKE) cohort 2B	190	Anti-PD-(L)1 ± chemo vs Anti-PD-(L)1 ± chemo + SRS	**CNS-PFS** (iRANO)	–
	Global	NCT02831959	270	Anti-PD-(L)1 + SRS vs Anti-PD-(L)1 + SRS → TTFields	**iTTP**	**iORR,** **TT-Neurocognitive failure** (HVLT-R, TMT, COWA)
ICI + FUS	USA & Canada	NCT05317858	20	Pembrolizumab vs Pembrolizumab + Exablate FUS	ORR, AEs	**CNS-ORR, CNS-TTR** (RANO-BM)

FOCUS ULTRASOUND FOR BRAIN METS: PRINCIPLE





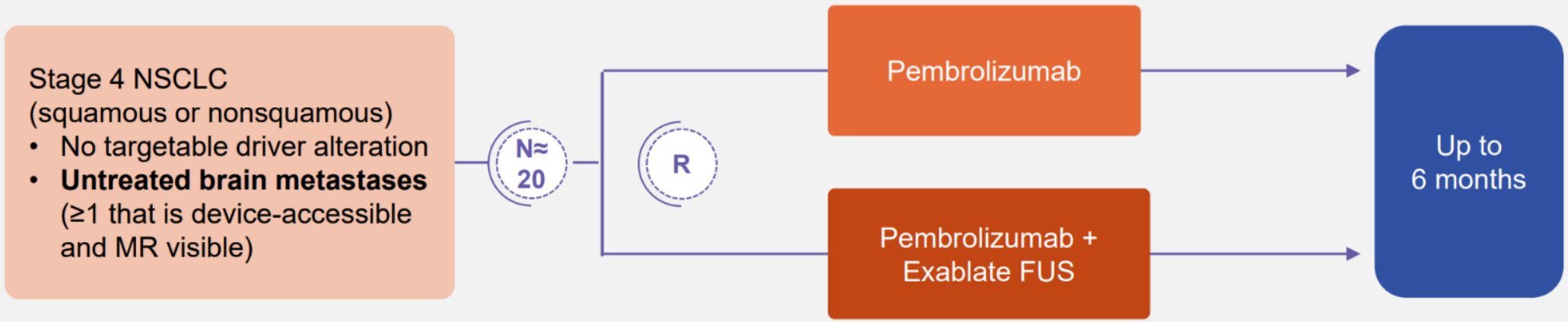
Size-dependent BBB permeation

Normal state
Drug/mAb entrance into the brain is restricted by tight junctions of the BBB

FUS exposure
Microbubble cavitation widens BBB junctions allowing some drugs/mAbs to cross

Ohta Sci Rep 2020

PHASE III (?) RCT (NCT05317858)
PEMBRO VS FUS & PEMBRO



Endpoints

Primary endpoints
– **AEs, ORR**

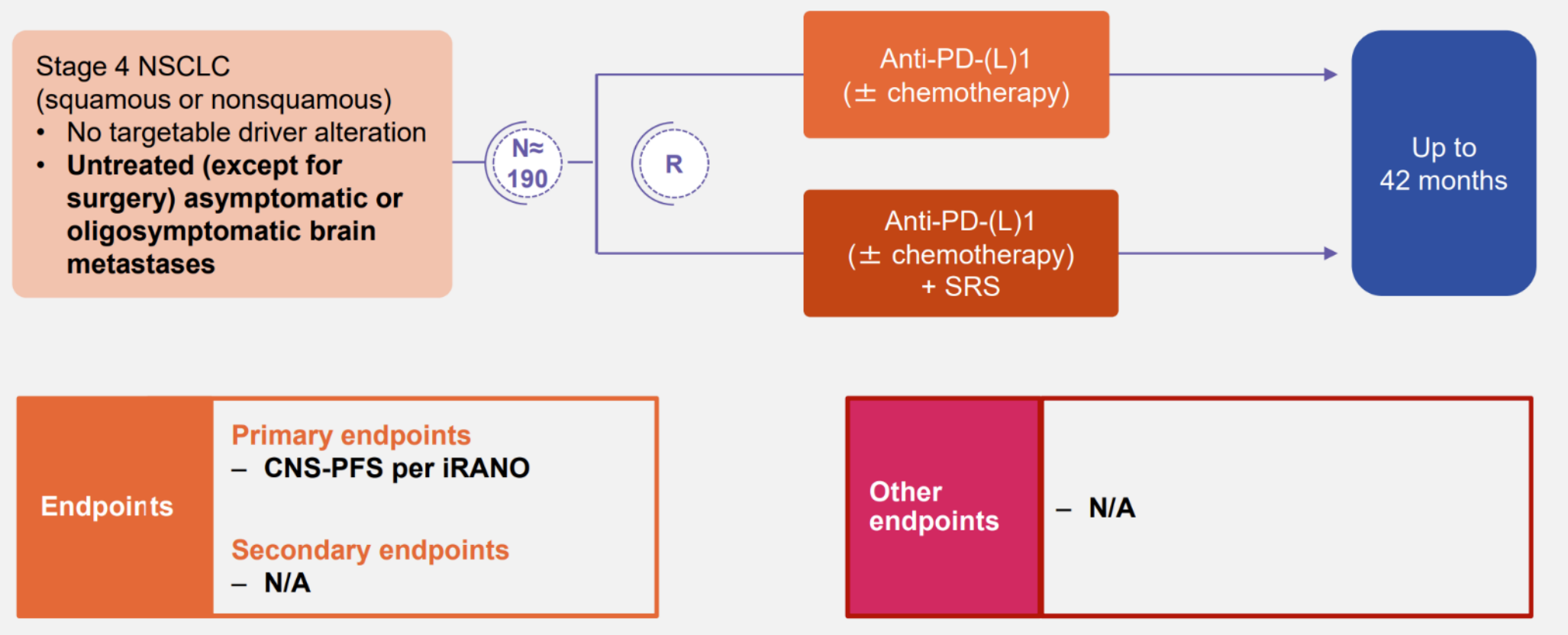
Secondary endpoints
– **RANO-BM ORR & TTR**

Other endpoints

– **Patient reported QoL**
– **Measurement of BBB disruption**

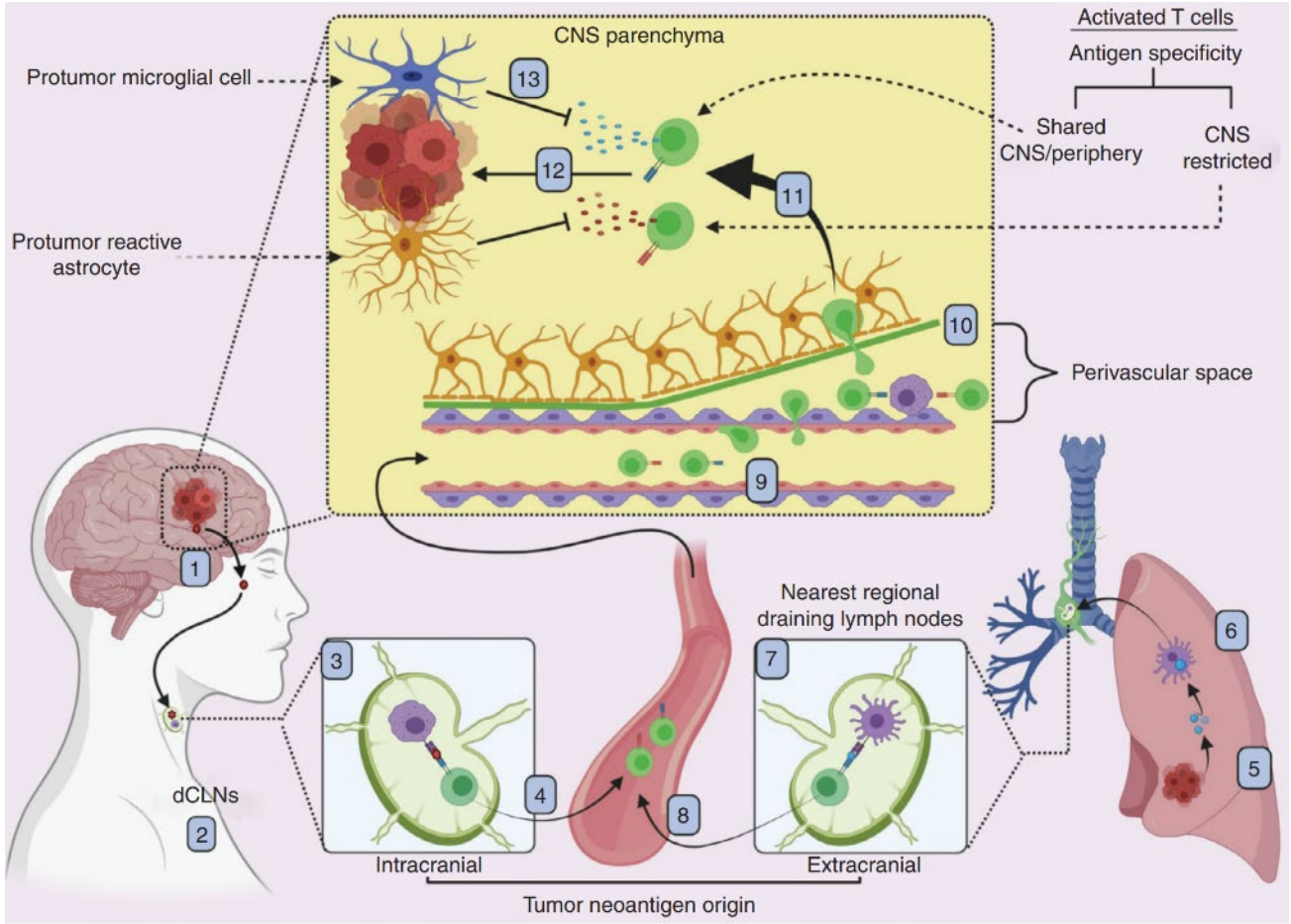
USZ-STRIKE (NCT05522660): PHASE III RCT EVALUATING SEQUENCE OF TREATMENT

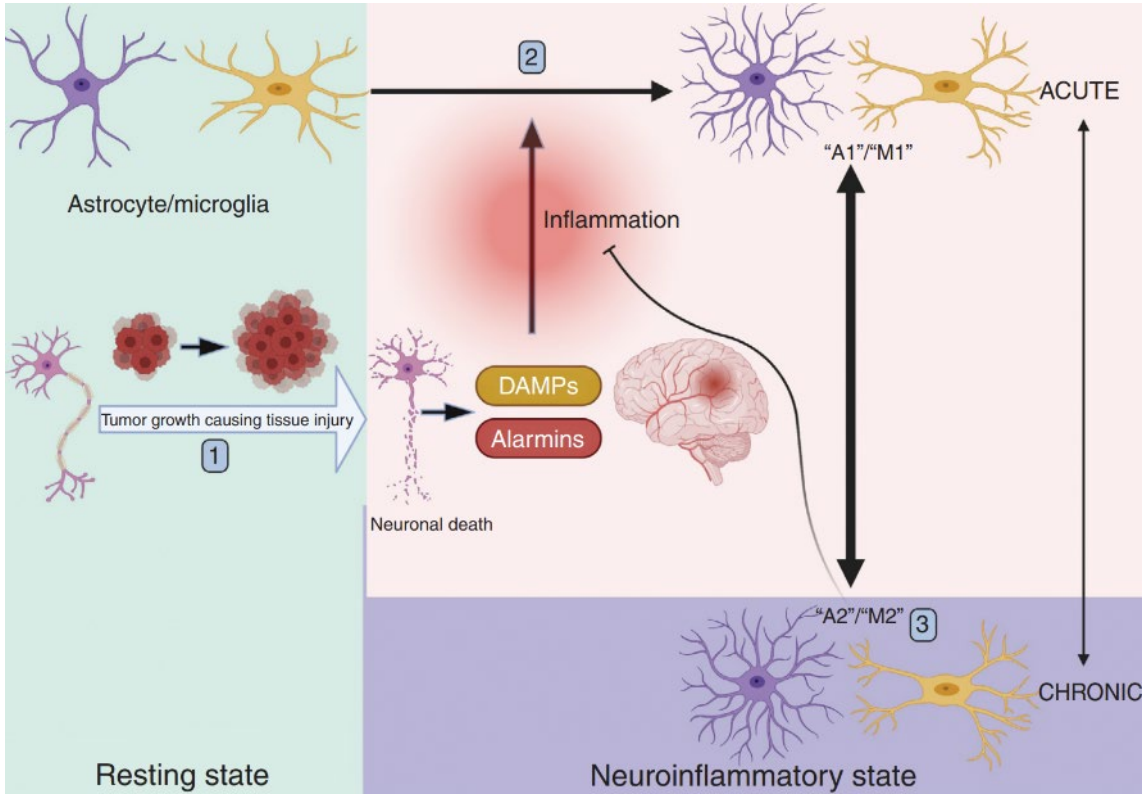
Cohort 2B: ICI +/- SRT for NSCLC brain mets



WE NEED TO UNDERSTAND THE CNS TME TO IMPROVE TREATMENT

CNS T-cell response, role astrocytes, microglia, bone marrow derived macrophages





L Hendriks

Strickland & Brastianos Cancer Disc 2022

TO READ AND IMPLEMENT: FDA BRAIN METS RECOMMENDATIONS

Document prior CNS therapies on CRF + timing of these therapies

Stratify for prior therapy

Assess with MRI brain, specify when pretreated BM is eligible

Baseline imaging of CNS for all patients + follow up same time as extraCNS disease

Apply accepted CNS response criteria + document neurological complaints + therapy

Define appropriate endpoint

GUIDANCE DOC = NECESSARY!
recommendations seldom already incorporated

FDA guidance doc July 2021; Schoenmaekers & Hendriks CROH 2021; Corbett JAMA Oncol 2021

CONCLUSIONS AND TAKE HOME MESSAGES

Brain metastases occur frequent in NSCLC

Historically, survival was poor

Although TME is less favourable vs extracranial, immunotherapy can result in long-lasting responses

Research needed to evaluate the best treatment sequence and to better understand the CNS TME

Dedicated trials needed

GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Thank you for your attention

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